IV. 3. Effect of Stereotactic Pallidal Surgery on Dopamine D2 Receptor in Advanced Parkinson's Disease


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Introduction

Parkinson’s disease (PD) is characterized by degeneration of the dopaminergic neurons originated from the substantia nigra pars compacta\(^1\). Administration of levodopa has been established as a standard therapy. However long-term treatment with levodopa leads to a decline in its therapeutic efficacy with fluctuating response to treatment\(^2\).

Stereotactic pallidal surgery has been established as an alternative therapy for advanced PD patients\(^3\). Although several studies have demonstrated that posteroventral pallidotomy (PVP) or deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) could relieve drug-induced symptoms in advanced PD\(^4,5\), the physiological mechanism of these procedures has not been understood yet.

Several studies showed up-regulated D2 function as measured as the binding potential (BP) in the putamen in early PD and its reduction in advanced stage\(^6,7\). Recent study disclosed a decrease of BP in extrastriatal regions such as anterior cingulate cortex, dorsolateral prefrontal cortex and the thalamus in advanced PD patients\(^8\). These findings imply the crucial role of dopaminergic system as a definitive factor of symptoms in PD.

We have quantified BP of striatal and extrastriatal dopamine D2 receptor before and after pallidal surgery using positron emission tomography (PET) and \(^{11}C\)-nemonapride, which is selective antagonist to dopamine D2 receptor, to investigate physiological changes of dopaminergic system induced by the stereotactic pallidal surgery.

Subjects and methods

Subject

Six patients with advanced PD (3 men and 2 women, mean age 56.2±10.2 years) were included in this study. All the patients have undergone either PVP or DBS of the GPi because of both PD symptoms of rigidity-dominance and severe fluctuating response to levodopa treatment with drug induced dyskinesia. The patients were rated according to the
Unified Parkinson’s Disease Rating Scale (UPDRS) before and after the surgery. The clinical characteristics of the patients are presented in Table 1.

**PET imaging**

We performed PET studies before and after the surgical treatment. PET scan was carried out using Shimadzu HEADTOME-V scanner in 3-D data acquisition mode. The subjects lay comfortably in the scanner couch with their eyes closed in a dim room in quiet environment. All scans were performed at ‘off’ state, levodopa administration was suspended at least 9 hours before the PET scanning.

$^{11}$C-nemonapride was synthesized according to the method previously described$^9)$. Radiochemical purity was more than 99 %, and the specific activity ranged from 250 mCi/μmol to 1200 mCi/μmol at the end of the synthesis.

The tracer was injected intravenously in 3 - 5 ml of saline over a period of 60 seconds. The maximal mass dose of nemonapride was below either 0.25 nmol/kg body weight or 12.5 nmol/whole body weight, which is estimated to occupy less than 5 % of D2 receptors in human. Emission scan was performed for 90 minutes starting 30 seconds after the administration of the ligand: 6 x 60 s scans, 8 x 180 s scans, 6 x 300 s scans, 3 x 600 s scans.

**Image analysis**

Regions of interest (ROI) analysis was carried out on average $^{11}$C-nemonapride images of 70 to 90 minutes after injection. Irregular ROIs were set on the bilateral striatum, frontal cortex, dorsolateral prefrontal cortex in each hemisphere with reference to the patients’ MR images. We also set ROIs on occipital cortex as reference region since little specific binding was observed in the occipital cortex$^9)$. We adopt an equilibrium model where the BP is expressed as follows.

$$BP = \frac{Cs}{Cr} - 1$$

Where Cs and Cr express radioactivity in the specific region and reference region respectively.

**Statistical analysis**

The differences of changes in the clinical score and BP between before and after pallidal surgery were statistically analyzed using paired t-test.

**Results**

The UPDRS score were obviously improved after the pallidal surgery. The UPDRS total was $73.5\pm35.4$ (average±SD) before operation and $55.8\pm30.8$ after operation (p<0.05). UPDRS III, an index of motor function, also improved significantly, $38.5\pm20.9$ to
29.1 ± 19.4 (p < 0.05). Though all the patients developed drug-induced dyskinesia before the operation, the symptom was significantly improved in all patients after surgery (data not shown).

Significant decrease of BP was found in the striatum (p < 0.01), dorsolateral prefrontal cortex (p < 0.05), frontal cortex (p < 0.05) in the operated-side, while these regions did not reveal significant changes in contralateral hemisphere (Table 2).

**Discussion**

Deterioration of dopaminergic system and subsequent pathological dysfunction in the basal ganglia-thalamocortical circuit is believed to be the cause of the symptoms of PD. Previous studies showed that BP of dopamine D2 receptor in the striatum is up-regulated to compensate exhausted endogenous dopamine in early PD patients\(^7\). However, it significantly reduced to 82 % of normal levels in the advanced stage\(^6\). Furthermore in vivo study using PET revealed existence of D2 receptor in the extrastriatal brain regions\(^10\) and much attention has been paid on its roles in schizophrenia and Parkinson's disease. Kaasinen et al disclosed that BP of D2 receptor in medial thalamus, anterior cingulate cortex and dorsolateral prefrontal cortex were deteriorated, as the severity of PD progressed\(^8\). This finding indicated that not only striatal but also extrastriatal dopaminergic system contributed to the pathogenesis of PD.

