The impact of stereotactic pallidal surgery on the dopamine D₂ receptor in Parkinson disease: a positron emission tomography study

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Object. The aim of this study was to estimate the impact of stereotactic pallidal surgery on the binding potential of dopamine D₂ receptors in patients with advanced Parkinson disease (PD).

Methods. Six patients with advanced PD (three men and three women; mean age 56.7 ± 9.8 years, Hoehn and Yahr stage 3.3 ± 1.3 [on/off scores], mean ± standard deviation) underwent stereotactic pallidal surgery. One underwent right posteroventral pallidotomy (PVP), one received left PVP, three were treated with deep brain stimulation (DBS) of the left globus pallidus internus (GPi), and one with bilateral DBS of the GPi. The binding potential of the dopamine D₂ receptors of these patients was determined before and after surgery by using positron emission tomography scanning with ¹¹C-nemonapride and it was compared with the value in eight healthy volunteers. The authors also examined whether changes in the D₂ receptor binding potential were correlated with the clinical outcome. The clinical symptoms, especially those in the off state, were significantly improved after surgery. Preoperatively, the D₂ receptor binding potential in the putamen was elevated by 27% (p < 0.01) and that in the thalamus was 29% lower than that in controls (p < 0.01). The D₂ receptor binding potential in the putamen and thalamus returned to control levels after surgery. The preoperative level of the D₂ receptor binding potential in the anterior cingulate cortex was comparable to that of controls, but it declined significantly after surgery, whereas the D₂ receptor binding potential in other regions of both hemispheres showed no significant changes after surgery. Although the D₂ receptor binding potential did not correlate with the Hoehn and Yahr stage, the Schwab and England score, or the Unified PD Rating Scale (UPDRS) score, a positive correlation was seen between the percent improvement rate of the total UPDRS score in the off state and the percentage change of the D₂ receptor binding potential in the putamen (r = 0.773, p = 0.0417 according to the Pearson linear correlation).

Conclusions. The altered dopamine D₂ receptor binding potential in the putamen might play a crucial role in clinical improvement after PVP or DBS of the GPi in advanced PD.

KEY WORDS • Parkinson disease • positron emission tomography • dopamine D₂ receptor • pallidotomy

Although the mechanism of motor disturbances in PD is not fully understood, a functional schema has been proposed for the regulation of motor activities (Fig. 1; modified from DeLong). According to this schema, dopaminergic neurons in the substantia nigra pars compacta act on the striatal GABAergic neurons consisting of two subpopulations with distinct dopamine receptors, one dominated by D₁ receptors (D₁ neurons) and the other by D₂ receptors (D₂ neurons). The D₂ neurons are directly connected to the GPi (direct striatopallidal pathway), whereas the D₂ neurons have an indirect connection with the GPi and the SNr through the GABAergic neurons in the globus pallidus externus and the glutamatergic neurons in the STN (indirect striatopallidal pathway). On stimulation with dopamine, the D₂ neurons exert an inhibitory effect on the release of GABA from the GPi and SNr, whereas the D₁ neurons facilitate GABA release from the GPi and SNr through an indirect action on glutamatergic neurons in the STN connected to the GPi and SNr.

A state of dopamine deficiency, as is found in PD, appears to be associated with hyperactivity of the indirect striatopallidal pathway and hypoactivity of the direct striatopallidal pathway, resulting in an excessive release of GABA from the GPi and SNr, and these conditions ultimately lead to suppression of motor activities. Thus, the D₂ neurons seem to play a key role in motor disturbances in a dopamine-deficient state.

