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PMMA-stimulus generalization to the optical isomers of MBDB and 3,4-DMA

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Abstract

Psychoactive phenylisopropylamines can produce one or more of several different stimulus effects in animals. These effects are typified by the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), the central stimulant amphetamine, and by N-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA), an agent whose actions are not yet well understood. The optical isomers of two phenylisopropylamines known to lack DOM and amphetamine-stimulus character, that is N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminobutane (MBDB) and 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-DMA), were examined in rats trained to discriminate 1.25 mg/kg of PMMA from vehicle. The PMMA stimulus ($ED_{50} = 0.4$ mg/kg) generalized to all four agents: $S(+)$-MBDB ($ED_{50} = 0.8$ mg/kg), $R(-)$-MBDB ($ED_{50} = 2.0$ mg/kg), $S(+)$-3,4-DMA ($ED_{50} = 2.6$ mg/kg) and $R(-)$-3,4-DMA ($ED_{50} = 3.9$ mg/kg). The results show that these agents produce stimulus effects similar to those produced by PMMA. Both isomers of MBDB have been previously demonstrated to substitute for N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) in rats trained to discriminate MDMA from vehicle, but MBDB-trained animals failed to recognize DOM or amphetamine. Similar results were obtained with the 3,4-DMA optical isomers in the present investigation using rats trained to discriminate MDMA, DOM or (+)-amphetamine from vehicle; both isomers of 3,4-DMA substituted for an MDMA stimulus, but not for a DOM or amphetamine stimulus. Taken together, the evidence suggests that PMMA, $S(+)$-MBDB, $R(-)$-MBDB, $S(+)$-3,4-DMA, $R(-)$-3,4-DMA, and $S(+)$-MDMA can produce common stimulus effects in rats. The present findings also better define the PMMA stimulus and the structural requirements necessary to produce this type of stimulus effect. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: PMMA; Amphetamine; MBDB; 3,4-DMA; MDMA; DOM; Hallucinogens; Designer drugs

1. Introduction

Phenylisopropylamines represent a very broad and interesting series of psychoactive substances that produce one or more of several different discriminative stimulus effects in animals depending upon the identity of substituent groups in the molecule (Glennon, 1989). For example, the stimulus produced by 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), a hallucinogenic agent, is different from that produced by amphetamine, a central stimulant. A third type of stimulus effect is that produced by N-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA) (Glennon et al.,

1997) (see Fig. 1 for chemical structures). Although the stimulus effects of PMMA are poorly understood, it is clear that they are different from those of either DOM or amphetamine (Glennon et al., 1997). The goal of the present investigation was to better define the PMMA stimulus. To this extent, we examined the stimulus effects of the optical isomers of N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminobutane (MBDB) and 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-DMA) in rats trained to discriminate PMMA from saline vehicle.

N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA; also known as Ecstasy, XTC, X and e), classified as a Schedule I substance, is a very popular and widely used phenylisopropylamine (Schedules of Controlled Substances, 1986). For example, it has been estimated that 0.5% to 3% of the adult population of Europe has experienced MDMA (Christophersen, 2000). In humans,

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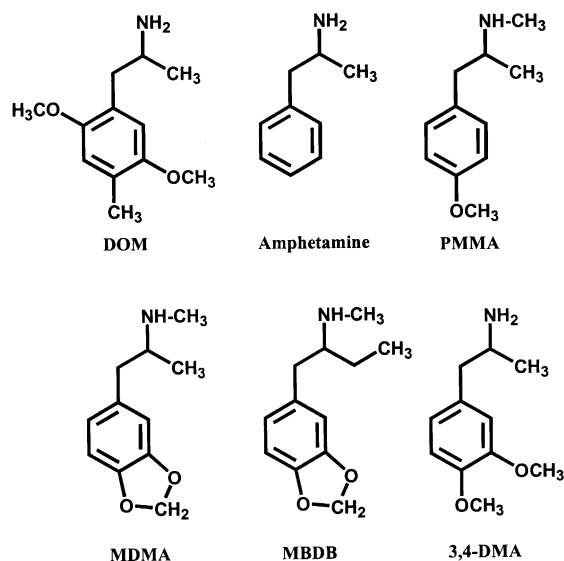*E-mail address*: glennon@hsc.vcu.edu (R.A. Glennon).

