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Treatment With a Serotonin-Depleting Regimen of MDMA Prevents Conditioned Place Preference to Sex in Male Rats

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Abstract

Among young adults, 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) is a popular drug of abuse, and anecdotal evidence indicates that repeated use of MDMA may result in impairments in sexual function and decreased sex drive in human users. There has been little investigation of the effects of MDMA on sexual function in rodents. In the present study, the authors determined that in male rats (*Rattus norvegicus*) tested in a sexually naïve or a sexually experienced state, administration of a serotonin (5-HT)–depleting regimen of MDMA did not produce a change in mount, intromission, and ejaculation latency or in mount and intromission frequency compared with such latency and frequency in vehicle-treated control rats. In contrast to vehicle-treated rats, MDMA-treated rats did not form a conditioned place preference (CPP) to sex. Failure of MDMA-treated rats to form CPP to sex may be due to MDMA-induced impairments in circuits mediating sexual reward.

Keywords

MDMA; sex behavior; reward; associative learning

Among the young adult population, 3,4-methylenedioxy-methamphetamine (MDMA, “ecstasy”) is a popular drug of abuse, with 10% of college students at one large U.S. university reporting use and only alcohol and marijuana cited as more commonly abused substances (Boyd, McCabe, & d’Arcy, 2003). Studies in rodents have shown that repeated high-dose administration of MDMA produces selective long-term reduction in striatal 5-HT concentration (Battaglia, Yeh, & De Souza, 1988; Schmidt, 1987), tryptophan hydroxylase activity (Schmidt & Taylor, 1987; Stone, Merchant, Hanson, & Gibb, 1987; Stone, Stahl, Hanson, & Gibb, 1986), and the number of 5-HT reuptake sites (Battaglia et al., 1987), which are thought to indicate toxicity to 5-HT nerve terminals. Studies in human users have indicated a decrease in the concentration of cerebrospinal fluid 5-HT metabolite compared with the 5-HT metabolite concentration in nonuser control subjects (McCann, Ridenour, Shaham, & Ricaurte, 1994; Ricaurte, DeLanney, Wiener, Irwin, & Langston, 1988) as well as alterations in glucose uptake in the brains of MDMA users in regions including the hippocampus, amygdala, putamen, and caudate nucleus (Obrocki et al., 1999). Studies in which MDMA users have undergone positron emission tomography (PET) have reported decreases in global

serotonin transporter (SERT) density (McCann et al., 2005) as well as decreased SERT binding in brain regions, including the mesencephalon, thalamus, caudate, hippocampus, occipital cortex, temporal lobes, and posterior cingulate gyrus (Buchert et al., 2004). Additionally, single photon emission computer tomography (SPECT) results have indicated decreased SERT binding that may be related to gender, with one study reporting decreased SERT binding only in female users of ecstasy (Reneman et al., 2001), whereas another study has reported decreased SERT binding in male users of ecstasy (Semple, Ebmeier, Glabus, O'Carroll, & Johnstone, 1999). Although these study results may be indicative of toxicity to 5-HT nerve terminals following use of ecstasy, additional data suggest that this toxicity may not be long term, because there is a significant relation between SERT binding and duration of abstinence (McCann et al., 2005), and no differences in SERT binding have been noted between drug-naïve subjects and ecstasy users who have abstained from use of the drug for a minimum of 20 weeks (Buchert et al., 2004).

