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(±)-3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') increases social interaction in rats

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Abstract

A series of experiments administered a low dose range (0, 1.25, 2.5 and 5 mg/kg) of (±)-3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') to rats and assessed them in a variety of standard tests of anxiety. These tests included the emergence and elevated plus-maze tests, social interaction, cat odor avoidance and footshock-induced ultrasonic vocalizations. MDMA increased anxiety-related behaviours in the emergence and elevated plus-maze tests at all dose levels. A 5 mg/kg dose of MDMA also significantly reduced the time spent in close proximity to an anxiogenic cat odor stimulus. The 5 mg/kg dose also significantly reduced footshock-induced ultrasonic vocalizations. In the social interaction test, MDMA decreased aggressive behaviours at all doses tested, while the highest dose (5 mg/kg) also significantly increased the duration of social interaction. These results indicate that MDMA has both anxiogenic and anxiolytic effects depending upon the test situation employed. The facilitation of social interaction produced by MDMA in rats concurs with human experience of MDMA as a uniquely prosocial drug.

Keywords: MDMA ((±)-3,4-Methylenedioxymethamphetamine); Ecstasy; Anxiety; Odor, cat; Social interaction; Ultrasonic vocalization

1. Introduction

The illicit drug (±)-3,4-methylenedioxymethaphetamine (MDMA, 'Ecstasy') has been the subject of considerable recent interest. Extensive recreational consumption of the drug by young people in many western countries (Forsyth, 1996; Peroutka, 1987; Topp et al., 1999) and the occurrence of several associated fatalities associated with MDMA use (Henry et al., 1992) have resulted in intense recent media and scientific attention.

The most commonly reported positive effects of MDMA are euphoria and an increased feeling of closeness towards others (Peroutka, 1990; Shulgin, 1990; Solowij et al., 1992). However, adverse emotional effects are also commonly reported. Pathological anxiety is one such adverse effect, with several case studies reporting anxiogenic and panicogenic properties of the drug in human users (McCann and Ricaurte, 1992; Solowij et al., 1992; Whitaker-Azmitia and Aronson, 1989; Windhaber et al., 1998). Such findings appear to conflict with results in clinical settings where anxiolytic effects of the drug have been reported (Greer and Tolbert, 1986). Other studies have observed decreased anxiety with certain subjects and increased anxiety with others (Liester et al., 1992). Interestingly, Vollenweider et al. (1998) found that while MDMA heightened openness and a sense of closeness towards other people, a moderate increase in anxiety also occurred. This suggests that MDMA may have a dual effect, wherein social anxieties are diminished but generalised or free-floating anxiety is exaggerated.

Results from animal studies investigating acute effects of MDMA on anxiety are rather unclear. An anxiogenic effect of medium to high doses of the drug has been reported in rats using the elevated plus-maze test (Bhattacharya et al., 1998). In mice, however, a mixed effect was reported with higher doses of the drug having a mild anxiolytic effect in this test (Lin et al., 1999). Anxiogenic effects of high doses of MDMA have also been demonstrated in the social interaction test in rats (Bhattacharya et al., 1998). In mice, however, MDMA exhibits an anti-aggressive profile during social interaction, characterized by a reduction of threat and attack (Miczek and Haney, 1994; Navarro and Maldonado, 1999). MDMA also decreases the number of ultrasonic vocalizations produced by rat pups

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during maternal separation, suggesting a panicolytic effect of the drug (Winslow and Insel, 1990). Unfortunately, many of these studies employed doses of MDMA that are well above the doses typically consumed by humans.

The present study sought to further investigate the acute effects of MDMA on anxiety in rats using a low to moderate dose range (0, 1.25, 2.5 and 5 mg/kg) similar to those typically used by humans (1–4 mg/kg) (Boot et al., 2000; Topp et al., 1999; Vollenweider et al., 1998). A battery of different anxiety tests were employed, which are thought to model different anxiety states in humans (File, 1995). These consisted of: the emergence (Crawley and Goodwin, 1980) and elevated plus-maze tests (Pellow et al., 1985); the social interaction test (File, 1980); the cat odor avoidance test (Dielenberg et al., 1999); and a test of footshock-induced ultrasonic vocalizations (DeVry et al., 1993).

