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BRIEF COMMUNICATION

Contrasting Effects of Dopaminergic Blockade on MDMA and *d*-Amphetamine Conditioned Taste Aversions

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LIN, H. Q., I. S. McGREGOR, D. M. ATRENS, M. J. CHRISTIE AND D. M. JACKSON. *Contrasting effects of dopaminergic blockade on MDMA and* d*-amphetamine conditioned taste aversions.* PHARMACOL BIOCHEM BEHAV 47(2) 369–374, 1994.—A series of experiments examined the role of dopamine in the conditioned taste aversion (CTA) produced by 3,4-methylenedioxymethamphetamine (MDMA) and *d*-amphetamine in rats. The CTA induced by MDMA (1.0 mg/kg) was unaffected by the D_1 dopamine receptor antagonist SCH23390 (0.3 or 0.6 mg/kg), the D_2 receptor antagonist raclopride (0.3 or 0.6 mg/kg), SCH23390 and raclopride combined (both 0.3 or 0.6 mg/kg), or the D_1/D_2 receptor antagonist haloperidol (0.4 mg/kg). In contrast, the CTA produced by *d*-amphetamine (0.5 mg/kg) was attenuated by SCH23390 and raclopride combined (both 0.3 mg/kg) as well as haloperidol (0.4 mg/kg), but not by SCH23390 (0.3 or 0.6 mg/kg) or raclopride (0.3 or 0.6 mg/kg) alone. These results suggest that dopamine plays different roles in MDMA and amphetamine CTAs, and that the D_1 and D_2 receptors independently mediate the aversive effect of amphetamine in CTA.

Conditioned taste aversion MDMA Amphetamine SCH23390 Raclopride Haloperidol
Dopamine D_1 receptor D_2 receptor

MUCH recent speculation has centred on the fact that psychoactive drugs that are readily self-administered by laboratory animals possess aversive stimulus properties in these same animals when tested in a conditioned taste aversion (CTA) paradigm [see (23) for a review]. One possible explanation of this apparent paradox is that the positive and negative reinforcement may occur at different doses of a given drug. For example, Booth et al. (7) showed that cocaine had only low potency in the CTA paradigm at doses that produced pronounced behavioural stimulation. Similarly, Goudie and Newton (15) found that the potency of cathinone in CTA is not in proportion to its other behavioural effects. Nonetheless, many other drugs such as *d*-amphetamine seem to have both positively reinforcing and aversive properties over the same dose range [for references see (23)].

Another explanation of the apparent paradox is that the appetitive and aversive effects of self-administered drugs may be mediated by different neurotransmitter systems. However, the evidence does not support such a contention. Hunt and Amit (23) have noted that suppression of catecholaminergic activity can similarly disrupt both the reinforcing and aversive actions of amphetamine, morphine, and ethanol. In the case of amphetamine, dopaminergic antagonists appear to suppress the positively reinforcing properties of amphetamine and attenuate its CTA-inducing properties across similar dose ranges (13,19,27,29,34).

The focus of the present study is on the "designer drug" MDMA. MDMA is a phenethylamine derivative with a chemical structure similar to amphetamine. MDMA, like amphetamine, has abuse potential in humans (28) and causes amphetamine-like behavioural stimulation (14). MDMA is positively reinforcing in laboratory animals as shown in the conditioned place preference (4), self-administration (2), and self-stimulation (22; Lin et al., submitted) paradigms.

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MDMA's aversive stimulus properties have recently been demonstrated in a CTA paradigm (26). In these experiments the minimally effective dose of MDMA in CTA was similar to those found effective in conditioned place preference and self-stimulation (3,22; Lin et al., submitted). These data suggest some shared mechanism in the reinforcing and aversive effects of the two drugs. It was therefore of interest to investigate whether the reinforcing and aversive properties of MDMA and amphetamine are mediated by the same neurochemical processes.

