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CX. Classification of Receptors for
5-hydroxytryptamine; Pharmacology and Function**

Nicholas M Barnes, Gerard P Ahern, Carine Becamel, Joël Bockaert, Michael Camilleri, Séverine Chaumont-Dubel, Sylvie Claeysen, Kathryn A Cunningham, Kevin C Fone, Michael Gershon, et al.

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International Union of Basic and Clinical Pharmacology. XXX: Classification of receptors for 5-hydroxytryptamine; pharmacology and function

Nicholas M. Barnes, Gerard P. Ahern, Carine Becamel, Joël Bockaert, Michael Camilleri, Severine Chaumont-Dubel, Sylvie Claeysen, Kathryn A. Cunningham, Kevin C. Fone, Michael Gershon, Giuseppe Di Giovanni, Nathalie M. Goodfellow, Adam Halberstadt, Rachel M. Hartley, Ghérici Hassaine, Katharine Herrick-Davis, Ruud Hovius, Michael T. Klein, Enza Lacivita, Evelyn K. Lambe, Marcello Leopoldo, Finn Olav Levy, Sarah C.R. Lummis, Philippe Marin, Luc Maroteaux, Andrew C. McCreary, David L. Nelson, John F. Neumaier, Adrian Newman-Tancredi, Hugues Nury, Alexander Roberts, Bryan L. Roth, Anne Roumier, Gareth J. Sanger, Milt Teitler, Trevor Sharp, Carlos M. Villalón, Horst Vogel, Stephanie W. Watts, Daniel Hoyer

Neuropharmacology Research Group, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT UK (N.M.B., A.R.); Department of Pharmacology and Therapeutics, School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Victoria 3010, Australia (N.M.B., D.H.); Department of Pharmacology, Georgetown University Medical Center, 3900 Reservoir Road, Washington DC, 20007, USA (G.P.A.); IGF, CNRS, INSERM, Univ Montpellier, Montpellier, France (C.B., J.B., S.C-D., S.C., P.M.); INSERM, U1191, F-34094 Montpellier, France (C.B., J.B., S.C-D., S.C., P.M.); Université de Montpellier, F-34094 Montpellier, France (C.B., J.B., S.C-D., S.C., P.M.); C.E.N.T.E.R. Division of Gastroenterology and Hepatology Mayo Clinic, Rochester, Minnesota 55905, USA (M.C.); Center for Addiction Research and Department of Pharmacology and Toxicology, University of Texas Medical Branch, 301 University Boulevard, Galveston, Texas 77555, USA (K.A.C., R.M.H.); School of Life Sciences, Medical School, Queen's Medical Centre, The University of Nottingham, Nottingham NG7 2RD UK (K.C.F.); Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, 650 West 168th Street, New York, NY 10032, USA (M.G.); Laboratory of Neurophysiology, Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta MSD2080 (G.D.G.); Department of Physiology, Department of Obstetrics and Gynaecology, Department of Psychiatry, University of Toronto, Toronto, ON M5S 1A8 Canada (N.M.G., E.K.L.); Department of Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0804, USA (A.H.); Theranynx, 163 Avenue de Luminy, Marseille, France (G.H.); Department of Neuroscience

and Experimental Therapeutics, Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA (K.H-D.); Ecole Polytechnique Fédérale de Lausanne, Institute of Chemical Sciences and Engineering, Lausanne, Switzerland (R.H., H.V.); Center for Neuropharmacology & Neuroscience, Albany Medical College, Albany, New York 12208, USA (M.T.K., M.T.); Department of Pharmacy - Drug Science, University of Bari Aldo Moro, Via Orabona 4, 70125 Bari, Italy (E.L., M.L.); Department of Pharmacology, Faculty of Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway; Center for Heart Failure Research, Faculty of Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway (F.O.L.); Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge CB2 1QW UK (S.C.R.L.); INSERM UMR-S 839, F75005, Paris, France; Université Pierre et Marie Curie, F75005, Paris, France; Institut du Fer à Moulin, F75005, Paris, France (L.M., A.R.); Drug Development, Grunenthal GmbH, Aachen, Germany (A.C.M.); Neuroscience Discovery Research and Discovery Chemistry, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA (D.L.N.); Departments of Psychiatry & Behavioral Sciences and Pharmacology, University of Washington, Seattle, WA 98104, USA (J.F.N.); Neurolix Inc., Dana Point, CA 92629, USA (A.N-T.); Université Grenoble Alpes, IBS, Grenoble, France (H.N.); CNRS, IBS, Grenoble, France (H.N.); CEA, DSV, IBS, Grenoble, France (H.N.); Department of Pharmacology, University of North Carolina, Chapel Hill, NC 27599, USA (B.L.R.); Blizzard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK (G.J.S.); Department of Pharmacology, University of Oxford, Oxford, OX1 3QT UK (T.S.); Cinvestav-Coapa, Pharmacobiology, Mexico City, Tlalpan, Mexico (C.M.V.); Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824-1317, USA (S.W.W.); The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, 30 Royal Parade, Parkville, VIC, 3052, Australia (D.H.); Department of Molecular Medicine, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA (D.H.).

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Corresponding author: Professor Nicholas M. Barnes PhD, FBPhS, Neuropharmacology Research Group, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT UK; Email: n.m.barnes@bham.ac.uk

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List of abbreviations

(+)-5-FPT: (+)-5-(2'-fluorophenyl)-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine

1-PP: 1-(2-pyrimidinyl)-piperazine

25CN-NBOH: (N-(2-hydroxybenzyl)-2,5-dimethoxy-4-cyanophenethylamine)

2-AG: 2-arachidolyglycerol

2S,6S-DMBMPP: ((+)-(2S,6S)-trans-2-(2,5-dimethoxy-4-bromobenzyl)-6-(2-methoxyphenyl)piperidine

5-CT: 5-Carboxamidotryptamine

5-HIAA: 5-hydroxyindole acetic acid

5-HT: 5-hydroxytryptamine

5-HTBP: 5-HT binding protein

5-MeO-DMT: 5-methoxy-N,N-dimethyltryptamine

8-OH DPAT: (\pm)-8-Hydroxy-2-dipropylaminotetralin

AC: Adenyl cyclase

ACC: Anterior cingulate cortex

AChE: Acetylcholinesterase

ACTH: Adrenocorticotrophic hormone

AD: Alzheimer's disease

ADAR: RNA-specific adenosine deaminase

ADHD: Attention deficiency hyperactivity disorder

AIWG: Antipsychotic-induced weight gain

AKAP: A Kinase Anchoring proteins

AngII: Angiotensin II

ANLN: Anillin

ANT-1: Adenine nucleotide translocator

AP1: Activator protein 1

AP-2: Activator protein 2

APA: Adrenocortical aldosterone-producing adenoma

AP-MS: Affinity purification-mass spectrometry

APP: Amyloid precursor protein

ARF1: ADP-ribosylation factor 1

ASD: Autism spectrum disorder

AT1: Angiotensin II receptor type 1

ATL: Adult T-cell leukemia

A β : Amyloid- β

BAC: Bacterial artificial chromosome

BBB: Blood brain barrier

BDNF: Brain derived neurotrophic factor

BFU: Erythroid burst-forming units

BIS: Behavioral inhibition system

BMI: Body mass index

BNP: Brain natriuretic peptide

BPAD: Bipolar affective disorder

BRET: Bioluminescence resonance energy transfer

BSS: Behavioral satiety sequence

cAMP: Cyclic adenosine monophosphate

CART: Cocaine- and amphetamine-regulated transcript

CCI: Chronic constriction injury

CD: Cluster of differentiation

CDK5: Cyclin-dependent kinase 5

CFU-E: Hematopoietic colony forming unit

CFU-GEMM: Early stem/progenitors

cGMP: Cyclic guanosine monophosphate

CGRP: Calcitonin gene-related peptide

CHO: Chinese Hamster Ovary

CIPP: Channel interacting PDZ protein,

cNOS: Constitutive nitric-oxide synthase

CNS: Central nervous system

COPD: Chronic obstructive pulmonary disease

COX: Cyclooxygenase

CpG: Methyl-cytosine-phosphate-guanine

CRE: cAMP response element

CREB: cAMP response element binding

CRF: Corticotropin-releasing factor

CRMP: Collapsing response mediator protein

CRP: C-reactive protein

CXCL: Chemokine ligand

CYP: Cyanopindolol

DA: Dopamine
DAG: Diacylglycerol
DARPP₃₂: Dopamine and cAMP regulated phosphoprotein
DCX: Doublecortin
DHE: Dihydroergotamine
DOB: 2,5-Dimethoxy-4-bromoamphetamine
DOCA: Deoxycorticosterone
DOI: 2,5-Dimethoxy-4-iodoamphetamine
DOM: 2,5-dimethoxy-4-methylphenyl-2-aminopropane
DRG: Dorsal root ganglion
DRN: Dorsal Raphe nucleus
EB: Embryoid body
EC: Enterochromaffin cells
ECD: Extracellular domain
ECL2: Extracellular loop 2
EEDQ: N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EEG: Electroencephalography
EGFP: Enhanced Green fluorescent protein
EGFR: Epidermal growth factor receptor
eIF3k: Eukaryotic Initiation of translation Factor 3, subunit k
EMDT: 2-Ethyl-5-methoxy-N,N-dimethyltryptamine
ENS: Enteric nervous system
EPS: Extrapyramidal side effects
ER: Endoplasmic reticulum
ERG-1: Early growth response protein 1
ERK: Extracellular Signal-regulated Kinase
ES: Embryonic stem

FDA: Food and Drug Administration

FFA2: Free fatty acids

Fmr1: Fragile X mental retardation 1

FMRP: Fragile X mental retardation protein

FR: Fixed ratio

FRET: Fluorescence Resonance Energy Transfer

FST: Forced swim test

FXS: Fragile X syndrome

GABA: gamma-Aminobutyric acid

GAERS: Genetic Absence Epilepsy Rat from Strasbourg

GAP: GTPase activating protein

GASPs: GPCR-associated sorting proteins

GDNF: Glial cell-derived neurotrophic factor

GEF: Guanine nucleotide exchange factor

GH: Growth hormone

GI: Gastrointestinal

GIP: Glucose-dependent insulinotropic peptide

GIP: GPCR interacting protein

GIRK: G protein-coupled inwardly-rectifying potassium channel

GlcNAc: N-acetylglucosamine

GLIC: Gloeobacter ligand-gated ion channel

GluCl: Glutamate-gated chloride channels

GM-CSF: Granulate-macrophage colony-stimulating factor

GPCR: G-protein coupled receptor

GPRIN1: G protein inducer of neurite growth 1

GR: Glucocorticoid receptor

GRK: G-protein-coupled receptor protein kinase

GSK3: Glycogen synthase kinase-3

GTI: Carboxymethylglycyl iodotyrosinamide

GTP: Guanosine-5'-triphosphate

GTPase: Guanosine triphosphate hydrolase enzyme

HB-EGF: Heparin-binding EGF-like growth factor

HCC: Hepatocellular carcinoma

HCN: Hyperpolarization-activated cyclic nucleotide-regulated channels

HDAC: Histone deacetylase

hERG: Human Ether-ago-go-Related Gene

HR: High responder

HSC: Hepatic stellate cells

HUVEC: Human umbilical endothelial cells

IBS: Irritable bowel syndrome

IBS-C: IBS with constipation

IBS-D: IBS with diarrhea

ICC: Interstitial cells of Cajal

ICD: Intracellular domain

IDO: indoleamine 2,3-dioxygenase

IEG: Immediate-early gene

IG: Immunoglobulin

I_h: Hyperpolarization activated current

IKBKE: Inhibitor of nuclear factor kappa-B kinase subunit epsilon

IL: Interleukin

iNOS: Inducible nitric-oxide synthase

IP: Intraperitoneal

IP₃: Inositol-1,4,5-triphosphate

IPANs: Intrinsic afferent neurons

ISHH: In situ hybridization histochemistry

ITTP: Intrathymic T progenitor

IUPHAR: International Union of Basic and Clinical Pharmacology

NfκB α : Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha

JAK: Janus kinase

JCV: John Cunningham Virus/polyomavirus

KIF5B: Kinesin family member 5B

L-DOPA: levodopa

LDT: Laterodorsal tegmental area

LID: L-DOPA-induced dyskinesia

LPS: Lipopolysaccharide

LR: Low responder

LSD: Lysergic acid diethylamide

LSTc: Sialic acid receptor motif α 2,6-linked lactoseries tetrasaccharide c

LTD: Long term depression

M1: Pro-inflammatory macrophage

M2: Anti-inflammatory macrophage

MAGI2: Membrane-associated guanylate kinase with inverted domain structure 2,

Man: Mannoses

MAO: Monoamine oxidase

MAP: Microtubule-associated protein

MAP1B-LC1: light chain 1 subunit of MAP1B protein

MAPK: Mitogen-activated protein kinase

MCHR1: Melanin-concentrating hormone receptor 1

MCP-1: Monocyte chemoattractant protein-1

mCPP: M-chlorophenylpiperazine

M-CSF: Macrophage colony-stimulating factor

MDA: 3,4-methylene dioxyamphetamine

MDC: Macrophage-derived chemokine

MDMA: 3,4-methylenedioxy methamphetamine

MeCP2: Methyl-CpG-binding protein 2

MEF2: Myocyte enhancer factor-2 proteins

mEPSCs: Miniature excitatory postsynaptic currents

Micro PET: Micro positron emission tomography

MK: Megakaryocyte

MMC: Migrating motor complex

MMP: Matrix metalloproteinase

MMVD: Myxomatous mitral valve disease

mPER2: Period circadian protein homolog 2

mPFC: Medial prefrontal cortex

MPP2: MAGUK p55 subfamily member

MPPF: 2'-methoxyphenyl--p-fluoro-benzamidoethylpiperazine

mRNA: Message Ribonucleic acid

mTor: Mechanistic target of rapamycin

mTORC1: mTOR complex 1

MUPP1: Multi-PDZ Domain Protein 1

NAc: Nucleus accumbens

NADP: Nicotinamide adenine dinucleotide phosphate,

NAL: Neutral allosteric ligands

NAM: Negative allosteric modulators

NCAM: Neural cell adhesion molecule

ND2: Adaptor protein NADH dehydrogenase subunit 2

NE: Norepinephrine

NF: Neurofibromin

NF-1: Nuclear factor 1

NFAT: Nuclear factor of activated T-cells

NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells

NF- κ B: Nuclear factor- κ B

NHE-1: Type1 sodium-proton exchanger

NHERF: Na⁺/H⁺ exchanger regulatory factor

NK: Neurokinin

NMDA: N-methyl-D-aspartic acid

NO: Nitric oxide

NOS: Nitric oxide synthase

NOX: NADPH oxidase

NR1: NMDA receptor subunit 1

NREM: Non-rapid eye movement sleep

NUDR/DEAF-1: nuclear DEAF-1-related / Drosophila Deformed epidermal autoregulatory factor-1

OCD: Obsessive-compulsive disorder

P2: Purinergic2 receptors

PAH: Pulmonary arterial hypertension

PAK: p21 activated kinases

PAM: Positive allosteric modulator

PCP: Phencyclidine

PCR: Polymerase chain reaction

PD: Parkinson's disease

PDE: Phosphodiesterase

PDGFR: Platelet derived growth factor receptor

PDZ 10: MUPP1 PDZ domain 10

PDZ: PSD-95/Disc large/Zonula occludens

pEC₅₀: Negative log of 50% effective concentration

PET: Positron emission tomography

PFC: Prefrontal cortex

PG12: Prostacyclin
PGIS: Prostacyclin synthase
PI3K: Phosphatidylinositol-3 kinase
PICOT: Protein kinase C interacting cousin of thioredoxin
PKA: Protein kinase A
PKC: Protein Kinase C
PLA₂: Phospholipase A₂
PLAC-24: Protein that Localizes At Cell-cell Contacts
PLC: Phospholipase C

PLC β : Phospholipase C beta
PLD: phospholipase D
PML: Multifocal leukoencephalopathy
POMC: Pro-opiomelanocortin

POV: Post-operative vomiting
PPAR: Peroxisome proliferator-activated receptors
PPI: Prepulse inhibition
PPT: Pedunculopontine tegmental area
PR: Progressive ratio
PRAS40: Proline-rich Akt substrate of 40 kDa
PSD: Postsynaptic marker

PSD-95: Postsynaptic density-95

PTEN: Phosphatase and tensin homolog deleted on chromosome 10

PTSD: Post-traumatic stress disorder
PWE: Patients with epilepsy
qPCR: Quantative polymerase chain reaction
REM: Rapid eye movement sleep

Rheb: Ras homolog enriched in brain
RNA: Ribonucleic acid

ROS: Reactive oxygen species

RSK2: P90 ribosomal S6 kinase 2

RT-PCR: Reverse transcriptase polymerase chain reaction

RTT: Rett syndrome

SAP97: Synapse-associated protein 97

SAR: Structure activity relationship

SCFAs: Short-chain fatty acids

SCN: Suprachiasmatic nucleus

SERT: Serotonin transporter

Sf9: Spodoptera frugiperda 9 cells

SGZ: Sub-granular zone

siRNA: Small interfering RNA

SN: Substantia nigra

SNC: Substantia nigra pars compacta

SNP: Single nucleotide polymorphism

SNX: Sorting nexin family member

SOD1: Superoxide dismutase 1

SPARC: Secreted protein acidic and rich in cysteine

SRF: Serum response factor

SRI: Serotonin reuptake inhibitor

SSRI: Selective serotonin reuptake inhibitor

STAT: Signal Transducer and Activator of Transcription

SW: Slow wave

SWS: Slow wave sleep

TACE, ADAM-17: Tumor necrosis factor-alpha (TNF- α) converting enzyme

TASK-1: Acid-Sensitive Potassium Channel Protein-1

TCB-2: (4-Bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine

TFMPP: 3-trifluoromethylphenylpiperazine

TG: Tissue transglutaminase

TGF- β 1: Transforming growth factor beta 1

Th: T helper cells

TH2: T helper cell 2

THC: Δ^9 -tetrahydrocannabinol

TLE: Temporal lobe epilepsy

TLR: Toll-like receptors

TM: Trans-membrane domains

TMD: Transmembrane domain

TNAP: Tissue-non specific alkaline phosphatase

TNF: Tumour necrosis factor

TPH: Tryptophan hydroxylase

TRPC: Transient receptor potential channels

TrpV1: Transient receptor potential cation channel subfamily V member 1

TSC: Tuberos sclerosis

TST: Tail suspension test

TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

VGlut1: Vesicular glutamate transporter 1

VMAT: Vesicular monoamine transporter

VTA: Ventral Tegmental Area

WASP: Wiskott-Aldrich syndrome protein

WAVE-1: WASP-family verprolin homologous protein 1

WBC: White blood cell

WT: Wild type

Yif1B: Yip1 interacting factor homolog B

α -Me-5-HT: α -methyl-5-HT

Table of Contents

Abstract

I. Introduction

II. 5-HT_{1A} receptor

II. A. Introduction

II. B. 5-HT_{1A} receptor identification and expression

II. C. Pharmacology

II. D. Biased agonism: differential activation of 5-HT_{1A} receptor subpopulations

II. E. 5-HT_{1A} intracellular signal transduction

II. F. Function

II. F. 1. Differential function of 5-HT_{1A} receptors at cellular, tissue and *in vivo* level

II. F. 1.a. 5-HT_{1A} receptors in depression and anxiety

II. F. 1.b. 5-HT_{1A} receptor activation for improved antipsychotic action

II. G. 5-HT_{1A} receptors and some emerging treatment areas

II. G. 1. Parkinson's disease

II. G. 3. Pain

II. G. 4. Attention Deficiency Hyperactivity Disorder

II. G. 5. Autism Spectrum Disorder

II. G. 6. Respiratory control

II. G. 7. Sexual dysfunction

II. G. 8. Food intake, and eating disorders

II. G. 9. Aggressive behaviour

II. G. 10. Neuroplasticity and neuroprotection

III. 5-HT_{1B} receptors

III. A. Introduction

III. B. Pharmacology

III. C. Receptor structure and transduction

III. D. Distribution and function

III. E. Radioligand binding

IV. 5-HT_{1D} receptors

IV. A. Introduction

IV. B. Pharmacology

IV. C. Receptor structure and transduction

IV. D. Distribution and function

IV. E. Radioligand binding

V. 5-HT_{1e} receptors

V. A. Introduction

V. B. Cloning and distribution of 5-HT_{1e} receptors

V. C. Pharmacology

V. D. Functions

VI. 5-HT_{1F} receptors

VI. A. Introduction

VI. B. Cloning and structure

VI. C. Distribution

VI. C. 1. mRNA

VI. C. 2. Radioligand binding

VI. C. 3. Immunoreactivity

VI. D. Pharmacology

VI. D. 1. Agonists

VI. D. 2. Partial agonists and antagonists

VI. E. Signal transduction

VI. F. Function

VI. G. Clinical relevance and therapeutics

VII. 5-HT_{2A} receptors

VII. A. Introduction

VII. B. Cloning of the gene

VII. B.1. Regulation of 5-HT_{2A} receptor gene expression

VII. C. Distribution

VII. D. Post-translational modifications and impact

VII. E. Pharmacology

VII. F. Function

VII. F. 1. Signalling

VII. F. 2. Action in cells, tissues and *in vivo*

VII. G. Clinical relevance

VIII. 5-HT_{2B} receptor

VIII. A. Introduction

VIII. B. Expression profile

VIII. B. 1. Peripheral expression

VIII. B. 2. Central expression

VIII. C. Post-translational modifications and impact

VIII. C. 1. Gene structure

VIII. C. 2. Gene regulation

VIII. C. 3. Receptor isoforms

VIII. D. Protein structure

VIII. E. Heteromeric receptor associations

VIII. F. Pharmacology

VIII. F. 1. Agonists

VIII. F. 2. Antagonists

VIII. F. 3. Allosteric modulators

VIII. G. Transduction system(s)

VIII. G. 1. Transfected cells

VIII. G. 2. Primary cell cultures

VIII. H. Regulatory mechanisms

VIII. H. 1. Internalization

VIII. H. 2. Interacting proteins

VIII. I. Function at cellular, tissue and *in vivo* level

VIII. I. 1. Hematopoiesis

VIII. I. 2. Pancreas

VIII. I. 3. Adipocytes

VIII. I. 4. Cardio-vascular and pulmonary

VIII. I. 5. Endothelial cells

- VIII. I. 6. Aorta
- VIII. I. 7. Liver
- VIII. I. 8. Gut
- VIII. I. 9. Central autonomic nervous system
- VIII. I. 10. Peripheral autonomic nervous system
- VIII. I. 11. Amygdala and anxiety
- VIII. I. 12. Sleep
- VIII. J. Clinical relevance
 - VIII. J. 1. Feeding and anorexigens
 - VIII. J. 2. Raphe and antidepressant
 - VIII. J. 3. Dopamine and antidepressant
 - VIII. J. 4. Serotonin (5-HT) syndrome
 - VIII. J. 5. Drug of abuse
 - VIII. J. 6. Impulsivity
 - VIII. J. 7. Fragile X syndrome
 - VIII. J. 8. Cardiovascular diseases
 - VIII. J. 9. Pulmonary arterial hypertension
 - VIII. J. 10. Vascular hypertension
 - VIII. J. 11. Fibrosis
 - VIII. J. 12. Valvular heart disease
 - VIII. J. 13. Acute Pain
 - VIII. J. 14. Chronic pain
 - VIII. J. 15. Neuropathic pain
 - VIII. J. 16. Spasticity in amyotrophic lateral sclerosis
 - VIII. J. 17. Migraine
 - VIII. J. 18. Visceral pain
 - VIII. J. 19. Bones
 - VIII. J. 20. Teeth development
 - VIII. J. 21. Cancers
 - VIII. J. 21. a. Carcinoid tumors
 - VIII. J. 21. b. Breast tumors
 - VIII. J. 21. c. Melanoma
 - VIII. J. 21. d. Prostate cancer

- VIII. J. 21. e. Adrenocortical carcinoma
- VIII. J. 21. f. Hepatocellular carcinoma
- VIII. J. 21. g. T-cell Leukemia
- VIII. J. 21. h. Myosarcoma
- VIII. J. 21. i. Tumor angiogenesis
- VIII. J. 22. Clinical relevant knowledge gained from the gene
- VIII. J. 22. a. The human 5-HT_{2B} receptor gene

- IX. 5-HT_{2C} receptor
- IX. A. Introduction
- IX. B. Expression profile
- IX. C. Post-transcriptional and post-translational modifications
- IX. C. 1. RNA editing
- IX. C. 2. RNA splicing
- IX. C. 3. Single nucleotide polymorphisms
- IX. C. 4. Glycosylation
- IX. C. 5. Phosphorylation
- IX. C. 6. Dimerization
- IX. D. Pharmacology
- IX. E. Signal transduction
- IX. E. 1. Phospholipase C
- IX. E. 2. Phospholipase D
- IX. E. 3. Phospholipase A₂
- IX. E. 4. Cyclic nucleotides
- IX. E. 5. Extracellular signal-regulated kinases (ERK_{1/2})
- IX. E. 6. Ion channels
- IX. F. The 5-HT_{2C} receptor as an oncogene
- IX. G. Clinical relevance of the 5-HT_{2C} receptor
- IX. G. 1. Substance use disorders (addiction)
- IX. G. 2. Appetite, satiety and obesity
- IX. G. 3. Schizophrenia
- IX. G. 4. Mood disorders and anxiety
- IX. G. 5. Epilepsy

IX. G. 6. Sleep

IX. G. 7. Clinical impact of RNA editing of the 5-HT_{2C} receptor

X. 5-HT₃ receptor

X. A. Introduction

X. B. Expression

X. C. Post-translational modifications

X. D. Pharmacology

X. E. Function

X. F. Clinical relevance

XI. 5-HT₄ receptors

XI. A. Introduction

XI. B. Gene and primary structure

XI. C. Expression profile

XI. C. 1. Central nervous system

XI. C. 2. Periphery

XI. C. 2. a. Cardiac system

XI. C. 2. b. Gastro-intestinal (GI) tract

XI. C. 2. c. Adrenal gland

XI. C. 2. d. Salivary glands

XI. C. 2. e. Urinary bladder

XI. C. 2. f. Lung

XI. D. Post-translational modifications

XI. D. 1. *N*-Glycosylation

XI. D. 2. Palmitoylation

XI. D. 3. Phosphorylation

XI. E. Pharmacology

XI. E. 1. Agonists

XI. E. 2. Antagonists

XI. E. 3. Inverse agonists

XI. E. 4. Multifunctional ligands

XI. E. 5. 5-HT₄ receptor radioligands

XI. F. Function

XI. F. 1. Physiological function

XI. F. 2. Cellular function

XI. F. 2. a. G-protein coupling of 5-HT₄ receptors and primary signalling events

XI. F. 2. b. G-protein independent coupling of 5-HT₄ receptors

XI. F. 2. c. GPCR interacting proteins (GIPs) associated with 5-HT₄ receptors

XI. F. 3. Gastro-intestinal (GI) tract

XI. F. 4. Visceral pain

XI. F. 5. ENS development and ENS adult neurogenesis

XI. F. 6. Central nervous system

XI. F. 6. a. Learning and memory

XI. F. 6. b. Control of mood, role of 5-HT₄ receptor agonists

XI. F. 6. c. Feeding behaviour

XI. F. 6. d. Cardiac system

XI. F. 6. e. Respiratory system

XI. F. 6. f. Adrenal gland

XI. F. 6. g. Urinary bladder

XI. G. Clinical relevance

XI. G. 1. Gastro-intestinal pathologies

XI. G. 2. Learning, memory and Alzheimer's disease

XI. G. 3. Anxiety and depression

XI. G. 4. Heart disease

XI. G. 5. Respiratory system

XI. G. 6. Adrenocortical hyperplasias and tumors

XI. G. 7. Feeding behaviour

XII. 5-HT_{5A} Receptors

XII. A. Introduction

XII. B. Gene and primary structure

XII. C. Expression profile

XII. D. Post-translational modifications and impact

XII. E. Pharmacology

XII. F. Function

- XII. F. 1. Cellular function
- XII. F. 2. G-protein coupling of the 5-HT_{5A} receptor *in vitro*
- XII. F. 3. G-protein coupling of the 5-HT_{5A} receptor *ex vivo*
- XII. F. 4. 5-HT_{5A} receptor function in the spinal cord
- XII. F. 5. Function *in vivo*
- XII. G. Clinical relevance
 - XII. G. 1. Psychosis and depression
 - XII. G. 2. Memory and circadian rhythm

- XIII. 5-ht_{5b} Receptors
 - XIII. A. Introduction
 - XIII. B. Receptor structure
 - XIII. C. Expression profile
 - XIII. D. Regulatory mechanisms and post-translational modifications
 - XIII. E. Pharmacology
 - XIII. F. Function at cellular, tissue and *in vivo* level
 - XIII. G. Clinical relevance

- XIV. 5-HT₆ receptors
 - XIV. A. Introduction
 - XIV. B. Expression
 - XIV. C. Pharmacology
 - XIV. D. Post-translational modifications and protein interactions
 - XIV. E. Signaling pathways
 - XIV. F. Function
 - XIV. F. 1. Electrophysiology
 - XIV. G. Clinical Relevance

- XV. 5-HT₇ receptors
 - XV. A. Introduction
 - XV. B. Cloning of the gene
 - XV. C. Expression
 - XV. C. 1. mRNA

- XV. C. 2. Radioligand binding
- XV. C. 3. Immunoreactivity
- XV. D. Pharmacology
 - XV. D. 1. Agonists
 - XV. D. 2. Antagonists
 - XV. D. 3. Allosteric modulators
- XV. E. Signalling
- XV. F. Post-translational modifications
 - XV. F. 1. Regulatory mechanisms
 - XV. F. 2. Interacting proteins
 - XV. F. 3. Homo and heteromeric receptor associations
- XV. G. Function
 - XV. G. 1. Thermoregulation
 - XV. G. 2. Learning and Memory
 - XV. G. 3. Anti-psychotic potential
 - XV. G. 4. Antidepressant-like behavior
 - XV. G. 5. Sleep
 - XV. G. 6. Autism Spectrum Disorders
 - XV. G. 7. Epilepsy
 - XV. G. 8. Drug Abuse
 - XV. G. 9. Pain
- XV. H. Clinical relevance
 - XV. H. 1. Depression
 - XV. H. 2. Sleep

- XVI. High resolution structure of 5-HT receptors
 - XVI. A. 5-HT GPCRs
 - XVI. B. 5-HT LGIC

- XVII. 5-HT GPCRs and their interacting proteins

XVII. A. Introduction

XVII. B. A survey of 5-HT receptor GIPs

XVII. B. 1. 5-HT_{1A} receptor

XVII. B. 2. 5-HT_{1B} receptor

XVII. B. 3. 5-HT_{2A} receptor

XVII. B. 4. 5-HT_{2B} receptor

XVII. B. 5. 5-HT_{2C} receptor

XVII. B. 6. 5-HT₄ receptors

XVII. B. 7. 5-HT₇ receptor

XVII. C. 5-HT₆ receptor receptosome: toward new signalling mechanisms underlying its control of cognition and neurodevelopmental processes

XVII. C. 1. Introduction

XVII. C. 2. Fine tuning of 5-HT₆ receptor trafficking and signal transduction by GIPs

XVII. C. 3. Recruitment of mTOR complex 1 by 5-HT₆ receptor: potential role in cognitive deficits associated with schizophrenia

XVII. C. 4. Recruitment of Cdk5 by 5-HT₆ receptor: an essential step in its control of neuronal migration and differentiation

XVIII. 5-HT receptors and the brain

XVIII. A. Introduction

XVIII. B. 5-HT receptor signalling in neurons

XVIII. C. Expression of 5-HT receptors in the brain

XVIII. C. Presynaptic 5-HT receptors

XVIII. D. Postsynaptic 5-HT receptors

XVIII. E. Cellular localisation of CNS 5-HT receptors

XVIII. F. Behavioural roles of 5-HT receptors in the brain

XVIII. F. 1. Introduction

XVIII. F. 2. 5-HT₁ receptor family

XVIII. F. 2. a. 5-HT_{1A} receptors

XVIII. F. 2. b. 5-HT_{1B} receptors

XVIII. F. 3. 5-HT₂ receptor family

XVIII. F. 3. a. 5-HT_{2A} receptors

XVIII. F. 3. b. 5-HT_{2B} receptors

XVIII. F. 3. c. 5-HT_{2C} receptors

XVIII. F. 4. 5-HT₃ receptors

XVIII. F. 5. 5-HT₄ receptors

XVIII. F. 6. 5-HT₅ receptors

XVIII. F. 7. 5-HT₆ receptors

XVIII. F. 8. 5-HT₇ receptors

XIX. 5-HT receptors and the cardiovascular system

XIX. A. Introduction

XIX. B. 5-HT in cardiovascular tissues

XIX. C. Cardiovascular effects mediated by 5-HT receptors

XIX. C. 1. 5-HT_{1A} receptors

XIX. C. 2. 5-HT_{1B} receptors

XIX. C. 3. 5-HT_{1D} receptors

XIX. C. 4. 5-HT_{1E} receptors

XIX. C. 5. 5-HT_{1F} receptors

XIX. C. 6. 5-HT_{2A} receptors

XIX. C. 7. 5-HT_{2B} receptors

XIX. C. 8. 5-HT_{2C} receptors

XIX. C. 9. 5-HT_{3A} and 5-HT_{3AB} receptors

XIX. C. 10. 5-HT₄ receptors

XIX. C. 11. 5-HT₅ receptors

XIX. C. 12. 5-HT₆ receptors

XIX. C. 13. 5-HT₇ receptors

XIX. C. 14. Receptor-independent actions of 5-HT

XX. 5-HT receptors and the gastro-intestinal tract

XX. A. Introduction

XX. B. Functions of 5-HT

XX. B. 1. Movements of the hungry stomach

XX. B. 2. Movements and sensations of the stomach and duodenum after meals

XX. B. 3. Movements of the small intestine

XX. B. 4. Movements of the colon

XX. B. 4. a. 5-HT_{2A} receptors

XX. B. 4. b. 5-HT_{2B} receptors

XX. B. 4. c. 5-HT₃ receptors

- XX. B. 4. d. 5-HT₄ receptors
- XX. B. 4. e. 5-HT₇ receptors
- XX. C. 5-HT in GI pathology
 - XX. C. 1. Emesis
 - XX. C. 2. Eating disorders
 - XX. C. 3. Carcinoid diarrhea
 - XX. C. 4. Functional GI disorders
 - XX. C. 5. Functional dyspepsia
 - XX. C. 6. IBS
 - XX. C. 7. Other GI Disorders
- XX. D. Therapeutic benefits of 5-HT receptor agonists
 - XX. D. 1. 5-HT₄ receptor agonists
 - XX. D. 2. Other 5-HT receptor agonists

XXI. 5-HT receptors and the immune system

- XXI. A. Introduction
 - XXI. B. How do immune cells encounter 5-HT?
 - XXI. C. 5-HT and hematopoiesis
 - XXI. D. 5-HT and the immune tolerance
 - XXI. E. 5-HT and the innate immune response
 - XXI. F. 5-HT and adaptive immunity
- ## XXII. General summary and conclusions

Acknowledgements

References

Abstract

5-HT receptors expressed throughout the human body are targets for established therapeutics and various drugs in development. Their diversity of structure and function reflects the important role 5-HT receptors play in physiological and pathophysiological processes. The present review offers a framework for the official receptor nomenclature and a detailed understanding of each of the fourteen 5-HT receptor subtypes, their roles in the systems of the body and where appropriate the (potential) utility of therapeutics targeting these receptors.

Significance Statement

This review provides a comprehensive account of the classification and function 5-HT receptors including how they are targeted for therapeutic benefit.

I. Introduction

Classification of 5-HT receptors extends back to the middle of the last century when Gaddum and Picarelli (1957) suggested that the 5-HT-induced contraction of guinea pig ileum was mediated by two different receptors: a neurotropic “M” receptor located on parasympathetic ganglia (effect blocked by morphine and atropine; now known to be the 5-HT₃ receptor) and a musculotropic “D” receptor located on smooth muscles (effect blocked by dibenzyline, lysergide, 2-bromolysergide and dihydroergotamine; now known to be the 5-HT_{2A} receptor). This original classification served well for around two decades although, from time to time, it was reported that some 5-HT-induced effects (e.g. vasoconstriction in the canine carotid arterial bed) were not mediated by “M” or “D”, but by “special” receptors (Saxena, 1974). Then, Bennett and Aghajanian (1974) reported the first successful radioligand binding study of 5-HT receptors using [³H]lysergide and subsequent studies using [³H]5-HT, [³H]spiperone and [³H]lysergide enabled Peroutka and Snyder (1979) to identify two 5-HT “receptors”, named 5-HT₁ (nM affinity for 5-HT) and 5-HT₂ (μM affinity for 5-HT). Subsequently, 5-HT₁ “receptors” were subdivided pharmacologically into 5-HT_{1A} and 5-HT_{1B} receptors (Pedigo et al., 1981), and 8-OH-DPAT was designated as a selective 5-HT_{1A} ligand (Gozlan et al., 1983; Middlemiss and Fozard, 1983). However, at these times 5-HT receptors were being classified by various names (e.g. “D”, “M”, 5-HT₁, 5-HT₂, S₁, S₂), and hence the clear need for a uniform terminology. This effort culminated in the Bradley et al. (1986) publication, classifying 5-HT receptors into: “5-HT₁-like” (equivalent to some “D” or 5-HT₁), 5-HT₂ (equivalent to most “D” or 5-HT₂) and 5-HT₃ (equivalent to “M”) receptors. The authors emphasized that this classification was a “general framework”, which would be regularly updated with new findings. Indeed, with the explosion in new findings around the time, it was clear a new classification was required that gave rise to the 5-HT receptor IUPHAR sub-committee sanctioned classification of 5-HT receptors into 5-HT₁ (“5-HT₁-like”, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}), 5-HT₂ (5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}), 5-HT₃, 5-HT₄, recombinant (5-HT_{5a/5b}, 5-HT₆, 5-HT₇) and “orphan” receptors (Hoyer et al., 1994). This new classification scheme was based on the conjunction of structural (molecular structure), transductional (intracellular transduction mechanisms) and operational (selective agonists and antagonists and ligand binding affinities) criteria. This first IUPHAR review on 5-HT receptors (Hoyer et al, 1994) was a landmark for the then rather complex 5-HT receptor field and the associated diversity of nomenclature used by operators in the field. In the 1994 review, we noted that the authors had a cumulated 100 years of active 5-HT research to share. A number of our colleagues have in the meantime retired from active research, or have moved to other professional priorities. The

present review provides a comprehensive overview of each of the recognized 5-HT receptors (Table 1) as well as reviewing the roles of 5-HT receptors in the major organs. There is a lot of new “blood” authors on board to reflect the growing diversity of the research, which is currently performed in many different academic and industrial centers; the combined years in 5-HT research of the present authors has increased considerably, partly due to the expansion of authors to ensure a comprehensive review of 5-HT receptors guided by the IUPHAR sub-committee on 5-HT receptors Chaired by Nicholas Barnes and Danny Hoyer.

In the present review, we address each receptor separately, as was performed previously, and then have sections that deal with specific aspects in more details, such as the structures of 5-HT receptors, their functions in the major systems, as well as translational/clinical outcomes arising from 5-HT research. Readers are also directed to a website (Barnes et al. <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=1>) and the Concise Guide to Pharmacology (Alexander et al., 2017).

II. 5-HT_{1A} receptor

II. A. Introduction

5-HT_{1A} receptors have attracted particular interest because of their negative feedback on 5-HT neurons, thus inhibiting 5-HT release and having broad influence on 5-HT tone. Additionally, 5-HT_{1A} receptors are widely distributed in terminal areas of the brain, where they are expressed as post-synaptic heteroreceptors in a variety of different brain regions influencing a range of neuropsychopharmacological sequelae (Albert and Fiori, 2014). After outlining the molecular structure, tissue expression and the tools that can aid in the delineation of 5-HT_{1A} receptor function, the focus will be on the diverse therapeutic fields in which 5-HT_{1A} receptors have become a target. Accordingly, substantial efforts have focused on targeting 5-HT_{1A} receptors for pharmacotherapy of a variety of neurological and psychiatric disorders including major depressive disorder, anxiety and schizophrenia. In addition, activation or blockade of 5-HT_{1A} receptors has been implicated in control of diverse other effects, including cognition, pain, fear, substance use disorder, Parkinson's disease and more recently in emerging clinical opportunities such as female sexual dysfunction and the treatment of respiratory deficits. The complexity of the effects of 5-HT_{1A} receptors presents both a challenge and a considerable opportunity for investigation of 5-HT function and for the potential identification of novel and improved therapeutic drugs.

II. B. 5-HT_{1A} receptor identification and expression

The introduction of tritiated [³H] receptor binding techniques revealed the existence of 5-HT₁ (and 5-HT₂) receptor families in the prefrontal cortex (PFC) of the brain (Peroutka and Snyder, 1979) and extended studies indicated the existence of different 5-HT₁ receptor populations, designated – for the first time - 5-HT_{1A} and 5-HT_{1B} receptors (Middlemiss and Fozard, 1983; Pedigo et al., 1981), leading to a much greater understanding of the pharmacological and functional role of the 5-HT_{1A} receptor in health and disease.

The cloning of the 5-HT_{1A} receptor from various species confirmed the existence of 5-HT_{1A} receptors as distinct gene products that correlated with pharmacologically defined receptor responses (Table 2).

The 5-HT_{1A} receptor has been located in a wide variety of peripheral and central targets. In the periphery, immunohistochemical studies have demonstrated that the receptor is located in human and rat kidney: medulla and cortical ascending limbs, the convoluted tubules, connecting tubule cells and the principal cells of the initial collecting tubule (Raymond et al., 1993); and murine peritoneal macrophages (Freire-Garabal et al., 2003). However, other techniques have revealed a wider distribution: Western blotting found the receptor in human benign and malignant prostate tissue (Dizeyi et al., 2004) whereas RT-PCR demonstrated the presence of 5-HT_{1A} receptors in rat taste buds (Kaya et al., 2004). However, the receptor is relatively poorly expressed in human coronary arteries, heart atrium, heart ventricles and epicardium (Nilsson et al., 1999). The brain and spinal cord have particularly dense populations of 5-HT_{1A} receptors, consistent with the role of this receptor in neuropsychiatric disease. The use of 5-HT_{1A} receptor agonists has been linked with the management of pain, accordingly radioligand-binding and *in-situ* hybridization studies have indicated the presence in the human and rat dorsal and ventral horns (Laporte et al., 1996; Pompeiano et al., 1992) and rat superior cervical ganglia (Pierce et al., 1996). In the brain, a wide distribution of the receptor has been described in both terminal regions as post-synaptic sites, and in the raphe nuclei where it has a somatodendritic autoreceptor function (Fornal et al., 1994; Jacobs and Azmitia, 1992). Generally, there is much conservation in regional expression across species although rat-human cortical and hippocampal differences in laminar organisation were reported (Barnes and Sharp, 1999; Burnet et al., 1995). Within the brain different techniques including receptor binding, RT-PCR, *in situ* hybridisation (Figure 1), Western and Northern blotting and immunohistochemistry have localised the receptor to the septum, thalamus, hippocampus, entorhinal cortex, interpeduncular nucleus, olfactory bulb, amygdala, hypothalamic sub-nuclei and sub-areas of the cortex and raphe nuclei (Albert et al., 1990; Chalmers and Watson, 1991; Daval et al., 1987; Dourish et al., 1986; Francis et al., 1992; Gozlan et al., 1983; Hall et al., 1985; Hamon et al., 1988; Hirose et al., 1990; Hoyer et al., 1986; Khawaja, 1995; Kung et al., 1995; Lemoine et al., 2010; Lemoine et al., 2012; Miquel et al., 1992; Pazos and Palacios, 1985; Pike et al., 1995; Pompeiano et al., 1992; Radja et al., 1991; Verge et al., 1986; Weissmann-Nanopoulos et al., 1985). More particularly, 5-HT_{1A} receptors are located on septal cholinergic neurones, cortical and hippocampal glutamatergic pyramidal neurones and granule cells (Burnet et al., 1995; Francis et al., 1992; Pompeiano et al., 1992) and also calbindin- and parvalbumin positive neurones (Aznar et al., 2003).

II. C. Pharmacology

In view of the involvement of 5-HT_{1A} receptors in a wide variety of physiological responses, the pharmacological profile of these receptors has been investigated extensively using an impressive variety of ligands, with varying degrees of selectivity. These range from drugs preferentially targeting 5-HT_{1A} receptors to non-selective compounds that have broad pharmacological activities. Examples of the latter are atypical antipsychotic drugs such as clozapine, ziprasidone or aripiprazole, which interact with many receptor subtypes. Notably, there are currently no selective 5-HT_{1A} receptors drugs approved for therapeutic use. This is somewhat surprising, in view of the broad therapeutic interest of 5-HT_{1A} receptors but likely reflects the difficulty of identifying chemical scaffolds that engage selectively this target. For example, the anxiolytic agent, buspirone, and its chemical analogues such as ipsapirone and gepirone, lack selectivity over some other receptors (for example buspirone displays sub- μ M affinity for dopamine D₂, D₃ and D₄ receptors, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₆ and 5-HT₇ receptors and α 1 adrenoceptors). Similarly, several antagonist ligands have been proposed but few have proved to be selective 'silent antagonists'. Nevertheless, some recent 'full agonists' (notably befiradol) have been identified that exhibit good selectivity for 5-HT_{1A} receptors and as such may constitute first-in-class therapeutic agents.

Tables 3 and 4 summarise the receptor binding properties of many 5-HT_{1A} receptor ligands that have been described over the last decades. It is also worth noting that even though certain compounds do display measurable receptor binding affinity, this may be too low to induce functional responses at the 5-HT_{1A} receptor. Such an example is olanzapine, which displays affinity at the 5-HT_{1A} receptor, yet fails to elicit electrophysiological actions at the level of somatodendritic autoreceptors, in contrast to ziprasidone and clozapine (Sprouse et al., 1999). Many of the ligands have been decisive in the operational definition of biochemical and pharmacological function at a basic science level, and in key disease models. In addition to the receptor agonists and antagonists there is some evidence for the existence of allosteric modulators, such as zinc, Galphimine-B and RS-30199 (Barrondo and Salles, 2009; Jimenez-Ferrer et al., 2011; Spedding et al., 1998).

The use of [³⁵S]GTPγS binding, a non-hydrolysable analogue of GTP that binds to agonist-activated G-proteins, has proved useful for investigating 5-HT_{1A} receptor signalling and pharmacology (Barr and Manning, 1997; Cosi and Koek, 2000; Dupuis et al., 1999a; Dupuis et al., 1999b; Gonzalez-Maeso et al., 2000; McLoughlin and Strange, 2000; Newman-Tancredi et al., 1996b; Newman-Tancredi et al., 1997b; Newman-Tancredi et al., 1998; Odagaki and Toyoshima, 2005a; Odagaki and Toyoshima, 2005b; Odagaki and Toyoshima, 2007; Pauwels et al., 1997; Shen et al., 2002; Sim et al., 1997; Stanton and Beer, 1997). Notably, the use of [³⁵S]GTPγS binding enabled the investigation of both positive and negative efficacy ligands at 5-HT_{1A} receptors. Thus, whereas a range of ligands efficaciously stimulated G-proteins, other drugs, such as spiperone and methiothepin, markedly inhibited the [³⁵S]GTPγS basal binding in both membranes prepared from 5-HT_{1A} receptor transfected CHO cells and native tissue, confirming the capacity of 5-HT_{1A} receptors to elicit constitutive activation of G-proteins *in vitro* (Corradetti et al., 2005; Martel et al., 2007; McLoughlin and Strange, 2000; Newman-Tancredi et al., 1997a; Stanton and Beer, 1997). In contrast to spiperone, WAY1000635 exhibited neither positive nor negative efficacy, yet blocked the actions of both agonists and inverse agonists, consistent with “neutral antagonist” properties (Martel et al., 2007) also evident *in vivo* using electrophysiological procedures (e.g. Fornal et al., 1996). This was important because other compounds claimed as antagonists at 5-HT_{1A} receptors, such as NAN190, BMY7378, SDZ216,525 and even WAY100135, were found to display partial agonist properties when tested in systems that exhibit high degrees of receptor reserve (Greuel and Glaser, 1992; Routledge, 1996); changes in receptor expression level can markedly affect functional responses, and this is important when considering the nature of ligand engagement and the notion that different brain areas exert distinct physiological influence (Newman-Tancredi et al., 1997c). A three-fold increase in receptor:G-protein ratio almost doubled relative efficacy of the partial agonist eltoprazine (53% to 93%), without a change potency, whereas 5-HT exhibited a two-fold increase in potency (decrease in EC₅₀ value) (Newman-Tancredi et al., 1997c). In addition to these changes, the increase in 5-HT_{1A} receptor:G-protein ratio roughly doubled the negative efficacy of spiperone. These data therefore lead to the supposition that the targeting of agonist-efficacy *in vivo* at different receptor populations is possible, which may offer therapeutic benefits.

II. D. Biased agonism: differential activation of 5-HT_{1A} receptor subpopulations

The term “biased agonism” (“functional selectivity” or “agonist-directed signalling”) (Berg and Clarke, 2006; Evans et al., 2010; Kenakin, 2010; Tzingounis et al., 2010) was coined to denote a pattern of agonist signalling that was distinct from the concept of ‘intrinsic activity’. Whereas the latter posits that receptor activation is an outcome of the ‘intrinsic’ properties of the agonist, the concept of “biased agonism” is based on the capacity of agonists to preferentially mediate receptor signalling via specific pathway(s), whilst not affecting, or even blocking other secondary messenger pathways coupled to the same receptor. If the different signalling cascades mediate distinct functionality (e.g. therapeutic *versus* side-effects), then biased agonism will offer a strategy to potentially target different mechanisms with the opportunity to potentially develop more effective, better-tolerated drugs.

An early study at 5-HT_{1A} receptors suggested that different agonists displayed differential G α i2 and G α i3 activation, determined using a photoreactive GTP analogue (4-azidoanilido-[α -³²P]GTP) (Gettys et al., 1994). Rauwolscine displayed similar EC₅₀ values for activation of the two G-protein subtypes, ipsapirone showed a nearly four-fold lower EC₅₀ for G α i3 activation. 5-HT and 8-OH-DPAT had intermediate EC₅₀ (Gettys et al., 1994). In another study, the presence of anti-G α i3 antibodies almost completely suppressed G-protein activation by pindolol, a 5-HT_{1A} receptor partial agonist, preferentially elicits activation of G α i3, a property that may underlie its preferential occupancy of midbrain 5-HT_{1A} autoreceptors (Hirani et al., 2000; Martinez et al., 2001; Newman-Tancredi et al., 2002). Drug differences were also seen in transduction experiments on native rat raphe: buspirone elicited G α i2, G α i3 and G α o mediated-responses as well as inhibition of adenylyl cyclase, whereas 8-OH-DPAT only elicited coupling to G α i3 and did not elicit the other responses (Valdizan et al., 2010).

Together, these data support that different 5-HT_{1A} receptor agonists possess different G-protein activation “fingerprints”, backing the biased agonist concept, and hence suggesting that 5-HT_{1A} receptor subpopulation targeting is possible (Figure 2). Compounds such as the biased 5-HT_{1A} receptor agonists, F15599 and F13714, reversed immobility in the rat forced swim test via actions at presumed post-synaptic receptors. Similarly, anxiolytic-like

actions were seen in the rat ultrasonic vocalization test (USV) (Assie et al., 2010; De Vry et al., 1993). However, in animal tests related to side-effects, F15599 exhibited a better profile compared to F13714 (Assie et al., 2010; Gaggi et al., 1997; Prinssen et al., 2000) further supporting the potential for improved potential therapeutics utilising biased agonists to target the appropriate 5-HT_{1A} receptor subpopulation (Table 5), which includes potential to improve the cognitive state of patients with schizophrenia (Depoortere et al., 2010; Horiguchi and Meltzer, 2012).

II. E. 5-HT_{1A} receptor intracellular signal transduction

The transfection (Fargin et al., 1988) and heterologous expression of 5-HT_{1A} receptors in various different cellular environments (including COS7, HeLa, CHO, NIH3T3, Sf9 and *Escherichia coli* cells) enabled the study of their G-protein coupling to secondary messenger systems (Raymond et al., 1999). A well-characterised intracellular functional response is the inhibition of adenylyl cyclase (AC) activity and has been extensively used to differentiate ligands for this receptor, their agonist and partial agonist actions or their degree of antagonism (Bockaert et al., 1987; De Vivo and Maayani, 1986; Dumuis et al., 1988; Fargin et al., 1989; Markstein et al., 1986; Raymond et al., 2006; Shenker et al., 1987; Varrault and Bockaert, 1992). 5-HT_{1A} receptors can also activate G-protein inward rectifying potassium channels (GIRK), high conductance anion channels to inhibit calcium conductance modulating intracellular calcium mobilisation; stimulate nitric oxide synthase (NOS) and a nicotinamide adenine dinucleotide phosphate (NADP) oxidase-like enzyme (Adayev et al., 2003; Hsiung et al., 2005; Polter and Li, 2010). The receptor can affect metabolism and arachidonic acid production (Raymond et al., 1999), activate protein kinase C production, Src kinase, and mitogen activated protein kinases (MAPKs), and activate activate or inhibit phosphoinositol hydrolysis and stimulate ROS production (superoxide and peroxide) (Raymond et al., 1999). Together the elucidation of this diverse pattern has led to important developments in establishing test systems to probe receptor and drug function.

II. F. Function

II. F. 1. Differential function of 5-HT_{1A} receptors at cellular, tissue and *in vivo* level

The functional properties of 5-HT_{1A} receptors have been extensively investigated. The overall conclusion from these studies is that subpopulations of 5-HT_{1A} receptors expressed in different brain regions exhibit specific patterns of receptor signalling, with differing impact on central function. These diverse properties indicate that separate subpopulations of 5-HT_{1A} receptors mediate particular responses and may constitute therapeutic targets in their own right (see also Figure 2). For example, agonist activation of somatodendritic 5-HT_{1A} autoreceptors expressed on serotonergic neurons in the raphe elicits inhibition of 5-HT release in terminal regions such as the hippocampus and cortex. In contrast, activation of post-synaptic cortical 5-HT_{1A} hetero-receptors expressed on glutamatergic pyramidal cells and/or gamma-aminobutyric acid (GABAergic) interneurons, elicits different neurochemical responses, including stimulation of dopamine release in frontal cortex (Bortolozzi et al., 2010; Santana et al., 2004).

Activation of 5-HT_{1A} autoreceptors induces anxiolytic activity in rodent behavioural tests, (Akimova et al., 2009; De Vry et al., 2004), whereas antidepressant-like responses are seen upon activation of 5-HT_{1A} heteroreceptors (De Vry et al., 2004). These data obtained in rat behavioural experiments are consistent with observations in transgenic mice overexpressing raphe 5-HT_{1A} autoreceptors: accentuated depressive-like behaviour was observed and diminished response to antidepressant treatment (Richardson-Jones et al., 2010). These data support the interpretation that desensitization of pre-synaptic 5-HT_{1A} receptors is necessary before antidepressant efficacy may be achieved (Artigas et al., 2006; Millan, 2006), consistent with the relatively long latency (typically 3-4 weeks) to clinical responsiveness in depressed patients treated with 5-HT reuptake inhibitors.

Diverse responses to 5-HT_{1A} receptor agonists are also observed in tests of cognition / memory function relevant to numerous neuropsychiatric diseases including major depressive disorder, schizophrenia, Parkinson's disease, Alzheimer's disease etc. Interestingly, the prototypical 5-HT_{1A} receptor agonist, 8-OH-DPAT, facilitated rat passive avoidance at low doses, whereas higher doses impaired performance (Luttgen et al., 2005; Madjid et al., 2006). This suggests that opposite responses are mediated by 5-HT_{1A} receptor subpopulations i.e. improved performance is elicited by 5-

HT_{1A} autoreceptors whereas impairment is due to activation of hippocampal 5-HT_{1A} heteroreceptors (Ogren et al., 2008). This interpretation is supported by local administration experiments in which the 5-HT_{1A} receptor weak partial agonist/antagonist, S15535, was microinjected into the hippocampus. The compound reversed the memory deficit elicited by systemic injection of 8-OH-DPAT in a spatial discrimination task (Millan et al., 2004), indicating that activation of post-synaptic receptors in this brain region was detrimental to mnemonic performance.

Given that only a single 5-HT_{1A} receptor gene has been identified in human and rat and that it is intron-less and hence without splice variants (Albert et al., 1990; Fargin et al., 1988), the variety of responses described above are attributable likely to regional '*receptor interactome*' differences including coupling to distinct G-protein subtypes (see below)(Mannoury la Cour et al., 2006), regulators of G-protein signalling (RGS) (Talbot et al., 2010) or transcriptional regulation.

At a molecular level, 5-HT_{1A} receptor inactivation studies using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) demonstrated the existence of receptor reserve in the raphe for inhibition of 5-HT synthesis (Meller et al., 1990). In contrast, receptor reserve was not evident in the hippocampus for the inhibition of adenylyl cyclase or for control of hypothermia (Meller et al., 1992; Yocca et al., 1992).

The agonist radioligand, [³H]8-OH-DPAT, which preferentially recognizes 5-HT_{1A} receptors when coupled to G-proteins, displayed five-fold higher affinity for hippocampal compared to raphe binding sites (Johnson et al., 1997), supporting differing receptor-G-protein coupling state between the two brain regions. Further, whereas 5-HT_{1A} receptors are coupled to inhibition of adenylyl cyclase in hippocampus, such coupling was not detected in raphe homogenates (Clarke et al., 1996). Further support that 5-HT_{1A} receptors couple to different G-protein subtypes depending on brain region arises from immuno-precipitation studies where raphe 5-HT_{1A} receptors couple preferentially to G α i3 subtypes whereas they couple preferentially to G α o in hippocampus and to a combination of G-proteins in cortex and hypothalamus (Mannoury la Cour et al., 2006).

Functional ($[^{35}\text{S}]\text{GTP}\gamma\text{S}$) autoradiography experiments also support the contention that regional variations exist in native brain activation of G-proteins by 5-HT_{1A} receptors. Indeed, whilst 5-HT_{1A} receptor density is similar in the raphe and hippocampus, agonist-induced $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ labelling was markedly lower in the former (Hensler, 2003; see also Newman-Tancredi et al., 2003 for relevant evidence).

An additional level of complexity of 5-HT_{1A} receptor signalling has been reported, i.e., the existence of receptor homo-, hetero-, and potentially trimers with a variety of targets. Firstly, 5-HT_{1A} homodimers may be formed constitutively (Lukasiewicz et al., 2007; Renner et al., 2012), and are affected by the presence of specific ligands such as 8-OH-DPAT, which enhanced dimerization, while methysergide reduced dimer formation potentially via a mechanism modulated by G α s subunits. The 5-HT₇ receptor, like the 5-HT_{1A} receptor, has also been reported to play a role in depression, formed homodimers, but also heterodimerized with the 5-HT_{1A} receptor and may have functional consequence insofar as 5-HT_{1A}-5-HT₇ heterodimerization reduces GIRK currents in a heterologous cell system and potentially affecting 5-HT_{1A} receptor internalisation in the hippocampus (Naumenko et al., 2014; Renner et al., 2012). Heterodimerization with a novel negative response element of 5-HT_{1A} receptors has been suggested with glucocorticoid and mineralocorticoid receptors, which may also be key players in depression (Ou et al., 2001). Galanin receptors form heteromers with a variety of targets, including galanin receptor-5-HT_{1A} heteromers and trimers (Fuxe et al., 2012). With potential relevance to the influence of 5-HT_{1A} receptors in ascending and central pain perception, heterodimerization has also been demonstrated with 5-HT_{1A} receptors and μ -opioid receptors *in vitro*, and further data suggested that both receptors could exert effects on ERK1/2 phosphorylation (Cussac et al., 2012).

II. F. 1.a. 5-HT_{1A} receptors in depression and anxiety

The key role of 5-HT_{1A} receptors in major depression and anxiety has been recognized for nearly four decades (see Barnes and Sharp, 1999; Albert et al., 2014). Accordingly, animal behavioural models of fear, anxiety, depression and cognition have been used to identify potential antidepressant and clinically-active anxiolytics such as the partial agonists buspirone, gepirone, ipsapirone and tandospirone (Gilbert and Dourish, 1987; Peroutka, 1985; Taylor et al., 1985). Buspirone and tandospirone were both clinically developed and received marketing approval for treating anxiety. However, their azapirone chemical structures are associated with only limited selectivity (e.g. versus α_1 adrenoceptors and D₂ dopamine receptors) and they also

exhibit relatively poor metabolic stability and generate pharmacologically active metabolites, such as 1-(2-pyrimidinyl)-piperazine (1-PP), that is an α_2 adrenoceptor antagonist (Cao and Rodgers, 1997; Garattini et al., 1982; Sugimoto et al., 2005; Wong et al., 2007; Zuideveld et al., 2002). Consequently, the therapeutic usefulness of selective 5-HT_{1A} receptor agonists still remains to be determined.

Indeed, data suggest that the phenotypic expression of normal behaviour, anxiety or depression may be influenced by the differential 5-HT_{1A} receptor-sensitive circuitry at the level of the PFC; the balance between 5-HT_{1A} receptor stimulation of glutamatergic pyramidal cells and GABAergic interneurons may impact the expression of anxiety (Goodfellow et al., 2009; Albert et al., 2014) although juvenile development processes play a key role in determining vulnerability to mood disorders (Donaldson et al., 2014; Garcia-Garcia et al., 2014; Leonardo and Hen, 2008). In depression the neurobiology appears different. Therefore, activation of pyramidal neurones by stimulation of 5-HT_{1A} receptors has antidepressant action, while the interneurons are weakly activated by 5-HT_{1A} receptor activation. This interneurone population could then potentially be recruited by additional activation, in-turn further activating the “antidepressant” pyramidal neurones (Albert et al., 2014). It is interesting to note that the rapid antidepressant activity of ketamine appears to be partly mediated via 5-HT_{1A} receptor activation. Indeed, ketamine inhibits 5-HT reuptake *in vivo* (Martin et al., 1982; Martin and Smith, 1982) and elicits its prolonged antidepressant-like effects in rodents via a 5-HT-dependent mechanism (Gigliucci et al., 2013). This is likely to involve indirect activation of 5-HT_{1A} receptors, as exemplified by the fact that the effects of ketamine in the novelty-suppressed feeding test are blocked by a 5-HT_{1A} receptor antagonist (Fukumoto et al., 2014).

Additional evidence that 5-HT_{1A} receptors are involved in affective disorders comes from genetic studies. The expression of 5-HT_{1A} receptors is differentially regulated by a single nucleotide polymorphism (SNP) in the promoter region of the 5-HT_{1A} receptor gene (C-1019G substitution) (Albert and Francois, 2010; Lesch and Gutknecht, 2004). This SNP impairs repression of the 5-HT_{1A} promoter by the NUDR/DEAF-1 transcription factors in raphe cells, consistent with over-expression of pre-synaptic 5-HT_{1A} receptors (Lemondé et al., 2004; Parsey et al., 2006). Thus, C-1019G polymorphism is associated with higher levels of symptom remission failure and suicidal behaviour in depressed patients, consistent with impaired antidepressant efficacy due to excessive feed-back inhibition by pre-synaptic 5-HT_{1A} receptors.

Taken together, the above considerations indicate that 5-HT_{1A} receptors remain promising targets for the pharmacotherapy of affective disorders both as a somatodendritic and post-synaptic receptor target in the brain. Accordingly, various efforts have been made to incorporate 5-HT_{1A} receptor activity in antidepressant / anxiolytic drug candidates. For example, SB-649915-B is a 5-HT reuptake inhibitor (SSRI) that also acts as a 5-HT_{1A} receptor antagonist (Hughes et al., 2007; Starr et al., 2007) based on the rationale that accelerated antidepressant response may be achieved by avoiding feed-back inhibition of terminal 5-HT release by blocking the activation of 5-HT_{1A} autoreceptors (Artigas et al., 2006; Gartside et al., 1999; Portella et al., 2011). However, whilst antidepressant efficacy may be enhanced by 5-HT_{1A} autoreceptor antagonism the blockade of post-synaptic 5-HT_{1A} receptors likely opposes antidepressant activity (Berrocoso and Mico, 2009; De Vry et al., 2004). Accordingly, a clinical trial in which a selective 5-HT_{1A} receptor antagonist was administered as adjunct to fluoxetine did not show any acceleration of antidepressant onset of efficacy (Scorza et al., 2011), likely due to its concurrent blockade of both pre- and post-synaptic 5-HT_{1A} receptors. In contrast, adjunct treatment with pindolol, which preferentially occupies 5-HT_{1A} autoreceptors (Martinez et al., 2001), appears to reliably elicit acceleration of antidepressant efficacy (Artigas et al., 2006; Portella et al., 2011). Compounds such as vilazodone, vortioxetine and VN2222 are SRIs possessing partial agonist actions at 5-HT_{1A} receptors (Alvarez et al., 2012; Dawson and Watson, 2009; Mork et al., 2009; Romero et al., 2003) that might assist in engaging diverse frontal circuitry leading to better treatment of the disease.

II. F. 1.b. 5-HT_{1A} receptor activation for improved antipsychotic action

A noteworthy development in the study of 5-HT_{1A} receptors has been the increasing therapeutic interest for this target in psychotic disorders. This has stemmed from extensive clinical and pre-clinical observations (see McCreary and Newman-Tancredi, 2015 for review).

Schizophrenia, which shares some symptoms with other neuropsychiatric diseases, and includes positive symptoms (auditory and visual hallucinations, delusions, conceptual disorganization, thought disorders, and some motor disturbances), negative symptoms (affective blunting, social withdrawal, anhedonia, avolition, and poverty of thought and speech), cognitive impairments such as working memory abnormalities, deficits of

cognitive processing, and attention and affective disorders (depression and anxiety) (Meltzer, 1999). 5-HT_{1A} receptors appear involved both in the pathophysiology and in functionality of potential novel treatments. Thus the newer generation antipsychotics clozapine, ziprasidone, quetiapine, aripiprazole, lurasidone and cariprazine, possess (partial) agonist effects at 5-HT_{1A} receptors, although interestingly risperidone and olanzapine do not (McCreary and Newman-Tancredi, 2015). In patients, changes in 5-HT_{1A} receptor binding or functional activity have been identified (Bantick et al., 2004; Billard et al., 2014; Burnet et al., 1996; Frankle et al., 2006; Kasper et al., 2002; Lerond et al., 2013; Yasuno et al., 2003), along with short nucleotide polymorphisms (SNPs) at loci ss212928868 and rs6294, which are associated with the clinical outcome in paranoid schizophrenic women (Zhou et al., 2012). Polymorphisms were also associated with much of the depression and negative treatment outcomes (Newman-Tancredi and Albert, 2012; Reynolds et al., 2006). Preliminary studies assessing cytosine methylation at a site close to this rs6295 polymorphism, suggested that this was associated with a lower incidence of negative symptoms (Reynolds et al., 2006; Tang et al., 2014), reinforcing the importance of this site in the negative symptoms of schizophrenia. Taken together, these accumulated data support the assertion that there is involvement of 5-HT_{1A} receptors in the pathophysiology and treatment-related facets of the disease, particularly negative symptomatology.

A net hypofunctionality of the PFC, a brain area key in working memory, decision and attentional processing, has been proposed in schizophrenia (McCreary et al., 2007; Weinberger and Lipska, 1995). It is therefore interesting that many atypical antipsychotic drugs may impact this deficit (McCreary and Newman-Tancredi, 2015). It may therefore be relevant that the 5-HT_{1A} receptor agonist agents possessing antipsychotic properties (SSR181507, adopraxine and lurasidone) augment extracellular microdialysate dopamine and acetylcholine levels in the PFC, to “normalise” hypofrontal tone (Claustre et al., 2003; Huang et al., 2014; McCreary et al., 2007) to promote potential therapeutic outcomes. This is supported by preclinical evidence (Depoortere et al., 2007) and clinical evidence with the partial agonist, tandospirone, which improved cognitive symptoms in patients with schizophrenia treated with neuroleptics (Sumiyoshi et al., 2001a; Sumiyoshi et al., 2001b; Sumiyoshi et al., 2007). Additionally, blonanserin, tandospirone, lurasidone and buspirone reduced MK-801-induced novel object recognition deficits (Horiguchi and Meltzer, 2012; Horiguchi and Meltzer, 2013) and PCP-induced reversal learning was attenuated by 5-HT_{1A} receptor activation (McLean et al., 2009). In the social interaction test, a model for negative symptoms, aripiprazole, SSR181507, and F-15063 induced a 5-HT_{1A} receptor-dependent performance

improvement (Boulay et al., 2004; Bruins Slot et al., 2005; Depoortere et al., 2007; Snigdha and Neill, 2008). In addition, administration of 5-HT_{1A} receptor (partial) agonists reversed PCP-induced decreases of tickling-induced 50-kHz ultrasound vocalization in juvenile rats, a model for negative symptoms and improved attentional processing in a 5-choice serial reaction time task (Boulay et al., 2013; Winstanley et al., 2003). In conclusion, data from pre-clinical and clinical findings support that 5-HT_{1A} receptor activation will benefit the treatment of cognitive, attentional and negative symptom domains.

An additional complication of antipsychotic treatment are so-called extrapyramidal side-effects induced by the typical antipsychotics, such as haloperidol, which can reduce striatal output and lead to a parkinsonian phenotype. Such symptoms in preclinical models can be reduced by 5-HT_{1A} receptor agonists (McCreary et al., 2007). Compounds such as adopraxine, bifeprunox and F-15063 have reduced catalepsy unduced by e.g. haloperidol. However, treatment, with WAY-100635 unmasked this blockade of catalepsy, indicating a key role of 5-HT_{1A} receptors (Bardin et al., 2006; Kleven et al., 2005). Consistently, mesolimbic selectivity, and therefore the ability to treat the positive symptoms, was supported with electrophysiological studies demonstrating depolarization block of VTA, but not SNC, dopaminergic neurones was mediated by 5-HT_{1A} receptor agonists (McCreary et al., 2007; Nakamura et al., 2006) and that PFC 5-HT_{1A} receptors influenced VTA cell firing by indirectly affecting pyramidal cell afferents to the VTA, thereby increasing dopamine cell firing (Llado-Pelfort et al., 2012a; Santana et al., 2012). Therefore, indirectly influencing mesoaccumbal dopaminergic output and impacting positive symptoms. Some clinical meta-analytical studies support this assertion and suggest a trend for improved cognitive symptoms following the addition of 5-HT_{1A} receptor partial agonists, together with a trend for improved positive symptoms (Kishi et al., 2013), but more extensive clinical studies are warranted. It is interesting to speculate that fully efficacious agents might offer added benefit. Moreover, benefit in other symptom domains might be expected, particularly mood. Accordingly, bifeprunox, SSR181507, and adopraxine (SLV313) all demonstrated anxiolytic-like and antidepressive-like properties (Depoortere et al., 2003) and 5-HT_{1A} receptors appear mediate the antidepressant effects of ketamine and metabotropic glutamate (2/3) receptor antagonists (Fukumoto et al., 2014). Moreover, 5-HT_{1A} gene loci polymorphism linkage studies support this in schizophrenic patients with depression, which are partly supported by linkage studies in depression (Albert, 2012).

Taken together, these data support a role for the 5-HT_{1A} receptor in schizophrenia. This is particularly interesting in light of the clinical development and marketing approval of lurasidone and cariprazine, which possess dopamine D2 and 5-HT_{1A} receptor agonist action (Ishibashi et al., 2010; Kiss et al., 2010). Indeed, pharmacodynamic studies support the described 5-HT_{1A} receptor-mediated mechanisms in the actions of lurasidone on augmented PFC-dopamine and acetylcholine levels and cognitive actions (Horiguchi and Meltzer, 2012; Huang et al., 2012; Huang et al., 2014). Consistently, clinical benefit in a variety of symptom domains was evident (Citrome et al., 2013; Veselinovic et al., 2013; Durgam et al., 2014; Loebel et al., 2014a; Loebel et al., 2014b).

II. G. 5-HT_{1A} receptors and some emerging treatment areas

II. G. 1. Parkinson's disease

Parkinson's disease (PD) is characterized by a loss of nigrostriatal dopaminergic neurones resulting in the cardinal motor symptoms (Schapira et al., 2006). Symptomatic treatment ultimately relies on the gold-standard medication and dopamine precursor levodopa (L-DOPA) (Jenner et al., 2011). However, over time the effects of L-DOPA are prone to wearing-off i.e. there is a tolerance to the actions of L-DOPA, and patients develop dose-limiting dyskinesia (Jenner et al., 2011). The treatment of L-DOPA-induced dyskinesia (LID) has been hampered by a lack of approved medications. Recently, the 5-HT system has emerged as a key player in the induction of LID. 5-HT neurones possess the enzymes necessary to convert exogenous L-DOPA to dopamine (DA) and mediate its vesicular storage and *'false neurotransmitter'* release. However, 5-HT neurons lack appropriate control mechanisms to regulate synaptic DA levels (e.g. via presynaptic D₂ receptors or dopamine transporters), resulting in excessive DA release and pulsatile (over) stimulation of post-synaptic dopamine receptors that generate dyskinesia. Theoretically, it might be possible to mitigate dopamine release from serotonergic neurones by suppressing serotonergic tone by the application of 5-HT_{1A} (or 5-HT_{1B}) receptor agonists, which suppress neurotransmission by influencing the negative feedback somatodendritic (or terminal autoreceptors). Indeed 5-HT_{1A} receptor agonist treatment does reduce LID in both rat and non-human primate models (Bibbiani et al., 2001; Eskow et al., 2007; Eskow et al., 2009; Huot, 2015; Iderberg et al.,

2015a; Munoz et al., 2009) and appear to translate in clinical studies using the partial agonists buspirone and the mixed 5-HT_{1A}/5-HT_{1B} agonist eltoprazine (Svenningsson et al., 2015). However, other clinical attempts to target the 5-HT_{1A} receptor have been disappointing, with compounds such as sarizotan and tandospirone also impairing the antiparkinsonian activity (Bonifati et al., 1994; Goetz et al., 2007; Kannari et al., 2002; Olanow et al., 2004), whereas eltoprazine showed only modest effects (Svenningsson et al., 2015). Together, this suggests that while 5-HT_{1A} receptors can reduce dyskinesia, compounds tested to date may be less than optimal (Hamik et al., 1990; Newman-Tancredi et al., 1997c; Newman-Tancredi et al., 1998; Newman-Tancredi et al., 2003). Interestingly, only full agonists succeed in completely reversing haloperidol-induced catalepsy, whereas partial agonists failed to do so (Prinssen et al., 2002), suggesting that maximal efficacy may be required. The selective 5-HT_{1A} receptor 'biased agonist' F13714, which preferentially targets raphe 5-HT_{1A} autoreceptors, completely abolished abnormal involuntary movements (AIMs) along with inhibiting 5-HT release (Inderberg et al., 2015a). Comparable findings were evident with Befiradol (McCreary et al., 2015).

In addition, 'full agonist' activity at 5-HT_{1A} receptors may also provide beneficial influence on non-motor symptoms of PD, such as the mood deficits likely elicited by deficient 5-HT neurotransmission (Eskow Jaunarajs et al., 2010; Politis, 2010). Indeed, whereas treatment of depressive symptoms in PD using 5-HT reuptake inhibitors is poorly effective, direct activation of post-synaptic (cortical) 5-HT_{1A} receptors is associated with potent antidepressant actions (Celada et al., 2004). In restless legs syndrome, another movement disorder typically managed with low doses of dopamine receptor agonists or L-DOPA, 5-HT_{1A} receptor agonists may also display clinical benefit (Shioda et al., 2006).

II. G. 2. Pain

There is good evidence for the involvement of the 5-HT system in chronic pain (Millan, et al. 2002), which is not surprising given their expression by descending pathways of the dorsal horn and other relevant structures. The receptors of the dorsal horn appear pivotally involved in the pronociceptive effects (Avila-Rojas et al., 2015; Colpaert, 2006; Fasmer et al., 1986; Millan, 1994; Millan et al., 1996; Sagalajev et al., 2015; You et al., 2005; Millan, 2002) and may also influence antinociception (Millan et al., 1996; Millan, 2012). Recent evidence suggests that the newer generation antipsychotic agent, e.g. aripiprazole, which possess 5-HT_{1A} receptor partial agonist actions displays antinociceptive effects (Fei et al., 2012; Almeida-

Santos et al., 2015). Moreover, the ability of 5-HT_{1A} receptors to form heterodimers with μ -opioid receptors (Cussac et al., 2012) suggests 5-HT_{1A} receptor targeting as an adjunct to opioid strategies may be useful.

II. G. 3. Attention Deficiency Hyperactivity Disorder

In animal models of impulse control, 5-HT_{1A} receptor stimulation reduced the impulsivity suggesting potential benefit in diseases such as attention deficiency hyperactivity disorder (ADHD; Winstanley et al., 2003). Furthermore, in an isolation rearing model - which models some components of ADHD - 5-HT_{1A} receptor binding sites were altered in a region specific manner (Preece et al., 2004). Pharmacological study using the agonists SSR181507 (Terranova et al., 2005) and sarizotan (Danysz et al., 2015) suggest efficacy in animal models of ADHD. It is also relevant that a HTR1A rs10042486 polymorphism is associated with ADHD (Park et al., 2013). Indeed bupirone may benefit ADHD management (Levin, 2015), although to a lesser extent than methylphenidate (Mohammadi et al., 2012).

II. G. 4. Autism Spectrum Disorder

Pre-clinical studies reveal altered central 5-HT_{1A} receptor activity in a rat valproate model of autism (Wang et al., 2013) and in BTBR mice, which have a phenotype paralleling that of autism spectrum disorder, elevated [³⁵S]GTP γ S binding is evident corresponding to enhanced 5-HT_{1A} receptor functional activity that potentially contributes to poor social behaviour (Gould et al., 2011). Clinical data are limited, but anti-5-HT_{1A} receptor antibodies have been identified in the blood of an autistic boy (Todd and Ciaranello, 1985). Furthermore, a 5-HTR1A C-1019G polymorphism in autism may influence clinical outcome (Egawa et al., 2012).

II. G. 5. Respiratory control

5-HT_{1A} receptor agonists increased respiration in rats and cats (Edwards et al., 1990; Rose et al., 1995) and morphine-induced ventilatory depression was reduced by the 5-HT_{1A} receptor agonist, repinotan (Guenther et al., 2010). Electrophysiological studies support a modulatory role of the 5-HT_{1A} receptor in the bursting activity of respiratory neurones (Onimaru et al., 1998) and 5-HT_{1A} receptors activate bronchio-constrictor vagal

preganglionic neurones and phrenic nerve neurones (Bootle et al., 1998; Valic et al., 2008). These, and other data have led to the suggestion that 5-HT_{1A} receptor agonists display potential to treat sleep apnoea (Futuro-Neto et al., 1993; Dando et al., 1998; Khater-Boidin et al., 1996; Khater-Boidin et al., 1999; Sahibzada et al., 2000) that may translate to the clinic given an evident reduction in apnoea evoked by buspirone (Wilken et al., 1997). In addition, activation of 5-HT_{1A} receptors may be beneficial to reverse compromised respiration; for instance, in a transgenic mouse model of Rett syndrome that also models the disordered breathing, (+)8-OH DPAT and sarizotan reduced the apnoeic frequency to restore the respiratory pattern (Abdala et al., 2010; Abdala et al., 2014c; Levitt et al., 2013). Furthermore, the 5-HT_{1A} receptor biased agonist, F15599, impacts apnoea and respiration frequency in Mecp2 null male and heterozygous female mice (Levitt et al., 2013). Clinical experiences investigating the 5-HT_{1A} receptor role in Rett syndrome are limited, but buspirone administered with fluoxetine, reduced the frequency of hyperventilation and apnoeic attacks (Gokben et al., 2012).

II. G. 6. Sexual dysfunction

5-HT_{1A} receptors may be a promising target in the treatment of sexual dysfunction. The 5-HT_{1A} receptor agonist, flibanserin (which also possesses 5-HT_{2A} receptor antagonist and dopamine D₄ receptor partial agonist properties; Borsini et al., 2002; Heusler et al., 2009; Mendelson and Gorzalka, 1986; Stahl, 2015) is a treatment for female hypo-active sexual desire disorder (Clayton et al., 2010; Jayne et al., 2012; Katz et al., 2013; Thorp et al., 2012) and is the culmination of research indicating a role for 5-HT_{1A} receptors in sexual function (e.g. Mendelson and Gorzalka, 1986; Olivier et al., 2011; Aubert et al., 2012; Gelez et al., 2013; Snoeren et al., 2014a; Snoeren et al., 2014b) although its clinical effects are likely not exclusively related to actions at 5-HT_{1A} receptors (Allers et al., 2010; Stahl et al., 2011; Stahl, 2015). However, inclusion of 5-HT_{1A} agonist actions in the profile of activity of psychotropic drugs has been reasoned to potentially alleviate the sexual dysfunction seen in some patients treated with antidepressant or antipsychotic agents.

II. G. 7. Food intake, and eating disorders

The role of 5-HT in modulating food-intake and satiety has been investigated extensively (Blundell et al., 1995; Halford et al., 2007). Early studies demonstrated 5-HT_{1A} receptor activation induces hyperphagia suggesting agonists may help treat patients with eating disorders such as bulimia and/or anorexia nervosa (Dourish et al., 1987). *In vivo* imaging studies suggest 5-HT_{1A} receptor binding increases in cortical and limbic structures of the brain of patients with anorexia and/or bulimia, consistent with a potential role in anxiety, behavioural inhibition and body ideation (Bailer et al., 2007; 2011; Bailer and Kaye, 2011; Galusca et al., 2008; Kaye et al., 2005). Although clinical pharmacology studies are limited, and restricted to case studies, the partial agonist tandospirone improved the weight gain of patients with anorexia nervosa (restricting and binge-eating/purging subtypes) and also improved scores on the Eating Disorder Examination Questionnaire following treatment for up to 6 months (Okita et al., 2013). The mechanistic basis for this may involve control of mood: the anxiolytic effects of 5-HT_{1A} receptor agonists are likely to be beneficial (Crow and Mitchell, 1994) and potentially contribute to treatment outcome.

II. G. 8. Aggressive behaviour

5-HT_{1A} receptor activation appears to reduce aggressive behaviour in pre-clinical and clinical (buspirone) settings (Bell and Hobson, 1994; Olivier and Mos, 1992; Takahashi et al., 2012) with animal models indicating impact at the level of the dorsal raphe, and hence a reduction in 5-HT neurotransmission, may underlie the response (Mos et al., 1993). This is supported by results generated with S15535, a preferential autoreceptor agonist and, possibly, via blockade of hypersensitive post-synaptic 5-HT_{1A} heteroreceptors (de Boer et al., 2000; Millan et al., 1997). Indeed, elevated post-synaptic 5-HT_{1A} heteroreceptors in the forebrain are associated with aggressive behaviour (Korte et al., 1996), although direct administration of F15559 into ventral orbital PFC reduces aggression in male mice (Stein et al., 2013).

II. G. 9. Neuroplasticity and neuroprotection

5-HT_{1A} receptor agonists evoke neurogenesis and synaptogenesis in the adult hippocampus, thereby improving cognitive performance in this structure that is important for mnemonic function (Mogha et al., 2012; Schreiber and Newman-Tancredi, 2014; Vines et al., 2012). Moreover, 5-HT_{1A} receptor stimulation can lead to long term potentiation or depression (Meunier et al., 2013) with consequent elevated BDNF expression to influence neurogenesis (Luoni et al., 2013; Quesseveur et al., 2013).

In addition to the effects of 5-HT_{1A} receptor agonists on neuroplasticity, targeting this receptor may also have a beneficial role in neuroprotection. Indeed, there is considerable data supporting this assertion: repinotan reduced staurosporine-induced apoptosis (Suchanek et al., 1998), 8-OH-DPAT reduced the impact of excitotoxic doses of NMDA *in vivo* (Oosterink et al., 1998), and further may protect neurones via protective effects of astrocytes; conversely, 5-HT_{1A} receptor antagonism by WAY100635 increased damage (Ramos et al., 2004). Similarly, the selective 5-HT_{1A} receptor agonist, F13714 and the antipsychotic drugs clozapine, ziprasidone and aripiprazole, attenuated kainic acid-induced lesion volume in the striatum – effects that were reversed by WAY100635 (Cosi et al., 2005).

In models of Parkinson's disease, 5-HT_{1A} receptor agonists may slow neuronal damage (Bezard et al., 2006), and limit astrogliosis (Miyazaki et al., 2013). In the experimental autoimmune encephalopathy model of multiple sclerosis and *in vitro* cell-based models, the efficacy of a novel arylpiperazine D₂/5-HT_{1A} receptor ligand suggested this was due to combined action of the compound to limit inflammation and neuroprotective actions (Popovic et al., 2015), and buspirone appears to exert some efficacy against apoptosis in multiple sclerosis (O'Sullivan et al., 2008). Interestingly, repinotan was developed for activity in ischemic stroke and traumatic brain injury (Berends et al., 2005; Guenther et al., 2010; Lutsep, 2002; Mauler and Horvath, 2005); therapeutic areas that are historically very difficult for drug development. However, repinotan failed to show efficacy in acute ischemic stroke, and its development was discontinued (Teal et al., 2009).

III. 5-HT_{1B} receptors

III. A. Introduction

The 5-HT_{1B} receptor and its counterpart the 5-HT_{1D} receptor have experienced a complex and debated history (Figure 3) that is explained here. The two receptors are clearly closely related and result probably from gene duplication, which explains that in most species their pharmacological profiles are almost indistinguishable (however this is less evident in some species such as rat, mouse, hamster or opossum, see below). In addition: (i) expression levels of the 5-HT_{1D} receptor are very low as compared to those of the 5-HT_{1B} receptor; (ii) the two receptors tend to be expressed together in many brain regions (although not in the periphery; Figure 4); and (iii) 5-HT_{1B} and 5-HT_{1D} receptors are co-expressed and may form heterodimers in certain brain cells. In essence, the 5-HT_{1B} receptor is predominant and, in the absence of selective compounds, it is very challenging to identify a separate population of 5-HT_{1D} receptors in the brain. Except in rodents, hamster and opossum, where both receptors display somewhat different pharmacological profiles, the 5-HT_{1B} receptor is still largely predominant in terms of expression and function.

The 5-HT_{1B} receptor was originally defined according to operational and transductional criteria, and initially thought to be a rodent specific receptor (for references see Hoyer et al., 1994). In the 1970s, Peroutka and Snyder (1979) and others postulated that while [³H]5-HT labelled 5-HT₁ binding sites, [³H]spiperone (and later [³H]ketanserin) labelled 5-HT₂ binding sites, whereas [³H]LSD labelled both 5-HT₁ and 5-HT₂ binding sites. In 1981, Nelson and colleagues (Pedigo et al, 1981) proposed that 5-HT₁ binding sites were a heterogeneous population, since [³H]5-HT was displaced biphasically by spiperone; accordingly, the high affinity site for spiperone was called 5-HT_{1A}, and the low affinity 5-HT_{1B}. Middlemiss and colleagues (1977) had reported earlier that certain indole β -blockers displayed high affinity for some 5-HT receptors. In 1983, a breakthrough was reached when Hjorth et al. (1983) and Middlemiss and Fozard (1983) described 8-OH-DPAT as a selective 5-HT_{1A} ligand. Further, Gozlan et al. (1983) reported the selective labelling of 5-HT_{1A} sites using [³H]8-OH-DPAT. This allowed a clear definition of the 5-HT_{1A} pharmacological profile and, by extension, of the features of non-5-HT_{1A} sites (see Pazos et al, 1984a, 1984b; Hoyer et al, 1985a, 1985b). Thus, Palacios, Hoyer and colleagues at Sandoz in Basel, characterised [³H]mesulergine binding in the choroid plexus (Pazos et al, 1984a; Hoyer et al, 1985b), which 5-HT competed for with high affinity, but the relatively low affinity of ketanserin and spiperone suggested a 5-HT₁ receptor pharmacology. The features of [³H]mesulergine-labelled sites were

different from classical 5-HT₂ binding sites as labelled with e.g. [³H]ketanserin. The novel [³H]mesulergine-labelled binding site was named 5-HT_{1C} (now 5-HT_{2C}). Indeed, [³H]mesulergine binding was also markedly different from 5-HT_{1B} binding as evidenced in radioligand binding and autoradiographic studies (Pazos and Palacios, 1985; Pazos et al, 1985; Hoyer et al, 1986a, 1986b; Pazos et al, 1987a, 1987b). More specifically in rodents, 5-HT_{1B} binding sites were characterised extensively with the iodinated version of cyanopindolol, [¹²⁵I]ICYP (Engel et al, 1981), a potent β-blocker with high affinity for 5-HT_{1B} binding sites. These sites displayed high affinity for 5-HT, 5-CT, some β-blockers, some ergolines, LSD and RU24969 (Hoyer et al, 1985a; Engel et al, 1986; Hoyer et al, 1986a). Species differences in receptor pharmacology soon became evident with [³H]mesulergine, which had different binding profiles in rodents, pigs and humans; this pattern would repeat itself with a number of 5-HT receptors, most prominently with the 5-HT_{1B} receptor (Hoyer et al, 1988; Waeber et al, 1988). The Sandoz group used rat, mouse, hamster, rabbit, guinea pig, cat, dog, bovine, human and more atypical for research species such as pigeons, opossum and trout (e.g. Waeber et al, 1988a; 1988b; 1989a; 1989b) to investigate the pharmacology of 5-HT_{1A}, 1B, 1C and 5-HT₂ receptor binding sites. In addition, the pharmacology, transduction and distribution of non 5-HT_{1A/1B/1C} receptor binding sites, identified initially in calf and human brain and then most other species investigated, was termed 5-HT_{1D} receptor binding sites (Hoyer et al, 1998; Waeber et al, 1988a; 1988b; Hoyer and Schoeffter, 1988; Schoeffter et al, 1988). Although the pharmacology of 5-HT_{1B} and 5-HT_{1D} binding sites/receptors displayed some distinct differences, their distribution pattern in brain was similar (if not overlapping), and they shared transductional and functional responses (Hoyer and Schoeffter 1988; Schoeffter and Hoyer, 1989; 1990). Therefore, rodent ‘5-HT_{1B}’ and non-rodent ‘5-HT_{1D}’ receptors were proposed initially to represent species homologues (Hoyer & Middlemiss, 1989), a view that was unequivocally confirmed when genetic and structural information became available with the cloning of these receptors (Voigt et al, 1991; Adham et al, 1992; Hartig et al., 1992; Hamblin et al, 1992; Levy et al., 1992b; Maroteaux et al, 1992; Mochizuki et al, 1992).

However, matters were further complicated when Weinshank et al. (1992) identified two structurally distinct genes encoding human 5-HT₁ receptors with at the time almost overlapping pharmacological profiles, both resembling the 5-HT_{1D} receptor. Earlier on, a canine “orphan” clone called RDC4 (later named 5-HT_{1Dα}) had been reported to display a 5-HT_{1D}-like pharmacological profile (Libert et al, 1991; Hamblin and Metcalf, 1991; Maenhaut et al, 1991; Zgombick et al, 1991). A human receptor, initially called S12, was cloned independently and differed in sequence from the canine RDC4, yet displayed 5-HT_{1D}-like pharmacology (Levy et al, 1992b). Since the operational profiles of these two new receptors were mostly indistinguishable, they

were called 5-HT_{1D α} (canine RDC4 and species homologues) and 5-HT_{1D β} receptors (human S12 and species homologues). It soon became evident that, however, that in spite of some fundamental differences in their pharmacological profiles (see below), the 5-HT_{1D β} receptor was a human homologue of the rodent 5-HT_{1B} receptor (displaying 96% overall sequence homology; Adham et al., 1992). The subsequent identification of the 5-HT_{1D α} gene in rats confirmed that 5-HT_{1B} and 5-HT_{1D} receptors represent just two different receptor classes (Hartig et al., 1992), which prompted a realignment of 5-HT receptor nomenclature to recognise primacy (pre-eminence) of the human genome (Hartig et al., 1996). As a result, the 5-HT_{1D β} receptor was renamed 5-HT_{1B} (subsuming the rodent 5-HT_{1B} receptor), while the 5-HT_{1D α} nomenclature was abandoned for 5-HT_{1D} in recognition of the fact that this gene product encodes the 5-HT_{1D} receptor (see Figure 3; Hartig et al., 1996). This nomenclature for 5-HT_{1B} and 5-HT_{1D} receptors has been used since 1996 and remains to date.

III. B. Pharmacology

The 5-HT₁-like receptor mediating smooth muscle contraction and inhibition of noradrenaline release showed close similarities to the 5-HT_{1B} and/or 5-HT_{1D} receptors; however, the lack of selective ligands at these receptors made it difficult to distinguish these receptors with confidence hampering research for quite some time (Hoyer, 1988; Hoyer et al., 1994). Clitherow et al. (1994) reported the properties of several compounds including a piperazinybenzanilide derivative, GR127935, which shows a high affinity for and selective antagonist activity at 5-HT_{1B/1D} receptors. But more importantly the subsequent identification of potent and relatively selective antagonists at either the 5-HT_{1B} (SB224289; Hagan *et al.*, 1997; Gaster *et al.*, 1998) or 5-HT_{1D} (BRL15572; Price *et al.*, 1997) receptors, allowed responses to be attributed to either 5-HT_{1B} or 5-HT_{1D} receptors; for example the sumatriptan-induced contraction of vascular smooth muscle mediated via the 5-HT_{1B} receptor (e.g. De Vries et al., 1998, 1999; Verheggen et al., 1998).

Despite the 96% amino acid sequence homology in the transmembrane regions (Adham et al., 1992), the rodent 5-HT_{1B} receptor displays a distinct pharmacology compared to the 5-HT_{1B} receptor in other species (Hartig et al., 1996). The differences in the pharmacology of these species

homologues are largely attributed to the mutation of a single amino acid in the transmembrane spanning region Asp¹²³ to Arg¹²³ (Adham et al, 1994). Thus, CP93129 is a selective agonist at the rodent 5-HT_{1B} receptor, whereas some β -adrenoceptor antagonists, such as cyanopindolol, (-)-pindolol and (-)-propranolol, are selective antagonists at the rodent 5-HT_{1B} receptor, but not in other species. Unfortunately, no selective agonist is thus far available for the non-rodent 5-HT_{1B} receptor.

III. C. Receptor structure and transduction

The 5-HT_{1B} receptor gene is intronless, encoding for a 386-amino acid protein in rat and mouse and 390 amino acids in humans that displays the typical structure of a 7-transmembrane spanning GPCR. The human, mouse and rat 5-HT_{1B} receptor genes are located on chromosomes 6q13, 9E1 and 8q31, respectively. The rat receptor has 96% homology in the TMR with the human receptor, but the rat and mouse receptor (Voigt et al, 1991; Maroteaux et al., 1992; Adham et al, 1992) exhibit the typical 5-HT_{1B} receptor operational profile in contrast to the human receptor, which is close to the 5-HT_{1D} receptor operational profile (Levy et al., 1992b; Weinschank et al., 1992).

The 5-HT_{1B} receptor couples negatively to adenylyl cyclase (Bouhelal et al, 1988; Hoyer and Schoeffter, 1988; 1991; Adham et al., 1992; Maroteaux et al., 1992). Native 5-HT_{1B} receptors expressed in OK cells also mediate elevation of intracellular calcium (Zgombick and Branchek, 1998).

It is noteworthy that 5-HT_{1B} (and 5-HT_{2B}) receptors have been crystallised (Wang et al, 2013; Wacker et al, 2013; McCorvy and Roth, 2015; see Section XVI. A) that increases greatly knowledge of the structure-pharmacology of the receptor. Indeed, the conformation of a number of agonists is different when bound to 5-HT_{1B} or 5-HT_{2B} receptors, in spite of very similar orthosteric binding sites (Wacker et al, 2013; Wang et al, 2013; McCorvy and Roth, 2015). Sumatriptan and a range of other triptans fit well into the orthosteric pocket of the human 5-HT_{1B} receptor (in contrast to the 5-HT_{2B} receptor), thus confirming the high affinity and potency reported for the triptans at 5-HT_{1B} (and 5-HT_{1D}) receptors. Some ergolines (LSD, metergoline, DHE, ergotamine) bind to an accessory, possibly allosteric site, which is located outside of the orthosteric pocket. It has been proposed that a short peptide, 5-HT-moduline, is a negative allosteric modulator of both 5-HT_{1B} and 5-HT_{1D} receptors (Rousselle et al, 1998); research

concerning this peptide appears to have waned in recent years; the interested reader is directed to previous reviews on the subject (Fillion, 2000; Moret et al., 2003).

III. D. Distribution and function

Autoradiographic studies performed in various species showed that both 5-HT_{1A} and 5-HT_{1C} (now named 5-HT_{2C}) receptor binding was evident, in addition to 5-HT₂ receptor binding. However, what was then called 5-HT_{1B} binding site was apparently absent in pig, calf and human brain, in contrast to rodent brain. This observation was extended to the guinea-pig, and then to an increasing number of other species (Hoyer et al., 1988; Waeber et al, 1988a, 1988b, Hoyer and Middlemiss, 1989). Eventually, it was found that only rat, mouse, hamster and opossum had a 5-HT₁ receptor with a classical 5-HT_{1B} profile (see Hoyer et al, 1985a, 1985b). By contrast, other species expressed what was called 5-HT_{1D} receptors in the brain, i.e. guinea-pig, bovine, dog, rabbit, monkey and humans (see Waeber et al, 1988a; 1989a; 1989b; Hoyer et al, 1992; Hoyer and Schoeffter, 1989). It was subsequently shown that [³H]sumatriptan and a number of other triptans label both 5-HT_{1B} and 5-HT_{1D} sites. However, they may also label 5-HT_{1F} sites (Waeber and Moskowitz, 1995b). It also became evident when using specific antagonists, that both 5-HT_{1B} and 5-HT_{1D} receptors could be detected in a single species (Bruinvels et al, 1993a; 1993b; 1994a; Domenech et al, 1997; Bonaventure et al, 1997; Napier et al, 1999; Varnas et al, 2001), but 5-HT_{1D} receptor levels were minor when compared to the 5-HT_{1B} receptor.

An elegant study demonstrated the rat brain autoreceptors mediating inhibition of 5-HT release displayed the pharmacology of the 5-HT_{1B} receptor (Engel et al, 1986). In various other species, including humans, inhibitory autoreceptors displayed 5-HT_{1D} receptor pharmacology (Schlicker et al, 1989). 5-HT_{1B} receptors were also reported to mediate inhibition of GABA, cholinergic and glutamatergic neurotransmission (Maura and Raiteri, 1986; Johnson et al, 1992; Singer et al, 1996; Chadha et al, 2000; Morikawa et al, 2000). The 5-HT_{1B} receptor is highly concentrated in the substantia nigra, and was shown to be negatively coupled to adenylyl cyclase activity (Bouhelal et al, 1988; Hoyer and Schoeffter, 1988, 1991).

Both 5-HT_{1B} and 5-HT_{1D} receptors have a neuronal localisation (Waeber et al, 1990; Bruinvels et al, 1911; 1992a, 1992b; 1993; 1994a; 1994b; Sari et al, 1999), including in the trigeminal ganglia (Bruinvels et al, 1992a; Bruinvels et al, 1994a, 1994b; Hou et al, 2001; Ma, 2001; Potrebic et al, 2003). There is also evidence that both receptors colocalise and may form heterodimers (Ma, 2001; Xie et al, 1999).

Evidence from radioligand binding experiments using 5-HT neuronal lesions is equivocal regarding the location of the rat 5-HT_{1B} receptor, with some studies finding that the lesion causes an upregulation of 5-HT_{1B} binding sites, and others finding a down regulation in the same areas. However, it is now clear that, like the 5-HT_{1A} receptor, the 5-HT_{1B} receptor functions as a presynaptic autoreceptor (see also section XVIII). *In situ* hybridisation studies have located mRNA encoding the 5-HT_{1B} receptor in the dorsal and median raphé nuclei (Bruinvels et al, 1994a; Bonaventure et al, 1998). Furthermore, 5-HT_{1B} receptor mRNA in the raphé nuclei is markedly reduced by a 5-HT neuronal lesion. Together, these data suggest that 5-HT_{1B} receptors are located both presynaptically (inhibitory autoreceptor) and postsynaptically (heteroreceptor) relative to 5-HT neurones (see Waeber et al, 1990b); as an example of the latter, 5-HT_{1B} heteroreceptors inhibit CGRP release from sensory perivascular nerves in the rat systemic vasculature (González-Hernández et al., 2010).

5-HT_{1B} receptors are also located on cerebral arteries and other vascular tissues mediating direct vasoconstriction (see Villalón et al., 2003; Villalón and Centurión, 2007). Further, it seems that the receptor may be “silent” in a number of vascular preparations; becoming responsive in conditions such as atherosclerosis or when co-stimulated with “priming” factors (Sahin Erdemli et al, 1991; Kaumann et al, 1993; 1994). Other peripheral effects have also been described, such as: (i) inhibition of noradrenaline release from sympathetic nerves in vena cava (Göthert et al., 1986) and systemic vasculature (Villalón et al., 1998); and (ii) inhibition of plasma extravasation produced by trigeminal ganglion stimulation (Buzzi et al., 1991). 5-HT_{1B} receptors also mediate vasoconstriction in the rat caudal arteries (Craig and Martin, 1993) and the canine external carotid circulation (De Vries et al., 1998) or guinea-pig iliac artery (Sahin Erdemli et al, 1991), although endothelium-mediated relaxation has also been reported (Schoeffter and Hoyer, 1989; 1990). Interestingly 5-HT_{1B} receptor mRNA is more abundant within vascular smooth muscle cells, as compared to 5-HT_{1D} receptor mRNA (Branchek et al., 1995; Bouchelet et al., 1996; Sgard et al., 1996). The latter was reinforced by evident 5-HT_{1B}, but not 5-HT_{1D} receptor immunoreactivity in cranial blood vessels (Longmore et al., 1997). Consistent with these findings, the subsequent advent of the potent and relatively selective antagonists at either the 5-HT_{1B} (SB224289; Hagan *et al.*, 1997; Gaster *et al.*, 1998) or 5-HT_{1D} (BRL15572; Price *et al.*, 1997) receptors, made it

possible to demonstrate that the 5-HT_{1B}, but not the 5-HT_{1D}, receptor mediates the sumatriptan-induced contraction of vascular smooth muscle (e.g. De Vries et al., 1998, 1999; Verheggen et al., 1998).

III. E. Radioligand binding

Autoradiographic studies using [³H]-5-HT (in the presence of 8-OH-DPAT), [¹²⁵I]ICYP (in the presence of isoprenaline) or [¹²⁵I]-GTI demonstrated a high density of 5-HT_{1B} sites in the rat basal ganglia, (particularly the substantia nigra, globus pallidus, ventral pallidum and entopeduncular nucleus), but also in many other regions (Hoyer, 1988; Hoyer et al., 1994; Mengod et al, 2010). The discrimination of 5-HT_{1B} and 5-HT_{1D} receptors in both rodent and non-rodent species has become more straightforward with the availability of a new 5-HT_{1B/1D} radioligand, namely, [³H]-GR-125743 (Domenech et al, 1997; Varnas et al, 2001) or various triptans (Leysen et al, 1996; Bonaventure et al, 1997; Napier et al, 1999), as well as cold ligands which discriminate 5-HT_{1B} and 5-HT_{1D} receptors (Price et al, 1997; Middlemiss et al, 1999).

IV. 5-HT_{1D} receptors

IV. A. Introduction

To re-cap, following the cloning of 5-HT_{1D α} and 5-HT_{1D β} receptor genes in various species, 5-HT_{1D α} was renamed the 5-HT_{1D} and 5-HT_{1D β} became the 5-HT_{1B}, receptor keeping in mind that 5-HT_{1D} expression levels are generally low as compared to the 5-HT_{1B} receptor (see Section III for more detail).

IV. B. Pharmacology

As noted in Section III, the pharmacological distinction of 5-HT_{1B} from 5-HT_{1D} receptors was a challenge until the advent of selective and silent antagonists (devoid of intrinsic activity) for 5-HT_{1B} and 5-HT_{1D} receptors (Hagan *et al.*, 1997).

A series of isochroman-6-carboxamide derivatives, including PNU109291 (Ennis *et al.*, 1998), PNU142633 (McCall, 1999; McCall *et al.*, 2002) and L775606 (MacLeod *et al.*, 1997), have been reported to be selective 5-HT_{1D} receptor agonists, although they display low intrinsic efficacy at primate 5-HT_{1D} receptors in GTP γ ³⁵S binding assays (Pregenzer *et al.*, 1999).

The 5-HT_{1D} receptor is potently antagonised by the 5-HT_{1B/1D} receptor antagonist GR127935 (Clitherow *et al.*, 1994; Skingle *et al.*, 1996) and by the selective 5-HT_{1D} receptor antagonist, BRL15572 (Price *et al.*, 1997). Additionally, some 5-HT₂ receptor antagonists (e.g. ketanserin and ritanserin) can discriminate the 5-HT_{1D} receptor from 5-HT_{1B} and 5-HT_{1F} receptors (Hoyer *et al.*, 1994), although this is highly species dependent (see Branchek *et al.*, 1995; Zgombick *et al.*, 1995; 1997; Bard *et al.*, 1996). Sumatriptan and the second-generation triptans are potent agonists at the 5-HT_{1D} receptor (but also interact with 5-HT_{1B} and 5-HT_{1F} receptors; Villalón *et al.*, 2003; Table 6). It has been demonstrated that the 5-HT_{1D} receptor is located preferentially on neuronal, rather than vascular, tissues (Ullmer *et al.*, 1995; Sgard *et al.*, 1996; Longmore *et al.*, 1997).

Given the cardiovascular liabilities of triptans potentially via 5-HT_{1B} receptors expressed by vasculature (Nilsson *et al.*, 1999a; 1999b), which is not the case for 5-HT_{1D} receptors (Nilsson *et al.*, 1999b), it was hypothesised that selective 5-HT_{1D} receptor agonists may treat migraine, with reduced

cardiovascular side effects. Unfortunately, this has not translated to the clinic; 5-HT_{1D} receptor agonist PNU-142633 was ineffective in the acute treatment of migraine (Gómez- Mancilla et al, 2001) although the intrinsic activity of this compound may complicate interpretation.

IV. C. Receptor structure and transduction

The 5-HT_{1D} receptor gene, like the 5-HT_{1B} receptor gene, is intronless. The human 5-HT_{1D} receptor gene is located on chromosome 1p34.3-p36.3, codes for a 377 amino acid protein and possesses 63% overall structural homology with the 5-HT_{1B} receptor; the mouse and rat receptor genes are located on chromosomes 4D3 and 5q36 and code for 374 amino acid proteins. These receptors are made of a single polypeptide chain that spans the membrane seven times, with the amino terminus being extracellular and the carboxyl terminus intracellular in the manner typical of GPCRs (Hamblin and Metcalf, 1991; Weinshank et al, 1992; Hamblin et al, 1992; Weydert et al, 1992). The receptor is negatively coupled to adenylyl cyclase activity (Weinshank et al, 1992).

IV. D. Distribution and function

The distribution of 5-HT_{1D} receptors is known but understood with less confidence because protein levels are low along with the relative difficulty of radioligands to discriminate this receptor from the 5-HT_{1B} receptor. Receptor autoradiographic studies in rat (CP93129-insensitive [¹²⁵I]-GTI binding) or human (ketanserin-insensitive [³H]-sumatriptan binding) brain clearly indicate 5-HT_{1D} receptor site is in the basal ganglia (globus pallidus, substantia nigra and caudate putamen) and also the hippocampus and cortex (Pineyro et al, 1995; Hou et al, 2001; Potrebic et al, 2003; Mengod et al, 2010).

In situ hybridisation experiments allow a greater confidence of gene expression albeit not at the level of protein. Thus 5-HT_{1D} mRNA is present in rat brain including the caudate putamen, nucleus accumbens, olfactory cortex, dorsal raphe nucleus and locus coeruleus (e.g. Bruinvels et al, 1994a; Mengod et al, 2010; Figure 4). The mRNA shows low abundance in all regions and was undetectable in the globus pallidus, ventral pallidum and

substantia nigra where as noted above 5-HT_{1D} receptor sites appear to be present; perhaps indicative of the 5-HT_{1D} receptor being located predominantly on axon terminals of both 5-HT and non-5-HT neurones.

In the periphery, the presence of 5-HT_{1D} receptors is rather limited with evidence of presence in autonomic and trigeminal nerve terminals/ganglia (Jones et al., 1995; Molderings et al., 1996; Shephard et al., 1997; Villalón et al., 1998).

The function of the 5-HT_{1D} receptor still remains to some extent enigmatic. There is little evidence supporting the role of the 5-HT_{1D} receptor in any pathology. The availability of suitable tools for investigation *in vivo* has limited the investigations into the importance of 5-HT_{1D} receptors; they have been identified as autoreceptors in the dorsal raphe (Pineyro et al, 1995) or terminal brain regions. Thus, given their autoreceptor activity, 5-HT_{1D} receptor antagonists may have antidepressant potential and to maximize 5-HT release in terminal brain regions, 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1A} receptors must be blocked simultaneously.

Operationally, 5-HT_{1D} receptors mediate inhibition of noradrenaline release in human atrium (Schlicker *et al.*, 1997). Additionally, the 5-HT_{1D} receptor seems to be involved in the inhibition of guinea-pig dural plasma protein extravasation (Waeber *et al.*, 1997; Ennis *et al.*, 1998) and the central trigeminal inhibitory effects by some antimigraine compounds (Mills *et al.*, 1995; Goadsby & Knight, 1997; Cumberbatch *et al.*, 1998; De Vries et al., 1999a,b; Villalón et al., 2003).

It has been proposed that the 5-HT_{1D} receptor modulates growth hormone release (Mota et al, 1995; Whale et al, 1999) although this requires clearer pharmacological verification.

V. 5-ht_{1e} receptors

V. A. Introduction

There has been a relative lack of research on the 5-ht_{1e} receptor with an apparent lack of expression in rodents complicating pre-clinical studies. The lack of functional data concerning natively expressed 5-ht_{1e} receptors means by convention lower case appellation is still used for nomenclature.

With hindsight the 5-ht_{1e} receptor was likely discovered by virtue of an atypical pharmacology of a [³H]5-HT binding site in human frontal cortex (Leonhardt et al., 1989), which was sensitive to guanyl nucleotides suggesting association with the GPCR family. The high affinity [³H]5-HT displays for the binding sites and the low affinity for drugs displaying affinity for the 5-HT₂ receptor (e.g. mesulergine) supported membership of the 5-HT₁ receptor family. However, the low affinity of 5-carboxamidotryptamine (5-CT), the prototypical 5-HT₁ receptor agonist, and detailed pharmacological characterization of the new [³H]5-HT binding site in human and bovine cortical homogenates highlighted this site likely represented a further member of the 5-HT₁ family and hence it was given that next available name: 5-HT_{1E} (Leonhardt et al., 1989; now reclassified as 5-ht_{1e} until a functional response in native tissue/cell preparation can be attributed).

V. B. Cloning and distribution of 5-ht_{1e} receptors

Soon after the 5-ht_{1e} receptor binding site was pharmacologically characterized by radioligand binding in human and bovine brain tissue, a human GPCR gene, termed S31, was cloned (Levy et al., 1992a; see h5-ht_{1e} in Figure 5 for sequence) and assigned to human chromosome 6q14-q15 (Levy et al., 1994). When S31 was expressed in cell lines, the gene product was found to have pharmacological properties similar to the tissue-expressed 5-ht_{1e} receptor binding site, and the conclusion was this gene encodes the protein for the receptor binding site discovered by Leonhardt *et al.* (Leonhardt et al., 1989; McAllister et al., 1992; Zgombick et al., 1992; Gudermann et al., 1993). However, the 5-HT_{1F} receptor, discovered subsequent to these early reports on the 5-ht_{1e} receptor, shares a high degree of sequence homology with the 5-ht_{1e} receptor compared to other 5-HT receptors (see Figure 5 for h5-ht_{1e} and h5-HT_{1F} amino acid sequence alignment) and bears a pharmacological profile very similar to the 5-ht_{1e} receptor (Adham et al., 1993;

Lovenberg et al., 1993). A careful examination of the binding data presented in the original report on the 5-ht_{1e} receptor (Leonhardt et al., 1989) suggests the binding site identified in this report is likely a composite of both 5-ht_{1e} and 5-HT_{1F} receptor binding sites. Drugs that can discriminate between these receptor subtypes were not identified until after a number of studies were published that attempted to identify the distribution of 5-ht_{1e} receptors via radioligand binding and autoradiography methodologies (Barone et al., 1994; Beer et al., 1993; Fugelli et al., 1997; Miller and Teitler, 1992; Stanton et al., 1996). This resulted in reports that incorrectly attributed [³H]5-HT radioligand binding to the 5-ht_{1e} receptor in both rat and mouse brain tissue; species that were later identified to lack the 5-ht_{1e} receptor gene (Bai et al., 2004). Even those reports that utilized tissue from species that do express a 5-ht_{1e} receptor gene (e.g. humans, monkeys, guinea pigs, and bovine) were, in hindsight, confounded by the labeling of 5-HT_{1F} receptors, and thus need to be viewed as data that reflects a mixture of 5-ht_{1e} and 5-HT_{1F} receptor populations. Subsequent pharmacological isolation of 5-ht_{1e} receptors (Klein and Teitler, 2012) has shown the following pattern of expression of the 5-ht_{1e} receptor binding sites; olfactory bulb=hippocampus>frontal cortex>hypothalamus=cerebellum>brainstem-thalamus=striatum (Figure 6). Issues impacting the ability to define with confidence the distribution of the 5-ht_{1e} receptor, were to some extent overcome with the development of an antibody recognizing the 5-ht_{1e} receptor protein (Klein and Teitler, 2012) allowing protein expression to be revealed in native tissue. Such immunohistochemical studies revealed that the 5-ht_{1e} receptor-immunoreactivity was expressed in the olfactory bulb (glomerula cells) whereas in the hippocampus expression is limited to the dentate gyrus (Klein and Teitler, 2012). Interestingly, 5-ht_{1e} receptor-immunoreactivity was also expressed in cerebral arteries (guinea pig; Klein and Teitler, 2012).

V. C. Pharmacology

Bai and coworkers demonstrated that the rhesus monkey, pig, rabbit, and guinea pig express a homolog of the human 5-ht_{1e} receptor gene (Bai et al., 2004). Due to the relative utility in pre-clinical models, the guinea pig 5-ht_{1e} receptor (gp5-ht_{1e}) sequence was cloned for further study. The guinea pig homolog shares 88% nucleic acid and 95% amino acid sequence homology with the human 5-ht_{1e} receptor. The pharmacological properties of the guinea pig recombinant 5-ht_{1e} receptor correlate well with the human counterpart in terms of affinity ($R^2 = 0.99$) and potency ($R^2 = 0.96$) indicating a high degree of evolutionary conservation for the receptor.

Quantitative RT-PCR of guinea pig brain regions revealed high levels of gp5-ht_{1e} receptor mRNA in the cortex, hippocampus, and olfactory bulb and moderate expression in some other regions, similar to the expression pattern in the human brain (Bai et al., 2004). Thus, the structural and pharmacological similarities of the human and guinea pig receptors, along with comparable patterns of expression in gross brain regions, lend a great deal of support to the guinea pig as a valid model to study the functionality of the h5-ht_{1e} receptor.

Some attempts have been made to develop selective pharmacological tools for the h5-ht_{1e} receptor (Dukat et al., 2004) although failed to identify 5-ht_{1e} receptor ligands with affinities substantially higher than 5-HT. A relatively selective high affinity 5-ht_{1e} receptor ligand has been identified, BRL54443 (Brown et al., 1998) although this drug displays similar affinities for the h5-ht_{1e} and h5-HT_{1F} receptors but more usefully at least 60-fold lower affinities for other 5-HT, dopamine, and adrenergic receptors. Few published reports exist regarding the pharmacology of this compound, and the reports of BRL54443 action *in vivo* have utilised species which do not express the 5-ht_{1e} receptor (mice and rats; Adham et al., 1994; Brown et al., 1998; Granados-Soto et al., 2010; Hisadome et al., 2009; McKune and Watts, 2001; Watts et al., 2001).

A high throughput screening study conducted at the Scripps Research Institute's Molecular Screening Center in collaboration with Milt Teitler's laboratory, with the aim of identifying highly potent, selective agonists or antagonists for the 5-ht_{1e} receptor has been performed (PubChem BioAssay Database, AID: 567; 574; 613; 718; 726; 730). Nearly 65,000 compounds from a broad range of structural classes were screened for agonist and antagonist properties at the h5-ht_{1e} receptor and counter-screened at the 5-HT_{1A} receptor as an assessment of selectivity. Whilst none of the compounds were highly selective for the h5-ht_{1e} receptor, a number of high potency agonists (EC₅₀ low nM) were identified that displayed some structural similarity to BRL54443. In a more recent study comparing 51 tryptamine-based compounds for affinities at the human 5-ht_{1e} and 5-HT_{1F} receptors, no drugs were identified that showed a significant preference for the 5-ht_{1e} receptor over the 5-HT_{1F} receptor, again demonstrating the difficulties in attempting to identify 5-ht_{1e} receptor-selective drugs (Klein et al., 2011).

V. D. Functions

Recombinant expression of the 5-HT_{1e} receptor in cell lines demonstrate the coupling to G_{i/o} signaling pathways (Adham et al., 1994) although no signalling pathways have been identified in native tissues and in the absence of a recognised functional response the lower case appellation nomenclature is retained.

VI. 5-HT_{1F} receptors

VI. A. Introduction

Although the first published reports for the 5-HT_{1F} receptor occurred in 1992-93 (Amlaiky et al., 1992; Adham et al., 1993a; Lovenberg et al., 1993), there is still only limited information about this receptor. Much of the current literature centers on possible roles for the 5-HT_{1F} receptor in the treatment of migraine despite the 5-HT_{1F} receptor displaying a broad distribution within the central nervous system (CNS) and also appears to be expressed in the periphery.

VI. B. Cloning and structure

The 5-HT_{1F} receptor was discovered as the result of homology cloning strategies. The first report of the cloning of the human 5-HT_{1F} receptor was in a patent application by Synaptic Pharmaceuticals, Inc., (Weinshank et al., US patent #5,360,735, filed in 1992, issued in 1994). Amlaiky et al. (1992) reported the cloning of the mouse receptor (initially called 5-HT_{1Eβ}) that same year, followed by a peer-reviewed report on the human receptor (Adham et al., 1993a), and the cloning of both the rat and human versions (initially called 5-HT_{1E-like}) of the receptor in 1993 (Lovenberg et al., 1993) (Table 7).

The 5-HT_{1F} receptor gene is intronless, coding for a GPCR of 366 amino acids that conform to the classic GPCR structure and has been sequenced in a number of species (mouse, rat, guinea pig, pig, human; Amlaiky et al., 1992; Adham et al., 1993a; Lovenberg et al., 1993; Adham et al., 1997; Bhalla et al., 2002b). In mouse and rat, it appears that the 5-HT_{1F} receptor is encoded by three different mRNA transcripts (Guptan et al., 1997), which differ in their 3' untranslated regions.

VI. C. Distribution

VI. C. 1. mRNA

The initial studies of 5-HT_{1F} receptor distribution located 5-HT_{1F} receptor mRNA, either by the reverse transcription polymerase chain reaction (RT-PCR) or *in situ* hybridization (Figure 7; Table 8). 5-HT_{1F} receptor mRNA has a rather broad distribution within the brain; the cerebral cortex shows a relatively dense band of expression within the internal layers (approximately layers IV-VI), and hippocampal areas CA1-CA3 display relatively high expression, as do the thalamus and striatum.

