



**HAL**  
open science

## Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders

Anil Annamneedi, Caroline Gora, Ana Dudas, Xavier Leray, Véronique Bozon, Pascale Crépieux, Lucie P. Pellissier

### ► To cite this version:

Anil Annamneedi, Caroline Gora, Ana Dudas, Xavier Leray, Véronique Bozon, et al.. Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders. *British Journal of Pharmacology*, 2023, 2023, pp.1-24. 10.1111/bph.16216 . hal-04220553

**HAL Id: hal-04220553**

**<https://hal.science/hal-04220553v1>**

Submitted on 28 Sep 2023





**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders

Anil Annamneedi<sup>1,2,3</sup>  | Caroline Gora<sup>1</sup> | Ana Dudas<sup>1</sup> | Xavier Leray<sup>1,4</sup>  |  
Véronique Bozon<sup>1</sup> | Pascale Crépieux<sup>1,4</sup>  | Lucie P. Pellissier<sup>1</sup> 

<sup>1</sup>Team Biology of GPCR Signaling Systems (BIOS), CNRS, IFCE, INRAE, Université de Tours, Nouzilly, France

<sup>2</sup>LE STUDIUM Loire Valley Institute for Advanced Studies, Orléans, France

<sup>3</sup>Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu, India

<sup>4</sup>Inria, Inria Saclay-Ile-de-France, Palaiseau, France

## Correspondence

Lucie P. Pellissier, Team Biology of GPCR Signaling Systems (BIOS), CNRS, IFCE, INRAE, Université de Tours, PRC, F-37380, Nouzilly, France.

Email: [lucie.pellissier@inrae.fr](mailto:lucie.pellissier@inrae.fr)

## Funding information

H2020 European Research Council, Grant/Award Number: 851231; Agence Nationale de la Recherche, Grant/Award Number: ANR-18-CE45-0003

## Abstract

Autism spectrum disorders (ASDs) are diagnosed in 1/100 children worldwide, based on two core symptoms: deficits in social interaction and communication, and stereotyped behaviours. G protein-coupled receptors (GPCRs) are the largest family of cell-surface receptors that transduce extracellular signals to convergent intracellular signalling and downstream cellular responses that are commonly dysregulated in ASD. Despite hundreds of GPCRs being expressed in the brain, only 23 are genetically associated with ASD according to the Simons Foundation Autism Research Initiative (SFARI) gene database: oxytocin OTR; vasopressin V<sub>1A</sub> and V<sub>1B</sub>; metabotropic glutamate mGlu<sub>5</sub> and mGlu<sub>7</sub>; GABA<sub>B2</sub>; dopamine D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub>; serotonergic 5-HT<sub>1B</sub>; β<sub>2</sub>-adrenoceptor; cholinergic M<sub>3</sub>; adenosine A<sub>2A</sub> and A<sub>3</sub>; angiotensin AT<sub>2</sub>; cannabinoid CB<sub>1</sub>; chemokine CX<sub>3</sub>CR1; orphan GPR37 and GPR85; and olfactory OR1C1, OR2M4, OR2T10 and OR52M1. Here, we review the therapeutic potential of these 23 GPCRs, as well as 5-HT<sub>2A</sub> and 5-HT<sub>7</sub>, for ASD. For each GPCR, we discuss its genetic association, genetic and pharmacological manipulation in animal models, pharmacopoeia for core symptoms of ASD and rank them based on these factors. Among these GPCRs, we highlight D<sub>2</sub>, 5-HT<sub>2A</sub>, CB<sub>1</sub>, OTR and V<sub>1A</sub> as the more promising targets for ASD. We discuss that the dysregulation of GPCRs and their signalling is a convergent pathological mechanism of ASD. Their therapeutic potential has only begun as multiple GPCRs could mitigate ASD.

## KEYWORDS

autism spectrum disorder, brain, G protein-coupled receptors, neurotransmitter, signalling pathways, social interaction

**Abbreviations:** ASD, autism spectrum disorder; cKO, conditional knock-out; CNV, copy number variant; FXS, fragile X syndrome; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; NAM, negative allosteric modulator; OR, olfactory receptor; PAM, positive allosteric modulator; PD, Parkinson's disease; RTT, Rett syndrome; UTR, untranslated region.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *British Journal of Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

## 1 | INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder diagnosed around the age of 3 with a worldwide prevalence of around 1/100 child births (Zeidan et al., 2022). Core clinical symptoms are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013): social interaction and communication deficits and stereotyped behaviours, restrained or compulsive activities and interests. ASD is often associated with comorbid symptoms, such as anxiety, epilepsy, sleep disturbances, motor coordination impairment, gastrointestinal disorders, or intellectual disability. Its aetiology is partially resolved, because 70% of cases remain sporadic, highlighting the polygenic, epigenetic and environmental complexity of the disease (Cheroni et al., 2020; Lacivita et al., 2017; Saxena et al., 2020). To date, no pharmacological treatment exists for the core social symptoms of ASD. Currently, only **risperidone** and **aripiprazole** antipsychotics are approved for irritability, aggressive behaviours and self-injury comorbid symptoms, and they frequently present side effects (McCracken et al., 2002; McDougle et al., 2005; Owen et al., 2009; Varni et al., 2012). Administration of antidepressant compounds (e.g., **fluoxetine**) improves stereotyped and repetitive behaviours and compulsive activities in patients, despite having limited efficacy and important side effects (Lacivita et al., 2017). Early behavioural intervention programmes have shown some efficacy on core social symptoms. However, they are costly, they are highly demanding to children and their families, they need intensive training, they should start as early as possible and their outcome remains uncertain (Estes et al., 2015; Linstead et al., 2017; Smith et al., 2015). Therefore, the discovery of new and effective drugs relies on the identification of new targets that remain the main gaps in the ASD field so far.

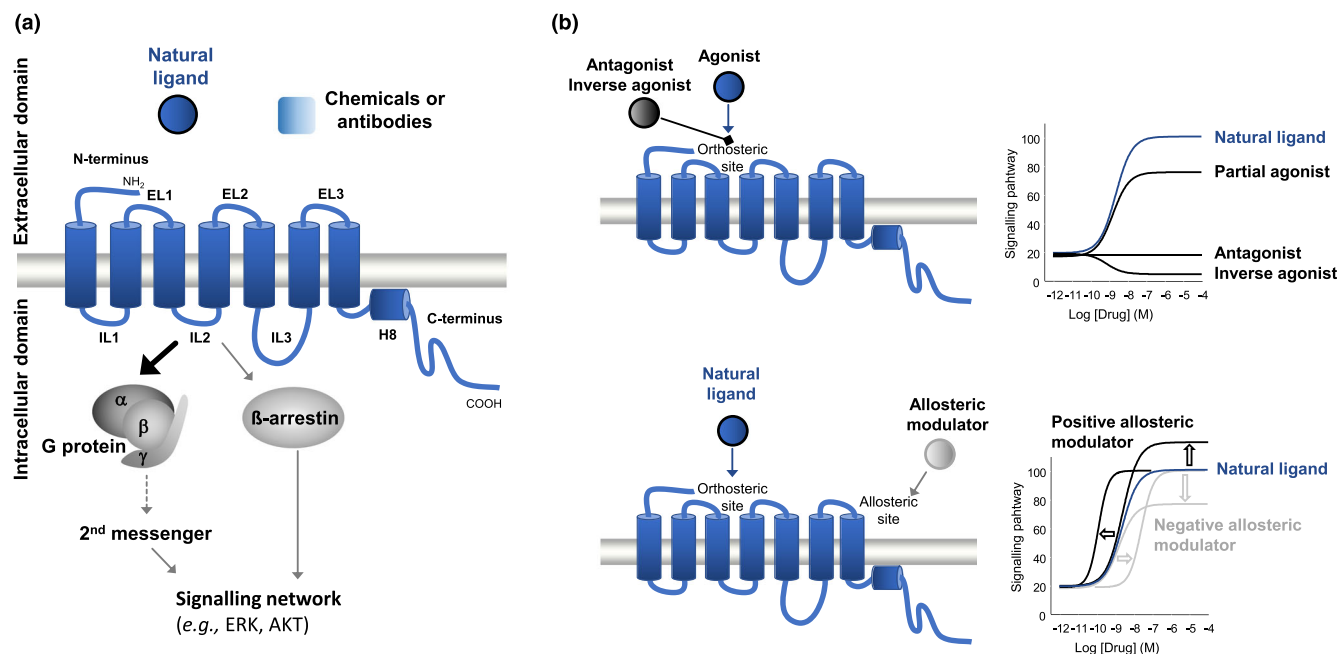
Various types of ionotropic (**NMDA**, **nicotinic acetylcholine** and **GABA<sub>A</sub>** receptors), metabotropic or G protein-coupled receptors (**GPCRs**) (**glutamate**, **GABA<sub>B</sub>**, **serotonin** and **oxytocin (OT)-vasopressin** systems), **Toll-like (TLR)** and **insulin growth factor 1 (IGF1)** receptors or intracellular signalling molecules (**mTOR**, **ROCK** and **GSK3B**) have been targeted in ASD preclinical and clinical trials (Lacivita et al., 2017). So far, these clinical trials have failed at the phase 2b/3 stage of clinical trials, because of an important placebo effect, lack of efficacy, and/or the large heterogeneity of patients (Daniels et al., 2023; Lacivita et al., 2017). New advances need to overcome these challenges. First, subtypes of patients determined on their genetic or neuropathological mechanism profile should be tested rather than patients from the whole spectrum. Second, the identification of robust therapeutic targets and the development of potent drugs should thwart the placebo effect. More than a thousand candidate genes are listed in the Simons Foundation Autism Research Initiative (SFARI) database (<https://gene.sfari.org>), and rather than a single mutation, accumulation of deleterious alleles and copy number variants (CNVs) may underlie the pathological process among affected individuals (Manoli & State, 2021). Recent genome wide association studies of large ASD cohorts robustly identified hundreds of candidate genes that fall in two main convergent neurobiological mechanisms,

namely 'gene expression regulation' or 'neuronal communication, signalling or plasticity' (De Rubeis et al., 2014; Satterstrom et al., 2020; Pintacuda et al., 2023). GPCRs are master regulators of these convergent mechanisms. In addition, their fine-tuned pharmacology and diversity may represent the greatest therapeutic potential for ASD, leading to successful clinical trials. In this review, we demonstrate why this receptor family meets all criteria of convergent therapeutic targets for ASD.

### 1.1 | GPCRs and their signalling are dysregulated in ASD

Canonical GPCRs display an extracellular domain composed of the N-terminus and three extracellular loops (EL1–3) that connect seven transmembrane (TM) helices. Occupancy of the ligand binding pocket leads to conformational changes in the helices that transmit activation to the intracellular domain, that is composed of three intracellular loops (IL1–3) and a C-terminus region with an eighth helix parallel to the plasma membrane (Figure 1). This intracellular domain is involved in the recruitment and activation of direct transducers that activate downstream intracellular signalling. GPCRs are translated inside the membrane of the endoplasmic reticulum (ER) and are actively exported to the plasma membrane. Due to their molecular complexity, they are often prone to misfolding or lack of ER export, which may result in cell toxicity (Beerepoot et al., 2017). Most GPCRs and their transducers are expressed in the central nervous system (CNS) (Marti-Solano et al., 2020; Regard et al., 2008), with over 200 variants in GPCR genes associated with ASD (SFARI). Furthermore, transcriptomic data and meta-analysis from prefrontal cortex tissue showed that GPCRs are the most frequently dysregulated genes in ASD and revealed around 200 GPCRs potentially linked to ASD (Hormozdiari et al., 2015; Monfared et al., 2021). Among these genes, serotonin **HTR2A**, adenosine **ADORA1** and adrenergic **ADRA1D** are the most dysregulated.

GPCRs and their downstream signalling pathways are also affected in ASD. Upon activation, GPCRs couple to several heterotrimeric G proteins (comprising  $\alpha$ ,  $\beta$  and  $\gamma$  subunits) and recruit  $\beta$ -arrestins that impact on the kinetics of intracellular signalling pathways, such as extracellular signal-regulated kinases (**ERKs**) or promote receptor endocytosis (Figure 1a).  $G_{\alpha_{s/olf}}$  protein activates **adenylyl cyclases** that hydrolyse **ATP** into **cAMP**, which is degraded by **phosphodiesterases** into **AMP**. cAMP activates the exchange protein activated by cAMP (**EPAC**), **calcium ion channels** ( $Ca_v$ ) and protein kinase A (**PKA**). Conversely,  $G_{\alpha_{i/o}}$  inhibits adenylyl cyclases and cAMP production and mostly modulates calcium channels.  $G_{\alpha_{q/11}}$  proteins activate **phospholipases C $\beta$** , which hydrolyses phosphatidylinositol-4,5-bisphosphate (**PIP<sub>2</sub>**) into diacylglycerol (DAG) and inositol-1,4,5-triphosphate (**IP<sub>3</sub>**). Released **IP<sub>3</sub>** binds to **ryanodine receptors** (RyRs) on the ER, which leads to calcium release from this subcellular location. Both calcium and DAG activate protein kinase C (**PKC**) and its effectors, such as **Akt** (protein kinase B, PKB) or ERK.  $G_{\alpha_{12/13}}$  activates Rho guanine nucleotide exchange factor (**GEF**) and RhoA, which



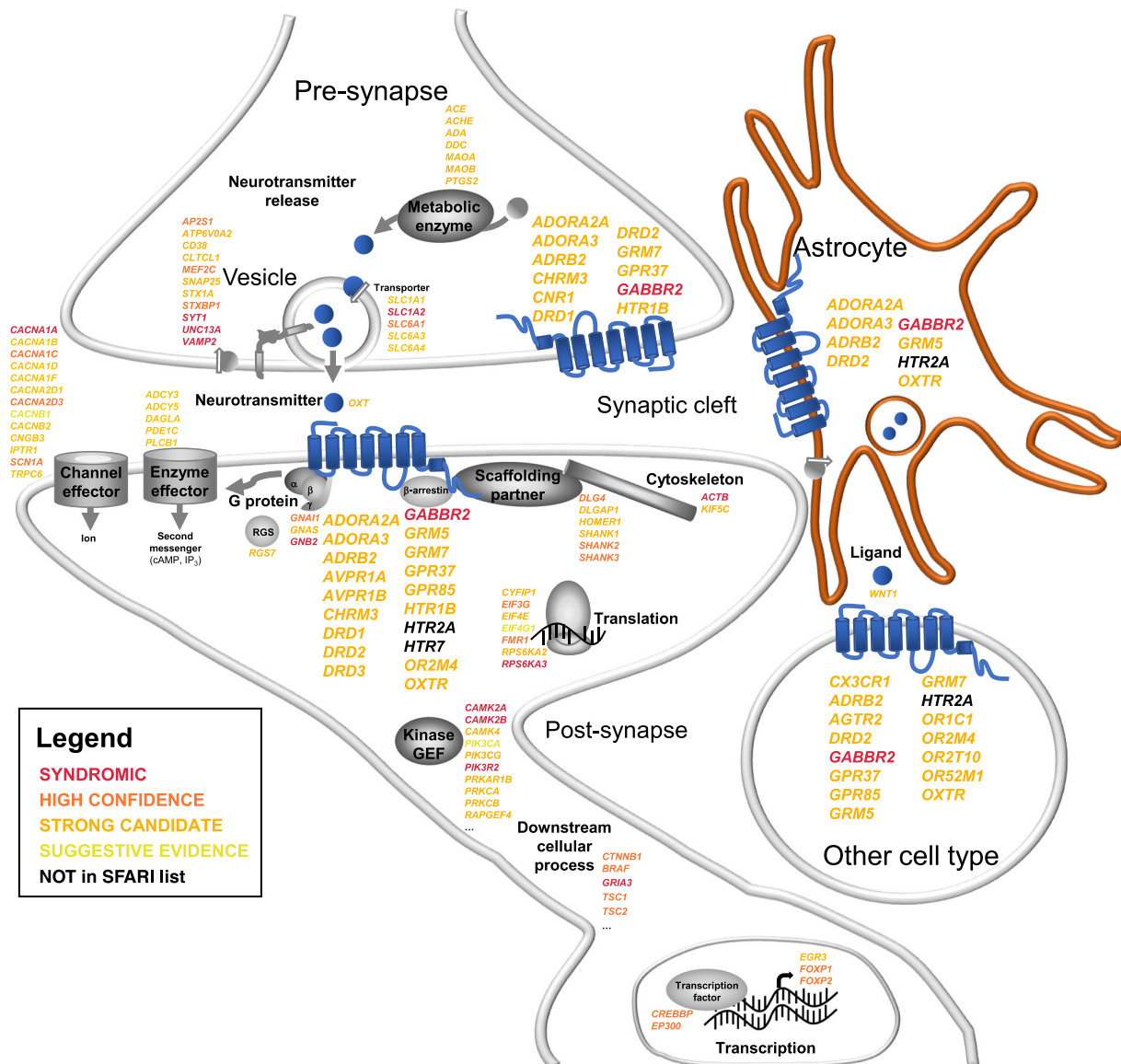
**FIGURE 1** G protein-coupled receptor (GPCR) signalling and pharmacology. (a) GPCRs are composed of seven transmembrane domains connecting the extracellular domain (N-terminus and extracellular loops [EL] 1–3) where various ligands bind the receptor (e.g., natural ligands and chemicals/antibodies), to the intracellular domain (intracellular loops [IL] 1–3, helix H8 and C-terminus) that recruit the direct transducers, which activate a signalling network (e.g., Akt and extracellular signal-regulated kinase [ERK]) and integrated cellular processes. A biased ligand has the particular pharmacological profile to favour signalling pathways within the complex receptor signalling network. Here, a G protein-biased ligand that favours G protein coupling (black arrow) over  $\beta$ -arrestin recruitment (grey arrow) is shown. (b) GPCRs display a rich pharmacopoeia of ligands, with agonists, antagonists and inverse agonists that bind to the orthosteric binding site (e.g., the binding site of the natural ligand) to, respectively, activate or prevent the agonist binding and inactivate the receptor. Other ligands bind to allosteric sites that increase or decrease the efficacy and/or potency of the natural ligand, respectively, called positive or negative allosteric modulators.

acts on the cytoskeleton to promote neurite formation. G $\beta\gamma$  proteins also participate in downstream signalling through activation of G protein-coupled inwardly rectifying potassium channels (GIRK) and other ion channels. The most affected transducers in ASD are G $\alpha_i$  and G $\alpha_{12/13}$  proteins (Monfared et al., 2021). Following activation, GPCRs are internalised in intracellular compartments (e.g., endosomes) together with their transducers and participate in the signalling cascades (Villardaga et al., 2023). Downstream intracellular signalling networks lead to integrated cellular processes, translation of specific mRNAs (León et al., 2014; Musnier et al., 2012; Tréfier et al., 2018) and gene transcription. The profile of gene expression and transcript translation depends on the specific activation of GPCRs and the cellular context. For example, G $\alpha_s$ -dependent GPCRs activate the transcription factor cAMP-responsive element binding protein (CREB), among many others. Globally, GPCRs are key upstream regulators of Wnt/ $\beta$ -catenin, ERK, PKC, PI3K/Akt, CREB, PTEN and mTOR intracellular pathways that are convergently dysregulated in ASD (Gazestani et al., 2019; O'Roak et al., 2012; Pintacuda et al., 2023). In an attempt to estimate their potential as master regulators of genes involved in ASD, we confronted 'Kyoto Encyclopedia of Genes and Genomes' (KEGG) pathways, 'Reactome' pathways, 'Gene Ontology' (GO) terms and our knowledge (Supporting Information) to the 1045 ASD candidate genes from the SFARI list. In this list, we identified 23 GPCRs and 129 genes linked to GPCRs (Figure 2 and

Table S1), accounting for at least 15% of all the candidate genes. Interestingly, two orphan GPR37 and GPR85 and four olfactory OR1C1, OR2M4, OR2T10 and OR52M1 receptors with relatively unknown functions in the brain belong to this list. This proportion of candidate genes might increase with future knowledge on signalling and cellular processes under the control of GPCRs, especially their effect on translation and transcription.

