Original Article

Effects of Electrical Stimulation and Lidocaine Injection of Lateral Habenula Nucleus in the Addicted Rats with Morphine Self-administration

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Abstract

Background: Addiction is one of the critical problems in public health. The lateral habenula (LHb) is a brain structure that plays an important role in sleep, reward-based decision-making, punishment avoidance, and stress. Based on the function of the LHb in addiction, this study examined the impacts of electrical stimulation (ES) and temporary inactivation of the LHb by lidocaine on the process of morphine addiction. **Methods:** The anesthetized animals were placed in the stereotaxic device. A cannula and electrode were inserted into the LHb for stimulation at both low and high intensities (LI: 25 and HI: 150 μA), and injecting lidocaine, respectively. Then, jugular vein was catheterized. After recovery, an 11-day self-administration protocol was performed. Animals received morphine or saline during each session. Finally, the counts of both active and passive lever presses, along with the instances of self-infusions, were documented and assessed. **Results:** Morphine led to an increase in the number of active lever presses in the morphine group compared to the saline group ($P < 0.001$). HI-ES and lidocaine injection decreased the changes compared to the morphine group ($P < 0.001$). In addition, the number of infusions in the morphine group was higher than the saline group after the 6th day ($P < 0.001$); HI-ES and lidocaine injections reduced the alterations relative to the morphine group ([$P < 0.006$], [$P < 0.001$], respectively). **Conclusion:** The results indicate that HI-ES of the LHb and lidocaine injection into this region reduce morphine self-administration and active lever pressing. These findings underscore the prominent role of the LHb in regulating reward-related behaviors and drug consumption.

Keywords: *Addictive, behavior, electric stimulation, lateral habenula, lidocaine, morphine*

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Introduction

Addiction, a chronic relapsing brain disorder, significantly impacts both individual and public health.[1] Disruptions in brain regions, such as the habenula, can intensify reward-seeking behaviors, leading to addiction.[2] The habenula is an important center for reward and addiction, containing dopaminergic neuron cell bodies that project to other brain regions and influence brain function.[3] Furthermore, the habenular complex establishes an essential pathway between the forebrain and other parts of the brain (midbrain/hindbrain).[4] Based on the anatomical connection of cellular composition, the lateral habenula (LHb) and medial habenula have been recognized in the habenular complex.[5] The LHb influences the function of all important monoaminergic nuclei located in the mid-brain due to receiving some inputs from the basal ganglia and limbic forebrain.[6] The LHb plays a primary role in processing negative feedback related to seeking behavior.[7] In this regard, the activation of LHb leads to the inhibition of dopaminergic neurons in the ventral tegmental area (VTA), which is considered a crucial reward pathway within the brain.[8] Also, it has proposed a close relation between LHb and dorsal raphe nucleus (DRN).[8] DRN is a critical center for the synthesis and release of 5-HT,[9] and the microinjection of lidocaine into the habenula may lead to the inactivation of the LHb inhibitory effect on the LHb-DRN pathway,[10] and the effect induces to increase in the 5-HT and improves depression behaviors.[11]

Electrical stimulation (ES) of the brain is presented as an approach for the induction of therapeutic effects in the central nervous system. This is possible by the implantation

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of electrode into particular neural nucleus.[12] Currently, ES is utilized to treat several neurological disorders, including obsession, depression,[13] and Parkinson's disease (PD).[14,15] In this respect, ES of the subthalamic nucleus can ameliorate the disease symptoms and attenuated the desire of dopaminergic drug administration in the PD patients.[16] In addition, ES modulates neural circuits related to reward, influencing the activity of key brain regions such as accumbens and amygdala to reduce cravings and alter drug-seeking behavior in addiction.[17,18]

Given that previous research has primarily investigated the effects of conditioned place preference and ES of LHb,[19] these studies have not directly examined addiction-related behaviors such as active substance seeking and consumption. Instead, they have largely focused on assessing the rewarding properties of substances, which are influenced by memory and conditioning processes. Notably, the impact of LHb stimulation on morphine self-administration behavior remains unexplored. This method provides a more direct measure of dependence on addictive substances. Therefore, the novelty of the present study lies in its investigation of the role of LHb stimulation in morphine self-administration, which could offer valuable insights into the neural mechanisms underlying morphine addiction and contribute to the development of novel therapeutic strategies.

