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Influence of histamine, cimetidine and pyrilamine on naloxone-induced jumping in morphine-dependent mice

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Abstract

In the present study, the effects of histamine on naloxone-induced jumping in the presence or absence of adrenoceptor or acetylcholine receptor antagonists in morphine-dependent mice were examined. In these experiments, the drugs were used before s.c. injection of naloxone (2 mg/kg), to test their effects on the expression of jumping. The i.c.v. administration of histamine (5–20 μg/mouse) 15 min before naloxone injection decreased the number of jumps in mice. When the histamine H_2 receptor antagonist, cimetidine (5–20 mg/kg), and the histamine H_1 receptor antagonist, pyrilamine (5–20 mg/kg), were administered i.p. to morphine-dependent mice, only cimetidine enhanced the jumping behaviour. Administration of cimetidine (20 mg/kg, i.p.), 30 min, of the β-adrenoceptor antagonist, propranolol (2.5–10 mg/kg, i.p.), 15 min but not of pyrilamine (20 mg/kg, i.p.), 30 min before naloxone injection, decreased the histamine effect. The i.p. administration of an acetylcholine receptor antagonist, atropine (5 and 10 mg/kg, i.p.), the α_1-adrenoceptor antagonist, prazosin (0.5, 1 and 2 mg/kg, i.p.), and α_2-adrenoceptor antagonist, yohimbine (0.5, 1 and 2 mg/kg, i.p.), 15 min before naloxone injection, had no effect on the histamine response. Single administration of propranolol, atropine or prazosin decreased, while yohimbine increased the naloxone-induced jumping. It is concluded that the histamine H_2 receptor mechanism may be involved in the influence of histamine on the expression of naloxone-induced jumping in morphine-dependent mice.

Keywords: Jumping; Histamine; Morphine; Naloxone; Adrenoceptor agent; (Mouse)

1. Introduction

Repeated treatment with opioids may induce drug dependence (Gutstein and Akil, 2001). Several neurotransmitters, including catecholamines, serotonin, acetylcholine, γ-aminobutyric acid (GABA), or peptidergic transmission have been reported to have an important role in the expression of the somatic signs of withdrawal or abstinence syndrome of opioids (see Maldonado, 1997).

Increasing evidence indicates that histamine may function as a neurotransmitter in the brain. A histaminergic neuronal system (Hough, 1988) and specific pre- and postsynaptic histamine receptor subtypes (Schwartz et al., 1986; Watanabe et al., 1990) have been identified. There are reports indicating that intracerebral injection of the agent may induce antinociception via histamine H_2 receptors and also increase the analgesic effect of morphine (Chung et al., 1984; Suzuki et al., 1994; Thoburn et al., 1994; Eriksson et al., 2000). However, other reports suggest that histamine inhibits the analgesic effect of morphine, mainly by a histamine H_1 receptor mechanism (Arrigo-Reina, 1990; Suzuki et al., 1994). There may be also some functional relationships between central morphine action and the release of histamine in the brain. Morphine has been shown to release histamine in the periaqueductal gray and induces analgesia (Barke and Hough, 1992, 1993). Acute morphine treatment enhances histamine release via opioid receptors. It also releases histamine from a non-neuronal pool(s) in the mouse brain (Nishibori et al., 1985). Furthermore, it has been reported that, during withdrawal of morphine in opioid dependence in rats, the levels of histamine can be reduced (Mazurkiewicz-Kwilecki and Henwood, 1976). Intracerebroventricular injection of histamine has been reported to elicit withdrawal signs similar to those of opioids (Glick and Crane, 1978). On

