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Interaction between histamine and morphine at the level of the hippocampus in the formalin-induced orofacial pain in rats

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Abstract:
The present study explored the interaction between histaminergic and opioidergic systems at the level of the hippocampus in modulation of orofacial pain by intra-hippocampal microinjections of histamine, pyrilamine (an antagonist of histamine H_1 receptors), ranitidine (an antagonist of histamine H_2 receptors), morphine (an opioid receptor agonist) and naloxone (an opioid receptor antagonist) in separate and combined treatments. Orofacial pain was induced by subcutaneous (*sc*) injection of formalin (50 µl, 1%) in the upper lip region and the time spent face rubbing was recorded in 3 min blocks for 45 min. Formalin (*sc*) produced a marked biphasic (first phase: 0–3 min, second phase: 15–33 min) pain response. Histamine and morphine suppressed both phases of pain. Histamine increased morphine-induced antinociception. Pyrilamine and ranitidine had no effects when used alone, whereas pretreatments with pyrilamine and ranitidine prevented histamine- and morphine-induced antinociceptive effects. Naloxone alone non-significantly increased pain intensity and inhibited the antinociceptive effects of morphine and histamine. The results of the present study indicate that at the level of the hippocampus, histamine through its H_1 and H_2 receptors, mediates orofacial region pain. Moreover, morphine *via* a naloxone-reversible mechanism produces analgesia. In addition, both histamine H_1 and H_2 receptors, as well as opioid receptors may be involved in the interaction between histamine and morphine in producing analgesia.

Key words:
histamine, histamine H_1 and H_2 receptors, morphine, naloxone, hippocampus, orofacial formalin test, rats

Abbreviations: *icv* – intracerebroventricular, PAG – periaqueductal gray, SNO – subnucleus oralis

Introduction

The hippocampus is involved in a variety of biological functions including learning and memory, stress, immunity, energy intake, body weight regulation and pain modulation [11, 21–24, 48]. Histaminergic endings and its H_1, H_2 and H_3 receptors are distributed in various parts of limbic system [37], and mediate some of functions of the hippocampus such as anxiety, arousal state, hibernation, neurotransmission, learning and memory [2, 36, 49]. On the other hand, opioid receptors are expressed in the hippocampal formation and are involved in mediation of hippocampal functions including adult neurogenesis, the action of gonadal hormones, development of neonatal transmitter system and pain [12, 13, 18].

The trigeminal nerve relays the sensory information including acute and chronic pains arising from orofacial structures including facial skin, teeth, tongue, lips and temporomandibular joint to the higher regions and nuclei of brain such as trigeminal sensory nuclei, nucleus tractus solitarious (NTS), inferior and superior colliculus, periaqueductal gray (PAG), thalamus, hippocampus, striatum and cerebral cortex [41]. The orofacial formalin test was introduced by Clavelou et al. [9] and was completed by Clavelou et al. [8], and thereafter has been frequently used with success in the brain modulation of orofacial region pain [1, 7, 15].

Some interactions exist between histamine and opioid receptors in mediating the brain functions. The histamine precursor L-histidine potentiated, while zolantidine (central histamine H_2-receptor antagonist), but not pyrilamine (central histamine H_1-receptor antagonist) attenuated the discriminative stimulus effects of morphine (an opioid antagonist) [30]. Moreover, pyrilamine, but not ranitidine, increased the inhibitory effect of morphine on drinking behavior in rats [16]. Intrathecal administration of cyproheptadine (an antagonist of histamine H_1 receptors) and ranitidine attenuated the inhibition of the tail-flick response induced by intrathecally-administered morphine in mice [39]. There are a few studies describing the supraspinal interactions between histamine and morphine in mediating pain and analgesia mechanisms. However, pyrilamine (a centrally acting histamine H_1 receptor antagonist) potentiated, whereas zolantidine (a centrally acting histamine H_2 receptor antagonist) inhibited *icv*-injected morphine-induced antinociception in the hot plate test in the mouse [40].

The present study was aimed to investigate the hippocampal interaction between histamine and morphine by intra-hippocampal microinjections of histamine, pyrilamine, ranitidine, morphine and naloxone in separate and combined treatments using orofacial formalin test in rats.

