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Effects of histamine and opioid systems on memory retention of passive avoidance learning in rats

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Abstract

The present study investigated the effect of interactions between histamine receptor agents and the opioid peptidergic system on memory retention of passive avoidance learning in rats. Post-training intracerebroventricular (i.c.v.) injections were carried out in all the experiments. Administration of histamine (20 μg/rat) reduced, but the histamine H_1 receptor antagonist, pyrilamine (20 and 50 μg/rat), and the histamine H_2 receptor antagonist, cimetidine (10 and 50 μg/rat), increased memory retention in rats. The histamine receptor antagonists decreased the response induced by histamine. Morphine (1–10 μg/rat) reduced, while pentazocine (5 and 10 μg/rat) or the opioid receptor antagonist, naloxone (5 and 15 μg/rat), increased memory retention. The combination of histamine with morphine showed potentiation. Effects of pyrilamine and cimetidine were attenuated by morphine. The responses to pentazocine and naloxone also were decreased by histamine. It is concluded that the histaminergic system has an interaction with opioidergic system that is involved in the memory retention process.

Keywords: Retention; Passive avoidance; Histaminergic agent; Opioid, rat

1. Introduction

Histamine as a central neurotransmitter (Haas et al., 1991; Schwarts et al., 1991; Onodera et al., 1994) is concentrated in the tuberomammillary nucleus of the posterior hypothalamus, with efferent varicose fibers to almost all parts of the brain (Panula et al., 1984; Watanabe et al., 1984). There is agreement that histamine and the histaminergic system have an important role in several physiological processes in the brain (Alvarez and Banzan, 1995; Onodera et al., 1994; Frisch et al., 1998b; Zimmermann et al., 1999). A role of histamine and its receptors in some specific brain processes such as cognition and novel environment-motivated exploration has also been characterized (Alvarez et al., 2001). Further, there is evidence that endogenous histamine plays an important role in learning and memory (Kamei and Tasaka, 1991; Flood et al., 1998).

Furthermore, there is evidence that opioids may modulate neural processes that are essential to memory consolidation. Stimulation of κ-opioid receptors has been shown to attenuate memory dysfunctions resulting from the blockade of muscarinic M_1 receptors (Ukai et al., 1997), while treatment with morphine and other opioid receptor agonists may disrupt memory (Izquierdo et al., 1980). However, there is also a report indicating that endogenous opioid systems do not play a major role in modulating neural mechanisms that maintain accurate spatial memory (Beatty, 1983). Since morphine has been shown to elicit an increase in histamine release (Brake and Hough, 1992), the aim of the present study was to show the effects of the interaction of opioids with histamine on memory retention.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 200–250 g were used in these experiments. The animals were maintained under a 12/12-h light–dark cycle, with light beginning at 7 a.m.

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The rats were maintained at a constant temperature (22 ± 2 °C), with food and water freely available in their home cages. The animals were housed five per cage. Each animal was used once only. Eight animals were used in each experiment.

2.2. Cannula guide implantation

For central administration of drugs, the animals were implanted with a 21-gauge (0.8 mm) stainless steel guide cannula aimed at the lateral ventricle (David Koft Instruments, USA). Implantation was done under ketamine–xylazine (100 mg/kg ketamine–5 mg/kg xylizine) anesthesia, using stereotaxic coordinates taken from the atlas of Paxinos and Watson (1986), and was performed at least 5 days before behavioral testing. The coordinates used were 0.8 mm posterior to the bregma, 1.6 mm lateral to the midline, and 3.4 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 patent prior to injections.

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 with 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

A learning box consisted of two rooms, one light (white opaque resin, 20 × 20 × 30 cm) and the other dark (black opaque resin, 20 × 20 × 30 cm). A guillotine door opening (7 × 9 cm) was made on the floor in the center of the partition between the two rooms. Stainless steel grids (2.5 mm in diameter) were placed at 1-cm intervals (distance between the centers of grids) on the floor of the dark room to produce foot shock. Intermittent electric shocks (50 Hz, 1.5 s, 2 mA intensity) were delivered to the grid floor of the dark room by an insulated stimulator.

2.5. Training

All animals were allowed to habituate in the experimental room for 1 h prior to testing. 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. Animals that waited more than 100 s to cross to the other side were 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 was followed after the same interval by the acquisition trial during which the guillotine door was closed and a foot shock (50 Hz, 2 mA and 1.5 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 during 120 s, successful acquisition of 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. After retesting, if the rat acquired acquisition of passive avoidance successfully, it was removed from the apparatus and injected via the guide cannula.

