Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, Nos. 2/3, pp. 345-351, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00393-9

Task Difficulty Determines the Differential Memory-Impairing Effects of EAA Antagonists in Gerbils

S. A. MAURER, F. E. STORCH, R. R. LAFORGE AND C. A. BOAST[1]

Wyeth-Ayerst Research, Princeton, NJ

Received 20 August 1992

MAURER, S. A., F. E. STORCH, R. R. LAFORGE AND C. A. BOAST. *Task difficulty determines the differential memory-impairing effects of EAA antagonists in gerbils.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 345-351, 1995.— Excitatory amino acid antagonists (EAAAs) have been shown to disrupt learning and memory in a variety of cognitive tasks. EAAAs have been reported to produce differential effects on working memory (WM) and reference memory (RM) or to have no effect at all. Apparent selective effects of EAAAs on WM and/or RM may have been due to differences between the effects of competitive and noncompetitive EAAAs, dose selection, or to different task requirements for the WM and RM components. In the present experiments, we assessed the effects of a noncompetitive EAAA (MK-801), a competitive EAAA (CPP), and the muscarinic antagonist scopolamine in two cognitive tasks, the split-stem T-maze and the eight-arm radial maze. In these two tasks, the WM and the RM components differed in their relative degree of difficulty. Gerbils were trained on either the T-maze, where WM was more difficult than RM, or on the radial arm maze, where RM was more difficult than WM. In the T-maze, MK-801 (0.1 mg/kg, IP, 30 min prior), CPP (30.0 mg/kg, IP, 2 h prior) and scopolamine (0.3 mg/kg, IP, 30 min prior) impaired both WM and RM, but the magnitude of the impairing effect was statistically greater for the WM component, the more difficult of the two components. Lower doses of these three compounds produced either selective effects on WM or no effect at all. In the radial arm maze all three drugs impaired both components, but the magnitude of the impairing effect was statistically greater for the RM component, the more difficult of the two components. These data indicate that a) the class of EAAA does not appear to contribute to previously reported differential effects on WM or RM, b) differential effects of a drug on WM or RM can be the result of dose selection, and c) task difficulty as defined by the degree and rate of acquisition can influence the apparent selectivity of the memory impairment produced by a given drug.

T-maze Radial arm maze Working memory Reference memory MK-801 CPP Scopolamine

THE ROLE of *N*-methyl-D-aspartate (NMDA) receptors in learning and memory has been studied extensively. Interference with normal NMDA function, whether pharmacologically or through ischemic insult, produces a disruption in learning and memory, in both rodents (1,4,8,12) and humans (12). Specifically, treatment with excitatory amino acid antagonists (EAAAs) has been shown to disrupt learning and memory in a variety of cognitive tasks (4,8,10,13). In some reports, it appears that EAAAs disrupt either working memory alone (13), both working and reference memory (10), or neither working nor reference memory (10). Resolution of the effects of EAAAs as being either selective or not is important to understanding the role of EAAs in memory formation and possibly to understanding mechanisms that differentially contribute to memory processes. We reasoned that differences in experimental outcome in previous experiments may have been due to differences between the effects of competitive and noncompetitive EAAAs, dose selection, or different task requirements for working and reference memory components. In the present experiments, we assessed the effects of various doses of a noncompetitive EAAA, dizocilpine (MK-801) [(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine maleate], a competitive EAAA, 3-[(+)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid (CPP), and the muscarinic antagonist, scopolamine, in two cognitive tasks. The tasks used were the split-stem T-maze (5) and the eight-arm radial maze (7), both with working and reference memory components that vary in the relative degree of difficulty of the two components. In our studies the relative degree of difficulty was determined using the degree and rate of acquisition.

[1] Requests for reprints should addressed to C. A. Boast, Wyeth-Ayerst Research, CN8000, Princeton, NJ 08543-8000.

Our purpose was to determine whether the apparent selective effects of EAAAs on either working or reference memory might be due to the class of EAAA used, the dose selected, or the degree of difficulty of each component of a given task.

METHODS

Subjects

Female Mongolian gerbils (Tumblebrook Farms, West Brookfield, MA), weighing 40–60 g on arrival, were group-housed with food and water available ad lib for a minimum of 1 week. Gerbils were then singly housed and began a restricted diet of Results precision pellets (Bioserv, Frenchtown, NJ) to reduce them to 85% of their free-feeding body weight.

