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Anticonflict Effect of MK-801 in Rats: Time Course and Chronic Treatment Studies

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XIE, Z. C., E. BUCKNER AND R. L. COMMISSARIS. *Anticonflict effect of MK-801 in rats: Time course and chronic treatment studies.* PHARMACOL BIOCHEM BEHAV 51(4) 635–640, 1995.—The present study examined the time course and chronic treatment effects of the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist, MK-801 (dizocilpine), on conflict behavior in the conditioned suppression of drinking (CSD) paradigm, a repeated-measures conflict task. In daily 10-min sessions, water-restricted rats drank from a tube that was occasionally electrified (0.25- or 0.5-mA shocks signaled by a tone). Trained subjects (4 weeks of CSD testing) exhibited stable baselines for both punished responding and unpunished responding. In the first experiment, the effects of MK-801 administered IP were determined in female and male rats following a range of pretreatment intervals (i.e., 0.5–48 h). In female rats, 0.2 mg/kg MK-801 exerted an anticonflict effect at pretreatment intervals of 10–36 h, but not before 10 h or after 36 h. In male rats, qualitatively similar results were obtained; MK-801 (0.4 mg/kg) exerted anticonflict effects following pretreatment intervals of 6–14 h, but not before 6 or after 14 h. In the second experiment, chronic treatment of female rats with 0.04, 0.1, or 0.2 mg/kg MK-801 resulted in a dose-dependent anticonflict effect in CSD paradigm, which remained stable over the course of 5 weeks of chronic treatment. Punished responding returned to pretreatment levels within 2–3 days after discontinuation of chronic treatment with MK-801. These data suggest that MK-801 exerts a delayed anticonflict effect in both female and male rats with a qualitatively similar pattern, and that there is no tolerance to the anticonflict effect of MK-801 with chronic treatment.

MK-801 NMDA receptor complex Conflict behavior Time course Chronic treatment Anxiolytics Sex differences

EXCITATORY amino acids, especially those acting through the *N*-methyl-D-aspartate (NMDA) receptor complex, have been reported to be involved in many CNS functions and disorders, such as convulsions (4,10,37), schizophrenia (7), learning/memory deficits (13,24–26), neurotoxicity (28), and anxiety (18,34). The compound MK-801 (dizocilpine) has been perhaps the most extensively studied of the NMDA compounds; the results of studies with this noncompetitive NMDA antagonist have been used to assess the involvement of NMDA neurotransmission in these conditions (13). This agent has been reported to exert actions in tests for anticonvulsant (6,21–23,35), neuroprotection (8,29,32), and learning/memory deficits (13,24–26). With respect to anxiety-like behavior, MK-801 has been studied in several conflict paradigms for its possible anticonflict (i.e., anxiolytic-like) effects. Whereas some authors have reported that MK-801 exerts an anticonflict (i.e., anxiolytic-like) effect (2,17,20,30,31), a nearly equal number of authors have reported that MK-801 does not exert an anticonflict effect (2,3,9,15).

It is possible that these discrepancies may relate to the differences in the pretreatment intervals examined in the various studies. Using a modified Vogel (36) task, Clineschmidt et al. (2) found that moderate to high doses of MK-801 (0.125–0.5 mg/kg) did not exhibit a significant anticonflict effect until 2–4 h after oral treatment in male rats; they did not investigate the possible anticonflict effect of MK-801 after pretreatment intervals of 8 h or more, nor did these investigators study female rats. In female rats, Xie and Commissaris (38) reported that MK-801 (administered IP) increased punished responding in the conditioned suppression of drinking (CSD) conflict paradigm (a modification of the Vogel acute conflict task) at pretreatment intervals of 20–36 h, but not at pretreatment intervals less than 20 h or greater than 36 h (38); these investigators did not report on the effects of MK-801 in

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male rats. Thus, comparative data regarding the time course for the effects of MK-801 on conflict behavior in both female and male rats is lacking.

