Original Article

Involvement of Basolateral Amygdala Dopamine D1 Receptors in the Acquisition and Expression of Morphine-Induced Place Preference in Rats

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Abstract

Background: In the present study, the effects of intra-basolateral amygdala (BLA) blockade of dopamine D1 receptor on morphine-induced conditioned place preference (CPP) were investigated in male Wistar rats. **Materials and Methods:** A 5-day CPP paradigm was used. Morphine was injected subsequently at effective (5 mg/kg) and ineffective (0.5 mg/kg) doses. SCH 23390 (0.5– μg/rat), as a selective D1 receptor antagonist, was microinjected bilaterally into the BLA. **Results:** Effective dose of morphine induced a significant CPP, and increased the locomotor activity during the testing phase. The results showed that morphine-induced CPP was significantly suppressed by D1 receptors antagonist in BLA in the acquisition phase and caused an aversion even at high doses. The antagonist also significantly prevented CPP expression. Morphine increased the motor activity, but the D1 receptors blockade, significantly reduced it. **Conclusions:** The findings of this study suggest a possible role for BLA dopamine D1 receptors in reward responses in morphine dependency.

Keywords: *Addiction, basolateral amygdala, dopamine-D1 receptor, morphine*

Introduction

Opioid analgesics are used to treat chronic pain, but it has important side effects such as tolerance, abnormal behaviors, and ultimately addiction. Patients first use opiates to relieve their pain, but over time they must increase the dose of these drugs.[1] According to the report of the World Health Organization, the number of deaths due to the overdose of opioids has significantly increased during these years.[2] Long-term treatment with morphine causes tolerance and also causes symptoms of withdrawal syndrome in patients. As a result, its use has been tried to be limited in the clinic.[3,4]

Addictive substances have been shown to cause long-term changes in brain function, and exert their effects by activating various mechanisms, including activating the mesolimbic dopamine pathway.[5] This pathway that mediates pleasure in the brain and has function in emotion and reward systems, originates in the ventral tegmental area (VTA), and innervates the amygdala, pyriform cortex, lateral septal nuclei, and the nucleus accumbens (NAc).[6]

Until recently, it was believed that the amygdala was only involved in aversive learning and fear conditioning, but recent studies have shown that the amygdala is also very important in reward responses.[7] The amygdala is also important in many behavioral disorders such as addiction, autism, and anxiety.[8] The amygdala is very important in reward responses and studies showed that lateral amygdala (LA) lesions prevent amphetamine conditioned place preference (CPP),[9] and central amygdala (CeA) lesions prevent conditioned responses to reward factors.[10] The basolateral amygdala (BLA) has different neural circuits involved in positive and negative stimuli.[11] These circuits are involved in responding to reward factors, including natural and pharmacological rewards, as well as reward-related behaviors.[12,13]

There are four main dopaminergic neural circuits in the mammalian nervous system; nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways.[14] These pathways are involved in learning and memory, motor functions, attention, controlling the secretion of the pituitary and hypothalamic endocrine systems.[6] The mesolimbic pathway plays an important role in the reward system.[15] Dopamine

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receptors are divided into two subgroups based on structural and pharmacological characteristics. D1-like receptors including D1,[16] D5[17] receptors, stimulate and increase intracellular levels of cyclic AMP. D2-like receptors that inhibit intracellular cyclic adenosine monophosphate (cAMP) levels, and are include, D2,[18] D3,[19] and D4[20] receptors. D1 and D2 receptors are abundantly expressed in the brain.[17,21] It has previously been reported that both systemic and local injection of the D1 receptors (D1R) antagonist (SCH23390) into the NAc inhibits cocaine-induced CPP.[22] It was also found that injection of SCH23390 into the CeA or the CA1 region of the hippocampus reduces morphine-induced CPP.[23,24] However, it has been revealed that blockade of the D1R in NAc, or dorsal hippocampus, induces conditioned place aversion[25] or reduces CPP, respectively.[26,27]

Previous studies have shown conflicting roles of D1Rs in the development of reward-related responses in the reward pathways. Therefore, due to the role of the BLA in creating motivational responses and the lack of sufficient documentation regarding the involvement of D1Rs in this region, our aim in this study was to evaluate the role of BLA D1Rs in morphine addiction and dependency in the rat.

Materials and Methods

Subjects

Subjects were male adult Wistar rats (Pasteur Institute; Tehran, Iran), weighing 250–300 g. Four animals were kept per cage, in a 12/12 h light/dark cycle, with water and food *ad libitum* and controlled temperature (22°C–25°C). The Ethics Committee of Animal Use of the Isfahan University of Medical Sciences approved the study (IR.mui.MED.REC.1398.369), and all experiments were executed, in accordance with the guidelines for Animal Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23), revised in 2010.

