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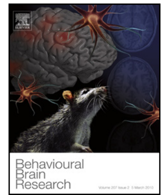

Research report

High frequency stimulation of subthalamic nucleus results in behavioral recovery by increasing striatal dopamine release in 6-hydroxydopamine lesioned rat

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HIGHLIGHTS

- We studied the effect of HFS-STN on 6-OHDA-lesioned rats.
- Increased dopamine levels induced by HFS-STN were observed in 6-OHDA-lesioned rats.
- HFS-STN improved the motor symptoms without rescuing nigral dopaminergic neurons.
- HFS-STN increased striatal dopamine release by modulating the expression of TH.

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective medical therapy in alleviating motor symptoms in moderate to severe Parkinson's disease (PD) patients. However, there are still remaining questions regarding the mechanisms of this action. In this experiment, using 6-hydroxydopamine (6-OHDA) PD rat model we investigated the effect of high frequency stimulation (HFS)-STN on improvement of the motor symptoms, DA release in the striatum and to elucidate the underlying mechanisms. Our results showed that HFS-STN improved the motor symptoms of 6-OHDA lesioned rat model of PD via inducing a significant increase in the extracellular dopamine levels and directly evoked dopamine release in the striatum of normal and partially 6-OHDA lesioned rats. In addition, we found the tyrosine hydroxylase (TH) positive cells in the substantia nigra pars compacta (SNpc) did not increase after HFS-STN, while the expression of TH in the substantia nigra increased significantly compared to the 6-OHDA lesioned group. This suggested that STN-HFS could reverse motor deficits against 6-OHDA-induced lesion through increasing striatal dopamine release by modulating the expression of TH, without rescuing dopaminergic neurons in the SNpc.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which leads to severe dopaminergic denervation of the striatum [1–3]. Researchers have reported that deep brain stimulation (DBS) is an effective medical therapy in alleviating disability in moderate to severe PD patients [4–10]. In the past three decades, the introduction of DBS of different targets, mainly including the ventro-intermediate nucleus of thalamus (VIM) [11], the globus pallidus internum (GPi) [12] and the subthalamic nucleus (STN) [13,14], has attracted numerous interests. Though randomized comparisons of GPi DBS and STN

Abbreviations: 6-OHDA, 6-hydroxydopamine; DBS, deep brain stimulation; DOPAC, dihydroxyphenylacetic acid; FCV, fast cyclic voltammetry; HPLC, high-performance liquid chromatography; HVA, homovanillic acid; PD, Parkinson's disease; SNpc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase.

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DBS demonstrated no difference in motor outcomes [15], the general trend is that treating the STN improves all symptoms, directly (akinesia and rigidity) or indirectly (dyskinesias), making it the best target for DBS for the treatment of PD [16,17].

However, the mechanisms underlying the neurosurgical interventions on STN to improve the symptoms of PD are not well understood. It was reported that striatal dopaminergic metabolism was increased by high frequency stimulation (HFS)-STN in 6-hydroxydopamine (6-OHDA) lesioned rats [18,19]. Moreover, in clinical, the response to levodopa before surgery is the best predictor of the outcome of STN stimulation [20,21]. STN-HFS is effective for the Parkinsonian patients who respond well to L-DOPA. This suggested the clinical benefit might be associated with the contents of dopamine. Therefore, we hypothesized that STN-HFS can activate surviving nigrostriatal dopaminergic neurons to evoke significant DA release in the striatum. In addition, this DA release might be associated with the behavioral recovery of PD. Therefore, to address this issue we use electrochemical techniques, including fast cyclic voltammetry (FCV), which would provide detailed temporal information about the coupling of STN-HFS and DA release, to demonstrate whether STN-HFS can evoke striatal DA release in PD rats in vivo. Moreover, high-performance liquid chromatography (HPLC) was used to determine whether STN stimulation enhanced the concentration of DA and its metabolites: dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum. At the same time, western blots and immumohistochemical staining were used to detect the changes of tyrosine hydroxylase (TH) and the numbers of TH-positive neurons in the substantia nigra (SN) of 6-OHDA-induced PD rats to investigate the mechanisms underlying the DA release evoked by STN-HFS in PD.

2. Materials and methods

2.1. Materials

6-OHDA, apomorphine, dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), cresyl violet, rabbit anti-rat tyrosine hydroxylase (TH) antibody, and anti β-actin monoclonal antibody were from Sigma Chemical Co. (St. Louis. MO, USA). DAB kit was from Beijing biosynthesis biotechnology CO., Ltd (Beijing, China).

