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Anxiolytic-Like Effects of the Noncompetitive NMDA Antagonist MK 801

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XIE, Z. AND R. L. COMMISSARIS. *Anxiolytic-like effects of the noncompetitive NMDA antagonist MK 801.* PHARMACOL BIOCHEM BEHAV 43(2) 471–477, 1992. – The present study examined the effects of the noncompetitive NMDA antagonist, MK 801 (dizocilpine), on behavior in the conditioned suppression of drinking (CSD) punished drinking paradigm, a repeated-measures conflict task. In daily 10- or 15-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 (approximately 40 or 100 shocks received/session at the 0.5- and 0.25-mA shock intensities, respectively) and unpunished (approximately 15 ml/session water intake at either shock intensity) responding. Over a wide range of doses, (+) MK 801 did not increase punished responding when administered using a 10-min, 4-h, or 48-h pretreatment. However, at a 24-h pretreatment (+) MK 801 (0.04–0.4 mg/kg, IP) produced a dramatic and dose-dependent increase in punished responding. The "inactive" (−) isomer of MK 801 did not produce a significant anxiolytic-like effect in the CSD paradigm at doses up to 2 mg/kg when tested using a 24-h pretreatment. These data suggest that the anticonvulsant agent (+) MK 801 also may exert antianxiety effects in humans.

MK 801 Anxiolytics NMDA antagonist Conflict behavior Anxiety

IN the late 1950s, Curtis et al. (5) reported that L-glutamate and a number of other naturally occurring acidic amino acids excited single neurons in the mammalian brain. Since this pioneering discovery, considerable evidence has accumulated suggesting that one or more of these excitatory amino acids (EAAs) or related analogs may function as excitatory neurotransmitters in the mammalian CNS. In a recent review, Collingridge and Lester (2) indicated that EAAs, particularly (*N*-methyl-D-aspartate (NMDA), may play an important role in the etiology and/or expression of many CNS disorders, including neuronal cell death, learning and memory, seizure activity, and anxiety-like behaviors.

Conflict paradigms represent perhaps the most frequently used animal models for the study of anxiety and antianxiety treatments. Therefore, it is not surprising that the noncompetitive NMDA antagonist (+) MK 801 (dizocilpine) has been studied for its possible anxiolytic-like effects in several conflict paradigms and in several species. Although most reports in which experimental subjects are pigeons or primates would suggest that (+) MK 801 is not effective in reducing conflict (1,10,12), the majority of the studies in rats conclude that (+) MK 801 increases punished responding (1,13,15–17). However, even in rats the magnitude of the anticonflict effect produced by (+) MK 801 appears to be somewhat limited relative to the increase in punished responding produced by barbiturates and benzodiazepines (1,16,17). It also should be noted that Clineschmidt et al. (1) reported that (+) MK 801 exhibits only minimal anticonflict effects after short pretreatment intervals (i.e., less than 2 h) and greater anticonflict effects following longer pretreatment intervals (i.e., 2–4 h). There are no other reports on the time course for the effects of (+) MK 801 on conflict behavior.

Another conflict procedure that has been used extensively in the study of anxiety and/or antianxiety agents is the conditioned suppression of drinking (CSD) (3,8,14), a modification of the Geller–Seifter conditioned conflict test (9) and the Vogel acute conflict task (20). Although this conflict procedure has been used in numerous studies examining the anxiolytic-like effects of benzodiazepines (3,8,14), barbiturates (3,14), buspirone (14,18), and chronic antidepressant treatment (6,7), there are no reports on the effects of (+) MK 801 on CSD conflict behavior. The purpose of the present study, therefore, was to examine both time course and dose–response curves for the effects of the noncompetitive NMA receptor antagonist, (+) MK 801, on CSD conflict behavior in the rat.

