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Review Article

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The Serotonin-6 Receptor as a Novel Therapeutic Target

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Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that is found in both the central and peripheral nervous systems. 5-HT mediates its diverse physiological responses through 7 different 5-HT receptor families: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors. Among them, the 5-HT_6 receptor (5-HT_6R) is the most recently cloned serotonin receptor and plays important roles in the central nervous system (CNS) and in the etiology of neurological diseases. Compared to other 5-HT receptors, the 5-HT_6R has been considered as an attractive CNS therapeutic target because it is expressed exclusively in the CNS and has no known isoforms. This review evaluates in detail the role of the 5-HT_6R in the physiology and pathophysiology of the CNS and the potential usefulness of 5-HT_6R ligands in the development of therapeutic strategies for the treatment of CNS disorders. Preclinical studies provide support for the use of 5-HT_6R ligands as promising medications to treat the cognitive dysfunction associated with Alzheimer's disease, obesity, depression, and anxiety.

Key words: depression, Alzheimer, cognitive disorders, Fyn, Jab1, ST1936

SEROTONIN (5-HT) AND 5-HT RECEPTORS

Serotonin (5-hydroxytryptamine, 5-HT), one of best known neurotransmitters, modulates neural activities and a wide range of neuropsychological processes [1]. The first step in 5-HT synthesis is the catalysis of tryptophan to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (TPH); this is the rate-limiting step in 5-HT synthesis. Two TPH enzymes are known; TPH1 is found in several tissues, while TPH2 is a brain-specific enzyme. The enzyme 5-HTP decarboxylase next converts 5-HTP to 5-HT [2]. In the brain, 5-HT is taken and stored from cytoplasm to synaptic vesicles by vesicular monoamine transporters. 5-HT is released into the synapse through a Ca^{2+}-dependent mechanism, and its reuptake from the synapse is induced by the serotonin transporter (SERT). SERT is the principal site of action of many antidepressants (mainly selective serotonin reuptake inhibitors, SSRI; serotonin norepinephrine reuptake inhibitors, SNRI; tricyclic antidepressants, TCA) and represents a primary target of interest in antidepressant pharmacogenetics. Interestingly, alteration of tryptophan metabolism elicited by proinflammatory cytokines has recently gained attention as a new concept to explain the etiological and pathophysiological mechanisms of major depression [3-5].

5-HT plays an important role in the regulation of many pivotal functions, including emotion, mood, cognition, sleep, circadian rhythm, motor function, reproductive behaviors, thermoregulation, and endocrine functions, as well as in pathological states such as depression, anxiety, Alzheimer's diseases, schizophrenia, drug addiction, autism, and obesity [6-8]. Therefore, the components of the 5-HT system have developed as important therapeutic targets in the clinic. 5-HT mediates its diverse physiological responses through its receptors. Based on structural, biochemical, and pharmacological differences, 5-HT receptors (5-HTR) are classi-

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fied into 7 distinct receptor families: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors. The complexity of the 5-HT system is further increased by alternative splicing and mRNA editing of several 5-HT receptors [9, 10]. With the exception of the 5-HT_3 receptors (consists of the 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} receptors), which are ligand-gated ion channels, all 5-HT receptors are G-protein-coupled receptors (GPCR), transmitting their signals via G-proteins (Table 1) [11].

As a brief introduction to each 5-HT receptor (5-HTR), the 5-HT_1R and 5-HT_5R are negatively coupled to adenylate cyclase via Gi/o proteins, and they induce inhibition of cAMP formation. The 5-HT_1R family comprises the subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptors, which are known to play roles in the brain as well as the heart and gastrointestinal tract. The 5-HT_5R family consists of 2 subtypes: the 5-HT_{5A} and 5-HT_{5B}. Although the 5-HT_{5A}R has been found on neurons and neuronal-like cells of the carotid body, both receptors are limited in distribution to the CNS [12]. However, the 5-HT_5R family has not been extensively characterized pharmacologically. The 5-HT_2R couples to Gq/11 proteins and activates phospholipase C leading to the production of inositol-1,4,5-trisphosphate, intracellular Ca^{2+} release, and protein kinase C activation. The 5-HT_2R family currently comprises 3 receptor subtypes, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}, and has important roles in the brain, heart, gastrointestinal tract, platelets, and smooth muscle [11, 13-15]. The 5-HT_3R family members are non-selective cation ligand-gated ion channels. Their effects are excitatory, and they exist mainly in the peripheral nervous system, particularly on nociceptive afferent neurons and on autonomic and enteric neurons. 5-HT_3R antagonists (e.g. ondansetron and tropisetron) are used predominantly as anti-emetic drugs [16]. The 5-HT_4R, 5-HT_6R, and 5-HT_7R are positively coupled to adenylate cyclase via G_S proteins and they elevate cAMP formation. The 5-HT_4R consists of multiple subtypes (5-HT_{4A}, 5-HT_{4B}, 5-HT_{4C}, 5-HT_{4D}, 5-HT_{4E}, 5-HT_{4F}, 5-HT_{4G}, 5-HT_{4H}, and 5-HT_{4HB} receptors), and the 5-HT_7R consists of 4 subtypes (5-HT_{7A}, 5-HT_{7B}, 5-HT_{7C}, and 5-HT_{7D} receptors) [9, 17]. The 5-HT_4R and 5-HT_7R play roles in the CNS as well as other systems. The 5-HT_6R is known to have important functions specifically in the CNS due to its exclusive distribution in the CNS [6, 11, 18].

