High frequency stimulation of the subthalamic nucleus decreases cFOS expression in the nucleus accumbens shell

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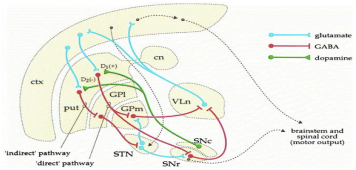
INTRODUCTION

In the face of the rising heroin and prescription opioid epidemic, novel treatments are being investigated for individuals who are resistant to traditional therapies such as cognitive behavioral therapy and pharmacological treatment. Interest in using deep brain stimulation (DBS) to manage and treat drug addiction is increasing due to success seen in Parkinson's Disease patients with unrelated compulsive disorders. It has previously been shown that both lesions of the subthalamic nucleus (STN) and stimulation of the STN decrease cocaine responding in a progressive ratio (PR) session, as well as the time spent in a cocaine-paired chamber in a conditioned place preference test. Evidence that STN stimulation also excites GABAergic and glutamatergic outputs from the STN supports the idea that the effects of STN stimulation on cocaine intake may be extended to other drugs of abuse. Indeed, inactivation of the STN through high frequency stimulation decreases compulsive-like self-administration of heroin.

Our objective was to investigate the consequences of STN high frequency stimulation on the neuronal network associated with the STN and addiction-related brain regions.

BASAL GANGLIA CIRCUITRY



Henderson and Dunnett, 1998 *Brain Research Bulletin*

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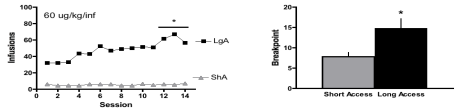
Wade CL, Hernandez DO, Breysse E, de Guglielmo G, Crawford E, Koob GF, Baunez C, George O. Attenuation of compulsive-like heroin self-administration with high frequency stimulation of the subthalamic nucleus. *Submitted to Neuropsychopharmacology*

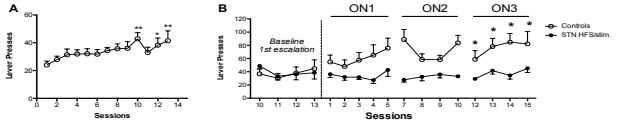
BACKGROUND

Compulsive heroin self-administration



Compulsive Heroin Self-Administration (1): A) Infusion rates of animals in the long access (12 hours) group doubled over the course of the experiment while infusion rates of animals given one hour access to heroin remained stable. B) Animals in the long access group show increased motivation to work for successive infusions, demonstrated by increased breakpoint in a progressive ratio schedule of reinforcement.

Self-Administration before DBS (escalation) and during DBS (re-escalation)



Escalation Re-Escalation

Deep Brain Stimulation in Heroin Self-Administration (2): Animals were allowed to self-administer heroin (60 ug/kg/inf) in daily 10hr (long access) sessions. Animals were divided into stimulated and non-stimulated groups, where the stimulated groups were stimulated for the first 4 hours of each self-administration session. Animals that were in the stimulated group self-administered heroin to a lesser degree than animals in the non-stimulated groups throughout the duration of the experiment. Escalation was defined as a significant increase in infusions as measured by repeated measures ANOVA. (* = $p < 0.05$)

METHODS

Surgery and stimulation: Teflon-insulated platinum wires were implanted bilaterally in the STN (bregma: anterior/posterior, -3.7 mm, lateral, ±2.4 mm, dorsal/ventral, -8.3 mm (from skull), incisor bar set at -3.3 mm) and one week following surgery animals were stimulated for 30 minutes at a 130 Hz frequency and 60 µs pulse width. 60 minutes following stimulation, the animals (along with non-stimulated controls) were sacrificed and perfused for immunohistochemistry (IHC).

IHC: The brains were sectioned into 40 µm slices and preserved prior to processing and mounting. The sections were incubated in rabbit anti c-*fos* polyclonal antibody diluted 1:2500 (Cell Signaling) and ImmPRESS anti-rabbit immunoglobulin G (IgG) peroxidase-linked secondary antibody (Vector Labs). Immunoreactivity was visualized using a DAB substrate kit (Vector Labs). The sections were mounted on coated glass slides and permounted. All of the experimental groups were processed in parallel using the same immunohistochemical procedures.

cFos visualization: Bright-field images of Fos immunoreactivity in the brain areas were captured using a charge-coupled device camera and QImaging EXi Aqua attached to a Zeiss Axioskop 2 microscope. Images for counting labeled cells were captured at 20× magnification. Labeled cells from three sections per rat were bilaterally and automatically counted using IPLab 3.9.4 r5 software for Macintosh (Scanalytics) and iVision 4.0.15 software for Macintosh (BioVision). Counts from all images from each rat were averaged, so that each rat was an *n* of 1.

cFOS EXPRESSION FOLLOWING DBS

Electrode Placement

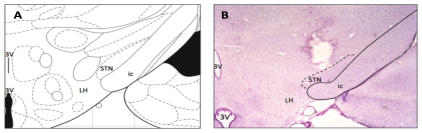
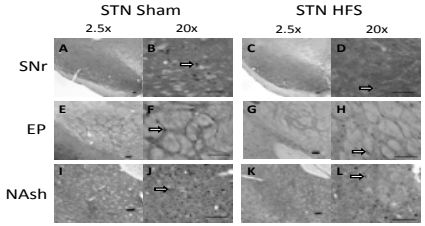
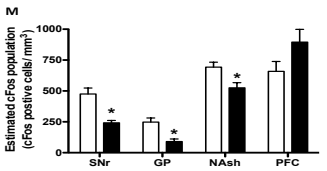


Image of the tip of the electrode at the subthalamic nucleus using Cresyl violet staining.





Orientation was noted at 2.5x (left panels) and cell counts taken at 20x (right panels). Arrows highlight a typical Fos-positive neuron for each section. Scale bars indicate 100um.

CONCLUSIONS

1) As predicted, STN high frequency stimulation decreases cFos expression in the direct output regions of the substantia nigra pars reticulata, and the globus pallidus.

2) Neuronal activity was decreased in the shell of the nucleus accumbens, suggesting that inactivity of the STN has the ability to alter the perception of reward and positive reinforcement.

3) This study provides anatomical support to behavioral data suggesting that deep brain stimulation has potential to treat heroin addiction in medication-resistant patients