Pharmacology Biochemistry and Behavior, Vol. 65, No. 4, pp. 725–730, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(99)00255-5

The NMDA Antagonist EAA 494 Does Not Impair Working Memory in an Operant DNMTP Task in Rats

THERESA M. BALLARD[1] AND KEVIN H. MCALLISTER

Novartis Pharma Inc., Nervous Systems Department, WSJ-386.226, CH-4002, Basel, Switzerland

Received 6 September 1999; Revised 28 October 1999; Accepted 11 November 1999

BALLARD, T. M. AND K. H. MCALLISTER. *The NMDA antagonist EAA 494 does not impair working memory in an operant DNMTP task in rats*. PHARMAC BIOCHEM BEHAV **65**(4) 725–730, 2000.—There is contrasting evidence for an impairment of spatial working memory in operant delayed matching/or nonmatching to position (DMTP/DNMTP) tasks, as both delay-dependent and -independent disruption of choice accuracy has been found following *N*-methyl-D-aspartate (NMDA) receptor blockade. Using a within-subjects experimental design, the effect of the competitive NMDA receptor antagonist, EAA 494 (D-CPP-ene) (1, 1.5, 2 mg/kg IP 30 min prior), on working memory was investigated in male Lister Hooded rats pretrained to the DNMTP task (0–16-s delay in intervals). Metal barriers were inserted between the food magazine and levers to inhibit the use of mediating strategies, such as orientation towards the correct lever during the delay interval, because this behavior may contribute to the delay-dependent disruption noted in previous studies. It was found that EAA 494 did not modify working memory either in the presence or absence of barriers. However, a dose-dependent impairment of task performance was recorded, notably in the presence of barriers. These results indicate that competitive blockade of NMDA receptors with EAA 494 does not result in impaired working memory in rats and parallel the lack of effect of the compound upon working memory in humans. Activation of NMDA receptors does not appear to be essential for the performance of spatial tasks requiring working memory. © 2000 Elsevier Science Inc.

Delayed nonmatching-to-position task Working memory Mediating behavior
EAA494 NMDA antagonist Rat

THE *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors has been hypothesized to play a major role in the induction of long-term potentiation in the hippocampus, a physiological mechanism hypothesized to underlie learning and memory (3). Preclinical studies have provided evidence for an involvement of NMDA receptors in the acquisition (11,18) and working memory (5,17) of spatial tasks. However, there is conflicting evidence for a specific impairment of spatial working memory following NMDA receptor blockade in operant delayed-matching-to-position (DMTP) and delayed-nonmatching-to-position (DNMTP) tasks. The competitive NMDA receptor antagonist, CPP, produced a delay-dependent reduction in choice accuracy in a DMTP task, suggesting a selective disruption of working memory (4). However, the noncompetitive NMDA receptor-associated ion channel blocker, MK-801 (4,14,15) and the competitive NMDA receptor antagonist, CGS 19755 (14), have both been found to significantly disrupt choice accuracy delay independently, indicating that the compounds do not have a selective effect on working memory, but may impair the ability to perform the task (7). It has also been found that CPP and MK-801 reduced choice accuracy delay independently in nonspatial delayed-matching-to-sample (12) and conditional discrimination (16) tasks, respectively. Interestingly, it has been shown that spatial working memory in humans given EAA 494 (D-CPP-ene), the unsaturated analogue of CPP and also competitive receptor antagonist (1) is relatively spared compared to a robust impairment memory in verbal and nonverbal memory tasks (13).

Requests for reprints should be addressed to Kevin H. McAllister, Novartis Pharma Inc., Nervous System Department, WSJ-386.226, CH-4002 Basel, Switzerland.
[1]Present address: F. Hoffman–La Roche Ltd., Pharmaceutical Division, Preclinical Research, CH-4070 Basel, Switzerland.

The purpose of the present study was to examine the effects of EAA 494 upon working memory in the DNMTP task, as this compound has greater potency in vitro and in vivo than CPP (1,9). Furthermore, the present study assessed the effects of EAA 494 in the DNMTP task in both the absence and presence of metal barriers inserted between the food magazine and levers. The insertion of barriers has been used to prevent the rats using positional strategies or mediating behavior to solve the task (6,14). One potential reason for the contrasting effects of CPP (4) and CGS 19755 (14) on choice accuracy in the DMTP task may have been due to the use of barriers in the latter study. It has been suggested that compounds that modify motor behavior, produce delay-dependent disruption by impairing mediating behavior and nonworking memory (8). The test procedure of the study described below is sensitive to delay-dependent impairments of working memory by the muscarinic antagonist scopolamine, which is reversible by coadministration of the acetylcholinesterase inhibitor ENA 713 [Exelon®; (2)]. This study used a within-subjects design to control for the behavioral histories of the subjects, and to allow a more sensitive detection of changes in behavior, and employed a number of performance measures to control for nonspecific motor effects of EAA 494, which may impact upon the interpretation of drug effects upon working memory.

