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Effects of MK-801 on Learning and Memory as Assessed Using a Novel Water Maze[1,2]

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KANT, G. J., W. L. WRIGHT, T. N. ROBINSON, III AND C. P. D'ANGELO. *Effects of MK-801 on learning and memory as assessed using a novel water maze.* PHARMACOL BIOCHEM BEHAV **39**(2) 479–485, 1991.—The effects of the NMDA receptor antagonist MK-801 {(+)-10,11-dihydro-5-methyl-5H-dibenzo [a,d]-cyclohepten-5,10 imine hydrogen maleate} on learning and memory were assessed using a water maze. The maze was a traditional type of maze with alleys and choices between various paths, but set inside a pool of water to a height of 25 cm. Different mazes could be configured by altering the arrangement of open vs. closed doors. Both the time required to reach an out-of-the-water exit platform and the errors made during the swim from start to finish were recorded. Learning was assessed during the first 10 to 20 trials in a new maze configuration, while memory was tested after the maze was well learned. Three experiments, some with several phases, were performed. These experiments compared the effects of 0.1 mg/kg of either (+)-MK-801, or (−)-MK-801 vs. saline on learning new maze configurations as well as swimming well-learned mazes. Neither of the MK-801 isomers impaired performance of a previously learned maze. (+)-MK-801 clearly slowed learning of new mazes as measured by both maze completion time and errors committed, while (−)-MK-801 had a significant but smaller effect on learning. Rats given (+)- or (−)-MK-801 (0.1 mg/kg) for 16 days while learning one maze and then challenged to learn a new maze without drug administration performed no differently on the new maze than controls, suggesting that the acute effect of MK-801 on learning is not long lasting.

MK-801 N-Methyl-D-aspartate (NMDA) Water maze Learning Memory

THERE has been much recent interest in the role of glutamate, an excitatory neurotransmitter, in neuronal cell death following injury, ischemia or seizures. MK-801 {(+)-10,11-dihydro-5-methyl-5H-dibenzo [a,d]-cyclohepten-5,10 imine hydrogen maleate} is a noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) subclass of glutamate receptors (26–28). Various NMDA antagonists, including MK-801, have shown positive effects as anticonvulsant, anti-ischemic and neural protective drugs (4, 6, 9, 16, 18, 19).

However, in addition to these potential beneficial effects of NMDA antagonists, there have been reports of adverse neurobehavioral effects of these drugs (3, 8, 14, 15, 17, 25, 29). MK-801 has been shown to impair learning of passive avoidance, brightness and olfactory discriminations, and acquisition of a radial arm maze (3, 5, 8, 22–24, 29). In addition, several reports have used the Morris water maze task to assess effects of NMDA antagonists on learning and memory and have generally found that these compounds impair acquisition but not memory in this spatial task (10, 14, 17, 25).

In the Morris water maze task, the rat is challenged to learn and remember the location of an under-the-water platform hidden in an open opaque pool. While the time to reach the platform is easily recorded, other performance data is more difficult to quantify (e.g., errors), although video recordings of the rat's swim often reveal interesting differences in the swim paths taken by control and drug-treated or lesioned animals. Our laboratory has utilized another water performance task very unlike the Morris water maze to assess the effects of various compounds on learning and memory (11–13, 20, 21). In this maze, described more fully below, an arrangement of alleys and doors is configured so that the rat must learn and remember a series of choices through open doors to swim a path from a starting point to an out-of-the-water platform. The difficulty of the task can be altered by varying the number of door choices that the rat must correctly make on the way to the "finish." Also, several mazes of approximately equal difficulty can be quickly configured by changing the start, finish and/or combination of open doors. This flexibility allows for retesting learning in the same group of rats. Both the time to reach the finish and errors made along the way can be easily quantified. The ability to assess errors, as well as speed, is helpful in distinguishing deficits in motor, motivational and cognitive impairments.

We have found that this water maze is more quickly learned than an identical "dry" maze where the reward for reaching the finish is a desired food (11) and drug-induced changes in appetite do not confound performance testing in a water maze. Using this water maze task, we have reported performance deficits after administration of psychoactive drugs and blood substitutes (12, 13, 21).

In the present report, we have carried out a series of experi-

[1]The views of the author(s) do not purport to reflect the position of the Department of the Army or the Department of Defense, (para 4-3, AR 360-5).

[2]Research was conducted in compliance with the Animal Welfare Act, and other Federal statutes and regulations relating to animals and experiments relating to animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, NIH publication 86-23.

ments with MK-801 to determine the effects of this drug on learning and memory using this water maze.

