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Microinjection of histamine into the dentate gyrus produces antinociception in the formalin test in rats

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ABSTRACT

The present study was aimed to investigate the effects of microinjection of histamine, chlorpheniramine (a histamine H_1 receptor antagonist), ranitidine (a histamine H_2 receptor antagonist) and thioperamide (a histamine H_3 receptor antagonist) into the dentate gyrus on the formalin-induced pain. A biphasic pattern (first phase: 0–5 min and second phase: 15–60 min) in nociceptive responses was induced after subcutaneous injection of formalin (50 μl, 2.5%) into the ventral surface of the right hind paw. Microinjection of histamine (1 and 2 μg) into the dentate gyrus decreased the intensity of nociceptive responses. Intra-dentate gyrus microinjection of chlorpheniramine and ranitidine at the same doses of 1 and 4 μg had no effects, whereas thioperamide at a dose of 4 μg suppressed both phases of formalin-induced pain. Pretreatments with chlorpheniramine and ranitidine at the same dose of 4 μg prevented histamine (2 μg)-induced antinociception, while thioperamide (4 μg) increased histamine (2 μg)-induced antinociception. These results indicated that activation of brain neuronal histamine at the levels of dentate gyrus produced antinociception. The post-synaptic H_1, H_2 receptors and pre-synaptic H_3 receptors of histamine may be involved in the histamine-induced antinociception at the level of the dentate gyrus.

1. Introduction

Some studies have suggested a role for the dentate gyrus of hippocampal formation in central pain modulation. Microinjection of acetylcholine and pilocarpine into the dentate gyrus decreased the discharge frequency of pain-excited neurons, and increased the discharge frequency of pain-inhibited neurons in the sciatic nerve electrical stimulation model of nociception in rats (Jiao et al., 2009). Moreover, intra-dentate gyrus microinjection of AP5, a competitive NMDA receptors antagonist, and MK801, a non-competitive NMDA receptor antagonist, suppressed both phases of formalin-induced pain in rats (Mckenna and Melzack, 2001; Soleimannejad et al., 2007). Besides, lidocaine, a local anesthetic, produced analgesia in the formalin test of rats when microinjected into the dentate gyrus (McKenna and Melzack, 1992).

Evidence taken from acute and chronic pain tests suggests that the brain histamine via H_1, H_2 and H_3 receptors influences the central perception of pain. Central administration of histamine has been shown to produce antinociception in both phases of the formalin test in mice and rats (Tamaddonfard and Rahimi, 2004; Mojtahedin et al., 2008). Co-administration of temelastine (a histamine H_1 receptor antagonist) and tiotidine (a histamine H_2 receptor antagonist) with histamine into the periaqueductal gray inhibited histamine-induced analgesia in the hot plate test in rats (Thoburn et al., 1994). Moreover, it was found that central injection of ranitidine and thioperamide (a histamine H_3 receptor antagonist), but not pyrilamine (a histamine H_1 receptor antagonist), enhanced the nociceptive threshold in a rat model of neuropathic pain (Huang et al., 2007). More recently, the involvement of histamine H_1 and H_2 receptors on the histamine-induced antinociception at the hippocampus was reported in the formalin-induced orofacial pain in rats (Erfanparast et al., 2010).

Formalin test has been used frequently to study pain mechanisms in laboratory animals and according to these studies a biphasic pattern of pain-related behaviors was produced by subcutaneous injection of small amounts (20–100 μl) of dilute solutions (0.1–10%) of formalin into the various parts of the body (Tjolsen et al., 1992; Raboisson and Dallel, 2004). The first phase in turn may be attributed to a direct algogenic effect of formalin on the nociceptors and the second phase to the release of local inflammatory mediators responsible for sensitization of primary and spinal sensory neurons and subsequent signal transduction into the brain (Tjolsen et al., 1992; Raboisson and Dallel, 2004; Porro and Cavazzuti, 1993).

Despite the demonstration of the implication of the histaminergic system in central perception of pain, nothing has been published on the effects of histamine in the dentate gyrus in pain modulation. Therefore, the present study was aimed at investigating the implication of histaminergic system in pain perception by microinjection of histamine and its H_1, H_2 and H_3 receptor antagonists into the dentate gyrus using formalin test in rats.

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2. Materials and methods

2.1. Animals

Healthy adult male Wistar rats, weighing 300–350 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 (22 ± 0.5 °C) and under a 12 h light–dark cycle (lights on from 07:00 h). Six rats were used in each experiment. Experiments were performed between 12:00 h and 15:00 h. All research and animal care procedures were approved by the Veterinary Ethics Committee of the Faculty of Veterinary Medicine of Urmia University and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Drugs

Drugs used in the present study included histamine dihydrochloride, chlorpheniramine maleate, ranitidine hydrochloride and tioperamide maleate. The drugs were purchased from Sigma–Aldrich Inc., St Louis, MO, USA. All drugs were dissolved in sterile normal saline 30 min before intra-dentate gyrus microinjection.

