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Effect of PMA optical isomers and 4-MTA in PMMA-trained rats☆

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Abstract

1-(4-Methoxyphenyl)-2-aminopropane (PMA) and its sulfur analog, 1-(4-methylthiophenyl)-2-aminopropane (4-MTA), have been misrepresented as the controlled substance analog, N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA; ''Ecstasy''). Because MDMA has been shown to produce both amphetamine-like and *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA)-like stimulus effects in rats, we examined *S*(+)PMA, *R*(−)PMA and 4-MTA in rats trained to discriminate either PMMA (1.25 mg/kg) or (+)amphetamine (1.0 mg/kg) from saline vehicle. The sulfur analog of PMMA (i.e., 4-MTMA) was also examined. The PMMA stimulus generalized to *R*(−)PMA (ED_{50} = 0.4 mg/kg), whereas *S*(+)PMA produced a maximum of 72% PMMA-appropriate responding. 4-MTA (ED_{50} = 0.3 mg/kg) also substituted for PMMA, but 4-MTMA produced a maximum of only 36% PMMA-appropriate responding. None of the four agents substituted for (+)amphetamine. Hence, like MDMA, *R*(−)PMA and 4-MTA are capable of producing PMMA stimulus effects in rats, but unlike MDMA, neither agent substituted for (+)amphetamine.

Keywords: MDMA; Amphetamine; Designer drugs

1. Introduction

Illicit use of the controlled substance analog (i.e., designer drug), *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA; ''Ecstasy,'' ''X,'' ''e''), is reaching epidemic proportions (Hall, 2001). Several other phenylalkylamines gaining recent notoriety on the clandestine market are either being misrepresented as MDMA, are being used to lace tablets or capsules of MDMA or are simply claimed to be new designer drugs (Byard et al., 1998; Dal Cason, 2001; Felgate et al., 1998; Poortman and Lock, 1999). Included among these are: 1-(4-methoxyphenyl)-2-aminopropane (PMA; ''Chicken Yellow,'' ''Chicken Powder,'' ''White Mitsubishi,'' ''Death''), its *N*-monomethyl analog, *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA; ''Doone''), and its sulfur analog, 1-(4-methylthiophenyl)-2-aminopropane (4-MTA; ''Flatliners,'' ''Golden Eagles''). Poisonings and deaths have been associated with the use of PMA (Felgate et al., 1998; James and Dinan, 1998; Ling et al., 2001; Lora-Tamayo et al., 1997), PMMA (Lora-Tomayo et al., 1997) and 4-MTA (Elliott, 2000), and both PMA and PMMA have been shown to be neurotoxic in animals (Steele et al., 1992). 4-MTA purportedly lacks the neurotoxic actions of PMA (Huang et al., 1992). In Australia, in particular, much of the available MDMA is actually PMA (Irvine, 2001), and PMA is responsible for most of the deaths attributed to MDMA (Irvine, 2001; Ling et al., 2001). PMA is already classified as a Schedule 1 controlled substance, whereas 4-MTA is currently being considered for scheduling (Federal Register, 2001).

These agents are closely related in structure (see Fig. 1 for chemical structures). That is, 4-MTA is the sulfur analog of PMA, and PMA is the *N*-desmethyl analog of PMMA. These, in turn, are structurally related to the heterocyclic phenylalkylamine, MDMA. These agents are not new and each has been in the scientific literature for a decade or more. For example, in the early 1960s, it was shown that PMA is a weak locomotor stimulant in mice (van der Schoot et al., 1961). PMMA, however, seemingly lacks significant stimulant action (Glennon et al., 1988a,b). PMA and its optical isomers nonselectively block reuptake and cause the release of the monoamines serotonin (5-HT), dopamine and norepinephrine (e.g., Loh and Tseng, 1978; Tseng et al., 1976), but are relatively weak with respect to their dop-

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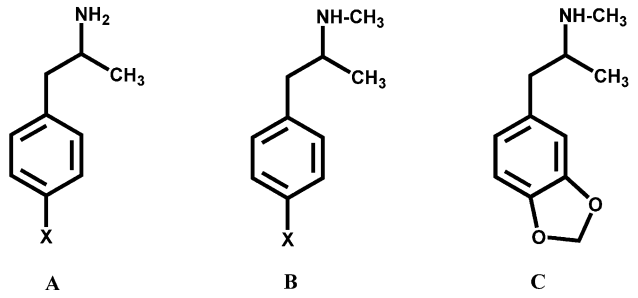

