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Evaluation of different classes of histamine H_1 and H_2 receptor antagonist effects on neuropathic nociceptive behavior following tibial nerve transection in rats

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Chemical compounds studied in this article:
Chlorpheniramine maleate (PubChem CID: 8231)
ranitidine hydrochloride (PubChem CID: 3033332)
fexofenadine hydrochloride (PubChem CID: 63002)
famotidine hydrochloride (PubChem CID: 56841564)
gabapentin (PubChem CID: 3446)
carboxymethylcellulose (PubChem CID: 24748)
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ABSTRACT

It seems that histamine release in the site of neuronal injury could contribute to the neuropathic pain mechanism. In the present study, we investigated the anti-allodynic effects of chronic administration of different classes of histamine H_1 and H_2 receptor antagonists on neuropathic nociceptive behavior following tibial nerve transection (TNT) in rats.

Peripheral neuropathy was induced by TNT surgery. We performed acetone tests (AT) to record cold allodynia, Von Frey tests (VFT) to measure mechanical allodynia, double plate test (DPT) to evaluate thermal place preference/avoidance and open field test (OFT) for evaluation of animal activity.

TNT rats showed a significant mechanical and cold allodynia compared to the sham group. Chlorpheniramine (5 and 15 mg/kg, i.p) significantly attenuated cold allodynia and prevented cold plate avoidance behavior and at the dose of 15 mg/kg remarkably decreased mechanical allodynia. Fexofenadine (10 and 30 mg/kg, p.o) significantly attenuated the mechanical allodynia and prevented cold plate avoidance. Ranitidine (5 and 15 mg/kg, i.p) significantly prevented cold plate avoidance behavior and at the dose of 15 mg/kg notably improved mechanical and cold allodynia. Famotidine (1 and 3 mg/kg, p.o) was ineffective on all nociceptive tests. Gabapantin (100 mg/kg, p.o) significantly improved all types of nociceptive behaviors.

These results indicate that both blood brain barrier penetrating (chlorpheniramine) and poorly penetrating (fexofenadine) histamine H_1 receptor antagonists could improve the neuropathic pain sign, but only the blood brain barrier penetrating histamine H_2 receptor antagonist (ranitidine) could produce anti-allodynic effects in the TNT model of neuropathic pain in rats.

1. Introduction

According to the new definition of the International Association for the Study of Pain (IASP), pain caused by lesion or disease of the somatosensory system is defined as neuropathic pain (Jensen et al., 2011).

Histamine appears to be involved in the both inflammatory and neuropathic models of pain (Rudick et al., 2008; Marchand et al., 2005; Moalem and Tracey, 2006). Large numbers of resident mast cells are identified in the peripheral nervous system which accumulate rapidly at the site of the nerve injury (Zochodne et al., 1994). The mast cell granules as an important pool for peripheral histamine, which were degranulated for up to fourteen days or even months under certain conditions of nerve injury (Zuo et al., 2003; Hayashi et al., 2008). Pharmacological and electrophysiological evidences showed that histamine could sensitize or activate unmyelinated afferent C-fibers, provoking itching in normal skin (Schmelz et al., 1997) however, induces spontaneous burning pain instead of itch in the skin of neuropathic patients (Baron et al., 2001). Most of C-fibers identified in the rat neuroma are sensitive to histamine. Moreover, the activation of these C-fibers may be responsible for autotomy behavior following sciatic and saphenous neurectomy (Seltzer et al., 1991).

Histamine could activate histamine-sensitive C-fibers in the rat sensory neurons by induction of Ca^{2+} influx via the PLA_2/lipoxygenase/TRPV1 pathway (Kim et al., 2004). In addition, histamine could contribute to neuropathic pain mechanism by upregulation of Nav1.8 expression in primary afferent neurons (Yue et al., 2014). It has been reported that topical application of histamine or capsaicin in

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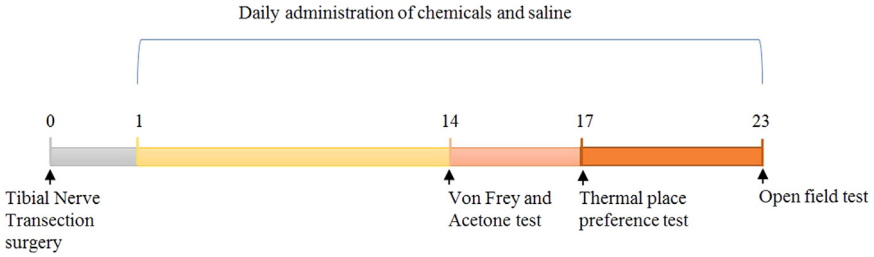

Fig. 1. Schematic representation of the experimental timeline.

postherpetic neuralgia patients enhanced heat hyperalgesia indicating that C-nociceptors are abnormally sensitized to histamine and capsaicin in the affected skin area (Petersen et al., 2000; Baron et al., 2001).