Apparatus

T-Maze. The T-maze (Fig. 1A) was constructed of black Plexiglas with an open top. The start box, 21 × 20 cm, opened into two 40 × 10-cm walkways: a blind alley on the right and an open one on the left. This stem portion of the maze was separated from the start box by a black plastic curtain with approximately 1-cm strips cut vertically to facilitate passage. The stem of the maze opened to the T portion of the maze with the arms of the T forming a rectangle of 122 × 10 cm. Each arm ended in a goal box that was 20 × 10 cm and contained a circular depression in which bait, 45-mg chocolate pellets (BioServ), could be placed. Each goal box could be closed off manually by a 21 × 10-cm black Plexiglas guillotine door. The walls of the maze were 15 cm high. The maze was located in a room with black and white geometric posters on each wall to serve as visual cues. For all testing phases, white noise was audible (~70 dB).

Radial arm maze. The radial arm maze (Fig. 1B) was adapted from Peele and Baron (9). The maze was elevated to a height of 75.5 cm and was composed of a circular area surrounded by eight arms radiating away from the center, equidistant from each other. Each arm was 58 cm long × 10 cm wide and was enclosed in clear Plexiglas. Food cups were located at the end of each arm. A Plexiglas cylinder could be lowered to enclose the animal in the center portion of the maze before the start of the session. Each arm of the maze was equipped with three sets of photocells interfaced to a data acquisition unit (Hewlett Packard 3497A), which in turn was interfaced to an HP Vectra ES/12. An in-house program compiled and stored the data. The maze was located in a testing room with black and white geometric posters on each wall to serve as visual cues. During all training and testing procedures, white noise was audible (~70 dB).

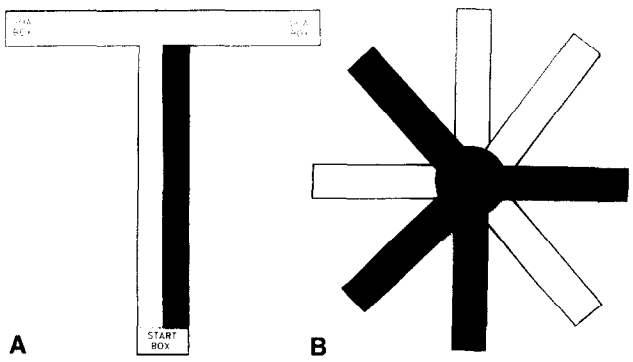

FIG. 1. Testing apparatus. (A) Split-stem T-maze: The food was located in the goal boxes at the end of each arm. Food location was alternated between trials. The darkened portion of the diagram indicates a blind alley that was never baited. Working memory error = entry into an arm that was not baited. Reference memory error = entry into the blind alley. (B) Radial arm maze: Four arms were always baited and four arms were never baited. Working memory error = reentry into a previously visited arm. Reference memory = entry into an arm that was never baited.

Materials

(±)CPP hydrate and (+)MK-801 were obtained from Research Biochemicals, Inc. Scopolamine HBr was obtained from Sigma Chemical.

Behavioral Training

T-Maze. The gerbils were habituated to the T-maze for 6 days. On days 1–4 of the habituation phase, two gerbils at a time were placed on the maze for 15 min/day. Initially, 45-mg chocolate pellets were scattered liberally throughout all areas of the maze except the blind alley and start box. On each day pellets were reduced (e.g., to the choice point and arms only, and finally only in the goal box). On day 4, as each gerbil entered a goal box, the door was closed and the gerbil was allowed to eat there for the remainder of the 15 min. On days 5 and 6 each gerbil was placed on the maze individually for 10 min/day. On day 5 the goal box was filled with pellets, whereas on day 6 only five pellets were available. Habituation was followed by a forced alternation phase.

During the first trial of the forced alternation phase, both goal boxes were baited with a 45-mg chocolate pellet and access was permitted to both. After the animal chose a goal box, the door was closed as the animal ate. For four subsequent trials, the animal was permitted to access only the goal box opposite the one of the previous trial, each time baited with one 45-mg chocolate pellet. Consecutive trials were separated by a 30-s intertrial interval in which the gerbil waited in a plastic holding bin while the maze was wiped with water. Animals were advanced to a forced-free choice phase after 3–15 days of forced alternation testing. The first five trials of the forced-free choice phase were identical to the forced alternation phase (i.e., one free choice trial followed by four alternating forced choice trials). On the sixth trial, the arm opposite to the one baited in trial 5 was baited and the doors of both goal boxes were raised. The door of the baited arm was shut after entry and while the animal ate. For trials 7–15, food placement alternated between sides, with access to both goal boxes and opportunity for correction. The following data were recorded or calculated for trials 6–15: a) stem errors [the number of entries into the blind alley (reference memory parameter)]; b) choice errors [the number of entries into the unbaited arm of the maze (working memory parameter)]; and c) percent correct trials (the number of correct trials as a percent of trials 6–15).

