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Effects of Chlorpheniramine and Ranitidine on the Visceral Nociception Induced by Acetic Acid in Rats: Role of Opioid System

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Abstract: In this study, effects of chlorpheniramine (H_1-receptor blocker), ranitidine (H_2-receptor blocker), morphine (an opioid agonist) and naloxone (an opioid antagonist) in separate and combined treatments were investigated on the visceral nociception in rats. Visceral nociception was induced by intraperitoneal injection of acetic acid (1 mL, 1%). The latency time to the beginning of the first abdominal wall contraction (first writhe) was measured and the numbers of writhes were counted for 1 h after acetic acid injection. Intraperitoneal injections of chlorpheniramine and ranitidine significantly ($p < 0.05$) increased the latency time to the beginning of the first writhe and also significantly ($p < 0.05$) decreased the numbers of writhes. The same results were obtained after subcutaneous injection of morphine. Subcutaneous injection of naloxone did not change the intensity of visceral nociception, but significantly ($p < 0.05$) prevented the morphine-induced antinociception. Intraperitoneal injection of chlorpheniramine significantly ($p < 0.05$) enhanced the morphine-induced analgesia, but did not reverse the effect of naloxone on nociceptive responses. Intraperitoneal injection of ranitidine, with no effect on the morphine -induced antinociception, significantly ($p < 0.05$) reversed the effect of naloxone on pain responses. These results suggest that both chlorpheniramine and ranitidine exert antinociceptive effect in the visceral nociception. In addition, morphine through a naloxone-dependent mechanism produces visceral antinociception. Moreover, the endogenous opioid system may participate in the chlorpheniramine- but not in the ranitidine-induced antinociception.

Key words: Chlorpheniramine, ranitidine, morphine, naloxone, visceral nociception, rats

INTRODUCTION

Pain arising from a distension, ischemia and inflammation of the viscera such as the stomach, kidney, gallbladder, urinary bladde and intestines constitute a large part of clinically treated pains (Al-Chear and Traub, 2002). Visceral pain is diffuse and poorly localized. A classical feature of visceral pain is that the sufferer perceives the pain as arising from somatic sites distant from the area of visceral pain source. This phenomenon of referred pain attenuates a real source of pain and complicates a diagnostic of disorders (Janig and Habler, 2002). Over the past few years, a number of animal models have been developed that, to a large extent, mimic the nociception originating in the viscera (Ness, 1999; Le Bars et al., 2001). Intraperitoneal injections of irritant agents produce a very stereotyped behavior in mice and rats which characterized by abdominal muscles contraction accompanied by a hind limb extensor motion.

This visceral nociceptive test has been known as the writhing test (Ness, 1999; Le Bars et al., 2001).

Histamine is known to function as a physiological messenger through the body because it is synthesized in a wide variety of cells including mast cells, basophils, platelets, entrochromafin-like cells, endothelial cells and neurons (Rangachari, 1992). Histamine has been shown to stimulate nociceptive afferent fibers in a variety of tissues such as heart, joints, jejunum and skin (Fu et al., 2005; Ting et al., 2007; Kreis et al., 1998; Lang et al., 1990). It is evident that several histamine H_1, H_2, H_3 and H_4 antagonists, but not all, produce an antinociceptive effect in some animal models of pain. Intraperitoneal injections of cimetidine produced antinociception in the formalin test in mice (Tamaddonfard and Mojtahedin, 2004). It was reported that imepip (H_3-receptor agonist) attenuated formalin-induced pain and peripheral and central pretreatments with thioperamide (H_3-receptor antagonist) reversed the suppressive effect of imepip (Cannon et al.,

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2007). Histamine H_4-receptor antagonists such as JNJ7777120 and VUF6002 has been reported to reduce the hyperalgesia provoked by subplantar injection of carrageenan in rats (Coruzzi *et al.*, 2007).

It is well known that endogenous opioid and non-opioid systems modify the sensation of pain. Morphine (an opioid agonist) and naloxone (an opioid antagonist) are frequently used to explore the involvement of endogenous analgesic systems activated by novel analgesics (Ananthan, 2006; Trescot *et al.*, 2008; Yoshimatsu and Furue, 2006). Using somatic tests of nociception, it has been demonstrated that histamine H_1 and H_2 antagonists interact with non-opioid analgesic systems such as GABAergic, serotonergic and adrenergic mechanisms as well as with opioid analgesic system to produce antinociception (Gogas and Hough, 1989; Leza *et al.*, 1990; Suzuki *et al.*, 1994; Wong, 1985).

