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A 5-HT_{2C} receptor-mediated interaction between 2,5-dimethoxy-4-methylamphetamine and citalopram in the rat

J.R. Eckler, C.J. Reissig, R.A. Rabin, J.C. Winter*

Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo, 102 Farber Hall, Buffalo, NY 14214-3000, USA

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Abstract

Previous studies conducted in our laboratory have shown that acute administration of the selective serotonin re-uptake inhibitor (SSRI), citalopram, potentiates the stimulus effects of the phenethylamine hallucinogen [−]-2,5-dimethoxy-4-methylamphetamine (DOM) in the rat while neither substituting for the DOM stimulus when administered alone nor altering brain levels of DOM. The present investigation was designed to determine the mechanism by which citalopram acts on DOM-induced stimulus control. To that end, we tested the following hypotheses: (a) citalopram blocks the transport of DOM by the serotonin transporter, (b) citalopram acts via the 5-HT_{1A} receptor, and (c) citalopram acts via the 5-HT_{2C} receptor. Hypothesis (a) was rejected on the basis of equilibrium saturation studies of [^{3}H]citalopram binding, which revealed no significant affinity of DOM for the 5-HT transporter of rat brain membranes. Hypotheses (b) and (c) were tested in a group of 20 rats in which stimulus control was established with DOM (0.6 mg/kg; 75 min pretreatment time). A two-lever, fixed ratio 10 (FR10), positively reinforced task with saline controls was employed. Hypothesis (b), a role for the 5-HT_{1A} receptor, was rejected on the basis of an absence of antagonism of the effects of citalopram on DOM by the selective 5-HT_{1A} receptor antagonist, WAY-100635. In contrast, Hypothesis (c), a role for the 5-HT_{2C} receptor, gained support from the observation of significant antagonism of the effects of citalopram on DOM by the selective 5-HT_{2C} receptor antagonist, SB-242084.

Keywords: Drug discrimination; Citalopram; DOM; Potentiation; Rat

1. Introduction

Previous studies conducted in our laboratory have shown that acute administration of the selective serotonin re-uptake inhibitor (SSRI), citalopram, potentiates the stimulus effects of the phenethylamine hallucinogen [−]-2,5-dimethoxy-4-methylamphetamine (DOM) in the rat (Eckler et al., 2002) while neither substituting for the DOM stimulus when administered alone nor altering brain levels of DOM (Eckler et al., 2001). In addition, we have demonstrated that subchronic treatment with citalopram does not diminish the potentiation of DOM by citalopram (Winter et al., 2002).

Following its synthesis by Shulgin (1964), the hallucinogenic effects of DOM were reported independently by Hollister et al. (1969) and Snyder et al. (1968). DOM is one of a family of psychoactive phenethylamines, including amphetamine, methamphetamine, and 3,4-methylenedioxy-methamphetamine (MDMA). Methamphetamine and MDMA both are known to interact with monoamine transporters (Rothman et al., 2000). More specifically, MDMA is believed to block serotonin re-uptake and to induce the release of both serotonin and dopamine. However, the effect on dopamine appears to be secondary to the release of 5-HT, as indicated by the fact that fluoxetine, an SSRI, inhibits the elevations of dopamine levels following MDMA administration (Nash and Brodkin, 1991). In addition, both MDMA and methamphetamine are taken up by the 5-HT transporter and released inside of the presynaptic cell. Finally, the release of

* Corresponding author. Tel.: +1 716 829 3239; fax: +1 716 829 2801.
E-mail address: jcwinter@buffalo.edu (J.C. Winter).

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serotonin is characteristic of all substituted amphetamines, including methamphetamine (Malberg and Bonson, 2001). Thus, it has been concluded that the pharmacological effects of MDMA are dependent upon the 5-HT transporter (Bengel et al., 1998). In light of the structural similarities of DOM and MDMA, we hypothesized that the previously observed potentiation of the stimulus effects of DOM by citalopram are due to the blockade of the presynaptic uptake of DOM with a resultant increase in synaptic levels of DOM. For this hypothesis to be true, the serotonin transporter should display appreciable affinity for DOM.