METHODS

Subjects

Twenty-three male Lister Hooded rats (Harlan, The Netherlands), weighing 220–240 g at the start of the study, were singly housed under a 12 L:12 D cycle (lights on 0700–1900 h). Water was available ad lib, but food intake was restricted (12–15 g/day) so that rats were maintained at 85–90% of their free-feeding body weight, throughout the duration of the experiment. The following experiments were undertaken in accordance with the Tierschutzgesetz (9.3.78) and Tierschutzverordnung (27.5.81), Switzerland.

Apparatus

Six rodent operant chambers (CeNeS Cognition, UK) housed in large, sound-attenuating boxes, were connected to an Acorn Risc PC 700 computer via a Paul Fray interface. Each chamber was fitted with two retractable levers positioned either side of a central food magazine. The food magazine was covered by a hinged Perspex panel, which registered nose pokes. A house light was positioned in the center of the ceiling, two stimulus lights were above each lever, and another light illuminated the food tray. Reinforcement was provided by 45-mg food pellets (Rodent diet formula A, Bioserv), which were dispensed individually to the food tray. Aluminium barriers, height 22 cm, width 1 mm and extending 12 cm into the operant chamber, could be attached with screws to the wall either side of the food magazine. The barriers extended from the grid floor to the ceiling and from the wall into the chamber so that the rats had to move back and around the barriers to perform the task.

Training Procedure

All rats were pretrained to the DNMTP task modified from the procedure originally published (7), until a stable baseline had been achieved. The training procedure involved three stages, and barriers were only inserted into the chambers when the subjects had achieved the performance criterion in the DNMTP task.

Habituation to Operant Chambers

The initial part of training involved habituating subjects to the operant chambers and to eat food pellets from the magazine tray, followed by learning to associate pressing a lever with obtaining a food reward. On day 1, the hinged Perspex panel of the food magazine was taped back, and approximately 5 g of food pellets were placed in the tray. The rats were placed in the operant chambers for 15 min, with the house light illuminated. From day 2 onward, the rats were placed in the chambers and trained to a continuous reinforcement procedure. A trial began when both levers were inserted into the chamber. If the rat pressed one of the levers, both levers retracted and one food pellet was dispensed into the food tray. Once rats had learned to press a lever, they were then tested in sessions where only one lever was presented during each trial, to encourage responding on both left and right levers. The number of trials per session was increased until rats reached a criterion of 96 food pellets per session over several consecutive days.

Nonmatching to Position (NMTP) Training

The subjects were trained to learn the NMTP rule. At the start of each trial one lever was presented (the "sample"), if the rat pressed the lever, then the lever was retracted and the food magazine was illuminated. The rat had to nose poke the panel covering the food magazine prior to the extension of both levers into the chamber, when the rat had to make a choice. If it pressed the nonmatching lever (i.e., opposite to the "sample"), the a correct response was recorded, both levers were retracted and the rat was rewarded with a food pellet. If the rat pressed the same lever as the "sample" (i.e., matching), then an incorrect response was recorded, both levers were retracted, and the animal was not rewarded. Each trial was followed by an intertrial interval (ITI) of 5 s with the house light illuminated and each session consisted of 96 trials. During each trial the rat had 20 s to respond to the "sample" lever, and if the lever was not pressed during this period, then it was retracted and the house light extinguished for 20s ("time-out" period). This was followed by an ITI of 5 s with the house light on. Failing to respond to a lever is termed a missed trial or omission. The NMTP stage took 2–3 weeks for rats to reach criteria: (i) >95% correct responses; (ii) no or few omissions; (iii) no bias for a lever, i.e., 50–60% left-hand side preference.

