Original Article

Repeated Histamine Pretreatment Decreased Amnesia Induced by Post-training Administration of the Drug in a Step-down Inhibitory Avoidance Test in Mice

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Abstract:

Background: Repeated administration of certain drugs could result in an enhancement of the behavioral effects of those drugs. In the present study, the effect of repeated administration of histamine on amnesia induced by post-training administration of the drug was examined.

Methods: A single trial step-down inhibitory (passive) avoidance task was used for memory assessment in male NMRI mice.

Results: The results showed that post-training administration of different doses of histamine (5, 10, and 20 µg/mouse, i.c.v.) decreased the step-down latency on the test day. Repeated pretreatment of histamine (10 and 20 µg/mouse) for three days followed by five days of no drug treatment prevented amnesia due to post-training histamine (20 µg/mouse). In contrast, repeated administration of histamine H1 receptor antagonist, pyrilamine (5, 10, and 20 mg/kg) or histamine H2 receptor antagonist, ranitidine (12.5 and 25 mg/kg) 10 minutes prior to histamine injections, decreased the effect of repeated histamine administration. Moreover, a similar pattern was seen in animals which received dopamine D1 receptor antagonist, SCH 23390 (0.025, 0.5, and 1 mg/kg) or dopamine D2 receptor antagonist, sulpiride (0.2, 1, and 5 mg/kg) 10 minutes prior to histamine injections during the repeated pretreatment.

Conclusion: The results indicated that both the histamine and dopamine receptor mechanisms may be involved in the effects of repeated pretreatment of histamine on drug induced amnesia.

Keywords: Amnesia - administration - histamine - pyrilamine - ranitidine - repeated - SCH23390 - sulpiride

Introduction

Histamine plays an important role as a neurotransmitter in the central nervous system and participates in several physiological functions through specific receptors including the H1, H2, H3, and H4 histamine receptors.[1–6] The H1, H2, and H3 subtypes are expressed in the central nervous system whereas the H4 subtype is only detected in the periphery, particularly in bone marrow and leukocytes.[6–9] The H1 and H2 receptors are located postsynaptically and excite neurons or potentiate excitatory inputs,[10,11] while H3 receptors are presynaptic where they usually mediate histamine synthesis and release.[7]

It has been determined that the histaminergic system in the brain plays a crucial role in learning and memory functions.[12–14] Some investigators have demonstrated that histamine has powerful positive effects on memory processes.[15–17] Conversely, other investigators have reported that histamine exerts a negative influence on learning and memory formation.[18,19] Consistent with the later report, we have shown that pre- or post-training histamine administration induced amnesia in inhibitory avoidance tasks in mice and rats, respectively.[20,21]

Furthermore, it has been reported that repeated administration of certain drugs could cause an enhancement in the behavioral effects of those drugs.[22,23] For example, it has been reported that repeated adminis-

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tration of morphine induced locomotor sensitization through enhancement of the dopamine D1 and D2 receptor function.[24,25] Previously, we have reported a state-dependent learning for histamine which was affected by repeated administration of morphine and apomorphine.[26] Interestingly, histamine could substitute for morphine in the state-dependent learning induced by the latter drug.[20,27] In addition, involvement of dopamine receptors has been shown in morphine-induced state-dependent learning.[28]

Considering the above cited data it is logical to suggest that histamine may act via mechanisms similar to morphine on inhibitory avoidance memory. Therefore, the aim of the present study was to investigate the influence of repeated administration of histamine on amnesia induced by post-training administration of the drug. Subsequently, the receptor mechanisms involved in the histamine effect were evaluated by repeated co-administration of histamine H1 and H2 receptor antagonists, and dopamine D1 and D2 receptor antagonists with histamine.

Patients and Methods

Animals

Male albino NMRI mice (Pasteur Institute; Tehran, Iran) weighing 20 – 25 g were used. The animals were maintained under a 12/12-hr light-dark cycle (light beginning at 7:00 a.m.) and in a controlled temperature (22±2°C). They had free access to food and water and were housed, ten mice per cage. Each experimental group consisted of ten animals, and each animal was used once. All procedures were carried out in accordance with Institutional Guidelines for Animal Care and Use.

