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Research article

Acute morphine administration alters the power of local field potentials in mesolimbic pathway of freely moving rats: Involvement of dopamine receptors

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ABSTRACT

Increasing number of evidence support the role of ventral tegmental area (VTA) and nucleus accumbens (NAc) in mediating the opiate effects as the two critical components of brain reward pathway. It is believed that VTA to NAC dopaminergic projections mediate the reinforcing effects induced by opioid drugs. Although numerous studies have investigated mechanisms of reward processing in these brain regions, alterations of local field potentials (LFPs), as an index of total synaptic currents, has not been previously addressed.

In the present study, thin metal electrodes were implanted in both VTA and shell sub-region of NAc to simultaneously record the spontaneous LFPs in freely moving rats. After one week recovery period, a single dose of morphine was systemically administered and the LFP recording was performed 15, 30, 45 and 60 post-injection. Also, in order to assess the role of dopamine system, two groups of animals were pre-treated by selective antagonists of dopamine type-1 and type-2 receptors 15 min prior to morphine injection.

The obtained results indicated that in VTA, acute morphine administration potentiates the power of all LFP frequency bands (i.e. delta, theta, alpha, beta and gamma). However, in NAc shell, theta wave was significantly attenuated by morphine and other components were not affected. In addition, pre-treatment with both antagonists prevented the observed effect of morphine on LFP power suggesting the involvement of dopamine receptors in this process. Future studies should address mechanisms of dopamine-morphine interactions. It is also valuable to focus on acute and chronic effects of morphine on LFP power and assessment of the observed effects following naloxone challenge.

1. Introduction

The mesocorticolimbic system, also known as the brain reward system, is composed of dopaminergic projections from the ventral tegmental area (VTA) to several brain regions including the nucleus accumbens (NAc), hippocampus, amygdala and prefrontal cortex [1]. Currently, it is well established that the mentioned pathways play critical roles in mediating motivation, reinforcement processing and expression of reward-related behaviors [2].

Various brain structures have been found to be involved in induction of adverse effects by drugs of abuse [3,4,5,6,7,8,9]. More specifically, a growing number of evidence support the involvement of VTA-NAc dopaminergic pathway (known as the mesolimbic system) in mediating the opiate effects [10,11,12,13]. In this regard, direct intra-VTA microinjection of morphine has been shown to elicit potent reinforcing effects as assessed by several behavioral tests such as place conditioning and self-administration [12,14,15,16]. Consistently, the extracellular level of dopamine has been shown to be significantly increased in NAc following intra-VTA morphine administration in rats [10]. It is noteworthy that the shell sub-region of NAc is also significantly associated with drug-induced reward processing [17,18,19,20]. Interestingly there are evidence suggesting that drug-induced neuroadaptations first occurs in NAc shell and then develops in NAc core [1,21]. Behavioral studies performed in rats have demonstrated that animals learn to self-administer reward-inducing drugs such as cocaine, amphetamine and dopamine receptor agonists into the

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NAC shell but not the NAc core [19,22,23,24,25]. Also, administration of DA receptor antagonists into the shell region of NAc, rather than the core, has been found to attenuate the nicotine- and morphine-induced conditioned place preference [26,27].

In a recent electrophysiological study, it was observed that activity of NAC shell neurons is regulated by the baseline activity of VTA neurons and transient inactivation of VTA function can attenuate the neuronal responses of NAc shell to morphine [28]. Also, there is an evidence indicating that the spontaneous firing of neurons in nucleus accumbens septi is markedly suppressed following intra-VTA microinfusion of morphine in anesthetized rats. The mentioned inhibitory effect of morphine has been found to be reversed by dopamine (DA) antagonists, suggesting the involvement of DA receptors [29]. In another study, it has been observed that the spontaneous but not the evoked activity of NAS cells can be inhibited by iontophoretic application of morphine implying that the systemic effects of opiates on NAS activity can be mediated by directly affecting the NAS cells and through affecting the VTA inputs as well [30]. Although the effect of opiates on spike activity of mesolimbic components have been investigated in animal models, opioid-induced alterations of local field potentials (LFPs) and the involvement of dopamine (DA) system in this process has not been previously addressed. For this purpose, changes of LFP power in VTA and NAc shell was assessed following systemic injection of morphine in freely moving rats. Also, the role of DA system in mediating morphine-induced effects was investigated.

