The Role of mGluR4 Receptors Within the Nucleus Accumbens in the Acquisition and Expression of Morphine-induced Conditioned Place Preference in Male Rats

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Abstract

Background: Several studies have shown that glutamate neurotransmission in the nucleus accumbens (NAc) is required for the development of morphine-induced conditional place preference (CPP). Also, metabotropic glutamate receptors (mGluRs) into the NAc play important roles in the reward pathways. However, the precise role of mGluR4 in different steps of the morphine-induced CPP is less well known. In the present study we investigated the effect of bilateral intra-accumbal infusion of VU0155041, as a specific mGluR4 agonist on the acquisition and expression of morphine induced CPP in male Wistar rats. Animals were bilaterally implanted with guide cannulae above the NAc. In the first part of the study, the VU0155041 was administered at doses of 10, 30 and 50 µg/0.5 µL saline per side into the NAc during the 3 days of morphine (5 mg/kg) conditioning (acquisition) phase of morphine-induced CPP. In the next part of the study, the rats bilaterally received VU0155041 at the dose of 50 µg/0.5 µL, 5 min before the post-conditioning test to check the effect of VU0155041 on the expression of morphine-induced CPP.

Results: The results showed that the intra-accumbal injection of VU0155041 inhibits the acquisition of morphine-induced CPP in a dose dependent manner, but had no effect on expression Our data indicated that intra-NAc administration of VU0155041 dose-dependently blocks the establishment of morphine-induced CPP and reduces the rewarding properties of morphine.

These effects may be related to changes in glutamate activity in the NAC and/or learning dependent mechanism of glutamate neurotransmission in reward pathway(s).

Background

Reward is the attractive and motivational property of a stimulus that induces appetitive behavior and usually creates a conscious experience of pleasure (1). The positive reinforcing (rewarding) effects of some drugs such as alcohol, nicotine, cocaine, morphine, and heroin play a chief role in the initiation and maintenance of the drug-taking habit (2). Drug addiction is a chronic disorder characterized by cravings and recurrence of drug abuse after prolonged abstinence (3). The reward pathway (especially the mesolimbic reward pathway) links the ventral tegmental area (VTA) of the midbrain and the nucleus accumbens (NAc) of the striatum via the medial forebrain bundle (4). The NAc is located inside the ventral striatum and is one of the most important neural elements in the reward pathway (5, 6).

Studies have shown that several neurotransmitters such as dopamine, glutamate (Glu) and GABA are involved in the neural circuitry of reward and that dopaminergic and glutamatergic systems are the most important of these pathways (7, 8). Anatomical and electrophysiological studies suggest that glutamatergic neurons projecting from the medial prefrontal cortex, VTA, and amygdala to NAc play an important role in addictive behaviors (8, 9).

The actions of glutamate are mediated by ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs respectively) (10–12). The mGluRs are G-protein coupled receptors and have eight subtypes and are classified into three groups including; group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3),

and group III (mGluR4, mGluR6, mGluR7, and mGluR8) depending on their signal transduction pathways, sequence homology, and pharmacological selectivity. The group III of mGluRs are coupled with the Gi/o proteins (13). In our previous works we identified the role mGluR2/3, mGluR5 and mGluR7 in NAc on acquisition and expression of morphine-induced conditioned place preference (CPP) in rats (7, 14, 15). We showed that intra-NAc microinjection of the LY379268 (as a mGluR2/3 agonist) inhibits the acquisition and expression (7), and attenuates extinction latencies and the reinstatement of morphine-induced CPP in rats (16). Also, we reported that blockade of mGluR5 in the NAc reduces rewarding properties of morphine (15). Moreover, we reported that intra-accumbal administration of AMN082, a metabotropic glutamate receptor type 7 allosteric agonist, inhibits the acquisition of morphine-induced CPP in rats (14). Also, it has been shown that mGluR7 orthosteric agonist, LSP2-9166 blocked morphine CPP expression and reinstatement after extinction (17). It is indicated that activation of mGluR4 has an important effect on the rewarding properties of alcohol (18) and recently Zaniewska et al. showed that mGluR4 activation reduces cocaine-, but not nicotine-induced locomotor sensitization (19). mGluR4 receptors are widely distributed in different parts of the brain, including the cerebellar cortex, globus pallidus and ventral pallidum (VP), olfactory tubercle, striatum, entopeduncular nucleus, the sensory relay nuclei of the thalamus, neocortex, piriform cortex, hippocampus, lateral and basolateral amygdaloid nuclei and in the superficial grey of the superior colliculus (20, 21). Specifically, the mGluR4 has high density in brain regions involved in reward circuits such as NAc, ventral pallidum (VP), and VTA (20, 22–24). This anatomical distribution of mGluR4 suggests that this receptor may plays a critical role in drug dependence. The mGluR4 is primarily localized presynaptically in GABAergic and glutamatergic terminals and is involved in the regulation of Glu and GABA release (20, 24) and acts as inhibitory presynaptic receptor and reduces synaptic transmission (25).