Delayed-Nonmatching-to-Position (DNMTP) Training

In the final stage of training a variable interval was introduced between the sample and choice stage. The delay range included 0, 1, 2, 4, 6, and 8 s until rats were performing to criteria, and then the range was increased to 0, 1, 2, 4, 8, and 16 s. The trials followed the same procedure as the NMTP training, except that when the rat pressed the sample lever, there was a variable delay interval before both levers were presented. The presentation of lever and delay interval was randomized. The food tray was illuminated during the delay. Rats required 2–3 weeks to reach the criteria of: (i) >90% correct at 0 delay; (ii) >50% correct at 16 s delay; (iii) few or no omissions; (iv) between 40–60% left-hand side preference. Once criteria had been achieved, metal barriers were then inserted into the operant chamber and DNMTP training continued for 2–3 weeks

until the rats attained the same criteria in the presence of barriers. This design was used to control for the behavioral histories of the subjects, because a between-subjects design would have required the training of one group to criterion in the absence of barriers followed by the insertion of barriers, while the other group would be trained only in the absence of barriers. Thus, both groups would have different histories of training and potentially different baselines of performance.

Drugs

EAA 494 [(*E*)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid] was dissolved in 0.9% saline and administered in a volume of 1 ml/kg. The concentrations of the compound were calculated as the weight of the base. The doses of EAA 494 were selected based on the results of preliminary experiments in the DNMTP task.

Treatment Protocol

Subjects were administered either EAA 494 or saline IP 30 min prior to testing. The four treatment groups were control (saline), 1, 1.5, and 2 mg/kg EAA 494.

Experimental Procedure

Subjects were divided into two groups; one group ($n = 12$) was tested in chambers without barriers, and the other group ($n = 11$) was tested in the presence of barriers. All rats received each of the treatments on 2 test days per week, separated by at least 48-h interval. Training was continued between testing to ensure that rats were performing at baseline. Once all doses had been tested, the groups were crossed over and retrained for at least 3 days to the new situation, i.e., either chambers with or without barriers. All rats were again tested with each treatment, as described previously.

Statistical Analysis

Subjects that failed to complete half of the 96 trials during one test session were excluded from the statistical analysis. The percent correct responses (choice accuracy), the latency to press the correct lever (correct latency), and the number of nose pokes per second (rate of nose poking) were measured at each delay interval and analyzed using a three-way ANOVA with repeated measures on all factors [barriers, dose, and delays; (19)]. The latency to press the same lever (latency to sample) was measured prior to the delay interval, and the latency to collect the reward from the food magazine (magazine latency) was measured following a response to the correct lever. Therefore, the data for the latency to sample and magazine latency were analyzed as a single value within an experimental session using a two-factor ANOVA with repeated measures on all factors (barriers and dose). The data was also analyzed using paired *t*-tests with Bonferroni correction for multiple comparisons between the treatments, in the absence or presence of barriers.

The total number of omissions was recorded. Because the data did not meet the assumptions of parametric analysis, nonparametric statistics were employed. Delay dependency was analyzed within each treatment group using a Friedman two-way ANOVA. The total number of omissions made during an experimental session were analyzed over treatments using a Kruskal–Wallis ANOVA and in significant cases, Mann–Whitney *U*-tests were used to compare two groups. Statistical significance was assumed when $p < 0.05$.

RESULTS

One of the 23 subjects did not complete more than half of the 96 trials during a test session following administration of 2 mg/kg EAA 494 in the presence of barriers. The data for this subject were excluded from the analysis.

Choice Accuracy

Choice accuracy significantly decreased across the delays in both situations, $F(5, 105) = 156.2$, $p < 0.001$. The presence of barriers did not significantly alter the choice accuracy, $F(1, 21) = 1.2$ (Fig. 1), and there was no interaction between barriers and dose, $F(3, 63) = 0.4$, and barriers and delay, $F(5, 105) = 0.3$. EAA 494 did not significantly modify choice accuracy, $F(3, 63) = 1.2$, NS.

