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An NMDA Antagonist Impairs Copulation and the Experience-Induced Enhancement of Male Sexual Behavior in the Rat

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Sexual experience facilitates subsequent male sexual behavior; activation of the *N*-methyl-D-aspartate (NMDA) glutamate receptor may play a role in this experience-induced enhancement. In this article, the authors report that systemic injections of MK-801, an NMDA receptor antagonist, impaired male sexual behavior in sexually naive and sexually experienced male rats. Furthermore, saline-treated rats that received 7 daily exposures to an inaccessible estrous female instead of sexual experience displayed enhancement of copulation on the following day. Injections of MK-801 before each of these exposures inhibited the experience-induced enhancement on the drug-free test on Day 8. These data suggest that stimulation of NMDA receptors enhances sexual performance immediately and mediates the experience-induced enhancement of subsequent copulatory behavior.

With sexual experience, male sexual behavior becomes more efficient and more resistant to various insults. Experienced male rats show an increased preference for receptive females rather than males (Matuszczyk & Larsson, 1994) and require fewer mounts and intromissions to elicit ejaculation and less time to mount, intromit, and ejaculate (Bialy, Rydz, & Kaczmarek, 2000; Dewsbury, 1969; Larsson, 1978); they also take less time to resume copulation after ejaculating (Larsson, 1959). Copulation to one ejaculation also elicits more neural activation (measured as *fos* immunoreactivity) in the medial preoptic area of experienced males compared with naive males (Lumley & Hull, 1999). Finally, compared with naive males, experienced males are more resistant to impairment due to lesions of the medial preoptic area (rats: de Jonge et al., 1989), of the medial amygdala (rats: Kondo, 1992), of the bed nucleus of stria terminalis (rats: Claro, Segovia, Guillamon, & Del Abril, 1995) or of the vomeronasal organ (hamsters: Meredith, 1986; rats: Saito & Moltz, 1986); and due to castration (hamsters: Lisk & Heimann, 1980; cats: Rosenblatt & Aronson, 1958).

The physiological changes that accompany the experience-induced facilitation of sexual behavior are not well understood. The neurotransmitter glutamate, through activation of *N*-methyl-D-aspartate (NMDA) receptors, plays an important role in various types of neural plasticity, including long-term potentiation (reviewed in Malenka & Nicoll, 1999; Martin, Grimwood, & Morris, 2000), the acquisition of bird song (reviewed in Nordeen, 1997), fear conditioning (LeDoux, 2000), the fear-potentiated startle response (Miserendino, Sananes, Melia, & Davis, 1990), and memory of a novel environment (Carey, Dai, & Gui, 1998). NMDA receptors may also play a role in the experience-induced facilitation of sexual behavior. Fleming and Kucera (1991) reported that systemic administration of the NMDA antagonist dizocilpine maleate (MK-801) to male rats prior to initial sexual experience blocked the experience-induced enhancement of sexual behavior on drug-free tests 3, 6, or 9 days later. A different NMDA antagonist, CGP40116, blocked both the sexual experience-induced increase in precopulatory 50-kHz vocalizations and the decrease in ejaculation latency (Bialy et al., 2000).

The current experiments were designed to further elucidate the role of glutamate and NMDA receptors in the experience-induced facilitation of sexual behavior. These experiments first tested whether systemic injections of the noncompetitive NMDA antagonist MK-801 prior to initial sexual experience would attenuate the enhancement of sexual behavior during a subsequent test. Because MK-801 impaired sexual behavior on the initial experience in Experiment 1, we tested the effects of several doses of MK-801 in sexually experienced males in Experiment 2. Finally, to avoid possible confounding effects of impaired copulation during the initial experience tests due to MK-801, in Experiment 3, we tested whether systemic injections of MK-801 would attenuate the enhancement of copulation observed after repeated exposures to an inaccessible receptive female.

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General Method

Subjects

Adult male Long-Evans/Blue Spruce rats (Harlan Sprague-Dawley, Indianapolis, IN) were housed individually in large plastic cages. Rats were housed in a climate-controlled room, on a 14:10-hr light–dark cycle, with lights off at 1100 and on at 2100. Food and water were available ad libitum.