2.3. Surgical procedure

To deliver the compounds to be tested, rats were bilaterally implanted with two guide cannulas in the dentate gyrus. In brief, each rat was anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) injected intraperitoneally, and then placed in a stereotaxic apparatus (Stoelting, Wood Lane, IL, USA). The scalp was incised, and the skull was leveled off around the bregma. Two 23 gauge, 12 mm stainless-steel guide cannulas were bilaterally implanted into the right and left dentate gyrus. The tip of cannulas was aimed at the following coordinates: −3.8 mm posterior to the bregma, 2 mm left and right sides of the midline and 3.6 mm below the top of the skull (Paxinos and Watson, 1997). The cannulas were then fixed to the skull using three screws and dental acrylic (Acropars, Tehran, Iran). A 12 mm stylet was inserted to each cannula to keep them patent prior to injection. At least 14 days was allowed for recovery from the surgery.

2.4. Intra-dentate gyrus injection protocol

For intra-dentate gyrus microinjections of normal saline (control), histamine (0.25, 0.5, 1 and 2 μg), mepyramine, ranitidine and thioperamide at the same doses of 1 and 4 μg, a 30 gauge, 12 mm injection needle was attached to a 30 cm polyethylene tube fitted to a 5 μl Hamilton syringe. Then, the rat was placed on a wooden plate for a period of 15 min, thereafter the stylet was withdrawn, and the injection needle was inserted into the guide cannula. The volume of the drug solution to be injected into each dentate gyrus was 0.5 μl and the injection was slowly made over a period of 1 min. The injection needle was left in place for a further 1 min after completion of injection to facilitate diffusion of the drug. Intra-dentate gyrus microinjection of mepyramine, rantidine and thioperamide was performed 10 min before intraplantar injection of formalin. Histamine was injected 5 min before induction of pain by formalin.

2.5. Nociceptive testing

Formalin test was used for induction of pain. Before rats were pain tested, they were placed in a plexiglass observation chamber (30 × 30 × 25 cm) for 30 min on three successive days to minimize stress-activated pain suppressive mechanisms (Abbott and Bonder, 1997). The formalin test was applied as follows. Fifty microliters of 2.5% formalin was injected subcutaneously into the ventral surface of the right hind paw using a 29-gauge injection needle (Guidon et al., 2007; Heughan and Sawynok, 2002; Lee and Jeong, 2002; Marcil et al., 2006). Following formalin injection, the rat was immediately put back in the observation chamber. Nociceptive behaviors including licking, biting and shaking of the injected paw were observed with the help of a mirror angled at 45° below the observation chamber. Observation of animal's behavior was made every 5 min and 60 min, starting after formalin administration (Tjolsen et al., 1992). Licking, biting and shaking of the injected paw were chosen as measures of pain, because they are supraspinally mediated behaviors (Porro and Cavazzuti, 1993). The frequency, duration and level of formalin-induced pain behaviors depend on the specific concentration used and the site of injection (Capone and Aloisi, 2004). In the present study, data collected between 0 and 5 min after formalin injection represented the first (early) phase and data collected between 15 and 60 min after injection of formalin represented the second (late) phase (Tjolsen et al., 1992; Capone and Aloisi, 2004; Heughan and Sawynok, 2002).

2.6. Cannula verification

At the end of each experiment, 0.5 μl methylene blue was injected into each dentate gyrus. The animals were killed with high dose ether, and perfused intracardially with physiological saline followed by 10% formalin solution. Brains were removed and placed in formalin (10%) solution. At least 3 days later, the brains were sectioned coronally (50–100 μm), and viewed under a loop to localize the injection site (Fig. 1) (Paxinos and Watson, 1997). The results obtained from rats with guide cannula outside the dentate gyrus or with excessive damage to the dentate gyrus beyond the site of the cannula were eliminated from the data analysis.

2.7. Statistical analysis

To evaluate significant differences among intra-dentate gyrus treated groups, one-way analysis of variance (ANOVA) and Duncan's test were applied. In figures, all values are expressed as mean ± SEM. A value of $P<0.05$ was considered statistically significant.

3. Results

3.1. Cannula tip placements

The placements of the tip of the cannulas in the dentate gyrus of rats are shown in Fig. 1. The rat brain section was modified from the atlas of Paxinos and Watson, 1997 (Fig. 1A). The location of the cannula tip placements in the dentate gyrus was confirmed with intra-dentate gyrus injection of methylene blue (Fig. 1B).