The present study was designed to investigate the effects of chlorpheniramine (H_1-receptor antagonist) and ranitidine (H_2-receptor antagonist) on the acetic acid-induced visceral nociception in rats. In addition, effects of morphine (an opioid agonist) and naloxone (an opioid antagonist) on visceral nociception were also examined. Moreover, to identify the mechanism that possibly mediating the effects of chlorpheniramine and ranitidine on pain, the contribution of the endogenous analgesic opioid system was assessed using morphine and naloxone with chlorpheniramine and ranitidine.

MATERIALS AND METHODS

Animals: Healthy adult male albino Wistar rats weighing 220-250 g were maintained in polypropylene cages with 6 rats in each cage with food and water available *ad libitum*, in a laboratory with controlled ambient temperature (20- 23°C) and under a 12 h light-dark cycle (lights on 07.00 h). Six rats were used in each treatment. The experimental protocol was approved by the Laboratory Animal Care and Use Center of Urmia University.

Drugs and treatments: Drugs used in the present study were chlorpheniramine maleate (Sigma-Aldrich Co., Steinheim, Germany), ranitidine hydrochloride (Sigma-Aldrich), morphine sulfate (Temad, Tehran, Iran) and naloxone dihydrochloride (Sigma-Aldrich). All drugs were dissolved in normal saline. Chlorpheniramine at the doses of 2.5, 5 and 10 mg kg^{-1} b.wt. and ranitidine at the doses of 20, 40 and 80 mg kg^{-1} b.wt., were intraperitoneally injected 30 min before induction of visceral pain. Morphine (0.25, 0.5 and 1 mg kg^{-1} b.wt.) and naloxone (1 mg kg^{-1} b.wt.) were subcutaneously administered 20 and 40 min before induction of visceral nociception,

respectively. In the combined treatments, intraperitoneal injections of chlorpheniramine (5 mg kg^{-1} b.wt.) and ranitidine (40 mg kg^{-1} b.wt.) were performed 10 min before morphine (0.5 mg kg^{-1} b.wt., s.c.) and 10 min after naloxone (1 mg kg^{-1} b.wt., s.c.) administrations. Naloxone (1 mg kg^{-1} b.wt., s.c.) was injected 20 min before subcutaneous injection of morphine (0.5 mg kg^{-1} b.wt.). Drug solutions were intraperitoneally injected in a volume of 1 mL kg^{-1} b.wt. using a 25-gauge injection needle. Subcutaneous injections of drug solutions were performed in a constant volume 0.2 mL rat^{-1} at the neck region using a 27-gauge injection needle.

Induction of visceral nociception: For induction of visceral nociception, each rat was placed inside a cleared plexiglass chamber (40×30×20 cm) for an acclimation period of 30 min. At the end of this period and after drug solution treatments according to time schedule mentioned in the drugs and treatments, 1 mL of 1% acetic acid were intraperitoneally injected using a 27-gauge injection needle. Immediately after injection of acetic acid, the latency time to the beginning of the first abdominal wall contraction (first writhe) was measured and the numbers of writhes were counted for a period of 1 h. A writhe was defined as a wave of the contraction of the abdominal musculature followed by extension of the hind limbs (Tamaddonfard *et al.*, 2008; Tajik *et al.*, 2008). In control rats the intraperitoneal injection of appropriate amount of normal saline was performed.

Statistical analysis: Data were expressed as Mean±SEM. Differences among treated groups were statistically evaluated using the one-way analysis of variance (ANOVA) followed by Duncan's test. Differences were considered significant at p<0.05.

RESULTS AND DISCUSSION

The latency time to the beginning of the first writhe and the numbers of writhes obtained from intraperitoneal injection of acetic acid 30 min after intraperitoneal injection of normal saline were 6.4±0.8 and 45.7±6.4, respectively (Table 1, 2).

Intraperitoneal injections of chlorpheniramine (2.5 mg kg^{-1} b.wt.) and ranitidine (20 mg kg^{-1} b.wt.) produced no significant effect on the pain responses. Chlorpheniramine (5 and 10 mg kg^{-1} b.wt., i.p.) and ranitidine (40 and 80 mg kg^{-1} b.wt., i.p.) significantly (p<0.05) increased the latency time to the beginning of the first writhe and significantly (p<0.05) decreased the numbers of writhes induced by intraperitoneal injection of acetic acid (Table 1).

