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BRIEF COMMUNICATION

Comparison of Conditioned Taste Aversions Produced by MDMA and *d*-Amphetamine

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LIN, H. Q., D. M. ATRENS, M. J. CHRISTIE, D. M. JACKSON AND I. S. McGREGOR. *Comparison of conditioned taste aversions produced by MDMA and* d-*amphetamine.* PHARMACOL BIOCHEM BEHAV **46**(1) 153–156, 1993. – Many drugs of abuse such as *d*-amphetamine support the development of taste aversion in a conditioned taste aversion paradigm. However, it has yet to be established whether methylenedioxymethamphetamine (MDMA), an amphetamine-like stimulant, has this property. A direct comparison was made between MDMA and *d*-amphetamine over a dose range of 0.125–2.0 mg/kg (SC). Two pairings of either drug with saccharin produced dose-related taste aversions to saccharin that were retained for at least three successive testing trials. The minimally effective dose was 1 mg/kg for MDMA and 0.5 mg/kg for *d*-amphetamine. The relative potency of MDMA to amphetamine was 4.5, similar to that previously reported for drug discrimination and self-stimulation.

MDMA *d*-Amphetamine Conditioned taste aversion Reinforcement

SINCE the 1970s, the conditioned taste aversion paradigm has been widely used in investigating the reinforcing effects of drugs. It is not surprising that drugs such as lithium and copper sulfate that have emetic effects support taste aversion. However, it is somewhat surprising that drugs such as morphine, amphetamine, and barbiturates that may be shown to be positively reinforcing in other paradigms also support conditioned taste aversion. This suggests that even positively reinforcing drugs may have aversive properties (8). Thus, the conditioned taste aversion method plays an important role in analysing the complex motivational properties of psychoactive drugs.

Methylenedioxymethamphetamine (MDMA) is a ring-substituted derivative of *d*-amphetamine with considerable abuse potential in human beings (15). Recent research has shown that laboratory animals will self-administer MDMA (13) and that it produces conditioned place preference (2) and enhances reinforcement in the self-stimulation paradigm (10). All of these effects suggest a commonality with the parent compound, *d*-amphetamine. MDMA is similar to *d*-amphetamine in a variety of other behavioural tests including locomotor activity (6), drug discrimination (5), and conditioned locomotion (7). However, it is not known whether this commonality extends to the conditioned taste aversion paradigm.

Reports that a drug's potency in producing a conditioned taste aversion is not necessarily parallel to its potency in other behavioural procedures indicate that the positively and negatively reinforcing properties of drugs of abuse may be independent. For example, cocaine is a powerful behavioural stimulant but supports only a weak conditioned taste aversion (3). In contrast, fenfluramine is a weak behavioural stimulant but is potent in inducing conditioned taste aversion (3). The present study was designed to determine whether MDMA supports the establishment of conditioned taste aversion and its relative magnitude with reference to *d*-amphetamine.

METHOD

Subjects

Subjects were 59 experimentally naive, male Wistar rats weighing between 300 and 500 g. Rats were housed individually in a colony room maintained at approximately 22°C with a 14 L : 10 D cycle. Food was available ad lib. On the last baseline day, rats were allocated to dosage groups (n = 6–11) that were matched for mean and variance of body weight and water intake during the baseline phase.

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Procedure

Throughout the experiment, rats were deprived of water for 23.5 h each day. They were allowed access to water in their home cages for the remaining 0.5 h. The experiment consisted of three phases. In the baseline phase (days 1–7), rats were given 0.5-h access to two bottles of tapwater and briefly handled after drinking. On day 7, the water intake for each rat was recorded as baseline data. In the conditioning phase (days 8–11) for half the rats 0.1% saccharin solution (w/v) was given immediately following an injection of drugs on days 8 and 10 and tapwater was presented immediately following an injection of 0.9% sterile saline on days 9 and 11. For the other half of the rats, tapwater was provided immediately after injecting saline on days 8 and 10 and saccharin was provided immediately after drug administration on days 9 and 11. Thus, rats in the drug groups received two drug–saccharin pairings and two saline–tapwater pairings. Rats in the control groups had two saline–saccharin pairings and two saline–tapwater pairings.

