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Stimulus Properties of 1-(3,4-Methylenedioxyphenyl)-2-Aminopropane (MDA) Analogs

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GLENNON, R. A., M. YOUSIF AND G. PATRICK. *Stimulus properties of 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) analogs.* PHARMACOL BIOCHEM BEHAV **29**(3) 443–449, 1988.— Using a standard two-lever operant procedure, groups of rats were trained to discriminate intraperitoneal doses of the phenylisopropylamines (+)amphetamine (1.0 mg/kg) or racemic 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; 1.0 mg/kg) from saline using a VI 15-sec schedule of reinforcement for food reward. Once trained, the animals were administered doses of several methylenedioxy analogs (MDAs) of phenylisopropylamine including the N-monomethyl [S(+)MDMA and R(−)MDMA], N-monoethyl [(±)MDE, S(+)MDE, and R(−)MDE], and the N-hydroxyl [(±)N-OH MDA] derivatives. The DOM-stimulus did not generalize to any of these agents. The amphetamine-stimulus generalized to S(+)MDMA, S(+)N-ethylamphetamine and (±)N-hydroxyamphetamine, but not to R(−)MDMA, (±)MDE, S(+)MDE, R(−)MDE, or N-OH MDA. The present results are consistent with other reports in the literature suggesting that the psychoactive effects of certain MDA derivatives may be other than simply amphetamine- or DOM-like.

Amphetamine Hallucinogens DOM MDA MDMA MDE Discrimination

SIMPLE 3,4-methylenedioxy derivatives of phenylisopropylamine (i.e., those bearing no aromatic substituents other than the methylenedioxy group) have recently gained widespread notoriety because of (a) their possible, though controversial, utility as adjuncts to psychotherapy [5, 19, 24, 36], (b) their potential abuse liability [1,20] and (c) their neurotoxic effects [27, 30, 31]. The structurally simplest and best known member of this family of agents is 1-(3,4-methylenedioxyphenyl)-2-aminopropane (3,4-MDA; "MDA"). Other members of this series with demonstrated activity in humans include the N-monomethyl (MDMA; "Ecstasy," "Adam"), N-monoethyl (MDE; MDEA, "Eve"), and N-hydroxyl (N-OH MDA) analogs of MDA [3,4]. A structurally related agent, alpha-desmethyl MDA (des-Me MDA, HPA), appears to lack psychoactive properties in humans [32].

With the exception of MDA, relatively little is known concerning the stimulus properties of these methylenedioxy derivatives. Although we have previously trained animals to discriminate MDA [11,12] and MDMA [17] from saline, we have found it convenient to examine the stimulus properties of these agents using animals trained to recognize more conventional agents. For example, using a two-lever drug discrimination paradigm with rats trained to discriminate the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) from saline, 5-OMe DMT-stimulus generalization occurred with (±)MDA and R(−)MDA but not with S(+)MDA [13]. This was our first indication that the isomers of MDA might be producing dissimilar stimulus effects. In subsequent studies with groups of rats trained to discriminate either the stimulant phenylisopropylamine (+)amphetamine (AMPH) or the hallucinogenic phenylisopropylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline, we found that stimulus generalization occurred with racemic MDA in both groups of animals [12,15]. However, the amphetamine-stimulus generalized to S(+)MDA but not to R(−)MDA, whereas the DOM-stimulus generalized to R(−)MDA but not to S(+)MDA suggesting that each optical isomer of MDA is responsible for a different stimulus effect [12,15].

MDMA has recently been placed in Schedule I of the Controlled Substances Act. Since then, there has been an increased occurrence of the clandestine synthesis and illicit use of some of the other methylenedioxy derivatives [28]. In the present study, for purposes of comparison, we examine the remaining members of this series in groups of animals trained to discriminate the same two phenylisopropylamines, (+)amphetamine and DOM, from vehicle.

METHOD

Drug Discrimination Studies

Thirteen male Sprague-Dawley rats (ca. 250–300 g) were used in the present study. The animals were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals'

body weights were maintained at this reduced level by partial food deprivation; in their home cages, the animals were allowed drinking water ad lib. The animals were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of either 1.0 mg/kg of (+)amphetamine sulfate (n=7) or 1.0 mg/kg of DOM hydrochloride (n=6) from vehicle (sterile 0.9% saline) under a variable interval 15-sec schedule of reinforcement for food (sweetened powdered milk) reward. Standard two-lever operant chambers (Coulbourn Instruments model E10-10) were used. The amphetamine-trained rats are essentially the same animals that we used in an earlier study [16] (two of the original animals died and were replaced by three new animals). The six rats trained to discriminate DOM from saline were trained as previously described in greater detail [15]. In general, daily training sessions were conducted with both training drugs (in their respective group of animals) or 1.0 ml/kg of saline; on every fifth day, learning was assessed during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. For approximately half the animals, the left lever was designated the drug-appropriate lever whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the stimulus generalization studies until they made greater than 80% of their responses on the drug-appropriate lever after administration of training drug, and less than 20% of their responses on the same drug-appropriate lever after administration of saline, for three consecutive weeks. The animals were placed in the operant chambers no more than once per day and were in their home cages except during training and extinction sessions.

