Available online at www.sciencedirect.com

SCIENCE DIRECT®

Pharmacology, Biochemistry and Behavior 78 (2004) 263–268

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Modulation of the stimulus effects of (+)amphetamine by the 5-HT$_6$ antagonist MS-245

Manik Pullagurla, Tatiana Bondareva, Richard Young, Richard A. Glennon*

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia Campus, Virginia Commonwealth University, 554A Smith Building, 410 North 12th Street, Richmond, VA 23298-0540, USA

Received 13 March 2004; received in revised form 13 March 2004; accepted 24 March 2004
Available online 13 May 2004

Abstract

5-HT$_6$ serotonin receptors are distributed within some dopamine terminal regions in the brain leading to suggestions that they might influence dopaminergic function. In the present study, the 5-HT$_6$ antagonist 5-methoxy-*N*,*N*-dimethyl-N_1-benzenesulfonyltryptamine (MS-245) was without effect when administered (3.0–7.5 mg/kg) to rats trained to discriminate (+)amphetamine (1.0 mg/kg) from saline vehicle in a two-lever drug discrimination task. Administered in combination, 0.3 mg/kg (i.e., the ED$_{50}$ dose) of (+)amphetamine plus 5.0 mg/kg of MS-245 elicited 95% amphetamine-appropriate responding. Similar studies were conducted using rats trained to discriminate cocaine (8.0 mg/kg) from saline vehicle, but a combination of 2.0 mg/kg (i.e., the ED$_{50}$ dose) of cocaine together with relatively low doses of MS-245 resulted in the percent response (approximately 50%) expected from administration of this dose of cocaine or in disruption of the animals' behavior. The present results confirm findings from other laboratories that 5-HT$_6$ antagonists can modulate amphetamine-induced behavioral actions, and further extend these findings to an example of a different structural class of 5-HT$_6$ antagonists and to a different behavioral paradigm. Taken together, the data suggest that 5-HT$_6$ serotonin agents (or at least MS-245) could have potential clinical application in therapies that involve modulation of dopamine neurotransmission.

Keywords: Amphetamine; Cocaine; Drug abuse; Dopamine; Parkinsonism

1. Introduction

5-HT$_6$ receptors represent one of seven major subfamilies (5-HT$_1$–5-HT$_7$) of serotonin (5-hydroxytryptamine, 5-HT) receptors (Hoyer et al., 2002). Most of the early characterization of 5-HT$_6$ receptor function was conducted in the absence of selective agents. Recent studies, however, have described several purported 5-HT$_6$ receptor antagonists, including 4-amino-*N*-(2,6-*bis*methylaminopyrimidin-4-yl) benzenesulfonamide (Ro 04-6790), 5-chloro-*N*-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl)-2-benzothiophenesulfonamide (SB-271046), 5-chloro-*N*-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-3-methylbenzothiophene-2-ylsulfonamide (SB-258510), and 5-methoxy-*N*,*N*-dimethyl-N_1-benzenesulfonyltryptamine (MS-245; for review, see Glennon, 2003). The availability of these agents might now allow a better understanding of 5-HT$_6$ pharmacology.

A specific function for 5-HT$_6$ receptors has yet to be delineated but it has been suggested that they might play a role in the action of typical and atypical antipsychotic agents, appetite control, and in cognitive dysfunction (for review, see Glennon, 2003; Russell and Dias, 2002; Slassi et al., 2002). The 5-HT$_6$ receptors seem to have a modulatory effect on multiple neurotransmitter systems (Dawson et al., 2001; Glennon, 2003), and of particular interest to the present investigation is their influence on the dopaminergic system. On the basis that 5-HT$_6$ receptors are distributed within dopamine terminal regions, Dawson et al. (2002) examined the effect of acute subcutaneous administration of SB-271046 on basal dopamine levels (rat striatum) and found no effect. However, the effect of (+)amphetamine (0.3 mg/kg) was potentiated by SB-271046. On the basis of these studies, it was concluded that the 5-HT$_6$ antagonist does not exert an effect on the tonic modulation of dopamine, but that it has a modulatory influence when dopaminergic neurotransmission is enhanced. Likewise, Frantz et al. (2000) showed that SB-258510 had no effect on rat motor activity by itself, but potentiated the locomotor

* Corresponding author. Tel.: +1-804-828-8487; fax: +1-804-828-7404.
E-mail address: glennon@hsc.vcu.edu (R.A. Glennon).

