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Effects of the NMDA Antagonists CPP and MK-801 on Radial Arm Maze Performance in Rats

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WARD, L., S. E. MASON AND W. C. ABRAHAM. *Effects of the NMDA antagonists CPP and MK-801 on radial arm maze performance in rats.* PHARMACOL BIOCHEM BEHAV **35**(4) 785–790, 1990.—The dose- and time-dependent effects of N-methyl-D-aspartate receptor/channel antagonists on radial 8-arm maze performance were examined in rats. Both CPP (1.0–30 mg/kg), a competitive NMDA antagonist, and MK-801 (0.1–1.0 mg/kg), a noncompetitive NMDA antagonist, produced dose-dependent increases in the number of errors made to sample all 8 baited arms. The effective doses of both drugs produced maximal performance impairments 2 hr after IP injection, and no effects after 24 hr. In a second radial arm maze task where only 4 arms were baited, CPP (10 mg/kg) had a somewhat greater effect on the number of working memory errors than on reference memory errors. MK-801 (0.1, 0.33 mg/kg) had no effects on either this task or on a task involving a 1-hr delay between correct choices 4 and 5 on the 8 choice task. CPP (10 mg/kg), however, impaired performance on this latter task. These results indicate that doses of NMDA antagonists, sufficient to block hippocampal long-term potentiation, also disrupt radial arm maze performance.

Hippocampus N-Methyl-D-aspartate Spatial memory Radial arm maze Long-term potentiation CPP MK-801

THE N-methyl-D-aspartate (NMDA) subclass of glutamate receptor has been shown to be critically involved in various types of synaptic plasticity including long-term potentiation (LTP) in the hippocampus (5,6), enhanced synaptic transmission in the visual cortex (3,12), the kindling model of epilepsy (16,23) and vestibular compensation after unilateral labyrinthectomy (24). These data are suggestive of a role for NMDA receptors in the learning and retention of behavioral tasks, insofar as these experimental phenomena represent neural changes that normally mediate the behavioral adaptation of an organism to its changing environment.

One way to address the extent to which these experimental models of plasticity, and NMDA receptors generally, participate in normal learning and/or memory is to test various NMDA antagonists on task performance, and to compare any dose-dependent effects on behaviour with those on neural plasticity. It has been shown, for instance, that intraventricular or intrahippocampal 2-amino-5-phosphonovalerate (APV, a competitive NMDA antagonist) impaired performance on a Morris water maze task, at doses that also blocked LTP in the dentate gyrus of the hippocampus (17,19). Visual discrimination learning, on the other hand, was unimpaired. These data raise the possibility that the behavioral effects of APV may be at least in part the result of a block of LTP in the hippocampus, since a similar dissociation of effects on task performance occurs with hippocampal lesions (18,20).

In the present study, we tested systemic injections of a competitive NMDA antagonist [3-3(2-carboxypiperazine-4-yl-propyl-1-phosphonic acid, CPP] and a noncompetitive NMDA antagonist [(+)-5-methyl-10,11-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate, MK-801], on performance by rats on a radial 8-arm maze. The radial maze, like the Morris water maze, is considered a spatial task in that it is solved largely on the basis of a mix of extramaze cues, and performance on this task is rather sensitive to hippocampal lesions (21). As we have already tested the dose effectiveness of the above compounds systemically applied [both are known to cross the blood-brain barrier (9,14)] on LTP in the dentate gyrus in vivo (2), we were able to test for drug effects on maze performance using doses with known effects on LTP.

METHOD

Subjects

The animals used in this study were male Sprague-Dawley rats (220–300 g at beginning of training), maintained in individual cages with a 12-hr light-dark cycle. Prior to any behavioral testing, the rats were gradually reduced over a 2-week period to 85% of their free-feeding weight, and then kept on a restricted diet (food was freely available for two hours daily) for the rest of the experiment. Water was available ad lib in the home cage.