Abbreviations used in this paper: ACC = anterior cingulate cortex; DBS = deep brain stimulation; GABA = γ-aminobutyric acid; GPi = globus pallidus internus; PD = Parkinson disease; PET = positron emission tomography; PVP = posteroventral pallidotomy; ROI = region of interest; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; UPDRS = Unified PD Rating Scale; 3D = three-dimensional.
amelioration of akinesia with dopaminergic drugs is associated with an increase in the activity of abnormally depressed supplementary motor and premotor cortices,13,21 the areas involved in the initiation of movements.13 From this observation we infer that dopamine reduces the excessive inhibitory outflow from neurons in the basal ganglia. Indeed, a high firing rate in the GPi in patients with PD diminishes after administration of a potent D1 and D2 dopamine receptor agonist, apomorphine, in doses that reverse parkinsonism.21

Apparently, this schema is not complete. The thalamotomy, with its consequent diminution of thalamic activation of the cortex, should worsen PD, and the pallidotomy at GPi, by diminishing inhibitory outflow from neurons in the basal ganglia, should produce hemiballism, as occurs with spontaneous lesions in the STN. Neither of these predictions has been borne out by surgical experience. These inaccurate predictions of surgical response may reflect the fact that the schema considers only neuronal discharge rates rather than the more complex neuronal firing patterns, potentially more important neuromodulation through dopamine D1 and D2 receptors, or the fact that the circuit may behave in a manner different from that expected in the chronic dopamine-deficient state.

In this study we have assessed the effect of PVP or DBS of the GPi on the D2 receptor binding potential by using PET scanning with 11C-nemonapride, and we have also correlated the clinical outcome of the surgical treatment with alterations in the D2 receptor binding potential. Nemonapride is a selective D2 antagonist that is being used in PET studies to assess the postsynaptic D2 receptor function in experimental animals15–17,19 and humans.3,20,22,32,42–45,47

Clinical Material and Methods

Patient Population

Stereotactic pallidal surgery was performed in six patients with advanced PD (three men and three women). The mean age of the patients was 56.2 ± 9.8 years and the average duration of symptoms was 16.8 ± 10.4 years. The patients with rigidity–akinesia dominant symptoms, severely fluctuating response to levodopa, and dopa-induced dyskinesia were selected because PVP or DBS of the GPi has been effective for such cases.30 These patients received either DBS of the GPi or PVP: one on the right side, four on the left, and one bilaterally. Before and after the operation, the severity of symptoms in the on and off states was assessed by identifying the Hoehn and Yahr stage, the UPDRS score, and the Schwab and England score.31 Clinical features of these patients are summarized in Table 1.

Eight healthy male volunteers with a mean age of 59.5 ± 8.1 years were recruited after obtaining written informed consent in accordance with the guidelines approved by Tohoku University and the Declaration of Human Rights (Helsinki, 1975). These individuals were deemed healthy after a review of their medical history, physical examination, and blood and urine analyses, in addition to magnetic resonance images of the brain. None of them was receiving any medication. The protocol of this study was approved by the Clinical Committee on Radioisotope Use of Tohoku University.

Protocol for PET Studies

The PET studies were performed using a 3D PET scanner with 32 ring detectors (model SET2400W; Shimadzu, Inc., Kyoto, Japan). Spatial resolution was 3.9 mm at full

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>PD Duration (yrs)</th>
<th>Preop (on/off)</th>
<th>Postop (on/off)</th>
</tr>
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<tr>
<td></td>
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<td>H &amp; Y Stage</td>
<td>UPDRS Score</td>
</tr>
<tr>
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<td>64, F</td>
<td>10</td>
<td>2.5/3</td>
<td>29/59</td>
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<td>6</td>
<td>48, M</td>
<td>9</td>
<td>4/5</td>
<td>73/112</td>
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* H & Y = modified Hoehn and Yahr; S & E = Schwab and England.
† This patient had autosomal recessive–juvenile parkinsonism.
width at half maximum, and the axial field of view was 200 mm. The participants lay comfortably on a scanner couch with their eyes closed in a quiet, dimly lit room. All medications were discontinued at least 9 hours before the PET scans were obtained. Transmission scanning was also performed for 10 minutes by using a 68 Ge/68 Ga external rotating line source (370 MBq at purchase) to correct the tissue attenuation of emission photons. Acquired data were reconstructed into 128×128–matrix images for a set of 3D volume images by applying a filtered 3D back-projection algorithm with the Tohoku University supercomputer (SX-4/128H4).

