

Effects of administration of histamine and its H₁, H₂, and H₃ receptor antagonists into the primary somatosensory cortex on inflammatory pain in rats

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ABSTRACT

Objective(s): The present study investigated the effects of microinjection of histamine and histamine H₁, H₂, and H₃ receptor antagonists, chlorpheniramine, ranitidine and thioperamide, respectively into the primary somatosensory cortex (PSC) on inflammatory pain.

Material and Methods: Two stainless steel guide canulas were bilaterally implanted into the PSC of anaesthetized rats. Inflammatory pain was induced by subcutaneous (SC) injection of formalin (50 µl, 2.5%) in the ventral surface of right hind paw. Time durations of licking/biting of the injected paw were recorded as a pain measure.

Results: Formalin produced a biphasic pattern of licking/biting of the injected paw. Histamine at doses of 0.5, 1, and 2 µg decreased the intensity of pain. 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. Antinociceptive effects were observed when thioperamide at doses of 1 and 4 µg was used with 0.25 and 1 µg of histamine, respectively. The antinociceptive effects induced by histamine (2 µg) and thioperamide (4 µg) were prevented by prior treatment with naloxone (4 µg).

Conclusion: These results indicate that at PSC levels, histamine through post-synaptic H₁, H₂, and pre-synaptic H₃ receptors might be involved in pain modulation. The endogenous opioid system may be involved in histamine- and thioperamide-induced antinociception.

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Introduction

Pain is a multidimensional phenomenon that encompasses sensory-discriminative, affective-motivational, and cognitive-emotional components mediated by different mechanisms and processed in a neural network (1, 2). Recent years have seen progressive unraveling of the neuroanatomical circuits and cellular mechanisms underlying the induction of pain (3, 4). Contrary to the traditional view that the cerebral cortex is not involved in pain perception, multiple cortical areas including the anterior cingulate cortex, the granular insular cortex, the ventrolateral orbital cortex (VLOC), the motor cortex, and the PSC and secondary somatosensory cortex (SSC) have major roles in the representation and modulation of pain (5, 6). Extracellular unit recording techniques have demonstrated that monkey and cat PSC neurons in the deeper lamina encode the intensity of noxious, mechanical, thermal,

and chemical stimulation (7). Besides, PSC neurons responded to nociception induced by CO₂ laser-heat irradiation of the middle part of the tail in rats (8). Recently, it has been reported that formalin injection in the hind paw of rats resulted in metabolic increases in the cortical structures including PSC (9).

Histamine via its H₁, H₂ and H₃ receptors participates in modulation of pain. Central administration of histamine produced antinociception in the formalin test in mice and rats (10, 11). Co-administration of temelastine (a histamine H₁ receptor antagonist) and tiotidine (a histamine H₂ receptor antagonist) with histamine into the periaqueductal gray inhibited the histamine-induced analgesia in the hot plate test in rats (12). Moreover, central injection of ranitidine and thioperamide (a histamine H₃ receptor antagonist), but not pyrilamine (a histamine H₁ receptor antagonist), enhanced the nociceptive threshold in a rat model of neuropathic pain (13).

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More recently, the involvement of histamine H₁, H₂, and H₃ receptors in the histamine-induced antinociception was reported in the formalin-induced pain at the level of the dentate gyrus in rats (14, 15).

The present study was aimed at investigating the implication of histaminergic system in pain perception by microinjection of histamine and its H₁, H₂, and H₃ antagonists into the PSC using formalin test in rats. In addition, we assessed the contribution of the endogenous analgesic opioid system by microinjection of naloxone prior to histamine and thioperamide.

Materials and Methods

Animals

Healthy adult male Wistar rats, weighing 250–280 g, were used in this study. Rats were maintained in groups of six per cage in a light-dark cycle (light on at 07:00 hr) at a controlled ambient temperature (22 ± 0.5°C) with *ad libitum* food and water. Six rats were used for each experiment. 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.

Drugs

Drugs used in the present study included histamine dihydrochloride, chlorpheniramine maleate, ranitidine hydrochloride, thioperamide maleate, and naloxone hydrochloride. The drugs were purchased from Sigma-Aldrich Inc., St Louis, MO, USA. All drugs were dissolved in sterile normal saline 30 min prior to intra-primary somatosensory (intra-PSC) cortex microinjection.