METHOD

Animals

Male Sprague-Dawley rats were purchased from Zivic-Miller. The average weight of rats at the beginning of Experiment 1 was 283 grams (range: 268 to 300) and separate groups of rats were used for Experiment 2 (average weight 415; range: 368 to 477 grams) and Experiment 3 (average weight 393; range 364 to 423). Rats were maintained in individual hanging cages with food and water freely available in a light-controlled animal room (lights on from 0700 to 1900 h).

Drugs

The MK-801 used in the first experiment was a gift from Dr. Alberto Martinez-Arizala who obtained it from Merck Sharp and Dohme Research Laboratories, West Point, PA. This compound was supplied as the (+) isomer {(+)-10,11-dihydro-5-methyl-5H-dibenzo [a,d]-cyclohepten-5,10 imine hydrogen maleate}. Both the (+)- and (−)-MK-801 hydrogen maleate used in the second and third experiments were purchased from Research Biochemicals Inc., Natick, MA. Drugs were dissolved in 0.9% saline immediately prior to use each day. Drugs were administered IP, 30 min prior to each swim trial. The dose of 0.1 mg/kg of MK-801 was selected from the literature as a dose less than that required to cause gross locomotor changes or ataxia (5,25).

Maze

As shown in Fig. 1, the maze consisted of concentric squares set inside a 5 ft dia. child's swimming pool. The maze walls were white opaque plastic and removeable doorways set in the center of the walls allowed for different maze configurations. The maze was located in an open laboratory with overhead lighting and numerous available spatial room cues including laboratory equipment and the position of the investigator. Water (24°C) filled the maze to a depth of 25 cm. Maze A was the first maze configured. Rats were placed into the center of the maze and given a maximum of 5 min to find the out-of-the water exit platform located at the "finish." Both the time required and the number of errors (whole body entries through doorways not leading to the exit platform) were recorded for each trial. Rats not reaching the platform in 5 min were gently pushed with a paddle and guided through the correct path until they reached the platform. Rats were tested once daily.

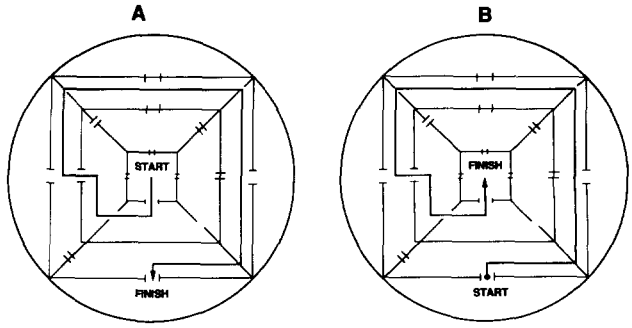

FIG. 1. Schematic diagram of mazes A and B. An out-of-the-water platform was placed at the "finish." Rats were placed at the "start" and given a maximum of 5 min to swim to the platform. Whole body entries through doors not on the correct path were counted as errors.

Experiment 1

Twenty-four male rats served as subjects. Twelve rats received (+)-MK-801 (0.1 mg/kg, IP; the compound obtained

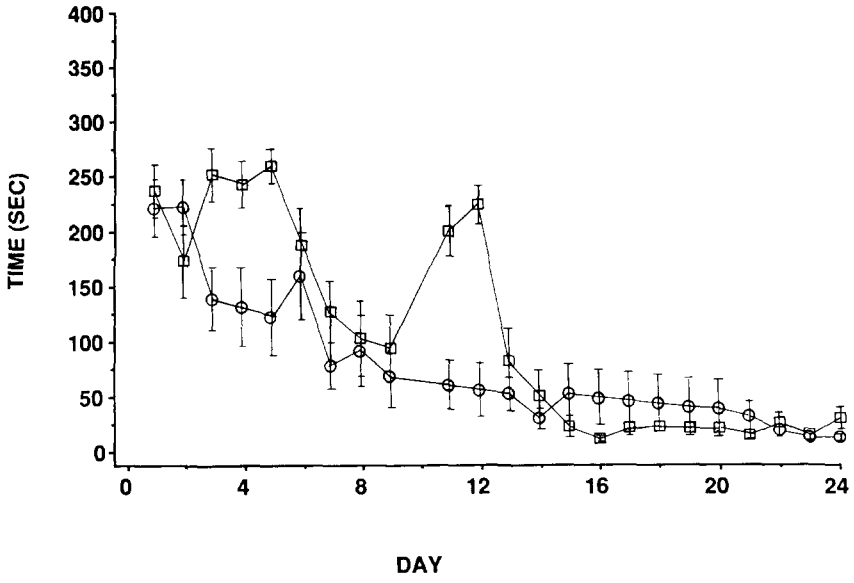

FIG. 2. Experiment 1, phase 1. Effects of (+)-MK-801 (0.1 mg/kg IP, 30 min prior to swim) on time required to swim from the start to the finish on daily trials while learning maze A. Circles are controls (saline-injected) and squares are MK-801-treated rats. n = 11 or 12/group (one saline group animal did not swim; it always grasped the doorway and was deleted from the experiment). Values represent the mean ± SEM. Trial 10 was aborted due to severe pool leak.

