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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 312–317
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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The stimulus effects of 8-OH-DPAT: Evidence for a 5-HT_{2A} receptor-mediated component

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Received 12 June 2007; received in revised form 29 August 2007; accepted 6 September 2007
Available online 19 September 2007

Abstract

A previous investigation in our laboratory found that the stimulus effects of the 5-HT_{2A} agonist, LSD, are potentiated by 5-HT_{1A} receptor agonists including the prototypic agonist, 8-OH-DPAT. Also suggestive of behaviorally relevant interactions between 5-HT_{1A} and 5-HT_{2A} receptors are behavioral analyses of locomotor activity, head-twitch response, forepaw treading and production of the serotonin syndrome; in some instances effects are augmented, in other, diminished. These observations led us in the present investigation to test the hypothesis that stimulus control by 8-OH-DPAT [0.2 mg/kg; 15 min pretreatment time] is modulated by 5-HT_{2A} ligands. Stimulus control was established with 8-OH-DPAT in a group of 10 rats. A two-lever, fixed ratio 10, positively reinforced task with saline controls was employed. As shown previously, stimulus control by 8-OH-DPAT and the generalization of 8-OH-DPAT to the 5-HT_{1A} partial agonist, buspirone, was completely blocked by the selective 5-HT_{1A} antagonist, WAY-100635. In contrast, antagonism by the selective 5-HT_{2A} antagonist, M100907 [0.1 mg/kg; 30 min pretreatment time], of 8-OH-DPAT and of the generalization of 8-OH-DPAT to buspirone was statistically significant but less than complete. In light of our previous conclusions regarding the interactions of 5-HT_{1A} agonists with LSD-induced stimulus control, the present data suggest that the interaction between 5-HT_{1A} and 5-HT_{2A} receptors is bidirectional in drug discrimination studies.

Keywords: 8-OH-DPAT; 5-HT_{2A} receptor; Stimulus control; M100907; 5-HT_{1A}

1. Introduction

The 5-HT_{1A} receptor may be the best characterized of the fourteen serotonergic receptor subtypes (Pucadyil et al., 2005). 5-HT_{1A} receptors have been implicated in psychiatric disorders such as depression (Celada et al., 2004) and schizophrenia (Millan, 2000; Yasuno et al., 2004) as well as the formation of memory (Winter and Petti, 1987) and neural development (del Olmo et al., 1998; Pazos et al., 1998). The 5-HT_{1A} receptor has been proposed as the pharmacological target of the azapirone anxiolytics (Cunningham et al., 1987) and may contribute to the therapeutic effects of the novel antipsychotic aripiprazole (Marona-Lewicka and Nichols, 2004). Thus, insight concerning 5-HT_{1A} function will offer knowledge applicable across a wide spectrum of research interests.

Dysfunction of a second serotonergic receptor subtype, 5-HT_{2A}, may also underlie a variety of central nervous system disorders including impulsive behavior (Nomura et al., 2006), Alzheimer's disease (Lorke et al., 2006), schizophrenia (Dean, 2003), and depression (de Angelis, 2002). Although selective 5-HT_{2A} antagonists have yielded disappointing results in the treatment of schizophrenia (de Paulis, 2001), 5-HT_{2A} antagonism may contribute to the lower side effect profile and increased efficacy of atypical antipsychotic drugs (Meltzer, 1999; Meltzer et al., 2003) and improve the efficacy of selective serotonin reuptake inhibitors (SSRI's) (Boothman et al., 2006). In light of these observations, manipulation of 5-HT_{2A} receptor function and the resultant behavioral effects have considerable therapeutic potential.

There is ample evidence supporting functional interactions between 5-HT_{1A} and 5-HT_{2A} receptors. *In vivo* analyses have examined these interactions using a variety of behavioral paradigms including the head-twitch response (Arnt and Hyttel, 1989; Yocca

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doi:10.1016/j.pbb.2007.09.011

et al., 1990), forepaw treading (Arnt and Hyttel, 1989; Backus et al., 1990), production of the serotonin syndrome (Backus et al., 1990), and locomotor activity (Krebs-Thomson and Geyer, 1998). However, conflicting results have emerged as some of these studies have shown additive or potentiating interactions between 5-HT_{1A} and 5-HT_{2A} receptors (Arnt and Hyttel, 1989; Backus et al., 1990), while others have shown functional opposition or antagonistic interactions (Krebs-Thomson and Geyer, 1998; Yocca et al., 1990).