Materials and Methods

Animals

In this research, male Wistar rats weighting between 250 and 300 g were used. The animals were proved from Isfahan University of Medical Sciences. They were kept in the animal house of the Medical School in polycarbonate cages under standard conditions (temperature of 22°C ± 2°C with a 12 h dark/12 h light cycle), and with ample water and food available. All animal experiments received approval from the Ethics Committee at Kazeroon Azad University (IR.IAU.KAU.REC.1400.112). In addition, this study adhered to the guidelines set forth by the National Institute of Health for the care and use of laboratory animals (NIH Publication, No. 85-23, revised 2010).

Drugs

The substances administered during the experiment included morphine sulfate (5 mg/ml; Temad Factory Co, Iran), Ketamine (100 mg/kg; Trittau Co, Germany), Xylazine (10 mg/kg; Inter chemie Co, Holland), sodium chloride (saline 0.9%), (0.3 µl/rat; Iranian pharmaceutical Co, Iran), lidocaine hydrochloride 2% (0.3 µl/rat; Caspian Tamin Pharmaceutical Co, Iran), gentamicin (6 mg/kg; Alborz Darou Co, Iran), urethane (1.7 g/kg; Sigma Co, USA).

Surgery procedure

Rats were anesthetized using ketamine (100 mg/kg) and xylazine (10 mg/kg) via intraperitoneal injection. After fixing in a stereotaxic device (RWD Life Science, China) and cutting the scalp with a median incision, the skull was exposed. Then, the bregma and lambda areas were cleaned and dried. After determining the location of LHb according to the coordinates of anterior–posterior: −2.2 mm, medial–lateral: −0.7 mm, and dorsal–ventral: −5.2 mm,[20] both cannula and electrode were inserted into the LHb then fixed on the skull by screws and dental acrylic cement. Following the stereotaxic surgery, the right jugular vein was catheterized by a cannula (Polyethylene tubing, PE-50), filled with heparin-saline solution. The rest of the cannula was passed through the skin and came out from behind the animal. To avert infection, the animals were administered gentamicin (6 mg/kg; subcutaneously). Following the completion of the surgery, each animal was placed in individual housing and permitted to recover for a period of 7 days before the experiment.[21] To habituate the animals to the experimental conditions, the dark/light cycle was reversed before the experiment for 3 days.

Experimental design

The animals were randomly assigned to five experimental groups (n = 6) as follows:

- Morphine + ES: ES of LHb with different intensities (LI: 25 and HI: 150 µA) that stimulation was performed 10 min before each morphine self-administration sessions (5 mg/mL morphine sulfate dissolved in saline)
- Morphine + lidocaine group: receiving lidocaine (0.3 µL/Rat) into LHb, which was injected before each morphine selfadministration sessions
- Morphine group: animals had similar protocol to lidocaine group, except saline was injected instead of lidocaine
- Saline group: animals had similar protocol to the morphine group, except saline was infused into jugular vein instead of morphine (0.1 ml saline) [Figure 1].

Self-administration device and procedure

The self-administration apparatus consisted of a standard operant conditioning chamber situated in a soundproofed environment. There was an active lever and a passive lever on the opposite walls in the chamber. In addition, the device was equipped by a red light positioned above the active lever to facilitate the learning process. When animal pressed the active lever, it received a defined food amount (approximately 45 mg) as a reward. After the recovery period, each animal was located in a room with an inversed light/dark cycle (12 h light/12 h dark) followed by starvation for 30 h. The length of the starvation period gradually decreased (6 h daily) until the starvation period was completely removed in the 5th day. The self-administration period was 11 days. Each animal was housed in the self-administration device for 2 h each day. The animal was allowed to move in the device. When the active lever was pressed, the animal was administered 0.1 ml of morphine sulfate (5 mg/ml) or saline with equal volume by a peristaltic pump via cannula implanted into jugular vein for 10 s. By activating the passive lever, the animal did not receive

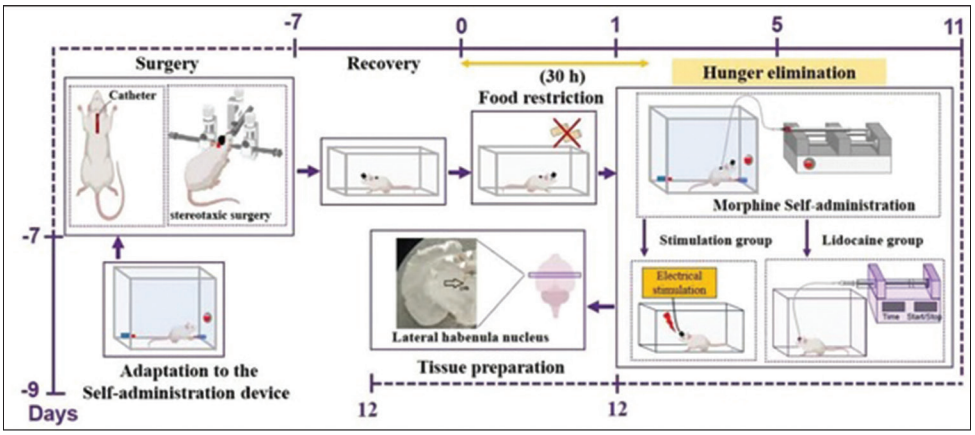

Figure 1: Illustrative diagram depicting the experimental protocol for the electrical stimulation method and lidocaine injection into the lateral habenula of rats addicted to morphine through self-administration

