Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 4, pp. 1049–1056, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)00249-5

Tolerance to and Dependence on MK-801 (Dizocilpine) in Rats

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Received 21 February 1994

WESSINGER, W. D. *Tolerance to and dependence on MK-801 (dizocilpine) in rats.* PHARMACOL BIOCHEM BEHAV 49(4) 1049–1056, 1994. – Rats were trained to respond under a fixed-ratio 30 schedule for food presentation during four daily 0.5-h sessions occurring every 6 h. After stable baseline response was established, osmotic minipumps were implanted that infused vehicle or (+)-5 methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (dizocilpine; MK-801), SC. Behavioral sessions continued to be conducted daily. After 10 days the infusion pumps were removed. Vehicle and 0.10 mg/kg per day MK-801 did not affect behavior during infusions or after cessation of dosing. Dosing with 0.32 and 0.56 mg/kg per day initially suppressed responding, but tolerance developed to these effects. After the infusions were stopped, a dose-dependent disruption of operant behavior occurred. Response rates for the 0.32 and 0.56 mg/kg per day infusion groups were suppressed to 41 and 27% of preinfusion control response rates, respectively, the day after dosing stopped; however, no physical signs of abstinence were observed. Response rates recovered toward control over the next 2–4 days. In a separate experiment, the suppression of response produced by abstinence from 0.32 mg/kg per day of MK-801 (SC) for 10.5 days was reversed by readministration of MK-801 (IP). These results demonstrate that MK-801 produces dependence, as evidenced by the emergence of a behavioral abstinence syndrome after cessation of dosing.

Rats Behavioral pharmacology Schedule-controlled behavior Fixed-ratio MK-801 Dizocilpine Drug dependence Drug tolerance

MK-801 ([+]-5 methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate; dizocilpine) has many properties in common with phencyclidine (PCP). Although structurally dissimilar from PCP, both agents have a common binding site, termed the PCP receptor (21), which is associated with the *N*-methyl-D-aspartate (NMDA) receptor–ion channel complex. Both PCP and MK-801 act as noncompetitive antagonists of NMDA receptor by binding to the PCP receptor and blocking the NMDA receptor–gated ion channel (e.g., 1,13,27,37). However, MK-801 appears to be more selective for this site than PCP, which also has affinity for the σ site and the dopamine uptake transporter (21).

In numerous behavioral assays there is a striking similarity in the effects of these two drugs. Both produce similar stereotypy in rodents (16,26), PCP-like catalepsy in pigeons (16), and similar gross behavioral effects in rhesus monkeys (16). Consistent with the hypothesis that they act by antagonizing NMDA receptor–mediated actions, both have been shown to block NMDA-induced convulsions (8,26). MK-801 and PCP are also effective as anticonvulsants in other models (6,11,26).

In drug discrimination procedures, MK-801 substitutes for PCP in PCP-trained pigeons (16,19), rats (12,27,34), and rhesus monkeys (4). The substitution appears to be symmetrical in that PCP engenders drug stimulus–appropriate response in rats (5,7,26) and rhesus monkeys (9) trained to discriminate MK-801 from vehicle. The self-administration of these compounds by laboratory animals may depend on drug self-administration history. PCP has been reported to maintain self-administration when substituted for ketamine, but not when substituted in monkeys maintained on codeine (39). Likewise, MK-801 is self-administered by rhesus monkeys with recent histories of ketamine (16) or PCP (4) self-administration, but not in monkeys maintained on cocaine self-administration (4). However, MK-801 failed to maintain self-administration in rats when substituted for ketamine (18).

These similarities in the behavioral effects of PCP and MK-801 suggest that the latter might have a similar abuse potential. Among the factors considered to be important in human drug abuse is the dependence liability of self-administered drugs. The physical dependence-producing properties of PCP (as evidenced by the emergence of overt physiologic signs after withdrawal) have been well documented in laboratory animals (e.g., 2,23,24). With the use of lower doses for continuous administration of PCP, disruptions in operant behavior have been shown to occur after cessation of dosing in monkeys (22) and rats (3,30,33), sometimes in the

absence of any discernible physiologic signs of drug withdrawal. The present study was undertaken to investigate the dependence-producing properties of MK-801 using operant behavior as a quantitative measure of abstinence. Of interest in this regard are recent reports that MK-801 prevents the development of tolerance to (10,17,25,28) and dependence on (28) morphine, tolerance to ethanol (15,38), and the sensitizing effects of repeated administration of stimulants (14,35,36).

