Pharmacology, Biochemistry and Behavior 98 (2011) 169–172

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Mini-review

5-HT$_6$ pharmacology inconsistencies

Franco Borsini *, Fabio Bordi, Teresa Riccioni

Sigma-tau Industrie Farmaceutiche Riunite s.p.a., Via Pontina km. 30,400, 00040 Pomezia (Roma), Italy

ARTICLE INFO

Article history:
Received 24 December 2009
Received in revised form 27 October 2010
Accepted 16 December 2010
Available online 28 December 2010

Keywords:
5HT6
Receptors
MRNA
Neurochemistry and behavior

ABSTRACT

5-HT$_6$ receptors are relatively recently-discovered receptors. After an uncertain beginning, where results were ambiguous, findings are now apparently more congruent. Nevertheless, discrepancies still exist. The aim of the present manuscript is to point out some of these discrepancies, in order to reflect on the current status of the field of the 5-HT$_6$ receptor neuropharmacology, and where the field should move next. Examples of 5-HT$_6$ receptor ligand-induced changes in behavior, neurochemistry and binding highlight areas where discrepancies remain and further experimental attention is needed. Possible methodological as well as conceptual issues underlying the inconsistencies are considered in an effort to increase awareness of the need for more thorough consideration of these aspects in future research.

1. Introduction

Despite considerable research as summarized in several thorough reviews on serotonin type-6 (5-HT$_6$) receptor physiopharmacology within the past decade (Branchek and Blackburn, 2000; Geldenhuys and Van der Schyl, 2008; Glennon et al., 2010; Heal et al., 2008; Holenz et al., 2006; Johnson et al., 2008; Lane et al., 2008; Russell and Diaz, 2002; Woolley et al., 2004), the functional role of 5-HT$_6$ receptors remains ambiguous. For example, it is not yet understood why putative 5-HT$_6$ receptor agonists and antagonists may share some odd similarities in their pharmacological properties, as in the case of their potential antidepressant (Carr et al., 2010; Hirano et al., 2009; Svenningsson et al., 2007; Wesolowska, 2007; Wesolowska and Nikiforuk, 2007; Wesolowska et al., 2007) or cognitive effects (Branchek and Blackburn, 2000; Burnham et al., 2007; Fone, 2008; Geldenhuys and Van der Schyl, 2009; Kendall et al., 2010; Liu and Robichaud, 2009; Schechter et al., 2004). Underlying some of these behavioral discrepancies are, we believe, ambiguous results on some basic aspects of 5-HT$_6$ receptor pharmacology. The discrepancies in the literature began even before the identification of selective 5-HT$_6$ receptor ligands, in work with antisense oligonucleotides to critical portions of the 5-HT$_6$ receptor.

2. A 5-HT$_6$ behavioral syndrome (yawning, stretching and chewing)?

A particular behavior syndrome resulting from blockade of 5-HT$_6$ receptors was characterized by Bourson et al. (1995). Lacking selective 5-HT$_6$ receptor antagonists, Bourson et al. (1995) utilized 5-HT antisense oligonucleotides (AO) complementary to bases 1 to 18 of the rat 5-HT$_6$ cDNA. After intracerebroventricular oligonucleotide administration twice a day at 6 or 12 μg/rat for four days, AO-treated animals displayed a dose-dependent specific behavioral syndrome consisting of yawning, stretching and chewing 16 h after the final treatment, which continued for the following 7–8 days. This syndrome was dose-dependently attenuated by the antimuscarinic compound atropine, but unaffected by the dopamine antagonist haloperidol. Food-intake, body temperature, body weight, and heat sensitivity were unchanged by AO administration. The regimen of AO treatment was found to reduce the number of 5-HT$_6$ receptors by 30% in the frontal cortex, without modifying 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor binding sites. AO administration also did not affect striatal dopamine and DOPAC levels.

However, subsequently the same group (Bentley et al., 1997) reported that intracerebreventricular AO for 5-HT6 receptors reduced body weight and food intake, in apparent contrast to their prior publication. Moreover, Yoshioka et al. (1998) administered intracerebroventricularly 14 μg/rat/day AO with an osmotic pump for 7 days and also found a reduction in 5-HT$_6$ receptors by 30% in membranes coming from whole brain, with no specific behavioral signs observed after AO administration. Similarly, Hamon et al. (1999) and Otano et al. (1999) with AO administration regimens lasting 4–7 days also did not observe the specific behavioral syndrome first reported by Bourson et al. (1995). Several years later, Wolley et al. (2001) again found no evidence of the specific behavioral syndrome after AO twice daily for 6 days, and again in contrast to the initial Bourson et al. (1995) results, they reported an effect on food intake and body weight reduction after AO administration.

