Dopaminergic Function and Dopamine Transporter Binding Assessed With Positron Emission Tomography in Parkinson Disease

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Background: Measuring progression of Parkinson disease (PD) using positron emission tomography may help demonstrate the efficacy of neuroprotective treatments. To date, 18F-dopa has been the gold standard to measure presynaptic dopaminergic function in PD, but this tracer might overestimate the rate of neuronal death in PD because its uptake also depends on dopamine turnover rather than exclusively on the density of dopaminergic terminals in the striatum. The latter might be assessed using newly developed ligands of the membrane dopamine transporter.

Objective: To compare the striatal uptakes of 18F-dopa and 76Br-FE-CBT, a dopamine transporter ligand, in patients with PD.

Patients and Methods: The striatal uptakes of 76Br-FE-CBT and 18F-dopa were compared using positron emission tomography in 10 patients with early PD and 8 with advanced PD. Correlation of uptakes with motor performance was investigated.

Results: The reduction in 76Br-FE-CBT binding to 43% of control values was more severe than the reduction in 18F-dopa uptake (63% of control values) in the putamen of patients with early PD. No significant difference was found between either tracer’s uptake in the putamen of patients with advanced PD. Motor performance was highly correlated to 18F-dopa uptake, whereas correlation to 76Br-FE-CBT binding was weak.

Conclusions: Uptake of 18F-dopa may be up-regulated in early PD, suggesting a compensatory increase of dopamine synthesis in surviving dopaminergic terminals. Positron emission tomography dopamine transporter ligands and 18F-dopa give complementary information on the presynaptic status of the nigrostriatal dopaminergic system and might be associated to investigate the efficacy of neuroprotective treatments in PD.

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PATIENTS AND METHODS

PATIENTS

Eighteen patients (mean ± SD age, 53.7 ± 6.0 years) fulfilling the UK Parkinson’s Disease Brain Bank criteria for prospective diagnosis of PD were selected. They were divided into 2 groups: (1) 10 patients with early PD (mean ± SD age, 51.7 ± 4.4 years; mean ± SD disease duration, 1.9 ± 0.6 years; Hoehn and Yahr stage I-II) without atypical signs who were drug naive at the time of the PET study but responded to treatment after it was initiated and (2) 8 patients with more advanced PD (mean ± SD age, 56.1 ± 6.6 years; mean ± SD disease duration, 12.5 ± 6.7 years; Hoehn and Yahr stage ≥III) who were all dopa responders according to the criteria of the Core Assessment Program for Intracerebral Transplantations and the Core Assessment Program for Surgical Intervenational Therapies (Table 1).

All patients were assessed in the “defined off” state using the Unified Parkinson’s Disease Rating Scale 3 (UPDRS-3) motor score and the Purdue Pegboard task. The latter estimates bradykinesia and has been shown to correlate with striatal dopaminergic function. Briefly, for this task, patients were asked to put as many unmarked rods as possible into aligned holes using a single hand in 30 seconds. The number of rods accurately placed was registered.

Patients were scanned using 2 different PET tracers: (1) 18F-dopa and (2) 76Br-FE-CBT (fluorethyl-methyl-2-carboxymethoxy-3β-4-bromophenyl-tropane), a ligand of the presynaptic plasma membrane DAT. This highly specific tracer has the advantage of reaching an equilibrium 30 minutes after injection. Patients with PD were compared with 25 control subjects (22 men and 3 women; mean ± SD age, 49.7 ± 13.0 years) with no neurological history, no clinical abnormality, and normal findings on brain magnetic resonance imaging. Of these 25 controls, 7 were examined with 18F-dopa only, 8 with 76Br-FE-CBT only, and 10 with both PET tracers. All patients and controls were part of ongoing protocols in our center (Orsay, France) that were approved by the local ethics committee, and they gave their written informed consent after the nature of the procedure had been fully explained.

