Published in final edited form as:

Synapse. 2014 July ; 68(7): 321–323. doi:10.1002/syn.21744.

Olfactory Tubercle Neurons Exhibit Slow-Phasic Firing Patterns During Cocaine Self-Administration

BRENDAN M. STRIANO¹, DAVID J. BARKER¹, ANTHONY P. PAWLAK¹, DAVID H. ROOT^{1,2}, ANTHONY T. FABBRICATORE¹, KEVIN R. COFFEY, JOSHUA P. STAMOS, and MARK O. WEST^{1,*}

¹Department of Psychology, Rutgers University, 152 Frelinghuysen Road, Piscataway, New Jersey 08854

²Neural Networks Section, Integrative Neuroscience Research Branch, National Institute on Drug Abuse, 251 Bayview Blvd., Baltimore, Maryland 21224

Keywords

addiction; dopamine; ventral striatum; cocaine

INTRODUCTION

The Olfactory Tubercle (OT) shares many relevant similarities to the Nucleus accumbens (NAcc). While both the structures have been implicated in the rewarding properties of drugs, the OT has not been as thoroughly investigated with regard to reward processing. Anatomical and cellular studies have revealed that both the NAcc and OT share continuous stretches of medium spiny neurons. Moreover, projections from the hippocampus and piriform cortex terminate in both the NAcc and OT, both NAcc and OT project to ventral pallidum, and both structures exhibit similar reactions to acetyl-cholinesterase staining, distinct from other structures in close proximity (Heimer and Wilson, 1975; Shipley et al., 1995; Ikemoto, 2007). Because of the cellular, afferent, and efferent similarities between the OT and the NAcc, Heimer and Wilson suggested both brain regions to be part of the ventral striatal system. Furthermore, they believed the OT and NAcc to contribute to the same neurobehavioral processes.

The roles of the OT and NAcc in processing rewarding stimuli involve dopaminergic projections from the ventral tegmental area (VTA). Accordingly, the OT has been shown to support intracranial self-administration (S-A) of dopamine (DA) agonists: cocaine and amphetamine (Ikemoto et al., 2007), as does the medial shell subregion of the NAcc (Ikemoto et al., 2007; Carlezon et al., 1995). Moreover, 6-OHDA depletion of DAergic

© 2014 WILEY PERIODICALS, INC.

*Correspondence to: Mark O. West, Department of Psychology, Rutgers University, 152 Frelinghuysen Road, Piscataway, NJ 08854. markwest@rutgers.edu.

The authors have no financial interests to be disclosed.

Additional Supporting Information may be found in the online version of this article.

fibers from the VTA causes a significant decrease in the DAergic innervation of the ventral striatum, as well as in the rewarding efficacy of intracranial self-stimulation (Fibiger et al., 1987). Concordantly, the DAergic innervation of the OT has been found to be crucial in the development of a conditioned place preference for methylphenidate (Sellings et al., 2006a,b) and manipulations of DA have proven to be crucial for producing rewarding effects in both regions (Ikemoto et al., 2007).

A large body of electrophysiological research has focused on the role of the NAcc in reward processing. These studies have demonstrated that neurons show slow-phasic changes in firing rate for minutes surrounding an infusion. The “progressive-reversal” slow phasic pattern is characterized by a postinfusion firing change during cocaine S-A (Fig. 1B) followed by a reversal that is correlated with the cycle of self-infusion (Peoples and West, 1996). These firing rate changes are both unrelated to the cycle of locomotor behavior (Peoples et al., 1998) and correlated with estimated cocaine levels (Nicola and Deadwyler, 2000). Evidence that such NAcc firing patterns are pharmacologically mediated suggests that they may help transduce fluctuating cocaine levels during S-A into neural signals that may guide drug seeking.

Despite the body of work suggesting a similar role for the OT, patterns of OT neuron firing during cocaine S-A have not been previously reported. As the aforementioned similarities suggest, basal fore-brain processing of not only DA altering drugs, but also general reward processing are not likely restricted to the NAcc, but may also be under the control of the OT. Therefore, in an effort to explore the contribution of the OT to downstream processing, as well as gain a better conceptual understanding of the entire ventral striatum’s role in mediating reward, it is important to assess whether cocaine-sensitive firing patterns are observed in the OT.

