DIALOGUES IN CLINICAL NEUROSCIENCE
2025, VOL. 27, NO. 1, 112–128
https://doi.org/10.1080/19585969.2025.2502028

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REVIEW ARTICLE

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5-HT6 receptors: Contemporary views on their neurobiological and pharmacological relevance in neuropsychiatric disorders

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ABSTRACT

Despite the relatively limited number of serotonergic neurons in humans, serotonin plays a key role in neurophysiological functions, including sleep, pain perception, learning, memory, cognition, emotion, reward, and mood regulation. Altered serotonergic neurotransmission is linked to conditions such as anxiety, depression, anorexia, migraine, insomnia, schizophrenia, Alzheimer's disease (AD), and cognitive impairments. The 5-HT6 receptor (5-HT6R), mainly found in brain regions involved in cognition, is a promising therapeutic target for cognitive deficits in neuropsychiatric disorders, particularly AD and schizophrenia. Preclinical studies have shown that 5-HT6R antagonists improve cognitive function. 5-HT6R interacts dynamically with an extensive intracellular protein network, regulating the localisation, trafficking, and signalling of these proteins. Proteomic and genetic studies have revealed interactions with mTOR kinase and neurofibromin, both of which are crucial for synaptic plasticity, learning, and memory. Fyn kinase is also associated with 5-HT6Rs, reinforcing receptor expression and G-protein coupling. Notably, the G protein-regulated inducer of neurite outgrowth 1 (GPRIN1) interacts with 5-HT6Rs independently of agonists, enhancing receptor activity. This review highlights the clinical testing of 5-HT6R ligands as regulators of these complex signalling properties, underscoring their therapeutic potential in addressing cognitive impairments associated with neuropsychiatric disorders.

ARTICLE HISTORY
Received 8 October 2024
Revised 2 April 2025
Accepted 30 April 2025

KEYWORDS
5-HT6 receptor; neuropsychiatric disorders; cognitive impairment; learning; memory

1. Introduction

The 5-HT6 receptor (5-HT6R), a member of the serotonin (5-HT) receptor family, is an attractive target for the treatment of neuropsychiatric disorders (Johnson et al. 2008; Quiedeville et al. 2014). It is primarily located in the central nervous system of mammals (Chaumont-Dubel et al. 2020). Although the striatum has the highest density, 5-HT6Rs are also found in other brain regions, such as the cortex, hippocampus, ventrolateral orbital cortex (VLO), and spinal cord (Chaumont-Dubel et al. 2020; Zhang et al. 2020). A growing focus on 5-HT6R over the past two decades has emerged as a potential therapeutic target for cognitive enhancement. The growing interest is marked by the continuous development of newer 5-HT6R compounds reaching the clinic.

5-HT6R, like other 5-HTRs and more generally other G-protein coupled receptors (GPCR), is at the forefront of new pharmacological concepts of drug effects. Initially described as a GPCR coupled to Gs protein stimulating adenylyl cyclase in the presence of 5-HT (Ruat et al. 1993), molecular data have shown that 5-HT6R interacts with multiple partners, sometimes independently of an interaction with Gs (Chaumont-Dubel et al. 2020). Among the molecular partners, we describe the interactions with mammalian target of rapamycin (mTOR) kinase, neurofibromin, tyrosine-protein kinase Fyn (Fyn kinase), and G protein-regulated inducer of neurite outgrowth 1 (GPRIN1) (Dayer et al. 2015). The action of compounds on these targets could be important for the activity of 5-HT6R, ultimately leading to an impact on synaptic plasticity, learning, and memory.

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Additionally, like other 5-HTRs (De Deurwaerdère et al. 2020), 5-HT6R can display agonist-independent activity (constitutive activity) towards its intracellular signalling pathways (Kohen et al. 2001; Mokhtar et al. 2023). This implies distinct responses of 5-HT6R agonists, neutral antagonists, and inverse agonists (drugs that can block the constitutive activity of receptors). It is an important aspect to cover with 5-HT6R drugs, as both agonists and antagonists (most of them being inverse agonists) have been proposed as cognitive enhancers (Fone 2008; Bokare et al. 2018).

These pharmacological aspects are essential to consider in view of the diseases for which 5-HT6R ligands have been proposed, including Alzheimer's disease (AD), schizophrenia, mood disorders, neuropathic pain, and epilepsy to cite a few. Despite clear preclinical evidence of their potential benefits, clinical trials reaching stage III for some of them are still disappointing. To gain a more comprehensive understanding of the biological effects of 5-HT6R, it is essential to investigate the intricate intracellular protein networks associated with the receptor that regulate receptor targeting to specific cellular compartments, trafficking in and out of the plasma membrane, and signalling. This review focuses on the biological effects of 5-HT6R and some of its specific partners and addresses the pharmacology of 5-HT6R. This review focuses on the biological roles of 5-HT6R and some of its key interacting partners.

2. Distribution of 5-HT6 receptors

5-HT6Rs are gaining attention as potential therapeutic targets for neurological and psychiatric conditions because of their involvement in cognition, mood regulation and neurotransmitter modulation. Their presence in crucial brain areas, such as the nucleus accumbens (NAc), islands of Calleja, striatum, olfactory tubercle, and hippocampus, indicates their role in dopamine and glutamate signalling. These pathways are essential in disorders such as schizophrenia, AD, and depression (Helboe et al. 2015).

5-HT6Rs are found alongside dopamine D1 and D2 receptors in the striatum and NAc, suggesting their involvement in dopamine-serotonin interactions (Helboe et al. 2015). Certain atypical antipsychotics act on 5-HT6Rs, and their modulation can improve treatment effectiveness while minimising extrapyramidal side effects by affecting glutamatergic and cholinergic pathways (Meltzer and Bobo 2006; Nirogi et al. 2023).

5-HT6Rs are found in brain areas essential for learning and memory, and blocking these receptors has been shown to boost cholinergic and glutamatergic activity (Ward and Dorsa 1996). The detection of 5-HT6Rs in both cortical interneurons and pyramidal cells indicates their potential involvement in neurodevelopmental conditions such as autism and Attention-Deficit/Hyperactivity Disorder (Helboe et al. 2015). Furthermore, their participation in serotonin-driven signalling suggests a role in mood regulation, which may be relevant to depression and anxiety (Fukuyama et al. 2023). Recent studies have emphasised the presence of 5-HT6Rs in neuronal cilia, where they influence local serotonin release and activate RhoA signalling, potentially affecting epigenetic processes (Sheu et al. 2022). Studies using transgenic mice with GFP-tagged 5-HT6Rs have confirmed their primary localisation in primary cilia and limited expression in interneurons (Dupuy et al. 2023). Moreover, a truncated, non-functional variant of 5-HT6R has been discovered in the caudate and substantia nigra, indicating a complex regulatory system (Hannon and Hoyer 2008).

3. Canonical 5-HT6R coupling to Gs

G protein-coupled receptors (GPCRs) exhibit constitutive activity (De Deurwaerdère et al. 2020). 5-HT6R is a remarkable example of a GPCR with high constitutive activity, even when expressed at endogenous levels (Chaumont-Dubel et al. 2020).