Radial arm maze. Gerbils were habituated to the maze for a minimum of 4 days. On day 1 of the habituation phase, gerbils were placed on the maze in pairs for 10 min with 45-mg chocolate pellets scattered liberally throughout four of the eight arms. Two arm sequences were used; either arms 2, 4, 5, and 7 only, or arms 1, 3, 6, and 8 only, were the baited arms for each gerbil. Arms that were always baited represented the working memory parameter, whereas arms that were never baited represented the reference memory parameter. On days 2–4 of habituation, each gerbil was placed individually on the maze for a 10-min period and pellets were reduced daily (e.g.,

from the middle photocell to the food cup of the working memory arms only, then only in and around the food cups, and finally each gerbil was allowed 5 min to collect one pellet from each working memory arm). The gerbil was trained to enter each baited arm once. Reentry into a previously entered arm was considered a working memory error whereas entry into an arm in which food was never found was considered a reference memory error. Training continued until a gerbil had made fewer than two total errors on three consecutive daily sessions.

Drug Trials

T-Maze. The criterion to begin drug treatment was that each animal had to reach at least 80% correct trials on 3 consecutive days. Vehicle injections were used in conjuncton with each dose condition. To receive vehicle, an animal had to reach at least 80% correct trials on the previous baseline day. On the day following the vehicle injection, the animal had to reach 80% correct trials to receive a drug dose the next day. Some animals did not receive all compounds because of a failure to reach either of these criteria. Therefore, group size varied from 11–17/group among doses. The drugs were administered intraperitoneally in the following doses: 0.01, 0.03, or 0.1 mg/kg (+)MK-801; 1.0, 3.0, 10.0, or 30.0 mg/kg (±)CPP hydrate; or 0.1 or 0.3 mg/kg scopolamine HBr. The drugs were administered in the order listed previously, but the order of doses for each drug was chosen randomly. MK-801 and scopolamine were administered in saline; CPP was administered in distilled water. The dose volume was 10 ml/kg, injected 30 min before the start of a test session, except for 30.0 mg/kg CPP, which was injected 2 h before a test session.

Radial arm maze. Several doses of MK-801, CPP, and scopolamine were initially examined in the T-maze task. Table 1 summarizes the results of those doses on working and reference memory. Doses that produced a statistically significant impairment of both working and reference memory were selected for testing in the radial arm maze. The criterion to begin drug treatment in the radial arm maze was that the animal made fewer than two total errors on three consecutive daily sessions. Test compounds were administered in random order and were injected intraperitoneally. The following doses were tested: 0.1 mg/kg MK-801, 30.0 mg/kg CPP, and 0.3 mg/kg scopolamine. MK-801 and scopolamine were administered in saline; CPP was administered in distilled water. The dose volume was 10 ml/kg, injected 30 min before the start of a test session, except for 30.0 mg/kg CPP, which was injected 2 h before a test session.

Data Analysis

For the T-maze, working and reference memory errors for vehicle and drug days were compared using a one-way analysis of variance (ANOVA) test for each dose group, followed by a Bartlett's analysis for homogeneity of variance. This test revealed that the standard deviations of the groups differed significantly, warranting the use of nonparametric statistics. Therefore, the data for vehicle and drug days were first ranked and then compared using a one-way ANOVA test. In the radial arm maze task, a one-way repeated measures ANOVA was used to compare vehicle vs. drug scores. To compare the magnitude of the effect of each drug on working and reference memory in both the T-maze and the radial arm maze tasks, difference scores for each component were obtained by subtracting errors made after vehicle treatment from those made after drug treatment. The difference scores obtained from these two conditions were then analyzed by a paired *t*-test to determine whether errors were greater for either the working or reference memory component. In all analyses, a probability of < 0.05 was considered to be indicative of a significant difference.