DISCOVERY, GENETICS, AND DISTRIBUTION OF THE 5-HT_6R

The 5-HT_6R is one of the most recently discovered 5-HT receptors. The history of 5-HT_6R was started with the finding of a novel 5-HT receptor in the brain since a 5-HT-stimulated adenylate cyclase activity was detected in the striatum which did not fit with any of the known classes of 5-HT receptors. Furthermore, some neuroblastoma cells (NCB-20 and N18TG2) showed 5-HT-stimulated cAMP production that was sensitive to antipsychotics in a manner suggestive of a novel receptor [19, 20]. The rat 5-HT_6R was identified and sequenced by 2 groups in 1993 [21, 22], and in 1996, the human gene was cloned and shown to have 89% sequence homology with its rat equivalent [23]. The recombinant human 5-HT_6R is positively coupled to adenylate cyclase and has

Table 1. The classification and their signal pathways of 5-HT receptor subtypes

Receptor		Major signal pathway	Other G-proteins	Main signal pathways	Agonists**	Antagonists**
5-HT_1	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}	Gi/o	Gz	↓ cAMP	8-OH-DPAT, Buspirone Anpirtoline, CP 94253	WAY-100635 SB-224289, GR-127935
5-HT_2	5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	Gq/11	Gi/o, G12, and G13	PLC, Ca^{2+}, and PKC (+)*	DOI, m-CPP, R0 600175	Ketanserin, M100907 Mesulergine, SB-200907
5-HT_3	5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}, 5-HT_{3E}	Ion channel	–	Depolarization	mCPBG, 2-CH3-5-HT	Ondansetron, Tropisetron
5-HT_4	5-HT_{4A} - 5-HT_{4H}, 5-HT_{4HB}	Gs	G13	↑ cAMP	BIMU-8, RS 67333, Cisapride	GR-113808, SB-204070
5-HT_5	5-HT_{5A}, 5-HT_{5B}	Gi/o	NT	↓ cAMP	–	–
5-HT_6	–	Gs	NT	↑ cAMP	EMDT, WAY 181187, WAY 208466	SB-399885
5-HT_7	5-HT_{7A}, 5-HT_{7B}, 5-HT_{7C}, 5-HT_{7D}	Gs	G12	↑ cAMP	8-OH-DPAT	Amisulpiride, SB-269970

*(+), stimulation; NT, not tested; PLC, phospholipase C; PKC, protein kinase C. **Agonists and antagonists were adapted from Carr and Lucki [3].

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pharmacological properties similar to the rat receptor, exhibiting high affinity for several typical and atypical antipsychotics, including clozapine. The 5-HT_6R protein is a glycoprotein comprising 440 amino acids in humans and mice, and 438 amino acids in rats. All known 5-HT_6R homologues have 7 transmembrane domains that form 3 intracellular and 3 extracellular loops [24].

The gene for the human 5-HT_6R maps to the chromosome region 1p35-p36 and has an open reading frame of 1,320 bp [23]. The gene has 3 exons, which are separated by a 1.8-kb intron at position 714 and a second intron of 193 bp at position 873, corresponding to intracellular loop 3 and extracellular loop 3. In contrast to the complexity of the 5-HT receptor isoforms generated by alternative splicing and mRNA editing, as shown in Table 1, the 5-HT_6R has no known isoforms. A non-functional truncated splice variant of the 5-HT_6R has been identified, but it appears to have no physiological significance.

