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# A Preliminary Behavioral Investigation of PMMA, the 4-Methoxy Analog of Methamphetamine

RICHARD A. GLENNON,* ABD EL-KADER M. ISMAIEL,* BILLY MARTIN,† DOUGLAS POFF* AND MICHAEL SUTTON*

**Department of Medicinal Chemistry, School of Pharmacy*
*†Department of Pharmacology & Toxicology*
*Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298*

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GLENNON, R. A., A. E.-K. M. ISMAIEL, B. MARTIN, D. POFF AND M. SUTTON. *A preliminary behavioral investigation of PMMA, the 4-methoxy analog of methamphetamine.* PHARMACOL BIOCHEM BEHAV 31(1) 9–13, 1988.—The controlled-substance analog N-monomethyl-l-(4-methoxyphenyl)-2-aminopropane (PMMA) may be viewed as being either the 4-methoxy analog of methamphetamine or the N-methyl analog of l-(4-methoxyphenyl)-2-aminopropane (PMA). Because of its abuse potential, PMMA was examined with regard to (a) its stimulus properties in rats trained to discriminate either 1.0 mg/kg of (+)amphetamine or (±)DOM from saline, (b) its toxicity (isolated and aggregated) in mice relative to (±)PMA, and (c) its locomotor stimulant activity in mice relative to (±)amphetamine, (±)methamphetamine, and (±)PMA. Racemic PMMA produced neither DOM-like nor, unlike PMA, amphetamine-like stimulus effects. There was no significant difference between the 24-hr isolated ($LD_{50}$=63 mg/kg) and aggregated ($LD_{50}$=53 mg/kg) toxicity, and PMMA did not produce significant locomotor stimulation at doses of up to 30 mg/kg. The present results suggest that while PMMA may produce central effects it does not appear to behave as a simple amphetamine-like agent.

Amphetamine Paramethoxymethamphetamine Paramethoxyamphetamine Methamphetamine
CNS Stimulants PMA PMMA

AMPHETAMINE and related phenylisopropylamine derivatives can produce a variety of central effects (12). Certain N-alkyl phenylisopropylamines (particularly N-monomethyl phenylisopropylamines) have recently attracted widespread attention because of their abuse potential. Of these controlled-substance analogs (i.e., "designer drugs"), one of the best recognized agents is the N-methyl derivative of l-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) or MDMA (i.e., "Ecstasy"). The recent scheduling (Controlled Substances Act) of MDMA (9) has prompted the clandestine synthesis of other N-alkyl phenylisopropylamine derivatives and we have begun a systematic investigation of certain of these agents (14,15). A new controlled-substance analog that was recently confiscated from several different clandestine laboratories is the N-methyl derivative of l-(4-methoxyphenyl)-2-aminopropane (PMA) or PMMA ("paramethoxy methamphetamine") (23) (see Fig. 1 for structures). PMMA was first synthesized in 1938 (16) and, though it is a positional isomer of methoxyphenamine (Orthoxine, Ortodrinex) and is a synthetic precursor of the sympathomimetic agent pholedrine (Veritol) (3,19), its pharmacology has not been well investigated. PMMA produces cardiovascular and other sympathomimetic effects by what is believed to be an indirect mechanism (3, 10, 19). PMMA also produces a peculiar cataleptic effect in cats and rats when administered by the intracisternal or intraventricular route; this effect, though less marked, was also observed in mice given PMMA (18,19). Little else is known about the central effects of this agent.

We have previously examined the stimulus properties of N-methyl phenylisopropylamine derivatives using rats trained to discriminate either the stimulant phenylisopropylamine (+)amphetamine, or the hallucinogenic phenylisopropylamine DOM [i.e., l-(2,5-dimethoxyphenyl)-2-aminopropane], from saline [e.g., (14,15)]. In the present investigation, we conducted similar studies with PMMA. Because PMMA is structurally similar to amphetamine, and is related to PMA in the same manner that methamphetamine is related to amphetamine (Fig. 1), we further examined PMMA, with regard to its aggregated toxicity and spontaneous activity in mice.