Compared with other 5-HTRs, the orthosteric binding sites of 5-HT6R and 5-HT2R show significant structural similarities. Gαs plays an important role in mediating the 5-HT6R signalling pathway by increasing cyclic AMP (cAMP) levels (Schoeffter and Waeber 1994; Kang et al. 2005; Romero et al. 2006). However, antibody immunocapture and scintillation proximity assay (SPA) methods have shown that 5-HT6R binds to other Gα protein subunits (Gαi/o or Gαq) and intracellular proteins (Dupuis et al. 2008; Chaumont-Dubel et al. 2020; Bockaert et al. 2021). Among the various neuronal adenylyl cyclase (AC) subtype isoforms discovered to date, the most abundant is AC5. Gs-sensitive ACs are present in all brain regions, with the highest expression in the striatum and NAc. *In vivo*, two specific neuronal cyclases, AC1 and AC8, can be activated independently of the Gs protein and are sensitive to calmodulin. AC5 specifically binds to 5-HT6R expressed in HEK-293 cells; however, this binding is not shared by AC1 or AC8 (Baker et al. 1998). AC1 is located in the hippocampus, whereas AC8 is located in both the hippocampus and hypothalamus (Baker et al. 1998; Schaefer et al. 2000).

3.1. Dynamic interactions between 5-HT6R and its protein partners

5-HT6R exhibits intrinsic constitutive activity, which is facilitated by specific structural determinants that can be modulated by protein interactions (He et al. 2023). This constitutive activation lasts longer than that induced by agonists. As a result, the intracellular GPCR-interacting proteins (GIP)-dependent activation of GPCRs can be 'permanent', as shown by the constitutive activation of 5-HT6R resulting from its interaction with neurofibromin-1, or can last for hours, as with the activation of the mGlu1/5 receptor by Homer1a. Thus, GIP protein turnover is a key factor in determining the dynamics of constitutive receptor activity.

In addition to canonical G protein-coupled signalling, GPCRs can recruit various downstream effectors that are independent of G proteins (Weis and Kobilka 2018). Proteomic and genetic studies have identified several 5-HT6R proteins (Luo et al. 2024). These include neurofibromin, which functions as a Ras GTPase-activating protein, and the mechanistic target of rapamycin (mTOR). The association between mTOR and 5-HT6R involves the last 49 C-terminal amino acids of the receptor; however, the C-terminal domain of the receptor alone is insufficient to recruit mTOR (Meffre et al. 2012).

3.1.1. Role of GPRIN1 in modulating 5-HT6R activity

The association of G protein-regulated inducer of neurite outgrowth 1 (GPRIN1) with 5-HT6R enhances the constitutive activity of the receptor in the Gs signalling pathway. GPRIN1 activates Gs signalling by either increasing the recruitment of activated Gαs or changing the conformational state of the receptor.

GPRIN1 is a member of the GPRIN family (which comprises three gene products: GPRIN1–GPRIN3) (Ge et al. 2009). GPRIN1 is the sole member of the GPRIN protein family identified in the 5-HT6R interactome and is expressed in the central nervous system in neurons but not in glial cells (Pujol et al. 2020). As a substrate of Cyclin-Dependent Kinase 5 (Cdk5), it is involved in neurodevelopmental processes by promoting neurite extension through selective binding to activated G proteins (Nordman et al. 2014) (Figure 1D). Although GPRIN1 is not present in primary cilia, it colocalizes with 5-HT6R in the cell body, where it promotes the coupling of the receptor to Gs (Pujol et al. 2020). The 5-HT6R-GPRIN1 complex requires both the C-terminal domain of the receptor and its ability to activate G proteins. Co-immunoprecipitation of 5-HT6R with GPRIN1 is physiologically relevant because it increases cAMP generation and facilitates neurite growth and branching *via* a PKA-dependent mechanism. The dynamic interplay between 5-HT6R and GPRIN1 highlights the allosteric regulation of GPCRs by protein partners and shows how these interactions regulate dendritic arborisation and other processes related to nervous system development (Pujol et al. 2020).

During neuronal differentiation, 5-HT6R interacts sequentially with Cdk5 and GPRIN1. 5-HT6R-operated Cdk5-Cdc42 signalling promotes the initiation of neurite outgrowth (Figure 1D), whereas the interaction between 5-HT6R and GPRIN1 induces neurite extension and branching (Nordman and Kabbani 2012; Nordman et al. 2014). This occurs in an agonist-independent but adenosine 3′, 5′-monophosphate (cAMP)-dependent manner in both neuroblastoma cells and primary striatal neurons (Pujol et al. 2020). Immunohistochemical investigations of newborn mice revealed the presence of the 5-HT6R-GPRIN1 complex in cortical and striatal neurons. This complex was found in the soma but not in primary cilia. Additional evidence from cultured neurons indicates that a subset of 5-HT6R has a somatodendritic location and colocalizes with GPRIN1, which differs from the pattern observed in adult mice (Pujol et al. 2020).

Phosphorylation of 5-HT6R at Ser^{350} by Cdk5 affects its binding partners (Figure 1B). The non-phosphorylatable mutant (S350A) showed increased GPRIN1 interaction, whereas the phosphomimetic mutant (S350D) did not recruit GPRIN1. Likewise, the overexpression of p35, a Cdk5 coactivator, decreases the ability of 5-HT6R to bind to GPRIN1, further supporting the notion that the phosphorylation of Ser^{350} by Cdk5 inhibits the 5-HT6R-GPRIN1 interaction and that the association of Cdk5 and GPRIN1 with the receptor is exclusive (Pujol et al. 2020).

In summary, the canonical coupling of 5-HT6R to G proteins and its specific interaction with different forms of neuronal adenylate cyclase form a crucial foundation for understanding the diverse roles of the receptor across various brain regions. This understanding paves the way for investigating its dynamic protein interactions and broader functional significance in the future.

3.1.2. Functional consequences of GPRIN1 involvement in 5-HT6R signalling

The association between GPRIN1 and 5-HT6R occurs in the absence of an agonist and is reduced by the antagonist/inverse agonist SB271046, suggesting a conformation-dependent interaction between the two.