Drugs

The drugs used in this study were morphine sulfate (Temad, Tehran, Iran), SCH-23390 (R (+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, (Sigma: D1 receptor antagonist), all dissolved in 0.9% saline just before the experiments. Morphine was injected subcutaneously. Control animals received vehicle (saline).

Surgery and drug microinjection

Rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) (i.p.), and positioned in a stereotaxic device (Stoelting, USA). Two stainless steel guide cannulae (23 gauge) were bilaterally implanted 1 mm above the BLA (AP = −2.8 mm; L= ±3.6 mm; DV= −8.6 mm),[28] and fixed to the skull with dental cement. Two stainless steel stylets (30 gauge) were inserted into the guide cannula, to be kept free of debris. Each rat was housed individually in the cage and allowed to recover for 5—7 days. For drug microinjections, stylets were withdrawn and 30-gauge injector needles were located 1 mm below the tip of the guide cannula, into the BLA. Subsequently, different doses of the antagonists (0.5, 1, 2, 4 μg/rat) or the vehicle were administered bilaterally in a total volume of 0.6 μl/rat (0.3 μl per site), over 60 s period (n = 6-8).

Apparatus

CPP apparatus consisted of three chambers (A, B, and C). Two large chambers (A and B) with equal size. The walls and floor of the A chamber were black with a grid floor, while they were white and checkered, respectively, with a smooth floor in the B chamber. The C chamber was smaller and it is connected to other chambers by guillotine door. The time animal spent in each chamber and its locomotor activity was recorded by a video track software (ANYmaze), Place conditioning was performed, using a biased procedure, in which the animal was allocated to the nonpreferred chamber, following morphine administration. The behavioral procedure of CPP is done in five continuous days with three distinct phases: preconditioning, conditioning, postconditioning.[29]

Preconditioning

On the 1st day, each rat was put into the C chamber, while the guillotine door was open and the rat is allowed to move freely for 10 min. A video camera was located directly over the apparatus, recording the activity of the animal.

Conditioning

It consisted of a 3-day plan that contained six sessions (3 for saline and 3 for morphine), and each session lasts 30 min. Guillotine door was closed and daily injection was performed in two stages, with a 6 h interval. In the morning of the 2nd and 4th days, after injection of morphine, rats were confined to nonpreferred chamber and in the evening, after injection of saline, to the preferred chamber. On the 3rd day, rats received saline in the morning and morphine in the evening.

Postconditioning

On the 5th day, same to the 1st day, each rat was put into the C chamber for 10 min, while the guillotine door was open. The conditioning score calculated as, the time spent in the morphine-paired chamber on the 5st day minus the spent time at the same chamber on the 1st day.[29]

Locomotor activity

Using the software, ANY maze was evaluated the locomotor activity. The time animal spent in each chamber and its locomotor activity was recorded by a video track

software (ANYmaze). Locomotion was measured as the distance traveled in the CPP device with a scale meter, in the postconditioning phase.

Experimental design

Dose–response curve for morphine

We examined the different doses of morphine (0.5, 2.5, 5, 7.5, and 10 mg/kg, s. c.), on the CPP in this experiment. Rats were given saline (1 ml/kg, s. c), in the vehicle group in both chambers (A and B).

Intra-BLA microinjection of SCH23390

To evaluate the effects of these antagonist on acquisition (during 3-day conditioning phase) and expression (only on the 5th day) of morphine-induced CPP, different doses of SCH23390 (0.5, 1, 2, and 4 μg/rat) combinations of their effective (5 μg/rat) and ineffective (0.5 μg/rat) doses, were bilaterally injected into the BLA, 5 min before subcutaneous injection of morphine. In the saline, paired-chamber was microinjected into the BLA instead of antagonists.

Histology

At the end of the experiments, the rats were deeply anesthetized and perfused transcardially with a 10% formalin solution. Then, the brain was dissected and fixed in 10% formalin for at least 3 days. To verify the position of the cannula in the BLA, transverse sections through the brain were cut, using a freezing microtome, and examined under a microscope[28] [Figure 1].

Statistic

The data were analyzed statistically using one-way ANOVA, following a significant F-value, *post hoc* analyses (Tukey test), and unpaired *t*-test for comparing specific groups. All data are expressed as mean ± standard error of the mean. $P < 0.05$ were considered statistically significant (n = 5–8).

