Attenuation of fluctuating striatal synaptic dopamine levels in patients with Parkinson disease in response to subthalamic nucleus stimulation: a positron emission tomography study

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Object. The “wearing-off” phenomenon often hampers the treatment of Parkinson disease (PD). Although deep brain stimulation (DBS) of the subthalamic nucleus (STN) is known to ameliorate the wearing-off phenomenon, the mechanism by which it does this remains unclear. As part of an inquiry into the mechanism of STN DBS, the authors measured synaptic dopamine levels in the striatum by performing positron emission tomography (PET) with [11C]raclopride.

Methods. Three patients with PD who were experiencing the wearing-off phenomenon underwent PET scanning before and after DBS of the STN. The clinical features in these patients were evaluated by applying the Hoehn and Yahr, United Parkinson’s Disease Rating, and Schwab and England Activities of Daily Living Scales. Before and after surgery, PET scans were obtained using [11C]raclopride prior to and 1 hour following an oral administration of levodopa. Regions of interest for the [11C]raclopride binding potential (RacloBP) were set in the bilateral putamen and the caudate nucleus.

All clinical scores were dramatically improved postoperatively. Deep brain stimulation of the STN reduced the baseline RacloBP in both the putamen and caudate nucleus, but the differences between the pre- and postoperative levels were insignificant. Before DBS of the STN, the levodopa administration significantly reduced RacloBP in the putamen (p < 0.0001). Postoperatively the drug-induced reduction in RacloBP became statistically insignificant. The drug-induced increase in synaptic dopamine concentrations in the putamen preoperatively was estimated to be approximately four times higher than that after surgery (p < 0.01). The drug-induced RacloBP change in the caudate nucleus was similar to that in the putamen, although the magnitude of the change was lower (p < 0.05). The drug-induced increase in the caudate nucleus was also reduced postoperatively (p < 0.05).

Conclusions. Deep brain stimulation of the STN induces the stabilization of synaptic dopamine concentrations in the striatum and may attribute to the alleviation of levodopa-related motor fluctuations.

KEY WORDS • Parkinson disease • subthalamic nucleus • deep brain stimulation • positron emission tomography • dopamine turnover • wearing-off phenomenon

Many patients with PD experience changes in the therapeutic response to levodopa and dopamine agonists such as apomorphine.22,23,40 Fluctuations in their motor responses, such as “wearing-off” and “on–off” fluctuations as well as levodopa-induced dyskinesias, are commonly seen in patients with advanced stages of PD. Modifications of the dosing schedule can initially alleviate the wearing-off fluctuation. In a course of a long-term therapy, however, patients with wearing-off fluctuations often display oscillations in mobility unrelated to the timing of levodopa ingestion as well as levodopa-induced dyskinesias.

Despite many efforts, the mechanism of wearing-off fluctuations is poorly understood.24 Both presynaptic2 and postsynaptic3 mechanisms are postulated. It has been speculated that this end-of-dose deterioration reflects the severity of the damage to the nigrostriatal dopaminergic system.6 As the number of nigral cells declines with disease progression, the capacity of the nigrostriatal system to synthesize and store dopamine from exogenous levodopa would diminish. Motor fluctuation, however, does not seem to correlate to the degree of damage in the nigrostriatal dopaminergic system. An [18F]fluorodopa PET study revealed a considerable overlap in the [18F]fluorodopa uptake rate between wearing-off and non–wearing-off fluctuation.53

Abbreviations used in this paper: ADL = activities of daily living; ANOVA = analysis of variance; BP = binding potential; DBS = deep brain stimulation; PD = Parkinson disease; PET = positron emission tomography; RacloBP = [11C]raclopride BP; ROI = region of interest; SD = standard deviation; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale.
Dopamine turnover following DBS of the STN

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration (yrs)</th>
<th>Preop Score (on/off medication state)</th>
<th>Postop Score (on/off medication state)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>H &amp; Y UPDRS</td>
<td>Motor UPDRS</td>
</tr>
<tr>
<td>1</td>
<td>47, M</td>
<td>8</td>
<td>2.5/4</td>
<td>26/59</td>
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<tr>
<td>2</td>
<td>65, M</td>
<td>13</td>
<td>4/5</td>
<td>52/61</td>
</tr>
<tr>
<td>3</td>
<td>70, F</td>
<td>22</td>
<td>3/4</td>
<td>48/84</td>
</tr>
</tbody>
</table>

* Ama = amantadine; Cab = cabergoline; H & Y = Hoehn and Yahr Scale; LD = levodopa; Per = pergoline; S & E = Schwab and England ADL Scale.

