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REVIEW

Serotonin Type 6 and 7 Receptors as a Novel Therapeutic Target for the Treatment of Schizophrenia

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Abstract: Schizophrenia is a serious disease of the central nervous system that affects a person's ability to think, feel and behave clearly. Even though the pathophysiological hypothesis of the disease is not clearly understood, dysfunction of dopamine, glutamate, serotonin and other neurotransmitters is widely believed to be involved. Serotonin within the synaptic vesicles functions as neurotransmitter and neurohormone in regulation of emotion, learning, memory, hormone release, cognition and motor function. Dysfunction of normal brain activity of serotonin is associated with schizophrenia. The role of serotonin 6 and 7 receptors in schizophrenia, interaction with neurotransmitters and the effect of drugs on those receptors in schizophrenia are the goal of this review. The aim of this review was to provide information for researchers and other scholars to identify the possible intervention points in the management of schizophrenia. The serotonin 6 and 7 receptors are associated with schizophrenia via modulating cyclic adenosine monophosphate, regulation of Fyn kinase and induction of structural plasticity. The above modulatory effects affect cholinergic, dopaminergic, glutamatergic, adrenergic and GABAergic systems. Recently, diverse numbers of selective agonist and antagonist ligands were developed for both receptors. SGS-518, ABT-354, Lu AE58054, SB-742,457, S-518, AVN-211, AVN-322, SYN-114 and SYN-120 are serotonin 6 receptor antagonists and aripiprazole-controlled release serotonin 7 receptor agonists under clinical trial for schizophrenia. Thus, research on novel drugs that act on serotonin 6 and 7 receptors likely facilitates the intervention into schizophrenia patients seeking better quality of life in the future.

Keywords: serotonin 6 receptor, serotonin 7 receptor, agonist, antagonist, schizophrenia

Introduction

Normal and impaired memory uses different signalling mechanisms with a variety of neurotransmitters. One of those is serotonin (5-HT), which is synthesized from tryptophan in the cell bodies of the dorsal raphe nucleus of brain stem.[1]

Serotonin is transported from the cytoplasm into synaptic vesicles to function as a neurotransmitter and neurohormone[2] in regulation of emotion, learning, memory,[3] mood, nociception, feeding, hormone release,[4] cognition,[5] sexual behaviour, circadian rhythm[6] and motor function.[7] In addition it mediates a variety of peripheral activities like gastrointestinal motility, inflammatory response and nociception modulation.[8]

Dysfunction of normal brain activity of 5-HT is associated with schizophrenia,[9] autism,[10] Alzheimer's diseases,[11] depression,[12] anxiety,[13] drug addiction[14] and

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obesity.[15] This paper will try to summarize the possible connection of 5-HT6 and 5-HT7 receptors with schizophrenia, interaction with inhibitory and excitatory neurotransmitters and progress in ligands that targeted those receptors, especially chemicals under preclinical and clinical trials.

Serotonin Receptors

Based on their structural, biochemical and pharmacological differences serotonin receptors (5-HTRs) have seven distinct receptor families with more than twenty subpopulations (Table 1).[16] All serotonin receptors are G-protein-coupled receptors (GPCRs) with the exception of 5-HT3R, which is ligand-gated ion channel.[2,17]

Even though 5-HT6 and 5-HT7 receptors are less extensively studied receptors because of their more recent identification, selective agonists and antagonists (Table 2) along with 5-HT 6 and 7 receptor knock-out mice have revealed the involvement of those receptors in central nervous system activities.[18] Additionally, their localization in brain areas associated with memory, locomotion and behaviour and their higher affinity to second generation antipsychotics and various antidepressants suggest a possible connection between those receptors and particular psychiatric disorders like schizophrenia.[19]

Distribution of Serotonin 6 and 7 Receptors

Data from in situ hybridization indicate exclusive 5-HT6Rs expression within brain mainly in diencephalon, striatum, nucleus accumbens, olfactory tubercle and cortex and moderately expressed in the amygdala, hypothalamus, thalamus and cerebellum.[20,21] In situ and northern blot analysis shows 5-HT7Rs distribution in human brain in thalamus, hypothalamus, hippocampus and cortex, and this is in good correlation with distribution in rodents.[22]