Documentation of the presence of 5-HT_{1F} receptor mRNA in peripheral tissues is limited to a few single reports in different species including human, bovine, pig, rat, and rabbit (Table 8). Overall, there is still a need for a systematic mapping of the peripheral distribution of 5-HT_{1F} receptors. Peripheral blood vessels such as the coronary artery have been reported to express 5-HT_{1F} message, although the findings in human coronary appear variable, with Ishida et al. (1999) finding none, Nilsson et al. (1999b) reporting a strong signal, and Bouchelet et al. (2000) reporting a weak signal in about 40% of patients. Bhalla et al. (2002) found a 5-HT_{1F} receptor mRNA signal in porcine coronary artery. Regardless, the 5-HT_{1F} receptor agonist, LY334370 did not elicit contractions in human coronary artery (Nilsson et al., 1999b). 5-HT_{1F} receptor transcripts are also present in vascular preparations from the CNS (Table 8). However, when the brain microvessel preparations were treated to yield cultures of either smooth muscle or endothelial cells, no 5-HT_{1F} receptor mRNA was detected (Cohen et al., 1999).

In contrast to peripheral tissues, evidence for the presence of 5-HT_{1F} receptor mRNA in the peripheral nervous system is clear; thus, multiple studies in trigeminal ganglia and dorsal root ganglia (fresh or cultured) have identified 5-HT_{1F} receptor mRNA (Table 8).

VI. C. 2. Radioligand binding

The first localization studies of 5-HT_{1F} receptor binding sites used [³H]sumatriptan, which displays high affinity for 5-HT_{1F} receptors as well as 5-HT_{1B/1D} receptors. This radioligand has been used to map the 5-HT_{1F} receptor in a variety of species (including of 'cold' competing ligands e.g. 5-CT or methiothepin prevent radiolabelling of 5-HT_{1B} and 5-HT_{1D} receptors; Waeber and Moskowitz, 1995b; Mengod et al., 1996; Scarr et al., 2004; Dean et al., 2006). Although [³H]5-HT can be used to label heterologous expression of 5-HT_{1F} receptors in cultured cells (Adham et al., 1993a), lack

of selectivity makes 5-HT_{1F} receptor localization studies with [³H]5-HT challenging Fugelli et al. (1997). A second useful radioligand to label the 5-HT_{1F} receptor is [³H]LY334370, albeit in the presence of 5-HT_{1A} receptor ligands e.g. 8-OH-DPAT to prevent labeling of the latter receptor (Wainscott et al., 2005). It is probably noteworthy that with all 5-HT_{1F} receptor labelling studies, the lack of a selective radioligand necessitating the use of ‘cold’ blocking drugs to better isolate radioligand binding to the 5-HT_{1F} receptor may underestimate the reported levels of 5-HT_{1F} receptors or conversely the specific radioligand binding signal consists of a heterogeneous population of sites that includes the 5-HT_{1F} receptor; either way, interpretation should be made with caution.

VI. C. 3. Immunoreactivity

Relatively few studies have utilized antibodies to localize 5-HT_{1F} receptors (Table 9). The antibody studies of Ma (2001) and Classey et al. (2010) are consistent with investigations showing 5-HT_{1F} receptor mRNA in trigeminal ganglia and dorsal root ganglia (Table 8). Classey et al. (2010) describe 5-HT_{1F} receptor-like immunoreactivity in dorsal root ganglia from all regions examined, cervical, thoracic and lumbar. Ma (2001) reported co-localization of 5-HT_{1F} receptor with glutamate-containing neurons of the trigeminal ganglion, and Ahn et al. (2009) showed co-localization of 5-HT_{1F} receptors with CGRP in neurons of rat vestibular nuclei. Garrett et al. (2014) provide a unique perspective on the 5-HT_{1F} receptor, showing the presence of both mRNA (Table 8) and protein (Table 9) in the rabbit renal proximal tubule.

VI. D. Pharmacology

VI. D. 1. Agonists

The 5-HT_{1F} receptor, like the other members of the 5-HT₁ family, has high affinity for 5-HT itself. This characteristic has driven much of the structural work devoted to developing high-affinity, selective 5-HT_{1F} receptor agonists.

Compared to 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors, the pharmacology described for 5-HT_{1F} receptors is rather sparse. Because of a potential link between 5-HT_{1F} receptor activation and the treatment of migraine (see below), most of the effort to develop selective compounds has focused on the development of orthosteric agonists. No selective orthosteric 5-HT_{1F} receptor antagonists have been reported. Likewise, there are no literature descriptions of allosteric 5-HT_{1F} receptor ligands.

Almost all of the structure activity relationship (SAR) work has come from the laboratories of Eli Lilly and Company, which had exclusive rights to the 5-HT_{1F} receptor through a collaborative agreement with the patent holder, Synaptic Pharmaceutical Corporation. Table 10 summarizes published named compounds showing selectivity for the 5-HT_{1F} receptor. Lasmiditan (COL-144, LY573144) and LY344864 display very good selectivity for the 5-HT_{1F} receptor relative to all other 5-HT receptors, as does LY334370, except that it is only about 8-9 fold selective over 5-HT_{1A} receptor. LY302148 was an early molecule that showed selectivity for the 5-HT_{1F} receptor relative to other 5-HT₁ subtypes. However, it also has high affinity for 5-HT_{2A} and 5-HT_{2B} receptors (Table 10) and is illustrative of the difficulty in identifying 5-HT receptor subtype selectivity in simple indole-based compounds.

Lasmiditan (COL-144, LY573144) is a departure from the other structures in that it contains no indole nucleus. The progression from a bicyclic aromatic nucleus (indole) to the monocyclic nucleus of lasmiditan apparently involved some serendipity, as Zhang et al. (2015) describe how, in the process of producing a homolog of LY334370, a monocyclic intermediate was formed that had moderately good affinity for the 5-HT_{1F} receptor. Expanding an SAR around this finding, they discovered several compounds that had high affinity and good selectivity for the 5-HT_{1F} receptor (Zhang et al., 2015). Replacing the indole to eventually generate lasmiditan resulted in a highly selective 5-HT_{1F} receptor agonist.

Several additional studies have generated significant SAR for 5-HT_{1F} receptor agonists (Xu et al., 2001; Filla et al., 2003; Zhang et al., 2004; and Mathes et al., 2004). The most potent and selective compounds are included in Table 11. These molecules represent riffs on the indoleethylamine core of 5-HT. For example, compound A (Table 11) employs N,N-dimethyltryptamine as its core, resulting in a molecule that has slightly lower

affinity for the 5-HT_{1F} receptor compared to LY334370, but overall greater selectivity. Compounds B, C, D, and E illustrate that the indole nucleus can be replaced with other bicycles (e.g., azaindole, indazole, and indoline), resulting in compounds with very good 5-HT_{1F} receptor affinity and selectivity.

VI. D. 2. Partial agonists and antagonists

There are no published SAR studies for 5-HT_{1F} receptor antagonists. Methiothepin has been used in *in vitro* functional studies, but it is nonselective and of only moderate affinity for the 5-HT_{1F} receptor (Adham et al., 1993a). 1-NP (1-naphthylpiperazine) and metergoline were described as partial agonists to inhibit adenylyl cyclase activity (Adham et al., 1993b). Other compounds have been reported as partial agonists at 5-HT_{1F} receptor-stimulated [³⁵S]GTPγS binding, e.g. dihydroergotamine (68% of 5-HT; Wainscott et al., 1998), LY302148 (17% of 5-HT; Wainscott et al., 1998), frovatriptan (46% of 5-HT; Nelson et al., 2010), 2-thienyl-LYX (61% of 5-HT; Filla et al, 2003), and 2-pyridyl-LYX (63% of 5-HT; Filla et al., 2003). The prototypical triptan, sumatriptan, has relatively high affinity for the 5-HT_{1F} receptor, and for comparison with the selective 5-HT_{1F} compounds, Table 6 lists the affinities of a number of triptans across the 5-HT receptor subtypes. Efficacy studies using a [³⁵S]GTPγS binding system to measure functional activity at the 5-HT₁ family of receptors, naratriptan, rizatriptan, sumatriptan, and zolmitriptan were found to act as full agonists at all the 5-HT₁ receptors that they stimulated. Frovatriptan, the only carbazole (i.e. a three-ring system containing indole), was a full agonist at 5-HT_{1B} and 5-HT_{1D} receptors, but only a partial agonist at 5-HT_{1A} and 5-HT_{1F} receptors (Nelson et al., 2010). Hence several triptans have high affinity for the 5-HT_{1F} receptor and may activate 5-HT_{1F} receptors *in vivo* at doses sufficient to also activate 5-HT_{1B/1D} receptors (as well as other receptors; Table 6).

VI. E. Signal transduction

The 5-HT_{1F} receptor inhibits forskolin-stimulated adenylyl cyclase activity in recombinant cell systems (Amlaiky et al., 1992; Adham et al 1993a), with later studies suggesting coupling through Gi/Go proteins based on pertussis toxin sensitivity (Adham et al., 1993b). The human 5-HT_{1F} receptor can also mediate inositol phosphate production and calcium flux through a pertussis toxin-sensitive mechanism in a recombinant system (Adham et al., 1993b). There are no reports on the transduction mechanisms affected by the 5-HT_{1F} receptor in native tissues.

VI. F. Function

As noted above, signal transduction studies with heterologously expressed 5-HT_{1F} receptor readily identify responses; inhibition of forskolin-stimulated adenylyl cyclase activity (Amlaiky et al., 1992; Adham et al., 1993a), stimulation of inositol phosphate production and cellular calcium flux (Adham et al., 1993b), stimulation of [³⁵S]GTPγS binding (Wainscott et al., 1998).

Neurogenic dural inflammation has been used as a model for the development of anti-migraine drugs, in which the triptans display efficacy. Early dogma considered that the mechanism of action of the triptans was exclusively through the activation of 5-HT_{1B/1D} receptors (Buzzi and Moskowitz., 1991; Humphrey, 2007). Yet other studies (Johnson et al., 1997; Wainscott et al., 1998) demonstrate that the pharmacologic profile for the inhibition of neurogenic dural inflammation in the guinea pig correlated better with the pharmacology of the 5-HT_{1F} receptor. Several additional studies support that 5-HT_{1F} receptor selective agonists inhibit neurogenic dural inflammation; LY344864 and lasmiditan inhibit neurogenic dural inflammation in the rat (Phebus et al., 1997; Nelson et al., 2010), and 'Compound A, B & C' likewise in the guinea pig (Xu et al., 2001; Filla et al., 2003).

Several studies have examined the effects of 5-HT_{1F} receptor agonists on *c-fos* levels in the trigeminal system. Intra-cisternal administration of capsaicin in rats stimulates *c-fos* production in the trigeminal nucleus caudalis, an effect that is inhibited by pretreatment with either sumatriptan or LY344864 (Mitsikostas et al., 1999). The effect of sumatriptan but importantly not that of LY344864, was blocked by a rat 5-HT_{1B} receptor antagonist. The inhibition of capsaicin-induced *c-fos* production by LY344864 and sumatriptan was also reproduced in the mouse (Mitsikostas et al., 2002). Electrical stimulation of the trigeminal ganglion in the rat induces *c-fos* production in the nucleus caudalis, which was blocked by lasmiditan in a dose-dependent fashion (Nelson et al., 2010). LY334370 was also active in this model.

Other models of neuronal stimulation have shown that 5-HT_{1F} receptor agonists produce inhibitory effects. For example, LY344864 inhibited a CGRP-mediated vasodepressor response produced by electrical stimulation of primary sensory nerves in the rat (González-Hernández et al., 2011). It did not affect vasodepressor responses induced by exogenously administered CGRP, consistent with the concept that prejunctional 5-HT_{1F} receptors inhibit CGRP release. LY344864 inhibited potassium-stimulated release of CGRP in the dura mater of the rat, but not in the trigeminal ganglion or trigeminal nucleus caudalis (Amrutkar et al., 2012). Additionally, LY344864 inhibited activation of second-order neurons in the trigeminal nucleus caudalis elicited by electrical stimulation of the dura mater in rats (Shepherd et al., 1999).

Little work has been devoted to potential peripheral actions of 5-HT_{1F} receptors. Granados-Soto et al. (2010) have suggested that 5-HT_{1F} receptors are involved in peripheral pain mechanisms, since LY344864 blocked nociception induced by formalin injection into the rat paw. In a more direct examination of peripheral tissues LY334370 and LY344864 stimulated the production of markers of mitochondrial biogenesis in isolated rabbit renal proximal tubules, which was diminished when the tubule preparation was subject to 5-HT_{1F} receptor knockdown by siRNA transfection (Garrett et al., 2014). Administration of LY344864 *in vivo* to mice also led to an increase in a panel of markers for mitochondrial biogenesis in renal cortex, heart, and liver (Garrett et al., 2014).

Extensive study has failed to demonstrate 5-HT_{1F} receptors contract blood vessels (e.g. Johnson et al., 1997; Cohen and Schenck, 1999, 2000; Razzaque et al., 1999; Shepherd et al., 1999; Bouchelet et al., 2000; Nelson et al., 2010). As detailed in Section III, this contrasts functions associated with the 5-HT_{1B} receptor, through which triptans act to contract certain vascular tissues, including coronary artery, that can present serious adverse effects for patients. Hence the optimism for 5-HT_{1F} receptor agonists as treatments for migraine with a reduced side-effect profile (see below).

VI. G. Clinical relevance and therapeutics

As discussed above, since 5-HT_{1F} receptor agonism correlates with the pharmacology of the inhibition of a model of neurogenic dural inflammation – combined with the apparent absence of the 5-HT_{1F} receptor to contract vasculature - much of the translatable work concerning the 5-HT_{1F} receptor has centered on the treatment of migraine. This led, ultimately, to the development of LY334370, the first selective 5-HT_{1F} receptor agonist examined

clinically where efficacy to treat the pain of acute migraine attacks was noted (Goldstein et al., 2001). However, development of LY334370 was terminated due to safety concerns identified in animal toxicology studies (Ramadan et al., 2003; Ramadan and Buchanan, 2006). Further efforts to search for a more selective 5-HT_{1F} receptor agonist with pre-clinical toxicology issues, identified LY573144. This molecule was subsequently out-licensed to CoLucid Pharmaceuticals (becoming COL-144; lasmiditan; Table 10), although the acquisition of CoLucid in 2017 by Eli Lilly returned the molecule to the parent company.

Lasmitidan is efficacious in alleviating symptoms of acute migraine in clinical trials. The first peer-reviewed published trial was a proof of concept investigation that demonstrated the efficacy of lasmiditan given intravenously (Ferrari et al., 2010). The primary efficacy measure was headache relief two hours after administration; a significant dose-response effect on efficacy separated lasmitidan from placebo. A trial using oral lasmiditan used the same primary efficacy measure, and all doses significantly improved headache response at 2 hours compared with placebo (Färkkilä et al., 2012). The most common side effects were dizziness, fatigue, vertigo, and paraesthesia. Positive results from two pivotal Phase III trials of lasmitidan (Kuca et al., 2018; Loo et al., 2019) led to subsequent marketing approval in 2019.

VII. 5-HT_{2A} receptors

VII. A. Introduction

The 5-HT_{2A} receptor (formerly 5-HT₂) was first identified as a binding site in rat brain with high (nanomolar) affinity for [³H]spiperone and [³H]ketanserin and low (micromolar) affinity for 5-HT (Peroutka and Snyder, 1979; Leysen et al., 1981). Soon after its discovery, the 5-HT_{2A} receptor was found to mediate several effects of 5-HT in the periphery, including platelet aggregation (De Clerck et al., 1982) and smooth muscle contraction (Cohen et al., 1981; Maayani et al., 1984; Engel et al., 1985). The peripheral 5-HT_{2A} receptors were originally classified as “D-type” 5-HT receptors based on pharmacological evidence (Bradley et al., 1986). The 5-HT_{2A} receptor was also the first 5-HT receptor found to couple to stimulate PI hydrolysis (Conn and Sanders-Bush, 1984).

VII. B. Cloning of the gene

The first 5-HT_{2A} receptor clone was isolated from rat brain cDNA libraries by homology screening based on the sequence of structurally related 5-HT_{2C} receptor (Pritchett et al., 1988; Julius et al., 1990). Functional expression of the cloned receptor confirmed coupling to phosphoinositide hydrolysis and Ca²⁺ mobilization. The human 5-HT_{2A} receptor was subsequently cloned by Saltzman et al. (1991), and displayed 87% homology with the rat receptor. The receptor contains 471 amino acids, with 5 potential glycosylation sites in the N-terminal extracellular domain and 11 potential phosphorylation sites in the C-terminal intracellular domain. The *HTR2A* gene encoding the human 5-HT_{2A} receptor has been mapped to chromosome 13q14–q21 (Sparkes et al., 1991). Analysis of the genomic structure of the human 5-HT_{2A} receptor revealed that it contains three exons separated by two introns, spanning more than 20 kilobases (kb) (Chen et al., 1992; Stam et al., 1992). Other species from which the 5-HT_{2A} receptor has been cloned include hamster (Obberghen-Schilling et al., 1991), mouse (Yang et al., 1992), and pig and rhesus monkey (Johnson et al., 1995) (Table 12). Sequence alignments for the 5-HT_{2A} receptor from eight species are shown in Figure 8.

VII. B.1. Regulation of 5-HT_{2A} receptor gene expression

The structure of the 5-HT_{2A} promoter region has been characterized in humans, rats and mice; the promoters lack canonical TATA or CAAT boxes. Fragments of a 1.6 kb segment from the 5' flanking region of the human gene showed promoter activity when transfected into receptor-expressing human cell lines (Zhu et al., 1995). The human promoter sequence contains multiple transcription initiation sites, along with several binding sites for transcription factors, including Sp1 (simian virus 40 promoter factor 1), PEA3 (polyomavirus enhancer activator 3), CRE (cAMP response element), and E-box binding proteins. There was also evidence that the 5' flanking sequence contains an alternative promoter, as well as a silencing element upstream from the translation start codon. Falkenberg et al. (2011) subsequently demonstrated that the human promoter contains a glucocorticoid receptor (GR) binding site at position -1,420. Furthermore, the A-allele of the -1,438G/A (rs6311) polymorphism is believed to create a binding site for the transcription factor Th1/E47, which reportedly increases promoter activity (Smith et al., 2008).

Multiple *cis* elements in the mouse 5-HT_{2A} promoter act in a dynamic manner to regulate transcription. The 5' flanking region of the mouse 5-HT_{2A} receptor gene contains a basal promoter (located -0.6 kb to -2.3 kb from the translational start site), which includes 11 transcription initiation sites, and binding sites for AP-2 (activating protein 2), PEA3, and Sp1 transcription factors (Ding et al., 1993; Toth et al., 1994). The activity of the basal promoter is attenuated in non-neuronal cells by two upstream repressor elements (extending from -2.3 kb to -4.2 kb), domains that presumably contain binding sites for transcription-inhibiting factors present in non-neuronal but not in neuronal cell types. Repressed genes can be reactivated in particular cell types via cell-specific activators, which may be responsible for 5-HT_{2A} receptor expression in certain non-neuronal cells. For example, Ding et al. (1993) identified a domain located upstream (-4.2 kb to -5.6 kb) from the repressor elements that reactivates transcription of the 5-HT_{2A} gene in C6 glioma cells.

The organization of the rat 5-HT_{2A} promoter is similar to that of mice, containing multiple negative and positive regulatory elements. Garlow et al. (1994) identified a primary transcription initiation site -1,173 from the translational start site, and a minimal promoter sequence in the 0.2 kb

sequence immediately upstream from the primary initiation site. The activity of the minimal promoter is enhanced by proximal positive transitional elements 0.2 to 1.1 kb from the initiation site, and attenuated by two distal negative domains located further upstream (1.1–2.2 and 2.3–2.5 kb from the initiation site, respectively). Analysis of the promoter and enhancer sequences revealed the presence of binding sites for the transcription factors NF-1, AP-1, AP-2, and Egr 1, as well as a GR element (Garlow et al., 1994; Garlow and Ciaranello, 1995). Experiments with transfected promoter-reporter plasmids showed that dexamethasone and AP-1 affected transcription of the promoter (Garlow and Ciaranello, 1995). The GR element appears to regulate 5-HT_{2A} receptor transcription in rat brain, as evidenced by the significant increase in 5-HT_{2A} mRNA expression induced by GR knockdown (Islam et al., 2004). AP-1 may play a role in agonist-induced upregulation of the 5-HT_{2A} receptor in rat cerebellar granule cells (Chalecka-Franaszek et al., 1999). In contrast, Du et al. (1994, 1995) reported that the primary 5-HT_{2A} transcriptional start site in rat myometrial smooth muscle cells is located at position –1,120 from the translational start site. They also identified a basal promoter and two upstream repressor domains, but no enhancer region was detected. These discrepant findings may reflect cell type-specific differences in the function of the rat 5-HT_{2A} promoter.

VII. C. Distribution

Many cell types in peripheral tissues express 5-HT_{2A} receptors, including platelets, fibroblasts, lymphocytes, and myocytes. In the CNS, neurons are the main site of localization although the presence of 5-HT_{2A} receptors on non-neuronal cells types (glia, astrocytes) has also been reported (see below). The localisation of 5-HT_{2A} receptors in the brain has been mapped by a combination of receptor autoradiography, in situ hybridisation, immunocytochemistry, and more recently PET neuroimaging. Receptor autoradiography studies using [³H]spiperone, [³H]ketanserin, [¹²⁵I]DOI and [³H]MDL 100907 as radioligands, have revealed high levels of 5-HT_{2A} receptor binding sites in many forebrain regions, including cortical and hippocampal areas, the basal ganglia and olfactory tubercle, and the pattern is similar across species (eg. Pazos et al., 1987 and López-Giménez et al., 1997). The distribution of 5-HT_{2A} receptor binding sites agrees well with that of 5-HT_{2A} mRNA (Mengod et al., 1990, Morilak et al., 1994, Burnet et al., 1995), suggesting that 5-HT_{2A} receptors are largely expressed in the region of the somatodendritic and not trafficked along axons although there are some conflicting immunohistochemical data (for review see Weber and Andrade, 2010; Nocjar et al., 2015). Moreover, much 5-HT_{2A} receptor immunoreactivity in rat neocortex has been detected in the cytoplasmic rather than membrane bound compartments (Cornea-Hebert et al., 1999;

Cornea-Hebert et al., 2002); which might reflect a high intracellular reserve of the 5-HT_{2A} receptors, which could be useful for the dynamic insertion of these receptors into the membrane.

A combination of immunocytochemical and *in situ* hybridisation studies have investigated the cell types expressing the 5-HT_{2A} receptor in cerebral cortex (Figure 9). Early data demonstrated the presence of 5-HT_{2A} receptors in cortical glutamatergic pyramidal (projection) neurons (Burnet et al., 1995), which have subsequently been mapped to specific cortical pathways (Vázquez-Borsetti et al, 2009; Mocci et al, 2014). Most such studies indicate that these cortical 5-HT_{2A} receptors are predominantly postsynaptic and localized to either the apical dendrites or soma of pyramidal neurons. However, 5-HT_{2A} receptors have also been detected in GABAergic interneurons in the cortex (Morilak et al., 1994; Burnet et al., 1995; Mengod et al, 2015) and amygdala. There has also been an immunohistochemical analysis of 5-HT_{2A} receptor localisation in the ventral tegmental area and the majority of immunolabeling was colocalized with tyrosine hydroxylase, suggesting that the receptors are expressed on dopaminergic neurons, although there is also evidence for localization on VTA GABA neurons (Doherty and Pickel, 2000; Nocjar et al., 2002).

More recently 5-HT_{2A} receptor localisation has been mapped using BAC transgenic mice engineered to express a fluorescent reporter (EGFP) under the control of the 5-HT_{2A} receptor promoter, thus revealing 5-HT_{2A} expression (Weber and Andrade, 2010). These data show a striking pattern of 5-HT_{2A} receptor distribution at the regional and cellular levels. Mapping within the cortical microcircuitry revealed 5-HT_{2A} receptor expression in specific laminae and in both pyramidal and interneurons. Interestingly, and in agreement with previous observations (Puig et al, 2010), expression was marked in cortical parvalbumin positive interneurons which underpin the formation of certain network oscillations (gamma frequency) thought critical for sensory information processing. The BAC (bacterial artificial chromosome) transgenic mouse study and previous immunocytochemical studies (Stein et al., 2000; Weber and Andrade, 2010) also find 5-HT_{2A} receptors is located on parvalbumin-containing interneurons in the basolateral nucleus of the amygdala. This finding is consistent with data from electrophysiological studies showing that in the amygdala, 5-HT acts on 5-HT_{2A} receptors to potentiate GABAergic inhibition, including the GABA input to pyramidal neurons in this region (Jiang et al., 2009; Bocchio et al, 2015).

The study of BAC transgenic mice with EGFP under the control of the 5-HT_{2A} receptor promoter (Weber and Andrade, 2010) did not report the presence of 5-HT_{2A} receptors in non-neuronal cells, as suggested in earlier immunocytochemical studies (Xu and Pandey, 2000) although further confirmation is awaited. Co-localisation of 5-HT_{2A} receptors with other 5-HT receptor subtypes has been reported (5-HT_{1A}, 5-HT_{2C}; eg. Puig et al, 2010; Stephens et al., 2014; Nocjar et al, 2015; Mengod et al, 2015; Tian et al., 2016), providing further evidence of potential cross-talk in 5-HT signaling at the receptor level.

The development of a number of 5-HT_{2A} receptor-selective radioligands has been useful as research tools including the imaging of 5-HT_{2A} receptors in humans with the most successful including the SPECT radioligand [¹²³I]R91150, and the PET radioligands [¹⁸F]setoperone, [¹⁸F]altanserin, and [¹¹C]MDL 100,907 (Paterson et al, 2013; Herth and Knudsen, 2015). The first 5-HT_{2A} receptor agonist PET ligand, [¹¹C]N-(2-methoxybenzyl)-2,5-dimethoxy-4-bromophenethylamine ([¹¹C]Cimbi-36), has recently been reported (Ettrup et al, 2014) and raised the interesting possibility that this may be displaceable by endogenous 5-HT and therefore provide an index of 5-HT release. [¹⁸F]Altanserin PET has also been used to quantify 5-HT release (Quednow et al, 2012). A potential confound for the development of 5-HT_{2A} receptor PET ligands is the reported high levels of 5-HT_{2A} receptors in the intracellular compartment (see above). If the significant levels of PET binding is intracellular, then it is less likely to be in a position to be displaced by endogenous 5-HT. However, collectively these imaging studies confirm the cross-species localisation of 5-HT_{2A} receptor but more importantly have opened the way for investigations of 5-HT_{2A} receptors in disease states.

VII. D. Post-translational modifications and impact

N-Glycosylation is known to regulate the intracellular sorting, surface expression, ligand binding, and signal transduction of GPCRs (Rads et al., 1990; Couvineau et al., 1996; Michineau et al., 2004; Transky et al., 2007). The extracellular *N*-terminus of the 5-HT_{2A} receptor contains 5 potential *N*-glycosylation sites; glycosylation is apparently required for the 5-HT_{2A} receptor to be targeted to the cell surface (Maginnis et al., 2010). Multiple proteins have been shown to interact with the 5-HT_{2A} receptor (Table 13; see also Section XVII).

VII. E. Pharmacology

The three members of the 5-HT₂ receptor family share significant sequence homology (Figure 10). Depending upon the species examined, the seven transmembrane domains of 5-HT_{2A} and 5-HT_{2C} receptors display 79–80% amino acid sequence conservation. Because of the high degree of structural homology, not surprisingly 5-HT_{2A} and 5-HT_{2C} receptor binding affinities are highly correlated (Glennon et al., 1992a,b, 1994; Nelson et al., 1999). It is now recognized that most of the antagonists that have traditionally been used to block 5-HT_{2A} receptors, including *N*-alkylpiperidines (e.g. ketanserin, ritanserin, pirenperone, altanserin), ergolines (e.g. methysergide, metergoline, LY53857), and tricyclic benzocycloheptenes (e.g. cyproheptadine, pizotifen), are also active at 5-HT_{2C} receptor (Newton et al., 1996; Hoyer, 1988*a,b*). For example, altanserin is only 20-fold selective for 5-HT_{2A} vs. 5-HT_{2C} receptor sites (Table 14). Ketanserin has been used extensively for reported pharmacological definition of 5-HT_{2A} receptor responses and does show some selectivity for 5-HT_{2A} receptor ($pK_i = 8.7$) compared with 5-HT_{2B} ($pK_i = 6.4$) and 5-HT_{2C} ($pK_i = 6.8$) receptors (Wainscott et al., 1996). However, ketanserin also has moderate affinity for adrenergic (α_1) and histaminergic (H₁) receptors, as well as 5-HT_{1D} receptors and the vesicular monoamine transporter (Erickson et al., 1996; Leysen et al., 1996; Bucholtz et al., 1999; Yoshio et al., 2001), which can complicate interpretation of arising data. Ritanserin is even less selective for 5-HT_{2A} versus 5-HT_{2C} receptors and also interacts with 5-HT_{1D}, 5-HT₆, 5-HT₇, D₂, D₃, D₄, H₁ and α_1 sites (Bard et al., 1993; Monsma et al., 1993; Shen et al., 1993; Leysen et al., 1996; Seeman and Tallerico, 1998; Yoshio et al., 2001). The butyrophenone neuroleptic spiperone displays 500-2000-fold selectivity for 5-HT_{2A} versus 5-HT_{2C} and has often been used to discriminate those receptors, but it binds to numerous other receptors, including dopaminergic D₂, D₃, and D₄, adrenergic α_1 and α_2 , and 5-HT_{1A} and 5-HT₇ receptors (Ruat et al., 1993; Tang et al., 1994; Metwally et al., 1998; Corradetti et al., 2005). The spiperone derivative AMI-193 (8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is twice as selective as spiperone for 5-HT_{2A} versus 5-HT_{2C}, but retains nanomolar affinity for D₂ and 5-HT_{1A} (Ismail et al., 1993). Atypical antipsychotics such as risperidone, olanzapine and clozapine block 5-HT_{2A} receptors with high affinity but generally have limited selectivity versus 5-HT_{2C} and dopamine receptors. By contrast, haloperidol and other typical antipsychotics have higher affinity for dopamine D₂ receptors than for 5-HT_{2A} receptors.

The 4-carbinolpiperidines volinaserin (MDL 100,907, M100907) and glemaserin (MDL 11,939) were the first truly selective 5-HT_{2A} receptor antagonists. Volinaserin has subnanomolar affinity for 5-HT_{2A} and 50-100-fold lower affinity for 5-HT_{2C} and α_1 receptors, with negligible affinity for other investigated sites (Palfreyman et al., 1993; Kehne et al., 1996). In contrast to most 5-HT_{2A} receptor antagonists, the selectivity of M100907 for 5-HT_{2A} versus 5-HT_{2C} receptors has been verified in mice (Canal et al., 2013). Compared with volinaserin, glemaserin displays even greater selectivity for 5-HT_{2A} receptor ($K_i = 2.893$ nM) versus 5-HT_{2B} ($K_i = 1419$ nM), 5-HT_{2C} ($K_i = 853.6$ nM), and α_1 ($K_i = 588$ nM) receptor sites (Dudley et al., 1988; Pehek et al., 2006). Like most drugs that block 5-HT_{2A} receptor responses, volinaserin and glemaserin were initially thought to be neutral antagonists but are now known to act as inverse agonists (Weiner et al., 2001; Aloyo et al., 2009). Although it was previously difficult to conclusively discriminate responses mediated by individual 5-HT₂ receptor subtypes *in vitro* and *in vivo*, volinaserin or glemaserin at appropriate concentrations in combination with selective 5-HT_{2B} and 5-HT_{2C} receptor antagonists such as RS-127,445 and SB-242,084, respectively, allow such pharmacological investigations.

In contrast to initial reports, it is now recognized that the 5-HT_{2A} receptor has high affinity for 5-HT. For example, 5-HT competes for the agonist radioligand [³H]DOB with a K_i of 6.13 nM (Titeler et al., 1985), and [³H]5-HT reportedly radiolabels the 5-HT_{2A} receptor with $K_d = 1.3$ nM (Sleight et al., 1996). In contrast, competition binding experiments with antagonist radioligands tend to underestimate the affinity of 5-HT_{2A} receptor agonists; 5-HT_{2A} receptors exist in low-affinity and high-affinity agonist binding conformations depending on whether they are coupled to G proteins, and only a small fraction of 5-HT_{2A} receptors are in the G protein-coupled, agonist high-affinity conformation at any given time. 5-HT_{2A} receptor antagonists bind to both conformations with equal affinity (Lyon et al. 1987; Glennon et al. 1988). Therefore, the apparent affinity of 5-HT_{2A} receptor agonists varies depending on the intrinsic activity of the radioligand used to label the receptor, with agonists displaying 10–100-fold higher affinity for agonist-labeled receptors vs. antagonist-labeled receptors (Titeler et al. 1987; Glennon et al. 1994; Sleight et al., 1996).

Numerous 5-HT_{2A} receptor agonists are available (Table 15). Tryptamines such as α -methyl-5-HT (α -Me-5-HT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) are widely used as 5-HT_{2A} receptor agonists, but they tend to activate 5-HT receptors non-selectively and can inhibit the 5-HT transporter at μ M concentrations (Ismail et al., 1990; Nagai et al., 2007; Blough et al., 2014). 2,5-Dimethoxy-4-iodoamphetamine (DOI) and its structural analogues DOM, DOB, and TCB-2 have high affinity and selectivity for 5-HT₂ receptors, but do not discriminate between the three 5-HT₂ receptor subtypes. In contrast to most phenylalkylamines, which are nonselective for 5-HT_{2A} versus 5-HT_{2C} receptors, 25CN-NBOH (*N*-(2-hydroxybenzyl)-2,5-dimethoxy-4-cyanophenethylamine) is reportedly 100-fold selective for 5-HT_{2A} ($K_i = 1.3$ nM) vs 5-HT_{2C} receptors ($K_i = 132$ nM) (Hansen et al., 2014). The conformationally restricted phenethylamine 2*S*,6*S*-DMBMPP ((+)-(2*S*,6*S*)-*trans*-2-(2,5-dimethoxy-4-bromobenzyl)-6-(2-methoxyphenyl)piperidine) displays even greater selectivity for 5-HT_{2A} receptors, binding to 5-HT_{2C} receptors with 124-fold lower affinity (Juncosa et al., 2013). Racemic *trans*-DMBMPP is less selective but still shows 98-fold higher affinity for 5-HT_{2A} over 5-HT_{2C} receptors.

VII. F. Function

VII. F. 1. Signalling

The G α_q -PLC β cascade is the canonical signaling pathway coupled to 5-HT_{2A} receptor activation (Conn and Sanders-Bush, 1984; Kendall and Nahorski, 1985), resulting in the hydrolysis of membrane phospholipids to inositol-1,4,5-triphosphate (IP₃) and diacylglycerol (DAG). In turn, IP₃ elevates the concentration of Ca²⁺ in the cytosol by releasing it from the endoplasmic reticulum, whereas DAG activates protein kinase C (PKC) and facilitates its translocation from the cytosol to the membrane. Both PKC and Ca²⁺ are known to have widespread and far-reaching influences on intracellular signaling: PKC phosphorylates various target proteins while Ca²⁺ is known to modulate the activity of enzymes (e.g., Ca²⁺/calmodulin-dependent kinases) and ion channels.

In addition to the classical signaling mediated by the PLC-IP₃ cascade, the 5-HT_{2A} receptor can activate a variety of other effector mechanisms. For example, the 5-HT_{2A} receptor has been shown to stimulate phospholipase A₂ (PLA₂), resulting in increased production of the second messenger arachidonic acid (AA) (Felder et al., 1990; Berg et al., 1996). The 5-HT_{2A} receptor also increases release of the endocannabinoid 2-arachidolylglycerol

(2-AG) (Parrish and Nichols, 2006). The 5-HT_{2A} receptor can also couple to mitogen activated protein kinases (MAPK) such as extracellular-regulated kinase (ERK)1/2 (Hershenson et al., 1995; Watts, 1996; Greene et al., 2000). Other signaling molecules that have been linked to 5-HT_{2A} activation in native tissues and in cell lines expressing the receptor include Akt (Johnson-Faley et al., 2005), phospholipase D1 (PLD) (Barclay et al., 2011), JAK/STAT (Guillet-Deniau et al., 1997; Banes et al., 2005), nitric oxide synthase (Miller et al., 1997), CREB (Chalecka-Franaszek et al., 1999), calmodulin (Turner and Raymond, 2005), and glycogen synthase kinase-3 β (GSK3 β) (Li et al., 2004).

Some of the aforementioned signaling pathways are coupled to the 5-HT_{2A} receptor in a G α_q -independent manner. The ability of the 5-HT_{2A} receptor to stimulate PLD is mediated by the monomeric G protein ADP-ribosylation factor-1 (ARF1), which interacts directly with the receptor (Barclay et al., 2011). The coupling of the 5-HT_{2A} receptor to PLA₂ in NIH3T3 cells appears to be mediated by two independent signaling cascades. In the first case, activation of *Srv* by G $\alpha_{i/o}$ -associated G $\beta\gamma$ subunits results the formation of a ternary complex between SHC/GRB/SOS, which in turn activates the Ras–Raf–MEK1/2–ERK1/2 cascade. In the second, activation of RhoA by G $\alpha_{12/13}$ stimulates p38 MAP kinase (Kurrasch-Orbaugh et al., 2003b). Reports also indicate PLC and PKC are not involved in the ERK activation produced by 5-HT_{2A} receptor agonists in PC12 and vascular smooth muscle cells (Florian and Watts, 1998; Banes et al., 1999; Quinn et al., 2002). Nevertheless, in certain cell types, the coupling of ERK1/2 to 5-HT_{2A} receptors *is* dependent on G α_q . Activation of the Ras–Raf–MEK–ERK1/2 cascade by 5-HT_{2A} receptors in tracheal smooth muscle cells and mesangial cells is downstream from G α_q and dependent on PKC (Hershenson et al., 1995; Watts, 1996; Greene et al., 2000). The coupling of the 5-HT_{2A} receptor to MAPK may actually be ligand-specific. In mouse embryonic fibroblasts transfected with the 5-HT_{2A} receptor, the stimulation of ERK1,2 by DOI is dependent on PLC whereas the stimulation by 5-HT is PLC-independent and requires β -arrestin2 (Schmidt et al., 2008).

The 5-HT_{2A} receptor was one of the first receptors shown to display functional selectivity. According to Berg et al. (1998), 5-HT_{2A} receptors activate PLC and PLA₂ independently in CHO cells, and the relative efficacies of agonists differ depending on which response is measured. Subsequent studies confirmed the PLC–IP₃ and PLA₂–AA pathways coupled to 5-HT_{2A} receptor in NIH3T3 cells have different receptor reserves, indicating they

are activated independently (Kurrasch-Orbaugh et al., 2003a). It has been proposed that 5-HT_{2A} receptor functional selectivity (biased signaling) may explain why certain 5-HT_{2A} receptor agonists produce hallucinogenic effects whereas other agonists such as lisuride are non-hallucinogenic (Gonzales-Maseo et al., 2007). Specifically, although both hallucinogenic and non-hallucinogenic 5-HT_{2A} receptor agonists increase the expression of the immediate-early gene (IEG) *c-fos* by activating G α_q , only agonists with hallucinogenic effects increase the cortical expression of the IEG *egr-2* by activating G $\alpha_{i/o}$ and *Src*. Another group has reported that the activation of the 5-HT_{2A} receptor by 5-HT and hallucinogens results in vastly different downstream signaling responses (Schmid and Bohn, 2010). The behavioral response to 5-HT in mice requires Akt phosphorylation and formation of a complex between Akt, *Src*, and β -arrestin2, whereas the response to hallucinogens is independent of Akt and β -arrestin2.

It is now apparent that many 5-HT_{2A} receptor antagonists act in a functionally-selective manner. Like most GPCRs, the 5-HT_{2A} receptor is downregulated by exposure to agonists. Somewhat paradoxically, however, prolonged exposure to certain 5-HT_{2A} receptor antagonists also induces 5-HT_{2A} receptor downregulation (Leysen et al., 1986; Eison et al., 1989; Pranzatelli, 1991; Moreno et al., 2013). The anomalous downregulation of 5-HT_{2A} receptors induced by antagonists is not a consequence of altered gene transcription (Roth and Ciaranello, 1991) but is likely caused by redistribution of the receptor from the cell surface to intracellular compartments (Willins et al., 1998, 1999; Bhatnagar et al., 2001). Interestingly, although the 5-HT_{2A} receptor antagonists ketanserin, clozapine, and olanzapine reduce 5-HT_{2A} immunoreactivity and [³H]ketanserin binding in mouse frontal cortex, M100907, MDL 11,939, and altanserin do not alter receptor expression (Yadav et al., 2011). These findings indicate that certain 5-HT_{2A} receptor antagonists have agonist-like effects on the signaling pathways responsible for promoting receptor internalization. For example, although ketanserin and risperidone act as inverse agonists on the 5-HT_{2A}–PLC and 5-HT_{2A}–ERK pathways, they also act as 5-HT_{2A} receptor agonists by stimulating β -arrestin translocation (Clark et al., 2013). Nevertheless, it appears that 5-HT_{2A} receptor antagonists can promote 5-HT_{2A} receptor internalization through multiple mechanisms because clozapine does not recruit β -arrestin (Schmid et al., 2014). Clozapine does act in a functionally-selective manner—it has been shown to induce Akt phosphorylation in cortical neuronal cultures via the 5-HT_{2A} receptor (Schmid et al., 2014); but the mechanism by which clozapine promotes receptor down-regulation remains to be determined.

Adding to the complexity of 5-HT_{2A} receptor signaling is the discovery that it can oligomerize with other GPCRs, potentially allowing the 5-HT_{2A} receptor to couple to an even wider range of effector mechanisms. Gonzalez-Maseo and colleagues have reported that 5-HT_{2A} and mGlu₂ receptors form heterocomplexes, providing a mechanism whereby 5-HT_{2A} receptors can modulate G $\alpha_{i/o}$ signaling (Gonzalez-Maseo et al., 2008). Heteromers between 5-HT_{2A} and D₂ receptors (Borrito-Escuela et al., 2010; Lukasiewicz et al., 2010) and 5-HT_{2A} and CB₁ receptors (Vinals et al., 2015) have also been detected in transfected cells but the functional significance of these interactions and the extent to which they occur in native tissues is unclear.

VII. F. 2. Action in cells, tissues and *in vivo*

5-HT_{2A} receptor activation produces a variety of physiological effects in peripheral tissues and in the CNS. There is evidence for 5-HT_{2A} receptor involvement in the proliferation, differentiation, and contraction of vascular and extravascular smooth muscle (Maayani et al., 1984; Watts and Cohen, 1992; Fanburg and Lee, 1997; Shum et al., 2002; Itoh and Kajikuri, 2011), as well as increased contractility of cardiac muscle, where it is expressed in neonatal and reexpressed in failing and hypertrophic heart (Qvigstad et al., 2005c; Brattelid et al., 2007a,b; Birkeland et al., 2007b; Levy et al., 2008; Brattelid et al., 2012). Similarly, the 5-HT_{2A} receptor increases the proliferation and synthesis of extracellular matrix proteins by glomerular mesangial cells (Kasho et al., 1998; Gööz et al., 2006). 5-HT_{2A} receptor antagonists inhibit the platelet aggregation and shape change induced by 5-HT, DOB, and DOI (de Clerck et al., 1982, 1984; Seggel et al., 1987). The neuroendocrine effects of DOI in rats, including increases in the release of ACTH, corticosterone, oxytocin, renin, and prolactin, appear to be mediated by 5-HT_{2A} (Calogero et al., 1990; van der Kar et al., 2001; Zhang et al., 2002). 5-HT_{2A} receptor activation produces sympathoexcitatory effects and increases arterial pressure through a combination of central and peripheral effects (Tadepelli et al., 1975; McCall et al., 1987; Alper, 1990; Dedeoglu and Fisher, 1991; Chaouche-Teyara et al., 1994).

5-HT_{2A} receptor activation produces long-lasting increases in the excitability and firing rate of glutamatergic and GABAergic neurons, resulting in increased excitatory and inhibitory network activity (McCormick and Wang, 1991; Sheldon and Aghajanian, 1991; Cumming-Hood et al., 1993; Pessia et al., 1994; Marek and Aghajanian, 1996; Aghajanian and Marek, 1997; Shen and Andrade, 1998; Zhou and Hablitz, 1999; Lambe and Aghajanian, 2006a; Beique et al., 2007; Lambe and Aghajanian, 2007; Benekareddy et al., 2010; Gullede and Avesar, 2012; but see also Carr et al., 2002; Tian et

al., 2016). These electrophysiological effects are absent in Htr2A knockout mice and are restored upon conditional cortical rescue of 5-HT_{2A} receptors (Weisstaub et al., 2006). Reductions in resting K⁺-conductances are thought to contribute to many of the excitatory effects of 5-HT_{2A} receptor activation. For example, 5-HT_{2A} receptor activation induces membrane depolarization, reduces afterhyperpolarization, and evokes a slow afterdepolarization in layer V pyramidal neurons in the prefrontal cortex (PFC), effects thought to be mediated by inhibition of the Ca²⁺-activated K⁺-current $I_{K(Ca)}$ and activation of the Ca²⁺-dependent non-selective cation current I_{CAN} (Araneda and Andrade, 1991; Tanaka and North, 1993; Villalobos et al., 2005, 2011; Zhang and Arsenault, 2005). The ability of 5-HT_{2A} receptor activation to enhance motoneuron excitability is mediated by inhibition of a leak K⁺-current ($I_{K(leak)}$) and enhancement of the hyperpolarizing-activated nonselective cation current I_h (Garratt et al., 1993; Hsiao et al., 1997; Larkman and Kelly, 1998; Xu et al., 2009). TASK-1 and TASK-3 two-pore domain K⁺-channels are believed to be responsible for $I_{K(leak)}$ in motoneurons (Talley et al., 2000; Larkman and Perkins, 2005). Likewise, the 5-HT_{2A} receptor-mediated depolarization produced by 5-HT in entorhinal cortex interneurons occurs as a consequence of TASK-3 channel inhibition (Deng and Lei, 2008). 5-HT_{2A} has been shown to depolarize nucleus accumbens medium spiny neurons by inhibiting an inwardly-rectifying K⁺-current (North and Uchimura, 1989). There is also evidence that 5-HT_{2A} receptor-induced arterial constriction is mediated by inhibition of Kv channels (Cogolludo et al., 2006; Sung et al., 2013). Other ion channels known to couple to the 5-HT_{2A} receptor include rapidly inactivating and persistent voltage-dependent Na⁺-channels (Carr et al., 2002), CaV 1.2 L-type Ca²⁺-channels (Day et al., 2002), Kv1.2 K⁺-channels (Lambe and Aghajanian, 2001), and voltage-independent Ca²⁺-channels (Hagberg et al., 1998).

VII. G. Clinical relevance

5-HT_{2A} receptors are clinically relevant to numerous CNS disorders, ranging from mood disorder and schizophrenia to drug dependence. The links between the 5-HT_{2A} receptor and the causes of such CNS disorders are not well understood. Early life stress has been shown trigger strong upregulation of the functional effects of 5-HT_{2A} receptors on electrophysiology, signalling, and gene expression in prefrontal cortex (Benekareddy et al., 2010). Emerging findings regarding 5-HT_{2A} gene polymorphisms and epigenetic regulation of 5-HT_{2A} receptor expression are also of great interest. The association between the 5-HT_{2A} receptor and successful treatment of certain CNS disorders is strong, and there is an ongoing active research

interest into the therapeutic potential of 5-HT_{2A} receptor ligands. The majority of these studies have had a particular focus on schizophrenia and depression, and the actions of antipsychotic and antidepressant drugs.

In schizophrenia there are reports of reduced 5-HT_{2A} receptor binding in frontal cortex of post-mortem brains, and there is supporting evidence from PET imaging studies for similar changes as recently reviewed (Selvaraj et al, 2014). However, given that not all the PET studies used 5-HT_{2A} receptor selective radiotracers and that there are inconsistencies in the post-mortem studies, the extent to which impaired cortical 5-HT_{2A} receptor function contributes to the symptoms of schizophrenia is unclear.

The psychotomimetic effects of hallucinogens such as LSD and psilocybin are undoubtedly linked to activation of 5-HT_{2A} receptors (Halberstadt, 2015). Furthermore, commonly used second generation antipsychotics such as clozapine, risperidone, and sertindole are potent 5-HT_{2A} receptor antagonists in addition to having affinity at other 5-HT receptor subtypes and receptors for other neurotransmitters (Meltzer, 2012). 5-HT_{2A} receptor blockade has been linked to the antipsychotic efficacy of second-generation antipsychotics and also a reduced side effect profile (Meltzer and Massey, 2011). This provided support for the idea that selective 5-HT_{2A} receptor antagonists might be useful as a monotherapy for some psychoses and as antipsychotic augmenting agents, although schizophrenia trials with the selective 5-HT_{2A} receptor antagonist MDL 100,907 were disappointing. Nevertheless, the subsequent discovery that 5-HT_{2A} receptor inverse agonists have antipsychotic actions in preclinical models (Weiner et al, 2001) suggests an alternative way to treat psychosis. This thinking advanced to the clinical development of pimavanserin (Vanover et al, 2006) for the treatment of psychosis in Parkinson's disease patients (Meltzer and Roth, 2013). In 2016, pimavanserin was approved by the US FDA as a treatment for hallucinations and delusions associated with Parkinson's disease. Although the degree of inverse agonism required for an antipsychotic effect is uncertain, 5-HT_{2A} receptor inverse agonists are currently considered as a potential new generation of antipsychotic agents.

In post-mortem studies of suicide victims there is evidence of an upregulation in 5-HT_{2A} receptors in cortex (for review see Meyer, 2013). This finding parallels results from PET imaging studies that report increased 5-HT_{2A} receptor binding in depressed patients particularly in association with

severe pessimism (Meyer et al. 2003; Bhagwagar et al. 2006). The latter observations fit with findings in healthy subjects, that individuals with high scores for pessimistic personality had higher cortical 5-HT_{2A} receptor binding (Frokjaer et al. 2008). It has been hypothesized that the increase in cortical 5-HT_{2A} receptor binding in depression is associated with severe pessimism and arises as an adaptive response to chronic 5-HT deficiency (Meyer, 2013).

The above findings in depressed patients link to evidence that certain antidepressants, and particularly tricyclics, have high affinity for 5-HT_{2A} receptors (eg. Millan, 2006). Whilst tricyclic antidepressants have high affinity for multiple receptors, it can be argued that evidence of the superior therapeutic efficacy of tricyclic antidepressant drugs over other antidepressant drug classes particularly in the treatment of severe melancholic depression, is linked in part to their ability to block 5-HT_{2A} receptors. Thus, 5-HT_{2A} receptor antagonists augment the effect of 5-HT uptake inhibitors in preclinical models (Marek et al., 2005; Boothman et al, 2006), and drugs with 5-HT_{2A} receptor antagonist properties are advocated as an add-on to antidepressant therapy in treatment resistant cases (Marek et al, 2003); all a possible link to evidence of an inhibitory 5-HT_{2A} receptor-mediated feedback on 5-HT neurons (Sharp et al, 2007).

Aside from schizophrenia and depression, 5-HT_{2A} receptors are relevant to the pathophysiology of many other CNS disorders. Currently there is large and ongoing research effort to understand the importance of polymorphic variation in the 5-HT_{2A} receptor gene to a large variety of psychiatric disorders (eg. Smith et al, 2013; Paquette and Marsit, 2014). Despite the many reports of associations between 5-HT_{2A} gene polymorphisms and neuropsychiatric disorders, some of which are subject to careful meta-analysis, effect sizes are at best modest and the role of genetic 5-HT_{2A} variability in mental health continues to be uncertain. This work is expanding to incorporate recent findings of epigenetic variation of the 5-HT_{2A} receptor gene, and specifically methylation sites near the gene promoter region (for review see Paquette and Marsit, 2014).

Ligands for 5-HT_{2A} receptors have a current untapped potential for the management of cognitive dysfunction. There are well established links between the receptor and the formation of different memory types, including recognition (Morici et al., 2015) and fear memories (Bombardi and

Giovanni, 2013; Zhang and Stackman, 2015). The latter connects with the considerations of ecstasy and other similar psychotomimetics for the management of PTSD (Smith et al, 2014; Sessa and Nutt, 2015). There are also very interesting links between the 5-HT_{2A} receptor and impulse control; in animal models 5-HT_{2A} receptor antagonists consistently reduce measures of impulsivity (Higgins et al., 2003; Winstanley et al, 2004; 2011; Fletcher et al., 2007) and attenuate abuse-related effects of cocaine (Howell and Cunningham, 2014). This raises the possibility that 5-HT_{2A} antagonists/inverse agonists may have utility in the control of addictions, and disorders of impulse control more generally.

5-HT_{2A} receptors are required for entry of JC polyomavirus (JCV) into cells (Elphick et al., 2004). JCV causes progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease. JCV attaches to the sialic acid receptor motif α 2,6-linked lactoseries tetrasaccharide c (LSTc) on the cell surface and then undergoes endocytosis with the 5-HT_{2A} receptor (Assetta et al., 2013). 5-HT_{2A} antagonists have been found to inhibit infection of cell by JCV (O'Hara and Atwood, 2008). Furthermore, treatment with mirtazepine, an antidepressant that acts as a 5-HT_{2A} receptor antagonist, has proven beneficial in patients infected with JCV (Verma et al., 2007; O'Hara and Atwood, 2008; Cettomai and McArthur, 2009; Park et al., 2011).

5-HT_{2A} receptor agonists have ocular hypotensive effects. *R*-(-)-DOI, 5-MeO-DMT, and α -Me-5-HT have been shown to lower intraocular pressure in a cynomolgus monkey model of ocular hypertension (May et al., 2003). 5-HT_{2A} receptors have been identified in tissues involved in the regulation of aqueous humor dynamics, including ciliary muscle (Lograno et al., 2003; Sharif et al., 2006a), ciliary epithelium (Inoue-Matsuhisa et al., 2003), and trabecular meshwork (Sharif and Senchyna, 2006; Sharif et al., 2006b). Studies have not completely elucidated the mechanism for the reduction of intraocular pressure by 5-HT_{2A} receptor agonists, but increased uveoscleral outflow may play a role (Gabelt et al., 2005). This effect led to the evaluation of 5-HT_{2A} receptor agonists as potential treatments for glaucoma. In order to reduce the potential for psychotropic side-effects, much of the work to develop 5-HT_{2A} receptor agonists as ocular hypotensive agents has focused on compounds with limited blood brain barrier (BBB) permeability. Several 5-HT_{2A} receptor agonists with limited BBB permeability have been shown to lower intraocular pressure following topical ocular administration to monkeys, including AL-34662 (1-[(2*S*)-2-aminopropyl]-1*H*-indazol-6-ol) (May et al., 2006; Sharif et al., 2007), (8*R*)-1-[(2*S*)-2-

aminopropyl]-8,9-dihydro-7*H*-pyrano[2,3-*g*]indazol-8-ol (May et al., 2015); phenylisopropylamines incorporating α -hydroxy or α -methoxy substituents (Glennon et al., 2004), and benzodifuran derivatives (Feng et al., 2007).

Ketanserin can reportedly lower interocular pressure in patients with glaucoma (Costagliola et al., 1991, 1993; Takenaka et al., 1995; Mastropasqua et al., 1997). However, the ocular hypotensive effect of ketanserin is attenuated in unilaterally sympathectomized rabbits and therefore is thought to be mediated by blockade of α_1 -adrenoceptors (Chang et al., 1985).

VIII. 5-HT_{2B} receptor

VIII. A. Introduction

5-HT-induced contractions of rat stomach fundus strips were used as a sensitive bioassay for 5-HT, long before more specific analytical assays became available (Vane, 1957), however the 5-HT receptor was only defined more than three decades later as the 5-HT_{2B} receptor. Early pharmacological studies suggested a strong similarity to the 5-HT_{2C} receptor, in line with the high potency of 5-HT and blockade by 5-HT₂ receptors antagonists. However, 5-HT_{2C} receptor mRNA was absent and molecular cloning identified the new receptor; first in rat and mouse (Foguet et al., 1992a; Foguet et al., 1992b; Kursar et al., 1992; Loric et al., 1992; Wainscott et al., 1993) and then in humans (Choi et al., 1994; Kursar et al., 1994; Schmuck et al., 1994; Wainscott et al., 1996). Initially given the tissue associated primarily with the functional receptor, the receptor was named the 5-HT_{2F} receptor, but it was reclassified subsequently to the 5-HT_{2B} receptor to better fit 5-HT receptor nomenclature. The pharmacological characterization of this receptor in various species confirmed its close relationship to both 5-HT_{2C} and 5-HT_{2A} receptors, as expected from their closely related structural and transductional features. The physiological and pathophysiological functions of the 5-HT_{2B} receptor both in the peripheral and central nervous systems are rather unique.

VIII. B. Expression profile

VIII. B. 1. Peripheral expression

5-HT_{2B} receptor mRNA and/or protein are detected in the stomach fundus, intestine, liver, kidney, pancreas, spleen, lung and heart in rats, mice and humans (Choi et al., 1994; Choi and Maroteaux, 1996; Kursar et al., 1994; Kursar et al., 1992). Functionally active 5-HT_{2B} receptors are present in human uterine smooth muscle (Kelly and Sharif, 2006). The 5-HT_{2B} receptor is also expressed in the vasculature, in various smooth muscle cells (Ullmer et al., 1995), endothelial cells of pig pulmonary arteries (Glusa and Pertz, 2000), human meningeal blood vessels (Schmuck et al., 1996), and rat jugular vein (Ellis et al., 1995). The 5-HT_{2B} receptor is expressed in rat spleen, thymus, peripheral blood lymphocytes (Stefulj et al., 2000), in rat

osteocytes, osteoblasts and periosteal fibroblasts containing osteoblast precursor cells (Bliziotis et al., 2001; Westbroek et al., 2001). The 5-HT_{2B} receptor gene is expressed in human and rodent anagen, but not telogen skin, in various melanomas and Mel A melanocytes (Slominski et al., 2004; Slominski et al., 2003). Finally, the 5-HT_{2B} receptor is expressed in c-kit⁺ bone-marrow cells (Launay et al., 2012). All together, the very heterogeneous expression of the 5-HT_{2B} receptor suggests very diverse physiological and pathophysiological roles.

VIII. B. 2. Central expression

The 5-HT_{2B} receptor is expressed in human cerebral cortex, cerebellar nuclei and their projection areas, lateral septum, dorsal hypothalamus and medial amygdala (Choi et al., 1994; Choi and Maroteaux, 1996; Kursar et al., 1994; Kursar et al., 1992). The presence of 5-HT_{2B} receptor mRNA was reported in several mammalian brain nuclei including the dorsal raphe (Bonaventure et al., 2002). 5-HT_{2B} receptor expression (determined by qPCR) was confirmed in the human frontal, temporal, parietal, and occipital lobes, the olfactory region, cerebellum, diencephalon, hippocampus, thalamus, pituitary gland, pons, medulla oblongata and nucleus accumbens (Bevilacqua et al., 2010). 5-HT_{2B} receptor mRNA was reported in rat cultured astrocytes (Osredkar and Krzan, 2009; Sanden et al., 2000). Microglial expression of 5-HT_{2B} receptors was documented in primary cultured and acutely isolated adult microglia, using two photon microscopy on brain slices (Kolodziejczak et al., 2015) and patch-clamp studies in cultured microglia (Krabbe et al., 2012), suggesting 5-HT_{2B} receptor may mediate modulation of microglial functions such as phagocytosis and migration, synaptogenesis and neuronal death.

The 5-HT_{2B} receptor modulates the release of rat growth hormone (GH) in the pituitary (Papageorgiou and Deneff, 2007). The 5-HT_{2B} receptor is expressed in the spinal cord (Helton et al., 1994; Holohean and Hackman, 2004), the rat organ of Corti lateral wall and spiral ganglion subfractions (Oh et al., 1999), and is upregulated in ageing mice cochlea (Tadros et al., 2007). 5-HT_{2B} receptor mRNA is expressed predominantly in the human retina, ciliary body, ciliary epithelium, choroid, conjunctiva, and iris. 5-HT_{2B} receptor mRNA was also documented in optic nerve tissue of human donors trabecular meshwork cells (Sharif and Senchyna, 2006).

VIII. C. Post-translational modifications and impact

VIII. C. 1. Gene structure

The 5-HT_{2B} receptor gene is composed of four Exons, including one 5' non-coding exon and three coding exons in all vertebrates that have been sequenced.

VIII. C. 2. Gene regulation

The transcriptional regulation of the 5-HT_{2B} receptor gene is not well understood. In breast tumors, the c-Myc transformation induces an increased 5-HT_{2B} receptor expression (Pai et al., 2009). In human umbilical endothelial cells (HUVEC), Wnt2 down-stream targets the 5-HT_{2B} receptor gene (Klein et al., 2009). The 5-HT_{2B} receptor expression is down regulated *via* NF- κ B (RelAp65-p52), in C-reactive protein-stimulated pulmonary arterial endothelial cells (Wynants et al., 2013). In pulmonary artery smooth muscle cells, 5-HT induces 5-HT_{2B} receptor mRNA expression, which is inhibited by peroxisome proliferator activated receptor (PPAR) γ activation and suggests the suppression of AP-1 activity (Liu et al., 2012; Maroteaux, 2013). The presence of retinoic acid response elements in the 5-HT_{2B} receptor promoter, suggests a negative regulatory relationship between retinoic acid and 5-HT signaling at sites of epithelio-mesenchymal interaction (Bhasin et al., 2004).

VIII. C. 3. Receptor isoforms

Only a few studies have investigated putative splice variants in the 5-HT_{2B} receptor. In puffer fish 5-HT_{2B} receptor splicing variants have been identified (De Lucchini et al., 2001): Splice variant 1 contains a 136 bp deletion that eliminates a portion of exon 2 by alternative splice sites located within trans-membrane regions I and II, which results in a premature stop codon to produce a very short truncated 31 aa protein. Splice variant 2 contains a 201 bp deletion due to an exon-skipping mechanism that eliminates exon 3 (which is also found in human and mice). The resulting RNA retains the same open reading frame. Splice variant 3 contains a 19 bp deletion probably by an alternative 5' splice site upstream of the canonical 5' splice site of intron C; this leads to a frame shift and a premature termination codon, which was also found in human and mice. This short variant results in a putative 177 amino acids protein, with 28 specific residues at the carboxyl terminus. The functions of these splice variant remain to be

defined. Finally, an exon-skipping mechanism that eliminates exon 3 was found in fish, humans and rodents; this leads to a truncated receptor containing only the first transmembrane domain.

VIII. D. Protein structure

The 5-HT_{2B} receptor displays the characteristic structure of a GPCR receptor, with a relatively long N-terminus of about 55 amino-acids. The human 5-HT_{2B} receptor has 481 aa (479 aa in rat or mouse), with 79% and 82% homology for human vs. rat and mouse respectively. The 5-HT_{2B} receptor N-terminus may act as a negative modulator, affecting both constitutive and agonist-stimulated activity (Belmer et al., 2014).

The ergotamine-bound 5-HT_{2B} receptor crystal structure exhibits some conformational features of both the active and inactive states: an active-like state in the helix VII conformation, but only partial changes in helix VI, which mirror the strong β -arrestin bias of ergotamine seen in functional assays (Wacker et al., 2013; Wang et al., 2013). A structural explanation for the distinct conformational features and the biased pharmacology of ergotamine can be seen in the extracellular loop 2 (ECL2) junction with helix V, E212-R213-F214 forming an additional helical turn stabilized by a structured water molecule at the extracellular tip of helix V. The segment of ECL2 connecting helices III and V *via* the conserved disulfide bond is, therefore, shortened and creates a conformational constraint on the extracellular tip of helix V (Martí-Solano et al., 2014). However, this structured water molecule involved in ECL2 junction with helix V has been challenged since differential interactions of ergotamine with the top of helices V and VI could determine the rotational freedom of helix VI (Liu et al., 2013). For more discussion of the crystal structure see Section XVI.A.

VIII. E. Heteromeric receptor associations

In cardiac fibroblasts, angiotensin AT1 receptors and 5-HT_{2B} receptors, which share common signaling pathways, could exist in heterodimeric complexes as shown by co-immunolocalization and a pull-down assay (Jaffre et al., 2009), but experimental confirmation is lacking.

VIII. F. Pharmacology

VIII. F. 1. Agonists

Biased agonism is evident with a range of drugs that impact the 5-HT_{2B} receptor and the influence of this phenomenon on the pharmacological profile of agonists can be profound (see for example Huang et al., 2009). Hence when defining the action of agonists at the 5-HT_{2B} receptor – at least in terms of their potency and efficacy – the particular readout (e.g. [Ca²⁺]_i, arrestin, ERK, IP₃) and the nature of the receptor preparation needs to be taken into account. Against this background, the pharmacology of agonists will be described.

BW723C86: 1-methyl-2-[5-(2-thienylmethoxy)-1H-indole-3-yl] ethylamine hydrochloride, has 10- and 100-fold selectivity for the human 5-HT_{2B} receptor over the human 5-HT_{2C} and 5-HT_{2A} receptors respectively. (recommended use : ≤100 nM concentration or ≤3 mg/kg ip in rodents Cussac et al., 2008; Jerman et al., 2001; Knight et al., 2004; Porter et al., 1999). α-Methyl-5-HT is a full agonist with high potency for the 5-HT_{2B} receptor (pEC₅₀=8.4) and lower potency for both 5-HT_{2C} and 5-HT_{2A} receptors. 5-Methoxytryptamine is also 25- and 400-fold selective over the 5-HT_{2A} and 5-HT_{2C} receptors, respectively. Nor-dexfenfluramine (metabolite of dexfenfluramine), methylethylergonovine (metabolite of methysergide), and Ro 60-0175: 2(S)-1-(6-chloro-5-fluoro-1H-indol-1-yl)-2-propanamine fumarate are all somewhat preferential 5-HT_{2B} receptor agonists with about 10 fold selectivity over 5-HT_{2C} receptor.

The 5-HT_{2B} receptor displays high affinity to 5-HT (K_d ~10 nM) and many non-selective 5-HT₂ receptor active compounds, including some metabolites of therapeutics and drugs of abuse. Such agonists include MDA (3,4-methylene dioxyamphetamine-MDA, a metabolite of 3,4-methylenedioxy methamphetamine-MDMA) (Setola et al., 2003), MDMA ('ecstasy') itself, tryptamine, and lysergic acid diethylamide (LSD). 2,5-dimethoxy-4-iodoamphetamine (DOI) is a nearly full agonist at 5-HT_{2B} receptors but with similar affinity to 5-HT_{2A} and 5-HT_{2B} receptors (Cussac et al., 2008; Jerman et al., 2001; Knight et al., 2004; Porter et al., 1999).

Many substances known as "legal highs" display notable affinity for 5-HT_{2B} receptors, including 5-APB commonly 'marketed' as 'benzofury' (K_i = 14 nM) and 6-APB (K_i = 3.7 nM), and 5-iodo-aminoindane (K_i = 70 nM). 5-APB and 6-APB act as potent (i.e., nanomolar EC₅₀ values) full agonists at

5-HT_{2B} receptors (Iversen et al., 2013; Rickli et al., 2015). 5-APB, contracts the rat stomach fundus, and is antagonised by the 5-HT_{2B} receptor antagonist, RS127445 (Dawson et al., 2014). Other such drugs, show sub-micromolar affinities for the 5-HT_{2B} receptor (mephedrone, naphyrone, 1-naphyrone and methylenedioxy-aminotetralin). Indeed, there is a correlation in a series of phenyliso-propylamines between hallucinogenic activity and affinity for the 5-HT_{2B} receptor (Nelson et al., 1999), although 5-HT_{2A} receptor agonism is still also considered to play a major role in “psychedelics”, such as LSD or psilocibine. Activation of the 5-HT_{2B} receptor appears to play a key role in the behavioral stimulant and 5-HT releasing effects of MDMA (Doly et al., 2008) and in the reinforcing effects of MDMA in mice (Doly et al., 2009).

VIII. F. 2. Antagonists

The first highly 5-HT_{2B} selective antagonist is LY266097: 1-(2-chloro-3,4- dimethoxybenzyl)- 6-methyl- 1,2,3,4-tetrahydro- 9Hpyrido [3,4-b]indole hydrochloride with a pK_i of 9.7 for the human cloned 5-HT_{2B} receptor and a 100-fold greater selectivity over human 5-HT_{2C} and 5-HT_{2A} receptor binding sites (recommended use: 20 nM concentration *in vitro* or 0.5 mg/kg ip in rodents; Audia et al., 1996). SB204741: N-(1-methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl)urea is another selective 5-HT_{2B} receptor antagonist with approximately 100-fold selectivity over the 5-HT_{2C} and 5-HT_{2A} sites, but with rather low potency (K_i around 100 nM) (recommended use: 500 nM concentration *in vitro* or 10 mg/kg ip in rodents; Bonhaus et al., 1995). The tetrahydro-β-carboline, LY272015: 6-chloro-5-methyl -N-(5-quinolinyl) -2,3-dihydro -1H-indole-1-carboxamide is also a fairly selective and highly potent antagonist (recommended use: 50 nM concentration *in vitro* or 1.0 mg/kg ip in rodents; Cohen et al., 1996). RS127445: 2-amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine has sub-nanomolar affinity for the 5-HT_{2B} receptor (pK_i = 9.5) and 1,000 fold selectivity compared to numerous other receptors and ion channels and appears as the most selective, high affinity 5-HT_{2B} receptor antagonist suitable now (Bonhaus et al., 1999). Recommended use: 20 nM concentration or 0.25 mg/kg ip in rodents. The methoxythioxanthene BF-1 is a highly selective and potent 5-HT_{2B} receptor antagonist lacking high affinities for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, histamine H₁, dopamine D₁ and D₂ as well as muscarinic M₁ and M₂ receptors (Schmitz et al., 2015). S33526: 6-chloro-2,3,4,9-tetrahydro-1H-b-carbolin-1-yl)-phenyl-acetic acid ethyl ester, is a high affinity and relatively selective antagonist at 5-HT_{2B} receptors (Cussac et al., 2002). SB215505: 6-chloro-5-methyl-N-(5-quinolinyl)-2,3-dihydro-1H-indole-1-carboxamide behaves as

a high affinity and preferential inverse agonist at 5-HT_{2B} receptors. SB206553: 5-methyl-N-(3-pyridyl)-1,2,3,5-tetrahydrobenzo[1,2-b:4,5-b']dipyrrole-1-carboxamide is a mixed 5-HT_{2C}/5-HT_{2B} receptor inverse agonist with 50- to 100-fold lower affinity for the 5-HT_{2A} and other sites.

Nonselective 5-HT₂ receptor antagonists such as ritanserin and metergoline antagonize 5-HT_{2B} receptor-mediated effects. Furthermore, the α_2 adrenergic receptor antagonists yohimbine and rauwolscine are potent 5-HT_{2B} antagonists, with low affinity for the 5-HT_{2C} and 5-HT_{2A} receptors. Atypical antipsychotics have also fairly high affinity for 5-HT_{2B} receptors including clozapine, asenapine, or cariprazine (Kiss et al., 2010; Millan et al., 2003; Shahid et al., 2009; Wainscott et al., 1996). Aripiprazole (OPC-14597) is a novel atypical antipsychotic, with high antagonist affinity (EC₅₀ = 11 nM) for the human 5-HT_{2B} receptor (Shapiro et al., 2003).

VIII. F. 3. Allosteric modulators

No selective 5-HT_{2B} allosteric modulator has been definitely identified. In the crystal, ergotamine binds to two distinct sites at the 5-HT_{2B} receptor, the orthosteric site, where the indole nucleus of ergotamine resides, and the “extended” binding site, to which the tripeptide portion of the ergoline binds. This potential allosteric site is also present in the muscarinic M2 receptor at the same extracellular region. The similarities in both the M2 and 5-HT_{2B} receptors suggest that the location of the extracellular allosteric site for Class A GPCRs is rather similar and conserved: these common features suggest that ergotamine and other ergolines, may function as “bitopic” ligands, acting at both the orthosteric and the putative extracellular allosteric site in the 5-HT_{2B} receptor. It is thought that a sodium ion allosterically modulates the binding pocket to reduce G-protein signaling, thus favoring β -arrestin recruitment, (McCorvy and Roth, 2015).

VIII. G. Transduction system(s)

VIII. G. 1. Transfected cells

5-HT_{2B} receptors expressed in mouse fibroblast L-cells, stimulate GTPase activity and inositol 1,4,5- triphosphate production upon agonist stimulation. This GTPase activation is mediated by G $\alpha_{q/11}$, but not by G α_s or G α_i . The GTPase activation was also blocked by anti- β 1-4, or anti- γ 2

subunit antibodies. The 5-HT_{2B} receptor couples to phospholipase A2 (PLA2)-mediated release of arachidonic acid (Tournois et al., 1998). In addition, stimulation of the 5-HT_{2B} receptor triggers intracellular cGMP production through dual activation of constitutive nitric-oxide synthase (cNOS) and inducible NOS (iNOS). The group I PDZ motif at the carboxy terminus of the 5-HT_{2B} receptor is required for cNOS transduction pathways, whereas iNOS stimulation is Gα13-dependent (Manivet et al., 2000). The 5-HT_{2B} receptor shares the C-terminal E-X-V/I-S-X-V sequence with the 5-HT_{2C} receptors and also binds MUPP1-PDZ domains *in-vitro* (Becamel et al., 2001). Agonist-induced stimulation of the 5-HT_{2B} receptor promotes rapid and transient activation of the proto-oncogene product p21^{ras}, as measured by an increase in GTP bound-Ras (Launay et al., 1996). 5-HT_{2B} receptor stimulation activates the mitogen-activated protein kinases (MAPKs) p42^{mapk}/p44^{mapk}, as well as extracellular signal-regulated kinase 2 and 1 (ERK2/ERK1). It results in the formation of foci and to the formation of tumors from these foci in nude mice (Launay et al., 1996). The 5-HT_{2B} receptor-dependent cell cycle progression happens through retinoblastoma protein hyperphosphorylation and the activation of both cyclin D1/cdk4 and cyclin E/cdk2 kinases. The induction of cyclin D1, but not that of cyclin E expression, is under MAPK control, indicating an independent regulation of these two cyclins in 5-HT_{2B} receptor-induced mitogenesis. Similarly, platelet derived growth factor receptor (PDGFR) kinase activity is essential for 5-HT_{2B}-triggered MAPK/cyclin D1, but not cyclin E, signaling pathways. 5-HT_{2B} receptor activation also increases activity of the Src family kinases c-Src, Fyn and c-Yes. Strikingly, c-Src, but not Fyn or c-Yes, is the crucial link between the Gq protein-coupled 5-HT_{2B} receptor and the cell cycle regulators (Nebigil et al., 2000b). Inhibition of c-Src activity is sufficient to abolish 5-HT-induced PDGFR tyrosine kinase phosphorylation and MAPK activation, cyclin D1 and cyclin E expression levels and thymidine incorporation. Thus, c-Src activation by the 5-HT_{2B} receptor controls cyclin E induction, and in concert with PDGFR, induces also cyclin D1 expression *via* the MAPK/ERK pathway (Nebigil et al., 2000b). The 5-HT_{2B} signal transduction pathways are thus quite diverse and are similar to those of 5-HT_{2A/2C} receptors. On the other hand, the NOS pathway seems to be 5-HT_{2B} receptor-specific.

VIII. G. 2. Primary cell cultures

In cultivated cardiac fibroblasts, angiotensin II- (AngII) or 5-HT-dependent cytokine release is critical for the expression of HB-EGF and Src activity *via* endogenous AT1 and 5-HT_{2B} receptors (Jaffre et al., 2009). Matrix metalloproteinases (MMPs) are responsible for HB-EGF shedding and

subsequent EGF-receptor transactivation induced by AngII or 5-HT. Tumor necrosis factor-alpha (TNF- α) converting enzyme (TACE, ADAM-17), controls HB-EGF shedding in fibroblasts and is directly regulated by 5-HT_{2B} receptors (Pietri et al., 2005). Blockade of one of the two receptors prevents cytokine release induced by the other receptor (Jaffre et al., 2009). These findings also indicate that AT1 and 5-HT_{2B} receptors share common EGF receptor-dependent signaling pathways in adult cardiac fibroblasts, and the two receptors were shown to interact in a common cell compartment. Together the data support AT1 and 5-HT_{2B} receptors exist as heterodimers that may play a key role in receptor maturation and trafficking to the plasma membrane and/or signaling (Bulenger et al., 2005) to drive common signaling regulating hypertrophic factors in the heart (Jaffre et al., 2009).

5-HT_{2B} receptor stimulation in hepatic stellate cells (HSC) activates the expression of TGF β 1 (a powerful suppressor of hepatocyte proliferation) *via* ERK/JunD signaling. 5-HT_{2B} receptor antagonists decrease the mRNA levels of TGF β 1, connective growth factor, plasminogen activator inhibitor-1, Smad-3 and JunD in lung and skin fibroblasts (Dees et al., 2011). 5-HT_{2B} receptor activation leads to sustained phosphorylation of two downstream targets of mTOR, p70S6K and 4E-BP1, thereby facilitating survival and inhibiting autophagy of hepatocellular carcinomas (Soll et al., 2010). The 5-HT_{2B} receptor protects newborn post-mitotic cardiomyocytes against serum deprivation-induced apoptosis as manifested by DNA fragmentation, nuclear chromatin condensation, and TUNEL labeling. 5-HT prevents cytochrome c release and caspase-9 and -3 activation after serum deprivation *via* cross-talks between phosphatidylinositol-3 kinase (PI3K)/Akt and ERK1/2 signaling pathways. 5-HT_{2B} receptor-activated ERK kinases inhibit Bax expression induced by serum deprivation. 5-HT activates nuclear factor- κ B (NF- κ B) *via* PI3K/Akt required for the regulation of the mitochondrial adenine nucleotide translocator (ANT-1) and mitochondrial permeability. Thus, 5-HT *via* the 5-HT_{2B} receptor is a novel survival factor targeting mitochondria (Nebigil et al., 2003). Interestingly, NF- κ B regulation by 5-HT_{2B} receptors is confirmed in a large screen for genes regulating NF- κ B and the MAPK pathways (Matsuda et al., 2003).

Primary osteoblasts from mutant 5-HT_{2B} receptor KO mice show reduced proliferation and delayed differentiation; calcium incorporation is markedly reduced in osteoblasts after 5-HT_{2B} receptor inactivation (by genetic invalidation or by pharmacological inhibition; Collet et al., 2008). A functional

link between the 5-HT_{2B} receptor and the activity of the tissue-nonspecific alkaline phosphatase (TNAP) was established in an osteoprogenitor C1 cell line (Baudry et al., 2010). During osteogenic differentiation, both 5-HT_{2B} receptor and TNAP mRNA translations are delayed with respect to extracellular matrix deposition. Once the receptor is expressed, it constitutively controls TNAP activity at a post-translational level along the entire period of mineral deposition. The lack of 5-HT_{2B} receptors is associated with a 10-fold over-production of prostacyclin (PGI₂) in osteoblasts primary cultures. A specific prostacyclin synthase (PGIS, CYP8A1) inhibitor (U51605) totally rescued osteoblast aggregation and matrix mineralization in 5-HT_{2B} receptor KO osteoblasts without any effect on WT osteoblasts. Prostacyclin is the endogenous ligand of the nuclear receptor PPAR- β/δ , and its inhibition in 5-HT_{2B} KO cells rescued totally the alkaline phosphatase *TNAP* and osteopontin *SPP1* mRNA levels, cell-cell adhesion, and matrix mineralization. The absence of 5-HT_{2B} receptors leads to the overproduction of prostacyclin, inhibiting osteoblast differentiation due to PPAR- β/δ -dependent target regulation and defective cell-cell adhesion and matrix mineralization (Chabbi-Achengli et al., 2013), supporting a physiological negative control of PGIS by 5-HT_{2B} receptors. Thus, endogenously expressed 5-HT_{2B} receptors can modulate various transduction pathways including Src, MMPs, pLA2 activities in a cell type-dependent manner.

VIII. H. Regulatory mechanisms

VIII. H. 1. Internalization

In transfected cells, prior exposure to 5-HT results in a rapid and considerable (up to 80%) 5-HT_{2B} receptor desensitization (Porter et al., 2001). Internalization of 5-HT_{2B} receptors is caveolin1-independent and clathrin- and β -arrestin2-dependent (Janoshazi et al., 2007).

Some ergot derivatives are 'slow' 5-HT_{2B} receptor binders, with very slow association and dissociation rates. The compounds have apparent lower potency to increase intracellular concentrations of calcium ions relative to inositol phosphate accumulation assays. Similarly, the potency of ergolines to activate ERK1/2 is highly time-dependent. In addition, a number of ergot derivatives produce 'wash-resistant' 5-HT_{2B} receptor signaling that persists for hours without appreciable loss of potency, which is not explained simply by slow receptor-dissociation kinetics. Thus, this persistent signaling has been proposed to originate from internalized or sequestered receptors (Unett et al., 2013). The 5-HT_{2B} receptor crystal structure (Huang

et al., 2009), reveals an intermediate state of activation stabilized by the extracellular-facing tripeptide portion of ergotamine, which likely drives β -arrestin bias and is not seen in unbiased ligands such as 5-HT itself. Thus, the long duration of action of some ergolines may be explained by a combination of very slow kinetics at the receptor, coupled with persistent intracellular signaling.

VIII. H. 2. Interacting proteins

Proteins known to interact with the 5-HT_{2B} receptor include constitutive and inducible NOS, G α _q, G α ₁₁, and G α ₁₃, involved in signaling of the receptor and MUPP1 a multivalent PDZ scaffolding protein. (Becamel et al., 2001).

For more details on proteins that interact with the 5-HT_{2B} receptor see Section XVII.B.4.

VIII. I. Function at cellular, tissue and *in vivo* level

VIII. I. 1. Hematopoiesis

5-HT promotes megakaryocytes (MKs) proliferation and reduces cell apoptosis *via* activation of the 5-HT_{2B} receptor and Akt pathway (Liu and Yang, 2006). 5-HT increases proplatelet bearing MKs and polymerizes actin *via* ERK1/2 (Ye et al., 2014). *Tpb1*^{-/-} mice are deficient in peripheral 5-HT and display features of ineffective erythropoiesis. The central event starts in the bone marrow where the absence of 5-HT inhibits the terminal differentiation of erythroid precursors expressing 5-HT_{2A} and 5-HT_{2B} receptors. In addition, red blood cells from 5-HT-deficient mice are more sensitive to macrophage phagocytosis and have a shortened *in-vivo* half-life (Amireault et al., 2011). In addition, the 5-HT_{2B} receptor is expressed in c-kit⁺ bone-marrow cells (Launay et al., 2012). The 5-HT_{2B} receptor antagonist RS127445 decreases colony-forming capacity, with inhibition of both CFU-GEMM and BFU-E formation attributed to a reduction of cell proliferation and/or an apoptotic effect. By contrast, 5-HT significantly enhances the expansion of CD34⁺ cells to early stem/progenitors (CFU-GEMM) and committed progenitors (BFU/CFU-E) (Yang et al., 2007).

In human macrophages, 5-HT inhibits the LPS-induced release of proinflammatory cytokines, to upregulate the expression of M2 polarization-associated genes, and to reduce the expression of M1-associated genes. 5-HT_{2B} receptors mediate the pro-M2 skewing effect of 5-HT. Blockade of this receptor during *in-vitro* monocyte-to-macrophage differentiation preferentially modulates the acquisition of M2 polarization markers. 5-HT_{2B} receptor mRNA is preferentially expressed by anti-inflammatory M2 (M-CSF) macrophages, is detected *in-vivo* in liver Kupffer cells and in tumor-associated macrophages (de Las Casas-Engel et al., 2013). 5-HT_{2B} receptor expression is found in postnatal microglia, suggesting that 5-HT participates in microglial functions (Kolodziejczak et al., 2015). 5-HT_{2B} receptor mRNA expression is evident in spleen, thymus, and peripheral blood lymphocytes (Stefulj et al., 2000). Immature dendritic cells express 5-HT_{2B} receptor mRNA, and 5-HT_{2B} receptor stimulation induces intracellular Ca²⁺ mobilization in immature, but not mature, dendritic cells. Thus, 5-HT stimulates, in a maturation-dependent manner, different signaling pathways in dendritic cells (Idzko et al., 2004).

A proper balance between different T helper (Th) cell subsets is necessary for normal functioning of the adaptive immune system. Th cells (from human umbilical cord blood) differentiated *in vitro* into Th1 or Th2 cells reveal the latter express 5-HT_{2B} receptor mRNA (Aijö et al., 2012). In gene expression profiles during human CD41 T cell differentiation, 5-HT_{2B} receptor mRNA, was found to be SP4-specific (~10-fold) among the sixteen transcripts expressed in SP4 thymocytes at levels 3-fold or higher than in any other isolated T cell subpopulation (Lee et al., 2004).

Treatment with aggregated (1-40 or 1-42) and oligomeric (1-42) amyloid β (A β -found in Alzheimer's disease) promoted differentiation of bone marrow-derived mesenchymal stem cells without toxic effects. The effect of A β was shown to be mediated by the neuropeptide Y1 receptor and the 5-HT_{2B} receptor, *via* PI3K-dependent activation of the MAPK/ERK1/2 pathway (Jin et al., 2009). Thus, the 5-HT_{2B} receptor among others, mediates the balance among various hematopoietic lineages.

VIII. I. 2. Pancreas

A strong lactogen-dependent upregulation of 5-HT biosynthesis takes place in a subpopulation of mouse islet β -cells during pregnancy (Schraenen et al., 2010). Pancreatic islet cells express the genes encoding all of the products necessary for synthesizing, packaging, and secreting 5-HT, including both isoforms of the 5-HT synthetic enzyme tryptophan hydroxylase (TPH) and the archetypal 5-HT transcription factor Pet1. In β -cells, Pet1 can bind to the 5-HT relevant genes but also to a conserved insulin gene regulatory element. Mice lacking Pet1 display reduced insulin production and secretion and impaired glucose tolerance (Ohta et al., 2011). Inhibition of 5-HT synthesis blocks β -cell expansion and induced glucose intolerance in pregnant mice without affecting insulin sensitivity. Expression of the 5-HT_{2B} receptor in maternal islets has been reported to increase during pregnancy and to normalize just before parturition. Blocking 5-HT_{2B} receptor signaling in pregnant mice may also block β -cell expansion and cause glucose intolerance (Kim et al., 2010).

VIII. I. 3. Adipocytes

By inhibiting 5-HT_{2B} receptor signaling during adipogenesis using RS127445, an increased fat accumulation was observed similar to the knock-down phenotype (Söhle et al., 2012). In adipocytes, 5-HT_{2B} receptors favor lipolysis by increasing phosphorylation and activity of hormone-sensitive lipase (Sumara et al., 2012).

VIII. I. 4. Cardio-vascular and pulmonary systems

5-HT_{2B} receptor inactivation in mice leads to partial embryonic lethality due to major defects in heart development (Monassier et al., 2010). Neonates exhibit a second wave of partial lethality due to cardiac dilation resulting from contractility deficits and structural deficits at the intercellular junctions between cardiomyocytes. Echocardiography and electrocardiography studies in animals that live past the first week and survive until adulthood, confirm the presence of left ventricular dilation and decreased systolic function. 5-HT, *via* the 5-HT_{2B} receptor, regulates heart differentiation and proliferation during development as well as cardiac structure and function in adults (Nebigil et al., 2000a). The 5-HT_{2B} receptor is functionally coupled to reactive oxygen species synthesis through NADPH oxidase (NOX) stimulation in 1C11 cells (Schneider et al., 2006) and in angiotensin II and isoproterenol-induced cardiac hypertrophy (Monassier et al., 2008). In human atrial myocytes, 5-HT reduces the amplitude of L-type calcium currents

and affects the strength of gap junctional intercellular communication, which is markedly reduced by blocking receptors: showing that activation of 5-HT_{2B} receptors inhibit gap junctional intercellular communication (Derangeon et al., 2009). Upon pulmonary artery banding, the 5-HT_{2B} receptor antagonist SB204741 reduces right ventricular fibrosis and improves heart function in mice (Janssen et al., 2015).

A model in which 5-HT_{2B} receptor signaling promotes cardiac hypertrophy by stimulating calcineurin/NFAT signaling, suggests the recruitment of histone acetyl transferases to regulatory regions of NFAT target genes. 5-HT_{2B} receptor agonist-induced hypertrophy of cardiac muscle cells results from a signaling pathway involving calcineurin and a kinase-dependent mechanism that inactivates class II histone deacetylases (HDAC), which act as repressors of cardiac growth (Bush et al., 2004). Since it also stimulates nuclear export of class II HDACs, MEF2 may play a role in the mechanism by which 5-HT_{2B} receptor signaling triggers cardiac remodeling (McKinsey and Olson, 2005). A cDNA encoding the 5-HT_{2B} receptor was found in a screen for genes encoding HDAC5 modulators and the ability of 5-HT_{2B} receptors to promote HDAC5 phosphorylation and cardiomyocyte hypertrophy was confirmed (McKinsey and Olson, 2005). The 5-HT_{2B} receptor-triggered intracellular calcium ion release and PKC activation, accounts at least in part, for the overexpressed receptor-induced HDAC5 phosphorylation (Chang et al., 2005).

VIII. I. 5. Endothelial cells

In human pulmonary artery endothelial cells, 5-HT_{2B} receptors stimulate calcium ion release from intracellular stores (Ullmer et al., 1996). 5-HT_{2B} receptors mediate the endothelium-dependent relaxation of rat jugular vein (Ellis et al., 1995) and pig pulmonary artery (Glusa and Pertz, 2000). Activation of 5-HT_{2B}/5-HT_{1B} receptors stimulates NO production in human coronary artery endothelial cells (Ishida et al., 1998). Compared with non-stimulated pulmonary artery endothelial cells, CRP-stimulated cells show downregulation of 5-HT_{2B} receptor by 25%, of inhibitor of NF-κB kinase subunit epsilon (IKBKE) by 30%, and of toll-like receptor-4 and -6 by 18 and 39%, respectively (Wynants et al., 2013). A cardioprotective function of the 5-HT_{2B} receptor in an integrated model of heart failure with preserved ejection fraction can be explained by a contribution of the endothelial 5-HT_{2B} receptors to coronary vasodilatation (Ayme-Dietrich et al., 2015).

VIII. I. 6. Aorta

In normotensive rats, 5-HT-induced contraction of the aorta is primarily 5-HT_{2A} receptor-dependent, however in hypertensive rats, it is mediated by both 5-HT_{2A} and 5-HT_{2B} receptors. The endothelium-denuded isolated superior mesenteric artery of hypertensive (DOCA-salt) rat displays a marked increase in maximum arterial contraction to 5-HT_{2B} receptor agonists when compared with control rats, confirming that the 5-HT_{2B} receptor plays a greater role in 5-HT-induced contraction in arteries from hypertensive rats (Banes and Watts, 2003; Watts and Fink, 1999).

VIII. I. 7. Liver

5-HT is a potent growth factor for liver development and regeneration. The expression of both 5-HT_{2A} and 5-HT_{2B} receptors in the liver increases following hepatectomy. 5-HT₂ receptor inhibition by ketanserin blocks liver regeneration when administered close to the G1/S transition point suggesting 5-HT as a cofactor for DNA synthesis (Papadimas et al., 2006). In *Tph1*^{-/-} mice, the failure of liver regeneration is rescued by reloading 5-HT-free platelets with a 5-HT precursor molecule (Lesurtel et al., 2006). Elderly mice have decreased ability of the liver to restore normal volume after partial hepatectomy. The 5-HT₂ receptor agonist DOI reverses the age-related pseudocapillarization of old liver and improves hepatosinusoidal blood flow (Furrer et al., 2011), it also enhances hepatocyte proliferation after liver transplantation in mice. 5-HT_{2B} receptor activation significantly improves survival in recipients of a small, otherwise non-viable graft by enhancing liver regeneration and hepatic microcirculation, thereby reducing ischemia/reperfusion injury (Tian et al., 2011). 5-HT protects the liver in an IL-6-independent manner. The protective effects of DOI is lost in animals treated with SB206553, a 5-HT_{2B/2C} receptor antagonist. DOI may thus preserve microcirculation and accelerate liver regeneration via 5-HT_{2B} receptors, thus preventing the liver parenchyma from further injury (Tian et al., 2011). However in a pathophysiological setting, the regenerative influence of 5-HT acting through 5-HT_{2A} receptors on hepatocytes may be subjected to opposite anti-regenerative effects arising from 5-HT acting through 5-HT_{2B} receptors in hepatic stellate cells (Ebrahimkhani et al., 2011). In hepatocytes, signaling through 5-HT_{2B} receptors also promotes gluconeogenesis (Sumara et al., 2012).

VIII. I. 8. Gut

The 5-HT_{2B} receptor was initially characterized as the receptor contracting the rat stomach fundus (Vane, 1957). The 5-HT_{2B} receptor is expressed by smooth muscles in the small intestine, the stomach and by enteric neurons. 5-HT, stimulating 5-HT_{2B} receptors, affects the fate of the large subset of enteric neurons that arises after the development of endogenous sources of 5-HT (Fiorica-Howells et al., 2000). High levels of both 5-HT_{2B} receptor mRNA and protein are found predominantly in the muscle layers and in the myenteric nerve plexus throughout the colon, where they cause neuronally-mediated contractions of longitudinal muscle (Borman et al., 2002) and tonically regulate colonic motility (Bassil et al., 2009).

Ghrelin, an orexigenic peptide present in the stomach, has gastroprokinetic properties. *In-vivo*, the ghrelin receptor antagonist D-Lys(3)-GHRP-6 reduces food intake and delays gastric emptying in rodents. D-Lys(3)-GHRP-6, contracts stomach strips, an effects blocked by methysergide and yohimbine, suggesting an interaction with 5-HT_{2B} receptors (Depoortere et al., 2006).

Normal gastrointestinal motility requires functional interstitial cells of Cajal (ICC) that proliferate in adult mice. 5-HT_{2B} receptor activation increases the proliferation of ICC *in-vivo*. On the other hand, lack of 5-HT_{2B} receptor signaling reduces the density of ICC networks in mature mice. Targeting 5-HT_{2B} receptors may protect ICC networks from injury and/or help repair them after injury (Tharayil et al., 2010).

VIII. I. 9. Central autonomic nervous system

5-HT_{2B} and 5-HT_{2A} receptors are expressed in ponto-medullary respiratory motor centres. They are co-localized in the Kolliker-Fuse and parabrachial regions of the pons, and in the Bötzing and pre-Bötzing complex of the ventral medulla with a stronger expression of 5-HT_{2A} receptors in all regions. BW723C86 applied in the pre-Bötzing complex increases respiratory frequency, and is blocked by the 5-HT_{2B} receptor selective antagonist, LY272015. Hence, endogenous 5-HT appears to support tonic action on respiratory rhythm generation *via* 5-HT_{2B} receptors. However, respiratory activity is unaffected in 5-HT_{2B} receptor-deficient mice: BW723C86 and LY272015 had no effects, whereas ketanserin blocked rhythmic activity. Thus, endogenous 5-HT_{2B} receptor activation has a stimulatory role at the pre-Bötzing complex and hypoglossal motoneurons that can be substituted by 5-HT_{2A} receptors in the absence of 5-HT_{2B} receptors. The presence of functional 5-HT_{2B} receptors in the neonatal medullary breathing

center suggests a potential convergent regulatory role of 5-HT_{2B} and 5-HT_{2A} receptors on the central respiratory network (Günther et al., 2006). When 5-HT_{2A} and 5-HT_{2B} receptor agonists are applied concurrently, there is a frequency increase that exceeds the effects of either agonist alone. This is an expected outcome if frequency-controlling neurons are preferred targets for 5-HT_{2B} receptor modulation in the ponto-medullary respiratory compartment (Niebert et al., 2011).

Phrenic motor neurons express 5-HT_{2B} receptors and acute intermittent hypoxia induces phrenic long-term facilitation via spinal 5-HT₂ receptor activation and NOX activity. Pre-treatment with NOX inhibitors blocks 5-HT_{2B} receptor-induced phrenic motor facilitation (Macfarlane et al., 2011). Episodic spinal 5-HT receptor activation alone, without changes in oxygenation, is sufficient to elicit NOX-dependent phrenic motor facilitation. Intrathecal BW723C86 elicits progressive and sustained phrenic motor facilitation, blocked by the 5-HT_{2B} receptor antagonist, SB206553. Spinal nNOS activity is necessary for acute intermittent hypoxia-induced phrenic long-term facilitation (Macfarlane et al., 2014). Thus, episodic spinal NO elicits phrenic long-term facilitation via 5-HT_{2B} receptor activation and NOX-derived ROS formation.

VIII. I. 10. Peripheral autonomic nervous system

Heart rate control originates in parasympathetic preganglionic cardiac vagal neurons in the nucleus ambiguus. 5-HT₂ receptors modulate spontaneous and respiratory-evoked GABAergic neurotransmission to cardioinhibitory vagal neurons within the nucleus ambiguus as well as rhythmic fictive inspiratory-related activity. Neurons in the rat nucleus tractus solitarius are affected differently by 5-HT₂ receptor ligands, in regard to their vagal postsynaptic location, the type of cardio-pulmonary afferent they receive and the nature of the 5-HT₂ receptor. 5-HT_{2B} receptors are excitatory, whereas 5-HT_{2C} receptors are inhibitory (Jordan, 2005). In neurons of the nucleus tractus solitarius receiving vagal afferent input, the selective 5-HT_{2B} receptor antagonist, LY202715, significantly reduced the excitatory actions of BW723C86 on 'intermediate' and 'polysynaptic' cells (Sevoz-Couche et al., 2000).

Multiple, as opposed to single, applications of α -methyl-5-HT, cause a long-lasting inhibition of both spontaneous and fictive inspiratory-related GABAergic neurotransmission to cardioinhibitory vagal neurons, which are prevented by the 5-HT_{2B} receptor antagonist, SB204741 (Dergacheva et al., 2008). BW723C86 reversibly increases both the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs) in cardiac vagal neurons. The facilitation evoked by α -methyl-5-HT is blocked by the 5-HT_{2B/2C} receptor antagonist, SB206553. Interestingly, the blockade of both NMDA and non-NMDA glutamatergic receptors did not prevent α -methyl-5-HT-evoked facilitation of mEPSCs; however, the responses were blocked by P2 receptor antagonists (Dergacheva et al., 2008). These results indicate that activation of 5-HT₂ receptors facilitates excitatory purinergic, but not glutamatergic, neurotransmission to cardiac vagal neurons.

VIII. I. 11. Amygdala and anxiety

Animals administered the 5-HT_{2B} receptor agonist, BW723C86, exhibit anxiolytic-like behaviour in both the rat social interaction test and two conflict models of anxiety; the rat Geller-Seifter and marmoset conflict test (Kennett et al., 1995). Adult rat neurons in the medial amygdoloid nucleus express 5-HT_{2B} receptors protein (Figure 11) where local application of a 5-HT_{2B} receptor agonist displays anxiolytic activity in the social interaction model, but has little effect on behavior in a punished conflict model of anxiety (Kennett et al., 1996). This 5-HT_{2B} receptor agonist also increased the time spent in feeding behavior of freely-fed rats in observation cages over 15 min. The effect was also likely to be 5-HT_{2B} receptor-mediated, as no response to BW723C86 was evident in freely fed rats pretreated with the 5-HT_{2C/2B} receptor antagonist, SB206553. BW723C86 also reduced the frequency of grooming bouts of rats in observation cages (Kennett et al., 1997). Finally, BW723C86 increased the number of punishments accepted in a rat Vogel drinking conflict paradigm over 3 min, as do anxiolytic benzodiazepine drugs. The anti-punishment effect of BW723C86 was blocked by the 5-HT_{2B/2C} receptor antagonists SB206553 or SB215505, but not by the selective 5-HT_{2C} receptor antagonist, SB242084. Thus, the anti-punishment action of BW723C86 is likely to be 5-HT_{2B} receptor mediated (Kennett et al., 1998).

VIII. I. 12. Sleep

5-HT_{2A} and 5-HT_{2C} receptors modulate deep (slow wave) sleep and low-frequency EEG power in humans and rodents. Antagonists of 5-HT_{2A} and/or 5-HT_{2C} receptors have a well-known slow wave sleep enhancing effect. In contrast, blockade of 5-HT_{2B} receptors increases motor activity and wakefulness along with decreased theta activity during wakefulness and REM sleep. The 5-HT_{2B} receptor antagonist, SB215505, dose-dependently increases wakefulness at the expense of the intermediate stage of sleep, REM sleep and slow wave sleep and reduces low-frequency (<8 Hz) EEG power. In REM sleep, the 5-HT_{2B} receptor antagonist, SB215505, dose-dependently decreases EEG power solely in the theta (6-9 Hz) band, primarily affecting the peak power value (7 Hz) (Kantor et al., 2004). 5-HT exerts a 5-HT_{2B} receptor-mediated facilitation of NREM sleep, and an influence that is, respectively, inhibitory on NREM sleep and facilitatory on sleep apnea generation, *via* 5-HT_{2A} receptors (Popa et al., 2005). *Htr_{2B}^{-/-}* mice exhibited significantly increased wakefulness, with less NREM sleep while REM sleep is not affected. Chronic oral intake of haloperidol restored the balance between wakefulness and NREM sleep in *Htr_{2B}^{-/-}* mice (Pitychoutis et al., 2015). Activation of 5-HT_{2B} receptors may thus contribute to initiation of sleep and to theta generation during wakefulness and REM sleep under physiological conditions. However, it should be kept in mind that clinically there have been no successes in insomnia/ sleep disorders, with 5-HT₂ receptor antagonists in spite of multiple attempts, at least with 5-HT_{2A} receptor antagonists.

VIII. J. Clinical relevance

VIII. J. 1. Feeding and anorexigens

The hypophagic response to the anorexigen and 5-HT releaser, dexfenfluramine, observed in wild-type mice is absent in *Htr_{2B}^{-/-}* mice or in wild-type mice treated with RS127445. The dexfenfluramine-induced hypothalamic peak of 5-HT release is strongly reduced in *Htr_{2B}^{-/-}* awake mice compared with control mice. Dexfenfluramine-induced 5-HT release is observed in synaptosomal preparation from wild type, but absent in *Htr_{2B}^{-/-}* mice (Banas et al., 2011). 5-HT_{2B} receptor-induced NO production phosphorylates SERT and maximizes 5-HT uptake in raphe neuron primary culture. 5-HT_{2B} receptor- PKC coupling promotes additional phosphorylation of both SERT and Na⁺, K⁺-ATPase α -subunit, impairing the electrochemical gradient necessary for 5-HT uptake. Such 5-HT_{2B} receptor-mediated control of SERT activity operated in primary neurons from the raphe nuclei (Launay et

al., 2006). Thus, activation of 5-HT_{2B} receptors is a limiting step in the SERT dependent-releasing effect of dexfenfluramine, whereas other 5-HT receptors may act downstream with respect to feeding behavior.

VIII. J. 2. Raphe and antidepressant activity

5-HT neurotransmission is tightly regulated by autoreceptors that fine-tune 5-HT neurotransmission through negative feedback inhibition at the cell bodies (predominantly 5-HT_{1A}) or at the axon terminals (predominantly 5-HT_{1B}), although 5-HT_{2B} receptors may play different roles (McDevitt and Neumaier, 2011). The therapeutic effects induced by 5-HT-selective reuptake inhibitor (SSRI) antidepressants are initially triggered by blocking the SERT and rely on long-term adaptations of pre- and post-synaptic receptors. Long-term behavioral and neurogenic SSRI effects were abolished after either genetic or pharmacologic inactivation of 5-HT_{2B} receptors (Diaz et al., 2012). Conversely, direct agonist stimulation of 5-HT_{2B} receptors induced an SSRI-like response in behavioral and neurogenic assays. The 5-HT_{2B} receptor is expressed in raphe serotonergic neurons. The SSRI-induced increase in hippocampal extracellular 5-HT concentration is strongly reduced in the absence of functional 5-HT_{2B} receptors hence selective 5-HT_{2B} activation mimicks SSRI effects (Diaz et al., 2012). Thus, the 5-HT_{2B} receptor modulates 5-HT neurone activity and may be required for the therapeutic actions of SSRIs.

VIII. J. 3. Dopamine and anti-depressant activity

Agomelatine, a potent melatonin MT₁/MT₂ receptor agonist, is an effective antidepressant, and a potent 5-HT_{2B/2C} receptor antagonist (Millan et al., 2003). Twice daily melatonin increases the number of spontaneously active dopamine neurons without affecting noradrenaline neurons. Long-term administration of either melatonin or the 5-HT_{2C} receptor antagonist, SB242084, has no effect on the firing rate and burst parameters of 5-HT and dopamine neurons, whereas their combination, enhances the number of spontaneously active dopamine neurons, while leaving the firing of 5-HT neurons unchanged. The addition of the 5-HT_{2B} receptor antagonist, LY266097, to the previous regimen, which by itself is devoid of effect, increases the activity of dopamine neurons (Chenu et al., 2014). Hence, the combination of melatonin receptor activation, 5-HT_{2C} and 5-HT_{2B} receptor blockade results in a disinhibition of dopamine neurons, reproducing the antidepressant effect of agomelatine.

VIII. J. 4. Serotonin (5-HT) syndrome

The 5-HT syndrome occurs in humans after a combination of drugs inducing a massive increase in extracellular 5-HT or direct targeting of several 5-HT receptor subtypes (see Scotton et al, 2019). *Htr_{2B}^{-/-}* mice are more prone to develop the 5-HT syndrome symptoms after administration of high dose of SSRI or the 5-HT precursor, 5-hydroxytryptophan (5-HTP), although increases in 5-HT plasma levels are similar in both genotypes (Diaz and Maroteaux, 2011).

VIII. J. 5. Drug of abuse

The "club drug" MDMA ('ecstasy') inhibits SERT activity, releasing 5-HT stores from nerve terminals. The subsequent activation of postsynaptic 5-HT receptors by released 5-HT is critical for the unique psychostimulatory effects of MDMA. Acute pharmacological inhibition or genetic ablation of the 5-HT_{2B} receptor in mice completely abolishes MDMA-induced hyperlocomotion and 5-HT release in nucleus accumbens and ventral tegmental area. The MDMA-stimulated release of endogenous 5-HT from superfused midbrain synaptosomes is 5-HT_{2B} receptor- dependent (Doly et al., 2008). *Htr_{2B}^{-/-}* mice show no behavioral sensitization or conditioned place preference following MDMA. In addition, MDMA-induced reinstatement of conditioned place preference and locomotor sensitization are both abolished by RS127445 in mice, whereas MDMA-induced dopamine D1 receptor-dependent phosphorylation of extracellular regulated kinase in nucleus accumbens is abolished in mice lacking functional 5-HT_{2B} receptors. These results underpin the importance of 5-HT_{2B} receptors in the reinforcing properties of MDMA (Doly et al., 2009).

The selective 5-HT_{2B} receptor antagonist, LY266097, reduces dopamine outflow in the ventral striatum /nucleus accumbens, but not in the dorsal striatum (Auclair et al., 2010). The locomotor response of *Htr_{2B}^{-/-}* mice to both dizocilpine and amphetamine is significantly enhanced as compared with control mice (Pitychoutis et al., 2015). 5-HT_{2B} receptor antagonists reduce cocaine-induced hyperlocomotion independently of changes of subcortical dopamine outflow supporting a regulatory control exerted by this receptor on ascending dopamine pathways (Devroye et al., 2015). Thus 5-HT_{2B} receptors may also exert, in addition to 5-HT neurons, a facilitatory control on mesoaccumbens dopamine pathway activity.

VIII. J. 6. Impulsivity

A functional stop codon in the human 5-HT_{2B} receptor gene enhances impulsive behavior (Bevilacqua et al., 2010). Especially under conditions where control is impaired, the carriers of the stop codon are more vulnerable to alcohol and more impulsive upon drinking. Similarly, *Htr_{2B}^{-/-}* mice display more impulsive choice in delayed discounting tasks, sought novelty, and are more active after receiving a D1 dopamine receptor agonist (Bevilacqua et al., 2010). Interestingly, early-onset schizophrenia is more prevalent in human 5-HT_{2B} receptor gene Q*20 carriers. Domains related to the positive, negative and cognitive symptom-clusters of schizophrenia are affected in *Htr_{2B}^{-/-}* mice, with deficits in sensorimotor gating, selective attention, social interactions, learning and memory processes. *Htr_{2B}^{-/-}* mice show enhanced locomotor response to dizocilpine and amphetamine and alterations in sleep architecture. 5-HT_{2B} receptor ablation induces a region-selective decrease of dopamine and glutamate concentrations in the dorsal striatum. Importantly, selected schizophrenic-like phenotypes and endophenotypes are rescued by chronic haloperidol treatment (Pitychoutis et al., 2015). The phenotypes of *Htr_{2B}^{-/-}* mice result from a combination of both the direct absence of 5-HT_{2B} receptor signaling and the resultant neural adaptations.

VIII. J. 7. Fragile X syndrome

Fragile X syndrome, caused by the loss of *Fmr1* gene function, is the most common form of inherited mental retardation, with no current effective treatment. 5-HT_{2B} receptor activation moderately enhances Ras-PI3K/PKB signaling input, GluA1-dependent synaptic plasticity, and learning in *Fmr1* knockout mice without causing anxiety-related side effects (Lim et al., 2014).

VIII. J. 8. Cardiovascular diseases

5-HT_{2B} receptors are overexpressed in heart tissue from patients with congestive heart failure, in parallel to increased cytokine and norepinephrine plasma levels (Jaffre et al., 2009). 5-HT plasma levels are also increased in patients with heart failure and in rodents with cardiac hypertrophy induced by aortic constriction. Thus, 5-HT-induced cardiac hypertrophy and/or heart failure may be 5-HT_{2B} receptor dependent, or at least responses likely exacerbated via the 5-HT_{2B} receptor. In support of which, 5-HT_{2B} receptor KO mice do not develop isoproterenol-induced left ventricular

hypertrophy (Jaffré et al., 2004). Mice expressing the 5-HT_{2B} receptor exclusively in cardiomyocytes, similarly to global 5-HT_{2B} receptor-null mice, are resistant to isoproterenol-induced cardiac hypertrophy and dysfunction, as well as to isoproterenol-induced increases in plasma cytokine levels (Jaffre et al., 2009). In primary culture of cardiac fibroblasts, angiotensin II- and isoproterenol- stimulated NOX activity is prevented by the selective 5-HT_{2B} receptor antagonist (SB215505). SB215505 prevents the increase in cardiac superoxide generation and hypertrophy in two models of cardiac hypertrophy, i.e., angiotensin II and isoproterenol infusions in mice (Monassier et al., 2008). A functional interaction between AT1 and 5-HT_{2B} receptors *via* a trans-inhibition mechanism, may involve heterodimeric receptor complexes and trigger cytokine release in cardiac fibroblasts (Jaffre et al., 2009).

The 5-HT_{2B} receptor is involved in cardiac hypertrophy by acting directly on cardiac myocytes. After two weeks of aortic banding surgery, 5-HT_{2B} receptor mRNA and protein expression is increased. SB215505 significantly reduces the arising increase in heart weight, heart wall thickness, left ventricular mass and expression of the brain natriuretic peptide (BNP), but does not attenuate the up-regulation of 5-HT_{2B} receptor protein expression in rats after aortic banding. Following *in-vitro* mechanical stretch of cardiomyocytes and incubation with 5-HT, the level of 5-HT_{2B} receptors and BNP protein increases time-dependently. 5-HT_{2B} receptor siRNA applied to cardiomyocytes, reversed both the increase of NF-κB translocation and BNP protein induced by 5-HT incubation plus mechanical stretch (Liang et al., 2006). 5-HT_{2B} receptors are involved in the generation of apoptotic events associated with cardiac remodeling during increased adrenergic stimulation (Bai et al., 2010). Thus, there is a dual role for 5-HT_{2B} receptors on both cardiomyocytes and cardiac fibroblasts in regulating cardiac hypertrophy *in-vivo*.

VIII. J. 9. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive and often fatal disorder that results from increased pulmonary blood pressure associated with abnormal vascular proliferation. 5-HT is associated with the pathogenesis of PAH (Chan and Loscalzo, 2008). Therapeutics with PAH as a side effect, e.g. dexfenfluramine, are potent 5-HT releasers acting at SERT and/or 5-HT_{2B} receptor agonists (Weir et al., 2008). The blockade of 5-HT_{2B} receptors either by genetic (*Htr_{2B}^{-/-}*) or pharmacologic inactivation (5-HT_{2B} receptor antagonist, RS127445), completely prevent the development of hypoxia-

induced pulmonary hypertension in mice and lung remodeling, the increase in vascular proliferation, elastase activity and transforming growth factor- β -1 (TGF β 1) levels (Launay et al., 2002). In the monocrotaline-induced pulmonary hypertension model, a number of 5-HT_{2B} receptor antagonists (terguride, PRX-08066, or C-122) reduce pulmonary pressure, arterial wall thickening and lumen occlusion but maintained cardiac function (Dumitrascu et al., 2011; Porvasnik et al., 2010; Zopf et al., 2011). Pulmonary hypertension is associated with a substantial increase in 5-HT_{2B} receptor expression in the pulmonary arteries of both rodents and humans (Dumitrascu et al., 2011; Launay et al., 2002). Activation of 5-HT_{2B} receptors appears to be, therefore, a limiting step in the development of pulmonary hypertension. However, the restricted expression of 5-HT_{2B} receptors to bone-marrow cells is necessary and sufficient for pulmonary hypertension to develop *via* an action at hematopoietic stem cell differentiation (Launay et al., 2012). There appears to be a limiting role of 5-HT_{2B} receptors in PAH development; thus, the contribution of 5-HT to PAH may be an extrapulmonary, and specifically hematopoietic event.

VIII. J. 10. Vascular hypertension

Mesenteric arteries from deoxycorticosterone- (DOCA) salt hypertensive rodents, predominantly contract *via* 5-HT_{2B} receptors; they display an increase in 5-HT_{2B} receptor mRNA and receptors (Watts et al., 1996). The isolated endothelium-denuded superior mesenteric artery of DOCA-salt rats display a marked increase in the maximal contraction to the 5-HT_{2B} receptor agonist, BW723C86. In chronically instrumented rats, the 5-HT_{2B}-receptor antagonist, LY272015, significantly reduces mean blood pressure (Watts and Fink, 1999). LY272015 also inhibited 5-HT-induced contractions in aorta from rats made hypertensive by exposure to the nitric-oxide synthase inhibitor N(omega)-nitro-L-arginine, whereas ketanserin was inactive (Russell et al., 2002). Thus, the 5-HT_{2B} receptor appears to play an important role in 5-HT-induced contraction in hypertensive rodent arteries.

VIII. J. 11. Fibrosis

5-HT increases proliferation and collagen synthesis of lung fibroblasts. 5-HT concentrations in lung homogenates increase significantly following bleomycin-induced fibrosis, paralleled with an increased expression of 5-HT_{2A} and 5-HT_{2B} receptors (Königshoff et al., 2010). Blockade of 5-HT_{2B}

receptors by SB215505 reduces bleomycin-induced lung fibrosis, with reduced lung collagen levels and procollagen 1 and 3 mRNA expression. 5-HT_{2B} receptor antagonists decrease levels of lung TGFβ1 mRNA, connective growth factor and plasminogen activator inhibitor-1 and JunD mRNA, consistent with their anti-fibrotic activity. Interestingly, the 5-HT_{2B} receptor is strongly overexpressed in fibroblastic foci in human idiopathic pulmonary fibrosis (Fabre et al., 2008). Thus, it is likely that 5-HT-induced lung fibrosis is controlled by 5-HT_{2B} receptors regulating TGFβ1 levels.

In the liver, fibrogenic hepatic stellate cells (HSC), which are negative regulators of hepatocyte regeneration, are known to express both 5-HT_{2A} and 5-HT_{2B} receptors, which may regulate TGFβ1 and Smad signalling (Li et al., 2006). HSCs play a key role in hepatic wound healing and fibrosis. After HSC activation, expression of 5-HT_{2A} and 5-HT_{2B} receptors is around 100 and 50-fold that of quiescent cells, respectively. The 5-HT_{2B} receptor expression is strongly associated with fibrotic tissue in diseased liver. 5-HT₂ receptor antagonists treated HSCs display suppressed proliferation and increased apoptosis. 5-HT synergizes with platelet-derived growth factor to stimulate HSC proliferation (Ruddell et al., 2006). In contrast to quiescent cells, activated HSCs exhibit [Ca²⁺]_i transients following treatment with 5-HT, which is inhibited by ritanserin. Expression of type 1 inositol-5'-triphosphate receptor and type 2 sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase is also increased during activation of HSCs and serves as the major isotype for endoplasmic reticulum (ER) Ca²⁺ storage and release in activated HSCs. ER Ca²⁺ binding chaperone proteins, including calreticulin, calnexin and calsequestrin, are up-regulated following activation of HSCs (Park et al., 2011). 5-HT_{2B} receptor stimulation of HSCs increases the expression of TGFβ1 (a powerful suppressor of hepatocyte proliferation) *via* ERK/JunD signaling. Similar effects are evident in mice lacking 5-HT_{2B} receptor or JunD or when HSCs have been selectively depleted. 5-HT_{2B} receptor blockade attenuates fibrogenesis and improves liver function in disease models in which fibrosis is pre-established and progressive (Ebrahimkhani et al., 2011). Therefore, the hepatic 5-HT_{2B} receptor appears to have a dual role, promoting regeneration in physiological conditions and fibrosis in pathological conditions.

Dermal fibrosis is reduced in *Htr_{2B}^{-/-}* mice using both inducible and genetic models of fibrosis. Pharmacologic inactivation of the 5-HT_{2B} receptor effectively prevents the onset of experimental fibrosis and ameliorates established fibrosis by decreasing mRNA levels of TGFβ1, connective growth factor, plasminogen activator inhibitor-1 and Smad-3 (Dees et al., 2011). Moreover, inhibition of platelet activation prevents fibrosis in models of skin

fibrosis. In TPH1 deficient mice, the rate-limiting enzyme for 5-HT production outside the central nervous system, show reduced experimental skin fibrosis (Dees et al., 2011). Skin fibrosis is thus controlled by 5-HT_{2B} receptors via regulation of TGFβ1 levels.

Treatment of neonatal rat cardiac fibroblasts with 5-HT increases the expression of smooth muscle α -actin, a marker of fibroblast differentiation into myofibroblasts and stimulated cardiac fibroblast migration. 5-HT enhances secretion of TGFβ1 and expression of MMPs in cardiac fibroblasts (Yabanoglu et al., 2009). 5-HT- or AngII-stimulated cytokine release and secretion of TGFβ1 in adult cardiac fibroblasts is sensitive to 5-HT_{2B} receptor blockade. Treatments with epidermal growth factor receptor (EGFR, ErbB1/4)-selective inhibitors or with selective inhibitors of MMPs also abolished AngII- and 5-HT-induced cytokine release. Finally, the use of *HB-EGF*^{-/-} cardiac fibroblasts confirmed that EGFR stimulation is absolutely required for AngII- and 5-HT-dependent cytokine release (Jaffre et al., 2009). Collectively, these results highlight a convergent action of NE, AngII and 5-HT *via* interactions between AT1 and 5-HT_{2B} receptors co-expressed by non-cardiomyocytes are limiting key events in cardiac hypertrophy.