Materials and Methods

Animals

Healthy adult male Wistar rats (280–330 g) were used throughout the study. Rats were maintained in groups of 6 per cage in a 12 h light-dark cycle (lights on at 07:00 h) at a controlled ambient temperature (22 ± 0.5°C) with *ad libitum* food and water. Six rats were used in each experiment. Experiments were performed between 12:00 h and 15:00 h. The experimental protocol was approved by the Veterinary Ethics Committee of the Faculty of Veterinary Medicine of Urmia University and was 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, mepyramine maleate (pyrilamine), ranitidine hydrochloride, naloxone dihydrochloride (Sigma-Aldrich Chemical Co., St. Louis, MO, USA) and morphine sulfate (Temad, Tehran, Iran). All drugs were dissolved in sterile normal saline 30 min before intra-hippocampal microinjection.

Surgery

After a 15-day adaptation period, each rat was anesthetized 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 Lane, IL, USA). Two 23 gauge, 12 mm stainless-steel guide cannulas were bilaterally implanted into the right and left dorsal hippocampus at the following coordinates: 3.6 mm posterior to the bregma, 2.4 mm left and right sides of the midline and 2.7 mm below the top of the skull [33]. The cannulas were then fixed to the skull using three screws and dental acrylic. A 29-gauge, 12 mm stylet was inserted to each cannula to keep them patent prior to injection. At least 14 days were allowed for recovery from the surgery.

Intra-hippocampal microinjection

Intra-hippocampal microinjections of normal saline (control), histamine (0.5, 1 and 2 μg), pyrilamine and ranitidine at the same doses of 1 and 4 μg, morphine (0.5, 1 and 2 μg) and naloxone (4 μg) were performed using a 30 gauge, 12 mm injection needle attached to

a 5 µl Hamilton syringe. The volume of the drug solution to be injected into each dorsal hippocampus was 0.5 µl and the injection was slowly made over a period of 45 s. The injection needle was left in place for a further 45 s after completion of injection to facilitate diffusion of the drug. Histamine and naloxone were injected 5 min before induction of pain. Orofacial formalin-induced pain was induced 10 min after intra-hippocampal microinjections of pyrilamine, ranitidine and naloxone. In the case of intrahippocampal co-microinjection of histamine and morphine, histamine and morphine were microinjected 6 and 4 min before induction of orofacial pain, respectively. The drug doses used here were closer to other investigations in which the used dose ranges were reported 2–20 µg for histamine H_1 and H_2 antagonists and 0.2–5 µg for morphine [15, 22, 32, 49].

Orofacial formalin test

Orofacial formalin test was performed according to the method described by Raboisson and Dallel [34]. Each rat was placed in Plexiglas observation chamber (30 cm × 30 cm × 30 cm) with a mirror mounted at 45° beneath the floor to allow an unobstructed view of the orofacial region. After a 30-min adaptation period, 50 µl of 1% diluted formalin solution was injected into the left side of upper lip *sc* just lateral to the nose using a 30-gauge injection needle. Immediately following formalin injection, the rat was returned into the observation chamber. The time each animal spent face rubbing with ipsilateral forepaw was recorded (using a stopwatch), in consecutive 3-min bins over a period of 45 min, and was considered as an index of nociception. Formalin injection induced a stereotyped response characterized by two well distinct phases [8, 34]. In the present study, data collected between 0 and 3 min post-formalin injection represented the first (early) phase and data collected between 15 and 33 min after injection of formalin represented the second (late) phase. All the observers were blinded to the protocol of the study.

Cannula verification

At the end of each experiment, 0.25 µl of methylene blue was injected into the each side of hippocampus. Animals were killed with the high dose diethyl ether, and perfused intracardially with physiological saline followed by 10% formalin solution. The brains were removed and placed in a formalin solution (10%). After 24 h, the brains were sectioned coronally (50–100 µm) and viewed under a loup to localize the injection site according to the atlas of Paxinos and Watson [33]. The results obtained from rats with guide cannulas outside the hippocampus were eliminated from the data analysis.