Tests of stimulus generalization were conducted in order to determine if the MDA analogs would substitute for the (+)amphetamine or racemic DOM stimulus. During this phase of the study, maintenance of the training drug discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On one of the two days before a generalization test, approximately half of the animals would receive training drug 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 non-reinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of the challenge drugs were administered in a random order, using a 15-min presession injection interval, to groups of 3–6 rats. If a particular dose of a challenge drug resulted in disruption of behavior, only lower doses would be evaluated in subsequent weeks. Stimulus generalization was said to have occurred when the animals, after a given dose of challenge drug, made ≥80% of their responses on the drug-appropriate lever. Animals making fewer than 5 total responses during the 2.5-min extinction session were considered as being disrupted. Where stimulus generalization occurred, ED50 values were calculated by the method of Finney [7]. The ED50 doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

Solutions of all drugs were made fresh daily in 0.9% sterile saline. All drugs were administered via the intraperitoneal route 15 min prior to testing.

Locomotor Activity Studies

The spontaneous locomotor activity of mice was determined by quantitating the number of interruptions of a photocell light beam (Autotron Inc., Danville, IL) in a 13×7×3" plastic cage as previously described [21]. Ambulatory movement of the mice interrupted the light beam which traversed the cage. Gross movement was measured at a time interval of 5–15 min after injection of test drug. This time period was selected because of its rough correspondence to the 15-min presession injection interval used in the drug discrimination studies. Eight to 14 mice were used for each dose with two animals per chamber. The mice were injected intraperitoneally with saline (control) or with solutions of the test drugs in saline.

Drugs

N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDMA) and its R(−) and S(+) optical isomers (as their hydrochloride salts) were synthesized in our laboratory as previously reported [14]. N-Hydroxy-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (N-OH MDA) was synthesized according to the method of Braun *et al.* [3]. 2-(3,4-Methylenedioxyphenyl)-1-aminoethane hydrochloride (des-Me MDA) was available from an earlier study [15]. N-Hydroxyl-1-phenyl-2-aminopropane oxalate (N-OH AMPH) was prepared according to the method of Gilsdorf and Nord [9] and (+)N-ethyl-1-phenyl-2-aminopropane hydrochloride (N-Et AMPH) was prepared by the method of Schaeffer *et al.* [29] except that lithium aluminum hydride was used in place of sodium bis(2-methoxyethoxy) aluminum hydride as the reducing agent. Racemic N-ethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDE) and its optical isomers (as their hydrochloride salts) were obtained as gifts from NIDA.

RESULTS

The (+)amphetamine-stimulus generalized to S(+)MDMA (ED50=0.6 mg/kg; Table 1), but not to R(−)MDMA; at that dose of S(+)MDMA where generalization occurred (i.e., 0.8 mg/kg) the animals' response rates were reduced to approximately 50% of control levels. The (+)amphetamine-stimulus did not generalize to MDE, nor to either of its optical isomers, but did generalize to (+)N-Et amphetamine. Likewise, the (+)amphetamine-stimulus did not generalize to N-OH MDA but did generalize to N-OH amphetamine (ED50=0.38 mg/kg; 1 μmole/kg). Again, response rates were depressed at those doses where generalization occurred. The alpha desmethyl analog of MDA (des-Me MDA) produced saline-appropriate responding at doses of up to 15 mg/kg and disruption of behavior at 20 mg/kg (Table 1).

In the DOM-trained animals, drug-appropriate responding after administration of MDE, or of either optical isomer of MDE, never exceeded 20%; at the highest non-disruptive doses evaluated, response rates were severely depressed.

