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The role of histamine H_1 receptors in the thermoregulatory effect of morphine in mice

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Abstract

Morphine is known to release histamine from mast cells and increase the turnover of neuronal histamine. It is also known that histamine receptors mediate some of the morphine effects. The contribution of histamine H_1 and H_2 receptors to the thermoregulatory effect of morphine in mice was investigated in the present experiments. Morphine produced a hypothermic effect, especially at the dose of 10 mg/kg. Although the histamine H_1 receptor antagonist, dimethindene (0.1 mg/kg, i.p.), attenuated the hypothermic effect of morphine (10 mg/kg), a histamine H_2 receptor antagonist, ranitidine (100 mg/kg, i.p.), had no effect. These results suggest that the hypothermic effect of morphine in mice is mediated, at least partly, through histamine H_1 receptors.

Keywords: Morphine; Histamine; Colonic temperature; Histamine receptor antagonist

1. Introduction

Morphine is known to have pronounced and complex effects on body temperature in animals (Adler et al., 1988; Clark and Lipton, 1985). Depending on several factors, such as the environmental temperature, the dose, the sex of the animal or the handling procedure, morphine causes either a fall or a rise in body temperature (Burks and Rosenfeld, 1979; Glick, 1975). In a series of studies concerning the thermoregulatory effect of morphine and other opiate and opioid receptor agonists/antagonists in mice, it has been shown that opiate agonists produce either hypothermia or hyperthermia, depending on the dose used and the ambient temperature (Rosow et al., 1980, 1982a,b,c)

Although histamine is now widely accepted as a transmitter or modulator in the central nervous system, it is only recently that there have been some investigations of its role (Scherkl et al., 1991; Schwartz, 1975; Schwartz et al., 1980). Brain histamine is localized in both neurons and mast cells (Goldschmidt et al., 1985; Lewis et al., 1986; Schwartz, 1975). Acute morphine treatment is known to increase the turnover of neuronal histamine and to release histamine from mast cells in peripheral tissues (Ellis et al., 1970; Rosow et al., 1982d; Nishibori et al., 1985).

Histamine receptors are known to play important roles in morphine-stimulated locomotion and morphine antinociception (Gogas et al., 1989; Mickley, 1986). A role of histamine in the other effects of morphine, such as thermoregulation, can also be expected.

We therefore studied changes in the thermoregulatory effect of morphine in the presence of dimethindene, a histamine H_1 receptor antagonist, and ranitidine, a histamine H_2 receptor antagonist.

2. Materials and methods

2.1. Animals

Male albino mice (Eczacıbası, Turkey) weighing 25–30 g were used. The animals were housed in a quiet room at an ambient temperature of 22 ± 1°C, with food and water ad libitum, and a 12 h light/dark cycle (lights on at 6:00 a.m. and off at 6:00 p.m.). All animals were well used to handling and to measuring of colonic temperature for the day before the experiments. Because there is an age-dependent increase of histamine content in mast cells (Okudaria et al., 1980), all mice chosen were 4 months old.

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The experiments had been approved by the 'Center of the Laboratory Animals – Animal Care Ethics Committee' of our faculty.

2.2. Measurements of colonic temperature

The temperature was measured to the nearest 0.1°C with an Ellab thermometer. This was done by inserting the probe (2 mm diameter) for 2.5 cm into the rectum of mice. The probe was left in place until steady readings were obtained (20–25 s). During temperature measurement, maximum care was taken to avoid stress due to handling.

2.3. Experimental procedure

Colonic temperature was measured in the mice once, before a single i.p. injection of morphine (0.01, 0.1, 1, 10 and 100 mg/kg), and again 15, 30, 45, 60, 90, 120 min after the injections. Changes in colonic temperature induced by morphine were also evaluated after a single i.p. injection of dimethindene (0.1 mg/kg), ranitidine (100 mg/kg) or saline (0.1 ml/10 g) 10 min before morphine (10 mg/kg) administration. At least seven animals per group were used. Each animal was used only once. Histamine H_1 and H_2 receptor antagonists were tested in doses that were used several times by other investigators and us (Gogas et al., 1989; Scherkl et al., 1991; Ulugöl et al., unpublished data; Karadağ et al., unpublished data).

2.4. Drugs

Morphine hydrochloride (Haver, İstanbul), dimethindene (Fenistil, Ciba-Geigy, Istanbul) and ranitidine (Ulcuran, Abfar-Zyma, Istanbul) were diluted from commercial preparations. All chemicals were dissolved in isotonic NaCl and administered intraperitoneally in a volume of 0.1 ml/10 g body weight. The control group received 0.1 ml/10 g saline intraperitoneally.