Statistical analysis

Data obtained from the subcutaneous injections of normal saline and formalin were analyzed using repeated measure ANOVA and Duncan test. To evaluate significant differences among intra-hippocampal microinjection treated groups, one-way analysis of variance (ANOVA) and Duncan's test were applied. In figures, all values are expressed as the mean ± SEM. Statistical significance was set at $p < 0.05$.

Results

The placements of the tip of the cannulas in the dorsal hippocampus of rats are shown in Figure 1. The rat brain section was modified from the atlas of Paxinos and Watson [33] (Fig. 1A). The locations of the cannula tip placements in the hippocampus were confirmed with intra-hippocampal injection of methylene blue (Fig. 1B).

Subcutaneous injection of normal saline into the rat upper lip produced a negligible nociceptive response only in the first 3-min block (Fig. 2). Diluted formalin, when subcutaneously injected into the upper lip, produced a typical pattern of face rubbing behavior. Repeated measure ANOVA revealed a significant difference in face rubbing between first, 6^{th}, 7^{th}, 8^{th}, 9^{th} 10^{th} and 11^{th} with the other 3-min blocks after subcutaneous injection of formalin ($F(5,70) = 42.361$, $p < 0.05$). Therefore, the formalin-induced nociceptive behavior showed a biphasic time course: the first phase began immediately after formalin injection and declined in approximately 10 min, while the second phase began about 15 min after formalin injection and lasted about 18 min and declined to the end of recording period (45 min) (Fig. 2).

Figure 3 shows the intra-hippocampal microinjections of histamine, mepyramine and ranitidine on the formalin-induced orofacial pain. Intra-hippocampal

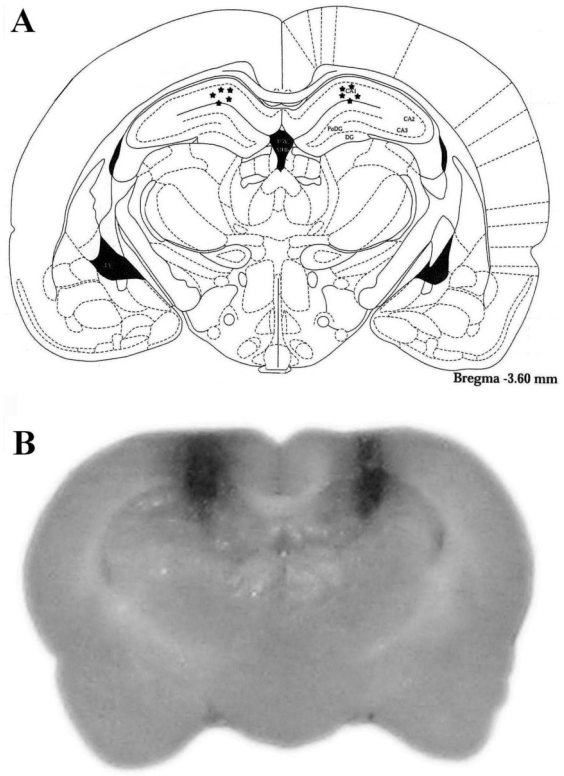

Fig. 1. Schematic illustration of coronal section of the rat brain showing the approximate location of the dorsal hippocampus microinjection sites (black stars) in the experiments (**A**). Location of the injection cannulas tip in the dorsal hippocampus of all rats included in the data analysis (**B**). Atlas plate adapted from Paxinos and Watson [33]. CA1, CA2, CA3: fields CA1, CA2, CA3 of hippocampus, DG: dentate gyrus, PoDG: polymorph layer of dentate gyrus

microinjection of histamine at a dose of 1 and 2 μg, but not at a dose of 0.5 μg, significantly decreased the intensity of nociceptive response in the first phase of formalin-induced nociception ($F(3,20) = 7.163$, $p < 0.05$, one-way ANOVA). The second phase of formalin-induced pain was significantly suppressed by intra-hippocampal microinjection of histamine at doses of 0.5, 1 and 2 μg ($F(3,20) = 12.267$, $p < 0.05$, one-way ANOVA) (Fig. 3A). Intra-hippocampal microinjection of pyrilamine at doses of 1 and 4 μg alone did not change the intensity of first and second phases of pain. Pretreatment with pyrilamine (4 μg) significantly inhibited the antinociceptive effects of histamine (1 μg) in the first ($F(4,25) = 3.124$, $p < 0.05$, one-way ANOVA) and second ($F(4,25) = 5.789$, $p < 0.05$, one-way ANOVA) phases of formalin-induced orofacial pain (Fig. 3B). Microinjection of ranitidine into the dorsal hippocampus alone at doses of 1 and 4 μg alone did not change the intensity of first and second phases of pain. Pretreatment with ranitidine (4 μg) significantly inhibited the antinociceptive effects of histamine (1 μg) in the first ($F(4,25) = 3.483$, $p < 0.05$, one-way ANOVA) and second ($F(4,25) = 8.105$, $p < 0.05$, one-way ANOVA) phases of formalin-induced orofacial pain (Fig. 3C).