2. Materials and methods

2.1. Animals

A total number of 28 male Wistar rats (250–300 g) were used in this study. Animals were kept in transparent Plexiglas cages (four per cage) in a colony room under stable temperature and on 12-h light/dark cycles with free access to food (pellet chow) and water. An effort was made to minimize the animal suffering during experimental procedures. All experiments were performed according to the guidelines for the care and use of laboratory animals determined by the ethical committee of Institute for Cognitive Science Studies (ICSS). Our study included five groups of rats as follows: Groups 1 and 2: Animals received acute intraperitoneal (i.p.) injection of morphine (0.6 mg/kg, n = 11) or its vehicle (saline, n = 8) respectively, 15 min prior to the beginning of LFP recording. Groups 3 and 4: Animals received i.p. injection of DA receptor type-1 or type-2 antagonist (SCH-23390 or sulpirde, respectively) 15 min prior to morphine administration (i.e. 45 min before the beginning of LFP recording, n = 5 for each group). Group 5: Animals received i.p. injection of antagonist vehicle 15 min prior to morphine injection (n = 5). The time line of experimental protocol is shown in Fig. 1B.

2.2. Drugs

Drugs and chemical reagents used in this study were as follows: morphine sulfate (Temad, Tehran, Iran), SCH-23390 and sulpiride, selective D1 and D2 receptor antagonists respectively (Tocris Bioscience, USA), dimethyl sulfoxide (DMSO), as sulpiride vehicle (Sigma–Aldrich, Germany). Also, for anesthesia induction, ketamine 10% and xylazine 2% (Alfasan, Woerden, Holland) were co-administered intraperitoneally.

2.3. Electrode implantation surgery and LFP recording

Following the induction of general anesthesia by combination of ketamine (100 mg/kg) and xylazine (10 mg/kg), animals were fixed in the stereotaxic instrument (Stoelting, USA) by two specific blunt ear bars and a tooth piece adjusted at -3.3 mm. A small incision was made on the scalp along the midline and the skull surface was exposed and cleaned. Then, the stereotaxic coordinates for VTA and NAc shell were found on the right side and marked accordingly (for VTA: 5 mm posterior to bregma, 0.5 mm lateral to midline, 8.5 mm vertical from the skull and for NAc shell: 2 mm anterior to bregma, 0.7 mm lateral to midline, 7 mm vertical from the skull). Afterwards, two minute holes were carefully drilled on the marked spots to be used for electrode implantation. In addition, two small stainless steel screws were fixed on the skull surface near to each hole each of which were connected to a reference wire (Fig. 1A). Also, in order to provide further structural support, two similar screws were additionally anchored in the skull.

Unipolar recording electrodes were prepared by tightly twisting two pieces of teflon-coated wires together (125 μm in diameter; DC resistance = 8.7 Ω, A.M. system Inc., USA) to reach the required level of rigidity. Obviously, the tips of these electrodes on both sides (recording tip and connection end) were not insulated [31]. As aforementioned, two reference electrodes were also connected to the screws anchored in the left side of the skull surface. Two small pins were attached to the electrode ends (for both recording and reference wires) and then inserted to a small socket. The prepared recording electrodes were gently lowered down into the regions of interest (i.e. VTA and NAc shell) and the whole structure was finally secured on the skull by dental cement. Animals were given a 7 days post-operative recovery period and during three consecutive days before the test, they were placed in the recording chamber (1 h in each day) to get accustomed to the novelty of lab environment. Then, the socket, fixed on the animal's head, was connected to the recording system. Spontaneous local field potentials of VTA and NAc shell neurons were simultaneously recorded by two distinct channels and digitized (at 200 Hz, Fig. 3) using a commercial data acquisition board (D3111 model, Science Beam Co., Tehran, Iran).