The emergence test and elevated plus-maze test both rely on the conflict between the desire to explore and the desire to avoid open spaces (Crawley and Goodwin, 1980; Pellow et al., 1985). Both tests are thought to model generalised anxiety states in humans (Handley and McBlane, 1993; Hascoet and Bourin, 1998). The social interaction test measures the duration of social interaction between two rodents meeting for the first time and is thought to be a model of social anxiety in humans (File, 1980, 1985). The cat odor avoidance model relies upon the innate fear rodents possess for the odor of natural predators such as cats (Dielenberg et al., 1999), and the anxiety provoked by cat odor has been suggested to bear some resemblance to phobic anxiety in humans (Zangrossi and File, 1994). Finally, the 22 kHz ultrasonic vocalizations that are elicited in rats during exposure to shock are reduced by panicolytic drugs, suggesting that the anxiety produced in his model may have some resemblance to panic disorder in humans (DeVry et al., 1993; Molewijk et al., 1995).

Of particular interest in this study was the notion that MDMA might exhibit an anxiolytic effect in models involving social behaviour, while exaggerating anxiety in tests involving novel, painful, predatory or other non-social stimuli.

2. Materials and methods

2.1. Subjects

A total of 88 inbred male albino Wistar rats (Concord Hospital, Sydney, Australia) were used in the experiments, aged between 85 and 95 days old and weighing between 276 and 483 g at the start of testing. The rats were housed in groups of eight per cage in a temperature-controlled environment (average temperature 22°C). A 12-h reversed light cycle was in operation (lights off at 8:30 AM) and all testing took place in the dark cycle. Food and water were freely available. All the experiments were approved by the University of Sydney Animal Ethics Committee.

A total of 48 rats were initially used as subjects in the emergence and elevated plus-maze tests. Two weeks later, these same rats, plus an additional eight, were given further doses of MDMA or vehicle and tested in the social interaction ($n = 56$), locomotor activity ($n = 56$) and cat odor avoidance tests ($n = 40$). Finally, 32 experimentally naive rats were used to test footshock-induced ultrasonic vocalizations. All rats were subjected to extensive handling before the start of testing.

2.2. Apparatus and procedure

2.2.1. Emergence test

The emergence apparatus consisted of a white Perspex walled rectangular arena ($96 \times 100 \times 40$ cm). The floor was divided into 16 marked squares, and a black wooden hide box ($24 \times 40 \times 15$ cm) was placed in the top left corner of the arena. The open field was illuminated with red light (40 W) and a video camera was mounted above the arena. The experimenter remained outside the room during testing.

Rats were injected with MDMA ($n = 12$/dose) or vehicle ($n = 12$) 20 min before being placed in the hide box of the emergence apparatus. Testing continued for 5 min. Subsequent video analysis by two "blind" observers scored emergence latency, emergence frequency, duration of time spent in the open field and defecation (number of fecal boli). The average of the two observers' scores was used for analysis. In between each test session, the apparatus was thoroughly wiped down with a damp cloth containing 10% ethanol.

2.2.2. Elevated plus-maze test

The elevated plus-maze apparatus was made of white Perspex and consisted of two open arms (50×10 cm) and two closed arms (50×10 cm). The closed arms had 50-cm high walls. The open and closed arms were connected by a central square (10×10 cm). The maze was elevated to a height of 59 cm. A miniature video camera was mounted on the top of one of the closed arms, vertically above the central square, sending images to a monitor and video recorder in an adjacent room. Photocell detectors (two infrared transmitters and two receivers) were placed at the far ends of each of the four arms with output from the receivers directed to a Macintosh computer running "WorkbenchMac" data acquisition software (McGregor, 1996). Placement of photocells allowed for the determination of the amount of time spent in and the number of entries to the closed and open arms and the central square. The room was illuminated by a red light (40 W) and the experimenter remained outside the room during testing.

