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ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 203 – 207
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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The 5-HT$_3$ receptor partial agonist MD-354 (*meta*-chlorophenylguanidine) enhances the discriminative stimulus actions of (+)amphetamine in rats

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Received 6 November 2006; received in revised form 5 March 2007; accepted 22 March 2007
Available online 30 March 2007

Abstract

The effect of the 5-HT$_3$ receptor partial agonist MD-354 (*meta*-chlorophenylguanidine) was examined on the discriminative stimulus produced by (+)amphetamine. Using male Sprague–Dawley rats trained to discriminate 1.0 mg/kg (i.p.) of (+)amphetamine from saline vehicle (VI 15-s schedule of reinforcement) in a two-lever operant procedure for appetitive reward, tests of stimulus generalization (substitution) and antagonism showed that MD-354 neither substituted for, nor antagonized, the amphetamine stimulus at the doses evaluated. Administration of (+) amphetamine doses in combination with a fixed (i.e., 1.0 mg/kg) dose of MD-354 shifted the (+)amphetamine dose–response curve to the left such that, following 0.3 mg/kg of (+)amphetamine, stimulus generalization occurred. Furthermore, MD-354 doses of 0.1, 0.3 and 1.0 mg/kg, but not doses of 0.01, 0.5, 1.5 or 3.0 mg/kg (i.p.), administered in combination with the ED$_{50}$ dose (0.33 mg/kg) of (+)amphetamine resulted in stimulus generalization (i.e., >80% drug-appropriate responding). It is concluded that even though MD-354 lacks amphetamine-like central stimulant actions of its own it can modulate the discriminative stimulus effects of (+)amphetamine in rats.

Keywords: (+)Amphetamine; MD-354; *meta*-Chlorophenylguanidine; 5-HT$_3$ receptors; 5-HT$_3$ antagonists; Drug discrimination

1. Introduction

Although the discriminative stimulus produced by (+) amphetamine in rats seems to be, primarily, dopaminergically-mediated (Brauer et al., 1997; Young and Glennon, 1986), the neurotransmitter serotonin has been implicated as a modulator of this effect. For example, whereas the 5-HT$_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) failed to substitute for (+)amphetamine (Marona-Lewicka and Nichols, 1997), and the 5-HT$_2$ antagonists ketanserin and MDL 100,907 had no effect on the stimulus actions of (+)amphetamine (Moser et al., 1996; West et al., 1995), the stimulus effects of doses of amphetamine lower than those used as training dose were potentiated by DOI pretreatment (Marona-Lewicka and Nichols, 1997). In addition, the 5-HT$_{1A/7}$ serotonin receptor agent 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (8-OH DPAT) also failed to either substitute for, or antagonize, a (+)amphetamine stimulus (Przegalinski and Filip, 1997; Young et al., 2006) yet, administered together with low doses of training drug, 8-OH DPAT effectively enhanced the stimulus actions of (+)amphetamine in rats (Young et al., 2006). Likewise, the 5-HT$_6$ receptor antagonist MS-245 failed to substitute for, or antagonize, a (+) amphetamine stimulus, but enhanced the actions of low doses of the training drug when given in combination (Pullagurla et al., 2004). To date, there is mounting evidence that particular subpopulations of 5-HT receptors might be involved in modulating the discriminative stimulus effects of (+)amphetamine in rats.

In addition to a possible role for 5-HT$_2$, 5-HT$_{1A/7}$ and 5-HT$_6$ receptors, there is evidence that 5-HT$_3$ receptors also might influence the stimulus actions of (+)amphetamine. 5-HT$_3$ receptors are associated with release of dopamine in several brain areas (reviewed: Grant, 1995) making this receptor subpopulation of particular interest in investigations of agents whose various actions might involve a dopaminergic mechanism. However, of several 5-HT$_3$ antagonists examined (including MDL-72,222, ondansetron, tropisetron, and zacopride), none was

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0091-3057/$ - see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.pbb.2007.03.008

shown to either substitute for, or antagonize, the stimulus effects of (+)amphetamine in rats (Glennon et al., 1992; Moser, 1992; West et al., 1995). Nevertheless, tropisetron potentiated the discriminative stimulus effects of a low dose of (+)amphetamine in (+)amphetamine-trained rats when given in combination (West et al., 1995). Thus, 5-HT_3 receptors might play a modulatory role in the discriminative stimulus actions of amphetamine.

