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1-(2,3-METHYLENEDIOXYPHENYL)-2-AMINOPROPANE (2,3-MDA): A PRELIMINARY INVESTIGATION

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Abstract—1. Rats trained to discriminate saline from either (+)-amphetamine, (±)-DOM, or (±)-3,4-MDA in a two-lever drug discrimination paradigm were administered doses of a novel positional isomer of 3,4-MDA, i.e. 2,3-MDA.

2. The novel isomer produced neither amphetamine-appropriate nor DOM-appropriate responding: the 3,4-MDA stimulus did, however, generalize to 2,3-MDA.

INTRODUCTION

There are two possible positional isomers of the phenylisopropylamine 1-(methylenedioxyphenyl)-2-aminopropane (methylenedioxyamphetamine; MDA), i.e. 2,3-MDA and 3,4-MDA. The psychoactive agent 3,4-MDA has been studied both in human (Shulgin, 1978) and non-human (Marquardt *et al.*, 1978; Glennon and Young, 1983) subjects and has been demonstrated to produce both amphetamine-like and hallucinogen-like effects. 2,3-MDA has only recently been synthesized (Soine *et al.*, 1983) and even though its pharmacological properties have not yet been investigated, it is listed under Schedule I of the Federal Comprehensive Drug Abuse and Control Act (Shulgin, 1978). Because various phenylisopropylamine derivatives are known to produce amphetamine-like and/or hallucinogenic effects (Shulgin, 1978), it was of interest to evaluate the effects of 2,3-MDA in a drug discrimination paradigm employing animals trained to discriminate a phenylisopropylamine stimulant (i.e. amphetamine), a phenylisopropylamine hallucinogen (i.e. DOM), or a phenylisopropylamine with dual effects (i.e. 3,4-MDA) from saline.

MATERIALS AND METHODS

Subjects

Male Sprague–Dawley rats, weighing 250–300 g at the start of training, were used; body weights were reduced to approximately 80% of expected free-feeding weights by partial food deprivation. The animals were individually housed and had free access to water.

Apparatus

Commercially-available operant chambers (Coulbourn Instruments) housed with sound and light attenuated outer chambers were used. A single dipper situated between the two levers delivered 0.01 ml of sweetened condensed milk (diluted 2:1 with tapwater). Other details on the apparatus and recording of data have been described (Young *et al.*, 1983).

Procedure

We have previously trained animals (rats) to discriminate saline from either (+)-amphetamine (Glennon and Young, 1983) or DOM (Young *et al.*, 1981). The procedures used herein are identical to those reported and will only be described in brief. The animals trained to discriminate saline from 1.5 mg/kg 3,4-MDA are the same group of animals recently reported by Glennon and Young (1984). The animals were initially trained to respond to a variable interval 15-sec schedule of reinforcement. When rates of responding had stabilized, the animals were trained to discriminate intraperitoneal (i.p.) injections of either 1.0 mg/kg of (+)-amphetamine sulfate ($N = 4$) or 1.0 mg/kg of (±)-DOM ($N = 6$) from vehicle (sterile saline, 1.0 ml/kg). A pre-session injection interval of 15 min was used; training sessions were also of 15 min duration. Saline or drug was administered on a double-alteration schedule. Discrimination learning was assessed every fifth day during a 2.5-min non-reinforced (extinction) session; this was followed by a 12.5 min training session. Data collected during the extinction session included percent correct responding on the drug-appropriate lever (number of responses on the drug designated lever as a percent of total number of responses) and response rate (resp/min). Once discrimination training was stable in each group, i.e. more than 93% drug-appropriate responding after administration of the training dose of the training drug and less than 10% drug-appropriate responding after administration of saline (response rates = 13–15 and 12–15 resp/min for the training dose of amphetamine and DOM, respectively, and 13–15 resp/min after saline), substitution investigations were begun. During the substitution (generalization) studies, various doses of (±)-2,3-MDA were administered during 2.5-min extinction sessions that were interposed between discrimination training sessions. After this 2.5-min period, the animals were returned to their home cages. Again, a 15-min presession injection interval was employed and doses of 2,3-MDA were administered (i.p.) in a random sequence.

Drugs

Racemic amphetamine sulfate was on hand as a result of earlier studies. Racemic MDA hydrochloride and DOM hydrochloride were gifts from NIDA, while (±)-2,3-MDA hydrochloride was synthesized according to the method of Soine *et al.* (1983). All solutions were prepared fresh daily in sterile 0.9% saline.

