

THE EFFECT OF HISTAMINE H₁ RECEPTOR ANTAGONISTS ON THE MORPHINE-INDUCED ANTINOCICEPTION IN THE ACUTE TRIGEMINAL MODEL OF NOCICEPTION IN RATS

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ABSTRACT

Objective: In this study, the effect of different classes of histamine H₁ receptor antagonists (chlorpheniramine, cetirizine, and fexofenadine), μ opioid receptor agonist (morphine), and opioid receptor antagonist (naloxone) in separate and combined treatments were investigated on the acute trigeminal model of pain in rats.

Methods: Eye wiping test used for induction of acute trigeminal pain by putting a drop of NaCl, 5 M solution (40 μ l) on the corneal surface of the eye, and the number of eye wipes counted during the first 30 seconds.

Results: Intraperitoneal injection of both chlorpheniramine and cetirizine at doses of 10 and 20 mg/kg significantly inhibited the acute trigeminal pain. However, fexofenadine did not change corneal pain response. Morphine at doses of 1.25, 2.5, and 5 mg/kg reduced eye wipe responses. Administration of both chlorpheniramine and cetirizine but not fexofenadine before morphine-enhanced morphine analgesic activity, also pretreatment of animals with naloxone inhibited morphine, chlorpheniramine, and cetirizine-induced analgesia in the acute corneal pain.

Conclusion: Our results showed that chlorpheniramine as a histamine H₁ antagonist that efficiently Penetrates blood-brain barrier (BBB) and cetirizine with less penetration of BBB but not fexofenadine (an H₁ receptor antagonist with a negligible brain-accessibility) could induce analgesia in the acute corneal pain via opioidergic mechanism. Coadministration of morphine with chlorpheniramine or cetirizine could enhance its analgesic activity in the acute trigeminal model of pain in rats.

Keywords: Trigeminal pain, Morphine, Histamine H₁ receptor antagonists, Naloxone, Rats.

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INTRODUCTION

The evidence suggests that different classes of histamine H₁ receptor antagonists have an antinociceptive effect in animals and men. For example, ReN-1869 is a novel selective H₁ receptor antagonist that has been developed for analgesic purpose [1]. It has been reported that histamine H₁ receptor knockout mice showed decreased sensitivity to nociceptive stimuli [2]. In the periphery, histamine release from the injured tissue, mast cells, and basophils led to activation of pain-transmitting nerve fibers and also increases the release of pain-related neuropeptides [3]. The central histaminergic system plays an important role in the pain modulation. Histamine showed dual analgesic and pronociceptive roles in the central nervous system [4-6].

Fexofenadine is a selective nonsedating H₁ receptor antagonist with a negligible brain-accessibility. There is no approved evidence for its analgesic properties, but there are some evidences about its anti-inflammatory activity. Fexofenadine inhibits cytokine release from nasal epithelial cells following eosinophil activation [7]. Fexofenadine inhibited the release of chemotransmitters from isolated human basophils [8]. Furthermore, fexofenadine decreased carrageenan-induced paw edema and decreased pain score following intraplantar injection of formalin in rats [9]. Cetirizine is another selective H₁ receptor antagonist used for allergic conditions such as rhinitis, urticaria, and conjunctivitis. Priya *et al.* (2013) reported an analgesic effect of cetirizine in the tail immersion, tail flick, and tail pinch test in rats [10].

The analgesic effects of morphine in behavioral studies are well established [11]. It is believed that the opioid system may interact in

the antihistamine-induced antinociception. It has been reported that intramuscular injection of hydroxyzine combined with morphine in postoperative patients, can potentiate the antinociceptive activity of morphine [12]. Intraperitoneal (IP) administration of chlorpheniramine enhanced analgesic effect of morphine on the visceral nociceptive responses [13].

Spinal trigeminal nucleus process corneal sensory input in the rat [14]. Corneal pain would be very severe and incapacitating. Corneal nociceptor density has been estimated to be 20-40 times greater than dental pulp and 300-600 times higher than skin [15]. These polymodal nociceptors mostly respond to a range of noxious stimuli such as cold, heat, high threshold touch, chemicals, and protons. Moreover, there is a wide range of conditions including dry eye, post-herpetic neuralgia, trigeminal neuralgia, contaminated environments, contact lens wear, and new surgical techniques for the correction of refractive defects that cause ocular discomfort and pain [16].

