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The Anxiogenic-Like and Anxiolytic-Like Effects of MDMA on Mice in the Elevated Plus-Maze: A Comparison With Amphetamine

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LIN, H. Q., P. M. BURDEN, M. J. CHRISTIE AND G. A. R. JOHNSTON. *The anxiogenic-like and anxiolytic-like effects of MDMA on mice in the elevated plus-maze: A comparison with amphetamine.* PHARMACOL BIOCHEM BEHAV **62**(3) 403–408, 1999.—Many abused substances have been found to possess anxiogenic-like or/and anxiolytic-like properties. Discrepancies about the effects of MDMA, one of the most popular recreational drugs in recent years, on anxiety have been seen in the literature, and almost all of the data in this respect were derived from retrospective studies. The present study was thus designed to examine the drug's actions by using an animal model of anxiety, the elevated plus-maze test in male mice. Intraperitoneal MDMA at 1 mg/kg was ineffective, at 4 mg/kg decreased the percent of open arm entries ($p < 0.01$), and increased enclosed entries ($p < 0.05$), at 12 mg/kg had no significant effect, and at 20 mg/kg induced an increase of percent of open time ($p < 0.01$). As control drugs, amphetamine (0.5–4 mg/kg, IP) produced a dose-dependent, anxiogenic-like effect and diazepam (1 mg/kg, IP) induced an anxiolytic-like effect in the test. The results indicate that MDMA has anxiogenic-like properties at lower doses and anxiolytic-like at higher doses. The effects of MDMA and amphetamine on the mouse's responses to the plus-maze are compared. These findings provide a possible explanation for the controversies over MDMA's effects on anxiety in the literature. © 1999 Elsevier Science Inc.

MDMA Amphetamine Anxiety Elevated plus-maze Mice

A variety of abused substances have been found to be capable of modulating the expression of anxiety. Some of these substances are known as anxiogenics, such as marijuana, amphetamine, cocaine, and caffeine. In contrast, ethanol, nicotine, diazepam, and phenobarbitone are reported to possess anxiolytic-like properties, though they may elicit anxiety-like responses to withdrawal from chronic or subchronic use. Such findings have led to establishment of a link between anxiety disorders and drug abuse.

3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a bicyclic amphetamine derivative with abuse potential. Despite the evidence for MDMA's strong serotonergic toxicity in animals, and despite the legislative restriction of its use in several countries, MDMA has become a popular recreational drug over the last decade. Controversies over MDMA's effects on anxiety have been seen in literature. Schifano (35) reported a case of chronic use of MDMA, in which a high level of anxiety was observed. In a survey of 500 MDMA users, Cohen (5) discovered that 16% of subjects had experienced immediate anxiety following oral administration of the drug. Peroutka (29), in a university campus survey, reported 12% of students studied suffered anxiety, worry or fear 24 h after ingestion of MDMA. Paradoxically, Liester et al. (18) conducted a retrospective study on 20 volunteer psychiatrists who had used MDMA previously, and found 15% reporting decreased anxiety but 25% indicating increased anxiety. Moreover, Greer and Tolbert (12) reported that in a clinical setting some subjects felt less anxious after two doses of MDMA, and

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Battaglia et al. (2), in a review article, considered MDMA a drug with "anxiolytic-like" effects. It is noteworthy that most of the existing conclusions about MDMA's effects on anxiety are based on retrospective studies. Usually, these studies had no clear objective measures and/or lacked control of many variables, for example, dose, purity of MDMA, frequency of MDMA use, set and setting, etc. Therefore, the main purpose of the present study was to examine the pharmacological actions of MDMA on anxiety by using an animal model to provide objective and more precise data in this regard.

Both MDMA and amphetamine are phenethylamine derivatives. The similarity of their chemical structures has provoked continuous research interest in the comparison of the drugs' behavioral effects as well as relevant neural mechanisms (4,10,26). Previously, we found that MDMA was less potent than amphetamine in producing conditioned taste aversion (19), and that these taste aversions seemed to be mediated by different neurotransmitter systems (21). We also demonstrated that, in accumbal self-stimulation, MDMA and amphetamine had similar effects on reinforcement but different effects on performance (20). A recent survey has indicated that both drugs caused a range of adverse effects including anxiety in drug users and the adverse effects of amphetamine seemed more severe than those of MDMA (38). A direct comparison under the same experimental conditions would produce more accurate data in regard to the two drugs' pharmacological effects on anxiety.

