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Antidepressant and anxiolytic effects of selective 5-HT₆ receptor agonists in rats

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Abstract

Rationale—Although selective serotonin reuptake inhibitors (SSRIs) produce clinical therapeutic effects on depression and anxiety through augmentation of serotonergic neurotransmission, there is little known about the potential contributions of the 5-HT₆ receptor in the treatment of mood disorders.

Objectives—The aim of this study was to test the potential antidepressant-like and anxiolytic-like effects of the 5-HT₆ receptor agonists WAY-208466 and WAY-181187 using established behavioral tests in rats.

Methods—In order to determine if the 5-HT₆ receptor agonists possess antidepressant-like activity, rats were treated with WAY-208466 or WAY-181187 and tested in the modified rat forced swim test (FST). Also, the potential anxiolytic-like effects of WAY-208466 and WAY-181187 were measured using the defensive burying (DB) test and novelty-induced hypophagia (NIH) test.

Results—WAY-208466 and WAY-181187 produced both antidepressant-like and anxiolytic-like effects. Both compounds decreased immobility and increased swimming behavior in the FST. The effects of the 5-HT₆ receptor agonists were similar to those seen after treatment with the SSRI fluoxetine. Both 5-HT₆ receptor agonists also decreased burying duration in the DB test, indicative of anxiolytic activity in the test. The anxiolytic effects of WAY-208466 were reproduced in the NIH test. Assessment of the anxiolytic effects of WAY-181187 in the NIH was confounded by alterations in home cage feeding behavior.

Conclusions—These findings suggest that 5-HT₆ receptor agonists may represent a new class of potential antidepressant and anxiolytic compounds and could possess a number of advantages over currently available treatments, including rapid onset of anxiolytic efficacy.

Keywords

Serotonin; Depression; Anxiety; 5-HT₆ receptor; Antidepressants; Forced swim test; Novelty-induced hypophagia; Defensive burying

Introduction

The most widely prescribed pharmacological treatments for depression and anxiety are the selective serotonin reuptake inhibitors (SSRIs) (Montgomery et al. 2007; Nutt 2005). The principal acute pharmacological action of these compounds is the direct blockade of the serotonin (5-HT) transporter which causes increased extracellular levels of 5-HT (Frazer 1997). Despite extensive clinical use of SSRIs for the treatment of depression and anxiety, it is still unclear which of the 5-HT receptor subtypes contribute to the therapeutic actions of SSRIs. Early studies identified postsynaptic 5-HT_{1A} receptors as an important target for antidepressant activity as selective 5-HT_{1A} receptor agonists reproduce many of the effects of SSRIs (Lucki et al. 1994; De Vry 1995) and blockade or genetic deletion of 5-HT_{1A} receptors prevent the effects of acute and chronic administration of SSRIs (Mayorga et al. 2001; Santarelli et al. 2003). However, selective 5-HT_{1A} receptor agonists have not demonstrated equivalent clinical antidepressant efficacy to SSRIs (Blier and Ward 2003). In view of the positive effects of numerous selective 5-HT receptor agonists and antagonists reported on tests for antidepressant activity, the therapeutic effects of SSRIs may be the product of the activation of multiple 5-HT receptors (Carr and Lucki 2010).

The 5-HT₆ receptor is a G-protein-coupled receptor that positively stimulates adenylate cyclase activity (Gerard et al. 1997; Monsma et al. 1993; Ruat et al. 1993; Ward et al. 1995). 5-HT₆ receptor mRNA is located most abundantly in the olfactory tubercle, frontal and entorhinal cortices, dorsal hippocampus, nucleus accumbens, and striatum (Gerard et al. 1997; Ward et al. 1995). Other studies have shown a similar distribution pattern for 5-HT₆ receptor protein in the brain (Hamon et al. 1999; Roberts et al. 2002). 5-HT₆ receptors are thought to serve as heteroreceptors as they are not found on 5-HT cell bodies or terminals (Gerard et al. 1996). Signaling through the 5-HT₆ receptor has been shown to regulate the release of other neurotransmitters in the brain. Specifically, 5-HT₆ receptor antagonists increase extracellular levels of acetylcholine, glutamate, and norepinephrine in forebrain regions (Dawson et al. 2000, 2001; Riemer et al. 2003).

A role for the 5-HT₆ receptor system has been proposed in the regulation of cognitive function. 5-HT₆ receptor antagonists have been shown to improve performance in tasks involving learning and memory in rodents (Hirst et al. 2006; Loiseau et al. 2008; Rogers and Hagan 2001; Woolley et al. 2003). Additionally, 5-HT₆ receptor antagonists also produce anxiolytic-like and antidepressant-like effects in rodents (Hirano et al. 2009; Wesolowska 2007, 2008; Wesolowska and Nikiforuk 2007; Wesolowska et al. 2007). These compounds are promising therapeutic agents as the combination of these effects could be especially useful for the treatment of diseases, like Alzheimer's disease, characterized by cognitive deficits and mood alterations (for review, see Fone 2008; Mitchell and Neumaier 2005).

