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Effects of α-adrenoceptor agonists and antagonists on histamine-induced impairment of memory retention of passive avoidance learning in rats

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Abstract

The effect of α-adrenoceptor agents on the impairment induced by histamine was measured for memory retention of passive avoidance learning in rats. Post-training intracerebroventricular (i.c.v.) injection was carried out in all the experiments. Histamine (5, 10 and 20 μg/rat) reduced, while a histamine H_1 receptor antagonist, chlorpheniramine (0.1, 1 and 10 μg/rat), increased memory retention. The histamine H_2 receptor antagonist, ranitidine (0.1, 1, 10 and 20 μg/rat), did not elicit any response in this respect. Different doses of chlorpheniramine but not ranitidine reversed the histamine-induced impairment of memory. Clonidine and prazosin decreased, but yohimbine and phenylephrine increased, memory retention. Yohimbine decreased the inhibitory response to histamine. Phenylephrine, clonidine and prazosin did not alter the histamine effect. It is concluded that a histamine-induced impairment of memory retention through histamine H_1 receptors and an α_2-adrenoceptor mechanism may be involved in the histamine response.

Keywords: Passive avoidance learning; Histaminergic agent; α-Adrenoceptor agent; (Rat)

1. Introduction

Accumulating evidence has established histamine as a central neurotransmitter (Haas et al., 1991; Schwartz et al., 1991; Ondodera et al., 1994). The tuberomammillary nucleus in the posterior hypothalamus is the major source of neuronal histamine, which projects to numerous brain regions, including neostriatum, hippocampus, and tectum (Niigawa et al., 1988; Schwartz et al., 1991). Furthermore, the tuberomammillary nucleus has been implicated in both the processes underlying the functional recovery from brain damage and in the mechanisms of reinforcement, learning, and memory (Huston et al., 1997). However, the functions of the central histaminergic neurons in memory and learning are controversial (Cacabelos and Alvarez, 1991). Histamine functions through three different histamine receptor subtypes; postsynaptic histamine H_1 and H_2 receptors in addition to presynaptic histamine H_3 receptors which control the release of neuronal histamine (Prell and Green, 1986; Schwartz et al., 1986; Haas, 1992) and many other neurotransmitters (Schlicker et al., 1994). It was shown that adrenoceptors (Hill and Straw, 1988; Gulat-Marnay et al., 1989a) and muscarinic receptors (Gulat-Marnay et al., 1989b) influence the release of labeled histamine from decreases histamine release from hypothalamic neurons (Prast and Heistracher, 1991). However, endogenous noradrenaline does not play a physiological role in the release of histamine (Gulat-Marnay et al., 1989a), and no interactions between histamine receptor and α-adrenoceptor systems in learning and memory have not been described. In the present study, depolarized slices of brain cortex. It has also been shown that yohimbine increases and clonidine the possibility of an interaction between the α-adrenoceptor system and histamine H_1 and H_2 receptor agents was investigated.

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2. Materials and methods

2.1. Animals

Male Wistar rats weighing 200–250 g were used in these experiments. The animals were housed five per cage at room temperature (22–24 °C) with a 12-h light/12-h dark cycle, and food and water ad libitum. Ten animals were used for each experiment.

2.2. Cannula guide implantation

The animals were anesthetized with ketamine hydrochloride (50 mg/kg) plus xylazine (rompun; 4 mg/kg). The skull of the rat was fixed to a stereotaxic frame (with David Koft Instruments, USA) and a permanent stainless-steel guide cannula (21 gauge, 0.8 mm) was implanted stereotaxically at the right lateral ventricle. The tip of the cannula was aimed at the following coordinates: $A = -0.8$ mm, $L = 1.6$ mm, $V = 3.7$ mm from the bregma (Paxinos and Watson, 1986). The cannula was fixed to the skull using a screw and dental acrylic cement. A stylet was inserted into the cannula to keep it patent prior to injections. The animals were allowed 1 week of recovery before initiation of behavioural experiments. The experimental protocol was approved by the Research and Ethics Committee of the Sciences and Research Campus, Azad University, Tehran (2000).

