Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 4, pp. 935-940, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in the USA. All rights reserved
0091-3057/94 $6.00 + .00

0091-3057(94)E0057-O

Acute Behavioral Effects of MK-801 in Rhesus Monkeys: Assessment Using an Operant Test Battery

ELIZABETH A. BUFFALO,* MICHAEL P. GILLAM,* RICHARD R. ALLEN† AND MERLE G. PAULE*‡[1]

*Division of Neurotoxicology, and †Computer Based Systems, Inc., National Center for Toxicological Research, Jefferson, AR 72079-9502
‡Departments of Pharmacology and Toxicology, and Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR 72205

Received 30 July 1993

BUFFALO, E. A., M. P. GILLAM, R. R. ALLEN AND M. G. PAULE. *Acute behavioral effects of MK-801 in rhesus monkeys: Assessment using an operant test battery.* PHARMACOL BIOCHEM BEHAV **48**(4) 935-940, 1994.—The acute effects of MK-801, a selective, noncompetitive NMDA receptor antagonist, were assessed using an operant test battery (OTB) of complex food-reinforced tasks that are thought to depend upon relatively specific brain functions such as motivation to work for food (progressive ratio, PR), learning (incremental repeated acquisition, IRA), color and position discrimination (conditioned position responding, CPR), time estimation (temporal response differentiation, TRD), and short-term memory and attention (delayed matching-to-sample, DMTS). Endpoints included response rates (RR), accuracies (ACC), and percent task completed (PTC). MK-801 (0.003-0.075 mg/kg, IV), given 15 min pretesting, produced significant dose-dependent decreases in measures of IRA and TRD performance at doses ≥0.03 mg/kg. In both tasks, MK-801 produced significant decreases in accuracy at doses lower than those required to affect response rate. MK-801 also produced statistically significant decreases in PR, CPR, and DMTS measures, but only at higher doses (≥0.056 mg/kg) that caused significant decreases in both response rates and accuracies. These results indicate that, in monkeys, performance of operant tasks designed to model learning and time estimation is more sensitive to the disruptive effects of MK-801 than performance of tasks that model motivation, color, and position discrimination, and short-term memory and attention.

MK-801 *Macaca mulatta* Operant behavior Time estimation Incremental repeated acquisition Learning Color and position discrimination Temporal response differentiation Delayed matching-to-sample Short-term memory Motivation Attention Food reinforcement

(+)-5-METHYL-10,11-dihydro-5H-dibenzo-[a,d]cyclo-hepten-5,10-imine maleate (MK-801) is a selective, noncompetitive *N*-methyl-d-aspartate (NMDA) receptor antagonist that blocks NMDA-induced excitation by interacting with open ion channels linked to the NMDA receptor (3,7,17). The NMDA receptor has been shown to play a critical role in the induction of the phenomenon known as long-term potentiation (LTP) (2). This receptor mediates calcium influx across the postsynaptic membrane and it is this calcium influx that is believed to lead to the development of LTP. LTP has been described as a substantial increase in synaptic efficacy that can be induced by tetanic stimulation (3,26) and it is believed that the mechanisms involved in the induction and maintenance of LTP are fundamental to learning and memory processes (1). Therefore, we predicted that MK-801 (an LTP antagonist) would selectively impair performance in tasks that model learning and memory.

Some of the behavioral effects of MK-801 are qualitatively similar to those of PCP, ketamine, and other PCP-like compounds, with the most striking difference being the longer duration of action of MK-801 (25). In nonhuman primates, PCP and MK-801 induce similar effects such as calming, ataxia, salivation, and slight respiratory depression (27). Also, certain similarities in effects on cortical EEG have been ob-

[1] To whom requests for reprints should be addressed.

served (8). In studies of its discriminative stimulus properties, MK-801 has been shown to substitute completely for PCP (6). PCP acts on both NMDA and sigma opiate receptors, while MK-801 acts primarily at the NMDA receptor (7). Therefore, it would be useful to compare the effects of these drugs on monkey performance in the operant test battery (OTB) to provide information on the importance of the different receptors to specific OTB behaviors.