The behavioral literature concerning the effects of 5-HT₆ receptor agonists in models of depression-like and anxiety-like behavior is small, most likely due to the paucity of selective agonists (Schechter et al. 2008; Svenningsson et al. 2007). Preclinical studies showed that the 5-HT₆ receptor agonist 2-ethyl-5-methoxy-*N,N*-dimethyltryptamine (EMDT) produced antidepressant-like effects in the mouse tail suspension test, and the 5-HT₆ receptor antagonist SB-271046 blocked the effects of EMDT and partially blocked the effects of the SSRI fluoxetine (Svenningsson et al. 2007). Recently, two selective 5-HT₆ receptor

agonists, WAY-208466 and WAY-181187, were synthesized and neuro-chemically characterized (Cole et al. 2007; Schechter et al. 2008). These compounds demonstrate greater than 100-fold selectivity for the 5-HT₆ receptor over a number of other receptors found in the CNS. Acute and chronic systemic administration of these compounds in rats increase extracellular GABA levels in multiple brain regions, decrease 5-HT and dopamine levels in the frontal cortex, and decrease stimulated glutamate release without affecting basal glutamatergic tone (Schechter et al. 2008). In behavioral studies, WAY-181187 decreases adjunctive drinking maintained by schedule-induced polydipsia, a model of obsessive-compulsive behavior (Schechter et al. 2008). Chronic treatment with SSRIs also decreases schedule-induced polydipsia (Woods et al. 1993) suggesting that SSRIs and 5-HT₆ receptor agonists may produce similar behavioral effects.

In the current study, we tested the hypothesis that activation of the 5-HT₆ receptor would produce antidepressant-like and anxiolytic-like effects in rats. We utilized the modified rat forced swim test (FST) to examine potential antidepressant effects of the two selective 5-HT₆ receptor agonists, WAY-208466 and WAY-181187, because this version of the test has been shown to reliably detect the antidepressant activity of SSRIs and other agents that produce their effects through activation of the 5-HT system (Cryan et al. 2005). The novelty-induced hypophagia (NIH) test and defensive burying (DB) tests were used to measure any potential anxiolytic-like effects of these compounds (De Boer and Koolhaas 2003; Dulawa and Hen 2005). These tests were chosen because of the complementary nature of the anxiety-like responses produced in the tests. The DB test involves the initiation of an active behavior in response to an aversive stimulus whereas the NIH test involves the suppression of active behavior in response to the novel arena. Anxiolytic drugs produce complementary effects on behavior, reducing burying behavior in DB test and increasing approach to the food in the NIH test. This approach provides additional information when employed as a pair of tasks used to measure anxiety-related behaviors.

Materials and methods

Animals

Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA), weighing 225–250 g upon arrival, were housed two per cage in a temperature-controlled (22°C) colony room under a 12-h light/dark schedule (lights on at 0700 hours). Food and water were freely available. The care and use of animals was in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Drugs

WAY-208466 (*N*-[2-[3-(3-fluorophenylsulfonyl)-1H-pyr-olo[2,3-*b*]pyridin-1-yl]ethyl]-*N,N*-dimethylamine), WAY-181187 *N*-1-(6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl)tryptamine (Wyeth Research, Princeton, NJ), chlordiazepoxide hydrochloride (Sigma-Aldrich, St. Louis, MO), and fluoxetine hydrochloride (BIOTREND Chemicals, Zurich, Switzerland) were all dissolved in distilled water. All drug solutions were injected s.c. at a volume of 2 ml/kg subcutaneously. Control groups in all experiments were given an injection of 0.9% saline at an equivalent volume.

Behavioral procedures

Forced swim test—The modified rat FST utilized in these experiments is similar to a protocol used frequently in this lab (Detke et al. 1995). Rats were exposed to two swim sessions. The first session was 15 min in duration, and the second session was 5 min in duration and given 24 h after the first session. WAY-208466 (7.5, 15, and 30 mg/kg), WAY-181187 (3, 10, and 17 mg/kg), and fluoxetine (20 mg/kg) were administered three

times between the 15- and 5-min swim sessions (23.5, 5, and 1 h before the 5-min swim). The 5-HT₆ agonist drug doses were chosen to span doses previously shown to modulate extracellular neurotransmitter levels (Schechter et al. 2008). The swim tests were conducted in a glass cylinder (20 cm diameter) filled to a depth of 30 cm with fresh water (23–25°C). The 5-min test was videotaped and scored for the frequency of climbing, swimming, and immobility behaviors using a time-sampling method by an observer blind to treatment.

Locomotor activity—General locomotor activity was measured in a Plexiglas open-field arena (L 46 cm×W 38 cm×H 38 cm) located in a room lit by two 15-W light bulbs, aimed away from the testing arena to produce a total illumination level of 75 lx in the testing arena. Total distance traveled (centimeters) was measured over a 30-min time period using the SMART video tracking system (San Diego Instruments, San Diego, CA). WAY-208466 (30 mg/kg) and WAY-181187 (17 mg/kg) were administered 23.5, 5, and 1 h before the testing session in order to mimic the treatment regimen used in the FST experiments.

