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The interaction between histamine H_1 receptor and μ- opioid receptor in scratching behavior in ICR mice

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ABSTRACT

In this study, we examined the interaction between histamine H_1 receptor and μ-opioid receptor in scratching behavior in ICR mice. Both histamine and morphine caused scratching and simultaneous injection of histamine and morphine had an additive effect. Chlorpheniramine and naloxone inhibited histamine-induced scratching behavior. These two drugs also inhibited morphine-induced scratching behavior. Simultaneous injection of chlorpheniramine and naloxone caused a significant inhibition of histamine-induced scratching compared with separate injections. The same findings were also noted for morphine-induced scratching. These results strongly indicate a close relationship between histamine H_1 receptor and μ-opioid receptor in scratching behavior in ICR mice.

1. Introduction

It is well-recognized that histamine causes itching, a sensation causing the urge to scratch, through H_1 receptor in humans (Cormia, 1952; Rhoades et al., 1975). As with human beings, experimental animals also show scratching behavior when some pruritogenic agents such as histamine, serotonin, compound 48/80 and substance P are injected into the rostral back (Kuraishi et al., 1995; Thomsen et al., 2001; Sugimoto et al., 1998; Inagaki et al., 2010). Therefore, scratching behavior in some experimental animals, especially mice, has been widely used as a useful model for developing new anti-pruritic agents and for investigating the mechanism of itching. Inagaki et al. (2001) reported that the ICR mouse is a good responder for scratching behavior against various stimuli, especially histamine, and they concluded that ICR mice are suitable for studying mediators for and/or the mechanism of itching. Consequently, ICR mice are frequently used in the study of scratching behavior. Togashi et al. (2002) demonstrated that chlorpheniramine, a representative histamine H_1 receptor antagonist, inhibited histamine-induced scratching behavior in ICR mice.

It is well known that morphine also sometimes induces itching in humans and experimental animals, and that μ- opioid antagonists attenuate itching. For instance, Yamamoto et al. (2010) demonstrated that morphine caused scratching behavior when injected intradermally into ICR mice. They described that this scratching behavior was inhibited by not only naloxone but also chlorpheniramine. However, it was concluded that morphine-induced scratching behavior did not occur mainly via the histamine H_1 receptor, from the finding that a high dose of chlorpheniramine is required to inhibit morphine-induced scratching behavior compared with histamine-induced scratching (Maekawa et al., 2000). Nevertheless, we may assume that histamine H_1 receptor antagonists have some interaction with morphine-induced scratching behavior.

In order to clarify the interaction between histamine H_1 receptor and μ-opioid receptor for itching, we examined the effects of chlorpheniramine and naloxone on both histamine-induced and morphine-induced scratching behavior using ICR mice.

2. Materials and methods

2.1. Animals

Eight-week-old male ICR mice weighing 30–35 g were obtained from Charles River, Shizuoka, Japan. The animals were housed in an air conditioned room maintained at 24 ± 2 °C with relative humidity of $55 \pm 15\%$. They were given standard laboratory rodent chow (Oriental Yeast, Tokyo, Japan) and water *ad libitum*. All procedures involving animals were conducted in accordance with the Guidelines for Animal Experiments at Yasuda Women's

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2.2. Drugs

The drugs used in the experiments were obtained from the sources shown in parentheses: histamine dihydrochloride (Wako, Tokyo, Japan), D-chlorpheniramine maleate (Wako, Tokyo, Japan), morphine hydrochloride (Takeda, Osaka, Japan), naloxone hydrochloride (Sigma-Aldrich, St Louis, MO, USA). Histamine dihydrochloride and morphine hydrochloride were dissolved in saline and administered intradermally (i.d.) in a volume of 0.02 ml into the rostral back (neck) of mice. Histamine was used at doses of 10 nmol (1.11 μg)/site, 30 nmol (3.33 μg)/site and 100 nmol (11.1 μg)/site. Morphine was used at doses of 10 nmol (2.85 μg)/site, 30 nmol (8.55 μg)/site and 100 nmol (28.5 μg)/site. Naloxone hydrochloride was dissolved in saline and administered subcutaneously (s.c.) in a volume of 0.05 ml/10 g 15 min before histamine and morphine injections. D-chlorpheniramine was suspended in 5% gum arabic solution and administered orally (p.o.) in a volume of 0.1 ml/10 g 1 h before histamine and morphine injections.