Fig. 1. Chemical structures of racemic DOM, amphetamine, PMMA, MDMA, MBDB, and 3,4-DMA.

MDMA produces what is commonly referred to as an empathogenic effect (increased sociability, enhanced feelings of empathy, openness of communication) (Hegadoren et al., 1999; Peroutka, 1990). Administered to animals trained to discriminate either DOM, (+)-amphetamine, or PMMA from vehicle, MDMA failed to substitute for DOM, but substituted for (+)-amphetamine (Glennon et al., 1982) and PMMA (Glennon et al., 1997). MDMA serves as a discriminative stimulus in animals (reviewed in Glennon, 1989; Nichols and Oberlender, 1989). Whereas the MDMA-stimulus failed to generalize to DOM, it generalized to (+)-amphetamine and PMMA (Glennon et al., 1997). MDMA, then, seems to possess more than a single component of stimulus action, and shares stimulus character both with amphetamine and PMMA (Glennon et al., 1997).

Attempts have been made to define the MDMA stimulus by determining which structural features of MDMA contribute to its stimulus actions. Questions being addressed include: What structurally related agents are capable of producing MDMA-stimulus effects, and what are the minimal structural requirements necessary to produce these effects? The issue is somewhat confounded by the finding that MDMA possesses some amphetaminergic character. But, structural manipulation of the MDMA molecule can reduce or eliminate amphetaminergic properties (Nichols et al., 1986). For example, unlike MDMA, its α-ethyl homolog MBDB (Fig. 1) has been reported to be a more selective substance in that it lacks the amphetaminergic actions of MDMA. This agent has been extensively investigated by Nichols and Oberlender (1989) and Nichols et al. (1986). Examined in rats trained to discriminate either MDMA, (+)-amphetamine or a hallucinogen from vehicle, MBDB substituted only for MDMA (Nichols and Oberlender, 1989). Similar results were obtained when S(+)-MBDB was used as training drug; that is, an S(+)-MBDB stimulus general-

ized to MDMA, but not to DOM or (+)-amphetamine (Oberlender and Nichols, 1990). Hence, MBDB and PMMA represent phenylisopropylamines that lack DOM and amphetamine stimulus character, but it is not known if they share common stimulus effects.

Another related phenylisopropylamine that failed to substitute for either a (+)-amphetamine or DOM stimulus is 3,4-DMA (Fig. 1) (Glennon et al., 1982) — also a Schedule I substance (Schedules of Controlled Substances, 1986). Due to its structural similarity to PMMA and MDMA, it was thought that 3,4-DMA might substitute for PMMA in PMMA-trained animals, but, interestingly, administration of racemic 3,4-DMA resulted only in a maximum of 70% PMMA-appropriate responding (Glennon et al., 1997). Despite the fact that 3,4-DMA does not produce stimulus effects similar to those produced by the hallucinogen DOM or the stimulant (+)-amphetamine, it does produce stimulus effects similar to those of MDMA's structural parent MDA [i.e., 1-(3,4-methylenedioxyphenyl)-2-aminopropane], an agent that produces DOM-like, (+)-amphetamine-like, and MDMA-like stimulus effects in animals (Glennon and Young, 1984). In fact, 3,4-DMA may be viewed as a ring-opened analog of MDA.

The purpose of the present investigation was to better characterize the PMMA stimulus, by examining in PMMA-trained animals two phenylisopropylamines (i.e., MBDB and 3,4-DMA), which possess structural similarity to PMMA but which lack amphetaminergic stimulus character. Because differences might exist in the actions of racemates and their optical isomers, we synthesized and evaluated the individual optical isomers of the two agents. We have already intimated that a PMMA stimulus might generalize to MBDB (Glennon et al., 1997). Furthermore, the high degree of substitution seen with racemic 3,4-DMA in PMMA-trained animals suggests that at least one of the optical isomers of 3,4-DMA might produce stimulus effects similar to those produced by PMMA. Nichols and Oberlender (1989) have previously demonstrated that MDMA-stimulus generalization occurs to both optical isomers of MBDB.