2.6. Retention test

Twenty-four hours after training, a retention test was performed to determine long-term memory. Each animal was placed in the light compartment for 5 s, the door was opened, and the step-through latency was measured for entering into the dark compartment. 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.

2.7. Drugs

The drugs included histamine dihydrochloride (Merck, Germany), pyrilamine maleate, the histamine H_1 receptor antagonist (Sigma, Poole, UK), cimetidine, the histamine H_2 receptor antagonist (Richter, Hungary), morphine sulphate, the opioid receptor agonist (Temad, Iran), naloxone dihydrochloride, the opioid receptor antagonist (Akzonobel, Netherlands) and pentazocine, the partial agonist (mixed agonist/antagonist) (Fis, Fabbrica, Italy). All the drugs were dissolved in saline. The drugs were used (i.c.v.) in a volume of 2 μl/rat.

2.8. Data analysis

Overall treatment effects of behavioral experiments were examined using a repeated-measures two-way analysis of variance (ANOVA). The criterion for statistical significance was $P < 0.05$.

2.9. Histology

Immediately after the retention test, all rats were given 2 μl of methylene blue in a lateral ventricle, and then were

anaesthetized with a high dose of ether and perfused transcardically with a phosphate-buffered saline solution (pH = 7.4) and then formaldehyde (10%). All rats were decapitated and the brains were removed and placed in formaldehyde (4%). After 3 days, the brains were sliced into 60-μm-thin slices. Data from rats with incorrect placement were excluded from the analysis.

3. Results

Fig. 1 shows the effect of morphine alone or in combination with histamine on memory retention. Two-way ANOVA indicated that different doses of morphine (1, 2.5 and 5 μg/rat) interact with histamine (2.5 μg/rat) [morphine, $F(3,56) = 11.4$, $P < 0.0001$; histamine, $F(1,56) = 54.1$, $P < 0.0001$; morphine × histamine, $F(3,56) = 2.8$, $P < 0.05$]. Further analysis showed that post-training injections of histamine and morphine attenuated memory retention and histamine potentiated the morphine-induced effect. Both pyrilamine and cimetidine reduced the histamine-induced impairment (data not shown).

Fig. 2 shows the effect of pentazocine or naloxone on the histamine-induced response. Two-way ANOVA indicates that pentazocine (5 and 10 μg/rat) and naloxone (5 and 15 μg/rat) interacted with histamine (20 μg/rat) [pentazocine, $F(2,42) = 9.2$, $P < 0.001$; histamine, $F(1,42) = 106.8$, $P < 0.0001$; pentazocine × histamine $F(2,42) = 3.3$, $P < 0.05$ and naloxone, $F(2,42) = 12.8$, $P < 0.0001$; histamine, $F(1,42) = 111.6$, $P < 0.0001$; naloxone × histamine $F(2,42) = 7.5$, $P < 0.01$]. Further analysis showed that post-training injections of both pentazocine and naloxone potentiated memory retention, while histamine attenuated this response. On the other hand, histamine could decrease naloxone or pentazocine-induced effects. Naloxone attenuated the response to morphine but not that to pentazocine (data not shown).