Taken together, although the precise role of mGluR4 in morphine-induced CPP is unclear. It seems that there is a type specificity in the role of mGluRs in different steps of drug abuse Therefore, the goal of the current study was to assess the involvement of intra-accumbal mGluR4 in the acquisition and expression of morphine-induced CPP in male rats.

Results

The dose–response for morphine on conditioned place in the CPP paradigm was examined and as previous studies, the minimum effective dose of morphine was 5 mg/Kg (7, 14, 15).

Effects of intra-accumbal microinjection of mGluR4 receptor agonist, VU0155041, on the acquisition of morphine-induced CPP

To investigate the effects of mGluR4 agonist on the acquisition of morphine-induced CPP, intra-accumbal injection of VU0155041 (10, 30 and 50 µg/0.5 µL) was bilaterally done 5 min prior to each morphine injection during the 3-day conditioning phase (Fig. 2). In this study, the saline group animals received subcutaneous injection of saline (as a solvent of morphine) instead of morphine during the conditioning

phase. The vehicle group animals received subcutaneous injection of morphine (5 mg/kg) during the conditioning phase along with intra-NAc microinjection of saline (as a solvent of VU0155041).

As depicted in Fig. 1, a one-way ANOVA, followed by Newman–Keuls multiple comparison test, indicated that there were significant differences in the CS between the experimental groups [$F(3, 32) = 2.26$, $P = 0.0149$]. The results revealed that there was a significant difference between the saline and vehicle group ($P < 0.01$). The concurrent administration of intra-accumbal VU0155041 and systemic morphine during the acquisition period attenuated the rewarding attributes of morphine in the CPP paradigm in a dose dependent manner ($P < 0.05$). Also, administration of the highest dose of VU0155041 (50 µg/0.5 µL) alone did not affect the CS in saline-treated animals (which received saline instead of morphine during the conditioning phase) (Fig. 1).

Effects of intra-accumbal microinjection of mGluR4 receptor agonist, VU0155041, on the expression of morphine-induced CPP.

As depicted in Fig. 2, a one-way ANOVA (followed by Newman–Keuls multiple comparison test) indicated a difference between experimental groups [$F(2, 16) = 3.718$, $P = 0.0472$]. But, intra-accumbal administration of VU0155041 (50 µg/µL) had no effect on the expression of morphine-induced CPP in morphine treated animals, compared to the saline group ($P > 0.05$). It means that VU0155041 (50 µg/µL) could not fully reverse the morphine place preference.

The effect of VU0155041 injection into the nucleus accumbens on motor activity of rats

One-way ANOVA followed by Newman-Keuls multiple comparison test [$F(5, 45) = 0.3644$, $P = 0.8702$] indicated that VU0155041 did not change the traveled distance during the 10 min test period (on the post-test day) in comparison with the vehicle and saline groups (Fig. 3).

Discussion

In the present study, the effect of VU0155041 as a selective mGluR4 allosteric agonist within the NAc on development of morphine-induced CPP was investigated in rats. Main findings of the present study can be expressed as :a) bilateral intra-accumbal microinjection of VU0155041 dose-dependently reduced the acquisition of morphine-induced CPP, b) after conditioning, intra-accumbal activation of mGluR4 by VU0155041 at highest dose of 50 µg / 0.5 µL, did not affect the expression of morphine-induced CPP in the rats, c) administering the highest dose of VU0155041 into the NAc alone could not induce CPP, and d) VU0155041 did not affect locomotor activity.

Previous studies have shown that mGluRs are involved in the acquisition and expression of morphine-induced CPP; mGluR2/3, (7) mGluR5 (15) and mGluR7 (14) in NAc on acquisition and expression of morphine-induced conditioned place preference (CPP) in rats. This is the first study which investigated the effects of intra-accumbal microinjection of mGluR4 agonist on the acquisition and expression of morphine-induced CPP.