Our study disclosed that pallidal surgery led to a significant BP decrease in the striatum, dorsolateral prefrontal cortex and frontal cortex of the operated hemisphere. According to the theory of 'cortico-basal ganglia-thalamocortical circuit', the GPi has inhibitory output to the ventrolateral thalamus using γ-aminobutyric acid as a neurotransmitter and the thalamic nucleus has excitatory project to motor, premotor, supplementary motor and prefrontal cortex\(^11,12\). Thus PVP or DBS of GPi might have reduced inhibitory output to the thalamus, subsequently leading to increased excitatory projection to the cortex. Some authors have investigated the effects of pallidal manipulations on the primary motor cortex. Activation studies using H\(_2\)O PET demonstrated that PVP and DBS had potential to improve motor performance and enhance the cerebral blood flow associated to the motor task\(^13\). This phenomenon may lead the concept that artificial manipulation of GPi can modify the cortical functions through the basal ganglia-thalamocortical network. Furthermore previous reports demonstrated that the striatum received an excitatory, glutamatergic input from all of cerebral cortex except for primary visual and auditory area\(^14\). The cortical afferents to striatum terminate primarily on the shafts of the dendritic spines of medium spiny neurons\(^15\). In addition to that, dopaminergic input from substantia nigra pars compacta also terminate the spines of medium spiny neuron in striatum and subsequently modulates the cortical inputs to the neurons\(^16\). The mechanism underlying the decreasing change of BP in the operated-side striatum could not be clearly elucidated. However, it is possible that the pallidal surgery
leads the activation of the cortex that subsequently enhances the cortical input to striatal neurons though the basal ganglia-thalamo-cortical circuit and this functional alternation modulates the physiological status of medium spiny striatal neuron and its dopaminergic system. Some authors reported that drug-induced dyskinesia is due to unbalanced interaction between exogenous dopamine and dopaminergic system in striatum. Therefore physiological changes of BP in striatum demonstrated in our study might be strongly relevant to the clinical improvement of drug-induced dyskinesia.

We also found BP decreases in the frontal cortex and dorsolateral prefrontal cortex of the operated hemisphere. The reciprocal neural network between mediodorsal nuclei of the thalamus and prefrontal cortices, such as the frontal eye field, the superior frontal convexity and the dorsolateral prefrontal cortex has been reported\(^7\). This circuit has been acknowledged to be pathophysiologically important role in schizophrenia. Furthermore Robbins demonstrated that the network participated in psychiatric and cognitive function in PD and proposed 'frontostriatal dementia' as a more apt description\(^8\). Correlation between the function of D2 like receptor in dorsolateral prefrontal, anterior cingulate, medial thalamus and cognitive function in PD was also reported\(^9\). In our series such adverse complications have not been observed. However, surgery-related alterations in D2 receptors possibly related to the 'frontostriatal circuit' may not completely exclude disturbances in patient's cognitive function occasionally developed after pallidotomy.

This study demonstrated that the dopaminergic neural circuit including extrastriatal areas such as prefrontal cortex has an important role in modulating the pathophysiological status in PD patients. Pallidal surgery has potential to modulate this network relating to the 'cortico-basal ganglia-thalamocortical circuit' and consequently improves the motor related disorders and drug-induced dyskinesia. PET study using \(^11\)C-nemonapride has successfully disclosed the physiological changes of dopaminergic system underlying the clinical effects of the stereotactastic surgical treatment in advanced PD.

References


Table 1. Clinical feature of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Age at onset</th>
<th>H&amp;Y</th>
<th>UPDRS total</th>
<th>UPDRS motor</th>
<th>DID</th>
<th>Surgical site</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>50 M</td>
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<td>3</td>
<td>58</td>
<td>25</td>
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<tr>
<td>2</td>
<td>65 F</td>
<td>55</td>
<td>2.5</td>
<td>59</td>
<td>36</td>
<td>1</td>
<td>right</td>
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<tr>
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<td>55 F</td>
<td>33</td>
<td>3</td>
<td>78</td>
<td>47</td>
<td>2</td>
<td>right</td>
</tr>
<tr>
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<td>48 M</td>
<td>40</td>
<td>2</td>
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<tr>
<td>5</td>
<td>72 F</td>
<td>55</td>
<td>5</td>
<td>113</td>
<td>53</td>
<td>3</td>
<td>bilateral</td>
</tr>
<tr>
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<td>38</td>
<td>4</td>
<td>112</td>
<td>64</td>
<td>2</td>
<td>left</td>
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</tbody>
</table>

M = male; F = female; H&Y = Hoehn and Yahr scale
UPDRS = Unified Parkinson's Disease Rating Scale; DID = drug induced dyskinesia

Table 2. Binding potentials (Bmax/Kd) at before and after the operation

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Operation side</th>
<th>Contralateral side</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>Striatum</td>
<td>1.86±0.44</td>
<td>*</td>
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<tr>
<td></td>
<td>1.72±0.43</td>
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<tr>
<td>Frontal cortex</td>
<td>0.28±0.16</td>
<td>†</td>
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<tr>
<td></td>
<td>0.20±0.11</td>
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<tr>
<td>Dorsolateral prefrontal</td>
<td>0.16±0.08</td>
<td>†</td>
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<tr>
<td>cortex</td>
<td>0.10±0.08</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* p < 0.01
† p < 0.05