nothing.[22] Experimental groups received lidocaine (0.3 µl/rat) or saline before each session selfadministration. The experiments were performed in the dark cycle due to more activating at night. During the test, the number of levers pressed as well as the number of infusions was recorded by a computer and measured.

Electrical stimulation

The LHb was stimulated using a stimulator device A36O (25 and 150 µA current intensity, 0.4 ms stimulus duration, 5 s interburst interval with a frequency of 25 Hz, for 10 min; World Precision Instruments, CO, USA), and the delivering current of setup was tested with an oscilloscope (8203 SAIRAN). ES was applied for 10 min before the start of the self-administration sessions. The choice of 25 µA and 150 µA intensities was based on prior findings from our lab and existing literature, indicating these levels as the minimal effective and optimal upper therapeutic currents for addiction-related interventions without inducing adverse effects.[23,24]

Microinjection procedure

The microinjection technique was carried out using a 30-gauge injection needle, which was inserted into the guide cannula. This needle was linked to a 10-µl Hamilton syringe through a polyethylene tube (PE-20) that was connected to a syringe pump. Lidocaine or saline (0.3 µl/rat) was administered slowly over 60 s by the syringe pump (KD Scientific Inc, USA).[23]

In addition, the needle was maintained within the guide cannula for a further 60 s to allow the diffusion of lidocaine or saline and to prevent fluid backflow.

Histology procedure

After ending experiment, the rats were deeply anesthetized with urethane (1.7 g/kg). Next, the animals were transcardially perfused with the solutions of saline and formalin 10%. After decapitating, the brains were extracted and stored in a 10% formalin solution for 7 days. Then, the brain tissue sections (a thickness of 60 µm) were made by a freeze-microtome. For confirming the stimulating electrode or cannula site in the LHb, the slices were investigated by a light microscopy [Figure 2].[24]

Statistical analysis

Data are expressed as the mean ± standard error of the mean (SEM). Repeated measures analysis, followed by Tukey's post hoc test, was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

Results

Effect of lateral habenula electrical stimulation on active lever pressing

As shown in Figure 3, the statistical analysis using repeated measures indicated that the number of active lever pressing showed a significant increase across all groups during the first 5 days of the experiment. This initial rise likely reflects the subjects' acclimatization to the operant conditioning environment and their growing motivation to obtain the rewards associated with lever pressing.

From days 6 to 11, the morphine group exhibited a substantial increase in active lever pressing compared to the saline group, with statistical significance noted $F(1,10) = 44.936$, ($P < 0.0001$) [Figure 3a]. This finding suggests that morphine administration enhances motivation and reinforces drug-seeking behavior.

In contrast, the groups receiving HI-ES demonstrated a notable reduction in the number of active lever pressing when compared to the morphine group $F(3,19) = 39.546$, ($P < 0.0001$) [Figure 3b]. The statistical analysis indicated that the differences in active lever pressing across groups were statistically significant.

Effect of lidocaine injection into lateral habenula on active lever pressing

In the case of lidocaine injections, the results mirrored those of the HI-ES group. The number of active lever pressing

was significantly lower in the lidocaine group compared to the morphine group F (3,19) = 39.546, ($P < 0.0001$) [Figure 3b]. Similarly, this reduction implies that lidocaine, like HI-ES, could contribute to diminishing the reinforcing effects of morphine on drug-seeking actions.

Effect of lateral habenula electrical stimulation on number of infusions

The results illustrated in Figure 4 further demonstrate that the number of infusions closely paralleled the trends observed in active lever pressing. All experimental groups experienced an increase in the number of infusions until day 5.