Using the selective 5-HT$_6$ antagonist Ro04-6790 (Sleight et al., 1998; Bentley et al., 1999), stretching and chewing were observed but

* Corresponding author. Tel.: +39 06 91393325; fax: +39 06 91393988.
E-mail address: franco.borsini@sigma-tau.it (F. Borsini).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.12.021

not yawning. Similar observations were made by other researchers at Hoffman–LaRoche, by using a different 5-HT_6 receptor antagonist (Bos et al., 2001). Lindner et al. (2003) found that, in contrast to cholinesterase inhibitor physostigmine, Ro04-6790 and the other 5-HT_6 receptor antagonist SB-271046 induced stretching, whereas chewing was increased by Ro04-6790 and physostigmine but not by SB-271046; neither Ro04-6790 nor SB-271046 nor physostigmine modified yawning. Marcos et al. (2008) found that oral SB-271046 induced yawning, a behavior that was also maintained after 7 days of repeated administrations. However, no behavioral syndrome was observed by Reavill and Rogers (2001) with SB-271046, as well as by Stean et al. (2002) after oral SB-357134 (at doses ranging between 0.1 and 30 mg/kg, either after single or 7-day administration). Compound 4, a claimed 5-HT_6 receptor antagonist, also failed to induce yawning, stretching and chewing (Russell and Diaz, 2002).

Although the majority of results with AO showed that rats did not display the behavioral syndrome, some of the studies with 5-HT_6 receptor antagonists indicate the induction of at least some elements of the behavioral syndrome with the drugs tested. However, in general, the overall behavioral syndrome (stretching, yawning and chewing) is not a consistent phenomenon observed with either AO or 5-HT_6 receptor antagonists in rats. This points out how the interpretation of the interaction between ligands and 5-HT_6 receptors may possibly defect of better understanding of 5-HT_6 receptor ligands, both in their pharmacodynamic and pharmacokinetics/metabolic properties.

3. Pharmacokinetic and pharmacodynamic profiles of 5-HT_6 receptor antagonists

There are several 5-HT_6 receptor antagonists with high affinity for cloned human 5-HT_6 receptors: Ro04-6790 (Ki = 55 nM; Sleight et al., 1998), Ro63-0563 (Ki = 12 nM; Sleight et al., 1998), Ro65-7199 (Ki = 20 nM; Bos et al., 2001), SB271046 (Ki = 1.3 nM; Bromidge et al., 1999), SB-357134 (Ki = 0.3 nM; Bromidge et al., 2001), SB-699929 (Ki = 2.5 nM; Ahmed et al., 2005), SB-399885 (Ki = 0.9 nM; Hirst et al., 2006). However, not all of them can appreciably cross the blood-brain barrier (Sleight et al., 1998).

Chemical structures acting as 5-HT_6 receptor agonists were also synthesized. EMDA (2-ethyl-5-methoxy-N,N-dimethyltryptamine) possesses, however, higher affinity for 5-HT_4 receptors (Mattsson et al., 2005), and compounds 16 and 18 have similar affinity for 5-HT_{1A} and 5-HT_{1B} receptors (Mattsson et al., 2005). Cole et al. (2005) found some compounds (compounds 13c, 13f, 15c and 15e) that were full agonists on cAMP production in cloned cells, but unselective. E-6801, in addition to 5-HT_6 receptors, also binds to 5-HT_{1A} receptors (Kendall et al., 2010). The 5-HT_6 receptor agonist WAY-181187 seems quite selective, even if a certain degree of variability was found for 5-HT_7 receptors (Cole et al., 2007; Schechter et al., 2008).

Despite the fact that 5-HT_6 receptor ligands have affinity for 5-HT_6 receptors, may cross the blood-brain barrier and have metabolic stability, their relationship between PK/PD is unclear. 1) SB-357134, which crosses blood-brain barrier better than SB-271046 and Ro04-6790, did not induce behavioral syndrome (Stean et al., 2002); 2) however, oral SB-357134 induced anticonvulsant effects that were at their peak at 4–6 h, but blood and brain concentrations were at their peak after around 1 h (Stean et al., 2002); 3) the anticonvulsant effects induced by oral SB-271046 appeared in less than 30 min, without appreciable blood and brain levels at that timepoint (Routledge et al., 2000); 4) oral SB-399885 had a peak anticonvulsant effect 6 h after administration and on extracellular acetylcholine in the cortex after 1 h, but the maximum concentration in the blood and in the brain was achieved at 3 and 4 h, respectively (Hirst et al., 2006); and 5) compound 11 induced the maximum effect on extracellular levels of acetylcholine after 20 min from oral administration, despite its plasmatic Tmax was at 2 h and its $t_{1/2}$ was at 3 h (Riemer et al., 2003).

