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RAPID COMMUNICATION

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[1]

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GLENNON, R. A. AND B. R. MISENHEIMER. *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**(4) 909–912, 1989.—Tests of stimulus generalization were conducted using rats trained to discriminate 1.5 mg/kg of N-monomethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA) from saline in order to determine if two structurally related analogs (MDE and N-OH MDA) would produce similar stimulus effects. The MDMA-stimulus (MDMA, ED_{50} value = 0.76 mg/kg) generalized both to MDE (ED_{50} value = 0.73 mg/kg) and N-OH MDA (ED_{50} value = 0.47 mg/kg). Administration of (+)amphetamine resulted in partial generalization (maximum of 49% MDMA-appropriate responding) in the MDMA-trained animals. Taken together with our previous studies showing that MDMA substitutes for the phenylisopropylamine stimulant (+)amphetamine, but that neither MDE nor N-OH MDA substitute for (+)amphetamine or for the phenylisopropylamine hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), the present results [i.e., MDMA-stimulus generalization to MDE, N-OH MDA, but not to (+)amphetamine] suggest that 1) MDMA produces effects other than those that may be considered amphetamine-like, and 2) MDE and N-OH MDA are MDMA-like agents with even less of an amphetamine-like component of action than MDMA itself.

MDMA MDE N-OH MDA MDA Amphetamine Drug discrimination

PSYCHOACTIVE phenylisopropylamines may consist of several behavioral subclasses (6,9). We have suggested, for example, that certain phenylisopropylamines might exist on an amphetamine-like/hallucinogen continuum (10,12), and that aromatic, side-chain, and terminal amine substituents determine where a particular agent lies on this continuum (6).

MDMA or N-monomethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane ("XTC," "Ectasy," "Adam") is a phenylisopropylamine that is claimed to be of benefit as an adjunct to psychotherapy; however, due to its abuse potential, it has been recently classified as a Schedule I controlled substance (17). 1-(3,4-Methylenedioxyphenyl)-2-aminopropane (MDA), the structural parent of MDMA, produces in human subjects both central stimulant and hallucinogenic effects (22). Likewise, in tests of stimulus control of behavior in animals, stimulus generalization occurs upon administration of MDA to animals trained to discriminate either the phenylisopropylamine central stimulant (+)amphetamine or the phenylisopropylamine hallucinogenic agent

[1]A preliminary account of this work was presented at the NIDA-sponsored Technical Review of Controlled Substance Analogs, Washington DC, August, 1988.

1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline (7, 8, 11). Conversely, stimulus generalization occurs both to amphetamine and DOM in animals trained to discriminate MDA from saline (8,11). MDA, then, may lie somewhere near the center of the amphetamine-like/hallucinogen continuum.

According to existing structure-activity relationships (6), N-monomethylation of MDA, to afford MDMA, should reduce its hallucinogenic properties, but should have relatively little effect on amphetamine-like character. To this extent, MDMA produces stimulus effects similar to those of (+)amphetamine (4, 7, 15, 16), but fails to result in stimulus generalization in rats trained to discriminate DOM from saline (11). Two closely related structural analogs of MDMA, N-monoethyl MDA (MDE, "Eve") and N-hydroxy MDA (N-OH MDA), are reported to elicit effects in humans similar to those produced by MDMA (2,3). MDE is slightly less potent, and N-OH MDA slightly more potent, than MDMA (2,3), such that N-OH MDA is nearly twice as potent as MDE. Furthermore, both agents are currently being considered for classification as Schedule I drugs. Based on the above mentioned structure-activity relationships, MDE and N-OH MDA would be expected to produce stimulus effects similar to those of (+)amphetamine, but dissimilar to those of DOM. Indeed, neither agent results in stimulus generalization in DOM-trained rats (15). Interestingly, however, a (+)amphetamine-stimulus also failed to generalize to MDE and N-OH MDA (15). That is, both agents elicited saline-appropriate responding in (+)amphetamine-trained rats (at doses of up to 1.8 and 0.7 mg/kg, respectively), or, at slightly higher doses, resulted in disruption of behavior (i.e., no responding) (15). This is particularly difficult to understand in light of the fact that both N-monoethylamphetamine and N-OH amphetamine produce (+)amphetamine-like stimulus effects (15). Evidently, neither MDE nor N-OH MDA is a simple amphetamine-like agent. Apart from any amphetamine-like effects, Nichols (18) has suggested that MDMA can produce a unique spectrum of nonamphetamine effects that may account for its utility in psychotherapy. Thus, the possibility is raised that MDE and N-OH-MDA behave more like MDMA than like amphetamine or DOM. Several years ago, we demonstrated that MDMA serves as an effective discriminative stimulus in rats (13); since then, others have also trained rats to discriminate MDMA from saline (19,21). In order to test the hypothesis that MDE and N-OH MDA might produce MDMA-like effects, we trained another group of rats to discriminate MDMA from saline and conducted tests of stimulus generalization with MDE, N-OH MDA, and (+)amphetamine.

