Involvement of dopamine receptors within the dorsal hippocampus in suppression of the formalin-induced orofacial pain

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\textbf{A B S T R A C T}

It is widely established that the dopaminergic system has profound effects on pain modulation in different regions of the brain including the hippocampus, the salient area for brain functions. The orofacial region is one of the most densely innervated (by the trigeminal nerves) areas of the body susceptible to acute and chronic pains. In this study, we tried to examine the effects of dopamine receptors located in the dorsal hippocampus (CA1) region upon the modulation of orofacial pain induced by the formalin test. To induce orofacial pain in male Wistar rats, 50 μl of 1% formalin was subcutaneously injected into the upper lip. In control and experimental groups, two guide cannulae were stereotaxically implanted in the CA1, and SKF-38393 (0.25, 0.5, 1 and 2 μg/0.5 μl saline) as a D1-like receptor agonist, SCH-23390 (1 μg/0.5 μl saline) as a D1-like receptor antagonist, Quinpirole (0.5, 1, 2 and 4 μg/0.5 μl saline) as a D2-like receptor agonist and Sulpiride (3 μg/0.5 μl DMSO) as a D2-like receptor antagonist or vehicles were microinjected. For induction of orofacial pain, 50 μl of 1% formalin was subcutaneously injected into the left side of the upper lip. Results indicated that SKF-38393 at the dose of 1 and 2 μg significantly reduced pain during the first and second phases of observed pain while SCH-23390 reversed such analgesic effect. Moreover, there is a significant difference between groups in which animals received 2 and 4 μg quinpirole or vehicle in the first phase (early phase) of pain. The three high doses of this compound (1, 2 and 4 μg) appeared to have an analgesic effect during the second (late) phase. Furthermore, Sulpiride could potentially reverse the observed analgesic effects already induced by an agonist. Current findings suggest that the dorsal hippocampal dopamine receptors exert an analgesic effect during the orofacial pain test.

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1. Introduction

Although hippocampus is a brain region primarily appreciated for its role in learning and memory function, cumulative and empirical evidence has postulated its great contribution to many other behaviors including anxiety, goal-directed behaviors, information processing, olfactualion and spatial navigation and orientation (Hansen and Manahan-Vaughan, in press; Kenney and Gould, 2008). Recent studies have strongly substantiated that the morphological alterations and gene expressions in the hippocampus which occur during induction of neuropathic pain refer to the involvement of the hippocampus in the process of pain sensation (del Rey et al., 2011; Gao et al., 2012; Soleimannejad et al., 2006). It has been shown that the intra-hippocampal GABAergic inhibitory interneurons mediate formalin-induced suppression of the dorsal hippocampal (CA1 region) pyramidal cell discharge (Zheng and Khanna, 2008) while morphine reverses the formalin-induced CA1 pyramidal cell inhibition through an effect on the hippocampal neural processing (Khanna and Zheng, 1999).

The complex multifaceted nature of pain necessitates the contribution of numerous factors in such experience. Several neurotransmitter systems are involved in the modulation of nociceptive information. Amongst them, the possible role of GABA, histamine and dopamine systems has appealed to many researchers’ interest (Nowak et al., 2013). Animal studies have proposed the participation of dopaminergic system in chronic and acute pain processing (Carta et al., 1999; Hagelberg et al., 2003a) for which the role of the hippocampal dopaminergic system is well articulated. Dopamine is the predominant catecholamine neurotransmitter in the mammalian brain. Given the fact that many pathological conditions are known to be associated with dopaminergic transmission, this neurotransmitter system turned to the focus of some investigations over the past years (Missale et al., 1998). Dopamine agonists such as apomorphine, d-amphetamine and cocaine produce analgesia during the formalin test in rats (Haghparast et al., 2012; Zarrindast et al.,
1999). Dopamine D1 and D2 receptors are shown to mediate the inhibitory role of dopamine in animal models of persistent pain (Hagelberg et al., 2003a). Dopamine D2 receptor agonist (quinpirole for instance) enhances the antinociceptive effect of morphine, whereas the blockade of D1/D2 dopamine receptors within the nucleus accumbens reduces the antinociceptive effects of cannabinoid receptor agonist in the basolateral amygdala (Haghabrast et al., 2012; Tricklebank et al., 1984; Zarindsay et al., 1999). At molecular level, the hippocampal dopaminergic signal transduction molecular markers such as CREB are known to be increased once the neuro-pathic pain is triggered (Hebert and O’Callaghan, 2000).