To our knowledge, the effect of histamine H₁ antagonists on the analgesic action of morphine in the corneal pain was not described until now. We hypothesized that the combination of histamine H₁ antagonists with morphine can enhance the analgesic effect of morphine and reduce the morphine dose in the patients with corneal or trigeminal pain symptoms.

Hence, the present study was planned to investigate the analgesic effect of sedating and nonsedating H₁ receptor antagonists on the hypertonic saline-induced corneal pain (acute trigeminal pain). Naloxone pretreatment was performed to clarify the involvement of the opioidergic system in H₁ antagonists-induced analgesia. The effect of

histamine H₁ antagonists on the morphine-induced analgesia was also examined.

METHODS

Animals

Adult male Wistar rats, weighing 250-280 g, were used in this study. They were randomly housed in polyethylene cages with ad libitum access to food and water in a room with controlled temperature (22±1°C) and under a 12 h light-dark cycle (lights on from 07:00 a.m.). Six rats were used in each group. All experiments were performed between 11 am and 3 pm. All research and animal care procedures were approved by the Veterinary Ethics Committee of the Faculty of Veterinary Medicine, University of Tabriz and were performed in accordance with the current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental pain in conscious animals [17].

Drugs

Morphine sulfate was purchased from Toliddarou Co (Tehran, Iran). Cetirizine hydrochloride, fexofenadine hydrochloride, chlorpheniramine maleate, naloxone hydrochloride, and carboxymethylcellulose (CMC) were purchased from the Sigma-Aldrich Chemical Co (St. Louis, MO, USA). NaCl was purchased from Merck Chemicals (Darmstadt, Germany). Fexofenadine dissolved in CMC (5%), other drugs and chemicals were dissolved in physiological saline only NaCl dissolved in distilled water.

Eye wiping test

Each rat was placed on a 50×50×1 cm wooden table and after a 15 minutes habituation period, one drop (40 µl) of NaCl 5 M solution was put into the right or left cornea using a pipette (Transferpette® S 10-100 µl Brand Co., Germany), and then the numbers of eye wipes performed with ipsilateral forepaw were counted during the 30 seconds. Furthermore, each burst of hind paw scratches was counted as one wipe [18,19].

The first eye wiping test (pre-drug wiping test) of each animal was measured 10 minutes before all chemicals administration. The second eye wiping test (post-drug wiping test) was performed 30 or 40 minutes after drug administration, depending on the type of treatment.

The maximal possible effect (MPE%) was calculated for each animal according to the following formula:

$$\text{MPE}\% = 100 \times \frac{[\text{postdrug wipes count} - \text{predrug wipes count}]}{[0 - \text{predrug wipe count}]}$$

Experimental protocol

We used IP injection for the administration of all chemicals and drugs in this study. Saline (200 µl), CMC (5%, 200 µl), chlorpheniramine (5, 10, and 20 mg/kg), cetirizine (5, 10, and 20 mg/kg), fexofenadine (5, 10, and 20 mg/kg), and morphine (1.25, 2.5, and 5 mg/kg) were injected 30 minutes before the second eye wiping test. Naloxone (1 mg/kg) was administered 40 minutes before the second eye wiping test. Co-administration of chlorpheniramine (5 mg/kg), cetirizine (5 mg/kg), and fexofenadine (5 mg/kg) together with morphine (2.5 mg/kg) were done 30 minutes before the second eye wiping test. Naloxone was administered 10 minutes before IP injection of morphine (5 mg/kg), chlorpheniramine (20 mg/kg), and cetirizine (20 mg/kg).

Statistical analysis

Statistical differences were determined by one-way analysis of variance followed by Tukey honest significant difference *post-hoc* test using IBM® SPSS® software version 19 (IBM company, USA). In figures, all values are expressed as mean±standard error of the mean. A value of $p < 0.05$ was considered statistically significant.

