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Short communication

Involvement of histaminergic system in the discriminative stimulus effects of morphine

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Abstract

The interactions between morphine and the histaminergic system are not yet fully clarified. More especially, the involvement of the histaminergic system in the discriminative stimulus effects of morphine has not been determined. Therefore, the effects of histamine-related compounds on the discriminative stimulus effects of morphine were examined in rats. Combination tests using histamine-related compounds with morphine were initiated in rats trained to discriminate between 3.0 mg/kg morphine and saline. Zolantidine (central histamine H_2-receptor antagonist), but not pyrilamine (central histamine H_1-receptor antagonist) or ranitidine (peripheral histamine H_2-receptor antagonist), significantly attenuated the discriminative stimulus effects of morphine. The histamine precursor L-histidine significantly potentiated the discriminative stimulus effects of morphine. These results suggest that the discriminative stimulus effects of morphine are, at least in part, mediated through the central activation of histamine H_2-receptors in rats.

Keywords: Discriminative stimulus effect; Morphine; Histamine; H_2-receptor

1. Introduction

Morphine is widely used for the treatment of moderate to severe pain in cancer and after surgery. When self-administered intravenously, morphine induces subjective effects which might be related to its reinforcing effects (Bigelow and Preston, 1995). The drug discrimination procedure has been used to determine the mechanisms of the discriminative stimulus effects of drugs, and it is believed that the discriminative stimulus effects of psychoactive drugs in rats are related to their subjective effects in humans.

Histamine is widely distributed throughout the mammalian central nervous system and is regarded as a neurotransmitter or a neuromodulator. Histaminergic neurons in the central nervous system have been suggested to be involved in the control of pain as well as other behavioral disorders (Onodera et al., 1994; Yamatodani et al., 1991).

A considerable amount of evidence has been demonstrated that morphine increases the release of histamine from nerve terminals (Onodera et al., 1994; Yamatodani et al., 1991), suggesting that the histaminergic system is involved in some behavioral effects of morphine. Morphine-induced antinociceptive effects are attenuated by the histamine H_2-receptor antagonist zolantidine, and this effect is potentiated by histamine H_1-receptor antagonists. In contrast, we previously demonstrated that the rewarding effects of morphine and pentazocine were significantly potentiated by either histamine H_1- or H_2-receptor antagonists (Suzuki et al., 1991, 1995a). However, little is known about the involvement of the histaminergic system in the discriminative stimulus effects of morphine. The present study was thus designed to investigate the effects of histamine-related compounds on the discriminative stimulus effects of morphine in rats trained to discriminate between 3.0 mg/kg morphine and saline.

2. Materials and methods

2.1. Animals

Seven male Fischer 344 rats (Charles River Japan, Yokohama, Japan) were maintained at 200–230 g (80%

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free-feeding weight). Water was available ad libitum for all of the rats in their home cages. The rats were housed in individual cages at a room temperature of 23 ± 1 °C with a 12-h-light–dark cycle (light on 8:00 a.m. to 8:00 p.m.).

2.2. Discrimination training

Experiments were conducted according to our previous reports (Suzuki et al., 1995b). Briefly, we used operant-conditioning chambers equipped with two levers. Rats were trained to press either the right or the left lever under a fixed-ratio (FR) 1 reinforcement schedule. After the response rates had stabilized (the FR requirement was increased steadily to a reinforcement schedule of FR 10), both levers were presented in the chamber. In the discrimination training session, morphine (3.0 mg/kg) or saline was administered subcutaneously 30 min before each session in a daily sequence of SDDSSDDSSD (D = drug, S = saline). Rats were required to respond on the stimulus-appropriate lever to obtain reinforcement; there were no programmed consequences for responding on the incorrect lever. Training sessions were 15 min in duration, and this phase of training continued until all of rats performed to the required criterion [accuracy of at least 83% (First Food Pellet [10 correct responses] ≦ 12 responses) for five consecutive sessions]. Discrimination training was continued even after the criterion was attained.

