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

Zanbouri, A.; Tamaddonfard, E.* and Mojtahedin, A.

Department of Basic Sciences, Faculty of Veterinary Medicine, Urmia University, Urmia-Iran.

Key Words:
Brain; histamine; chlorpheniramine; ranitidine; visceral nociception; rats.

Correspondence
Tamaddonfard, E.,
Division of Physiology, Department of Basic Sciences, Faculty of Veterinary Medicine, Urmia University,
P.O. Box 57135-1177, Urmia-Iran.
Tel: +98 (441) 2770508,
Fax: +98 (441) 2771926
E-mail: e.tamaddonfard@mail.urmia.ac.ir

Received 21 October 2008,
Accepted 21 April 2009

Abstract

In the present study, the effects of intracerebroventricular (ICV) injections of histamine, chlorpheniramine (H_1-receptor antagonist) and ranitidine (H_2-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 writhe) 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 writhe 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 H_1 and H_2 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 (O'Mahony *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. Intracerebroventircular (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; Mojtahedin *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 H_1, H_2, H_3 and H_4 histamine receptors (Brown *et al.*, 2001; Haas *et al.*, 2003). Co-administration of temelastine (a H_1-receptor antagonist) and tiotidine (H_2-receptor blocker) with histamine into the preaquductal 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 H_3-receptor agonist) attenuated formalin-induced pain, and peripheral and central pretreatments with thioperamide (a H_3-receptor antagonist) reversed the suppressive effect of imepip (Cannon *et al.*, 2007). In addition, histamine H_4-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 H_1-receptor antagonist) or ranitidine (a H_2-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 stylet 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 writhe) was measured, and the numbers of writhes were counted for 1 h. A writhe was defined as a wave of contraction of the abdominal musculature followed by 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 writhe). Histamine (40 µg) significantly increased the latency time to the beginning of the first writhe ($p<0.05$; 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 induce 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 writhe 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.

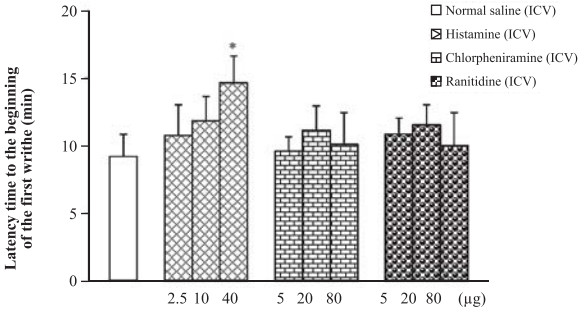


Figure 2: Effect of ICV pretreatment with chlorpheniramine and ranitidine before the ICV injection of histamine on the latency time to the beginning of the first writhe that was induced by IP injection of acetic acid in rats. n=6 rats for each treatment. ICV: intracerebroventricular, IP: intraperitoneal,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

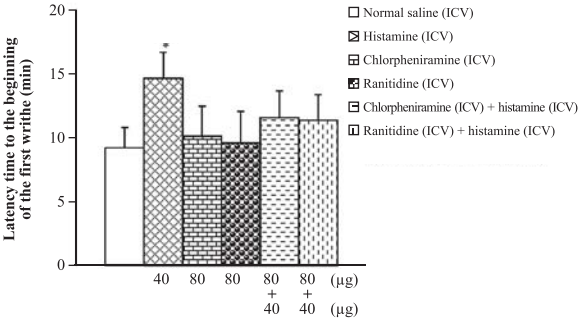


Figure 3: Effect of ICV injection of histamine, chlorpheniramine or ranitidine on the numbers of writhes induced by IP injection of acetic acid in rats. *p<0.05 as compared to normal saline, n=6 rats for all experimental groups. ICV: intracerebroventricular, IP: intraperitoneal, µg: microgram.

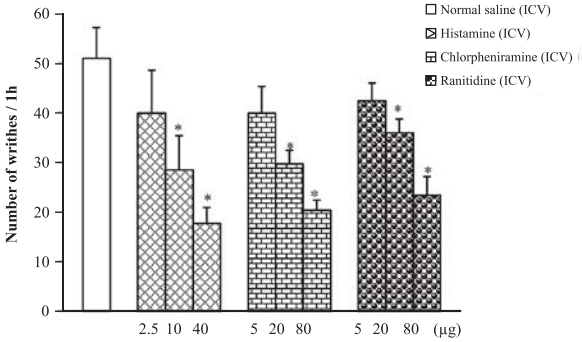
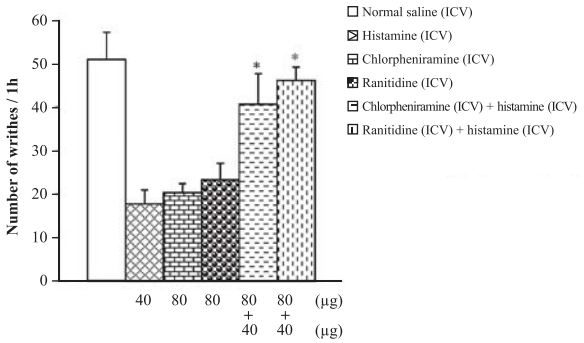


Figure 4: Effect of ICV pretreatment with chlorpheniramine or ranitidine before the ICV injection of histamine on the numbers of writhes induced by an IP injection of acetic acid in rats. *p<0.05 as compared to histamine, n=6 rats for each treatment. ICV: intracerebroventricular, IP: intraperitoneal, µg: microgram.