Surgical procedure

To deliver the compounds to be tested, rats were bilaterally implanted with two guide cannulas in each PSC. In brief, each rat was anaesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) injected intraperitoneally (IP), and then placed in a stereotaxic apparatus (Stoelting, Wood Dale, IL, USA). The scalp was incised, and the skull was leveled off around the bregma. Two 24 gauge, 10 mm stainless-steel guide cannulas were bilaterally implanted into the right and left PSCs. The tip of cannulas was aimed at the following coordinates: -0.80 mm posterior to the bregma, 1.8 mm left and right sides of the midline, and 1.2–1.4 mm below the top of the skull (16). The cannulas were then fixed to the skull using three screws and dental acrylic (Acropars, Tehran, Iran). A 10 mm stylet was inserted into each cannula to keep it patent prior to microinjection. All animals were allowed 14 days to recover from surgery.

Intra-PSC microinjection

For intra-PSC microinjections of normal saline (control), histamine (0.25, 0.5, 1, and 2 µg), chlorpheniramine, ranitidine, and thioperamide at the same doses of 1 and 4 µg and naloxone at a dose of 4 µg, a 30 gauge, 10 mm injection needle was attached to a 30 cm polyethylene tube fitted to a 1 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 PSC was 0.25 µl, and the injection was slowly made over a period of 60 sec. The injection needle was left in place for a further 60 sec after the completion of the injection to facilitate the diffusion of the drug. Microinjections of chlorpheniramine, ranitidine, thioperamide, and naloxone were performed 10 min before induction of pain, whereas histamine was microinjected 5 min before intraplantar (IPL) injection of formalin. In the case of intra-PSC co-administration of naloxone plus histamine and naloxone plus thioperamide, naloxone was microinjected 2 min before microinjection of histamine and thioperamide. The drug doses used here were calculated according to our previous studies (14, 15, 17–19).

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 (20). The formalin test was applied as follows: Fifty µl of 2.5% formalin was injected (SC) into the ventral surface of right hind paw using a 30-gauge injection needle; Following formalin injection, the rat was immediately put back in the observation chamber. Nociceptive behaviors including licking/biting 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 for 60 min, starting after formalin administration (21). Licking/biting behaviors of the injected paw were chosen as measures of pain, because they are supraspinally mediated behaviors (22). The frequency, duration and level of formalin-induced pain behaviors depend on the specific concentration used and the site of injection (23). In the present study, data collected between 0–5 min after formalin injection represented the first (early) phase and data collected between 15–60 min after injection of formalin represented the second (late) phase (21–23).

Cannula verification

At the end of each experiment, 0.25 µl of methylene blue was injected into each side of PSC.

Animals were killed with high dose ether, and perfused intracardially with physiological saline followed by 10% formalin solution. Brains were removed and placed in the formalin (10%) solution. At least 3 days later, the brains were sectioned coronally (50-100 μ m) and viewed under a loupe to localize the injection site (16). The results obtained from rats with guide cannula outside the PSC (hindlimb region) were eliminated from the data analysis.

Statistical analysis

Data obtained from five min blocks, after (IPL) injection of formalin and normal saline, were analyzed using factorial ANOVA followed by Duncan's test. To evaluate significant differences among intra-PSC treated groups on the first and second phases of formalin-induced pain, one-way analysis of variance (ANOVA) and Duncan's test were applied. In figures, all values are expressed as the mean \pm SEM. A value of $P < 0.05$ was considered statistically significant.

Results

The placements of the cannula tips in the PSC of rats are shown in Figure 1. The rat brain section was modified from the atlas of Paxinos and Watson (16) (Figure 1A). The locations of the cannula tip placements in the PSC were confirmed with intra-PSC injection of methylene blue (Figure 1B).

Figure 2 shows the durations of licking/biting of normal saline and formalin (2.5%) injected paw at five min blocks. Normal saline produced a negligible response at the first five min block. IPL injection of formalin (2.5%) significantly ($P < 0.05$) produced pain responses at 1st and 4th-12th five min blocks (Figure 2).

