3485

Psychopharmacology 67, 311–312 (1980)

Psychopharmacology

Short Report

MDA and DOM: Substituted Amphetamines that do not Produce Amphetamine-Like Discriminative Stimuli in the Rat

Harlan E. Shannon
National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, KY 40583, U.S.A.

Abstract. 3,4-Methylenedioxyamphetamine (MDA) and 2,5-dimethoxy-4-methylamphetamine (DOM) are amphetamine congeners that produce both amphetamine-like and LSD-like effects. To evaluate whether MDA and DOM should be classed with amphetamine, their capacity to produce amphetamine-like discriminative stimuli was assessed. Rats were trained to discriminate between saline and 1.0 mg/kg *d*-amphetamine in a two choice, discrete trial shock avoidance paradigm. Neither MDA nor DOM produced any amphetamine-appropriate responding when tested over a 30-fold dose range. The specificity of the procedure to detect amphetamine-like effects was demonstrated by the failure of LSD to produce any amphetamine-appropriate responding. These results suggest that neither MDA nor DOM should be classed as amphetamine-like agents.

Key words: *d*-Amphetamine – MDA – DOM – LSD – Discriminative stimuli

3,4-Methylenedioxyamphetamine (MDA) and 2,5-dimethoxy-4-methylamphetamine (DOM) are substituted amphetamines which produce both amphetamine-like and LSD-like effects (Martin et al., 1978). This mixed spectrum of effects makes pharmacologic classification difficult. Such classification is important in assessing abuse liability as well as in determining whether MDA and DOM have amphetamine-like or LSD-like modes of action or both or if they represent a unique class of drugs. Evaluation of the discriminative stimulus properties of drugs is a useful means of classification within other drug classes (Barry, 1974 for review). Therefore, to determine if MDA and DOM should be classed with their parent chemical compound, amphetamine, experiments were conducted to determine whether they produce amphetamine-like discriminative stimuli in the rat.

Offprint requests to: H. E. Shannon

Materials and Methods

Subjects. The subjects were male CFE rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) weighing 275–300 g at the start of discrimination training. The rats were housed in a large colony room where they had continuous access to food and water. The lights in the colony room were turned off 6 p.m.–6 a.m.

Apparatus. A two-lever rat chamber (model 1111-L, Grason-Stadler Co., Bolton, Massachusetts) was modified by suspending from the ceiling a 25 cm long omnidirectional lever midway along the wall opposite the original levers (the choice response levers) and 2.5 cm from the wall. Other details of the experimental chamber and environmental enclosure were described previously (Shannon and Holtzman, 1976). Schedule contingencies were controlled by a SCAT 3002 system (BKP Scientific, Berlin, Massachusetts).

Procedure. The procedure for training rats to discriminate between *d*-amphetamine and saline was similar to that described in detail elsewhere (Shannon and Holtzman, 1976). Briefly, rats were trained in a two choice, discrete trial shock avoidance task that required the animals to respond first on the omnidirectional lever and then on the appropriate choice response lever to terminate each trial and avoid or escape from a 1.0 mA electric shock delivered to their feet.

d-Amphetamine (1.0 mg/kg) or saline was injected SC 30 min before the start of training sessions, which were conducted 5 days a week. Each session ended after 21 trials or 30 min, whichever came first. The amphetamine and saline sessions were given in double alternation and then in random alternation until responding was at least 95% correct for four consecutive sessions (two were amphetamine and two were saline sessions). When a rat met this criterion, the next amphetamine and saline sessions were conducted as test sessions where a response on either choice lever terminated a trial. An animal was said to have acquired the discrimination if at least 18 of 20 trials (exclusive of the first trial) were to the appropriate choice lever during both test sessions. Once an animal met the acquisition criteria, training sessions, with only once choice lever being 'correct', were conducted at least 3 days a week with amphetamine and saline sessions given in double alternation across training sessions. Test sessions, with both choice levers being 'correct', were conducted on Tuesday and Friday if responding was at least 90% correct on all training sessions since the previous test day. All drugs and saline were

0033-3158/80/0067/0311/$01.00

administered SC 30 min before the start of a session. The order in which the doses and control injections were administered within each drug series was randomized.

Drugs. The following drugs were used in this study: *d*-amphetamine sulfate; lysergic acid diethylamide tartrate (LSD); *d,l*-3,4-methylenedioxyamphetamine HCl (MDA); and 2,5-dimethoxy-4-methylamphetamine HCl (DOM). All drugs were dissolved in 0.9% saline and injected SC in a volume of 1.0 ml/kg. Drug doses are expressed in terms of the free base except for DOM which is expressed in terms of the salt.

Results

d-Amphetamine produced a dose-related increase in the number of trials completed on the amphetamine-appropriate lever when tested over a 30-fold dose range. Saline and *d*-amphetamine (0.1, 0.3, 1.0, and 3.0 mg/kg) produced mean levels of responding on the drug-appropriate lever of 3, 4, 44, 96, and 95%, respectively ($N = 5$). In contrast, the substituted amphetamines MDA ($N = 5$; 0.1, 0.3, 1.0, and 3.0 mg/kg) and DOM ($N = 4$; 0.3, 1.0, 3.0, and 10 mg/kg) failed to produce levels of greater than 10% responding on the amphetamine-appropriate choice lever. Likewise, the prototypic hallucinogen LSD ($N = 6$; 0.003, 0.01, 0.03, and 0.1 mg/kg) also failed to produce greater than 10% responding on the drug-appropriate lever. When the rats were administered 1.0 mg/kg amphetamine during each of these latter three drug series, every rat completed greater than 90% of the trials on the drug-appropriate lever. Thus, the failure of these animals to respond on the amphetamine lever after the administration of MDA, DOM, or LSD was not due to a loss of stimulus control by amphetamine. Higher doses of MDA and DOM could not be tested safely because they disrupted bar-pressing behavior and tended to produce convulsions after prolonged periods of repetitive shock delivery.