Stimulus female rats of the same strain were ovariectomized under ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (4 mg/kg)

anesthesia. Females were brought into behavioral estrus with 10 μg estradiol benzoate 48 hr and 500 μg of progesterone 4 hr before they were used as stimulus females. Behavioral receptivity was confirmed by placing the female with a stud male shortly before she was to be used in an experiment. All procedures were in accordance with the National Institutes of Health guidelines for the use of animals and were approved by the local Institutional Animal Care and Use Committee.

Drug

Merck Research Laboratories (White House Station, NJ) generously provided the MK-801 used in all experiments. MK-801 was dissolved in isotonic saline and was administered in the following concentrations: 0.05 mg/kg (Experiment 2), 0.10 mg/kg (Experiments 1 and 2), and 0.20 mg/kg (Experiments 2 and 3).

Copulatory Measures

The following measures were recorded or calculated for all copulation tests: mount and intromission latency (ML and IL; time from the introduction of the female to the first mount or intromission); ejaculation latency (EL; time from the first intromission to the first ejaculation); postejaculatory interval (PEI; time from the first ejaculation to the subsequent intromission); total mount (MF), intromission (IF), and ejaculation frequencies (EF); first ejaculatory series mount (MF_1) and intromission frequencies (IF_1); first ejaculatory series intromission ratio (IR_1; number of intromissions divided by the number of mounts and intromissions during the first series); and total intromission ratio (IR_T; number of intromissions divided by the number of mounts and intromissions during the entire test). If a rat did not display sexual behavior, measures of latency for that rat were set to 1,800 s.

Experiment 1

Method

Procedures. Methods for Experiment 1 were adapted from Fleming and Kucera (1991). Prior to placing the sexually naive male rat with a sexually receptive female, subject males received injections of either 0.1 mg/kg ip of MK-801 (MK-801 group; $n = 10$) or vehicle saline solution (vehicle group; $n = 10$). Subject males were then taken to a test room; 15 min later the receptive female was placed into the male's home cage, and they were allowed to copulate (experience day). The initial experience meeting lasted 90 min; during this time, sexual behaviors were observed and recorded. Four days later, a similar procedure was performed, except males were tested while in a drug-free condition (drug-free day). The drug-free tests lasted 30 min from the first intromission or 30 min total if the animal failed to intromit (see Figure 1).

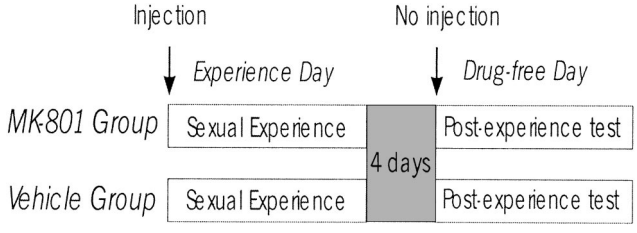

Figure 1. Diagram of the experimental design for Experiment 1. On experience day, the MK-801 group received an injection of MK-801, and the vehicle group received saline. Four days later, both groups were tested in a drug-free condition.

Statistics. Two × two (Group × Testing Day) analyses of variance (ANOVAs) with repeated measures across tests were used to analyze ML, IL, EL, and IR_T. Frequency data were not analyzed using a two-way repeated measures ANOVA because the experience day exposure duration was 90 min, and the drug-free day exposure duration was only 30 min. Numbers of mounts and intromissions preceding ejaculation could not be analyzed on the experience day because only one rat in the MK-801 group ejaculated. All other measures were compared separately for the experience day and test day using independent *t* tests. A Fisher exact statistic was used to determine whether the number of rats that ejaculated on the experience day was different between groups. If rats did not display a behavior, the latency for that behavior was set to 1,800 s. Rats that did not intromit on their first experience test were excluded from statistical analysis, which left 7 rats in each group. In all experiments, a two-tailed $p < .05$ was considered significant.