As many of the aforementioned psychiatric disorders manifest themselves as alterations of cognitive function, similarly complex behavioral measures must be employed toward their investigation. To this end, drug discrimination has proven useful in determining the neuropharmacological mechanism underlying a diverse array of psychoactive substances (Koek et al., 1992; Winter, 1974, 1994). Of particular interest are drug discrimination studies showing that hallucinogens whose stimulus effects are mediated primarily by 5-HT_{2A} receptors (Fiorella et al., 1995a; Fiorella et al., 1995b; Winter et al., 2004) are potentiated by 5-HT_{1A} agonists (Reissig et al., 2005). This finding suggests that 5-HT_{1A} receptor stimulation enhances 5-HT_{2A} receptor function in the drug discrimination paradigm.

Because drug discrimination studies have found that 5-HT_{1A} receptor agonists potentiate the stimulus effects of hallucinogens whose effects are mediated by actions at 5-HT_{2A} receptors (Reissig et al., 2005), we hypothesized that 5-HT_{2A} receptors may have a modulatory effect on the stimulus effects of 8-OH-DPAT. Thus, in the present study, the 5-HT_{2A} antagonist M100907 was evaluated for its ability to modulate the stimulus effects of 8-OH-DPAT. This will further characterize functional interactions between 5-HT_{1A} and 5-HT_{2A} receptors using drug discrimination, a technique able to model the subjective effects of drug-receptor interactions.

2. Materials and methods

2.1. Subjects

Ten male Fischer 344 rats were obtained at an age of approximately 6 weeks from Harlan Sprague-Dawley Inc. [Indianapolis, IN, USA], housed in pairs under a 12-h light–dark cycle beginning at 6:00 a.m., and allowed free access to water in their home cages. All training and testing took place during the light cycle. Subjects were fed standard rat chow. Caloric restriction was used to maintain a body weight of approximately 275 g. Caloric restriction has been shown to lengthen the life span and decrease the incidence of pathologies in Fischer 344 rats (Keenan et al., 1994). Based on a recent sample of 25 rats, the average life span under these conditions is 34.3 months [S.E.M. = 1.1]. Animals used in these studies were maintained in accordance with U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals as amended August 2002. All experimental protocols were approved by the Institutional Animal Care Unit.

2.2. Drug discrimination training

Six small animal test chambers (MED Associates ENV-008) were used for experiments. These were housed in larger light-proof, sound-insulated boxes, which contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a microcomputer using operant control software (MED-PC State Notation, Version IV). Subjects were trained to discriminate 8-OH-DPAT from saline (0.2 mg/kg, 15-min pretreatment time, intraperitoneal injection). A fixed ratio 10 (FR10) schedule of reinforcement was employed. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever. After stimulus control was established, tests were conducted once per week in each animal so long as performance did not fall below the criterion level of 83% correct responding in any of the three previous training sessions. The 8-OH-DPAT training dose produced 99.3% drug-appropriate responding during training sessions conducted throughout the course of this study. In contrast, less than 3% drug-appropriate responding was observed in training sessions that were preceded by the injection of saline.

2.3. Test procedures

After stimulus control with 8-OH-DPAT was established, combination and substitution tests were conducted once per week in each animal if the criterion for drug-induced stimulus control were met. Tests were balanced between subjects trained on the previous day with saline and 8-OH-DPAT, respectively. During test sessions, no responses were reinforced and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time. Data for any subjects failing to emit 10 responses within the constraints of the 10-min test session were not considered in the calculation of the percent drug-appropriate responding but were included in analysis of response rates.