In the testing phase (days 12–14), tapwater and 0.1% saccharin solutions were simultaneously presented for all rats and no injections were given. To control for the influence of position preference, the position of the bottles was counterbalanced; for half the rats, the saccharin solution was placed on the right-hand side and for the other half on the left. The intake of tapwater and saccharin solution for each rat was measured to the nearest 0.1 g and the percentage of saccharin consumption was determined.

Dose-Response Studies

Doses of MDMA (0.125, 0.5, 1.0, and 2.0 mg/kg) and *d*-amphetamine (0.125, 0.5, and 2.0 mg/kg) were selected on the basis of previous work and preliminary experiments. Slopes of log dose–effect curves for the scores of the three testing trials were determined by linear regression analyses. Such analyses were conducted only on the approximately linear portion of the log dose–effect curve for each drug. This was done to avoid confounding "floor" and "ceiling" effects. Following this, a test for parallelism of the two curves was carried out. If the slopes did not differ significantly from each other, two corresponding parallel lines were constructed according to the common slope of the curves. The logarithmic value of the relative potency was derived from the horizontal distance between the parallel lines dropping perpendiculars to the abscissa from the equally effective values on each line. The relative potency was finally determined from the inverse logarithmic value (19). In addition, the ED_{50} (i.e., the dose corresponding to the saccharin intake level of 50% of the saline control group) was estimated by interpolation from the above-described parallel regression lines.

Drugs

MDMA HCl (National Institute on Drug Abuse, Rockville, MD) and *d*-amphetamine sulfate (Charles MacDonald) were dissolved in 0.9% sterile saline (Astra, Södertälje, Sweden) and injected SC. All injections were given in a volume of 1 ml/kg body weight. Doses of the drugs were expressed as the weight of their salt forms.

RESULTS

The conditioned taste aversions induced by MDMA and *d*-amphetamine on three consecutive testing trials are shown in Fig. 1. Analysis on these results with two-factor (eight groups × three trials) analysis of variance (ANOVA), with repeated measures over trials, confirmed a significant group effect, $F(7, 51) = 17.057$, $p < 0.0001$, a significant trial effect, $F(2, 102) = 5.975$, $p < 0.01$, but a nonsignificant interaction, $F(14, 102) = 0.999$, $p > 0.05$. Simple effects revealed that the group effects were statistically reliable across the three testing trials (all $p < 0.001$). Further multiple comparisons with Duncan's test indicated that saccharin preference scores of Groups MDMA 1 and 2 and *d*-amphetamine 0.5 and 2 mg/kg were significantly less than that of the saline control (all $p < 0.01$). The percentage of saccharin consumption in Trial 1 was markedly lower than that in Trial 2 ($p < 0.05$) and Trial 3 ($p < 0.01$).

Separate statistical analysis upon the amount of liquid consumed showed no significant differences among all groups on the last baseline day, $F(7, 51) = 1.695$, $p > 0.05$ (one-way ANOVA), or on all the three testing trials, $F(7,51) = 1.247$, $p > 0.05$ (group effect in two-way ANOVA). These results confirmed that all groups matched in their water consumption amount on baseline phase and imply that the drugs used in this experiment did not cause notable effects on drinking itself.

Figure 2 shows log dose–effect curves, analysed with linear regression lines, for MDMA and *d*-amphetamine upon mean scores of the three testing trials. Slopes (mean ± SE) were -72.30 ± 8.59 and -68.48 ± 8.58 for MDMA and *d*-amphetamine, respectively. An analysis of parallelism revealed no significant difference between the slopes, $t(113) = 0.1287$, $p > 0.05$. The ED_{50} was 1 and 0.22 mg/kg for MDMA and *d*-amphetamine, respectively. The relative potency (MDMA/amphetamine) was 4.5.