Apparatus

The apparatus was an elevated radial 8-arm maze made of clear Plexiglas. The arms were 9 cm wide and extended 68 cm beyond the 33 cm diameter center. A 6 cm edge ran around the entire ap-

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paratus. At the end of each arm there was a food cup to hold the bait, which was either a single 45 mg Noyes pellet early in the study, or a single Kellogg Cocoa Puff in the later experiments. The entire maze was elevated 53 cm above the floor. Behavioral testing was conducted in the animal vivarium, with a variety of extramaze cues surrounding the maze.

Behavioral Training

The rats were shaped over a 2-week period to run to the end of the arms and consume the bait. The bait was initially available throughout the maze, but gradually was restricted to the food wells. For the next 2–4 weeks, 1–2 training trials were given per day wherein the bait in the wells was not replaced. The trial continued until all bait had been located and consumed. The rats were trained until they had made 7/8 correct arm entries (i.e., entering arms not previously chosen on that particular trial) on 4 consecutive training trials. In Experiment 1, performance was then tested on this standard maze task at various times after various doses of either CPP or MK-801, as described below.

The rats used in Experiments 2 and 3 were given pretraining additional to that for Experiment 1. In Experiment 2 they were trained on a working memory/reference memory task, wherein the same 4 arms were baited on each training trial. The other 4 arms were never baited. The animals were trained to a criterion of making the 4 correct arm entries in 5 choices for 4/5 consecutive trials. Learning this procedure took 2–6 weeks. In Experiment 3 they were trained on a task involving a delay after sampling 4 baited arms, imposed by removing the rat from the maze and placing him back in his home cage for 1 hr. Training continued to a criterion of choosing the remaining 4 baited arms within the first 5 choices after the delay, for 4/5 consecutive trials. Learning this procedure required 2–3 weeks of training.

Drug Administration

The drugs used in this study were CPP (Tocris Neuramin; 0.33, 1, 3.3, 10, 30 mg/kg in a 0.9% saline vehicle) and MK-801 (donated by Merck Sharp and Dohme; 0.1, 0.33, 0.5, 1.0 mg/kg in distilled water vehicle). Both drugs and vehicle solutions were injected IP, in a volume of 3 ml/kg, with the experimenter blind to the drug dose during testing.

In Experiment 1, 9 rats were given each of the various doses of CPP. One month following the final CPP administration, these same 9 rats plus 3 others began testing with MK-801. Behavioral testing was done daily, with injections being given on alternate days. For the CPP study, behavioral testing occurred 30 min, 2 hr and 6 hr following the drug or vehicle injection. Testing occurred only once on the following day when no injection was given, with the exception that no rat was run on the day following saline injection. The 9 rats tested were divided into 3 groups of 3 rats, each group receiving a different order of the drug doses and saline. The experimental protocol was similar for MK-801 testing, except that the 30-min condition was not run.

In Experiments 2 and 3, new groups of 6 rats each were used. These were also run on consecutive days, with injections being given on alternate days for the delayed spatial task (Experiment 2) and on every third day on the working/reference memory task (Experiment 3). For each task the rats were divided into two groups of three, one group being given an ascending series of drug doses, and one given a descending series (vehicle solutions were treated as dose 0). In both tasks, all doses of CPP were given before testing with MK-801 was begun one week later. CPP and MK-801 were administered 2 hr prior to behavioral testing.

Data Analysis

Both error and running time data were collected and collapsed across the order of drug administration. To enable the use of parametric statistics on the error data which were skewed due to a performance ceiling, the error data were ranked and then subjected to analysis of variance (ANOVA, using the GENSTAT and SAS statistical packages), according to the method of Conover and Iman (7). The time data were also skewed and therefore normalized by a log-transformation, and then analyzed by ANOVA.