The NAc is a key brain region that receives and integrates convergent emotional, motivational and reward-related signals that aid in regulating behavioral output (26). These signals are thought to be mediated, in part, by glutamatergic inputs from several brain regions including the VTA, basolateral amygdala, medial prefrontal cortex and the ventral hippocampus (27, 28). Excitatory afferents to the NAc are thought to facilitate reward seeking by encoding reward-associated cues. Recent optogenetic studies, for example, have revealed that activation of glutamatergic inputs from the Amygdala or the ventral Hippocampus to NAc facilitates reward seeking (28, 29). On the other hand, it has been reported that morphine eliminates the inhibitory effects of dopamine on glutamatergic inputs to NAc neurons and enhances glutamate activity on this nucleus (30). The mGluR4 is primarily localized presynaptically in glutamatergic terminals (24) and acts as inhibitory presynaptic receptor and reduces synaptic transmission (25). Based on the results presented in this study, it can be concluded that VU0155041 blocks the rewarding properties of morphine by reducing glutamate release form glutamatergic inputs to the NAc. Interestingly, Barrett et al. (2012) suggest that the specific pathway releasing glutamate is not as important as the amount of glutamate that is released (28). We cannot completely exclude that observed effect of VU0155041 injections on acquisition of morphine CPP is specific to intra accumbal infusion of the drug rather than diffusion/action of at other brain regions

Studies on mGluR4 have shown that mGluR4 is involved in locomotor activity and regulation of motor stimulation induced by intraperitoneal injection and oral administration of ethanol (18). Despite the importance of glutamate in drug dependence, only a few studies have demonstrated anti-addictive activity in the group III of mGluRs (mGluR4, mGluR6, mGluR7, and mGluR8).

The NAc include two main parts, core and shell. The NAc core is responsible for the evaluation of reward and initializing reward-related motor action (31–33). Also, The NAc core is essential for acquiring drug-taking behaviors and cue-elicited drug-seeking responses. For psychostimulant drugs, learning drug reward associations is largely dependent on dopaminergic and glutamatergic signaling within the NAc core, whereas reinstatement is mostly driven by glutamate (34, 35). In our study we injected the selective mGluR4 allosteric agonist (VU0155041) into the NAc and because of injection site, VU0155041 may affected both parts of the NAc and we can’t exclude the role of each part. However, the inhibitory effects of mGluR4 activation on morphine induced CPP acquisition can be mostly related to these receptors in NAc core which remained to be elucidated.

Group III mGluRs are generally located presynaptically and regulate neurotransmitter release and activation of these receptors cause glutamate release inhibition (36). mGluR4 receptors have been identified as attractive targets for treating anxiety disorders (37). In addition Davis and colleagues in 2012 have shown that mice lacking or deficient in mGluR4 were associated with increased anxiety (38). Their data suggest that pharmacological activation of the mGluR4 may be useful in reducing anxiety alterations in fear learning mechanisms likely participate in the development and/or maintenance of anxiety disorders. Anxiety disorders and substance use disorders often occur together, but the strength of this association and their apparent order of onset differ across studies (39, 40). Morphine dependent animals' have been shown to have enhanced anxiety levels (41). Because rats’ performance in CPP

apparatus is related to the learning and anxiety mechanisms (42), some effects of mGluR4 activation into the NAc on acquisition of morphine induced CPP may related to the role of this receptor on anxiety state.

We showed that after conditioning, intra-accumbal activation of mGluR4 by VU0155041 did not affect the expression of morphine-induced CPP in the rats. In contrast to our observations, Zaniewska and colleagues have shown that administration of either mGluR4 orthosteric agonist LSP1-2111 or a positive allosteric modulator of mGluR4 Lu AF21934 attenuated the expression of cocaine sensitization (19). One explanation for the difference in the effects of mGluR4 receptor agonists on the behavioral responses to cocaine and morphine could be that these two substances have different neuropharmacological mechanisms and neuroanatomical sites of action. Also, this incongruity could be explained by the animal species used, behavioural model of substance abuse and/or by the type and dose of agonists.

Conclusion

In conclusion, our data extend present knowledge about the effects of pharmacological stimulation of mGluR4 on the behavioral responses to morphine in rats and demonstrate that activation of mGluR4 in NAc confers an inhibitory effect on the acquisition of morphine induced CPP while it had no effect on the expression of morphine-induced CPP. Elevation of glutamate level in NAc may be involve in this effect although future studies are needed to characterize the specific mechanisms of action of mGluR4 in acquisition and expression of morphine-induced place preference in rats.

Materials And Methods

Ethics statement

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences (Ethic code: IR.UMSHA.REC.1397.784) and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All efforts were made to minimize suffering. The operations that could cause pain and distress were performed in another room in the absence of other animals.

Animal

Male Wistar rats (200–250g) were obtained from animal breeding colony of Hamadan University of Medical Sciences (Hamadan, Iran). They were maintained on 12/12h light/dark cycle (light on at 7 AM) and had access to freely available food and water in their home cages (temperature 22°C ± 2°C).

