Pharmacology Biochemistry and Behavior, Vol. 57, Nos. 1/2, pp. 151–158, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00306-1

Initial Characterization of PMMA as a Discriminative Stimulus[1]

RICHARD A. GLENNON, RICHARD YOUNG, MALGORZATA DUKAT, AND YULIN CHENG

Department of Medicinal Chemistry, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0540

Received February 5 1995; Accepted April 30 1996

GLENNON, R. A., R. YOUNG, M. DUKAT, AND Y. CHENG. *Initial characterization of PMMA as a discriminative stimulus.* PHARMACOL. BIOCHEM. BEHAV. **57**(1/2) 151–158, 1997.—The phenylisopropylamine PMMA or *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane, a structural hybrid of paramethoxyamphetamine (PMA) and methamphetamine, has been previously shown to unexpectedly lack amphetamine-like or hallucinogen-like stimulus properties in animals. For example, in tests of stimulus generalization, neither a (+)amphetamine stimulus nor a DOM stimulus generalized to PMMA. It has also been shown, however, that stimulus generalization does occur in animals trained to discriminate the designer drug MDMA ("Ecstasy" or *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane) from vehicle. In order to further characterize this unique agent, we trained a group of six Sprague-Dawley rats to discriminate 1.25 mg/kg of PMMA (ED50 = 0.44 mg/kg) from saline vehicle. The PMMA stimulus failed to generalize to the phenylisopropylamine stimulant (+)amphetamine, or to the phenylisopropylamine hallucinogen DOM. Stimulus generalization occurred to (±)MDMA (ED50 = 1.32 mg/kg) and S(+)MDMA (ED50 = 0.48 mg/kg). Partial generalization occurred with R(−)MDMA, PMA, 3,4-DMA, and fenfluramine. The PMMA stimulus also generalized to the α-ethyl homolog of PMMA (EH/PMMA, ED50 = 1.29 mg/kg). Taken together, the results of these studies suggest that PMMA is an MDMA-like agent that lacks the amphetamine-like stimulant character of MDMA. These findings support our previous suggestion that PMMA be considered the structural parent of the MDMA-like family of designer drugs. © 1997 Elsevier Science Inc.

PMMA PMA MDMA MDA DOM Amphetamine Designer drugs Drug discrimination

PMMA, also known as paramethoxymethamphetamine or *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (see Fig. 1), is a structural hybrid of two phenylisopropylamine stimulants: PMA (or paramethoxyamphetamine) and methamphetamine. PMA is a weak central stimulant, whereas methamphetamine is at least as potent as amphetamine (23). For example, in a drug discrimination task using rats trained to discriminate (+)amphetamine (ED50 = 1.8 μmol/kg) from saline vehicle, both PMA and methamphetamine (ED50 = 9.5 and 1.5 μmol/kg, respectively) substitute for amphetamine (23). Thus, it might be expected that PMMA would also be an amphetamine-like agent. Interestingly, PMMA failed to engender >10% amphetamine-appropriate responding in amphetamine trained rats, and lacked quantifiable central stimulant character in mice (13). Certain methoxy-substituted phenyliospropylamines are considered to be classical hallucinogens; these agents result in stimulus generalization in rats trained to discriminate the prototypical phenylisopropylamine hallucinogen DOM (or 1-(2,5dimethoxy-4-methylphenyl)-2-aminopropane) from vehicle (2). DOM-stimulus generalization is highly dependent upon the location and number of methoxy groups present in the phenylisopropylamine (2); PMMA does not meet the structural requirements necessary for producing DOM-like effects. Moreover, PMMA failed to produce > 10% DOM-appropriate responding in DOM-trained rats (13). There is a third category of psychoactive phenylisopropylamines to which PMMA bears some structural similarity; this class of agents is typified by the designer drug MDMA (or *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane) (see Fig. 1). MDMA, although possessing some amphetamine-like stimulant character, is perhaps best described as an empathogen. That is, MDMA facilitates communication, induces feelings of empathy, and has seen some application as an adjunct to psychotherapy (2,18). Because all MDMA-like agents known at the time our studies began contained a methylenedioxy group, it was not expected that PMMA would pro-

[1]Presented in part at the Phoenix, Arizona CPPD Meeting, June 1995.

