Pharmacology Biochemistry & Behavior, Vol. 22, pp. 723–729, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Structure-Activity Studies on Methoxy-Substituted Phenylisopropylamines Using Drug Discrimination Methodology

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Received 29 June 1984

GLENNON, R. A., R. YOUNG AND A. E. HAUCK. *Structure-activity studies on methoxy-substituted phenylisopropylamines using drug discrimination methodology.* PHARMACOL BIOCHEM BEHAV 22(5)723–729, 1985.—Eighteen rats were trained to discriminate 1.0 mg/kg of (+)-amphetamine sulfate from saline in a two-lever operant procedure. Once responding was stable, these animals were administered various doses of sixteen different methoxy-substituted phenylisopropylamines in tests of stimulus generalization. Of three possible mono-methoxyphenylisopropylamines, all three produced amphetamine-appropriate responding, but none was as potent as racemic amphetamine. The amphetamine-stimulus did not completely generalize to any of the di- or tri-methoxyphenylisopropylamines.

Amphetamine Phenylisopropylamines Structure-activity studies CNS stimulants Drug discrimination Hallucinogens

CERTAIN phenylisopropylamines, such as amphetamine, are known to behave as CNS stimulants [8], whereas others, e.g., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane or DOM, are hallucinogenic in humans. We [2,4], and others [6,9], have previously used a drug discrimination procedure to investigate the mechanism of action and structure-activity relationships (SAR) of hallucinogenic phenylisopropylamines. In these studies, rats were first trained to discriminate racemic DOM from saline. Subsequent administration of various neurotransmitter antagonists provided mechanistic information while administration of structural modifications of DOM afforded SAR data. More recently, we have undertaken an investigation of amphetamine-like SAR employing animals trained to discriminate (+)-amphetamine from saline. In our initial study, we investigated the effects of four types of gross structural modification on amphetamine-appropriate responding [5]. These modifications of the amphetamine molecule included (a) benz-fusion of the aromatic nucleus, (b) α-demethylation of the alkyl side chain, (c) conversion of the benzylic methylene to a carbonyl group, and (d) conformational restriction of the side chain. Because a number of methoxy-substituted phenylisopropylamines are known to be centrally active [8], the present study investigated the stimulus effects of various mono-, di- and tri-methoxyphenylisopropylamines in order (a) to determine which derivatives are capable of producing discriminative stimulus effects similar to those of amphetamine, and (b) to extend the present state of knowledge concerning the SAR of phenylisopropylamines.

METHOD

Subjects

The animals used in this study were twenty-six male Sprague-Dawley rats. Ten of the animals had been previously trained to discriminate 1.0 mg/kg of (+)-amphetamine sulfate from saline [5]. In the present study, eight additional animals were similarly trained and were added to the original group. In addition, eight rats were trained to discriminate 1.0 mg/kg of racemic DOM hydrochloride from saline following the procedure used by Young *et al.* [12].

Apparatus

Behavioral testing was conducted in standard operant chambers (Model E10-10, Colbourn Instruments, Lehigh Valley, PA) housed within light- and sound-attenuating outer chambers. One wall of each operant chamber was fitted with two levers and a dipper (centered equidistant between the levers) for delivery of reinforcement (0.01 ml of sweetened milk). The recessed area in which the dipper was located was illuminated by a white light when the dipper was activated. Illumination of each chamber was provided by an overhead 28 V houselight. Solid state and electromechanical programming and recording equipment were used, and these were housed in the same room as the operant chambers.