2.3. Testing procedure

After the animals attained the criterion, dose–response, generalization and combination tests were initiated; test sessions were performed only when First Food Pellet × 12 responses in at least three consecutive discrimination training sessions. During the test session, rats were placed in the operant chamber until they had made 10 responses on either lever, or 5 min had elapsed. In the dose–response test, rats were tested for lever selection after the administration of various doses of morphine. In the combination test, several doses of drugs that produced less than 20% drug-lever responses in the generalization tests or saline were adminis-

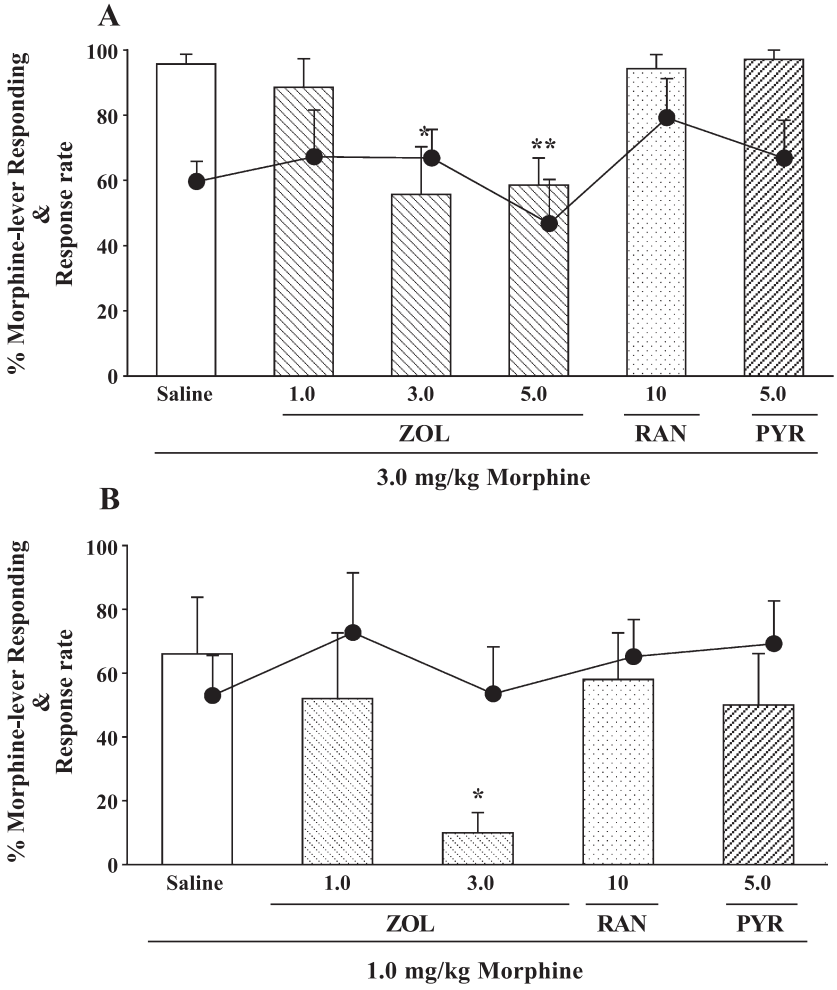

Fig. 1. Effects of zolantidine (ZOL), ranitidine (RAN), pyrilamine (PYR), or saline on the discriminative stimulus effects of (A) 3.0 and (B) 1.0 mg/kg morphine in rats trained to discriminate between 3.0 mg/kg morphine from saline. Each column and point are the mean percentage of morphine-appropriate responding and the mean response rates with S.E.M. for seven animals, respectively. *$P < 0.05$, **$P < 0.01$ vs. saline control group.

tered in combination with morphine, and then rats were tested. The pretreatment times of the drugs used were 30 min for morphine, pyrilamine (central histamine H_1-receptor antagonist), ranitidine (peripheral histamine H_2-receptor antagonist) and zolantidine (central histamine H_2-receptor antagonist), and 60 min for L-histidine (a histamine precursor). The doses and pretreatment time of drugs were based on the reports by Mori et al. (2002) and Suzuki et al. (1995b, 1997). If the rats did not make 10 responses during each component, the response was judged to have been disrupted.

During the test sessions, performance was expressed in terms of the number of drug-appropriate responses as a percentage of the total responses on completion of FR 10. Response rate was calculated as the total number of responses before the completion of 10 responses on the either lever divided by the time (minutes) taken. The paired Student's *t*-test was used to compare the percentage of drug-lever responding or response rates during the combination tests. The dose needed to produce 50% morphine-appropriate responding (ED_{50}) was estimated by linear interpolation of the dose–response curve.

2.4. Drugs

Morphine hydrochloride (Sankyo Co., Tokyo, Japan), pyrilamine maleate (Sigma-Aldrich Co., St. Louis, MO, USA), zolantidine dimaleate (Smith Kline French Lab., France) and ranitidine hydrochloride (Research Biochemicals International, Natick, MA, USA) were dissolved in saline and injected in a volume of 1.0 ml/kg. L-Histidine hydrochloride (Wako Pure Chemical Ind., Ltd., Osaka, Japan) was suspended in 0.5% Tween 80 in a volume 100 mg/ml.