RESULTS

General Behavioral Effects of Systemically Administered NMDA Antagonists

At the highest doses CPP (30 mg/kg) and MK-801 (1 mg/kg) produced a similar profile of overt behavioral symptoms. These included hyperexcitability to environmental stimuli, ataxia and motor incoordination, behavioral activation when placed on the maze, and stereotyped behavior. This last symptom was usually evidenced as a continual running between 2 arms of the maze, generally ones that were opposite to each other. When showing this behavior, the rats would not necessarily consume the food it came upon. In some extreme cases, they would not stop at the end of the maze but would continue off the end of an arm onto the floor. Data was discarded on those trials where the rats did not eat the food or did not remain on the maze throughout the session.

Experiment 1: CPP Effects on Standard Maze Performance

To determine the effects of CPP on standard radial maze performance, measures were made of the number of errors in the first 8 choices and the total number of errors before all arms were sampled. The time to make the first 8 choices was also recorded to see if changes in motor performance were correlated with changes in memory performance.

A two-way ANOVA with repeated measures revealed a significant effect of both time and dose on the number of errors in the first 8 choices. Extraction of orthogonal polynomials showed the dose main effect to be linear, $F(1,24) = 27.49$, $p<0.001$, with no significant quadratic or cubic component. The time main effect was quadratic in nature, $F(1,74) = 4.39$, $p<0.05$. A significant dose $\times$ time interaction was also observed, $F(8,74) = 2.17$, $p<0.05$. These results are shown graphically in Fig. 1A. There was a slight but nonsignificant trend toward facilitation of performance (i.e., fewer errors) 30 min after the 1 mg/kg dose. At 10 and 30 mg/kg, an impairment of performance (i.e., increased errors) was observed that was maximal at 2 hr but still evident 6 hr postinjection. These drug effects were no longer evident 24 hr postinjection.

There was a similar dose- and time-dependency for CPP's effects on the total number of errors to make all 8 arm choices [dose linear, $F(1,24) = 18.56$, $p<0.001$; dose $\times$ time interaction, $F(8,74) = 2.50$, $p<0.05$], although in this case there was no significant time main effect. Again there was an impairment of performance at the 10 and 30 mg/kg doses and a trend toward a slight early facilitation at the 1 mg/kg dose (Fig. 1B).

CPP also had effects on the time taken to sample the first 8 arms [dose cubic, $F(1,24) = 5.56$, $p<0.05$; time linear, $F(1,74) = 11.77$, $p<0.05$; dose $\times$ time interaction, $F(8,74) = 2.58$, $p<0.05$]. However, these effects bore no resemblance to the drug effects on the error scores (Fig. 1C). When the error data (for the first 8 choices) were subjected to an analysis of covariance, using running time as the covariate, the dose and time main effects plus their interaction remained statistically significant.

