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Review Article

Drug discovery targets: 5-HT$_6$ receptor

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Abstract

The serotonergic (5-HT) nervous system has been implicated in cognitive function and feeding behavior. At present, there are a number of compounds undergoing biological testing for 5-HT$_6$ receptor antagonism. Preclinical data have confirmed potent and selective antagonism for several compounds *in vitro* at the rat and human 5-HT$_6$ receptor. Favorable cognition-enhancing effects have been demonstrated in rats, with significant improvement in memory retention, consolidation and spatial learning. Therefore, 5-HT$_6$ antagonism has been proposed as a promising approach for treating cognitive impairment associated with neuropsychiatric disorders (*e.g.*, Alzheimer's disease, schizophrenia). Furthermore, these compounds facilitate a reduction in food intake, fat absorption and body weight in genetic and dietary models of obesity. This review summarizes the progress with 5-HT$_6$ receptor antagonists as a therapeutic strategy for Alzheimer's disease- and schizophrenia-associated cognitive dysfunction and obesity.

Introduction

Serotonin is a vasoactive amine found widely throughout the body which acts on 5-hydroxytryptamine (5-HT) receptors. 5-HT receptors are divided into seven families (5-HT$_1$ to 5-HT$_7$) according to structural and functional homologies, with different subtypes in some families (1). This has facilitated the investigation of subtype-specific physiological/pathophysiological roles.

Figure 1 illustrates the current therapeutic impact of 5-HT$_6$ receptor antagonists. Tables I, II and III show the 5-HT$_6$ receptor binding affinity of compounds from patents, compounds from the literature and antipsychotic agents, respectively. As can be seen, compounds with 5-HT$_6$ receptor-antagonist properties have a predominantly sulfone or sulfonamide structure. A number of agents are undergoing biological testing for those conditions outlined in Figure 1, but in particular, preclinical data have been generated for several potent and selective 5-HT$_6$ receptor antagonists as procognitive and antiobesity treatments. This review will therefore focus on the role of 5-HT$_6$ receptors in cognition and feeding behavior and outline the experimental progress to date.

The 5-HT$_6$ receptor as a target for cognitive dysfunction

Alzheimer's disease and schizophrenia are associated with chronic and severe cognitive deficits. Alzheimer's disease is the most common cause of dementia in the elderly. This brain disorder is a slow disease that progresses as nerve cell damage, neuritic plaques and neurofibrillary tangles (2) extend to different parts of the brain that control thought, memory and language. Early symptoms include mild cognitive impairment with a decline in

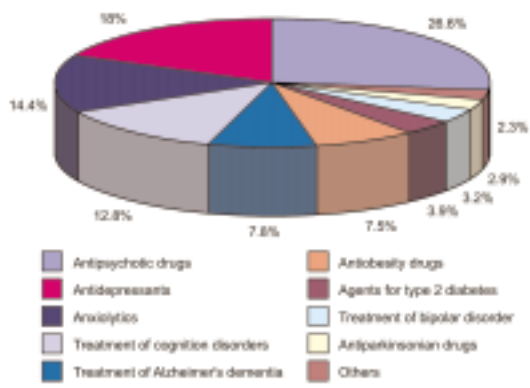
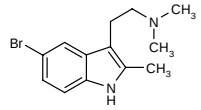
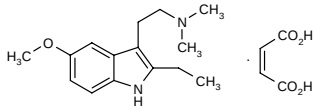
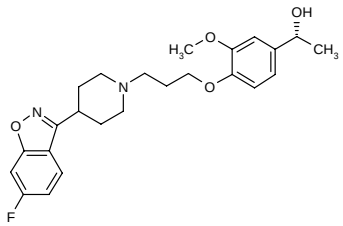
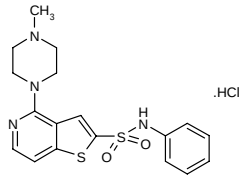
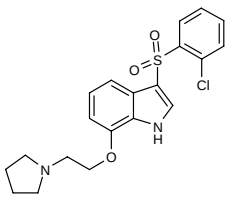
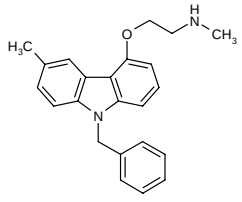
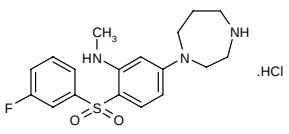