For purposes of discussion of these data, definitions were according to Winter et al. (2000). Complete generalization of the training drug to a test drug is said to be present when (a) a mean of 80% or more of all test responses occurs on the drug-appropriate lever; (b) there is no significant difference between the response distributions of the training drug and the test drug; and (c) there is a statistically difference between the response distributions of the test drug and saline control sessions. Partial generalization or antagonism is defined as being present when the mean response distribution after a test drug or combination of drugs is less than 80% drug-appropriate responding and is statistically significantly different from both training conditions Finally, when the response distribution after a test drug is not different from that in saline control sessions, an absence of generalization of the training drug to the test drug is assumed Similar criteria are applied to the definitions of full, partial and no antagonism. Thus, full antagonism is assumed to be present when (a) less than 20% of

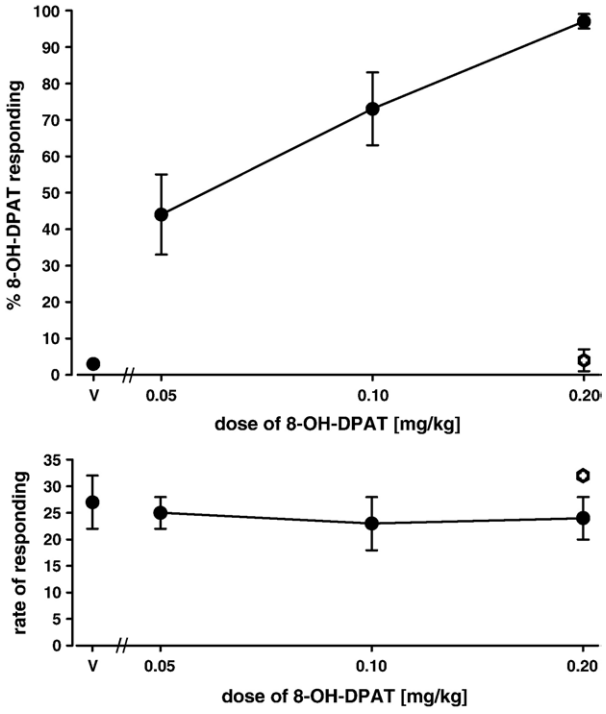

Fig. 1. Dose-response relationship for 8-OH-DPAT alone and in combination with WAY-100,635. Circles represent the effects of 8-OH-DPAT alone in rats trained with 8-OH-DPAT as a discriminative stimulus (0.2 mg/kg; 15 min pretreatment time). Each point represents the mean of two determinations in each of 10 rats, with the exception of WAY-100,635 where a single determination is shown. The *open hexagon* represents the effects of WAY-100 635 (0.3 mg/kg 30 min pretreatment) in combination with the training dose 8-OH-DPAT. The point at V is for vehicle controls.

all test responses are on the training drug-appropriate lever; (b) there is no significant difference between the response distributions in the test of antagonism and the saline control, and (c) there is a statistically significant difference between the response distributions of the test drug alone and in combination with an antagonist.

Substitution tests were performed with buspirone [1.0 mg/kg] given 15 min before testing. The effects of antagonists on 8-OH-DPAT-induced stimulus control were assessed by co-administration of either M100907 [0.1 mg/kg] or WAY-100,635 [0.3 mg/kg] 30 min before testing and an agonist (buspirone) 15 min before testing.

2.4. Drugs

8-hydroxy-2-(di-*N*-propylamino)tetralin, WAY-100,635, and buspirone were purchased from Tocris [Ellisville, MO, USA]. M100907 was synthesized at the Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Disorders at the National Institutes of Health [Bethesda, MD, USA]. A stock solution of M100907 [0.5 mg/ml] was made by dissolving M100907 in a minimal volume of 0.2% w/v tartaric acid and diluting with water. All other drugs were dissolved in 0.9% saline. Doses are expressed as mg/kg of the salts. The IP route was employed for all drugs with the exception of WAY-100,635 which was administered SC. An injection volume of 0.25 ml was employed for all drugs.

2.5. Statistical analysis

The statistical significance of tests of antagonism with M100907 and 8-OH-DPAT were determined using two-way ANOVA with dose of 8-OH-DPAT and pretreatment with M100907 as factors. Other behavioral data were assessed for statistical significance using one-way analysis of variance [ANOVA] followed by pair-wise comparisons using the Student–Newman–Keuls method. Differences were considered statistically significant if the probability of their having arisen by chance was ≤ 0.05. All analyses were conducted using SigmaStat for Windows™ (Jandel Scientific Software, San Rafeal, CA).