## METHOD

### *Discrimination Studies*

The drug discrimination studies were performed as we have previously reported, using rats that had already been trained to discriminate either 1.0 mg/kg of (+)amphetamine sulfate of 1.0 mg/kg or racemic DOM HCl from 0.9% saline (14). Male Sprague-Dawley rats (200–300 g) were trained to respond on both levers of a standard two-lever operant chamber (Coulbourn Instruments model E10-10) for food (sweetened powdered milk) reward and were then trained

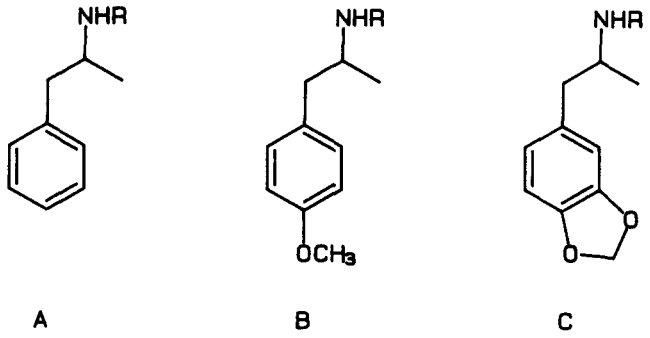


FIG. 1. Structures of amphetamine (A, R=H), methamphetamine (A, R=$CH_3$), PMA (B, R=H), PMMA (B, R=$CH_2$), MDA (C, R=H), and MDMA (C, R=$CH_3$).

to discriminate one of the training drugs from saline using a variable interval 15-sec schedule of reinforcement; see Glennon *et al.* (14) for greater detail. Unless otherwise noted, all drugs were administered via the intraperitoneal route 15 min prior to testing. During the stimulus generalization studies, maintenance of the drug/saline discrimination was insured by continuing the training sessions throughout this period. Training sessions were conducted with drug or saline during the four days prior to a generalization test; that is, the animals would be administered either drug or saline and the proper responses were reinforced during a 15-min training session. On one of these days, the animals' learning would be assessed by allowing the animals to respond, under each condition, during a 2.5-min extinction session followed by a 12.5-min training session. Animals not discriminating drug from saline (i.e., animals not making >80% of their responses on the drug-appropriate lever following administration of training drug, or animals making >20% of their responses on the drug-appropriate lever following administration of saline) were not used in the immediately subsequent generalization test. In the stimulus generalization test sessions, animals were administered doses of either PMA or PMMA and were allowed 2.5 min to respond under extinction conditions; the animals were then returned to their individual home cages. Doses of these agents were generally administered in a random sequence with the proviso that once disruption of behavior (i.e., no responding) occurred, only lower doses would be evaluated. Criterion for stimulus generalization was ≥80% of total responses on the drug-appropriate lever; disruption of behavior was said to have occurred if an animal failed to make at least five responses during the 2.5-min extinction session.

*Locomotor Studies*

ICR male mice (Dominion Laboratories, Dublin, VA) were placed in individual clear plastic cages (16.5×28 cm), and six cages were placed in a sound-attenuated chamber such that each cage was traversed with a single photocell beam. The animals were allowed to acclimate for 20 min. The mice were removed from these cages and given an intraperitoneal injection of either saline or drug. The animals were returned to the activity cages and interuptions of the photocell beams were recorded for 40 min with accumulated counts being recorded at 10-min intervals.