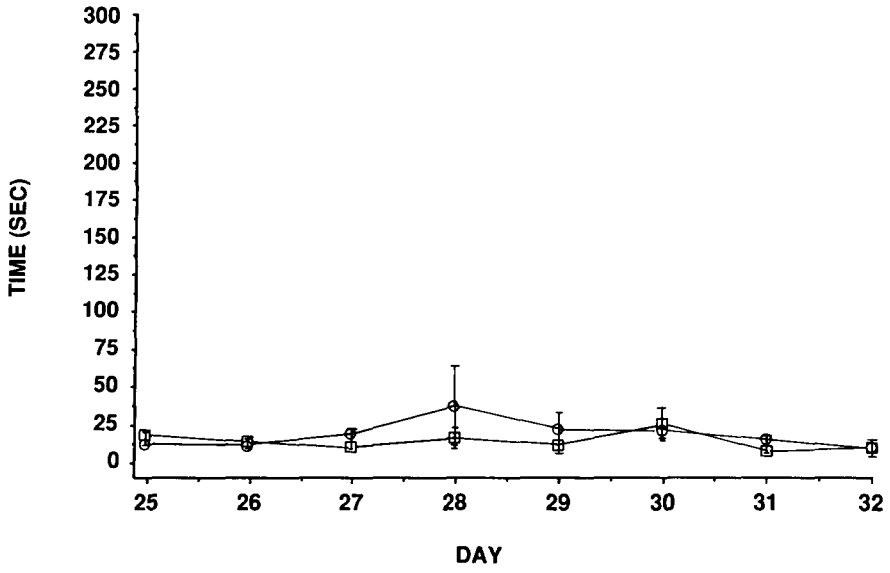

FIG. 3. Experiment 1, phase 2. Effects of (+) MK-801 (0.1 mg/kg IP, 30 min prior to swim) on time required to swim maze A after this task was well learned. All animals are from the saline group of phase 1 (Fig. 2). Five of the 11 animals from phase 1 were injected with MK-801 and the other six continued to receive saline. Values represent the mean ± SEM. Circles are saline injected and squares are (+) MK-801 injected.

from Merck Sharp and Dohme) and twelve rats received a similar volume (approximately 0.3 ml) of saline 30 min prior to each single daily learning trial on maze A (Fig. 1), a particular maze configuration with the start in the center of the maze, 4 sequential choices between open doors and an out-of-the-water exit located near the outside rim of the pool. This first learning phase of the experiment was conducted for 24 days.

During the second phase of this first experiment, the saline group of 12 animals from phase 1 was divided into 2 subgroups. Of the 12 animals administered saline in phase 1, 6 continued to receive saline in phase 2 (saline/saline group) and 6 were administered MK-801 in phase 2 (saline/MK-801 group). These 2 groups were then retested for a period of 8 days in the well-learned maze A of phase 1 to determine the effects of MK-801 on retention or memory, by comparing the performance of the saline/saline group with the saline/MK-801 group. Following 8 days of memory testing, the groups continued in the same treatment groups and were challenged to learn a new maze configu-

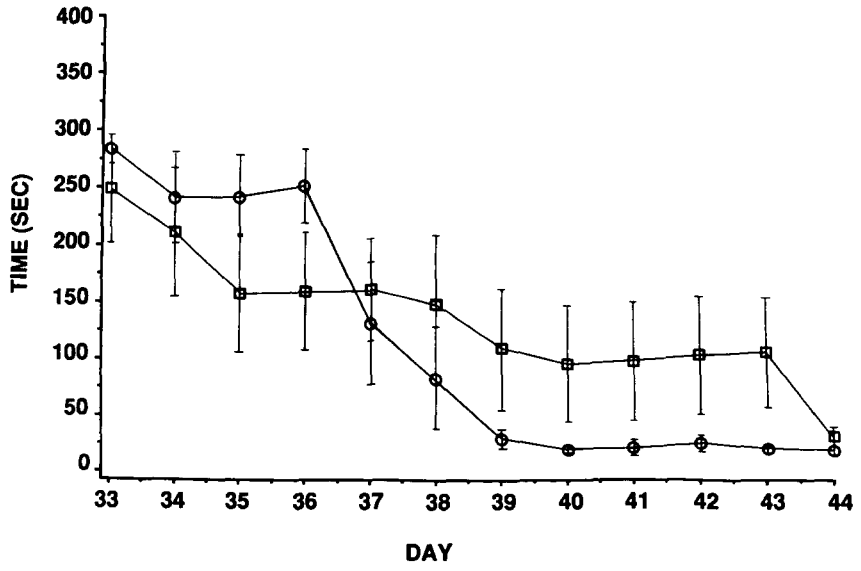

FIG. 4. Experiment 1, phase 3. Same animals and treatment as Fig. 3, but rats are learning a new maze, maze B.

