Central effect of histamine on acetic acid-induced visceral nociception in rats

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Abstract
In the present study, the effects of intracerebroventricular (ICV) injections of histamine, chlorpheniramine (H1-receptor antagonist) and ranitidine (H2-receptor antagonist) were investigated on visceral nociception induced by an intraperitoneal (IP) injection of acetic acid in rats. The latency time to the beginning of the first abdominal wall contraction (the first writh) was recorded and the number of writhes was counted for 1 h after the IP injection of acetic acid (1 ml, 1%). All treatments (histamine: 2.5–80 μg, chlorpheniramine and ranitidine: 5–80 μg) did not influence the latency time to the beginning of the first writh significantly except for the 40 μg dose of histamine, which significantly increased the latency time (p<0.05). Doses of histamine of 10 and 40 μg and doses of chlorpheniramine and ranitidine of 20 and 80 μg significantly decreased the number of writhes (p<0.05). Pretreatments with chlorpheniramine or ranitidine at the dose of 80 μg significantly prevented histamine-induced (40 μg) antinociception (p<0.05). These results indicate that brain histamine may mediate the perception of visceral antinociception through both central H1 and H2 receptors.

Introduction

Pain that arises from distension, ischemia and inflammation of the viscera, such as the stomach, kidneys, gallbladder, urinary bladder and intestines, constitute a large amount of the pain that requires clinical treatment (Al-Chaer and Traub, 2002). Over recent years, a number of animal models have been developed that, to a large extent, mimic the nociceptive stimuli that originate from the viscera. Intraperitoneal (IP) injections of irritant agents, such as acetic acid and phenylquinone, which irritate serous membranes, produce a highly stereotypical behavior in the mouse and rat. This behavior is characterized by contractions of the abdominal muscles, a reduction of body movements, and twisting of the dorsoabdominal muscles that is accompanied by hind limb extensor movements. The test is sometimes called the abdominal constriction test, or stretching test, but more recently it has become known as the writhing test (LeBars et al., 2001; Ness, 1999).

Many of central nervous system (CNS) nuclei and regions, such as the nucleus gracilis, the ventroposterolateral nucleus of the thalamus, the locus coeruleus/subcoeruleus (LC/SC), the anterior and posterior cingulated cortex, and the somatosensory cortex participate in the central perception of visceral pain (Wood, 2007; Wu et al., 2008; Liu et al., 2008).

Brain chemical messengers that include serotonin, noradrenaline, dopamine, opiates, cytokines and glutamate are involved in the central neural modulation of visceral nociception (OMahony et al., 2006; Fiaramonti and Bueno, 2002; Wood, 2007; Wu et al., 2008).

Several lines of evidence suggest that brain histamine may be involved in the central perception of pain. Intracerebroventricular (ICV) injections of histamine produced antinociception in both the hot plate and paw pressure nociceptive tests in rats (Malmberg-Aiello et al., 1994). In the formalin test in mice, rats and rabbits, an ICV injection of histamine attenuated pain responses (Tamaddonfard and Rahimi, 2004; Mojlahedin et al., 2008; Tamaddonfard et al., 2006). The central administration of histamine was reported to produce an inhibitory effect on the pain threshold of neuropathic pain in rats (Huang et al., 2007). ICV injection of histamine also decreased the number of eye wipes after the topical corneal application of hypertonic saline in rats (Tamaddonfard et al., 2008).

It is recognized that the action of histamine in the brain on pain modulation is mediated through the H1, H2, H3, and H4 histamine receptors (Brown et al., 2001; Haas et al., 2003). Co-administration of temelastine (a H1-receptor antagonist) and tiotidine (H2-receptor blocker) with histamine into the preaquaductal grey
(PAG) matter inhibited histamine-induced analgesia in the hot plate test in rats (Thoburn et al., 1994). Moreover, it was reported that imepip (a H₁-receptor agonist) attenuated formalin-induced pain, and peripheral and central pretreatments with thiopental (a H₂-receptor antagonist) reversed the suppressive effect of imepip (Cannon et al., 2007). In addition, histamine H₂-receptor antagonists, such as JNJ7777120 and VUF6002, reduced the hyperalgesia provoked by subplantar injection of carrageenan in rats (Coruzzi et al., 2007).

In the present study, the effects of ICV injections of histamine, chlorpheniramine (a H₁-receptor antagonist) or ranitidine (a H₂-receptor antagonist) were investigated with regards to the acute visceral nociception induced by the IP injection of acetic acid in rats.

Materials and Methods

Healthy adult male Wistar rats that weighed between 200 and 220 g were used in this study. Rats were maintained in polyethylene cages with food and water available ad libitum in a laboratory with controlled ambient temperature (23 ± 0.5°C) and a 12 h light-dark cycle (lights on from 07:00). Experiments were carried out between 09:00 h and 13:00 h. The experimental protocol was approved by the Laboratory Animal Care and Use Center of the College of Veterinary Medicine of Urmia University.