Immediately following emergence testing, rats were placed in the center of the elevated plus-maze, with their head facing a closed arm. Testing continued for 5 min,

during which open and closed arm times and number of open and closed entries were recorded by computer. Risk assessment behaviours (head poking, rearing and stretching/arch back, (see Blanchard and Blanchard, 1989) were determined from video at a later date by two "blind" observers. The average of the two observers' scores was used for subsequent statistical analysis. In between each test session, the maze was thoroughly wiped down with a damp cloth of 10% ethanol.

2.2.3. Social interaction test

Exactly 2 weeks after the emergence and plus-maze tests, rats were tested in the social interaction, cat odor avoidance and locomotor activity tests. For this second set of tests, rats were reassigned to treatment conditions (0, 1.25, 2.5 and 5 mg/kg MDMA) in a way that ensured that no rat received the same treatment in the preceding experimental phase.

This re-allocation meant that many rats were receiving MDMA for the second time when tested on the social interaction, cat odor avoidance and locomotor activity tests. While it is possible that such repeat exposure to MDMA may result in tolerance or sensitization to the effects of the drug (e.g. Kalivas et al., 1998), we found no difference in behaviour in these tests comparing rats given MDMA for the first time (i.e. rats given vehicle in the first test phase) and those given MDMA for the second time.

The social interaction test arena was a square, clear Perspex box ($52 \times 52 \times 40$ cm) dimly lit with red light (40 W). The floor was marked with masking tape to divide it into four equally sized squares. A miniature video camera was placed vertically above the box and a second video camera was placed adjacent to the arena. These two cameras sent their signal into two video recorders and monitors in a neighbouring room where the interactions of the rats were recorded onto tape. The experimenter remained outside the test room during testing.

Rats were split into pairs of approximately equal body weight; with the rats in each pair receiving the same drug treatment. There were seven pairs for each treatment condition. Rats were injected with MDMA 20 min before being placed in the test arena for a 10-min session. The total duration of social interaction was recorded for each pair by two "blind" observers and the average scores used for subsequent analysis.

Behaviours considered as social interaction included sniffing, adjacent lying, following, crawling under/over and mutual grooming (File, 1980). Aggressive-type behaviours (e.g. kicking, aggressive grooming, biting, boxing and jumping on; see Guy and Gardner, 1985) were also scored. These were treated as separate entities because such behaviours are modulated by different pharmacological agents than social behaviours (Miczek and Winslow, 1987). The number of squares crossed was also recorded as a measure of locomotor activity. The arena was wiped down with 10% ethanol between each test session.

2.2.4. Cat odor avoidance test

Cat odor avoidance testing occurred in chambers which comprised a rectangular arena with Perspex walls ($60 \times 26 \times 36$ cm) and a metal grid floor, which was raised 2 cm above a tray containing wood shavings (Dielenberg et al., 1999). At one end of the chamber was a small wooden hide box ($21 \times 24 \times 22$ cm) with a small (6×6 cm) square hole allowing rats to enter the box. On the opposite wall of the apparatus to the hide box was an alligator clip (4 cm above the metal grid floor) with a piece of cat collar attached. A domestic cat had worn the collar for 3 weeks. The worn collar was stored in an air-tight plastic container and kept in a freezer. Before testing, the collar, handled only with plastic gloves, was warmed, attached to the alligator clip and left to stand for 30 min. Photocell detectors were placed at opposite ends of the chamber, which fed output to a Macintosh computer running "WorkbenchMac" data acquisition software. Placement of photocells allowed for the determination of the amount of time spent in the hide box ("hide time") and the amount of time rats spent in close vicinity to the cat collar (approach time). Testing took place in darkness and the researcher remained outside the room during testing.

