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Research report

Local field potentials in the ventral tegmental area during cocaine-induced locomotor activation: Measurements in freely moving rats

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ABSTRACT

The ventral tegmental area (VTA) has been established as a critical nucleus for processing behavioral changes that occur during psychostimulant use. Although it is known that cocaine induced locomotor activity is initiated in the VTA, not much is known about the electrical activity in real time. The use of our custom-designed wireless module for recording local field potential (LFP) activity provides an opportunity to confirm and identify changes in neuronal activity within the VTA of freely moving rats. The purpose of this study was to investigate the changes in VTA LFP activity in real time that underlie cocaine induced changes in locomotor behavior. Recording electrodes were implanted in the VTA of rats. Locomotor behavior and LFP activity were simultaneously recorded at baseline, and after saline and cocaine injections. Results indicate that cocaine treatment caused increases in both locomotor behavior and LFP activity in the VTA. Specifically, LFP activity was highest during the first 30 min following the cocaine injection and was most robust in Delta and Theta frequency bands; indicating the role of low frequency VTA activity in the initiation of acute stimulant-induced locomotor behavior. Our results suggest that LFP recording in freely moving animals can be used in the future to provide valuable information pertaining to drug induced changes in neural activity.

1. Introduction

The ventral tegmental area (VTA) has been established as a critical nucleus for processing the effects of psychomotor stimulants such as cocaine. The VTA is a structure in the mesolimbic system that projects to the nucleus accumbens in the ventral striatum as well as other areas such as the amygdala and hypothalamus (Adinoff, 2004; Sesack and Grace, 2010; Russo and Nestler, 2013). The administration of psychostimulants such as cocaine induces an increase in locomotor behavior in rats (Henry and White, 1992), which is quantifiable (Cornish and Kalivas, 2001; Rebec, 2006). Cocaine-induced locomotor activity has been associated with changes in neural activity of mesolimbic structures including the VTA, which is a critical nucleus for the initiation phase of drug induced changes in behavior (Henry and White, 1992; Pierce and Kalivas, 1997). The administration of cocaine results in transient cellular changes in the VTA which have been extensively studied. Briefly, the VTA is richly innervated with a large population of heterogeneous dopaminergic cell bodies, comprising approximately 60–65% of the cells in the VTA (Sesack and Grace, 2010). Cocaine increases the dopamine at the postsynaptic receptor site by blocking the dopamine transporter (DAT), which results in dopamine failing to reabsorb back into the presynaptic neuron (Adinoff, 2004; Soderman and Unterwald, 2008; Sabeti et al., 2003). Repeated administration of the dopamine re-uptake inhibitor (GBR 12909) into the VTA results in sensitization of the behavioral locmotor effects of cocaine (Cornish and Kalivas, 2001). Thus, alterations in cellular functioning of neurons in the VTA, in part, underlie psychostimulant-induced changes in behavior and increase in dopamine activity in the area (Byrnes et al., 2000).

The VTA also contains approximately 30–35% of GABAergic neurons (Sesack and Grace, 2010). The release of GABA in the VTA is influenced by D_1 receptors; cocaine administration changes the pre-synaptic regulation of GABA transmission (Pierce and Kalivas, 1997). Other cellular mechanisms in the VTA play important roles in the psychostimulant augmentation of locmotion such as: synthesis

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of the retrograde messenger nitric oxide (Byrnes et al., 2000), orexin A facilitation of VTA neurons (Borgland et al., 2006), endogenous mu opiod receptor activation (Soderman and Unterwald, 2008), brain derived neurotrophic factor support of dopimanergic cells (Horger et al., 1999) and the necessary activation of NMDA receptors in the area (Vanderschuren and Kalivas, 2000). Taken together, many cellular mechanisms are activated during cocaine induced locomotor changes and certainly contribute to the oscillation of electrical activity in the vicinity of the VTA.

Psychostimulant-induced changes in locomotor activity can be impeded by lesions to the VTA (Byrnes et al., 2000), while repeated electrical stimulation of the area results in sensitization of locomotor effects after injection of amphetamine (Ben-Shahar and Ettenberg, 1994). Furthermore, Borgland et al. (2004) found that cocaine induced locomotor behaviors were correlated with synaptic enhancement in the VTA in post-mortem tissue. Although these studies established that the VTA is necessary for the initiation phase of cocaine-induced locomotor activity, our current knowledge of how that activity changes in real time is limited.

Local field potential (LFP) recording is a measure of the low-frequency neuron activity in the vicinity of the tip of the electrode, providing information about activity in real time (Lindén et al., 2011). The LFP measure reflects activity within an average range of 200–400 μm (Katzner et al., 2009; Xing et al., 2009). The development of our custom-designed wireless recording module presents an opportunity to assess LFP changes in the VTA of freely moving rats during the initiation phase of cocaine-induced locomotor activation (Ativanichayaphong et al., 2008; Farajidavar et al., 2012; Zuo et al., 2012).