2.3. Intracerebroventricular (i.c.v.) injections

The rats were gently restrained by hand, the stylet was withdrawn from the guide cannula and a 27-gauge injection needle (0.5 mm beyond the tip of the implanted guide cannula) was inserted. The injection needle was attached by a polyethylene tube to a 5-μl Hamilton syringe. The injection solutions were administered in a total volume of 2 μl. The injection needle was retained in the guide cannula for an additional 30 s after the injection to facilitate diffusion of the drugs.

2.4. Passive avoidance apparatus

The passive avoidance apparatus consisted of a light (Plexiglass) and dark (black) compartment of the same size ($20 \times 20 \times 30$ cm each) separated by a guillotine door (7×9 cm). The floor of the dark compartment was made of stainless-steel rods (2.5-mm diameter) separated by a distance of 1 cm. Intermittent electric shocks (50 Hz, 5 s), 1.5-mA intensity were delivered to the grid floor dark compartment from an insulated stimulator.

2.5. Training

The rats were allowed to habituate to the laboratory environment for 1 h before each of the training or testing sessions. All training and testing was done between 08.00 and 14.00 h. All experimental groups were first habituated to the apparatus. Each animal was gently placed in the light compartment for 5 s, after which the guillotine door was lifted and the latency with which the animal crossed to the dark (shock) compartment was timed. If an animal waited more than 100 s to cross to the other side, it was eliminated from the experiment. Once the animal crossed with all four paws to the next compartment, the door was closed and the rat was taken from the dark compartment into the home cage. The habituation trial was repeated after 30 min and followed after the same interval by the acquisition trial during which the guillotine door was closed and a foot shock (50 Hz, 1.5 mA and 5 s) was delivered immediately after the rat had entered the dark compartment. After 20 s, the rat was removed from the apparatus and placed temporarily into the home cage. Two minutes later, the rat was retested in the same way as before; if the rat did not enter the dark compartment in 120 s, successful aquisition of a passive avoidance response was recorded. Otherwise, when the rat entered the dark compartment, a second time, the door was closed and the rat received the same shock as above. Then the rat was removed from apparatus and injected intracerebroventricularly via the guide cannula.

2.6. Retention test

Twenty-four hours after training, a retention test was performed to evaluate long-term memory. Each animal was placed in the light compartment for 5 s, the door was opened, and the step-through latency for entering into the dark compartment was measured. The test session ended when the animal entered the dark compartment or remained in the light compartment for 300 s (criterion for retention). During these sessions, no electric shock was applied. Increase or decrease in step-through latencies indicated an increase or decrease in memory retention, respectively.

2.7. Drugs

The drugs used were histamine dihydrochloride (Merck, Germany), the histamine H_1 receptor antagonist, chlorpheniramine, the histamine H_2 receptor antagonist, ranitidine, the α_1-adrenoceptor agonist, phenylephrine hydrochloride, the α_1-adrenoceptor antagonist, prazosin hydrochloride, the α_2-adrenoceptor agonist, clonidine hydrochloride and the α_2-adrenoceptor antagonist, yohimbine (Sigma, Poole, UK). All drugs were dissolved in saline only and were used intracerebroventricularly (i.c.v.) in a volume of 2 μl/rat. The control groups received saline.

2.8. Data analysis

Analysis of variance (ANOVA) followed by the Newman–Keuls test was used to evaluate the data. The criterion for statistical significance was $P < 0.05$.

2.9. Histology

At the end of the experiment, each animal was given a lethal dose of chloroform and was transcardially perfused with a phosphate-buffered saline solution (pH 7.4). The brain was removed, cut coronally in 60-μm sections and stained with cresyl violet to determine injection locations. Data from rats with incorrect placement were excluded from analysis.

3. Results

3.1. Effect of histamine receptor agonist and antagonists on memory retention in rats

Fig. 1 shows the effects of histamine and histamine receptor antagonists when given intracerebroventricularly (i.c.v.), immediately after the training session. One-way ANOVA indicates a significant difference between results obtained with histamine (5, 10 and 20 μg/rat), the histamine H_1 receptor antagonist, chlorpheniramine (0.1, 1 and 10 μg/rat) and the histamine H_2 receptor antagonist, ranitidine (0.1 1, 10 and 20 μg/rat) [$F(11,108)=9.3$, $P<0.0001$]. Further analysis showed that histamine decreased, while chlorpheniramine increased the memory retention in rats. Ranitidine did not elicit any response.