Testing consisted of two phases which were spaced 24 h apart. In the first phase ("habituation"), all rats were injected with vehicle and 30 min later, were exposed to the testing apparatus for 20 min in the presence of a "virgin" cat collar that has not been worn by a cat. This allowed the rats to habituate to the novel apparatus and testing proce-

Table 1
Effects of MDMA in the emergence test

Groups	Emergence latency (s)	Emergence frequency (*n*)	Time in open field (s)	Defecation (*n*)
Vehicle	123.13 ± 35.15	3.79 ± 1.25	41.17 ± 14.43	0.00 ± 0.00
MDMA (1.25)	276.08 ± 23.92^{a}	0.25 ± 0.25^{a}	2.29 ± 2.29^{b}	0.42 ± 0.15^{c}
MDMA (2.5)	254.88 ± 30.42^{a}	0.88 ± 0.79^{a}	5.54 ± 4.67^{a}	0.92 ± 0.34^{a}
MDMA (5)	281.38 ± 18.63^{b}	0.17 ± 0.17^{b}	2.33 ± 2.33^{b}	1.92 ± 0.45^{b}

Data represent mean ± SEM.
Maximum emergence latency = 300 s due to 5-min test.
[a] $P < 0.01$, relative to vehicle treatment, Mann–Whitney *U*-test.
[b] $P < 0.001$, relative to vehicle treatment, Mann–Whitney *U*-test.
[c] $P < 0.05$, relative to vehicle treatment, Mann–Whitney *U*-test.

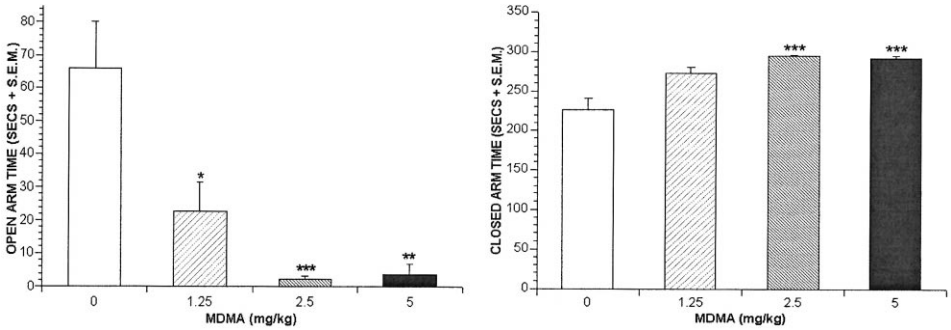

Fig. 1. Mean (+SEM) time spent in the open arms (left) and closed arms (right) of the elevated plus-maze by rats tested with MDMA or vehicle. $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$, relative to vehicle treatment, Mann–Whitney *U*-test.

dure. In the second phase ("test"), the rats were placed in the apparatus for 20 min in the presence of a worn cat collar. This phase occurred immediately after the social interaction test, meaning that rats were tested in this model 30 min after MDMA administration. In between each test, the testing chambers were thoroughly cleaned with a 10% ethanol solution and the wood shavings under the grid floor were replaced.

2.2.5. Locomotor activity test

Locomotor activity was measured in standard operant chambers (30 × 50 × 25.5 cm) with an aluminum side and back walls and Perspex front wall (see McGregor et al., 1996). The floor of the chamber consisted of 16 metal bars. A single count occurred when the rat changed its position on any one bar relative to the others. Counts were recorded by a Macintosh computer running "WorkbenchMac" data acquisition software. Each test chamber was placed inside a wooden sound attenuation box, which provided masking noise via a cooling fan and darkness during testing.

Immediately following the cat odor testing, each rat was placed in an individual locomotor activity testing chamber and assessed for activity over a 60 min period. Activity was therefore measured 50 min after drug administration. Following this test, the rats were returned to their home cages.

2.2.6. Footshock-induced ultrasonic vocalization test

Testing of footshock-induced ultrasonic vocalizations took place in an operant chamber, of the same type as was used for locomotor activity testing. The 16 metal floor bars were connected to a Coulbourn shock generator. An ultrasonic microphone was embedded in the aluminum roof of the test chamber. The microphone was connected to an S-25 BAT detector (Ultrasound Advice, London, UK) which sent high-frequency output to a customized signal detection device. The device generated a digital output whenever it detected an incoming signal in the frequency band of 20–30 kHz. This digital output was sent to a Macintosh computer running "WorkbenchMac" software, allowing the number and duration of signals received to be recorded. Testing was carried out under bright white illumination.