Surgery

Animals were anesthetized with a ketamine-xylazine mixture (100 mg/kg – 10 mg/kg, respectively) and submitted to a stereotaxic frame. A middle incision was made and after removal of the underlying periosteum, a 23-gauge stainless steel guide cannula was implanted to aim at 0.5 mm above the right lateral ventricle, and then anchored to the skull by dental cement. The coordinates were: 0.9 mm posterior to the bregma, 1.5 mm lateral to the midline, and 2 mm below the top of the skull.[29] A stylet was inserted into the guide cannula to keep it patent prior to injections. Surgery was performed five days before beginning of behavioral experiments.

Drugs

The drugs used in the study were histamine dihydrochloride, ranitidine hydrochloride, SCH 23390 (R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hy-drochloride), and sulpiride (Sigma, St. Louis, USA). Pyrilamine maleate was a gift from Osve, Tehran, Iran. All drugs were dissolved in sterile 0.9% saline immediately prior to the experiments, with the exception of sulpiride which was dissolved in one drop of glacial acetic acid and made up to a volume of 2 mL with sterile 0.9% saline before diluting to the required volume.

Inhibitory avoidance task

The inhibitory avoidance apparatus was a (30×30×40 cm high) wooden box, the floor of which consisted of parallel stainless steel bars (0.3 cm in diameter and spaced 1 cm apart). A wooden platform (4×4×4 cm high) was placed on the center of the grid floor.

In the training session, animals were gently placed on the platform and their latency to step down on the grid with all four paws was recorded. Immediately after stepping down on the grid, animals received an electric shock (1 Hz, 0.5 s, 45V DC) continuously for 15 s. The shock was delivered to the grid floor by an isolated stimulator (Grass S44, West Warnick, RI, USA). The testing session was carried out 24 hours later and was procedurally identical to the training, except that no shock was given. Step-down latency on the test day was recorded as an index of inhibitory avoidance memory. An upper cut-off time of 300 seconds was set. The training and testing sessions were carried out between 8:00 a.m. and 2:00 p.m. during the light phase.

Drug treatments

All drugs with the exception of histamine were given intraperitoneally (i.p.) and the doses were adjusted so that each animal received a volume of 10 mL/kg. Since a peripheral injection of histamine does not cross the blood brain barrier, the drug was administered through the intracerebroventricular (i.c.v.) route. The animals were gently restrained by hand, then the stylet was withdrawn from the guide cannula and a 30-gauge injection needle was

Table 1. Time table for days and drug treatments during the experiments (experiments began after five days recovery from surgery)

Days	Treatment
3–1	Repeated administration of drugs
8–4	Five days of no drug treatment
9	Training session and post-training administration
10	Testing session

inserted. The injection needle was attached, with a polyethylene tube, to a 2-μL Hamilton syringe. The injection solution was administered in a total volume of 1 μL/mouse during 60 seconds, followed by an additional 60 seconds to facilitate diffusion of the drugs from the tip of the guide cannula.

The protocol and time of drug administration used were as Table 1; three days of repeated administration of drugs followed by five days of no drug treatment. On day nine of the experiments, after inhibitory avoidance task training, the animals were administered histamine immediately following training and were tested 24 hours later for inhibitory avoidance step-down latency.

Experimental design

Experiment 1

This experiment examined effects of post-training administration of histamine on the step-down latency on the test day. One group of animals received an i.c.v. injection of saline (1 μL/mouse) and three groups received histamine (5, 10, and 20 μg/mouse, i.c.v.), immediately after training. All animals were tested 24 hours after the training.