As an alternative to the possible effects of citalopram on the transport of DOM, we may consider what is known of the stimulus effects of citalopram. In studies by Millan et al. (1999), it was concluded that stimulus control by citalopram in the rat is the result of agonistic effects at the 5-HT_{2C} receptor. Thus, citalopram is mimicked by the selective 5-HT_{2C} receptor agonist, Ro 60-0175, and blocked by the selective 5-HT_{2C} receptor antagonist, SB-242084. Based on these observations, it may be hypothesized that the potentiation of the stimulus effects of DOM by citalopram is mediated by the actions of citalopram at the 5-HT_{2C} receptor. Although it is generally assumed that agonist interactions at 5-HT_{2A} receptors mediate the stimulus effects of both indoleamine and phenethylamine hallucinogens (Ismaiel et al., 1993; Schreiber et al., 1994, Fiorella et al., 1995b), suggestive evidence for a modulatory role for 5-HT_{2C} receptors has been presented previously (Glennon et al., 1991; Fiorella et al., 1995b; Winter et al., 1999).

The blockade of the re-uptake of 5-HT by citalopram would be expected to increase the levels of the neurotransmitter at all serotonergic synaptic receptors, including those of the 5-HT_{1A} subtype. It was reported by Glennon (1991) that the selective 5-HT_{1A} agonist 8-hydroxydipropylaminotetralin (DPAT) potentiates the stimulus effects of DOM, and we have replicated this finding (see Table 2). In addition, it has been observed that citalopram potentiates the effects of DPAT when trained as a discriminative stimulus (Wolff and Leander, 1998) and that hypothermia induced by citalopram is mediated by agonist activity at the 5-HT_{1A} receptor (Oerther and Ahlenius, 2001). Taken together, these observations prompted us to hypothesize that citalopram potentiates stimulus control by DOM via a process mediated by the 5-HT_{1A} receptor.

The goal of the present study was to test the hypotheses outlined above regarding the possible mechanisms by which the stimulus effects of DOM are potentiated by the coadministration of citalopram. To that end, stimulus control was established with DOM in rats, and tests were conducted with combinations of DOM with selected ligands at 5-HT_{1A} and 5-HT_{2C} receptors. In addition, the affinities of DOM and related drugs for the 5-HT transporter were determined.

2. Materials and methods

2.1. Subjects

Male Fischer 344 rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN, USA) and were housed with free access to food and water in a temperature-controlled room under a constant 12:12-h light–dark cycle. All experiments were conducted during the light phase. Subjects were fed following the experimental sessions. Caloric intake was controlled to yield a mean body weight of about 300 g. The animals used in these studies were maintained in accordance with the 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 and Use Committee of the University at Buffalo.

2.2. Discrimination training

Six small animal test chambers (MED Associates ENV-008) were used for all 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). Twenty subjects were trained to discriminate DOM from saline using a dose and pretreatment time (0.6 mg/kg, 75-min pretreatment time, intraperitoneal injection) based on previous work in our laboratory (Fiorella et al., 1995a). 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. DOM-induced stimulus control were established after 25–30 training sessions. The DOM 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 was established with the training agents, 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 one of the previous three training sessions. Half of the test sessions were conducted the day after saline training sessions, with the remainder following DOM training sessions. 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 a 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 on both levers by the elapsed time prior to 10 responses on either lever. Throughout the text, pretreatment times refer to the elapsed time between drug administration and testing; for example, a 90-min pretreatment time for citalopram means that it was given 15 min before DOM when the latter was given using its usual 75-min pretreatment time.

2.4. Binding studies

Binding of [^{3}H]citalopram to the 5-HT transporter was measured according to the method of D'Amato et al. (1987). Briefly, whole brains minus cerebellum were maintained at 4 °C and were homogenized (Dounce tissue grinder) in 20 volumes of ice-cold 50 mM Tris–HCl buffer (pH 7.4 at 25 °C) containing 120 mM NaCl and 5 mM KCl, and the homogenates were centrifuged at 40,000×g for 15 min at 4 °C. The resulting pellet was resuspended in fresh buffer and recentrifuged. This washing procedure was repeated again, and the final pellet was suspended in 1.5 volumes of Tris–HCl buffer. Assays were carried out for 60 min at 23 °C in a final volume of 1 ml, consisting of 0.75 ml of tissue suspension, 0.1 ml of appropriate drug solution, 0.1 ml buffer, and 0.05 ml of radioligand. A concentration range of 0.15–6.0 nM [^{3}H]citalopram was used for the equilibrium saturation studies, while 0.7 nM [^{3}H]citalopram (specific activity 55 Ci/mmol) was used for the competition studies. Specific binding was defined by the difference in the amount of radioactivity bound in the absence and presence of 0.33 μM fluoxetine. Reactions were terminated by the addition of ice-cold 50 mM Tris–HCl buffer (pH 7.4 at 25 °C, with 120 mM NaCl and 5 mM KCl), and membranes were collected by vacuum filtration (Brandel cell harvester) using Whatman GF/B glass fiber filters presoaked in 0.3% polyethylenimine. Filters were rinsed three times with ice-cold Tris buffer, and the amount of bound radioactivity was determined by liquid scintillation spectrometry after an overnight incubation in scintillation cocktail. The affinity of the unlabeled compounds for the serotonin transporter was calculated by nonlinear regression using the program EBDA/LIGAND (Elsevier Biosoft).