All these results suggest a possible role of metabolite(s) in the mechanism of action of some 5-HT_6 receptor antagonists. Indeed, SB-271046 was reported to be an active metabolite of SB-258510A (Frantz et al., 2002). More detailed pharmacokinetic information on the different molecules used in the in vivo studies would certainly help in understanding the results obtained so far. Unfortunately, information on pharmacokinetics and metabolic characteristics of 5-HT_6 receptor ligands is poorly described (Ahmed et al., 2005; Bos et al., 2001; Bromidge et al., 1999, 2001; Cole et al., 2007; Liu et al., 2009; Trani et al., 2008). The inconsistencies found in PK/PD might not solely depend on metabolic characteristics but also on other pharmacological activities of 5-HT_6 ligands, as information on in-vitro selectivity is often poor (Arnt et al., 2010; De Foubert et al., 2007; Hirst et al., 2006; Isaac et al., 2000; Ivachtchenko et al., 2010; Kendall et al., 2010; Schechter et al., 2008; Zhou et al., 2005).

4. Affinity and functional in-vitro assays

The radioligands mostly used with recombinant systems expressing the 5-HT_6 receptor are the unselective lysergic acid diethylamide, either iodinated ([^{125}I]LSD) or tritiated ([^{3}H]LSD) and the tritiated serotonin ([^{3}H]5-HT), for both saturation and competition experiments. 5-HT and LSD seem to interact differently on 5-HT_6 receptors, the latter having higher affinity but being capable of only partially activating rat and human receptors (Boess et al., 1997; Dupuis et al., 2008). Particularly, tryptamine derivatives appear more affine to binding sites labelled with 5-HT than LSD, whereas the contrary is true for ergotamine derivatives (Boess et al., 1997). That compounds may bind to the 5-HT_6 receptors with different interactions is also suggested by the fact that in contrast to SB-357134, Ro04-6790 failed to displace [^{3}H]LSD from mouse 5-HT_6 receptors transiently expressed in HEK cells (Hirst et al., 2003). Moreover, when the more selective 5-HT_6 receptor antagonists [^{3}H]Ro63-0563 and [^{125}I]SB-258585 were used, the number of 5-HT_6 receptors in human recombinant cloned cells ranged from 1.6 pmol/mg with [^{3}H]Ro63-0563 (Boess et al., 1998), to 6.1 pmol/mg with [^{125}I]SB-258585 (Hirst et al., 2000), in comparison with 2.8 pmol/mg with [^{3}H]5-HT (Boess et al., 1997) and 3.9 pmol/mg with [^{3}H]LSD (Hirst et al., 2000). As a whole, these findings suggest that the 5-HT_6 receptor population is bound at different sites by radiolabelled compounds. However, saturation analysis revealed a single binding site (Hirst et al., 2000) or at least cannot be explained with the presence of multiple binding sites (Boess et al., 1998). Another important aspect is the difference in 5-HT_6 receptor density between native tissues and recombinant cells, being the density in native tissue about 30 times lower than in cloned cells (Hirst et al., 2000). As the definition of agonist/antagonist depends on receptor and G protein density, the use of cloned cells for such definition may be misleading (Codony et al., 2010). Additionally, more information on compound selectivity is needed to clarify possible effects that do not seem mediated by 5-HT_6 receptors. However, it is difficult to ascertain the meaning of Ki affinity values or receptor density when these values are reported without an index of variability of the measurement. Thus, if 1.6 and 6.1 pmol/mg protein as 5-HT_6 receptor density measurement (see above) is really different remains an open issue. In line with the unclear information on 5-HT_6 receptor characteristics, the specific binding in striatal membranes was around 65% with [^{125}I]SB-258585 (Hirst et al., 2000) and around 20% with [^{3}H]Ro63-0563 (Boess et al., 1998).

Finally, one should consider another characteristic of 5-HT_6 receptors. Max et al. (1995) observed that the cloned rat 5-HT_6 receptor in HEK-293 cells undergoes fast desensitization, without receptor down-regulation, with a $t_{1/2}$ of less than 1 h with maximal desensitization occurring between 2 and 4 h of treatment. Thus, some activities of 5-HT_6 agonists might also depend on their agonistic

properties at shorter times, but, due to rapid receptor desensitization, an antagonistic action may appear at longer times.