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES

| Agent | Dose (mg/kg) | PSII* (min) | N† | Drug-Appropriate Responding (±SEM)‡ | Mean Responses Per Min (±SEM)‡ |
|---|---|---|---|---|---|
| | | (+)Amphetamine-Trained Rats | | | |
| PMMA | 0.3 | 15 | 5/5 | 6% (2) | 9.1 (1.7) |
| | 0.5 | 15 | 5/5 | 10% (4) | 5.8 (2.2) |
| | 0.6 | 15 | 2/5 | — | |
| | 0.7 | 15 | 1/5 | — | |
| | 0.8 | 15 | 1/4 | — | |
| | 1.0 | 15 | 0/4 | — | |
| | 0.8 | 5 | 4/4 | 2% (1) | 8.5 (3.1) |
| | 0.8 | 10 | 4/4 | 0% | 4.8 (1.2) |
| | 0.8 | 30 | 3/4 | 2% (1) | 6.0 (2.2) |
| | 0.5 | 5 | 4/4 | 1% (1) | 7.8 (1.7) |
| | 0.8 | 5 | 4/4 | 2% (1) | 8.5 (3.1) |
| | 0.9 | 5 | 2/5 | — | |
| | 1.0 | 5 | 2/5 | — | |
| | 1.2 | 5 | 0/4 | — | |
| (+)AMPH | 1.0 | 15 | 5/5 | 94% (2) | 14.4 (2.2) |
| (±)PMA¶ | 2.25 | 5 | 4/6 | 83% | 4.5 |
| Saline | 1 ml/kg | 15 | 5/5 | 8% (4) | 14.2 (3.0) |
| | | DOM-Trained Rats | | | |
| PMMA | 0.05 | 15 | 4/4 | 7% (2) | 7.4 (1.1) |
| | 0.2 | 15 | 3/4 | 8% (6) | 3.4 (1.0) |
| | 0.4 | 15 | 0/3 | — | |
| | 0.6 | 15 | 0/3 | — | |
| DOM | 1.0 | 15 | 4/4 | 90% (4) | 11.6 (1.0) |
| Saline | 1 ml/kg | 15 | 4/4 | 10% (4) | 11.0 (1.2) |

*PSII=Pretession injection interval. †N=Number of animals responding/number of animals administered drug. ‡Determined during the 2.5-min extinction session. §Disruption of behavior. ¶Data previously reported (13).

*Toxicity Studies*

The method employed essentially followed the procedure described by Moore (20). Male albino mice (ICR; Dominion Labs) weighing 18–24 g were used. The animals were housed in groups of ten in standard animal facilities and had free access to food and water. Prior to an experiment, individual animals were isolated for 4 hr and were denied access to food and water. Animals were administered drug via the intraperitoneal route and were placed in small transparent chambers that were covered with a wire mesh screen: 1 per chamber in the "isolated" series and 4 per chamber in the "aggregated" series. The floor area of the chambers was held constant at 44 $cm^2$ per mouse. Isolated toxicity studies employed 6–7 animals per dose and the aggregated sudies employed 8 animals (two groups of four) per dose. During the toxicity study, the room was fully illuminated by overhead lights and the room temperature was maintained at 24±1°C. The animals were denied access to food and water during this time and

TABLE 2
ACUTE 4-HOUR AND 24-HOUR $LD_{50}$ VALUES FOR PMA AND PMMA

| Agent | Series | 4-Hour $LD_{50}$ (mg/kg)* | 24-Hour $LD_{50}$ (mg/kg)* |
|---|---|---|---|
| PMA | Isolated | 52 (40–66) | 39 (33–46) |
| | Aggregated | 40 (28–57) | 29 (24–35) |
| PMMA | Isolated | 68 (56–81) | 63 (51–77) |
| | Aggregated | 53 (42–66) | 53 (42–66) |

*$LD_{50}$ value followed by 95% confidence limits.

were routinely observed during the first two hours and then again at hours 4 and 24. Mortality was determined by recording the number of fatalities at the end of the 4-hr and 24-hr period. $LD_{50}$ values (at 4 and 24 hr) were calculated by the method of Litchfield and Wilcoxon (17). Solutions of all drugs were prepared fresh daily in 0.9% sterile saline just prior to their use.