2.5. Drugs

The initial demonstrations of the hallucinogenic properties of DOM in human subjects (Hollister et al., 1969; Snyder et al., 1968) and much subsequent work in animals employed a racemic mixture. Subsequently, however, it was found that the [−]-isomer is significantly more potent both in humans (Shulgin, 1973) and in rats (Benington et al., 1973; Silverman, 1977). Indeed, Shulgin and Shulgin (1991) suggest that the major contribution of the [+]-isomer of DOM may be unwanted amphetamine-like effects. For this reason, the present experiments have employed [−]-DOM.

All drugs used in the behavioral experiments were dissolved in 0.9% saline solution and injected in a volume of 1.0 ml/kg bodyweight. The intraperitoneal route was employed for all drugs. [−]-DOM and LSD were supplied by the National Institute on Drug Abuse (Rockville, MD, USA). The following drugs were generously provided by the organizations indicated: [±]-fluoxetine HCl (Lilly Research Laboratories, Indianapolis, IN, USA), citalopram hydrobromide (H. Lundbeck, Copenhagen, Denmark), fluvoxamine maleate (Solvay Duphar, Weesp, The Netherlands), WAY-100635 (Wyeth-Ayerst Research, Princeton, NJ, USA), SB-242084 (GlaxoSmithKline, United Kingdom). The following drugs were purchased from the commercial sources indicated: serotonin HCl and [+]-8-hydroxy-dipropylaminotetraline HBr (DPAT; Research Biochemicals International, Natick, MA, USA), [^{3}H] citalopram (PerkinElmer Life Sciences, Boston, MA, USA), and [[+]-8-OH-DPAT], *m*-chlorophenylpiperazine (mCPP; Aldrich Chemical, Milwaukee, WI, USA).

2.6. Statistical analysis

Behavioral data were assessed for statistical significance using individual applications of paired Student's t test and one-way repeated-measures analysis of variance (ANOVA), followed by pair-wise comparisons using the Holm–Sidak method. Differences were considered statistically significant if the probability of their having arisen by chance was <.05. All analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, San Rafael, CA, USA).

3. Results

3.1. Affinity of DOM for the 5-HT transporter

In equilibrium saturation studies of [^{3}H]citalopram binding, the data indicate a single population of binding sites, with a K_D of 0.77 nM (pK_D=9.11) and a B_{max} equal to 372.0 (±8.73) fmol/mg. This K_D value for [^{3}H]citalopram is consistent with values previously observed in the male Fisher 344 rat (D'Amato et al., 1987). The affinities for the serotonin transporter of agents used in competition studies (Fig. 1) are shown in Table 1. The affinities observed for the SSRIs are consistent with previously reported values. The data indicate that neither LSD nor DOM possesses significant affinity for the 5-HT transporter.

3.2. Potentiation of DOM by citalopram

Previous studies in our laboratory established that the stimulus effects of DOM are potentiated by citalopram (1.0

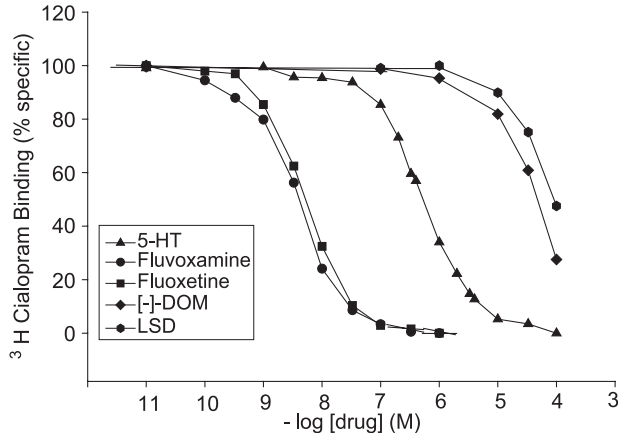

Fig. 1. Competition plots for the binding of [^{3}H]citalopram to rat brain. Membranes were incubated with 0.7 nM [^{3}H]citalopram and various concentrations of serotonin, fluvoxamine, fluoxetine, DOM, or LSD, as described in the Materials and methods. Nonspecific binding was defined with 0.33 μM fluoxetine. Results are expressed as the percentage of specific [^{3}H]citalopram bound in the absence of unlabeled drug and are presented as the average of duplicate determinations from three to four separate experiments.

