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Effects of St-587 and Prazosin on Water Maze and Passive Avoidance Performance of Scopolamine-Treated Rats

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PUUMALA, T., J. SIRVIÖ, S. RUOTSALAINEN AND P. RIEKKINEN, SR. *Effects of St-587 and prazosin on water maze and passive avoidance performance of scopolamine-treated rats.* PHARMACOL BIOCHEM BEHAV **55**(1) 107–115, 1996.—The present experiments were designed to investigate whether the alpha-1 adrenergic and muscarinic cholinergic systems interact in the regulation of spatial navigation behavior in the Morris water maze test and passive avoidance performance. Pretraining administration of scopolamine, a muscarinic antagonist, markedly impaired the acquisition of water maze task (a hidden platform version) as well as retention of this task. The drug also impaired slightly navigation to a visible platform. Pretraining subcutaneous administration of St-587 (alpha-1 agonist) at 2000 μg/kg slightly improved the water maze navigation to a hidden platform in control rats, but its effect was not augmented in scopolamine-treated rats. Pretraining administration of prazosin (alpha-1 antagonist) 1000 μg/kg or 2000 μg/kg did not significantly potentiate the scopolamine (muscarinic cholinergic antagonist)-induced (doses 200 μg/kg and 100 μg/kg, pretraining intraperitoneal injection) deficit in water maze navigation. Pretraining administration of prazosin at doses 1000 μg/kg and 2000 μg/kg or St-587 at doses 1000 μg/kg and 2000 μg/kg did not have any significant influence on scopolamine-induced (200 μg/kg or 400 μg/kg) disruption in passive avoidance performance. These findings suggest that alpha-1 adrenergic mechanisms do not participate or are not the most important component of the noradrenergic system in the interaction between noradrenaline and muscarinic receptors in the modulation of learning and memory. The analysis of results indicates that activation of alpha-1 adrenoceptors might facilitate the acquisition of water maze task in its initial phase, for instance, switching from wall hugging strategy to an active exploration strategy. Furthermore, the present data suggest that muscarinic cholinergic blockade may affect both mnemonic and nonmnemonic processes in rats.

Noradrenaline Alpha-1 adrenoceptors Muscarinic receptors Scopolamine Learning Memory Rat

RELATIONAL memory as assessed with the water maze (WM) task, seems to involve *N*-methyl-D-aspartate (NMDA) (36) and metabotropic type of glutamate receptors (40). NMDA receptors are also crucial for the induction of long-term potentiation (LTP), a model of synaptic plasticity, in several areas of the hippocampal formation and neocortex (3,8,9,28,30). Furthermore, metabotropic glutamate receptors are involved in the induction and reversal process of LTP (4,40,51).

The ascending systems, especially neurones releasing acetylcholine and noradrenaline, modulate signal transmission as well as synaptic and behavioral plasticity (5,9,15,18,20,21,26, 31,33). In those functions, acetylcholine and noradrenaline have synergistic effects, and those neurotransmitters may interact in processes involved in spatial learning (11,41).

Noradrenaline exerts its functions through alpha and beta adrenoceptors that are divided into subclasses (34,47). A considerable body of evidence points to the role of beta-1 adrenergic receptors, which are linked to the synthesis of cyclic adenosine monophosphate (cAMP) (13), as being involved in synaptic and behavioral plasticity (14,20,25,26,46). cAMP may regulate the ceiling of LTP expression (1). On the other hand, the role of postsynaptic alpha-adrenoceptors in plasticity has been proposed to be only minor. However, pharmacological evidence suggests that the stimulation of alpha-1 adrenoceptors can potentiate NMDA and metabotropic receptor-mediated effects of glutamate (29,50). This suggests that the stimulation of alpha-1 adrenoceptors may facilitate encoding of information in the hippocampus.

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Previously, it has been shown that β-adrenergic and muscarinic cholinergic mechanisms can interact in learning and memory as assessed using water maze and passive avoidance tasks (10). In the present study, the question was asked whether alpha-1 adrenergic and muscarinic cholinergic mechanisms interact in experiments assessing learning and memory. Thus, the effects of concurrent administration of alpha-1 adrenoceptor active agents and scopolamine on the acquisition of WM task and the retention of passive avoidance task were investigated in rats.

METHOD

Animals

Male Han:Wistar rats (n = 336) were used in the experiment. The rats were 14–17 weeks old at the beginning of behavioral testing. The rats were housed in pairs in stainless steel shoebox cages (44 × 27 × 15 cm, l × w × h) with elevated coverings. The cages were placed in a temperature (20 ± 1°C), humidity (55 ± 10%) and light period (lights on 0700–1900 h)-controlled environment. Food pellets (Astra-Ewos, Sweden) and water were available ad lib except during testing.

Drugs

The drugs used in this study were St-587, an alpha-1 agonist (1000 and 2000 μg/kg), prazosin, an alpha-1 antagonist (1000 and 2000 μg/kg), and scopolamine hydrobromide, a muscarinic cholinergic antagonist (100 and 200 μg/kg). St-587 has been considered to be a selective alpha-1 adrenoceptor agonist, but it has also been shown to have alpha-2 antagonistic properties (12,37). Prazosin (Research Biochemicals International, USA) was dissolved in deionized water (1 mg/ml) and injected subcutaneously. St-587 (Boehringer Ingelheim KG, Germany) and scopolamine (Merck, Germany) were dissolved in saline and injected subcutaneously and intraperitoneally, respectively [1 ml/kg (SC) and 2 ml/kg (IP)]. Prazosin and scopolamine were administered 30 min before the training session when the interaction between muscarinic cholinergic and alpha-1 adrenergic systems was studied. St-587 was injected 45 min before daily training. For controls (vehicle-treated) deionized water (SC 1 ml/kg or 2 ml/kg), saline SC (1.0 ml/kg), and IP (2.0 ml/kg) were injected on each consecutive day.