Experiment 1: MK-801 Effects on Standard Maze Performance

Four doses of MK-801 (0, 0.1, 0.5, 1.0 mg/kg) were tested on

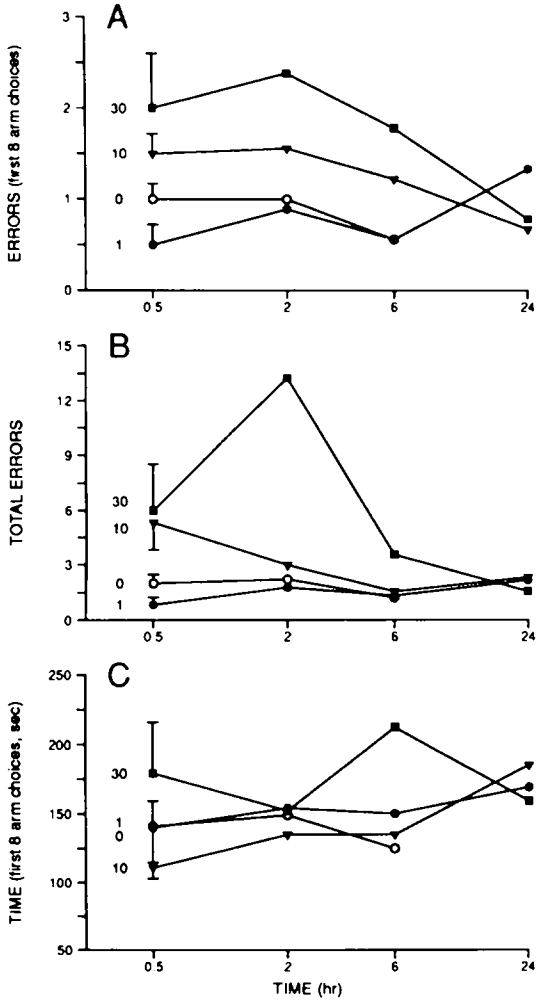

FIG. 1. Time- and dose-dependent effects of CPP on standard radial arm maze performance. Results are group means, plus standard error bars for the first data point for each dose. The drug effects on arm choice errors (A, B) was not accounted for by changes in running time (C). Doses are provided at the left of each line drawing and time on the x-axis (log scale) refers to time postinjection. No data were obtained 24 hr following saline (dose 0) injection.

standard radial maze performance. The same performance measures were made as for CPP. However, the data for the 1 mg/kg dose had to be discarded because of the extreme behavioral activation and stereotypy induced by this dose.

MK-801 produced both dose- and time-dependent effects on the number of errors made in the first 8 choices. ANOVA with polynomial extractions showed a linear effect of dose, $F(1,22) = 12.57$, $p<0.01$, plus a linear main effect for time, $F(1,66) = 13.02$, $p<0.01$. No significant quadratic components were detected for either main effect. A significant dose × time interaction was also observed, $F(4,66) = 6.31$, $p<0.001$. As seen in Fig. 2A, the largest impairment of performance was observed 2 hr after the 0.5 mg/kg dose. No evidence for facilitation was observed at any of the times tested.

A similar pattern of results was seen for total number of errors [dose linear, $F(1,22) = 10.53$, $p<0.01$; time linear, $F(1,66) = 12.75$, $p<0.01$; dose × time interaction, $F(4,66) = 5.59$, $p<0.001$]. Again the performance impairment was greatest 2 hr after the 0.5 mg/kg dose (Fig. 2B).

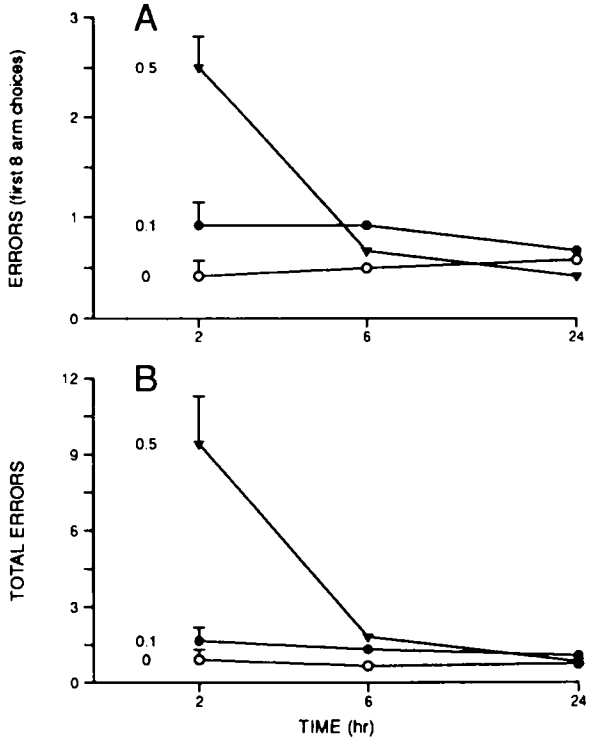

FIG. 2. Time- and dose-dependent effects of MK-801 on standard radial arm maze performance. Results are presented as in Fig. 1.

