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BRIEF COMMUNICATION

The Effects of Repeated Administration of MDMA on the Expression of Sexual Behavior in the Male Rat

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DORNAN, W. A., J. L. KATZ AND G. A. RICAURTE. *The effects of repeated administration of MDMA on the expression of sexual behavior in the male rat.* PHARMACOL BIOCHEM BEHAV **39**(3) 813–816, 1991.—3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a potent neurotoxin which preferentially produces 5-HT nerve terminal degeneration in the CNS in both rodents and primates. Timely research on the behavioral effects of acute and long term treatment of MDMA is critical due to the neuropathological effects of MDMA and its abuse liability. Presently, there are no published reports that have systematically examined the effects of acute or chronic treatment of MDMA on animal sexual behavior. Accordingly, the effects of repeated systemic administration of MDMA on a variety of parameters of male sexual behavior in sexually vigorous male rats were studied. Treatment consisted of subcutaneous injections of MDMA (40 mg/kg) or saline (1 ml/kg) every 12 hours for 4 consecutive days. In addition, neurochemical assessments of brain 5-HT and 5-HIAA depletion following repeated MDMA treatment were also conducted using reverse phase liquid chromatography. The results of this study revealed that repeated systemic administration of MDMA to sexually vigorous male rats produced a transient disruption of the expression of male copulatory behavior. In addition, in MDMA-treated males that did display copulatory behavior, both the ejaculation latency and postejaculatory interval were dramatically lengthened when compared to saline injected controls. Suprisingly, one week after the first behavioral test, copulatory behavior in MDMA treated rats appeared unaffected despite a marked depletion of 5-HT and 5-HIAA content in the striatum, and hippocampus.

3,4-Methylenedioxymethamphetamine MDMA Ecstasy 5-HT Male rat sexual behavior Neurotoxicity

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "Ecstasy"), an amphetamine analog, is one of the recent "designer drugs" to surface on the illicit drug market [for review see (12)]. First synthesized in Germany in 1914 for use as an anorexiant, it became popular in the 1970s and early 1980s as psychotherapeutic adjunct, based on MDMA's apparent ability to enhance emotional insight, which in turn was claimed to facilitate communication between client and therapist (5, 12, 13). As a result of its abuse liability and suspected neurotoxicity, however, on July 1st 1986, MDMA was assigned emergency Schedule I status by the United States Drug Enforcement agency (DEA).

Currently, MDMA has attracted a great deal of attention as it is one of a number of designer drugs which is being increasingly abused on university campuses in the United States (9,10). These reports are particularly alarming, as MDMA has been revealed to have neurotoxic effects (1, 2, 11, 17). For example, acute of chronic MDMA administration to rodents as well as to nonhuman primates results in reductions of brain concentrations of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), as well as a preferential degeneration of 5-HT nerve terminals, as revealed by profound decreases in the density of 5-HT uptake sites (2,11).

Presently, little is known about the behavioral effects of repeated MDMA treatment. In one recent study, using rodents and primates, Slikker et al. (15) reports that following repeated administration of MDMA for 4 consecutive days, no significant decreases in complex maze behavior (rodents) or spontaneous behavioral changes (primates) were observed despite a significant decrease (50%) in 5-HT forebrain concentrations when compared to saline injected controls. The authors speculate that perhaps one of the reasons for the discrepancy between the neurochemical and behavioral results was that their behavioral tests were not sensitive enough to assess the functional consequences of the 5-HT depletion.

The sexual behavior of the male rat has been shown to be extremely sensitive to pharmacological manipulation (6,16). Consequently, a systematic approach assessing the effects of MDMA

on rat sexual behavior would be a logical form of MDMA research. This is particularly relevant given that there are conflicting empirical and anecdotal reports on the effects of MDMA on sexual performance in humans (3, 5, 7, 12). Presently, however, there are no published reports of studies that have systematically examined the effects of acute or chronic treatment of MDMA on animal sexual behavior. Accordingly, in this preliminary study we examined the effects of repeated administration of MDMA on sexual behavior in the male rat. In addition, neurochemical assessments of brain 5-HT and 5-HIAA depletion following repeated MDMA treatment were also conducted using reverse phase liquid chromatography.

METHOD

Subjects

Thirty Long-Evans adult male rats were used in the following experiment. Animals weighed between 350-475 grams at the time of injections. They were housed singly in a controlled environment at 21°C, with a reversed light cycle (lights off 2:00 p.m.). Throughout the experiments, food and water were available ad lib. Animals were handled daily so as to minimize stress during injections.

Procedure

Each male was given sexual screening tests in which it was placed with a sexually receptive female on alternate days until one ejaculation was achieved during a 30 minute test. Males were tested on alternate days until they had ejaculated in at least three of these tests. Only males that satisfied this criterion were subsequently used. This type of behavioral paradigm produces highly sexually vigorous males (4). After successful completion of the last screening test, males were randomly divided into two groups. One group was administered subcutaneously 40 mg/kg of MDMA every 12 hours for 4 consecutive days. This schedule has been shown to produce maximum 5-HT neurotoxicity (11). The other group received injections of saline.