MAGNETIC RESONANCE IMAGING AND PET ACQUISITION

Brain magnetic resonance images were obtained using a 1.5-T imager (Signa; General Electric Co, Milwaukee, Wis). T2-weighted images from each patient were used to reveal brain lesions and signal abnormalities in the basal ganglia. In addition, a T1-weighted SPGR (spoiled gradient acquisition at the steady state) acquisition with inversion recovery was performed to allow 3-dimensional reconstruction of magnetic resonance images.

Positron emission tomographic examinations in patients with early PD were performed using the ECAT EXACT HR+ tomograph (CTI-Siemens, Knoxville, Tenn), which collects 63 simultaneous 2.4-mm-thick slices with an intrinsic in-plane resolution of 4.3 mm. Patients with advanced PD were studied using the ECAT 953B/31 tomograph (CTI-Siemens), which acquires 31 simultaneous 3.4-mm-thick slices with an intrinsic transaxial resolution of 6.0 mm. For all PET examinations, patients were positioned in the tomograph using 3-dimensional laser alignment and a thermoplastic mask molded to each patient’s face to restrain head movements. Tissue attenuation was measured using 3 68Ge rod sources.

For 18F-dopa studies, patients with advanced disease discontinued taking antiparkinsonian medications at least 12 hours before PET examination. In all patients, 100 mg...
investigated the correlations between these tracers’ uptakes and motor performances of these patients.

**18F-DOPA** and **76Br-FE-CBT IN PATIENTS AND CONTROLS**

**Figure 1** shows examples of images obtained in a control subject, a patient with early PD, and a patient with advanced PD for 18F-dopa Ki and 76Br-FE-CBT BnP. Because Ki and BnP values were normalized to the mean of control values (Table 2), they are expressed as percentages of the normal mean.

In patients with early PD, normalized Ki values averaged over both hemispheres were reduced to 87%±13% in the caudate nucleus and 63%±21% in the putamen, and the corresponding BnP values were 70%±14% and 43%±17%. In patients with advanced disease, Ki values were 46%±11% and 33%±9% of control values in the caudate and putamen, respectively, whereas BnP values were decreased to 32%±7% and 27%±5% in these regions. The calculation of the striatal binding potential (BnP) values of this tracer using the graphical analysis described by Logan et al27 and using the occipital activity as a non-specific input function.

Considering that patients were studied using 2 different scanners, the Ki and BnP values obtained in each patient were normalized to the mean Ki and BnP values obtained in age-matched controls studied using the same tomograph. Specifically, the values obtained in patients with early PD were normalized to values obtained using the ECAT EXACT HR+ in 7 controls (mean±SD age, 49.4±12.2 years) for 18F-dopa uptake and 6 controls (mean±SD age, 53.3±7.2 years) for 76Br-FE-CBT, whereas the values obtained in patients with more advanced PD were normalized to values in 10 controls (mean±SD age, 49.9±14.2 years) for 18F-dopa uptake and 10 controls (mean±SD age, 53.9±5.6 years) for 76Br-FE-CBT.

**STATISTICAL ANALYSIS**

The 3 groups (controls and patients with early and severe PD) were compared for Ki and BnP values in the caudate and putamen using a Kruskal-Wallis test (1-way nonparametric analysis of variance). For that purpose, values obtained in the right and left hemispheres were averaged. In addition, normalized Ki values were compared with normalized BnP values in the putamen of patients on the more and less affected hemispheres using a Friedman test (2-factor nonparametric analysis of variance). Finally, correlations between Ki and BnP values and motor performance (motor score of the UPDRS-3 scale and Purdue Pegboard) were analyzed using the nonparametric Spearman test. For the latter analysis between PET values and Purdue Pegboard scores, right and left values were averaged to avoid any statistical bias related to the lack of independence of the variables. Data are given as mean±SD.

Kruskal-Wallis analysis of variance comparing patients with early PD, patients with severe PD, and controls revealed significant differences among groups for Ki values (caudate: H=18.50; putamen: H=18.97) and BnP values (caudate: H=18.21; putamen: H=18.12) (P<.001 for all).