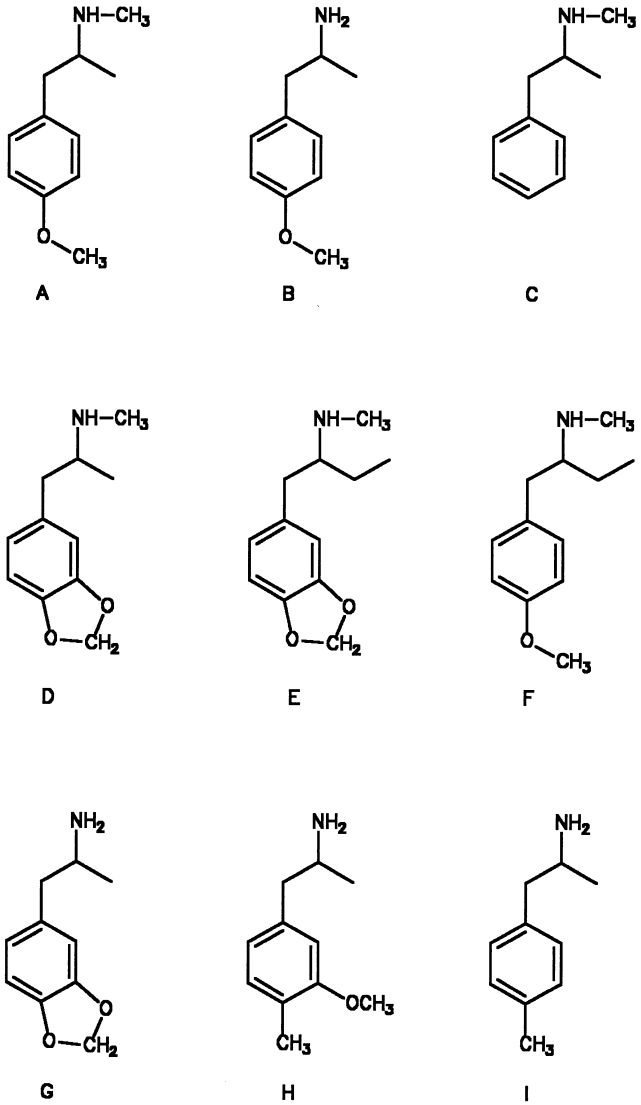

FIG. 1. Structural relationships among PMMA (A), PMA (B), methamphetamine (C), MDMA (D), MBDB (E), EH/PMMA (F), MDA (G), 1-(3-methoxy-4-methylphenyl)-2-aminopropane (H), and p-TAP (I).

duce MDMA-like effects. Nevertheless, due to the structural relationship between PMMA and MDMA, and the even greater structural similarity between PMMA and various MDMA metabolites (5), PMMA was evaluated in animals trained to discriminate MDMA from vehicle. Not only did PMMA substitute for MDMA, PMMA was three times more potent than MDMA (5). Furthermore, PMMA was the first phenylisopropylamine lacking a methylenedioxy ring shown to produce MDMA-like stimulus effects; as such, this expanded our knowledge of the structure-activity relationships of MDMA-like substances.

Psychoactive phenylisopropylamines with demonstrated abuse potential, then, can be divided into three categories: central stimulants, hallucinogens, and a third type typified by MDMA (2). In drug discrimination studies using animals trained to discriminate examples of each category of phenylisopropylamine, (i.e., (+)amphetamine, DOM, MDMA) from vehicle, it has been demonstrated that each agent is associated

TABLE 1

RESULTS OF PUBLISHED STIMULUS GENERALIZATION STUDIES USING THE PHENYLISOPROPYLAMINES S(+)AMPH, DOM AND MDMA AS TRAINING DRUGS†

	Training Drug		
Test Drug	S(+)AMPH	DOM	MDMA
S(+)AMPH	GEN [23]	NG [11]	49% [6]
DOM	32% [23]	GEN [10]	NG [2]
MDMA	GEN [7]	52% [12]	GEN [3]
S(+)MDMA	GEN [10]	33% [12]	GEN [3]
R(−)MDMA	33% [10]	29% [12]	GEN [3]
PMA	GEN [23]	NG [11]	50% [5]
3,4-DMA	NG [9]	46% [12]	67% [5]
PMMA	NG [13]	NG [13]	GEN [5]
Fenfluramine	NG [23]	GEN [23]	GEN [21]

†GEN: Stimulus generalization (i.e., > 80% drug-appropriate responding). NG: No stimulus generalization (i.e., <20% drug-appropriate responding at the highest dose evaluated). In some cases, certain agents produced an effect that fell somewhere between GEN and NG; in those instances, the highest percent drug-appropriate responding is provided. For the purpose of comparison, we have cited only our studies (i.e., numbers in brackets), where possible, even though other investigators may have examined some of these same agents. Other studies are cited in the text.

with a distinctive stimulus generalization profile (see Table 1). PMMA is most similar to MDMA. Nevertheless, PMMA differs somewhat from MDMA in that it is not recognized by (+)amphetamine-trained animals (Table 1). Because PMMA lacks appreciable amphetamine-like character, it may be "cleaner" than MDMA itself. Furthermore, because PMMA is structurally related to, and is more potent yet structurally simpler than, MDMA, we have suggested that PMMA might represent the parent member of the MDMA family of phenylisopropylamines (8). Consequently, we trained a group of rats to discriminate PMMA from vehicle in order to examine its stimulus generalization profile.