The purpose of the current study was to examine the effect of a 5-HT_3 receptor agonist, specifically MD-354 (*meta*-chlorophenylguanidine; *m*CPG) (Dukat et al., 1996, 2007), on a (+) amphetamine stimulus. The measured partition coefficient of MD-354 (Log*P*=−0.64) is such that it might not be expected to readily penetrate the blood–brain barrier (Rahman et al., 2003). However, the structurally related 5-HT_3 agonist *meta*-chlorophenylbiguanide (*m*CPBG) possesses a similar partition coefficient (Log*P*=−0.38) (Rahman et al., 2003) and has been shown to be brain penetrant (Kilpatrick and Rogers, 1993) in rats, although not in mice (Bachy et al., 1993). Furthermore, MD-354 served as an effective discriminative stimulus in rats (Dukat et al., 2000) and the MD-354 stimulus was potently antagonized by the 5-HT_3 receptor antagonists tropisetron and zacopride, but not by tropisetron methiodide — a quaternary amine analog of tropisetron that retains 5-HT_3 antagonist action but that does not readily penetrate the blood–brain barrier (Dukat et al., 2000). These results suggested that the MD-354 stimulus is 5-HT_3-receptor mediated, and is probably of a central nature (Dukat et al., 2000). It was also shown that MD-354, depending on the doses employed, can act both as an agonist and an antagonist in a shrew emesis assay, further suggesting that MD-354 is a 5-HT_3 receptor partial agonist (Dukat et al., 2000).

In the present investigation, we sought to determine whether MD-354 would either substitute for, or antagonize, an amphetamine stimulus in rats trained to discriminate (+) amphetamine from saline vehicle. In addition, the effect of MD-354 in combination with low doses of (+)amphetamine was examined to determine if it might modulate the amphetamine stimulus.

2. Materials and methods

2.1. Drug discrimination studies

A turnover in personnel resulted in rats being trained to discriminate (+)amphetamine from saline vehicle in two stages. The first group of four animals was employed in the MD-354 stimulus generalization and antagonism studies. A second group of animals (n=7) was later trained to discriminate 1.0 mg/kg of (+)amphetamine from saline vehicle, and was used for the remainder of the studies described here; their training is described below. The procedures employed in the training of each group of animals were identical.

Seven male Sprague–Dawley rats (Charles River Laboratories), weighing 250–300 g at the beginning of the study, were trained to discriminate (15-min pre-session injection interval) 1.0 mg/kg of (+)amphetamine from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reinforcement for sweetened condensed milk reward using standard, two-lever, Coulbourn Instruments (Allentown, PA) operant equipment. Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

In brief, animals were partially food-restricted to maintain body weights of approximately 80% that of their free-feeding weight, but were allowed free access to water in their individual home cages. Daily training sessions were conducted with either the training dose of (+)amphetamine or saline. For approximately half the animals, the right lever was designated as the drug-appropriate lever, whereas the situation was reversed for the remainder of the animals. Learning was assessed every fifth day during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. Data collected during the extinction session included number of responses on the drug-appropriate (i.e., amphetamine-appropriate) lever (expressed as a percent of total responses) and response rate (i.e., responses per minute). Animals were not used in subsequent stimulus generalization or combination studies until they consistently 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 0.9% saline vehicle. During the testing (i.e., stimulus generalization or drug combination) phase of the study, maintenance of the training drug/saline discrimination was insured by continuation of the training sessions on a daily basis