VIII. J. 12. Valvular heart disease

Valvular heart disease occurs in over 65% of carcinoid syndrome patients and is characterized by fibrous thickening of cardiac valves, leading to heart failure (for review see Roth, 2007). High plasma 5-HT levels correlate with valvular abnormalities detected by cardiac catheterization and echocardiography (Robiolio et al., 1995). The similarity of lesions in carcinoid heart disease and in methysergide-associated valvular disease suggested a direct stimulation of myofibroblast growth by an unknown 5-HT receptor agonism (Hendrikx et al., 1996). The increase in fenfluramine-associated valvular heart disease raised concerns that other 5-HT relevant medications might also increase the risk of valvular heart disease (Connolly et al., 1997). Dexfenfluramine had been approved in the United States for long-term use as an appetite suppressant until it was associated with valvular heart disease. The valvular changes (myofibroblast proliferation) are histopathologically indistinguishable from those observed in carcinoid disease or following long-term exposure to 5-HT₂ receptor-preferring ergot drugs (ergotamine, methysergide). The amphetamine derivative, MDMA ("Ecstasy") and its N-demethylated metabolite, 3,4-methylenedioxyamphetamine (MDA) both preferentially bind to and activate human recombinant 5-HT_{2B} receptors. Like fenfluramine and norfenfluramine, they elicit mitogenic responses in human valvular interstitial cells *via* likely activation of 5-HT_{2B}

receptors (Setola et al., 2003). Based on these strikingly similar echocardiographic and histopathologic features, it is now considered that ergot-derived dopamine agonists (e.g. pergolide, cabergoline) cause a valvular heart disease nearly identical to that seen in patients with carcinoid syndrome (Horvath et al., 2004). Population studies of patients with Parkinson's disease compared with non-parkinsonian controls show that pergolide and cabergoline have a similar risk of inducing fibrotic changes in cardiac valve leaflets. Pergolide and cabergoline have high affinity for the 5-HT_{2B} receptors. The frequency of moderate-to-severe regurgitation in at least one heart valve was higher in patients receiving cabergoline or pergolide compared to patients taking non-ergot agonists or controls, and the incidence of new-onset valvulopathy was relatively high in patients taking the ergot-derived drugs (Antonini and Poewe, 2007; Roth, 2007). A simultaneous mitral bioprosthesis hypertrophic scarring and native aortic valve fibrosis was recently reported following benfluorex therapy. The bioprosthesis and aortic valves exhibit similar histopathological lesions. Thickening and plaque deposits made by smooth muscle α -actin- and vimentin-positive cells in a glycosaminoglycan matrix were observed supporting that activation of the 5-HT_{2B} receptor by norfenfluramine may trigger the development of drug-induced heart disease (Ayme-Dietrich et al., 2012).

5-HT_{2B} and 5-HT_{2A} receptor transcripts are reported to be present in heart valves, while no 5-HT_{2C} receptor transcript is detectable. Preferential stimulation of valvular 5-HT_{2B} receptors (with or without accompanying 5-HT_{2A} receptor activation) may contribute to valvular fibroplasia in humans (Fitzgerald et al., 2000). Mitral valve regurgitation has been associated with increased mRNA expression of valvular 5-HT_{2B} receptors and SERT in pigs (Cremer et al., 2015b). Canine myxomatous mitral valve disease (MMVD) was associated with higher expression of 5-HT_{2B} receptors in mitral valve (Cremer et al., 2015a).

These findings suggest that 5-HT_{2B} receptor signaling links vascular damage and platelet activation to tissue remodeling and identify the 5-HT_{2B} receptor as a novel potential therapeutic target to treat valvular heart diseases. As a result of these investigations, the development of 5-HT_{2B} receptor agonists have been banned by the FDA.

VIII. J. 13. Acute Pain

5-HT released from mast cells or platelets in peripheral tissues is an important inflammatory mediator of pain. The involvement of 5-HT in pain is complex because it can inhibit or facilitate nociceptive transmission, due to the presence of multiple functionally opposing 5-HT receptors on peripheral and central nociceptors. An acute injection of 5-HT or the 5-HT₂ receptor, agonist α -methyl-5-HT, into hindpaws of mice induces significant hyperalgesia to mechanical stimuli, which can be inhibited by the 5-HT_{2B/2C} receptor antagonist, SB206553, which also blocks 5-HT-induced transient [Ca²⁺] signaling in DRG neurons. 5-HT_{2B} receptors are involved in mechanical hyperalgesia in mice (Lin et al., 2011). 5-HT released from descending pain modulation pathways to the dorsal horn is crucial in spinal nociception processing. Local peripheral ipsilateral, but not contralateral, administration of RS127445 significantly prevents formalin-induced flinching behavior. Moreover, local peripheral ipsilateral, but not contralateral, administration of the 5-HT₂ receptor agonist, DOI, augmented formalin-induced nociception. The local pronociceptive effect of DOI is prevented by local RS127445. Moreover, intrathecal RS127445 also prevented formalin-induced nociception. By contrast, spinal DOI increases flinching behavior induced by formalin. The spinal pronociceptive effect of DOI is prevented by intrathecal RS127445 (Cervantes-Durán et al., 2012). It is therefore evident that 5-HT_{2B} receptors play a pronociceptive role in peripheral as well as spinal sites in the rat formalin test.

VIII. J. 14. Chronic pain

In rats subjected to spinal nerve ligation, the 5-HT_{2B} receptor agonist, BW723C86, enhances evoked potentials, whereas the 5-HT_{2B} receptor antagonist SB204741 depresses them. Spinal hyperexcitation promoted by 5-HT_{2B} receptors has been proposed as a pathogenic pathway contributing to pain (Aira et al., 2010). Plasticity of spinal serotonergic neurotransmission selectively reduces spinal μ -opioid receptor mechanisms via increased expression of 5-HT_{2B} receptors in dorsal horn neurons also expressing the μ -opioid receptor (Aira et al., 2012). The involvement of glutamate receptors in dorsal neuron hyperexcitation can also be promoted by 5-HT_{2B} receptor after spinal nerve ligation. Augmentation of C-fiber-evoked potentials by spinal superfusion with the 5-HT_{2B} receptor agonist, BW723C86, in nerve-ligated rats is impeded by co-administration of NMDA receptor antagonist. Evoked potentials are increased by NMDA receptor agonist in nerve-injured rats, irrespective of simultaneous 5-HT_{2B} receptor blockade by SB204741. In uninjured rats, NMDA receptor agonist enhances evoked potentials in the presence of BW723C86, but not if administered alone. Blockade of 5-HT_{2B} receptors with the selective antagonist, SB204741, after spinal nerve ligation bilaterally decreases phosphorylation of the

NMDA receptor subunit, NR1 (pNR1), in the synaptic fraction, and co-localization of both PKC γ and pNR1 with postsynaptic marker PSD-95. Delivery of SB204741 bilaterally attenuates thermal and mechanical allodynia occurring after spinal nerve ligation, at early time period, day 2 post injury. The transient activation of the PKC γ /NMDA receptor pathway is critically involved in 5-HT_{2B} receptor-mediated facilitation in the spinal nerve ligation model (Aira et al., 2013). The adaptor protein NADH dehydrogenase subunit 2 (ND2) is involved in NR1-phosphorylation and spinal hyperexcitability secondary to peripheral nerve injury. Spinal nerve ligation is followed by increased co-localization of ND2 with pNR1. C fiber-evoked dorsal horn field potentials are increased after spinal nerve ligation by superfusion with an NMDA receptor agonist. This increased postsynaptic up-regulation of ND2/pNR1 can be prevented by prior administration of selective 5-HT_{2B} antagonist, SB204741 (Aira et al., 2014). Thus, NMDA receptor phosphorylation is instrumental in coupling 5-HT_{2B} receptor-mediated input to NMDA receptor expressing synapses in spinal hyperexcitation involved in pain.

VIII. J. 15. Neuropathic pain

5-HT has also implicated in a rat model of neuropathic pain evoked by chronic constriction injury (CCI) of the sciatic nerve. 5-HT_{2B} receptor activation has been reported to both prevent and reduce CCI-induced allodynia at 3 weeks post-injury. Intrathecal administration of the 5-HT_{2B} receptor agonist, BW723C86, attenuated established mechanical and cold allodynia, an effect prevented by co-injection of RS127445. A single application of BW723C86 on the sciatic nerve concomitantly to CCI dose-dependently prevented mechanical allodynia and reduced cold allodynia 17 days after CCI. This behavioral effect is accompanied with a marked decrease in macrophage infiltration into the sciatic nerve and, in the DRG, with an attenuated abnormal expression of several markers associated with local neuroinflammation and neuropathic pain. CCI results in a marked upregulation of 5-HT_{2B} receptor expression in sciatic nerve and DRG. In the latter structure, it is biphasic, consisting of a transient early increase 2 days after surgery (around 23-fold) before neuropathic pain emergence, followed by a steady (around 5-fold) increase, that remains relatively constant until the pain disappeared. In DRG and sciatic nerve, 5-HT_{2B} receptors are immunolocalized on sensory neurons and infiltrating macrophages (Urtikova et al., 2012).

It thus appears that 5-HT_{2B} receptor involvement in pain takes place at various sites and time periods, early events being more pronociceptive while at later stages this receptor contribution may be more antinociceptive, although this varies according to the animal models.

VIII. J. 16. Spasticity in amyotrophic lateral sclerosis

Spinal cord injury leads to an initial phase of hyporeflexia followed by hyperreflexia, often referred to as spasticity. Spasticity is a common and disabling symptom also observed in patients with amyotrophic lateral sclerosis, a disease that can affect both upper and lower motor neurons. A rat tail-spasticity model with a caudal spinal transection demonstrates 5-HT_{2B} receptor downregulation at 21 days post-injury (Wienecke et al., 2010). Motoneurons, which recover from denervation, function autonomously exhibiting large persistent calcium currents that help with functional recovery and contribute to uncontrolled muscle spasms. Application of agonists relatively selective to 5-HT_{2B} receptors (including BW723C86) increase persistent calcium currents. 5-HT_{2B} receptors on motoneurons ultimately contribute to recovery of motoneuron function and emergence of spasms (Murray et al., 2011). In amyotrophic lateral sclerosis, spasticity is traditionally thought to be the result of degeneration of the upper motor neurons in the cerebral cortex, although degeneration of other neuronal types, in particular 5-HT neurons, might also underlie the spasticity. In SOD1 (G86R) mice, a transgenic model of amyotrophic lateral sclerosis, 5-HT levels are decreased in brainstem and spinal cord before onset of motor symptoms. Furthermore, there is noticeable atrophy of 5-HT neuronal cell bodies along with neuritic degeneration at disease onset. In SOD1 (G86R) mice, tail muscle spastic-like contractions occur at end-stage. Importantly, they are abolished by the 5-HT_{2B/2C} receptors inverse agonist, SB206553. In keeping with this, 5-HT_{2B} receptor expression is strongly increased at disease onset (Dentel et al., 2013). In summary, 5-HT_{2B} receptors on motoneurons can become constitutively active after injury and ultimately contribute to some recovery of motoneuron function and emergence of spasms.

VIII. J. 17. Migraine

A role for 5-HT in migraine is supported by changes in circulating levels of 5-HT and its metabolites during the phases of a migraine attack. A migraine headache is thought to be transmitted by the trigeminal nerve from the meninges and their associated blood vessels. Correlation of the receptor affinities with the potencies of drugs used in migraine prophylaxis demonstrates correlations with the 5-HT_{2B} receptor and various human

meningeal tissues express 5-HT_{2B} mRNAs (Schmuck et al., 1996). The 5-HT_{2B} receptor can activate the release of the smooth muscle relaxant NO and induce relaxation of the cerebral arteries and the jugular vein. 5-HT_{2B} receptors expressed by endothelial cells of meningeal blood vessels may trigger migraine headache through the formation of NO, which results in the dilation of cerebral blood vessels and the concomitant activation of sensory trigeminovascular afferents, thus initiating the manifestation of head pain (Johnson et al., 2003). In addition, a genetic study identified 5-HT_{2B} receptors as a susceptibility gene to migraine (Corominas et al., 2010). Endothelial 5-HT_{2B} receptors may thus trigger dilation of meningeal blood vessels, which by activating sensory trigeminovascular afferents induces head pain.

VIII. J. 18. Visceral pain

5-HT_{2B} receptors are involved in signaling from the colon in rats in which there is visceral hypersensitivity. Oral administration of RS127445, inhibits visceral hypersensitivity provoked by restraint stress without significant effect on the visceral nociceptive threshold of naïve rats (Ohashi-Doi et al., 2009). Moreover, when administered intracerebroventricularly, RS127445 also decreases the number of pain behaviors during noxious colorectal distension. A selective 5-HT_{2B} receptor antagonist has thus been proposed to have therapeutic potential for the treatment of gut disorders characterized by visceral hypersensitivity (O'Mahony et al., 2010). The 5-HT_{2B} receptor appears thus to be involved in regulating sensory pathways but only under hyperalgesic conditions, suggesting the possible utility of 5-HT_{2B} receptor antagonism in reducing visceral hypersensitivity in patients with irritable bowel syndrome and other hypersensitivity conditions.

VIII. J. 19. Bones

5-HT_{2B} receptor mRNA, which is undetectable in anaplastic osteoblasts, appears in differentiated and matured osteoblasts (Bliziotis et al., 2001; Westbroek et al., 2001). The differentiation and maturation of osteoblasts might thus be regulated by 5-HT_{2B} receptor activation (Hirai et al., 2009). Of interest, *Htr_{2B}^{-/-}* female mice display reduced bone density from the age of 4 months and intensifies by 12 and 18 months. This histomorphometrically confirms that osteopenia is due to reduced bone formation (Collet et al., 2008). Using the osteoprogenitor cell line C1, blockade of 5-HT_{2B} receptor intrinsic activity affects the efficiency of mineralization by decreasing calcium incorporation. Optimal bone matrix

mineralization involves both NO and PLA2 signaling pathways and the 5-HT_{2B} receptor promotes prostaglandin E2 production through cyclooxygenase (COX) activation. When C1 osteoblasts undergo conversion into osteocyte-like cells, COX activity is quenched. The 5-HT_{2B} receptor contributes in an autocrine manner to osteogenic differentiation (Locker et al., 2006). There is a functional link between the 5-HT_{2B} receptor and the activity of the tissue nonspecific alkaline phosphatase (TNAP). Agonist stimulation of the receptor increases TNAP activity during the initial mineralization phase, whereas inhibition of 5-HT_{2B} receptor intrinsic activity prevents TNAP activation. In contrast, agonist stimulation of the receptor further increased TNAP activity during the initial mineralization phase. The 5-HT_{2B} receptor couples to PLA2 pathway and prostaglandin production at the beginning of mineral deposition. The 5-HT_{2B} receptor also controls leukotriene synthesis *via* PLA2 at the terminal stages of differentiation. These two 5-HT_{2B} receptor-dependent eicosanoid productions delineate distinct time-windows of TNAP regulation during the osteogenic program. Finally, prostaglandins or leukotrienes relay the post-translational activation of TNAP via stimulation of the phosphatidylinositol-specific phospholipase C. In agreement with this, primary calvarial osteoblasts from *Htr_{2B}^{-/-}* mice exhibit defects in TNAP activity (Baudry et al., 2010). Brain 5-HT may favor indirectly bone mass accrual following activation of 5-HT_{2C} receptors on ventromedial hypothalamic neurons and 5-HT_{2B} receptors on arcuate neurons (Yadav et al., 2009). Compared to control osteoblasts, the lack of 5-HT_{2B} receptors is associated with a 10-fold over-production of prostacyclin (PGI₂) and the specific prostacyclin synthase inhibitor (U51605) rescues totally osteoblast aggregation and matrix mineralization in *Htr_{2B}^{-/-}* osteoblasts without effect on WT osteoblasts. Prostacyclin is the endogenous ligand of PPAR- β/δ , and its inhibition in *Htr_{2B}^{-/-}* cells totally rescues the alkaline phosphatase and osteopontin mRNA levels, cell-cell adhesion, and matrix mineralization. The absence of 5-HT_{2B} receptors leads to the overproduction of prostacyclin, inducing reduced osteoblast differentiation due to PPAR- β/δ - dependent target regulation and defective cell-cell adhesion and matrix mineralization (Chabbi-Achengli et al., 2013). Of relevance, the 5-HT_{2A} receptor is expressed only in osteoblasts, whereas 5-HT_{2B} receptor expression increases from precursor to mature osteoclasts (Hodge et al., 2013). The 5-HT_{2B} receptor therefore appears to contribute in an autocrine manner to osteogenic differentiation.

VIII. J. 20. Teeth development

Periodontal diseases occur in patients treated with antidepressants such as SSRIs (e.g. fluoxetine). In the molar teeth of *Htr_{2B}^{-/-}* mice, rod curvatures and twisting are altered compared to WT mice, suggesting involvement of the 5-HT_{2B} receptor at early stages of enamel formation. The volume of the enamel layer in *Htr_{2B}^{-/-}* mice is also reduced, with smaller crystallite thickness. The outer aprismatic enamel border is 1.5- to 2-fold larger in *Htr_{2B}^{-/-}* compared to WT mice. Finally, although no noticeable difference is observed in dentin, the micro-CT three-dimensional pulp reconstruction reveals a decrease in both length and width of dentin formation in the root canals of the *Htr_{2B}^{-/-}* mice (Dimitrova-Nakov et al., 2014). Therefore, 5-HT_{2B} receptors may mediate some harmful of the effects of long-term use of SSRIs on bone and teeth regeneration.

VIII. J. 21. Cancers

VIII. J. 21. a. Carcinoid tumors

5-HT_{2B} receptor expression is observed in spontaneous human carcinoid tumors, along with coupling to p21^{ras} activation (Launay et al., 1996). The tumor proliferative activity of small intestinal neuroendocrine tumors (including cell growth and the development of desmoplasia) is associated with the particular microenvironment in the peritoneum and tumor cells support this necessary milieu through the secretion of profibrotic/angiogenic factors (Svejda et al., 2010).

VIII. J. 21. b. Breast tumors

Increased 5-HT biosynthetic capacity accompanied by multiple changes in 5-HT receptor expression and signaling favor malignant progression of human breast cancer cells. Among them, expression of 5-HT_{2B} receptors is increased (Pai et al., 2009). 5-HT_{2B} receptor mRNA expression is lower in basal estrogen receptor (ER) negative tumors, compared with luminal tumors, which are most commonly ER positive. 5-HT_{2B} receptor mRNA is elevated in carcinomas, and increased with tumor stage, and higher in lymph node-positive tumors as compared to node-negative tumors. c-Myc transformation induces an increase in 5-HT_{2B} receptor expression (Pai et al., 2009). In human breast cancer, there is a significant correlation of 5-HT_{2B} receptor expression with estrogen receptor- α (ER- α) expression (Kopparapu et al., 2013).

VIII. J. 21. c. Melanoma

Uveal (ocular) melanoma is an aggressive cancer that often forms undetectable micrometastases before diagnosis of the primary tumor. High increases in 5-HT_{2B} receptor mRNA are evident in all uveal melanomas with monosomy 3 compared with low expression in all tumors with disomy 3. As monosomy 3 is associated with metastatic disease, 5-HT_{2B} receptor expression has been proposed as a marker to identify patients with poor prognosis (Tschentscher et al., 2003). The 5-HT_{2B} receptor gene is among the genes showing the highest overexpression in class 2 uveal melanoma (van Gils et al., 2008). A PCR-based 15-gene assay comprising 12 discriminating genes including the 5-HT_{2B} receptor gene is now part of a prognostic assay, which provides an important addition to help manage patients with uveal melanoma (Onken et al., 2010) by distinguishing whether uveal melanomas contain liver metastases and thus aid in the diagnosis and prevention of uveal melanoma liver metastases, based on their different features (Zhang et al., 2014).

VIII. J. 21. d. Prostate cancer

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men. Despite this fact, many of the genetic changes that coincide with prostate cancer progression remain enigmatic. The 5-HT_{2B} receptor has been shown to be upregulated in tumors (Magee et al., 2001). Overexpression of receptors to neuroendocrine cell products may contribute to development of hormone-refractory prostate cancer. Immunostaining for the 5-HT_{2B} receptor is evident in low-grade and high-grade tumors, prostatic intra-epithelial neoplastic and benign prostatic hyperplasia cells, and in vascular endothelial cells. Antagonists for the 5-HT_{2B} receptor inhibit proliferation of prostate cancer cells in a dose-dependent manner (Dizeyi et al., 2005).

VIII. J. 21. e. Adrenocortical carcinoma

Gene expression profiles of adrenocortical tumors demonstrate underexpression of 5-HT_{2B} receptor mRNA as a marker of malignant adrenocortical carcinoma (Fernandez-Ranvier et al., 2008). Analysis of biomarkers of malignancy of adrenocortical cancers in a meta-analysis suggests the combination of overexpressed anillin (*ANLN*) and underexpressed 5-HT_{2B} receptor mRNA to be the best predictor of malignancy (Zsippai et al., 2011). However, in adrenocorticotropin-dependent adrenal hyperplasias, the mechanisms responsible for the ectopic adrenal expression of glucose-

dependent insulinotropic peptide (GIP) receptor (*GIPR*) in GIP-dependent Cushing's syndrome are unknown. Chronic adrenal stimulation by GIP in GIP-dependent ACTH-independent macronodular adrenal hyperplasia leads to the significant induction of genes for the GPR54, 5-HT_{2B}, GPR4, and endothelial differentiation sphingolipid EDG8 receptor (Lampron et al., 2006).

VIII. J. 21. f. Hepatocellular carcinoma

Among 64 genes for which mRNA expression differed between non-hepatitis B, non-hepatitis C compared to hepatitis C-type hepatocellular carcinoma (HCC), the most affected is gene for the 5-HT_{2B} receptor (Iizuka et al., 2004). The function of 5-HT as a survival factor of HCC cells has been demonstrated: activation of the 5-HT_{2B} receptor leads to sustained phosphorylation of two downstream targets of mTOR, p70S6K and 4E-BP1, thereby facilitating survival and inhibiting autophagy. Inhibiting the 5-HT_{2B} receptor reduces cancer cell growth *in-vitro* and *in-vivo*. The presence of 5-HT_{2B} receptors in HCC and the activation of autophagy-related mechanisms provide novel insights of 5-HT in cancer biology and propose 5-HT-mediated signaling as a therapeutic target (Soll et al., 2010). 5-HT_{1B} and 5-HT_{2B} receptors are expressed, respectively, in around 32% and 35% of the patients with hepatocellular cancer. Both receptors are associated with an increased proliferation index (Soll et al., 2012). The 5-HT_{2B} receptor mediates 5-HT-induced proliferation in the serum-deprived HCC Huh7 cells. Additionally, selective 5-HT_{2B} receptor antagonism using SB204741 in Huh7 cells decreases the expression of FOXO3a (Liang et al., 2013).

VIII. J. 21. g. T-cell Leukemia

A proteasome inhibitor, bortezomib, is a potential therapeutic agent to treat adult T-cell leukemia (ATL). A network including the 5-HT_{2B} receptor was identified that converges upon the secreted protein acidic and rich in cysteine (*SPARC*) gene, a tumor-invasiveness related gene, which may act as a modulator of bortezomib-induced cell death in ATL cells (Ohyashiki et al., 2008).

VIII. J. 21. h. Myosarcoma

In the pathogenesis of uterine leiomyosarcoma, there is a fourfold overexpression of the 5-HT_{2B} receptor gene and is one of the most overexpressed genes (Arslan et al., 2005; Matsumura et al., 2006).

VIII. J. 21. i. Tumor angiogenesis

5-HT does not enhance colon cancer tumor cell proliferation but may act as a regulator of angiogenesis by reducing the expression of MMP-12, and lower levels of angiostatin—an endogenous inhibitor of angiogenesis (Nocito et al., 2008). 5-HT stimulates the phosphorylation of ERK1/2 in bovine endothelial cells, and the 5-HT_{2B} receptor plays a role in the activation of eNOS in human endothelial cells. In SB204741-treated mice, the selective blockade of the 5-HT_{2B} receptor results in the reduction of tumor angiogenesis and growth through the inhibition effect of ERK1/2 and eNOS (Asada et al., 2009). Therefore, the 5-HT_{2B} receptor may participate in tumor angiogenesis.

VIII. J. 22. Clinically relevant knowledge gained from the gene

VIII. J. 22. a. The human 5-HT_{2B} receptor gene

The human 5-HT_{2B} receptor gene (MIM 601122) is located on chromosome 2q37.1 (Le Coniat et al., 1996). The human 5-HT_{2B} receptor gene rate of evolution displays high conservation in primates (Andrés et al., 2007). Within the 23 sites that are highly conserved among primates and that have changed on the modern human lineage after separation from Denisovan ancestors, one (D216N) is found in ECL2 of the 5-HT_{2B} receptor, suggesting that crucial aspects of synaptic transmission involving the receptor may have changed in modern humans (Meyer et al., 2012). There is evidence of the contribution of 5-HT_{2B} receptor gene variants to intelligence quotation, intellectual disability and language onset delay in autism spectrum disorders (ASD) patients (Hervas et al., 2014).

The 5-HT_{2B} receptor gene was identified as a susceptibility gene for impulsivity disorders: one single nucleotide polymorphism (SNP) introducing a stop codon after amino-acid 21 (Q21*) was found more frequently in severely impulsive individuals, presenting suicidal behavior (Bevilacqua et al., 2010). In the same cohort, early-onset schizophrenia was more prevalent in 5-HT_{2B} receptor gene Q*20 carriers. Other work testing SNPs within the

5-HT_{2B} receptor gene for potential associations with the behavioral inhibition system (BIS) and the three components of the behavioral approach systems (BAS: fun seeking, drive, and reward responsiveness) in a Han Chinese sample found four 5-HT_{2B} receptor gene SNPs significantly associated with BAS fun seeking (Zhu et al., 2012).

Several SNPs confer a double-mutant R6G/E42G of the receptor protein associate with drug abuse, suggesting that 5-HT_{2B} receptor contributes to pathways that are involved in drug dependence (Lin et al., 2004). Peripheral blood DNA methylation levels of CpGs in the promoter regions were examined in African Americans and European Americans. In European Americans, 6 CpGs in the 5-HT_{2B} receptor gene promoter are significantly hypermethylated in Alcohol-Dependent cases (Zhang et al., 2013).

An association study on susceptibility to migraine in a Spanish population supports the involvement of the 5-HT_{2B} receptor gene and the MAO_A gene in the genetic predisposition to migraine without aura (Corominas et al., 2010). Finally, by investigating the 5-HT_{2B} receptor gene in patients who developed pulmonary hypertension after use of fenfluramine, a heterozygous mutation was identified in one female patient who five years earlier had followed a nine month anorexigen treatment (Blanpain et al., 2003). This heterozygous mutation R393X in the 5-HT_{2B} receptor generates a carboxy terminus-truncated receptor characterized by a switch of coupling from G α _q/11 to G α ₁₃, reduced nitric oxide synthase (NOS) activation and an increase in cell proliferation, modifications relevant to pathophysiological vasoconstriction (Deraet et al., 2005).

IX. 5-HT_{2C} receptor

IX. A. Introduction

The 5-HT_{2C} receptor is a G protein-coupled receptor (GPCR) with the characteristic seven-transmembrane domain structure with an extracellular N-terminus and intracellular C-terminus. Binding of 5-HT to the 5-HT_{2C} receptor results in a conformational change that catalyzes the diffusion of multiple second messenger effectors. The canonical G protein-dependent signaling through the 5-HT_{2C} receptor is engendered by 5-HT-stimulated coupling predominantly to G $\alpha_{q/11}$ to activate the enzyme phospholipase C (PLC) which generates phosphoinositide hydrolysis and intracellular calcium (Ca_i²⁺) mobilization (Conn and Sanders-Bush, 1986a; Hoyer et al., 1989; Chang et al., 2000). The 5-HT_{2C} receptor also signals through other second messengers which can include phospholipase D (PLD) and phospholipase A₂ (PLA₂), cyclic nucleotides, and extracellular signal-regulated kinases (Berg et al., 1994; Kaufman et al., 1995; Berg et al., 1998b; Werry et al., 2005). Landmarks in the progress of 5-HT_{2C} receptor research are illustrated in Figure 12.

The gene for the human 5-HT_{2C} receptor (*HTR2C*) was cloned and localized to the X chromosome (Xq24) in the early 1990s (Milatovich et al., 1992; Stam et al., 1994; Xie et al., 1996; Yu et al., 1991). The genomic DNA for the 5-HT_{2C} receptor is divided into six exons with five introns (Xie et al., 1996), while the coding region contains four exons with three introns (Stam et al., 1994). The gene encodes a 458 amino acid protein in humans and 460 amino acid protein in rats, which share 90% amino acid homology (Saltzman et al., 1991). The 5-HT_{2C} receptor is the only GPCR known to undergo RNA editing, resulting in the functional expression of multiple isoforms of the receptor that differ in their distribution, pharmacology and signaling capabilities.

The 5-HT_{2C} receptor was first identified in choroid plexus tissue by receptor autoradiography as a highly expressed binding site with high affinity for radioligands that bind to the 5-HT₁ receptor family (Pazos et al., 1984; Yagaloff and Hartig, 1985). This binding site displayed a different pharmacological profile from the known 5-HT_{1A} receptor and 5-HT_{1B} receptor and thus was originally named 5-HT_{1C} receptor. It was cloned by

functional expression of choroid plexus RNA injected into *Xenopus* oocytes (Lubbert et al., 1987; Julius et al., 1988). The genomic organization of the 5-HT_{1C} receptor (with the presence of introns), a 50% overall homology to the 5-HT_{2A} receptor, and similar signal transduction mechanisms as 5-HT_{2A} receptor and 5-HT_{2B} receptor, indicated that the 5-HT_{1C} receptor was more similar to members of the 5-HT₂ receptor family than the intronless, adenylyl cyclase-coupled members of the 5-HT₁ receptor family. Therefore, the 5-HT_{1C} receptor was reclassified as a member of the 5-HT₂ receptor family and renamed 5-HT_{2C} receptor (Hoyer et al., 1994).

Early autoradiography studies reported a predominant localization of this receptor in choroid plexus tissue, while subsequent *in situ* hybridization studies revealed a widespread distribution throughout the basal ganglia, limbic system and prefrontal cortex (Hoyer et al., 1986; Hoffman and Mezey, 1989; Molineaux et al., 1989; Mengod et al., 1990; Figure 13). In fact, 5-HT_{2C} receptor mRNA has been reported to be more abundant and widespread throughout the central nervous system (CNS) than mRNA of the closely related 5-HT_{2A} receptor (Pompeiano et al., 1994; Wright et al., 1995). Thus, the 5-HT_{2C} receptor, largely thought of as “the choroid plexus receptor”, is actually well positioned throughout the CNS to mediate many of the central actions of 5-HT including regulation of appetite, cognition, mood, movement, and sleep (for reviews) (Berg et al., 2008a; Di Giovanni et al., 2010). The 5-HT_{2C} receptor has been implicated in addiction, anxiety, depression, epilepsy, schizophrenia, and obesity. Therefore, the 5-HT_{2C} receptor is a therapeutic target of great interest (for reviews see Bubar and Cunningham, 2006; Howell and Cunningham, 2015; Sullivan et al., 2015; Di Giovanni and De Deurwaerdere, 2016).

IX. B. Expression profile

The 5-HT_{2C} receptor mRNA is differentially overexpressed in neurons relative to astrocytes and oligodendrocytes in the postnatal mouse forebrain (Cahoy et al., 2008). Regional analyses indicate that the 5-HT_{2C} receptor mRNA is present in high levels in the choroid plexus, hippocampus, and the subthalamic and lateral habenular nuclei (Hoffman and Mezey, 1989; Molineaux et al., 1989; Mengod et al., 1990). Brain regions with moderate to high levels of 5-HT_{2C} receptor mRNA include the amygdala, nuclei of the basal ganglia [nucleus accumbens (NAc), striatum, ventral tegmental area (VTA), substantia nigra, internal globus pallidus], cortex, hypothalamus, dorsal raphe, brain stem and spinal cord (Hoffman and Mezey, 1989;

Molineaux et al., 1989; Mengod et al., 1990). The 5-HT_{2C} receptor mRNA is found in regions containing the major dopaminergic cell bodies including the substantia nigra (SN) and the ventral tegmental area (VTA) (Mengod et al., 1990; Pompeiano et al., 1994; Eberle-Wang et al., 1997; Bubar and Cunningham, 2007; Bubar et al., 2011), cholinergic cell bodies (Lopez-Gimenez et al., 2001) as well as in enkephalin, substance P and dynorphin containing neuropeptidergic neurons in the dorsal and ventral striatum (Ward and Dorsa, 1996), and in neuropeptide Y containing neurons in the lateral and basolateral amygdala (Bonn et al., 2013). The 5-HT_{2C} receptor mRNA is not present in neurons expressing 5-HT transporter (SERT) mRNA in the raphe nuclei, but is localized to γ -aminobutyric acid (GABA) interneurons in this region (Serrats et al., 2005).

There is good agreement between mRNA and protein distribution in the majority of brain regions, suggesting that the 5-HT_{2C} receptor is predominantly localized in somatodendritic compartments (Mengod et al., 1990; Abramowski et al., 1995; Abramowski and Staufenbiel, 1995; Eberle-Wang et al., 1997; Clemett et al., 2000; Anastasio et al., 2010). The exceptions are the subthalamic nucleus in which 5-HT_{2C} receptor mRNA expression is high while its protein levels are low, and the external globus pallidus where the 5-HT_{2C} receptor is present but 5-HT_{2C} receptor mRNA is absent.

Early radioligand binding studies suggested that the 5-HT_{2C} receptor is located on the apical surface of epithelial cells in the choroid plexus (Hartig et al., 1990). More recently, confocal microscopy and fluorescence correlation spectroscopy were used to directly visualize native 5-HT_{2C} receptor and reveal their expression as homodimers on the apical surface of choroid epithelial cells (Herrick-Davis et al., 2015).

The 5-HT_{2C} receptor is widely distributed throughout the basal ganglia and limbic-cortico-striatal circuit. The 5-HT_{2C} receptor is located postsynaptic to serotonergic neurons on GABAergic, glutamatergic, dopaminergic, neuropeptidergic, and cholinergic neurons. For example, the 5-HT_{2C} receptor is expressed on GABAergic interneurons in the raphe nuclei (Serrats et al., 2005) and on GABAergic projection neurons in the NAc and striatum (Alex and Pehek, 2007). They are also found on GABAergic neurons in the substantia nigra (Eberle-Wang et al., 1997; Invernizzi et al., 2007) and VTA (Di Giovanni et al., 2001; Bubar and Cunningham, 2007; Bubar et al., 2011). Since the 5-HT_{2C} receptor stimulates IP turnover (Conn and Sanders-Bush,

1986a; Hoyer et al., 1989; Chang et al., 2000) and increases Ca_i^{2+} levels resulting in membrane depolarization and neuronal firing (Stanford et al., 2005), activation of the 5-HT_{2C} receptor on GABAergic neurons would be expected to increase the firing of these neurons which have an inhibitory influence in that region. For example, stimulation of the 5-HT_{2C} receptor in the VTA increases the firing rate of GABAergic interneurons resulting in a decreased firing rate of dopaminergic neurons (Prisco et al., 1994; Di Giovanni et al., 2001). Conversely, 5-HT_{2C} receptor antagonism has been reported to increase dopaminergic neurotransmission and dopamine levels in the NAc and prefrontal cortex (Di Giovanni et al., 1999; Di Matteo et al., 1999; Gobert et al., 2000). However, the story is likely to be more complicated as the 5-HT_{2C} receptor has also been shown to be expressed on a subset of dopaminergic neurons in the VTA, with higher expression in the middle relative to the rostral and caudal regions (Bubar and Cunningham, 2007; Bubar et al., 2011). These findings suggest the possibility that activation of the 5-HT_{2C} receptor may directly enhance dopamine neurotransmission within specific subnuclei of the VTA in a region-specific manner.

5-HT neurons from the raphe terminate in layers V and VI of the medial prefrontal cortex, adjacent to GABAergic interneurons that express the 5-HT_{2C} receptor (Liu et al., 2007; Nocjar et al., 2015). In turn, the GABAergic interneurons terminate on pyramidal efferents (likely glutamatergic), which may also express the 5-HT_{2C} receptor (Vysokanov et al., 1998; Carr et al., 2002; Liu et al., 2007; Nocjar et al., 2015). In the prefrontal cortex, the 5-HT_{2C} receptor associates with PSD-95 in postsynaptic densities (Anastasio et al., 2010) and co-localize with the 5-HT_{2A} receptor on GABAergic interneurons (Nocjar et al., 2015). In the hypothalamus, the 5-HT_{2C} receptor is expressed on pro-opiomelanocortin (POMC) neurons in the arcuate nucleus where they stimulate the release of the anorectic peptide alpha-melanocyte stimulating hormone (Heisler et al., 2002).

Previous studies provide little evidence that the 5-HT_{2C} receptor is expressed outside the CNS. However, portions of the *HTR2C* gene are expressed outside the CNS. Exons I and II of the *HTR2C* gene are located in the 5' untranslated region and the translational start site for the 5-HT_{2C} receptor protein is located in the middle of exon III (Xie et al., 1996). Exons I-III of the *HTR2C* gene have been reported to be expressed in non-neuronal cells, along with four different microRNAs (miRNA) generated from intron II (Zhang et al., 2013b). Expression of these miRNAs is regulated by the small nucleolar RNAs (SNORD) SNORD 115/MBII-52 and SNORD 116/MBII-85. Patients with Prader-Willi syndrome lack MBII-52 and MBII-

85 and express different levels of the 5-HT_{2C} receptor miRNAs than control subjects (Zhang et al., 2013b). While the function of these miRNAs is not fully understood, it is possible that their dysregulation may contribute to the Prader-Willi syndrome phenotype as explored in 5-HT_{2C} receptor transgenic mouse models.

Since the 5-HT_{2C} receptor mRNA in human brain includes exons I-VI and the mRNA found outside the CNS contains exons I-III, it was hypothesized that a transcriptional termination signal prior to exon IV may be employed in non-neuronal cells outside the CNS (Zhang et al., 2013b). In contrast, a 185 base-pair fragment of 5-HT_{2C} receptor mRNA was identified by quantitative RT-PCR from rat adipocyte visceral tissue (Stunes et al., 2011). The expression level of the 5-HT_{2C} receptor mRNA was only 5% of the expression level of the β -actin housekeeping gene control, and Western blots revealed that 5-HT_{2C} receptor expression in undifferentiated adipocytes was negligible compared to expression in rat brain (Stunes et al., 2011). However, expression of 5-HT_{2C} receptor mRNA and protein expression could be induced in cultured adipocytes. In addition, low levels of 5-HT_{2C} receptor mRNA and protein have been reported in rat pancreatic islet cells (Zhang et al., 2013a). Further research is required to elucidate the physiological role of the 5-HT_{2C} receptor in the function of adipocytes (Stunes et al., 2011) and potentially pancreatic β -cells (Zhang et al., 2013a).

IX. C. Post-transcriptional and post-translational modifications

IX. C. 1. RNA editing

The 5-HT_{2C} receptor is the only GPCR reported to undergo RNA editing. The 5-HT_{2C} receptor pre-mRNA is unique in containing a region of exonic and intronic sequence complementarity between the distal half of exon V and the beginning of intron V (Burns et al., 1997). This results in base pairing between the exonic and intronic sequences, giving the pre-mRNA a double-stranded, stem loop structure. The secondary structure of the 5-HT_{2C} receptor pre-mRNA influences the pattern of editing (Fukuda et al., 2015) as well as splicing (Shen et al., 2013). The double-stranded RNA is a substrate for adenosine deaminases that act on RNA, RNA-specific adenosine deaminase (ADAR) ADAR1 and ADAR2 (Burns et al., 1997; Liu et al., 1999). These enzymes catalyze the deamination of adenosine to inosine, which is read as guanosine when the RNA is translated into protein. Adenosine to inosine RNA editing can occur at up to five different locations (termed A-E) within exon V (Burns et al., 1997; Fitzgerald et al., 1999;

Niswender et al., 1999; Wang et al., 2000) and one site located in intron V (Flomen et al., 2004). The editing sites in exon V are located in the second intracellular loop of the receptor in close proximity to the highly conserved “DRY” motif at the base of transmembrane domain III. The resulting adenosine to guanosine conversions change the coding potential of amino acids I156, N158 and I160 from INI (isoleucine, asparagine, isoleucine) in the unedited isoform to VSV (valine, serine, valine) or VGV (valine, glycine, valine) in the fully edited isoforms.

The RNA editing of the *HTR2C* gene can produce up to 32 different 5-HT_{2C} receptor pre-mRNAs encoding 24 different proteins. There are seven predominant 5-HT_{2C} receptor isoforms that are expressed in a region-specific manner in human and rodent brain (Burns et al., 1997; Fitzgerald et al., 1999; Niswender et al., 1999; Wang et al., 2000; Dracheva et al., 2009; Abbas et al., 2010; Morabito et al., 2010b). The more highly edited isoforms are the predominant isoforms expressed in whole brain with VSV and VNV being the most prominent. Regions such as the hypothalamus, hippocampus, striatum and cortex predominantly express the edited VNV, VSV and VSI isoforms, while the choroid plexus and cerebellum express significantly higher levels of the unedited INI and partially edited INV and ISV isoforms.

Since RNA editing occurs in the second intracellular loop of the receptor, a region known to play an important role in G protein activation, it has profound effects on the pharmacology and signaling capabilities of the 5-HT_{2C} receptor. RNA editing decreases agonist binding affinity and G protein coupling efficiency (Burns et al., 1997; Fitzgerald et al., 1999; Herrick-Davis et al., 1999; Niswender et al., 1999; Wang et al., 2000; Berg et al., 2001). In these studies, the fully edited VSV and VGV isoforms displayed a 5 to 40 fold decrease in 5-HT binding affinity and potency for stimulating phosphoinositide production compared to the unedited INI isoform, and displayed decreased affinity and potency for a variety of different agonists. When expressed in COS-7 cells at levels similar to native 5-HT_{2C} receptor in choroid epithelial cells, the unedited INI isoform displayed high constitutive activity that was successively diminished by RNA editing to very low levels of constitutive activity in the fully edited VSV and VGV isoforms (Herrick-Davis et al., 1999; Niswender et al., 1999). In addition to regulating the level of basal activity, RNA editing alters the specificity of G protein coupling and second messenger activation. For example, the unedited INI isoform can signal through G_q, G₁₃, and G₁₅, but the fully edited VSV and VGV isoforms predominantly couple to and signal through G_q (Price et al., 2001; McGrew et al., 2002; McGrew et al., 2004). The 5-HT_{2C}

receptor has been shown to signal in an agonist-specific manner to differentially regulate phosphoinositide and arachadonic acid production (Berg et al., 1998b) and the phosphorylation of ERK_{1/2} (Werry et al., 2005), effects which are diminished following RNA editing (Berg et al., 2001; Berg et al., 2008b; Werry et al., 2008). In addition to impacting signaling, RNA editing also influences receptor desensitization and trafficking (Marion et al., 2004).

The 5-HT_{2C} receptor pre-mRNA editing is regulated by ADAR1 and ADAR2 (Burns et al., 1997). Both *in vitro* and *in vivo* studies have reported that RNA editing at amino acid 156 of the 5-HT_{2C} receptor is predominantly accomplished by ADAR1, editing at amino acid 160 requires ADAR2, and that both enzymes participate in editing at amino acid 158 (Liu et al., 1999; Wang et al., 2000; Hartner et al., 2004; Wang et al., 2004). ADAR1 and ADAR2 may act in a concerted manner whereby ADAR1 editing at amino acid 156 enhances ADAR2 pre-mRNA binding and subsequent editing at amino acids 160 and 158 (Carmel et al., 2012). In addition, factors that regulate the alternative splicing of the ADAR1 and ADAR2 pre-mRNAs have been reported to influence 5-HT_{2C} receptor RNA editing (Liu et al., 1999; Schmauss et al., 2010). Alterations in ADAR activity or pattern of expression can result in altered 5-HT_{2C} receptor isoform expression. Studies using neuronal cell cultures showed that factors that increase ADAR1 expression, such as treatment with interferon, increase 5-HT_{2C} receptor editing at amino acid 156 (Yang et al., 2004) and that reduced ADAR1 expression abolished editing at amino acid 156 (Sukma et al., 2005). *In vivo* evidence supporting this hypothesis is provided by a recent study reporting a down-regulation in ADAR2 expression following spinal cord injury in rats, which resulted in decreased 5-HT_{2C} receptor RNA editing at amino acid 160 (Di Narzo et al., 2015). Conversely, RNA editing has been reported to be increased in transgenic mice over-expressing ADAR2, which resulted in an increase in the expression of the more fully edited, and a decrease in expression of the unedited, 5-HT_{2C} receptor isoforms (Singh et al., 2011). The results of these studies indicate that alterations in ADAR activity and expression patterns alter the degree and pattern of 5-HT_{2C} receptor editing, resulting in changes in 5-HT_{2C} receptor isoform expression and signal transduction.

IX. C. 2. RNA splicing

Three different variants of the 5-HT_{2C} receptor are produced by RNA splicing, only one of which is expressed on the plasma membrane and is fully functional. The full length, functional 5-HT_{2C} receptor (2Cfl) is generated following splicing at the traditional exon / intron boundaries to remove introns III-V (Xie et al., 1996). There are two alternative donor splice sites flanking the traditional donor splice site located at the exon V / intron V boundary: one located in the middle of exon V (Canton et al., 1996; Xie et al., 1996) and an infrequently used site located within intron V (Wang et al., 2000; Flomen et al., 2004). The splice sites are conserved across rat, mouse and human species. Splicing at either one of the alternative splice sites produces an RNA that encodes a prematurely truncated protein. Use of the donor splice site located in the middle of exon V results in the deletion of the last 95 nucleotides of exon V, including the RNA editing sites, and causes a frame shift mutation with stop codon. The result is a truncated protein (2Ctr) containing the N-terminus and first three transmembrane domains followed by 96 unique amino acids (Canton et al., 1996; Xie et al., 1996; Wang et al., 2000). In human brain tissue, 2Ctr mRNA is found in all brain regions containing 2Cfl mRNA. While Western blots of membrane extracts from 2Ctr-transfected NIH3T3 cells revealed immunoreactive bands the predicted size of 2Ctr protein, radioligand binding and phosphoinositide production were not observed in the transfected cells (Canton et al., 1996; Wang et al., 2000). The 2Ctr protein is not expressed on the plasma membrane, but is retained within the endoplasmic reticulum where the 2Ctr can form heterodimers with 2Cfl (Herrick-Davis and Farrington, 2011; Martin et al., 2013). Thus, one possible function of 2Ctr is to regulate 5-HT_{2C} receptor signaling by forming heterodimers with 2Cfl and trapping 2Cfl in the endoplasmic reticulum (Herrick-Davis and Farrington, 2011; Martin et al., 2013).

Factors that influence splice site selection will impact 5-HT_{2C} receptor function and signaling by altering the relative balance between 2Cfl and 2Ctr within a given brain region. RNA editing, and factors that influence RNA editing such as ADAR1 and ADAR2 activity, have been shown to influence splice site selection (Rueter et al., 1999; Maas et al., 2001; Flomen et al., 2004; Tohda et al., 2004; Dracheva et al., 2008a). Increased editing of the 5-HT_{2C} receptor pre-mRNA, generating the more fully edited and less active isoforms, promotes the use of the traditional donor splice site at the exon V / intron V boundary and favors the generation of 2Cfl over 2Ctr (Flomen et al., 2004). On the other hand, the unedited and highly active INI isoform is associated with increased use of the alternative donor splice site in the middle of exon V, increasing the production of 2Ctr. The preferred splicing of the INI isoform into 2Ctr (Flomen et al., 2004) may explain the higher plasma membrane expression levels of 2Cfl observed in transgenic

mice expressing the VGV isoform compared with mice expressing the INI isoform of the 5-HT₂R (Kawahara et al., 2008). These results are consistent with the original studies in which 2Ctr was first identified and was reported to be most abundant in the choroid plexus (Canton et al., 1996; Xie et al., 1996), the same brain region that was subsequently reported to express the highest levels of unedited and partially edited isoforms of the 5-HT_{2C} receptor (Burns et al., 1997; Niswender et al., 1999; Wang et al., 2000).

Several studies have provided evidence for a link between 5-HT_{2C} receptor RNA editing and splicing *in vivo*. In postmortem brain samples from patients who committed suicide, RNA editing was increased along with the ratio of 2Cfl to 2Ctr, with increased expression of the less active 5-HT_{2C} receptor isoforms (Dracheva et al., 2008a). In malignant gliomas from human brain, decreased ADAR2 activity (predicted to reduce RNA editing) was positively correlated with increased alternative splicing and the production of 2Ctr (Maas et al., 2001). In several of the gliomas examined and in glioma derived cells lines 2Ctr was predominant and 2Cfl was mostly absent (Maas et al., 2001; Tohda et al., 2004). In light of these findings, it is interesting to note that patients with glioblastoma have an increased incidence of seizures, as do 5-HT_{2C} receptor knockout mice.

Small nucleolar RNAs (snoRNAs) also regulate 5-HT_{2C} receptor RNA splicing. The snoRNA MBII-52 binds to exon V of the *HTR2C* gene in the region containing the alternative splice site and the RNA editing sites (Kishore and Stamm, 2006; Kishore et al., 2010). MBII-52 reduces RNA editing and the use of the alternative splice site, thereby favoring the production of the full length, unedited and more active 5-HT_{2C} receptor isoforms. In mice lacking MBII-52, RNA editing is increased, leading to increased expression of the edited and less active 5-HT_{2C} receptor isoforms (Doe et al., 2009). These mice display phenotypic and behavioral changes similar to those observed in Prader-Willi syndrome (Doe et al., 2009). Consistent with these findings, transgenic mice expressing only the fully edited VGV isoform display characteristics of Prader-Willi syndrome (Morabito et al., 2010a). The human homolog HBII-52 has been shown to be absent in patients with Prader-Willi syndrome and 5-HT_{2C} receptor RNA editing is increased in patients with Prader-Willi syndrome (Kishore and Stamm, 2006). These studies highlight the important roles that RNA editing and splicing play in the regulation of 5-HT_{2C} receptor activity and demonstrate how deregulation of this system can have profound phenotypic and behavioral consequences.

IX. C. 3. Single nucleotide polymorphisms

The 5-HT_{2C} receptor not only achieves diversity through RNA editing and splicing, but also through the incorporation of single nucleotide polymorphisms (SNPs), substitutions of a novel nucleotide for a wild-type nucleotide, a common type of genetic variation (Wang et al., 1998). These SNPs can produce an unstable conformation that alters the protein structure of a GPCR and affects its ultimate functional properties (Wenkert et al., 1996). A number of *HTR2C* SNPs have been reported in the literature: three polymorphisms as well as a GT nucleotide repeat variation have been identified in the promoter (Xie et al., 1996); three polymorphisms have been reported within intronic regions (Gibson et al., 2004); one polymorphism has been reported in the coding region resulting in the replacement of cysteine with serine at amino acid 23 (C23S) in the amino-terminus of the receptor (Lappalainen et al., 1995); and there is one polymorphism in the 3' untranslated region (Song et al., 1999). Few studies are reported that have ascertained the impact of these *HTR2C* SNPs on function at either the cellular or whole organism level. The impact of the S23 variant, when expressed in insect cells, was reported to have slightly higher affinity for 5-HT than the C23 variant and to alter 5-HT_{2C} receptor desensitization/resensitization mechanisms (Okada et al., 2004; Walstab et al., 2011). However, this finding remains controversial as other studies have reported no difference between the C23 and S23 variants with respect to agonist binding affinity or potency, G-protein coupling, constitutive activity, and homodimerization (Lappalainen et al., 1995; Fentress et al., 2005). Given suggestions that the C23 variant may have clinical implications (Lappalainen et al., 1995; Okada et al., 2004; Piva et al., 2011; Walstab et al., 2011), further studies of this and other *HTR2C* SNPs are required.

IX. C. 4. Glycosylation

The rat 5-HT_{2C} receptor is reported to be glycosylated and bands with different molecular weights were observed on Western blot of brain and cells expressing the receptor (Abramowski and Staufenbiel, 1995). Antibodies raised against the third and fourth cytoplasmic domain of the 5-HT_{2C} receptor identified an *N*-glycosylated polypeptide with a 60-kDa apparent molecular mass. Polypeptides were detected in immunoprecipitates from extracts of pig choroid plexus upon Western blot and binding assays with [³H]-mesulergine. A signal sequence was cleaved during membrane insertion resulting in a 38-kDa polypeptide. During further maturation, the receptor was *N*-glycosylated at two sites via a 48-kDa intermediate, which was more abundant in choroid plexus than in hippocampus. However, there may be more glycosylated species, since following transfection of 5-HT_{2C} receptor

cDNAs into cultured cells, polypeptides were observed that differed from the ones found in brain. Similarly, the *N*-glycosylated 5-HT_{2C} receptor was identified in solubilized extracts from cell lines and rat brain (Backstrom et al., 1995). Extracts from NIH3T3 fibroblasts stably expressing rat 5-HT_{2C} receptor contained immunoreactive proteins of 51-52 kDa and 58-68 kDa. In the brain, immunoreactive proteins were identified from choroid plexus extracts with masses of 51 kDa and 58-62 kDa. On the other hand, the major 58-62 kDa and minor 51 kDa proteins were not detected in extracts prepared from the hippocampus, striatum, or frontal cortex prepared under the same conditions. The association of asparagine-linked (*N*-linked) oligosaccharides with the receptors was also examined. Cells grown in the presence of tunicamycin to inhibit *N*-linked glycosylation resulted in proteins with masses of 40 and 41 kDa. Extracts prepared from NIH3T3 cells and choroid plexus incubated with *N*-glycosidase F showed proteins of 41 and 42 kDa from NIH3T3 cells and 41 kDa from choroid plexus. Neuraminidase treatment, to cleave sialic acid, reduced the mass of the 51 kDa and 58-62 kDa proteins from the choroid plexus to 50 kDa and 54-58 kDa, whereas the proteins from NIH3T3 cells were not affected by neuraminidase. Altogether, the 5-HT_{2C} receptor contains *N*-linked sugars and it is suggested that sialic acid residues associate with the receptor from the choroid plexus, but not from other brain regions. These oligosaccharide moieties contribute up to approximately 30% of the relative mass of the receptor, and may affect the functional properties of the 5-HT_{2C} receptor.

IX. C. 5. Phosphorylation

The constitutively active 5-HT_{2C} receptor is phosphorylated under basal conditions and phosphorylation is increased by agonist treatment (Westphal et al., 1995). Pretreatment of cells with 5-HT resulted in 5-HT_{2C} receptor desensitization, which was blocked by calcineurin (presumably by its phosphatase activity) (Boddeke et al., 1993). It was subsequently shown that S458 and S459 are phosphorylated (Backstrom et al., 2000). Phosphorylation of a mutant 5-HT_{2C} receptor that lacks the carboxyl-terminal PDZ recognition motif [Ser(458)-Ser-Val-COOH; DeltaPDZ] was not detectable, although these cells produced similar amounts of phosphoinositide and Ca_i²⁺ with similar kinetics as wild-type cells. Alanine mutations, S458A or S459A, decreased phosphorylation to 50% of wild-type receptor levels. Subsequent Ca_i²⁺ responses of S459A receptors were diminished relative to S458A and wild-type receptors. Thus, desensitization may occur in the absence of 5-HT_{2C} receptor phosphorylation, suggesting that receptor phosphorylation at S459 enhances resensitization of 5-HT_{2C} receptor responses. Agonist-induced phosphorylation of the 5-HT_{2C} receptor

was later established to regulate the receptor interaction with multiple PDZ protein 1 (Parker et al., 2003), also known as MUPP1 (Ullmer et al., 1998). MUPP1 is a putative scaffolding protein containing 13 PSD-95, Dlg, ZO-1 (PDZ) domains, identified by a yeast two-hybrid screen as one of a series of 5-HT_{2C} receptor -interacting proteins. The MUPP1 PDZ domain 10 (PDZ 10) associates with Ser458-Ser-Val of the 5-HT_{2C} receptor. An Asp mutation at Ser458 significantly decreased receptor interaction with PDZ 10. Also, 5-HT treatment of 5-HT_{2C} receptor-NIH3T3 cells reduced receptor interaction with PDZ 10, an effect that was blocked by a 5-HT_{2C} receptor antagonist.

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) interacts within several amino acids of the third intracellular loop (termed 3L4F) of the 5-HT_{2C} receptor (Ji et al., 2006). The tumor suppressor PTEN is widely distributed in the brain (Lachyankar et al., 2000). The PTEN and 5-HT_{2C} receptor proteins co-immunoprecipitate in fractions of the VTA (Ji et al., 2006; Anastasio et al., 2013). Employing a proximity ligation assay, the assembly of the 5-HT_{2C} receptor:PTEN complex, and the ability of 3L4F to disrupt the complex, was validated under native conditions within intact, live cells (Anastasio et al., 2013). A peptide fragment of the 5-HT_{2C} receptor third intracellular loop (3L4F), labelled with the cell-penetrating peptide TAT, disrupts the 5-HT_{2C} receptor:PTEN complex and PTEN-mediated dephosphorylation of the 5-HT_{2C} receptor in PC12 cells (Ji et al., 2006) as well as enhances 5-HT-mediated Ca^{2+} release in Chinese Hamster Ovary (CHO) cells stably transfected with the human 5-HT_{2C-IN1} receptor (but not the 5-HT_{2A} receptor) (Anastasio et al., 2013). Interestingly, the cell-adhesion molecule close homology of L1 (CHL1) protein also binds to the third intracellular loop of the 5-HT_{2C} receptor (amino acids 292-304) and may regulate the 5-HT_{2C} receptor association with PTEN and β -arrestin₂ to control its phosphorylation (Kleene et al., 2015).

Systemic administration of the TAT-3L4F peptide suppresses the Δ^9 -tetrahydrocannabinol (THC) induced increase in firing rate of VTA dopaminergic neurons in the rat (Ji et al., 2006) and suppresses the place association conditioned to Δ^9 -THC and nicotine in rats (Ji et al., 2006). In more recent studies, while TAT-3L4F had no effect alone, the combination of ineffective doses of TAT-3L4F *plus* WAY163909 synergize to suppress motor impulsivity, a primary symptomatic element of multiple neuropsychiatric disorders (American Psychiatric Association, 2013) which is consistently suppressed by pretreatment a selective 5-HT_{2C} receptor agonist (Winstanley et al., 2004; Fletcher et al., 2007; Fletcher et al., 2011;

Anastasio et al., 2013; Cunningham et al., 2013). In addition, TAT-3L4F augments 5-HT_{2C} receptor agonist-mediated suppression of spontaneous locomotor activity, effects which are consistent with positive allosteric modulation of 5-HT_{2C} receptor function (Anastasio et al., 2013; Wild et al., 2014; Wild, 2016). Together, coupled with the findings that Tat-3L4F did not affect spatial learning and memory (Maillet et al., 2008) or generate the total behavioral profile of 5-HT_{2C} receptor agonists (Ji et al., 2006; Anastasio et al., 2013), inhibition of the PTEN:5-HT_{2C} receptor interface and, thus, 5-HT_{2C} receptor dephosphorylation, is a novel pharmacological approach with therapeutic potential in substance use disorders (Ji et al., 2006; Muller and Carey, 2006; Maillet et al., 2008; Anastasio et al., 2013; Cunningham and Anastasio, 2014).

IX. C. 6. Dimerization

Homodimerization for many GPCRs is thought to be a post-translational event that occurs within the endoplasmic reticulum as a prerequisite for the transport and expression of functional receptors on the plasma membrane (for review see Milligan, 2010). Many members of the 5-HT receptor family, including the 5-HT_{2C} receptor, have been reported to form homodimers (for review see Herrick-Davis, 2013). Using a confocal microscopy-based resonance energy transfer technique, 5-HT_{2C} receptor homodimer formation was visualized within the endoplasmic reticulum during receptor biosynthesis (Herrick-Davis et al., 2006). The 5-HT_{2C} receptor is transported through the Golgi complex to the plasma membrane as a homodimer.

The 5-HT_{2C} receptor forms detergent-sensitive homodimers (Herrick-Davis et al., 2004) that do not dissociate or associate to form higher order complexes following agonist or inverse agonist treatment (Herrick-Davis et al., 2007). Co-expression of wild-type receptors with inactive, mutant receptors provided evidence that the 5-HT_{2C} receptor homodimer interacts with a single G protein, that both protomers participate in signaling, and that both protomers must be functional in order for signaling to occur (Herrick-Davis et al., 2005). Time-lapse fluorescence confocal microscopy provided direct visualization of β -arrestin₂ recruitment to the plasma membrane following 5-HT binding to the homodimer (Herrick-Davis et al., 2007; Herrick-Davis et al., 2012). Homodimerization was observed for both the unedited INI and the fully edited (VSV and VGV) isoforms (Herrick-Davis et al., 2007; Herrick-Davis et al., 2012).

Advanced imaging techniques with near single molecule sensitivity have been employed more recently in an attempt to distinguish between dimers and higher order oligomers. Fluorescence correlation spectroscopy studies report that the 5-HT_{2C} receptor expressed in HEK293 cells exists as homodimers, with no evidence for monomers, tetramers or higher order oligomers (Herrick-Davis et al., 2012). Spatial intensity distribution analysis was used to monitor the oligomer status of the 5-HT_{2C} receptor over a wide range of receptor expression levels (Ward et al., 2015). In this study, the 5-HT_{2C} receptor was expressed as a mixture of monomers, dimers and tetramers; treatment with a 5-HT_{2C} receptor antagonist for 90 minutes converted the majority of dimers and tetramers to monomers. However, it should be noted that tetramers were prominent only when 5-HT_{2C} receptor expression exceeded 100 receptors/ μm^2 (Ward et al., 2015), greatly in excess of physiological expression levels for native GPCRs (Hegener et al., 2004; Herrick-Davis et al., 2015). Similarly, the homodimer was the predominant species observed for biogenic amine receptors when expressed within their normal physiological range in HEK293 cells (Herrick-Davis et al., 2013).

Only one study to date has examined the 5-HT_{2C} receptor endogenously expressed in its native cellular environment. The native 5-HT_{2C} receptor, endogenous to the choroid plexus, is expressed as homodimers on the apical surface of the epithelial cells at a density of 32 receptors/ μm^2 (Herrick-Davis et al., 2015). While this is similar to a reported density of 20 receptors/ μm^2 for native β_2 -adrenergic receptors in alveolar epithelial cells, expression levels in neurons were much lower at 4.5 receptors/ μm^2 (Hegener et al., 2004). The study by Herrick-Davis and colleagues found no evidence for monomers or tetramers of the native 5-HT_{2C} receptor in choroid epithelial cells or when the 5-HT_{2C} receptor was expressed at normal physiological levels in HEK293 cells. In this study, the signaling properties of the 5-HT_{2C} receptor homodimer were investigated using agonists that bind in a wash-resistant manner to one or both protomers of the 5-HT_{2C} receptor homodimer. Agonist binding to one protomer stimulated a half-maximal phosphoinositide response, while binding to both protomers was required to produce a maximal response (Herrick-Davis et al., 2015). These experiments provide pharmacological evidence supporting the hypothesis that the 5-HT_{2C} receptor functions as a homodimer.

Heterodimers can form between the different isoforms of the 5-HT_{2C} receptor generated by RNA editing (Herrick-Davis and Farrington, 2011). In HEK293 cells, positive resonance energy transfer was observed between the INI/VSV, INI/VGV and VSV/VGV isoform pairs. However, the

influence of heteromer pairs of edited 5-HT_{2C} receptor isoforms on receptor signaling and neural function *in vivo* are yet to be demonstrated. In terms of heterodimers between the 5-HT_{2C} receptor and other members of the 5-HT receptor family, the 5-HT_{2A} receptor would be the most likely candidate given their similarity in structure (for review see Hannon and Hoyer, 2008). Immunohistochemical analyses indicate that the 5-HT_{2A} receptor and 5-HT_{2C} receptor protein co-localize in the same GABAergic neurons as well as in a population of pyramidal projection neurons in the rat medial prefrontal cortex (mPFC) (Nocjar et al., 2015). Co-immunoprecipitation studies suggest that the 5-HT_{2A} receptor and 5-HT_{2C} receptor are found in the same protein complex in the rat mPFC (Anastasio et al., 2015). Further analyses of the structural and biological significance of a possible heteromeric protein complex incorporating both the 5-HT_{2A} receptor and 5-HT_{2C} receptor is required to understand its potential role in behavior and neuropsychiatric disorders.

Selective 5-HT_{2A} receptor antagonists and selective 5-HT_{2C} receptor agonists have been noted to suppress a wide range of behaviors which are particularly well-studied in preclinical models of addictive disorders (Bubar and Cunningham, 2008; Cunningham and Anastasio, 2014; Howell and Cunningham, 2015). The combination of low doses of the selective 5-HT_{2A} receptor antagonist M100907 *plus* the preferential 5-HT_{2C} receptor agonist MK212 evoked modest effects, but resulted in an approximately additive suppression of cocaine-evoked hyperlocomotion and Fos expression in the caudate putamen (Pockros et al., 2012). In a second study, combination of subthreshold doses of M100907 *plus* the selective 5-HT_{2C} receptor agonist WAY163909 synergistically suppressed inherent and cocaine-evoked motor impulsivity as well as cocaine-induced hyperactivity and cocaine-seeking behavior (Cunningham et al., 2013). These data raise the possibility that the 5-HT_{2A} receptor and 5-HT_{2C} receptor may act in concert to regulate the neural bases for behavior. Further analyses of the structural and functional interactions between the 5-HT_{2A} receptor and 5-HT_{2C} receptor are necessary to disentangle the manner in which these GPCRs interact at neuronal and circuit levels.

Microinfusion of the preferential 5-HT_{2A} receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) into the mPFC enhances (Wischof et al., 2011) while intra-mPFC infusion of M100907 (Winstanley et al., 2003) suppresses motor impulsivity. The density of 5-HT_{2A} receptor (Fink et al., 2015) as well as 5-HT_{2C} receptor protein expression in the mPFC (Anastasio et al., 2014b) predicts the level of motor impulsivity in outbred rats. High

impulsive rats exhibit a greater 5-HT_{2A} receptor-mediated head twitch response and are more sensitive to the suppressive effects of the selective 5-HT_{2A} receptor antagonist M100907 on motor impulsivity (Fink et al., 2015). The levels of 5-HT_{2A} receptor and 5-HT_{2C} receptor protein predicted the intensity of motor impulsivity and the ratio of the 5-HT_{2A} receptor to 5-HT_{2C} receptor protein in mPFC positively correlated with levels of motor impulsivity in individual outbred rats (Anastasio et al., 2015). High phenotypic motor impulsivity associated with a diminished mPFC synaptosomal 5-HT_{2A}R:5-HT_{2C} receptor protein:protein interaction assessed by co-immunoprecipitation (Anastasio et al., 2015). Knockdown of 5-HT_{2C} receptor in the mPFC resulted in increased motor impulsivity and triggered a compensatory upregulation of 5-HT_{2A} receptor protein expression in mPFC and a leftward shift in the potency of M100907 to suppress impulsive behavior (Anastasio et al., 2015). These data further support the concept that an interactive relationship between the mPFC 5-HT_{2A} receptor and 5-HT_{2C} receptor is behaviorally relevant. The manner in which a potential 5-HT_{2A} receptor and 5-HT_{2C} receptor heteromeric protein complex in the mPFC contributes to high levels of inherent motor impulsivity remains to be uncovered.

The 5-HT_{2C} receptor has also been reported to form heterodimers with ghrelin GHS-R1a receptor when overexpressed in HEK293 cells and to co-localize with the GHS-R1a in cultured primary hypothalamic and hippocampal neurons from the rat (Schellekens et al., 2015). In this study, activation and blockade of 5-HT_{2C} receptor *in vivo* attenuated and potentiated, respectively, the orexigenic effects of ghrelin. Heterodimers between 5-HT_{2C} receptor and melatonin MT₂ receptors have also been reported in transfected cells as well as human cortex and hippocampus (Kamal et al., 2015). Interestingly, the novel antidepressant agomelatine demonstrates biased signaling and displays 5-HT_{2C} receptor and MT₂ receptor agonist properties, suggesting the heterodimer as a potential target for the development of a novel class of therapeutics for the treatment of psychiatric disorders as well as eating disorders and obesity.

Immunohistochemical studies demonstrated that the NMDA receptor GluN2A co-localizes with the 5-HT_{2C} receptor in rat spinal cord neurons while co-immunoprecipitation analysis of synaptosomal fractions suggests formation of a 5-HT_{2C} receptor and GluN2A protein complex (Bigford et al., 2012). Stimulation of the 5-HT_{2C} receptor enhanced NMDA-evoked motoneuron depolarization through involvement of Src tyrosine kinase (Bigford

et al., 2012). These results support the assembly of a functionally relevant 5-HT_{2C} receptor and NMDA receptor complex in the spinal cord, although the presence of this complex in the brain and its involvement in higher order neural function is unexplored.

IX. D. Pharmacology

For the 5-HT_{2C} receptor, the identification of selective orthosteric ligands relative to the close family members, 5-HT_{2A} receptor and 5-HT_{2B} receptor, is challenged by their ~50% overall homology which rises to ~80% in the transmembrane domains comprising the orthosteric receptor binding pocket (Hoyer et al., 2002). Because of this challenge, the earliest preclinical and clinical research employed “preferential” 5-HT_{2C} receptor ligands which frequently displayed affinity (agonists, antagonists) and/or efficacy (agonists) at the 5-HT_{2A} receptor and 5-HT_{2B} receptor. Due to the lack of selectivity of available agonists [e.g., MK212, *m*-chlorophenylpiperazine (mCPP)] and antagonists (e.g., ketanserin), experimental outcomes with such compounds initially led to ambiguous conclusions concerning the biological roles for the 5-HT_{2C} receptor, particularly *in vivo*. Furthermore, with the understanding that 5-HT_{2A} receptor or 5-HT_{2B} receptor agonists may evoke hallucinations (Nichols, 2004) or cardiac valvulopathy (Fitzgerald et al., 2000; Roth, 2007), respectively, the need for 5-HT_{2C} receptor orthosteric agonists that lack demonstrable efficacy at 5-HT_{2A} receptor or 5-HT_{2B} receptor is recognised. In 1997, the chemists at SmithKline Beecham synthesized and characterized SB242084 as the first selective 5-HT_{2C} receptor antagonist (Bromidge et al., 1997; Kennett et al., 1997). Because the 5-HT_{2C} receptor exhibits constitutive activity dependent upon the edited isoform and the *in vitro* and *in vivo* conditions employed for analyses, SB242084 and other compounds in this series (e.g., SB206553, SB243213) (Bromidge et al., 1997; Kennett et al., 1997) have been noted to act as inverse agonists to attenuate constitutive 5-HT_{2C} receptor activity (for reviews see Aloyo et al., 2009; Sullivan et al., 2015). Atypical antipsychotic drugs are also reported to act as inverse agonists with the ability to inhibit 5-HT_{2C} receptor constitutive activity (Herrick-Davis et al., 2000; Rauser et al., 2001) and Spampinato and colleagues have identified the role of 5-HT_{2C} receptor constitutive activity in the control of dopamine corticoaccumbens function (Aloyo et al., 2009; Leggio et al., 2009b).

A body of knowledge has been developed around several useful 5-HT_{2C} receptor agonists which have been available to scientists for the last 10 years. The compound RO60-0175 (Knight et al., 2004) has generated a great deal of information concerning the biological role of the 5-HT_{2C} receptor

(Millan et al., 1998; Di Matteo et al., 2000; Grottick et al., 2000; Filip and Cunningham, 2002; Tomkins et al., 2002; Leggio et al., 2009a; Fletcher et al., 2012). RO60-0175 exhibits affinity and efficacy for all three 5-HT₂ receptor subtypes, although many of its effects *in vivo* are blocked by SB242084 (Martin et al., 1998; Porter et al., 1999; Knight et al., 2004). Lorcaserin is a selective, high-efficacy 5-HT_{2C} receptor agonist marketed as Belviq® for weight reduction in patients with a body-to-mass (BMI) index of >30 or with a BMI >27 comorbid with type-2 diabetes, hypertension or dyslipidemia (www.us.eisai.com/). The availability of lorcaserin for clinical research has prompted a growing number of studies, particularly focused on addictive disorders (Rezvani et al., 2014; Higgs et al., 2015; Harvey-Lewis et al., 2016; for review see Higgins et al., 2020). The preliminary results of a clinical trial (<http://www.eisai.com/news/news201465.html>) demonstrated the efficacy of lorcaserin to increase abstinence from nicotine, a highly abused psychostimulant while preclinical studies continue to promote the prospects of lorcaserin as a tool to reduce substance use disorders (Levin et al., 2011; Cunningham and Anastasio, 2014; Rezvani et al., 2014; Higgins et al., 2017; Howell and Cunningham, 2015; Harvey-Lewis et al., 2016; for review see Higgins et al., 2020). Strikingly, Di Giovanni's group has also recently shown that lorcaserin is very effective as an anticonvulsant in both animal models of generalized non-convulsive absence epilepsy and temporal lobe epilepsy (Orban et al., 2014; Venzi et al., 2016).

A compound series developed at Wyeth Research includes vabicaserin (SCA-136) which acts as a selective 5-HT_{2C} receptor full agonist ($K_i = 3$ nM; efficacy 100% relative to 5-HT), a 5-HT_{2B} receptor antagonist ($IC_{50} = 29$ nM) and a weak 5-HT_{2A} receptor antagonist ($IC_{50} = 1,650$ nM) (Rosenzweig-Lipson et al., 2007a; Tong et al., 2010; Dunlop et al., 2011). A randomized, double-blind, placebo-controlled study suggested the efficacy, safety and tolerability of vabicaserin in the treatment of acute schizophrenia (Shen et al., 2014), although few preclinical analyses of this compound are published. WAY163909 is chemically-similar to vabicaserin with high affinity ($K_i=10.5$ nM) and full efficacy (90% relative to 5-HT) at the 5-HT_{2C} receptor. WAY163909 exhibits a lower affinity ($K_i=212$ nM) and no efficacy at the 5-HT_{2A} receptor, and is a weak partial agonist at the 5-HT_{2B} receptor (Dunlop et al., 2005). WAY163909 has been employed as a tool compound to test hypotheses related to the involvement of the 5-HT_{2C} receptor in animal models of addiction, depression, impulsivity, and schizophrenia (Dunlop et al., 2006; Marquis et al., 2007; Rosenzweig-Lipson et al., 2007b; Navarra et al., 2008; Cunningham et al., 2011; Anastasio et al., 2013; Cunningham et al., 2013; Navailles et al., 2013b; Anastasio et al., 2014a). More recently, rational medicinal chemistry approaches have been employed to craft novel, highly selective 5-HT_{2C} receptor agonists (Storer

et al., 2014; Cheng et al., 2015; Rouquet et al., 2015). Some of these newer 5-HT_{2C} receptor agonists have been made commercially available (e.g., PF-3246799, PF-4479745 from Pfizer) (Storer et al., 2014) which will allow their increasing employment in *in vitro* and *in vivo* studies and provide greater breakthroughs in our understanding of 5-HT_{2C} receptor biology.

The orthosteric site of a GPCR at which the endogenous agonist binds has been the traditional target for ligand discovery, but the chemical space for GPCR neuroprobes and therapeutics has greatly expanded with the discovery of allosteric ligands for many GPCR subfamilies. An allosteric modulator is a ligand that binds to a spatially-distinct allosteric site(s) and alters the receptor conformation to modulate its interaction with other ligands and/or signal transduction molecules (for reviews see Conn et al., 2009; Christopoulos et al., 2014). Allosteric sites are expected to exhibit higher sequence divergence across receptor subtypes relative to the highly-conserved orthosteric domain (Kenakin, 2009; Kenakin and Miller, 2010). For example, a positive allosteric modulator (PAM) can increase the affinity and/or efficacy of the orthosteric ligand (Conn et al., 2009) and, thus, has the potential to improve its therapeutic index and diminish negative side effects. Such allosteric modulation is saturable (comes to a finite magnitude when the allosteric site is fully occupied) and probe dependent (varies dependent upon the orthosteric ligand) with the prospects for separate control of affinity and efficacy, making allosteric ligands intriguing therapeutic chemical targets (Kenakin, 2010). At present, allosteric modulators are defined operationally as positive (PAM), negative allosteric modulators (NAM) or neutral allosteric ligands (NAL) with the possibility of the additional property of allosteric agonism (agonist effects consequent to binding to allosteric sites; Christopoulos et al., 2014).

Adron Harris and colleagues were the first to identify the effects of the fatty acid amide oleamide to positively modulate 5-HT_{2C} receptor-mediated activity in *Xenopus* oocytes (Huidobro-Toro et al., 1996), and further analyses have identified oleamide as a member of a family of amphipathic lipid metabolites that allosterically promote 5-HT receptor signaling through other receptors (e.g. 5-HT_{2A} receptor, 5-HT₇ receptor; Thomas et al., 1997; Thomas et al., 1998; Alberts et al., 2001), but also exhibit a myriad of additional effects on receptor signaling (Leggett et al., 2004). In 2003, chemical library screening at Pharmacia (now Pfizer) resulted in the discovery and characterization of PNU-69176E as a PAM highly selective for the 5-HT_{2C} receptor over the 5-HT_{2A} receptor, 5-HT_{2B} receptor, 5-HT₇ receptor and dopamine receptors (Im et al., 2003). In 2012, Zhou and colleagues

optimized the synthetic route to generate PNU-69176E and its diastereomer (Ding et al., 2012). A series of new molecules based on the 4-alkylpiperidine-2-carboxamide scaffold were designed, synthesized, and pharmacologically evaluated as 5-HT_{2C} receptor PAMs (Wild et al., 2018). Several analogues, potentiated 5-HT-evoked Ca_i²⁺ in 5-HT_{2C} receptor -CHO cells, but not in 5-HT_{2A} receptor -CHO cells; one compound was further evaluated *in vivo* and exhibited a favorable overall pharmacokinetic and behavioral profile in rats (Wild et al., 2018). In addition, two predicted allosteric sites were identified by molecular docking to a 5-HT_{2C} receptor homology model (Wild et al., 2018). Taken together, these data provide proof-of-concept that allosteric modulation of 5-HT_{2C} receptor may be a viable strategy toward the discovery of novel neurotherapeutics. Recent preclinical indications of the efficacy of allosteric modulators in disease models, coupled with the launch of cinacalcet and maraviroc as the first marketed GPCR allosteric modulators, provide strong validation of the potential clinical utility of allosteric modulators (Conn et al., 2009). Ultimately, further analyses of novel allosteric modulators will improve understanding of 5-HT_{2C} receptor function and how allosteric modulators may provide gain (or loss) of function in this system.

IX. E. Signal transduction

Intracellular signaling cascades stimulated by the 5-HT_{2C} receptor have been assessed predominantly in recombinant cellular models and to a lesser extent within natural cellular environments (e.g., choroid plexus epithelial cells). Multiple G proteins (e.g., G $\alpha_{q/11}$, G $\alpha_{12/13}$ and G $\alpha_{i/o}$) and activation of second messengers such as phospholipases, cyclic nucleotides, and extracellular signal-regulated kinases 1 and 2 (ERK_{1/2}) are essential mediators of 5-HT_{2C} receptor actions in cells. By the late 1990s, structurally diverse 5-HT_{2C} receptor agonists (Berg et al., 1994; Berg et al., 1998a; Moya et al., 2007) were noted to differentially activate intracellular signaling pathways, variably referred to as “agonist-directed trafficking of receptor stimulus,” biased agonism (signaling), stimulus trafficking, collateral efficacy, and functional selectivity (Berg, 2009; Whalen et al., 2011; Kenakin and Christopoulos, 2013). Recent modeling studies suggest that 5-HT_{2C} receptor ligands with fewer docking poses may stabilize a structural conformation contributory to a specific signaling pathway (Canal et al., 2011). Thus, distinct conformational states may differentially modulate the receptor interaction with immediate effectors (e.g., G proteins vs. β -arrestins), resulting in biased intracellular signal transduction patterns depending on the recruited effector (Gesty-Palmer et al., 2006; Whalen et al., 2011; Kenakin and Christopoulos, 2013). For example, G protein-dependent signaling pathways result in

activation of specific downstream signaling effectors (e.g., pERK_{1/2}), while β -arrestin₂-dependent signaling can result in a different subset of downstream effectors as well as subcellular distribution of shared effectors (e.g., cytoplasmic vs. nuclear pERK_{1/2}). These signaling profiles can then lead to distinct overall effects of GPCR activation (Gesty-Palmer et al., 2006). Targeting G protein- vs. β -arrestin₂-dependent mechanisms can allow for selectively inducing certain outcomes of receptor activation and perhaps not only reducing undesired side effects, but providing new therapeutic possibilities (Luttrell et al., 2015), a hypothesis which is supported for the 5-HT_{2C} receptor system (Berg, 2009) as well as for other GPCR signaling systems (Gesty-Palmer et al., 2006; Masri et al., 2008; Allen et al., 2011; Lovell et al., 2015; Marti-Solano et al., 2015).

IX. E. 1. Phospholipase C

The 5-HT_{2C} receptor is characterized to stimulate phospholipase C (PLC) signaling through pharmacological analyses in heterologous expression systems (Westphal and Sanders-Bush, 1996; Briddon et al., 1998; Herrick-Davis et al., 1999; Rosendorff et al., 2000; Devlin et al., 2004), choroid plexus cells (Conn and Sanders-Bush, 1986b; Conn et al., 1986; Sanders-Bush and Conn, 1986) as well as corticostriatal regions of the brain (Wolf and Schutz, 1997). In this regard, the 5-HT_{2C} receptor is largely thought to act through pertussis toxin-insensitive $G\alpha_{q/11}$ proteins (Conn et al., 1986; Berg et al., 1994; Chang et al., 2000), although there is evidence that pertussis toxin-sensitive $G\alpha_{i/o}$ G proteins may couple the 5-HT_{2C} receptor to PLC in *Xenopus laevis* oocytes (Chen et al., 1994) and HEK293 cells (Alberts et al., 1999). Thus, the canonical G protein-dependent signaling through the 5-HT_{2C} receptor is engendered by 5-HT-stimulated coupling to $G\alpha_{q/11}$ to activate the enzyme phospholipase C $_{\beta}$ (PLC $_{\beta}$) which generates the intracellular second messenger inositol-1,4,5-trisphosphate (IP₃), accumulation of the downstream IP₃ metabolite inositol monophosphate (IP₁), and diacylglycerol (DAG). IP₃ interacts with the IP₃ receptor leading to increased Ca^{2+} into the cytoplasm; Ca^{2+} mobilization, measured with calcium-binding fluorescent dyes, and IP₁ levels, assessed with [³H]-inositol, are well-characterized to be elevated following activation of the 5-HT_{2C} receptor (for reviews) (Raymond et al., 2001; Millan et al., 2008). Utilizing cell-permeable, small peptide disruptors mimicking the C-terminal of $G\alpha_q$, Sanders-Bush and colleagues demonstrated that a $G\alpha_q$, but not a G_s , disruptor was able to block 5-HT_{2C} receptor-mediated phosphoinositide hydrolysis in choroid

plexus endothelial cells (Chang et al., 2000). Furthermore, a PLC β_1 , but not a PLC β_2 , peptide blocked 5-HT $_{2C}$ receptor activation suggesting that 5-HT $_{2C}$ receptor-evoked phosphoinositide hydrolysis is mediated through a G α_q and PLC β_1 dependent mechanism (Chang et al., 2000).

Hydrolysis of phosphoinositides generates the signaling lipid DAG, leading to activation of protein kinase C (PKC) and downstream stimulation of the mitogen-activated protein kinase (MAPK) cascade resulting in phosphorylation of ERK $_{1/2}$ (Werry et al., 2005). In fact, 5-HT $_{2C}$ receptor-transfected CHO cells were shown to couple ERK $_{1/2}$ via a PLD- and PKC-dependent pathway likely through G $\alpha_{12/13}$ proteins (Werry et al., 2005). The PLD and PKC involvement in ERK $_{1/2}$ phosphorylation evoked by 5-HT $_{2C}$ receptor stimulation was recently validated in a hypothalamic cell line (mHypoA-2/10) derived from the periventricular nucleus of an adult male mouse (Lauffer et al., 2016). These further analyses indicated that the native 5-HT $_{2C}$ receptor activates the cellular transcription factor cAMP response element (CRE) binding protein (CREB) via PKC-induced ERK $_{1/2}$ activation in this cellular model (Lauffer et al., 2016).

Desensitization and resensitization processes regulate the functional activity of 5-HT $_{2C}$ receptor. Agonist-dependent desensitization is associated with 5-HT $_{2C}$ receptor phosphorylation involving G protein receptor kinase $_2$ (GRK $_2$) (Berg *et al.*, 2001), binding of β -arrestins and uncoupling of the receptor from the G protein to result in receptor internalization into endosomes; resensitization and recycling to the plasma membrane occurs with dephosphorylation (Marion et al., 2004; Schlag et al., 2004). The interaction of the 5-HT $_{2C}$ receptor with the C-terminal domain of PSD-95/Disc large/Zonula occludens (PDZ) domain-containing proteins (Becamel et al., 2002; Becamel et al., 2004; Anastasio et al., 2010; Anastasio et al., 2014b) is known to play an important role in 5-HT $_{2C}$ receptor desensitization/resensitization processes and trafficking (Gavarini et al., 2006). Intracellular Ca $_i^{2+}$ release in mouse cortical neurons in primary culture is regulated by the PDZ proteins postsynaptic density-95 (PSD-95) and MAGUK p55 subfamily member 3 (MPP3) (Gavarini et al., 2006; Moller et al., 2013). While PSD-95 and MPP3 do not modify the efficacy of 5-HT $_{2C}$ receptor signaling triggered by a single 5-HT exposure, PSD-95 increases signal desensitization and trafficking upon repeated agonist exposure, an effect which is blocked by a peptidyl mimetic of the 5-HT $_{2C}$ receptor C-terminus which disrupts the interaction between the 5-HT $_{2C}$ receptor and PSD-95 (Gavarini et al., 2006). On the other hand, MPP3 stabilizes the 5-HT $_{2C}$ receptor at the plasma membrane and prevents desensitization of the 5-HT $_{2C}$

receptor-mediated Ca^{2+} release (Gavarini et al., 2006). This regulation correlates with surface expression of the receptor and indicates that 5-HT_{2C} receptor signaling is highly regulated by PDZ proteins.

IX. E. 2. Phospholipase D

The 5-HT_{2C} receptor also activates phospholipase D (PLD), an enzyme which catalyzes the conversion of phosphatidylcholine to choline and phosphatidic acid; phosphatidic acid transduces most of PLD-evoked activity, while soluble choline diffuses into the cytosol, but has little second messenger activity (for reviews see Frohman, 2015; Nelson and Frohman, 2015). The activation of PLD can occur through the canonical receptor/G protein/effector signal transduction cascade via $G\alpha_{12/13}$. In rat choroid plexus epithelial cells, 5-HT evoked PLD activation occurs at levels similar to PLC activation, however PLD activation is not downstream to G protein-linked PLC activation (McGrew et al., 2002). The 5-HT_{2C} receptor antagonist SB206553 and a peptide targeting the $G\alpha_{13}$, but not the $G\alpha_q$, subunit blocked 5-HT-evoked PLD activation (McGrew et al., 2002). Inactivation of RhoA guanosine triphosphate (GTP) hydrolase enzyme (GTPase) in NIH3T3 cells stably expressing the 5-HT_{2C} receptor by the C3 exoenzyme from *Clostridia botulinum* blocks 5-HT_{2C} receptor-evoked PLD, but not PLC, signaling (McGrew et al., 2002). Also, in a NIH3T3 cell line derived from $G\alpha_{q/11}$ -deficient mice, 5-HT_{2C} receptor-dependent stress fiber formation is dependent on $G\alpha_{13}$ and Rho signaling (Gohla et al., 1999). The PLD signaling was not seen in cells transfected with the 5-HT_{2C-VGV} receptor; this highly-edited isoform has a diminished ability to couple to $G\alpha_{13}$ and is unable to promote Rho GTPase activity (McGrew et al., 2004). Together, these studies suggest that 5-HT_{2C} receptor-mediated PLD signaling is dependent on $G\alpha_{13}$ activation of Rho, a property of this receptor which is affected by pre-RNA editing.

IX. E. 3. Phospholipase A₂

Stimulation of the 5-HT_{2C} receptor is thought to activate cytosolic phospholipase A₂ (PLA₂) which hydrolyzes arachidonic acid-containing phospholipids to produce free arachidonic acid and a host of its metabolites (for reviews see Burke and Dennis, 2009a; Burke and Dennis, 2009b). In an early study, 5-HT was demonstrated to stimulate the release of arachidonic acid through activation of PLA₂, but not phosphoinositide turnover, in hippocampal neurons co-cultured with glial cells, but not in glial cultures alone; the studies supported the involvement of the 5-HT₂ receptor subtype

in the PLA₂ activation (Felder et al., 1990). In 5-HT_{2C} receptor -transfected CHO cells, 5-HT increases the release of arachidonic acid, an effect which is blocked by the PLA₂ inhibitor mepacrine which had no effect on 5-HT_{2C} receptor -mediated phosphoinositide hydrolysis (Berg et al., 1996). The G protein effector is sensitive to pertussis toxin inactivation, but the exact G proteins(s) involved are as of yet unknown (Felder et al., 1990). This research was extended to demonstrate that the relative efficacy of agonists is distinct for the PLA₂-arachidonic acid vs. PLC-phosphoinositide pathways. For example, DOI acts as a full agonist to stimulate arachidonic acid release (equivalent to 5-HT) while 3-trifluoromethylphenylpiperazine (TFMPP) and *d*-lysergic acid diethylamide (LSD) preferentially activate the PLC-phosphoinositide and PLA₂-arachidonic acid pathway, respectively (Berg et al., 1998b). In addition, arachidonic acid release, while sensitive to pretreatment with 5-HT, is not as sensitive as phosphoinositide hydrolysis, suggesting that arachidonic acid release may be more difficult to demonstrate *in vivo* as a 5-HT_{2C} receptor -mediated output when compared to phosphoinositide hydrolysis (Berg et al., 1998b). The involvement of arachidonic acid stimulation in 5-HT₂ receptor signaling *in vivo* is supported by the observation that systemic administration of DOI resulted in increased incorporation of labelled arachidonic acid into brain membranes (Qu et al., 2005). The increases were seen in brain regions with the highest densities of 5-HT_{2A} receptor (e.g., cerebral cortex), but not in the choroid plexus which expresses the highest 5-HT_{2C} receptor density (choroid plexus). Future studies are necessary to clarify the relative roles of the 5-HT_{2A} receptor and 5-HT_{2C} receptor in the control of arachidonic acid incorporation *in vivo* (Basselin et al., 2012).

IX. E. 4. Cyclic nucleotides

Signaling through cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), are also reported to be engaged by the 5-HT_{2C} receptor. Activation of the 5-HT_{2C} receptor inhibits forskolin-stimulated cAMP production in AV12 fibroblast cells that stably express the receptor at high density (~12 pmol/mg membrane protein); at low 5-HT_{2C} receptor density (~150 fmol/mg of membrane protein), 5-HT couples to the PLC-IP pathway, but evokes a stimulation rather than an inhibition of cAMP production (Lucaites et al., 1996). Upon pertussis toxin treatment, a modest 5-HT_{2C} receptor stimulatory effect on cAMP accumulation as well as its potential dependence on the G_{i/o} family of G proteins was observed (Lucaites et al., 1996). In *Xenopus* oocytes transfected with the 5-HT_{2C} receptor and G proteins, the 5-HT_{2C} receptor was

shown to couple to G_o in addition to G_q (Quick et al., 1994). Since there is limited evidence that the 5-HT_{2C} receptor links to cAMP in cells natively expressing the receptor (porcine choroid plexus) (Palacios et al., 1986), further analyses as to its biological significance *in vitro* and *in vivo* is required.

The antimigraine medication dihydroergotamine, which inhibits [³H]-mesulergine binding to the 5-HT_{2C} receptor and is a full 5-HT_{2C} receptor agonist in porcine choroid plexus (Brown et al., 1991), elevates cGMP levels in LMTK⁻ fibroblasts stably expressing the 5-HT_{2C} receptor (Schaefer et al., 2003). 5-HT rapidly elevates cGMP production in the 5-HT_{2C} receptor -enriched porcine choroid plexus tissue slices (Kaufman et al., 1995) with an efficacy similar to PI turnover (Conn et al., 1986); the potencies of antagonists that suppress 5-HT-mediated cGMP formation align with their affinity for the 5-HT_{2C} receptor (Kaufman et al., 1995). The pertussis toxin-insensitive 5-HT_{2C} receptor -mediated cGMP formation is dependent upon calcium and PLA₂-arachidonate release as well as lipoxygenase (Kaufman et al., 1995). Thus, the 5-HT_{2C} receptor appears to exhibit efficacy to evoke cGMP formation in a native tissue in a PLA₂-dependent manner (Kaufman et al., 1995) as well as regulate NMDA-mediated production of nitric oxide and elevation of cGMP (Marcoli et al., 1997).

IX. E. 5. Extracellular signal-regulated kinases (ERK_{1/2})

The activation of the 5-HT_{2C} receptor can diverge to influence several G protein-dependent downstream cascades and may also converge on others, such as members of the MAPK class, P42 and 44 (p44/p42-MAPK), also known as ERK_{1/2}. In fact, there is evidence to suggest that phosphorylation of ERK_{1/2} is an important integrator of the multiple upstream signaling events for the 5-HT_{2C} receptor. In CHO cells stably expressing the 5-HT_{2C} receptor, 5-HT stimulated phosphorylation of ERK_{1/2} which is inhibited by the 5-HT_{2C} receptor antagonist mianserin (Werry et al., 2005). While PKC and PLD inhibitors suppress 5-HT-mediated phosphorylation of ERK_{1/2}, PLC and PLA₂ inhibitors are ineffective, suggesting the 5-HT_{2C} receptor -mediated pERK_{1/2} is dependent upon PKC and PLD signaling (Werry et al., 2005). Activation of ERK_{1/2} by 5-HT_{2C} receptor ligands is not solely mediated by coupling of the 5-HT_{2C} receptor to G proteins and can, in fact, be mediated by coupling to other protein transducers. The C-terminus of the 5-HT_{2C} receptor contains a calmodulin domain that is critical for β -arrestin recruitment and ERK_{1/2} signaling (Labasque et al., 2008). A calmodulin mutant prevented phosphorylation of ERK_{1/2} in cortical neurons and choroid plexus epithelial cells, suggesting that the calmodulin

interaction is critical for G protein-independent signaling (Labasque et al., 2008). In HEK293 cells transiently expressing the 5-HT_{2C} receptor, pERK_{1/2} levels were increased over non-transfected cells, suggesting the expression of constitutive activity of the 5-HT_{2C} receptor (Labasque et al., 2008). This elevated basal pERK_{1/2} was inhibited by a 5-HT_{2C} receptor inverse agonist towards PLC (Labasque et al., 2008), again suggesting that pERK_{1/2} activity is PLC mediated. Interestingly, this activity was unaffected by depletion of G α_{12} or G α_{13} proteins while, in cells lacking β -arrestin or calmodulin, basal pERK_{1/2} levels were decreased, providing the first evidence of constitutive activity of a G protein-coupled receptor towards a G protein-independent, β -arrestin dependent signaling mechanism (Labasque et al., 2008).

IX. E. 6. Ion channels

The impact of 5-HT_{2C} receptor on the function of ion channels has been addressed extensively in the choroid plexus which controls the composition and secretion of cerebrospinal fluid, a function in which chloride (Cl⁻) and potassium (K⁺) channels play a key role (Millar et al., 2007). 5-HT acting through the 5-HT_{2C} receptor has been noted to activate Cl⁻ and inhibit K⁺ channels in mouse and rat choroid plexus epithelium (Hung et al., 1993; Speake et al., 2004) and the 5-HT_{2C} receptor has been shown to inhibit K⁺ channels through a PKC-dependent pathway in rat choroid plexus epithelial cells (Speake et al., 2004). Activation of the 5-HT_{2C} receptor leads to G-protein-dependent PLC activation, IP₃ and DAG production and the release of Ca_i²⁺ from the endoplasmic reticulum which triggers the opening of calcium-activated Cl⁻ channels in *Xenopus* oocytes (Julius et al., 1988; Panicker et al., 1991; Woodward et al., 1992; DiMagno et al., 1996). The G α and G_q subunits may be involved in the generation of this calcium-activated Cl⁻ current which also involves PLC β production (Quick et al., 1994; DiMagno et al., 1996). Upon co-expression of the 5-HT_{2C} receptor and a brain-derived K⁺ channel in *Xenopus* oocytes, 5-HT suppresses K⁺ conductance through a calcium/calmodulin-activated phosphatase thought to dephosphorylate the K⁺ channel in a kinase-dependent manner, evoking its closure (Hoger et al., 1991).

The 5-HT_{2C} receptor also modulates the Kv1.5 channel through a PLC-dependent pathway in *Xenopus* oocytes (Panicker et al., 1991), which contrasts the observation that the 5-HT_{2C} receptor inhibits K⁺ channels through a PKC-dependent pathway in rat choroid plexus epithelial cells (Speake et al., 2004). The 5-HT_{2C} receptor also inhibits the GABA_A receptor in *Xenopus* oocytes through a calcium-dependent, phosphorylation-independent

mechanism (Huidobro-Toro et al., 1996) and by suppressing an inwardly rectifying K⁺ current in striatal cholinergic interneurons and rat brain slices (Blomeley and Bracci, 2005; Blomeley and Bracci, 2009). The 5-HT_{2C} receptor was G α_q -coupled to PLC activation and phosphoinositide hydrolysis to directly inhibit inwardly-rectifying K⁺ (GIRK) channels in POMC neurons of the arcuate (Qiu et al., 2007) as well as in lateral (but not basolateral) amygdala neurons (Yamamoto et al., 2014), which are known to stabilize resting membrane potential and therefore polarization of these neurons (Delmas and Brown, 2005). Hence while stimulation of 5-HT_{2C} receptor significantly modulates ion channel function, the involvement of specific signal transduction molecules in the processes is variable and underexplored at present.

IX. F. The 5-HT_{2C} receptor as an oncogene

5-HT is known to act as a mitogen to regulate the proliferation and differentiation of a variety of cells through its binding to several 5-HT receptors and control of downstream signaling (for review) (Fanburg and Lee, 1997). The NIH3T3 mouse fibroblast cells are often used to identify oncogenes (genes that can transform a cell to a tumor cell), because they display several well-characterized phenotypes that are indicative of cellular transformation, including the formation of foci (regions of dense cell growth within an otherwise confluent monolayer) (Land et al 1983). Stimulation of NIH3T3 cells transfected with the 5-HT_{2C} receptor leads to the generation of transformed foci, maintenance of which requires the activation of the 5-HT_{2C} receptor as a 5-HT_{2C} receptor antagonist blocks foci formation (Julius et al., 1988; Julius et al., 1989). Upon injection of these cells into nude mice, tumors form, a finding which led to the initial conclusion that the 5-HT_{2C} receptor is a proto-oncogene (Julius et al., 1989). The constitutive activity of the 5-HT_{2C} receptor also stimulated cell division in the transfected NIH3T3 cells and these data further suggested that multiple G proteins and signaling pathways were engaged in the cell division generated by agonist-evoked and constitutively active receptor signaling (Westphal and Sanders-Bush, 1996).

IX. G. Clinical relevance of the 5-HT_{2C} receptor

The 5-HT_{2C} receptor is widely distributed throughout the basal ganglia, limbic system and prefrontal cortex (Hoyer et al., 1986; Hoffman and Mezey, 1989; Molineaux et al., 1989; Mengod et al., 1990) and is well-poised to mediate 5-HT-dependent appetite, cognition, mood, movement, and sleep,

while dysfunctional 5-HT_{2C} receptor signaling has been implicated in neuropsychiatric (e.g., addiction, anxiety, depression) and neuropathological conditions (e.g., schizophrenia) as well as obesity and metabolic disorders (Berg et al., 2008a; Di Giovanni et al., 2010; Figure 14). Therefore, the 5-HT_{2C} receptor is a therapeutic target of great interest (for other reviews see Cunningham and Anastasio, 2014; Howell and Cunningham, 2015; Sullivan et al., 2015; Di Giovanni and De Deurwaerdere, 2016; Figure 12). The behavioral pharmacology of 5-HT_{2C} receptor ligands as well as the clinical relevance of a dysfunctional 5-HT_{2C} receptor system has recently been reviewed recently in detail (Cunningham and Anastasio, 2014; Howell and Cunningham, 2015; Sullivan et al., 2015; Di Giovanni and De Deurwaerdere, 2016), and an overview of clinical implications of the 5-HT_{2C} receptor system is provided here.

IX. G. 1. Substance use disorders (addiction)

The pharmacological and molecular mechanisms underlying the effects of abused drugs have been the subject of extensive study. As early work unfolded, a central concept emerged that the dopamine pathway projection from the VTA to the nucleus accumbens plays a mechanistic role in the rewarding and incentive-salience value of abused drugs (for reviews) (Koob and Volkow, 2010; Volkow et al., 2010). As the research progressed, the field began to recognize that the transition to problematic drug abuse and substance use disorder (addiction, dependence) involves an “expanding cycle of dysfunction” (Koob and Volkow, 2010), engaging multiple neurotransmitter substrates within limbic-corticostriatal circuitry, including 5-HT (for reviews) (Kalivas and Volkow, 2005; Koob and Volkow, 2010; Volkow et al., 2010; Cunningham and Anastasio, 2014; Muller and Homberg, 2015; Di Giovanni and De Deurwaerdere, 2016; Wolf, 2016). Much of the research has focused on abused drugs as rewarding substances and the evoked, long-lasting dysregulation of the dopamine mesoaccumbens pathway (for reviews) (Koob and Volkow, 2010; Volkow et al., 2010). However, a second focus has evolved toward identifying genotypic and phenotypic drivers of individual differences in vulnerability to substance use disorders and relapse since drug abuse culminates in addiction in only a subset of users (SAMHSA, 2015). Impulsivity, a predisposition toward rapid unplanned reactions to stimuli without regard to the negative consequences, is one such phenotype that contributes to initial drug use and is perpetrated by continued use of the abused drug (for reviews) (Moeller et al., 2001a; Moeller et al., 2001b; Cunningham and Anastasio, 2014). The impact of impulsivity in psychostimulant addiction is best described with roles for 5-HT and dopamine prominently identified (for reviews) (Moeller et al.,

2001a; Dalley and Roiser, 2012; Bari and Robbins, 2013; Cunningham and Anastasio, 2014; Logue and Gould, 2014). Cue reactivity, the sensitivity to cues previously linked with the drug-taking experience, is a second such phenotype which plays a prominent role in craving and relapse in humans (Carter and Tiffany, 1999; Drummond, 2001; O'Brien, 1998). The extended limbic-corticostriatal circuitry underlies both impulsivity and cue reactivity with multiple neurotransmitters involved (Childress et al., 1999; Bechara, 2005; Goldstein et al., 2007; Liu et al., 2012). Thus, addiction involves the generation of drug use within a background of vulnerability (e.g., propensity for impulsive behavior), and progresses with repeated drug exposure, neuronal plasticity and the entrainment of addictive behaviors. In particular, the role of the 5-HT_{2C} receptor in various aspects of these addictive processes has been well-studied for the class of psychostimulants; several studies have reported the efficacy of 5-HT_{2C} receptor agonists to suppress nicotine intake and nicotine-seeking (Grottick et al., 2001; Levin et al., 2011; Higgins et al., 2012). Relevant to this are the extensive studies of the role of the 5-HT_{2C} receptor in the rewarding and incentive-salience value of cocaine as well as factors involved in vulnerability to addiction and relapse, especially impulsivity and cue reactivity.

Cocaine is a psychomotor stimulant that inhibits 5-HT reuptake (Koe, 1976). Employing the self-administration assay, the preclinical model with the best validity for human drug-taking, studies demonstrated that voluntary cocaine administration elevates 5-HT efflux in the nucleus accumbens (Parsons and Justice, 1993; Parsons et al., 1995; Howes et al., 2000). Depletion of forebrain 5-HT induces compulsive cocaine-seeking, which is reversed by a 5-HT_{2C} receptor antagonist (Pelloux et al., 2012). Constitutive knockout of the 5-HT_{2C} receptor increases the motivation to take cocaine and enhances cocaine-induced elevation in dopamine in the nucleus accumbens (but not the dorsal striatum) of mice (Rocha et al., 2002). Pretreatment with a 5-HT_{2C} receptor agonist, systemically or into the VTA, enhances while systemic administration of a 5-HT_{2C} receptor antagonist inhibits the elevated dopamine efflux in the NAc evoked by non-response contingent cocaine administration (Navailles et al., 2004; Navailles et al., 2008; Cathala et al., 2015). The 5-HT_{2C} receptor control over dopamine function is thought to mediate in large part the efficacy of a selective 5-HT_{2C} receptor agonist (e.g., RO60-0175, WAY163909) to suppress the voluntary intake of cocaine (Grottick et al., 2000; Fletcher et al., 2002a; Fletcher et al., 2004; Neisewander and Acosta, 2007; Cunningham et al., 2011).

Stimulation of the 5-HT_{2C} receptor also dose-dependently suppresses reinstatement induced by cocaine and cocaine-associated cues as measures of cue reactivity (Grottick et al., 2000; Neisewander and Acosta, 2007; Burbassi and Cervo, 2008; Fletcher et al., 2008; Cunningham et al., 2011; Swinford-Jackson et al., 2016). Conversely, systemic administration of 5-HT_{2C} receptor antagonists have been shown to exert effects opposite to those following agonist administration, thus enhancing cocaine self-administration (Fletcher et al., 2002a) and cue reactivity (Fletcher et al., 2002a; Pelloux et al., 2012). In non-human primates, a 5-HT_{2C} receptor agonist attenuated the stimulant, reinforcing and reinstatement effects of cocaine, effects reversed by the selective 5-HT_{2C} receptor antagonist SB242084 (Manvich et al., 2012a; Manvich et al., 2012b; Ruedi-Bettschen et al., 2015). Interestingly, SB242084 induced modest stimulant effects and exhibited reinforcing effects in primates (Manvich et al., 2012a; Manvich et al., 2012b), but see contrasting results (Ruedi-Bettschen et al., 2015).

The efficacy of 5-HT_{2C} receptor agonists to suppress cue reactivity upon systemic administration is mirrored following intracranial microinjection of a 5-HT_{2C} receptor agonist into the mPFC which attenuates both cocaine- and cue-induced reinstatement (Pentkowski et al., 2010). These data highlight the importance of the 5-HT_{2C} receptor in regulation of cortical substrates underlying cocaine-associated cue reactivity specifically as 5-HT_{2C} receptor agonist microinfusions did not alter cocaine intake (Pentkowski et al., 2010). Thus, the 5-HT_{2C} receptor provides inhibitory tone over cocaine reward and cue reactivity as well as the neurochemical effects of cocaine (for reviews) (Cunningham and Anastasio, 2014; Howell and Cunningham, 2015; Di Giovanni and De Deurwaerdere, 2016), and mPFC-localized 5-HT_{2C} receptor underlie in part the generation of cue reactivity.

Cocaine administered non-response contingently has been reported to result in 5-HT_{2C} receptor neuroadaptations (Zayara et al., 2011; Craige et al., 2015) as well as regulation of the brain-specific snoRNA MBII-52 which is involved in the regulation of the 5-HT_{2C} receptor pre-mRNA (Chen et al., 2014). Abstinent cocaine users exhibit lower sensitivity to the effects of a 5-HT_{2C} receptor agonist (Lee and Meltzer, 1994; Buydens-Branchey et al., 1997; Patkar et al., 2006) while the highest cue reactivity was observed in those cocaine-dependent subjects carrying the C23S SNP in the 5-HT_{2C} receptor gene (Anastasio et al., 2014a), which may be associated with diminished 5-HT_{2C} receptor signal transduction (Lappalainen et al., 1995; Okada et al., 2004; Piva et al., 2011; Walstab et al., 2011). Further evidence that the functional status of the 5-HT_{2C} receptor in the mPFC (Lopez-Gimenez et

al., 2001; Liu et al., 2007; Nocjar et al., 2015) influences the incentive-motivational effects of cocaine and cocaine-associated cues has accumulated in rats (Anastasio et al., 2014a; Anastasio et al., 2014b; Swinford-Jackson et al., 2016). Cunningham and colleagues found that the highest levels of cocaine cue reactivity correlated with the lowest levels of mPFC 5-HT_{2C} receptor protein and a blunted sensitivity to the suppressive effects of the selective 5-HT_{2C} receptor agonist WAY163909 (Anastasio et al., 2014a; Swinford-Jackson et al., 2016). The efficacy of WAY163909 to suppress high levels of cue reactivity associated with extended forced abstinence (“incubation”) was also reduced at a timepoint (30 days) at which lower synaptosomal expression of 5-HT_{2C} receptor protein was observed in the mPFC (Swinford-Jackson et al., 2016), a key site involved in incubation phenomena (Koya et al., 2009; Whitfield et al., 2011; Ma et al., 2014). Further, a greater proportion of the expressed 5-HT_{2C} receptor protein was sequestered in the cytoplasmic (vs. membrane) compartment of the mPFC at prolonged *vs.* early forced abstinence, and there was an inverse correlation of the membrane to cytoplasmic 5-HT_{2C} receptor ratio in the mPFC with levels of cocaine cue reactivity. Collectively, these outcomes indicate that the functional status of the 5-HT_{2C} receptor system in the mPFC is a key contributor to cocaine cue reactivity and its incubation.

Cocaine-dependent subjects who express high cocaine cue reactivity express high impulsivity (Liu et al., 2011) and a similar relationship has been observed in cigarette smokers (Doran et al., 2007; Doran et al., 2008). In outbred rats, lower mPFC 5-HT_{2C} receptor membrane protein levels and an increase in edited 5-HT_{2C} receptor mRNA variants with reduced 5-HT_{2C} receptor signaling capacity distinguish high impulsive rats from low impulsive rats (Anastasio et al., 2014b) as well high and low responders to novelty, another model of addiction vulnerability (Dracheva et al., 2009). The virally-mediated knockdown of the 5-HT_{2C} receptor localized to the mPFC also results in elevated impulsivity and cue reactivity relative to controls (Anastasio et al., 2014b), suggesting that reduced 5-HT_{2C} receptor tone in the mPFC confers vulnerability to these interlocked behaviors (Anastasio et al., 2014b). The status of 5-HT_{2C} receptor function in the orbitofrontal cortex may also be a contributor to the vulnerability of impulsive rats to cocaine reward and cue reactivity (Besson et al., 2013). Together, these data suggest that the functional status of the cortical 5-HT_{2C} receptor system may be a mechanistic driver in the generation of cocaine use disorder and relapse phenomena.

The body of knowledge in support of a role of the 5-HT_{2C} receptor in regulating the rewarding properties and voluntary intake of other abused substances is less well-developed than that of cocaine and nicotine. However, stimulation of the 5-HT_{2C} receptor has been noted to suppress ethanol self-administration (Maurel et al., 1999; Tomkins et al., 2002; Kasper et al., 2013; Rezvani et al., 2014) and reinstatement in rodents (Kasper et al., 2013). Exposure to ethanol vapor for several days is associated with increased expression of the 5-HT_{2C} receptor transcript in several corticostriatal and hypothalamic nodes (Yoshimoto et al., 2012), higher levels of the 5-HT_{2C} receptor protein in the NAc (Yoshimoto et al., 2012) and enhanced pre-mRNA editing of the 5-HT_{2C} receptor (Watanabe et al., 2014), suggesting that neuroadaptations in the 5-HT_{2C} receptor function are mechanistically involved in ethanol preference behavior.

Pretreatment with 5-HT_{2C} receptor ligands have been shown to impact various behavioral sequela associated with *d*-amphetamine (O'Neill et al., 1999; Rippberger et al., 2015; Wöhr et al., 2015), MDMA (Bankson and Cunningham, 2002; Fletcher et al., 2002b), methamphetamine (Steed et al., 2011; Graves and Napier, 2012), and the marijuana alkaloid Δ^9 -THC (Ji et al., 2006), suggesting that rich prospects remain to explore the potential therapeutic value of selective 5-HT_{2C} receptor agonists in addictive processes engaged by these abused drugs remain.

5-HT is involved in the pharmacology of opioid abused drugs (including heroin and prescription opioids) (Tao and Auerbach, 1994; Tao et al., 1998; Singh et al., 2003) and systemic administration of a 5-HT releaser (e.g. dexfenfluramine) was shown to suppress heroin self-administration in rats (Wang et al., 1995). Pretreatment with a selective 5-HT_{2C} receptor agonist also reduced opioid-induced behavioral sensitization (Wu et al., 2015; Zhang et al., 2016). Recent studies have further demonstrated that lorcaserin significantly decreases the reinforcing effects of oxycodone and shifts the oxycodone dose-effect curve downwards at doses that do not alter motor activity (Neelakantan, 2017). Thus, 5-HT_{2C} receptor agonists may prove therapeutically useful to promote recovery and extend abstinence from several classes of abused drugs.

IX. G. 2. Appetite, satiety and obesity

Hunger is the physiological need for food. Appetite (the desire for food), satiation (the end of the desire for food during a meal), and satiety (the feeling of ‘fullness’ that prevents further eating before the return of hunger) include both internal (e.g., glucose homeostasis) and conditioned factors (e.g., hedonics) (Blundell, 1999). 5-HT in the CNS has long been implicated in the control of the processes involved in satiation and satiety (Lucki, 1998; Halford and Blundell, 2000; Saper et al., 2002; Voigt and Fink, 2015). The 5-HT releaser *d*-fenfluramine, employed clinically for weight loss (until withdrawn in 1997), its metabolite *d*-norfenfluramine and preferential 5-HT_{2C} receptor agonists (e.g. mCPP) evoke hypophagia in rodents, which is associated with increased satiety, an effect blocked by 5-HT_{2C} receptor antagonists or constitutive knockdown of the 5-HT_{2C} receptor (Kennett and Curzon, 1988; Tecott et al., 1995; Halford et al., 1997; Vickers et al., 1999; Dalton et al., 2006; Nonogaki et al., 2008). Selective 5-HT_{2C} receptor agonists (e.g., lorcaserin, RO60-0175) have been consistently demonstrated to suppress food intake (Clifton et al., 2000; Somerville et al., 2007; Thomsen et al., 2008; Grottick et al., 2015; Higgs et al., 2015; for review see Higgins et al., 2020). In fact, the selective 5-HT_{2C} receptor agonist WAY163909 dose-dependently decreases food intake in normal Sprague–Dawley rats, obese Zucker rats and mice with diet-induced obesity (Dunlop et al., 2005) without the anxiogenic profile of mCPP (Dunlop et al., 2006). Tecott and colleagues reported that the constitutive 5-HT_{2C} receptor knockout mouse exhibited hypophagia and increased body mass in the context of both insulin resistance and late-onset obesity (Tecott et al., 1995; Nonogaki et al., 2008), while weight gain as well as a greater relative risk of metabolic dysfunction and diabetes develops with the chronic treatment of atypical antipsychotics with 5-HT_{2C} receptor antagonist properties (e.g., olanzapine) in humans and animals (Wirshing et al., 1999; Kirk et al., 2009). Interestingly, a selective 5-HT_{2C} receptor antagonist has been reported to variably increase (Bonhaus et al., 1997) or decrease food intake depending upon the preclinical model employed (Kennett et al., 1997; Murotani et al., 2011).

The behavioral satiety sequence (BSS) describes the orderly process through which eating transitions to other behaviors (e.g., grooming, resting) and is a well validated model for analyzing satiation (meal termination) and satiety (post-ingestive inhibition of food intake) in rodents and humans (for review) (Rodgers et al., 2010). Consistent with the proposed role of 5-HT to promote satiety, *d*-fenfluramine, its metabolite analogs, preferential and selective 5-HT_{2C} receptor agonists (Halford et al., 1998; Clifton et al., 2000; Hewitt et al., 2002; Dalton et al., 2006; Somerville et al., 2007) accelerate the BSS without disruption of its integrity (for review) (Rodgers et al., 2010). For example, *d*-fenfluramine and RO60-0175 reduced the rate of feeding

and meal size as well as increased the latency to feed consistent with enhanced satiety (Clifton et al., 2000). The effects of *d*-fenfluramine on the BSS was markedly reduced in mice constitutively lacking the 5-HT_{2C} receptor (Vickers et al., 1999). In contrast, appetite-enhancing drugs (e.g. cyproheptadine) (Chinuck et al., 2007) disrupt the satiety sequence (Bergen, 1964; Ishii et al., 2003). A recent microstructural analysis of ingestive behavior found that lorcaserin reduced the number of bouts of licking behavior (Higgs et al., 2016) indicative of the promotion of satiety (Davis et al., 2001). Thus, the 5-HT_{2C} receptor is an important mediator of food intake through the control of satiety mechanisms (for reviews) (Lucki, 1998; Halford and Blundell, 2000; Voigt and Fink, 2015).

Investigations of 5-HT involvement in the mechanisms underlying satiety have focused predominantly on neural loci in the hypothalamus and midbrain/hindbrain circuits which synchronize energy balance and glucose homeostasis in concert with peripheral systems (for reviews) (Saper et al., 2002; Gautron et al., 2015; Voigt and Fink, 2015). The 5-HT neurons in the dorsal and median raphe innervate multiple hypothalamic subnuclei (van de Kar and Lorens, 1979; Peyron et al., 1998) which richly express 5-HT_{2C} receptor mRNA and protein (Hoffman and Mezey, 1989; Molineaux et al., 1989; Mengod et al., 1990). A subpopulation of arcuate POMC neurons express the 5-HT_{2C} receptor and are activated by *d*-fenfluramine and mCPP (Heisler et al., 2002; Lam et al., 2008). Elmquist and colleagues elegantly demonstrated that the activation of the 5-HT_{2C} receptor localized to POMC neurons stimulates POMC synthesis and its cleavage into α -melanocyte stimulating hormone, which acts on melanocortin 4 receptors in the paraventricular nucleus of the hypothalamus to promote satiety, weight loss and glucose regulation (Heisler et al., 2007a; Zhou et al., 2007; Xu et al., 2008; Berglund et al., 2013). Stimulation of the 5-HT_{2C} receptor following application of mCPP depolarized a subpopulation of POMC neurons potentially via PLC-dependent activation of transient receptor potential channels (TRPC), independent of GIRK channel activity (Sohn et al., 2011). In mice that selectively lack the 5-HT_{2C} receptor in POMC neurons, body weight was normal, however these mice were insensitive to *d*-fenfluramine- or mCPP-evoked hypophagia and developed metabolic dysfunction, including hyperinsulinemia, hyperglucagonemia, hyperglycemia, and insulin resistance (Berglund et al., 2013). Rescue of 5-HT_{2C} receptor in POMC neurons of 5-HT_{2C} receptor null mice normalized food intake, adiposity and body weight as well as the anorexigenic effects of *d*-fenfluramine and mCPP (Xu et al., 2008). Interestingly, POMC expression within 5-HT_{2C} receptor-expressing neurons in the arcuate regulates whole body energy balance, body weight and adiposity in male, but not female, mice; these

authors proposed that this molecular mechanism may explain in part sex differences in the prevalence of obesity (Burke et al., 2016). This provocative idea requires further investigation, however, the observations corroborate the conclusion that the 5-HT_{2C} receptor in POMC neurons is a required component of the neural mechanisms that control energy and glucose homeostasis.

The adipocyte-derived *ob* gene product leptin (Halaas et al., 1995) acts via the leptin receptor (Tartaglia et al., 1995) to regulate long-term energy stores and homeostasis (Friedman, 2014). This landmark discovery marshalled in an era of advanced understanding of the CNS circuits involved in obesity (for review see Friedman, 2014). It was not long before genetic deletion of the leptin receptor in neurons was shown to result in hyperphagia and obesity (Cohen et al., 2001), while the rescue of central leptin receptor signaling corrects the obesity and diabetes phenotype of *db/db* mice which possess mutations in the leptin receptor (de Luca et al., 2005). Mice deficient for both leptin and the 5-HT_{2C} receptor exhibited a synergistic disruption of glucose homeostasis and a profound diabetes phenotype (Wade et al., 2008). On the other hand, transgenic mice that overexpress leptin but lack the 5-HT_{2C} receptor exhibited a lean phenotype on a chow diet; however, on a high fat diet, these mice developed diet-induced obesity (Wang and Chehab, 2006). In POMC neurons, pharmacological stimulation of the 5-HT_{2C} receptor was shown to activate the same POMC neurons activated by leptin (Qiu et al., 2010). Lastly, co-administration of the preferential 5-HT_{2C} receptor agonist mCPP plus leptin was recently shown to have an additive effect on reducing body weight in diet-induced obese mice (Yan et al., 2015). The growing knowledge of the interface between leptin and 5-HT regulatory systems prompted Halford and Blundell to propose that these systems function independently, but coordinate within the hypothalamus, to control satiety and energy reserves (Halford and Blundell, 2000).