Discrimination Procedure

Briefly, all rats were trained to respond on both of two

levers for sweetened milk under a variable interval 15-second (VI-15 sec) schedule of reinforcement. After lever-responding was established, each daily session was preceded by an intraperitoneal (IP) injection of either S(+)-amphetamine sulfate (1.0 mg/kg), DOM hydrochloride (1.0 mg/kg) or 0.9% saline (1.0 ml/kg). The total number of animals trained with the (+)-amphetamine/saline discrimination was eighteen. Eight animals were trained to discriminate an IP injection of either (±) DOM hydrochloride (1.0 mg/kg) or 0.9% saline (1.0 ml/kg). For both groups of animals, a pre-session injection interval of 15 min was employed; during this period, the animals were in their home cages. Training sessions were of 15 min duration. Responding on one of the levers was reinforced after administration of drug, while responses on the opposite lever were reinforced after administration of saline; treatment conditions were counterbalanced within each group. Saline or drug was administered on a double-alternation schedule (i.e., two days saline, two days drug). On every fifth day the rats' discrimination learning was assessed during an initial 2.5-min non-reinforced (extinction) period, followed by a 12.5-min training session. Data collected during the extinction period included total responses (expressed as mean responses per min) and percent drug (amphetamine or DOM)-appropriate responding (i.e., number of responses on the drug-designated lever as a percent of the total number of responses).

After thirty-five training sessions, discrimination performance was stable under each treatment condition. That is, drug-appropriate responding was greater than 80% after administration of drug, and less than 20% after administration of 1.0 ml/kg of saline.

Generalization Tests

Maintenance of the drug/saline discrimination was insured in all twenty-six animals by continuation of training sessions throughout the generalization testing period. Discrimination training sessions were conducted with drug or 1.0 ml/kg of saline during the two days prior to any generalization test. On one of these days, half the animals would receive training drug (i.e., amphetamine or DOM) whereas the other half would be administered saline; after a 2.5 min non-reinforced session, training was continued for an additional 12.5 min. Animals not discriminating drug (i.e., less than 80% drug-appropriate responding when given drug) from saline (i.e., more than 20% drug-appropriate responding when given saline) were excluded from the immediately subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the discrimination training sessions. The animals were allowed 2.5 min to respond under non-reinforcement conditions; the animals were then removed from the operant chamber and returned to their home cages. An odd number of training sessions (not less than three) separated any two test sessions. Generalization tests investigated the ability of the training drug stimulus to generalize to the various challenge drugs. Doses of these agents were administered in a random sequence using a 15-min pre-session injection interval (unless stated otherwise). Stimulus generalization was defined, in this study, as being 80% or greater drug-appropriate responding. That is, stimulus generalization was said to occur when the animals, after given a dose of challenge drug, made 80% or greater of their total responses on the drug-appropriate lever. Animals making less than five total responses during the entire 2.5-min extinction session were reported as being disrupted. For those compounds where generalization occurred, ED_{50} values were determined from the dose-response data by the method of Finney [1]. These ED_{50} values are doses at which the animals would be expected to make approximately 50% of their responses on the drug-appropriate lever.

Drugs

(+)-Amphetamine was used as its sulfate salt, whereas all of the other agents were used as their hydrochloride salts. 4-Methoxyamphetamine hydrochloride (PMA) and 1-(2,5-dimethoxy-4-methylphenyl)-2-amino-propane hydrochloride (DOM) were obtained from NIDA; all of the other racemic phenylisopropylamines were prepared in our laboratories using reported procedures and include 2-methoxy- (OMA), 3-methoxy- (MMA), 2,3-dimethoxy- (2,3-DMA), 2,4-dimethoxy- (2,4-DMA), 2,5-dimethoxy- (2,5-DMA), 2,6-dimethoxy- (2,6-DMA), 3,4-dimethoxy- (3,4-DMA), and 3,5-dimethoxyphenylisopropylamine (3,5-DMA). The following trimethoxyphenylisopropylamines were also prepared: 2,3,4-trimethoxy- (2,3,4-TMA), 2,3,5-trimethoxy- (2,3,5-TMA), 2,4,5-trimethoxy- (2,4,5-TMA), 2,4,6-trimethoxy- (2,4,6-TMA), and 3,4,5-trimethoxyphenylisopropylamine (3,4,5-TMA). All compounds were dissolved in sterile saline immediately before use and were administered by intraperitoneal injection.

