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Effects of combined block of α_1-adrenoceptors and NMDA receptors on spatial and passive avoidance behavior in rats

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Abstract

The present study was designed to investigate the interactions between α_1-adrenoceptors and NMDA receptors in modulating spatial navigation and passive avoidance behavior in rats. Pretraining treatment with prazosin, an α_1-adrenoceptor antagonist, at 2 mg/kg i.p., impaired acquisition performance in a water maze navigation test and had no effect on passive avoidance behavior. Posttraining and pretest injections of prazosin had no effect on water maze or passive avoidance behavior. Pretraining treatment with ((±))-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), a competitive NMDA receptor antagonist, dose dependently (3 and 10 mg/kg) impaired passive avoidance and water maze behavior. Posttraining treatment with CPP had no effect on water maze and passive avoidance behavior. A pretraining combination of subthreshold doses of CPP (1 mg/kg) and prazosin (1 mg/kg) impaired water maze behavior. A combination of subthreshold doses of CPP (3 mg/kg) and prazosin (1 mg/kg) injected posttraining or pretest had no marked effect on water maze or passive avoidance performance. A control experiment showed that CPP 3 mg/kg or CPP 1 mg/kg and prazosin 1 mg/kg injected pretraining had no effect on cue navigation to a clearly visible platform, but CPP 10 mg/kg markedly impaired performance. The present results indicate that α_1-adrenoceptors and NMDA receptors may synergistically regulate acquisition of spatial navigation performance. Therefore, it would be interesting to study the effects of combined stimulation of α_1-adrenoceptors and NMDA receptors on age-related memory defects.

Keywords: α_1-Adrenoceptor; NMDA receptor; Water maze; Passive avoidance; Prazosin; CPP ((±))-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid)

1. Introduction

Neurochemical and neuropathological studies conducted using post-mortem brain samples of patients suffering from Alzheimer disease have shown that ascending neuromodulatory systems, such as cholinergic cells of the basal forebrain and noradrenaline cells of the brainstem, are adversely affected (Soininen et al., 1992; Francis et al., 1994). Another typical neurochemical abnormality observed in Alzheimer disease is the degeneration of glutamate containing projections in areas important for memory functioning, such as hippocampus and surrounding medial temporal lobe structures (Francis et al., 1994).

Experimental pharmacological studies support the importance of the impaired noradrenergic and glutamate activity in the development of memory defects associated with aging and Alzheimer disease. For example, treatment with an α_2-adrenoceptor agonist that decreases the firing rate of noradrenergic neurons, the release of noradrenaline in the forebrain and the stimulation of postsynaptic α_1- and β-adrenoceptors impairs water maze spatial learning and passive avoidance in young rats (Decker and Gallagher, 1987; Decker et al., 1990; Riekkinen Jr. et al., 1990a; Devagues and Sara, 1991; Harley, 1991; Sirviö et al., 1991, 1992; Brocher et al., 1992). Destruction of presynaptic noradrenaline fibers with noradrenergic neurotoxins, such as systemically injected DSP-4 or with 6-hydroxydopamine infusion into the dorsal noradrenergic bundle, had no effect on spatial learning in the water maze or radial arm maze, but aggravated the performance failure caused by treatment with scopolamine, a muscarinic acetylcholine receptor antagonist (Decker and Gallagher, 1987; Riekkinen Jr. et al., 1990a). Furthermore, in aged rats a near-complete destruction of central noradrenergic

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systems impaired water maze navigation, but in young rats noradrenaline depletion had no measurable effect on water maze learning (Sirviö et al., 1991).