RESULTS

Acquisition

The acquisition of the working and reference memory components of both the T-maze and radial arm maze tasks are

TABLE 1

DOSE RESPONSE INFORMATION FOR MK-801, CPP AND SCOPOLAMINE IN THE T-MAZE AND RADIAL ARM MAZE

Compound	Dose (mg/kg)	Mean Working Errors		Mean Reference Errors	
		Vehicle	Drug	Vehicle	Drug
MK-801					
	0.01	0.88	1.81*	0.31	0.56
T-maze	0.03	1.12	2.18*	0.29	0.24
	0.1	0.69	4.81*	0.25	1.81*
Radial arm maze	0.1	0.09	1.0*	0.55	3.1*
CPP					
	1	1.07	1.00	0.07	0.07
T-maze	3	1.00	1.75	0.19	0.44
	10	0.69	1.54	0.08	0.15
	30	0.75	4.25*	0.33	2.42*
Radial arm maze	30	0.17	5.33*	0.67	9.33*
Scopolamine					
	0.1	0.58	3.17*	0.08	0.58
T-maze	0.3	1.00	4.00*	0.09	0.73*
Radial arm maze	0.3	0.08	1.25*	0.5	3.75*

*$p > 0.05$ vs. vehicle scores.

depicted in Figs. 2 and 3. Once an animal met criteria in the T-maze or radial arm maze it was eligible for dosing. As animals met criteria and began receiving test compounds, their data could no longer be considered acquisition data, so they could not be included in the group acquisition mean. However, to exclude them entirely would mean that the *n*/day would continue to decrease as additional animals met criteria. Thus, to avoid these serial reductions in group size or the inclusion of drug data, acquisition scores for the remaining weeks were automatically entered as two total errors for those animals who had met criteria and were receiving test compounds. This was done for graphing purposes only.

The working memory component of the radial arm maze was apparently learned quickly, as evidenced by the low mean errors that remained stable from week 1 of training. This probably reflected acquisition that occurred during the habituation phase of the procedures, although errors were not recorded during that portion of the experiment. The working memory component of the T-maze, however, took longer to acquire, as seen by the higher mean error, which did not reach asymptote until week 9, at two errors. The reference memory component of the T-maze task dropped to one error by week 3 of training and to zero errors by week 9, whereas mean reference errors in the radial arm maze task were elevated over 13 weeks of training. The acquisition data provide evidence that the relative degree of difficulty of the working and reference memory component in the T-maze and radial arm maze differ. Specifically, the working memory component is more difficult in the T-maze and the reference memory component is more difficult in the radial arm maze.

Drug Trials

MK-801 (0.01, 0.03, or 0.1 mg/kg), CPP (1.0, 3.0, 10.0, or 30.0 mg/kg), or scopolamine (0.1 or 0.3 mg/kg) was initially examined in the T-maze task. Table 1 summarizes working

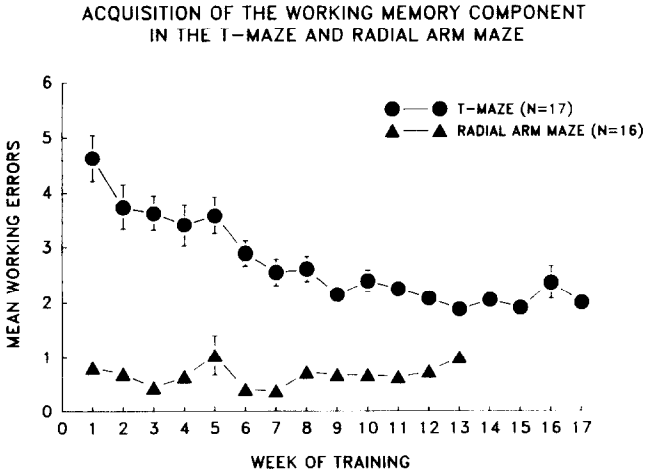

FIG. 2. Acquisition data for the working memory component in the T-maze and the radial arm maze. The working memory component of the radial arm maze took less time to acquire and stabilized at a lower level, in contrast to the working memory component of the T-maze, in which errors remained elevated over several weeks of training. These data provide evidence that the working memory component in the T-maze is more difficult than in the radial arm maze.

