



HAL
open science

The Serotonin 4 Receptor Subtype: A Target of Particular Interest, Especially for Brain Disorders

Véronique Sgambato

► **To cite this version:**

Véronique Sgambato. The Serotonin 4 Receptor Subtype: A Target of Particular Interest, Especially for Brain Disorders. *International Journal of Molecular Sciences*, 2024, 25 (10), pp.5245. <10.3390/ijms25105245>. <hal-04845433>

HAL Id: hal-04845433

<https://hal.science/hal-04845433v1>

Submitted on 18 Dec 2024

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 CC BY 4.0 - Attribution - International License



Review

The Serotonin 4 Receptor Subtype: A Target of Particular Interest, Especially for Brain Disorders

Véronique Sgambato ^{1,2}

¹ Institut des Sciences Cognitives Marc Jeannerod (ISCMJ), Unité Mixte de Recherche 5229 du Centre National de la Recherche Scientifique (CNRS), 69675 Bron, France; veronique.sgambato@inserm.fr; Tel.: +33-4379-11249

² UFR Biosciences, Université de Lyon 1, 69100 Villeurbanne, France

Abstract: In recent years, particular attention has been paid to the serotonin 4 receptor, which is well expressed in the brain, but also peripherally in various organs. The cerebral distribution of this receptor is well conserved across species, with high densities in the basal ganglia, where they are expressed by GABAergic neurons. The 5-HT₄ receptor is also present in the cerebral cortex, hippocampus, and amygdala, where they are carried by glutamatergic or cholinergic neurons. Outside the central nervous system, the 5-HT₄ receptor is notably expressed in the gastrointestinal tract. The wide distribution of the 5-HT₄ receptor undoubtedly contributes to its involvement in a plethora of functions. In addition, the modulation of this receptor influences the release of serotonin, but also the release of other neurotransmitters such as acetylcholine and dopamine. This is a considerable asset, as the modulation of the 5-HT₄ receptor can therefore play a direct or indirect beneficial role in various disorders. One of the main advantages of this receptor is that it mediates a much faster antidepressant and anxiolytic action than classical selective serotonin reuptake inhibitors. Another major benefit of the 5-HT₄ receptor is that its activation enhances cognitive performance, probably via the release of acetylcholine. The expression of the 5-HT₄ receptor is also altered in various eating disorders, and its activation by the 5-HT₄ agonist negatively regulates food intake. Additionally, although the cerebral expression of this receptor is modified in certain movement-related disorders, it is still yet to be determined whether this receptor plays a key role in their pathophysiology. Finally, there is no longer any need to demonstrate the value of 5-HT₄ receptor agonists in the pharmacological management of gastrointestinal disorders.

Keywords: serotonin; 5-HT₄ receptor; depression; anxiety; cognitive decline; movement disorders; eating disorders; constipation



Citation: Sgambato, V. The Serotonin 4 Receptor Subtype: A Target of Particular Interest, Especially for Brain Disorders. *Int. J. Mol. Sci.* **2024**, *25*, 5245. <https://doi.org/10.3390/ijms25105245>

Academic Editor: Elena E. Voronezhskaya

Received: 15 March 2024

Revised: 22 April 2024

Accepted: 7 May 2024

Published: 11 May 2024



Copyright: © 2024 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Serotonin (5-HT, 5-hydroxytryptamine) is a monoamine synthesized from an essential amino acid, L-tryptophan. L-tryptophan can cross the blood–brain barrier and be converted by the enzyme tryptophan hydroxylase 2 (TPH2) into L-5-hydroxytryptophan. The latter is then converted to 5-HT after decarboxylation by aromatic amino acid decarboxylase (AADC). TPH2 is specific to serotonergic neurons in the central nervous system and is responsible for 5-HT synthesis in the brain [1,2], while AADC is localized in many cell types. In the brain, the majority of the cell bodies of serotonin-containing neurons are located in the brain stem and grouped into nine nuclei (named B1 to B9) which are, in turn, divided into the rostral or superior group and the caudal or inferior group [3,4]. The rostral group is located in the pons and midbrain and consists of both the dorsal nucleus (DRN) and medial nucleus (MRN) of the raphe [5,6]. The caudal group is located in the medulla and consists of nuclei projecting mainly to the spinal cord [5]. Although, in many brain territories, projections from serotonergic neurons originate from both the DRN and MRN, in some regions, 5-HT innervation originates solely or preferentially from the DRN or MRN. This is the case, for example, of the hippocampus, the dorsal part of which receives serotonergic

innervation from the MRN [7]. On the other hand, the 5-HT fibers of the striatum, globus pallidus, lateral septum, and amygdala, including the prefrontal cortex, come from the DRN [8]. Along with the MRN, the DRN innervates the ventral part of the hippocampus and the prefrontal cortex [8] and certain nuclei of the thalamus [7,9,10]. There are also dense serotonergic projections between the DRN and MRN [11]. The central nervous system therefore contains a small number of 5-HT neurons grouped together in nuclei, but these neurons release serotonin diffusely throughout the brain at chemical synapses or by volume transmission [4,12]. Serotonin can therefore exert a modulating action on a wide variety of neuronal circuits and therefore functions [13,14]. The action of serotonin is complicated by the identification of seven families of serotonin receptor subtypes (5-HT₁ to 5-HT₇ receptors) in the brain [15]. Six of these are metabotropic G-protein-coupled receptors and one (the 5-HT₃ receptor) is a ligand-gated ion channel (ionotropic receptor) [16]. This leads to the existence of eighteen 5-HT receptor subtypes plus a number of isoforms resulting from alternative mRNA splicing [17]. While all 5-HT receptor subtypes have post-synaptic expression on target cells, some subtypes, such as 5-HT_{1A}, 5-HT_{1B/D}, and 5-HT_{2B}, are also localized pre-synaptically on the 5-HT neurons themselves (autoreceptors). Finally, 5-HT receptors also differ in their brain expression profiles in the brain [18] and in their interactions with other neurotransmitter systems.

In recent years, particular attention has been focused on the serotonin 4 receptor subtype [19–21], originally identified and cloned in rodents [22,23]. This receptor is positively coupled to adenylate cyclase via a G_s-type G protein leading to the canonical activation of the cAMP/PKA pathway [24]. But activation of the 5-HT₄ receptor can also lead to the activation of the ERK signaling pathway independently of G proteins [25]. In addition to the fact that the 5-HT₄ receptor has a constitutive activity, which is expressed at low receptor levels, another important feature of the receptor is that it can establish homodimers or heterodimers with several other proteins. These dimers functionally impact the signaling pathways on which they act [26]. In the brain, the 5-HT₄ receptor is mainly located on neurons and has a dual somatodendritic and axonal localization [27]. Its cerebral distribution is highly conserved across species [27,28] with the highest densities in basal ganglia, particularly in the striatum [29,30] and the substantia nigra [31]. The 5-HT₄ receptor is expressed by GABAergic neurons, as neurotoxic lesions of rodent basal ganglia components lead to dramatic decreases in 5-HT₄ receptor binding in these regions [27,32]. The post-synaptic expression of the 5-HT₄ receptor seems independent of dopaminergic neurons, as a dopaminergic lesion induced by intranigral injection of the 6-hydroxydopamine in rodents does not induce decreases in its expression in the striatum or the substantia nigra [27,32]. Similarly, the lesion of serotonergic neurons by intra-raphe injection of the 5,7-dihydroxytryptamine upregulates the 5-HT₄ receptor binding in the basal ganglia and hippocampal regions [32]. The 5-HT₄ receptor is also highly expressed in the cerebral cortex, hippocampus, and amygdala, where it may be carried by glutamatergic or cholinergic neurons, depending on the region [33,34]. The distribution of this receptor has also been studied in the post-mortem human brain by *in situ* hybridization and ligand binding studies and has been found to be high in basal ganglia regions and moderate to low in hippocampal formation and the cortical mantle [28]. Substantial evidence from preclinical and clinical studies have indicated an inverse relationship between the central 5-HT tonus and the density of the 5-HT₄ receptor. In animals, 5-HT depletion or 5-HT boosting by the use of antidepressants, or again serotonin transporter gene manipulation, all lead to alterations of the 5-HT₄ receptor binding in the brain [35–37]. In humans, the polymorphism of the serotonin transporter also results in different 5-HT levels and to different expression levels of the 5-HT₄ receptor [38]. And as it has been demonstrated that the density of the 5-HT₄ receptor adapts to the variations in brain extracellular 5-HT levels induced by antidepressant treatment, the central 5-HT₄ receptor binding is now used as an *in vivo* biomarker of serotonergic tonus [39]. Outside the central nervous system, the 5-HT₄ receptor is known to be also expressed in the gastrointestinal tract, the cardiovascular system, the bladder, and the adrenal glands [40].