3.2. Effect of intra-dentate gyrus microinjection of histamine on the formalin-induced pain

Fig. 2 shows the effects of intra-dentate gyrus microinjection of histamine at doses of 0.25, 0.5, 1 and 2 μg on the first and second phases of formalin-induced licking/biting and shaking of the injected paw. One-way ANOVA revealed that intra-dentate gyrus microinjection of histamine at doses of 1 and 2 μg, but not at doses of 0.25 and 0.5 μg, significantly decreased the duration of licking/biting in the first phase of pain ($F_{(4,25)}=3.325$, $P<0.05$). The second phase of formalin-induced licking/biting was significantly suppressed by intra-dentate gyrus microinjection of histamine at doses of 0.5, 1 and 2 μg (one-way ANOVA, $F_{(4,25)}=9.320$, $P<0.05$) (Fig. 2A). Intra-dentate gyrus microinjection of histamine at doses of 1 and 2 μg significantly decreased the number of paw shakes in the first (one-way ANOVA, $F_{(4,25)}=3.323$, $P<0.05$) and second (one-way ANOVA, $F_{(4,25)}=4.021$, $P<0.05$) phases of pain (Fig. 2B).

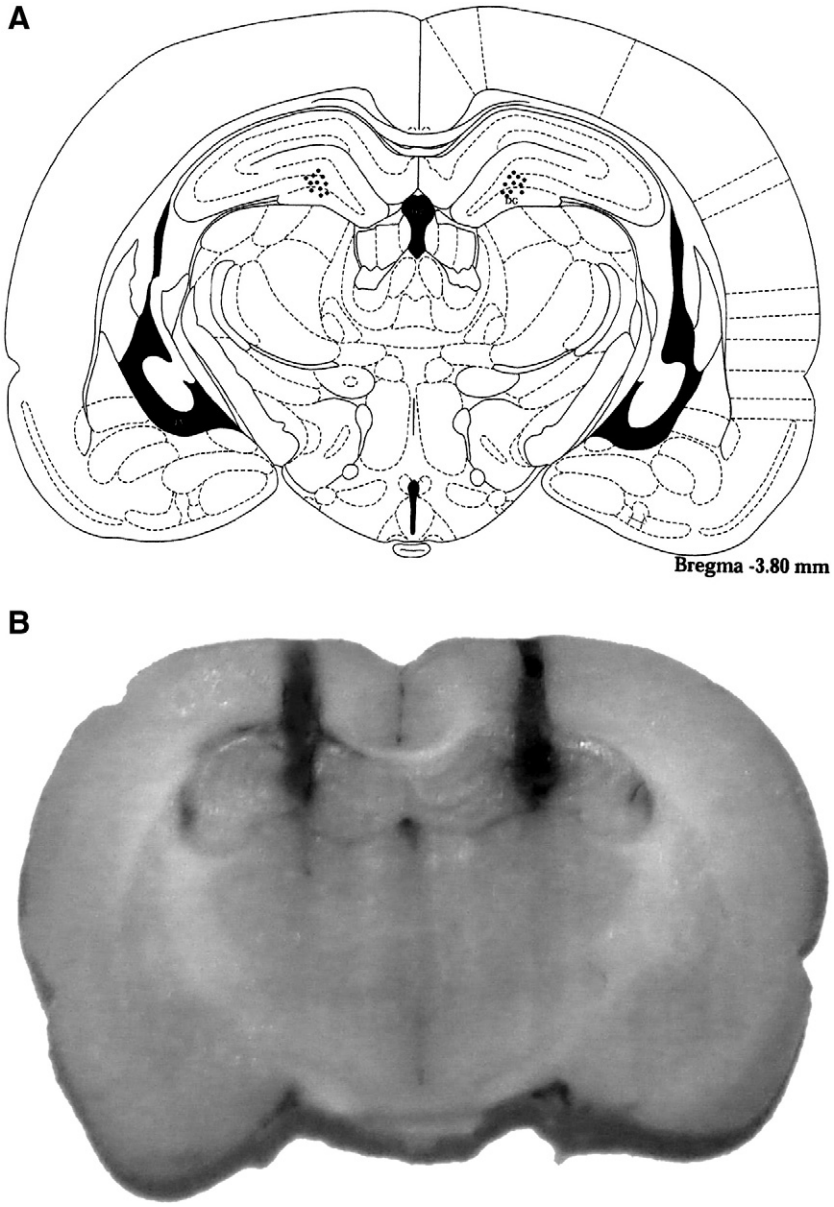

Fig. 1. Schematic illustration of coronal section of the rat brain showing the approximate location of the dentate gyrus microinjection sites (black circles) in the experiments (A). Location of the injection cannulas tip in the dentate gyrus of all rats included in the data analysis (B). Atlas plate adapted from Paxinos and Watson (1997). DG: dentate gyrus.