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES USING RATS TRAINED TO DISCRIMINATE EITHER (+)AMPHETAMINE OR (±)DOM FROM SALINE

Agent	Dose (mg/kg)	N*	Drug-Correct Responding†	Mean Responses Per Minute†
		(+) Amphetamine-Trained Animals		
(±)MDA‡		ED50=2.29 mg/kg		
S(+)MDA‡		ED50=0.90 mg/kg		
R(−)MDA‡		Disruption >2.0 mg/kg		
(±)MDMA‡		ED50=1.64 mg/kg		
S(+)MDMA	0.1	4/6	0%	8.0 (2.2)
	0.35	5/5	3% (2)	6.9 (1.6)
	0.5	4/5	34% (16)	10.0 (1.6)
	0.8	4/5	80% (5)	8.2 (2.1)
	0.9	1/4	—§	8.2 (2.1)
	1.0	0/4	—§	
	1.4	0/4	—§	
	1.6	0/5	—§	
	2.0	0/4	—§	
		ED50=0.60 (0.44–0.80) mg/kg¶		
R(−)MDMA	1.0	4/4	9% (3)	10.2 (2.8)
	2.0	2/4	33% (8)	18.2 (1.4)
	2.5	3/5	22% (12)	8.4 (2.8)
	2.7	0/4	—§	
(±)MDE	0.15	4/4	3% (2)	18.1 (6.8)
	0.4	3/3	0%	20.0 (8.1)
	0.5	3/3	21% (12)	16.5 (1.6)
	0.8	3/4	17% (2)	13.6 (7.6)
	1.2	3/3	15% (9)	8.1 (2.2)
	1.8	3/4	25% (8)	10.8 (1.2)
	2.0	0/3	—§	
S(+)MDE	0.5	4/4	12% (6)	13.5 (3.3)
	0.7	4/4	24% (12)	10.8 (3.4)
	1.0	3/5	5% (3)	7.6 (3.4)
	1.5	3/5	3% (3)	8.1 (1.4)
	2.0	3/6	14% (1)	6.8 (4.4)
	2.3	2/6	—§	
R(−)MDE	1.0	4/5	4% (3)	11.8 (3.9)
	1.5	3/4	6% (5)	7.6 (1.6)
	1.7	3/3	2% (2)	10.8 (2.5)
	2.0	3/3	0%	16.3 (3.2)
	4.0	3/4	15% (8)	13.0 (4.3)
	4.5	3/4	28% (17)	6.0 (2.0)
	5.0	4/5	19% (13)	7.2 (2.7)
	5.5	1/4	—§	
	6.0	0/4	—§	
	7.0	1/4	—§	
S(+)N-Et AMPH	0.5	3/3	7% (6)	5.7 (1.6)
	0.7	5/7	38% (8)	7.0 (1.7)
	1.0	4/7	55% (16)	6.8 (1.1)
	1.2	5/7	82% (11)	6.3 (1.0)
		ED50=0.87 (0.65–1.17) mg/kg		
(±)N-OH MDA	0.04	3/4	12% (3)	4.2 (1.0)
	0.1	3/4	0%	2.6 (0.2)
	0.2	3/4	0%	3.2 (0.6)
	0.4	3/4	0%	3.2 (0.6)
	0.6	4/5	11% (9)	4.2 (0.9)
	0.7	3/4	12% (3)	3.8 (1.1)
	0.8	1/4	—§	

TABLE 1
(CONTINUED)

Agent	Dose (mg/kg)	N*	Drug-Correct Responding†	Mean Responses Per Minute†
(±)N-OH AMPH	0.2	4/5	19% (3)	8.4 (2.2)
	0.3	4/4	41% (14)	11.2 (1.6)
	0.5	4/4	63% (16)	12.4 (5.0)
	1.0	4/5	93% (4)	5.2 (1.5)
		ED50=0.38 (0.21–0.66) mg/kg		
Des-Me MDA	1.0	4/4	2% (1)	18.3 (3.4)
	4.0	4/4	7% (4)	17.4 (1.4)
	10.0	3/3	4% (3)	16.9 (1.7)
	15.0	4/4	6% (2)	6.3 (1.7)
	20.0	0/3	—§	
S(+)AMPH	1.0	7/7	91% (5)	14.6 (2.3)
Saline (1 ml/kg)		7/7	12% (4)	14.2 (3.1)
		(±)DOM-Trained Animals		
(±)MDA‡		ED50=1.68 mg/kg		
S(+)MDA‡		Disruption >1.5 mg/kg		
R(−)MDA‡		ED50=0.81 mg/kg		
(±)MDMA‡		Disruption >2.0 mg/kg		
S(+)MDMA‡		Disruption >2.0 mg/kg		
R(−)MDMA‡		Disruption >2.0 mg/kg		
(±)MDE	0.2	4/4	6% (5)	8.2 (4.0)
	0.5	3/4	2% (1)	9.0 (1.7)
	0.6	4/6	2% (2)	4.3 (1.3)
	0.8	0/4	—§	
S(+)MDE	0.05	3/3	0%	11.1 (2.6)
	0.2	3/4	0%	7.2 (3.2)
	0.4	4/4	5% (3)	3.1 (0.5)
	0.6	0/3	—§	
R(−)MDE	0.5	3/6	0%	7.5 (2.9)
	0.7	3/5	5% (4)	5.3 (3.8)
	1.0	3/5	4% (2)	6.3 (2.1)
	1.5	3/4	5% (3)	5.9 (1.9)
	2.0	3/3	19% (9)	6.0 (2.1)
	2.5	0/4	—§	
	3.5	0/4	—§	
(±)N-OH MDA	0.5	3/4	4% (2)	17.0 (1.4)
	0.7	4/5	20% (13)	15.5 (1.0)
	0.8	5/5	27% (10)	10.3 (2.9)
	1.0	1/3	—§	
	1.5	3/5	21% (6)	3.9 (0.6)
	1.8	0/3	—§	
(±)DOM	1.0	6/6	94% (3)	10.8 (0.8)
Saline (1 ml/kg)		6/6	8% (2)	11.4 (1.1)