2.4. Histological verification

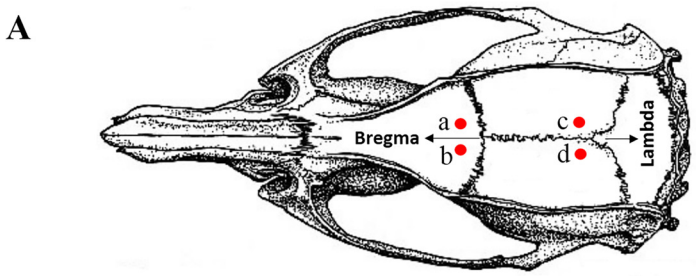
In order to ensure the accuracy of electrode implantation, rats were deeply anaesthetized by i.p. injection of urethane (1.2 g/Kg) at the end of each experiment. Then, a direct current was applied to both recording electrodes using a 9 V battery during 5 s. Animals were finally decapitated, brains were removed and submerged in phosphate-buffered formalin solution for 48 h. The fixed brain tissues were glued on the cutting platform of a vibrating microtome (Campden Co., USA) and coronal slices of 200 μm thickness were prepared. Dark lesion sites (caused by the aforementioned application of electrical current) were visually observed on slices (Fig. 2) and compared to the corresponding sections in the rat brain atlas of Paxinos and Watson [32]. Animals with misplaced lesion trace were excluded from the study.

2.5. Spectral analysis

The recorded LFP signals for each animal were analyzed offline using a custom-written MATLAB code. Power spectra were calculated for the predefined frequency components of the LFP waveform (Delta: 0–3 Hz, Theta: 4–8 Hz, Alpha: 8–13 Hz, Beta: 13–30 Hz, and Gamma: 30–45 Hz) by means of Welch's periodogram (built-in MATLAB *pwelch* function). Relative power spectral density (rPSD) was calculated by dividing the PSD of each frequency range by the sum PSD of the whole frequency. Phase coherence was analyzed using the mscohere.m function from the Signal Processing Toolbox.

2.6. Statistics

Statistical analysis was performed by GraphPad Prism software, version 6.01 for Windows (GraphPad Software, USA). The obtained results were compared among different experimental groups by one-way ANOVA followed by Tukey's post hoc test. Data are indicated as mean ± standard error of the mean (SEM). In all experiments, statistical significance was considered as the $P < 0.05$.



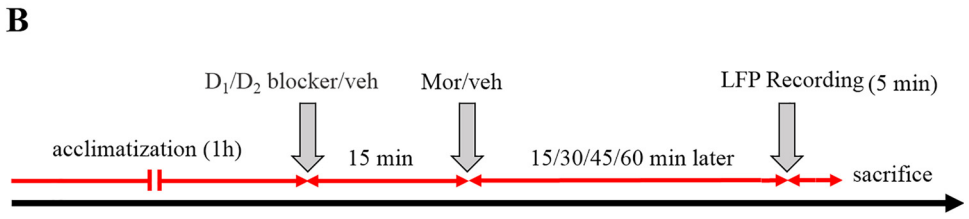


Fig. 1. Schematic representation of electrode implantation sites and the timeline of experimental protocols. A) Indicates the site of electrode insertion on rat skull surface as follows: NAc shell recording and reference electrodes (a and b, respectively), VTA recording and reference electrodes (c and d, respectively). B) Indicates the time line of experimental protocols for drug application and LFP recording. Veh: Vehicle and Mor: Morphine.