METHOD

Animals

Subjects were female Sprague–Dawley rats (Charles River, Inc., Cambridge, MA) housed in groups of two to four in a climate-controlled room with a 12 L : 12 D cycle (lights on

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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 testing was conducted in an apparatus similar to that described by Commissaris et al. (3,4) and McCloskey et al. (14). 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

For the first few sessions, water-restricted subjects (food provided ad lib) were placed in the experimental chamber and allowed to consume water freely without the shock contingency. After 1 week of nonshock sessions, the tone/shock contingency was initiated. The 7-s tone periods were presented at regular [29-s intershock interval (ISI)] intervals to subjects. During the latter 5 s of these tone periods, contact between the floor and the metal drinking tube 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). The shock intensities used were 0.5 and 0.25 mA. 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 during the silent periods and made relatively few and very brief contacts with the tube during the tone, receiving a consistent number of shocks per session. Day-to-day coefficients of variation for punished responding were approximately 30% for individual rats. Subjects were tested individually in all experiments. Except for one experiment (36- and 48-h MK 801 pretreatment study), CSD testing was conducted in 10-min sessions at the same time of day Tuesday through Friday and subjects were allowed free access to water from Friday p.m. until Monday a.m. This schedule of 4-day/week testing was maintained throughout the course of drug testing.

Specific Experiments Conducted

Experiment 1: Effects of (+) MK 801 on CSD conflict behavior—0.25-mA shock intensity. Subjects were trained as described above for CSD testing using a 0.25-mA shock intensity. The acute effects of various doses of (+) MK 801 were determined using a standard crossover procedure as described by McCloskey et al. (14). On the Thursday test days, half the subjects received a dose of (+) MK 801 and half received vehicle (saline). These treatments were reversed on the Friday test days. Thus, each animal served as its own control for the effects of a given drug dose. (+) MK 801 doses or saline were administered 10 min prior to CSD testing. Each week, the effects of a different dose of (+) MK 801 were determined; the order of doses tested was randomized.

Examination of the data obtained using the crossover design revealed what appeared to be a significant delayed anxiolytic-like effect observed 24 h after (+) MK 801 administration (i.e., 10 min after acute saline challenge on the following day). To test for this possibility, the effects of various doses of (+) MK 801 on CSD behavior were determined using a crossover procedure and a 24-h pretreatment interval. For these studies, (+) MK 801 or vehicle administration was accomplished immediately after CSD testing on Wednesday or Thursday. That is, half the subjects received (+) MK 801 on Wednesday immediately after CSD testing (24 h prior to the Thursday test session), and the other half received vehicle on Wednesday after testing. These treatments were reversed after CSD testing on Thursday (24 h prior to the Friday test session). As mentioned above, each week the effects of a different dose of (+) MK 801 were determined; the order of doses tested was randomized.

Experiment 2: Parametric studies on the effects of MK 801 on CSD conflict behavior—0.5-mA shock intensity. Following completion of Experiment 1, shock intensity was increased to 0.5 mA, and control CSD testing was continued (4 days/week) for 3 weeks. After this 3-week period, baseline behavior had stabilized and further parametric investigations with MK 801 were initiated at this shock intensity. These studies did not utilize a crossover design. Rather, studies in Experiment 2 utilized a procedure in which the data obtained on the first 3 days in any given week (Tuesday, Wednesday, Thursday) were averaged and served as the baseline from which a drug or vehicle effect was determined. Using this procedure, the dose-response curve for the effects of various doses of (+) MK 801 or vehicle were determined following a 10-min, a 4-h, and a 24-h pretreatment (drug or vehicle administered immediately after CSD testing on Thursday, i.e., 24 h prior to CSD testing on Friday).

Subsequent to the dose-response determinations described above, the time course (2–24 h) for the effects of a single dose of (+) MK 801 (0.04 mg/kg) was determined over the course of several weeks of CSD testing. In the time course studies, subjects were always tested in the CSD paradigm between 1600 and 1800 h; subjects received 0.04 mg/kg (+) MK 801 at various times (0–22 h) after the CSD session on Thursday as a pretreatment for the Friday CSD session.

After completion of the studies described above, a series of studies was undertaken to determine the effects of (+) MK 801 when administered at pretreatment intervals of 36 and 48 h. To accomplish these studies, CSD testing was conducted only on Mondays, Wednesday, and Fridays each week. The duration of these CSD sessions was increased to 15 min to allow for greater water intake during the test sessions. In these studies, the data from the Monday and Wednesday test sessions were averaged and served as the baseline. (+) MK 801 was injected at selected times after the Wednesday session (i.e., 36 and 48 h prior to the Friday CSD sessions).

The last part of Experiment 2 was designed to determine the effects of the inactive (−) isomer of MK 801 on CSD conflict behavior. In this study, the effects of a range of doses of (−) MK 801 (0.2–2 mg/kg) on CSD conflict behavior were determined following a 24-h pretreatment. The design used was similar to that described above for determination of the dose-response curve for the effects of the (+) isomer.