Intra-PSC microinjection of histamine at doses of 0.5, 1, and 2 μ g, but not at a dose of 0.25 μ g, significantly decreased the intensity of nociceptive response in the first ($P < 0.05$) and second ($P < 0.05$) phases of formalin-induced pain (Figure 3).

No significant differences were observed between intra-PSC microinjection of normal saline and chlorpheniramine, at doses of 1 and 4 μ g, in pain response. Pretreatment with chlorpheniramine (4 μ g) significantly ($P < 0.05$) prevented the suppressive effects of histamine (2 μ g) on licking/biting of the injected paw in the first and second phases (Figure 4).

Intra-PSC microinjection of normal saline and ranitidine at doses of 1 and 4 μ g produced no significant effects on pain intensity. The suppressive effects, induced by intra-PSC microinjection of histamine (2 μ g), on licking/biting of the injected paw in the first and second phases were significantly ($P < 0.05$) prevented by prior microinjection of ranitidine (4 μ g) into the same site (Figure 5).

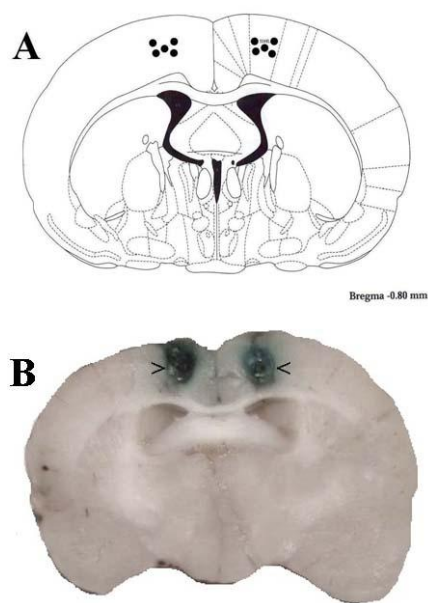


Figure 1. Schematic illustration of coronal section of the rat brain showing the approximate location of the PSC microinjection sites (black circles) in the experiments (A). Locations of the injection cannula tips in the PSC of all rats included in the data analysis (B). Atlas plate adapted from Paxinos and Watson (16)

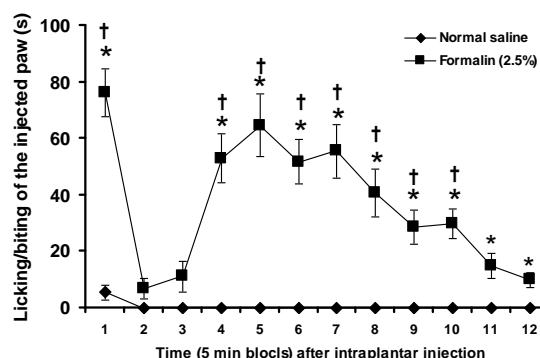


Figure 2. Duration of licking/biting of the hindpaw after IPL injection of normal saline and formalin. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs normal saline. † $P < 0.05$ denotes significant difference vs other five min blocks (factorial ANOVA and Duncan's test)

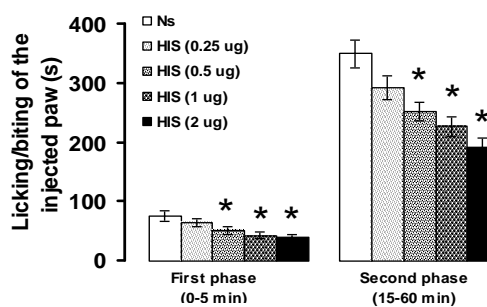


Figure 3. Effect of intra-PSC microinjections of saline normal (Ns) and histamine (HIS) on the formalin-induced pain. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs normal saline (one-way ANOVA and Duncan's test)