DISCUSSION

The present study shows that rats will reduce their intake of saccharin solution when the saccharin has been previously paired with injections of MDMA. This effect was dose related, with effective doses of 1–2 mg/kg and a threshold dose of 0.5 mg/kg and the aversive effects were retained over at least three consecutive testing trials. This demonstration of conditioned taste aversion complements previous reports of MDMA's positive reinforcing effects (2,10,13). This suggests that MDMA has aversive as well as appetitive properties that further extend its commonality with its parent compound, *d*-amphetamine.

The fact that the minimally effective dose of MDMA (1 mg/kg, SC) in conditioned taste aversion is similar to those obtained elsewhere for conditioned place preference (2 mg/kg, SC) (2) and self-stimulation (0.5–2 mg/kg, SC) (10) in rats suggests a possible relation between the positively and negatively reinforcing properties of MDMA. In this sense, MDMA is similar to *d*-amphetamine and morphine [see (11) for references] but dissimilar to cocaine and fenfluramine (3).

Comparing MDMA and *d*-amphetamine shows that MDMA is less potent in inducing conditioned taste aversion. The ED_{50} was 1 mg/kg for MDMA and 0.22 mg/kg for *d*-amphetamine. The ED_{50} for *d*-amphetamine here is close to the 0.20 mg/kg in Goudie and Newton's report (9) and lower than the 0.47 mg/kg reported by Booth et al. (3). This may reflect the fact that the calculation method in the present study is more similar to the former than to the latter. In comparison of the ED_{50} of MDMA vs. *d*-amphetamine, a relative potency of 4.5 was obtained. The potency ratio is basically consistent with previous studies [(14); Lin et al., submitted].

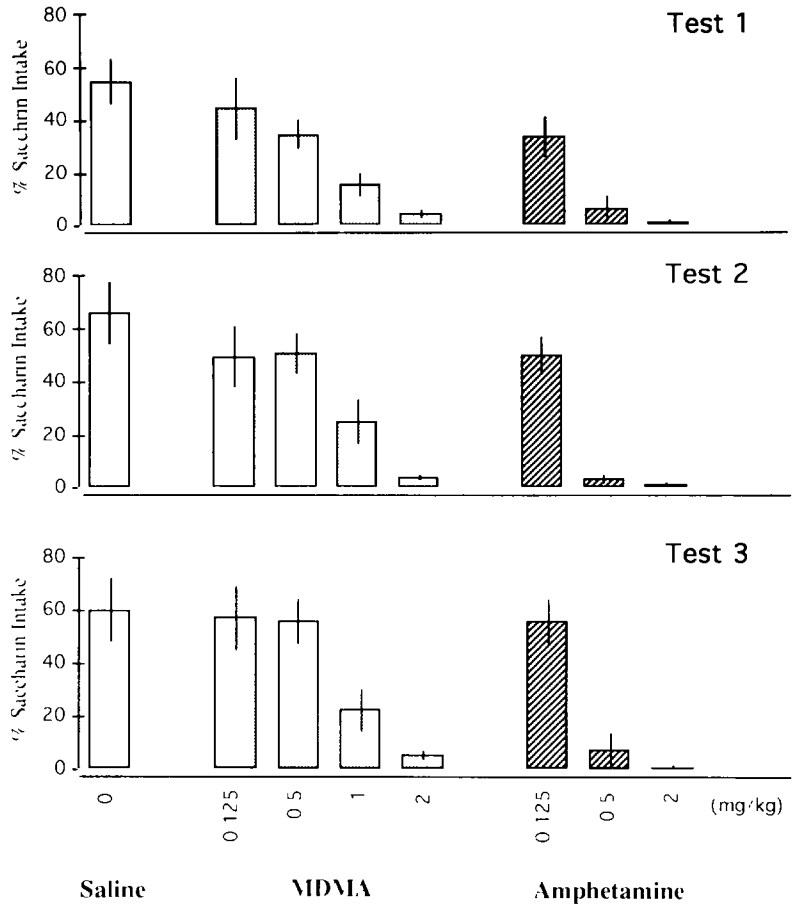

FIG. 1. Conditioned taste aversions produced by methylenedioxymethamphetamine (MDMA) and *d*-amphetamine after two drug-saccharin pairings. Values are the mean ± SEM for percent saccharin intake in testing Trials 1 (Test 1), 2 (Test 2), and 3 (Test 3). Saline group, $n = 6$; MDMA 0.5-mg/kg group, $n = 11$; other groups, $n = 7$.