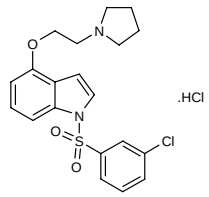
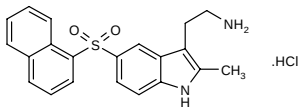
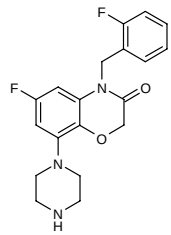
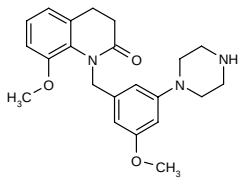
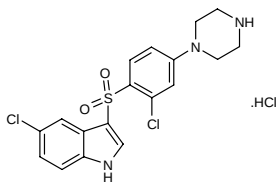
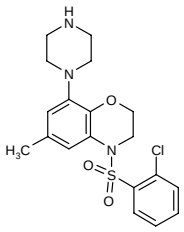
Fig. 1. Therapeutic impact of 5-HT$_6$ receptor antagonists (from Prous Science Integrity®).

Table I: Serotonin 5-HT$_6$ receptor binding affinities of representative patent compounds (from Prous Science Integrity®).

Compound (entry number, EN)[1]	5-HT$_6$ affinity (pK_i)[2,3]	Source	Patent
 (332626)	**7.49**	Sigma-Tau	WO 2003000252
 (286390)	**7.80** (7.70-7.80)	Virginia Commonwealth Univ.	WO 2000034242
 (337465)	**8.10** (7.80-8.10)	Novartis	WO 2003020707
 (359100)	**8.35** (7.49-8.35)	Biovitrum	WO 2004000828
 (374775)	**8.40** (7.70-8.40)	Roche	WO 2004050085
 (302572)	**8.66** (7.92-8.66)	Pfizer	WO 2001017963
 (314968)	**8.85** (8.31-8.85)	Pfizer	WO 2001098279

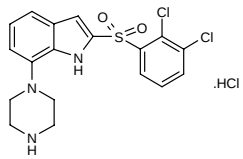
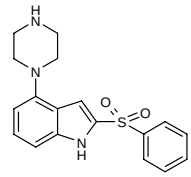
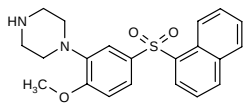
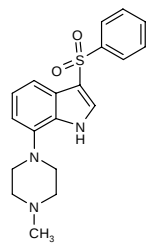
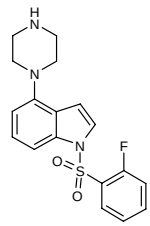
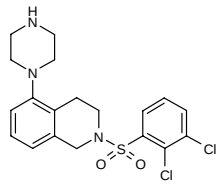
Continuation

Table I: Serotonin 5-HT$_6$ receptor binding affinities of representative patent compounds (from Prous Science Integrity®).

Compound (entry number, EN)[1]	5-HT$_6$ affinity (pK_i)[2,3]	Source	Patent
 (358397)	**8.90** (8.80-8.90)	Roche	WO 2003104193
 (335707)	**9.05** (8.40-9.05)	Pfizer	WO 2003011284
 (369890)	**9.17** (9.04-9.17)	Roche	WO 2004041792
 (383361)	**9.49** (8.78-9.49)	Roche	WO 2004080969
 (370039)	**9.61** (9.00-9.61)	Roche	WO 2004035047
 (355495)	**9.70** (8.50-9.70)	Roche	WO 2003095434

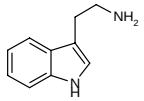
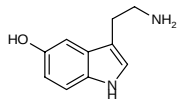
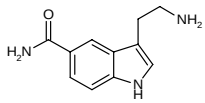
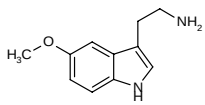
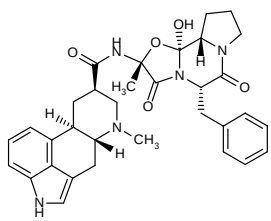
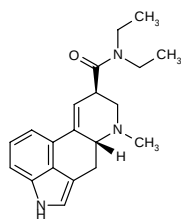
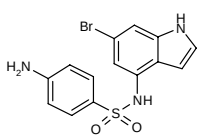
Continuation

Table I: Serotonin 5-HT$_6$ receptor binding affinities of representative patent compounds (from Prous Science Integrity®).