A number of experiments have also described that proper activation of NMDA receptors is a prerequisite for effective performance in several tests used to assess memory functions. Pharmacological studies have reported an impairment of memory following systemic, intracerebroventricular and hippocampal infusion of NMDA receptor antagonists (Morris et al., 1986; Clissold et al., 1991; Lyford and Jarrard, 1991; Cole et al., 1993). Initially Morris et al. (1986) found that intracerebroventricular infusion of NMDA antagonist impaired the development of long-term potentiation and the acquisition of spatial navigation in the water maze, but not the acquisition of visual discrimination. Furthermore, Cole et al. (1993) reported that systemic treatment with a competitive NMDA receptor antagonist, (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) at 10 mg/kg i.p., delay-dependently impaired short-term working memory in an operant-delayed matching to position task. Ward et al. (1990) reported also that CPP 10 and 30 mg/kg impaired performance in a standard eight-arm radial arm maze and also impaired retention of information when a 1-h delay was introduced. However, the behavioral defects caused by NMDA receptor antagonists are not restricted to spatial paradigms. Lyford and Jarrard (1991) found that CPP disrupted performance of both place and cue tasks in a radial arm maze, and Clissold et al. (1991) reported that competitive and non-competitive NMDA receptor antagonists impaired behavior in a nonspatial operant discrimination task.

NMDA receptors and noradrenergic mechanisms may also jointly regulate memory trace formation in the hippocampus (Mueller et al., 1982; Collingridge et al., 1983; Hopkins and Johnston, 1988; Mynlieff and Dunwiddie, 1988; Collingridge and Singer, 1990; Dunwiddie et al., 1992; Bliss and Collingridge, 1993; Malenka and Nicoll, 1993; Scanziani et al., 1993). Electrophysiological studies aiming to elucidate the neurochemical regulation of synaptic memory in a model, long-term potentiation, have found that the induction of NMDA-dependent long-term potentiation in the dentate gyrus is facilitated by activation of α_1- and β-adrenoceptors (Hopkins and Johnston, 1988; Dunwiddie et al., 1992). However, the possible behavioral interactions between NMDA and α_1-adrenoceptors have largely not been studied.

We designed the present study to investigate the hypothesis that NMDA and α_1-adrenoceptors (Pichler and Kobinger, 1985; Minneman and Esbenshade, 1994) may jointly modulate memory trace formation. Therefore, we investigated the effects of single and combined treatment with an α_1-adrenoceptor antagonist, prazosin, and a competitive NMDA receptor antagonist, CPP, on water maze and passive avoidance behavior. The effect of pretraining, posttraining and pretest drug injections on water maze and passive avoidance behavior was studied to investigate the time course of the possible α_1-adrenoceptor–NMDA interaction. Finally, the effect of single and combined prazosin and CPP on cue navigation (clearly visible platform) was studied to investigate the possible non-cognitive effects of single and combined drug treatments, as NMDA receptor antagonists may also disrupt non-spatial behavior.

2. Materials and methods

2.1. Animals

Young (3.5–4 months old; $n = 8–12$/group) male Han:Wistar rats were used in the present study. The rats were housed in a controlled environment with food and water ad libitum (temperature 22 ± 2°C, lights on/off = 07:00–19:00 h, humidity 60%).

2.2. Drugs

Prazosin (Research Biochemicals) doses of 0.1, 0.3, 1 and 2 mg/kg were selected as in our preliminary study we found that pretraining injection of prazosin 2 mg/kg significantly impaired water maze navigation. CPP ((±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) (Research Biochemicals) doses of 1, 3 and 10 mg/kg were selected as delayed non-matching to position working memory was impaired following CPP 10 mg/kg injections. CPP and prazosin were dissolved in NaCl 0.9% (4 ml/kg) and injected i.p. 45 min before testing. For control purposes NaCl 0.9% injections (4 ml/kg) were used.

2.3. Water maze

The swimming patterns of rats were monitored with a computerized video tracking system (Riekkinen Jr. et al., 1990b). The computer calculated the mean of daily swimming speed (cm/s) and escape distance (cm) (daily total distance/number of daily trials) to a hidden, submerged platform. The mean daily escape values of the groups were stored for statistical analysis of the effects of drug treatment on water maze acquisition. The starting locations, which were labelled north, south, east and west, were located arbitrarily on the pool rim. Rats were placed in the water, facing the wall, at one of the starting points in a random manner. The training consisted of 5 consecutive days of training (3 trials/day; each trial 70 s) for the studies investigating the effects of pretraining and 4 consecutive days of training for the studies investigating the effects at posttraining treatments on spatial navigation. A 3-day paradigm (3 trials/day; each trial 70 s) was used to assess the effects of study drugs on cue navigation to a clearly visible platform. The groups involved in the study investigating the effects of pretest treatment on spatial bias performance were initially trained for 5 days (3 trials/day;

each trial 70 s) without any drug treatment and then the rats were divided into groups matched for water maze learning. During the sixth day a trial with no platform in the pool was assessed and the time spent (s) in the previous training quadrant was used to measure spatial bias (the more time spent in the previous goal quadrant, the better bias). If the rats failed to find the platform, they were placed on it for 5 s. The rats that escaped to the platform by themselves were allowed to stay on it for 5 s. A 30-s recovery period was allowed between the trials. During the training trials the platform was clearly visible or hidden (see for the details the Results section).