Drugs

The active (+) and inactive (−) isomers of MK 801 were obtained from Research Biochemicals Inc. (RBI, Natick, MA). The drugs were prepared in saline and were injected IP in a volume of 1 ml/kg body weight.

Statistical Analyses

For the data from Experiment 1 (crossover design), the effects of individual doses of (+) MK 801 on the change in

shocks received and the change in water intake were compared to vehicle controls using *t*-tests for paired values. For the data from Experiment 2 (noncrossover design), the effects of individual doses of MK 801 or its vehicle [or the effects of 0.04 mg/kg (+) MK 801 at various pretreatment intervals] were compared to baseline control values (e.g., Tuesday through Thursday average) using t-test for paired values. In all statistical comparisons, $p < 0.05$ was used as the criterion for statistical significance (19).

RESULTS

Baseline (i.e., nondrug) punished responding in the CSD paradigm was 98 ± 12 and 41 ± 5 shocks/session at the 0.25- and 0.5-mA shock intensities, respectively (values represent the mean ± SEM obtained from all vehicle treatment days). Baseline water intake in the CSD paradigm was 15.6 ± 0.5 and 14.0 ± 0.7 ml water/session at the 0.25- and 0.5-mA shock intensities, respectively. Baseline responding in the CSD paradigm (0.5 mA) when test sessions were 15 min in duration and were conducted 48 h apart was 59 ± 7 shocks/session and 18.6 ± 1.0 ml/session. It should be noted that even at the lowest shock intensity the number of tube contacts during the shock component was insignificant when compared to the number of tube contacts during the unpunished components (2,500–3,000 per session). Thus, the volume of water consumed accurately reflects unpunished responding in the CSD.

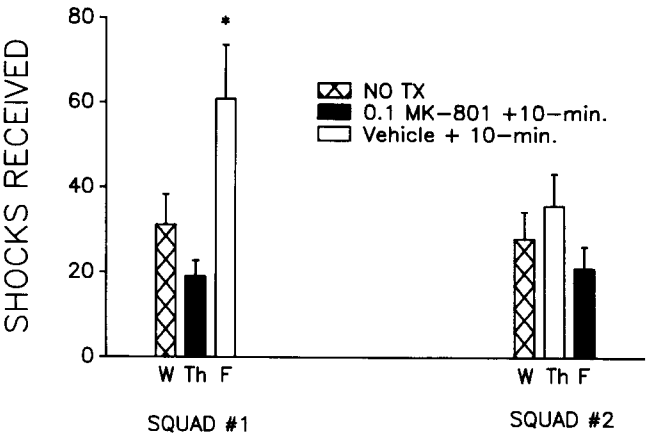

FIG. 1. Delayed anxiolytic-like effect of 0.1 mg/kg (+) MK-801. Subjects in squad 1 received no treatment on Wednesday, 0.1 mg/kg (+) MK-801 10 min prior to testing on Thursday, and saline 10 min prior to testing on Friday; subjects in squad 2 received no treatment on Wednesday, saline on Thursday, and 0.1 mg/kg (+) MK-801 10 min prior to testing on Friday. Each symbol and bar represents the mean ± SEM ($n = 8$) number of shocks received. *The number of shocks received on the indicated day is significantly different from no treatment (Wednesday), $p < 0.05$, paired *t*-test.

Experiment 1: Effects of (+) MK 801 on Conflict Behavior—0.25-mA Shock Intensity

Table 1 illustrates the effects of (+) MK 801 on CSD behavior using a 10-min or 24-h pretreatment interval and a crossover design. When CSD testing was conducted following a 10-min pretreatment, (+) MK 801 did not increase punished responding; rather, it decreased both punished responding and water intake at several doses. At no dose was a selective anxiolytic-like or anxiogenic-like effect observed with (+) MK 801 at a 10-min pretreatment. In contrast, when administered with a 24-h pretreatment interval (+) MK 801 increased punished responding at several doses (0.1 and 0.2 mg/kg) but did not significantly affect water intake.

Figure 1 illustrates the delayed anxiolytic-like effect of 0.1 mg/kg (+) MK 801 when CSD testing was conducted using a "crossover" design and a 10-min pretreatment. For subjects in squad 2, there was no difference between CSD behavior on Wednesday (no treatment) and Thursday (vehicle, 10-min pretreatment). In contrast, subjects in squad 1 exhibited an apparent increase in punished responding following vehicle administration on Friday [24 h after (+) MK 801 administration on Thursday] relative to Wednesday. For subjects in both squads, (+) MK 801 administration at a 10-min pretreatment resulted in a decrease in punished responding relative to Wednesday (i.e., no treatment).