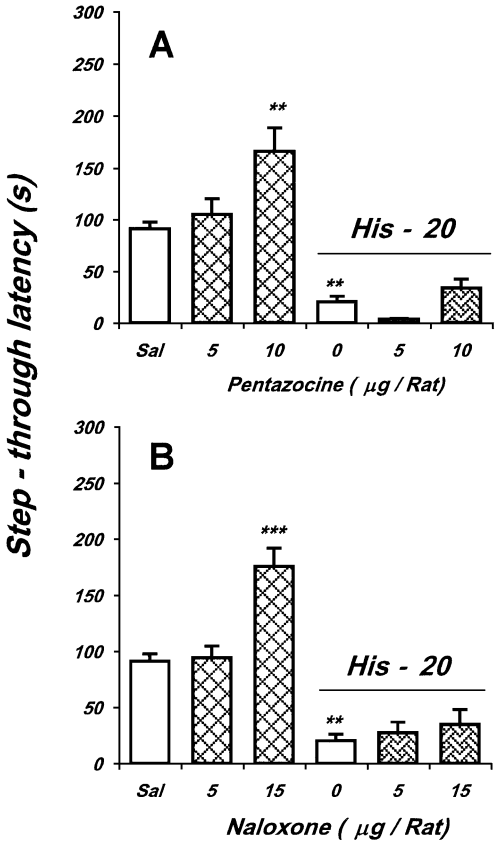

Fig. 2. Effect of pentazocine (A) or naloxone (B) in the presence or absence of histamine on memory retention. Animals were injected (i.c.v.) either with saline (2 μl/rat) or different doses of pentazocine (5 and 10 μg/rat) or naloxone (5 and 15 μg/rat) immediately after training session. Histamine (His, 20 μg/rat) administered 5 min after injection of pentazocine or naloxone and retention latencies were tested 24 h later. Each column represents the Mean ± S.E.M. of eight rats. $**P < 0.01$, $***P < 0.001$ different from saline control group.

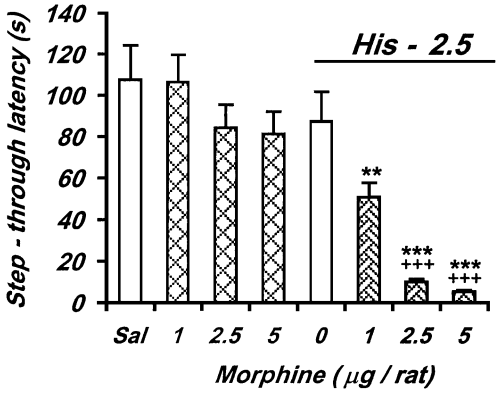

Fig. 1. Effect of morphine in the presence or absence of histamine on memory retention. Animals were injected (i.c.v.) either with saline (2 μl/rat) or different doses of morphine (1, 2.5 and 5 μg/rat) immediately after post-training session. Histamine (His, 2.5 μg/rat) administered 5 min after injection of morphine and retention latencies were tested 24 h later. Each column represents the Mean ± S.E.M. of eight rats. $**P < 0.01$, $***P < 0.001$ different from saline group. $+++P < 0.001$ different from morphine control group.

Fig. 3 shows the effect of the histamine receptor antagonists on the morphine-induced effect on memory retention. Two-way ANOVA indicates that pyrilamine (20 and 50 μg/rat) interacted with morphine (10 μg/rat) [pyrilamine, $F(2,42) = 21.5$, $P < 0.0001$; morphine, $F(1,42) = 67.1$, $P < 0.0001$; pyrilamine × morphine $F(2,42) = 3.3$, $P < 0.05$]. Cimetidine (10 and 50 μg/rat) also showed an interaction with morphine (10 μg/rat) [cimetidine, $F(2,42) = 50.5$, $P < 0.0001$; morphine, $F(1,42) = 294.5$, $P < 0.0001$; cimetidine × morphine $F(2,42) = 25.1$, $P < 0.0001$]. Further analysis showed that post-training injections of both pyrilamine and cimetidine have potentiating effects on memory retention, while morphine decreased this response. On the other hand,