## 1.2 | GPCRs are relevant druggable targets for ASD

GPCRs respond to diverse natural signals ranging from photons, amino acids, peptides up to large glycosylated proteins. This receptor family comprises more than 800 GPCRs, subdivided into five classes according to the International Union of Basic & Clinical Pharmacology (IUPHAR) nomenclature and classification (Alexander et al., 2021): the largest rhodopsin-like class A, the secretin/class B, the glutamate/class C, the Frizzled class and the adhesion class. Sensory GPCRs (olfactory, vision, taste and pheromone receptors), which account for most GPCR genes, are included mostly in class A and a few in class C. Although hundreds of GPCRs remain without any identified ligand, 24% of these so-called 'orphan receptors' (including olfactory receptors [ORs]) are dysregulated in ASD. In addition to natural ligands,



**FIGURE 2** At least 15% of Simons Foundation Autism Research Initiative (SFARI) genes participate in G protein-coupled receptor (GPCR) activity and signalling processes. GPCR ligands are synthesised by metabolic enzymes, loaded by their transporters into synaptic vesicles that fuse with the presynaptic membrane upon increase of intracellular calcium, leading to neurotransmitter release in the synaptic cleft. These neurotransmitters or ligands are either recaptured by membrane transporters, degraded or bind and activate their cognate GPCR. Even in the absence of ligand, GPCRs are present in preformed higher complexes with scaffolding partners, channels, cytoskeleton and signalling transducers. Upon GPCR activation, transducers activate enzyme and channel effectors to produce second messengers. These second messengers activate major kinases and guanine nucleotide exchange factor (GEF) that tune up or down downstream cellular processes, including translation and transcription. Syndromic (in red), high confidence (Category 1 in dark orange), strong candidate (Category 2 in light orange) and suggestive evidence (Category 3 in green) genes are coloured according to SFARI gene scoring and colour code ([gene.sfari.org/about-gene-scoring](http://gene.sfari.org/about-gene-scoring); Table S1) and additional GPCR genes are in black. GPCRs are localised at presynaptic and/or postsynaptic compartment of neurons, in astrocytes or in unknown or other cell types (see text and Figure 3 for their widespread or specific expression pattern in the different structures).

drugs can modulate GPCR activity, inducing diverse pharmacological profiles (Figure 1b). They can either be chemical compounds, peptides, large autoantibodies and more recently, antibody fragments (Mujic-Delic et al., 2014). Orthosteric agonists, inverse agonists and antagonists occupy the natural ligand binding pocket and activate, inactivate the receptor and/or prevent the binding of the endogenous ligand respectively. In contrast, by binding to allosteric sites, positive

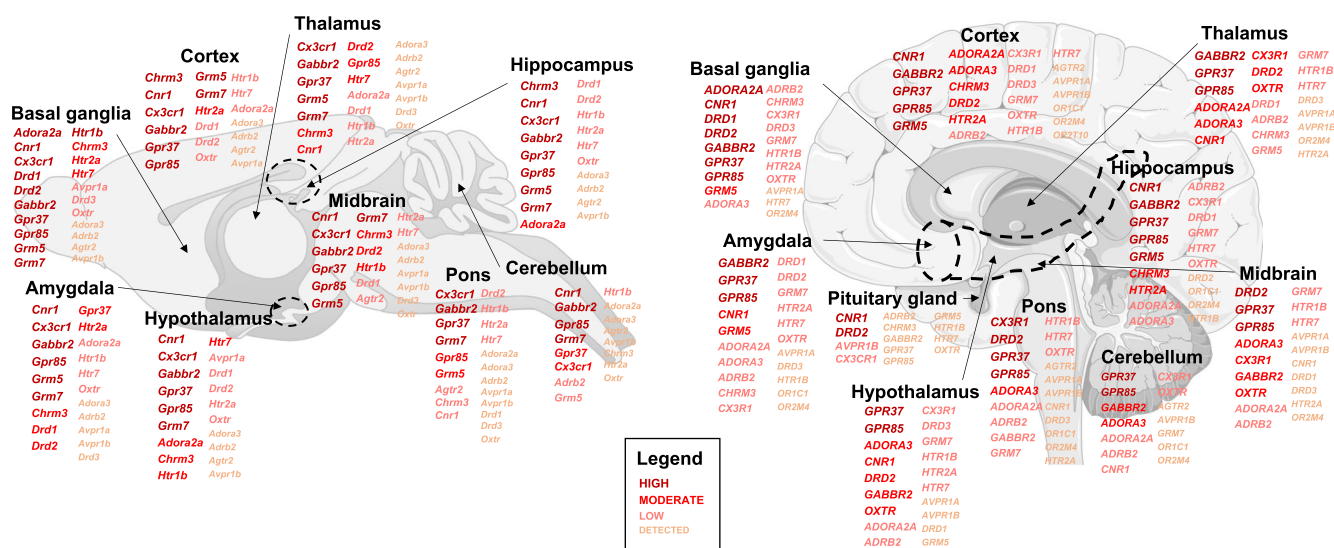
(PAM) or negative (NAM) allosteric modulators enhance or decrease GPCR activity only in the presence of agonists. While their intrinsic instability has been a major issue for resolving their three-dimensional structure, many GPCR structures in inactive, intermediate and active conformations became available with the development of cryo-electron microscopy. These recent advances facilitate in silico design of more selective drugs. Finally, GPCRs are modulated by interacting

partners. They can form cell-specific homo- or hetero-oligomers depending on the GPCR composition and subcellular localisation in a particular cell type. Each GPCR in the oligomer, or co-expressed in the same cell, may influence the signalling network of other GPCRs, opening a new area of GPCR pharmacology. Their activity also is modulated through reciprocal functional interactions with scaffolding protein partners (e.g., Shank1–3), **ion channels** and **tyrosine kinase receptors**. Different ligands may favour one coupling or protein partner interaction, leading to what is called ‘signalling bias’ (Figure 1a). This pharmacological property of GPCRs may be of great interest for therapeutic applications, because one biased drug can promote one signalling cascade over all others, hence possibly avoiding side effects. Considering their unique characteristics, GPCRs offer many levels of leveraging as therapeutic targets for neurological disorders. More than 30% of the drugs approved on the global market target GPCRs in various disorders, including neurological conditions by 20% of them (Alexander et al., 2021; Hauser et al., 2017). This proportion will increase because nearly half of GPCRs in the CNS remain orphan. So far, no pharmaceutical agent has reached the market to improve core symptoms of ASD. The few GPCRs that have been tested in clinical trials are **mGlu<sub>5</sub>**, **GABA<sub>B</sub>**, **V<sub>1A</sub>** and **CB<sub>1</sub>**, all of which are listed in the SFARI database (Table S1). Therefore, the therapeutic potential of GPCRs has only begun. In this review, we explored the therapeutic values of 23 GPCRs identified above and in the SFARI list. We further included 5-HT<sub>2A</sub> and 5-HT<sub>7</sub> receptors because both receptors are associated with ASD and they are listed in another autism database (<http://autism.mindspec.org/autdb>). We studied the potential deleterious effect of different variants associated with ASD and their dysregulation in ASD post-mortem tissues to conclude on their potential

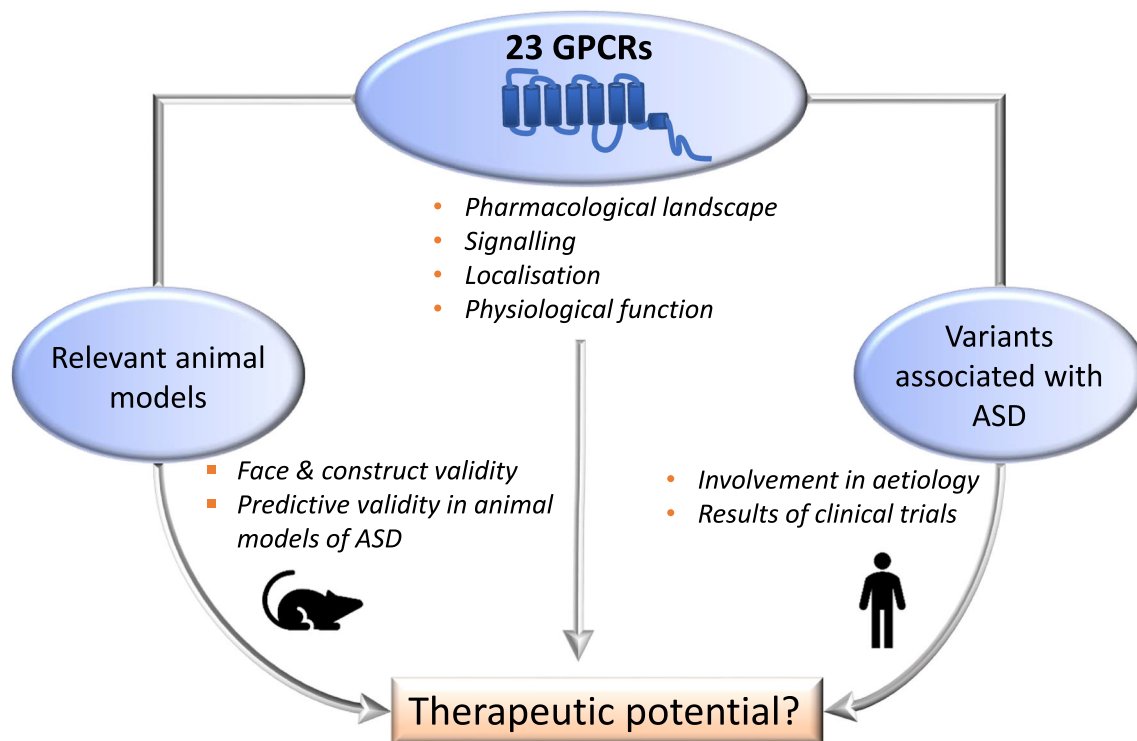
contribution in the aetiology of ASD (Table S2). We addressed the behavioural consequences of their genetic and pharmacological manipulation in animal models (Table S3) and whether these models fulfil the validity criteria defined for psychiatric diseases applied to ASD (Chadman et al., 2019). We analysed their pharmacological landscape (e.g., specific drugs on the market or in clinical trials), the availability of GPCR structures and where available, the results of clinical trials (Table S4). We also reported their known downstream signalling and their interacting partners (Table S5). Finally, we reviewed their expression profile in the different brain cell types and structures (widespread vs. specific localisation; Figures 2 and 3 and Table S6). Based on this evidence, we conclude on the therapeutic potential of 25 candidate GPCRs (Figure 4).

## 2 | OXYTOCIN AND VASOPRESSIN RECEPTORS

**Oxytocin** (OT) was first described in the 1960s for its effects on reproduction and maternal behaviours (Froemke & Young, 2021). In the mammalian CNS, OT and its paralogue **arginine vasopressin** (AVP) modulate social recognition and memory, defensive behaviours, trust, empathy and maternal attachment (Macdonald & Macdonald, 2010; Rae et al., 2022). Mice lacking OT peptide (Oxt knock-out [KO] mice) display aggressive and anxious-like behaviours and social memory impairment (Table S3) (DeVries et al., 1997; Ferguson et al., 2000; Ragnauth et al., 2005; Winslow et al., 2000), but these phenotypes vary across laboratories and parental genotypes. Administration of OT in the lateral ventricles or in the medial amygdala of Oxt KO mice



**FIGURE 3** G protein-coupled receptor (GPCR) localisation and expression in the human and mouse brain. Relative expression and localisation of the 25 GPCRs are presented on the murine and human brain templates from the protein atlas database ([www.proteinatlas.org](http://www.proteinatlas.org)). After comparison with protein expression for consistency (only available for the 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>7</sub>, A<sub>2A</sub>, V<sub>1B</sub>, M<sub>3</sub>, CB<sub>1</sub>, CX<sub>3</sub>CR<sub>1</sub>, D<sub>2</sub>, GABA<sub>B2</sub> and GPR37), relative RNA levels are represented as high (brown, over 20 normalised transcript expression values [nTPM]), moderate (red, 10–20 nTPM), low (pink, 2–10 nTPM) and just detectable (light pink, 0.1–2 nTPM) expression in the CNS (expression in the other organs are indicated in Tables S4 and S6). Brain templates are from Servier Medical Art.



**FIGURE 4** Workflow to assess the relevance to autism spectrum disorder (ASD) of G protein-coupled receptor (GPCR) genes extracted from the Simons Foundation Autism Research Initiative (SFARI) database and their therapeutic potential.

restores anxious-like behaviour and social recognition (Ferguson et al., 2001; Mantella et al., 2003). Brattleboro rats, which carry a frameshift deletion in the *Avp* gene and loss of AVP, display social preference impairment (Surget & Belzung, 2008) whereas *Avp* full deletion in mice is lethal in the absence of peripheral AVP administration (Zelena, 2017).

Many studies have investigated the therapeutic potential of either OT or AVP for ASD, because they regulate social behaviours and OT plasma levels are lower in ASD children (Cataldo et al., 2018; John & Jaeggi, 2021; Rae et al., 2022). Administration of OT or AVP normalises social skills and/or stereotyped behaviours in *Cdh8*, *Pogz*, *Cntnap2*, *Oxtr*, *Magel2* and *Fmr1* KO mouse models of ASD but not in 16p11.2 deletion and *Shank3* KO mice (Cherepanov et al., 2021; Kitagawa et al., 2021; Lindenmaier et al., 2022; Meziane et al., 2015; Peñagarikano et al., 2015; Sala et al., 2011). Differences in dose, acute versus chronic treatment, and/or way of administration in these studies prevent generalising the beneficial effects reported. Furthermore, chronic exposure to OT abolishes sociability and induces stereotyped behaviours in wild-type (WT) animals (Bales et al., 2013; Zhang et al., 2015). Intranasal administration of OT at low dose improves emotion recognition in young men with ASD (Guastella, Einfeld, et al., 2010), increased trust and interactions in adults with ASD (Andari et al., 2010), and reduced severe repetitive behaviours (Hollander et al., 2003). Unexpectedly, administration of OT failed to improve social abilities over placebo in phase 2 clinical trials and induced frequent side effects in several studies (Leppanen et al., 2018; Sikich et al., 2021; Witte et al., 2022). In fact, OT

administration may not be effective in all patients but rather only in subtypes of patients with OT deficiency, or should be combined with behavioural intervention programmes (Daniels et al., 2023). Interestingly, administration of AVP in healthy men improves the recognition of happy and angry social faces compared with neutral faces (Guastella, Kenyon, et al., 2010). A phase 2 clinical trial showed that 4 weeks of intranasal administration of AVP in 30 ASD children improved their social skills and reduced anxiety and repetitive behaviours, with minimal side effects (Parker et al., 2019). Whereas AVP remains to be tested in a large cohort of patients, the first results indicate that it might be more efficient than OT to provide pro-social effects. Thus, despite mixed results, the OT-AVP family remains of interest for ASD. Actually, OT and AVP might not be ideal treatments. Both peptides bind and activate with nanomolar affinity the four highly conserved OT receptor (OTR), vasopressin  $V_{1A}$  and  $V_{1B}$  receptors in the CNS and  $V_2$  receptor in the periphery. Therefore, in the following section, we review the therapeutic potential of OTR,  $V_{1A}$  and  $V_{1B}$  for ASD.

## 2.1 | OTR

The OTR gene (*OXTR*) spans over four exons and encodes five splicing transcript variants that differ in their 5' untranslated region (UTR) leading to only one receptor, OTR. Decades of research have identified several agonists of OTR (Table S4), such as the potent peptide agonist **Thr<sup>4</sup>Gly<sup>7</sup>-OT** (TGOT) (Elands et al., 1988), the  $G_{\alpha_q}$ -biased

agonist **carbetocin** (Passoni et al., 2016) and the first chemical agonist **LIT001** (Frantz et al., 2018). However, all these ligands also bind to vasopressin receptors. OTR expression is found in CNS regions critical for the regulation of social behaviour and emotion (Figure 3) and might be sexually dimorphic depending on the brain region and species (Dumais et al., 2013). In humans, *OXTR* transcript levels peak after birth, during all infancy and reduce in adolescents and adults (Kang et al., 2011). This corresponds to oxytocinergic neuron development in the same critical period in mice (Soumier et al., 2022). OTR is involved in complex social behaviours, like maternal care, social recognition, aggression, mating and pair bonding. It also favors empathy and can exert anxiolytic effects (Jurek & Neumann, 2018). *Oxtr* KO mice or conditional KO (cKO) in forebrain neurons have an autism-like phenotype, with both social and communication deficits and stereotyped behaviours, whereas heterozygous mice express only social deficits (Table S3) (Lee et al., 2008; Pobbe et al., 2012; Sala et al., 2013; Takayanagi et al., 2005). However, results in self-grooming, anxious-like behaviours and cognitive inflexibility vary through laboratories or mouse lines. In addition, *Oxtr* KO in monogamous prairie voles leads to deficits only in social novelty and increased compulsive behaviours but no impairment in social interactions, vocalisations or maternal behaviour (Berendzen et al., 2023; Horie et al., 2019). Interestingly, intraventricular administration of either OT or AVP restores the social deficits in *Oxtr* KO mice via  $V_{1A}$  receptors (Sala et al., 2011). This finding highlights the crosstalk within this GPCR family. More than 20 variants in the *OXTR* gene have been associated with ASD (Table S2). Interestingly, variants are mostly located outside the receptor coding region, leading to potential receptor expression dysregulation.

## 2.2 | Vasopressin $V_{1A}$ and $V_{1B}$ receptors

AVP is well known as the antidiuretic hormone via the activation of  $V_2$  receptors, but also binds to  $V_{1A}$  and  $V_{1B}$  receptors in the CNS. *AVPR1A* and *AVPR1B* genes encode only one transcript variant each and their  $V_{1A}$  and  $V_{1B}$  receptors, respectively.

$V_{1A}$  receptor is involved in maternal care, social recognition, affiliative behaviour and pair bonding (Koshimizu et al., 2012). Administration of the  $V_{1A}$  antagonist **d(CH<sub>2</sub>)<sub>5</sub>Tyr(Me)AVP** into the medial amygdala of rats affects maternal memory (Nephew & Bridges, 2008). Furthermore, *Avpr1a* KO mice and hamsters display defective social memory, interaction and communication, reduced anxious-like behaviours and inconsistent levels of aggressive behaviour across species (Table S3) (Bielsky et al., 2004, 2005; Egashira et al., 2007; Taylor et al., 2022; Wersinger et al., 2007). Several studies have associated the length of the promoter and the 5'UTR of the *AVPR1A* gene, which regulate  $V_{1A}$  expression levels, with important social deficits. Indeed, most variants associated with ASD risk are identified in these regions (Table S2), which influence human relationships and altruism (Meyer-Lindenberg et al., 2009; Walum et al., 2008), personality in non-human primates (Hopkins et al., 2012) or social behaviour in rodents (Hammock et al., 2005). Recently, administration of the selective  $V_{1A}$  antagonists, either **RG7713** or **balovaptan**, improved

socialisation and communication in men with ASD (Bolognani et al., 2019; Schnider et al., 2020; Umbricht et al., 2017). Despite these promising results in phase 2 clinical trials, balovaptan failed to improve social abilities over placebo in phase 3 trials (Jacob et al., 2022). Further investigations are still required to understand the therapeutic potential of the  $V_{1A}$  receptor because it remains unclear if either activation or inhibition would improve social skills.

$V_{1B}$  receptor deletion in mice (*Avpr1b* KO) leads to increased dominance, impaired aggressive behaviour, vocalisations, social motivation and memory (Table S3) (Albers, 2012; Scattoni et al., 2008; Wersinger et al., 2007). Three independent studies have identified variants in the *AVPR1B* gene linked to ASD (Table S2), mood disorders and aggressive behaviour. Accordingly, administration of the antagonist **nelivaptan** (Table S4) normalises aggressive, chasing and anxious-like behaviours in rodents (Blanchard et al., 2005; Salomé et al., 2006). Oral administration of nelivaptan is currently in clinical trials for anxiety and depression.

In conclusion, data in animals and humans support that OTR and  $V_{1A}$  receptors may be involved in the aetiology of autism and are major therapeutic targets for ASD, whereas  $V_{1B}$  might be of interest for aggressive and anxious-like behaviours. Nevertheless, so far, clinical trials failed to bypass the placebo effect observed in patients. Regarding their conservation, their crosstalk and the existence of homo- and hetero-oligomers of these three receptors (Dekan et al., 2021; Terrillon et al., 2003), further investigations are needed to identify the most suitable targets (e.g., which receptor or oligomer, which signalling pathway).

## 3 | METABOTROPIC GLUTAMATE AND GABA RECEPTORS

**Glutamate** and  $\gamma$ -aminobutyric acid (**GABA**) are the two major neurotransmitters in the CNS. They bind to their cognate class C GPCRs, the metabotropic glutamate mGluRs and GABA<sub>B</sub> receptors, respectively. In contrast to class A GPCRs, glutamate and GABA bind to the large extracellular N-terminal domain called the Venus Fly Trap, which closes upon activation. In addition, they form constitutive oligomers, which lead to specific rearrangements of subunits during activation. They are mainly expressed in presynaptic and postsynaptic compartments in the brain (Figures 2 and 3) and participate in the excitatory and inhibitory balance in the CNS (Nelson & Valakh, 2015), which is hypothesised to be dysregulated in ASD.

### 3.1 | mGlu<sub>5</sub>

The *GRM5* gene encodes two splice variants of mGlu<sub>5</sub> (mGlu<sub>5a</sub> and mGlu<sub>5b</sub>), with the mGlu<sub>5b</sub> receptor expressed predominantly during the adult stage (Table S6). Activation of mGlu<sub>5</sub> induces synaptic plasticity, which requires de novo mRNA translation through phosphorylation of eukaryotic initiation factor-2 (eIF2 $\alpha$ ) (Di Prisco et al., 2014). *Grm5* KO mice display ASD-related core symptoms (Table S3), deficits



in social interaction, increased stereotyped and compulsive behaviours (Xu et al., 2021). Furthermore, they show hyperactivity, reduced anxious-like behaviours and sensorimotor gating deficits (Brody et al., 2004; Xu et al., 2021). Five independent studies have identified over 20 rare variants in the *GRM5* gene of ASD patients (Table S2), highlighting *GRM5* as one of the most susceptible genes in ASD (Nisar et al., 2022). Alterations in mGlu<sub>5</sub> receptor signalling or expression affect synaptic and neuronal development, trademarks of ASD and intellectual disability (D'Antoni et al., 2014). Thus, administration of the selective antagonist  **mavoglurant**  and the NAM  **basimglurant**  in the fragile X syndrome (FXS) mouse model (*Fmr1* KO) (Table S4) improved its broad range of phenotypes (Scharf et al., 2015). However, administration of these compounds failed to provide similar therapeutic benefits in FXS patients in phase 2b/3 clinical trials (Jacquemont et al., 2011, 2014; Lozano et al., 2015). These compounds are still in clinical trials for dyskinesia, obsessive-compulsive disorders and depression. Altogether, data favour the role of mGlu<sub>5</sub> in ASD pathogenesis. However, targeting mGlu<sub>5</sub> with a selective negative allosteric modulator did not pass the placebo effect in patients. Variations in mGlu<sub>5</sub> expression levels in patients might result from insufficient inhibition of excitatory outputs. Indeed, higher mGlu<sub>5</sub> protein expression was reported in different brain regions including cerebellar vermis region and superior frontal cortex in children with ASD (Fatemi et al., 2011) whereas higher and lower expression was observed in the prefrontal cortex of patients with FXS and ASD patients, respectively (Chana et al., 2015; Lohith et al., 2013). In addition, *GRM5* is one of the GPCR genes that display the highest number of variants altering drug efficacy (Hauser et al., 2018).