RESULTS

In the present study, application of one drop (40 µl) of NaCl, 5 M solution on the surface of the cornea produced eye wiping (pre eye wiping

numbers: 15.66±2.26 and post eye wiping numbers: 15.33±2.18) response. None of the tested animals reacted to topically applied NaCl, 0.9% solution (normal saline). Thus, the obtained results (0±0) are not shown in the figures.

Chlorpheniramine at a dose of 5 mg/kg had no effect, whereas, at doses of 10 and 20 mg/kg, this histamine H₁ receptor antagonist significantly showed an inhibitory effect on the eye wiping response (37.47±6.27% $p < 0.001$ and 49.22±9.13% $p < 0.0001$, respectively) compared to vehicle-treated group (Fig. 1).

Cetirizine at a dose of 5 mg/kg did not produce significant analgesia, whereas, at doses of 10 and 20 mg/kg, it significantly showed an inhibitory effect on eye wiping response (38.75±6.19% $p < 0.001$ and 44.45±6.62% $p < 0.0001$, respectively) compared to control group (Fig. 2).

As shown in the Fig. 3, IP administration of all doses of fexofenadine (5, 10, and 15 mg/kg) did not produce analgesia (4.76±3.94%, 3.33±2.13, and 10.41±4.22, respectively) in the acute trigeminal model of pain in rats.

In addition, all doses of morphine (1.25, 2.5, and 5 mg/kg, IP) produced an analgesic effect on eye wiping response (30.83±6.05% $p < 0.05$, 35.15±10.06% $p < 0.01$, and 71.90±6.63% $p < 0.0001$, respectively) compared to control group (Fig. 4).

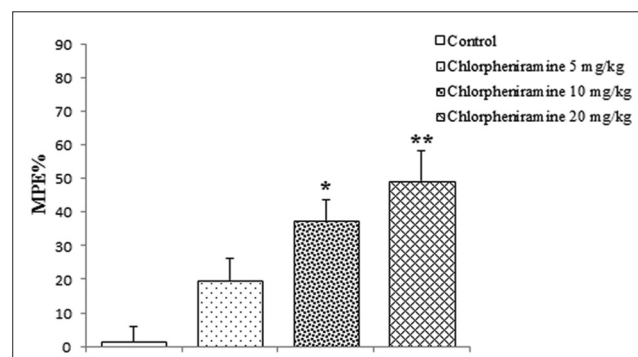


Fig. 1: Analgesia produced by intraperitoneal injection of different doses of chlorpheniramine on corneal pain response induced by NaCl 5 M solution applied to the corneal surface in rats. The values are expressed as mean±standard error of the mean (n=6/group). The data are compared with one-way analysis of variance followed by Tukey honest significant difference *post-hoc* test; * $p < 0.01$, ** $p < 0.0001$ versus control

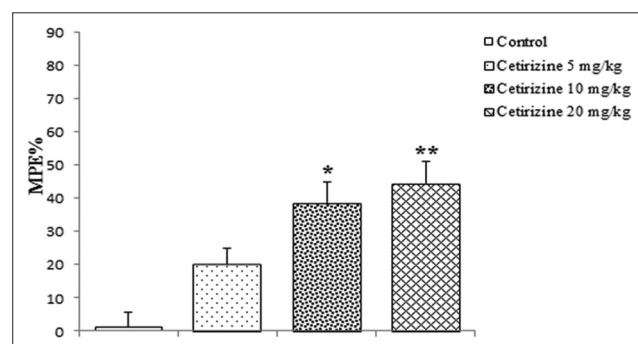


Fig. 2: Analgesia produced by intraperitoneal injection of different doses of cetirizine on corneal pain response induced by NaCl 5 M solution applied to the corneal surface in rats. The values are expressed as mean±standard error of the mean (n=6/group). The data are compared with one-way analysis of variance followed by Tukey honest significant difference *post-hoc* test; * $p < 0.001$, ** $p < 0.0001$ versus control