3. Results

3.1. The effect of morphine on LFP power of VTA and NAc shell neurons: role of dopamine receptors

As aforementioned, morphine was acutely injected (0.6 mg/Kg, i.p.) and 15 min later, spontaneous LFPs were recorded from VTA and NAc shell in freely moving rats at 15 min intervals (Fig. 1B). As indicated in Fig. 4, morphine significantly increased the relative power spectral density (rPSD) of LFPs for all frequency bands in VTA (i.e. delta, theta, alpha, beta and gamma) compared to the vehicle group. However, in NAc shell, morphine reduced the rPSD in theta range, but did not affect other components (Fig. 5). In the next step, in order to reveal whether the observed morphine-induced effects on LFP power are mediated by dopaminergic system, selective dopamine typ-1 and type-2 (D_1 and D_2) receptor antagonists (SCH-23390 and sulpiride, respectively) were separately administered 15 min prior to morphine injection and LFP changes were evaluated in VTA and NAc shell 15, 30, 45 and 60 min later. The obtained results indicated that morphine-induced potentiation of LFP power in VTA is significantly prevented in rats pre-treated with D_1 and D_2 blockers. In other words, rPSD of LFPs in these animals were not significantly different from that of the control (vehicle-treated) group. Also, looking at the Fig. 4, there seems to be a potential difference in effect of the D1 and D2 antagonists on the beta component, however this is not statistically significant. In NAc shell, morphine-induced attenuation of theta band was not affected by antagonist pre-treatment. The coherence between VTA and NAc shell, as an index of neural synchronization [33] was not affected following morphine injection in any oscillatory range, however, morphine enhanced the coherence in two frequency ranges (alpha and beta) when animals were pre-treated by the D1 receptor antagonist SCH-23390 (Fig. 6).

4. Discussion

There are several lines of evidence indicating that acute opioid exposure can trigger the occurrence of rapid tolerance and dependence to these drugs [34,35,36]. More specifically, in a previous electrophysiological study, it was observed that even a single dose of morphine can persistently alter the activity of VTA dopaminergic (DA) neurons in rats [37]. In another report, acute administration of morphine (1 mg/

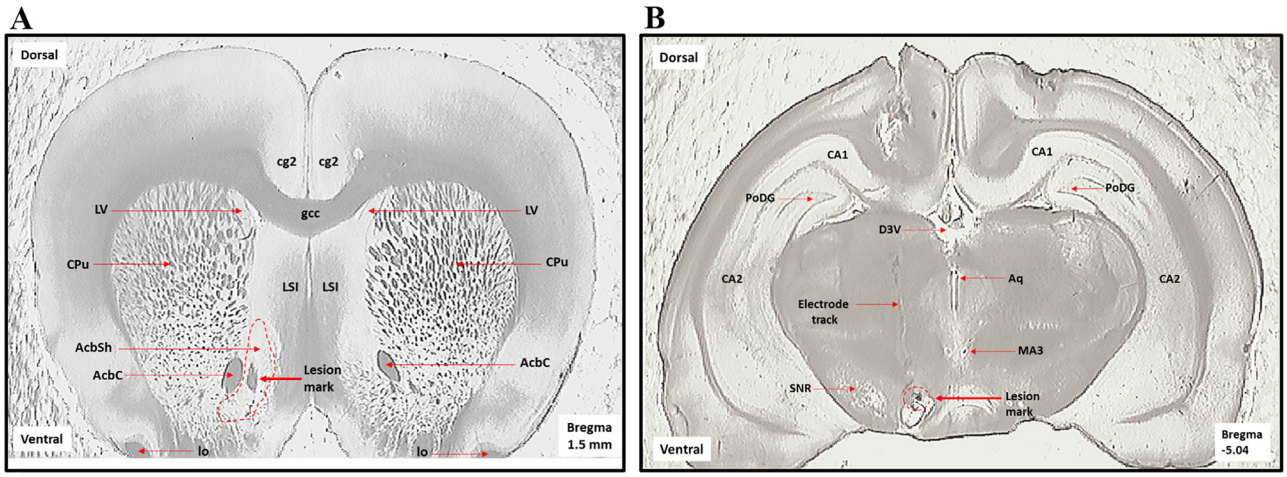


Fig. 2. Histological verification of electrode tips. Sample photomicrographs indicating the electrical lesion sites (left as dark marks) on NAc shell (A) and VTA (B) in coronal rat brain slices compared to the corresponding sections on rat brain atlas of Paxinos and Watson. A) AcbC: accumbens nucleus core; AcbSh: nucleus accumbens shell; lo: lateral olfactory tract; LSI: lateral septal nucleus intermediate; gcc: genu of the corpus callosum; Cg2: cingulate cortex area 2; CPu; caudate putamenand; LV: lateral ventricle, B) SNR: substantia nigra, reticular part; MA3: medial accessory oculomotor nucleus; D3V: dorsal 3rd ventricle; Aq: aqueduct; PoDG: polymorph layer dentate gyrus; CA: field CA1 of the hippocampus; CA2: field CA2 of the hippocampus.