Defensive burying test—The shock-probe defensive burying test, adapted from the procedure developed by Treit and colleagues (1981), was conducted in a clear polycarbonate cage, 48 cm L×26 cm W×20 cm H, with a 1-cm diameter hole located 7 cm from the base at one end of the cage to accommodate the shock-probe. The test was conducted in a room with standard fluorescent lighting set to 130 lx. Fresh bedding (Bed o’Cobs, The Andersons, Maumee, OH) lined the cage to a depth of 5 cm. The shock probe was a 1.0-cm diameter glass rod wrapped with two alternating, non-touching 18-gauge copper wires. The probe extended 6 cm into one end of the cage and 2 cm above the surface of the bedding. The probe was attached to a shock generator (SGS-004, BRS-LVE, Laurel, MD) set to deliver 4.0 mA of current when the probe was touched. Rats were treated with WAY-208466 (15 or 30 mg/kg), chlordiazepoxide (5 mg/kg), or WAY-181187 (10 or 17 mg/kg) 30 min before the start of testing. At the beginning of the test, rats were placed in the cage at the end opposite the shock probe, facing away from the probe. Rats typically approached the probe to investigate within 10–15 s, making contact with their paw or snout. The 15-min test period began when the rat contacted the probe and received a shock. The probe remained electrified for the duration of the session. Test sessions were videotaped for subsequent analysis. After each test, the cage was replaced with an identical clean testing cage containing fresh bedding. Burying consisted of burrowing into the bedding with the snout and upper body and then pushing or flicking the bedding toward the probe using the forepaws. In addition to the total time spent burying, the latency to contact the probe and shock reactivity on a four-point scale (Treit and Pesold 1990) was also measured.

Novelty-induced hypophagia—Rats were trained to consume a palatable food (Graham cracker crumbs) in their home cage for eight consecutive days. Ninety minutes prior to the daily feeding sessions, an opaque Plexiglas divider was inserted into the home cage, separating the two cage mates. Each rat was individually presented with 8–10 g of Graham cracker crumbs (Kraft Foods, Inc., Northfield, IL) for 15 min. This training period allowed for the development of stable levels of food intake and feeding latencies (Bechtholt et al. 2007). The day after the end of training, rats were given a home cage test. The home cage test was identical to the training sessions except that the rats were treated with either WAY-208466 (15 or 30 mg/kg) or WAY-181187 (10 or 17 mg/kg) 30 min before they were given access to the Graham cracker crumbs. The home cage test was videotaped for later analysis. Novelty-induced hypophagia was assessed by presenting the familiar graham cracker crumbs to individual rats in a novel environment. The novel cage test was conducted 1 day after the home cage test. The novel environment consisted of a polycarbonate cage of the same dimensions as the home cage (48 cm L×26 cm W×20 cm H) that was brightly lit (1,345 lx) and had a wire, rather than bedding, lined floor. Rats were again treated with

WAY-208466 or WAY-181187 30 min before testing. The novel cage test was also videotaped. Latency to begin eating and amount of food consumed were measured in both the home and novel cage tests.

Statistical analyses

PASW 17.0 software (SPSS, Inc., Chicago, IL) was used for all data analysis. The forced swim tests using the 5-HT₆ agonists, locomotor activity tests, DB tests, and NIH tests were analyzed using one-way ANOVA. Follow-up analysis of significant main effects was conducted using Bonferroni's post hoc test. The data from the FST experiment with fluoxetine was analyzed using a Student's *t* test.

Results

Effects of 5-HT₆ receptor agonists in the forced swim test

The 5-HT₆ receptor agonist WAY-208466 produced antidepressant-like effects in the modified rat FST (Fig. 1a). WAY-208466 treatment produced a significant reduction in immobility [$F(3, 39)=3.62, p<0.05$]. The 30-mg/kg dose significantly lowered immobility compared to the saline-treated group ($p<0.05$). WAY-208466 treatment also produced a complementary increase in swimming behavior [$F(3, 39)=2.83, p=0.05$]. The 30-mg/kg dose increased swimming behavior compared with saline ($p=0.05$). There were no significant effects of drug treatment on climbing behavior.

Antidepressant-like effects were produced by administration of WAY-181187 (Fig. 1b). Treatment with WAY-181187 decreased immobility [$F(3, 27)=3.18, p<0.05$] and increased swimming behavior [$F(3, 27)=3.42, p<0.05$]. The 17-mg/kg dose significantly decreased immobility ($p<0.05$) and increased swimming ($p<0.05$). Administration of WAY-181187 did not produce any changes in climbing behavior.

The antidepressant-like effects of these two compounds were not due to a general increase in locomotor activity, as neither drug produced hyperactivity in the open field (Table 1). Also, the magnitude and response pattern of the antidepressant activity produced by the 5-HT₆ agonists was similar to that seen after treatment with the clinically effective SSRI fluoxetine (Fig. 1c), which decreased immobility [$t(18)=3.06, p<0.01$] and increased swimming behavior [$t(18)=3.70, p<0.01$].