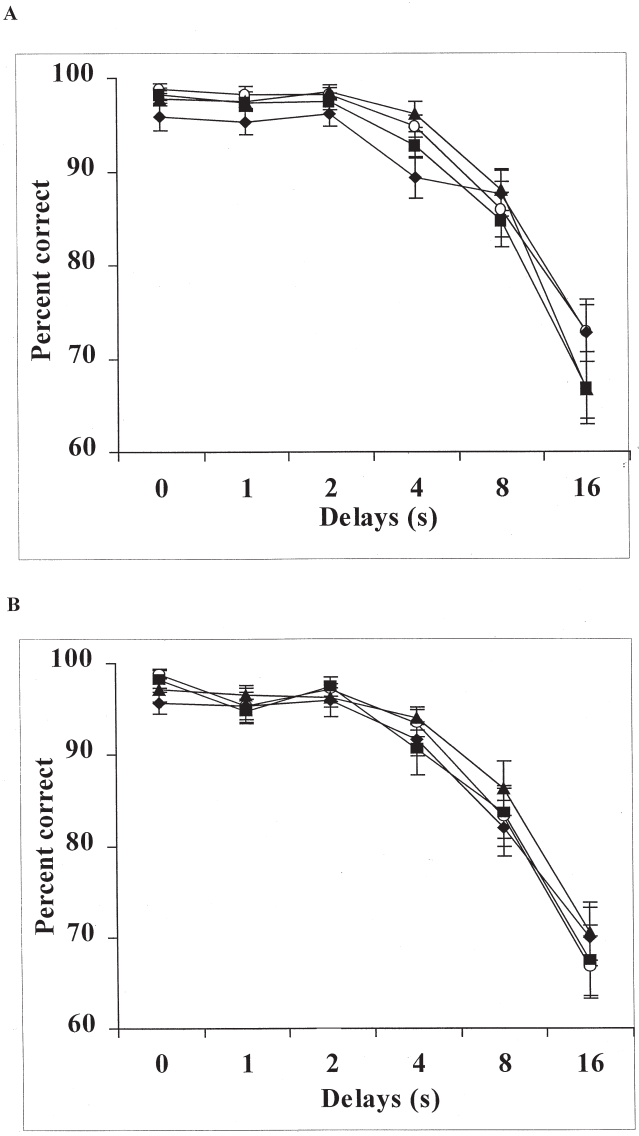

FIG. 1. Percent correct responses (choice accuracy) at each delay interval in an operant DNMTP task in the absence (A) and presence (B) of barriers, following: (○) vehicle, (■) 1 mg/kg, (▲) 1.5 mg/kg, or (◆) 2 mg/kg EAA 494. Data are presented as mean ± SEM.

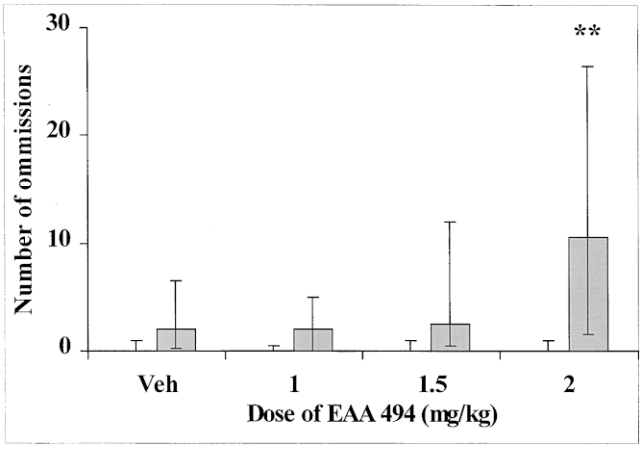

FIG. 2. The effect of EAA 494 on the total number of omissions in the absence (white bars) and presence (shaded bars) of barriers. Data are presented as medians and interquartile ranges (**$p < 0.01$, compared to vehicle).

Number of Omissions

EAA 494 did not affect the total number of omissions during the session in chambers without barriers ($H = 2.9$). In the presence of barriers, EAA 494 showed a significant increase in the total number of omissions ($H = 11.1$, $p < 0.05$, Fig. 2). Mann–Whitney *U*-tests revealed that 2 mg/kg EAA 494 significantly increased the total number of omissions compared to controls ($U = 124.0$, $p < 0.01$). Friedman two-way ANOVA showed there was no significant effect of treatment on number of omissions across delay intervals in the absence or presence of barriers.

Latency to Sample

There was a significant effect of barriers, $F(1, 21) = 176.6$, $p < 0.001$, dose, $F(3, 63) = 27.8$, $p < 0.001$, and a significant barriers × dose interaction, $F(3, 63) = 20.0$, $p < 0.001$. Multiple comparisons tests showed that EAA 494 significantly increased the latency to press the sample lever at 2 mg/kg in the absence of barriers ($p < 0.05$) and at 1 ($p < 0.05$), 1.5 ($p < 0.001$) and 2 ($p < 0.001$) mg/kg in the presence of barriers (Fig. 3).