METHODS

The general methods for this study were similar to those used previously to study the behavioral effects of PCP dependence in monkeys (22) and rats (3,30,33).

Animals and Apparatus

Twenty-eight experimentally naive male Sprague–Dawley rats (Charles River Breeding Laboratories, Wilmington, MA) that weighed between 221 and 415 g at the beginning of operant training (average weight ± SD = 286 ± 50 g) served as experimental subjects. The experiments were conducted in standard rat operant test chambers (Model G7322; Gerbrands Corp., Arlington, MA) located inside sound- and light-attenuating enclosures (Model G7210; Gerbrands) equipped with a fan that provided air circulation and masked noise. Each test chamber had two response levers mounted below a pair of stimulus lights (28 VDC), an overhead pair of houselights (28 VDC), and a speaker. Water was continuously available in a water bottle mounted on a side wall of the test chamber. Between the levers was a food tray into which a pellet feeder (Model G5100; Gerbrands) delivered 97-mg food pellets (Formula A; P. J. Noyes Co., Lancaster, NH) when schedule contingencies were met. The houselights were illuminated between 0700 and 1900 h to simulate the normal day–night cycle. All experimental conditions and data acquisitions were controlled by an IBM-compatible microcomputer programmed using Medstate Notation (MED Associates, East Fairfield, VT) and operated through an interface (Med-PC, MED Associates).

Procedure for Dose-Effect Study

After an overnight fast, rats were placed into the test chambers, where they remained for the duration of the experiment. Beginning at 1400 h and every 6 h thereafter (i.e., 1400, 2000, 0200, and 0800 h), a 30-min response period ensued, which was signaled by a speaker tone and illumination of the stimulus lights over the right lever. During response periods only the right-hand lever was active; responses on the left lever were counted but had no scheduled consequences. The first response on the right lever turned off the speaker tone until the next response period, but the stimulus lights remained on. For initial training the response requirement was set to a fixed-ratio 1 (FR1); thus, during the response periods a food pellet was delivered after every lever response. After response for food was established under the FR1 schedule of reinforcement (usually 1–2 days), the response requirements were gradually increased to the terminal value of FR30 over the next 3–5 days. The food pellets provided for a complete rodent diet, and subjects obtained all of their daily food during the four 30-min response periods. Daily, after the fourth response period and between the hours of 1100 and 1300, routine chamber maintenance was performed. During this period, the rats were removed from the chambers, weighed, and observed for unusual behaviors or signs of ill health.

After stable baseline rates of response were obtained under the FR30 schedule (i.e., when the range of daily session response rates varied by < 15% for three consecutive 5-day periods) the rats were implanted SC with an osmotic minipump that delivered drug solutions or vehicle (Alza Corp., Palo Alto, CA). About 1200 h, approximately 2 h before the next daily session, the rats were anesthetized with ether. A SC incision (~2 cm) was made in a shaved, cleansed area in the mid-dorsal region and an SC pocket was formed by blunt dissection; the filled pump was inserted portal end first, and the incision was closed using two or three wound clips. The rats were allowed to recover in a warmed enclosure before being returned to the test chambers. The osmotic pumps delivered a constant (beginning approximately 4 h after implantation) SC infusion of MK-801 or vehicle (sterile water). For the dose-effect study, four groups of five rats each were infused with vehicle, 0.1, 0.32, or 0.56 mg/kg per day of MK-801; three rats were infused with the highest dose of MK-801, 1.0 mg/kg per day. Regular daily sessions were conducted over the next 10 days (except for the three rats infused with 1.0 mg/kg per day of MK-801). Then the pumps were removed to stop the infusions, again under ether anesthesia approximately 2 h before the next daily session. The entire implantation–explantation procedure took from 3–5 min, and the rats were usually mobile within 10 min after closure of the incision. After removal of the pumps, regular daily sessions were conducted for another 10 days (again, except for the 1.0 mg/kg per day group). During and after the 10-day infusion period the rats were monitored closely for weight loss. If body weights fell below 80%, supplemental food (30–100 Noyes food pellets) was provided.