Compound (entry number, EN)[1]	5-HT$_6$ affinity (pK$_i$)[2,3]	Source	Patent
 (368591)	**9.70** (9.30-9.70)	Roche	WO 2004026830
 (367528)	**9.90** (9.10-9.90)	Roche	WO 2004026831
 (336175)	**9.90** (9.14-9.90)	Roche	WO 2003014097
 (331938)	**10.00** (7.65-10.00)	Roche	WO 2002098857
 (332547)	**10.28** (9.81-10.28)	Roche	WO 2002102774
 (382031)	**10.37** (9.28-10.37)	Roche	WO 2004078176

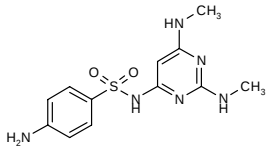
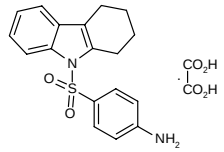
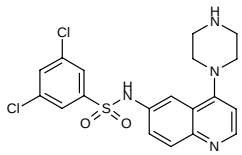
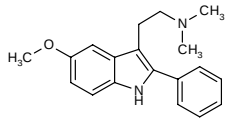
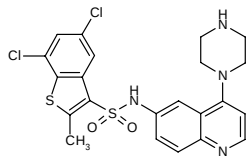
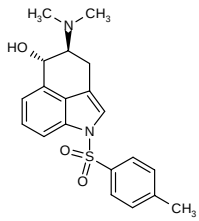
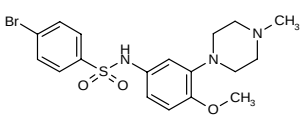
[1]The entry number (EN) is an internal code of Prous Science. [2]The value shown in bold is the pK$_i$ of the most active compound, *i.e.*, the compound in the table. [3]The values in parentheses are the range of pK$_i$ values for all compounds tested in the patent.

Table II: Serotonin 5-HT$_6$ receptor binding affinities (pK$_i$) for selected 5-HT$_6$ antagonists compared to reference agonist compounds (from Prous Science Integrity®).

Compound	5-HT$_6$ affinity (pK$_i$)	Source	Ref.
Agonists			
 Tryptamine	7.15		38
 5-Hydroxytryptamine (5-HT, serotonin)	7.18 (6.87-7.80)		18, 32, 38, 56, 57
 5-Carboxamidotryptamine (5-CT)	6.54 (6.14-6.87)		37, 38, 56
 5-Methoxytryptamine	7.57 (7.16-8.00)		18, 37, 38, 56
 Dihydroergotamine	8.27		56
 LSD (Lysergic acid diethylamide)	8.64		18
Antagonists			
 Ro-65-7199	7.30	Roche	58

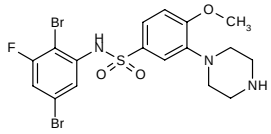
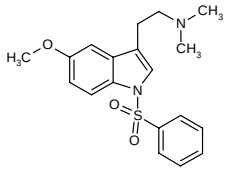
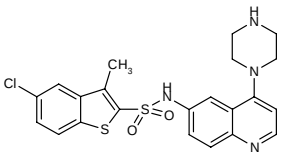
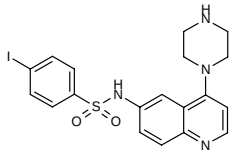
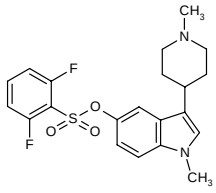
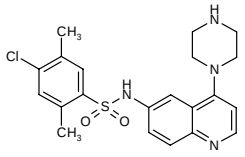
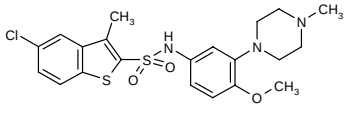
Continuation

Table II: Serotonin 5-HT$_6$ receptor binding affinities (pK$_i$) for selected 5-HT$_6$ antagonists compared to reference agonist compounds (from Prous Science Integrity®).

Compound	5-HT$_6$ affinity (pK$_i$)	Source	Ref.
Antagonists			
 Ro-04-6790	7.33 (7.26-7.52)	Roche	18, 27, 32, 59
 JCF-177	7.54	Case Western Reserve Univ.; Virginia Commonwealth Univ.	60
 304842	7.60	GlaxoSmithKline	61
 286392	7.70	Virginia Commonwealth Univ.	14
 304846	8.10	GlaxoSmithKline	61
 310562	8.14	Merck Sharp & Dohme	62
 SB-214111	8.55	GlaxoSmithKline	18

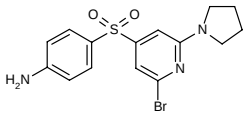
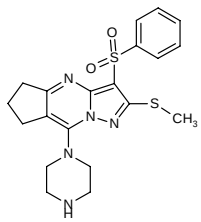
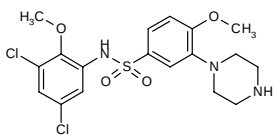
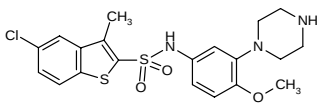
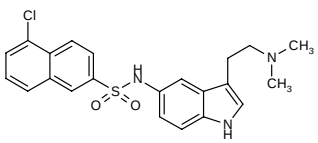
Continuation

Table II: Serotonin 5-HT$_6$ receptor binding affinities (pK$_i$) for selected 5-HT$_6$ antagonists compared to reference agonist compounds (from Prous Science Integrity®).