The purpose of this experiment was to detail the effects of MK-801 on performance of complex operant behaviors in rhesus monkeys and, thus, explore the role of the NMDA receptor (and possibly LTP) in the performance of tasks thought to model motivation to work for food, learning, color and position discrimination, time estimation, and short-term memory and attention. We have previously used behavior in the National Center for Toxicological Research (NCTR) OTB to evaluate the neurobehavioral effects of a variety of psychoactive drugs (4,5,11,15). Furthermore, Paule et al. (10,13,14) have used a modified version of the OTB to assess the performance of children and have found human and nonhuman primate performance to be remarkably similar. Thus, results obtained in the monkey model will likely have relevance for the effects of MK-801 and similar compounds in humans.

METHOD

Subjects

Seven male rhesus monkeys (*Macaca mulatta*) between 3 and 10 years of age and weighing from 4.5 to 10.0 kilograms at the beginning of the study served as subjects. All animals had previously been trained under the schedules in the OTB for at least 2 years and had been used in previous studies of acute drug effects (16,19–23). Animal housing, feeding, etc., were as described previously (12). Access to food (Purina Hi Protein Monkey Chow, Ralston Purina, St. Louis, MO) supplemented with fresh fruit and chewable multiple vitamins with iron (Arkansas Cooperative Assoc. Inc., North Little Rock, AR) given after daily behavior sessions was restricted such that animals gained approximately 0.05 to 0.10 kg/month. The monkeys were housed singly under a 12 L : 12 D cycle (lights on at 0600 h) with temperature and relative humidity of 25 ± 2°C and 50 ± 4%, respectively. Animal care and procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAA-LAC) guidelines and approved by the Institutional Care and Use Committee of the National Center for Toxicological Research.

Apparatus

The apparatus have been described in detail elsewhere (18) and consisted of portable primate restraint chairs, sound-attenuated behavioral chambers, operant panels, and computer consoles. The operant panels were equipped with three rear-projection press plates, four retractable levers, six serial position indicator lights, and correct and incorrect response indicator lights. The press plates, levers, and indicator lights were aligned horizontally, with the press plates and serial position indicator lights located above the levers. Symbols and/or colors were projected onto the press plates from the rear and, when pressed, each press plate and lever effected a switch closure. Serial position and correct and incorrect indicator lights were illuminated from behind the panel with various colors. A trough for reinforcement (190 mg banana-flavored food pellet) delivery was centered below the levers.

Operant Schedules

The use and description of the tasks contained in the OTB have been reported in detail and a diagram of the behavioral test panel has been published elsewhere (18). A brief description of each task follows.

Progressive ratio (PR). For the PR task, only the far right lever was used. Subjects were required to increase the number of lever presses for each subsequent reinforcement. Initially, three to eight lever presses (depending upon the individual monkey but the same for each subject every test session throughout this study) resulted in reinforcement delivery. The number of responses required for the next reinforcement was increased by the initial number of lever presses required for the first reinforcement. Thus, if three lever presses were required for the initial reinforcement, six lever presses were required for the next, then nine, 12, etc. These initial ratios were chosen such that marked periods of pausing or cessation of responding generally occurred during each baseline or vehicle PR session.

Incremental repeated acquisition (IRA). The IRA task used all four response levers and required subjects to learn a new sequence of lever presses each test session. IRA began with the presentation of a one-lever response sequence (IRA1). Each response on the correct lever resulted in reinforcement delivery and after 20 correct responses (criterion performance), a 1 min timeout period was followed by the presentation of an incremented two-lever sequence (IRA2), such that a response on a different lever was required before a response on the original correct lever produced food. After the 20th errorless two-lever sequence (i.e., no errors made between the first and last correct lever press of the required sequence), the task was incremented to a three-lever sequence and so on, up to six-lever sequences or until the task time ended. The serial position indicator lights signaled position in the response sequence from left to right, indicating the remaining number of correct responses necessary for reinforcement delivery. Incorrect responses were followed by a 2-s timeout (incorrect response light indicator on) but did not reset the response requirement; thus, error correction was permitted. Correct responses were followed by illumination of the next rightmost serial position indicator light and the final correct response in a sequence was followed by a 1-s timeout, during which the correct response indicator light was illuminated.