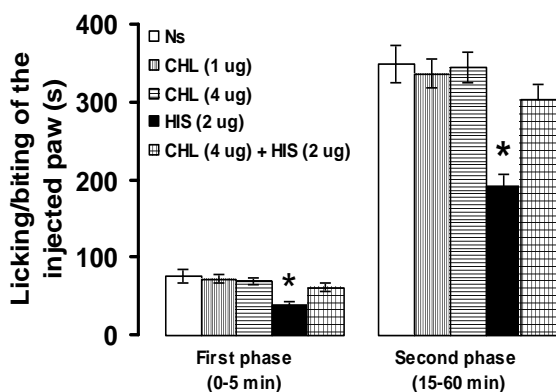


Figure 4. Effect of intra-PSC microinjections of normal saline (Ns), chlorpheniramine (CHL) alone and before histamine (HIS) on the formalin-induced pain. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs other groups (one-way ANOVA and Duncan's test)

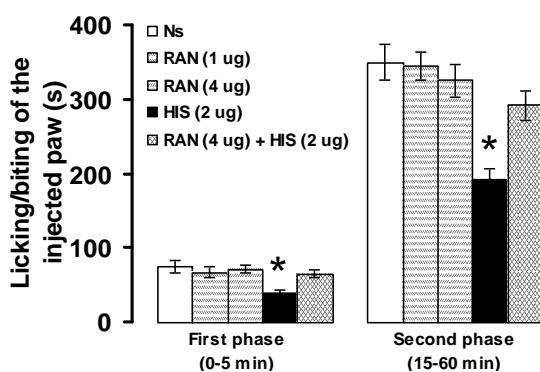


Figure 5. Effect of intra-PSC microinjections of normal saline (Ns), ranitidine (RAN) alone and before histamine (HIS) on the formalin-induced pain. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs other groups (one-way ANOVA and Duncan's test)

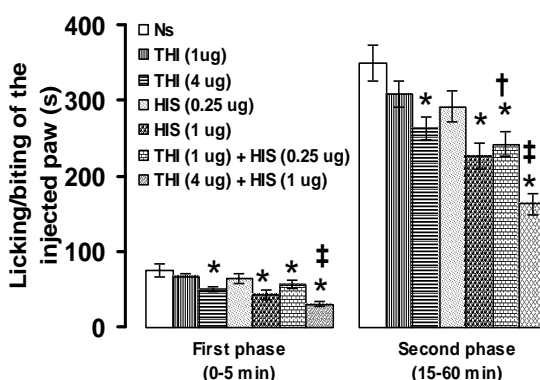


Figure 6. Effect of intra-PSC microinjections of normal saline (Ns), thioperamide (THI) alone and before histamine (HIS) on the formalin-induced pain. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs other groups. † $P < 0.05$ denotes significant difference vs thioperamide (1 μ g) and histamine (0.25 μ g). ‡ $P < 0.05$ denotes significant difference vs thioperamide (4 μ g) and histamine (1 μ g). (one-way ANOVA and Duncan's test)

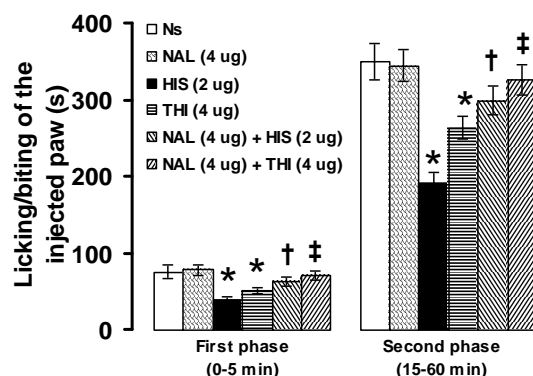


Figure 7. Effect of intra-PSC microinjections of normal saline (Ns), naloxone (NAL) alone and before histamine (HIS), and thioperamide (THI) on the formalin-induced pain. Data are presented as mean \pm SEM (n = 6). * $P < 0.05$ denotes significant difference vs other groups. † $P < 0.05$ denotes significant difference vs histamine (2 μ g). ‡ $P < 0.05$ denotes significant difference vs thioperamide (4 μ g). (one-way ANOVA and Duncan's test)

Microinjection of thioperamide into the PSC at a dose of 4 μ g, but not at 1 μ g, significantly decreased the duration of licking/biting of the formalin-injected paw in the first and second phases. Thioperamide (1 μ g) plus histamine (0.25 μ g) significantly ($P < 0.05$) decreased the second phase of pain intensity. Thioperamide (4 μ g) plus histamine (1 μ g) produced antinociception in the first and second phases of formalin-induced pain (Figure 6).

