Behavioural Brain Research 356 (2019) 266–270

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Short communication

Activation of the ventral subiculum reinvigorates behavior after failure to achieve a goal: Implications for dopaminergic modulation of motivational processes

David Lindenbach*, Jeremy K. Seamans[1], Anthony G. Phillips[1]

Djavad Mowafaghian Centre for Brain Health, Department of Psychiatry, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Keywords:
Dopamine
Nucleus accumbens
Ventral subiculum
Motivation
Depression
Schizophrenia
Deep brain stimulation
Microdialysis

ABSTRACT

Previous studies confirm that brief electrical stimulation of glutamatergic afferents from the ventral subiculum (vSub) can significantly enhance dopamine release in the ventral striatum for an extended duration (> 20 min). However, the functional significance of this effect on motivated behavior remains to be specified. Here we tested the hypothesis that brief electrical stimulation of the ventral subiculum (20 Hz for 10 s) might increase effort expenditure for food rewards. Motivation was assessed by a progressive ratio lever pressing task, which requires continuous escalation of the numbers of lever presses to receive each subsequent sucrose pellet, eventually resulting in the failure to achieve the required ratio for a food reward. vSub stimulation at the start of a session did not affect the rate or total number of lever presses prior to reaching the "break point". In contrast, stimulation of the vSub with identical parameters on a post break point trial resulted in a significant increase in total responses. These findings demonstrate that activation of the vSub with parameters that modulate dopamine efflux in the nucleus accumbens can re-activate goal-directed behavior after failure to achieve a goal. Our data highlight a possible role for the vSub in the pathophysiology and potential treatment of motivational processes linked to psychiatric disease.

Research conducted with both human and animal subjects confirms a critical role for dopamine (DA) in motivating and sustaining goal-directed behaviors when task requirements become onerous [1–3]. Motivation to work for a reward is often assessed using progressive ratio (PR) tasks that require participants to increase the number of lever press responses to obtain each food reward. The maximum effort a subject is willing to expend is defined by the highest ratio of presses achieved to receive the final food pellet (the "break point" [BP]; [4]).

Deficits in motivation are common in many psychiatric disorders, most notably depression and schizophrenia [3,5]. Patients with major depression or schizophrenia with prominent negative symptoms exert less effort on PR schedules, consistent with a diminished motivational state [6,7]. This research is paralleled in animal models of depression that also report reduced PR responding [8,9]. Neurotoxic lesions or pharmacological blockade of the nucleus accumbens (NAc) DA system greatly reduce the BP on PR tasks [10]. Thus, the motivational deficits observed in schizophrenia and depression could be due to altered NAc DA transmission [11]. This hypothesis is supported by the observation that electrical ("deep brain") stimulation of the NAc improved motivation in a small sample of severely depressed patients [12]. Other case studies report that NAc stimulation can reverse the negative symptoms of schizophrenia and formal clinical trials using this intervention are currently underway ([13]; ClinicalTrials.gov ID: NCT02377505).

There is a growing appreciation of the importance of glutamatergic projections from the ventral hippocampus in the modulation of DA function [11,14]. Importantly, glutamatergic afferents from the ventral subiculum (vSub) regulate the number of tonically active DA axons in the NAc [1,15]. Furthermore, brief trains (10 s) of electrical activation of the vSub increase DA efflux in the NAc for 30+ min [16,17]. Behavioral correlates of this sustained increase in DA function have focused exclusively on locomotor activity and therefore more general effects on motivational processes remain to be determined.

We hypothesized that vSub stimulation-evoked increases in NAc DA efflux would alter performance on a PR schedule of reinforcement either by achieving a higher BP response ratio required to obtain the final food reward, or by reinvigorating the effort expended to obtain food

* Corresponding author at: Mathison Centre for Mental Health Research and Education, Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada.
E-mail addresses: david.lindenbach@ucalgary.ca (D. Lindenbach), jeremy.seamans@ubc.ca (J.K. Seamans), aphillips@psych.ubc.ca (A.G. Phillips).
[1] These authors are considered senior authors.

https://doi.org/10.1016/j.bbr.2018.09.002
Received 3 August 2018; Received in revised form 30 August 2018; Accepted 5 September 2018
Available online 07 September 2018
0166-4328/