3.3. Effect of intra-dentate gyrus microinjection of chlorpheniramine on formalin-induced pain

Fig. 3 shows the effects of intra-dentate gyrus microinjection of chlorpheniramine on the formalin-induced nociceptive behaviors. One-way ANOVA revealed no significant differences between intra-dentate gyrus microinjection of normal saline and chlorpheniramine at doses of 1 and 4 μg on the first and second phases of formalin-induced licking/biting and shaking of the injected paw. Pretreatment with chlorpheniramine (4 μg) significantly prevented the suppressive effects of histamine (2 μg) on licking/biting and shaking of the injected paw in the first phase (licking/biting: one-way ANOVA, $F_{(4,25)}=3.809$, $P<0.05$; shaking: one-way ANOVA, $F_{(4,25)}=2.936$, $P<0.05$) (Fig. 3A). One-way ANOVA revealed that the second phase suppression of licking/biting and shaking induced by intra-dentate gyrus microinjection of histamine (2 μg) was significantly prevented by chlorpheniramine (4 μg) pretreatment (licking/biting: $F_{(4,25)}=7.481$, $P<0.05$; shaking: $F_{(4,25)}=4.199$, $P<0.05$) (Fig. 3B).

3.4. Effect of intra-dentate gyrus microinjection of ranitidine on the formalin-induced pain

Fig. 4 shows the effects of intra-dentate gyrus microinjection of ranitidine on the formalin-induced nociceptive behaviors. One-way ANOVA revealed no significant differences between intra-dentate gyrus microinjection of normal saline and ranitidine at doses of 1 and 4 μg on the first and second phases of formalin-induced licking/biting and shaking of the injected paw. Pretreatment with ranitidine (4 μg) significantly prevented the suppressive effects of histamine (2 μg) on licking/biting and shaking of the injected paw in the first phase (licking/biting: one-way ANOVA, $F_{(4,25)}=3.702$, $P<0.05$; shaking: one-way ANOVA, $F_{(4,25)}=3.605$, $P<0.05$) (Fig. 4A). The suppressive effects induced by intra-dentate gyrus microinjection of histamine (2 μg) on the licking/biting and shaking of the second phase were significantly prevented by pretreatment with ranitidine (licking/biting: one-way ANOVA, $F_{(4,25)}=6.822$, $P<0.05$; shaking: one-way ANOVA, $F_{(4,25)}=4.203$, $P<0.05$) phases (Fig. 4B).