Conditioned position responding (CPR). For the CPR task, only the three press plates were used. At the start of each trial, the center plate was illuminated with either a solid red, yellow, blue, or green color (side press plates were dark). Subjects continued each trial by making an observing response (a press) to the center plate, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate color had been either blue or green, a response to the right press plate resulted in reinforcement delivery. If the center press plate had been either red or yellow, a response to the left press plate resulted in reinforcement delivery. Responding to the incorrect position initiated a 10-s timeout period followed by the initiation of a new trial. The sequence of color presentation was random.

Temporal response differentiation (TRD). For the TRD task, only the far left retractable lever was extended. Subjects were required to hold the lever in the depressed position for a minimum of 10 s but no longer than 14 s. Releasing the lever within this 4-s window resulted in reinforcement delivery. Releasing the lever too early or too late had no programmed consequences and the monkey could immediately start another trial.

Delayed matching-to-sample (DMTS). For the DMTS task, only the three press plate manipulanda were used. At the start of each trial, one of seven white-on-black geometric symbols (the sample) was randomly projected onto the center plate (side press plates were dark). To continue the trial, each monkey was required to make an observing response (a press to the sample on the center plate). After the observing response was made, the center plate was extinguished for one of six time delays presented pseudorandomly (2, 8, 16, 32, 48, or 64 s). After each time delay, all three plates were illuminated, each with a different symbol, only one of which matched the sample. A response to the match resulted in reinforcement delivery and initiation of a new trial with another sample stimulus (presented randomly). A nonmatching response was followed by a 10-s timeout period (all press plates darkened) and then initiation of a new trial.

Behavioral Testing Procedure

Behavioral test sessions were conducted daily (Monday-Friday), and lasted approximately 50 min. Monkeys were rotated through nine identical behavior chambers such that, generally, no monkey was placed in the same chamber for 2 consecutive test days. Behavioral schedules alternated daily. For example, PR (10 min), IRA (35 min), and CPR (5 min) were presented on one test day; TRD (20 min) and DMTS (30 min) were presented the next test day.

Drugs and Dosing Procedure

MK-801 (Research Biochemicals Incorporated, Natick, MA) was dissolved in sterile bacteriostatic (0.9% benzyl alcohol) saline (Elkins-Sinn Inc., Cherry Hill, NJ) such that the final injection volume was 0.1 ml/kg. Doses of MK-801 were administered IV in a semirandomized order. MK-801 injections were given on Tuesdays and/or Fridays while saline injections were given on Tuesdays, Thursdays, and/or Fridays. Mondays and Wednesdays served as noninjected baseline days. Due to the daily alternation of the presentation of the behavioral tasks, all doses were given twice to provide dose-response data for each set. Approximately 15 min following injections, subjects were placed into operant chambers and behavioral sessions began 1 min later.

Data Analysis

The endpoints measured in each task have been described in detail elsewhere (4,18–20). Two fundamental measures were monitored for each task: percent task completed and response rate and/or latency. Accuracy data are used in all except the PR task (no errors possible). Percent task completed data are measures of a predetermined criteria of performance (i.e., completing 60 or 120 correct trials would represent 100% task completed for the CPR and the DMTS tasks, respectively) and are functions of both response rates and accuracies. Percent task completed values are calculated by dividing the total number of reinforcements earned by the total number of reinforcements possible for a given task and multiplying this quotient by 100. The percent task completed endpoint is a convenient and comprehensive measure showing intraanimal stability and is useful for comparing drug effects on performance across tasks. For the TRD task, the mean duration of lever holds and the frequency of lever hold durations were also monitored. For the PR task, the breakpoint (number of lever presses made for the last reinforcement earned) was also measured. The interresponse times (calculated from press to press) were measured in the CPR and PR tasks. For the IRA task, between-sequence errors (incorrect presses before a correct response on the first lever of a sequence) and within-sequence errors (incorrect responses made between the first correct response of a sequence and reinforcement) were measured.