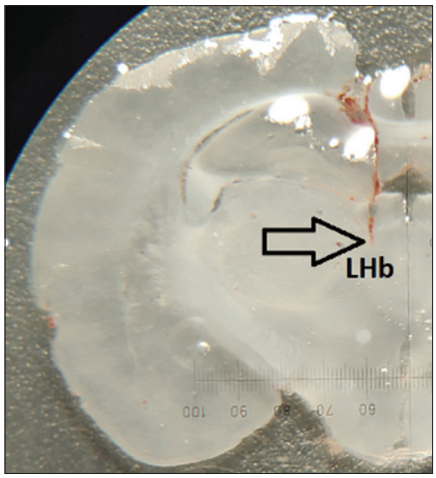

Figure 2: Location of electrical stimulation or injection in the lateral habenula (LHb) of rat brain. The arrow indicates the LHb location (4×)

During the subsequent 6 days, the morphine group exhibited a significantly higher number of infusions compared to the saline group F (1,10) = 17.710, ($P < 0.002$) [Figure 4a]. This increase in drug intake aligns with the rise in active lever pressing, reinforcing the idea that morphine escalates both the motivation to press the lever and the overall consumption of the drug. The repeated measures showed the number of infusions in the HI-ES group was significantly lower during days 6–11 compared to morphine group F (3, 20) = 17.072, ($P < 0.001$) [Figure 4b].

Effect of lidocaine injection into lateral habenula on number of infusions

Conversely, the infusion counts in the lidocaine injection group were considerably lower during days 6–11 compared to the morphine group F (3, 20) = 17.072, ($P < 0.001$) [Figure 4b]. The repeated measures indicated statistically significant differences in infusion counts among the groups, highlighting the effectiveness of lidocaine in reducing morphine-induced drug-seeking behavior. This correlation between active lever pressing and infusion counts suggests that both behaviors are similarly influenced by the treatments, underscoring the reinforcing properties of morphine and the potential for lidocaine to diminish these effects.

Effect of lateral habenula electrical stimulation and lidocaine injection on passive lever pressing

As shown in Figure 5, the number of passive lever pressing displayed a fluctuating and irregular pattern throughout the study. Notably, no significant differences were found

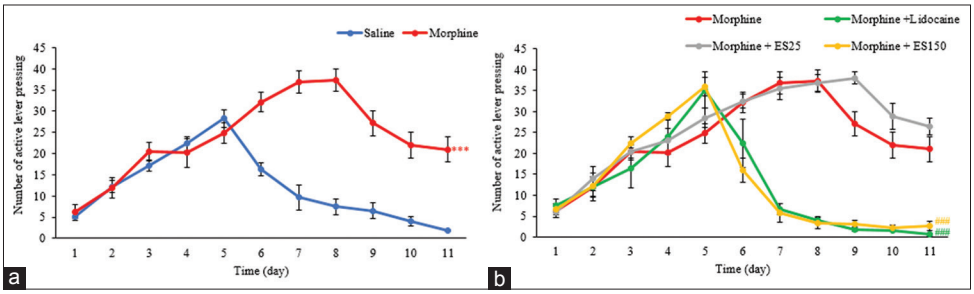

Figure 3: The number of active lever pressing during the experiment in all groups. (a) Saline versus Morphine; (b) electrical stimulation groups and lidocaine group in comparison with the morphine group. Data were presented as mean ± standard error of the mean. ***$P < 0.001$ and ###$P < 0.001$ indicate significant differences in comparison to saline and morphine groups, respectively

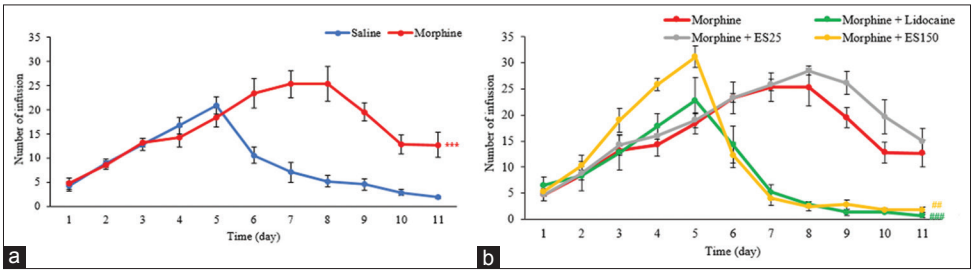

Figure 4: The number of infusions during the experiment in all groups. (a) Saline versus Morphine. (b) electrical stimulation groups and lidocaine group in comparison with the morphine group. Data were presented as mean ± standard error of the mean. ***$P < 0.001$, ###$P < 0.001$ and ##$P < 0.006$ indicate significant differences in comparison to saline and morphine groups, respectively