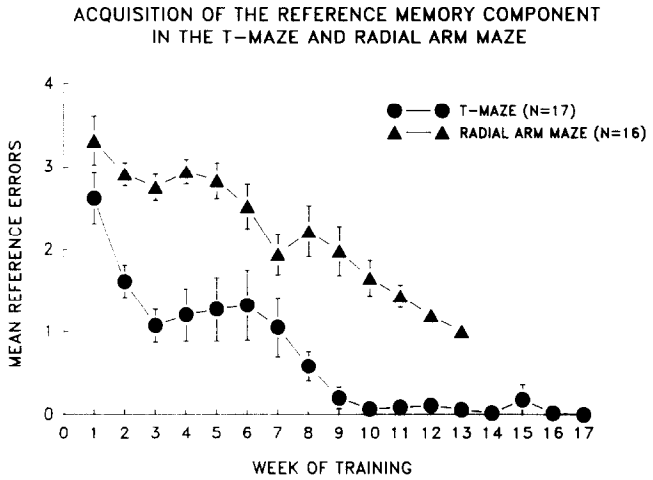

FIG. 3. Acquisition data for the reference memory component in the T-maze and radial arm maze. The reference memory component of the T-maze took less time to acquire and stabilized at a lower level, compared to the reference memory component of the radial arm maze, in which errors remained elevated over several weeks of training. These data provide evidence that the reference memory component in the radial arm maze is more difficult than in the T-maze.

and reference memory errors obtained under vehicle and drug conditions in that initial study. The two lowest doses of MK-801 (0.01 and 0.03 mg/kg) selectively impaired working memory, whereas the highest dose tested (0.1 mg/kg) impaired both working and reference memory. Scopolamine at 0.1 mg/kg impaired working memory only, but 0.3 mg/kg of scopolamine impaired both working and reference memory. CPP at 1.0, 3.0, and 10.0 mg/kg administered 30 min before the test session had no effect on either working or reference memory. A 30.0-mg/kg dose of CPP was initially administered to some animals 30 min before the test session, but they displayed preconvulsive tremors and some degree of ataxia; therefore, the 30.0-mg/kg dose was given 2 h before testing. This dose of CPP impaired both working and reference memory. Working memory errors obtained under vehicle were always numerically greater than the reference memory errors obtained under vehicle, further emphasizing that the working memory component is the more difficult of the two types of memory in the T-maze task.

A summary of working and reference errors obtained under vehicle and drug conditions in the radial arm maze is included in Table 1. MK-801 (0.1 mg/kg), CPP (30 mg/kg), and scopolamine (0.3 mg/kg) each impaired both working and reference memory.

Figure 4 compares the impairing effects of MK-801 in the T-maze and radial arm maze tasks. In the T-maze, MK-801 (0.1 mg/kg) produced a statistically significant increase in both working and reference memory errors. Although MK-801 had an impairing effect on both working and reference memory, analyses comparing difference scores revealed that the magnitude of the increase was statistically greater for the working memory component, the more difficult parameter ($\bar{x}$ difference score working = 4.13 ± 0.4; $\bar{x}$ difference score reference = 1.56 ± 0.61). In the radial arm maze task, MK-801 (0.1 mg/kg) also produced a statistically significant increase in both working and reference memory errors. Analysis