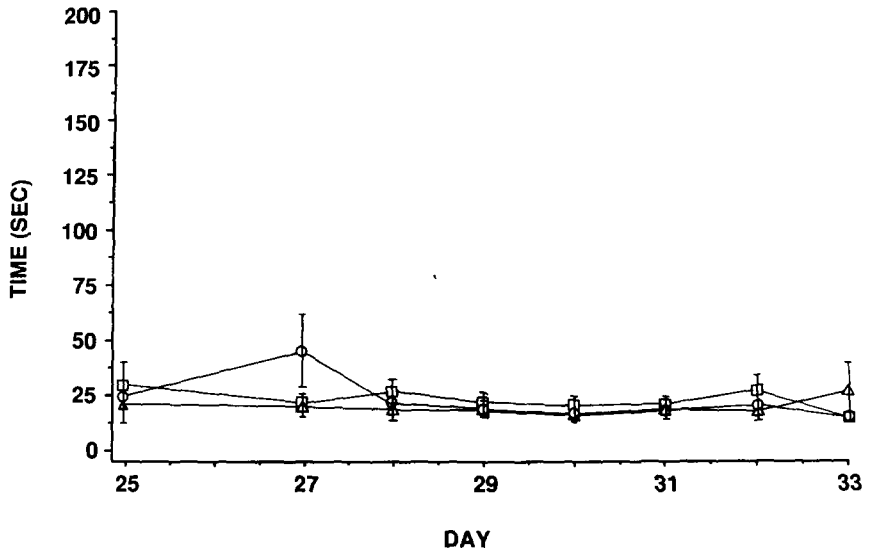

FIG. 5. Experiment 2. Effects of (+)-MK-801 (squares) vs. (−)-MK-801 (triangles) vs. saline-injected controls (circles) on swimming an already learned maze A (all 24 animals had learned maze A without any drug administration). Eight animals per group. Values represent the mean ± SEM. All drugs were injected IP 30 min prior to swim. MK-801 isomers were administered at 0.1 mg/kg.

ration, maze B, which is the exact reverse of maze A with the start located at the site of the maze A out-of-water-platform and the platform located at the maze A start.

Experiment 2

Twenty-four male Sprague-Dawley rats served as subjects. All 24 were first trained on maze A for 18 daily trials without any drug administration, and then given saline injections IP 30 min prior to maze testing for 3 days. Three groups of eight rats each were formed based upon the 3-day average maze time for the saline injection trials, such that group maze completion times each averaged approximately 25 seconds. Then one group received (+)-MK-801 (0.1 mg/kg), another group received (−)-MK-801 (0.1 mg/kg), and the third group received an equivalent

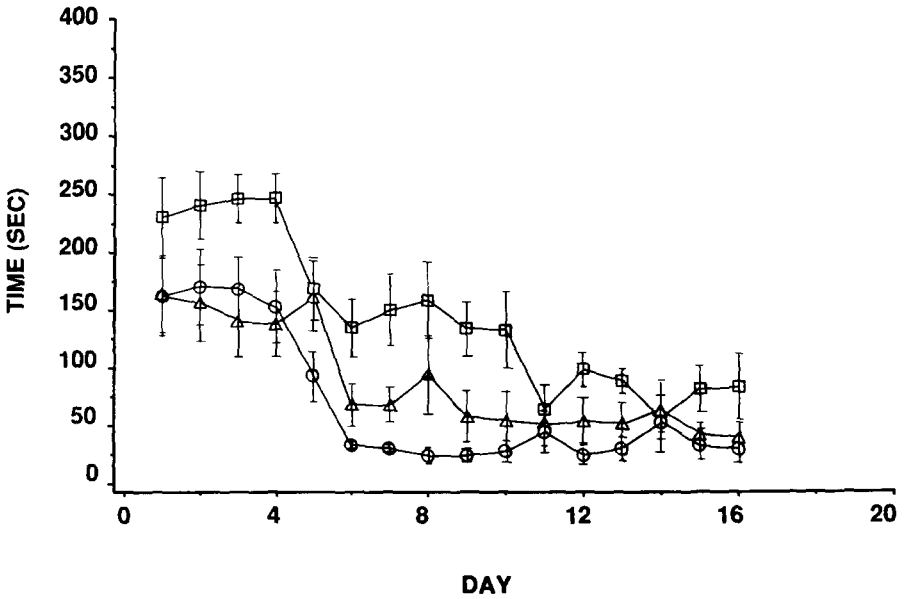

FIG. 6. Experiment 3, phase 1. Effects of (+)-MK-801 (squares) vs. (−)-MK-801 (triangles) vs. saline-injected controls (circles) on learning a new maze (A). Drug doses and timing are the same as for Experiment 2, but the animals are different. Both MK-801 groups have 8 animals per group. The saline group consisted of 7 animals. Values represent the mean ± SEM.