In the patient groups, we compared the normalized Ki values with the normalized BnP values in the putamen contralateral to the less and more clinically affected sides (Figure 2). The Friedman analysis of variance revealed that Ki values were significantly higher than BnP values in patients with early PD in the less affected (Ki=74%±19% and BnP=48%±14%) and more affected (Ki=51%±23% and BnP=37%±20%) hemispheres (χ2=20.43; P<.001). In patients with severe PD, the difference between Ki and BnP values was not significant in the less affected (Ki=34%±12% and BnP=27%±5%) and more affected (Ki=31%±9% and BnP=27%±5%) hemispheres (χ2=3.75; P=.29).

**CORRELATIONS**

The Ki values in the putamen averaged over both hemispheres in patients with PD were significantly corre-
lated with motor performance, measured using the motor score of the UPDRS-3 scale \((r = -0.78; P < .003, \text{Spearman})\) and the Purdue Pegboard \((r = 0.78; P < .005)\) \((\text{Figure 3})\). There was a trend toward a correlation between the corresponding BnP values and the motor scores \((\text{UPDRS-3}: r = -0.61; P = .01; \text{Purdue Pegboard}: r = 0.51; P = .05)\) \((\text{Figure 3})\), although the latter correlations were not significant after Bonferroni correction. Patient 2 has high Ki and BnP normalized values and good motor performance \((\text{Figure 3})\) and therefore might be considered an outlier. However, this patient has clear parkinsonian symptoms, including a rest tremor. If we make the correlation analysis after excluding patient 2, Ki values are correlated with UPDRS-3 \((r = -0.73; P = .003)\) and Pegboard \((r = 0.74; P = .006)\) scores, whereas BnP values are correlated with UPDRS-3 \((r = -0.54; P = .03)\) but not Pegboard \((r = 0.41; P = .12)\) scores.

**COMMENT**

In this study, we compared the striatal binding of 2 different presynaptic dopaminergic PET tracers: \(^{18}\text{F}-\text{dopa}\), which has been widely used to study striatal dopaminergic function, and \(^{76}\text{Br}-\text{FE-CBT}\), a recently developed highly specific ligand of the membrane DAT. The binding of both tracers is reduced in parkinsonian patients, but this reduction is significantly greater with \(^{76}\text{Br}-\text{FE-CBT}\) than with \(^{18}\text{F}-\text{dopa}\). Specifically, in the putamen of drug-naive patients with early PD, \(^{18}\text{F}-\text{dopa}\) uptake is decreased to 63\% of control values on average, whereas \(^{76}\text{Br}-\text{FE-CBT}\) BnP is reduced to 43\% of control values. For each tracer, this value estimates the symptomatic threshold, which is the level of tracer uptake for which the clinical signs of PD appear. The symptomatic threshold found using \(^{18}\text{F}-\text{dopa}\) is similar to that reported in previous PET studies.\(^{12,13,28,29}\) Only 2 PET studies\(^{12,13}\) have compared \(^{18}\text{F}-\text{dopa}\) and a PET DAT ligand in the same parkinsonian patients. As in the present study, it was reported that the binding of the DAT ligand was significantly lower than the \(^{18}\text{F}-\text{dopa}\) uptake in the putamen of patients with early PD.\(^{12,13}\) Altogether, these results confirm that DAT ligands are more sensitive than \(^{18}\text{F}-\text{dopa}\) to detect the early stages of PD because they reflect the loss of dopaminergic nerve terminals.\(^{14-16}\) Indeed, the mean 57\% reduction in \(^{76}\text{Br}-\text{FE-CBT}\) in the putamen of patients with early PD is in line with the decrease in dopaminergic neurons in the substantia nigra pars compacta extrapolated from the postmortem analysis of brains from patients with PD.\(^{30,31}\) In addition, in our group of patients with advanced PD with a mean disease duration of 12.1 years, the 73\% loss of \(^{76}\text{Br}-\text{FE-CBT}\) in the putamen of patients with early PD is in line with the decrease in dopaminergic neurons in the substantia nigra pars compacta extrapolated from the postmortem analysis of brains from patients with PD.\(^{30,31}\)
Br-FE-CBT uptake in the putamen is comparable to the 75% nigral cell loss observed by German et al. in patients with an average disease duration of 14 years. Comparatively, 18F-dopa uptake seems to be upregulated in the surviving dopaminergic terminals of patients with early PD. The striatal 18F-dopa uptake depends on the integrity of the nigrostriatal dopaminergic pathway and on the activity of the aromatic L-amino acid decarboxylase in these nerve terminals. An L-amino acid decarboxylase overactivity is supposed to occur in the surviving dopaminergic terminals of patients with PD to compensate for the loss of dopaminergic neurons. This compensatory mechanism might be similar to that observed in normal aging, in which the progressive loss of nigrostriatal dopaminergic neurons is associated with a decrease in striatal DAT ligand binding, without any reduction of 18F-dopa uptake.