TABLE 1

SUMMARY OF EFFECTS OF MK-801 ON OTB RESPONDING

Task	Endpoint	0.003 mg/kg	0.01 mg/kg	0.03 mg/kg	0.056 mg/kg	0.075 mg/kg
Color and position discrimination	Percent Task Completed	–	–	–	*	*
	Response Rate	–	–	–	*	*
	Observing Response Latency	–	–	–	*	*
	Choice Response Latency	–	–	–	–	*
	Accuracy	–	–	–	*	*
Learning	Percent Task Completed	–	–	*	*	*
	Response Rate	–	–	–	*	*
	Accuracy	–	–	*	*	*
Short-term memory	Percent Task Completed	–	–	–	*	*
	Response Rate	–	–	*	*	*
	Observing Response Latency	–	–	–	*	*
	Choice Response Latency	–	–	–	–	*
	Accuracy	–	–	–	*	*
Motivation	Percent Task Completed	–	–	–	*	*
	Breakpoint	–	–	–	*	*
Time estimation	Percent Task Completed	–	–	*	*	*
	Response Rate	*	–	–	–	–
	Accuracy	–	–	*	*	*
	Average Hold	–	–	–	*	–

*Indicates significant difference from saline (control) data. For the short-term memory task and the learning task, all end-points except percent task completed are combined across delays or components, respectively.

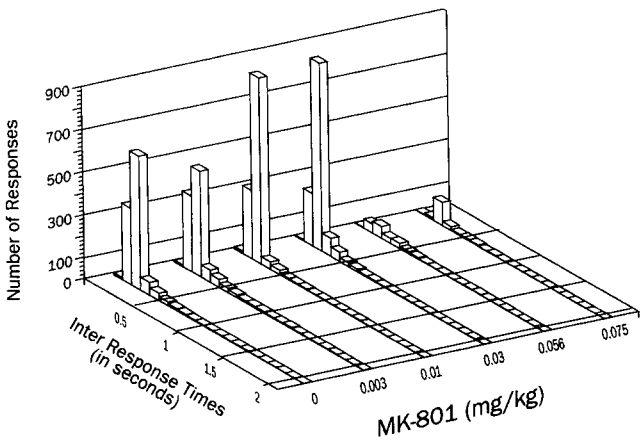

FIG. 1. Effects of MK-801 on PR interresponse times, 0.0 mg/kg, n = 4–7 obs/6 animals; 0.003 mg/kg, n = 5; 0.010 mg/kg, n = 7; 0.030 mg/kg, n = 9; 0.056 mg/kg, n = 4; 0.075 mg/kg, n = 5. The ordinate is the number of occurrences of the indicated interresponse times.

Statistical Analysis

Only those monkeys exhibiting stable performance (standard deviations of percent task completed values after saline injections were less than 15% of mean PTCs) were included in the statistical analyses. For an individual data session to be included in the TRD and CPR accuracy analyses, the monkey must have completed a minimum of three trials. For inclusion in the DMTS and IRA accuracy analyses, a minimum of 10 trials must have been completed. For each behavioral endpoint in each task, the overall effect of drug treatment on performance was determined using a one-way repeated measures analysis of variance (ANOVA). If overall significance was evident ($p \leq 0.05$), then performance at each dose was compared to saline control performance using a Bonferroni correction (9).

RESULTS

Overall Effect of Saline Vehicle

Saline vehicle injections produced no statistically significant effects on any measures when compared to noninjected baseline data.

Progressive Ratio (PR)

MK-801 produced dose-dependent decreases in PR percent task completed, breakpoint, and response rate (Table 1) with significant effects at doses ≥0.056 mg/kg. At the low doses (0.003, 0.01, and 0.03), MK-801 increased the interresponse times (Fig. 1).

Incremental Repeated Acquisition (IRA)

MK-801 produced a significant disruption in IRA percent task completed at doses ≥0.03 mg/kg (Table 1). Accuracy was significantly decreased at these doses, while response rate was not significantly decreased at doses <0.056 mg/kg (Table 1). Learning curves for IRA2 (number of errors made during acquisition of the correct sequence) are shown in Fig. 2 where it can be seen that at ≥0.03 mg/kg errors were generally above the 95% confidence interval for control data. For two-lever sequences (IRA2), MK-801 decreased error commission at the low doses of 0.003 and 0.010 mg/kg; errors at these doses were generally below the 95% confidence interval for control data (Fig. 2). Similar findings were noted for all IRA components at the 0.01 mg/kg dose only.