Water Maze Experiments

The WM apparatus was a circular, black painted fiberglass tank, 150 cm in diameter, 74 cm deep, and filled to height of 52 cm with water at room temperature (20 ± 1°C). The platform (diameter 10 cm) was made of a Plexiglas tube and its top surface was composed of black rubber. The platform top was 1.5 cm below the water line. The pool was divided into four quadrants and three annuli of equal surface area. The starting locations were called north, east, south, and west, and they were arbitrarily at equal distances on the pool rim. The swim paths were monitored by a video camera linked to a computer through an image analyzer. The timing of the trial was started and ended by the experimenter by pressing an air button.

The rats were placed into the water, with the nose pointing toward the wall, at one of the four starting points that were ordered in a semirandom manner. The first swim of the day was always started from one of the points located farthest from the platform (north, east). The starting point of the second swim of the day was chosen randomly between south and west, and the third trial was started always from the farthest point (east, north). If the first trial was started from north then east was selected as the starting point of third trial and vice versa. During the training period of the task, rats were trained three times/day for 7 days (maximum trial duration 70 s, 10 s reinforcement on the platform, 30 s recovery period between trials) to find a submerged platform, located in the middle of the south-west quadrant of the pool. Rats that failed to find the submerged platform were placed onto it for 10 s. The computer calculated the escape latency (s) and distance (cm) to find the hidden platform. Control rats showed a clear acquisition of this task, and escape latencies were 10–20 s at the end of training period. The probe trial was assessed on the eighth day of behavioral testing (two experiments) and the time spent in training counter was recorded. The training counter was determined as an area around the place where the escape platform had been set during training. The training counter was set to be three times the diameter of the escape platform (counter diameter 30 cm). Drugs were also administered before the probe trial. To control whether an acquisition deficit was due to impaired visual acuity (discrimination), a visible platform version of the task was used. In this version of the task the platform top was 2 cm above water line and the platform was painted white. Naive rats were used in each water maze experiment.

Passive Avoidance

The passive avoidance apparatus consisted of a rectangular Plexiglas box (length, 90 cm; height 15 cm), divided into two compartments by a sliding guillotine door (length of the dark compartment, 60 cm; length of the illuminated compartment 30 cm). The dark compartment had a metal grid floor, to which a shock generator (Campden Instruments Ltd, UK) was connected. In the training of the task, the rat was placed on the lighted side. After 30 s, the door was opened into the dark compartment. Five seconds after the entry of the rat into the dark chamber, a 0.5 mA shock was initiated and maintained for 3 s. Entry latency was measured during the training trial. In the retention test (24 h after training), the rat was placed in the lighted side of the apparatus, and the door was opened 30 s later. The session was continued until the rat had entered the dark compartment (maximum time 360 s). The latency to enter the dark chamber (testing latency) was recorded.

The rats used in passive avoidance experiments were animals that were initially tested in the WM task (n = 240). Animals were given a 2-week (14 days) wash-out period after the last injection, which had been given before the last WM-testing session. Rats were allocated into the same groups as those used in water maze test in the passive avoidance training and testing. Thus, for example, rats that had been injected with scopolamine prior to daily WM were given scopolamine also before the passive avoidance training trial, and animals that were injected with scopolamine and prazosin before daily WM testing were given the same drugs prior to the passive avoidance training trial.

Statistical Analysis of Data

Multivariate analysis of variance (MANOVA) was used to analyze WM distance, latency, as well as speed (distance/latency) values. The one-way ANOVA followed by Duncan's multiple group comparison was used to analyze group differences of the data collected during probe trials. The Kruskal–Wallis one-way ANOVA was used to analyze overall group effects of the passive avoidance data. In further analysis of differences between groups, Mann–Whitney U-test was used.

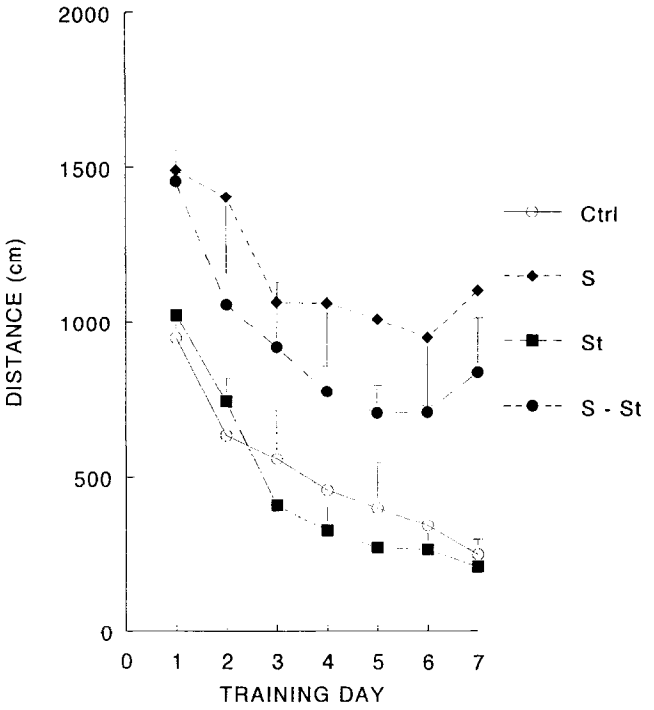

FIG. 1. Effects of St-587 and scopolamine on water maze escape distance values (y-axis, centimeters (cm)). Training days 1–7 are shown on the x-axis. Three trials were given during every training day. The platform was hidden under the water. The results are expressed as group mean ± SEM of daily training trials. Error bars of the 1st, 3rd, 5th, and 7th, or 2nd, 4th, and 6th training days are shown. Ctrl, vehicle (n = 12); S, scopolamine 200 μg/kg (n = 12); St, St-587 1000 μg/kg (n = 12); S-St, scopolamine 200 μg/kg + St-587 1000 μg/kg (n = 12).