Experiment 2: Parametric Studies on the Effects of MK 801 on CSD Conflict Behavior—0.5-mA Shock Intensity

The dose-response curve for the effects of (+) MK 801 on CSD behavior at the 0.5-mA shock intensity (not a crossover design) at a 24-h pretreatment is depicted in Fig. 2. As can be seen in the upper panel of this figure, vehicle treatment did not affect the number of shocks received whereas (+) MK 801 administration increased punished responding at several

TABLE 1

(+) MK 801 EFFECTS ON CSD BEHAVIOR: CROSSOVER DESIGN

	10-min Pretreatment		24-h Pretreatment	
MK-801 Dose (mg/kg)	Change in Shocks Received*	Change in Water Intake†	Change in Shocks Received*	Change in Water Intake†
0.004	−5 ± 5	0.0 ± 0.6	−10 ± 7	−1.1 ± 1.1
0.01	−11 ± 8	−2.4 ± 1.1	0 ± 11	0.4 ± 0.6
0.02	−1 ± 9	−1.9 ± 1.2	2 ± 5	−0.4 ± 0.7
0.04	+4 ± 7	−2.0 ± 0.5‡	19 ± 9	−0.5 ± 0.7
0.10	−14 ± 5‡	−6.0 ± 2.0‡	25 ± 8‡	0.6 ± 1.0
0.20	−72 ± 31	−8.5 ± 1.8‡	40 ± 11‡	1.1 ± 0.7

*Data represent the mean ± SEM ($n = 8$) change in shocks received relative to vehicle treatment.

†Data represent the mean ± SEM ($n = 8$) change in water intake (in milliliters) relative to vehicle treatment.

‡The indicated dose is significantly different from vehicle control, $p < 0.05$, paired *t*-test.

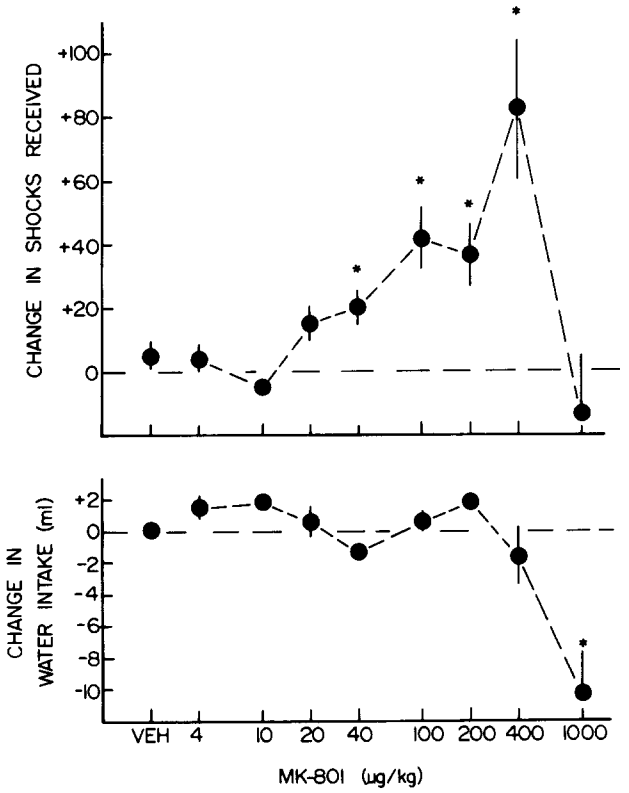

FIG. 2. Dose-effect curve for the effects of (+) MK 801 on CSD conflict behavior in the rat following a 24-h pretreatment interval. Upper panel: Change in shocks received (punished responding) following (+) MK 801 (0.004–1.0 mg/kg) at a 24-h pretreatment. Lower panel: Change in water intake (unpunished responding) following (+) MK 801 (0.004–1.0 mg/kg) at a 24-h pretreatment. Each symbol and vertical bar represents the mean ± SEM change in shocks received or water intake obtained from eight subjects. *The indicated dose is significantly different from predrug baseline values, $p < 0.05$, paired t-test.

doses relative to baseline. This increase in punished responding was dose dependent, with a maximal increase observed following 0.4 mg/kg (+) MK 801. The dose of 1.0 mg/kg (+) MK 801 did not significantly increase punished responding, largely because of the prominent ataxic effects of this dose even 24 h after administration.