2.3. Scratching behavior

Scratching behavior was measured according to the method of Kuraishi et al. (1995). Briefly, 10 min before testing, the mouse was placed in an observation cage (cylindrical, diameter 12 cm, height 18 cm) for acclimation. The number of scratching episodes was counted for 1 h by a laboratory assistant who was blinded to the experimental conditions. Mice generally scratched for about 1 s, and a series of these movements was counted one episode of scratching.

2.4. Statistical analysis

Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Dunnett's test. A probability (P) value less than 0.05 was considered significant. The data represent the means ± standard error of the mean (S.E.M.). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria, Kanda, 2013). Effective dose $(ED)_{50}$ and inhibitory dose $(ID)_{50}$ values were calculated by the Probit method.

3. Results

3.1. Scratching behavior induced by histamine and morphine

Histamine caused a dose-dependent increase in the number of scratching episodes at doses of 10, 30 and 100 nmol/site (i.d.). Significant effects were observed at doses of 30 and 100 nmol/site (i.d.). (Fig. 1A). ED_{50} was 25.0 (15.5–37.2) nmol/site (i.d.). Morphine also caused a dose-dependent increase in the number of scratching episodes at doses of 10, 30 and 100 nmol/site (i.d.). Significant effects were observed at doses of 30 and 100 nmol/site (i.d.). (Fig. 1B). ED_{50} was 27.3 (13.2–49.9) nmol/site (i.d.). ED_{50} was defined as the dose that elicited more than twice the number of scratching episodes counted in the control group.

3.2. Scratching behavior induced by simultaneous injection of histamine and morphine

As shown in Fig. 2, simultaneous injection of histamine (30 nmol/site, i.d. which showed a significant effect at $P < 0.05$ compared with control) and morphine (30 nmol/site, i.d. which showed a significant effect at $P < 0.05$ compared with control) resulted in a significant increase ($P < 0.05$) in the number of scratching episodes compared with when injected separately.

3.3. Effects of chlorpheniramine and naloxone on scratching behavior induced by histamine

Chlorpheniramine caused a dose-dependent inhibitory effect on histamine-induced scratching. A significant effect was observed at a dose of 1 mg/kg (p.o.). A dose of 3 mg/kg (p.o.) also showed a significant effect (Fig. 3A). ID_{50} was 2.08 (1.34–4.67) mg/kg (p.o.). ID_{50} was defined as the dose that elicited less than half the number of scratching episodes counted in the control group. Naloxone also caused a dose-dependent inhibition of histamine-induced scratching. Significant effects were observed at doses of 0.3 and 1 mg/kg (s.c.) (Fig. 3B). ID_{50} was 1.70 (0.86–10.7) mg/kg (s.c).

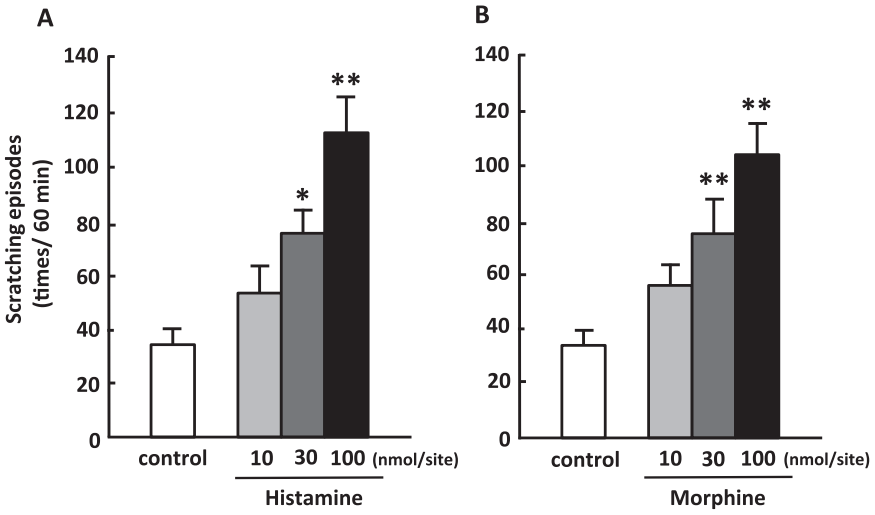

Fig. 1. Histamine- and morphine-induced scratching behavior in ICR mice. (A) Histamine. (B) Morphine. Histamine and morphine were injected intradermally (i.d.) into the rostral back (neck), and the number of scratching episodes was counted for 1 h. Each column and vertical bar represents the means ± S.E.M. (n = 10).*,**: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively (Dunnetts' test).