The 5-HT₄ receptor is involved in several functions. It mediates a positive feedback effect on the 5-HT neurons themselves. Indeed, the 5-HT₄ receptor in the prefrontal cortex has a positive influence on the rate of discharge of 5-HT neurons in the raphe and increases the probability of action potential emissions via the positive feedback loop from the prefrontal cortex to the dorsal raphe [41,42]. The administration of 5-HT₄ agonists also activates raphe 5-HT neurons [41,43]. It also releases 5-HT in the hippocampus [44]. The action of 5-HT₄ receptors in the hippocampus plays an important role in the regulation of synaptic plasticity and related memory mechanisms [45]. Apart from the serotonergic system, the modulation of the 5-HT₄ receptor has effects on the homeostasis of other neurotransmitter systems such as acetylcholine or dopamine [46]. The stimulation of the 5-HT₄ receptor facilitates the release of acetylcholine in the frontal cortex of awake rats [47]. Similarly, the 5-HT₄ receptor has been shown to facilitate dopamine release in the rat striatum both in vitro and in vivo [48]. The fact that modulation of the 5-HT₄ receptor can affect the release of different neurotransmitters highlights the importance of this receptor as a potential therapeutic player in a variety of pathological conditions.

1.1. Mood and Anxiety Disorders

One of the major interests of this receptor is its potential involvement in mood and anxiety disorders (Table 1). It has already been shown that the 5-HT₄ receptor expression is altered in various rodent models of depression. Some studies have reported a decrease in 5-HT₄ receptor expression [35,49], while others have observed an increase [50]. It is highly probable that these divergent results are due to the use of different animal models of depression. On the contrary, similar results were obtained by studies modulating 5-HT₄ receptor activation. Drugs that activate the 5-HT₄ receptor play a fast-acting beneficial role on behavioral markers of depression or anxiety [51]. Electrophysiological, molecular, morphological, and behavioral changes that have previously been specifically linked to beneficial long-term treatment with selective serotonin reuptake inhibitors are already present after only 3 days of treatment when using 5-HT₄ agonists in rodents [52]. The lack of 5-HT₄ receptor modulates mood-like disorders [53] and further impacts the response to antidepressants in rodents [54]. Overexpression of the 5-HT₄ receptor in the medial prefrontal cortex leads to antidepressant effects [55], whereas its functional ablation throughout the brain [54] or only in the hippocampus [53] causes anxiety and mood disorders. The pharmacological modulation of the 5-HT₄ receptor located in the lateral habenula also produces antidepressant effects, via changes in monoamine levels in the prefrontal cortex and hippocampus in parkinsonian rats [56]. Yet, links have been shown between the antidepressant action of 5-HT₄ receptor agonists and mechanisms of synaptic plasticity or gene regulation in the hippocampus. For example, the administration of 5-HT₄ receptor agonists leads to the upregulation of mRNAs encoding BDNF (brain-derived neurotrophic factor) in the hippocampus. This increase results from activation of the CREB (cAMP-response element-binding protein) signaling pathway, which stimulates the expression of various neurotrophic factors in the hippocampus, including BDNF [57]. Furthermore, it has been shown that the stimulation of the 5-HT₄ receptor drives neurogenesis in the hippocampus, while the lack of or the antagonism toward the 5-HT₄ receptor reduces these effects [58–61]. Furthermore, it has been shown that the activation of the 5-HT₄ receptor boosts the formation and the function of dendritic spines [62,63] and more generally acts as a unique modulator of synaptic plasticity mechanisms in the hippocampus [64].

In support of these preclinical data, several human studies have also shown that expression levels of the 5-HT₄ receptor are altered in mood disorders and/or depression (Table 1). Autopsy results of brain tissue from antidepressant-free, violent suicide victims have shown a high density of the 5-HT₄ receptor in the frontal cortex and caudate nucleus compared with control subjects [65]. In vivo PET (positron emission tomography) data have shown a lower cerebral 5-HT₄ receptor binding in patients with major depressive disorder than in healthy subjects [66,67]. And concomitant anxiety in patients suffering from depression is also negatively associated with 5-HT₄ receptor brain binding [68]. There

is also an association between brain 5-HT₄ receptor binding and reactivity to emotional faces in depressed and healthy individuals: the higher the concomitant anxiety, the lower the binding in the brain [69]. The global brain binding of this receptor has also been positively linked to high trait aggression in men [70]. Finally, a polymorphism in the 5-HT₄ receptor in its C-terminal region has been linked to unipolar depression in humans [71], suggesting that genomic variations of this gene may confer susceptibility to mood disorders. A more recent study aimed to assess the association of the 5-HT₄ receptor polymorphism (rs1345697) with depressive symptom improvement after 6 months of antidepressant treatment and found that there is an impact of this rs1345697 polymorphism on the improvement in depressive symptoms and remission of these symptoms after antidepressant treatment [72]. Taken together, these preclinical and clinical data tend to show that there is rather a drop in expression of the 5-HT₄ receptor associated with mood and anxiety disorders, and that the use of agonists of this receptor could reduce them.

1.2. Cognitive Disorders

Another attraction of the 5-HT₄ receptor subtype is that its activation can improve learning and memory (Table 2). Several preclinical experimental paradigms have evidenced such pro-cognitive properties [73,74]. Significant and reproducible improvements in a delayed matching to sample task accuracy are observed following an oral administration of a 5-HT₄ agonist in both younger and older monkeys [73]. In rodents, activation of the 5-HT₄ receptor leads to an increase in acetylcholine release, which counteracts memory deficits [21,46]. And it has been shown that the 5-HT₄ receptor plays a specific and unique role in modulating the long-term potentiation of synapses in the hippocampus [75] and thus the memory mechanisms dependent on this structure [64]. It also promotes here the maturation of neuronal dendritic spines [63]. In humans, PET imaging studies have shown an inverse relationship between brain 5-HT₄ receptor binding and memory performance in healthy subjects [76,77]. Even weaker brain binding is associated with memory dysfunction in untreated depressive patients compared with healthy individuals [67]. Finally, as in animals, stimulation of the 5-HT₄ receptor by prucalopride improves cognitive performance in healthy subjects [78,79]. This beneficial effect is achieved by enhancing the resting-state functional connectivity between regions involved in cognitive networks while reducing that of the default mode network [80].

Table 1. List and main characteristics of preclinical and clinical studies involving the 5-HT₄ receptor in mood and anxiety disorders.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models	Main Results	Reference	
5-HT ₄ receptor polymorphism	Polymorphism	Bipolar or depressed individuals	C-terminal region linked to mood disorders *	[71]	
		Major depressed individuals	Genotype GG of rs1345697 polymorphism associated with lower remission rates	[72]	
5-HT ₄ receptor expression	Binding assays	Violent suicide human victims	↑↑	in frontal cortex *	[65]
			↑↑	in caudate nucleus *	
	Autoradiography	Rat depression model	↓	in the hippocampus	[35]
			↓	in hippocampus and basal ganglia under chronic paroxetine	
			↓	in hippocampus, hypothalamus, and lateral globus pallidus after 5-HT depletion	
			↓		
	Deletion	KO mouse	↑↑	in ventral hippocampus	[50]
			↑↑	in caudal caudate putamen	
	qRT-PCR, Western blot	KO mouse		Attenuation of “dematuration” of hippocampal granule cells	[58]
				Anxiety and anhedonia induced and responses to antidepressant impacted	[54]
Rat depression models		↓	in hippocampus associated with anhedonia	[49]	
		↑	in prefrontal cortex associated with anti-depressant-like phenotype	[55]	
In situ hybridization		KO mouse		Fluoxetine-induced neurogenesis abolished	[61]
Overexpression		Mouse		Anti-depressant-like phenotype	[55]
PET imaging		Healthy individuals	↓	in striatum and limbic regions negatively correlated with number of first-degree relatives treated for major depression	[66]
				Positive correlation with high trait aggression, only in males	[70]
	Anxious and depressed individuals	↓	in global brain	[68]	
	Depressed individuals	↓	Negative correlation with concomitant anxiety *	[69]	
		↓	in global brain *	[67]	

Table 1. Cont.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models		Main Results	Reference
5-HT ₄ receptor modulation	5-HT ₄ receptor agonist	Rat depression models	↓	Depressive-like behavioral responses	[52]
		Rat	↓	Depressive- and anxiety-like behavioral responses	[57]
		Rat model of Parkinson's disease	↓	Depressive-like behavioral responses	[56]
		KO mouse		Antidepressant behavioral responses	[53]

* in comparison with healthy individuals. Up arrows indicate an increase, down arrows a decrease.