RESULTS

The (+)-amphetamine stimulus generalized to all three of the mono-methoxy phenylisopropylamines (i.e., OMA, MMA and PMA) (Table 1). The 3-substituted derivative MMA (ED_{50}=3.44 mg/kg) was found to be approximately twice as potent as its 2-substituted positional isomer OMA (ED_{50}=7.82 mg/kg), but only about one-fifth as potent as the unsubstituted derivative (±)-amphetamine (ED_{50}=0.62 mg/kg). Using the standard pre-session injection interval of 15 min, PMA produced only partial generalization (followed by disruption of behavior at higher doses). Interestingly, PMA was the only compound to produce partial generalization (60–62%) without a significant reduction in response rate. For this reason, the pre-session injection interval was varied from the standard 15-min interval. Using a 60-min interval, 2.0 mg/kg of PMA produced only 18% amphetamine-appropriate responding (as opposed to 62% appropriate responding using the 15-min interval) (Table 1). The use of a shorter interval (i.e., 5 min) resulted in stimulus generalization (ED_{50}=1.91 mg/kg).

Of the six positional isomers of dimethoxyphenylisopropylamine (DMA), none produced effects identical to those produced by amphetamine. 2,3-DMA and 3,4-DMA produced saline-like effects at 5.5 and 6.5 mg/kg, respectively, and disruption of behavior at higher doses. 2,4-DMA and 2,5-DMA produced partial generalization, followed, at higher doses, by disruption of behavior, while 2,6-DMA and 3,5-DMA produced saline-like effects at 10–20 times the ED_{50} dose of (±)-amphetamine. In addition, neither S(+)-2,5-DMA nor the N-monomethyl derivative of 2,5-DMA (i.e., N-Me 2,5-DMA) resulted in amphetamine-stimulus generalization at the doses evaluated.

The trimethoxyphenylisopropylamines (TMA's) can be divided into two groups: those that produced saline-like effects followed by disruption of behavior (i.e., 2,3,4-TMA and 2,3,5-TMA), and those that produced partial generalization

TABLE 1

RESULTS OF GENERALIZATION STUDIES USING (+)-AMPHETAMINE AS TRAINING DRUG

Agent	Dose (mg/kg)	N*	Amphetamine Appropriate Responding† (±SEM)	Mean Resp Per Min† (±SEM)
(±)-Amphetamine§		ED_{50}=0.62 mg/kg		
(+)-Amphetamine	1.0	18/18	92% (2.8)	13.0 (2.3)
Saline (1.0 ml/kg)		18/18	8% (2.8)	13.6 (1.6)
(±)-OMA	2.0	4/4	7% (3.4)	11.3 (1.0)
	3.0	4/4	8% (1.2)	9.7 (2.4)
	4.0	4/4	20% (10.4)	10.3 (2.6)
	6.0	3/4	24% (8.1)	7.6 (1.4)
	8.0	3/4	49% (17.4)	6.7 (1.2)
	10.0	3/4	61% (14.2)	7.1 (2.1)
	13.0	3/4	73% (9.3)	7.3 (1.8)
	15.0	3/4	89% (8.6)	5.3 (1.0)
		ED_{50}=7.82 (4.80–12.73) mg/kg‡		
(±)-MMA	2.0	4/4	15% (5.6)	10.3 (1.8)
	3.0	4/4	36% (16.6)	10.0 (1.7)
	3.5	4/4	42% (13.2)	10.3 (1.9)
	4.0	4/4	46% (18.4)	9.3 (2.1)
	4.5	3/4	72% (8.5)	9.1 (1.3)
	4.75	3/4	82% (9.7)	7.0 (1.0)
	4.85	3/4	89% (5.2)	6.3 (1.9)
	5.0	1/4	—¶	
		ED_{50}=3.44 (2.64–4.48) mg/kg		
(±)-PMA	0.5	5/5	12% (4.0)	11.8 (2.9)
	0.75	5/5	13% (3.5)	10.8 (2.6)
	1.0	4/5	26% (11.6)	8.8 (1.5)
	1.5	4/4	35% (14.6)	12.7 (2.1)
	1.8	4/4	60% (10.4)	11.3 (2.3)
	2.0	4/4	62% (14.3)	10.0 (2.5)
	2.1	4/5	37% (10.4)	9.0 (2.1)
	2.25	3/6	13% (9.3)	5.1 (1.6)
	2.5	1/4	—¶	
(±)-PMA**	1.5	4/4	20% (9.3)	11.3 (4.3)
	2.0	4/4	18% (7.1)	13.3 (2.3)
	3.5	0/4	—¶	
(±)-PMA††	1.5	4/5	19% (19.0)	12.3 (1.0)
	1.75	4/5	27% (10.4)	8.6 (1.4)
	2.0	4/5	51% (5.4)	9.6 (1.9)
	2.25	4/6	83% (14.3)	4.5 (1.7)
		ED_{50}=1.91 (1.59–2.29) mg/kg		
(±)-2,3-DMA	2.0	4/4	10% (4.6)	9.6 (1.4)
	3.0	4/4	14% (5.7)	8.6 (2.1)
	4.0	3/4	18% (6.7)	6.0 (1.2)
	5.5	3/4	14% (4.0)	7.4 (1.0)
	6.0	1/4	—¶	
	6.5	1/4	—	