Conditioned Position Responding (CPR)

MK-801 produced dose-dependent decreases in CPR percent task completed, response rate, and accuracy with significant effects noted at doses ≥0.056 mg/kg (Table 1).

Temporal Response Differentiation (TRD)

MK-801 produced significant dose-dependent decreases in TRD percent task completed and accuracy (Table 1) at doses ≥0.03 mg/kg. TRD response rate was significantly decreased at ≥0.056 mg/kg (Table 1). At 0.056 mg/kg, the mean duration that the subjects held the lever in the depressed position was significantly decreased and at 0.075, the animals did not respond (Fig. 3).

Delayed Matching-to-Sample (DMTS)

MK-801 significantly disrupted DMTS percent task completed and accuracy (Table 1) at doses ≥0.056 mg/kg. Re-

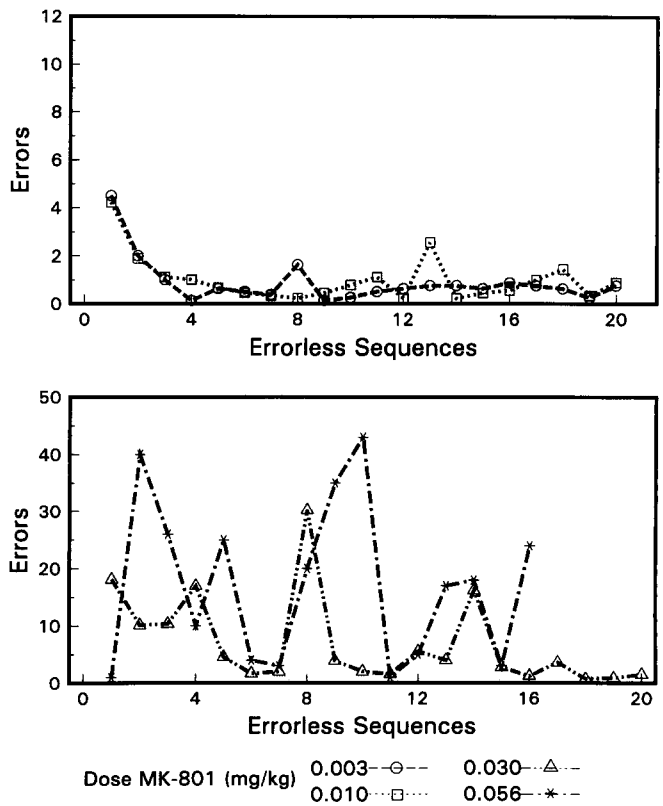

FIG. 2. Effects of MK-801 on learning curves for IRA at level 2, control, n = 4–7 obs/6 animals; 0.003 mg/kg, n = 8; 0.010 mg/kg, n = 9; 0.030 mg/kg, n = 9; 0.056 mg/kg, n = 1; 0.075 mg/kg, n = 3. Shaded area represents the 95% confidence interval for control data. Each point represents the mean total errors committed for completion of each of the 20 errorless sequences.