Effects of 5-HT₆ receptor agonists in the DB test

WAY-208466 significantly decreased burying duration in the DB test [$F(3, 42)=4.88, p<0.01$] at 15 mg/kg ($p<0.05$), but not at 30 mg/kg (Fig. 2a). The magnitude of the effect for WAY-208466 (15 mg/kg) was similar in magnitude to the effect produced by the reference anxiolytic compound chlordiazepoxide. There were no significant differences between the groups in reactivity score or latency to contact the probe suggesting that the treatment effects were not due to insensitivity to the shock or locomotor deficits (Table 2).

WAY-181187 significantly decreased burying duration in the DB test [$F(2, 26)=12.72, p<0.001$] (Fig. 2b). Both the 10- and 17-mg/kg doses produced significant decreases in burying duration ($p<0.01$ and $p<0.001$, respectively). The high dose of WAY-181187 almost eliminated all burying behavior as eight of the nine rats tested did not bury at all. As with WAY-208466 treatment, WAY-181187 did not alter reactivity score or latency to contact probe (Table 2).

Effects of 5-HT₆ receptor agonists in the NIH test

WAY-208466 produced significant reductions in the latency to begin feeding in the novel cage portion of the NIH test [$F(2, 20)=4.36, p<0.05$]. As shown in Fig. 3a, the compound produced decreases in novel cage latency at the 15-mg/kg doses ($p<0.05$). As seen in the DB test, the high dose of WAY-208466 did not significantly alter behavior in the NIH test. There were no differences in novel cage food consumption, home cage latency, or home cage consumption (Table 3).

WAY-181187 did not produce significant reductions in approach latency at either dose tested in the NIH test (Fig. 3b). WAY-181187 treatment had a significant effect on food consumption as the compound decreased home cage consumption [$F(2, 26)=3.87, p<0.05$] (Table 3). The difference in consumption was significant at the 17-mg/kg dose ($p<0.05$ compared to saline-treated control group).

Discussion

The selective 5-HT₆ receptor agonists WAY-208466 and WAY-181187 were tested for potential antidepressant activity in the modified FST because this version of the test has been widely demonstrated to measure the antidepressant-like effects of SSRIs and selective 5-HT receptor agonists (Lucki 1997; Cryan et al. 2005). Both 5-HT₆ receptor agonists produced antidepressant-like effects in the modified rat FST. The pattern of response in the FST, increased swimming, was also similar to the effects of other serotonergic compounds (Detke et al. 1995). This response pattern suggests that 5-HT₆ receptor agonists may have potential activity as antidepressants in agreement with previous research in mice (Svenningsson et al. 2007).

Paradoxically, 5-HT₆ receptor agonists and antagonists have been reported to produce similar effects in animal models of depression and anxiety (Svenningsson et al. 2007; Wesolowska 2007, 2008; Wesolowska and Nikiforuk 2007; Wesolowska et al. 2007). 5-HT₆ receptor agonists and antagonists also appear to produce convergent behavioral effects in tests of cognitive function as both classes of compounds improve performance in attentional set-shifting tasks in rats (Burnham et al. 2010; Hatcher et al. 2005). It is possible that 5-HT₆ receptor agonists and antagonist happen to produce similar behavioral effects but through different neurochemical mechanisms, although actions mediated in different brain regions can provide another reason. Supporting the first explanation, antidepressant-like effects of 5-HT₆ receptor antagonists could be produced through non-serotonergic mechanisms as they have been demonstrated using versions of the FST that would ordinarily not be sensitive to SSRIs (Borsini 1995; Wesolowska 2007; Wesolowska and Nikiforuk 2008). Indeed, the antidepressant-like and anxiolytic-like effects of the 5-HT₆ antagonist SB-399885 were shown to persist after 5-HT depletion suggesting that the effects were not dependent on serotonergic neurotransmission but could involve another neurotransmitter (Wesolowska 2007, 2008).

SSRIs are also administered for the treatment of anxiety disorders (Nutt 2005). The 5-HT₆ receptor agonists used in these studies have been shown to increase extracellular concentrations of GABA in multiple brain regions (Schechter et al. 2008) and activation of GABA receptors is associated with anti-anxiety effects (Shiah and Yatham 1998). The reduced adjunctive drinking maintained by schedule-induced polydipsia, a heuristic model of compulsive behavior, by WAY-181187 could be indicative of antianxiety effects (Schechter et al. 2008). Accordingly, the effects of 5-HT₆ receptor agonists were examined on two anxiety-related behavior tests, defensive burying and novelty-induced hypophagia.