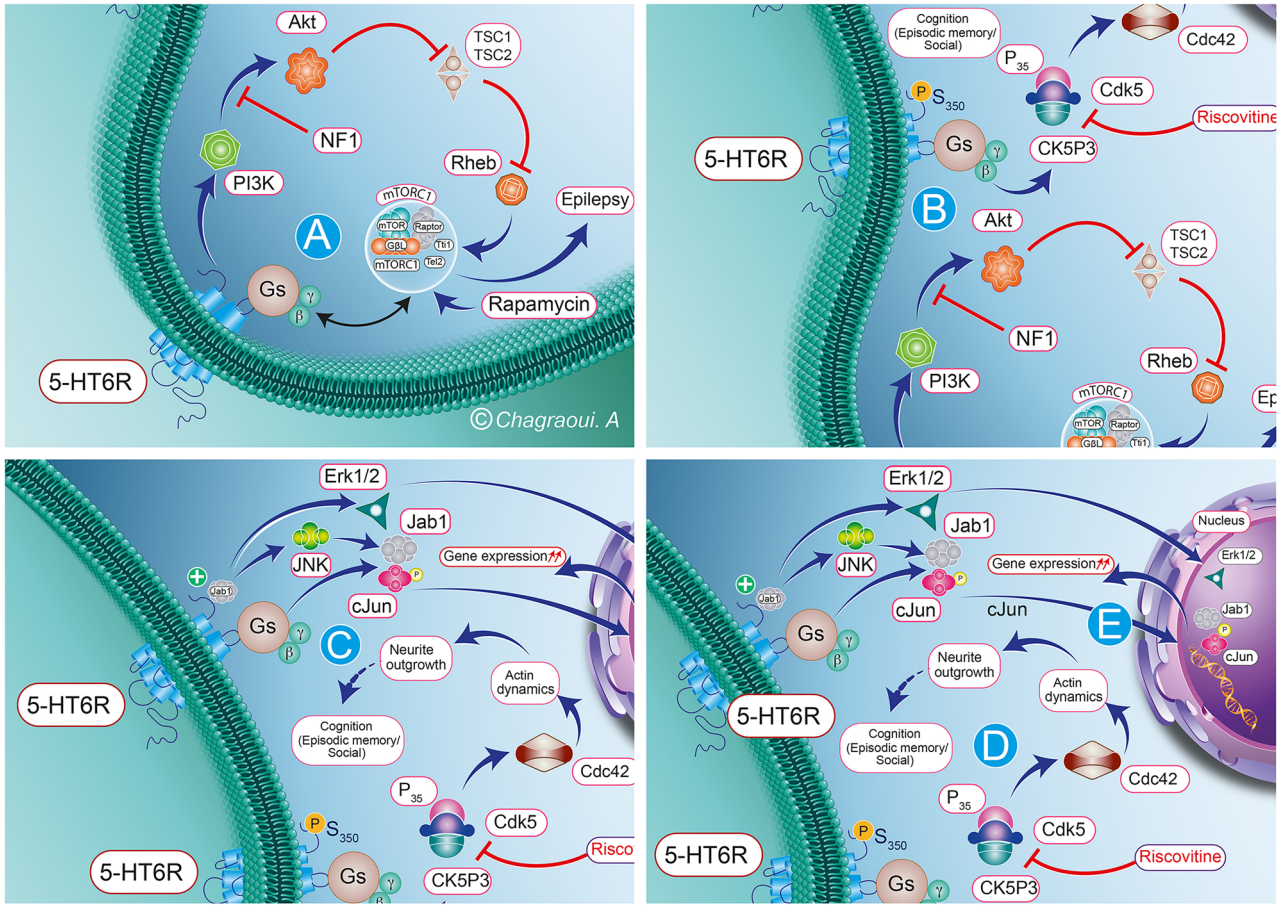

Figure 1. (A) 5-HT6R-induced mTOR signalling occurs *via* the PI3K/Akt/Rheb pathway, which is typically activated by insulin and other growth factors. 5-HT6R overexpression affects mTOR signalling, which modulates epileptic activity. (B) Agonist-independent engagement of Cdk5-Cdc42 signalling depends on receptor phosphorylation at Ser350 by receptor-bound Cdk5. (C) 5-HT6R interacts with Jun-1 activation domain-binding protein (Jab1). In addition, 5-HT6R activation increased c-Jun phosphorylation and Jab1-c-Jun association.(D) As a substrate of Cdk5, it is involved in neurodevelopmental processes by promoting neurite extension through selective binding to activated G proteins. (E) Translocation of Jab1 into the nucleus of the cells.

AC: Adenylyl Cyclase; Akt: Protein kinase B (PKB), also known as Akt, Cdc42: Cell Division Cycle 42, Cdk5: Cyclin-dependent kinase 5, cJun: Proto-oncogene c-Jun, Erk1/2: Extracellular signal-Regulated Kinases 1 et 2, GPRIN1: G Protein-Regulated Inducer of Neurite Outgrowth 1, Jab1: Jun activation domain-binding protein 1, JNK: c-Jun N-terminal Kinase, mTOR: mechanistic Target Of Rapamycin, NF1: Neurofibromin 1, PI3K: Phosphoinositide 3-Kinase, Rheb: Ras homolog enriched in the brain, TSC1: Tuberous Sclerosis Complex 1, TSC2: Tuberous Sclerosis Complex 1.

This interaction enhances the constitutive activity of 5-HT6R, which is an important characteristic of 5-HT6R. This suggests allosteric activation of the receptor by GIPs, highlighting a unique mode of receptor modulation. Interestingly, this interaction did not alter the agonist-dependent responses. Moreover, it contributes to neuronal differentiation by promoting neurite elongation and facilitating branching, which are crucial for establishing neuronal connectivity (Pujol et al. 2020).

3.2. Recruitment of mTOR pathway proteins by 5-HT6R

mTOR plays a pivotal role in the development of the nervous system and is involved in several processes, including the initiation of cell differentiation (Easley et al. 2010). Evidence indicates that 5-HT6R directly interacts with mTOR and other proteins in the mTOR pathway (Meffre et al. 2012). Moreover, in HEK-293 cells, 5-HT6R induced mTOR signalling *via* the PI3K/Akt/Rheb pathway, reminiscent of mTOR activation by insulin and other growth factors (Swiech et al. 2008; Zhou and Huang 2010; Wang and Proud 2011) (Figure 1A).

Previous studies have identified two proteins that are critical for the assembly and function of the mTORC1 protein complex, namely Tti1 and Tel2 (Kaizuka et al. 2010), which are also recruited by 5-HT6R. Three additional proteins identified in the 5-HT6R interactome, namely Ras homolog enriched in the brain (Rheb), neurofibromin 1, and Vps34, have been implicated in mTOR activation pathways (Swiech

et al. 2008; Zhou and Huang 2010), along with mTOR and GβL (G protein β-subunit-like protein, also known as mLST8), which is part of the rapamycin-sensitive mTOR complex 1 (mTORC1) (Park et al. 2024).

3.2.1. Functional consequences of 5-HT6R-operated mTOR signalling

Increased 5-HT6R levels were observed in both human epileptic tissues and animal models of epilepsy (Figure 1A). Overexpression of 5-HT6R affects mTOR signalling, which modulates epileptic activity (Wang et al. 2015). Additionally, the 5-HT6R antagonist SB-399885 reduced both seizures and mTOR activity in a pilocarpine-induced rat model of epilepsy. These findings suggest that increased 5-HT6R expression may be associated with increased mTOR activity, which underlies the pathophysiology of epilepsy.

Knockdown of Disc1, a key gene implicated in schizophrenia, in adult-born dentate granule neurons results in cognitive and affective deficits associated with a non-physiological increase in mTOR signalling (Zhou et al. 2013). The results showing an increase in mTOR activity in the prefrontal cortex of adult rats reared in social isolation or treated with phencyclidine during the neonatal period, two models used to address specific symptoms of schizophrenia in rodents are consistent with these observations (Meffre et al. 2012). Furthermore, 5-HT6R antagonists abolished the increase in mTOR signalling, and rapamycin, similar to 5-HT6R antagonists, prevented the impaired social cognition and episodic memory observed in both developmental schizophrenia models.

Evidence suggests that chronic THC exposure during adolescence induces sustained activation of the mTOR pathway in the prefrontal cortex (PFC) *via* 5-HT6Rs (Berthoux et al. 2020). This activation affects the excitatory/inhibitory balance of the PFC and the activity of layer V pyramidal neurons, leading to cognitive deficits (Berthoux et al. 2020). Similar to observations made in neurodevelopmental models of schizophrenia, cognitive deficits induced by chronic THC exposure in mice during adolescence can be reversed by either rapamycin or 5-HT6R antagonists (Berthoux et al. 2020), highlighting the potential therapeutic benefits of targeting both mTOR and 5-HT6Rs.