Several studies have indicated that MDMA acts as an agonist at both serotonergic and dopaminergic receptors (33,35). There is evidence for dopaminergic mediation of MDMA's reinforcing effects in self-stimulation (5) and a role for 5-HT_3 receptors in MDMA-induced conditioned place preference (4). However, little is known about the neural mechanism of MDMA's aversive properties as measured in CTA. On the other hand, as noted above, there is clear evidence of dopaminergic involvement in both the positive and negative reinforcing properties of amphetamine. In particular, amphetamine-induced CTA is attenuated by coadministration of the dopamine receptor antagonist haloperidol (29) or pimozide (19). If MDMA has amphetamine-like effects in the CTA paradigm, this effect should also be attenuated by DA receptor blockade.

An important issue that is yet to be clarified with respect to amphetamine-induced CTA is that of the respective roles of the D_1 versus D_2 dopamine receptors in mediating the effect. The fact that haloperidol and pimozide can attenuate the effect suggests D_2 involvement. However, both the selective D_1 agonist SKF 38393 and the selective D_2 agonist quinpirole also produce CTAs (1).

The present study investigated the involvement of D_1 and D_2 receptors in MDMA- and amphetamine-induced CTAs by examining the ability of the specific D_1 antagonist SCH 23390 and the specific D_2 antagonist raclopride to reverse amphetamine- and MDMA-induced CTAs. In addition, the influence of haloperidol on MDMA- and amphetamine-induced CTAs was investigated to replicate previous findings (29) and to examine whether haloperidol can also attenuate MDMA-induced CTA.

MATERIALS AND METHODS

Subjects

The subjects were a total of 137 experimentally naive, male Wistar rats, approximately 120 days of age. They were housed individually in plastic cages on wood shavings and were maintained at a constant temperature (22 ± 1°C) and regular light (0600–2000)/dark (2000–0600) cycle. Commercial rodent chow was available ad lib. Water was available at all times except during the experimental procedure as described below.

Drugs

(±)-Methylenedioxymethamphetamine HCl (MDMA) (National Institute on Drug Abuse, USA), (+)-amphetamine sulfate (May & Baker, UK), SCH23390 (Research Biochemicals, Natick, MA), raclopride (Astra Research Labs, Södertälje, Sweden), and haloperidol (Research Biochemicals) were dissolved in 0.9% sterile saline (Astra, NSW, Australia). Drugs were SC injected in a volume of 1 ml/kg body weight and the doses are expressed as salt forms.

Procedure

Rats were placed on a 23.5-h water deprivation schedule and allowed access to drinking in their home cages for 30 min per day throughout the experiment. The liquid was contained in white plastic bottles (about 250 ml in volume) and presented in the front portion of cage lids. All experiments were conducted during the light period, from approximately 1400 to 1700.

In the baseline phase (days 1–6) rats were given access to tap water and briefly handled after drinking. On day 6 the water intake for each rat was recorded as the baseline and the rats were assigned to treatment groups matched on this baseline water intake.

In the conditioning phase (days 7–8) the 30-min water drinking was immediately followed by appropriate injections. Ingestion of 0.1% saccharin solution (w/v) was paired with drug treatments on one day and ingestion of tap water was paired with 0.9% sterile saline injection on the other day. To equalise the possible stress-inducing effects of the injection procedure per se, half the animals in each group received drug treatment on day 7 and saline treatment on day 8; the other half received drug and saline treatments in the reverse sequence.

In the testing phase (day 9) one bottle of tap water and one bottle of 0.1% saccharin solution were simultaneously presented. To eliminate the influence of position preference, saccharin location (i.e., left or right) was counterbalanced across animals. The intake of tap water and saccharin solution for each rat was respectively measured to the nearest 0.1 ml and the percentage of saccharin consumption computed.