Drugs

In the current study the following drugs were used: Morphine sulfate (Temad, Iran) was dissolved in normal saline (0.9% NaCl); cis-2-[[(3,5-Dichlorophenyl)amino]carbonyl]cyclohexanecarboxylic acid (VU0155041) (Tocris, UK), a selective mGluR4 allosteric agonist, was also dissolved in normal saline (0.9% NaCl). In this study, the saline group animals received subcutaneous injection of saline (as a solvent of morphine) instead of morphine during the conditioning phase (1 ml/kg; s.c.; n = 6/group). The vehicle group animals received subcutaneous injection of morphine (5 mg/kg; s.c.; n = 7) during the conditioning phase along with intra-accumbal microinjection of saline (instead of VU0155041).

Stereotaxic Surgery and Drug Administration

Subjects were anesthetized by Xylazine (10 mg/kg) and Ketamine (100 mg/kg) and placed in the stereotaxic apparatus (Stoelting, USA) with the incisor bar set at approximately 3.3 mm below horizontal zero in order to achieve a flat skull position. Then, an incision was made to expose the rat's skull and two points were determined and drilled into the skull at stereotaxic coordinates of 1.45 ± 0.3 mm anterior to bregma, ±1.5 mm lateral to the sagital suture. Two guide cannulae (23-Gauge) with 12 mm length were inserted into the holes aiming at the NAc, 6.5 mm down from top of the skull according to the atlas of rat brain (Paxinos and Watson, 2007). The guiding cannulae were anchored with a jeweler's screw and the incision was closed with dental cement. After surgery, dummy inner cannulae that extended 0.5 mm beyond the guiding cannulae were inserted into the guiding cannulae and left in place until injections were made. All rats were allowed to recover for one week before starting the behavioral testing.

Intra-accumbal Injection

The rats were gently restrained by hand and the dummy cannulae were removed from the guiding cannulae. Drugs were directly injected into the NAc through the guiding cannulae using injector cannulae (30- gauge, 1 mm below the tip of the guiding cannula). Polyethylene tubing (PE-20) was used for attaching the injector cannula to the 1-µl Hamilton syringe. Selective mGluR4 allosteric agonist, VU0155041, was administered into the NAc at doses (10 µg/0.5 µL saline (n = 11), 30 µg/0.5 µL saline (n = 10) and 50 µg/0.5 µL saline (n = 8) per side) (43, 44). The injection volume into the NAc was 0.5 µl/side for all groups. Injections were made bilaterally over a 50s period and the injection cannulae were left in the guiding cannulae for an additional 60s in order to facilitate the diffusion of the drugs.

Place Conditioning Apparatus and Protocol

A three-compartment CPP apparatus was used in the experiments. The apparatus was divided into two equal-sized compartments (30 cm × 30 cm × 40 cm) with the third section (30 cm × 15 cm × 40 cm) being the null section which connected the two equal-sized sections. Both compartments had white backgrounds with black stripes in different orientations (vertical vs. horizontal). To provide a tactile difference between the compartments, one of them had a smooth floor, while the other compartment had a net-like floor. The CPP protocol has been previously described (14). An unbiased allocation was used. Rats with a neutral preference (45–55% for either side) were randomly allocated their drug-paired side (unbiased allocation). In the CPP paradigm, the conditioning score (CS) and distance traveled were

calculated based on a video recorded by a CCD camera with 30 frames per second (30 fps) resolution. The camera was placed 2m above the CPP boxes and the locomotion tracking was measured by Maze Router homemade software, a video tracking system for automation of behavioral experiments. CPP paradigm took place for 5 continuous days, which consisted of three distinct phases: pre-conditioning, conditioning and post-conditioning (14, 15).

Pre-conditioning Phase

On day 1, each rat was separately placed in the apparatus for 10 min, with free access to all compartments. Animal movements were recorded by Maze Router tracking software and analyzed on the same day. Rats with any compartment preference were omitted from the experiment. 3 rats were excluded from this study due to compartment preference. Then rats were randomly assigned to one of the two groups (odd and even) for place conditioning (14).

Conditioning Phase

The morphine conditioning phase, also known as the acquisition phase, were conducted on days 2,3 and 4. Each group of animals was randomly divided into even or odd. Odd animals received subcutaneous (SC) injection of saline and morphine (5mg/kg) pairing in alternative morning and afternoon design with an interval of 6 h. The vice versa program for even animals was done. This phase consisted of a 3-day schedule of conditioning sessions. A total of six sessions (30 min each) was carried out. During these 3 conditioning days, in 3 sessions, animals were confined to one compartment, under the drug influence. During other three sessions, they were injected with saline while confined to the other compartment. Access to the other compartments was blocked on these days. Place preference was calculated as a preference score (time spent in drug paired zone – time spent in the saline paired zone) (14, 15). During this phase, saline group animals received saline in both compartments during alternative morning and afternoon design with an interval of 6 h. Locomotor data were also collected throughout CPP testing in order to assess the development of behavioral sensitization.