The drive to eat palatable foods, comprised essentially of high fat and/or sugars, involves hedonic mechanisms which are also important to maintaining the homeostatic nutritional requirements for energy balance (for reviews see Saper et al., 2002; Volkow et al., 2012). These foods activate limbic-cortico-striatal systems which mediate reward and motivation (for reviews) (Gautron et al., 2015; Voigt and Fink, 2015) and hedonic eating has been identified as a contributor to the obesity epidemic (Saper et al., 2002; Volkow et al., 2012). Preclinical analysis of the rewarding (reinforcing) and motivational effects of food self-administration can be evaluated on a fixed ratio (FR) and a progressive ratio (PR) schedule, respectively, in either

freely-fed or food-restricted animals. Performance under PR schedules is thought to reflect the motivational “efficacy” of the food given that deprivation level as well as reinforcer magnitude can increase breakpoints on the PR schedule (Hodos and Kalman, 1963). The preferential (mCPP, MK212) and selective 5-HT_{2C} receptor agonists (R0 60-0175) decrease the breakpoint for a grain reinforcer on a PR schedule in food-restricted pigeons (Wolff and Leander, 2000). WAY163909 dose-dependently reduces self-administration of sucrose on an FR schedule in freely-fed rats, an effect blocked by pretreatment with SB242084 (Cunningham et al., 2011) while mCPP decreases the breakpoint for Ensure in freely-fed mice (Ward et al., 2008). Lorcaserin efficaciously suppresses the rewarding effects of food in food-restricted rats based upon its 5-HT_{2C} receptor agonist actions (Higgins et al., 2012; for review see Higgins et al., 2020). Interestingly, while 5-HT_{2C} receptor agonists effectively suppress cocaine-seeking (for reviews see Cunningham and Anastasio, 2014; Howell and Cunningham, 2015), WAY163909 failed to affect sucrose-seeking (Cunningham et al., 2011), suggesting that the 5-HT_{2C} receptor differentially regulates the incentive-salience value of cocaine- vs. sucrose-associated cues. Thus, there is evidence that the 5-HT_{2C} receptor system controls the hedonic, rewarding aspects of palatable food; the brain locus of action for the 5-HT_{2C} receptor to control these behaviors requires further evaluation (Pratt et al., 2009; Pratt et al., 2012; Clissold et al., 2013).

Multiple lines of investigation suggest a relationship between 5-HT_{2C} receptor SNPs and obesity, antipsychotic-induced weight gain, and transcriptional activity of the *HTR2C* gene. Eight *HTR2C* gene polymorphisms have been reported in the literature: three polymorphisms, as well as a GT nucleotide repeat variation, have been identified in the promoter (Xie et al., 1996); three polymorphisms have been reported within intronic regions (Gibson et al., 2004); one polymorphism has been reported in the coding region resulting in the replacement of cysteine with serine at amino acid 23 (C23S) in the amino-terminus of the receptor (Lappalainen et al., 1995); and there is one polymorphism in the 3' untranslated region (Song et al., 1999).

The C23S SNP occurs with a frequency of approximately 10-15% in the human population (Lappalainen et al., 1995). However, there is no evidence for an association of this SNP with obesity (Lentes et al., 1997; Gibson et al., 2004). The promoter haplotype -995A/-759T/-697C has been reported to be associated with obesity in a Japanese population (Yuan et al., 2000) and the -759C allele to be more common in obese than non-obese

Caucasian women (Pooley et al., 2004). Several studies suggest that the -759T allele may be associated with less weight gain following antipsychotic drug treatment (Reynolds et al., 2003; Miller, 2005; Templeman et al., 2005). While additional research has reported no association between antipsychotic-induced weight gain (AIWG) and *HTR2C* promoter polymorphisms (Basile et al., 2002; Tsai et al., 2002; Theisen et al., 2004; Templeman et al., 2005), others have reported an association of the -759C allele with AIWG (Wallace et al., 2011). It is interesting to note that greater promoter activity, resulting in increased *HTR2C* transcription, has been reported to be associated with the -759T allele (Yuan et al., 2000). Also, in a luciferase-based reporter assay, *HTR2C* promoter haplotypes containing the -759C allele showed lower transcriptional activity than those containing the -759T haplotype (Buckland et al., 2005). While these studies suggest that the -759C/T polymorphism may regulate gene transcription *in vitro*, a subsequent study reported that 5-HT_{2C} receptor mRNA levels in the frontal cortex of 43 subjects are unaffected by -759C/T status (Pooley et al., 2004).

IX. G. 3. Schizophrenia

Both selective 5-HT_{2C} receptor agonists and 5-HT_{2C} receptor antagonists have been suggested for the treatment of schizophrenia. Antipsychotic medications with a profile as a 5-HT_{2C} receptor antagonist seem to be effective to suppress positive symptoms, while 5-HT_{2C} receptor agonists appear useful for inhibition of the negative symptoms and cognitive impairments in schizophrenia (Wood et al., 2001; Rosenzweig-Lipson et al., 2007a; Rosenzweig-Lipson et al., 2012) with fewer motor side effects (Di Giovanni et al., 2006; Di Giovanni and De Deurwaerdere, 2016). The therapeutic potential of a specific antipsychotic would depend indirectly on the opposite modulation that these receptors exert on dopaminergic systems and the preferential 5-HT_{2C} receptor modulation of the mesocortical and limbic system vs. the nigrostriatal system (Di Giovanni et al., 2006; Di Giovanni and De Deurwaerdere, 2016). Moreover, the analysis of the pharmacological profile of some atypical antipsychotics led to 5-HT_{2C} receptor blockade as a valuable strategy to improve the efficacy of dopamine antagonists in long-term treatments (Meltzer, 1999). Vabicaserin is a novel antipsychotic and anorectic agent with high agonist efficacy at the 5-HT_{2C} receptor (Dunlop et al., 2011) and has been shown to be effective in treating schizophrenia, improving positive symptoms (Shen et al., 2014). Unfortunately, the clinical development of vabicaserin by Pfizer was terminated since the drug failed to meet the primary efficacy endpoint in clinical trials (<https://clinicaltrials.gov/ct2/show/results/NCT00563706?term=vabicaserin&rank=2>).

Sertindole, a newer antipsychotic (Juruena et al., 2011) alternatively exerts a potent inverse agonist activity at the 5-HT_{2C} receptor (Herrick-Davis et al., 2000), along with dopamine D₂, α_1 -adrenergic receptor and 5-HT_{2A} receptor blockade (Hietala et al., 2001). Sertindole is effective in reducing anxiety, improving cognition/memory and brain plasticity, most probably by reducing 5-HT_{2C} receptor tonic activation (Hietala et al., 2001).

Several lines of evidence have identified the 5-HT_{2C} receptor in the origin of some side effects, both motor and metabolic, associated with the chronic use of antipsychotic drugs. For instance, 5-HT_{2C} receptor blockade seems to contribute to anti-psychotic-induced weight gain (AIWG), one of the most common and debilitating side effects induced by chronic treatment with these medications (Reynolds et al., 2005; Shams and Muller, 2014). Therefore, 5-HT_{2C} receptor agonists may have an antipsychotic activity without inducing AIWG and alterations of glucose homeostasis caused by atypical antipsychotics. However, agomelatine as a 5-HT_{2C} receptor antagonist has a more favorable profile and does not influence body weight in depressed patients (Pompili et al., 2013).

Other important side effects induced by the chronic use of antipsychotics that may be related to the activation of the 5-HT_{2C} receptor are the movement disorders, such as dystonia, acute Parkinsonism and tardive dyskinesia, referred to globally as antipsychotic-induced extrapyramidal side effects (EPS) (Tarsy and Baldessarini, 1984; Tarsy et al., 2002; Janno et al., 2004). The inverse agonism at the 5-HT_{2C} receptor evoked by some atypical antipsychotics might indeed explain their fewer EPS effects (Herrick-Davis et al., 2000). Consistently, ritanserin, a non-selective 5-HT₂ antagonist, limits the occurrence of EPS in patients treated with typical neuroleptic drugs (Bersani et al., 1990). Moreover, the affinity of typical antipsychotics towards the 5-HT_{2C} receptor inversely correlates to the EPS severity (Richtand et al., 2007; Richtand et al., 2008). Nevertheless, experimental evidence suggests that concurrent 5-HT_{2C} receptor agonism might increase the efficacy of typical and atypical antipsychotics, allowing dose-sparing with a reduction of side-effects (Grauer et al., 2009).

IX. G. 4. Mood disorders and anxiety

Depression and anxiety are complex illnesses that have in common an altered central 5-HT tone. Compelling evidence accumulating over more than four decades has indicated the 5-HT_{2C} receptor is critically involved in the serotonergic regulation of these pathological states. Indeed, mCPP and MK-212 induce anxiogenic-like behaviors in animals (Kennett et al., 1989; Benjamin et al., 1990; Shepherd et al., 1994; Bilkei-Gorzo et al., 1998; Millan, 2005; Martin et al., 2013) and induce anxiety and panic when administered in humans (Lowy and Meltzer, 1988; Kahn and Wetzler, 1991; Sevy et al., 1994; Southwick et al., 1997; Gatch, 2003). These anxiogenic effects are likely due to the activation of the 5-HT_{2C} receptor. In agreement, Tecott and colleagues showed that 5-HT_{2C} receptor knockout mice exhibit an anxiolytic-like phenotype not attributable to locomotor alterations (Heisler et al., 2007b). Moreover, desensitization of the 5-HT_{2C} receptor in SERT knockout mice has been shown to contribute to the moderation of the anxiety phenotype (Martin et al., 2015) and to the antidepressant effects (Prisco and Esposito, 1995; Di Giovanni et al., 2006). On the other hand, mCPP induced anxiolytic effects in mice (Nic Dhonnchadha et al., 2003), but showed antidepressant-like properties in the anhedonia model in rats (Moreau et al., 1996) and was recently observed to be anorexigenic without inducing anxiety/depression in humans (Thomas et al., 2014). Moreover, RO60-0175 presented an antidepressant profile or an anxiolytic/anti-compulsive profile in some tests (Cryan and Lucki, 2000; Nic Dhonnchadha et al., 2003). Interestingly, anxiogenic responses induced by RO60-0175 (Martin et al., 2013; Martin et al., 2014) are sometimes related to its sedative properties (Kennett et al., 2000). CP809101 is ineffective in some models (Siuciak et al., 2007) and anxiogenic in others (Strong et al., 2009; Christianson et al., 2010; Strong et al., 2011).

Consistent with proposed anxiogenic effects of 5-HT_{2C} receptor activation, 5-HT_{2C} receptor antagonists display anxiolytic/antidepressant properties in numerous tests (Kennett et al., 1994; Kennett et al., 1996; Kennett et al., 1997; Wood et al., 2001; Millan, 2005; Harada et al., 2006). Interestingly, there are models in which both 5-HT_{2C} receptor agonists and antagonists display anxiolytic/antidepressant properties, including the chronic mild stress-induced anhedonia model and the activity consequent to olfactory bulbectomy. The tendency is that selective 5-HT_{2C} receptor agonists would be more appropriate in the treatment of depression, obsessive-compulsive disorder or panic attacks, while the antagonists would be better suited for generalized anxiety and obsessive-compulsive disorder (Jenck et al., 1998; Millan, 2003; Millan, 2005). On the contrary, the atypical antidepressants mirtazapine and mianserin (Hayasaka et al., 2015) and a recently developed new antidepressant agomelatine (Millan et al., 2003; Millan, 2005; Millan et

al., 2011) have clear antagonistic 5-HT_{2C} receptor profiles. The lack of selectivity of the pharmacological 5-HT_{2C} receptor tools employed to date as well as the limited appreciation of 5-HT_{2C} receptor function and its unique molecular mechanisms (e.g. edited and spliced 5-HT_{2C} receptor isoforms, constitutive activity, biased signaling) complicate final conclusions at present.

The paradoxical efficacy of both 5-HT_{2C} receptor agonists and antagonists is likely due to the complex neurobiological basis of depression/anxiety and the fact that different behavioral responses involve different areas expressing the 5-HT_{2C} receptor, of which activation produces opposite effects (Millan et al., 2005). Indeed, local activation of the 5-HT_{2C} receptor in the basolateral part of the amygdala induces anxiety (Campbell and Merchant, 2003), while the activation of those in the dorsal periaqueducal grey triggers anxiolytic responses (Yamashita et al., 2011). Thus, the long-term antidepressant effect of compounds such as SSRIs may be related to a region-dependent desensitization of the 5-HT_{2C} receptor in determined regions (Prisco and Esposito, 1995; Di Giovanni et al., 2006; Martin et al., 2014).

In summary, selective 5-HT_{2C} receptor antagonists may present promising molecules for developing new antidepressants/anxiolytic drugs. These could be considered as monotherapy or for augmentation strategies to improve other antidepressant responses (Cremers et al., 2004; Cremers et al., 2007) with the ability to reverse several SSRI-induced side effects.

IX. G. 5. Epilepsy

Early evidence implicated a 5-HT involvement in the pathophysiology of epilepsy (Bonnycastle et al., 1957). Since then, evidence has accumulated clearly showing that there is a direct link between 5-HT levels and epilepsy. Increasing 5-HT levels in the CNS is generally antiepileptic, while a decrease favors epileptogenesis and seizure generation (for reviews see Bagdy et al., 2007; Guiard and Di Giovanni, 2015). Moreover, a common 5-HT dysfunction might underlie both epilepsy and comorbid depression seen in patients with epilepsy (Kanner et al., 2012; Guiard and Di Giovanni, 2015).

The 5-HT_{2C} receptor is thought to be involved in seizure generation and cell excitability (Jakus et al., 2003; Isaac, 2005). Tecott and colleagues showed that 5-HT_{2C} receptor knockout mice display spontaneous convulsive generalized seizures which cause their high mortality rate (Tecott et al., 1995) and a reduced threshold for various convulsing stimuli (Applegate and Tecott, 1998; Heisler et al., 1998). Conversely, 5-HT_{2C} receptor activation increased the threshold of general convulsion induced by pentylenetetrazole and electroshock in mice (Upton et al., 1998). The 5-HT_{2C} receptor also negatively controls non-convulsive generalized seizures. Di Giovanni and colleagues showed that, in the polygenic animal model of absence epilepsy, the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) (Danober et al., 1998), RO60-0175 (unpublished observation), lorcaserin and CP809101 were capable of blocking spike and wave discharges (Venzi et al., 2016). Interestingly, as expected, SB242084 blocked the effect of lorcaserin and CP809101, but also showed some anti-absence effects. One possible mechanism by which 5-HT_{2C} receptor activation exerts antiepileptic effects is via the normalization of the aberrant GABA_A receptor tonic inhibition in the ventrobasal thalamus seen in different animal models of absence epilepsy (Cope et al., 2009; Crunelli and Di Giovanni, 2014; Crunelli and Di Giovanni, 2015). Findings with the GAERS animal model of absence epilepsy are in agreement with those obtained in another model of absence epilepsy, the Wistar Albino Glaxo/Rij-rat in which mCPP decreases the cumulative duration of spike and wave discharges via the activation of the 5-HT_{2C} receptor (Jakus et al., 2003; Jakus and Bagdy, 2011).

The 5-HT_{2C} receptor system seems devoid of any modulatory role in partial seizures, or paradoxically, have a pro-epileptic role in this type of epilepsy. Indeed, observations from Di Giovanni's group show that mCPP and lorcaserin, but not RO60-0175, were able to halt hippocampal after discharges in a rat model of temporal lobe epilepsy (TLE), an effect potentiated and insensitive to SB242084 pretreatment (Orban et al., 2014). These data indicate that other 5-HT receptors are involved in the antiepileptic effect of mCPP and lorcaserin, probably the 5-HT_{1A/7} receptor (Orban et al., 2013) or unknown targets, confirming previous findings (Damjanoska et al., 2003; Navailles et al., 2013a; Orban et al., 2014).

In summary, 5-HT_{2C} receptor agonists may have new therapeutic utility in epilepsy. In particular, the FDA-approved lorcaserin may be useful for the treatment of human generalized convulsive and non-convulsive epilepsy, very important in consideration of the fact that epileptic drug pipeline is

limited. Moreover, activation of the 5-HT_{2C} receptor may also be useful for treating comorbid neuropsychiatric comorbidity commonly seen in patients with epilepsy (Di Giovanni and De Deurwaerdere, 2016; Venzi et al., 2016).

IX. G. 6. Sleep

A role for 5-HT in the sleep-wake cycle is well documented as 5-HT has been shown to promote wakefulness and reduce rapid eye movement (REM) sleep (for review see Monti, 2011). In general, non-selective 5-HT_{2A/2C} receptor agonists and selective 5-HT_{2C} receptor agonists increase wakefulness and decrease slow wave (SW) and/or rapid eye movement (REM) sleep following systemic administration in rats, while non-selective 5-HT_{2A/2C} receptor antagonists and selective 5-HT_{2C} receptor antagonists tend to decrease wakefulness and promote SW with reduced REM sleep (for review see Monti, 2011). In contrast to what may be anticipated, 5-HT_{2C} receptor knockout mice display increased wakefulness with reduced SW and non-REM sleep (Frank et al., 2002). The increased wakefulness and reduced SW sleep have been attributed to compensatory mechanisms, possibly including the enhanced dopaminergic and adrenergic neurotransmission that occurs as a result of the constitutive knockout of the 5-HT_{2C} receptor (Frank et al., 2002).

The non-selective 5-HT_{2C/2A} receptor antagonists ritanserin and ketanserin enhanced SW sleep in a dose-dependent manner in human subjects with normal sleep patterns (Sharpley et al., 1990; Idzikowski et al., 1991). Similar results were observed following treatment with seganserin, ICI169369, and SR46349B (Dijk et al., 1989; Landolt et al., 1999). In addition, ritanserin has been reported to improve SW sleep in subjects with insomnia (Adam and Oswald, 1989), major depression (Staner et al., 1992) and generalized anxiety disorder (da Roza Davis et al., 1992). In patients with schizophrenia, typical and atypical antipsychotic drugs with non-selective 5-HT_{2C/2A} receptor antagonist properties tend to increase total sleep time and efficiency, but reduce the latency and duration of REM sleep (Taylor et al., 1991; Nofzinger et al., 1993; Wetter et al., 1996; Sharpley et al., 2000; Muller et al., 2004). Taken together, these results indicate an involvement of the 5-HT_{2C} receptor in the maintenance of normal sleep architecture and suggest possible avenues for future research and medications development for the treatment of insomnia.

IX. G. 7. Clinical impact of RNA editing of the 5-HT_{2C} receptor

Many studies have attempted to analyze 5-HT_{2C} receptor RNA editing profiles in postmortem samples from patients with psychiatric disorders. The majority of these reported that 5-HT_{2C} receptor RNA editing in postmortem prefrontal cortex samples from patients with schizophrenia or bipolar disorder is not altered (Niswender et al., 2001; Dracheva et al., 2003; Iwamoto and Kato, 2003; Dracheva et al., 2008b; Zhu et al., 2012). In contrast, mixed results were obtained from postmortem prefrontal cortex samples from patients with major depression, with some studies reporting no change (Niswender et al., 2001; Zhu et al., 2012; Lyddon et al., 2013) and other studies reporting a decrease (Gurevich et al., 2002b) or increase in 5-HT_{2C} receptor RNA editing (Iwamoto and Kato, 2003). Several studies have reported that psychiatric patients who committed suicide had increased 5-HT_{2C} receptor RNA editing with increased levels of the less active 5-HT_{2C} receptor isoforms (Niswender et al., 2001; Gurevich et al., 2002b; Iwamoto and Kato, 2003; Dracheva et al., 2008b; Lyddon et al., 2013; Di Narzo et al., 2014) as well as increased expression of ADAR1 (Simmons et al., 2010). However, there were notable differences in the patterns of 5-HT_{2C} receptor RNA editing that were reported in these studies. In a similar fashion, there is great variation in the reported effects of antipsychotic and antidepressant medications on RNA editing (Sodhi et al., 2005; Abbas et al., 2010; Iwamoto et al., 2011; Martin et al., 2014) and the effect of altered synaptic 5-HT levels on 5-HT_{2C} receptor RNA editing (Gurevich et al., 2002a; Abbas et al., 2010; Lyddon et al., 2010; Moya et al., 2011). These variations in results highlight the requirement of a large sample size and the need to analyze hundreds of sequences per sample to obtain an accurate profile of all possible RNA editing events. In some of the more recent studies, the statistical power of the results has been increased by employing high-throughput sequencing methods that allow larger numbers of samples to be processed, in a more timely and less expensive manner, along with the ability to analyze hundreds or even thousands of sequences from a single sample (Lanfranco et al., 2009; Abbas et al., 2010; Morabito et al., 2010b; O'Neil and Emeson, 2012; Zhu et al., 2012; Lyddon et al., 2013; Anastasio et al., 2014b; Di Narzo et al., 2014). While these studies have reported changes in 5-HT_{2C} receptor RNA editing patterns following chronic drug treatment in rodent models or changes in editing in patients with psychiatric disorders who committed suicide, the magnitude of the observed change is small, typically less than 10%. This raises several important questions. Could such a small change in 5-HT_{2C} receptor editing be physiologically relevant? Could there be larger changes in 5-HT_{2C} receptor RNA editing occurring within discrete neuronal populations and could these changes be underestimated or masked when sampling an entire brain region?

A few of the studies described in the preceding paragraph examined RNA editing in both cortical and subcortical regions, while many studies examined RNA editing only in the prefrontal cortex of patients with psychiatric illnesses. Since the 5-HT_{2C} receptor is located within mesolimbic and mesostriatal regions that have been shown to regulate the activity of ascending dopamine, it still remains possible that changes in RNA editing occurring within discrete populations of neurons in cortical and/or subcortical regions could play a role in the etiology of psychiatric disorders. Future studies capable of examining RNA editing profiles of individual neuronal populations within localized sub-regions will provide a more accurate picture of the relationship between 5-HT_{2C} receptor RNA editing, 5-HT_{2C} receptor isoform expression, and the functional regulation of 5-HT and dopamine neurotransmission in psychiatric disorders.

X. 5-HT₃ receptor

X. A. Introduction

The 5-HT₃ receptor is a Cys-loop ligand-gated ion channel, which is structurally and functionally distinct from the other six classes of 5-HT receptors whose metabotropic actions are mediated via G-proteins. 5-HT₃ receptors are pentameric assemblies of five identical or non-identical subunits that pseudo-symmetrically surround the ion pore (Boess et al., 1992; Green et al., 1995). Each subunit has a large extracellular domain (ECD), four transmembrane domains (TMD I-IV), and an intracellular domain (ICD) between M3 and M4.

The ECD contains the agonist binding site, which is located at the interface of two adjacent subunits and is formed by three loops (A-C) from one (the principal) subunit and three β -strands (referred to as loops D-F) from the adjacent or complementary subunit; key residues that contribute to the binding pocket in these loops have been identified from structural data (Hassaine et al., 2014) and these are supported by a range of functional studies (for reviews see Barnes et al., 2009; Thompson et al., 2010). The binding site contains the aromatic box, which is found in all Cys-loop receptors, and in the homomeric 5-HT_{3A} receptor is constituted of W183 (loop B), W90 (loop D), Y153 (loop E), F226 (loop C) and Y234 (loop C).

The transmembrane domain of each 5-HT₃ receptor subunit is composed of four (M1-M4) transmembrane α -helices, with short loops between M1 and M2 (intracellular), and M2 and M3 (extracellular). The M2 α -helices line the ion pore and pore facing residues contribute to ion flux and selectivity. M1, M3 and M4 both protect M2 from the surrounding membrane lipids, and play a role in receptor function. The conserved proline in M1, for example, is essential for activation, and the receptor is expressed but cannot function when this proline is replaced by alanine, glycine or leucine (Dang et al., 2000). However, substitution with non-canonical amino acids that lack hydrogen bond donor activity yields active channels similar to wild-type receptors. These suggest flexibility in secondary structure in this region of M1 is a key element in channel gating.

The ICD is formed primarily by the large M3-M4 intracellular loop; this region is responsible for receptor modulation, and also plays a role in trafficking. Deletion studies reveal the ICD is not essential, as the mouse 5-HT₃A receptor subunit ICD can be replaced by the heptapeptide M3-M4 linker of GLIC without loss of function (Jansen et al., 2008). Further evidence that the ICD can function as a separate domain comes from studies where it was added to the GLIC linker peptide, resulting in modification of function by the intracellular protein RIC-3 (Goyal et al., 2011).

ICD structural details are sparse, but each subunit is known to possess an α -helix which contributes to openings, known as portals, just below the level of the membrane. The residues that line these portals are important for ion conductance: when the 5-HT₃A subunit residues are replaced with those found in the 5-HT₃B subunit, the single channel conductance, which is very low in the homomeric 5-HT₃A receptor, is increased to that of the heteromeric 5-HT₃AB receptor (Kelley et al., 2003).

Only 5-HT₃A subunits can form functional homomeric 5-HT₃ receptors. These subunits have been cloned from a range of species including human hippocampus, amygdala, and colon (Belelli et al., 1995) (Miyake et al., 1995) guinea pig small intestine (Lankiewicz et al., 1998), ferret colon (Mochizuki et al., 2000) and dog brain (Jensen et al., 2006), but homologues are absent from invertebrates (although there is a related 5-HT-gated anion selective receptor). Multiple isoform of 5-HT₃A subunits are known: Alternative splicing of the transcript encoding guinea pig, mouse, and rat, (but not dog, ferret, or human) 5-HT₃A subunits results in 'long' (5-HT₃A(a)) and short (5-HT₃A(b)) isoforms, where the 5-HT₃A(b) isoform lacks 5 or 6 amino acid residues within the M3-M4 intracellular loop, which results in some subtle differences in receptor properties (Hope et al., 1993) (Lankiewicz et al., 1998) In the human 5-HT₃A subunit, three different splice variants have been described. Two of these (5-HT₃AL, HT₃Rext) would result in larger proteins, while the other (5-HT₃AT) codes for a truncated subunit containing only a single transmembrane domain. 5-HT₃Rext has not yet been functionally evaluated, but 5-HT₃AT and 5-HT₃AL, while not functional when expressed alone, form receptors with modified functional properties when co-expressed with canonical 5-HT₃A subunits (Bruss et al., 2000).

A range of other 5-HT₃ receptor subunit have been identified (B-E) of which only the 5-HT₃B subunit has been extensively investigated (Dubin et al., 1999) (Davies et al., 1999) (Niesler et al., 2003). Co-expression of this subunit with the 5-HT₃A subunit to yield heteromeric 5-HT₃AB receptors resulted in functional receptors with properties that more closely represented those found in some native neuronal receptors; relatively high single channel conductance and relatively low Ca²⁺ permeability compared to homomeric 5-HT₃A receptors.

The stoichiometry of heteromeric receptors is still not clear, although the presence of at least one 5-HT₃A subunit appears to be obligatory in heteromeric receptors (Holbrook et al., 2009; Niesler et al., 2008). 5-HT₃AB receptors were originally suggested to possess a 3B:2A subunit ratio, and using atomic force microscopy with tagged subunits indicated a BABBA arrangement (Barrera et al., 2005). The physiological relevance of this, however, has been questioned in more recent studies, where the presence of an AA interface was clearly demonstrated (Lochner and Lummis, 2010) (Thompson et al., 2011b) and fluorescently tagged subunits indicate a 3A:2B arrangement at the plasma membrane (Miles et al., 2013). This is also consistent with the near identical orthosteric binding site pharmacology when comparing h5-HT₃A and h5-HT₃AB receptors (Brady et al., 2001). The arrangement and number of 5-HT₃C, 5-HT₃D and 5-HT₃E subunits in functional receptors has not yet been determined, although there are many potential 5-HT₃ receptor isoforms arising from the utilization of multiple subunits in different combinations.

For more information of the structure of the 5-HT₃ receptor see Section XVI. B. 5-HT LGIC.

X. B. Expression

5-HT₃ receptors are located in many brain areas including the hippocampus (Figure 15), entorhinal cortex, frontal cortex, cingulate cortex, dorsal horn ganglia, amygdala, nucleus accumbens, substantia nigra, and ventral tegmental area (Parker et al., 1996; Barnes et al., 2009). The dorsal vagal complex in the brainstem, which is key to the vomiting reflex and contains the area postrema and nucleus tractus solitarius, has the highest levels, consistent with the potent anti-emetic properties of 5-HT₃ receptor antagonists (Pratt et al., 1990; Parker et al., 1996; Figure 16).

The functional studies are supported by expression studies, with 5-HT_{3A} receptor mRNA and protein being observed in regions of the CNS known to have 5-HT₃ receptors. Such studies also indicate 5-HT₃ receptors expression in a wide range of other tissues, including peripheral and sensory ganglia, and the gastrointestinal tract (e.g. Michel et al., 2005; Barnes et al., 2009; Figure 17). In addition expression of the 5-HT_{3A} subunit has been reported in immune cells such as monocytes, chondrocytes, T-cells, synovial tissue and platelets (Fiebich et al., 2004; Stratz et al., 2008).

There was initial controversy as to the presence of 5-HT_{3B} subunits in brain, but later studies show it is expressed here (e.g. Brady et al., 2007), with a preference for distinct 'brain-type' isoforms. The longer canonical 5-HT_{3B} subunit is broadly expressed in many tissues including kidney, liver, and the gastrointestinal tract, with relatively high levels in spleen, colon, small intestine, and kidney, (Tzvetkov et al., 2007) (Holbrook et al., 2009).

5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E} receptor subunits were first identified in humans, and genes for these proteins have now been shown to exist in a range of species, although not in rodents (Niesler et al., 2008) (Holbrook et al., 2009). Initial studies suggested that the 5-HT_{3D} and 5-HT_{3E} subunits had a very restricted expression in the GI tract but more recent data suggests all these subunits have a relatively widespread distribution. Studies examining protein levels have lagged behind the genetic work, but expression of 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} subunits at the protein level in the GI tract has recently been confirmed (Kapeller et al., 2011).

X. C. Post-translational modifications

The human 5-HT_{3A} subunit has four consensus sequence *N*-glycosylation sites in the N-terminal ECD domain and all can be *N*-glycosylated (Monk et al., 2004). *N*-glycosylation is essential for export from the ER, cell surface expression and radioligand binding, although is not necessary to preserve a ligand binding site once the receptor has matured (Boyd et al., 2003) (Green et al., 1995) (Quirk et al., 2004). Three of the four *N*-glycosylation sites are conserved between a range of species (N104, N170 and N186) and appear to be critical, while the *N*-glycosylation site at residue 28 is less important and indeed absent in rodents (Monk et al., 2004).

The other subunits have been less well studied but it has been shown that 5-HT₃B receptor subunits, when expressed alone, fail to exit the ER, providing a possible explanation as to why these subunits cannot form functional homomeric receptors. ER retention is due, at least in part, to a CRAR retention motif which forms part of the M1-M2 intracellular loop (Boyd et al., 2003). Co-expression with the 5-HT₃A subunit may shield this ER retention motif allowing heteromeric 5-HT₃AB receptors to reach the cell surface. There is some evidence that the 5-HT₃B subunit forces a preference for expression of the heteromeric 5-HT₃ receptor, as co-expression of the 5-HT₃A and 5-HT₃B subunits in tsA-201 cells did not indicate the presence of homomeric 5-HT₃A receptors (Barrera et al., 2005), although the physiological relevance of this finding is not yet clear.

BiP, calnexin, and RIC-3 have been identified as ER chaperone proteins that associate with the 5-HT₃ receptor, and are likely to promote correct folding, oligomerisation, post-translational modification and/or export from the ER (Boyd et al., 2003). RIC-3 has been the most widely studied but has different effects depending on the subunits, the species they originated from, and the expression system (Cheng et al., 2007) (Castillo et al., 2005) (Cheng et al., 2005). Expression of human homomeric 5-HT₃A receptors in transfected mammalian cells, for example, is enhanced by RIC-3, but it causes inhibition of heteromeric (5-HT₃AB) receptor expression, and mouse 5-HT₃A receptor expression in oocytes is completely abolished (Cheng et al., 2005). This apparent discrepancy may be due to other proteins which could influence 5-HT₃ receptor expression. Cyclophilin A, for example, promotes 5-HT₃A receptor expression in the cell membrane *via* an integral peptidyl prolyl isomerase activity (Helekar and Patrick, 1997), and there may be a range of other proteins yet to be identified which can modify 5-HT₃ receptor expression.

Similar to the human 5-HT₃A subunit, the human 5-HT₃B subunit has a number of consensus sequences for *N*-glycosylation sites in the N-terminal ECD domain (five; Massoura et al., 2011) and all can be *N*-glycosylated (Massoura et al., 2011). *N*-glycosylation of the human 5-HT₃B subunit at each of the five consensus sites facilitates export from the ER and efficient cell surface expression when the 5-HT₃B subunit is co-expressed with the human 5-HT₃A subunit to generate heteromeric 5-HT₃AB receptors (Massoura et al., 2011).

X. D. Pharmacology

There are many selective and potent compounds that act at 5-HT₃ receptors. Many 5-HT₃ receptor agonists have in common a basic amine, an aromatic ring, a hydrophobic group and two hydrogen bond acceptors; potent agonists include 2-methyl-5-HT, phenylbiguanide, and m-chlorophenylbiguanide (Cockcroft et al., 1995) (Kilpatrick et al., 1990). Data from AChBP suggest that agonists tend to be relatively small compounds, as they need to allow the C loop to close over the binding site, initiating the gating process; the structure of 5-HTBP, a modified version of AChBP which binds 5-HT and granisetron, supports a similar mechanism of action for the 5-HT₃ receptor (Kesters et al., 2012) (Tsetlin and Hucho, 2009).

A range of highly selective 5-HT₃ receptor partial agonists with a range of intrinsic activities are available (e.g. Manning et al., 2011; 2014; Roberts et al., 2020) that have been proposed as therapeutics to treat the symptoms for example of IBS-d and carcinoid syndrome (Roberts et al., 2020).

5-HT₃ receptor competitive antagonists, which bind at the orthosteric (agonist) binding site, are usually larger than agonists; they require an aromatic part, a basic moiety and an intervening hydrogen bond acceptor. For most antagonists these are a rigid aromatic or heteroaromatic ring system, a basic amine, and a carbonyl group (or isosteric equivalent) that is coplanar to the aromatic system (Evans et al., 1991), and there are slightly longer distances between the aromatic and amine group when compared to the agonist pharmacophore. Only small substituents, such as a methyl group, can be accommodated on the charged amine (Schmidt and Peroutka, 1989). Many potent antagonists of 5-HT₃ receptors have 6.5 heterocyclic rings, and the most potent compounds contain an aromatic 6-membered ring. Morphine and cocaine (Gaddum and Picarelli, 1957) were the first antagonists used to characterize the 5-HT₃ receptor, with more selective 5-HT₃ receptor antagonists being developed in the 1980s: MDL72222 or bemestron, (Fozard, 1984) and ICS 205-930 or tropisetron (Donatsch et al., 1985). Other compounds that were developed include ondansetron, granisetron and zacopride, which act at nanomolar concentrations, and there is now a wide range of similarly potent compounds, with many containing bicyclic heteroaromatic structures, that is, quinoxalines, quinazolines or quinolines (Verheij et al., 2012). Data indicate that these compounds, and therefore possibly all ligand that bind to the orthosteric site, are stabilized in the binding pocket by interaction with water molecules.

Some 5-HT₃ receptor inhibitors act by blocking the channel; picrotoxin, which was originally considered to be relatively selective for the GABA_A receptor also blocks the 5-HT₃ receptor channel; the binding of picrotoxinin (the active component of picrotoxin) has been localised to the 6' position of M2 (Das and Dillon, 2003) (Thompson et al., 2011a). Compounds structurally similar to picrotoxin, such as the ginkgolides and bilobalide, act similarly (Thompson et al., 2011a). Diltiazem, which blocks voltage-gated calcium channels, is also known to block the 5-HT₃ receptor pore, and acts close to the 7' and/or 12' residues in homomeric receptors (Gunthorpe and Lummis, 1999) (Thompson et al., 2011a). Morphine and its analogue methadone, and the antimalarial compounds quinine and mefloquine may also exert their inhibitory effects via binding to the pore, highlighting the common mechanisms that many of these drugs share, and also the promiscuity that many of these compounds display (Brady et al., 2001) (Baptista-Hon et al.) (Deeb et al., 2009)

There are a number of allosteric modulators that effect 5-HT₃ receptor function including n-alcohols, anaesthetics, antidepressants, cannabinoids, opioids, steroids, and natural compounds; these can inhibit or enhance receptor activity and many also modulate other Cys-loop receptors, although not always in the same direction (see reviews by Parket et al., 1996; Davies, 2011; Machu, 2011; Walstab et al., 2010). Specific binding sites for these compounds have mostly not yet been confirmed, although some may bind in an inter-subunit binding cavity at the top of the TMD (Trattnig et al., 2012). The effects of these compounds have mostly been studied on 5-HT_{3A} receptors (see Downie et al., 1995; Parker et al., 1996; but see Bentley and Barnes, 1998 for impact upon native 5-HT₃ receptors), although alcohols and inhaled anaesthetics have been shown to have reduced sensitivity at 5-HT_{3AB} receptors, while the effects of etomidate, propofol and pentobarbital are similar at 5-HT_{3A} and 5-HT_{3AB} receptors (Solt et al., 2005) (Rusch et al., 2007; Stevens et al., 2005).

A further pharmacological phenomenon termed cryptic orthosteric modulation was identified using the human 5-HT_{3A} receptor as a model (Powell et al., 2016); this pharmacological mechanism may convey therapeutic benefits when targeting ligand-gated ion channels (LGICs; Powell et al., 2016).

X. E. Function

The 5-HT₃ receptor pore is a relatively non-selective cation channel, constructed of five pseudo-symmetrically arranged M2 α -helices (one from each of the five subunits). The residues that line the ion-accessible face of M2 are predominantly non-polar, and are the major controlling influence on ion flux (McKinnon et al.; Panicker et al., 2002; Reeves et al., 2001). Currents are primarily carried by Na⁺ and K⁺ ions, although divalent and small organic cations are also permeable (Derkach et al., 1989) (Maricq et al., 1991; Yang, 1990).

Ionic selectivity is predominantly mediated via residues in M2: A triple mutant receptor with a proline insertion at -1', and the substitutions E-1'A and V13'T resulted in an anion permeable mouse 5-HT_{3A} receptor (Gunthorpe and Lummis, 2001), although subsequent studies showed that the replacement of only two residues (E-1', S19'R) was needed to invert ion selectivity (Thompson and Lummis, 2003). Changing -1'E alone resulted in non-selective channels indicating that the rings of charge at either end of M2 charge make the most critical contribution (Thompson and Lummis, 2003). Equivalent residues participate in the selectivity filters of other Cys-loop (Thompson et al., 2010).

5-HT_{3A} receptors are almost equally permeable to monovalent and divalent cations ($P_{Ca}/P_{Cs} = 1.0 - 1.4$; (Brown et al., 1998) (Davies et al., 1999) (Livesey et al., 2011). However human 5-HT_{3AB} receptors have lower Ca²⁺ permeability ($P_{Ca}/P_{Cs} = 0.6$ (Davies et al., 1999)), possibly the consequence of the 20' residue being neutral (Asn and not Asp) in human 5-HT_{3B} subunits. Consistent with this, a D20'A substitution in 5-HT_{3A} subunits reduces Ca²⁺ relative permeability ($P_{Ca}/P_{Cs} = 0.4$ (Livesey et al., 2008). Recent studies suggest that the ICD may also play a role in Ca²⁺ permeability as substitutions of charged residues in this region can have a major effect on Ca²⁺ permeability (Livesey et al., 2011).

The single channel conductance of the homomeric receptor is low: values of 0.4 - 0.76 pS have been reported (Davies et al., 1999; Gunthorpe et al., 2000; Kelley et al., 2003). The presence of Lys in the M2 regions was originally considered a possible explanation, but substitutions here revealed this was not the case (Gunthorpe et al., 2000). Subsequent work revealed that the low conductance was due to Arg residues located in the amphipathic helix of the M3-M4 loop, which forms holes, known as portals, through which ions can cross between the intracellular vestibule of the receptor and the cell interior (Kelley et al., 2003).

Heteromeric 5-HT₃AB receptors show a range of distant biophysical characteristics when compared to 5-HT₃A receptors: their desensitization is more rapid, and concentration response curves reveal lower EC₅₀s and Hill slopes; their voltage dependence is linear, and their divalent cation permeability is much reduced; most noticeable, however, is the large single channel conductance (13-16 pS) (Peters et al., 2005). This has been shown to be due to the substitution of Arg residues in the M3-M4 helical region of the 5-HT₃A subunit by neutral or negative charged residues in the 5-HT₃B subunit (Kelley et al., 2003).

Other heteromeric receptors have not yet been extensively investigated, but studies to date indicate that they are more similar to homomeric 5-HT₃A receptors.

The gate of the 5-HT₃A receptor channel is located centrally within M2 (Panicker et al., 2002), consistent with the 'hydrophobic girdle' model of channel gating, the hydrophobic girdle being a region in the centre of M2 that is less than 3.5 Å diameter over a distance of ~8 Å; the residues that face the pore here are hydrophobic (13[']Val and 9[']Leu) making it effectively impermeable to ions in the closed conformation (Miyazawa et al., 2003). Data consistent with this hypothesis are substitution of Val13['] residues in the 5-HT₃A receptor by threonine or serine, which causes an increase in agonist potency (Dang et al., 2000), or spontaneous channel openings (Bhattacharya et al., 2004), and substitutions of Leu9['] by a range of amino acids, which affected agonist potency and desensitization rates (Yakel et al., 1993).

X. F. Clinical relevance

Studies implicate the malfunction of 5-HT₃ receptors in a range of neurological and gastrointestinal disorders (Niesler, 2011) (Walstab et al., 2010). Selective 5-HT₃ receptor antagonists (e.g. first generation selective antagonists like ondansetron and granisetron and second generation antagonists such as palonosetron) have revolutionised the control of emesis particularly in patients receiving high aggressive cytotoxic anti-cancer chemotherapy (e.g. cisplatin) and radiotherapy. Thus the release of substantial amounts of 5-HT from enterochromaffin cell stores in the gastro-intestinal tract as a

consequence of anti-mitotic anti-cancer therapy activates local (vagal) and central (chemoreceptor trigger zone) 5-HT₃ receptors to evoke nausea and vomiting. Simple antagonism of these 5-HT₃ receptors offers substantial relief to patients. See Section XX for further discussion of the 5-HT₃ receptor and emesis.

The identification of 5-HT₃ receptors in immune cells also suggests a possible role of 5-HT₃ receptors in immunological processes and inflammation, and suggests that they may plausibly be involved in diseases like atherosclerosis, tendomyopathies and fibromyalgia (Fiebich et al., 2004) (Stratz et al., 2008).

Some SNPs have been identified in patients with bipolar affective disorder (BPAD) or schizophrenia, disorders which segregate with cytogenetic abnormalities involving a region on chromosome 11 that harbours the HTR3A gene (Weiss et al., 1995). Further studies are needed with two SNPs found in schizophrenic patients (R344H and P391R) to determine if they contribute to disease in these patients, but a significant association was found in BPAD with a P16S mutation in the 5-HT_{3A} subunit, with reporter constructs indicating this mutant could modulate expression levels. (Niesler et al., 2001) (Krzywkowski et al., 2007) (Thompson et al., 2006). Additional SNPs in the HTR3A gene result in the 5-HT_{3A}(A33T) and 5-HT_{3A}(M257I) subunit variants, both of which are associated with reduced levels of cell surface expression, and the 5-HT_{3A}(S253N) variant which does not appear to compromise plasma membrane expression (Krzywkowski et al., 2007). The significance of these is yet to be determined.

In the 5-HT_{3B} subunit there has been an extensive investigation into a very common SNP, Y129S, which is linked both to BPAD and major depression in women (Krzywkowski, 2006) (Hammer et al., 2012). Unusually, the Y129S variant is a gain of function mutation, as 5-HT_{3AB}(Y129S) receptors have an increased maximal response to 5-HT, decreased desensitization and deactivation kinetics and a 7-fold increase in mean channel open time in comparison to heteromeric receptors containing the wild-type 5-HT_{3B} subunit (Krzywkowski et al., 2008). An intermediate effect is apparent for receptors assembled from a mixture of wild-type 5-HT_{3A}, wild-type 5-HT_{3B} and 5-HT_{3B}(Y129S) subunits, suggesting that signaling via the 5-HT_{3AB} receptor in heterozygous, as well as homozygous, individuals is altered by this SNP (Krzywkowski et al., 2008).

Studies in the more recently discovered HTR3C, HTR3D and HTR3E genes also indicate possible involvement in disease. A SNP in the 5-HT_{3C} gene (N163K) is has been correlated with irritable bowel syndrome (IBS), and expression studies suggest it causes an increase in receptor density (Kapeller et al., 2011). Increased expression has also been associate with a SNP in the 3'UTR of the HTR3E gene, also associated with IBS, which inhibits the binding of a micro RNA as described above (Kapeller et al., 2008).

IBS-d is another disorder in which 5-HT₃ receptor antagonists can be effective therapeutic agents although side-effects associated with a high level of 5-HT₃ receptor inhibition supports the development of 5-HT₃ receptor partial agonists (e.g. Roberts et al., 2020). See Section XX for discussion of the role of the 5-HT₃ receptor and IBS.

Additional studies suggest that a wide range of other diseases have the potential to be treated with 5-HT₃ receptor selective drugs, including addiction, pruritis, migraine, chronic heart pain, bulimia, and neurological phenomena such as anxiety, psychosis, nociception and cognitive function (Thompson and Lummis, 2007) (Walstab et al., 2010).

See Sections XVIII, XIX, XX and XXI for further discussion of the clinical relevance of the 5-HT₃ receptor.

XI. 5-HT₄ receptors

XI. A. Introduction

An atypical 5-HT receptor was initially identified to be positively coupled to adenylate cyclase both in colliculi neurons (Dumuis et al., 1988) and guinea-pig hippocampus (Bockaert et al., 1990) and human and porcine cardiac atria (Kaumann et al., 1990; Kaumann 1990; Villalon et al., 1990). This receptor was insensitive to 5-HT₁ receptor and 5-HT₂ receptor antagonists and was antagonised (but with a relatively low affinity) by tropisetron (at the time thought to be a relatively selective 5-HT₃ receptor antagonist), but not by another 5-HT₃ receptor antagonist, MDL 72222. This new 5-HT receptor was named the "5-HT₄" receptor.

XI. B. Gene and primary structure

The cloning of the rat cDNA by Gerald *et al.* revealed the first primary sequence of 5-HT₄ receptor (Gerald et al., 1995). It is a classical GPCR with 7 trans-membrane domains (TM). Two splice variants sequences were found initially (5-HT_{4S} and 5-HT_{4L} later renamed 5-HT_{4(a)} and 5-HT_{4(b)}) coding for proteins of 387 and 388 amino acids, respectively. The splicing occurs within the C-terminal domain following the splicing site coding for the leucine 358 (L³⁵⁸). This splicing site at position L³⁵⁸ was subsequently found in the majority of the numerous splice variants transcripts sequenced in rodents, pig and human (Blondel et al., 1998; Bach et al., 2001; Brattelid et al., 2004a; Bockaert et al., 2006; Claeysen et al., 1999; Coupar et al., 2007). Subsequently in human, additional splice variants differing in their C-terminal sequences following L³⁵⁸ have been identified (a, b, c (a shorter non-relevant form of the c variant has been reported that is due to a sequencing error), d, e, f, g, i and n; Bockaert et al., 2006; Coupar et al., 2007; Figure 18). For a complete analysis of intron/exon junctions of the human gene see Bockaert et al. (2004a). Another splice variant (h) occurs in the second extracellular loop (Bender et al., 2000). In pig, at least nine other different splice variants, not described in humans, have been reported including a functional homo-fusion variant (De Maeyer et al., 2008a). The coding sequence of the 5-HT₄ receptor gene (*HTR4*) extends over more than 200 kb (Genes, Ensembl release 82) and is localized on chromosome 5 (5q31-q33) (Claeysen et al., 1997). It contains at least 14 exons. Each of the C-terminal variant sequences contains one of the exon 8 to 13 (Bockaert et al., 2006). The variant h is the only form that results from expression of

exon 6. The presence or not of exon 1 in the 5-HT_{4(a)} transcript is debated (Hodge et al., 2013) since the ATG starting site is localized in exon 2. Recently, a novel transcript has been found in human brain in which exon 1 and 2 are substituted for a novel exon (N) containing an expected ATG starting site, the C-terminal sequence being identical to the 5-HT_{4(b)} receptor splice variant (Hodge et al., 2013). The predicted protein sequence for this 5-HT₄ receptor variant should have a different N-terminus sequence being longer and the N-linked glycosylation site at N2 instead of N7 (Hodge et al., 2013). Similar additional N-terminal exons have been identified in mouse brain and heart (Azim et al., 2012). However, further studies to clone the complete cDNA sequences, express and functionally characterize them are required before concluding on the physiological importance of this splice variant. As some exons (such as h or i) do not present any in frame stop codons, many additional combinations probably remain to be discovered (Brattelid et al., 2004a). SNP within the non-coding region of *HTR4* gene have been associated with chronic obstructive pulmonary disease (COPD) and asthma/airways obstruction (Hodge et al., 2013; Repapi et al., 2010). The locus present features consistent with a regulatory region and involve SNP that alter significantly the binding motifs of a transcription factor regulating lung development (Foxp1) (Hodge et al., 2013). Consistent with this finding, mice devoid of the 5-HT₄ receptor have an altered baseline lung function (House et al., 2015).

XI. C. Expression profile

XI. C. 1. Central nervous system

Brain distribution of 5-HT₄ receptors has been studied using radiolabeled antagonists [³H]GR 113808, [¹²⁵I]SB 207710 and [3H]R116712 in many species including mouse, rat, guinea-pig, monkey and human (Bockaert et al., 1997; Eglen et al., 1995b; Bonaventure et al., 2000; Figure 19). Generally, a heterogeneous and comparable distribution is found in the adult brain of these various species with some inter-species differences in the globus pallidus, the substantia nigra and the interpeduncular nucleus. The highest receptor densities are found in several regions of the limbic system (islands of Calleja, olfactory bulbs, striatum, ventral pallidum, septum, hippocampus, amygdala) or in areas belonging to several pathways such as hippocampo-habenulo-interpeduncular and striato-nigro-tectal pathways (Jakeman et al., 1994; Waeber et al., 1996; Waeber et al., 1993; Waeber et al., 1994). Abundant localization of 5-HT₄ receptor mRNA in the rat brain was reported in the olfactory system, striatum, medial habenula and the hippocampus (Ullmer et al., 1996). In the rat striatum, lesion studies showed the presence of 5-HT₄ receptor on the cell bodies of neurons that

project to the substantia nigra and/or globus pallidus (Compan et al., 1996), whereas *in situ* hybridization experiments performed in guinea pig reported a localization of 5-HT₄ receptors on the terminals of the striatopallidal and striatonigral projections (Mengod et al., 1996). In the rat brain, comparison of mRNA distribution with [¹²⁵I]SB 207710 binding sites confirmed that 5-HT₄ receptors are localized both somatodendritically (caudate putamen) and on axon terminals (substantia nigra and globus pallidus) (Vilaro et al., 1996). Bonaventure *et al.* performed a mapping analysis of both 5-HT₄ receptor mRNA and binding sites in post-mortem human brains and reported combined receptor detection in caudate nucleus, putamen, nucleus accumbens and hippocampus with moderate to low densities in the cortex (Bonaventure et al., 2000). Mismatches between absence of 5-HT₄ receptor mRNA with high densities of receptor binding sites in the globus pallidus and the substantia nigra suggested that the receptors may be localized on axonal projections originating from the striatum (Bonaventure et al., 2000).

In the cortex, hippocampus and amygdala 5-HT₄ receptors were described on cholinergic neurons, where they stimulate the release of acetylcholine as well as on the glutamatergic neurons (King et al., 2008). In the striatum and nucleus accumbens the receptors have been found on the intrinsic GABA neurons (spiny neurons) but also on glutamatergic neurons (King et al., 2008). Work using dual label *in situ* hybridization precised the localization of 5-HT₄ receptors in relation with the cholinergic system. In the basal forebrain, 5-HT₄ receptor mRNA was not detected in the cholinergic cell population but in parvalbumin synthesizing, and glutamatergic cells (Penas-Cazorla and Vilaro, 2015). Thus, non-cholinergic cell populations within the basal forebrain, hippocampal and cortical areas that express 5-HT₄ receptors (likely glutamatergic cells) would mediate the 5-HT₄ receptor mediated enhancement of acetylcholine (Penas-Cazorla and Vilaro, 2015) and other neurotransmitters like the increase in 5-HT release in the hippocampus (Ge and Barnes, 1996).

Localization of 5-HT₄ receptor splice variants in rodents appears to be similar within brain areas and concordant to the binding studies, with a low level of 5-HT₄ receptor mRNA in the cerebellum, where no receptor-binding site is detected (Claeyssen et al., 1999; Vilaro et al., 1996). A complex pattern of human 5-HT₄ receptor isoforms, which depends not only on the region studied but also on each individual brain, requires analysis of a larger cohort to be conclusive (Bender et al., 2000). However, the variations in C-terminal domain of the 5-HT₄ receptor influence its constitutive

activity (Claeyssen et al., 1999), internalization properties (Mnie-Filali et al., 2010) and subcellular localization via interacting partners (Joubert et al., 2004) (see e.1). The distribution of 5-HT_{4(a)} receptors in the juvenile rat brain and spinal cord recently achieved using a polyclonal antibody have produced global data in accordance with the literature. However, striking staining of cerebellum cells raises a doubt on the specificity of the antibody used, which has not been tested on animals devoid of 5-HT₄ receptor (KO) (Suwa et al., 2014).

5-HT₄ receptor are also located on the respiratory Pre-Boetzing complex in the ventrolateral medulla of the brainstem, where they modulate spontaneous respiratory activity (Manzke et al., 2003; Richter et al., 2003).

XI. C. 2. Periphery

XI. C. 2. a. Cardiac system

In porcine and human heart, 5-HT₄ receptors are mainly expressed in the atria myocytes and their expression was long believed to be atria-specific (Kaumann and Levy, 2006; Kaumann et al., 1991; Ouadid et al., 1992). However, expression was later also found in human and porcine ventricle (Bach et al., 2001; Brattelid et al., 2004a), and during heart failure and cardiac hypertrophy, their mRNA level and expression increase in the porcine, rat and human ventricles (Brattelid et al., 2004a; Qvigstad et al., 2005a,b,c), possibly reflecting reactivation of a foetal gene expression pattern (Brattelid et al., 2012).

XI. C. 2. b. Gastro-intestinal tract

In rodents, 5-HT₄ receptors are expressed in the smooth muscles of the oesophagus. In many species, they are present on the intrinsic afferent neurons (IPANs), motor neurons and enterocytes of the gastrointestinal tract (Hegde and Eglen, 1996). The expression of 5-HT₄ receptors on excitatory motor neurons in the gut facilitates acetylcholine release, which stimulates gastrointestinal motility (Gershon and Tack, 2007; Liu et al., 2005; Ren et al., 2008). In the human colon, 5-HT₄ receptors are also expressed on circular smooth muscles cells, where they induce relaxation (McLean et al., 1995). The 5-HT_{4(b)} receptor variants appears to be predominantly expressed in porcine GI mucosa suggesting their contribution to

the 5-HT₄ receptor-mediated mucosal effects of 5-HT (Priem et al., 2013). In human colon, RT-PCR analysis shows that 5-HT_{4(d)} and 5-HT_{4(g)} receptor splice variants are significantly less likely to be detected in mucosa and longitudinal muscle compared to the 5-HT_{4(a), 4(b), 4(c), 4(n)} splice variants (Yaakob et al., 2015).

XI. C. 2. c. Adrenal gland

5-HT₄ receptors are present in glomerulosa and zona fasciculata of the adrenal cortex (Lefebvre et al., 1992; Lefebvre et al., 1998). RT-PCR study demonstrated that 5-HT₄ receptor are overexpressed in adrenocortical aldosterone-producing adenoma (APA) tissues in comparison with normal adrenal cortex (Cartier et al., 2005). Moreover, a different splicing mechanism seems to occur in these tumors, where the 5-HT_{4(a)} and 5-HT_{4(b)} receptor splice variants, usually present in normal adrenal cortex, are absent and the 5-HT_{4(d)}, a rare isoform, is over-represented (Cartier et al., 2005).

XI. C. 2. d. Salivary glands

In the rat submandibular gland, expression of 5-HT_{4(b)} but not 5-HT_{4(a)} receptors was demonstrated and linked to cyclic AMP formation and regulation of volume and protein content of saliva, together with 5-HT₇ receptors (Turner et al., 1996; Bourdon et al., 2000).

XI. C. 2. e. Urinary bladder

In the bladder, 5-HT₄ receptors are present on cholinergic/purinergic neurons that innervate the smooth muscle (detrusor) (Candura et al., 1996). Their stimulation with cisapride enhances human bladder contraction with without affecting urethral contractions or relaxations (Kullmann et al., 2013).

XI. C. 2. f. Lung

5-HT₄ receptor mRNA has been detected at low density in human alveolar epithelial cells type II, airway epithelial cells lines and human airway smooth muscle (Bayer et al., 2007; Einstein et al., 2008; Hodge et al., 2013).

XI. D. Post-translational modifications

Post-translational modifications of 5-HT₄ receptors and their related functional consequences have been studied on receptors expressed in heterologous cells rather than native tissues.

XI. D. 1. N-Glycosylation

There are two putative *N*-linked glycosylation sites in the extracellular side of 5-HT₄ receptors that conform to the consensus sequence N-X-S/T, where X can be any amino acid except a Pro residue (N-terminal N7 and second extracellular loop N180; Figure 18). The pattern of glycosylation is dependent on the nature of the cell in which 5-HT₄ receptors are expressed. Salom *et al.* report that glycosylation pattern of 5-HT₄ receptors ectopically expressed in mouse rod cells *in vivo*, is more homogeneous than the glycosylation pattern of 5-HT₄ receptors expressed artificially in HEK293 cells (Salom et al., 2012). The h5-HT_{4(b)} receptors expressed in mouse rod cell display high mannose type and complex type of sugars at both N7 and N180 sites. Most of the oligosaccharides had the core structure of three mannoses (Man) and two *N*-acetylglucosamine (GlcNAc) residues (23 species for N7, and 8 species for N180). This *N*-glycosylation pattern is much complex than for others GPCRs expressed in mouse rod cells.

XI. D. 2. Palmitoylation

The first crystal structure of rhodopsin reveals that after the TM7 there is a fourth intracellular loop (I-4) with α -helical structure. Thus, this I-4 loop is also called helix 8 and terminates with 2 palmitoyled cysteines that are well conserved in many GPCRs as in the 5-HT₄ receptors (C³²⁸ and C³²⁹). The palmitoylation/depalmitoylation of those cysteines are associated with the wide spectrum of GPCRs biological activities: from coupling to G-proteins and regulated endocytosis to receptor phosphorylation and desensitization. Ponimaskin *et al.* were the first to show that, in insect Sf9 cells, palmitoylation of the 5-HT_{4(a)} is a reversible process and that agonist increases the turnover rate for receptor-bound palmitate (Ponimaskin et al., 2002a). They identified C³²⁸/C³²⁹ as potential acylation sites in the 5-HT_{4(a)} receptor but, in contrast to most other palmitoyled GPCRs, an additional

cysteine residue C³⁸⁶, located in the very distal portion of the C-terminal domain was also identified as a palmitoylation site. Therefore, "complete" palmitoylation of the 5-HT_{4(a)} may result in the formation a putative additional intracellular loop (I-5). Mutation of the proximal palmitoylation sites (C³²⁸S and C³²⁹S) increased the capacity of the receptor to convert from the inactive (R) to the active (R*) form in the absence of agonists, whereas the mutation of C³⁸⁶S had no effect on this parameter. 5-HT₄ receptors expressed, in rod cells *in vivo* are palmitoylated either on C³²⁸ or C³²⁹ (Salom et al., 2012).

XI. D. 3. Phosphorylation

The 5-HT₄ receptor C-terminal sequence, common to all splice variants (upstream of L³⁵⁸), contains a remarkable cluster of serine and threonine residues (S³⁴⁷T³⁴⁸T³⁴⁹I³⁵⁰G³⁵¹S³⁵²T³⁵³H³⁵⁴V³⁵⁵L³⁵⁶), which are potential phosphorylated sites for G-protein-coupled receptor protein kinases (GRK). This cluster is absolutely required for β -arrestin/dynamin-dependent receptor endocytosis, but not for receptor uncoupling (Barthet et al., 2005). This cluster is also required for β -arrestin binding to the receptor (Barthet et al., 2005). Like many GPCRs, 5-HT₄ receptors stimulates ERK (extracellular signal-regulated kinase). However, this stimulation is G_s/G_q/G_i/G_o/cAMP/PKA independent as well as β -arrestin independent. In contrast, this stimulation requires activation of Src tyrosine kinase (Barthet et al., 2007). This G_s independent Src-mediated ERK activation is inhibited by GRK5, physically associated with the proximal region of the C-terminus (upstream of the S/ T cluster) (Barthet et al., 2009). Tandem mass spectra of the stimulated 5-HT₄ receptors, in HEK293 cells expressing GRK5, revealed a peptide (R³³⁶-R³⁵⁰) found under a non-phosphorylated and three phosphorylated forms with one, two and three phosphates attached, respectively (Barthet et al., 2009). Loss of phosphate on fragmentation indicated phosphorylation of S354 in the mono-phosphorylated peptide and the presence of an additional phosphorylated residue within the S³⁴⁷T³⁴⁸T³⁵⁰ motif. The tri-phosphorylated peptide incorporated an additional phosphate within the S³⁴⁷T³⁴⁸T³⁵⁰ motif. This indicates that GRK5 sequentially phosphorylates the peptide, first on S³⁵⁴ and then in the S³⁴⁷T³⁴⁸T³⁵⁰ motif. The same 5-HT₄ receptor peptide was found to be phosphorylated in receptors expressed in mouse rods (0 to 5 phosphorylated residues) (Salom et al., 2012). In the same model, another peptide was found to be phosphorylated within the I-3 loop (A²³² to R²⁵⁰). S²³⁵, S²³⁶, S²³⁸ and S²⁴² residues were the targets for phosphorylation as well as S²⁴⁷ or T²⁴⁸ (Salom et al., 2012).

XI. E. Pharmacology

XI. E. 1. Agonists

Very early, benzamides substituted by 2-methoxy-4-amino-5-chloro such as metoclopramide, renzapride, cisapride or zacopride were identified as potent agonists of the 5-HT₄ receptors (for reviews see Bockaert et al., 2004a; 2008; Bockaert et al., 1997; Langlois and Fischmeister, 2003)). This was an important step in the pharmacological characterization of 5-HT₄ receptors (Clarke et al., 1989) and prompted a number of pharmaceutical companies to develop specific ligands for this receptor.

The first class of 5-HT₄ receptor agonists includes indoles derivatives such as tryptamines (including 5-HT) and indoles carbazimidamines derivatives. Tegaserod, prescribed to treat irritable bowel syndrome (IBS) in women suffering from constipation, belongs to this class. This compound has been withdrawn from the market in 2007 because of cardiovascular side effects although it has made a recent return to the market, albeit with limitations on use.

The second class includes benzamide derivatives such as metoclopramide, which was commercialized as an anti-emetic (action via dopamine D₂ receptors and 5-HT₃ receptors at higher doses) and stimulating gastrointestinal transit (action via 5-HT₄ receptors). Mosapride, which acts also as a 5-HT₄ receptor agonist is used to treat gastrointestinal disorders as it accelerates gastric emptying (Curran and Robinson, 2008; Tack et al., 2012) but a main metabolite is pharmacologically active and antagonises the 5-HT₃ receptor.

The benzofurane carboxamide, prucalopride is selective for the 5-HT₄ receptor (Briejer et al., 1999) and has been approved for the treatment of chronic constipation, in case of laxative resistance, in Europe (2009) and in Canada (2011) (Tack et al., 2013).

Lead of benzoates class is ML10302, which presents a high affinity for 5-HT₄ receptor and weak affinity for 5-HT₃ receptors (Yang et al., 1997).

ML10302 was described as the first potent and selective 5-HT₄ receptor agonist but further investigation *in vivo* was limited by its susceptibility to hydrolysis.

Benzodioxane class is represented by only one product, the SL65.0155, particularly pro-active as a mnemonic in several species. This compound has reached Phase IIb for the treatment of Alzheimer's disease (Moser et al., 2002). It was abandoned for undisclosed reasons that may be related to its low efficacy and very partial agonist profile on 5-HT₄ receptors.

The sixth class includes aryl ketones, which were developed to overcome the metabolic lability related to the related 5-HT₄ receptor ester ligands. These compounds have a high bioavailability and easily pass the blood-brain barrier. RS 67333 (Eglen et al., 1995a), containing a large alkyl group, was widely used *in vivo* in rodent and particularly for behavioral studies demonstrating the pro-cognitive effects of 5-HT₄ receptor agonists (Fontana et al., 1997; Kulla and Manahan-Vaughan, 2002; Lamirault and Simon, 2001; Lelong et al., 2001; Marchetti et al., 2000).

The 7th class is represented by a carboxamide pyridine, PRX-03140 (also known in the literature as VRX-03011), another partial 5-HT₄ receptor agonist and pro-mnemonic substance that reached Phase IIb for the treatment of Alzheimer's disease (Mohler et al., 2007) in 2008 although development of the drug was then stopped.

Benzimidazolone derivatives constitutes the 8th class with BIMU1 and BIMU8 as examples, which are potent and efficacious 5-HT₄ receptor agonists with good brain penetrating properties (Dumuis et al., 1991; Rizzi et al., 1992). However, their affinity for 5-HT₃ and σ_2 receptors limits their utility (Bonhaus et al., 1993).

The last two classes include naphthalimides derivatives (Eglen et al., 1994) (RS 56532 and RS 66332) and the quinoline derivative, velusetrag (Beattie et al., 2008). Velusetrag displays promising efficacy in patients with constipation (e.g. Nelson et al., 2017) and may also be useful in Alzheimer's

disease.

Other 5-HT₄ receptor agonists are listed in Table 16, indicating key pharmacological parameters.

XI. E. 2. Antagonists

GR 113808, belonging to the indole class, was the first specific 5-HT₄ receptor antagonist presenting low affinity for 5-HT₃ receptors (Gale et al., 1994) and the first tritiated radioligand commercially available. This molecule enabled the accurate definition of pharmacological characteristics and localization of 5-HT₄ receptors, especially in the brain (Grossman et al., 1993). Other antagonists are benzoate derivatives (such as SDZ 205557), or benzoate dioxane derivatives such as SB 204070 that by substitution of the chlorine by a radioactive iodine leads to [¹²⁵I]SB 207710, another excellent radioligand (Kaumann et al., 1995). Other antagonist classes include benzimidazolones, imidazolpyridines and aryl ketones.

5-HT₄ receptor antagonists have been mainly developed for binding studies purpose and in situ labeling using radioligands. Recent work include the development of imaging probes for Positron Emission Tomography (PET) (Buiter et al., 2013; Dubost et al., 2012; Tavares et al., 2014). However, due to the presence of 5-HT₄ in the failing heart, some antagonists have be designed for cardioprotective purpose, trying to avoid CNS penetration and improving oral administration route (Brudeli et al., 2013; Brudeli et al., 2014).

Some 5-HT₄ receptor antagonists are listed in Table 16, indicating key pharmacological parameters.

XI. E. 3. Inverse agonists

Inverse agonists of the 5-HT₄ receptor (Claeyssen et al., 2000; Joubert et al., 2002) have been generated by Roche in collaboration with Bockaert's group (RO 116-0086, RO 116-1148 and RO 116-2617; Figure 20). SB 207266, which is a carboxylate indole derivative is also an inverse agonist at the 5-HT₄ receptor (Figure 20).

XI. E. 4. Multifunctional ligand

Dallemagne et al. reported the synthesis and characterization of donecopride, a multi-target directed molecule combining 5-HT₄ receptor agonist properties with acetylcholinesterase (AChE) inhibition (Lecoutey et al., 2014); the drug may display disease modifying actions by increasing sAPP α release as well as pro-cognitive effects (Lecoutey et al., 2014; Rochais et al., 2015).

XI. E. 5. 5-HT₄ receptor radioligands

The first tritiated or iodinated 5-HT₄ receptor compound, mainly antagonists were particularly useful to determine brain regional distribution of the receptor (Grossman et al., 1993; Waeber et al., 1996; Waeber et al., 1993; Waeber et al., 1994), [³H]GR 113808 and [¹²⁵I]SB 207710 being the lead compounds (Kaumann et al., 1995). Then, several [¹¹C]-labeled compounds have been developed for a use in positron emission tomography (PET) (Buiter et al., 2013; Gee et al., 2008; Xu et al., 2010), enabling live imaging studies in animals (Kornum et al., 2009) and in humans (Madsen et al., 2011; Marner et al., 2009). New [¹²⁵I]-labeled antagonists have also been developed for use as PET tracers (Dubost et al., 2012). More recently, promising fluoride radioligands have been described: [¹⁸F]MNI-698 and [¹⁸F]MNI-699 (Caille et al., 2013; Tavares et al., 2014).

XI. F. Function

XI. F. 1. Physiological function

The 5-HT₄ receptors have many physiological functions. They are implicated in learning and memory and in the stimulation of the non-amyloidogenic cleavage of APP (Bockaert et al., 2008; 2011; Claeysen et al., 2015). Thus, they are potential targets to treat Alzheimer's disease.

A role of 5-HT₄ receptors in feeding behaviour is now clear. Agonists and antagonists have hypo- and hyper-phagic properties, respectively (Bockaert et al., 2011; Jean et al., 2007).

5-HT₄ receptor stimulation has rapid antidepressant action and may contribute to the actions of SSRI (Lucas, 2009; Samuels et al., 2014).

In the periphery, the role of 5-HT₄ receptors in gastro-intestinal tract is well established. 5-HT₄ receptors are implicated in gastric emptying, peristaltic reflex, intestinal motility, inhibition of hyper-sensibility, short free fatty acid-stimulated HCO₃⁻ secretion and importantly enteric nervous system development and adult neurogenesis of enteric plexus (Akiba et al., 2015; Gershon, 2011; 2013; Hoffman et al., 2012; Matsuyoshi et al., 2010). For further discussion see Section XX.

5-HT₄ receptor antagonists may be useful in those cardiac pathologies (Birkeland et al., 2007a; Kjekshus et al., 2009).

Although 5-HT₄ receptors are weakly expressed in whole lung, airways epithelial cells, and airways smooth muscle cells, GWAS meta-analyses indicate that intronic SNPs in *HTR4* gene are associated with some pulmonary diseases (Hancock et al., 2010; Hodge et al., 2013; Repapi et al., 2010; Soler Artigas et al., 2011).

5-HT₄ receptors are present in cortico-adrenal gland, where they stimulate aldosterone production, in salivary glands, where they modify the volume and protein content of saliva (Turner et al., 1996; Bourdon et al., 2000) and in urinary bladder (Hegde and Eglen, 1996; Lefebvre et al., 2015).

XI. F. 2. Cellular function

XI. F. 2. a. G-protein coupling of 5-HT₄ receptors and primary signalling events

5-HT₄ receptors stimulate the adenylate cyclase in colliculi neurons as well as in hippocampus (Dumuis et al., 1988). This coupling has also been found in nucleus accumbens (Jean et al., 2007) and in heart atrium (Kaumann et al., 1990; Ouadid et al., 1992) and ventricle (Afzal et al., 2008). Thus, in native tissues, the 5-HT₄ receptor-mediated G_s/cAMP/PKA signalling pathway is well established. In primary cortical neurons and HEK293 cells, cAMP produced by 5-HT₄ receptors also activates the exchange factor Epac. Epac, via an Epac/Rap1/Ras pathway, activates an α -secretase and the

release of sAPP α (soluble amyloid precursor protein) (Cochet et al., 2013; Lezoualc'h and Robert, 2003).

In transfected cell lines, several signalling pathways have been found including coupling to G_{i/o}, G_q and G₁₃ (Bockaert et al., 2006; Ponimaskin et al., 2002b; Woehler and Ponimaskin, 2009). Expression of different 5-HT₄ receptor splice variants, in heterologous cells (COS and HEK293 cells, rodent cardiac myocytes), have identified putative differences in their signalling coupling. One clear difference is their constitutive activities measured on G_s coupling. Generally, the shorter is the C-terminal, the highest is the constitutive activity (Claeyssen et al., 1999). In addition, it has been reported that, in HEK293 cells and adult cardiac myocytes, 5-HT_{4(b)} but not 5-HT_{4(a)} or 5-HT_{4(d)} are coupled to both G_s and G_{i/o} (Pindon et al., 2002). In similar heterologous systems, activation of transiently expressed 5-HT_{4(a)} receptors by 5-HT and other agonists induce both cAMP and inositol phosphate accumulation (Chang et al., 2007; Gaven et al., 2013).

Following PKA activation, a series of ionic currents are modulated in colliculi and CA1 hippocampal neurons (Andrade and Chaput, 1991; Ansanay et al., 1995). These include a long-lasting inhibition of K⁺ currents including Ca²⁺-activated K⁺ channels (mediated by a PKA dependent inhibition of phosphatases), which generates neuronal excitability and a decrease in spike accommodation (Ansanay et al., 1995) and activation of the hyperpolarization activated current (I_h) known to adjust repetitive discharge behaviour in CA1 neurons (Andrade and Chaput, 1991). In prefrontal cortex pyramidal neurons, GABA_A current and GABAergic transmission are either stimulated or inhibited by 5-HT₄ receptors. A role of PKA and AKAP (A Kinase Anchoring Proteins) has been reported (Cai et al., 2002). 5-HT₄ receptors also activate L-type Ca²⁺ channels in human and porcine atrial myocytes via a cAMP/PKA pathway (Kaumann and Levy, 2006; Ouadid et al., 1992).

The receptor-G_s uncoupling phase of 5-HT₄ receptors desensitization is very rapid and efficient in colliculi neurons (Ansanay et al., 1992) and rat oesophagus (Ronde et al., 1995) and is specifically dependent on the presence of a high expression of GRK2 but not of its catalytic activity (Barthet et al., 2005). In contrast, the β -arrestin/dynamin dependent endocytosis of 5-HT₄ receptors in HEK293 cells does not require a high expression of GRK2 and is dependent of the S/T cluster upstream of L²⁵⁸ (Barthet et al., 2005).

XI. F. 2. b. G-protein independent coupling of 5-HT₄ receptors

5-HT₄ receptors activate ERK in a G protein and β -arrestin independent manner both in colliculi neurons and HEK293 cells (Barthet et al., 2007). The first step in 5-HT₄ receptor-ERK activation is the phosphorylation-activation of the tyrosine kinase Src bound to the receptor (Barthet et al., 2007). This G-protein independent activation of Src by 5-HT₄ receptors has also been described in epithelial cell lines (Gill et al., 2005). Indeed, in the enterocyte cell line Caco 2, 5-HT₄ receptor-induced Src activation was required to activate the PLC γ 1 pathway and to inhibit Na⁺/H⁺ exchanger (Gill et al., 2005).

5-HT₄ receptor-operated Src/ERK pathway, but not the G_s pathway, was negatively regulated by GRK5 physically pre-associated with the proximal C-terminal region of the receptor in both human HEK293 cells and mouse colliculi neurons (Barthet et al., 2009). This desensitization requires two sequences of events: the association of β -arrestin1 to the phosphorylated S/T cluster already described and the phosphorylation, by GRK5, of β -arrestin1 (at S⁴¹²) bound to the receptor. Phosphorylated β -arrestin1, in turn, prevented the activation of Src constitutively bound to 5-HT₄ receptors (Barthet et al., 2009).

XI. F. 3. Gastro-intestinal (GI) tract

5-HT₄ receptors localisation and functions, in GI tract, have been extensively studied in many species including guinea-pig, pig, dog, mice, rat and human (Craig and Clarke, 1990; Gershon and Tack, 2007; Hegde and Eglen, 1996; McLean et al., 1995; Poole et al., 2006; Priem et al., 2013; Sanger, 2008).

That 5-HT₄ receptors are pro-kinetic on GI and stimulate guinea-pig ileum contractions is concomitant to discovery of 5-HT₄ receptors (Craig and Clarke, 1990). Subsequently 5-HT₄ receptor facilitation of the peristaltic reflex has been identified (Hegde and Eglen, 1996; Grider et al., 1998). The mechanism by which 5-HT₄ receptors stimulate peristaltic reflex is debated. Two proposals have been provided. 1. Within circular muscles of colon

(human) 5-HT₄ receptors stimulate the release the inhibitory (descending relaxation) and excitatory (ascending contractions) neurotransmitters (nitric oxide and acetylcholine respectively) (Cellek et al., 2006; Liu et al., 2005; Ren et al., 2008; Tonini et al., 1989). 2. 5-HT₄ receptors localized on the luminal surface of epithelial cells including enterochromaffin cells and goblet cells, stimulate the peristaltic effect via secreted mucus, 5-HT, and fluid secretion (Hegde and Eglen, 1996). Luminal HCO₃⁻ secretion is an important component of normal colonic fluid and electrolyte movement and is a major fraction of the fluid secreted in several diarrheal diseases. It has been recently found that short-chain fatty acids (SCFAs) stimulate HCO₃⁻ secretion. This effect involves several steps including the following ones. SCFA via the stimulation of a GPCR receptor localized on enterochromaffin cells (FFA2) increases 5-HT release and 5-HT₄ receptors localized on epithelial cells and afferent neurons stimulate HCO₃⁻ secretion (Akiba et al., 2015).

XI. F. 4. Visceral pain

Tegaserod, a 5-HT₄ receptor agonist, administered orally in human reduces abdominal pain and discomfort (De Maeyer et al., 2008b; Sanger, 2008). Since tegaserod is also a 5-HT_{2B} receptor antagonist, its exact mechanism of action is not clear. Hoffman *et al.* found that, on a colorectal distension model of visceral pain, a more specific 5-HT₄ receptor agonist (naronapride) is also active and that both tegaserod and naronapride effects were blocked by a 5-HT₄ receptor antagonist (Hoffman et al., 2012). The mechanism of this anti-visceral pain action of 5-HT₄ receptor agonists is unknown.

XI. F. 5. ENS development and ENS adult neurogenesis

5-HT₄ receptors are important in the early development of enteric neurons whose number increases through 4 months of age (Gershon, 2013). In mice lacking 5-HT₄ receptors (KO), the early increase fails and the later decline is more severe. 5-HT₄ receptors specifically protect cultured enteric neurons from apoptosis and also activate CREB (Liu et al., 2009). In adult, 5-HT₄ receptors are also able to stimulate neurogenesis in mouse (Gershon, 2011). Adult neurogenesis appears to only start when ENS is injured, either following rectal transection and end-to-end anastomosis or chemical ablation with for example benzalkonium chloride (Laranjeira et al., 2011; Matsuyoshi et al., 2010). In the former model, mosapride, a 5-HT₄

receptor agonist, promoted the regeneration of the neural circuit in the impaired myenteric plexus and the recovery of the defecation reflex in the distal gut (Kawahara et al., 2012; Matsuyoshi et al., 2010).

XI. F. 6. Central nervous system

XI. F. 6. a. Learning and memory

One of the first roles of 5-HT₄ receptors *in vivo* was their promnesic effect in rat, mouse, monkey and human (Bockaert et al., 2008; 2011; Eglen et al., 1995b; Haahr et al., 2013; Meneses, 2015). Pro-cognitive effects of 5-HT₄ receptor agonists have been described, both on short-term memory (such as social olfactory memory) and on long-term olfactory memory (such as olfactory associative memory). Acute treatments with 5-HT₄ receptor agonists induced an increase in memory acquisition in autoshaping task, object and social recognition, Morris water-maze, task with long inter-trial intervals (two hours), delayed matching performance and impeded spontaneous alteration scores (Bockaert et al., 2011; King et al., 2008). Chronic treatments also improve memory performance (Quiedeville et al., 2015). They also increase working memory. Old rats have poor memory relative to adult rats which can be upgraded with 5-HT₄ receptor agonists, which are also reported to antagonize atropine- or scopolamine-induced learning and memory deficits in a variety of tasks such as spatial navigation in Morris water maze, spontaneous alternation and olfaction (King et al., 2008; Lamirault and Simon, 2001; Lelong et al., 2003; Marchetti et al., 2011). In 5-HT₄ receptor KO mice, the loss of learning and memory appears to be circumvented by adaptative changes in cholinergic systems (Buhot et al., 2003).

Hippocampal 5-HT₄ receptor expression correlates inversely with human memory (Haahr et al., 2013). The cellular basis of such learning and memory effects may be an increase in acetylcholine release found in frontal cortex and hippocampus, a complex modulation of synaptic plasticity (LTP and LTD) an a potentiation of learning-induced spine growth in the hippocampus (see (Bockaert et al., 2011; Kemp and Manahan-Vaughan, 2004; King et al., 2008)). Interestingly, the 5-HT₄ receptor agonist, SL65.0155 enhances simultaneous olfactory discrimination performance and potentiates learning-induced dendritic spine growth in the mouse hippocampus (Restivo et al., 2008). Finally, an association between 5-HT₄ receptor mRNA and protein expression in cortical areas, hippocampus, olfactory tubercles on one hand and memory consolidation on the other hand has

been reported (Manuel-Apolinar et al., 2005).

XI. F. 6. b. Control of mood, role of 5-HT₄ receptor agonists

SSRIs are common drugs to treat of depression that eventually increase tonic 5-HT release in relevant limbic structures such as the hippocampus. It has been established that stimulation of 5-HT₄ receptors localized on pyramidal mPFC stimulate the activity of a fraction DRN 5-HT neurons (responders neurons with high frequency discharges), an effect expected to result in a positive effect on mood behaviour (Lucas, 2009; Lucas and Debonnel, 2002). Thus, 5-HT₄ receptor agonists may be relatively fast antidepressant actions or may be used in combination to reduce the delay of action of SSRIs when given alone (Samuels et al., 2014).

5-HT₄ receptors interact with p11, a protein, which is down-regulated in brain of depressed patients. This interaction is particularly clear in brain regions important for anxiety/depression and cognition such as the hippocampus (Egeland et al., 2011; Warner-Schmidt et al., 2009). The antidepressant-like activity of RS 67333, a 5-HT₄ receptor agonist, was abolished in p11-KO mice, which are known to have a depressive-like phenotype (Warner-Schmidt et al., 2009).

Adult hippocampal neurogenesis in the sub-granular zone (SGZ) has gained considerable attention in relationship with mood and depression. The hypothesis is that a decrease in new-born dentate granule cells production leads to depression, whereas enhanced neurogenesis (proliferation, survival, and maturation) is required for treatment of depression (Duman and Monteggia, 2006; Samuels et al., 2014). Chronic antidepressant treatments, including SSRIs, stimulate adult hippocampal neurogenesis (proliferation of new-born cells as well as the survival and maturation of the young neurons. 5-HT₄ receptor agonists can also induce a rapid neurogenesis in the hippocampus in adult rodents (Duman and Monteggia, 2006; Ishizuka et al., 2014; Pascual-Brazo et al., 2012) and the synthesis of BDNF, a key growth factor implicated in antidepressant actions and neurogenesis. Interestingly, the 5-HT₄ receptor antagonist GR 125487 partially blocks the neurogenic effects of chronic fluoxetine treatment and its antidepressant and anxiolytic effects (Mendez-David et al., 2014), which may relate to a reduced hippocampal 5-HT release evident with 5-HT₄ receptor antagonists

(Ge and Barnes, 1996). In addition to neurogenesis, SSRIs can reverse neuronal maturation in the adult hippocampal granular cell neurons via 5-HT₄ receptor-mediated signaling (Kobayashi et al., 2010).

XI. F. 6. c. Feeding behaviour

In 5-HT₄ receptor KO mice, the stress-induced hypophagia and novelty-induced exploratory activity were reduced (Compan et al., 2004). This suggests that 5-HT₄ receptors may be involved in stress-induced anorexia. Anorexia and bulimia are motivation disorders, which may implicate a reward structure such as nucleus accumbens that displays relatively high expression of 5-HT₄ receptors. Direct stimulation of 5-HT₄ receptors in the nucleus accumbens reduced the physiological drive to eat and increased the mRNA of the anorectic peptide CART (cocaine- and amphetamine-regulated transcript) in WT but not KO mice (Jean et al., 2007; 2012). 5-HT₄ receptors control CART mRNA expression via a cAMP/PKA signalling pathway. Finally, intra-accumbal injection of 5-HT₄ receptor antagonists or siRNA-mediated 5-HT₄ receptors KO decrease satiety (Jean et al., 2007).

XI. F. 6. d. Cardiac system

5-HT via 5-HT₄ receptors induces cardio-excitation in atrial but not in ventricles of healthy humans and pig (Jahnel et al., 1992; Kaumann, 1990; Kaumann et al., 1991). However, an inotropic effect can also be found in human and porcine cardiac ventricle under phosphodiesterase inhibition (Brattelid et al., 2004a). In the atrium, 5-HT₄ receptor activate and phosphorylate L-type Ca²⁺ channels via a cAMP/PKA signalling pathway (Kaumann and Levy, 2006; Ouadid et al., 1992). It has been proposed that atrial fibrillation, mediated by 5-HT₄ receptors, may occur in case of altered circulation for example during ageing (Kaumann and Levy, 2006). 5-HT₄ receptors expressed in sino-atrial node in piglets, and possibly in humans, may be responsible for some 5-HT-mediated arrhythmias (Sanders and Kaumann, 1992). In addition, in failing human heart of either man and pig (Brattelid et al., 2004b), there is an up-regulation of 5-HT₄ receptor mRNA level in ventricles accompanied by a 5-HT₄ receptor-mediated positive inotropic response to 5-HT. Similar observations have been reported in both infarcted, failing and hypertrophic rat hearts (Brattelid et al., 2007; Qvigstad et al., 2005a,c). Note that 5-HT₄ receptors are not expressed in healthy rat ventricles. Since in those pathologies there is an increase in plasma 5-HT concentration, likely released from platelets, this may result in cardio-toxic effects mediated via 5-HT₄ receptors.

Cardiac remodelling in heart failure is characterized by activation of a foetal gene program. Indeed, Brattelid *et al.* found, in rat, that 5-HT₄ receptor mRNA expression and 5-HT₄ receptor-mediated inotropic response are augmented, not only in heart failure, but also in ventricles during late foetal development (Brattelid *et al.*, 2012). In rodent cardiomyocytes, prucalopride responses, characterized by a high propensity to trigger diastolic Ca²⁺ events, absent in controls, can be achieved following BDNF and imipramine treatments (Meschin *et al.*, 2015). Since both treatments increase expression of p11, the authors are logically proposing that it is p11 which up-regulates 5-HT₄ receptor responses as seen in the brain. This is likely, but not formally demonstrated in the report. The difference in p11 expression in human and rodent cardiomyocytes could explain their different responsiveness to 5-HT₄ receptor agonists. This remains to be demonstrated.

For further discussion see Section XIX.

XI. F. 6. e. Respiratory system

At the level of the brainstem central respiratory centre, the Pre-Boetzing complex, 5-HT_{4(a)} receptors via a cAMP signalling pathway, control respiration (Manzke *et al.*, 2003). They stimulate phrenic nerve activity and respiratory minute volume. Thus, 5-HT₄ receptors are able to avert opioid-induced breathing depression, likely by having an opposing effect on the cAMP decrease induced by those drugs in the respiratory centre (Manzke *et al.*, 2003). Although noncoding variants SNPs in *HTR4* are associated with pulmonary diseases in human GWASs (Hancock *et al.*, 2010; Hodge *et al.*, 2013; Repapi *et al.*, 2010; Soler Artigas *et al.*, 2011), the relatively low expression of 5-HT₄ receptors in lungs cast some doubt on the functional impact of 5-HT₄ receptors in pulmonary functions (Hodge *et al.*, 2013). However, 5-HT₄ receptor KO mice display an altered baseline lung function (lung resistance, tissue resistance and tissue elastance) and an increase in methacholine and 5-HT-induced airway hyper-responsiveness (House *et al.*, 2015).

XI. F. 6. f. Adrenal gland

In the human adrenal gland, 5-HT₄ receptors are mainly localized on zona glomerulosa (Lefebvre et al., 2015), which is consistent with 5-HT stimulating preferentially aldosterone secretion rather than cortisol *in vitro*. Similarly, 5-HT₄ receptor agonists administered to healthy individuals increases plasma aldosterone levels without any change in plasma cortisol concentrations (Lefebvre et al., 2015).

XI. F. 6. g. Urinary bladder

Neuromuscular cholinergic transmission in human isolated detrusor muscle is facilitated by neural 5-HT₄ receptors (Tonini et al., 1994). In contrast, in urinary bladder strips from Rhesus and Cynomolgus monkeys, experiments using direct electrical stimulation of bladder smooth muscle indicate that the 5-HT₄ receptors are located post-junctionally (Waikar et al., 1994).

XII. 5-HT_{5A} Receptors

XII. A. Introduction

In the early 1990's, the genes encoding the human and rodent 5-HT_{5A} receptor genes were cloned and localized. Subsequent work in the mid-1990's revealed the primary protein structure, expression pattern and cellular function of the receptor using *in vitro* preparations (Rees et al., 1994; Plassat et al., 1992; Erlander et al., 1993; Matthes et al., 1993; Rees et al., 1994). Yet, the function of the receptor *in vivo* remained elusive until the early 2000's. By generating the *Htr5A* receptor knockout mouse, Grailhe and colleagues were the first to provide evidence of 5-HT_{5A} receptor function *in vivo* (Grailhe et al., 1999; Graillhe et al., 2001). Subsequently, an *ex vivo* approach was used to characterize the electrophysiological effects of 5-HT_{5A} receptors in native mouse and rat cortical brain tissue and the consequences of its deletion (Goodfellow et al., 2012), which led to the Receptor Nomenclature Committee promoting to receptor status (i.e. 5-ht_{5a} to 5-HT_{5A} receptor). While further investigations have been pursued *in vivo* (Curtin et al., 2013; Muñoz-Islas et al., 2014; Yamazaki et al., 2014; 2015), clinical examination has been severely limited by the lack of selective ligands.

XII. B. Gene and primary structure

The human *HTR5A* is located on chromosome 7, at position 7q36 (Matthes et al., 1993). Partial sequencing revealed an intron-exon boundary located in the middle of the third cytoplasmic loop at exactly the same position as in the mouse and rat 5-HT_{5A} genes (Rees et al., 1994; Grailhe et al., 2001). The homologous mouse *Htr5A* is located on chromosome 5, at position 5B (Matthes et al., 1993). Partial sequence analysis revealed that the 5-HT_{5A} receptor gene contains an intron in the third cytoplasmic loop (Matthes et al., 1993), of approximately 8 kb in length (Matthes et al., 1993). The human 5-HT_{5A} receptor, comprised of a 1071 bp open reading frame, displays approximately 82% nucleotide homology with the mouse 5-HT_{5A} gene (Grailhe et al., 2001; Rees et al., 1994).

Polymorphisms in the 5-HT_{5A} receptor have been reported, including two nucleotide substitutions in the 5' untranslated region and two synonymous substitutions in the coding region, as well as a Pro15Ser amino acid substitution near the N-terminal (Shimron-Abarbanell et al., 1997; Iwata et al.,

1998; Birkett et al., 2000; Iwata et al., 2001; Arias et al., 2001; Dubertret et al., 2004). The latter polymorphism is proximal to a phosphorylation site and is located in a region likely involved in agonist-induced downregulation (Iwata et al., 1998; Thomas, 2006). Additional polymorphisms in the promoter region of the 5-HT_{5A} receptor have been identified (Zhang et al., 2010).

Hydropathy analysis revealed that the 5-HT_{5A} receptor contains seven hydrophobic domains (numbered I-VII), a classic feature of GPCRs (Plassat et al., 1992; Erlander et al., 1993; Matthes et al., 1993; Rees et al., 1994; Grailhe et al., 2001; Thomas et al., 2004). Sequencing analysis of the 5-HT_{5A} receptor protein uncovered a single long open reading frame and a poly A tail (Plassat et al., 1992; Matthes et al., 1993; Grailhe et al., 2001; Thomas et al., 2004; Hurley et al., 1998). The length of the 5-HT_{5A} receptor protein is 357 amino acids for the human, mouse and rat proteins (Plassat et al., 1992; Erlander et al., 1993; Matthes et al., 1993; Rees et al., 1994; Hurley et al., 1998; Grailhe et al., 2001) but 356 amino acids in length in for the guinea pig receptor (Thomas et al., 2004). In all species, the 5-HT_{5A} receptors display *N*-linked glycosylation sites on the amino-terminals as well as consensus phosphorylation sites for protein kinase C and protein kinase A on the presumed cytoplasmic domains (Plassat et al., 1992; Erlander et al., 1993; Grailhe et al., 2001).

XII. C. Expression profile

The 5-HT_{5A} receptor is expressed widely in in the central nervous system (Plassat et al., 1992; Rees et al., 1994; Pasqualetti et al., 1998a; Grailhe et al., 2001; Kinsey et al., 2001; Tanaka et al., 2012; Figure 21) but seemingly not in peripheral organs (Plassat et al., 1992; Rees et al., 1994; Grailhe et al., 2001). There is some controversy over its expression in the peripheral nervous system (Chen et al., 1998; Pierce et al., 1996; Wang et al., 2000; Nicholson et al., 2003; Avila-Rojas et al., 2015).

In the human brain, the 5-HT_{5A} receptor mRNA expression has been reported in many regions of the cerebral cortex, including prefrontal, parietal, temporal, occipital and entorhinal cortices (Pasqualetti et al., 1998b; Grailhe et al., 2001; Lambe et al., 2011; Figure 22). The 5-HT_{5A} mRNA was also detected in the hippocampus, the amygdala, the cerebellum, the striatum, the caudate nucleus and the substantia nigra (Rees et al., 1994; Pasqualetti et

al., 1998a; Grailhe et al., 2001; Figure 22). Similar expression patterns have been reported in the mouse (Plassat et al., 1992; Tanaka et al., 2012) and the rat (Erlander et al., 1993; Kinsey et al., 2001; García-Alcocer et al., 2010; Lopez-Esparza et al., 2015). Expression was also noted in the suprachiasmatic nucleus of the hypothalamus, raphe nuclei, the ventral tegmental area, and the locus coeruleus (Oliver et al., 2000; Duncan et al., 2000). Since the 5-HT_{5A} receptor mRNA has not been detected in astrocytes (Hirst et al., 1998), expression of this receptor in the central nervous system is likely restricted to neuronal cells, consistent with the morphology of cells expressing 5-HT_{5A} receptor immunoreactivity (Oliver et al., 2000).

XII. D. Post-translational modifications and impact

Treatment with the *N*-glycosylation inhibitor tunicamycin fails to alter [³H]5-HT binding to the 5-HT_{5A} receptor yet results in re-distribution of the 5-HT_{5A} receptor from the cell membrane to the intracellular compartment suggesting that the *N*-glycosylation sites may play a role in targeting the 5-HT_{5A} receptor to the cell membrane (Dutton et al., 2008). Whilst both the N6 and N21 residues appear *N*-glycosylated within the mature human receptor protein, amino acid mutagenesis demonstrates that *N*-glycosylation of only the N6 residue results in protein insertion into the cell membrane (Dutton et al., 2008), a presumed prerequisite for receptor function.

XII. E. Pharmacology

The psychedelic hallucinogen LSD binds to and stimulates the 5-HT_{5A} receptor with high affinity as does another non-selective 5-HT receptor agonist, 5-CT. However, the quest to characterize the functions of the 5-HT_{5A} receptor in native tissue has been limited by a lack of selective agonists. Such characterization has relied on non-selective agonists in the presence of antagonists for other 5-HT receptors (Goodfellow et al., 2012).

Among selective antagonists for 5-HT_{5A} receptors, SB699551 (Corbett et al., 2005) has been most widely used in the literature (Table 17). It is important to note, however, that while SB-699551 possesses high affinity for the human and guinea pig 5-HT_{5A} receptor (\sim pKi 8.3), it displays a 100-fold lower affinity for the rat and mouse 5-HT_{5A} receptor (pKi 6.3; Thomas et al., 2006) limiting its utility in preclinical studies.

Other 5-HT_{5A} receptor antagonists have been proposed, including A-842377 (Garcia-Ladona et al., SFN abstract, 2006) and 2-aminodihydroquinazolines (Peters et al., 2008). However, only SB699551 and a series of compounds, ASP5736 (Yamazaki et al., 2014; 2015), AS2030680 and AS2674723 (Yamazaki et al., 2015) have extensive published pharmacological validation. Non-selective antagonists for the 5-HT_{5A} receptor include methiothepin and ritanserin (Thomas et al., 2004).

Based on rank order of affinity alone, the following *in vitro* pharmacological profile can be suggested for the human and mouse 5-HT_{5A} receptors: LSD (human pKi 8.40-8.70; mouse pKi 9.10) > 5-CT (human pKi 7.6-8.28; mouse pKi 7.8) > 5-HT (human pKi 6.7-7.40; mouse pKi 6.6-7.12) > 8-OH-DPAT (human pKi 5.6-6.07; mouse pKi 6.13-5.9) (Plassat et al., 1992; Rees et al., 1994; Francken et al., 1998; Grailhe et al., 2001; Thomas et al., 2004). By contrast, the human and mouse 5-HT_{5A} receptors display low affinity for ketanserin, norepinephrine, dopamine or spiperone (pKi < 5) (Plassat et al., 1992; Rees et al., 1994; Francken et al., 1998).

XII. F. Function

XII. F. 1. Cellular function

Functional effects of 5-HT_{5A} receptors have been examined in cell systems, in native tissue, and *in vivo*. Broadly, these data suggest that the 5-HT_{5A} receptor can activate pertussis toxin-sensitive G proteins (Francken et al., 1998; Hurley et al., 1998; Thomas et al., 2004) and suppress adenylyl cyclase and production of cAMP (Francken et al., 1998; Hurley et al., 1998; Thomas et al., 2000; Noda et al., 2003). Electrophysiological examination in native rodent cerebral cortex is consistent with coupling to G $\alpha_{i/o}$ proteins that activate Kir3 channels (Goodfellow et al., 2012). Studies *in vivo* indicate 5-HT_{5A} receptors may influence cognitive function and memory (Yamazaki et al., 2014; 2015; Gonzalez et al., 2013; Nikiforuk et al., 2016), participate in acoustic startle circuitry (Curtin et al., 2013) and potentially antinociception (Muñoz-Islas et al., 2014).

XII. F. 2. G-protein coupling of the 5-HT_{5A} receptor *in vitro*

To elaborate on the functional work in cell systems, treatment of cell lines transfected with the 5-HT_{5A} receptor with either 5-HT or 5-CT increases labelled GTPγS binding (Francken et al., 1998; Hurley et al., 1998; Thomas et al., 2004), an effect that could be abolished by pretreatment with pertussis toxin (Francken et al., 1998; Thomas et al., 2004). Conversely, pre-treatment of the non-hydrolysable GTP analogue, Gpp(NH)p, reduced the high affinity binding of [³H]5-CT in transfected HEK 293 cells (Francken et al., 1998). Moreover, stimulation of the 5-HT_{5A} receptor with 5-HT can reduce the basal activity of adenylyl cyclase (Noda et al., 2003) and inhibit forskolin-induced formation of cAMP in both C6 glioma and HEK-293 cell lines (Francken et al., 1998; Hurley et al., 1998; Thomas et al., 2000; Noda et al., 2003). Moreover, pretreatment with pertussis toxin prevented this 5-HT-elicited inhibition of basal adenylyl cyclase activity (Noda et al., 2003). These findings are also consistent with the 5-HT_{5A} receptor coupling to a Gαi/o protein pathway. However, this inhibitory effect of the 5-HT_{5A} receptor on cAMP could not be replicated in transfected HeLa or COS-M6 cells (Erlander et al., 1993). Similarly, in both HEK and NIH-3T3 cell lines stimulation of the transfected 5-HT_{5A} receptors had no detectable effect in basal cAMP levels, forskolin-induced cAMP levels, or accumulation of inositol phosphates (Grailhe et al., 2001). In C6 glioma cells, 5-HT_{5A} receptor has been shown to inhibit ADP-ribosyl cyclase activity in response to 5-HT, an effect that was abolished following pretreatment with pertussis toxin (Noda et al., 2003).

XII. F. 3. G-protein coupling of the 5-HT_{5A} receptor *ex vivo*

Research in native tissue has shown that cerebral cortical 5-HT_{5A} receptors couple to G proteins and has assessed the electrophysiological consequences of such coupling. In the presence of clozapine and spiperone, cortical slices from wild type mice display a rightward shift of the [³H]5-CT binding following pretreatment with Gpp(NH)p suggesting that in the native system the 5-HT_{5A} receptor is coupled to G proteins (Waeber et al., 1998). The 5-HT_{5A} receptor-activated ion current has been characterized in native prefrontal cortical tissue of both rats and mice (Goodfellow et al., 2012). The native 5-HT_{5A} receptor produces a small outward current that has a potent inhibitory effect on excitability of layer V pyramidal neurons of the prefrontal cortex. 5-HT has sub-micromolar potency at the native 5-HT_{5A} receptor and activates inwardly-rectifying potassium channels (Goodfellow et al., 2012).

XII. F. 4. 5-HT_{5A} receptor function in the spinal cord

Spinal 5-HT_{5A} receptors are upregulated by painful stimuli (Muñoz-Islas et al., 2014) and have been suggested to participate in antinociception and pain (Doly et al., 2004; Muñoz-Islas et al., 2014; Avila-Rojas et al., 2015). Their spinal localization suggests possible motor, somatosensory, and autonomic functions (Doly et al., 2004).

XII. F. 5. Function *in vivo*

Grailhe and colleagues (1999) generated 5-HT_{5A} receptor knockout mice. In terms of its biological phenotype, the central nervous system of the 5-HT_{5A} receptor knockout mice appeared normal. There were no major differences in the cytoarchitectonic divisions, neuronal morphology or distribution of glia (Grailhe et al., 1999). Moreover, 5-HT_{5A} receptor knockout mice display no differences in the distribution of neuronal markers for the monoaminergic system, calcium binding protein, neuropeptides, nitric oxide synthase or amino acid receptor subunits (Grailhe et al., 1999).

There appears to be the potential for significant cross talk between 5-HT_{5A} receptors and 5-HT_{1A} receptors in cerebral cortex given their electrophysiological function (Goodfellow et al., 2012; Goodfellow et al., 2014). In mice constitutively deleted for *Htr5A*, however, there were striking, supra-compensatory changes in the magnitude of the prefrontal 5-HT_{1A} receptor currents, with 5-HT_{5A} receptor knockout mice displaying nearly a doubling of the 5-HT_{1A} receptor outward current in layer V neurons from the prefrontal cortex (Goodfellow et al., 2012). The mechanism underlying this homeostatic plasticity is unknown. Further electrophysiological examination of 5-HT_{5A} receptor knockout mice revealed no difference in GABA_B receptor-mediated outward current, 5-HT_{1A} receptor protein levels or cell intrinsic properties in the adult prefrontal cortical neurons (Goodfellow et al., 2012).

Mice deleted for *Htr5A* display an increase of explorative-like behaviors, rather than anxiety-like behaviors, on the open field, the elevated plus maze and the marble burying task (Grailhe et al., 1999). Moreover, 5-HT_{5A} receptor knockout mice display greater increase in the number of entries into the central region after the introduction of the novel object into the center of the open field suggesting an increase in 'inspective' explorative-like

behaviors (Grailhe et al., 1999). In addition, 5-HT_{5A} receptor knockout mice displayed a reduction on LSD-elicited increase in locomotion in the open field (Grailhe et al., 1999). These changes occurred in the absence of any difference in motor activity (Grailhe et al., 1999). Given the evident considerable homeostatic plasticity detected in the cerebral cortex of the 5-HT_{5A} receptor knockout mice (strong upregulation of 5-HT_{1A} receptor mediated effects; Goodfellow et al., 2012), the behavioural characterization of the 5-HT_{5A} receptor knockout may underestimate its behavioural effects.

XII. G. Clinical relevance

The 5-HT_{5A} receptors are positioned neuroanatomically to play a role in emotional regulation, cognition, antinociception, and control of circadian rhythms and metabolism (Plassat et al., 1992; Pasqualetti et al., 1998a; Pasqualetti et al., 1998b; Oliver et al., 2000; Duncan et al., 2000; Grailhe et al., 2001; Doly et al., 2004; Lambe et al., 2011; Tanaka et al., 2012). Unfortunately, clinical examination of 5-HT_{5A} receptors has been restricted by the lack of selective ligands.

XII. G. 1. Psychosis and depression

A nonsynonymous single nucleotide polymorphism (Pro15Ser) in the *HTR5A* gene has been linked to schizophrenia (Iwata et al., 2001; Dubertret et al., 2004) and depression (Birkett et al., 2000), and polymorphisms in the promoter region of the 5-HT_{5A} receptor link to elevated triglyceride levels (Zhang et al., 2010). The high affinity of the psychedelic hallucinogen LSD for the 5-HT_{5A} receptor also underscores a potential link to psychosis (Thomas, 2006), keeping in mind that LSD, like many other ergolines, has affinity for multiple 5-HT receptors, of which only the 5-HT_{2A} receptor has been shown to play a significant role in hallucinations or psychosis. Yet in additional relevance to schizophrenia, 5-HT_{5A} receptors have been suggested to participate in pre-pulse inhibition of the acoustic startle response (Curtin et al., 2012). This effect was demonstrated in goldfish with SB-699551 and also with A-843277. The latter compound has been reported to have antipsychotic and antidepressant properties in rodent models, in line with the distribution of the receptor in higher cortical and limbic regions (Garcia-Ladona et al., 2004; Garcia-Ladona et al., SFN abstract, 2006; but see Kassai et al., 2012). Recent work suggests that blocking 5-HT_{5A} receptors may ameliorate positive symptoms in a rodent model of schizophrenia,

and will potentially enhance cognition and social behaviour in such models (Yamazaki et al., 2014; Nikiforuk et al., 2016). It may be relevant that the atypical anti-psychotic drug, asenapine, has high affinity for h5-HT_{5A} receptors (along with a number of other receptors; Shahid et al., 2009).

XII. G. 2. Memory and circadian rhythm

Yamazaki and colleagues demonstrated the 5-HT_{5A} receptor antagonists (ASP5736, AS2030680 and AS2674723; Table 17) benefit memory (Yamazaki et al., 2014; 2015) supporting a role for 5-HT_{5A} receptors in memory consolidation (Gonzalez et al., 2013). Additional preclinical work focuses on the localization of 5-HT_{5A} receptors in the hypothalamus, where it is densely expressed in the suprachiasmatic nucleus (Oliver et al., 2000; Duncan et al., 2000) suggesting potential roles in circadian rhythm and metabolism.

XIII. 5-ht_{5b} Receptors

XIII. A. Introduction

The genes encoding the human and rodent 5-ht_{5b} receptor were identified in 1993. The human 5-ht_{5b} receptor gene *HTR5B* is located on chromosome 2 at position 1q11-13 (Matthes et al., 1993). However, this gene contains stop codons in exon I resulting in a transcriptional product likely yielding a presumed non-functional truncated protein (Grailhe et al., 2001). The mouse 5-ht_{5b} receptor gene *Htr5B* is located on chromosome 1 at position 1F (Matthes et al., 1993) and forms a functional protein upon heterologous expression. Partial sequence analysis revealed that the 5-ht_{5b} receptor gene contained an intron in the third cytoplasmic loop (Matthes et al., 1993; Grailhe et al., 2001).

XIII. B. Receptor structure

Using hydropathy analysis, the predicted 5-ht_{5b} receptor protein has been shown to contain seven hydrophobic domains (numbered I-VII), a classic feature of GPCRs (Plassat et al., 1992; 1992; Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993; Rees et al., 1994; Grailhe et al., 2001). Sequencing analysis of the 5-ht_{5b} receptor protein revealed a single long open reading frame and a poly A tail (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993). The length of the 5-ht_{5b} receptor is 370 amino acids in both the rat and mouse protein (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993).

XIII. C. Expression profile

The 5-ht_{5b} receptor has a restricted expression profile within the central nervous system. In the rodent, expression of the 5-ht_{5b} receptor is exclusively found in the CA1 field of the hippocampus, the habenula, the inferior olivary nucleus, and the raphe nuclei (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993; Kinsey et al., 2001; Serrats et al., 2004; 2004; Tanaka et al., 2012; Figure 23). Interestingly, the 5-ht_{5b} receptor mRNA was strongly expressed in the medial portion of the raphe nuclei and was found to have high co-expression with 5-HT transporter, suggesting that this receptor may be localized on 5-HT producing neurons (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993; Serrats et al., 2004; Figure 24).

Expression of the 5-ht_{5b} receptor has not been detected in any peripheral organs including the heart, kidney, lung, liver or intestine (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993). Evidence for the 5-ht_{5b} receptor being expressed primarily in endosomes rather than the cell membrane raises potentially novel mechanisms of the functional relevance of this protein (Niebert et al., 2017) by impacting cell membrane expression of the 5-HT_{1A} receptor via intracellular direct protein-protein interaction.

XIII. D. Regulatory mechanisms and post-translational modifications

The 5-ht_{5b} gene expression is regulated by the transcription factor ATF-7, which can directly bind to the 5-ht_{5b} promoter region, resulting in histone methylation and, ultimately, silencing of the receptor gene transcription (Maekawa et al., 2010). The 5-ht_{5b} receptor displays *N*-linked glycosylation sites on the amino-terminal end as well as consensus phosphorylation sites for protein kinase C and protein kinase A on the presumed cytoplasmic domains (Erlander et al., 1993; Matthes et al., 1993; Wisden et al., 1993).

XIII. E. Pharmacology

To date, selective ligands for the 5-ht_{5b} receptor have not been reported. Non-selective agonists include LSD and 5-CT, and a nonselective antagonist is methiothepin. Based on affinity alone, the following *in vitro* pharmacological profile can be suggested for rodent 5-ht_{5b} receptors: LSD (rat pK_i 7.49), 5-CT (mouse pK_i 7.4; rat pK_i 6.26-8.88) and methiothepin (mouse pK_i 7.8; rat pK_i 7.35-8.87) but low affinity for ketanserin, dopamine and norepinephrine (Matthes et al., 1993).

XIII. F. Function at cellular, tissue and *in vivo* level

The transduction pathway of the 5-ht_{5b} receptor has not been well examined. Pretreatment with Gpp(NH)p reduced [³H]5-CT binding in 5-ht_{5b} transfected COS1 cells suggesting that the 5-ht_{5b} receptor readily couples to G protein (Wisden et al., 1993). However, this receptor had no effect on basal cAMP levels in either HeLa or COS-M6 cell lines (Erlander et al., 1993) although high levels of 5-ht_{5b} expression in mouse brain is associated with low cAMP levels (Vogelgesang et al., 2017).

It is speculated that the 5-ht_{5b} receptor acts as an inhibitory autoreceptor on 5-HT neurons in the raphe in rodents. However, neither an electrophysiological nor pharmacological profile has been described for the 5-ht_{5b} receptor in native tissue.

In a mouse model of Rett syndrome, there is a relatively high level of 5-ht_{5b} receptor expression in the brainstem due to a failure to downregulate receptor expression (Vogelgesang et al., 2017) with further studies suggesting a role for the 5-ht_{5b} receptor in the modulation of the complex breathing phenotype of the mouse model of Rett syndrome (Vogelgesang et al. 2018) as well a potential link to the native receptor inhibiting generation of cAMP.

XIII. G. Clinical relevance

Functional 5-ht_{5b} receptors are likely not expressed in humans (Grailhe et al., 2001), which limits interest in this receptor particularly from the pharmaceutical industry.

XIV. 5-HT₆ receptors

XIV. A. Introduction

The 5-HT₆ receptor has moderately high affinity for 5-HT, with an apparent binding affinity of approximately 30 nM. The gene for the 5-HT₆ receptor was originally cloned from rat in the early 1990's (Monsma et al., 1993; Ruat et al., 1993) and later from human (Kohen et al., 1996) and mouse (Kohen et al., 2001) cDNA libraries; the human gene being located on chromosome 1 (Kohen et al., 1996). For each known species, the complete gene contains three exons and has a total length of around 14 kb with a coding sequence of approximately 1.4 kb. The receptor protein is comprised of 440 amino acids in humans and mice and 436 amino acids in rats; a sequencing error in the originally published rat sequence was later corrected (Kohen et al., 1996). In humans, there is one described polymorphism (a C267T variant; Masellis et al., 2001)) as well as a truncated, non-functional splice variant (Olsen et al., 1999). No replicated polymorphisms in the human gene have been associated with human diseases including schizophrenia, methamphetamine-associated psychosis, tardive dyskinesia, Alzheimer's disease, obesity, or antidepressant drug responsiveness.

The protein structure of the 5-HT₆ receptor conforms to the typical motif of GPCRs with the typical seven transmembrane domain configuration. There have been no detailed investigations of whether this receptor exists in dimers or higher order oligomers.

XIV. B. Expression

5-HT₆ receptor mRNA is expressed primarily in the brain (Figure 25) being detectable in rat brain by day 12 of embryogenesis (Grimaldi et al., 1998). Originally, northern blot analyses detected RNA transcripts in brain tissue with the following regional density profile: hypothalamus > hippocampus = mesencephalon > cerebral cortex = olfactory bulb > olfactory tubercle (Monsma et al., 1993). Ruat and colleagues (1993) also reported a very similar distribution, noting highest expression in dorsal and ventral striatum, olfactory tubercle, and hippocampus, with lower expression in stomach, and very low to no expression detected in a variety of other peripheral tissues. Radioligand binding and immunohistochemical localization supported a similar distribution in rat and human brain (Gerard et al., 1997; Marazziti et al., 2013b). Using RT-PCR, Hirst and colleagues (2003) detected a

similar distribution of 5-HT₆ receptor mRNA in various regions of rat and human brain, whereas mouse brain had much lower apparent levels of 5-HT₆ receptor mRNA and unlike in other species, no enrichment in the basal ganglia. Specific binding of [¹²⁵I]-SB258585, a highly selective 5-HT₆ receptor radioligand, displayed the same patterns of regional localization with substantially higher levels of 5-HT₆ receptors in striatum than in other regions in rats and humans, but fairly homogenous levels of expression in all of the mouse brain regions that expressed 5-HT₆ receptors. Differences in 5-HT₆ receptor pharmacology between these species were evident, but did not explain the disparate distributions of receptor expression highlighting important species differences in 5-HT₆ receptor distribution (and pharmacology).

The cellular profile of expression has been examined in some detail in several brain regions. In the hippocampus and cortex, 5-HT₆ receptor mRNA is present in glutamatergic neurons containing vGluT1 mRNA as well as a subset of GABAergic interneurons that co-express the 5-HT_{3A} receptor; 5-HT₆ receptor mRNA is also detected in other classes of interneurons at a lower frequency (Helboe et al., 2015). 5-HT₆ receptor immunoreactive glial cells have also been reported in human cortex (Lorke et al., 2006; Marazziti et al., 2013b). In striatum, 5-HT₆ receptor mRNA is expressed in both direct and indirect pathway medium spiny neurons (Helboe et al., 2015; Ward and Dorsa, 1996) and occasionally in cholinergic interneurons (Bonsi et al., 2007; Helboe et al., 2015).

5-HT₆ receptors are not presynaptic autoreceptors on 5-HT neurons since 5-HT₆ receptor mRNA in rat is not altered by ablation of the DRN with 5,7-dihydroxytryptamine (Gerard et al 1996) and is not co-localized with SERT mRNA (Helboe et al 2015). Nonetheless their abundant expression on forebrain cortical neurons thought to project to DRN 5-HT neurons may explain how 5-HT₆ receptor ligands can modify 5-HT neuronal firing (see electrophysiology below).

The localization of 5-HT₆ receptors within neurons is still somewhat controversial, perhaps because of differences in antibody specificity. Initial studies described 5-HT₆ receptors in the neuropil and electron microscopy suggested that immunolabeling was predominantly associated with dendrites (Gerard et al., 1997). A subsequent electron microscopy study revealed that 5-HT₆ receptor immunolabeling is not only associated with

dendrites, but also with primary neuronal cilia (Brailov et al., 2000; Hamon et al., 1999). This is a surprising result because there are few GPCRs that localize to primary neuronal cilia (e.g. somatostatin sst3 receptor), and the 5-HT₆ receptor is the only 5-HT receptor that may do so (Berbari et al., 2008). The ciliary localization may require the presence of key amino acids in the third intracellular loop of the receptor, which is the case for 5-HT₆ receptors in mice, rats, and humans (Berbari et al., 2008). This subcellular distribution may have implications for interactions with other signaling proteins, such as adenylyl cyclase 3, which is localized exclusively in primary cilia (Baker et al., 1998) and resultant functional consequences of 5-HT₆ receptor signaling. However, the distribution and function of 5-HT₆ receptors that are heterologously expressed may be strongly dependent on a number of factors including the differentiation state of the neuron and the amount of receptor expressed. As an example, exogenous overexpression of transfected 5-HT₆ plasmid DNA has a strong effect on cilia localization, with heavy expression leading to increased rates of non-ciliary localization.

XIV. C. Pharmacology

There are important species differences between mammalian 5-HT₆ receptors. The mouse 5-HT₆ receptor has similar sequence homology to the homologous receptor of human, pig or rat, but the pharmacological profile is much closer between human and rat than mouse (Setola and Roth, 2003). Hirst and colleagues detected marked differences in the affinity of a number of ligands for the 5-HT₆ receptor in these three species (Hirst et al., 2003). For example, the antagonist compound Ro 04-6790 binds to recombinant rat or human 5-HT₆ receptors with similar affinity ($pK_i \sim 7.4$) but has relatively very low affinity for mouse 5-HT₆ receptor ($pK_i < 4$); several other antagonists (including SB-258585 and mianserin) have lower affinities (5 and 12 fold, respectively) at mouse compared to rat or human receptors (Hirst et al., 2003); these differences are explained to some degree by variances in the binding pocket as demonstrated by site directed mutagenesis. On the other hand, several highly selective agonists have similar affinities for mouse, human and rat 5-HT₆ receptors.

There are relatively far lower levels of 5-HT₆ receptor radioligand binding sites in mouse brain, with lesser density variation across regions, than is evident in rat and human brain. Importantly, this reduced level of receptor binding and rather homogenous density across the mouse brain, is

method-independent as it is equally observed using a variety of techniques to localize the receptors. Differences in residues 188 in TM5 and 290 in TM6 contribute to these species differences.

A null mutation (“knockout”) for the mouse 5-HT₆ receptor results in only subtle changes to the physiological and behavioral phenotype (Bonasera et al., 2006), consistent with a limited contribution of the 5-HT₆ receptor to baseline mouse behavior. Thus, rats may be a more useful model for studying the pharmacological and (patho)physiological roles of 5-HT₆ receptors in relation to humans, whereas the availability of a knockout strain make mice very useful for studying other aspects of the biology of this receptor.

Several strategies for radiolabeling 5-HT₆ receptor have been described: [¹²⁵I]-SB258585 (Hirst et al., 2006) is the most selective, commercially available option; other radioligands require masking of non-5-HT₆ receptor sites, and include [³H]-LSD (Sleight et al., 1998), [³H]-clozapine (Glatt et al., 1995), and [¹¹C]-GSK215083 (Parker et al., 2012; Parker et al., 2015).

