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Research Report

Activation of the NMDA receptor involved in the alleviating after-effect of repeated stimulation of the subthalamic nucleus on motor deficits in hemiparkinsonian rats

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ABSTRACT

To test the hypothesis that the cellular mechanism whereby chronic deep brain stimulation of the subthalamic nucleus (STN-DBS) induces the improvement of motor deficits lasting after stimulation in the hemiparkinsonian (hemi-PD) rat involves the NMDA receptor-dependent processes in neurons receiving afferents from the STN, we examined whether the NMDA receptor antagonist prevents the alleviating after-effect of repeated STN-DBS on motor deficits in hemi-PD. The cylinder test was performed before and after repeated STN-DBS over 3 days in hemi-PD that received a unilateral injection of 6-OHDA into the medial forebrain bundle 3 weeks prior to STN-DBS experiments. No significant improvement in the reduced frequency of forelimb use and forelimb-use asymmetry was seen in the cylinder test after the single STN-DBS, while, when the STN-DBS was applied three times at intervals of 24 h, the improvement became apparent and significant only in the reduced frequency of forelimb use (akinesia) after termination of the stimulation, suggesting the alleviating after-effect of chronic stimulation. Then, the effects of intraperitoneal administration of the non-competitive NMDA receptor antagonist MK-801 and the competitive NMDA receptor antagonist CPP on the alleviating after-effect of the STN-DBS were examined in cylinder tests performed before and after repeated STN-DBS for 3 days in hemi-PD. Both MK-801 (0.1 mg/kg) and CPP (0.5 mg/kg) completely prevented the improvement of the akinetic motor deficit after repeated STN-DBS. These results support the hypothesis that activation of the NMDA receptor and subsequent cellular processes in neurons receiving the afferents from the STN may involve in the mechanism underlying the alleviating after-effect of chronic STN-DBS on the akinetic motor deficit in hemi-PD.

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Abbreviations: PD, Parkinson's disease; DBS, deep brain stimulation; STN, subthalamic nucleus; STN-DBS, deep brain stimulation at the subthalamic nucleus; GPe, external segment of globus pallidus; SNr, substantia nigra pars reticulata; hemi-PD, hemiparkinsonian rats; NMDA, N-methyl-d-aspartate; 6-OHDA, 6-hydroxydopamine; MK-801, dizocilpine; CPP, 3-{(+)-2carboxypiperazin-4-yl}-propyl-1-phosphonic acid; MFB, medial forebrain bundle; LIDs, levodopa-induced dyskinesias

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms, such as tremors, reduction and slowness of movement (akinesia), rigidity, deficit of postural reflex, or deficit of motor coordination. A large variety of therapeutic treatments for PD has been developed. Among them, the pharmacological treatment, which includes the administration of levodopa, has markedly improved the motor symptoms (Lang and Lozano, 1998). However, the long-term treatment with levidopa induces severe side effects, such as dyskinesias (Obeso et al., 2000). It has been reported that deep brain stimulation (DBS) applied at the internal segment of the globus pallidus, the subthalamic nucleus (STN), or the ventral nuclei of the thalamus improves the motor deficits of PD patients and permits the reduction of dopaminergic medications, leading to fewer drug-induced side effects (Dostrovsky and Lozano, 2002). In particular, DBS of the STN (STN-DBS) alleviates the three major motor symptoms of PD patients, such as tremors, akinesia, and rigidity (Krack et al., 1998), while the STN-DBS may impair certain aspects of cognitive processing as well as produce untoward emotional responses (Perlmutter and Mink, 2006). To enhance the benefit from the STN-DBS and avoid the cognitive and emotional impairment exacerbated by the STN-DBS, the precise mechanism of the ameliorative action of the STN-DBS on motor deficits in PD should be elucidated.