Having synthesized both optical isomers of 3,4-DMA, we also took advantage of their availability to also examine them in rats trained to discriminate MDMA from vehicle. These isomers have not been previously examined in MDMA-trained animals. A demonstration of similarity among the stimulus properties of PMMA, MDMA, MBDB, and 3,4-DMA would provide a greater understanding of the structural requirements necessary to produce PMMA-stimulus effects, and would allow better characterization of the PMMA stimulus. It would also provide a link among the stimulus properties of these structurally similar, yet structurally distinct, agents. Furthermore, although neither a (+)-amphetamine stimulus nor a DOM stimulus generalized to racemic 3,4-DMA, the optical isomers of 3,4-DMA have never been examined. To complete the present study, we investigated the

effect of $S(+)$- and $R(-)$-3,4-DMA in (+)-amphetamine-trained animals and in DOM-trained animals to determine if either isomer produces (+)-amphetamine or DOM-stimulus effects.

In brief, we conducted this investigation (a) to determine which, if either, optical isomer of MBDB would substitute for PMMA in PMMA-trained animals, (b) to determine which, if either, optical isomer of 3,4-DMA would substitute for PMMA in PMMA-trained animals, and (c) to determine if substitution would occur with 3,4-DMA optical isomers in groups of animals trained to discriminate either 1.5 mg/kg of MDMA, 1.0 mg/kg of (+)-amphetamine, or 1.0 mg/kg of DOM from saline vehicle.

2. Methods

2.1. Drug discrimination studies

The subjects were 25 male Sprague–Dawley rats (Charles River Laboratories) weighing 250–300 g at the beginning of the study. The animals were divided into four groups and trained to discriminate either 1.25 mg/kg of PMMA ($n=9$), 1.5 mg/kg of MDMA ($n=5$), 1.0 mg/kg of (+)-amphetamine ($n=6$), or 1.0 mg/kg of DOM ($n=5$) from saline vehicle as previously described (Glennon and Young, 2000; Glennon et al., 1982, 1985, 1988a, 1997). In brief, the animals were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this reduced level by partial food deprivation; the animals were allowed drinking water ad lib in their home cages. The rats were trained (15 min training session) to discriminate intraperitoneal injections (15 min presession injection interval) of either 1.25 mg/kg of PMMA, 1.5 mg/kg of MDMA, 1.0 mg/kg of (+)-amphetamine, or 1.0 mg/kg of DOM from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard two-lever operant equipment as previously described (Glennon and Young, 1984; Glennon et al., 1997). Daily training sessions were conducted with training drug or saline; on every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. For approximately half the animals, the left lever was designated the drug-appropriate lever whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percentage 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.

Tests of stimulus generalization (i.e., substitution) were conducted in order to determine if the training drug stimulus would generalize to the MBDB or 3,4-DMA optical isomers. During this 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; see below). On one of the two days before a generalization test, approximately half of the animals would receive the training dose of the 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 criteria (i.e., >80% of total responses on the drug-appropriate lever after administration of training drug, and <20% of total responses on the same lever after administration of saline) during the extinction session were excluded from the next 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; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of the test drugs were administered in a random order, using a 15-min presession injection interval, to groups of rats. Stimulus generalization was said 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. Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (1952). The ED_{50} doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

2.2. Drugs

N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA) and N-methyl-1-(4-methoxyphenyl)-2-aminopropane HCl (PMMA) were previously synthesized in our laboratories, and (+)-amphetamine sulfate was available from earlier investigations. $S(+)$- and $R(-)$-MBDB were synthesized as previously reported (Nichols et al., 1986). The individual optical isomers of 3,4-DMA have been previously reported (Schrecker, 1957); they were prepared by a literature procedure (Nichols et al., 1973) and used as their HCl salts. DOM was a gift from NIDA. Doses refer to the weight of the salt. All solutions

were prepared fresh daily and intraperitoneal injections were made 15 min prior to testing.