2.4. Passive avoidance

The passive avoidance box consisted of a bright (40 × 25 × 30 cm/length, height, width) and dark (110 × 25 × 30 cm/length, height, width) compartment. During the training trial the rats were placed into the bright compartment. The guillotine door separating the two compartments was opened 30 s later and the time to enter the dark compartment was measured. After the rats had entered the dark compartment a shock was delivered (0.5 mA, 3 s). During the testing trial 24 h later the rats were again placed into the bright compartment, the guillotine door was opened, and the latency to re-enter the dark compartment was measured (maximum duration is 360 s). Short entry latencies indicated bad performance.

2.5. Statistics

The one-way-analysis of variance followed by Duncan's post-hoc multiple group comparison was used to analyze passive avoidance and spatial bias group differences. Multiple analysis of variance tests were used to measure the effects of drug treatments on water maze acquisition performance. $P < 0.05$ was accepted as significant.

3. Results

3.1. Hidden platform

3.1.1. Pretraining injection of CPP and prazosin

The effects of daily pretraining injection of CPP (groups: control, CPP 1, CPP 3 or CPP 10 mg/kg), prazosin (groups: control, prazosin 0.1 mg/kg, prazosin 0.3 mg/kg, prazosin 1 mg/kg, prazosin 2 mg/kg) and combined CPP + prazosin (groups: control, CPP 1 mg/kg, prazosin 1 mg/kg, CPP + prazosin 1 mg/kg) on water maze and passive avoidance behavior were studied. Fig. 1 shows the water maze results of these experiments. Rats were trained for 5 days to find the hidden platform.

CPP dose dependently at 3 and 10 mg/kg impaired water maze navigation and increased the escape distance (overall group effect: $F(3,31) = 8.2$, $P < 0.05$). At the highest dose the rats were markedly affected. Furthermore,

