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Original Article

Intracerebroventricular Injection of Histamine Induces State-Dependency through H_1 Receptors

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Abstract

The aim of the present study was to investigate whether and by which mechanism; histamine can induce state-dependent retrieval of passive avoidance task. The pre-training or pre-test intracerebroventricular (i.c.v.) injection of histamine (20μg/mouse) impaired retrieval, when it was tested 24 h later. In the animals, which retrieval was impaired due to histamine pre-training administration, pre-test administration of histamine, with the same dose, restored retrieval. The H_1 blocker, pyrilamine (20 μg/mouse, i.c.v.), but not the H_2 blocker; ranitidine prevented the restoration of retrieval by pre-test histamine. A pre-test administration of histamine H_3 receptor antagonist, clobenprobit, also reversed hitamine-induced impairment of memory retention. In conclusion, histamine can induce state-dependent retrieval through the H_1 receptor H_1 mechanism.

Keywords: Histamine; Histamine receptor antagonist; Memory; State-dependent retrieval; Mouse.

Introduction

The central neurotransmitter histamine (1-3) is concentrated in the tuberomammillary nucleus of the posterior hypothalamus, with efferent varicose fibers to almost all parts of the brain (4, 5). A role for histamine and its' receptors in learning and cognition processes in the rat brain has been suggested (6). There is also evidence that endogenous histamine plays an important role in learning and memory (7, 8). Moreover, stimulation of histaminergic neurons attenuates the rewarding effect of morphine (9). The hypothermic effect of morphine is also mediated, at least partly, through the histamine H1 receptors (10). It has also been shown that histamine increases morphine-induced impairment in rats (11).

Three subtypes of histamine receptors (H1, H2 and H3) have been characterized pharmacologically and are widespread through the brain in both neuronal and glial cells (12, 13). Histamine synthesis and release are under the control of inhibitory histamine H3 auto-receptors located on the somata and axon terminals of histamine neurons (14).

Drug-induced State-dependent learning

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(StD) has been known since 1830 (15, 16). It is a phenomenon in which the retrieval of newly acquired information is possible only if the subject is in the same sensory context and physiological state as during the encoding phase (17- 19). StD retrieval has been demonstrated with a variety of drugs, including opioids. Previously, we have shown that histamine mimicked morphine-induced memory improvement by a mechanism independent of the μ-opioid receptors (20). Considering the similarity between morphine and histamine, induction of StD by histamine and the histamine receptors involved in this phenomenon have been tested in the present study.

Experimental

Materials

The materials used in this study included: histamine dihydrochloride (Merck, Germany), pyrilamine (mepiramine) maleate, the histamine H1 receptor antagonist and histamine H3 receptor clobenprobit (Sigma, Poole, Dorset, UK) and ranitidine hydrochloride, the histamine H_2 receptor antagonist (Kimidaru, Iran) that was used i.c.v. in a volume of 5 μl/mouse. All the drugs were dissolved in saline. The drug doses and the time course of the drugs' actions used in our experiments are based on a pilot study and those used previously (11, 21).

Methods

Subjects

Male albino NMRI mice weighing 20–30 g were used in this study. The animals were kept in an animal house with a 12/12-h light–dark cycle and controlled temperature (22 ± 2° C). They were housed ten per cage and had free access to food and water. Ten animals were used in each experimental group. Each animal was used once only. All the procedures were carried out in accordance with the institutional guidelines for animal care and use.

Cannula guide implantation

For central administration of drugs, the animals were implanted with a 23-gauge stainless steel guide cannula aimed 0.5 cm above the lateral ventricle. Implantation was performed under ketamine–xylazine (100 mg/kg ketamine + 5 mg/kg xylizine) anesthesia, and carried out at least 5 days before the behavioral testing. The coordinates used were 0.9 mm posterior to the bregma, 1.5 mm lateral to the midline, and 2.5 mm below the top of the skull. The cannula was fixed to the skull using one screw and dental acrylic. A stylet was inserted into the cannula to keep it open prior to injections.

Intracerebroventricular (i.c.v.) injections

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

Passive avoidance task

The apparatus was a wooden box (30×30×40 cm high), with its' floor consisting of parallel caliber stainless steel bars (0.3 cm diameter spaced 1 cm apart). A wooden platform (4×4×4 cm) was placed on the center of the grid floor.