3. Results

Rats required approximately 20 sessions to acquire the morphine–saline discrimination. Once rats attained the criterion, morphine–saline discrimination stabilized and was maintained with a high degree of accuracy. During the dose–response test, morphine (0.3–3.0 mg/kg) produced a dose-related increase in drug-appropriate responses, and the training dose of morphine elicited more than 80% drug-appropriate responses in all of the rats. ED_{50} value (with 95% confidence intervals) of morphine was 0.89 (0.68–1.18) mg/kg. In the combination tests, 3.0 and/or 5.0 mg/kg zolantidine, but not 10 mg/kg ranitidine and 5.0 mg/kg pyrilamine, significantly attenuated the discriminative stimulus effects of both 1.0 and 3.0 mg/kg morphine (Fig. 1A and B). These histamine-related compounds did not affect the response rate when used in combination with morphine. In contrast, 400 mg/kg L-histidine, but not 200 mg/kg, significantly potentiated the discriminative stimulus effects of 0.3 mg/kg morphine (Fig. 2). L-Histidine slightly attenuated the response rates; however, these changes were not significant. In the generalization tests, histamine-related compounds used in the present study engendered less than 20% morphine-appropriate responding.

4. Discussion

Pharmacological, behavioral and biochemical studies of the histaminergic system have revealed the existence of two types of postsynaptic histamine receptors, histamine H_1- and H_2-receptors. In the present study, we found that the histamine H_2-receptor antagonist zolantidine, which readily penetrates the blood–brain barrier (Calcutt et al., 1988), significantly attenuated the discriminative stimulus effects of morphine. Neither pyrilamine, a central histamine H_1-receptor antagonist, nor the other histamine H_2-receptor antagonist ranitidine, which cannot penetrate the blood–brain barrier, affected the discriminative stimulus effects of morphine. However, the histamine precursor L-histidine significantly potentiated the discriminative stimulus effects of morphine. These results strongly suggest

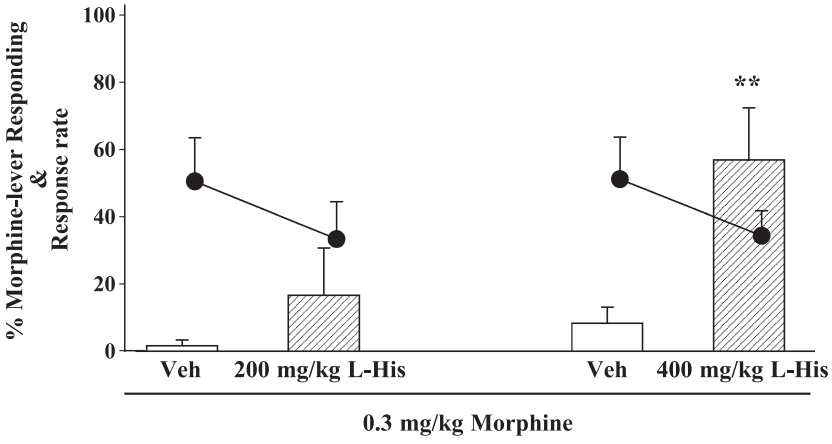

Fig. 2. Effects of L-histidine (L-His) or vehicle (Veh) on the discriminative stimulus effects of 0.3 mg/kg morphine in rats trained to discriminate 3.0 mg/kg morphine from saline. Each column and point are the mean percentage of morphine-appropriate responding and the mean response rates with S.E.M. for seven animals, respectively. $^{**}P<0.01$ vs. Veh control group.

that the discriminative stimulus effects of morphine are, at least in part, mediated by the activation of central histamine H_2-receptors. With regard to these results, zolantidine potentiated the rewarding effects of morphine (Suzuki et al., 1995a,b), but not the discriminative stimulus effects of morphine. Therefore, it is likely that the mechanisms of the discriminative stimulus effects of morphine in rats might not merely reflect its rewarding effects.

A previous study demonstrated that the antinociceptive effects of morphine were significantly attenuated by zolantidine (Hough and Nalwalk, 1992). Morphine increased histamine release from the periaqueductal gray and other brain regions (Barke and Hough, 1992; Onodera et al., 1994; Yamatodani et al., 1991). It is well known that the activation of μ-opioid receptors in the periaqueductal gray plays an important role in the antinociceptive effects of morphine. Similarly, microinjection of morphine into the periaqueductal gray (Rosecrans and Krynock, 1977) partially generalized to the discriminative stimulus effects of morphine. Such mechanisms may explain why the discriminative stimulus effects of morphine were attenuated by zolantidine in the present study. Our findings appear to highlight the importance of histamine H_2-receptors in the discriminative stimulus effects of morphine.

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