Compound	5-HT$_6$ affinity (pK$_i$)	Source	Ref.
Antagonists			
 **SB-357134**	8.59	GlaxoSmithKline	18
 295303	8.64	NPS Pharmaceuticals	62
 SB-331711	8.70	GlaxoSmithKline	61
 304848	8.80	GlaxoSmithKline	61
 diF-BAMPI	8.89	Lilly	36
 304847	8.90	GlaxoSmithKline	61
 SB-258510	8.99	GlaxoSmithKline	18

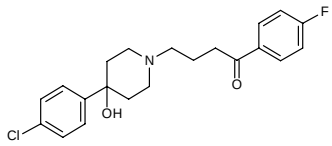
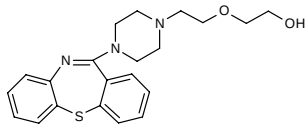
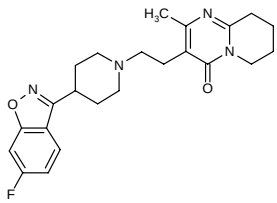
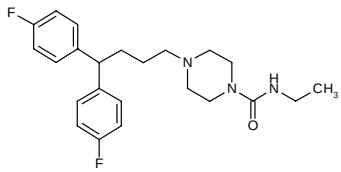
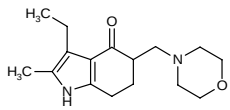
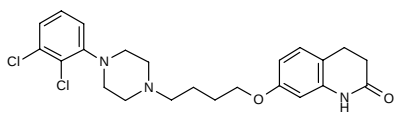
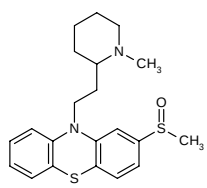
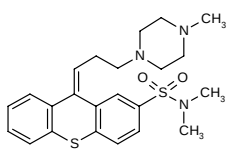
Continuation

Table II: Serotonin 5-HT$_6$ receptor binding affinities (pK$_i$) for selected 5-HT$_6$ antagonists compared to reference agonist compounds (from Prous Science Integrity®).

Compound	5-HT$_6$ affinity (pK$_i$)	Source	Ref.
Antagonists			
 Ro-66-0074	9.00	Roche	59
 Ro-65-7674	9.07	Roche	29
 SB-399885	9.11	GlaxoSmithKline	35
 SB-271046	9.14 (8.90-9.88)	GlaxoSmithKline	18, 30, 31, 32, 63
LY-483518 (Not available)	9.22	Lilly	64
 397674	9.70	Esteve	65

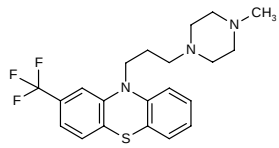
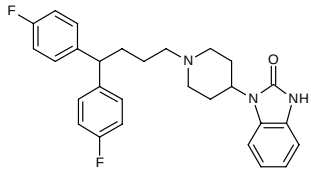
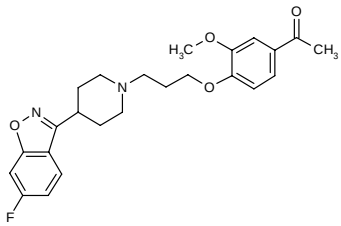
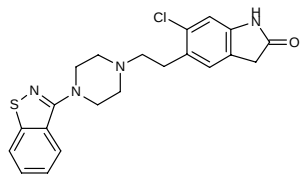
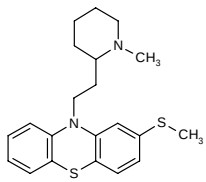
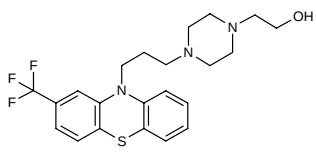
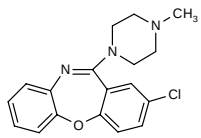
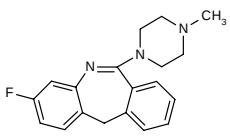
Affinities (pK$_i$) obtained in competitive binding assays by displacement of [^{3}H]-5-HT or [^{3}H]-LSD in cells transfected with the recombinant human 5-HT$_6$ receptor; when more than one value from different studies was available, mean values were calculated and the range is shown in parentheses.

Table III: Human 5-HT$_6$ receptor binding affinities of antipsychotic drugs (from Prous Science Integrity®).