3. Results

The two optical isomers of MBDB and 3,4-DMA were synthesized and examined in rats trained to discriminate 1.25 mg/kg of PMMA from vehicle. The optical isomers of 3,4-DMA were also examined in rats trained to discriminate 1.5 mg/kg of MDMA, 1.0 mg/kg of (+)-amphetamine, or 1.0 mg/kg of DOM from vehicle. Administration of PMMA to the PMMA-trained animals (Fig. 2) showed a dose-dependent effect and PMMA was as potent ($ED_{50} = 0.4$ mg/kg; 95% CL = 0.3–0.7 mg/kg) as previously reported (i.e., $ED_{50} = 0.44$ mg/kg) (Glennon et al., 1997).

Administration of doses of both optical isomers of MBDB (five doses of the *S*-isomer and six doses of the *R*-isomer) to the PMMA-trained animals resulted in stimulus generalization (Fig. 2): *S*(+)-MBDB, $ED_{50} = 0.8$ (95% CL = 0.5–1.3) mg/kg; *R*(−)-MBDB, $ED_{50} = 2.0$ (95% CL = 1.1–3.6) mg/kg. Likewise, both isomers of 3,4-DMA substituted for the PMMA stimulus: *S*(+)-3,4-DMA, $ED_{50} = 2.6$ (95% CL = 1.3–4.1) mg/kg; *R*(−)-3,4-DMA, $ED_{50} = 3.9$ (95%CL = 2.1–7.4) mg/kg. In general, the animals' response rates were not very different from the response rates (9.7 ± 2.9 responses/min) following administration of the training dose of the training drug to the animals. Following administration of 4.0 mg/kg of *S*(+)-MBDB or 7.0 mg/kg of *R*(−)-3,4-DMA, the animals' responses rates were depressed by 30% to 50%, whereas following administration of 6.0 mg/kg of *S*(+)-3,4-DMA, the animals' response rates were doubled.

Administration of 1.5 mg/kg of MDMA to the MDMA-trained animals resulted in the animals making 93($\pm$3)% of their responses on the MDMA-appropriate lever, whereas

the animals made 5($\pm$2)% of their responses on the same lever following administration of saline (Fig. 3, upper panel). The animals' response rates following MDMA administration was 7.1 ± 1.8 responses/min and, following administration of saline, 10.4 ± 2.8 responses/min. The MDMA stimulus generalized both to *S*(+)-3,4-DMA ($ED_{50} = 6.1$ mg/kg; 95% CL = 4.5–8.4 mg/kg) and *R*(−)-3,4-DMA ($ED_{50} = 5.4$ mg/kg; 95% CL = 3.2–9.2 mg/kg). The animals' response rates following the administration of the 3,4-DMA isomers were similar to that following administration of 1.5 mg/kg of training drug except that 7.0 and 8.0 mg/kg of *S*(+)-3,4-DMA and 8.0 mg/kg of *R*(−)-3,4-DMA reduced the animals' response rates by approximately 50%.