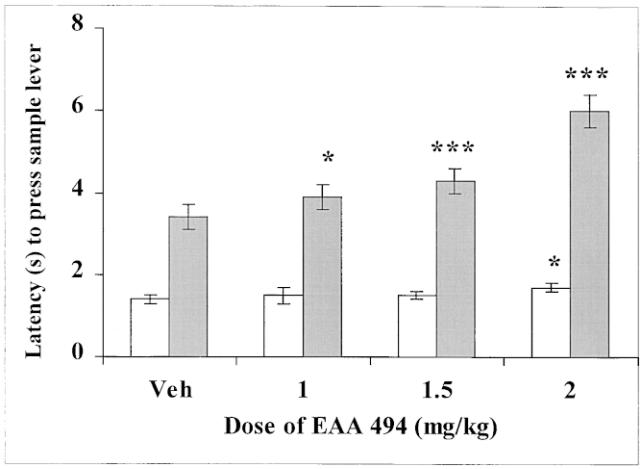

FIG. 3. The latency (seconds) to press the sample lever (latency to sample) in the absence (white bars) and presence (shaded bars) of barriers. Data are presented as mean ± SEM (*$p < 0.05$, ***$p < 0.001$, compared to vehicle).

Rate of Nose Poking

The presence of barriers did not significantly, $F(1, 21) = 0.12$, affect the rate of nose poking, and there was no interaction effects with dose, $F(3, 63) = 0.13$, or delays, $F(4, 84) = 0.7$, or a barriers × dose × delays interaction, $F(12, 252) = 1.9$. There was a significant effect of dose, $F(3, 63) = 34.3$, $p < 0.001$, delays, $F(4, 84) = 96.1$, $p < 0.001$, and a significant dose × delays interaction, $F(12, 252) = 4.1$, $p < 0.001$. Multiple comparisons tests showed that in the absence of barriers (Fig. 4A), EAA 494 significantly reduced nose poking at a 1-s delay following 1 mg/kg, at 1–8-s delays following 1.5 mg/kg, and at all delay intervals following 2 mg/kg. In the presence of barriers (Fig. 4B), 1 mg/kg significantly reduced nose poking at 4-, 8-, and 16-s delays, 1.5 mg/kg significantly reduced nose

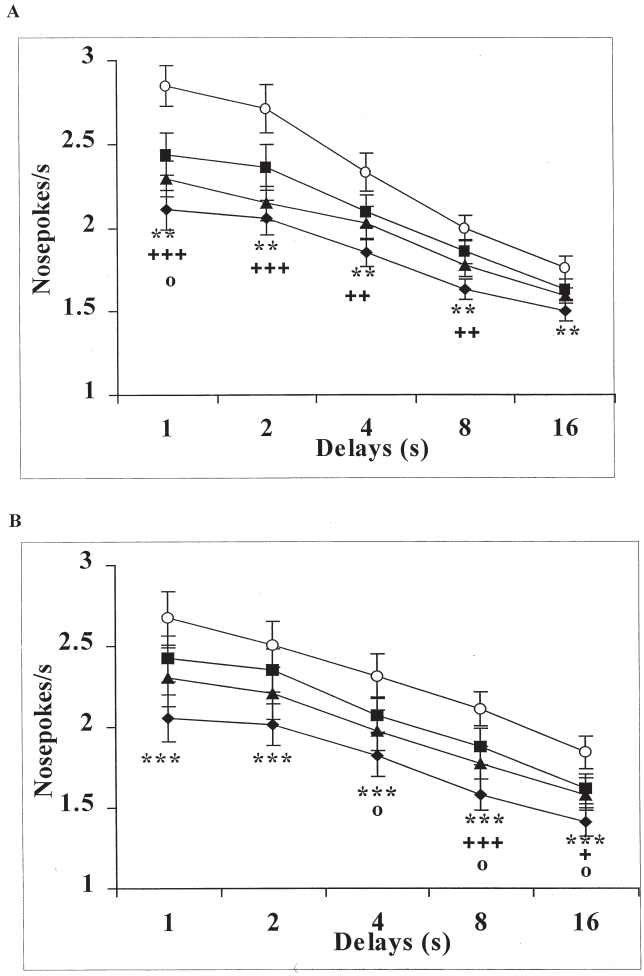

FIG. 4. The number of nose pokes per second (rate of nose poking) at each delay interval in the absence (A) and presence (B) of barriers, following (○) vehicle, (■) 1 mg/kg, (▲) 1.5 mg/kg, or (◆) 2 mg/kg EAA 494. Data are presented as mean ± SEM ($^{o}p < 0.05$, 1 mg/kg EAA 494 compared to vehicle; $^{+}p < 0.05$, $^{++}p < 0.01$, $^{+++}p < 0.001$, 1.5 mg/kg EAA 494 compared to vehicle; ***$p < 0.001$, 2 mg/kg compared to vehicle).

poking at 8- and 16-s delays, whereas 2 mg/kg EAA 494 significantly reduced the rate of nose poking at all delay intervals.