Subthalamic nucleus stimulation has become an effective treatment option for patients with advanced PD, particularly for those who experience motor fluctuations such as the wearing-off phenomenon, but the mechanism of the symptom amelioration remains to be elucidated. Recently, de la Fuente-Fernandez, et al., demonstrated that fluctuation of synaptic dopamine concentrations in the putamen precedes the clinically apparent wearing-off phenomenon and suggested that an increased dopamine turnover might be involved in levodopa-related motor complications.

In the present study, we estimated the effects of DBS of the STN on the concentration of dopamine in the putamen and caudate nucleus of patients with advanced PD. Recently, [11C]raclopride PET has been used to assess levels of dopamine D2 receptor occupancies by different doses of levodopa or typical and atypical antipsychotics and to assess the relation between levels of occupancy and both therapeutic effectiveness and side effects. Because raclopride is sensitive to competition with endogenous dopamine, due to its relatively low affinity for the dopamine D2 receptor, [11C]raclopride has been used to assess relative changes in synaptic dopamine induced by levodopa or psychostimulant drugs. Drug-induced changes in [11C]raclopride striatal binding are interpreted as reflecting changes induced by the dopamine occupancy of D2 receptors secondary to changes in the concentration of synaptic dopamine. This measure has been used as an indication of the responsivity of the dopamine system to a pharmacological challenge. Using this strategy, this PET technique has been used to measure synaptic dopamine concentrations in the putamen.

**Clinical Material and Methods**

**Patient Selection**

Stereotactic STN stimulation was performed bilaterally in three patients with advanced PD (two men and one woman). The mean age of the patients was 60.6 years and the mean duration of symptoms was 14.3 years. All patients met the precise clinical criteria for PD. They had responded well to treatment with levodopa, and displayed severe motor fluctuations such as those known as the wearing-off phenomenon and dominant symptoms of rigidity–akinesia. Two of the patients also had mild or moderate levodopa-induced dyskinesia. These patients received bilateral DBS to the STN, which was delivered during a stereotactic procedure performed using a semimicrorecording technique. After physiological refinement of the target, a quadripolar DBS lead (3387; Medtronic, Inc., Minneapolis, MN) was implanted. A test stimulation was performed to assure the relief of symptoms and to evaluate the individual patient’s threshold for adverse effects. After the patient had been prepared for surgery and general anesthesia had been induced, an Implantable Pulse Generator (Soletra; Medtronic, Inc.) was placed in an infraclavicular subcutaneous pocket. Before and after the operation, the modified Hoehn and Yahr Scale, the UPDRS, and the Schwab and England ADL Scale were used to determine the severity of symptoms during “on” and “off” states. Neurological evaluations were performed by two neurologists (S.S. and T.O.) independently. The clinical features identified in these patients and the medications they were given are shown in Table 1.

**Positron Emission Tomography Protocol**

Before and 6 months after surgery, all patients underwent two consecutive [11C]raclopride PET studies on the same day: the first scanning session (baseline) was performed 12 to 18 hours after withdrawal of levodopa and at least 48 hours after withdrawal of the dopamine agonist; the second scanning session was performed 1 hour after oral administration of 250 mg of levodopa or 25 mg of carbidopa to an empty stomach. Because it has been reported in patients with PD that, in those with severe wearing-off phenomenon, the estimated synaptic dopamine level 1 hour after levodopa administration is three times higher than that in patients without motor fluctuations, we compared the baseline dopamine level with that measured 1 hour after levodopa administration.