Results

Two-way ANOVAs (Group × Test Day) revealed significant main effects of test day for several measures. There were significant decreases across tests for ML, $F(1, 12) = 10.26$; IL, $F(1, 12) = 9.09$; and EL, $F(1, 12) = 6.47$; all ps $< .05$; indicating a facilitative effect of experience on sexual behavior. However, there was no significant interaction. On the experience day, the vehicle group displayed significantly more ejaculations, $t(12) = 2.38$, $p < .05$ (Figure 2a); and a higher intromission ratio, IR_T, $t(11) = 3.91$, $p < .01$ (Figure 2b); than the MK-801 group; these data indicate an impairment of copulation caused by MK-801 on the experience day. There were also more rats that ejaculated in the vehicle group than in the MK-801 group ($p < .05$). On the drug-free test, there were no significant differences between groups; however, there were nonsignificant trends for rats in the MK-801 group to display longer ML, IL, and EL compared with those in the vehicle group (see Table 1).

Experiment 2

Method

Procedures. Because results of Experiment 1 indicated that MK-801 impaired sexual behavior on the experience day, Experiment 2 established a dose-response curve for the effects of MK-801 on the sexual behavior of sexually experienced male rats using a counterbalanced design. Twenty min before behavioral testing, 14 sexually experienced males that had been used in Experiment 1 received injections of either 0.05 mg/kg, 0.10 mg/kg, or 0.20 mg/kg ip of MK-801 or saline vehicle in counterbalanced order. As in Experiment 1, male rats were tested in their home cages; tests lasted 30 min from the first intromission or 30 min total if the rat failed to intromit.

Statistics. One-way repeated measures ANOVAs with Newman–Keuls pairwise comparisons were used to calculate significance for the following measures: ML, IL, and EL; and MF_T, IF_T, EF, and IR_T. In addition, first ejaculatory series data were analyzed for rats that ejaculated in all conditions ($n = 11$). In several analyses, the distribution of scores did not meet the requirements for normality; in those cases, ANOVAs on ranks were used. Statistics for the following measures were calculated only for rats that ejaculated in all four conditions ($n = 7$): MF_1, IF_1, and IR_1.

Results

MK-801 produced dose-dependent decreases in EF, $F(3, 36) = 3.10$, $p < .05$ (Figure 3A); and IR_T, $F(3, 36) = 4.96$, $p < .01$ (Figure 3B); and an increase in MF_T, $\chi^2(3, N = 14) = 14$, $p < .01$ (Figure 3C).

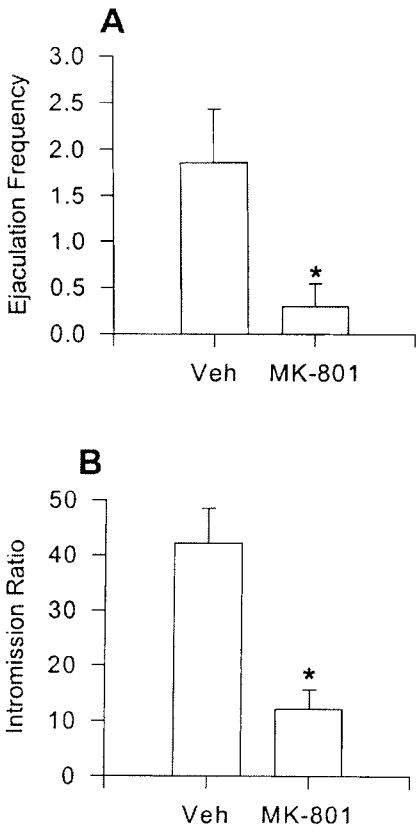

Figure 2. Mean (+*SEM*) ejaculation frequency (A) intromission ratio (B) for rats receiving MK-801 or vehicle injections on experience day in Experiment 1. The vehicle (Veh) group displayed more ejaculations and achieved a higher intromission ratio compared with the MK-801 group. * $p < .05$.