The above brain areas with higher distribution of 5-HT 6 and 7 receptors are associated with schizophrenia, as well as playing an important role in working memory and cognitive flexibility thought to be fundamental in schizophrenia.[19]

Methods

A reference database was collected from PubMed and Google scholar with the following search terms: serotonin 6 receptors AND schizophrenia, serotonin 7 receptors AND schizophrenia, serotonin 6 receptors agonist AND schizophrenia AND clinical trial, serotonin 7 receptors AND schizophrenia AND clinical trial, serotonin 6 receptors agonist AND serotonin 7 receptors schizophrenia agonist AND schizophrenia. Only English language articles from animal studies and clinical human studies were included. We narrowed our results by searching in conjunction with more specific terms, such as definition, mechanisms, agonist, antagonist and clinical trials. The content of the search results was divided into the following sections: ligands, mechanism of action, modulation of neurotransmitters pathway and role in schizophrenia.

Results

Ligands for 5-HT6R

Although several non-selective agonist and antagonist agents that strongly bind to serotonin 6 and 7 receptors were discovered long ago, the availability of selective ligands was increased in number and diversity after the discovery of human serotonin 6 and 7 receptors (Table 2).

Mechanism Action of 5-HT 6 and 5-HT 7 Receptors

Cyclic Adenosine Monophosphate (cAMP) Pathway

Serotonin 6 receptor activates cyclic adenosine monophosphate pathway (cAMP) signalling pathways through adenylate cyclase stimulation. This increases phosphorylation of dopamine and cAMP-regulated phosphoprotein by protein kinase A (PKA).[2,23] In addition, the receptor stimulates the extracellular signal regulated kinase (ERK) through PKA and Ras monomeric GTPase-dependent mechanism.[24] ERK1/2 activation is PKA and Ras-dependent but Rap_1-independent and involved one or more Raf isoforms which is almost similar to 5-HT6 cAMP-mediated signalling mechanism. Activation of

Table 1 Serotonin 6 and 7 Receptors Distribution, Mechanism of Action and Potential Effect[80,81]

Receptor Type	Receptor Subtype	Main Function	Signaling Pathway	Potential Effect
5-HT_6		Anxiety, Cognition, Learning, Memory, Mood	↑ cAMP	Excitatory
5-HT_7	$5\text{-HT}_{7(A\text{-}D)}$	Thermoregulation, Mood, Respiration, Circadian rhythm, Anxiety, Memory, Sleep	↑ cAMP	Excitatory

Table 2 Agonist and Antagonist Serotonin 6 and 7 Receptor Ligands

Receptor Type	Nature of Interaction	Action	Examples	Reference
5-HT6R	Agonist	Partial agonist	EMD386088 (20-fold selectivity), E-6801 and E-6837	[82–84]
		Fully agonist	R-13c (50-fold selectivity), EMDT, WAY-466, WAY-208,466, E-6837, WAY-181,187 and LY586713	
	Antagonist		• Ro 04–6790 (100-fold selectivity)*, SB-271,046 (50-fold selectivity)*, Ro 63–0563 and SB-258,585 (100-fold selectivity), SB-399,885 (200-fold selectivity), SB-699,929, SB-357,134 and SB-399,885 • [11C]-GSK215083**, AVN-322, BVT-74,316, PRX-07034, R-1485, SYN-114, SYN-120 and SUVN-502 are under clinical trial phase I • AVN-211, SAM-531, SB-742,457 and SGS-518 under clinical trial phase II	[85–89]
5-HT7R	Agonist	Partial agonist	AS-19, MSD-5a and LP-44 (are selective agonists)	[26,90,91]
		Fully agonist	5-CT and 8-OH-DPAT (non-selective for 5-HT7 and 1), E-55,888, E-57,431, LP-211, LP-12 are selective agonists of 5-HT7R	
	Antagonist		DR-4004 (non-selective), SB-258,719, SB-258,741, SB-269,970, SB-656,104, JNJ-18,038,683 are selective antagonists	[90,92]

Notes: *Orally active because of poor capacity to cross blood–brain barrier, **Radiolabelled antagonist developed as serotonin 6 receptor tracer.