0091-3057/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.03.017

actions of (+)amphetamine. In that same study, SB-258510 potentiated the reinforcing properties of (+)amphetamine and increased amphetamine-induced dopamine efflux in rat frontal cortex. Interestingly, doses of SB-258510 that altered amphetamine-induced behaviors and neurochemistry failed to modify cocaine-induced actions (Frantz et al., 2000). This dichotomy of effect was explained by the action of amphetamine being primarily to release dopamine whereas that of cocaine is predominantly one of dopamine reuptake inhibition, and that the actions of the latter might be more dependent on impulse activity than those of amphetamine. Taken together, the overall conclusions of the above studies indicate that 5-HT_6 receptors (i) are behaviorally silent under drug-free conditions (Frantz et al., 2000), and (ii) can regulate amphetamine-induced, but not cocaine-induced dopaminergic behavior or function. As such, continued investigation of 5-HT_6 receptor pharmacology could assist in the further elucidation of mechanisms contributing to stimulant abuse, and might also be useful targets in the development of agents (i.e., 5-HT_6 agonists and partial agonists) for the treatment of amphetamine dependence.

Given that 5-HT_6 antagonists have been shown to modulate some amphetamine-induced behaviors but do not seem to affect cocaine-induced activities, the goal of the present study was to determine if similar results could be demonstrated in a drug discrimination task, a highly sensitive and relatively specific behavioral assay that provides both qualitative and quantitative information about a drug (e.g., Glennon et al., 1991). In this procedure, for example, animals can be trained to respond on one lever, in a two-lever operant chamber, following administration of a particular dose of a given training drug, and on the opposite lever following administration of saline vehicle. Once trained, animals can be administered doses of a challenge drug to determine if it can mimic (i.e., substitute for or generalize to) or antagonize the training drug stimulus. For a general review see, for example, Colpaert and Slangen (1982) and Glennon et al. (1991). In the current investigation, it was hypothesized that a 5-HT_6 receptor antagonist would potentiate the discriminative stimulus effects of (+)amphetamine, but not those of cocaine, in groups of rats trained to discriminate each of these agents from vehicle. The purported high-affinity (Ki = 1.5 nM) 5-HT_6 receptor antagonist, MS-245, developed earlier in our laboratories (Glennon et al., 2000) was used to evaluate this hypothesis.

2. Materials and methods

2.1. Drug discrimination studies

Ten male Sprague–Dawley rats (Charles River Laboratories), weighing 250–300 g at the beginning of the study, were trained to discriminate (15-min presession injection interval) either 1.0 mg/kg of (+)amphetamine sulfate ($n = 5$) or 8.0 mg/kg of cocaine hydrochloride ($n = 5$) from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard two-lever Coulbourn Instruments operant equipment as previously described (Glennon et al., 1995; Young and Glennon, 1993). The animals' body weights were maintained at 80% of their free-feeding weights by food restriction; animals had free access to water in their individual home cages. Animals were maintained in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals and studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

Daily training sessions were conducted with the training dose of the training drugs, or saline, administered on a random schedule with the proviso that no more than two consecutive sessions occur with drug or vehicle. Stimulus control was assessed every fifth day during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. Data collected during the extinction session included response rate (i.e., responses per minute) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the subsequent stimulus generalization studies until they made >80% of their responses on the drug-appropriate lever after administration of training drug and <20% of their responses on the same drug-appropriate lever after administration of saline for three consecutive weeks. During the stimulus generalization (i.e., substitution) phase of the study, maintenance of the training-drug/saline discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day). On 1 of the 2 days before a generalization test, approximately half the animals would receive the training dose of training drug and the remainder would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original training criteria during the extinction session were excluded from the subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions. An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of test drugs were administered in a random order, using a 15-min presession injection interval, to the groups of rats. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made $\geq$80% of their responses (group mean) on the training drug-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Response rate data refer only to animals making $\geq$5 responses during the extinction session. ED_{50} doses for (+)amphetamine and cocaine were determined from previous studies (Glennon et al., 1995; Young and Glennon, 1993); in the present investigation, these calculated doses were administered to serve as control.