5. Neurochemistry

In vivo, the 5-HT_6 receptor antagonist SB-399885 increased extracellular acetylcholine (ACh) levels in the rat brain (Hirst et al., 2006), an effect also reported for another 5-HT_6 receptor antagonist (compound 11; Riemer et al., 2003). However, the antagonist Ro04-6790 was unable to increase extracellular Ach levels in hippocampus (Shirazi-Southall et al., 2002).

Regarding brain catecholamines, SB-271046 was reported to increase extracellular levels of dopamine (DA) and noradrenaline (NA) in the cortex when given orally (Lacroix et al., 2004), but not when given subcutaneously (Dawson et al., 2000). The authors themselves explained such difference in term of different subregions, primary motor cortex vs. prelimbic/infralimbic, of the cortex. An alternative explanation might be that, in contrast to subcutaneous route, oral administration allows the compound to pass initially through the intestine and liver where it may be metabolized, and, therefore, some active metabolite(s) produced during first-pass metabolism might explain the activity of SB27106 after oral administration. However, the injection of intraperitoneal SB-258510A, a pro-drug of SB-271046 (Frantz et al., 2002), and of subcutaneous SB-399885 (Li et al., 2007) did not induce any increase in extracellular levels of DA in the cortex. It is worth noting that, in contrast to Dawson et al. (2000), Frantz et al. (2002) and Li et al. (2007), Lacroix et al. (2004) used neostigmine, a reversible acetylcholinesterase inhibitor, in the dialyses fluid. Thus, one cannot exclude that the effect on cortical extracellular levels of DA may be observable only when Ach is increased. This hypothesis, however, needs experimental support.

With regard to the in vivo effects induced by 5-HT_6 receptor agonism, a lack of readily available selective 5-HT_6 agonists has limited research advances to date. In the recent European Behavioural Pharmacology Society Meeting in Rome, we presented microdialysis data on the new 5-HT_6 agonist, ST1936 (Borsini et al., 2008). This agonist increased extracellular DA and NA, but not 5-HT levels in medial prefrontal cortex and in the shell of the nucleus accumbens in a dose-dependent manner, and another study confirmed these effects and reported that they were reversed by the antagonist SB-271046, which was inactive by itself (Valentini et al., 2009; additional experiments to extend such effects are ongoing — G. Di Chiara, personal communication). Such data are in contrast with those obtained with another 5-HT_6 receptor agonist, WAY-181187, which reduced 5-HT and DA levels in frontal cortex, but left NA content unchanged (Schechter et al., 2008). This latter microdialysis study on freely moving rats also showed increases in extracellular levels of GABA in the frontal cortex and dorsal hippocampus upon the administration of the 5-HT_6 receptor selective agonist WAY-181187 (Schechter et al., 2008). Thus, in the recent and very limited in vivo experiments that utilize 5-HT_6 receptor agonists, inconsistencies about the effects of 5-HT_6 receptor modulation on monoamine systems in the brain also are evident.

In conclusion, much remains to be clarified about the modulation of 5-HT_6 receptors on other neurotransmitter systems and more tools are necessary for this feat.

6. Conclusions

Although experimental inconsistencies also exist for other 5-HT receptors, i.e. 5-HT_{1A} (Marazziti et al., 2002) and 5-HT_{2C} (Millan, 2005), the marked paucity of information on 5-HT_6 receptors, due to the insufficient data on 5-HT_6 receptor ligands, particularly hampers our understanding of 5-HT_6 receptor pharmacology.

However, the picture of 5-HT_6 receptors is more complex than expected, as their interaction with 5-HT_6 ligands might also depend on neuroanatomical region. In fact, there is even a report (de Foubert et al., 2007) that shows that the up-regulation in **a**ctivity-**r**egulated **c**ytoskeleton-associated protein (Arc) mRNA expression caused by subcutaneous administration of the purported agonist LY586713 is blocked by the subcutaneous administration of the antagonist/inverse agonist SB-271046 in hippocampus and parietal cortex but not in cingulate and orbital cortex. Moreover, in the latter brain regions, the antagonist SB-271046 increased Arc mRNA expression similarly to the agonist LY-586713. Thus, regional brain differences also may then account for some of the inconsistencies. Such regional difference may well account for the discrepancies in microdialysis studies as well. Additionally, it remains to document whether the G proteins linked to 5-HT_6 receptors (Codony et al., 2010) are differently expressed in the different brain regions.

In the field of 5-HT_6 receptors there are several inconsistent findings in need of further study. We think that experimental and procedural flaws might be, at least in part, at the source of these inconsistencies and such inconsistencies could be avoided if some precautions were taken. These include: 1) the use of different radioligands which can provide quite different results in affinity characterization studies; 2) the use of different tissues receptor density and biochemical readouts as these may affect the definition of a compound as silent antagonist, agonist or inverse agonist; 3) more information on possible active metabolites and/or pharmacokinetic differences across compounds that may produce vastly different in vivo neurochemical and behavioral profiles; and 4) more information on receptor selectivity.