The elevated plus-maze test is one of the most commonly used animal models of anxiety in recent years. The maze consists of two opposing open arms and two opposing enclosed arms, elevated from the floor. The test is based on the drive conflict of rodents, a desire to explore the surroundings and a fear of the open and high places. Lister (22) has validated the model in mice with different classes of drugs, and demonstrated that the test was effective for investigating anxiogenic-like and anxiolytic-like effects of agents. In the past decade, a large number of pharmacological studies on anxiety have been done with the method. There is good evidence for the neuropharmacological and neuroantomical parallels between rodent emotionality and human anxiety. The plus-maze test with outbred mice was, therefore, used to assess the acute effects of MDMA and amphetamine on anxiety in the present study. Diazepam, an anxiolytic, served as a control drug. Although there has been an increasing interest in using genetical techniques in anxiety studies, for a general drug assessment, conclusions derived from outbred animals would be more relevant to normal human population than those from inbred or mutant animals.

METHOD

Subjects

Eight to 11-week-old, male Quackenbush Swiss (QS) mice (an outbred strain obtained from the University of Sydney SPF facility, Little Bay, Australia) were used. They were group ($n = 10$) housed in plastic cages with free access to water and standard laboratory chow. The animal house was maintained at 21 ± 1°C and a 12 L:12 D cycle. The experiments were conducted from 1030–1630 h, and the testing order for different treatments were counterbalanced to limit the time effect. Each animal was used once only.

Apparatus and Procedures

The elevated plus-maze consisted of two opposing open arms (30 × 5 cm) and two enclosed arms (30 × 5 cm), which joined at a square central area (5 × 5 cm). Each enclosed arm was enclosed by three transparent walls (15 cm in height). The floor of the maze was made of black Plexiglas and raised 40 cm above the room floor by means of a stand. Three white 40-W fluorescent tubes hung from the ceiling provided the only source of light in the testing room. A video camera was mounted vertically about 1.5 meters above the plus-maze for recording behavioral responses.

Age-matched mice were randomly assigned to 12 experimental groups. They were transferred into an injection room at least 1 h before testing. Immediately following an injection, the mice were separately detained in a small cage (29 × 16 × 11 cm) and then individually tested in a testing room. At testing time, a single mouse was placed onto the central area of the maze facing an open arm, and its responses were recorded for 5 min by the video camera. After removal of each animal, the maze was cleaned with wet cloth and wiped dry. The behaviors of mice recorded on videotapes were later scored by a trained observer blinded to the treatments.

Behavioral measures included percent time spent in open arms (% open time) expressed as a percentage of total time on both open and enclosed arms, percent entries into open arms (% open entries) expressed as a percentage of the total number of arm entries, and the number of entries into enclosed arms (enclosed entries) (22). Arm entry was defined as two front paws having crossed the dividing line between an arm and the central area.

Drugs

(±)-MDMA hydrochloride (National Institute on Drug Abuse, USA) and *d*-amphetamine sulfate (May and Baker, UK) were dissolved in 0.9% saline. Diazepam (Roche Products, Australia) was dissolved in a vehicle consisting of propylene glycol, Tween 80, and 0.9% saline (15:2:83). The drug solutions or vehicle were injected intraperitoneally in a volume of 10 ml/kg, 30 min prior to behavioral testing. The doses of MDMA (1, 4, 12, and 20 mg/kg) employed in the present study were referred to previous behavioral experiments with rats, conditioned taste aversion (0.125–2 mg/kg) (19), self-stimulation (0.5–4 mg/kg) (20), and ultrasonic vocation (20 mg/kg) (39). The dose range of amphetamine (0.5, 2, and 4 mg/kg) was based on that (1, 2, and 4 mg/kg) used by Lister (22) in the plus-maze test in mice. The single dose of diazepam (1 mg/kg) was an effective anxiolytic-like dose found in our pilot study.

Statistical Analyses

Raw data for the highest dose of MDMA as well as those for diazepam were subjected to an unpaired Student *t*-test, and the other were analyzed with an a priori multiple comparison procedure, a Bonferroni *t*-test (15).