Fig. 2 shows the effect of histamine in the presence or absence of chlorpheniramine. Two-way ANOVA indicates that chlorpheniramine 0.1 μg/rat [$F(3,72)=5.5$, $P<0.01$], 1 μg/rat [$F(3,72)=4.4$, $P<0.01$] and 10 μg/rat [$F(3,72)=6.8$, $P<0.001$] showed interactions with the histamine response (5, 10 and 20 μg/rat). Further analysis indicated that chlorpheniramine reversed the histamine effect. However, ranitidine 0.1 μg/rat [$F(3,72)=0.5$, $P>0.05$], 1 μg/rat [$F(3,72)=0.7$, $P>0.05$], 10 μg/rat [$F(3,72)=0.16$, $P>0.05$] and 20 μg/rat [$F(3,72)=1.5$, $P>0.05$] did not alter the response to histamine (Fig. 3).

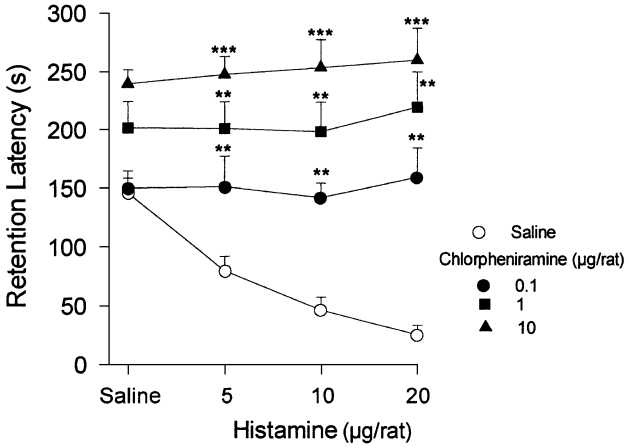

Fig. 2. Effect of histamine in the presence or absence of chlorpheniramine on memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus chlorpheniramine 0.1 (●), 1 (■) and 10 (▲) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. $^{**}P<0.01$, $^{***}P<0.001$ different from saline control group.

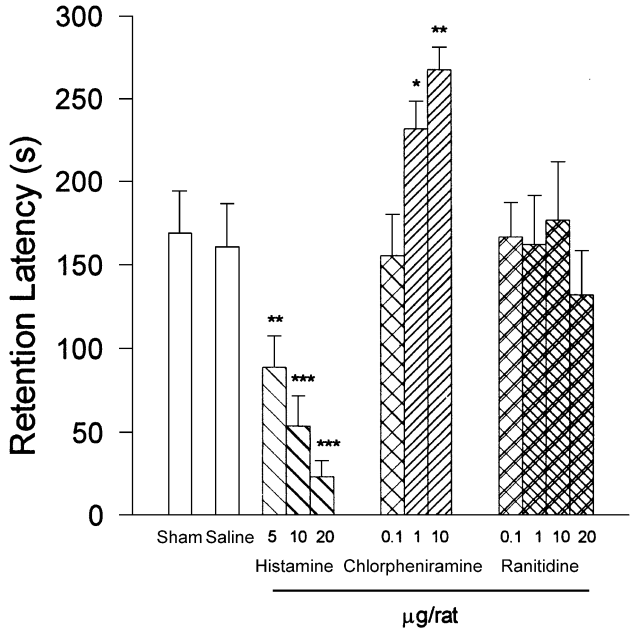

Fig. 1. Effect of histamine and histamine receptor antagonists on memory retention in rats. The animals were injected intracerebroventricularly (i.c.v.) either with saline (2 μl/rat), different doses of histamine (5, 10 and 20 μg/rat), chlorpheniramine (0.1, 1 and 10 μg/rat) or ranitidine (0.1, 1, 10 and 20 μg/rat) immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ different from saline control group.

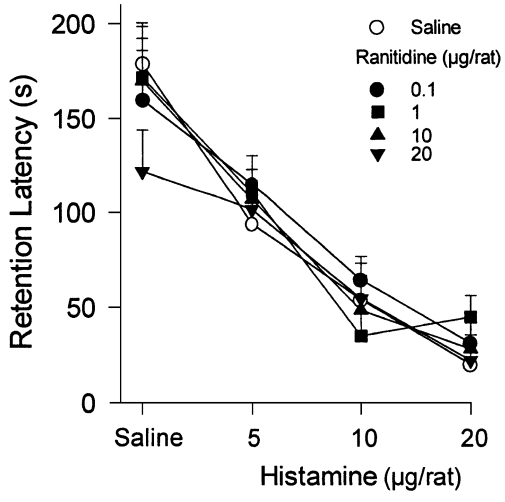

Fig. 3. Effect of histamine in the presence or absence of ranitidine on memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus ranitidine 0.1 (●), 1 (■), 10 (▲) and 20 (▼) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. Ranitidine did not alter the response to histamine (F values mentioned in Results).