Three to five behavioral test chambers were used for these experiments at any given time. Initial studies in three rats used 1.0 mg/kg per day as the infusion dose of MK-801. Because this dose proved to be behaviorally toxic, lower doses of MK-801 or vehicle infusions were studied in 20 subjects. Over the subsequent course of the experiments, the doses infused to rats occupying the chambers concurrently were counterbalanced to the extent possible, and at least one subject was chronically infused with vehicle (which served as control) at any given time.

Procedures for Reversal Study

After the dose-effect experiments were completed, five additional rats were trained and subsequently infused (as described earlier) with 0.32 mg/kg per day MK-801 for 10.5 days to test the ability of MK-801 to reverse the abstinence syndrome induced by removal of the pumps. The pumps were removed at midnight, 2 h before the regularly scheduled 0200-h response period. Immediately after the 0800-h response period (when behavioral disruptions were usually apparent in the previously studied group), two additional 30-min trials were conducted. An IP injection of 0.1 mg/kg MK-801 was administered 10 min before the initiation of each of these repeat response periods.

Drugs and Osmotic Minipumps

(+)-MK-801 hydrogen maleate ([+]-dizocilpine hydrogen maleate; [5R,10S]-[+]-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5,10-imine hydrogen maleate) was purchased from Research Biochemicals (Natick, MA). The drug was dissolved in sterile water to the appropriate concentrations and placed into the osmotic minipumps (Alzet Model 2ML2; Alza Corp.) as per the manufacturer's instructions. The 2ML2