Cocaine HCl was purchased from Sigma-Aldrich (St Louis, MO) and MS-245 as the oxalate salt was prepared in our laboratory as previously described (Glennon et al., 2000). Amphetamine sulfate was available in our laboratories from previous studies. Doses refer to the weight of the salts. All solutions were prepared fresh daily.

2.2. Statistical methods

Student's t test was used to determine the statistical significance ($P < .05$) between the animals' response (i.e., percent drug-appropriate lever responding, response/min) to the ED_{50} dose of (+)amphetamine or cocaine and the combination of the highest (nondisruptive) dose of MS-245 with the respective ED_{50} dose.

2.3. Binding profile

MS-245 was examined in about 40 different radioligand binding assays by the NIMH Psychoactive Drug Screening Program (PDSP). Assays employed the standard PDSP binding protocols. The agent was initially screened in quadruplicate at a concentration of 10,000 nM; where MS-245 produced >50% inhibition, a Ki value was determined in quadruplicate. For details of the binding assays and radioligands employed, see http://kidb.cwru.edu/pdsp.php.

3. Results

Administered to rats trained to discriminate (+)amphetamine from saline vehicle, MS-245 doses of 3.0, 5.0, and 7.5 mg/kg produced a maximum of 2% (+)amphetamine-appropriate responding (Fig. 1). However, when administered in combination with the ED_{50} dose of (+)amphetamine (0.3 mg/kg, 56 ± 10% drug-appropriate responding), 5.0 mg/kg of MS-245 resulted in stimulus generalization [i.e., 95% (+)amphetamine-appropriate responding] that was determined to be a statistically significant increase ($t = 3.77$, $df = 6$, $P < .01$). The animals' response rate at this dose combination (8.9 responses/min) was not statistically different ($t = 0.96$, $df = 6$, $P > .05$) from that produced by 0.3 mg/kg of (+)amphetamine (9.6 responses/min).

In the cocaine-trained animals, MS-245 produced vehicle-appropriate responding at doses of 1.0, 2.0, and 3.0 mg/kg (Fig. 2) and resulted in behavioral disruption at 5.0 mg/kg (i.e., at the latter dose, only one of five animals made ≥5 responses during the entire 2.5-min extinction session). Administration of the ED_{50} dose of cocaine (2.0 mg/kg) resulted in the animals making 40 ± 15% of their responses on the cocaine-designated lever. Administration of 1.0 mg/kg of MS-245 in combination with 2.0 mg/kg of cocaine produced 49% cocaine-appropriate responding, which was not a statistically significant increase ($t = 0.39$, $df = 8$, $P > .05$). The animals' response rate at this dose combination (13.4 responses/min) was not statistically different ($t = 0.35$, $df = 8$, $P > .05$) from that produced by 2.0 mg/kg of cocaine alone (11.8 responses/min). The combination of 2.0 mg/kg of MS-245 with 2.0 mg/kg of cocaine resulted in behavioral disruption.