The two 5-HT₆ receptor agonists reduced burying behavior in the DB test and WAY-208466 decreased approach latency in the NIH test, effects that are similar to those of established anti-anxiety drugs (Treit et al. 1981; Bodnoff et al. 1989) and chronic treatment with antidepressants in these tests (Bechtholt et al. 2008; Bodnoff et al. 1988; Bondi et al. 2007; Dulawa et al. 2004). In the DB test, there were slight differences in the behavioral responses produced by the 5-HT₆ receptor agonists. The most effective dose of WAY-208466 in our study was the low dose (15 mg/kg) tested which produced a roughly 50% decrease in burying behavior. The anxiolytic-like effect produced by WAY-208466 was similar in magnitude to the effect produced by the benzodiazepine chlordiazepoxide. The high dose (30 mg/kg) did not significantly reduce burying compared to saline treatment. On the other hand, WAY-181187 produced a stepwise dose-response and the high dose tested virtually eliminated burying behavior. The reduction of burying behavior appeared to be an anxiolytic-like effect since this dose of WAY-181187 did not produce any significant alterations in general locomotor activity, reactivity to shock, or latency to contact probe.

There were also differences between the two 5-HT₆ receptor agonists in their behavioral effects in the NIH test. Again, the 15 mg/kg dose of WAY-208466 tested produced greater effects than the high dose on approach latency in the novel cage. WAY-208466 treatment did not increase food consumption in the novel cage, an effect found in rats after chronic fluoxetine treatment (Bechtholt et al. 2008). This may represent a partial anxiolytic phenotype that could be enhanced with repeated treatment. In contrast, WAY-181187 did not decrease approach latency in the novel environment, an effect that could be related to a decrease in appetitive behaviors as drug treatment also reduced food consumption in the home cage. Interestingly, a reduction in food consumption has been shown after treatment with the 5-HT₆ receptor agonist E-6837 (Fisas et al. 2006). Another possible explanation for the decrease in food consumption could be secondary activation of the 5-HT_{2c} receptor. WAY-181187 exhibits roughly three-fold greater affinity for the 5-HT_{2c} receptor than WAY-208466 (Cole et al. 2007; Schechter et al. 2008), and activation of the 5-HT_{2c} receptor has been shown to decrease the motivation to consume palatable foods (Ward et al. 2008).

A major drawback of clinical treatment with many SSRIs is a side-effect profile that includes increased anxiety, nausea, and inhibition of sexual motivation due to the generalized effects of globally increasing 5-HT transmission (Frazer 1997). The development of selective 5-HT₆ receptor agonists as antidepressants could substantially improve the treatment of affective disorders if similar clinical efficacy could be achieved without these common side effects. Additionally, 5-HT₆ receptors are almost exclusively expressed in the CNS (Ruat et al. 1993), thereby reducing the potential for peripheral side effects.

In conclusion, the acute activation of the 5-HT₆ receptors, through the administration of the agonists WAY-208466 and WAY-181187, produces antidepressant-like and anxiolyticlike effects in rats. These behavioral effects, combined with neurochemical data that show a convergence of effects between 5-HT₆ receptor agonist administration and chronic SSRI treatment (Schechter et al. 2008), support further study of 5-HT₆ receptor agonists as potential treatments for depression and anxiety. Elucidation of the full behavioral and neurochemical profile of 5-HT₆ receptor agonists, especially following chronic treatment, is necessary in order to determine a suitable recommendation for their potential use in clinical settings.

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References

- Bechtholt AJ, Hill TE, Lucki I. Anxiolytic effect of serotonin depletion in the novelty-induced hypophagia test. *Psychopharmacology (Berl)* 2007;190:531–540. [PubMed: 17165096]
- Bechtholt AJ, Valentino RJ, Lucki I. Overlapping and distinct brain regions associated with the anxiolytic effects of chlordiazepoxide and chronic fluoxetine. *Neuropsychopharmacology* 2008;33:2117–2130. [PubMed: 17987061]
- Blier P, Ward NM. Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biol Psychiatry* 2003;53:193–203. [PubMed: 12559651]
- Bodnoff SR, Suranyl-Cadotte B, Aitken DH, Quirion R, Meaney MJ. The effects of chronic antidepressant treatment in an animal model of anxiety. *Psychopharmacology* 1988;95:298–302. [PubMed: 3137614]
- Bodnoff SR, Suranyl-Cadotte B, Quirion R, Meaney MJ. A comparison of the effects of diazepam versus several typical and atypical antidepressant drugs in an animal model of anxiety. *Psychopharmacology* 1989;97:277–279. [PubMed: 2567028]
- Bondi CO, Barrera G, Lapid MD, Bedard T, Mahan A, Morilak DA. Noradrenergic facilitation of shock-probe defensive burying in lateral septum of rats, and modulation by chronic treatment with desipramine. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:482–495. [PubMed: 17188790]
- Borsini F. Role of the serotonergic system in the forced swimming test. *Neurosci Biobehav Rev* 1995;19:377–395. [PubMed: 7566740]
- Burnham KE, Baxter MG, Bainton JR, Southam E, Dawson LA, Bannerman DM, Sharp T. Activation of 5-HT₆ receptors facilitates attentional set shifting. *Psychopharmacology (Berl)* 2010;208:13–21.
- Carr, GV.; Lucki, I. Role for serotonin in depression. In: Muller, C.; Jacobs, B., editors. *Handbook of the behavioral neurobiology of serotonin*. Academic; Amsterdam: 2010. p. 493-505.
- Cole DC, Stock JR, Lennox WJ, Bernotas RC, Ellingboe JW, Boikess S, Coupet J, Smith DL, Leung L, Zhang GM, Feng X, Kelly MF, Galante R, Huang P, Dawson LA, Marquis K, Rosenzweig-Lipson S, Beyer CE, Schechter LE. Discovery of N1-(6-chloroimidazo[2, 1-b][1, 3]thiazole-5-sulfonyl)tryptamine as a potent, selective, and orally active 5-HT₆ receptor agonist. *J Med Chem* 2007;50:5535–5538. [PubMed: 17948978]
- Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neurosci Biobehav Rev* 2005;29:547–569. [PubMed: 15893822]
- Dawson LA, Nguyen HQ, Li P. In vivo effects of the 5-HT₆ antagonist SB-271046 on striatal and frontal cortex extracellular concentrations of noradrenaline, dopamine, 5-HT, glutamate and aspartate. *Br J Pharmacol* 2000;130:23–26. [PubMed: 10780993]
- Dawson LA, Nguyen HQ, Li P. The 5-HT₆ receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology* 2001;25:662–668. [PubMed: 11682249]
- De Boer SF, Koolhaas JM. Defensive burying in rodents: ethology, neurobiology and psychopharmacology. *Eur J Pharmacol* 2003;463:145–161. [PubMed: 12600707]
- Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. *Psychopharmacology (Berl)* 1995;121:66–72. [PubMed: 8539342]
- De Vry J. 5-HT_{1A} receptor agonists: recent developments and controversial issues. *Psychopharmacology (Berl)* 1995;121:1–26. [PubMed: 8539333]
- Dulawa SC, Hen R. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. *Neurosci Biobehav Rev* 2005;29:771–783. [PubMed: 15890403]