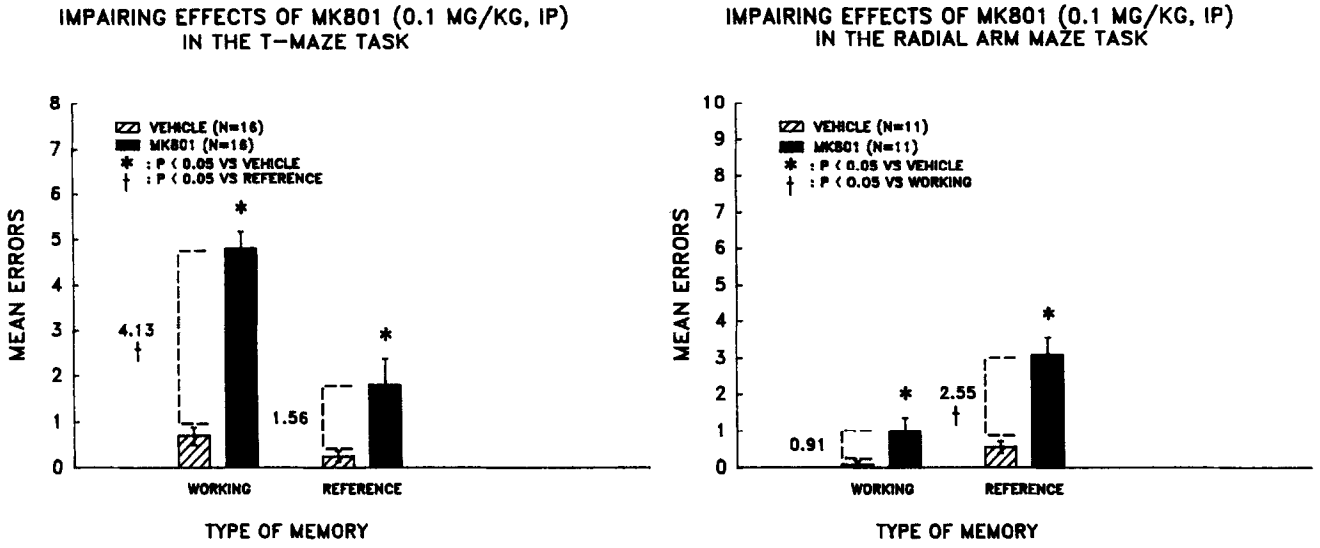

FIG. 4. In both the T-maze and radial arm maze tasks, MK-801 (0.1 mg/kg) produced a statistically significant increase in both working and reference memory errors; however, the magnitude of the increase was statistically greater for the working memory component in the T-maze and the reference memory component in the radial arm maze.

of the difference scores revealed that the magnitude of the increase was statistically greater for the reference memory component, the more difficult parameter ($\bar{x}$ difference score reference = 2.55 ± 0.49; $\bar{x}$ difference score working = 0.91 ± 0.37). In summary, although MK-801 (0.1 mg/kg) impaired both working and reference memory in both the T-maze and radial arm maze tasks, there was a statistically greater impairment of the component that was more difficult.

Figure 5 compares the impairing effects of CPP in the T-maze and radial arm maze tasks. In the T-maze, CPP (30.0 mg/kg) produced a statistically significant increase in both working and reference memory errors. Although CPP had an impairing effect on both working and reference memory, analysis of the difference scores revealed that the magnitude of the increase was statistically greater for the working memory component, the more difficult parameter ($\bar{x}$ difference score working = 3.5 ± 0.72; $\bar{x}$ difference score reference = 2.1 ± 0.78). In the radial arm maze task, CPP (30.0 mg/kg) also produced a statistically significant increase in both working and reference memory errors. Analysis of the difference scores revealed that the magnitude of the increase was statistically greater for the reference memory component, the

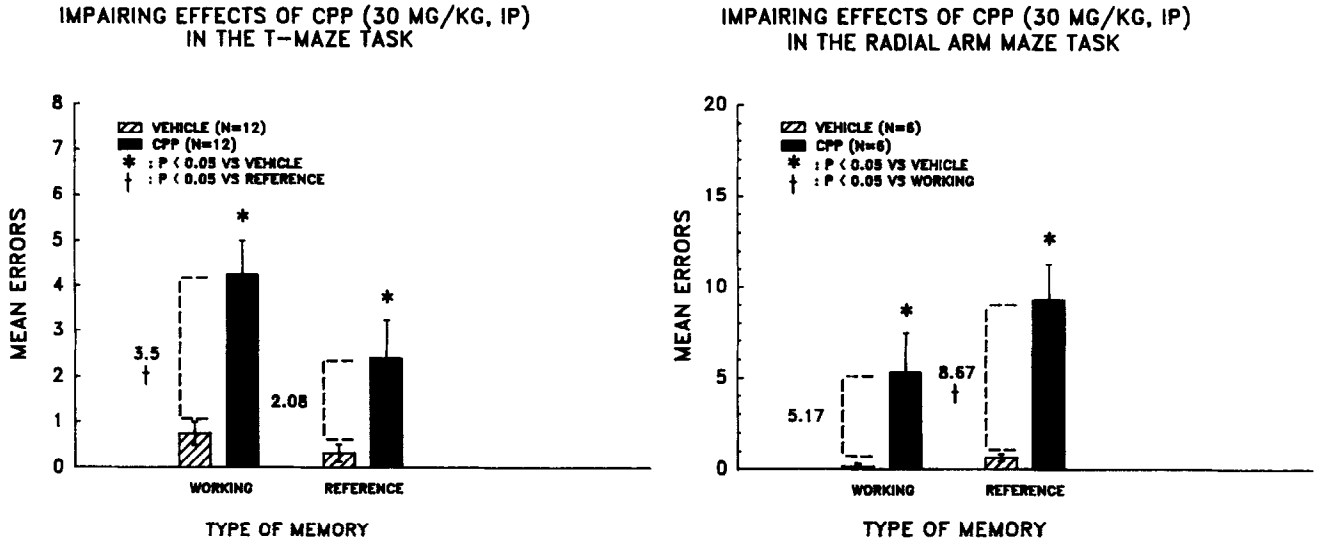

FIG. 5. In both the T-maze and radial arm maze tasks, CPP (30.0 mg/kg) produced a statistically significant increase in both working and reference memory errors; however, the magnitude of the increase was statistically greater for the working memory component in the T-maze and the reference memory component in the radial arm maze.