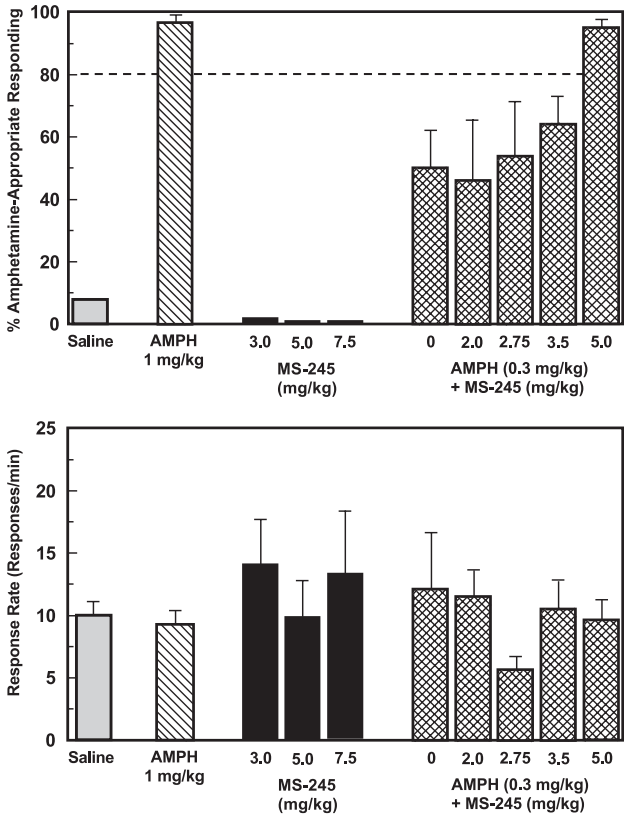

Fig. 1. Mean percent drug-appropriate responding (± S.E.M.) following saline, training dose of training drug [1.0 mg/kg of (+)amphetamine ($n = 5$)], doses of MS-245, and doses of MS-245 in combination with 0.3 mg/kg of (+)amphetamine (upper panel). Animals' response rates under the different conditions are shown in the lower panel.

3.1. Binding profile

MS-245 (h5-HT_6 Ki = 1.5 nM) was submitted to the NIMH PDSP so that a receptor-binding profile could be obtained. Evaluation of MS-245 at about 40 receptors/transporters revealed it to be relatively selective, showing 15- to 30-fold selectivity over human (h) dopamine D_1 (Ki = 25 ± 13 nM) receptors and rat (r) 5-HT_{2C} (Ki = 50 ± 10 nM) receptors, and greater than 100-fold selectivity over h5-HT_{1A} (Ki = 1640 ± 450 nM), r5-HT_{1B} (Ki = 4220 ± 400 nM), h5-HT_{1D} (Ki = 9200 ± 3600 nM), h5-HT_{2A} (Ki = 200 ± 45 nM), 5-HT_3 (Ki = 2400 ± 140 nM), h5-HT_{5A} (Ki 2020 ± 160 nM), h5-HT_7 (Ki = 600 ± 180 nM), human α_{1A}-(Ki = 1325 ± 175 nM), α_{1B}-(Ki = 1830 ± 450 nM), α_{2A}-(Ki = 240 ± 65 nM), α_{2B}-(Ki = 260 ± 25 nM), α_{2C}-(Ki = 700 ± 100 nM), β_1-(Ki>10,000 nM), and β_2-adrenergic (Ki>10,000 nM), $r D_2$ dopamine (Ki = 540 ± 50 nM), $h D_3$ (Ki = 320 ± 30 nM), $r D_4$ (Ki = 2830 ± 750 nM), and $h D_5$ (Ki>10,000 nM). MS-245 lacked measurable affin-