This procedure involved a single 20-min test session. Rats were placed in the test chamber and received a 1 mA shock of 1 s duration at 2, 4, 6 and 8 min. Then, they remained in the test chamber, without further shock, until 20 min had elapsed. For the purpose of statistical analysis, the session was split into an initial 10-min "shock" period and a second 10-min "post-shock period".

2.3. Drug

(±)-3,4-Methylenedioxymethamphetamine (MDMA) was obtained from NIDA (USA). The drug was dissolved

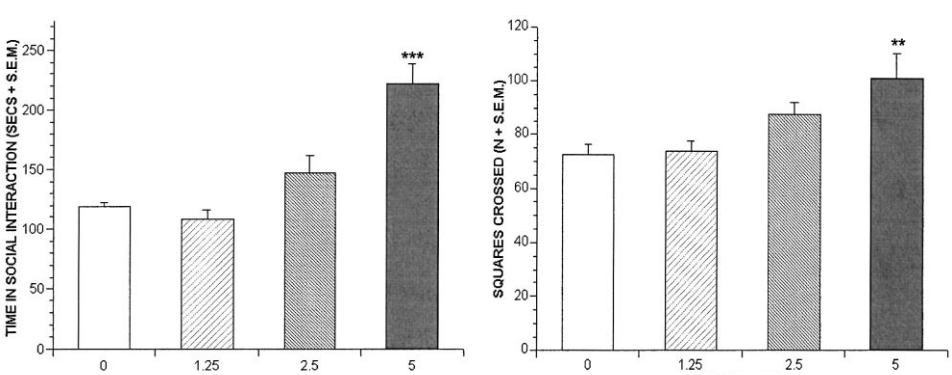

Fig. 2. Mean (+SEM) time spent in social interaction and mean (±SEM) number of squares crossed by rats tested with MDMA or vehicle. $^{**}P < 0.01$, $^{***}P < 0.001$, relative to vehicle treatment, Bonferroni planned contrasts.

Table 2
Effects of MDMA in the cat odor avoidance test

Groups	Habituation		Test	
	Hide time (s)	Approach time (s)	Hide time (s)	Approach time (s)
Vehicle	355.19 ± 22.05	118.80 ± 68.21	846.79 ± 68.13	68.21 ± 16.63
MDMA (1.25)	334.49 ± 27.18	114.54 ± 94.65	713.62 ± 44.40	94.65 ± 19.05
MDMA (2.5)	298.37 ± 28.75	125.88 ± 50.13	762.82 ± 19.83	50.13 ± 9.02
MDMA (5)	347.70 ± 27.21	107.33 ± 12.7	1047.05 ± 73.16	12.70 ± 3.07[a]

Data represent mean ± SEM.
[a] $P < 0.05$, relative to vehicle treatment, Bonferroni planned contrasts.

in 0.9% saline and injected intraperitoneally at a volume of 1 mg/kg. Doses used were 1.25, 2.5 and 5 mg/kg. Control rats received equivalent injections of saline.

2.4. Statistical analysis

Statistical analysis involved comparing the effect of each of the MDMA treatments (1.25, 2.5 and 5 mg/kg) individually with the vehicle treatment. This was done using planned contrasts with Bonferroni correction, except in the case where data were not normally distributed. In this case, Mann–Whitney *U*-tests were employed. A probability level of 0.05 was considered as statistically significant for all experiments.

3. Results

3.1. Emergence test

The results and statistical analysis of the emergence test are shown in Table 1. Mann–Whitney *U*-tests revealed that, relative to vehicle, all doses of MDMA decreased the frequency of emergence and caused a concomitant increase in emergence latency. Each dose also decreased the amount of time spent in the open field and increased the amount of defecation. An inter-rater reliability of 0.98 was obtained with scoring of emergence latency, 0.96 for open field time and 0.98 for emergence number (Pearson correlation coefficients).