Experiment 3

Method

Procedures. Experiment 3 was similar to Experiment 1, but instead of copulating on an experience day, sexually naive male rats were repeatedly exposed to an inaccessible receptive female. Twenty min prior to exposure to the female, males received injections of either 0.2 mg/kg ip of MK-801 (MK-801 group, $n = 9$) or saline (vehicle group, $n = 9$). A sexually receptive female in a wire mesh cage (12.5 × 26 × 15 cm) was then placed above the male's home cage for 30 min per day for 7 days. During exposure, the male could see, smell, and hear the female but could not copulate with her. A third group was given saline injections and no exposure to females (control group, $n = 9$). On the 8th day, all rats copulated in a drug-free condition. Copulation tests were in the males' home cages and lasted 30 min from the first intromission or 30 min total if the animals failed to intromit.

Statistics. One-way ANOVAs with Newman–Keuls pairwise comparisons were used to calculate significance of ML, IL, EL, MF_T, IF_T, EF, and IR_T on the drug-free test day.

Table 1
Mount, Intromission, and Ejaculation Latencies for Rats in the MK-801 and Vehicle Groups During the Drug-Free Test in Experiment 1

Action	Vehicle	MK-801
Mount	52.60 ± 13.80	90.40 ± 31.45
Intromission	95.40 ± 29.63	392.90 ± 237.35*
Ejaculation	775.20 ± 208.85	1,177.90 ± 256.37*

Note. Data are presented as mean (±*SEM*) latencies in seconds.
* $.05 < p < .10$, compared with vehicle.

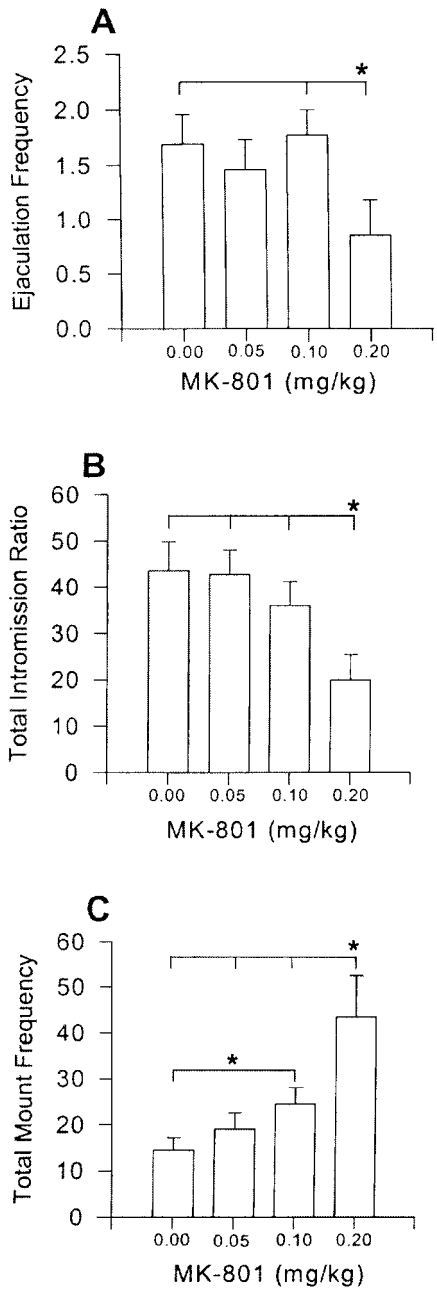

Figure 3. Mean (+*SEM*) ejaculation frequency (A), total intromission ratio (B), and total mount frequency (C) for sexually experienced rats receiving 0.00, 0.05, 0.10, or 0.20 mg/kg MK-801 in Experiment 2. MK-801 produced a dose-dependent impairment of all three measures. * $p < .05$.

Results

To avoid the confounding effects of impaired copulation during the initial experience tests due to MK-801, in Experiment 3, we tested whether systemic injections of MK-801 would attenuate any enhancement of copulation observed after repeated exposures to an inaccessible receptive female. Rats exposed to females following vehicle injections displayed decreased IL, $F(2, 24) = 8.48$ (Figure 4A); decreased EL, $F(2, 24) = 15.2$ (Figure 4B); and increased IR_T, $F(2, 24) = 4.82$ (Figure 4C); all $ps < .05$; compared with unexposed controls. MK-801 blocked this facilitation because the MK-801 group displayed lengthier intromission and ejaculation latencies (Figures 4A and 4B) and achieved fewer ejaculations, $F(2, 24) = 3.43$ (Figure 4D); compared with the vehicle group (all $ps < .05$). No other behavioral parameters were significantly altered. Although time spent sniffing the female rat during the experience days was not quantified, the MK-801-treated rats appeared to spend similar amounts of time investigating the female compared with controls.