Within the 5-HT_6R gene, there is a silent polymorphism at bp position 267 within a tyrosine codon, where a cytidine is substituted for a thymidine (C267T variant). Based on a number of genetic linkage studies, the distribution of C and T alleles appears to be more or less equal among the general population. Although this polymorphism does not affect the identity of the tyrosine codon, it has been further analyzed for biased distribution in several human diseases. In this regard, several studies have investigated whether 5-HT_6 polymorphisms are associated with brain-related variables, such as neuropsychiatric disorders. Because several antipsychotic agents (notably clozapine) and antidepressants have high affinity for and are antagonists of 5-HT_6Rs, several genetic studies have examined the possible association of 5-HT_6 polymorphisms with schizophrenia and depression [25]. No association of the C267T polymorphism with schizophrenic was found in studies of Japanese and French patients. In addition, when pharmacogenetic studies were undertaken to assess the association between the C267T polymorphism and the response of schizophrenic patients to atypical antipsychotic drugs, no significant association was observed for patients taking clozapine. However, risperidone caused greater improvement in positive symptoms in patients carrying a thymidine substitution at the 267 position [26]. The association of the C267T polymorphism with patients suffering from depression has also been investigated, but failed to show a significant correlation [27]. A subsequent study reported that patients with major depressive disorder carrying the C267T polymorphism showed a better response to antidepressant medications [28]. Several additional genetic studies have been performed to investigate the association of this polymorphism and other 5-HT_6R polymorphisms on with bipolar disorder, Alzheimer's disease, and Parkinson's disease. However, the results of these studies have not been reproducible and their significance remains to be established [25].

The 5-HT_6R is expressed earlier in brain development than other 5-HT receptors. High levels of 5-HT_6R are first expressed on embryonic day 12 (E_{12}) in the rat brain, expression decreases slightly on E_{17}, and then remains stable through to adulthood. This expression pattern coincides with the emergence of serotonergic neuron, implying a role for 5-HT_6Rs early in the neuronal growth process involving the serotonergic system [29]. Rat and human 5-HT_6R mRNA is detected in the striatum, amygdala, nucleus accumbens, hippocampus, cortex and olfactory tubercle, but has not been found in peripheral organs. Using the highly specific radiolabelled 5-HT_6R antagonist [^{125}I] SB-258585, autoradiographic binding studies in the rat brain show high receptor levels in caudate-putamen, nucleus accumbens, striatum, and olfactory tubercles, and choroid plexus. Moderate recptor levels are seen in the hippocampus, thalamus, cerebral cortex, and frontal and parietal cortex [24, 30]. Similarly, immunohistochemical staining shows high receptor levels in nucleus accumbens, striatum, olfactory tubercles, cortex, hippocampus, and hypothalamus [31, 32]. In *in situ* hybridization and RT-PCR analyses [22, 31], 5-HT_6R levels exhibit a similar pattern in rats and humans. However, relatively little 5-HT_6R expression has been demonstrated in the mouse, and it is not clear why the mouse 5-HT_6R homolog does not exhibit the widespread brain expression seen in rats and humans. Indeed, many 5-HT_6R antagonists that induce enhanced cognition in rats have very little effect in mice, which may be due to the low expression in mice or to differences in ligand affinity across species [33]. Immunohistochemical staining for the 5-HT_6Rs has revealed that on neurons it is localized on dendrites, cell bodies, and postsynaptic sites, and is expressed in GABAergic, cholinergic, and glutamatergic neurons [24, 32].

5-HT_6R AGONISTS AND ANTAGONISTS

Although there are several well-known non-selective 5-HT ligands that bind strongly to 5-HT_6Rs, such as lysergic acid diethylamide (LSD), for many years there were no selective 5-HT_6R agonists or antagonists available. Since the discovery of the human 5-HT_6R by Kohen et al. [23], an increasing number and diversity of selective and novel 5-HT_6R ligands have been developed using 5-HT_6R-specific high-throughput screening technologies [34, 35]. The synthesis of 5-HT_6R ligands, especially 5-HT_6R antagonists, has been very successful, with a number of highly potent ligands being reported.