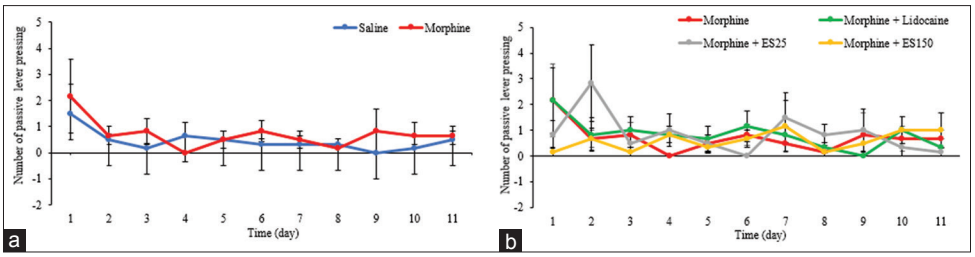

Figure 5: The number of passive lever pressing during the experiment in all groups. (a) Saline versus Morphine. (b) electrical stimulation groups and lidocaine group in comparison with the morphine group. Data were presented as mean ± standard error of the mean. There were no significant differences among groups

between the different groups in terms of passive lever pressing. The statistical analysis confirmed that the variations in passive lever pressing were not significant, indicating that this behavior remained stable and unaffected by the administered treatments.

Discussion

The present study assessed the impact of ES and temporary inactivation of the LHb in addicted rats with morphine self-administration. The findings suggest that HI-ES and temporary inactivation of the LHb may attenuate morphine self-administration, as evidenced by a decrease in the number of active lever presses and infusions. These results indicate a potential reduction in the reinforcing effects of morphine. Our results demonstrated that morphine administration increased the number of active lever presses [Figure 3] and infusions [Figure 4]. This supports the idea that morphine acts as a positive reinforcer, directing behavior toward drug-seeking. Notably, morphine administration did not significantly affect passive lever pressing, further suggesting that the observed behavioral changes were specific to the drug's reinforcing properties. These findings align with previous studies showing that LHb stimulation can reduce drug intake, such as cocaine consumption.[14] The LHb is believed to play a crucial role in negative reinforcement and reward processing.[15] Previous research suggests that lesions in the LHb can alter normal function and motivation related to drug reward.[14] While the exact mechanisms remain unclear, LHb is known to have glutamatergic projections that influence key brain regions involved in addiction, such as the VTA, DRN, and locus coeruleus.[8,25] The VTA, in particular, regulates dopaminergic and GABAergic neurons, which are critical for neurotransmitter balance.[26] It has been proposed that repeated morphine administration disrupts this balance by reducing inhibitory control of GABA interneurons on dopaminergic neurons in the VTA, potentially leading to enhanced drug-seeking behavior.[27,28] Although we did not measure neurotransmitter levels in this study, previous research suggests that ES and inactivation of LHb could modulate neurotransmitter systems involved in addiction, including glutamate, serotonin, and dopamine.[6,29] For instance, serotonin has been implicated in regulating addictive substance consumption, and increasing its levels may reduce drug intake.[30] Studies have also suggested that ES might influence serotonin and endogenous opioid levels in the DRN,[25,31] which could contribute to the observed behavioral effects. Furthermore, some pharmacological interventions, such as 18-methoxycoronaridine, have been shown to reduce morphine self-administration, possibly through modulation of nicotinic receptors in the LHb and interpeduncular nucleus.[13] In addition, our findings suggest that lidocaine injection into the LHb could decrease morphine self-administration. Lidocaine, a pharmacological blocker of the LHb, has been reported to have analgesic effects and may inhibit glutamatergic projections to the VTA.[11] This inhibition could potentially reduce dopamine release in the VTA and subsequently attenuate morphine-seeking behavior.[32] Moreover, previous studies have indicated that lidocaine injection into the central amygdala might ameliorate morphine-induced addiction,[22] and its local application in the habenula may increase serotonin levels in the DRN.[11] Overall, while our study did not directly measure neurotransmitter changes, the observed behavioral effects suggest that ES and inactivation of the LHb may influence neurobiological pathways involved in addiction. Further research is necessary to elucidate the precise molecular mechanisms underlying these effects. Further research is necessary to elucidate the precise molecular mechanisms underlying these effects. One limitation of the current study is the lack of a locomotor control test, such as the open field test, which could help distinguish between motivational and motor effects. Although our focus was on self-administration behavior, incorporating such assessments in future studies would provide a more comprehensive understanding of the behavioral outcomes.

Conclusion

In summary, ES of LHb and the temporary inactivation of LHb by lidocaine injection may reduce morphine self-administration. This effect is likely related to changes in decision-making patterns and individual motivations. Further studies are needed to understand better the behavioral mechanisms involved, especially studies that examine the effects of neurotransmitters as well as receptor stimulation or blockade to clarify the role of LHb in addiction-related behaviors.

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Conflicts of interest

There are no conflicts of interest.

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