Experiment 2

This experiment examined the effect of repeated administration of histamine on the amnesia induced by post-training administration of the drug. There were five groups of animals used in this experiment. One group of animals received saline (1μL/mouse) as controls during both the repeated administration and post-training treatments. The other four groups received saline (1 μg/mouse) or histamine (5, 10, and 20 μg/mouse) during repeated drug administration, and on the training day they received histamine (20 μg/mouse) after training. The test session was carried out 24 hours after training.

Experiment 3

This experiment examined the effect of repeated co-administration of histamine H1 and H2 receptor antagonists with histamine on the amnesia induced by post-training histamine. Nine groups of animals were used in this experiment. Two groups of the animals during repeated drug administration received saline (1 μL/mouse), and on the training day they received saline (1 μL/mouse) or histamine (20 μg/mouse) after training. The other seven groups of animals received repeated administrations of saline or pyrilamine (5, 10, and 20 mg/kg) or ranitidine (6.25, 12.5, and 25 mg/kg), 10 minutes prior to histamine injections (20 μg/mouse). All of these animals received post-training histamine (20 μg/mouse), and were tested 24 hours later.

Experiment 4

This experiment examined the effect of repeated co-administration of dopamine D1 and D2 receptor antagonists with histamine on the amnesia induced by post-training histamine. Nine groups of animals were used in this experiment. Two groups of the animals received repeated administration of saline (1 μL/mouse), and on the training day they received post-training saline (1 μL/mouse) or histamine (20 μg/mouse). The other seven groups, during repeated administration, received either saline (1 μL/mouse), SCH23390 (0.25, 0.5, and 1 mg/kg) or sulpiride (0.2, 1, and 5 mg/kg), 10 minutes prior to injections of histamine (20 μg/mouse). All of these animals received post-training histamine (20 μg/mouse), and were tested 24 hours later.

Data analysis

The data were analyzed with the Kruskal-Wallis nonparametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann-Whitney's U-test. The Holmes-Bonferroni Sequential Correction test was used for paired comparisons. The step down latencies on the test day for ten animals were expressed as median and inter-quartile ranges for each experimental

group. In all statistical evaluations, $P<0.05$ was used as the criterion for statistical significance.

Results

Effect of post-training administration of histamine on the step-down latency on the test day

Figure 1 shows that post-training administration of histamine altered the step down latency on the test day [Kruskal-Wallis nonparametric ANOVA, H(3)=24.6, $P<0.001$]. Post *hoc* analysis by Mann-Whitney's U-test indicated that post-training administration of histamine (5, 10, and 20 µg/mouse) significantly decreased the step down latency compared to the saline group; i.e. the animals which received post-training histamine showed amnesia on the test day (Figure 1).

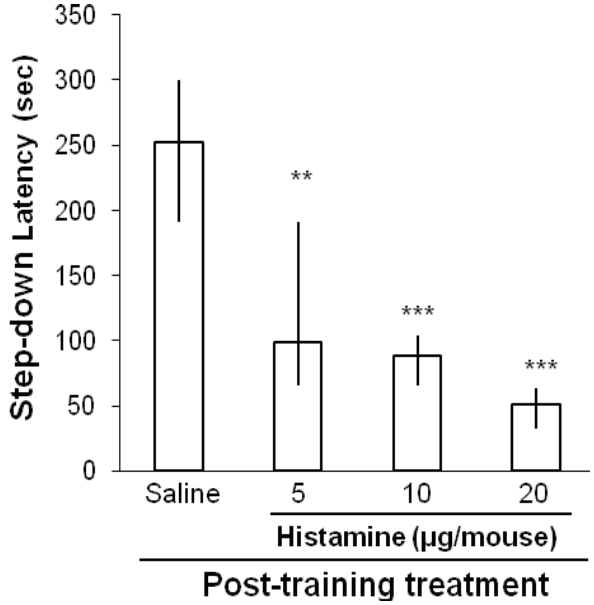

Figure 1. Influence of post-training histamine on the step down latency on the test day. One group of animals received intracerebroventricular injection of saline (1 µL/mouse) and other groups received histamine (5, 10 and 20 µg/mouse, i.c.v.), after training. All animals were tested 24 hours after training. Each value represents median and interquatile ranges for ten animals. $^{**}P<0.01$, $^{***}P<0.001$ different from saline control group.

