Physiology & Behavior 145 (2015) 112–117

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Cocaine exposure alters dopaminergic modulation of prefronto-accumbens transmission

Xiusong Wang [a,1], Lei Liu [b,1], Wendy Adams [c], Shouxin Li [d], Qian Zhang [d], Bingjin Li [b], Min Wang [a,*,2], Ranji Cui [b,**,2]

[a] Key Laboratory of Animal Resistance of Shandong Province, Department of Anatomy and Physiology, College of Life Science, Shandong Normal University, Jinan, China
[b] The Second Hospital of Jilin University, Changchun, China
[c] Department of Psychology, University of British Columbia, Vancouver, Canada
[d] Department of Psychology, Shandong Normal University, Jinan, China

HIGHLIGHTS

- We record NAc field potentials after electrically stimulating the PFC and VTA.
- Stimulation of the VTA is paired at different time intervals to that of the PFC.
- VTA stimulation at −100 ms before PFC stimulation inhibits PFC–NAc transmission.
- Concurrent VTA stimulation with PFC stimulation potentiates PFC–NAc transmission.
- This process of timing-dependent modulation is blunted by prior cocaine experience.

ARTICLE INFO

Article history:
Received 1 January 2015
Received in revised form 28 March 2015
Accepted 30 March 2015
Available online 31 March 2015

Keywords:
Dopamine
Prefrontal cortex
Nucleus accumbens
Ventral tegmental area
Cocaine self-administration

ABSTRACT

In the nucleus accumbens (NAc), dopamine transmission modulates glutamatergic input from the prefrontal cortex (PFC). This neuromodulatory action of dopamine can be disrupted by repeated exposure to psychostimulants such as cocaine. However, it is unclear whether this modulation depends on the precise timing of transmission at the same medium spiny neurons (MSNs) and if so, then whether this timing related modulation is also influenced by cocaine experience. Here, combining cocaine self-administration and *in vivo* extracellular recordings in anesthetized rats, we show that dopamine efflux in the NAc evoked by electrically stimulating the ventral tegmental area (VTA) exerted timing-dependent regulation of the excitatory accumbens response to stimulation of the medial prefrontal cortex (mPFC), and also that this modulation was blunted following prolonged abstinence from cocaine self-administration. These data indicate that dopaminergic timing-dependent dysregulation of mPFC–NAc glutamatergic transmission is implicated in cocaine addiction and might contribute to vulnerability to drug relapse after prolonged abstinence.

1. Introduction

The nucleus accumbens (NAc) receives excitatory glutamatergic afferents from cortical and limbic structures, such as the prefrontal cortex (PFC), hippocampus and basolateral amygdala [18,37,53]. Among these excitatory afferents, the PFC–NAc circuit has been proposed to mediate motivation and reward-related behavior [26]. Several lines of evidence show that prefrontal afferents in the NAc are modulated by dopaminergic inputs from the ventral tegmental area (VTA) [15,42]. Indeed, dopaminergic modulation of the prefronto-accumbens projection is considered critical for goal-directed behaviors and reward processes [15,48].

The timing of different inputs to a synapse is crucial for signal processing and computation. For example, spike timing-dependent plasticity refers to the process where the relative timing between presynaptic stimulation and postsynaptic action potentials controls the direction of synaptic plasticity [11]. In the NAc, the precise temporal sequence of activity of those excitatory inputs has been shown to be critical for signal processing and output functioning of the NAc medium spiny neurons (MSNs) [15,17], however, whether the timing of VTA dopaminergic input activity, relative to PFC glutamatergic input activity, influences PFC–NAc transmission or plasticity has not yet been investigated. Therefore, using *in vivo* extracellular field potential recordings in anesthetized

* Correspondence to: M. Wang, Department of Anatomy and Physiology, College of Life Science, Shandong Normal University, Jinan 250014, China.
** Correspondence to: R. Cui, The Second Hospital of Jilin University, Changchun 130041, China.
E-mail addresses: wangmin78@yahoo.com (M. Wang), cuiranji@jlu.edu.cn (R. Cui).
[1] These authors contributed equally to this work.
[2] These corresponding authors contributed equally to this work.

http://dx.doi.org/10.1016/j.physbeh.2015.03.042
0031-9384/

rats, we set out to explore timing-dependent dopaminergic modulation induced by directly stimulating the VTA on neural responses in the NAc evoked by stimulation of the medial prefrontal cortex (mPFC).

Long-term administration of drugs of abuse, such as cocaine or heroin, induces changes in synaptic transmission or plasticity of mPFC glutamatergic synapses on NAc MSNs [36,44], as well as decreases phasic dopamine release in the ventral striatum [52]. In addition, one previous study using *in vivo* intracellular recording showed that repeated methamphetamine administration abolished the ability of VTA train stimulation to dampen PFC-evoked responses in NAc [4]. However, whether prior exposure to cocaine alters timing-dependent effects of dopaminergic modulation on this circuit remains to be examined. Taken together, we hypothesized that timing-dependent dopaminergic modulation of mPFC–NAc transmission exists and that this process might be altered by prior exposure to cocaine.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (80–100 g) were purchased from Jilin University (Changchun, Jilin, China) at the age of 20–28 days. Rats were housed under conditions of controlled temperature (22 ± 1 °C) and relative humidity (60 ± 5%) with a 12 h light/dark cycle (on at 7:00, off at 19:00). Rats were allowed to acclimate in the vivarium for at least 1 week prior to surgeries, and had access to food and water *ad libitum* throughout the experiment. All procedures were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee at Jilin University.