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the other hand, it has been reported that the brain histamine level is highly stable, irrespective of the development of morphine dependence or the induction of withdrawal symptoms. However, the turnover of brain histamine is elevated as seen from the increase of histamine metabolite (Oishi et al., 1988). Histamine and histaminergic receptors have also been implicated in morphine withdrawal jumping in mice (Leza et al., 1990). It was shown that adrenoceptors (Hill and Straw, 1988; Gulat-Marnay et al., 1989a) and muscarinic receptors (Gulat-Marnay et al., 1989b) influence the release of labeled histamine from depolarized slices of brain cortex. One of the important anatomical areas, which seems to represent a site of origin of the opioid withdrawal syndrome, is the locus coeruleus (Maldonado et al., 1992) and a noradrenergic pathway (Maldonado, 1997). The α_2-adrenoceptor antagonist, yohimbine, increases and the α_2-adrenoceptor agonist, clonidine, decreases histamine release from hypothalamic neurons (Prast et al., 1991). It is proposed that interactions between histaminergic and cholinergic neurons constitute an important circuit in cortical activation (Lin et al., 1996). A cholinergic mechanism may be involved in the morphine withdrawal signs (Buccafusco et al., 2000). An interaction between the histaminergic plus the adrenergic system and/or the cholinergic system in jumping withdrawal has not been described. In the present study, the effects of histamine receptor subtypes on naloxone-induced jumping and the influence of adrenoceptor and acetylcholine receptor antagonists on the histamine response were investigated.

2. Materials and methods

2.1. Animals

Male NMRI mice (25–30 g) were used in all experiments. The animals were housed 10 per cage in an animal room maintained at 24–25 °C on a 12-h light/dark cycle. Food and water were available at all times except during the experiments. The experiments were done between 10:00 and 12:00 AM. Each animal was used once only and was killed immediately after the experiment. The experimental protocol was approved by the Ethical Committee of the Azad University of Tehran (21 June 2002).

2.2. Drugs

The following drugs were used: histamine dihydrochloride (Sigma, UK), atropine sulphate (Merck, Germany), morphine sulphate (Temad, Iran), naloxone hydrochloride ampoules (Tolidaru, Iran), prazosin hydrochloride and yohimbine hydrochloride (Sigma, Poole, UK), propranolol hydrochloride (ICI, UK), Ketamine hydrochloride (Rotex, Germany) and xylazine hydrochloride (Bayer, Germany). The drugs were dissolved in saline and were injected i.p. in a volume of 10 ml/kg, except morphine and naloxone, which were administered s.c. in a volume of 10 ml/kg. Histamine was injected i.c.v. (2 μl/mouse). The control groups received saline. The doses of the drugs used had been shown to be active in previous studies (Zarrindast et al., 1999, 2000).

2.3. Chronic guide cannula implantation

The animals were anesthetized with ketamine hydrochloride (50 mg/kg) plus xylazine hydrochloride (4 mg/kg). The skull of the rat was fixed to a stereotaxic frame (David Kopf Instruments, USA) and permanent stainless-steel guide cannulas (23 gauge) were implanted under anesthesia 3 days before the experiments.

The guide cannulas were implanted in the lateral ventricle at the following coordinates: 2 mm lateral and 0.9 mm caudal to the bregma and to the depth of 3 mm from the surface of the skull. The drugs were injected in a volume of 2 μl during a period of 2 min, by means of an internal cannula (30 gauge) connected by polyethylene tubing to a 5-μl Hamilton syringe. The injection cannula was left in place for a further 1 min before being slowly withdrawn.

2.4. Induction of dependence

The mice were made dependent on morphine, based on the method we used previously (Zarrindast and Farzin, 1996). Morphine sulphate was injected subcutaneously three times daily at 8, 12 and 16 h on the following dosage schedule. The first three doses were 50, 50 and 75 mg/kg, respectively. The higher dose of the third daily injection was aimed to minimize any overnight withdrawal. Morphine administration was carried out over a maximum of 3 days for any group of mice. A dose of 50 mg/kg of morphine sulfate was also injected on the 4th day (2 h before naloxone injection). Hyperactivity and the Straub tail effect were seen after morphine injections. Loss of weight (5–6%) and death (0.5–1%) were observed with chronic administration of morphine sulphate.