The orofacial region is one of the most densely innervated (by the trigeminal nerves) areas of the body thus a common site for acute and chronic pains (Raboison and Dallel, 2004). The orofacial formalin test was introduced and developed successfully by Clavelou and colleagues (Clavelou et al., 1989, 1995) currently considered as a reliable way of producing and quantifying nociception in the trigeminal region of the rat. In chronic orofacial pain, decreased DOPA uptake has been observed in the different brain regions including the hippocampus (Hagelberg et al., 2003a). In the current study, we aimed to scrutinize the effects of dopamine and its dorsal hippocampal receptors of rats’ brain upon pain responses induced by the subcutaneous injection of formalin in the upper lip (orofacial formalin test). The study was designed to investigate the possible role of the hippocampal dopamine receptors in the modulation of orofacial pain.

2. Materials & methods

2.1. Animal

Adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 230–280 g were used in these experiments. Animals were housed in groups of three per cage in a 12/12 h light/dark cycle (light on between 7:00 a.m. and 7:00 p.m.) with access to chow and tap water. The animals were randomly allocated to different experimental groups. Each animal was used only once. Rats were habituated to their new environment and handled for 1 week before the experimental procedure started. All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti and Rafsanjan Universities of Medical Sciences.

2.2. Drugs

In our study the following drugs were used: (±)-1-Phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol hydrochloride, SKF-38393, as a D1-like receptor agonist, R(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, SCH-23390, as a D1-like receptor antagonist, (4aR,8aR)-5-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]quinoline, quinpirole, as a D2-like receptor agonist, (±)-5-(aminosulfonyl)-N-[(1-ethylpyrrolidin-2-yl)[methyl]-2-methoxybenzamide, sulpiride, as a D2-like receptor antagonist. Control animals received normal saline or 10% dimethyl sulfoxide, DMSO (Sigma-Aldrich, Germany) as a vehicle.

2.3. Stereotaxic surgery

Rats were anesthetized by intraperitoneal (i.p.) injection of xylazine (10 mg/kg) and ketamine (100 mg/kg), and were placed in the stereotaxic device (Stoelting, USA). Lidocaine with epinephrine (0.2 ml) was injected in several locations around the area that the incision was to be made. Our incisions were made along the midline, and the area surrounding bregma was cleaned and dried following the retraction of the scalp. Stainless steel guide cannulae were stereotaxically implanted bilaterally into the CA1 region of the hippocampus. The coordinates for this region determined by rat brain atlas (Paxinos and Watson, 2007) were AP = −2.8 mm caudal to bregma, Lat = −1.5 mm lateral to midline and DV = −2.8 mm ventral from the skull surface (cannula 23-gauge, 11 mm in length, guide cannulae were 1 mm above the appropriate injection place). Jewelers’ screws and dental acrylic cement were applied to secure the cannulae. After the cement was completely dried and hardened, two stainless steel stylets were used to occlude the guide cannulae during recovery period. Penicillin-G 200,000 IU/ml (0.2–0.3 ml/rat, single dose, intramuscular) was administered immediately after surgery. Animals were individually housed and allowed to recover for 5–7 days before the experiments.

Microinjections were performed by 30-gauge injector cannulae (1 mm below the tip of the guide cannulae). Polyethylene tubing (PE-20) was used to attach injector cannula to the 1-μl Hamilton syringe. The animals were gently restrained in hand, stylets were removed from the guide cannulae and replaced by 30-gauge injector cannulae through which drugs were infused. All drug (SKF-38393, SCH-23390, quinpirole and sulpiride) solutions were administered slowly at a total volume of 0.5 μl over a period of 60 s. Injection needles were left in place for an additional 60 s to prevent the backflow of drugs, which was then followed by reinserting the stylets into the guide cannulae.