- Dulawa SC, Holick KA, Gundersen B, Hen R. Effects of chronic fluoxetine in animal models of anxiety and depression. *Neuropsychopharmacology* 2004;29:1321–1330. [PubMed: 15085085]
- Fisas A, Codony X, Romero G, Dordal A, Giraldo J, Merce R, Holenz J, Vrang N, Sorensen RV, Heal D, Buschmann H, Pauwels PJ. Chronic 5-HT₆ receptor modulation by E-6837 induces hypophagia and sustained weight loss in diet-induced obese rats. *Br J Pharmacol* 2006;148:973–983. [PubMed: 16783408]
- Fone KC. An update on the role of the 5-hydroxytryptamine₆ receptor in cognitive function. *Neuropharmacology* 2008;55:1015–1022. [PubMed: 18655798]
- Frazer A. Pharmacology of antidepressants. *J Clin Psychopharmacol* 1997;17(Suppl 1):2S–18S. [PubMed: 9090573]
- Gerard C, el Mestikawy S, Lebrand C, Adrien J, Ruat M, Traiffort E, Hamon M, Martres MP. Quantitative RT-PCR distribution of serotonin 5-HT₆ receptor mRNA in the central nervous system of control or 5,7-dihydroxytryptamine-treated rats. *Synapse* 1996;23:164–173. [PubMed: 8807744]
- Gerard C, Martres MP, Lefevre K, Miquel MC, Verge D, Lanfumey L, Doucet E, Hamon M, el Mestikawy S. Immunolocalization of serotonin 5-HT₆ receptor-like material in the rat central nervous system. *Brain Res* 1997;746:207–219. [PubMed: 9037500]
- Hamon M, Doucet E, Lefevre K, Miquel MC, Lanfumey L, Insausti R, Frechilla D, Del Rio J, Verge D. Antibodies and antisense oligonucleotide for probing the distribution and putative functions of central 5-HT₆ receptors. *Neuropsychopharmacology* 1999;21(Suppl):68S–76S. [PubMed: 10432491]
- Hatcher PD, Brown VJ, Tait DS, Bate S, Overend P, Hagan JJ, Jones DN. 5-HT₆ receptor antagonists improve performance in an attentional set shifting task in rats. *Psychopharmacology (Berl)* 2005;181:253–259. [PubMed: 15846482]
- Hirano K, Piers TM, Searle KL, Miller ND, Rutter AR, Chapman PF. Procognitive 5-HT₆ antagonists in the rat forced swimming test: potential therapeutic utility in mood disorders associated with Alzheimer's disease. *Life Sci* 2009;84:558–562. [PubMed: 19302808]
- Hirst WD, Stean TO, Rogers DC, Sunter D, Pugh P, Moss SF, Bromidge SM, Riley G, Smith DR, Bartlett S, Heidbreder CA, Atkins AR, Lacroix LP, Dawson LA, Foley AG, Regan CM, Upton N. SB-399885 is a potent, selective 5-HT₆ receptor antagonist with cognitive enhancing properties in aged rat water maze and novel object recognition models. *Eur J Pharmacol* 2006;553:109–119. [PubMed: 17069795]
- Loiseau F, Dekeyne A, Millan MJ. Pro-cognitive effects of 5-HT₆ receptor antagonists in the social recognition procedure in rats: implication of the frontal cortex. *Psychopharmacology (Berl)* 2008;196:93–104. [PubMed: 17922111]
- Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behav Pharmacol* 1997;8:523–532. [PubMed: 9832966]
- Lucki I, Singh A, Kreiss DS. Antidepressant-like behavioral effects of serotonin receptor agonists. *Neurosci Biobehav Rev* 1994;18:85–95. [PubMed: 8170624]
- Mayorga AJ, Dalvi A, Page ME, Zimov-Levinson S, Hen R, Lucki I. Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine (1B) receptor mutant mice. *J Pharmacol Exp Ther* 2001;298:1101–1107. [PubMed: 11504807]
- Mitchell ES, Neumaier JF. 5-HT₆ receptors: a novel target for cognitive enhancement. *Pharmacol Ther* 2005;108:320–333. [PubMed: 16005519]
- Monsma FJ Jr, Shen Y, Ward RP, Hamblin MW, Sibley DR. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol Pharmacol* 1993;43:320–327. [PubMed: 7680751]
- Montgomery SA, Baldwin DS, Blier P, Fineberg NA, Kasper S, Lader M, Lam RW, Lepine JP, Moller HJ, Nutt DJ, Rouillon F, Schatzberg AF, Thase ME. Which antidepressants have demonstrated superior efficacy? A review of the evidence. *Int Clin Psychopharmacol* 2007;22:323–329. [PubMed: 17917550]
- Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectr* 2005;10:49–56. [PubMed: 15618947]