5-HT6R stimulates cAMP-dependent pathways involving PKA then followed by Ras, several Raf, MEK and ERK1/2.[25]

Serotonin 7 receptor stimulates ERK in two ways. Firstly, using a cAMP-activated guanine nucleotide exchange factor (Epac) which is a PKA-independent pathway, that leads to Ras-dependent activation of the extracellular, signal-regulated kinases. Secondly, 5-HT7R directly stimulates ERK in hippocampal neurons which is important for hippocampal function and mood regulation.[26] ERK1/2 activation through 5-HT7Rs was inhibited in cells pre-treated with the PKA inhibitor H89. This indicates the involvement of PKA in 5-HT7R-mediated signalling mechanism.[27]

In neurons, where 5-HT 6 and 7 receptors mainly operate, the activation of ERK1/2 is involved in cell morphological changes associated with neuroplasticity, such as the formation of synapses or dendritic spine maturation, thus contributing to learning, memory, cognition and other neural activities.[28]

Regulation of Fyn Kinase

Fyn is a non-receptor protein tyrosine kinase and is expressed to a high degree in neurons, glia and oligodendrocytes.[29] 5-HT6Rs and Fyn are co-localized on the cell surface and on intracellular membranes.[30] The carboxyl terminus of 5-HT6Rs directly interacts with Fyn, leading to Fyn phosphorylation that further activates ERK1/2 through Ras and MEK-dependent pathways.[31] 5-HT6Rs–Fyn protein complexes play important roles in mammalian neuronal functions such as schizophrenia.[25,31]

Induction of Structural Plasticity

Neuronal circuit, cyto-architecture and plasticity of the brain neurons during development are shaped by both 5-HT6 and 7 receptors through proliferation, migration, differentiation, neurotic growth and synaptogenesis modulation. The 5-HT6Rs antagonists SB-271,046, SB-399,885 and SB-742,457 have all been shown to induce the expression levels of polysialylated neuronal cell adhesion molecule (PSA-NCAM) in the dentate gyrus of the rat. PSA-NCAM is indicator of neuronal development and synaptogenesis in immature brain and contributes to morpho-functional reorganization of adult brain. PSA creates physical hindrance to provide antiadhesive properties that reduce the binding affinity between opposite membranes of NCAM on neuronal processes, thus promoting structural plasticity.[32] Thus, an increment in PSA-NCAM neurons by 5-HT6Rs antagonist supports their involvement in neuronal plasticity regulation.[33]

Serotonin 7 receptor activation affects the morphology of neurons, excitation of neurons and neuronal plasticity. This strongly suggests its modulator action in

remodelling neuronal morphology and circuitry in the mature brain.[34] In hippocampus neurons of mouse 5-HT7Rs activation stimulated the small GTP-ases RhoA and Cdc42 and enhanced neurite elongation, dendritic spine density, the number of synaptic contacts and the amount of AMPA receptors expressed at synapses, leading to increased synaptic efficacy.[35] This is also supported by recent data that show that 5-HT7Rs agonists 8-OH-DPAT and LP-211 stimulated neurite outgrowth in primary cultures of mouse and rat striatal and cortical neurons by activation of the cyclin-dependent protein-kinase 5 (Cdk5), a kinase playing an important role in microtubule assembly and cytoarchitecture rearrangements.[36]