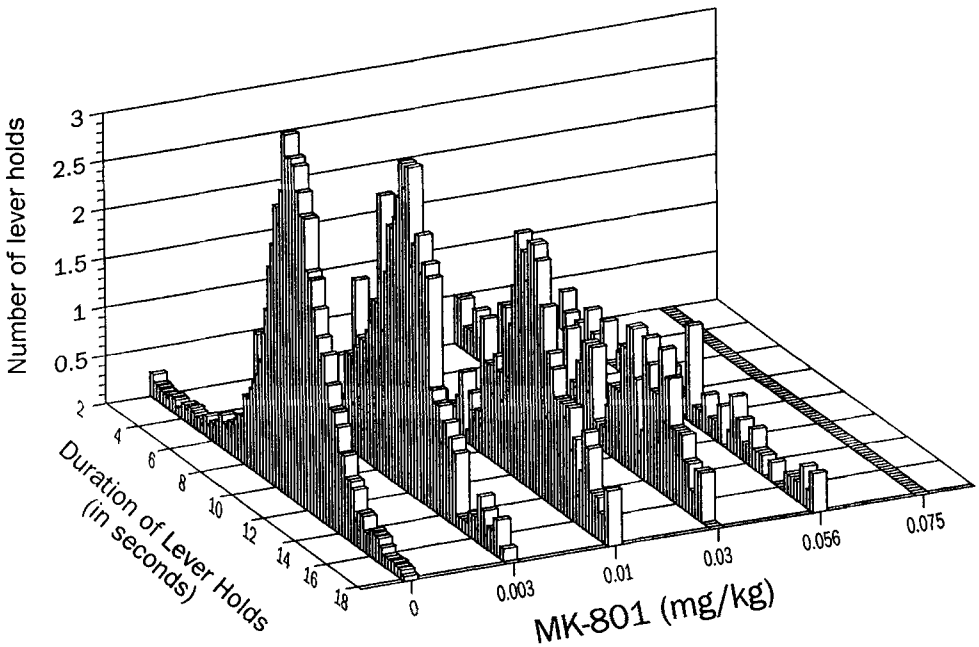

FIG. 3. Effects of MK-801 on lever hold duration for the TRD task, 0.0 mg/kg, n = 4–7 obs/6 animals; 0.003 mg/kg, n = 8; 0.010 mg/kg, n = 7; 0.03 mg/kg, n = 4; 0.056 mg/kg, n = 5; 0.075 mg/kg, n = 1. Shown is the frequency of lever holds of the indicated durations.

sponse rate (Table 1) was affected at doses >0.03 mg/kg. The effects on accuracy, however, were not delay-dependent and, thus, did not appear to be selective for short-term memory processes (Fig. 4).

Task Comparison

Table 1 summarizes of the effects of MK-801 on OTB responding. Significant deficits in performance are first noted at 0.03 mg/kg in the IRA, MTS, and TRD tasks. A significant enhancement was found in TRD response rate at 0.003 mg/kg; however, this was caused by the unusual performance of one animal on one test day. Asterisks indicate significant difference from vehicle controls determined by Bonferroni's t-test ($p < 0.05$).

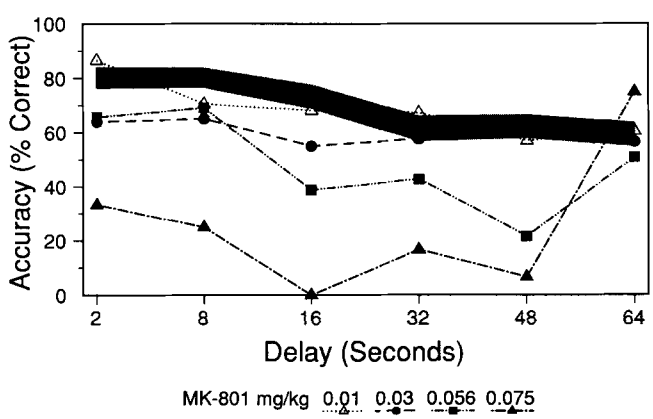

FIG. 4. Effects of MK-801 on forgetting (DMTS decay curve), control, n = 4–7 obs/6 animals; 0.010 mg/kg, n = 6; 0.030 mg/kg, n = 6; 0.056 mg/kg, n = 4; 0.075 mg/kg, n = 3. Shaded area represents the 95% confidence interval for control data. Each point represents the mean percent accuracy at each recall delay.

DISCUSSION

MK-801 altered rhesus monkey performance in the behaviors contained in the NCTR operant test battery by producing a selective disruption of accuracy in the learning (IRA) and time estimation (TRD) tasks at a dose (0.03 mg/kg) that did not affect response rates. Performance in the short-term memory (DMTS), color and position discrimination (CPR), and motivation (PR) tasks was generally unaffected at this dose.

