The role of pallidal serotonergic function in Parkinson’s disease dyskinesias: a positron emission tomography study

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ARTICLE INFO
Article history:
Received 30 August 2014
Received in revised form 19 November 2014
Accepted 29 December 2014

Keywords:
Parkinson’s disease
Serotonin
Globus pallidus
Dyskinesia
Positron emission tomography

ABSTRACT
We have investigated the role of globus pallidus (GP) serotonergic terminals in the development of levodopa-induced dyskinesias (LIDs) in Parkinson’s disease (PD). We studied 12 PD patients without LIDs, 12 PD patients with LIDs, and 12 healthy control subjects. We used 11C-DASB positron emission tomography (PET), a marker of serotonin transporter availability, and 11C-raclopride PET to measure changes in synaptic dopamine levels following levodopa administration. PD patients without LIDs showed a significant reduction of GP serotonin transporter binding compared with healthy controls although this was within the normal range in PD patients with LIDs. Levels of GP serotonin transporter binding correlated positively with severity of dyskinesias. 11C-raclopride PET detected a significant rise in GP synaptic dopamine levels of patients with LIDs after a levodopa challenge but not in patients with a stable response. Our findings indicate that LIDs in PD are associated with higher GP serotonergic function. This increased serotonin function may result in further dysregulation of thalamocortical signals and so promote the expression of dyskinesias.

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1. Introduction
Levodopa remains the most effective oral treatment for Parkinson’s disease (PD) despite the introduction of newer oral therapies. However, as the disease advances, 80% of PD patients develop fluctuating responses to levodopa accompanied by involuntary movements known as levodopa-induced dyskinesias (LIDs) (Horstink et al., 2006; Lees et al., 1977). Progressive degeneration of nigrostriatal dopaminergic projections is the main pathologic hallmark of PD (Forno, 1996); however, degeneration of serotonergic, noradrenergic, and cholinergic neurons also occurs (German et al., 1992; Jellinger, 1991; Kish et al., 2008; Politis et al., 2010a, 2011, 2014; Rylander et al., 2010).

Previous positron emission tomography (PET) studies have reported that serotonergic function is affected in PD but to a lesser extent compared with the loss of striatal dopaminergic function (Politis et al., 2010a). Animal lesion models of PD have suggested that serotonergic neurons play a role in the development of LIDs via the aberrant release of striatal dopamine as a false transmitter after levodopa administration (Carlsson et al., 2007; Carta et al., 2007, 2010). A similar mechanism has been suggested in PD patients who received intrastriatal transplantation of fetal ventral mesencephalic tissue. These patients developed graft-induced dyskinesias that were associated with excessive serotonergic innervation within their grafts (Politis et al., 2010b, 2011). A recent PET study has demonstrated that relative preservation of striatal serotonergic terminals of advanced PD patients was associated with the development of LIDs (Politis et al., 2014).

Although most of the studies have focused on the striatum, other brain structures within the basal ganglia network are important in the control of movement. The internal globus pallidus (GPi) is the main output nucleus balancing excitatory activity from the direct and inhibitory activity from the indirect striatal pathways.
Dopamine modulates these pathways by exciting the direct pathway’s striatopallidal neurons via D1 receptors and by inhibiting the indirect pathway’s striatopallidal neurons via D2 receptors. The Gpi also receives a direct dopaminergic input from the medial substantia nigra (Parent and Cossette, 2001).

Although dopamine is a major modulatory neurotransmitter, the globus pallidus (GP) also receives serotonergic input from the dorsal raphe nucleus (Kita et al., 2007). A postmortem study with 

$^3$H-citalopram has shown increased levels of serotonin transporters (SERT) in the putamen and GP of PD patients with dyskinasias compared with PD patients without a history of dyskinasias (Rylander et al., 2010). In nigral lesion animal models of PD, levodopa exposure induced synaptic sprouting of serotonin neurons in the striatum, suggesting that the increased transporter expression reflects terminal upregulation (Rylander et al., 2010). This has since been corroborated by findings in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated marmosets (Zeng et al., 2010). However, it is unknown whether SERT and serotonin function is altered in patients with PD and LIDs.

We hypothesized that serotonin terminal function in GP would be relatively upregulated in PD with LIDs, so further dysregulating the signaling cascade in the network responsible for the control of movement. We sought to investigate this using $^{11}$C-DASB PET, a marker of SERT binding, and $^{11}$C-raclopride PET, a marker of dopamine D2 receptor availability which is influenced by rises in synaptic dopamine levels after a medication challenge with levodopa.