(Continued)

TABLE 1
(Continued)

Agent	Dose (mg/kg)	N*	Amphetamine Appropriate Responding† (±SEM)	Mean Resp Per Min† (±SEM)
(±)-2,4-DMA	2.0	4/4	0%	12.0 (1.8)
	4.5	3/5	21% (8.7)	5.2 (1.1)
	5.0	4/4	22% (9.1)	3.5 (1.0)
	5.5	4/5	27% (1.8)	3.8 (0.9)
	6.25	3/5	45% (14.3)	3.6 (1.0)
	6.75	4/5	50% (11.7)	3.0 (0.5)
	7.0	1/5	—¶	
(±)-2,5-DMA	0.5	4/4	3% (2.8)	15.0 (2.2)
	1.0	5/5	15% (9.0)	7.8 (1.0)
	3.0	5/5	13% (2.8)	5.4 (1.0)
	3.5	4/5	19% (8.8)	4.0 (1.1)
	3.9	4/5	20% (7.2)	4.3 (1.3)
	4.4	4/5	23% (6.8)	4.5 (1.7)
	5.0	5/5	14% (5.4)	5.4 (1.1)
	6.5	4/5	14% (4.6)	5.2 (1.2)
	8.0	4/5	36% (14.8)	5.7 (1.4)
	11.0	4/5	41% (13.2)	5.3 (1.0)
	13.0	3/4	49% (15.9)	4.1 (1.1)
	13.5	4/5	43% (5.1)	3.7 (1.2)
	13.9	1/6	—¶	
	14.2	1/5	—	
	15.0	1/5	—	
S(+)-2,5-DMA	6.0	5/5	13% (9.4)	8.6 (1.0)
	9.0	4/4	22% (10.0)	8.4 (2.5)
(±)-N-Me 2,5-DMA	8.0	3/3	5% (2.6)	8.4 (1.0)
	12.0	3/3	6% (1.9)	9.6 (1.2)
	13.5	4/5	21% (5.1)	3.7 (1.0)
	14.25	4/5	18% (5.0)	3.9 (1.0)
	15.0	1/5	—¶	
(±)-2,6-DMA	5.0	5/5	15% (6.4)	11.0 (1.4)
	8.0	5/5	13% (3.0)	12.5 (1.2)
	12.0	5/5	16% (5.8)	10.8 (2.4)
	15.0	4/5	12% (1.8)	7.3 (1.4)
(±)-3,4-DMA	1.0	4/4	8% (5.0)	13.3 (2.7)
	3.0	4/4	5% (2.3)	10.6 (1.8)
	5.0	4/4	6% (5.6)	8.3 (1.3)
	6.25	3/4	6% (4.3)	8.1 (1.0)
	6.5	3/4	7% (3.8)	8.0 (1.4)
	6.65	1/4	—¶	
	6.8	1/4	—	
	7.5	0/4	—	
(±)-3,5-DMA	2.0	4/4	6% (5.7)	10.3 (1.2)
	3.0	4/4	10% (6.9)	10.2 (1.8)
	4.0	3/4	14% (9.9)	8.0 (2.5)
	5.5	3/4	12% (4.4)	7.3 (1.2)
	6.5	3/4	8% (2.3)	5.4 (2.1)
	7.0	3/4	9% (3.4)	6.2 (2.1)