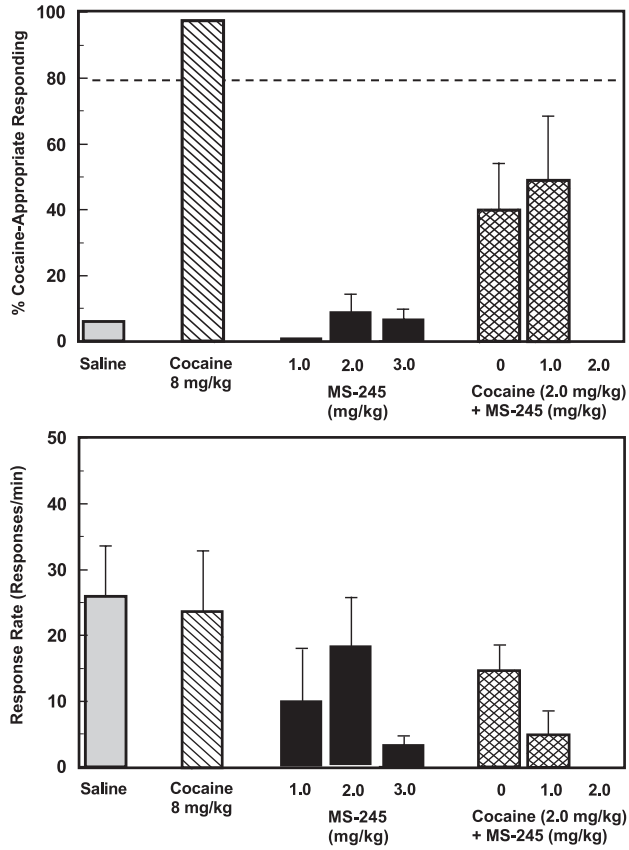

Fig. 2. Mean percent drug-appropriate responding (± S.E.M.) following saline, training dose of training drug [8.0 mg/kg of cocaine ($n = 5$)], doses of MS-245, and doses of MS-245 in combination with 2.0 mg/kg of cocaine (upper panel). MS-245 administered to cocaine-trained animals at 5.0 mg/kg, or administered at 2.0 mg/kg in combination with 2.0 mg/kg of cocaine, resulted in behavioral disruption. Animals' response rates under the different conditions are shown in the lower panel.

ity (i.e., Ki>10,000 nM) for human μ and κ opioid receptors, m_1-m_5 muscarinic receptors, *r*BZ receptors, *r*PCP receptors, *r*NMDA receptors, and the serotonin (SERT), norepinephrine (NET), and dopamine (DAT) transporters.

4. Discussion

It is well established that central stimulants, such as (+)amphetamine and cocaine, serve as effective discriminative stimuli in animals and that their stimulus effects are dependent, at least in part, on dopamine systems (Goudie, 1991; Woolverton, 1991; Young and Glennon, 1986). In the present study, neither stimulus generalized to MS-245 (Figs. 1 and 2). The lack of stimulus generalization between the training drug stimuli and that produced by the 5-HT_6 antagonist MS-245 indicates that the qualitative effects of MS-245 are different from those of the stimulants. This might not have been unexpected because biochemical studies have shown that administration of 5-HT_6 receptor antagonists, by themselves, have little effect on dopamine function (Dawson et al., 2002; Frantz et al., 2000). It also has been reported that 5-HT_6 receptor antagonists enhance amphetamine-induced, but not cocaine-induced, dopaminergic actions (Dawson et al., 2002; Frantz et al., 2000). The results presented here indicate that the administration of various doses of MS-245 in combination with the calculated ED_{50} dose of (+)amphetamine (which produced 56% amphetamine-appropriate responding when administered alone) resulted in increased amphetamine-appropriate responding; MS-245 enhanced the effect of (+)amphetamine (Fig. 1). That is, although the (+)amphetamine stimulus did not generalize to various doses of MS-245, administration of 5.0 mg/kg of MS-245 together with the ED_{50} dose of (+)amphetamine resulted in dose-related stimulus generalization. Apparently, MS-245 made (+)amphetamine appear more amphetamine-like to the (+)amphetamine-trained animals. In contrast, the administration of various doses of MS-245 in combination with the ED_{50} dose of cocaine (which produced 40% cocaine-appropriate responding when administered alone) failed to result in stimulus generalization (Fig. 2).