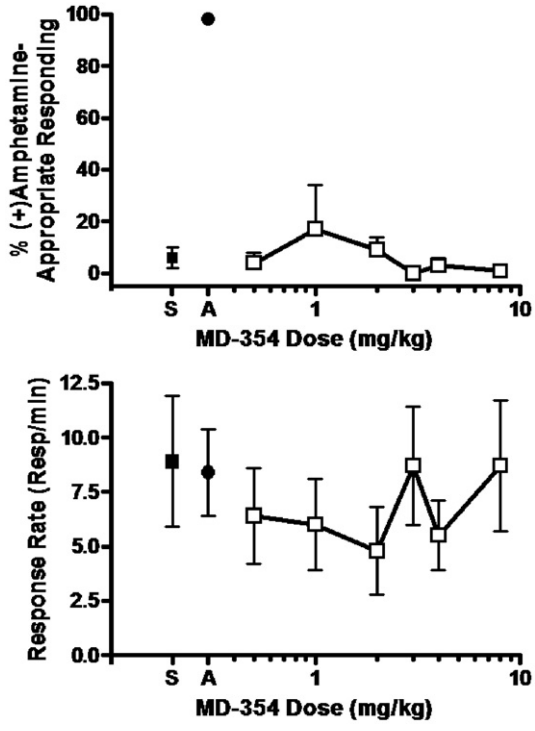

Fig. 1. Results of stimulus generalization studies in rats (n=4) trained to discriminate 1.0 mg/kg of (+)amphetamine from saline vehicle. Shown is the mean (±S.E.M.) percent drug-appropriate responding following administration of MD-354 doses (upper panel); *S* = effect of saline (1 ml/kg), and *A*=effect of (+)amphetamine (1 mg/kg). The animals' response rates (±S.E.M.) are shown in the lower panel.

(except on a test day). On one of the two days prior to a generalization or combination test, approximately half the animals would receive the training dose of (+)amphetamine and the remainder would receive saline; after a 2.5-min extinction session, training was continued for an additional 12.5 min. Animals not meeting the original training criteria during the extinction session were excluded from the subsequent antagonism, combination, or generalization test session. During investigations of stimulus generalization, or in combination tests, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under non-reinforcement conditions. An odd number of training sessions (usually 5) separated any two test sessions. Doses of test drug were administered to the rats in a random order using, generally, a 15-min pre-session injection interval. (+)Amphetamine and saline were always administered 15 min prior to testing. MD-354 was administered 15 prior to testing in the stimulus generalization study shown as Fig. 1, but in combination studies MD-354 was administered 15 min prior to administration of (+) amphetamine. [It might be noted that a few MD-354 doses were examined alone in the (+)amphetamine-trained animals using a 30-min pretreatment time and the results were consistent with what was observed at the 15-min interval (i.e., <10% drug-appropriate responding).] A determination of complete, partial, or no generalization (or antagonism) was predicated on previously described criteria (Glennon et al., 1983; Young and Glennon 1986). Thus, stimulus generalization was considered to have occurred (i.e., is defined as) when the animals, after a given dose of drug, or drug combination, made ≥80% of their responses (group mean) on the training drug-appropriate lever, whereas antagonism was considered to have occurred when the animals made ≤20% (group mean) drug-appropriate responding following a drug combination. Animals making fewer than 5 total responses during the 2.5-min extinction session were considered as being behaviorally disrupted. Percent drug-appropriate responding and response rate data refer only to animals making ≥5 responses during the extinction session (Young and Glennon, 1986). If >50% of the animals were disrupted following administration of a given drug dose, or dose combination, data were not plotted. Where applicable, an ED_{50} dose was calculated by the method of Finney (1952). The ED_{50} dose represents the drug dose where animals would be expected to make 50% of their responses on the drug-appropriate lever.