2.5. Naloxone-induced jumping

Groups of nine mice were tested for the occurrence of jumping after their tenth injection of morphine on day 4. Two hours after the last dose of morphine (50 mg/kg, s.c.), abstinence was precipitated by administration of naloxone (2 mg/kg, s.c.). Then the animals were placed individually in a Perspex observation cylinder (15 cm diameter, 50 cm height). The number of jumps was recorded immediately after injection of naloxone over a 30-min period.

2.6. Drug treatment

The animals received 10 injections of morphine as described in Section 2.4, in order to develop dependence on morphine. The number of jumps induced by naloxone was compared to those of mice that received 10 injections of saline instead of morphine.

2.6.1. Experiment 1

The morphine-dependent animals received either i.c.v. injection of histamine (5, 10 and 20 μg/mouse), 15 min or i.p. administration of pyrilamine (5, 10 and 20 mg/kg) or cimetidine (5, 10 and 20 mg/kg), 30 min before naloxone (2 mg/kg, s.c.) administration. The results are given in Results (Fig. 1).

2.6.2. Experiment 2

All the animals were made dependent on morphine. Three groups of animals received either saline (10 ml/kg, i.p.), pyrilamine (20 mg/kg, i.p.) or cimetidine (20 mg/kg, i.p.), 30 min and different doses of histamine (2.5, 5 and 10 μg/mouse, i.c.v.) 15 min before naloxone (2 mg/kg, s.c.) injection, to test the effect of the histamine receptor antagonists on the response to histamine in the expression of jumping behaviour (Fig. 2).

2.6.3. Experiment 3

The effect of the α_1-adrenoceptor antagonist, prazosin, in the absence or presence of histamine was tested on the expression of naloxone-induced jumping in morphine-dependent animals. One group of animals received prazosin (0.5, 1 and 2 mg/kg, i.p.), 15 min before naloxone (2 mg/kg, s.c.) injection. The second group of animals received prazosin plus histamine (5 μg/mouse, i.c.v.), 15 min before naloxone administration, on day 4 (Fig. 3).

2.6.4. Experiment 4

The effect of the α_2-adrenoceptor antagonist, yohimbine in the absence or presence of histamine, was tested on the expression of naloxone-induced jumping in morphine-dependent animals. One group of animals received yohimbine (0.5, 1 and 2 mg/kg, i.p.), 15 min before naloxone (2 mg/kg, s.c.) injection. The second group of animals received yohimbine plus histamine (5 μg/mouse, i.c.v.), 15 min before naloxone administration, on day 4 (Fig. 4).

2.6.5. Experiment 5

The effect of the β-adrenoceptor antagonist, propranolol, in the absence or presence of histamine was tested on the expression of naloxone-induced jumping, in morphine-dependent animals. One group of animals received propranolol (2.5, 5 and 10 mg/kg, i.p.), 15 min before naloxone (2 mg/kg, s.c.) injection. The second group of animals received

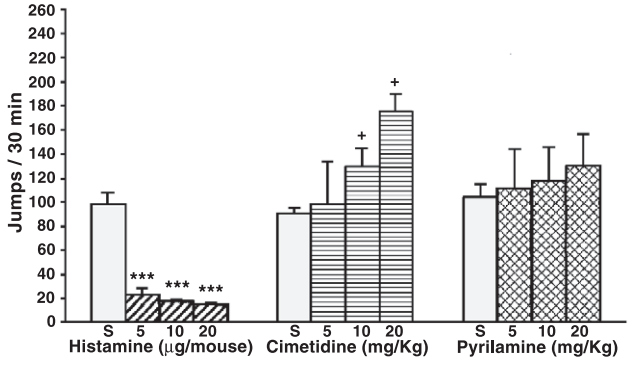

Fig. 1. Effect of histamine, cimetidine or pyrilamine on the expression of naloxone-induced jumping in morphine-dependent mice. Animals were made dependent as described in Materials and methods. All the dependent animals received naloxone s.c. (2 mg/kg) to induce jumping. The animals received i.c.v. different doses of histamine (5, 10 and 20 μg/mouse), and also saline and different doses of cimetidine (5, 10 and 20 mg/kg) or pyrilamine (5, 10, 20 mg/kg) i.p. 30 min before naloxone administration. Each group comprised of nine mice. Data are means ± S.E.M. ***$P<0.001$; compared with histamine control group, +$P<0.05$; compared with cimetidine control group.