mg/kg) using a pretreatment time of 90 min, i.e., 15 min prior to the administration of DOM (0.1 mg/kg) and 75 min prior to testing (Eckler et al., 2002). A replication of these experiments yielded the data shown in Table 2, with a value for DOM alone of 32% DOM-appropriate responding and, following the combination of DOM and citalopram, a value of 76%. Subsequent experiments evaluated the role of agonist activity at 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors, respectively, in the observed potentiation of DOM by citalopram. The 5-HT$_{1A}$ receptor agonist, DPAT, and the 5-HT$_{2C}$ receptor agonist, mCPP, did not, at the doses selected, mimic the stimulus effects of DOM. However, in combination with an intermediate dose of DOM, both DPAT and mCPP were seen to increase DOM-appropriate responding. Simultaneous comparison of DOM, DOM+citalopram, and DOM+citalopram+WAY-100635 by one-way repeated-measures ANOVA failed to reveal statistically significant differences [$F(2, 21)=2.205$; N.S.]. In contrast, simultaneous comparison of DOM, DOM+citalopram, and DOM+citalopram+SB-242084 indicated a significant antagonism by SB-242084 of the potentiation of DOM by citalopram the selective 5-HT$_{2C}$ receptor antagonist, SB-242084 [$F(2,27)=8.305$, $P=.002$]. Pair-wise comparisons revealed a significant difference between DOM+citalopram and DOM+citalopram+SB-242084, but no significant difference between the latter and DOM alone.

Table 1
Affinity for the 5-HT transporter

Drug	
K_I (S.E.) in nM	
Fluvoxamine	2.27 (0.14)
Fluoxetine	3.56 (0.24)
Serotonin	323 (26.7)
IC_{50} (S.E.) in μM	
DOM	53.1 (1.82)
LSD	86.4 (9.69)

Equilibrium dissociation constants (K_I) for fluvoxamine, fluoxetine, and serotonin were determined by nonlinear regression analysis (EBDA/LIGAND) using the data from Fig. 1. Because of their low affinity, data for the hallucinogens LSD and DOM are expressed as the concentration of drug causing a 50% inhibition (IC_{50}) of the specific binding of 0.7 nM [^{3}H]citalopram. Results are presented as the mean (S.E.) of three to four separate experiments.

Table 2
Potentiation by citalopram of stimulus control by DOM and interactions with ligands at 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors

Treatment[a]	*N*	% DOM[b] responding	Significance (*P*)	Rate[b] RS/min
DOM	20[c]	32 (9)		15 (7)
DOM+citalopram	16[c]	76 (6)	<.001	22 (3)
DPAT	9	8 (4)	N.S.[d]	19 (4)
DOM+DPAT	9	72 (10)	<.01[e]	18 (7)
WAY-100635+ DOM+citalopram	12	63 (14)	N.S.[f]	5 (3)
mCPP	8	14 (7)	N.S.[d]	16 (7)
DOM+mCPP	13	64 (12)	<.05[e]	5 (1)
SB-242084+DOM	9	32 (15)	N.S.	13 (5)
SB-242084+ DOM+citalopram	9	47 (12)	<.05[f]	14 (2)

[a] DOM: 0.1 mg/kg, −75 min; citalopram: 1.0 mg/kg, −90 min; DPAT: 0.05 mg/kg, −15 min; WAY 100635: 3.0 mg/kg, −60 min; mCPP: 0.2 mg/kg, −15 min; SB-242084: 0.1 mg/kg, −90 min.
[b] Mean; S.E.M. in parentheses.
[c] Mean of two determinations in each subject.
[d] Compared with vehicle (paired *t* test).
[e] Compared with DOM alone (paired *t* test).
[f] Compared with DOM+citalopram (ANOVA; see text).