Post-conditioning Phase

On the 5th day, the partition was removed and the rats could access the entire apparatus. The mean time spent for each rat in both compartments during a 10-min period was recorded. In order to calculate the conditioning score, the difference in the time spent for the drug- and saline-paired places was considered as the preference criteria. In the acquisition tests, no injection was given on the post-conditioning day.

Experimental Design

The effect of intra-accumbal administration of mGluR4 allosteric agonist (VU0155041) on the acquisition of morphine-induced CPP

To investigate the effects of mGluR4 agonist on the acquisition of morphine-induced CPP, bilaterally intra-accumbal injection of VU0155041 (10, 30 and 50 µg/0.5 µL) (45) was done 5min prior to each morphine

injection during the conditioning phase (once daily for 3 days). During this phase, vehicle group animals received saline (0.5 µL) instead of VU0155041 into the NAc, prior to SC injection of morphine (5 mg/kg; SC). Moreover, to rule out the possibility that VU0155041 administration alone had rewarding or aversive effects on the CPP, a separate group of rats received the highest dose (50 µg/0.5 µL) of VU0155041 prior to saline injection (1mL/kg; SC) instead of morphine during the conditioning days.

The effects of intra-accumbal VU0155041injection on the expression of morphine-induced CPP

In order to examine the effects of the highest dose of VU0155041 (50 µg/ 0.5µL saline, n = 6) on the expression of morphine-induced CPP, the rats were bilaterally given VU0155041 in the NAc 5min prior to CPP test. In addition, vehicle group animals (n = 7) received saline (0.5µL) through the NAc instead of VU0155041 before CPP test on post-conditioning phase. Animals in the saline group received saline instead of morphine during the conditioning phase (n = 6).

Locomotor Activity Measurement

The locomotor activity of each rat was recorded using the locomotion tracking apparatus by a video tracking system (Router maze software). In these experiments, the total distance traveled (in centimeters) by each rat was measured in pre- and post-tests for all groups.

Histology

After the behavioral tests and data collection, rats were anesthetized with Ketamine and Xylazine and then sacrificed in order to investigate the correct placement of cannulae in the brain regions. Brain of rats were removed and then fixed in 10% formalin solution. 50 µm coronal sections of brain tissue were cut using a rotatory microtome. The correct placement of cannulae was investigated using rat brain atlas. Only the rat brains with correct cannulae placement (Fig. 1a and b) were chosen for final data analysis. Animals with cannula misplacement (n = 7) were excluded from the study.

Statistics

Data were processed by commercially available software GraphPad Prism® 8.0.2 In order to compare the conditioning scores (CS) and the traveled distance obtained from morphine CPP animals, one-way analysis of variance (ANOVA) followed by post hoc analysis (Newman–Keuls multiple comparison test) was used. Multiple student's t-test was used to compare pre-conditioning with saline or highest dose of VU0155041 (50 µg/0.5 µL). P-values less than 0.05 ($P < 0.05$) were considered to be statistically significant (14, 15).

Declarations

Authors' contributions

AS, AK and SAK designed the project, wrote the manuscript and performed the statistical analysis, revised the manuscript and supervised the project. ZE, NK, SAK and AS were involved in laboratory works and experimental design of the work. AS, AK and MN were involved in data collection and lab assessments, and study designing. All authors read and approved the final

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data are available for any scientific use with kind permission.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences (Code of Ethics Committee: Grant Number: IR.UMSHA.REC.1397.784) and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

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Declarations of interest

there are no conflict of interest.