Serotonin 6 and 7 Receptor Modulation on Neurotransmitter Pathways

Cholinergic Pathway

Serotonin 6 receptor activation has an inhibitory role on acetylcholine release and is associated with cognitive impairment through cholinergic hypofunction. Selective 5-HT6Rs antagonists have provided direct evidence for the ability of 5-HT6Rs blockade to elevate cholinergic neurotransmission in different brain regions of freely moving adult rats, including the prefrontal cortex (RO-66-0074 and SB-39,988) and the dorsal hippocampus (SB-271,046).[32,37,38] Atropine, a cholinergic antagonist, also attenuated behavioural phenomena associated with 5-HT6Rs inhibition including stretching and yawning. Treatment of rat with 5-HT6Rs antagonist antisense oligonucleotides produces a behavioural alteration that alters by atropine but not haloperidol. This shows the modulatory effect of 5-HT6Rs on Ach release. An effect of 5-HT6Rs on the activity of nigrostriatal pathway by modulation of Ach release is also observed in lesioned rats.[39] Combined 5-HT6Rs antagonist and cholinesterase inhibitor galantamine improves cognitive symptoms in schizophrenic patients.[40] Those findings indicate the positive influence of 5-HT6Rs antagonist in the release of acetylcholine. However, 5-HT7 heteroreceptors have a facilitator role for release of acetylcholine by coupling positively with adenyl cylase.[41]

Glutamate Pathway

Serotonin 6 receptors activation has inhibitory effect on release of glutamate.[42] Chronic treatment with glutamatergic receptor antagonists resulted in a decrease in striatal mRNA levels of 5-HT6Rs. SB-271,046, a 5-HT6Rs antagonist, induces the release of the excitatory neurotransmitter glutamate in the dorsal hippocampus and frontal cortex, as well as aspartate in the frontal cortex.[43]

Clozapine has high affinity for 5-HT6Rs that enhance glutamate levels in the frontal cortex, and this neurochemical effect contributes to the efficacy of this drug in improving negative symptoms and cognitive dysfunction observed in patients with schizophrenia.[40]

Acute and chronic activations of 5-HT7Rs have opposite results on glutamate result. The effect of acute activation of 5-HT7Rs in hippocampus is in the post-synaptic terminals and increases the basal glutamate transmission by increasing AMPA receptors expression and NMDA-evoked current.[44]

However, long-term activation of 5-HT7Rs up-regulates platelet-derived growth factor (PDGF)-β receptor expression and activity which inhibits the membrane expression of NMDA receptors. This activation of PDGFβ receptors selectively inhibits NMDA receptor currents and is involved in neuroprotection by protecting neurons against NMDA-induced excitotoxicity.[45]

Gamma-Amino Butyric Acid (GABA) Pathway

Within the striatum 5-HT6Rs mRNA is expressed extensively on GABAergic striatopallidal neurons and striatonigral neurons. This localization and effect of 5-HT6R with GABAergic neurons was confirmed by WAY-466 5-HT6Rs agonist.[32] Tonic activation of 5-HT6Rs expressed on GABAergic neurons leads to the induction of GABA release and in turn the inhibition of downstream cholinergic and glutamatergic neurons. Blockade of 5-HT6Rs effectively removes this tonic GABAergic inhibition of downstream neurons, resulting in enhanced neurotransmission of Ach and glutamate.[32]

The carboxyl terminal of the 5-HT6Rs recruits Cdk5, a signaling protein, which is implicated in schizophrenia. This 5-HT6/Cdk5-dependent signalling pathway affects neuronal migration, neurite growth and dendritic structure through phosphorylation of the Cdk5 substrate histone H1.[46]

Additionally, serotonin 6 receptor forms complexes with proteins that regulate developmental processes including mTOR pathway. The mTOR pathway plays a crucial role in cell proliferation, synaptogenesis and growth of dendrites and axons. Its disturbance in

prefrontal and medial frontal cortex results in cognitive symptoms of schizophrenia.[47]

Modulation of GABAergic transmission in raphe nuclei by 5-HT7Rs activation decreases serotonin release.[47] In the raphe nuclei 5-HT7Rs are not localized directly on serotonin cells but rather on GABAergic and glutamatergic neurons. The activation of 5-HT7Rs enhances the excitability of GABAergic neurons in globus pallidus neurons.[48] 5-HT7Rs-mediated GABA release and activation of spontaneous inhibitory postsynaptic currents frequency is partially due to increase in glutamate release from excitatory terminals located on interneurons through activation of 5-HT7Rs located on glutamatergic neurons and partially due to 5-HT7Rs localized on GABAergic cells.[49]