2.4. Nociceptive testing (orofacial formalin test)

Orofacial formalin test was performed according to the method described by Raboison and Dallel (2004). A plexiglass observation chamber (30 × 30 × 30 cm) was prepared with a mirror based at 45° below the floor to allocate an unobstructed view of the experimental region. Rats were held about 30 min in chambers for adaptation. Then, a 29-gauge injection needle was used to inject 50 μl of 1% diluted formalin into the left side of the upper lip subcutaneously just lateral to the nose. The rat returned into the observation chamber immediately after the formalin injection. Index of nociception was considered as a time each animal spent face rubbing with the ipsilateral forepaw. This time was recorded with a stopwatch in a repeated 3-min block over a period of 45 min. Two definite distinct phases have been induced in formalin injection. In this study, data obtained between 0 and 3 min postformalin injection were considered as the first (early or acute) phase and data obtained between 15 and 33 min after formalin injection correspond to the second (late or chronic) phase. All the observers were blind to the study protocol.

2.5. Experiment design

2.5.1. Effects of the intra-CA1 administration of D1-like agonist on orofacial pain modulation

In order to observe the effects of D1-like agonist in the CA1 region on orofacial pain modulation, four different doses (0.25, 0.5, 1 and 2 μg/0.5 μl Saline) of SKF-38393, D1-like receptor agonist, were administered to this region while the control group received normal saline. Then, orofacial formalin test was performed and data were collected in two phases of pain. To specify the effects of D1-like receptor agonist on orofacial pain, we used pre-treatment of SCH-23390, D1-like receptor antagonist, with 0.5 μg dose prior to the administration of SKF-38393 at the dose of 1 μg. The orofacial pain test was then repeated. Control groups received normal saline in all respective experiments.

2.5.2. Effects of the intra-CA1 administration of D2-like agonist on orofacial pain modulation

To determine the effects of D2-like agonist in the CA1 region on orofacial pain modulation, four different doses (0.5, 1, 2 and 4 μg/0.5 μl saline) of quinpirole, D2-like receptor agonist were administered into this region. The early and late phases of orofacial pain process were examined during the formalin test. We used 3 μg of sulpiride, D2-like receptor antagonist, as a pre-treatment before the administration of quinpirole (at the dose of 2 μg) to specify the role of D2-like receptor
in the CA1 region of the hippocampus. The orofacial formalin test was then repeated. Control groups received normal saline and 10% DMSO in this set of experiments.

2.6. Histological verifications

Upon the completion of the tests, animals were deeply anesthetized with ketamine and xylazine followed by transcardial perfusion with 0.9% saline and 10% formalin solution. The brains were removed, post-fixed and sliced coronally in 50 μm sections through the cannulae placements. The neuroanatomical location of cannulae tip placements (Fig. 1) was confirmed using rat brain atlas (Paxinos and Watson, 2007). Only the data for the animals with correct cannulae placements were considered in our analysis.

2.7. Statistics

The face rubbing time in each block is expressed as mean ± SEM (standard error of mean). Data were processed by commercially available software GraphPad Prism® 5.0. The repeated measures two-way analysis of variance (ANOVA) followed by post-hoc analysis Bonferroni test were used in order to compare the face rubbing time obtained in all time set intervals. The face rubbing time values in the early and/or late phases of orofacial pain responses in all groups were subjected to the one-way ANOVA followed by protected Newman–Keuls test for multiple comparisons. P-values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Nociceptive behavior

