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High frequency stimulation of the subthalamic nucleus increases c-fos immunoreactivity in the dorsal raphe nucleus and afferent brain regions

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ABSTRACT

High frequency stimulation (HFS) of the subthalamic nucleus (STN) is the neurosurgical therapy of choice for the management of motor deficits in patients with advanced Parkinson's disease, but this treatment can elicit disabling mood changes. Our recent experiments show that in rats, HFS of the STN both inhibits the firing of 5-HT (5-hydroxytryptamine; serotonin) neurons in the dorsal raphe nucleus (DRN) and elicits 5-HT-dependent behavioral effects. The neural circuitry underpinning these effects is unknown. Here we investigated in the dopamine-denervated rat the effect of bilateral HFS of the STN on markers of neuronal activity in the DRN as well as DRN input regions. Controls were sham-stimulated rats. HFS of the STN elicited changes in two 5-HT-sensitive behavioral tests. Specifically, HFS increased immobility in the forced swim test and increased interaction in a social interaction task. HFS of the STN at the same stimulation parameters, increased c-fos immunoreactivity in the DRN, and decreased cytochrome C oxidase activity in this region. The increase in c-fos immunoreactivity occurred in DRN neurons immunopositive for the GABA marker parvalbumin. HFS of the STN also increased the number of c-fos immunoreactive cells in the lateral habenula nucleus, medial prefrontal cortex but not significantly in the substantia nigra. Collectively, these findings support a role for circuitry involving DRN GABA neurons, as well as DRN afferents from the lateral habenula nucleus and medial prefrontal cortex, in the mood effects of HFS of the STN.

1. Introduction

Currently, high frequency stimulation (HFS) of the subthalamic nucleus (STN) is the neurosurgical therapy of choice for treatment-resistant patients with advanced Parkinson's disease (PD). Randomized controlled trials have shown that HFS of the STN was superior over best medical treatment (Deuschl et al., 2006; Weaver et al., 2009; Williams et al., 2010). Despite improving motor disability, in some patients HFS of the STN induces mood disorders such as depression and increased impulsivity (Berney et al., 2002; Houeto et al., 2002; Temel et al., 2006a). In addition, evidence suggests that the risk of suicide and suicide attempts increases significantly (Soulas et al., 2008; Voon et al., 2008). These mood-related side-effects often mitigate the positive effects on motor symptoms and negatively influence the quality of life of patients and their families (Schrag et al., 2000; Troster et al., 2003).

Depression, impulsivity and suicide are associated with a dysfunctional 5-hydroxytryptamine (5-HT; serotonin) system (Mann, 2003; Smith et al., 1997). Recently we found that, in a rat model of PD, bilateral HFS of the STN inhibited the firing rate of 5-HT neurons of the dorsal raphe nucleus (DRN) and induced 5-HT-dependent changes in depressive-like behavior (Hartung et al., 2011; Temel et al., 2007). Furthermore, in microdialysis studies HFS of the STN was reported to decrease 5-HT release in the rat

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forebrain (Navailles et al., 2010), and we have observed this effect in similar studies (Tan et al., 2010a). These findings support the idea that changes in mood induced by HFS of the STN are caused by reduced 5-HT function.

The neural circuitry underpinning the effect of HFS of the STN on 5-HT neurons is not known but likely involves indirect projections from the STN to the DRN. Thus, although there is no direct projection from the STN to the DRN (Peyron et al., 1998), projections from the STN target regions with major inputs to the DRN including the medial prefrontal cortex (mPFC), lateral habenula nucleus (LHb) and substantia nigra reticulata (SNr) and compacta (SNc) (Aghajanian and Wang, 1977; Hajos et al., 1998; Jankowski and Sesack, 2004; Kirouac et al., 2004; Varga et al., 2001). GABA neurons in the DRN may be a key part of the circuitry because they inhibit nearby 5-HT neurons (Liu et al., 2000) and are selectively targeted by inputs from the mPFC and LHb (Hajos et al., 1998; Varga et al., 2003, 2001).

The present study used molecular markers of neural activity to test the hypothesis that HFS of the STN alters the function of GABA neurons in DRN, as well as DRN input regions. The principle marker used was the activity-dependent immediate early gene c-fos, supplemented by measurements of the metabolic enzyme cytochrome C oxidase. Initial experiments established STN stimulation parameters that would evoke behavioral changes in 5-HT-dependent tests of emotionality.

2. Material and methods

2.1. Animals

Male Lewis rats (280–320 g, Maastricht University) were housed individually under conditions of constant temperature (20–22 °C) and humidity (60–70%) with a reversed light/dark cycle (lights on 17h–05h). Rats had access to water and food *ad libitum*. Experiments were ethically reviewed and approved by the Animal Experimental Committee of Maastricht University.