Several selective 5-HT₆ receptor agonists are available. EMDT was the first moderately selective agonist developed (Glennon et al., 2000); it is brain penetrant and has >10 fold selectivity for 5-HT₆ compared to other 5-HT receptors. More selective agonists include WAY181187, WAY208466 (Schechter et al., 2008), and ST1936 (Borsini et al., 2015). Some of these ligands display partial agonism under certain circumstances, e.g. EMD386088 (Jastrzebska-Wiesek et al., 2013) and E6801 (Romero et al., 2006); many non-selective 5-HT receptor agonists are either full or partial agonists at 5-HT₆ receptors, which can be useful tools in specific cases, but care must be given to rule out actions at other 5-HT receptors. For instance, EMD386088 has moderate affinity (IC₅₀ = 34nM) for the 5-HT₃ receptor (Mattson et al., 2005) and ST1936 has moderate affinity for 5-HT₇, 5-HT_{2B} and alpha2-adrenoceptors (K_i = 168, 245 and 300nM, respectively; Riccioni et al, 2011). However, the contribution of partial agonism to the behavioral or physiological effects of 5-HT₆ receptor ligands has not been thoroughly characterized.

A number of clinically effective drugs have affinity for 5-HT₆ receptors, but also for other receptor targets. Several antidepressants and antipsychotics have high affinity for 5-HT₆ receptors (Monsma et al., 1993; Ruat et al., 1993); but none of these are selective for the receptors. After the discovery of the 5-HT₆ receptor, a number of modestly selective antagonists were reported based on high throughput screening of chemical libraries, although these often shared affinity for other 5-HT or dopamine receptors (Upton et al., 2008). The first CNS penetrant selective 5-HT₆ receptor antagonists were produced by Roche (e.g. Ro 04-6790; Sleight et al 1998) and GlaxoSmithKline (e.g. SB-271046; Bromidge et al 1999). Subsequently, more highly selective 5-HT₆ receptor antagonists were developed, which are useful for both *in vitro* and *in vivo* experimentation. Among these are SB258585, SB399885 (Hirst et al., 2003), Ro4368554 (Lieben et al., 2005).

In heterologous systems expressing wild-type or constitutively active 5-HT₆ receptors, a number of the selective agonists may show partial agonist activity, whereas numerous antagonists display inverse agonist properties (Purohit et al., 2003; Romero et al., 2006).

The first 5-HT₆ receptor somewhat selective PET ligand, [¹¹C]-GSK215083 (with approximately 5-fold-lower affinity for the 5HT_{2A} receptor) demonstrates 5-HT₆ receptor occupancy in the human striatum (Parker et al 2012; Parker et al 2015) and will no doubt help to investigate the role of this receptor in human pathology and in therapeutic response /target engagement of existing or new therapeutics or drugs.

XIV. D. Post-translational modifications and protein interactions

There is a predicted glycosylation site in the amino terminal of the 5-HT₆ receptor and a number of predicted phosphorylation sites (Kohen et al., 2001; Kohen et al., 1996; Monsma et al., 1993; Ruat et al., 1993), although none of these have been examined systematically. However, phosphorylation of serine 350 appears to be mediated by cyclin-dependent kinase 5 (Cdk5); treatment of NG108 cells with a 5-HT₆ receptor selective agonist leads to co-immunoprecipitation of 5-HT₆ receptor and Cdk5 whereas the 5-HT₆ receptor-selective antagonist, SB258585, reduces the receptor phosphorylation and co-immunoprecipitation with Cdk5 (Duhr et al., 2014). Furthermore, bioluminescence energy transfer experiments confirm the direct interaction of this receptor and Cdk5 in transfected NG108 cells, which is also inhibited by the 5-HT₆ receptor antagonist

SB258585. Duhr and colleagues (2014) demonstrated that Cdk5-dependent phosphorylation of the 5-HT₆ receptor leads to activation of Cdc42 (a Rho GTPase), which can in turn activate further downstream mechanisms. The role of serine 350 phosphorylation was confirmed by site-directed mutagenesis, which may result in constitutive activity of the receptor in the absence of agonist and inhibition of phosphorylation and downstream events by the 5-HT₆ receptor selective antagonist SB258585. These signaling events may enhance NG108 cell differentiation and neurite outgrowth both in this cell line and in striatal and cultured hippocampal and striatal neurons.

Using HEK-293 cells transfected with epitope tagged 5-HT₆ receptors, Marin's group also detected direct interactions of this receptor with mTOR and several related proteins in the mTOR complex 1 (Meffre et al., 2012). 5-HT₆ receptor selective agonists induce mTOR activation, social cognition impairments in mice and object recognition impairment in rats that could be blocked with the mTOR antagonist, rapamycin. In summary, these data suggest that direct protein-protein interactions involving the 5-HT₆ receptor may lead to activation of multiple signaling cascades in addition to the canonical G_s-mediated activation of adenylate cyclase (see Section XVII. C. for further discussion of protein-protein interactions with the 5-HT₆ receptor).

While not examined in detail, dimerization of 5-HT₆ receptors can be inferred from the immunoprecipitation and western blot analysis (Duhr et al., 2014; Meffre et al., 2012).

XIV. E. Signaling pathways

There is growing appreciation of the complexity of the pharmacological and signaling properties of the 5-HT₆ receptor. The ability of the 5-HT₆ receptor to activate adenylate cyclase in a G_s-dependent manner was first described when the receptor was originally cloned and expressed heterologously, as well as in native tissues (Choi et al., 2007; Kim et al., 2014; Monsma et al., 1993; Ruat et al., 1993; Sebben et al., 1994; Unsworth and Molinoff, 1994). 5-HT₆ receptors can activate several adenylate cyclase isoforms, including AC3, AC5, and AC8, but not AC1 or AC8 (Baker et al., 1998). Since 5-HT₆ receptors activate adenylate cyclase, thereby increasing cAMP and therefore protein kinase A activity, a number of additional

downstream signaling consequences can be presumed, although these have not been systematically examined. Svenningsson and colleagues (2002) examined the potential synergistic interactions between 5-HT₆ and D₁ dopamine receptors: 5-HT₆ receptor activation in striatum regulates DARPP₃₂, an enzyme previously associated mainly with dopaminergic neurotransmission. Selective 5-HT₆ receptor agonists modulate the DARPP₃₂ phosphorylation state in a manner consistent with increasing this enzyme's activity; phosphorylation of DARPP₃₂ is blocked by selective 5-HT₆ receptor antagonists; 5-HT-mediated c-Fos activation and motor activity is blunted in DARPP₃₂ knockout mice (Svenningsson et al., 2002). However, 5-HT regulation of DARPP₃₂ is unlikely to involve exclusively 5-HT₆ receptors, since 5-HT₄ and 5-HT₇ receptors can also activate DARPP₃₂. This pathway is an interesting regulatory node that potentially integrates 5-HT and dopamine signaling in neurons that co-express 5-HT₆ and D₁ receptors, such as striatonigral (direct pathway) medium spiny neurons.

The 5-HT₆ receptor induces fyn kinase activation. (Riccioni et al., 2011; Yun et al., 2007). Fyn is a src tyrosine kinase family member, present in both cilia and neuronal soma. Fyn is expressed in the same brain regions as 5-HT₆ receptor. Phosphorylated-Fyn is thought to activate Erk1/Erk2 kinases via the Ras-Raf-MEK pathway. Direct protein interactions with Cdk5 also predict that 5-HT₆ receptors signal through this kinase pathway, which was shown to regulate neurite outgrowth in NG108 cells and primary neurons (Duhr et al., 2014). This pathway regulates neuronal migration in both slice cultures and *in vivo* (Jacobshagen et al., 2014). 5-HT₆ receptor activation phosphorylates doublecortin and focal adhesion kinase, two mediators of neuronal migration, is Cdk5 dependent although additional or alternative mediators may be at play. Similarly, mTOR interactions were predicted based on studies of protein interactions, and 5-HT₆ receptor agonists induce phosphorylation of mTOR into the active form, which is blocked by selective 5-HT₆ receptor antagonists both *in vitro* and *in vivo* (Meffre et al., 2012).

The constitutive activity of 5-HT₆ receptors represents an intriguing issue. Constitutive activity implies that the receptor couples to and activates downstream effectors in the absence of the agonist; the clearest evidence for this with 5-HT₆ receptors comes from heterologous expression systems and with activation of Cdk5, Fyn, and mTOR signaling events (Duhr et al., 2014; Jacobshagen et al., 2014; Meffre et al., 2012; See Section XVII.C). However, it has been more difficult to confirm this in systems that are dependent upon activation of 5-HT₆ receptors expressed in native cells or

tissues. For example, Sebben and colleagues described 5-HT₆ receptor mediated cAMP accumulation in primary cultured mouse striatal neurons, and several full agonists, such as 5-HT and LSD, caused cAMP production, but no constitutive activity was apparent (Sebben et al., 1994). Since the cell type, signal transduction pathway(s), and the level of receptor expression may all affect the extent of constitutive activity, its contribution to 5-HT₆ function likely varies a great deal depending on the cellular context; hence it still remains to be demonstrated with natural expression levels *in vivo*. However, the 5-HT₆ receptor clearly has a propensity to display constitutive activity and many of the available antagonists are in fact inverse agonists, meaning that they will reduce 5-HT₆ signaling if constitutive activity is present (Purohit et al., 2003).

XIV. F. Function

Prior to the availability of selective 5-HT₆ receptor antagonists, antisense oligonucleotides were used to reduce expression/ function of the 5-HT₆ receptor: yawning and stretching behavior (Bourson et al 1995), weight loss and reduced retention of spatial learning in the Morris water maze were reported following receptor knock-down (Woolley et al 2001), later replicated by the use of selective antagonists. Interestingly, the extent of 5-HT₆ receptor knock-down was limited (20-30% using [³H]LSD binding) and it is only more recently that knock-out mice have been available. Tecott and Brennan (2000) produced the first 5-HT₆ receptor knock-out mouse and reported weight loss in a patent, which triggered the exploration of 5-HT₆ receptor antagonists as appetite suppressants (Heal et al 2008; Higgs et al., 2016). More recently germ-line knockout of 5-HT₆ receptors produced no changes in viability, health, weight or longevity of the null mutant mice (Bonasera et al., 2006), no deficits in fertility or maternal behavior. Furthermore, no overt changes in circadian activity, emotional behavior, sensorimotor gating or cognition were detected. The only behavioral change evident was a reduced sensitivity to the sedative and ataxic effects of acute ethanol administration. However, mouse 5-HT₆ receptor KO may underestimate the potential roles of 5-HT₆ receptors in any of these effects, since mice have much lower 5-HT₆ receptor expression than many other mammalian species (Hirst et al., 2003) as discussed above.

While 5-HT₆ null mutant mice seem to develop normally, there are very interesting effects of acute modulation of 5-HT₆ receptors during cortical development. Using both *in vivo* and explant culture models, Dayer and colleagues have shown that modulating 5-HT₆ receptor signaling produces

deficits in neuronal migration. The 5-HT₆ receptor partial agonist, EMD386088, delays the rate of pyramidal neuron and interneuron migration (Riccio et al., 2011; Riccio et al., 2009), which can be blocked by the antagonist SB 258585, although the concentrations of drugs used are rather high questioning receptor classification.

The effect of activation vs. inhibition of 5-HT₆ receptor activity is complex, though, as shRNA knockdown of endogenous 5-HT₆ receptors produces deficits in neuronal speed and extent of neuronal migration (Jacobshagen et al., 2014). This deficit is partially rescued by co-expressing 5-HT₆ receptors or overexpressing Cdk5, but not by co-expressing 5-HT₆ receptor mutants that disrupt Gs-coupling and thus adenylate cyclase activation. Further, 5-HT₆ receptor mediated Cdk5 signaling facilitates dendritic outgrowth. There may be additional mechanisms of 5-HT₆ receptor mediated developmental effects as the selective agonist, WAY181187, activates mTOR in mouse cortex and this is blocked by SB258585 (Meffre et al., 2012). The psychomimetic drug phencyclidine, which models aspects of the development and symptoms of schizophrenia, induces mTOR activation in neonatal rat cortex and impairs social cognition in the adult mice; both of which are blocked by the mTOR inhibitor rapamycin, or the 5-HT₆ receptor selective antagonist, SB258585. Interestingly, both drugs also reverse visual recognition impairments associated with isolation rearing in rats (Marsden et al., 2011; Meffre et al., 2012). While adenylate cyclase, mTOR, Cdk5, and fyn kinase signaling are complex and impacted by many parallel pathways, the potential that multiple signaling pathways emanating from 5-HT₆ receptors play a crucial role in establishing normal cortical circuitry has far-reaching implications given that drugs that modulate 5-HT dynamics (such as SSRIs and other antidepressants) or that directly interact with 5-HT₆ receptors (whether exclusively so or not) may produce alterations in cortical development. These issues need to be examined more fully to understand the consequences of 5-HT drug treatments during gestation or in adolescence.

It is reasonable to conclude that 5-HT₆ receptors may increase the excitability of neurons as this is the expected result following activation of adenylate cyclase. The 5-HT₆ receptor agonist WAY181187 increases fos-like immunoreactivity in cortex (Burnham et al., 2010) and the 5-HT₆ receptor antagonist Ro4368554 reduces scopolamine-induced increase of fos-like immunoreactivity in lateral amygdala (Mitchell et al., 2009);

however, both of these manipulations produce complex behavioral and pharmacological changes that make it difficult to conclude that the effects are directly related to 5-HT₆ receptors or are more indirect consequences of circuitry level events.

5-HT₆ receptors modulate many different neurotransmitter systems (Dawson, 2011; Mitchell and Neumaier, 2005). Impact upon extracellular levels of acetylcholine, glutamate, GABA, dopamine, and norepinephrine have been reported using microdialysis. Selective 5-HT₆ receptor ligands alter neuronal firing in a variety of brain regions, but it is difficult to conclude whether these effects are direct or indirect. In any event, it appears that 5-HT₆ receptor ligands modulate numerous brain regions and neurotransmitter systems.

There is a rich literature addressing the potential cognitive effects of 5-HT₆ receptor modulation (Codony et al., 2011; King et al., 2008; Marsden et al., 2011; Meneses, 2015; Mitchell and Neumaier, 2005; Wooley et al 2004). In most cases 5-HT₆ receptor antagonists display pro-cognitive effects in a variety of rodent memory tasks such as spatial learning, novel object recognition, social discrimination, and autoshaping (Mitchell and Neumaier, 2005). Generally, these experiments used parenteral drug administration either just before or just after a memory “training” session that was then assessed after a short interval. The procognitive effects of 5-HT₆ receptor antagonists have often been shown to be associated with changes in other neurotransmitter systems, especially acetylcholine, glutamate or GABA release. However, it is difficult to reach mechanistic conclusions based on the correlative nature of these observations. At this time, it is not possible to attribute the memory enhancing effects of 5-HT₆ receptor antagonists to a single brain region or neurotransmitter system and it seems likely that multiple mechanisms are responsible.

While there are numerous reports that inhibiting 5-HT₆ receptors promotes (or restores) memory, there is some apparent inconsistency in the cognitive role of 5-HT₆ receptor agonists. For example, WAY117187 (an agonist) impaired social recognition in an antagonist sensitive manner whether given systemically or locally into frontal cortex (Loiseau et al., 2008); EMD386088 or WAY466 impaired memory in the autoshaping or social recognition tasks, respectively (Meneses et al., 2008; Schechter et al., 2008). However, other reports have observed pro-cognitive effects of 5-HT₆ receptor agonists (Kendall et al., 2011; Pereira et al., 2015; Woods et al., 2012). There are several potential explanations for these discrepancies.

One explanation is that 5-HT₆ receptor activation in some brain regions is pro-cognitive whereas inhibition of 5-HT₆ receptors in other brain regions is also pro-cognitive. Another possible explanation is that the effect of increased or decreased 5-HT₆ receptor activity is entirely dependent on the specific cognitive domain being tested. A third possibility is that either high or low levels of 5-HT₆ receptor activity enhance cognition in specific regions albeit by different neurochemical mechanisms (e.g. facilitating glutamatergic function in states with a relative deficit or facilitating GABAergic function in states of excessive glutamatergic activity). Even when the same cognitive task has been used, each laboratory likely performs these tests in at least slightly different ways - with or without amnesic maneuvers (such as using scopolamine to disrupt memory function), in young or old animals, short vs. long interval testing; thus, it seems unlikely that agonists or antagonists will “win” this battle, but rather there may be a role for both 5-HT₆ receptor agonists and antagonists for different cognitive problems in different pathological states.

The effects of striatal 5-HT₆ receptors on autoshaping and related instrumental learning tasks have been investigated based on the early observations that 5-HT₆ receptor antagonists facilitate cholinergic function (Mitchell and Neumaier, 2005); it was thought that these drugs facilitate consolidation of memory by cortical or hippocampal mechanisms. However, since 5-HT₆ receptors are most heavily expressed in medium spiny neurons in striatum, these neurons might also be an important site of 5-HT₆ receptor action in cognition. Since the autoshaping task used extensively by Meneses' group was clearly sensitive to 5-HT₆ receptor antagonism, this task was studied in mice with striatum-specific increased 5-HT₆ receptor expression (Mitchell et al., 2007). High 5-HT₆ receptor density in dorsomedial striatum impaired the acquisition, but not the expression of previously learned instrumental learning. This effect is unlikely to involve memory consolidation as the deficit is only reversed by giving a 5-HT₆ receptor antagonist before but not after the training session. The operant conditioning parameters were altered to allow single session acquisition; increased 5-HT₆ receptor expression interfered with learning under these conditions (Eskenazi and Neumaier, 2011b). Further, the type of learning affected by increasing the local expression of 5-HT₆ receptors depended entirely on the subregion of striatum targeted (Eskenazi and Neumaier, 2011a; b; Ferguson et al., 2008; Mitchell et al., 2007). These studies do not exclude a role of 5-HT₆ receptors in cholinergic interneurons in striatum, as the focus was on the direct and indirect striatal output pathways, which have generally opposing effects on behavior (Yager et al., 2015). Increased 5-HT₆ receptor expression in indirect pathway medium spiny neurons is sufficient to disrupt instrumental learning in dorsomedial striatum or to facilitate

learning of new behavior in over-trained animals when the dorsolateral striatum was targeted (Eskenazi et al., 2015). Indeed, 5-HT₆ receptors tend to oppose the effects of dopamine on striatal-based behaviors including learning since they are expressed in both output pathways, whereas D₁ and D₂ dopamine receptors are differentially expressed in these pathways (Gerfen and Surmeier, 2011). These subtleties illustrate how 5-HT₆ receptors can have diverse effects on behavior depending on the cells that express these receptors. Thus, a full understanding of how 5-HT₆ receptors modulate learning and memory in a specific cognitive disorder may depend, at least in part, on how that disorder changes 5-HT receptor signaling.

In addition to effects on cognition, 5-HT₆ receptors have been proposed to promote satiety and reduce feeding and body weight (Fisas et al., 2006; Higgs et al., 2016; Voigt and Fink, 2015; Woolley et al., 2001); however, not all studies report effects of chronic 5-HT₆ receptor antagonism on body weight in rats or humans (Mitchell et al., 2009; Quiedeville et al., 2015; Wilkinson et al., 2014). Most of these studies used animals with normal body weight, whereas the 5-HT₆ receptor antagonist idalopirdine reduced feeding, peritoneal fat, and body weight when rats were fed a high fat diet (Dudek et al., 2015). This metabolic profile might be advantageous clinically as reducing feeding only in obese individuals would mitigate the risks of the drug when used for treating individuals with dementia. Furthermore, since several atypical antipsychotics that have high affinity for 5-HT₆ receptors (along with many other sites) are associated with increased appetite, weight gain, and the development of the metabolic syndrome, the preclinical and limited clinical data available suggest that 5-HT₆ receptor antagonism is unlikely to be responsible for these adverse effects, which are more likely due at least in part to 5-HT_{2C} receptor antagonism.

The 5-HT₆ receptor has also been examined in relation to drug dependence, given their dense expression in the striatum, a key mediator of reward seeking and habit formation. However, some reports have found no effect of a systemic 5-HT₆ receptor ligands on cocaine self-administration (Fijal *et al*, 2010; Frantz *et al*, 2002; Valentini *et al*, 2012) while others suggest that cocaine reinforcement or reinstatement is regulated by 5-HT₆ receptor activity (van Gaalen *et al*, 2010; Valentini *et al*, 2012). Increased striatal 5-HT₆ receptors modulate learning of drug-associated behaviors as well as the stability of habitual responding (Eskenazi et al., 2015; Eskenazi and Neumaier, 2011a; Ferguson et al., 2008) but selectively increasing 5-HT₆ receptors

in the indirect pathway medium spiny neurons in ventral striatum increases the sensitivity to the reinforcing properties of self-administered cocaine (Brodsky et al., 2015).

5-HT₆ receptors may also play a role in the development and treatment of epilepsy (Hirst et al., 2006). Increased 5-HT₆ receptor levels were detected in brain tissue surgically removed from humans with epilepsy and in the pilocarpine model of epilepsy in rats (Wang et al., 2015). The selective antagonist, SB399885, reduces mTOR activation and epileptic activity in this animal model. Further, the co-localization of 5-HT_{3A} and 5-HT₆ receptors in a subset of cortical interneurons (Helboe et al., 2015) is intriguing given the potential role of these interneurons in cortical excitability for both normal cognition as well as pathological states.

XIV. F. 1. Electrophysiology

Much of the electrophysiological data concerning 5-HT₆ receptors concerns *in vivo* recording primarily, the cellular mechanisms are difficult to infer. The selective 5-HT₆ receptor agonist, WAY181187, increases excitability and spiking by rat medium spiny neurons in acutely prepared striatal slices in a SB258585-reversible manner; but this has not been sufficiently explored identify whether this is a direct or indirect phenomenon. In whole cell patch clamp mode, the 5-HT₆ receptor agonist ST1936 reduces spontaneous excitatory post synaptic currents in striatal medium spiny neurons and cortical pyramidal neurons, which is prevented by SB258585 (Tassone et al 2011). Thus, the agonist-induced reduction in glutamatergic neuronal activity (consistent with microdialysis reports of enhanced glutamate overflow following microinfusion of 5-HT₆ receptor antagonists; Upton et al 2008; Dawson 2011) might be indirect by modulation of GABAergic interneurons in these brain areas. Although systemic administration of 5-HT₆ receptor agonists to anaesthetized rats produced both excitation and inhibition of ventral tegmental area (VTA) dopamine neurons, only excitation is observed following microiontophoretic application (Borsini et al, 2015), suggesting a direct excitatory activation, which may be relevant for cognitive and addictive properties of 5-HT₆ receptor ligands.

Moderate levels of 5-HT₆ receptors are also expressed in the DRN and local injection of the agonist, WAY-208466, decreases REM sleep and increases wakefulness (Monti et al, 2013). Single unit recording in the anaesthetized rat shows that systemic application of the full agonist, WAY-181187, increases and the antagonist, SB-399885, decreases firing of putative DRN 5-HT neurons; further studies are needed to establish if this involves cortical feedback loops, interneurons and/or a direct effect on 5-HT neurons, as proposed by the authors (Brouard et al, 2015). Consistent with this idea of indirect modulation of 5-HT release in the raphe, the 5-HT₆ receptor antagonist, SB399885, inhibits spontaneous firing of GABA-ergic interneurons (expressing 5-HT₆ receptor mRNA) in the DRN in mouse brain slices (Asaoka et al, 2015). This mechanism may be relevant to the action of antipsychotic drugs since the effect is mirrored by olanzapine.

XIV. G. Clinical Relevance

Treatment of cognitive impairment is a leading potential application of 5-HT₆ receptor ligands in humans. There is ample evidence that manipulation of 5-HT₆ receptors can improve cognitive function based on preclinical animal models. While schizophrenia is associated with positive and negative symptoms that can respond to available antipsychotic drugs, cognitive impairment is an often disabling and persistent problem that typically does not respond well to antipsychotic medications. While there are some preliminary clinical trials in schizophrenia, these trials had technical limitations since the 5-HT₆ receptor ligands investigated were as add on to treatments already underway; and in some cases, the on-going treatments were atypical antipsychotic drugs that possess potent antagonist properties at 5-HT₆ receptors, making it unlikely that additional benefits from 5-HT₆ receptor blockade could be readily detected. Early clinical studies with 5-HT₆ receptor ligands are reviewed elsewhere (Heal 2008; Codony et al 2001). A double-blind, placebo-controlled Phase II trial for treatment of dementia associated with Alzheimer's Disease (Wilkinson et al., 2014) investigated whether the addition of Lundbeck's idalopirdine, a selective 5-HT₆ receptor antagonist, to an established treatment (donepezil; a cholinesterase inhibitor) delays the progression of dementia. This study was successful in two important ways: addition of idalopirdine was well tolerated and also led to improved cognitive function as compared to addition of placebo. However, disappointingly idalopirdine suffered a late-stage failure in a pivotal Phase III trial. Along the same lines, intepirdine, previously known as RVT-101, a 5-HT₆ receptor antagonist originally developed by GSK displayed positive effects in patients with AD in Phase II clinical trial. A subsequent Phase III trial of the drug after it was acquired by Axovant, failed to

achieve any of its main efficacy targets in mild-to-moderate AD patients. Intepirdine did not improve symptoms compared to placebo on two widely used AD symptom measures - the ADAS-Cog and ADCSADL scales. Subsequently, intepirdine was evaluated in clinical trial of patients with dementia with Lewy bodies (DLB) also without success leading to a halt in the development of this drug. Hence whilst the availability of new, effective treatments for dementia is a crucial health imperative, it would appear that 5-HT₆ receptor antagonism may not transfrom the preclinical promises into clinical practice; understanding the mechanisms that underlie this apparent failure is important and may allow opportunity for patient stratification to better identify patients that may respond favourably to 5-HT₆ receptor ligands.

Several other pathologies might also be amenable to treatment with 5-HT₆ receptor ligands, since preclinical data suggests that other progressive dementing disorders, depression, obesity, and epilepsy have potential to become indications for 5-HT₆ receptor ligands. As now appreciated, the multiple signal transduction pathways engaged by 5-HT₆ receptors, and various 5-HT₆ receptor ligands with differing degrees of intrinsic efficacy, the role of agonism, partial agonism, antagonism, and inverse agonism as well as biased signaling needs to be considered in future development of 5-HT₆ receptor therapeutic agents. Such pharmacological complexity may also account for the apparent opposing actions of 5-HT₆ receptor ligands in pre-clinical behavioural models as discussed above.

XV. 5-HT₇ receptors

XV. A. Introduction

The 5-HT₇ receptor was the last 5-HT receptor to be discovered. In 1993, several research groups almost at the same time identified the 5-HT₇ receptor from the screening of cDNA libraries from various species, including humans. 5-HT₇ receptor mRNA is localized in discrete areas of the mammalian brain, including thalamus, hippocampus, and cortex, and matched with the expression of 5-HT₇ receptor protein. Based on its distribution in the CNS, the 5-HT₇ receptor is proposed to be involved in thermoregulation, circadian rhythm, learning and memory, hippocampal signaling, and sleep. Since various drugs (clozapine, cyproheptadine, amitriptyline) and pharmacological tools (5-CT, 8-OH-DPAT) bind to 5-HT₇ receptor poses the question whether some of the effects of these compounds are mediated, at least in part, by 5-HT₇ receptor. Initially, the lack of selective 5-HT₇ receptor agonists and antagonists slowed down the elucidation of the (patho)physiological role of the receptor, especially because of the high sequence homology in the transmembrane domains of 5-HT₇ and 5-HT_{1A} receptors. Moreover, the two receptors are distributed in the same areas of the CNS and, at the cellular level, they may have opposite effects: the 5-HT₇ receptor is positively coupled to adenylyl cyclase whereas the 5-HT_{1A} receptor is negatively coupled. After 2000, various selective antagonists (SB-258719, SB-269970) and agonists (AS-19, LP-211, E-55888) became available, providing the scientific community with powerful pharmacological tools to get deeper insights on the role of 5-HT₇ receptors in health and disease.

XV. B. Cloning of the gene

The 5-HT₇ receptor, is a class A GPCR, cloned by screening of cDNA libraries from mouse (Plassat et al., 1993), rat (Lovenberg et al., 1993a, Meyerhof et al., 1993, Ruat et al., 1993b; Shen et al., 1993), human (Bard et al., 1993), guinea pig (Tsou et al., 1994), *Xenopus laevis* (Nelson et al., 1995), pig (Bhalla et al., 2002a), *Caenorhabditis elegans* (Hobson et al., 2003) and honeybee (Schlenstedt et al., 2006).

The open reading frame of the human cDNA codes for a protein of 445 amino acids with 57% sequence identity within the transmembrane regions in comparison with the *Drosophila melanogaster* 5-HT_{dro1} receptor, and 39-53% homology with human 5-HT₁, 5-HT₂, 5-HT₅, and 5-HT₆ receptors (Bard et al. 1993). The gene encoding the human 5-HT₇ receptor is located on chromosome 10 (q21-q24) (Gelernter et al., 1995) and contains several introns in the coding region (Ruat et al., 1993b, Erdmann et al., 1996; Heidmann et al., 1997). The guinea pig 5-HT₇ receptor has 466 amino acids, with an amino acid homology within the transmembrane regions with other 5-HT receptors of 34 and 48% (Tsou et al. 1993). The mouse brain 5-HT₇ receptor cDNA has one long open reading frame for 448 amino acids. The homology with other 5-HT receptors is low, with the best score with the 5-HT_{dro1} receptor (42%), the next closest homology being with 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1E} receptors (Plassat et al. 1993). The 5-HT₇ receptor was cloned from rat by four groups which reported different amino acid lengths ranging from 404 to 448. Shen et al. (1993) reported the sequencing of a full length clone isolated from a rat hippocampal cDNA library revealing a 404 amino acids protein with seven hydrophobic regions. Within these regions, rat 5-HT₇ receptor is 44-50% identical with members of the 5-HT₁, 5-HT₅, and 5-HT₆ subfamilies, with lower homology to the 5-HT₂ receptor subtypes (37-40%). Lovenberg et al. (1993a) isolated and determined the nucleotide sequence of a clone showing an open reading frame that encoded a 435 amino acids protein. Within the conserved transmembrane domains of known 5-HT receptors, the rat 5-HT₇ receptor exhibited the greatest identity with the 5-HT_{dro1} receptor (54%). Instead, the entire coding sequence showed low identity (33-39%) with 5-HT_{dro1}, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, 5-HT₅ receptor subtypes. Ruat et al. (1993b) reported the characterization of a nucleotide sequence containing an open reading frame encoding a 448 amino acids protein. This rat 5-HT₇ receptor showed the highest sequence homology in the hydrophobic regions with the 5-HT_{dro1} receptor (60%). In the transmembrane domains the homologies with other 5-HT receptors were as follows: 5-HT_{1A}: 51%; 5-HT_{1B}: 55%; 5-HT_{1D}: 52%; 5-HT_{1E}: 53%; 5-HT_{1F}: 52%; 5-HT_{2A}: 43%; 5-HT_{2B}: 40%; 5-HT_{2C}: 42%; 5-HT₅: 48%; 5-HT₆: 45%. The rat 5-HT₇ receptor reported by Meyerhof et al. (1993), has an open reading frame encoding a 448 amino acids protein, showing the highest sequence homology with 5-HT_{dro1} receptor (36% identity). The 5-HT₇ receptor from pig (Bhalla et al. 2002a), encoded an open reading frame of a 447 amino acids protein, that showed high homology (92-96%) with the 5-HT₇ receptor protein cloned from the other species.

The presence of introns in the 5-HT₇ receptor gene, results in a number of functional splice variants. While no alternative splicing has been reported for the first intron, located in the sequence encoding the second intracellular loop of the receptor, alternative splicing at the second intron, which is

located in the sequence encoding the C-terminal end, generates a number of splice variants, namely 5-HT_{7(a), (b), (c), (e)} receptors in rat and 5-HT_{7(a), (b), (d)} receptors in man (Heidmann et al., 1998; Krobert et al., 2001; Liu et al., 2001). Splice variants in dog, marmoset and zebrafish are to be found in the www.ensembl.org database, but no related reports are available in the literature. In the mouse, two additional splice variants have been described, named 5-HT_{7(b)} and 5-HT_{7(c)} in analogy with the rat (Gellynck et al., 2008). In guinea pig and pig, the 5-HT₇ receptor is homologous to the human 5-HT_{7(a)} variant. Although the splice variants differ in the lengths of their carboxy terminal ends, they do not show major differences in their membrane localization nor significant differences in their respective pharmacology and signal transduction properties or functional coupling to Gs protein (see below).

A transcribed human 5-HT₇ receptor pseudogene has been identified by a degenerate PCR approach. The original clone (S771) has homology greater than 90% to the 5-HT₇ receptor sequence: expression of the pseudogene transcript is detected throughout the brain and peripheral tissues, in general agreement with 5-HT₇ receptor mRNA localization. However, the transcript was also detected in tissues not known to express the 5-HT₇ receptor (i.e. liver and kidney) (Olsen et al 1999).

There is as yet no crystal structure of the 5-HT₇ receptor, but molecular modelling and site-directed mutagenesis has identified essential residues for ligand binding and activation of the human receptor (Impellizeri et al, 2015).

XV. C. Expression

XV. C. 1. mRNA

The distribution of mRNA encoding the 5-HT₇ receptor protein has been studied in several species using various techniques, as summarized in Tables 18 and 19. In all species, high levels of 5-HT₇ receptor mRNA are expressed in the CNS (hypothalamus, thalamus, and hippocampus; Figure 26). In peripheral tissues, 5-HT₇ receptor mRNA is present in the ileum, spleen, endocrine glands, and arteries. In blood vessels and the gastrointestinal tract, 5-HT₇ receptor mRNA expression is generally present smooth muscle cells.

The relative abundance of the three human 5-HT₇ isoforms, 5-HT_{7(a)}, (b), (d) within brain (fetal brain, caudate, hippocampus) and peripheral tissues (uterus, trachea, small intestine, stomach, saphenous vein) has been examined (Krobert et al., 2001; Guthrie et al., 2005). These tissues expressed all three isoforms. Although the 5-HT_{7(b)} isoform is most prevalent, the relative amounts of 5-HT_{7(a)} and 5-HT_{7(d)} differed by tissue type, with the 5-HT_{7(d)} isoform being most abundant in smooth muscle and least common in brain tissues (Krobert et al. 2001; Guthrie et al. 2005). In the rat, the 5-HT_{7(a)} receptor isoform is most prevalent in both the CNS (cerebellum, cortex, hippocampus, hindbrain, thalamus) and the periphery (heart, kidney, spleen) (Heidmann et al., 1997; 1998).

XV. C. 2. Radioligand binding

Radioligand binding assays have been used to study the distribution of 5-HT₇ receptor protein in native tissues. A first study to define 5-HT₇ receptor binding sites in rat hypothalamic membranes was performed using [³H]5-HT in the presence of 100 nM pindolol that blocks the binding of the radioligand to 5-HT_{1A} and 5-HT_{1B} receptors. The pharmacology of the identified binding sites correlated well with that of rat recombinant 5-HT₇ receptors (Sleight et al., 1995). A subsequent study showed that 100 nM pindolol does not completely mask 5-HT_{1A} and 5-HT_{1B} receptors and that the population of pindolol-insensitive receptors labeled by [³H]5-HT in rat hypothalamus appeared to be heterogeneous (Gobbi et al., 1996). Also, [³H]5-CT failed to define a homogeneous population of 5-HT₇ binding sites in rat hypothalamus homogenates even in the presence of various masking agents (pindolol, sumatriptan, DOI) (Stowe & Barnes 1998). [³H]5-CT has been used to label 5-HT₇ receptors in guinea pig brain cortex membranes in the presence of sumatriptan and cyanopindolol (To et al. 1995). The pharmacology of these binding sites was well correlated to that of the guinea pig cloned 5-HT₇ receptor. Because affinity values of reference compounds were consistently lower in the binding assay performed in native tissue, the authors hypothesized that sumatriptan and cyanopindolol were likely to occupy, at least in part, the 5-HT₇ receptors. [³H]Mesulergine labels 5-HT₇ receptors in guinea-pig ileal longitudinal muscle in the presence of several masking agents (cinanserin, prazosin, raclopride, RS 102221, and yohimbine). However, under these same conditions no binding was detected in the rat jejunum (Hemedah et al., 1999).

[³H]SB-269970 is the first selective radioligand to label with high affinity 5-HT₇ receptors in rat, mouse, guinea pig, pig, marmoset and human brain homogenates. Guinea pig brain homogenate displays markedly higher 5-HT₇ receptor expression in comparison to rat, mouse, and pig brain homogenates (Thomas et al. 2002).

Autoradiographic studies on the localization of 5-HT₇ receptors have been performed by using various radioligands. [³H]5-CT has been used in the presence of various masking agents (To et al., 1995; Mengod et al., 1996; Waeber & Moskowitz, 1995; Gustafson et al., 1996). In guinea pig and rat brain, the distribution of the 5-HT₇ receptor binding sites was largely consistent with that reported for 5-HT₇ receptor mRNA. The highest densities were in the medial thalamic nuclei and related limbic and cortical regions. However, as the detected densities were very low, it was hypothesized that the masking compounds might have sufficient affinity for 5-HT₇ receptor sufficient to compete with [³H]5-CT to some degree for the 5-HT₇ receptor. In a subsequent study, the localization of 5-HT₇ receptor was studied in 5-HT_{1A} receptor knockout and 5-HT_{1A/B} receptor double knockout mice by using [³H]5-CT (5-HT_{1A}, 5-HT_{1B}, 5-HT₇ agonist) and [³H]8-OH-DPAT (5-HT_{1A} and 5-HT₇ agonist) (Bonaventure et al. 2002b). [³H]8-OH-DPAT was better than [³H]5-CT for measuring 5-HT₇ receptor binding sites, even if it displays lower 5-HT₇ receptor affinity than [³H]5-CT in tissue homogenates. The anatomical distribution of the [³H]8-OH-DPAT-labelled sites observed in these knockout mice was in agreement with the distribution of 5-HT₇ receptor mRNA and immunoreactivity reported previously. Within the hippocampal formation, strong labeling was found in the CA3 region, whereas low binding was found in CA1 region. 5-HT₇ receptors were also found within the dorsal raphe and the hypothalamus, including the suprachiasmatic nucleus.

The selective high-affinity radioligand [³H]SB-269970 was used to localize the 5-HT₇ receptors in human brain (Varnäs et al., 2004; Figure 27). The distribution of the 5-HT₇ receptors was largely similar to that shown by the autoradiographic studies in rat (Gustafson et al., 1996), guinea pig (To et al., 1995), and mouse (Martin-Cora & Pazos, 2004). High receptor density was detected in thalamus, hypothalamus and hippocampus. However, unlike in rodents, human brain 5-HT₇ receptors were also found in high levels in caudate nucleus, putamen and substantia nigra (Varnäs et al., 2004). Eventually, using [³H]SB-269970, Horisawa et al. (2013) reported that 5-HT₇ receptor distribution in rat brain was similar to that in human (Varnas et al., 2004), with small differences in regions with an intermediate to low density of 5-HT₇ receptors.

XV. C. 3. Immunoreactivity

Rabbit polyclonal antibodies raised against amino acid sequence 8–23 of the rat 5-HT₇ receptor are commercially available. Immunocytochemistry has been used to localize the distribution of 5-HT₇ receptors in rat forebrain (Neumaier et al., 2001), which were detected in the cortex, hippocampal formation, tenia tecta, thalamus, and hypothalamus, in agreement with the localization reported for the 5-HT₇ receptors mRNA. In particular, in the suprachiasmatic nucleus both cell bodies and proximal fibers were strongly stained, suggesting a somatodentric subcellular distribution of the receptor. The presence of 5-HT₇ receptors was also reported in both pre- and postsynaptic GABA, vasoactive intestinal polypeptide, and vasopressin processes in the suprachiasmatic nucleus in mouse (Belenky & Pickard, 2001). 5-HT₇ receptors are detected in Purkinje cells of rat cerebellum, but not in the cerebellar cortex or in deep nuclei (Geurts et al., 2002).

5-HT₇ receptor immunolabeling was detected mainly in the two superficial laminae of the dorsal horn and in small and medium-sized dorsal root ganglion cells in the rat spinal cord (Doly et al. 2005), consistent with a predominant role of 5-HT₇ receptor in nociception. In addition, moderate labeling was found in the lumbar dorsolateral nucleus (Onuf's nucleus), suggesting an involvement of the receptor in the control of pelvic floor muscles (Doly et al., 2005). Electron microscopic examination of the dorsal horn shows three main localizations of the receptor: 1) a postsynaptic localization on peptidergic cell bodies in laminae I–III and in numerous dendrites; 2) a presynaptic localization on unmyelinated and thin myelinated peptidergic fibers; 3) in lamina I and II in astrocytes (Doly et al., 2005). 5-HT₇ receptors have been localized to numerous myenteric neurons, some submucosal neurons, and a few smooth muscle cells of guinea pig ileum (Tonini et al., 2005) and in human corneal epithelium and endothelium (Grueb et al., 2006). An upregulated expression of 5-HT₇ receptors was detected during maturation of bone marrow-derived dendritic cells, suggesting a critical role of 5-HT₇ receptors in the regulation of immune cell polarization and, thus, in the peripheral inflammatory processes (Holst et al., 2015).

XV. D. Pharmacology

XV. D. 1. Agonists

Various selective 5-HT₇ receptor agonists have been identified (Table 20). The aminotetraline derivative AS-19, has a K_d of 0.6 nM at human cloned 5-HT₇ receptors, with high selectivity over all the others 5-HT receptor subtypes (> 100-fold) except 5-HT_{1D} receptors (11-fold). However AS-19 behaves as a potent partial 5-HT₇ receptor agonist (EC_{50} = 9 nM) with a maximal effect reaching 77% of that of 5-HT in a functional assay measuring cAMP stimulation in HEK293F cells overexpressing human 5-HT₇ receptors (Brenchat et al. 2009), which can complicate interpretation of arising data using tissue and *in vivo* preparations.

E-55888 is another potent and selective 5-HT₇ receptor agonist with high efficacy, displaying high affinity for 5-HT₇ receptors (K_d = 2.5 nM), low affinity for 5-HT_{1A} (K_d = 700 nM), and no significant affinity for the other 5-HT receptors. E-55888 behaves as a full agonist (EC_{50} = 16 nM) and increases cAMP levels in HEK-293F expressing human 5-HT₇ receptors (Brenchat et al. 2009). Another selective 5-HT₇ receptor agonist is LP-211 with high although different affinities for rat and human recombinant 5-HT₇ receptors (K_d = 0.58 and 15.0 nM, respectively) and moderate to low affinity for other 5-HT receptors, including 5-HT_{1A} (Hedlund et al. 2010, Leopoldo et al. 2008). LP-211 induces 5-HT₇-mediated relaxation of substance P-stimulated guinea pig ileum contracture (82% of the maximal effect elicited by 5-CT). However, in HEK293 cells stably expressing human 5-HT₇ receptor (Atanes et al. 2013), LP-211 displayed insurmountable antagonism of 5-CT-stimulated cAMP signaling. These results were unexpected since LP-211 have been extensively characterized as a 5-HT₇ receptor agonist in several *ex vivo* and *in vivo* studies (for review see Di Pilato et al. 2014). The authors suggested that the inhibitory effects of LP-211 are due to an irreversible stabilization of an inactive conformational state of the receptor that is tightly associated with Gs protein, independent of agonist binding (Bruheim et al. 2003, Andressen et al. 2006).

XV. D. 2. Antagonists

Various selective 5-HT₇ receptor antagonists have been identified (Table 20). The first was SB-258719, which displays useful 5-HT₇ receptor affinity (K_i = 31.6 nM) with 100-fold selectivity against all the other 5-HT receptors (Forbes et al. 1998). In HEK293 cells stably expressing the human 5-HT₇ receptor, SB-258719 did not stimulate basal adenylate cyclase activity suggesting a lack of agonist activity, but produced a surmountable antagonism of the response 5-CT response with a pK_B of 7.0. Further chemical optimization of SB-258719 led to SB-269970, which is the prototype 5-HT₇ receptor antagonist (Hagan et al. 2000). SB-269970 displays high affinity at both human cloned 5-HT₇ receptors (pK_i = 8.9) and in guinea-pig cortex

($pK_i = 8.3$). The compound is at least 100-fold selective against a wide range of receptors, except for the human 5-HT_{5A} receptor (about 50-fold). SB-269970 displays potent antagonism in both HEK293 cells stably expressing the 5-HT₇ receptor ($pA_2 = 8.5$) and in the guinea-pig hippocampal membranes ($pK_B = 8.3$). SB-269970 also produces a small inhibition of basal adenylyl cyclase activity in the absence of added 5-CT, consistent with inverse agonism (Hagan et al. 2000). Subsequent studies led to the identification of the antagonist SB-656104, which is as potent as SB-269970 ($K_i = 2$ nM; $pA_2 = 8.4$), but displays only 10-fold selectivity over the 5-HT_{1D} receptor. Both SB-269970 and SB-656104 are brain penetrant and the latter is more stable metabolically (Thomas et al. 2003).

XV. D. 3. Allosteric modulators

Oleamide, an amidated fatty acid, is an allosteric modulator of the 5-HT₇ receptor (Thomas et al. 1999; Thomas et al. 1997a; Thomas et al. 1997b; Hedlund et al. 1999, Alberts et al. 2001). In cells expressing the 5-HT₇ receptor, oleamide increases cAMP accumulation in a concentration-dependent manner, but with a lower efficacy than 5-HT. In the presence of 5-HT, oleamide displayed the opposite effect on cAMP, causing insurmountable antagonism of 5-HT, suggesting that oleamide acts at an allosteric site on the 5-HT₇ receptor. In receptor binding studies, oleamide modulated the binding properties of 5-HT₇ receptors expressed *in vitro* (Hedlund et al. 1999). In addition, the binding of both agonists and antagonists at human recombinant 5-HT₇ receptors stably expressed in HEK293 cells was allosterically inhibited by zinc (Satała et al. 2017).

XV. E. Signalling

The 5-HT₇ receptor is positively coupled to adenylate cyclase through activation of G_s, resulting in intracellular increase in cAMP (Bard et al. 1993; Lovenberg et al. 1993a; Ruat et al. 1993b). The human, rat, and mouse splice variants all activate adenylate cyclase (Krobert et al. 2001; Krobert & Levy 2002; Heidmann et al. 1998; Gellynck et al. 2008) and do not show evident differences in their respective pharmacology and signal transduction properties or functional coupling to G_s protein (Heidmann et al., 1998; Krobert et al., 2001). The only reported functional difference is that the human 5-HT_{7(Δ)} receptor displays a differential pattern of receptor internalization (Guthrie et al. 2005). Furthermore, variation in the length of the C-terminal tails and in the number of consensus sites for phosphorylation by protein kinases PKA and PKC raises the possibility that the splice variants

can display different desensitization or trafficking properties (Heidmann et al., 1997). Moreover, the human 5-HT_{7(b)} and the rat 5-HT_{7(b)} and 5-HT_{7(c)} receptor splice variants contain recognition sites for PDZ domain-containing proteins (Hamblin et al., 1998), suggesting that these splice variants may be targeted to active zones within cells and may couple to alternative signaling pathways.

Stimulation of the human 5-HT_{7(a)} receptor in HEK293 cells co-expressed with various adenylyl cyclase isoforms revealed that this receptor not only activates the G_s-sensitive AC5 isoform, but also the G_s-insensitive and Ca²⁺/calmodulin-stimulated AC1 and AC8 isoforms (Nielsen et al. 1996; Xia and Storm 1997; Baker et al. 1998).

5-HT₇ receptor expression density does not appear to influence agonist or partial agonist potency (or efficacy) suggesting the absence of receptor reserve effects (Bruheim et al. 2003; Andressen et al. 2006) implying independence from receptor-G_s stoichiometry, that may suggest the 5-HT₇ receptor is preassociated with G_s (Adham et al. 1998; Alberts et al., 2001; Krobert et al. 2001), which is supported by a more recent study investigating receptor-immobilized fluorescence recovery after photobleaching and FRET (Andressen et al., 2017) to compare the G_s-coupling of the 5-HT₇ and 5-HT₄ receptors.

Prolonged stimulation by 5-HT induces both homo and heterologous desensitization of G_s signaling in HEK293 cells. A similar effect is seen upon prolonged incubation with the inverse agonists SB-269970 and methiothepin, implying that desensitization is independent of G_s activation (Krobert et al. 2006).

Clozapine and olanzapine, which are 5-HT₇ receptor inverse agonists (see Krobert and Levy 2002), display functional selectivity at the human 5-HT₇ receptor i.e. different ligands at the same receptor elicit different functional effects (Andressen et al., 2015). Thus, clozapine and olanzapine downregulate 5-HT₇ receptors expressed in HEK293 cells, an effect normally evident for agonists, but not for antagonists or inverse agonists. This inverse agonist-mediated receptor downregulation may be mediated by interaction with the G-protein-associated sorting protein GASP-1 (Manfra et al. 2015).

In rat hippocampal neurons, 5-HT₇ stimulation leads to the activation of serine/threonine kinases ERK1 and ERK2 and most of this activity is mediated by 5-HT₇ receptors (Errico et al. 2001). A protein kinase A (PKA)-dependent pathway for 5-HT₇ receptor-mediated ERK1 and ERK2 activation has been proposed (Norum et al. 2003, 2005). 5-HT₇ receptor activation increases intracellular cAMP levels to activate PKA, which phosphorylates the guanine nucleotide exchange factor (GEF) Ras-GRF1 that controls the activity of Ras, an upstream activator of c-Raf (or Raf-1; a member of the Raf kinase family; Norum et al. 2003). Consequently, c-Raf phosphorylates and activates various kinases including MEK1, and further downstream ERK1/2. An alternative pathway could involve the activation of GEF proteins Epac1 and Epac2 by cAMP which in turn activate the Rap1 proteins through GDP-GTP exchange. GTP-bound Rap1 proteins can bind and activate different members of the Raf kinase family (i.e. B-Raf, A-Raf, and c-Raf) leading to ERK1/2 activation (Norum et al. 2005). The contribution of these GEFs in the ERK1/2 activation pathway mediated by 5-HT₇ receptor has been demonstrated in the pheochromocytoma PC12 cells stably overexpressing 5-HT₇ receptor and in rat hippocampal neurons (Lin et al. 2003; Johnson-Farley et al. 2005). Moreover, ERK1/2 seems to be required for normal neuronal function, such as neurotrophin-stimulated neuronal differentiation and neuroprotection as well as regulation of neurite outgrowth and formation of neuronal networks (Hetman et al. 1999; Speranza et al. 2013, 2015).

Stimulation of 5-HT₇ receptor expressed in HEK293 cells increases intracellular Ca²⁺ levels (Baker et al. 1998). However, the exact mechanism for this increase is not known. In rat adrenal glomerulosa cells, this 5-HT₇ receptor-mediated increase of intracellular Ca²⁺ levels is mediated by T-type Ca²⁺ channels in a cAMP/PKA-dependent manner (Lenglet et al. 2002a, b), which is likely to contribute to ERK1/2 activation (Lin et al. 2003; Norum et al. 2003; Johnson-Farley et al. 2005).

The 5-HT₇ receptor interacts with the G12 member of the G protein family (Kvachnina et al. 2005; Kobe et al. 2012) which can activate multiple signaling pathways. The prominent downstream effectors are members of the Rho family of small GTPases (Rho, Rac, and Cdc42). 5-HT₇ receptor-mediated stimulation of G12-protein results in Rho-dependent activation of the transcription factor serum response factor (SRF), which binds to the serum response element (SRE). The stimulation of 5-HT₇ receptor increases SRE-driven gene expression even in the presence of a PKA-inhibitor or pertussis toxin, suggesting that the receptor-mediated SRE activation is not PKA dependent (Kvachnina et al. 2005). Stimulation of 5-HT₇

receptor/G12 signaling pathway selectively activates both RhoA and Cdc42 (Kvachnina et al. 2005), suggesting a crosstalk between Cdc42 and RhoA pathways. The 5-HT₇ receptor/G12 signaling pathway in cultured hippocampal neurons promotes formation of dendritic spines and accelerates synaptogenesis, leading to enhanced spontaneous synaptic activity (Kobe et al. 2012). A morphogenic action of the 5-HT₇ receptor is confirmed in neuronal primary cultures from the cortex, hippocampus and striatal complex of embryonic rat or mouse brain (Speranza et al. 2013, 2015) and postnatal cortical and striatal neurons (Speranza et al. 2017). The involvement of mTOR, Cdc42, Cdk5, and ERK in this process suggests these proteins to be downstream targets of G12 (Speranza et al. 2013, 2015). In the hippocampus, the 5-HT₇ receptor/G12 signaling pathway undergoes strong developmental regulation. In organotypic hippocampal cultures from juvenile mice, G12 signaling potentiates formation of dendritic spines, increases the basal neuronal excitability, and modulates synaptic plasticity. In contrast, in preparations from older mice, 5-HT₇ receptor stimulation had no effect on neuronal morphology, synaptogenesis, and synaptic plasticity (Kobe et al. 2012). Consistently, the expression level of both 5-HT₇ receptor and G12 proteins in the hippocampus progressively decreases during postnatal development (Kobe et al. 2012).

XV. F. Post-translational modifications

XV. F. 1. Regulatory mechanisms

The 5-HT₇ receptor appears to undergo *N*-glycosylation and palmitoylation. The receptor is *N*-glycosylated at the asparagine residues N5 and N66 (Gellynck et al. 2012) but this does not appear to influence agonist binding, potency or efficacy. Furthermore, immunocytochemical studies revealed the presence of the *N*-glycosylation mutants at the cell surface.

The mouse 5-HT₇ receptor expressed in Sf9 insect cells undergoes dynamic palmitoylation in an agonist-dependent manner (Kvachnina et al. 2009). Mutation analysis shows that cysteines located in the C-terminal receptor domain at positions 404, 438 and 441 represent the main potential palmitoylation sites. Palmitoylation-deficient mutants reveal that agonist-induced activation of Gs- and G12-proteins is unaffected. Instead, mutation of the Cys404 alone or in combination with Cys438/Cys441 increases Gs-mediated constitutive activity of the 5-HT₇ receptor (agonist-independent), while the activation of G12-protein is not affected. Thus, palmitoylation of 5-HT₇ receptors might be directly involved in the isomerization of the

receptor from the inactive to the active form in the absence of agonists. Considering that the 5-HT₇ receptor is coupled to both G_s- and G₁₂-proteins, dynamic palmitoylation may represent a molecular mechanism responsible for selective G_s- or G₁₂-mediated signaling.

XV. F. 2. Interacting proteins

Apart from G proteins, only a few 5-HT₇ receptor interacting proteins have been described. Interacting proteins mostly act as adaptor or scaffolding proteins and help in trafficking of the receptor, not only to the plasma membrane but also in receptor internalization, recycling, and degradation. Among the many regulatory proteins that are involved in GPCR desensitization and down-regulation, GPCR-associated sorting proteins (GASPs) participate in the sorting of several receptors toward the degradation pathway (Bornert et al. 2013). GASP-1 and GASP-2 interact with several GPCRs, including 5-HT₇ receptors, through interaction of C-terminal tails containing two critical amino acid residues within the sequence that corresponds to helix 8 in the three-dimensional structure of rhodopsin (Simonin et al. 2004).

PLAC-24 (Protein that Localizes At Cell-cell Contacts), also known as eIF3k (the eukaryotic Initiation of translation Factor 3, subunit k) is another intracellular interaction partner for all three splice variants of the human 5-HT₇ receptor (De Martelaere et al. 2007). PLAC-24 might be involved in the transport of newly synthesized 5-HT₇ receptors towards the plasma membrane, since this transport is hampered by the overexpression of certain domain constructs of PLAC-24. PLAC-24 has been proposed to be additionally involved in the stabilisation of the receptor at the cell surface by anchoring it at the actin cytoskeleton, as PLAC-24 might be part of a multisubunit complex that links the actin and microtubule cytoskeleton and causes an increase in the expression of the receptor.

Periplakin (an actin- and intermediate filament-binding protein) and the neurite-outgrowth promoting protein, neurochondrin, strongly interact with the C-terminal tail of 5-HT₇ receptor. The functional consequences of these specific interactions are not yet known (Ward et al. 2009).

RhoBTB3, a member of the Ras superfamily of small guanosine triphosphatases (GTPases), is expressed in several brain regions where the 5-HT₇ receptor is also localized, including hippocampus and nucleus accumbens. The physical interaction between the 5-HT_{7a} receptor and RhoBTB3 has been demonstrated through yeast two hybrid, GST pull down, and co-immunoprecipitation assays (Matthys et al. 2012). Not only the C-terminal tail,

but also the third intracellular loop of the 5-HT_{7a} receptor seem to be involved in the interaction. The 5-HT_{7a} receptor may be targeted for proteasomal degradation following endocytosis at the plasma membrane and RhoBTB3 appears to strongly inhibit proteasomal degradation of the receptor.

S100B is a Ca²⁺-regulatory protein that controls Ca²⁺ homeostasis in various cell types, including astrocytes. S100B also regulates the activity of adenylate cyclase in preparations from rat brain and skeletal muscle (Donato et al. 2009). S100B physically interacts with 5-HT₇ receptors; it negatively regulates cAMP accumulation in 5-HT₇-transfected HeLa cells and mouse cortical astrocytes. Overexpression of S100B causes brain region-specific dysregulation of cAMP pathways *in vivo* that may relate to depressive-like behavior, which can be normalized by 5-HT₇ receptor blockade by SB-269970 (Stroth and Svenningsson, 2015).

For further discussion of interacting proteins see Section XVII.B.

XV. F. 3. Homo and heteromeric receptor associations

GPCRs can form oligomers and it is now widely accepted that homo- and heterodimerization provides an additional mechanism for regulating cellular processes through the fine tuning of receptor-mediated signaling (Devi 2001; Bulenger et al. 2005). The 5-HT₇ receptor forms homodimers in both intact HEK-293 cells and neuroblastoma N1E-115 cells transfected with 5-HT₇ receptor and rat cortical astrocytes (Teitler et al. 2010; Smith et al. 2011; Renner et al. 2012; Teitler and Klein 2012).

Heterodimerization between 5-HT_{1A} and 5-HT₇ receptors has been demonstrated by co-immunoprecipitation and by FRET approaches (Renner et al. 2012); the co-immunoprecipitation studies in mouse brain provide direct evidence that 5-HT_{1A} and 5-HT₇ receptors can form heterodimers *in vivo*. Such heterodimerization alters the signalling properties of the 5-HT_{1A} receptor by attenuating the ability of 5-HT_{1A} receptor to activate Gi protein, in contrast to 5-HT₇-receptor mediated activation of Gs protein, which is not affected. In addition, heterodimerization reduces the ability of 5-HT_{1A}

receptors to activate G-protein-gated potassium (GIRK) channels, an effect mediated through the G $\beta\gamma$ -subunits of Gi-proteins (Reuveny et al. 1994, Kofuji et al. 1995). The inhibitory effect of heterodimerization on GIRK currents is also evident in mouse hippocampal neurons, suggesting a physiological relevance *in vivo*.

Heterodimerization between the 5-HT_{1A} and 5-HT₇ receptors appears to promote agonist-mediated internalization of the 5-HT_{1A} receptor (5-HT_{1A} receptors expressed alone are relatively resistant to the agonist-induced internalization). The pharmacological blockade of 5-HT₇ receptors, but not of 5-HT_{1A} receptors, abolishes internalization of both 5-HT₇ homo- and heterodimers suggesting that 5-HT₇-receptor-mediated signaling is an initial step responsible for 5-HT_{1A} receptor co-internalization. Once internalized, 5-HT_{1A} receptors can activate G-protein-independent signaling pathways such as a β -arrestin-mediated coupling to MAPK. Thus, depending on the relative amount of 5-HT_{1A} receptors participating in dimers, stimulation by 5-HT can activate distinct ERK-mediated pathways (i.e. G-protein-dependent or β -arrestin-dependent) further implicating the physiological relevance of heterodimerization.

XV. G. Function

Hedlund et al. (2003) first reported on the generation of 5-HT₇ KO mice by targeted disruption within exon II of the 5-HT₇ receptor gene, thus inactivating all known splice variants of the receptor. 5-HT₇ KO mice (Roberts et al. 2004; Guscott et al. 2005) grow and reproduce normally suggesting that the receptor does not play an essential role during development. These mice also have normal body weight and basal rectal temperature and appear to be in good health (Guscott et al. 2005). No differences are detected between 5-HT₇ KO mice and the wild type littermates in general motor ability, visual acuity, pain sensitivity, anxiety-like behavior, or the capacity to show freezing behavior in the habituation, conditioning or cued components of the cued and contextual conditioning procedure (Roberts et al., 2004). Also, in the prepulse inhibition (PPI) paradigm, no difference is observed in the 5-HT₇ receptor KO mice (Guscott et al. 2005; Semenova et al. 2008).

XV. G. 1. Thermoregulation

5-HT₇ agonists induces a considerable hypothermic response *in vivo* in various species (Sugimoto et al. 1991; Yamada et al. 1988; Won and Lin, 1988; Guscott et al., 2003; Hedlund et al. 2003; 2004; Naumenko et al. 2011). Initially, the 5-HT_{1A} receptor was thought responsible, largely on the basis of data obtained using the 5-HT_{1A} receptor agonist 8-OH-DPAT (Hjorth, 1985) before this drug was also recognized as a 5-HT₇ receptor agonist (Guscott et al., 2003; Hedlund et al. 2003; 2004). It appears the 5-HT₇ receptor is more important at lower 5-HT concentrations, playing a role in the fine tuning of temperature homeostasis, whereas the 5-HT_{1A} receptor is activated at higher 5-HT concentrations, possibly as a defense against hyperthermia (Hedlund et al. 2004), such that both 5-HT_{1A} and 5-HT₇ receptors are important (Brenchat et al., 2012a).

XV. G. 2. Learning and Memory

5-HT₇ receptor KO mice under certain types of examination can display specific impairments in contextual learning. Two forms of place learning, spatial (Barnes maze) and contextual (fear conditioning), in addition to three hippocampus-dependent learning tests have been studied (motor, cued conditioning and operant conditioning) to demonstrate effects of 5-HT₇ receptor KO mice in contextual fear conditioning whereas no evident effect in the other learning tests. Of potential relevance, electrophysiological studies on hippocampal slices from 5-HT₇ receptor KO mice demonstrate deficits in long term potentiation (LTP; Roberts et al. 2004).

Further behavioural studies demonstrate hippocampus-associated spatial memory deficit in 5-HT₇ receptor KO mice (impairments in memory compilation required for resolving spatial tasks), which result in impaired hippocampus-dependent allocentric memory (Sarkysian and Hedlund 2009), while no effect was evident in the novel object recognition test. Egocentric spatial memory, which is striatum-dependent, remains intact. On the other hand, 5-HT₇ receptor KO mice do not exhibit learning impairments and/or dysfunctions in short term memory, if the environment remains static such as in the Barnes maze test. In the same test, 5-HT₇ receptor KO mice have no impairment in long-term memory or memory consolidation.

XV. G. 3. Anti-psychotic potential

5-HT₇ receptor antagonists have been evaluated in animal models used to test antipsychotic-like activity. The selective 5-HT₇ receptor antagonist SB-258741 reverses hyperactivity induced by PCP in rats (Pouzet et al., 2002). SB-269970 partially but significantly blocks hyperactivity induced by ketamine in mice (Galici et al., 2008). Further, 5-HT₇ receptor KO mice display less pronounced deficits in the PCP-induced prepulse inhibition as

compared to WT mice (Semenova et al., 2008), although this effect was not replicated by SB-269970 treatment (Semenova et al., 2008). Collectively, the available data suggest that the antipsychotic-like activity elicited by selective 5-HT₇ receptor blockade is weaker than that obtained with clinically proven antipsychotic drugs (Thomas and Hagan, 2004).

Current antipsychotic drugs are not very effective to reverse the cognitive deficits associated with schizophrenia. Cognitive impairments induced by sub-chronic PCP administration in rats are believed to mimic cognitive deficits in schizophrenia (Javitt and Zukin, 1991; Jentsch and Roth, 1999). PCP selectively impairs performance in reversal learning test (Abdul-Monim et al., 2006, 2007; McLean et al., 2009a), attentional set-shifting test (McLean et al., 2008a), and novel object recognition test (a paradigm for studying visual episodic memory) (Grayson et al., 2007). The acute administration of SB-269970 reverses sub-chronic PCP-induced deficits in a reversal learning task in rats (McLean et al., 2009b) and in the novel object recognition test in rats (Horiguchi et al., 2011). Pre-treatment with SB-269970 or lurasidone reverses the sub-chronic PCP-induced deficit in reversal learning in mice (Rajagopal et al. 2016). This effect was not elicited by the agonist AS-19, confirming that antagonism, but not agonism, at 5-HT₇ receptors restores function in principal cortical neurons impaired by NMDA receptor blockade.

Cognitive deficits in mice induced by dizocilpine are also used to model impaired working memory in schizophrenia. SB-269970 reverts dizocilpine-induced cognitive deficit in a translational behavioral model of working memory, the delayed non-matching to position task. At a neurochemical level, SB-269970 normalizes the dizocilpine-induced glutamate efflux, but not dizocilpine-induced dopamine extracellular levels in the cortex of freely moving rats (Bonaventure et al., 2011). SB-269970 also reverses dizocilpine-induced memory deficits in an autoshaping Pavlovian instrumental learning task in rats (Meneses, 2004). Moreover, 5-HT₇ receptor blockade by another antagonist SB-656104, reverses dizocilpine-induced learning and memory impairments in the passive avoidance and Morris water maze tests in rats (Horisawa et al., 2011).

Ketamine-based animal models represent a valuable tool in preclinical research because ketamine is commonly used in the clinic to model the transient neurocognitive impairments in healthy volunteers (Krystal et al., 1994). Acute administration of SB-269970 in rats ameliorates ketamine-induced cognitive deficits in the attentional set-shifting task (a measure of cognitive flexibility) and the novel object recognition test (Nikiforuk et al.,

2013). SB-269970 reverses memory deficits in an autoshaping Pavlovian instrumental learning task in rats after an intra-prefrontal infusion of ketamine (Liy-Salmeron and Meneses, 2008).

Experimental evidences suggest a role of 5-HT₇ receptor blockade in the pro-cognitive actions of the atypical antipsychotics amisulpride and lurasidone. Both drugs ameliorate the PCP-induced deficits in the novel object recognition task in rats (Horiguchi et al., 2011). This effect is reversed by co-administration of the selective 5-HT₇ agonist AS-19. Lurasidone attenuates the dizocilpine-induced deficits in the passive avoidance test in rats. Also, in this case AS-19 abolishes the effect of lurasidone (Horisawa et al., 2013).

The pharmacological blockade of 5-HT₇ receptors may also have therapeutic implications for the treatment of negative symptoms in schizophrenia since SB-269970 ameliorates ketamine-induced social withdrawal in rats (Nikiforuk and Popik, 2013). Consistently, acute administration of amisulpride reverses ketamine-induced social withdrawal. The pro-social efficacy of amisulpride is abolished by the agonist AS-19. Finally, co-administration of subactive doses of SB-269970 and amisulpride results in pro-social effects in rats (Hołuj et al., 2015).

XV. G. 4. Antidepressant-like behavior

5-HT₇ receptor KO mice have an antidepressant-like behavior, with reduced immobility in commonly used preclinical animal models of depression, such as the tail suspension test (TST) and the forced swim test (Hedlund et al. 2005; Guscot et al. 2005; Sarkisyan et al. 2010). The decreased immobility in both models is most likely not due to a general increase in motor activity, since no genotype difference in locomotor activity or motor learning were evident between 5-HT₇ receptor KO and WT mice (Roberts et al 2004).

Since 5-HT₇ receptor KO mice display an antidepressant-like behavior, the potential role of the 5-HT₇ receptor was also investigated in obsessive-compulsive disorder (OCD) models: it is recognized OCD involves the 5-HT system and patients may benefit from antidepressant therapy. Thus, 5-HT₇ receptor KO mice have been tested in three models believed to mimic some of the stereotypic aspects of OCD (Hedlund and Sutcliffe 2007). Inactivation of the 5-HT₇ receptor leads to decreased marble burying, a model linked to OCD and anxiety. However, there is no difference between

5-HT₇ receptor KO and WT mice in the two other models (i.e. head dipping and plastic-mesh screen chewing models). Thus, a possible role of the receptor in OCD remains an open question.

XV. G. 5. Sleep

Overall, a normal sleep pattern is observed in 5-HT₇ receptor KO mice although during rest, 5-HT₇ receptor KO mice spend less time in REM sleep (with less frequent, but longer REM episodes) compared with WT mice (Hedlund et al., 2005). There is no difference between the genotypes in time spent awake or in slow wave sleep, and the frequency of slow wave sleep episodes is not altered. These sleep patterns of 5-HT₇ receptor KO mice is in agreement with the antidepressant-like profile observed in this genotype.

A variety of circadian parameters in 5-HT₇ receptor KO mice, including rate of entrainment and photic responsiveness have been investigated. There are no evident differences in the average number of days that 5-HT₇ receptor KO mice need to reach entrainment to an advance of 6 h in the light/dark cycle compared with WT mice (Gardani and Biello 2008). Both groups of mice display minimal effects to light stimulation during the subjective day, whereas, during the early night, light induces phase delays and later in the subjective night results in advances of the circadian phase.

Similarly, administration of the 5-HT₇ receptor antagonists SB-269970 and SB-656104 to rats reduces the total amount of REM sleep, whereas wake and slow wave sleep (SWS) are not affected (Hagan et al., 2000, Thomas et al., 2003; Monti and Jantos, 2006). Furthermore, both genetic inactivation and pharmacological blockade of 5-HT₇ receptor augmented the effects of SSRIs on REM sleep suppression (Bonaventure et al., 2007, Shelton et al., 2009).

As for the effect of 5-HT₇ receptor agonists on sleep, systemic administration of LP-211 during the light phase increases wakefulness in rats and reduces REM sleep duration and periods. In order to assess the potential neural sites that mediate the changes in REM and wake in the rat, LP-211 was microinjected into the brain regions involved in sleep - wake regulation. Local administration of LP-211 into the DRN, locus coeruleus, lateral basal forebrain, and laterodorsal tegmental nucleus suppressed REM sleep, and microinjection of LP-211 into the basal forebrain augmented wake (Monti et al., 2014). The authors proposed that activation of 5-HT₇ receptors expressed by GABAergic interneurons decreases the activity of REM

sleep-promoting cholinergic neurons in the laterodorsal and pedunculopontine tegmental (LDT/PPT) nuclei and reduces REM sleep. Suppression of REM sleep was observed also when LP-44, another 5-HT₇ receptor agonist, was microinjected into the DRN (Monti 2008).

A possible explanation for these apparently contradictory findings is that 5-HT₇ receptors can stimulate GABAergic neurons only in the absence and/or at low concentrations of 5-HT, whereas at high 5-HT concentrations, 5-HT₇ receptors inhibit these GABAergic neurons. Therefore, a concentration-dependent switch in 5-HT₇ receptor signaling could explain why inhibition of 5-HT₇ receptor activity, or elevated 5-HT concentrations or administration of 5-HT₇ receptor agonist at high concentration, prevent 5-HT₇ receptor-mediated stimulation of the REM stimulatory GABAergic neurons.

5-HT₇ receptors have also been implicated in the regulation of the mammalian circadian clock located in the suprachiasmatic nucleus (SCN). Studies have demonstrated that 8-OH-DPAT induces non-photic phase resetting through activation of 5-HT₇ receptors *in vitro* and *in vivo*. This effect is reversed by genetic inactivation or pharmacological blockade by the antagonists SB-269970, DR-4004, and JNJ-18038683 (Guscott et al., 2005; Sprouse et al., 2004; Shelton et al., 2014). Consistently, the agonist LP-211 induced a phase advancement of the circadian rhythm in mice (Adriani et al., 2012). Moreover, activation of 5-HT₇ receptors by the partial agonist AS19 shortens the period length of oscillation of clock gene mPER2 expression in the SCN. mPER2 expression is used to monitor changes in circadian period length and amplitude (Westrich et al., 2013).

XV. G. 6. Autism Spectrum Disorders

Clinical studies suggest a deficient brain 5-HT system as a causal mechanism in autism spectrum disorders (Boccutto et al., 2013, McDougle et al., 1996). Moreover, the lack of 5-HT during early stages of development may contribute to disrupt the wiring architecture of the brain (Azmitia et al., 2011).

5-HT₇ receptor activation corrects molecular, electrophysiological, and behavioral manifestations in mice models of Fragile X syndrome (FXS) and Rett syndrome (RTT), both genetic forms of intellectual disabilities associated with autistic behavior (Costa et al., 2012, 2015; De Filippis et al., 2014,

2015). FXS is the most common inherited intellectual disability; it is caused by silencing of the *Fmr1* gene coding for the Fragile X Mental Retardation Protein (FMRP) (Pieretti et al., 1991).

Activation of 5-HT₇ receptors by the agonists 8-OH-DPAT and LP-211 rescues mGluR-LTD in *Fmr1* knockout mice and restores LTD levels to those of WT mice (Costa et al., 2012, 2015). This might have important functional consequences, since long-term synaptic plasticity plays a fundamental role in shaping the structure and function of brain circuits. LTD is crucially involved in learning and memory, in novelty detection and in the extinction of previously acquired memories and is believed to underlie behavioral flexibility (Collingridge et al., 2010). On that basis, Costa et al. (2012; 2015) suggested that selective activation of 5-HT₇ receptors, by restoring mGluR-mediated synaptic plasticity to normal levels, might also rescue cognitive functions and behavioral flexibility in the mouse model of FXS.

De Filippis et al. (2014) have demonstrated that the selective 5-HT₇ agonist LP-211 rescues the behavioral impairments in MeCP2-308 male mice, a mouse model of RTT. RTT is a rare neurodevelopmental disorder characterized by severe behavioral symptoms, including autistic-like behaviors, anxiety, motor disturbances, stereotypic hand movements, and severe cognitive dysfunction (Hagberg et al., 2002; Ricceri et al., 2012). Mutations in the methyl-CpG-binding protein 2 (MeCP2) gene have been identified as the main genetic cause of RTT. MeCP2 encodes a multifunctional protein that binds to methylated DNA and mainly acts as a key transcriptional regulator. Systemic treatment with LP-211 rescues RTT-related defective performance: anxiety-related profiles in a light/dark test, motor abilities in a dowel test, the exploratory behavior in the marble burying test, as well as memory in the novelty preference task. At a molecular level, LP-211 administration in MeCP2-308 mice restores levels of the Rho GTPases effector molecules PAK and cofilin, which both are key regulators of actin cytoskeleton dynamics and, thus, crucially involved in neuronal plasticity. A follow-up study reported similar effects in MeCP2-308 heterozygous female mice, the genetic and hormonal milieu of these mice more closely resemble those of RTT patients (De Filippis et al., 2015). In addition, targeting 5-HT₇ receptors can rescue brain mitochondrial dysfunction in heterozygous female MeCP2-308 and MeCP2-Bird mice (a more severely affected model). Moreover, LP-211 treatment completely restores the radical species overproduction by brain mitochondria in the MeCP2-308 model and partially recovers the oxidative imbalance in MeCP2-Bird mice (Valenti et al. 2017).

A core symptom of autism spectrum disorder is repetitive and stereotypic behavior. The dual 5-HT_{1A}/5-HT₇ partial agonist (+)-5-FPT reduces or eliminates stereotypy in three different mouse models of stereotypy: idiopathic jumping, repetitive body rotations after treatment with the NMDA antagonist dizocilpine, and repetitive head-twitching after treatment with the 5-HT₂ receptor agonist DOI (Canal et al., 2015) without altering locomotor behavior.

Finally, it has been proposed that the reduced behavioral inflexibility elicited by 5-HT₇ receptor antagonists (Nikiforuk, 2012; Nikiforuk and Popik, 2013) might be of relevance in autism spectrum disorder, since reduced behavioral flexibility (i.e, a reduced ability to replace a previously acquired rule with a new one in adaptation to a new environmental context) is a typical feature of this pathology (Ciranna and Catania, 2015).

There is a suggestive link between a *HTR7* genetic abnormality, which encodes the 5-HT₇ receptor, and neurodevelopmental disorders (Helsmoortel et al., 2016). The whole genome sequencing of a severely affected dizygotic twin with an autism spectrum disorder and intellectual disability revealed a compound heterozygous mutation in the *HTR7* gene as the only variation,.

XV. G. 7. Epilepsy

The involvement of 5-HT₇ receptors in epilepsy has been actively investigated. The 5-HT₇ receptor antagonist, SB-258719, reduces spontaneous epileptic activity in the WAG/Rij rat model of absence epilepsy (Graf et al., 2004). In pilocarpine-induced rat models of temporal lobe epilepsy, SB-269970 also reduces the number of seizures (Yang et al., 2012). Consistently, in epileptic rats, the presumed activation of 5-HT₇ receptors by AS-19 increases the number of seizures (Yang et al., 2012). In contrast to the above data, inactivation of the 5-HT₇ receptor gene caused a generalized threshold reduction in electrical- or chemical-induced seizures (Witkin et al., 2007).

It has been suggested that the evident seizure-prone phenotype of 5-HT₇ receptor KO mice may be due to adaptive changes to the loss of perinatal 5-HT₇ receptor-induced depolarization. In line with these data, the 5-HT₇/5-HT_{1A} receptor agonist 5-CT increased the seizure threshold for picrotoxin

in stressed mice (Pericic and Svob Strac, 2007), which is abolished by SB-269970, but not by the 5-HT_{1A} receptor antagonist, WAY-100635 (Pericic and Svob Strac, 2007).

XV. G. 8. Drug Abuse

The link between the 5-HT₇ receptor and substance abuse has been under explored. Hauser et al. (2015) suggest that 5-HT₇ receptors may play a key role in addiction, on the basis of neuroanatomical, biochemical, physiological, and behavioral observations.

Interestingly, genomic studies in humans suggest a link between variants in the gene encoding the 5-HT₇ receptor and alcoholism (Zlojutro et al., 2011; Kim et al., 2014). In this respect, mice exposed to alcohol vapors present increased expression of 5-HT₇ receptors in brain areas specifically involved in dependence (Yoshimoto et al., 2012). However, blockade of 5-HT₇ receptors with SB-258719 does not alter alcohol drinking behavior in the mice exposed to alcohol vapor (Yoshimoto et al., 2012).

XV. G. 9. Pain

Much effort has been made to investigate the potential (patho)physiological role of 5-HT₇ receptors in nociception and chronic pain. Early studies suggested a peripheral pro-nociceptive action of 5-HT through 5-HT₇ receptor activation (Meuser et al., 2002). The pain promoting effect of 5-HT or 5-CT injection into a hindpaw on formalin-induced local nociceptive responses is blocked by SB-269970 (Rocha-González et al., 2005).

In rat models of neuropathic pain (i.e. chronic constriction injury to the sciatic nerve or spinal nerve ligation) systemic administration of SB-269970 reduces hyperalgesia and tactile allodynia (Amaya-Castellanos et al., 2011; Viguier et al., 2012). Intrathecal administration of SB-269970 also reduces tactile allodynia in spinal nerve-ligated rats, suggesting the involvement of 5-HT₇ receptors in pronociceptive mechanisms at the spinal level (Amaya-Castellanos et al., 2011). A pro-nociceptive effect of 5-HT₇ receptor stimulation has been reported at the trigeminal level. SB-656104 significantly decreases the c-Fos immunostaining in the spinal nucleus of the trigeminal nerve in response to intracisternal injection of capsaicin (Martínez-García et al., 2011).

However, such findings appear in contradiction with the data from Brenchat et al. (2009, 2010) where systemic administration of SB-269970 or SB-258719 enhance mechanical hypersensitivity associated with capsaicin-induced hyperalgesia or nerve injury in mice. Interestingly, local injection of SB-269970 or SB-258719 in control mice, does not promote hypersensitivity, suggesting that 5-HT₇ receptors might be involved in some pronociceptive modulatory mechanisms only under neuronal sensitization conditions.

In addition to possible species differences, the selected model of neuropathic pain might also have relevance with respect to the aforementioned contradictions.

The antinociceptive potential of 5-HT₇ receptor antagonists would suggest a pronociceptive effect of 5-HT₇ receptor agonists for which there is some support (Brenchat et al., 2010; Martínez-García et al., 2011). However, other studies report 5-HT₇ receptors mediate antinociceptive effects. Thus blockade of spinal 5-HT₇ receptors by intrathecal injection of SB-269970 prevents the antinociceptive effects of systemic administration of morphine, tramadol or cannabinoids in the tail flick test (Dogrul and Seyrek, 2006; Dogrul et al., 2009; Yanarates et al., 2010) and intrathecal administration of E-57431 and E-55888 inhibit mechanical hypersensitivity caused by capsaicin injection or nerve injury-induced mechanical hypersensitivity in both mice and rats (Brenchat et al., 2011; Viguier et al., 2012). Furthermore, systemic treatment with 5-HT₇ receptor agonists produce marked reductions in mechanical and thermal hypersensitivity in various chronic pain models with central and/or peripheral sensitization (Brenchat et al., 2009, 2010, 2012a, 2012b; Ulugol et al., 2012; Viguier et al., 2012, 2013).

XV. H. Clinical relevance

XV. H. 1. Depression

Multiple experimental approaches tend to support the hypothesis that 5-HT₇ receptor blockade or genetic inactivation displays an antidepressant-like activity (Guscott et al., 2005; Hedlund et al., 2005; Sarkisyan et al., 2010). In agreement with mouse KO data, the pharmacological blockade of 5-HT₇ receptors results in antidepressant-like effects in the TST (Hedlund et al., 2005; Bonaventure et al., 2007; Wesolowska et al., 2006a) and in the FST in both mice (Hedlund et al., 2005; Wesolowska et al., 2006b) and rats (Wesolowska and Kowalska et al., 2008, Mnie-Filali et al., 2011).

The 5-HT₇ receptor antagonist, SB-269970, was assessed in the olfactory bulbectomy paradigm, which is considered as a ‘chronic’ behavioral model of depression in which classical antidepressants require the administration for 2-3 weeks before any antidepressant-like effects can be observed (Song and Leonard, 2005). SB-269970 induced a faster antidepressant-like response when compared to 1-week treatment with the SSRI, fluoxetine (Mnie-Filali et al., 2011). 5-HT₇ receptor blockade may also augment the effects of antidepressant drugs; thus the combination of an ineffective dose of SB-269970 with an ineffective dose of one of several antidepressants, results in a synergistic reduction in immobility in both FST and TST (Wesolowska et al., 2006b; Bonaventure et al., 2007; Wesolowska and Kowalska, 2008; Sarkisyan et al., 2010) that correlates with increases in 5-HT release in the frontal cortex (Bonaventure et al., 2007; Wesolowska and Kowalska, 2008). Besides the prefrontal cortex, the hippocampus has also been implicated in the effects of SB-269970 and imipramine, since intra-hippocampal SB-269970 administration reduces immobility in the rat FST (Wesolowska et al., 2006b).

Preclinical tests in mice suggest that the clinically established antidepressant effect of the atypical antipsychotic drugs amisulpride, aripiprazole or lurasidone may be due to 5-HT₇ receptor blockade. Thus, amisulpride, aripiprazole and lurasidone are potent but non-selective 5-HT₇ receptor antagonists that have clear antidepressant actions (Lecrubier et al., 1997; Smeraldi, 1998; Lawler et al., 1999; Shapiro et al., 2003; Nakamura et al., 2009; Ishibashi et al., 2010; Citrome, 2011) which reduce immobility in the TST and the FST in WT, but not in 5-HT₇ KO mice (Abbas et al., 2009; Sarkisyan et al., 2010; Cates et al., 2013), strongly suggesting a role for the 5-HT₇ receptor.

The 5-HT₇ receptor antagonist, JNJ-18038683 (Bonaventure et al., 2012) reduces immobility in mice in the TST. Co-administration of subeffective doses of citalopram and JNJ-18038683 elicits an antidepressant effect. However, JNJ-18038683 when tested in patients with major depressive disorder, produced no statistically significant improvement over placebo on the Montgomery-Åsberg Depression Rating Scale (MADRS), although escitalopram in that same study was also inactive, complicating interpretation.

XV. H. 2. Sleep

The potent and selective 5-HT₇ receptor antagonist, JNJ-18038683, prolonged REM latency and decreases REM sleep duration in healthy volunteers (Bonaventure et al., 2012). Furthermore, JNJ-18038683 appeared to enhance REM sleep suppression induced by citalopram.

XVI. High resolution structure of 5-HT receptors

XVI. A. 5-HT GPCRs

Since the initial cloning of a 5-HT receptor in 1988 (Julius et al., 1988) it has been appreciated that the G-protein coupled 5-HT receptors would have a topology similar to other members of the GPCR superfamily (Kroeze et al., 2003). These features included a predicted 7-transmembrane helical arrangement with an orthosteric binding pocket near the upper 1/3rd of the helical array (Choudhary et al., 1992; Choudhary et al., 1993; Choudhary et al., 1995). Indeed, early molecular models—bolstered by site-directed mutagenesis studies—predicted that 5-HT and serotonergic drugs such as ergolines and ergopeptines would be anchored by a highly conserved aspartic acid in Helix III and aromatic residues in Helix VI (Choudhary et al., 1993; Choudhary et al., 1995; Sealfon et al., 1995; Wang et al., 1993).

These predictions were confirmed in 2013 with the publication of the first high resolution structures of the human 5-HT_{1B} (Wang et al., 2013) and 5-HT_{2B} (Wacker et al., 2013) receptors—both in complex with the ergopeptine ergotamine (Figure 28). Additionally, the 5-HT_{1B} receptor was also solved in complex with dihydroergotamine (Wang et al., 2013) revealing an essentially identical ligand orientation. Perhaps not surprisingly—and as predicted many years ago (Choudhary et al., 1995)—ergotamine was anchored by the highly conserved TMIII aspartic acid residue and stabilized by hydrophobic and edge-on-face interactions with aromatic residues in helix VI (Wacker et al., 2013; Wang et al., 2013).

Given the large differences between 5-HT_{1B} and 5-HT_{2B} receptors in terms of pharmacology, signal transduction and amino acid sequence, the high resolution structures of both receptors allowed the investigators to identify both important structural commonalities and dissimilarities between these two distinct 5-HT receptor families (Wacker et al., 2013; Wang et al., 2013); the orthosteric binding pockets of both receptors are nearly identical with only two amino acids in the conserved orthosteric binding site differing (Wang et al., 2013). This high degree of conservation readily explains why many serotonergic drugs are promiscuous. Indeed, LSD was found to be a potent agonist at every G-protein coupled 5-HT receptor except the 5-HT₇ (Wacker et al., 2013).

Subtle differences in the general region of the binding pocket were able to explain heretofore puzzling aspects of 5-HT receptor pharmacology. For instance, the apparent preference of rodent versions of the 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} receptors for β -adrenergic antagonists (Adham et al., 1994) was now apparent based on structural, mutagenesis and modeling studies (Wang et al., 2013). Thus a Thr^{7.39}->Asn^{7.39} mutation—changing the human to rodent version—led to the formation of a polar interaction network now favoring the binding of the propanolamine moiety of adrenergic antagonists. Additionally, the high affinity of norfenfluramine for 5-HT_{2B} receptors—which may lead to valvular heart disease (Rothman et al., 2000)—was explained by the orientation of a non-conserved methionine residue (M^{5.39}) which was oriented in the binding pocket in the 5-HT_{2B} receptor and absent in all other 5-HT receptors (Wang et al., 2013). Finally distinctly different patterns of signaling by ergotamine at 5-HT_{1B} receptors—where it is unbiased—and 5-HT_{2B} receptors—where it shows arrestin bias, led to explication of the structural features responsible for functional selectivity (Wacker et al., 2013). Thus the apparent arrestin-biased signaling by ergotamine at 5-HT_{2B} receptors is due to a preferential stabilization of inactive states of particular G-protein conformational micro-switches (which are essential for mediating canonical signaling) and the preferential allowance of conformations responsible for arrestin-dependent signaling (Wacker et al., 2013).

More recent studies have clarified the mechanisms responsible for the differential activation of G-protein vs arrestin signaling (Wacker et al., 2017a) at 5-HT_{2A} (Wacker et al., 2017b) and 5-HT_{2B} receptors (McCorvy et al., 2018) (Wacker et al., 2017b). In particular, a detailed study of several 5-HT_{2B} receptor structures (McCorvy et al., 2018) (Wacker et al., 2017b) disclosed that key interactions with A^{5.46} and T^{5.37} are essential for canonical G protein signaling while interactions with extracellular loop residue L^{7.35} is essential for arrestin-ergic signaling. Additionally, other structures of an intermediate-active state of the 5-HT_{2C} receptor (Peng et al., 2018; Figure 28) and the G-protein heterotrimer-stabilized active state of the 5-HT_{1B} receptor (Garcia-Nafria et al., 2018) implicated a key ‘trigger motif’ P-I-F as being essential for the active-inactive switch and biased signaling (McCorvy et al., 2018) (Wacker et al., 2017a).

XVI. B. 5-HT LGIC

5-HT₃ receptors are ion channels of the Cys-loop receptor family (Thompson et al., 2010; Corringer et al., 2012). Thus they share a common architecture with other members: e.g. nicotinic acetylcholine, ionotropic γ -aminobutyric, and glycine receptors. All of them are composed of five subunits, symmetrically disposed around a central ionic pore axis, forming an urn-like architecture (Figure 29). Each subunit has three functional domains (Figure 29): a large extracellular domain harboring the neurotransmitter binding pocket, a four-helix transmembrane domain establishing the ion channel and an intracellular domain which mediates the receptors interaction with intracellular proteins.

Recent years have seen the emergence of a solid structural framework to help interpret functional and pharmacological studies. First 5-HT₃, granisetron and palonosetron have been crystallized in complex with a soluble model protein (termed 5-HT Binding Protein, 5-HTBP; Kesters et al., 2013; Price et al., 2016), providing possible orientations of ligands and adding up to the huge variety of nicotinic receptor ligands co-crystallized with the same type of model protein. Second, the initial mouse 5-HT_{3A} receptor X-ray structure (Hassaine et al., 2014) has provided an almost complete picture (\sim 60 unstructured residues missing in the intracellular domain) of a 5-HT₃ receptor but with empty neurotransmitter sites capped by stabilizing llama antibodies instrumental to crystallization. Third, a series of distinct conformations of the full-length murine receptor imaged by cryo-EM (Polovinkin et al., 2018; Basak et al., 2018a; Basak et al. 2018b) has shed light on its gating mechanism and revealed how 5-HT and anti-emetic drugs such as tropisetron bind in the neurotransmitter site. Specialized reviews discuss Cys-loop receptor structure at length (da Costa et al., 2013; Nys, et al., 2013; Sauguet et al., 2015; Wu et al., 2015; Nemezc et al., 2016).

The five equivalent neurotransmitter binding pockets of the homopentameric 5-HT_{3A} receptor are located in electronegative clefts at interfaces between two adjacent subunits (Figure 30). Three loops of the principal subunit and four portions of beta strands of the complementary subunit contribute to the pocket (Figure 30). Therefore the shape of the binding pocket arise from the combination of the quaternary arrangement (how one subunit is oriented relative to its neighbor) and of the local conformation of loops and side-chains. During activation of Cys-loop receptors and gating of the channel, both global subunit/subunit orientation and more local conformation changes take place (Du et al., 2015; Sauguet et al., 2013; Basak et al. 2018b; Polovinkin et al., 2018). The 5-HTBP and other model proteins present a stiff quaternary structure where the subunit/subunit orientation is fixed and in that respect they are imperfect models for ligand binding.

The binding cleft of the 5-HT_{3A} receptor is surrounded by aromatic residues forming a 10-Å wide box, including W156 (loop B), W63 (loop D), Y126 (loop E), F199 and Y207 (loop C). W156 (W145 in 5-HTBP) lies at the bottom of the cleft and has cation- π interaction with 5-HT (Beene et al., 2002). This part of the site looks rigid with many intra- and inter-subunit interactions. In contrast the mouth of the cleft seems prone to reorganization. The C loop adopts different conformations in the apo, the antagonist-bound and 5-HT-bound (Figure 30). Other important residues lining the site include N101 (loop A), T152 and T154 (loop B), R65 (loop D), D177, S179, I180 (loop F), D42 and I44 (loop G).

A picture of the molecular mechanism of 5-HT₃ receptors starts to emerge from the accumulated structural data. The closed apo conformation resembles those of the receptor inhibited by small molecules (anti-emetics such as tropisetron) or by the inhibitory VHH15. Upon 5-HT binding the receptors undergo a transition to the open state characterized by: 1- a compaction of the neurotransmitter pocket due to quaternary reorganization of the extracellular domain; and 2- an opening of the transmembrane pore linked to the pivot of each subunit transmembrane domain. Two independent cryo-EM studies have captured a second 5-HT-bound state featuring a closed pore similar to that of the resting state (Basak et al. 2018b; Polovinkin et al., 2018). Based on functional experiments, this state was tentatively described as pre-active rather than desensitized (Polovinkin et al., 2018).

There is no direct structural data on allosteric modulation sites of 5-HT₃ receptors. Nevertheless allosteric sites identified on homologous Cys-loop receptors are relevant to the 5-HT₃ pharmacology. For instance PU-02, a selective inhibitor of the 5-HT₃ receptor acting in the micro-molar range, binds to a transmembrane inter-subunit site (orange in Figure 29) that correlates to the ivermectin site of the *C. elegans* GluCl receptor (Hibbs et al., 2011) and to the ethanol and bromoform sites of the model bacterial GLIC receptor (Sauguet et al., 2013). In the 5-HT_{3A} receptor structure, a deep cleft between subunits is indeed accessible from the lipid bilayer and lined by residues determining PU-02 activity [16]: L266, S270, G282, V288 on the (+) side and S226, I268 and T272 on the (-) side (Figure 29). A second membrane-accessible site, this time located within a single subunit (Figure 29), has been identified as the site of action of the positive allosteric modulator TMPPAA (Gasiorek et al., 2016; Polovinkin et al., 2018) and might be involved in anesthetics inhibition (Lopreato et al., 2003). Some compounds acting as physical blockers of the ion flux binds directly in the channel lumen. A variety of sites have been identified at different depths in the pore, spanning almost the whole transmembrane part, from divalent cations

binding close to the intracellular mouth to TEA and lidocaine in the middle (Hilf et al., 2010) and memantine that binds close to the extracellular mouth (between 13' and 16')(Rammes et al., 2001; Ulens et al., 2014).

The 5-HT₃ receptor structures also shed light on the neglected intracellular domain. Only part of it is seen in the structures: a short helical stretch after the M3 transmembrane helix and a long helix MA continuous with the M4 transmembrane helix (Figure 29 and 31). At their N-terminal side, MA helices form a tight pentameric bundle stabilized by hydrophobic interactions (Figure 31). Further up, and closer to the mouth of the transmembrane pore, they carry charged residues whose mutations were shown to profoundly affect the channel conductance. At this level the spacing between MA helices results in lateral fenestrations, plugged in the closed-pore structures by the loop linking M3 and MA (Figure 31). Recent cryo-EM structures have shown that this intracellular region is drastically re-organized in the open-pore state, with wide portals, and displays flexibility. The ion exit pathway and how the ion flux depends on the flexibility and the local electrostatic environment remain to be fully described (Di Maio et al., 2015).

Molecular dynamics simulations established the existence of a de-wetted zone in the transmembrane pore in the closed-pore conformations; and its conversion to a fully hydrated pore permeant to cations in the open conformations (Yuan et al., 2016; Polovinkin et al., 2018).

XVII. 5-HT GPCRs and their interacting proteins

XVII. A. Introduction

The history of cell signalling started more than 60 years ago with the seminal discovery of cAMP by Earl Sutherland (Nobel prize in 1971). The mechanisms by which some receptors activate the production of second messengers has been revealed by Martin Rodbell (Nobel Prize 1994) in the 1970s when he showed that the receptors do not directly stimulate second messenger synthesizing enzymes but indirectly, *via* an allosteric activation of G proteins. The G protein-coupled receptors (GPCRs) ternary complex consisting of a receptor, a G protein and an effector, enzyme or channel, was born. Surprisingly, 5 decades later, the nature and functions of the huge protein complexes comprising GPCRs and GPCR interacting proteins (GIPs) still remain poorly characterized. During their cellular journey, GPCRs are assisted by GIPs for their proper folding, targeting to proper subcellular compartments, trafficking to and out of the plasma membrane, and to select several alternative signalling pathways, including G protein-independent pathways. In addition, GIPs are able to allosterically modify the pharmacology of associated GPCR and even to activate some GPCRs in absence of ligands. This section of the review is dedicated to GIPs of 5-HT receptors, which are among the GPCRs for which those proteins are the most extensively characterized, mainly thanks to proteomics screens. Given the large number of 5-HT receptor GIPs identified, it provides a wide overview of their role in GPCR physiology. Recent advances in the role of GIPs in fine-tuning of 5-HT₆ receptor signalling and associated physiological functions including neurodevelopment and cognition are particularly highlighted.

The evolution of multicellular organisms has been closely linked to their capacity to communicate with their environment and to develop sophisticated communications between their own cells. Most of these communications involve chemical messengers (e.g. hormones, neurotransmitters, growth factors) that interact with one or several transmembrane receptors. Among those receptors, GPCRs are the most numerous ones (Bockaert and Pin, 1999). Around 1,000 genes encode such receptors in the human genome (representing 3-4 % of the genome), of which ~300 are non-olfactory receptors (Fredriksson et al., 2003). 5-HT receptors are particularly well represented in this important receptor family. The diversity of 5-HT GPCRs is certainly due to molecular tinkering from one ancestral gene and has been instrumental for the implication of 5-HT

in a large number of physiological and pathophysiological functions both in the central nervous system (CNS) and peripheral tissues. Due to their structural diversity, 5-HT₁ receptors are able to trigger a large panel of signalling events (Marin et al., 2012). Many of them are transduced by different G proteins. In addition, signalling events elicited by 5-HT₁ receptor activation as well as by many GPCRs are triggered or finely modulated through their interaction with multiple intracellular proteins ‘GIPs’ and are assembled into functional complexes designated as “receptosomes” (Bockaert et al., 2004; Bockaert et al., 2003; Bockaert et al., 2010; Marin et al., 2012; Maurice et al., 2011). GIPs are not only involved in GPCR signalling but also in their targeting to subcellular compartments including axonal and dendritic compartments, in their trafficking in and out of the plasma membrane, through the endoplasmic reticulum, Golgi apparatus, endosomal, and lysosomal compartments (Bockaert et al., 2004; Bockaert et al., 2003; Bockaert et al., 2010; Marin et al., 2012; Maurice et al., 2011). Several reviews have been published on GIPs, including two dedicated to 5-HT₁ receptor GIPs (Allen et al., 2008; Marin et al., 2012). Accordingly, only a brief description of the nature, cellular and physiological functions of 5-HT₁ receptor GIPs will be provided here (see Table 21) focussing on intracellular GIPs and not consider 5-HT₁ receptor association with other GPCRs (homodimer/heteromer formation). A more detailed account of proteins interacting with the 5-HT₆ receptor is presented to highlight the interest of a comprehensive description of GIPs for a given receptor to unravel novel mechanisms underlying GPCR activation and physiological functions controlled by those receptors.

XVII. B. A survey of 5-HT receptor GIPs

XVII. B. 1. 5-HT_{1A} receptor

The 5-HT_{1A} receptor recruits and activates both G_{i3} and G_o (Bockaert et al., 2006; Marin et al., 2012). Coupling to G_{i3} is predominant in the soma of 5-HT raphe neurons and mainly leads to adenylyl cyclase (AC) inhibition, whereas coupling to G_o prevails in hippocampus and leads to inhibition of G protein-coupled inwardly-rectifying potassium (GIRK) channels (Mannoury la Cour et al., 2006), see also (Marin et al., 2012) for a detailed review of G_i/G_o-mediated signalling events elicited by 5-HT_{1A} receptor and their physiological impact. The molecular basis of the difference in G protein coupling is unknown. Only two GIPs are known to interact with 5-HT_{1A} receptors, namely calmodulin (Della Rocca et al., 1999; Turner et al., 2004) and Yif1B (Al Awabdh et al., 2012; Alterio et al., 2015; Carrel et al., 2008). The Ca²⁺-calmodulin complex binds to two distinct sites located the third intracellular loop (i₃) of the receptor (Turner et al., 2004) while Yif1B (Yip1 interacting factor homolog B) associates with its short C-terminal domain (Ct). Ca²⁺-calmodulin is implicated in receptor internalization, Erk1,2 activation and modulation of protein kinase C (PKC)-dependent receptor phosphorylation (Della Rocca et al., 1999; Turner et al., 2004). In addition, Ca²⁺-calmodulin contributes to receptor-operated Janus kinase 2 (Jak2) and type 1 sodium-proton exchanger (NHE-1) activation (Turner et al., 2007). 5-HT_{1A} receptor activation leads to the assembly of a ternary signalling complex that includes activated Jak2, Ca²⁺-calmodulin and NHE-1, in which calmodulin is activated by tyrosine phosphorylation instead of cellular Ca²⁺ elevation. This results in tighter interaction of calmodulin with NHE-1, NHE-1 conformational change and increased NHE-1 transport activity (Turner et al., 2007). Yif1B is a protein implicated in the traffic of proteins from the endoplasmic reticulum (ER) to the Golgi (Alterio et al., 2015) that plays a key role in the specific targeting of 5-HT_{1A} receptors to dendrites (Carrel et al., 2008). It has been proposed that Yif1B serves as a scaffold allowing the recruitment of 5-HT_{1A} receptor to a complex comprising Rab6, kinesin family member 5B (KIF5B) and dynein that coordinates its anterograde traffic to terminal dendrites (Al Awabdh et al., 2012).

XVII. B. 2. 5-HT_{1B} receptor

In addition to its coupling to G_i/G_o (Bockaert et al., 2006; Marin et al., 2012), the 5-HT_{1B} receptor interacts *via* its i₃ loop with a particularly interesting

GIP, named p11 (Svenningsson et al., 2006; Svenningsson and Greengard, 2007). p11 (also known as S100A10) is a member of the S100 EF-hand protein family. S100 proteins are small acidic proteins (10–12 kDa) characterized by two calcium-binding sites that have helix-loop-helix ("EF-hand type"). p11 increases cell surface density of 5-HT_{1B} receptor and, thus, receptor-operated signalling (Svenningsson et al., 2006). Reduction in p11 level has been found in post-mortem human tissue from depressed individuals and suicide victims as well as in a rodent model of depression, while its level in rodent brain is increased by antidepressants or electroconvulsive therapy (Svenningsson et al., 2006; Svenningsson and Greengard, 2007). Furthermore, invalidation of the gene encoding p11 induces a depression-like phenotype, reduces response to antidepressants and emotional memory, and enhances dependence to cocaine (Eriksson et al., 2013; Svenningsson, 2014; Svenningsson and Greengard, 2007; Svenningsson et al., 2013).

XVII. B. 3. 5-HT_{2A} receptor

The 5-HT_{2A} receptor is mainly coupled to G_q/G₁₁ proteins. 5-HT_{2A} receptors also engage G_i/G_o-mediated signalling upon stimulation by hallucinogenic agonists, including lysergic acid diethylamide (LSD) and synthetic agonists, such as 2,5-dimethoxy-4-iodoamphetamine (DOI) (Bockaert et al., 2006; Gonzalez-Maeso et al., 2007; Karaki et al., 2014; Marin et al., 2012). Like many GPCRs, the 5-HT_{2A} receptor also recruits β -arrestins following agonist stimulation (Bhattacharya et al., 2010). Intriguingly, it has been found that β -arrestin 2 is specifically involved in the hallucinogenic-like effects elicited by high concentrations of 5-HT (or its metabolites) but not in those induced by DOI (Schmid et al., 2008). These hallucinogenic-like effects are mediated by the activation, *via* β -arrestin 2, of a phosphoinositide 3-kinase (PI3K)/Src/Akt signalling cascade (Schmid and Bohn, 2010). Likewise, β -arrestins are required for Erk1,2 activation by 5-HT, but not by DOI (Schmid et al., 2008).

The 5-HT_{2A} receptor (like several other 5-HT receptors including 5-HT_{2B} and 5-HT_{2C} receptors, see below) expresses a canonical recognition motif for PSD-95/Disc large/Zonula occludens-1 (PDZ) domain containing proteins at its C-terminal extremity. PDZ domain containing proteins (or PDZ proteins) are scaffolding proteins containing one or several PDZ domains, in addition to other protein-protein interaction domains. PDZ domains have been classified according to their specificity for PDZ motifs (or PDZ ligands): class I PDZ domains preferentially bind to -S/Tx ϕ , class II to - ϕ x ϕ and class III to -E/Dx ϕ motifs (where ϕ represents a hydrophobic residue and X any residue), respectively. The 5-HT_{2A} receptor PDZ

ligand (-SCV) clearly belongs to class I. Several PDZ proteins have been found to interact with the 5-HT_{2A} receptor. The majority of them have been identified thanks to affinity purification coupled to mass spectrometry (AP-MS) proteomic strategies or two-hybrid screens. These include Multi-PDZ protein1 (MUPP1), PSD-95, Membrane-associated guanylate kinase with inverted domain structure2 (MAGI2), synapse-associated protein (SAP)97, Channel interacting PDZ protein (CIPP), MAGUK p55 subfamily member 2 (MPP2) and 3 (MPP3) (Becamel et al., 2001; Becamel et al., 2004; Pichon et al., 2010). Amongst the 5-HT_{2A} receptor GIPs identified, PSD-95 is certainly the most extensively studied with respect to the functional impact of its association with the receptor. PSD-95, which is located in post-synaptic spine membranes together with other receptor PDZ partners, is required for dendritic targeting of the receptor (Allen et al., 2008; Xia et al., 2003). In addition, microtubule-associated protein (MAP)1A may scaffold the receptor to the microtubule cytoskeleton and facilitate its trafficking to apical dendrites (Allen et al., 2008). PSD-95, like SAP97 and MUPP1, increases receptor cell surface density likely by inhibiting receptor endocytosis (Allen et al., 2008; Jones et al., 2009). The impact of the 5-HT_{2A} receptor/PSD-95 complex upon receptor-operated signalling is less clear. On the one hand, 5-HT_{2A} receptor-mediated downstream signalling is impaired in PSD-95 deficient mice (Abbas et al., 2009), suggesting that the interaction promotes receptor-operated signal transduction. On the other hand, acute disruption of 5-HT_{2A} receptor/PSD-95 association with an interfering peptide increases receptor-mediated cytosolic Ca²⁺ increase and its antihyperalgesic effects in models of neuropathic and inflammatory pain in the rat (Pichon et al., 2010; Wattiez et al., 2013), suggesting that this interaction inhibits receptor-operated signalling. These opposite effects of sustained (PSD-95 knock out) and acute (interfering peptide) disruption of the 5-HT_{2A} receptor/PSD-95 interaction may reflect long-term adaptive changes in PSD-95 knockout mice. In line with the antihyperalgesic effects produced by disruption of 5-HT_{2A} receptor/PSD-95 interaction with a peptide, docking simulation studies identified a series of substituted indoles as potential small molecule inhibitors of this interaction. One of them efficiently inhibited mechanical hyperalgesia in an experimental model of traumatic neuropathic pain in the rat (Vogrig et al., 2013). Collectively, these studies identify the 5-HT_{2A} receptor/PSD-95 complex as a new therapeutic target for the treatment of neuropathic pain, which remains poorly controlled by currently available analgesics. Consistent with the inhibition of 5-HT_{2A} receptor-operated signalling in PSD-95 deficient mice, the hallucinogenic-like effects of drugs are impaired in these mice (Abbas et al., 2009). Likewise, deletion of PSD-95 renders ineffective atypical antipsychotics like clozapine, which act as 5-HT_{2A} receptor inverse agonists, against PCP-induced disruption of prepulse inhibition, a widely used pharmacological model of schizophrenia (Abbas et al., 2009). Na⁺/H⁺ exchanger

regulatory factor (NHERF) 3 is another PDZ protein that interacts with the 5-HT_{2A} receptor but, surprisingly, in a PDZ-independent manner (Walther et al., 2015). NHERF3 negatively regulates 5-HT_{2A} receptor endocytosis and positively influences 5-HT_{2A} receptor-stimulated inositol phosphate formation (Walther et al., 2015).

Several 5-HT_{2A} receptor interacting proteins have been identified in addition to PDZ proteins. Targeting of 5-HT_{2A} receptor to caveolae microdomains is ensured by its interaction with the multi-functional proteins caveolins (Allen et al., 2008). Moreover, association of the receptor with caveolins has a profound impact upon receptor-operated signal transduction and functions: interaction of 5-HT_{2A} receptor with caveolin-1 within lipid raft/caveolae membranes enhances receptor-mediated signal transduction by facilitating its coupling to G α_q protein in C6 glioma cells (Bhatnagar et al., 2004), while its interaction with caveolin-3, the predominant caveolin isoform in heart, upon 5-HT stimulation, negatively regulates receptor-mediated hypertrophy in cardiomyoblasts and neonatal cardiomyocytes (Mialet-Perez et al., 2012).

ADP-ribosylation factor (ARF)1 and, to a lesser extent, ARF6, associate with the i₃ loop and Ct of the 5-HT_{2A} receptor (Robertson et al., 2003). This association is enhanced by GTP loading and is essential for 5-HT_{2A} receptor-mediated phospholipase D (PLD) activation, which seems to be independent of G $_{q/11}$ (Robertson et al., 2003). 5-HT_{2A} receptors also bind to the tyrosine kinase Jak2, in foetal myoblasts (Guillet-Deniau et al., 1997). This is accompanied by Jak2 auto-phosphorylation, the recruitment of the transcription factor *signal transducer and activator of transcription* (STAT)3 and its translocation to the nucleus (Guillet-Deniau et al., 1997). P90 ribosomal S6 kinase 2 (RSK2) interacts with 5-HT_{2A} receptor i₃ loop and exerts a tonic brake on receptor-operated signalling (Allen et al., 2008; Sheffler et al., 2006). RSK2 phosphorylates 5-HT_{2A} receptor at Ser³¹⁴ located in the i₃ loop. Ser³¹⁴ phosphorylation underlies heterologous desensitization of the receptor elicited by growth factors (Allen et al., 2008; Strachan et al., 2009). A role of 5-HT_{2A} receptors in symptoms associated with Coffin–Lowry syndrome (due to null mutations in *RSK2* gene), such as moderate to severe mental retardation, movement disorders and schizophrenia-like psychosis in heterozygote females has been proposed (Allen et al., 2008). Calmodulin interacts in a Ca²⁺-dependent manner with consensus binding motifs located in 5-HT_{2A} receptor i₂ loop and Ct. This association inhibits receptor coupling to G $_q$ (Turner and Raymond, 2005).

XVII. B. 4. 5-HT_{2B} receptor

The 5-HT_{2B} receptor is mainly coupled to G_q (see also (Bockaert et al., 2006; Marin et al., 2012) for detailed review of G_i/G_o-mediated signalling events elicited by this receptor).

A number of recognised signalling proteins interact with the 5-HT_{2B} receptor include constitutive and inducible NOS and the G-proteins; Gα_q, Gα₁₁, and Gα₁₃. The 5-HT_{2B} receptor also binds to the multivalent PDZ scaffold protein, MUPP1; this is in common with the other 5-HT₂ receptors, 5-HT_{2A} and 5-HT_{2C} receptors. 5-HT_{2A} and 5-HT_{2B} receptors also bind MUPP1-PDZ domains *in-vitro* and share the C-terminal -E-X-V/I-S-X-V sequence (Becamel et al., 2001). This PDZ motif is also required for the recruitment of the constitutive NO synthase cNOS (Manivet et al., 2000).

Ubiquitin ligases (E3s) confer specificity to ubiquitination by recognizing target substrates. The Ligand of Numb protein X (LNX) family of E3s, is a group of PDZ domain-containing RING-type E3 ubiquitin ligases. The substrate recognition mechanism of LNX E3s involves their specific PDZ domains by binding to the C-termini of the target proteins. The human C-terminal LNX1 PDZ3-binding motifs of the 5-HT_{2B} receptor promotes ubiquitination by LNX1ΔPDZ4 (Guo et al., 2012).

XVII. B. 5. 5-HT_{2C} receptor

The 5-HT_{2C} receptor activates phospholipase C (PLC) *via* G_{q/11}, PLD *via* G₁₃, phospholipase A2 (PLA2) and Akt / glycogen synthase kinase (GSK)3β *via* G_{i3} (Bockaert et al., 2006). 5-HT_{2C} receptors also activate Erk1,2 signalling *via* a mechanism entirely independent of G proteins but dependent of its interaction with both Ca²⁺/calmodulin and β-arrestin 2 (Labasque et al., 2008; Marin et al., 2012). As already mentioned, the receptor expresses a canonical Class I PDZ ligand at its C-terminal extremity. MUPP1 was the first PDZ protein identified as a partner of the 5-HT_{2C} receptor in 1998, using the yeast two hybrid system (Ullmer et al., 1998). MUPP1 contains thirteen PDZ domains (it is the PDZ protein that contains the

largest number of PDZ domains identified) and selectively interacts with the receptor *via* its 10th PDZ domain (Becamel et al., 2001). This interaction is dynamically regulated by agonist-dependent receptor phosphorylation at Ser⁴⁵⁸ located in the PDZ binding motif (Parker et al., 2003). The gene encoding MUPP1 (*Mpdz*) has been identified as a quantitative trait underlying physical dependence to drugs of abuse (Shirley et al., 2004). Additional PDZ partners of 5-HT_{2C} receptor have been identified by means of AP-MS proteomic strategies (Becamel et al., 2002; Becamel et al., 2004). These include PSD-95, SAP102, MPP3 and the ternary complex Veli3/CASK/Mint1. These studies revealed that in spite of their similar PDZ binding motifs, 5-HT_{2A} and 5-HT_{2C} receptors bind to different sets of PDZ proteins that differ in their synaptic localizations: 5-HT_{2A} receptors preferentially interact with PDZ proteins exclusively located at the post-synapse (e.g. PSD-95, SAP97 and CIPP), whereas 5-HT_{2C} receptors associate with PDZ proteins exhibiting both presynaptic and post-synaptic localizations such as the ternary complex Veli3/CASK/Mint1, consistent with their different distribution at the synapse (Becamel et al., 2004). 5-HT_{2C} receptor PDZ partners differentially regulate receptor endocytosis and desensitization: PSD-95 increases both constitutive and agonist-induced receptor endocytosis and desensitization, whereas MPP3 stabilizes the receptor at the plasma membrane and prevents its desensitization (Gavarini et al., 2006). Note that PSD-95 has an opposite effect on 5-HT_{2A} and 5-HT_{2C} receptor endocytosis (Gavarini et al., 2006; Xia et al., 2003).

5-HT_{2C} receptors also interact *via* their i₃ loop with Phosphatase and TENsine homologue (PTEN), a phosphatase that negatively controls the Akt/PkB signalling pathway and thus is a tumor suppressor (Ji et al., 2006). The 5-HT_{2C} receptor/PTEN interaction was established in the Ventral Tegmental Area (VTA), the site of inhibition of the rewarding effects of many drugs of abuse by 5-HT_{2C} receptor agonists. This inhibition is linked to the ability of receptors to prevent the increase in the firing rate of VTA dopaminergic neurons projecting to the nucleus accumbens elicited by drugs. Disrupting the 5-HT_{2C} receptor-PTEN interaction with a cell-penetrating interfering peptide reduced the firing rate of VTA dopaminergic neurons and prevented rewarding effects of drugs of abuse such as tetrahydrocannabinol (THC) and nicotine, suggesting that this interaction might be a relevant target for the treatment of drug addiction (Ji et al., 2006). 5-HT_{2C} receptors also interact with PICOT, a PKC theta-interacting protein with a thioredoxin homology domain involved in the regulation of the thioredoxin system (Becamel et al., 2002). The functional consequence of this interaction remains to be established.

XVII. B. 6. 5-HT₄ receptors

5-HT₄ receptors engage signalling pathways through multiple G proteins, especially G_s and in some cell lines G₁₃, G_q and G_i (for reviews, see (Bockaert et al., 2008; Coupar et al., 2007)). In addition, 5-HT₄ receptors stimulate Erk1/2 in a G protein- and β -arrestin-independent mechanism that requires activation of the tyrosine kinase Src constitutively associated with 5-HT₄ receptor (Barthet et al., 2007; Bockaert et al., 2011; Gill et al., 2005). This pathway is also implicated in the activation of PLC γ 1-mediated inhibition of NHE-1 in intestinal epithelial cells (Gill et al., 2005). Furthermore, GPCR kinase (GRK)5 interacts with the proximal Ct of 5-HT₄ receptors and phosphorylates β -arrestin 1. This prevents Src activation and underlies desensitization of Src-dependent Erk1,2 activation by 5-HT₄ receptors (Barthet et al., 2009; Bockaert et al., 2008).

Like 5-HT_{1B} receptors, 5-HT₄ receptors interact with p11 *via* their i₃ loop (Warner-Schmidt et al., 2009). p11 enhances receptor cell surface localization and signal transduction (Warner-Schmidt et al., 2009). Given the extensive data showing that p11 is down-regulated in depressive states (Svenningsson and Greengard, 2007) and that activation of 5-HT₄ receptors has antidepressant effects (Ge and Barnes, 1996; Bockaert et al., 2011), this interaction might be of particular interest for the treatment of depression.

The 5-HT₄ receptor interacts, directly or indirectly, with the α -secretase ADAM10. This interaction might be an important step in the constitutive (agonist-independent) activation of non-amyloidogenic cleavage of amyloid precursor protein (APP) and release of soluble sAPP α fragment elicited by the receptor (Cochet et al., 2013). sAPP α has neurotrophic and neuroprotective properties and its release upon constitutive (and agonist-dependent) receptor activation might contribute to receptor-mediated reduction of amyloid pathology observed in several mouse models of Alzheimer's disease (Claeyssen et al., 2015; Cochet et al., 2013; Pimenova et al., 2014; Tesseur et al., 2013).

The 5-HT₄ receptor is one of the GPCRs for which alternative mRNA splicing generates the most variants that differ in their Ct, with some variants (a, e and f) expressing canonical PDZ ligands, suggesting that these receptors may recruit specific GIPs, including different sets of PDZ partners. Ten

proteins have been shown to interact with the Ct of the 5-HT_{4(a)} receptor. Most of them are PDZ proteins that associate with its canonical class I PDZ motif (-SCF) (Joubert et al., 2004). These include SNX27a, a member of the sorting nexin family, which targets 5-HT_{4(a)} receptors to early endosomes in cell lines (Joubert et al., 2004). A more recent study showed that SNX27 associates with β_2 -adrenergic receptor PDZ ligand, and that this interaction is essential for PDZ-directed receptor recycling (Temkin et al., 2011). It also showed that SNX27 serves as an essential adaptor protein linking PDZ motif containing cargo to the retromer. SNX27 also directly interacts with endosomes through its lipid binding phox homology (PX) domain. A similar role of SNX27a in endocytic 5-HT₄ receptor trafficking is likely. The interaction of the 5-HT_{4(a)} receptor with the PDZ protein NHERF promotes its recruitment to microvilli, where it localizes with activated ezrin, consistent with a role of 5-HT₄ receptors in cytoskeleton remodelling (Joubert et al., 2004). The Ct of the 5-HT_{4(a)} receptor also recruits CRMP2, a member of the collapsing response mediator protein (CRMP) family through a PDZ-independent mechanism (Joubert et al., 2004). 5-HT₄ receptors cause G₁₃- and RhoA-dependent neurite retraction and cell rounding in neuroblastoma cells (Ponimaskin et al., 2002). Their association with CRMP2 might also contribute to regulation of neuronal architecture.

Three GIPs associate with the class II PDZ ligand (-VPV) of the 5-HT_{4(e)} receptor. These include two PDZ partners, namely CIPP and neuronal nitric oxide synthase (nNOS), the only NOS isoform expressing a PDZ domain. The third protein that binds to the Ct of 5-HT_{4(e)} receptor is Sec23A, a protein of the COPII complex, which is likely involved in its trafficking from the ER to the Golgi (Joubert et al., 2004). The 5-HT_{4(b)} receptor interacts with the phosphodiesterases PDE3A1 and PDE4D3, which may thereby regulate receptor-operated cAMP signalling (Weninger et al., 2014).