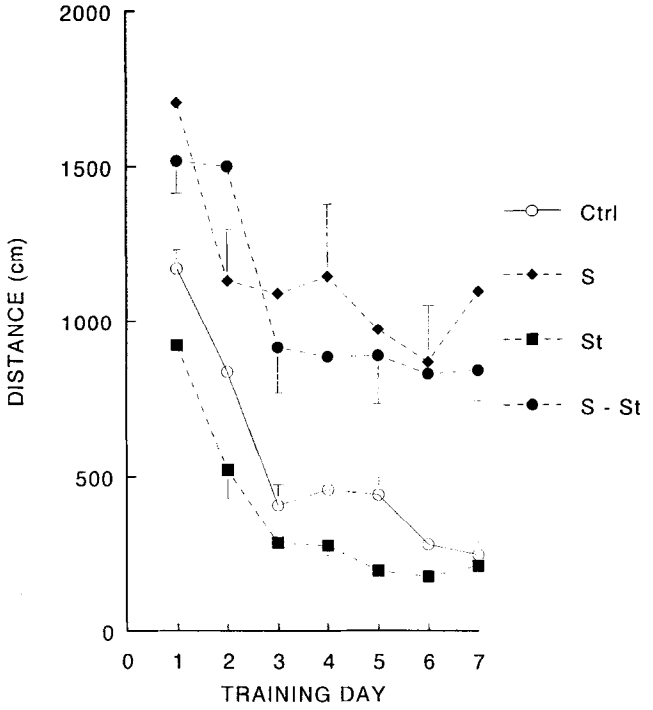

FIG. 2. Effects of St-587 and scopolamine on water maze escape distance values (y-axis, centimeters (cm)). Training days 1–7 are shown on the x-axis. Three trials were assessed during every training day and the escape platform was hidden under the water. Results are expressed as group mean ± SEM of daily training trials. Error bars of the 1st, 3rd, 5th, and 7th, or 2nd, 4th, and 6th training days are shown. Ctrl, vehicle (n = 12); S, scopolamine 200 μg/kg (n = 12); St, St-587 2000 μg/kg (n = 12); S-St, scopolamine 200 μg/kg + St-587 2000 μg/kg (n = 12).

$p < 0.05$ was accepted as significant. The data were analyzed using SPSS/PC+ software in a personal computer.

RESULTS

Effects of Combined Alpha-1 Adrenergic Stimulation and Muscarinic Cholinergic Blockade

Pretraining Administration of St-587 1000 μg/kg and Scopolamine 200 μg/kg, Hidden Platform. In the analysis of WM escape distance values, a significant overall group effect was observed, $F(3, 44) = 7.64$, $p < 0.001$. In further analysis of treatment effects on WM escape distance values, it was observed that scopolamine treatment significantly impaired the performance, $F(1, 44) = 20.97$, $p < 0.001$. Further analysis of escape distance values revealed that scopolamine 200 μg/kg administered on its own and combined with St-587 1000 μg/kg significantly impaired the performance of these rats in comparison with controls, $F(1, 22) = 9.65$, $p < 0.01$, and $F(1, 22) = 6.73$, $p < 0.05$, respectively. Rats treated with a combination of scopolamine 200 μg/kg and St-587 1000 μg/kg did not significantly differ from rats receiving scopolamine alone, $F(1, 22) = 1.24$, $p > 0.1$. Pretraining administration of St-587 at a dose of 1000 μg/kg did not significantly affect the WM navigation of rats in comparison with controls, $F(1, 22) = 0.18$, $p > 0.1$ (Fig. 1).

Pretraining Administration of St-587 2000 μg/kg and Scopolamine 200 μg/kg, Hidden Platform. Analysis of WM escape distance values revealed a significant overall group effect, $F(3, 44) = 19.33$, $p < 0.001$. In further analysis of escape distance values, it was found that pretraining administration of St-587 2000 μg/kg significantly improved the performance of rats when compared with controls, $F(1, 22) = 9.4$, $p < 0.01$. (The data of the first training day was also analysed separately, and a significant group difference was observed in distances of the first three swims between St-587 2000 μg/kg-treated rats and controls, $F(1, 22) = 6.31$, $p < 0.05$ (data not shown). Shorter escape latencies were also observed in the group of St-587–treated animals when compared with controls, but the difference did not reach statistical significance, $F(1, 22) = 2.89$, $p = 0.103$ (data not shown). Furthermore, scopolamine 200 μg/kg administered on its own, $F(1, 22) = 16.91$, $p < 0.001$, or concurrently with St-587 2000 μg/kg, $F(1, 22) = 7.55$, $p < 0.05$, impaired the performance in comparison with controls. No significant difference was observed between scopolamine and combination-treated groups, $F(1, 22) = 0.30$, $p > 0.1$ (Fig. 2). When analyzing data gathered during the probe trial, a significant overall group effect was observed in time spent in the training counter, $F(3, 44) = 6.43$, $p = 0.001$. Rats treated with scopolamine 200 μg/kg or scopolamine 200 μg/kg plus St-587 2000 μg/kg spent significantly less time in the correct (training) counter ($p < 0.05$, Duncan's post hoc test) in comparison with the control group or St-587 2000 μg/kg-treated animals (Fig. 3A).