To test whether or not slow-phasic firing patterns exist in the OT, male Long Evans rats ($N = 14$) were implanted with indwelling catheters into the jugular vein and sixteen channel microwire arrays targeting the ventral striatum. Animals were trained to self-administer cocaine for 6-h per day by responding on a lever under an FR1 schedule (0.24 mg/0.2 ml/infusion over 7.5 s; $\sim 0.67 - 0.77$ mg/kg). Drug availability was signaled by a stimulus-light located above the lever. A 7.5 s tone signaling cocaine infusion coincided with the infusion pump. Infusions were followed by a 40 s schedule timeout during which responses had no programmed consequences. Before electrophysiological recordings, it was verified that animals had acquired S-A behavior as evidenced by increases in both the number of responses and daily drug intake over days. Following 2-weeks of training, single-units were recorded. Each channel was recorded for one session (Supporting Information 1.1).

Following neural recordings, animals’ brains were extracted and processed to verify microwire placements into the OT. A total of 224 wires were aimed toward the ventral striatum. Microwires were localized to both the NAcc and the OT (Supporting Information 1.2). Data from microwires localized to the NAcc were previously published (Fabbri et al., 2010). Thirty-three microwires exhibiting a single-unit were localized to the OT (Fig. 1A, Supporting Information 1.3).

Patterns of firing in the minutes surrounding each infusion were identified using a principle components analysis (Tabachnick and Fidell, 1989) as described previously (Root et al., 2012; Supporting Information 1.4). Briefly, this analysis allows for the creation of a taxonomy (or typology) of different firing patterns in response to cocaine infusions. Previous studies of slow phasic firing rate data in our laboratory have defined two directions of postinfusion changes in firing rate (increase and decrease) and three different kinds of reversal patterns (early, progressive, and late), which correspond to the time course of the observed change. Progressive-reversal neurons show an initial increase or decrease in postinfusion firing rate followed by a gradual reversal of the postinfusion change (e.g., Fig. 1B).

Nearly all recorded OT neurons (78.8%) exhibited a postinfusion change and subsequent reversal over the interinfusion interval. The most common reversal type in the OT was a progressive-reversal ($n = 19$; 57.6%). Forty-five percent of all neurons exhibited a postinfusion decrease with a progressive reversal, whereas 12 percent of neurons a postinfusion increase with a progressive reversal (Fig. 2). Drug-levels were estimated using first-order pharmacokinetics (described in Supporting Information 1.5; Root et al., 2012). Significant correlations between estimated drug level and firing rate were observed in 42 percent ($n = 14$) of OT neurons (mean $r = 0.51 \pm 0.03$, $P < 0.001$). All 14 of the neurons exhibiting correlations between estimated drug-level and firing rate were of the progressive-reversal type firing pattern. Thus, 74 percent of progressive-reversal neurons exhibited correlation with estimated drug-level (Supporting Information 2.0).

These data demonstrate unequivocally that OT neurons exhibit progressive-reversal firing patterns during cocaine S-A. Identification of these firing patterns draws yet another similarity between the NAcc and OT, suggesting that both process fluctuating levels of cocaine in a similar manner, as does their common target, ventral pallidum (Root et al., 2010) (NAcc and OT further compared in Supporting Information 3.1). Our results add to a growing literature supporting a role for the OT in the rewarding action of psychostimulants. Furthermore, these results also add to mounting evidence that the progressive-reversal pattern is a product of the pharmacological time-course of cocaine's actions in the brain. Notably, evidence from our laboratory has suggested that fluctuations in estimated levels of cocaine also correspond to changes in drug-related affective processing (Barker et al., 2014). Finally, as the first single-unit recording study of the OT during self-administration, the results of this study lay the groundwork for future exploration of the OT's role in drug abuse and motivated behavior and suggest that future studies of the OT are necessary in order to fully explore ventral striatal contributions to reward processing and drug abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Thomas Grace, Linda King, Sisi Ma, Olivia Kim, and Dana Silagi for excellent assistance. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contract grant sponsor: National Institute on Drug Abuse Grants; Contract grant numbers: DA006886 (MOW) and DA032270 (DJB).