General Discussion

In Experiment 1, animals receiving MK-801 injections prior to sexual experience displayed impaired copulation during the initial-experience test. Thus, the slight (nonsignificant) impairment observed during the drug-free test (Table 1) may have resulted from less sexual experience rather than impaired consolidation of behavioral elements. A similar impairment on the experience day may have occurred in the Fleming and Kucera (1991) experiment. They reported that administration of MK-801 (0.1 mg/kg, the same dose used in Experiment 1) before a 2-hr sexual experience blocked the copulatory improvement seen in vehicle-treated animals. Although in their experiment there were no significant differences in latencies on the experience day, 27% of the animals treated with MK-801 were removed from the analysis because they failed to intromit; no saline-treated animals were removed. Thus, the NMDA antagonist apparently resulted in an acute impairment of copulation. Bialy et al. (2000) did not observe an acute impairment by CGP 40116 on the first copulatory experience of their male rats. However, female rats treated with 0.1 mg/kg MK-801

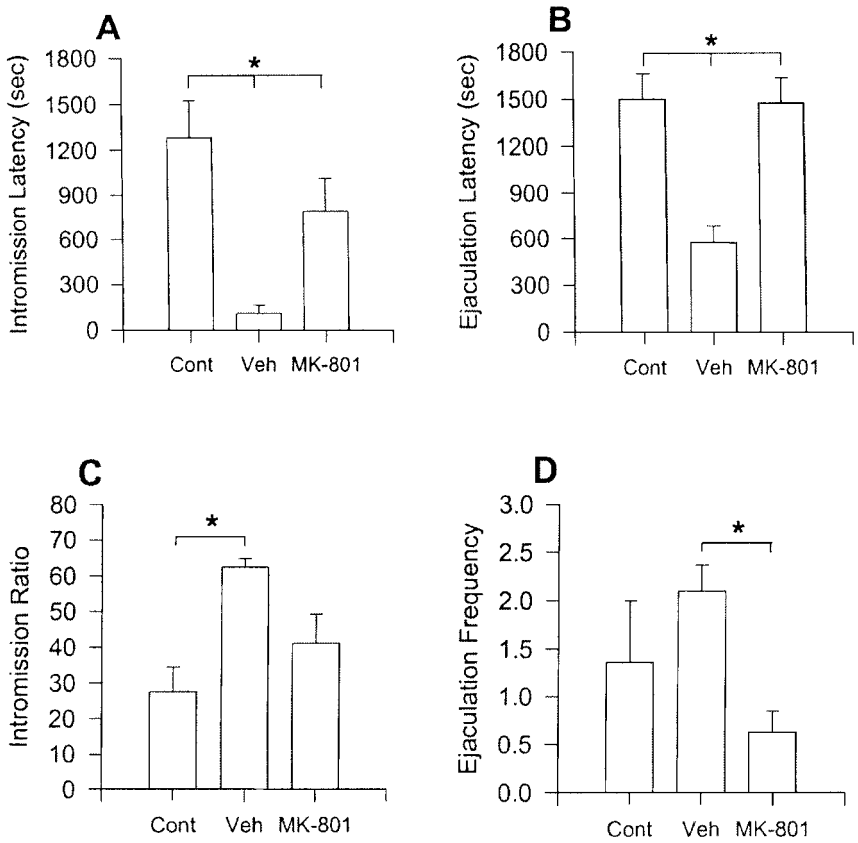

Figure 4. Mean (+*SEM*) intromission latency (A), ejaculation latency (B), intromission ratio (C), and ejaculation frequency (D) observed for drug-free tests in Experiment 3. Rats received vehicle (Veh) or MK-801 injections prior to repeated exposure to an inaccessible estrous female; the control (Cont) group received no exposure. Compared with controls, rats receiving vehicle injections displayed decreased intromission and ejaculation latencies and increased total intromission ratio during drug-free copulation testing. Compared with rats receiving MK-801, rats receiving vehicle injections also displayed decreased intromission and ejaculation latencies and achieved more ejaculations. * $p < .05$.

showed an inhibition of female sexual behavior and also less rearing but more locomotor activity; higher doses (up to 0.4 mg/kg) produced dose-related impairments of locomotion (Fleischmann, Vincent, & Etgen, 1991).