Effects of Combined Alpha-1 Adrenergic and Muscarinic Cholinergic Blockade

Pretraining administration of prazosin 1000 μg/kg and scopolamine 200 μg/kg, hidden platform. In the analysis of WM

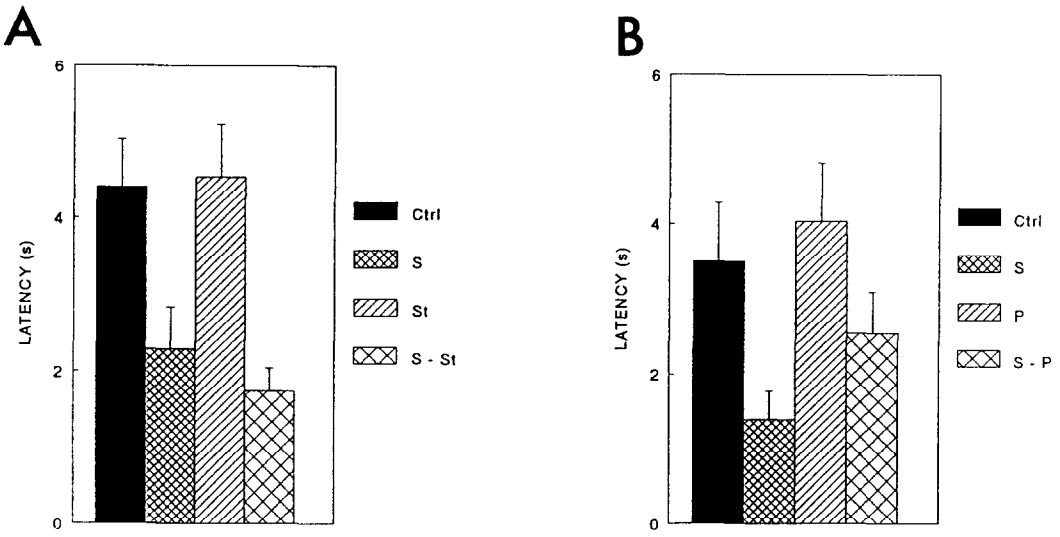

FIG. 3. Effects of pretraining administration of St-587 and scopolamine or prazosin and scopolamine on water maze probe trial time spent in training counter [time shown on the y-axis, seconds (s)]. The results are expressed as group mean + SEM. Each group consisted of 12 (n = 12) rats. (A) Ctrl, vehicle; S, scopolamine 200 μg/kg; St, St-587 2000 μg/kg; S-St, scopolamine 200 μg/kg + St-587 2000 μg/kg. (B) Ctrl, vehicle; S, scopolamine 200 μg/kg; prazosin 2000 μg/kg; S-P, scopolamine 200 μg/kg + prazosin 2000 μg/kg.

escape distance values, a significant overall group effect was observed, $F(3, 44) = 24.18$, $p < 0.001$. In further analysis of escape distance values, it was observed that scopolamine 200 μg/kg-treated rats and rats treated concurrently with scopolamine 200 μg/kg plus prazosin 1000 μg/kg were impaired when compared with the controls. Further analysis of treatment effects on escape distance values revealed that scopolamine 200 μg/kg significantly impaired the learning of the position of the hidden platform, $F(1, 44) = 70.14$, $p < 0.001$, whereas prazosin 1000 μg/kg given separately or concurrently with scopolamine 200 μg/kg had no significant effect on the performance of the rats, $F(1, 44) = 2.22$, $p > 0.1$, and $F(1, 44) = 0.2$, $p > 0.1$, respectively. An interaction between time (training day) and drug treatment occurred when rats were treated concurrently with prazosin 1000 μg/kg and scopolamine 200 μg/kg, $F(6, 264) = 2.30$, $p < 0.05$ (Fig. 4).

Pretraining Administration of Prazosin 1000 μg/kg and Scopolamine 100 μg/kg, Hidden Platform. In the analysis of WM escape distance values, a significant overall group effect was found, $F(3, 92) = 8.11$, $p < 0.001$. In the further analysis of treatment effect on escape distance values, it was observed that scopolamine 100 μg/kg significantly impaired the WM performance, $F(1, 92) = 22.35$, $p < 0.001$. Concurrent administration of prazosin 1000 μg/kg and scopolamine 100 μg/kg slightly interacted with time (training day), modifying the trend of the escape distance curve in comparison with the other treatments, $F(6, 552) = 1.99$, $p = 0.066$) (Fig. 5).

Pretraining Administration of Prazosin 2000 μg/kg and Scopolamine 200 μg/kg, Hidden Platform. Analysis of WM escape distance values revealed a significant group effect, $F(3, 44) = 19.16$, $p < 0.001$, in the overall comparison. Group comparisons revealed that scopolamine and combined scopolamine plus prazosin administration impaired the performance of rats, $F(1, 22) = 17.1$, $p < 0.001$, and $F(1, 22) = 15.06$, $p = 0.001$, respectively, but no significant difference was observed between these groups, $F(1, 22) = 0.43$, $p > 0.1$. Prazosin 2000 μg/kg injected on its own did not significantly affect the navigation performance of rats, $F(1, 22) = 0.55$, $p > 0.1$. As observed