Administration of *S*(+)-3,4-DMA to the (+)-amphetamine-trained animals resulted in a maximum of 28% (+)-amphetamine-appropriate responding and, at 9.0 mg/kg only half of the animals made >5 responses during the entire extinction session (Fig. 3, middle panel). *R*(−)-3,4-DMA produced a maximum of 30% (+)-amphetamine-appropriate responding, and at 6.0 mg/kg, fewer than half of the animals made >5 responses during the extinction session. The training dose of (+)-amphetamine elicited 97($\pm$1)% drug-appropriate responding. Response rates following administration of the various drug doses were similar to those observed following 1.0 mg/kg of (+)-amphetamine (9.3 ± 1.9 responses/min). In the DOM-trained animals, *S*(+)-3,4-DMA produced 30% DOM-appropriate responding (response rate = 9.3 ± 5.5 responses/min) at 5.0 mg/kg and 53% DOM-appropriate responding at 6.5 mg/kg (response rate = 4.4 ± 0.9 responses/min) (Fig. 3), and disrupted the animals' responding at 6.75 and 7.0 mg/kg, with only two of five animals responding at the latter two doses. *R*(−)-3,4-DMA produced 44% DOM-appropriate responding at 4.0 mg/kg and disrupted the animals at 4.25, 4.5, and 5.0 mg/kg with zero of five, one of five, and one of five animals responding, respectively, at each of these latter three doses.
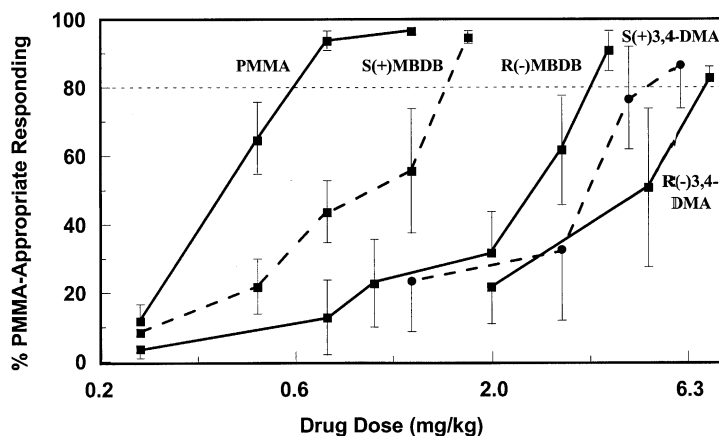

Fig. 2. Results of stimulus generalization studies with MBDB and 3,4-DMA optical isomers in rats trained to discriminate 1.25 mg/kg of PMMA from saline vehicle. Administration of 1.25 mg/kg of PMMA (**D**) elicited 97(± 1)% PMMA-appropriate responding whereas administration of saline (**S**) elicited 7(± 3)% responding on the same drug-appropriate lever.
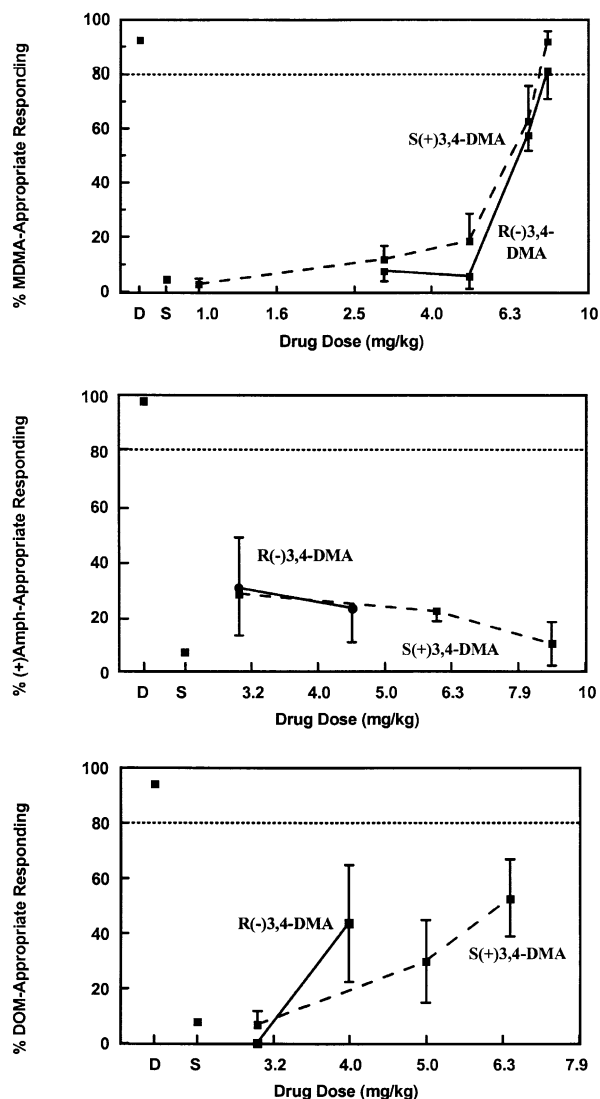
Fig. 3. Results of stimulus generalization studies with optical isomers of 3,4-DMA in rats trained to discriminate either 1.5 mg/kg of MDMA (upper panel), 1.0 mg/kg of (+)-amphetamine (middle panel), or 1.0 mg/kg of DOM (lower panel) from saline vehicle. In each case, **D** designates the effect of the training dose of the training drug whereas **S** designates the effect of saline vehicle.