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Figures

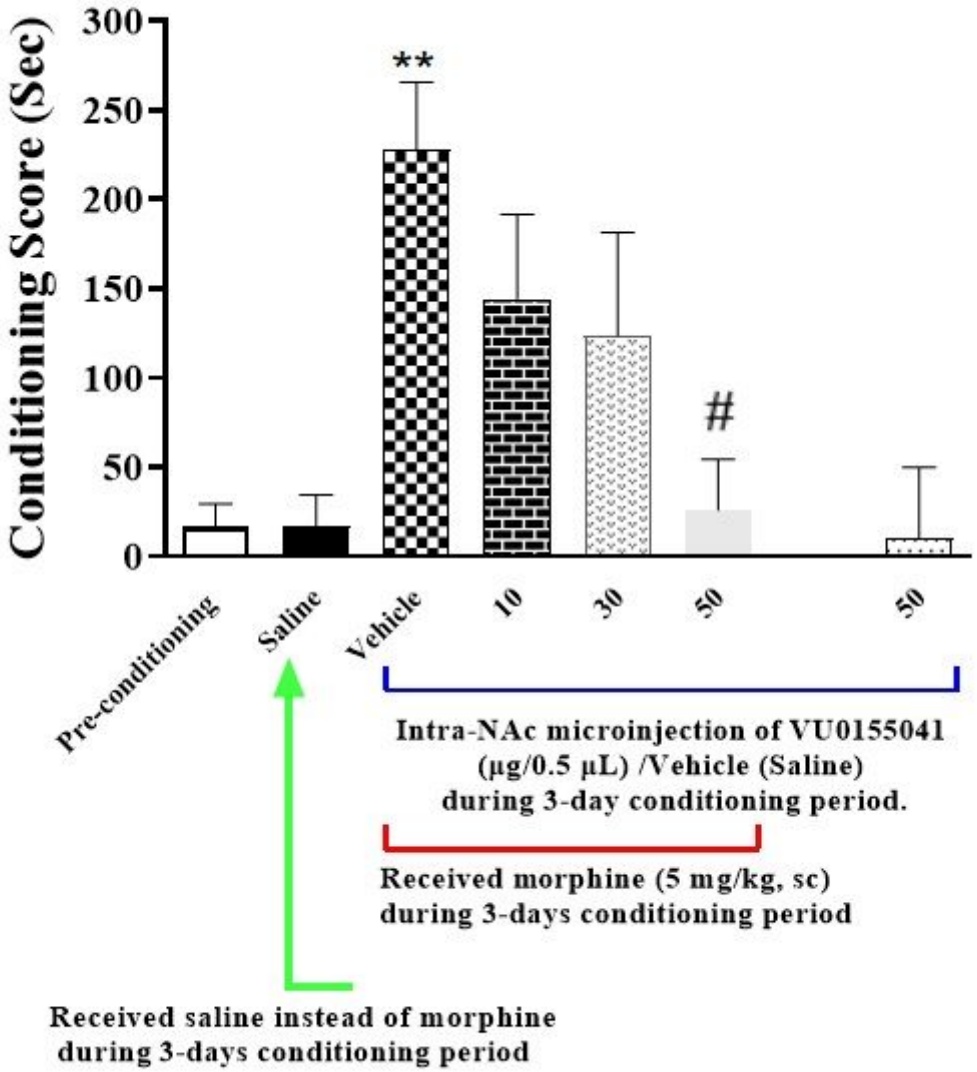

Figure 1

The effects of the administration of different doses of VU0155041, as a potent and selective mGluR4 agonist, (10, 30 and 50 µg/0.5 µL) into the NAc, 5 min before the injection of morphine (5 mg/kg, sc) and administration of maximum dose of VU0155041 into the NAc region alone, in the conditioning days. Each point shows the mean ± SEM. **P < 0.01 as compared with the saline group. # P < 0.05 as compared with the vehicle group. (One-way ANOVA followed by Student-Newman-Keuls post-test).