The lower panel of Fig. 2 illustrates the effects of (+) MK 801 on water intake in the CSD paradigm when administered at a 24-h pretreatment. As can be seen, vehicle treatment did not affect water intake. Except for the highest dose examined (1 mg/kg) at a 24-h pretreatment interval, (+) MK 801 failed to depress water intake; indeed, there was a slight increase in water intake observed at several doses of (+) MK 801.

Table 2 summarizes the effects on CSD conflict behavior of (+) MK 801 when administered at pretreatment intervals of 10 min, 4 h, and 48 h using a noncrossover design. As can be seen, with the exception of the 0.2-mg/kg dose tested with a 48-h pretreatment, no dose of (+) MK 801 significantly increased punished responding when tested at these pretreatment intervals. Indeed, a dramatic and dose-related decrease in punished responding was found with (+) MK 801 at the 4-h pretreatment interval. This effect likely was the result of the dramatic disruption of unpunished responding (reduced water intake) produced by (+) MK 801 at this pretreatment interval.

Figure 3 illustrates the time course for the effects of 0.04 mg/kg (+) MK 801 on CSD behavior. As can be seen in the top panel of this figure, at 2-, 4-, and 8-h pretreatment intervals 0.04 (+) MK 801 did not increase punished responding. There was a tendency for an increase in punished responding at the 12-, 16-, and 20-h pretreatment intervals, but none of these effects were statistically significant. However, when tested using a 24-h or 36-h pretreatment interval (36-h pretreatment data determined using the alternate-day, 15-min session testing procedure) (+) MK 801 did significantly increase punished responding. Finally, this dose of (+) MK 801 failed to increase punished responding when tested using a 48-h pretreatment interval.

The bottom panel of Fig. 3 illustrates the time course for the effects of 0.04 mg/kg (+) MK 801 on water intake in the CSD paradigm. As can be seen, except for the 4-h pretreatment interval (+) MK 801 increased water intake slightly or had no affect on this parameter.

Table 3 depicts the effects of the inactive (−) isomer of MK 801 on CSD behavior when tested using a 24-h pretreatment interval. As can be seen, even at the dose of 2 mg/kg the (−) inactive isomer of MK 801 did not significantly increase punished responding. Except 2 mg/kg, the (−) inactive isomer of MK 801 did not change water intake significantly.

DISCUSSION

The present studies constitute a parametric evaluation of the effects of the noncompetitive NMDA antagonist, MK 801, on behavior in the CSD conflict paradigm. When adminis-

TABLE 2

MK 801 EFFECTS ON CONFLICT BEHAVIOR: NONCROSSOVER DESIGN

Dose (mg/kg)	Change in Shocks Received*	Change in Water Intake†
10-min pretreatment		
VEH	+4 ± 3	+1.9 ± 0.6‡
0.02	+6 ± 3	+1.4 ± 0.8
0.04	+6 ± 9	+2.3 ± 1.1
0.10	−6 ± 7	+0.5 ± 1.0
4-h pretreatment		
VEH	+10 ± 6	+1.8 ± 0.7‡
0.02	+17 ± 13	−1.1 ± 0.7
0.04	−8 ± 12	−2.8 ± 1.3
0.10	−5 ± 6	−8.7 ± 1.6‡
0.20	−59 ± 19‡	−14.9 ± 1.0‡
48-h pretreatment		
VEH	1 ± 8	1.3 ± 0.9
0.02	10 ± 4	1.0 ± 0.4
0.04	−4 ± 1	1.4 ± 0.7
0.10	−3 ± 13	1.0 ± 0.6
0.20	20 ± 5‡	2.3 ± 1.1
0.40	7 ± 8	−1.6 ± 0.6‡

*Data represent the mean ± SEM (n = 8) change in shocks received relative to pretreatment baseline.

†Data represent the mean ± SEM (n = 8) change in water intake (in milliliters) relative to pretreatment baseline.

‡The indicated dose is significantly different from baseline values, $p < 0.05$, paired t-test.