In the training session, animals were placed on the platform and their latencies to step down on the grid with all four paws were measured. Immediately after stepping down on the grid, animals received an electric shock (1 Hz, 0.5 s, 50V DC), continuously for 15 s. The shocks were delivered to the grid floor by an isolated stimulator (Grass S44, USA). The retention test session was carried out 24 h after training and was procedurally identical to training, except that no shock was presented. Step-down latency was used as a measurement of the retrieval or passive avoidance performance. An upper cut-off time of 300 s was set. The experiments were carried out between 8:00 a.m. and 2: 00 p.m.

Drug treatment

Histamine was injected 10 min before testing or training. Other drugs were injected 10 min before testing.

Experiment 1

This experiment examined the histamine state dependent (StD) learning. In this experiment six groups of animals were used. Two groups of these animals were trained with saline administered 10 min before training, and 24 h later they received saline (1 µl/mouse, i.c.v.) or histamine (20 µg/mouse, i.c.v.) as a pre-test treatment. The other four groups of animals received histamine, 10 min before training and 24 h later the animals received saline or histamine (5, 10 and 20 µg/mouse, i.c.v.), 10 min before testing (Figure 1).

Experiment 2

This experiment examined the effects of pre-test administration of the histamine H1 receptor antagonist, pyrilamine, on the retrieval of a task learned under the influence of histamine. In this experiment four groups of animals were used. All the animals were trained 10 min after histamine (20 µg/mouse) injection. On the test day, one group of animals received saline (1 µl/mouse), and the other three groups received different doses (5, 10 and 20 µg/mouse) of pyrilamine in the presence of histamine, before testing (Figure 2).

Experiment 3

This experiment examined the effects of pre-test administration of histamine H2 receptor antagonist, ranitidine, on the retrieval of a task learned under the influence of histamine. Animals were trained after histamine (20 µg/mouse) injection and 24h later; they received saline (1 µl/mouse), or different doses of ranitidine (5, 10 and 20 µg/mouse) in the presence of histamine, before testing (Figure 3).

Experiment 4

This experiment examined the effects of pre-test administration of saline or clobenprobit, histamine H3 receptor antagonist, on a task learned following pre-training histamine injection. The first group of animals received saline (5 µl/mouse), both before training and testing. The four other groups of animals received saline or clobenprobit (5, 10 and 20 µg/mouse) 10 min before testing (Figure 4).

Data analysis

The retention latencies are expressed as the median and interquartile range. Data were analyzed using the Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney's U-test, followed by Bonferoni correction for the paired comparisons. In all the statistical evaluations, $P<0.05$ was used as the criterion for statistical significance.

Results

Effect of intracerebroventricular (i.c.v.) administration of histamine on passive avoidance performance

Figure 1 shows the effect of histamine on passive avoidance performance. There was a significant difference between the responses induced by pre-training and/or pre-test administration of histamine [Kruskal–Wallis nonparametric ANOVA, $H(5)=16.47$, $P<0.01$]. Post hoc analysis by Mann-Whitney's U-test indicated that histamine (20 µg/mouse), when administered before training and pre-test, impaired the passive avoidance performance. Pre-test administration of histamine (20 µg/mouse) restored the performance in

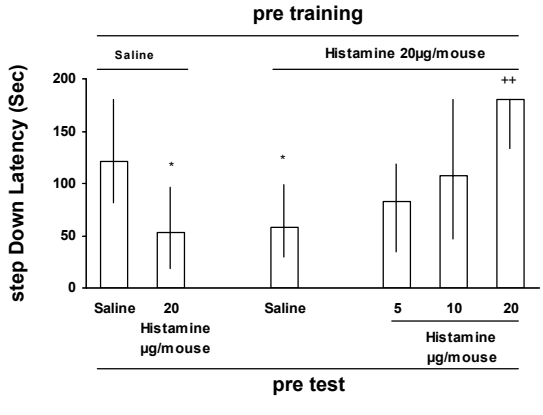

Figure 1. Figure1.The effects of pre-test administration of different doses of histamine following pre-training treatment with saline or histamine (20µg/mouse). Six groups of animals were used. Two groups of animals received pre-training saline on the test day. They received saline or histamine (20µg/mouse) pre-test administration. The other four groups received histamine (20 µg/mouse) 10 min before training, and either saline or different doses of histamine (5, 10 and 20 µg/mouse) 10 min before testing.