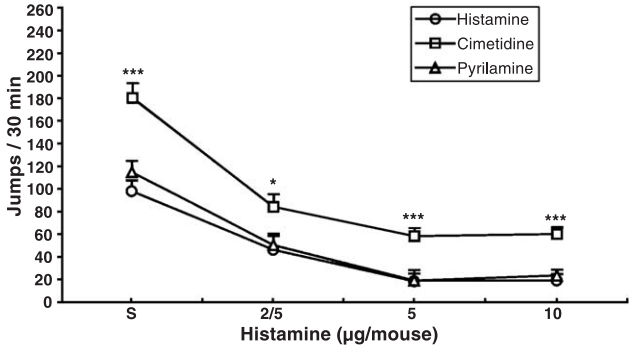

Fig. 2. Effect of cimetidine or pyrilamine on the influence of histamine on the expression of naloxone-induced jumping in morphine-dependent mice. All the dependent animals received naloxone (2 mg/kg, s.c.) to induce jumping. The animals received cimetidine (20 mg/kg, i.p.) or pyrilamine (20 mg/kg, i.p.) 15 min before histamine (2.5, 5 and 10 μg/mouse, i.c.v.), administration. Histamine was administered 15 min before naloxone administration. Each group comprised of nine mice. Data are means ± S.E.M. *$P<0.05$; ***$P<0.001$; compared with the histamine control group.

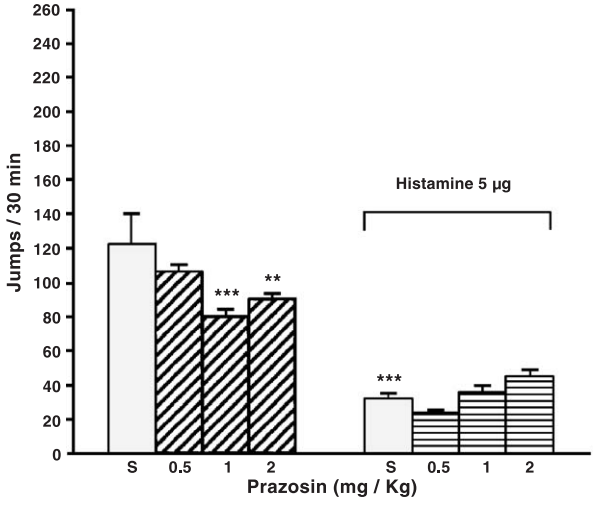

Fig. 3. Effect of prazosin with or without histamine on the expression of naloxone-induced jumping in morphine-dependent mice. All the dependent animals received different doses of prazosin (0.5, 1 or 2 mg/kg, i.p.) or prazosin plus histamine (5 μg/mouse, i.c.v.), 15 min before naloxone injection. Each group comprised of nine mice. Data are means ± S.E.M. **$P<0.01$; ***$P<0.001$; compared with the saline control group.