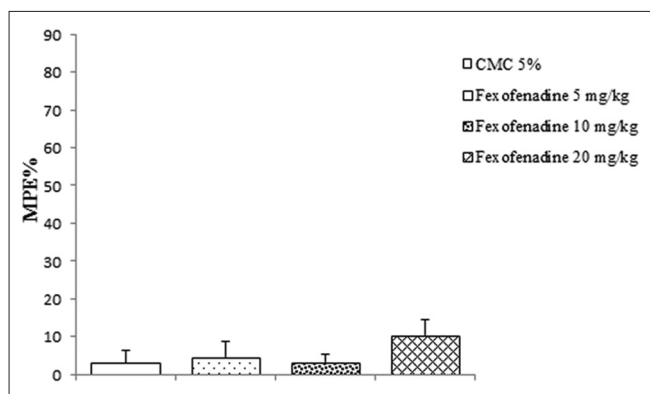


Fig. 3: The maximal possible effect of intraperitoneally administered fexofenadine on corneal pain response induced by NaCl 5 M solution applied to the corneal surface in rats. (n=6/group). CMC: Carboxymethylcellulose

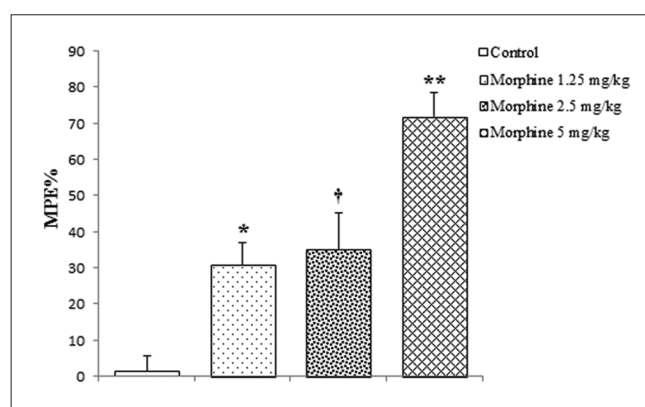


Fig. 4: Analgesia produced by intraperitoneal injection of different doses of morphine on corneal pain response induced by NaCl 5 M solution applied to the corneal surface in rats. The values are expressed as mean±standard error of the mean (n=6/group). The data are compared with one-way analysis of variance followed by Tukey honest significant difference *post-hoc* test; *p<0.05, †p<0.01 and **p<0.0001 versus control

Coadministration of chlorpheniramine (5 mg/kg) with morphine (2.5 mg/kg) enhanced (63.52±7.27%, p<0.0001) the antinociceptive effect of morphine (2.5 mg/kg) in the eye wiping response (Fig. 5).

Coadministration of cetirizine (5 mg/kg) with morphine (2.5 mg/kg) enhanced (60.49±9.16% p<0.0001) the antinociceptive effect of morphine (2.5 mg/kg) in the eye wiping response (Fig. 5).

Coadministration of fexofenadine (5 mg/kg) with morphine (2.5 mg/kg) did not alter the antinociceptive effect of morphine (2.5 mg/kg) in the eye wiping response (34.06±1.97%, p<0.05) in comparison with the control group (Fig. 5).

On the other hand, IP administration of naloxone (1 mg/kg, IP) alone had no effect on eye wiping response in comparison with the control group. However, pretreatment of animals with naloxone inhibited the antinociceptive effects of morphine (2.5 mg/kg), chlorpheniramine (20 mg/kg), and cetirizine (20 mg/kg) in the eye wiping response (Fig. 6).

DISCUSSION

Topical administration of one drop NaCl 5 M solution into the corneal surface-induced acute chemical pain response in this study. It has been