Chronic treatment with MK-801 has been reported to result in tolerance for some, but not all, measures. For example, Dall'olio et al. (5) reported that in rats, repeated administration of MK-801 (0.25 mg/kg, IP, daily for 21 days) produced a dramatic and nearly complete tolerance to the hypermotility induced by MK-801 administration. This tolerance was observed after as little as 7 days of repeated administration and was maintained even 5 days after discontinuation of chronic treatment. In contrast, however, Kuribura et al. (16) reported that repeated MK-801 administration to mice resulted in only slight tolerance to the locomotor stimulatory effects of MK-801; at some doses, a slight but statistically significant sensitization was observed. Tricklebank and coworkers (27) have reported that repeated administration of MK-801 (0.5 mg/kg, SC, daily for 6 days) to mice resulted in a tolerance to some effects of MK-801 (frequency of head weaving produced by MK-801), but this chronic treatment failed to result in tolerance to the increased locomotor (sensitization was observed), ataxic, or antiseizure effects of MK-801. This group also reported that chronic MK-801 administration results in regionally specific neurochemical tolerance; that is, chronic treatment with MK-801 resulted in tolerance to the effects of MK-801 to increase concentrations of dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens, but not in the medial prefrontal cortex (12). The effects of chronic administration of MK-801 on conflict behavior have not been reported.

The present studies were designed 1) to compare in male and female rats the full time course for the effects of MK-801 on conflict behavior, and 2) to determine the effects of chronic treatment with MK-801 on CSD conflict behavior.

METHOD

Animals

Subjects were female and male Sprague-Dawley rats (Charles River, Inc., Cambridge, MA) housed in groups of two to four in a climate-controlled room with a 12L : 12D cycle (lights on 0700–1900 h). Animals were given ad lib access to food with restricted water (details of the water restriction are provided below in the General Procedure section).

Apparatus

Conditioned suppression drinking (CSD) testing was conducted in an apparatus similar to that described by Xie and Commissaris (38) and McCloskey et al. (19). The testing chamber was a rectangular box with Plexiglas sides and a metal floor and top. Recessed into one wall was a metal drinking tube to which a calibrated (0.5-ml units) length of polyethylene tubing was attached for measuring the volume of water consumed.

General Procedure

Subjects were tested individually in the CSD conflict paradigm Monday through Friday (Experiment 1) or Monday through Thursday (Experiment 2). Subjects received ad lib water on nontest days. All CSD conflict sessions were conducted after a period of 24 h without access to water. For the first week of sessions, water-restricted subjects were placed in the experimental chamber and were allowed to consume water freely without the shock contingency. After 1 week of nonshock sessions, the tone/shock contingency was initiated. TONE ON periods (7 s in duration) were presented at regular [30-s interstimulus interval (ISI)] intervals to subjects. There were 20 occurrences of the TONE ON : NO TONE alternations during every 10-min test session. During the latter 5 s of each TONE ON period, contact between the floor and the metal sipper tube (i.e., drinking) completed a circuit that resulted in the delivery of a shock to the mouth of the rat. Shocks were applied using a Coulbourn Instruments, Inc. (Lehigh Valley, PA) Two-Pole, Small Animal Shocker (Model E13-02). The duration of the shock received was equal to the duration of the tube contact (less than 200 ms). Previous work has indicated that female rats are more sensitive to the shock than are males. Therefore, to obtain more comparable control levels of punished responding, the shock intensities used were 0.25 and 0.5 mA for female and male rats, respectively. Programming for the test sessions was controlled by solid-state modular programming equipment (Coulbourn Instruments).

Initially, the shock inhibited fluid consumption in the test chamber. After several days, however, all subjects learned to consume stable volumes of water (primarily during the silent periods) and made less frequent and very brief contacts with the tube during the tone, receiving a relatively consistent number of shocks per session. Day-to-day coefficients of variation for punished responding were approximately 30% for individual rats.

