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Stimulus Properties of PMMA: Effect of Optical Isomers and Conformational Restriction

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YOUNG, R., M. DUKAT, L. MALMUSI AND R. A. GLENNON. *Stimulus properties of PMMA: Effect of optical isomers and conformational restriction.* PHARMACOL BIOCHEM BEHAV **64**(2) 449–453, 1999.—*para*-Methoxymethamphetamine (PMMA), a structural hybrid of two central stimulants, lacks stimulant properties but behaves in a manner similar to that of MDMA [*N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane]. PMMA has been established as a training drug in drug discrimination studies, and in the present investigation we sought to determine which optical isomer of PMMA is primarily responsible for its stimulus effects. Because PMMA is a conformationally flexible molecule, it was also of interest to determine what conformation is most important for its actions., Accordingly, we prepared and examined *S*(+)PMMA, *R*(−)PMMA, and conformationally restricted forms of PMMA: PMMA-AT, TIQ-1, and TIQ-2. *S*(+)PMMA (ED_{50} = 0.32 mg/kg) was found to be at least as potent as PMMA (ED_{50} = 0.41 mg/kg), whereas *R*(−)PMMA failed to result in complete stimulus generalization. An aminotetralin-like conformation, as found in PMMA-AT (ED_{50} = 0.29 mg/kg), seems to better account for the actions of PMMA than a tetrahydroisoquinoline-like conformation because TIQ-1 and TIQ-2 failed to result in stimulus generalization. The results of the present study further support the concept that PMMA and MDMA share considerable similarity with respect to their stimulus properties in animals except that PMMA lacks the amphetaminergic stimulant component of action associated with MDMA. © 1999 Elsevier Science Inc.

PMMA *para*- Methoxymethamphetamine MDMA Methamphetamine Stimulants Aminotetralins Drug discrimination Tetrahydroisoquinolines

BOTH methamphetamine and *para*-methoxyamphetamine (PMA) are phenylalkylamine central stimulants; *para*-methoxymethamphetamine (PMMA) is a hybrid structure of methamphetamine and PMA (7) (see Fig. 1 for chemical structures). Surprisingly, however, PMMA lacks appreciable central stimulant activity. For example, PMMA is not a locomotor stimulant in mice, and PMMA produces <20% (+)amphetamine-appropriate responding in rats trained to discriminate (+)amphetamine from saline vehicle (6). PMMA also bears a close structural resemblance to the controlled substance analog MDMA ("Ecstasy"; "XTC") or *N*- methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane. An MDMA stimulus has been demonstrated to generalize to PMMA, and PMMA was found to be three times more potent than MDMA (5). PMMA itself has been used as a training drug in drug discrimination studies (7). The PMMA stimulus failed to generalize to (+)amphetamine; however, the PMMA stimulus did generalize to MDMA and, again, PMMA was three times more potent than MDMA (7). Because MDMA possesses some amphetamine-like stimulant character, PMMA has been proposed to be a "cleaner" MDMA-like agent than MDMA itself (7); that is PMMA lacks the amphetaminergic central stimulant character of MDMA. We have been investigating the structure–activity relationships for PMMA-like activity, and in the present study we address two specific questions: (a) are the stimulus effects of PMMA stereoselective or stereospecific, and (b) what is the preferred conformation for PMMA-like stimulus action. Accordingly, we prepared the two optical isomers of PMMA, *S*(+)PMMA and *R*(−)PMMA, and three conformationally restricted analogs of PMMA (Fig. 1). Once prepared, these compounds were examined in animals trained to discriminate PMMA from vehicle.