### 2. Methods

#### 2.1. Participants

We recruited 24 nonmedicated and nondepressed PD patients from UK university hospital movement disorder clinics who fulfilled the UK Brain Bank criteria for PD (Hughes et al., 1992). Imaging findings were compared with a group of 12 age- and gender-matched control subjects without history of neurologic or psychiatric disease. None of the subjects were on antidepressant medication known to interfere with the serotonergic system. Informed consent was obtained from all participants in the study in accordance with the Declaration of Helsinki. Clinical details are specified in Table 1.

<table>
<thead>
<tr>
<th>Characteristics for normal control subjects, Parkinson’s disease patients with stable response to levodopa (PD stable) and with levodopa-induced dyskinasias (PD LIDs)</th>
<th>Normal control subjects</th>
<th>PD stable</th>
<th>PD LIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/2</td>
<td>9/3</td>
<td>10/2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.3 ± 7.0</td>
<td>65.6 ± 6.9</td>
<td>65.2 ± 8.2</td>
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<tr>
<td>Disease duration (y)*</td>
<td>—</td>
<td>5 ± 1.6</td>
<td>12.0 ± 4.0***</td>
</tr>
<tr>
<td>UPDRS-III—OFF medication</td>
<td>—</td>
<td>23.9 ± 13.1</td>
<td>44.7 ± 7.5***</td>
</tr>
<tr>
<td>Daily LED (mg)</td>
<td>—</td>
<td>444 ± 105</td>
<td>1080 ± 735**</td>
</tr>
<tr>
<td>Lifetime LED (g)</td>
<td>—</td>
<td>295 ± 174</td>
<td>2184 ± 1372***</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.4 ± 0.7</td>
<td>29.3 ± 1.2</td>
<td>29.6 ± 0.8</td>
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<tr>
<td>Hoehn and Yahr-stage</td>
<td>—</td>
<td>2.3 ± 0.7</td>
<td>3.4 ± 0.8**</td>
</tr>
</tbody>
</table>

Data represent mean ± SD. Student t test. **p < 0.01, ***p < 0.001.

* Disease duration has been accounted from the time of first appearance of PD motor symptoms.

#### 2.2. Imaging procedures

The PD patients (12 with LIDs; 12 without dyskinasias) were assessed clinically ON and OFF levodopa, after overnight PD medication withdrawal. Motor disability and LIDs were rated with the Unified Parkinson’s disease rating scale (UPDRS) and Abnormal Involuntary Movements Scale (AIMS). On separate mornings, patients received either a $^{11}$C-DASB PET scan or the $^{11}$C-raclopride PET scans (the first OFF medication, a second 60 minutes after levodopa administration). Furthermore, a 1.5 T volumetric T1 magnetic resonance imaging (MRI) scan was performed for aiding the analysis of the PET data.

Twelve normal control subjects underwent clinical assessment; baseline $^{11}$C-raclopride and $^{11}$C-DASB PET scans and a 1.5 T volumetric T1 MRI scan, for anatomic colocalization purposes. PET imaging was performed at Hammersmith Hospital, London. Hammersmith Imanet plc, UK supplied the radiotracers. The details of the MRI and PET scanners and data analysis have been described in earlier studies (Politis et al., 2014). In brief, we acquired $^{11}$C-raclopride and $^{11}$C-DASB PET images using an ECAT EXACT HR+ scanner (Siemens, Erlangen, Germany). A short attenuation scan preceded the intravenous bolus injection of a mean dose of 250 MBq of $^{11}$C-raclopride or 450 MBq of $^{11}$C-DASB. We obtained images as 20 dynamic time frames over a period of 60 minutes for $^{11}$C-raclopride and as 28 time frames over 90 minutes for $^{11}$C-DASB. All PET and clinical assessments were performed in a pseudorandomized fashion.

#### 2.3. Clinical procedures for levodopa challenge

All PD patients were given a levodopa challenge (levodopa 250/ carbidopa 25) after overnight withdrawal from their medication for 18 hours. We rated LIDs using the AIMS every 15 minutes over a period of 150 minutes. We rated dyskinasias on a 0–4 point scale, and the highest amplitude or frequency was reported (Smith et al., 1978). A description of the calculation of lifetime levodopa equivalent exposure has been described previously (Politis et al., 2014).