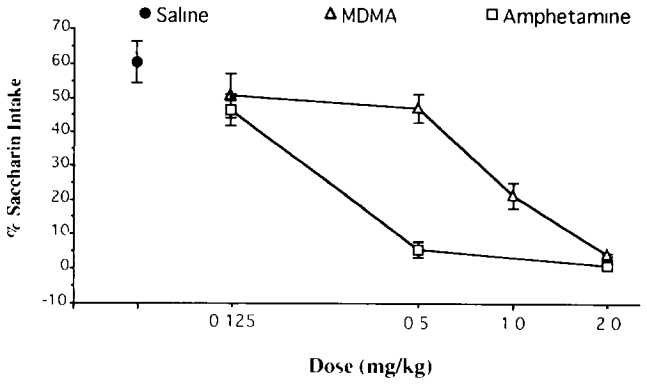

FIG. 2. Log dose-effect curves for methylenedioxymethamphetamine (MDMA) and *d*-amphetamine in taste aversion conditioning. Values are mean ± SEM of raw saccharin preference scores for three testing trials. Sizes of dosage groups are as in Fig. 1.

Indirect comparisons of dose-response relations suggest that *d*-amphetamine is generally more potent than MDMA in other behavioural tests, such as conditioned place preference (2,18), brain self-stimulation [(4); Lin et al., submitted], and locomotion activity (1,6). Also, other direct comparisons have shown that the relative potency of MDMA vs.*d*-amphetamine was 2.5 for training dose-response curves in drug discrimination (14) and 4.4 in rate-frequency function for self-stimulation (Lin et al., submitted). Thus, it can be seen that the relative potency of these two stimulants in conditioned taste aversion is similar to those in a series of other behavioural paradigms.

The common underlying mechanisms for the aversive effects of drugs have long been a puzzle. MDMA, *d*-amphetamine, and cathinone are structurally similar compounds. Previous studies have shown that the MDMA cue is able to generalise to *d*-amphetamine (5) and *l*-cathinone (16) in drug discrimination tests, indicating these drugs share some common components in their behavioural effects. Other behavioural tests also provided evidence of the pharmacological similarities between *d*-amphetamine and MDMA (2,6,10,13) or between *d*-amphetamine and cathinone [see (9) for refer-

ences]. The relative potency derived from such behavioural paradigms ranges from 2.5–4.4 for MDMA vs.*d*-amphetamine [(14); Lin et al., submitted] and 2.0–3.0 for cathinone vs.*d*-amphetamine [see (9)]. Nevertheless, the relative potency in conditioned taste aversion paradigm is 4.5 for MDMA vs. *d*-amphetamine (the present study) and 17 for cathinone vs. *d*-amphetamine (9). These data indicate that in other behavioural paradigms the resemblance between MDMA and *d*-amphetamine is parallel to that between cathinone and *d*-amphetamine, but in conditioned taste aversion MDMA seems more similar to *d*-amphetamine than does cathinone.

It is difficult to associate the effects of *d*-amphetamine, cathinone, and MDMA on conditioned taste aversion with their activity on neurotransmitter systems. *d*-Amphetamine and cathinone act primarily on catecholaminergic systems (12) while MDMA has more powerful serotonergic and only relatively weak dopaminergic effects (17). These considerations suggest that the effects of cathinone and *d*-amphetamine on conditioned taste aversion should be similar whereas those of MDMA should be different. In fact, in the taste aversion paradigm MDMA is more similar to *d*-amphetamine than is cathinone. This finding is in agreement with that of Booth et al. (3) and thus accentuates the enigma of the neurochemical mechanism(s) underlying conditioned taste aversion. These findings suggest that there is no single mechanism involved and that conditioned taste aversion induced by different drugs may only be superficially similar. The fact that rats do not drink as much of a normally preferred solution says nothing about the basis for this acquired aversion.