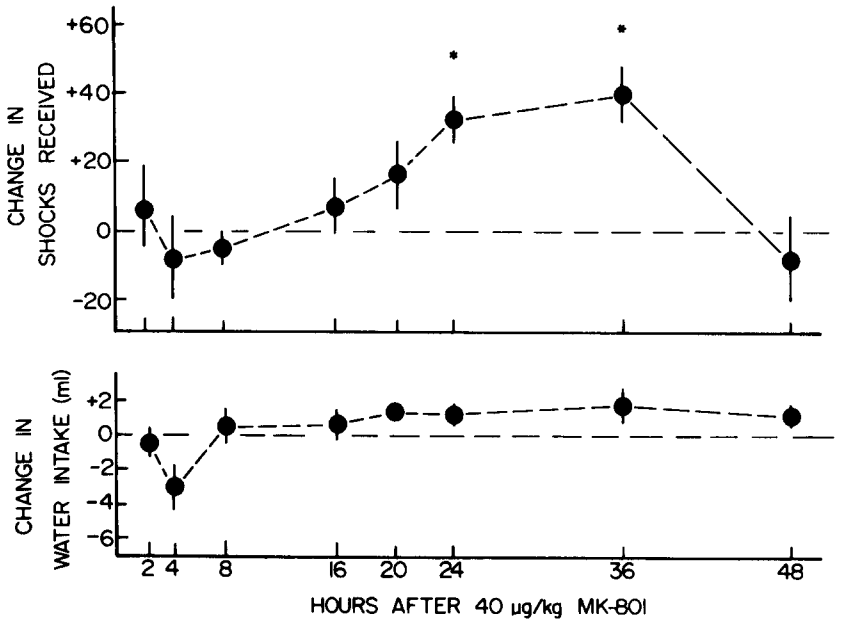

FIG. 3. Time course for the effects of 0.04 mg/kg (+) MK 801 on CSD conflict behavior in the rat. The change in shocks received (upper panel) and change in water intake (lower panel) produced by 0.04 mg/kg (+) MK 801 at various pretreatment intervals are plotted. Each symbol and vertical bar represents the mean ± SEM obtained from eight subjects. *The effect of 0.04 mg/kg (+) MK 801 is significantly different from predrug baseline values at the indicated pretreatment interval, $p < 0.05$, paired t-test.

tered using a 10-min pretreatment and a crossover design, (+) MK 801 did not result in an anxiolytic-like effect in the CSD paradigm; rather, it decreased both punished responding and water intake at several doses. This effect was in part the result of a delayed anxiolytic-like effect, because when it was administered using a 24-h pretreatment (+) MK 801 exerted an anxiolytic-like effect in the CSD paradigm at several doses. Similarly, when tested using a noncrossover design (+) MK 801 did not exert an anticonflict effect when administered at either a 10-min or 4-h pretreatment interval. As with the crossover procedure, however, robust and dose-dependent anticonflict effects were produced by (+) MK 801 when administered 24 h prior to conflict testing. Finally, the inactive (−) isomer of MK 801 did not affect CSD conflict behavior at doses up to 2 mg/kg at this 24-h pretreatment interval.

TABLE 3

(−) MK 801 EFFECTS ON CONFLICT BEHAVIOR: NONCROSSOVER DESIGN AND 24-h PRETREATMENT

Dose (mg/kg)	Change in Shocks Received*	Change in Water Intake†
0.2	+4 ± 3	+2.0 ± 0.9
0.4	+23 ± 21	−1.6 ± 0.9
1.0	+2 ± 9	+0.4 ± 1.0
2.0	+6 ± 11	+2.7 ± 0.8‡

*Data represent the mean ± SEM (n = 8) change in shocks received relative to pretreatment baseline.

†Data represent the mean ± SEM (n = 8) change in water intake (in ml) relative to pretreatment baseline.

‡The indicated dose is significantly different from pretreatment baseline values; $p < 0.05$, paired t-test.

As mentioned in the introductory section, literature reports on the effects of (+) MK 801 are somewhat inconsistent. (+) MK 801 generally does not exert anticonflict effects in pigeons and nonhuman primates (10,12), although the effects of long pretreatment intervals have not been determined in these species. In rats, anticonflict effects generally are reported; the magnitude of the anticonflict effects reported, however, are somewhat modest when compared to the magnitude of the anticonflict effects produced by barbiturates ad benzodiazepines (1,16,17). In the present study, the magnitude of the maximal anticonflict effect of (+) MK 801 was indeed quite impressive (an increase of approximately 80 shocks over baseline at the 0.4-mg/kg dose), an increase in punished responding usually observed only following barbiturate or benzodiazepine treatment in this paradigm (14).