METHODS

The subjects were six male Sprague-Dawley rats (Charles River Laboratories) weighing 250–300 g at the beginning of the study. The animals were first trained to lever-press for sweetened milk reward using standard two-lever operant chambers (Coulbourn Instruments, Lehigh Valley, PA, model E10-10) housed within sound- and light-attenuating outer chambers. Once lever-pressing behavior was acquired, the animals were trained to discriminate intraperitoneal (IP) injections of PMMA (1.25 mg/kg) from 0.9% sterile saline (1.0 mL/kg). That is, rats were trained to respond on a variable-interval 15-s (VI 15s) schedule of reinforcement; once rates of responding stabilized, the animals received an injection of PMMA or saline 15 min prior to each session. Drug or saline vehicle was administered on a double-alternation schedule (i.e., two days drug, two days saline) and training sessions were of 15 min duration. For half of the animals, the right lever was designated the drug-appropriate lever; the situation was reversed for the remaining animals. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. We have used this procedure routinely in the past to train

animals to discriminate an agent from vehicle (23). Data collected during the extinction period included percent drug-appropriate responding (i.e., the number of responses on the drug-designated lever divided by the total number of responses, expressed as a percent), and the total number of responses made during the 2.5-min extinction session (recorded as responses per minute).

Once the rats consistently (i.e., for three consecutive weeks) made >80% of their responses on the drug-appropriate lever after administration of 1.25 mg/kg of PMMA, and <20% of their responses on the same lever after administration of 1.0 ml/kg of saline, stimulus generalization studies were begun. During these investigations, test sessions were interposed among the training sessions; however, after the 2.5-min extinction period, the animals were returned to their individual home cages. During generalization studies, animals were injected with doses of test compound, returned to their home cage for 15 min, and were then tested under extinction conditions for 2.5 min. Stimulus generalization was said to have occurred when the animals made >80% of their responses on the drug-appropriate lever. In these instances, an ED50 value (i.e., calculated dose at which the animals would be expected to make 50% of their responses on the drug-appropriate lever) was calculated by the method of Finney (1). Animals making <5 responses during the entire 2.5-min extinction session were reported as being disrupted.

Drugs

PMMA hydrochloride, PMA hydrochloride, MDMA hydrochloride, R(−)MDMA hydrochloride, S(+)MDMA hydrochloride, and 3,4-DMA or 1-(3,4-dimethoxyphenyl)-2-aminopropane hydrochloride were previously synthesized in our laboratory and were available from earlier studies. (+)-amphetamine sulfate was purchased from Sigma (St. Louis) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane or DOM hydrochloride was obtained from NIDA. Fenfluramine hydrochloride was obtained from A.H. Robins (Richmond, VA).

The α-ethyl homolog of PMMA, EH/PMMA or *N*-monomethyl-1-(4-methoxyphenyl)-2-aminobutane hydrochloride, was synthesized from 1-(4-methoxyphenyl)-2-aminobutane (22). The amine was allowed to react with an equivalent of ethyl chloroformate in tetrahydrofuran and triethylamine under a nitrogen atmosphere at 0°C for 30 min; the *N*-carboethoxy intermediate was isolated as a yellow oil and was used without further characterization. A tetrahydrofuran solution of the oil was reduced with lithium aluminum hydride (4 h) under standard conditions to afford an overall 52% yield of EH/PMMA hydrochloride as a white solid; mp 117–120°C after recrystallization from absolute ethanol. The assigned structure was consistent with spectral data; elemental analysis for C, H, and N was within 0.4% of theory.

All solutions were prepared fresh daily and all agents were administered 15 min prior to testing via i.p. injection in a 1.0 ml/kg injection volume.

RESULTS

Six rats were trained to discriminate 1.25 mg/kg of PMMA from saline vehicle. Administration of PMMA doses lower than the training dose resulted in decreased responding on the PMMA-appropriate lever; response rates were not significantly different (see Table 2) following the different doses of PMMA or 1 ml/kg of saline. The ED50 dose for PMMA was calculated to be 0.44 mg/kg. The PMMA stimulus failed to generalize to either (+)amphetamine or DOM. In both instances, 1 mg/kg of drug produced vehicle-appropriate (i.e, <20% PMMA-appropriate) responding, and higher doses resulted in disruption of behavior (Table 2). PMA, the *N*-desmethyl counterpart of PMMA, produced a maximum of 63% PMMA-appropriate responding at the highest nondisruptive dose evaluated (i.e., 1.25 mg/kg); at this dose, the animals' response rates were depressed by about 60%. Higher doses of PMA resulted in disruption of behavior. The PMMA stimulus generalized to racemic MDMA (ED50 = 1.32 mg/kg) and S(+)MDMA (ED50 = 0.48 mg/kg), but not to R(−)MDMA (Table 2). At MDMA doses that produced ≥80% PMMA-appropriate responding, the animals' response rates were reduced by about 25% and 50% (for racemic and S(+)MDMA, respectively). At 3.5 mg/kg, R(−)MDMA elicited 68% PMMA-appropriate responding, with severely depressed response rates; it might be noted that the three animals responding at this dose made 100%, 90%, and 14% of their responses on the PMMA-appropriate lever. A slightly higher dose of R(−)MDMA (i.e., 3.75 mg/kg) resulted in disruption of behavior.

The α-ethyl homolog of PMMA, or EH/PMMA, produced PMMA-like stimulus effects. Stimulus generalization occurred at 2 mg/kg (ED50 = 1.29 mg/kg).