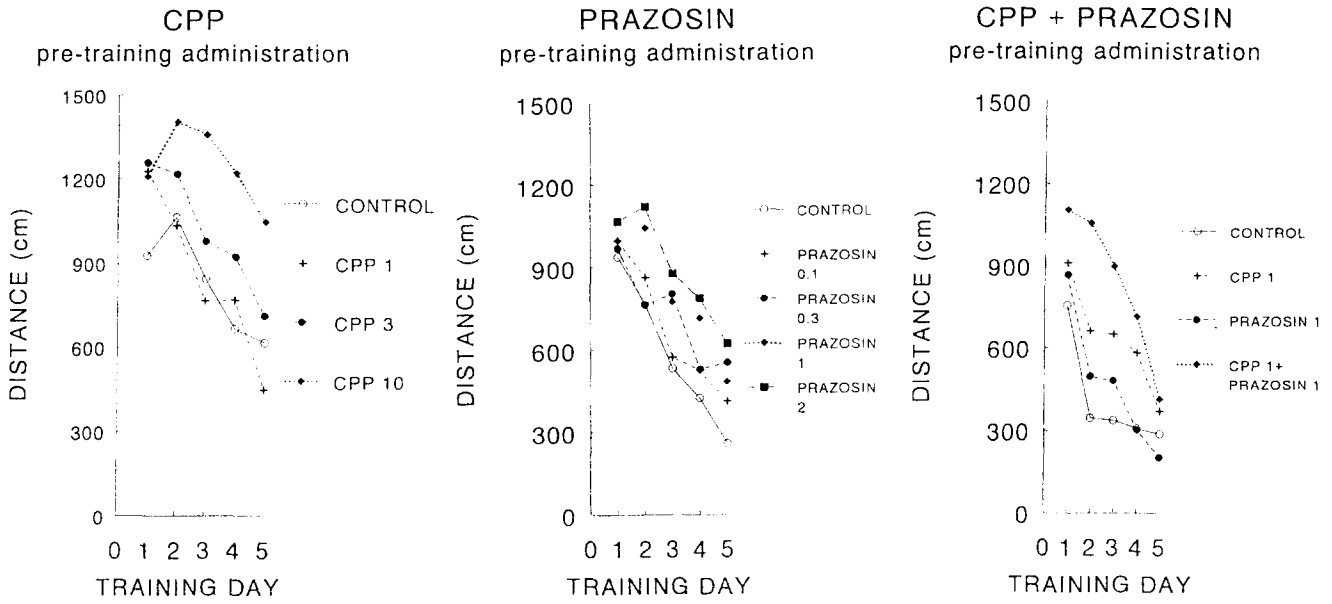

Fig. 1. Pretraining treatment with single injection of CPP 1, 3 or 10 mg/kg (left), prazosin 0.1, 0.3, 1 or 2 mg/kg (middle) or combined injection of CPP + prazosin 1 mg/kg (right) on water maze spatial navigation to a hidden escape platform. CPP dose dependently and markedly impaired water maze navigation. Prazosin induced a defect only at the highest dose used. A combination of subthreshold doses of prazosin (1 mg/kg) and CPP (1 mg/kg) impaired navigation in the water maze pool. *Y*-axis: escape distance to the hidden platform in cm. The values represent daily group means. *X*-axis: training days 1–5.

CPP 10 mg/kg treated rats tended to jump off the platform after an experimenter had placed them on it or the rats had found it. A dose of 1 mg/kg had no effect on water maze behavior ($F(1,18) = 0.4$, $P > 0.05$). The analysis of swimming speed also revealed that CPP 10 mg/kg markedly decreased the speed of swimming (data not shown) (overall group effect: $F(3,31) = 5.5$, $P < 0.05$; controls vs. CPP 10 mg/kg: $F(1,18) = 5.7$, $P < 0.05$). However, the smaller CPP doses had no measurable effect on the swimming speed. Passive avoidance training trial entry latencies were not affected by CPP at any of the doses tested (data not shown) (overall group effect: $F(3,30) = 0.4$, $P > 0.05$). However, 3 and 10 mg/kg impaired passive avoidance testing trial latencies (mean ± S.D.: controls = 344 ± 23 s, CPP 1 mg/kg = 342 ± 35 s, CPP 3 mg/kg = 202 ± 55 s, CPP 10 mg/kg = 151 ± 66 s) (overall group effect: $F(3,30) = 7.2$, $P < 0.05$).

Prazosin only at the highest dose of 2 mg/kg increased the water maze escape distance and impaired spatial navigation performance (overall group effect: $F(4,43) = 5.8$, $P < 0.05$; controls vs. prazosin 2 mg/kg: $F(1,18) = 8.8$, $P < 0.05$). Analysis of swimming speed showed that prazosin decreased swimming speed at the 2 mg/kg dose (overall group effect: $F(4,43) = 5.0$, $P < 0.05$; controls vs. prazosin 2 mg/kg: $F(1,18) = 7.3$, $P < 0.05$) (data not shown). Passive avoidance training and testing trial behavior remained unaffected by the prazosin doses used (means ± S.D.: controls = 334 ± 24 s, prazosin 0.1 mg/kg = 345 ± 33 s, prazosin = 0.3 mg/kg = 351 ± 14 s, prazosin 1 mg/kg = 323 ± 45 s, prazosin 2 mg/kg = 351 ± 33 s; overall group effect: $F(4,42) = 0.4$, $P > 0.05$ for both comparisons).