2.2. Experimental groups

Rats were randomly assigned to one of three groups: i) neurosurgical sham-control without STN electrode implants ($n = 6$), ii) dopamine lesion without STN electrode implants ($n = 10$) and iii) dopamine lesion with STN electrode implants ($n = 12$).

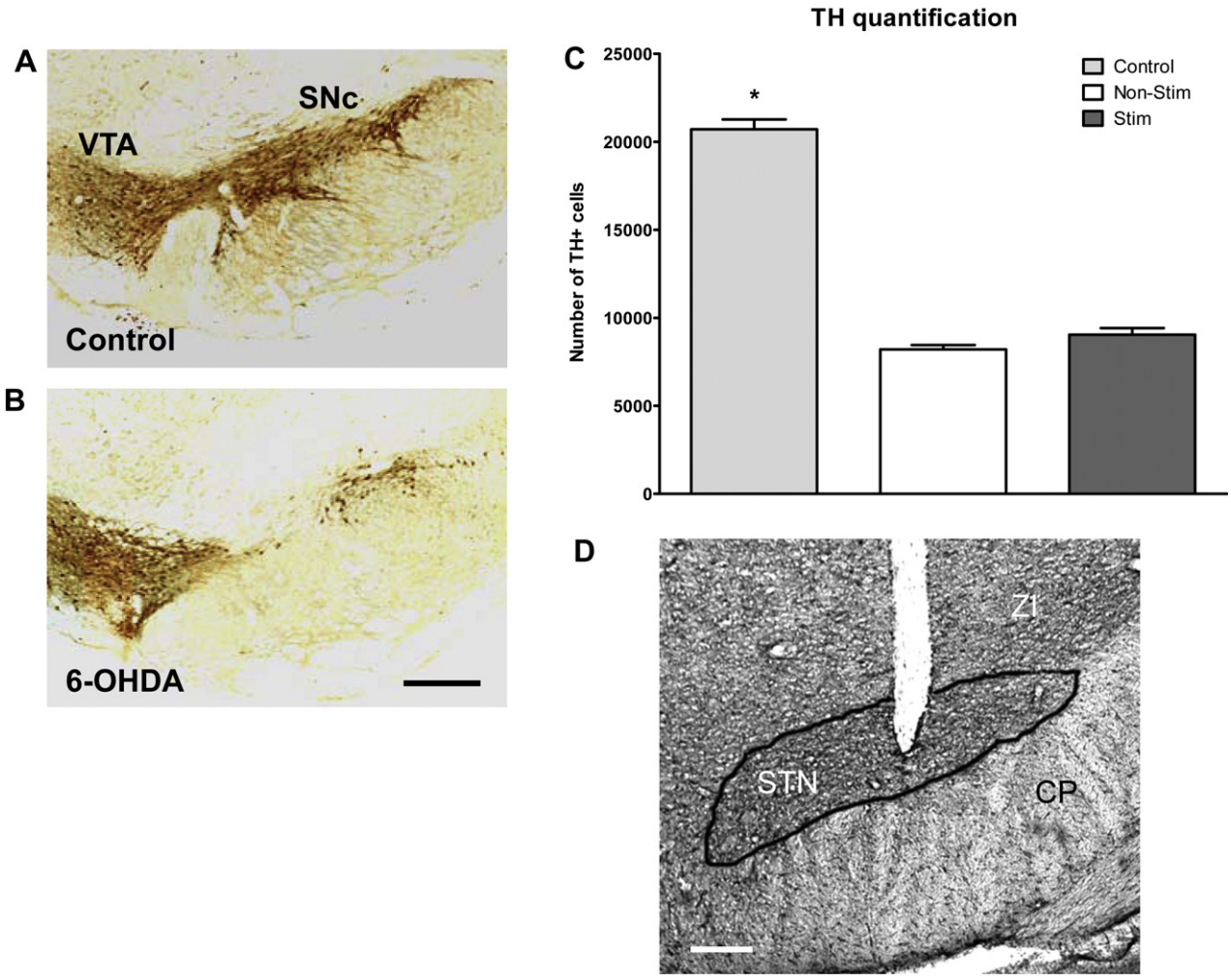

Fig. 1. Effect of 6-OHDA lesions on TH expression in the SNc. TH immunocytochemistry of a control rat (A) and a 6-OHDA treated rat (B) (SNc = substantia nigra compacta; VTA = ventral tegmental area; scale bar = 500 μm). Grouped data for TH-positive neurons in the SNc presented in means ± s.e.m (C), $^*p < 0.05$ control versus non-stim and stim groups. Illustrative coronal section that shows the histological verification of the electrode location in the STN (CP = cerebral peduncle; STN = subthalamic nucleus; ZI = zona incerta; bar = 150 μm) (D).