XVII. B. 7. 5-HT₇ receptor

The 5-HT₇ receptor is coupled to G_s and G₁₂ (Bard et al., 1993; Ruat et al., 1993). 5-HT₇ receptor stimulation promotes neurite outgrowth and SRE-mediated gene transcription through G α_{12} -dependent activation of RhoA and Cdc42 GTPases (Guseva et al., 2014; Kvachnina et al., 2005). The 5-HT₇ receptor Ct interacts with neurochondrin, a protein expressed in bone and brain that promotes neurite growth. Neurochondrin interacts with several GPCRs, including melanin-concentrating hormone receptor 1 (MCHR1), orexin-1 and thromboxane A₂ receptors, and the mGlu5

metabotropic glutamate receptor (Marin et al., 2012; Ward et al., 2009). Generally, neurochondrin inhibits GPCR coupling to G proteins. The 5-HT₇ receptor Ct also recruits the intermediate filament periplakin which, like neurochondrin, inhibits receptor-operated Ca²⁺ signalling (Ward et al., 2009). The role of neurochondrin in neurite outgrowth elicited by 5-HT₇ receptor stimulation remains unexplored.

5-HT₇ receptors, *via* their i₃ loop, interact with S100B, a member of the S100 family, and that S100B negatively regulates 5-HT₇ receptor-induced cAMP production (Stroth and Svenningsson, 2015). S100B seems to play a role in the antidepressant effects of fluoxetine (Baudry et al., 2010) and its serum concentration may serve as a biomarker predicting response to antidepressant treatment (Arolt et al., 2003). Notably, 5-HT₇ receptor antagonists have been reported to display rapid antidepressant action, making the receptor a promising target for antidepressants with improved onset of clinical efficacy, compared with most of the currently available treatments (Mnie-Filali et al., 2011). Suggestive of a possible influence of 5-HT₇ receptor/S100B interaction in the pathogenesis of mood disorders and their treatment, transgenic female mice overexpressing S100B show depressive-like behaviour that is normalized by administration of a 5-HT₇ receptor antagonist (Stroth and Svenningsson, 2015).

The human and rat genes coding for the 5-HT₇ receptors generate different splice variants (Heidmann et al., 1997). One of them (5-HT_{7(b)} receptor) is common to rat and human and expresses at its extreme Ct a canonical Class II PDZ ligand (-FVL). To date, no PDZ partner of 5-HT_{7(b)} receptor has been identified.

XVII. C. 5-HT₆ receptor receptosome: toward new signalling mechanisms underlying its control of cognition and neurodevelopmental processes

XVII. C. 1. Introduction

The 5-HT₆ receptor has early been considered as a promising target for psychiatric diseases in line with its near exclusive expression in the central nervous system (Hirst et al., 2003). Although initial studies suggested that 5-HT₆ receptors are almost exclusively localized on GABA interneurons, more recent studies including some in human brain indicate that they are also present on pyramidal glutamatergic neurons in prefrontal cortex and

hippocampus (Marazziti et al., 2013; Woolley et al., 2004). A more detailed study of 5-HT₆ receptor mRNA distribution showed highest expression in both D₁ and D₂ receptor-containing medium size spiny neurons of caudate putamen and nucleus accumbens, and confirmed consistent expression in glutamatergic neurons of hippocampus and cerebral cortex expressing vGluT1 (Helboe et al., 2015). It also showed the presence of 5-HT₆ receptor mRNA in a minor fraction of GABAergic cortical neurons, including mainly neurons co-expressing 5-HT_{3A} receptor and a subset of calbindin and calretinin positive neurons (Helboe et al., 2015). 5-HT₆ receptors thus display an ideal distribution to regulate the balance between excitatory and inhibitory signalling in brain regions implicated in cognition, which is altered in schizophrenia (Uhlhaas and Singer, 2010). The pharmacology of 5-HT₆ receptors includes a great number of ligands exhibiting agonist or antagonist activities. Some of them have shown putative interest for treating cognitive deficits, depression, anxiety, sleep and feeding disorders as well as pain (Fone, 2008; Karila et al., 2015; Ly et al., 2013; Mitchell and Neumaier, 2005; Pereira et al., 2015; Svenningsson et al., 2007; Claeysen et al., 2015; Wilkinson et al., 2014). Unfortunately Phase III clinical trial results for treating cognitive impairment have been disappointing. An increase in our understanding of how the cellular and molecular events associated with the 5-HT₆ receptor translate to behavioural responses may inform and support stratified medicine approaches.

The 5-HT₆ receptor is positively coupled to G_s and, like many GPCRs, activates Erk1,2 (Ruat et al., 1993; Sebben et al., 1994) (Figure 32). As G_s/cAMP and Erk1,2 pathways can have a positive influence upon cognition, it was unlikely that their inhibition would mediate the pro-cognitive effects of 5-HT₆ receptor antagonists. This suggested that alternative coupling mechanisms might be involved. Likewise, the cellular mechanisms controlling 5-HT₆ receptor functional activity remained largely unexplored until the use of unbiased strategies to identify 5-HT₆ receptor interacting proteins. These included two-hybrid screens (Kim et al., 2014; Yun et al., 2010; Yun et al., 2007) and AP-MS proteomics strategies based on different methods to purify receptor partners, such as co-immunoprecipitation (Meffre et al., 2012) or pull-down assays using particular receptor sequences as baits (Duhr et al., 2014; Ha et al., 2015).

XVII. C. 2. Fine tuning of 5-HT₆ receptor trafficking and signal transduction by GIPs

The non-receptor tyrosine kinase Fyn was the first GIP discovered for 5-HT₆ receptor, thanks to a two-hybrid screen using the receptor Ct as bait

(Figure 32). Fyn is a member of the Src family of tyrosine kinases that highly expressed in brain and involved in synaptic plasticity. Several lines of evidence suggest that Fyn might be implicated in Alzheimer's disease pathogenesis: Fyn phosphorylates Tau at Tyr¹⁸ and controls its association with microtubules (Lee et al., 2004); it has also been involved in A β -induced synaptic deficits and neurotoxicity (Yang et al., 2011). In addition, Fyn plays a key role in neurodevelopmental processes: in combination with Src, Fyn controls cortical lamination, the formation of the Purkinje cell plate and thus neuronal migration (Kuo et al., 2005). It is involved in netrin-1-mediated axon attraction of cortical neurons *via* the phosphorylation of Trio, a Rho/Rac-guanine nucleotide exchange factor (GEF) (DeGeer et al., 2013), and in the maturation of GABAergic synapses elicited by neural cell adhesion molecule (NCAM) (Chattopadhyaya et al., 2013). Fyn binds to 5-HT₆ receptor Ct (likely to the conserved polyproline sequence PXhPXR where X represents any amino-acid and h an hydrophobic amino acid) *via* its SH3 domain (Yun et al., 2007). Functional studies showed that Fyn increases 5-HT₆ receptor cell surface localization and consequently receptor-operated G protein signalling (Yun et al., 2007). Conversely, 5-HT₆ receptor activation triggers Fyn phosphorylation, as assessed by an increase in Tyr⁴²⁰ phosphorylation, an event contributing to 5-HT₆ receptor-induced activation of the Ras/Erk1,2 pathway (Figure 32) (Yun et al., 2007). Whether 5-HT₆ receptor-mediated Fyn activation is involved in neuronal migration, attraction and maturation of GABAergic synapses remains to be elucidated.

Further two-hybrid screens identified two other 5-HT₆ receptor interacting proteins that control receptor trafficking. The first one is Jun activation domain-binding protein (Jab)1, a protein initially isolated as a c-Jun and Jun D binding partner that stabilizes their binding to activator protein 1 (AP-1) sites and potentiates them as transcription factors (Claret et al., 1996; Yun et al., 2010). Jab1 interacts with both i₃ loop and Ct of the receptor (Yun et al., 2010). Jab1 stabilizes surface expression of 5-HT₆ receptor and is necessary to maintain activity of endogenous receptors. In turn, 5-HT₆ receptor stimulation increases nuclear translocation of Jab1, suggesting that they may play a role in the regulation of gene expression *via* Jab1 (Figure 32) (Yun et al., 2010). Furthermore, 5-HT₆ receptors and Jab1 are up-regulated following middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Likewise, exposure of cultured cells to hypoxic insults increased expression of both protein partners, which in turn reduce cell death induced by hypoxia (Figure 32) (Yun et al., 2010). The second protein identified is light chain 1 (LC1) subunit of MAP1B protein (MAP1B-LC1), a microtubule-associated protein highly expressed in the brain (Kim et al., 2014). MAP1B-LC1 interacts with the Ct of the receptor, reduces receptor

endocytosis and thereby increases its cell surface expression and signal transduction activity (G_s coupling and Erk1,2 activation) (Kim et al., 2014).

The 5-HT₆ receptor i₃ loop recruits several proteins of the endocytic machinery such as dynamin, AP-2, amphiphysin and epsin, as well as SNX14 (Ha et al., 2015). Like SNX27, SNX14 belongs to the sorting nexin family, predicted to have a role in protein sorting and vesicular trafficking (Carlton et al., 2005). It contains a putative regulator of G protein signalling (RGS) domain and a phox homology (PX) domain, an N-terminal hydrophobic region and a PX-associated (PXA) domain of unknown function. SNX14 is expressed at high level in the nervous system (Carroll et al., 2001) and plays a critical role in both excitatory and inhibitory transmissions (Huang et al., 2014). SNX14 was found to inhibit 5-HT₆ receptor-dependent signalling *via* two different mechanisms: 1) it specifically binds to and sequesters $G\alpha_s$, thus inhibiting the G_s -cAMP pathway and 2) it promotes 5-HT₆ receptor endocytosis and degradation (Figure 32) (Ha et al., 2015). Furthermore, protein kinase A (PKA) phosphorylates SNX14 at two serine residues located in the RGS domain. SNX14 phosphorylation strongly reduces its affinity for $G\alpha_s$ and thereby prevents $G\alpha_s$ sequestration. Accordingly, phosphorylated SNX14 preferentially associates with 5-HT₆ receptor and can thereby enhance receptor internalization (Ha et al., 2015). Therefore, SNX14 has been considered as a dual, sequential, negative regulator of 5-HT₆ receptor-operated signalling, firstly by sequestering $G\alpha_s$ and secondly by inducing receptor endocytosis (Ha et al., 2015). Collectively, these findings indicate that 5-HT₆ receptor functional activity is finely modulated by its association with GIPs that exert contrasting effects upon receptor trafficking and receptor-mediated signal transduction.

XVII. C. 3. Recruitment of mTOR complex 1 by 5-HT₆ receptor: potential role in cognitive deficits associated with schizophrenia

Using a proteomics strategy combining co-immunoprecipitation of full length receptor and tandem mass spectrometry, Meffre *et al.* identified 28 proteins, which specifically associate with the 5-HT₆ receptor (Meffre et al., 2012). This 'receptosome' showed a remarkable enrichment in proteins of the mammalian target of rapamycin (mTOR) pathway (Meffre et al., 2012). These include mTOR itself, Raptor (regulatory associated protein of TOR), an activator of mTOR which together with mTOR and proline-rich Akt substrate of 40 kDa (PRAS40) constitutes the mTOR complex 1 (mTORC1), the small GTPase Rheb (Ras homolog enriched in brain), which directly activates mTOR when bound to GTP, the Tti1/Tel2 complex, required for assembly and stability of mTOR complexes, and the Ras GTPase activating protein (GAP) Neurofibromin (NF1), an upstream negative

regulator of the pathway leading to mTOR activation (Figure 33) (Meffre et al., 2012). This ‘receptosome’ also includes Vps34, a protein of the class III phosphatidylinositol 3-kinase (PI3K) family implicated in autophagosome formation (Bockaert and Marin, 2015). In line with this remarkable enrichment of the 5-HT₆ receptor complex in proteins of the mTOR pathway, agonist stimulation of the receptor results in the activation of the mTOR pathway both in a transfected cell line and in rodent brain, particularly in prefrontal cortex and striatum (Meffre et al., 2012). Notably, 5-HT₆ receptor-elicited mTOR activation depends on both its physical association with mTOR and the canonical PI3K/Akt/TSC/Rheb pathway involved in activation of mTORC1 by tyrosine kinase receptors (Figure 33) (Meffre et al., 2012).

An over-activation of mTOR is observed in many genetic diseases in which mental retardation or cognitive deficits are observed (for a review see (Bockaert and Marin, 2015)). One classical example is tuberous sclerosis (TSC) caused by mutations in the *TSC1* or *TSC2* genes, which encode proteins of the TSC complex, namely hamartin and tuberin, respectively. The TSC complex is the main GAP for Rheb. Mutations in *TSC1* or *TSC2* result in inactivation of TSC, a process leading to non-physiological mTOR activation. About 50% of TSC patients show intellectual disabilities as well as deficits in memory, attention, and executive functions, and 20–60% display autism spectrum disorder (ASD) (Bockaert and Marin, 2015). Moreover, the mTORC1 inhibitor rapamycin rescues cognitive deficits in a mouse model of TSC (*Tsc2*^{+/-} mice). Likewise, systemic administration of rapamycin prevents deficits in social cognition and novel object recognition induced by a 5-HT₆ receptor agonist in the rat (Meffre et al., 2012). In two neurodevelopmental rodent models of schizophrenia, the neonatal PCP model and the social isolation model (isolation after weaning), a sustained, 5-HT₆ receptor-mediated, mTOR activation that persists at the adult stage, occurs specifically in prefrontal cortex (Meffre et al., 2012). Again, cognitive impairment observed in both models is reversed by an acute injection of rapamycin at the adult stage (Meffre et al., 2012). These findings suggest a critical role of mTOR activation not only in rare autism-related genetic disorders, such as TSC, but also in schizophrenia, a more frequent, multi-factorial and debilitating disorder. The mechanisms by which non-physiological mTORC1 activation induces cognitive deficits remain largely unknown. A recent report has shown that enhanced activity of mTORC1 in post-mortem brain of ASD patients is associated with a decrease in autophagy, an increase in spine density and a reduction of developmental spine pruning in layer V pyramidal neurons (Tang et al., 2014). Spine defects are likewise observed in *Tsc2*^{+/-} mice (Bockaert and Marin, 2015). Whether inhibition of mTOR pathway contributes to the pro-cognitive

effects of 5-HT₆ receptor antagonists in Alzheimer's disease patients remains to be explored. Non-physiological mTOR activation, under the control of 5-HT₆ receptor, might also be involved in epilepsy. Indeed, an increase in 5-HT₆ receptor expression was found both in human epileptic tissue and the brain of rats treated with pilocarpine, a model of temporal lobe epilepsy (Wang et al., 2014). mTOR is also overactivated in the pilocarpine model and a 5-HT₆ receptor antagonist prevents mTOR activation, increases latency of seizures and reduces their severity (Wang et al., 2014). This suggests that blocking the 5-HT₆/mTOR pathway might be a valuable therapeutic strategy for epilepsy treatment.

XVII. C. 4. Recruitment of Cdk5 by 5-HT₆ receptor: an essential step in its control of neuronal migration and differentiation

The 5-HT₆ receptor is implicated in early steps of brain development including neurulation and neuronal migration within the cortex (Dayer et al., 2015; Jacobshagen et al., 2014). Although the cAMP pathway contributes to the control of neuronal migration by 5-HT₆ receptors, a PKA inhibitor only partially reversed the effect of its stimulation upon neuronal migration (Riccio et al., 2009), suggesting that other signalling pathways might be involved. Cyclin-dependent kinase (Cdk)5, which has been identified as a 5-HT₆ receptor partner by different AP-MS proteomics strategies (Figure 33; Duhr et al., 2014; Meffre et al., 2012), was an obvious candidate. Indeed, Cdk5 is known to control actin cytoskeleton dynamics and various neuro-developmental processes such as neuronal migration (including migration of cortical pyramidal neurons), neurite growth and synapse morphogenesis (Jessberger et al., 2009; Lalioti et al., 2010). Moreover, the 5-HT₆ receptor recruits, *via* its Ct, not only Cdk5 and its activator p35, but also a network of proteins functionally connected with Cdk5, including Wiskott-Aldrich syndrome protein (WASP)-family verprolin homologous protein 1 (WAVE-1) and G protein inducer of neurite growth 1 (GPRIN1), two Cdk5 substrates, phosphatase 2A, which dephosphorylates and activates WAVE-1, and the Arp2/3 complex, which is also known to be activated by WAVE-1 (Duhr et al., 2014). Several lines of evidence indicate a role of Cdk5, under the control of the 5-HT₆ receptor, in the migration of pyramidal neurons: *in utero* electroporation of a 5-HT₆ receptor shRNA at E14.5 induces a mispositioning of these neurons, which can be rescued by electroporation of plasmids encoding wild type 5-HT₆ receptor or 5-HT₆ receptors unable of coupling to G_s or to bind to 5-HT (Jacobshagen et al., 2014). This indicates that the effect of 5-HT₆ receptors on pyramidal neuron migration is agonist-independent and is not mediated by the G_s-adenylyl cyclase pathway. Defect in migration elicited by silencing 5-HT₆ receptor expression is rescued by electroporation of plasmids expressing Cdk5 and its activator p35 (Jacobshagen et al., 2014). Moreover, 5-HT₆

receptor knockdown significantly reduces phosphorylation of doublecortin (DCX, at Ser²⁹⁷) and focal adhesion kinase (FAK, at Ser⁷³²) in primary cortical neurons, two Cdk5 substrates known to control migration of pyramidal neurons (Tanaka et al., 2004; Xie et al., 2003). Collectively, these findings indicate that 5-HT₆ receptors control migration of cortical pyramidal neurons through an agonist-independent, Cdk5-dependent, mechanism (Dayer et al., 2015; Jacobshagen et al., 2014).

Beyond neuronal migration, the 5-HT₆/Cdk5 complex also controls neurite outgrowth and neuronal differentiation (Figure 33). Its role in neurite growth was not only established in neuroblastoma-glioma NG108-15 cells, a commonly used cellular mode for investigating mechanisms underlying neuronal development, but also in primary neurons and brain explants (Duhr et al., 2014; Seo and Tsai, 2014). Reminiscent of its control of neuronal migration, the growth promoting effects of the receptor is G_s- and agonist-independent. They are reversed by the specific 5-HT₆ receptor antagonist SB258585, which thus behaves as an inverse agonist in this model (Duhr et al., 2014). Likewise, SB258585 inhibits Cdk5 association with the 5-HT₆ receptor, indicating a specific recruitment of Cdk5 by a constitutively active receptor conformation. 5-HT₆ receptor-elicited neurite growth also depends on receptor phosphorylation at Ser³⁵⁰ by associated Cdk5. This suggests a reciprocal interplay between 5-HT₆ receptor and Cdk5 whereby the receptor stimulates Cdk5 activity and is itself a Cdk5 substrate. The signalling events downstream of the 5-HT₆/Cdk5 complex contributing to neurite growth have been partially characterized and involve Cdk5-dependent activation of the Rho GTPase cell division cycle (Cdc)42, a key regulator of actin cytoskeleton dynamics (Figure 33) (Duhr et al., 2014). The precise mechanisms that control 5-HT₆ receptor/Cdk5 interaction, including the potential influence of other receptor partners, and the cellular events downstream of the 5-HT₆/Cdk5/Cdc42 pathway remain to be explored. As already mentioned, the regulatory role of Cdk5 during brain development extends to synapse formation. Whether 5-HT₆ receptor-dependent activation of Cdk5 controls synaptogenesis in addition to neuron migration and shaping also remains to be investigated.

XVIII. 5-HT receptors and the brain

XVIII. A. Introduction

The diversity of 5-HT receptor signalling pathways and associated functional complexity in the brain is greater than any other tissue or organ. For historical perspectives on the contribution of neurophysiology, pharmacology and molecular biology to the discovery of 5-HT receptor subtypes in the brain, see the following reviews (Bradley *et al.*, 1984; Barnes and Sharp, 1999; Bockaert *et al.*, 2010).

XVIII. B. 5-HT receptor signalling in neurons

All 5-HT receptor subtypes found in the brain are also found in the periphery except 5-ht_{1e}, 5-HT_{2C} and 5-HT₆ receptors for which there is little evidence for functional expression outside the CNS. The signalling properties of 5-HT receptors in the brain are identical to those in the periphery. Thus, the metabotropic 5-HT receptors couple to the 3 canonical signalling pathways, namely G_i, G_s and G_{q/11}, which elicit the expected second messenger cascades, and this is proven to occur in neurons in most cases.

The G_i-coupled 5-HT receptors which inhibit adenylate cyclase and cause a fall in cAMP encompass the 5-HT₁ receptor family, comprising 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, and 5-HT_{1F} subtypes. Evidence suggests that the 5-HT₅ receptor family, 5-HT_{5A} and 5-ht_{5b}, is also G_i-coupled, although to date this has only been demonstrated in cultured cells and not native neurons. Excellent reviews on the signalling (Hannon & Hoyer, 2008; Bockaert *et al.*, 2010; McCorvy & Roth, 2015) and consequent electrophysiological (Lamb & Aghajanian, 2006; Andrade & Beck, 2010; Marek, 2010) properties of 5-HT₁ receptors can be found elsewhere.

Independent of the involvement of a decrease in cAMP, 5-HT₁ receptors also open G-protein-gated inwardly rectifying potassium channels (GIRKs) to hyperpolarise neurons and inhibit the opening of voltage-gated calcium channels; this is best understood for 5-HT_{1A} receptors (eg. Montalbano *et al.*, 2015). 5-HT₁ receptors are also likely to elicit other (non-canonical) G-protein-dependent signals including via extracellular signal-regulated kinase

(ERK) and Akt kinase, again as exemplified by studies of the 5-HT_{1A} receptor. Adding further complexity, it is well established that 5-HT_{1A} receptors have different properties depending on their pre- or postsynaptic localization. In particular, agonists tend to have greater efficacy at presynaptic 5-HT_{1A} receptors, and the latter have greater tendency to desensitize than postsynaptic 5-HT_{1A} receptors. The reason for these differences are uncertain, but as discussed elsewhere (Clarke *et al.*, 1996; Barnes & Sharp, 1999; Mannoury la Cour *et al.*, 2006; Garcia-Garcia *et al.*, 2014), could relate to presynaptic versus postsynaptic differences in 5-HT_{1A} receptor reserve, efficiency of G-protein coupling, non-G-protein dependent signalling, or even biased agonism - that is the generation of signals that are ligand-dependent. In regards to the latter, emerging data strongly support the view that selective 5-HT_{1A} receptor agonists can preferentially direct receptor signalling to particular intracellular pathways in a brain region-specific manner (Becker *et al.*, 2016).

The 5-HT₂ receptor family, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}, comprise G_{q/11}-coupled receptors that activate phospholipase C leading to increased formation of inositol trisphosphate and diacylglycerol, and then mobilisation of intracellular calcium and protein kinase C (PKC) activation. 5-HT₂ receptor stimulation also results in neuronal excitation in a variety of brain regions, likely involving the closure of potassium channels. A 5-HT₂ receptor-mediated increase in excitatory postsynaptic currents is also often observed, which is thought to be mediated either directly or indirectly through increased release of glutamate (Lambe & Aghajanian, 2006a, 2006b; Marek, 2010).

It is now recognised that 5-HT₂ receptor signalling goes well beyond activation of the phospholipase C/PKC pathway. For instance, non-canonical signalling pathways associated with 5-HT_{2A} receptor activation include phospholipase A₂, the ERK pathway and signalling via small G proteins (eg. Rho A, Rab4), and there are similar such findings for 5-HT_{2B}, and 5-HT_{2C} receptors (for review see Bockaert *et al.*, 2010; Halberstadt, 2015; McCorvy & Roth, 2015; Maroteaux *et al.*, 2016). Interesting findings are emerging regarding non-canonical signalling by 5-HT₂ receptors. Specifically, the 5-HT_{2C} receptor is able to activate ERK via a G protein-independent mechanism through recruitment of calmodulin and β -arrestin (Labasque *et al.*, 2008). Furthermore, recent studies on non-canonical signalling by the 5-HT_{2B} receptor found evidence of ligand-dependent signals, and then used the crystal structure of the receptor to identify high resolution, structural basis for the biased signalling (Wacker *et al.*, 2013; Wacker *et al.*, 2017). This

evidence of ligand-dependent signalling through 5-HT₂ receptors has relevance to the psychotropic effects of 5-HT_{2A} receptor agonists, some of which are hallucinogenic but not all (Gonzalez-Maeso *et al.*, 2007), and may also explain the long lasting effects of LSD which are difficult to explain on the basis of pharmacokinetics alone (Wacker *et al.*, 2017). However, the signalling pathways mediating the characteristic effects of hallucinogens have not been identified conclusively. Biased agonism at 5-HT₂ receptors offers intriguing possibilities for therapeutic potential (eg. avoidance of hallucinogenic properties) although this is yet to be explored, keeping in mind that 5-HT_{2A} receptor agonists have profound effects on vascular and other smooth muscle in addition to their psychotropic effects. Also, findings of the existence of constitutive activity at 5-HT_{2A} and 5-HT_{2C} receptors, and 5-HT₂ receptor ligands with inverse agonist properties, provides further avenues for 5-HT₂ receptor drug development (eg. Aloyo *et al.*, 2009).

The remaining metabotropic 5-HT receptors to be considered, specifically 5-HT₄, 5-HT₆, and 5-HT₇ receptors, are G_s-coupled and thus activate adenylyl cyclase to increase cAMP. At the electrophysiological level, 5-HT₄ receptor activation on neurons is associated with a slow membrane depolarization mediated by a reduction of a slow after-hyperpolarization potential, and facilitation of L-type calcium channels through protein kinase A activation (Andrade & Chaput, 1991; Birnstiel & Beck, 1995). Similarly, the neuronal 5-HT₇ receptor is also frequently associated with a direct depolarizing or excitatory effect, also likely mediated by actions on slow after-hyperpolarization and L-type calcium channels (Bacon & Beck, 2000; Andrade, 2006).

As with the other metabotropic 5-HT receptors, the 5-HT₄ receptor generates a diversity of signals independent of the second messenger. In addition, both the 5-HT₄ and 5-HT₆ receptors provide further examples of metabotropic 5-HT receptors that are capable of non-canonical signalling. For example, 5-HT₄ receptor stimulation activated ERK in cultured cells and neurons in a manner that was G protein-independent (G_q, G_i, G_o) but rather, dependent on Src tyrosine kinase (Barthet *et al.*, 2007; Bockaert *et al.*, 2010), and there are analogous observations for 5-HT₆ receptors (Yun *et al.*, 2007).

As a complement to the slow signalling elicited by metabotropic 5-HT receptors, the ionotropic 5-HT₃ receptor mediates rapid synaptic transmission. All five human 5-HT₃ receptor genes (*5-HT3A-3E*) are homologous with other members of the Cys - Cys loop ligand-gated channel superfamily, e.g. nicotinic, GABA_A, glutamate or glycine receptors (Barnes *et al.*, 2009). Although there is uncertainty regarding the composition of the native 5-HT₃ receptor(s) in the brain, pentameric co-assemblies of 5-HT_{3A} and 5-HT_{3B} subunits is a likely common occurrence (for reviews see Niesler, 2011; Thompson & Lummis, 2013). Allosteric modulators of the 5-HT₃ receptor are emerging to add to the possibilities for 5-HT₃ receptor manipulation for therapeutic benefit (e.g. Trattnig *et al.*, 2012; Newman *et al.*, 2013).

Overall the complexity of neuronal signalling events elicited by 5-HT receptors is yet to be fully revealed. The metabotropic 5-HT receptors are clearly capable of both G protein-dependent and G protein-independent signalling, and it is also clear that the diverse signals generated by these receptors can be biased according to the agonist used. Moreover, as covered elsewhere, further complexity arises from the large number of protein partners influencing cellular localization and trafficking as well as signal tuning of 5-HT receptors, their homo- or heterodimerization with other GPCRs, and the alternative RNA splicing and editing of certain 5-HT receptors (especially 5-HT_{2C}, 5-HT₄ and 5-HT₇ receptors) to generate variability in function (Hannon & Hoyer, 2008; Bockaert *et al.*, 2010; McCorvy & Roth, 2015).

XVIII. C. Expression of 5-HT receptors in the brain

Application of a combination of techniques such as receptor autoradiography, *in situ* hybridisation and immunocytochemistry has revealed maps of 5-HT receptor subtype distribution in the brain, that are largely similar across a range of vertebrate species (although of note the 5-HT_{1e} receptor is not expressed in rodents, forebrain 5-HT₃ receptors are differentially expressed across species and the full length 5-HT_{5b} receptor is not expressed in man). The use of BAC transgenic mice engineered to express a fluorescent or coloured reporter genes under the control of specific 5-HT receptor promoters, for instance as in the case of 5-HT_{2A} receptor (Weber & Andrade, 2010), reveals further anatomical detail of 5-HT receptor distribution. Although the 5-HT receptor maps are largely based on data collected from the rodent brain, a high-resolution PET atlas of four 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT₄ receptors) and the 5-HT transporter was recently described for the human brain (Beliveau *et al.*, 2017). It is now clear

from these mapping studies that each 5-HT receptor subtype has a unique distribution pattern in the brain although one that often overlaps with that of other 5-HT receptor subtypes. These differential distribution patterns suggest that different 5-HT receptor subtypes are likely associated with distinct CNS functions amenable to manipulation using 5-HT receptor subtype selective pharmacological agents.

XVIII. C. Presynaptic 5-HT receptors

Two of the 14 5-HT receptors are highly expressed presynaptically (i.e. expressed by 5-HT neurons themselves). Thus, 5-HT_{1A} receptors are located on the soma and dendrites of 5-HT neurons, whereas 5-HT_{1B} receptors are expressed at the soma but then trafficked down the axons to the terminals (Riad *et al.*, 2000). It is firmly established from both *in vitro* and *in vivo* models that 5-HT_{1A} and 5-HT_{1B} receptors function as autoreceptors and exert direct inhibitory control over the firing of 5-HT neurons and terminal 5-HT release, respectively. Thus, studies over 40 years ago finding that 5-HT itself, or non-selective 5-HT agonists such as LSD, inhibited the efflux of preloaded radiolabelled 5-HT from rodent brain slice preparations where followed up by extensive pharmacological analysis which identified that this effect was mediated by 5-HT_{1B} receptors located on 5-HT nerve terminals (Gothert & Weinheimer, 1979; Mounsey *et al.*, 1982; Engel *et al.*, 1986; Fink & Gothert, 2007). Similarly detailed pharmacological studies using electrophysiological recordings of 5-HT neurons and *in vivo* microdialysis measurements of 5-HT release characterised the autoreceptor function of somatodendritic 5-HT_{1A} receptors (e.g. Vandermaelen & Aghajanian, 1983; Sharp *et al.*, 1989; Adell & Artigas, 1998).

There are more recent reports of the presence of other 5-HT receptor subtypes in the midbrain raphe nuclei, in particular 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_{5A}. However, with the exception of 5-HT_{2C} (located on raphe GABAergic interneurons and not 5-HT neurons), expression levels of these receptors in the midbrain raphe are low and their functional significance in terms of 5-HT neuron control is not certain. Nevertheless, recent findings have discovered that feedback control of 5-HT neurons is not likely limited to 5-HT₁ autoreceptors but includes 5-HT receptors located on postsynaptic targets that have the physiological effects of 5-HT autoreceptors but use additional 5-HT receptor subtypes, and operate via neural inputs to 5-HT neurons. For example, evidence supports a role for postsynaptic 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors in the inhibitory control of 5-HT neurons, whereas 5-HT₄ and 5-HT₆ receptors are excitatory in this regard (Ge and Barnes, 1996; Sharp *et al.*, 2007; Sharp, 2010; Brouard *et al.*,

2015). Many of these feedback pathways appear to be localised on cortical pathways projecting back to the midbrain raphe nuclei (5-HT_{1A}, 5-HT_{2A}, 5-HT₄, 5-HT₆ receptors) although contributions from non-5-HT neurons such as habenula inputs to the raphe (5-HT_{2C} receptors) further emphasise the complexity of 5-HT neuron control.

XVIII. D. Postsynaptic 5-HT receptors

5-HT receptor mapping studies demonstrate that the majority of 5-HT receptor subtypes are located postsynaptically (ie expressed by non-5-HT neurons, sometimes referred to as heteroreceptors; including the receptor subtypes involved in feedback control of 5-HT neurons) and that each 5-HT receptor subtype has an expression pattern that is distinct but often overlaps with that of other 5-HT receptors. Even 5-HT receptors from the same family have different CNS distributions (eg 5-HT_{2A} versus 5-HT_{2C}, 5-HT_{1A} versus 5-HT_{1B}). Some 5-HT receptors are expressed at higher levels than others, in particular 5-HT_{1A} and 5-HT_{2A} receptors are amongst the most abundant whereas in comparison levels of 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2B} and 5-HT_{5A} receptors are much less abundant. Detailed maps of 5-HT receptor binding sites, protein and mRNA distribution in the brain are reported in a number of review articles (Mengod *et al.*, 2006; Mengod *et al.*, 2010; Palacios, 2016).

At the macro-level, and in keeping with the widespread 5-HT innervation of the brain, 5-HT receptors of different types are expressed in many brain regions that play key roles in numerous CNS functions. For example, regions rich in 5-HT receptors include cortical and limbic areas, (5-HT_{1A}, 5-HT_{2A/2C}, 5-HT₃, 5-HT₄, 5-HT₆ receptors), the basal ganglia (5-HT_{1B}, 5-HT₄, 5-HT₆ receptors), mesolimbic pathways (5-HT_{1B}, 5-HT_{2A/2C}, 5-HT₄ receptors), hypothalamus (eg. paraventricular and arcuate nuclei; 5-HT_{2C} receptor), suprachiasmatic nucleus (5-HT₇ receptor), trigeminal nucleus (5-HT_{1B/1D} receptors), dorsal vagal complex (encompassing the area postrema and nucleus tractus solitarius; 5-HT₃ receptor), as well as the spinal cord (dorsal root ganglia; 5-HT_{2B/2C}, 5-HT₃ receptors). This list depicting 5-HT receptor distribution is of course not exclusive, and does not take into account the relative density of receptors in the different regions (e.g. in many regions 5-HT_{2C} receptors are present at much lower densities than 5-HT_{2A} receptors [with the remarkable exception of the choroid plexus], and this is also the case for 5-HT_{1D} compared to 5-HT_{1B} receptors).

XVIII. E. Cellular localisation of CNS 5-HT receptors

The principal cellular location of CNS 5-HT receptors is neurons; indeed, evidence for the expression of 5-HT receptors by adult native non-neural cells such as glial cells is at best, inconsistent – for example, reports of glial cell expression of 5-HT_{1A} and 5-HT_{2A} receptors appear to be dependent on the antibody used. However, emerging evidence suggests that activated microglia may express 5-HT_{2B} and other 5-HT receptors (Krabbe *et al.*, 2012; Kolodziejczak *et al.*, 2015). Nevertheless, 5-HT receptors are undoubtedly present in cells of the cerebrovasculature as most evident for 5-HT_{1B} receptors (Riad *et al.*, 1998).

On the whole, the expression of specific 5-HT receptors is not restricted to particular neuron types. For example, amongst the complex microcircuitry of the cerebral cortex, hippocampus and amygdala, 5-HT_{1A} and 5-HT_{2A} receptors are expressed both on pyramidal neurons (glutamatergic) and certain classes of GABAergic interneurons (in particular those expressing parvalbumin). Elsewhere in the brain 5-HT_{1A} receptors are localised on 5-HT neurons in the raphe nuclei (see above) and cholinergic neurons in the septum, whereas 5-HT_{2A} receptors are expressed by midbrain dopamine neurons. On the other hand, 5-HT₃ receptors in rodent cortex and hippocampus mark a specific population of GABA interneurons with distinct chemical, morphological and anatomical properties (Lee *et al.*, 2010), and these receptors are also present in pyramidal neurons, particularly in humans (Brady *et al.*, 2007). In comparison, cortical 5-HT₆ receptors are preferentially (although not exclusively) expressed by pyramidal cells (Helboe *et al.*, 2015).

Not surprisingly there are multiple interactions between 5-HT and other neurotransmitter systems, and particular attention has been paid to 5-HT interactions with the other monoamines, noradrenaline and dopamine. These interactions are highly complex involving multiple 5-HT receptor subtypes located at pre- and postsynaptic sites within complicated, overlapping circuitry, such that prediction of the overall effect of 5-HT is often not possible. However, at the level of individual receptors the rules can be more straightforward. For example, the distribution of 5-HT_{2A} and 5-HT_{2C} receptors within the mesolimbic dopamine system has allowed the general consensus that 5-HT_{2A} receptors stimulate and 5-HT_{2C} receptors inhibit dopamine transmission (Howell & Cunningham, 2015).

Given the differential expression patterns of the 5-HT receptors, it is highly unlikely that all 14 5-HT receptors are expressed by a single neuron. Evidence from earlier double and triple labelling *in situ* hybridisation studies support the idea that a single postsynaptic synapse may express a combination of 2-3 5-HT receptors (Mengod *et al.*, 2010). Studies combining whole-cell patch clamp recordings with single cell reverse transcriptase polymerase chain reaction (RT-PCR) to characterize 5-HT receptor expression, are in keeping with this idea. Thus, analysis of the 5-HT receptor mRNA content of neurons of the bed nucleus of the stria terminalis revealed that individual neurons could be subdivided according to the prominent expression of 2-3 distinct 5-HT receptor transcripts in largely excitatory/inhibitory combinations (eg. 5-HT_{1A}/5-HT₇, 5-HT₃/5-HT₇, 5-HT_{1B}/5-HT₄, 5-HT_{1A}/5-HT_{1B}/5-HT_{2A}, and 5-HT_{1A}/5-HT_{2A} receptors) that matched electrophysiological observations (Hazra *et al.*, 2012). A similar analysis of the 5-HT receptor mRNA content of single neurons of the preoptic nucleus revealed two types of neurons that predominantly expressed a combination of inhibitory (5-HT_{1A}) and excitatory (5-HT_{2C}, 5-HT₄, 5-HT₇) 5-HT receptors whereas others expressed excitatory 5-HT receptors alone, again in keeping with electrophysiological findings (Sangare *et al.*, 2016). This evidence of 5-HT receptor expression conferring both excitatory and inhibitory signalling effects of 5-HT at the single cell level is born out more generally in electrophysiological experiments recording the effects of either bath application of 5-HT or electrical and optogenetic activation of 5-HT neurons (Andrade, 2006; Andrade & Beck, 2010; Sengupta *et al.*, 2017).

Generally speaking, there is a very good match between 5-HT receptor mRNA and protein (e.g. Mengod *et al.*, 2010), suggesting that the majority of 5-HT receptor proteins are not trafficked significantly along axons and reside largely at the levels of the neuronal soma and dendrites. Notable exceptions to this rule are 5-HT_{1B} and 5-HT₃ receptors. The former are trafficked either to nerve terminals of 5-HT neurons where they function as autoreceptors, or to nerve terminals of other neurons and especially GABA neurons where they modulate GABA release. On the other hand, it is estimated that about 70–80% of the 5-HT₃ receptors are located on nerve endings where their role is also to modulate neurotransmitter release e.g. dopamine, cholecystokinin, glutamate, acetylcholine and GABA (Hannon & Hoyer, 2008; Walstab *et al.*, 2010). A final point of note is that unusually, 5-HT₆ receptors are expressed on neuronal primary cilia (Hamon *et al.*, 1999), the functions of which remain obscure.

At the ultrastructural level, electron microscopy studies show that all metabotropic 5-HT receptors visualised thus far are located extrasynaptically, which has reinforced the idea that 5-HT principally signals via volume transmission (Descarries *et al.*, 2006). However, synaptic localisation of 5-HT receptors cannot be excluded as these are challenging studies which are often limited by the properties and specificity of available antibodies. Moreover, it is beyond doubt that 5-HT is present in vesicles that are synaptic as well as non-synaptic. An additional complexity in signalling at 5-HT synapses is co-transmission, with co-released glutamate is emerging as a key player (e.g. Sengupta *et al.*, 2017).

XVIII. F. Behavioural roles of 5-HT receptors in the brain

XVIII. F. 1. Introduction

Knowledge of the regional and cellular location of 5-HT receptors in the brain has been immensely helpful in understanding a vast literature on the behavioural effects of pharmacological and genetic manipulation of 5-HT receptors. Collectively these developments are casting light on the likely behavioural functions of 5-HT receptors. As yet no behavioural response can be confidently ascribed to activation of the CNS 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F} or 5-HT₅ receptors.

XVIII. F. 2. 5-HT₁ receptor family

XVIII. F. 2. a. 5-HT_{1A} receptors

The behavioural functions of 5-HT_{1A} receptors have been the focus of much research given the widespread and high CNS expression of these receptors, combined with the availability of a large number of selective 5-HT_{1A} receptor ligands. It has long been known that in rodents, administration of 8-OH-DPAT and other 5-HT_{1A} receptor agonists causes a wide range of behavioural and physiological effects including changes in motor function (especially induction of the 5-HT behavioural syndrome), hyperphagia, hypothermia, altered sexual behaviour and changes in pain threshold. Also, there is a large literature demonstrating that 5-HT_{1A} receptor agonists have antidepressant and anxiolytic activity, and influence a range of cognitive domains relevant to symptoms of schizophrenia (for review see Traber & Glaser, 1987; Handley, 1995; Newman-Tancredi, 2010). These findings accord with preclinical and clinical evidence implicating changes in 5-HT_{1A} receptors in the pathophysiology of a variety of psychiatric

illnesses, including depression, anxiety and other stress-related disorders, and schizophrenia. Appropriate 5-HT_{1A} receptor function also appears critical for antidepressant drug efficacy (Richardson-Jones *et al.*, 2010; Samuels *et al.*, 2016). The diverse behavioural effects of 5-HT_{1A} receptor agonists are likely to involve an action at 5-HT_{1A} receptors in multiple forebrain and midbrain sites; the contribution of presynaptic and postsynaptic 5-HT_{1A} receptors to specific behavioural effects of 5-HT_{1A} receptor agonists is not always certain and indirect effects on other transmitter systems, in particular noradrenaline and dopamine, may often be involved.

Despite these complexities, a significant body of evidence links the decrease in 5-HT transmission evoked by 5-HT_{1A} autoreceptor activation to anxiolytic effects whereas an increase in 5-HT transmission evoked by activation of postsynaptic 5-HT_{1A} receptors is associated with antidepressant effects (see Barnes & Sharp, 1999 and Section II in the present review). Much of the evidence for this has come from psychopharmacological studies in animals and humans, and it is being increasingly reinforced by studies using advanced genetic mouse models which have the power to make targeted manipulation of pre- versus postsynaptic 5-HT_{1A} receptors. In particular, genetic mouse constructs with selective knockdown of 5-HT_{1A} autoreceptor expression generates an increase in anxiety phenotypes (Richardson-Jones *et al.*, 2011). In contrast, selective knockdown of postsynaptic 5-HT_{1A} receptors is associated with depressive-like phenotype, suggesting a differential impact of pre- versus postsynaptic 5-HT_{1A} receptors on anxiety and depression mechanisms. Paradoxically, although these phenotypes associated with genetic manipulation can be reproduced by pharmacological means, they are only observed when 5-HT_{1A} receptor suppression is initiated in early life and not during adulthood. Thus, these data point to a developmental mechanism, that is, altered pre- and postsynaptic 5-HT_{1A} receptor signalling during development causing an adult behavioural phenotype through impacting on the normal formation of anxiety/depression circuitry (Richardson-Jones *et al.*, 2011; Garcia-Garcia *et al.*, 2014; Garcia-Garcia *et al.*, 2016). An analogous theory has been posited to explain the behavioural phenotype of 5-HT transporter mutant mice (Ansoorge *et al.*, 2004). Consideration of developmental mechanisms may therefore be appropriate when interpreting the behavioural phenotype of other mouse models with altered 5-HT receptor expression (Gingrich *et al.*, 2003; Berger & Tecott, 2006; O'Leary & Cryan, 2010).

Aside from the interesting picture emerging through genetic models, there is increasing evidence that behavioural effects of 5-HT_{1A} agonist administration are dependent on the agonist used. Divergent effects of certain 5-HT_{1A} agonists have been reported across a range of models of cognition and emotional behaviour, as well as in relevant neurochemical and neurophysiological paradigms. These findings raise the possibility that different behaviours are being evoked by different signals due to biased agonism, and differential sensitivity of pre- and postsynaptic 5-HT_{1A} receptors to the agonists may be a contributing factor. Thus, functionally and anatomically distinct subpopulations of 5-HT_{1A} receptors combined with an emerging diversity of biased 5-HT_{1A} receptor agonists, forecasts new categories of 5-HT_{1A} drugs for selective behavioural manipulation and thereby potential multiple therapeutic applications.

XVIII. F. 2. b. 5-HT_{1B} receptors

Preclinical studies on the behavioural effects of the 5-HT_{1B} receptor ligands have been hampered by the lack of drug tools with sufficient selectivity or brain penetration, and this continues to be somewhat problematic in the case of 5-HT_{1B} receptor agonists. Early studies on the behavioural effects of 5-HT_{1B} receptor agonists and antagonists in rodents have been extensively reviewed (Lucki, 1992; Middlemiss & Tricklebank, 1992; Barnes & Sharp, 1999). These earlier findings, combined with more recent preclinical and clinical studies, emphasise a role for 5-HT_{1B} receptors in depression and anxiety behaviours on the one hand (for review see Ruf & Bhagwagar, 2009; Fakhoury, 2016) and aggression and impulse control on the other (for review see Nautiyal *et al.*, 2015). Moreover, the role of pre- versus postsynaptic 5-HT_{1B} receptors in these behaviours is beginning to be addressed utilising tissue-specific and time-dependent conditional 5-HT_{1B} receptor mutant mice.

Evidence from earlier neuropharmacological studies suggests on the whole that 5-HT_{1B} receptor agonists have antidepressant effects in animal models whereas 5-HT_{1B} receptor antagonists are anxiolytic (Fakhoury, 2016). The findings with 5-HT_{1B} receptor antagonists are to some extent consistent with evidence that mice with a global 5-HT_{1B} receptor knockout demonstrate anxiolytic and antidepressant-like phenotypes (Mayorga *et al.*, 2001; Jones & Lucki, 2005; Bechtholt *et al.*, 2008). Moreover, it is reported these phenotypic effects can be recapitulated in genetic mice with selective loss of 5-HT_{1B} autoreceptors (Nautiyal *et al.*, 2015). The latter group argue that relative to 5-HT_{1B} autoreceptors, postsynaptic 5-HT_{1B} receptors may

have an opposing effect on anxiety and depressive behaviours, thereby potentially accounting for the divergent actions of 5-HT_{1B} receptor agonists and antagonists noted above. Importantly, an anxiolytic and antidepressant-like phenotype was generated by knockout of 5-HT_{1B} autoreceptors in adulthood and not during early postnatal life, thereby making a developmental mechanism unlikely (Nautiyal *et al.*, 2015). Collectively, these data suggest that drugs that selectively block 5-HT_{1B} autoreceptors may be useful for the treatment of anxiety and depression. Currently there are no drugs with this property although developments with biased 5-HT_{1A} receptor agonists (see above) offer the potential for such agents in the future.

Another interesting phenotype of mice with a global 5-HT_{1B} receptor knockout is increased aggression and impulsivity. This finding fits in with earlier evidence that certain 5-HT_{1B} receptor agonists ('serenics') have anti-aggressive properties (Olivier *et al.*, 1995). Moreover, these data fit with a consistent line of evidence associating reduced brain 5-HT transmission with high levels of impulsivity and aggression. The recently available conditional 5-HT_{1B} receptor knockout mice has allowed further examination of the role of pre- versus postsynaptic 5-HT_{1B} receptors in aggression and impulsivity (Nautiyal *et al.*, 2015). It was found that heightened aggression and impulsivity was linked to loss postsynaptic 5-HT_{1B} receptors and not 5-HT_{1B} autoreceptors. However, whilst the increase in aggression involved a development mechanism (i.e. recapitulated by early life knockout), the increase in impulsivity was separable and was linked to loss of postsynaptic 5-HT_{1B} receptors in adulthood. These data raise the possibility that pharmacologic agents targeting 5-HT_{1B} receptors may be therapeutically effective in disorders associated with loss of impulse control. At least in the case of 5-HT_{1B} receptor agonists, these agents have been widely used in the clinic since the first development of sumatriptan for the acute treatment of migraine (Humphrey, 2008). It may be argued at length whether the effects of triptans in migraine involve a neuronal component versus vascular/inflammatory mechanisms (Humphrey & Goadsby, 1994), triptans are considered safe in terms of CNS adverse effects.

XVIII. F. 3. 5-HT₂ receptor family

The behavioural effects of 5-HT₂ receptor agonists in rodents are many, ranging from changes in both unconditioned (e.g. head-twitches, increased motor activity, hypophagia, hyperthermia) and conditioned responses (e.g. punished responding, drug discrimination) (for review see Koek *et al.*, 1992; Barnes & Sharp, 1999; Halberstadt, 2015). It has become possible to identify the role of the different 5-HT₂ receptor subtypes in these

behaviours with some degree of confidence, through the availability of highly selective antagonists (for each of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors) and agonists (especially 5-HT_{2C} receptor agonists) as well as mutant mice with the different receptors selectively knocked out (for review see Berger & Tecott, 2006; O'Leary & Cryan, 2010; Halberstadt, 2015; Di Giovanni & De Deurwaerdere, 2016).

XVIII. F. 3. a. 5-HT_{2A} receptors

It is clear from detailed pharmacological analysis that the 5-HT_{2A} receptor mediates the effects of serotonergic hallucinogens such as LSD and psilocybin in various behavioural models in animals including drug discrimination, the head-twitch response, and locomotion (Halberstadt, 2015). The evidence is equally strong that the 5-HT_{2A} receptor mediates the hallucinogenic effects of these drugs in humans. Prior to their prohibition in the late 1960s, psychedelic drugs like LSD and psilocybin were used extensively in the treatment of major depression as well as anxiety-related disorders and addictions, and results were generally encouraging. Despite the restrictions that remain in place around these agents, there has been renewed interest in their use for experimental medicine studies and therapeutic purposes. Psilocybin in particular has been subject to investigation in a range of human psychopharmacological and brain imaging studies, which have contributed proof-of-principle and dose/safety data for clinical trials (Nutt, 2016). Moreover, recent clinical data demonstrate that acute administration of psilocybin (combined with psychological support) causes a sustained lowering of depression and anxiety ratings in cancer patients (Ross et al, 2016; Griffiths et al 2016) and treatment resistant-depression (Carhart-Harris *et al.*, 2016), which is likely to encourage further studies in these and other patient groups.

The potent 5-HT_{2A} receptor antagonist properties of many second generation antipsychotics has been linked to the reported superior antipsychotic efficacy and reduced side effect profile of these agents compared to early drugs (Meltzer & Massey, 2011). Although selective 5-HT_{2A} receptor blockade is unlikely to be sufficient to generate a useful antipsychotic effect *per se*, evidence that the 5-HT_{2A} receptor inverse agonist pimavanserin has antipsychotic actions in relevant animal models (Vanover *et al.*, 2006) and in certain patient populations (Fox, 2014) suggests a novel alternative way to treat psychosis.

Recent reports that 5-HT_{2A} receptor antagonists augment the effect of 5-HT uptake inhibitors in preclinical models (Marek *et al.*, 2003; Marek *et al.*, 2005; Boothman *et al.*, 2006), may link to evidence that drugs with 5-HT_{2A} receptor antagonist properties are helpful as augmenting agents in treatment resistant depression (Marek *et al.*, 2003). Although the mechanism behind this effect of 5-HT_{2A} receptor blockade is not certain, it may link to evidence of an inhibitory 5-HT_{2A} receptor-mediated feedback on 5-HT neurons (Sharp *et al.*, 2007). 5-HT_{2A} receptor blockade has also been associated with impulse control; thus, selective 5-HT_{2A} receptor antagonists decrease impulsivity in animal models (Winstanley *et al.*, 2004; Winstanley, 2011) and there is support for this action from psychopharmacological studies in humans (Rock *et al.*, 2013). Interestingly, both lithium and the organoselenium compound, ebselen, which like lithium blocks signalling through phosphoinositide pathway, inhibit 5-HT_{2A} receptor function and both agents reduce impulsivity in animal models and humans (Singh *et al.*, 2013; Masaki *et al.*, 2016). This raises the possibility that 5-HT_{2A} receptor antagonists/inverse agonists as well as novel lithium mimetics may have utility in the control of disorders of impulse control.

XVIII. F. 3. b. 5-HT_{2B} receptors

The combination of low 5-HT_{2B} receptor expression in the brain and the lack of selective 5-HT_{2B} receptor ligands has hampered progress in establishing whether these receptors are able to elicit robust behavioural effects. This situation has moved forward with the development of 5-HT_{2B} knockout mice, which have striking phenotypes across a range of modalities including deficits in sensorimotor gating, social interaction, attention, learning and memory, as well as elevated impulsivity and altered sleep patterns (Pitychoutis *et al.*, 2015). Furthermore, some of these effects (sleep, sensorimotor gating) can be phenocopied by administration of a selective 5-HT_{2B} receptor antagonist. However, 5-HT_{2B} knockout is also associated with severe cardiac abnormalities and embryonic and postnatal lethality, which might lead to neurodevelopment issues in surviving animals that could confound the interpretation of these adult CNS phenotypes (as noted above). Although studies involving conditional 5-HT_{2B} knockout strategies and further pharmacological phenocopying are awaited, these data raise interesting possibilities regarding the functional role of CNS 5-HT_{2B} receptors. As noted elsewhere (Hutcheson *et al.*, 2011), 5-HT_{2B} receptor agonism as a therapeutic approach is fraught by clinical evidence that such agents may induce valvulopathies, pulmonary hypertension that can have lethal consequences: thus, many therapeutic agents with 5-HT_{2B} receptor agonist properties (eg. fenfluramine, pergolide, cabergoline) have now been withdrawn from the market (Hutcheson *et al.*, 2011). Nevertheless, recent data

showing biased agonism at the 5-HT_{2B} receptor (Wacker *et al.*, 2013) offers the potential for future 5-HT_{2B} receptor agonists that may be devoid of these systemic adverse effects.

XVIII. F. 3. c. 5-HT_{2C} receptors

Early studies recognised that several behavioural responses were likely associated with activation of central 5-HT_{2C} receptors including hypolocomotion, hypophagia, anxiety, penile erection and hyperthermia (for review see Barnes & Sharp, 1999). Initially these associations were largely based on observations using non-selective 5-HT_{2C} receptor ligands. However, with increased availability of 5-HT_{2C} receptor selective compounds and the creation of 5-HT_{2C} knock out mice, evidence for the involvement of the 5-HT_{2C} receptor in many of these responses is now compelling (for review see Di Giovanni & De Deurwaerdere, 2016). Moreover, these developments expanded the CNS processes likely to be under 5-HT_{2C} receptor control to include various behaviours and cognitions linked to compulsive drug- and food-seeking, as well as the central control of energy homeostasis, oral dyskinesia, wakefulness and even control seizure threshold.

In the last decade or so there has been considerable research interest in the link between 5-HT_{2C} receptors and addictive behaviours associated with food and psychostimulant drugs (Higgins & Fletcher, 2015; Howell & Cunningham, 2015). It is now clear that 5-HT_{2C} receptor agonists reduce palatable food consumption and other effects associated with obesity (increased body mass and fat content; Heisler *et al.*, 2006; Heisler *et al.*, 2007; Lam *et al.*, 2008; Higgs *et al.*, 2011; 2016). These agents can also disrupt various steps in the sequence of events leading up to compulsive use of addictive drugs such as cocaine and nicotine (including stimulant action, positive reinforcement, behavioural sensitization, reinstatement). The mechanism in part is likely to involve a 5-HT_{2C} receptor-mediated decrease in mesolimbic dopamine function but interactions with other transmitter systems (especially cortical glutamate) are likely to play a role. In addition, the lowering of food intake and metabolism by 5-HT_{2C} receptor agonists is likely to involve an action on hypothalamic nuclei that promote satiety and regulate energy balance pathways (Heisler *et al.*, 2006; Heisler *et al.*, 2007; Lam *et al.*, 2008).

Interestingly, separate studies have revealed a link between 5-HT_{2C} receptors and impulse control; thus 5-HT_{2C} receptor agonists reduce premature responses whereas 5-HT_{2C} receptor antagonists have the opposite effect (Higgins *et al.*, 2003; Winstanley *et al.*, 2004; Fletcher *et al.*, 2007). Given that impulsivity may influence many aspects of addictive behaviour, 5-HT_{2C} receptors may modulate addiction indirectly via its effects on impulsive behaviour.

Many of these experiments detect opposing interactions between 5-HT_{2C} receptors and 5-HT_{2A} receptors (e.g. 5-HT_{2A} receptor antagonists also lower impulsivity), that were detected in earlier neuropharmacological studies (Berendsen & Broekkamp, 1990). This opposing interaction between 5-HT_{2C} and 5-HT_{2A} receptors could explain the poor efficacy in drug addiction models of drugs that elevate 5-HT itself (SSRIs, fenfluramine). Consequently, it is proposed that an optimal way to control addictive behaviour (and also avoid potential adverse effects associated with 5-HT_{2C} receptor agonists that have off-target effects at 5-HT_{2A} and 5-HT_{2B} receptors) may be a drug which combines in the same molecule agonist activity at the 5-HT_{2C} receptor and antagonist activity at the 5-HT_{2A} receptor (Anastasio *et al.*, 2015; Higgins & Fletcher, 2015). Additional approaches for future investigation could include 5-HT_{2C} receptor agonists with biased agonist properties or positive allosteric modulators of the 5-HT_{2C} receptor.

XVIII. F. 4. 5-HT₃ receptors

Outside of the well-established role of central (as well as peripheral) 5-HT₃ receptors in the control of emesis, 5-HT₃ receptors have been linked to multiple behavioural effects, ranging from changes in anxiety and cognition to altered pain processing and sensitivity to addictive drugs. Most of the original evidence for this comes from reports of the behavioural effects of 5-HT₃ receptor ligands (mostly antagonists) in animal models; these and more recent findings are extensively reviewed elsewhere (Costall & Naylor, 1992; Bentley & Barnes, 1995; Barnes & Sharp, 1999; Walstab *et al.*, 2010; Gupta *et al.*, 2016). However, many of the behavioural effects observed in preclinical investigations are not confirmed by studies of selective 5-HT₃ receptor antagonists in clinical populations (Bentley & Barnes, 1995; Walstab *et al.*, 2010). The apparent failure for the translation of these preclinical findings could in part be explained by sub-optimal clinical dosing, since a bell-shaped dose-response curves are often observed for 5-HT₃ receptor antagonists, particularly in relation to CNS effects. Nevertheless, the involvement of 5-HT₃ receptors in some of these behaviours receives support

from more recent studies of mutant mice with altered 5-HT_{3A} receptor expression. In particular, support for a role for 5-HT₃ receptors in depression/anxiety-related behaviours, learning and memory, and pain processing comes from the phenotypic analysis of transgenic mice with 5-HT_{3A} receptor knockout or overexpression (Harrell & Allan, 2003; Kelley *et al.*, 2003; Berger & Tecott, 2006). However, interpretation of the phenotypes of these mice is complicated by findings that, i) they are not always phenocopied by pharmacological agents, ii) they are dependent on the mouse background strain, and iii) over-expression and deletion of the 5-HT_{3A} receptor sometimes produced similar effects (for review see Berger & Tecott, 2006; O'Leary & Cryan, 2010).

More recent evidence associating 5-HT₃ receptors with emotional behaviours and cognition comes from findings with vortioxetine, which has a complex pharmacology leading to potent inhibition of 5-HT₃ receptors, although the drug is also a 5-HT₇ and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and 5-HT transporter inhibitor. Vortioxetine has significant antidepressant and procognitive activity in both rodent models and clinical trials (Mork *et al.*, 2012; Sanchez *et al.*, 2015) and is currently marketed as an antidepressant with cognition enhancing properties. In spite of vortioxetine's polymodal pharmacology, inhibition of 5-HT₃ receptors is thought to play a prominent role in its mechanism of action. Thus, in rodents vortioxetine preferentially occupies 5HT₃ receptors and the 5-HT transporter at low doses, and either 5-HT₃ receptor blockade alone produces similar effects to vortioxetine or effects of vortioxetine can be replicated by co-administration of an SSRI and a 5-HT₃ receptor antagonist (Mork *et al.*, 2012; Sanchez *et al.*, 2015). One current mechanistic explanation of these findings is that blockade of 5-HT₃ receptors on specific populations of GABA interneurons in the cerebral cortex contributes to vortioxetine's action (Riga *et al.*, 2016).

XVIII. F. 5. 5-HT₄ receptors

Early preclinical studies detected positive effects of 5-HT₄ receptor agonists on cognitive performance, and also a reduction in anxiety-related behaviours (for review see Barnes & Sharp, 1999), and these observations have proved consistent in later work as recently reviewed by others (Bockaert *et al.*, 2011; Claeysen *et al.*, 2015; Hagen & Manahan-Vaughan, 2016). Stemming in part from studies of 5-HT₄ knockout mice (Compan *et*

al., 2004), a role of 5-HT₄ receptors in feeding behaviour is also seems clear, with 5-HT₄ receptor agonists and antagonists have hypo- and hyperphagic properties, respectively (Jean *et al.*, 2007; Bockaert *et al.*, 2011).

Pro-cognitive effects of 5-HT₄ receptor agonists have been described across a range of species and in a variety of experimental paradigms that model different aspects of short- and long-term memory, many of them dependent on hippocampus where 5-HT₄ receptors are reasonably abundant (Hagena & Manahan-Vaughan, 2016). These agents also reverse the cognitive deficits induced by factors such as ageing, pharmacological interventions (e.g. muscarinic antagonists) and Alzheimer's disease-like pathology. The mechanisms underlying the procognitive effects of 5-HT₄ receptor agonists are not certain but may be mediated by one or more of increased release of acetylcholine, induction of synaptic plasticity, increased synaptic spine formation and altered hippocampal network properties (see Boddeke & Kalkman, 1990; Claeysen *et al.*, 2015; Hagena & Manahan-Vaughan, 2016). Administration of 5-HT₄ receptor agonists is also associated with increased amyloid precursor protein cleavage, which has lead to speculation that these agents may be useful in the management of Alzheimer's disease (Claeysen *et al.*, 2015). A contribution from 5-HT₄ receptors in hippocampus seems likely as noted above but a role for other circuits such as cortico-striatal connectivity which is abundant in 5-HT₄ receptors, seems likely.

Administration of 5-HT₄ receptor agonists is also associated with rapid antidepressant effects in animal models (Lucas *et al.*, 2007), and there is preclinical evidence that 5-HT₄ receptor activation plays an important role in the action of SSRIs (Mendez-David *et al.*, 2014). Thus, 5-HT₄ receptor agonists induce a number of responses in common with repeated antidepressant treatment (e.g. efficacy in models of depression, increased expression of neural plasticity markers) but with a rapid onset of action (Vidal *et al.*, 2014; Samuels *et al.*, 2016). Moreover, antidepressant administration causes adaptive changes in 5-HT₄ receptor expression and function (Licht *et al.*, 2010a). Part of the mechanism involved in the antidepressant effects of 5-HT₄ receptor agonists may be activation of a positive feedback control of midbrain 5-HT neurons via 5-HT₄ receptor located in the frontal cortex (Lucas *et al.*, 2005; Licht *et al.*, 2010b).

The full interpretation of this literature on the behavioural effects of 5-HT₄ receptor ligands is somewhat hampered by the current lack of reports concerning the effect of these agents on mood or cognitive performance in man, although there is early evidence that a 5-HT₄ receptor agonist improved the cognitive performance in non-human primates (Terry *et al.*, 1998). Concerns about the potential for 5-HT₄ receptor agonists to elicit adverse gastrointestinal and cardiac effects are likely to have held back the transition to clinical studies, but these do not appear to be effects common to all 5-HT₄ receptor agonists (Claeyssen *et al.*, 2015), which is encouraging for future clinical studies.

XVIII. F. 6. 5-HT₅ receptors

To date there are few studies on the CNS effects of 5-HT₅ receptor ligands, and the main indications regarding the functions of this receptor currently come from studies on the phenotype of 5-HT_{5A} receptor knockout mice (Grailhe *et al.*, 1999). It is reported that these mice display increased exploratory activity in the open field and various other tests without evidence of altered anxiety levels. Without data from phenocopying experiments using 5-HT₅ receptor antagonists or other controls for developmental origins of the phenotype, it remains uncertain whether these behaviours are driven by the absence of 5-HT₅ receptor in the adult brain. Intriguingly, in 5-HT_{5A} receptor knockout mice the locomotor activation induced by LSD was blunted, suggesting that 5-HT_{5A} receptor activation might contribute to the psychotropic effects of psychedelic agents.

XVIII. F. 7. 5-HT₆ receptors

Despite the identification of the 5-HT₆ receptor over twenty years ago, the functions of this receptor have been somewhat obscure until recently. Largely through studies on the effects of 5-HT₆ receptor ligands (agonists and antagonists) in animal behavioural models, it has been discovered that the receptor likely plays an important role in cognition.

The evidence for procognitive effects of 5-HT₆ receptor ligands is in keeping with the predominant localisation of 5-HT₆ receptors in cortico-striatal circuitry, and reviewed elsewhere (King *et al.*, 2008; Codony *et al.*, 2011; Meneses, 2015); see also Section XIV). There are consistent findings that 5-HT₆ receptor antagonists enhance learning and memory mechanisms in a variety of preclinical models ranging from novel object and social

recognition to spatial memory tasks. These effects are observed in naive animals and in those with memory deficits, for example induced by pharmacological means such as cholinergic antagonists.

The mechanism underlying this effect of 5-HT₆ receptor blockade is uncertain. An interaction with the cholinergic system was proposed in early studies, and this is supported by more recent data. In particular, treatment with a 5-HT₆ receptor antagonist augments the effects of an acetylcholinesterase inhibitor on cognitive measures in both animal models and patients with Alzheimer's disease (Wilkinson *et al.*, 2014; Kucinski *et al.*, 2017; although 5-HT₆ receptor antagonists have failed in larger Phase III clinical trial of patients with pathological cognitive deficits) and there is neurophysiological and neurochemical evidence that this drug combination has a synergistic effect on cholinergic function (Herrick *et al.*, 2016). However, recent data show that 5-HT₆ receptors are not expressed by cholinergic neurons (Helboe *et al.*, 2015), which would invoke an indirect mechanism. A mechanism involving increased information processing through cortico-striatal circuits was recently proposed (Kucinski *et al.*, 2017).

A further complication in understanding the procognitive effects of 5-HT₆ receptor antagonists is the paradoxical observation that 5-HT₆ receptor agonists are also reported to have procognitive effects in some, albeit not all, studies (e.g. Schechter *et al.*, 2008; Burnham *et al.*, 2010; Kendall *et al.*, 2011; Meneses *et al.*, 2011). It is difficult to see how this paradox can be reconciled by inferring subtleties in subpopulations of 5-HT₆ receptor at the neural circuit level. Part of the explanation could lie in the cognitive domain being measured, and to date few studies have systematically compared 5-HT₆ receptor agonists and antagonists in the same model. There also remains the intriguing possibility that the full answer lies in the pharmacology of 5-HT₆ receptor ligands, and that their categorisation in terms of partial agonist, inverse agonist and even biased agonist is not yet complete (e.g. Romero *et al.*, 2006).

XVIII. F. 8. 5-HT₇ receptors

As with the 5-HT₆ receptor, the functions of the 5-HT₇ receptor are only now beginning to be revealed. This has largely come about through developments in 5-HT₇ receptor pharmacology and genetic mouse models. Preclinical data link the 5-HT₇ receptor to a variety of CNS processes

including regulation of circadian rhythms, body temperature, mood, cognitions, seizure threshold and pain processing as well as mechanisms of addiction, and this is extensively reviewed elsewhere and will only be briefly discussed here (Hedlund, 2009; Hauser *et al.*, 2014); see also Section XV).

The link between the 5-HT₇ receptor and circadian rhythms was established in early studies which recognised that the circadian phase shift of neurons of the suprachiasmatic nucleus evoked by the 5-HT_{1A} receptor agonist 8-OH-DPAT was mediated by 5-HT₇ and not 5-HT_{1A} receptors (Lovenberg *et al.*, 1993). Indeed, in this light, re-evaluation of the hypothermic effect of 8-OH-DPAT using 5-HT₇ receptor knockout mice and selective antagonists revealed the involvement of 5-HT₇ receptors, although 5-HT_{1A} receptors appear to mediate the hypothermic effect of higher doses of the drug (Hedlund *et al.*, 2004). This hypothermic effect of 5-HT₇ receptor activation is sufficiently robust to make it a useful test of 5-HT₇ receptor agonist activity *in vivo* (Di Pilato *et al.*, 2014).

The discovery that 5-HT₇ receptor knockout mice have an antidepressant-like phenotype contributed to evidence that 5-HT₇ receptors have a role for in emotional control. This feature of the mice is phenocopied by selective 5-HT₇ receptor antagonists which were shown to have antidepressant effects in a range of models in rats and mice. These agents also augment the effect of SSRI and other antidepressants in behavioural and neurochemical models. These findings have translated into clinical trials of the 5-HT₇ receptor antagonist, JNJ-18038683 (Bonaventure *et al.*, 2012), although as yet a clear conclusion regarding efficacy of this agent has not been reached. It is interesting that in animal models, the antidepressant efficacy of amisulpiride is 5-HT₇ receptor-dependent. Many other antidepressant and antipsychotic drugs (tricyclics, lurasidone, aripiprazole, etc) in clinical use have 5-HT₇ receptor antagonist properties, though the contribution of this receptor to their clinical effects is not known.

A final point of interest, selective brain penetrant 5-HT₇ receptor agonists are becoming available as pharmacological tools (Di Pilato *et al.*, 2014) to help further define the function of the 5-HT₇ receptor and open up new therapeutic avenues.

XIX. 5-HT receptors and the cardiovascular system

XIX. A. Introduction

Cardiovascular effects of 5-HT are complex: when infused into the rat circulation, 5-HT produces a triphasic response with a short lasting hypotensive phase, followed by a hypertensive phase and then a long lasting hypotensive phase mediated by respectively: 5-HT₃, 5-HT₂ and 5-HT₁ receptors (Kalkman et al, 1984). The cardiovascular effects of 5-HT have been known since the middle ages when ergots produced devastating peripheral vasoconstriction, which resulted in gangrene and limb loss due to consumption of rye bread polluted with fungi that produced ergots. For a long time, the general view was that 5-HT₂ receptors are largely responsible for vasoconstrictor effects, which would be blocked by 5-HT₂ receptor antagonists, such as ketanserin. However, the situation was much more complex and it was known that depending vessel and species, compounds such as the ergolines (ergotamine, dihydroergotamine (DHE), metergoline) would produce very complex responses: often vasoconstriction, but not infrequently, vasodilation could be observed as well. Even before the full repertoire of 5-HT receptors were known it was suspected that “5-HT₁-like” receptors would at least mediate some of these effects. One of the most important tools for probing “5-HT₁-like receptor”-mediated effects was 5-carboxamidotryptamine (5-CT), which became available in the early 1980's. 5-CT (i) potently contracted the dog saphenous vein (Feniuk et al., 1981); (ii) inhibited the release of noradrenaline and 5-HT from sympathetic and central 5-HT neurons, respectively (Feniuk et al., 1981; Engel et al., 1983); and (iii) displayed nM affinity for the 5-HT₁ receptor recognition sites (Engel et al., 1983). Furthermore, several 5-CT-induced responses (associated with “5-HT₁ like” receptor recognition sites) were blocked by methiothepin and/or methysergide, but not by ketanserin, including relaxation of smooth muscle, contraction of dog saphenous vein, long-lasting hypotension in the rat and tachycardia in the cat (see Kalkman et al, 1984; Bradley et al., 1986; Saxena and Villalón, 1990a). The migraine programme led by Pat Humphrey at Glaxo, used 5-CT as a template to study such effects with the idea to develop a new migraine medication that would be selective for the craniovascular bed. This research culminated with the discovery and development of sumatriptan (and other ‘triptans’ that followed). It was then realised that sumatriptan had high affinity and potency at 5-HT_{1D} receptor sites, before the actual receptors were cloned (Peroutka et al, 1989; Schoeffter and Hoyer 1989a, 1989b, Hoyer et al, 1990). The high affinity of sumatriptan for 5-HT_{1D} receptor recognition sites suggested that the sumatriptan-induced vasoconstriction was mediated by “5-HT₁-like”

receptors resembling the 5-HT_{1D} receptor subtype (Martin, 1994). However, the concept of “5-HT₁-like” receptor remained alive for some time (Hoyer et al., 1994). One of the main reasons for this uncertainty, was that metergoline, a potent 5-HT_{1D} receptor ligand, was less active as an antagonist both *in vitro* (e.g. canine, human and rabbit saphenous vein, and rabbit renal and cerebral arteries; Deckert et al., 1994; Hoyer et al., 1994) and *in vivo* (porcine and canine carotid vascular beds; Den Boer et al., 1992b; Villalón et al., 1995c) than methiothepin as may have been anticipated from metergoline’s affinity at the then defined 5-HT_{1D} receptor recognition sites. However, the experimental conditions used to detect 5-HT_{1D} receptor binding (Waeber et al., 1988) allowed binding to, at the time unknown, 5-HT_{1E}, 5-HT_{1F} and 5-HT₇ receptors, which clearly complicated interpretation. The cloning of 5-HT_{1Dα} and 5-HT_{1Dβ} receptors combined with their relatively high affinity for sumatriptan, and the eventual distinction between 5-HT_{1B} and 5-HT_{1D} receptors, including the species differences, allowed some order to the complexity (Weinshank et al., 1992) along with an appreciation of a need for subtype-selective 5-HT₁ receptor agonists and antagonists. Eventually it was realised that the loosely defined “5-HT₁-like receptor” covered at least three structurally distinct receptors, namely, the 5-HT_{1B}, 5-HT_{1D} and 5-HT₇ receptors. Here, basic and more recent knowledge as to the involvement of each 5-HT receptor in the cardiovascular system in normal physiological and pathophysiological conditions will be discussed (the cardiovascular system to include the heart, blood, vasculature, kidneys, adrenals as well as the peripheral and central nervous systems involved in cardiovascular system regulation).

XIX. B. 5-HT in cardiovascular tissues

The majority of 5-HT in the body is made by 1) the gastrointestinal system and 2) the neurons of the raphe complexes in the brainstem. 5-HT makes its way to all body organs by storage in blood platelets following SERT uptake, and through free 5-HT being released from the enterochromaffin cells of the intestine. Free 5-HT – external to the platelet – is measurable in the plasma of all species examined (Watts et al, 2012). 5-HT has been detected in all rat tissues examined (Linder et al, 2009) and cannot be accounted for by the presence of platelets given that electron microscopic images show no platelet adhesion to the tissues used for measuring 5-HT. Moreover, 5-hydroxyindole acetic acid (5-HIAA) can be detected in these same tissues. 5-HIAA is a metabolite of 5-HT, the product of monoamine oxidase, a mitochondrial enzyme i.e. 5-HT has to be inside the cell to be converted to 5-HIAA. Interestingly, many cardiovascular tissues express SERT and, at least in the rat, SERT-dependent uptake of 5-HT takes place in peripheral

tissues that include arteries, heart, and adrenals (Linder et al, 2009). The SERT KO rat, created by Edwin Cuppen (Homberg et al, 2007), has been particularly useful in these studies. Moreover, certain tissues of the cardiovascular system synthesize 5-HT, independent of the gastrointestinal system and brain using tryptophan hydroxylase (TPH), of which two forms exist, TPH1 and TPH2, the latter being neuron-specific.

XIX. C. Cardiovascular effects mediated by 5-HT receptors

XIX. C. 1. 5-HT_{1A} receptors

One of the best-known peripheral actions of 5-HT_{1A} receptor stimulation in rodents is inhibition of stress-evoked cardiovascular responses, reducing the tachycardia and renal sympathoexcitation that accompany stress (Horiuchi et al, 2005, 2011; Nalivaiko and Sgoifo, 2009). Stress models investigated include restraint stress, fear-conditioned stress, cold exposure and elevated plus maze (anxiety-producing). Interestingly, 5-HT_{1A} receptor agonists can be given systemically to produce their anxiolytic effects independent of sympathoinhibition (Vianna and Carrive, 2009). 5-HT_{1A} receptors also mediate increased vagal drive (Ramage et al, 1990).

5-HT_{1A} receptor agonists lower blood pressure in the normal (non-hemorrhaged, non-stressed) rat. 8-OH-DPAT given in the ventral medulla of the normal rat causes hypotension and bradycardia (Helke et al, 1993). Similarly, 8-OH-DPAT, flesinoxan and other 5-HT_{1A} receptor agonists reduce blood pressure in both the spontaneously hypertensive rat (SHR) and Wistar Kyoto (WKY) rat (see e.g. Doods et al, 1988). The 5-HT_{1A} receptor agonist flesinoxan has been suggested to inhibit sympathetic nerve activity, at least in part through renal nerves, to lower blood pressure in rats (Chamienia and Johns, 1994) and in cats (Ramage et al, 1992; Wouters et al, 1988). Collectively, these studies point to the central role of 5-HT_{1A} receptors modifying autonomic responses as one of the greatest contributions made by this receptor subtype. Interestingly, peripheral 5-HT_{1A} receptors can also mediate inhibition of the sympathetic vasopressor outflow in pithed rats (Morán et al., 1998; Villalón et al., 1998).

In contrast to the decrease in blood pressure caused in a normal rat, 8-OH-DPAT increases whole body venous tone to protect against hemorrhagic shock (Tiniakov and Scrogin, 2009), described as a sympathetic mediated venoconstriction. 5-HT_{1A} receptors are not highly expressed in the

vasculature, and direct effects within the vasculature are uncommon (Villalón and Centurión, 2007; Ramage and Villalón, 2008). Flesinoxan and other 5-HT_{1A} receptor agonists have been developed as blood pressure lowering agents, but no clinical success has been reported and these programmes were abandoned.

XIX. C. 2. 5-HT_{1B} receptors

5-HT_{1B} receptors are found on cerebral arteries and other vascular tissues mediating direct vasoconstriction (see Villalón et al., 2003; Villalón and Centurión, 2007). Further, it seems that the receptor may be silent and may become responsive in conditions such as atherosclerosis (Ishida et al, 2001, Geerts et al, 2000). Peripheral effects in rats have been described, such as: (i) inhibition of noradrenaline release from sympathetic nerves in vena cava (Göthert et al., 1986) and systemic vasculature (Villalón et al., 1998); and (ii) inhibition of plasma extravasation produced by trigeminal ganglion stimulation (Buzzi et al., 1991). 5-HT_{1B} receptors also mediate vasoconstriction in the rat caudal arteries (Craig and Martin, 1993) and the canine external carotid circulation (De Vries et al., 1998).

5-HT_{1B} receptors are expressed in vascular smooth muscle of several different arteries, including: rat aorta (Banes and Watts, 2003), aortic vasavasorum (Cohen et al, 2002), tail artery (Craig and Martin, 1993) and middle cerebral artery (Kovacs et al, 2012); human arteries and veins, including central, pulmonary and coronary arteries (Morecroft et al, 1999; Nilsson et al, 1999a,b; Tanaka et al 2008; van den Broek et al, 2002; Verheggen et al, 1998) as well as coronary endothelial cells (Ishida et al, 1998); canine internal (Centurión et al., 2001) and external (Centurión et al., Valdivia et al, 2004) carotid artery beds; rabbit saphenous vein, basilar artery (Bhattacharya et al, 2004) and renal artery (Hill et al, 2000); porcine coronary artery (Schoeffter and Hoyer, 1989; 1990); bovine pulmonary artery (McKenzie et al, 2010); and guinea-pig isolated iliac artery (Sahin Erdemli et al, 1991; Jahnichen et al, 2004). Next to the 5-HT_{2A} receptor, the 5-HT_{1B} receptor is the best studied and most frequently reported in the vasculature. Expression in cerebral arteries has been a significant focus given the potential involvement of these receptors in the pathophysiology of migraine (e.g. Villalón et al., 2003; Villalón and Centurión, 2007).

The 5-HT_{1B} receptor mediates vasoconstriction in a variety of blood vessels, although some 5-HT_{1B} receptors have been described as ‘silent’, meaning that a vessel needs to be primed with a depolarizing stimulus such as high K⁺ before a functional receptor is observed (‘unmasking’) (Froldi et al, 2008; Movahedi and Purdy, 1998). By contrast, functional 5-HT_{1B} receptors, coupled to nitric oxide synthase, have been reported in cultured bovine aortic endothelial cells (McDuffie et al, 1999). There is thus the potential for 5-HT_{1B} receptors to serve opposing actions in the blood vessel; contraction through smooth muscle and relaxation through the endothelium (Schoeffter and Hoyer, 1989; 1990; Sahin Erdemli et al, 1991).

Functional 5-HT_{1B} receptors are also found in the trigeminocervical complex of cats and dogs, where activation of the receptor inhibits: (i) the ‘nociceptive traffic’ within this complex in the former (Goadsby and Clasey, 2003); and (ii) capsaicin-sensitive trigeminal sensory nerves innervating the external carotid bed in the latter (Muñoz-Islas et al., 2006; 2009). 5-HT_{1B} receptor agonists inhibit the release of sensory neuropeptides (particularly calcitonin gene-related peptide) in migraine, providing the basis for an effective treatment in addition to the craniovascular vasoconstrictor effects (Ma et al., 2001; Gupta and Villalón, 2010; Villalón and Olesen, 2009). Finally, prejunctional 5-HT_{1B} receptors inhibit (by peripheral mechanisms): (i) norepinephrine release in blood vessels (Molderings et al, 1990, 1996; Villalón et al., 2001); (ii) the vasopressor (Villalón et al., 1998) and cardioaccelerator (Sánchez-López et al., 2004) sympathetic outflow; and (iii) the vasodepressor sensory CGRPergic outflow in rats (González-Hernández et al., 2010). Thus, the expression and function of 5-HT_{1B} receptors is complex and at multiple levels, even within just the vasculature.

In the vasculature, the 5-HT_{1B} receptor is best known for its upregulation and elevated function in pulmonary hypertension (Keegan et al, 2001). The 5-HT_{1B} receptor contractile function is also enhanced in rabbit atherosclerotic coronary arteries (Ishida et al, 2001) and rabbit carotid arteries from animals subjected to a carotid collar (Geerts et al, 2000). Also well established is the use of 5-HT_{1B/1D/1F} receptor agonists (the triptans) for the abortive treatment of migraine attacks (e.g. Villalón et al., 2003). Though useful in causing a cerebral vasoconstriction that is thought to be associated with improved symptoms, the triptans can also cause a coronary artery constriction that limits their use in the treatment of migraine in patients with a cardiac condition, although long-term surveillance shows a remarkably low incidence of serious side effects (Chan et al., 2011). Exploration for anti-

migraine mechanisms have expanded beyond the 5-HT_{1B} receptor (there are a multitude of triptans available) with interest on the role of the 5-HT_{1F} receptor playing a potentially non-vascular role (Chan et al., 2011; Rizzoli, 2014) with compounds such as lasmiditan.

XIX. C. 3. 5-HT_{1D} receptors

The external carotid vasoconstrictor responses to 5-HT and sumatriptan are antagonised by the selective 5-HT_{1B} receptor antagonist, SB224289, but not the selective 5-HT_{1D} receptor antagonist, BRL15572 (De Vries et al., 1998) indicating that 5-HT_{1B} receptors mediate this vasoconstrictor response. It must be noted that sumatriptan and second generation triptans do not distinguish between 5-HT_{1B} and 5-HT_{1D} receptors (Villalón et al., 2003; Villalón and Centurión, 2007).

A series of isochroman-6-carboxamide derivatives, including PNU-109291 and PNU-142633, have been described as highly selective 5-HT_{1D} receptor agonists (Ennis et al., 1998; McCall et al., 2002). These 5-HT_{1D} receptor agonists do not produce vasoconstriction in *in vivo* (Centurión et al., 2001) or *in vitro* preparations (cerebral arteries; Bouchelet et al., 2000).

At the peripheral level, the presence of 5-HT_{1D} receptors seems to be rather limited to autonomic and trigeminal nerve terminals/ganglia (Jones et al., 1995; Molderings et al., 1996; Shephard et al., 1997; Villalón et al., 1998).

There were attempts to develop 5-HT_{1D} receptor agonists for migraine therapy (for references see Villalón et al., 2003; Chan et al., 2011); these compounds are active in the trigeminal inflammation / plasma extravasation models yet would presumably be less prone to side effects, since the cardiovascular effects are largely negligible (Villalón et al., 2003; Chan et al., 2011). However, when tested in the clinic to treat migraine there was little success and development has been abandoned.

XIX. C. 4. 5-HT_{1E} receptors

The receptor has been immunohistochemically localized to the cerebral vasculature of humans, but mice and rats do not express a functional 5-HT_{1e} receptor (Klein and Teitler, 2012). There is no evidence for a physiological role for 5-HT_{1e} receptors (Hoyer *et al.*, 1994; Hoyer and Martin, 1997; Villalón and Centurión, 2007; Ramage and Villalón, 2008).

XIX. C. 5. 5-HT_{1F} receptors

5-HT_{1F} receptor mRNA and the corresponding protein is preferentially expressed in neuronal tissues rather than vascular smooth muscle (Ullmer *et al.*, 1995; Bouchelet *et al.*, 1996). Accordingly, 5-HT_{1F} receptor agonists appear devoid of direct vasoconstrictor properties (Cohen *et al.*, 1998; Bouchelet & Hamel, 1999; Villalón *et al.*, 1999).

Most recently, lasmiditan was developed as a 5-HT_{1F} receptor agonist (Rizzoli, 2014); it did not contract rabbit saphenous vein, frequently used as a surrogate for the human coronary artery for which crossover effects of migraine drugs (triptans) can be identified (Nelson *et al.*, 2010). This is consistent with a lack of contractile response via the 5-HT_{1F} receptor generally in this preparation (Cohen and Schenck, 2000) as well as with human cerebral and meningeal arteries (Razzaque *et al.*, 1999; Bouchelet *et al.*, 2000).

XIX. C. 6. 5-HT_{2A} receptors

The 5-HT_{2A} receptor is the original 'D' receptor of Gaddum and Piccarrelli (1957). It is expressed in vascular smooth muscle, cardiac muscle and platelets in multiple species including humans (Ullmer *et al.*, 1995; Derangeon *et al.*, 2010; Watts *et al.*, 2012).

The 5-HT_{2A} receptor mediates contraction in arteries and veins from most species (Villalón and Centurión, 2007), including rat (Sung *et al.*, 2013), both directly and indirectly through regulation of sympathetic nerves (Blessing and Seaman, 2003). It promotes platelet aggregation and gap junctional coupling in heart myocytes (Derangeon *et al.*, 2010), induces the activation of cardiac fibroblasts (Yabanoglu *et al.*, 2009), and within the nucleus tractus solitarius stimulates a depressor and bradycardic response (Comet *et al.*, 2007). Moreover, the direct component of 5-HT-induced tachycardia

in reserpinised pithed rats is mediated by activation of 5-HT_{2A} receptors (Centurión et al., 2002). The receptor mediates increases in contractility in rat cardiac atrium (Läer et al., 1998) and ventricle, but the latter only in heart failure and cardiac hypertrophy (Läer et al., 1998; Qvigstad et al, 2005c; Brattelid et al, 2007a,b; Birkeland et al, 2007b) .

In most vascular diseases, isolated blood vessels are hyper-responsive to 5-HT via the 5-HT_{2A} receptor. Similar to the 5-HT_{1B} receptor, upregulation of the 5-HT_{2A} receptor has been implicated in elevated vascular tone in pulmonary hypertension (Delaney et al, 2013). The 5-HT_{2A} receptor antagonist sarpogrelate blocked the development of pulmonary hypertension induced by monocrotaline and increased survival rate for this highly fatal disease (Hironaka et al, 2003).

The 5-HT_{2A} receptor has been targeted for the treatment of hypertension; thus ketanserin had been developed for this indication, but further research revealed that the antihypertensive effects of ketanserin were actually mediated by alpha₁ adrenoceptor blockade. Interestingly, relatively selective 5-HT_{2A} receptor antagonists (e.g. ritanserin) are devoid of antihypertensive potential in humans.

XIX. C. 7. 5-HT_{2B} receptors

The 5-HT_{2B} receptor, originally described in the stomach fundus, is expressed throughout the cardiovascular system, including vascular smooth muscle (many beds), endothelial cells, cardiac myocytes, fibroblast and valves (Choi and Maroteaux, 1996, Jaffré et a., 2009).

In systemic arteries from normotensive rats, the 5-HT_{2B} receptor is expressed but is apparently not functional (Banes and Watts, 2002, 2003). The endothelial 5-HT_{2B} receptor mediates a nitric oxide-mediated relaxation in normal vessels (Ellis et al, 1995; Glusa and Pertz, 2000; Jahnichen et al, 2005). Strong support for the interaction of the 5-HT_{2B} receptor with NOS was provided by Manivet et al, (2000). In endothelial cells isolated from human coronary artery, 5-HT elevates nitric oxide production through the 5-HT_{2B} receptor (Ishida et al, 1998). The receptor also mediates calcium

release in human pulmonary arterial endothelial cells (Ullmer et al, 1996). The 5-HT_{2B} receptor would appear necessary for cardiomyocyte survival (Nebigil et al, 2003a, b); receptor ablation leads to a cardiomyopathy without hypertrophy (Nebigil et al 2000, 2001).

The 5-HT_{2B} receptor is critical to development of hypoxia-induced pulmonary hypertension (Esteve et al, 2007; Launay et al, 2002), monocrotaline-induced pulmonary hypertension (Zopf et al, 2011) and becomes functional in a number of models of experimental hypertension (Watts et al 1995, 1996; Watts and Fink, 1999; Russell et al, 2002; Banes and Watts, 2002, 2003). Inhibition of the 5-HT_{2B} receptor appears to block valvular myofibroblast differentiation, a process involved in calcification of the aortic valves (Hutcheson et al, 2012). The question remains whether this role of the 5-HT_{2B} receptor also applies to pulmonary hypertension in humans, where the 5-HT_{1B} receptor seems to have a central role (Maclean and Dempsey, 2010). However, the use of the anorectic combination fenfluramine-phentermine (fen-phen) precipitated pulmonary hypertension and valvular heart disease, with evidence of mediation via the 5-HT_{2B} receptor (Fitzgerald et al, 2000; Rothmann et al, 2000). Valvulopathy is also observed with other 5-HT_{2B} receptor agonists (e.g. norfenfluramine, benfluorex, pergolide, cabergoline, ergotamine, most of which have been withdrawn from a majority of markets due to concerns around these adverse side-effects). As a consequence of these findings, preclinical safety screens for 5-HT_{2B} receptor agonism have become mandatory in an attempt to avoid the potential risk of valvulopathy (Hutcheson et al, 2011; Reid et al, 2013). Valvulopathy induced by serotonergic compounds did not begin with fen-phen, it has been observed with ergots over the centuries in central and eastern Europe and even in ancient Egypt (Eadie, 2003; Hauck et al 1990) as well as in patients with carcinoid tumors (Druce et al, 2009). Finally, 5-HT_{2B} receptors appear essential for isoproterenol-induced cardiac hypertrophy in the mouse (Jaffre et al, 2004) and overexpression of the 5-HT_{2B} receptor lead to cardiac hypertrophy in the mouse (Nebigil et al, 2003b). It should also be kept in mind that MDMA (ecstasy) and its metabolite MDA, as well as a number of MDMA analogues act as 5-HT_{2B} receptor agonists and thus carry the risk of valvulopathies, if consumed (Setola et al, 2003).

XIX. C. 8. 5-HT_{2C} receptors

This receptor has not been localized to peripheral tissues with confidence, though a few reports suggest this may be so. The 5-HT_{2C} receptor is, however, expressed in cardiovascular controlling areas of the central nervous system (e.g. nucleus tractus solitarius) and may elevate blood pressure (Austgen et al, 2012; Ferreira et al, 2005).

XIX. C. 9. 5-HT₃A and 5-HT₃AB receptors

An important action of 5-HT₃ receptors in the cardiovascular system is the ability to elicit the neuronally mediated transient von Bezold-Jarisch reflex (for references see Kalkman et al, 1984; Saxena and Villalón, 1990; Villalón and Centurión, 2007).

Alternatively, activation of some peripheral 5-HT₃ receptors evokes tachycardic responses that may involve: (i) noradrenaline release from postganglionic cardiac sympathetic neurons (Saxena and Villalón, 1990); (ii) a direct action on the cardiac pacemaker (Wilson et al., 1990); and (iii) CGRP release from cardiac sensory nerves (Nishio et al, 2002).

5-HT₃ receptors in sympathetic ganglia may sustain chronic stress-induced hypertension in the rat (Nalivaiko and Sgoifo, 2009).

XIX. C. 10. 5-HT₄ receptors

Cardiac expression is well established for the 5-HT₄ receptor, with earliest papers of 5-HT₄-like receptors in human atria dating back to 1989 (Kaumann and Levy 2006). The 5-HT₄ receptor is functional in fetal hearts (Brattelid et al 2012), normally expressed in human and porcine atrium and ventricle (Bach et al, 2001; Brattelid et al, 2004a,b; Weninger et al, 2012) and splice variants of the receptor exist in the human heart (Kaumann and Levy 2006; Bach et al., 2001; Brattelid et al, 2004a; Krobert et al, 2005). Endothelial cells also express 5-HT₄ receptors (Machida et al, 2013; Nishikawa et al, 2010), as does the adrenal gland (Vilaro et al, 2002).

5-HT₄ receptors mediate positive inotropic, chronotropic and lusitropic effects in human and porcine atrium (Kaumann et al., 1990; Kaumann 1990; Villalón et al., 1990; 1991; Kaumann, 1993; Kaumann and Levy 2006, Krobert et al, 2005; De Maeyer et al, 2006; Gergs et al, 2009; Weninger et al, 2012; Chai et al, 2012) and positive inotropic and lusitropic effects in human and porcine ventricular myocardium (Brattelid et al, 2004; Afzal et al 2008).

5-HT₄ receptors also mediate arrhythmogenesis in human atria (Kaumann 1994; Pino et al., 1998), modulation of angiogenesis in cultured human umbilical vein endothelial cells (Nishikawa et al, 2010; Profirovic et al, 2013) and aldosterone secretion from the adrenal gland (Lefebvre et al, 1998, 2000). Interestingly, a model of cardiac overexpression of the human 5-HT₄ receptor in the mouse heart has been developed in order to test for arrhythmogenesis as a cardiac side effect (Gergs et al, 2010).

As pointed out earlier, only 5-HT_{2A} receptors mediate 5-HT-induced cardiostimulation in healthy rats (Centurión et al., 2002), but both 5-HT₄ and 5-HT_{2A} receptors mediate this effect after development of congestive heart failure (Qvigstad et al., 2005a,b). Accordingly, 5-HT₄ receptors: (i) become functional in ventricles during heart failure (Birkeland et al, 2007b; Brattelid et al, 2004a; 2007a, 2012; Qvigstad et al., 2005a,c); and (ii) may contribute to human atrial fibrillation (Kaumann et al., 1994; Lezoualc'h et al, 2007). Thus, 5-HT₄ receptor antagonists may have potential therapeutic usefulness for improvement of cardiac function. In line with a proposed arrhythmogenic effect of stimulation of atrial 5-HT₄ receptors (Kaumann, 1994), antiarrhythmic effects of a 5-HT₄ antagonist was demonstrated in a porcine model of atrial fibrillation (Rahme et al, 1999). However, although atrial 5-HT₄ expression levels increase in human chronic atrial fibrillation (Lezoualc'h et al, 2007), the arrhythmic potential of 5-HT₄ receptors may be reduced in established human atrial fibrillation (Christ et al 2014).

By analogy with the use of betablockers to improve prognosis in heart failure (Lohse et al, 2003), the use of 5-HT₄ receptor antagonists was proposed (Qvigstad et al., 2005, Levy et al, 2008) and delivered improvement in a rat model (Birkeland et al, 2007). 5-HT₄ receptors are functional in human

failing ventricle (Brattelid et al., 2004a; Afzal et al., 2008), and apparent clinical benefits of 5-HT₄ receptor antagonism have been detected (Kjekshus et al, 2009).

XIX. C. 11. 5-HT₅ receptors

The knowledge about cardiovascular responses mediated by 5-HT₅ receptors is very limited (see Ramage and Villalón, 2008). It is suggested that putative 5-HT₅ receptors can mediate: (i) the 5-HT-induced cardiac sympatho-inhibition (together with 5-HT_{1B/1D}) receptors in pithed rats (Sánchez-López et al., 2003); and (ii) the GR-127935-sensitive mechanism mediating hypotension in anesthetized rats (Sánchez-Maldonado et al., 2014).

XIX. C. 12. 5-HT₆ receptors

These receptors have not been localized or found to be functionally relevant within the cardiovascular system (Villalón and Centurión, 2007; Ramage and Villalón, 2008).

XIX. C. 13. 5-HT₇ receptors

The 5-HT₇ receptor most probably is encompassed with the originally designated “5-HT₁-like” receptor that mediates direct (endothelium-independent) vasorelaxation, the late vasodepressor response (i.e. the tertiary component of the triphasic response) following intra-venous administration of 5-HT (Kalkman et al, 1984; Saxena and Villalón, 1990; 1991).

5-HT₇ receptors are primarily located in vascular smooth muscle of most species (Ullmer et al., 1995; Villalón and Centurión, 2007, Ramage and Villalón, 2008). The 5-HT₇ receptor mediates direct vasorelaxation in multiple vascular beds (e.g. Cushing et al, 1996; Terrón, 1996; Villalón et al., 1997a, 2001; Jahnichen et al., 2005; Seto et al., 2009; Watts et al., 2015).

XIX. C. 14. Receptor-independent actions of 5-HT

It is recognized that 5-HT can exert a (patho)physiological role which is independent of cell surface 5-HT receptors.

For instance various groups have reported that animals lacking SERT or in which SERT was pharmacologically inhibited, are protected from pulmonary hypertension (Elangbam et al, 2008; Fanburg and Lee, 2000; Guignabert et al, 2005; Marcos et al, 2003; Wang et al, 2012). Similarly, rodents overexpressing SERT develop pulmonary hypertension (Guignabert et al, 2006). It is known that intracellular 5-HT is able to modify proteins, a phenomenon known as 'serotonylation' of proteins (Lin et al, 2014). Such protein modification may mediate mitogenic and profibrotic effects of 5-HT independent of receptor activation (Guilluy et al, 2009; Liu et al, 2011; Penumatsa and Fanburg, 2014; Wei et al, 2012). This covalent modification of target proteins by 5-HT is mediated by the enzyme transglutaminase, of which the tissue transglutaminase isoform (TG II, tTG) is abundant in vascular tissue. Targets for serotonylation include Akt (Penumatsa et al, 2014), small GTPases such as Ras, Rab 4 and Rho (Ahmed et al, 2008; Lin et al, 2013; Mercado et al, 2011; Walther et al, 2003, 2011), fibronectin (Hummerich et al, 2012; Liu et al, 2011) and smooth muscle α -actin (Watts et al, 2009).

XX. 5-HT receptors and the gastro-intestinal tract

XX. A. Introduction

The GI tracts of mammals contain a huge store of 5-HT (Gershon and Tack, 2007), melatonin (a derivative of 5-HT; Stone and Darlington, 2002) and also kynurenine derivatives of tryptophan which can interact with 5-HT receptors on GI muscle (Pomfret et al., 1987). This 5-HT is released to act within the GI tract (all known 5-HT receptors are expressed within the GI tract; see below) and externally into the blood, playing various roles in metabolism, osteogenesis, immunity, neurogenesis and neuroprotection (Gershon, 2012; 2013). Indeed, about 95% of the 5-HT in the human body comes from the GI tract, with 90% being in enterochromaffin (EC) cells in the mucosal epithelium and 5% in the neural structures intrinsic to the bowel wall; in common with the rest of the epithelium, EC cells are continually shed and replaced. Large amounts of 5-HT are also present in mast cells of rats and mice, but human intestinal mast cells usually contain no 5-HT (Buhner and Schemann, 2012); a subset of mast cells in patients with colon carcinoma and ulcerative colitis has been reported to contain 5-HT (Stoyanova and Gulubova, 2002). In the human GI tract, the highest amounts of 5-HT are present in the duodenum and rectum, whereas the lowest is found in the esophagus and ileum (Spiller et al., 2008a). In rats, the greatest amount of 5-HT is in the caecum (Hansen and Witte, 2008). 5-HT is also present in a limited (2-3%) number of myenteric descending interneurons (with variation among species; Gershon, 2003; Gershon and Tack, 2007) potentially regulating secretion and circular muscle movements in guinea-pig jejunum (Neal and Bornstein, 2007), and also in enteric sensory and motor neurons of mouse colon (Okamoto et al., 2014).

There are two GI 5-HT pools, each dependent on a different isoform of TPH (Li et al., 2011b). The larger pool is present in EC cells and is TPH1-dependent. The smaller pool, present in neurons is TPH2-dependent, as is CNS 5-HT. These two pools can thus be selectively depleted. Thus, TPH1 knockout (TPH1KO) depletes EC cells, whereas TPH2KO depletes neuronal 5-HT.

5-HT is released from EC cells by mechanical and chemical stimuli (e.g. pH, bile acids, and nutrients such as glucose and short-chain fatty acids) applied to the luminal surface of the bowel. 5-HT release is modulated by neuronal and hormonal inputs acting at numerous receptors (including 5-

HT receptors; see below) expressed by EC cells (Gershon, 2003; Hansen and Witte, 2008). The junctions between EC cells and intrinsic and extrinsic sensory nerve terminals in the mucosa are not morphologically like traditional synapses (Wade and Westfall, 1985). Indeed, 5-HT secreted by EC cells acts locally in a paracrine fashion, although the nerves it activates may be situated far from the EC cells (Wade and Westfall, 1985). In addition, EC cells are in constant motion from the crypts to the surface, they turn over and are replaced by stem cells both in the small and large intestines. As a result of the movement and transient nature of EC cells, traditional synapses are not found (nerves are not good at innervating moving targets) and EC cells do not focus the 5-HT released as precisely as do neurons (see Gershon and Tack, 2007). Similarly, EC cells are located in relatively close proximity to mucosal lymphocytes (Yang and Lackner, 2004).

The 5-HT released into the mucosa and/ or lumen does not normally penetrate to the muscle of the GI tract because of two reasons: first, 5-HT has poor ability to cross lipid layers of cell membranes, and second, because 5-HT is readily taken up by neurones and enterocytes via either SERT or organic cation transporters (Chen et al., 1998; Wade et al., 1996). 5-HT is also removed into the vasculature where it is taken up into blood platelets, which lack TPH and thus cannot synthesise 5-HT. Mucosal 5-HT thus does not gain access to the muscle layers of the bowel, except in pathological conditions where high plasma concentrations are reached (Sanger, 2008).

The released 5-HT can potentially act at multiple 5-HT receptors (see Costa et al, 2003; Beattie and Smith, 2008; Hansen and Witte, 2008; Sanger, 2008; Chetty et al., 2009; Li et al, 2011b; Hoffman et al., 2012; Alexander et al, 2015a, b) which are expressed by several elements of the GI tract:

- Isolated enteric crest-derived cells (mRNA for all known 5-HT receptors)
- EC cells (5-HT_{2C}, 5-HT₃, 5-HT₄)
- Goblet cells (5-HT₄)
- Enterocytes (5-HT_{1A}, 5-HT_{2A}, 5-HT₃, 5-HT₄)
- Muscle (5-HT_{1B/1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT₄, 5-HT₇)
- Interstitial cells of Cajal (5-HT₃, 5-HT₄)

- Motor (5-HT_{1A}, 5-HT_{1B/1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT₃, 5-HT₄) and sensory (5-HT₃, 5-HT₄, 5-HT₇) neurons of the myenteric and submucosal plexus
- Terminals of GI extrinsic sympathetic and/ or parasympathetic nerves (5-HT_{1A}, 5-HT₃, 5-HT₄ in rodents)

The genes encoding the 5-HT_{3A} and 5-HT_{3B} subunits of the 5-HT₃ receptor are widely expressed by different mammalian tissues. In humans, expression of 5-HT_{3C} and 5-HT_{3E} mRNA is greatest within the GI tract (5-HT_{3C} is also present elsewhere), whereas 5-HT_{3D} mRNA is largely restricted to the kidney, colon and liver (Niesler et al., 2003; Holbrook et al., 2009; Yaakob et al., 2015). Notably, genes encoding 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} are found in humans and other mammals, but not in rodents (Holbrook et al., 2009).

5-HT_{3A} mRNA has been found in the mucosa, circular and longitudinal (*taenia*) muscle of human colon, whereas 5-HT_{3B} mRNA may be more common in muscle and 5-HT_{3E} mRNA in the mucosa (Chetty et al., 2009; Yaakob et al., 2015). Importantly, 5-HT_{3A} and 5-HT_{3B} mRNA and immunoreactivity are co-expressed with neuronal cell markers in the submucosal plexus of human intestine and therefore potentially form heteromeric 5-HT_{3AB} receptors in these nerves (Michel et al., 2005). Others report that in cell bodies of human colon myenteric neurons, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} mRNA co-express with 5-HT_{3A}, whereas mRNA for 5-HT_{3A} and 5-HT_{3D} co-express in the submucosal plexus (Kapeller et al., 2011). The physiological significance of these different expression patterns is not clear. However, the absence of genes encoding 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} in rodents has been linked to the specific divergence of rodents away from the primate evolutionary line and the peculiar lack of an emetic reflex in rodents (a function strongly linked in humans with 5-HT₃ receptors; see below and Holbrook et al., 2009). Here it may be of interest to note that selective 5-HT₃ receptor antagonists do not necessarily affect GI functions in the same way (e.g. Banner and Sanger, 1995) but whether such anomalies are explained by an ability to distinguish between different 5-HT₃ receptor subunits (see Thompson and Lummis, 2013 for examples) is still unknown.

Among the 5-HT GPCRs, splice variants exist in human colon for 5-HT_{2B}, 5-HT₇ and 5-HT₄ receptors (Coupar et al., 2007; Chetty et al., 2009; Yaakob et al., 2015), although their roles are poorly understood. It has been speculated that the efficiency of 5-HT₄ receptor intracellular coupling

and/or the desensitization liability and affinity of this receptor for particular ligands depends on which COOH-terminal splice variant is expressed by a particular cell (Coupar et al., 2007; Beattie and Smith, 2008; Sanger, 2009). This would explain why 5-HT₄ receptor agonists facilitate GI cholinergic functions with high intrinsic activity (leading to increased GI motility) whereas in cardiac muscle and other tissues, the intrinsic activity of the same agonist is low (De Maeyer et al, 2006). Notably, the 5-HT_{4(d)} isoform is specifically expressed within human intestine (in addition to 5-HT_{4(b)} and 5-HT_{4(a)} which are widely expressed) and the GI prokinetic renzapride (a non-selective 5-HT₄ receptor agonist; Sanger 1987a) acts as a full agonist at this isoform, but only as a partial agonist at the 5-HT_{4(g)} isoform (Mialet et al., 2000).

Certain 5-HT GPCRs may modulate ion channel functions within the GI tract. Sugiuar et al (2004) showed that in mouse colon, the functions of TRPV1 channels were facilitated by both 5-HT_{2A} and 5-HT₄ receptor activation. In rat colon, a synergistic link between 5-HT₄ and 5-HT₃ receptors has been suggested (Smith et al., 1999). A proposed intracellular ‘crosstalk’ between 5-HT₃ and NK₁ receptors may also provide a pathway via which certain selective 5-HT₃ receptor antagonists can influence the receptor in an allosteric manner (e.g. palonsetron) to inhibit substance P-mediated responses and thereby exert greater anti-emetic activity (Rojas et al., 2014; see later).

Finally, it should be noted that 5-hydroxyindalpine, an agonist mimicking certain atypical 5-HT-mediated responses (said to be mediated by a putative 5-HT_{1P} receptor, as yet undefined as a molecular entity despite considerable research; see Galligan, 2007), facilitated peristalsis in mouse colon, but had no meaningful affinity for human 5-HT_{1A}, 1B, 1D, 2A, 2B, 2C, 3, 4, 6, and 7 receptors or for other monoamine (adrenoceptor, dopamine, histamine) receptors (Mitchell et al., 2009). It has been speculated that at least some ‘atypical 5-HT’ responses’ may be the result of ligands acting at allosteric binding sites and/or at GPCR heterodimers, such as a 5-HT_{1B/1D} and dopamine D₂ receptor heterodimer (Galligan, 2007).

XX. B. Functions of 5-HT

Of the many proposed roles for endogenous 5-HT in GI physiology, the most widely studied relate to its involvement in GI movements, secretion, reflex functions and sensations. Several of these functions are mediated via 5-HT₃ and 5-HT₄ receptors; other receptors may also have important

roles although the available data is often limited. It is important to appreciate that GI functions can differ markedly between species, especially between rodents and humans (Sanger et al., 2011a; 2013), and this can greatly change the functions of 5-HT and thereby complicate the translational value of certain animal models.

Additional developmental roles for endogenous 5-HT have also been reported, acting as an enteric neurotrophic or neuroprotective agent via 5-HT_{2B} and 5-HT₄ receptors or when released from enteric neurons, to promote epithelial growth via 5-HT_{2A} receptors on submucosal cholinergic neurons (Fiorica-Howells et al., 2000; Liu et al., 2009; Li et al., 2011b; Gross et al., 2012; Gershon, 2013; Mawe and Hoffman, 2013; Takaki et al., 2014). The absence of neuronal 5-HT during development in mice lacking TPH2, for example, is associated with a profound ENS hypoplasia and slow GI transit (Li et al., 2011b). Neurons that are born (become post-mitotic) after enteric serotonergic neurons, in the sequence of ENS neurogenesis, are 5-HT-dependent and are particularly deficient in these animals. Thus, 5-HT is a growth factor that is required for enteric neuronal development. The mucosa was also defective in TPH2KO mice, suggesting that neuronal 5-HT promotes division of transit amplifying cells in intestinal crypts (Gross et al., 2012). Further, the normal post-natal accretion of enteric neurons and growth of mice during the first 4 months of life also does not occur in animals in which 5-HT₄ receptors have been deleted (Liu et al., 2009).

One possibility is that neuroprotective functions of neuronal 5-HT might be integrated with a pro-inflammatory role of mucosal 5-HT. For example, mucosal 5-HT enhances and triggers inflammation (Bischoff et al., 2009; Ghia et al., 2009; Haub et al., 2010; Li et al., 2011a; Margolis et al., 2014), probably by stimulating dendritic cells (Li et al., 2011a). Inflammation is potentially toxic to enteric neurons (Gulbransen et al., 2012) but it is also important in protecting the bowel from microbial invasion. Mucosal 5-HT may therefore enhance the strength of the innate immune response to danger while at the same time neuronal 5-HT may protect enteric neurons from being damaged by the response; 5-HT can thus serve both as a sword and a shield of the gut (Gershon, 2012).

XX. B. 1. Movements of the hungry stomach

During hunger, the release of 5-HT from the upper GI tract, together with the hormone motilin, has a potential role in initiating a repeating pattern of upper GI movements known as the migrating motor complex (MMC) also associated with changes in blood flow, gall-bladder emptying, gastric and pancreatic secretions.

The MMC, which in humans repeats every 80-120 minutes, is characterised by a relatively long period of quiescence (Phase I), irregular, non-propulsive movements (Phase II) and then a short burst (5–8 min) of high amplitude propulsive contractions (Phase III) initiated by the vagus nerve in stomach, duodenum and jejunum, but rapidly recovering (Phase IV) while migrating to the terminal ileum where the movement is terminated. Phase III removes undigested material and prevents bacterial overgrowth; it can be disrupted by disease and may help develop feelings of hunger (Sanger and Lee, 2008; Sanger et al., 2011b; Deloos et al., 2012; Tack et al., 2014). In dogs (Nakajima et al., 2010) a gradual release of 5-HT from duodenal enterochromaffin cells during Phase I eventually activates 5-HT₄ receptors within the myenteric plexus to increase GI motility (Phase II), releasing more 5-HT from enterochromaffin cells to initiate Phase III via 5-HT₃ receptors in the stomach (also Morita et al., 2013, and in humans (Luiking et al., 2002; Wilmer et al., 1993) and 5-HT₄ receptors in the intestine (dogs: Davidson et al., 1990; Nakajima et al., 2010). The vagus also increases motilin release from human mucosal enteroendocrine cells (Wilmer et al., 1993) to re-enforce gastric phase III activity by greatly facilitating cholinergic motor nerve activity in a short-lasting manner (Broad et al., 2012).

XX. B. 2. Movements and sensations of the stomach and duodenum after meals

In healthy volunteers, little or no influence of endogenous 5-HT has been detected on gastric accommodation, compliance, sensation and motility, or on the rate of gastric emptying after ingestion of a meal, at least by acting at 5-HT₃ (e.g. Gore et al., 1990; Kuo et al., 2002; Netzer et al., 2002; Janssen et al., 2011a; Kusakabe et al., 2014) or 5-HT₄ receptors (e.g. Bharucha et al., 2000). In contrast, 5-HT₃ receptor antagonism can increase gastric emptying in rodents (e.g. Costall et al., 1987; Miyata et al., 1995), although an ability of ondansetron, a racemate, to facilitate cholinergic activity in guinea-pig ileum via an unknown, non-5-HT₃-mediated mechanism, should also be noted (Miyata et al., 1995; González & Puig, 1997). However, in

the mouse, elimination of neuronal 5-HT as a result of the knockout of TPH2, accelerates gastric emptying (Li et al., 2011b) and 5-HT deletion or antagonism impairs vagal relaxation of the guinea pig stomach (Bülbring and Gershon, 1967).

If a meal is rich in glucose, amino acids and/ or lipids, high concentrations of these nutrients and/ or gastric acid within the lumen of the duodenum can release 5-HT from enterochromaffin cells (and other mediators such as cholecystokinin (CCK), potentially acting synergistically together; Hayes et al., 2005) to activate 5-HT₃ receptors upon abdominal vagal nerve terminals to induce satiety (Feinle and Read, 1996; Savastano and Covasa, 2007) and if necessary, nausea (see below). In rodents a clear reduction in gastric emptying has also been observed, but in humans, intra-duodenal infusion of glucose or a high fat meal caused only a small 5-HT₃ receptor-mediated reduction in gastric antrum movements and gastric emptying (Stacher et al., 1990; Raybould et al., 2003; Savoye et al., 2007). In rats, 5-HT₄ receptors on intrinsic cholinergic neurons may be activated to increase duodenal bicarbonate secretion for a neutralizing action against gastric acid (Akiba et al., 2014).

XX. B. 3. Movements of the small intestine

It has long been known that 5-HT is released into the intestinal lumen by mechanical stimuli to the mucosa, leading to facilitation of the peristaltic reflex (e.g., Bülbring and Lin, 1958; Foxx-Orenstein et al., 1996; Bertrand et al., 2000; Pan and Gershon, 2000; Patel et al., 2007; Bertrand et al., 2008). However, it seems unlikely that this mechanism has a major physiological influence on human small intestinal movements, at least via 5-HT₃ (Gore et al., 1990; Houghton et al., 2000) and 5-HT₄ receptors (Bharucha et al., 2000). Nevertheless, this does not rule out the possibility that under certain non-physiological conditions (e.g. prevention of 5-HT reuptake by use of a SSRI), small intestinal movements can be stimulated by the released 5-HT (Grover & Camilleri, 2013; Bundeff & Woodis, 2014; see section XX.C 5-HT in GI pathology, for discussion). Further, it should be noted that 5-HT is probably released from EC cells into the lamina propria underlying these cells. Nerve fibres from intrinsic primary afferent neurons are found in this location, as are sensory nerves derived from the vagus and dorsal root ganglia. Since the entire enteroendocrine system, including EC cells secretes basolaterally, not apically, the luminal appearance of 5-HT is likely to result from spillover (5-HT is a relatively small

molecule so it can diffuse into the lumen after its release into the lamina propria). It might thus be expected that endogenous 5-HT release in the small intestine would not affect motility.

XX. B. 4. Movements of the colon

Endogenous 5-HT acting at 5-HT₃ receptors plays a physiological role in controlling normal movements of the colon via extrinsic and/ or intrinsic nerve pathways, depending on the species of mammal. Additionally, and in certain species, 5-HT_{2B} and 5-HT₇ receptors may play similar roles (see below). However, the exact role of 5-HT on movements of the colon remain uncertain due in part to the high complexity of both the 5-HT system and the movements of colon in different species. This uncertainty has been discussed in a series of ‘cross-talk’ articles (Heredia et al., 2013; Smith and Gershon, 2015a; b; Spencer et al., 2015a; b).

XX. B. 4. a. 5-HT_{2A} receptors

5-HT_{2A} receptor knock-out mice, from which 5-HT can no longer cause contraction of the isolated colon, display apparently normal GI transit and colorectal motility patterns (Fiorica-Howells et al., 2002).

XX. B. 4. b. 5-HT_{2B} receptors

Propulsive movements of the colon and faecal output *in vivo* are reduced by 5-HT_{2B} receptor antagonism in rodents (Bassil et al., 2009) but not in dogs (Morita et al., 2013). The receptor has been implicated in enteric nerve and in ICC development (Fiorica-Howells et al., 2000; Tharayil et al., 2010). Although exogenously-applied 5-HT can cause contraction of human colon via 5-HT_{2B} receptor activation (Borman et al., 2002), a role for endogenous 5-HT acting at the 5-HT_{2B} receptor to affect human colonic functions has yet to be established.

XX. B. 4. c. 5-HT₃ receptors

5-HT₃ receptor antagonists slow colonic motility and induce mild constipation in several species but the mechanisms of action may vary. In humans, the ability to slow colonic motility (e.g. Gore et al., 1990; Talley et al., 1990; Houghton et al., 2000) is at least partly due to inhibition of the gastrocolic reflex, thought to be a vagus nerve-mediated colonic contractile response associated with eating, but specifically evoked by distension of the gastric antrum or inclusion of lipids within the lumen of the duodenum (Prior and Read, 1993; von der Ohe et al., 1994; Björnsson et al., 1998; 2002). In these studies, the ascending and descending components of the peristaltic reflex were unaffected by 5-HT₃ receptor antagonism. The latter is consistent with an inability to detect 5-HT-mediated fast synaptic potentials in the myenteric plexus of human colon (Brookes et al., 1987) but seems at variance with the ability of local application of 5-HT to excite submucosal neurons (but not chloride ion secretion) in human small and large intestine via 5-HT₃ receptors (where 5-HT_{3A} and 5-HT_{3B} receptor subunits are expressed; Michel et al., 2005).

In rodents, 5-HT₃ receptors appear to influence colonic movements via more 'local' mechanisms. Thus, the ability of 5-HT₃ receptor antagonists (granisetron and tropisetron, but not ondansetron) to dose-dependently inhibit faecal pellet excretion by guinea-pigs could be at least partly mimicked in guinea-pig mid-to-distal isolated colon, in which granisetron and tropisetron prevented movement and expulsion of endogenous faecal pellets (recovered by application of naloxone; Sanger and Wardle, 1994). Similar data were reported by Jin et al (1999) using artificial faecal pellets and approximately the same region of colon after application of different 5-HT₃ and 5-HT₄ receptor antagonists. However, in guinea-pig distal colon, movements of artificially-inserted faecal pellets were unaffected or only transiently reduced when 5-HT₄ or 5-HT₃ receptor antagonists (including granisetron and ondansetron) were applied individually but were inhibited, albeit for only a short period of time, when the antagonists were given together (Kadowaki et al., 1996). In rats, proximal colon transit (measured via an indwelling cannula) and 5-HT-induced diarrhoea in mice, were unaffected by 5-HT₄ or 5-HT₃ receptor antagonists (ondansetron) applied separately but were inhibited when applied together (Nagakura et al., 1997). In contrast, Yu et al (2015) demonstrated an ability of 5-HT₃ receptor antagonism to abolish propulsive movements of rat isolated colon, again supporting a local role for 5-HT in the control of rodent colonic movements.