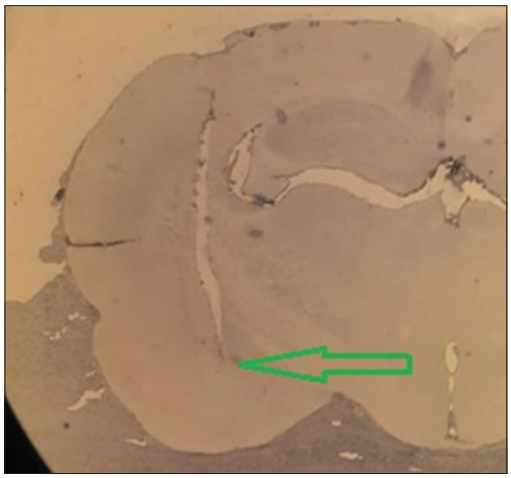

Figure 1: Coronal photomicrograph of microinjection site in the basolateral amygdala

Results

Effect of different doses of morphine on the conditioned place preference

The results showed that there was a significant increase in CPP acquisition in all doses of morphine except 0.5 mg/kg, compared to the saline group (F [5, 47] =6.476; $P < 0.001$), indicating that morphine with doses 2.5, 5, ($P < 0.01$) 7.5, and 10 mg/kg ($P < 0.05$) has induced the CPP [Figure 2a]. Morphine in doses 5, 7.5, and 10 mg/kg increased the locomotor activity in comparison with that of the saline control group [$P < 0.01$, $P < 0.05$ and $P < 0.01$, respectively; Figure 2b].

Effects of blockade of dopamine d1 receptors within the basolateral amygdala on the acquisition of morphine-induced conditioned place preference

Statistical analysis indicated a significant difference in conditioning scores [F (8, 61) =59.086, $P < 0.001$; Figure 3a], and in locomotor activity [F (8, 61) =12.835, $P < 0.001$; Figure 3b], among the groups, in the acquisition of CPP. The results revealed that blockade of dopamine d1 receptors (0.5, 1, 2, and 4 μg/rat) prevented the morphine-induced CPP in rats [$P < 0.001$ in both doses of morphine; Figure 3a] with respect to morphine-vehicle rats and also decreased the locomotor activity, compared to the morphine (0.5

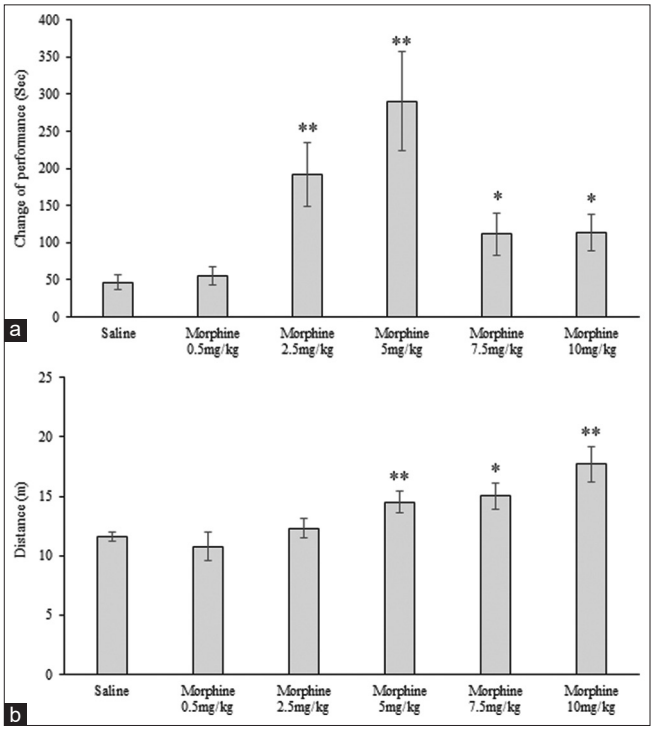

Figure 2: Morphine dose-response curve in the conditioned place preference pattern. The preference of score was calculated as the difference between the time spent in the drug-paired compartment on the 5th and 1st day (a), and locomotor activity on the testing day (b). Data are expressed as mean ± standard error of mean. *$P < 0.05$, **$P < 0.01$ different from the saline control group (n = 6–8)

and 5 mg/kg)-vehicle rats [$P < 0.05$ and $P < 0.001$, respectively; Figure 3b].