*P<0.05 compared to saline/saline group, ++ P<0.01 different from the histamine/saline group.

the animals whose memory performance were impaired due to histamine pre-training administration.

Effect of intracerebroventricular (i.c.v.) administration of pyrilamine, on the passive avoidance performance

Figure 2 indicates the effects of histamine H1 receptor antagonist, pyrilamine on histamine-induced restoration of performance. ANOVA indicated that pyrilamine reduced restoration of performance by pre-test administration of histamine [Kruskal-Wallis ANOVA, H (3) =13.47, P<0.05]. Further analysis indicated that only pre-training administration of pyrilamine reduced restoration of performance by histamine (20 µg/mouse), when compared to the saline/ saline group.

The effect of ranitidine on histamine-induced reinstatement of passive avoidance performance

Figure 3 indicates the effect of ranitidine, (a histamine receptor antagonist), on the histamine-induced reinstatement of the passive avoidance performance. When administered 10 min before testing, ranitidine (25, 50 and 100 µg/ mouse) had no significant effect on performance [Kruskal–Wallis nonparametric ANOVA, H (3)=6.74, P>0.05].

The effect of clobenprobit on passive avoidance performance

Figure 4 indicates the effect of clobenprobit, a H_3 histamine receptor antagonist, on the passive avoidance performance. When administered 10 min before testing, clobenprobit (25, 50 and 100 µg/mouse) significantly attenuated the impairment of passive avoidance performance induced by pre-training histamine (20 µg/mouse) [Kruskal–Wallis nonparametric ANOVA, H (4)= 17.1, P<0.01].

Discussion

Memory, as measured by changes in an animal·s behavior some time after learning, reflects many processes including acquisition, consolidation, retention, retrieval and performance. Histaminergic neurons are concentrated in the posterior hypothalamus of the rat brain, projecting their fibers to different brain structures such as the hippocampus and nucleus accumbens (21, 22). Histaminergic systems have an important role in several

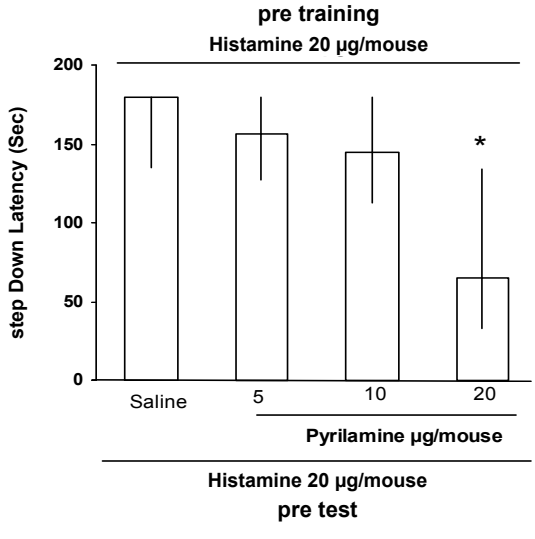

Figure 2. The effect of pre-test administration of pyrilamine on histamine state-dependent retrieval. Animals were trained 10 min after histamine injection (20µg/mouse), and received histamine (20µg/mouse) in combination with pyrilamine (5, 10 and 20µg/mouse) 10 min before the test on the test day. Pyrilamine significantly prevented histamine-induced restoration of retrieval. *P<0.05 compared to the histamine-histamine group.