Effects of repeated administrations of histamine on the amnesia induced by post-training administration of the drug

As shown in Figure 2, histamine-induced amnesia was significantly altered in animals which had previously received repeated injections of histamine (10 and 20 µg/mouse) for a three day period, compared to mice pretreated with saline [Kruskal-Wallis non-parametric ANOVA, H(3)=16.3, $P<0.01$]. Repeated injections of histamine appear to affect the histaminergic system of the brain, so the step down latency was markedly and dose-dependently increased (Figure 2).

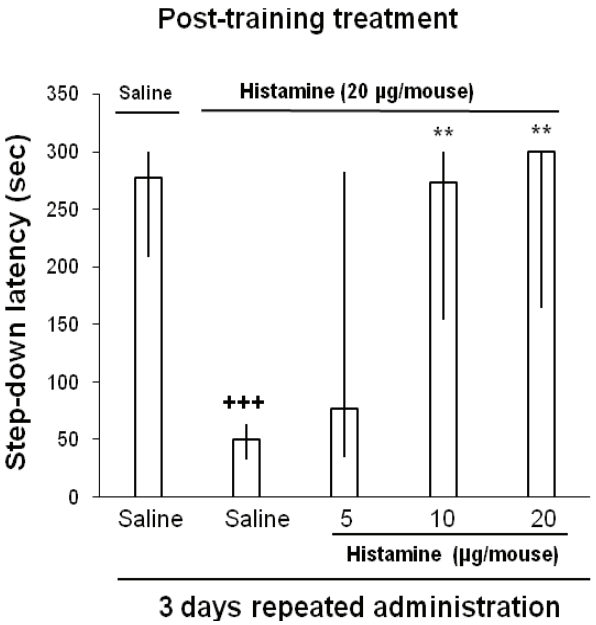

Figure 2. Effect of repeated administration of histamine on histamine-induced amnesia. Five groups of animals were used in this experiment. Two groups of the animals received saline (1µL/mouse) as control and other three groups received histamine (5, 10, and 20 µg/mouse) during repeated drug administration. On the training day, one group of animals with repeated pretreatment of saline (1 µL/mouse) received saline and the other four groups received histamine (20 µg/mouse) after training. The test session was carried out 24 hours after training. Each value represents median and interquatile ranges for ten animals. +++ $P<0.001$ compared to post-training saline control group. $^{**}P<0.01$ compared to histamine post-training group which was pretreated with saline.

Effects of repeated co-administration of histamine H1 and H2 receptor antagonists with histamine on the amnesia induced by the later drug after training

The results of experiment 3 indicated that co-administration of pyrilamine and ranitidine prevented the effect of repeated administration of histamine on histamine-induced amnesia (Figure 3). Thus, in animals which had received co-administration of pyrilamine and histamine compared to the group which received saline and histamine, the step down latency was markedly and dose-dependently reduced [Kruskal-Wallis non-parametric ANOVA, H(3)=14.9,

P<0.0]. A similar pattern was seen in animals which received co-administrations of ranitidine and histamine [Kruskal-Wallis non-parametric ANOVA, H(3)=22, P<0.001].