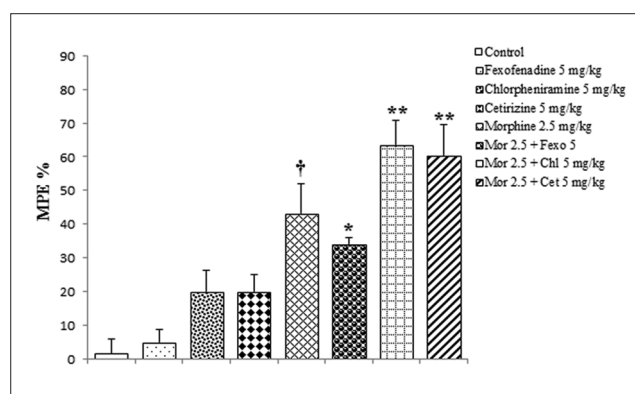


Fig. 5: Analgesia produced by coadministration of sub analgesic doses of chlorpheniramine and cetirizine with morphine on the corneal pain response in rats. Values are expressed as the mean±standard error of the mean (n=6/group). *p<0.05, †p<0.01 and **p<0.0001 compared with control. Mor: Morphine, Chl: Chlorpheniramine, Cet: Cetirizine, Fexo: Fexofenadine

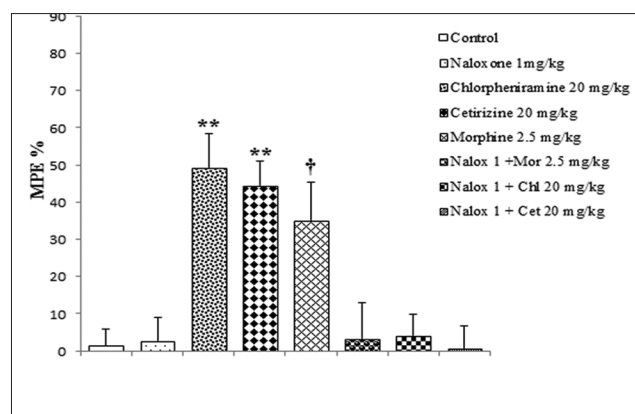


Fig. 6: Effect of pretreatment with naloxone on the antinociceptive activity of chlorpheniramine, cetirizine, and morphine in corneal pain response induced by NaCl 5 M solution applied to the corneal surface in rats. The values are expressed as mean±standard error of the mean (n=6/group). The data are compared with one-way analysis of variance followed by Tukey honest significant difference *post-hoc* test; **p<0.0001, †p<0.01 versus control. Nalox: Naloxone, Chl: Chlorpheniramine, Cet: Cetirizine

shown that the application of NaCl, capsicum, and nicotine into the corneal surface produce a vigorous response in the nociceptive neurons in the trigeminal subnucleus caudalis in rat [20]. Hyperosmotic solution like NaCl by activating transient receptor potential (TRP) vanilloid 1 and TRP melastatin 8 receptors on corneal nociceptors could induce chemical nociception [21,22].

According to the present results, it is clear that chlorpheniramine and cetirizine produced antinociception in the acute trigeminal model of pain as an acute model of corneal chemical pain while IP administration of fexofenadine did not alter acute trigeminal pain in rats.

Fexofenadine is a highly selective non-sedating histamine H₁ receptor antagonist [23]. Tissue distribution studies in rats revealed that fexofenadine does not cross the blood-brain barrier [24,25]. We used fexofenadine in this study because it is very selective for H₁ receptor and only occupied peripheral histamine H₁ receptors, whereas chlorpheniramine as a first-generation of antihistamines have been attributed to poor H₁-receptor specificity and also easily crossing the blood-brain barrier (BBB) and acts on the both peripheral and central receptors [26].

Cetirizine is a second-generation antihistamine with reduced brain-penetrating activity and more H₁ binding selectivity in comparison with the first-generation of antihistamine [26].

Tashiro *et al.* (2002) reported that the administration of cetirizine 20 mg/kg in the human subjects could cause occupation of 30% of histamine H₁ receptors in the cerebral cortex [25].

These results indicated that only antihistamines with the BBB penetrating activity could cause analgesia in the NaCl-induced acute corneal pain in rats.