Although a variety of highly selective 5-HT_6R ligands has been

reported, the major efforts have focused on antagonism because of the positive effects of 5-HT$_6$R antagonists in several animal models, as discussed below. Before the discovery of such 5-HT$_6$R antagonists, 5-HT$_6$Rs were known to have high affinity for various atypical antipsychotic drugs and tricyclic antidepressants, but they displayed no clear selectivity [36]. Currently, more than 20 selective 5-HT$_6$R antagonists have been discovered. The most potent and selective 5-HT$_6$R antagonists are Ro 04-6790 (displays 100-fold selectivity for 5-HT$_6$R over other 5-HT receptors), Ro 63-0563 (100-fold selectivity), SB-271046 (50-fold selectivity), SB-258585 (100-fold selectivity), and SB-399885 (200-fold selectivity) [37-39]. Although Ro04-6790 and SB-271046 were the first identified and the most studied 5-HT$_6$R antagonists, respectively, they have limited capacity to cross the blood-brain barrier and appear to be orally active [37, 39]. Other 5-HT$_6$R antagonists such as SB-699929, SB-357134, and SB-399885 appear to have better pharmacokinetical and pharmacological profiles than SB-271046 and SB-258585 [40]. AVN-322, BVT-74316, PRX-07034, R-1485, SYN-114, SYN-120, and SUVN-502 are additional 5-HT$_6$R antagonists that are being developed for the treatment of cognitive disorders and are currently in phase I clinical trials [41]. Several 5-HT$_6$R antagonists including AVN-211, SAM-531, SB-742457, and SGS-518 have reached phase II clinical trials for cognitive disorders [41]. [^{11}C]-GSK215083 is a radiolabeled 5-HT$_6$R antagonist being developed as a PET radiotracer for the 5-HT$_6$R, and is in phase I trials [42].

Compared to the 5-HT$_6$R antagonists, considerably fewer compounds claim to be selective 5-HT$_6$R agonists. Examples are 2-ethyl-5-methoxy-N,N-dimethyltryptamine (EMDT), EMD386088, WAY-466, E-6801, LY586713, WAY-208466, WAY-181187, and R-13c [40]. EMD386088 displays 20-fold selectivity for the 5-HT$_6$R over other 5-HT-binding receptors, including the 5-HT transporter protein and dopamine receptors [43]. R13-c displays 50-fold selectivity over other 5-HT and dopamine receptors [44]. E-6801and E-6837 are potent partial agonists of the 5-HT$_6$R [45]. Thus, there are few 5-HT$_6$R agonists, and only WAY-181187 (displays 50-fold selectivity against serotonergic and other receptors) has been characterized and widely used [46, 47]. Recently, a new 5-HT$_6$R agonist, ST1936, has been reported and compared with the characteristics of WAY-181187 [48].

THE ROLES OF THE 5-HT$_6$R IN THE CNS

Taken together, the high affinity of the 5-HT$_6$R for atypical antipsychotic drugs and tricyclic antidepressants, and its abundant distribution in the brain (cortex, hippocampus, striatum, and hypothalamus) imply that the 5-HT$_6$R plays important roles in the CNS and in the etiology of neurological diseases. The 5-HT$_6$R shares a signaling mechanism with 5-HT$_4$R and 5-HT$_7$R in that they are the three 5-HT receptors positively coupled to Gs proteins, inducing cAMP production through stimulation of adenylate cyclase activity. However, since the 5-HT$_6$R is almost exclusively expressed in the brain compared with the expression patterns of the 5-HT$_4$R and 5-HT$_7$R, recently developed selective 5-HT$_6$R ligands may represent attractive new therapeutic options for several types of diseases.

Depression

Many of the current treatments for depression act by increasing serotonergic neurotransmission with selective serotonin reuptake inhibitors (SSRIs), and data from SSRIs form the basis for the monoamine hypothesis of affective disorders [3]. However, a causative role of perturbed 5-HT function in depression has been difficult to prove, and the specific serotonergic receptors responsible for antidepressant efficacy are poorly defined. Preclinical data suggests a possible role for 5-HT$_6$Rs in depression; however, the results of pharmacological studies are equivocal since both blockade and stimulation of 5-HT$_6$Rs may evoke antidepressant-like effects.

Research in mice and rats has shown that 5-HT$_6$R agonists produce antidepressant effects in a number of tests. As mentioned above, the first 5-HT$_6$R agonists (LY-586713 and WAY-466) have been identified and are being evaluated as potential treatments for depression. Antidepressants such as the SSRIs upregulate brain-derived neurotrophic factor (BDNF) gene expression [49], and the 5-HT$_6$R is a candidate for mediating these changes. The selective 5-HT$_6$R agonist, LY-586713, upregulates BDNF mRNA in the hippocampus and cortex. This effect was observed at 1 mg/kg LY-586713 and was completely blocked by pre-treatment with the selective 5-HT$_6$R antagonist SB-271046 (10 mg/kg) [50]. The 5-HT$_6$R agonist EMDT reduced immobility in tail suspension tests in mice, whereas the 5-HT$_6$R antagonist SB-271046 prevented the antidepressant effects of EMDT and that of the antidepressant fluoxetine [51]. It was also recently shown that the selective 5-HT$_6$R agonists WAY-181187 and WAY-208466 have antidepressant-like effects in established behavioral tests such as the forced swim test in rats [52]. These findings suggest that 5-HT$_6$R agonists may represent a new class of antidepressant compounds that possess a number of advantages over currently available treatments. Paradoxically, selective 5-HT$_6$R antagonists have also been reported to produce antidepressant-like effects. Using the forced swim and tail suspension tests, the 5-HT$_6$R antagonist SB-399885 produced anti-depressant-like effects in both rats and mice [53]. SB-399885 also augmented the anti-immobility effects of antidepressants in the forced swim test [54].