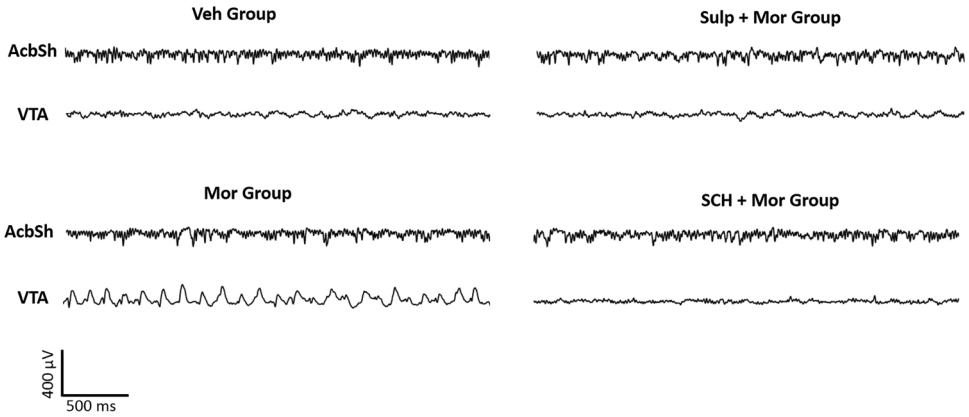


Fig. 3. Sample traces of LFP recording in different experimental groups. AcbSh: nucleus accumbens shell, VTA: ventral tegmental area.

kg. i.v.) in naïve rats was found to increase both the firing rate and the burst discharge of VTA DA neurons [38]. Acute morphine injection has also been shown to increase dopamine release within the nucleus accumbens [39]. The dose of morphine used in our study (i.e. 0.6 mg/kg) is very close to the dose previously reported to induce potent positive reinforcing effect measured by self-administration experiments in rats (i.e. 0.56 mg/kg) [40]. Consistently, this dose of morphine has been found to significantly increase the expression of reward-related behavioral manifestations such as locomotor activity in naïve rats [41].

Mechanistically, opioid-induced activation of VTA dopaminergic neurons has been attributed to a disinhibitory mechanism. In other words, suppression of GABAergic transmission within the VTA by opioids leads to the activation of VTA to NAc dopaminergic afferents [42,43]. Increased LFP power of VTA neurons following morphine injection in our study is in line with the results of a previous study indicating that morphine-induced enhancement of VTA firing rate and burst activity is temporally associated with elevation in power of slow LFP oscillations [37]. These rhythmic activities, which are believed to be mainly dependent on the inputs from prefrontal cortex [44], are known to regulate the pattern of firing rate in VTA dopaminergic neurons [45]. Interestingly around 40% of VTA GABAergic neurons have been found to exhibit oscillatory activity in their power spectra in response to sensory stimuli [46]. Given that GABAergic neurons of VTA are the fundamental modulators of VTA dopaminergic projections, acute morphine challenge may induce a rhythmic activity in these GABAergic cells and therefore cause a similar oscillation in DA neurons and the subsequent alteration of dopamine release in VTA targets. In addition, the effect of morphine administration on LFP power has previously been investigated within the mesolimbic pathway. For example, systemic injection of morphine was found to potentiate the LFP power of NAc (Gamma band) and enhance the VTA-NAc coherence in mice [45]. No significant change in LFP power of VTA or other components of NAc has been reported in this study. In contrast, our results demonstrated the enhancement of all LFP frequency bands in VTA following morphine injection with almost no (except theta) alteration in NAc shell as well as the mentioned coherence. These inconsistencies may result from the difference in animal models used (mice vs. rats), dose of morphine (5 and 15 mg/kg vs. 0.6 mg/kg) and most probably, the recording region (NAc core vs. NAc shell). In this regard, there are evidence indicating that drug-induced neuroadaptations develop