Discussion

The present results suggest that MDA should not be classified as an amphetamine-like drug, even though it is closely related to amphetamine structurally and produces a number of effects in common with amphetamine, including maintenance of self-administration behavior (Griffiths et al., 1976) and anorexia (Griffiths et al., 1976; Martin et al., 1978), as well as mydriasis, bradycardia, and facilitation of the flexor reflex (Martin et al., 1978). On the other hand, MDA reportedly produces psychotomimetic effects in man and has been abused presumably for these effects rather than its amphetamine-like effects (Martin et al., 1978). However, the LSD-like effects of MDA in the chronic spinal dog are not blocked by the LSD antagonist cyproheptadine, and exhibit only partial cross-tolerance to LSD (Martin et al., 1978). Thus, the majority of the evidence, including the present findings, suggests that MDA may have neither an amphetamine-like nor an LSD-like mode of action and, therefore, may represent a unique class of drugs.

Several lines of evidence suggest that DOM has predominantly an LSD-like mode of action. In drug discrimination stidies, the present findings as well as those of Huang and Ho (1974) agree that the discriminative stimuli of DOM are not generalized to those of amphetamine. Similarly, Tilson et al. (1975) reported that lower but not higher doses of DOM produce amphetamine-appropriate responding. Further, Winter (1975) demonstrated that the stimuli produced by DOM but not amphetamine are generalized to those produced by mescaline. In addition, DOM produces predominantly LSD-like effects in the chronic spinal dog, including elicitation of the stepping reflex, and these effects of DOM exhibit virtually complete cross-tolerance to LSD (Martin et al., 1978). These latter findings are particularly strong evidence that DOM has an LSD-like rather than an amphetamine-like mode of action.

References

Barry, H., III: Classification of drugs according to their discriminable effects in rats. Fed. Proc. **33**, 1814–1824 (1974)

Griffiths, R. R., Winger, G., Brady, J. V., Snell, J. D.: Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. Psychopharmacology **50**, 251–258 (1976)

Huang, J., Ho, B. T.: Discriminative stimulus properties of *d*-amphetamine and related compounds in rats. Pharmacol. Biochem. Behav. **2**, 669–673 (1974)

Martin, W. R., Vaupel, D. B., Nozaki, M., Bright, L. D.: The identification of LSD-like hallucinogens using the chronic spinal dog. Drug Alcohol Depend. **3**, 113–123 (1978)

Shannon, H. E., Holtzman, S. G.: Evaluation of the discriminative effects of morphine in the rat. J. Pharmacol. Exp. Ther. **198**, 54–65 (1976)

Tilson, H. A., Baker, T. G., Gylys, J. A.: A comparison of the discriminative stimulus properties of R-2,5-dimethoxy-4-methylamphetamine (R-DOM) and S-amphetamine in the rat. Psychopharmacologia **44**, 225–228 (1975)

Winter, J. C.: The effects of 2,5-dimethoxy-4-methyl amphetamine (DOM), 2,5-dimethoxy-4-ethylamphetamine (DOET), *d*-amphetamine, and cocaine in rats trained with mescaline as a discriminative stimulus. Psychopharmacologia **44**, 29–32 (1975)

Received May 21, 1979; Final Version October 18, 1979

3485

191/987 26456V

P s.c. dex'amphetamine' 'LSD' 'psychotomimetic' 2,5-dimethoxy-4-methylamphetamine methylenedioxyamphetamine as 'reflex-motive' discrimination cue rat /XXVI/ /XXXII/ /E/

Psychopharmacology 67, No.3, 311-12 /1980/

Shannon H E /Lexington,Ky.,USA/

MDA and DOM: Substituted Amphetamines that do not Produce Amphetamine-Like Discriminative Stimuli in the Rat.

The discriminative stimulus properties of amphetamine (A), 3,4-methylenedioxy-A (MD), 2,5-dimethoxy-4-methyl-A (DO) and LSD were compared.

Methods

Male CFE rats (275-300 g) were trained to discriminate between d-A (1 mg/kg, s.c.) and saline in order to avoid a 1 mA electric shock delivered to the feet. Discrimination between LSD tartrate (0.003, 0.01, 0.03 and 0.1 mg/kg), MD (0.1, 0.3, 1.0 and 3.0 mg/kg), DO (0.3, 1.0, 3.0 and 10.0 mg/kg), A (0.1, 0.3, 1.0 and 3.0 mg/kg) and saline, all administered s.c. in random order were tested in trained rats.

Results

D-A at 0.1, 0.3, 1.0 and 3.0 mg/kg produced mean levels of responding on the drug-appropriate shock-termination lever of 3.4, 44, 96, and 95%, respectively. Responding to MD, DO or LSD was never above 10%, even though the response to D-A at 1.0 mg/kg inserted into any drug series was greater than 90%. Higher doses of MD and DO disrupted bar-pressing behavior and tended to produce convulsions after prolonged periods of repetitive shock delivery.

7 Ref.

W19/MCB/WJA

National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, KY 40583, U.S.A.