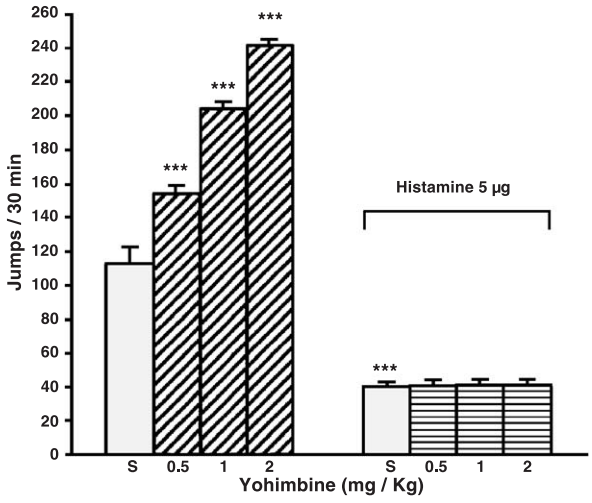

Fig. 4. Effect of yohimbine with or without histamine on the expression of naloxone-induced jumping in morphine-dependent mice. All the dependent animals received different doses of yohimbine (0.5, 1 or 2 mg/kg, i.p.) or yohimbine plus histamine (5 µg/mouse, i.c.v.), 15 min before naloxone injection. Each group comprised of nine mice. Data are means ± S.E.M. ***$P<0.001$; compared with the saline control group.

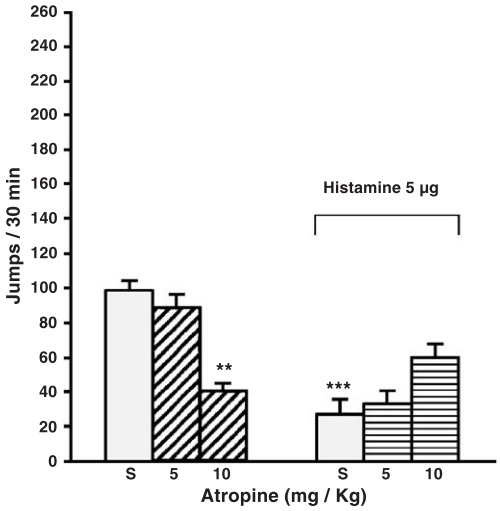

Fig. 6. Effect of atropine with or without histamine on the expression of naloxone-induced jumping in morphine-dependent mice. All the dependent animals received different doses of atropine (5, 10 mg/kg, i.p.) or atropine plus histamine (5 µg/mouse, i.c.v.), 15 min before naloxone injection. Each group comprised 9 mice. Data are means ± S.E.M. **$P<0.01$; ***$P<0.001$; compared with the saline control group.

propranolol plus histamine (5 µg/mouse, i.c.v.), 15 min before naloxone administration, on day 4 (Fig. 5).

2.6.6. Experiment 6

The effect of the acetylcholine receptor antagonist, atropine, in the absence or presence of histamine, was tested on the expression of naloxone-induced jumping in morphine-dependent animals. One group of animals received atropine (5 and 10 mg/kg, i.p.), 15 min before naloxone (2 mg/kg, s.c.) injection. The second group of animals received atropine plus histamine (5 µg/mouse, i.c.v.), 15 min before naloxone administration, on day 4 (Fig. 6).

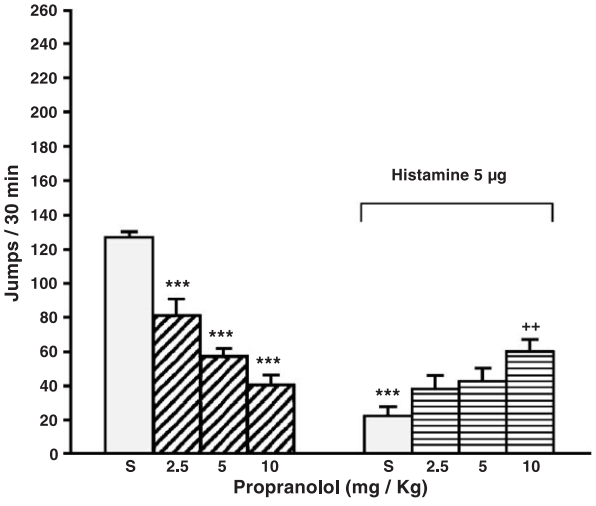

Fig. 5. Effect of propranolol with or without histamine on the expression of naloxone-induced jumping in morphine-dependent mice. All the dependent animals received different doses of propranolol (2.5, 5 or 10 mg/kg, i.p.) or propranolol plus histamine (5 µg/mouse, i.c.v.), 15 min before naloxone injection. Each group comprised of nine mice. Data are means ± S.E.M. ***$P<0.01$; compared with the saline control group. ++$P<0.01$; compared with the propranolol control group.