3.2. Elevated plus-maze test

The results and statistical analysis of the elevated plus-maze test are shown in Fig. 1. Mann–Whitney *U*-tests showed that all doses of MDMA significantly decreased the amount of time spent on the open arm of the maze. Both the 2.5 and 5 mg/kg doses of MDMA also produced significant increases in the amount of closed arm time. Mean total arm entries also showed a significant decrease with increasing MDMA dose (data not shown). No significant treatment effect occurred with any of the risk assessment measures for all doses tested ($P > 0.05$).

3.3. Social interaction test

The results for the social interaction test are shown in Fig. 2. Planned contrasts with Bonferroni correction revealed no significant effect of 1.25 and 2.5 mg/kg MDMA on duration of interaction or number of squares crossed in the test chamber. However, MDMA (5 mg/kg) increased the time spent in social interaction ($F(1,24) = 38.74$, $P < 0.001$) and the number of squares crossed ($F(1,24) = 13.09$, $P < 0.01$). Mann–Whitney *U*-tests revealed a significant decrease in the duration of aggressive behaviours with MDMA for all doses tested (vehicle = 20.86 ± 10.05, all MDMA groups = 0.00 (s); $P < 0.001$). An inter-rater reliability of 0.93 occurred with social interaction and 0.97 with aggressive behaviours (Pearson correlation coefficients).

3.4. Cat odor avoidance test

The data for hide time and approach time during the habituation and test phases of the cat odor avoidance test are shown in Table 2. One-way analysis of variance (ANOVA) revealed that the treatment groups did not differ in hide and approach times during the habituation phase when an unworn cat collar was presented ($F < 1$). Planned contrasts revealed that MDMA (1.25, 2.5 or 5 mg/kg)

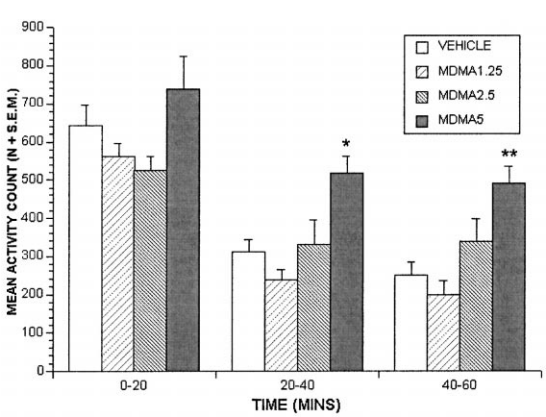

Fig. 3. Mean locomotor activity counts (+SEM) across consecutive 20-min bins for rats treated with MDMA or vehicle. * $P < 0.05$; ** $P < 0.01$, relative to vehicle treatment, Bonferroni planned contrasts.

Table 3
Effects of MDMA on ultrasonic vocalizations (UVs)

Groups	UVs during shock period (*n*)	UVs during post-shock period (*n*)
Vehicle	36.60 ± 2.65	66.00 ± 25.79
MDMA (1.25)	31.00 ± 8.52	49.75 ± 19.36
MDMA (2.5)	21.37 ± 16.79	25.63 ± 15.00
MDMA (5)	6.25 ± 4.26[a]	10.50 ± 4.82

Data represent mean ± SEM.
[a] $P < 0.01$, relative to vehicle treatment, Mann–Whitney *U*-test.

produced no significant differences from vehicle in hide times ($F(1,36) = 2.43$, 0.97, 5.49, respectively; $P > 0.05$) but that the 5 mg/kg dose caused a significant decrease in approach times ($F(1,36) = 8.47$; $P < 0.05$).

3.5. Locomotor activity test

The results for the 60 min locomotor activity test are shown in Fig. 3. Planned contrasts revealed no significant differences between groups and during the first 20 min ($Fs < 2.1$). MDMA (5 mg/kg), but not the two lower doses, produced significantly greater activity than vehicle treatment during the 20–40 min period ($F(1,52) = 10.99$, $P < 0.01$), and also during the 40–60-min period ($F(1,52) = 15.02$; $P < 0.001$).