RESULTS

The effects of MDMA on responses to the plus maze are depicted in Fig. 1. In a dose-related fashion, the actions of MDMA varied from anxiogenicity to anxiolysis with increasing dose. At the dose of 1 mg/kg, MDMA did not have any significant effect on all measures. When the dose was increased to 4 mg/kg, the drug markedly reduced % open entries ($p < 0.01$) and significantly increased enclosed entries ($p < 0.05$), indicating an anxiogenic-like and an stimulant effect, respectively. At the dose of 12 mg/kg, no significant effect was observed. Finally, at the highest dose level, 20 mg/kg,

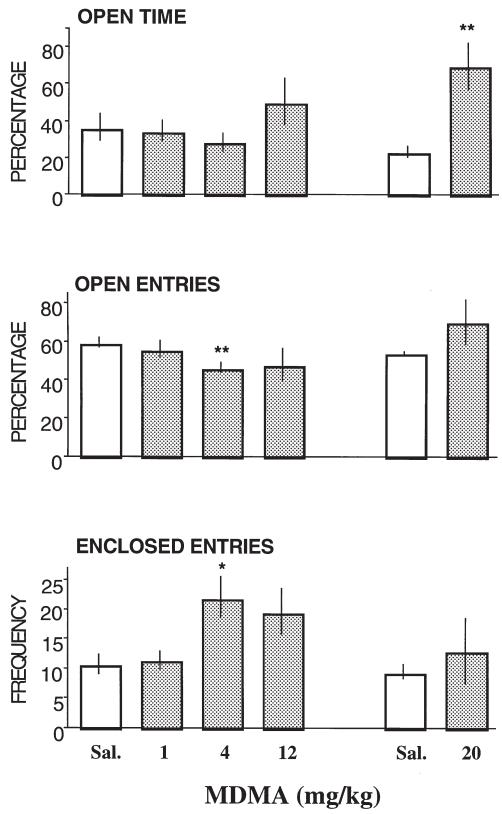

FIG. 1. The effect of MDMA on responses to the elevated plus-maze. Each column and vertical bar represent the mean ± SEM for eight to nine mice. *$p < 0.05$, **$p < 0.01$, compared with the vehicle control.

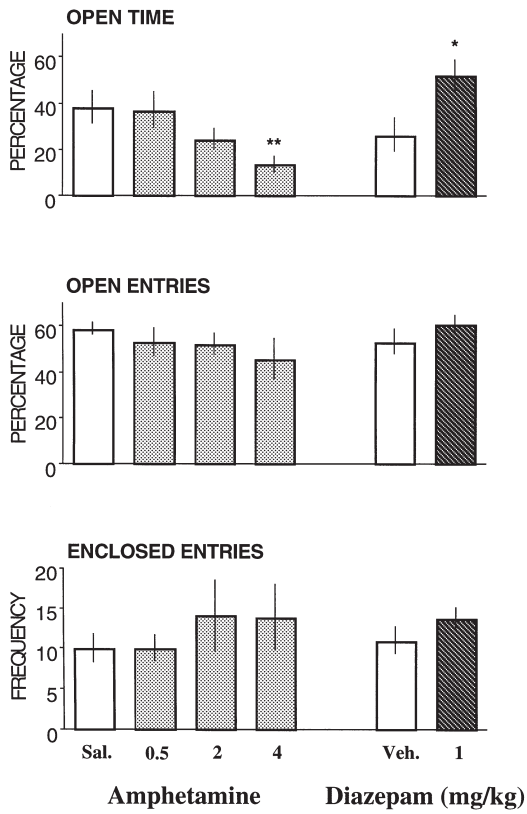

FIG. 2. The effects of amphetamine and diazepam on responses to the elevated plus-maze. Each column and vertical bar represent the mean ± SEM for eight to nine and seven mice for amphetamine and diazepam, respectively. *$p < 0.05$, **$p < 0.01$, compared with the vehicle control.

MDMA induced a significant increase of % open time ($p < 0.01$), suggesting an anxiolytic-like effect for the drug.

The effects of amphetamine and diazepam are shown in Fig. 2. In a dose-dependent manner, amphetamine significantly decreased % open time ($p < 0.01$), implying a reliable anxiogenic-like effect in the test. Consistently, the drug tended to decrease % open entries, although this measure failed to reach the statistically significant level. The slight increase of enclosed entries by the higher doses of amphetamine were not significantly different from the saline control. Diazepam produced a reliable increase of % open time ($p < 0.05$), indicating that the drug exerted an anxiolytic-like action in the plus maze test.