One effective approach to prevent cognitive impairment in adulthood is the administration of 5-HT6R antagonists during early adolescence. In addition, stimulation of 5-HT6R enhances mTOR signalling in neurons located in the prefrontal cortex, a critical area for social cognition. Activation of 5-HT6R increases the efficacy of GABAergic neurotransmission, consistent with the presence of receptors in GABAergic neurons. The mTOR inhibitor rapamycin successfully prevented the cognitive abnormalities caused by 5-HT6R agonists. This establishes a clear link between mTOR signalling and cognitive impairment in the brain. In addition, the mTOR pathway interferes with autophagy in AD by phosphorylating key autophagy triggers, resulting in the accumulation of harmful proteins in the brain. This dysregulation is amplified by the presence of tau and beta-amyloid proteins, which stimulate mTOR signalling. Thus, the activation of 5-HT6R, which stimulates the mTOR pathway, may play a role in autophagy deficiency. Therapeutic approaches that rely on 5-HT6R inhibition may provide novel methods for restoring autophagic function in AD.

3.3. Role of neurofibromin in modulating 5-HT6R activity

Neurofibromin, a Ras GTPase-activating protein (Ras-GAP) (Xu et al. 1990) encoded by the *NF1* gene, plays a role in pathways leading to mTOR activation. 5-HT6R is known for the sustained activation of the Gs/adenylyl cyclase signalling pathway, which is influenced by its interaction with neurofibromin (Deraredj Nadim et al. 2016). The constitutive activity of 5-HT6R in Gs signalling requires the interaction of the receptor with the pleckstrin homology (PH) and C-terminal (CTD) domains of neurofibromin (Deraredj Nadim et al. 2016). Reducing neurofibromin expression in HeLa cells and striatal neurons leads to a decrease in constitutive 5-HT6R activity in Gs signalling (Deraredj Nadim et al. 2016).

Neurofibromatosis type 1 (Nf1) is a genetic disease caused by mutations in the *NF1* gene. It affects skin pigmentation and leads to the development of benign skin tumours and mild tumours in the central and peripheral nervous systems. Additionally, it may result in learning difficulties, attention deficiencies, and issues related to visuospatial abilities (Ozonoff 1999). The interaction between neurofibromin and 5-HT6R results in a notable increase in the constitutive activity of 5-HT6R in Gs signalling. Inhibiting the interaction between neurofibromin-1 and 5-HT6Rs using a specific peptide decreased the constitutive activity of 5-HT6Rs in primary neurons. These findings indicate that the physical interaction of receptors with molecular partners, such as neurofibromin-1, strengthens their inherent connections with Gs (Deraredj Nadim et al. 2016). Mutations affecting the PH domain disrupt interactions with 5-HT6R without enhancing constitutive activity. Nevertheless, the expression of the PH domain could

potentially restore cAMP signalling *via* 5-HT6R in neurofibromin-deficient cells. The role of neurofibromin in constitutive receptor activity is also supported by a decrease in CREB phosphorylation observed in the prefrontal cortex of *Nf1*$^{+/-}$ mice, suggesting a reduction in agonist-independent Gs signalling. Furthermore, systemic administration of an inverse agonist (SB271046) disrupts the interaction between 5-HT6R and neurofibromin, resulting in decreased CREB phosphorylation in the prefrontal cortex of wild-type mice but not in *Nf1*$^{+/-}$ mice (Deraredj Nadim et al. 2016).

The complex interplay between neurofibromin and 5-HT6R in controlling receptor activity provides valuable insights into the cellular signalling pathways. However, when mutations occur in neurofibromin, particularly in the context of neurofibromatosis type 1 (NF1), it raises important questions regarding the broader implications of neurofibromin mutations on 5-HT6R function and the resulting neuronal abnormalities in patients with Neurofibromatosis type 1 (Nf1). Investigating the effects of neurofibromin mutations on 5-HT6R function and neuronal abnormalities in patients with Nf1 could enhance our understanding of the physical interaction between neurofibromin and 5-HT6R and its impact on receptor activity.

Deraredj Nadim et al. found that the brains of *Nf1*$^{+/-}$ mice (Nf1 model) exhibited a significant decrease in constitutive receptor activity compared to WT mice (Deraredj Nadim et al. 2016). This emphasises the importance of the interaction between 5-HT6R and neurofibromin in constitutive receptor activity.

3.4. Role of Fyn in modulating 5-HT6R activity

Fyn, a member of the Src family of tyrosine kinases, phosphorylates numerous proteins, influencing cellular processes such as migration and cell proliferation. This phosphorylation attaches a phosphate group to the PKA catalytic subunit, enhancing its activity and suggesting a broader role for Fyn in regulating the signalling pathways (Schmoker et al. 2018). 5-HT6R interacts with Fyn's SH3 domain *via* its carboxyl-terminal region. (Yun et al. 2007).

Neurons, glia, and oligodendrocytes express high levels of Fyn (Semba et al. 1986). Fyn KO mice exhibit abnormalities, including spatial memory deficits and anxiety (Grant et al. 1992; Miyakawa et al. 1994). Fyn is physically associated with 5-HT6R (Figure 2C), thereby enhancing the localisation of cell surface receptors and G protein coupling. 5-HT6R activation increases Fyn kinase activity, as evidenced by increased Fyn Tyr420 phosphorylation (Yun et al. 2007). This regulation requires the interaction of Fyn's SH3 domain interaction with 5-HT6R's carboxyl terminus, leading to Tyr-420 autophosphorylation and Fyn activation (Chaumont-Dubel et al. 2020; Bockaert et al. 2021). Fyn is involved in Netrin-121-mediated cortical neuronal axon growth (DeGeer et al. 2013) and NCAM-mediated GABAergic synapse maturation (Chattopadhyaya et al. 2013). Evidence suggests that Fyn plays an important role in brain development (Schmoker et al. 2018; Liu et al. 2022; Zhu et al. 2024). Deletion of both Fyn and Src genes in mice impairs cerebellar Purkinje cell