#### 2.4. Imaging analysis

We corrected all PET images for motion artefacts using frame-by-frame realignment (Montgomery et al., 2006; Turkheimer et al., 1999). We generated parametric images of $^{11}$C-raclopride nondisplaceable binding potential (BP$_{ND}$) from the dynamic $^{11}$C-raclopride scans using a basis function implementation of the simplified reference tissue model, with the cerebellum as the reference tissue for nonspecific binding (Gunn et al., 1997). We then coregistered and resliced the data to the corresponding volumetric T1-weighted MRI using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK) implemented in Matlab. We calculated the input function for the $^{11}$C-DASB PET images from the nonspecific tracer-binding signal in the posterior cerebellar gray matter cortex, avoiding inclusion of the vermis (Kish et al., 2005). We then calculated volume of distribution ratios for regions-of-interest (ROI) using the graphical analysis method of Logan (Logan et al., 1996), and the BP$_{ND}$ was calculated as VDR-1 (Ginovart et al., 2001). We acquired meteorological data for the periods of $^{11}$C-DASB PET to correct for any confounding factors of weather and seasonal changes on $^{11}$C-DASB binding as previously described (Politis et al., 2010a,c). We saw no influence of weather conditions on our SERT results (data not shown), and thus, results were not corrected for this.

ROIs were traced on the individual coregistered MRIs by Ruben Smith and Thomas Hart who were blinded to the data, and then used the ROIs to sample the parametric PET images. GP ROIs were adapted
not to capture signal from the nearby putamen. We further calculated in ROIs 11C-raclopride BP\textsubscript{ND} percentage changes between the practically defined OFF-medication phase (baseline) and following administration of levodopa (de la Fuente-Fernandez et al., 2004).

2.5. Statistical analysis

We used Graph Pad Prism 6.0 or SPSS for Macintosh for statistical comparisons. After testing for normality using D’Agostino and Pearson omnibus normality test, we performed correlations using Pearson correlations because our data were normally distributed. For comparison of radioligand binding and disease duration, UPDRS scores and levodopa equivalent dose-exposure multiple regression analyses with correction for multiple comparisons were performed in SPSS. For other comparisons, we used Student t test or 1- or 2-way analysis of variance with or without repeated measurements as applicable. Multiple comparison corrections were performed using Bonferroni multiple comparisons test for each separate analysis. The α-value was set to 0.05. Results are presented ± standard error of the mean.

3. Results

3.1. SERT binding in globus pallidus

In PD patients with a stable response to levodopa, 11C-DASB BP\textsubscript{ND} was significantly reduced compared with control subjects in both the GPe (−20.2%) and the GPi (−24.2%) (F\textsubscript{(2,66)} = 10.24, p = 0.0001; GPe = 0.89 ± 0.05 vs. 0.71 ± 0.05, p < 0.05 and GPi = 0.66 ± 0.05 vs. 0.50 ± 0.05, p < 0.05).

PD patients with LIDs, however, had 11C-DASB BP\textsubscript{ND} levels similar to control subjects both in the GPe (þ2.3%) and the GPi (þ4.6%) (F\textsubscript{(2,66)} = 10.24, p = 0.0001; GPe = 0.89 ± 0.05 vs. 0.91 ± 0.04, p = n. s. and GPi = 0.66 ± 0.05 vs. 0.69 ± 0.05, p = n. s.).

Levels of 11C-DASB BP\textsubscript{ND} were relatively higher in patients with dyskinesias compared with those with a stable response to levodopa (GPe p < 0.01, GPi p < 0.05) (Fig. 1).

3.2. Correlations

We correlated regional brain 11C-DASB BP\textsubscript{ND} with average and maximum AIMS scores. For both GPe and GPi, higher 11C-DASB BP\textsubscript{ND} correlated significantly with higher AIMS scores (average: GPe r = 0.73, p < 0.01 and GPi r = 0.63, p < 0.05; maximum: GPe r = 0.70, p < 0.05 and GPi r = 0.57, p = 0.051) (Fig. 2A–D) in PD LIDs group.

To correct for possible influences of disease duration, UPDRS scores or total levodopa exposure on the 11C-DASB BP\textsubscript{ND} or 11C-raclopride BP\textsubscript{ND} multiple linear regression analyses were performed on the data. No significant influences of the former were seen. GPe DASB (F\textsubscript{(3,20)} = 1.26; p = 0.32), GPe DASB (F\textsubscript{(3,20)} = 0.97; p = 0.43), GPe RAC (F\textsubscript{(3,20)} = 0.35; p = 0.79), and GPe RAC (F\textsubscript{(3,20)} = 0.44; p = 0.73).