2.5. Statistical analysis

The results were expressed as the means ± S.E. and analyzed with two-way repeated measures ANOVA (analysis of variance), followed by the Student-Newman-Keuls test for all pairwise comparisons and Dunnett's test for multiple comparisons versus to the control.

3. Results

3.1. Effects of morphine on colonic temperature

The colonic temperature of mice receiving saline showed no change, compared to that before injection. In order to select the hypo- and/or hyperthermic doses of morphine to use in the experiments with dimethindene or ranitidine, we tested the influence of single i.p. doses of the opiate on colonic temperature. Fig. 1 outlines the effects of morphine (0.01–100 mg/kg, i.p.) on colonic temperature at time intervals ranging from 15 to 120 min. Colonic temperature decreased for 30 min after injection and then gradually returned to its baseline level at the 1 mg/kg and 10 mg/kg doses of morphine. Morphine 0.1 mg/kg produced a decrease in colonic temperature beginning from 90 min after injection. However, as seen from this experiment, 10 mg/kg of morphine produced a more significant effect. Therefore, the dose of 10 mg/kg of morphine was

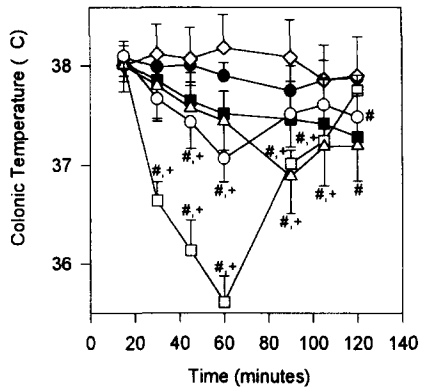

Fig. 1. Changes in colonic temperature after injections of different doses of morphine. Morphine injections were (■) 0.01 mg/kg ($n = 9$), (△) 0.1 mg/kg ($n = 10$), (○) 1 mg/kg ($n = 10$), (□) 10 mg/kg ($n = 10$) and (◇) 100 mg/kg ($n = 7$). Control mice were given saline alone (●) ($n = 10$). Vertical lines indicate S.E.M. Values of # and + ($P < 0.05$) were significantly different from those before injection and of control mice, respectively.

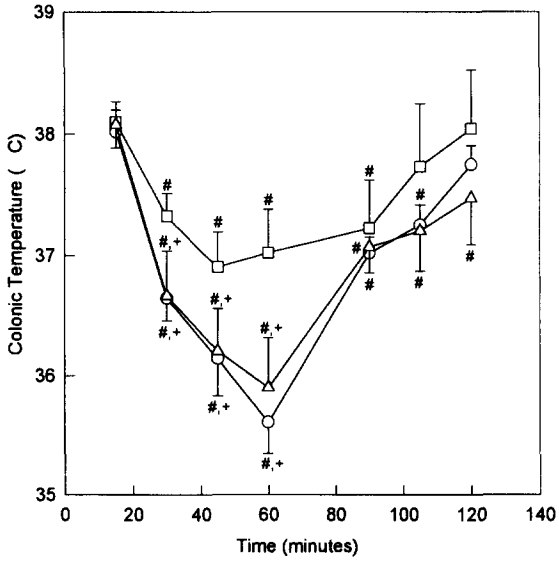

Fig. 2. Effects of dimethindene and ranitidine on colonic temperature changes produced by morphine. ○, morphine (10 mg/kg), $n = 10$; □, morphine (10 mg/kg) + dimethindene (0.1 mg/kg), $n = 9$; △, morphine (10 mg/kg) + ranitidine (100 mg/kg), $n = 10$. Vertical lines indicate S.E.M. Values marked # and + ($P < 0.05$) were significantly different from those before injection and for control mice, respectively.

chosen for the subsequent experiments in which we assessed the effects of histamine receptor antagonists on morphine-induced hypothermia.

3.2. Effects of histamine receptor antagonists on morphine-induced hypothermia

Each of the histamine receptor antagonists was evaluated at a dose which itself produced no effect on temperature, and a higher dose of ranitidine was used since it is a poorly brain-penetrating compound. The histamine receptor antagonists were used 10 min prior to administration of morphine (10 mg/kg). As seen in Fig. 2, the histamine H_1 receptor antagonist, dimethindene (0.1 mg/kg), attenuated the hypothermic effect of morphine significantly, but not completely ($P < 0.05$). However, the histamine H_2 receptor antagonist, ranitidine (100 mg/kg), had no effect on the morphine hypothermic effect.