Antipsychotic drug	Structure	5-HT$_6$ affinity (pK$_i$)	Ref.
Haloperidol		5.31 (5.18-5.44)	37, 66
Quetiapine		5.73	66
Risperidone		5.77 (5.62-5.92)	37, 66
Amperozide		5.80	37
Molindone		6.00	66
Aripiprazole		6.18 (6.11-6.24)	66, 67
Mesoridazine		6.42	37
Thiothixene		6.59 (6.50-6.68)	37, 66

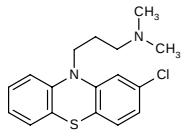
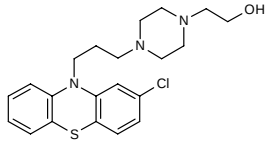
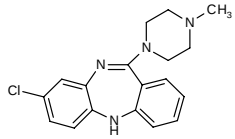
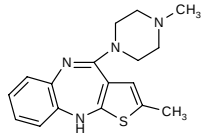
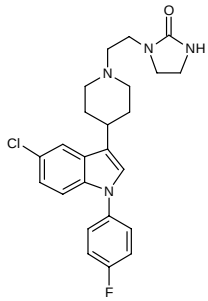
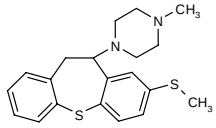
Continuation

Table III: Human 5-HT$_6$ receptor binding affinities of antipsychotic drugs (from Prous Science Integrity®).

Antipsychotic drug	Structure	5-HT$_6$ affinity (pK_i)	Ref.
Trifluoperazine		6.85 (6.77-6.93)	37, 66
Pimozide		7.15	66
Iloperidone		7.20	68, 69
Ziprasidone		7.22	66
Thioridazine		7.24	66
Fluphenazine		7.42	37, 66
Loxapine		7.53 (7.48-7.57)	37, 66
Fluperlapine		7.54	37

Continuation

Table III: Human 5-HT$_6$ receptor binding affinities of antipsychotic drugs (from Prous Science Integrity®).

Antipsychotic drug	Structure	5-HT$_6$ affinity (pK$_i$)	Ref.
Chlorpromazine		7.71 (7.70-7.72)	37, 66
Perphenazine		7.77	66
Clozapine		7.97 (7.77-8.20)	14, 18, 32, 37, 66
Olanzapine		8.10 (8.00-8.20)	37, 66
Sertindole		8.27	66
Methiothepin		9.43 (8.85-10.1)	18, 32, 37, 56, 68

Affinities (pK$_i$) obtained in competitive binding assays by displacement of [^{3}H]-5-HT or [^{3}H]-LSD in cells transfected with the recombinant human 5-HT$_6$ receptor; when more than one value from different studies was available, mean values were calculated and the range is shown in parentheses.

the ability to perform simple everyday tasks. Over time, patients can no longer think clearly or make judgements, language skills are diminished, and mood and personality changes may occur. Eventually, with severe brain atrophy they become completely unresponsive and require total care (3). It is a major health problem worldwide, with the incidence estimated to be between 15 and 18 million individuals. This is expected to increase to 45 million people by 2050 (4).

In contrast, the symptoms of schizophrenia typically emerge in late adolescence or early adulthood, and often persist throughout the rest of the patient's life. This condition affects approximately 24 million people worldwide (5, 6). Although the etiology of schizophrenia is not well understood, in general, it is thought to be a disorder of developmental maturation rather than of neurodegeneration (7). Cognitive dysfunction, ranging from impaired attention to abnormal executive function, as well as

depression and/or anxiety, may present prior to positive and negative symptoms, and can change over time. Although antipsychotic agents are commonly utilized in the treatment of schizophrenia, it is now thought that targeting cognitive deficits, the method for treating Alzheimer's disease, may generate more favorable outcomes.

In the past, a great deal of emphasis has been placed on abnormalities within the cholinergic system as a focus for procognitive therapies for Alzheimer's disease and schizophrenia. However, cholinesterase inhibitors are associated with severe side effects and unsatisfactory results (8, 9). More recently, studies have identified an important role for 5-HT$_6$ receptors in cognitive function.

The 5-HT neuronal system projects to virtually every brain region that subserves cognition (10) and there is evidence indicating that a 5-HT system decline is associated with cognitive dysfunction (11). It has been shown that 5-HT$_6$ receptor expression is abundant in brain regions associated with learning and memory, including the hippocampus, cerebral cortex and amygdala (12, 13). Prior to the development of selective 5-HT$_6$ ligands, early studies identified the therapeutic potential of 5-HT$_6$ receptor modulation for cognitive dysfunction via the use of antisense oligonucleotides designed to reduce the expression of 5-HT$_6$ receptors. Intracerebroventricular injection of antisense oligonucleotides over 6 days to rats facilitated progressive enhancement of memory retention in the water maze memory task (14). Correspondingly, there is evidence for 5-HT$_6$ receptor-mediated inhibitory control over acetylcholinesterase (15) and the induction of behaviors in rodents that are mediated by an increase in cholinergic neurotransmission in the CNS (16).