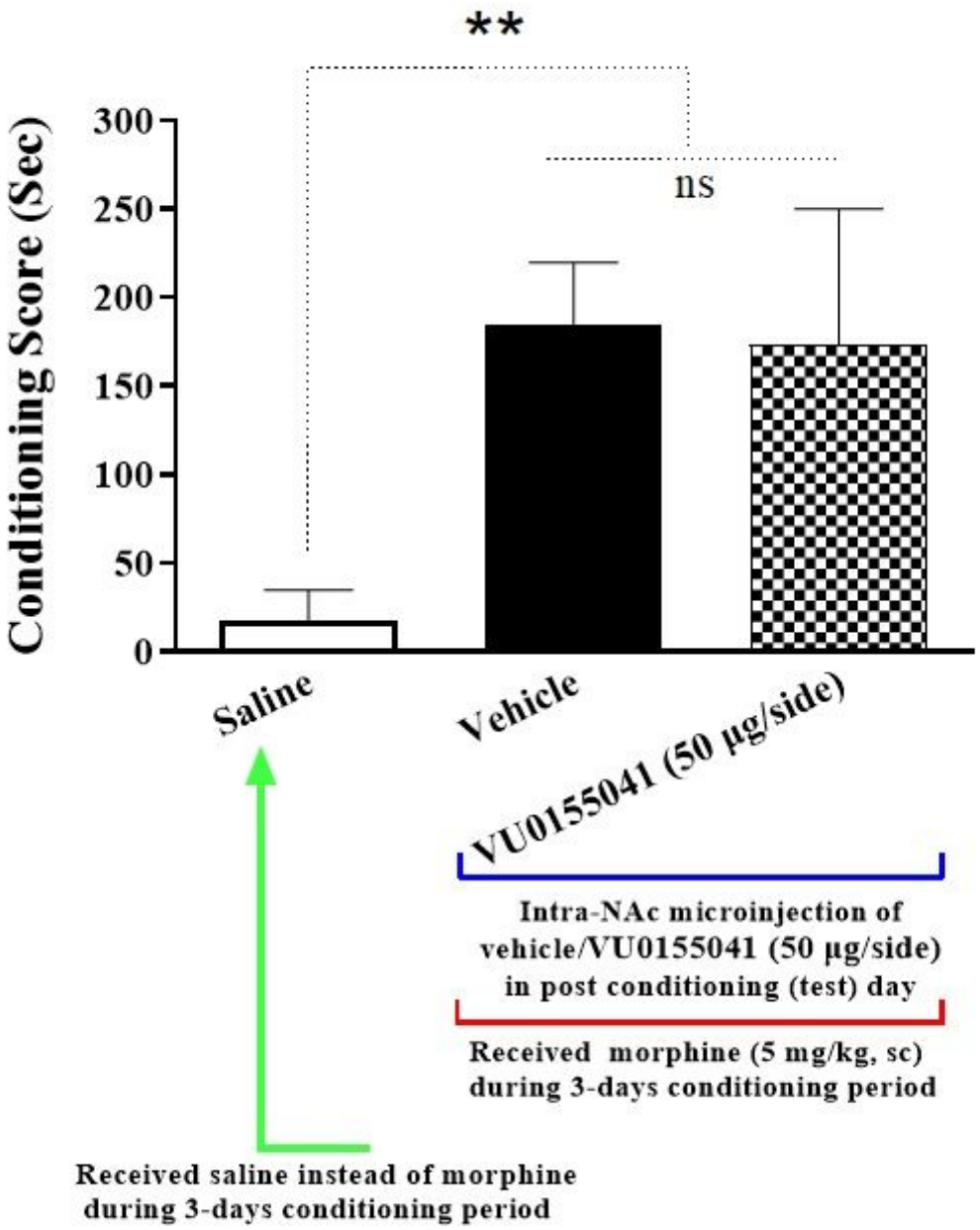

Figure 2

The effects of the administration of highest dose of VU0155041, as a potent and selective mGluR4 agonist, (50 µg/µL) into the NAc, 5 min before the test on the post-conditioning day. Each point shows the mean ± SEM. **p< 0.05 as compared with the saline group. ns: not significant as compared with the vehicle group (One-way ANOVA followed by Newman-Keuls post-test).

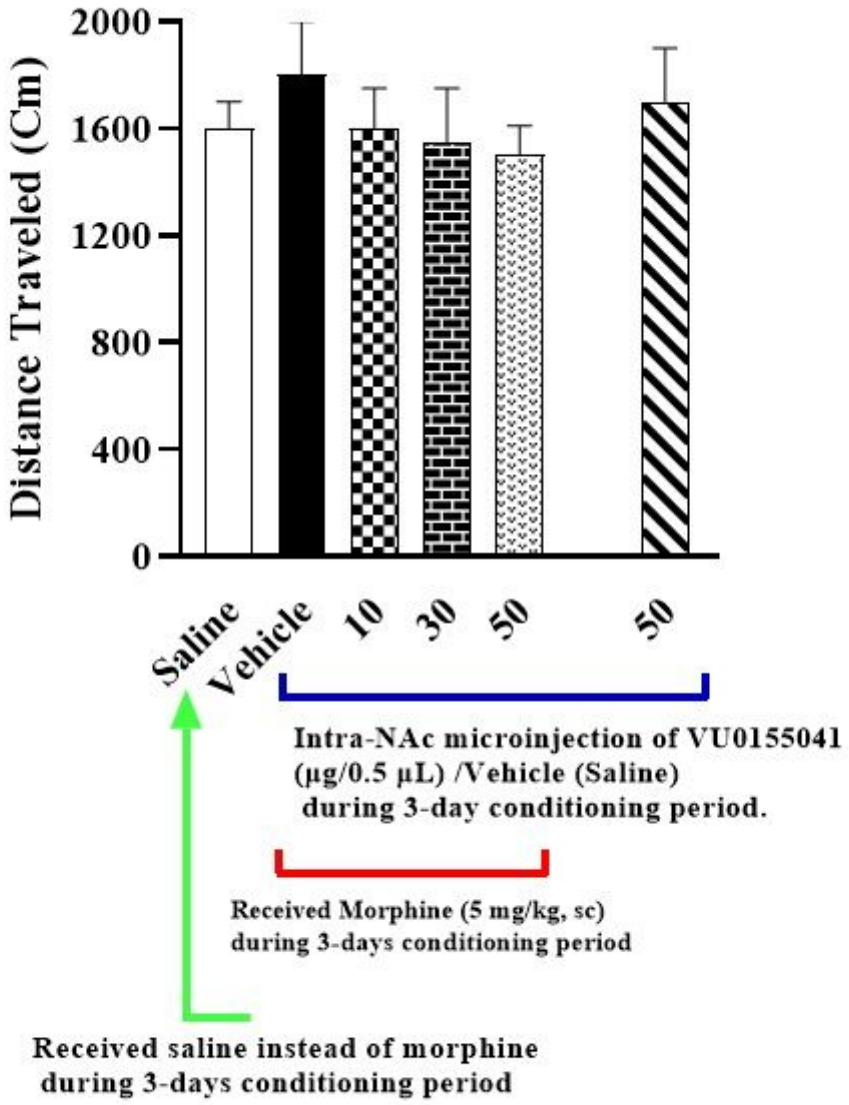

Figure 3

The effect of VU0155041 injection into the NAc on locomotor activity during morphine-induced CPP.