Additionally, only very few studies (de Foubert et al., 2007; Schechter et al., 2008; Valentini et al., 2009) use a 5-HT_6 receptor antagonist to block the effect of an 5-HT_6 receptor agonist. The reverse (5-HT_6 receptor agonist against an effect mediated by 5-HT_6 receptor antagonist) has never been assessed. If the 5-HT_6 ligands competitively bind to the same site, the effect of an agonist should be counteracted by an antagonist, and vice versa.

References

Ahmed M, Briggs MA, Bromidge SM, Buck T, Campbell L, Deeks NJ, et al. Bicyclic heteroarylpiperazine as selective brain penetrant 5-HT_6 receptor antagonists. Bioorg Med Chem Lett 2005;15:4867–71.

Arnt J, Bang-Anderson B, Grayson B, Bymaster FP, Cohen MP, DeLapp NW, Giethlen B, Kreilgaard M, McKinzie DL, Neill JC, Nelson DL, Nielsen SM, Poulsen MN, Schaus JM, Witten LM. LuAE58054, a 5-HT6 antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats. Int J Nuropsychopharmacol 2010;13:1021–33.

Bentley JC, Sleight AJ, Marsden CA, Fone KCF. 5-HT_6 antisense oligonucleotide i.c.v. affects rat performance in the water maze and feeding. J Psychopharmacol 1997;11:A64.

Bentley JC, Bourson A, Boess FG, Fone KCF, Marsden CA, Petit N, Sleight AJ. Investigation of stretching behaviour induced by the selective 5-HT_6 receptor antagonist, Ro04-6790, in rats. Br J Pharmacol 1999;126:1537–42.

Boess FG, Monsma Jr FJ, Carolo C, Meyer V, Rudler A, Zwingelstein C, et al. Functional and radioligand binding characterization of rat 5-HT_6 receptors stably expressed in HEK293 cells. Neuropharmacology 1997;36:713–20.

Boess FG, Riemer C, Bos M, Bentley J, Bourson A, Sleight AJ. The 5-hydroxytryptamine6 receptor-selective radioligand [^{3}H]Ro63-0563 labels 5-hydroxytryptamine receptor binding sites in rat and porcine striatum. Mol Pharmacol 1998;54:577–83.

Borsini F, Stasi MA, Minetti P, Riccioni T, Mennini T. Effect of ST1936, a 5HT6 ligand, on rodent adenylate cyclase and forced swimming test. Int J Neuropsychopharmacol 2008;11(Suppl. 1):123–4.

Bos M, Sleight AJ, Godel T, Martin JR, Riemer C, Stadler H. 5-HT_6 receptor antagonists: lead optimisation and biological evaluation of N-aryl and N-heteroaryl 4-amino-benzene sulfonamides. Eur J Med Chem 2001;36:165–78.

Bourson A, Borroni E, Austin RH, Monsma FJ, Sleight AJ. Determination of the role of the 5-HT_6 receptor in the rat brain: a study using antisense oligonucleotides. J Pharmacol Exp Ther 1995;274:173–80.

Branchek TA, Blackburn TP. 5-HT_6 receptors as emerging targets for drug discovery. Ann Rev Pharmacol 2000;40:319–34.

Bromidge SM, Brown AM, Clarke SE, Dodgson K, Gagewr T, Grassam HL, et al. 5-choro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): a potent selective, and orally bioavailable 5-HT_6 receptor antagonist. J Med Chem 1999;42:202–5.

Bromidge SM, Clarke SE, Gager T, Griffith K, Jeffrey P, Jenning AJ, et al. Phenyl benzensulfonamides are novel and selective 5-HT6 antagonists: identification of N (2, 5-dibromo-3-fluorophenyl)-4-methoxy-3-pioperqzin-a-ylbenzensulfonamide (SB-357134). Bioorg Med Chem Lett 2001;11:55–8.

Burnham KE, Baxter MG, Bainton J, Southam E, Dawson LA, Sharp T, Bannerman DM. The 5-HT6 receptor agonist WAY181187 enhances extradimensional set-shifting in the rat. Br J Pharmacol 2007;5(2):27P.

Carr GV, Schechter LE, Lucki I. Antidepressant and anxiolytic effects of selective 5-HT(6) receptor agonists in rats. Psychopharmacology 2010 Mar 9 doi:10.1007/s00213-010-1798-7 [Epub ahead of print].