Correct Latency

The use of barriers significantly affected the correct latency, $F(1, 21) = 186.1$, $p < 0.001$. The dose of EAA 494 significantly modified correct latency, $F(3, 63) = 28.3$, $p < 0.001$, and there was a significant interaction between barriers × dose, $F(3, 63) = 18.8$, $p < 0.001$. There was a significant effect of delays, $F(5, 105) = 4.2$, $p < 0.01$, and a significant barriers × delays interaction, $F(5, 105) = 3.04$, $p < 0.05$, but no significant interaction between dose and delays, $F(15, 315) = 0.6$. There was not a significant interaction between barriers and dose and delays, $F(15, 315) = 1.06$. Multiple comparisons tests showed that in the absence of barriers (Fig. 5A), 2 mg/kg EAA 494 significantly increased the correct latency at the 8-s delay only. In the presence of barriers (Fig. 5B), 1 mg/kg increased the correct latency at the 1-s delay, 1.5 mg/kg increased the correct latency at the 0–8-s delays, and 2 mg/kg EAA 494 significantly increased the correct latency at all delay intervals.

Magazine Latency

There was a significant effect of barriers, $F(1, 21) = 292.9$, $p < 0.001$, dose, $F(3, 63) = 22.5$, $p < 0.001$, and a significant barriers × dose interaction, $F(3, 63) = 19.7$, $p < 0.001$. Multiple comparisons tests showed that 2 mg/kg EAA 494 significantly increased the latency to reach the food magazine in the presence of barriers only (Fig. 6).

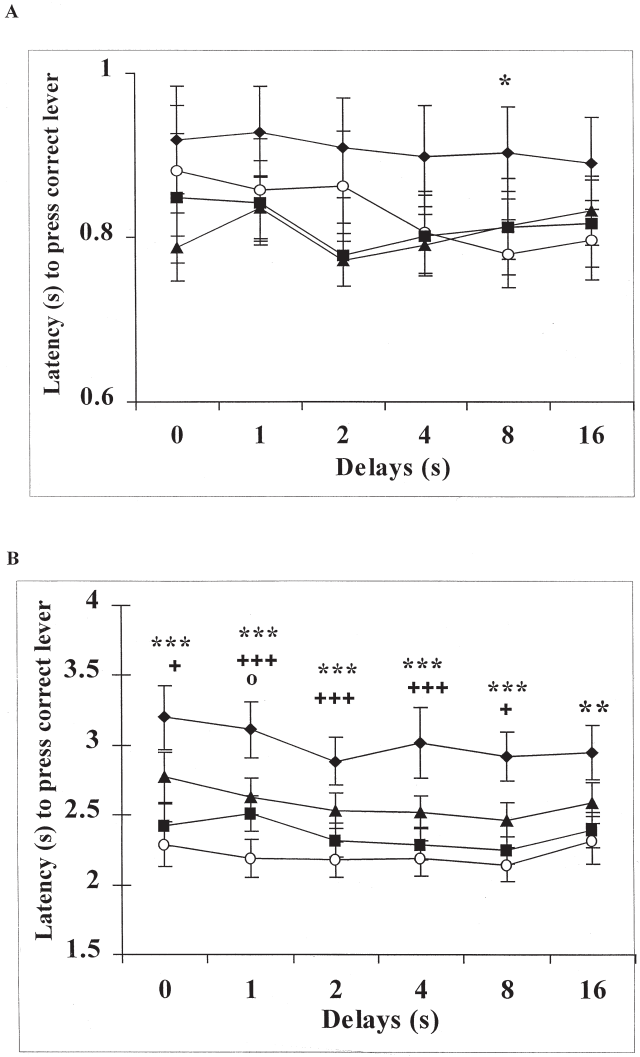

FIG.5. The latency (seconds) to press the correct lever (correct latency) at each delay interval in the absence (A) and presence (B) of barriers, following (○) vehicle, (■) 1 mg/kg, (▲) 1.5 mg/kg, or (◆) 2 mg/kg EAA 494. Data are presented as mean ± SEM ($^{o}p < 0.05$, 1 mg/kg EAA 494 compared to vehicle; $^{+}p < 0.05$, $^{+++}p < 0.001$, 1.5 mg/kg EAA 494 compared to vehicle; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, 2 mg/kg compared to vehicle).