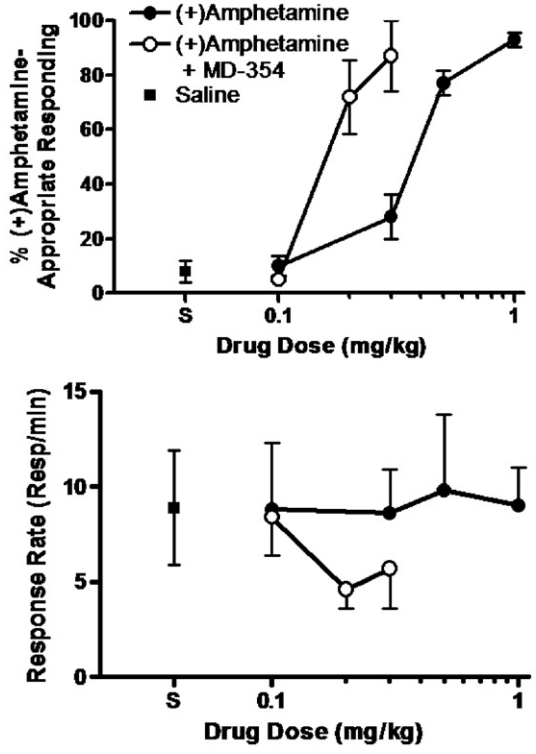

Fig. 2. Results of stimulus generalization studies in rats ($n=7$) trained to discriminate 1.0 mg/kg of (+)amphetamine from saline vehicle with (+) amphetamine alone, or (+)amphetamine in combination with 1 mg/kg of MD-354. Shown is mean (±S.E.M.) percent drug-appropriate responding; S = effect of saline (1 ml/kg) (upper panel). The animals' response rates (±S.E.M.) are shown in the lower panel.

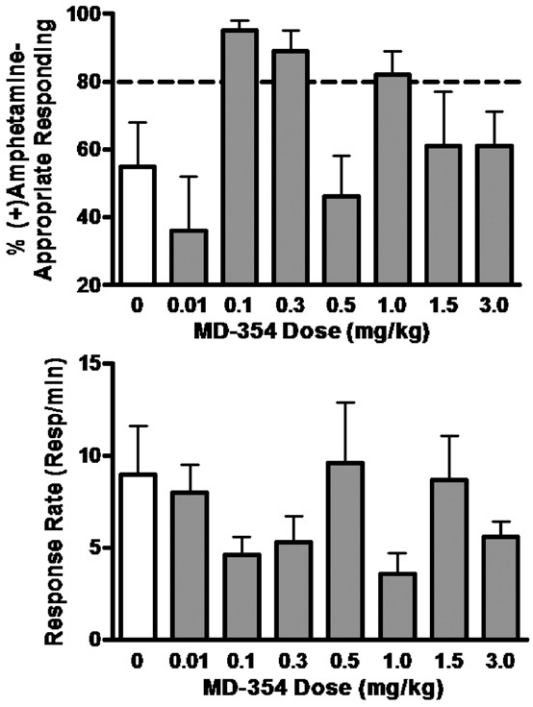

Fig. 3. Results of combination studies in rats ($n=7$) trained to discriminate 1.0 mg/kg of (+)amphetamine from saline vehicle. Shown is the mean (±S.E.M.) percent drug-appropriate responding following administration of the ED_{50} dose of (+) amphetamine (0.33 mg/kg) alone (i.e., where the MD-354 dose=0) and in the presence of MD-354 doses (upper panel). The animals' response rates (±S.E.M.) are shown in the lower panel.

2.2. Drugs

(+)Amphetamine sulfate (Sigma-Aldrich; St. Louis, MO) was available from previous studies conducted in our laboratories and *meta*-chlorophenylguanidine nitrate (MD-354) was synthesized in our laboratories as previously described (Dukat et al., 1996). Doses refer to the weight of the salts. Solutions in sterile 0.9% saline were freshly prepared each day and administered by intraperitoneal (i.p.) injection using an injection volume of 1.0 ml/kg.