ANOVA of the drug effect on the time to sample the first 8 arms showed no dose main effect, but a significant dose × time interaction, $F(4,66) = 4.19$, $p<0.01$. However, as for CPP, this effect did not account for the drug effect on errors, as determined by an analysis of covariance (data not shown).

Experiment 2: NMDA Antagonists' Effects on Delayed Maze Performance

In this experiment, a delay of 1 hr was interposed between the fourth and fifth correct arm choices. In all drug conditions there was perfect choice performance when selecting the first 4 arms. Thus, data is presented only for the number of errors made when completing the arm sampling after the 1-hr delay.

CPP produced a dose-dependent effect on errors made after the 1-hr delay period, $F(4,12) = 5.02$, $p<0.05$, $N = 6$. Post hoc paired t-tests showed there was an increase in the number of errors made after the 10 mg/kg dose and a decrease in the number of errors at the 3.3 mg/kg dose (Fig. 3A). The increased mean number of errors after 10 mg/kg was greater for this task (3.25 errors more than vehicle control) than for the standard task (0.8 errors, Experiment 1).

MK-801 (0.1 and 0.33 mg/kg, $N = 6$) had no effect on the number of errors in this task, $F(2,6) = 0.31$, n.s. (Fig. 3B,C). Data from the 1.0 mg/kg dose were not collected because of the resulting extreme behavioral activation and stereotypy.

Experiment 3: NMDA Antagonists' Effects on Working Memory/ Reference Memory

To examine whether NMDA antagonists affected specifically

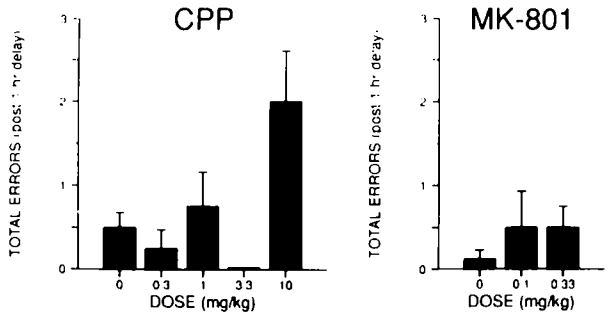

FIG. 3. Effects of CPP and MK-801 on the number of errors made while choosing the last four correct arms, after a 1-hr delay was imposed between choices 4 and 5. CPP (3.3 mg/kg) decreased errors (no errors were made by any rat at this dose), while the 10 mg/kg dose increased errors. MK-801 had no significant effects on performance.

either working memory or reference memory in this radial arm maze task, rats were trained to select only those 4 arms that were baited on each trial. Measures were made of the total number of errors to sample all 4 baited arms, the number of working memory errors (entering an arm containing food but previously entered) and reference memory errors (entering an arm that was not baited).

CPP, injected 2 hr prior to testing, produced a dose-dependent increase in the total number of errors made, $F(2,10)=8.52$, $p<0.01$, $N=6$. Post hoc paired t-tests showed this was largely due to an increased error rate at the 10 mg/kg dose (although only minimal ataxia and no stereotypy occurred). At 1 mg/kg, there was a small, nonsignificant reduction in the number of errors (Fig. 4C).

When the errors were subdivided into the working memory and reference memory categories, CPP showed a strong effect on the number of working memory errors, $F(2,10)=9.60$, $p<0.01$. This effect was dose-dependent, with the impairment evident only at the 10 mg/kg dose (Fig. 4A). There was a similar magnitude, but statistically weaker effect of CPP on the number of reference memory errors, $F(2,10)=2.99$, $0.5<p<0.1$ (Fig. 4B).

In this experiment, MK-801 was again tested only at doses of 0.1 and 0.33 mg/kg, given 2 hr prior to testing. There were no significant drug effects, at these doses, on the total number of errors, $F(2,6)=0.65$, n.s., $N=4$, nor on specifically working or reference memory errors.