Based upon the hypothesis that the NMDA-receptor complex is involved in and/or necessary for the induction of Long-Term Potentiation (LTP) and that LTP is involved in learning and memory processes, we predicted that MK-801 (an LTP antagonist) would selectively impair performance in those tasks that model learning and short-term memory. This prediction was not totally supported by our findings. Likewise, it was predicted that those OTB behaviors supported most by the induction of LTP (or at least tonic activity at NMDA receptors) would be identified as those that were the most sensitive to disruption by MK-801.

We found the learning (IRA) task more sensitive to disruption by MK-801 than the short-term memory (DMTS) task. These findings parallel those from other studies that have shown that NMDA antagonists selectively disrupt acquisition or consolidation of new information. It has been reported that an intoxicating dose (0.2 mg/kg) of MK-801 was required to disrupt performance of a memory task in a radial arm maze in rats previously trained in the task. However, a nonintoxicating dose (0.1 mg/kg) disrupted the acquisition of new information (28). Others have reported that MK-801 impaired the acquisi-

tion of both working and reference memory in naive rats, but did not affect the performance of either memory type in rats previously trained in a radial maze task (24).

In comparing the effects of MK-801 reported here to those of PCP obtained previously [in (12)], we find that these drugs have different behavioral profiles. The learning (IRA) and time estimation tasks (TRD) were the most sensitive to disruption by both PCP and MK-801. However, the motivation task (PR) was equally sensitive to PCP while it was less sensitive to MK-801. These data would suggest that performance in the PR task is disrupted by PCPs action at sigma opiate receptors, while disruption of performance in the IRA and TRD tasks is caused by NMDA antagonism. PCP also blocks dopamine uptake at the doses tested while MK-801 does not. Therefore, dopaminergic stimulation could explain the differences in task sensitivity.

The evidence from the present experiment supports the hypothesis that the NMDA-receptor complex (and, thus, possibly the phenomenon of LTP) is more important to those processes subserving the functions of learning (IRA) and time estimation (TRD) than those subserving short-term memory and attention (DMTS), color and position discrimination (CPR), and motivation to work for food (PR).

ACKNOWLEDGEMENTS

The authors wish to thank Eric Allen and Kat Wheeler for their outstanding graphics assistance and the NCTR primate husbandry crew: Betty White, Randy Thompson, James Henderson, Josephine Watson, O. T. Watson, Arnold Tripp, Henry Baughman, and Rodney Hogan for their excellent maintenance and handling of the animals. Part of this work was completed by E. A. Buffalo during ORISE and NCTR-sponsored summer internships.