3. Results

3.1. Drug discrimination studies

MD-354 was administered to the first group of (+) amphetamine-trained animals alone, and in combination with the training dose of (+)amphetamine. MD-354 doses ranging from 0.5 to 8.0 mg/kg failed to elicit >20% drug-appropriate responding (Fig. 1). Administration of a higher (i.e., 10 mg/kg) dose of MD-354 to the (+)amphetamine-trained animals resulted in behavioral disruption (data not plotted). Administration of 2.0 mg/kg of MD-354 together with 1.0 mg/kg of (+) amphetamine produced 99(±1)% drug-appropriate responding, whereas following a dose of 4.0 mg/kg of MD-354 in combination with 1.0 mg/kg of (+)amphetamine, the animals failed to respond (data not shown).

In the second group of animals trained to discriminate 1.0 mg/kg of (+)amphetamine (ED_{50}: 0.33 (95%CL=0.18–0.61) mg/kg) from vehicle, the animals were pretreated with 1.0 mg/kg of MD-354, and the effect of various (+) amphetamine doses was examined (Fig. 2). The MD-354 pretreatment resulted in a leftward shift of the (+)amphetamine dose–effect curve such that an amphetamine dose of 0.3 mg/kg, a dose nearly comparable to the ED_{50} dose of (+)amphetamine when administered alone, elicited 87% drug-appropriate responding under these conditions.

Administration of the ED_{50} dose (i.e., 0.33 mg/kg of (+) amphetamine to the animals produced 55% drug-appropriate responding (Fig. 3). MD-354 doses ranging from 0.01 to 3.0 mg/kg were administered in combination with the ED_{50} dose of (+)amphetamine (Fig. 3). Following MD-354 doses of 0.1, 0.3, and 1.0 mg/kg in combination with the ED_{50} dose of (+)amphetamine, the animals made >80% of their responses on the drug-appropriate lever. However, following MD-354 doses of 0.5, 1.5, and 3.0 mg/kg, the animals made 46%–61% of their responses on the drug-appropriate lever. One animal failed to respond at each of the two highest MD-354 doses examined. MD-354 doses of 0.5 and 1.0 mg/kg were subsequently reinvestigated on separate occasions. The results of the re-examination replicated the results of the initial experiment: the animals made 58(±16)% and 87(±13)% of their responses on the drug-appropriate lever following MD-354 doses of 0.5 and 1.0 mg/kg, respectively, in combination with the ED_{50} dose of (+)amphetamine.

4. Discussion

The present investigation examined the effect of MD-345, a 5-HT_3 (partial) agonist, on a (+)amphetamine stimulus. It was found that MD-354 neither substituted for (Fig. 1) nor antagonized the stimulus effects of the training drug. However, in three separate experiments, it was found that co-administration of certain doses of MD-354 with a low dose of (+) amphetamine resulted in increased percent drug-lever responding. That is, co-administration of these MD-354 doses with a dose of (+)amphetamine (0.3 or 0.33 mg/kg) equivalent (or nearly so) to its ED_{50} dose, resulted in stimulus generalization. Taken together, the findings are similar to the results reported previously for the effect(s) of the 5-HT_3 receptor antagonist tropisetron in amphetamine-trained animals: tropisetron neither substituted for nor antagonized the stimulus effects of (+) amphetamine in rats whereas its co-administration with a low dose of (+)amphetamine resulted in enhanced drug-appropriate responding (West et al., 1995).