3. Results

3.1. 8-OH-DPAT dose effect relationship

Fig. 1 shows an orderly, dose-related increase in 8-OH-DPAT-appropriate responding in rats trained and tested with 8-OH-DPAT. When the training dose of 8-OH-DPAT (0.2 mg/kg) was tested in rats pretreated with WAY-100,635 (0.3 mg/kg), 8-OH-DPAT appropriate responding was completely blocked. Pretreatment with WAY-100,635 caused a significant decrease in drug-appropriate responding ($p<0.001$), although response rate was not altered.

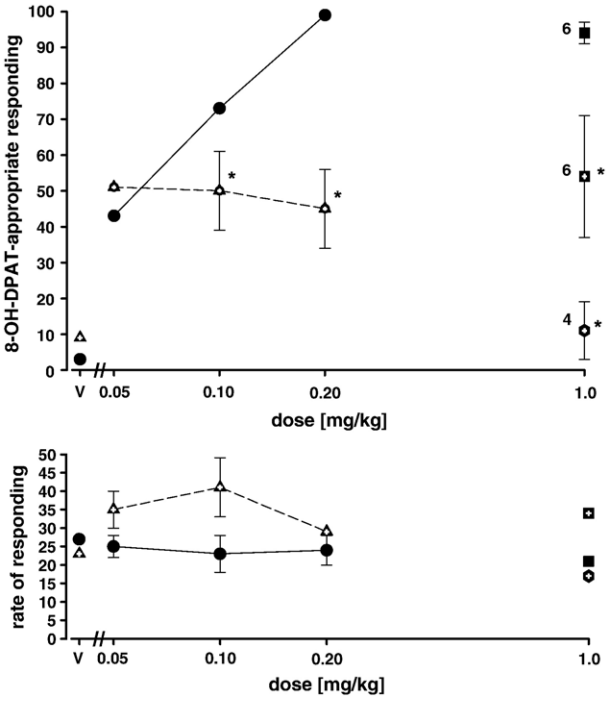

Fig. 2. Dose-response relationship for 8-OH-DPAT alone and in combination with M100907. *Circles* represent the effects of 8-OH-DPAT alone in rats trained with 8-OH-DPAT as a discriminative stimulus (0.2 mg/kg; 15 min pretreatment time). Each point represents the mean of two determinations in each of 10 rats, unless otherwise noted. *Triangles* represent the effects of M100907 (0.1 mg/kg 30 min. pretreatment) in combination with 8-OH-DPAT. The points at V are for either vehicle controls [*circle*] or M100907 alone [*triangle*]. The *closed square* represents the effects of buspirone (1.0 mg/kg 15 min pretreatment). The *open square* represents the effects of buspirone given in combination with M100907. The *hexagon* represents the effects of buspirone in combination with WAY-100,635. An asterisk indicates a statistically significant difference from 8-OH-DPAT given alone.

3.2. Substitution and combination tests with buspirone, M100907 and WAY-100,635

Fig. 2 shows the results of substitution tests with buspirone and combination tests using the selective 5-HT_{2A} antagonist M100907 (Marek and Aghajanian, 1994; Sorensen et al., 1993) and the 5-HT_{1A} antagonist WAY-100,635. It is seen that M100907 attenuates the stimulus effects of the training dose (0.2 mg/kg), and an intermediate dose (0.1 mg/kg), but not the lowest dose (0.05 mg/kg) of 8-OH-DPAT tested. Two-way ANOVA revealed that the overall level of 8-OH-DPAT appropriate responding was decreased by pretreatment with M100907 ($F_{2,118}=9.006$; $p=0.003$). Pretreatment with M100907 also produced a significant increase in the subject's rate of responding ($F_{2,118}=5.534$; $p=0.003$).

A 1.0 mg/kg dose of buspirone substituted completely for 8-OH-DPAT. This substitution was significantly decreased by pretreatment with M100907 and WAY-100,635 as revealed by one-way ANOVA ($F_{2,46}=99.743$; $p<0.001$).

4. Discussion

The data in Fig. 1 demonstrate that the stimulus effects of 8-OH-DPAT are completely blocked by the selective 5-HT_{1A} antagonist WAY-100,635 (Fletcher et al., 1993; Fletcher et al., 1996; Forster et al., 1995). These results are in agreement with previous reports suggesting that 5-HT_{1A} stimulation is the primary component of the 8-OH-DPAT stimulus cue (Celada et al., 2004; Cunningham et al., 1987; Sanger and Schoemaker, 1992; Tricklebank et al., 1987).