Histamine H₁ receptors play an important role in both somatic and visceral pain perception since mutant mice lacking the histamine H₁ receptors showed fewer nociceptive responses in various pain test [2]. Our previous results have shown that intracerebroventricular injection of chlorpheniramine significantly decreases the number of eye wipes in the acute model of trigeminal pain [4]. It has been reported that ReN 1869 (H₁ antagonist) produces antinociception in chemical (formalin and capsaicin) but not in thermal (hot plate and tail flick) nociceptive test [1]. Moreover, it was reported that pyrilamine (H₁ antagonist) without any effect in the formalin test, produced antinociception in acetic acid-induced writhing in mice [27]. More recently, Priya *et al.* (2013) reported analgesic activity for cetirizine in some models of acute pain (tail flick, tail immersion, and tail clip methods) in the mice [10]. Furthermore, IP injection of chlorpheniramine and ranitidine significantly increased the latency time to the beginning of the first writhe and also significantly decreased the number of writhes in acetic acid (1%) induced visceral pain in rats [13]. It has been reported that the activation of H₁ receptors by 2-(3-trifluoromethylphenyl)-histamine, a selective histamine H₁ receptor agonist not only prevents the antinociception induced by the H₁ receptor antagonist but also increased sensitivity to noxious stimuli in rodents [5]. Farzin and Nosrati reported (2007) that IP injection of (20 and 30 mg/kg) dexchlorpheniramine (H₁ receptor antagonist) had an antinociceptive effect in both phases of formalin-induced pain and at a dose of 10 mg/kg antagonized the hyperalgesia induced by intracerebroventricular injection of histamine-trifluoromethyltoluidine (histamine H₁ agonist) [28]. Furthermore, activation of central Gi-protein by peripheral administration of diphenhydramine, pyrilamine, and promethazine suggested as one of the mechanisms that contribute in the analgesic activity of these first-generation antihistamines in the acute model of pain (hot plate test) in mice [29].

In the present study, morphine-induced antinociception in the acute chemical model of corneal pain and naloxone prevented the morphine-induced analgesia. Coadministration of chlorpheniramine or cetirizine but not fexofenadine with morphine enhanced morphine-induced antinociception in this model of pain. Moreover, chlorpheniramine- and cetirizine-induced analgesia were blocked by pretreatment of animals with opioid receptor antagonist naloxone. This means that activation of the central endogenous opioid system may contribute in the morphine-, cetirizine-, and chlorpheniramine-induced analgesia in this model of nociception.

It is believed that opioid system and histaminergic agents may interact in pain modulation. Zanoori *et al.* (2008) reported that coadministration of chlorpheniramine but not ranitidine with morphine potentiate the antinociceptive activity of morphine in the acetic acid-induced visceral pain model in rats [13]. In addition, Sun *et al.* (1985) reported that H₁ antagonists produced antinociception in the modification of Haffner's tail-clamp procedure when given alone to mice and also caused potentiation when combined with morphine [30]. On the other hand, it has been reported that mepyramine (histamine H₁ receptor antagonist) do not affect the morphine-induced analgesia in p-benzoquinone-induced visceral nociception [31].

Another explanation for the potentiation of morphine analgesic activity by histamine H₁ receptor antagonists may be related to its pharmacokinetic modifications occurs in the transfer through the

BBB. P-glycoprotein (P-gp) is an adenosine-5'-triphosphate-dependent transmembrane efflux pump which acts as a drug transporter. This carrier systemically expressed on several barrier epithelia not only in the blood-brain barrier but also in some others tissues, including the intestine, testis, adrenal glands, liver, and kidney [32]. P-gp is responsible for several antihistamines and morphine absorption and distribution [33]. Hamabe *et al.* (2007) reported a negative correlation between morphine-induced antinociception and P-gp expression levels in the brain [34]. This means that morphine could produce a better analgesic activity in the individuals with the lower expression of P-gp transporter. More recently, Mesgari Abbasi *et al.* (2016) reported that cetirizine has a P-gp inhibitory activity [35]. The inhibition of P-gp by cetirizine may be one of the reasons that cause enhancement of morphine-induced analgesia in the combination therapy.

Meanwhile, longer and repeated administration of the antihistaminics such as diphenhydramine, promethazine, and pyrilamine (opposite of morphine, baclofen, and oxotremorine) did not promote the development of tolerance to the analgesic activity of these agents [36].

CONCLUSION

Finally, it is concluded that chlorpheniramine and cetirizine but not fexofenadine produced analgesia via activation of central opioid receptors in the hypertonic saline-induced corneal pain. Chlorpheniramine and cetirizine but not fexofenadine enhanced the antinociceptive action of morphine in the trigeminal model of pain in rats.