The 11C-nemonapride was synthesized as described previously. 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 radiotracer was injected through a cannula placed in the antecubital vein. The 11C-nemonapride, an average dose of 280 MBq in 3 to 5 ml of saline, was injected intravenously over a period of 60 seconds. The PET scanning was performed for 90 minutes starting 30 seconds after the administration of the ligand: six 60–second scans, eight 180–second scans, six 300–second scans, and three 600–second scans. Neither excessive agitation nor body movement was observed during the scanning period.

**Evaluation of the Binding Potential of Dopamine Receptors**

Seven hemispheres that underwent surgical intervention, five unilaterally and one bilaterally, and five hemispheres without intervention were subjected to the binding potential analysis. An ROI analysis was conducted using average 11C-nemonapride–enhanced images obtained 70 to 90 minutes after injection of the tracer. As shown in Fig. 2, in each hemisphere, ROIs were defined in the putamen, thalamus, dorsolateral prefrontal cortex (Brodmann areas 9 and 46), ACC (Brodmann areas 23 and 31), temporal cortex (Brodmann areas 21, 22, 37, and 38), and parietal cortex (Brodmann areas 7, 39, and 40). The positioning of ROIs was guided by findings on the magnetic resonance images of the patients and volunteers. The occipital cortex served as a reference region because little specific binding has been detected in this region.

The following equilibrium model was used for the assessment of the binding potential: binding potential = Cs/Cr, where 

\[ \text{binding potential} = \frac{C_s}{C_r} \]

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Assessment of Clinical Correlation With D2 Receptor Binding Potential

Changes in the Hoehn and Yahr stage, total UPDRS score, and motor (items 18–31) and dopa-induced dyskinesia (items 32 and 33) subscores of the UPDRS and Schwab and England score were correlated with the alteration in D2 receptor binding potential after the surgical intervention. In addition, the percent improvement rate of clinical features was correlated with the percentage change of the D2 receptor binding potential in the putamen and thalamus as follows: percent improvement rate of clinical features = (preoperative score − postoperative score)/preoperative score × 100, and the percentage change of D2 receptor binding potential = (preoperative binding potential − postoperative binding potential)/preoperative binding potential × 100.

**Statistical Analysis**

Statistical analyses were performed using commercial-
ly available software (StatView 5.0J; SAS Institute, Inc., Cary, NC). The comparison of Hoehn and Yahr stage, total UPDRS, and Schwab and England scores before and after the surgery was performed using the Student t-test, and a probability value of 0.05 or less was considered to be significant. The D2 receptor binding potential in patients with PD was compared with that in normal volunteers by using analysis of variance with the Bonferroni post hoc comparison. A probability value of 0.0167 or less was considered significant. The D2 receptor binding potential in the hemispheres in which no intervention was performed was compared before and after the surgery by using the Mann–Whitney U-test. A probability value of 0.05 or less was considered significant. To determine significant variables for the D2 receptor binding potential, multivariate logistic regression was performed on ordinal data.

Results

Clinical Outcome

The patients’ clinical symptoms were remarkably improved after the surgery. The Hoehn and Yahr stage was significantly lower in the off state (p < 0.05), and the Schwab and England score in the off state increased significantly (p < 0.05). The total UPDRS score was also improved in both on and off states (p < 0.01). The clinical outcome of the surgery is summarized in Table 2.

Binding Potential of the Dopamine D2 Receptor

Before the surgery, the D2 receptor binding potential in the putamen of the patients (1.815 ± 0.256; all values given in arbitrary units) was significantly higher than that in healthy volunteers (1.43 ± 0.185, p < 0.01). On the other hand, the D2 receptor binding potential in the thalamus (0.364 ± 0.077) was significantly lower than that in healthy volunteers (0.513 ± 0.067, p < 0.01). No significant difference was seen in other regions.

The D2 receptor binding potential in the putamen and thalamus was returned to the level found in healthy volunteers after surgery (Fig. 3A and B). In addition, the D2 receptor binding potential in the ACC (0.067 ± 0.054) was significantly lower than that in healthy volunteers (0.175 ± 0.078, p < 0.01; Fig. 3C). No significant postoperative changes were observed in other areas, and the postoperative changes in hemispheres with no intervention were not significant (data not shown).