Dopamine and Norepinephrine Pathway

Differentiation of serotonin and dopamine neurons during the normal development requires sonic hedgehog (SHH) and fibroblast growth factor 8 (FGF-8) interactions, but serotonin is through a third signal, FGF-4, that modifies SHH and FGF-8 response. Addition of FGF-4 to ventral midbrain increases ectopic serotonin neuron development and inhibits endogenous dopamine neuron development. Therefore, serotonin antagonist increases dopamine synthesis by inhibiting serotonin.[50]

In schizophrenia, ascending serotoninergic pathways from the dorsal raphe nuclei to the substantia nigra and from the rostral raphe nuclei to the neocortex, limbic regions and basal ganglia are upregulated, leading to dopaminergic hypo-function. It is believed that the symptoms of schizophrenia are at least in part due to this interconnectivity between 5-HTergic and dopaminergic systems.[51]

Medial prefrontal cortex is abundantly innervated by catecholaminergic neurons, and is associated with cognitive function, temporal organization of behaviour and behavioural flexibility. 5-HT6Rs activation in this brain region results in inhibition of dopamine and norepinephrine release, but selective antagonist increases those neurotransmitters.[32] For example, a study conducted on rat using systemic administration of ST1936 5-HT6R agonist shows increasing dopamine and noradrenalin in the prefrontal cortex.[25]

In addition, generation of dopamine neurons in neurospheres of mesencephalic precursors increases by inhibition of glial 5-HT7Rs. This is confirmed by an increase in generation of dopamine neurons after elimination of the 5-HT neurons or reduction of 5-HT levels using methiothepin (5-HT1,2,5,6,7 receptor antagonist), and the 5-HT7Rs antagonist SB 269,970.[52]

Blockade of 5-HT7Rs by SB-269,970 increases 5-HT levels in cortical terminals. Since SB-269,970 has no affinity for dopamine and adrenergic receptors, nor does it show any dopamine and noradrenalin reuptake inhibition activity, its effect is through indirect modulating action of released serotonin on dopamine and noradrenalin neurons via 5-HT7 heteroreceptors localized on dopamine and noradrenalin neurons.[53]

Role of 5-HT 6 and 5-HT 7 Receptors in Schizophrenia

The 5-HT 6 and 7 receptors are associated with a number of psychiatric disorders, including schizophrenia.[54] Significant reduction of 5-HT7Rs at prefrontal cortex in post mortem studies of schizophrenic patients and positive genetic correlation between 5-HT7Rs gene with schizophrenia are the suggestive points for the role of 5-HT7Rs in schizophrenia pathophysiology.[55] In addition to this, high affinity of multiple antipsychotics drugs like clozapine and risperidone for 5-HT7Rs and their anatomical distribution within the brain increase the motive to study their role in schizophrenia.[56]

Antipsychotics (risperidone, ziprasidone, pimozide, sertindole, zotepine, clozapine and olanzapine), antidepressants (amitriptyline) and 5-HT2 receptor antagonists (mesulergine, ritanserin and LY215840) have a high affinity for 5-HT 6 and 7 receptors.[28]

In animal models of psychosis, SB-271,406, a 5-HT6Rs antagonist, selectively increases extracellular concentrations of both dopamine and epinephrine,[38] hippocampus glutamate and aspartate within the frontal cortex,[57] PSA-NCAM in hippocampus and dose-dependently reversed amphetamine-induced prepulse inhibition disruption.[58] SB-399,885, a 5-HT6Rs antagonist, increases dopamine, norepinephrine, acetylcholine concentration and hippocampus PSA-NCAM.[55] On top of this, enhancement of GABA and reduction of glutamate in hippocampus by way-466, a 5-HT6Rs antagonist, in combination with increasing of DRAPP-2 phosphorylation by EMDT, suggest that 5-HT6Rs antagonists may have some therapeutic utility in the treatment of schizophrenia.[59]

The distribution of 5-HT6Rs mRNA in the limbic and cortical regions of the human brain together with the high affinity of many antipsychotic agents could suggest a role in the development of schizophrenia. It may be possible

that SB271046, a selective 5-HT6Rs antagonist, can improve cognition through facilitation of cortical and hippocampal glutamatergic activity and acetylcholine release. Although 5-HT6Rs distribute most densely in the STR and NAC, SB271046, a selective 5-HT6Rs antagonist, has been reported to increase glutamate release but not dopamine release in the mPFC and dorsal hippocampus without an effect in the NAC or STR.[60]