Effects of blockade of D1ARs within the basolateral amygdala on the expression of morphine-induced conditioned place preference

Statistical analysis indicated a significant difference in conditioning scores, among the groups, in the expression of CPP [F (3, 29) = 97.06, $P < 0.001$; Figure 4a]. The results revealed that microinjection of D1A (4 μg/rat) within BLA in both morphine groups with doses of 0.5 and 5 mg/kg, decreased expression in CPP [$P < 0.05$ and $P < 0.001$, respectively; Figure 4a] with respect to morphine-vehicle rats. Microinjection of D1A (4 μg/rat) had no effects on locomotor activity [F (3, 29) =2.132, $P = 0.12$; Figure 4b].

Discussion

In this study, same to previous studies,[30] morphine was able to induce CPP, which showed that rats became dependent on morphine. For further evaluation, we used morphine at a dose of 0.5 mg/kg as an ineffective dose and 5 mg/kg as an effective dose. Our results showed that blockade of BLA-D1Rs with different doses of SCH23390 inhibited the acquisition of morphine-induced CPP in a dose-dependent manner, and even at high doses, it was able to cause aversion in both effective and ineffective doses of morphine [Figure 3]. Furthermore, inhibition of D1R in BLA in both effective and ineffective doses of morphine suppressed CPP expression [Figure 4]. This suggests that the BLA dopaminergic system, especially through D1Rs, plays a significant role in mediating and inducing the addictive effects of morphine.

Dopaminergic neurons in the VTA project to the prefrontal cortex (PFC), BLA, and NAc medial shell and core.[31] Studies have shown the presence of dopamine transmission and D1Rs in BLA, and it has been shown that dopamine levels are increased in BLA during learning and in response to stressful stimuli.[32,33] BLA can play a significant role in synaptic plasticity and the development of NAc-induced motivational behaviors by sending glutamatergic projections to NAc in close relation with the dopaminergic system.[13]

The role of the amygdala in reward responses has been shown, and following the amygdala lesions, it has been revealed that these lesions also eliminate reward-based behaviors.[34] Lesion of LA prevents amphetamine-induced CPP[9] and lesions of the CeA inhibit the conditioned orientation responses.[35]

Both mesolimbic and mesocortical dopaminergic systems are involved in emotion-related behavior, including motivation and reward.[36] The dopaminergic projections of this pathway originate in the VTA and then enters to the NAc, amygdala, and other area of the brain.[6] D1Rs are abundant in the mesolimbic pathway and play several

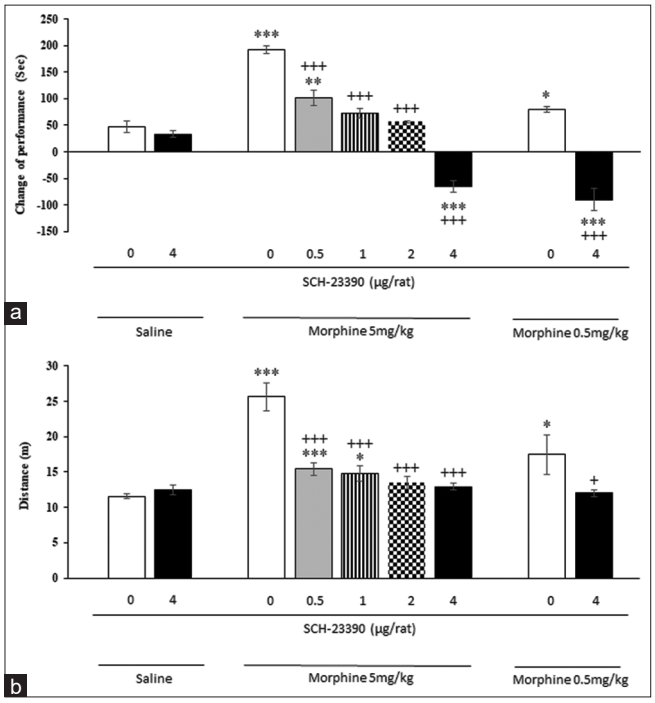

Figure 3: Effect of bilateral administration of dopamine D1 receptor antagonists (SCH-23390) within the basolateral amygdala on the acquisition of morphine-induced conditioned place preference (a), and locomotor activity (b). The change of preference was calculated as the difference between times spent in the drug-paired compartment on the 5th day and 1st day. Data are expressed as mean ± standard error of mean. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ different from the saline-vehicle group. +$P < 0.05$, +++$P < 0.001$ different from the morphine-vehicle group (n = 6–8)