Discussion

In the present study, ICV injections of histamine at difference 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 preaquductal 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).

In the present study, both histamine H_1 and H_2 receptor blockers, chlorpheniramine and ranitidine, produced antinociception in the absence of histamine; however, in the presence of histamine, these drugs prevented histamine-induced antinociception. This indicates that both H_1 and H_2 antagonists may have analgesic properties. Histamine H_1 and H_2 post-synaptic and H_3 pre-synaptic receptors are distributed throughout all of regions of the CNS and are involved in the central neurological actions of histamine

(Schwartz *et al.*, 1991; Brown *et al.*, 2001; Farzin and Nosrati, 2007). Both histamine H_1 and H_2 receptors may involve CNS-mediated antinociception induced by histamine, since mutant mice that lack histamine H_1 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-triflouromethylphenyl) histamine dihydrogenmaleate, 2-thiazolylethylamine (both H_1-receptor agonists) and pyrilamine (a H_1-receptor antagonist) produce hypernociception and antinociception, respectively, which suggests that H_1 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 H_1 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 H_2 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 (H_1–receptor antagonist) and cimetidine into the preaqueductal grey or into the raphe nucleus prevented histamine-induced antinociception (Thoburn *et al.*, 1994). In addition, subcutaneous (SC) injections of mepyramine (a H_1-receptor antagonist) and zolantidine (a H_2-receptor antagonist), which cross the blood-brain barrier, produced antinociception in the acetic 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 H_1 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 H_2 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 H_2 receptors (Netti *et al.*, 1988). However, in the central action of cimetidine on pain perception, the possible involvement of other mechanisms such as serotonergic, muscarinic, nicotinic, dopaminergic, gabaergic 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 H_1 and H_2 receptors of histamine may be involved in the histamine-induced visceral antinociception.

References

1. Al-Chaer, E.D.; Traub, R.J. (2002) Biological basis of visceral pain: recent development. Pain 96: 221–225.
2. Brooks, J.; Tracey, I. (2005) From nociception to pain perception: imaging the spinal and supraspinal pathways. J. Anat. 207: 19–33.
3. Brown, R.E.; Stevens, D.R. and Haas, H.L. (2001) The physiology of brain histamine. Prog. Neurobiol. 63: 637–672.
4. Cannon, K.F.; Leurs, R. and Hough, L.B. (2007) Activation of peripheral and spinal histamine H3 receptors inhibits formalin-induced inflammation and nociception, respectively. Pharmacol. Biochem. Behav. 88: 122–129.
5. Coruzzi, G.; Adami, M.; Guaita, E.; de Esch, I.J. and Leurs, R. (2007) Antiinflammatory and antinociceptive effects of the selective histamine H4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. Eur. J. Pharmacol. 563: 240–244.
6. Farzin, D., Nosrati, F. (2007) Modification of formalin-induced nociception by different histamine receptor agonists and antagonists. Eur. Neuropsychopharmacol. 17: 122–128.
7. Fiaramonti, J.; Bueno, L. (2002) Centrally acting agents and visceral sensitivity. Gut 51: 191–195.
8. Girard, P.; Pansart, Y.; Coppe, M.C.; Verniers, D. and Gillardin, J.M. (2004) Role of histamine system in nefopam-induced antinociception in mice. Eur. J. Pharmacol. 503: 63–69.
9. Haas, H.L.; Pannula, P. (2003) The role of histamine and the tuberomammillary nucleus in the nervous system. Nat. Rev. Neurosci. 4: 121–130.
10. Hough, L.B.; Nalwalk, J.W.; Barnes, W.G.; Leurs, R.; Menge-Wiro, M.P.B.; Timmerman, H. and Wentdland, M. (2000) A third life for burimamide: discovery and characterization of a novel class of non-opioid analgesics derived from histamine antagonists. Ann. N. Y. Acad. Sci. 909: 25–40.
11. Hough, L.B.; Nalwalk, J.W.; Leurs, R.; Menge-Wiro, M.P.B. and Timmerman, H. (2001) Significance of gabaergic system in the action of improgan, a non-opioid analgesic. Life Sci. 68: 2751–2757.
12. Huang, L.; Adachi, N.; Nagaro, T.; Liu, K. and Arai, T. (2007) Histaminergic involvement in neuropathic pain produced by partial ligation of the sciatic nerve in rats. Reg. Anesth. Pain Med. 32: 124–129.
13. LeBars, D.; Gozariu, M. and Cadden, S.W. (2001) Animal models of nociception. Pharmacol. Rev. 53: 597–652.
14. Liu, L.; Tsuruoka, M.; Maeda, M.; Hayashi, B.; Wang, X. and Inoue, T. (2008) Descending modulation of visceral