Again, single injections of CPP and prazosin at 1 mg/kg were ineffective in the water maze study, as the escape distance was not affected by the treatments (overall group effect: $F(3,36) = 68.8$, $P < 0.05$; $F(1,18) < 0.8$, $P > 0.05$ for both comparisons with the controls). In contrast, a combination of CPP and prazosin, 1 mg/kg, markedly impaired water maze spatial navigation and increased the escape distance ($F(1,18) = 8.8$, $P < 0.05$) and a significant CPP × prazosin treatment interaction was found on the escape distance ($F(1,36) = 10.1$, $P < 0.05$). We found that prazosin 1 mg/kg, CPP 1 mg/kg and the combination of CPP 1 mg/kg + prazosin 1 mg/kg had no effect on the speed of swimming (data not shown) (overall group effect: $F(3,36) = 0.3$, $P > 0.05$). Furthermore, the combination of subthreshold doses of CPP (1 mg/kg) and prazosin (1 mg/kg) did not have a significant effect on passive avoidance behavior (means ± S.D.: controls = 344 ± 22 s, CPP 1 mg/kg = 353 ± 11 s, prazosin 1 mg/kg = 351 ± 10 s, CPP 1 mg/kg + prazosin 1 mg/kg = 344 ± 18 s) (overall group effect: $F(3,36) = 0.6$, $P > 0.05$).

3.1.2. Posttraining injections of CPP and prazosin

The effect of daily posttraining injections of CPP, prazosin and CPP + prazosin (groups: controls, prazosin 1 and 2 mg/kg, CPP 3 and 10 mg/kg, CPP 3 mg/kg + prazosin 1 mg/kg) was investigated on water maze and passive avoidance behavior. Fig. 2 shows the water maze results of this experiment. Rats were trained for 4 days to find the hidden platform.

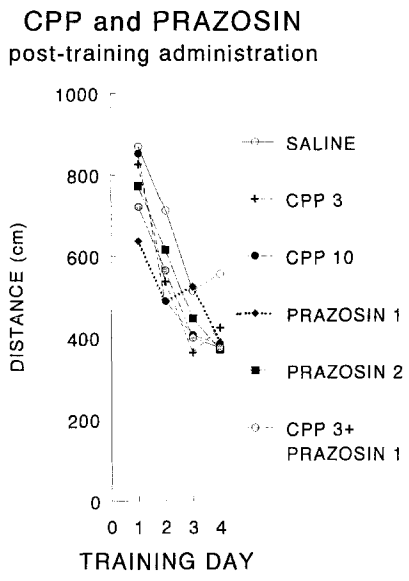

Fig. 2. Posttraining treatment with single injection of CPP 3 or 10 mg/kg, prazosin 1 or 2 mg/kg or combined injection of CPP 3 mg/kg + prazosin 1 mg/kg on water maze spatial navigation to a hidden escape platform. Posttraining CPP and/or prazosin did not induce a defect of water maze navigation. *Y*-axis: escape distance to the hidden platform in cm. The values represent daily group means. *X*-axis: training days 1–4.

Analysis of the escape distances of this study showed that CPP impaired performance ($F(5,64) = 0.8$, $P > 0.05$). Posttraining injections of CPP 10 mg/kg and CPP 3 mg/kg had no marked effect on water maze spatial navigation ($F(1,18) = 1.5$, $P > 0.05$). Posttraining prazosin was ineffective in disrupting water maze spatial navigation at 1 or 2 mg/kg ($F(1,18) < 1$, $P > 0.05$ for both comparisons). Furthermore, a combination of subthreshold doses of CPP 3 mg/kg and prazosin 1 mg/kg had no effect on water maze behavior ($F(1,18) = 0.01$, $P > 0.05$). No effect on swimming speed was observed (data not shown) ($F(5,65) = 0.3$, $P > 0.05$). Posttraining CPP 3 and 10 mg/kg, single prazosin (1 or 2 mg/kg) and combined prazosin 1 mg/kg + CPP 3 mg/kg were ineffective in impairing passive avoidance testing or training trial performance (mean ± S.D.: controls = 344 ± 24 s, CPP 3 mg/kg = 334 ± 31 s, CPP 10 mg/kg = 352 ± 12 s, prazosin 1 mg/kg = 334 ± 25 s, prazosin 2 mg/kg = 341 ± 27 s, prazosin 1 mg/kg + CPP 3 mg/kg = 334 ± 32 s) (overall effect: $F(5,63) = 0.02$, $P > 0.05$).