Effects of SCH 23390 and Raclopride on MDMA- and d-Amphetamine-Induced CTAs

The aim of this experiment was to determine whether dopaminergic systems are involved in the CTA established by MDMA and *d*-amphetamine. Accordingly, the effects of the D_1 antagonist SCH23390 (24) and the D_2 antagonist raclopride (25) were investigated on MDMA- and *d*-amphetamine-induced CTAs. The rats (n = 102) were divided into 17 groups of five to seven and given the following drug treatments.

MDMA groups (nine groups):

Saline + saline
Saline + MDMA 0.35 mg/kg
Saline + MDMA 1.0 mg/kg
SCH23390 0.3 + MDMA 1.0 mg/kg
SCH23390 0.6 + MDMA 1.0 mg/kg
Raclopride 0.3 + MDMA 1.0 mg/kg
Raclopride 0.6 + MDMA 1.0 mg/kg
SCH23390 0.3 + raclopride 0.3 + MDMA 1.0 mg/kg
SCH23390 0.6 + raclopride 0.6 + MDMA 1.0 mg/kg.

Amphetamine groups (eight groups):

Saline + saline
Saline + amphetamine 0.5 mg/kg
SCH23390 0.3 + amphetamine 0.5 mg/kg
SCH23390 0.6 + amphetamine 0.5 mg/kg
Raclopride 0.3 + amphetamine 0.5 mg/kg
Raclopride 0.6 + amphetamine 0.5 mg/kg
SCH23390 0.3 + raclopride 0.3 + amphetamine 0.5 mg/kg
SCH23390 0.6 + raclopride 0.6 + amphetamine 0.5 mg/kg.

Injection of antagonists immediately preceded administration of MDMA or amphetamine. When SCH23390 and raclopride were used together, they were made up separately and

mixed in syringe before coadministration, ensuring the injection was kept in a volume of 1 ml/kg.

Effects of Haloperidol on MDMA- and Amphetamine-Induced CTAs

Thirty-five rats, in five groups of 6–8, were used in this experiment. The dose of haloperidol was selected on the base of previous studies (1,29). The drug treatments were:

Saline + saline
Saline + MDMA 1.0 mg/kg
Haloperidol 0.4 + MDMA 1.0 mg/kg
Saline + amphetamine 0.5 mg/kg
Haloperidol 0.4 + amphetamine 0.5 mg/kg.

Data Analysis

Raw scores of liquid intake or saccharin preference score were analysed using a one-way analysis of variance (ANOVA) between subjects. The results showing significant overall differences were subjected to Duncan multiple comparison test to identify the differences between particular groups.

RESULTS

Effects of SCH23390 and Raclopride on MDMA-Induced CTA

Group means of water intake on the sixth baseline day (range 15.9–17.4 ml) for the nine groups did not significantly differ from each other, $F(8, 45) = 0.45, p > 0.05$. Similarly, there were no significant differences in group means of saccharin solution intake (range 13.8–17.7 ml), $F(8, 45) = 1.592$, $p > 0.05$, on the conditioning day.

A one-way ANOVA on percent saccharin intake revealed significant differences in drug treatments, $F(8, 45) = 16.7$, $p < 0.0001$. Post hoc comparisons indicated a reliable reduction of saccharin intake after the dose of MDMA 1.0 mg/kg ($p < 0.01$ vs. saline controls), but not at the lower dose of MDMA 0.35 mg/kg ($p > 0.05$ vs. saline controls, data not shown), confirming the establishment of a dose-dependent CTA by MDMA.

The effects of SCH23390 or/and raclopride on the CTA induced by MDMA 1.0 mg/kg are depicted in Fig. 1 (upper). Duncan's test showed that none of the antagonist treatments (one antagonist alone or both combined) was able to reverse the CTA (all *p*s > 0.05 vs. MDMA alone).

Effects of SCH23390 and Raclopride on Amphetamine-Induced CTA

There were no significant differences in mean water intake on the sixth baseline day for the eight groups, which ranged from 15.2 to 18.1 ml, $F(7, 41) = 0.568$, $p > 0.05$. Group means of saccharin solution intake on the conditioning day, which ranged from 16.0 to 21.1 ml, also failed to reach significance, $F(7, 41) = 1.924, p > 0.05$.