Drugs used in the present study included histamine dihydrochloride (Merck, Darmstadt, Germany), chlorpheniramine maleate and ranitidine hydrochloride (Sigma-Aldrich Co., Steinheim, Germany). The drugs were dissolved in normal saline 1 h before the ICV injections.

After a 15-day adaptation period, each rat was anaesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg), which was administered by an IP injection. The rat was then placed in a stereotaxic apparatus (Stoelting, Wood Lane, IL, USA). The scalp was incised and the skull was leveled off around the bregma. A 22-gauge, 12-mm stainless-steel guide cannula was inserted in the right lateral ventricle of the brain. The tip of the cannula was aimed at the following coordinates: 0.8 mm posterior to the bregma, 2 mm lateral to the midline and 4 mm below the top of the skull (Paxinos and Watson, 1997). The cannula was then fixed to the skull using three screws and dental acrylic. A 12.5-mm stylect was inserted through the cannula to keep it patent prior to the IP injection. Animals were allowed a 10-day recovery period before the experiments began.

For the ICV injections of normal saline (control), histamine (2.5, 10 and 40 µg), chlorpheniramine and ranitidine (at the same doses of 5, 20 and 80 µg), a 28-gauge, 12.5-mm injection needle was attached to a 30-cm polyethylene tube that was fitted to a 5-µL Hamilton syringe. The rat was then restrained by hand, the stylet was withdrawn, and the injection needle was inserted into the guide cannula. The volume of the solutions to be injected into the lateral ventricle was 1 µL, and the injection was made over a period of 60 s. One specific group of rats was assigned to one specific drug treatment condition and each group comprised six rats. Therefore, each rat received two or three treatments and five days were allowed between ICV injections.

The induction of visceral nociception was performed using the writhing test. For this purpose, each rat was placed inside a plexiglass chamber (40×30×20 cm) for an adaptation period of 30 min. At the end of this period, 1 ml of 1% acetic acid was injected into the peritoneum using a 25-gauge injection needle. Immediately after the IP injection of acetic acid, the latency time to the beginning of the first contraction of the abdominal musculature (the first writh) was measured, and the numbers of writhes were counted for 1 h. A writh was defined as a wave of contraction of the abdominal musculature following the extension of the hind limbs (LeBars et al., 2001; Ness, 1999; Tamaddonfard et al., 2008). In control rats, the IP injection of the equivalent volume of normal saline was performed.

During the surgery and before the ICV injections, the rising of the cerebrospinal fluid through the cannula was observed. For additional confirmation of the placement of the cannula in the lateral ventricle of the brain, the rats were ICV injected with 10 µl methylene blue at the end of the experiment and were then anaesthetized deeply with a high dose of ether and decapitated. The brains were removed and placed in formaldehyde (10%) solution. After 24 h, the brains were sliced into 1 mm slices and the place of the tip of the cannula and distribution of the dye in the lateral ventricle were assessed visually. Data from rats with an incorrect placement of the cannula were excluded from analysis.

All the values were expressed as the means ± SEM. The data were analyzed by using a factorial analysis of variance (ANOVA) followed by Duncan's test. Statistical significance was set as p<0.05.

Results

ICV injections of histamine at doses of 2.5 and 10 µg and chlorpheniramine or ranitidine at the doses of 5, 20 and 80 µg produced no significant effects on the latency time to the beginning of the first abdominal wall contraction (first writh). Histamine (40 µg) significantly increased the latency time to the beginning of the first writh (p<0.05; Fig. 1).

ICV pretreatments with either chlorpheniramine or ranitidine at the dose of 80 µg did not significantly reduce the increase in the latency time induced by 40 µg histamine (Fig. 2). An ICV injection of histamine at a
dose of either 10 or 40 μg, but not at the dose of 2.5 μg, significantly decreased the number of writhes induced by acetic acid (p<0.05). Both chlorpheniramine and ranitidine at the doses of 20 and 80 μg, but not at the dose of 5 μg, significantly suppressed the visceral nociceptive response (p<0.05; Fig. 3). ICV pretreatments with either chlorpheniramine or ranitidine at the dose of 80 μg significantly prevented the suppressive effect of 40 μg histamine on the number of writhes (p<0.05; Fig. 4).

Figure 1: Effect of ICV injections of histamine, chlorpheniramine or ranitidine on the latency time to the beginning of the first writhing that was induced by an IP injection of acetic acid in rats. *p<0.05 compared to normal saline. All groups consisted of six rats. ICV: intracerebroventricular, IP: intraperitoneal, μg: microgram.