3.1.3. Pretest injection of CPP and prazosin

The effect of pretest injection of CPP, prazosin and CPP + prazosin (groups: controls, CPP 3 and 10 mg/kg, prazosin 1 and 2 mg/kg, CPP 3 mg/kg + prazosin 1 mg/kg) on water maze and passive avoidance behavior

was studied. Fig. 3 shows the water maze results of this experiment. Rats were trained for 5 days to find the hidden platform. Then groups that were matched for their learning ability during the 5-day training period were tested 70 s on the 6th day with no platform in the pool.

Analysis of spatial bias data revealed treatment-induced effects on performance (one-way ANOVA $F(5,64) = 8.8$, $P < 0.05$). Analysis of water maze spatial bias revealed that CPP 10 mg/kg (Duncan's test: $P < 0.05$) disrupted retention trial performance and the lower dose of 3 mg/kg (Duncan's test: $P < 0.05$) was ineffective. Pretest single injection of prazosin at 1 or 2 mg/kg was ineffective in disrupting water maze retention performance (Duncan's test: $P < 0.05$). Furthermore, a combination of subthreshold doses of prazosin 1 mg/kg and CPP 3 mg/kg did not significantly modulate water maze retention performance (Duncan's test: $P < 0.05$). The highest dose of CPP 10 mg/kg and prazosin 2 mg/kg significantly decreased the swimming speed of the rats (data not shown) (one-way ANOVA $F(5,64) = 10.1$, $P < 0.05$; Duncan's test: $P < 0.05$ for both comparison). Passive avoidance testing trial performance was not impaired by single or combined prazosin and CPP (mean ± S.D.: controls = 344 ± 34 s, CPP 3 mg/kg = 313 ± 55 s, CPP 10 mg/kg = 356 ± 12 s, prazosin 1 mg/kg = 301 ± 56 s, prazosin 2 mg/kg = 323 ± 42 s, CPP 3 mg/kg + prazosin 1 mg/kg = 351 ± 12 s) (one-way ANOVA $F(5,64) = 0.3$, $P > 0.05$).

3.2. Visible platform

The effects of pretraining injection of CPP, prazosin and CPP + prazosin (groups: controls, prazosin 1 and 2 mg/kg, CPP 3 and 10 mg/kg and CPP 3 mg/kg + prazosin 1 mg/kg) on cue navigation to a clearly visible platform were studied. Fig. 4 shows the results of this experiment. The rats were tested for 3 days (3 trials/day; each trial 70 s) for their ability to find a clearly visible platform.

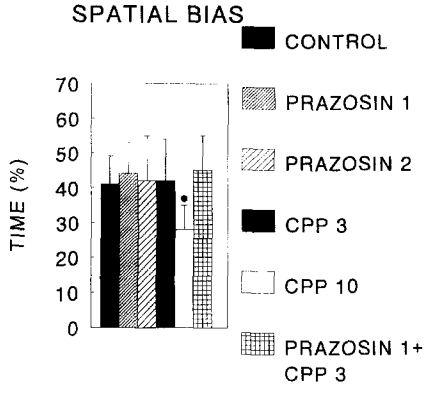

Fig. 3. Pretest treatment with single injection of CPP 3 or 10 mg/kg, prazosin 1 or 2 mg/kg or combined injection of CPP 3 mg/kg + prazosin 1 mg/kg on water maze spatial bias test (no platform in the pool) performance. Spatial bias was calculated as the time spent in the previous location of the escape platform during a 70-s trial. Pretest CPP at the higher dose impaired water maze spatial bias. Prazosin alone or in combination with a subthreshold dose of CPP (3 mg/kg) had no marked effect on spatial bias in the water maze pool. *Y*-axis: spatial bias in s. The values represent group means ± S.D. * $P < 0.05$ vs. controls, Duncan's post-hoc multiple group comparison.