Figure 4 shows the microinjections of morphine, naloxone, histamine plus morphine, naloxone plus histamine, mepyramine plus morphine and ranitidine plus morphine on the formalin-induced orofacial pain.

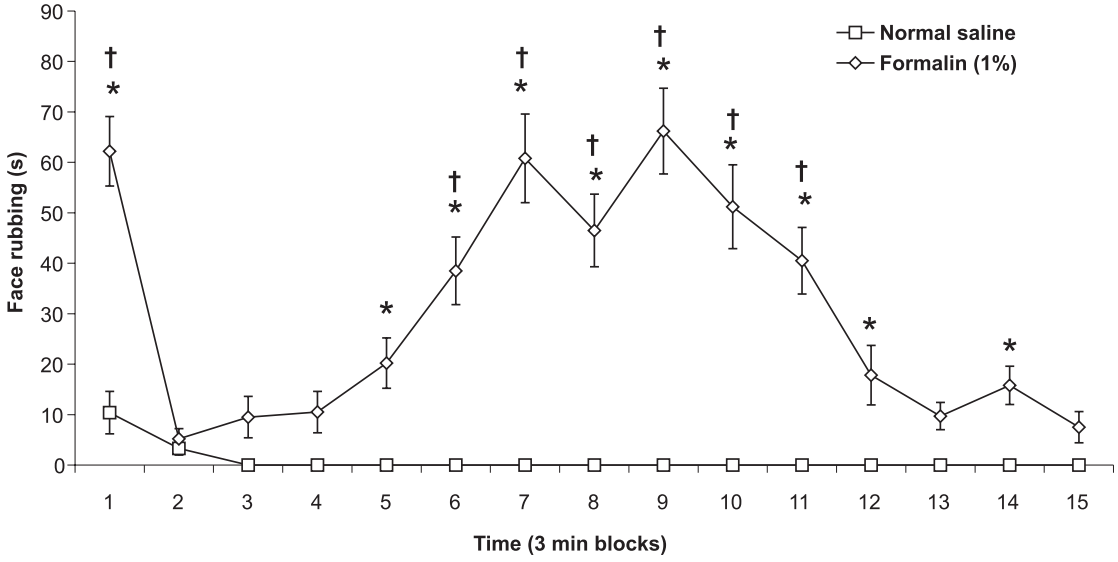

Fig. 2. The orofacial pain response induced by subcutaneous injection of normal saline and formalin in the upper lip in rats. The time of face rubbing was recorded immediately after administrations of normal saline and formalin. Values are the mean ± SEM of six rats per group; * $p < 0.05$ as compared to normal saline treated group, † $p < 0.05$ as compared to other 3-min blocks