More recent studies confirmed a local release of 5-HT from mouse colon in response to a maintained presence of a faecal pellet, an ability of 5-HT₃ receptor activation to promote pacemaker activity generated in mouse ileum by the interstitial cells of Cajal (Liu et al., 2011) and an ability of 5-HT₃ receptor antagonism to prevent colonic migrating motor contractions (e.g. Bush et al., 2001; Heredia et al., 2008; 2013; Dickson et al., 2010). The question of whether the 5-HT comes from interneurons or from enterochromaffin cells to evoke these movements – or even if endogenous 5-HT is required at all – is the subject of debate, raising interesting questions about methods, the role of mucosal versus stretch-induced reflexes, putative constitutive expression of receptors (Smith et al., 2010; Heredia et al., 2013; Sia et al., 2013; Smith et al., 2014) and mouse strain differences (Neal et al., 2009). Despite the controversy surrounding the function of colonic 5-HT, myenteric 5-HT neurons project so extensively in the colon that these cells have been called “the central processing unit in the colon” (Okamoto et al., 2014).

XX. B. 4. d. 5-HT₄ receptors

5-HT₄ receptor antagonists have little (Morita et al., 2013) or no ability to inhibit colon movements in dogs (Nagakura et al., 1996) or rodents (Kadowaki et al., 1966; Nagakura et al., 1997; Sanger et al., 1998; 2000) although reduced GI activity was observed in 5-HT₄ receptor knock-out mice, arguably related to loss of 5-HT₄ receptor-mediated promotion of survival of enteric neurons (Gershon and Liu, 2007). In human volunteers there were no changes in colonic transit (a trend towards delayed transit was not statistically significant), fasting or postprandial motor activity, compliance or sensations evoked by transverse and sigmoid colon distension after 10–12 days administration with pharmacologically-effective doses of a 5-HT₄ receptor antagonist (Bharucha et al., 2000).

XX. B. 4. e. 5-HT₇ receptors

Activation of 5-HT₇ receptors expressed by human intestinal muscle causes muscle relaxation (Prins et al., 1999; Coupar et al., 2007; Irving et al., 2007). In guinea-pig ileum, 5-HT₇ receptors are localised both to muscle and to myenteric and submucosal neurons (Tonini et al., 2005). In this tissue, the release of 5-HT from enterochromaffin cells is thought to activate 5-HT₇ receptors on intrinsic sensory neurones (defined as Dogiel type II neurons) to evoke slow depolarisation (Monro et al., 2005) and perhaps also, to facilitate a descending inhibitory motor pathway to relax the muscle,

increasing its ability to accommodate and thereby reducing the likelihood of inducing peristalsis by intraluminal distension (Tuladhar et al., 2003; Tonini et al., 2005). By a similar process, endogenous 5-HT may activate 5-HT₇ receptors in mouse colon to promote descending inhibitory interneurons and contribute to the generation of spontaneous colonic migrating motor complex (Dickson et al., 2010).

XX. C. 5-HT in GI pathology

The large amount of 5-HT in the GI tract and the expression of all 5-HT receptors on several, functionally different types of GI cells (see above) creates the interesting situation of being able to use selective 5-HT receptor antagonists to treat disease caused by release of *endogenous* 5-HT, and also use 5-HT receptor agonists (*exogenous* 5-HT) to treat other diseases. This section discusses the involvement of *endogenous* 5-HT in the mechanisms of disease.

Increased release or availability of 5-HT from EC cells is associated with various GI disorders, including diarrhoea (e.g. induced by cholera and other bacterial toxins and also by carcinoid tumours), inflammatory bowel disease and functional disorders such as IBS (Gershon and Tack, 2007; Spiller, 2008b; Bertrand and Bertrand, 2010; Spiller, 2011 - for discussion on expression of 5-HT receptors by human dendritic and immune cells, see Idzko et al., 2004 and Shajib and Khan, 2014). More recently, the release of 5-HT from enterochromaffin cells of the rat duodenum has been shown to increase following exposure to short chain fatty acids (Akiba et al., 2015), potentially caused by increased TPH1 transcription (Reigstad et al., 2015). 5-HT release is also increased by cytotoxic anti-cancer treatments, following generation of free radicals in enterochromaffin cells; (Torri et al., 1993; Minami et al., 2003) and acute stress, via agents such as CRF (Sanger et al., 2000; Von Mentzer et al., 2007). Increases in 5-HT availability in 5-HT transporter knockout mice can change the level of expression and sensitivity of enteric 5-HT₃ receptors (Gershon, 2003).

In GI disease, an increased availability of 5-HT has marked effects on certain autonomic functions (e.g. emesis), GI movements (e.g. diarrhoea) and perhaps, conscious perceptions of discomfort and/ or pain. Several studies have investigated the role of 5-HT release into the circulation, 5-HT in tissue (typically by immunohistochemistry), mRNA expression of *5-HTTLPR* gene (which determines SERT levels) in rectal mucosa and platelets and

DNA polymorphisms in *5-HTTLPR* gene. In summary, the most consistent findings are elevated postprandial plasma 5-HT in IBS with diarrhea (IBS-D) and reduced levels in IBS with constipation (IBS-C) (Spiller, 2008; Camilleri, 2014; Zhang et al., 2014; El-Salhy et al., 2012; Mawe and Hoffman, 2013).

XX. C. 1. Emesis

There are no ‘universal’ anti-emetic drugs and multiple stimuli evoke emesis via different pathways, not all of which involve the release of 5-HT. The stimuli which involve the release of 5-HT and which have been studied most often are discussed below. In this discussion the term ‘emesis’ is taken to represent the combined act of vomiting (and dry retching) as well as nausea. It is, however, increasingly appreciated that the sensation of nausea is not fully explained by the pathways that induce vomiting. For example, 5-HT₃ and NK₁ receptor antagonists are both more effective against vomiting than they are against nausea, implying that different mechanisms are involved (Andrews and Sanger, 2014) and hence different approaches to treatment are required (Sanger et al., 2013).

Since the pioneering studies with animals (Miner and Sanger, 1986; Costall et al., 1986; Miner et al., 1987), the use of selective 5-HT₃ receptor antagonists as anti-emetic drugs has revolutionised treatment of cancer by making chemo- and radio-therapeutic treatments more tolerable (emesis is now viewed as something which can be treated rather than needs to be tolerated, and anti-cancer drugs can now be given in family-orientated out-patient clinics), by enabling the delivery of more aggressive treatments, and by actually reducing health care costs (Currow et al., 1997; Warr and DeAngelis, 2009). Following identification of this role for the 5-HT₃ receptor, it rapidly became standard practice to co-administer a 5-HT₃ receptor antagonist with the corticosteroid dexamethasone, to achieve even better relief from emesis evoked by moderate to severe emetogenic treatments. Later, the ‘triple-therapy’ of 5-HT₃ receptor antagonism, dexamethasone and NK₁ receptor antagonism has achieved a further benefit in patients receiving treatments classified as ‘highly emetogenic’, controlling the appearance of both ‘acute’ emesis (during the first 24h after initiation of treatment), but even more importantly, now controlling the ‘delayed emesis’ which in these patients can occur 24 – 48 h after the start of treatment (Warr, 2012).

5-HT₃ receptor antagonists prevent cytotoxic-associated vomiting by blocking the ability of released 5-HT (Barnes et al., 1990; Cubeddu et al., 1990), likely from EC cells, to activate 5-HT₃ receptors on abdominal vagal nerve terminals and thereby effectively ‘desensitise’ the vagus to the pro-emetic stimulatory actions of other substances (e.g. prostanoids) released during the cytotoxic treatment (see Sanger and Andrews, 2006). Most recently, evidence is emerging that a long-lasting 5-HT₃ receptor antagonist (palonosetron) may provide further improvements in emesis control by a mechanism not yet clearly understood, but argued to involve inhibition of substance P-mediated responses via a unique interaction with the 5-HT₃ receptor (Rojas et al., 2014).

Depending partly on the population studied, a minority of patients treated with moderate-to-highly emetogenic chemotherapy do not respond well to treatment with a 5-HT₃ receptor antagonist. This may be due to mutations in a P-glycoprotein efflux transporter in intestinal epithelia and capillaries of the blood-brain barrier, affecting the availability and target engagement of these and other drugs (Perwitasari et al., 2011; Tsuji et al., 2013; He et al., 2014; Zoto et al., 2014), and/ or differences in rates of metabolism of ondansetron and tropisetron associated with polymorphisms of the gene encoding CYP2D6 (Kaiser et al., 2002). Genetic variants of the 5-HT_{3B}, but not the 5-HT_{3A} subunit, are also reported to alter anti-emetic efficacy in a small number of patients (Tremblay et al., 2003; Kaiser et al., 2004; de Wit et al., 2005).

In patients at the end of life, perhaps with far advanced cancer when chemo- or radio-therapy is no longer provided, emesis can remain a severe problem for reasons associated with the use of drugs, cranial, electrolytic or metabolic causes, bowel obstruction, uremia and/ or sepsis. In these patients, 5-HT₃ receptor antagonists have often provided effective control of emesis (e.g. Currow et al., 1997; Mystakidou et al., 1998; Buchanan and Muirhead, 2007). Exactly where the 5-HT comes from is not always clear and 5-HT₃ receptors expressed both peripherally (vagus nerve terminals) and centrally within the brainstem are likely to be involved (Sanger and Andrews, 2006).

Selective 5-HT reuptake inhibitors (SSRIs) can induce nausea and vomiting that is reduced by 5-HT₃ receptor antagonism and associated with polymorphisms of the HTR3B gene but not with genes encoding the 5-HT transporter, the 5-HT_{2A} receptor or the 5-HT_{3A} receptor subunit (Sugai et al., 2006; Tanaka et al., 2008). Such drugs also stimulate small but not large bowel motility and have been evaluated as potential treatments of IBS, improving general wellbeing (Grover and Camilleri, 2013; Bundeff and Woodis, 2014).

Notably, there are many drugs and experimental tools other than the SSRIs that increase (e.g. 5-HTP, non-selective SSRIs, MAO inhibitors) or decrease 5-HT availability (e.g. fenfluramine; depletion following the initial increase), sometimes with additional abilities to antagonise certain 5-HT receptors, and these can induce or reduce emesis. The receptors include 5-HT_{1A}, 5-HT_{2A} and 5-HT₃ but which receptors are involved are not always clear and studies with more selective ligands are required to understand mechanisms of action (Johnston et al., 2014).

Post-operative vomiting (POV) is caused by multiple stimuli, but can be reduced by 5-HT₃ receptor antagonism (e.g. Chun et al., 2014). The exact mechanism is not clear (Horn et al., 2014). Genetic variations in the HTR3A and HTR3B genes may be associated with the risk of developing POV but given the multifactorial causes of POV, larger studies are required to determine the true clinical significance of these observations (Rueffert et al., 2009; Ma et al., 2013).

XX. C. 2. Eating disorders

The 5-HT₃ receptor antagonist ondansetron reduces binge-eating, vomiting and depressive symptoms in patients with severe bulimia nervosa, leading to a return of normal eating, possibly by modulating cyclic increases in vagal nerve activity (Faris et al., 2006). Arguably, an ability of 5-HT₃ receptor antagonism to increase the threshold before satiation is reached (Janssen et al., 2011) could also play a role. Variants of the HTR3B gene have been associated with the restrictive subtype of anorexia nervosa (Hammer et al., 2009). It may also be possible to achieve long-term regulation of body weight by modulating different aspects of gastric motility (Janssen et al., 2011), perhaps with drugs that act at different 5-HT receptors (see below).

XX. C. 3. Carcinoid diarrhea

Carcinoid tumours in the colon can generate high levels of circulating 5-HT, causing diarrhoea by stimulating colonic motor functions (von der Ohe et al., 1993), via 5-HT₃ receptors (see above) and chloride ion secretion in human colon via 5-HT_{2A} and 5-HT₄ (ascending colon) and 5-HT_{2A} (descending colon) receptors (Borman and Burleigh, 1996). This is primarily treated with loperamide or a somatostatin analogue, such as octreotide, but 5-HT₃ receptor antagonists have helped, at least when given acutely, as have 5-HT_{2A} (ketanserin) receptor antagonists and methysergide, a non-selective 5-HT₁/ 5-HT₂ receptor agonist/ antagonist (Camilleri and von der Ohe, 1994; Schworer et al., 1995; Spiller, 2008a). Given that TPH1 is responsible for 5-HT production, perhaps its inhibition may represent a new treatment paradigm in carcinoid tumors (See Camilleri, 2011).

XX. C. 4. Functional GI disorders

These are a grouping of GI disorders that cannot be explained by structural or tissue abnormalities and as such are defined by symptoms. They include functional dyspepsia, irritable bowel syndrome (IBS) and several others (Longstreth et al., 2006).

XX. C. 5. Functional dyspepsia

The rationale for treatment of functional dyspepsia with a 5-HT receptor antagonist has not been established. Single doses of a 5-HT₄ receptor antagonist did not affect symptoms (Van Lelyveld et al., 2006) although an ability of 5-HT₄ receptor antagonism to prevent HCO₃⁻ release in rat duodenum by short-chain fatty acids (SCFA) has suggested a role when high levels of SCFAs occur in the upper GI tract during bacterial overgrowth (Akiba et al., 2014). More promisingly, a pilot study with patients dosed for twelve weeks with a 5-HT₃ receptor antagonist showed some improvement in 'adequate relief of pain or discomfort' (Talley et al., 2001) and an association between symptoms and 5-HT_{3A} receptor gene polymorphism has been suggested (Mujakovic et al., 2011). Arguably, these data find some consistency with an ability of 5-HT₃ receptor antagonism to prevent the experience of nausea in healthy volunteers induced by intraduodenal infusion of lipids (see Gershon and Tack, 2007), since early satiety and nausea are common symptoms in this group of patients (Vanheel et al., 2013), but are at variance with the lack of ability of 5-HT₃ receptor antagonism to change sensitivity to gastric distension (see Gershon and Tack, 2007).

XX. C. 6. IBS

In some pilot studies 5-HT₃ receptor antagonism reduced sensations caused by bowel distension in patients with IBS (e.g. Prior & Read, 1993; Goldberg et al., 1996), perhaps as a consequence of increased compliance to distension (Delvaux et al., 1998). These studies, together with the known ability to reduce colonic movements, prompted the evaluation and initial success of the 5-HT₃ receptor antagonist alosetron as a treatment for IBS patients with symptoms of diarrhoea as well as abdominal discomfort and/ or pain. The subsequent occurrence of ischaemic colitis in a small number of treated patients restricted use of alosetron and almost entirely stopped research into this area. It has since been concluded that ischaemic colitis is 2- to 4- times more likely to occur in patients with IBS regardless of treatment (Lewis 2011), suggesting that any future treatments of this form of IBS should not induce severe constipation to potentially exacerbate such a liability. Further, it should be noted that an ability of 5-HT₃ receptor antagonists to reduce sensations evoked by bowel distension has not been consistently observed (e.g. Hammer et al., 1993, and Zigelboim et al., 1995 in patients without ‘psychological disorders’), perhaps arguing for greater emphasis of future research on colonic movement disorders. Any association between IBS and *HTR3* subunit gene mutations remains uncertain (Niesler, 2011). Nevertheless, in patients with diarrhoea-predominant IBS the ability of alosetron to reduce colonic transit may be associated with long (LL) polymorphisms of the 5-HT transporter gene *5-HTTLPR*, which is associated with increased synthesis of SERT (SLC6A4) and inactivation of endogenous 5-HT (Camilleri et al., 2002). Also in this group of IBS patients, symptoms were improved in a pilot study using the 5-HT₃ receptor antagonist ramosetron, an activity correlating with increased expression of TPH1 and with *TPH1* gene polymorphism (Shiotani et al., 2014).

The 5-HT₄ receptor antagonist SB-207266 reduced stress-induced defecation in mice (Sanger et al., 2000) and in a pilot study with diarrhoea-predominant IBS patients, tended to reduce rectal sensitivity and reduced small intestinal transit (Houghton et al., 1999). However, lack of significant efficacy in larger studies stopped further development for this indication (De Ponti, 2004).

In some countries the 5-HT₄ receptor agonist tegaserod was registered for treatment of IBS and chronic constipation (see below for discussion on the potential use of 5-HT₄ receptor agonists in the treatment of IBS) but was then withdrawn because of potential cardiovascular liability and poor overall efficacy (Schiller and Johnson, 2008). Tegaserod has since been shown to act as a potent 5-HT_{2B} receptor antagonist (Beattie et al., 2004), reducing colonic motility (in rodents, not dogs; see above) and exerting a visceral anti-nociceptive activity in rodents (Ohashi-Doi et al., 2010; O'Mahoney et al., 2010). The extent to which each of these different activities translates to humans and/ or IBS patients is not clear. In parallel with the evidence that LL polymorphisms of the 5-HT transporter gene *5-HTTLPR* results in greater changes in colonic transit with alosetron, a clinical trial has shown that LL polymorphism is associated with reduced clinical efficacy of tegaserod in patients with constipation (Li et al., 2007).

LX1031, a locally acting TPH inhibitor, that does not cross the blood-brain barrier, has been found to be safe and well tolerated in an exploratory 4 week phase 2 study in patients with symptomatic, non-constipating IBS (Brown et al, 2011). Thus, reduction of mucosa-derived 5-HT may positively influence symptoms common to non-constipating IBS. A relationship was observed between symptom improvement and a reduction in 24-hour urinary 5-HIAA: thus, 5-HIAA can serve as a biomarker to estimate the rate of 5-HT synthesis and target engagement by the TPH inhibitor LX1031. However data from any further clinical development of this drug is lacking and the company Lexicon have confirmed development has been terminated.

Any involvement of the 5-HT₇ receptor in the mechanisms of visceral pain, following a proposed role in somatic pain (Andrews and O'Neill, 2011), is as yet unknown. Similarly, any involvement of 5-HT in the mechanisms of mucosal inflammation (see earlier) in patients with IBS has yet to be demonstrated.

XX. C. 7. Other GI Disorders

In colon from patients with diverticular disease, 5-HT₄ mRNA expression was reduced in the muscle but increased in the mucosa; expression of 5-HT_{2B} and 5-HT_{3A} mRNA was unchanged. The authors speculate that these changes could influence the intestinal motor disturbances associated with this disease (Böttner et al, 2014).

XX. D. Therapeutic benefits of 5-HT receptor agonists and antagonists

This section discusses the use of 5-HT receptor agonists (*exogenous* 5-HT) to treat diseases where any involvement of *endogenous* 5-HT in the mechanism of the disease is absent or unclear. The class of 5-HT₃ receptor antagonists (e.g. alosetron, ondansetron) for IBS-D and 5-HT₄ receptor agonists for chronic constipation or IBS-C (e.g. prucalopride) are extensively used in clinical practice and constitute first or second line therapeutic agents for these conditions. Efficacy and safety are documented by systematic reviews and meta-analyses (Andresen et al., 2008; Ford et al., 2009; Shin et al., 2014). The risk of ischemic colitis with alosetron (not observed with ondansetron) is estimated at about 1 in 1000 patients; however, there is also evidence that IBS itself is a risk factor the development of ischemic colitis (Huerta et al., 2011).

XX. D. 1. 5-HT₄ receptor agonists

At present, 5-HT₄ receptors appear to have little or no major roles in disorders of GI hypomotility, e.g. in idiopathic gastroparesis there were no overall changes in 5-HT₄ receptor expression apart from a reduced expression of the 5-HT_{4(c)} splice variant (van Lelyveld et al., 2008), yet 5-HT₄ receptor agonists have long been used to treat such disorders. This began with metoclopramide, a derivative of procaine found to have surprising anti-emetic and gastric prokinetic properties. Understanding the mechanisms of action of metoclopramide directly led to the discovery of the anti-emetic role of the 5-HT₃ receptor (Miner and Sanger, 1986) and in the description of a novel '5-HT-like' receptor affecting GI motility (Sanger, 1987b), later named as the 5-HT₄ receptor by Bockaert and colleagues who used similar ligands in CNS studies (Dumuis et al., 1988). Subsequently, a number of different 5-HT₄ receptor agonists were launched as prokinetic agents but none of the early examples are selective in their action, leading to cardiovascular complications (Sanger, 2009). Nevertheless, the selective 5-HT₄ receptor agonist prucalopride is now marketed as a treatment of chronic idiopathic constipation; others are in development and the potential use of such agents in the treatment of upper GI disorders associated with

gastric and/ or esophageal hypomotility is still being explored (Sanger, 2009; Broad et al., 2014a,b; Kessing et al., 2014). Interestingly, a low dose of the 5-HT₄ receptor agonist mosapride has been shown to increase human gastric accommodation in healthy volunteers (Amano et al., 2015), perhaps reflecting the ability of 5-HT₄ receptor agonists to increase nitrergic as well as cholinergic activity (Cellek et al., 2006), the former potentially increasing gastric fundus accommodation and the latter, gastric antrum motility and emptying. Since impaired gastric accommodation may contribute to the aetiology of symptoms in patients with post-prandial functional dyspepsia (e.g. early satiety and/ or nausea; Talley 2015), these data support the argument that such symptoms can be relieved by selective 5-HT₄ receptor agonists (Janssen et al., 2011b; Sanger et al., 2013).

In human colon, 5-HT₄ receptor activation is an effective prokinetic principle as it facilitates excitatory cholinergic and inhibitory nitrergic motor nerve activities (representing the ascending excitatory and descending inhibitory components of a peristaltic reflex), decreases muscle tension and increases chloride secretion from the mucosa into the lumen (Borman and Burleigh, 1996; Prins et al., 2000; Cellek et al., 2006; Broad et al., 2013). Evidence for facilitation of enteric sensory nerve activity remains uncertain (Gershon and Tack, 2007). More recent attention has been drawn to the possibility that 5-HT₄ receptor activation might stimulate bicarbonate secretion in rat proximal colon (Kaji et al., 2015) and might also reduce nociception in rats exposed to colo-rectal distension (Hoffman et al., 2012; Gilet et al., 2014). The latter activity could depend on a synergistic interaction with 5-HT₃ receptors in the mechanisms of allodynia (Smith et al., 1999), but also contrasts with the findings of Sugiuar et al (2004), who showed that the nociceptive functions of TRPV1 channels were facilitated by 5-HT₄ receptor activation in mouse colon. Similar responses have not yet been confirmed to occur in human colon but if successfully translated, 5-HT₄ agonists may be useful as suppositories or enemas, for treating IBS (Kale-Pradhan and Wilhelm, 2007; Mawe and Hoffman, 2013). To date, only the 5-HT₄ receptor agonist tegaserod has been fully tested as a potential treatment of IBS but poor efficacy at the 5-HT₄ receptor, potential confounding cardiovascular complications and the existence of additional ability to antagonist at the 5-HT_{2B} receptor (see above for discussion) greatly complicate the use of such data to argue for or against the use of 5-HT₄ receptor agonists as a treatment of any form of IBS.

Finally, the possibility that 5-HT₄ receptor activation might promote neurogenesis in adults has received support from studies using mice (increased bromodeoxyuridine incorporation into neurons, neural precursors or stem cells; Liu et al., 2011), guinea-pigs, rats and mice (regeneration of neural circuitry or recovery of reflex activity after rectal transection and anastomosis, accompanied by increased neurofilament and neural stem cell markers; Takaki et al., 2014) suggesting potential use of 5-HT₄ receptor agonists in treatments of disorders associated with intestinal aganglia.

XX. D. 2. Other 5-HT receptor agonists

Different 5-HT_{1A} receptor agonists, including buspirone, may reduce emesis induced by different stimuli in animals, including cisplatin and motion, although species differences in actions complicates the interpretation of data (Johnston et al., 2014). In patients with functional dyspepsia, repeat-dosing with the 5-HT_{1A} receptor agonist R137696 did not reduce dyspeptic symptoms or gastric accommodation (Tack et al., 2009).

When given acutely after meals to patients with functional dyspepsia, the 5-HT_{1B/1D} receptor agonist sumatriptan delayed gastric emptying, improved gastric accommodation and reduced the perception of gastric distension and early satiety (Tack et al., 2004). The suggestion that this receptor may be involved in the mechanisms of vomiting has not yet been resolved (Johnston et al., 2014), especially since sumatriptan may act on the yet to be defined 5-HT_{1P} receptor.

Partial 5-HT₃ receptor agonists (e.g. pumosetrag; CSTI-300) have been identified for treatment of patients with diarrhoea-predominant IBS (e.g. Moore et al., 2013; Roberts et al., 2020). CSTI-300 displays comparable efficacy to alosetron in a rat model of colon distension (Roberts et al., 2020). Pumosetraghas been evaluated in patients with gastro-esophageal reflux disease (Choung et al., 2014), reducing the rate of acid reflux events but not symptoms.

A summary of some 5-HT drugs in development for GI therapeutics is summarized in Table 22 and reviewed elsewhere (Valentin et al., 2015).

XXI. 5-HT receptors and the immune system

XXI. A. Introduction

The defense against pathogens is mediated by innate and adaptive immune mechanisms that act in the periphery and the central nervous system (CNS). 5-HT regulates inflammation and immunity by acting on 5-HT receptors that are differentially expressed on immune cells, both in rodents and humans. 5-HT acts as a potent chemoattractant, recruiting innate immune cells to sites of inflammation. 5-HT also alters the production and release of cytokines and cell activation/proliferation. Some immune cells, including mast cells and T lymphocytes, have the capacity to synthesize and release 5-HT, expanding the range of tissues for 5-HT signaling.

XXI. B. How do immune cells encounter 5-HT?

Although 5-HT is largely studied as a neurotransmitter, enterochromaffin cells of the gut produce most of the body's 5-HT that functions as a local hormone. These cells express tryptophan hydroxylase TPH1, a rate-limiting enzyme for 5-HT production (Walther et al., 2003). A second TPH isoform, TPH2, synthesizes 5-HT in the CNS and gut enteric nerves (Walther et al., 2003). 5-HT concentrations in blood and tissues are normally kept relatively low. Immune cells, however, may encounter 5-HT released in the gut mucosa or from platelets that sequestered 5-HT via the 5-HT transporter, SERT (SLC6A4). In turn, platelets can release accumulated 5-HT at sites of injury and inflammation. Platelet-derived 5-HT is important for attracting innate immune cells such as neutrophils to inflamed tissue (Duerschmied et al., 2013). In addition to platelets, dendritic cells (professional antigen-presenting cells) and B lymphocytes express SERT and thus, accumulate and release 5-HT. Interestingly, recent studies indicate that some immune cells are capable of 5-HT biosynthesis. Mast cells (tissue-resident cells) in rodents and humans express TPH1 and levels of 5-HT are elevated in patients with mastocytosis, who have greatly elevated mast cell numbers (Kushnir-Sukhov et al. 2007, Nowak et al. 2012). Further, T lymphocytes (O'Connell *et al.* 2006, León-Ponte *et al.* 2007; Urbina, 2014) also express TPH1 upon mitogen or T-cell receptor activation and can synthesize 5-HT. Interestingly, expression of TPH1 and 5-HT production is greater in CD8⁺ compared with CD4⁺ T cells (Chen et al., 2015).

XXI. C. 5-HT and hematopoiesis

It has been proposed that 5-HT acts at hematopoietic stem cell progenitors directly or via modulation of the bone-marrow microenvironment (Yang et al., 2007). Mice deficient in peripheral 5-HT (*Tph1*^{-/-}) display morphological and cellular features reminiscent of ineffective erythropoiesis (Amireault et al., 2011). Other data show that the bone-marrow composition of *Htr2b*^{-/-} mice displays a significant increase in Cd11b⁺/Gr⁺ cells that represents granulocyte precursors. This is associated with a significant reduction in Cd11b⁻/Cd31⁺ population that corresponds to immature endothelial progenitor cells in 5-HT_{2B}^{-/-} mice (Launay et al., 2012). These observations support the hypothesis that 5-HT signaling controls the differentiation of myeloid precursor cells, in particular, in the monocyte/macrophage lineages.

XXI. D. 5-HT and the immune tolerance

One well-documented way to control immunity and tolerance is through the regulation of nutrients in the microenvironment of immune cells. Best described is tryptophan deficiency mediated by the catabolic enzyme indoleamine 2,3-dioxygenase (IDO), which locally depletes tryptophan and liberates immunoregulatory metabolites known as kynurenines. T cell activation is exquisitely sensitive to local tryptophan catabolism, and thus this enzyme exerts profound protective effects in allo-fetal rejection, autoimmunity, and inflammation (Munn and Mellor, 2013). Although IDO is thought to be the major tryptophan-catabolizing enzyme outside of the liver, TPH1 shares a similar K_M to IDO (~20 μ M) (Mckinney et al., 2005) and can also potentially exhaust tryptophan to regulate immune tolerance. Indeed, in models of skin allograft tolerance, tumor growth and experimental autoimmune encephalomyelitis (multiple sclerosis), *Tph1* deficiency was shown to break allograft tolerance, to induce tumor remission, and to intensify neuroinflammation independent of the downstream product, 5-HT (Nowak et al., 2012).

XXI. E. 5-HT and the innate immune response

Innate immune system function involves monocytes, macrophages, dendritic cells, neutrophils, eosinophils, mast cells and natural killer cells that act immediately in the area of infection, leading to the destruction of pathogens. Innate immunity is primarily responsible for recognizing and eradicating

“non-self” molecules presented by pathogens, and is therefore confined to recognizing extracellular pathogens (bacteria vs. viruses). This response is nonspecific with respect to particular invaders, but provides immediate host defense against pathogens via pattern recognition by toll-like receptors (TLRs). Pathogen-associated molecular patterns (e.g. peptidoglycans, bacterial lipopolysaccharides-LPS, double-stranded viral RNAs) bind TLRs on antigen-presenting cells, namely, dendritic cells and macrophages. Antigen-presenting cells then phagocytose pathogens and display pathogen-derived peptides via the major histocompatibility complex (MHC) on their cell surface for recognition by leukocytes of the “adaptive” immune system. Antigen-presenting cells also secrete pro-inflammatory cytokines (e.g., IL1 β , IL-6, TNF α), prostaglandins, and histamine, which further activate physiological responses, alerting the body to infection/invasion. In addition to cellular protective mechanisms, innate immunity also includes the complement system, activated by foreign substances, antigen–antibody complexes (classical pathway), and Gram-negative bacteria (alternative pathway). This system leads to cell lysis, increased vascular permeability (allowing antibodies, innate immune cells, and fluid to enter tissues), and chemotaxis. The complement system also helps to activate antigen-presenting cells, namely, dendritic cells and B cells during specific immune responses. Innate immunity also functions to communicate the presence of pathogens to cells involved in adaptive immune responses (Baganz and Blakely, 2013). The local environment and the presence of stimulatory signals determine whether monocytes acquire dendritic cell or macrophage characteristics and functions. 5-HT receptors are expressed by a broad range of inflammatory cell types, including monocytes, macrophages and dendritic cells.

Neutrophils are the most abundant white blood cell and serve an essential role in innate immunity, particularly against bacteria. Duerschmied and colleagues (2013) reported that *Tpb1*^{-/-} mice show mild leukocytosis, e.g. elevated WBC (white blood cells) numbers compared with wild-type (WT) mice, primarily driven by an elevated neutrophil count. Despite this, 50% fewer leukocytes rolled on unstimulated mesenteric venous endothelium of *Tpb1*^{-/-} mice. Diminished rolling in *Tpb1*^{-/-} mice resulted in reduced firm adhesion of leukocytes after LPS treatment, and neutrophil extravasation into lung, peritoneum and skin wounds was reduced in *Tpb1*^{-/-} mice. 5-HT alone did not induce neutrophil migration *in vitro*, suggesting that endothelial adhesion was the primary deficit. Consequently, survival from LPS-induced endotoxic shock was improved in *Tpb1*^{-/-} mice. In conclusion, platelet 5-

HT promotes the recruitment of neutrophils in acute inflammation (Duerschmied et al., 2013), however, the nature of the 5-HT receptor(s) underlying these effects is unknown.

In human CD14 monocytes, mRNA expression of 5-HT_{1e}, 5-HT_{2A}, 5-HT₃, 5-HT₄ and 5-HT₇ receptors has been revealed (Dürk et al., 2005). 5-HT modulates the release of IL-1 β , IL-6, IL-8/CXCL8, IL-12p40 and TNF- α , while it has no effect on the production of IL-18 and IFN- γ in LPS-stimulated human blood monocytes. Moreover, 5-HT modulates mRNA levels of IL-6 and IL-8/CXCL8, but not of IL-1 β and TNF- α . Pharmacologic experiments suggested that signaling through the 5-HT₃ receptor up-regulates the LPS-induced production of IL-1 β , IL-6 and IL-8/CXCL8, but not that of TNF- α and IL-12p40. Furthermore, activation of the Gs-coupled 5-HT₄ and 5-HT₇ receptors increases secretion of IL-1 β , IL-6, IL-12p40 and IL-8/CXCL8, but in contrast, inhibits LPS-induced TNF- α release. Interestingly, 5-HT_{1e} and 5-HT_{2A} receptor agonists do not modulate the LPS-induced cytokine production in human monocytes (Dürk et al., 2005). Instead, 5-HT modulates cytokine production via activation of 5-HT₃, 5-HT₄ and 5-HT₇ receptors.

5-HT has been shown to upregulate the activity of peritoneal macrophages and to increase the *in vitro* activity of phagocytosis in a concentration-dependent manner via 5-HT_{1A/7} receptors and nuclear factor κ B (NF- κ B) (Freire-Garabal et al., 2003). Gene expression profiling of pro-inflammatory M1 (GM-CSF) and anti-inflammatory M2 (M-CSF) macrophages revealed that 5-HT_{2B} and 5-HT₇ receptor mRNAs are preferentially expressed by M2 macrophages, whereas the 5-HT₇ receptor is the only 5-HT receptor expressed in M1 macrophages (de Las Casas-Engel et al., 2013). The 5-HT_{2B} receptor is preferentially expressed by anti-inflammatory M2 macrophages and is also detected *in vivo* in liver Kupffer cells and in tumor-associated macrophages. Expression of 5-HT_{2C} receptors was also reported in alveolar macrophages, where 5-HT induces a rise in intracellular Ca²⁺ concentration and an increased expression of CCL2 (MCP-1) mRNA (Mikulski et al., 2010). LPS, the archetypal macrophage-activating stimulus that signals via TLR4, was shown to regulate the expression of 5-HT_{2B} receptors in mouse macrophages. 5-HT_{2B} receptor mRNA is increased 20-fold in murine thioglycollate-elicited peritoneal macrophages (Lattin et al., 2008). 5-HT was shown to inhibit the LPS-induced release of pro-inflammatory cytokines, to upregulate expression of macrophage M2 polarization-associated genes and to reduce the expression of M1-associated genes. Only 5-

HT₇ receptors mediate the inhibitory action of 5-HT on the release of pro-inflammatory cytokines. Both 5-HT_{2B} and 5-HT₇ receptors mediate the pro-M2 skewing effect of 5-HT. Blockade of both receptors during *in vitro* monocyte-to-macrophage differentiation preferentially modulates the acquisition of M2 polarization markers (de Las Casas-Engel et al., 2013).

In mice, it has been established that 5-HT is an important regulator of microglia, the brain resident macrophages, which derive from yolk sac hematopoietic stem cell precursors. In the presence of 5-HT, the microglial processes moved more rapidly towards a lesion, which is considered a chemotactic response. Similarly, the chemotactic response of cultured microglia to ATP is enhanced by 5-HT. Phagocytic activity determined by the uptake of microspheres reveals that 5-HT application decreases phagocytic activity of amoeboid microglia. The presence of microglial 5-HT_{2B}, 5-HT_{5A} and 5-HT₇ receptors was confirmed by patch-clamp experiments in culture and amoeboid microglia and by qPCR analysis of RNA isolated from primary cultured and acutely isolated adult microglia (Krabbe et al., 2012). This was recently confirmed by two-photon microscopy, showing that microglial processes moved rapidly toward the source of 5-HT via activation of the 5-HT_{2B} receptor (Kolodziejczak et al., 2015). Modulation of microglial functions like phagocytosis and migration is fundamental for the CNS since microglia can influence the balance of synaptogenesis and neuronal death during development and in pathology.

Platelet activation was reported in patients with various allergic disorders. Platelet-derived factors may influence monocytic differentiation into dendritic cells. Indeed, 5-HT alters differentiation of monocytes into dendritic cells (triggered by granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4), leading to dendritic cells with reduced expression of co-stimulatory molecules and CD1a, and higher expression of CD14. These 5-HT-triggered dendritic cells exhibit significantly reduced stimulatory activity toward allogeneic T cells. However, they show enhanced cytokine-producing capacity, including for IL-10 but not IL-12. 5-HT-induced alteration of dendritic cells phenotype and the reduction in antigen-presenting capacity are mediated via 5-HT_{1c}/5-HT₇ receptors (Kato et al., 2006).

Immature dendritic cells preferentially express mRNA for 5-HT_{1B}, 5-HT_{1c} and 5-HT_{2B} receptors, while mature dendritic cells mostly express 5-HT₄ and 5-HT₇ receptors. The mRNA expression level of the ligand-gated cation channel 5-HT₃ and the GPCR 5-HT_{2A} receptors are not modified during maturation. 5-HT stimulates 5-HT₃-dependent Ca²⁺ influx in both immature and mature dendritic cells. The 5-HT_{1B/1E} and 5-HT_{2A/2B} receptor stimulation induces intracellular Ca²⁺ mobilization via Gi/Gq proteins in immature, but not mature, dendritic cells. Activation of 5-HT_{4/7} receptors induces cAMP elevation in mature dendritic cells. Functional studies indicate that activation of 5-HT₄ and 5-HT₇ receptors enhances the release of the cytokines IL-1 β and IL-8, while reducing the secretion of IL-12 and TNF- α in mature dendritic cells (Idzko et al., 2004).

5-HT is able to induce oriented migration in immature but not in LPS-matured dendritic cells via activation of 5-HT_{1B/1E} and 5-HT_{2A/2B} receptors. Accordingly, 5-HT also increases migration of pulmonary dendritic cells to draining lymph nodes *in vivo*. By binding to 5-HT₃, 5-HT₄ and 5-HT₇ receptors, 5-HT up-regulates the production of the pro-inflammatory cytokine IL-6. Additionally, 5-HT influenced chemokine release by human monocyte-derived dendritic cells: production of the potent T helper cells Th1 chemoattractant IP-10/CXCL10 was inhibited in mature dendritic cells, whereas CCL22/MDC secretion was up-regulated in both immature and mature dendritic cells. Furthermore, dendritic cells matured in the presence of 5-HT switched to a high IL-10 and low IL-12p70 secreting phenotype. Consistently, 5-HT favored the outcome of a Th2 immune response both *in vitro* and *in vivo* (Müller et al., 2009). A recent study using *Htr7*^{-/-} mice confirmed 5-HT₇ receptor expression in CD103⁺CD11c⁺ dendritic cells found in colon (and spleen), and its importance in immune activation and gut inflammation (Kim et al., 2013).

Interestingly, like platelets, dendritic cells can take up 5-HT from the microenvironment and the antidepressant, fluoxetine, inhibits this uptake. Expression of 5-HT transporters (SERTs) is regulated by dendritic cell maturation, exposure to microbial stimuli, and physical interactions with T cells. Significantly, 5-HT sequestered by dendritic cells is stored within LAMP-1⁺ vesicles and subsequently released via Ca²⁺-dependent exocytosis, as confirmed by amperometric recordings (O'Connell et al., 2006).

5-HT is chemotactic for eosinophils. Notably, allergic asthma is characterized by infiltration of eosinophils, and plasma levels of 5-HT are elevated in symptomatic asthma patients. There is solid evidence that 5-HT contributes to this eosinophil recruitment. Indeed, 5-HT alone can stimulate in vitro migration of murine and human eosinophils (Boehme et al., 2004) (Kang et al., 2013). Although several 5-HT receptor subtypes are expressed, 5-HT_{2A} is the most prominent, and 5-HT_{2A} receptor antagonists inhibit 5-HT-induced, but not eotaxin-induced migration. Further, eosinophils roll in response to 5-HT in venules under conditions of physiological shear stress (Boehme et al., 2004) (Kang et al., 2013). Signaling via 5-HT_{2A} receptors is associated with changes in cell shape/morphology via activation of specific intracellular signaling molecules (ROCK, MAPK, PI3K and the PKC-calmodulin pathway) (Kang et al., 2013).

Mast cells have the capacity to synthesize and accumulate 5-HT (Kushnir-Sukhov et al., 2007). In turn, this stored 5-HT can be released upon IgE cross-linking. Further, mast cells express mRNA for multiple 5-HT receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT₆, and 5-HT₇ receptors (Kushnir-Sukhov et al., 2006). 5-HT can induce mast cell adherence to fibronectin and stimulate cell migration. However, there is no evidence that 5-HT degranulates mast cells or modulates their activation by IgE. Mast cells from the 5-HT_{1A} receptor knockout mouse (*Htr1A*^{-/-}) do not respond to 5-HT indicating a principal role for this receptor. Importantly, 5-HT attracts mast cells to sites of inflammation; injection of 5-HT into the skin enhances the accumulation of mast cells in wild-type but not in 5-HT_{1A} receptor-null mice.

Natural killer cells are large lymphocytes with innate killing capacity. Addition of 5-HT to mixtures of target cells and CD56⁺ natural killer-enriched human mononuclear cells strongly augmented natural killer cell cytotoxicity via 5-HT_{1A} receptors. This effect was indirect and involved 5-HT signaling at accessory monocytes. The cytotoxicity-enhancing effect of 5-HT was additive to that induced by IFN- α , IFN- γ , or IL 2, but not to histamine (Hellstrand and Hermodsson, 1987).

XXI. F. 5-HT and adaptive immunity

The response of a second immune system division, termed the adaptive, or specific, immune system, occurs within hours of an infection and involves antigen-specific recognition and destruction of pathogens by T and B lymphocytes. The two components of the adaptive immune system involve cell-mediated and humoral immunity. Cell-mediated immunity is carried out by T cells located in the thymus, lymph nodes, and circulation. Antigen presenting cells that migrate to lymph nodes will prime and educate T cells as to the nature of the pathogen. T cells then proliferate and differentiate into for example CD4⁺ T-helper inflammatory cells (Th1) that activate macrophages, CD4⁺ Th2 cells that aid antibody responses, or CD8⁺ cytotoxic cells that target cells infected with intracellular microbes. The second component of adaptive immunity involves the contributions of B cells, located in lymph tissue, spleen and in the circulation. Upon stimulation, B cells become plasma cells (with or without the help of Th2) that produce and secrete antibodies (immunoglobulins). Memory T and B cells recognize specific antigens and respond quickly. Thus, the adaptive immune system is distinguished from the innate immune system by its ability to identify, remember, and eliminate pathogens that have been designated as nonself. Adaptive immunity is triggered at the immune synapse, where peptide major histocompatibility complexes and co-stimulatory molecules expressed by dendritic cells are physically presented to T cells (Baganz and Blakely, 2013).

The mRNA expression of 5-HT receptors in lymphoid tissues of the rat, *ex vivo* isolated spleen, thymus, and peripheral blood lymphocytes include 5-HT_{1B}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT₆ and 5-HT₇ receptor mRNAs. Mitogen-stimulated spleen cells additionally expressed mRNA corresponding to the 5-HT₃ receptor (Stefulj et al., 2000). In the rhesus macaque, SERT positive cells were found among CD4⁺, CD3⁺, and CD3⁺CD4⁺ lymphocytes respectively (Yang et al., 2007). Fluoxetine significantly increases the number of lymphocytes expressing SERT, and stimulates an enrichment of CD8⁺ T cells, decreasing the CD4⁺/CD8⁺ ratio. Fluoxetine administration elevates the levels of IL-4 at 1, 2 and 3 weeks; and of IL-2, at 2 and 3 weeks. IL-4/IL-2 ratio is significantly increased in fluoxetine group respecting the controls and is similar during the 3 weeks of treatment (Fazzino et al., 2009).

There is long standing evidence that 5-HT can influence T-cell activation. Notably, mice treated with a selective, irreversible inhibitor of TPH1, para-chlorophenylalanine, exhibit a reduction in the number of CD25-positive T cells (Young *et al.* 1993, León-Ponte *et al.* 2007), suggesting that 5-HT

contributes physiologically to T cell activation. A screen for 5-HT receptor subtypes in murine T cells revealed expression of three subtypes; naïve T cells selectively express 5-HT₇ receptors while following T-cell activation there is a strong upregulation of 5-HT_{1B} and 5-HT_{2A} receptors (León-Ponte *et al.* 2007). Significantly, exogenous 5-HT induces rapid phosphorylation of extracellular signal-regulated kinase-1 and -2 (ERK1/2) and IκBα in naïve T cells, that is inhibited by preincubation with a selective 5-HT₇ receptor antagonist. Thus, 5-HT signaling via the 5-HT₇ receptor may contribute to early T cell activation. Yin *et al.* (2006) showed that 5-HT_{1B} receptor antagonists impaired the proliferation of helper CD4⁺ T cells in mouse and human. Inoue *et al.* (2011) showed that a 5-HT_{2A} receptor agonist enhanced Concavalin-A induced activation of murine CD4⁺ and CD8⁺ T cells, whereas a 5-HT_{2A} receptor antagonist blocked T-cell receptor mediated interleukin-2 and interferon-gamma production. Consistent with these data, Akiyoshi *et al.* (2006) showed that treatment with a 5-HT_{2A} receptor antagonist enhanced the survival of cardiac allograft in mice. Thus, these mouse data strongly support involvement of 5-HT receptors (5-HT₇, 5-HT_{1B} and 5-HT_{2A}) during early and late stage T cell activation.

Interestingly, although not detected in mouse, the 5-HT_{2B} receptor is found in human T cells. Gene expression profiles during human CD4⁺ T cell differentiation, identified the 5-HT_{2B} receptor with 10-fold greater expression in CD3^{high}CD4⁺CD8⁻ SP4 thymocytes over intrathymic T progenitor cells, CD3⁻CD4⁺CD8⁺ ‘double positive’ thymocytes (ITTP), CD3⁺CD4⁺CD8⁻CD45RA⁺CD62L⁺ ‘naïve’ T cells from cord blood (CB4) and CD3⁺CD4⁺CD8⁻CD45RA⁺CD62L⁺ ‘naïve’ T cells from adult blood (AB4) (Lee *et al.*, 2004). Further, 5-HT_{2B} receptors are differentially expressed among Th subsets. In human umbilical cord blood, Th cells cultured in the presence of cytokines promoting Th2 differentiation were found to increase 5-HT_{2B} receptor expression along with 50 Th2 differentially expressed genes (Aijö *et al.*, 2012).

5-HT may also modulate migration of human T cells. Human, but not mouse T cells, express functional 5-HT₃ receptors. 5-HT₃ receptor agonists selectively decrease T cell migration towards gradients of the chemokine CXCL12, but not to other chemokines such as CCL2 and CCL5. Interestingly, CXCL12 is highly expressed on vascular endothelium and inhibits T cell migration across endothelium and extravasation. In transmigration experiments, 5-HT₃ receptor stimulation reverses this effect of endothelial-bound CXCL12 on T cell migration (Magrini *et al.*, 2011). These data suggest that 5-HT can stimulate trafficking of T cells from blood to tissues.

T cells have the capacity to synthesize 5-HT and levels of TPH1 expression increase following T-cell activation (O'Connell *et al.* 2006, León-Ponte *et al.* 2007; Urbina, 2014; (Chen *et al.*, 2015). The precise signaling role for T-cell produced 5-HT is uncertain. Conceivably, TPH1 activity in T cells could act to exhaust tryptophan as has been proposed for mast cells (Nowak *et al.*, 2012). On the other hand, 5-HT produced by T cells might act in an autocrine or paracrine manner. Indeed, T cells express the type 1 vesicular monoamine transporter (VMAT1) responsible for vesicular storage of 5-HT, and VMAT1 expression increases following T-cell activation concomitant with TPH1. Further, Ca²⁺ elevations in T cells can trigger secretion of 5-HT. Interestingly, levels of TPH1 and monoamine oxidase A, the principal catabolic enzyme for 5-HT are greater in CD8⁺ compared to CD4⁺ T cells suggesting a specific biological role for 5-HT synthesis in this T-cell subset (Chen *et al.*, 2015). B lymphocytes have the capacity to sense and sequester 5-HT via SERT. 5-HT increases mitogen-stimulated CD19⁺ B lymphocyte proliferation in a concentration- and time-dependent manner. These effects are reproduced by a 5-HT_{1A} receptor agonist. 5-HT-induced increases in proliferation are blocked by 5-HT_{1A} receptor antagonists. Moreover, LPS-activated mouse spleen cells express specific binding sites for 5-HT_{1A} receptor, suggesting that 5-HT upregulates mitogen-stimulated B lymphocyte proliferation through 5-HT_{1A} receptors (Iken *et al.*, 1995). Further, mitogen-activated B-lymphocytes express higher levels of 5-HT_{1A} receptor mRNA and protein than resting cells. This upregulation is seemingly dependent upon NF-κB transcription factors, as specific inhibitors of this pathway prevent the increase in mRNA expression for the 5-HT_{1A} receptor (Abdoun *et al.*, 2001).

B lymphocytes express SERT and uptake of 5-HT leads to apoptosis of Burkitt lymphoma (BL) cells (Serafeim *et al.*, 2002). 5-HT may induce apoptosis via the intracellular serotonylation signaling pathway. Further, long-term treatment with SSRIs in humans leads to enhanced (~30%) numbers of B lymphocytes (Hernandez *et al.*, 2010). Interestingly, higher doses of SSRIs directly promote apoptosis of BL cells by inhibiting DNA synthesis, whereas normal peripheral and tonsillar B cells are relatively resistant to SSRI-induced apoptosis (Serafeim *et al.*, 2003). SERT has been detected in a variety of B-cell lines (Meredith *et al.*, 2005), revealing SERT as a potential target for a broad range of B-cell malignancies.

XXII. General summary and conclusions

The first official IUPHAR review on 5-HT receptors (Hoyer et al, 1994) was a landmark for the then rather complex 5-HT receptor field: it has come of age and has been cited well over 3000 times (Google Scholar). It followed a number of initiatives and meetings in the late 1980's, when the 5-HT receptor nomenclature committee was established (by our esteemed colleague and friend Paul Vanhoutte in 1987, who sadly died in 2019). The committee was constituted and met formally the first time in 1990 at the occasion of the 5-HT meeting in Basel (a satellite to the 1990 IUPHAR main meeting): a number of recommendations were made adapting to the new findings in transduction mechanisms and molecular biology of the receptors over the subsequent decade (Humphrey et al, 1993; Hoyer et al, 1994; Hartig et al, 1996; Hoyer and Martin, 1997; Martin et al, 1998; 2000; Hoyer et al, 2002). It is remarkable that the recommendations made at the time have, 1) been largely accepted by a community that was used to very different nomenclatures or even definitions of receptors, and 2) that very little needed to be changed or added to these recommendations. In the 1994 review, it was noted that the authors had a cumulated 100 years of active 5-HT research to share. A number of our colleagues have in the meantime retired from active research, or have moved to other professional priorities. There is a lot of new "blood" now on board to reflect the growing diversity of the research, which is currently performed in many different academic and SME (small or medium enterprise) pharmaceutical centers; the combined years in 5-HT research accumulated by the authorship has increased due to the considerably more authors on the present paper to address a more diverse range of complex issues.

What has clearly changed though, is the relative representation from Industry, which compared to the 1994 version is very much reduced. In 1994, there were six out of the eight authors who worked in 'big Pharma', whereas there are none for the present review. This is explained by the lesser interest for exploratory 5-HT research in Industry on the one hand, with less emphasis on 5-HT translational research, and a shift of research towards SME/Biotech; on the other hand, there is an increased interest in very basic aspects of 5-HT research, such as structural biology or the more recent advances in the immunological aspects, which were hardly addressed in the previous review of 1994. The shift in emphasis and thus authorship, was very much needed as the 5-HT receptor field has become more complex and possibly less the subject of "classical" pharmacologists as it was in the latter decades of the last century.

The apparent good news is that no new receptors have been identified, except for some additional 5-HT₃ receptor subunits whose function still remain to be defined clearly. On the other hand, there have been major advances with respect to 5-HT_{1B/1D} receptors: as far as can be told, all triptans act as 5-HT_{1B/1D} receptor agonists, and in the meantime, many different triptans have reached the market primarily for the acute treatment of migraine. Some of them e.g. sumatriptan may also act as 5-HT_{1F} receptor agonists. Thus, the 5-HT_{1B} receptor is most probably the main and sole target for triptans in the treatment of migraine, whereas the 5-HT_{1D} receptor, which is comparatively less abundant, may only play a minor role. Indeed, a study in migraine with a selective 5-HT_{1D} receptor agonist (PNU142633), was not conclusive; it can be argued that the compound was only a partial agonist and that target engagement may not have been optimal. Thus, the jury is still out to define a role for the 5-HT_{1D} receptor in physiology and disease. Because of the triptans, of which many starting with sumatriptan have affinity for it, the 5-HT_{1F} receptor has attracted quite some attention and there is clinical evidence (with lasmiditan) that this constitutes another target for the treatment of migraine. This is especially true for patients that want to avoid vascular side effects, since in contrast to the 5-HT_{1B} receptor, the 5-HT_{1F} receptor is not expressed in vascular tissues. The 5-HT_{1A} receptor is still actively investigated, especially since newer highly selective 5-HT_{1A} receptor ligands show very different patterns of pathway selectivity and thus may have clinical application in diseases as different as chronic pain, Parkinson's disease or Rett Syndrome and other forms of autistic disorders / mental retardation, as illustrated by the relatively recent FDA approval for compounds such as flibanserin, cariprazine, vortioxetine, for the treatment of female sexual desire deficit, schizophrenia and depression, respectively. Although these compounds have other activities, they all share 5-HT_{1A} receptor agonism with possible differences in receptor engagement in different brain regions. An interesting aspect with some of the newer 5-HT_{1A} receptors, is their variety of activities at different transduction systems, i.e. these compounds have various degrees of biased agonism or signaling. This is not unique to 5-HT_{1A} receptors, as probably most 5-HT GPCR agonists show different levels of biased signaling depending on their preferential activation of one or the other multiple combinations of receptor/ G protein and accessory proteins. This has become even more evident now that crystal structures exist for both 5-HT_{1B} and 5-HT_{2B} receptors, which show that various ligands can occupy different conformation in the same orthosteric pocket, which may explain why certain 5-HT_{2A} receptor agonists produce hallucinations where others do not. In addition, it has become evident that the orthosteric binding pocket is not a unique target for ligands, a number of ergolines (e.g. ergotamine or

DHE), may bind an accessory (allosteric site?), which has been well described for some metabotropic GPCRs (e.g. mGlu or GABA_B receptors) opening the possibility for allosteric 5-HT receptor modulators (some of which have already been proposed for e.g. 5-HT_{1B/1D} or 5-HT₃ receptors).

The aspect of species differences is a recurrent theme as illustrated by the amply documented and well-accepted differences in the pharmacology of 5-HT_{1B} receptors (explained by a single amino acid change in the core structure of the ligand binding site), or the multiple differences observed with splice variants of the 5-HT₄ or 5-HT₇ receptors. A potential function for the 5-HT_{1e} receptor in native tissue or cells is still to be identified; absence from rodents hinders the research and has made 5-HT_{1e} receptor drug discovery relatively unattractive in the absence of a link to disease. A similar point can be made about the 5-HT₅ receptors, where both a relative lack of tools and the absence of a link to disease also hinders progress, although recent advances in knowledge concerning the 5-HT_{5A} receptor may promote further research. However, as the 5-HT_{5B} receptor appears to be non-functional in humans, this likely prevents interest as a therapeutic target.

Significant progress has been made in the 5-HT₂ receptor family. The potential role played by 5-HT_{2B} receptors in valvulopathies led to many of the drugs acting as agonists at these receptors being withdrawn from the market since the early 2000's (fenfluramine, norfenfluramine, benfluorex, pergolide), keeping in mind that MDMA ('ecstasy') and its active metabolites act as 5-HT_{2B} receptor agonists, as may also be the case for a number of "designer" drugs. As a consequence, there is significant emphasis on screening for 5-HT_{2B} receptor agonism in preclinical safety studies and the 'red flag' on further clinical development of such compounds. It has been established that the 5-HT_{2C} receptor comes in a variety of edited forms (up to 24 possible variants in the human brain) that may be linked to disease (e.g. depression, suicide, impulsivity, addiction, spinal cord injury and obesity as induced by some antipsychotic drugs). The edited forms of the receptor can display different coupling ability, lower affinity for agonists and lower constitutive activity compared to the non-edited isoform, that can couple to multiple G proteins. In addition, both agonists (lorcaserin) and antagonists (agomelatine), have been / are being developed to treat obesity / schizophrenia/ addiction and depression / generalized anxiety disorder, respectively. Interestingly, in spinal cord injury, the 5-HT_{2C} receptor is less edited and expression is increased, resulting in constitutive activity and muscle spasms in the absence of any endogenous 5-HT, which can be reversed by inverse 5-HT_{2C} receptor antagonists. The 5-HT_{2A} receptor may be

less investigated, since early claims that linked 5-HT_{2A} to hypertension or sleep, did not result in clinical success. However, it should be kept in mind that all three, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{1B} receptors play a role in pulmonary hypertension, a disease with unmet need for treatment, since neither endothelin antagonists, nor PDE inhibitors are highly effective, although commonly prescribed. On another note, 5-HT_{2B} receptors appear to play a significant role in fibrosis, be it in the lung, liver and especially in the heart. 5-HT_{2A} receptor antagonism is a major component of second generation anti-psychotics (in combination with dopamine D₂ receptor antagonism and often many other pharmacological activities, e.g. blonanserin) and there is evidence that a 5-HT_{2A} receptor antagonist may show efficacy in certain sub-populations of schizophrenic patients. It may also be relevant that the 5-HT - glutamate link in schizophrenia may be related to the existence of heterodimers between 5-HT_{2A} and mGlu₂ receptors, although *in vivo* proof of concept remains to be established. Along these lines, there is evidence that 5-HT_{2A} receptors are able to form homodimers, similarly to 5-HT_{1B} or 5-HT_{1D} receptors; however, the latter two may also form heterodimers, which may explain the co-distribution that has been consistently observed for these two receptors. The 5-HT_{2C} receptor is also capable of dimerization *in vitro*, it may even form tetra or octamers, and it may form heteromers with the ghrelin or the melatonin 2 receptor.

Clearly receptor homo- and hetero-dimerisation is an ongoing subject of interest with respect to 5-HT receptors. In addition to information incorporated within relevant sections of this review, the reader is also directed to specialized papers on this subject (e.g. Lee et al., 2000; Herrick-Davis, 2013; Moreno et al., 2016; Moutkine et al., 2017; Maroteaux et al., 2019).

In the 5-HT₃ receptor field, similarly to what has been long known and accepted for other members of the Cys-loop ligand-gated ion channel superfamily (e.g. nicotine acetylcholine receptors), homomeric and heteromeric 5-HT₃ receptors are evident and new receptor molecular isoforms are still being investigated. Clinically, alosetron has been developed for the treatment of IBS with diarrhea, in contrast to 5-HT₄ receptor agonists, where the primary indication remains IBS with constipation, or primary constipation, in spite of the withdrawal of tegaserod from most markets. Obviously, the anti-emetic effects of 5-HT₃ receptor antagonists, whether in the short term or in the longer term following chemotherapy or possibly surgically-induced, are still a very salient feature of these drugs, even if in the meantime, combination therapy (with e.g. NK1 receptor antagonists), becomes the

accepted treatment. There has been a lot of research dealing with 5-HT₆ receptor antagonists in memory / dementia (e.g. idalopirdine) although the Phase III clinical data has been disappointing, whereas the 5-HT₇ receptor is somewhat less actively investigated as a clinical target. The mystery of the putative 5-HT_{1P} receptor in the gastro-intestinal tract remains, although heterodimerisation remains a favoured potential explanation albeit without clear direct evidence.

The more troubling news is that whereas receptors used to be defined based on structural, operational and transductional features, it becomes clear that some refinements are needed:

(1) In terms of structural knowledge, progress has been relatively slow: X-ray diffraction data from crystals exist for the 5-HT₃ receptor and also for example the 5-HT_{1B} and 5-HT_{2B} receptors. One of the limitations of this approach for GPCRs is that the conformation of the ligand-receptor complex is very much dependent on the G-protein heterotrimer associated with the receptor. In more recent years, we have learned that many receptors are able to couple to various pathways, and even are able to signal in the absence of G-proteins. In addition, there are multiple GPCR interacting proteins that may affect both signal transduction and receptor-ligand conformation, thus the pharmacological signature.

(2) The operational definition of a receptor (pharmacological profile based on rank orders of affinity of agonists and antagonists), which was the primary feature of receptors up to the 1990s, is now recognized as increasingly complex due to the dependence on the G-protein associated with the receptor under study, and other GPCR interacting proteins. Indeed, a number of drugs will have different affinities and potencies depending on the transduction system studied. Such variations may seem artificial and linked to the expression of receptors and transduction components in engineered cells, but we know that an endogenously expressed receptor can react very differently to a given ligand in a cell- and system-dependent manner (e.g. 5-HT₄ receptors in the GIT). Thus, the concept of functional selectivity or biased agonism/ antagonism is a reality (see so-called β -blocker which have rather different clinical features depending on their signaling characteristics e.g. carvedilol compared to propranolol, pindolol, nadolol). In contrast to other receptors, e.g. muscarinic or GABA receptors, there is little research addressing allosteric modulation for 5-HT receptors, with the possible exception of the 5-HT₃ receptor. However, it becomes clear from X-ray structural studies performed with some ergolines, that in addition to the

classical orthosteric binding pocket, some 5-HT receptors have an extended binding “site”, which is very reminiscent of that described for muscarinic allosteric ligands. Such molecular targets may offer attractive strategies for novel therapeutics.

The relatively recently recognized importance of the microbiome continues to grow (Gilbert et al., 2018) and one aspect of this relevant to the present paper is the regulation of 5-HT receptors by bacteria-derived metabolites (e.g. Yano et al., 2015; Bhattarai et al., 2017; Cohen et al., 2017); understanding the ‘physiological’ and ‘pathological’ consequences of such modulation will no doubt provide impetus for developing therapeutic strategies harnessing these mechanisms.

In conclusion, it is a clear understatement to say a lot has been learnt since 1994, but still some old questions remain unanswered, and many new questions will keep 5-HT researchers busy for years to come. The appreciated complexity of the 5-HT system relates less to the number of 5-HT receptor classes, families and subtypes which *per se* was a conceptual challenge for some researchers in the 1980s and 1990s, than to the actual complex nature of the ligand / receptor / G protein / arrestin and/or other interacting protein complexes that vary according to species, organ, cells, gender and disease state. This intricacy renders the pharmacological definition of a given receptor, or a ligand, challenging since it may all depend on the nature and environment of the supramolecular complex, which is being specifically addressed.

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Figure 1. *In situ* hybridisation detection of 5-HT_{1A} receptor mRNA expression in rat (A) and human brain (B) at the level of the hippocampus. CA1, dentate gyrus (DG) of the hippocampus and para-hippocampal gyrus (PHG). Adapted from Burnet et al., 1995 (with permission).

Figure 2. Biased agonism at the 5-HT_{1A} receptor offers the potential to target subpopulations of 5-HT_{1A} receptors.

Figure 3. The evolution of “5-HT₁-like” receptors into the different sumatriptan-sensitive 5-HT₁ receptor subtypes and the sumatriptan-insensitive 5-HT₇ receptor. Modified from Saxena et al. (1998). For references see Hartig et al. (1996); Hoyer and Martin (1997); Villalón et al. (1997); Villalón and Centurión (2007).

Figure 4. *In situ* hybridisation detection of 5-HT_{1B} and 5-HT_{1D} receptor mRNA in rat brain (and 5-HT_{1B} receptor mRNA in the posterior communicating artery [reverse autoradiogram; K]). 5-HT_{1B} (B-K) and 5-HT_{1D} (B²-J') receptor mRNA. Anterior olfactory nucleus (AON), frontal cortex (FrCx [layer VI]), caudate putamen (CPu), nucleus accumbens (Ace), cingulate cortex (CgCx), parietal motor cortex (layers III and V), antero-ventral thalamic nucleus (AV), CA1 region of the hippocampus (CA1), arcuate hypothalamic nucleus (Arc), basolateral amygdaloid nucleus (BL), subthalamic nucleus (STh), posterior communicating artery (PCA), superficial grey layer of the superior colliculus (SuG), interpeduncular nucleus (IP) and Purkinje cells of the cerebellum (Pur), primary olfactory cortex (PO), olfactory tubercle (Tu), reuniens nucleus (Re), nucleus of Darkschewitsch (DK), red nucleus (R), inner posterior subnucleus of the interpeduncular nucleus (IPIP) and medial vestibular nucleus (MVe). Scale bar is 5 mm (except K where is 0.5 mm). Adapted from Bruinvels et al., 1994 (with permission).

Figure 5. Alignment of human 5-HT_{1e} and 5-HT_{1F} receptor amino acid sequences. Sequence homology is assessed by Basic Local Alignment Search Tool (BLAST, copyright National Library of Medicine) for protein sequences. Transmembrane domains (TMD 1 -7) were determined previously (Bai et al., 2004) and highlighted by yellow rectangles. **Nonpolar**, **uncharged polar**, **acidic polar**, and **basic polar** amino acids are labeled by corresponding color.

Figure 6. 5-ht_{1e} receptor expression in guinea pig and rat brain.

Top; immunohistochemical staining of the 5-ht_{1e} receptor in the hippocampus A: Coronal section of guinea pig hippocampus at the septal pole of the DG. B; Coronal section of guinea pig hippocampus near the temporal pole of the DG. C; Coronal section of rostral guinea pig hippocampus shows a lack of 5-ht_{1e} receptor staining in the CA3-CA2 region. D; Rat hippocampus (coronal section of DG septal pole) does not stain for 5-ht_{1e} receptors. Molecular layer (ML), granular cell layer (GCL), polymorphic layer (PML). Scale bars = 100 μm.

Bottom; histogram of radioligand 5-ht_{1e} receptor binding sites in homogenates of guinea pig brain. High levels of 5-ht_{1e} receptor binding sites are detected in the hippocampus and olfactory bulb (*p<0.05 compared to “Whole Brain”, one-way ANOVA with Dunnett’s post-test). Data are the means ± SEM of three independent experiments performed in triplicate. Adapted from Klein and Teitler (2012; with permission).

Figure 7. *In situ* hybridisation detection of 5-HT_{1F} receptor mRNA expression in guinea pig brain.

Frontal cortex (FRCX), anterior olfactory nucleus (AON), cingulate cortex (CGCX), septo-hippocampal nucleus (SHI), olfactory tubercle(TU), primary olfactory cortex (PO), claustrum (CL), medial amygdaloid nucleus (ME), supraoptic hypothalamic nucleus (SO), layerIV of the parietal motor cortex (IV), dentate gyrus (DG) and CA1-3 field (CA1-3) of the hippocampus. Adapted from Bruinvels et al., 1994 (with permission).

Figure 8. Primary structure of 5-HT_{2A} receptors from various species.

Figure 9. *In situ* hybridisation detection of 5-HT_{2A} receptor mRNA expression in rat and human brain.

Reverse autoradiograms of the rat (A) and human brain (B-F). Human section; hippocampus and surrounding cortex (B), orbitofrontal cortex (Brodmann area 11; C), striate cortex (Brodmann area 17; D), superior temporal gyrus (Brodmann area 22; E) and brainstem at the level of the raphe nucleus (F; not lack of 5-HT_{2A} receptor mRNA evident). Adapted from Burnet et al. (1995; with permission).

Figure 10. Primary structure of human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors.

Figure 11. 5-HT_{2B} receptor immunoreactivity in rat brain.

Immunohistochemical detection of 5-HT_{2B} receptor immunoreactivity within Purkinje cells in the cerebellum (A), multipolar neurons in the lateral septum (B), multipolar and bipolar neurons in the medial amygdala (C), cells in the dorsal hypothalamic nucleus (D). In each case the staining was abolished in adjacent sections by co-incubation with synthetic 5-HT_{2B} receptor peptide (not shown). Adapted from Duxon et al. (1997; with permission).

Figure 12. Landmarks in 5-HT_{2C} receptor research and development

Identification and characterization of the 5-HT_{2C} receptor and the development of 5-HT_{2C} receptor-directed ligands has evolved over the last 40 years (black text). The 5-HT_{1C} receptor was reclassified as the 5-HT_{2C} receptor in the mid-1990s (purple text). Examples of novel pharmacological tools (blue text) as well as the first-in-class selective 5-HT_{2C} receptor agonist approved for obesity (red text) are illustrated in the timeline. Refer to the text for details; superscripted numbers indicate literature citations:

1. Peroutka and Snyder 1979)
2. Pazos, Hoyer et al. 1984; Yagaloff and Hartig 1985
3. Closse, 1983
4. Pazos et al., 1984; Pazos and Palacios, 1985; Pazos et al., 1985; Hoyer et al., 1986
5. Conn et al., 1986; Conn and Sanders-Bush, 1986a; Hoyer et al., 1989; Chang et al., 2000
6. (rat) Lubbert et al., 1987; Julius et al., 1988; (human) Saltzman et al., 1991; Milatovich et al., 1992; Stam et al., 1994; Xie et al., 1996; (mouse) Yu et al., 1991; Foguet et al., 1992
7. Hoffman and Mezey, 1989; Molineaux et al., 1989; Mengod et al., 1990
8. Millar et al., 2007
9. Hoyer, 1988; Humphrey et al, 1993; Hoyer, 1994Hoyer et al., 1994
10. Tecott et al., 1995
11. Berg et al., 1994; Berg et al., 1998a
12. Burns et al., 1997
13. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm>
14. Bromidge et al., 1997; Kennett et al., 1997
15. Herrick-Davis et al., 1999
16. Di Giovanni et al., 1999; Di Matteo et al., 1999; Gobert et al., 2000
17. Becamel et al., 2002; Becamel et al., 2004
18. Basile et al., 2002; Tsai et al., 2002; Theisen et al., 2004; Templeman et al., 200)
19. Herrick-Davis et al., 2006; Herrick-Davis et al., 2007
20. Rosenzweig-Lipson et al., 2007a; Tong et al., 2010; Dunlop et al., 2011; Dunlop et al., 2005
21. Xu et al., 2008
22. Leggio et al., 2009b
23. Kawahara et al., 2008; Morabito et al., 2010a
24. Kishore and Stamm, 2006; Doe et al., 2009;Kishore et al., 2010
25. Ji et al., 2006; Anastasio et al., 2013
26. Im et al., 2003; Ding et al., 2012; Wild et al., 2016
27. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm>; Thomsen et al., 2008; Smith et al., 2009;Smith et al., 2010

28. <http://www.eisai.com/news/news201465.html>; Cunningham and Anastasio, 2014; Rezvani et al., 2014; Higgs et al., 2015; Howell and Cunningham, 2015; Harvey-Lewis et al., 2016
29. Nocjar et al., 2015; Anastasio et al., 2015
30. Herrick-Davis et al., 2015
31. Schellekens et al., 2015; Kamal et al., 2015
32. Di Giovanni and De Deurwaerdere, 2016; Venzi et al., 2016
33. Xu et al., 2016

Figure 13. 5-HT_{2C} receptor expression in rat brain.

In situ hybridisation detection of 5-HT_{2C} receptor mRNA (A-D) and 5-HT_{2C} receptor autoradiography (A'-D') from adjacent sections. Nucleus accumbens (Acb), anterior olfactory nucleus (AON), bed nucleus stria terminalis (BST), hippocampus CA1 field (CA1), central gray (CG), choroid plexus (ChP), caudate-putamen (CPu), dentate gyrus (DG), globus pallidus (GP), lateral habenular nucleus (Lhb), medial geniculate nucleus (MG), posterior cingulate cortex (PCg), primary olfactory cortex (PO), subiculum (S), substantia nigra (SN), subthalamic nucleus (STh). Scale bar = 1 mm. Adapted from Mengod et al. (1990; with permission).

Figure 14. Regional CNS localization 5-HT_{2C} receptors and functional correlates

The full-length 5-HT_{2C} receptor is localized exclusively in the central nervous system with good agreement between mRNA and protein distribution in the majority of brain regions. The postulated signaling components (shown in normal text), neurochemical and/or neurophysiological correlates (shown in *italic* text) and *in vivo* effects (shown in CAPITAL text) are illustrated.

Figure 15. Immunohistochemical detection of 5-HT_{3A} and 5-HT_{3B} receptor subunit expression in human hippocampus. 5-HT_{3A} and 5-HT_{3B} subunit immunoreactivity brown immunoreaction product in whole hippocampal section (large plates) is shown with fields of the hippocampus CA1-CA3, hilus (CA4) and dentate gyrus (DG), which are also shown at higher magnification (small plates; scale bars represent 50 μ m). Immunoreactivity was not detected when either primary antibody was replaced by pre-immune serum (No 1^o) or following pre-absorption with the immunising peptide (Peptide block). Subsequent to the detection of immunoreactivity, sections were histologically stained with haematoxylin to aid identification of hippocampal fields. Adapted from Brady et al. (2007; with permission).

Figure 16. 5-HT₃ receptor autoradiography in the human brainstem.

Left: [³H]-(S)-zacopride binding to the 5-HT₃ receptor in coronal section of human brainstem at the level of the chemoreceptor trigger zone (area postrema [AP], nucleus tractus solitarius [NTS] and dorsal motor nucleus of the vagus nerve [X]). Right: Adjacent section stained for acetylcholinesterase (hypoglossal nerve nucleus). [³H]-(S)-zacopride binding in the presence of ondansetron (1.0 μM) was absent (not shown).

Figure 17. 5-HT₃ receptor protein expression (5-HT3A and 5-HT3B subunits) in human gut.

(A) Immunolabeling of a ganglion in the human submucous plexus with an antibody against the 5-HT3A subunit. (B) The same ganglion as in A stained with an antibody against the human neuronal protein HuC/HuD, which labels all neurons. All anti-HuC/HuD—positive neurons are immunoreactive for the 5-HT3A antibody. (C) Immunolabeling of another human submucous ganglion with an antibody against the 5-HT3B subunit. (D) The same ganglion as in C stained with anti-HuC/HuD. All anti-HuC/HuD—positive neurons were immunoreactive for the 5-HT3B antibody. Scale bar in A applies also for B–D. (E) Detection of h5-HT3B immunoreactivity by SDS polyacrylamide gel electrophoresis/Western blot. Lane 1, HEK293 cells stably expressing with h5-HT3A subunit; lane 2, HEK293 cells stably expressing both the h5-HT3A and h5-HT3B subunits; lane 3, human large intestine; lane 4, human small intestine. Numbers are the positions of the molecular weight markers (kDa). Adapted from Michel et al. (2005; with permission).

Figure 18. Primary structure of human 5-HT₄ receptors.

The amino acid sequences of the identified splice variants are depicted. 5-HT₄ receptors have identical sequences up to L³⁵⁸ and differ by the length and composition of their C-terminal domain. The 5-HT_{4(h)} variant, which presents an insertion of 14 residues in the second extracellular loop, has been isolated in combination with the b isoform and it is called 5-HT_{4(hb)}. N-glycosylation sites on N⁷ and N¹⁸⁰ are indicated. Palmytoylation sites on C³²⁸, C³²⁹ (common to all splice variants) and C³⁸⁶ (in the a isoform) are schematized. This figure has been established in accordance with the last human genome assembly (Genes, Ensembl release 82) and modified from (Padayatti et al., 2013).

Figure 19. 5-HT₄ receptor expression in the human brain.

In situ hybridisation detection of 5-HT₄ receptor mRNA (B-D) and 5-HT₄ receptor autoradiography of radioligand binding sites (³H]R116712 total binding [G-H] and non-specific binding [J-K]). Nucleus accumbens (Acc), hippocampal fields (CA1-3), caudate nucleus (Cd), dentate gyrus (DG), entorhinal cortex (Ent Cx), internal capsule (Ic), putamen (Pu), subiculum (S), substantia nigra (SN; no mRNA evident), tail of caudate nucleus (TCd). Adapted from Bonaventure et al. (2000; with permission).

Figure 20. Structure and activities of 5-HT₄ receptor inverse agonists.

The inverse agonist activity was studied according to the ability of the compounds to inhibit the constitutive activity (activity in the absence of agonists). 5-HT_{4(a)} receptors were expressed in COS-7 cells (1500 ± 130 fmol/mg). The constitutive cAMP production in presence of the receptor is equal to $720 \pm 50\%$ of the activity obtained in the absence of receptor. From (Joubert et al., 2002).

Figure 21. *In situ* hybridisation detection of 5-HT_{5A} receptor mRNA expression in mouse brain.

Dark field of the emulsion autoradiograph of an horizontal section through an adult mouse brain. Cerebral cortex (Cx), olfactory bulb (OB), hippocampus (H), cerebellum (Cb), CA fields of the hippocampus CA (CA1-3), dentate gyrus (DG), granule cell layer of the cerebellum (G). Adapted from Plassat et al. (1992; with permission).

Figure 22. *In situ* hybridisation detection of 5-HT_{5A} receptor mRNA expression in human brain.

i and ii: Dark-field autoradiographs of coronal sections of human hippocampus and surrounding regions. CA1, CA3 fields and the dentate gyrus (DG) of hippocampus, entorhinal cortex (EC) and subiculum (S). Scale bars, 0.2 cm.

A: Dark-field autoradiograph of a coronal section of the cerebellar cortex: the Purkinje cells are heavily labelled (high magnification of Purkinje cells in bright-field (B) and dark-field (C). Scale bars 600 μm (A), 500 μm (B) and 900 μm (C).

Adapted from Pasqualetti et al. (1998; with permission).

Figure 23. *In situ* hybridisation detection of 5-HT_{5b} receptor mRNA expression in rat brain.

Coronal (A) and horizontal (E) rat brain sections. C: Nissl stain of the section used to generate the autoradiogram in A. F: Radioactive oligonucleotide probe in the presence of excess unlabelled probe. CA1 and CA3; CA fields of the hippocampus; Cb, cerebellum; CPu, caudate-putamen; Ctx, cortex; DG, dentate granule cells; Ent, entorhinal cortex; Hy, hypothalamus; MHb, medial habenula. Adapted from Wisden et al. (1993; with permission).

Figure 24. Evidence for 5-HT raphe neurones expressing the 5-ht_{5b} receptor.

Top row: Visualization of 5-HTT and 5-ht_{5b} receptor mRNAs in the dorsal raphe. A; a consecutive section to B and C stained with cresyl violet for anatomical reference. The approximate limits of the dorsal raphe (DR) and its subdivisions—lateral wings and medial portion—are depicted. B; a bright-field photomicrograph where numerous cell profiles express 5-HTT mRNA are visualized using digoxigenin-labelled oligonucleotide probes. C; a dark-field photomicrograph from an emulsion-dipped tissue section displaying 5-ht_{5b} receptor mRNA signal in the DR. Medial longitudinal fasciculus (mlf), periaqueductal gray (PAG). Scale bar = 0.5 mm.

Bottom row: Schematic representations of the rat lower midbrain and upper pons showing the sub-regional location of cells co-expressing 5-ht_{5b} receptor mRNA and 5-HTT mRNA (filled circles) and cells expressing only 5-HTT mRNA (empty circles) in the DR and central superior nucleus (CS or median raphe). Anterior tegmental nucleus (AT), cerebral aqueduct (AQ), decussation of the superior cerebellar peduncle (dscp), interpeduncular nucleus (IPN), tectospinal pathway (tsp), ventral tegmental area (VTA), ventral tegmental nucleus (VTN). Adapted from Serrats et al. (2004; with permission).

Figure 25. *In situ* hybridisation detection of 5-HT₆ receptor mRNA expression in rat brain.

Autoradiographic visualization of 5-HT₆ receptor mRNA in rat brain (A, B, C and D) and relative absence of signal when adjacent sections probed with the sense control (c and d). Anterior nucleus accumbens (ANA), cingulate cortex (CgCx), cortex (Cx), dentate gyrus (DG), habenula (Hb), hippocampus (Hp), olfactory tubercle (OT), prefrontal cortex (PfCx), pyriform cortex (PyCx). Adapted from Ward et al. (1995; with permission).

Figure 26. 5-HT₇ receptor mRNA and protein expression in rat brain.

Comparative *in situ* hybridization localization of 5-HT₇ receptor mRNA (ISHH; A, C, E and G) and immunocytochemical location of 5-HT₇ receptor protein (ICC; B, D, F, H), respectively. Amygdala (amyg), anteroventral thalamic nucleus (av), anterior thalamic nuclei (atn), hippocampus (hip), lateral septal nuclei (lsn), neocortex (neo), medial preoptic area (mpa), piriform cortex (pir), paraventricular thalamic nuclei (pvn), posterior paraventricular nucleus (pvp), retrosplenial cortex (rc), suprachiasmatic nuclei (scn), striatum (str), tenia tecta (tt). Adapted from Neumaier et al. (2001; with permission).

Figure 27. 5-HT₇ receptor binding sites in human brain.

Autoradiographic detection of [³H]SB-269970 binding to 5-HT₇ receptors in the human brain. Autoradiograms showing the distribution of 5-HT₇ receptors at the level of the thalamus (left column) and dorsal striatum (right column). B plates; total binding. C plates; non-specific binding (inclusion of 5-HT, 10 μM). A plates; line drawings of brain hemisphere contours with square showing location of sections for the autoradiograms below. Anterior cingulate gyrus (ACG), amygdala (Amg), anterior thalamus (Ath), caudate nucleus (Ca), dentate gyrus (DG), dorsal raphe (DR), hippocampus (Hi), substantia nigra (SN), posterior cingulate gyrus (PCG), putamen (Pu), thalamus (Th). Adapted from Varnas et al. (2004; with permission).

Figure 28. Structures of 5-HT_{1B}, 5-HT_{2B} and 5-HT_{2C} receptors

PyMol renderings of the 5-HT_{1B} receptor in complex with ergotamine (Left: Wang et al., 2013; Wacker et al., 2013) and the 5-HT_{2B} receptor in complex with LSD (Wacker et al., 2017) demonstrating different binding pockets for ergotamine and LSD (see Wacker et al., 2017 for details). The figure also shows inactive-state structure of the 5-HT_{2C} receptor (Peng et al, 2018) and the G-protein coupled state of the 5-HT_{1B} receptor (Garcia-Nafra et al, 2018)

Figure 29. Architecture and ligand binding sites of 5-HT₃ receptors

a, Cartoon representation of a single subunit viewed parallel to the plane of the membrane.

b, Cartoon representation of the entire pentameric receptor, in the same orientation (the subunit of panel (a) is equivalent to the yellow subunit). One out of the five stabilizing VHH15 single-chain llama antibodies is shown in pale green and labeled VHH15.

c, Surface representation of the receptor highlighting binding clefts in blue (neurotransmitter site), yellow (anesthetics intra-subunit site), orange (PU-02 and anesthetics inter-subunit site), purple (extracellular allosteric pocket) and olive (pore blockers site). The subunit equivalent to the one of panel (a) appears in darker grey.

Figure 30. The neurotransmitter binding site of the 5-HT₃ receptor

a, Global view of the site, at the interface between two subunits represented as cartoons, viewed from parallel to the plane of the membrane. Binding elements of the principal subunit (A, B, C) and of the complementary subunit (D, E, F, G) are color-coded.

b, Surface view representing the electrostatic potential in the same orientation. The surface has been removed around to yellow loop C that would cover it, for clarity. The inset illustrates motions of loop C associated with binding of an agonist (blue, contracted conformation, PDB 2BYQ), an antagonist (grey, extended conformation, PDB 2C9T) or the stabilizing llama antibody VHH15 (salmon).

c, Close-up views of the binding site with essential residues, including those of the aromatic box. On the right panel the 5-HT_{3A} receptor structure is superimposed with the 5-HTBP structure co-crystallized with granisetron (in yellow). The principal subunits are superimposed and as a consequence of different subunit/subunit orientation, the strands of the complementary subunit are shifted. This superimposition illustrates the diversity and complementarity of structural templates.

Figure 31. The intracellular domain of the 5-HT₃ receptor

a, Surface representation of the intracellular domain viewed parallel to the membrane plane. The left part shows the external surface while the right part shows a cut-through and thus depicts the intracellular vestibule, the lateral obstructed portal and the constriction along the pore axis. The arrow indicates the plausible exit for ions

b, Backbone representation of MA-M4 helices (grey, two subunits shown) with the numerous charged residues (blue and red for positively and negatively charged residues) depicted as sticks. The green cartoon shows for one subunit the M3 and MX helices and their connecting loop that plug the portal (yellow oval). The hydrophobic residues that create the tight bundle of MA helices are in yellow, and the triplet of arginine determinant for channel conductance are labeled in bold font.

Figure 32: Role of Fyn, Jab1 and SNX 1 recruitment by 5-HT₆ receptor in receptor-operated signalling and functions

Association of Fyn with 5-HT₆ receptor C_t increases receptor cell surface localization and, consequently, receptor-operated G protein signalling. Fyn is also involved in Erk1/2 activation by 5-HT₆ receptors. Fyn phosphorylates Tau to control its association with microtubules and is involved in neuronal migration and A β -induced synaptic deficits and neurotoxicity. Association of 5-HT₆ receptor with Jab1 stabilizes surface expression of the receptor and is essential for its activity. 5-HT₆ receptor stimulation increases nuclear translocation of Jab1, a process that might reduce cell death induced by hypoxia. The 5-HT₆ receptor also interacts with SNX14, which inhibits receptor functions by sequestering G α_s and promoting receptor endocytosis and degradation.

Figure 33. Engagement of Cdk5 and mTOR signalling pathways by 5-HT₆ receptor and their role in neurodevelopmental processes and cognition

Left panel: The 5-HT₆ receptor constitutively interacts with Cdk5 (and its activator p35), which phosphorylates the receptor at Ser³⁵⁰. This enables 5-HT₆ receptor to promote neurite growth *via* the activation of the Rho GTPase Cdc42. Cdk5 activity, under the control of 5-HT₆ receptor, also enables migration of pyramidal cortical neurons, likely *via* the phosphorylation of doublecortin (DCX) and FAK. These effects are agonist-independent and prevented by inverse agonists. *Right panel:* The 5-HT₆ receptor recruits several proteins of the mTOR pathway, including mTOR itself and Raptor, two protein components of the mTORC1 complex, neurofibromin (NF1), Vps34 and Rheb. Prefrontal 5-HT₆ receptors engage mTOR signalling upon agonist stimulation and in rat neurodevelopmental models of schizophrenia to compromise social cognition and episodic memory, while 5-HT₆ receptor blockade by antagonists or direct mTOR inhibition by rapamycin rescue cognitive deficits in these models.

Table 1. Nomenclature for 5-HT receptors

5-HT receptor groups	Nomenclature for 5-HT receptors in the group	Comments
5-HT ₁ receptors		
	5-HT _{1A} receptor	
	5-HT _{1B} receptor	
	5-HT _{1D} receptor	
	5-ht _{1e} receptor	Lower case appellation used by convention since a functional response in native cells of tissues has not been identified.
	5-HT _{1F} receptor	
5-HT ₂ receptors		
	5-HT _{2A} receptor	
	5-HT _{2B} receptor	
	5-HT _{2C} receptor	
5-HT ₃ receptors	Native receptors of unknown stoichiometry: 5-HT ₃ receptor Heterologous expression of known subunits e.g. Homomeric receptor: 5-HT _{3A} receptor Heteromeric receptor: 5-HT _{3AB} receptor 5-HT _{3AC} receptor etc	Five known subunits: 5-HT3A, 5-HT3B, 5-HT3C, 5-HT3D, 5-HT3E 5-HT ₃ receptors are pentameric complexes with the presence of 5-HT3A subunits a prerequisite for function ie only the homomeric 5-HT _{3A} receptor is functional. Heteromeric 5-HT ₃ receptors are likely to require at least two 5-HT3A subunits.
5-HT ₄ receptor	5-HT ₄ receptor	
5-HT ₅ receptors	5-HT _{5A} receptor	
	5-ht _{5b} receptor	Lower case appellation is used by convention since a functional response in native cells of tissues has not been identified.
5-HT ₆ receptor		
5-HT ₇ receptor		

Table 2. Overview of the amino acid structure, gene loci and symbols and gene name of the human, mouse, rat, dog and rhesus macaque monkey for 5-HT_{1A} receptors.

Species	Bp	AA	AA Homology with human (%)	Chromosome Location	Gene Symbol
Human ^{1,2}	1269	422	100 %	5q11.2-q13	HTR1A
Mouse ³	1266	421	88 %	13 D2.1	Htr1a
Rat ^{4,5}	1269	422	90 %	2q16	Htr1a
Dog ⁶	1272	423	92 %	?	HTR1A
Monkey*	1266	421	98 %	6.122.4cr	HTR1A

**Macaca mulatta*

High receptor homology, but homology in binding receptor domains is higher. References: ¹(Fargin et al., 1988); ²(Stam et al., 1992); ³(Charest et al., 1993); ⁴(Albert et al., 1990); ⁵(Fujiwara et al., 1990), ⁶(Van den Berg et al., 2003), Partly adapted from (Andrade, 2015). AA, number of amino acids; Bp, coding base pairs. Homologues described for other non-human primates, mosquito, *Gallus gallus domesticus*, *Danio rerio*, *Caenorhabditis elegans*, *Drosophila melanogaster*, *Bos taurus*, *Xenopus laevis*, *Cavia porcellus*, *Equus caballus* etc. 160 species have orthologues of the human receptor. [https://www.ncbi.nlm.nih.gov/gene/?Term=ortholog_gene_3350\[group\]](https://www.ncbi.nlm.nih.gov/gene/?Term=ortholog_gene_3350[group]); [http://www.ncbi.nlm.nih.gov/probe/?term=479890\[unistsid\]](http://www.ncbi.nlm.nih.gov/probe/?term=479890[unistsid]).

Table 3. Receptor binding characteristics of 5-HT_{1A} receptor agonists.

Agonist	Agonist Action	Affinity	Units	Clinical Utility
1-naphthylpiperazine	Full	8	pK _i	
5-CT	Full	9.4 – 10.3	pK _i	
5-hydroxytryptamine	Full	9.1 – 9.7	pK _i	
7-methoxy-1-naphthylpiperazine	Full	8.6	pK _i	
8-OH-DPAT	Full	8.4 – 9.4	pK _i	
(R)-UH 301	Partial	8.6	pK _i	
Adoprazine (SLV313)	Full/Partial	8.64-9.1	pK _i	Schizophrenia
Apomorphine	Partial	6.9	pK _i	PD, erectile dysfunction
Aripiprazole	Full	8.2	pK _i	Schizophrenia
Asenapine	Full	8.0 – 8.3	pK _i	Schizophrenia
BMY-7378	Partial	6.8 – 8.0	pIC ₅₀	
BMY-1480	Full	7.2	pK _i	
Befiradol	Full	9.1	pK _i	PD dyskinesia
Bifeprunox	Partial	7.19-8.95	pK _i	Schizophrenia
Brexiprazole	Partial	9.92	pK _i	Schizophrenia
BRL-15572	Partial	7.7	pK _i	
Bromocriptine	Partial	7.9	pK _i	PD
Buspiron	Partial	7.7 – 8.0	pK _i	Anxiety
Cabergoline	Full	7.7	pK _i	PD
Capeserod	Partial	6	pK _i	
Cariprazine	Partial	8.59	pK _i	Schizophrenia
Clozapine	Full	6.8 – 6.9	pK _i	Schizophrenia
CP 93129	Full	6.1	pK _i	
Donitriptan	Full	7.6	pK _i	<u>Migraine</u>
Eletriptan	Full	7.4	pK _i	
Eltoprazine	Partial	8.03	pK _i	
EMDT	Full	6.8	pK _i	
F13714	Full	10.1	pK _i	
F15063	Partial	8.24	pK _i	
F15599	Full	8.6	pK _i	<u>Rett syndrome</u>
FG-5893	Full	8.7	pK _i	
Flesinoxan	Full	9.3	pK _i	<u>Major depression</u>
Flibanserin	Agonist	9	pK _i	Female hypoactive sexual desire
Fluparoxan	Partial	6.8	pK _i	
Frovatriptan	Agonist	7.2	pK _i	
GR127935	Partial	7.1 – 7.2	pK _i	
Ipsapirone	Partial	8.6 – 8.8	pK _i	
L-694,247	Full	9.3	pK _i	
L-772,405	Full	7.2	pIC ₅₀	
Lisuride	Full	9.7 – 9.8	pK _i	Migraine
LP-12	Agonist	7.2	pK _i	
LP-44	Agonist	7.3	pK _i	
LP-211	Agonist	6.7	pK _i	
LSD	Full	9	pK _i	
Lurasidone	Full	8.17	pK _i	Schizophrenia
LY293284	Full	10.1	pK _i	
LY334370	Full	7.8	pK _i	

LY344864	Full	6.3	pK_i	
LY 165,163	Full	8.9	pK_i	
Nafadotride	Full	7.3	pK_i	
Naratriptan	Full	7.1 – 7.6	pK_i	Migraine
Nemonapride	Partial	8.35	pK_i	Schizophrenia
Ocaperidone	Full	8	pK_i	
Olanzapine	Full	5.6 – 5.8	pK_i	Schizophrenia
Pardoprunox (SLV308)	Full	8.5	pK_i	PD
Pergolide	Partial	8.7	pK_i	PD
Piribedil	Partial	6.4	pK_i	PD
Quetiapine	Full	6.5 – 6.6	pK_i	Schizophrenia
Quinpirole	Full	5.8	pK_i	
Repinotan	Full	9.4	pK_i	
Rizatriptan	Full	6.4	pK_i	Migraine
Roxindole	Partial	9.4 – 9.9	pK_i	
RU 24969	Full	9	pK_i	
S 16924	Partial	8.4	pK_i	
S-14506	Full	9.6 – 9.7	pK_i	
S-14671	Full	10.2 – 10.5	pK_i	
S-15535	Partial	9.2	pK_i	
Sarizotan	Partial	8.65	pK_i	PD dyskinesia
SB 216641	Partial	6.3	pK_i	
Spiroxatrine	Full	8.8	pK_i	
SSR181507	Partial	8.53	pK_i	
Sumatriptan	Full	6	pK_i	Migraine
Tandospirone	Partial	8.2	pK_i	Anxiety
Terguride	Partial	8.5	pK_i	PD
U92016A	Full	9.7	pK_i	
Vilazodone	Partial	9.7	pK_i	Depression
Vilazodone	Partial	9.5	pIC_{50}	Depression
Vortioxetine	Partial	7.8	pK_i	Depression
WAY-100135	Partial	8	pK_i	
Xanomeline	Full	7.2	pK_i	
Zalospirone	Full	8.1	pK_i	
Ziprasidone	Partial	7.9 – 8.9	pK_i	Schizophrenia
Zolmitriptan	Full	6.6	pK_i	Migraine

Data are extracted and adapted from: (Andrade, 2015; Colpaert et al., 2002; Glennon et al., 2006; McCreary et al., 2007; McCreary and Newman-Tancredi, 2015).

Table 4. Receptor binding characteristics of 5-HT_{1A} receptor antagonists

Antagonist	Affinity	Units
(+)-butaclamol	6.4	p <i>K</i> _i
(-)-propranolol	7.5	p <i>K</i> _i
(-)-tertatolol	8.2	p <i>K</i> _i
(R)-flurocarazolol	6.5	p <i>K</i> _i
(S)-flurocarazolol	7.5	p <i>K</i> _i
(S)-UH 301	7.9	p <i>K</i> _i
[³ H]p-MPPF	8.4	p <i>K</i> _d
[³ H]robalzotan	9.8	p <i>K</i> _d
[³ H]WAY100635	9.5	p <i>K</i> _d
[¹¹ C]WAY100635	-	-
chlorpromazine	6.2	p <i>K</i> _i
cyamemazine	6.3	p <i>K</i> _i
Fluspirilene	7.2	p <i>K</i> _i
GR 125,743	7.3	p <i>K</i> _i
GR 218,231	6.8	p <i>K</i> _i
haloperidol	5.7 – 5.8	p <i>K</i> _i
iloperidone	6.8-7	p <i>K</i> _i
ketanserin	5	p <i>K</i> _i
mesoridazine	7	p <i>K</i> _i
methiothepin	7.8 – 8.1	p <i>K</i> _i
MPDT	5.8	p <i>K</i> _i
NAN 190	9.4	p <i>K</i> _i
p-[¹⁸ F]MPPF	-	-
p-MPPI	8.4	p <i>K</i> _i
pimozide	6.8	p <i>K</i> _i
pindolol	8.1	p <i>K</i> _i
pipamperone	5.6	p <i>K</i> _i
pizotifen	7.4	p <i>K</i> _i
raclopride	5.2	p <i>K</i> _i
Rec 15/3079	9.7	p <i>K</i> _i
Risperidone	6.2 – 6.5	p <i>K</i> _i
9-OH-risperidone	6.2	p <i>K</i> _i
ritanserin	5.2 – 5.5	pIC ₅₀
robalzotan	9.2	p <i>K</i> _i
SB 272183	8	p <i>K</i> _i
SB 649915	8.6	p <i>K</i> _i
SB 714786	6.5	p <i>K</i> _i
SDZ-216525	7.8 – 8.2	pIC ₅₀
Sertindole	6.4 – 6.6	p <i>K</i> _i
spiperone	6.7 – 8.8	p <i>K</i> _i
thioridazine	7.1	p <i>K</i> _i
tiospirone	8.3	p <i>K</i> _i
WAY-100635	7.9 – 9.2	p <i>K</i> _i
yohimbine	7.3	p <i>K</i> _i
Zotepine	6.5	p <i>K</i> _i

Table adapted from (Andrade, 2015).

Table 5. Comparison of properties of 5-HT_{1A} receptor ‘biased agonists’, F15599, F13714 and befiradol, and the reference agonists 8-OH-DPAT and 5-HT

Agonist	In vitro affinity/selectivity ¹	Cellular Transduction pathways ²	Target brain regions ³	Read-out in vivo ⁴	Relevant therapeutic indications
F15599	Nanomolar Highly selective	Preferential pERK activation	Cortex, brain stem	Reverses PCP-induced cognitive deficits, active in antidepressant and anxiolytic tests. Normalizes breathing in MeCP2 ^{+/-} mice	Cognitive deficits, mood disorders, respiratory difficulties (Rett syndrome)
F13714	Sub-nanomolar Highly selective	Multiple (pERK, receptor internalization, G-protein, cAMP, Ca ²⁺ release)	Mid-brain, Thalamus, hippocampus,	Potently eliminates L-DOPA-induced AIMs, active in antidepressant and anxiolytic tests	Not clinically tested (research tool)
Befiradol	Nanomolar Highly selective	Multiple (pERK, receptor internalization, G-protein, cAMP, Ca ²⁺ release)	Mid-brain, cortex, thalamus, hippocampus	Potently eliminates L-DOPA-induced AIMs, active in antidepressant and anxiolytic tests	Dyskinesias in Parkinson’s disease, mood deficits, chronic pain
8-OH-DPAT	Nanomolar Binds 5-HT ₇	Preferential pERK activation	Hippocampus, mid-brain, cortex, thalamus, brain stem	Disparate effects on cognition tests, active in antidepressant and anxiolytic tests, reduces L-DOPA-induced AIMs	Not clinically tested (research tool)
5-HT	Nanomolar Non-selective	Multiple (pERK, receptor internalization, G-protein, cAMP, Ca ²⁺ release)	All 5-HT projection areas		N/A

Based on the publications indicated below. Target brain regions are those identified in microPET imaging and neurochemical experiments. In vivo read-outs are non-exhaustive and focus on the primary activities of the biased agonists.

¹(Colpaert et al., 2002; Newman-Tancredi et al., 2009a); ²(Buritova et al., 2009; Colpaert et al., 2002; Newman-Tancredi et al., 2009b; Pauwels and Colpaert, 2003); ³(Lemoine et al., 2010; Lemoine et al., 2012; Llado-Pelfort et al., 2010; Llado-Pelfort et al., 2012b; Vidal, 2014); ⁴(Assie et al., 2010; Depoortere et al., 2010; Iderberg et al., 2015b; Levitt et al., 2013; van Goethem et al., 2015).

Table 6. pK_i values of sumatriptan and second-generation triptans at human (except when stated otherwise) 5-HT receptors.

Receptor	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Eletriptan	Almotriptan	Frovatriptan	F11356
5-HT _{1A}	6.4 ^a 6.9 ^b 6.0 ^c	6.6 ^c 6.5 ^d	7.6 ^b 7.1 ^c 7.1 (rat) ^e	6.4 ^c	7.4 ^c	6.3 ^f	7.3 ^g	7.6 ^h
5-HT _{1B}	7.8 ^a 7.4 ^c 8.3 ⁱ	7.7 ^c 8.3 ^d	8.1 ^c 8.7 ^e	6.9 ^c 7.7 ^j 8.1 ^k	8.0 ^c	8.0 ^f	8.6 ^g	9.4 ^h
5-HT _{1D}	8.5 ^a 8.0 ^c	8.9 ^c 9.2 ^d	8.4 ^c 8.3 ^e	7.9 ^c 8.6 ^k	8.9 ^c	8.0 ^f	8.4 ^g	9.3 ^h
5-HT _{1E}	5.8 ^a 5.8 ^c 5.6 ^l	7.7 ^c 8.0 ^k	7.7 ^c	6.8 ^c	7.3 ^c		<6.0 ^g	5.9 ^h
5-HT _{1F}	7.9 ^a 7.9 ^c 7.6 ^l	7.5 ^c 7.2 ^d	8.2 ^c	6.8 ^c	8.0 ^c		7.0 ^g	5.5 ^h
5-HT _{2A}	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c		<5.3 ^g	6.7 ^h
5-HT _{2B}	6.9 ^m	7.2 ^m		6.6 ^m				
5-HT _{2C}	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c		<5.3 ^g	
m5-HT ₃	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c		<6.0 ^g	<5.0 ^h
gp5-HT ₄	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c			5.7 ^h
5-HT _{5A}	<5.5 (rat) ^c	6.4 (rat) ^c	5.5 (rat) ^c	5.3 (rat) ^c	5.8 (rat) ^c			6.1 ^h
5-HT ₆	<5.5 ^c	<5.5 ^c	<5.5 ^c	<5.5 ^c	6.3 ^c			5.6 ^h
5-HT ₇	5.9 ^c	7.0 ^c	<5.5 ^c	5.7 ^c	6.7 ^c	<6.5 ^f	6.7 ^g	6.4 ^h

Data taken from: ^a, Leysen *et al.* (1996); ^b, Newman-Tancredi *et al.* (1997); ^c, Napier *et al.* (1999); ^d, Martin *et al.* (1997); ^e, Connor *et al.* (1997); ^f, Bou *et al.* (1997); ^g, Brown *et al.* (1996); ^h, John *et al.* (1999); ⁱ, Beer *et al.* (1998); ^j, Wurch *et al.* (1997); ^k, Pauwels, P.J., personal communication; ^l, Adham *et al.* (1993); ^m, Gupta, P., personal communication. m, Mouse; gp, guinea-pig.

Table 7: Chromosomal location of the 5-HT_{1F} receptor gene^a

Species	Locus	Name
Human ^b	3p12	HTR1F
Rat	11p12	Htr1f
Mouse	16 C1.3	Htr1f

^aThe chromosomal location of 5-HT_{1F} receptor genes can be found in these databases:

<http://www.ncbi.nlm.nih.gov/gene/?term=HTR1F%5Bsym%5D>;

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=5>

^bMaassen Vandenbrink et al., 1998

Table 8: Localization of 5-HT_{1F} Receptor mRNA^a

Tissue or Cells	Species	Method	Reference
Forebrain, hindbrain, spinal cord, cerebellum	Mouse	RT-PCR	Amlaiky et al., 1992
CA1, CA2, CA3 of the hippocampus	Mouse	ISHH	Amlaiky et al., 1992
Brain, uterus, mesentery	Human	RT-PCR	Adham et al, 1993a
Layer V of cerebral cortex (pyramidal cells) layer VI non-pyramidal cells, CA1-CA3 of the hippocampus (pyramidal cells), Dorsal raphe (large neurons), Dentate gyrus (granule cells)	Guinea pig	ISHH	Adham et al, 1993a
Cerebral cortex, striatum, hippocampus, thalamus, pons, hypothalamus, cerebellum.	Rat	RT-PCR	Lovenberg et al, 1993
Olfactory, cingulate, frontal, and entorhinal cortex (esp. layer V), hippocampus (CA1, CA2, CA3 and dentate gyrus)	Guinea Pig	ISHH	Bruinvels et al., 1994
Clastrum, cerebral cortex, thalamus, striatum	Guinea Pig	ISHH	Mengod et al., 1996
Trigeminal ganglion	Human	RT-PCR	Bouchelet et al., 1996
Cerebral blood vessels	Human	RT-PCR	Bouchelet et al., 1996
Trigeminal ganglion	Guinea pig	ISHH	Johnson et al., 1997
Dorsal root ganglia, trigeminal ganglion	Guinea pig	ISHH	Adham et al., 1997
Dorsal root ganglia	Human	RT-PCR	Pierce et al., 1997
Cerebral cortex, hippocampus, cerebellum; brain stem	Mouse	Northern blot	Guptan et al , 1997
Hippocampus, cerebral cortex	Rat	Northern blot	Guptan et al , 1997
Dorsal root ganglia (cultured)	Rat	RT-PCR	Chen et al., 1998
Neonatal and cultured astrocytes	Rat	RT-PCR	Hirst et al., 1998
Coronary arteries, atrium, ventricle and epicardium.	Human	RT-PCR	Nilsson et al., 1999b
Brain cortical microvessels and capillaries	Human	RT-PCR	Cohen et al., 1999
Astrocytes (cultured)	Human	RT-PCR	Cohen et al., 1999
Immune Tissue: spleen, thymus, mitogen- activated spleen cells, and peripheral blood lymphocytes	Rat	RT-PCR	Stefulj et al., 2000
Lumbar dorsal root ganglia	Rat	RT-PCR	Wu et al., 2001
Cerebral cortex, trigeminal ganglion	Pig	RT-PCR	Bhalla et al, 2002
Coronary artery, pulmonary artery, saphenous vein	Pig	RT-PCR	Bhalla et al, 2002
Lumbar dorsal root ganglia	Rat	RT-PCR	Liu et al., 2005
Intestine (4 separate regions)	Bovine	RT-PCR	Engel et al., 2006
Various forebrain areas of embryonic brain, including cerebral cortex, amygdala, globus pallidus, caudate putamen, hippocampus, dentate gyrus	Mouse	ISHH	Bonnin et al., 2006
Midbrain periaqueductal grey	Rat	RT-PCR	Jeong et al., 2008
Neonatal rat: cerebellum, cortex, cortical astrocytes Adult rat: cerebellum, cortex	Rat	RT-PCR	Osredkar and Kržan, 2009

Trigeminal ganglion, trigeminal nucleus caudalis	Rat	RT-PCR	Amrutkar et al., 2012
Renal proximal tubule cells	Rabbit	RT-PCR	Garrett et al., 2014
Heart, liver	Mouse	RT-PCR	Garrett et al., 2014

^aThe most intensely labelled regions or areas of unique interest from the different references are listed in this table. See the original references for a more complete expression profile.

Table 9: Localization of 5-HT_{1F} Receptor Protein Using Antibodies

Tissue or Cells	Species	Method	Reference
Trigeminal ganglion neurons	Rat	Immunohistochemistry	Ma, 2001
Superior, lateral, spinal, and medial vestibular nuclei	Rat	Immunohistochemistry	Ahn et al., 2009
Neurons of trigeminal ganglia, and dorsal root ganglia (C2, C5, T5, and L5 levels)	Rat	Immunohistochemistry	Classey et al., 2010
Renal proximal tubule cells	Rabbit	Immunoblot	Garrett et al., 2014

Table 10: Affinities of selective 5-HT_{1F} receptor agonists at cloned human 5-HT receptors^a

	LY302148	LY306258	LY334370 ^b	LY344864 ^c	LY397584	Lasmiditan ^b (COL-144, LY573144)
Receptor	K _i , nM	K _i , nM	K _i ± SEM, nM	K _i , nM	K _i , nM	K _i ± SEM, nM
5-HT _{1A}	12.0 ^g	5370 ^g	16.4 ± 2.7 (9)	530	1046 ^c	1053 ± 134 (8)
5-HT _{1B}	53.7 ^d	1698 ^d	189 ± 25 (10)	549	723 ^c	1043 ± 124 (8)
5-HT _{1D}	21.9 ^d	794.3 ^d	281 ± 58 (10)	575	724 ^c	1357 ± 156 (8)
5-ht _{1e}	50.1 ^g	73.6 ^f	176 ± 34 (8)	1415	776 ^g	594 ± 59.1 (6)
5-HT_{1F}	2.5^d	10.2^d	1.87 ± 0.34 (10)	6	5.5^c	2.21 ± 0.22 (8)
5-HT _{2A}	5.89 ^g	1072 ^g	1530 ± 200 (3)	3935	3890 ^g	>5 μM (6)
5-HT _{2B}	6.17 ^g	1072 ^g	1280 ± 90 (3)	1695	6166 ^g	>2 μM (6)
5-HT _{2C}	13.5 ^g	813 ^g	3250 ± 930 (3)	3499	309 ^g	>3 μM (6)
5-HT ₆			>3 μM (2)			>4 μM (6)
5-HT ₇			1550 ± 260 (5)	4851		>3 μM (6)

^aBinding values are expressed as K_i in nM (± SEM where available) from studies using cloned human receptors. Values in parentheses are the number of individual determinations from the cited references.

^bTaken from Nelson et al., 2010

^cTaken from Ramadan et al., 2003 (structure not reported)

^dTaken from Johnson et al., 1997

^eTaken from Phebus et al., 1997

^fTaken from Flaugh et al., 1998

^gTaken from Johnson, 2005

Table 11. Affinities of Selective 5-HT_{1F} Receptor Agonists from SAR studies at Cloned Human 5-HT Receptors^a

	Compound A ^b	Compound B ^c	Compound C ^d	Compound D ^e	Compound E ^f
Receptor	K _i ± SEM, nM	K _i ± SEM, nM	K _i ± SEM, nM	K _i , nM	K _i , nM
5-HT _{1A}	265 ± 99	620 ± 37	1000 ± 270	870	240
5-HT _{1B}	1060 ± 204	270 ± 47	720 ± 220	2300	>10 μM
5-HT _{1D}	1620 ± 100	250 ± 38	720 ± 55	3100	2300
5-HT _{1E}	>4830	660 ± 110	770 ± 80		
5-HT_{1F}	8.2 ± 1.2	5.0 ± 0.5	5.5 ± 0.6	3.9	9
5-HT _{2A}	1000 ± 85	4800 ± 2000	3400 ± 1600		
5-HT _{2B}	676 ± 118	>10000	>10000		
5-HT _{2C}	2200 ± 390	1900 ± 1600	310 ± 41		
5-HT ₄		4000 ± 350	2400 ± 740		
5-HT ₆	380 ± 40	>10000	1120 ± 203		
5-HT ₇	1770 ± 130	>5000	Not determined		

^aBinding values are expressed as K_i in nM from studies using cloned human receptors.

^bN-[3-(2-(dimethylamino)-ethyl)-2-methyl-1H-indol-5-yl]-4-fluorobenzamide, from Xu et al., 2001

^cN-(3-(1-methyl-4-piperidinyl)-1H-pyrrolo(3,2-b)pyridin-5-yl)acetamide, from Filla et al., 2003

^dN-[3-(1-Methyl-4-piperidinyl)-1H-pyrrolo[3,2-b]pyridin-5-yl]propanamide, from Filla et al., 2003

^e4-Fluoro-N-[3-(1-methyl-4-piperidinyl)-1H-indazol-5-yl]benzamide, from Zhang et al., 2004

^f4-Fluoro-N-[3-(1-methyl-4-piperidinyl)-2,3-dihydro-1H-indol-5-yl]benzamide, from Zhang et al., 2004

Table 12. 5-HT_{2A} receptor genes, transcripts, and proteins.

Organism	Gene		mRNA transcript		Receptor protein	
	Location	Ensembl Gene ID	NCBI RefSeq ID	Base pairs	NCBI RefSeq ID	Amino acids
<i>Bos taurus</i> (cow)	Ch 12: 16.82–16.88 Mb	ENSBTAG00000013498	NM_001001157	3562 bp	NP_001001157	470 aa
<i>Equus caballus</i> (horse)	Ch 17: 23.89–23.95 Mb	ENSECAG00000024282	NM_001081784	1413 bp	NP_001075253	470 aa
<i>Homo sapiens</i> (human)	Ch 13: 46.83–46.89 Mb (13q14–q21)	ENSG00000102468	NM_000621	5429 bp	NP_000612	471 aa
<i>Macaca mulatta</i> (rhesus macaque)	Ch 17: 25.98–26.05 Mb	ENSMMUG00000004210	NM_001032966	1438 bp	NP_001028138	471 aa
<i>Mus musculus</i> (mouse)	Ch 14: 74.64–74.70 Mb	ENSMUSG00000034997	NM_172812	2971 bp	NP_766400	471 aa
<i>Rattus norvegicus</i> (rat)	Ch 15: 56.66–56.73 Mb (15q11)	ENSRNOG00000010063	NM_017254	1566 bp	NP_058950	471 aa
<i>Sus scrofa</i> (pig)	Ch 11: 20.89–20.95 Mb	ENSSSCG00000009406	NM_214217	1432 bp	NP_999382	470 aa

Table 13. Proteins reported to interact with the 5-HT_{2A} receptor

Interacting protein	Region of the 5-HT _{2A} receptor ¹	Reference
ADP ribosylation factor 1 (Arf1)	C-terminus (NPxxY motif)	Robertson et al., 2003; Johnson et al., 2006
β-Arrestin	ICL3, C-terminus (ASK motif ²)	Gelber et al., 1999; Bhattacharya et al., 2010
Calmodulin (CaM)	ICL2, C-terminus	Turner and Raymond, 2005
Caveolin-1 (Cav-1)	ND	Bhatnagar et al., 2004
Glutamine synthetase	ICL3	Sheffler et al., 2006
Jak2 kinase	ND	Guillet-Deniau et al., 1997
Microtubule-associated protein 1A (MAP1A)	ICL3	Sheffler et al., 2006
Multi-PDZ domain protein 1 (MUPP1)	C-terminus (PDZ domain)	Jones et al., 2009
Na ⁺ /H ⁺ exchange regulatory factor 3 (NHERF3)	ND	Walther et al., 2015
Nucleoside-diphosphate kinase 3 (NME3)	ICL3	Sheffler et al., 2006
Paraoxonase 2 (PON2)	ICL3	Sheffler et al., 2006
Postsynaptic density protein 95 kDa (PSD-95)	C-terminus (PDZ domain)	Xia et al., 2003a
Protein phosphatase 5 (PP-5)	ICL3	Sheffler et al., 2006
Ribosomal S6 kinase 2 (RSK2)	ICL3	Sheffler et al., 2006
Synapse-associated protein 97 (SAP97)	C-terminus (PDZ domain)	Dunn et al., 2014

¹C-terminus, carboxyl-terminus; ICL2, second intracellular loop; ICL3, third intracellular loop; ND, not determined.

²Specific to the human and monkey 5-HT_{2A} receptor.

Table 14. Affinities of 5-HT_{2A} receptor antagonists

Ligand	h5-HT _{2A} K _i (nM)	r5-HT _{2A} K _i (nM)	h5-HT _{2C} K _i (nM)	r5-HT _{2C} K _i (nM)	hα _{1A} K _i (nM)	hα _{1B} K _i (nM)	References
Spiperone	1.4	0.43	661	871	5.0	0.6	A,B
Ketanserin	3.2	1.3	200	63	6.3	6.3	B,C
Ritanserin	0.25	0.30	0.25	2.7	4.0	10	A,B
Pirenpirone	1.08		77				D
Resperidone	1.1	0.16	12	32	4.0	10	B,E,F,G
Altanserin	0.51	0.3		6.0			H,I
MDL11,939	6.06	2.893	1020	853.6	1876	1579	D,J
MDL100907	1.50	1.92		88	128	424.7	J,K

h, human; r, rat.

References: (A) Bonhaus et al., 1997; (B) Yoshio et al., 2001; (C) Bonhaus et al., 1995; (D) Waincott et al., 1996; (E) Roth et al., 1992; (F) Kongsamut et al., 1996; (G) Schotte et al., 1996; (H) Smith et al., 1998; (I) Tan et al., 1999; (J) Pehek et al., 2006; (K) Kehne et al., 1996.

Table 15. Affinities of 5-HT_{2A} receptor agonists.

Ligand ¹	h5-HT _{2A} K _i (nM) [³ H]ketanserin	h5-HT _{2A} K _i (nM) [³ H]mesulergine	Reference
(±)-DOI	3.2	19.1	Canal et al., 2013
Cimbi-5 (25I-NBOMe)	0.52	0.69	Nichols et al., 2015
Cimbi-36 (25B-NBOMe)	0.19	4.0	Juncosa et al., 2013
(+)-(2 <i>S</i> ,6 <i>S</i>)- DMBMPP	2.5	310	Juncosa et al., 2013
25CN-NBOH (NBOH-2C-CN)	2.2	49.8	Halberstadt et al., 2016

¹Alternative names are shown in parentheses.

Table 16. Affinities and efficacies of several 5-HT₄ receptor ligands in radioligand binding (pK_i) and functional (pEC₅₀) studies

Compounds	Affinity (pK _i)	Efficacy		References
		(pEC ₅₀ or pIC ₅₀)	(E _{max} or I _{max})	
Agonists				
PF-00885706	8.4	8.2 to 8.4	78% to 84%	(Komada et al., 2009)
PF-01354082	8.7	8.1 to 8.5	74% to 66%	(Mikami et al., 2009)
Compound 26	7.9	9.4	63%	(McKinnell et al., 2009)
ATI-75025 (Naropride)	8.9			(Bowersox et al., 2011; Camilleri et al., 2007)
Compound 2d	9.3 to 9.8	9.2 to 9.6	7% to 33%	(Brodney et al., 2012)
Compound 3	8.1 to 8.6	8.7 to 9.1	21% to 63%	(Brodney et al., 2012)
TD-2749	8.0	8.6	85%	(Long et al., 2012)
PF-4995274 (TBPI)	9.5	9.0	19%	(Sawant-Basak et al., 2013)
SSP-002392	9.1 to 9.2	10.4 to 10.8	≈100%	(Tesseur et al., 2013)
TD-8954	9.4	8.6	55%	(McKinnell et al., 2013)
Dual ligands				
5-HT ₄ agonist/5-HT ₃ antagonist – Cpd 17	6.7 (5-HT ₄ R) 7.4 (H ₃ R)	7.3 (H ₃ R)		(Lepailleur et al., 2014)
Donecopride 5-HT ₄ agonist/ AChE inhibitor	8.1 (5-HT ₄)	9.0 (5-HT ₄) 7.8 (pIC ₅₀ AChE)	48% (5-HT ₄)	(Lecoutey et al., 2014; Rochais et al., 2015)
Antagonists				
Compound 34d	8.8	9.2	80% to 100%	(Lemaitre et al., 2009)
Compound 30	8.8	7.9 (pK _b)		(Brudeli et al., 2010)
Compound 12g	8.7	8.6	100%	(Furlotti et al., 2012)
Compound 20	11.9	10.6 (pK _b)		(Brudeli et al., 2013a)
Compound 9	9.9	8.6 (pK _b)		(Brudeli et al., 2013b)
Compound 25	10.1	9.1 (pK _b)		(Brudeli et al., 2014)

Table 17. Affinities of selective antagonists at 5-HT_{5A} and other 5-HT receptors.