Preclinical evidence for cognitive improvement via 5-HT$_6$ antagonism is, however, contradictory and thought to be hindered by the diversity among 5-HT$_6$ receptors in humans, rats and mice. Although 5-HT$_6$ receptors share a high degree of homology (over 84%), differences in receptor profiles have been described in binding studies using [^{125}I]-SB-258585. Although this radioligand displays high affinity for rat and human brain 5-HT$_6$ receptors, a very low level of specific binding has been observed in the mouse brain (17). Further investigation has shown that 5-HT$_6$ receptor expression is considerably lower in the mouse brain compared to rat and human brains, and while 5-HT$_6$ receptors accumulate in the basal ganglia and limbic structures in rats and humans, expression is very low in the basal ganglia of mice. Distinct pharmacological profiles have also been demonstrated with differences in rat/human and mouse receptor residues for ligand binding to the 5-HT$_6$ receptor (18). Therefore, it has been suggested that the evaluation of 5-HT$_6$ receptor antagonist efficacy in mice should be interpreted with caution.

The 5-HT$_6$ receptor as a target for obesity

Obesity refers specifically to the excessive accumulation of fat in adipose tissue, to the extent that health and wellbeing are adversely affected. Because obesity increases the risk for other health disorders, it has a major impact on mortality. Life span is often significantly reduced with the concurrent diagnosis of conditions including type 2 diabetes, hypertension, coronary heart disease, dyslipidemia, sleep apnea, blood clots and ischemic stroke (19, 20). It also increases the risk of several types of cancer (colon, endometrial, prostate and postmenopausal breast cancers), gallbladder disease, musculoskeletal disorders, pulmonary dysfunction, infertility in women and depression (21). Obesity has become a chronic problem among adults. The incidence has doubled since 1980, and the number of overweight adolescents has tripled.

As treatment for this condition is often invasive, drugs that reduce energy intake, increase energy expenditure, decrease the absorption of fat or stimulate fat mobilization (22-24) would be important antiobesity pharmacotherapies. Early studies demonstrated that chronic administration of 5-HT$_6$ receptor antisense oligonucleotides produced a significant reduction in food intake and body weight in rats (25). 5-HT$_6$ receptor knockout mice are also resistant to weight gain when exposed to a high-fat diet (26).

Experimental pharmacology of 5-HT$_6$ receptor antagonists

Binding data

In vitro binding studies have demonstrated the different receptor binding profiles of 5-HT$_6$ receptor antagonists (see Table II). The first selective 5-HT$_6$ receptor antagonists, Ro-04-6790 and Ro-63-0563, were described by Roche. In binding assays with [^{3}H]-LSD, these compounds displayed mean pK_i values at the rat 5-HT$_6$ receptor of 7.35 and 7.83, respectively, and pK_i values at the human 5-HT$_6$ receptor of 7.26 and 7.91, respectively. Both compounds were found to be over 100-fold selective for the 5-HT$_6$ receptor relative to a panel of other receptor binding sites. However, brain permeability was extremely limited (< 1%) (27). This work led to the development of Ro-65-7674, which displayed good potency for the 5-HT$_6$ receptor (pK_i = 9.07) and high selectivity over a number of other binding sites (28, 29).

Subsequent compounds were reported by the former SmithKline Beecham (now GlaxoSmithKline). SB-271046 displayed excellent 5-HT$_6$ receptor affinity in transfected HeLa cells (pK_i = 8.9), with > 200-fold selectivity over 50 other receptors, enzymes and ion channels (30). In experiments in native brain tissues using [^{3}H]-LSD and [^{125}I]-SB-258585 as radioligands, SB-271046 presented pK_i values of 8.9 and 9.1, respectively. The compound also displaced [^{125}I]-SB-258585 from rat and pig striatal and human caudate putamen membranes with pK_i values of 9.02, 8.55 and 8.8, respectively, and over 200-fold selectivity for the human 5-HT$_6$ receptor as compared to 55 other receptors, enzymes and ion channels (31). As described above, differences in affinity according to

species have also been shown, as SB-271046 displays similar potency at the human and rat receptors but a 4-fold lower affinity for the mouse receptor (32).

However, as SB-271046 showed low brain penetration, a derivative of this compound, SB-399885, was selected for further evaluation (33). SB-399885 displayed high affinity for both rat and human 5-HT_6 receptors, with pK_i values ranging from 8.81 to 9.11. Investigation of a further analogue, SB-357134, also demonstrated potent inhibition of [^{125}I]-SB-258585 and [^{3}H]-LSD binding in a HeLa cell line expressing human 5-HT_6 receptors (pK_i = 8.6 and 8.54, respectively). Furthermore, SB-357134 inhibited [^{125}I]-SB-258585 binding in human caudate putamen and in rat and pig striatal membranes (pK_i = 8.82, 8.44 and 8.61, respectively). The compound also displayed over 200-fold selectivity for the 5-HT_6 receptor *versus* 72 other receptors and enzymes (34), and 4 h postadministration it inhibited *ex vivo* [^{125}I]-SB-258585 binding in the rat with an ED_{50} of 4.9 mg/kg p.o. (34). *In vivo* studies established that oral SB-399885 binds specifically to the 5-HT_6 receptor in the striatum of rats with an ED_{50} of 2 mg/kg (35).