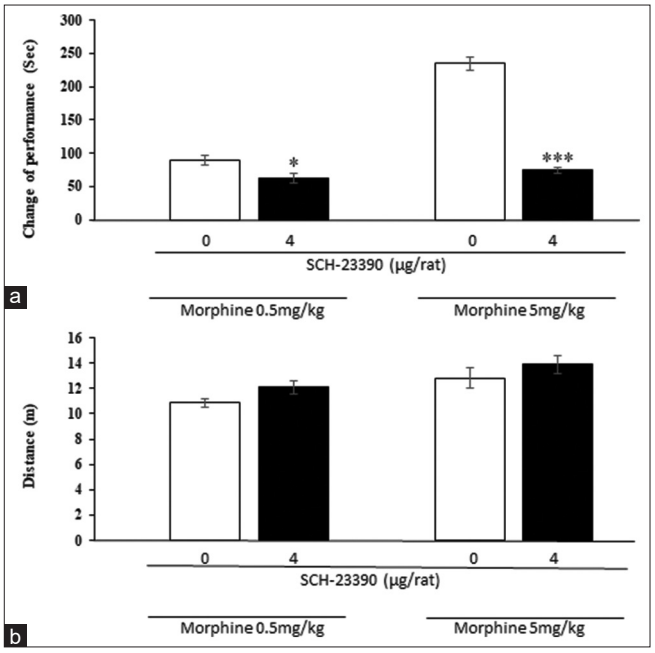

Figure 4: Effect of bilateral administration of dopamine D1 receptor antagonists (SCH-23390) within the basolateral amygdala on the expression of morphine-induced conditioned place preference (a), and locomotor activity (b). The change of preference was calculated as the difference between times spent in the drug-paired compartment on the 5th day and 1st day. Data are expressed as mean ± standard error of mean. *$P < 0.05$, ***$P < 0.001$ different from the morphine (0.5 or 5 mg/kg)-vehicle group (n = 6–8)

roles in generating behavioral responses related to pleasure, reward, and addiction.[37] D1Rs appear to be involved in movement control,[38] and cognitive functions.[39]

It is specified that D1Rs are involved in reward-dependent learning,[40] and blockade of these receptors appears to reduce CPP induction by attenuating and eliminating the rewarding effects of addictive substances. D1Rs in various parts of the brain are essential in drug seeking[40] as well as conditional reward.[41] However, blockade of D1Rs in different areas of the brain and mesocorticolimbic pathways has had conflicting effects on drug dependency. Previous studies have shown that the blockade of D1Rs in some sites in the brain causes conditioned preference aversion[7,42] Antagonizing of these receptors in the pre-limbic cortex, caudate nucleus, putamen, shell part of the NAc (but not the core), changed the seeking behavior of opiates,[43] and in the central part of the amygdala, hippocampus or the NAc reduced expression phase of amphetamine-induced CPP.[44] It also had a reducing effect on ethanol-induced CPP[42] and cocaine-seeking behavior.[45,46] However, in other studies, blockade of D1Rs had no effect on the induction of CPP by morphine[29] and cocaine.[47] In a study, it has been revealed that blockade of D1Rs in the CeA has no effect on cocaine-seeking behavior.[47]

One of the obvious behavioral effects of some addictive substances,[48] same to opioids,[49] is affecting motor activity. In this study, it was found that morphine in effective doses, increased locomotor activity. These increases were significantly suppressed by inhibiting D1Rs in the BLA.

This finding is similar to the studies that show, inhibition of D1Rs reduces the increased motor activity following cocaine and amphetamine application.[47,50] This shows that D1Rs are involved in voluntary movement and motion, and their inhibition causes reduction in movement. However, previous studies have shown that inhibition of D1Rs in the CeA following morphine application has different effects on locomotor activity.[23] This suggests that different regions of the amygdala have different circuits and behavioral effects.

The dopaminergic system innervates different brain areas that are involved in cognitive functions, including working memory and learning.[51] Some of these areas same to NAc are involved in cognitive functions, processes of motivation, movement, and reward.[52] The NAc receives stimulatory glutamatergic inputs from PFC, hippocampus and amygdala, as well as dopaminergic inputs from the VTA.[53,54] Thus, BLA may mediate the effects of morphine to some extent along with the areas involved in locomotor activity.

Conclusions

The results of the present study showed that morphine dependency and addiction can be largely mediated by the BLA. This region has a variety of connections with other areas involved in controlling responses to pleasure and reward, and the dopaminergic system probably manages much of this interaction. D1Rs in BLA plays a significant role in morphine addiction and related behaviors.

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Conflicts of interest

There are no conflicts of interest.

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