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However, the same authors recently reported that the 5-HT_6R agonist EMD386088 produces antidepressant effects in rats after intrahippocampal administration [55]. This effect was fully blocked by the selective 5-HT_6R antagonist SB-399885 when administered at a dose that had been reported as inactive in their previous studies [53, 54].

Thus, both 5-HT_6R agonists and antagonists show antidepressant-like effects in preclinical studies, although the reason for their analogous effects is currently unclear. One likely explanation for the paradoxical effects of 5-HT_6R agonists and antagonists is that their similar behavioral effects are mediated through different neurochemical mechanisms. The antidepressant-like effects of 5-HT_6R antagonists could be produced through non-serotonergic mechanisms while the activation of 5-HT_6Rs would likely produce behavioral effects similar to those of SSRIs through global stimulation of postsynaptic 5-HT receptors. Supporting this explanation, microdialysis studies suggest that the 5-HT_6R antagonist SB-271046 increases dopamine and noradrenaline concentrations in rat medial prefrontal cortex [56]. The involvement of these neurotransmitters in the anti-immobility action of 5-HT_6R antagonist has been supported by a study demonstrating that a selective 5-HT_6R antagonist enhanced the anti-immobility action of the noradrenaline reuptake inhibitor desipramine and the dopamine reuptake inhibitor bupropion in forced swim tests [54]. The antidepressant-like action of a 5-HT_6R antagonist has also been attributed to its action at dopamine D_1 and D_2 receptors and α_2-adrenoceptors [57]. Indeed, the antidepressant-like effects of the 5-HT_6R antagonist SB-399885 persisted after 5-HT depletion, suggesting that the effects of this compound were not dependent on endogenous serotonergic neurotransmission [57].

Anxiety

There are surprisingly only few studies that have explored 5-HT_6R activity in anxiety compared with the involvement of other 5-HT receptor subtypes. Both 5-HT_6R agonists and antagonists show anxiolytic-like effects, similar to their actions in depression [58]. When the selective 5-HT_6R agonist WAY-181187 was administered acutely, it effectively decreased water intake by rats that had not been water-deprived in the schedule-induced polydipsia test, a model considered to be predictive for efficacy in obsessive-compulsive disorder [47]. However, blockade of 5-HT_6Rs can also produce anxiolytic activity. Wesolowska and Nikiforuk [53] have observed that the selective 5-HT_6R antagonist SB-399885 produced specific anxiolytic-like activity in animal models of anxiety, such as the conflict drinking (Vogel) and elevated plus maze tests in rats and the four-plate test in mice.

Current therapeutic agents for the treatment of anxiety disorders include benzodiazepines and SSRIs that act either directly or indirectly to modulate GABAergic neurotransmission. Benzodiazepines, which act as positive allosteric modulators of the $GABA_A$ receptor/Cl^- ion channel complex, enhance GABA signaling following receptor stimulation. SSRIs may enhance levels of GABA as predicted from recent imaging studies in humans. Interestingly, immunohistochemical studies suggest that the 5-HT_6R colocalizes with GABAergic neurons. In neurochemical studies, both WAY-181187 and WAY-466 consistently elevate levels of GABA in many regions of the brain regions associated with anxiety, including the frontal cortex and amygdala [47]. The ability of 5-HT_6R agonists to enhance extracellular GABA levels and decrease stimulated glutamatergic neurotransmission seems to support the hypothesis that 5-HT_6R agonists may be effective agents for the treatment of anxiety. Unfortunately, there are no neurochemical studies on the effect of SB-399885 on GABA release. Therefore, further studies are necessary to explain the anxiolytic-effects of 5-HT_6R antagonists and to demonstrate the effect of 5-HT_6R agonists and antagonists in various animal models of anxiety.