### 3.2 | mGlu<sub>7</sub>

The *GRM7* gene encodes two isoforms (mGluR<sub>7a</sub> and mGluR<sub>7b</sub>) that differ in their C-terminus, potentially leading to different protein-protein interactions and receptor coupling. mGlu<sub>7</sub> is expressed during the critical neurodevelopmental period, when it augments synapse formation and stabilisation (Song et al., 2021). Compared with other mGluRs, mGlu<sub>7</sub> has lower affinity for glutamate, hence is considered as an 'emergency brake'. mGlu<sub>7</sub> receptors are predominantly localised at presynaptic sites and regulate neurotransmitter release of glutamate or GABA. Interestingly, the non-selective mGlu<sub>4/6/7</sub> agonist  **L-AP4**  negatively regulates glutamate or GABA release whereas the selective PAM  **AMN082**  positively affects the extracellular glutamate levels and negatively the GABA levels (Li et al., 2008; Manahan-Vaughan & Reymann, 1995; Mitsukawa et al., 2005). *Grm7* KO mice display intact social interaction, but social memory deficits (Table S3) (Fisher et al., 2020), which might be explained by their global learning defects. Overall, *Grm7* KO mice and mice carrying the Ile154Thr mGlu<sub>7</sub> mutation identified in ASD patients recapitulate comorbid symptoms, such as anxious-like behaviours, motor coordination impairment and seizures (Fisher et al., 2020, 2021). Twenty-one single-nucleotide polymorphisms (SNPs) and CNVs in the *GRM7* gene have been associated with ASD (Table S2). In particular, the Ile154Thr,

Arg658Trp and Thr675Lys mutants lead to reduced mGlu<sub>7</sub> surface expression and/or degradation. Dysregulated levels of mGlu<sub>7</sub> results in lack of axonal growth due to altered cAMP-PKA-ERK signalling and reduced number of synapses in primary neuronal cultures, which is rescued by the PAM AMN082 (Song et al., 2021). This is in line with reduced expression of mGlu<sub>7</sub> in post-mortem motor cortex samples from patients with Rett syndrome (RTT) and in a mouse model of RTT (*Mecp2* KO) (Bedogni et al., 2016; Gogliotti et al., 2017). In conclusion, mGlu<sub>7</sub> is a promising target because it could contribute to ASD pathogenesis. Furthermore, selective agonists or PAMs (e.g.,  **AMN082** ) already exist and normalise comorbid symptoms in mouse models of ASD via the regulation of glutamate and GABA release and possibly in patients as well.

### 3.3 | GABA<sub>B</sub> receptor

Metabotropic GABA<sub>B</sub> receptors are obligatory hetero-oligomers of  **GABA<sub>B1</sub>**  and  **GABA<sub>B2</sub>**  through their C-terminus coiled-coiled domain. Presynaptic GABA<sub>B</sub> receptors suppress neurotransmitter release whereas postsynaptic receptors induce slow inhibitory postsynaptic currents, which shunt the excitatory currents (Lüscher et al., 1997). GABA<sub>B</sub> receptor deletion in mice (*Gabbr1-Gabbr2* double KO) leads to emotional disturbances and increased anxious- and anti-depressive-like behaviours (Table S3) (Mombereau et al., 2005). The effect of *Gabbr2* deletion alone has not been reported yet on core ASD symptoms. However, *Xenopus tropicalis* tadpole larvae carrying the Ala567Thr, Ser695Ile and Ile705Asn GABA<sub>B2</sub> mutants identified in ASD and epileptic patients, display increased seizure-like behaviour and altered swimming patterns that are partially rescued by the selective GABA<sub>B</sub> agonist  **baclofen**  (Yoo et al., 2017). Of note, when expressed heterologously in HEK293 cells, these three mutants disrupt GABA<sub>B</sub> activation. Four genomic studies revealed an association of the *GABBR2* gene with ASD and RTT (Table S2). Administration of baclofen normalises the behaviours observed in a mouse model of FXS, in an idiopathic BTBR mouse model of ASD and in the C58 inbred mouse strain (Henderson et al., 2012; Silverman et al., 2015). Despite its first beneficial effect and its good tolerance in FXS and ASD patients, baclofen clinical trials were discontinued after phase 2 for its lack of efficacy (Berry-Kravis et al., 2012; Veenstra-VanderWeele et al., 2017). Nevertheless, baclofen is currently tested for irritability as an adjuvant therapy to risperidone (Mahdavinassab et al., 2019). Finally, in agreement with the unbalanced GABA and glutamate transmission hypothesis in ASD, reduced expression levels of the GABA<sub>B</sub> receptor were observed in the cerebellum, in the cingulate cortex and in the fusiform gyrus of ASD patients (Fatemi et al., 2009; Oblak et al., 2010).

In conclusion, GABA<sub>B</sub> receptor remains a promising therapeutic target for ASD according to the genomic and genetic data in patients and in animal models. However, its efficacy might be greater in combination with the administration of other ligands, such as risperidone for irritability or drugs targeting mGluRs to restore the excitatory and inhibitory balance.

## 4 | BIOGENIC AMINE RECEPTORS

Biogenic amine receptors are class A GPCRs that interact with endogenous aminergic ligands, such as **adrenaline**, **noradrenaline**, **dopamine** and serotonin (5-hydroxytryptamine [5-HT]).

### 4.1 | Dopamine receptors

Dopaminergic D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) receptors regulate broad functions: locomotion including voluntary movement, reward processing, learning, motivated behaviour, action selection, sleep, attention, and decision making (Mishra et al., 2018), some of which, when dysregulated, are comorbid symptoms of ASD (DiCarlo et al., 2019).

D<sub>1</sub> receptors are particularly enriched in D<sub>1</sub> striato-nigral GABAergic medium spiny neurons of the striatum. They have the lowest dopamine affinity among all the dopaminergic receptors, suggesting that they are activated by high phasic dopamine release, while D<sub>2</sub>-like receptors might detect low tonic dopamine levels (Beaulieu & Gainetdinov, 2011). D<sub>1</sub> receptors may have a role, although controversial, in social behaviours (Campi et al., 2014; Scerbina et al., 2012). Rats carrying the Ile116Ser mutation in the D<sub>1</sub> receptor and KO mice display deficits in social interaction and communication and reduced stereotyped behaviours and comorbid symptoms, respectively (Homberg et al., 2016; McNamara et al., 2003), while excessive activation of D<sub>1</sub> receptors in the dorsal striatum exhibits both symptoms in WT mice (Table S3) (Lee et al., 2018). Unbalanced D<sub>1</sub> over D<sub>2</sub> medium spiny neuron outputs on the circuitry probably explains this finding. Administration of the D<sub>1</sub> receptor antagonist **SCH23390** ameliorated stereotyped behaviours in mice lacking the **tyrosine hydroxylase** that catalyses dopamine synthesis (Chartoff et al., 2001). The D<sub>1</sub>/D<sub>5</sub> antagonist **ecopipam** is currently in phase 2 clinical trials for the treatment of Tourette's syndrome, characterised by repetitive tics (Gilbert et al., 2018). Lastly, one study reported that three common SNPs located in the 5'UTR of the *DRD1* gene (Table S2) are associated with severe impairments in social interaction, non-verbal communication and increased motor stereotypies.

D<sub>2</sub> receptors encoded by the *DRD2* gene comprise two splicing isoforms, short D<sub>2S</sub> and long D<sub>2L</sub> differing in their IL3 loops. D<sub>2S</sub> serves as an auto-receptor regulating dopamine release and dopamine synthesis whereas D<sub>2L</sub> is a postsynaptic receptor (Negyessy & Goldman-Rakic, 2005). These receptors are mainly expressed in neurons, with the highest levels in GABAergic indirect D<sub>2</sub> striato-pallidal medium spiny neurons of the striatum, and in astrocytes and oligodendrocytes (Figure 2). *Drd2* KO mice show great impairments in social interaction and communication, social olfaction and stereotyped behaviours (Table S3) (Lee et al., 2018). Moreover, *Drd2* heterozygous mice exposed to early maternal separation stress also display social interaction deficits and stereotyped behaviours (Lee & Han, 2019). This phenotype seems exclusively mediated by the dorsal striatum as specific knock-down of the D<sub>2</sub> receptors in this structure is sufficient to recapitulate all the behavioural impairments

reported in *Drd2* KO mice (Lee et al., 2018). Conversely, D<sub>2</sub> receptor overexpression in the striatum and olfactory tubercle revealed impairment in sociability and communication only in female mice (Kabitzke et al., 2015). Among the dopamine receptors, the *DRD2* gene displays the highest number of SNPs associated with ASD (Table S2). Currently, the only approved drugs for comorbid ASD symptoms, aripiprazole or risperidone, antagonise the D<sub>2</sub> receptors as their primary target (Table S4) (McDougle et al., 2005; Varni et al., 2012). Antipsychotics might normalise the exacerbated activity of D<sub>2</sub> in the dorsal striatum of ASD patients (Brandenburg et al., 2020). Additionally, two other D<sub>2</sub> antagonists, **pimozide** and **olanzapine**, are antipsychotics used in clinics for schizophrenia and Tourette's syndrome, leading to potential amelioration of speech impairment (Maguire et al., 2004; Pringsheim & Marras, 2009).

D<sub>3</sub> receptor expression is conserved between humans and rodents and controls habituation to novelty (Mishra et al., 2018). *Drd3* KO mice display hyperactive and addictive behaviours, with particular vulnerability to alcohol and drug abuse (Table S3). Their social skills or stereotyped behaviours have not been reported yet. Three independent studies identified three SNPs in the *DRD3* gene associated with ASD (Table S2). The antipsychotic **cariprazine**, a partial agonist for D<sub>3</sub> that also binds D<sub>2</sub> receptors with lower affinity, is approved for the treatment of schizophrenia and bipolar disorder. Interestingly, administration of cariprazine improved social behaviours in a dose-dependent way, in male rat models of ASD exposed to **valproic acid** in utero (Román et al., 2021), which makes this ligand a potential treatment for ASD.

In conclusion, alteration in any of these three dopaminergic receptors results in autistic-like symptoms in animal models and in genetic association with ASD. However, approved ligands targeting the D<sub>2</sub> receptor are already on the market to ameliorate comorbid symptoms and could be tested for core symptoms. Nonetheless, other dopamine receptors might be of interest; for example, the less known *DRD5* gene that displays the highest number of distinct missense and loss of function variants in the general population (Hauser et al., 2018).

### 4.2 | Serotonin receptors

Dysregulation in 5-HT levels in different CNS structures has been observed in ASD (Pourhamzeh et al., 2022), whereas enhanced 5-HT release restores social deficits in several ASD mouse models (Walsh et al., 2021). The dup15q11-q13 mouse model of ASD displays reduced serotonergic activity in the dorsal raphe nucleus, associated with low 5-HT levels in all CNS regions and impaired social interaction (Farook et al., 2012; Nakai et al., 2017). Because more than 25% of the ASD patients show increased 5-HT blood levels, 5-HT is considered as a biomarker for a subgroup of patients (Gabriele et al., 2014; Muller et al., 2016). All 14 serotonin receptors occur as a GPCR, except the ion channel receptor 5-HT<sub>3</sub>. These GPCRs modulate cognition, memory, sleep, appetite, respiration, thermo-regulation and mood (Berger et al., 2009).

The **5-HT<sub>1B</sub> receptor** belongs to the 5-HT<sub>1</sub> receptor family that are encoded by seven genes (*HTR1A-F*). It exerts a consistent effect on anxious-like behaviours in rodents, because administration of the selective full agonist **CP94253** or antagonists **SB 216641** and **GR 127935** (Table S4) leads to either anxiogenic or anxiolytic effect, respectively. In addition, administration of CP94253 reduced aggressive behaviour in resident male mice, whereas anpirtoline, which also targets **5-HT<sub>3</sub>** channels, restored isolation-induced impairments, increased pain threshold and exerted anti-depressive effects in mice (Fish et al., 1999; Schlicker et al., 1992). In agreement with pharmacological studies, *Htr1b* KO mice display decreased anxious-like behaviours, exacerbated aggressive behaviour, deficits in maternal behaviour, improved cognitive flexibility and vulnerability to drug abuse (Table S3) (Bouwknicht et al., 2001; Brunner et al., 1999). So far, only two variants associated with ASD have been reported from two independent studies (Table S2).

The **5-HT<sub>2A</sub> receptor**, together with **5-HT<sub>2B</sub>** and **5-HT<sub>2C</sub>** receptors, modulates the activity of neurotransmitters, such as glutamate, dopamine, **acetylcholine** and noradrenaline. Mice lacking the 5-HT<sub>2A</sub> receptor (*Htr2a* KO) display reduced anxious-like behaviour (Table S3), which can be normalised by restoration of 5-HT<sub>2A</sub> expression in the cortex or reversed to depression-like behaviour by chronic exposure to corticosterone (Petit et al., 2014; Weisstaub et al., 2006). In addition, administration of **M100907**, a selective 5-HT<sub>2A</sub> antagonist, reduces repetitive grooming in the BTBR mouse model of ASD (Amodeo et al., 2016). Two SNPs in the *HTR2A* gene are associated with ASD (Table S2). The most frequent SNP is the rs6311 variant located within the promoter region (Liu et al., 2021; Smith et al., 2014), which probably influences 5-HT<sub>2A</sub> receptor levels. In addition, imaging and post-mortem studies revealed lower densities of 5-HT<sub>2A</sub> in the fusiform gyrus, the cingulate cortex and the thalamus in ASD patients (Beversdorf et al., 2012; Goldberg et al., 2009; Murphy et al., 2006; Oblak et al., 2013). In particular, *HTR2A* transcripts are reduced in the platelets of patients with ASD as well as in patients with gastrointestinal disorders (Kazek et al., 2010). Because serotonin receptors tightly control gastrointestinal motility, it might explain the co-occurrence with this comorbid symptom. Finally, targeting 5-HT<sub>2A</sub> receptors offers promise for ASD. On the one hand, the only two approved drugs for ASD, aripiprazole and risperidone (Table S4), antagonise 5-HT<sub>2A</sub> (Alexander et al., 2021; McCracken et al., 2002; McDougle et al., 2005; Varni et al., 2012). On the other hand, psychedelics (e.g., **MDMA**, **LSD**, and **psilocybin**) that activate the receptor have beneficial effects in animal models and in case studies of ASD patients (Kwan et al., 2022). Regular clinical trials are required, notably to assess the risk associated with their administration.

**5-HT<sub>7</sub> receptors** encoded by the *HTR7* gene display three splicing isoforms that differ in their C-terminal domain (Marti-Solano et al., 2020). 5-HT<sub>7</sub> receptors promote neurite growth and synaptogenesis through their signalling (Table S5) (Kvachnina et al., 2005; Speranza et al., 2017). This serotonin receptor is involved in cognition, sleep, pain, circadian rhythm, hypothermia and mood. Deletion of 5-HT<sub>7</sub> in mice (*Htr7* KO) leads to decreased compulsive behaviours associated with reduced depressive-like behaviours and pain

thresholds and increased epileptic seizures and anxious-like behaviours (Table S3) (Hedlund & Sutcliffe, 2007). Moreover, activation of 5-HT<sub>7</sub> normalises repetitive and anxious-like behaviours in *Fmr1* and *Mecp2* KO mice (Costa et al., 2018; De Filippis et al., 2014). Whereas only one SNP in the coding sequence of the *HTR7* gene has been associated with ASD (Table S2) (Cukier et al., 2014), several selective 5-HT<sub>7</sub> ligands have been developed and/or are currently in clinical trials (Table S4). Administration of serodolin, a selective  $\beta$ -arrestin-biased agonist for inflammatory pain (El Khamlichi et al., 2022), might be beneficial in preclinical models, and eventually in patients, as  $\alpha_5$ -biased agonist increased self-grooming in *Shank3* KO mice (Lee et al., 2021).

Apart from the *HTR1B* gene, evidence highlights that the *HTR2A* and *HTR7* genes might also fulfil the criteria to be candidate genes in the SFARI database. Regarding the major 5-HT system dysfunctions in ASD, potentially all the 14 serotonin receptors are of interest. For example, targeting **5-HT<sub>6</sub>** using a selective antagonist SLV improves core social symptoms in mouse models of ASD (de Bruin et al., 2016) and variants in the *HTR6* gene are associated with autism susceptibility (Hervás et al., 2014). Highly promising drugs targeting multiple 5-HT receptors, such as arylpiperazine derivative drugs (Lacivita et al., 2021) and the first 5-HT<sub>7</sub> biased agonist (El Khamlichi et al., 2022), could be tested to improve core ASD symptoms. Currently, the administration of antipsychotics (aripiprazole and risperidone) to treat irritability, aggressive and repetitive behaviours in ASD patients partially activates 5-HT<sub>1A</sub> and inhibits 5-HT<sub>2A</sub>.

### 4.3 | $\beta_2$ -Adrenoceptor

Noradrenaline and adrenaline activate the  $\alpha_1$ -,  $\alpha_2$ -,  $\beta_1$ -,  $\beta_2$ - and  $\beta_3$ -**adrenoceptors** with different potencies. In the CNS, they control cognition, memory, emotions and stress-induced behaviours. Only the *ADRB2* gene is present in the SFARI list and encodes the  **$\beta_2$ -adrenoceptor**. Despite its vital cardiac function, *Adrb2* KO mice are viable and fertile. They display increased anxious-like behaviours and decreased depressive-like behaviours (Table S3). Increased adrenergic neuron activity from the locus coeruleus or increased noradrenaline plasma concentration has been associated with aberrant attention and decreased interest in ASD individuals (Bast et al., 2018; Beversdorf, 2020). Accordingly, two common SNPs associated with ASD (Table S2) show enhanced **isoprenaline**-induced response. Furthermore, studies have suggested an association between prenatal exposure to  $\beta_2$ -adrenoceptor agonists and ASD (Gidaya et al., 2016). Interestingly, administration of the approved  $\beta_2/\beta_3$ -adrenergic antagonist **propranolol** improves verbal responses and social interactions and decreases anxiety in ASD patients (Hegarty et al., 2017). Therefore, the  $\beta_2$ -adrenoceptor is an interesting target for ASD, and the approved  $\beta_1/\beta_2$ -adrenoceptor antagonist propranolol (Table S4) may help to normalise core social symptoms. Further investigations also should address the potential interest in other members of this family, such as *ADRA1D*, one of the most down-regulated genes in the

prefrontal cortex of ASD patients (Monfared et al., 2021), whose targeting with **clonidine** improves hyperarousal, hyperactivity and social relationships in individuals with ASD (Ming et al., 2008).

## 5 | OTHER CLASS A RECEPTORS

### 5.1 | Adenosine receptors

**Adenosine receptors** are divided into four subtypes, namely,  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$ , among which  $A_1$  and  $A_{2A}$  show the highest affinity for adenosine (Alexander et al., 2021). Adenosine receptors in the CNS have important roles in neuroplasticity, sleep–wake cycle, locomotion and cognition (Wei et al., 2011).

$A_{2A}$  receptor, which is encoded by the *ADORA2A* gene, stimulates glutamate release at presynaptic terminals and myelination by oligodendrocytes (De Nuccio et al., 2019). Postsynaptic  $A_{2A}$  receptors are highly enriched in  $D_2$  GABAergic striato-pallidal medium spiny neurons of the striatum, to modulate locomotion and anxious-like behaviours (Coelho et al., 2014). Accordingly, *Adora2a* KO mice display motor impairment and anxious-like behaviours (Table S3).  $A_{2A}$  might act as a regulator of other GPCRs (Table S5), because it forms many different hetero-oligomers with  $D_2$ , mGlu<sub>5</sub>,  $\delta$  opioid receptors and orphan **GPR88** (Ciruela et al., 2011; Laboute et al., 2020; Pellissier et al., 2018). During brain development, GABAergic synapses, which release **adenosine** and ATP in addition to GABA, are the first synapses to be formed and are crucial for the construction of the neural network. Activation of  $A_{2A}$  receptors is necessary and sufficient to prune GABAergic synapses during this period (Gomez-Castro et al., 2021). In contrast, any impairment in  $A_{2A}$  signalling or expression may result in GABAergic synapse alteration and cognitive deficits in adults, as observed in animals administered with  $A_{2A}$  antagonists during development. Spontaneous stereotypies often result from unbalanced cortical glutamatergic and GABAergic afferences (glutamate hyperactivity) on the striatum and decreased activation of the efferent subthalamic nucleus, as observed in ASD patients and animal models (Li & Pozzo-Miller, 2020). Consistently, administration of the selective  $A_{2A}$  agonist **CGS21680** normalises aberrant vertical repetitive behaviours in BTBR and C58 inbred mice (Amodeo et al., 2018; Lewis et al., 2019) via its action on  $D_2$  medium spiny neurons, which in turn restore the neurotransmission of efferent subthalamic nucleus. So far, only one study has associated four SNPs in the *ADORA2A* gene with autism and severe anxiety (Table S2).

The  $A_3$  receptor promotes expression of the serotonin transporter (**SERT**) to the cell surface (Campbell et al., 2013). Thus, lack of  $A_3$  signalling decreases SERT cell-surface expression and leads to extracellular accumulation of serotonin, as observed in ASD patients (see Section 4.2 on serotonin). Actually, two variants in the *ADORA3* gene are associated with ASD (Table S2), with impaired adenosine binding (Campbell et al., 2013). However, the effect of *Adora3* deletion has not been studied for core or comorbid symptoms (Table S3).

In conclusion,  $A_{2A}$  shows the greatest promise in mitigating repetitive behaviours and anxiety in ASD. However, most  $A_{2A}$  agonists

have failed in clinical trials (Guerrero, 2018) due to severe side effects, including CNS excitotoxicity (Table S4). Only a few of them have been approved, such as the agonist **regadenoson**. An alternative strategy would be to consider other members of this family, such as the *ADORA1* gene, which is one of the most down-regulated GPCR genes in patients (Monfared et al., 2021) and whose targeting in combination to  $A_{2A}$  agonists improves stereotyped behaviours (Lewis et al., 2019). A better specificity also could be achieved by targeting  $A_{2A}$  hetero-oligomers such as  $D_2$ - $A_{2A}$ -mGluR<sub>5</sub> to avoid side effects.