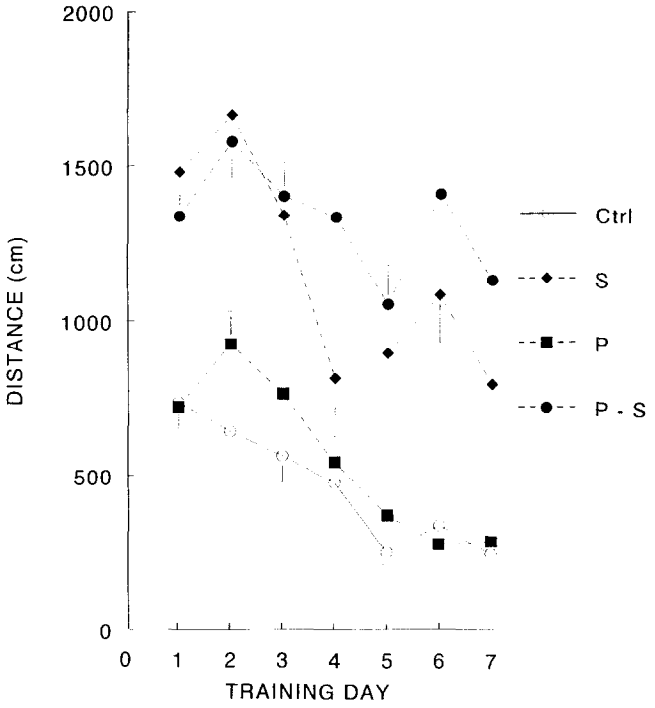

FIG. 4. Effects of prazosin and scopolamine on water maze escape distance values (shown on the y-axis, centimeters (cm)). Drug injections were made 30 min before daily training. Three trials were given every training day and the platform was hidden under the water. Ctrl, vehicle (n = 12); S, scopolamine 200 μg/kg (n = 12); P, prazosin 1000 μg/kg (n = 12); S-P, scopolamine 200 g/kg + prazosin 1000 μg/kg (n = 12).

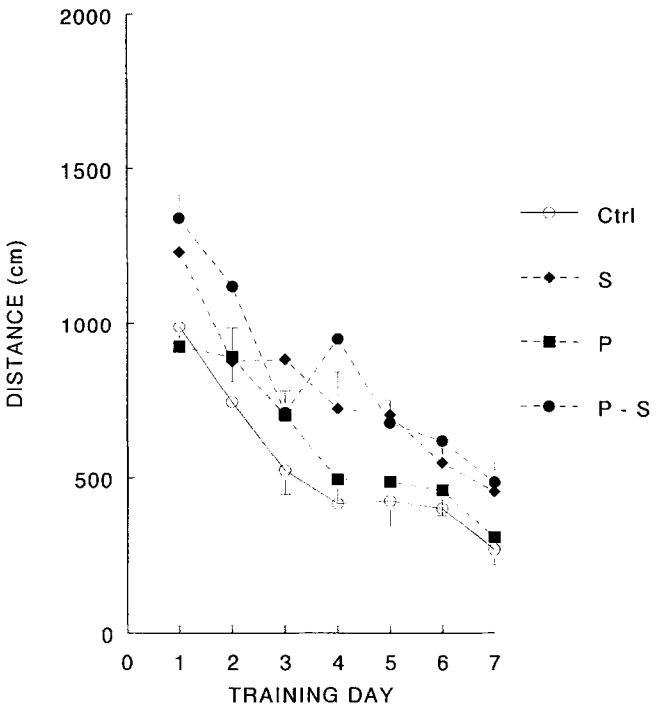

FIG. 5. Effects of prazosin and scopolamine on water maze escape distance values (shown on the y-axis, centimeters (cm)). Drug injections were made 30 min before daily training trials (three trials/day). The escape platform was hidden under the water. Ctrl, vehicle (n = 24); S, scopolamine 100 μg/kg (n = 24); P, prazosin 1000 μg/kg (n = 24); S-P, scopolamine 100 μg/kg + prazosin 1000 μg/kg (n = 24).

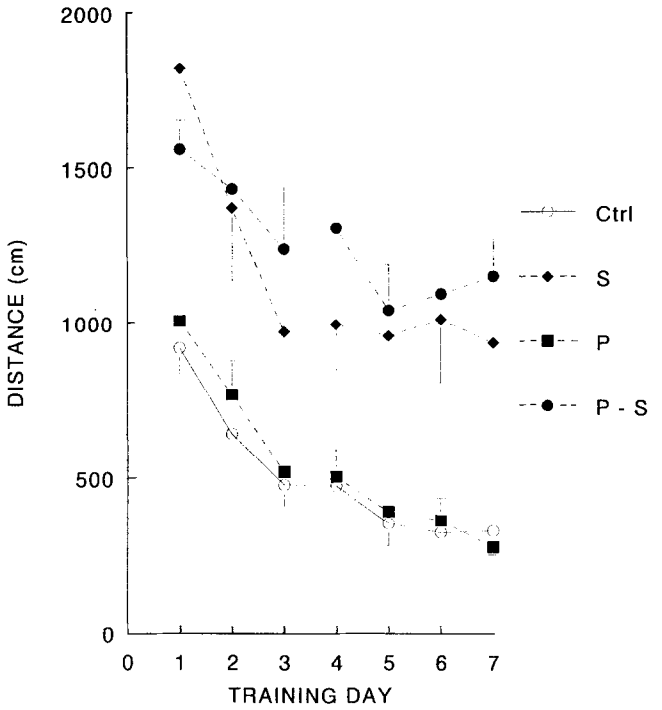

FIG. 6. Effects of prazosin and scopolamine on water maze escape distance values (y-axis, centimeters (cm)). Drug injections were made 30 min before daily training (three trials/day). The escape platform was hidden under the water. Ctrl, vehicle (n = 12); S, scopolamine 200 μg/kg (n = 12); P, prazosin 2000 μg/kg (n = 12); S-P, scopolamine 200 μg/kg + prazosin 2000 μg/kg (n = 12).

above, scopolamine 200 μg/kg treatment significantly impaired the performance of rats, $F(1, 44) = 56.65$, $p < 0.001$, but other treatments had no significant effects on performance (Fig. 6). In the analysis of the probe trial time spent in the correct (training) counter, a significant overall group effect was found, $F(3, 44) = 3.25$, $p < 0.05$, and further analysis of this data revealed that scopolamine 200 μg/kg-treated rats were impaired when compared with the control group ($p < 0.05$, Duncan's post hoc multiple group comparison) (Fig. 3B).