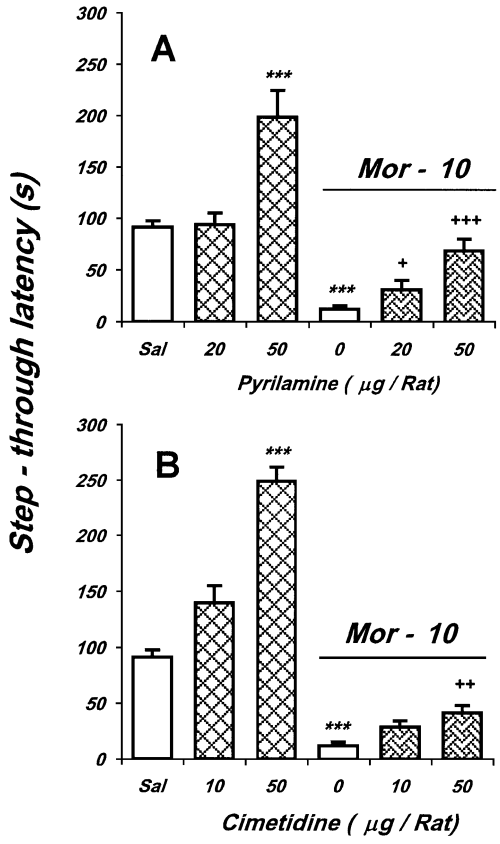

Fig. 3. Effect of pyrilamine (A) or cimetidine (B) in the presence or absence of morphine on memory retention. Animals were injected (i.c.v.) either with saline (2 μl/rat) or different doses of pyrilamine (20 and 50 μg/rat) or cimetidine (10 and 50 μg/rat) immediately after training session. Morphine (Mor, 10 μg/rat) administered 5 min after pyrilamine or cimetidine injection and retention latencies were tested 24 h later. Each column represents the Mean ± S.E.M. of eight rats. $***P<0.001$ different from saline control group. $+P<0.05$, $++P<0.01$, $+++P<0.001$ different from morphine control group.

morphine attenuated histamine receptor antagonists-induced responses.

4. Discussion

The present data indicate that post-training administration of different doses of histamine attenuated memory retention. The data are agreement with results of others (Kamei and Tasaka, 1991; Flood et al., 1998). Three subtypes of histamine receptors (H_1, H_2 and H_3) have been characterized pharmacologically and are widespread throughout the brain in both neuronal and glial cells (Arrang, 1994; Inagaki and Wada, 1994). Histamine synthesis and release are under the control of inhibitory histamine H_3 auto-receptors located on the somata and axon terminals of histamine neurons (Prast et al., 1994). In addition, histamine release in target regions is under the control of inhibitory muscarinic M_1 receptors (Prast et al., 1994), α_2-adrenoceptors (Arrang et al., 1991), 5-HT_{1A} (Oishi et al., 1992), κ-opioid receptors (Arrang et al., 1991), as well as facilitatory μ-opioid receptors (Itoh et al., 1988). Our data showed that the histamine H_1 receptor antagonist, pyrilamine, or the histamine H_2 receptor antagonist, cimetidine, potentiated memory retention. Both antagonists attenuated the histamine-induced response, which has also been shown previously (Tasaka et al., 1985). In agreement with others (Frisch et al., 1998b), the present results may indicate that the activation of histamine H_1 receptors attenuated the histamine-induced memory impairment. However, other data show that histamine H_1 receptor activation increased memory recall (DeAlmeida and Izquierdo, 1986), whereas activation of the histamine H_2 receptor was ineffective (Kamei and Tasaka, 1991). In contrast, there is a report indicating that the histamine H_2 receptors appear to exert some type of modulating effect on the inhibitory action of histamine H_1 receptor activity (Alvarez et al., 2001). Moreover, it has been proposed that different versions of avoidance learning (active, passive and inhibitory avoidance) have been used to study the associations between histamine and memory and reinforcement. The conclusions from these studies are contradictory (Frisch et al., 1998a,b; Huston et al., 1997; Seguro-Torres et al., 1996), although the present results can be added to a wide range of data which, in recent years, has supported an inhibitory effect of histamine.

Our present results also showed that post-training injection of morphine reduced, while injection of the opioid receptor antagonist, naloxone or pentazocine, the partial agonist (mixed agonist/antagonist) increased memory retention. The data also showed that naloxone reduced the morphine-induced effect. In agreement with other findings (see McGaugh and Cahill, 1997), the data may indicate an inhibitory role of the opioid system in memory retention.

In the present study, the effect of the interaction of opioid and histaminergic systems on memory retention was studied. In order to study the interactions of two systems, the effects of opioid agents were compared to those of histamine or histamine receptor antagonists in passive avoidance task. The data indicate that histamine potentiates morphine-induced impairment of memory retention, while histamine receptor antagonists reduce the morphine response, indicating that histamine and opioid systems have a close interaction, which is supported by reports that high doses of morphine can induce increased histamine release in the rat central gray (Brake and Hough, 1992), and that opioids enhance brain turnover of histamine that can be blocked by naloxone (Itoh et al., 1988). It should be also considered that histamine H_2 receptor antagonists but not histamine H_1 receptor antagonists block morphine-induced locomotor hyperactivity in mice (Mickley, 1986). Moreover, several histamine H_1 receptor antagonists have been shown to have potentiating effects when administered both alone (Wauquier and Niemegeers, 1981; Zimmermann et al., 1997) and in combination with other opioids and even tend to augment the pleasurable effects of the latter (Shannon and Su, 1982; Suzuki et al., 1995).

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