### 5.2 | Angiotensin AT<sub>2</sub> receptor

**Angiotensin receptors** are divided into  $AT_1$  and  $AT_2$  subtypes. They are activated by different maturation products of angiotensinogen peptides, namely, **angiotensin II** and **angiotensin III**. Only the  $AT_2$  receptor is implicated in different neurological disorders, such as ASD, schizophrenia, Parkinson's disease (PD) and Alzheimer's disease (Firouzabadi et al., 2016; Szczepanska-Sadowska et al., 2022). Its functions in the brain remain elusive. To date, no data from genetic or pharmacological manipulation supports a role of  $AT_2$  in social or stereotyped behaviours (Table S3). However, *Agtr2* KO mice show impaired reward processing and locomotion. Interestingly, administration of the  $AT_2$  receptor selective agonist **C21/M024** improves cognition in a mouse model of Alzheimer's disease (Jing et al., 2012). Finally, four independent studies have associated the *AGTR2* gene on the chromosome X with ASD and X-linked intellectual disability (Table S2). Therefore, together with its unknown expression and function in the CNS, further studies are required to conclude on the therapeutic potential of  $AT_2$ .

### 5.3 | Cannabinoid CB<sub>1</sub> receptor

Endogenous cannabinoids regulate many brain functions, including learning and memory, locomotor activity or appetite (Irving et al., 2002). In dopamine circuits, they are crucial for reward processes, linked to addiction (Zhang et al., 2004). Cannabinoid receptors are composed of  $CB_1$  and  $CB_2$ .  $CB_1$  mediates the central effects of cannabis and its derivatives and modulates synaptic transmission through its effect on neurotransmitter release. *Cnr1* KO mice show deficits in social interaction and communication, two core symptoms of ASD (Table S3) (Haller et al., 2004; Litvin et al., 2013). They also exhibit anxiogenic, context-dependent social aggressive and depressive-like behaviours and improved social memory. Interestingly, administration of anandamide **fatty acid amide hydrolase** (FAAH) inhibitor improves social interactions and cognitive deficits in BTBR and *Fmr1* KO mice and *Fmr1* $\Delta$ *exon8* rats, whereas administration of a  $CB_1$  antagonist in the amygdala reverses only social impairment in the FXS rats (Schiavi et al., 2023; Wei et al., 2016). Three independent studies have reported more than 30 variants in the *CNR1* gene associated with ASD (Table S2). Some states in the United States have already authorised cannabis to treat self-injury or aggressive behaviours in ASD patients.

The first results of clinical trials with a combination of **cannabidiol** and **Δ9-THC** showed no side effects, but also mixed results (Aran et al., 2021). Few case studies have shown improvement of core and comorbid symptoms in children (Carreira et al., 2022). Thus, further testing is required and administration of CB<sub>1</sub> NAM cannabidiol or an endocannabinoid mix are currently in clinical trials for ASD (Aran et al., 2021). In conclusion, evidence highlights that the CB<sub>1</sub> receptor as one of the most promising GPCR targets to treat core and comorbid symptoms in ASD.

## 5.4 | Chemokine CX<sub>3</sub>CR1 receptor

**Chemokine receptors** are a vast family of GPCRs involved in the immune system. Both secreted and membrane-bound chemokine **CX3CL1** activate the C-X<sub>3</sub>-C motif chemokine receptor 1 (**CX<sub>3</sub>CR1**, or GPR13). In humans, the **CX3CR1** gene encodes four transcript variants and two protein isoforms that differ in their N-terminus domain (Marti-Solano et al., 2020). CX<sub>3</sub>CR1 is expressed on microglia where it is activated by CX3CL1 released from neurons upon inflammatory response and during synaptic maturation and pruning (Jung et al., 2000; Soriano et al., 2002; Zhan et al., 2014). *Cx3cr1* KO mice display social interaction deficits and increased motor stereotypies (Table S3) associated with decreased functional brain connectivity from the prefrontal cortex, similarly to observations in ASD patients (Pirainen et al., 2021; Zhan et al., 2014; Zhou et al., 2020). Moreover, in mice exposed to social isolation, levels of *Cx3cr1* transcripts were increased in the prefrontal cortex, nucleus accumbens and hippocampus (Zhou et al., 2020). Three rare missense deleterious mutations in the **CX3CR1** gene have been associated with schizophrenia and ASD (Table S2).

In conclusion, CX<sub>3</sub>CR1 plays a major role in neuron–microglia mutual interaction, highlighting the growing evidence of microglia in neurodevelopmental disorders, including ASD (Lukens & Eyo, 2022). CX<sub>3</sub>CR1 is a promising target to treat ASD. However, development of specific compounds will be necessary to demonstrate its beneficial effect.

## 5.5 | Muscarinic acetylcholine M<sub>3</sub> receptor

In addition to ionotropic receptors, acetylcholine activates five **muscarinic** M<sub>1</sub>–M<sub>5</sub> GPCRs. Whereas many receptor ligands, including allosteric modulators, have been reported, few of them are selective for a receptor subtype (Table S4). The **CHRM3** gene is complex, spans over 550 kbp and includes seven exons, with only Exon 7 encoding the **M<sub>3</sub> receptor**. It has 10 described, and 21 predicted, transcript variants. Like other muscarinic receptors, M<sub>3</sub> modulates excitatory transmission, neuronal development including cellular proliferation and survival, neuronal differentiation, and controls food intake, learning and memory (Poulin et al., 2010; Yamada et al., 2001). *Chrm3* KO mice or knock-in of a mutant receptor whose IL3 loop cannot be phosphorylated, significantly altered hippocampus-dependent contextual fear

memory formation and decreased paradoxical sleep (Table S3). However, no study has investigated the ASD-like symptoms in these animals nor the therapeutic potential of muscarinic ligands. Seven variants have been associated with ASD in six independent studies (Table S2), suggesting the potential involvement of M<sub>3</sub> in ASD aetiology. Interstitial deletion in the 1q43 region, which mostly affects the **CHRM3** gene, is associated with ASD, intellectual disability, seizures, microcephaly and congenital malformations (Hiraki et al., 2008; van Bever et al., 2005). Whereas reduced cholinergic enzyme activity has been observed in cortical areas of ASD patients (Perry et al., 2001), further evidence is needed to conclude on the potential interest of muscarinic receptors as therapeutic targets for ASD.

## 6 | ORPHAN AND OLFACTORY RECEPTORS

Hundreds of orphan and olfactory GPCRs are expressed in the CNS and represent new potential therapeutic targets for neurological disorders (Khan & He, 2017) including ASD. Interestingly, orphan GPR37 and GPR85 are the top dysregulated GPCR genes in ASD tissues (Monfared et al., 2021). Except their classification by sequence homology to the class A of GPCRs, the study of orphan or olfactory receptors remains challenging due to the lack of any identified ligand or poorly known function.

### 6.1 | GPR37

GPR37 or parkin-associated endothelin-like receptor (Pael-R) is closely related to endothelin GPCRs. Several potential natural peptides have been reported to activate GPR37 (Table S4), but this remains to be confirmed. GPR37 is characterised by a poor export from ER to plasma membrane in heterologous cell lines, which is either rescued by deletion of its long N-terminus domain, oligomerization with A<sub>2A</sub> or D<sub>2</sub> receptors, or interaction with syntenin 1 through their PDZ domain (Dunham et al., 2009; Hertz et al., 2019). GPR37 is up-regulated during oligodendrocyte differentiation, where it inhibits late-stage differentiation and myelination (Yang et al., 2016). GPR37 is also located in dopaminergic axon terminals of the substantia nigra, where it controls dopamine release through a direct interaction with the **dopamine transporter** (SLC6A3) (Marazziti et al., 2007). *Gpr37* KO mice display obsessive compulsive behaviours, decreased locomotion, reduced colon motility and abnormal sensorimotor gating (Table S3) (Imai et al., 2007; Mandillo et al., 2013; Marazziti et al., 2007, 2011). They may have increased anxious-like behaviours, but this phenotype varies depending on the tests, sex, and housing conditions. Conversely, transgenic mice overexpressing *Gpr37* show increased **methamphetamine**-induced stereotyped behaviours, motor coordination and locomotion (Imai et al., 2007). Although social interaction deficits remain to be investigated, *Gpr37* mice display a variety of comorbid symptoms of ASD that are associated with altered striatal dopamine signalling (Li & Pozzo-Miller, 2020). Interestingly, variants

of the dopamine transporter gene, its direct interactor, are also associated with ASD (DiCarlo et al., 2019) and lead to similar alterations of dopamine transmission in the striatum. The *GPR37* gene has been identified in the first autism locus (AUTS1) on chromosome 7q31–33. Since then, nine variants in this gene have been associated with ASD (Table S2). Therefore, several pieces of evidence confirm that *GPR37* may be an interesting target for ASD. However, selective ligands should be developed and tested in preclinical models to further strengthen its therapeutic potential for ASD.

## 6.2 | GPR85

*GPR85/SREB2* belongs to the super-conserved receptor expressed in the brain (SREB) family. The *GPR85* gene encodes seven predicted and three transcript variants due to alternative splicing of the 3'UTR. They all encode the extremely conserved *GPR85*, which shares 100% homology and strong expression throughout the CNS in humans and mice (Figure 3). It is expressed in all types of neurons and microglia (Figure 2). At the molecular level, *GPR85* directly interacts with SHANK3 or PSD95 scaffolding partners through its PDZ domain in its C-terminus and indirectly with *neuroligin* through PSD95 (Fujita-Jimbo et al., 2015; Jin et al., 2018). In the adult hippocampus, *GPR85* negatively regulates neurogenesis and dendritic morphology, thus controlling brain size (Chen et al., 2012). *Gpr85* KO mice display increased neurogenesis associated with enlarged brain size and increased cognitive abilities in spatial tasks (Table S3). Conversely, mice overexpressing *Gpr85* in forebrain neurons show core symptoms of ASD, social interaction deficits and restrictive behaviours, in addition to cognitive inabilities, abnormal sensorimotor gating and reduced dendritic arborisation (Chen et al., 2012; Matsumoto et al., 2008). Two independent studies reported five variants in the human *GPR85* gene in Japanese ASD patients (Table S2), including one variant in the 3'UTR. Furthermore, two studies have found down-regulated *GPR85* transcripts and decreased *GPR85* splicing events in the cortex of ASD patients (Monfared et al., 2021; Voineagu et al., 2011). Interestingly, increased *Gpr85* mRNA levels have been found in the striatum and prefrontal cortex of mice overexpressing *Shank3* (Jin et al., 2018). Although studies on *GPR85* remain sparse and no drugs are available, data from mice and patients converge on its therapeutic potential to improve social interaction deficits.

## 6.3 | ORs

In humans, 387 genes encode ORs in addition to 462 pseudogenes. ORs, which are encoded by a single exon, are subdivided in aquatic ancestry class I receptors clustered on human chromosome 1 (OR1–15) and the largest terrestrial ancestry class II (OR51–56) located on different chromosomes (Olender et al., 2020). They detect odorant volatile molecules, although most of them remain orphans. Since their discovery, growing evidence has shown OR expression outside the olfactory epithelium, first in testis, then in most tissues, including

the CNS. Their roles in development, chemotaxis, tissue injury and regeneration are starting to be deciphered. While the strongest association with ASD for ORs has been observed in the *OR1C1* gene, few studies have associated the *OR2M4*, *OR2T10* and *OR52M1* genes with ASD (Table S2). Furthermore, other OR genes were identified in association studies (Ruzzo et al., 2019), in particular with schizophrenia. Often qualified as 'ectopic' outside the olfactory epithelium, their expression is rather conserved among species (De la Cruz et al., 2009; Olender et al., 2016). *OR1C1*, *OR2M4* and *OR2T10* are present in the CNS, in contrast to *OR52M1*, which is conserved between humans and rodents (Figures 2 and 3 and Table S4). *OR1C1* and *OR2T10*, specific to apes, are both detected in the cortex, with *OR1C1* also found in the pons, cerebellum, hippocampus and amygdala (Table S6). *OR2M4* is conserved in apes, cows and pigs and is detected in neurons of most CNS areas. Their function remains to be elucidated in the CNS because no ligands nor animal models are available. In conclusion, the function of orphans and ORs is only starting to be elucidated in the CNS, but they could be of interest for ASD in the future with the development of selective drugs.

## 7 | GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we highlighted the contribution of different GPCRs in the aetiology of ASD and emphasised their potential role as therapeutic targets. First, we analysed the effect of GPCR variants associated with ASD based on their level of expression, ligand binding, receptor folding or activation of downstream signalling pathways (Table S2). SNPs or CNVs located in introns, untranslated regions or coding regions of *mGlu7*, *5-HT<sub>2A</sub>*, *CB<sub>1</sub>*, *GPR37* and *GPR85* receptor genes are consistent with the decreased levels of transcript expression observed in patients (Monfared et al., 2021). Based on evidence in ASD patients, their function, localisation (Figures 2 and 3 and Tables S2 and S6) and their behavioural predictive validity in animal models (Table S3), we identified *OTR*, *V<sub>1A</sub>*, *mGlu<sub>5</sub>*, *D<sub>2</sub>*, *5-HT<sub>2A</sub>*, *CB<sub>1</sub>* and *GPR37* for their contribution to ASD aetiology. *V<sub>1A</sub>* receptors display a clear potential for improving social interaction, *D<sub>2</sub>* and *GPR37* for normalising stereotyped behaviours and *mGlu<sub>5</sub>*, *OTR*, *CB<sub>1</sub>* and *5-HT<sub>2A</sub>* for both core ASD symptoms. Overall, it is surprising that out of around 800 GPCRs, only 23 are included in the SFARI list, and that these genes are only classified in the second category, namely, 'strong candidate gene'. We propose to move *OTR*, *CB<sub>1</sub>* and *V<sub>1A</sub>* receptors to the first category 'high confidence genes' and add *5-HT<sub>2A</sub>* and *5-HT<sub>7</sub>* to the list. We also propose *GABA<sub>B1</sub>*, *5-HT<sub>6</sub>*, *D<sub>4</sub>* and *D<sub>5</sub>* as potential candidates that deserve further consideration for their contribution to ASD. Overall, further investigation is required to identify all the GPCRs that contribute to the aetiology of the spectrum or subtypes of autism. Increasing evidence highlights functional crosstalk between GPCRs within a cell type to control a specific function, such as *D<sub>2</sub>*, *A<sub>2A</sub>* and *mGlu<sub>5</sub>* for the control of motor activity (Ciruela et al., 2011). In fact, independently of their physical interaction, GPCRs are not individual entities but should rather be considered as combinations of

GPCRs and isoforms working together in a cell to orchestrate the different signals and regulate downstream signalling networks and related cellular processes. Up to hundreds of GPCRs are expressed in the same brain structures or cell types, with the highest diversity in the striatum, cortex and hypothalamus (Marti-Solano et al., 2020; Vassilatis et al., 2003). Over 30 thousands of missense variants and CNVs have been identified in GPCR genes in the global population (Hauser et al., 2018). Considering the potential impact of GPCR on downstream signalling and cellular processes (Table S5) that are altered in ASD (De Rubeis et al., 2014; Hormozdiari et al., 2015; Gazestani et al., 2019), any slight modification in a GPCR (van der Westhuizen, 2023) or combinations of GPCRs may lead to important signalling defects and neuronal pathogenicity in a given cell type and circuitry. Here, we found that at least 15% of the genes listed in the SFARI database are involved in the signalling networks and cellular downstream processes of GPCRs. Therefore, rather than individual gene, combinations of GPCRs expressed in a cell type or circuit that control signalling networks should be considered in order to understand the global contribution of GPCRs to ASD aetiology. These analyses would allow us to identify an exhaustive list of GPCRs. Therefore, the impact of GPCRs for autism research has only begun to be highlighted.

GPCRs meet the criteria of therapeutic targets for ASD to bypass the placebo effect observed in clinical trials. They contribute to the polygenic ASD aetiology, pathogenic variants are recessive, they are therapeutically rescuable, and they are *per essence* membrane receptors that display a large pharmacopoeia of safe and efficient drugs. Nevertheless, targeting GPCRs, that are not involved in ASD aetiology but could normalise core symptoms, would also offer therapeutic opportunities across the spectrum without loss of efficacy. Here, we analysed the therapeutic potential of 25 GPCRs and categorised them as 'high', 'moderate' and 'low' candidates, based on (1) the expected pharmacological profile for ASD, (2) drug development status (approved or tested for a related disorder; Table S4), (3) their beneficial effects in animal models of ASD or in clinical trials (Tables S3 and S4) and (4) their safety (see Tables S4 and S6) and/or potential therapeutic window of efficacy (e.g., during development or in adults). We classified mGlu<sub>5</sub>, GABA<sub>B</sub>, D<sub>2</sub> and 5-HT<sub>2A</sub> as 'high' candidates and OTR, V<sub>1A</sub>, mGlu<sub>7</sub>, D<sub>1</sub>, 5-HT<sub>1B</sub>, M<sub>3</sub>, 5-HT<sub>7</sub> and CB<sub>1</sub> as 'moderate' candidates. We excluded β<sub>2</sub>-adrenoceptors, A<sub>2A</sub> and AT<sub>2</sub> and mGlu<sub>5</sub> and GABA<sub>B</sub> as toxicity and lack of efficacy have been reported in clinical trials, respectively. We did not exclude OTR and V<sub>1A</sub>, because more selective compounds or other pharmacological profiles remain to be tested, especially in combination with behavioural intervention programmes (Daniels et al., 2023). Furthermore, Hauser et al. (2018) reported hundreds of missense variants and CNVs in GPCR genes, including mGlu<sub>5</sub>, V<sub>1B</sub>, D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, 5-HT<sub>2A</sub>, β<sub>2</sub>-adrenoceptors and GABA<sub>B</sub>. This area of research based on receptor bias is known as pharmacogenomics (e.g., all variants that might influence ligand binding or transducer recruitment; Table S2). In particular, variants reported in mGlu<sub>5</sub> and 5-HT<sub>2A</sub> compromise their responsiveness to drugs (Hauser et al., 2018), which may explain why mGlu<sub>5</sub>-targeted clinical trials did not reach significant results. Finally, despite their strong potential, orphan and olfactory receptors belong to the

'low' category as there are no natural ligands or drugs clearly identified. We also ranked CX3CR<sub>1</sub>, V<sub>1B</sub>, D<sub>3</sub> and A<sub>3</sub> as 'low' candidates, as no data on pharmacological and genetic manipulation in animals is available. Finally, based on their involvement in ASD aetiology and their 'high' or 'moderate' therapeutic potential (Figure 4), we conclude that D<sub>2</sub>, 5-HT<sub>2A</sub>, CB<sub>1</sub>, OTR and V<sub>1A</sub> remain the most promising targets. Nevertheless, investigations or trials are still ongoing (or should be done) for these targets (e.g., CB<sub>1</sub> on social scale).

In the future, targeting oligomers or multiple GPCRs in a given cell type or administration of allosteric modulators or biased compounds should offer great promise for ASD drug development. Whereas allosteric modulators have already been tested for widespread targets (e.g., mGlu<sub>5</sub> or GABA<sub>B</sub>) in ASD, administration of biased agonists has only begun. The effect of one particular signalling pathway to a specific physio-pathological process (known as functional selectivity) has started to be unravelled (Kolb et al., 2022), including for ASD. Several examples of the effect of biased agonists showed very promising properties with limited side effects for other CNS applications. For example, β-arrestin-biased D<sub>2</sub> partial agonists normalised positive, negative and cognitive symptoms in two mouse models of schizophrenia, including social deficits, with reduced cataleptic side effects (Park et al., 2016). Gα<sub>i</sub>-biased μOR agonists have been developed for pain, without tolerance and addictive values (Crowley et al., 2020; Stahl et al., 2021). In addition, functional selectivity could be fully addressed for the 5-HT<sub>7</sub> as both β-arrestin and Gα<sub>s</sub>-biased agonists have been developed (El Khamlichi et al., 2022; Lee et al., 2021). Targeting oligomers or combinations of GPCRs in a given cell type using combination of drugs or a drug targeting multiple GPCRs would act synergically to achieve local and specific therapeutic effects. Such drugs already exist. For example, aripiprazole, risperidone, cariprazine or arylpiperazine derivatives target multiple dopamine, serotonin, histamine and/or adrenoceptors (Table S4) (Lacivita et al., 2021). The emergence of high throughput screening by DNA-based bar-coded chemical libraries should boost the identification of new drugs to target GPCRs with appropriate pharmacological profiles, including orphan and olfactory receptors (Madsen et al., 2020). Furthermore, the recent development of antibody fragments targeting GPCRs (Mujčić-Delić et al., 2014) offers multiple therapeutic advantages. They display all types of pharmacological profiles, and in addition, acting as chaperones, they could rescue deficient GPCR cell-surface expression. Furthermore, when reformatted in bi-specific or bivalents, they can target oligomers of GPCRs. Based on their fine-tune pharmacology and their diversity, GPCRs represent the greatest therapeutic options for ASD and hold the promise for successful clinical trials.

## 7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <https://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22: G protein-coupled receptors (Alexander et al., 2021).

## AUTHOR CONTRIBUTIONS

All authors contributed to the review. *Conceptualization*: Anil Annamneedi and Lucie P. Pellissier. *The literature search, data analysis and writing—original draft preparation*: Anil Annamneedi, Caroline Gora, Ana Dudas, Xavier Leray, Véronique Bozon, Pascale Crépieux and Lucie P. Pellissier. *Writing—review and editing*: Anil Annamneedi, Pascale Crépieux and Lucie P. Pellissier. *Funding acquisition, project administration and supervision*: Lucie P. Pellissier. All authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

This project has received funding from the H2020 European Research Council research and innovation programme (Grant 851231). Ana Dudas and Caroline Gora acknowledge the LabEx MablImprove (Grant ANR-10-LABX-53-01) for financial support of their PhD co-fund. Xavier Leray has received a postdoctoral fellowship from Agence Nationale de la Recherche (Grant ANR-18-CE45-0003). We thank Dr Romain Yvinec and Dr Scott Love for their advice on the manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

N/A-Review.