How might these different results with (+)amphetamine and cocaine in combination with MS-245 be reconciled? In drug discrimination studies, symmetrical generalization occurs between (+)amphetamine and cocaine regardless of which is used as training drug (reviewed: Goudie, 1991; Woolverton, 1991). Although the occurrence of stimulus generalization suggests that a challenge drug can produce stimulus effects similar to those of a particular dose of training drug, the agents need not share an identical mechanism of action. For example, although (+)amphetamine and cocaine substitute for one another, they are thought to produce their stimulus effects, to a significant extent, by different indirect actions on dopamine receptors: amphetamine primarily via release of presynaptic dopamine, and cocaine primarily via inhibition of dopamine reuptake (Goudie, 1991; Woolverton, 1991; Young and Glennon, 1986; for a general review of the mechanism of action of psychostimulants, see Webster, 2001). Perhaps 5-HT_6 receptor antagonists exert a modulatory effect on a dopamine-mediated discriminative stimulus when dopamine activity is enhanced as a result of increased levels of dopamine, but not the blockade of the dopamine reuptake process. In any case, the present results are consistent with other reports that 5-HT_6 receptor antagonists potentiate amphetamine-induced, but not cocaine-induced, behaviors, while at the same time having little effect on these behaviors when administered alone. Furthermore, the present results also extend previous findings (Dawson et al., 2002; Frantz et al., 2000) to include the discriminative stimulus actions of (+)amphetamine and cocaine, and broaden the structural types of 5-HT_6 antagonists that can influence the behavioral effects of (+)amphetamine to include MS-245.

Might MS-245 influence the amphetamine stimulus via a non-5-HT_6 mechanism? To this end, we obtained an extensive binding profile for MS-245. Although MS-245 is a high-affinity (Ki = 1.5 nM) and fairly selective 5-HT_6 receptor antagonist, it binds with only about 10-fold

selectivity for human 5-HT_6 versus dopamine D_1 receptors (Ki = 25 nM). In addition, there is evidence for involvement of a D_1 mechanism in the stimulus actions of amphetamine. For example, D_1 antagonists have been consistently shown to antagonize the stimulus effects of amphetamine in amphetamine-trained rats (e.g. Arnt, 1988; Callahan et al., 1991; Filip and Przegalinski, 1997; Furmidge et al., 1991; Nielsen et al., 1989) and to antagonize the stimulus effects of cocaine when administered in combination with cocaine to rats trained to discriminate cocaine from vehicle (e.g., Barrett and Appel, 1989, Callahan et al., 1991; Elliot et al., 2003; Filip and Przegalinski, 1997; Witkin et al., 1991). However, D_1 agonists generally fail to substitute for amphetamine (e.g., Arnt, 1988; Callahan et al., 1991; Filip and Przegalinski, 1997; Furmidge et al., 1991; Nielsen et al., 1989) or for cocaine (Callahan et al., 1991; Chausmer and Katz, 2002; Filip and Przegalinski, 1997; Witkin et al., 1991). The general consensus is that both D_1 and D_2 receptors are involved (at least in part) in the stimulus actions of amphetamine and cocaine, but that activation of D_1 dopamine receptors alone is not sufficient to produce the drug-like stimulus effects. Nevertheless, the possibility cannot be dismissed that the amphetamine-enhancing actions of MS-245 involve, at least to some extent, a D_1 agonist mechanism. Does this explain the difference seen upon coadministration of MS-245 with amphetamine and cocaine? Coadministration of a D_1 agonist in combination with cocaine in cocaine-trained animals has been demonstrated to have either little to no effect (e.g., Chausmer and Katz, 2002; Costanza and Terry, 1998; Rachna and Nader, 2001), to right-shift the cocaine dose–response curve (Chausmer and Katz, 2002; Spealman et al., 1997), or to left-shift the cocaine dose–response curve (Chausmer and Katz, 2002), depending upon the particular agonist employed. Consequently, the question is difficult to answer at this time. Additional studies will be required to determine if the potentiating action of MS-245 involves a direct D_1 agonist component of action. However, there is no indication that other 5-HT_6 antagonists (e.g., SB-271046 and SB-258510) act via a direct D_1 mechanism; that is, they influence dopaminergic mechanisms in an indirect manner. MS-245 also binds at 5-HT_6 receptors only with 30-fold selectivity over 5-HT_{2C} (Ki = 50 nM) receptors. Filip and Cunningham (2003) have recently demonstrated that 5-HT_{2C} ligands can modulate the stimulus effects of cocaine in rats, with a 5-HT_{2C} agonist producing a rightward shift of the cocaine dose–response curve, and an antagonist producing a leftward shift of the curve. Because MS-245 had no effect upon coadministration with cocaine, it does not seem very likely that 5-HT_{2C} mechanisms are involved in its actions. Considering the above findings, MS-245 is either producing its effects solely by a 5-HT_6 antagonist mechanism, or via a combination of indirect (i.e., 5-HT_6 antagonist) and direct (i.e., D_1 activation) dopaminergic mechanisms. Further investigation of possible involvement of the D_1 (and perhaps 5-HT_{2C}) aspects of the actions of MS-245 are certainly warranted.