Table 1: Effects of normal saline, chlorpheniramine and ranitidine on the visceral nociception induced by acetic acid in rats

Treatment	Latency time[a] (min)	No. of writhes[b]
Normal saline (i.p.)	6.4±0.8	45.7±6.4
Chlorpheniramine (i.p., 2.5 mg kg^{-1})	7.1±0.7	40.8±5.7
Chlorpheniramine (i.p., 5 mg kg^{-1})	11.3±1.1*	35.5±4.8*
Chlorpheniramine (i.p., 10 mg kg^{-1})	12.8±0.9*	25.7±3.4*
Ranitidine (i.p., 20 mg kg^{-1})	7.3±1.5	39.7±5.0
Ranitidine (i.p., 40 mg kg^{-1})	12.2±0.9*	30.7±2.3*
Ranitidine (i.p., 80 mg kg^{-1})	13.5±1.1*	21.5±3.6*

[a]Measured after acetic acid administration (1 mL, 2%), [b]Counted in an 1 h observation period after acetic acid administration. Values are Mean±SEM, n = 6 in each group, *p<0.05 vs. normal saline group, one way ANOVA followed by Duncan's test, i.p: Intraperitoneal

Table 2: Effects of normal saline, morphine and naloxone on the visceral nociception induced by acetic acid in rats

Treatment	Latency time[a] (min)	No. of writhes[b]
Normal saline (i.p.)	6.4±0.8	45.7±6.4
Morphine (s.c., 0.25 mg kg^{-1})	11.9±1.2*	30.8±5.2*
Morphine (s.c., 0.5 mg k^{-1})	15.7±1.2*	23.3±3.0*
Morphine (s.c., 1 mg kg^{-1})	20.1±1.4*	10.2±1.2*
Naloxone (s.c., 1 mg kg^{-1})	7.7±1.0	47.5±7.1
Naloxone (s.c., 1 mg kg^{-1}) Morphine (s.c., 0.5 mg kg^{-1})	8.6±0.8	42.3±5.5

[a]Measured after acetic acid administration (1 mL, 2%), [b]Counted in an 1 h observation period after acetic acid administration. Values are Mean±SEM, n = 6 in each group, *p<0.05 vs. other groups, one way ANOVA followed by Duncan's test, i.p.: Intraperitoneal, s.c.: Subcutaneous

Subcutaneous injection of morphine at the doses of 0.25, 0.5 and 1 mg kg^{-1} b.wt., significantly (p<0.05) increased the latency time to the beginning of the first writhe and significantly (p<0.05) decreased the numbers of writhes. Naloxone (1 mg kg^{-1} b.wt., s.c.) produced no significant effect on the intensity of visceral pain, but significantly (p<0.05) blocked the effect of morphine (0.5 mg kg^{-1} b.wt., s.c) on visceral nociceptive responses (Table 2).

Intraperitoneal injection of chlorpheniramine (5 mg kg^{-1} b.wt.) significantly (p<0.05) enhanced the effect of morphine (0.5 mg kg^{-1} b.wt., s.c.), but did not influence the effect of naloxone (1 mg kg^{-1} b.wt., s.c.) on the visceral nociceptive responses. Intraperitoneal injection of ranitidine (40 mg kg^{-1} b.wt.) did not changed the antinociception induced by morphine (0.5 mg kg^{-1} b.wt., s.c.), whereas significantly (p<0.05) reversed the effect of naloxone (1 mg kg^{-1} b.wt., s.c.) on the numbers of writhes (Table 3).

The results presented here indicate that histamine H_1- and H_2-receptor antagonists, chlorpheniramine and ranitidine, respectively, produced antinociception in the acetic acid-induced visceral nociception. Intraperitoneal administrations of agents such as acetic acid and

Table 3: Effects of chlorpheniramine and ranitidine on the visceral nociceptive changes induced by morphine and naloxone in the visceral nociception induced by acetic acid in rats

Treatment	Latency time[a] (min)	No. of writhes[b]
Morphine (s.c., 0.5 mg kg^{-1})	15.7±1.2	23.3±3.0
Naloxone (s.c., 1 mg kg^{-1}) Chlorpheniramine (i.p., 5 mg kg^{-1})+	7.7±1.0	47.5±7.1
Morphine (s.c., 0.5 mg kg^{-1}) Naloxone (s.c., 1 mg kg^{-1})+	21.9±3.7*	15.0±2.6*
Chlorpheniramine (i.p., 5 mg kg^{-1}) Ranitidine (i.p., 40 mg kg^{-1})+	8.8±1.0	41.3±5.3
Morphine (s.c., 0.5 mg kg^{-1}) Naloxone (s.c., 1 mg kg^{-1})+	12.0±2.1	30.8±3.8
Ranitidine (i.p., 40 mg kg^{-1})	8.5±0.8	30.3±4.9†