METHOD

The animals employed in this investigation were previously trained to discriminate PMMA, and are those used in an earlier study; their training has been reported (7). The animals were housed individually and during the entire course of the study, the animals' body weights were maintained at 80% of their free-feeding body weights. In their home cages, the animals were allowed drinking water ad lib. Briefly, the six male Sprague–Dawley rats used in the study were originally trained (15-min training session) to discriminate the intraperi-

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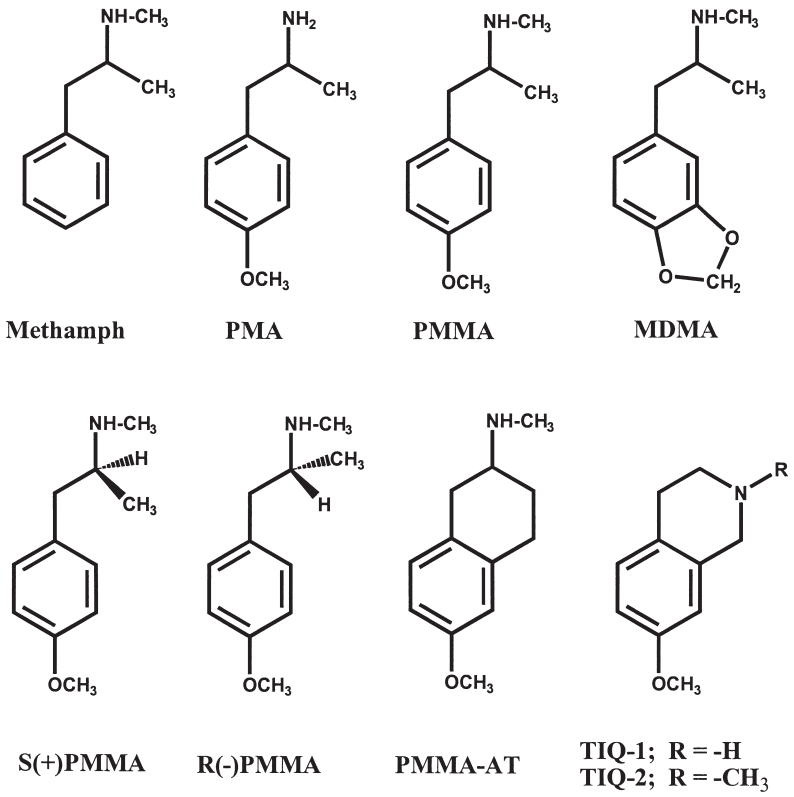

FIG. 1. Chemical structures showing the structural relationships between methamphetamine (Methamph), *para*-methoxyamphetamine (PMA), *para*-methoxymethamphetamine (PMMA), *N*-methyl-1-(3,4-methylene-dioxyphenyl)-2-aminopropane (MDMA), the two optical isomers of PMMA—*S*(+)PMMA and *R*(−)PMMA—the aminotetralin analog of PMMA (PMMA-AT), and the tetrahydroisoquinoline analogs of PMMA (TIQ-1 and TIQ-2).

toneal injections (15-min presession injection interval) of 1.25 mg/kg of PMMA from vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard two-lever operant chambers (7). For half of the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining animals. Daily training sessions were conducted with PMMA, and learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. Data collected during extinction sessions included response rates (i.e., resp/min) and number of responses on the drug-appropriate lever (expressed as a percent of total responses).

Tests of stimulus generalization were conducted to determine if the PMMA stimulus would generalize to the following agents: *S*(+)PMMA, *R*(−)PMMA, PMMA-AT, TIQ-1, and TIQ-2. During this phase of the study, maintenance of the PMMA–saline discrimination was ensured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On 1 of the 2 days before a generalization test, half of the animals would receive PMMA and half 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 immediately 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; 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 session. Doses of the test drugs were administered in a random order, using a 15-min presession injection interval, to groups of four to six rats. If a particular dose of a challenge drug resulted in disruption of behavior (i.e., no responding), only lower doses would be evaluated in subsequent weeks. Stimulus generalization was considered to have occurred when the animals, after a given dose of challenge drug, made ⩾80% of their responses on the PMMA-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted, and were not used in calculating mean percent PMMA-appropriate responding and mean responses per minute. Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (2). The ED_{50} doses are doses at which the animals would be expected to make 50% of their responses on the drug- appropriate lever.

Drugs

PMMA HCl was previously prepared in our laboratories (6). The individual optical isomers of PMMA were prepared from the isomers of *para*-methoxyamphetamine (PMA) (9).