Cognitive dysfunction associated with Alzheimer's disease

Significant reductions in 5-HT_6R density have been found in cortical areas of the brains of Alzheimer's disease patients, although the reductions were unrelated to the cognitive status before death. As 5-HT_6R blockade induces acetylcholine release, the observed reductions in 5-HT_6R density may represent an effort to restore acetylcholine levels in a deteriorated cholinergic system [25]. Based on these findings, there has been increasing interest in the role of the 5-HT_6R in higher cognitive processes such as memory. An increasing number of recent studies support the use of 5-HT_6R antagonism as a promising mechanism for treating cognitive dysfunction. Most studies, in healthy adult rats, report that 5-HT_6R antagonists enhance retention of spatial learning in the Morris water maze, improve consolidation in autoshaping tasks, and reverse natural forgetting in object recognition. 5-HT_6R antagonists appear to facilitate both cholinergic and glutamatergic neurotransmission, reversing scopolamine-induced and NMDA receptor antagonist-induced memory impairments. Thus, there is current interest in the role of 5-HT_6Rs in cognitive enhancement as a therapeutic approach in Alzheimer's diseases [59, 60]. Based on the preclinical data demonstrating their beneficial effect on cognition [41, 61], a number of 5-HT_6R antagonists have undergone successful phase I clinical studies, and some have been evaluated in phase II clinical studies for the treatment of Alzheimer's disease. PRX-07034 and SB-742457 are the 5-HT_6R antagonists currently in phase I and II studies, respectively [62]. Other phase II trials are being performed with SB-742457, SGS-

518, or SAM-531, either alone or as add-on therapy with the acetylcholine esterase inhibitor, donepezil [41].

Compared with 5-HT_6R antagonists, there have been few studies on the role of 5-HT_6R agonists in cognition. In a recent study, selective 5-HT_6R agonists and antagonists were administered either alone, after a scopolamine-induced impairment, or combined with sub-effective doses of the acetylcholinesterase inhibitor, donepezil, or the glutamate NMDA receptor antagonist, memantine, in a novel object discrimination paradigm in adult rats [63]. The authors reported that the 5-HT_6R agonist E-6801 produced significant and dose-dependent increases in novel object exploration, indicative of memory enhancement. More intriguing were the results obtained when combining non-active doses of the 5-HT_6R agonist E-6801 and the 5-HT_6R antagonist SB-271046, which produced an improvement in novel object discrimination. However, more behavioral experiments using diverse and selective 5-HT_6R agonists are required to elucidate the role of 5-HT_6R agonists in cognition.

NEUROCHEMICAL MECHANISMS OF 5-HT_6RS

As a member of the Gs-GPCR family, it is well known that engagement of the 5-HT_6R activates cAMP signaling pathways through adenylate cyclase stimulation. In addition, Svenningsson et al. [64] reported that the activation of 5-HT_6Rs increases phosphorylation of dopamine- and cAMP-regulated phosphoprotein of molecular weight 32,000 (DARPP-32) by protein kinase A. However, there are still insufficient studies on the mechanisms of 5-HT_6R-mediated signal transductions to understand the receptor's various roles in physiological and pathological states in the CNS, including Alzheimer's disease, depression, cognition, and obesity. This is mainly due to the lack of pharmacological tools able to selectively activate 5-HT_6Rs in the CNS. The selective 5-HT_6R agonists have only recently been developed and characterized [47, 48, 65]. This lack of appropriate tools has also contributed to the inconsistent observations on the pharmacological and neurochemical effects of 5-HT_6R antagonists.

To identify the mechanism of 5-HT_6R function and its cellular mechanisms in the CNS, we employed a yeast two-hybrid screening system on a human brain cDNA library, with the 5-HT_6R intracellular loop 2 (iL2), intracellular loop 3 (iL3), and the carboxyl terminus as bait (Fig. 1). We first reported that Fyn, a member of the Src family of non-receptor protein-tyrosine kinases, is bound to the carboxyl terminus of the 5-HT_6R [32]. The expre-