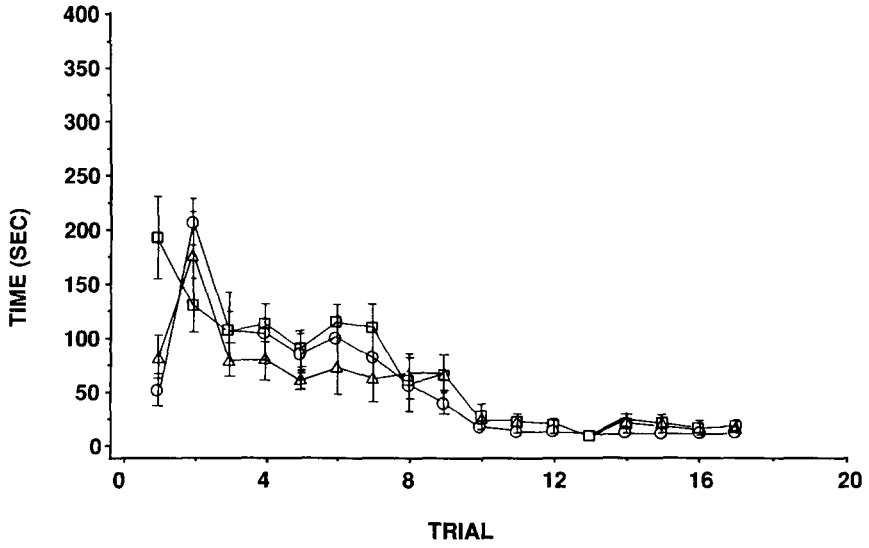

FIG. 7. Experiment 3, phase 2. All drugs were discontinued and animals from phase 1 (Fig. 6) were tested for learning a new maze (B).

volume of saline 30 min before daily retesting in maze A for 8 days.

Experiment 3

Twenty-four rats served as subjects. One group of 8 rats received (+)-MK-801 (0.1 mg/kg) 30 min prior to daily trials on maze A while a second group of 8 rats received (−)-MK-801 (0.1 mg/kg) and a third group received saline. Following 16 trials on maze A, the rats were trained on a new maze (B) without any drug administration.

Data Analysis

Data were analyzed by two-way analysis of variance (ANOVA) using BMDP software programs. Preselected follow-up comparisons were made using Student's *t*-test. Results were considered to be significant at $p<0.05$.

RESULTS

In these experiments, maze completion times and errors committed were similarly affected by all treatments and showed a similar learning curve over trials. Therefore, only the measurement of maze completion time will be presented in figures, but the statistical analyses for both the maze completion times and the errors will be presented.

Experiment 1: Effects of (+)-MK-801 on Learning and Memory

Animals given (+)-MK-801 in phase 1 took longer to complete the maze (Fig. 2) and made more errors (data not shown) than animals given saline. One saline animal never swam and was omitted from the analysis (this animal clung to the doorways). Two-way analysis of variance showed significant effects of trial, $F(22,480)=20.6$, $p<0.0001$, and treatment, $F(1,480)=18.4$, $p<0.0001$, as well as a significant trial × drug interaction, $F(22,480)=3.7$, $p<0.0001$, for maze completion time. Similar results were seen with respect to errors for the main effects of trial, $F(22,479)=11.96$, $p<0.0001$, and treatment, $F(1,479)=18.74$, $p<0.0001$, and their interaction, $F(22,479)=1.93$, $p<0.01$. Trial 10 was aborted due to a severe pool leak and data from this trial was not included in the data analysis. Interestingly, the effect of this "missed day" appeared to set back the learning of the MK-801 group, but not of the controls.

In phase 2 of this experiment, half of the saline treatment group from phase 1 continued to receive daily saline injections ($n=6$), while the other 5 animals were switched to daily MK-801 injections. In this testing of performance on a well-learned task, there were no significant performance differences between the saline/saline and saline/MK-801 groups for either maze completion time, $F(1,86)=1.16$, $p>0.05$, as shown in Fig. 3 or errors committed, $F(1,86)=1.00$, $p>0.05$ (data not shown).