Pretraining Administration of Prazosin 2000 μg/kg and Scopolamine 200 μg/kg, Visible Platform. In the analysis of WM escape distance values, a significant overall group effect was observed, $F(3, 44) = 7.67$, $p < 0.001$. Scopolamine 200 μg/kg-treated rats and rats treated concurrently with scopolamine 200 μg/kg and prazosin 2000 μg/kg were significantly impaired when compared with controls, $F(1, 22) = 9.74$, $p < 0.01$, and $F(1, 22) = 32.26$, $p < 0.001$, respectively. In the analysis of treatment effects on WM escape distance values, it was observed that administration of scopolamine 200 μg/kg caused a significant impairment of performance, $F(1, 44) = 21.29$, $p < 0.001$. The other treatments had no significant effects on escape distance values (Fig. 7).

Pretraining administration of scopolamine significantly increased the speed of animals in all WM experiments [e.g., scopolamine 100 μg/kg, $F(1, 92) = 66.22$, $p < 0.001$, and scopolamine 200 μg/kg, $F(1, 44) = 114.09$, $p < 0.001$. Prazosin did not affect swimming performance in control rats or scopolamine-treated rats, $F(1, 46) = 2.42$, $P > 0.1$; $F(1, 46) = 0.53$, $p > 0.1$, respectively.

The Effects of Combined Alpha-1 Adrenergic and Muscarinic Cholinergic Blockade, Passive Avoidance

Pretraining Administration of Scopolamine 400 μg/kg and Prazosin 1000 μg/kg. Analysis of the passive avoidance acquisition trial data revealed nosignificant overall group effect ($p > 0.1$, Kruskal–Wallis test). A significant group effect was observed in the analysis of the passive avoidance testing trial entry latency data ($p < 0.01$, Kruskal–Wallis test). Scopolamine-treated rats and rats treated with the combination of scopolamine and prazosin 1000 μg/kg were impaired when compared with the control group ($p < 0.05$ for 400 μg/kg scopolamine and $p < 0.01$ for combined scopolamine 400 μg/kg and prazosin 1000 μg/kg administration; Mann–Whitney U) (Fig. 8A).

Pretraining Administration of Scopolamine 400 μg/kg and Prazosin 2000 μg/kg. In the analysis of passive avoidance acquisition trial data, a significant group effect was found ($p < 0.01$, Kruskal–Wallis test). The further analysis of the data revealed that prazosin 2000 μg/kg-treated rats and rats treated concurrently with scopolamine 400 μg/kg and prazosin 2000 μg/kg had significantly longer latencies to entry ($p < 0.01$ and $p < 0.05$, respectively, Mann–Whitney U). Analysis of passive avoidance testing trial entry latency data revealed a significant group effect ($p < 0.01$, Kruskal–Wallis test). Similar significant group differencies as observed in the previous experiment were detected ($p < 0.05$ for scopolamine 400 μg/kg and $p < 0.01$ for combination of scopolamine 400 μg/kg and prazosin 2000 μg/kg, Mann–Whitney U) (Fig. 8B).

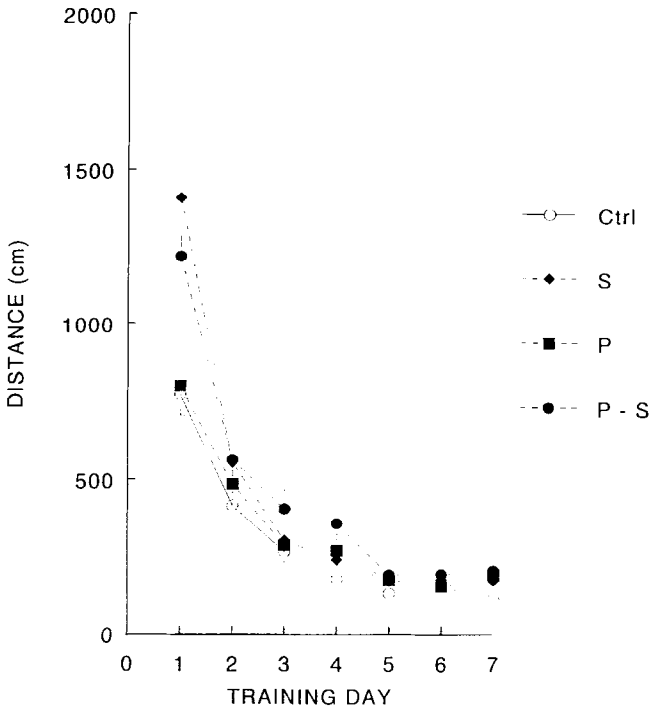

FIG. 7. Effects of prazosin and scopolamine on water maze escape distance values (y-axis, centimeters (cm)). Drugs were injected 30 min before daily training (three trials/day). The escape platform was clearly visible. Ctrl, vehicle (n = 12); S, scopolamine 200 μg/kg (n = 12); P, prazosin 2000 μg/kg (n = 12); S-P, scopolamine 200 μg/kg + prazosin 2000 μg/kg (n = 12).

Pretraining Administration of Scopolamine 200 μg/kg and Prazosin 1000 μg/kg. In the analysis of passive avoidance acquisition data, no significant group differences were observed ($p > 0.1$, Kruskal–Wallis test). In the analysis of passive avoidance testing trial entry latency data, a significant overall group effect was found ($p < 0.001$, Kruskal–Wallis test). Group comparisons revealed that scopolamine 200 μg/kg-treated rats and the group treated concurrently with scopolamine 200 μg/kg and prazosin 1000 μg/kg were significantly impaired ($p < 0.01$ and $p < 0.001$, respectively; Mann–Whitney U) (Fig. 8C).