Specific Experiments Conducted

Experiment 1: Time course for the effects of MK-801 on CSD conflict behavior in male and female rats. Trained subjects were tested individually in 10-min CSD conflict sessions Monday through Friday at same time of day (1300–1500 h). For the Monday, Tuesday, and Wednesday test sessions each week, no treatments were administered. The average of shocks received (and water intake) on these sessions was considered as the pretreatment baseline for punished responding and unpunished responding, respectively. At various times after the Wednesday test session, MK-801 (0.2 mg/kg for female rats and 0.4 mg/kg for male rats) was administered IP so that the pretreatment intervals for Thursday would be 0.5, 2, 4, . . . 20, 22, and 24 h before testing on Thursday. Thus, on Thursday, the MK-801 effects on CSD conflict behavior were examined after pretreatment intervals from 0.5 to 24 h; on Friday, the MK-801 effects on CSD conflict behavior were examined in these animals after pretreatment intervals from 24.5 to 48 h, again in 2-h increments. Forty rats of each sex were divided into five squads/sex of eight subjects/squad. The effects of MK-801 at various pretreatment intervals were determined in these different squads, with each pretreatment interval examined in only one squad. MK-801 was administered only one time each week. Thus, over the course of several weeks, the effects MK-801 were examined over a variety of pretreatment intervals. In addition, on various occasions, acute challenges with vehicle (saline) were conducted in a similar manner using 30-min, 6-h and 12-h pretreatments; these challenges did not affect CSD conflict behavior (data not shown). The doses of MK-801 used in males and females were selected because pilot studies had indicated that MK-801 is approximately twofold more potent in females compared to males.

Experiment 2: The effects of chronic treatment with MK-801 on CSD conflict behavior. The subjects (32 naive female rats) were trained and were tested as described above (conflict testing at 1600–1800 h Monday-Thursday). After 3 weeks of CSD conflict testing without drug treatment, subjects were divided into four squads with comparable pretreatment base-

lines for shocks received and water intake. Subjects in the various squads received either 0.0 (saline), 0.04, 0.1, or 0.2 mg/kg MK-801 each afternoon shortly after conflict testing (i.e., 24 h prior to the next day's conflict session). This pretreatment interval (24 h) was selected because it is roughly the midpoint for the delayed anticonflict effect produced by MK-801 in female rats. Although subjects were not tested on Friday, Saturday, and Sunday, injections were made in the late afternoon on these days. Daily posttest injections and 4 days/week conflict testing were continued for 5 weeks; 4 days/week conflict testing was continued during the 3-week period immediately following discontinuation of chronic MK-801 or vehicle treatment.

Drug

(+)-MK-801 was obtained from Research Biochemical Inc. (RBI, Natick, MA). The drug was prepared in saline and was injected IP in a volume of 1 ml/kg body weight.

Statistical Analyses

The dependent variables in these experiments were the number of shocks received (punished responding) and the volume of water consumed (unpunished responding); the effects of the various treatments on these two variables were analyzed separately. In Experiment 1, the difference between the number of shocks received on Thursday or Friday and that of baseline (average of Monday, Tuesday, and Wednesday test sessions) reflected the effects of MK-801 on punished responding in the CSD conflict paradigm. Similarly, the difference between the volume of water consumed on Thursday or Friday and that of baseline reflected the effects of MK-801 on unpunished responding in the CSD conflict paradigm. Paired *t*-tests were used to analyze the change in shocks received and the change in water intake produced by MK-801 at various pretreatment intervals in male and female rats. In Experiment 2, pretreatment baselines (i.e., the Monday prior to initiation of chronic treatment) for shocks received and water intake in the four treatment groups were compared using one-way ANOVAs. The effects of chronic MK-801 administration over the first 3 days of repeated administration (i.e., onset) were examined using 4 × 4 factorial ANOVAs with repeated measures [main effects: treatments (0, 0.04, 0.1, 0.2 mg/kg MK-801); test days (Monday = pretreatment, Tuesday, Wednesday, and Thursday)]. The effects of chronic MK-801 over the course of repeated administration were analyzed using 4 × 4 factorial ANOVAs with repeated measures (main effects: treatments, test Weeks 2–5). Finally, the effects of treatment discontinuation were analyzed using 4 × 4 factorial ANOVAs with repeated measures [main effects: treatments; test days (Monday = before discontinuation, Tuesday (D/C day 1), Wednesday (D/C day 2), and Thursday (D/C day 3)]. Post hoc comparisons were made using the least significant differences (lsd) test. In all statistical comparisons, $p < 0.05$ was used as the criterion for statistical significance (33).