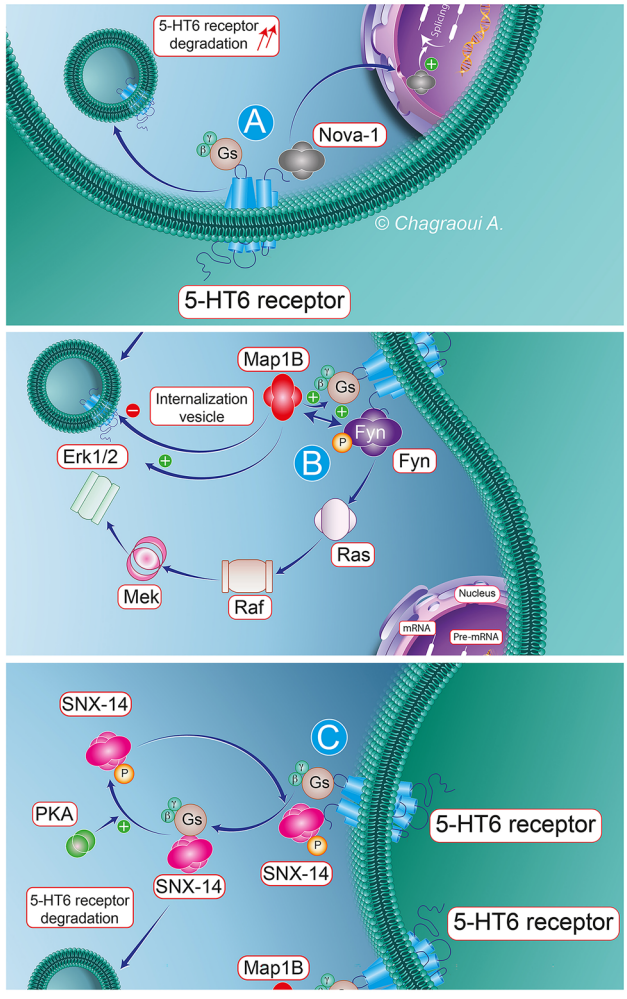

Figure 2. (A) Nova-1 plays a role in 5-HT6R-operated signalling *via* its direct interaction with the C-terminus (CT) of 5-HT6R. (B) 5-HT6R directly interacts with Fyn, Jab 1, and MAP1B *via* the C-terminal region. (C) Physical association of Fyn with 5-HT6R enhances cell surface receptor expression and G-protein coupling. Additional 5-HT6R partner proteins include SNX14, which influences both the signalling and trafficking of 5-HT6R.

Fyn: Fyn proto-oncogene; Map1B:Microtubule-Associated Protein 1B; Mek: Mitogen-Activated Protein Kinase; Nova-1: Neuro-Oncological Ventral Antigen 1; PKA: Protein Kinase A; Raf: Rapidly Accelerated Fibrosarcoma; Ras: Rat Sarcoma; SNX-14: Sorting Nexin 14.

migration and causes inverted cortical plaques. Suppressing Src alone results in a normal brain appearance, whereas Fyn loss alone generates an intermediate phenotype, highlighting the link between Fyn, Src, and reelin signalling pathways (DeGeer et al. 2013).

Tau protein has many proline-rich motifs that are crucial for its interaction with the SH3 domain of Fyn kinase. This interaction relies on the fifth and sixth PXXP motifs of the tau protein. Phosphorylation at S214 in these motifs impairs Tau binding to Fyn, indicating that phosphorylation may control this interaction (Jos et al. 2024). *In vivo* experiments have shown that the lack of Fyn results in reduced tau hyperphosphorylation and aggregation, indicating Fyn's role in tau pathology progression, irrespective of amyloid-β (Aβ) (Briner et al. 2020). Fyn directly influences tau phosphorylation at specific sites, such as Tyr18, which is crucial for tau's pathological role in AD, affecting its solubility and aggregation propensity (Lau et al. 2016). In frontotemporal dementia, tau's ability to bind Fyn increases with the phosphorylation levels of 4 R-tau or mutant 4 R proteins, leading to increased neurodegeneration (Bhaskar et al. 2005). Phosphorylation significantly influences the Fyn–4R-tau interaction, with implications for AD pathology. Although phosphorylation can enhance or inhibit this interaction depending on the specific site, Fyn plays a pivotal role in modulating the pathological state of tau. Understanding these molecular dynamics offers promising directions for developing targeted therapies for AD and related tauopathies.

Phosphorylation of Tau on the Y18 epitope of Fyn is key to its fibrillation, emphasising the critical role of Fyn in Tau aggregation (Briner et al. 2020). The regulatory impact of Fyn extends beyond phosphorylation, as its interaction with Tau depends on the conformation of Tau, influencing nanoclustering and signalling mechanisms (Martínez-Mármol et al. 2023).

3.4.1. Functional consequences of Fyn involvement in 5-HT6R signalling

Combining the modulation of 5-HT6R with Fyn kinase inhibitors has the potential to enhance the therapeutic outcomes of AD by addressing both the symptoms and underlying mechanisms (Czarnota-Łydka et al. 2022). Activation of Fyn kinase by amyloid-β oligomers results in synaptic dysfunction, emphasising its role in AD (Lewis 2012). In addition, studies have shown that Fyn inhibition can reduce phospho-Tau accumulation and enhance memory performance in tauopathies (Tang et al. 2020). The interaction between 5-HT6R and Fyn exacerbates synaptic dysfunction through pathways involving the modulation of amyloid-β and NMDA receptors. This further links these proteins to cognitive decline associated with AD (Lewis 2012). Thus, targeting Fyn with 5-HT6R antagonists may help mitigate cognitive deficits in AD by reducing neuroinflammation and excitotoxicity.

3.5. Role of Nova-1 in modulating 5-HT6R activity

Additional 5-HT6R partner proteins include neurooncological ventral antigen 1 (Nova-1), a splicing regulator that is highly expressed in the brain and plays a role in splicing several pre-mRNAs, including GlyRa2, GnRH GABA A, and Rg2 (Kim et al. 2019). These pre-mRNAs are important for synaptic activity and neuronal development (Ratti et al. 2008; Xin et al. 2017). 5-HT6R directly interacts with Nova-1 (Figure 2A), as evidenced by yeast two-hybrid assays, GST pull-down assays, and co-immunoprecipitation tests. This interaction was confirmed in both cell lines and rat brain tissue. Overexpression of 5-HT6R caused Nova-1 to move from the nucleus to the cytoplasm, subsequently reducing Nova-1 splicing activity (Figure 2B) (Kim et al. 2019). Conversely, an increase in Nova-1 expression resulted in a reduction in both the activity and protein levels of 5-HT6R, indicating a reciprocal interplay between the two partner proteins (Kim et al. 2019).

Nova-1 is an RNA-binding protein that contains three RNA-binding domains, known as K-homology (KH) motifs (Kim et al. 2019). The KH3 domain is required for binding pre-mRNA targets and mediating alternative RNA splicing (Buckanovich and Darnell 1997; Jensen et al. 2000b). Nova-1 contributes to mRNA maturation by regulating pre-mRNA splicing. The pre-mRNA targets of this protein mainly encode proteins involved in synapse formation and synaptic transmission, such as the inhibitory GABAA receptor γ2 (GABAARγ2) and the glycine receptor α2 (GlyRα2) (Jensen et al. 2000a; Dredge and Darnell 2003; Ule et al. 2006; Ule and Darnell 2006; Racca et al. 2010). Additionally, Nova-1 null animals display apoptotic neuronal death and splicing abnormalities in GABAARγ2 (Dredge and Darnell 2003) and GlyRα2 (Jensen et al. 2000a) and die shortly after their birth. Disruption of the RNA-binding function of Nova-1 can significantly affect the post-transcriptional processing of target RNAs, which is essential for modulating protein expression and function. Proteomic and genetic investigations have implicated the abnormal function of RNA-binding proteins in various human diseases, including neurological disorders (Zhou et al. 2014).

The interaction between Nova-1 and 5-HT6R may affect neural cell survival and inhibitory synaptic transmission, in line with their crucial roles in inhibitory

synapses, preventing excessive neuronal firing, and maintaining excitatory-inhibitory balance in the brain.

3.5.1. Functional consequences of Nova-1 involvement in 5-HT6R signalling

The significance of subcellular translocation of Nova-1 remains unclear, as its expression levels remain unchanged. Some studies have suggested that translocation weakens the binding of Nova-1 to its RNA splicing targets in the nucleus. The regulation of 5-HT6R activity appears to be dependent on Nova-1 levels. Overexpression of Nova-1 reduced Ca^{2+} levels stimulated by 5-HT. This involves the activation of 5-HT6R and ERK1/2 phosphorylation. Consequently, 5-HT6R is susceptible to degradation, leading to reduced 5-HT6R levels and activity (Kim et al. 2019). However, the mechanism by which Nova-1 leads to 5-HT6R degradation remains unclear (Kim et al. 2019).