(Continued)

TABLE 1
(Continued)

Agent	Dose (mg/kg)	N*	Amphetamine Appropriate Responding† (±SEM)	Mean Resp Per Min† (±SEM)
(±)-2,3,4-TMA	5.0	5/5	9% (5.0)	12.5 (1.5)
	7.5	4/5	2% (1.9)	9.2 (2.2)
	10.0	1/5	—¶	
(±)-2,3,5-TMA	5.0	4/5	17% (8.4)	7.1 (2.5)
	7.0	4/5	3% (2.1)	5.1 (1.1)
	10.0	1/5	—¶	
(±)-2,4,5-TMA	1.0	4/5	14% (6.7)	8.7 (1.3)
	2.0	3/6	35% (7.4)	5.3 (1.0)
	3.0	4/6	46% (18.2)	3.4 (0.5)
	3.3	1/5	—¶	
(±)-2,4,6-TMA	3.0	4/4	24% (11.5)	12.6 (1.6)
	5.0	5/5	25% (7.2)	8.8 (1.0)
	6.0	4/5	58% (18.9)	5.6 (1.1)
	6.75	5/5	52% (13.5)	4.6 (1.0)
	8.0	3/5	51% (9.2)	4.2 (0.5)
	8.5	1/5	—¶	
(±)-3,4,5-TMA	2.0	4/4	10% (4.7)	10.8 (1.4)
	3.5	4/4	50% (16.5)	9.3 (2.1)
	4.5	4/5	46% (8.6)	5.9 (1.2)
	4.75	3/5	45% (6.3)	5.2 (1.1)
	5.0	1/5	—¶	
	5.25	1/5	—	

*Number of animals responding/number of animals to receive drug.
†Data obtained during 2.5-min extinction session.
‡ED_{50} value with 95% confidence limits in parenthesis.
§Data previously reported [3]; included for comparative purposes.
¶Disruption of behavor (i.e., no responding).
**A 60-min pre-session injection interval was used.
††A 5-min pre-session injection interval was used.

followed by disruption of behavior (i.e., 2,4,5-TMA, 2,4,6-TMA and 3,4,5-TMA). Thus, of the sixteen methoxyphenylisopropylamines evaluated, the amphetamine-stimulus generalized only to the three monomethoxy derivatives. Where generalization occurred, response rates (at the dose where stimulus generalization was observed) were approximately 50% of those produced by the training dose of the training drug and/or saline.

The (±)-DOM-stimulus did not generalize to (±)-PMA. Administration of 2.0 and 2.25 mg/kg of PMA resulted in 33% and 20% drug-appropriate responding, respectively. The administration of 2.5 mg/kg of PMA resulted in disruption of behavior.

DISCUSSION

Amphetamine and DOM both possess a phenylisopropylamine skeleton and yet, whereas amphetamine is a central stimulant, DOM is a hallucinogenic agent. Furthermore, these agents produce dissimilar discriminative stimulus effects in animals. That is, administration of amphetamine to animals trained to discriminate DOM from saline does not result in stimulus generalization, and, vice versa [3, 4, 9]. We have previously investigated the effects of methoxy-substituted phenylisopropylamines in DOM-trained (1.0 mg/kg) animals; this has led to the formulation of SAR for DOM-like activity [4]. In this present study, we have examined the same methoxy-substituted derivatives in animals trained to discriminate (+)-amphetamine from saline.