Pretraining Administration of Scopolamine 400 μg/kg and St-587 1000 μg/kg or 2000 μg/kg. No significant group effect was observed in the analysis of passive avoidance training trial latency data ($p > 0.1$, both experiments, Kruskal–Wallis test). In the analysis of the latencies to cross into the dark compartment during the retention test, a significant group effect was observed ($p < 0.001$, Kruskal–Wallis test). Further analysis of group differences revealed that scopolamine 400 μg/kg significantly impaired the retention test performance and the performance was impaired also when St-587 1000 μg/kg (Fig. 8D) or 2000 μg/kg (data not shown) were administered concurrently with this scopolamine dose ($p < 0.01$ and $p < 0.01$, respectively, Mann–Whitney U).

DISCUSSION

The main purpose of this research was to investigate whether alpha-1 adrenergic and muscarinic cholinergic mechanisms interact in learning and memory.

The impaired acquisition of water maze task in animals pretreated with scopolamine is consistent with a large body of research supporting a role for cholinergic mechanisms in the performance in tasks assessing spatial learning and memory (6,7,11,39,41,42,44,48,49). In addition, scopolamine increased swimming speed of rats as found previously. Interestingly, pretraining administration of scopolamine (200 μg/kg) slightly impaired the WM navigation to a visible platform suggesting that sensory and motor factors are involved in the effects of scopolamine on escape performance. Furthermore, results from other experimental pharmacological studies have suggested that muscarinic cholinergic blockade (with scopolamine) may also affect nonmnemonic cognitive functions, such as attentional processes (24,27,48). When they are trying to solve the visible platform version of the water maze task normal, nontreated rats use distal cues during the initial portion of the swim, and then use the local visible cue to guide them during the last part of the swim (48). However, scopolamine-treated animals seemed to have a disruption of their behavioral strategy because these rats circled more around the pool and around the visible platform whereas normal rats swam more directly to reach the platform.

Furthermore, the observation that scopolamine induced an impairment in passive avoidance retention performance when administered prior to the training session is also consistent with previous research. Pharmacological blockade of muscarinic cholinergic receptors (42,44) or lesion of the nucleus basalis magnocellularis, which is the source of the cholinergic input to the amygdala and neocortex, produce impairments in passive avoidance performance (16,35,43,44). The passive avoidance paradigm is thought to assess recently formed memories (45), and acquisition and retention of the passive avoidance task is critically dependent on the nucleus basalis cholinergic system. Both muscarinic and nicotinic receptors located in the amygdala may mediate some of the effects of muscarinic and nicotinic cholinergic active drugs on passive avoidance performance (44).

According to the present results, a systemically administered alpha-1 antagonist did not markedly potentiate the scopolamine-induced navigation deficit, though a slight impairment was seen. Furthermore, St-587 injection did not ameliorate scopolamine-evoked disruption of spatial navigation performance, even though it did facilitate acquisition of the task in controls. These results suggest that alpha-1 adrenergic and muscarinic cholinergic systems might act additively so that blockade of alpha-1 adrenergic receptors would slightly potentiate the effects of muscarine receptor antagonism. However, prazosin did not significantly abolish the scopolamine-evoked locomotor hyperactivity (increased swimming speed) or injection of prazosin on its own did not consistently affect the swimming speed of rats (data not shown). Previously, it has been shown that the disrupting effects of scopolamine (doses from 400 μg/kg to 1000 μg/kg) on water maze performance can be abolished by peripheral pretraining administration of d-cycloserine (escape distance) (39) and aggravated, for example, by administrating propranolol prior to training (escape latency) (10) or by lesioning rats with DSP-4 treatment (escape latency) (41). Therefore, it is known that the water maze testing paradigm used is sensitive to the potentiating or abolishing effects of drugs on the scopolamine-induced impairment on water maze acquisition and that these results are not due to the insensitivity of the paradigm.

Pretraining injection of St-587 2000 μg/kg slightly improved the spatial navigation of rats. St-587–treated rats had significantly shorter escape distances (three trials) as early as the