To clarify the acute effects of MK-801 on copulation, we produced a dose-response curve for the effects of MK-801 on sexual behavior of sexually experienced males in Experiment 2. MK-801 dose dependently decreased IR_T and EF compared with rats receiving vehicle injections. These data suggest that MK-801 administration does indeed impair some measures of copulation, even in experienced males.

The acute impairment of copulation by MK-801 in Experiments 1 and 2 may have resulted in part from impairment of genital sensory or motor processing. In both experiments, the ability to achieve an intromission, as measured by intromission ratio [intromissions / (mounts + intromissions)], was decreased, and in Experiment 2, the number of mounts was increased. Thus, impaired genital sensitivity or motor responsiveness may have interfered with the ability to intromit, which in turn decreased the number of ejaculations.

Another factor may have been decreased production of nitric oxide (NO). NMDA receptor activation is known to promote the production of NO in several brain areas that have been implicated in male sexual behavior, including the nucleus accumbens (Ohno, Arai, & Watanabe, 1995) and the paraventricular nucleus (PVN; Melis, Succu, Spano, & Argiolas, 2000). Blocking NMDA receptors in the PVN resulted in a decrease in noncontact penile erections, as well as decreased NO production (Melis et al., 2000). Furthermore, decreased NO production in the nucleus accumbens may have resulted in decreased dopamine release (Ohno et al., 1995), which may have diminished motivation or behavioral activation. Finally, NO is important for both basal (Lorrain & Hull, 1993) and female-stimulated (Lorrain, Matuszewich, Howard, Du, & Hull, 1996) dopamine release in the medial preoptic area. In turn, medial preoptic area dopamine is important for sexual motivation, copulatory efficiency, and genital reflexes (reviewed in Hull et al., 1999; Hull, Meisel, & Sachs, 2002). Therefore, administration of MK-801 in the present experiments may have inhibited an NO-mediated enhancement of copulation.

To test the effects of MK-801 on experience-induced enhancement of sexual behavior and to avoid the confounding effects of impaired copulation during the initial sexual experience, we repeatedly exposed sexually naive rats in Experiment 3 to an inaccessible receptive female. Female exposure on the experience days facilitated sexual behavior during the subsequent drug-free test in rats receiving vehicle injections but not in rats receiving MK-801, which performed similarly to rats that were not exposed to a female. Although time spent sniffing the female was not quantified, drug-treated males appeared to investigate the female similarly to the saline-treated males. These data are consistent with a previous report that exposure to an inaccessible estrous female facilitated subsequent sexual behavior (de Jonge, Oldenburger, Louwerse, & Van De Poll, 1992); furthermore, they suggest that the glutamate NMDA receptor is important for the mediation of this experience-induced enhancement of copulation.

Although auditory and visual stimuli from the female rats were available during the female exposures in Experiment 3, the primary cues responsible for the experience-induced enhancement of copulation were probably chemosensory. Pheromonal and olfactory cues are very important for successful copulation in rodent species, including the rat. Removal of the rat's olfactory bulbs decreased the number of males that initiated copulation (Edwards, Griffs, & Tardival, 1990; Larsson, 1969; Meisel, Lumia, & Sachs, 1980; Wang & Hull, 1980) and also decreased the ability to achieve ejaculation among those that did begin to copulate (Meisel et al., 1980). Noncontact erections elicited by an inaccessible female were also eliminated by olfactory bulbectomy (Kondo, Tomihara, & Sakuma, 1999). Thus, blocking NMDA receptors in chemosensory pathways may have impaired the processing or consolidation of relevant cues.