METHOD

Drug Discrimination Studies

Six 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 weights. The animals' body weights were maintained at this reduced level throughout the study by partial food deprivation. In their home cages, the animals were allowed free access to drinking water. Using standard two-lever operant chambers (Coulbourn Instruments Model E10-10), the animals were first trained to lever-press for food (sweetened powdered milk) reward and were then trained to discriminate 1.5 mg/kg of MDMA hydrochloride from 1 ml/kg of 0.9% saline using a variable-interval 15-sec schedule of reinforcement. For half of the animals, the right lever was designated as the drug-correct lever, whereas for the other half, the left lever was designated the drug-correct lever. Animals were administered drug or saline in a double alternation sequence (i.e., two days drug, two days saline) once per day in a 15-min training session and all drugs were administered via the intraperitoneal route 15 min prior to testing. Once per week, discrimination learning was assessed under each condition during an initial 2.5-min nonreinforced (i.e., extinction) session followed by a 12.5-min training session. Data collected during the extinction session included responses per min (i.e., response rate) and the number of responses (as a percent of total responses) made on the drug-appropriate lever. Once the animals consistently made greater than 80% of their responses on the drug-appropriate lever following administration of 1.5 mg/kg of MDMA, and fewer than 20% of their responses on the same lever following 1.0 ml/kg of saline, they were used in the stimulus generalization studies.

Stimulus generalization studies were conducted in order to determine if the MDMA-stimulus would generalize to nontraining doses of MDMA, or to doses of MDE, N-OH MDA, and (+)amphetamine. Discrimination training continued (as above) during this phase of the study, and only those animals meeting the original criteria were used in a subsequent stimulus generalization experiment. During these generalization studies, test sessions were interposed among the training sessions on a once per week basis. The animals were allowed to respond under extinction conditions for 2.5 min and were then returned to their individual home cages. Generally, four training sessions separated any two generalization sessions. MDE, N-OH MDA, and (+)amphetamine were administered via the intraperitoneal route 15 min prior to testing. Stimulus generalization was said to have occurred when the animals made greater than 80% of their total responses on the drug-appropriate lever following administration of drug. Animals making fewer than five total responses during the entire 2.5-min extinction session were recorded as being disrupted. Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (5) and reflect the dose at which the animals would be expected to make 50% of their responses on the drug-appropriate lever. Two of the rats died shortly after initiation of the stimulus generalization studies.

Drugs

Both N-monomethyl- and N-hydroxy-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDMA and N-OH MDA, respectively) were previously prepared in our laboratory [15]. N-Monoethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDE) was obtained from NIDA and (+)amphetamine sulfate was purchased from Sigma Chemical Company (St. Louis, MO). All solutions were prepared fresh daily in sterile 0.9% saline.

RESULTS

Table 1 shows that the MDMA-stimulus generalized to MDE and N-OH MDA in a dose-related manner. MDE (ED_{50} value = 0.73 mg/kg) is essentially equipotent with MDMA (ED_{50} value = 0.76 mg/kg); N-OH MDA (ED_{50} = 0.47 mg/kg) is slightly more potent than either MDE or MDMA. The MDMA-stimulus did not generalize to (+)amphetamine (Table 1); doses of 0.8 and 1.0 mg/kg of (+)amphetamine produced a maximum of about 50% MDMA-appropriate responding, and doses of 1.2 and 2.0 mg/kg resulted in disruption of behavior.

DISCUSSION

MDMA produces amphetamine-like stimulus effects in (+)amphetamine-trained animals regardless of whether rats (8), pigeons (4), or monkeys (16) are used as subjects. This effect is accompanied, however, by a decrease in response rates at doss where stimulus generalization occurs (4, 8, 16). Consistent with these observations, stimulus generalization also occurs upon administration of MDMA to rats trained to discriminate either apomor-

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES WITH RATS TRAINED TO DISCRIMINATE MDMA (1.5 mg/kg) FROM SALINE