RESULTS

Experiment 1: Time Course for the Effects of MK-801 on CSD Conflict Behavior in Male and Female Rats

Baseline (i.e., no drug treatment) punished responding in the CSD conflict paradigm in Experiment 1 was 49 ± 7 (mean ± SEM shocks/session) and 69 ± 11 for female and male rats, respectively. Baseline water intake in the CSD conflict paradigm was 12.9 ± 0.5 ml/session (mean ± SEM ml water/session) and 14.5 ± 0.4 for female and male rats, respectively. These rats exhibited an approximately 5- to 10-fold level of behavioral suppression in this conflict task (e.g., unpunished responding for males: 2500 unpunished licks/23 s × 20 occurrences = 5.4 licks/second; punished responding for males: 70 punished licks/5 s × 20 occurrences = 0.7 licks/second). It should be noted that the total number of tube contacts during the shock component (TONE ON; approximately 50–70/session) was relatively insignificant when compared to the total number of tube contacts during the unpunished component (NO TONE; 2500–3000 contacts/session); thus, the volume of water consumed reflects unpunished responding in the CSD conflict paradigm.

Figure 1 illustrates the time course for the effects of MK-801 on CSD conflict behavior in female (left panel) and male (right panel) rats. The upper panel shows the change in shocks received and lower panel shows the change in water intake. In female rats (left panel), 0.2 mg/kg MK-801 failed to exert an anticonflict effect when tested at pretreatment intervals up to 10 h and also at pretreatment intervals greater than 36 h. MK-801 treatment did result in significant anticonflict effects in the majority of the intervals between 10 and 36 h. MK-801 also significantly reduced water intake at pretreatment intervals up to 10 h in female rats.

Compared to female rats, MK-801 (0.4 mg/kg) administration to male rats (right panels) resulted in a qualitatively similar, but much more abbreviated, time course in the CSD conflict paradigm. MK-801 treatment failed to exert an anti-

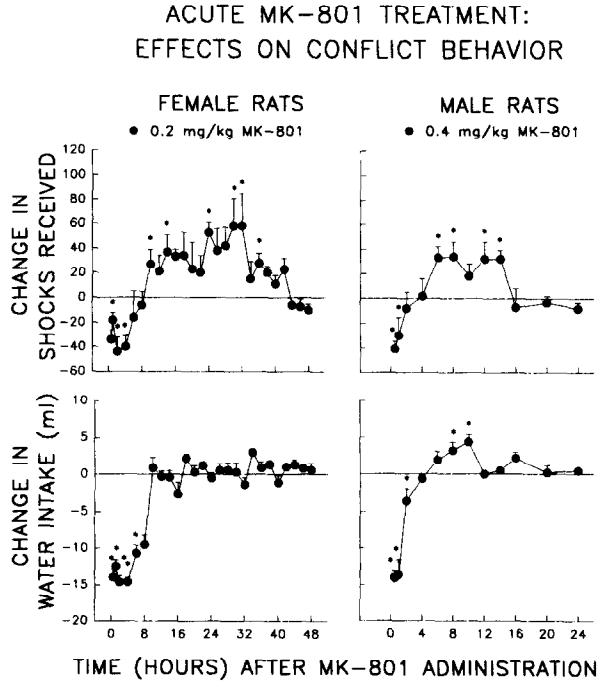

FIG. 1. Time course for the effects of MK-801 on CSD conflict behavior in male and female rats. Plotted are the change in shocks received (upper panels) and the change in water intake (lower panels) produced by 0.2 mg/kg MK-801 in female rats (left panels) and 0.4 mg/kg in male rats (right panels) at various pretreatment intervals. Each symbol and vertical bar represents the mean ± SEM obtained from eight subjects. *The effect of MK-801 at the indicated pretreatment interval is significantly different from control (i.e., pretreatment) values, $p < 0.05$, paired *t*-test.

conflict effect when tested at pretreatment intervals of up to 4 h and at pretreatment intervals greater than 14 h. However, this dose of MK-801 did result in a significant anticonflict effect in the majority of the intervals between 6 and 14 h. As in female rats, 0.4 mg/kg MK-801 in male rats also significantly reduced water intake when tested at pretreatment intervals up to 4 h.