Subcutaneous injection of normal saline in the upper lip of the rats produced slight pain in the first 3-min interval time. To stimulate an orofacial pain, we injected diluted formalin subcutaneously in the upper lip and the typical pattern of face-rubbing was observed to measure the induced pain behaviors. Repeated measures two-way ANOVA followed by Bonferroni test [Formalin effect: \( F(1,195) = 447.3, P < 0.0001 \); Time effect: \( F(14,195) = 18.69, P < 0.0001 \); Formalin × time effect: \( F(14,195) = 17.83, P < 0.0001 \)] revealed a significant difference in the face rubbing time (sec) among the 3rd, 18th, 21st, 24th, 27th, 30th and 33rd min intervals with the other time blocks of the experiment after the injection of formalin representing a biphasic time course in the formalin-induced nociceptive behavior (Fig. 2). The first phase was initiated immediately after the subcutaneous injection of formalin and declined in about 9 min, while the second phase began 18 min after formalin injection and declined at the end of the experiment.

3.2. Effects of the intra-CA1 administration of D1-like receptor agonist on formalin-induced orofacial pain

To distinguish the effects of SKF-38393 (D1-like receptor agonist), four different doses (0.25, 0.5, 1 and 2 μg) were administrated into the CA1 region while the control group received normal saline. One-way

![Fig. 1. Three coronal schematic sections of rat’s brain showing the histological reconstruction of the injection sites into the dorsal hippocampus (CA1 region). Dots indicate the location of needle injections (Paxinos and Watson, 2007).]
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Fig. 2. The time-course responses of orofacial pain-related behaviors after subcutaneous injections of 1% formalin or normal saline in the upper lip in rats. Immediately after saline and formalin administrations, for each rat, the duration of face rubbing with the ipsilateral paw was recorded. Each point represents the mean ± SEM (n = 7–8). * P < 0.05 and ** P < 0.01 indicate significant difference as compared with the previous 3-min block in normal saline- or formalin-treated animals. † P < 0.05, †† P < 0.01 and ††† P < 0.001 indicate significant difference as compared to the respective 3-min block in normal saline group.

ANOVA followed by Dunnett’s multiple comparison test showed that SKF-38393 (at the dose of 1 and 2 μg) significantly reduces the formalin-induced orofacial pain in the first phase [F(4,34) = 3.547, P = 0.0175; Fig. 3A left panel] and the second phase [F(4,34) = 3.547, P = 0.0175; Fig. 3A left panel]. There was no significant difference between the animals treated with other doses of SKF-38393 and saline-treated groups.

To study the role of the D1-like receptor in observed antinociceptive effects, SCH-23390 (0.5 μg) as a D1-like receptor antagonist was administered prior to SKF-38393 (1 μg) administration. The obtained data were analyzed through one-way ANOVA followed by Newman–Keuls multiple comparison test. As shown in Fig. 3B, there is a significant difference in the face rubbing time between SCH-23390-, SKF-38393- and saline-treated groups in the first [F(3,27) = 3.943, P = 0.0203; Fig. 3B left panel] and second phase [F(3,27) = 6.786, P = 0.0018; Fig. 3B left panel]. Therefore, antinociceptive effects were shown to be fully suppressed following pre-treatment with antagonist. Nonetheless, no significant difference in the face rubbing time was observed between antagonist- and saline-treated groups.

3.3. Effects of the intra-CA1 administration of D2-like receptor agonist on formalin-induced orofacial pain

To examine the effects of quinpirole (D2-like receptor agonist), four different doses (0.5, 1, 2 and 4 μg) were administered in the CA1 region while the control group received normal saline. One-way ANOVA followed by Dunnett’s multiple comparison test revealed a significant difference in the face rubbing time as compared to groups which received 1, 2 and 4 μg of quinpirole and the saline control group (Fig. 4A right panel). Face rubbing time was decreased significantly in all mentioned groups in comparison to controls. In addition, to test the role of D2-like receptors in analgesic effects, sulpiride (3 μg) as a D2-like receptor antagonist was administered into the CA1 region prior to the treatment with quinpirole (2 μg). One-way ANOVA followed by Newman–Keuls multiple comparison test demonstrated a difference in face rubbing time between sulpiride–quinpirole and quinpirole-treated groups during the first [F(3,27) = 7.494, P = 0.001; Fig. 4B left panel] and second phase [F(3,27) = 5.784, P = 0.0004; Fig. 4B left panel]. Meanwhile there was no significant difference in the face rubbing time between antagonist- and DMSO-treated groups. The antinociceptive effect of quinpirole was completely reversed by antagonist pre-treatment.