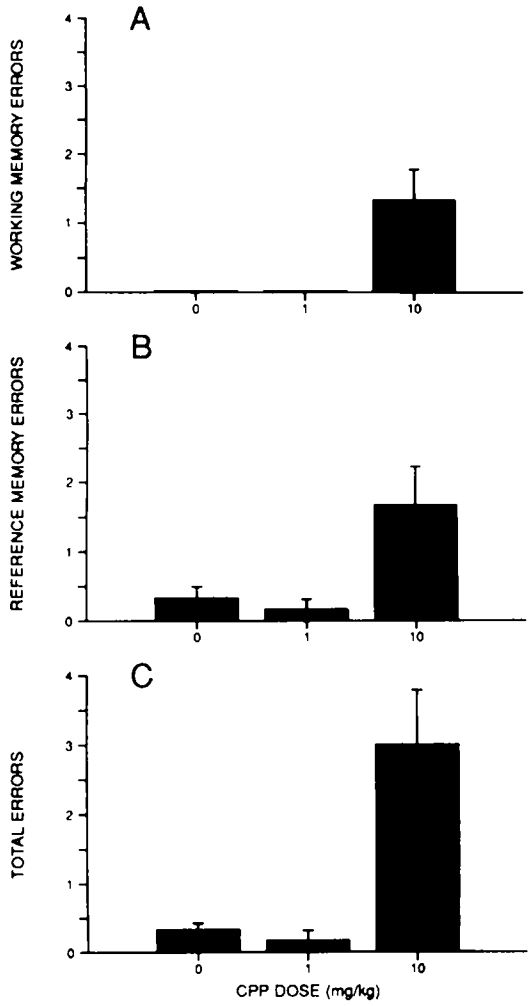

FIG. 4. Effects of CPP on errors made in the working memory/reference memory task. A dose-dependent increase of working memory errors (A) and total errors (C) was found, while a similar magnitude but statistically weaker increase in reference memory errors (relative to working memory errors) was also observed (B). No working memory errors were made by any animal at the 0 and 1 mg/kg doses.

DISCUSSION

The present experiments show that both CPP, a competitive NMDA receptor antagonist, and MK-801, a noncompetitive NMDA receptor antagonist can produce a dose- and time-dependent disruption of radial arm maze performance. These effects were noticeable for CPP at the higher doses 30 min after injection, and were maximal for both compounds after 2 hr. The MK-801 effects were somewhat shorter lasting than for CPP, which still produced a behavioral impairment at 6 hr, but no significant drug effects were observed for either compound 24 hr after administration. These results support and extend the findings from other studies where 2-amino-5-phosphonovalerate (APV, a competitive NMDA antagonist) impaired water maze performance (17,19), and phencyclidine (a noncompetitive NMDA receptor antagonist that binds to the MK-801 site) and APV impaired radial arm maze performance (8).

Parallels Between Drug Effects on LTP and Behavior

It is interesting to compare the present behavioral findings with our previously reported drug effects on hippocampal LTP (2), particularly since hippocampal damage generally is known to disrupt radial arm maze performance (21). The parallel is particularly strong for CPP. The 10 mg/kg dose of CPP completely blocked dentate gyrus LTP 2 and 6 hr postinjection, times when this dose also produced some behavioral impairment in the standard radial maze. This dose was also shown to impair both working and reference memory. Lower doses of the drug impaired neither LTP nor maze performance. It is harder to draw parallels for MK-801, since the dose required to block LTP (1 mg/kg) caused such behavioral excitation and stereotypy that its effect on maze performance could not be assessed. However, MK-801 at 0.5 mg/kg produced about a 50% block of LTP and this dose also impaired radial arm maze performance. No significant effects were seen at lower doses on either behavior or LTP.