Experiment 2: The Effects of Chronic Treatment With MK-801 on CSD Conflict Behavior

Figure 2 illustrates the effects of chronic treatment with MK-801 on CSD conflict behavior. The upper panel depicts the number of shocks received and the lower panel depicts the volume of water consumed. Data on the far left represent the data from the first week of chronic treatment (onset); data in the middle represent conflict behavior during weeks 2-5 of chronic treatment; data on the far right represent conflict behavior during the first week following treatment discontinuation. Pretreatment baselines (Monday of week 1) for both shocks received and water intake were not significantly different [for shocks: $F(3, 16) < 1.0$, NS; for water: $F(3, 16) < 1.0$, NS). As can be seen, chronic saline treatment for 5 weeks did not affect CSD conflict behavior. As can be seen on the left side of Fig. 2, the anticonflict effect of 0.2 mg/kg MK-801 was not maximal on the first day of treatment (Tuesday); rather, maximal anticonflict effect was seen on the second day of repeated treatment (Wednesday). Statistically, this was supported by a significant treatment × test day interaction, $F(3, 16) = 4.42$, $p < 0.05$. The anticonflict effects of 0.04 and 0.1 mg/kg MK-801 were far less dramatic and did not exhibit an increase across days of repeated treatment. There were no significant effects of any treatment on water intake during the first week of treatment, $F(3, 16) < 1.0$, NS).

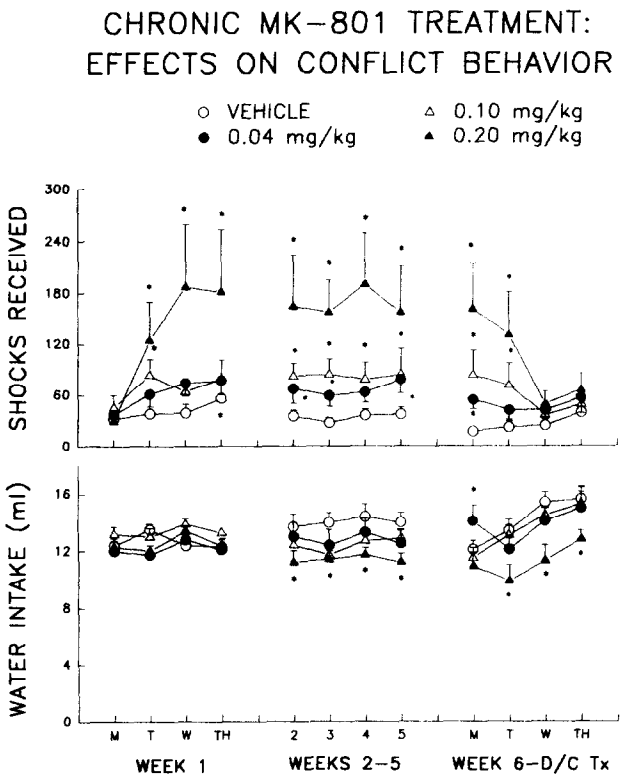

FIG. 2. The effects of chronic treatment with MK-801 on CSD conflict behavior in female rats. Plotted are the number of shocks received (upper panels) and the volume of water consumed (lower panels) in rats receiving 0.0 (saline; open circles), 0.04 mg/kg (filled circles), 0.1 mg/kg (open triangles), or 0.2 mg/kg (filled triangles) MK-801 daily for 5 weeks. Data presented in the far left are daily averages for the day before (Monday) and the first 3 days of chronic treatment; the first MK-801 treatment was administered immediately after testing on Monday. Data presented in the middle are weekly averages for test weeks 2-5 of chronic treatment. Data presented in the far right are daily averages for the last day of chronic treatment (Monday) and the first 3 days following discontinuation of chronic treatment; MK-801 chronic treatment was discontinued following the Monday test of week 6. Each symbol and vertical bar represents the mean ± SEM obtained from eight subjects. *The effect of MK-801 treatment at the indicated dose is significantly different from saline controls at the indicated time, $p < 0.05$, post hoc lsd test following 4 × 4 factorial ANOVA.