The stimulus-enhancing effect of MD-354 also seems to be multi-phasic. That is, whereas MD-354 doses of 0.1, 0.3, and 1.0 mg/kg enhanced the stimulus actions of (+)amphetamine, doses of 0.5, 1.5, and 3.0 mg/kg did not (Fig. 3). Previous studies have shown that 5-HT_3 receptor antagonists often produce bi-phasic dose–effect curves in various pharmacological assays (e.g. Costall et al., 1990). The reasons for this remain to be determined. Because there is some evidence that MD-354 is a 5-HT_3 receptor partial agonist (Dukat et al., 2000), MD-354 might be acting as a 5-HT_3 receptor antagonist when given in combination with (+)amphetamine. Indeed, MD-354 already has been shown to function in some assays as a 5-HT_3 receptor antagonist (Dukat and Wesolowska, 2005). One possibility, then, is that the partial agonist MD-354 is acting as a 5-HT_3 receptor antagonist to enhance the stimulus effects of (+) amphetamine. Another possibility is that at some doses MD-354 behaves as a 5-HT_3 agonist and at other doses as a 5-HT_3 antagonist to result in the observed bi-phasic response. Obviously, this explanation will require further investigation.

Although MD-354 is a reasonably selective 5-HT_3 receptor ligand, it also binds with nearly equivalent affinity at α_{2B}-adrenoceptors (Wesolowska et al., 2004). Thus, the possibility exists that the effects seen in the present investigation might involve an adrenergic rather than (or in addition to) a 5-HT_3 serotonergic mechanism. Although it has been reported that neither activation nor blockade of adrenoceptors is sufficient to alter the discriminative stimulus properties of (+)amphetamine (West et al., 1995), arguments can be made for, or against, this concept. For example, various α- and β-adrenoceptor agents are without effect on the stimulus actions of (+)amphetamine in the rat; examples of agents examined include prazosin (α_1-adrenoceptor antagonist), clonidine (α_2-adrenoceptor agonist), idazoxan (α_2-adrenoceptor antagonist), yohimbine (α_2-adrenoceptor antagonist), salbutamol (β-adrenoceptor agonist), and propranolol (β-adrenoceptor antagonist) (Sanger, 1988; Schechter and Cook, 1975; West et al., 1995). On the other hand, these studies examined adrenergic agents for substitution or antagonism of the training doses of (+)amphetamine, but not the possibility that they might exert a modulatory influence on doses of (+)amphetamine lower than those of the training dose. This is something that will need to be addressed in the future.

The present investigation adds further support to the concept that serotonergic interactions might influence the stimulus actions of (+)amphetamine. Furthermore, taken together, the modulatory effects of several types of serotonergic agents seem to be comparable in (+)amphetamine- and (+)methamphetamine-trained rats. For example, i) (+)methamphetamine-stimulus generalization failed to occur to 8-OH DPAT, DOI, or tropisetron, ii) neither 8-OH DPAT, ketanserin, nor tropisetron antagonized the (+)methamphetamine stimulus, but iii) pretreatment of the

animals with 8-OH DPAT, DOI, or tropisetron resulted in a leftward shift of the (+)methamphetamine dose–response curve (Munzar et al., 1999).

Overall, then, it was shown in the present investigation that although the 5-HT_3 partial agonist MD-354 neither substitutes for nor antagonizes a (+)amphetamine stimulus in rats (at the doses and dose combinations examined), it enhances the discriminative stimulus effects of low doses of (+)amphetamine in rats. This latter effect was demonstrated by examining several doses of MD-354 with a fixed dose of (+)amphetamine, and by examining several doses of (+)amphetamine with a fixed dose of MD-354. A parsimonious explanation for the present results is that MD-354 is acting through a 5-HT_3 receptor mechanism. Given that MD-354 is a partial agonists that can function as a 5-HT_3 receptor antagonist in some assays, together with the similarity of the present results with the findings of West et al. (1995) using a 5-HT_3 receptor antagonist, it seems likely that the (+)amphetamine stimulus-enhancing effect of MD-354 involves, at least in part, an antagonist action at 5-HT_3 receptors.

Acknowledgments

This work was supported in part by DA 01642 (RAG) and by J-778 from the Jeffress Foundation (MD).

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