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European Journal of Pharmacology 279 (1995) 109–113

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Effects of a histamine H_2 receptor agonist and antagonist on restraint-induced antinociception in female mice

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Received 3 October 1994; revised 22 February 1995; accepted 24 February 1995

Abstract

Restraint for 1 h induced significant antinociceptive activity, as assessed by the hot plate test, in female mice. The antinociceptive activity was significant throughout the 1 h period of observation starting immediately after restraint. Prior administration of the histamine H_2 receptor agonist dimaprit (1.5–6.0 mg/kg s.c.) 15 min before restraint further enhanced the restraint-induced antinociceptive activity. Furthermore, the induction of antinociceptive activity by restraint was antagonised by prior administration of histamine H_2 receptor antagonists, cimetidine (2.5–10.0 mg/kg s.c.) or zolantidine (2.5–10.0 mg/kg s.c.). However, when these drugs were administered immediately after restraint for 1 h, the antinociceptive activity observed was similar to those restrained animals receiving saline injection. The histamine receptor agonist and antagonists, at the doses used in the present study, did not affect the response of unrestrained animals to the hot plate test. These results demonstrate that the effect of a histamine H_2 receptor agonist and antagonists on restraint-induced antinociception is dependent upon their time of administration and may act by altering the intensity of stress, thus affecting the antinociceptive activity induced.

Keywords: Antinociception; Histamine H_2 receptor; Restraint; Hot plate test

1. Introduction

It has previously been shown that stress can induce antinociception in experimental animals (Kelly, 1982; Hart et al., 1983). Our previous studies have implicated a sex difference in the response of mice to swim-induced antinociception (Wong, 1987a,b,1988). In these studies, it was shown that the swim-induced antinociception is insensitive to the effect of naloxone in the male mice while in the female animals it is antagonised dose dependently by prior administration of naloxone. A similar observation of sex difference in swim-induced antinociception in mice has been recently reported by Mogil et al. (1993). Gender difference in opioid mediation of swim-induced antinociception was also demonstrated in rats (Romero et al., 1988). Recently, these findings have also been confirmed in restraint-induced antinociception in mice (Wong, 1992). It was shown that naloxone given either before or after restraint for 1 h would suppress the antinociceptive activity induced by restraint in the female but not in the male mice, implying a possible sex difference in the involvement of the opioid systems in stress-induced antinociception.

There is accumulating evidence that histamine turnover is altered under physiological stress (Mazurkiewicz-Kwilecki and Prell, 1986) and that it induces corticosterone and adrenocorticotrophic hormone secretion in stressed rats (Bugajski and Gadek, 1983; Seltzer et al., 1986). In a recent study, we reported the involvement of histamine H_2 receptors in restraint-induced antinociception in male mice (Wong, 1993). In the present study, experiments were carried out to investigate the possible role of histamine H_2 receptors in restraint-induced antinociception in female mice and report the interesting finding that the effects of histamine H_2 receptor agonist and antagonists on restraint-induced antinociception are dependent on the time of administration of the drugs in relation to restraint.

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SSDI 0014-2999(95)00129-8

2. Materials and methods

2.1. Animals

Female Swiss albino CFLP (Carworth Farm Lane-Petter) mice weighing between 20–25 g were used for all experiments. The animals were kept in the Bioresources Unit under a 12 h light (08:00 h–20:00 h)/dark cycle and were allowed free access to standard laboratory diet and tap water until experimentation. All studies were carried out during the light cycle between 10:00 h–14:00 h. Each animal was used only once.

2.2. Restraint stress

Animals were restrained individually by putting them in a cylindrical tube with holes along the whole length for ventilation. Inside the tube the animals would have only a limited degree of movement (Wong and Bentley, 1979). The animals were restrained for 1 h. Despite the limited movement for up to 1 h, in the present study all animals appeared to be in good physical condition after the restraint.

2.3. Antinociceptive assay

Antinociceptive activity was assessed by the hot plate test. Animals were individually placed on a hot plate maintained at 55 ± 1° C. The time latency before the animal licked or lifted its hind paw was measured. For those animals not responding within 15 s the test was terminated to avoid tissue damage. Animals were tested for antinociceptive activity at 0, 10, 20, 40 and 60 min after restraint. The histamine H_2 receptor agonist dimaprit and antagonists cimetidine and zolantidine were given s.c. either 15 min before restraint or immediately after restraint for 1 h. Control animals received saline injection 10 ml/kg at the corresponding time. At least 16 animals were used for each treatment.

2.4. Drugs

The following drugs were used: dimaprit dihydrochloride (Smith, Kline and Beecham), cimetidine (Smith, Kline and Beecham) and zolantidine dimaleate (Smith, Kline and Beecham). All doses refer to the weight of the salts used. Cimetidine was dissolved in 0.15 M hydrochloric acid with saline and then adjusted to neutral pH with drops of 1 M sodium hydroxide. All other drugs were dissolved in physiological saline solution and administered subcutaneously in a volume of 10 ml/kg.