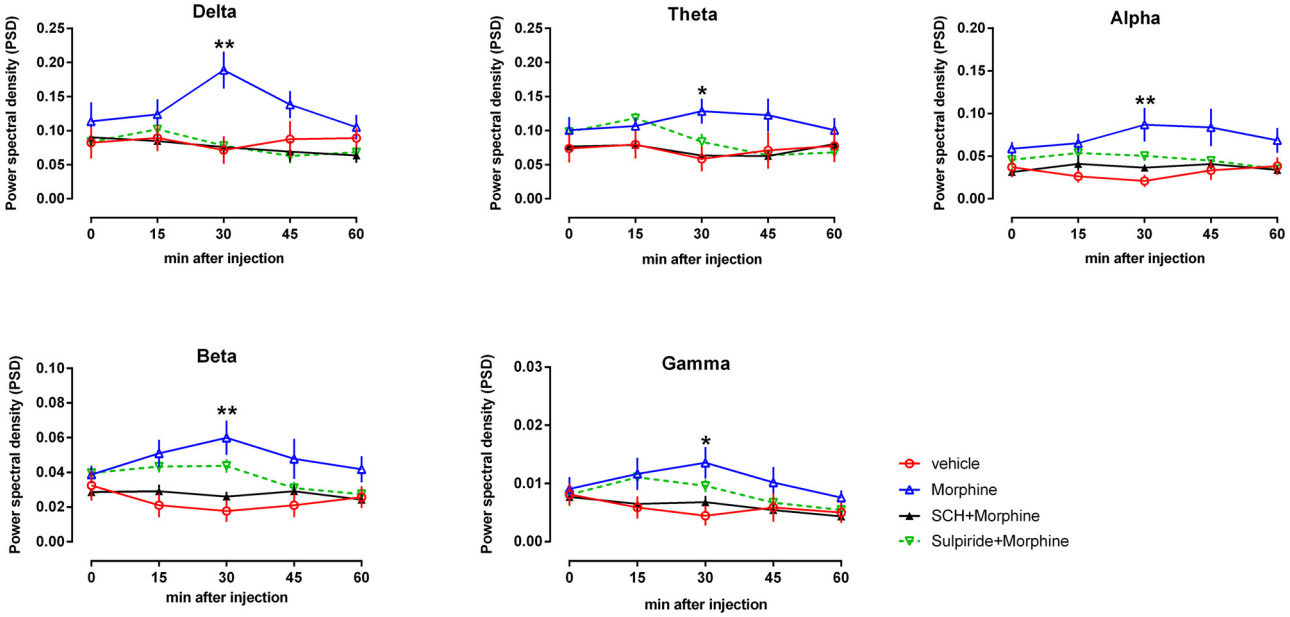


Fig. 4. Power spectral analysis of LFP frequency bands in VTA among different experimental groups. Data are expressed as ± standard error of the mean (SEM). * $p < 0.05$ and ** $p < 0.01$ compared to the vehicle group. One way ANOVA followed by post-hoc Tukey's test. Delta: $F(3, 25) = 6.825$, $P = 0.0016$; Theta: $F(3, 25) = 3.901$, $P = 0.0205$; Alpha: $F(3.25) = 3.967$, $P = 0.0193$; Beta: $F(3, 25) = 5.878$, $P = 0.0035$; Gamma: $F(3, 25) = 3.432$, $P = 0.0323$. The numbers in the parenthesis after the F value represent DFn (degree of freedom in numerator) and DFd (degree of freedom in denominator), respectively. DFn = (number of groups)-1 and DFd = (total number of subjects) - (number of groups). The time point 0 represents baseline recording.