Fig. 2 shows that antagonism of 5-HT_{2A} receptors attenuates the stimulus effects of the training dose (0.2 mg/kg) and an intermediate dose (0.1 mg/kg), but not the lowest dose (0.05 mg/kg) of 8-OH-DPAT tested. These results are interesting in light of a previous investigation which failed to attenuate the 8-OH-DPAT stimulus cue using the 5-HT_2 antagonist ketanserin (Cunningham et al., 1987). However, the latter study used a higher dose of the training agent (0.4 mg/kg), different strain of rat (Sprague-Dawley), and different FR schedule (FR=20). Additionally, ketanserin may exhibit affinity for other brain receptors including 5-HT_{2C} receptors, α1 receptors, and dopamine receptors (Leysen et al., 1985). The present study employed M100907, a more selective 5-HT_{2A} antagonist which has a >100-fold higher affinity for 5-HT_{2A} versus 5-HT_{2C} receptors (Johnson et al., 1996; Kehne et al., 1996). Our finding that 8-OH-DPAT generalizes completely to the 5-HT_{1A} agonist buspirone (Peroutka, 1985; Riblet et al., 1982) and that this substitution is blocked by WAY-100,635 demonstrates that this is not an idiosyncratic event unique to 8-OH-DPAT.

Previous behavioral studies have yielded inconclusive results regarding the complex interaction between 5-HT_{2A} and 5-HT_{1A} receptor subtypes. For example, the head-twitch response, a behavior typically associated with 5-HT_{2A} receptor stimulation (Green et al., 1983; Schreiber et al., 1995) is variably affected by 5-HT_{1A} agonists. While quipazine-induced head twitches are increased by administration of the 5-HT_{1A} agonist gepirone (Yocca et al., 1991), DOI-mediated head twitches (Darmani et al., 1990) are decreased by 8-OH-DPAT. Further complicating matters is a report demonstrating the ability of 8-OH-DPAT to increase 5-MeO-DMT-induced, but not 5-hydroxytryptophan-induced, head twitches in rats (Goodwin and Green, 1985). Thus, it appears that the interaction between 5-HT_{1A} and 5-HT_{2A} receptors on the head-twitch response is dependent upon the compounds used to investigate this interaction.

In vitro evidence also suggests an interaction between 5-HT_{1A} and 5-HT_{2A} receptors. Electrophysiological studies have shown that 5-HT_{1A} and 5-HT_{2A} receptors mediate opposite responses on pyramidal neuron membrane excitability (Araneda and Andrade, 1991; Ashby et al., 1994). This antagonistic interaction can be extended to include 5-HT release, where stimulation of 5-HT_{2A} receptors causes 5-HT release in mice (Bortolozzi et al., 2003) and rats (Martin-Ruiz et al., 2001), an effect that is reversed by 5-HT_{1A} agonism.

Other behavioral analyses have yielded similar, contradictory results regarding 5-HT_{2A} and 5-HT_{1A} receptor interactions. Isobolographic analysis suggests that 5-HT_{1A} and 5-HT_{2A} receptors act antagonistically with regards to their locomotor suppressing effects (Krebs-Thomson and Geyer, 1998). An antagonistic 5-HT_{1A}/5-HT_{2A} interaction is also seen in the regulation of body temperature in rats (Gudelsky et al., 1986). However, 8-OH-DPAT-induced forepaw treading is increased by the 5-HT_{2A} agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane (DOI) suggesting additive effects between 5-HT_{1A} and 5-HT_{2A} receptors (Arnt and Hyttel 1989). It may be argued however, that all of these behavioral measures are components of the serotonin syndrome, a condition thought to be caused by excessive serotonin at 5-HT_{1A} (Darmani and Ahmad, 1999) and 5-HT_2 receptors (Pranzatelli and Pluchino, 1991).