2.5. Statistical analysis

Data were analysed by the analysis of variance. When statistical significance was indicated among groups, the data of individual groups were compared with the unpaired Student's t-test at a significance level of $P < 0.05$.

3. Results

3.1. The effects of prior administration of a histamine H_2 receptor agonist and antagonist on restraint-induced antinociception

Restraint for 1 h induced significant antinociceptive activity in female mice. Immediately after restraint the mean response latency of restraint animals was 10.21 ± 0.77 s versus 5.02 ± 0.33 s in non-restraint controls ($P < 0.05$). The antinociceptive activity was significant throughout the 1 h post-restraint period of observation (Figs. 1–4). Administration of saline 10 ml/kg s.c. before or after restraint did not affect the antinociceptive activity induced by restraint. Prior administration of the histamine H_2 receptor agonist dimaprit (1.5–6.0 mg/kg s.c.) 15 min before restraint further enhanced the antinociceptive activity (Fig. 1). For the dimaprit 6.0 mg/kg s.c. pretreated group, the mean response latency measured immediately after restraint was 13.01 ± 0.63 s versus 10.01 ± 0.69 s for saline pretreated restraint controls ($P < 0.05$). The enhancement was dose dependent on the dimaprit given 15 min before restraint. The enhanced antinociceptive activity in-

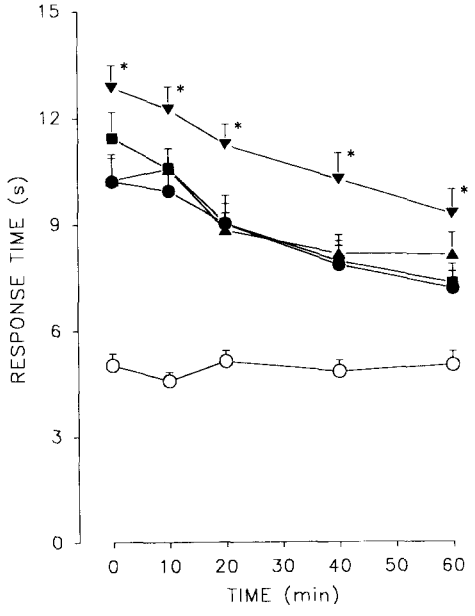

Fig. 1. The effect of dimaprit s.c. 15 min before restraint for 1 h on the induced antinociception in female mice. (○) Non-restraint control; (●) saline 10 ml/kg + restraint 1 h; (▲) dimaprit 1.5 mg/kg + restraint 1 h; (■) dimaprit 3.0 mg/kg + restraint 1 h; (▼) dimaprit 6.0 mg/kg + restraint 1 h. Values are means ± S.E.M. ($n = 16$). $^*P <$ 0.05 compared with the corresponding saline + restraint control values.

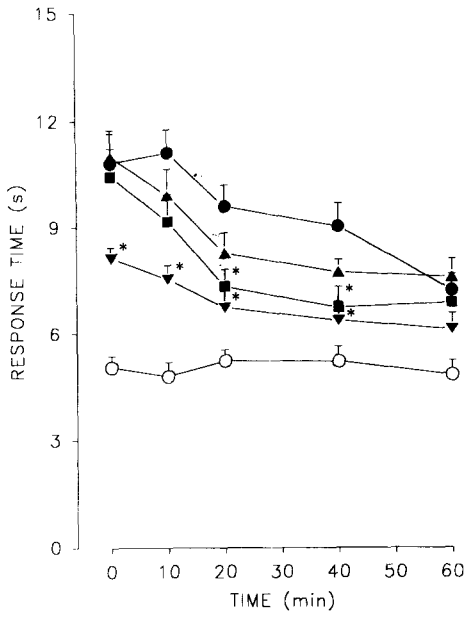

Fig. 2. The effect of cimetidine s.c. 15 min before restraint for 1 h on the induced antinociception in female mice. (○) Non-restraint control; (●) saline 10 ml/kg + restraint 1 h; (▲) cimetidine 2.5 mg/kg + restraint 1 h; (■) cimetidine 5.0 mg/kg + restraint 1 h; (▼) cimetidine 10.0 mg/kg + restraint 1 h. Values are means ± S.E.M. ($n = 16$). $^*P < 0.05$ compared with the corresponding saline + restraint control values.