REFERENCES

1. Carlson, N. R. Physiology of behavior. Boston: Allyn and Bacon; 1991:Chapt. 15.
2. Collingridge, G. L.; Kehl, S. J.; McLennan, H. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. J. Physiol. 334: 33–46; 1983.
3. Collingridge, G. L.; Lester, R. A. J. Excitatory amino acid receptors in the vertebrate central nervous system. Pharmacol. Rev. 40:143–210; 1989.
4. Ferguson, S. A.; Paule, M. G. Acute effects of chlorpromazine in a monkey operant behavior test battery. Pharmacol. Biochem. Behav. 42:333–341; 1991.
5. Ferguson, S. A.; Paule, M. G. Acute effects of pentobarbital in a monkey operant behavioral test battery. Pharmacol. Biochem. Behav. 45:107–116; 1993.
6. Koek, W.; Colpaert, F. C. Selective blockade of *N*-methyl-D-aspartate (NMDA) induced convulsions by NMDA antagonists and putative glycine antagonists: Relationship with phencyclidine-like behavioral effects. J. Pharmacol. Exp. Ther. 252:349–357; 1990.
7. Lodge, D.; Johnson, K. M. Noncompetitive excitatory amino acid receptor antagonists. Trends Pharmacol. Sci. 11:81–86; 1990.
8. 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.
9. Miller, R. G. Simultaneous statistical inference. New York: McGraw Hill; 1966.
10. Paule, M. G.; Cranmer, J. M.; Wilkins, J. D.; Stern, H. P.; Hoffman, E. L. Quantitation of complex brain function in children: Preliminary evaluation using a nonhuman primate behavioral test battery. Neurotoxicology 9(3):367–378; 1988.
11. Paule, M. G.; Schulze, G. E.; Slikker, W., Jr. Complex brain function in monkeys as a baseline for studying the effects of exogenous compounds. Neurotoxicology 9:463–472; 1988.
12. Paule, M. G.; Allen, R. R.; Gillam, M. P. The effects of phencyclidine (PCP) on rhesus monkey performance in an operant test battery (OTB). Psychopharmacology (Berlin) 101:42; 1990.
13. Paule, M. G.; Cranmer, J. M. Complex brain function in children as measured in the NCTR monkey operant test battery. In: Johnson, B. L., ed. Advances in neurobehavioral toxicology: Applications in environmental and occupational health. Chelsea: Lewis Publishers; 1990:433–447.
14. Paule, M. G.; Forrester, T. M.; Maher, M. A.; Cranmer, J. M.; Allen, R. R. Monkey vs. human performance in the NCTR operant test battery. Neurotox. Teratol. 12:503–507; 1990.
15. Paule, M. G.; Gillam, M. P. Effects of physostigmine on rhesus monkey performance in an operant test battery (OTB). Toxicologist 11(1):164; 1991.
16. Paule, M. G.; Allen, R. R.; Bailey, J. R.; Scallet, A. C.; Ali, S. F.; Brown, R. M.; Slikker, W., Jr. Chronic marijuana smoke exposure in the rhesus monkey II: Effects on progressive ratio and conditioned position responding. J. Pharmacol. Exp. Ther. 260(1):210–222; 1992.
17. Robinson, G. S., Jr.; Crooks, G. B., Jr.; Shinkman, P. G.; Gallagher, M. Behavioral effects of MK-801 mimic deficits associated with hippocampal damage. Psychobiology 17(2):156–164; 1989.
18. Schulze, G. E.; McMillan, D. E.; Bailey, J. R.; Scallet, A. C.; Ali, S. F.; Slikker, W., Jr.; Paule, M. G. Acute effects of delta-9-tetrahydrocannabinol (THC) in rhesus monkeys as measured by performance in a battery of complex operant tests. J. Pharmacol. Exp. Ther. 245:178–186; 1988.
19. Schulze, G. E.; McMillan, D. E.; Bailey, J. R.; Scallet, A. C.; Ali, S. F.; Slikker, W., Jr.; Paule, M. G. Acute effects of marijuana smoke in rhesus monkeys as measured by performance in a battery of complex operant tests. Life Sci. 45:465–175; 1989.
20. Schulze, G. E.; Slikker, W., Jr.; Paule, M. G. Multiple behavioral effects of diazepam in rhesus monkeys. Pharmacol. Biochem. Behav. 34:29–35; 1989.
21. Schulze, G. E.; Paule, M. G. Acute effects of *d*-Amphetamine in a monkey operant behavioral test battery. Pharmacol. Biochem. Behav. 35:759–65; 1990.
22. Schulze, G. E.; Paule, M. G. Effects of morphine sulfate on operant behavior in rhesus monkeys. Pharmacol. Biochem. Behav. 38:77–83; 1991.
23. Schulze, G. E.; Gillam, M. P.; Paule, M. G. Effects of atropine on operant test battery performance in rhesus monkeys. Life Sci. 51(7):487–497; 1992.
24. Shapiro, M. L.; Caramanos, Z. NMDA antagonist MK-801 impairs acquisition but not performance of spatial working memory. Psychobiology 18(2):231–243; 1990.
25. Sircar, R.; Rappaport, M.; Nichtenhauser, R.; Zukin, S.R. The novel anticonvulsant MK-801: A potent and specific ligand of the brain phencyclidine/sigma receptor. Brain Res. 435:235–240; 1987.
26. Tomita, J.; Shibata, Y.; Sakurai, T.; Okada, Y. Involvement of a protein kinase C-dependent process in long-term potentiation formation in guinea pig superior colliculus slices. Brain Res. 536: 146–152; 1990.
27. Willetts, J.; Balster, R. L.; Leander, J. D. The behavioral pharmacology of NMDA receptor antagonists. Trends Pharamcol. Sci. 11:423–428; 1990.
28. 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.