[a]Measured after acetic acid administration (1 mL, 2%), [b]Counted in an 1 h observation period after acetic acid administration. Values are mean±SEM, n = 6 in each group, *p<0.05 vs. morphine group, †p<0.05 vs. naloxone group, one way ANOVA followed by Duncan's test, s.c.: Subcutaneous, i.p.: Intraperitoneal

phenylquninone that irritate serous membranes provoke a very stereotyped behavior in the mouse and in the rat which characterized by abdominal contractions, movements of body as a whole, twisting of dorsoabdominal muscles and a reduction in motor activity (Ness, 1999; Le Bars et al., 2001). Possible mediators involving in the acetic acid-induced inflammatory pain are not well known. It has been reported that bradykinin, neurokinins and prostanoids involve in the sensory C-fibers activation after intraperitoneal injection of propionic, lactic and acetic acids (Ikeda et al., 2001). In another study, release of histamine from mast cells has been reported after incubation of Peritoneal Cell-derived Mast Cells (PCMC) with trichloroacetic acid (Malbec et al., 2007). Moreover, in the peripheral tissues such as joint, skin and visceral organs, histamine stimulates nociceptive afferent fibers (Ting et al., 2007; Lang et al., 1990; Akoev et al., 1996). Using gene knockout mice, the role of histamine H_1 and H_2 receptors in modulation of somatic and visceral nociceptive tests has been revealed (Mobarakeh et al., 2000, 2002, 2006). In the p-benzoquinine- writing test in mice, the antinociceptive effect of mepyramine (H_1-receptor blocker), ReN 1869 (a selective histamine H_1 receptor antagonist) and famotidine (H_2-receptor blocker) was reported by Abacioglu et al. (1993) and Olsen et al. (2002). In addition, it was found that subcutaneous injections of pyrilamine (H_1-receptor blocker) and famotidine (H_2-receptor blocker) produced antinociception in the mouse acetic acid-induced writing test (Girard et al., 2004). Moreover, both celemastine (H_1-receeotor antagonist) and cimetidine (H_2-receptor antagonist) inhibited the excitatory effect of histamine on the mesenteric nerve of small intestine (Akoev et al., 1996). However, the visceral antinociception induced by

histamine H_1 and H_2 blockers, observed in this study, confirms the fact that in rats as well as in mice, histamine may be involved in visceral pain modulation.

In the present study, morphine produced visceral antinociception and naloxone prevented the morphine-induced antinociception. It has been reported that intraperitoneal injection of morphine suppresses and naloxone pretreatment inhibits the morphine-induced antinociception in the abdominal writhing evoked by acetic acid in mice (Reichert *et al.*, 2001). In addition, both morphine and fentanyl attenuated writhing response in the gerbil (Gallantine and Meert, 2004).

The results of the present study showed that chlorpheniramine enhanced, but ranitidine blocked the morphine-induced antinociception and ramitidine but not chlorpheniramine reversed the effect of naloxone on pain response. This means that the endogenous opioid system is involved in the chlorpheniramine- but not in the ranitidine-induced antinociception. It was reported that diphenhydramine (H_1-receptor blocker) and ranitidine blocked the antinociceptive effect of morphine in the hot plate test of nociception in mice (Leza *et al.*, 1990). In addition, in the hot plate test in mice the potentiation and inhibitory effects of pyrilamine and zolantidine, respectively, on the morphine-induced analgesia was reported by Suzuki *et al.* (1994). On the other hand, results of Abacioglu *et al.* (1993) revealed that mepyramine and famotidine non-significantly potentiated the antinociceptive effect of morphine in the p-benzoquinine-writhing test in mice. Moreover, Olsen *et al.* (2002) reported a potentiation effect between ReN 1869 and morphine to producing analgesia in the p-benzoquinine-writhing test in mice. In the visceral pain induced by acetic acid, morphine-induced antinociception increased in histamine H_2-receptor gene knockout mice, compared to the wild type mice (Mobarakeh *et al.*, 2006). In the acetic acid-induced abdominal constriction test in mice, pretreatments with diphenhydramine (H_1-receptor antagonist), ranitidine and cimetidine altered neither the antinociceptive effect of morphine nor the antagonistic activity of naloxone (Wong, 1985). Intrathecal co-administration of chlorpheniramine and morphine enhanced the effects of morphine in thermal, mechanical and chemical nociceptive tests in mice (Mobarakeh *et al.*, 2002). The differences between the findings would be related to the kind of H_1-receptor blocker used.

Finally, the results of the present study showed that chlorpheniramine and ranitidine suppressed the visceral nociception induced by acetic acid. In addition, morphine via a naloxone-sensitive mechanism induced visceral antinociception. Moreover, endogenous opioid system may involve in the antinociceptive effect of

chlorpheniramine, but in the ranitidine-induced antinociception, the endogenous opioid system may not have a role.

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