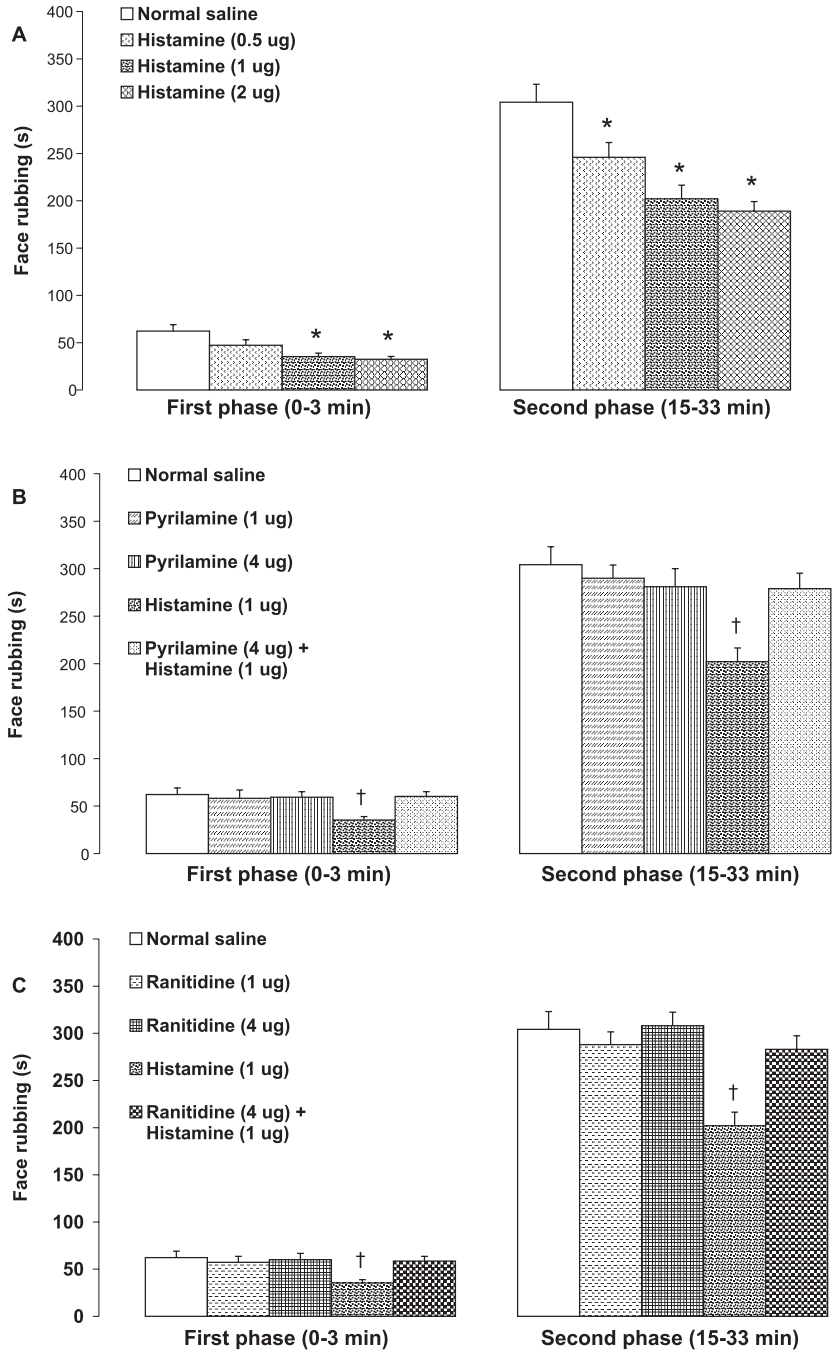

Fig. 3. Effect of intra-hippocampal microinjection of histamine (**A**), pyrilamine (**B**) and ranitidine (**C**) on the orofacial pain induced by formalin. The time of face rubbing was recorded 10 and 5 min after intra-hippocampal microinjections of histamine antagonists and histamine, respectively. Values are the mean ± SEM of six rats per group. * $p < 0.05$ as compared to normal saline treated group. † $p < 0.05$ as compared to other groups

Microinjection of morphine into the dorsal hippocampus at a dose of 0.5 μg had no effect on pain response, whereas morphine at doses of 1 and 2 μg significantly suppressed both first ($F(5,30) = 3.272$, $p < 0.05$, one-way ANOVA) and second ($F(5,30) = 5.655$, $p < 0.05$, one-way ANOVA) phases of pain. Naloxone (4 μg) alone non-significantly increased pain response, and reversed the antinociceptive effects of morphine (2 μg) in the first ($F(5,30) = 3.272$, $p < 0.05$, one-way ANOVA) and second ($F(5,30) = 5.655$, $p < 0.05$, one-way ANOVA) phases of pain (Fig. 4A). No antinociceptive effect was observed in the first phase of formalin-induced pain, when intra-hippocampal microinjection of histamine (0.5 μg) was used with morphine (0.5 μg). Intra-hippocampal microinjections of histamine at doses of 1 and 2 μg with morphine (0.5 μg) produced antinociceptive effects when compared with normal saline and morphine (0.5 μg)