The analgesic effects of some histamine H_1 and H_2 receptor antagonists are well documented in different models of nociception (Medhurst et al., 2008; Farshchi et al., 2009; Zanboori et al., 2010; Ortiz, 2016; Khalilzadeh et al., 2017). In previous studies, we showed that central and peripheral administration of chlorpheniramine as a histamine H_1 antagonist could induce analgesia in the acute model of corneal nociception in rats (Tamaddonfard et al., 2008; Khalilzadeh et al., 2017). Also, we recently reported that co-administration of morphine with chlorpheniramine or cetirizine could enhance its analgesic activity in the acute trigeminal model of pain in rats (Khalilzadeh et al., 2017). However, to the best of our knowledge, there are not any reports about the positive effects of histamine H_1 and H_2 receptor antagonists in the tibial nerve transected model of neuropathic pain symptoms. Therefore, we thought it would be worthwhile to investigate the effect of pharmacological inhibition of these histamine receptors on mechanical allodynia, cold allodynia, thermal place preference/avoidance, and animal activity following tibial nerve transection model of neuropathy in rats. In this study, we used blood-brain barrier crossing and non-crossing H_1 and H_2 receptors antagonists to determine which kind of these antagonists may have more potent effect on neuropathic pain allivation.

2. Materials and methods

2.1. Chemicals

Chlorpheniramine maleate, ranitidine hydrochloride, fexofenadine hydrochloride famotidine hydrochloride, gabapentin and carboxymethylcellulose (CMC) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Ketamine hydrochloride and xylazine hydrochloride were purchased from Alfasan (Woerden, Holland).

2.2. Experimental animals

Adult male Wistar rats, weighing 240–270 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 test group. All experiments were performed between 10 a.m. till 3 p.m.. 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 (Zimmermann, 1983).

2.3. Preparation of chemicals

Chlorpheniramine (5 and 15 mg/kg), ranitidine (5 and 15 mg/kg) and gabapentin (100 mg/kg) were dissolved in sterile normal saline for intraperitoneal injection, but fexofenadine (10 and 30 mg/kg), famotidine (1 and 3 mg/kg) suspension were prepared in vehicle (0.5% carboxymethylcellulose in sterile normal saline) and were administered orally using an oral gavage needle.

A total of 200 µl solution was used for each administration. All treatments started 24 h after TNT surgery and lasted until the end of the experiment. All animals received chemicals, once a day and treatment was performed between 9 a.m. and 11 a.m. On the test day, intraperitoneal administration of chemicals was performed 30 min prior to each test whereas oral administration of chemicals was performed 60 min prior to each test.

2.4. Experimental design

The animals were randomly allocated into groups of 6 rats each. The experimental timeline is shown in Fig. 1.

2.5. Tibial nerve transection-induced neuropathic pain model

Peripheral neuropathic pain was induced by transection of tibial branch of the sciatic nerve as described previously (Hofmann et al., 2003). Briefly, animals were anesthetized by intraperitoneal administration of mixture of ketamine (80 mg/kg, Alfasan, Woerden, Holland) and xylazine (10 mg/kg, Alfasan, Woerden, Holland), then the lateral surface of the left thigh was shaved and its skin was incised and blunt dissection was performed between the gluteus maximus and biceps femoris muscles till sciatic nerve was exposed. Sciatic nerve was gently freed from the surrounding connective tissue and its three branches (the sural, common peroneal, and tibial nerves) were exposed. The tibial nerve was identified and slightly elevated by a curved forceps, then it was tightly ligated at two locations before trifurcation using silk suture (4 − 0) and 2 mm section of the tibial nerve (between the two ligatures) transected using Vannas scissors. The other two nerves remained intact.

2.6. Von Frey filament test

14 days after surgery, mechanical sensitivity was assessed by von Frey test as described by Tal and Bennett (1994). After a minimum of 60 min habituation in the test room, animals were placed into a Plexiglas test box (25 × 25 × 30 cm) with a wire mesh floor for further 15 min of adaptation. Ascending stiffness von Frey filaments (4, 6, 8, 10, 15, 26 and 60 g) (Stoelting, Wood Dale, USA) were firmly applied to the mid-plantar surface of left hind paws and the number of positive responses to 5 touches were recorded. Von Frey filaments were applied to the animal paw only when the rat was immobile and standing on all four paws. The lowest force of the von Frey hairs that elicited at least three withdrawal responses in five consecutive tests were recorded as the touch threshold.

2.7. Acetone test

14 days after surgery, cold allodynia was assessed by the acetone test according the method described by Sakurai et al., 2009 with little modifications (Sakurai et al., 2009). After a minimum of 60 min habituation in the test room, the animals were placed into a Plexiglas test