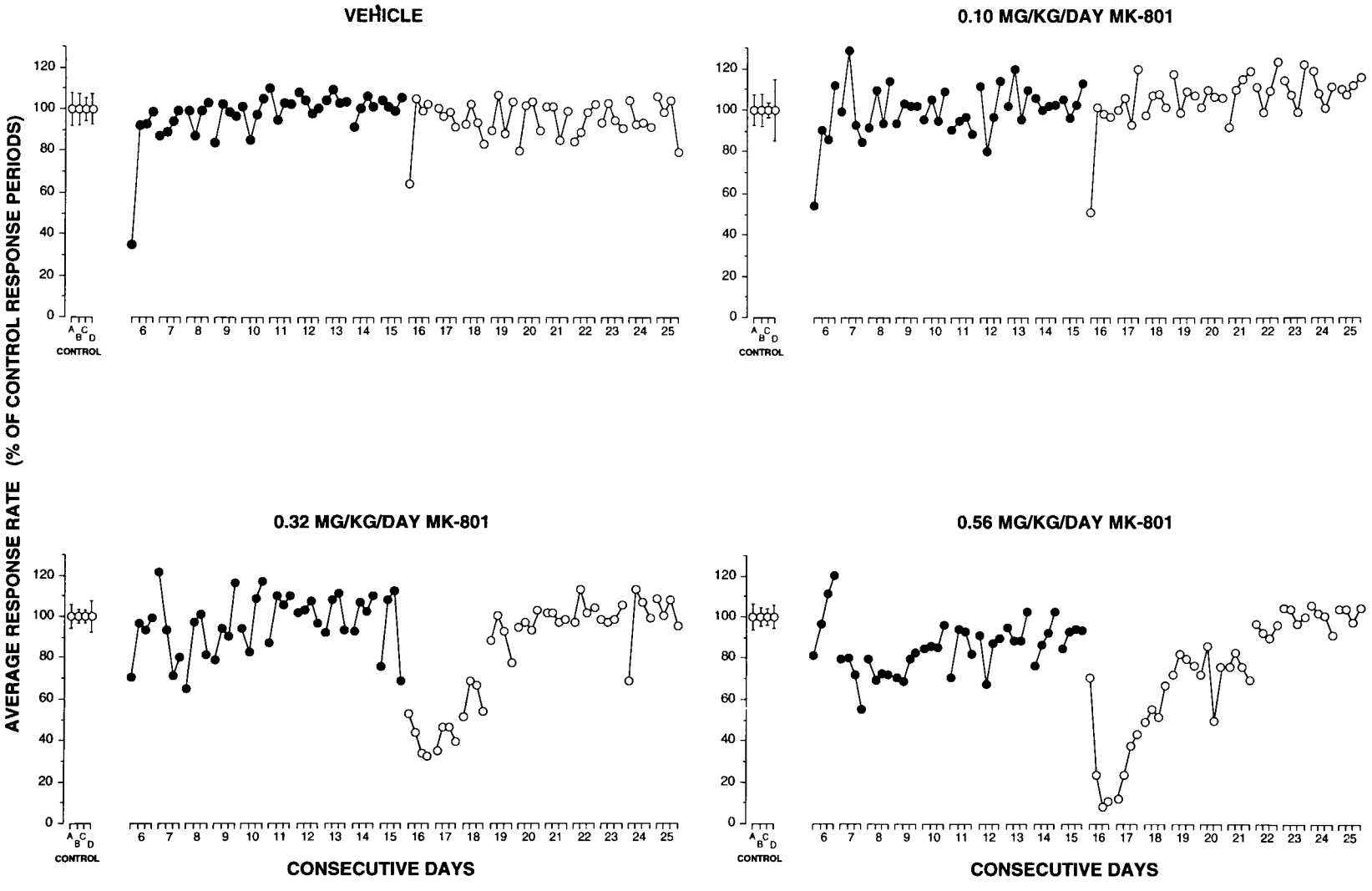

FIG. 1. Average response rates for each of the four daily half-hour response periods (as a percentage of control rates for each response period) during 10 days of vehicle or (+)-5 methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate (MK-801) infusions (solid points, days 6–15), and for 10 days after cessation of infusions (open points, days 16–25). The response rates for each response period (A, B, C, and D) over the 5 days preceding infusions served as control (100% ± SD). Response rates from subsequent response periods (days 6–25) are shown as a percentage of the response period control rates. Sets of four connected points correspond to daily data from response periods A, B, C, and D. Each point is the average of five subjects, except for control points, which are the average of five subjects over 5 days (± SD).

pump has a reservoir capacity of approximately 2 ml and delivers solutions at a constant rate of approximately 5 μl/h for up to 14 days (Alza Corp.). All doses are expressed as milligrams per kilogram per day and were calculated on the basis of the salt.

Data Analysis

Response period response rate (responses per second) was determined by dividing the number of responses occurring during a half-hour response period by 1800 s. Data for response periods are presented in Fig. 1 as a percentage of control response periods averaged for each treatment group. The response rates for the control response periods (A, B, C, and D in Fig. 1, which occurred at 1400, 2000, 0200, and 0800 h, respectively) that occurred during days 1-5 were averaged and set at 100% (±SD); subsequent response periods were also expressed as a percentage of the control response period values. Session response rate (responses per second) refers to the response rate over a 24-h session, and was determined by dividing the sum of the responses occurring during the four half-hour response periods by 7200 s. Fig. 2 shows the 24-h session response rates, averaged for each treatment group. The reversal data are shown in Fig. 3, expressed as a percentage of the averaged (days 1-5) control response period A (i.e., the 1400-h response period) values. Data are shown for response period A on the last day of infusion, for the next response period A (i.e., 14 h after stopping the infusion during withdrawal), and for the two subsequent reversal trials that immediately followed response period A.

RESULTS

Dose-Effect Study

The initial experiments on MK-801 dependence in three rats used an infusion rate of 1.0 mg/kg per day. This dose was selected as a starting point because drug discrimination experiments in pigeons showed MK-801 to be approximately four times more potent than PCP (19), and because in similar dependence experiments infusions of 10 mg/kg per day of PCP were sufficient reliably to produce behavioral dependence (33). This dose of MK-801 proved to be behaviorally toxic. The rats ceased responding for food after 2-3 days and rapidly lost weight despite supplemental feeding. During the infusions chromodacryorrhea and ataxia were noted in all subjects. Out of concern for the health of the rats, the infusions were terminated after 8 days. However, they continued to lose weight and were subsequently sacrificed 3-6 days later. Because of the limited number of subjects studied at 1.0 mg/kg per day and the procedural differences, further details from these three subjects are not reported.