DISCUSSION

Discriminative Stimulus Profile

PMMA is a structurally simple, yet pharmacologically interesting molecule. Although it bears significant structural similarity to other phenylisopropylamine stimulants, and although it would be anticipated on the basis of established structure-activity relationships (23) to be a central stimulant, early studies failed to demonstrate any quantifiable amphetamine-like stimulant character for this agent (13). Likewise, PMMA was shown to be pharmacologically distinct from the phenylisopropylamine hallucinogen DOM (13). Nevertheless, doses of <0.5 mg/kg were shown to disrupt animals trained to discriminate (+)amphetamine or DOM from vehicle, indicating that PMMA may possess some type of potent central activity (13). PMMA has also been confiscated from clandestine laboratories, suggesting that there might be some interest in this agent on the illicit market (13). Subsequently, an MDMA-stimulus was found to generalize to PMMA (5); furthermore, PMMA (ED50 = 0.2 mg/kg) was shown to be several times more potent than racemic MDMA (ED50 = 0.76 mg/kg) (5).

Of the three different types of psychoactive phenylisopropylamines (i.e., stimulant, hallucinogenic, and MDMA-like), PMMA seemed to behave most like MDMA (see Table 1). MDMA is considered to be an early member of a novel class of phenylisopropylamines whose effects in humans are primarily of an empathogenic nature (18). Although there is considerable support for this concept, it appears that MDMA is also capable of producing some amphetamine-like effects (2,10,20). That is, MDMA retains some amphetamine-like character, and this may be associated primarily with its S(+)enantiomer (2). Additionally, although MDMA is not generally considered to be hallucinogenic, it partially substitutes for a DOM-stimulus (Table 1), and there is at least one documented report where high doses of MDMA have produced visual hallucinations (17). In general, homologation of the α-methyl substituent of a stimulant phenylisopropylamine or of an hallucinogenic phenylisopropylamine to an α-ethyl group severely diminishes or abolishes its stimulant or hallucinogenic nature

TABLE 2

RESULTS OF THE STIMULUS GENERALIZATION STUDIES EMPLOYING PMMA-TRAINED RATS

Agent	Dose	N[a]	% DAR(SEM)[b]	Response Rate (Resp/min)
PMMA	0.25	5/5	16 (4.6)	12.6 (1.8)
	0.50	5/5	52 (13.5)	10.9 (2.4)
	0.75	5/5	88 (6.9)	9.7 (2.1)
	1.00	5/5	92 (4.6)	10.7 (2.4)
	1.25	6/6	98 (1.2)	12.5 (1.8)
	ED50 = 0.44 (0.27–0.73) mg/kg[c]			
Saline (1 ml/kg)		6/6	3 (1.2)	12.3 (1.0)
(+)Amphetamine	0.25	5/5	6 (2.2)	11.6 (1.9)
	0.50	5/5	18 (6.3)	12.4 (1.7)
	0.75	4/5	10 (4.5)	8.6 (1.9)
	1.00	3/5	11 (5.7)	4.2 (2.2)
	1.25	1/4	d	
	1.50	0/4	d	
DOM	0.25	5/5	0	13.4 (1.7)
	0.50	5/5	5 (2.1)	12.6 (2.1)
	0.75	4/5	12 (6.3)	8.7 (1.6)
	1.00	3/5	15 (9.5)	4.1 (1.0)
	1.25	1/4	d	
	1.50	0/3	d	
PMA	0.20	4/4	10 (6.3)	14.1 (2.1)
	0.40	4/4	15 (7.8)	13.7 (1.8)
	0.60	4/4	34 (8.1)	14.4 (2.1)
	0.75	4/4	54 (16.5)	8.7 (1.9)
	1.00	3/4	60 (12.9)	5.9 (2.6)
	1.25	3/4	63 (18.3)	4.7 (1.1)
	1.50	1/4	d	
	1.75	0/4	d	
(±)MDMA	0.50	5/5	13 (5.1)	13.1 (1.7)
	1.00	5/5	39 (3.9)	12.7 (2.5)
	1.50	5/5	41 (12.7)	11.9 (1.7)
	2.00	5/5	56 (18.3)	12.6 (2.1)
	2.50	5/5	83 (6.2)	9.3 (1.1)
	2.75	4/5	93 (4.7)	7.8 (2.1)
	ED50 = 1.32 (0.87–2.10) mg/kg			

(4,18). It has been demonstrated that homologation of MDMA (to MBDB or *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminobutane) has little effect on MDMA-like activity (18,20). Thus, this one structural change is capable of distinguishing MDMA-like phenylisopropylamines from stimulant or hallucinogenic phenylisopropylamines (20). Armed with this information, as well as with the different stimulus generalization profiles shown in Table 1, we trained a group of animals to discriminate PMMA from vehicle in order to characterize its stimulus effects.