- Riemer C, Borroni E, Levet-Trafit B, Martin JR, Poli S, Porter RH, Bos M. Influence of the 5-HT₆ 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-HT₆ receptor antagonist. *J Med Chem* 2003;46:1273–1276. [PubMed: 12646038]
- Roberts JC, Reavill C, East SZ, Harrison PJ, Patel S, Routledge C, Leslie RA. The distribution of 5-HT(6) receptors in the rat brain: an autoradiographic binding study using the radiolabelled 5-HT(6) receptor antagonist [(125)I]SB-258585. *Brain Res* 2002;934:49–57. [PubMed: 11937069]
- Rogers DC, Hagan JJ. 5-HT₆ receptor antagonists enhance retention of a water maze task in the rat. *Psychopharmacology (Berl)* 2001;158:114–119. [PubMed: 11702084]
- Ruat M, Traiffort E, Arrang JM, Tardivel-Lacombe J, Diaz J, Leurs R, Schwartz JC. A novel rat serotonin (5-HT₆) receptor: molecular cloning, localization and stimulation of cAMP accumulation. *Biochem Biophys Res Commun* 1993;193:268–276. [PubMed: 8389146]
- Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003;301:805–809. [PubMed: 12907793]
- Schechter LE, Lin Q, Smith DL, Zhang G, Shan Q, Platt B, Brandt MR, Dawson LA, Cole D, Bernotas R, Robichaud A, Rosenzweig-Lipson S, Beyer CE. Neuropharmacological profile of novel and selective 5-HT₆ receptor agonists: WAY-181187 and WAY-208466. *Neuropsychopharmacology* 2008;33:1323–1335. [PubMed: 17625499]
- Shiah IS, Yatham LN. GABA function in mood disorders: an update and critical review. *Life Sci* 1998;63:1289–1303. [PubMed: 9768867]
- Svenningsson P, Tzavara ET, Qi H, Carruthers R, Witkin JM, Nomikos GG, Greengard P. Biochemical and behavioral evidence for antidepressant-like effects of 5-HT₆ receptor stimulation. *J Neurosci* 2007;27:4201–4209. [PubMed: 17428998]
- Treit D, Pesold C. Septal lesions inhibit fear reactions in two animal models of anxiolytic drug action. *Physiol Behav* 1990;47:365–371. [PubMed: 1970655]
- Treit D, Pinel JP, Fibiger HC. Conditioned defensive burying: a new paradigm for the study of anxiolytic agents. *Pharmacol Biochem Behav* 1981;15:619–626. [PubMed: 6117086]
- Ward RP, Hamblin MW, Lachowicz JE, Hoffman BJ, Sibley DR, Dorsa DM. Localization of serotonin subtype 6 receptor messenger RNA in the rat brain by in situ hybridization histochemistry. *Neuroscience* 1995;64:1105–1111. [PubMed: 7753378]
- Ward SJ, Lefever TW, Jackson C, Tallarida RJ, Walker EA. Effects of a Cannabinoid1 receptor antagonist and Serotonin2C receptor agonist alone and in combination on motivation for palatable food: a dose-addition analysis study in mice. *J Pharmacol Exp Ther* 2008;325:567–576. [PubMed: 18256173]
- Wesolowska A. Study into a possible mechanism responsible for the antidepressant-like activity of the selective 5-HT₆ receptor antagonist SB-399885 in rats. *Pharmacol Rep* 2007;59:664–671. [PubMed: 18195455]
- Wesolowska A. The anxiolytic-like effect of the selective 5-HT₆ receptor antagonist SB-399885: the impact of benzodiazepine receptors. *Eur J Pharmacol* 2008;580:355–360. [PubMed: 18096153]
- Wesolowska A, Nikiforuk A. Effects of the brain-penetrant and selective 5-HT₆ receptor antagonist SB-399885 in animal models of anxiety and depression. *Neuropharmacology* 2007;52:1274–1283. [PubMed: 17320917]
- Wesolowska A, Nikiforuk A. The selective 5-HT₆ receptor antagonist SB-399885 enhances anti-immobility action of anti-depressant in rats. *Eur J Pharmacol* 2008;582:88–93. [PubMed: 18234190]
- Wesolowska A, Nikiforuk A, Stachowicz K. Anxiolytic-like and antidepressant-like effects produced by the selective 5-HT₆ receptor antagonist SB-258585 after intrahippocampal administration to rats. *Behav Pharmacol* 2007;18:439–446. [PubMed: 17762512]
- Woods A, Smith C, Szewczak M, Dunn RW, Cornfeldt M, Corbett R. Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. *Psychopharmacology (Berl)* 1993;112:195–198. [PubMed: 7871019]