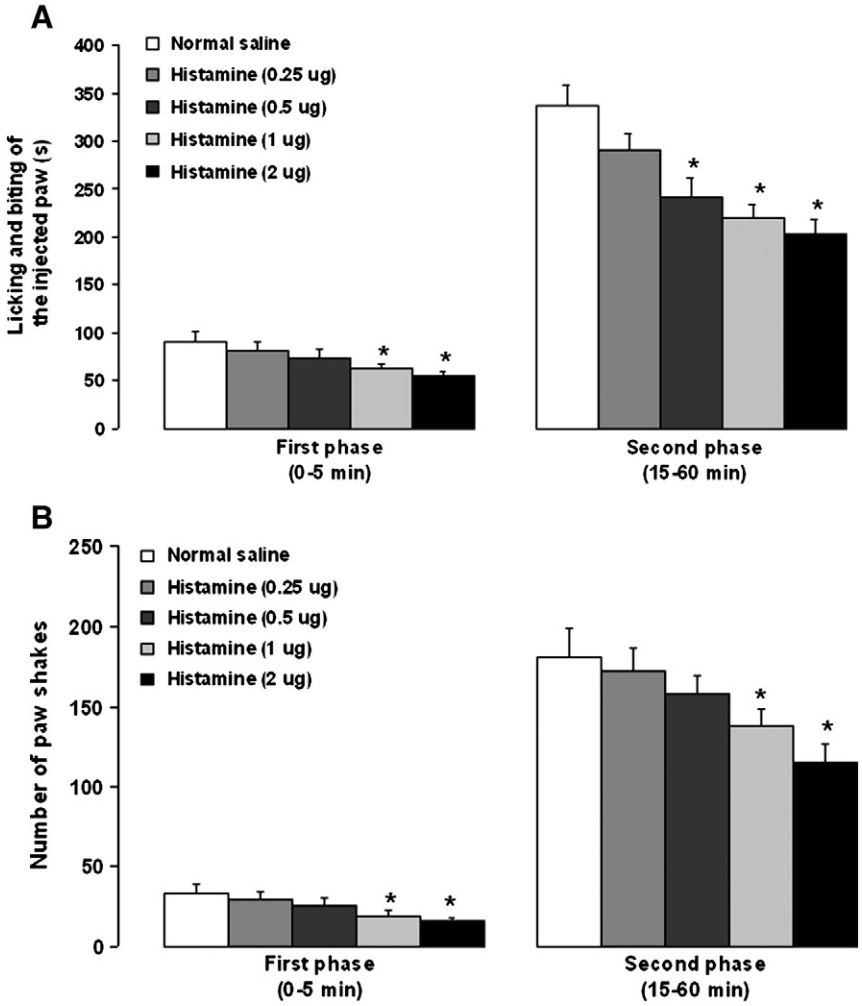

Fig. 2. Effect of intra-dentate gyrus microinjection of histamine on the licking/biting (A) and shaking (B) behaviors induced by intraplantar injection of formalin. The licking/biting and shaking of the injected paw were recorded 5 min after intra-dentate gyrus microinjection of histamine. Each column represents the mean ± SEM ($n=6$). *$P<0.05$ as compared to normal saline treated group (one-way ANOVA followed by Duncan test).

3.5. Effect of intra-dentate gyrus microinjection of thioperamide on the formalin-induced pain

Fig. 5 shows the effects of intra-dentate gyrus microinjection of thioperamide on the formalin-induced nociceptive behaviors. Intra-dentate gyrus microinjection of thioperamide at a dose of 4 μg, but not at a dose of 1 μg, significantly decreased the duration of licking/biting of the formalin-injected paw in the first and second phases. Thioperamide at a dose of 4 μg significantly increased the suppressive effects of histamine (2 μg) on the first (one-way ANOVA, $F_{(4,25)}=11.309$, $P<0.05$) and second (one-way ANOVA, $F_{(4,25)}=22.507$, $P<0.05$) phases of formalin-induced licking/biting of the injected paw (Fig. 5A). The suppressive effects of histamine (2 μg) on shaking of the formalin-injected paw were also increased with thioperamide (4 μg) in the first (one-way ANOVA, $F_{(4,25)}=7.970$, $P<0.05$) and second (one-way ANOVA, $F_{(4,25)}=12.376$, $P<0.05$) phases (Fig. 5B).

4. Discussion

In the present study, intra-dentate gyrus microinjection of histamine produced antinociception in the formalin test. Histamine involves in mediating formalin-induced pain at the local peripheral, spinal and supraspinal levels. Hong and Abbott (1994) reported a small number of flinches following intraplantar injection of histamine in rats. In addition, intraplantar injection of chlorpheniramine and cimetidine decreased formalin-induced pain responses in rats (Parada et al., 2001). Although nothing has been published on the direct intrathecal injection effect of histamine in formalin-induced pain, Sakurada et al. (2003) reported a pain-like behavior consisting of scratching, biting and licking following intrathecal administration of histamine in conscious mice. At the supraspinal level, the antinociceptive effects of histamine have been reported in the formalin test in rats and mice. Centrally administered histamine attenuated pedal edema, nociception as well as protein concentration in edema fluid induced by intraplantar injection of formalin in rats (Dumka et al. 1996). Moreover, intracerebroventricular injection of histamine decreased licking and biting induced by intraplantar injection of formalin in mice (Tamaddonfard and Rahimi, 2004) and rats (Mojtahedin et al., 2008). In addition, intra-hippocampal microinjection of histamine suppressed both the first and the second phases of formalin-induced orofacial pain in rats (Erfanparast et al., 2010).

In this study, chlorpheniramine and ranitidine did not produce any effect on pain intensity when used alone, but pretreatment with chlorpheniramine and ranitidine prevented histamine-induced antinociception. This indicates that histamine, through its post-synaptic H_1 and H_2 receptors, modulates pain in the dentate gyrus of the brain.