In contrast to the numerous studies documenting neurochemical effects of MDMA, few studies have examined the behavioral consequences associated with administration of this drug in rodents. MDMA has been shown to increase social interaction in rats tested immediately after drug administration (Morley & McGregor, 2000), yet it decreases social interaction in rats tested 20 days after drug administration (Bull, Hutson, & Fone, 2003). Discrepancies also exist between conclusions regarding the anxiogenic or anxiolytic properties of MDMA. Rats undergoing behavioral testing immediately after MDMA administration have been reported to show both an increase in anxiogenic behaviors—including decreased aggression and increased avoidance (Lin, Burden, Christie, & Johnston, 1999; Maldonado & Navarro, 2001)—and an increase in anxiolytic behaviors (Lin et al., 1999). It has been suggested that this discrepancy may be related to dose, with lower doses of MDMA producing acute anxiogenic effects and higher doses producing acute anxiolytic effects (Lin et al., 1999). Furthermore, studies that have examined the long-term effects of MDMA on anxiety-like behaviors have found that MDMA may produce either an increase (Gurtman, Morley, Li, Hunt, & McGregor, 2002; Morley, Gallate, Hunt, Mallet, & McGregor, 2001) or a decrease (Mechan et al., 2002) in anxiogenic behaviors 2–3 months after MDMA administration. Again, these discrepancies may be related to differences in dosing or behavioral testing paradigms. In view of the postulated role of 5-HT in the neurobiology of reward (Higgins & Fletcher, 2003), other studies have focused on the rewarding properties of drugs of abuse in rats previously exposed to a 5-HT-depleting regimen of MDMA, and there are equally conflicting reports in this area. Pretreatment with MDMA results in facilitation of cocaine self-administration (Fletcher, Robinson, & Slippoy, 2001) and slows acquisition of self-administration of a low dose of amphetamine (Morley, Cornish, Li, & McGregor, 2004). Studies in which the conditioned place preference (CPP) paradigm has been used have found that for rats, treatment with MDMA enhances the rewarding properties of cocaine (Fone et al., 2002; Horan, Gardner, & Ashby, 2000), reduces the rewarding properties of alcohol (Cole, Sumnall, O'Shea, & Marsden, 2003), and has no apparent effect on the rewarding properties of amphetamine or heroin (Cole et al., 2003).

In recent years, it has been suggested that drugs of abuse and natural rewards activate the same neural pathways (Di Chiara, Acquas, Tanda, & Cadoni, 1993; Kelley & Berridge, 2002); yet few, if any, studies have examined the effect of MDMA on natural reward, such as that produced by food or sex. Anecdotal evidence indicates that human abusers of MDMA may experience impairments in both sexual function (Buffum & Moser, 1986; Zemishlany, Aizenberg, & Weizman, 2001) and sex drive (Parrott, Milani, Parmar, & Turner, 2001; Topp, Hando, Dillon, Roche, & Solowij, 1999), suggesting that MDMA may cause alterations in the rewarding properties of sex. In the present study, we used the CPP paradigm to determine the rewarding properties of sex in male rats previously exposed to a 5-HT-depleting regimen of

MDMA. Additionally, parameters of sexual performance were measured in MDMA-pretreated rats.

Method

Animals and Drug Treatment

Adult male Sprague–Dawley rats (*Rattus norvegicus*, Harlan, Indianapolis, IN; 200–230 g at the start of the experiment) were housed in Plexiglass cages on a 12-hr reverse light–dark cycle (lights off at 1000) for the duration of the experiment. Seven days after arrival in the animal colony, group-housed male rats were treated with a multiple-dose regimen of MDMA (10 mg/kg ip administered every 2 hr for a total of four injections) or vehicle (0.9% sodium chloride ip) beginning 2 hr after the start of the light cycle. Males were maintained at an elevated room temperature (24–25 °C) 2 hr before and during drug treatment and were group housed (2 rats per cage) up to 1 day prior to initiation of behavior testing, at which point rats were single housed for the remainder of the study. Food and water were available ad libitum, and rats were handled and weighed daily.

Adult female Sprague–Dawley rats (200–220 g) used in mating behavior experiments were bilaterally ovariectomized and received a subcutaneous implant containing 5% estradiol benzoate and 95% cholesterol. Sexual receptivity in female rats was induced by subcutaneous administration of 500 µg progesterone in 0.1 mL sesame oil 5 hr prior to the start of behavior testing. All procedures adhered to the policies set forth in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996) and were approved by the University of Cincinnati Institutional Animal Care and Use Committee.

Sexual Behavior

Twelve or thirteen days following administration of MDMA ($n = 10$) or vehicle ($n = 8$), sexually naïve male rats were tested for sexual behavior and mating-induced CPP (described below). In particular, MDMA- or vehicle-pretreated males received a receptive female in their home cage and were allowed to mate to one ejaculation, after which they were gently removed from the home cage and placed in the conditioning chamber of the CPP apparatus (described below). Males were again allowed to mate to one ejaculation or for 60 min, whichever occurred first, with a receptive female in their home cages 26, 33, and 40 days following MDMA or vehicle treatment. During each test (except for the test 33 days following treatment), the number of mounts and intromissions, as well as the latency to first mount and intromission (i.e., the time from presentation of the receptive female to the first mount or intromission) and ejaculation (i.e., the time from the first intromission to ejaculation), were recorded. Repeated measures analysis of variance (ANOVA) and Student–Newman–Keuls or t tests were used in post hoc analysis (with 5% significance levels) to compare the two groups on latencies to mount, intromission, and ejaculation and on numbers of mounts and intromissions before ejaculation. In addition, latencies and numbers of mounts and intromissions were averaged over the three behavioral tests for each animal, and group means were compared with unpaired t tests and 5% significance levels.