We had already shown that PMMA produces <10% drug-appropriate responding in rats trained to discriminate either (+)amphetamine or DOM from vehicle (13). Consistent with these observations, in the present study it was found that (+)amphetamine and DOM fail to produce >20% PMMA-appropriate responding. That is, regardless of which of the three agents is used as the training drug, PMMA was consistently shown to be unique. Also consistent with our previous report of MDMA-stimulus generalization to PMMA (5), the PMMA stimulus generalized to MDMA. In both studies, PMMA was approximately three times more potent than MDMA. Both optical isomers of MDMA are capable of producing "MDMA-like" effects (18); S(+)MDMA is more potent than its R(−)enantiomer (2,18). In the present study S(+)MDMA was found to be equipotent with PMMA, whereas R(−)MDMA, at a dose higher than that of S(+)MDMA that resulted in PMMA-stimulus generalization (i.e., 1.25 mg/kg), produced only 17% PMMA-appropriate responding; higher doses were necessary to produce partial generalization. Taken together, these results clearly demonstrate that PMMA lacks amphetamine-like and DOM-like effects, but is similar to MDMA. Furthermore, it may be the

TABLE 2 (*Continued*)

Agent	Dose	*N*[a]	% DAR(SEM)[b]	Response Rate (Resp/min)
S(+)MDMA	0.25	4/4	20 (4.5)	13.6 (2.6)
	0.50	4/4	45 (10.9)	12.3 (3.9)
	0.75	4/4	63 (11.6)	7.4 (2.7)
	1.00	3/4	94 (5.2)	6.3 (1.3)
	ED50 = 0.48 (0.25–0.91) mg/kg			
R(−)MDMA	0.25	5/5	26 (14.9)	15.6 (3.4)
	0.75	6/6	23 (11.5)	17.4 (3.0)
	1.25	6/6	17 (8.0)	17.7 (4.4)
	2.00	3/5	52 (24.0)	11.7 (4.0)
	2.50	4/6	59 (14.9)	12.9 (6.0)
	3.50	3/5	68 (27.2)[e]	4.1 (1.5)
	3.75	1/5	d	
3,4-DMA	1.00	5/5	3 (1.2)	13.1 (1.7)
	3.00	5/5	24 (12.7)	12.5 (2.5)
	4.00	4/5	45 (7.6)	8.7 (2.0)
	6.00	5/5	58 (8.6)	10.2 (5.6)
	8.00	4/5	69 (13.8)	8.1 (3.4)
	8.25	3/5	71 (23.3)[f]	5.6 (2.3)
	8.50	1/5	d	
	9.00	1/5	d	
	10.00	0/5	d	
Fenfluramine	0.25	5/5	26 (13.5)	17.9 (6.4)
	0.50	4/5	33 (12.7)	13.8 (6.2)
	0.75	4/5	65 (13.4)	9.4 (3.3)
	1.00	3/5	66 (15.3)	16.3 (3.6)
	1.25	5/6	51 (16.5)	10.1 (4.1)
	2.00	4/5	34 (13.6)	7.4 (2.6)
EH/PMMA	1.00	5/5	28 (14.2)	11.1 (3.4)
	1.50	5/5	59 (12.9)	13.0 (1.2)
	2.00	4/5	90 (9.7)	11.5 (0.6)
	ED50 = 1.29 (0.91–1.81) mg/kg			

[a]*N* = Number of animals responding/number of animals administered drug.
[b]% DAR = percent drug-appropriate responding followed, in parenthesis, by SEM.
[c]Where stimulus generalization occurred, an ED50 dose is provided. ED50 dose followed, in parenthesis, by 95% confidence limits.
[d]Disruption of behavior; majority of animals failed to make ≥5 responses during testing.
[e]Individual % DAR for the three animals was 100%, 90%, and 14%.
[f]Individual % DAR for the three animals was 100%, 88%, and 23%.

partial amphetamine-like nature of MDMA and S(+)MDMA that accounts for the depression in response rates at the doses where stimulus generalization occurred.

Nichols and co-workers (15) have reported that the 3-methoxy-4-methyl derivative of amphetamine, 1-(3-methoxy-4-methylphenyl)-2-aminopropane (see Fig. 1 for structure), is an MDMA-like agent (equipotent with MDMA in animals trained to discriminate MDMA from vehicle) that lacks amphetamine-like properties. This observation is quite intriguing because its 3-desmethoxy counterpart, p-TAP [1-(4-methylphenyl)-2-aminopropane], has been reported to be an amphetamine-like agent to which a (+)amphetamine stimulus generalizes (14). Thus, here is another example of where a minor structural alteration converts an agent from being amphetamine-like to one that is MDMA-like. Unlike PMMA, 1-(3-methoxy-4-methylphenyl)-2-aminopropane lacks an oxygen atom at the nuclear 4-position. It would seem that either a 4-position oxygen atom (e.g. PMMA) or a 3-position oxygen atom may be a major contributor to MDMA-like actions. 3,4-DMA, or 1-(3,4-dimethoxy-4-methylphenyl)-2-aminopropane, is a phenylisopropylamine that possesses two oxygenated functions, one at the 3-position and another at the 4position. It might be noted that 3,4-DMA has already been demonstrated to lack amphetamine-like actions in (+)amphetamine-trained animals but results in partial generalization in MDMA-trained animals (5). Accordingly, we evaluated 3,4-DMA in the PMMA-trained animals. As in MDMA-trained animals (Table 1), it was found (Table 2) that partial (71%) generalization occurs with 3,4-DMA. At the highest nondisruptive dose examined (8.25 mg/kg), two of the three animals

made >80% of their responses on the PMMA-appropriate lever; nevertheless, even if it is concluded that 3,4-DMA is somewhat PMMA-like, it is still considerably less potent than PMMA.