Overall, there appears to be a rough parallel for both drugs between those doses effective on LTP and those that impair performance on this spatial maze task. The LTP experiments were conducted with anesthetized rats and thus the dose correspondence must be treated with some caution. However, we have now done

some limited testing of CPP (10 mg/kg) and MK-801 (1 mg/kg) in awake rats chronically implanted with electrodes and found that these doses are only slightly less effective in blocking LTP than in the anesthetized state (10).

Despite the parallel effects of NMDA antagonists on radial arm maze performance and hippocampal LTP, and the known sensitivity of this task to hippocampal lesions, other drug actions may be partly or completely responsible for the present results. APV, for instance, has been shown to affect hippocampal pyramidal cell spontaneous complex spike firing (1) and hippocampal theta rhythm (13), in addition to its effects on LTP, while both CPP and MK-801 can affect dentate granule cell responsiveness to synchronous afferent input (2). Thus, we cannot yet specify the relevant physiological mechanisms responsible for the drug effects on behavior. In a similar vein, since the drugs will spread throughout the nervous system following peripheral injection, action in brain regions other than the hippocampus may contribute to their behavioral effects. Areas relevant to radial maze performance include, for example, the septal nuclei, medial frontal cortex, entorhinal cortex, parietal cortex and nucleus basalis magnocellularis (11,22). The working memory effects may, for instance, relate to drug action in the hippocampus (15), while the reference memory effect may be due to drug action in the neocortex (11). At a minimum, however, our present behavioral results strongly suggest a functional importance of NMDA receptors for normal performance of the radial arm maze task.

NMDA Antagonist Effects: Spatial Memory Versus Stimulus Processing

Tasks such as the radial arm maze and the Morris water maze are frequently used to assess lesion or drug effects on spatial memory processing. The fact that the NMDA antagonists produce effects on radial arm maze performance makes it tempting therefore to suggest that the behavioral effects are due to changes in spatial memory processing. This idea receives some support from our showing, as in other studies (4), a large drug effect on spatial working memory, despite the disadvantage of a possible floor effect resulting from the fact that working memory errors never occurred after vehicle or low dose (CPP) injections. It is also interesting to note that CPP had a greater effect on the number of arm entries required to make the last 4 correct choices when a 1-hr delay was interposed between the fourth and fifth correct choices, suggesting an interaction between the drug effect and the memory retention interval.

Despite the above considerations, the performance impairments caused by NMDA antagonists could in principle also be due to effects on functions other than memory, such as stimulus processing, motivation or movement. To distinguish these possibilities, it is common to test the drugs on a variety of tasks. This is particularly important for treatments affecting radial maze performance, since it is extremely difficult to dissociate effects on memory from, for example, effects on stimulus processing in this task. (We were, however, able to observe performance decrements in the absence of obvious motor impairments.) Morris *et al.* (17) showed that intraventricular APV impaired water maze performance but not visual discrimination learning, suggesting a possible drug selectivity for the spatial memory task.

Recently, we tested CPP and MK-801 on performance of an auditory delayed conditional discrimination task (25). Here we were able to separate drug effects on stimulus discriminability from those on memory retention over a 30-sec interval, using a signal detection analysis applied to the data (27). Our results indicated that the performance impairments produced by both CPP and MK-801 were in fact due to impaired discrimination of stimuli, rather than to a more rapid decay of memory. These effects were observed for both drugs at the same doses required to produce radial arm maze impairments or block LTP. These data support the recent finding (26) that a variety of NMDA antagonists could impair performance of a brightness discrimination task.

Clearly there are important differences in stimulus presentation and response requirements for the radial arm maze versus the stimulus discrimination tasks. Furthermore, the radial maze task often requires the animal to hold previous arm choices in working memory for longer than 30 sec, and it is therefore possible that the drugs may have greater effects on memory retention over longer intervals. Thus, it remains to be investigated further whether the radial arm maze impairments produced by NMDA antagonists are largely due to impaired stimulus processing or to impaired spatial memory storage or retrieval processes.

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