The STN, which has become the most commonly used target for DBS in the treatment of PD, serves as an excitatory center in the basal ganglia circuitry via the glutamatergic projection neurons (Kitai and Deniau, 1981; Kitai and Kita, 1987; Parent and Hazrati, 1995; Mink and Thach, 1993; Kita et al., 2005). In general, the glutamatergic excitatory synapses

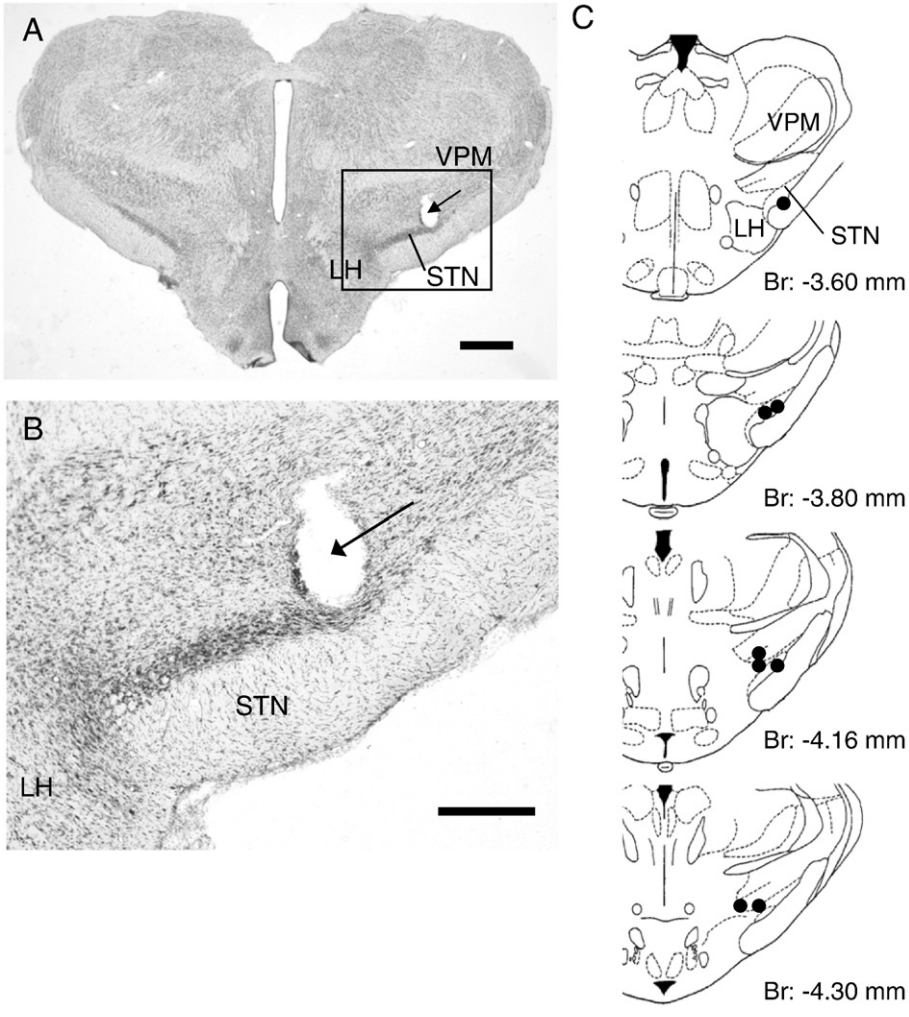

Fig. 1 – Location of the tip-site of the stimulating electrode. (A) Tip-site of a stimulating electrode indicated by the hole-like scar (arrow) in Nissl-stained coronal section of the midbrain from the hemi-PD that received the STN-DBS applied three times at intervals of 24 h over 3 days. (B) Enlarged view of the hole-like scar (arrow) locating just above the STN. (C) Schematic drawing of coronal sections of the midbrain at four different levels, depicting all the tip-sites (filled circle) identified by the hole-like scar which were obtained from 8 out of 12 hemi-PD in the STN-DBS experiment. The rest (4 out of 12 rats) was eliminated from analysis because of the far departure of their tip-site from the target structure for the stimulation. STN, subthalamic nucleus; LH, lateral hypothalamic area; VPM, ventral postero-medial thalamic nucleus. Scale bar: 1000 μm for A and 500 μm for B.