3.2. Effects of histaminergic agents in the presence or absence of adrenoceptor agonists or antagonists

Fig. 4 shows the effects of the α_2-adrenoceptor agonist, clonidine, on the histamine-induced impairment of the memory retention. Two-way ANOVA indicates that clonidine 0.5 μg/rat [$F(3,72)=4.3$, $P<0.01$], 1 μg/rat [$F(3,72)=7.0$, $P<0.001$] and 2 μg/rat [$F(3,72)=7.9$, $P<0.0001$] interacted with the effect of various doses of histamine (5, 10 and 20 μg/rat). However, post hoc analysis showed that clonidine did not alter the histamine effect. Different doses of clonidine (1 μg/rat [$F(1,72)=6.7$, $P<0.05$] and 2 μg/rat [$F(1,72)=20.1$, $P<0.0001$]) itself also reduced memory retention.

Fig. 5 shows the effects of the α_2-adrenoceptor antagonist, yohimbine, on the impairment of memory retention induced by histamine. Two-way ANOVA indicates that yohimbine 1 μg/rat [$F(3,72)=5.4$ $P<0.01$], 2 μg/rat [$F(3,72)=10.8$, $P<0.0001$] and 4 μg/rat [$F(3,72)=13.7$, $P<0.0001$] but not 0.5 μg/rat [$F(3,72)=0.9$, $P>0.05$] reduced the histamine-induced impairment of memory. Different doses of yohimbine (0.5 μg/rat [$F(1,72)=6.9$, $P<0.05$], 1 μg/rat [$F(1,72)=70.1$, $P<0.0001$], 2 μg/rat [$F(1,72)=167.5$, $P<0.0001$] and 4 μg/rat [$F(1,72)=406.7$, $P<0.0001$]) itself also increased memory retention.

Fig. 6 shows the effects of the α_1-adrenoceptor agonist, phenylephrine, on the impairment of memory retention induced by histamine. Two-way ANOVA indicates that phenylephrine 0.05 μg/rat [$F(3,72)=0.06$, $P>0.05$], 0.1 μg/rat [$F(3,72)=0.04$, $P>0.05$] and 0.2 μg/rat [$F(3,72)=0.5$, $P>0.05$] did not alter the response to histamine (5, 10 and 20 μg/rat). However, phenylephrine (0.1 μg/rat [$F(1,72)=18.9$, $P<0.0001$] and 0.2 μg/rat [$F(1,72)=54.1$, $P<0.0001$] itself increased memory retention.

Fig. 7 shows the effects of the α_1-adrenoceptor antagonist, prazosin, on the impairment of memory retention induced by histamine. Two-way ANOVA indicates that prazosin 1 μg/rat. [$F(3,72)=3.1$, $P<0.05$] but not 0.1 μg/rat [$F(3,72)=0.23$, $P>0.05$] or 0.5 μg/rat [$F(3,72)=0.9$, $P>0.0$] altered the response to histamine (5, 10 and 20 μg/

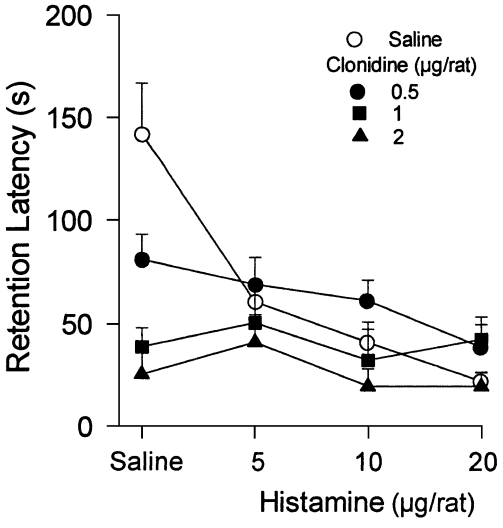

Fig. 4. Effect of histamine in the presence or absence of clonidine on memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus clonidine 0.5 (●), 1 (■) and 2 (▲) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. Clonidine plus histamine was different from histamine alone (F values mentioned in Results), but post hoc analysis showed that clonidine did not alter the response to histamine.