In the third phase of testing, group treatments remained as in phase 2, but rats were challenged to learn a new maze (maze B, the reverse of maze A). As shown in Fig. 4, performance of the MK-801-treated animals was similar to that of controls for the first 5 trials; in fact, there was a tendency for the MK-801 animals to take less time for the first few trials, although this difference was not statistically significant. When data from all trials was analyzed there was a significant effect of MK-801 on errors, $F(1,130)=3.95$, $p<0.05$, but not time, $F(1,130)=1.1$, $p>0.05$. If only data from trials 37 to 44 are used for analysis, then MK-801 significantly increased both errors, $F(1,86)=15.7$, $p<0.001$, and maze completion time, $F(1,86)=11.0$, $p<0.01$.

Experiment 2: Effects of (+)-MK-801 vs. (−)-MK-801 on Performance of a Well-Learned Task

In the first phase of this second experiment, no drugs were given to the 24 rats learning maze A, and all rats learned the maze as shown by decreased time for maze completion and decreased errors over trials (data not shown). In a second phase, memory was then assessed by testing each rat on maze A 30 min following injection of (+)-MK-801, or (−)-MK-801 or saline for 8 daily trials. There were no significant effects of trial or drug treatment on this memory testing phase as shown in Fig. 5. Analysis of variance showed no effect of treatment group for

either time, $F(2,160)=0.59$, $p>0.05$, or errors, $F(2,160)=0.30$, $p>0.05$.

Experiment 3: Effects of (+)-MK-801 and (−)-MK-801 on Learning a New Maze

As shown in Fig. 6, both (+)-MK-801 and (−)-MK-801 impaired learning of maze A with (+)-MK-801 having a more pronounced effect. Two-way analysis of variance showed significant effects of trial and treatment group for both time, $F(2,336)=44.5$, $p<0.0001$, and errors, $F(2,336)=46.4$, $p<0.0001$. Follow-up comparisons by Student's t-test showed significant differences between either MK-801 treatment group vs. controls ($p<0.05$) for the variable time and a significant difference between the (+)-MK-801 group and control for the variable, errors ($p<0.05$). The comparison between (−)-MK-801 and controls was not statistically significant for errors ($p<0.10$).

When drug administration was discontinued and all rats were challenged to learn a different maze, no differences in learning speed were seen among the groups (Fig. 7).

DISCUSSION

MK-801 is a prototype of an exciting new group of potential therapeutic compounds acting via the NMDA receptor complex. Several beneficial uses for these types of drugs, including anticonvulsant, anti-ischemic, and neural protective effects of these compounds, have been demonstrated (4, 6, 9, 16, 18, 19). However, NMDA receptor antagonists have also been shown to have some undesirable properties. MK-801 and AP5, for example, have been reported to impair learning in various paradigms including the Morris water maze, the radial arm maze, and passive avoidance (3, 5, 8, 10, 14, 17, 22, 24, 25, 29). PCP, which binds to the ion channel associated with NMDA, has well-known psychotomimetic effects. MK-801 has also been shown to inhibit hippocampal long-term potentiation associated with learning (1, 7, 17). The purpose of the present report was to further explore and characterize the effects of MK-801 on learning and memory using a novel water maze characterized by our laboratory (11–13, 20, 21). Since the (+) and (−) isomers might have qualitative as well as quantitative differences with respect to effects on neural protection vs. effects on learning and memory, these isomers were compared in the present report.

In the first experiment, we found that (+)-MK-801 impaired learning a novel maze, but did not impair performance on the identical maze if MK-801 was first administered after the task was well learned. However, even in animals with experience with swimming a maze after receiving MK-801, performance on learning a new maze was impaired by MK-801 administration. These data suggest that animals do not become pharmacologically tolerant to MK-801 with respect to the effects on learning, at least not at these doses and with this dosing regimen. This is perhaps not surprising considering that rats given continuous exposure to the NMDA antagonist AP5 via an indwelling pump for more than 1 week still were measurably impaired in learning the Morris water maze (17). Other data suggest, however, that tolerance may develop to some of the ataxic effects of high doses of MK-801 (25). In addition, tolerance to the response rate decreasing effects of low doses of MK-801 on fixed interval schedules has been seen [Ray Genovese, Psychopharmacology (Berlin), in press].