Fig. 1. Chemical structures of PMA (A, X = $-OCH_3$), 4-MTA (A, X = $-SCH_3$), PMMA (B, X = $-OCH_3$), 4-MTMA (B, X = $-SCH_3$) and MDMA (C).

aminergic actions relative to their serotonergic effects (Daws et al., 2000). PMA and PMMA also possess action as selective Type A monoamine oxidase inhibitors (Green and El Hait, 1980; Mash et al., 2001). 4-MTA is a monoamine oxidase inhibitor and a relatively selective 5-HT-releasing agent (e.g., Scorza et al., 1999).

Each of the above agents has been examined in tests of stimulus generalization using animals trained to discriminate various training drugs from saline vehicle. For example, racemic PMA has been variously shown to substitute (Glennon et al., 1985; Huang and Ho, 1974) or partially substitute (Corrigall et al., 1991) for (+)amphetamine in rats, but not in monkeys (Woolverton and English, 1997). PMMA does not substitute for (+)amphetamine (Glennon et al., 1988b). Substitution occurs upon administration of 4-MTA to MDMA-trained rats (Huang et al., 1992). PMA (Winter, 1984) and PMMA (Glennon et al., 1988a,b; Young et al., 1999) have even been used as training drugs, although results with PMA are relatively limited. On the other hand, it was shown that PMMA stimulus generalization failed to occur with (+)amphetamine (Glennon et al., 1997). Hence, regardless of which of the two agents was used as training drug, PMMA and (+)amphetamine produce stimulus effects that are clearly dissimilar. In contrast, stimulus generalization occurs between PMMA and MDMA independent of which is used as training drug (Glennon and Higgs, 1992; Glennon et al., 1997). There are similarities and distinct differences between PMMA and MDMA. PMMA is structurally related to — but is structurally simpler than — MDMA, the agents result in cross-generalization, and in both cases, PMMA is three times more potent than MDMA (Glennon et al., 1997). However, unlike what was seen with PMMA, stimulus generalization occurs upon administration of MDMA to (+)amphetamine-trained animals. That is, MDMA possesses an amphetaminergic component of stimulus action that is lacking with PMMA. Consistent with these results, the α-ethyl homolog of MDMA (i.e., MBDB, another MDMA-like agent that lacks amphetaminergic action) substitutes for training drug in animals trained to discriminate either MDMA (Oberlender and Nichols, 1990) or PMMA (Rangisetty et al., 2001) from vehicle.

Due to the structural similarities among PMA, 4-MTA and PMMA, we conducted the present investigation to determine whether or not stimulus similarities exist among these three agents. Because 4-MTA is the sulfur counterpart of PMA, we also prepared and evaluated the sulfur counterpart of PMMA (i.e., 4-methylthiomethamphetamine, 4-MTMA). Specifically, we examined *S*(+)PMA, *R*(−)PMA, 4-MTA and 4-MTMA in rats trained to discriminate either PMMA or (+)amphetamine from saline vehicle.

2. Methods

2.1. Drug discrimination studies

The subjects were 17 male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 250–300 g at the beginning of the study. The animals were divided into two groups and trained to discriminate either 1.25 mg/kg PMMA ($n = 9$) or 1.0 mg/kg (+)amphetamine ($n = 8$) from saline vehicle, as previously described (Glennon et al., 1985; Rangisetty et al., 2001). 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 libitum in their home cages. The rats were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of training drug 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., 1985). 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. The left lever was designated the drug-appropriate lever for approximately half the animals, 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 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.

Tests of stimulus generalization (i.e., substitution) were conducted in order to determine if the training drug stimulus would generalize to the challenge drugs. 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 2 days before a generaliza-