In summary, MDMA is an actively aversive agent in conditioned taste aversion although it is not as potent as its parent compound, *d*-amphetamine. The relative potency of MDMA to *d*-amphetamine in producing conditioned taste aversion seems to be similar to their potency ratios in positive reinforcement and behavioural stimulation. Further work would be of interest to compare the neurochemical basis of the aversive effects of MDMA and *d*-amphetamine in the conditioned taste aversion paradigm.

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REFERENCES

1. Bauer, R. H. The effects of *l*-, *d*-, and parahydroxyamphetamine on locomotor activity and wall climbing in rats of different ages. Pharmacol. Biochem. Behav. 13:155–165; 1980.
2. Bilsky, E. L.; Hui, Y.; Hubbell, C. L.; Reid, L. D. Methylenedioxymethamphetamine's capacity to establish conditioned place preference and modify intake of an alcoholic beverage. Pharmacol. Biochem. Behav. 37:633–638; 1990.
3. Booth, D. A.; Pilcher, C. W. T.; D'Mello, G. D.; Stolerman, I. P. Comparative potency of *d*-amphetamine, fenfluramine and related compounds in taste aversion experiments in rats. Br. J. Pharmacol. 61:669–677; 1977.
4. Gallistel, C. R.; Freyd, G. Qualitative determination of the effects of catecholaminergic agonists and antagonists on the reward efficacy of brain stimulation. Pharmacol. Biochem. Behav. 26: 731–741; 1987.
5. Glennon, R. A.; Young, R. Further investigations of the discriminative stimulative properties of MDA. Pharmacol. Biochem. Behav. 20:501–504; 1984.
6. Gold, L. H.; Hubner, C.B.; Koob, G. F. A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA. Psychopharmacology (Berl.) 99:40–47; 1989.
7. Gold, L. H.; Koob, G. F. MDMA produces stimulant-like conditioned locomotor activity. Psychopharmacology 99:352–356; 1989.
8. Goudie, A. J. Aversive stimulus properties of drugs. Neuropharmacology 18:971–979; 1979.
9. Goudie, A. J.; Newton, T. The puzzle of drug-induced conditioned taste aversion: Comparative studies with cathinone and *d*-amphetamine. Psychopharmacology (Berl.) 87:328–333; 1985.
10. Hubner, C. B.; Bird, M.; Rassnick, S.; Kornetsky, C. The threshold lowering effects of MDMA (ecstasy) on brain-stimulation reward. Psychopharmacology (Berl.) 95:49–51; 1988.
11. Hunt, T.; Amit, Z.; Conditioned taste aversion induced by self-administered drugs: Paradox revisited. Neurosci. Biobehav. Rev. 11:107–130; 1987.
12. Kalix, P. Cathinone, an alkaloid from khat leaves with an *d*-amphetamine-like releasing effects. Psychopharmacology (Berl.) 74: 269–270; 1981.
13. Lamb, R.; Griffiths, R. Self-injection of *d,l*-3,4-methylenedioxymethamphetamine (MDMA) in the baboon. Psychopharmacology (Berl.) 91:268–272; 1987.
14. Oberlender, R.; Nichols, D. E. Drug discrimination studies with MDMA and *d*-amphetamine. Psychopharmacology (Berl.) 95:71–76; 1988.
15. Peroutka, S. J. Recreational use of MDMA. In: Peroutka, S. J., ed. Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Boston: Kluwey Academic; 1990: 53–62.
16. Schechter, M. Discriminative profile of MDMA. Pharmacol. Biochem. Behav. 24:1533–1537; 1986.
17. Schechter, M. D. Serotonergic–dopaminergic mediation of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol. Biochem. Behav. 31:817–824; 1989.
18. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Res. 253:185–193; 1982.
19. Tallarida, R. J.; Murray, R. B. Manual of pharmacological calculations with computer programs. 2nd ed. New York: Springer-Verlag; 1987:16–26, 35–38.