DISCUSSION

The present study clearly demonstrates dose-dependent, "paradoxical" effects of MDMA in the elevated plus-maze test. These effects can be summarized as follows: a 1-mg/kg dose was inactive, 4 mg/kg exerted an anxiogenic-like action as well as a hyperactive effect, 12 mg/kg seemed to be a transient dose level between anxiogenicity and anxiolysis, and 20 mg/kg gave rise to anxiolysis. The results suggest that MDMA possesses dual pharmacological properties, capable of activating both excitatory and inhibitory neural mechanisms in the control of anxiety. The results also show that amphetamine, in a dose-related fashion, elicited a reliable, anxiogenic-like effect, while diazepam induced a significant, anxiolytic-like effect in the test. The data from these two established drugs confirm that the experimental settings in the present study were appropriate for detecting drug effects in both anxiogenic-like and anxiolytic-like directions.

Previous clinical observation (35) and retrospective studies (5,29,38) have indicated that MDMA may cause anxiety problems in drug users. In the present study MDMA, at a lower dose, elicited anxiety-like behaviors in mice. The consistency of human and animal studies substantiates the notion that MDMA possesses anxiogenic-like properties. Rewarding and reinforcing effects of MDMA have been shown in animal models such as conditioned place preference (34), self-administration (16), and self-stimulation (20). Interestingly, the anxiogenic-like dose of MDMA in the plus-maze test (4 mg/kg in mice) (the present study) is close to its reinforcing doses in conditioned place preference (1.5 mg/kg in rats) (34) and in self-stimulation (4 mg/kg in rats) (20). This suggests that the euphoric effect of MDMA may be accompanied by its anxiogenic-like effect. Peroutka (30) has pointed out that MDMA was used at longer intervals than the classic addictives (e.g., morphine, cocaine, and amphetamine), and can be voluntarily given up by users after a considerably long period of recreational use. A similar phenomenon has been seen with marijuana abuse. Users with panic anxiety spontaneously stopped smoking marijuana because it enhanced their anxiety (37). Whether this is a reason for the specific pattern of MDMA

use described by Peroutka (30) remains to be further investigated.

The anxiolytic-like effect of MDMA is indicated by its increase of % open time in the plus-maze test at the highest dose. This result is consistent with Liester et al.'s (18) and Greer and Tolbert's (12) finding that MDMA reduced anxiety in a proportion of human subjects. Moreover, Winslow, and Insel (39) found that repeated administration of MDMA resulted in decreased vocalization in rat pups without affecting locomotor behavior. Reduction of ultrasonic calls has been considered to be an index of relief of anxiety (14). Miczek and Haney (23) also reported that MDMA dose dependently decreased the mouse's aggressive behavior towards an intruder. Under the experimental conditions, the aggressive behavior may contain an anxiety component. These data derived from human and animal studies provide evidence for the anxiolytic-like properties of MDMA. Surprisingly, the anxiolytic-like dose of MDMA is relatively high, several times that producing anxiogenic-like (the present study) and reinforcing (20,34) effects. Based on these dose–effect relationships, it is conceivable that seeking a more preferable pharmacological state with MDMA, i.e., euphoria with anxiolysis, would lead to much higher dosing of the drug. Cases involving lethal misuse of MDMA have been repeatedly reported. It is, therefore, worthwhile to consider whether the anxiolytic-like property of MDMA is related to high-dose misuse of the drug.

This is the first animal study to compare the effects of MDMA and amphetamine on anxiety. Within a low dose range (1 and 4 mg/kg for the former and 0.5–4 mg/kg for the latter), the dose–response relationship of the two drugs were mostly parallel, revealing a similarity in their anxiogenic-like actions. However, with higher doses, the two drugs caused differential responses. MDMA at 20 mg/kg eliciting a significant antianxiety effect (the present study). In contrast, QS mice could not tolerate higher doses of amphetamine. In a pilot study, we found that amphetamine at 6, 12, and 20 mg/kg resulted in convulsive seizure in one of three, two of five and three of five mice, respectively. These results extend our previous findings that MDMA was only in part similar to amphetamine in conditioned taste aversion (19,21) and brain self-stimulation (20). Such partial similarities of the two drugs have also been observed in monoamine transmitter release (8), locomotor activity (11), and schedule-controlled behavior (9). Moreover, the potency of MDMA is generally weaker than amphetamine in several other behavioral tests (9,19,20), but its anxiogenic-like potency seems comparable with amphetamine's in the sense that both drugs had a common minimal effective dose (4 mg/kg) in producing anxiety on the plus-maze (the present study). Taken together, these data support the concept that MDMA belongs to an independent drug class (25), although its chemical structure is closely similar to amphetamine, and it was sometimes considered an amphetamine-like stimulant.