Conditioned Place Preference (CPP) Paradigm

The CPP paradigm used in this study was based on paradigms described in previous reports (Agmo & Berenfeld, 1990; Agmo & Gomez, 1993; Pfaus, Kippin, & Centeno, 2001). The same males used for sex behavior testing described above were used for the analysis of mating-induced CPP.

Apparatus—The CPP apparatus (MED Associates, St. Albans, VT) consisted of three tactilely and visually distinct chambers: Two large conditioning chambers (28 cm long × 21

cm wide × 21 cm high)—one with white plastic walls and a metal grid floor and one with black plastic walls and a metal rod floor—were separated from one another by a small neutral chamber (12 cm long × 21 cm wide × 21 cm high) constructed of gray plastic walls and floor. The three chambers were connected by opaque guillotine doors, such that the rat could be confined to one chamber or allowed free access to all three chambers. Each chamber was covered by a hinged clear polycarbonate lid to allow videotaping. The apparatus was thoroughly cleaned with 70% ethanol solution after each rat's use to minimize olfactory cues.

Pretest phase—Ten days following the administration of MDMA or vehicle, male rats were removed from their home cages, introduced into the CPP apparatus, and allowed free access to the entire apparatus for 15 min; then the rats were returned to their home cage. We recorded the pretest on videotapes and then scored the tapes using a Microsoft (Redmond, WA) Excel custom macro program to determine in which large chamber of the apparatus each rat spent more time. The chamber in which a rat spent the greater amount of time was defined as the *initially preferred chamber*. Conversely, the chamber in which a rat spent less time was defined as the *initially nonpreferred chamber*.

Conditioning phase—Conditioning assignments were based on the results of the pretest, such that each animal was conditioned to associate sex with the chamber of the CPP apparatus that was initially not preferred. In a balanced design, 2 days after the pretest phase (12 days after MDMA or saline vehicle treatment), male rats either received a receptive female in their home cage and were allowed to copulate until one ejaculation (for details, see above), after which they were immediately removed from the home cage and confined to the chamber of the CPP apparatus that they did not initially prefer (referred to as the *sex-paired chamber*) or were removed from their home cage without receiving sex and placed in the chamber of the CPP apparatus that they initially did prefer (referred to as the *control chamber*). Confinement lasted for 30 min, and the rats were subsequently returned to the home cage. On the following day (13 days after MDMA or vehicle treatment), the rats received the opposite behavior treatment and associated chamber confinement. At this time, the sex behavior parameters detailed above were recorded for these sexually naïve rats.

Test phase—One day following the end of the conditioning phase, rats were once again placed in the CPP apparatus and allowed free access to all three chambers for 15 min. We videotaped and subsequently scored the behavior to determine the time spent in individual chambers of the apparatus. The pretest and posttest data collected from the CPP experiment were expressed as the preference score (the percentage of time spent in the sex-paired chamber) and the difference score (time spent in the sex-paired chamber – time spent in the control chamber). We compared statistical differences in the pretest and posttest data for each treatment group using a paired *t* test, with a 5% significance level. Formation of CPP for each treatment group was defined as a significant increase in both preference score and difference score in the posttest compared with the pretest (i.e., after the conditioning phase in which rats were trained to associate individual chambers of the apparatus with the sex or no-sex experience). In addition, the difference in the time that males spent in the sex-paired chamber between the posttest and the pretest was calculated for each animal. Using paired *t* tests with 5% significance levels, we calculated and compared group means for vehicle- and MDMA-treated males.