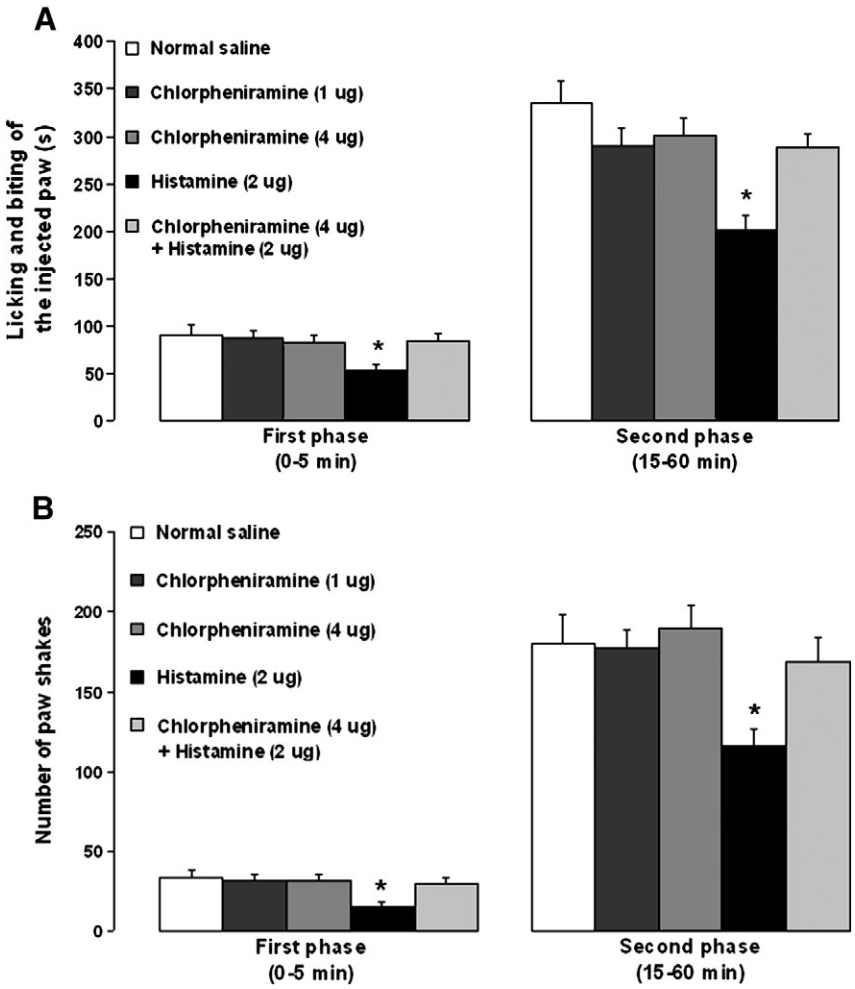

Fig. 3. Effect of intra-dentate gyrus microinjection of chlorpheniramine alone and before histamine on the licking/biting (A) and shaking (B) behaviors induced by intraplantar injection of formalin. The licking/biting and shaking of the injected paw were recorded 10 and 5 min after intra-dentate gyrus microinjection of chlorpheniramine and histamine, respectively. Each column represents the mean ± SEM ($n = 6$). *$P < 0.05$ as compared to other treated groups (one-way ANOVA followed by Duncan test).

The distribution of histamine H_1 and H_2 receptors in the dentate gyrus has been reported (Midzyanovskaya and Tuomisto, 2003; Karlstedt et al., 2001). Histamine post-synaptic H_1 and H_2 receptors are involved in mediating dentate gyrus functions. It has been shown that the histaminergic system modulates information flow through the dentate gyrus in a complex manner involving both histamine H_1 and H_2 receptors (Manahan-Vaughan et al., 1998). Central histamine H_1 and H_2 receptors are involved in the non-opiate mediation of stress-induced analgesia (Paul et al., 2002). In the hot plate test, Thoburn et al. (1994) reported the involvement of histamine H_1 and H_2 receptors at the levels of periaqueductal gray and dorsal raphe nucleus in rats. In addition, it has been reported that histamine central H_2, but not H_1 receptors are involved in the centrally administered histamine-induced antinociception in an acute model of trigeminal pain in rats (Tamaddonfard et al., 2008). There are a few data regarding the involvement of supraspinal histamine H_1 and H_2 receptors in the formalin-induced pain. Mojtahedin et al. (2008) reported the preventive effects of centrally administered mepyramine and famotidine on the histamine-induced antinociception in the formalin test in rats. Moreover, intra-hippocampal microinjection of mepyramine and ranitidine prevented histamine-induced antinociception in the formalin-induced orofacial pain in rats (Erfanparast et al., 2010).

In this study, intra-dentate gyrus microinjection of thioperamide alone produced antinociception, and increased histamine-induced antinociception when used before histamine. Histamine H_3 receptors act as pre-synaptic auto-receptors and post-synaptic hetero-receptors (Arrang et al., 1987; Pollard et al., 1993). Activation of histamine H_3 auto-receptors by selective agonists such as R-α-methylhistamine, imepipe and imetit results in the inhibition of histamine synthesis and release from histaminergic neurons, whereas blockade of histamine H_3 auto-receptors with selective antagonists including clobenpropit, ciproxifan and thioperamide can increase the release of histamine from histaminergic endings (Brown et al., 2001; Haas et .al., 2008). Although the majority of histamine H_3 receptors are located in the brain (Pillot et al., 2002), histamine H_3 receptor mRNA is also found in various non-brain tissues including the skin, stomach, intestines, brown adipose tissue, dorsal root ganglion and spinal cord (Cannon et al., 2007a; Karlstedt et al., 2003). The evidence taken from acute and chronic pain tests has suggested peripheral, spinal and supraspinal roles for histamine H_3 receptor in mediating pain and analgesia. Local activation of histamine H_3 receptor with subplantar injection of R-α-methylhistamine potentiated the suppressive effect of fentanyl in thermal hyperalgesia induced by subplantar injection of Complete Ferund's adjuvant in mice (Fernandez-Duenas et al., 2010). Administration of immepip and thioperamide to the cholestatic rats increased and decreased tail-flick latencies, respectively (Hasanein, 2010). It has been reported that activation of histamine H_3 receptors by immepip on peripheral and spinal sites of pain pathways attenuates formalin-induced