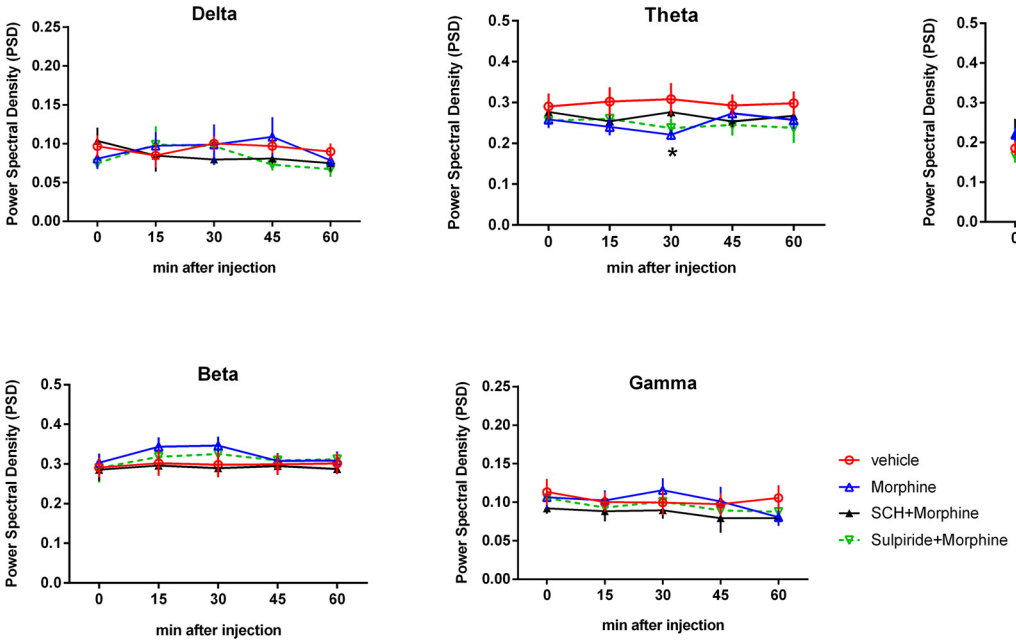


Fig. 5. Power spectral analysis of LFP frequency bands in NAc shell among different experimental groups. Data are expressed as ± standard error of the mean (SEM). * $p < 0.05$ compared to the vehicle group. One way ANOVA followed by post-hoc Tukey's test. Delta: $F(3, 25) = 0.09011$, $P = 0.9648$; Theta: $F(3, 25) = 2.726$, $P = 0.0646$; Alpha: $F(3, 25) = 0.9340$, $P = 0.4389$; Beta: $F(3, 25) = 1.173$, $P = 0.3397$; Gamma: $F(3, 25) = 0.4796$, $P = 0.6992$. The time point 0 represents baseline recording.

differently in time within the NAc core and shell [1,21]. Consistently, dopaminergic transmission in the two mentioned sub-regions has been shown to be mediated through functionally distinct mechanisms [47]. Although the involvement of VTA and NAc shell in modulation of reward processing has been addressed, the role of DA system in mediating the opiate effects on LFPs has not been previously investigated in freely moving state. Our results indicated that acute morphine administration enhances the LFP power in all frequency bands within the VTA and attenuates only one component (theta) in NAc shell region. With this in mind, the mentioned morphine-induced excitation of VTA dopaminergic neurons [30] might be associated with our current observation i.e., morphine-induced enhancement of LFPs in this brain structure.

Another interesting finding was that although morphine injection does not affect the coherence per se, it can enhance this index in two frequency ranges (alpha and beta) when animals are pre-treated by the D1 receptor antagonist SCH-23390 (Fig. 6). To our knowledge, this observation has not been reported in literature and is in line with the results of previous studies emphasizing locale-specific disparities among the VTA-NAc core/shell reward pathways [28].