A second factor that could have contributed to the diminished copulatory performance in Experiment 3 is decreased testosterone levels. NMDA receptors contribute to the amplitude but not timing of pulsatile gonadotropin release in male rats (Ping, Mahesh, & Brann, 1995). It is unlikely that the impairment by acute injections of MK-801 in Experiments 1 and 2 was mediated by decreased hormones, because tests began 15 min after injection and were completed either 90 (Experiment 1) or 30 (Experiment 2) min later. However, the daily injections in Experiment 3 may have inhibited gonadotropin and subsequently testosterone release. On the other hand, testosterone is usually present in male rats in much greater quantities than is necessary to stimulate sexual behavior (Damassa, Smith, Tennent, & Davidson, 1977). Furthermore, copulation frequently proceeds normally for a week or longer after castration (Davidson, 1966). Therefore, moderate reductions in hormone levels should not have appreciably affected copulatory ability in these experiments.

The results of Experiment 3 suggest that stimulation of NMDA receptors is important for experience-induced enhancement of copulation in male rats. Indeed, glutamate, acting via NMDA receptors, is critical for numerous forms of learning and neural plasticity (reviewed in Malenka & Nicoll, 1999; Martin et al., 2000). Glutamate, released from a presynaptic terminal, binds to both alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors on the postsynaptic membrane. However, the ion channel associated with the NMDA receptor is normally blocked by Mg^{2+}, rendering it functionally inactive. Activation of AMPA receptors opens Na^+ channels and depolarizes the postsynaptic cell, which results in displacement of the Mg^{2+}. As a result, Na^+ and Ca^{2+} can flow into the postsynaptic cell through the ion channel associated with the NMDA receptor. The resultant increase in intracellular Ca^{2+} triggers a cascade of intracellular processes that result in long-term potentiation. As a result, stimuli that were previously ineffective in producing a neuronal response are now able to activate the postsynaptic neuron. Repeated exposure to sexually relevant stimuli may increase the efficiency of coupling between the stimuli and copulatory responses via just such a mechanism. Thus, glutamate, acting via NMDA receptors, may both promote immediate sexual behavior and also increase the likelihood and efficiency of its future occurrence.

Because the hippocampus is a major locus of mnemonic processes and contains many NMDA receptors, it is possible that hippocampal NMDA receptors mediated the experience-induced facilitation of copulation observed in Experiment 3. Indeed, oxytocin released in the hippocampus appears to mediate drug-induced penile erection (Melis, Stancampiano, & Argiolas, 1992). However, there is no direct evidence for a role of the hippocampus

in copulatory behavior. Mating induced c-*fos* expression (a measure of cellular activation) in several brain areas in male rabbits, but not in the hippocampus (Reyna-Neyra, Camacho-Arroyo, Cerbon, & Gonzalez-Mariscal, 2000). Furthermore, removal of the hippocampus, in addition to removal of most of the neocortex, did not further impair the ability of male rats to impregnate females compared with neocortex lesions alone (Whishaw & Kolb, 1983). Therefore, it is unlikely that blocking NMDA receptors in the hippocampus caused the present copulatory impairment.

A more likely site for experience-based (especially olfactory-based) enhancement of copulation is the medial amygdala. NO does promote long-term potentiation in the medial amygdala (Abe, Watanabe, & Saito, 1996), and the medial amygdala is important for both the performance of copulatory behavior and the ability of chemosensory stimuli to elicit copulation in numerous species (reviewed in Hull et al., 2002). However, consolidation of copulatory elements may occur in each of several sites that are critical for the control of male sexual behavior.

In summary, the NMDA antagonist MK-801, administered before an initial copulatory experience, impaired copulation during that experience. It also resulted in slight (statistically nonsignificant) deficits on a subsequent drug-free test. The acute effects of MK-801 were then tested in sexually experienced animals; MK-801 produced a dose-dependent impairment on several copulatory measures. Finally, to prevent the confounding effect of poorer performance on the initial experience, we repeatedly exposed male rats to an inaccessible estrous female. Such exposure facilitated copulation on a subsequent drug-free test in males that received saline before each exposure, but not in males that received MK-801 before the exposures. Therefore, stimulation of NMDA receptors both enhances sexual performance immediately and facilitates its future occurrence.

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