Each of the three mono-methoxy derivatives produced amphetamine-like effects. The presence of a single methoxy group appears to have an adverse effect on potency in that all three of the mono-methoxy phenylisopropylamines were less potent than amphetamine. The location of the methoxy group is important with respect to its influence on potency. Although it is difficult to make a strict potency comparison because of the different injection-to-test, or pre-session injection, interval employed for PMA, the general order of potency is: unsubstituted > 3-methoxy > 2-methoxy, or, (±)-amphetamine > MMA > OMA. This same order of po-

tency was observed with respect to the ability of these agents to produce locomotor stimulation in rats [10].

Using rats trained to discriminate 0.8 mg/kg of (+)-amphetamine sulfate from saline, Huang and Ho [6] had earlier demonstrated that an amphetamine stimulus generalizes to racemic PMA, but not to MMA. Interestingly, although a 15 min pre-session injection interval was employed, both a 5-min and a 10-min extinction session were used by these investigators. Comparing these results with those presented in Table 1 for PMA, it seems that temporal factors may be less important than they appear to be, and (in retrospect), that an exhaustive evaluation of PMA doses between 1.8 and 2.1 mg/kg may have resulted in stimulus generalization using a 15-min pre-session injection interval. With respect to MMA, the results obtained by Huang and Ho at the highest MMA dose evaluated (i.e., 4.0 mg/kg) are not dissimilar to those reported herein; however, it should be noted (Table 1) that amphetamine-stimulus generalization was not observed in the present study until the dose of MMA exceeded 4 mg/kg.

At the doses at which the mono-methoxy phenylisopropylamines produced amphetamine-appropriate responding, response rates were reduced to approximately 50% of those observed after administration of saline and/or 1.0 mg/kg of (+)-amphetamine. Tseng *et al.* [10] have suggested that mono-methoxy phenylisopropylamines might be capable of producing amphetamine-like and lysergic acid diethylamide (LSD)-like effects. However, to date, compelling evidence in support of this supposition for all three mono-methoxy derivatives has been lacking. For example, animals trained to discriminate 1.0 mg/kg of DOM from saline recognized LSD as being DOM-like, whereas DOM-stimulus generalization did not occur with OMA, MMA or PMA [4]. Nevertheless, to test the possibility that PMA might produce an immediate amphetamine-like effect followed, after a period of time, by a DOM-like effect, several doses of PMA were administered to a small group of rats trained to discriminate DOM from saline, and a 60-min pre-session injection interval was employed for the stimulus generalization test. The results shown in Table 2 suggest that even with the longer injection interval, DOM-stimulus generalization does not occur with PMA. Furthermore, employing rats trained to discriminate 3.0 mg/kg of racemic PMA from saline, Winter [11] has recently reported that administration of LSD to these animals produced an effect that was significantly different from either PMA or saline. Comparable results were obtained when doses of PMA were administered to LSD-trained animals [11]. On the other hand, it has been demonstrated that PMA, unlike amphetamine, does not produce stereotyped behavior in rodents, and that the unsubstituted and mono-methoxy phenylisopropylamines have different patterns of effects on neurotransmitter (e.g., serotonin, dopamine, norepinephrine) release [7,10]. Thus, at those doses of OMA, MMA and PMA where some decrease in response rates were noted, it is entirely possible that these agents may also be producing central effects other than those that might be termed amphetamine-like.