Saccharin preference scores following treatment with amphetamine or amphetamine plus antagonist(s) are illustrated in Fig. 1 (lower). There was a significant overall drug effect across the eight groups, $F(7, 41) = 13.71, p < 0.0001$. A post hoc Duncan's test confirmed that amphetamine 0.5 mg/kg produced a reliable CTA ($p < 0.01$ vs. saline controls). This CTA was attenuated by SCH23390 0.3 and raclopride 0.3 mg/kg combined ($p < 0.05$ vs. amphetamine alone; $p < 0.01$, vs. saline control), but was not affected by the other

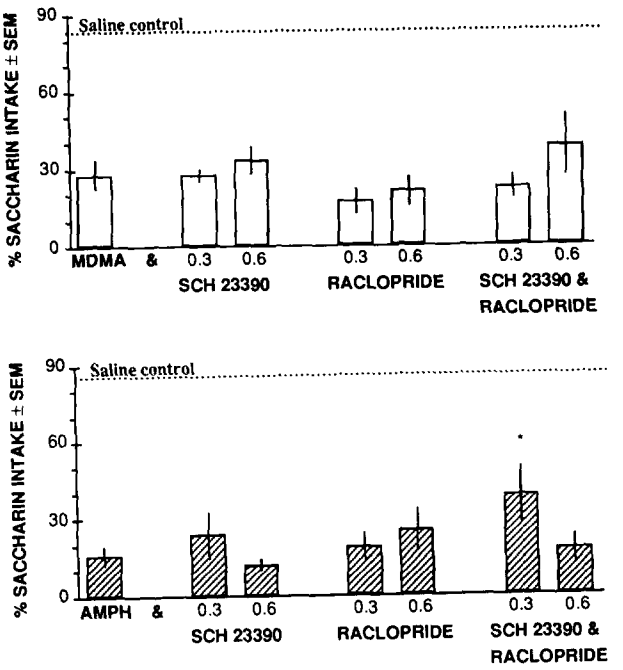

FIG. 1. Effects of dopaminergic antagonists SCH23390 and raclopride on conditioned taste aversions induced by MDMA 1.0 mg/kg (upper) or *d*-amphetamine (AMPH) 0.5 mg/kg (lower). Each column and vertical bar represent mean ± SE of percent saccharin intake for five to seven rats. *$p < 0.05$, compared to amphetamine control (post doc Duncan's test).

SCH23390 and/or raclopride treatments (all *p*s > 0.05 vs. amphetamine alone).

Effects of Haloperidol on MDMA and Amphetamine-Induced CTAs

The means of baseline water intake which ranged between 16.0 and 16.4 ml did not significantly differ among the five groups, $F(4, 30) = 0.103, p > 0.05$. The means of saccharin solution intake on the conditioning day, which ranged from

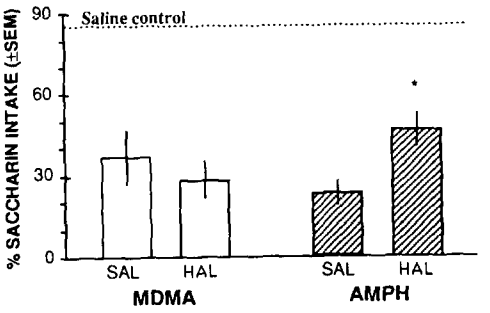

FIG. 2. Effects of haloperidol 0.4 mg/kg on conditioned taste aversions induced by MDMA 1.0 mg/kg or *d*-amphetamine 0.5 mg/kg. Each column and vertical bar represent mean ± SE of percent saccharin intake for six to eight rats. *$p < 0.05$, compared to amphetamine control (post doc Duncan's test). AMPH = *d*-amphetamine, HAL = haloperidol, SAL = saline.

