Opiate-like actions by intracerebroventricular histamine in mice and its antagonism by naloxone

Kenji Onodera and Yasumi Ogura

Department of Pharmacology (Chief: Prof. Yasumi Ogura), Tohoku University School of Dentistry, 4-1 Seiryo-machi, Sendai 980, Japan

[Accepted for publication: October 17, 1983]

Key words: analgesia / catalepsy / naloxone / opioid system / histamine

Introduction

In recent years increasing evidence has been advanced supporting the hypothesis that histamine is a neurotransmitter in the mammalian central nervous system. As histamine does not enter the blood brain barrier, neuropharmacological studies on histamine started with investigators who used the technique of intracerebroventricular (i.c.v.) injections and reported some behavioral effects in unanesthetized animals. Histamine has been known to have a role in the tolerance to and physical dependence on morphine. Morphine and opiate alkaloids also increase plasma histamine levels. In the current study, we examined the opiate-like actions of i.c.v. histamine, especially using catalepsy and analgesia as indexes, and its antagonism by naloxone was also examined.

Materials and Methods

Male ddY strain mice, weighing 18–24 g were used in this experiment. They were allowed free access to food and water except for the duration of measurements. The animals were housed in a room with a 12 hr day-night cycle and relative constant environment (22±2° and 60±5% humidity). The technique employed for i.c.v. injection to mouse was described by Brittain and Handley and modified according to Haley and MacCormick. Histamine dissolved in pyrogen-free Ringer's solution and adjusted to pH 6.0–6.5 was given to the animals in a volume of 20 µl per animal.

Analgesia assay; writhing response induced by 0.7% acetic acid was used in this experiment. Mice were given i.c.v. histamine, 10 min before intraperitoneal (i.p.) injection of 0.7% acetic acid. The number of writhings were counted at 5 min intervals for 0–30 min after the injection. The data were expressed as the inhibition percentage to the control group (only acetic acid-treated mice) by total counts during the observation periods.

Catalepsy test; catalepsy was examined by placing the whole forelimbs over a 5 cm high horizontal bar. The time taken from placing the mouse in this position until a forepaw touched the floor was measured with a stopwatch to the nearest seconds. The degree of catalepsy was assessed on a scale from 0 to 3 by measuring the cataleptic duration. A score of 0 indicates no cataleptic state, and scores of 1, 2 and 3 indicate 1–30 sec, 30–60 sec and more than 60 sec of catalepsy. Statistical differences among the groups were assessed by Mann-Whitney U-test.

Results and Discussion

Fig. 1 shows the effect of i.c.v. histamine on the writhing response induced by 0.7% acetic acid in mice. Although it was observed that higher concentrations of histamine injected into the skin of human subjects caused burning and sharp painful sensations, more than 5 µg of histamine inhibited significantly the writhing response induced by 0.7% acetic acid in this experiment (P<0.05 at 5 µg and P<0.01 at both 10 and 20 µg, respectively). Headache was observed by peripheral in-
K. Onodera, et al.: Opiate-like actions by i.c.v. histamine

Fig. 1 The effect of intracerebroventricular (i.c.v.) histamine on the writhing response induced by 0.7% acetic acid in mice. Statistical differences from control group (*P<0.05 and **P<0.01).

Injection13), whereas analgesia was observed when histamine was injected i.c.v. in mice in this experiment. The same tendency was reported on bradykinin13,14), substance P15,16) and prostaglandin D217).

Recently, Glick and Crane reported that histamine produced analgesia in rats when injected into dorsal raphe nucleus, or nearby in the periaqueductal gray region of brain18). Further investigations are needed to clarify this difference, although histamine behaved like an opiate.

Previously, we also found that i.c.v. histamine caused behavioral disorders such as hypothermia, sedation, catalepsy, and so on5,19). Opiates, endogenous peptides (β-endorphine, Met-enkephaline,…) are similar in effect to i.c.v. histamine20,21). It is also reported that β-endorphine caused naloxone-reversible cataleptic state even in relatively small doses20-22).

Firstly, we examined the effect of high doses of histamine (from 100 up to 1000 µg per mouse) on the cataleptic scores in mice. The data as shown in Fig. 2 were expressed as the percentage to the maximum scores during the four observation periods (Maximum scores were 12).

Even more than 500 µg of histamine did not reach the maximum scores, and it was suggested that high doses of histamine are attributed to activation of cholinergic mechanisms23). Therefore, we used 100 µg histamine for naloxone antagonism, as shown in Fig. 3.

Catalepsy test was carried out immediately before injection (0 min), and 5, 15, 30 and 120 min afterwards. After 100 µg of histamine, the cataleptic state was clearly evident in most animals after 30 min, but decreased by 120 min. Statistically significant reduction was observed in naloxone-pretreated mice at 5 and 10 mg/kg i.p. Naloxone was injected 30 min before histamine, but in case...
of 1 mg/kg did not have any influence. These results suggest that the action of histamine may be involved in or affect the opioid system in the brain.

We also reported that catalepsy induced by histamine is considered as a histamine H1-mediated phenomenon. In conclusion, catalepsy induced by histamine can be evoked by various independent mechanisms, i.e. activation of histamine H1-receptor, muscarinic cholinergic receptor, dopaminergic receptor, and opioid receptor in this experiment.

It is well documented in the literature that histamine has a stimulant action on the CNS in cats, dogs, mice and rats. Besides these actions, i.c.v. histamine caused depressive effects, such as catalepsy, analgesia in this experiment. These histamine effects need to be separated to study whether the actions are directly or indirectly related to histaminergic neurons in the mammalian brain.

Acknowledgement

This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientist, from the Ministry of Education, Science and Culture, Japan (No. 58770149).

References