REFERENCES

- Olsen UB, Eltorp CT, Ingvarsdn BK, Jørgensen TK, Lundbaek JA, Thomsen C, *et al.* ReN 1869, a novel tricyclic antihistamine, is active against neurogenic pain and inflammation. *Eur J Pharmacol* 2002;435(1):43-57.
- Mobarakeh JI, Sakurada S, Katsuyama S, Kutsuwa M, Kuramasu A, Lin ZY, *et al.* Role of histamine H(1) receptor in pain perception: A study of the receptor gene knockout mice. *Eur J Pharmacol* 2000;391(1-2):81-9.
- Raffa RB. Antihistamines as analgesics. *J Clin Pharm Ther* 2001;26(2):81-5.
- Tamaddonfard E, Khalilzadeh E, Hamzeh-Gooshchi N, Seiednejhad-Yamchi S. Central effect of histamine in a rat model of acute trigeminal pain. *Pharmacol Rep* 2008;60(2):219-24.
- Malmberg-Aiello P, Lamberti C, Ipponi A, Bartolini A, Schunack W. Evidence for hypernociception induction following histamine H1 receptor activation in rodents. *Life Sci* 1998;63(1):463-76.
- Khalilzadeh E, Tamaddonfard E, Farshid AA, Erfanparast A. Microinjection of histamine into the dentate gyrus produces antinociception in the formalin test in rats. *Pharmacol Biochem Behav* 2010;97(2):325-32.
- Abdelaziz MM, Devalia JL, Khair OA, Bayram H, Prior AJ, Davies RJ. Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1998;101(3):410-20.
- Amon U, Amon S, Gibbs BF. *In vitro* studies with fexofenadine, a new non-sedating histamine H1 receptor antagonist, on isolated human basophils. *Inflamm Res* 2000;49 Suppl 1:S13-4.
- Anoush M, Mohammad Khani MR. Evaluating the anti-nociceptive and anti-inflammatory effects of ketotifen and fexofenadine in rats. *Adv Pharm Bull* 2015;5(2):217-22.
- Priya M, Narayanan VS, Mohapatra S, Rani RJ. Screening of cetirizine for analgesic activity in mice. *Int J Basic Clin Pharmacol* 2013;2(2):187-92.
- Basbaum AI, Clanton CH, Fields HL. Opiate and stimulus-produced analgesia: Functional anatomy of a medullospinal pathway. *Neurobiology* 1976;73(12):4685-8.
- Hupert C, Yacoub M, Turgeon LR. Effect of hydroxyzine on morphine analgesia for the treatment of postoperative pain. *Anesth Analg* 1980;59(9):690-6.
- Zanoori A, Tamaddonfard E, Mojtahedain A. Effects of chlorpheniramine and ranitidine on the visceral nociception induced by acetic acid in rats: Role of opioid system. *Pak J Biol Sci*