2.2. Animals and experiments groups

All procedures were carried out in accordance with the NIH Guide for the care and use of laboratory animals and the guidelines for the use of animals in neuroscience research. Female Wistar rats weighing 200–220 g were given free access to food and water and kept in a 12 h light/dark cycle. Rats had free access to water and food ad libitum. The rats were randomly assigned to four groups: (i) Control group: normal female rats received saline containing 0.2 mg/mL L-ascorbate by injection into the left MFB and electrode implantation in the STN ("NOR"), (ii) 6-OHDA lesioned rats without STN electrode implantation ("LES"), (iii) 6-OHDA lesioned rats with STN electrode implantation given sham stimulation ("SHAM"), and (iv) 6-OHDA lesioned rats with STN electrode implantation and continuous HFS for 8 days ("STIM"). All animals were killed at 28 days. Experimental design was showed in Fig. 1A.

2.3. 6-OHDA treatment and rotational behavior tests

Surgery was performed under 8% chloral hydrate anaesthesia (8 g chloral hydrate in 100 mL normal saline, 4 mL/kg i.p.) and mounted onto a stereotactic frame. One burr hole (2.5 mm diameter) was drilled above the injection region of the left medial forebrain bundle (MFB) and the tip of the syringe lowered into the target. Rats were injected at two targets with coordinates in mm relative to Bregma according to the brain atalas of Paxions and Waston [22]). Inject 6-OHDA (Sigma Chemical Co., 3.6 mg/mL dissolved in saline containing 0.2 mg/mL ascorbic acid) with a microsyringe into the left medial forebrain bundles at two sites with the following stereotactic coordinates [23] (1) TB: −2.3 mm; AP: −4.4 mm; ML: 1.2 mm; V: −7.8 mm and (2) TB: +3.4 mm; AP: −4.0 mm; ML: 0.8 mm; V: −8.0 mm. Volume of 2.5 μL and 3.0 μL of 6-OHDA were microinjected at a rate of 1.0 μL/min, respectively. After the injection, the microinjection needle was left in place for a further 5 min before slowly extracting. Finally, the skin incision was sutured. After the surgery, the rats were given penicillin 10,000 u (i.m.) per day for 3 days continuously in order to prevent infection. The rotations of rats were assessed routinely at days 7, 14 (before electrode implantation), 21 (HFS-STN), 28 (after the last stimulation of STN) with apomorphine (APO, 0.05 mg/kg, s.c.) in automated "rotometer" bowls for 30 min.

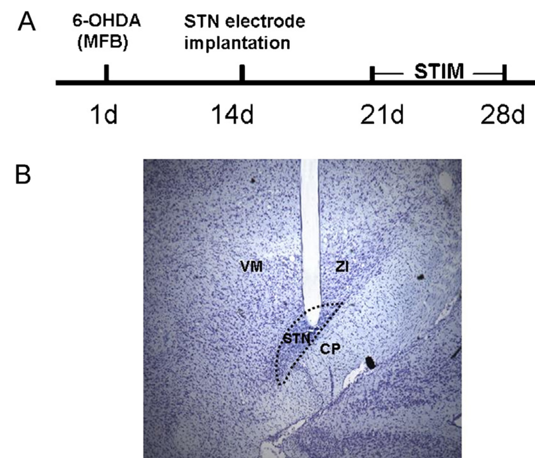

Fig. 1. (A) Experimental design. Animals were injected with 6-OHDA into the left medial forebrain bundles at two sites with the following stereotactic coordinates (1) TB: −2.3 mm; AP: −4.4 mm; ML: 1.2 mm; V: −7.8 mm and (2) TB: +3.4 mm; AP: −4.0 mm; ML: 0.8 mm; V: −8.0 mm. The rats were implanted electrode at day 14, received stimulation at day 21 and stopped stimulation at day 28. (B) Histological evaluation of the electrode localization. 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 = 200 μm). Approximate anatomical coordinate is −3.60 mm caudal from Bregma according to the stereotactic rat brain atlas by George Paxinos and Charles Watson [22].

2.4. STN electrode implantation and stimulation

Unilateral electrode implantation in the STN was performed 2 weeks after the 6-OHDA injection on the same brain side. Briefly, the rats were anesthetized and mounted onto the stereotaxic frame described previously. The stimulation electrode was implanted into the left STN (TB: −3.3 mm, AP: −3.8 mm, L: 2.5 mm, DV: −7.7 mm) [22]) and fixed in place using dental cement and skull screws. The rats were given penicillin as mentioned above. HFS was generated from a stimulator SEN-7203 (Nihonkoden, Tokyo, Japan) and started one week after the electrode implantation and lasted for 6 hrs daily continuously over a period of 21–28 days. STN-HFS was applied on freely moving rats with the following parameters over the stimulation period: frequency 130 Hz, pulse width 60 μs, intensity 100 μA.

2.5. Carbon fiber microelectrode and fast cyclic voltammetry (FCV)

There are several advantages of FCV compared with other methods like microdialysis. FCV can measure dopamine concentrations

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