16.9 to 18.2 ml, were also not significantly different, $F(4, 30) = 0.463, p > 0.05$.

The effects of haloperidol on CTAs produced by MDMA or amphetamine are depicted in Fig. 2. There was a significant effect of drug treatment, $F(4, 30) = 15.05, p < 0.0001$. The mean preference score (37.6 ± 9.6%) for MDMA 1.0 mg/kg alone did not significantly differ from that (23.5 ± 4.4%) for amphetamine 0.5 mg/kg alone ($p > 0.05$), suggesting similar strength of the two drugs. The preference scores of the two drugs were significantly lower than that of saline control (both $p < 0.01$), confirming the establishment of CTAs. The amphetamine-induced CTA was significantly attenuated by haloperidol ($p < 0.05$ vs. amphetamine alone; $p < 0.01$ vs. saline control). In contrast, the MDMA-induced CTA was not affected by haloperidol ($p > 0.05$ vs. MDMA alone).

GENERAL DISCUSSION

The present study confirms our previous demonstration that MDMA is capable of establishing a dose-dependent CTA (26) and shows that SCH23390 and raclopride administered alone do not interfere with the development of MDMA- or amphetamine-induced CTA (see Fig. 1). These results are unlikely to reflect inadequate dosage because the doses used are towards the high range of those shown to be effective in other behavioural paradigms (10,21,36). It is also unlikely that the present results reflect CTAs induced by the dopaminergic antagonists themselves, as previous studies have reported that SCH23390 (1) and the D_2 dopamine receptor antagonists by themselves [see (1,16,19,29)] do not support CTAs. An experiment in this laboratory has also shown that raclopride (0.6 mg/kg) alone does not produce a CTA.

The failure of raclopride to interfere with development of the CTA produced by amphetamine is interesting because both pimozide (19) and haloperidol (29, present study), which act primarily at the D_2 receptor, can attenuate amphetamine-induced CTA. Thus a relatively "pure" blockade of D_2 receptors may be insufficient to attenuate the CTA induced by amphetamine; some blockade of D_1 receptors must also be present for this attenuation to occur. Previous studies have shown haloperidol to act on both D_1 and D_2 receptors in certain instances, although it may have a high affinity for D_2 receptor (20). For example, Bo et al. (6) showed that separate administration of SCH23390 and raclopride did not cause sedation and cortical EEG changes, but coadministration produced sedation and synchronisation of EEG similar to that induced by haloperidol. Similarly, the present study has shown that SCH23390 and raclopride did not affect the CTA induced by amphetamine when administered alone and did attenuate the CTA when coadministered. Further, haloperidol reversed the CTA with a magnitude similar to that seen with the combination of SCH23390 and raclopride, suggesting in this case that haloperidol's attenuating effect on the CTA was mediated by both D_1 and D_2 receptors.

The ineffectiveness of either SCH23390 or raclopride alone on the CTA induced by amphetamine implies that the D_1 and D_2 receptors may independently mediate taste aversion responses. This notion is supported by other investigators' findings. For instance, Asin and Montana (1) have found that SCH23390 did not interrupt the aversion produced by the D_2 receptor agonist quinpirole, and haloperidol had no effects on induction of CTA by the D_1 agonist SKF38393. Moreover, haloperidol blocks the CTA-inducing effect of quinpirole (1) but merely attenuates the CTA induced by the nonselective D_1/D_2 agonist amphetamine (29, present study).

The present study shows that either haloperidol or SCH23390 plus raclopride attenuates, but does not block, the CTA produced by amphetamine. This is in agreement with previous reports using pimozide (19) and haloperidol (29). However, depletion of both noradrenaline and dopamine with alpha-methyl-para-tyrosine completely blocked the CTA induced by amphetamine (17). Central depletion of catecholamines by intraventricular injection of the neurotoxin 6-hydroxydopamine also blocked the CTA (32). These data indicate that the CTA induced by amphetamine may be mediated by multiple neurotransmitter systems (e.g., D_1/D_2 dopamine and noradrenaline receptors).