Codony X, Burgueño, J, Ramírez MJ, Vela JM. 5-HT6 receptor signal transduction. Second Messenger Systems. Int Rev Neurobiol 2010;94:89–110.

Cole DC, Lennox WJ, Lombardi S, Ellingboe JW, Bernotas RC, Tawa GJ, Mazandarani H, Smith DL, Zhang G, Coupet J, Schechter LE. Discovery of 5-arylsulfonamido-3-(oyrrolidin-2-ymethyl)-1H-indole derivatives as potent, selective 5-HT_6 receptor agonists and antagonists. J Med Chem 2005;48:353–6.

Cole DC, Stock JR, Lennox WJ, Bernotas RC, Ellingboe JW, Boikess S, Coupet J, Smith DL, Leung L, Zhang G-M, Feng X, Kelly MF, Galante R, Huang P, Dawson LA, Marquis K, Rosenweig-Lipson S, Beyer, Schechter LE. Discovery of N1-(6-chloroimidazo[2, 1-b][1, 3]thiazole-5-sulfoyl)tryptamine as a potent, selective, and orally active 5-HT6 receptor agonist. J Med Chem 2007;50:5535–8.

Dawson LA, Nguyen HQ, Li P. In vivo effects of the 5-HT_6 antagonist SB-271046 on striatal and frontal cortex extracellular concentrations of noradrenaline, dopamine, 5-HT, glutamate and aspartate. Br J Pharmacol 2000;130:23–6.

De Foubert G, O'Neill MJ, Zetterstrom TS. Acute onset by 5-HT_6 receptor-activation on rat brain-derived neurotrophic factor and activity-regulated cytoskeletal-associated protein mRNA expression. Neuroscience 2007;147:778–85.

Dupuis DS, Mannoury la Cour C, Chaput C, Verriele L, Lavielle G, et al. Actions of novel antagonists and antipsychotic agents at ricombinant rat 5-HT_6 receptors: a comparative study of coupling to GαS. Eur J Pharmacol 2008;588:170–7.

Fone KCF. An update on the role of the 5-hydroxytryptamine$_6$ receptor in cognitive function. Neuropharmacology 2008;55:1015–22.

Frantz KJ, Hansson KJ, Stouffer DG, Parson LH. 5-HT_6 receptor antagonism potentiates the behavioural and neurochemical effects of amphetamine but not cocaine. Neuropharmacology 2002;42:170–80.

Geldenhuys WJ, Van der Schyl CJ. Serotonin 5-HT_6 receptor antagonists for the treatment of Alzheimer's disease. Curr Top Med Chem 2008;8:1035–48.

Geldenhuys WJ, Van der Schyl CJ. The serotonin 5-HT6 receptor: a viable drug target for treating cognitive deficits in Alzheimer's disease. Expert Rev Neurother 2009;9:1073–85.

Glennon RA, Siripurapu U, Roth BL, Kolanos R, Bondarev ML, Sikazwe D, et al. The medicinal chemistry of 5-HT(6) receptor ligands with a focus on arylsulfonyltryptamine analogs. Curr Top Med Chem 2010;10:579–95.

Hamon M, Doucet E, Lefevre K, Miquel M-C, Lanfumey L, Insausti R, et al. Antibodies and antisense oligonucleotide for probing the distribution and putative functions of central 5-HT_6 receptors. Neuropsychopharmacology 1999;21:68S–76S.

Heal DJ, Smith SL, Fisas A, Codony X, Buschmann H. Selective 5-HT_6 receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. Pharmacol Ther 2008;117:207–31.

Hirano K, Piers TM, Searle KL, Miller ND, Rutter AR, Chapman PF. Procognitive 5-HT_6 antagonists in the rat forced swimming test: potential therapeutic utility in mood disorders associated with Alzheimer's disease. Life Sci 2009;84:558–62.

Hirst WD, Minton JAL, Bromidge SM, Moss SF, Latter AJ, Riley G, Routledge C, Middlemiss DN, Price GW. Characterization of [^{125}I]-SB-258585 binding to human recombinant and native 5-HT_6 receptors in rat, pig, and human brain tissue. Br J Pharmacol 2000;130:1597–605.

Hirst WD, Abrahamsen B, Blaney FE, Calver AR, Aloj L, Price GW, et al. Differences in the central nervous system distribution and pharmacology of the mouse 5-hydroxytryptamine-6 receptor compared with rat and human receptors investigated by radioligand binding, site-directed mutagenesis, and molecular modeling. Mol Pharmacol 2003;64:1295–308.

Hirst WD, Stean TO, Rogers DC, Sunter D, Pugh P, Moss SF, et al. SB-399885 is a potent, selective 5-HT_6 receptor antagonist with cognitive enhancing properties in aged rat water maze and novel recognition models. Eur J Pharmacol 2006;553:109–19.