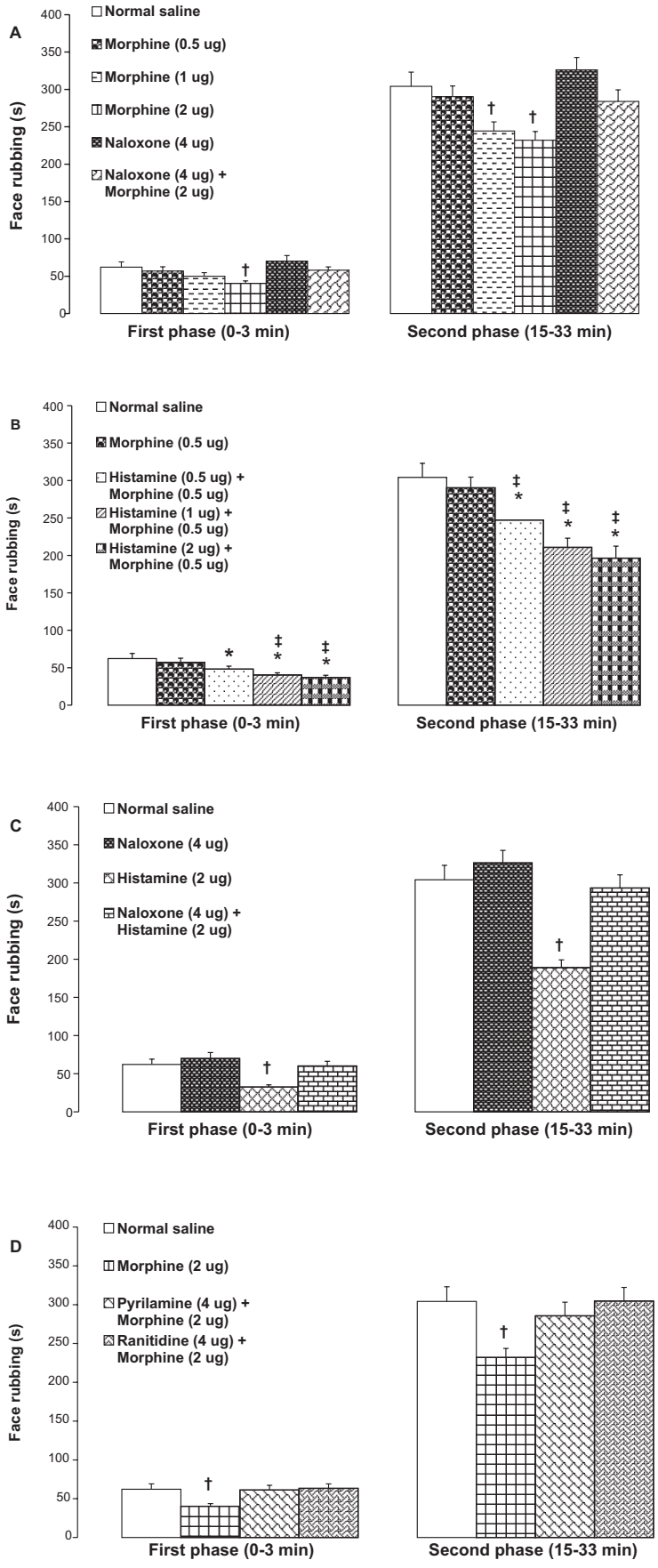

Fig. 4. Effects of intra-hippocampal microinjections of naloxone and morphine (**A**), histamine plus morphine (**B**), naloxone plus histamine (**C**) and histamine antagonists plus morphine (**D**) on the orofacial pain induced by formalin. The time of face rubbing was recorded 10 min after intrahippocampal microinjections of naloxone and histamine antagonists and 5 min after intra-hippocampal microinjection of morphine and histamine. In the case of histamine and morphine, histamine and morphine were microinjected 6 and 4 min before recording of face rubbing; * $p < 0.05$ as compared to normal saline treated group; † $p < 0.05$ as compared to other groups; ‡ $p < 0.05$ as compared to morphine (0.5 μg) treated group