Scientists from Lilly also recently presented data on a newly developed, potent and selective 5-HT_6 antagonist, diF-BAMPI, which binds to 5-HT_6 receptors with a K_i value of 1.3 nM (36).

Functional activity

5-HT_6 receptors are positively coupled to adenylyl cyclase via Gs (37). In functional studies, neither Ro-04-6790 nor Ro-63-0563 had any significant effect on basal levels of cyclic AMP (cAMP) accumulation in HeLa cells expressing the human 5-HT_6 receptor, suggesting that the compounds are neither agonists nor inverse agonists at this receptor. However, both Ro-04-6790 and Ro-63-0563 behaved as competitive antagonists, with mean pA_2 values of 6.75 and 7.10, respectively (27).

Functional analysis of the human cloned 5-HT_6 receptor has demonstrated that SB-271046 competitively antagonizes 5-HT-dependent increases in cAMP, with a pA_2 value of 8.71 (25). 5-HT-stimulated cAMP accumulation in cells expressing the human 5-HT_6 receptor was also competitively antagonized by SB-357134 (pA_2 = 7.63) (34).

Furthermore, *in vitro* studies in HEK cells transfected with the human 5-HT_6 receptor and using a chimeric G-protein (G-αq/G-αs) revealed that the antagonist SB-271046 exerts a concentration-dependent antagonist effect on Ca^{2+} responses evoked by 5-HT, with an IC_{50} value of 11 nM (38).

Neurochemistry

In vivo microdialysis studies have demonstrated the neurochemical effects of 5-HT_6 receptor antagonists in selected regions of the brain. Ro-65-7674 was proven to increase extracellular acetylcholine (ACh) content in the frontal cortex of freely moving rats at a dose of 30 mg/kg p.o. (28, 29). Interaction with monoaminergic receptors and a modest elevation in ACh efflux in the rat hippocampus have also been noted following administration of Ro-04-6790 (39). Administration of SB-271046 (10 mg/kg s.c.) produced a significant increase in extracellular levels of both glutamate and aspartate within the frontal cortex and hippocampus (40, 41). These neurochemical changes were tetrodotoxin-dependent but were not affected by coadministration of the muscarinic antagonist atropine, indicating on the one hand, an impulse-dependent origin, and on the other, that the enhanced excitatory neurotransmission observed was not a consequence of enhanced cholinergic function (41). The compound also evoked a significant increase in extracellular levels of dopamine and epinephrine in the prefrontal cortex, without altering 5-HT neurotransmission (42). Oral doses of 1, 3 or 10 mg/kg of SB-399885 increased the extracellular levels of noradrenaline, dopamine and ACh in the prefrontal cortex of freely moving rats (35).

Metabolism, pharmacokinetics and tolerability

In vitro studies have demonstrated that SB-271046 does not inhibit cytochrome (CYP) P-450 activity, which was confirmed in isoform-selective assays of major human isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) (30).

Pharmacokinetic studies in rats demonstrated low brain permeability for the Roche compounds Ro-04-6790 and Ro-63-0563 (< 1%) (27, 30). SB-271046 and SB-357134 showed higher, although only moderate, brain permeability, reaching 10% (30) and 19% (34, 42), respectively. SB-271046 has a low blood clearance rate (7.7 ml/min/kg) and an adequate half-life (4.8 h), with over 80% oral bioavailability (30). The bioavailability of SB-357134 reached 65% (34, 43), and when administered at 10 mg/kg p.o., peak blood and brain concentrations were 4.3 and 1.3 μM, respectively, 1 h postadministration (34).

Behavioral pharmacology

Cognition studies

Early studies demonstrated that Ro-04-6790 produced a behavioral response (stretching, yawning and chewing) similar to that seen following treatment with antisense oligonucleotides (27). Further investigation revealed that administration of nonselective muscarinic antagonists such as scopolamine and atropine inhibited stretching induced by Ro-04-6790. This indicates a useful functional correlation between cholinergic neurotransmission in the CNS and 5-HT_6 receptor blockade (44). In cognition studies, whereas Ro-04-6790 (10 or 30 mg/kg i.p.) alone had no effect on performance on the novel object discrimination task, it completely restored the

scopolamine-induced memory deficits (45), as did Ro-65-7674 (28, 29) and Ro-43-68554 (46). Further analysis of Ro-43-68554 demonstrated its activity in the reversal of object and social recognition deficits and in enhancing autoshape learning, whereas it was ineffective in the radial arm maze, step-through passive avoidance test and Morris water maze test in aged rats (46).