In both the new maze learning phases, the difference between the MK-801-treated rats and controls was not apparent in the first 2 (phase 1) to 5 (phase 3) trials. This data coupled with the rapid, relatively error free performance of the MK-801-treated rats in swimming a well-learned maze in phase 2 suggests that the learning performance deficit that became apparent after the initial trials in phases 1 and 3 was not due to some motor coordination or sensory deficit. This is important to note since MK-801 has been reported to affect activity and gross motor coordination, although the reported dose threshold for these effects varies considerably (5, 15, 25, 29). In the present study, the MK-801 rats swam as well as controls, but did not appear to consolidate the information derived from each daily trial as efficiently as controls. They therefore took longer to learn the task. All animals did eventually learn, however. This "slowed" learning is similar to what has been reported using other learning tasks whenever the experiment has been carried out long enough for the MK-801 animals to eventually learn the task. In the olfactory discrimination task reported by Staubli et al., the MK-801 animals learned as well as controls when the task was "easier," i.e., the odors were strong and trials were separated by short intertrial intervals. When the task was more difficult (weaker odors and longer intertrial intervals), the MK-801-treated animals did not learn the olfactory discrimination as well. Thus it appears that MK-801 impairs but does not prevent learning when used at doses that do not cause gross motor and sensory deficits.

The second experiment compared the effects of the (+)- and (−)-MK-801 isomers on performance of a well-learned task. Again, in this experiment [as in the phase 2 of Experiment 1 with the (+) isomer only], these drugs had no significant effect on performance of a previously learned task.

In the third experiment, both (+)-MK-801 and (−)-MK-801 impaired performance on learning a new maze task. The effects of (+)-MK-801 were more pronounced and the (+)-MK-801-treated animals were significantly impaired as assessed by either time or errors. The (−) isomer impaired learning as well, but the effects were only significant for time to completion. After 16 trials, the (+)-treated animals were still markedly impaired compared to controls; in contrast, after 16 trials the performance of the (−)-treated rats was similar to controls. The (−)-MK-801 isomer, however, is not inactive, but simply less potent. These in vivo data support the in vitro binding studies which demonstrate that the (+)-MK-801 isomer is the more potent (26,27). However, since only one dose of each isomer was tested, it is possible that differences other than potency may exist between the isomers.

The effects of MK-801 do not appear to be long lasting, since rats previously given daily injections of MK-801 for 16 days had no difficulty learning a new maze when the drugs were not given.

Clearly, the major finding of this report supports the conclusions reached by other investigators using other behavioral paradigms including the Morris water maze. MK-801 impairs learning but not memory and the (+) isomer is the more active in this regard.

These findings may be relevant to the purported role of long term potentiation (LTP) in the learning process. Induction of LTP in the hippocampus CA1 pyramidal cell region appears to involve activation of the NMDA receptor. NMDA antagonists have been shown to block LTP in vitro and block learning in vivo (1, 7, 17).

Although these findings do demonstrate an undesirable effect of MK-801 on learning, the lack of effect on memory and the apparent ability of the rats to learn new mazes with no difficulty once the drug administration is discontinued suggest that the neural protectant properties of this drug may outweigh the possibly limited and short-lasting negative side effects of this compound.