Table 2. List and main characteristics of preclinical and clinical studies involving the 5-HT₄ receptor in cognitive disorders.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models		Main Results	Reference
5-HT ₄ receptor expression	PET imaging	Subjects with early Alzheimer's disease	↑	In global brain and positively correlated with beta-amyloid accumulation	[81]
		Healthy young adult individuals		Inverse relationship with memory performance	[76]
		Depressed patients	↓	Inverse relationship with positive and neutral word recall performance	[77]
	Western blot	Rat model of Parkinson's disease	↑	in global brain * associated with memory dysfunction	[67]
5-HT ₄ receptor modulation	5-HT ₄ receptor agonist	Macaque young and old)		Learning improved	[73]
		Mouse		Memory improved	[74]
		Mouse model of scopolamine-induced deficit		Memory deficits counteracted	[46]
		Mouse model of Parkinson's disease		Restored facilitation of contextual fear extinction	[83]
	Rat model of Parkinson's disease		Working memory improved	[82]	
	Rat model of Alzheimer's disease		Memory deficits and associated mechanisms counteracted	[84]	
	Healthy young adult individuals		Pro-cognitive effects induced	[78]	
	Healthy young adult individuals		Mnesic performance improved associated with increased hippocampal activity	[79]	
5-HT ₄ receptor agonist and antagonist	ePet1-cre; Ai32 mouse		Memory formation modulated	[75]	

* in comparison with healthy individuals. Up arrows indicate an increase, down arrow indicates a decrease.

Stimulation of 5-HT₄ receptors is also proving promising in various pathological situations. In a rat model of Alzheimer's disease, the administration of a 5-HT₄ receptor agonist improves cognitive performance via a reduction in apoptotic neurons and an improvement in synaptic function in the hippocampus [84]. In humans with early Alzheimer's disease, a PET study elegantly showed that there is an increase in brain 5-HT₄ receptor binding (parietal cortex, lateral prefrontal cortex, lateral temporal cortex, posterior cingulate gyrus, and hippocampus), and that this global cerebral upregulation is positively correlated with the cortical detection of beta-amyloid accumulation [81]. These preclinical and clinical data indicate that upregulation of the 5-HT₄ receptor in the brain is beneficial, particularly in the hippocampus, where 5-HT₄ receptor stimulation favors synaptic plasticity and memory mechanisms. This also suggests that increased expression of this receptor is a compensatory mechanism designed not only to counteract the accumulation of amyloid plaques [85], but also to promote acetylcholine release [47] and improve cognition.

Pro-cognitive effects are also mediated by 5-HT₄ receptors in Parkinson's neurodegenerative disease and may be underpinned by similar mechanisms. Indeed, the systemic administration of a 5-HT₄ agonist improves the facilitation of contextual fear extinction, although without affecting hippocampal 5-HT₄ receptors at the mRNA level, in the parkinsonian mice [83]. But another study on the parkinsonian rat has shown that lesioning the dopaminergic neurons of the median forebrain bundle produces cognitive deficits which are associated with a hippocampal increase in the receptor protein expression. Moreover, the local modulation of this receptor can counteract the memory deficits displayed by the animal, notably via increases in dopamine and serotonin in the hippocampus and the amygdala [82]. This suggests that, once again, the increased expression of the 5-HT₄ receptor is a compensatory mechanism that stimulates the release of other neurotransmitters, thereby counteracting memory deficits.

Taken together, these data indicate that the stimulation of 5-HT₄ receptors triggers a number of possible mechanisms (release of acetylcholine, serotonin, or dopamine; stimulation of maturation and synaptic plasticity in the hippocampus; induction of mechanisms able to counteract the accumulation of toxic aggregates and neuronal apoptosis), aimed at improving cognitive impairments. They also strengthen the view that 5-HT₄ receptor agonists could be used in humans under different conditions: in subjects without a neurodegenerative pathology to improve memory deficits, and in elderly subjects affected by several evolutive diseases involving severe cognitive impairment [86].

1.3. Movement Disorders

Few studies have addressed the question of whether the 5-HT₄ receptor subtype is in any way involved in movement disorders (Table 3). However, some animal models exist for inducing motor deficits or complications, in which either the impact of the pharmacological modulation of this receptor or its potential alteration of expression has been analyzed. In a rat model of morphine-driven stereotyped behavior and haloperidol-induced catalepsy, the systemic pharmacological blockade of the 5-HT₄ receptor has no impact, suggesting that 5-HT₄ receptor antagonism does not modulate motor behaviors related to the change in dopamine transmission [87]. Similarly, the turning behavior induced by amphetamine in unilateral dopamine-denervated rats is not affected after antagonizing the 5-HT₄ receptor [88]. Divergent results were obtained in the parkinsonian mice. One study showed that the administration of 5-HT₄ receptor agonists did not improve motor impairment [83]. On the contrary, a 7-day administration of prucalopride, a 5-HT₄ agonist, induced a beneficial effect on motor deficits (bradykinesia, exploration, balance, and muscle strength) in the parkinsonian mice, by attenuating the striatal loss of dopamine [89]. Studies that have simply analyzed variations in receptor expression without using pharmacological ligands show divergent results. Changes in the striatal expression of the 5-HT₄ receptor are not observed after dopaminergic lesion induction, nor after a chronic levodopa treatment, leading to abnormal involuntary movements (i.e., dyskinesias) in a rat model of Parkinson's disease [90]. By contrast, using in vivo PET imaging and immunohistochemistry

on post-mortem tissue, we found that the 5-HT₄ receptor is upregulated in the striatum of parkinsonian macaques and rats, and further increased following chronic levodopa treatment, inducing dyskinesias in both animal species [91]. In humans, binding studies have not revealed any significant differences in 5-HT₄ receptor expression in the putamen or the substantia nigra between control subjects and Parkinson's sufferers, although there is a tendency for this receptor to increase in the putamen of patients [92,93]. By contrast, in Huntington's patients, who exhibit involuntary movements, a marked putaminal decrease in the 5-HT₄ receptor density is found [92]. However, a 3-week treatment with mosapride, a 5-HT₄ receptor agonist, improved motor functions in a small number of Parkinsonian patients [94]. Taken together, these results show that the question of possible links between altered 5-HT₄ receptor expression in the brain and movement disorders remains a largely open question. Further studies are sorely needed to elucidate whether or not this 5-HT₄ receptor plays a role in the pathophysiology of movement disorders.

Table 3. List and main characteristics of preclinical and clinical studies involving the 5-HT₄ receptor in movement disorders.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models	Main Results	Reference	
5-HT ₄ receptor expression	Binding assays	Patients affected by Huntington's disease	↓	in putamen *	[92,93]
		Patients affected by Parkinson's disease	↔	in putamen and nigra *	[92,93]
	In situ hybridization	Rat model of Parkinson's disease	↔	in striatum	[90]
	PET imaging immunohistochemistry		↑	in motor striatum	[91]
5-HT ₆ receptor modulation	5-HT ₄ receptor agonist	Patients affected by Parkinson's disease	Motor functions improved	[94]	
		Mouse model of Parkinson's disease	No motor improvement	[83]	
	5-HT ₄ receptor antagonist	Rat model of amphetamine-induced turning behavior	Motor deficits improved associated with rescued striatal dopamine levels	[89]	
			No impact	[88]	

* in comparison with healthy individuals. Up arrow indicates an increase, down arrow a decrease. Horizontal arrows indicate no change.

1.4. Food Disorders

Several studies, first in rodents and non-human primates, then in humans, have shown that the 5-HT₄ receptor is associated with the control of food intake (Table 4). In normal or food-deprived mice, the local stimulation of the 5-HT₄ receptor in the nucleus accumbens, a region involved in the reward system, inhibits food intake, an effect that is not obtained in 5-HT₄-receptor-deficient mice [95]. The same group has also shown that deletion or overexpression of the 5-HT₄ receptor in the medial prefrontal cortex induces overeating or hypophagia, respectively [96]. In obese rats, there is a higher level of the accumbal 5-HT₄ receptor, whose stimulation with an agonist reduces eating [97]. In normal macaque monkeys, here again, the modulation of this receptor reduces or enhances the motivation for food intake, following systemic administration of a 5-HT₄ receptor agonist or antagonist, respectively (personal communications). Similarly, in dopamine-lesioned macaques, the local injection of a 5-HT₄ agonist into the ventral striatum (the rodent equivalent of the nucleus accumbens) triggers a reduced motivation for food intake (personal communications). In humans, a PET imaging study found that obesity

is associated with the greater availability of this receptor in the nucleus accumbens and ventral pallidum of the brain reward circuit [98]. All these preclinical and clinical data point in the same direction and show that the high expression of 5-HT₄ receptors in the nucleus accumbens is associated with a high body mass index, and that the stimulation of 5-HT₄ receptors helps reduce the food intake.

Table 4. List and main characteristics of preclinical and clinical studies involving the 5-HT₄ receptor in food disorders.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models		Main Results	Reference
5-HT ₄ receptor expression	Autoradiography	Rat model of obesity	↑	In nucleus accumbens	[97]
	PET imaging	Normal to high body mass index individuals	↑	In nucleus accumbens, ventral pallidum, left hippocampus, and orbitofrontal cortex, associated with obesity	[98]
	Deletion	Mouse	↑	Food intake	[96]
	Overexpression	Mouse	↓	Food intake	[96]
	Food intake modulated	KO mouse	↓	Food intake	[96]
5-HT ₄ receptor modulation		Mouse		Food intake modulated	[95]
	5-HT ₄ receptor agonist or antagonist	Macaque		Modulated food intake	personal communications
	5-HT ₄ receptor agonist	Macaque model of Parkinson's disease	↓	Food intake	personal communications

Up arrows indicate an increase, down arrows a decrease.