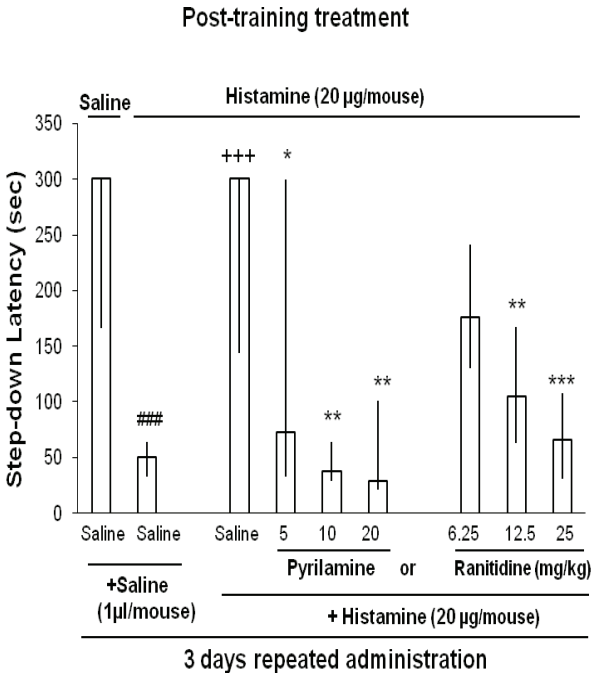

Figure 3. Effect of co-administration of histamine receptor antagonists with histamine during repeated pretreatment on histamine-induced amnesia. Nine groups of animals were used. Two groups of the animals, after three days of pretreatment with saline, received saline (1 µL/mouse) or histamine (20 µg/mouse) after training, and were tested 24 hours later. Seven groups received repeated administration of saline or pyrilamine (5, 10, and 20 mg/kg) or ranitidine (6.25, 12.5, and 25 mg/kg), 10 minutes prior to histamine injections (20 µg/mouse). All groups received histamine (20 µg/mouse) after training, and were tested 24 hours later. Each value represents median and interquatile ranges for ten animals. ###P<0.001 compared to the group which received saline as pretreatment and post-training treatment. +++P<0.001 compared to the group which received saline pretreatment and post-training histamine. *P<0.05, **P<0.01 and ***P<0.001 compared to the group which received saline+histamine during repeated administration and post-training histamine

Effects of repeated co-administration of dopamine D1 and D2 receptor antagonists with histamine on the amnesia induced by the later drug after training

The results of experiment 4 showed that co-administration of SCH23390 and sulpiride also prevented the effect of repeated administration of histamine on histamine-induced amnesia (Figure 4). In animals given histamine and saline, the median step down latency was 300 seconds, but in animals which had received SCH23390 plus histamine, the step down latency was significantly and dose-dependently attenuated [Kruskal-Wallis non-parametric ANOVA, H(3)=20.3, P<0.001]. In animals which received co-administration of sulpiride and histamine, the same effect was also observed [Kruskal-Wallis non-parametric ANOVA, H(3)=13.3, P<0.01].