References

- Barker DJ, Simmons SJ, Servilio LC, Bercovicz D, Ma S, Root DH, Pawlak AP, West MO. Ultrasonic vocalizations: Evidence for an affective opponent process during cocaine self-administration. *Psychopharmacology*. 2014; 231:909–918. [PubMed: 24197178]
- Carlezon WA, Devine DP, Wise RA. Habit-forming actions of nomifensine in nucleus accumbens. *Psychopharmacology*. 1995; 122:194–197. [PubMed: 8848536]
- Fabbriatore A, Ghitza U, Prokopenko VF, West MO. Electro-physiological evidence of mediolateral functional dichotomy in the rat accumbens during cocaine S-A II: Phasic firing patterns. *European J Neurosci*. 2010; 31:1671–1682. [PubMed: 20525080]
- Fibiger H, LePiane F, Jakubovic A, Phillips A. The Role of dopamine in intracranial self-stimulation of the ventral tegmental area. *J Neurosci*. 1987; 7(12):3888–3896. [PubMed: 3121802]
- Heimer, L.; Wilson, R. The subcortical projections of the allocortex: Similarities in the neural associations of the hippocampus, the piriform cortex, and the neocortex. In: Santini, Maurizio, editor. *Golgi Centennial Symposium: Perspectives in Neurobiology*. New York: Raven Press; 1975. p. 177-191.
- Ikemoto S. Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus-accumbens-olfactory tubercle complex. *Brain Res Rev*. 2007; 56:27–78. [PubMed: 17574681]
- Nicola SM, Deadwyler SA. Firing rate of nucleus accumbens neurons is dopamine-dependent and reflects the timing of cocaine-seeking behavior in rats on a progressive ratio schedule of reinforcement. *J Neurosci*. 2000; 20:5526–5537. [PubMed: 10884336]
- Peoples LL, West MO. Phasic firing of single neurons in the rat nucleus accumbens correlated with the timing of intravenous cocaine S-A. *J Neurosci*. 1996; 16:3459–3473. [PubMed: 8627379]
- Peoples LL, Gee F, Bibi R, West MO. Phasic firing time-locked to cocaine self-infusion and locomotion: Dissociable firing patterns of single nucleus accumbens neurons in the rat. *J Neurosci*. 1998; 18:7588–7598. [PubMed: 9736676]
- Root DH, Fabbriatore AT, Pawlak AP, Barker DJ, Ma S, West MO. Slow phasic and tonic activity of ventral pallidal neurons during cocaine S-A. *Synapse*. 2012; 66:106–127. [PubMed: 21953543]
- Sellings L, McQuade L, Clarke P. Evidence for multiple sites within rat ventral striatum mediating cocaine-conditioned place preference and locomotor activation. *J Pharmacol Exp Ther*. 2006a; 317:1178–1187. [PubMed: 16507711]
- Sellings LH, McQuade LE, Clarke PB. Characterization of dopamine-dependent rewarding and locomotor stimulant effects of intravenously-administered methylphenidate in rats. *Neuroscience*. 2006b; 141:1457. [PubMed: 16753267]
- Tabachnick, BG.; Fidell, LS. *Using multivariate statistics*. 2. New York, NY: HarperCollins Publishers; 1989.
- Shipley, M.; McLean, J.; Ennis, M. Olfactory system. In: Paxinos, G., editor. *The rat central nervous system*. 2. Sydney: Academic Press; 1995.

Fig. 1.

A: Schematic representation of wire placements (black dots). Numbers indicate the distance (mm) from bregma. Wires were verified to be $>150\ \mu\text{m}$ from all borders. **B:** An example progressive-reversal firing pattern with a schematic of estimated drug level over the interinfusion interval (black line). The x -axis shows time in relation to the infusion offset (seconds). Y -axis is an average of firing rate across 50 trials.

Fig. 2.

Patterns detected by the principal components analysis. Bold component traces are representative curves of activity within a group of neurons shown to fire similarly (Anderson–Rubin factor scores) and gray traces represent normalized firing rate (z-score) for individual neurons composing each taxon. Time in relation to the infusion offset (seconds) is shown on the x-axis (infusion at time zero). Plots **A**, **B**, and **C** correspond to decreasing (**A**) and increasing (**B–C**) progressive reversal (PR) patterns, which appear to be pharmacologically mediated by fluctuations in estimated drug level across the interinfusion interval. Plots **D–F** represent late-reversal (LR) and early-reversal (ER) patterns which may or may not be linked to pharmacological mediation. Plot **G** shows traces for neurons that did not load on any of the defined taxa (i.e., those which show no pattern across the interinfusion interval; NC).