3.6. Footshock-induced ultrasonic vocalization test

Results and statistical analysis from the footshock-induced ultrasonic vocalization test are shown in Table 3. Mann–Whitney *U*-tests revealed that the MDMA (5 mg/kg) group emitted fewer ultrasonic vocalizations than the vehicle group during this 10-min shock period. For all doses, there were no significant differences in ultrasonic vocalizations relative to vehicle for the second 10-min post-shock period, although there was a clear tendency for the higher MDMA dose to reduce ultrasonic vocalizations.

4. Discussion

MDMA produced several clear effects in the battery of anxiety tests, although different tests were associated with very different outcomes. In particular, MDMA had apparently anxiogenic properties in rats exposed to the emergence, elevated plus-maze and cat odor avoidance tests, while causing an apparent anxiolytic effect in the social interaction and footshock-induced ultrasonic vocalization tests.

All doses of MDMA tested had clear anxiogenic effects in the emergence test with a decrease in time spent in the open field, increased defecation and increased latency of rats to emerge from the hide box. Similarly, MDMA at all doses tested, decreased open arm time in the elevated plus-maze. This extends previous results obtained in the elevated plus-maze with higher doses of MDMA (Bhattacharya et al., 1998) to include results with low doses that are more comparable to those used by humans (Boot et al., 2000; Topp et al., 1999; Vollenweider et al., 1998). It is particularly notable that the effects of the lowest MDMA dose (1.25 mg/kg) were very pronounced in the emergence and elevated plus-maze models. This dose also significantly reduced aggressive behaviour in the social interaction test. This suggests that future behavioural studies of MDMA in rats could usefully explore even lower doses of the drug.

During cat odor exposure, rats treated with 5 mg/kg, but not lower doses of MDMA, significantly decreased the amount of time spent in close proximity to the odor stimulus (approach time). Time spent hiding was not significantly affected by MDMA. In past work (Dielenberg et al., 1999), we have found that approach time tends to be a more sensitive measure of cat odor-induced anxiety than hide time, so it is understandable that the former, but not the latter, was affected by MDMA. It is perhaps surprising that hide times were not affected, given the powerful anxiogenic effects of MDMA in the emergence model. However, it should be recalled that testing of cat odor avoidance took place in a dark and familiar apparatus, presumably where emergence from a hide box was not strongly anxiogenic. Further, in the cat odor avoidance model, hide times in the presence of cat odor are very high even under vehicle conditions (Dielenberg et al., 1999), making a drug-induced potentiation of hiding rather difficult to demonstrate.

A key result in the present study was that MDMA at a dose of 5 mg/kg increases social interaction, and at all doses tested, diminished aggressive behaviour in pairs of rats tested in an unfamiliar environment. The latter result parallels demonstrations that MDMA decreases offensive behaviours in mice (Navarro and Maldonado, 1999). The increase in social interaction seen here with 5 mg/kg MDMA contrasts with the finding by Bhattacharya et al. (1998) that the same dose of MDMA reduces social interaction in rats. The probable reason for this discrepancy is that this previous study tested MDMA in a familiar arena, while the present study used an unfamiliar arena. It is known that the effects of many drugs in the social interaction paradigm, including serotonergic agonists, are dependent upon the environmental conditions under which the test is conducted (File and Hyde, 1977; Higgins et al., 1992; Nadal et al., 1993). The present study suggests that the effects of MDMA on social interaction are similarly sensitive to environmental factors.

Prosocial and anti-aggressive effects in the social interaction test have also been reported with 5-HT_{1A} receptor agonists such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) under conditions when the test arena is unfamiliar (Picazo et al., 1995). A facilitation of social interaction in an unfamiliar environment has also been

reported following injection of the 5-HT_{2B} receptor agonist 1-[5-2(2-thienylmethoxy)-1H-3-indoly]propan-2-amine hydrochloride (BW 723C86) into the medial amygdala of rats (Duxon et al., 1997). This suggests that the social facilitation produced by MDMA may perhaps be mediated through an enhanced 5-HT action at 5-HT_{1A} or 5-HT_{2B} receptors.

In contrast, the anxiogenic effect of MDMA on the elevated plus-maze and emergence tests might reflect increased synaptic 5-HT acting at 5-HT_{2A} or 5-HT_{2C} receptors. It is well-known that 5-$HT_{2A/2C}$ receptor agonists such as *meta*-chlorophenylpiperazine are strongly anxiogenic in rats tested on the emergence and open field tests, and also increase free-floating anxiety in human volunteers (Broocks et al., 1997; Meert et al., 1997).