Besides the effects on cognition, 5-HT6Rs antagonists have potential effects on other comorbid conditions in schizophrenia, such as reduction of alcohol and nicotine addiction[61] and cocaine abuse[62] and had anxiolytic-like and antidepressant-like effects in rodents.[63]

Serotonin 6 receptor stimulation is associated with activation of mammalian target of rapamycin (mTOR) signalling. 5-HT6Rs-induced cognitive defects are inhibited by mTOR inhibitor drugs like raphamycin. This mTOR inhibition is associated with improvement in social cognation, working memory, executive function and episodic memory.[64] Additionally, combination of prazosin with 5-HT6R antagonist PRX-07034 enhances memory, which indicates its use in schizophrenia.[65]

Atypical antipsychotic, typical antipsychotic and antidepressant drugs show high affinity for 5-HT7Rs. For example, amisulpride is an effective antidepressant drug effective against schizophrenia, but it also shows modest 5-HT7Rs antagonist potency.[66] Additionally, postpartum studies from schizophrenic individuals show deficiency of 5-HT7Rs expression in cortex.[67] A genomewide study on schizophrenia also indicates linkage of 10q22 gene in close proximity with human 5-HT7Rs 10q21–24 gene.[68]

Animal models predictive of antipsychotic-like activity are used to evaluate 5-HT7Rs antagonists, through administration of amphetamine or antagonists of NMDA receptors like phencyclidine, ketamine or dizocilpine. Antagonists of the NMDA receptors evoke behaviours that reflect both positive symptoms and negative symptoms and cognitive impairments.[69]

The 5-HT7Rs antagonists SB-258,741 and SB-269,970 significantly blocked NMDA receptor antagonist amphetamine-induced hyperactivity. SB-269,970 decreases amphetamine and ketamine-induced hyperactivity and reverses amphetamine-induced prepulse inhibition disruption in mice, without changing startle amplitude.[70] It also reverses phencyclidine-induced deficits in the novel object recognition test in rats. 5-HT7 receptor antagonists ameliorate behavioural abnormalities in PACAP-deficient mice.[71] Together, these observations indicate that pharmacological blockade of the 5-HT7Rs has anti-schizophrenic effects.

Different 5-HT7Rs antagonists show precognitive effect (anticipation of future events after forced exposure during trial) in animals. This supports the possible use 5-HT7Rs antagonism as a target in the management of cognitive symptoms in schizophrenic patients. For example, scopolamine, MK-801 and PCP-induced learning and memory impairment is attenuated by lurasidone, and scopolamine and PCP-induced learning defect is attenuated by SB-269,970.[72] Additionally, LP-211, a selective 5-HT7Rs antagonist, improves spatial reference memory, motor coordination, synaptic plasticity and overall emotional memory.[73]

Dizocilpine-induced learning and memory impairments in the passive avoidance and Morris water maze tests in rats are reversed by 5-HT7Rs antagonist SB-656,104-A. This implies a role of 5-HT7Rs antagonist in cognitive defect of schizophrenia.[74] SB-258,741 ameliorates the PCP but not amphetamine-induced disruption of prepulse inhibition. This indicates that 5-HT7Rs affects the glutaminergic but not dopaminergic path of PCP. These data are in conflict with results in apomorphine and amphetamine-treated 5-HT7R knock-out mice.[56]

The pharmacological blockade of 5-HT7Rs also has therapeutic implications for the treatment of negative symptoms in schizophrenia. Although SB-25,874 had no beneficial effects on PCP-induced deficits in social interactions, SB-269,970 ameliorated ketamine-induced social withdrawal in rats.[75]

Several 5-HT 6 and 7 receptor ligands are under clinical trials (Table 3), and multiple mechanisms of action have been proposed for the different effects of 5-HT 6 and 7 receptor antagonists: Firstly, by enhancing dopamine, glutamate and Ach efflux[76] and decreasing GABA levels in the prefrontal cortex, 5-HT 6 and 7 receptor antagonists may decrease the release of GABA in the prefrontal cortex, which subsequently disinhibits glutamate and/or Ach release.