This compensatory process, suggested by results obtained in patients with early PD, seems not to persist in patients with advanced PD. The difference between 18F-dopa uptake and 76Br-FE-CBT BnP is less and is not significant in the putamen of patients with advanced disease (Figure 2). Recently, Lee et al. found that upregulation of 18F-dopa uptake was on average 18% of control values compared with DAT ligand binding in un-

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**Table 2. Individual Positron Emission Tomography Results in 18 Patients With Parkinson Disease**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>18F-Dopa</th>
<th>76Br-FE-CBT</th>
<th>18F-Dopa</th>
<th>76Br-FE-CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.90</td>
<td>0.67</td>
<td>0.72</td>
<td>0.61</td>
</tr>
<tr>
<td>2</td>
<td>1.17</td>
<td>1.15</td>
<td>0.93</td>
<td>0.89</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>0.86</td>
<td>0.81</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>1.08</td>
<td>0.60</td>
<td>0.68</td>
<td>0.48</td>
</tr>
<tr>
<td>5</td>
<td>0.82</td>
<td>0.74</td>
<td>0.57</td>
<td>0.45</td>
</tr>
<tr>
<td>6</td>
<td>0.84</td>
<td>0.76</td>
<td>0.70</td>
<td>0.76</td>
</tr>
<tr>
<td>7</td>
<td>0.89</td>
<td>0.83</td>
<td>0.59</td>
<td>0.52</td>
</tr>
<tr>
<td>8</td>
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<td>0.79</td>
<td>0.72</td>
<td>0.69</td>
</tr>
<tr>
<td>9</td>
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<td>0.68</td>
<td>0.80</td>
<td>0.74</td>
</tr>
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<td>10</td>
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<td>0.82</td>
<td>0.94</td>
<td>0.91</td>
</tr>
<tr>
<td>11</td>
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<td>0.26</td>
<td>0.52</td>
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<tr>
<td>12</td>
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<td>0.33</td>
<td>0.34</td>
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<tr>
<td>13</td>
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<td>0.44</td>
<td>0.29</td>
<td>0.22</td>
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<td>14</td>
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<td>0.27</td>
<td>0.26</td>
<td>0.20</td>
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<tr>
<td>15</td>
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<td>0.52</td>
<td>0.38</td>
<td>0.31</td>
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<td>16</td>
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<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>17</td>
<td>0.52</td>
<td>0.52</td>
<td>0.40</td>
<td>0.40</td>
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<tr>
<td>18</td>
<td>0.70</td>
<td>0.46</td>
<td>0.25</td>
<td>0.28</td>
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</tbody>
</table>