treated groups ($F(4,25) = 5.075$, $p < 0.05$, one-way ANOVA). In the second phase of formalin-induced pain, intra-hippocampal microinjection of histamine at doses of 0.5, 1 and 2 μg with morphine (0.5 μg) produced antinociceptive effects when compared with normal saline and morphine (0.5 μg) treated groups ($F(4,25) = 9.777$, $p < 0.05$, one-way ANOVA) (Fig. 4B). Intra-hippocampal microinjection of naloxone (4 μg) significantly prevented antinociceptive effects of histamine in both first ($F(3,20) = 6.957$, $p < 0.05$, one-way ANOVA) and second ($F(3,20) = 14.389$, $p < 0.05$, one-way ANOVA) phases of formalin-induced orofacial pain (Fig. 4C). Intra-hippocampal microinjections of pyrilamine and ranitidine at the same dose of 4 μg significantly inhibited morphine-induced antinociceptive effects in the first ($F(3,20) = 3.766$, $p < 0.05$, one-way ANOVA) and second ($F(3,20) = 3.970$, $p < 0.05$, one-way ANOVA) phases of formalin-induced orofacial pain (Fig. 4D).

Discussion

The present study shows that the subcutaneous injection of formalin into the upper lip produced a distinct biphasic pattern in the face rubbing performed by ipsilateral forepaw. Subcutaneous injection of formalin at the concentrations of 0.2–10% into the upper lip region induced a biphasic pattern in the face rubbing in rats [8]. During the orofacial formalin test, two distinct phases due to different mechanisms of nociception are produced, the first phase is associated to direct stimulation of C-nociceptors, whereas the second phase reflects integration between nociceptors and spinal and brainstem signaling [10]. Face rubbing with the ipsilateral forepaw due to formalin injection into the upper lip, has been mentioned as a specific nociceptive response [34]. Some researchers have reported vocalization, grooming and scratching due to electrical, mechanical, thermal and chemical (capsaicin, formalin) stimulation of the orofacial region in rats [1, 34, 46, 47]. However, nociceptive behavior obtained from the present study is in agreement with other investigations [5, 8, 34].

In this study intrahippocampal microinjection of histamine produced antinociception and histamine H_1 and H_2 antagonists, pyrilamine and ranitidine, respectively, prevented histamine-induced antinociception. The cell bodies of the histaminergic neuron system are concentrated in the tuberomammillary nucleus (TMN) of the hypothalamus, and send out axons to innervate the entire central nervous system [4, 37]. Hippocampal formation receives a weak to moderate histaminergic innervation, and the distribution of histamine H_1 and H_2 receptors in various parts of limbic system have been well documented [4, 37]. There is no report regarding the hippocampal changes of histamine and its H_1 and H_2 receptors in acute and chronic pain states. In other brain nuclei such as striatum, Huang et al. [20] reported an increase of histamine concentrations in a rat model of neuropathic pain. Moreover, an increase of histamine concentrations in the PAG was reported after intraplantar injection of paraformaldehyde solution in rats [31]. The involvement of brain histamine as a modulator of pain has been investigated by injection of the amine into the ventricles of brain or by microinjection of the amine into the brain nuclei. Central histamine H_1 and H_2 receptors involvement in the histamine-induced antinociception was reported in formalin test in mice and rats [29, 43], and in acute trigeminal pain in rats [42]. Microinjection of histamine into the PAG or into the dorsal raphe nucleus (DRN) produced antinociception in the rat hot plate test. Histamine-induced antinociception was inhibited by central pretreatment with temelastine (an antagonist of histamine H_1 receptors) and tiotidine (an antagonist of histamine H_2 receptors) [44]. In addition, microinjections of histamine into the dentate gyrus, a part of hippocampal formation, decreased licking/biting and shaking of the formalin-injected paw, and prior microinjections of chlorpheniramine (an antagonist of histamine H_1 receptors) and ranitidine into the same site inhibited the suppressive effects of histamine [22].