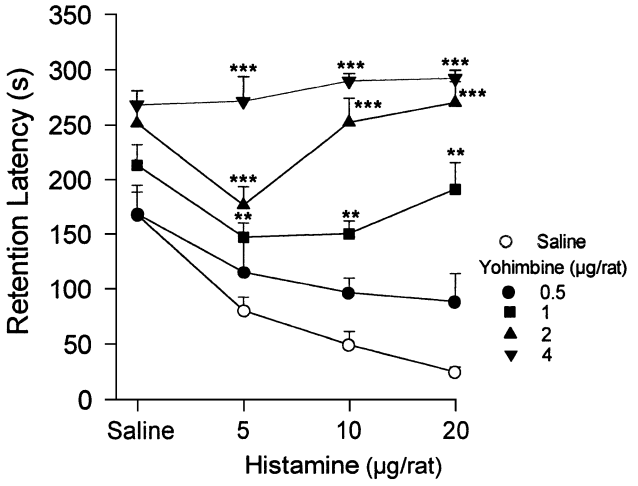

Fig. 5. Effect of yohimbine on histamine-induced impairment of memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus yohimbine 0.5 (●), 1 (■), 2 (▲), and 4 (▼) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. $^{**}P<0.01$, $^{***}P<0.001$ different from saline control group.

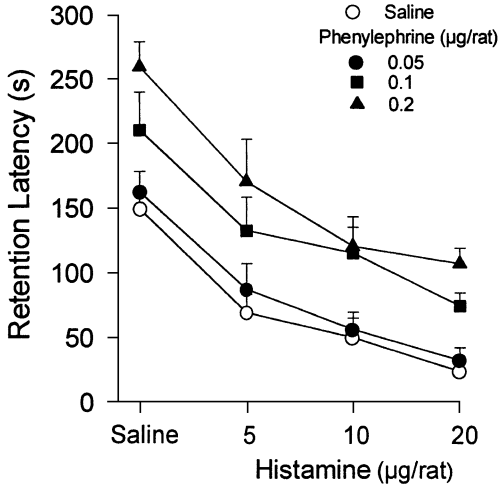

Fig. 6. Effect of phenylephrine on histamine-induced impairment of memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus phenylephrine 0.05 (●), 0.1 (■) and 0.2 (▲) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. Phenylephrine did not alter the response to histamine (F values mentioned in Results).

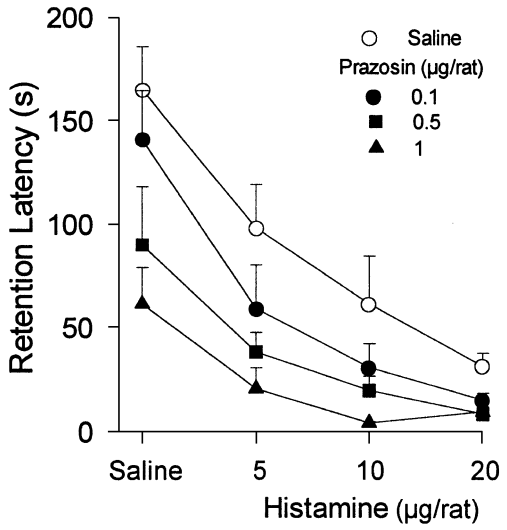

Fig. 7. Effect of prazosin on histamine-induced impairment of memory retention in rats. The animals were injected (i.c.v.) with different doses of histamine (○; 5, 10 and 20 μg/rat) alone, or histamine plus prazosin 0.1 (●), 0.5 (■) and 1 (▲) μg/rat, immediately after shock administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for 10 rats. Prazosin did not alter the response to histamine.

rat). Further analysis showed that prazosin (0.1 μg/rat) [$F(1,72)=6.3$, $P<0.05$], 0.5 μg/rat [$F(1,72)=21.4$, $P<0.0001$] and 1 μg/rat [$F(1,72)=47.6$, $P<0.0001$] itself reduced memory retention.