The results of the present investigation have potential ramifications in drug abuse studies and in the development of novel drug therapies. If the impact of 5-HT_6 receptor antagonists is primarily on agents that act via dopamine release rather than blockade of dopamine reuptake, then these antagonists might be used to investigate the stimulus effects (and mechanisms of action) of other abused substances that are thought to act through one of these two mechanisms. It is also tempting to speculate on the effects that might be seen upon administration of an amphetamine-related drug of abuse in combination with a 5-HT_6 agonist. Theoretically, such an application could result in a blockade (via a 5-HT_6 receptor agonist action) of the discriminative stimulus and/or reinforcing effects of the abused substance; of course, this remains to be investigated. Finally, a number of drug discrimination studies have suggested that a relationship might exist between drug-induced stimulus effects in animals and subjective effects in humans (Colpaert and Slangen, 1982; Young and Glennon, 1986). If so, some speculations can be made concerning the potential clinical applications of 5-HT_6 receptor antagonists. That is, 5-HT_6 receptor antagonists might be administered together with medications that enhance dopamine neurotransmission and, in so potentiating the effects of these agents, might result in fewer undesirable side effects than would be evident upon administration of a higher dose of the dopaminergic agent alone. For example, levodopa/carbidopa or amantadine are known to be effective in the treatment of Parkinson's disease, and amphetamine and amphetamine-related agents have found application as anorectic agents; administration of 5-HT_6 antagonists in combination with lower doses of these agents might form the basis of a new type of "low-dose dopamine therapy." Obviously, further investigation is necessary to determine the exact nature of the 5-HT_6/dopamine receptor interaction and whether 5-HT_6/dopamine drug combinations might be clinically useful.

Overall, the results suggest that 5-HT_6 antagonists might possess therapeutic potential for application in modulating dopamine-mediated actions. Additional study is required, however, to determine if MS-245 is unique among the 5-HT_6 antagonists in its ability to perhaps directly influence D_1 (and perhaps 5-HT_{2C}) receptor actions as well.

Acknowledgements

This work was supported in part by DA-01642 and MH-60599.

References

Arnt J. The discriminative stimulus properties of the D-1 agonist SK&F 38393 and the D-2 agonist (−)-NPA are mediated by separate mechanisms. Life Sci 1988;42:565–74.

Barrett RL, Appel JB. Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. Psychopharmacology 1989;99:13–6.

Callahan PM, Appel JB, Cunningham KA. Dopamine D1 and D2 mediation of the discriminative stimulus properties of D-amphetamine and cocaine. Psychopharmacology 1991;103:50–5.

Chausmer AL, Katz JL. Comparison of interactions of D_1-like agonists, SKF 81297, SKF 82958 and A-77636, with cocaine: locomotor activity and drug discrimination studies in rodents. Psychopharmacology 2002;159:145–53.

Colpaert FC, Slangen JL, editors. Drug discrimination: applications in CNS pharmacology. Amsterdam: Elsevier; 1982.

Costanza RM, Terry P. The dopamine D4 antagonist L-745,870: effects in rats discriminating cocaine from saline. Eur J Pharmacol 1998;345: 129–32.

Dawson LA, Nguyen HQ, Li P. The 5-HT_6 receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex. Neuropharmacology 2001;25:662–8.