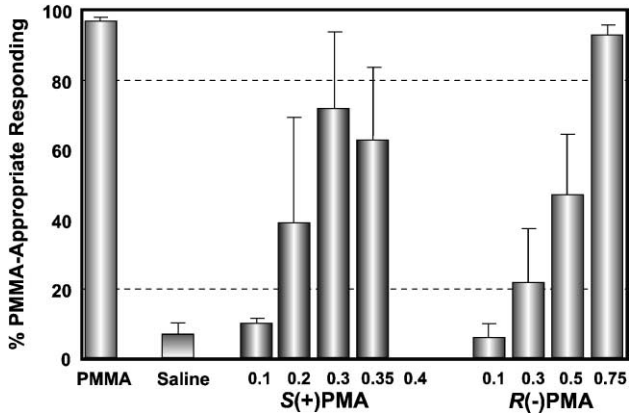

Fig. 2. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.25 mg/kg PMMA from saline vehicle following administration of either 1.25 mg/kg PMMA, 1 ml/kg 0.9% saline and doses of *S*(+)PMA and *R*(−)PMA. Animals administered *S*(+)PMA doses of ≥0.4 mg/kg failed to respond (see Table 1 for number of animals used and response rate data).

tion 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 test drugs were administered in a random order, using a 15-min presession injection interval, to the groups of rats with the proviso that if a particular dose of drug resulted in behavioral disruption, only lower doses would be investigated in subsequent sessions. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made ≥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.

2.2. Drugs

PMMA, and *S*(+)- and *R*(−)1-(4-methoxyphenyl)-2-aminopropane hydrochloride [*S*(+)PMA and *R*(−)PMA,

Table 1
Doses, number of animals and response rate data for the substitution studies

PMMA-trained animals				(+)Amphetamine-trained animals			
	Dose (mg/kg)	*N*[a]	Resp/min[b]		Dose (mg/kg)	*N*a	Resp/minb
PMMA saline	1.25	9/9	9.7 (2.9)	(+)AMPH saline	1.0	8/8	9.7 (2.1)
		9/9	14.8 (3.7)			8/8	13.1 (3.1)
(+)PMA	0.1	4/5	9.6 (3.2)	(+)PMA	0.5	4/4	13.8 (1.3)
	0.2	3/5	5.0 (2.1)		0.75	3/4	5.8 (2.0)
	0.3	3/5	5.2 (2.4)		0.85	3/4	7.9 (3.2)
	0.35	4/5	9.3 (3.5)		1.0	2/4	9.4 (0.9)
	0.4	1/5	–[c]		1.5	1/4	–[c]
	0.5	1/5	–[c]				
(−)PMA	0.1	6/9	11.4 (4.0)	(−)PMA	0.75	3/4	11.1 (1.9)
	0.3	7/9	9.9 (2.8)		1.5	3/4	5.1 (1.7)
	0.5	4/6	7.2 (1.6)		2.0	2/4	4.8 (2.1)
	0.75	4/6	6.3 (3.2)				
4-MTA	0.1	5/5	12.2 (4.2)	4-MTA	0.5	4/4	10.4 (3.3)
	0.3	5/5	10.4 (3.6)		1.0	4/6	7.3 (2.4)
	0.45	3/4	10.0 (3.9)		1.25	3/6	4.6 (0.9)
	0.6	4/7	5.4 (1.6)		1.5	1/6	–[c]
4-MTMA	0.1	4/4	11.6 (3.8)	4-MTMA	0.5	4/4	8.0 (2.7)
	0.3	4/4	14.0 (3.4)		1.0	4/6	5.3 (1.3)
	0.45	3/4	10.1 (4.7)		1.5	3/6	9.0 (4.3)
	0.55	4/4	7.3 (3.5)		2.0	3/6	5.9 (3.5)
	0.6	3/8	–[c]		2.25	3/6	6.7 (3.2)
					2.5	1/6	–[c]

[a] *N*=Number of animals responding/number of animals administered drug.
[b] Data obtained during a 2.5-min extinction session; reflect results only from animals making ≥5 responses during the extinction session.
[c] Disruption of behavior; majority of animals failed to make ≥5 responses during the extinction session.

respectively] were synthesized as previously described (Young et al., 1999). 4-MTA was synthesized as originally described by Holland et al. (1963). Its *N*-monomethyl derivative, *N*-methyl-1-(4-methylthiophenyl)-2-aminopropane hydrochloride (4-MTMA), was prepared by treatment of the free base of 4-MTA with ethyl chloroformate followed by reduction of the resulting carbamate with lithium aluminum hydride. The product was obtained in 31% overall yield as a white solid; mp 167–169 °C after recrystallization from absolute ethanol. 4-MTA and 4-MTMA analyzed within 0.4% of theory for C, H and N. The 4-MTMA proton magnetic resonance spectrum (300 mHz; DMSO-d_6) was consistent with the assigned structure. (+)Amphetamine sulfate was available from earlier investigations. All 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