As can be seen in the middle of Fig. 2, repeated administration MK-801 resulted in a dose-dependent increase in punished responding; this was supported by a significant main effect for treatment, $F(3, 16) = 14.47$, $p < 0.05$. There was no evidence for tolerance or sensitization over the course of test weeks 2-5, as evidenced by the lack of a significant main effect for test weeks, $F(3, 16) < 1.0$, NS, and the lack of a significant treatment × test week interaction, $F(3, 16) < 1.0$, NS. Over test weeks 2-5, MK-801 produced a modest but dose-dependent reduction in water intake, which was marginally significant, $F(3, 16) = 2.82$, $p < 0.05$ (one-tailed). There was no evidence for tolerance to this effect of MK-801 to reduce water intake, as evidenced by the lack of a significant test week × treatment interaction, $F(3, 16) < 1.0$, NS.

As can be seen in the right side of Fig. 2, discontinuation of MK-801 administration resulted in a return to saline treatment levels over the course of 2 test days. This was supported statistically by the significant test day × treatment interaction during this period, $F(3, 16) = 4.34$, $p < 0.05$. Post hoc lsd comparisons revealed that subjects withdrawn from 0.1 and 0.2 mg/kg MK-801 accepted significantly more shocks than did saline-treated rats on the first day after treatment discontinuation (Tuesday); by the second day after treatment discontinuation (Wednesday), there were no significant differences in shocks accepted in the various treatment groups. There was no evidence for a proconflict effect (i.e., a reduction in punished responding relative to vehicle controls) during the period of withdrawal from MK-801. Water intake in subjects that had received 0.04 or 0.2 mg/kg MK-801 was decreased slightly on the first day of withdrawal and increased over the subsequent 2 days; statistically, this was reflected as a significant main effect for test days, $F(3, 16) = 13.60$, $p < 0.05$.

DISCUSSION

The present studies investigated 1) the time course for the effects of MK-801 on conflict behavior in male and female rats, and 2) the effects of chronic treatment with MK-801 on conflict behavior in female rats. In the time course study, MK-801 exerted a delayed anticonflict effect that was qualitatively, but not quantitatively, similar in female and male rats. In both sexes, the effects of MK-801 administration were characterized temporally by 1) an initial decrease in water intake with a concomitant decrease in shocks received, 2) a later increase in punished responding associated with little or no effect on water intake, and finally 3) a return to control levels of both punished and unpunished responding. Compared to female rats, male rats exhibited a much more abbreviated time

course for both the increase in punished responding and the decrease in water intake following MK-801 administration. The observation of a dramatic delay to onset of anticonflict effect in female rats (middle of anticonflict period at approximately 24 h) is in agreement with our previous report on the effects of MK-801 in female rats in the CSD paradigm (38). The observation of a delay to onset of anticonflict in male rats is consistent with an earlier report by Clineschmidt et al. (2) on the effects of MK-801 administered orally in male rats using the Vogel acute conflict task; it should be noted, however, that the delay reported in the Clineschmidt et al. (2) study was considerably less than that observed in the present study. Given that the anticonflict effects of MK-801 exhibit a significant delay to onset in both male and female rats in the CSD conflict paradigm, it is possible that some the apparent inconsistencies in the literature regarding the effects of MK-801 on anxiety-like behaviors may relate to the pretreatment intervals used in the various studies. Thorough time course evaluations may resolve some of these apparent inconsistencies.