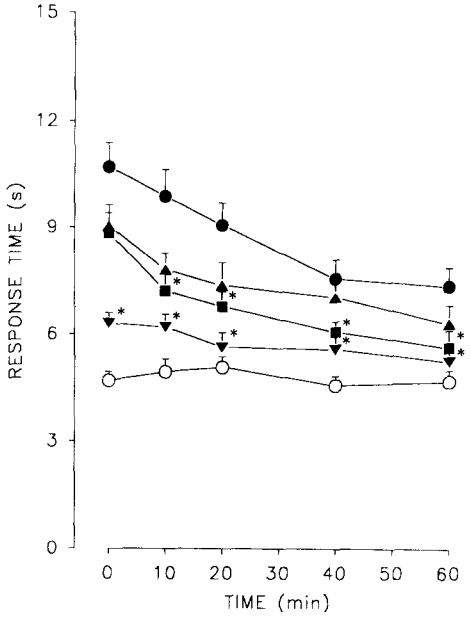

Fig. 3. The effect of zolantidine s.c. 15 min before restraint for 1 h on the induced antinociception in female mice. (○) Non-restraint control; (●) saline 10 ml/kg + restraint 1 h; (▲) zolantidine 2.5 mg/kg + restraint 1 h; (■) zolantidine 5.0 mg/kg + restraint 1 h; (▼) zolantidine 10.0 mg/kg + restraint 1 h. Values are means ± S.E.M. ($n = 16$). $^*P < 0.05$ compared with the corresponding saline + restraint control values.

duced by the highest dose of dimaprit used was still apparent at 60 min post-restraint.

On the other hand, prior administration of the histamine H_2 receptor antagonist cimetidine inhibited the development of antinociceptive activity induced by restraint (Fig. 2). At the highest dose of cimetidine used (10 mg/kg s.c.) the antinociceptive activity measured immediately after restraint was 8.12 ± 0.31 s versus 10.21 ± 0.77 s for restraint control ($P < 0.05$). The antinociceptive activity was significantly suppressed up to 40 min after restraint. Similar findings were obtained for another histamine H_2 receptor antagonist, zolantidine, which supposedly passes through the blood-brain barrier (Fig. 3). In this case, the highest dose of zolantidine (10 mg/kg s.c.) reduced the hot plate response time immediately after restraint to 6.31 ± 0.31 s versus 10.21 ± 0.77 s for restraint control ($P < 0.05$). The inhibition of antinociceptive activity was significant throughout the 1 h observation period.

3.2. The effects of a histamine H_2 receptor agonist and antagonist administered immediately after restraint on restraint-induced antinociception

When the same doses of the above mentioned drugs were administered immediately after restraint for 1 h, the antinociceptive activity observed was similar to those restrained animals receiving saline injection. Only the responses to the highest doses of the drugs used are shown in Fig. 4. The histamine receptor agonist and antagonist, at the doses used in the present study, did not affect the response of unrestrained animals to

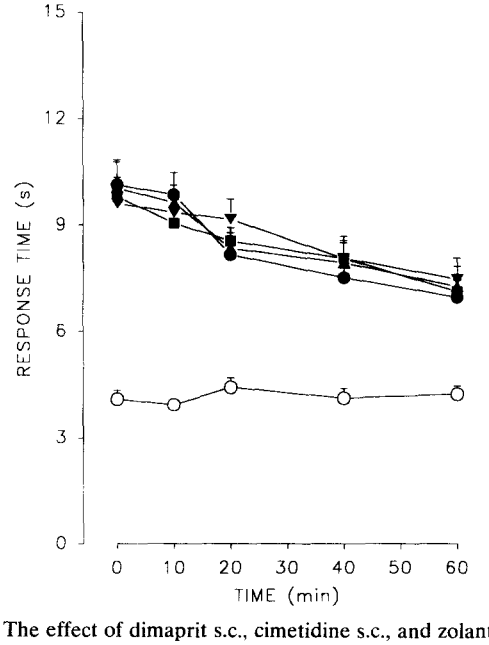

Fig. 4. The effect of dimaprit s.c., cimetidine s.c., and zolantidine s.c. immediately after restraint for 1 h on the induced antinociception in female mice. (○) Non-restraint control; (●) restraint 1 h + saline 10 ml/kg; (▲) restraint 1 h + dimaprit 6.0 mg/kg; (■) restraint 1 h + cimetidine 10.0 mg/kg; (▼) restraint 1 h + zolantidine 10.0 mg/kg. Values are means ± S.E.M. ($n = 16$).

the hot plate test throughout the same 1 h observation period.