Analysis of 5-HT Concentrations

The concentration of 5-HT in various brain regions, including the striatum, nucleus accumbens, cortex, hippocampus, and hypothalamus, was determined in separate groups of rats treated with vehicle (*n* = 5) or MDMA (*n* = 8) according to the treatment regimen described above. Tissue samples were dissected from 1-mm coronal sections of brain and were maintained at –80 °C until the time of 5-HT analysis. Tissue samples were homogenized in 50 volumes of

0.2 N-perchloric acid. Following centrifugation, an aliquot of the supernatant was subjected to high-performance liquid chromatography with electrochemical detection for the detection of 5-HT (Gudelsky, Yamamoto, & Nash, 1994). The mobile phase—consisting of 35 mM citric acid, 54 mM sodium acetate, 60 mg/L octanesulfonic acid, 50 mg/L ethylenediaminetetraacetic acid (EDTA), and 5% (volume/volume) methanol at pH 4.2—was pumped at 0.4 mL/min onto a C18 column connected to an LC-4C Amperometric Detector (Bioanalytical Systems, West Lafayette, IN). Peak heights were quantified with a Hewlett–Packard (Palo Alto, CA) integrator, and 5-HT concentrations (ng/mg tissue) were calculated. Consistent with previous findings (Matuszewich, Filon, Finn, & Yamamoto, 2002; Shankaran, Yamamoto, & Gudelsky, 2001), treatment with the aforementioned regimen of MDMA resulted in significant ($p < .005$) depletions of 5-HT of the following magnitude: striatum, 50%; cortex, 53%; hippocampus, 55%; hypothalamus, 43%; and nucleus accumbens, 40%. Values (ng/mg tissue) for 5-HT in each brain region for vehicle- and MDMA-treated rats, respectively, were the following: striatum, 0.33 ± 0.01 vs. 0.17 ± 0.01 ; cortex, 0.27 ± 0.02 vs. 0.13 ± 0.03 ; hippocampus, 0.29 ± 0.01 vs. 0.13 ± 0.01 ; hypothalamus, 0.83 ± 0.03 vs. 0.48 ± 0.05 ; and nucleus accumbens, 0.82 ± 0.06 vs. 0.49 ± 0.06 .

Results

Sexual Behavior

MDMA treatment did not greatly affect the expression of sexual behavior (Figures 1 and 2). Repeated measures ANOVA revealed a significant effect of repeated testing on mount latency ($p = .005$) and intromission latency ($p = .043$), but no significant effect of drug treatment or interaction between repeated testing and drug treatment was detected on any of the observed parameters. Post hoc analyses revealed that MDMA-treated males had shorter mount and intromission latencies during the third test than during the first test ($p = .03$ for mount latency and $p = .019$ for intromission latency). Although vehicle-treated males also had shorter latencies in the third test than in the first test, this difference failed to reach significance. Vehicle- and MDMA-pretreated males did not differ on the observed parameters of sexual behavior during any of the three behavioral tests, with the exception of a longer mount latency in MDMA-treated males during the second test (26 days following MDMA treatment: $p = .04$). Likewise, no differences between vehicle- and MDMA-pretreated males were detected when averages over the three tests for each parameter were analyzed (Figures 1D and 2C).

CPP

Male rats were conditioned to associate the experience of mating to one ejaculation (during the first mating test, 12 days after treatment with vehicle or MDMA) with one chamber of the conditioned place reference apparatus. Rats treated with vehicle exhibited a significant increase ($p = .00089$) in preference score (i.e., the percentage of time spent in the sex-paired chamber following the conditioning phase of the experiment; see Figure 3A) as well as an increase ($p = .00079$) in the difference score (i.e., the amount of time spent in the sex-paired chamber after the conditioning phase of the experiment, see Figure 3B). Thus, vehicle-treated rats formed a CPP to sex. In contrast, rats treated with MDMA exhibited no increase in preference score ($p = .96$; Figure 3A) or difference score ($p = .94$; Figure 3B), indicating that MDMA-treated male rats did not form CPP to sex under these conditions. Moreover, the time that the males spent in the sex-paired chamber between the posttest and pretest significantly differed between vehicle- and MDMA-treated rats ($p = .0014$). Whereas vehicle-treated males spent 63.4 ± 12.3 s more in the sex-paired chamber after conditioning, MDMA-treated animals instead spent 8.2 ± 15.2 s more in the control chamber.

Discussion

The purpose of this study was to determine the effects of a multiple-dose regimen of MDMA on sexual behavior in the male rat as well as to assess the effect of MDMA on the ability of the male rat to form CPP to a sexual reward. Treatment of rats with a regimen of MDMA that resulted in long-term 5-HT depletion had no significant effect on subsequent sexual behavior in either sexually naïve or sexually experienced rats. Moreover, MDMA pre-treatment and serotonin depletion did not affect the experience-associated decreases in mount and intromission latencies (Camacho, Sandoval, & Paredes, 2004). However, male rats that had been treated with MDMA were unable to form CPP to sex, suggesting an altered perception of sexual reward following MDMA treatment.