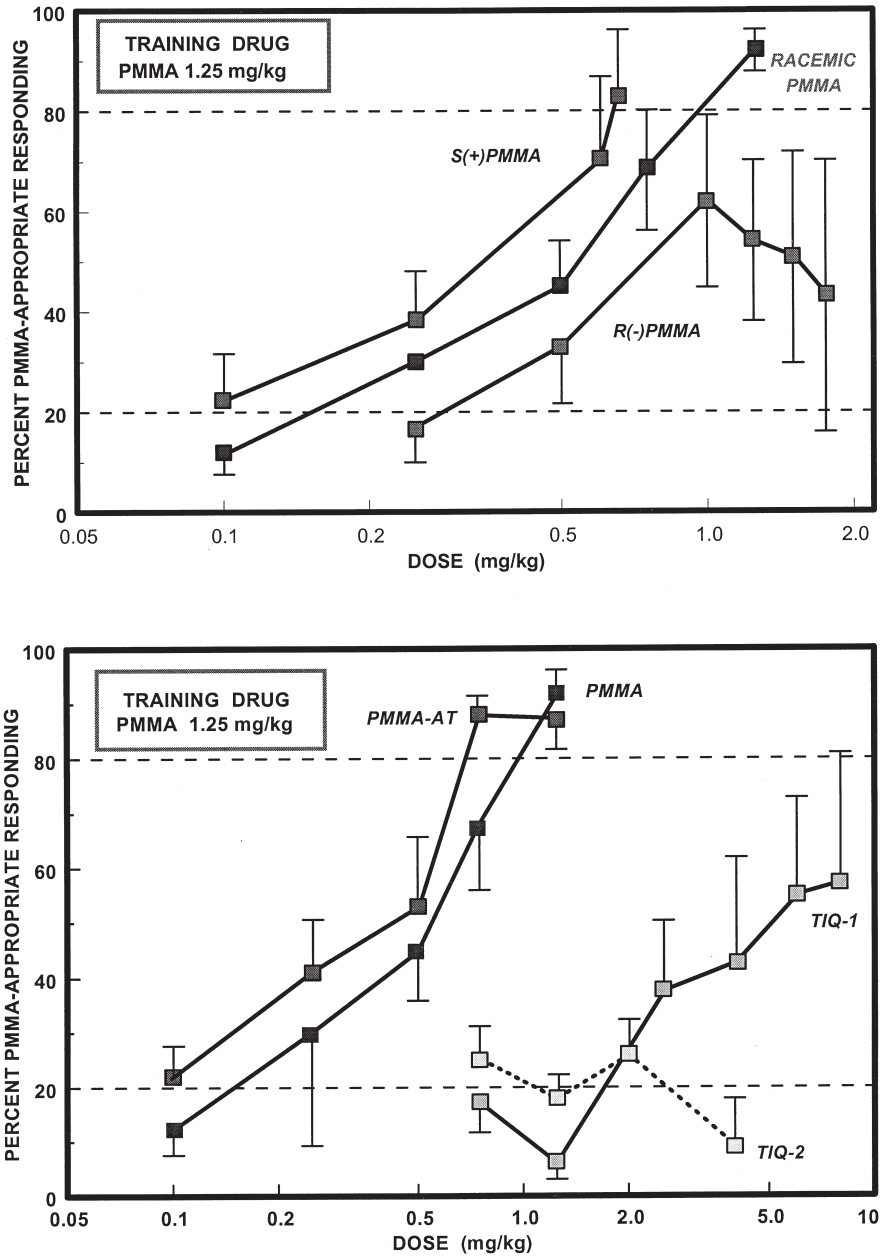

FIG. 2. Upper panel: Results of stimulus generalization studies with PMMA, *S*(+)PMMA, and *R*(−)PMMA in PMMA-trained animals. Lower panel: Results of stimulus generalization studies with conformationally restricted analogs of PMMA: PMMA-AT, TIQ-1, and TIQ-2; the dose–response curve for PMMA is reproduced in the lower panel for purpose of comparison.