4. Discussion

This study was performed to examine the role of dopamine receptors located in the dorsal hippocampus (CA1) region in pain responses induced by the subcutaneous injection of formalin. The major findings were: (a) SKF-38393, as a D1-like receptor agonist, had analgesic effects both during the first and second phases of pain induced by the formalin test while SCH-23390, as a D1-like receptor antagonist, reversed the antinociceptive effects of SKF-38393; (b) Quinpirole, as a D2-like receptor agonist, also produced analgesia in the first and second phases of pain induced by subcutaneous injection of formalin and (c) Sulpiride, as a D2-like receptor antagonist, abrogated the quinpirole effect.

Reduction of formalin-induced pain via SKF-38393 administration suggests involvement of dopamine D1-like (including D1 and D5) receptors in pain modulation. As demonstrated in our work, 1 and 2 μg of SKF-38393 caused analgesia in both first and second phases of formalin-induced pain sensation in upper lip of rat indicating that D1-like receptor agonist considerably reduced pain. The analgesic effect in the second phase of formalin-induced orofacial pain was more
significant in comparison with that of the first phase. Although the first phase of pain was significantly diminished in rats receiving 1 and 2 μg of agonist compared to those which received saline, more pronounced effects were seen in the second phase indicating that D1-like receptors in the CA1 region of the hippocampus may play a crucial role in antinociceptive effects, mostly in inflammatory pain. In our next experiment, rats were pretreated with SCH-23390 as a D1-like receptor antagonist, to specify the role of D1-like receptors in observed analgesic effects. Different neurotransmitters and neuromodulators play significant roles in pain modulation within the hippocampus. For example, Pilocarpine as a cholinergic agent, Muscimol, GABAergic agent, and morphine, opioidergic agent, caused antinociception in shock-induced pain response in guinea pigs (Favaron Mendes and Menescal-de-Oliveira, 2008). Sensory information including acute and chronic pain ascends from orofacial structures and is transmitted via the trigeminal nerve up to the higher regions such as the hippocampus (Takemura et al., 2006). In the orofacial pain model, there is a biphasic pattern of the face rubbing behavior produced by the subcutaneous injection of 0.2–10% of formalin into the upper lip (Clavelou et al., 1995). The analgesic effects were observed at lower doses of the agonist in the second phase in comparison with the first phase, it might be inferred that the D2-like agonist was potentially involved in inflammatory and chronic pain processes. To clarify the specific role of D2-like receptors in the observed analgesic effect, rats were pre-treated with Sulpiride, as a D2-like receptor antagonist. Data obtained from this experiment clearly demonstrated that sulpiride could reverse the antinociceptive effect of quinpirole suggesting that this agonist plays its role through D2-like (including D2, D3 and D4) dopamine receptors. In addition, there was a significant difference between the agonist-treated and antagonist pre-treated groups showing that sulpiride completely reverses the antinociceptive effect of quinpirole. Dopaminergic systems are involved in pain modulation in some parts of the brain such as the cortical, limbic and striatal regions (Altier and Stewart, 1998; Burkey et al., 1999; Lin et al., 1981). Earlier works have demonstrated that dopamine acts through 5 receptors divided into two groups of D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors (Missale et al., 1998; Neve et al., 2004). There are a number of studies substantiating that dopaminergic systems are involved in pain modulation in different areas of the brain (Lin et al., 1981; Magnusson and Fisher, 2000; Paalzow and Paalzow, 1983). Intra-striatum or intra-cerebroventricular administration of non-selective dopamine receptor agonists are known to decrease the pain responses (Ben-Sreti et al., 1983; Lin et al., 1981). It has been shown that the tonic pain may be decreased with increased dopamine release in the nucleus accumbens and that the administration of dopamine antagonist can inhibit the antinociceptive effects of dopamine release (Altier and Stewart, 1998; Gear et al., 1999). In support of the involvement of dopamine receptors in nociception, it was reported that dopamine receptors suppress constant pain pathway (Morgan and Franklin, 1991), and the left putamen D2 receptor accessibility is enhanced in patients with atypical facial pain (Hagelberg et al., 2003a). Moreover, patients with burning mouth syndrome have higher dopamine receptors representing the modulatory role of dopamine receptors and the dopaminergic system (Hagelberg et al., 2003b). High pain sensitivity correlates with the low dopaminergic neurons activity and vice versa (Treister et al., 2009). It has also been documented that dopamine blocks the electrical activity of pain excitation, and improves the activity of pain-inhibitory systems in morphine-dependent rats (Zhang et al., 2012).