It could be argued that the increased social interaction in rats following MDMA is merely an artifact of the hyperactivity induced by the drug. Indeed, the 5 mg/kg dose that increased social interaction in the current study, also increased the number of squares crossed in the social interaction test arena and also increased locomotor activity in a neutral test environment. This dose also caused significant hyperactivity in a previous study from our laboratory (Stephenson et al., 1999). However, video observation in the present study indicated that the increased social interaction elicited by 5 mg/kg MDMA reflected an increase in passive rather than active social behaviours. Thus, the increased interaction occurred, not when the rats were involved in locomotion, but during relatively static behaviours like adjacent lying and sniffing.

It is also prudent to ask whether changes in locomotor activity might underlie the apparent changes in anxiety-like behaviours seen in the emergence and elevated plus-maze results. This seems very unlikely since only the highest dose of MDMA (5 mg/kg) affected locomotor activity, while the two lower doses (1.25 and 2.5 mg/kg) were clearly effective in the elevated plus-maze and emergence tests.

Anxiolytic effects of MDMA were also suggested by the results of the footshock-induced vocalization model, with a dose-dependent reduction in the number of vocalizations produced by shock. However, these results suffer a possible confound due to the analgesic effects of MDMA. A dose-dependent (0–6 mg/kg) analgesic effect of MDMA on the hot plate test, has been previously demonstrated (Crisp et al., 1989) suggesting that the decreased ultrasonic vocalizations seen in the present study may have been simply due to a reduced sensitivity to shock. On the other hand, MDMA decreases ultrasonic vocalizations in rat pups during maternal separation (Winslow and Insel, 1990), suggesting that the decreased vocalizations seen here may reflect something other than an analgesic effect of MDMA. Future research in which MDMA is administered in a shock-paired environment rather than during shock itself (see Molewijk et al., 1995) might help to resolve whether the decrease in ultrasonic vocalizations represents an anxiolytic or an analgesic effect.

What is apparent from the current study is that MDMA possesses a bimodal behavioural profile, in line with the recent proposition that MDMA is capable of activating both excitatory and inhibitory neural mechanisms in the control of anxiety (Lin et al., 1999). Interestingly, in the present study, MDMA had clear anxiogenic properties at doses that are clearly rewarding in the self-stimulation and conditioned place preference models (Lin et al., 1997; Marona-Lewicka et al., 1996). This profile is reminiscent of cocaine and amphetamine, both of which are anxiogenic in the elevated plus-maze (Lin et al., 1999; Rogerio and Takahashi, 1992), yet positively reinforcing in the self-administration, self-stimulation and place preference tests (e.g. Depoortere et al., 1999; Roberts et al., 1999).

However, MDMA seems unique in at least one respect, in that previous studies have found that abused drugs such as amphetamine and cocaine fail to affect social interaction, while other abused drugs such as phenyclidine (PCP) and cannabinoid receptor agonists induce social withdrawal (Arnold, McGregor and Morley, unpublished data; Corbett et al., 1995; Guy and Gardner, 1985; Rademacher et al., 1999; Sams-Dodd, 1995, 1998). This suggests that the strong facilitation of social interaction found in the present study may be a relatively unique property of MDMA.

There is clearly an element of consistency between the human experience of MDMA and the data reported here. Thus, MDMA has been reported to acutely increase human social contact and induce a strong desire to be with and converse with people (Peroutka, 1990; Shulgin, 1990; Solowij et al., 1992) but also to produce increases in generalised anxiety (Vollenweider et al., 1998) as well as occasional panic attacks (McCann and Ricaurte, 1992; Whitaker-Azmitia and Aronson, 1989; Windhaber et al., 1998). The current results and clinical literature accord with the suggestion that MDMA may have the capacity to induce both euphoria and anxiety with contextual or personality variables determining the outcome of the drug experience from one situation or individual to the next.

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