Considering the above data, our discrimination results do not lend themselves to easy interpretation. Our results showing that M100907 attenuates the stimulus effects of 5-HT_{1A} receptor agonists suggests the engagement of a complex synaptic circuit in the stimulus effects of 5-HT_{1A} agonists. It would appear that 5-HT_{2A} receptors are involved in producing this cue, but their exact role remains to be determined. In light of the previous report demonstrating the potentiating effects of 5-HT_{1A} agonists on LSD-induced stimulus control (Reissig et al., 2005); it appears that 5-HT_{2A} and 5-HT_{1A} agonists have a bidirectional, modulatory influence upon one another in the drug discrimination paradigm. As it has been shown recently that M100907 can function as a discriminative stimulus (Dekeyne et al., 2002) it would be interesting to determine the effects of 8-OH-DPAT and WAY-100,635 on this stimulus cue.

References

Araneda R, Andrade R. 5-Hydroxytryptamine2 and 5-hydroxytryptamine 1A receptors mediate opposing responses on membrane excitability in rat association cortex. Neuroscience 1991;40:399–412.

Arnt J, Hyttel J. Facilitation of 8-OHDPAT-induced forepaw treading of rats by the 5-HT2 agonist DOI. Eur J Pharmacol 1989;161:45–51.

Ashby Jr CR, Edwards E, Wang RY. Electrophysiological evidence for a functional interaction between 5-HT_{1A} and 5-HT_{2A} receptors in the rat medial prefrontal cortex: an iontophoretic study. Synapse 1994;17:173–81.

Backus LI, Sharp T, Grahame-Smith DG. Behavioral evidence for a functional interaction between central 5-HT2 and 5-HT_{1A} receptors. Br J Pharmacol 1990;100:793–9.

Boothman LJ, Mitchell SN, Sharp T. Investigation of the SSRI augmentation properties of 5-HT(2) receptor antagonists using in vivo microdialysis. Neuropharmacology 2006;50:726–32.

Bortolozzi A, Amargos-Bosch M, Adell A, Diaz-Mataix L, Serrats J, Pons S, et al. In vivo modulation of 5-hydroxytryptamine release in mouse prefrontal cortex by local 5-HT(2A) receptors: effect of antipsychotic drugs. Eur J Neurosci 2003;18:1235–46.

Celada P, Puig M, Amargos-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT_{1A} and 5-HT_{2A} receptors in depression. J Psychiatry Neurosci 2004;29:252–65.

Cunningham KA, Callahan PM, Appel JB. Discriminative stimulus properties of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OHDPAT): implications for understanding the actions of novel anxiolytics. Eur J Pharmacol 1987;138:29–36.

Darmani NA, Ahmad B. Long-term sequential determination of behavioral ontogeny of 5-HT_{1A} and 5-HT2 receptor functions in the rat. J Pharmacol Exp Ther 1999;288:247–53.

Darmani NA, Martin BR, Pandey U, Glennon RA. Do functional relationships exist between 5-HT_{1A} and 5-HT2 receptors? Pharmacol Biochem Behav 1990;36:901–6.

de Angelis L. 5-HT_{2A} antagonists in psychiatric disorders. Curr Opin Investig Drugs 2002;3:106–12.

de Paulis T. M-100907 (Aventis). Curr Opin Investig Drugs 2001;2:123–32.

Dean B. The cortical serotonin2A receptor and the pathology of schizophrenia: a likely accomplice. J Neurochem 2003;85:1–13.

Dekeyne A, Iob L, Hautefaye P, Millan MJ. The selective serotonin(2A) receptor antagonist, MDL100,907, elicits a specific interoceptive cue in rats. Neuropsychopharmacology 2002;26:552–6.

del Olmo E, Lopez-Gimenez JF, Vilaro MT, Mengod G, Palacios JM, Pazos A. Early localization of mRNA coding for 5-HT_{1A} receptors in human brain during development. Brain Res Mol Brain Res 1998;60:123–6.

Fiorella D, Helsley S, Lorrain DS, Rabin RA, Winter JC. The role of the 5-HT_{2A} and 5-HT_{2C} receptors in the stimulus effects of hallucinogenic drugs. III: the mechanistic basis for supersensitivity to the LSD stimulus following serotonin depletion. Psychopharmacology (Berl) 1995a;121:364–72.