- 2008;11(20):2428-32.
14. Meng ID, Hu JW, Benetti AP, Bereiter DA. Encoding of corneal input in two distinct regions of the spinal trigeminal nucleus in the rat: Cutaneous receptive field properties, responses to thermal and chemical stimulation, modulation by diffuse noxious inhibitory controls, and projections to the parabrachial area. *J Neurophysiol* 1997;77(1):43-56.
 15. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: Is it real? *Ocul Surf* 2009;7(1):28-40.
 16. Belmonte C, Acosta MC, Gallar J. Neural basis of sensation in intact and injured corneas. *Exp Eye Res* 2004;78(3):513-25.
 17. Zimmermann M. Ethical guidelines for investigations of experimental pain in conscious animals. *Pain* 1983;16(2):109-10.
 18. Farazifard R, Safarpour F, Sheibani V, Javan M. Eye-wiping test: A sensitive animal model for acute trigeminal pain studies. *Brain Res Brain Res Protoc* 2005;16(1-3):44-9.
 19. Khalilzadeh E, Hazrati R, Sayah GV, Hasannejad H. Opioidergic and cholinergic but not nitric oxide pathways are involved in antinociceptive activity of *Vitex agnus-castus* essential oil in the acute trigeminal model of pain in rat. *Asian J Pharm Clin Res* 2015;8(1):283-6.
 20. Carstens E, Kuenzler N, Handwerker HO. Activation of neurons in rat trigeminal subnucleus caudalis by different irritant chemicals applied to oral or ocular mucosa. *J Neurophysiol* 1998;80(2):465-92.
 21. Hirata H, Meng ID. Cold-sensitive corneal afferents respond to a variety of ocular stimuli central to tear production: Implications for dry eye disease. *Invest Ophthalmol Vis Sci* 2010;51(8):3969-76.
 22. Pan Z, Wang Z, Yang H, Zhang F, Reinach PS. TRPV1 activation is required for hypertonicity-stimulated inflammatory cytokine release in human corneal epithelial cells. *Invest Ophthalmol Vis Sci* 2011;52(1):485-93.
 23. Mason J, Reynolds R, Rao N. The systemic safety of fexofenadine HCl. *Clin Exp Allergy* 1999;29 Suppl 3:163-70.
 24. Dogan AS, Catafau AM, Zhou Y, Yanai K, Ravert H, Brasic J, et al. *In Vivo* Histamine Receptor Occupancy of Two Antihistamine Drugs: A ¹¹C-doxepin PET Study (Poster). Presented at Annual Meeting of the American College of Allergy, Asthma and Immunology, November 2000, Seattle, Washington. p. 58.
 25. Tashiro M, Mochizuki H, Iwabuchi K, Sakurada Y, Itoh M, Watanabe T, et al. Roles of histamine in regulation of arousal and cognition: Functional neuroimaging of histamine H1 receptors in human brain. *Life Sci* 2002;72(4-5):409-14.
 26. Slater JW, Zechin AD, Haxby DG. Second-generation antihistamines: A comparative review. *Drugs* 1999;57(1):31-47.
 27. Girard P, Pansart Y, Coppé MC, Verniers D, Gillardin JM. Role of the histamine system in nefopam-induced antinociception in mice. *Eur J Pharmacol* 2004;503(1-3):63-9.
 28. Farzin D, Nosrati F. Modification of formalin-induced nociception by different histamine receptor agonists and antagonists. *Eur Neuropsychopharmacol* 2007;17(2):122-8.
 29. Galeotti N, Ghelardini C, Bartolini A. Antihistamine antinociception is mediated by Gi-protein activation. *Neuroscience* 2002;109(4):811-8.
 30. Sun CL, Hui FW, Hanig JP. Effect of H1 blockers alone and in combination with morphine to produce antinociception in mice. *Neuropharmacology* 1985;24(1):1-4.
 31. Abacioglu N, Bediz A, Cakici I, Tunçtan B, Kanzik I. Antinociceptive effects of H1 - And H2-antihistaminics in mice. *Gen Pharmacol* 1993;24(5):1173-6.
 32. Tsuji A, Sakata A, Tamai I. Tissue distribution of the multidrug-resistance gene product P-glycoprotein and its physiological function. *Nihon Rinsho* 1997;55(5):1059-63.
 33. Ambudkar SV, Dey S, Hrycyna CA, Ramachandra M, Pastan I, Gottesman MM. Biochemical, cellular, and pharmacological aspects of the multidrug transporter. *Annu Rev Pharmacol Toxicol* 1999;39:361-98.
 34. Hamabe W, Maeda T, Kiguchi N, Yamamoto C, Tokuyama S, Kishioka S. Negative relationship between morphine analgesia and P-glycoprotein expression levels in the brain. *J Pharmacol Sci* 2007;105(4):353-60.
 35. Mesgari Abbasi M, Valizadeh H, Hamishekar H, Mohammadnejad L, Zakeri-Milani P. The effects of cetirizine on P-glycoprotein expression and function *in vitro* and *in situ*. *Adv Pharm Bull* 2016;6(1):111-8.
 36. Ghelardini C, Galeotti N, Bartolini A. No development of tolerance to analgesia by repeated administration of H1 antagonists. *Life Sci* 1998;63(22):PL 317-22.