Overexpression of 5-HT6Rs, which disrupts Nova-1 function, may negatively impact neuronal survival and inhibit synaptic transmission. 5-HT6Rs also promote cell survival (Yun et al. 2010). Additionally, 5-HT6Rs may mediate anti-apoptotic effects by activating Jab1. These data together suggest that dysregulation of Nova-1 or 5-HT6Rs may be linked to neurological diseases.

3.6. Role of Jab1 in modulating 5-HT6R activity

A yeast two-hybrid assay showed that human 5-HT6R interacts with Jun-1 activation domain-binding protein (Jab1) (Figure 1C). In addition, 5-HT6R activation increased c-Jun (Figure 1C) phosphorylation and Jab1-c-Jun association, resulting in Jab1 translocation into the nucleus (Figure 1E). Reducing Jab1 levels *via* small interfering RNA decreases 5-HT6R-mediated signalling and membrane expression, whereas Jab1 overexpression does not significantly alter these parameters (Yun et al. 2010).

3.6.1. Functional consequences of Jab1 involvement in 5-HT6R signalling

Administration of SB271046 (5-HT6R antagonist/inverse agonist) has been shown to reduce the occurrence of spontaneous recurrent seizures while improving associated learning and memory impairments in epileptic rats (Pilocarpine Model of Chronic temporal lobe epilepsy) (Liu et al. 2019). SB271046 appeared to act by normalising the activity of the Jab1/phospho-c-jun pathway (Figure 1C), suggesting the potential involvement of the Jab1/phospho-c-jun pathway in the regulation of 5-HT6Rs in status epilepticus. In addition, Jab1 has been identified as a possible factor involved in the progression of neurological disorders, including AD and Parkinson's disease. This is probably due to its interaction with the endoplasmic reticulum stress transducer, IRE1 (Oono et al. 2004).

The significant increase in 5-HT6R expression and Jab1/p-c-Jun pathway stimulation observed in epileptic mice (Pilocarpine Model of Chronic temporal lobe epilepsy) suggests a potential link between these alterations, seizure onset, and cognitive deficits. Moreover, the interaction between Jab1 and 5-HT6R may contribute to the progression of degenerative conditions observed in these animals (Liu et al. 2019).

4. Pharmacological implications and questions

5-HT6R is the only 5-HTR subtype expressed exclusively in the central nervous system, where it is primarily located in the primary cilium. However, it can also transiently or developmentally localise to other parts of the neuron, including cell bodies (Brailov et al. 2000; Dupuy et al. 2023). The primary cilium plays an essential role in regulating migration and determining cell fate (Arellano et al. 2012; Guo et al. 2017; Anvarian et al. 2019). The pharmacological profile of 5-HT6R may vary depending on its localisation, making it a promising therapeutic target for treating various neuropsychiatric disorders, including autism spectrum disorder, schizophrenia, and AD-related dementia (Chaumont-Dubel et al. 2023). While both agonists and antagonists of the 5-HT6R have demonstrated comparable behavioural outcomes in preclinical investigations (Tables 1 and 2), the majority of clinical assessments have primarily concentrated on antagonists. This focus is largely attributable to their potential therapeutic benefits in managing conditions such as schizophrenia and cognitive impairments associated with AD and other neurological disorders (Nirogi et al. 2023).

4.1. Effects of 5-HT6R agonists

Activation of 5-HT6Rs in the hippocampus improves emotional memory (Pereira et al. 2015) (Table 1). Administration of WAY208466 (a selective and potent 5-HT6R agonist) improved cognitive processing in mice during the passive avoidance test, presumably by facilitating neuronal plasticity in the caudate putamen, hippocampus, and prefrontal cortex (Pereira et al. 2015). 5-HT6R agonists Agonists of the 5-HT6R have shown protective effects against amyloid-β (Aβ) toxicity in neurons, a key feature of AD. For example, compound 15, which acts as a dual ligand for 5-HT6R and

Table 1. Agonists of 5-HT6R in preclinical models.

Disease	Main effects	References
Anxiety	Anxiolytic effects	(Pyka et al. 2024)
Depression	Effects similar to those of antidepressants	(Siwek et al. 2024)
Neuropathic pain	Reduced allodynia	(Zhang et al. 2020)
Alzheimer's disease	Improved cognitive function, reduced Aβ toxicity	(Pyka et al. 2024; Siwek et al. 2024)
Schizophrenia	Improvement of cognitive deficits, reduction in psychosis	(Nikiforuk et al. 2013; Suárez-Santiago et al. 2022)

SERT, provides neuroprotection by reducing the activity of pro-apoptotic enzymes caspase-3 and caspase-7. Moreover, the effects of MK-801-induced memory deficits were reversed, with outcomes similar to those observed with antidepressant medications. This finding suggests potential benefits for cognitive and mood-related symptoms in patients with dementia (Siwek et al. 2024). Studies have indicated that 5-HT6R agonists, such as WAY-181187, can increase brain-derived neurotrophic factor (BDNF) levels, which may enhance neuroplasticity and mitigate cognitive impairment (Ou et al. 2022). Moreover, 5-HT6R agonists containing selenium exhibit antioxidant properties and influence the expression of antioxidant genes, underscoring their potential neuroprotective effects (Pyka et al. 2024). E-6837, a 5-HT6R agonist, has also shown efficacy in reversing ketamine-induced cognitive deficits and its potential for the treatment of schizophrenia (Nikiforuk et al. 2013).

The 5-HT6R plays an important role in modulating synaptic plasticity, particularly in the hippocampus. Activation of 5-HT6Rs plays a critical role in controlling glutamate release and NMDA receptor function, both of which are essential for synaptic plasticity and learning (Meffre et al. 2012) (Table 1).

4.2. Effects of 5-HT6R antagonists

Numerous studies have demonstrated that 5-HT6R antagonists can improve cognitive performance in rats during various learning and memory tasks (Foley et al. 2004; Woods et al. 2012) (Table 2). The apparent discrepancy with 5-HT6R agonists could be attributed to the different mechanisms through which agonists and antagonists of the 5-HT6R receptor modulate neurotransmitter systems. Antagonists such as SB-271046 and SB-742457 have been shown to modulate the release of neurotransmitters, including acetylcholine and glutamate, which are essential for learning and memory (Rychtyk et al. 2019; Suárez-Santiago et al. 2022).

Table 2. Key effects of 5-HT6R antagonists in preclinical models.