Behavioral Testing

One week following the first MDMA or saline injection, all males were given their first behavioral test. A second behavioral test was given 7 days later (test 2). Copulatory behavior was tested as previously described (4). Briefly, each test lasted a maximum of 30 minutes or until one ejaculation followed by an intromission was achieved. If a male did not have an intromission within the first 15 minutes, the test was terminated, and the male was considered a "noncopulator." The following behavioral parameters were recorded; 1) number of mounts preceding ejaculation (MF); 2) number of intromissions preceding ejaculation (IF); 3) mount latency (ML); 4) intromission latency (IL); 5) ejaculation latency (EL); 6) postejaculatory interval (PEI).

Motor Activity

Throughout the experiment a random sample of MDMA (n=3) and saline injected males (n=3) were placed in rectangular test boxes (51 L×38 W×36 H cm) that had been partitioned into 60 squares. In an attempt to assess the effects of repeated MDMA on spontaneous motor activity, immediately after the sexual behavioral test, a male was placed in the box and the number of squares crossed during a five minute interval was recorded.

Drugs

MDMA provided by the National Institute on Drug abuse was dissolved in physiological saline. Both MDMA and saline injections (control) were given a volume of 1.0 ml/kg.

Serotonin Determination

Approximately two weeks from the first MDMA or saline injections, a random sample of 9 rats were killed and the hippocampus, and striatum were isolated and 5-HT as well as 5-HIAA concentrations in these brain areas were determined by reverse phase liquid chromatography coupled with electrochemical detection, as previously described by Ricaurte et al. (11). These areas were chosen based on results of previous result which has shown that MDMA injections significantly reduce 5-HT content in the hippocampus and striatum (1, 2, 11).

Statistical Analysis

The proportion of animals displaying ejaculation during a 30-minute test was assessed by McNemar's change test (14). With the exception of the motor activity (*t*-test), all other behavioral parameters were analyzed by the Wilcoxon matched-pairs signed rank test (8,14).

RESULTS

Motor Activity

The results of these tests revealed that when compared to controls (saline injections) MDMA had no effect on spontaneous activity ($t=0.067$, $p>0.05$, data not shown).

Mating Tests

Of the 30 animals that began the experiment, four MDMA-treated males died within the first week. Another seven did not satisfy behavioral criterion. That left 19 animals for data analysis (MDMA, n=9, saline, n=10). As can be seen from Fig. 1A, one week after the first MDMA injection (test 1) a significantly smaller percentage of MDMA-treated males displayed ejaculatory behavior when compared to the saline injected controls ($p<0.05$). Only three out of nine MDMA-treated males (33%) displayed ejaculatory behavior. In the three males that did ejaculate, MDMA clearly affected their pattern of sexual behavior. Although the increase in ejaculation latency in the MDMA-treated animals failed to reach statistical significance, the postejaculatory interval was significantly increased by repeated administration of MDMA compared to saline injected controls ($p<0.05$, see Fig. 1B). No other behavioral parameter was affected.

In contrast, one week later (or 2 weeks following the first injection), there was no significant difference between MDMA and saline injected controls on any parameter of sexual behavior (test 2, Fig. 1). One MDMA-treated male, however, remained a noncopulator on test 2.

5-HT Determination

As can been seen from Fig. 2, repeated systemic treatmen of MDMA (n=6) produced a significant depletion of 5-HT an

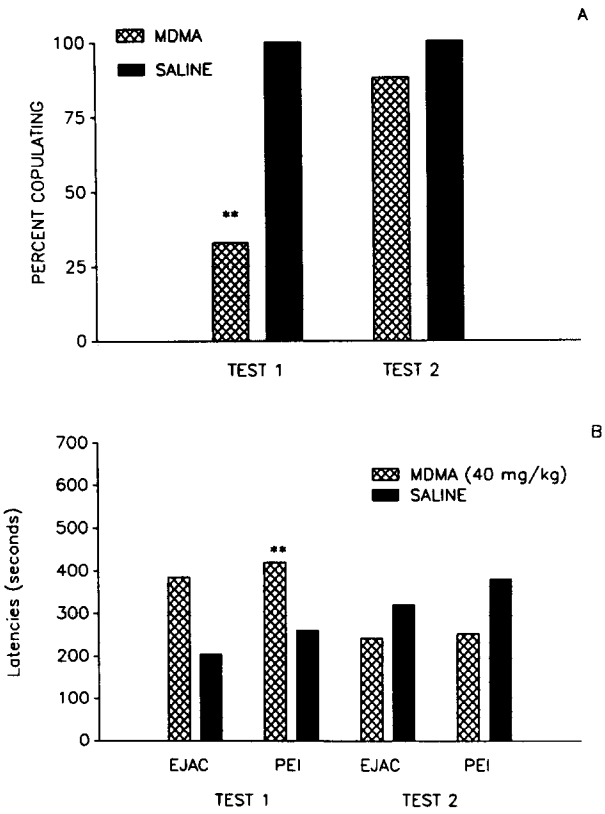

FIG. 1. Effect of subcutaneous injections of MDMA (40 mg/kg) or saline (1 ml/g) on the percent of sexually experienced male rats displaying ejaculatory behavior during two behavioral tests (A), and on the ejaculation latency and postejaculatory interval (B). MDMA, n=9; saline, n=10. $^{**}p<0.05$.