Following administration of the training dose of DOM, the animals made $95(\pm 2)\%$ of their responses on the DOM-appropriate lever, response rate $= 6.8 \pm 2.3$ responses/min.

4. Discussion

The purpose of this investigation was to better understand the structural requirements necessary for producing PMMA-stimulus effects in rats by determining whether there was any similarity between the stimulus effects of PMMA, MBDB, and 3,4-DMA. MBDB is a structurally modified analog of MDMA that lacks the amphetaminergic actions of MDMA; yet, MBDB substitutes for MDMA

regardless of which of the two is used as training drug (Nichols and Oberlender, 1989; Oberlender and Nichols, 1990). Stimulus generalization also occurs between PMMA, a structurally abbreviated analog of MDMA that lacks amphetaminergic character (Glennon et al., 1988a), and MDMA regardless of which is used as training drug (Glennon and Higgs, 1992; Glennon et al., 1997). On this basis, we felt that PMMA and MBDB might share common stimulus properties (Glennon et al., 1997). The present results provide evidence supporting this concept. The PMMA stimulus generalized to both optical isomers of MBDB, and $S(+)$-MBDB (ED$_{50} = 0.8$ mg/kg) was about twice as potent as $R(-)$-MBDB (ED$_{50} = 2.0$ mg/kg). Nichols and Oberlender (1989) have shown previously that in MDMA-trained and $S(+)$-MBDB-trained animals, $S(+)$-MBDB is approximately twice as potent as its $R(-)$-enantiomer. Hence, regardless of training drug [i.e., PMMA, MDMA, or $S(+)$-MBDB], both isomers of MBDB substitute for the training stimulus and $S(+)$-MBDB is the more potent isomer.

Perhaps due to its structural relationship to other drugs of abuse, 3,4-DMA has been the object of investigation since the 1960s. However, relatively little pharmacology has been published on 3,4-DMA or its optical isomers. 3,4-DMA possesses a phenylisopropylamine skeleton common to amphetamine; but, it neither produces amphetamine-like locomotor stimulation in mice (van der Schoot et al., 1961), nor does it produce amphetamine-appropriate responding in rats trained to discriminate (+)-amphetamine from vehicle (Glennon et al., 1985). Its structural similarity to PMMA led us to evaluate 3,4-DMA in PMMA-trained animals. The PMMA stimulus generalized to both optical isomers. Although less potent than PMMA (ED$_{50} = 0.4$ mg/kg) or $S(+)$-PMMA (ED$_{50} = 0.32$ mg/kg) (Young et al., 1999), $S(+)$-3,4-DMA and $R(-)$-3,4-DMA were nearly equipotent and were only two to three times less potent than the corresponding optical isomers of MBDB. It does seem peculiar, however, that stimulus generalization occurred to each individual isomer of 3,4-DMA when the racemate produced only 70% PMMA-appropriate responding (Glennon et al., 1997). Nevertheless, a similar inconsistency of effects already has been noted with this agent; it was reported that neither optical isomer of 3,4-DMA produced effects on conditioned avoidance responding in rats similar to that produced by racemic 3,4-DMA (Barfknecht and Nichols, 1972).

An MDMA stimulus generalized to both optical isomers of MBDB (Nichols and Oberlender, 1989). The MDMA stimulus also generalized to $S(+)$- and $R(-)$-3,4-DMA (Fig. 3, upper panel), and here too, the two isomers were nearly equipotent (ED$_{50} = 6.1$ and 5.4 mg/kg, respectively). This provides additional support that there exists some commonality of effect among these agents.