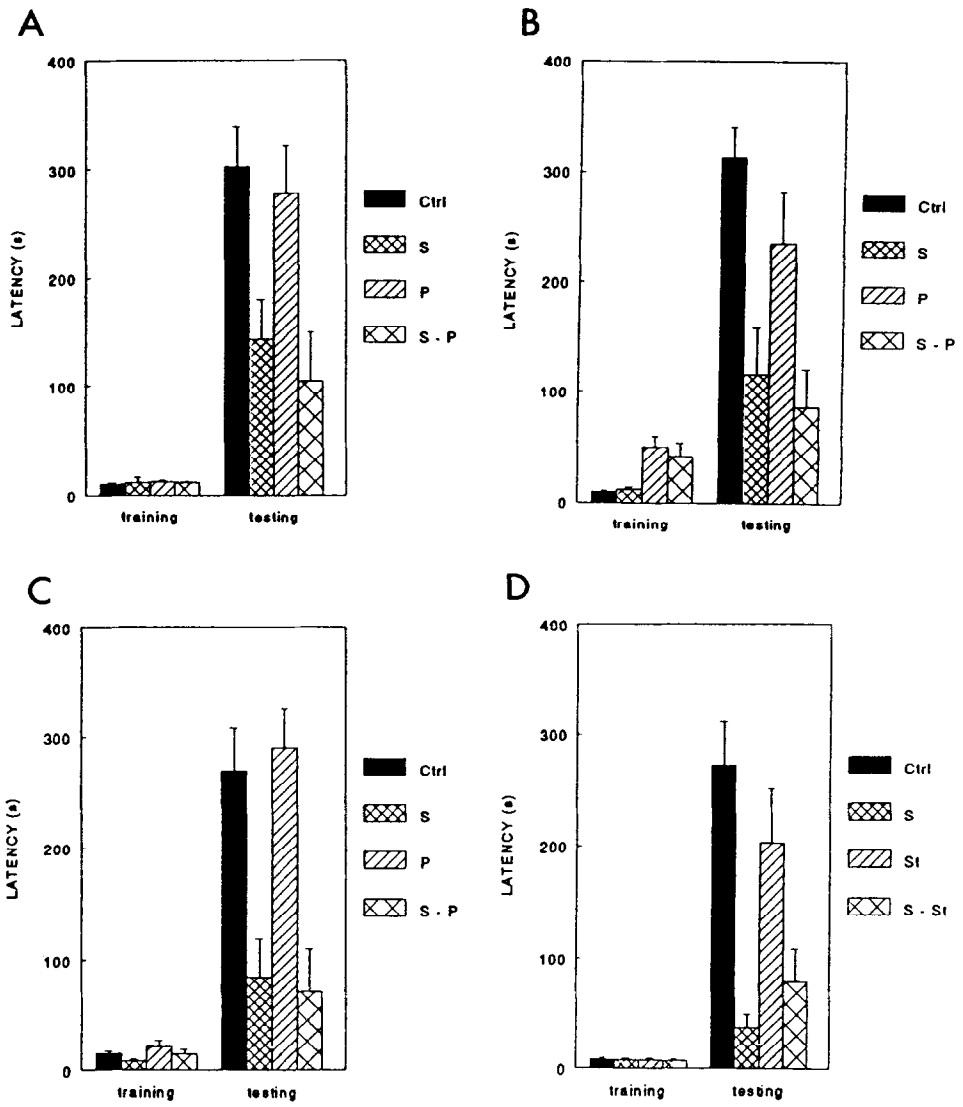

FIG. 8. The effects of pretraining administration of prazosin and scopolamine or St-587 and scopolamine on passive avoidance testing trial entry latencies (testing) and training trial entry latencies (training). Testing trial was given 24 h after training trial. The results are expressed as mean + SEM. Each group consisted of twelve rats. (A) Ctrl, vehicle; S, scopolamine 400 μg/kg; P, prazosin 1000 μg/kg; S-P, scopolamine 400 μg/kg + prazosin 1000 μg/kg. (B) Ctrl, vehicle; S, scopolamine 400 μg/kg; P, prazosin 2000 μg/kg; S-P, scopolamine 400 μg/kg + prazosin 2000 μg/kg. (C) Ctrl, vehicle; S, scopolamine 200 μg/kg; P, prazosin 1000 μg/kg; S-P, scopolamine 200 μg/kg + prazosin 1000 μg/kg. (D) Ctrl, vehicle; S, scopolamine 400 μg/kg; St, St-587 1000 μg/kg; S-St, scopolamine 400 μg/kg + St-587 1000 μg/kg.

first day of training when compared with the control group and moreover latencies of the first three swims were slightly shorter than those of control group. Possibly, enhanced water maze navigation is due to some kind of improvement in switching from wall hugging to circling and active exploration strategy.

The difficulties in the interpretation of the effects of systemically administered drugs include whether the effects are mediated centrally and/or peripherally. With respect to peripherally mediated effects, St-587 has been shown to dose dependently increase blood pressure in normotensive rats and cats, and this effect is thought to be mediated via peripheral postsynaptic alpha-1 adrenergic receptors on vascular smooth muscle cells (12) while central cardiovascular centers do not seem to be involved in this effect of St-587 treatment (12,38). It seems unlikely that the increased blood pressure would be the cause of the enhanced WM navigation performance.

In addition, we did not find any interaction between alpha-1 adrenergic and muscarininc cholinergic systems modulating the performance of rats in the passive avoidance task. Prazosin did not potentiate the scopolamine-evoked impairment in passive avoidance performance though this might also be due to a floor effect, for instance, scopolamine treatment induced such a profound impairment that any further disruption in performance could not have been possible. Drugs that act via alpha-1 adrenoceptors do not affect passive avoidance

retention trial latencies when injected on their own. These results agree with earlier findings, according to which alpha-1 adrenoceptors are not involved in the memory-enhancing effects of a lipophilic prodrug of epinephrine (dipivefrin) (23) and epinephrine (22,23). In addition, it has been proposed that naloxone-induced enhancement of memory is mediated through the activation of beta- but not alpha-adrenoceptors, which are located within the amygdala (32).

However, prazosin 2000 μg/kg increased the training entry latencies of vehicle- and scopolamine-treated rats. It is possible that the effects of prazosin to decrease motor activity could be the cause of the prolonged initial entry latencies (2). According to previous studies, prazosin at doses 500 and 1000 μg/kg was found to induce severe sedation (17), and this sedation is also a possible cause of longer training entry latencies. The prazosin 2000 μg/kg-treated group did not differ from controls when testing trial entry latencies were compared. However, it is most unlikely that these effects of prazosin to decrease motor activity are responsible for the increase in passive avoidance testing trial entry latencies, because prazosin was injected only before training. At low doses (50 μg/kg) prazosin has been shown to be anxiolytic, but this effect was not found at higher doses (up to 1000 μg/kg) (17). Thus, it is also possible that prazosin (2000 μg/kg) might have increased the timidness of the animals in a new environment, for instance, the passive avoidance testing apparatus, and thus lengthened the initial entry latencies of the rats. The decrease in blood pressure occurring after the administration of prazosin 2000 μg/kg might have accounted for the observed effects.

Previous results have demonstrated that a partial noradrenergic lesion can aggravate deficits in the performance of rats induced by muscarinic cholinergic blockade (scopolamine) in the radial arm maze (11) and WM tasks, which assess spatial memory (41). Furthermore, synergistic interactions between cholinergic manipulations and beta adrenergic blockade have also been reported (10,19). The present results suggest that the alpha-1 adrenergic system plays only a minor role in this interaction, especially in the passive avoidance task.

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