3.1. PMMA-trained animals

Six doses of *S*(+)PMA and four doses of *R*(−)PMA were examined in the PMMA-trained animals (Fig. 2; Table 1). *S*(+)PMA produced a maximum of 72% PMMA-appropriate responding (at 0.3 mg/kg); administration of 0.35 mg/kg of *S*(+)PMA elicited reduced PMMA-appropriate responding and higher doses disrupted the animals' lever pressing behavior. The number of animals responding at each drug dose and the animals' response rates are shown in Table 1. *R*(−)PMA substituted for PMMA in a dose-related manner (ED_{50} = 0.4 mg/kg; 95% CL: 0.2–0.7 mg/kg). At the dose of *R*(−)PMA where stimulus generalization occurred, the animals' response rate was reduced to about 65% of the PMMA-control response rate.

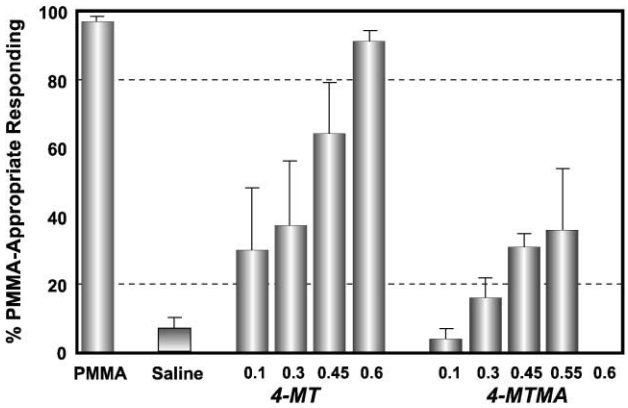

Fig. 3. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.25 mg/kg PMMA from saline vehicle following administration of either 1.25 mg/kg PMMA, 1 ml/kg 0.9% saline and doses of 4-MTA and 4-MTMA. The majority of animals administered 0.6 mg/kg 4-MTMA failed to respond (see Table 1 for number of animals used and response rate data).

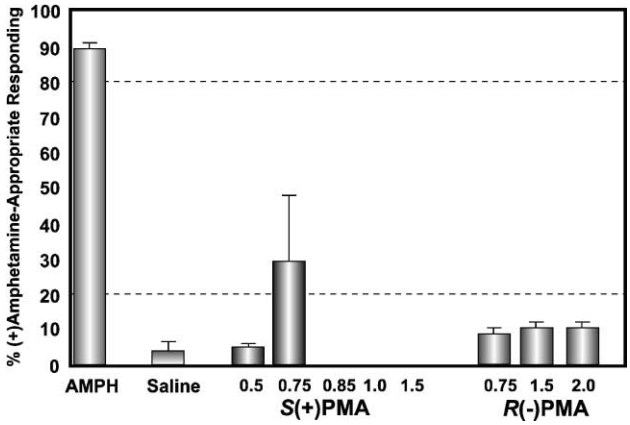

Fig. 4. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.0 mg/kg (+)amphetamine from saline vehicle following administration of either 1.0 mg/kg (+)amphetamine, 1 ml/kg 0.9% saline and doses of *S*(+)PMA and *R*(−)PMA. Animals administered 0.85 and 1.0 mg/kg *S*(+)PMA made 0% of their responses on the (+)amphetamine-appropriate lever, whereas the majority of animals administered 1.5 mg/kg *S*(+)PMA failed to respond (see Table 1 for number of animals used and response rate data).

Four doses of 4-MTA were examined (Fig. 3); 4-MTA substituted for PMMA in a dose-related manner (ED_{50} = 0.3 mg/kg; 95% CL: 0.1–0.6 mg/kg). At the 4-MTA dose eliciting >80% PMMA-appropriate responding, the animals' response rate was reduced to 60% of control. Five doses of 4-MTMA were examined and the animals made a maximum of 36% of their responses (at 0.55 mg/kg) on the PMMA-appropriate lever; a dose of 0.6 mg/kg produced disruption of behavior (no responding).