Controversies over amphetamine's effects in the plus-maze test have been seen in the literature, though the drug is known to possess anxiogenic-like effect in humans (13,38) and in animals (7). An anxiogenic-like effect of amphetamine on the plus-maze has been previously shown in rats (28) and in mice (17). These findings are in agreement with our present results. However, Lister (22) reported that amphetamine failed to alter indices of anxiety in mice, and Dawson et al. (6) claimed that the drug produced anxiolytic-like effect in rats. As an animal behavioral model, the plus-maze is susceptible to the influence of a variety of experimental variables such as animal strains, construction of the maze, lighting level, behavioral procedures, etc. At present, we do not have a clear explanation for the controversies that were based on variations in more than one of the variables.

An interesting finding in the present study is that MDMA significantly increased the enclosed entries in contrast to the nonsignificant effect of amphetamine [similarly, lack of significant effect of amphetamine on total arm entries has been previously reported (6,28)]. This seems to be in conflict with an earlier finding that amphetamine is more potent than MDMA in producing central stimulant effects (27). Our explanation for this phenomenon is that, in the plus-maze test, the measure of enclosed entries or total arm entries is not an accurate index of locomotor activity. Some researchers have thus suggested that the conventional measure of total arm entries should be replaced with a new measure, speed of movement, which is thought to be more sensitive in measuring locomotor activity (6), but this would demand more sophisticated analytical equipment. Moreover, amphetamine's inhibition of exploration of novel stimuli (31) may also contribute to its relatively weak stimulant effect in the plus-maze.

The elevated plus-maze test is an exploratory animal model of anxiety. Although early studies have argued for the specificity of the model in determining drugs' effects on anxiety (22,28), there are still concerns that changes in locomotor activity may influence the measures of anxiety. Typically, Dawson et al. (6) have shown that a lower dose of amphetamine generated an anxiolytic-like effect together with hyperactivity, and that higher doses of buspirone, an anxiolytic, elicited an anxiogenic-like response accompanied with decreased total entries. They thus concluded that the anxiogenic-like and anxiolytic-like effects of drugs in the plus-maze are confounded by changes in locomotor activity. In sharp contrast to Dawson et al.'s (6) observation on amphetamine, we found that MDMA at 4 mg/kg induced an anxiogenic-like rather than anxiolytic-like effect when it elevated enclosed entries (the present study). Pellow et al. (28) similarly discovered that caffeine reduced % open time and % open entries when it caused hyperactivity in the plus maze, while Lister (22) reported that amphetamine increased total entries without any significant effect on the anxiety measures. All these data show that drug-induced hyperactivity could be accompanied with anxiolysis, anxiogenicity, or noneffect on anxiety. Thus, it seems unlikely that there exists a clear, cause–effect relationship between drugs' stimulant and anxiolytic-like effects in the plus-maze test. On the other hand, the anxiety measurement appears to be susceptible to drug's depression of locomotion in the plus-maze. Similar to Dawson et al.'s finding with buspirone as mentioned above, we have observed a decrease of % open time and % open entries plus reduction of enclosed entries by a higher dose of diazepam (Lin et al., unpublished data). This may be ascribed to the sedative, hypnotic, or muscle-relaxant effects that can reduce animals' exploratory drive or impair their motor ability, and thus confound measurement of drugs' effects on anxiety.

MDMA is an active releaser of serotonin, dopamine, and noradrenalin (8) in addition to its moderate affinities for various receptor subtypes of these neurotransmitter systems (2). Serotonin (1), dopamine (36), and noradrenalin (32) have been thought to be important in the neural process of controlling anxiety. Also, much experimental evidence has suggested a role for these transmitter systems in the behavioral effects elicited by MDMA, for example, serotonergic modulation of a locomotor stimulant effect (4), dopaminergic mediation of a threshold-lowering effect in self-stimulation (3), both serotonergic and dopaminergic components in the stimulus proper-

ties in drug discrimination (33), and noradrenergic blockade of an inhibitory effect in schedule controlled behavior (24). It is, therefore, reasonable to question whether these three neurotransmitters play a role or interact with each other in mediating MDMA's anxiogenic-like and anxiolytic-like actions. Additional research along this line would provide insights into the multiple ways in which this complex drug may exert its effects on anxiety.

In summary, the present study reports that MDMA is able to produce an anxiogenic-like effect at lower doses and an anxiolytic-like effect at higher doses. The potency of MDMA as an anxiogenic seems close to that of amphetamine, although the effects of MDMA are generally weaker than amphetamine's in other behavioral tests (19,20,27). The finding of this animal study provides a possible explanation for the controversies over MDMA's effects on anxiety in human studies.

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