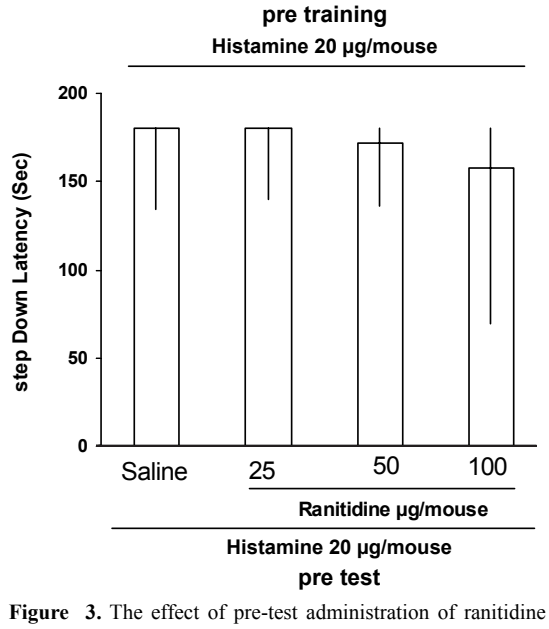

Figure 3. The effect of pre-test administration of ranitidine on histamine state-dependent retrieval. Animals were trained 10 min after histamine injection (20µg/mouse), and received histamine (20µg/mouse) in combination with ranitidine (25, 50 and 100µg/mouse) 10 min before testing.

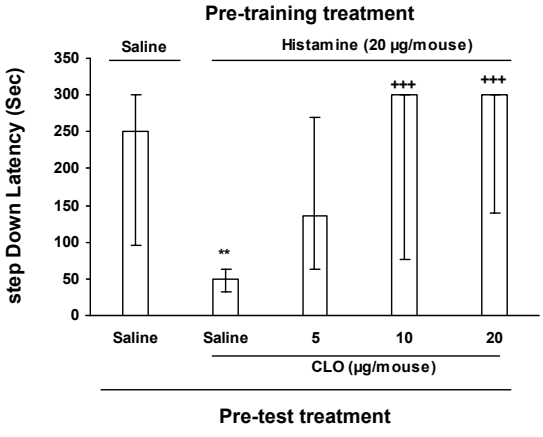

Figure 4. The effects of pre-test administration of different doses of clobenprobit following pre-training treatment with histamine (20µg/mouse). Five groups of animals were used. One group of animals received saline as pre-training and pre-test. Four other groups of animals received histamine 10 min before training, and either saline or different doses of clobenprobit (5, 10 and 20 µg/mouse) 10 min before testing. **P<0.01 different from the saline/saline group. +++P<0.01 different from the histamine/saline group.

physiological processes in the brain, such as learning and memory (7, 8). The available evidence regarding the effects of histamine on memory formation is very contradictory. Both the facilatory (23, 24) and inhibitory (25, 26) effects on memory have been reported. Several brain regions are likely to be involved in the memory modulating actions of histamine. Many of the paradigms that have been studied are partly or predominantly dependent on the hippocampal formation. Direct injection of histamine into the ventral hippocampus inhibits performance in an active avoidance task by acting on H1 receptors (27, 28). Moreover, in vitro studies on principal neurons in the hippocampus tend to suggest a memory-facilitating role for histamine [increased excitability, facilitation of NMDA receptors and LTP (29)].

Our present results show that pre-training or pre-test i.c.v. administration of histamine induces retrieval impairment in mice, which support our previous results that histamine impairs memory retention (11). The results also indicated a significant increase in retrieval, when histamine was taken at both pre-training and pre-test (His-His), compared to the conditions in which histamine was taken only at pre-training and saline at pre-test (His-Sal). A significant increase in retrieval was also found with His-His compared to the pre-training saline and pre-test histamine (Sal-His) group, with the maximum effect occurring with the same dose of histamine (20 µg/mouse) used during training and administered at the same time interval before testing. This phenomenon which is named state-dependent (StD) retrieval has also been seen with morphine (30, 31).

The StD retrieval has also been described for the histamine H1 receptor antagonist, chlorpheniramine (17). In our experiments, in the animals which were trained with histamine, and received the histamine receptor antagonists before histamine (20 µg/mouse) (His-His group) on the test day, the H1 receptor antagonist (pyrilamine), but not the H2 receptor antagonist (ranitidine) prevented histamine-induced restoration of retrieval. It should be considered that higher doses of ranitidine caused convulsions and it is not clear whether the doses used in the present study, were adequate enough to be effective. Moreover, our previous results showed that the histamine receptor antagonists, when used, had no intrinsic activity on retrieval (20). It seems possible that the histamine StD retrieval is at least in part due to histamine H1 receptors. The results of this study showed that the histamine H3 receptor antagonist, clobenprobit, when administered pre-test, similar to pre-test histamine, attenuated the impairment of passive avoidance performance by pre-training histamine. The response of histamine H3 receptor antagonist may be mediated through the release of histamine (32).

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