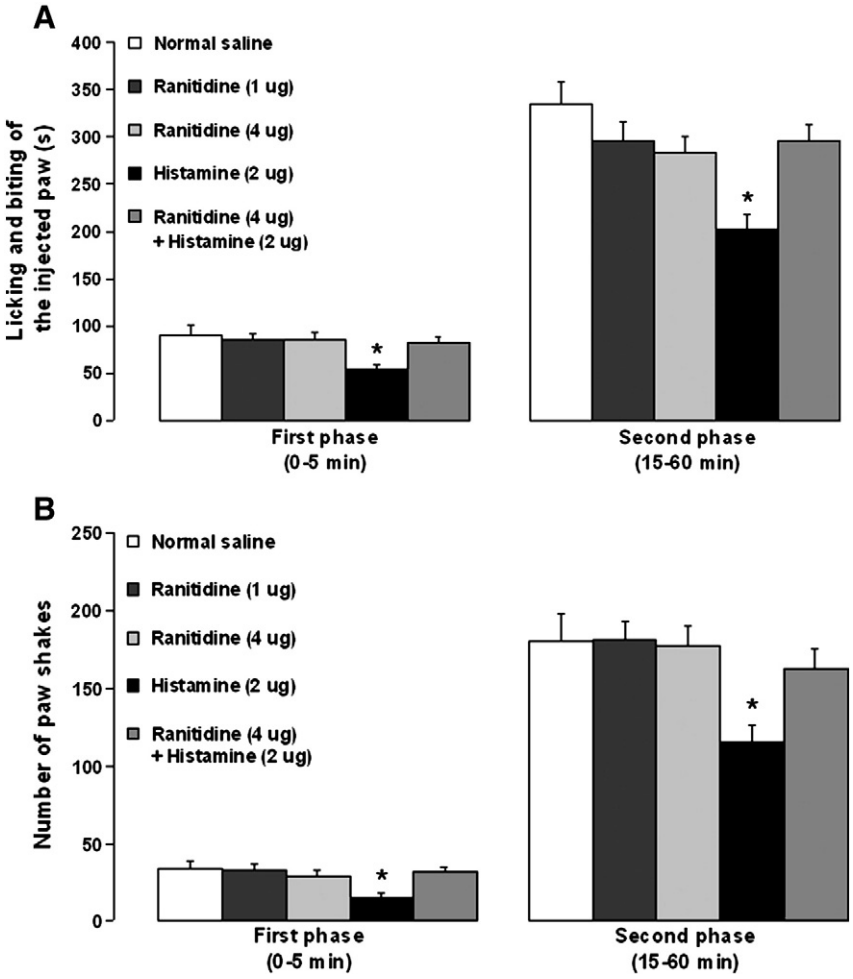

Fig. 4. Effect of intra-dentate gyrus microinjection of ranitidine alone and before histamine on the licking/biting (A) and shaking (B) behaviors induced by intraplantar injection of formalin. The licking/biting and shaking of the injected paw were recorded 10 and 5 min after intra-dentate gyrus microinjection of ranitidine and histamine, respectively. Each column represents the mean ± SEM ($n = 6$). *$P<0.05$ as compared to other treated groups (one-way ANOVA followed by Duncan test).

swelling and flinching (Cannon et al., 2007b). Using histamine H_3 receptor gene knockout mice, Mobarakeh et al. (2009) reported an inhibitory effect of histamine through its H_3 receptors on the morphine-induced antinociception in hot plate, tail-flick, paw-withdrawal and formalin tests of nociception at the spinal level. At the supraspinal level, intracerebroventricular injection of thioperamide increased the nociceptive threshold in a rat model of neuropathic pain (Huang et al., 2007). In contrast, intracerebroventricular injection of thioperamide did not exert any analgesic activities in the tail-flick and hot plate tests of nociception in rats (Hough et al., 1997). However, Malmberg-Aiello et al. (1994) reported analgesic and hyperalgesic effects after intracerebroventricular injection of thioperamide and R-α-methylhistamine, respectively, in rats and mice.