Baseline performance before beginning MK-801 infusions: days 1-5. During the 5-day control period before the implantation of osmotic minipumps, average session response rates (±SD) for individual rats ranged from 0.38 (±0.01) to 1.13 (±0.07) responses/s. Because of this wide individual animal variation, the response period data in Fig. 1 are expressed as a percentage of control response periods. The group averaged session response rates over the course of the experiment are shown in Fig. 2. Response rates for the different treatment groups were relatively stable over the 5 days preceding infu-

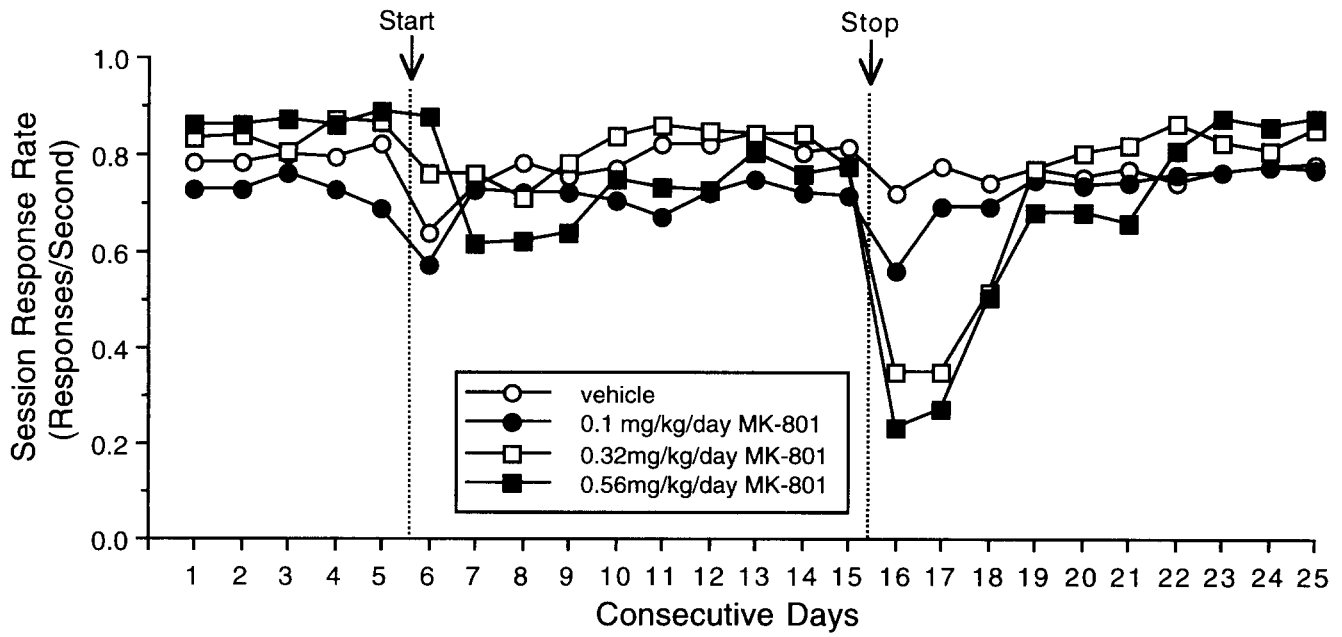

FIG. 2. Session response rates (responses per second) averaged for each treatment group (n = 5 per group) during each consecutive day of the experiment. For the first 5 days (days 1-5) there was no treatment. Osmotic pumps to administer vehicle or (+)-5 methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate (MK-801) (0.10-0.56 mg/kg per day) were implanted at noon, 2 h before the next response period on day 6. Vehicle or MK-801 was infused SC from days 6-15. To terminate the infusions the pumps were explanted at noon, 2 h before the next response period on day 16. There were no infusions from days 16-25.