All PET scans were obtained in the two-dimensional mode by using a PT-931 scanner (CTI Molecular Imaging, Inc., Knoxville, TN; axial/transaxial resolutions, 6.7 mm). A short cannula was placed in a radial artery for blood sampling. Each patient was positioned with the orbitomeatal line parallel to the detector rings, in accordance with brain slices depicted on MR images. A cross of light was projected to the marks on the patient’s head, which were set at the standard points of the 25 and 72 mm above and parallel to the orbitomeatal line.
A 10-minute transmission scanning study was performed with a \( ^{68} \text{Ge} / ^{68} \text{Ga} \) external ring source. Following an intravenous injection of \(^{11} \text{C} \)raclopride (mean 8.9 mCi), dynamic data acquisition was performed; this included ten 60-second scans and ten 5-minute scans. Data were simultaneously collected from each of seven contiguous axial sections. A total of 140 scans, each with a 6.7-mm thickness, were analyzed.

The BP (BP = Bmax/Kd) was determined using a graphic approach and a tissue input function described by Logan and colleagues.\(^{20,21} \) An integrated image was made from the emission data (40–60 minutes) for each subject. The ROIs were positioned in the caudate nucleus and putamen bilaterally, that is, in six hemispheres, and each mean ROI activity was measured. The background activity was averaged from a single ROI drawn over the cerebellum on each of two contiguous axial planes.

The estimated levodopa-induced change in the synaptic dopamine level (DA change) was calculated as follows:

\[
\text{DA change} \% = \frac{\text{Pre-BP} - \text{Post-BP}}{\text{Pre-BP}} \times 100 \%.
\]

All patients were recruited after we had obtained their written informed consent in accordance with the guideline approved by Tohoku University and the Declaration of Human Rights, Helsinki, 1975. The Clinical Committee of Radiosotope Use of Tohoku University approved the protocol for this study.

Statistical Analyses

Statistical analyses were performed with the aid of commercial software (StatView 5.0J; SAS Institute, Inc., Cary, NC). The BP was compared by using the one-way ANOVA with the Bonferroni comparison. A probability value of 0.0083 or less was considered significant in the one-way ANOVA with Bonferroni post hoc comparison. A probability value of 0.05 or less was considered significant in the paired t-test. Data are expressed as means ± SDs.

Results

Clinical Outcome

The effects of DBS to the STN on the patients’ Hoehn and Yahr, UPDRS, motor UPDRS, and Schwab and England ADL scores are summarized in Table 1. All scores, particularly the motor UPDRS score, were dramatically improved after surgery. The mean percentage improvement rates of the motor UPDRS score were 56.5% during the “on state” and 48.1% in the “off state.”

Striatal Synaptic Dopamine Levels Before and After Surgery

In the putamen, the baseline RacloBP decreased after STN DBS, but the difference between the pre- and postoperative values (3.01 ± 0.11 and 2.84 ± 0.06, respectively) was insignificant. Before surgery, the baseline RacloBP was significantly different from that after levodopa administration (3.01 ± 0.11 compared with 2.55 ± 0.16; \( p < 0.0001 \), ANOVA with Bonferroni post hoc comparison). After surgery, the drug-induced reduction in the RacloBP became insignificant (2.84 ± 0.06 compared with 2.72 ± 0.08) (Fig. 1).

In the caudate nucleus, the baseline RacloBP was reduced after DBS of the STN (2.11 ± 0.09 compared with 2.03 ± 0.13), but the difference was insignificant. Before

*Fig. 1. Boxplot showing the effect of DBS of the STN and levodopa administration on the RacloBP in the putamen. Values represent means ± SDs in arbitrary units. *\( p < 0.005 \), #\( p < 0.0001 \), ANOVA with the Bonferroni comparison with preoperation without levodopa administration. Circles indicate outliers. Pre&LD− = preoperation without levodopa administration; Pre&LD+ = preoperation with levodopa administration; Post&LD− = postoperation without levodopa administration; Post&LD+ = postoperation with levodopa administration.*

*Fig. 2. Boxplot showing the effect of DBS of the STN and levodopa administration on RacloBP in the caudate nucleus. Values represent means ± SDs in arbitrary units. *\( p < 0.005 \), $\ p < 0.001 $; ANOVA with the Bonferroni comparison with preoperation without levodopa administration. Circles indicate outliers.*
Dopamine turnover following DBS of the STN

DBS of the STN, a significant reduction was seen in the RacloBP after levodopa administration (2.11 ± 0.09 compared with 1.92 ± 0.06; p < 0.005, ANOVA with Bonferroni post hoc comparison). After surgery, the drug-induced decrease in the RacloBP after levodopa administration became insignificant (Fig. 2).