3.2. (+)Amphetamine-trained animals

Neither optical isomer of PMA substituted for (+)amphetamine (Fig. 4). *S*(+)PMA elicited a maximum of 33%

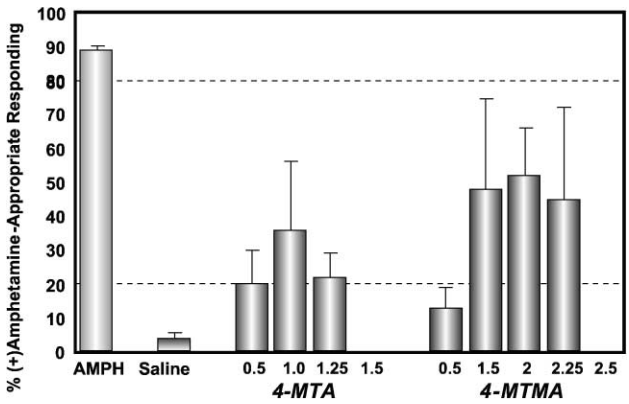

Fig. 5. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.0 mg/kg (+)amphetamine from saline vehicle following administration of either 1.0 mg/kg (+)amphetamine, 1 ml/kg 0.9% saline and doses of 4-MTA and 4-MTMA. The majority of animals administered 1.5 mg/kg 4-MTA or 2.5 mg/kg 4-MTMA failed to respond (see Table 1 for number of animals used and response rate data).

(+)amphetamine-appropriate responding (at 0.75 mg/kg); administration of 0.85 and 1.0 mg/kg produced 0% drug-appropriate responding and 1.5 mg/kg disrupted the animals' behavior. *R*(−)PMA produced a maximum of 12% (+)amphetamine responding; at 2.0 mg/kg of *R*(−)PMA, only two of four animals responded and the animals' response rate was reduced to <50% of the control rate (Table 1).

Neither 4-MTA nor 4-MTMA substituted for (+)amphetamine (Fig. 5). 4-MTA and 4-MTMA produced a maximum of 36% and 56% (+)amphetamine-appropriate responding, respectively. Administration of higher doses of either agent resulted in substantial decreases in response rates and, eventually, in disruption of behavior (Table 1).

4. Discussion

Stimulus generalization studies have demonstrated that MDMA is an agent that produces both (+)amphetamine and PMMA-like effects. Consistent with an amphetaminergic component of action, MDMA also acts as a locomotor stimulant in rodents (e.g., Glennon et al., 1988a,b). In contrast, PMMA produces a stimulus effect in rats that is similar to that produced by MDMA (Glennon and Higgs, 1992; Glennon et al., 1997) but different than that produced by (+)amphetamine (Glennon et al., 1988a,b). The present investigation addressed the question: Do PMA isomers, 4-MTA and 4-MTMA produce stimulus effects similar to those produced by PMMA, (+)amphetamine or both?

It would appear, on the basis of the results shown in Figs. 2 and 3, that *R*(−)PMA and 4-MTA are capable of producing PMMA-like stimulus effects in rats. As with PMMA, but unlike MDMA, *R*(−)PMA and 4-MTA failed to substitute for (+)amphetamine (Figs. 4 and 5). Evidently, under the current assay conditions, there exist some stimulus similarities between MDMA and PMMA, *R*(−)PMA and 4-MTA. However, due to the lack of stimulus generalization upon administration of PMMA (Glennon et al., 1997), *R*(−)PMA or 4-MTA to (+)amphetamine-trained animals, there also exist some differences. In terms of PMMA-like activity, *R*(−)PMA (ED_{50} = 1.9 μmol/kg) and 4-MTA (ED_{50} = 1.2 μmol/kg) are similar in potency to PMMA (ED_{50} = 1.9 μmol/kg) (Glennon et al., 1997) and several-fold more potent than MDMA (6.2 μmol/kg) (Glennon et al., 1997). Neither *S*(+)PMA nor 4-MTMA met stimulus generalization criteria upon administration to the PMMA-trained animals, nor did they substitute for (+)amphetamine.

Several curious results emerged from the present study. The *N*-methyl analog of 4-MTA, 4-MTMA, failed to substitute for PMMA even though it is the sulfur analog of PMMA (in the same manner that 4-MTA is the sulfur analog of PMA). This structural modification was not expected to abolish PMMA-like activity. One explanation for the result might be found in the optical activity of 4-MTMA. 4-MTMA possesses a chiral center and can thus exist as two optical isomers. Perhaps one of the optical isomers produces a disruptive effect that obscures stimulus generalization that might have occurred with its opposite enantiomer. Future studies might focus on the individual optical isomers of 4-MTMA.