1.5. Other Brain Disorders

Finally, one clinical study has reported an association between the methylation of the 5-HT₄ receptor promoter and autism spectrum disorder [99]. Another has linked hippocampal structural changes in psychosis to the distribution of the 5-HT₄ receptor [100], opening new avenues of research on this receptor. More recently, a study investigating the possible involvement of the serotonergic system in the pathophysiology of amyotrophic lateral sclerosis showed, using a transgenic mouse model, that systemic administration of a 5-HT₄ receptor antagonist worsened the disease's phenotype. It degraded motor function, without affecting disease progression. However, the 5-HT₄ receptor antagonist also induced an increase in the expression of proteins forming abnormal aggregates, as well as an increase in the number of glial cells at the expense of neurons, in these mice [101], suggesting that using 5-HT₄ receptors agonists might be of particular interest.

1.6. Gastrointestinal Disorders

Interestingly also, the 5-HT₄ receptor agonists have been evaluated as prokinetics in the gastrointestinal tract (Table 5). The gavage of prucalopride causes faster whole gut transit and colonic motility and these effects are blocked by a 5-HT₄ receptor antagonist and are not detected in 5-HT₄ receptor knockout mice [102]. Sacral nerve electrical stimulation can improve defecation and accelerate the recovery of colonic transmission functions in a rat model of constipation, and these effects involve an upregulation of the 5-HT₄ receptor in the colon [103]. The 5-HT₄ receptor agonists prucalopride and tegaserod have both been approved by the FDA (Food and Drug Administration) and are used to

treat various gastrointestinal-related conditions, including nausea, diarrhea, gastroparesis, constipation, and pain in irritable bowel syndrome [104]. In patients suffering from chronic idiopathic constipation [104], prucalopride is highly efficient, and other highly selective 5-HT₄ receptor agonists are still in advanced development [105]. In other pathologies, such as Parkinson's disease, 5-HT₄ receptor agonists can also improve non-motor symptoms such as constipation. This has been demonstrated both preclinically and clinically. Rats with bilateral lesions of nigral dopaminergic neurons exhibit a reduced 5-HT₄ receptor expression in the colonic muscular layer and manifest constipation, which is counteracted by a 5-HT₄ receptor agonist (cisapride) [106]. In the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated mice, a beneficial effect is obtained on the integrity of the intestinal barrier after intraperitoneal administration of prucalopride, the 5-HT₄ receptor agonist, for 7 days [89]. Clinical studies have also tested the effects of the pharmacological stimulation of the 5-HT₄ receptor on constipation in Parkinson's disease (see [107]) (Table 5). It has been shown that administration of the 5-HT₄ receptor agonist mosapride for 3 months improves the intestinal transit in patients without worsening their parkinsonian symptoms or causing serious side-effects [108]. Another study involving a small number of parkinsonian patients showed an increasing gastric motility during mosapride treatment [94]. These data are interesting insofar as constipation is a non-motor symptom that may precede the onset of motor symptoms in Parkinson's disease. We could therefore imagine that the therapeutic targeting of the 5-HT₄ receptor could be modulated according to the symptom (motor or non-motor), but also according to the stage of the pathology (early, advanced, or late).

Table 5. List and main characteristics of preclinical and clinical studies involving the 5-HT₄ receptor in gastrointestinal disorders.

Goal of the Study	Methods of 5-HT ₄ Receptor Investigation	Models	Main Results	Reference
5-HT ₄ receptor expression	ELISA, qRT-PCR, immunohistochemistry, Western blot	Rat model of constipation	↑	In colon after sacral nerve electrical stimulation [103]
	Western blot	Rat model of Parkinson's disease	↓	In colon, associated with constipation [106]
5-HT ₄ receptor modulation	5-HT ₄ receptor agonist	Patients affected by Parkinson's disease	↑	Intestinal transit [108]
			↑	Gastric motility [94]
	Rat model of Parkinson's disease	↑ ↓	In colon Constipation [106]	
	Mouse model of Parkinson's disease		Beneficial effect on intestinal barrier integrity [89]	
5-HT ₄ receptor agonist and antagonist	Naïve or KO mouse		Modulated gut transit and colonic motility [102]	

Up arrows indicate an increase, down arrows a decrease.

2. Conclusions

All these studies, both preclinical and clinical, highlight this 5-HT₄ receptor as a potential therapeutic target, especially for various brain disorders. While the benefits of activating this receptor have been well demonstrated at the preclinical level for certain conditions, such as depressive symptoms, memory deficits, food consumption, and constipation, there is still some way to go in terms of the interest in acting pharmacologically on this receptor in the field of movement disorders. In humans, the activation of this

receptor to counteract certain disorders is promising but remains to be validated, since only gastrointestinal disorders can be improved so far by using compounds acting toward this receptor. Further studies are sorely needed to unravel all the mysteries surrounding this receptor, both in terms of its functions and its potential therapeutic use.

Funding: Writing this review article was supported by the Fondation de France and the Agence Nationale de la Recherche. V.S. is supported by INSERM (Institut National de la Santé et de la Recherche Médicale).

Conflicts of Interest: The author declares no conflict of interest.

References

- Gutknecht, L.; Kriegebaum, C.; Waider, J.; Schmitt, A.; Lesch, K.-P. Spatiotemporal expression of tryptophan hydroxylase isoforms in murine and human brain: Convergent data from Tph2 knockout mice. *Eur. Neuropsychopharmacol.* **2009**, *19*, 266–282. [[CrossRef](#)] [[PubMed](#)]
- Walther, D.J.; Bader, M. A unique central tryptophan hydroxylase isoform. *Biochem. Pharmacol.* **2003**, *66*, 1673–1680. [[CrossRef](#)]
- Dahlström, A.; Fuxe, K. Localization of monoamines in the lower brain stem. *Experientia* **1964**, *20*, 398–399. [[CrossRef](#)] [[PubMed](#)]
- Hornung, J.P. The human raphe nuclei and the serotonergic system. *J. Chem. Neuroanat.* **2003**, *26*, 331–343. [[CrossRef](#)]
- Bjarkam, C.R.; Sørensen, J.C.; Geneser, F.A. Distribution and morphology of serotonin-immunoreactive neurons in the brainstem of the New Zealand white rabbit. *J. Comp. Neurol.* **1997**, *380*, 507–519. [[CrossRef](#)]
- Soares, J.G.; Cavalcanti, J.R.L.P.; Oliveira, F.G.; Pontes, A.L.B.; Sousa, T.B.; Freitas, L.M.; Cavalcante, J.S.; Nascimento, E.S.; Cavalcante, J.C.; Costa, M.S.M.O. Nuclear organization of the serotonergic system in the brain of the rock cavy (*Kerodon rupestris*). *J. Chem. Neuroanat.* **2012**, *43*, 112–119. [[CrossRef](#)]
- Azmitia, E.C.; Segal, M. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *J. Comp. Neurol.* **1978**, *179*, 641–667. [[CrossRef](#)]
- Michelsen, K.A.; Schmitz, C.; Steinbusch, H.W.M. The dorsal raphe nucleus- from silver stainings to a role in depression. *Brain Res. Rev.* **2007**, *55*, 329–342. [[CrossRef](#)] [[PubMed](#)]
- McQuade, R.; Sharp, T. Functional mapping of dorsal and median raphe 5-hydroxytryptamine pathways in forebrain of the rat using microdialysis. *J. Neurochem.* **1997**, *69*, 791–796. [[CrossRef](#)]
- McQuade, R.; Sharp, T. Release of cerebral 5-hydroxytryptamine evoked by electrical stimulation of the dorsal and median raphe nuclei: Effect of a neurotoxic amphetamine. *Neuroscience* **1995**, *68*, 1079–1088. [[CrossRef](#)]
- Jacobs, B.L.; Azmitia, E.C. Structure and function of the brain serotonin system. *Physiol. Rev.* **1992**, *72*, 165–229. [[CrossRef](#)] [[PubMed](#)]
- Abrams, J.K.; Johnson, P.L.; Hollis, J.H.; Lowry, C.A. Anatomic and functional topography of the dorsal raphe nucleus. *Ann. N. Y. Acad. Sci.* **2004**, *1018*, 46–57. [[CrossRef](#)] [[PubMed](#)]
- Berger, M.; Gray, J.A.; Roth, B.L. The expanded biology of serotonin. *Annu. Rev. Med.* **2009**, *60*, 355–366. [[CrossRef](#)] [[PubMed](#)]
- Fidalgo, S.; Ivanov, D.K.; Wood, S.H. Serotonin: From top to bottom. *Biogerontology* **2013**, *14*, 21–45. [[CrossRef](#)] [[PubMed](#)]
- Kroeze, W.K.; Kristiansen, K.; Roth, B.L. Molecular biology of serotonin receptors structure and function at the molecular level. *Curr. Top. Med. Chem.* **2002**, *2*, 507–528. [[CrossRef](#)] [[PubMed](#)]
- Nichols, D.E.; Nichols, C.D. Serotonin receptors. *Chem. Rev.* **2008**, *108*, 1614–1641. [[CrossRef](#)] [[PubMed](#)]
- Compan, V.; Laurent, L.; Jean, A.; Macary, C.; Bockaert, J.; Dumuis, A. Serotonin signaling in eating disorders. *Wiley Interdiscip. Rev. Membr. Transp. Signal* **2012**, *1*, 715–729. [[CrossRef](#)]
- Mengod, G.; Vilaró, M.T.; Raurich, A.; López-Giménez, J.F.; Cortés, R.; Palacios, J.M. 5-HT receptors in mammalian brain: Receptor autoradiography and in situ hybridization studies of new ligands and newly identified receptors. *Histochem. J.* **1996**, *28*, 747–758. [[CrossRef](#)] [[PubMed](#)]
- Bockaert, J.; Claeysen, S.; Compan, V.; Dumuis, A. 5-HT(4) receptors: History, molecular pharmacology and brain functions. *Neuropharmacology* **2008**, *55*, 922–931. [[CrossRef](#)]
- Rebholz, H.; Friedman, E.; Castello, J. Alterations of Expression of the Serotonin 5-HT4 Receptor in Brain Disorders. *Int. J. Mol. Sci.* **2018**, *19*, 3581. [[CrossRef](#)]
- Roux, C.M.; Leger, M.; Freret, T. Memory Disorders Related to Hippocampal Function: The Interest of 5-HT4Rs Targeting. *Int. J. Mol. Sci.* **2021**, *22*, 12082. [[CrossRef](#)] [[PubMed](#)]
- Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R.; Bockaert, J. A nonclassical 5-hydroxytryptamine receptor positively coupled with adenylate cyclase in the central nervous system. *Mol. Pharmacol.* **1988**, *34*, 880–887. [[PubMed](#)]
- Gerald, C.; Adham, N.; Kao, H.T.; Olsen, M.A.; Laz, T.M.; Schechter, L.E.; Bard, J.A.; Vaysse, P.J.; Hartig, P.R.; Branchek, T.A.; et al. The 5-HT4 receptor: Molecular cloning and pharmacological characterization of two splice variants. *EMBO J.* **1995**, *14*, 2806–2815. [[CrossRef](#)] [[PubMed](#)]
- Barthet, G.; Gaven, F.; Framery, B.; Shinjo, K.; Nakamura, T.; Claeysen, S.; Bockaert, J.; Dumuis, A. Uncoupling and endocytosis of 5-hydroxytryptamine 4 receptors. Distinct molecular events with different grk2 requirements. *J. Biol. Chem.* **2005**, *280*, 27924–27934. [[CrossRef](#)] [[PubMed](#)]