Finally, to determine whether either optical isomer of 3,4-DMA can produce amphetamine-like or DOM-like stimulus effects, the isomers were examined in rats trained

to discriminate either (+)-amphetamine or DOM from vehicle (Fig. 3). In no instance did stimulus generalization occur. Interestingly, the isomers of 3,4-DMA disrupted the animals' behavior at doses comparable to or slightly below those that resulted in PMMA-stimulus generalization.

The results of the present investigation reveal that PMMA-stimulus generalization occurs to $S(+)$-MBDB, $R(-)$-MBDB, $S(+)$-3,4-DMA, and $R(-)$-3,4-DMA. As demonstrated (see Introduction and summary in Table 1), these agents fail to substitute for (+)-amphetamine in tests of stimulus generalization using (+)-amphetamine-trained animals. We have also shown that the PMMA stimulus generalizes to ($\pm$)-MDMA and $S(+)$-MDMA (Glennon et al., 1997), agents that substitute for (+)-amphetamine. Hence, all of these agents — those that retain amphetamine character (i.e., MDMA) and those that do not (i.e., MBDB and 3,4-DMA) — produce a common PMMA-stimulus effect in rats. Furthermore, PMMA ($ED_{50} = 0.4$ mg/kg) is the most potent agent of the group.

Since psychoactive phenylisopropylamines can produce one or more of at least three distinct types of discriminative stimuli in animals, the present findings can be viewed from several perspectives. To account for the different stimulus actions of DOM, amphetamine, and PMMA, and because certain agents can produce more that one type of stimulus effect, we have proposed that their stimulus actions might be related in an overlapping fashion (Glennon et al., 1997). We have demonstrated that MDMA is best classified as producing both amphetamine-like and PMMA-like stimulus effects (Glennon et al., 1997). Results from the present investigation, together with previously published data (Nichols and Oberlender, 1989), suggest that MBDB and 3,4-DMA, although capable of producing MDMA-like stimulus effects, are probably best represented as being PMMA-like. In other words, it is unlikely that these three agents have in common an amphetaminergic component of action. To this end, we have further characterized the PMMA stimulus. It should be emphasized that the results are valid for the specific training doses that have been employed; use of different training doses could, conceivably, give somewhat different results. We have also obtained additional detail regarding the types of structures that can produce this effect. For example, 3,4-DMA is the first example of a primary amine to which a PMMA stimulus has been shown to generalize. We have also demonstrated that 3,4-DMA, an agent known to be behaviorally active but whose actions have not yet been fully characterized, produces PMMA-like and MDMA-like stimulus effects in animals. Taken together, our results demonstrate that $S(+)$-MBDB, $R(-)$-MBDB, $S(+)$-3,4-DMA, $R(-)$-3,4-DMA (present study), $S(+)$-PMMA (Young et al., 1999), and $S(+)$-MDMA (Glennon et al., 1997) are all capable of producing a common stimulus effect in animals trained to discriminate PMMA from vehicle.

Table 1
Stimulus generalization profiles of agents used in the present investigation.[a]

Agent	Training drug			
	DOM	(+)-AMPH	MDMA	PMMA
DOM	G	NG	NG	NG
(+)-AMPH	NG	G	G	NG
PMMA	NG	NG	G	G
$S(+)$-MDMA	NG	G	G	G
$R(-)$-MDMA	NG	NG	G	NG
$S(+)$-MBDB	NG[b]	NG[c]	G[c]	G
$R(-)$-MBDB	NG[b]	NG[c]	G[c]	G
$S(+)$-3,4-DMA	NG	NG	G	G
$R(-)$-3,4-DMA	NG	NG	G	G

[a] NG = No stimulus generalization (i.e., >80% drug-appropriate responding failed to occur); **G** = generalization (i.e., >80% drug-appropriate responding occurred). Shaded results are from the present study. Most other data are primarily from our laboratories and have been previously reported (Glennon, 1989; Glennon et al., 1988b, 1997).

[b] The hallucinogen LSD was used as training drug (Nichols and Oberlender, 1989).

[c] Data from Nichols and Oberlender (1989).

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