None of the dimethoxyphenylisopropylamines produced amphetamine-appropriate responding (Table 1); that is, the amphetamine-stimulus did not generalize to any of these derivatives. This does not necessarily mean that these agents are totally devoid of amphetamine-like properties. For example, at 6.75 mg/kg 2,4-DMA resulted in 50% amphetamine-appropriate responding; therefore, although this compound is DOM-like [2], it may, at the same time, possess some amphetamine-like character. This is consistent with the results of human trials with this agent [8]. As a group, dimethoxyphenylisopropylamines have received relatively little attention with respect to detailed investigations of their pharmacological properties. The one derivative that seems to have achieved some notoriety is 2,5-DMA; this agent produces DOM-like effects in rats trained to discriminate DOM from saline [2], and is hallucinogenic in humans [8]. However, in some studies, 2,5-DMA has also been reported to possess a stimulant component of action [8]. With regard to amphetamine-like stimulus effects S(+)-amphetamine is more potent than its racemate or enantiomer; also, N-methylation of amphetamine has little effect on its discriminative stimulus properties [3,6]. In contrast, N-methylation of phenylisopropylamine derivatives that produce DOM-like effects results in a decrease in potency, and, R(−)-isomers are more potent than their racemates or enantiomers [4]. In an attempt to suppress the DOM-like properties and/or to exaggerate (potential) amphetamine-like effects, we examined S(+)-2,5-DMA (of which only a limited supply was available) and N-Me 2,5-DMA. At the two doses evaluated, S(+)-2,5-DMA was, certainly, no more amphetamine-like than racemic 2,5-DMA. Likewise, N-Me 2,5-DMA did not produce amphetamine-stimulus generalization.

Of the remaining dimethoxy derivatives, DOM-stimulus generalization has been demonstrated only with 2,4-DMA [2]. At a dose of 6.0 mg/kg, 2,3-DMA produced disruption of behavior both in amphetamine-trained (Table 1) and in DOM-trained [2] animals. The other derivatives (i.e., 2,6-DMA, 3,4-DMA and 3,5-DMA) produced disruption of behavior, at high (10–15 mg/kg) doses, in DOM-trained animals [2], and either saline-like effects (2,6-DMA and 3,5-DMA) or disruption of behavior (3,4-DMA) in amphetamine-trained (Table 1) animals. None of the trimethoxyphenylisopropylamines resulted in complete amphetamine-stimulus generalization (Table 1), whereas they have all been demonstrated to produce DOM-appropriate responding in DOM-trained animals [2].

The results of the present study indicate that, in general, methoxy substitution on the aromatic nucleus of the phenyl-

TABLE 2

EFFECT OF (±)-PMA IN RATS TRAINED TO DISCRIMINATE 1.0 mg/kg OF DOM FROM SALINE

	Dose (mg/kg)	N†	DOM-Appropriate Responding‡ (±SEM)	Mean Responses Per Min‡ (±SEM)
(±)-PMA*	2.0	4/4	33% (4.7)	10.7 (2.6)
	2.25	4/4	20% (6.5)	12.8 (3.5)
	2.5	2/5	—	
(±)-DOM	1.0	8/8	94% (2.1)	10.1 (2.5)
Saline (1 ml/kg)		8/8	11% (3.0)	10.1 (1.8)

*A pre-session injection interval of 60 min was employed for the PMA generalization testing.

†Number of animals responding/number of animals to receive drug.

‡Data obtained during 2.5 min extinction session.

isopropylamine skeleton decreases amphetamine-like stimulus properties. Although mono-methoxy substitution is tolerated, OMA, MMA, and PMA are less potent than the unsubstituted phenylisopropylamine amphetamine. Increasing the number of methoxy groups beyond a single functionality tends to reduce amphetamine-like character and imparts a DOM-like stimulus profile, with activity and potency being related to the location of these methoxy groups. Nevertheless, certain of the di- and tri-methoxy derivatives, although DOM-like [4], produced partial generalization in the amphetamine-trained animals suggesting that they may possess some amphetamine-like properties.

ACKNOWLEDGEMENTS

This work was supported, in part, by PHS grant DA-01642 and by the A. D. Williams Fund.

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