25. Barthet, G.; Framery, B.; Gaven, F.; Pellissier, L.; Reiter, E.; Claeysen, S.; Bockaert, J.; Dumuis, A. 5-hydroxytryptamine 4 receptor activation of the extracellular signal-regulated kinase pathway depends on src activation but not on g protein or beta-arrestin signaling. *Mol. Biol. Cell* **2007**, *18*, 1979–1991. [[CrossRef](#)] [[PubMed](#)]
26. Mitroshina, E.V.; Marasanova, E.A.; Vedunova, M.V. Functional Dimerization of Serotonin Receptors: Role in Health and Depressive Disorders. *Int. J. Mol. Sci.* **2023**, *24*, 16416. [[CrossRef](#)]
27. Vilaró, M.T.; Cortés, R.; Mengod, G. Serotonin 5-HT₄ receptors and their mRNAs in rat and guinea pig brain: Distribution and effects of neurotoxic lesions. *J. Comp. Neurol.* **2005**, *484*, 418–439. [[CrossRef](#)] [[PubMed](#)]
28. Bonaventure, P.; Hall, H.; Gommeren, W.; Cras, P.; Langlois, X.; Jurzak, M.; Leysen, J.E. Mapping of serotonin 5-HT₄ receptor mRNA and ligand binding sites in the post-mortem human brain. *Synapse* **2000**, *36*, 35–46. [[CrossRef](#)]
29. Beliveau, V.; Ganz, M.; Feng, L.; Ozenne, B.; Højgaard, L.; Fisher, P.M.; Svarer, C.; Greve, D.N.; Knudsen, G.M. A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. *J. Neurosci.* **2017**, *37*, 120–128. [[CrossRef](#)]
30. Sgambato-Faure, V.; Tremblay, L. Dopamine and serotonin modulation of motor and non-motor functions of the non-human primate striato-pallidal circuits in normal and pathological states. *J. Neural Transm.* **2018**, *125*, 485–500. [[CrossRef](#)]
31. Waeber, C.; Sebben, M.; Nieoullon, A.; Bockaert, J.; Dumuis, A. Regional distribution and ontogeny of 5-HT₄ binding sites in rodent brain. *Neuropharmacology* **1994**, *33*, 527–541. [[CrossRef](#)] [[PubMed](#)]
32. Compan, V.; Daszuta, A.; Salin, P.; Sebben, M.; Bockaert, J.; Dumuis, A. Lesion study of the distribution of serotonin 5-HT₄ receptors in rat basal ganglia and hippocampus. *Eur. J. Neurosci.* **1996**, *8*, 2591–2598. [[CrossRef](#)] [[PubMed](#)]
33. Egeland, M.; Warner-Schmidt, J.; Greengard, P.; Svenningsson, P. Co-expression of serotonin 5-HT_{1B} and 5-HT₄ receptors in p11 containing cells in cerebral cortex, hippocampus, caudate-putamen and cerebellum. *Neuropharmacology* **2011**, *61*, 442–450. [[CrossRef](#)] [[PubMed](#)]
34. Peñas-Cazorla, R.; Vilaró, M.T. Serotonin 5-HT₄ receptors and forebrain cholinergic system: Receptor expression in identified cell populations. *Brain Struct. Funct.* **2015**, *220*, 3413–3434. [[CrossRef](#)]
35. Licht, C.L.; Marcussen, A.B.; Wegener, G.; Overstreet, D.H.; Aznar, S.; Knudsen, G.M. The brain 5-HT₄ receptor binding is down-regulated in the Flinders Sensitive Line depression model and in response to paroxetine administration. *J. Neurochem.* **2009**, *109*, 1363–1374. [[CrossRef](#)] [[PubMed](#)]
36. Vidal, R.; Valdizan, E.M.; Mostany, R.; Pazos, A.; Castro, E. Long-term treatment with fluoxetine induces desensitization of 5-HT₄ receptor-dependent signalling and functionality in rat brain. *J. Neurochem.* **2009**, *110*, 1120–1127. [[CrossRef](#)] [[PubMed](#)]
37. Jennings, K.A.; Licht, C.L.; Bruce, A.; Lesch, K.P.; Knudsen, G.M.; Sharp, T. Genetic variation in 5-hydroxytryptamine transporter expression causes adaptive changes in 5-HT₄ receptor levels. *Int. J. Neuropsychopharmacol.* **2012**, *15*, 1099–1107. [[CrossRef](#)] [[PubMed](#)]
38. Fisher, P.M.; Holst, K.K.; Mc Mahon, B.; Haahr, M.E.; Madsen, K.; Gillings, N.; Baaré, W.F.; Jensen, P.S.; Knudsen, G.M. 5-HTTLPR status predictive of neocortical 5-HT₄ binding assessed with [(11)C]SB207145 PET in humans. *Neuroimage* **2012**, *62*, 130–136. [[CrossRef](#)] [[PubMed](#)]
39. Haahr, M.E.; Fisher, P.M.; Jensen, C.G.; Frokjaer, V.G.; Mahon, B.M.; Madsen, K.; Baaré, W.F.; Lehel, S.; Norremolle, A.; Rabiner, E.A.; et al. Central 5-HT₄ receptor binding as biomarker of serotonergic tonus in humans: A [11C]SB207145 PET study. *Mol. Psychiatry* **2014**, *19*, 427–432. [[CrossRef](#)]
40. Hegde, S.S.; Eglén, R.M. Peripheral 5-HT₄ receptors. *FASEB J.* **1996**, *10*, 1398–1407. [[CrossRef](#)]
41. Lucas, G.; Compan, V.; Charnay, Y.; Neve, R.L.; Nestler, E.J.; Bockaert, J.; Barrot, M.; Debonnel, G. Frontocortical 5-HT₄ Receptors Exert Positive Feedback on Serotonergic Activity: Viral Transfections, Subacute and Chronic Treatments with 5-HT₄ Agonists. *Biol. Psychiatry* **2005**, *57*, 918–925. [[CrossRef](#)] [[PubMed](#)]
42. Conductier, G.; Dusticier, N.; Lucas, G.; Côté, F.; Debonnel, G.; Daszuta, A.; Dumuis, A.; Nieoullon, A.; Hen, R.; Bockaert, J.; et al. Adaptive Changes in Serotonin Neurons of the Raphe Nuclei in 5-HT₄ Receptor Knock-out Mouse. *Eur. J. Neurosci.* **2006**, *24*, 1053–1062. [[CrossRef](#)] [[PubMed](#)]
43. Moha ou Maati, H.; Bourcier-Lucas, C.; Veyssiere, J.; Kanzari, A.; Heurteaux, C.; Borsotto, M.; Haddjeri, N.; Lucas, G. The Peptidic Antidepressant Spadin Interacts with Prefrontal 5-HT₄ and MGluR2 Receptors in the Control of Serotonergic Function. *Brain Struct. Funct.* **2016**, *221*, 21–37. [[CrossRef](#)] [[PubMed](#)]
44. Ge, J.; Barnes, N.M. 5-HT₄ receptor-mediated modulation of 5-HT release in the rat hippocampus in vivo. *Br. J. Pharmacol.* **1996**, *117*, 1475–1480. [[CrossRef](#)] [[PubMed](#)]
45. Twarkowski, H.; Hagen, H.; Manahan-Vaughan, D. The 5-hydroxytryptamine 4 Receptor Enables Differentiation of Informational Content and Encoding in the Hippocampus. *Hippocampus* **2016**, *26*, 875–891. [[CrossRef](#)] [[PubMed](#)]
46. Hatat, B.; Yahiaoui, S.; Lecoutey, C.; Davis, A.; Freret, T.; Boulouard, M.; Claeysen, S.; Rochais, C.; Dallemagne, P. A Novel in vivo Anti-amnesic Agent, Specially Designed to Express Both Acetylcholinesterase (AChE) Inhibitory, Serotonergic Subtype 4 Receptor (5-HT_{4R}) Agonist and Serotonergic Subtype 6 Receptor (5-HT_{6R}) Inverse Agonist Activities, with a Potential Interest Against Alzheimer's Disease. *Front. Aging Neurosci.* **2019**, *11*, 148. [[PubMed](#)]
47. Consolo, S.; Arnaboldi, S.; Giorgi, S.; Russi, G.; Ladinsky, H. 5-HT₄ receptor stimulation facilitates acetylcholine release in rat frontal cortex. *Neuroreport* **1994**, *5*, 1230–1232. [[CrossRef](#)] [[PubMed](#)]
48. Steward, L.J.; Ge, J.; Stowe, R.L.; Brown, D.C.; Bruton, R.K.; Stokes, P.R.; Barnes, N.M. Ability of 5-HT₄ receptor ligands to modulate rat striatal dopamine release in vitro and in vivo. *Br. J. Pharmacol.* **1996**, *117*, 55–62. [[CrossRef](#)] [[PubMed](#)]