Theoretically, the destruction by PVP and stimulation by DBS are expected to exert different effects on the motor control system, and we compared the effect of the PVP and DBS on the D2 receptor binding potential separately. In reality, there was no apparent difference in the effect of the PVP and DBS on the D2 receptor binding potential, although the number of cases was small (PVP in two hemispheres and DBS in five hemispheres) and there were individual variations. The D2 receptor binding potential in the putamen changed from 2.023 ± 0.515 to 1.399 ± 0.472 (–29.9%) after PVP and from 1.73 ± 0.042 to 1.218 ± 0.13 (–29.6%) after DBS. Similarly, the D2 receptor binding potential in the thalamus ranged from 0.412 ± 0.027 to 0.346 ± 0.081 to 0.492 ± 0.091 (42.4%) after DBS. The alterations of D2 receptor binding potential in the ACC ranged from 0.134 ± 0.01 to 0.05 ± 0.034 (–60.7%) after PVP and from 0.169 ± 0.104 to 0.076 ± 0.063 (–54.8%) after DBS.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Preop On</th>
<th>Off</th>
<th>Postop On</th>
<th>Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>3.3 ± 1.1</td>
<td>3.9 ± 1.2</td>
<td>3.3 ± 1.1</td>
<td>3.3 ± 1.1</td>
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<tr>
<td>UPDRS</td>
<td>44.8 ± 27.8</td>
<td>73.5 ± 35.4</td>
<td>36.3 ± 24.9*</td>
<td>52.3 ± 29.1*</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>68.3 ± 29.3</td>
<td>48.3 ± 29.3</td>
<td>78.3 ± 23.1</td>
<td>65.0 ± 24.3*</td>
</tr>
</tbody>
</table>

* p < 0.05 according to the Student t-test in comparison with preoperative scores in the on or off state.
Correlation of D₂ receptor binding potential with clinical outcome

Correlation of Clinical Outcome With Binding Potential of the Dopamine D₂ Receptor

Because no apparent difference in the D₂ receptor binding potential was seen after the PVP and DBS, the results of PVP and DBS were combined in the comparison with clinical outcome. No correlation was seen between the D₂ receptor binding potential and the Hoehn and Yahr stage, total UPDRS score, motor and dopa-induced dyskinesia subscores of the UPDRS, and Schwab and England score in both the on and off states. There was a strong correlation, however, between percent improvement rates of total UPDRS scores in the off state and the percentage change of D₂ receptor binding potential in the putamen (Fig. 4; r = 0.773, p = 0.0417, Pearson linear correlation).

Discussion

Dopamine D₂ Receptor Binding Potential in the Putamen

Our study clearly showed that the D₂ receptor binding potential in the putamen of patients with advanced PD was significantly higher than that in healthy volunteers. The level of D₂ receptor binding potential in PD has been a matter of controversy. In some studies an elevation of D₂ receptor binding potential has been shown in the putamen, but in others contrary results have been reported. Moreover, in several studies it has been shown that the D₂ receptor binding potential was elevated in the early stage but not in the advanced stage.

The conflicting results might be partly due to the specificity of the tracer. In the past, ¹¹C-raclopride was commonly used but its binding specificity to the D₂ receptor is lower than that of ¹¹C-nemonapride. Nemonapride is a strong D₂ antagonist and its binding specificity to dopamine receptors is on the order of D₂ greater than D₃ greater than D₄. Thus, nemonapride can be expected to reflect the D₂ receptor binding potential more accurately than raclopride. The specificity of the ligand is crucial in this type of study because a 15% elevation of the D₂ receptor binding potential and a 40 to 45% reduction of the D₂ receptor binding potential are reported in the putamen of patients with advanced PD.

It is also noteworthy that the D₂ receptor binding potential is affected not only by the course of illness but also by various drugs, including levodopa, dopamine agonist, and monoamine oxidase-B inhibitor.