4. Discussion

A transmitter role for histamine in the mammalian brain had been suspected for a long time, and there is considerable biochemical and electrophysiological evidence to support this idea (Scherkl et al., 1991; Schwartz, 1975; Schwartz et al., 1980). A neurotransmitter and/or neuromodulator role of histamine in the regulation of neuroendocrine and neuroimmune functions, circadian rhythms, sleep-wakefulness cycle, body temperature, centrally mediated neurovegetative functions, cerebrovascular control, and behavior and learning has been suggested (Scherkl et al., 1991; Schwartz, 1975; Cacabelos, 1990).

The effect of histamine on body temperature has been studied extensively (Dey and Mukhopadhaya, 1986; Fujimoto et al., 1990; Hutchison and Spriesterbach, 1986; Kandasamy and Hunt, 1990; Mukhopadhyay and Dey, 1986). Like morphine, histamine may raise or lower body temperature, depending on the dose (Hutchison and Spriesterbach, 1986), the environmental temperature (Dey and Mukhopadhaya, 1986; Fujimoto et al., 1990), and the route of administration (Mukhopadhyay and Dey, 1986). It is suggested that histamine released from mast cells acting on H_2 receptors may play an important but indirect role in the thermogenic response of brown adipose tissue to stimulation of the ventromedial hypothalamic area, since the response was markedly reduced by cimetidine, a histamine H_2 receptor antagonist, but not by pyrilamine, a histamine H_1 receptor antagonist (Desautels et al., 1994). Hypothermia elicited from infusion of histamine into the lateral ventricle was prevented by pretreatment with the histamine H_1 receptor antagonist, mepyramine. The effect of infusion into the IVth ventricle, was prevented instead by the histamine H_2 receptor antagonist, cimetidine (Dey and Mukhopadhaya, 1986).

Brain histamine is localized in both neurons and mast cells and there is evidence that mast cells stores of histamine contribute significantly to the overall histamine content of the brain (Goldschmidt et al., 1985; Lewis et al., 1986; Schwartz, 1975). Acute morphine treatment is known to increase the turnover of neuronal histamine (Nishibori et al., 1985; Itoh et al., 1988). Moreover, morphine is also known to release histamine from mast cells in peripheral tissues (Ellis et al., 1970; Rosow et al., 1982d); therefore a morphine action on mast cells in the central nervous system should be taken into consideration.

Morphine has long been known to have potent effects on body temperature (Adler et al., 1988; Clark and Lipton, 1985). Although both hypothermia and hyperthermia are produced by morphine, depending on the species, the environmental temperature, dose and route of administration, the hypothermic effect of morphine is prominent with systemic administration (Burks and Rosenfeld, 1979; Glick, 1975). Our findings also indicate that morphine exerts hypothermic effects, especially at the dose of 10 mg/kg. Previous experiments with mice showed morphine to produce either hypothermia or hyperthermia or both, depending on the dose used and the ambient temperature (Rosow et al., 1980, 1982a,b,c). Our results are consistent with these findings, since morphine exerted hypothermic effects at lower doses and no effect at the dose of 100 mg/kg. The hypothermic effect of morphine was reduced when the dose of morphine was increased (personal observation). The thermoregulatory effects of morphine seem to be similar to its effects on convulsions, since the conditions under which morphine acts as a proconvulsant rather than an anticonvulsant agent are not understood (Frenk, 1983). Therefore, further experiments are needed to explain the bidirectional effect of morphine on thermoregulation.

Histamine H_1 and H_2 receptors are known to play important roles not only in the hemodynamic effects of morphine, but also in its effects on the central nervous system (Fahmy et al., 1983; Flacke et al., 1987; Gogas et al., 1989; Mickley, 1986). It has been reported that morphine antinociception is mediated by activation of brain histamine H_2 receptors in rats (Gogas et al., 1989), and morphine-stimulated locomotion of the C57BL/6J mouse may be partially mediated by histamine H_2 receptors of the nucleus accumbens (Mickley, 1986). Footshock-induced enhancement of brain histamine turnover in mice is mediated partly by activation of opioid-related mechanisms (Yoshitomi et al., 1986). It is suggested that, in the presence of morphine, brain histamine can provide bidirectional modulation of nociception and the direction of the modulation seems to depend upon the stress experience of the animal (Nalwalk and Hough, 1995). Moreover, the activation of histaminergic neurons may attenuate the rewarding effect of morphine, while the inhibition of histaminergic neurons may potentiate the rewarding effect of morphine (Suzuki et al., 1995). Our previous results have also shown that morphine exerts anticonvulsant effects via histamine H_1 receptors (unpublished data). Therefore, a

modulatory role of histamine on the thermoregulatory effects of morphine is to be expected.

As a result, our findings suggest that histamine also plays an important role in the hypothermic effect of morphine, similar to its role in morphine-induced locomotion, antinociception and anticonvulsant effects, and this effect is mediated, at least partly, through histamine H_1 receptors.

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