*N=Number of animals responding/number receiving drug.
†Followed by ±SEM.
‡Data previously reported [12,15]; included for comparative purposes.
§Disruption of behavior (i.e., no responding).
¶ED50 values followed by 95% confidence limits.

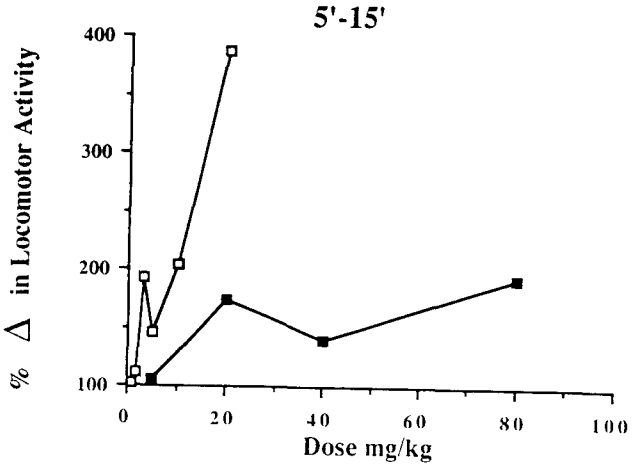

FIG. 1. The effect of the isomers of MDMA on spontaneous locomotor activity. Each point represents the mean percent change in number of photocell beam interruptions, relative to concomitantly tested control mice, in MDMA-treated mice during the interval of 5 to 15 minutes after IP injection. (N=4 to 7 cages per dose.) Black squares: R(−)MDMA; clear squares: S(+)MDMA.

Racemic N-OH MDA produced essentially saline-appropriate responding at the highest non-disruptive dose evaluated; here too, response rates were depressed (Table 1).

The effect of S(+)MDMA and R(−)MDMA on the locomotor activity of mice is shown in Fig. 1. The S(+)-isomer was significantly more potent than its R(−)enantiomer as a locomotor stimulant and its activity is essentially comparable to that of racemic MDMA (365% increase at 20 mg/kg; data not shown).

DISCUSSION

MDA is a rather unique agent in that it produces effects that are both amphetamine-like and hallucinogen-like (i.e., DOM- or LSD-like) (a) in drug discrimination studies using animals trained to discriminate either (+)amphetamine [12], DOM [15], or MDA [12], (b) in the chronic spinal dog [26], and (c) in various behavioral tests involving rodents [23]. Furthermore, the amphetamine-like properties of MDA appear to be associated primarily with the S(+)-isomer whereas the R(−)-isomer seems to be more responsible for the hallucinogen-like properties [10]. Distinct structure-activity relationships (SARs) have been formulated for phenylisopropylamine stimulants and phenylisopropylamine hallucinogens [10,37]; for example, for those phenylisopropylamines with central stimulant activity, the S-isomers are several times more potent than their R-enantiomers. Also, the presence of small alkyl groups on the terminal amine function has relatively little effect on amphetamine-like action but suppresses (or abolishes) hallucinogen-like activity [10]. A comparison of MDA with its N-methyl derivative MDMA provides results that are consistent with these SARs. Unlike racemic MDA and R(−)MDA, neither racemic MDMA, R(−)MDMA, nor S(+)MDMA produce DOM-like stimulus effects [15]. However, racemic MDMA does result in stimulus generalization when (+)amphetamine is used as the training drug regardless of the species of animal employed: rat [12], pigeon [6], monkey [22], and Table 1 shows that this amphetamine-like effect can be attributed primarily to S(+)MDMA. Likewise, the locomotor stimulation produced by MDMA also appears primarily attributable to the S(+)-isomer (Fig. 1). Interestingly, homologation of the alkyl group from methyl to ethyl results in an agent (i.e., MDE) that produces neither amphetamine-like nor DOM-like stimulus effects (Table 1). Furthermore, neither optical isomer of MDE results in amphetamine- or DOM-stimulus generalization (Table 1). This loss in amphetamine-like stimulus effects for MDE relative to MDMA cannot be attributed solely to homologation; though it is less potent than (+)amphetamine itself (ED50=0.43 mg/kg; 1.2 μmoles/kg), (+)N-Et amphetamine (ED50=0.87 mg/kg; 4.4 μmoles/kg) does produce amphetamine-like stimulus effects (Table 1). These results are also consistent with the previous findings that N-Et amphetamine, like amphetamine, is a potent locomotor stimulant [34] and is self-administered by monkeys [33,35].