Disease	Main effects	References
Cannabis-induced deficits	Prevention of cognitive deficits, inhibition of mTOR activation	(Berthoux et al. 2020)
Dementia	Neuroprotection and alleviation of neuropsychiatric symptoms	(Siwek et al. 2024)
Depression	Modulation of serotonin neurotransmission, improvement of mood	(Yun et al. 2015)
Epilepsy	Suppression of convulsive activity, reduction of mTOR signalling	(Wang et al. 2015)
Alzheimer's disease	Improved cognitive functions, reduced apoptosis and neuroprotection	(Hu et al. 2017)
Schizophrenia	antipsychotic potential and neuroprotective effects	(Marcos et al. 2008; Ivachtchenko et al. 2017)

Consistent with these findings, electrophysiological studies have revealed that the antagonistic effects of SB-271046 on 5-HT6Rs lead to an increase in basal excitatory synaptic transmission and the activation of NMDARs, which are two mechanisms involved in synaptic plasticity and memory consolidation (Lahogue et al. 2023). Blocking 5-HT6Rs receptors with SB357134 prevented amnesia induced by the non-competitive NMDAR antagonist of NMDARs, MK-801 (Márquez et al., 2023). These results suggest that 5-HT6R contributes to improved memory function, particularly in the hippocampus. Other preclinical studies have shown that the inhibition of 5-HT6Rs has beneficial effects on cognitive function. For instance, treatment with 5-HT6R inverse agonists, such as SB258585, in *Nf1*$^{+/-}$ mice, a model of neurofibromatosis type 1, has been shown to improve long-term social and associative memory by reducing mTOR pathway activity (Doucet et al. 2021). Memory consolidation and amnesia are believed to influence 5-HT6R expression in brain regions associated with memory, such as the prefrontal cortex, hippocampus, amygdala, and striatum (Meneses et al. 2007).

Bilateral intrahippocampal injections of the 5-HT6R antagonist SB271046 inhibited the CORT-induced enhancement of memory consolidation. In contrast to the agonist EMD386088, the antagonist SB271046 decreased a decrease 5-HT6Rin 5-HT6R receptor expression. These findings suggest an interaction between glucocorticoids, such as CORT, and 5-HT6R in the hippocampus, which may contribute to the modulation of memory consolidation associated with emotionally arousing experiences (Mohamad Rezaei et al. 2020) (Table 2).

5-HT6R antagonists have shown potential for improving learning and memory in various cognitive tasks. These beneficial effects are evident in both healthy animals and those with memory impairment, including deficits induced by anticholinergic agents (Woolley et al. 2003; Lieben et al. 2005). Moreover, in the MK-801 model of cognitive impairment, 5-HT6R antagonists alleviate key symptoms of schizophrenia, such as conditioned inhibitory reflex deficits (Gravius et al. 2011). In addition, concomitant blockade of 5-HT6R and 5-HT2AR ameliorates sensory gating, as measured by prepulse inhibition, mimicking the efficacy of the atypical antipsychotics clozapine and risperidone (Fijał et al. 2014). These convergent preclinical data demonstrating the procognitive effects of 5-HT6R blockade have led to the development of several ligands targeting 5-HT6Rs for the treatment of cognitive impairment in AD (Šimić et al. 2017).

Studies have found that 5-HT6R antagonists may be effective in addressing the cognitive impairments associated with cannabis use among adolescents. Early intervention with a 5-HT6R antagonist has been shown to effectively halts the prolonged activation of mTOR signalling within the prefrontal cortex, suggesting a potential therapeutic approach for managing cannabis-related cognitive challenges (Berthoux et al. 2020). Moreover, compounds that act on both 5-HT6R and serotonin reuptake transporters have shown potential for mitigating neuropsychiatric symptoms associated with dementia. These compounds offer protection against amyloid-β toxicity and mimic the effects of antidepressants, emphasising their potential in managing the behavioural and psychological symptoms associated with dementia (Siwek et al. 2024). However, challenges still need to be addressed (Berthoux et al. 2020) (Table 2).

4.3. Pharmacological considerations

The behavioural outcomes observed with 5-HT6R agonists and antagonists highlight the complex pharmacodynamics of this receptor, which is likely influenced by its subcellular positioning, receptor reserve, and downstream signalling mechanisms. Agonists appear to enhance synaptic plasticity and offer neuroprotection, particularly in hippocampal networks. Conversely, antagonists appear to facilitate cognitive enhancement by disinhibiting glutamatergic and cholinergic neurotransmissions. This paradoxical convergence suggests the potential for biased signalling or context-specific modulation, including variations in age, region, and pathologies. The interplay between 5-HT6R signalling and the mTOR pathway indicates that both excessive activation and inhibition may yield therapeutic advantages, depending on the neuropsychiatric condition being treated. Consequently, pharmacological approaches should consider the distinct characteristics of ligands (such as partial agonism, inverse agonism, and dual targeting with SERT) and the dynamic regulation of 5-HT6R expression in different disease states. These refined strategies, which emphasise a deeper understanding of ligand specificities, are expected to enhance translational success and mitigate the unsatisfactory outcomes observed in earlier clinical trials that predominantly focused on the antagonists.

5. Therapeutic implications

The potential therapeutic applications of 5-HT6R agonists span a wide range of neurological and neuropsychiatric disorders, including AD, schizophrenia, depression, anxiety, and neuropathic pain.

5.1. Alzheimer's disease

5-HT6R agonists have demonstrated the potential to enhance cognitive abilities and decrease neuroinflammation in preclinical AD models. Their capacity to mitigate Aβ toxicity and bolster neurotrophic support positions them as promising candidates for therapies aimed at modifying the disease (Więckowski et al. 2022; Pyka et al. 2024; Siwek et al. 2024).

A substantial body of research has been dedicated to investigated the cognitive-enhancing effects of 5-HT6R antagonists in AD. Compounds such as idalopirdine and intepirdine have been shown to be effective in mitigating cognitive impairments. However, larger phase 3 trials have yielded unsatisfactory results (Nirogi et al. 2023). Moreover, phase 3 trials of the leading compound idalopirdine, used in combination with the acetylcholinesterase inhibitor donepezil in patients with AD, have been unsuccessful (Atri et al. 2018). Conversely, novel agents such as AVN-211 and AVN-322 have shown significant cognitive improvements in preclinical models, underscoring their potential as therapeutic options (Ivachtchenko et al. 2016; 2017; Atri et al. 2018). Despite these challenges, the potential of 5-HT6R antagonists in addressing neuropsychiatric symptoms of dementia remains significant (Nirogi et al. 2023).

5.2. Schizophrenia

Research on schizophrenia has highlighted the efficacy of 5-HT6R agonists in reducing cognitive impairment and behaviours associated with psychosis. Their

capacity to modulate glutamatergic and GABAergic transmission makes them particularly effective in addressing the cognitive and perceptual symptoms associated with this disorder (Nikiforuk et al. 2013; Suárez-Santiago et al. 2022). 5-HT6R antagonists have shown potential in addressing residual psychotic symptoms and cognitive impairments. A clinical trial involving the antagonist Avisetron revealed notable improvements in female patients, suggesting possible sex-specific differences in treatment efficacy (Morozova et al. 2017). Additionally, another study using the 5-HT6 antagonist Dimebon reported enhancements in negative symptoms and cognitive abilities, such as working memory and attention, in individuals with schizophrenia (Morozova et al. 2012; de Bruin and Kruse 2015). Masupirdine, a targeted 5-HT6R antagonist, has demonstrated potential in alleviating agitation and aggressive-like behaviours in animal studies and has exhibited promising effects in a phase 2 clinical trial pertaining to agitation and psychosis associated with AD (Nirogi et al. 2023).

5.3. Depression and anxiety

5-HT6R agonists exhibit antidepressant and anxiolytic properties in various preclinical animal models. Their capacity to influence the serotonin and glutamate systems positions them as a promising alternative to existing antidepressant therapies (Czarnota-Łydka et al. 2022; Siwek et al. 2024).