more difficult parameter ($\bar{x}$ difference score reference = 8.67 ± 1.82; $\bar{x}$ difference score working = 5.17 ± 1.92). In summary, although CPP (30.0 mg/kg) impaired both working and reference memory in both the T-maze and radial arm maze tasks, there was a statistically greater impairment of the component that was more difficult.

Figure 6 compares the impairing effects of scopolamine in the T-maze and radial arm maze tasks. In the T-maze, scopolamine (0.3 mg/kg) produced a statistically significant increase in both working and reference memory errors. Although scopolamine had an impairing effect on both working and reference memory, analysis of the difference scores revealed that the magnitude of the increase was statistically greater for the working memory component, the more difficult parameter ($\bar{x}$ difference score working = 3.0 ± 0.36; $\bar{x}$ difference score reference = 0.64 ± 0.2). In the radial arm maze task, scopolamine (0.3 mg/kg) also produced a statistically significant increase in both working and reference memory errors. Analysis of the difference scores revealed that the magnitude of the increase was statistically greater for the reference memory component, the more difficult parameter ($\bar{x}$ difference score reference = 3.25 ± 0.45; $\bar{x}$ difference score working = 1.17 ± 0.53). In summary, although scopolamine (0.3 mg/kg) impaired both working and reference memory in both the T-maze and radial arm maze tasks, there was a statistically greater impairment of the component that was more difficult.

DISCUSSION

These data confirm the reports of others (4,8,10,13) that EAAAs can have detrimental effects on cognition. The pattern of effects in both the T-maze and the radial maze were similar regardless of whether the impairments were due to a competitive (CPP) or a noncompetitive (MK-801) EAAA. Thus, the class of EAAA does not appear to contribute to previously reported differential effects on working and reference memory. In fact, scopolamine, a muscarinic antagonist, also affected cognition in a similar way, suggesting that the observed effects can be generalized to various pharmacologic treatments.

Preliminary experiments in the T-maze showed that working memory could be selectively impaired at relatively low doses of both MK-801 and scopolamine. At higher doses of these drugs and at the impairing dose of CPP, both working and reference memory were impaired. Thus, in a given task different conclusions concerning the differential effects of a drug on working or reference memory can be the result of different doses studied. In our T-maze experiments, even at a dose that impairs both types of memory, the effect was greater for the working memory component—that is, the more difficult component.

When doses of MK-801, CPP, or scopolamine that impaired both memory components in the T-maze were tested in the radial maze, both components were again affected, but in this case the effect was greater for the reference memory component—that is, the more difficult component. Thus, the task can influence the apparent selectivity of memory impairment resulting from a given drug. In fact, because acquisition data for the two tasks used in the present experiments indicated that the working and reference memory components were reversed in degree of difficulty, the drugs apparently had selectivity for the most difficult component regardless of memory type. Again, this finding was independent of the class of EAAA used and was also apparent after scopolamine treatment, suggesting a more generalized effect.

Degree of difficulty, or task demand, has been recognized as an important factor in determining the relative susceptibility of memory to disruption (6). Few previous attempts have been made to determine the relative difficulty of the working and reference memory components of a given task. Thus, when conclusions have been reached regarding the selectivity of effects of various treatments on these two memory components, the conclusions may have been due to the relative degree of difficulty rather than underlying mechanisms subserving each component. For example, the role of glutamate or