Schechter (21) has shown that an MDMA stimulus generalizes to the serotonin releasing agent fenfluramine. The DOM stimulus, but not an amphetamine stimulus, also generalizes to fenfluramine (3). This latter finding is consistent with the currently accepted mechanism of action of DOM; that is, DOM appears to act via a serotonin, specifically 5-HT_2, receptor agonist mechanism (24). Because administration of racemic MDMA to DOM-trained animals results in partial (52%) generalization (see Table 1), it is perhaps not surprising that MDMA-trained animals recognize fenfluramine. Table 2 shows that administration of fenfluramine to PMMA-trained animals results only in partial (66%) generalization. Thus, the PMMA stimulus may involve, at least in part, a serotonergic mechanism. PMA, in addition to being an amphetamine-like agent, is also a 5-HT releasing agent (16,19). The partial (63%) generalization obtained with PMA (Table 2) upon administration to PMMA-trained animals is unlikely due to the amphetaminergic actions of PMA because the PMMA stimulus failed to generalize to (+)amphetamine. On the other hand, PMMA-stimulus generalization to PMA might involve release of 5-HT. MDMA has also been shown to release 5-HT (19). However, failure of the PMMA stimulus to completely substitute for fenfluramine and PMA, whereas it substitutes for MDMA, suggests that there is more to the PMMA stimulus than simply the release of 5-HT.

Other support for the unique (i.e., nonamphetamine-like and nonDOM-like) action of PMMA comes from studies with its α-ethyl homolog EH/PMMA. Nichols and Oberlender (18,20) have convincingly demonstrated that the α-ethyl homolog of MDMA, MBDB, lacks amphetamine-like and halluciongenic properties. They have further demonstrated that MDMA and MBDB produce similar stimulus effects, but that the α-ethyl homolog is about half as potent as MDMA (18). Accordingly, we prepared and evaluated the α-ethyl homolog of PMMA: EH/PMMA. The PMMA stimulus generalized to EH/PMMA, and the α-ethyl homolog was found to be about one-third as potent as PMMA. Thus, with respect both to stimulus effects and potency, EH/PMMA appears to be to PMMA what MBDB is to MDMA.

Proposal of a New Model

Comparing the stimulus properties of PMMA with those shown in Table 1, it is clear that PMMA is more like MDMA than like amphetamine or DOM. However, PMMA also differs from MDMA; one of the major differences between the two agents is that MDMA possesses some amphetamine-like qualities. That is, MDMA produces locomotor stimulation in rodents (10), whereas PMMA does not (13). In addition, the MDMA stimulus generalizes, or partially generalizes, to (+)amphetamine and cocaine (6,18). PMMA, then, appears to be an MDMA-like agent, but one that possesses minimal amphetamine-like character. Because PMMA is structurally related to, yet structurally simpler than, MDMA, it likely constitutes MDMA's structural parent (8). This hypothesis is supported by the following observations: (a) PMMA produces less amphetamine-like central stimulation than MDMA, (b) an amphetamine stimulus fails to generalize to PMMA, (c) a PMMA stimulus fails to generalize to (+)amphetamine, (d) a DOM stimulus fails to generalize to PMMA, (e) a PMMA stimulus fails to generalize to DOM, (f) an MDMA stimulus generalizes to PMMA, (g) a PMMA stimulus generalizes to MDMA, (h) PMMA is several times more potent than MDMA both in MDMA-trained and in PMMA-trained animals, (i) PMMA possesses a stimulus generalization profile that is more similar to MDMA than to (+)amphetamine or DOM, and (j) homologation of the α-methyl group of PMMA to an α-ethyl group (i.e., EH/PMMA) results in retention of PMMA stimulus properties.

We further propose now, with regard to the discriminative stimulus properties of these agents, that PMMA also be considered the prototype member of this family. It has been previously suggested that MBDB be considered the MDMA-family prototype due to its simplified pharmacology (i.e., lack of amphetaminergic and hallucinogenic character) (20). However, because MBDB is less potent than MDMA in drug discrimination studies (18) whereas PMMA is several times more potent than MDMA (this study), and because all important common structural elements (of MDMA, MBDB, PMMA, and related designer drugs such as, for example, *N*-ethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane or MDE, "Eve") are contained within the structurally simpler PMMA, PMMA would seem to be a better candidate for family prototype. On the other hand, PMMA can not be considered the pharmacophore for MDMA-like stimulus effects because, although it may constitute the pharmacophore for MDA, MDMA and related agents, 1-(3-methoxy-4-methylphenyl)-2-aminopropane, which has been shown to produce MDMA-like stimulus effects (15), lacks a 4-position oxygen atom. Moreover, because nonphenylisopropylamines, such as α-ethyltryptamine, also result in stimulus generalization in MDMA-trained animals (4), PMMA may be considered as a, not the, pharmacophore.