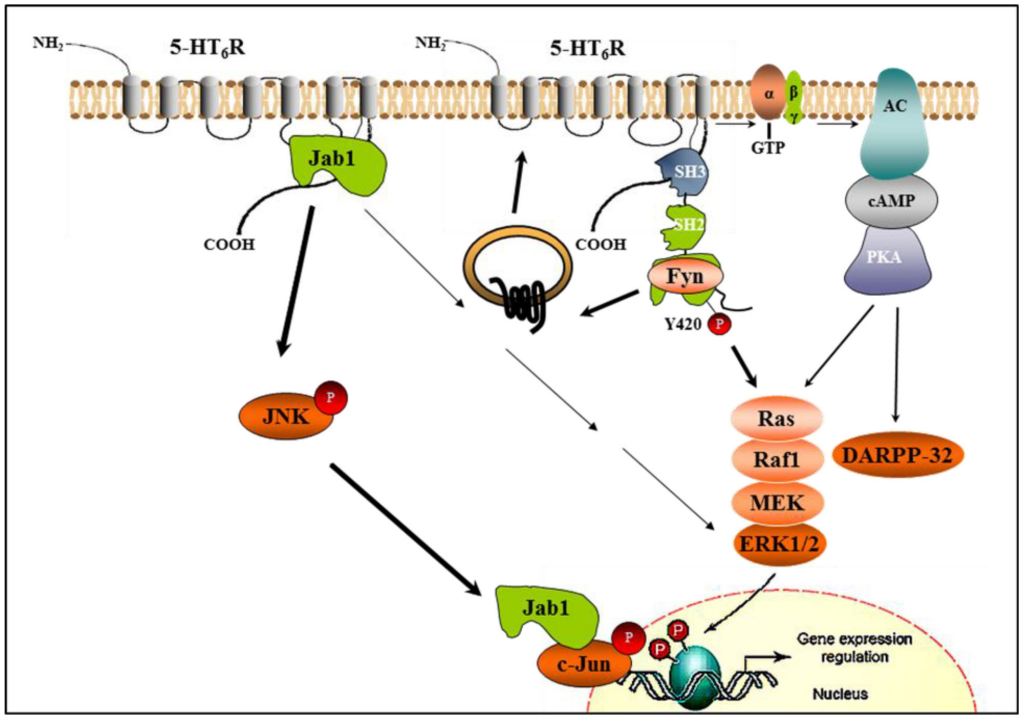

Fig. 1. 5-HT_6R-mediated signal transduction pathways. The activation of 5-HT_6R increases DARPP-32 activities by PKA [64] and ERK1/2 activities via Fyn- and PKA-dependent pathways [32]. Fyn also leads to the surface expression of 5-HT_6R via a direct interaction between Fyn and the carboxyl terminus of 5-HT_6Rs [32]. In addition, a novel interaction between human HT_6R (iL3 and the carboxyl terminus) and Jab1 was demonstrated by Yun et al. [68]. The expression of Jab1 mediates the modulation of the membrane expression and activity of 5-HT_6Rs. 5-HT_6Rs also affect the cytosol/nuclear distribution of Jab1 as well as the interaction between Jab1 and c-Jun, a target protein downstream of Jab1.

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ssion of Fyn increases 5-HT$_6$R activity by increasing receptor surface expression without changing total cellular expression of 5-HT$_6$R protein. Reciprocally, the activation of 5-HT$_6$Rs also increases Fyn phosphorylation at Tyr-420. Phosphorylation at Tyr-420 was blocked when the 5-HT$_6$R-Fyn interaction was blocked by overexpression of the Fyn SH3 domain, the best-characterized domain for Fyn-mediated protein-protein interactions. We further demonstrated that the activation of 5-HT$_6$Rs activated extracellular signal regulated kinase1/2 (ERK1/2) activity through Fyn- and PKA-dependent pathway. We recently showed that 2 selective 5-HT$_6$R agonists, ST1936 and WAY-181187, also increased Fyn phosphorylation [48]. Because Fyn is known to be involved in Alzheimer's disease through modulation of the microtubule-associated tau and amyloid-β proteins [66, 67], our observations may provide a cellular mechanism for 5-HT$_6$R-mediated cognition and mood changes in the brain. It is also interesting to note that the 5-HT$_6$R agonist, LY-586713, increases expression of cortical and hippocampal BDNF which could mediate its pro-cognitive effect; however, the cortical increase in BDNF was not antagonized by SB-271046 [50], suggesting the increased BDNF expression is mediated through a different mechanism.

Our group has also characterized a second 5-HT$_6$R-interacting protein: Jun activation domain-binding protein-1 (Jab1, Fig. 1). We recently discovered a novel interaction between human 5-HT$_6$R and Jab1, and we observed Jab1-mediated modulation of the membrane expression and activity of 5-HT$_6$Rs [68]. In addition, we found that 5-HT$_6$Rs affect the cytosolic and nuclear distribution of Jab1 as well as the interaction between Jab1 and c-Jun, a target protein downstream of Jab1. Furthermore, we demonstrated that 5-HT$_6$Rs and Jab1 play important roles under conditions of *in vitro* hypoxia and *in vivo* cerebral ischemia. A recent study has suggested that Jab1 is involved in the onset of neuronal diseases such as Alzheimer's disease and Parkinson's disease through interaction with the endoplasmic reticulum stress transducer IRE1 [69]. Therefore, these data provide new insights into the physiological roles of 5-HT$_6$Rs and Jab1 in the CNS at both the molecular and cellular levels. In addition to Fyn and Jab1 binding proteins, we are currently investigating 2 other proteins as candidate 5-HT$_6$R-binding proteins.