nociceptive transmission from the locus coeruleus/subcoeruleus in the rat. Brain Res. Bull. 76: 616–625.
15. Malmberg-Aiello, P.; Lamberti, C.; Ghelardini, C.; Giotti, A. and Bartolini, A. (1994) Role of histamine in rodent antinociception. Br. J. Pharmacol. 111: 1269–1279.
16. Malmberg-Aiello, P.; Lamberti, C.; Ipponi, A.; Bartolini, A. and Schunak, W. (1998) Evidence for hypernociception induction following histamine H1 receptor activation in rodents. Life Sci. 63: 463–467.
17. Malmberg-Aiello, P.; Lamberti, C.; Ipponi, A.; Hanninen, J.; Ghelardini, C. and Bartolini, A. (1997) Effects of two histamine-N-methyltransferase inhibitors, SKF 91488 and BW 301U in rodent antinociception. Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 354–360.
18. Mobarakeh, J.I.; Sakurada, S.; Katsuyama, S.; Kutsuwa, M.; Kuramasu, A.; Lin, Z.Y.; Watanabe, T.; Hashimoto, Y.; Watanabe, T. and Yanai, K. (2000) Role of histamine H1 receptor in pain perception: a study of the receptor gene knockout mice. Eur. J. Pharmacol. 391: 81–89.
19. Mobarakeh, J.I.; Takahashi, K.; Sakurada, S.; Kuramasu, A. and Yanai, K. (2006) Enhanced antinociceptive effects of morphine in histamine H2 receptor gene knockout mice. Neuropharmacology. 51: 612–622.
20. Mojtahedin, A.; Tamaddonfard, E. and Zanboori, A. (2008) Antinociception induced by central administration of histamine in the formalin test in rats. Indian J. Physiol. Pharmacol. 52: 249–254.
21. Ness, T.J. (1999) Models of visceral nociception. Inst. Lab. Anim. Res. J. 40: 119–128.
22. Netti, C.; Guidobono, F.; Sibilia, V.; Villa, I.; Cazzamalli, E. and Pecile, A. (1988) Central effects of the histamine H2 receptor agonist and antagonist on nociception in rats. Agents Actions. 23: 247–249.
23. Olsen, U.B.; Eltrop, C.T.; Ingvardsen, B.K.; Jorgensen, T.K.; Lundbaek, J.A.; Thamsen, C. and Hansen, A.J. (2002) Ren 1869, a novel tricyclic antihistamine, is active against neurogenic pain and inflammation. Eur. J. Pharmacol. 435: 43–57.
24. O'Mahony, S.; Dinan, T.G.; Keeling, P.W. and Chua, A.S.B. (2006) Central serotonergic and noradrenergic receptors in functional dyspepsia. World J. Gastroenterol. 12: 2681–2687.
25. Paxinos, G.; Watson, C. (1997) The rat brain in stereotaxic coordinates. 3rd edition, Academic Press, San Diego, USA.
26. Schwartz, J.C.; Arrang, J.M.; Garbarg, M.; Pollard, H. and Ruat, M. (1991) Histaminergic transmission in the mammalian brain. Physiol. Rev. 71: 1–51.
27. Tamaddonfard, E.; Azimpouran, A. and Behjat, B. (2006) Central effect of histamine on formalin-induced pain in rabbits: role of opioid system. J. Fac. Vet. Med. Univ. Tehran. 61: 83–90.
28. Tamaddonfard, E.; Khalilzadeh, E.; Hamzeh-Gooshchi, N. and Seiednejhad-Yamchi, S. (2008) Central effect of histamine in a rat model of acute trigeminal pain. Phamacol. Rep. 60: 219–224.
29. Tamaddonfard, E.; Rahimi, S. (2004) Central effect of histamine and peripheral effect of histidine on the formalin-induced pain response in mice. Clin. Exp. Pharmacol. Physiol. 31: 518–522.
30. Tamaddonfard, E.; Tajik, H. and Hamzeh-Gooshchi, N. (2008) Effects of curcumin and vitamin C on visceral nociception induced by acetic acid in rats. Med. Wet. 64: 883–885.
31. Thoburn, K.K.; Hough, L.B.; Nalwalk, J.W. and Mischler, S.A. (1994) Histamine-induced modulation of nociceptive responses. Pain. 58: 29–37.
32. Wood, J.D. (2007) Neuropathophysiology of functional gastrointestinal disorders. World J. Gastroenterol. 13: 1313–1332.
33. Woodward, J.K. (1995) Pharmacology of antihistamines. J. Allergy Clin. Immunol. 85:606–612.
34. Wu, X.; Gao, J.; Yan, J.; Fan, J.; Owyang, C. and Li, Y. (2008) Role for NMDA receptors in visceral nociceptive transmission in the anterior cingulated cortex of viscerally hypersensitive rats. Am. J. Physiol. 294: G918–G927.