The reason for the dramatic difference in the magnitude of the anticonflict effect in the present study relative to previous studies may relate to the pretreatment intervals examined. Most investigators have reported on the effects of (+) MK 801 on conflict behavior only following relatively short pretreatment intervals, with the only detailed time course study being that of Clineschmidt et al. (1). Using a modified Vogel task, these investigators reported that (+) MK 801 was *inactive* at 0.5- and 1.0-h pretreatment intervals, most active at 2- and 4-h pretreatment intervals, then inactive again at 6- and 8-h pretreatment intervals (1). The effects of (+) MK 801 at pretreatment intervals longer than 8 h were not reported. In the present studies, 0.04–0.2 mg/kg (+) MK 801 failed to increase punished responding at 10-min or 4-h pretreatment intervals, but did increase punished responding at a 24-h pre-

treatment interval. Moreover, in the time course determinations 0.04 mg/kg (+) MK 801 did not increase punished responding at pretreatment intervals up to 8 h, tended to increase punished responding at 16- and 20-h pretreatments, significantly increased punished responding when administered 24 or 36 h prior to conflict testing, and, finally, failed to increase punished responding when administered using a 48-h pretreatment interval. Thus, on a qualitative basis the present studies are in agreement with those of Clineschmidt et al. (1) regarding the delay in onset for the maximal anticonflict effect of (+) MK 801 in rats. The reason for the dramatic difference in the time to peak anticonflict effect reported in the present study, relative to that reported by Clineschmidt, remains undetermined. One possible explanation for the delayed anticonflict effect in both studies is that a metabolite of MK 801, rather than MK 801 itself, is exerting an anticonflict action. Indeed, the difference in the time to onset in the Clineschmidt et al. (1) study using male rats and the present experiments using female rats also would be consistent with this interpretation because male rats exhibit faster rates of hepatic drug metabolism than do female rats. Perhaps most important, the present studies and those of Clineschmidt suggest that a more thorough examination of the time course for the effects on conflict behavior of (+) MK 801 should be determined, particularly in pigeons and nonhuman primates, where (+) MK 801 frequently has been reported to be ineffective following short pretreatment intervals.

At the doses and pretreatment times used in the present study, (+) MK 801 and other noncompetitive NMDA antagonists have been reported to impair performance in tasks used to assess learning and memory. For example, in a passive avoidance task Jones et al. (11) reported that (+) MK 801, ketamine, or phencyclidine administered immediately after training resulted in a significant impairment of learning when tested for retention 24 h after training (also 24 h after drug treatment). There are two reasons that it is unlikely that an impairment of learning is responsible for the anticonflict effect of (+) MK 801 observed in the present study. First, as a repeated-measures conflict task experimental subjects in the CSD conflict paradigm have many months of training rather than a single session as in the passive avoidance task. It is unlikely, therefore, that any information learned (or not learned because of MK 801 treatment) following a single conflict test session contributes greatly to performance on the following day. Thus, any effect of (+) MK 801 to impair learning from the test session immediately preceding (+) MK 801 administration would be minimal. Second, if impairment of learning and/or memory was responsible for the anticonflict effect of (+) MK 801 then it would be expected that there would be no difference in the effects of (+) MK 801 when administered at either 24-h or 48-h pretreatment intervals. However, this is indeed *not* the case because (+) MK 801 failed to increase punished responding (except at the 0.2-mg/kg dose) when administered using a 48-h pretreatment interval. Thus, it seems unlikely that the anticonflict effects of (+) MK 801 in the present study are the result of an impairment of learning and/or memory.

In summary, when administered using either a 10-min or 4-h pretreatment (+) MK 801 did not result in an anxiolytic-like effect; rather, it decreased both punished responding and water intake at several doses. When administered using a 24-h pretreatment, however, (+) MK 801 increased punished responding in a robust and dose-dependent manner. When administered at pretreatment intervals less than 24 or more than 36 h, there was no significant increase in punished responding. Finally, the (−) isomer of MK 801 did not affect CSD conflict behavior. These data suggest that the anticonvulsant agent (+) MK 801 may possess antianxiety effects in humans. Further studies are needed to determine the mechanism for this delayed anxiolytic-like effect of (+) MK 801.

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