## ORCID

Anil Annamneedi  <https://orcid.org/0000-0002-6743-8627>

Xavier Leray  <https://orcid.org/0000-0003-2107-6082>

Pascale Crépieux  <https://orcid.org/0000-0002-2712-5271>

Lucie P. Pellissier  <https://orcid.org/0000-0001-7085-3242>

## REFERENCES

- Albers, H. E. (2012). The regulation of social recognition, social communication and aggression: Vasopressin in the social behavior neural network. *Hormones and Behavior*, *61*, 283–292.
- Alexander, S. P., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Southan, C., Davies, J. A., Abbracchio, M. P., Alexander, W., Al-Hosaini, K., Bäck, M., Barnes, N. M., Bathgate, R., ... Ye, R. D. (2021). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors. *British Journal of Pharmacology*, *178*(Suppl 1), S27–S156.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association.
- Amodeo, D. A., Cuevas, L., Dunn, J. T., Sweeney, J. A., & Ragozzino, M. E. (2018). The adenosine A2A receptor agonist, CGS 21680, attenuates a probabilistic reversal learning deficit and elevated grooming behavior in BTBR mice. *Autism Research*, *11*, 223–233.
- Amodeo, D. A., Rivera, E., Dunn, J. T., & Ragozzino, M. E. (2016). M100907 attenuates elevated grooming behavior in the BTBR mouse. *Behavioural Brain Research*, *313*, 67–70.
- Andari, E., Duhamel, J.-R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 4389–4394.
- Aran, A., Harel, M., Cassuto, H., Polyansky, L., Schnapp, A., Wattad, N., Shmueli, D., Golan, D., & Castellanos, F. X. (2021). Cannabinoid treatment for autism: A proof-of-concept randomized trial. *Molecular Autism*, *12*, 6. <https://doi.org/10.1186/s13229-021-00420-2>
- Bales, K. L., Perkeybile, A. M., Conley, O. G., Lee, M. H., Guoynes, C. D., Downing, G. M., Yun, C. R., Solomon, M., Jacob, S., & Mendoza, S. P. (2013). Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. *Biological Psychiatry*, *74*, 180–188. <https://doi.org/10.1016/j.biopsych.2012.08.025>
- Bast, N., Poustka, L., & Freitag, C. M. (2018). The locus coeruleus-norepinephrine system as pacemaker of attention—A developmental mechanism of derailed attentional function in autism spectrum disorder. *The European Journal of Neuroscience*, *47*, 115–125.
- Beaulieu, J.-M., & Gainetdinov, R. R. (2011). The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacological Reviews*, *63*, 182–217.
- Bedogni, F., Cobolli Gigli, C., Pozzi, D., Rossi, R. L., Scaramuzza, L., Rossetti, G., Pagani, M., Kilstrup-Nielsen, C., Matteoli, M., & Landsberger, N. (2016). Defects during Mecp2 null embryonic cortex development precede the onset of overt neurological symptoms. *Cerebral Cortex*, *26*, 2517–2529. <https://doi.org/10.1093/cercor/bhv078>
- Beerepoot, P., Nazari, R., & Salahpour, A. (2017). Pharmacological chaperone approaches for rescuing GPCR mutants: Current state, challenges, and screening strategies. *Pharmacological Research*, *117*, 242–251.
- Berendzen, K. M., Sharma, R., Mandujano, M. A., Wei, Y., Rogers, F. D., Simmons, T. C., Seelke, A. M., Bond, J. M., Larios, R., Goodwin, N. L., Sherman, M., Parthasarathy, S., Espineda, I., Knoedler, J. R., Beery, A., Bales, K. L., Shah, N. M., & Manoli, D. S. (2023). Oxytocin receptor is not required for social attachment in prairie voles. *Neuron*, *111*(6), 787–796.e4.
- Berger, M., Gray, J. A., & Roth, B. L. (2009). The expanded biology of serotonin. *Annual Review of Medicine*, *60*, 355–366.
- Berry-Kravis, E. M., Hessel, D., Rathmell, B., Zarevics, P., Cherubini, M., Walton-Bowen, K., Mu, Y., Nguyen, D. V., Gonzalez-Heydrich, J., Wang, P. P., Carpenter, R. L., Bear, M. F., & Hagerman, R. J. (2012). Effects of STX209 (arbaclofen) on neurobehavioral function in children and adults with fragile X syndrome: A randomized, controlled, phase 2 trial. *Science Translational Medicine*, *4*, 152ra127.
- Beversdorf, D. Q. (2020). The role of the noradrenergic system in autism spectrum disorders. Implications for treatment. *Seminars in Pediatric Neurology*, *35*, 100834. <https://doi.org/10.1016/j.spn.2020.100834>
- Beversdorf, D. Q., Nordgren, R. E., Bonab, A. A., Fischman, A. J., Weise, S. B., Dougherty, D. D., Felopulos, G. J., Zhou, F. C., & Bauman, M. L. (2012). 5-HT<sub>2</sub> receptor distribution shown by [<sup>18</sup>F] setoperone PET in high-functioning autistic adults. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *24*, 191–197. <https://doi.org/10.1176/appi.neuropsych.11080202>
- Bielsky, I. F., Hu, S.-B., Ren, X., Terwilliger, E. F., & Young, L. J. (2005). The V1a vasopressin receptor is necessary and sufficient for normal social recognition: A gene replacement study. *Neuron*, *47*, 503–513. <https://doi.org/10.1016/j.neuron.2005.06.031>
- Bielsky, I. F., Hu, S.-B., Szegda, K. L., Westphal, H., & Young, L. J. (2004). Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. *Neuropsychopharmacology*, *29*, 483–493. <https://doi.org/10.1038/sj.npp.1300360>
- Blanchard, R. J., Griebel, G., Farrokhi, C., Markham, C., Yang, M., & Blanchard, D. C. (2005). AVP V1b selective antagonist SSR149415 blocks aggressive behaviors in hamsters. *Pharmacology, Biochemistry, and Behavior*, *80*, 189–194. <https://doi.org/10.1016/j.pbb.2004.10.024>
- Bolognani, F., del Valle Rubido, M., Squassante, L., Wandel, C., Derks, M., Murtagh, L., Sevigny, J., Khwaja, O., Umbricht, D., & Fontoura, P. (2019). A phase 2 clinical trial of a vasopressin V1a receptor antagonist shows improved adaptive behaviors in men with autism spectrum disorder. *Science Translational Medicine*, *11*, eaat7838. <https://doi.org/10.1126/scitranslmed.aat7838>



- Bouwknicht, J. A., Hijzen, T. H., van der Gugten, J., Maes, R. A., Hen, R., & Olivier, B. (2001). Absence of 5-HT<sub>1B</sub> receptors is associated with impaired impulse control in male 5-HT<sub>1B</sub> knockout mice. *Biological Psychiatry*, 49, 557–568. [https://doi.org/10.1016/S0006-3223\(00\)01018-0](https://doi.org/10.1016/S0006-3223(00)01018-0)
- Brandenburg, C., Soghomonian, J.-J., Zhang, K., Sulkaj, I., Randolph, B., Kachadoorian, M., & Blatt, G. J. (2020). Increased dopamine type 2 gene expression in the dorsal striatum in individuals with autism spectrum disorder suggests alterations in indirect pathway signaling and circuitry. *Frontiers in Cellular Neuroscience*, 14, 577858. <https://doi.org/10.3389/fncel.2020.577858>
- Brody, S. A., Dulawa, S. C., Conquet, F., & Geyer, M. A. (2004). Assessment of a prepulse inhibition deficit in a mutant mouse lacking mGlu5 receptors. *Molecular Psychiatry*, 9, 35–41. <https://doi.org/10.1038/sj.mp.4001404>
- Brunner, D., Buhot, M. C., Hen, R., & Hofer, M. (1999). Anxiety, motor activation, and maternal-infant interactions in 5HT1B knockout mice. *Behavioral Neuroscience*, 113, 587–601. <https://doi.org/10.1037/0735-7044.113.3.587>
- Campbell, N. G., Zhu, C.-B., Lindler, K. M., Yaspan, B. L., Kistner-Griffin, E., NIH ARRA Consortium, Hewlett, W. A., Tate, C. G., Blakely, R. D., & Sutcliffe, J. S. (2013). Rare coding variants of the adenosine A3 receptor are increased in autism: On the trail of the serotonin transporter regulome. *Molecular Autism*, 4, 28. <https://doi.org/10.1186/2040-2392-4-28>
- Campi, K. L., Greenberg, G. D., Kapoor, A., Ziegler, T. E., & Trainor, B. C. (2014). Sex differences in effects of dopamine D1 receptors on social withdrawal. *Neuropharmacology*, 77, 208–216. <https://doi.org/10.1016/j.neuropharm.2013.09.026>
- Carreira, L. D., Matias, F. C., & Campos, M. G. (2022). Clinical data on cannabinoids: Translational research in the treatment of autism spectrum disorders. *Biomedicine*, 10, 796. <https://doi.org/10.3390/biomedicines10040796>
- Cataldo, I., Azhari, A., & Esposito, G. (2018). A review of oxytocin and arginine-vasopressin receptors and their modulation of autism spectrum disorder. *Frontiers in Molecular Neuroscience*, 11, 27. <https://doi.org/10.3389/fnmol.2018.00027>
- Chadman, K. K., Fernandes, S., DiLiberto, E., & Feingold, R. (2019). Do animal models hold value in autism spectrum disorder (ASD) drug discovery? *Expert Opinion on Drug Discovery*, 14, 727–734. <https://doi.org/10.1080/17460441.2019.1621285>
- Chana, G., Laskaris, L., Pantelis, C., Gillett, P., Testa, R., Zantomio, D., Burrows, E. L., Hannan, A. J., Everall, I. P., & Skafidas, E. (2015). Decreased expression of mGluR5 within the dorsolateral prefrontal cortex in autism and increased microglial number in mGluR5 knockout mice: Pathophysiological and neurobehavioral implications. *Brain, Behavior, and Immunity*, 49, 197–205. <https://doi.org/10.1016/j.bbi.2015.05.009>
- Chartoff, E. H., Marck, B. T., Matsumoto, A. M., Dorsa, D. M., & Palmiter, R. D. (2001). Induction of stereotypy in dopamine-deficient mice requires striatal D1 receptor activation. *Proceedings of the National Academy of Sciences of the United States of America*, 98, 10451–10456. <https://doi.org/10.1073/pnas.181356498>
- Chen, Q., Kogan, J. H., Gross, A. K., Zhou, Y., Walton, N. M., Shin, R., Heusner, C. L., Miyake, S., Tajinda, K., Tamura, K., & Matsumoto, M. (2012). SREB2/GPR85, a schizophrenia risk factor, negatively regulates hippocampal adult neurogenesis and neurogenesis-dependent learning and memory. *The European Journal of Neuroscience*, 36, 2597–2608. <https://doi.org/10.1111/j.1460-9568.2012.08180.x>
- Cherepanov, S. M., Gerasimenko, M., Yuhi, T., Furuhashi, K., Tsuji, C., Yokoyama, S., Nakayama, K. I., Nishiyama, M., & Higashida, H. (2021). Oxytocin ameliorates impaired social behavior in a Chd8 haploinsufficiency mouse model of autism. *BMC Neuroscience*, 22, 32. <https://doi.org/10.1186/s12868-021-00631-6>
- Cheroni, C., Caporale, N., & Testa, G. (2020). Autism spectrum disorder at the crossroad between genes and environment: Contributions, convergences, and interactions in ASD developmental pathophysiology. *Molecular Autism*, 11, 69. <https://doi.org/10.1186/s13229-020-00370-1>
- Ciruela, F., Gómez-Soler, M., Guidolin, D., Borroto-Escuela, D. O., Agnati, L. F., Fuxe, K., & Fernández-Dueñas, V. (2011). Adenosine receptor containing oligomers: Their role in the control of dopamine and glutamate neurotransmission in the brain. *Biochimica et Biophysica Acta*, 1808, 1245–1255. <https://doi.org/10.1016/j.bbame.2011.02.007>
- Coelho, J. E., Alves, P., Canas, P. M., Valadas, J. S., Shmidt, T., Batalha, V. L., Ferreira, D. G., Ribeiro, J. A., Bader, M., Cunha, R. A., & do Couto, F. S. (2014). Overexpression of adenosine A2A receptors in rats: Effects on depression, locomotion, and anxiety. *Frontiers in Psychiatry*, 5, 67. <https://doi.org/10.3389/fpsy.2014.00067>
- Costa, L., Sardone, L. M., Bonaccorso, C. M., D'Antoni, S., Spatuzza, M., Gulisano, W., Tropea, M. R., Puzzo, D., Leopoldo, M., Lacivita, E., Catania, M. V., & Ciranna, L. (2018). Activation of serotonin 5-HT7 receptors modulates hippocampal synaptic plasticity by stimulation of adenylate cyclases and rescues learning and behavior in a mouse model of fragile X syndrome. *Frontiers in Molecular Neuroscience*, 11, 353. <https://doi.org/10.3389/fnmol.2018.00353>
- Crowley, R. S., Riley, A. P., Alder, A. F., Anderson, R. J., Luo, D., Kaska, S., Maynez, P., Kivell, B. M., & Prisinzano, T. E. (2020). Synthetic studies of neoclerodane diterpenes from *Salvia divinorum*: Design, synthesis, and evaluation of analogues with improved potency and G-protein activation bias at the  $\mu$ -opioid receptor. *ACS Chemical Neuroscience*, 11, 1781–1790. <https://doi.org/10.1021/acchemneuro.0c00191>
- Cukier, H. N., Dueker, N. D., Slifer, S. H., Lee, J. M., Whitehead, P. L., Lalanne, E., Leyva, N., Konidari, I., Gentry, R. C., Hulme, W. F., Booven, D. V., Mayo, V., Hofmann, N. K., Schmidt, M. A., Martin, E. R., Haines, J. L., Cuccaro, M. L., Gilbert, J. R., & Pericak-Vance, M. A. (2014). Exome sequencing of extended families with autism reveals genes shared across neurodevelopmental and neuropsychiatric disorders. *Molecular Autism*, 5, 1. <https://doi.org/10.1186/2040-2392-5-1>
- Daniels, N., Moerkerke, M., Steyaert, J., Bamps, A., Debbaut, E., Prinsen, J., Tang, T., van der Donck, S., Boets, B., & Alaerts, K. (2023). Effects of multiple-dose intranasal oxytocin administration on social responsiveness in children with autism: A randomized, placebo-controlled trial. *Molecular Autism*, 14, 16. <https://doi.org/10.1186/s13229-023-00546-5>
- D'Antoni, S., Spatuzza, M., Bonaccorso, C. M., Musumeci, S. A., Ciranna, L., Nicoletti, F., Huber, K. M., & Catania, M. V. (2014). Dysregulation of group-I metabotropic glutamate (mGlu) receptor mediated signalling in disorders associated with Intellectual Disability and Autism. *Neuroscience and Biobehavioral Reviews*, 46(Pt 2), 228–241. <https://doi.org/10.1016/j.neubiorev.2014.02.003>
- de Bruin, N. M. W. J., van Loevezijn, A., Wicke, K. M., de Haan, M., Venhorst, J., Lange, J. H. M., de Groote, L., van der Neut, M. A. W., Prickaerts, J., Andriambelosen, E., Foley, A. G., van Drimmelen, M., van der Wetering, M., & Kruse, C. G. (2016). The selective 5-HT<sub>6</sub> receptor antagonist SLV has putative cognitive- and social interaction enhancing properties in rodent models of cognitive impairment. *Neurobiology of Learning and Memory*, 133, 100–117. <https://doi.org/10.1016/j.nlm.2016.06.020>
- de Filippis, B., Nativio, P., Fabbri, A., Ricceri, L., Adriani, W., Lacivita, E., Leopoldo, M., Passarelli, F., Fuso, A., & Laviola, G. (2014). Pharmacological stimulation of the brain serotonin receptor 7 as a novel therapeutic approach for Rett syndrome. *Neuropsychopharmacology*, 39, 2506–2518. <https://doi.org/10.1038/npp.2014.105>
- De la Cruz, O., Blekhan, R., Zhang, X., Nicolae, D., Firestein, S., & Gilad, Y. (2009). A signature of evolutionary constraint on a subset of ectopically expressed olfactory receptor genes. *Molecular Biology and Evolution*, 26, 491–494. <https://doi.org/10.1093/molbev/msn294>
- de Nuccio, C., Bernardo, A., Ferrante, A., Pepponi, R., Martire, A., Falchi, M., Visentin, S., Popoli, P., & Minghetti, L. (2019). Adenosine

- A<sub>2A</sub> receptor stimulation restores cell functions and differentiation in Niemann-Pick type C-like oligodendrocytes. *Scientific Reports*, 9, 9782. <https://doi.org/10.1038/s41598-019-46268-8>
- De Rubeis, S., He, X., Goldberg, A. P., Poultney, C. S., Samocha, K., Ercument Cicek, A., Kou, Y., Liu, L., Fromer, M., Walker, S., Singh, T., Klei, L., Kosmicki, J., Fu, S. C., Aleksic, B., Biscaldi, M., Bolton, P. F., Brownfeld, J. M., Cai, J., ... Buxbaum, J. D. (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*, 515, 209–215. <https://doi.org/10.1038/nature13772>
- Dekan, Z., Kremsmayr, T., Keov, P., Godin, M., Teakle, N., Dürbauer, L., Xiang, H., Gharib, D., Bergmayr, C., Hellinger, R., Gay, M., Vilaseca, M., Kurzbach, D., Albericio, F., Alewood, P. F., Gruber, C. W., & Muttenthaler, M. (2021). Nature-inspired dimerization as a strategy to modulate neuropeptide pharmacology exemplified with vasopressin and oxytocin. *Chemical Science*, 12, 4057–4062. <https://doi.org/10.1039/D0SC05501H>
- DeVries, A. C., Young, W. S., & Nelson, R. J. (1997). Reduced aggressive behaviour in mice with targeted disruption of the oxytocin gene. *Journal of Neuroendocrinology*, 9, 363–368. <https://doi.org/10.1046/j.1365-2826.1997.t01-1-00589.x>
- di Prisco, G. V., Huang, W., Buffington, S. A., Hsu, C.-C., Bonnen, P. E., Placzek, A. N., Sidrauski, C., Krnjević, K., Kaufman, R. J., Walter, P., & Costa-Mattoli, M. (2014). Translational control of mGluR-dependent long-term depression and object-place learning by eIF2 $\alpha$ . *Nature Neuroscience*, 17, 1073–1082. <https://doi.org/10.1038/nn.3754>
- DiCarlo, G. E., Aguilar, J. I., Matthies, H. J., Harrison, F. E., Bundschuh, K. E., West, A., Hashemi, P., Herborg, F., Rickhag, M., Chen, H., Gether, U., Wallace, M. T., & Galli, A. (2019). Autism-linked dopamine transporter mutation alters striatal dopamine neurotransmission and dopamine-dependent behaviors. *The Journal of Clinical Investigation*, 129, 3407–3419. <https://doi.org/10.1172/JCI127411>
- Dumais, K. M., Bredewold, R., Mayer, T. E., & Veenema, A. H. (2013). Sex differences in oxytocin receptor binding in forebrain regions: Correlations with social interest in brain region- and sex-specific ways. *Hormones and Behavior*, 64, 693–701. <https://doi.org/10.1016/j.yhbeh.2013.08.012>
- Dunham, J. H., Meyer, R. C., Garcia, E. L., & Hall, R. A. (2009). GPR37 surface expression enhancement via N-terminal truncation or protein-protein interactions. *Biochemistry*, 48, 10286–10297. <https://doi.org/10.1021/bi9013775>
- Egashira, N., Tanoue, A., Matsuda, T., Koushi, E., Harada, S., Takano, Y., Tsujimoto, G., Mishima, K., Iwasaki, K., & Fujiwara, M. (2007). Impaired social interaction and reduced anxiety-related behavior in vasopressin V1a receptor knockout mice. *Behavioural Brain Research*, 178, 123–127. <https://doi.org/10.1016/j.bbr.2006.12.009>
- el Khamlichi, C., Reverchon, F., Hervouet-Coste, N., Robin, E., Chopin, N., Deau, E., Madouri, F., Guimpied, C., Colas, C., Menuet, A., Inoue, A., Bojarski, A. J., Guillaumet, G., Suzenet, F., Reiter, E., & Morisset-Lopez, S. (2022). Serodolin, a  $\beta$ -arrestin-biased ligand of 5-HT<sub>7</sub> receptor, attenuates pain-related behaviors. *Proceedings of the National Academy of Sciences of the United States of America*, 119, e2118847119. <https://doi.org/10.1073/pnas.2118847119>
- Elands, J., Barberis, C., & Jard, S. (1988). [3H]-[Thr<sup>4</sup>,Gly<sup>7</sup>]OT: A highly selective ligand for central and peripheral OT receptors. *The American Journal of Physiology*, 254, E31–E38. <https://doi.org/10.1152/ajpendo.1988.254.1.E31>
- Estes, A., Munson, J., Rogers, S. J., Greenson, J., Winter, J., & Dawson, G. (2015). Long-term outcomes of early intervention in 6-year-old children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 580–587. <https://doi.org/10.1016/j.jaac.2015.04.005>
- Farook, M. F., DeCuyper, M., Hyland, K., Takumi, T., LeDoux, M. S., & Reiter, L. T. (2012). Altered serotonin, dopamine and norepinephrine levels in 15q duplication and Angelman syndrome mouse models. *PLoS ONE*, 7, e43030. <https://doi.org/10.1371/journal.pone.0043030>
- Fatemi, S. H., Folsom, T. D., Kneeland, R. E., & Liesch, S. B. (2011). Metabotropic glutamate receptor 5 upregulation in children with autism is associated with underexpression of both Fragile X mental retardation protein and GABA<sub>A</sub> receptor beta 3 in adults with autism. *Anatomical Record (Hoboken)*, 294, 1635–1645. <https://doi.org/10.1002/ar.21299>
- Fatemi, S. H., Folsom, T. D., Reutiman, T. J., & Thuras, P. D. (2009). Expression of GABA<sub>B</sub> receptors is altered in brains of subjects with autism. *Cerebellum*, 8, 64–69. <https://doi.org/10.1007/s12311-008-0075-3>
- Ferguson, J. N., Aldag, J. M., Insel, T. R., & Young, L. J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *The Journal of Neuroscience*, 21, 8278–8285. <https://doi.org/10.1523/JNEUROSCI.21-20-08278.2001>
- Ferguson, J. N., Young, L. J., Hearn, E. F., Matzuk, M. M., Insel, T. R., & Winslow, J. T. (2000). Social amnesia in mice lacking the oxytocin gene. *Nature Genetics*, 25, 284–288. <https://doi.org/10.1038/77040>
- Firouzabadi, N., Ghazanfari, N., Alavi Shoushtari, A., Erfani, N., Fathi, F., Bazrafkan, M., & Bahramali, E. (2016). Genetic variants of angiotensin-converting enzyme are linked to autism: A case-control study. *PLoS ONE*, 11, e0153667. <https://doi.org/10.1371/journal.pone.0153667>
- Fish, E. W., Faccidomo, S., & Miczek, K. A. (1999). Aggression heightened by alcohol or social instigation in mice: Reduction by the 5-HT<sub>1B</sub> receptor agonist CP-94,253. *Psychopharmacology*, 146, 391–399. <https://doi.org/10.1007/PL00005484>
- Fisher, N. M., AlHashim, A., Buch, A. B., Badivuku, H., Samman, M. M., Weiss, K. M., Cestero, G. I., Does, M. D., Rook, J. M., Lindsley, C. W., & Conn, P. J. (2021). A GRM7 mutation associated with developmental delay reduces mGlu7 expression and produces neurological phenotypes. *JCI Insight*, 6, 143324. <https://doi.org/10.1172/jci.insight.143324>
- Fisher, N. M., Gould, R. W., Gogliotti, R. G., McDonald, A. J., Badivuku, H., Chennareddy, S., Buch, A. B., Moore, A. M., Jenkins, M. T., Robb, W. H., Lindsley, C. W., Jones, C. K., Conn, P. J., & Niswender, C. M. (2020). Phenotypic profiling of mGlu7 knockout mice reveals new implications for neurodevelopmental disorders. *Genes, Brain, and Behavior*, 19, e12654. <https://doi.org/10.1111/gbb.12654>
- Frantz, M.-C., Pellissier, L. P., Pflimlin, E., Loison, S., Gandía, J., Marsol, C., Durroux, T., Mouillac, B., Becker, J. A. J., le Merrer, J., Valencia, C., Villa, P., Bonnet, D., & Hibert, M. (2018). LIT-001, the first nonpeptide oxytocin receptor agonist that improves social interaction in a mouse model of autism. *Journal of Medicinal Chemistry*, 61, 8670–8692. <https://doi.org/10.1021/acs.jmedchem.8b00697>
- Froemke, R. C., & Young, L. J. (2021). Oxytocin, neural plasticity, and social behavior. *Annual Review of Neuroscience*, 44, 359–381. <https://doi.org/10.1146/annurev-neuro-102320-102847>
- Fujita-Jimbo, E., Tanabe, Y., Yu, Z., Kojima, K., Mori, M., Li, H., Iwamoto, S., Yamagata, T., Momoi, M. Y., & Momoi, T. (2015). The association of GPR85 with PSD-95-neuroigin complex and autism spectrum disorder: A molecular analysis. *Molecular Autism*, 6, 17. <https://doi.org/10.1186/s13229-015-0012-5>
- Gabriele, S., Sacco, R., & Persico, A. M. (2014). Blood serotonin levels in autism spectrum disorder: A systematic review and meta-analysis. *European Neuropsychopharmacology*, 24, 919–929. <https://doi.org/10.1016/j.euroneuro.2014.02.004>
- Gazestani, V. H., Pramparo, T., Nalabolu, S., Kellman, B. P., Murray, S., Lopez, L., Pierce, K., Courchesne, E., & Lewis, N. E. (2019). A perturbed gene network containing PI3K-AKT, RAS-ERK and WNT- $\beta$ -catenin pathways in leukocytes is linked to ASD genetics and symptom severity. *Nature Neuroscience*, 22, 1624–1634. <https://doi.org/10.1038/s41593-019-0489-x>
- Gidaya, N. B., Lee, B. K., Burstyn, I., Michael, Y., Newschaffer, C. J., & Mortensen, E. L. (2016). In utero exposure to  $\beta$ -2-adrenergic receptor agonist drugs and risk for autism spectrum disorders. *Pediatrics*, 137, e20151316. <https://doi.org/10.1542/peds.2015-1316>
- Gilbert, D. L., Murphy, T. K., Jankovic, J., Budman, C. L., Black, K. J., Kurlan, R. M., Coffman, K. A., McCracken, J. T., Juncos, J.,