4. Discussion

Previous findings demonstrate that the SSRI citalopram potentiates the stimulus effects of DOM (Eckler et al., 2002; Winter et al., 2002). One possible explanation for this effect is that citalopram, by virtue of blocking the 5-HT transporter, increases the synaptic concentration of the hallucinogen. This explanation requires that DOM is a substrate for the 5-HT transporter. In support of this assumption, MDMA, which is structurally similar to DOM, is taken up by the 5-HT transporter (Bengel et al., 1998). However, the present data indicate that DOM lacks significant affinity for the 5-HT transporter. Thus, we must reject the hypothesis that citalopram blocks DOM uptake by the 5-HT transporter, resulting in an increase in the synaptic concentration of the hallucinogen.

As was noted above, we and others have observed potentiation of the stimulus effects of both racemic DOM (Glennon, 1991) and the [−]-isomer of DOM (unpublished) by the 5-HT$_{1A}$ selective agonist, DPAT. The latter observation was replicated in the present study (Table 2). Inasmuch as citalopram would be expected to increase the

levels of serotonin at all serotonin receptors, we tested the hypothesis that citalopram potentiates DOM by a process mediated by 5-HT_{1A} receptors. However, it is seen in Table 2 that the selective 5-HT_{1A} receptor antagonist WAY-100635, at a dose shown previously to block completely the stimulus effects of DPAT (Winter et al., 2000), does not significantly alter the interaction between DOM and citalopram. Thus, we must reject the hypothesis that citalopram acts indirectly at 5-HT_{1A} receptors to potentiate stimulus control by DOM.

When citalopram is used as a training agent in drug discrimination procedures, stimulus control appears to be mediated by 5-HT_{2C} receptors (Millan et al., 1999; Dekeyne et al., 2001). To evaluate a possible role for the 5-HT_{2C} receptor in the potentiation of DOM by citalopram, the interaction between DOM and the 5-HT_{2C} agonist, mCPP, was examined. It is seen in Table 2 that the stimulus effects of DOM are significantly augmented by the coadministration of mCPP. Although the present data do not permit a definitive conclusion, it appears from Table 2 that the potentiation of DOM by mCPP is of a lesser magnitude than that observed with citalopram. This may be explained by the nonspecificity of mCPP with respect to serotonergic receptors. Both biochemical (Conn and Sanders-Bush, 1987) and behavioral (Fiorella et al., 1995c) experiments suggest that mCPP acts not only as an agonist at 5-HT_{2C} receptors but also as an antagonist at 5-HT_{2A} receptors. The latter effect would serve to counter any facilitating action engendered by agonism at 5-HT_{2C} receptors (Fiorella et al., 1995b). Unfortunately, the more selective 5-HT_{2C} receptor agonist, Ro 60-0175, used by Millan et al. (1999) to characterize the stimulus effects of citalopram, was not available to us due to institutional constraints. Nonetheless, the observed effects of mCPP on DOM-induced stimulus control, together with the observation that potentiation of DOM by citalopram is significantly antagonized by the selective 5-HT_{2C} receptor antagonist, SB-242084 (Kennett et al., 1997; Table 2), support the hypothesis that citalopram acts to potentiate stimulus control by DOM via a 5-HT_{2C}-mediated mechanism. In separate experiments, it was found that the coadministration of DOM with a range of doses of SB-242084 (0.01–1.0 mg/kg) does not alter DOM-induced stimulus control (data not shown).