4. Discussion

The characteristics of stress-induced antinociception are dependent on the type and duration of stress and on the method by which antinociception is assessed (Kelly, 1982; Oluyomi and Hart, 1991). Furthermore, using the same stress parameter there is a gender difference in the underlying phenomena of stress-induced antinociception. In our previous studies, it was shown that swim at room temperature for 30 s induced antinociceptive activities as assessed by the abdominal constriction test in both male and female mice. However, naloxone only inhibited the swim-induced antinociceptive activity in female mice but not in male animals (Wong, 1987a,b). A similar sex difference was observed for restraint-induced antinociception assessed by hot plate test (Wong, 1992). The suppressing effect of naloxone on restraint-induced antinociception was observable whether the naloxone was given before or after the restraint. Others have shown gender difference in mice and rats using various stress parameters and antinociceptive assay methods (Mogil et al., 1993; Romero et al., 1988).

Brain histamine level has been suggested to be modulated by both stress and plasma corticosterone levels (Hough, 1988). The turnover rate of histamine in rodent brain is increased by exposure to various stressful situations (Taylor and Snyder, 1971, 1972; Itoh et al., 1989). In addition, histamine administration has been shown to elicit antinociception in both mice (Oluyomi and Hart, 1991) and rats (Bhattacharya and Parmer, 1985). Furthermore, it has been shown that a histamine H_2 receptor antagonist inhibits footshock-induced antinociception (Gogas and Hough, 1989) and morphine-induced antinociception in rats (Hough and Nalwalk, 1992). Recently, Malmberg-Aiello et al. (1994) have demonstrated the involvement of the histaminergic system in the modulation of nociceptive stimuli. Thus the possible roles of histamine in stress induced antinociception are being studied. In our recent study, it was reported that a histamine H_1 receptor agonist and antagonist had no effect on restraint-induced antinociception. However, the antinociceptive activity was enhanced by prior administration of a histamine H_2 receptor agonist and suppressed by prior administration of histamine H_2 receptor blockers (Wong, 1993). In the present study, the investigation was extended to female mice and also to the effect of drug administration after restraint for 1 h.

In the present study, prior administration of the histamine H_2 receptor agonist dimaprit enhanced while the antagonists cimetidine and zolantidine suppressed the development of antinociceptive activity induced by restraint. These findings are similar to those reported for male animals (Wong, 1993). This is a surprising finding as there is a gender difference in the effect of naloxone on restraint-induced antinociception in mice (Wong, 1992). In our previous report, it was shown that in male mice the restraint-induced antinociception was insensitive to naloxone antagonism while the female showed great sensitivity to naloxone, implicating the involvement of a non-opioid mechanism in male and an opioid mechanism in female mice in relation to restraint-induced antinociception. In the present and previous study (Wong, 1993), the ability of prior administration of a histamine H_2 receptor agonist to potentiate and the antagonist to suppress such antinociceptive activities would strongly suggest the involvement of the histaminergic system in this phenomenon in both male and female mice. Since histamine turnover has been shown to be enhanced under stress situations (Taylor and Snyder, 1971; Verdiere et al., 1977), it seems likely that restraint may activate the histaminergic pathway, which may then induce the development of antinociceptive activity through activation of endogenous opioid and non-opioid mechanisms by the histamine H_2 receptors. This may account for the lack of gender difference in response to a histamine H_2 receptor agonist and antagonist. If this is the case, prior blockade of the histamine H_2 receptors by cimetidine and zolantidine would suppress the development of the antinociceptive activity induced by restraint. Furthermore, increased stimulation of the histamine H_2 receptor by dimaprit before restraint would enhance the intensity of antinociceptive activity. However, both cimetidine and dimaprit penetrate the blood-brain barrier with difficulty so their actions are most probably restricted to the periphery. The effect of zolantidine, a histamine H_2 receptor blocker that readily crosses the blood-brain barrier (Calcutt et al., 1988), was also studied. At similar doses, zolantidine was more effective than cimetidine in blocking the development of restraint-induced antinociceptive activity. As the two histamine H_2 receptor antagonists have similar effects, it appears that the involvement of a histaminergic mechanism is most probably of peripheral origin with a possible central involvement.

As it has been previously shown that the antinociceptive activity induced by various forms of stressful stimuli is proportional to the intensity and duration of stress (Hart et al., 1983; Wong, 1987a, 1992), the role of peripheral and perhaps central histamine H_2 receptors may be mainly to increase the stress response in relation to stress intensity. The increased stress response would then result in the enhanced antinociceptive activity observed. If this is the case, it would explain the observations that histamine H_2 activation or blockade would enhance or block both naloxone-

sensitive and naloxone-resistant stress-induced antinociception as seen in the present and previous study (Wong, 1993). This postulation is further supported by the finding that the histamine H_2 receptor agonist and antagonist were ineffective in altering the antinociceptive activities when administered after the restraint in female mice in the present study and in male animals (unpublished observations). Further work is in progress to clarify the role of the histamine H_2 receptor in restraint-induced antinociception.

Acknowledgements

The author wishes to thank Smith, Kline and Beecham Co. for the gifts of zolantidine, cimetidine and dimaprit.

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