Several years ago, in an attempt to account for the pharmacological actions of different psychoactive phenylisopropylamines, we suggested that these agents exist on a trifurcated continuum, with agents such as amphetamine, DOM, and MDMA positioned at the three extremes, and representing three different pharmacological classes (2). A fourth agent, MDA or 1-(3,4-methylenedioxyphenyl)-2-aminopropane, was situated at the common intersect because MDA is capable of producing all three effects. It is now realized that S(+)MDA accounts for the stimulant character of racemic MDA whereas R(−)MDA represents the more DOM-like isomer (24); both isomers of MDA produce MDMA-like effects (18). Because MDMA results in partial generalization in DOM-trained animals, and in stimulus generalization in amphetamine-trained animals (see Table 1), and whereas the MDMA-like agent PMMA lacks these effects, we feel that the older trifurcated continuum model is no longer adequate and is in need of revision. We propose a new relationship between the three different classes of phenylisopropylamines; this is shown in Fig. 2.

Segment H of the Venn diagram (Fig. 2) represents the classical phenylisopropylamine hallucinogens and is typified by agents such as DOM; segment S represents the stimulants and is typified by (+)amphetamine. The third segment, referred to as "O", is represented by PMMA; because the effect of PMMA in humans is not yet fully documented, we can only refer to its effect as "other" to distinguish it from the hallucinogens and the stimulants. MBDB, an MDMA-like agent lacking hallucinogenic and stimulant character, could also fall into this category. MDMA, specifically S(+)MDMA, would best represent intersect 2; that is, it possesses both amphetamine-like and PMMA-like properties. Because S(+)MDA possesses similar qualities, it too might fall

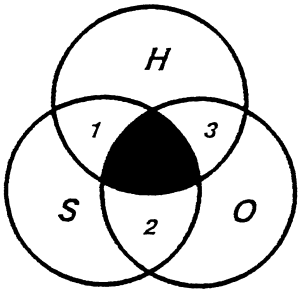

FIG. 2. Venn diagram showing proposed relationships between psychoactive phenylisopropylamines. H = Hallucinogenic actions, S = central stimulant or amphetamine-like actions, "O" = other psychoactive actions. Examples of agents falling into the H, S, and O category include DOM, (+)amphetamine, and PMMA, respectively. See text for further discussion.

into intersect 2. R(−)MDA, on the other hand, being DOM-like and MDMA- (and MBDB-)like, would best represent intersect 3. Racemic MDA best represents the common intersect (shaded area, Fig. 2). These representations may be an oversimplification of the pharmacology of the pyschoactive phenylisopropylamines. However, they provide us with a framework with which to begin a new understanding of the relationships amongst these agents. For example, they suggest the existence of three distinct, yet potentially overlapping, structure-activity relationships. They also provide a model that can generate testable hypotheses, and may also explain why partial generalization is so often noted in drug discrimination studies using animals trained to discriminate various phenylisopropylamines from vehicle.

SUMMARY

In conclusion, then, we have demonstrated that PMMA serves as a training drug in rats, that the stimulus properties of PMMA are dose-dependent, and that its stimulus generalization profile is more similar to that of MDMA than to those of (+)amphetamine or DOM. Lacking stimulant or hallucinogen-like stimulus qualities, PMMA may be considered to be qualitatively similar to MBDB. However, being structurally simpler than either MDMA or MBDB, and being several times more potent than MDMA as a discriminative stimulus, as determined in tests of stimulus generalization, PMMA may constitute a prototypic parent of the MDMA family of designer drugs. Obviously, additional work remains to be done. For example, the individual optical isomers of PMMA will need to be prepared and evaluated to determine if PMMA's actions are stereoselective or sterospecific. The stimulus effects of other agents will also need to be explored using PMMA-trained animals. Nevertheless, sufficient data are already available to allow the proposal of a new working model that should aid our understanding of the pharmacological and structural relationships among the psychoactive phenylisopropylamines.

ACKNOWLEDGEMENT

This work was supported, in part, by US PHS grant DA 01642.