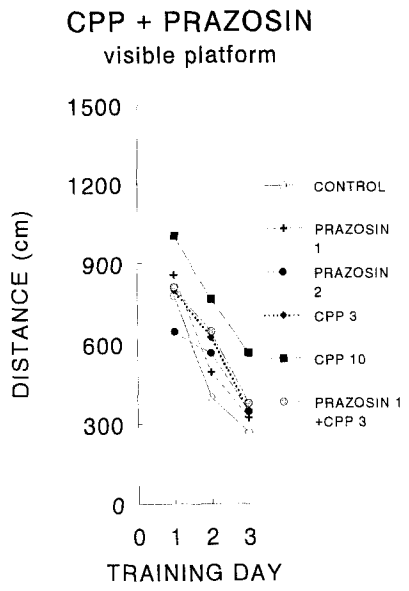

Fig. 4. Pretraining treatment with single injection of CPP 3 or 10 mg/kg, prazosin 1 or 2 mg/kg or combined injection of CPP 1 mg/kg + prazosin 1 mg/kg on water maze cue navigation to a clearly visible escape platform. CPP (10 mg/kg) markedly impaired cue water maze navigation. Single injection prazosin or a combination of subthreshold doses of prazosin (1 mg/kg) and CPP (3 mg/kg) had no effect on cue navigation in the water maze pool. *Y*-axis: escape distance to the visible platform in cm. The values represent daily group means. *X*-axis: training days 1–3.

Cue navigation performance was affected by the study drug treatments ($F(5,65) = 8.2$, $P < 0.05$). Again, the highest dose of CPP 10 mg/kg disrupted performance ($F(1,18) = 6.7$, $P < 0.05$), but the lower dose 3 mg/kg was not effective in impairing cue navigation ($F(1,18) = 0.5$, $P > 0.05$). Single injection of prazosin 1 and 2 mg/kg or combined injection of prazosin 1 mg/kg and CPP 1 mg/kg was not effective in impairing cue navigation in the water maze paradigm ($F(1,18) < 0.6$, $P > 0.05$ for all comparisons).

4. Discussion

The present results describing that the NMDA receptor antagonist, CPP, and the α_1-adrenoceptor antagonist, prazosin, impaired performance in water maze and passive avoidance paradigms is in good agreement with previous studies describing that NMDA receptors and noradrenergic systems may regulate performance in tests used to assess learning and memory processes. A more interesting and novel finding is that combined administration of prazosin and CPP impaired performance in the spatial navigation paradigm of the water maze test more severely than did the

drugs given individually, but the treatments did not have additive effects to disrupt swimming, passive avoidance performance, or cue navigation in water maze test.

The present result showing that pretraining CPP dose dependently (3 and 10 mg/kg) impaired spatial navigation to a hidden escape platform supports previous evidence showing that blockade of NMDA receptors impairs performance in paradigms used to measure different types of memory and learning (Morris et al., 1986; Venable and Kelly, 1990; Clissold et al., 1991; Cole et al., 1993). The spatial navigation performance of CPP 10 mg/kg-treated rats was severely disrupted as indicated by the markedly increased escape distance values during all of the training days. However, some of the performance-impairing effects of CPP 10 mg/kg are likely to be due to non-mnemonic factors, such as motor, attention or sensory defects, as rats swam slower, tended to jump off the platform (Pitkänen et al., 1996), and had an impaired cue navigation to a clearly visible platform. Furthermore, the learning curves of CPP 3 mg/kg treated and control rats were parallel, indicating that water maze performance was disrupted at the beginning of the test period. Thus, it is reasonable to believe that systemically injected CPP may disrupt water maze navigation by modulating non-cognitive processes important for accurate spatial performance. The present study also examined the time course of action of CPP and found that posttraining treatment had no effect on water maze performance, and only treatment with the high (10 mg/kg) dose disrupted spatial bias trial behavior. The lack of an effect of posttraining treatment to impair spatial navigation indicates that memory consolidation was not impaired by treatment with an NMDA receptor antagonist. In contrast, due to the non-mnemonic effects induced by CPP 10 mg/kg, the pretest treatment-induced impairment of spatial bias is difficult to interpret selectively as a defect of retrieval or retention. Indeed, it is likely that non-mnemonic defects may contribute to the impairing action of CPP 10 mg/kg. The passive avoidance study revealed also that the defects induced by CCP were dose and time dependent: pretraining treatment with 3 or 10 mg/kg disrupted retention trial performance, but posttraining or pretest treatments were ineffective.