In the present study, intra-hippocampal microinjection of morphine produced antinociceptive effect in the orofacial formalin test in rats, and naloxone reversed antinociception induced by morphine. The hippocampus expresses a high density of opioid receptors and is an important site of opioid action [14]. There is no report showing the changes in hippocampal opioid receptors under pain induced by subcutaneous injection of formalin in the lip. Using whole brain functional magnetic resonance imaging (fMRI), it has been reported that intraplantar injection of formalin (5%, 50 μl) increases blood oxygenation level-dependent (BOLD) signals in both cortical (cingulated and motor cortex) and subcortical (hippocampus, cau-

date putamen, PAG and thalamus) areas of brain [38]. In other regions of the brain, microinjections of morphine and naloxone have been used to explore the role of endogenous opioid system in supraspinal modulation of trigeminal pain. Microinjection of morphine into the subnucleus oralis (SNO), the rostral division of the spinal cord trigeminal nucleus, reduced face rubbing induced by *sc* injection of formalin in the upper lip in rats [25]. Naloxone reversed the antinociceptive effect of morphine when microinjected into the SNO [25]. Morphine, when microinjected into the nucleus raphe magnus (NRM) and nucleus reticularis paragigantocellularis (NRPg) of brain, produced analgesic effects in the orofacial formalin (chemical) and thermal pain tests in rats, respectively [15, 35].

In this study, histamine produced a synergistic effect on morphine in producing analgesia at the level of the hippocampus. Moreover, histamine H_1 and H_2 blockers inhibited the antinociception induced by morphine. These data therefore indicate that hippocampal histamine, through its H_1 and H_2 receptors, might have an excitatory effect on morphine function, and that opioid receptors might interact with histaminegic inhibitory effect on pain. Biochemical, pharmacological and behavioral findings have revealed that morphine, through opioid receptors, influences both release and function of histamine in the central nervous system. Morphine acts through μ-opioid receptors [45]. Opiate receptors, predominantly μ-, but not δ- and κ-opioid receptors are involved in the release of histamine from various brain regions. Morphine increased the release of histamine from nerve terminals in the PAG and striatum, and morphine induced-histamine release was blocked by naltrexone (an opioid antagonist) in the striatum [3, 6]. The *sc* injection of a selective κ-agonist, U-50, 488 and *icv* injection of a selective δ-agonist, [D-Pen2, D-Pen5]enkephalin, did not affect the release of histamine from the striatum in rats [6]. At the TMN, where the cell bodies of histaminergic neuron system are located, morphine depolarized and increased the firing of histaminergic neurons [17]. On the other hand, histamine H_1 and H_2 receptors may interact with morphine-induced antinociception. Using thermal (hot plate and tail flick), mechanical (tail pressure) and chemical (formalin and capsaicin) tests of nociception, the antinociceptive effects of intrathecally- and *icv*-administered morphine were enhanced in the histamine H_1 and H_2 receptor gene knockout mice, respectively [27, 28]. Moreover, pyrilamine (a centrally acting histamine H_1 receptor antagonist) potentiated, whereas zolantidine (a centrally acting histamine H_2 receptor antagonist) inhibited *icv*-injected morphine-induced antinociception in the hot plate test in the mouse [40]. In the present study, naloxone reversed histamine-induced antinociception. Naloxone is a competitive antagonist of μ-, κ- and δ-opioid receptors with higher affinity for the μ-opioid receptors [45]. Naloxone influences many functions of histamine in the central nervous system. Like the mepyramine and cimetidine, *icv* injection of naloxone antagonized the corticosterone secretion induced by *icv* injection of dimaprit (an agonist of histamine H_2 receptors) and histamine in rats [19]. Naloxone also inhibited the hypertensive response induced by *icv* injection of histamine in rats [26]. In addition, microinjection of naloxone into the PAG reversed the antinociceptive effect induced by the microinjection of histamine into the same site [44]. There is not any report describing the interaction between morphine and histamine at the level of the hippocampus, therefore, the results presented here could be the first report showing the interaction between morphine and histamine at the level of the hippocampus in mediating orofacial region pain.

In conclusion, the results of the present study suggest that at the level of the hippocampus the histaminergic and opioidergic systems interact with each other in mediating the pain originating from orofacial structures. Hippocampal opioid and histamine H_1 and H_2 receptors are involved in the interaction between histamine and morphine.

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