RESULTS AND DISCUSSION

In the amphetamine-trained group of animals, 2,3-MDA produced saline-like responding at doses of

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Table 1. Effects of 2,3-MDA in animals trained to discriminate either (+)-amphetamine, (±)-DOM or (±)-3,4-MDA from saline

Training drug	Dose of 2,3-MDA (mg/kg)	N[a]	% Drug-appropriate Responding[b] (± SEM)	Resp/min[b] (± SEM)
Amphetamine	1.0	4/4	16% (4.5)	11.3 (1.0)
	2.0	3/4	22% (5.4)	9.7 (1.3)
	2.5	3/4	24% (8.6)	8.6 (1.4)
	2.6	3/4	23% (9.6)	9.2 (1.6)
	2.75	2/4	12% (2.1)	6.3 (2.5)
	3.0	1/4	—[c]	
DOM	1.0	5/5	0%	14.5 (2.1)
	2.0	5/5	2% (1.8)	12.5 (1.0)
	4.0	4/5	5% (4.1)	5.5 (1.3)
	6.0	2/6	—[c]	
	8.0	1/5	—[c]	
3,4-MDA	2.0	4/4	15% (8.4)	10.8 (1.3)
	2.75	4/4	37% (13.0)	12.8 (2.1)
	3.15	4/4	56% (22.8)	11.8 (1.9)
	3.5	3/4	81% (9.8)	11.7 (2.2)
	5.0	3/4	100%	8.0 (1.5)

[a]Number of animals responding/number to receive particular dose of drug.
[b]Data obtained during 2.5-min extinction session. [c]Disruption of responding, i.e. majority of animals failed to respond.

2.75 mg/kg or less, and disruption of behavior (i.e. no responding) at 3.0 mg/kg (Table 1). Similar results were noted in the animals trained to discriminate DOM from saline; 2,3-MDA produced saline-like responding at doses at or below 4.0 mg/kg and disruption of behavior at doses of 6.0 and 8.0 mg/kg. Administration of 2,3-MDA to the 3,4-MDA-trained animals resulted in stimulus generalization (Table 1), $ED_{50} = 2.90$ mg/kg.

Amphetamine and DOM produce dissimilar stimulus effects regardless of what is used as the training drug (Silverman and Ho, 1980; Glennon *et al.*, 1983). However, both stimuli generalize to 3,4-MDA and vice versa (Glennon *et al.*, 1983; Glennon and Young, 1984). That is, racemic 3,4-MDA produces stimulus effects that appear to resemble those produced by both amphetamine and DOM. Interestingly, the positional isomer, 2,3-MDA, produces effects similar to 3,4-MDA, but effects that are dissimilar to either amphetamine or DOM. Furthermore, based on their ED_{50} values, 2,3-MDA is approximately one-fifth as active as 3,4-MDA ($ED_{50} = 0.65$ mg/kg; Glennon and Young, 1984) as a stimulus in 3,4-MDA-trained animals. The results of this preliminary study suggest that 2,3-MDA is not without central actions and, based on its unique stimulus properties, that it might be an interesting candidate for further pharmacological evaluation.

REFERENCES

Glennon R. A. and Young R. (1984) MDA: A psychoactive agent with dual stimulus effects. *Life Sci.* **34,** 379–383.

Glennon R. A., Rosecrans J. A. and Young R. (1983) Drug-induced discrimination: A description of the paradigm and a review of its specific application to the study of hallucinogenic agents. *Med. Res. Rev.* **3,** 289–340.

Marquardt G. M., Distefano V. and Ling L. L. (1978) Pharmacological effects of (±)- (S)- and (R)-MDA. In *The Psychopharmacology of Hallucinogens.* (Edited by Stillman R. C. and Willette R. E.). pp. 84–104. Pergamon, New York.

Shulgin A. T. (1978) Psychotomimetic drugs: Structure activity relationships. In *Handbook of Psychopharmacology.* (Edited by Iversen L. L., Iversen S. D. and Snyder S. H.) pp. 243–333. Plenum, New York.

Silverman P. B. and Ho B. T. (1980) The discriminative stimulus properties of 2,5-dimethoxy-4-methylamphetamine (DOM): Differentiation from amphetamine. *Psychopharmacology* **68,** 209–215.

Soine W. H., Shark R. E. and Agee D. T. (1983) Differentiation of 2,3-methylenedioxyamphetamine from 3,4-methylenedioxyamphetamine. *J. Forensic Sci.* **28,** 386–390.

Young R., Glennon R. A. and Rosecrans J. A. (1981) Discriminative stimulus properties of the hallucinogenic agent DOM. *Commun. Psychopharmac.* **4,** 501–506.

Young R., Rosecrans J. A. and Glennon R. A. (1983) Behavioral effects of 5-methoxy-N,N-dimethyltryptamine and dose-dependent antagonism by BC-105. *Psychopharmacology* **80,** 156–160.