Secondly, 5-HT 6 and 7 receptor antagonists may decrease GABAergic interneuron excitability, leading to disinhibition and a subsequent enhancement of synaptic plasticity in synapses and brain regions where 5-HT6Rs are expressed.[77]

Thirdly, chronic administration of 5-HT 6 and 7 receptor antagonists increased the number of NCAM PSA-immunoreactive neurons in the dentate gyrus and in the entorhinal and perirhinal regions of the cortex, which affects synaptic plasticity, possibly enhancing the ability of neurons to remodel their connections and contribute to ongoing adaptations in neuronal circuits.[78]

Table 3 Serotonin 6 and 7 Receptors Antagonist Under Clinical Trial

Compound	Indication	Clinical Trial Phase		Clinical Data and Status	Reference
Idalopirdine	Schizophrenia	Phase II	5-HT6R Antagonist	Well tolerated in both dose ranging and a multi-dose cohort	[93]
ABT-354	Schizophrenia and Alzheimer's	Phase III	5-HT6R antagonist	Tested in phase I and II clinical trials	[88]
Lu AE58054	Schizophrenia and Alzheimer's	Phase II	5-HT6R antagonist	The primary outcome measure was efficacy effect of treatment based on the Positive and Negative Syndrome Scale total score	[88,94]
AVN-211	Schizophrenia	Phase II	5-HT6R antagonist	Significant improvement of total Positive and Negative Syndrome in female patients	[95,96]
SYN-114	Schizophrenia and Alzheimer's	Phase I	5-HT6R antagonist	This product has completed phase I single and multiple ascending dose studies	[88]
PRX-07034	Schizophrenia	Phase II	5-HT6R antagonist	No recent reports of development identified for phase I development	[97]
SGS-518	Schizophrenia	Phase II	5-HT6R antagonist	Safe and well tolerated by patients with cognitive improvement. Terminated because of lack of efficacy	[32]
LY-483,518	Schizophrenia	Phase II	5-HT6R antagonist	No recent reports of development identified for phase II development in schizophrenia	[89,98]
SUVN-502	Schizophrenia	Phase I	5-HT6R antagonist	Satisfactory result and passed for phase II	[65,99]
RP5063 (RP5000)	Schizophrenia	Phase III	5-HT 6 and 7 receptor antagonist	Effective, well tolerated, and 100 mg oral dose is the maximum tolerated dose	[100]
Aripiprazole controlled release	Schizophrenia	Phase I	5-HT7R antagonist	No recent reports of development identified for phase I development in schizophrenia in Europe	[101]

Fourthly, 5-HT6Rs antagonists may have pro-cognitive effects through the decrease in mTOR signalling.[79] Fifthly, 5-HT 6 and 7 receptor antagonists may affect cognition through interaction of the 5-HT 6 and 7 receptors with the Fyn-tyrosine kinase: 5-HT6Rs agonists were shown to increase Fyn kinase activity, and 5-HT6Rs antagonists[79] antagonized effects. Finally, 5-HT 6 and 7 receptors interact with DARPP-32, which affects cognitive function and pathogenesis of schizophrenia.[55]

Conclusion

Recent neurohumoral study indicates that there is involvement of not only dopamine but also serotonin through its serotonin 6 and 7 receptors in the pathogenesis of schizophrenia. The different effects of 5-HT6 and 7 receptor antagonists on schizophrenia are by enhancing dopamine, glutamate and Ach efflux and decreasing GABA levels in the prefrontal cortex, increasing the number of NCAM PSA-immunoreactive neurons in the dentate gyrus and in the entorhinal and perirhinal regions of the cortex, which affects synaptic plasticity, possibly enhancing the ability of neurons to remodel their connections and contribute to on-going adaptations in neuronal circuits, through the decrease in mTOR signalling. Finally, serotonin 6 and 7 receptors antagonist plays a role in cognitive function and possibly in the pathogenesis of schizophrenia via interaction with DARPP-32.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in conception, study design, execution, acquisition of data, analysis and interpretation, or in all those areas; took part in drafting, revising or critical reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

There is no competing interest among the authors.

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