Woolley ML, Marsden CA, Sleight AJ, Fone KC. Reversal of a cholinergic-induced deficit in a rodent model of recognition memory by the selective 5-HT₆ receptor antagonist, Ro 04-6790. *Psychopharmacology (Berl)* 2003;170:358–367. [PubMed: 13680084]

Fig. 1.

Effects of serotonergic compounds in the FST: **a** Effects of the 5-HT₆ agonist WAY-208466 in the FST; $n=9-12$ /group. **b** Effects of the 5-HT₆ agonist WAY-181187 in the FST; $n=7-8$ /group. **c** Effects of the SSRI fluoxetine on behaviors measured in the modified rat FST. $n=10$ /group. Values indicate mean $\pm$ 1 SEM. * $p<0.05$ compared to saline group. ** $p<0.01$ compared to saline group. # $p=0.05$ compared to saline group

Fig. 2.

Effects of 5-HT₆ receptor agonists on the time spent burying in the DB test. **a** Effects of the 5-HT₆ receptor agonist WAY-208466 and the benzodiazepine chlordiazepoxide (*CDP*) on burying time in the DB test; $n=10-13/\text{group}$. **b** Effects of the 5-HT₆ receptor agonist WAY-181187 on burying time in the DB test. $n=8-12/\text{group}$. Values indicate mean+1 SEM. * $p<.05$, ** $p<.01$, and *** $p<.001$ compared to saline groups

Fig. 3. Effects of 5-HT₆ receptor agonists on approach latency in the novel cage in the NIH test. **a** Effects of the 5-HT₆ receptor agonist WAY-208466 on burying time in the DB test; $n=8$ /group. **b** Effects of the 5-HT₆ receptor agonist WAY-181187 on burying time in the DB test; $n=9-10$ /group. * $p<.05$ compared to saline group

Table 1Effects of 5-HT₆ receptor agonists on locomotor activity

Treatment	Distance traveled (cm)
Saline	5150±270
WAY-208466 (30 mg/kg)	5340±281
WAY-181187 (17 mg/kg)	5220±264

Values represent mean±1 SEM. *n*=7–8/group

Table 2

Effects of pharmacological treatment on shock reactivity and latency to contact the probe in the DB test

Treatment	Reactivity score	Latency to contact probe (s)
Saline	1.46±0.12	11.20±4.27
Chlordiazepoxide (5 mg/kg)	1.27±0.10	9.73±2.62
WAY-208466 (15 mg/kg)	1.32±0.09	5.89±1.79
WAY-208466 (30 mg/kg)	1.34±0.08	4.07±1.03
Saline	1.75±0.15	20.17±7.42
WAY-181187 (10 mg/kg)	1.40±0.14	13.75±4.87
WAY-181187 (17 mg/kg)	1.38±0.12	26.89±12.84

Values represent mean±1 SEM. *n*=8–13/group

Table 3

Effects of 5-HT₆ receptor agonists on food consumption and home cage latency in the NIH test

Treatment	Home cage latency (s)	Home cage consumption (g)	Novel cage consumption (g)
Saline	11.43±5.20	4.06±0.76	1.24±0.17
WAY-208466 (15 mg/kg)	8.00±1.49	4.80±0.53	1.19±0.36
WAY-208466 (30 mg/kg)	12.38±2.77	3.66±0.48	1.34±0.25
Saline	12.60±3.32	4.20±0.60	1.19±0.22
WAY-181187 (10 mg/kg)	15.30±3.79	2.76±0.47	1.33±0.32
WAY-181187 (17 mg/kg)	20.22±4.44	1.83±0.73*	0.41±0.19

Values represent mean±1 SEM. *n*=7–10/group

* *p*<.05 compared to saline-treated group