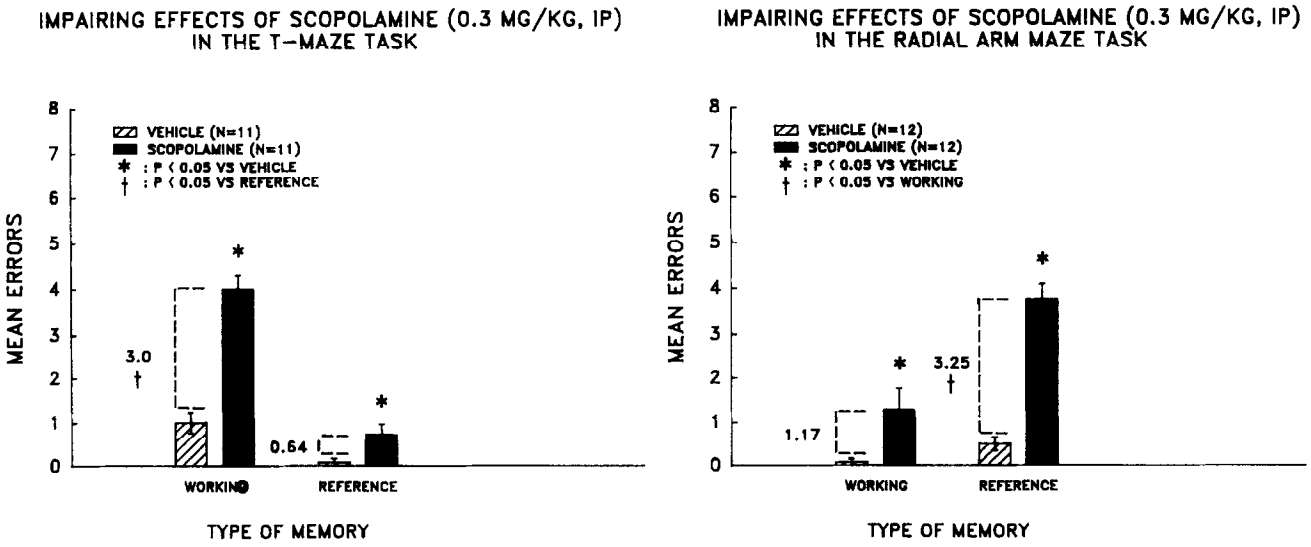

FIG. 6. In both the T-maze and radial arm maze tasks, scopolamine (0.3 mg/kg) produced a statistically significant increase in both working and reference memory errors; however, the magnitude of the increase was statistically greater for the working memory component in the T-maze and the reference memory component in the radial arm maze.

ACh in memory may not be restricted to either a working or a reference memory component, but may play a greater role in creating memories of difficult to learn experiences.

The term "difficulty" used here is related to accuracy of performance as measured by errors. This term can also be considered a measure of the level of stimulus control. Although there is extensive literature concerning drug effects and alterations in the level of stimulus control, a specific example in which reference and working memory components of an operant task were disrupted by scopolamine (11) supports the present interpretation. In those experiments, scopolamine affected both components equally when difficulty was equated, but had a greater effect on working memory when that component was more difficult. In contrast, others (14) reported a selective disruption of working memory by scopolamine in a paradigm in which reference and working memory errors appeared to be equated. More recently, Lydon and Nakajima (3) reported that by lowering reference memory baseline scores, effects of scopolamine on both memory components could be observed. Further, Feaseytruger et al. (2) reported that kindling stimulation disrupted reference memory selectively when baseline performance of reference and working memory components were equated. Thus, a variety of outcomes concerning selective effects on reference and working memory have been reported. Although baselines were often equated in these studies, there are no presentations of acquisition data that would enable conclusions concerning the relative degree of difficulty of reference and working memory components of the given task. Of course, it is also important to keep in mind that the results presented here were obtained using gerbils, whereas most other studies were performed on rats. It is possible that some real differences between these species have contributed to different outcomes in relative susceptibility of working and reference memory to disruption by specific treatments.

Although the present experiments focused on treatments that disrupt cognition, these results may also extend to agents that enhance cognition. If so, this may have important implications for the interpretation of the effects of potential therapeutic agents with regard to their target disease states and potential patient test populations. For example, instead of characterizing patients as having selective "short-term" memory impairments it may be useful to determine the level of difficulty for which a patient retains adequate cognitive function. Cognitive enhancing agents would then be useful if socially significant improvements in the degree of difficulty of cognitive processing were seen after treatment. Presumably, tests could be constructed that would assess cognitive function in terms of level of difficulty rather than the current emphasis on temporal or contextual processing. In any event, it is clear from our current data that the degree of difficulty of tests used in animal studies should be determined to allow intertest comparisons with respect to selective effects of pharmacologic agents.

ACKNOWLEDGEMENTS

The authors thank M. Weaver, C. Voorhees, and R. Syslo for apparatus construction, and M. Tufaro for her assistance in the preparation of the manuscript.

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