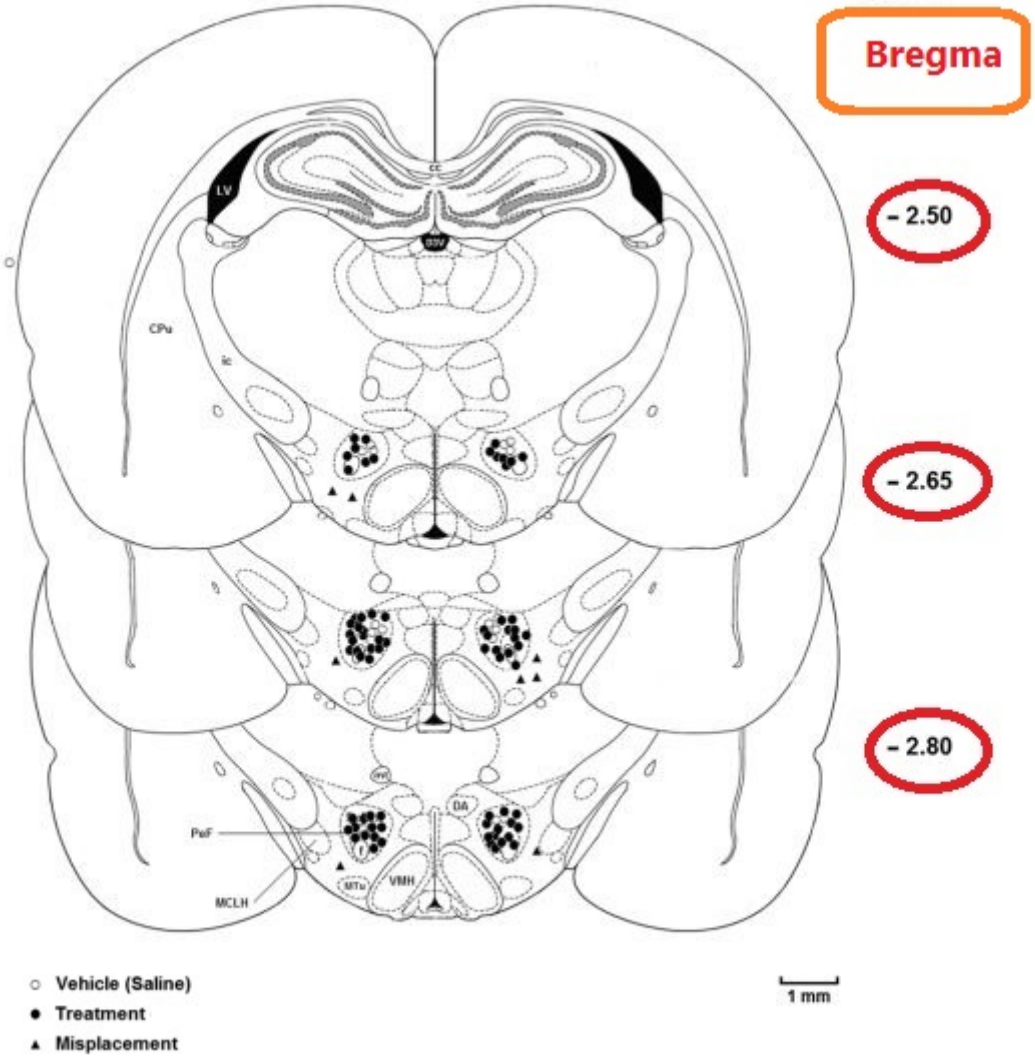

Figure 4

Histology. (A) Coronal photomicrograph of the bilateral microinjection sites in the nucleus accumbens (NAc) and (B) schematic illustration of rat brain coronal sections showing the approximate location of the NAc injection sites. The numbers indicate the anterior-posterior coordinates relative to bregma. Atlas plates were adapted from Paxinos and Watson (Paxinos and Watson, 2007). aca, anterior commissure, anterior part; CPu, caudate putamen (striatum); gcc, genu of the corpus callosum; NAc, nucleus accumbens; scale is 1 mm. The image shown here is our own work.

Supplementary Files

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