DISCUSSION

The competitive NMDA receptor antagonist, EAA 494, did not affect choice accuracy across delay intervals either in the absence or in the presence of barriers, up to doses that resulted in significant modification of the motor performance of the task. Previous studies with NMDA antagonists, such as MK-801 and CGS-19755, have described delay-independent impairment of choice accuracy, indicating that NMDA receptor blockade does not result in a selective impairment of working memory (4,14,15). In contrast to the present data, CPP has been shown to produce delay-dependent impairment of choice accuracy in an operant DMTP task (4). The discrepancy in these results is not a consequence of the level of training and baseline performance attained in the tasks, because in both studies the subjects were trained to a relatively high baseline to detect drug-induced disruption of the working memory curve. The lack of an effect of EAA 494 is not attributable to the present testing paradigm being insensitive because choice accuracy is delay-dependently impaired by scopolamine administration under the same experimental conditions (2).

Furthermore, the lack of effect of EAA 494 on working memory was not due to the choice of a low dose range, because similar doses shorten the retention latency in a passive avoidance task in mice, reverse haloperidol-induced catalepsy, and block maximal electroshock convulsions in rats (9,10). The highest dose of EAA 494 (2 mg/kg) resulted in the modification of motor behavior in the DNMTP task, particularly in the presence of barriers. Under this condition EAA

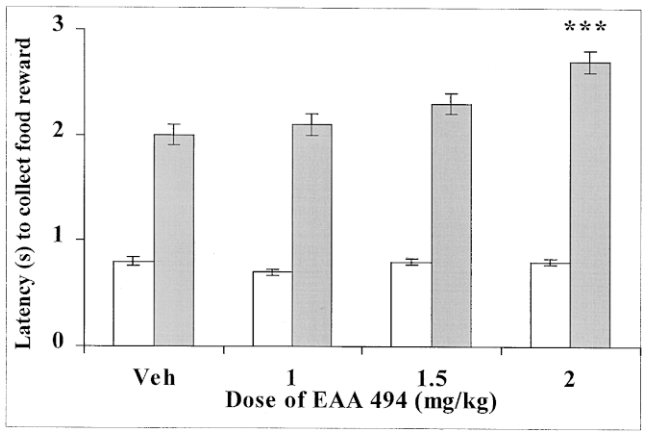

FIG. 6. The latency (seconds) to collect a food reward from the magazine (magazine latency) in the absence (white bars) and presence (shaded bars) of barriers. Data are presented as mean ± SEM ($***p < 0.001$, compared to vehicle).

494 significantly increased the total number of omissions, the latency to press the sample lever, the latency to press the correct lever, and the latency to collect a food reward from the magazine, and significantly decreased the rate of nose poking across delays. The lower doses tested also significantly increased the latency to press the sample lever and the latency to press the correct lever and significantly decreased the rate of nose poking. In chambers without barriers, EAA 494 significantly increased the latency to press the sample lever and reduced the rate of nose poking following administration of 1.5 and 2 mg/kg. Presumably, the increased demands upon motor behavior to perform the task in the presence of barriers provide a more sensitive readout of the motor-impairing effects of the compound. The effects of EAA 494 on motor performance are similar to those reported with CPP (10 mg/kg), in which a small increase in the latency to make a correct matching response, a decrease in the total number of nose pokes, and a slight increase in the number of omissions in an operant DMTP task were described (4). The differences in the doses of the NMDA receptor antagonists used in the two studies is consistent with the evidence that EAA 494 is a more potent NMDA receptor antagonist compared to CPP in vitro and in vivo (1,9,10). It is possible that the delay-independent effects of 10.0 mg/kg CGS-19755 were a consequence of biasing of the analysis, because 4 out of 10 rats were incapacitated, and the remaining subjects from which the measure of working memory was taken, completed fewer trials during the session (14). Doses of EAA 494 higher than 2 mg/kg could not be used in the present study because this results in severely disrupted task performance and a dramatic increase in the number of incompleted trials, hence decreasing the accuracy with which working memory could be measured (preliminary experiments, data not shown).

The impact of insertion of barriers to eliminate positional strategies, or mediating behavior, was to increase the time taken to perform the task (for instance, the latency to press the correct lever once the delay had ended). Choice accuracy was not affected. Although EAA 494 disrupted motor performance in the DNMTP task, there was no effect on the working memory curve either in the absence or presence of barriers. It cannot be inferred from the present data that the reported delay-dependent effect of CPP (4) was a consequence of impaired mediating strategies as hypothesized (see Introduction). It is possible, however, that in the training procedure in which all the animals were trained to criterion in the presence of barriers, the development of positional strategies was suppressed such that in the test situation in the absence of barriers, positional strategies were not employed by the animals.