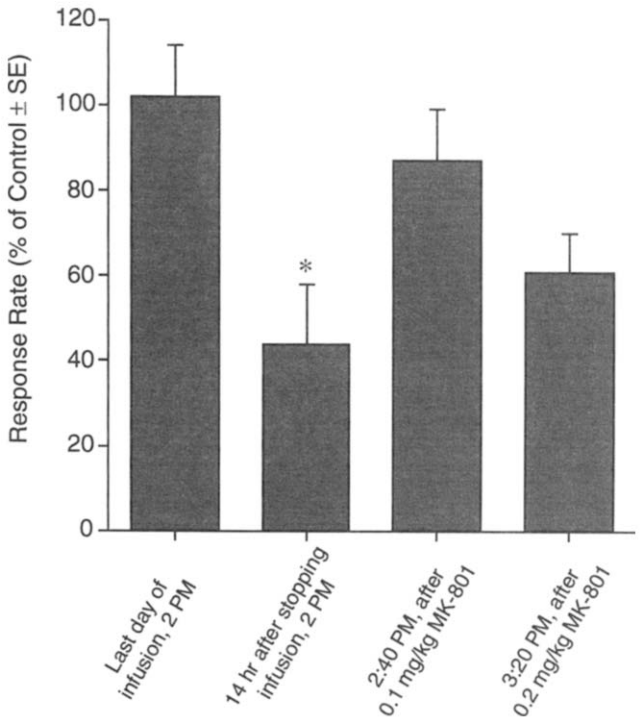

FIG. 3. Effects of readministering (+)-5 methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate (MK-801) after termination of osmotic pump infusions. Control data were the 5-day average of control response period A (1400 h [2:00 PM]) response period, days 1–5). Subsequent data shown here are the percentage of these control data. The left-most column shows the response rate during response period A on the last day of infusion. Pumps were removed at midnight, 10.5 days after starting the infusion. The second column shows the effects of withdrawal during response period A, 14 h after pump removal. (*Statistically different from control response rate, Bonferroni and Dunn; $p < 0.05$). The third column shows the effects of 0.1 mg/kg MK-801, IP, administered immediately after the first response period A (column 2). The right-most column shows the effects of a second dose of 0.1 mg/kg MK-801, IP, administered just after the second response period A (column 3), for a cumulative dose of 0.2 mg/kg MK-801.

sions. The session response rates, averaged (±SD) over the 5-day control period, were 0.80 (±0.26), 0.73 (±0.26), 0.84 (±0.15), and 0.87 (±0.13) response/s for the vehicle, 0.10, 0.32, and 0.56 mg/kg per day groups, respectively.

Before beginning drug infusions the rats obtained sufficient food during the daily sessions to maintain or increase body weight over their starting weights. For example, at the start of operant training the average weight (±SD) of the 20 rats that were used in the dose-effect study was 296 (±48) g. During the 5 days preceding pump implantation, after they were well trained, the rats gained approximately 2 g/day. Just before implantation of the pumps, the average weight of these rats was 360 (±66) g. Table 1 shows the average body weights before beginning infusions on day 6 for the different treatment groups. There were no significant differences between treatment groups at this time ($F(3, 16) = .81, p = 0.51$).

Effects of 10-day infusion of MK-801: days 6–15. The data for individual response periods in Fig. 1 reveal a clear effect of the surgical implantation of the osmotic pumps that occurred at noon, 2 h before the start of response period A (1400-h response period) on day 6. For the vehicle treatment group, this effect was gone by the second response period (B, 2000 h), occurring 8 h after surgery. Similar response rate decreases occurring in the response period just after surgery were observed in the three MK-801-treatment groups. Across the 10-day dosing period there was a modest decrease in response rate for the high-dose treatment group (0.56 mg/kg per day). Other than this effect, MK-801 generally had very little effect during the infusions, except for an increase in variability between response periods for the treatment groups compared with vehicle. When the data are expressed in terms of session response rate (i.e., the four individual daily response periods averaged; Fig. 2), a small decrease to about 90% of control session response rate (days 1–5) is evident for the 0.32 mg/kg dose group during days 7–9. A decrease to about 75% of control session response rates was observed during days 7–9 for the 0.56 mg/kg per day group. Over the course of MK-801 infusions, tolerance developed to these response rate–decreasing effects; during the last 3 days of infusions response rates had returned to control values in the 0.32 mg/kg per day group and to within about 90% of control values for the high-dose treatment group.

Rats in the vehicle group or the two low-dose treatment groups (0.10 and 0.32 mg/kg per day) continued to gain weight, at about the same rate as before infusions began, throughout the infusion period (Table 1). By the end of the infusion period, at the time the pumps were removed (at noon on day 16), the vehicle and two lowest treatment groups had gained between 9 and 12 g, and thus were clearly able to obtain sufficient food during the infusion period. In contrast, the 0.56 mg/kg per day dose group lost weight beginning on day 8 and subsequently did not regain weight until the second half of the infusion period. Other than weight loss in the high-dose group, there were no obvious observable effects of MK-801 at these doses (i.e., there were no signs of chromodacryorrhea, ataxia, piloerection, etc.).