Receptor	Species	SB699551	ASP5736	AS2030680	AS2674723
5-HT _{1A}	human	K _i = 501 nM	> 1000 nM	K_i = 21 nM	K _i = 84 nM
5-HT _{1B}	human	K _i = 316 nM	NR	NR	NR
5-HT _{1D}	human	K _i = 398 nM	NR	NR	NR
5-HT _{1E}	human	K _i > 1000 nM	NR	NR	NR
5-HT _{1F}	human	K _i > 1000 nM	NR	NR	NR
5-HT _{2A}	human	K _i = 794 nM	> 1000 nM	> 300 nM	> 300 nM
5-HT _{2B}	human	K _i = 1000 nM	> 1000 nM	K_i = 22 nM	> 300 nM
5-HT _{2C}	human	K _i = 398 nM	K _i = 287 nM	> 300 nM	> 300 nM
5-HT ₃	human	NR	> 1000 nM	> 100 nM	> 300 nM
5-HT ₄	guinea pig	NR	> 1000 nM	> 100 nM	> 300 nM
5-HT_{5A}	human	K_i = 3 - 6 nM	K_i = 4 nM	K_i = 1 nM	K_i = 1 nM
5-HT_{5A}	rat	K _i = 501 nM	K_i = 2 nM	K_i = 1 nM	K_i = 1 nM
5-HT_{5A}	mouse	K _i = 501 nM	K_i = 4 nM	K_i = 3 nM	K_i = 2 nM
5-HT ₆	human	K _i > 1000 nM	> 1000 nM	K _i = 39 nM	> 300 nM
5-HT ₇	human	K _i > 1000 nM	K _i = 123 nM	K_i = 10 nM	K_i = 7 nM

Adapted from data reported in Corbett et al., 2005 (for SB699551; compound 11a); Thomas, 2006 (for SB699551); Yamazaki et al., 2015 (for ASP5736, AS2030680, AS2674723). Values are binding IC₅₀ or K_i (where indicated), "NR" denotes not reported, and bold denotes high affinity bind at 5-HT_{5A} receptors (grey shading) or medium- to high-affinity nonselective binding. Note K_i values are given for the human, mouse, and rat cloned 5-HT_{5A} receptors; whereas the other values have been reported mainly for the human receptor (also see Thomas et al., 2004 for guinea pig values).

Table 18. Localization and relative abundance of 5-HT₇ receptor mRNA in the rat

Technique	Localization (Relative Abundance)
<i>In situ</i> hybridization ^a	hippocampus (+++), thalamus (+), hypothalamus (+)
<i>In situ</i> hybridization ^b	hippocampus, thalamus, enthorinal and piriform cortices, tenia tecta
<i>In situ</i> hybridization ^c	thalamus (+++), hippocampus (++), retrosplenial cortex (++), neocortex (+), hypothalamus (+) (not detected in suprachiasmatic nucleus)
<i>In situ</i> hybridization ^d	outer layer of the cortex, thalamus, hippocampus
<i>In situ</i> hybridization ^e	thalamus (+++), hippocampus (+++), retrosplenial cortex (+++), mammillary region (+++), posterior thalamic nucleus (+), suprachiasmatic nucleus (+)
<i>In situ</i> hybridization ^f	forebrain (+++), olfactory complex (+++), thalamus (+++), hippocampal formation (+++), hypothalamus (+++), suprachiasmatic nucleus (+++), septal region(++), amygdala (++), parvicellular (++)
<i>In situ</i> hybridization ^g	retrosplenial cortex (+++), hippocampus (+++), tenia tecta (+++), indusium griseum (+++), posterior hypothalamus (+++), medial amygdala nucleus (+++), thalamus (+++), cerebellum-Purkinje cell layer- (+++), pontine nuclei (+++), superior colliculus (+), raphe nucleus (+)
Northern Blot ^h	hypothalamus (+++), hippocampus (++), mesencephalon (++), cortex (++), olfactory bulb (+), olfactory tubercle (+), spleen (+) (not detected in retina, pituitary, testis, stomach, prostate, ovary, skeletal muscle, lung, liver, kidney, gut)
Northern Blot ^g	hypothalamus (+++), brainstem (+++), hippocampus (+++), stomach (+), ileum (+)
Northern Blot ^a	hypothalamus (+++), thalamus (+++), hippocampus (+), cortex (+) (not detected in urinary bladder, testis, liver, spleen, adrenal gland, kidney, lung, heart, pituitary)
Northern Blot ^c	hypothalamus (+++), thalamus (+++), hippocampus (++), cortex (++), medulla (++) (not detected in cerebellum, striatum, heart, liver, kidney, adrenal glands, testis, ovaries, spleen)
RT-PCR ⁱ	lumbar dorsal root ganglia, superior cervical ganglia, lumbar synpathetic ganglia
RT-PCR ^j	vena cava (+++), femoral vein (++), aorta (+), renal artery (+), portal vein (+) (not detected in jugular vein)
RT-PCR ^k	frontocortical astrocytes, hypothalamus
RT-PCR ^l	adrenal gland
RT-PCR ^m	submandibular gland
RT-PCR ⁿ	thymus, peripheral blood lymphocytes, spleen, mitogen activate spleen cells
RT-PCR ^o	adrenal cortex
RT-PCR ^p	jejunum, ileum, stomach fundus, oesophagus, colon

^aMeyerhof et al. (1993); ^bKinsey et al. (2001); ^cLovenberg et al. (1993); ^dMengod et al. (1996);

^eVenero et al. (1997); ^fNeumaier et al. (2001); ^gRuat et al. (1993); ^hShen et al. (1993); ⁱPierce et al.

(1997); ^jUllmer et al. (1995); ^kShimizu et al. (1996); ^lContesse et al. (1999); ^mBourdon et al. (2000);

ⁿStefulj et al. (2000); ^oLenglet et al. (2000); ^pLiu et al. (2001)

Table 19. Localization and abundance of 5-HT₇ receptor mRNA in guinea-pig, human, mouse, and pig

Species	Technique	Localization (Relative Abundance)
Guinea pig ^a	<i>In situ</i> hybridization	hippocampus (+++), periventricular thalamus (+++), superficial cortex (+++), cerebellar granule cells (+++)
Guinea pig ^b	<i>In situ</i> hybridization	medial thalamic nucleus (+++), hippocampal formation (+++), superficial layer cortex (++), medial geniculate nucleus (++), amygdala (++), hypothalamus (++), midbrain (+), hindbrain (+)
Guinea pig ^c	<i>In situ</i> hybridization	outer layer of the cortex, thalamus, hippocampus
Guinea pig ^d	Northern Blot	parietal cortex (+++), hippocampus (++), frontal cortex (++), cerebellum (+), ileum (+), spleen (+)
Guinea pig ^d	Northern Blot ^b	thalamus (+++), brainstem (+++), hypothalamus (+++), substantia nigra (+++), olfactory bulb (+++), olfactory tubercle (+++) (not detected in peripheral organs)
Hamster ^e	<i>In situ</i> hybridization	
Human ^f	RT-PCR	artery smooth cells (+++), pulmonay artery smooth cells (++) (not detected in coronary artery, pulmonary artery, aortic endothelial)
Human ^g	RT-PCR	dorsal root ganglia
Human ^b	RT-PCR	granulosa-lutein cells
Human ⁱ	RT-PCR	brain (+++), kidney (+), liver (+), pancreas (+), spleen (+), coronary artery (++) , stomach (++) , descending colon (++) , ileum (++)
Human ^j	RT-PCR	trigeminal ganglia
Human ^k	qPCR	colonic circular muscle
Mouse ^l	Northern Blot	not detected in brain, heart, kidney, lung, liver
Mouse ^l	RT-PCR	forebrain (+++), brain stem (+++), cerebellum (++) , colliculi (++) , intestine (+) , heart (+) , not detected in spleen, kidney, lung, liver
Mouse ^m	RT-PCR	substantia gelatinosa of the trigeminal subnucleus caudalis
Pig ^f	RT-PCR	pulmonary artery (++) , coronary artery (++) , cerebral artery (++) , cerebral vein (++)
Pig ⁿ	RT-PCR	myometrium
Pig ^o	RT-PCR	brain cortex, trigeminal ganglion, cerebellum, pulmonary artery, coronary artery, superior vena cava, saphenous vein, not detected in heart

^aTsou et al. (1994); ^bTo et al. (1994); ^cMengod et al. (1996); ^dRuat et al. (1993); ^eDuncan et al. (2007); ^fUllmer et al. (1995); ^gPierce et al. (1997); ^hGraveleau et al. (2000); ⁱBard et al. (1993); ^jTerron et al. (2001); ^kIrwing et al. (2007); ^lPlassat et al. (1993); ^mYang et al. (2014); ⁿKitazawa et al. (2001); ^oBhalla et al. (2002)

Table 20. Binding profile of the selective 5-HT₇ receptor agonists and antagonists.

Receptor	Affinity (K _i [nM])					
	Agonists/Partial agonists			Antagonists		
	E-55888 ^a	AS-19 ^a	LP-211 ^b	SB-258719 ^c	SB-269970 ^d	SB-656104 ^e
h5-HT₇	0.6	2.5	15	31.6	1.3	2.0
h5-HT _{1A}	89.7	700	379	>7900	>10000	562
h5-HT _{1B}	ND	ND	215	>5000	>1000	630
r5-HT _{1B}	490	n.s.	ND	ND	ND	ND
h5-HT _{1D}	6.6	n.s.	394	3162	1584	25
b5-HT _{1D}	n.s.	n.s.	ND	ND	ND	ND
h5-ht _{1e}	ND	ND	>10000	>10000	>6000	>5000
h5-HT _{2A}	n.s.	n.s.	626	>10000	>10000	63
h5-HT _{2B}	n.s.	n.s.	67	>5000	10000	91
h5-HT _{2C}	n.s.	n.s.	ND	>10000	10000	269
r5-HT _{2C}	ND	ND	91	ND	ND	ND
h5-HT ₃	n.s.	n.s.	>10000	ND	ND	ND
h5-HT ₄	ND	n.s.	ND	>10000	1259	1900
h5-HT _{5A}	98.5	n.s.	178	ND	63	182
h5-HT ₆	n.s.	n.s.	1571	>10000	6300	851
h5-HT transporter	n.s.	n.s.	812	ND	ND	ND

^aData taken from [Brenchat et al. 2009](#); ^bdata taken from [Hedlund et al. 2010](#); ^cdata taken from [Forbes et al. 1998](#); ^ddata taken from [Lovell et al. 2000](#); ^edata taken from [Thomas et al. 2003](#); ND not determined; n.s. not significant (K_i> 1 μM or % inhibition at 1.0 μM lower than 50%).

Table 21. 5-HT receptor interacting proteins and their cellular and physiological functions.

For each receptor, the nature of identified GIPs, their site of interaction, the function of their interaction with the receptor (if known) at the cellular (receptor targeting, trafficking and signal transduction) and physiological levels as well as their role in pathologies are indicated.

Receptor	GIP	Site of interaction	Cellular functions	Physiological/pathological functions	References
5-HT _{1A}	Calmodulin	i ₃ /Ct	Endocytosis PKC-dependent receptor phosphorylation Erk1,2 and Jun kinase activation NHE-1 activation	?	(Della Rocca et al., 1999; Turner et al., 2007; Turner et al., 2004)
	Yif1B	Ct	Anterograde trafficking Dendritic targeting	?	(Al Awabdh et al., 2012; Alterio et al., 2015)
5-HT _{1B/D}	p11	i ₃	↗ Cell surface density and signalling	↘ Depression in rodent models ↘ Emotional memory in rodents	(Eriksson et al., 2013; Svenningsson et al., 2006)
5-HT _{2A}	β-arrestin 2	?	↗ PI3K/Src/Akt signalling Delayed recycling (human receptor)	Hallucinogenic effects induced by high 5-HT concentration	(Bhattacharya et al., 2010; Schmid and Bohn, 2010; Schmid et al., 2008)
	MAP1A	?	Trafficking in apical dendrites		(Allen et al., 2008)
	Arf1-6	i ₃ /Ct	Coupling to phospholipase D		(Robertson et al., 2003)
	Jak/STAT3	?	↗ Transcription		(Guillet-Deniau et al., 1997)
	RSK2	i ₃	Receptor phosphorylation and desensitization	Putative implication in psychiatric disorders (Coffin-Lowry syndrome)	(Allen et al., 2008; Sheffler et al., 2006; Strachan et al., 2009)
5-HT _{2A}	Calmodulin	i ₂ /Ct	↘ Gq coupling		(Turner and Raymond, 2005)
	Caveolins	?	Targeting to lipid rafts Endocytosis		(Bhatnagar et al., 2004)

Receptor	GIP	Site of interaction	Cellular functions	Physiological/pathological functions	References
	PSD-95	Ct (PDZ ligand - SCV)	Dendritic targeting Post-synaptic localization ↗ Phospholipase C ↘ Endocytosis ↗ Cell surface density	- Hallucinogen effects in mice - Antipsychotic drug effects ↘ Inflammatory and neuropathic pain	(Abbas et al., 2009; Becamel et al., 2004; Pichon et al., 2010; Vogrig et al., 2013; Wattiez et al., 2013; Xia et al., 2003)
	SAP97	Ct (PDZ ligand -SCV)	↗ Gq signalling ↘ Endocytosis	?	(Allen et al., 2008)
	MUPP1	Ct (PDZ ligand -SCV)	Post-synaptic localization ↗ Cell surface density	Drug dependence	(Becamel et al., 2001; Jones et al., 2009; Shirley et al., 2004)
	MAGI2	Ct (PDZ ligand -SCV)	Post-synaptic localization	?	(Becamel et al., 2004)
	CIPP	Ct (PDZ ligand -SCV)	Post-synaptic localization	?	(Becamel et al., 2004)
	NHERF3	?	↗ Gq signalling ↘ Endocytosis	?	(Walther et al., 2015)
5-HT _{2B}	MUPP1	Ct (PDZ ligand -SYV/I)	?	?	(Becamel et al., 2001)
	PDZ protein	Ct (PDZ ligand -SYV/I)	NO synthesis	?	(Manivet et al., 2000)
	Calmodulin	Ct	↗ Erk1,2 signalling	?	(Becamel et al., 2002; Labasque et al., 2008)
5-HT _{2C}	β-arrestins	i ₂ /?	↗ Erk1,2 signalling Constitutive and agonist-dependent endocytosis	?	(Labasque et al., 2010; Labasque et al., 2008; Marion et al., 2004)
	MUPP1	Ct (PDZ ligand -SSV)	?	?	(Becamel et al., 2001; Parker et al., 2003)

Receptor	GIP	Site of interaction	Cellular functions	Physiological/pathological functions	References
	PSD-95	Ct (PDZ ligand -SSV)	↗ Endocytosis ↘ Signalling	?	(Becamel et al., 2002; Gavarini et al., 2006)
	MPP3	Ct (PDZ ligand -SSV)	↘ Endocytosis	?	(Becamel et al., 2002; Gavarini et al., 2006)
	Veli3/CASK/Mint MAGI2, SAP102, PSD93	Ct (PDZ ligand -SSV)	?	?	(Becamel et al., 2002)
5-HT _{2c}	PICOT	Ct	?	?	(Becamel et al., 2002)
	PTEN	i ₃	?	Rewarding effects of THC and nicotine	(Ji et al., 2006)
5-HT ₄	Src	?	↗ Erk1,2 signalling ↗ PLCγ1	?	(Barthet et al., 2009; Barthet et al., 2007; Gill et al., 2005)
	p11	i ₃	↗ Cell surface localization ↗ Signalling	↘ Depression in rodent models	(Warner-Schmidt et al., 2009)
	ADAM10	?	↗ sAPPα release	↘ β-amyloid plaques ↘ Neuroinflammation	(Cochet et al., 2013)
	GRK5	Ct	↘ Src activation ↘ Erk1,2 signalling	?	(Barthet et al., 2009)
5-HT _{4(a)}	SNX27a	Ct (PDZ ligand -SCF)	Targeting to endosomes Receptor recycling?	?	(Joubert et al., 2004)
	NHERF	Ct (PDZ ligand -SCF)	Targeting to microvilli - interaction with Ezrin	?	(Joubert et al., 2004)
	CRMP2	Ct	Neuronal architecture	?	(Joubert et al., 2004)
5-HT _{4(b)}	PDE3A1, PDE4D3	?	Regulation of cAMP signalling	?	(Weninger et al., 2014)
5-HT _{4(c)}	CIPP	Ct (PDZ ligand -VPV)	?	?	(Joubert et al., 2004)
5-HT _{4(e)}	nNOS	Ct (PDZ ligand -VPV)	?	?	(Joubert et al., 2004)

Receptor	GIP	Site of interaction	Cellular functions	Physiological/pathological functions	References
5-HT ₆	Fyn	Ct (PXHPXR)	<ul style="list-style-type: none"> ↗ Gs signalling ↗ Erk1,2 signalling ↗ Cell surface expression 	?	(Yun et al., 2007)
	Jab1	i ₃ /Ct	<ul style="list-style-type: none"> ↗ Gs signalling ↗ Cell surface expression ↗ c-Jun phosphorylation ↗ Cell surface expression 	↘ Cell death	(Yun et al., 2010)
	Map1B-LC1	Ct	<ul style="list-style-type: none"> ↘ Endocytosis ↗ Erk1,2 signalling 	?	(Kim et al., 2014)
	SNX14	i ₃	<ul style="list-style-type: none"> ↗ Endocytosis ↘ Gs signalling 	?	(Ha et al., 2015)
	mTORC1	Ct/unknown	↗ mTOR signalling	Cognitive impairment in neurodevelopmental models of schizophrenia	(Meffre et al., 2012)
	Cdk5, p35	Ct	Receptor phosphorylation Cdk5 signalling	Neurite growth Migration of pyramidal neurons	(Dayer et al., 2015; Duhr et al., 2014; Jacobshagen et al., 2014)
	5-HT ₇	Neurochondrin		?	?
Periplakin			?	?	(Ward et al., 2009)
S100B		i ₃	↘ cAMP	Behavioural despair	(Stroth and Svenningsson, 2015)

Table 22. Some novel 5-HT agents for GI indications

Drug Class	Example	Putative Action in humans	Pharmacodynamic in humans	Clinical Efficacy: Phase IIB or III	Safety issues, Approval, Other
TPH ₁ blocker	LX-1031	Inhibits synthesis of 5-HT by blocking TPH ₁	Inhibition of urine 5-HIAA excretion; no studies of PD efficacy	Phase IIB trial in non-C-IBS: 1000mg dose, improved adequate relief, stool consistency	Reported to be discontinued
5-HT ₃ receptor antagonist	Ramosetron	Inhibits secretion, motility, nociception	ND	Phase IIB 5 and 10 µg dose studies in IBS-D: benefit on global relief and bowel function	Approved in Asia, under investigation elsewhere; ischemic colitis with same drug class
5-HT ₄ receptor agonist	Prucalopride	Selective 5-HT ₄ receptor agonist; stimulates colonic motility	Accelerated colonic transit (CT) in health and chronic constipation (CC)	Multiple Phase II/III trials completed; open label experience of ~1000 cumulative patient-years; efficacy in CC (males and females in phase III and IV clinical trials), with consistent benefits shown by meta-analyses	No clinical cardiac AEs in clinical trials of >4000 humans; approved in virtually all countries except USA
5-HT ₄ receptor agonist	Velusetrag	Selective 5-HT ₄ receptor agonist; stimulates colonic motility	Accelerated CT in health in dose-related fashion	Phase IIB efficacy; no effect on QT in health or 400 patients with constipation	Under investigation (although last report 2017)
5-HT ₄ receptor agonist	Naronapride	Selective 5-HT ₄ receptor agonist; stimulates colonic motility	Accelerated CT in health	Under investigation	Under investigation (although last report 2018)
5-HT ₄ receptor agonist	Relenopride	Selective 5-HT ₄ receptor	Accelerated CT in functional	Phase II studies ongoing in IBS-C patients	May be discontinued (last active

		agonist; stimulates colonic motility	constipation	(ClinicalTrials.gov trial NCT02082457).	report 2015)
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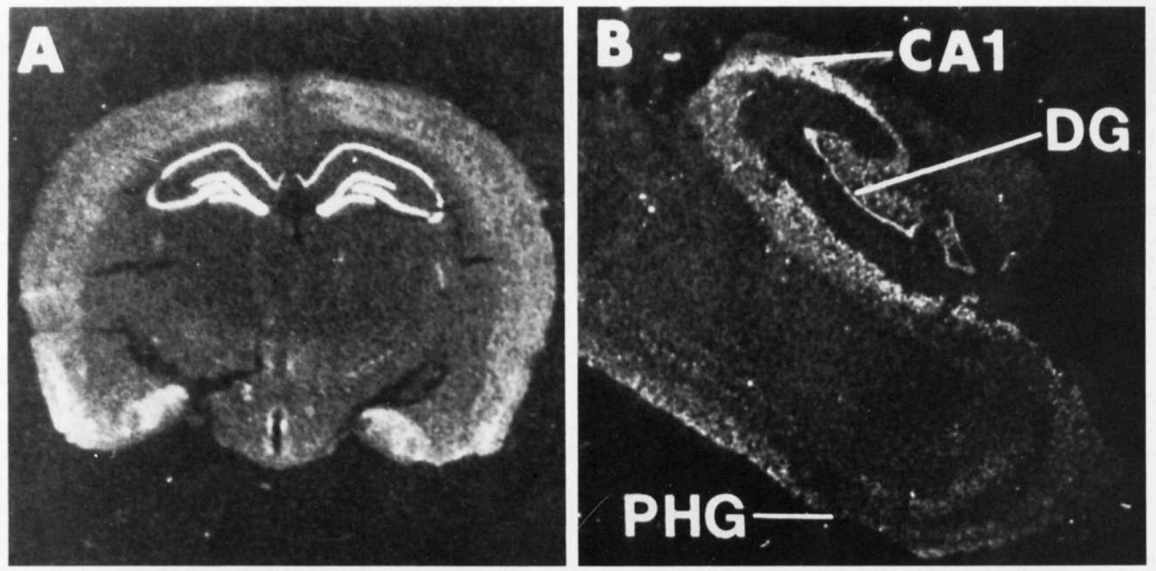


Figure 1.

Serotonin 5-HT_{1A} Receptor Subpopulations: Molecular, Neurochemical and Physiological Correlates

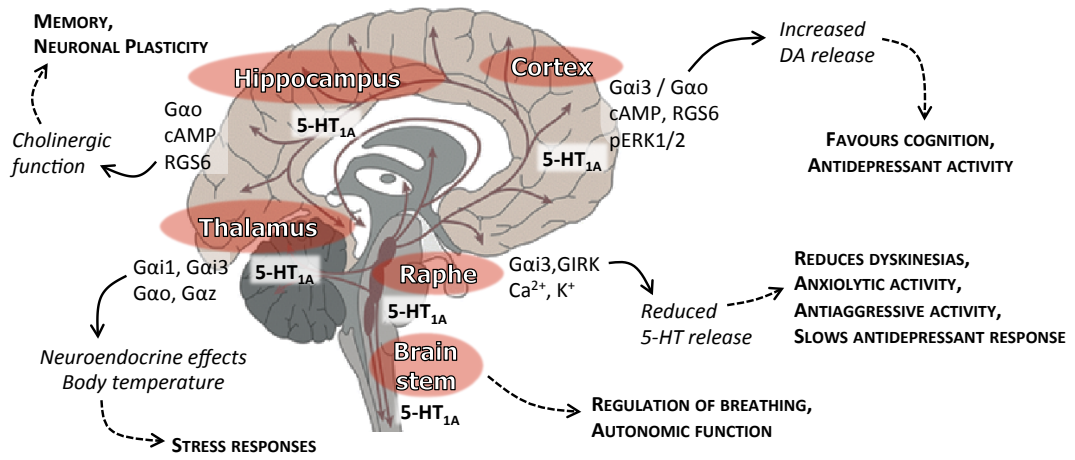
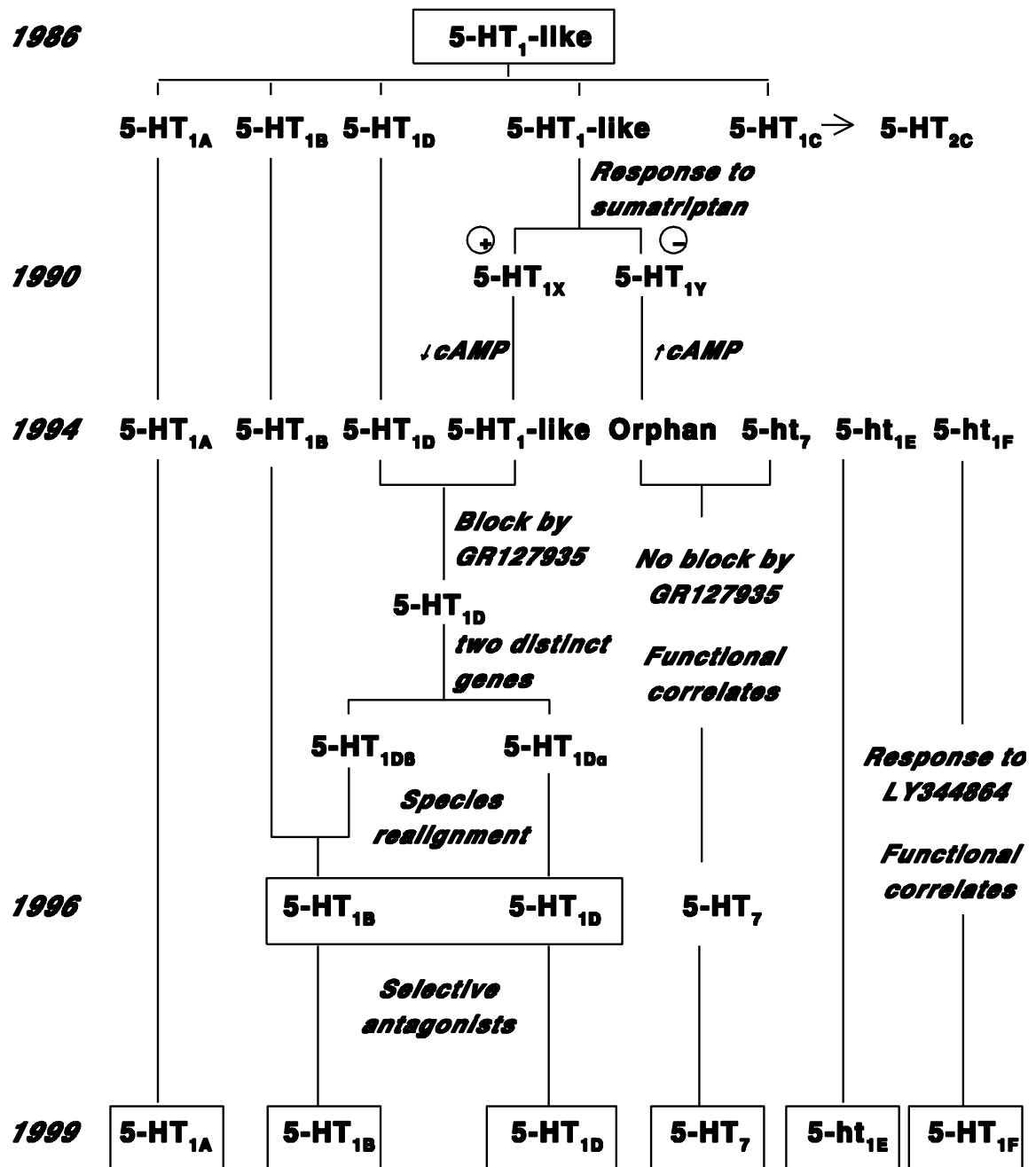


Figure 2.

Figure 3.



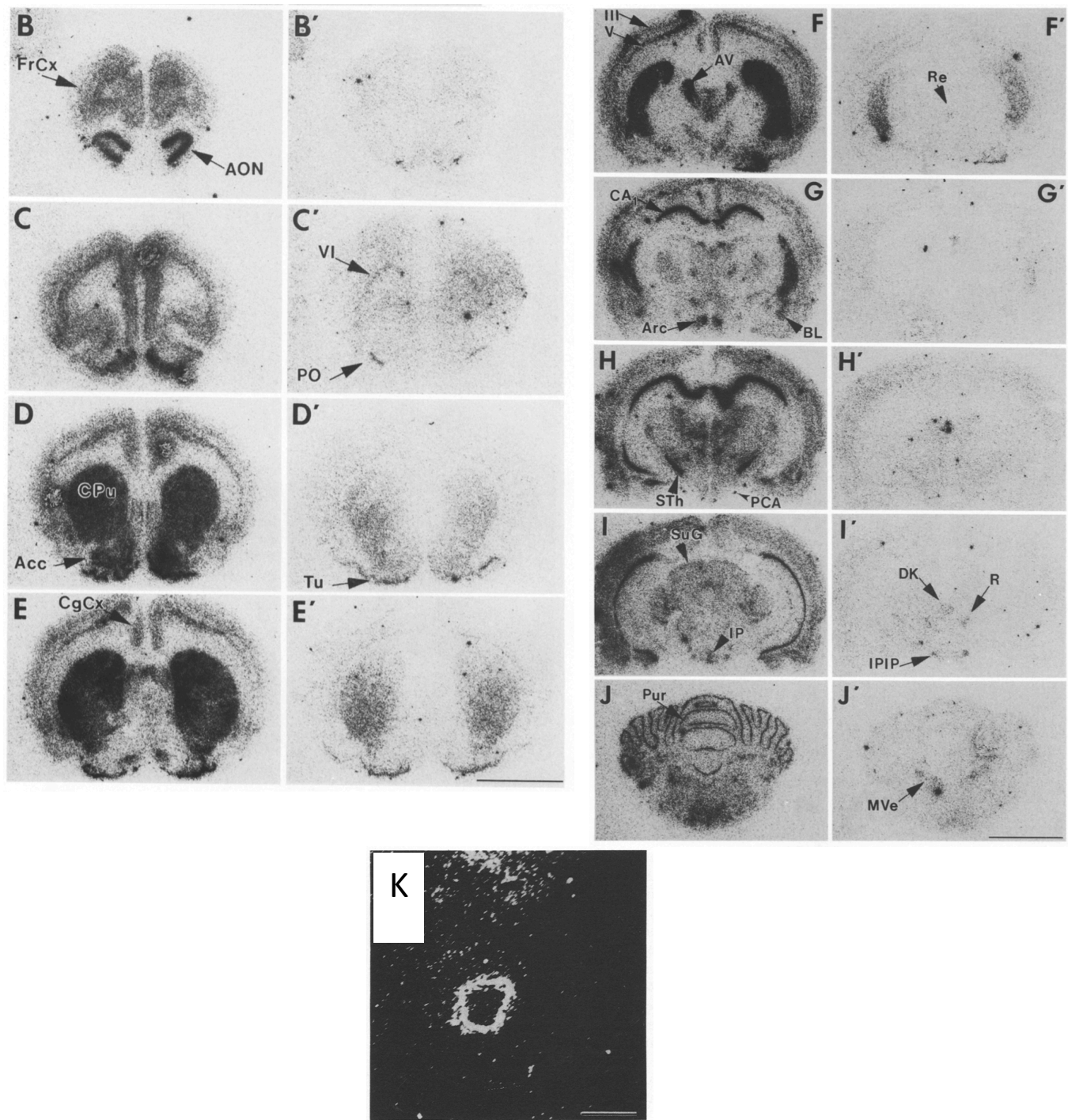


Figure 4.

Figure 5.

h5-HT_{1E} vs. h5-HT_{1F} Amino Acid Sequence

Identities = 207/363 (57%), Gaps = 12/363 (3%)

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h5-HT1E  -----MNI TNCTTEASMAIRPKTITEKMLICMTLVVITTLTLLNLAVI MAIGTTKKLHQ 55
h5-HT1F  MDFLNSSDQ·L·S·ELLNRM·-----S·I·VSL·SGLALM·TI·SL·A·IV·R·H 56

h5-HT1E  PANYLICSLAVTDLLVAVLVMPLSIIYIVMDRWKLG YFLCEVWLSVDMTCCTCSILHLCV 115
h5-HT1F  ············F··········F·V·RES·IM·QVV·DI··········I··········SA 116

h5-HT1E  IALDRYWAITNAIEYARKRTAKRAALMILTVWTFISIFISMPPLFWRS HRRLSPPPSQCTI 175
h5-HT1F  ·········R····D·V··········P·H·GI·TI·I·V···········-·QGT·-RDDE·I· 174

h5-HT1E  QHDHVIYTIYSTLGAFYIPLTLILILLYYRIYHAAKSLYQKRGSSRHL SNRSTDSQ----N 231
h5-HT1F  K····I·VS········F········A········K·R····T·H··QA··-IAKEEVNG·VLLES 233

h5-HT1E  SFASCKLTQTFCVSDFSTSDPTTEFEKFFHASIRIPPFNDLDHPGERQ QISSTRERKAAR 291
h5-HT1F  GEK·T·SVS·SY·LEK·L····S·D·D·I·STV·SLRSEFKHEKSWR·K·G········T 293

h5-HT1E  ILLGLILGAFILSWLPFFIKELIVGL-SIYTVSSEVADFLTWLGYVNSL INPLLYTSEF NED 350
h5-HT1F  T········VIC······V····V·NVCDKCKI·E·MSN·A····L····I·I···· 353

h5-HT1E  FKLAFKKLIRCREHT 365
h5-HT1F  ··K·Q·V····C-- 366

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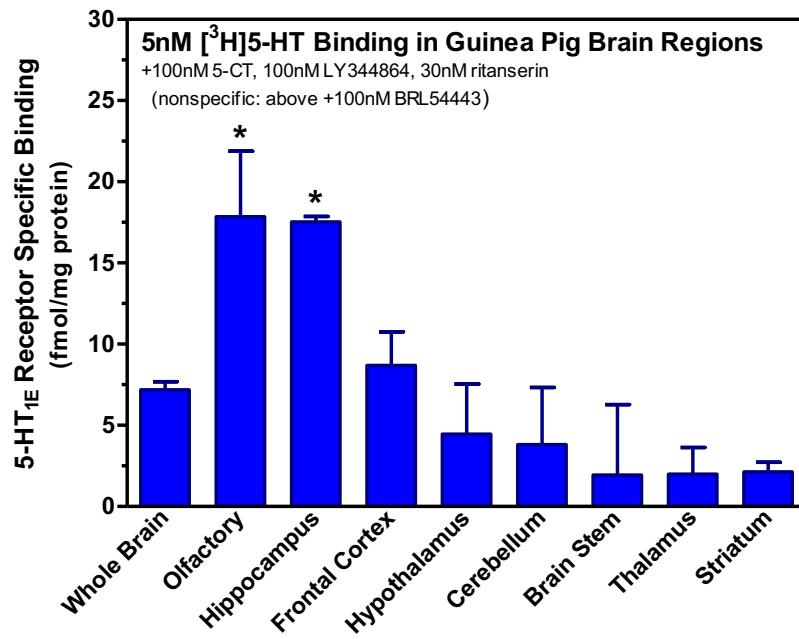
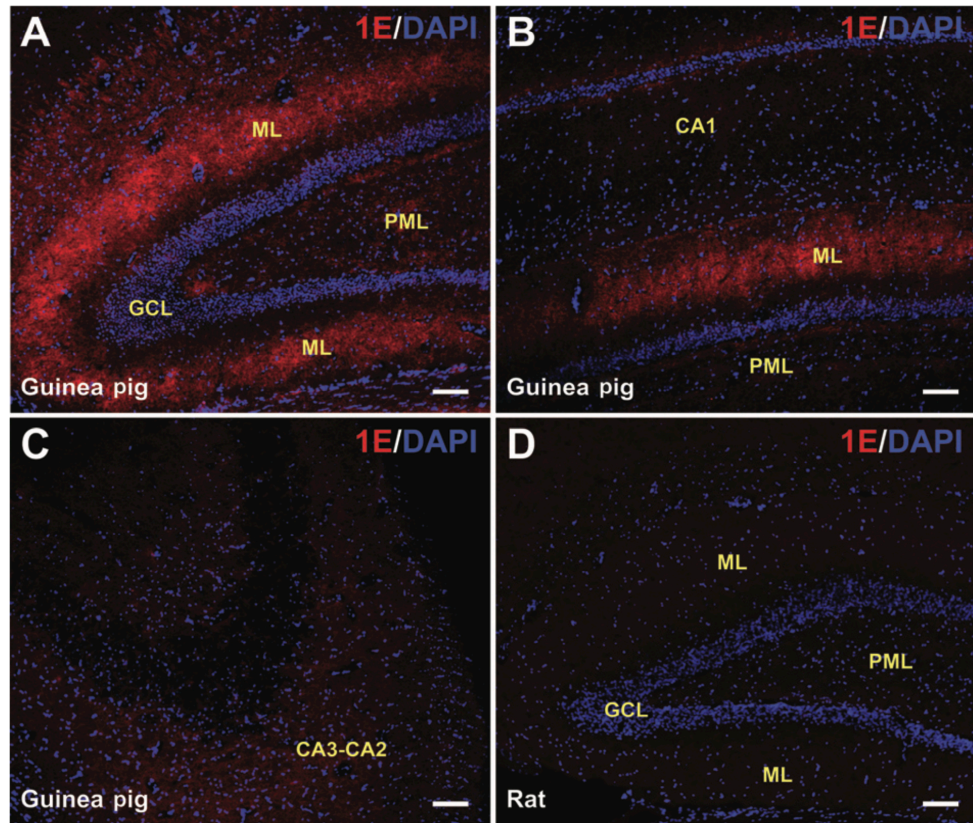


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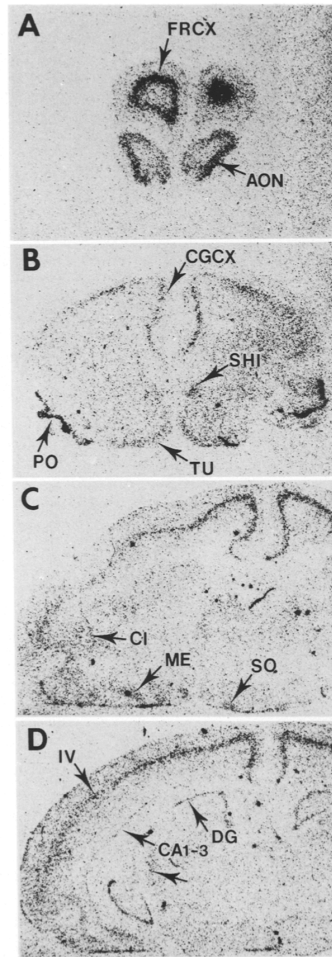
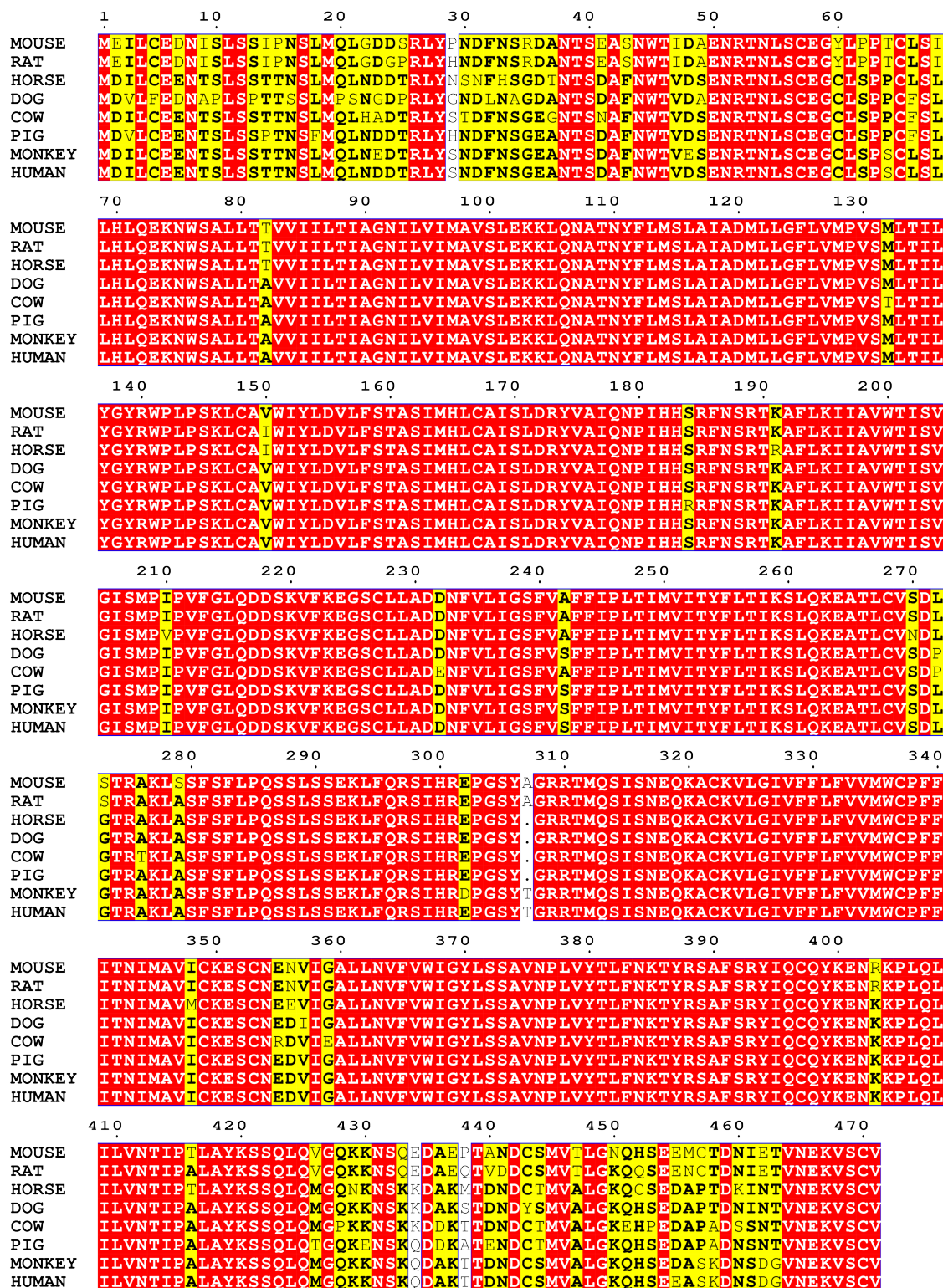


Figure 7.

Figure 8.



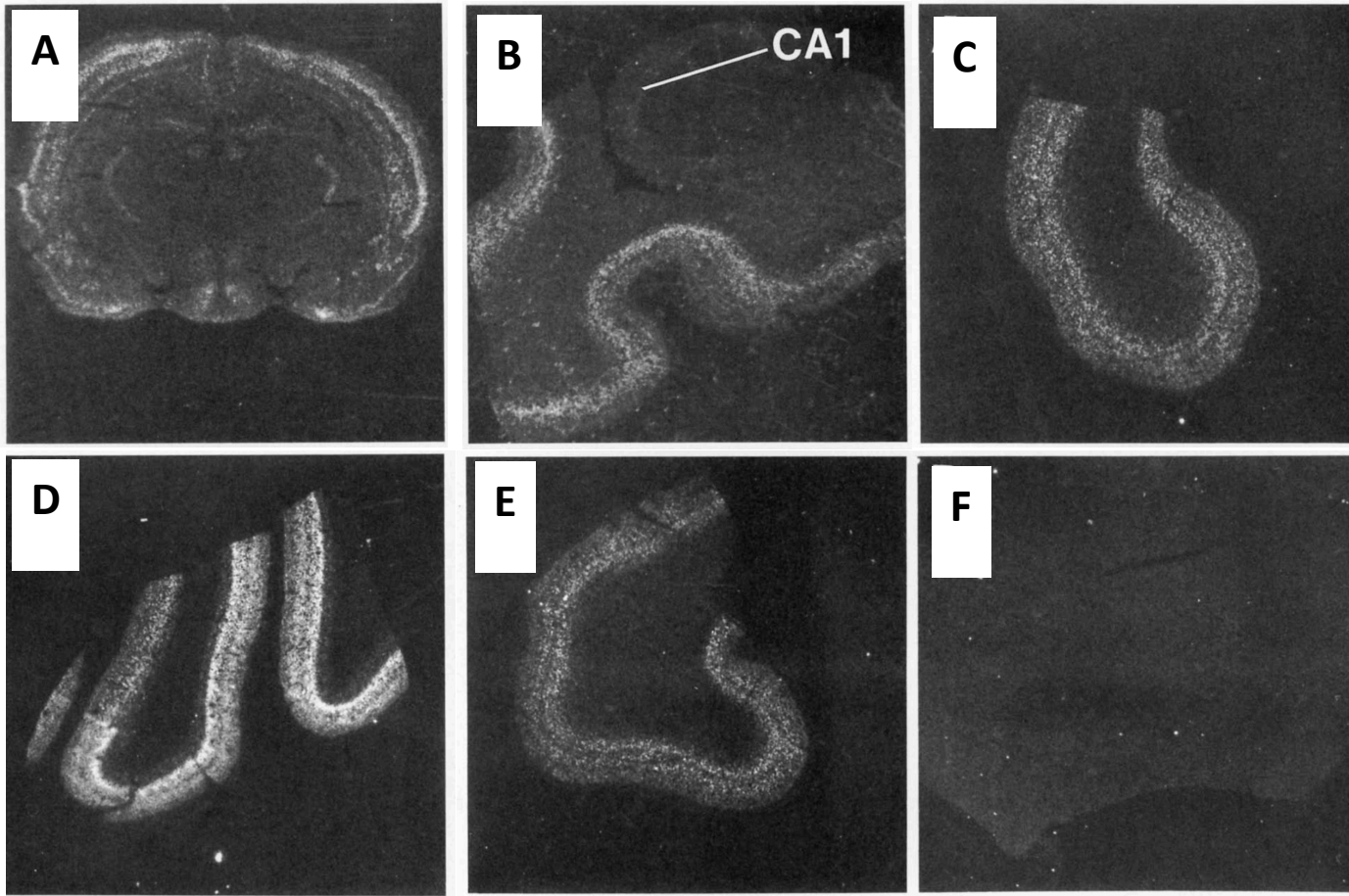


Figure 9.

Figure 10.

5-HT2B	1MALISYRVSELSQSTIPEHILQSTFVHVTI.SSNWSSLQ....
5-HT2A	1	MDILCEENTSLSSSTNSLMQLNDDTRLYS.....NDFNSGEANTSDAFNWTVDSENRT
5-HT2C	1MVNLRNAV.....HSFLVHLLIGLLVWQCDISVSP
5-HT2B	36TESIPEEMKQIVEEQGNKLHWAALLILMVIIPTIGGNLVLILAVSLEKKIQYA
5-HT2A	54	NLS.CEGCL..SPSCLSLHLQEKNWSALLTAVVITTIAGNIVIMAVSLEKKIQNA
5-HT2C	30	VAAIVTDIFNTSDGGRFKFPDGVQNWPAALSIIVITITMIGGNILVIMAVSMEKKLHNA
5-HT2B	89	TNYFLMSLAVADLLVGLFVMPIALLTIMFEAMWPLPLVLCPAWLF.LDVLFSTASIMHL
5-HT2A	109	TNYFLMSLAIADMLLGLFVMPVSMILTILYGYRWPLPSKLCVWIIYLDVLFSTASIMHL
5-HT2C	88	TNYFLMSLAIADMLVGLLVMPLSLLAILYDYYVWPLRYLCPVWISLDVLFSTASIMHL
5-HT2B	147	CAISVDRYTAIKKPIQANQYNSRATAFIKIVVWLISIGIAPVPIKGIETDVDNP.N
5-HT2A	167	CAISLDRYVAIQNPIHHSRFNSRTKAFILKIIVVWISVGISMPPIPVFGLQDDSKVFKKE
5-HT2C	146	CAISLDRYVAIRNPIEHSRFNSRTKALMKIIVVAISIGVSVPIPVIGLRDEEKVFN
5-HT2B	204	NITCVLTKERFGDFMLFGSLAAFFTPLAIMIVTYELTIHALQKKAYLVKNKPPQRITW
5-HT2A	225	.GSCILLADD...NFVLIGSFVSVFFIPLTIMVITYELTIKSLQKEATLCVSDLGTRAKL
5-HT2C	204	NITCVLNDP...NFVLIGSFVAFFIPLTIMVITYCLTIYVLRQQALMLLHGHTEEPFG
5-HT2B	262	LTVSTVVFQRDETPCSSPEKVMALDGSRKDKALPNSGDET.LMRRSTIIGKKSVCITISN
5-HT2A	279	ASF.....FLPOSSLS.....SEKLFQRSIHREPESYTRGRMTQISIN
5-HT2C	259	LSLD.....FLKCKRNRTAE.....EENSANPNQDNARRKKKERRPRGTMQAINN
5-HT2B	319	EQRASKVLGIVFFLFLMWCFFFITNITLVLCD.SCNQTTLQMLLEIFVWIGYVSSGV
5-HT2A	318	EQKACKVLGIVFFLVVMWCFFFITNIMAVICKESCNEVDVIGALLNVFVWIGYLVSSAV
5-HT2C	306	ERKASKVLGIVFFVFLIMWCFFFITNLSVLCESCNQKLMKLLNVFVWIGYVCSGI
5-HT2B	376	NPLVYTLEFNKTERDAFGRYITCNYRATKSVKTLRKRSSKIYFRNPMENSKFFKKGIT
5-HT2A	376	NPLVYTLEFNKTYRSAFSRYIQCYKENKKPLQLILVNTI.....P..ALAYKSSQL
5-HT2C	364	NPLVYTLEFNKIYRRAFSNYLRCNYKVEKKPVRRQIPRV.....A..AATALS GREIL
5-HT2B	434	RNGINPAMYQSPMRLRSSTIQSSSIILL...DTLLLTENEGDKTEEQVSYV
5-HT2A	425	QMGGKK...NSKQDAKTID.NDCSMVALGKQHSEEAASKDNSDGVNEKVS CV
5-HT2C	412	NVNIYRHT.NEPVIEKASD.NEPGIE.MQVE.NLELPVNPSSVVERISSV

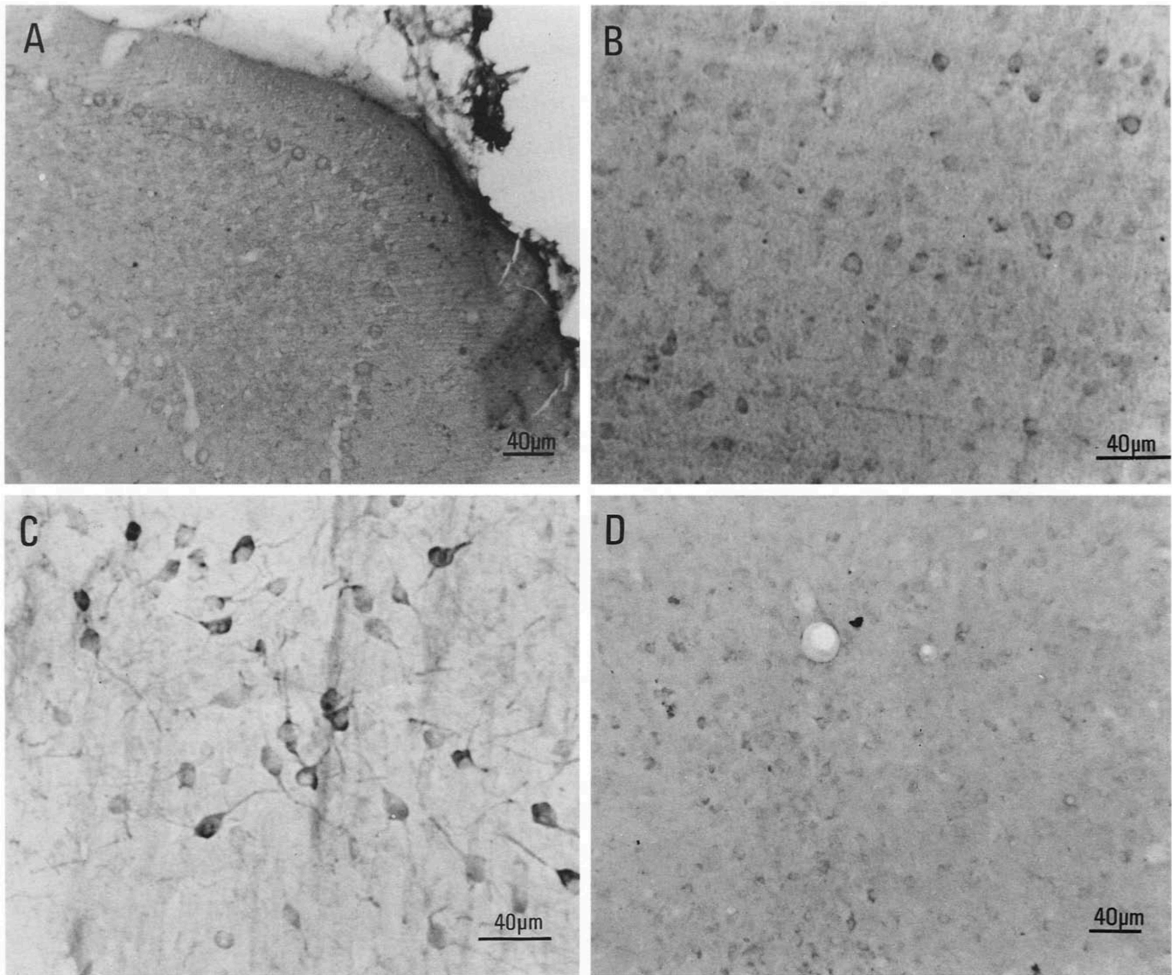
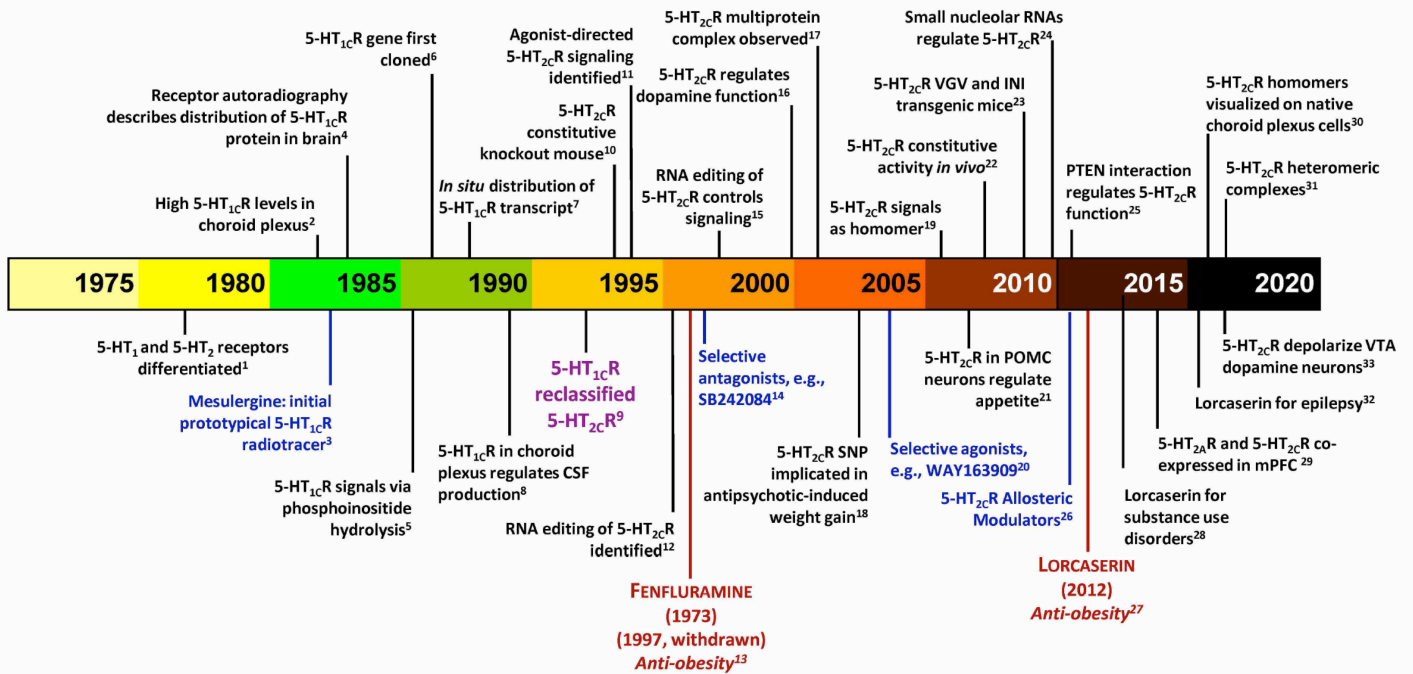


Figure 11.

Figure 12.

Landmarks in 5-HT_{2C} Receptor Research and Development



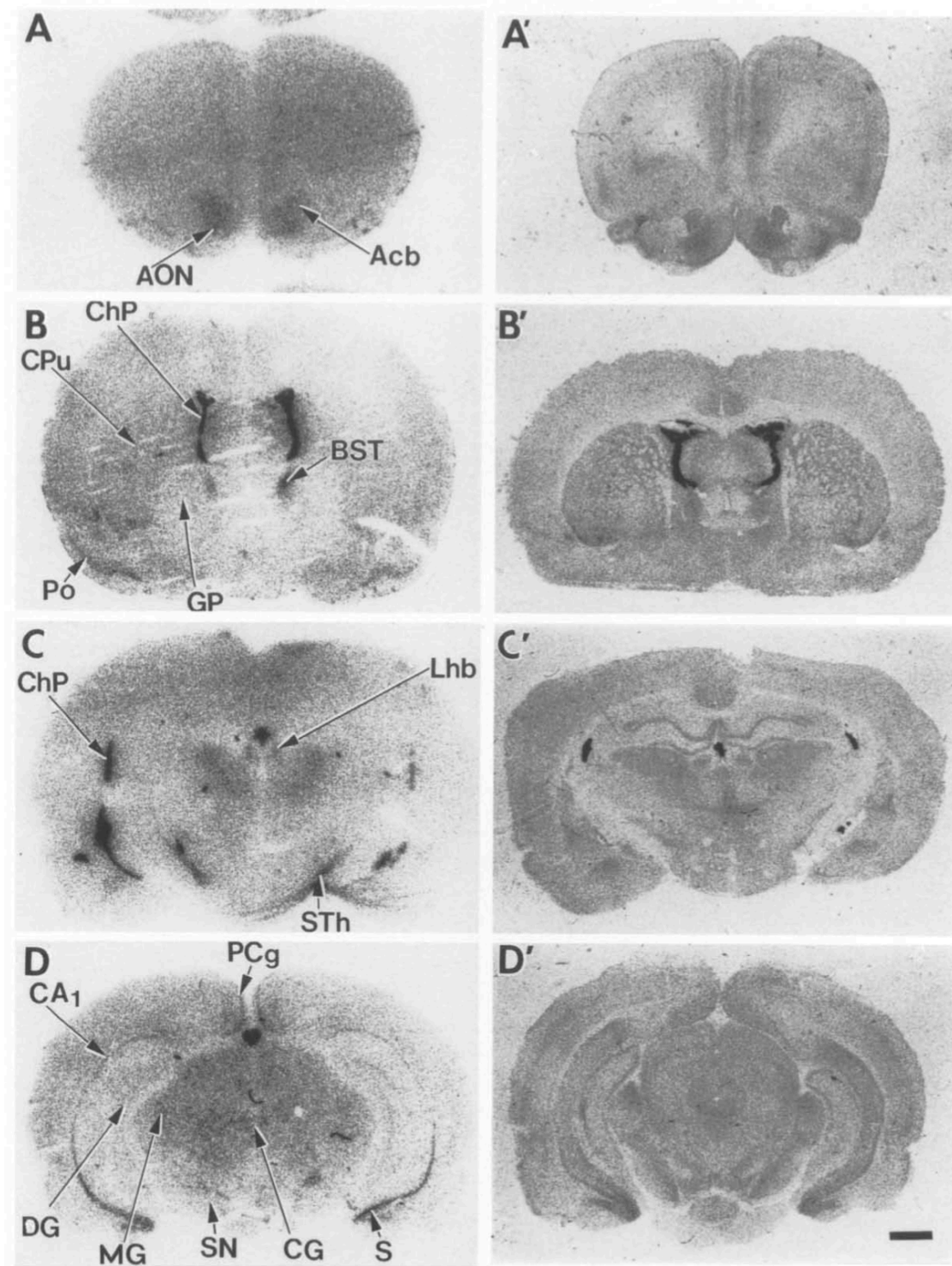
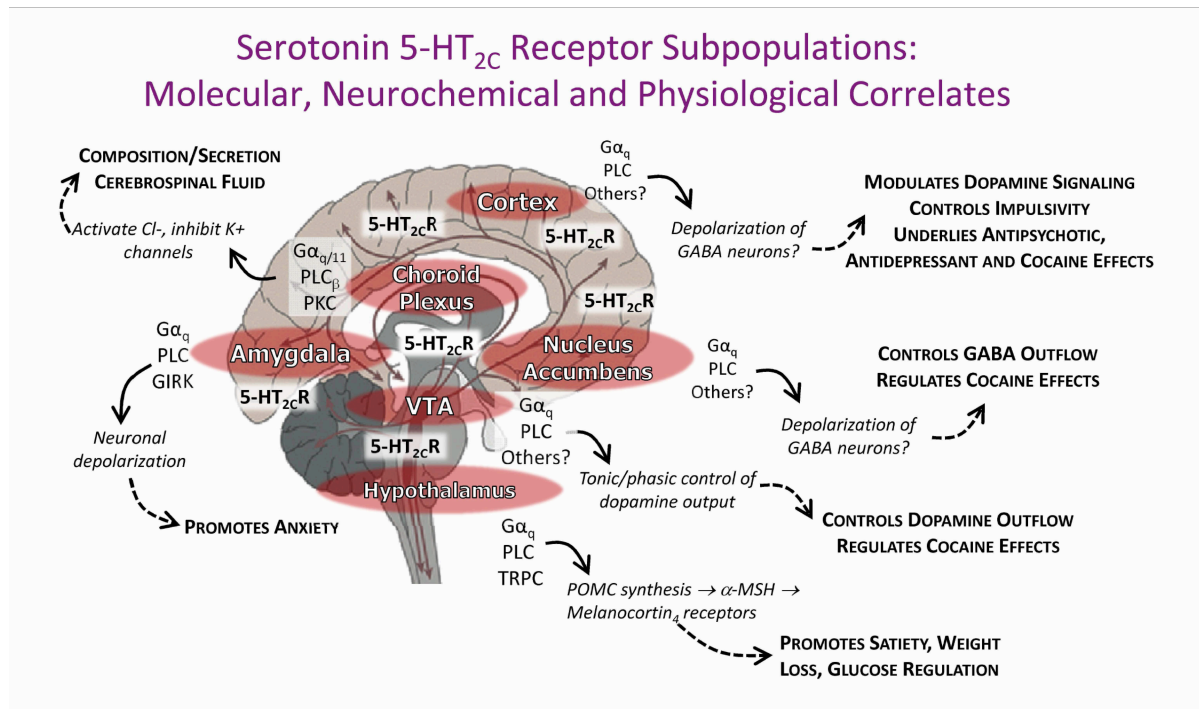


Figure 13.

Figure 14.



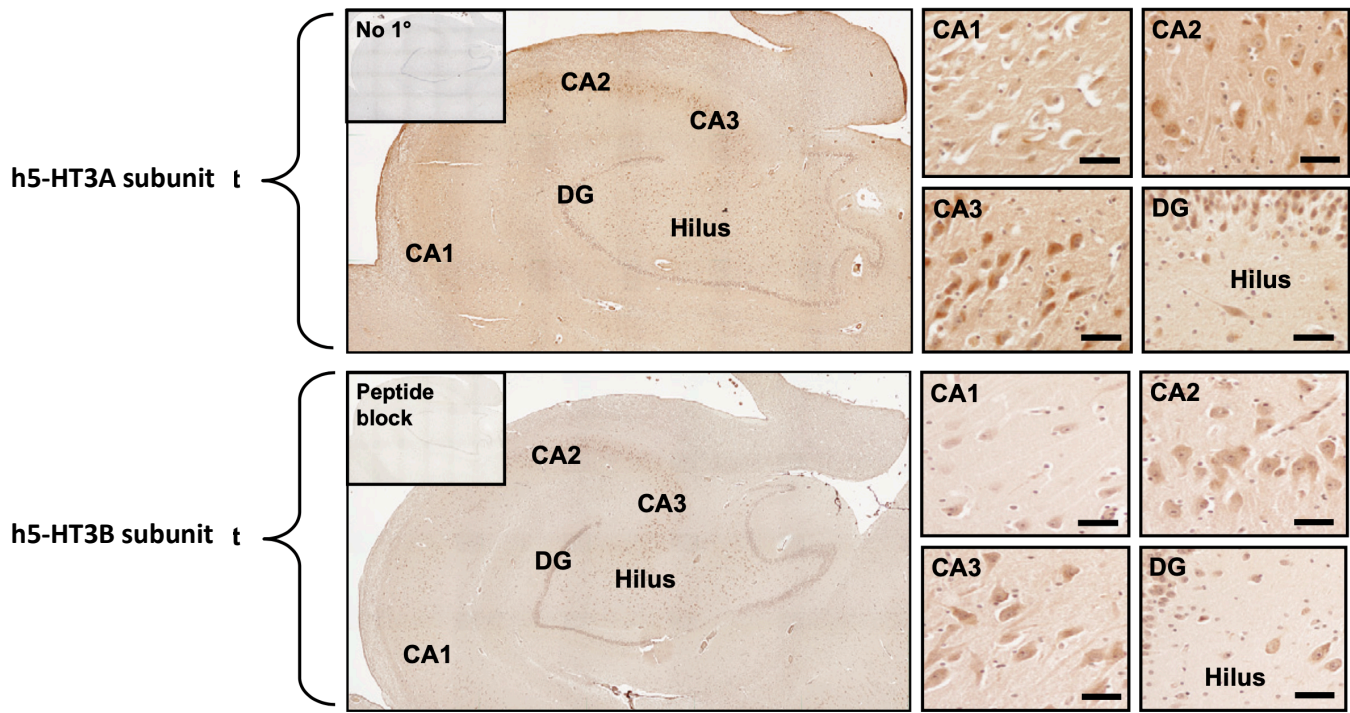


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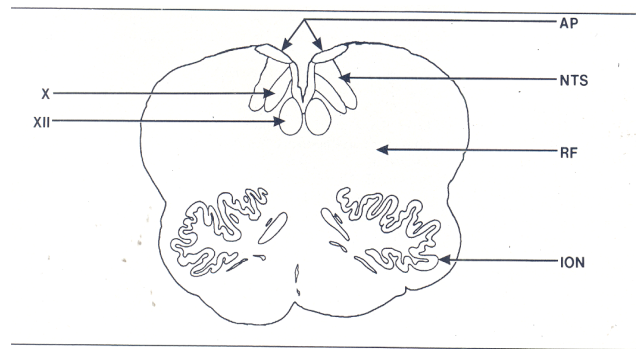
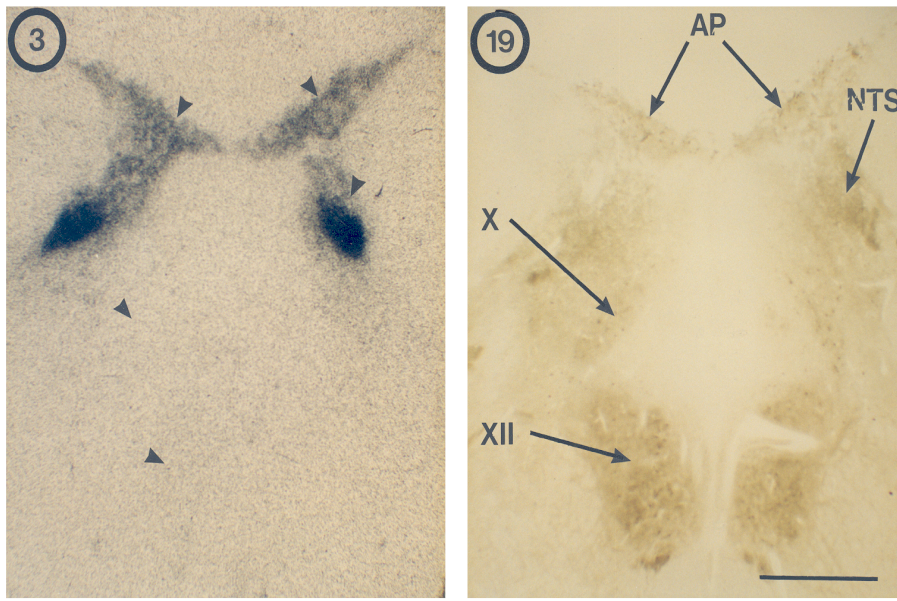


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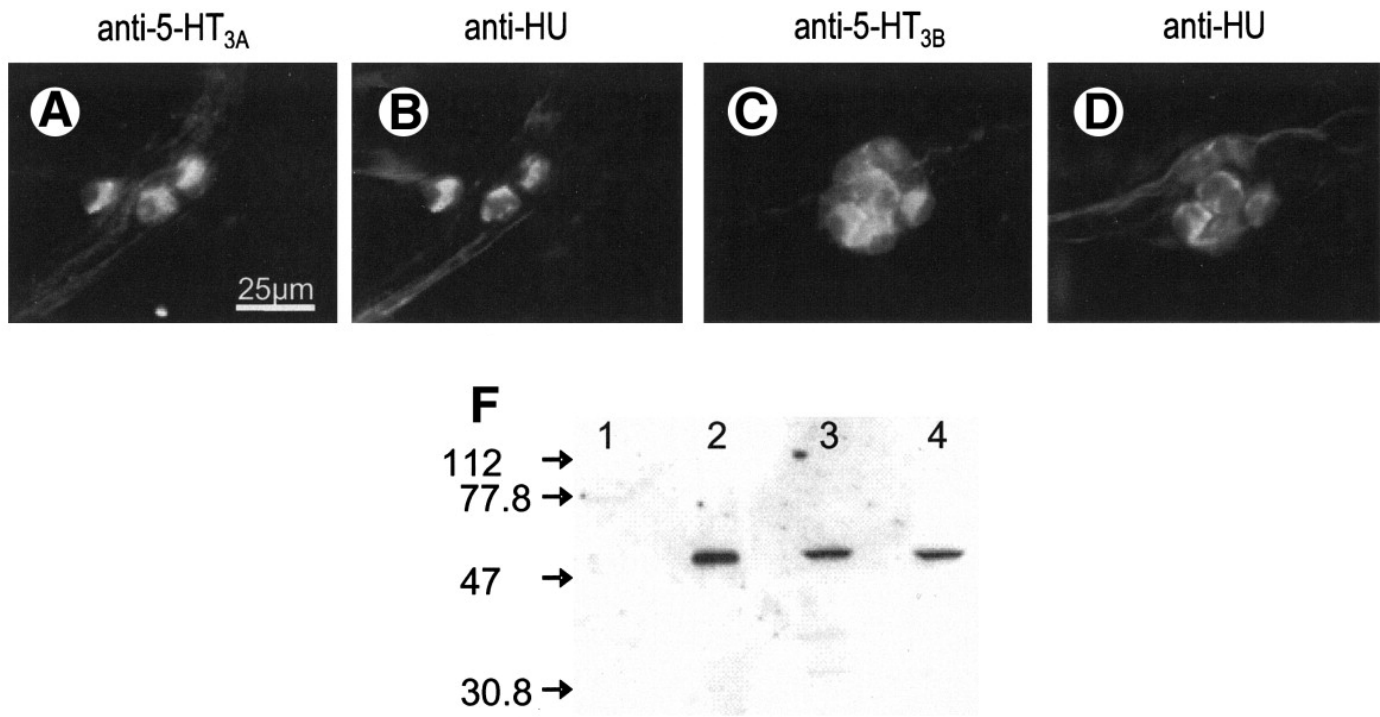
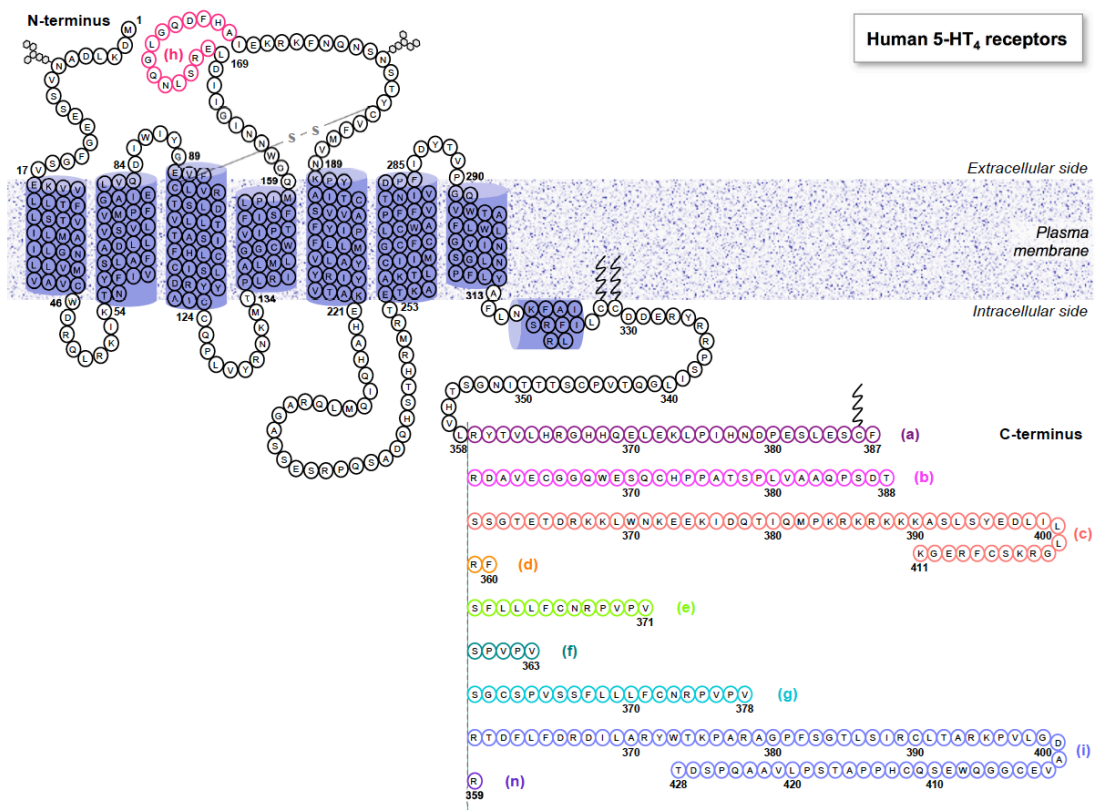


Figure 17.

Figure 18.



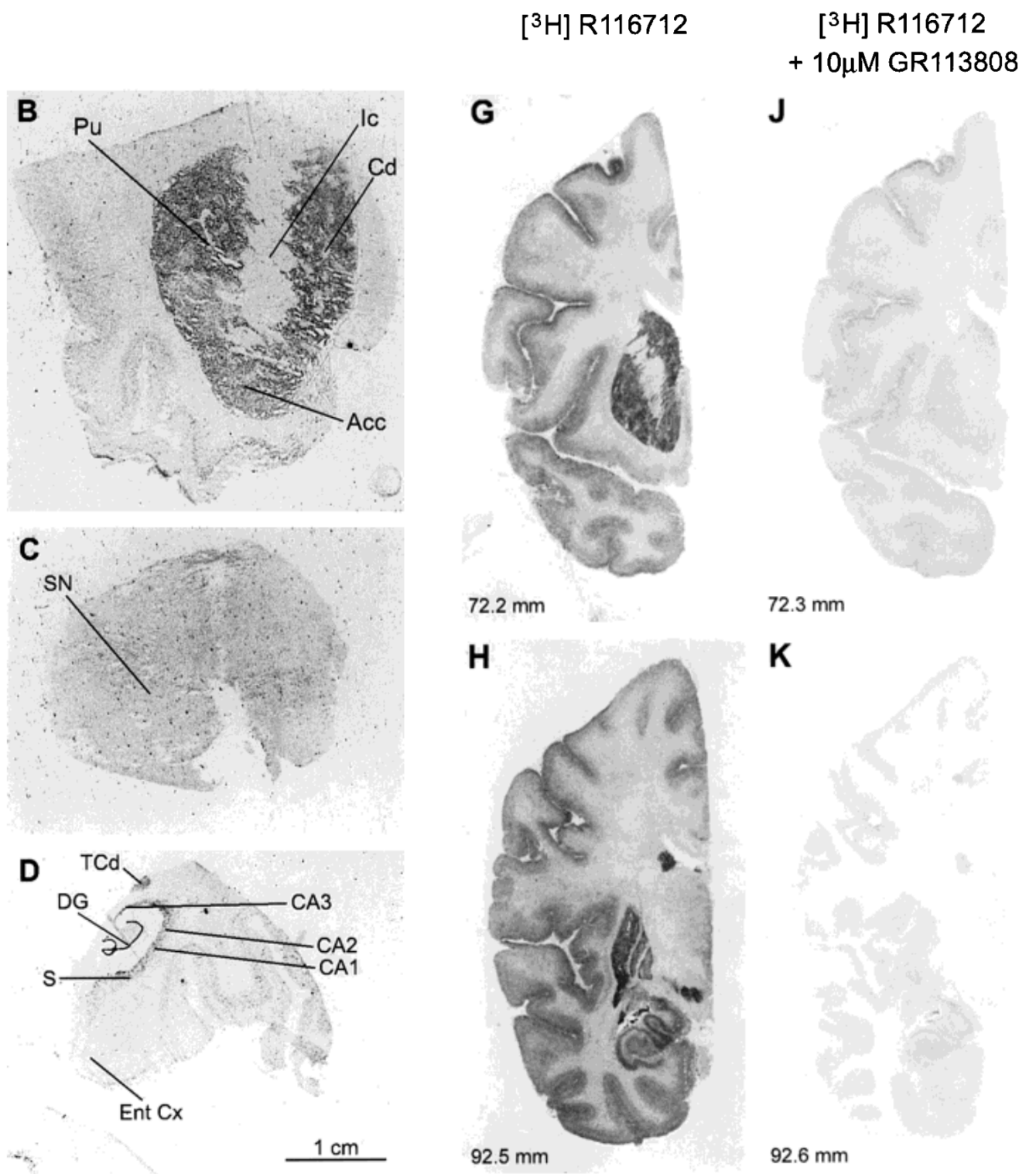


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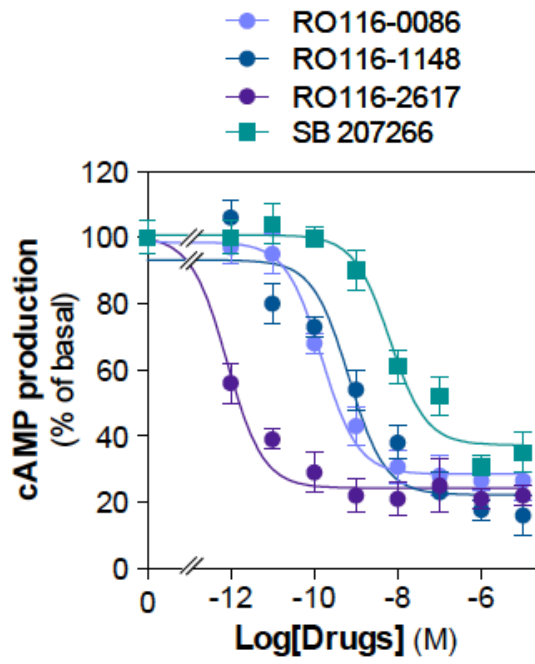
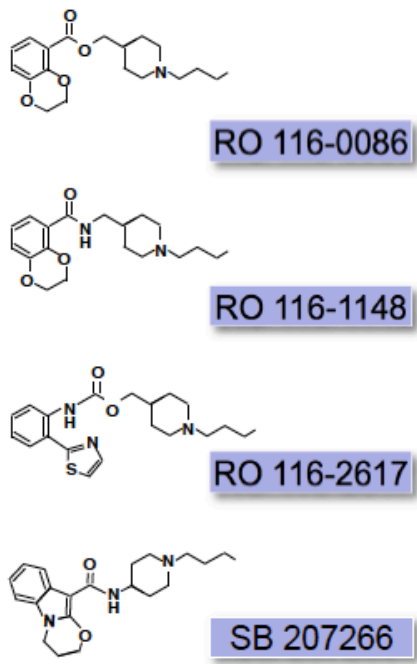


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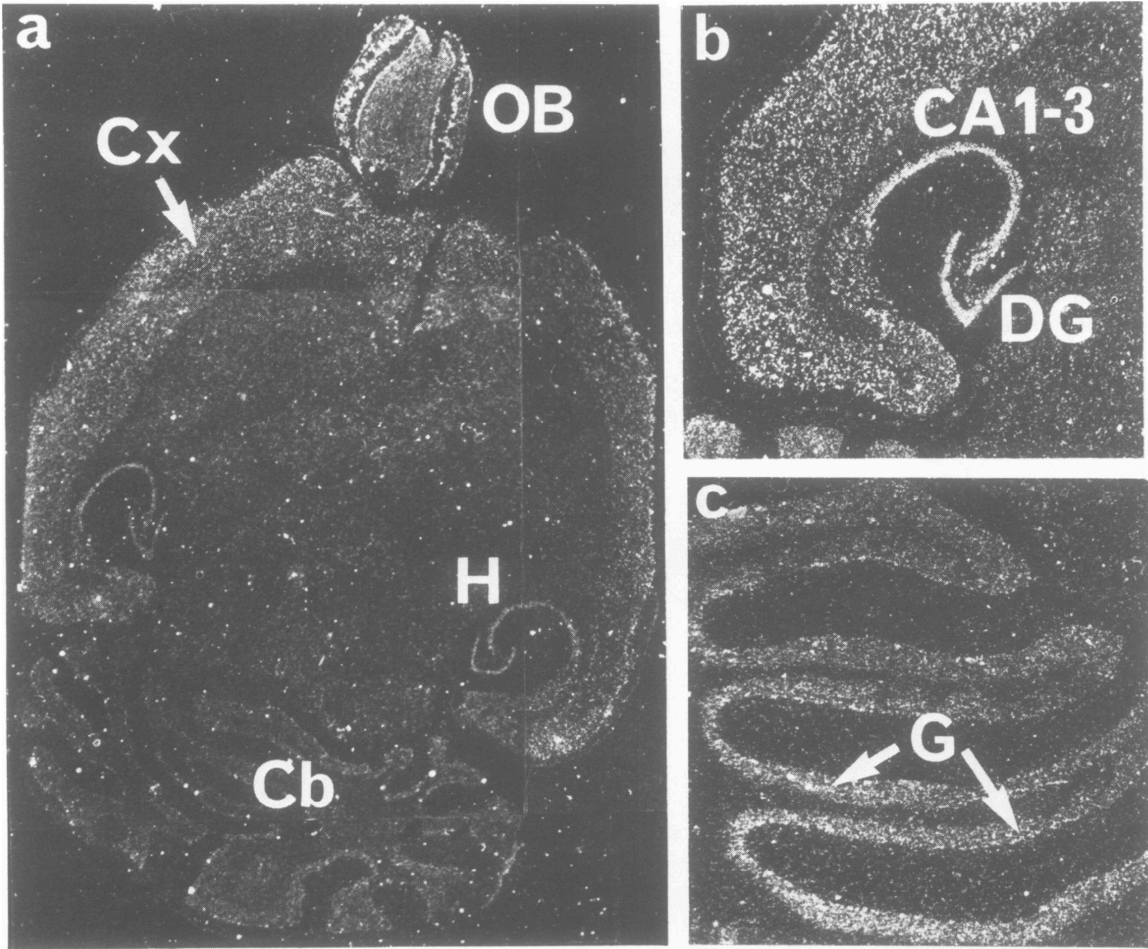


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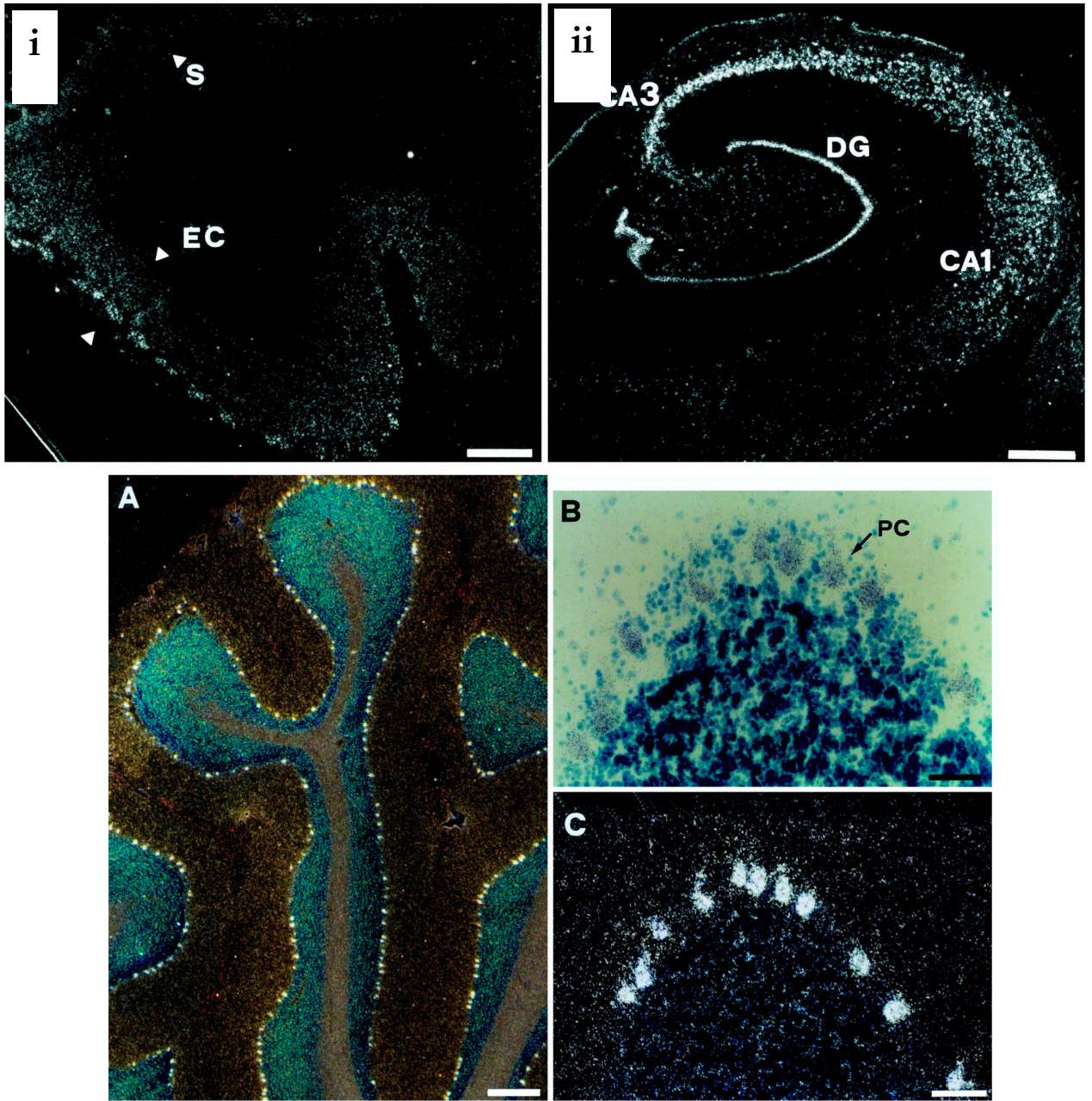


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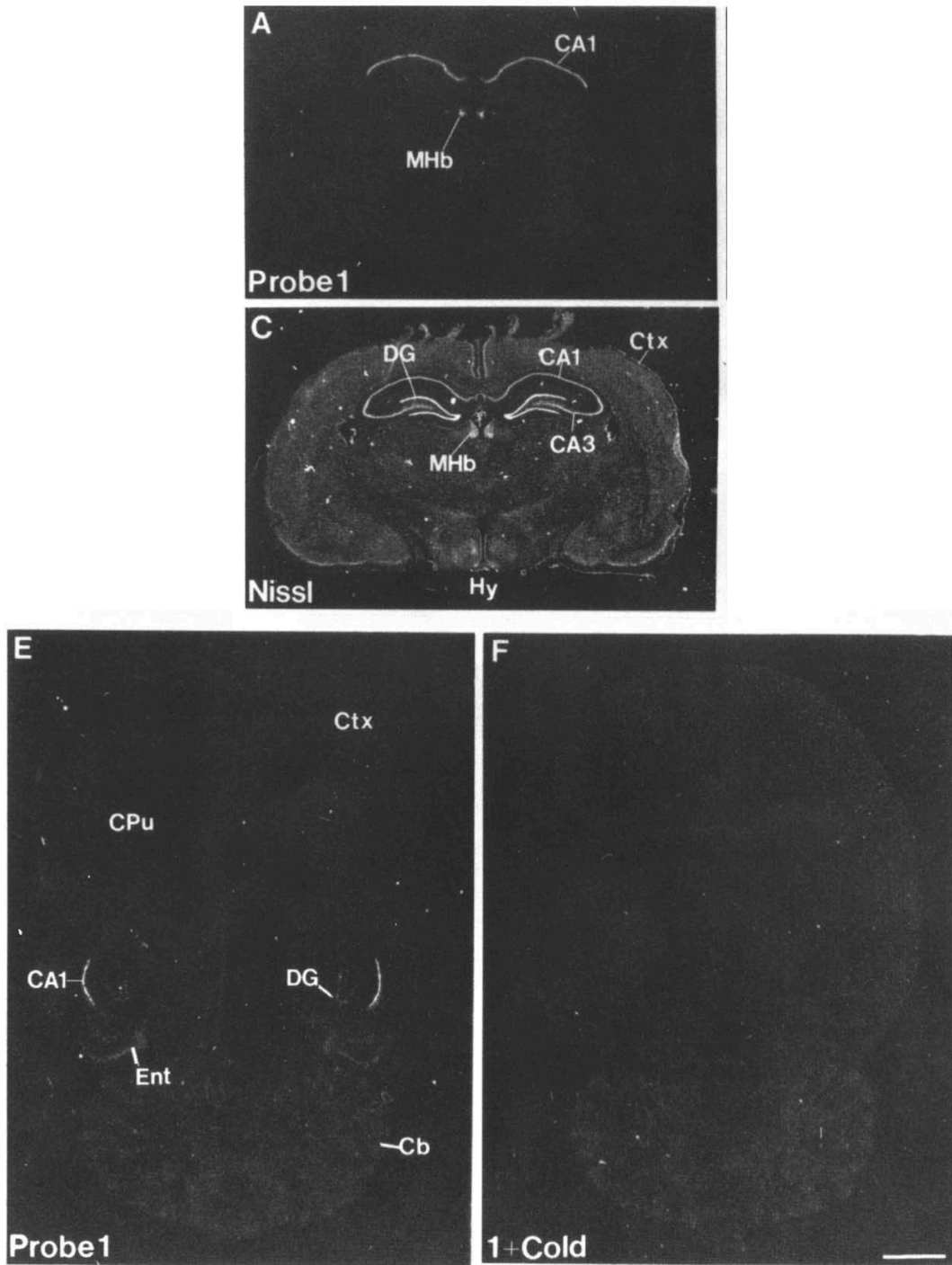


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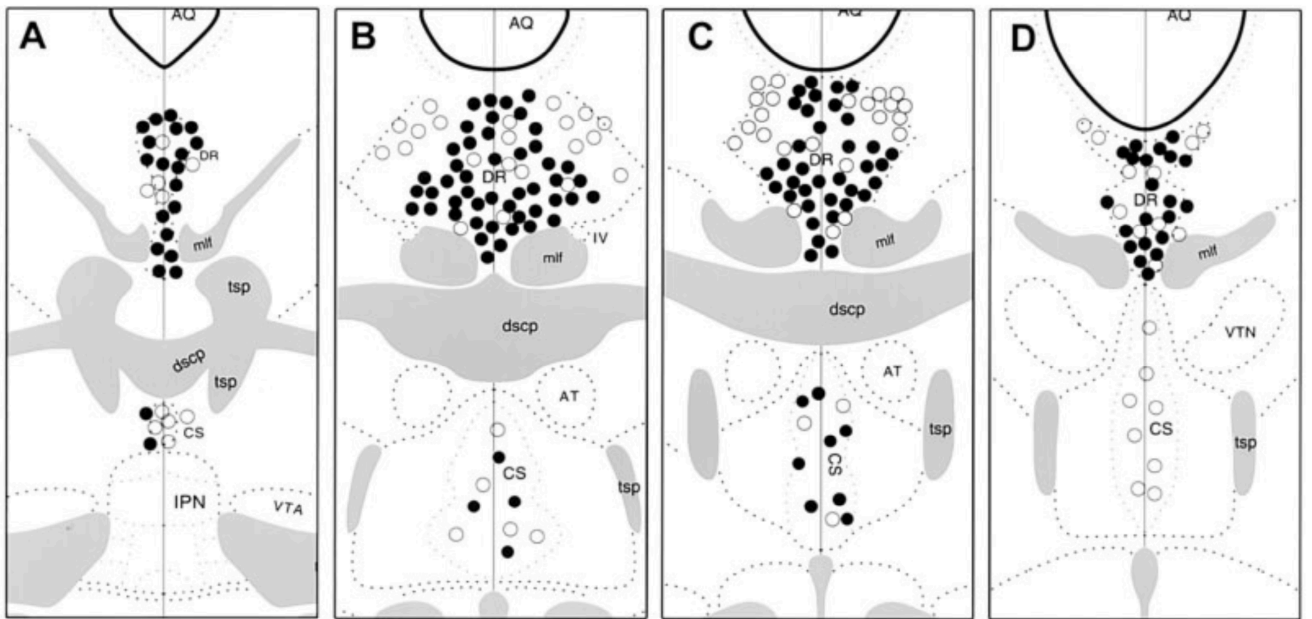
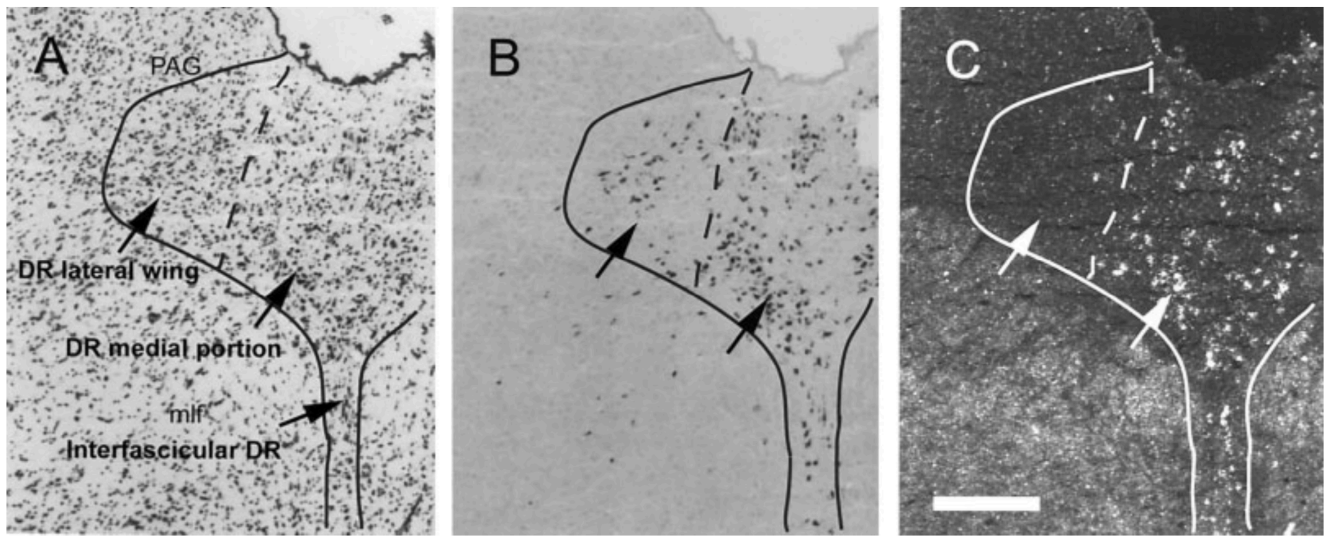


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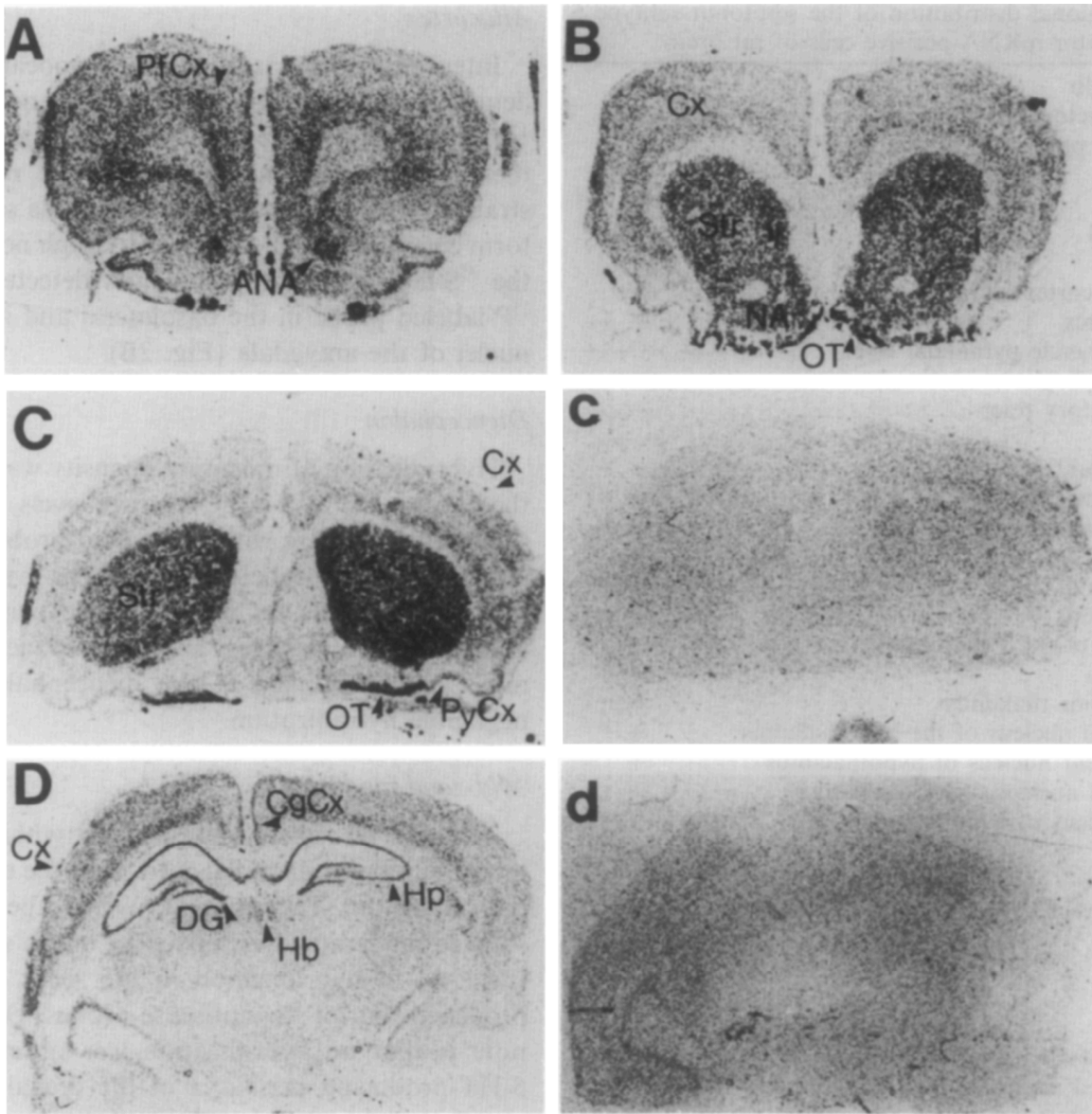


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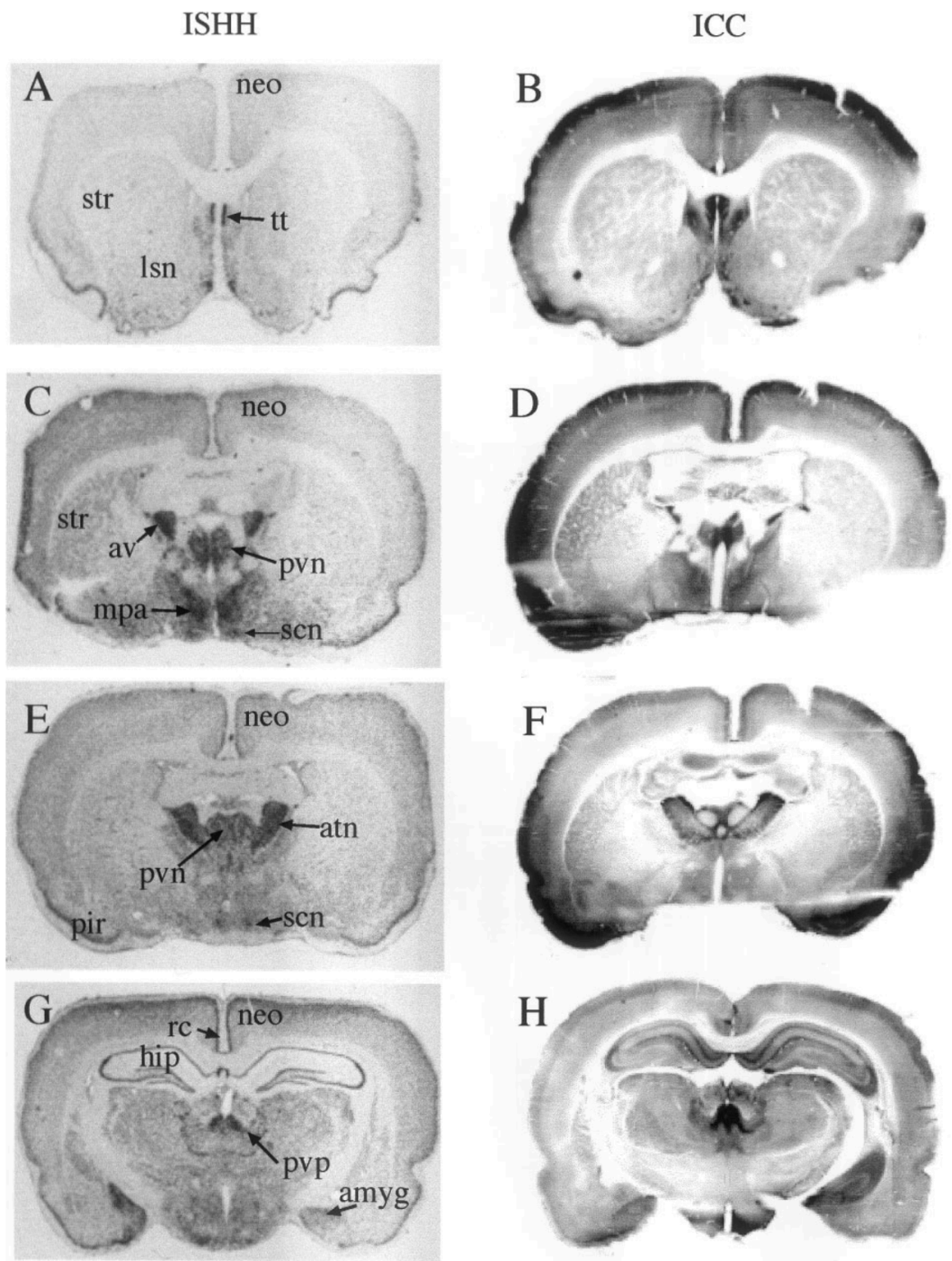


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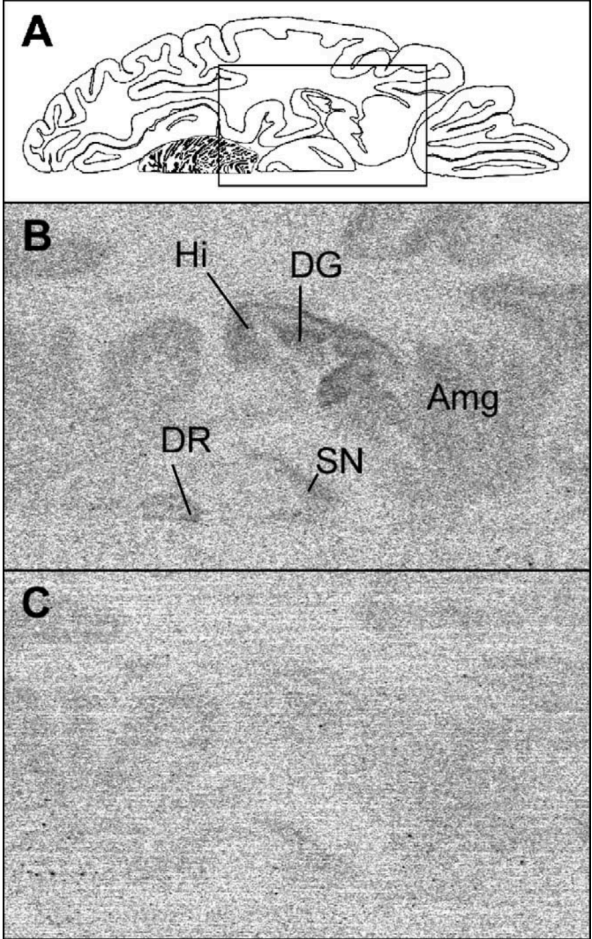
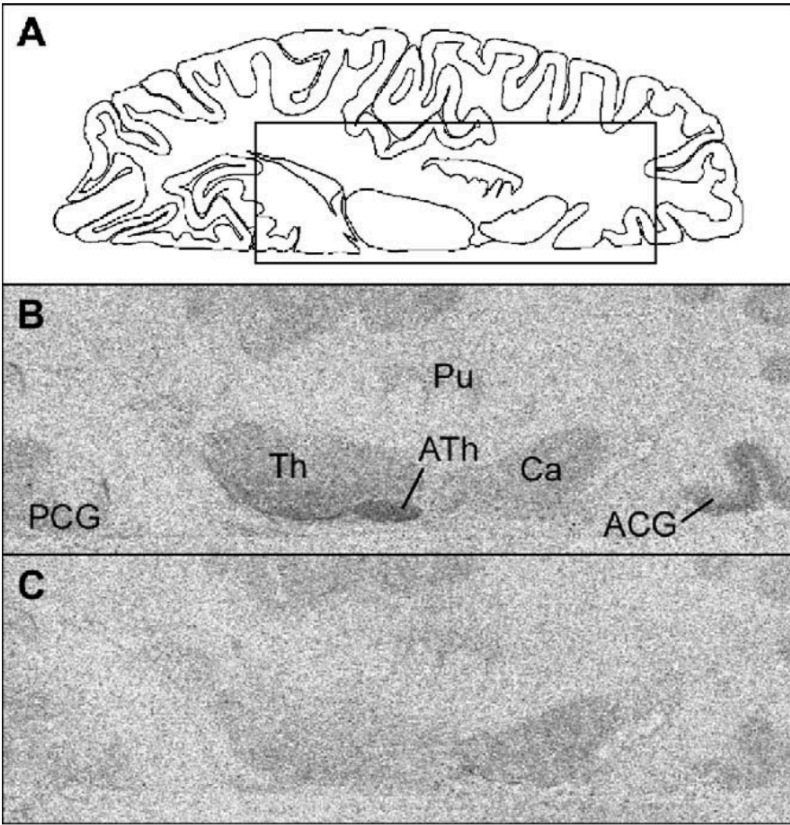


Figure 27.

Figure 28.

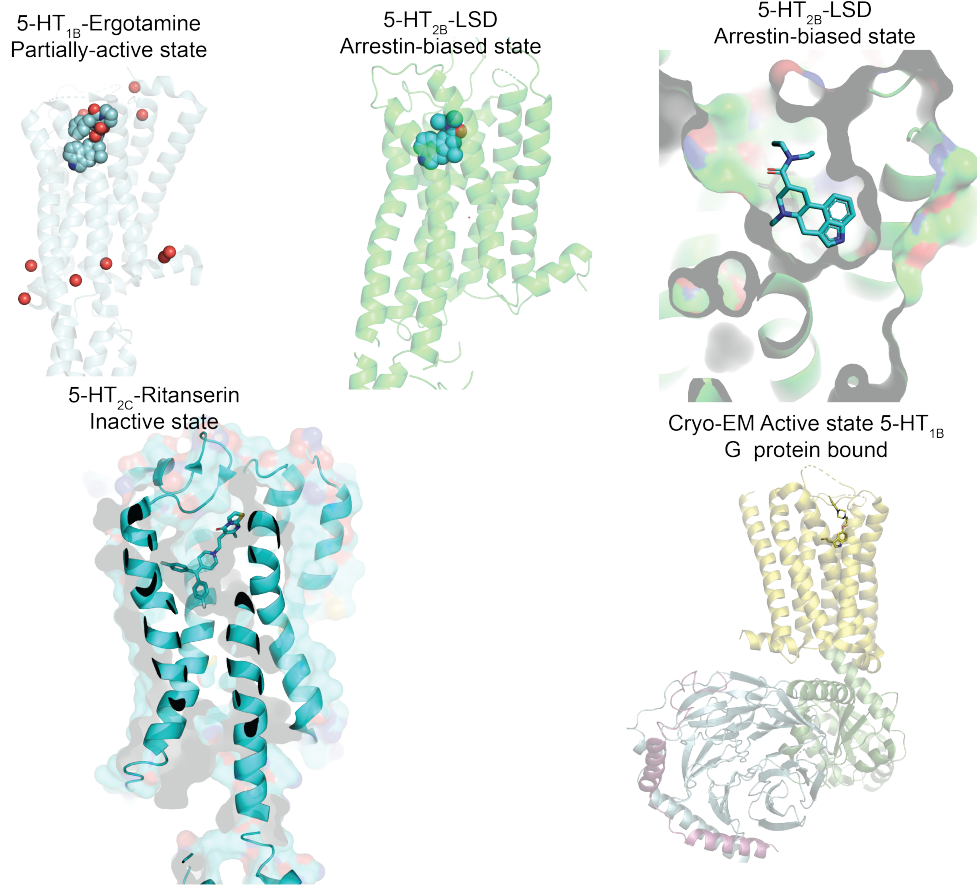


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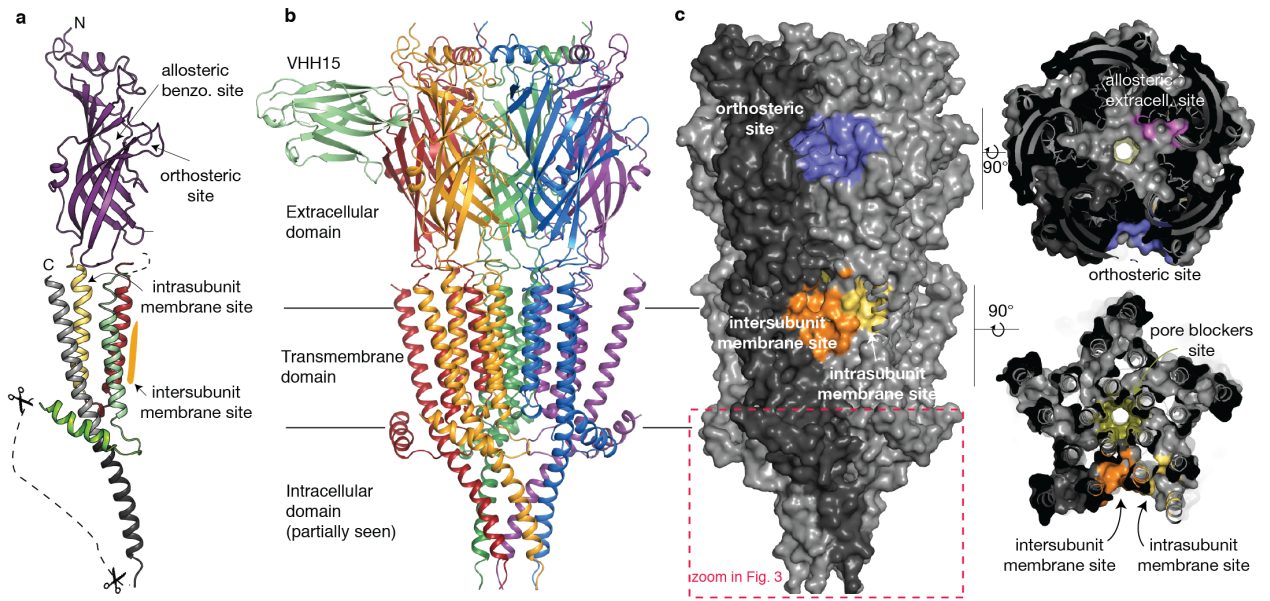


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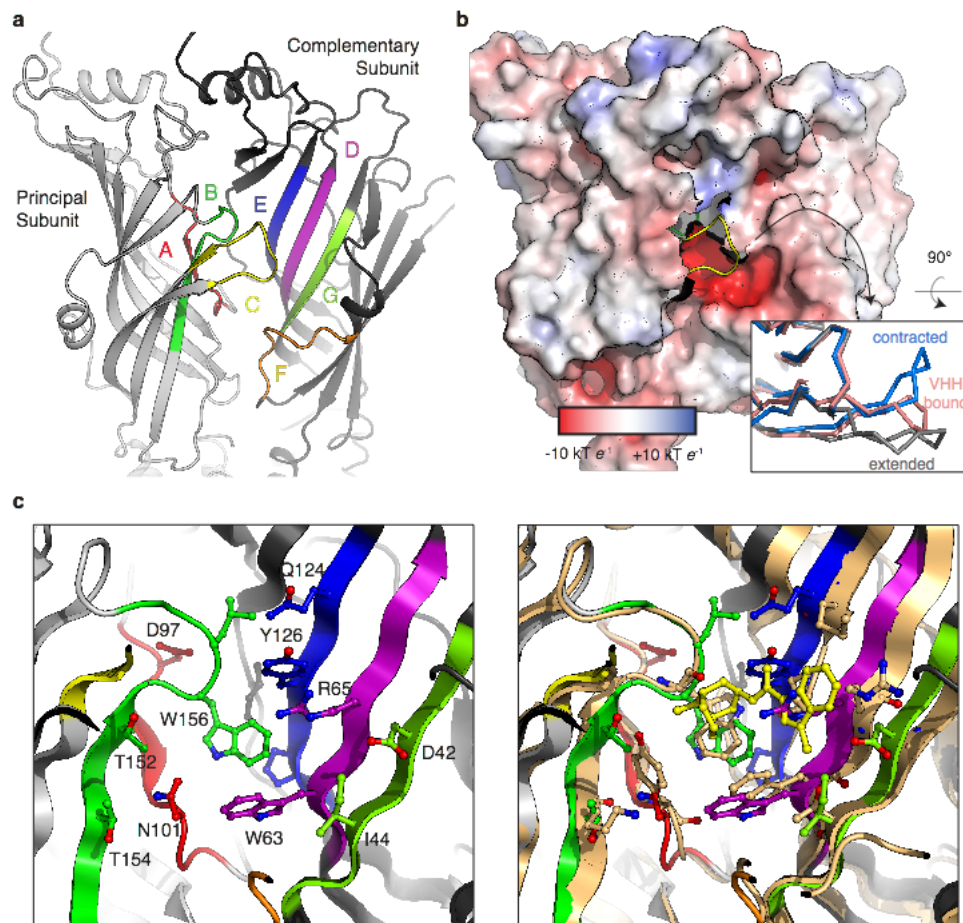


Figure 31.

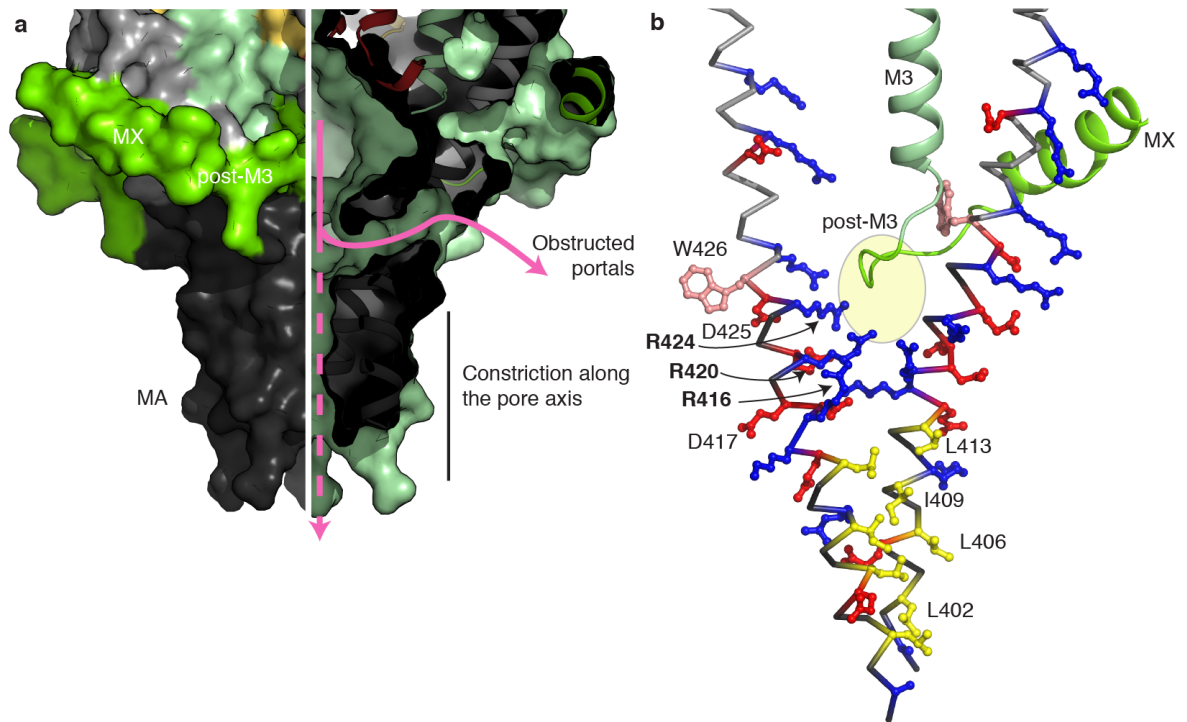


Figure 32.

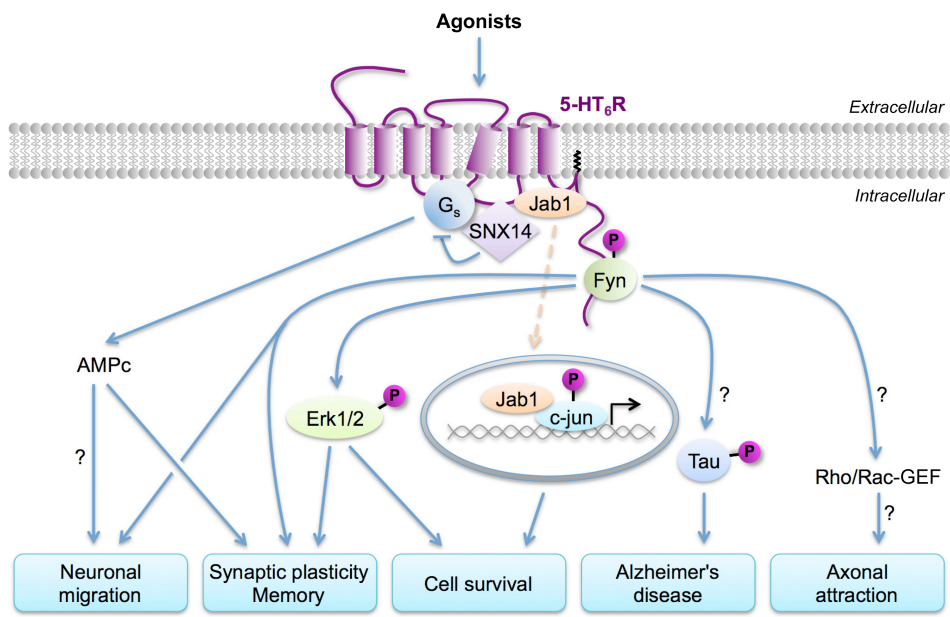


Figure 33.