In the present study, intra-dentate gyrus microinjections of histamine and thioperamide, without any significant effect on interphase (data not shown) suppressed the first and the second phases of formalin-induced licking/biting and shaking responses. This means that the microinjection of histamine and thioperamide in the dentate gyrus could modulate spinal mechanisms in the formalin test. The first phase of formalin-induced pain may be attributed to a direct algogenic effect of formalin on the nociceptors and the second phase to the release of local inflammatory mediators responsible for sensitization of primary and spinal sensory neurons and subsequent signal transduction into the brain (Tjolsen et al., 1992; Raboisson and Dallel, 2004; Porro and Cavazzuti, 1993). The interphase of formalin test is under active inhibition of spinal cord mechanisms (Henry et al., 1999). The pain-related behaviors can be associated with distinct brain structures, including spinal, brainstem and cerebrally mediated responses to nociceptive stimulation (Millan, 1999). Regarding the formalin-induced nocifensive behaviors including licking/biting and shaking of the injected paw, it was found that these behaviors are mediated by supraspinal structures (Porro et al., 2003). On the other hand, histaminergic neurons from tuberomammillary nucleus of the hypothalamus innervate the areas such as mesencephalic periventricular gray matter and external layers of the dorsal horn of the spinal cord, known to be involved in nociceptive control (Schwartz et al., 1991; Besson and Chaouch, 1987). It seems that the intra-dentate gyrus microinjected histamine-induced antinociception noted here may occur at the supraspinal level because Sakurada et al. (2003) reported a hyperalgesic effect of intrathecally administered histamine in mice. Moreover, spinal histamine H_3 receptor activation with selective agonists has been recommended for treatment of pain (Cannon et al., 2007b).

In conclusion, the results of the present study indicated that the activation of brain histamine in the dentate gyrus by exogenous administration of the amine produced antinociception in the formalin test in rats. The histamine post-synaptic H_1, H_2 and pre-synaptic H_3 receptors may be involved in mediating nociceptive information at the dentate gyrus level of the brain.

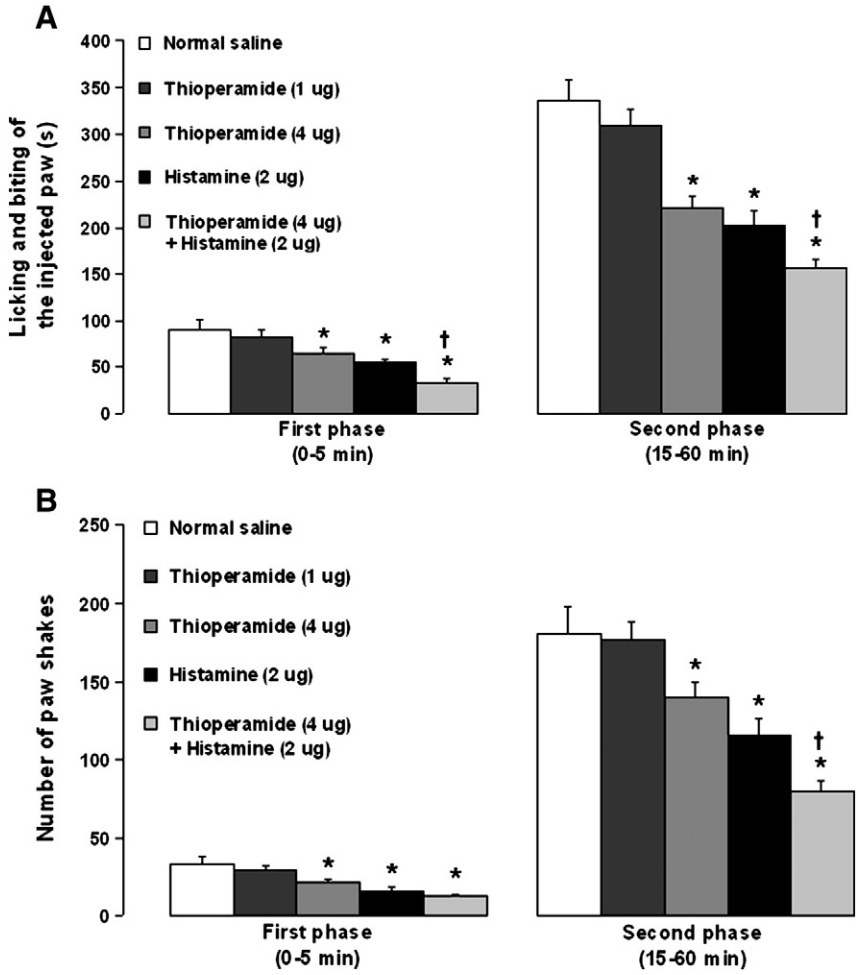

Fig. 5. Effect of intra-dentate gyrus microinjection of thioperamide alone and before histamine on the licking/biting (A) and shaking (B) behaviors induced by intraplantar injection of formalin. The licking/biting and shaking of the injected paw were recorded 10 and 5 min after intra-dentate gyrus microinjection of thioperamide and histamine, respectively. Each column represents the mean ± SEM ($n = 6$). *$P<0.05$ as compared to normal saline treated groups (one-way ANOVA followed by Duncan test). †$P<0.05$ as compared to histamine (2 μg) treated group (one-way ANOVA followed by Duncan test).

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