4. Discussion

There is evidence that histamine may play a role in learning and memory (Miyazaki et al., 1997) and in modulation of post-training memory processing (Flood et al., 1998).

The present data indicate that post-training administration of different doses of histamine reduced retention latencies. In agreement with the results obtained by other investigators (Kamei et al., 1993; Miyazaki et al., 1995; Alvarez and Banzan, 1996), the data may indicate an involvement of the central histaminergic system in memory. The role of the tuberomammillary-histaminergic system in learning and memory has been investigated pharmacologically, with contradictory results (Frisch et al., 1998). However, there are data showing that destruction of the tuberomammillary neurons could improve learning and memory (Klapdor et al., 1994), which may support our data. The histamine H_1 receptor antagonist, chlorpheniramine, but not the histamine H_2 receptor antagonist, ranitidine, increased memory retention, and reduced the response to histamine. It may be concluded that inhibition of memory retention by histamine could be mediated through a histamine H_1 receptor mechanism. This hypothesis gains support from reports that chlorpheniramine, but not ranitidine, can exert reinforcing and memory-promoting effect, when administered into different parts of the brain, including the nucleus basalis magnocellularis and nucleus accumbens (see Frisch et al., 1997). All parts of the tuberomammillary nucleus contain a dense network of fibers that are noradrenergic and make synaptic contacts with the dendrites, but not the somata, of tuberomammillary neurons. The lateral part of tuberomammillary nucleus receives an especially dense noradrenergic innervation (Eriksson et al., 2000). However, while the involvement of both brain adrenoceptors (Gold and Zornetzer, 1983) and histamine (Miyazaki et al., 1997; Flood et al., 1998) in memory modulation has been proposed, interactions between two systems have not been investigated.

The present results indicated that different doses of phenylephrine, an α_1-adrenoceptor agonist, and prazosin did not alter the response to histamine. The data may indicate that an α_1-adrenoceptor mechanism cannot influence the response to histamine. Our results also showed that phenylephrine itself increased memory retention. Such an effect has been reported previously following intra-amygdala infusion of norepinephrine (Liang and McGaugh, 1990; McGaugh, 1988) or when the drug was injected in the dentate gyrus (Lee et al., 1993). These data are consistent with the results obtained by other investigators that phenylephrine improves memory retrieval (Quartermain et al., 1988) and that norepinephrine improves retention (Introini-Collison et al., 1992; Lee et al., 1993). Thus, the involvement of an α_1-adrenoceptor mechanism in the improvement of memory retention seems likely. There are reports indicating that an α_1-adrenoceptor antagonist, prazosin, has no effect on memory retention (Riekkinen et al., 1996) or decreases acquisition of memory (Obersztyn and Kostowski, 1983; Riekkinen et al., 1996). However, the present data indicated that prazosin reduced retention latencies. Since prazosin also reduced the impairment of retention induced by phenylephrine, involvement of an α_1-adrenoceptor mechanism in the memory may be concluded (data not shown).

The present results indicate that the α_2-adrenoceptor agonist, clonidine did not alter the histamine-induced impairment of memory. However, we found in agreement with others (Lazarova-Bakarova et al., 1991) that clonidine itself also decreased memory retention. The α_2-adrenoceptor antagonist, yohimbine itself increased memory retention and reduced the response to histamine. However, there are data indicating that yohimbine itself increases memory retention (Chen et al., 1992). The antagonist also reduced the clonidine effect in the present study (data not shown). Our results show that an α_2-adrenoceptor mechanism(s) may influence the histamine response. One possible explanation is that alteration of histamine levels in the tuberomammillary nucleus by an α_2-adrenoceptor is involved. However, in contrast to our results, it has been shown that clonidine increases, while yohimbine decreases histamine release from hypothalamus (Prast and Heistracher, 1991).

The results could indicate that two adrenoceptors, α_1- and α_2, have opposite effects on memory retention, but

that only an α_2-adrenoceptor mechanism altered the histamine-induced impairment of memory retention. Therefore, it seems possible that a presynaptic α_2-adrenoceptor is present in the tuberomammillary nucleus on histaminergic neurons, which may modify the release of histamine (Eriksson et al., 2000). However, postsynaptic α_2-adrenoceptor involvement cannot be excluded and to clarify the exact mechanism(s) involved, more experiments are required.

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