Fiorella D, Rabin RA, Winter JC. The role of the 5-HT_{2A} and 5-HT_{2C} receptors in the stimulus effects of hallucinogenic drugs. I: antagonist correlation analysis. Psychopharmacology (Berl) 1995b;121:347–56.

Fletcher A, Bill DJ, Bill SJ, Cliffe IA, Dover GM, Forster EA, et al. WAY100135: a novel, selective antagonist at presynaptic and postsynaptic 5-HT_{1A} receptors. Eur J Pharmacol 1993;237:283–91.

Fletcher A, Forster EA, Bill DJ, Brown G, Cliffe IA, Hartley JE, et al. Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT_{1A} receptor antagonist. Behav Brain Res 1996;73:337–53.

Forster EA, Cliffe IA, Bill DJ, Dover GM, Jones D, Reilly Y, et al. A pharmacological profile of the selective silent 5-HT1A receptor antagonist, WAY-100635. Eur J Pharmacol 1995;281:81–8.

Goodwin GM, Green AR. A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. Br J Pharmacol 1985;84:743–53.

Green AR, Heal DJ, Johnson P, Laurence BE, Nimgaonkar VL. Antidepressant treatments: effects in rodents on dose-response curves of 5-HT- and dopamine-mediated behaviors and 5-HT2 receptor number in frontal cortex. Br J Pharmacol 1983;80:377–85.

Gudelsky GA, Koenig JI, Meltzer HY. Thermoregulatory responses to serotonin (5-HT) receptor stimulation in the rat. Evidence for opposing roles of 5-HT2 and 5-HT_{1A} receptors. Neuropharmacology 1986;25:1307–13.

Johnson MP, Siegel BW, Carr AA. [3H]MDL 100,907: a novel selective 5-HT_{2A} receptor ligand. Naunyn Schmiedebergs Arch Pharmacol 1996;354:205–9.

Keenan KP, Smith PF, Hertzog P, Soper K, Ballam GC, Clark RL. The effects of overfeeding and dietary restriction on Sprague-Dawley rat survival and early pathology biomarkers of aging. Toxicol Pathol 1994;22:300–15.

Kehne JH, Baron BM, Carr AA, Chaney SF, Elands J, Feldman DJ, et al. Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT_{2A} antagonist with a favorable CNS safety profile. J Pharmacol Exp Ther 1996;277:968–81.

Koek W, Jackson A, Colpaert FC. Behavioral pharmacology of antagonists at 5-HT2/5-HT_{1C} receptors. Neurosci Biobehav Rev 1992;16:95–105.

Krebs-Thomson K, Geyer MA. Evidence for a functional interaction between 5-HT_{1A} and 5-HT2 receptors in rats. Psychopharmacology (Berl) 1998;140:69–74.

Leysen JE, Gommeren W, Van Gompel P, Wynants J, Janssen PF, Laduron PM. Receptor-binding properties in vitro and in vivo of ritanserin: a very potent and long acting serotonin-S2 antagonist. Mol Pharmacol 1985;27:600–11.

Lorke DE, Lu G, Cho E, Yew DT. Serotonin 5-HT_{2A} and 5-HT6 receptors in the prefrontal cortex of Alzheimer and normal aging patients. BMC Neurosci 2006;7:36.

Marek GJ, Aghajanian GK. Excitation of interneurons in piriform cortex by 5-hydroxytryptamine: blockade by MDL 100,907, a highly selective 5-HT_{2A} receptor antagonist. Eur J Pharmacol 1994;259:137–41.

Marona-Lewicka D, Nichols DE. Aripiprazole (OPC-14597) fully substitutes for the 5-HT_{1A} receptor agonist LY293284 in the drug discrimination assay in rats. Psychopharmacology (Berl) 2004;172:415–21.

Martin-Ruiz R, Puig MV, Celada P, Shapiro DA, Roth BL, Mengod G, et al. Control of serotonergic function in medial prefrontal cortex by serotonin-2A receptors through a glutamate-dependent mechanism. J Neurosci 2001;21:9856–66.

Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999;21:106S–15S.

Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159–72.

Millan MJ. Improving the treatment of schizophrenia: focus on serotonin (5-HT) (1A) receptors. J Pharmacol Exp Ther 2000;295:853–61.