A half century ago, a serotonergic basis for the behavioral effects of LSD in humans was proposed on the basis of experiments using isolated smooth muscle (Gaddum, 1957; Wooley and Shaw, 1954). In the intervening years, data derived from both animal and human subjects extended this notion beyond LSD to include not only indoleamine hallucinogens, such as psilocybin and DMT, but also hallucinogens of the phenethylamine type, as exemplified by mescaline and DOM (for reviews, see Winter et al., 1999; Nichols, 2004). Concurrently, our conception of the serotonin receptor increased in complexity, until presently, there are seven distinct classes, 5-HT_1 to 5-HT_7, with multiple subtypes (for review, see Hoyer et al., 2002). From the time of its identification in porcine choroid plexus (Pazos et al., 1984) and its assignment to the 5-HT_2 class (Hoyer et al., 1985; Hoyer and Martin, 1997), the functional role of the 5-HT_{2C} receptor has remained uncertain (for reviews, see Pauwels, 2003; Giorgetti and Tecott, 2004). With respect to hallucinogen-induced stimulus control in the rat and, by extension, to hallucinogenesis in humans, interpretation is made difficult by the observation that all indoleamine and phenethylamine hallucinogens have affinity for 5-HT_{2A}, as well as 5-HT_{2C}, receptors. Nonetheless, a consensus has emerged that the activation of the 5-HT_{2A} receptor is necessary, although perhaps not sufficient, for hallucinogenesis (Fiorella et al., 1995b; Nichols, 2004). With respect to the 5-HT_{2C} receptor, previous work in our laboratory provided evidence that sensitization to the stimulus effects of LSD following serotonin depletion in the rat is accompanied by an up-regulation of the 5-HT_{2C} receptor (Fiorella et al., 1995d). That observation is completely compatible with the present data, suggesting that citalopram potentiates the stimulus effects of DOM by sensitizing or otherwise modifying the effects of DOM at 5-HT_{2C} receptors. It is expected that the details of functionally significant interactions between 5-HT_{2A} and 5-HT_{2C} receptors will be elucidated as more selective ligands are discovered.

In summary, the present data indicate that potentiation of the stimulus properties of DOM by citalopram is mediated neither by actions at the serotonin transporter nor via agonism at 5-HT_{1A} receptors. Instead, the data provide further evidence of a functionally significant role for 5-HT_{2C} receptors in the interaction between citalopram- and hallucinogen-induced stimulus control.

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References

Bengel D, Murphy DL, Andrews AM, Wichems CH, Feltner D, Heils A, et al. Altered brain serotonin homeostasis and locomotor insensitivity to 3,4-methylenedioxymethamphetamine ["Ecstasy"] in serotonin transporter-deficient mice. Mol Pharmacol 1998;53;649–55.

Benington F, Morin RD, Beaton J, Smythies JR, Bradley RJ. Comparative effects of stereoisomers of hallucinogenic amphetamines. Nature 1973; 242;185–6.

Conn PJ, Sanders-Bush E. Relative efficacies of piperazines at the phosphoinositide hydrolysis-linked serotonergic 5-HT_{1C} and 5-HT_2 receptors. J Pharmacol Exp Ther 1987;242;552–7.

D'Amato RJ, Largent BL, Snowman AM, Snyder SH. Selective labeling of serotonin uptake sites in rat brain by [^{3}H]citalopram contrasted to labeling of multiple sites by [^{3}H]imipramine. J Pharmacol Exp Ther 1987;242;364–71.

Dekeyne A, Loretta I, Millan MJ. Following long-term training with citalopram, both mirtazapine and mianserin block its discriminative stimulus properties. Psychopharmacology 2001;153;389–93.

Eckler JR, Greizerstein H, Rabin RA, Winter JC. A sensitive method for determining levels of 2,5,dimethoxy-4-methylamphetamine in brain tissue. J Pharmacol Toxicol Methods 2001;46;37–43.

Eckler JR, Doat MM, Rabin RA, Winter JC. Potentiation of DOM-induced stimulus control by fluoxetine and citalopram: role of pharmacokinetics. Life Sci 2002;71;1341–7.

Fiorella D, Palumbo PA, Rabin RA, Winter JC. The time-dependent stimulus effects of 2,5-dimethoxy-4-methylamphetamine [DOM]: implications for drug-induced stimulus control as method for the study of hallucinogenic agents. Psychopharmacology 1995a;119;239–45.

Fiorella D, Rabin RA, Winter JC. The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of hallucinogenic drugs: I Antagonist correlation analysis. Psychopharmacology 1995b;121;347–56.

Fiorella D, Rabin RA, Winter JC. The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of *m*-chlorophenylpiperazine. Psychopharmacology 1995c;119;222–30.

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 1995; 121;364–72.

Gaddum JH. Serotonin–LSD interaction. Ann N Y Acad Sci 1957;66; 562–75.

Giorgetti M, Tecott LH. Contributions of 5-HT_{2C} receptors to multiple actions of central serotonin systems. Eur J Pharmacol 2004;488;1–9.

Glennon RA. Discriminative stimulus properties of hallucinogens and related designer drugs. In: Glennon RA, Jarbe TUC, Frankenheim J, editors. Drug discrimination: applications to drug abuse research. NIDA Monograph, vol. 116. Washington (DC): USGPO; 1991. p. 29.