2.2. Self-administration surgery and training

Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p., Sigma, St. Louis, MO, USA) and xylazine (5 mg/kg, i.p., Sigma). The surgical protocol was derived from Wang et al. [51]. Briefly, the right jugular vein was isolated and one end of silicone tubing (inner diameter 0.51 mm, outer diameter 0.94 mm, Helix Medical, LLC, Carpinteria, CA, USA) was inserted 2 cm into the vein and sutured securely in place. The other end of the tubing was threaded subcutaneously to exit between the scapulae and connected to a custom harness. Rats were allowed to recover for at least 1 week before training, during which catheters were flushed daily with 0.1 ml of heparin (10 U/ml, Sigma) to help prevent catheter occlusion.

Self-administration training was conducted in operant-conditioning chambers enclosed within sound-attenuating cabinets (Med Associates, St. Albans, VT, USA). Training procedures were based on those used in our previous studies [8,33]. Briefly, each chamber contained active and inactive nose poke apertures that could be illuminated, a cocaine-infusion line controlled by a programmable syringe pump, and a house light. No food or water was provided in the chambers during the training sessions. On day 1, animals were placed in the self-administration chamber for an overnight training session on a fixed ratio (FR) 1 schedule. An active nose poke resulted in an infusion of saline or cocaine (0.75 mg/kg in 0.1 ml over 6 s), and the illumination of the light inside the nose poke hole (conditioned stimulus; 6 s). The house light was also illuminated for 20 s during which active nose pokes were counted but resulted in no further infusions. After the house light was extinguished, the next active nose poke resulted in another infusion of saline or cocaine. Nose pokes in the inactive hole were not reinforced but were recorded. Rats were subsequently allowed to self-administer cocaine or saline for 6 h/day for 5 consecutive days on a FR1 schedule. After a 21-day abstinence period in their home cages, rats were used for electrophysiological recordings.

2.3. In vivo extracellular field potential recording

The recording method was modified from previous studies [36,44]. Rats were anesthetized with urethane (1.5 g/kg, i.p.; Sigma) and mounted in a stereotaxic apparatus (Narishige, Tokyo, Japan); body temperature was maintained by a temperature control system (FHC, Bowdoin, ME, USA). During recording, supplemental urethane was administered to maintain a stable level of anesthesia. A concentric bipolar stimulating electrode (200 μm diameter with a tip separation of 500 μm, NE-100, Rhodes Medical Instruments, Summerland, CA, USA) was placed in the medial prefrontal cortex (mPFC; anteroposterior +3.0 mm; mediolateral +0.5 mm; dorsoventral −3.2 mm from brain surface); with these coordinates, the electrode tip ultimately terminated around the interface between the prelimbic and infralimbic mPFC. A second stimulating electrode was placed in the caudal ventral tegmental area (VTA; anteroposterior −6.8 mm; mediolateral +0.7 mm; dorsoventral −8.2 mm from skull surface, 10° angle from coronal plane). Each stimulating electrode was connected to a separated constant current stimulus isolator (Digitimer, Welwyn Garden City, Hertfordshire, England). A glass recording electrode (Warner Instruments, Hamden, CT, USA) pulled on a Narishige PE-2 puller (Narishige) was filled with 0.5 M sodium acetate and 2% pontamine sky blue (open tip resistance, 1–3 MΩ). The recording electrode was lowered into dorsomedial region of the nucleus accumbens (NAc; anteroposterior +1.0 mm; mediolateral +0.9 mm; dorsoventral −5.0 to 6.0 mm from brain surface, 10° angle from coronal plane) (see Fig. 1a); with these coordinates, the electrode tip ultimately targeted the border between the NAc core and shell. All coordinates were adapted according to the atlas of Paxinos and Watson [40]. Field potentials were amplified 100 times, Bessel-filtered at 1 or 3 kHz, and digitized at 10 kHz by a MultiClamp 700B amplifier and a Digidata 1440A digitizer (Molecular Devices, Sunnyvale, CA, USA). First, stable evoked field potentials in the NAc were obtained by stimulating the mPFC with a single pulse (pulse width, 0.3 ms) at 0.33 Hz. Field potential slope was measured offline (Fig. 1b) using Clampfit software (Molecular Devices). Then, basal stimulation intensity was determined, which corresponded to 40–50% of the minimum current intensity that evoked a maximum field response. About 1–2 h later, baseline data were recorded for 30 min before conducting the pairing protocol. The pairing protocol involved pairing VTA stimulation with a single pulse (intensity, about 0.6 mA; pulse width, 0.3 ms) at 0 ms or 100 ms before or after mPFC stimulation with a single pulse for 10 sweeps at 0.33 Hz (Fig. 1c). The timing parameters were chosen based on our pilot results and other studies [5]. All data were normalized to baseline and averaged over 5 sweeps (2.5 min) as one data point.

2.4. Histology

Histological verification of recording and stimulation sites was conducted after the recording procedure.

At the end of each recording session, 2% pontamine sky blue was iontophoretically injected into the NAc area to mark the recording position using the stimulus isolator (−40 μA, 5 min). To verify the stimulation sites, the mPFC and VTA were electronically lesioned (200 μA, 10 s). Rats were then transcardially perfused with 4% formalin, and brains were sectioned (100 μm) and placed onto slides for visualization of electrode tip positions.

2.5. Data analysis and statistics

Saline (n = 4) or cocaine (n = 12) self-administering rats were used for the *in vivo* electrophysiology experiment. Naïve rats were also used in this experiment. Since there were no differences between the electrophysiological responses of saline-treated and naïve rats (n = 18), they were pooled together as controls (n = 22). All data are expressed as mean ± standard error of the mean (SEM). Data were analyzed using