Agent	Dose (mg/kg)	N*	%-MDMA Responding†‡	Response Rate†§	ED_{50} (mg/kg)¶
MDMA	0.5	3/3	26% [± 8]	12.4 [±2.1]	
	0.7	3/3	31% [±15]	14.5 [±3.7]	
	1.0	3/3	76% [± 6]	12.2 [±2.1]	0.76
	1.5	6/6	92% [± 4]	12.8 [±2.6]	(0.47–1.21)
MDE	0.2	4/4	9% [± 6]	12.2 [±4.6]	
	0.5	3/3	30% [±20]	13.6 [±2.1]	
	1.0	4/4	65% [± 2]	14.8 [±4.3]	
	1.5	4/4	74% [± 2]	14.1 [±1.6]	0.73
	2.0	4/4	91% [± 6]	16.0 [±4.6]	(0.34–1.54)
N-OH MDA	0.1	3/3	8% [± 5]	12.6 [±2.2]	
	0.4	4/4	58% [±18]	18.0 [±4.4]	
	0.6	3/4	51% [± 5]	12.2 [±3.8]	
	1.0	3/3	71% [±17]	8.8 [±3.8]	0.47
	1.5	3/3	85% [± 5]	8.3 [±2.6]	(0.19–1.16)
(+)Amphetamine	0.5	4/4	28% [± 4]	15.7 [±3.1]	
	0.8	2/4	48% [± 8]	4.6 [±2.6]	
	1.0	4/4	49% [±10]	8.6 [±2.8]	
	1.2	1/4	—**		
	2.0	1/4	—**		
Saline (1 ml/kg)		6/6	13% [± 4]	11.7 [±2.2]	

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

†Data collected during 2.5-min extinction session.

‡Percent of responses on the MDMA-appropriate lever followed by S.E.M.

§Responses per min followed by S.E.M.

¶ED_{50} value followed by 95% confidence limits (in parentheses).

**Disruption of behavior (i.e., majority of animals made <5 total responses during the entire 2.5-min extinction session).

phine or (−)cathinone from vehicle (i.e., agents known to substitute for (+)amphetamine in amphetamine-trained animals) (20). However, Oberlender and Nichols failed to observe substitution of MDMA for (+)amphetamine in (+)amphetamine-trained rats (19). Nevertheless, there is ample evidence to suggest some similarity between the stimulus effects produced by MDMA and amphetamine. On the other hand, the MDMA-stimulus only partially generalized to (+)amphetamine (Table 1). Oberlender and Nichols found complete substitution of (+)amphetamine for MDMA in MDMA-trained animals, but only at a dose that disrupted more than half of the animals (19). Taken together, these results suggest that although there may be significant similarities between the stimulus effects of MDMA and amphetamine, there are probably some very significant differences.

Clearly, MDE and N-OH MDA are not simple amphetamine-like agents. MDE and N-OH MDA fail to elicit greater than 25% drug-appropriate responding in (+)amphetamine-trained rats (15). (Because both agents disrupt amphetamine-trained animals at low doses, the possibility cannot be excluded that these agents might produce some amphetamine-like effects at high doses.) In the present study, it is demonstrated for the first time that both agents are capable of producing MDMA-like stimulus effects in MDMA-trained animals. At those doses where stimulus generalization occurred, MDE produces no decrease in response rate, and N-OH MDA produces less than a 50% decrease in response rate.

Coupled with our previous results, and with results of studies from other laboratories, it appears that some substituted phenylisopropylamines are capable of producing either amphetamine-like (e.g., amphetamine), hallucinogen-like (e.g., DOM) or both amphetamine-like and hallucinogen-like (e.g., MDA) stimulus effects in animals. Certain structural modifications of MDA alter its spectrum of effects in a manner consistent with established structure-activity relationships and consistent with the amphetamine/hallucinogen continuum hypothesis. For example, N-monomethylation of MDA (i.e., MDMA) enhances its amphetamine-like character and diminishes (or abolishes) its hallucinogen-like character. Other structural modifications of MDA, such as N-ethylation and N-hydroxylation, afford agents that produce results inconsistent with established structure activity relationships. As previously suggested by Nichols (18), certain structural modifications (including N-monomethylation) of MDA may unveil a new type of nonamphetamine, nonhallucinogen-like activity. Nevertheless, MDMA seems to retain significant amphetamine-like character as evidenced not only by its stimulus properties (4, 8, 16), but also by its ability to produce locomotor stimulation in rodents (2, 3, 15), to disrupt schedule-controlled responding of mice (14), and to be self-administered by Rhesus monkeys (1). Likewise, MDE (but not N-OH MDA) is a fairly potent locomotor stimulant (3), but neither MDE nor N-OH MDA produce amphetamine-appropriate responding in (+)amphetamine trained rats (nor DOM-appropriate responding in DOM-trained rats) (15). Yet, the MDMA-stimulus generalized both to MDE and N-OH MDA (Table 1). Taken together, these results suggest: 1) that MDMA possesses significant amphetamine-like character, 2) that MDMA produces stimulus effects in addition to those that may be considered amphetamine-like, and 3) that the nonamphetamine, nonhallucinogen effects associated with MDMA are more pronounced in MDE and N-OH MDA than in MDMA itself.

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