49. Bai, M.; Zhu, X.-Z.; Zhang, Y.; Zhang, S.; Zhang, L.; Xue, L.; Zhong, M.; Zhang, X. Anhedonia Was Associated with the Dysregulation of Hippocampal HTR4 and MicroRNA Let-7a in Rats. *Physiol. Behav.* **2014**, *129*, 135–141. [[CrossRef](#)]
50. Licht, C.L.; Kirkegaard, L.; Zueger, M.; Chourbaji, S.; Gass, P.; Aznar, S.; Knudsen, G.M. Changes in 5-HT₄ Receptor and 5-HT Transporter Binding in Olfactory Bulbectomized and Glucocorticoid Receptor Heterozygous Mice. *Neurochem. Int.* **2010**, *56*, 603–610. [[CrossRef](#)]
51. Vidal, R.; Castro, E.; Pilar-Cuéllar, F.; Pascual-Brazo, J.; Díaz, A.; Rojo, M.L.; Linge, R.; Martín, A.; Valdizán, E.M.; Pazos, A. Serotonin 5-HT₄ Receptors: A New Strategy for Developing Fast Acting Antidepressants? *Curr. Pharm. Des.* **2014**, *20*, 3751–3762. [[CrossRef](#)] [[PubMed](#)]
52. Lucas, G.; Rymar, V.V.; Du, J.; Mnie-Filali, O.; Bisgaard, C.; Manta, S.; Lambas-Senas, L.; Wiborg, O.; Haddjeri, N.; Piñeyro, G.; et al. Serotonin(4) (5-HT₄) receptor agonists are putative antidepressants with a rapid onset of action. *Neuron* **2007**, *55*, 712–725. [[CrossRef](#)] [[PubMed](#)]
53. Karayol, R.; Medrihan, L.; Warner-Schmidt, J.L.; Fait, B.W.; Rao, M.N.; Holzner, E.B.; Greengard, P.; Heintz, N.; Schmidt, E.F. Serotonin receptor 4 in the hippocampus modulates mood and anxiety. *Mol. Psychiatry* **2021**, *26*, 2334–2349. [[CrossRef](#)] [[PubMed](#)]
54. Amigó, J.; Díaz, A.; Pilar-Cuéllar, F.; Vidal, R.; Martín, A.; Compan, V.; Pazos, A.; Castro, E. The absence of 5-HT₄ receptors modulates depression- and anxiety-like responses and influences the response of fluoxetine in olfactory bulbectomized mice: Adaptive changes in hippocampal neuroplasticity markers and 5-HT_{1A} autoreceptor. *Neuropharmacology* **2016**, *111*, 47–58. [[CrossRef](#)] [[PubMed](#)]
55. Castello, J.; LeFrancois, B.; Flajolet, M.; Greengard, P.; E Friedman, E.; Rebholz, H. CK2 regulates 5-HT₄ receptor signaling and modulates depressive-like behavior. *Mol. Psychiatry* **2018**, *23*, 872–882. [[CrossRef](#)] [[PubMed](#)]
56. Guo, Y.; Zhang, L.; Zhang, J.; Lv, S.-X.; Du, C.-X.; Wang, T.; Wang, H.-S.; Xie, W.; Liu, J. Activation and Blockade of Serotonin-4 Receptors in the Lateral Habenula Produce Antidepressant Effects in the Hemiparkinsonian Rat. *Neuropsychobiology* **2021**, *80*, 52–63. [[CrossRef](#)]
57. Pascual-Brazo, J.; Castro, E.; Díaz, Á.; Valdizán, E.M.; Pilar-Cuéllar, F.; Vidal, R.; Treceño, B.; Pazos, Á. Modulation of Neuroplasticity Pathways and Antidepressant-like Behavioural Responses Following the Short-Term (3 and 7 Days) Administration of the 5-HT₄ Receptor Agonist RS67333. *Int. J. Neuropsychopharmacol.* **2012**, *15*, 631–643. [[CrossRef](#)] [[PubMed](#)]
58. Kobayashi, K.; Ikeda, Y.; Sakai, A.; Yamasaki, N.; Haneda, E.; Miyakawa, T.; Suzuki, H. Reversal of Hippocampal Neuronal Maturation by Serotonergic Antidepressants. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 8434–8439. [[CrossRef](#)] [[PubMed](#)]
59. Mendez-David, I.; David, D.J.; Darcet, F.; Wu, M.V.; Kerdine-Römer, S.; Gardier, A.M.; Hen, R. Rapid Anxiolytic Effects of a 5-HT₄ Receptor Agonist Are Mediated by a Neurogenesis-Independent Mechanism. *Neuropsychopharmacology* **2014**, *39*, 1366–1378. [[CrossRef](#)]
60. Ishizuka, T.; Goshima, H.; Ozawa, A.; Watanabe, Y. Stimulation of 5-HT₄ Receptor Enhances Differentiation of Mouse Induced Pluripotent Stem Cells into Neural Progenitor Cells. *Clin. Exp. Pharmacol. Physiol.* **2014**, *41*, 345–350. [[CrossRef](#)]
61. Imoto, Y.; Kira, T.; Sukeno, M.; Nishitani, N.; Nagayasu, K.; Nakagawa, T.; Kaneko, S.; Kobayashi, K.; Segi-Nishida, E. Role of the 5-HT₄ Receptor in Chronic Fluoxetine Treatment-Induced Neurogenic Activity and Granule Cell Dematuration in the Dentate Gyrus. *Mol. Brain* **2015**, *8*, 29. [[CrossRef](#)] [[PubMed](#)]
62. Segi-Nishida, E. The Effect of Serotonin-Targeting Antidepressants on Neurogenesis and Neuronal Maturation of the Hippocampus Mediated via 5-HT_{1A} and 5-HT₄ Receptors. *Front. Cell. Neurosci.* **2017**, *11*, 142. [[CrossRef](#)] [[PubMed](#)]
63. Schill, Y.; Bijata, M.; Kopach, O.; Cherkas, V.; Abdel-Galil, D.; Böhm, K.; Schwab, M.H.; Matsuda, M.; Compan, V.; Basu, S.; et al. Serotonin 5-HT₄ receptor boosts functional maturation of dendritic spines via RhoA-dependent control of F-actin. *Commun. Biol.* **2020**, *3*, 76. [[CrossRef](#)]
64. Hagen, H.; Manahan-Vaughan, D. The serotonergic 5-HT₄ receptor: A unique modulator of hippocampal synaptic information processing and cognition. *Neurobiol. Learn. Mem.* **2017**, *138*, 145–153. [[CrossRef](#)] [[PubMed](#)]
65. Rosel, P.; Arranz, B.; Urretavizcaya, M.; Oros, M.; San, L.; Navarro, M.A. Altered 5-HT_{2A} and 5-HT₄ postsynaptic receptors and their intracellular signalling systems IP3 and cAMP in brains from depressed violent suicide victims. *Neuropsychobiology* **2004**, *49*, 189–195. [[CrossRef](#)] [[PubMed](#)]
66. Madsen, K.; Torstensen, E.; Holst, K.K.; Haahr, M.E.; Knorr, U.; Frokjaer, V.G.; Brandt-Larsen, M.; Iversen, P.; Fisher, P.M.; Knudsen, G.M. Familial risk for major depression is associated with lower striatal 5-HT₄ receptor binding. *Int. J. Neuropsychopharmacol.* **2014**, *18*, pyu034. [[CrossRef](#)]
67. Köhler-Forsberg, K.; Dam, V.H.; Ozenne, B.; Sankar, A.; Beliveau, V.; Landman, E.B.; Larsen, S.V.; Poulsen, A.S.; Ip, C.-T.; Jørgensen, A.; et al. Serotonin 4 Receptor Brain Binding in Major Depressive Disorder and Association With Memory Dysfunction. *JAMA Psychiatry* **2023**, *80*, 296–304. [[CrossRef](#)] [[PubMed](#)]
68. Köhler-Forsberg, K.; Ozenne, B.; Larsen, S.V.; Poulsen, A.S.; Landman, E.B.; Dam, V.H.; Ip, C.-T.; Jørgensen, A.; Svarer, C.; Knudsen, G.M.; et al. Concurrent anxiety in patients with major depression and cerebral serotonin 4 receptor binding. A NeuroPharm-1 study. *Transl. Psychiatry* **2022**, *12*, 273. [[CrossRef](#)] [[PubMed](#)]
69. Sankar, A.; Ozenne, B.; Dam, V.H.; Svarer, C.; Jørgensen, M.B.; Miskowiak, K.W.; Frokjaer, V.G.; Knudsen GM and Fisher, P.M. Association between brain serotonin 4 receptor binding and reactivity to emotional faces in depressed and healthy individuals. *Transl. Psychiatry* **2023**, *13*, 165. [[CrossRef](#)]
70. da Cunha-Bang, S.; Mc Mahon, B.; Fisher, P.M.; Jensen, P.S.; Svarer, C.; Knudsen, G.M. High trait aggression in men is associated with low 5-HT levels, as indexed by 5-HT₄ receptor binding. *Soc. Cogn. Affect. Neurosci.* **2016**, *11*, 548–555. [[CrossRef](#)]