S(+)PMA HCl was allowed to react with methyl chloroformate in the presence of triethylamine to afford the intermediate carbamate, which was subsequently reduced with lithium aluminum hydride in dry tetrahydrofuran. The crude product was isolated, converted to its HCl salt, and recrystallized from an absolute ethanol/anhydrous ether mixture to afford the desired product in 31% overall yield as a white cryatalline product; m.p. 203–205° C, $[\alpha]^{25}$ +13.0° (H_2O). The *R*(−)isomer of PMMA HCl was prepared in the same manner from *R*(−)PMA except that ethyl chloroformate was used as the acylating agent; the product was obtained as a white crystalline solid in 55% yield, m.p. 205–207°C, $[\alpha]^{25}$ −13.1° (H_2O). Both products were homogeneous as evidenced by thin-layer chromatography; proton magnetic resonance spectral data were consistent with the assigned structures, and both isomers analyzed correctly for C, H, and N to within 0.4% of theory (Atlantic Microlab, Norcross, GA).

7-Methoxy-1,2,3,4-tetrahydroisoquinoline HCl (TIQ-1) was prepared by condensation of 3-methoxy-benzaldehyde with aminacetaldehyde dimethylacetal followed by catalytic reduction under acidic conditions in a manner similar to that reported for the synthesis of related tetrahydroisoquinolines (8). The crude product was converted to its HCl salt and recrystallized from absolute ethanol to give the desired product

as white crystals; m.p. 230–231°C [lit (1) m.p. 233–234°C]. TIQ-1 was methylated using formaldehyde and sodium cyanoborohydride to afford TIQ-2 as an HCl salt in 81% yield after recrystallization from an absolute ethanol/anhydrous ether mixture; m.p. 201–202°C [lit (3) m.p. 201–202°C]. (±)*N*-Methyl-2-amino-6-methoxytetralin HCl (PMMA-AT) was prepared following a literature procedure (4) to give the desired product as a white solid; m.p. 169–170°C [lit (4) m.p. 172–174°C].

Solutions of all drugs were made fresh daily in 0.9% sterile saline, and all agents were administered via intraperitoneal injection in a 1.0 ml/kg injection volume. All doses refer to the weight of the salt.

RESULTS

A dose–response curve for PMMA is shown in Fig. 2 (racemic PMMA ED_{50} = 0.41 mg/kg; 95% CL = 0.18–0.93 mg/kg). Saline produced 4% PMMA-appropriate responding (data not shown). Mean response rate after administration of the training dose of PMMA was 12.5 (SEM ±1.8) responses per minute, and after administration of saline was 12.3 (SEM ±1.0) responses per minute. Dose–effect response rate data for each compound are shown in Table 1 and are calculated as percent of PMMA (based on the training dose of PMMA) responses per minute. Administration of doses of *S*(+)PMMA resulted in stimulus generalization (ED50) = 0.32 mg/kg; 95% CL = 0.15–0.68 mg/kg) (Fig. 2). Administration of *R*(−)PMMA resulted in the animals making a maximum of 62% of their responses on the PMMA-appropriate lever at 1 mg/kg; administration of 1.25, 1.50, and 1.75 mg/kg resulted in the animals making (with number of animals responding/number of animals administered drug) 54% (4 of 5), 51% (3 of 5), and 43% (3 of 5) of their responses on the drug-appropriate lever. Administration of higher doses of *R*(−)PMMA resulted in disruption of the animals' behavior. The animals' response rates after administration of the PMMA isomers were similar to the response rate obtained after administration of the training dose of PMMA except for a 26% decline in response rates after administration of 1.75 mg/kg of *R*(−)PMMA (Table 1).

Administration of PMMA-AT resulted in stimulus generalization (ED_{50} = 0.29 mg/kg; 95% CL = 0.14–0.64 mg/kg) (Fig. 2); at the highest dose of PMMA-AT (1.25 mg/kg) the animals' response rates were reduced to 53% of the PMMA response rate (Table 1). The PMMA stimulus failed to generalize to either TIQ analog (Fig. 2). TIQ-1 produced a maximum of 57% PMMA-appropriate responding at 8.0 mg/kg; at this dose, only three of five animals made >5 responses during the entire 2.5-min extinction session, and the response rate of the responding animals was reduced by 78% (Table 1). TIQ-2 resulted in a maximum of 26% PMMA- appropriate responding at 2.0 mg/kg; 4.0 mg/kg resulted in 9% PMMA-appropriate responding (42% reduction in response rates), and higher doses resulted in disruption of behavior.