- Grant, J. E., & Chipkin, R. E. (2018). Ecopipam, a D1 receptor antagonist, for treatment of Tourette syndrome in children: A randomized, placebo-controlled crossover study. *Movement Disorders*, 33, 1272–1280. <https://doi.org/10.1002/mds.27457>
- Gogliotti, R. G., Senter, R. K., Fisher, N. M., Adams, J., Zamorano, R., Walker, A. G., Blobaum, A. L., Engers, D. W., Hopkins, C. R., Daniels, J. S., Jones, C. K., Lindsley, C. W., Xiang, Z., Conn, P. J., & Niswender, C. M. (2017). mGlu7 potentiation rescues cognitive, social, and respiratory phenotypes in a mouse model of Rett syndrome. *Science Translational Medicine*, 9, eaai7459. <https://doi.org/10.1126/scitranslmed.aai7459>
- Goldberg, J., Anderson, G. M., Zwaigenbaum, L., Hall, G. B. C., Nahmias, C., Thompson, A., & Szatmari, P. (2009). Cortical serotonin type-2 receptor density in parents of children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39, 97–104. <https://doi.org/10.1007/s10803-008-0604-4>
- Gomez-Castro, F., Zappettini, S., Presse, J. C., Silva, C. G., Russeau, M., Gervasi, N., Figueiredo, M., Montmasson, C., Renner, M., Canas, P. M., Gonçalves, F. Q., Alcáda-Morais, S., Szabó, E., Rodrigues, R. J., Agostinho, P., Tomé, A. R., Caillol, G., Thoumine, O., Nicol, X., ... Lévi, S. (2021). Convergence of adenosine and GABA signaling for synapse stabilization during development. *Science*, 374, eabk2055. <https://doi.org/10.1126/science.abk2055>
- Guastella, A. J., Einfeld, S. L., Gray, K. M., Rinehart, N. J., Tonge, B. J., Lambert, T. J., & Hickie, I. B. (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry*, 67, 692–694. <https://doi.org/10.1016/j.biopsych.2009.09.020>
- Guastella, A. J., Kenyon, A. R., Alvares, G. A., Carson, D. S., & Hickie, I. B. (2010). Intranasal arginine vasopressin enhances the encoding of happy and angry faces in humans. *Biological Psychiatry*, 67, 1220–1222. <https://doi.org/10.1016/j.biopsych.2010.03.014>
- Guerrero, A. (2018). A2A adenosine receptor agonists and their potential therapeutic applications: An update. *Current Medicinal Chemistry*, 25, 3597–3612. <https://doi.org/10.2174/0929867325666180313110254>
- Haller, J., Varga, B., Ledent, C., Barna, I., & Freund, T. F. (2004). Context-dependent effects of CB1 cannabinoid gene disruption on anxiety-like and social behaviour in mice. *The European Journal of Neuroscience*, 19, 1906–1912. <https://doi.org/10.1111/j.1460-9568.2004.03293.x>
- Hammock, E. A., Lim, M. M., Nair, H. P., & Young, L. J. (2005). Association of vasopressin 1a receptor levels with a regulatory microsatellite and behavior. *Genes, Brain, and Behavior*, 4, 289–301. <https://doi.org/10.1111/j.1601-183X.2005.00119.x>
- Hauser, A. S., Attwood, M. M., Rask-Andersen, M., Schiöth, H. B., & Gloriam, D. E. (2017). Trends in GPCR drug discovery: New agents, targets and indications. *Nature Reviews. Drug Discovery*, 16, 829–842. <https://doi.org/10.1038/nrd.2017.178>
- Hauser, A. S., Chavali, S., Masuho, I., Jahn, L. J., Martemyanov, K. A., Gloriam, D. E., & Babu, M. M. (2018). Pharmacogenomics of GPCR drug targets. *Cell*, 172, 41–54.e19. <https://doi.org/10.1016/j.cell.2017.11.033>
- Hedlund, P. B., & Sutcliffe, J. G. (2007). The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. *Neuroscience Letters*, 414, 247–251. <https://doi.org/10.1016/j.neulet.2006.12.054>
- Hegarty, J. P., Ferguson, B. J., Zamzow, R. M., Rohowetz, L. J., Johnson, J. D., Christ, S. E., & Beversdorf, D. Q. (2017). Beta-adrenergic antagonism modulates functional connectivity in the default mode network of individuals with and without autism spectrum disorder. *Brain Imaging and Behavior*, 11, 1278–1289. <https://doi.org/10.1007/s11682-016-9604-8>
- Henderson, C., Wijetunge, L., Kinoshita, M. N., Shumway, M., Hammond, R. S., Postma, F. R., Brynczka, C., Rush, R., Thomas, A., Paylor, R., Warren, S. T., Vanderklisch, P. W., Kind, P. C., Carpenter, R. L., Bear, M. F., & Healy, A. M. (2012). Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABA<sub>B</sub> receptors with arbaclofen. *Science Translational Medicine*, 4, 152ra128. <https://doi.org/10.1126/scitranslmed.3004218>
- Hertz, E., Terenius, L., Vukojević, V., & Svenningsson, P. (2019). GPR37 and GPR37L1 differently interact with dopamine 2 receptors in live cells. *Neuropharmacology*, 152, 51–57. <https://doi.org/10.1016/j.neuropharm.2018.11.009>
- Hervás, A., Toma, C., Romarís, P., Ribasés, M., Salgado, M., Bayes, M., Balmaña, N., Cormand, B., Maristany, M., Guijarro, S., & Arranz, M. J. (2014). The involvement of serotonin polymorphisms in autistic spectrum symptomatology. *Psychiatric Genetics*, 24, 158–163. <https://doi.org/10.1097/YPG.0000000000000034>
- Hiraki, Y., Okamoto, N., Ida, T., Nakata, Y., Kamada, M., Kanemura, Y., Yamasaki, M., Fujita, H., Nishimura, G., Kato, M., Harada, N., & Matsumoto, N. (2008). Two new cases of pure 1q terminal deletion presenting with brain malformations. *American Journal of Medical Genetics. Part A*, 146A, 1241–1247. <https://doi.org/10.1002/ajmg.a.32275>
- Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., & Mosovich, S. (2003). Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. *Neuropsychopharmacology*, 28, 193–198. <https://doi.org/10.1038/sj.npp.1300021>
- Homberg, J. R., Olivier, J. D. A., VandenBroeke, M., Youn, J., Ellenbroek, A. K., Karel, P., Shan, L., van Bostel, R., Ooms, S., Balemans, M., Langedijk, J., Muller, M., Vriend, G., Cools, A. R., Cuppen, E., & Ellenbroek, B. A. (2016). The role of the dopamine D1 receptor in social cognition: Studies using a novel genetic rat model. *Disease Models & Mechanisms*, 9, 1147–1158. <https://doi.org/10.1242/dmm.024752>
- Hopkins, W. D., Donaldson, Z. R., & Young, L. J. (2012). A polymorphic indel containing the RS3 microsatellite in the 5' flanking region of the vasopressin V1a receptor gene is associated with chimpanzee (*Pan troglodytes*) personality. *Genes, Brain, and Behavior*, 11, 552–558. <https://doi.org/10.1111/j.1601-183X.2012.00799.x>
- Horie, K., Inoue, K., Suzuki, S., Adachi, S., Yada, S., Hirayama, T., Hidema, S., Young, L. J., & Nishimori, K. (2019). Oxytocin receptor knockout prairie voles generated by CRISPR/Cas9 editing show reduced preference for social novelty and exaggerated repetitive behaviors. *Hormones and Behavior*, 111, 60–69. <https://doi.org/10.1016/j.yhbeh.2018.10.011>
- Hormozdiari, F., Penn, O., Borenstein, E., & Eichler, E. E. (2015). The discovery of integrated gene networks for autism and related disorders. *Genome Research*, 25, 142–154. <https://doi.org/10.1101/gr.178855.114>
- Imai, Y., Inoue, H., Kataoka, A., Hua-Qin, W., Masuda, M., Ikeda, T., Tsukita, K., Soda, M., Kodama, T., Fuwa, T., Honda, Y., Kaneko, S., Matsumoto, S., Wakamatsu, K., Ito, S., Miura, M., Aosaki, T., Itohara, S., & Takahashi, R. (2007). Pael receptor is involved in dopamine metabolism in the nigrostriatal system. *Neuroscience Research*, 59, 413–425. <https://doi.org/10.1016/j.neures.2007.08.005>
- Irving, A. J., Rae, M. G., & Coutts, A. A. (2002). Cannabinoids on the brain. *Scientific World Journal*, 2, 632–648. <https://doi.org/10.1100/tsw.2002.139>
- Jacob, S., Veenstra-VanderWeele, J., Murphy, D., McCracken, J., Smith, J., Sanders, K., Meyenberg, C., Wiese, T., Deol-Bhullar, G., Wandel, C., Ashford, E., & Anagnostou, E. (2022). Efficacy and safety of balovaptan for socialisation and communication difficulties in autistic adults in North America and Europe: A phase 3, randomised, placebo-controlled trial. *Lancet Psychiatry*, 9, 199–210. [https://doi.org/10.1016/S2215-0366\(21\)00429-6](https://doi.org/10.1016/S2215-0366(21)00429-6)
- Jacquemont, S., Berry-Kravis, E., Hagerman, R., von Raison, F., Gasparini, F., Apostol, G., Ufer, M., Des Portes, V., & Gomez-Mancilla, B. (2014). The challenges of clinical trials in fragile X syndrome. *Psychopharmacology*, 231, 1237–1250. <https://doi.org/10.1007/s00213-013-3289-0>

- Jacquemont, S., Curie, A., des Portes, V., Torrioli, M. G., Berry-Kravis, E., Hagerman, R. J., Ramos, F. J., Cornish, K., He, Y., Paulding, C., Neri, G., Chen, F., Hadjikhani, N., Martinet, D., Meyer, J., Beckmann, J. S., Delange, K., Brun, A., Bussy, G., ... Gomez-Mancilla, B. (2011). Epigenetic modification of the *FMR1* gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056. *Science Translational Medicine*, 3, 64ra1. <https://doi.org/10.1126/scitranslmed.3001708>
- Jin, C., Kang, H., Ryu, J. R., Kim, S., Zhang, Y., Lee, Y., Kim, Y., & Han, K. (2018). Integrative brain transcriptome analysis reveals region-specific and broad molecular changes in *Shank3*-overexpressing mice. *Frontiers in Molecular Neuroscience*, 11, 250. <https://doi.org/10.3389/fnmol.2018.00250>
- Jing, F., Mogi, M., Sakata, A., Iwanami, J., Tsukuda, K., Ohshima, K., Min, L. J., Steckelings, U. M., Unger, T., Dahlöf, B., & Horiuchi, M. (2012). Direct stimulation of angiotensin II type 2 receptor enhances spatial memory. *Journal of Cerebral Blood Flow and Metabolism*, 32, 248–255. <https://doi.org/10.1038/jcbfm.2011.133>
- John, S., & Jaeggi, A. V. (2021). Oxytocin levels tend to be lower in autistic children: A meta-analysis of 31 studies. *Autism*, 25, 2152–2161. <https://doi.org/10.1177/13623613211034375>
- Jung, S., Aliberti, J., Graemmel, P., Sunshine, M. J., Kreutzberg, G. W., Sher, A., & Littman, D. R. (2000). Analysis of fractalkine receptor CX<sub>3</sub>CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. *Molecular and Cellular Biology*, 20, 4106–4114. <https://doi.org/10.1128/MCB.20.11.4106-4114.2000>
- Jurek, B., & Neumann, I. D. (2018). The oxytocin receptor: From intracellular signaling to behavior. *Physiological Reviews*, 98, 1805–1908. <https://doi.org/10.1152/physrev.00031.2017>
- Kabitzke, P. A., Simpson, E. H., Kandel, E. R., & Balsam, P. D. (2015). Social behavior in a genetic model of dopamine dysfunction at different neurodevelopmental time points. *Genes, Brain, and Behavior*, 14, 503–515. <https://doi.org/10.1111/gbb.12233>
- Kang, H. J., Kawasawa, Y. I., Cheng, F., Zhu, Y., Xu, X., Li, M., Sousa, A. M. M., Pletikos, M., Meyer, K. A., Sedmak, G., Guennel, T., Shin, Y., Johnson, M. B., Krsnik, Ž., Mayer, S., Fertuzinhos, S., Umlauf, S., Lisgo, S. N., Vortmeyer, A., ... Šestan, N. (2011). Spatio-temporal transcriptome of the human brain. *Nature*, 478, 483–489. <https://doi.org/10.1038/nature10523>
- Kazek, B., Huzarska, M., Grzybowska-Chlebowczyk, U., Kajor, M., Ciupińska-Kajor, M., Woś, H., & Marszał, E. (2010). Platelet and intestinal 5-HT<sub>2A</sub> receptor mRNA in autistic spectrum disorders—Results of a pilot study. *Acta Neurobiologiae Experimentalis (Wars)*, 70, 232–238.
- Khan, M. Z., & He, L. (2017). Neuro-psychopharmacological perspective of Orphan receptors of Rhodopsin (class A) family of G protein-coupled receptors. *Psychopharmacology*, 234, 1181–1207. <https://doi.org/10.1007/s00213-017-4586-9>
- Kitagawa, K., Matsumura, K., Baba, M., Kondo, M., Takemoto, T., Nagayasu, K., Ago, Y., Seiriki, K., Hayata-Takano, A., Kasai, A., Takuma, K., Hashimoto, R., Hashimoto, H., & Nakazawa, T. (2021). Intranasal oxytocin administration ameliorates social behavioral deficits in a *POGZ*<sup>WT/Q1038R</sup> mouse model of autism spectrum disorder. *Molecular Brain*, 14, 56. <https://doi.org/10.1186/s13041-021-00769-8>
- Kolb, P., Kenakin, T., Alexander, S. P. H., Bermudez, M., Bohn, L. M., Breinholt, C. S., Bouvier, M., Hill, S. J., Kostenis, E., Martemyanov, K. A., Neubig, R. R., Onaran, H. O., Rajagopal, S., Roth, B. L., Selent, J., Shukla, A. K., Sommer, M. E., & Gloriam, D. E. (2022). Community guidelines for GPCR ligand bias: IUPHAR review 32. *British Journal of Pharmacology*, 179, 3651–3674. <https://doi.org/10.1111/bph.15811>
- Koshimizu, T., Nakamura, K., Egashira, N., Hiroshima, M., Nonoguchi, H., & Tanoue, A. (2012). Vasopressin V1a and V1b receptors: From molecules to physiological systems. *Physiological Reviews*, 92, 1813–1864. <https://doi.org/10.1152/physrev.00035.2011>
- Kvachnina, E., Liu, G., Dityateva, A., Renner, U., Dumuis, A., Richter, D. W., Dityateva, G., Schachner, M., Voyno-Yasenetskaya, T. A., & Ponimaskin, E. G. (2005). 5-HT<sub>7</sub> receptor is coupled to G alpha subunits of heterotrimeric G12-protein to regulate gene transcription and neuronal morphology. *The Journal of Neuroscience*, 25, 7821–7830. <https://doi.org/10.1523/JNEUROSCI.1790-05.2005>
- Kwan, A. C., Olson, D. E., Preller, K. H., & Roth, B. L. (2022). The neural basis of psychedelic action. *Nature Neuroscience*, 25, 1407–1419. <https://doi.org/10.1038/s41593-022-01177-4>
- Laboute, T., Gandía, J., Pellissier, L. P., Corde, Y., Rebeillard, F., Gallo, M., Gauthier, C., Léauté, A., Diaz, J., Poupon, A., Kieffer, B. L., le Merrer, J., & Becker, J. A. J. (2020). The orphan receptor GPR88 blunts the signaling of opioid receptors and multiple striatal GPCRs. *eLife*, 9, e50519. <https://doi.org/10.7554/eLife.50519>
- Lacivita, E., Niso, M., Mastromarino, M., Garcia Silva, A., Resch, C., Zeug, A., Loza, M. I., Castro, M., Ponimaskin, E., & Leopoldo, M. (2021). Knowledge-based design of long-chain arylpiperazine derivatives targeting multiple serotonin receptors as potential candidates for treatment of autism spectrum disorder. *ACS Chemical Neuroscience*, 12, 1313–1327. <https://doi.org/10.1021/acscchemneuro.0c00647>
- Lacivita, E., Perrone, R., Margari, L., & Leopoldo, M. (2017). Targets for drug therapy for autism spectrum disorder: Challenges and future directions. *Journal of Medicinal Chemistry*, 60, 9114–9141. <https://doi.org/10.1021/acscimedchem.7b00965>
- Lee, H.-J., Caldwell, H. K., Macbeth, A. H., & Young, W. S. (2008). Behavioural studies using temporal and spatial inactivation of the oxytocin receptor. *Progress in Brain Research*, 170, 73–77. [https://doi.org/10.1016/S0079-6123\(08\)00407-X](https://doi.org/10.1016/S0079-6123(08)00407-X)
- Lee, J., Kwag, R., Lee, S., Kim, D., Woo, J., Cho, Y., Kim, H. J., Kim, J., Jeon, B., & Choo, H. (2021). Discovery of G protein-biased ligands against 5-HT<sub>7R</sub>. *Journal of Medicinal Chemistry*, 64, 7453–7467. <https://doi.org/10.1021/acscimedchem.1c00110>
- Lee, Y., & Han, P.-L. (2019). Early-life stress in D2 heterozygous mice promotes autistic-like behaviors through the downregulation of the BDNF-TrkB pathway in the dorsal striatum. *Experimental Neurobiology*, 28, 337–351. <https://doi.org/10.5607/en.2019.28.3.337>
- Lee, Y., Kim, H., Kim, J.-E., Park, J.-Y., Choi, J., Lee, J.-E., Lee, E. H., & Han, P. L. (2018). Excessive D1 dopamine receptor activation in the dorsal striatum promotes autistic-like behaviors. *Molecular Neurobiology*, 55, 5658–5671. <https://doi.org/10.1007/s12035-017-0770-5>
- León, K., Boulo, T., Musnier, A., Morales, J., Gauthier, C., Dupuy, L., Heyne, S., Backofen, R., Poupon, A., Cormier, P., Reiter, E., & Crépeux, P. (2014). Activation of a GPCR leads to eIF4G phosphorylation at the 5' cap and to IRES-dependent translation. *Journal of Molecular Endocrinology*, 52, 373–382. <https://doi.org/10.1530/JME-14-0009>
- Leppanen, J., Ng, K. W., Kim, Y.-R., Tchanturia, K., & Treasure, J. (2018). Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. *Journal of Affective Disorders*, 225, 167–179. <https://doi.org/10.1016/j.jad.2017.08.041>
- Lewis, M. H., Rajpal, H., & Muehlmann, A. M. (2019). Reduction of repetitive behavior by co-administration of adenosine receptor agonists in C58 mice. *Pharmacology, Biochemistry, and Behavior*, 181, 110–116. <https://doi.org/10.1016/j.pbb.2019.04.006>
- Li, W., & Pozzo-Miller, L. (2020). Dysfunction of the corticostriatal pathway in autism spectrum disorders. *Journal of Neuroscience Research*, 98, 2130–2147. <https://doi.org/10.1002/jnr.24560>
- Li, X., Gardner, E. L., & Xi, Z.-X. (2008). The metabotropic glutamate receptor 7 (mGluR7) allosteric agonist AMN082 modulates nucleus accumbens GABA and glutamate, but not dopamine, in rats. *Neuropharmacology*, 54, 542–551. <https://doi.org/10.1016/j.neuropharm.2007.11.005>
- Lindenmaier, Z., Ellegood, J., Stuiwe, M., Easson, K., Yee, Y., Fernandes, D., Foster, J., Anagnostou, E., & Lerch, J. P. (2022). Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy