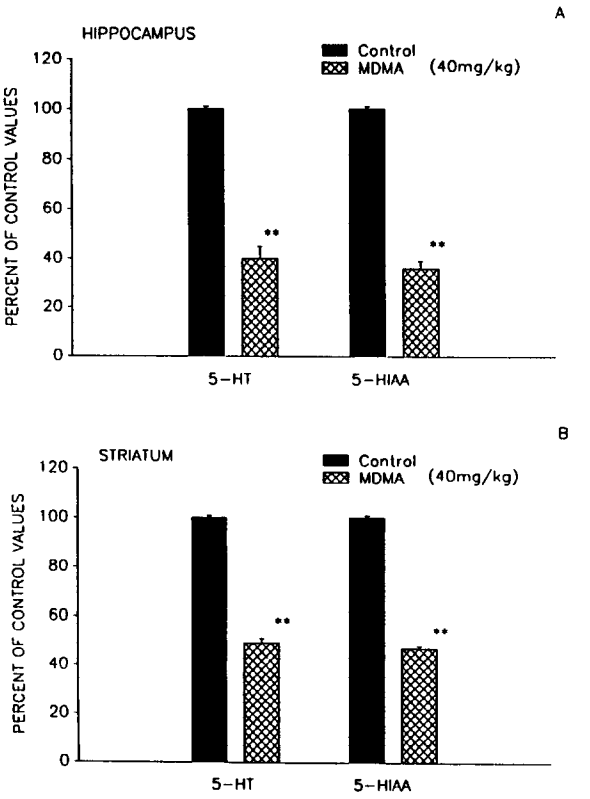

FIG. 2. Effect of subcutaneous injections of MDMA (40 mg/kg) or saline (1 ml/kg) on 5-HT and 5-HIAA in the hippocampus (A) and striatum (B) measured 17 days after the first injection. Treatment consisted of subcutaneous injections of MDMA (40 mg/kg) or saline (1 ml/kg) every 12 hours for 4 consecutive days. Data are plotted as percentage of control values in each brain region. Vertical bars represent ± standard errors of the mean. $^{**}p<0.05$.

5-HIAA in both brain areas examined when compared to saline-injected controls (n=3). It is noteworthy that 2 weeks from the first MDMA injection, no significant differences between MDMA-treated animals and controls were observed on copulatory behavior despite an overall mean 57 percent depletion of 5-HT in the MDMA-treated compared to control animals (see Figs. 1 and 2).

DISCUSSION

The major result of this experiment is that repeated administration of MDMA to sexually vigorous male rats produced a transient disruption of the expression of male copulatory behavior. In addition, in MDMA-treated males that did display ejaculatory behavior, both the ejaculation latency and postejaculatory interval were lengthened when compared to saline-injected controls. This is the first report to demonstrate that repeated administration of MDMA adversely affects male rat sexual behavior. Surprisingly, one week after the first behavioral test, copulatory behavior in MDMA-treated rats appeared unaffected despite a marked depletion of 5-HT content in the hippocampus, and striatum. Presently, the mechanisms which underlie this apparent recovery of male rat sexual behavior are not understood.

Although it is clear that the degree of 5-HT depletion in MDMA-treated males did not predict whether or not animals would express sexual behavior on the second test, interestingly, on test 1, males who did not copulate had an average 5-HT depletion of 64 percent. This is compared to only a 50 percent 5-HT depletion in males who did display copulatory behavior but had a prolongation of the ejaculation latencies and the postejaculatory behavior (data not shown). In addition, one subject only received one subcutaneous injection of MDMA (40 mg/kg). Although this subject's data was excluded from the analysis, it too failed to copulate one week following the first injection. Moreover, a 75% depletion of 5-HT and 5-HIAA content in the hippocampus was found in this subject suggesting that repeated administration of MDMA may not be necessary to produce 5-HT neurotoxicity. It is not clear what role sexual experience played in the full recovery of sexual behavior observed during the second test. This is presently being assessed by comparing groups of MDMA-treated males who receive a sexual behavioral test two weeks from the first MDMA injection with males tested using the identical behavioral paradigm in the present experiment.

Clearly, further research is required to fully elucidate the mechanism of action of MDMA on sexual behavior in the male rat. Future studies examining the effects on sexual behavior in both male and female rats following both acute and repeated central and peripheral administration of a variety of doses of MDMA are planned to fully characterize the effects of MDMA on the expression of sexual behavior in the rat.

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