A similar situation exists with N-OH MDA; the amphetamine-stimulus generalizes with (±)N-OH amphetamine but not with (±)N-OH MDA (Table 1) suggesting that it is not merely the presence of the N-hydroxyl group that alters activity. Indeed, others have previously reported that N-OH amphetamine produces amphetamine-like behavioral effects and that, in some assays, it is at least as potent as amphetamine [2,18].

The alpha desmethyl analog of MDA (i.e., des-Me MDA) is essentially inactive in both groups of animals (Table 1 and [15]). This is consistent with its lack of significant central effects in humans [32]. It may be speculated that the absence of the alpha methyl group renders the molecule more susceptible to oxidative deamination in vivo; similar effects are observed when amphetamine is compared with its alpha-des-methyl counterpart phenethylamine [37].

MDA produces both amphetamine-like and DOM-like stimulus effects. N-Monomethylation of MDA results in the retention of amphetamine-like stimulus effects but in loss of DOM-like stimulus effects. As with other stimulant phenylisopropylamines [10], it is the S(+)-isomer of MDMA that is the more potent (a) as a locomotor stimulant (Fig. 1), (b) in disrupting schedule-controlled operant responding [14], and (c) with respect to stimulus generalization in MDMA-trained rats [14,17]. S(+)MDMA also appears to be responsible for the amphetamine-like stimulus effects of MDMA (Table 1). Although these results might have been anticipated on the basis of available SAR, it cannot be overlooked that MDMA might undergo metabolism to MDA by demethylation in vivo. Indeed, we have recently demonstrated that in the rat MDA is a major metabolite of MDMA [8]. Nevertheless, because the stimulus profile of MDMA is different from that of MDA, it does not seem likely that this metabolite can account for the activity of MDMA within the time constraints employed in the drug discrimination study (unless racemic MDMA is preferentially metabolized to S(+)MDA).

Homologation of the methyl substituent to an ethyl group (i.e., MDE) and replacement of the methyl group by a hydroxyl group (i.e., N-OH MDA) result in agents to which neither the amphetamine- nor DOM-stimulus generalizes. It is particularly surprising that these agents (especially S(+)MDE) do not produce amphetamine-like stimulus effects since the amphetamine-stimulus generalizes to racemic MDA, S(+)MDA, S(+)N-Et amphetamine and N-OH amphetamine. It is also surprising that MDE and N-OH MDA should differ from what is observed for MDMA when it has been reported (although very limited data are available and these agents have not yet been thoroughly evaluated in humans) that all three agents share a common psychophar-

macological profile in humans [4]. Several explanations are possible. First, these agents may produce effects in rats that differ from those produced in humans; second, these agents may produce a central effect that interferes with or masks potential amphetamine-like or DOM-like stimulus effects (which might have been observed at higher doses had disruption of behavior not occurred at the lower doses). With regard to the latter possibility, we have previously suggested that psychoactive phenylisopropylamines might consist of several behavioral sub-classes [13] and it may be that MDE, N-OH MDA, and their relatives, are producing a pharmacological effect that is neither amphetamine-like nor DOM-like. The possibility also exists that these agents may constitute members of a new pharmacological class of psychoactive agents. Nichols and co-workers [25] have recently made such a claim for MDMA and, more specifically, for the alpha ethyl homolog of MDMA. In humans, these agents reportedly produce a state of introspection and the alpha ethyl homolog lacks amphetamine-like or hallucinogenic activity [25]. MDA and MDMA may share this activity but, at the same time, produce amphetamine-like and/or DOM-like effects as evidenced by the results of the drug discrimination studies. Obviously, additional studies (on both animal and human subjects) are necessary and warranted in order to better understand this interesting group of psychoactive agents.

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