The hippocampus is known to play a crucial role in several cognitive and non-cognitive functions such as learning and memory, stress, immuno- and pain modulation (Kennedy and Gould, 2008; Khalilzadeh et al., 2010; Khanna et al., 2004; Yang et al., 2008). There are several studies highlighting the role of the hippocampus in pain modulation. For instance, the hippocampal (CA1) injection of MK801, a competitive NMDA receptor antagonist is shown to suppress the second phase of the formalin-induced pain in rats suggesting the involvement of the CA1 region in pain modulation (Soleimannejad et al., 2007). The synaptic transmission along the dentate-CA3-CA1 axis is shown to be influenced by formalin-induced persistent nociception (Khanna et al., 2004). Different neurotransmitters and neuromodulators play significant roles in pain modulation within the hippocampus. For example, Pilocarpine as a cholinergic agent, Muscimol, GABAergic agent, and morphine, opioidergic agent, caused antinociception in shock-induced pain response in guinea pigs (Favaron Mendes and Menescal-de-Oliveira, 2008). Sensory information including acute and chronic pain ascends from orofacial structures and is transmitted via the trigeminal nerve up to the higher regions such as the hippocampus (Takemura et al., 2006). In the orofacial pain model, there is a biphasic pattern of the face rubbing behavior produced by the subcutaneous injection of 0.2–10% of formalin into the upper lip (Clavelou et al., 1995). The analgesic effects in the formalin test have also been observed following the administration of lidocaine into the dentate gyrus (McKenna and Melzack, 1992). The orofacial pain in humans is proposed to be related to the dopaminergic system dysfunction in the basal ganglia (Jaaskelainen et al., 2001). Dopamine receptors of the basal ganglia,
cerebral cortex and mid brain appear to be quite abundant while their expression in the hippocampus is by far less (Hall et al., 1994; Khan et al., 1998). It seems that D1-like agonists have an affinity toward D1 and D5 receptors and D2-like agonists toward the D2, D3 and D4 receptors (Missale et al., 1998). In some investigations, SKF 38393 and quinpirole have been used as non-selective dopamine receptor agonists (Belinsky et al., 2013; Manrique-Maldonado et al., 2013; Rossato et al., 2013), thus more studies seem to be required to specifically determine the effects of each type of dopamine receptors on orofacial pain. Finally, we demonstrated that dopamine receptors in the dorsal hippocampal (CA1) region could exert an analgesic effect during the orofacial pain test. However, more investigations need to clarify the exact pattern of the involved pain pathways within this region.

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References

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References

Alteri N, Stewart J. Dopamine receptor antagonists in the nucleus accumbens attenuate analgesia induced by ventral regional area substance P or morphine and by nucleus accumbens amphetamine. J Pharmacol Exp Ther 1998;285:208–15. Belinsky GS, Sirois CL, Rich MT, Short SM, Moore AR, Gilbert SE, et al. Dopamine receptors expression in the hippocampus is by far less (Hall et al., 1994; Khan et al., 1998). The authors would like to thank Dr Mohammad Torabi Nami for his comments and editing our manuscript. This study was supported by a grant from the Rafsanjan University of Medical Sciences, Rafsanjan, Iran.