Anecdotal evidence suggests that use of MDMA may result in impaired sexual function in humans (Buffum & Moser, 1986; Zemishlany et al., 2001); however, there are relatively few studies of the effects of MDMA on sexual behavior in rats. Dornan, Katz, and Ricaurte (1991) determined that multiple high-dose injections of MDMA in sexually experienced male rats produced an impairment in sexual function 3 days after drug treatment. However, this effect was transient, because there was no difference in sex behavior between the vehicle- and MDMA-treated rats 10 days after treatment. The present findings of a lack of impairment in sexual performance are consistent with those of Dornan et al. (1991) at the 10-day treatment interval. Brain 5-HT is considered to be inhibitory to sex behavior in the male rat (Hull et al., 1999; Hull, Muschamp, & Sato, 2004), and thus, removal of 5-HT inhibition would be expected to result in an increase in sexual behavior. Indeed, studies have shown that treatment of rats with drug regimens that result in increased 5-HT neurotransmission—including drugs that evoke 5-HT release, stimulate 5-HT synthesis, or inhibit 5-HT reuptake—results in a decrease in male copulatory behavior (Ahlenius & Larsson, 1991; Ahlenius, Larsson, & Svensson, 1980; Foreman, Hall, & Love, 1992). Conversely, drugs that reduce 5-HT neurotransmission by antagonizing postsynaptic 5-HT receptors or acting as agonists at 5-HT_{1A} autoreceptors facilitate sex behavior (Ahlenius, Larsson, & Arvidsson, 1989; Da Prada, Bonetti, Scherschlicht, & Bondiolotti, 1985; Fernandez-Guasti & Escalante, 1991). Furthermore, the administration of 5,7-dihydroxytryptamine or p-chloroamphetamine (drugs that selectively destroy 5-HT nerve terminals) also stimulates sexual behavior (Da Prada, Pieri, Keller, Pieri, & Bonetti, 1978; Fernandez-Guasti & Escalante, 1991; Sodersten, Berge, & Hole, 1978). However, it has been noted that an extensive lesion is necessary to achieve this behavioral effect (Sodersten et al., 1978). Thus, the approximate 40%–55% depletion in brain 5-HT produced by MDMA in the present study may not be sufficient to produce alterations in sex behavior.

The present finding that male rats are capable of forming CPP to sex confirms the findings of Agmo and Berenfeld (1990), who determined that a single ejaculation was sufficient to elicit formation of CPP. However, rats treated with a 5-HT-depleting regimen of MDMA failed to form CPP to sex. To our knowledge, this is the first demonstration that MDMA treatment impairs the formation of CPP to a natural reward.

The formation of CPP is dependent on the Pavlovian association of an appetitive stimulus (the unconditioned stimulus, i.e., food, sex, drug) with a single context (the conditioned stimulus, i.e., one chamber of the CPP apparatus). An increase in time spent in the paired context relative to a control value is viewed as evidence that the appetitive stimulus is rewarding (Bardo & Bevins, 2000). In the present study, rats treated with vehicle 12 or 13 days prior to conditioning spent more time in the CPP chamber associated with the experience of mating to one ejaculation, thus forming CPP to the sexual experience. In contrast, rats treated with MDMA 10 days prior to conditioning did not spend more time in the CPP chamber associated with the experience of mating and thus did not form CPP to sex. The failure of MDMA-treated rats to

form CPP to sex may be due to diminished rewarding properties of sex or impairments in associative learning.

The CPP paradigm has been used in previous studies to examine the effects of MDMA treatment on the reward associated with drugs of abuse, including alcohol (Bilsky, Hui, Hubbell, & Reid, 1990; Cole et al., 2003), cocaine (Cole et al., 2003; Fone et al., 2002; Horan et al., 2000), amphetamine, and heroin (Cole et al., 2003). The results of these studies are conflicting in that CPP to cocaine has been found to be enhanced (Fone et al., 2002; Horan et al., 2000), whereas CPP to amphetamine and heroin has been found to be unaffected (Cole et al., 2003) in rats previously treated with MDMA. However, treatment of rats with MDMA reduced formation of CPP to alcohol, an outcome that is similar to that observed for the formation of CPP to sex in this study. Given that drugs of abuse and natural rewards have been suggested to activate the same neural pathways (Di Chiara et al., 1993; Kelley & Berridge, 2002), it is possible that the mechanisms underlying the effect of MDMA on CPP to alcohol and sex are similar as well.