Dawson LA, Nguyen HQ, Li P. Potentiation of amphetamine-induced changes in dopamine and 5-HT by a 5-HT_6 receptor antagonist. Brain Res Bull 2002;59:513–21.

Elliot EE, Sibley DR, Katz JL. Locomotor and discriminative-stimulus effects of cocaine in dopamine D5 receptor knockout mice. Psychopharmacology 2003;169:161–8.

Filip M, Cunningham KJ. Hyperlocomotive and discriminative stimulus effects of cocaine are under control of serotonin$_{2C}$ (5-HT_{2C}) receptors in rat prefrontal cortex. J Pharmacol Exp Ther 2003;306:734–43.

Filip M, Przegalinski E. The role of dopamine receptor subtypes in the discriminative stimulus effects of amphetamine and cocaine in rats. Pol J Pharmacol 1997;49:21–30.

Frantz KJ, Hansson KJ, Stouffer DG, Parsons LH. 5-HT_6 receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. Neuropharmacology 2000;42:170–80.

Furmidge LJ, Exner M, Clark D. Role of dopamine D_1 and D_2 receptors in mediating the D-amphetamine discriminative cue. Eur J Pharmacol 1991;202:191–9.

Glennon RA. Higher end serotonin receptors: 5-HT_5, 5-HT_6, and 5-HT_7. J Med Chem 2003;46:2795–812.

Glennon RA, Jarbe TUC, Frankenheim J, editors. Drug discrimination: application in drug abuse research. NIDA Research Monograph, vol. 116. Washington (DC): U.S. Government Printing Office; 1991.

Glennon RA, Young AM, Martin BR, DalCason TA. Methcathinone (''Cat''): an enantiomeric potency comparison. Pharmacol Biochem Behav 1995;50:601–6.

Glennon RA, Lee M, Rangisetty JB, Dukat M, Roth BL, Savage JE, et al. 2-Substituted tryptamines: agents with selectivity for 5-HT_6 receptors. J Med Chem 2000;43:1011–8.

Goudie AJ. Discriminative stimulus properties of amphetamine, cathinone, and related agents. In: Glennon RA, Jarbe TUC, Frankenheim J, editors. Drug discrimination: applications to drug abuse research. NIDA Research Monograph, vol. 116. Washington (DC): U.S. Government Printing Office; 1991. pp. 45–60.

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

Nielsen EB, Randrup K, Andersen PH. Amphetamine discrimination: effects of dopamine receptor agonists. Eur J Pharmacol 1989;160: 253–62.

Rachna SS, Nader MA. Modulation of cocaine's discriminative stimulus effects by dopamine D1 agonists in rhesus monkeys. Pharmacol Biochem Behav 2001;68:301–9.

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

Slassi A, Isaac M, O'Brien A. Recent progress in 5-HT_6 receptor antagonists for the treatment of CNS diseases. Expert Opin Ther Pat 2002; 12:513–27.

Spealman RD, Bergman J, Rosenzweig-Lipson S. Differential effects of cocaine by low-efficacy and high-efficacy D_1 agonists. Psychopharmacology 1997;133:282–92.

Webster RA. Dopamine (DA). In: Webster RA, editor. Neurotransmitters, drugs and brain function. New York: Wiley; 2001. pp. 137–61.

Witkin JM, Nichols DE, Terry P, Katz JL. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J Pharmacol Exp Ther 1991;257:706–13.

Woolverton WL. Discriminative stimulus effects of cocaine. In: Glennon RA, Jarbe TUC, Frankenheim J, editors. Drug discrimination: applications to drug abuse research. NIDA Research Monograph, vol. 116. Washington (DC): U.S. Government Printing Office; 1991. pp. 61–74.

Young R, Glennon RA. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Med Res Rev 1986;6:99–130.

Young R, Glennon RA. Cocaine-stimulus generalization to two new designer drugs: methcathinone and 4-methylaminorex. Pharmacol Biochem Behav 1993;45:229–31.