The fact that the higher dose combination of SCH23390 and raclopride had no effects on the CTA induced by amphetamine initially seems puzzling. This may be due to the 5-HT_2-blocking effects of higher doses of SCH23390 (24). It has been suggested that 5-HT_2 receptors tonically inhibit dopaminergic brain systems (18). Thus the 5-HT_2 blockade produced by SCH23390 could potentiate the dopaminergic actions of amphetamine and enhance the dopamine-mediated CTA. The slight increase in amphetamine-induced CTA magnitude seen with administration of the higher dose of SCH23390 lends some support to this speculation (see Fig. 1, lower panel).

It is somewhat surprising that neither haloperidol nor SCH 23390 and raclopride combined affected the MDMA-induced CTA, considering that both of these treatments were effective on the CTA produced by amphetamine (present study) and in many aspects MDMA is considered an amphetamine-like drug (see the introductory section). Given that MDMA appears to act primarily on serotonergic systems and only weakly on dopaminergic transmission (33,35), attention might turn to the role of 5-HT systems in MDMA's CTA-inducing effect. Serotonergic mediation of CTA is suggested by several lines of evidence. Both central (8) and peripheral (12) administration of 5-HT can cause a CTA, and a number of serotonergically active drugs have been reported to induce CTAs [for references see (11)]. Nevertheless, preliminary studies in this laboratory have shown that the 5-HT_1/5-HT_2 receptor antagonist methysergide, the 5-HT_2 antagonist ketanserin, and the 5-HT_3 antagonist BRL43694 did not prevent formation of MDMA-induced CTA. These serotonergic blockade experiments were performed at 1100–1200. Based on these data, at least three possibilities can be considered: 1) The 5-HT receptor subtypes independently mediate the CTA-inducing properties of MDMA, just like the roles of D_1 and D_2 dopaminergic receptors in amphetamine-induced CTA; 2) the dopaminergic and serotonergic components of MDMA might independently activate the neural processes of the CTA; and 3) in addition to dopamine and serotonin there may be other neurotransmitter(s) mediating the CTA. To verify these speculations, it will be necessary to investigate the effects of nonselective serotonergic blockade as well as combined serotonergic–dopaminergic blockade on the CTA induced by MDMA.

An alternative interpretation of the failure of the antagonists to disrupt MDMA-induced CTA is based on the fact that the concentrations of dopamine and serotonin in the rat brain exhibit a circadian rhythm (30) and the rhythm can affect the actions of relevant agonists or antagonists [e.g., (9,31)]. However, in the present studies the influence of circadian rhythms appears unlikely to be a critical factor for three reasons: First, Campbell and Baldessarini (9) have shown that the preferential time for haloperidol's effect was at 1600, and the time (approximately 1400–1700) of administering dopaminergic antagonists in the present study was close to the

preferential time of haloperidol. Second, since MDMA and the related antagonists were concurrently administered, any circadian effects should be basically synchronic. Third, the dopaminergic blockers attenuated amphetamine-induced CTA, indicating that the regimens were sensitive enough to detect the pharmacological effects of the antagonists.

Finally, there are qualitative differences in the neurochemical mechanisms of MDMA- and amphetamine-induced CTAs. Dopaminergic blockade only interfered with the latter CTA, although both drugs can act similarly as dopaminergic agonists. Moreover, the dopaminergic blockade could merely attenuate but not completely block the amphetamine-induced CTA, and the D_1 and D_2 dopamine receptors seemed to independently mediate this CTA. These data together with the other result, that certain serotonergic blockers do not prevent development of MDMA-induced CTA (unpublished observations), are indicative of multiple neural mechanisms for CTAs induced by self-administered drugs such as MDMA and amphetamine.

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