Intra-PSC microinjection of naloxone (4 μ g), significantly ($P < 0.05$) prevented the antinociceptive effects induced by histamine (2 μ g) and thioperamide (4 μ g) in the first and second phases of formalin-induced pain (Figure 7).

Discussion

The results of the present study showed that IPL injection of formalin produced a biphasic pain response. Formalin test has been used frequently to study pain mechanisms in laboratory animals; according to these studies a biphasic pattern of pain-related behaviors was produced by SC injection of small amounts (20–100 μ l) of dilute solutions (0.1–10%) of formalin into the various parts of the body (21–24). The first phase in turn may be attributed to direct algogenic effect of formalin on the nociceptors and the second phase to release of local inflammatory mediators responsible for sensitization of primary and spinal sensory neurons and subsequent signal transduction into the brain (21–24). Various neurotransmitters and nuclei of the brain are involved in the modulation of formalin-induced pain at the supraspinal level (22).

In the present study, microinjection of histamine into the PSC produced antinociceptive effects in the first and second phases of formalin-induced pain. Histamine H_1 and H_2 antagonists, chlorpheniramine and ranitidine respectively, did not alter the intensity of pain when used alone, while pretreatments with

chlorpheniramine and ranitidine inhibited histamine-induced antinociception. These indicate that at PSC level, histamine through its post-synaptic H₁ and H₂ receptors, modulates formalin-induced pain. Histamine can modulate formalin-induced pain in the peripheral organs, spinal, and supraspinal structures. A small number of flinches were produced due to IPL injection of histamine (25); in addition, IPL injection of chlorpheniramine and cimetidine decreased formalin-induced pain responses in rats (26). At the level of the spinal cord, intrathecal (IT) administration of histamine produced a pain-like behavior consisting of scratching, biting, and licking in conscious mice. IT co-administration of chlorpheniramine or ranitidine with histamine prevented histamine-induced nociceptive behavior (27). At the supraspinal level, it has been reported that co-administration of temelastine or tiotidine with histamine into the periaqueductal gray (PAG) inhibits the histamine-induced analgesia in the hot plate test in rats (28). Moreover, microinjection of mepyramine (a histamine H₁ receptor antagonist) and ranitidine into the dorsal hippocampus inhibited the suppressive effects of histamine on pain behavior induced by SC injection of formalin in the upper lip region in rats (17). In addition, intra-dentate gyrus microinjections of chlorpheniramine and ranitidine prevented histamine-induced antinociception in the paw formalin test in rats (14). PSC has been thought to play an essential role in processing of the sensory-discriminative components of pain. These components include sensing the quality, intensity and spatial location of painful sensations (29). The distribution and function of histamine and its H₁ and H₂ receptors in the brain regions including cerebral cortex structures have been reported (30–32). In the cortical structures, histamine H₁ receptors are distributed in the middle (layers III and IV) and deep layers (layers IV and V), whereas superficial (layers I and II) and middle layer (predominantly layer III) contain histamine H₂ receptors (32). Using additional factor method and even related potentials recording, it has been found that the histaminergic system via its H₁ receptors, participates in sensory information processing; and histamine hypofunction in clinical disorders may cause impaired sensory processing (33). Moreover, it has been reported that intravenous (IV) injection of diphenhydramine (a histamine H₁ receptor antagonist) blocked the inhibitory effect of central amygdaloid nucleus conditioning stimulation on the tooth pulp-driven neuronal activity in the PSC in rats (34).