Glennon RA, Darmani NA, Martin BR. Multiple populations of serotonin receptors may modulate the behavioral effects of serotonergic agents. Life Sci 1991;48;2493–8.

Hollister LE, Macnicol MF, Gillespie HK. An hallucinogenic amphetamine analog [DOM] in man. Psychopharmacologia 1969;14;62–73.

Hoyer D, Martin G. 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacology 1997; 36;419–28.

Hoyer D, Engel G, Kalkman HO. Molecular pharmacology of 5-HT_1 and 5-HT_2 recognition sites in rat and pig membranes. Eur J Pharmacol 1985; 118;13–23.

Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological, and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71;533–54.

Ismaiel AM, De Los Angeles J, Titeler M, Ingher S, Glennon RA. Antagonism of the 1-[2,5-dimethoxy-4-methylphenyl]-2-aminopropane stimulus with a newly identified 5-HT2 versus 5-HT1C-selective antagonist. J Med Chem 1993;36;2519–25.

Kennett GA, Wood MD, Bright F, Trail B, Riley G, Holland V, et al. SB 242084, a selective and brain penetrant 5-HT_{2C} receptor antagonist. Neuropharmacology 1997;36;609–20.

Malberg J, Bonson KR. How MDMA works in the brain. In: Holland J, editor. Ecstasy: the complete guide. Rochester (VT): Park Street Press; 2001. p. 29–38.

Millan MJ, Girardon S, Dekeyne A. 5-HT2C receptors are involved in the discriminative stimulus effects of citalopram in rats. Psychopharmacology 1999;142;432–4.

Nash JF, Brodkin J. Microdialysis studies on 3,4-methylenedioxy-methamphetamine-induced dopamine release: effects of dopamine uptake inhibitors. J Pharmacol Exp Ther 1991;259;820–5.

Nichols DE. Hallucinogens. Pharmacol Ther 2004;101;131–81.

Oerther S, Ahlenius S. Involvement of 5-HT1A and 5-HT1B receptors for citalopram-induced hypothermia in the rat. Psychopharmacology 2001; 154;429–34.

Pauwels PJ. 5-HT receptors and their ligands. Tocris Rev 2003;25;1–10.

Pazos A, Hoyer D, Palacios JM. The binding of serotonergic ligands to the porcine choroid plexus: characterization of a new type of serotonin recognition site. Eur J Pharmacol 1984;106;539–46.

Rothman RB, Partilla JS, Baumann MH, Dersch CM, Carroll FI, Rice KC. Neurochemical neutralization of methamphetamine with high-affinity nonselective inhibitors of biogenic amine transporters: a pharmacological strategy for treating stimulant abuse. Synapse 2000;35;222–7.

Schreiber R, Brocco M, Millan MJ. Blockade of the discriminative stimulus effects of DOI by MDL 100,907 and the atypical antipsychotics, clozapine and risperidone. Eur J Pharmacol 1994;264;99–102.

Shulgin AT. Psychotomimetic amphetamines: methoxy 3,4-dialkoxy-amphetamines. Experientia 1964;20;1–4.

Shulgin AT. Stereospecific requirements for hallucinogens. J Pharm Pharmacol 1973;25;271–2.

Shulgin AT, Shulgin A, 1991. PiHKAL: a chemical love story. Berkley (MI): Transform Press; 1991. p. 640–1.

Silverman, P.B., Psychopharmacological study of 2,5-Dimethoxy-4-methylamphetamine [DOM]. PhD dissertation, University of Texas, Graduate School of Biomedical Sciences, Houston; 1977.

Snyder SH, Faillace LA, Weingartner H. DOM [STP], a new hallucinogenic drug, and DOET: effects in normal subjects. Am J Psychiatry 1968; 125;357–64.

Winter JC, Fiorella DJ, Timineri DM, Filipink RA, Helsley SE, Rabin RA. Serotonergic receptor subtypes and hallucinogen-induced stimulus control. Pharmacol Biochem Behav 1999;64;283–93.

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

Winter JC, Eckler JR, Doat MM, Rabin RA. The effects of acute and subchronic treatment with fluoxetine and citalopram on stimulus control by DOM. Pharmacol Biochem Behav 2002;74;95–101.

Wolff MC, Leander JD. Selective serotonin reuptake inhibitors potentiate 8-OH-DPAT-induced stimulus control in the pigeon. Eur J Pharmacol 1998;345;35–9.

Wooley DW, Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. Proc Natl Acad Sci U S A 1954; 40;228–35.