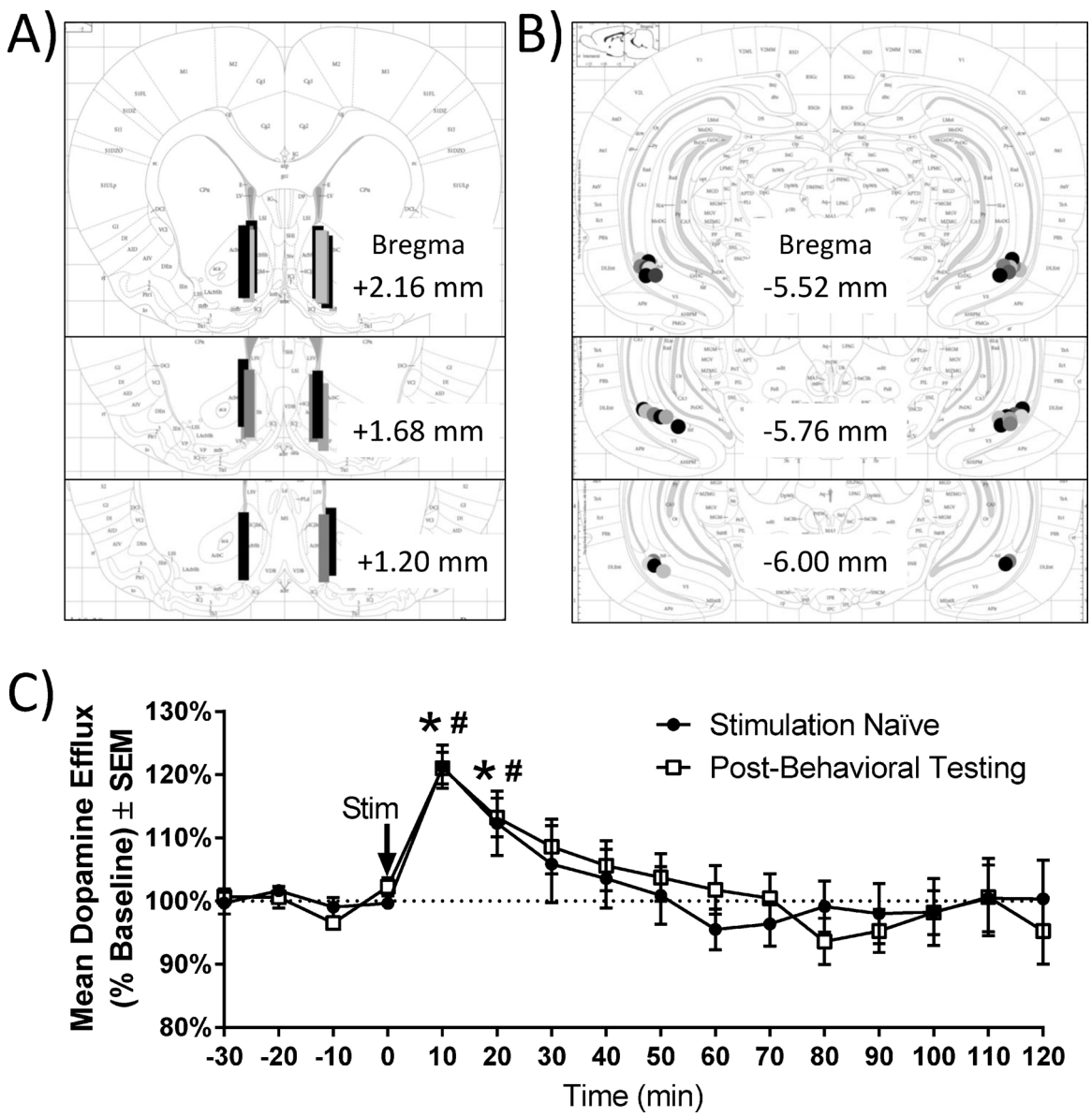

Fig. 1. (A) Placement of dialysis probes in the nucleus accumbens. (B) Placement of stimulating electrodes in the ventral subiculum. (C) Change in dopamine efflux (as percent of baseline) in rats after electrical stimulation of the ventral subiculum (20 Hz for 10 s; n = 9 per group; between-subjects). Stimulation was performed in animals that were stimulation naïve and in animals that had completed behavioral testing (thus, having received three trains of 20 Hz stimulation on two different days). Using Dunnett-corrected p-values compared to own baseline: * $p < .05$ Stimulation Naïve animals; # $p < .05$ Post-Behavioral Testing animals.

reward after failure.

The present study used Long-Evans rats (Charles River), which were 9–12 weeks old at the start of the experiment (n = 17). Animals were maintained on a 12 h light-dark cycle, with experiments performed during the dark cycle (0700–1900). All procedures were approved by the Animal Care Committee at the University of British Columbia and the Canadian Council of Animal Care. Rats were anaesthetized with isoflorane (2–3% for 1–2 h) and placed in a stereotaxic apparatus during surgery. Stainless steel guide cannulas were implanted dorsal to the lateral edge of the NAc shell using coordinates from the rat brain atlas of Paxinos and Watson (from bregma, 1.7 mm anterior, 1.1 mm lateral; from dura, 1 mm ventral; Fig. 1A). Stainless steel obdurators were used to maintain cannula patency. Twisted stainless steel stimulating electrodes (MS303/2B; Plastics One) were implanted in the vSub (from bregma, 5.76 mm posterior, 5.5 mm lateral; from dura, 6.8 mm ventral; Fig. 1B). Cannula and electrodes were stabilized using dental acrylic and four stainless steel screws. Rats were allowed to recover for at least one week prior to performing the microdialysis experiments.

Microdialysis experiments confirmed that vSub electrical stimulation parameters increased NAc DA levels, as in our past studies [16,17]. The microdialysis probes (2 mm length; 0.34 mm OD, 20 kDA pore) were implanted the day before sample collection, with the exposed membrane covering a depth of 5.8–7.8 mm below dura. Dialysate samples were collected every 10 min for at least 60 min before, and 120 min after, unilateral vSub stimulation (20 Hz; 10 s; 300 μA; 0.5 ms pulse width). Samples were analyzed for DA content using high pressure liquid chromatography with amperometric detection [16].

We compared evoked DA efflux using both stimulation-naïve animals and those that had previously received three trains of 20 Hz stimulation during behavioral testing (n = 9 probes per group, unilateral or bilateral placements, from a total of 13 rats). Data were analyzed using a 2-way ANOVA (Time [4 baselines + 12 post-treatment] * Group [Stimulation Naïve vs. Post-Behavioral Testing]). There was no effect of Group or Time*Group interaction, indicating that multiple stimulation sessions did not change the response of the DA system to vSub stimulation. A significant effect of Time ($F_{15,240} = 10.50$,