REFERENCES

1. Abraham, W. C.; Mason, S. E. Effects of the NMDA receptor/channel antagonists CPP and MK-801 on hippocampal field potentials and long-term potentiation in anesthetized rats. Brain Res. 462: 40–46; 1988.
2. Artola, A.; Singer, W. Long-term potentiation and NMDA receptors in rat visual cortex. Nature 330:649–652; 1987.
3. Benvenga, M. J.; Spaulding, T. C. Amnesic effect of the novel anticonvulsant MK-801. Pharmacol. Biochem. Behav. 30:205–207; 1988.
4. Braitman, D. J.; Sparenborg, S. MK-801 protects against seizures induced by the cholinesterase inhibitor soman. Brain Res. Bull. 23: 145–148; 1989.
5. Butelman, E. R. A novel NMDA antagonist, MK-801, impairs performance in a hippocampal-dependent spatial learning task. Pharmacol. Biochem. Behav. 34:13–16; 1989.
6. Clineschmidt, B. V.; Martin, G. E.; Bunting, P. R. Anticonvulsant activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug Dev. Res. 2:123–134; 1982.
7. Coan, E. J.; Saywood, W.; Collingridge, G. L. MK-801 blocks NMDA receptor-mediated synaptic transmission and long term potentiation in rat hippocampal slices. Neurosci. Lett. 80:111–114; 1987.
8. Danysz, W.; Wroblewski, J. T.; Costa, E. Learning impairment in rats by N-methyl-D-aspartate receptor antagonists. Neuropharmacology 27:653–656; 1988.
9. Gill, R.; Woodruff, G. N. The neuroprotective actions of kyneuric acid and MK-801 in gerbils are synergistic and not related to hypothermia. Eur. J. Pharmacol. 176:143–149; 1990.
10. Heale, V.; Harley, C. MK-801 and AP5 impair acquisition, but not retention, of the Morris milk maze. Pharmacol. Biochem. Behav. 36:145–149; 1990.
11. Kant, G. J.; Yen, M.; D'Angelo, C. P.; Brown, A. J.; Eggleston, T. Maze performance: A direct comparison of food vs. water mazes. Pharmacol. Biochem. Behav. 31:487–491; 1988.
12. Kant, G. J.; D'Angelo, C. P.; Robinson, T. N., III; Wright, W. L.; Wingfield, C. P.; Rigamonti, D. D. Effects of MK-801 on learning and memory as assessed using a novel water maze. Soc. Neurosci. Abstr. 16:767; 1990.
13. Kant, G. J.; D'Angelo, C. P.; Brown, A. J.; Myatt, C.; Lewis, E.; Robinson, T.; Eggleston, T. Effects of psychoactive drugs on learning and memory as assessed using a novel water maze. Soc. Neurosci. Abstr. 15:1170; 1989.
14. McLamb, R. L.; Williams, L. R.; Nanry, K. P.; Wilson, W. A.; Tilson, H. A. MK-801 impedes the acquisition of a spatial memory task in rats. Pharmacol. Biochem. Behav. 37:41–45; 1990.
15. Marquis, K. L.; Paquette, N. C.; Gussio, R. P.; Moreton, J. E. Comparative electroencephalographic and behavioral effects of phencyclidine, (+)-SKF-10,047 and MK-801 in rats. J. Pharmacol. Exp. Ther. 251:1104–1112; 1989.
16. Martinez-Arizala, A.; Rigamonti, D. D.; Long, J. B.; Kraimer, J. M.; Holaday, J. W. Effects of NMDA receptor antagonists following spinal ischemia in the rabbit. Exp. Neurol. 108:232–240; 1990.
17. Morris, R. G. M.; Anderson, E.; Lynch, G. S.; Baudry, M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319: 774–776; 1986.
18. Morrisett, R. A.; Rezvani, A. H.; Overstreet, D.; Janowsky, D. S.; Wilson, W. A.; Swartzwelder, H. S. MK-801 potently inhibits alcohol withdrawal seizures in rats. Eur. J. Pharmacol. 176:103–105; 1990.
19. Papagapiou, M. P.; Auer, R. N. Regional neuroprotective effects of the NMDA receptor antagonist MK-801 (dizocilpine) in hypoglycemic brain damage. J. Cereb. Blood Flow Metab. 10:27–276; 1990.
20. Przybelski, R. J.; Kant, G. J.; Leu, J. R.; Bounds, M. J.; Winslow, R. M. Rat maze performance after infusion with cross-linked hemoglobin solution. Biomater. Artif. Cells Artif. Organs 17:583–596; 1989.
21. Przybelski, R. J.; Kant, G. J.; Bounds, M. J.; Slayter, M. V.; Winslow, R. M. Rat maze performance after resuscitation with cross-linked hemoglobin solution. J. Lab. Clin. Med. 115:579–588; 1990.
22. Staubli, U.; Thibault, O.; DiLorenzo, M.; Lynch, G. Antagonism of NMDA receptors impairs acquisition but not retention of olfactory memory. Behav. Neurosci. 103:54–60; 1989.
23. Tang, A. H.; Ho, P. M. Both competitive and non-competitive antagonists of N-methyl-D-aspartate acid disrupt brightness discrimination in rats. Eur. J. Pharmacol. 151:143–146; 1988.
24. Ward, L.; Mason, S. E.; Abraham, W. C. Effects of the NMDA antagonists CPP and MK-801 on radial arm maze performance in rats. Pharmacol. Biochem. Behav. 35:785–790; 1990.
25. Whishaw, I. Q.; Auer, R. N. Immediate and long-lasting effects of MK-801 on motor activity, spatial navigation in a swimming pool and EEG in the rat. Psychopharmacology (Berlin) 98:500–507; 1989.
26. Wong, E. H. F.; Kemp, J. A., Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83: 7104–7108; 1986.
27. Wong, E. H. F.; Woodruff, G. N. The identification of a novel binding site for the anticonvulsant, MK-801, in rat brain membranes. Br. J. Pharmacol. Proc. Suppl. 89:530P; 1986.
28. Woodruff, G. N.; Foster A. C.; Gill, R.; Kemp, J. A.; Wong, E. H. F.; Iversen, L. L. The interaction between MK-801 and receptors for N-methyl-D-aspartate: functional consequences. Neuropharmacology 26:903–909; 1987.
29. Wozniak, D. F.; Olney, J. W.; Kettinger, L., III; Price, M.; Miller, J. P. Behavioral effects of MK-801 in the rat. Psychopharmacology (Berlin) 101:47–56; 1990.