One of the impressive findings in this study is the reversal of elevated D₂ receptor binding potential in the putamen after the surgery. The mechanism underlying this phenomenon is speculative. If the elevation of the D₂ receptor binding potential in the putamen in patients with advanced PD is compensatory for excessive inhibitory output from the GPi, the postoperative decline of the D₂ receptor binding potential in the putamen might be related to the reduction of an excessive inhibitory output from the GPi to the motor thalamus after the surgery. It would be accompanied by subsequent activation of the premotor and supplementary motor areas and amelioration of parkinsonism after PVP or DBS of the GPi.

Dopamine D₂ Receptor Binding Potential in the Thalamus

Before surgery, the D₂ receptor binding potential in the thalamus was lower than that in healthy volunteers. This observation is consistent with the report by Kaasinen, et al., who showed that the binding potentials of the D₂ and D₃ receptors in the medial thalamus were decreased by 17% compared with those in healthy volunteers. They examined the medial and lateral thalamus separately, and found that the decline of the D₂ receptor binding potential had occurred only in the medial thalamus. Kaasinen, et al., also suggested that cognitive disorders and emotional deficits in PD might be related to the decline of the binding potential of D₂ and D₃ receptors in the medial thalamus. Although Riordan, et al., showed improvement in cognitive and emotional deficits after PVP or DBS of the GPi, others reported no changes in cognitive and emotional deficits after surgery.

In our study, items 1 to 4 of the UPDRS, reflecting mood and depression, did not change after the surgery despite normalization of the D₂ receptor binding potential in the thalamus. Because the D₂ receptor binding potential of the thalamus is lower than that of the putamen, and the function of binding potential in the thalamus is poorly understood, the implication of a reduced D₂ receptor binding potential in PD and normalization of the D₂ receptor binding potential after PVP and DBS of the GPi remains to be elucidated.

Dopamine D₂ Receptor Binding Potential in the ACC

Unlike the report by Kaasinen, et al., the D₂ receptor binding potential in the ACC of our patients was not statistically different from that in healthy volunteers. This discrepancy might be attributable to the use of a different tracer. Kaasinen, et al., used FLB457, which is more useful for extrastriatal regions than nemonapride and raclopride. It is also possible that the clinical status of their patients was different from ours, but clinical details were not fully given in their paper.

The function of the ACC is not fully understood, but two functions are postulated. One is motor programming, akinesia associated with mesial frontal lesions is often attributed to impairment of the supplementary motor area, but monkeys with a lesion confined to this area are not akinetic. Thus, Playford, et al., suggested that additional involvement of the ACC was important in the genesis of akinesia. If this is the case, the postoperative reduction of the
D<sub>2</sub> receptor binding potential in the ACC might be related to improvement in akinesia after pallidal surgery.

On the other hand, the reduction of the D<sub>2</sub> receptor binding potential in the ACC is thought to be responsible for the impairment of working memory after pallidal surgery, because this area is activated during the performance of the Stroop color/word interference test and of a task involving a semantic decision in word sorting.

**Correlation Between Clinical Outcome and Binding Potential of the Dopamine D<sub>2</sub> Receptor**

In agreement with a previous report, clinical improvement in this study was more remarkable in the off than in the on state. Although there was no correlation between the level of D<sub>2</sub> receptor binding potential in the putamen and individual parameters of clinical symptoms, the percentage change in the D<sub>2</sub> receptor binding potential was positively correlated with the percent improvement rate of total UPDRS scores in the off state. We found that PVP or DBS of the GPi were highly effective for dopa-induced dyskinesia (an improvement rate of ≥80% was seen in contralateral dopa-induced dyskinesia). There was also an approximately 30% improvement in total motor scores; this change in the D<sub>2</sub> receptor binding potential was positive, with clinical symptoms in PD. Because an association between D<sub>2</sub> receptors in the putamen and thalamus, and it is accompanied by a semantic decision in word sorting.

**Conclusions**

Pallidal surgery alters the binding potential of dopamine D<sub>2</sub> receptors in the putamen and thalamus, and it is accompanied by the improvement of clinical symptoms in advanced PD.
Correlation of D₂ receptor binding potential with clinical outcome


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