Nomura M, Kusumi I, Kaneko M, Masui T, Daiguji M, Ueno T, et al. Involvement of a polymorphism in the 5-HT_{2A} receptor gene in impulsive behavior. Psychopharmacology (Berl) 2006;187:30–5.

Pazos A, Castro ME, del Olmo E, Romon T, del Arco C. Autoradiographic characterization, anatomical distribution, and developmental pattern of a new 5-HT site in human brain. Ann N Y Acad Sci 1998;861:262.

Peroutka SJ. Selective interaction of novel anxiolytics with 5-hydroxytryptamine1A receptors. Biol Psychiatry 1985;20:971–9.

Pranzatelli MR, Pluchino RS. The relation of central 5-HT_{1A} and 5-HT2 receptors: low dose agonist-induced selective tolerance in the rat. Pharmacol Biochem Behav 1991;39:407–13.

Pucadyil TJ, Kalipatnapu S, Chattopadhyay A. The serotonin1A receptor: a representative member of the serotonin receptor family. Cell Mol Neurobiol 2005;25:553–80.

Reissig CJ, Eckler JR, Rabin RA, Winter JC. The 5-HT_{1A} receptor and the stimulus effects of LSD in the rat. Psychopharmacology (Berl) 2005;182:197–204.

Riblet LA, Taylor DP, Eison MS, Stanton HC. Pharmacology and neurochemistry of buspirone. J Clin Psychiatry 1982;43:11–8.

Sanger DJ, Schoemaker H. Discriminative stimulus properties of 8-OH-DPAT: relationship to affinity for 5HT_{1A} receptors. Psychopharmacology (Berl) 1992;108:85–92.

Schreiber R, Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ. DOI-induced head-twitches in the rat are mediated by 5-HT_{2A} receptors: modulation by novel 5-$HT_{2A/2C}$ antagonists, D1 antagonists, and 5-HT_{1A} agonists. J Pharmacol Exp Ther 1995;273:101–12.

Sorensen SM, Kehne JH, Fadayel GM, Humphreys TM, Ketteler HJ, Sullivan CK, et al. Characterization of the 5-HT2 receptor antagonist MDL 100907 as a putative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. J Pharmacol Exp Ther 1993;266:684–91.

Tricklebank MD, Neill J, Kidd EJ, Fozard JR. Mediation of the discriminative stimulus properties of 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) by the putative 5-HT_{1A} receptor. Eur J Pharmacol 1987;133:47–56.

Winter JC. Hallucinogens as discriminative stimuli. Fed Proc 1974;33:1825–32.

Winter JC. The stimulus effects of serotonergic hallucinogens in animals. NIDA Res Monogr 1994;146:157–82.

Winter JC, Eckler JR, Rabin RA. Serotonergic/glutamatergic interactions: the effects of mGlu2/3 receptor ligands in rats trained with LSD and PCP as discriminative stimuli. Psychopharmacology (Berl) 2004;172:233–40.

Winter JC, Filipink RA, Timineri D, Helsley SE, Rabin RA. The paradox of 5-methoxy-N,N-dimethyltryptamine: an indoleamine hallucinogen that induces stimulus control via 5-HT_{1A} receptors. Pharmacol Biochem Behav 2000;65:75–82.

Winter JC, Petti DT. The effects of 8-hydroxy-2-(di-n-propylamino)tetralin and other serotonergic agonists on performance in a radial maze: a possible role for 5-HT1A receptors in memory. Pharmacol Biochem Behav 1987;27:625–8.

Yasuno F, Suhara T, Ichimiya T, Takano A, Ando T, Okubo Y. Decreased 5-HT1A receptor binding in amygdala of schizophrenia. Biol Psychiatry 2004;55:439–44.

Yocca FD, Wright RN, Margraf RR, Eison AS. 8-OH-DPAT and buspirone analogs inhibit the ketanserin-sensitive quipazine-induced head shake response in rats. Pharmacol Biochem Behav 1990;35:251–4.

Yocca FD, Eison AS, Hyslop DK, Ryan E, Taylor DP, Gianutsos G. Unique modulation of central 5-HT2 receptor binding sites and 5-HT2 receptor-mediated behavior by continuous gepirone treatment. Life Sci 1991;49:1777–85.