*Drugs*

Racemic amphetamine, methamphetamine, and l-(4-methoxyphenyl)-2-aminopropane (PMA) were previously prepared in our laboratory as their hydrochloride (HCl) salts. N-Methyl-l-(4-methoxyphenyl)-2-aminopropane HCl (PMMA) was prepared as follows: PMA (free base) was acylated with ethyl chloroformate in the presence of triethylamine and the resulting carbamate was isolated, purified, and subsequently reduced with lithium aluminum hydride. The HCl salt was prepared and recrystallized from ethanol; the melting point of the salt (m.p. 177–179°C) was consistent with that reported by Hildebrandt (16) (m.p. 174°C) and Michaux and co-workers (19) (m.p. 177–178°C) and the product was found to be homogeneous by chromatographic methods. The spectral data (infrared, proton magnetic resonance) obtained for PMMA were identical with that reported by Bailey and co-workers (1) and by Clark (7). (+)Amphetamine sulfate was purchased from Sigma and racemic l-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) was a gift from NIDA.

## RESULTS

*Discrimination Studies*

In the drug discrimination studies, the (+)amphetamine-stimulus failed to generalize to PMMA using the standard 15-min presession injection interval (Table 1). PMMA doses of up to 0.5 mg/kg produced saline-appropriate responding; higher doses resulted in disruption of behavior. Because we had earlier shown that the (+)amphetamine-stimulus generalizes to PMA when a 5-min, but not a 15-min, presession injection interval was used (13), the presession injection interval used in the present study was varied from 5 to 30 min. Table 1 also shows that with presession injection intervals of 5, 10, and 30 min, 0.8 mg/kg of PMMA produced saline-appropriate responding. Five different doses of PMMA were evaluated using a 5-min presession injection interval; doses of up to 0.8 mg/kg of PMMA produced saline-appropriate responding and higher doses resulted in disruption of behavior. At no time did the animals make greater than 10% of their responses on the amphetamine-appropriate lever. It should be noted, however, that the animals' response rates were depressed, relative to control values, even at the lowest PMMA doses evaluated. Four doses of PMMA were evaluated in the DOM-trained animals. As with PMA (12), PMMA did not result in DOM appropriate responding (Table 1). The above mentioned behavior-suppressing effect, however, was also evident in these animals.

*Toxicity Studies*

With regard both to the isolated and aggregated toxicities, PMA appears to be slightly more toxic at 24 hr than at 4 hr (Table 2); the differences in $LD_{50}$ values, however, are not statistically significant. The 4-hr and 24-hr toxicities of PMMA are essentially identical (Table 2). Likewise, there was no significant difference between the isolated and aggregated toxicities for either PMA or PMMA (Table 2; Fig. 2). Mice administered PMA displayed symptoms similar to those previously reported for this agent (8,22) including hyperactivity, increased respiration, limb (particularly hindlimb) abduction, profuse salivation, and tremor. In the aggregated series, periods of sporadic hyperactivity were punctuated by brief periods of rest (the groups' hyperactivity seemingly being in response to, or being initiated by, the activity of an individual animal). Fighting and increased vocalization was evident. Where death occurred, it was usually preceded by tremor and/or convulsions.

Although animals appeared relatively normal after doses of 30 and 50 mg/kg of PMMA in the isolated series, higher doses produced symptoms similar to those observed with PMA. Hyperactivity was normally evident within 5 min and, at 100 and 150 mg/kg, death occurred within 15 min after administration of drug. In the aggregated series, behavior was similar to that seen with PMA except that the animals seemed less aggressive as evidenced by fewer instances of fighting or biting.

*Locomotor Studies*

In the mouse locomotor studies (Table 3), 1 and 3 mg/kg of racemic amphetamine significantly increased 40-min cumulative locomotor activity relative to vehicle-treated controls. Similar resutls were obtained with the N-methyl analog of amphetamine, i.e., racemic methamphetamine. PMA significantly increased locomotor activity only at 30 mg/kg. Its N-methyl derivative, PMMA, was, likewise, relatively inactive at the doses evaluated (Table 3). Although there is an apparent decrease in locomotor activity for low doses of PMA and PMMA, these decreases were not statistically significant.