- and behavior of three autism-related mouse models. *NeuroImage*, 257, 119243. <https://doi.org/10.1016/j.neuroimage.2022.119243>
- Linstead, E., Dixon, D. R., Hong, E., Burns, C. O., French, R., Novack, M. N., & Granpeesheh, D. (2017). An evaluation of the effects of intensity and duration on outcomes across treatment domains for children with autism spectrum disorder. *Translational Psychiatry*, 7, e1234. <https://doi.org/10.1038/tp.2017.207>
- Litvin, Y., Phan, A., Hill, M. N., Pfaff, D. W., & McEwen, B. S. (2013). CB1 receptor signaling regulates social anxiety and memory. *Genes, Brain, and Behavior*, 12, 479–489. <https://doi.org/10.1111/gbb.12045>
- Liu, J., Fu, H., Kong, J., Yu, H., & Zhang, Z. (2021). Association between autism spectrum disorder and polymorphisms in genes encoding serotone and dopamine receptors. *Metabolic Brain Disease*, 36, 865–870. <https://doi.org/10.1007/s11011-021-00699-3>
- Lohith, T. G., Osterweil, E. K., Fujita, M., Jenko, K. J., Bear, M. F., & Innis, R. B. (2013). Is metabotropic glutamate receptor 5 upregulated in prefrontal cortex in fragile X syndrome? *Molecular Autism*, 4, 15. <https://doi.org/10.1186/2040-2392-4-15>
- Lozano, R., Martinez-Cerdeno, V., & Hagerman, R. J. (2015). Advances in the understanding of the GABAergic neurobiology of FMR1 expanded alleles leading to targeted treatments for fragile X spectrum disorder. *Current Pharmaceutical Design*, 21, 4972–4979. <https://doi.org/10.2174/1381612821666150914121038>
- Lukens, J. R., & Eyo, U. B. (2022). Microglia and neurodevelopmental disorders. *Annual Review of Neuroscience*, 45, 425–445. <https://doi.org/10.1146/annurev-neuro-110920-023056>
- Lüscher, C., Jan, L. Y., Stoffel, M., Malenka, R. C., & Nicoll, R. A. (1997). G protein-coupled inwardly rectifying K<sup>+</sup> channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron*, 19, 687–695. [https://doi.org/10.1016/S0896-6273\(00\)80381-5](https://doi.org/10.1016/S0896-6273(00)80381-5)
- Macdonald, K., & Macdonald, T. M. (2010). The peptide that binds: A systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*, 18, 1–21. <https://doi.org/10.3109/10673220903523615>
- Madsen, D., Azevedo, C., Micco, I., Petersen, L. K., & Hansen, N. J. V. (2020). An overview of DNA-encoded libraries: A versatile tool for drug discovery. *Progress in Medicinal Chemistry*, 59, 181–249. <https://doi.org/10.1016/bs.pmch.2020.03.001>
- Maguire, G. A., Riley, G. D., Franklin, D. L., Maguire, M. E., Nguyen, C. T., & Brojeni, P. H. (2004). Olanzapine in the treatment of developmental stuttering: A double-blind, placebo-controlled trial. *Annals of Clinical Psychiatry*, 16, 63–67. <https://doi.org/10.1080/10401230490452834>
- Mahdavinassab, S.-M., Saghazadeh, A., Motamed-Gorji, N., Vaseghi, S., Mohammadi, M.-R., Alichani, R., & Akhondzadeh, S. (2019). Baclofen as an adjuvant therapy for autism: A randomized, double-blind, placebo-controlled trial. *European Child & Adolescent Psychiatry*, 28, 1619–1628. <https://doi.org/10.1007/s00787-019-01333-5>
- Manahan-Vaughan, D., & Reymann, K. G. (1995). Regional and developmental profile of modulation of hippocampal synaptic transmission and LTP by AP4-sensitive mGluRs in vivo. *Neuropharmacology*, 34, 991–1001. [https://doi.org/10.1016/0028-3908\(95\)00081-G](https://doi.org/10.1016/0028-3908(95)00081-G)
- Mandillo, S., Golini, E., Marazziti, D., Di Pietro, C., Matteoni, R., & Tocchini-Valentini, G. P. (2013). Mice lacking the Parkinson's related GPR37/PAEL receptor show non-motor behavioral phenotypes: Age and gender effect. *Genes, Brain, and Behavior*, 12, 465–477. <https://doi.org/10.1111/gbb.12041>
- Manoli, D. S., & State, M. W. (2021). Autism spectrum disorder genetics and the search for pathological mechanisms. *The American Journal of Psychiatry*, 178, 30–38. <https://doi.org/10.1176/appi.ajp.2020.20111608>
- Mantella, R. C., Vollmer, R. R., Li, X., & Amico, J. A. (2003). Female oxytocin-deficient mice display enhanced anxiety-related behavior. *Endocrinology*, 144, 2291–2296. <https://doi.org/10.1210/en.2002-0197>
- Marazziti, D., Di Pietro, C., Mandillo, S., Golini, E., Matteoni, R., & Tocchini-Valentini, G. P. (2011). Absence of the GPR37/PAEL receptor impairs striatal Akt and ERK2 phosphorylation, DeltaFosB expression, and conditioned place preference to amphetamine and cocaine. *The FASEB Journal*, 25, 2071–2081. <https://doi.org/10.1096/fj.10-175737>
- Marazziti, D., Mandillo, S., Di Pietro, C., Golini, E., Matteoni, R., & Tocchini-Valentini, G. P. (2007). GPR37 associates with the dopamine transporter to modulate dopamine uptake and behavioral responses to dopaminergic drugs. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 9846–9851. <https://doi.org/10.1073/pnas.0703368104>
- Marti-Solano, M., Crilly, S. E., Malinverni, D., Munk, C., Harris, M., Pearce, A., Quon, T., Mackenzie, A. E., Wang, X., Peng, J., Tobin, A. B., Ladds, G., Milligan, G., Gloriam, D. E., Puthenveedu, M. A., & Babu, M. M. (2020). Combinatorial expression of GPCR isoforms affects signalling and drug responses. *Nature*, 587, 650–656. <https://doi.org/10.1038/s41586-020-2888-2>
- Matsumoto, M., Straub, R. E., Marengo, S., Nicodemus, K. K., Matsumoto, S.-I., Fujikawa, A., Miyoshi, S., Shobo, M., Takahashi, S., Yarimizu, J., Yuri, M., Hiramoto, M., Morita, S., Yokota, H., Sasayama, T., Terai, K., Yoshino, M., Miyake, A., Callicott, J. H., ... Weinberger, D. R. (2008). The evolutionarily conserved G protein-coupled receptor SREB2/GPR85 influences brain size, behavior, and vulnerability to schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 6133–6138. <https://doi.org/10.1073/pnas.0710717105>
- McCracken, J. T., McGough, J., Shah, B., Cronin, P., Hong, D., Aman, M. G., Arnold, L. E., Lindsay, R., Nash, P., Hollway, J., McDougle, C. J., Posey, D., Swiezy, N., Kohn, A., Scahill, L., Martin, A., Koenig, K., Volkmar, F., Carroll, D., ... McMahon, D. (2002). Risperidone in children with autism and serious behavioral problems. *The New England Journal of Medicine*, 347, 314–321. <https://doi.org/10.1056/NEJMoa013171>
- McDougle, C. J., Scahill, L., Aman, M. G., McCracken, J. T., Tierney, E., Davies, M., Arnold, L. E., Posey, D. J., Martin, A., Ghuman, J. K., Shah, B., Chuang, S. Z., Swiezy, N. B., Gonzalez, N. M., Hollway, J., Koenig, K., McGough, J. J., Ritz, L., & Vitiello, B. (2005). Risperidone for the core symptom domains of autism: Results from the study by the autism network of the research units on pediatric psychopharmacology. *The American Journal of Psychiatry*, 162, 1142–1148. <https://doi.org/10.1176/appi.ajp.162.6.1142>
- McNamara, F. N., Clifford, J. J., Tighe, O., Kinsella, A., Drago, J., Croke, D. T., & Waddington, J. L. (2003). Congenic D1A dopamine receptor mutants: Ethologically based resolution of behavioural topography indicates genetic background as a determinant of knockout phenotype. *Neuropsychopharmacology*, 28, 86–99. <https://doi.org/10.1038/sj.npp.1300008>
- Meyer-Lindenberg, A., Kolachana, B., Gold, B., Olsh, A., Nicodemus, K. K., Mattay, V., Dean, M., & Weinberger, D. R. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Molecular Psychiatry*, 14, 968–975. <https://doi.org/10.1038/mp.2008.54>
- Meziane, H., Schaller, F., Bauer, S., Villard, C., Matarazzo, V., Riet, F., Guillon, G., Lafitte, D., Desarmenien, M. G., Tauber, M., & Muscatelli, F. (2015). An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for *Magel2*, a gene involved in Prader-Willi syndrome and autism. *Biological Psychiatry*, 78, 85–94. <https://doi.org/10.1016/j.biopsych.2014.11.010>
- Ming, X., Gordon, E., Kang, N., & Wagner, G. C. (2008). Use of clonidine in children with autism spectrum disorders. *Brain and Development*, 30, 454–460. <https://doi.org/10.1016/j.braindev.2007.12.007>
- Mishra, A., Singh, S., & Shukla, S. (2018). Physiological and functional basis of dopamine receptors and their role in neurogenesis: Possible implication for Parkinson's disease. *Journal of Experimental Neurology*, 12, 1179069518779829. <https://doi.org/10.1177/1179069518779829>

- Mitsukawa, K., Yamamoto, R., Ofner, S., Nozulak, J., Pescott, O., Lukic, S., Stoehr, N., Mombereau, C., Kuhn, R., McAllister, K. H., van der Putten, H., Cryan, J. F., & Flor, P. J. (2005). A selective metabotropic glutamate receptor 7 agonist: Activation of receptor signaling via an allosteric site modulates stress parameters in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 18712–18717. <https://doi.org/10.1073/pnas.0508063102>
- Mombereau, C., Kaupmann, K., Gassmann, M., Bettler, B., van der Putten, H., & Cryan, J. F. (2005). Altered anxiety and depression-related behaviour in mice lacking GABA<sub>B(2)</sub> receptor subunits. *Neuroreport*, 16, 307–310. <https://doi.org/10.1097/00001756-200502280-00021>
- Monfared, R. V., Alhassen, W., Truong, T. M., Gonzales, M. A. M., Vachirakornpong, V., Chen, S., Baldi, P., Civelli, O., & Alachkar, A. (2021). Transcriptome profiling of dysregulated GPCRs reveals overlapping patterns across psychiatric disorders and age-disease interactions. *Cell*, 10, 2967. <https://doi.org/10.3390/cells10112967>
- Mujić-Delić, A., de Wit, R. H., Verkaar, F., & Smit, M. J. (2014). GPCR-targeting nanobodies: Attractive research tools, diagnostics, and therapeutics. *Trends in Pharmacological Sciences*, 35, 247–255. <https://doi.org/10.1016/j.tips.2014.03.003>
- Muller, C. L., Anacker, A. M. J., & Veenstra-VanderWeele, J. (2016). The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience*, 321, 24–41. <https://doi.org/10.1016/j.neuroscience.2015.11.010>
- Murphy, D. G. M., Daly, E., Schmitz, N., Toal, F., Murphy, K., Curran, S., Erlandsson, K., Eersels, J., Kerwin, R., Ell, P., & Travis, M. (2006). Cortical serotonin 5-HT<sub>2A</sub> receptor binding and social communication in adults with Asperger's syndrome: An in vivo SPECT study. *The American Journal of Psychiatry*, 163, 934–936. <https://doi.org/10.1176/ajp.2006.163.5.934>
- Musnier, A., León, K., Morales, J., Reiter, E., Boulo, T., Costache, V., Vourc'h, P., Heitzler, D., Oulhen, N., Poupon, A., Boulben, S., Cormier, P., & Crépieux, P. (2012). mRNA-selective translation induced by FSH in primary Sertoli cells. *Molecular Endocrinology*, 26, 669–680. <https://doi.org/10.1210/me.2011-1267>
- Nakai, N., Nagano, M., Saitow, F., Watanabe, Y., Kawamura, Y., Kawamoto, A., Tamada, K., Mizuma, H., Onoe, H., Watanabe, Y., Monai, H., Hirase, H., Nakatani, J., Inagaki, H., Kawada, T., Miyazaki, T., Watanabe, M., Sato, Y., Okabe, S., ... Takumi, T. (2017). Serotonin rebalances cortical tuning and behavior linked to autism symptoms in 15q11-13 CNV mice. *Science Advances*, 3, e1603001. <https://doi.org/10.1126/sciadv.1603001>
- Negyessy, L., & Goldman-Rakic, P. S. (2005). Subcellular localization of the dopamine D2 receptor and coexistence with the calcium-binding protein neuronal calcium sensor-1 in the primate prefrontal cortex. *The Journal of Comparative Neurology*, 488, 464–475. <https://doi.org/10.1002/cne.20601>
- Nelson, S. B., & Valakh, V. (2015). Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. *Neuron*, 87, 684–698. <https://doi.org/10.1016/j.neuron.2015.07.033>
- Nephew, B. C., & Bridges, R. S. (2008). Arginine vasopressin V1a receptor antagonist impairs maternal memory in rats. *Physiology & Behavior*, 95, 182–186. <https://doi.org/10.1016/j.physbeh.2008.05.016>
- Nisar, S., Bhat, A. A., Masoodi, T., Hashem, S., Akhtar, S., Ali, T. A., Amjad, S., Chawla, S., Bagga, P., Frenneaux, M. P., Reddy, R., Fakhro, K., & Haris, M. (2022). Genetics of glutamate and its receptors in autism spectrum disorder. *Molecular Psychiatry*, 27, 2380–2392. <https://doi.org/10.1038/s41380-022-01506-w>
- Oblak, A., Gibbs, T. T., & Blatt, G. J. (2013). Reduced serotonin receptor subtypes in a limbic and a neocortical region in autism. *Autism Research*, 6, 571–583. <https://doi.org/10.1002/aur.1317>
- Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2010). Decreased GABA<sub>B</sub> receptors in the cingulate cortex and fusiform gyrus in autism. *Journal of Neurochemistry*, 114, 1414–1423. <https://doi.org/10.1111/j.1471-4159.2010.06858.x>
- Olender, T., Jones, T. E. M., Bruford, E., & Lancet, D. (2020). A unified nomenclature for vertebrate olfactory receptors. *BMC Evolutionary Biology*, 20, 42. <https://doi.org/10.1186/s12862-020-01607-6>
- Olender, T., Keydar, I., Pinto, J. M., Tatarsky, P., Alkelai, A., Chien, M.-S., Fishilevich, S., Restrepo, D., Matsunami, H., Gilad, Y., & Lancet, D. (2016). The human olfactory transcriptome. *BMC Genomics*, 17, 619. <https://doi.org/10.1186/s12864-016-2960-3>
- O'Roak, B. J., Vives, L., Girirajan, S., Karakoc, E., Krumm, N., Coe, B. P., Levy, R., Ko, A., Lee, C., Smith, J. D., Turner, E. H., Stanaway, I. B., Vernot, B., Malig, M., Baker, C., Reilly, B., Akey, J. M., Borenstein, E., Rieder, M. J., ... Eichler, E. E. (2012). Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature*, 485, 246–250. <https://doi.org/10.1038/nature10989>
- Owen, R., Sikich, L., Marcus, R. N., Corey-Lisle, P., Manos, G., McQuade, R. D., Carson, W. H., & Findling, R. L. (2009). Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*, 124, 1533–1540. <https://doi.org/10.1542/peds.2008-3782>
- Park, S. M., Chen, M., Schmerberg, C. M., Dulman, R. S., Rodriguiz, R. M., Caron, M. G., Jin, J., & Wetsel, W. C. (2016). Effects of  $\beta$ -arrestin-biased dopamine D2 receptor ligands on schizophrenia-like behavior in hypoglutamatergic mice. *Neuropsychopharmacology*, 41, 704–715. <https://doi.org/10.1038/npp.2015.196>
- Parker, K. J., Oztan, O., Libove, R. A., Mohsin, N., Karhson, D. S., Sumiyoshi, R. D., Summers, J. E., Hinman, K. E., Motonaga, K. S., Phillips, J. M., Carson, D. S., Fung, L. K., Garner, J. P., & Hardan, A. Y. (2019). A randomized placebo-controlled pilot trial shows that intranasal vasopressin improves social deficits in children with autism. *Science Translational Medicine*, 11, eaau7356. <https://doi.org/10.1126/scitranslmed.aau7356>
- Passoni, I., Leonzino, M., Gliucci, V., Chini, B., & Busnelli, M. (2016). Carbetocin is a functional selective Gq agonist that does not promote oxytocin receptor recycling after inducing  $\beta$ -arrestin-independent internalisation. *Journal of Neuroendocrinology*, 28(4), 491. <https://doi.org/10.1111/jne.12363>
- Pellissier, L. P., Pujol, C. N., Becker, J. A. J., & Le Merrer, J. (2018). Delta opioid receptors: Learning and motivation. *Handbook of Experimental Pharmacology*, 247, 227–260. [https://doi.org/10.1007/164\\_2016\\_89](https://doi.org/10.1007/164_2016_89)
- Peñagarikano, O., Lázaro, M. T., Lu, X.-H., Gordon, A., Dong, H., Lam, H. A., Peles, E., Maidment, N. T., Murphy, N. P., Yang, X. W., Golshani, P., & Geschwind, D. H. (2015). Exogenous and evoked oxytocin restores social behavior in the *Cntnap2* mouse model of autism. *Science Translational Medicine*, 7, 271ra8. <https://doi.org/10.1126/scitranslmed.3010257>
- Perry, E. K., Lee, M. L., Martin-Ruiz, C. M., Court, J. A., Volsen, S. G., Merrit, J., Folly, E., Iversen, P. E., Bauman, M. L., Perry, R. H., & Wenk, G. L. (2001). Cholinergic activity in autism: Abnormalities in the cerebral cortex and basal forebrain. *The American Journal of Psychiatry*, 158, 1058–1066. <https://doi.org/10.1176/appi.ajp.158.7.1058>
- Petit, A.-C., Quesseveur, G., Gressier, F., Colle, R., David, D. J., Gardier, A. M., Ferreri, F., Lépine, J. P., Falissard, B., Verstuyft, C., Guiard, B. P., & Corruble, E. (2014). Converging translational evidence for the involvement of the serotonin 2A receptor gene in major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 54, 76–82. <https://doi.org/10.1016/j.pnpb.2014.04.013>
- Piirainen, S., Chithanathan, K., Bisht, K., Piirsalu, M., Savage, J. C., Tremblay, M.-E., & Tian, L. (2021). Microglia contribute to social behavioral adaptation to chronic stress. *Glia*, 69, 2459–2473. <https://doi.org/10.1002/glia.24053>
- Pintacuda, G., Hsu, Y.-H. H., Tsafou, K., Li, K. W., Martín, J. M., Riseman, J., Biagini, J. C., Ching, J. K. T., Mena, D., Gonzalez-Lozano, M. A., Egri, S. B., Jaffe, J., Smit, A. B., Fornelos, N., Eggen, K. C., & Lage, K.