Figure 2: Effect of ICV pretreatment with chlorpheniramine and ranitidine before the ICV injection of histamine on the latency time to the beginning of the first writhing that was induced by IP injection of acetic acid in rats. n=6 rats for each treatment. ICV: intracerebroventricular, IP: intraperitoneal, μg: microgram.

Figure 3: Effect of ICV injection of histamine, chlorpheniramine or ranitidine on the numbers of writhes induced by IP injection of acetic acid in rats. *p<0.05 as compared to normal saline, n=8 rats for all experimental groups. ICV: intracerebroventricular, IP: intraperitoneal, μg: microgram.

Discussion

In the present study, ICV injections of histamine at different doses produced antinociception against the visceral nociception induced by IP acetic acid injections in rats. The cell bodies of the histaminergic neuronal system are found only in the tuberomammillary nucleus (TMN) of the hypothalamus, and their fibers and terminals innervate the CNS (Schwartz et al., 1991). Specific areas in the nervous system, such as the external layers of the dorsal horn of the spinal cord, the preaquaductal grey and raphe nucleus, which are known to be involved in the control of nociception (Brooks and Tracey, 2005), are also innervated by the histaminergic system of the hypothalamus (Schwartz et al., 1991). Evidence taken from various studies on acute and chronic pain, such as the hot plate test (Malmberg-Aiello et al., 1994), formalin test (Tamaddonfard and Rahimi, 2004), neuropathic test (Huang et al., 2007), and trigeminal (Tamaddonfard et al., 2008) pain tests suggest that the brain histamine influences the central perception of pain. With regards to the central effect of histamine on visceral pain, it has been reported that the ICV injection of histamine produced antinociception in the abdominal constriction test in mice (Malmberg-Aiello et al., 1994). Moreover, the ICV injection of SKF 91488 (a histamine-N-methyltransferase inhibitor) suppressed nociception induced by the IP injection of acetic acid in mice (Malmberg-Aiello et al., 1997).
(Schwartz et al., 1991; Brown et al., 2001; Farzin and Nosrati, 2007). Both histamine H₁ and H₃ receptors may involve CNS-mediated antinociception induced by histamine, since mutant mice that lack histamine H₁ and H₂ receptors showed fewer nociceptive responses in various pain tests (Mobarakeh et al., 2000; Mobarakeh et al., 2006). It has been reported that ICV injection of 2-(3-trifluoromethylphenyl) histamine dihydrogenmalate, 2-thiazolylethylamine (both H₁-receptor agonists) and pyrilamine (a H₁-receptor antagonist) produce hypernociception and antinociception, respectively, which suggests that H₁ receptor activation increases the CNS sensitivity to noxious stimuli (Malmberg-Aiello et al., 1998). In addition, the tricyclic compound, REN 1869, which is a novel histamine H₁ receptor antagonist that penetrates the blood-brain barrier, has been found to induce antinociception in chemical (formalin, capsaicin and phenylquinone writhing) but not thermal (hot plate and tail flick) tests of nociception (Olsen et al., 2002). In the hot plate test in rats, ICV injections of a H₁ agonist (4-methylhistamine) and antagonists (cimetidine and ranitidine) enhanced the pain threshold (Netti et al., 1988). In another study, it was found that the intracerebral microinjection of temelastine (H₁-receptor antagonist) and cimetidine into the preaquaductal grey or into the raphe nucleus prevented histamine-induced antinociception (Thoburn et al., 1994). In addition, subcutaneous (SC) injections of mepyramine (a H₁-receptor antagonist) and zolantidine (a H₂-receptor antagonist), which cross the blood-brain barrier, produced antinociception in the acute acid-induced writhing test in mice (Girard et al., 2004).

The antinociception induced by the higher doses of chlorpheniramine (20 and 80 µg) that was observed in the present study may be related to its side effects. Chlorpheniramine belongs to the first class of H₁ antihistamines, which are known to produce the side effects of sedation, drowsiness and poor motor coordination (Woodward, 1995). In the present study, cimetidine produced analgesia in the absence of histamine. In the hot plate test in rats, the pain threshold enhancement was reported after ICV injections of histamine H₂ receptor agonists (4-methylhistamine and dimaprit) and antagonist (cimetidine). The results from that study suggested that the antinociceptive activity of cimetidine was not due to a specific blockade of H₂ receptors (Netti et al., 1988). However, in the central action of cimetidine on pain perception, the possible involvement of other mechanisms such as serotoninergic, muscarinic, nicotinic, dopaminergic, gabaaergic and adrenergic, as well as histaminergic, need to be considered (Hough et al., 2000; Hough et al., 2001).

The results of the present study indicate that activation of brain histamine by exogenous ICV injection of the amine produced an antinociceptive effect in the acetic acid-induced visceral pain. Both central H₁ and H₃ receptors of histamine may be involved in the histamine-induced visceral antinociception.

References