The failure of MDMA-treated rats to form CPP to sex may be due to a long-term effect of MDMA (e.g., 5-HT depletion) in diminishing the rewarding properties of sex. The neural circuits involved in sex-induced CPP are not clearly understood, and it is currently unknown whether 5-HT is involved in the acquisition or expression of sex-induced CPP. The release of 5-HT in the anterior lateral hypothalamic area after ejaculation has been hypothesized to contribute to the sexual quiescence following ejaculation (Hull et al., 2004). The results of the present study raise the possibility that sex-induced release of 5-HT may also be important for the formation of CPP. Spyraiki and Nomikos (1991) have provided evidence that 5-HT₂ receptor stimulation exerts a facilitatory role in drug-induced CPP. Accordingly, reduced 5-HT₂ receptor activation subsequent to diminished 5-HT release in MDMA-treated animals could be expected to result in a lack of CPP formation, as observed in the present study. It also is conceivable that MDMA treatment may affect CPP formation via diminished dopamine (DA) release in the mesolimbic pathway, given the role of DA in reward processing (Kelley & Berridge, 2002). However, activation of 5-HT_{2B/2C} receptors in the ventral tegmental area appears to be inhibitory to DA release in the mesolimbic pathway (Bankson & Yamamoto, 2003). On this basis, it might have been anticipated that depletion of 5-HT by MDMA would facilitate, not inhibit, formation of CPP to sex. However, it has been shown that treatment of rats with a DA antagonist has no effect on the formation of CPP to sex, suggesting that DA is of little importance in mediating the rewarding properties of sex (Agmo & Berenfeld, 1990).

The effects of MDMA treatment on the acquisition or expression of sex–CPP may potentially be explained by impairments in associative learning. However, data from other studies in which CPP was used suggest that MDMA does not produce decrements in associative learning in this particular paradigm, as studies have shown that pretreatment with MDMA actually enhances the formation of CPP to the appetitive stimulus cocaine (Fone et al., 2002; Horan et al., 2000). In addition, Schechter (1991) showed that MDMA pretreatment does not impair previously established CPP to MDMA. However, previous studies in humans and rodents have shown that administration of MDMA may result in impairments in associative learning in other learning paradigms. Abstinent human users show deficits in associative learning in a word-pairing task (Montgomery, Fisk, & Newcombe, 2005). Rats that are trained to discriminate between a low dose of MDMA and its vehicle and then are administered a high neurotoxic regimen of MDMA exhibit a decreased ability to discriminate interoceptive cues produced by MDMA in a challenge MDMA–vehicle discrimination task (Schechter, 1991).

In conclusion, this study has shown that treatment of rats with a 5-HT–depleting regimen of MDMA produces no change in parameters of sexual performance, yet does prevent the

formation of a CPP response to sex. Hence, these data suggest that MDMA treatment affects the perception of sexual reward.

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Figure 1.

Mount, intromission, and ejaculation latencies in male Sprague-Dawley rats during behavior tests 12 (Test 1 = Panel A), 26 (Test 2 = Panel B), and 40 (Test 3 = Panel C) days after treatment with 3,4-methylenedioxymethamphetamine (MDMA) or vehicle. Panel D illustrates average latencies over the three behavioral tests. * $p < .05$, compared with vehicle-treated rats.

Figure 2.

Number of mounts (Panel A) and intromissions (Panel B) in male Sprague–Dawley rats during behavior tests 12 (Test 1), 26 (Test 2), and 40 (Test 3) days after treatment with 3,4-methylenedioxymethamphetamine (MDMA) or vehicle. Panel C illustrates average number of mounts and latencies over the three behavioral tests.

Figure 3.

Impairment of conditioned place preference in male Sprague-Dawley rats treated with 3,4-methylenedioxymethamphetamine (MDMA). Preference score (Panel A; the percentage of time spent in the sex-paired chamber) and difference score (Panel B; time spent in the sex-paired-control chamber) are not significantly different between pre- and posttest in MDMA-treated males, in contrast to the scores in vehicle-treated males. * $p < .001$, compared with pretest score.