Effects of cessation of infusion of MK-801: days 16–25. Except for the effect of surgery similar to that seen after implantation of the osmotic pumps, both the vehicle and 0.10 mg/kg per day treatment groups showed little effect from the cessation of infusion (Figs. 1 and 2). The most dramatic effects were observed in the two highest-dose treatment groups after the osmotic pumps were removed to stop the 10-day infusions. These effects were larger than any seen during the infusions and were dose dependent. During the session after the pumps were removed (day 16), session response rates were suppressed to 41 and 27% of preinfusion control response rates for the 0.32 and 0.56 mg/kg per day groups, respectively. The 0.32 mg/kg per day group recovered gradually over the next 2 days and was within 97% of control values by day 20. Response rates remained suppressed for a longer duration in the high-dose group, but returned to within 93% of control values by day 22. There were no overt physical signs of withdrawal (e.g., seizures, tremor, piloerection, unkempt appearance, or refusal of food) after any of the infusion doses of MK-801.

After the infusions ceased, the vehicle group and the group infused with 0.10 mg/kg per day MK-801 remained unaffected by the treatments in terms of body weight. In contrast, the two high-dose treatment groups lost weight precipitously during the first 3 days after infusions stopped. Before the sessions starting on day 19 the 0.32 mg/kg per day group had lost 18 g

TABLE 1
CHANGES IN BODY WEIGHT FOR SELECTED DAYS

Treatment	Average Weight (g) on Day 6 (± SD)	Change in Average Weight on Selected Days			
		9	16	19	25
Vehicle	364 (93)	+1	+9	+9	+12
0.10 mg/kg/day	328 (81)	+8	+12	+16	+26
0.32 mg/kg/day	352 (29)	−1	+12	−6	+13
0.56 mg/kg/day	393 (42)	−11	−7	−32	−23

Average body weights (± SD) just before starting infusions of vehicle or (+)-5 methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801) (day 6) and changes in body weight from day 6 on selected days. Body weight on day 9 was measured before the fourth day of infusion, day 16 was measured at the time the pumps were removed, day 19 was before the fourth day after stopping infusions, and day 25 was the last day of the experiment. Subjects were infused with vehicle (H_2O) or doses of MK-801 (0.10, 0.32, or 0.56 mg/kg per day) for 10 days from days 6–15.

since the time the pumps were removed (day 16). The 0.56 mg/kg per day group lost 25 g over this period compared with their weights just before the infusions were stopped (Table 1). Subsequently, the 0.32 mg/kg per day group regained the lost weight by the end of the experiment. The high-dose group also regained some of the lost weight, but at a slower rate.

Reversal Study

During the five control sessions preceding implantation of osmotic pumps that delivered 0.32 mg/kg per day MK-801, the average session response rate (±SD) for the five rats used for the reversal study was 0.85 (±0.14) responses/s, which was similar to that seen during the dose-effect studies. The 5-day averaged control result for the first daily response period (response period A, 1400 h; ± SD), against which subsequent comparisons were made (Fig. 3), was 0.87 (±0.16) responses/s. During MK-801 infusion the effects (not shown) were similar to those reported earlier for the dose-effect study. Near the end of the infusion period, during the 1400-h response period before terminating the infusions, the average response rate was 0.86 (±0.17) responses/s. The left-most column in Fig. 3 shows these data expressed as the percentage of control response period A values averaged across individual animals (±SE). Pumps were removed at midnight during the 11th day of infusions; thus, a slightly longer (10.5 vs. 10 day) infusion period was used than in the dose-effect studies; however, the abstinence suppression observed after infusion stopped was also similar to the that of the previous study. Fourteen hours after the infusions were stopped, during the 1400-h response period the next day, response rates were significantly (Bonferroni and Dunn, $p < 0.05$) suppressed to 0.37 (±0.24) responses/s, which was 44% of the 5-day control value for response period A (Fig. 3). Immediately after this response period, 0.1 mg/kg MK-801 was administered IP, and 10 min later a second 0.5-h response period began. During this second trial, there was a reversal of the abstinence-induced behavioral suppression. Response rates increased to 87% of control values and were no longer different from control. Subsequent administration of an additional 0.1 mg/kg MK-801 did not further increase response rates toward control values, but resulted in a decrease to 61% of control.

