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THE SUBTHALAMIC ACTIVITY AND STRIATAL MONOAMINE ARE MODULATED BY SUBTHALAMIC STIMULATION

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Abstract—*Aims:* Not all the mechanisms by which subthalamic nucleus deep brain stimulation (STN-DBS) alleviates parkinsonian symptoms have been clarified as yet. The levels of striatal monoamine and the subthalamic beta activity might contribute to its efficacy. However, their direct relationship is unclear. We aimed to examine the correlation between the striatal monoamine and the STN beta activity induced by STN-DBS.

***Experimental procedures:* Experiments were performed under urethane anesthesia in normal ($n = 4$) and 6-hydroxydopamine hemi-lesioned Parkinson's disease (PD) model rats ($n = 5$). STN-DBS was applied to the left STN, and local field potential (LFP) was recorded before and after STN-DBS. Striatal extracellular fluid was collected before, during, and after STN-DBS. Spectral analysis of STN-LFP was performed, and the levels of monoamine were measured.**

***Results:* The levels of 3–4-dihydroxyphenylacetic acid (DOPAC) were significantly decreased after the cessation of stimulation in PD model rats. The levels of none of the monoamines were significantly affected in normal rats. The STN beta power was significantly elevated after the cessation of stimulation in normal rats but was significantly decreased in PD model rats. *Results:* The STN beta power and the levels of DOPAC and 5-HT was positively correlated in PD model rats, whereas the levels of dopamine and 5-HT showed positive correlation and the levels of DOPAC and Homovanillic acid (HVA) showed negative correlation in normal rats.**

***Conclusion:* STN-DBS could decrease the levels of DOPAC and the STN beta power in a PD model rat. The STN beta power and the levels of striatal monoamine might be differentially correlated between normal and PD model rats.**

Key words: Parkinson's disease, subthalamic nucleus, deep brain stimulation, local field potential, striatal monoamine.

INTRODUCTION

Subthalamic nucleus deep brain stimulation (STN-DBS) is the preferred surgical therapy in patients with advanced stage of Parkinson's disease (PD) (Benabid et al., 2009). However, its physiological mechanisms remain unclear (Perlmutter and Mink, 2006; Kringelbach et al., 2007; Humphries and Gurney, 2012).

Because only high-frequency (> 100 Hz) STN-DBS is clinically effective, STN-DBS has been postulated to alleviate pathological oscillation (especially that of the beta band: 15–35 Hz) in the basal ganglia of patients with PD (Brown, 2007; Eusebio et al., 2011; Giannicola et al., 2010; Hammond et al., 2007; Ray et al., 2008).

Another proposed mechanism is that STN-DBS affects neurotransmitter release in the basal ganglia (Windels et al., 2003, 2005; Gubellini et al., 2009). Some studies have examined the effect of STN-DBS on striatal dopamine (DA) release (Lacombe et al., 2007; Pazo et al., 2010). Although positron emission tomography (PET) measurements of [^{11}C]raclopride uptake during STN-DBS in humans failed to demonstrate any change in striatal DA (Hilker et al., 2003), several studies using a rodent model of PD revealed that STN-DBS increased striatal DA release (Meissner et al., 2001, 2002; Lacombe et al., 2007; Paul et al., 2000; Bruet et al., 2001; Pazo et al., 2010). However, stimulation parameters varied considerably among laboratories, and whether or not STN-DBS increases striatal DA is still unknown. Despite these controversial results, it is reasonable to postulate that STN-DBS might affect striatal DA release because it is effective in patients responsive to dopaminergic treatment.

Although both alleviation of pathological oscillation and influence on striatal DA release are plausible mechanisms of STN-DBS (Jenkinson and Brown, 2011), previous studies examined these issues separately. Recent review proposed the close relationships between the dopaminergic activity and beta activity in the basal ganglia, suggesting that beta activity might be elevated when the net DA level is at a low level (Jenkinson and Brown, 2011). We aimed to simultaneously examine the changes in the levels of striatal monoamine and the power in the beta activity of STN induced by STN-DBS

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 6-OHDA, 6-hydroxydopamine; DA, dopamine; DOPAC, 3–4-dihydroxyphenylacetic acid; EDTA, ethylenediaminetetraacetic acid; FFT, fast Fourier transform; H_2O_2, hydrogen peroxide; HPLC, high-performance liquid chromatography; HVA, Homovanillic acid; LFP, local field potential; PBS, phosphate-buffered saline; PBST, PBS containing 0.05% Tween-20; PD, Parkinson's disease; PSD, power spectral density; SNc, Substantia nigra pars compacta; STN-DBS, subthalamic nucleus deep brain stimulation.

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in normal and PD model rats. Since, both striatal monoamine and subthalamic beta power might be changed simultaneously by STN-DBS, we examined the correlation between the striatal monoamine and the beta activity in STN.

EXPERIMENTAL PROCEDURES

Animals and ethic statement

All experiments were performed on adult female Sprague–Dawley rats (14–16 weeks old, weighing 200–300 g) in accordance with the Chiba University Guideline for the Care and Use of Laboratory Animals. The experimental protocol was approved by the Animal Ethics Committee, Chiba University Graduate School of Medicine. All efforts were made to minimize animal suffering and reduce the number of animals used. The animals were housed in a room under standard environmental conditions with an alternating 12-h light/dark cycle.