Holenz J, Pauwels P, Diaz JL, Mercé R, Codony X, Buschmann H. Medicinal chemistry strategies to 5-HT_6 receptor ligands as potential cognitive enhancers and antiobesity agents. Drug Dis Today 2006;11:283–99.

Isaac M, Slassi A, Xin T, MacLean N, Wilson J, McCallum K, Wang H. Demchyshyn. 6-bicyclopiperazinyl-1-arylsulphonylindoles derivatives as novel, potent, and selective 5-HT_6 receptor antagonists. Bioorg Med Chem Lett 2000;10:1719–21.

Ivachtchenko AV, Mitkin OD, Tkachenko SE, Okun IM, Kysil VM. 8-Sulfonyl-substituted tetrahydro-1H-pyrido[4, 3-b]indoles as 5-HT6 receptor antagonists. Eur J Med Chem 2010;45:782–9.

Johnson CN, Ahmed M, Miller ND. 5-HT_6 receptor antagonists: prospective for the treatment of cognitive disorders including dementia. Curr Opin Drug Discov Dev 2008;11:642–54.

Kendall I, Slotten HA, Codony X, Burgueno J, Pauwels PJ, Vela JM, Fone KCF. E-6801, a 5-HT6 receptor agonist, improves recognition memory by combined modulation of cholinergic and glutamatergic neurotransmission in the rat. Psychopharmacology 2010 Pub ahead 20 April PMID: 20405281.

Lacroix LP, Dawson LA, Hagan JJ, Heidbreder CA. 5-HT_6 receptor antagonist SB-271046 enhances extracellular levels of monoamines in the rat medial prefrontal cortex. Synapse 2004;51:158–64.

Lane H-L, Liu Y-L, Huang C-L, Hsieh C-L, Chang Y-L, Chang L, et al. Prefrontal executive function and D_1, D_3, 5-HT_{2A} and 5-HT_6 receptor gene variations in healthy adults. J Psychiatry Neurosci 2008;33:47–53.

Li Z, Huang M, Prus AJ, Dai J, Meltzer HY. 5-HT_6 receptor antagonist SB-399885 potentiates haloperidol and risperidone-induced dopamine efflux in the medial prefrontal cortex or hippocampus. Brain Res 2007;1134:70–8.

Lindner MD, Hodges DB, Hogan JB, Orie AF, Corsa JA, Barten DM, et al. An assessment of the effects of serotonin 6 (5-HT_6) receptor antagonists in rodent models of learning. J Pharmacol Exp Ther 2003;307:682–91.

Liu KG, Robichaud AJ. 5-HT6 antagonists as potential treatment for cognitive dysfunction. Drug Dev Res 2009;70:145–68.

Liu KG, Lo JR, Comery TA, Zhang GM, Zhang JY, Kowal DM, Smith DL, Di L, Kerns EH, Schechter LE, Robichaud AJ. 1-Sulfonylindazoles as potent and selective 5-HT_6 ligands. Bioorg Med Chem 2009;19:2413–5.

Marazziti D, Palego L, Giromella A, Mazzoni MR, Borsini F, Mayer N, et al. Region-dependent effect of flibanserin and buspirone on adenylyl cyclase activity in the human brain. Int J Neuropsychopharmacol 2002;5:131–40.

Marcos B, Chuang TT, Ramirez MJ. Effects of 5-HT_6 receptor antagonism and cholinesterase inhibition in models of cognitive impairment in the rat. Br J Pharmacol 2008;155:434–40.

Mattsson C, Sonesson C, Sandahl A, Greiner HE, Gassen M, Plaschke J, Leibrock J, Bottcher H. 2-Alkyl-3-(1, 2, 3, 6-tetrahydropyridin-4-yl)-1H-indoles as novel 5-HT6 receptor agonists. Bioorg Med Chem Lett 2005;15:4230–4.

Max SI, Monsma FJ, Sibley DR. Agonist-induced desensitization of 5-HT_6 serotonin receptor-coupled adenylyl cyclase in stably transfected HEK-293 cells. J Serotonin Res 1995;2:101–16.

Millan MJ. Serotonin 5-HT_{2C} receptors as target for the treatment of depressive and anxious states: focus on novel therapeutic strategies. Therapie 2005;5:441–60.

Otano A, Frechilla D, Cobreros A, Cruz-Orive LM, Insausti A, Insausti R, et al. Anxiogenic-like effects and reduced stereological counting of immunolabelled 5-hydroxytryptamine$_6$ receptors in rat nucleus accumbens by antisense oligonucleotides. Neuroscience 1999;92:1001–9.