## DISCUSSION

The results of all three preliminary studies failed to demonstrate a significant amphetamine-like effect for PMMA (at doses lower than its $LD_{50}$ dose). In prior drug discrimination studies, we demonstrated that the (+)amphetamine-stimulus generalizes to (±)amphetamine ($ED_{50}$=0.71 mg/kg) and (±)methamphetamine ($ED_{50}$=0.49 mg/kg) (13). Although the (+)amphetamine-stimulus only partially generalized (62%) drug-appropriate responding) to PMA when a 15-min presession injection interval was used, stimulus generalization did occur with a 5-min presession injection interval ($ED_{50}$=1.9 mg/kg) (13). In the present study, the (+)amphetamine-stimulus failed to generalize to

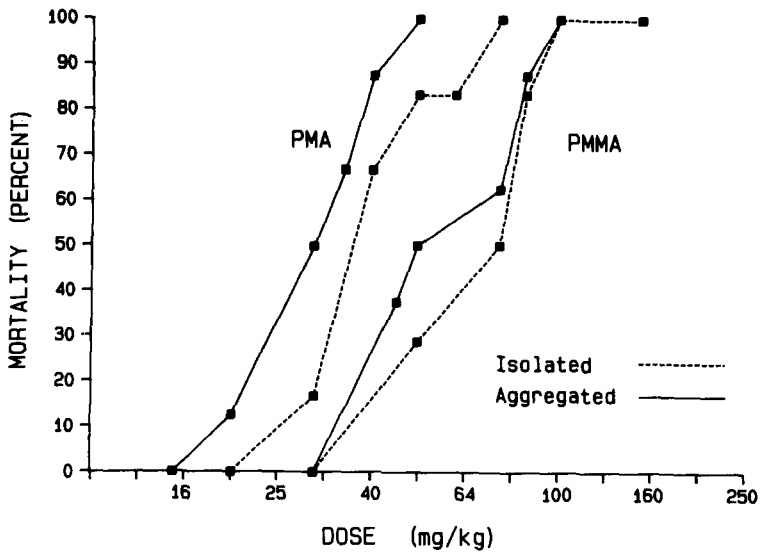


FIG. 2. Results of 24-hr toxicity study for PMA (left) and PMMA (right). In the isolated series (broken line), each dose was evaluated in 6–7 mice; in the aggregated series (solid line), each dose was evaluated in 8 mice.

TABLE 3

LOCOMOTOR STIMULATION PRODUCED BY AMPHETAMINE, METHAMPHETAMINE, PMA AND PMMA

| | | | Interruptions of Photocell at 10-Min Intervals (Means ± S.E.M.) | | | | |
|---|---|---|---|---|---|---|---|
| Treatment | Dose | N/group | 0–10 min | 10–20 min | 20–30 min | 30–40 min | 0–40 min |
| Vehicle | — | 56 | 62 ± 5 | 49 ± 4 | 44 ± 7 | 25 ± 6 | 179 ± 14 |
| Amph | 0.3 | 6 | 41 ± 7 | 26 ± 10 | 32 ± 12 | 25 ± 10 | 124 ± 35 |
| Amph | 1.0 | 12 | 109 ± 15* | 154 ± 21* | 163 ± 21* | 142 ± 20* | 505 ± 131* |
| Amph | 3.0 | 12 | 197 ± 11* | 137 ± 20* | 88 ± 19 | 82 ± 24* | 444 ± 81* |
| M-amph | 0.3 | 11 | 73 ± 10 | 50 ± 13 | 42 ± 15 | 35 ± 11 | 200 ± 46 |
| M-amph | 1.0 | 10 | 115 ± 18* | 81 ± 16 | 79 ± 11 | 76 ± 18 | 350 ± 47* |
| M-amph | 3.0 | 5 | 98 ± 22 | 124 ± 36* | 151 ± 39* | 137 ± 35* | 510 ± 129* |
| PMA | 1.0 | 6 | 47 ± 16 | 24 ± 7 | 8 ± 4 | 4 ± 1 | 83 ± 27 |
| PMA | 3.0 | 6 | 47 ± 16 | 12 ± 6 | 3 ± 2 | 16 ± 8 | 74 ± 30 |
| PMA | 10.0 | 6 | 24 ± 6 | 32 ± 20 | 42 ± 33 | 28 ± 16 | 126 ± 74 |
| PMA | 20.0 | 6 | 39 ± 6 | 77 ± 21 | 122 ± 33* | 104 ± 35* | 343 ± 85 |
| PMA | 30.0 | 12 | 77 ± 14 | 108 ± 16* | 151 ± 37* | 117 ± 23* | 453 ± 69* |
| PMMA | 1.0 | 6 | 45 ± 10 | 34 ± 10 | 24 ± 7 | 20 ± 6 | 123 ± 31 |
| PMMA | 10.0 | 5 | 30 ± 6 | 20 ± 4 | 31 ± 9 | 29 ± 12 | 110 ± 21 |
| PMMA | 20.0 | 6 | 78 ± 23 | 67 ± 33 | 53 ± 33 | 46 ± 26 | 244 ± 110 |
| PMMA | 30.0 | 5 | 112 ± 16* | 91 ± 13 | 79 ± 17 | 61 ± 19 | 343 ± 59 |