TABLE 1

MEAN RESPONSE RATE DATA FOR RACEMIC PMMA, ITS OPTICAL ISOMERS, AND THREE CONFORMATONALLY RESTRICTED PMMA ANALOGS (PMMA-AT, TIQ-1, AND TIQ-2)

Compound	Dose (mg/kg)	*n/N**	Response Rate† (as a % of PMMA resp/min)
(+)PMMA	1.25	6/6	100%
	0.75	6/6	86%
	0.50	6/6	78%
	0.25	6/6	87%
	0.10	6/6	101%
Saline	1 ml/kg	6/6	98%
S(+)PMMA	0.65	5/5	102%
	0.60	5/5	106%
	0.25	5/5	121%
	0.10	5/5	104%
R(−)PMMA	1.75	3/5	74%
	1.50	3/5	98%
	1.25	4/5	95%
	1.00	5/5	95%
	0.50	4/5	91%
	0.25	5/5	101%
PMMA-AT	1.25	4/5	53%
	0.75	5/5	51%
	0.50	5/5	77%
	0.25	5/5	76%
	0.10	5/5	85%
TIQ-1	8.00	3/5	22%
	6.00	4/5	30%
	4.00	4/5	70%
	2.50	4/5	58%
	1.25	4/5	75%
	0.75	4/5	96%
TIQ-2	4.00	5/5	58%
	2.00	4/5	89%
	1.25	4/5	78%
	0.75	4/4	70%

Response rates for each compound were calculated as percent of the PMMA (1.25 mg/kg) response rate.

*n/N = Number of animals responding/number of animals administered drug.

†Data collected during a 2.5–min extinction session.

DISCUSSION

The present results suggest that the PMMA stimulus may be stereospecific in that only one of the two optical isomers of PMMA resulted in complete PMMA-stimulus generalization. *S*(+)PMMA (ED_{50} = 0.32 mg/kg) was at least as potent as (±)PMMA (ED_{50} = 0.41 mg/kg), whereas *R*(−)PMMA resulted only in partial generalization. These results are consistent with the observation that *S*(+)MDMA (ED_{50} = 0.48 mg/kg) is more potent than (±)MDMA (ED_{50} = 1.32 mg/kg) in PMMA-trained animals, and that *R*(−)MDMA results only in partial (68%) generalization (7). Thus, PMMA not only produces stimulus effects similar to those of MDMA (7), like MDMA the stimulus effects of PMMA may be stereospecific in PMMA-trained animals and the *S*(+)isomer is the active isomer in both cases.

Multiple conformations of phenylalkylamines are possible. Two possibilities include an aminotetralin-like conformation and a tetrahydroisoquinoline-like conformation (8). We have previously demonstrated that the actions of MDMA are associated more with an aminotetralin-like conformation than with a tetrahydroisoquinoline-like conformation (8). Others (10) have also demonstrated that aminotetralin and related analogs of MDMA retain MDMA-like actions. Hence, we expected that PMMA-like activity would also be more associated with an aminotetralin than tetrahydroisoquinoline conformation. Indeed, the aminotetralin analog of PMMA, PMMA-AT (ED_{50} = 0.29 mg/kg), is at least as potent as PMMA (ED_{50} = 0.41 mg/kg) itself. In contrast, neither tet-

rahydroisoquinoline analog resulted in stimulus generalization. TIQ-1 produced a maximum of 57% PMMA-appropriate responding, whereas TIQ-2 produced a maximum of 26% PMMA-appropriate responding. Consistent with what was seen with MDMA, the aminotetralin conformation of PMMA appears to account for its stimulus actions .

In conclusion, the stimulus effects of PMMA are primarily associated with the *S*(+)isomer of PMMA, and an aminotetralin rather than tetrahydroisoquinoline conformation better explains its actions. In these respects, PMMA behaves like MDMA.

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