Reavill C, Rogers DC. The therapeutic potential of 5-HT6 receptor antagonists. Curr Opin Investig Drugs 2001;2:104–9.

Riemer C, Borroni E, Levet-Trafit B, Martin JR, Poli S, Porter RHP, et al. Influence of the 5-HT_6 receptor on acetylcholine release in the cortex: pharmacological characterization of 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine, a potent and selective 5-HT_6 receptor antagonist. J Med Chem 2003;46:1273–6.

Routledge C, Bromidge SM, Moss SF, Price GW, Hirst W, Newmann H, et al. Characterization of SB-271046: a potent, selective and orally active 5-HT_6 receptor antagonist. Br J Pharmacol 2000;130:1606–12.

Russell M, Diaz R. Memories are made of this (perhaps): a review of serotonin 5-HT_6 receptor ligand and their biological functions. Curr Top Med Chem 2002;2:643–54.

Schechter LE, Smith DL, Li P, Lin Q, Rosenweig-Lipson S, Robichaud A, Bernotas R, Beyer CE. WAY-466: pharmacological profile of a novel and selective 5-HT_6 receptor agonist. Soc Neurosci Meeting 2004:394.11.

Schechter LE, Lin Q, Smith DL, Zhang G, San Q, Polatt B, et al. Neuropharmacological profile of novel and selective 5-HT_6 receptor agonists: WAY-181187 and WAY-208466. Neuropsychopharmacology 2008;33:1323–35.

Shirazi-Southall S, Rodriguez DE, Nomikos GG. Effects of typical and atypical antipsychotics and receptor selective compounds on acetylcholine efflux in the hippocampus of the rat. Neuropsychopharmacology 2002;26:583–94.

Sleight AJ, Boess FG, Bos M, Levet-Trafit B, Riemer C, Bourson A. Characterization of Ro 04-6790 and Ro 63-0563: potent and selective antagonists at human and rat 5-HT_6 receptors. Br J Pharmacol 1998;1245:556–62.

Stean TO, Hirst WD, Thomas DR, Price GW, Rogers D, Riley G, et al. Pharmacological profile of SB-357134: a potent, selective, brain penetrant, and orally active 5-HT_6 receptor antagonists. Pharmacol Biochem Behav 2002;71:645–54.

Svenningsson P, Tzavara ET, Qi H, Carruthers R, Witkin JM, Nomikons GG, et al. Biochemical and behavioural evidence for antidepressant-like effects of 5-HT_6 receptor stimulation. J Neurosci 2007;27:4201–9.

Trani G, Baddeley SM, Briggs MA, Chuang TT, Deeks NJ, Johnson CN, et al. Tricyclic azepine derivatives as selective brain penetrant 5-HT_6 receptor antagonists. Bioorg Med Chem Lett 2008;18:5698–700.

Valentini V, De Luca MA, Borsini F, Frau R, Di Chiara G. Characterization of ST1936, a new 5-HT_6 agonist. Behav Pharmacol 2009;20(special issue 1):S36.

Wesolowska A. Study into a possible mechanism responsible for the antidepressant-like activity of the selective 5-HT_6 receptor antagonist SB-399885 in rats. Pharmacol Rep 2007;59:664–71.

Wesolowska A, Nikiforuk A. Effects of the brain-penetrant and selective 5-HT_6 receptor antagonists SB-3999885 in animal models of anxiety and depression. Neuropharmacology 2007;52:1274–83.

Wesolowska A, Nikiforuk A, Stachowicz K. Anxiolytic-like and antidepressant-like effect produced by the selective 5-HT_6 receptor antagonist SB-258585 after the intrahippocampal administration to rats. Behav Pharmacol 2007;18:439–46.

Woolley ML, Bentley JC, Sleight AJ, Marsden CA, Fone KCF. A role for 5-HT_6 receptors in retention of spatial learning in the Morris water maze. Neuropharmacology 2001;41:210–9.

Woolley ML, Marsden CA. Fone KCF. 5-HT_6 receptors. Curr Drug Targets 2004;3:59–89.

Yoshioka M, Matsumoto M, Togashi H, Mori K, Saito H. Central distribution and function of 5-HT_6 receptor subtype in the rat brain. Life Sci 1998;62:1473–7.

Zhou P, Yan Y, Bernotas R, Harrison BL, Huryn D, Robichaud AJ, Zhan GM, Smith DL, Schechter LE. 4-(2-Aminoethoxy)-N-(phenylsulphonyl)indoles as novel 5-HT_6 receptor ligands. Bioorg Med Chem Lett 2005;15:1393–6.