*Indicates significant difference from vehicle at $p<0.05$ by the Dunnett's $t$-test.

PMMA regardless of whether a 5-min or a 15-min presession injection interval was employed. Indeed, PMMA never engendered more than 10% drug-appropriate responding. As with PMA, PMMA did not (nor was it anticipated to) produce DOM-like effects.

Symptoms of excitement produced by phenylisopropylamine stimulants are much more pronounced in groups of mice than in mice housed individually. Chance (4,5) has investigated the effects of various environmental factors on the toxicity of amphetamine in mice and determined that aggregation (i.e., the presence of other mice) has the greatest single potentiating influence. Furthermore, within aggregated groups, as the area per mouse increases, toxicity decreases (4). Various studies have now shown that aggrega-

tion can potentiate the toxicity of amphetamine (and amphetamine-related agents) by a factor of as much as 10 [e.g., (4, 5, 20, 21, 25)] and this is thought to reflect social stress (i.e., "stress-enhanced toxicity"). The results of the present study do not reveal any difference in the toxicity of PMMA in mice under isolated versus aggregated conditions, suggesting a lack of amphetamine-like toxicity. Nevertheless, at doses greater than its $LD_{50}$ dose, PMMA did produce behavioral effects (e.g., hyperactivity, vocalization) similar to those observed with amphetamine.

Amphetamine and its N-methyl derivative, methamphetamine, are both known to produce locomotor stimulation in mice [e.g., (26)]. The results in Table 3 are consistent with these findings. PMA had been reported to be a very weak locomotor stimulant (26). The results for PMA in Table 3 are in agreement with previous reports in that PMA seems to produce little locomotor stimulation below doses of 30 mg/kg. The N-methyl derivative of PMA, PMMA, seems to be even less active at doses of up to 30 mg/kg.

In summary, PMMA does not appear to be a simple amphetamine-like stimulant. Nevertheless, it does seem to produce significant central effects. For example, in the drug discrimination studies, low doses of PMMA resulted in depressed rates of responding and/or in disruption of behavior. Although PMMA has been demonstrated to undergo N-demethylation in vitro (2), demethylation in vivo would not account for the differences observed for PMA and PMMA in the discrimination studies. An investigation of the neurochemical changes produced by PMMA, relative to for example PMA, amphetamine, or methamphetamine, might prove informative. The toxicity of PMMA is similar to that of PMA and it has been stated that, in humans, PMA can be a very treacherous drug to study (24); several human fatalities have been reported for PMA (6). Finally, PMMA is known to produce a cataleptic state in three species of animals. Taken together, these results suggest that human experimentation with PMMA should be discouraged and that further pharmacological studies are required to better understand this novel agent.

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