5.4. Neuropathic pain

The therapeutic potential of 5-HT6R agonists in neuropathic pain management of neuropathic pain has been investigated. The modulatory effects of these compounds on glutamatergic transmission in the ventrolateral orbital cortex represent a novel approach to address pain (Zhang et al. 2020). In diabetic neuropathy, constitutive 5-HT6R activity is thought to be uncontrolled, contributing to the sensation of persistent pain through high mTOR activity, which amplifies pain signals, creating a state of mechanical hyperalgesia in diabetic rats (Mokhtar et al. 2023). However, there is a lack of clinical data on the therapeutic potential of 5-HT6R receptor agonists in neuropathic pain treatment the treatment of neuropathic pain.

5.5. Epilepsy

Recent studies have investigated the effects of 5-HT6R antagonists on epilepsy. The selective 5-HT6R antagonist, SB-399885, SB-399885 suppressed epileptic seizures and decreased mTOR activity in a pilocarpine-induced epilepsy model (Wang et al. 2015). This indicates that 5-HT6R antagonists may influence seizure activity by affecting the mTOR pathway, suggesting a potential new treatment strategy for epilepsy. Currently, clinical evidence supporting the efficacy of 5-HT6R receptor antagonists in the management of epilepsy is lacking or remains limited.

5.6. Pharmacological considerations

The lack of effect of 5-HT6R antagonists on AD has been debated in the literature (Millan et al. 2020). The search for selectivity may not be the correct strategy for such a complex spectrum of cognitive issues. New ligands that concomitantly target dopamine D3Rs (Grychowska et al. 2019), 5-HT3Rs, and/or monoamine oxidase (MAO) (Grychowska et al. 2023) have been developed. A potentially relevant strategy would be to combine selective drugs targeting different mechanisms or neuronal processes (e.g., mTOR reduction through different pathways, as proposed with the combination of D3R and 5-HT6R antagonists (Millan et al. 2020)) and limit the oxidative metabolism associated with MAOB activity (Di Giovanni et al. 2016). These strategies, analogous to the treatment of schizophrenia with drugs that correct monoaminergic transmission at D2/D3Rs, 5-HT1A/2ARs, and possibly 5-HT2BRs (Di Giovanni et al. 2016), certainly warrant consideration.

However, there are still missing links to better address the strategy of targeting 5-HT6Rs in AD and, more generally, in diseases associated with cognitive defects. One challenge in addressing the cognitive deficits linked to 5-HT6R is understanding the pharmacological profile of agents targeting these receptors. This includes the differentiation between agonists, inverse agonists, and neutral antagonists. Determining the procognitive effects of 5-HT6R antagonists is a significant challenge, particularly given the potential of N-skatyltryptamines, which act as dual 5-HT6R/D2R ligands, to exhibit procognitive potential by modulating both 5-HT and DA receptors (Hogendorf et al. 2021). Recently reported neutral antagonists (CPPQ, PZ-1922) could also be interesting, with distinct preclinical effects compared to prototypical inverse agonists such as intepirdine (Grychowska et al. 2023). One could argue that the effects of agonists, inverse agonists, and neutral antagonists could vary according to the nature of the cognitive processes analysed and the underlying signalling pathways involved. However,

limited data are available comparing selective 5-HT6R agonists, inverse agonists, and antagonists in the same model and cognitive task. Another important point to consider is the physiological status of 5-HT6Rs (constitutively active, serotonergic tone, phasic transmission) in one or more brain regions involved in cognitive processes (Millan et al. 2020). Beyond these considerations, one may wonder whether the pharmacological evaluation of agonist/inverse agonist/neutral antagonist status is fully accurate for GPCRs such as 5-HT6R, which can directly interact with many partners beyond the Gs protein. Ligands can be considered complex regulators of receptor activity, which is governed by the cells expressing the receptor.

This highlights the need to address a new type of pharmacology beyond the classical picture of the pathophysiology of diseases associated with cognitive deficits. Regarding serotonergic tone, a decrease in 5-HT tone is anticipated, which could be associated with a decrease in 5-HT6Rs in AD (Šimić et al. 2017). These findings would support the use of 5-HT6Rs agonists. However, the status of the receptor, including its level of constitutive activity and specific localisation in the cell, also conditioning partnerships with intracellular signalling pathways, seems to be essential in the case of 5-HT6Rs. Although we can postulate that 5-HT6R ligands correct the aberrant activity of the receptor, the nature of this aberrant activity remains largely unknown in AD, schizophrenia, and epilepsy.

5.6.1. Neuroprotection in dementia

Compounds that act on both 5-HT6R and serotonin reuptake transporters have shown potential for mitigating neuropsychiatric symptoms associated with dementia. These compounds offer protection against amyloid-β toxicity and mimic the effects of antidepressants, emphasising their potential in managing the behavioural and psychological symptoms associated with dementia (Siwek et al. 2024). However, challenges still need to be addressed (Berthoux et al. 2020).

6. Conclusion

The development of new chemical scaffolds, such as partial or inverse agonists and neutral antagonists of 5-HT6R, could lead to the identification of ligands with unique pharmacological profiles, thereby offering promising candidates for future clinical trials targeting AD and other cognitive disorders. Numerous ligands that target 5-HT6R have been developed. These compounds have progressed to the early phases of clinical trials, and strategies combining these compounds with cholinesterase inhibitors have shown promise (de Jong and Mørk 2017). In particular, idalopirdine and RVT-101 have reached phase III clinical trials, demonstrating the therapeutic potential of 5-HT6R antagonists in AD treatment (Ferrero et al. 2017). Despite promising preclinical results, phase III clinical trials conducted with idalopirdine (STARSHINE, STARBEAM, and STARBRIGHT studies) and intepirdine (MINDSET study) failed to demonstrate a significant improvement in cognitive function. These repeated failures do not seem to be exclusively attributable to methodological limitations but could reflect the still insufficiently understood complexity of the pharmacology and mechanisms of action of the 5-HT6R (Khoury et al. 2018). Assessing the procognitive effects of 5-HT6R targeting (neutral antagonists/inverse agonists/biased agonists) remains a significant challenge, especially considering the potential of N-skatyltryptamines, which act as dual 5-HT6R/D2R ligands, to improve cognition by modulating both 5-HT and DA receptors (Hogendorf et al. 2021). 5-HT6R is functionally regulated by its interactions with various protein partners that influence the receptor-associated signalling cascades. Therefore, the broader context of GPCR signalling should be considered. 5-HT6R function can also be influenced by other factors, such as lipid rafts and adaptor proteins linked to the receptor, which can strongly influence the location of the receptor and the dynamics of its signalling (Björk et al. 2010). The complexity of these interactions highlights the necessity for further investigation into the role of 5-HT6R in brain physiology and its potential as a target for therapeutic interventions.

Acknowledgments

We would like to express our sincere gratitude to Dr. Philippe Marin (Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, Montpellier, France) for his invaluable assistance in editing and proofreading this manuscript.

Authors contributions

AC and PDD: Writing the original draft, reviewing, and editing. AC: Drawing figures in the manuscript. FT: Review and editing. All authors contributed substantially to the scientific process, leading to the review of this article.

Disclosure statement

The authors have no interests or activities that might influence the research (e.g., financial interests in a test or procedure and funding by pharmaceutical companies for research). All authors approved the final version of the manuscript.

Funding

This study received no specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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