REFERENCES

1. Finney, D. Probit Analysis. London: Cambridge University Press; 1952.
2. Glennon, R. A. Stimulus properties of hallucinogenic phenalkylamines and related designer drugs: Formulation of structure-activity relationships. In: Ashgar, K. and De Souza, E., eds. Pharmacology and Toxicology of Amphetamine and Related Designer Drugs. Washington, D.C.; U.S. Government Printing Office; 1989:43–67.
3. Glennon, R. A. Synthesis and evaluation of amphetamine analogues. In: Klein, M.; Sapienza, F.; McClain, H.; Khan, I. eds, Clandestinely Produced Drugs, Analogues, and Precursors. Washington D.C.: United States Department of Justice; 1989:39–65.
4. Glennon, R. A. MDMA-like stimulus effects of α-ethyltryptamine and the α-ethyl homolog of DOM. Pharmacol. Biochem. Behav. 46:459–462 (1993).
5. Glennon, R. A.; Higgs, R. Investigation of MDMA-related agents in rats trained to discriminate MDMA from saline. Pharmacol. Biochem. Behav. 43:759–763 (1992).
6. Glennon, R. A.; Misenheimer, B. R. Stimulus effects of *N*-monoethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDE) and *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-aminopropane (N-OH MDA) in rats trained to discriminate MDMA from saline. Pharmacol. Biochem. Behav. 33:909–912 (1989).
7. Glennon, R. A.; Young, R. Further investigation of the discriminative stimulus properties of MDA. Pharmacol. Biochem. Behav. 20:501–505 (1984).
8. Glennon, R. A.; Young, R.; Dukat, M. PMMA as a discriminative stimulus. Abstracts, CPPD Meeting, Phoenix AZ; June, 1995.
9. Glennon, R. A.; Young, R.; Hauck, A. E. Structure-activity studies on methoxy-substituted phenylisopropylamines using drug discrimination methodology. Pharmacol. Biochem. Behav. 22: 723–729 (1985).
10. Glennon, R. A.; Yousif, M.; Patrick, G. Stimulus properties of 1-(3,4-methylenedioxyphenyl)- 2-aminopropane (MDA) analogs. Pharmacol. Biochem. Behav. 29:443–449 (1988).
11. Glennon, R. A.; Young, R.; Benington, F.; Morin, R. D. Behavioral and serotonin receptor properties of 4-substituted derivatives of the hallucinogen 1-(2,5-dimethoxyphenyl)-2-aminopropane. J. Med. Chem. 25:1163–1168 (1982).
12. Glennon, R. A.; Young, R.; Rosecrans, J. A.; Anderson, G. M. Discriminative stimulus properties of MDA analogs. Biol. Psychiat. 17:807–814 (1982).
13. Glennon, R. A.; Ismaiel, A. M.; Martin, B.; Poff, D.; Sutton, M. A preliminary behavioral investigation of PMMA, the 4-methoxy analog of methamphetamine. Pharmacol. Biochem. Behav. 31: 9–13 (1988).
14. Higgs, R.; Glennon, R. A. Stimulus properties of ring-methyl amphetamine analogs. Pharmacol. Biochem. Behav. 37:835–837 (1990).
15. Johnson, M. P.; Frescas, S. P.; Oberlender, R.; Nichols, D. E. Synthesis and pharmacological examination of 1-(3-methoxy-4-methylphenyl)-2-aminopropane and 5-methoxy-6-methyl-2-aminoindan: Similarities to 3,4-(methylenedioxy)methamphetamine (MDMA). J. Med. Chem. 34:1662–1668 (1991).
16. Loh, H. H.; Tseng, L.-F. Role of biogenic amines in the actions of methoxyamphetamines, In: Stillman, R. C. and Willette, R. E., eds, The Psychopharmacology of Hallucinogens. New York; Pergamon Press; 1978:13–22.
17. McCann, U. D.; Ricaurte, G. A. Lasting neuropsychiatric sequelae of (±)methylenedioxymethamphetamine ('Ecstasy') in recreational users. J. Clin. Psychopharm. 11:302–305 (1991).
18. Nichols, D. E.; Oberlender, R. Structure-activity relationships of MDMA-like substances. In: Ashgar, K. and De Souza, eds. Pharmacology and Toxicology of Amphetamine and Related Designer Drugs. Washington, D.C.; U.S. Government Printing Office; 1989:1–29.

19. Nichols, D. E.; Lloyd, D. H.; Hoffman, A. J.; Nichols, M. B.; Yim, G. K. W. Effects of certain hallucinogenic amphetamine analogues on the release of [^{3}H]serotonin from rat brain synaptosomes. J. Med. Chem. 25:530–535 (1985).
20. Oberlender, R.; Nichols, D. E. (+)*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine as a discriminative stimulus in studies of 3,4-methylenedioxyamphetamine-like behavioral activity. J. Pharmacol. Exp. Ther. 255:1098–1106 (1990).
21. Schechter, M. D. Serotonergic-dopaminergic mediation of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). Pharmacol. Biochem. Behav. 31:817–824 (1989).
22. Vejdelek, Z.; Nemec, J.; Protiva, M. Synthesis of *N*-(1-phenyl-2-propyl)-2,5diphenylpentylamine and some related compounds as potential neurotropic and cardiovascular drugs. Collect. Czech. Chem. Commun. 51:1487–1493 (1986).
23. Young, R.; Glennon, R. A. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Med. Res. Rev. 6:99–130 (1986).
24. Glennon, R. A.; Young, R. A three-lever operant procedure differentiates the stimulus effects of R(−)MDA from S(+)MDA. J. Pharmacol. Exp. Ther. 276:594–601 (1996).