2.7. Statistical analysis

An analysis of variance (ANOVA) followed by the Newman–Keuls test was used for statistical evaluation of the data. Differences between means were considered statistically significant if $P<0.05$. Each point is the means ± S.E.M. for nine mice.

3. Results

3.1. Naloxone-induced jumping behaviour in morphine-dependent mice

The mice were divided randomly into two groups. One group received morphine (as described in Materials and methods) to induce dependence. The next group received saline (10 ml/kg), instead of morphine, subcutaneously. Naloxone (2 mg/kg, s.c.) increased the number of jumps (98.4 ± 9.5, $N=9$) in morphine-dependent mice as compared to the number of jumps (0.6 ± 0.3, $N=9$, $P<0.0001$) in nondependent mice. The results showed that naloxone could induce jumping in morphine-dependent mice. We considered jumping behavior as the sign of abstinence for further experiments in our study. Hyperactivity and Straub tail reaction were seen after morphine injections. Loss of weight (5–6%) and death (0.5–1%) occurred on chronic administration of morphine sulphate.

3.2. Effect of histamine and histamine receptor antagonists on the expression of naloxone-induced jumping behaviour in morphine-dependent mice

Fig. 1 shows a dose–response effect of histamine, cimetidine or pyrilamine on the jumping behaviour of mice. All animals received morphine (s.c.) three times daily for 3 days, in order to induce dependence on morphine as described earlier in Materials and methods. The animals were injected with different doses of histamine (5, 10 and 20 μg/mouse, i.c.v.) 15 min, cimetidine (5, 10 and 20 mg/kg, i.p.) or pyrilamine (5, 10 and 20 mg/kg, i.p.), 30 min before naloxone (2 mg/kg, s.c.) injection on day 4, and the numbers of jumps were then recorded. One-way ANOVA shows a significant difference between animals, after different doses of histamine [$F(3,32) = 52.43$, $P < 0.001$], and cimetidine [$F(3,32) = 3.5$, $P < 0.05$] but not pyrilamine [$F(3,32) = 0.18$, $P > 0.05$]. Further analysis indicates that histamine decreased while cimetidine increased the number of jumps, but pyrilamine did not elicit any response.

3.3. Effects of histamine with or without histamine receptor antagonists on the expression of naloxone-induced jumping in morphine-dependent mice

Fig. 2 shows the effect of histamine with or without histamine receptor antagonists, cimetidine and pyrilamine on the jumping behaviour of mice. The animals were made dependent on morphine as before, and received different doses of histamine (2.5, 5 and 10 μg/mouse, i.c.v.) 15 min, cimetidine (20 mg/kg, i.p.) or pyrilamine (20 mg/kg, i.p.), 30 min before naloxone (2 mg/kg, s.c.) injection on day 4. Two-way ANOVA indicates an interaction of histamine with cimetidine [$F(3,64) = 2.8$, $P < 0.05$] but not with pyrilamine [$F(3,64) = 0.3$, $P > 0.05$]. Further analysis indicates that histamine decreased, while cimetidine increased, naloxone-induced jumping.

3.4. Effect of adrenoceptor antagonists with or without histamine on jumping behaviour in morphine-dependent mice

Fig. 3 shows the effect of the α_1-adrenoceptor by itself or in combination with histamine on the expression of naloxone-induced jumping. The animals were made dependent on morphine as before, and received different doses of prazosin (0.5, 1 and 2 mg/kg, i.p.), histamine (5 μg/mouse, i.c.v.), 15 min before naloxone (2 mg/kg, s.c.) injection on day 4. Two-way ANOVA revealed an interaction between histamine and prazosin [$F(3,64) = 5.8$, $P < 0.01$]. Further analysis showed that two doses of prazosin (1 and 2 mg/kg) themselves decreased jumping behaviour, but did not alter the histamine response.