The purpose of this study was to investigate the changes in VTA LFP activity in real time that underlie cocaine induced changes in locomotor behavior. The hypothesis was that cocaine would provoke changes in VTA LFP activity concomitant with drug induced locomotor displays. Preliminary data were previously presented in abstract form (Harris et al., 2013).

2. Materials and methods

2.1. Animals

Eight adult female Sprague-Dawley rats weighing 247–305 g at 7–8 months of age were taken from the University of Texas at Arlington vivarium. Animals were housed in cages of 3–4 and given access to food and water ad libitum. They were kept on a 12 h light dark cycle from 7:30 a.m. to 7:30 p.m. Testing occurred during the light cycle (the animals active phase). All animal procedures were preapproved by the University of Texas Arlington Institutional Care and Use Committee (IACUC) and were in compliance with AAALAC standards.

2.2. Electrode implantation

After placement into a stereotaxic frame under sodium pentobarbital anesthesia (50 mg/kg, i.p.), subjects received a right unilateral VTA implant of a .23 mm bipolar stainless steel electrode (Plastics One, Roanoke VA). The electrode was attached to a plastic threaded pedestal. Electrodes were placed in the VTA using coordinates at 5.8 posterior to bregma, 2.0 mm lateral to the right, and 8.3 mm from the dura at an angle of 10° pointing towards the midline (Paxinos and Watson, 1998). Three stainless steel mounting screws (1.57 mm shaft diameter, Plastics One, Roanoke VA) were fixated on the skull and the electrode pedestal was permanently fixed in place by dental cement. The skin was stapled around the implant and animals were single housed after surgery. A period of 4 weeks for recovery was allotted before testing commenced. Animals were monitored each day after surgery for signs of infection or distress.

2.3. Locomotor and local field potential recordings

Our custom-built LFP module is a closed-loop digital wireless system that has both stimulating and recording subsystems, although just recording was used in this experiment (Zuo et al., 2012). On the test day, subjects were placed under isoflurane anesthesia (3% isoflurane/97% oxygen induction) and the wireless recording module (weighing less than 20g) was connected to the implanted electrode and mounted on a backpack worn by the rat along with a 3 V lithium battery. The module signal amplifies and transmits to a USB dongle on the host computer. The graphical user interface for displaying recorded activity was custom made through Labview. The rat was disconnected from the isoflurane for a period of 15 min and placed in locomotion test chamber to record LFP and locomotion simultaneously.

Locomotor activity was recorded in a single outer chamber of a three-chambered Med Associates Inc. (Georgia, VT) conditioned place preference apparatus (8.25″ W × 8.24″ H × 26.75″ L) that was lit by a single bulb. The chamber was equipped with 16 infrared photo beam detectors evenly spaced along each wall of the apparatus for automated data collection. Consecutive photo beam breaks (movement counts) were automatically recorded using Med Associates IV software (Med Associates; Georgia, VA). Locomotor behavior was regarded as the interruption of an infrared laser beam elicited by movement of the animal. A period of fifteen minutes was allotted for recovery from anesthesia before testing began in the following sequence (Fig. 1): (1) thirty minutes of baseline locomotor and LFP activity was recorded, (2) after an intraperitoneal NaCl injection (0.9% NaCl at 0.1 ml/kg), animals were promptly placed back into the chamber where recording was resumed for another 30 min, (3) following an intraperitoneal cocaine hydrochloride injection (10 mg/kg dissolved in 0.9% saline), animals were returned to the chamber for 60 min of recording.

2.4. Histological confirmation of electrode placement

After testing was completed, animals were sacrificed via carbon dioxide euthanasia. Brains were extracted and fixed in 33% formaldehyde for 48 h and then switched to a 30% sucrose solution for 48 h. Brains were sliced with a microtome (American Optical Corporation, Buffalo NY, Model 860) at 80 μm (coronal sections) and mounted to gelatin coated slides. Thionine staining was applied and slides were cover slipped with Shur/Mount Toluene based liquid mounting media (Triangle Biomedical Sciences). Electrode placement was analyzed under a microscope. Of the 8 animals that received an implant at the VTA region, 5 were included in the main analysis (see Fig. 2 for electrode placement). Three subjects were not included in the statistical analysis because placement of the electrode in the VTA could not be confirmed. Two observers analyzed placement of the electrodes.

2.5. Statistical analyses

Locomotor behavior was recorded as number of beam breaks per minute in the conditioned place preference chamber. The number of beam breaks per minute for each animal was exported from the conditioned place preference chamber MedPC file into Excel. Averages were computed for each time-point (baseline, saline, cocaine 0–30 min, cocaine 30–60 min) and imported into SPSS where a repeated-measures ANOVA was run to analyze locomotor changes over time. A significant effect ($p < .05$.) was analyzed further using post-hoc LSD test. All data are presented as mean ± SEM.