DISCUSSION

At appropriate doses MK-801 produced dependence, as evidenced by a dose-dependent suppression of operant behavior after termination of a 10-day infusion (Figs. 1 and 2). This abstinence-induced behavioral disruption was reversed by readministration of MK-801 14 h later (Fig. 3). The effects of stopping MK-801 infusions were generally much more profound than those seen during infusions. The dose-effect curve for the behavioral effects was steep; 0.10 mg/kg per day produced virtually no effect during or after infusions, whereas a 10-fold higher dose (1.0 mg/kg per day) was so toxic that the study of this dose was terminated. The effects of long-term MK-801 and withdrawal on body weight generally paralleled the effects on response for food. When response rates were unaffected the rats continued to gain weight normally, whereas when response rates were suppressed, resulting in decreased availability of food, body weight gain was slowed or weight was lost.

The author is unaware of other reports of the dependence-producing properties of MK-801. In contrast, the dependence-producing properties of PCP are well established under a variety of paradigms. In the present study, the dependence-producing properties of MK-801 were qualitatively and quantitatively similar to those produced by PCP under similar conditions. An intermediate dose of MK-801, 0.32 mg/kg per day, SC, produced reliable behavioral suppression after stopping a 10-day infusion that was similar to that seen after 10 days of 10 mg/kg per day, IV, of PCP. At these doses, both drugs initially produced only a modest suppression of response, to which tolerance quickly developed. After withdrawal of the drug, a 40–50% decrease in session response rates was observed on the first day of withdrawal, with recovery over the next 3–4 days (33).

Pharmacokinetics can play an important role in the onset and duration of the withdrawal effects of drugs. In addition to the other similarities between PCP and MK-801 discussed in the introduction, the pharmacokinetics of these compounds are similar. After a 10-day continuous SC infusion of 10.0 mg/kg per day of PCP·HCl in Sprague–Dawley rats, the terminal elimination half-life is 4.1 h (32). This is in contrast to the reported elimination half-life of PCP after an acute dose in Wistar rats of about 2 h (20). For MK-801, the terminal

elimination half-life after an acute dose of 2 mg/kg to Sprague–Dawley rats is 1.9 h (29). To the author's knowledge, the pharmacokinetics of chronic MK-801 has not been reported. Given these and other similarities between these drugs, it is perhaps not surprising that the time course and severity of withdrawal from PCP and MK-801 are similar as well.

Although several studies have employed long-term dosing of MK-801, most studies examined the effects of MK-801 on the development of tolerance and dependence to other drugs. Wu et al. (38) used a moving belt to examine motor impairment after daily MK-801 (0.25 mg/kg, IP) in rats. No tolerance to the motor-incoordinating effects developed over 14 days of treatment with MK-801 alone, although this same dose of MK-801 prevented the development of ethanol tolerance. Another report of repeated administration of MK-801 (0.25 mg/kg, IP) to rats did demonstrate the development of sensitization ("reverse tolerance") to the locomotor stimulant effects of MK-801, which persisted for at least 3 weeks. In addition, the same dose of MK-801 blocked the development of sensitization to amphetamine (36). In the present study, tolerance to the initial response rate–decreasing effects of 0.32 and 0.56 mg/kg per day of MK-801 developed over the 10-day infusion period (Figs. 1 and 2).

A number of studies have demonstrated that NMDA antagonists can block the development of tolerance to the analgesic effects of chronic opiates (10,17,25,28). Furthermore, the development of dependence to morphine was inhibited by MK-801 (28). These studies suggest a clinical use of these agents in the management of chronic pain. However, the present study, which demonstrates the dependence liability of relatively low doses of MK-801, indicates that some caution is warranted in the development of similar agents for this purpose.

ACKNOWLEDGEMENTS

The author thanks R. A. Dellinger and C. M. Healey for their expert technical assistance and Dr. T. F. Burke, Dr. P. R. Mayeux, and H. R. Garner for providing comments on the manuscript. This work was supported by a grant from the National Institute on Drug Abuse, DA04278. Portions of this data were presented at the 55rd Annual Meeting of the Committee on Problems of Drug Dependence, Palm Beach, FL, June, 1991 (31).

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