Our results show the time course and type of action of prazosin on spatial vs. cue navigation behavior. We found that only pretraining treatment with prazosin affected performance and that posttraining or pretesting treatments were ineffective. Again, the slope of the water maze learning curves did not differ from those of controls, indicating that non-mnemonic effects of prazosin may mediate this effect. Furthermore, prazosin only modestly decreased swimming speed and had no effect on cue navigation to a visible platform, which suggests that the α_1-adrenoceptor block brought about by the prazosin 2 mg/kg dose selectively impaired mechanisms supporting spatial navigation performance. It could be argued that the doses of prazosin used were too low to block the α_1-adrenoceptors and impair consolidation and retrieval of water maze behavior significantly. However, the highest dose of prazosin already had an adverse effect on swimming speed, and therefore higher doses were not used.

The studies investigating the behavioral profile of combined CPP 1 mg/kg and prazosin 1 mg/kg doses showed that spatial navigation was impaired by combined daily pretraining treatment, but cue navigation and passive avoidance behavior remained unaffected. The effects of injection of the drug combination at different time periods indicated that only pretraining treatments had a significant impairing action on water maze spatial behavior. Furthermore, following pretraining treatment a synergistic effect was observed only on the escape distance values and swimming speed was not decreased more severely following single or combined prazosin and CPP treatments, suggesting that the synergistic effect on escape distance values is not due to non-mnemonic factors, such as motor or motivational defects. However, it is possible that the impairment of attention or discrimination functions caused by disruption of noradrenaline and NMDA transmission may cause the performance defect in the spatial navigation paradigm of the water maze (Tang and Ho, 1988; Tan et al., 1989; Harley, 1991). Indeed, spatial navigation in the water maze test is dependent on the allocation of attention to and discrimination of distal extramaze cues. Thus, these results suggest that the brain mechanisms underlying acquisition of water maze spatial navigation are controlled by α_1-adrenoceptors and NMDA receptors, and that these receptor mechanisms do not jointly regulate consolidation or retrieval of spatial information, acquisition of cue navigation, avoidance behavior or motor behavior.

The validity of the passive avoidance test as a measure of memory is difficult to interpret as many non-mnemonic factors, such as alteration of sensitivity and reactivity to foot shock, arousal or attention, induced by pretraining treatment may modulate passive avoidance behavior. We observed that CPP impaired passive avoidance testing trial performance following pretraining treatment, but posttraining and pretest treatments did not affect performance. Thus, it is likely that the mechanisms underlying consolidation and retrieval of passive avoidance behavior remained unimpaired.

An interpretation of the time-dependent (pretraining treatment most effective in disrupting performance) impairment is that CPP, prazosin and CPP + prazosin treatments impair acquisition of spatial navigation and passive avoidance paradigms and that at a high dose CPP produced a non-mnemonic performance defect in the water maze test. This hypothesis is supported by previous studies showing that drugs acting via the noradrenergic system or NMDA receptors may, at an appropriate dose, selectively impair acquisition of long-term memory and also disrupt short-term working memory. However, the data are equally compatible with the hypothesis that the performance-impairing action of CPP, prazosin and combined CPP +

prazosin is dependent on the stimulus control. Indeed, the parallel shift upwards of the learning curves (even on day 1) of single and combined CPP and prazosin-treated animals suggests an effect on performance and not learning per se.

In conclusion, the present study described that combined partial block of α_1-adrenoceptors and NMDA receptors with subthreshold doses of antagonists may selectively impair mechanisms underlying performance in the spatial navigation test and have no effect on consolidation or retrieval of spatial navigation and passive avoidance behavior. Therefore, the present data may indicate that the activity of ascending noradrenergic input regulates NMDA receptor-mediated behavioral functions, such as acquisition of water maze spatial navigation performance. These results may have also some clinical relevance for neurological disorders associated with an impaired activation of α_1-adrenoceptors and NMDA receptors. It is possible that the degeneration of noradrenaline projections may aggravate dysfunctioning of NMDA receptors in the medial temporal lobe and aggravate memory acquisition failure in Alzheimer disease (Soininen et al., 1992; Francis et al., 1994). Therefore, future studies should investigate the effects of combined stimulation of α_1-adrenoceptor and NMDA receptors on acquisition performance in animal models of Alzheimer disease, and also the possible site(s) of the α_1-adrenoceptor–NMDA receptor interaction in the regulation of acquisition of novel memory traces.

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