*Less and more affected sides correspond to the hemispheres contralateral and ipsilateral, respectively, to the less and more clinically affected hemibodies. 18F-dopa uptake values (Ki) and binding potential (BnP) values have been normalized to the mean values in control subjects (see the “Image Analysis” subsection).
Thus, our results and those obtained in 2 recent PET studies suggest that compensatory mechanisms to dopaminergic neuronal degeneration are present in the early stages of the disease and might be less important in patients with more advanced PD, all of which are similar to observations made in a rat model of PD. Results of previous studies suggest that the compensatory increase of dopamine synthesis in PD mainly occurs at a later, although still presymptomatic, stage of neuronal degeneration. This hypothesis is based on the widely accepted observation that parkinsonian symptoms appear when striatal dopamine is reduced to 20% to 30% of normal levels, whereas dopaminergic neurons in the nigra are reduced to approximately 50% of normal values. However, measurements of postmortem striatal dopamine levels should be cautiously interpreted considering the instability of this molecule. In rats given PD using the 6-OHDA toxin, the level of striatal dopamine measured in vivo is much higher than that found in the postmortem analysis of the same animals. One simple explanation for this phenomenon is that dopamine turnover would rise in PD, leading to an increase in the dopamine released in the extracellular space but a decrease in the dopamine stored in the presynaptic vesicles, which is the dopamine measured in postmortem analyses. Accordingly, nearly all experimental and human studies have shown that the turnover of dopamine was increased in PD as demonstrated by the rise in the level of dopamine metabolites in the striatum. Thus, increased synthesis of dopamine in the surviving striatal terminals of patients with early PD would be accompanied by an increased transformation of 18F-dopa into 18F-dopamine in these terminals because of the overactivity of L-amino acid decarboxylase. The PET results fit with the latter hypothesis. Although this metabolic response might not be the only compensatory change during neuronal degeneration in early PD, it likely plays a role in delaying the onset of symptoms during the early stage of disease. Conversely, the loss of such metabolic compensations in more severely affected patients, which remain to be confirmed in further studies, might play a major role in the motor fluctuations observed in these patients. Prospective study of the striatal uptake of both tracers during disease progression may help confirm this.

Finally, in all patients with PD, the relationships between motor performance and putaminal tracer uptake were stronger with 18F-dopa than with 76Br-FE-CBT BnP. The correlations between 18F-dopa uptake and motor performance have been emphasized in several studies. In addition, correlations between PD severity and striatal uptake of DAT ligands have been reported using either PET or single-photon computed tomography. However, the relationships between the 2 different PET tracers and motor performance have not been analyzed previously in the same patients. The present results suggest that the motor abilities of patients with PD depend more on the functional status of putaminal dopaminergic terminals, measured using 18F-dopa, than on the density of these terminals, evaluated using a DAT ligand. This result, emphasizing the functional meaning of 18F-dopa uptake, is also in line with the hypothesis that the compensatory increase of dopamine synthesis in the early stages of PD might be responsible for delaying motor symptom onset in these patients.

Altogether, our results suggest that 18F-dopa and 76Br-FE-CBT are complementary markers of the presynaptic dopaminergic nigrostriatal system and thus may be useful to assess neuroprotection therapies. However, this is based on the hypothesis that there is no down-regulation of 76Br-FE-CBT binding in hyperactive dopaminergic neurons or in relation to dopaminergic medications. If this hypothesis is true, DAT ligands might more accurately measure dopaminergic neuronal degeneration than 18F-dopa and could be appropriate to evaluate neuroprotective strategies in PD.

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**Author contributions:** Study concept and design (Drs Vidailhet, Nguyen, Peschanski, Hantraye, Cesaro, Samson, and Remy); acquisition of data (Drs Ribeiro, Dupel, and Dollé and Messrs Loc’h and Ponchant); analysis and interpretation of data (Drs Ribeiro, Vidailhet, and Remy); drafting of the manuscript (Drs Ribeiro, Vidailhet, Dupel, Dollé, and Remy and Messrs Loc’h and Ponchant); critical revision of the manuscript for important intellectual content (Drs Vidailhet, Nguyen, Peschanski, Hantraye, Cesaro, Samson, and Remy); statistical expertise (Dr Remy); obtained funding (Drs Vidailhet, Dupel, Nguyen, Samson, and Remy); administrative, technical, and material support (Mr Loc’h and Dr Dollé); and study supervision (Drs Vidailhet, Peschanski, Hantraye, Cesaro, and Remy).

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REFERENCES