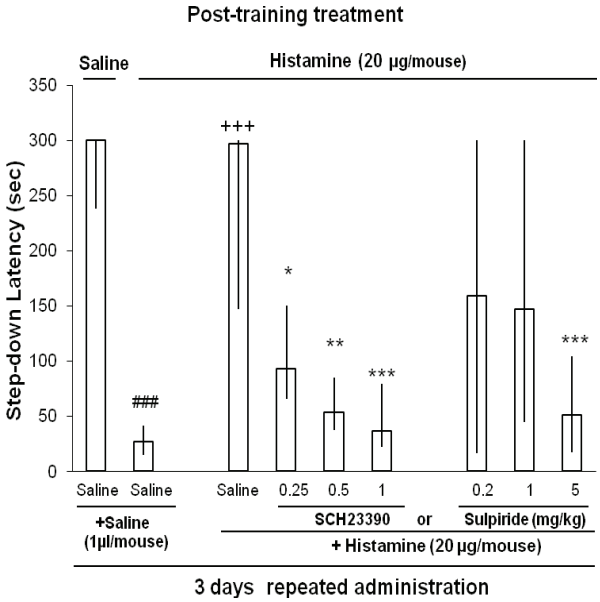

Figure 4. Effect of co-administration of dopamine receptor antagonists with histamine during repeated administration on histamine-induced amnesia. Nine groups of animals were used. Two groups of the animals, after pretreatment with saline, received saline (1 µL/mouse) or histamine (20 µg/mouse) after training, and were tested 24 hours later. Seven groups of the animals during repeated administration received saline or SCH23390 (0.25, 0.5, and 1 mg/kg) or sulpiride (0.2, 1, and 5 mg/kg) 10 minutes prior to histamine injections (20 µg/mouse). All animals received post-training histamine (20 µg/mouse), and were tested 24 hours later. Each value represents median and interquatile ranges for ten animals. ###P<0.001 compared to the group which received saline as pretreatment and post-training treatment. +++P<0.001 compared to the group which received saline pretreatment and post-training histamine. *P<0.05, **P<0.01 and ***P<0.001 compared to the group which received saline+histamine during repeated administration and post-training histamine

Discussion

The results of the present data showed that intracerbroventricular (i.c.v.) administration of histamine after training decreased the step-down latency in an inhibitory avoidance test. Although, there is some evidence that histamine has powerful positive effects on memory processes,[15,16,30] our results are in agreement with reports showing that histamine has

a negative influence on learning and memory.[18–20] It has been reported that in both of H1 and H2 receptor gene knockout mice compared to the respective wild-type mice, object recognition and Barnes maze performance were significantly impaired, while auditory and contextual freezing acquisition was improved.[31] Since different tasks are dependent on the function of different brain areas, therefore conflicting findings of both facilitory and inhibitory effects of neuronal histamine on learning and memory in different studies may result from using different tasks.[31]

To determine receptor mechanism(s) for the amnesic effect of post-training histamine, we examined effect of repeated pretreatment of histamine on amnesia induced by post-training administration of the drug. Our present results showed that the amnesia induced by post-training administration of histamine was significantly decreased in mice which had previously received repeated injections of histamine for three days followed by five days of no drug treatment. It was possible that repeated injections of histamine sensitized the animals and affected inhibitory avoidance memory.

The result of the present study indicated that co-administration of the histamine H1 and H2 receptor antagonist pyrilamine and ranitidine respectively, along with histamine, during repeated drug administration reduced the effect of the later drug on histamine-induced amnesia. Histaminergic neurons in the mammalian brain are located exclusively in the tuberomamillary nucleus of the posterior hypothalamus and send their axons throughout the central nervous system.[1,32,33] It has been reported that repeated administration of histamine H1 and H2 receptor antagonists significantly altered hypothalamic histamine levels.[34] The results of co-administration of pyrilamine and ranitidine with histamine in the present study may be due to altering histamine synthesis, as well as affecting histamine receptors and their subsequent effects. It has also been reported that the blockade of histamine H1 receptor improved learning and mnemonic ability in mice, raising the possibility that treatment with histamine antagonists may improve learning and mnemonic performance in certain patients with psychiatric diseases such as schizophrenic patients with cognitive dysfunction.[35] Therefore, both the H1 and H2 histamine receptors may be involved in the effect of repeated administration of histamine and subsequently its effect on histamine-induced amnesia.

It has been reported that histamine by mutual interaction with other transmitter systems is involved in higher brain functions such as learning and memory.[33] The present results also showed that co-administration of SCH23390 or sulpiride plus histamine during repeated drug administration prevented the effect of repeated pretreatment of histamine on amnesia induced by post-training histamine. Our previous study indicated that morphine-induced sensitization acts through dopamine receptor activation.[36] There are also some interactions between histamine and morphine in the brain.[37] Central histamine is demonstrated to have a stimulatory action on the release of beta-endorphin as well.[38] It has also reported that histamine exerts inhibitory effects on morphine-induced antinociception through H2 receptors in histamine H2 and H3 receptor gene knockout mice.[39,40] Our previous results also showed that morphine sensitization affected the impairment of memory by histamine through the dopaminergic system.[26] Therefore, it can be suggested that the effects of repeated administration of histamine on memory, like morphine, partly resulted from dopamine receptor mechanism(s). In conclusion, it is possible that the improvement of memory in the animals which received repeated pretreatment of histamine may be mediated through both the histamine and dopamine receptor mechanism(s).

Acknowledgements

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