The procognitive effects of SB-271046, which displays higher oral bioavailability and better brain penetration (25), have been investigated more extensively. In the rat, SB-271046 potentiated acetylcholinesterase inhibitor-induced behavior, facilitating cholinergic-mediated stretching, yawning and chewing (31, 32). Examination of spatial learning and memory in rats using a water maze demonstrated that oral administration of SB-271046 (10 mg/kg) improved retention, but it did not significantly alter learning facilitation. In contrast, the acetylcholinesterase inhibitor donepezil (0.1 and 0.3 mg/kg p.o.) had no effect, suggesting mechanisms independent of cholinergic neurotransmission in learning and memory processes (47). Further studies in aged rats receiving SB-271046 (0.3-0.6 mg/kg i.p.) over 3 days demonstrated equivalent dose-dependent improvements in retention performance (48). In contrast, another study which used SB-271046 at the optimal dose (10 mg/kg p.o.) failed to demonstrate any significant difference in memory acquisition or retention on water maze tasks (32).

Behavioral analysis of object discrimination revealed that acute SB-271046 (10 mg/kg i.p.) administered prior to and after familiarization trials completely reversed time delay-induced deficits in object discrimination, as rats preferred to explore novel rather than familiar objects. This indicated that SB-271046 is capable of enhancing memory consolidation (49). These observations of retention efficacy were also demonstrated in a dose-ranging study in young and aged rats. At 0.3-10 mg/kg i.p., SB-271046 produced a significant and dose-dependent increase in novel object exploration in young rats, with similar results seen in aged rats at doses of 0.3-3.0 mg/kg i.p. In this case, similar results were also seen with donepezil (0.3-3.0 mg/kg p.o.) (48).

The assessment of the efficacy of SB-271046 (0.3-10 mg/kg i.p.) in passive avoidance to footshock revealed a significant and complete reversal of memory deficits in aged rats, with equivalent results to donepezil (48). Subsequent studies in mature rats demonstrated that SB-271046 dose-dependently reversed scopolamine-induced amnesia in a passive avoidance paradigm, with significant effects at 3, 10 and 20 mg/kg p.o. Furthermore, chronic administration of SB-271046 enhanced spatial learning in aged animals in the water maze task and improved recall in the same task (50).

Analysis of the SB-271046 analogues SB-399885 and SB-357134 revealed that these compounds (10 mg/kg) also improved memory retention (34, 35, 47) and learning (34) using water maze tasks, while also reversing memory impairment induced by scopolamine in a novel object recognition paradigm (35).

Preliminary data recently presented on the behavioral effects of diF-BAMPI also demonstrated improved memory acquisition in rat models of cognition (36).

Saegis Pharmaceuticals has reported on the effectiveness of SGS-518, its novel and selective 5-HT$_6$ receptor antagonist, in behavioral studies of learning and memory. The compound also recently completed placebo-controlled, dose-ranging phase I clinical studies in healthy volunteers, indicating safety and good tolerability (51).

Feeding behavior studies

In vivo studies have also demonstrated a role for selective 5-HT$_6$ receptor antagonists in the regulation of feeding. Ro-04-6790 administered i.p. to rats over 3 days (30 mg/kg) facilitated a reduction in body weight (52). Further studies have revealed a dose-related reduction in food consumption following acute administration of Ro-04-6790 (ID_{50} = 18.6 mg/kg) and SB-271046 (ID_{50} = 14.45 mg/kg) to rats accustomed to a fixed daily feeding regimen (53).

BVT-5182 (3 mg/kg s.c.) potently reduced food intake in a genetic mouse model of obesity without affecting general motor activity or water intake. Chronic administration of BVT-5182 also reduced body weight and cumulative food intake by 9% and 11%, respectively, in mice fed a high-fat diet. Furthermore, the compound decreased serum leptin and epididymal fat in diet-induced obese mice and rats (54, 55). Similar results were observed following treatment with SB-271046 (54).

Conclusions

This review has outlined the evidence suggesting that drugs that selectively antagonize 5-HT$_6$ receptors could improve cognition and feeding behavior. Three potent and selective 5-HT$_6$ receptor antagonists have progressed to phase I clinical studies for the treatment of Alzheimer's disease-associated dementia and schizophrenia: SB-271046, SGS-518 and GlaxoSmithKline's 742457; the latter two are currently under active development and expected to reach phase II studies in 2005.

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