In this study, intra-PSC microinjection of thioperamide alone suppressed the pain and produced an antinociceptive effect when co-administered with histamine. This indicates that blockade of histamine H₃ receptors produced

antinociceptive effects. Histamine H₃ receptors act as pre-synaptic auto-receptors and post-synaptic hetero-receptors (35, 36). Activation of histamine H₃ auto-receptors by R- α -methylhistamine, imepipe, and imetit (histamine H₃ receptor agonists) results in the inhibition of histamine synthesis and release from histaminergic neurons, whereas blockade of histamine H₃ auto-receptors with histamine H₃ receptor antagonists such as clobenpropit, ciproxifan, and thioperamide can increase the release of histamine from histaminergic endings (37, 38). Recently, Munari *et al* (39) reported that ABT-239, a histamine H₃ receptor antagonist/inverse agonist, increased histamine release from the cortex when administered into the TMN of brain in Rats. Although the majority of histamine H₃ receptors are located in brain (31), histamine H₃ receptor mRNA is also found in various non-brain tissues including skin, stomach, intestines, brown adipose tissue, dorsal root ganglion, and spinal cord (40, 41). Thus, histamine H₃ receptors can influence pain modulation at peripheral local, spinal, and supraspinal levels (42). IPL injection of R- α -methylhistamine did not affect thermal hyperalgesia induced by the IPL injection of Complete Freund's adjuvant in mice (43). In contrast, the activation of spinal histamine H₃ receptors with IT injection of imemipip reduced the first and the second phases of formalin-induced flinching in rats, while the blockade of histamine H₃ receptors with thioperamide prevented imemipip-induced antinociception (44). At the supraspinal level, intracerebroventricular injection of thioperamide and R- α -methylhistamine produced analgesic and hyperalgesic effects, respectively, in the hot plate and writhing tests of nociception in rats and mice (45). Moreover, intra-dentate gyrus microinjection of thioperamide suppressed both the first and the second phases of formalin-induced nociception in rats and increased the antinociceptive effect of histamine when microinjected prior to histamine into the same site. The distribution of histamine H₃ receptors in the cortical structures (32), may confirm the antinociceptive effect induced by thioperamide that we observed in this study.

In the present study, naloxone inhibited the antinociceptive effects of histamine and thioperamide on the formalin-induced pain. This means that the opioid receptors may be involved in histamine-induced antinociception. Naloxone, as a competitive antagonist of mu-, kappa-, and sigma-opioid receptors with higher affinity for the mu-opioid receptors (46), has been frequently used to explore the role of endogenous opioid receptors in pain modulation. Microinjections of naloxone into the VLOC reversed the antinociceptive effects of morphine microinjected into the same site in the formalin test and in the L₅/L₆ spinal nerve ligation model of neuropathic pain in rats (47, 48). Several interactions exist between histaminergic agents and

opioid receptors in modulation of pain. Local activation of histamine H₃ receptor with IPL injection of R- α -methylhistamine potentiated the suppressive effect of fentanyl in thermal hyperalgesia induced by IPL injection of Complete Ferund's adjuvant in mice (43). Using the histamine H₃ receptors gene knockout mice, Mobarakeh *et al* (49) reported that histamine, through its H₃ receptors exerted inhibitory effects on the antinociceptive effects of morphine at the spinal level. In addition, the microinjection of naloxone into the PAG reversed the antinociceptive effect induced by the microinjection of histamine into the same site (12). The antinociception induced by microinjection of thioperamide into the dentate gyrus was inhibited by prior microinjection of naloxone into the same site (15).

Multiple neurotransmitters including GABA, glutamate, and opioid modulate the pain processing in the cortical structures (6). Both NMDA and AMPA/kainate receptors of glutamate have been found to contribute to PSC high-threshold responses evoked by noxious stimulation of the forepaw or hindpaw in rats (50). Microinjection of GABA_A agonist, muscimol, into the PSC significantly reduced the licking behavior in the first and second phases of formalin-induced pain (51). Thus, the neurotransmitters such as glutamate, GABA, opioids, and histamine can modulate pain by influencing the mechanisms of pain perception in the PSC. However, it needs more study with the agents that inhibited or stimulated the release or the synthesis of histamine at the synaptic site to clarify the exact roles of histamine and its receptors on supraspinal modulation of pain.

Conclusion

The results of the present study indicate that the activation of brain histamine in the PSC, by exogenous administration of the amine, produced antinociception in the formalin test in rats. The histamine post-synaptic H₁, H₂, and pre-synaptic H₃ receptors mediate histamine-induced antinociception at the PSC of the brain. Moreover, opioid receptors in the PSC may be involved in the antinociceptive effects of histamine and thioperamide.

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