71. Ohtsuki, T.; Ishiguro, H.; Detera-Wadleigh, S.D.; Toyota, T.; Shimizu, H.; Yamada, K.; Yoshitsugu, K.; Hattori, E.; Yoshikawa, T.; Arinami, T. Association between Serotonin 4 Receptor Gene Polymorphisms and Bipolar Disorder in Japanese Case-Control Samples and the NIMH Genetics Initiative Bipolar Pedigrees. *Mol. Psychiatry* **2002**, *7*, 954–961. [[CrossRef](#)]
72. Poinssignon, V.; Colle, R.; Asmar, K.E.; Mendez-David, I.; David, D.J.; Ait Tayeb, A.E.K.; Chappell, K.; Gressier, F.; Herrero, H.; Fève, B.; et al. The GG genotype of the serotonin 4 receptor genetic polymorphism, rs1345697, is associated with lower remission rates after antidepressant treatment: Findings from the METADAP cohort. *J. Affect. Disord.* **2022**, *299*, 335–343. [[CrossRef](#)] [[PubMed](#)]
73. Terry, A.V., Jr.; Buccafusco, J.J.; Jackson, W.J.; Prendergast, M.A.; Fontana, D.J.; Wong, E.H.; Bonhaus, D.W.; Weller, P.; Eglen, R.M. Enhanced delayed matching performance in younger and older macaques administered the 5-HT₄ receptor agonist, RS 17017. *Psychopharmacology* **1998**, *135*, 407–415. [[CrossRef](#)] [[PubMed](#)]
74. Quiedeville, A.; Boulouard, M.; Hamidouche, K.; Da Silva Costa-Aze, V.; Nee, G.; Rochais, C.; Dallemagne, P.; Fabis, F.; Freret, T.; Bouet, V. Chronic activation of 5-HT₄ receptors or blockade of 5-HT₆ receptors improve memory performances. *Behav. Brain Res.* **2015**, *293*, 10–17. [[CrossRef](#)] [[PubMed](#)]
75. Teixeira, C.M.; Rosen, Z.B.; Suri, D.; Sun, Q.; Hersh, M.; Sargin, D.; Dincheva, I.; Morgan, A.A.; Spivack, S.; Krok, A.C.; et al. Hippocampal 5-HT Input Regulates Memory Formation and Schaffer Collateral Excitation. *Neuron* **2018**, *98*, 992–1004. [[CrossRef](#)] [[PubMed](#)]
76. Haahr, M.E.; Fisher, P.; Holst, K.; Madsen, K.; Jensen, C.G.; Marner, L.; Lehel, S.; Baaré, W.; Knudsen, G.; Hasselbalch, S. The 5-HT₄ receptor levels in hippocampus correlates inversely with memory test performance in humans. *Hum. Brain Mapp.* **2013**, *34*, 3066–3074. [[CrossRef](#)] [[PubMed](#)]
77. Stenbæk, D.S.; Fisher, P.M.; Ozenne, B.; Andersen, E.; Hjordt, L.V.; McMahon, B.; Hasselbalch, S.G.; Frokjaer, V.G.; Knudsen, G.M. Brain serotonin 4 receptor binding is inversely associated with verbal memory recall. *Brain Behav.* **2017**, *7*, e00674. [[CrossRef](#)] [[PubMed](#)]
78. Murphy, S.E.; Wright, L.C.; Browning, M.; Cowen, P.J.; Harmer, C.J. A role for 5-HT₄ receptors in human learning and memory. *Psychol. Med.* **2020**, *50*, 2722–2730. [[CrossRef](#)] [[PubMed](#)]
79. de Cates, A.N.; Wright, L.C.; Martens, M.A.G.; Gibson, D.; Türkmen, C.; Filippini, N.; Cowen, P.J.; Harmer, C.J.; Murphy, S.E. Déjà-vu? Neural and behavioural effects of the 5-HT₄ receptor agonist, prucalopride, in a hippocampal-dependent memory task. *Transl. Psychiatry* **2021**, *11*, 497. [[CrossRef](#)]
80. de Cates, A.N.; Martens, M.A.G.; Wright, L.C.; Gibson, D.; Spitz, G.; Gould van Praag, C.D.; Suri, S.; Cowen, P.J.; Murphy, S.E.; Harmer, C.J. 5-HT₄ Receptor Agonist Effects on Functional Connectivity in the Human Brain: Implications for Pro-cognitive Action. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **2023**, *8*, 1124–1134. [[CrossRef](#)]
81. Madsen, K.; Neumann, W.J.; Holst, K.; Marner, L.; Haahr, M.T.; Lehel, S.; Knudsen, G.M.; Hasselbalch, S.G. Cerebral serotonin 4 receptors and amyloid- β in early Alzheimer's disease. *J. Alzheimers Dis.* **2011**, *26*, 457–466. [[CrossRef](#)]
82. Wang, J.-W.; Liu, J.; Wang, Z.-L.; Gao, F.; Yang, J.; Wang, X.-C.; Guo, Y.; Wang, Y.; Ma, B.-R.; Wang, H.-S.; et al. Activation and blockade of 5-HT₄ receptors in the dorsal hippocampus enhance working and hippocampus-dependent memories in the unilateral 6-hydroxydopamine lesioned rats. *Behav. Brain Res.* **2022**, *431*, 113952. [[CrossRef](#)] [[PubMed](#)]
83. Ishii, T.; Kinoshita, K.-I.; Muroi, Y. Serotonin 5-HT₄ Receptor Agonists Improve Facilitation of Contextual Fear Extinction in an MPTP-Induced Mouse Model of Parkinson's Disease. *Int. J. Mol. Sci.* **2019**, *20*, 5340. [[CrossRef](#)] [[PubMed](#)]
84. Hashemi-Firouzi, N.; Shahidi, S.; Soleimani Asl, S. Chronic stimulation of the serotonergic 5-HT₄ receptor modulates amyloid-beta-related impairments in synaptic plasticity and memory deficits in male rats. *Brain Res.* **2021**, *1773*, 147701. [[CrossRef](#)] [[PubMed](#)]
85. Cho, S.; Hu, Y. Activation of 5-HT₄ receptors inhibits secretion of beta-amyloid peptides and increases neuronal survival. *Exp. Neurol.* **2007**, *203*, 274–278. [[CrossRef](#)] [[PubMed](#)]
86. Barrett, M.J.; Cloud, L.J.; Shah, H.; Holloway, K.L. Therapeutic approaches to cholinergic deficiency in Lewy body diseases. *Expert Rev. Neurother.* **2020**, *20*, 41–53. [[CrossRef](#)] [[PubMed](#)]
87. De Deurwaerdère, P.; Cervo, L.; Stinus, L.; Spampinato, U. Central 5-HT(4) receptors and dopamine-dependent motor behaviors: Searching for a functional role. *Pharmacol. Biochem. Behav.* **2002**, *71*, 627–633. [[CrossRef](#)] [[PubMed](#)]
88. Reavill, C.; Hatcher, J.P.; Lewis, V.A.; Sanger, G.J.; Hagan, J. 5-HT₄ receptors antagonism does not affect motor and reward mechanisms in the rat. *Eur. J. Pharmacol.* **1998**, *357*, 115–120. [[CrossRef](#)] [[PubMed](#)]
89. Shi, Y.; Qiao, C.-M.; Zhou, Y.; Wu, J.; Cui, C.; Hong, H.; Jia, X.-B.; Huang, S.-B.; Yao, L.; Zhao, W.-J.; et al. Protective effects of prucalopride in MPTP-induced Parkinson's disease mice: Neurochemistry, motor function and gut barrier. *Biochem. Biophys. Res. Commun.* **2021**, *556*, 16–22. [[CrossRef](#)]
90. Padovan-Neto, F.E.; Patterson, S.; Voelkner, N.M.F.; Altwal, F.; Beverley, J.A.; West, A.R.; Steiner, H. Selective Regulation of 5-HT_{1B} Serotonin Receptor Expression in the Striatum by Dopamine Depletion and Repeated L-DOPA Treatment: Relationship to L-DOPA-Induced Dyskinesias. *Mol. Neurobiol.* **2020**, *57*, 736–751. [[CrossRef](#)]
91. Cirillo, R.; Duperrier, S.; Parekh, P.; Millot, M.; Li, Q.; Thiolat, M.L.; Morelli, M.; Xie, J.; Le Bars, D.; Redouté, J.; et al. Striatal serotonin 4 receptor is increased in experimental parkinsonism and dyskinesia. *J. Park. Dis.* **2024**, *14*, 261–267. [[CrossRef](#)]
92. Reynolds, G.P.; Mason, S.L.; Meldrum, A.; De Keczer, S.; Parnes, H.; Eglen, R.M.; Wong, E.H. 5-Hydroxytryptamine (5-HT)₄ receptors in post mortem human brain tissue: Distribution, pharmacology and effects of neurodegenerative diseases. *Br. J. Pharmacol.* **1995**, *114*, 993–998. [[CrossRef](#)]