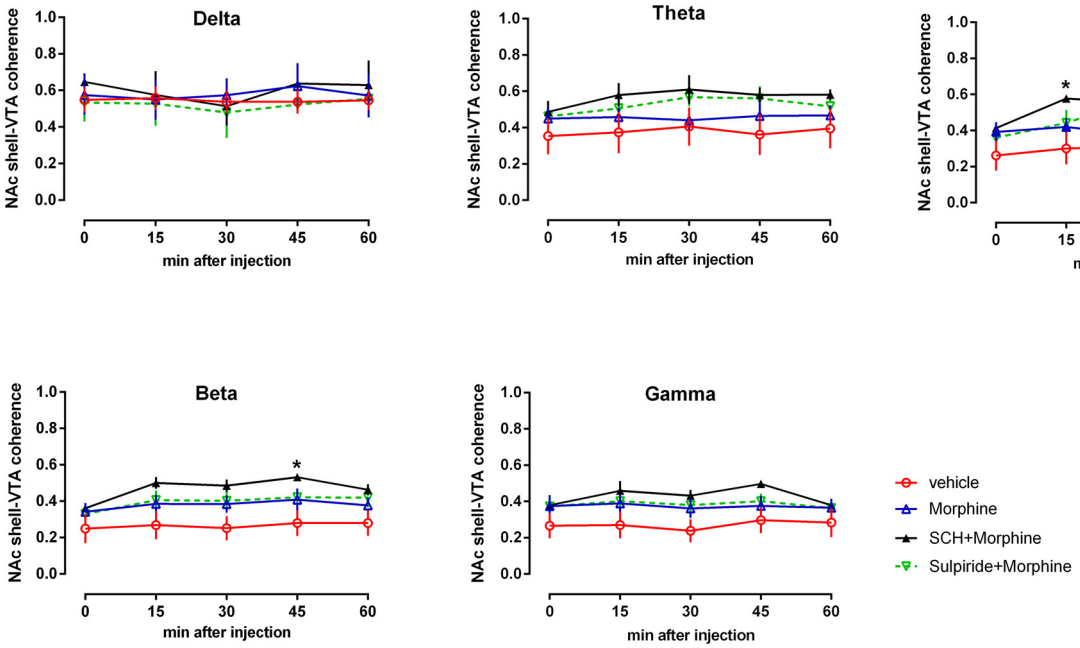


Fig. 6. NAc shell-VTA coherence values in various frequency bands of different experimental groups. Data are expressed as ± standard error of the mean (SEM). * $p < 0.05$ compared to the vehicle group. One way ANOVA followed by post-hoc Tukey's test. Alpha: $F(3, 25) = 2.439$, $P = 0.0880$; Beta: $F(3, 25) = 2.496$, $P = 0.0840$. The time point 0 represents baseline recording.

We also found that the observed morphine effect in VTA is mediated by D_1 and D_2 receptors, as the LFP power in rats pre-treated with selective blockers was not significantly different with that of the vehicle group. This is consistent with previous reports supporting the involvement of dopamine system in mediating opiate effect within the mesolimbic circuit [10,26,48,49].

For future works, we suggest to focus on mechanisms underlying dopamine-morphine interactions. Another line of study may focus on acute vs. chronic effects of morphine on LFP power and evaluation of the naloxone challenge as well. In addition, in the present study we did not record the behavioral manifestations of animals following pharmacological interventions. This is very important because morphine and dopamine antagonists can alter the locomotor activity and in turn affect LFPs regardless of morphine's direct impact. Also, it should be noted that repetitive morphine injection has been shown to induce different effects on NAc LFP power spectra [50], thus, the present results may not generalize to the addictive state when morphine exerts strong rewarding effects.

5. Conclusion

Our results indicate that a single dose of morphine can potentiate the power of LFPs in VTA and this effect is, at least in part, mediated by the activity of dopamine receptors throughout the CNS. Lack of morphine effect on most LFP frequency bands in NAc shell suggests the possibility that NAc sub-regions (core vs. shell) may differentially modulate the opioid-related reward processing within the mesolimbic pathway.

Conflict of interest

The authors declare no conflict of interest related to this work.

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