Fig. 4 shows the effect of the α_2-adrenoceptor antagonist, yohimbine, by itself or in combination with histamine on the expression of naloxone-induced jumping. The animals were made dependent on morphine as before, and received different doses of yohimbine (0.5, 1 and 2 mg/kg, i.p.), histamine (5 μg/mouse, i.c.v.), 15 min before naloxone (2 mg/kg, s.c.) injection on day 4. Two-way ANOVA revealed an interaction between histamine and yohimbine [$F(3,64) = 69.5$, $P < 0.0001$]. Further analysis showed that while yohimbine by itself increased jumping it did not alter the histamine response.

Fig. 5 shows the effect of the β-adrenoceptor antagonist, propranolol, by itself or in combination with histamine. The animals were made dependent on morphine as before, and received different doses of propranolol (2.5, 5 and 10 mg/kg, i.p.), histamine (5 μg/mouse, i.c.v.), 15 min before naloxone (2 mg/kg, s.c.) injection on day 4. Two-way ANOVA showed an interaction between propranolol and histamine [$F(3,64) = 29.7$, $P < 0.0001$]. Further analysis showed that all doses of propranolol decreased the histamine effect, and that propranolol by itself also decreased jumping behaviour.

Fig. 6 shows the effect of the acetylcholine receptor antagonist, atropine, by itself or in combination with histamine. The animals were made dependent on morphine as before, and received different doses of atropine (5 and 10 mg/kg, i.p.), histamine (5 μg/mouse, i.c.v.), 15 min before naloxone (2 mg/kg, s.c.) injection on day 4. Two-way ANOVA showed that the different doses of atropine have an interaction with histamine [$F(2.48) = 7.46$, $P < 0.01$]. Further analysis showed that while atropine by itself decreased jumping behaviour it did not decrease the histamine response.

4. Discussion

Histamine as a central neurotransmitter (Haas et al., 1991; Schwartz et al., 1991; Onodera et al., 1994) functions through three different histamine receptor subtypes. The histamine H_1 receptor acts via the excitation of Ca^{2+} while the H_2 receptor acts via cAMP. The H_3 receptor reduces histamine release (Arrang et al., 1983; Kanamaru et al., 1998; Rozniecki et al., 1999) and other neurotransmitters (Leurs et al., 1998). Fibers from the hypothalamic histaminergic cell bodies innervate several areas known to be important in antinociceptive mechanisms (Brown et al., 2001) including the periaqueductal gray (Panula et al., 1989b; Airaksinen and Panula, 1988) and the spinal cord (Panula et al., 1989a). All parts of the tuberomammillary nucleus contain dense networks of fibers which are noradrenergic and make synaptic contacts with the dendrites, but not the somata, of the tuberomammillary neurons. The lateral part of the tuberomammillary body receives an especially dense noradrenergic innervation (Eriksson et al., 2000). Furthermore, several neurotransmitters seem to be involved in morphine tolerance and dependence (Bhargava, 1994; Bourin et al., 1999).

In the present study, the effects of histamine, histamine H_1 and H_2 receptor antagonists and an adrenoceptor antagonist on naloxone-induced jumping in morphine-dependent mice,