6-Hydroxydopamine (6-OHDA) lesion (PD model rat)

Surgery was performed to Sprague–Dawley rats under sodium pentobarbital anesthesia (40 mg/kg, intraperitoneally). The animals received a unilateral injection of 2 μg/ml 6-OHDA (Sigma–Aldrich Japan, Tokyo, Japan) dissolved in 5 μl of 0.9% sterile saline containing 0.1% ascorbic acid into the left medial forebrain bundle at a rate of 1 μl/min. The stereotaxic coordinates of the injection site with respect to the bregma were as follows: anteroposterior, −3.6 mm; lateral, 2.0 mm; and dorsoventral, −8.8 mm.

Motor behavior

The extent of the DA neuron lesion was assessed 2 weeks after 6-OHDA injection by challenge with apomorphine (1 mg/kg, intraperitoneally; Sigma–Aldrich). The lesion was considered to be successful in animals that performed > 80 net contraversive rotations in 20 min.

STN-DBS and extracellular recordings of STN

STN-DBS and extracellular recordings of STN were performed in normal (Sprague–Dawley rats) (n = 4) and PD model (n = 5) rats under urethane anesthesia (0.7 g/kg, intraperitoneally). Experiments in PD model rats were performed 30–40 days after 6-OHDA injection.

A concentric platinum/iridium bipolar electrode (outer diameter, 125 μm; Pt/Ir; FHC, Bowdoin, ME, USA) was stereotaxically inserted into the left STN. The stereotaxic coordinates with respect to the bregma were as follows: anteroposterior, −3.8 mm; lateral, 2.4 mm; and dorsoventral, −8.1 mm.

Stimulation parameters were as follows: frequency, 130 Hz; intensity, 70 μA; pulse width, 80 μs; and stimulation time, 20 min (Fig. 1). Electrical rectangular stimulation was applied using a SEN-3401 stimulator (Nihon-Kohden, Tokyo, Japan).

Extracellular local field potential (LFP) recordings of STN were performed before and after stimulation for 20 min using the same Pt/Ir electrode (outer diameter, 125 μm; tip impedance, 9–12 MΩ) (Fig. 1). Extracellular recordings were performed between each pole of the concentric bipolar electrode. Extracellular signals were recorded (band-pass filtered, 0.3 Hz–10 kHz) and amplified (×10,000) through a high-performance extracellular amplifier (DAGAN 2400A, DAGAN, Minneapolis, MN, USA). At the end of each experiment, an electrical lesion was created in STN.

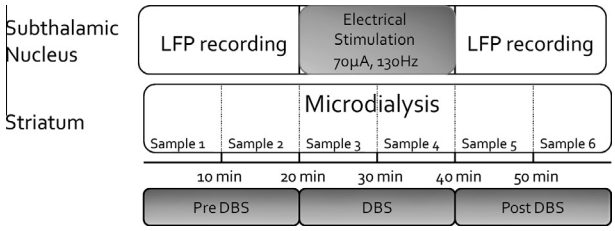

Fig. 1. Experimental protocol. In the subthalamic nucleus, local field potential (LFP) recordings were performed before and after subthalamic stimulation (pre- and post-DBS, respectively) for 20 min. Dialysates in the striatum were collected at 10-min intervals for 1 h.

Power spectrum analysis

The power spectrum of STN was analyzed off-line using LabChart software (AD Instrument Japan, Nagoya, Japan). Fast Fourier transforms (FFTs) were performed to analyze STN-LFPs data in the frequency domain from 0.3 to 50 Hz. Power spectral densities (PSDs) were estimated with 131072 FFT size, Hann window, and a 50% overlap, and normalized by log 10 (PSD).

In vivo microdialysis and high-performance liquid chromatography (HPLC) system

Striatal extracellular fluid was simultaneously collected before, during, and after subthalamic stimulation in normal rats (n = 4) and in PD model rats (n = 5) A concentric I-type dialysis probe (diameter, 0.22 mm; exposed membrane, 2.0 mm; A-I-12-02; Eicom Inc., Kyoto, Japan) was inserted stereotaxically into the left striatum, ipsilateral to the STN stimulation site. The stereotaxic coordinates with respect to the bregma were as follows: anteroposterior, +1 mm; lateral, ±3 mm; and dorsoventral, −5 mm. The perfusion rate was maintained at 2 μl/min using modified Ringer's solution (Na^+, 147 mM; K^+, 4 mM; Ca^{2+}, 2.3 mM; and Cl^-, 155.6 mM). Dialysates were collected 1 h after implantation of the dialysis probe. The collection was performed before, during, and after high-frequency subthalamic stimulation. The dialysates were collected at 10-min intervals for 1 h (Fig. 1A) and stored at −80 °C. The average levels of monoamines in the dialysates collected during the first 10 and 20 min before stimulation were defined as the basal levels, and the levels at the following points were evaluated as the ratios to the basal levels. The HPLC system used to determine monoamines was equipped with an electrochemical detector system (HTEC500; Eicom), and the mobile phase used was 0.1 M citric acid–0.1 M sodium acetate (pH 3.9) containing 140 mg/L sodium