- (2023). Protein interaction studies in human induced neurons indicate convergent biology underlying autism spectrum disorders. *Cell Genomics*, 3(3), 100250. <https://doi.org/10.1016/j.xgen.2022.100250>
- Pobbe, R. L. H., Pearson, B. L., Defensor, E. B., Bolivar, V. J., Young, W. S., Lee, H.-J., Blanchard, D. C., & Blanchard, R. J. (2012). Oxytocin receptor knockout mice display deficits in the expression of autism-related behaviors. *Hormones and Behavior*, 61, 436–444. <https://doi.org/10.1016/j.yhbeh.2011.10.010>
- Poulin, B., Butcher, A., McWilliams, P., Bourgognon, J.-M., Pawlak, R., Kong, K. C., Bottrill, A., Mistry, S., Wess, J., Rosethorne, E. M., Charlton, S. J., & Tobin, A. B. (2010). The M3-muscarinic receptor regulates learning and memory in a receptor phosphorylation/arrestin-dependent manner. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 9440–9445. <https://doi.org/10.1073/pnas.0914801107>
- Pourhamzeh, M., Moravej, F. G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., Ahadi, R., & Joghataei, M. T. (2022). The roles of serotonin in neuropsychiatric disorders. *Cellular and Molecular Neurobiology*, 42, 1671–1692. <https://doi.org/10.1007/s10571-021-01064-9>
- Pringsheim, T., & Marras, C. (2009). Pimozide for tics in Tourette's syndrome. *Cochrane Database of Systematic Reviews*, 2009, CD006996. <https://doi.org/10.1002/14651858.CD006996.pub2>
- Rae, M., Lemos Duarte, M., Gomes, I., Camarini, R., & Devi, L. A. (2022). Oxytocin and vasopressin: Signalling, behavioural modulation and potential therapeutic effects. *British Journal of Pharmacology*, 179, 1544–1564. <https://doi.org/10.1111/bph.15481>
- Ragnauth, A. K., Devidze, N., Moy, V., Finley, K., Goodwillie, A., Kow, L.-M., Muglia, L. J., & Pfaff, D. W. (2005). Female oxytocin gene-knockout mice, in a semi-natural environment, display exaggerated aggressive behavior. *Genes, Brain, and Behavior*, 4, 229–239. <https://doi.org/10.1111/j.1601-183X.2005.00118.x>
- Regard, J. B., Sato, I. T., & Coughlin, S. R. (2008). Anatomical profiling of G protein-coupled receptor expression. *Cell*, 135, 561–571. <https://doi.org/10.1016/j.cell.2008.08.040>
- Román, V., Adham, N., Foley, A. G., Hanratty, L., Farkas, B., Lendvai, B., & Kiss, B. (2021). Cariprazine alleviates core behavioral deficits in the prenatal valproic acid exposure model of autism spectrum disorder. *Psychopharmacology*, 238, 2381–2392. <https://doi.org/10.1007/s00213-021-05851-6>
- Ruzzo, E. K., Pérez-Cano, L., Jung, J.-Y., Wang, L.-K., Kashef-Haghighi, D., Hartl, C., Singh, C., Xu, J., Hoekstra, J. N., Leventhal, O., Leppä, V. M., Gandal, M. J., Paskov, K., Stockham, N., Polioudakis, D., Lowe, J. K., Prober, D. A., Geschwind, D. H., & Wall, D. P. (2019). Inherited and de novo genetic risk for autism impacts shared networks. *Cell*, 178, 850–866.e26. <https://doi.org/10.1016/j.cell.2019.07.015>
- Sala, M., Braidà, D., Donzelli, A., Martucci, R., Busnelli, M., Bulgheroni, E., Rubino, T., Parolaro, D., Nishimori, K., & Chini, B. (2013). Mice heterozygous for the oxytocin receptor gene (*Oxtr*<sup>+/-</sup>) show impaired social behaviour but not increased aggression or cognitive inflexibility: Evidence of a selective haploinsufficiency gene effect. *Journal of Neuroendocrinology*, 25, 107–118. <https://doi.org/10.1111/j.1365-2826.2012.02385.x>
- Sala, M., Braidà, D., Lentini, D., Busnelli, M., Bulgheroni, E., Capurro, V., Finardi, A., Donzelli, A., Pattini, L., Rubino, T., Parolaro, D., Nishimori, K., Parenti, M., & Chini, B. (2011). Pharmacologic rescue of impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: A neurobehavioral model of autism. *Biological Psychiatry*, 69, 875–882. <https://doi.org/10.1016/j.biopsych.2010.12.022>
- Salomé, N., Stemmelin, J., Cohen, C., & Griebel, G. (2006). Differential roles of amygdaloid nuclei in the anxiolytic- and antidepressant-like effects of the V1b receptor antagonist, SSR149415, in rats. *Psychopharmacology*, 187, 237–244. <https://doi.org/10.1007/s00213-006-0424-1>
- Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J.-Y., Peng, M., Collins, R., Grove, J., Klei, L., Stevens, C., Reichert, J., Mulhern, M. S., Artomov, M., Gerges, S., Sheppard, B., Xu, X., Bhaduri, A., Norman, U., ... Walters, R. K. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*, 180, 568–584.e23. <https://doi.org/10.1016/j.cell.2019.12.036>
- Saxena, R., Babadi, M., Namvarhaghighi, H., & Roulet, F. I. (2020). Role of environmental factors and epigenetics in autism spectrum disorders. *Progress in Molecular Biology and Translational Science*, 173, 35–60. <https://doi.org/10.1016/bs.pmbts.2020.05.002>
- Scattoni, M., McFarlane, H., Zhodzishsky, V., Caldwell, H., Young, W., Ricceri, L., & Crawley, J. (2008). Reduced ultrasonic vocalizations in vasopressin 1b knockout mice. *Behavioural Brain Research*, 187, 371–378. <https://doi.org/10.1016/j.bbr.2007.09.034>
- Scerbins, T., Chatterjee, D., & Gerlai, R. (2012). Dopamine receptor antagonism disrupts social preference in zebrafish: A strain comparison study. *Amino Acids*, 43, 2059–2072. <https://doi.org/10.1007/s00726-012-1284-0>
- Scharf, S. H., Jaeschke, G., Wettstein, J. G., & Lindemann, L. (2015). Metabotropic glutamate receptor 5 as drug target for Fragile X syndrome. *Current Opinion in Pharmacology*, 20, 124–134. <https://doi.org/10.1016/j.coph.2014.11.004>
- Schiavi, S., Manduca, A., Carbone, E., Buzzelli, V., Rava, A., Feo, A., Ascone, F., Morena, M., Campolongo, P., Hill, M. N., & Trezza, V. (2023). Anandamide and 2-arachidonoylglycerol differentially modulate autistic-like traits in a genetic model of autism based on FMR1 deletion in rats. *Neuropsychopharmacology*, 48, 897–907. <https://doi.org/10.1038/s41386-022-01454-7>
- Schlicker, E., Werner, U., Hamon, M., Gozlan, H., Nickel, B., Szelenyi, I., & Göthert, M. (1992). Anpirtoline, a novel, highly potent 5-HT<sub>1B</sub> receptor agonist with antinociceptive/antidepressant-like actions in rodents. *British Journal of Pharmacology*, 105, 732–738. <https://doi.org/10.1111/j.1476-5381.1992.tb09047.x>
- Schnider, P., Bissantz, C., Bruns, A., Dolente, C., Goetschi, E., Jakob-Roetne, R., Künnecke, B., Mueggler, T., Muster, W., Parrott, N., Pinard, E., Ratni, H., Risterucci, C., Rogers-Evans, M., von Kienlin, M., & Grundschober, C. (2020). Discovery of balovaptan, a vasopressin 1a receptor antagonist for the treatment of autism spectrum disorder. *Journal of Medicinal Chemistry*, 63, 1511–1525. <https://doi.org/10.1021/acs.jmedchem.9b01478>
- Sikich, L., Kolevzon, A., King, B. H., McDougale, C. J., Sanders, K. B., Kim, S.-J., Spanos, M., Chandrasekhar, T., Trelles, M. D. P., Rockhill, C. M., Palumbo, M. L., Witters Cundiff, A., Montgomery, A., Siper, P., Minjarez, M., Nowinski, L. A., Marler, S., Shuffrey, L. C., Alderman, C., ... Veenstra-VanderWeele, J. (2021). Intranasal oxytocin in children and adolescents with autism spectrum disorder. *The New England Journal of Medicine*, 385, 1462–1473. <https://doi.org/10.1056/NEJMoa2103583>
- Silverman, J. L., Pride, M. C., Hayes, J. E., Puhger, K. R., Butler-Struben, H. M., Baker, S., & Crawley, J. N. (2015). GABA<sub>B</sub> receptor agonist R-baclofen reverses social deficits and reduces repetitive behavior in two mouse models of autism. *Neuropsychopharmacology*, 40, 2228–2239. <https://doi.org/10.1038/npp.2015.66>
- Smith, R. M., Banks, W., Hansen, E., Sadee, W., & Herman, G. E. (2014). Family-based clinical associations and functional characterization of the serotonin 2A receptor gene (*HTR2A*) in autism spectrum disorder. *Autism Research*, 7, 459–467. <https://doi.org/10.1002/aur.1383>
- Smith, T., Klorman, R., & Mruzek, D. W. (2015). Predicting outcome of community-based early intensive behavioral intervention for children with autism. *Journal of Abnormal Child Psychology*, 43, 1271–1282. <https://doi.org/10.1007/s10802-015-0002-2>
- Song, J.-M., Kang, M., Park, D.-H., Park, S., Lee, S., & Suh, Y. H. (2021). Pathogenic GRM7 mutations associated with neurodevelopmental disorders impair axon outgrowth and presynaptic terminal development. *The Journal of Neuroscience*, 41, 2344–2359. <https://doi.org/10.1523/JNEUROSCI.2108-20.2021>

- Soriano, S. G., Amaravadi, L. S., Wang, Y. F., Zhou, H., Yu, G. X., Tonra, J. R., Fairchild-Huntress, V., Fang, Q., Dunmore, J. H., Huszar, D., & Pan, Y. (2002). Mice deficient in fractalkine are less susceptible to cerebral ischemia-reperfusion injury. *Journal of Neuroimmunology*, 125, 59–65. [https://doi.org/10.1016/S0165-5728\(02\)00033-4](https://doi.org/10.1016/S0165-5728(02)00033-4)
- Soumier, A., Habart, M., Lio, G., Demily, C., & Sirigu, A. (2022). Differential fate between oxytocin and vasopressin cells in the developing mouse brain. *iScience*, 25, 103655. <https://doi.org/10.1016/j.isci.2021.103655>
- Speranza, L., Labus, J., Volpicelli, F., Guseva, D., Lacivita, E., Leopoldo, M., Bellenchi, G. C., di Porzio, U., Bijata, M., Perrone-Capano, C., & Ponimaskin, E. (2017). Serotonin 5-HT7 receptor increases the density of dendritic spines and facilitates synaptogenesis in forebrain neurons. *Journal of Neurochemistry*, 141, 647–661. <https://doi.org/10.1111/jnc.13962>
- Stahl, E. L., Schmid, C. L., Acevedo-Canabal, A., Read, C., Grim, T. W., Kennedy, N. M., Bannister, T. D., & Bohn, L. M. (2021). G protein signaling-biased mu opioid receptor agonists that produce sustained G protein activation are noncompetitive agonists. *Proceedings of the National Academy of Sciences of the United States of America*, 118, e2102178118. <https://doi.org/10.1073/pnas.2102178118>
- Surget, A., & Belzung, C. (2008). Involvement of vasopressin in affective disorders. *European Journal of Pharmacology*, 583, 340–349. <https://doi.org/10.1016/j.ejphar.2007.11.065>
- Szczepanska-Sadowska, E., Wsol, A., Cudnoch-Jedrzejewska, A., Czarzasta, K., & Zera, T. (2022). Multiple aspects of inappropriate action of renin-angiotensin, vasopressin, and oxytocin systems in neuropsychiatric and neurodegenerative diseases. *Journal of Clinical Medicine*, 11, 908. <https://doi.org/10.3390/jcm11040908>
- Takayanagi, Y., Yoshida, M., Bielsky, I. F., Ross, H. E., Kawamata, M., Onaka, T., Yanagisawa, T., Kimura, T., Matzuk, M. M., Young, L. J., & Nishimori, K. (2005). Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 16096–16101. <https://doi.org/10.1073/pnas.0505312102>
- Taylor, J. H., Walton, J. C., McCann, K. E., Norvelle, A., Liu, Q., Vander Velden, J. W., Borland, J. M., Hart, M., Jin, C., Huhman, K. L., Cox, D. N., & Albers, H. E. (2022). CRISPR-Cas9 editing of the arginine-vasopressin V1a receptor produces paradoxical changes in social behavior in Syrian hamsters. *Proceedings of the National Academy of Sciences of the United States of America*, 119, e2121037119. <https://doi.org/10.1073/pnas.2121037119>
- Terrillon, S., Durrroux, T., Mouillac, B., Breit, A., Ayoub, M. A., Taulan, M., Jockers, R., Barberis, C., & Bouvier, M. (2003). Oxytocin and vasopressin V1a and V2 receptors form constitutive homo- and heterodimers during biosynthesis. *Molecular Endocrinology*, 17, 677–691. <https://doi.org/10.1210/me.2002-0222>
- Tréfier, A., Pellissier, L. P., Musnier, A., Reiter, E., Guillou, F., & Crépieux, P. (2018). G protein-coupled receptors as regulators of localized translation: The forgotten pathway? *Frontiers in Endocrinology (Lausanne)*, 9, 17. <https://doi.org/10.3389/fendo.2018.00017>
- Umbrecht, D., del Valle Rubido, M., Hollander, E., McCracken, J. T., Shic, F., Scahill, L., Noeldeke, J., Boak, L., Khwaja, O., Squassante, L., Grundschober, C., Kletzl, H., & Fontoura, P. (2017). A single dose, randomized, controlled proof-of-mechanism study of a novel vasopressin 1a receptor antagonist (RG7713) in high-functioning adults with autism spectrum disorder. *Neuropsychopharmacology*, 42, 1914–1923. <https://doi.org/10.1038/npp.2016.232>
- van Bever, Y., Rooms, L., Laridon, A., Reyniers, E., van Luijk, R., Scheers, S., Wauters, J., & Kooy, R. F. (2005). Clinical report of a pure subtelomeric 1qter deletion in a boy with mental retardation and multiple anomalies adds further evidence for a specific phenotype. *American Journal of Medical Genetics. Part A*, 135, 91–95.
- van der Westhuizen, E. T. (2023). Single nucleotide variations encoding missense mutations in G protein-coupled receptors may contribute to autism. *British Journal of Pharmacology*. <https://doi.org/10.1111/bph.16057>
- Varni, J. W., Handen, B. L., Corey-Lisle, P. K., Guo, Z., Manos, G., Ammerman, D. K., Marcus, R. N., Owen, R., McQuade, R. D., Carson, W. H., Mathew, S., & Mankoski, R. (2012). Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: A post hoc analysis of two controlled trials. *Clinical Therapeutics*, 34, 980–992. <https://doi.org/10.1016/j.clinthera.2012.02.023>
- Vassilatis, D. K., Hohmann, J. G., Zeng, H., Li, F., Ranchalis, J. E., Mortrud, M. T., Brown, A., Rodriguez, S. S., Weller, J. R., Wright, A. C., Bergmann, J. E., & Gaitanaris, G. A. (2003). The G protein-coupled receptor repertoires of human and mouse. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 4903–4908. <https://doi.org/10.1073/pnas.0230374100>
- Veenstra-VanderWeele, J., Cook, E. H., King, B. H., Zarevics, P., Cherubini, M., Walton-Bowen, K., Bear, M. F., Wang, P. P., & Carpenter, R. L. (2017). Arbaclofen in children and adolescents with autism spectrum disorder: A randomized, controlled, phase 2 trial. *Neuropsychopharmacology*, 42, 1390–1398. <https://doi.org/10.1038/npp.2016.237>
- Vilardaga, J.-P., Clark, L. J., White, A. D., Sutkeviciute, I., Lee, J. Y., & Bahar, I. (2023). Molecular mechanisms of PTH/PTHrP class B GPCR signaling and pharmacological implications. *Endocrine Reviews*, 44(3), 474–491.
- Voineagu, I., Wang, X., Johnston, P., Lowe, J. K., Tian, Y., Horvath, S., Mill, J., Cantor, R. M., Blencowe, B. J., & Geschwind, D. H. (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature*, 474, 380–384. <https://doi.org/10.1038/nature10110>
- Walsh, J. J., Llorach, P., Cardozo Pinto, D. F., Wenderski, W., Christoffel, D. J., Salgado, J. S., Heifets, B. D., Crabtree, G. R., & Malenka, R. C. (2021). Systemic enhancement of serotonin signaling reverses social deficits in multiple mouse models for ASD. *Neuropsychopharmacology*, 46, 2000–2010. <https://doi.org/10.1038/s41386-021-01091-6>
- Walum, H., Westberg, L., Henningson, S., Neiderhiser, J. M., Reiss, D., Igl, W., Ganiban, J. M., Spotts, E. L., Pedersen, N. L., Eriksson, E., & Lichtenstein, P. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 14153–14156. <https://doi.org/10.1073/pnas.0803081105>
- Wei, C. J., Li, W., & Chen, J.-F. (2011). Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. *Biochimica et Biophysica Acta*, 1808, 1358–1379.
- Wei, D., Dinh, D., Lee, D., Li, D., Anguren, A., Moreno-Sanz, G., Gall, C. M., & Piomelli, D. (2016). Enhancement of anandamide-mediated endocannabinoid signaling corrects autism-related social impairment. *Cannabis and Cannabinoid Research*, 1, 81–89. <https://doi.org/10.1089/can.2015.0008>
- Weisstaub, N. V., Zhou, M., Lira, A., Lambe, E., González-Maeso, J., Hornung, J.-P., Sibille, E., Underwood, M., Itoharu, S., Dauer, W. T., Ansorge, M. S., Morelli, E., Mann, J. J., Toth, M., Aghajanian, G., Sealon, S. C., Hen, R., & Gingrich, J. A. (2006). Cortical 5-HT2A receptor signaling modulates anxiety-like behaviors in mice. *Science*, 313, 536–540. <https://doi.org/10.1126/science.1123432>
- Wersinger, S. R., Caldwell, H. K., Martinez, L., Gold, P., Hu, S.-B., & Young, W. S. (2007). Vasopressin 1a receptor knockout mice have a subtle olfactory deficit but normal aggression. *Genes, Brain, and Behavior*, 6, 540–551.
- Winslow, J. T., Hearn, E. F., Ferguson, J., Young, L. J., Matzuk, M. M., & Insel, T. R. (2000). Infant vocalization, adult aggression, and fear behavior of an oxytocin null mutant mouse. *Hormones and Behavior*, 37, 145–155.



- Witte, A. M., de Moor, M. H. M., Majdandžić, M., Verhees, M. W. F. T., van IJzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2022). Effects of oxytocin and vasopressin administration on human fathers' sensitive and challenging parenting: A randomized within-subject controlled trial. *Hormones and Behavior*, 142, 105175.
- Xu, J., Marshall, J. J., Kraniotis, S., Nomura, T., Zhu, Y., & Contractor, A. (2021). Genetic disruption of *Grm5* causes complex alterations in motor activity, anxiety and social behaviors. *Behavioural Brain Research*, 411, 113378.
- Yamada, M., Miyakawa, T., Duttaroy, A., Yamanaka, A., Moriguchi, T., Makita, R., Ogawa, M., Chou, C. J., Xia, B., Crawley, J. N., Felder, C. C., Deng, C. X., & Wess, J. (2001). Mice lacking the M3 muscarinic acetylcholine receptor are hypophagic and lean. *Nature*, 410, 207–212. <https://doi.org/10.1038/35065604>
- Yang, H.-J., Vainshtein, A., Maik-Rachline, G., & Peles, E. (2016). G protein-coupled receptor 37 is a negative regulator of oligodendrocyte differentiation and myelination. *Nature Communications*, 7, 10884.
- Yoo, Y., Jung, J., Lee, Y.-N., Lee, Y., Cho, H., Na, E., Hong, J. Y., Kim, E., Lee, J. S., Lee, J. S., Hong, C., Park, S. Y., Wie, J., Miller, K., Shur, N., Clow, C., Ebel, R. S., DeBrosse, S. D., Henderson, L. B., ... Choi, M. (2017). *GABBR2* mutations determine phenotype in rett syndrome and epileptic encephalopathy. *Annals of Neurology*, 82, 466–478. <https://doi.org/10.1002/ana.25032>
- Zeidan, J., Fombonne, E., Scora, J., Ibrahim, A., Durkin, M. S., Saxena, S., Yusuf, A., Shih, A., & Elsabbagh, M. (2022). Global prevalence of autism: A systematic review update. *Autism Research*, 15, 778–790. <https://doi.org/10.1002/aur.2696>
- Zelena, D. (2017). Comparison of natural and artificial vasopressin deficiency: Why is the latter lethal? *Russian Journal of Genetics: Applied Research*, 7, 243–248.
- Zhan, Y., Paolicelli, R. C., Sforzini, F., Weinhard, L., Bolasco, G., Pagani, F., Vyssotski, A. L., Bifone, A., Gozzi, A., Ragozzino, D., & Gross, C. T. (2014). Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nature Neuroscience*, 17, 400–406. <https://doi.org/10.1038/nn.3641>
- Zhang, P.-W., Ishiguro, H., Ohtsuki, T., Hess, J., Carillo, F., Walther, D., Onaivi, E. S., Arinami, T., & Uhl, G. R. (2004). Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. *Molecular Psychiatry*, 9, 916–931. <https://doi.org/10.1038/sj.mp.4001560>
- Zhang, X., Li, Q., Zhang, M., Lam, S., Sham, P. C., Bu, B., Chua, S. E., Wang, W., & McAlonan, G. M. (2015). The effect of oxytocin on social and non-social behaviour and striatal protein expression in C57BL/6N mice. *PLoS ONE*, 10, e0145638. <https://doi.org/10.1371/journal.pone.0145638>
- Zhou, H., Wang, J., Zhang, Y., Shao, F., & Wang, W. (2020). The role of microglial CX3CR1 in schizophrenia-related behaviors induced by social isolation. *Frontiers in Integrative Neuroscience*, 14, 551676.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Annamneedi, A., Gora, C., Dudas, A., Leray, X., Bozon, V., Crépieux, P., & Pellissier, L. P. (2023). Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders. *British Journal of Pharmacology*, 1–24. <https://doi.org/10.1111/bph.16216>