In conclusion, the results of the present study indicate that competitive antagonism of NMDA receptors following administration of EAA 494 does not result in impaired spatial working memory in the DNMTP task even at doses that impair task performance. This result is consistent with the lack of a specific effect of competitive and noncompetitive NMDA antagonists, with the exception of CPP, upon spatial working memory in the same test and consistent with the results of a clinical study, in which EAA 494 did not significantly affect the performance of a spatial working memory test.

REFERENCES

1. Aebischer, G.; Frey, P.; Haerter H. P.; Herrling, P. L.; Mueller, W.; Olverman, H. H.; Watkins, J. C.: Synthesis and NMDA antagonistic properties of the enantiomers of 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (CPP) and of the unsaturated analogue (*E*)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid (CPP-ene). Helv. Chim. Acta 72:1043–1047; 1989.
2. Ballard, T. M.; McAllister, K. H.: The acetylcholinesterase inhibitor, ENA 713 (Exelon), attenuates the working memory impairment induced by scopolamine in an operant DNMTP task in rats. Psychopharmacology (Berlin) 146:10–18; 1999.
3. Bliss, T. V. P.; Collingridge, G. L.: A synaptic model of memory: Long-term potentiation in the hippocampus. Nature 361:31–39; 1993.
4. Cole, B. J.; Klewer, M.; Jones, G. H.; Stephens, D. N.: Contrasting effects of the competitive NMDA antagonist CPP and the non-competitive NMDA antagonist MK 801 on performance of an operant delayed matching to position task in rats. Psychopharmacology (Berlin) 111:465–471; 1993.
5. Danysz, W.; Wroblewski, J. T.; Costa, E.: Learning impairment in rats by *N*-methyl-D-aspartate receptor antagonists. Neuropharmacology 27:653–656; 1998.
6. Dawson, G. R.; Bayley, P.; Channell, S.; Iversen, S. D.: A comparison of the effects of the novel muscarinic receptor agonists L-689,660 and AF102B in tests of reference and working memory. Psychopharmacology (Berlin) 113:361–368; 1994.
7. Dunnett, S. B.: Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats. Psychopharmacology (Berlin) 87:357–363; 1985.
8. Herremans, A. H. J.; Hijzen, T. H.; Welborn, P. F. E.; Olivier, B.; Slangen, J. L.: Effects of infusion of cholinergic drugs into the prefrontal cortex area on delayed matching to position performance in the rat. Brain Res. 711:102–111; 1996.
9. Lowe, D. A.; Emre, M.; Frey, P.; Kelly, P. H.; Malanowski, J.; McAllister, K. H.; Neijt, H. C.; Rüdeberg, C.; Urwyler, S.; White, T. G.; Herrling, P. L.: The pharmacology of SDZ EAA 494, a competitive NMDA antagonist. Neurochem. Int. 25:583–600; 1994.
10. McAllister, K. H.: The competitive NMDA antagonist SDZ 220-581 reverses haloperidol-induced catalepsy in rats. Eur. J. Pharmacol. 314:307–311; 1996.
11. 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.
12. Pontecorvo, M. J.; Clossold, D. B.; White, M. F.; Ferkany, J. W.: *N*-Methyl-D-aspartate antagonists and working memory performance: Comparison with the effects of scopolamine, propanolol, diazepam, and phenylisopropyladenosine. Behav. Neurosci. 105: 521–535; 1991.
13. Rockstroh, S.; Emre, M.; Tarral, A.; Pokorny, R.: Effects of the novel NMDA-receptor antagonist SDZ EAA 494 on memory and attention in humans. Psychopharmacology (Berlin) 124:261–266; 1996.
14. Stanhope, K. J.; McLenachan, A. P.; Dourish, C. T.: Dissociation between cognitive and motor/motivational deficits in the delayed matching to position test: effects of scopolamine, 8-OH-DPAT and EAA antagonists. Psychopharmacology (Berlin) 122:268–280; 1995.
15. Stephens, D. N.; Cole, B. J.: AMPA antagonists differ from NMDA antagonists in their effects on operant DRL and delayed matching to position tasks. Psychopharmacology (Berlin) 126: 249–259; 1996.
16. Tan, S.; Kirk, R. C.; Abraham, W. C.; McNaughton, N.: Effects of the NMDA antagonists CPP and MK-801 on delayed conditional discrimination. Psychopharmacology (Berlin) 98:556–560; 1989.
17. Tonkiss, J.; Rawlins, J. N. P.: The competitive NMDA antagonist AP5, but not the non-competitive antagonist MK801, induces a delay-related impairment on spatial working memory in rats. Exp. Brain Res. 85:349–358; 1991.
18. 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.
19. Winer, B. J.: Statistical principles in experimental design. New York: McGraw-Hill; 1971.