Although the reason for the shorter delay to anticonflict onset and shorter duration of action of MK-801 in male rats compared to females is not known, sex differences in hepatic metabolism of MK-801 may contribute to these effects. Male rats typically exhibit greater cytochrome P450 drug metabolizing activity than do female rats. Hucker et al. (11) have reported that in male rats MK-801 is metabolized by hepatic P450 (specific subtype unknown) to 2-hydroxy-MK-801 and 8-hydroxy-MK-801. It is possible that one or more of these metabolites is responsible for the anticonflict effect observed. This explanation is somewhat unlikely, however, because Clineschmidt et al. (2) have indicated that these metabolites (single doses administered in pilot studies) do not appear to exert anticonflict effects in the Vogel task. Further study of the influence of P450 manipulations in male and female rats is needed to address this potential "prodrug" mechanism for the anticonflict effect of MK-801.

It is also possible that the delayed onset for the anticonflict effect of MK-801 is the result of behavioral interference produced by MK-801 at the earlier pretreatment intervals. In both male and female rats, when tested following relatively short pretreatment intervals, MK-801 treatment resulted in a decrease in water intake in the CSD paradigm; this decrease in water intake was associated with ataxia and locomotor stimulation, which were of considerable duration. In pilot studies, we have observed that 0.4 mg/kg MK-801 increases locomotor activity for up to 2 h in male rats and 0.2 mg/kg MK-801 increases locomotor activity for up to 6 h in females. It is possible that, even at short pretreatment intervals, MK-801 provides the necessary stimulus to produce an anticonflict effect, but the effect is simply masked by the stimulant and ataxic actions of MK-801 at these shorter pretreatment intervals. Although this may be an intriguing hypothesis, it should be noted that a significant delay to onset is observed even following administration of MK-801 at doses that do not dramatically reduce water intake (38).

In Experiment 2, repeated administration of MK-801 resulted in a dose-dependent anticonflict effect that did not exhibit tolerance over the course of 5 weeks of daily MK-801 administration. Interestingly, the magnitude of the anticonflict effect of 0.2 mg/kg MK-801 increased over the course of the first 2 days of repeated administration. Discontinuation of chronic treatment resulted in a return to pretreatment levels of punished responding. As with the onset, however, this return to pretreatment control levels occurred over a period of 2 test days in subjects that had received the highest dose of MK-801 chronically. There was no evidence for a withdrawal-induced proconflict (i.e., anxiogenic-like) effect, either during the first week of treatment discontinuation or for 3 additional weeks of testing (data not shown).

The observation that the anticonflict effect of MK-801 failed to exhibit tolerance over the course of 5 weeks of daily treatment is somewhat surprising, given previous reports indicating the development of tolerance to the hypermotility-inducing effects of MK-801 in rats (5) and tolerance to the effects of MK-801 to induce head-weaving behavior in mice (27). On the other hand, repeated administration of MK-801 failed to produce tolerance to its locomotor-stimulating, ataxia-inducing, or antiseizure effects in mice (27). Chronic administration of MK-801 in doses comparable to those used in the present study has been reported to result in significant upregulation of NMDA receptor sites (1); it has been suggested that this upregulation is responsible for the tolerance to the effects of MK-801 observed in some behaviors. Therefore, the observation that chronic MK-801 treatment did not result in tolerance in the present study suggests that the delayed anticonflict effect produced by MK-801 administration may not be the result of reduced NMDA transmission. Further studies with additional NMDA (and also sigma site) ligands might shed some light on this possibility.

In summary, MK-801 administration exerted a significant but notably delayed anticonflict effect in both male and female rats. In females, MK-801 exerted a significant anticonflict effect when tested at pretreatment intervals of 10–36 h, but not before or after this period. In males this pattern was qualitatively similar, but sooner in onset and shorter in duration (effective only at pretreatment intervals from 6–14 h). In female rats, repeated daily administration of MK-801 failed to exhibit tolerance or sensitization over the course of 5 weeks of chronic treatment. The exact mechanism for the delayed anticonflict effect of MK-801 is not known at the present time.

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