The drug-induced increase in synaptic dopamine concentrations in the putamen before surgery was estimated to be approximately four times higher than that after surgery (15.05 ± 3.55% compared with 3.89 ± 1.84%; p < 0.01, paired t-test; Fig. 3). The drug-induced increase in the percentage change of dopamine before surgery was estimated to be approximately twice as high as that after surgery in the caudate nucleus (8.95 ± 3.65% compared with 4.04 ± 3.52%; p < 0.05, paired t-test; Fig. 3).

Discussion

We believe that this is the first report on the effects of STN DBS on synaptic dopamine levels in the striatum of patients with advanced PD. The bilateral STN DBS significantly raised the baseline synaptic dopamine levels in both the putamen and caudate nucleus. Deep brain stimulation of the STN not only increased baseline dopamine levels but also attenuated an increase in dopamine levels after levodopa administration. The magnitude of the levodopa-induced changes in dopamine levels was reduced to that in patients without wearing-off fluctuations in comparison with data from de la Fuente-Fernandez, et al. As a result, the fluctuation of the synaptic dopamine concentration in the striatum was well stabilized after surgery. The stabilization of the dopamine level may be accompanied by a marked improvement in the patient’s clinical features. Although the number is small in our study, individual variations were relatively small. These findings may be congruent with the report by de la Fuente-Fernandez and colleagues who suggested the existence of a link between the instability of synaptic dopamine concentrations and the occurrence of wearing-off fluctuations.

The mechanism of the stabilization of synaptic dopamine concentrations remains undetermined, but it may be partly due to the restoration of autoregulation in presynaptic dopamine release in the striatum. Torstenson, et al. demonstrated that the effect of levodopa infusion on the striatal presynaptic dopaminergic activity differs significantly between the patients in early and advanced stages of PD. Moreover, Ekesbo and associates reported that in mild and stable PD, an upregulated presynaptic inhibitory feedback system maintained congruity within the dopaminergic system after administration of antiparkinsonian medication.

The functional tone of the nigrostriatal dopaminergic system seems to be regulated at two action sites: inhibitory autoreceptors located on presynaptic dopamine terminals, which control synthesis or release of dopamine, and those on the soma or dendrites of these neurons, which are involved in the regulation of impulse flow. This inhibitory feedback regulation is diminished with the progression of nigrostriatal degeneration. It seems plausible that DBS of the STN alters inputs from the STN to somatodendritic autoreceptors. Consequently, the functions of autoreceptors can be restored in the striatum.

Another possibility is that the relaxation of outputs from STN would activate the premotor and motor cortices, and the activation of the cortical activities would attenuate dopamine release in the striatum. Recently, investigators have shown that repetitive transcranial magnetic stimulation of the human motor cortex led to focal dopamine release in the ipsilateral putamen, supporting the corticostrial mode of dopamine release. As discussed earlier, DBS attenuates STN outputs, which results in the disinhibition of premotor and primary motor cortices. The finding of a reduced RacloBP in the known projection area of the disinhibited cortical site indicates that dopamine release was mediated by a direct effect of the corticostriatal neurons on striatal dopamine nerve terminals. As an example of cortical influence on the dopamine system, we have shown that the pallidotomy or pallidal stimulation altered the BP of postsynaptic dopamine D2 receptor in the striatum.

Although a direct corticostratial influence on striatal dopamine terminals is most likely to account for the spatial selectivity of the STN DBS effect in our study, we cannot exclude the involvement of other anatomical pathways. Frontal cortical neurons also project to the substantia nigra, where they can modulate the firing of dopamine neurons projecting to the striatum.

In accordance with a previous report, DBS of the STN modulated the dopamine concentration in the caudate nucleus after levodopa administration, although the degree of change was smaller than that in the putamen. The difference between the caudate nucleus and putamen may reflect the fact that the degree of the levodopa response is smaller than that in the putamen. This may be due to the fact that, in cases of PD, dopaminergic neurons in the caudate nucleus are
References


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Conclusions

The PET findings revealed that DBS of the STN significantly stabilized the synaptic dopamine concentration in the striatum, and that the stabilization of dopamine concentrations may be accompanied by a marked amelioration of wearing-off fluctuations. We hope that this study provides a new insight into the mechanism of DBS in patients with advanced PD.
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