93. Wong, E.H.F.; Reynolds, G.P.; Bonhaus, D.W.; Hsu, S.; Eglen, R.M. Characterization of [3H]GR 113808 binding to 5-HT 4 receptors in brain tissues from patients with neurodegenerative disorders. *Behav. Brain Res.* **1996**, *73*, 249–252. [[CrossRef](#)]
94. Asai, H.; Udaka, F.; Hirano, M.; Minami, T.; Oda, M.; Kubori, T.; Nishinaka, K.; Kameyama, M.; Ueno, S. Increased gastric motility during 5-HT4 agonist therapy reduces response fluctuations in Parkinson's disease. *Park. Relat. Disord.* **2005**, *11*, 499–502. [[CrossRef](#)]
95. Jean, A.; Conductier, G.; Manrique, C.; Bouras, C.; Berta, P.; Hen, R.; Charnay, Y.; Bockaert, J.; Compan, V. Anorexia induced by activation of serotonin 5-HT4 receptors is mediated by increases in CART in the nucleus accumbens. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16335–16340. [[CrossRef](#)] [[PubMed](#)]
96. Jean, A.; Laurent, L.; Delaunay, S.; Doly, S.; Dusticier, N.; Linden, D.; Neve, R.; Maroteaux, L.; Nieoullon, A.; Compan, V. Adaptive Control of Dorsal Raphe by 5-HT4 in the Prefrontal Cortex Prevents Persistent Hypophagia following Stress. *Cell Rep.* **2017**, *21*, 901–909. [[CrossRef](#)]
97. Ratner, C.; Ettrup, A.; Bueter, M.; Haahr, M.E.; Compan, V.; le Roux, C.W.; Levin, B.; Hansen, H.H.; Knudsen, G.M. Cerebral markers of the serotonergic system in rat models of obesity and after Roux-en-Y gastric bypass. *Obesity* **2012**, *20*, 2133–2141. [[CrossRef](#)] [[PubMed](#)]
98. Haahr, M.E.; Rasmussen, P.M.; Madsen, K.; Marnier, L.; Ratner, C.; Gillings, N.; Baaré, W.F.; Knudsen, G.M. Obesity is associated with high serotonin 4 receptor availability in the brain reward circuitry. *Neuroimage* **2012**, *61*, 884–888. [[CrossRef](#)]
99. Hu, Z.; Ying, X.; Huang, L.; Zhao, Y.; Zhou, D.; Liu, J.; Zhong, J.; Huang, T.; Zhang, W.; Cheng, F.; et al. Association of human serotonin receptor 4 promoter methylation with autism spectrum disorder. *Medicine* **2020**, *99*, e18838. [[CrossRef](#)] [[PubMed](#)]
100. Park, M.T.M.; Jeon, P.; Khan, A.R.; Dempster, K.; Mallar Chakravarty, M.; Lerch, J.P.; MacKinley, M.; Théberge, J.; Palaniyappan, L. Hippocampal neuroanatomy in first episode psychosis: A putative role for glutamate and serotonin receptors. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *110*, 110297. [[CrossRef](#)]
101. Jiang, S.S.; Gong, M.N.; Rao, W.; Chai, W.; Chen, W.Z.; Zhang, X.; Nie, H.B.; Xu, R.S. 5-Hydroxytryptamine: A potential therapeutic target in amyotrophic lateral sclerosis. *Neural Regen. Res.* **2023**, *18*, 2047–2055. [[PubMed](#)]
102. Konen, J.R.; Haag, M.M.; Guseva, D.; Hurd, M.; Linton, A.A.; Lavoie, B.; Kerrigan, C.B.; Joyce, E.; Bischoff, S.; Swann, S.; et al. Prokinetic actions of luminally acting 5-HT4 receptor agonists. *Neurogastroenterol. Motil.* **2021**, *33*, e14026. [[CrossRef](#)] [[PubMed](#)]
103. Zhu, Y.; Cheng, J.; Yin, J.; Yang, Y.; Guo, J.; Zhang, W.; Xie, B.; Lu, H.; Hao, D. Effects of sacral nerve electrical stimulation on 5 HT and 5 HT3AR/5 HT4R levels in the colon and sacral cord of acute spinal cord injury rat models. *Mol. Med. Rep.* **2020**, *22*, 763–773. [[CrossRef](#)] [[PubMed](#)]
104. Mahajan, R. Prucalopride: A Recently Approved Drug by the Food and Drug Administration for Chronic Idiopathic Constipation. *Int. J. Appl. Basic Med. Res.* **2019**, *9*, 1–2. [[CrossRef](#)] [[PubMed](#)]
105. Bassotti, G.; Satta, P.U.; Berti, G.; Lai, M.; Villanacci, V.; Bellini, M. Pharmacotherapeutic advances for chronic idiopathic constipation in adults. *Expert Opin. Pharmacother.* **2022**, *23*, 2053–2078. [[CrossRef](#)] [[PubMed](#)]
106. Zhang, X.; Li, Y.; Liu, C.; Fan, R.; Wang, P.; Zheng, L.; Hong, F.; Feng, X.; Zhang, Y.; Li, L.; et al. Alteration of enteric monoamines with monoamine receptors and colonic dysmotility in 6-hydroxydopamine-induced Parkinson's disease rats. *Transl. Res.* **2015**, *166*, 152–162. [[CrossRef](#)] [[PubMed](#)]
107. Mozaffari, S.; Nikfar, S.; Daniali, M.; Abdollahi, M. The pharmacological management of constipation in patients with Parkinson's disease: A much-needed relief. *Expert Opin. Pharmacother.* **2020**, *21*, 701–707. [[CrossRef](#)]
108. Liu, Z.; Sakakibara, R.; Odaka, T.; Uchiyama, T.; Uchiyama, T.; Yamamoto, T.; Ito, T.; Asahina, M.; Yamaguchi, K.; Yamaguchi, T.; et al. Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. *Mov. Disord.* **2005**, *20*, 680–686. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.