To explore the neurochemical mechanisms involved in 5-HT$_6$R functions, several microdialysis studies have been performed using selective 5-HT$_6$R ligands. In studies using *in vivo* microdialysis, increased acetylcholine levels were observed in the rat medial prefrontal cortex after acute administration of the 5-HT$_6$R antagonist SB-399885 [70] but not in the hippocampus after administration of another antagonist, Ro04-6790 [71]. Another selective 5-HT$_6$R antagonist, SB-357134, has been reported to increase high KCl-stimulated acetylcholine release *in vitro* in rat cortical and striatal slices [72]. However, no *in vitro* or *in vivo* microdialysis studies have yet been reported on acetylcholine release using selective 5-HT$_6$R agonists. Glutamate is a major excitatory neurotransmitter in the CNS. 5-HT$_6$R antagonists have been shown to increase the extracellular concentration of glutamate both *in vivo* by SB-271046 in the frontal cortex and hippocampus [73], and *in vitro* by SB-357134 in the cortex and striatum [72]. Interestingly, it was reported that the selective 5-HT$_6$R agonist WAY-181187 attenuated the stimulated glutamate levels elicited by sodium azide and high KCl *in vitro* but not *in vivo* [47]. A recent electrophysiological study using whole-cell patch-clamp recording showed that 5-HT$_6$R activation by ST1936 inhibits corticostriatal glutamatergic transmission, which was mimicked by a different agonist, WAY-181187 [65]. This finding is consistent with the reported *in vitro* microdialysis data using WAY-181187 [47].

Woolley et al. [24] reported on the immunohistochemical co-localization of 5-HT$_6$R with GABAergic neurons in many areas of the cortex, basal ganglia, hippocampus, thalamus, and cerebellum. These co-localization data together with the microdialysis data suggest that 5-HT$_6$R agonists/antagonists may modulate cholinergic and/or glutamatergic systems via disinhibition of GABAergic neurons. If 5-HT$_6$Rs do modulate cholinergic and/or glutamatergic systems in this manner, then 5-HT$_6$R antagonists should decrease GABA release. In fact, no study has yet reported on the modulation of GABA release by 5-HT$_6$R antagonists using microdialysis or electrophysiological methods. On the other hand, the 5-HT$_6$R agonist WAY-181187 has been shown to significantly increase extracellular GABA concentrations in the hippocampus, striatum, and amygdala, but had no effect on GABA levels in the nucleus accumbens or thalamus [47]. Another 5-HT$_6$R agonist, WAY-208466, also preferentially elevated cortical GABA levels following acute and chronic administration, indicating that neurochemical tolerance does not develop following repeated 5-HT$_6$R stimulation. These *in vivo* data were also confirmed by *in vitro* electrophysiological investigations. WAY-181187 increased the frequency of spontaneous inhibitory postsynaptic currents (sIPSC) recorded from hippocampal CA1 neurons [74]. This effect was blocked by the 5-HT$_6$R antagonist SB-399885, which confirmed it to be mediated by activation of 5-HT$_6$Rs. Collectively, the results of these microdialysis and electrophysiological experiments suggest that 5-HT$_6$R agonists/antagonists may modulate cholinergic, glutamatergic, and/or GABAergic systems.

PERSPECTIVES

The 5-HT$_6$R has gained increasing attention over the past decade,

and has become a promising target for the treatment of CNS diseases. Currently, consistent effects have been demonstrated with 5-HT_6R antagonists in preclinical models of cognition and 5-HT_6Rs have obvious pharmaceutical potential. Although the majority of 5-HT_6R research has focused on their pro-cognitive effects, the role of these receptors in depression and anxiety has also been postulated. However, the preclinical results are equivocal since blockade and stimulation of 5-HT_6Rs may evoke pro-cognitive, antidepressant-like, or anti-anxiety-like effects. The explanation for these paradoxical effects remains unclear. The function of the 5-HT_6R has been revealed to be much more complex than initially defined. Based on the existing data, and depending on the drug used, different cellular pathways may be activated. However, the full characterization of the functional profile of 5-HT_6Rs is still pending. The drug discovery process may benefit considerably from this complexity, in terms of the quantity and quality of potential new therapeutic molecules. Thus, the functions of 5-HT_6Rs must be studies at both molecular and cellular levels in order to understand their roles in the CNS and to develop novel drug targets for neurological diseases.

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