A finding that is more difficult to reconcile is that neither PMA isomer substituted for (+)amphetamine when it has been previously reported, at least in some studies, that racemic PMA substitutes for (+)amphetamine in rats (Glennon et al., 1985; Huang and Ho, 1974). Although it might not be unusual for the stimulus effects of a racemate to differ somewhat from those of the individual optical isomers, the present results indicate that neither isomer of PMA generated a semblance of the amphetamine-like effect produced by racemic PMA. It seems probable that other factors, such as training and testing conditions, might account for the different results. For example, PMA was shown to produce a maximum of only 30% (+)amphetamine-appropriate responding in one study using rats as subjects and lack of consistency with the earlier literature was attributed to procedural differences (Corrigall et al., 1991). The lack of stimulus generalization in the present study is consistent with what was reported to occur with racemic PMA in the latter study (Corrigall et al., 1991), and upon administration of racemic PMA to monkeys (Woolverton and English, 1997).

What is the mechanistic basis for the stimulus generalization that was observed? Racemic PMA is a nonselective monoamine-releasing agent and, in addition, is a nonselective inhibitor of monoamine reuptake. Although PMA is less potent than (+)amphetamine in its effects on dopamine and norepinephrine, PMA is more potent than (+)amphetamine with respect to 5-HT release and reuptake (Tseng et al., 1976). Furthermore, *R*(−)PMA and *S*(+)PMA are equipotent in stimulating 5-HT release, but *S*(+)PMA is more potent than *R*(−)PMA in blocking reuptake (Tseng et al., 1976). Subtle differences, between agents and between PMA isomers, might account for some of the results observed in the present study (i.e., different effect of the PMA isomers in PMMA-trained animals; effect of PMA isomers relative to racemic PMA in amphetamine-trained animals). In addition, consistent with its being structurally similar to amphetamine, racemic PMA has been shown to produce locomotor stimulation in rodents (van der Schoot et al., 1961)—an effect that might initially be considered related to its dopaminergic actions. However, PMA is, at best, only a weak dopamine-releasing agent or reuptake inhibitor (Daws et al., 2000; Loh and Tseng, 1978). Furthermore, due to differences in the gross behavior of the animals as compared to that seen following administration of amphetamine, Loh and Tseng (1978) have suggested that the effect of PMA on locomotor activity is the result of interactions at serotonergic receptors. Thus, even though PMA influences locomotor activity, it seems to do so in a manner that is different from that of amphetamine. 4-MTA

also acts as an indirect 5-HT agonist. It might be argued, then, that the serotonergic system could be involved, at least to some extent, in the stimulus actions of these agents. This remains to be fully investigated.

Finally, a sample of 4-MTA was submitted to the Drug Evaluation Committee of CPDD for evaluation. It was found that 4-MTA (CPDD-0056) substituted for (+)amphetamine in two of four rhesus monkeys when given via the intramuscular route, but failed to substitute when given orally (Harris, 2000). In addition, 4-MTA was not self-administered by rhesus monkeys maintained on cocaine (Harris, 2000). Coupled with the present results, there is a possibility that 4-MTA might possess some stimulant-like qualities, but a greater likelihood that it is more of a PMMA-like agent.

In conclusion, *R*(−)PMA and 4-MTA substituted for training drug in PMMA-trained rats but not in (+)amphetamine-trained rats, indicating stimulus similarity among PMMA, *R*(−)PMA and 4-MTA; the similarity is quantitative as well as qualitative. It should be emphasized, however, that training dose can influence outcomes (e.g., Appel et al., 1982; Glennon et al., 1982; Young et al., 1983). As with other drug discrimination studies, had other training doses been employed, the results might have been different. Nevertheless, on the basis of the present results, it is possible that *R*(−)PMA and 4-MTA can produce effects in humans that are, at least to some extent, similar to those of MDMA; however, lacking the amphetaminergic character of MDMA, it is likely that the actions of these agents are not identical to those of MDMA. Although the mechanism underlying this common effect has not yet been investigated, it might involve, at least in part, the interplay of these agents with monoamine release and, in particular, its effect on serotonergic systems.

Acknowledgments

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