were investigated. The data indicate that unilateral intracerebroventricular (i.c.v.) administration of different doses of histamine decreased naloxone-induced jumping, indicating the interaction of opioid and histamine receptor mechanisms. This can be supported by the suggestion of some investigators that histamine receptors are involved in the expression of precipitated withdrawal in morphine-dependent mice (El-Kadi and Sharif, 1996). Since morphine may reduce histamine levels during withdrawal (see Introduction), one could suggest that injection of histamine induces the opposite response. The histamine H_2 receptor antagonist, cimetidine, but not the histamine H_1 receptor antagonist, pyrilamine, reduced the histamine response. The data may indicate that a histamine H_2 receptor mechanism is involved in the attenuation of naloxone-induced jumping by histamine. This can also be supported by the results of other investigators that strongly suggest the importance of histamine H_2 receptors as mediators of the opiate antinociceptive response (Barke and Hough, 1992, 1993; Hough and Nalwalk, 1992). However, while our results are in agreement with data indicating that histamine H_2 receptors are involved in the expression of naloxone-induced jumping, they cannot support the results of other investigators which show histamine H_1 receptors are also involved in the withdrawal syndrome (El-Kadi and Sharif, 1996). Our data also showed that the single administration of cimetidine, but not of pyrilamine, increased jumping. The results are consistent with earlier reports showing that the histamine H_2 receptor antagonists increase the expression of jumping (Leza et al., 1990; El-Kadi and Sharif, 1996). However, the reports from these authors also indicate that the histamine H_1 receptor antagonists increase the other signs of the withdrawal syndrome. The response induced by H_2 receptor antagonists may also show that the brain histaminergic system may have an inhibitory role. H_2 receptor blockade has been suggested to produce a complex of neurobehavioural and gastroenteric syndromes. Therefore, it has been suggested that the drop in prolactin levels that occurs when cimetidine or ranitidine administration is interrupted may contribute to development of H_2 receptor antagonist withdrawal signs (Rampello et al., 1997; Rampello and Nicoletti, 1990).

It has been suggested that histamine receptors may function as modulators of noradrenergic neurotransmission in withdrawal signs (El-Kadi and Sharif, 1996). Our present results show that the α_1-adrenoceptor antagonist, prazosin, or α_2-adrenoceptor antagonist, yohimbine, did not alter the histamine-induced attenuation of naloxone-induced jumping. However, the single administration of prazosin decreased, while yohimbine increased, jumping behaviour. The data may show that the α_1- and α_2-adrenoceptors mechanisms themselves have various effects on jumping, but that they are not involved in the histamine effect. There is controversy about the yohimbine effect on withdrawal. It has been indicated that the drug exacerbated the expression of the withdrawal syndrome in mice (Sharif and El-Kadi, 1996a; Zarrindast et al., 2002) and the human (Stine et al., 2001, 2002) or attenuated jumping behavior when it is used during the development of dependence (Taylor et al., 1991; Iglesias et al., 1992; Ambrosio et al., 1997; Zarrindast et al., 2002), whereas other reports showed no response for the drug (Van der Laan, 1987). The contradictory responses found by different investigators may be due to differences in the doses of the drugs used, in animals or be a reflection of α_2-adrenoceptor agents' effect on presynaptic or postsynaptic sites of the adrenoceptor system. The yohimbine-induced increase in jumping in the present study may have been due to the inhibition of serotonin receptors or to the blockade of presynaptic α_2-adrenoceptors, which may in turn release noradrenaline. This can be supported by results showing that yohimbine potentiated naloxone-induced jumping in mice (Sharif and El-Kadi, 1996a) and elicited objective and subjective opioid withdrawal signs and increased the craving for opioid drugs in opioid-dependent patients (Stine et al., 2002).

On the other hand, propranolol (a β_1/β_2-adrenoceptor antagonist) itself decreased jumping behaviour and decreased the histamine effect. Thus, it is possible that a β-adrenoceptor mechanism is involved in the histamine response, which may agree with the concept that a β_2-adrenoceptor mechanism is involved in histamine-induced effects (Kjaer et al., 1995).

The results also showed that the administration of atropine sulphate 15 min before naloxone injection attenuated the jumping induced by naloxone in morphine-dependent mice. This result is in agreement with that of a previous study which showed that muscarinic receptor antagonists reduce naloxone-precipitated withdrawal symptoms (Sharif and El-Kadi, 1996b). However co-administration of atropine with histamine had no effect on the histamine influence on the expression of naloxone-induced jumping in morphine-dependent mice. The differences observed between effects of atropine alone and those of atropine in combination with histamine may be explained by the possibility that the drugs may be acting on different pathways.

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