![Fig. 1. 11C-DASB BP\textsubscript{ND} in globus pallidus. N = 12 per group. Mean values ± SEM. *p < 0.05. Abbreviations: BP\textsubscript{ND}, nondisplaceable binding potential; LIDs, levodopa-induced dyskinesias; PD, Parkinson’s disease; SEM, standard error of the mean.](image-url)

![Fig. 2. Correlations between 11C-DASB BP\textsubscript{ND}, AIMS scores. (A) 11C-DASB BP\textsubscript{ND} in GPe versus average AIMS in PD patients with LIDs. Pearson correlation: r = 0.7313, p < 0.01. (B) 11C-DASB BP\textsubscript{ND} in GPi versus average AIMS in PD patients with LIDs. Pearson correlation: r = 0.6322, p < 0.05. (C) 11C-DASB BP\textsubscript{ND} in GPe versus maximal AIMS in PD patients with LIDs. Pearson correlation: r = 0.6953, p < 0.05. (D) 11C-DASB BP\textsubscript{ND} in GPi versus maximal AIMS in PD patients with LIDs. Pearson correlation: r = 0.5746, p = 0.051. Abbreviations: AIMS, Abnormal Involuntary Movements Scale; BP\textsubscript{ND}, nondisplaceable binding potential; GPi, internal globus pallidus; LIDs, levodopa-induced dyskinesias; PD, Parkinson’s disease.](image-url)
2.2% for patients with stable disease and patients with LIDs (Politis et al., 2014). On the other hand, PD patients with a stable levodopa response show similar SERT reductions in GP (20%–24%) and striatal (20%–30%) SERT binding. These findings indicate that either the serotonin terminal function in the GP in patients with LIDs is spared or, that an adaptive terminal sprouting of remaining serotonergic projections occurs, or that there is an upregulation of SERT-binding sites in these patients.

Levels of GP $^{11}$C-DASB binding in PD correlated with LIDs severity as measured with AIMS, indicating that serotonergic innervation of the GP may play a role in the development of LIDs. Dopamine D2 receptor PET showed a significant decrease in GP $^{11}$C-raclopride binding of PD patients with LIDs after levodopa administration, but not in stable PD patients. These results indirectly indicate greater dopamine release after levodopa in the GP of PD patients experiencing LIDs.

The relative increase in GP $^{11}$C-DASB BPND in PD patients with LIDs is likely to be a regional effect, because levels of $^{11}$C-raclopride binding in the striatum were reduced to a similar extent in PD patients with stable disease and patients with LIDs (Politis et al., 2014). It has been shown that chronic levodopa exposure induces sprouting of serotonergic axon terminals in a rat lesion model of PD. Thus available animal data would suggest a sprouting of serotonergic terminals rather than solely increased protein translation or sparing of certain neuronal populations (Rylander et al., 2010).

Motor fluctuations and dyskinesias usually develop in patients with increasing disease duration (Ahlskog and Muenter, 2001), and in line with this, our study groups were different in terms of disease duration, disease severity, and levodopa exposure (Table 1). We therefore analyzed the interaction of disease duration, disease severity, and medication intake in $^{11}$C-DASB and $^{11}$C-raclopride PET data and found no such interaction.

Because it has been suggested that exogenous dopamine can be converted and stored in serotonergic terminals, and be released as a false neurotransmitter (Carta et al., 2010; Lindgren et al., 2010), we studied GP D2 receptor availability and indirectly dopamine release with a double $^{11}$C-raclopride PET experiment. We found no difference in GP D2 receptor availability between PD patients and healthy control subjects (Fig. 3A). After a levodopa challenge, there was a significant decrease of $^{11}$C-raclopride BPND in both the external and internal GP segments in PD patients with LIDs, indicating increased dopamine release. This was not the case in the group of stable PD patients. There were no statistically significant differences in $^{11}$C-raclopride BPND between stable PD patients and PD patients with LIDs at baseline or after the levodopa challenge. Dopamine D2 receptors are more abundant in the striatum than in the GP and the $^{11}$C-raclopride binding in GP is low, as is the signal to noise ratio.
This creates a variance that might in part explain that we do not discern any significant differences between groups. Although the changes in $^{11}$C-raclopride $B_{PN}$ after levodopa administration are small, a 10% reduction has been shown to correspond to a 4-fold increase in synaptic dopamine levels in the caudate nucleus of rhesus monkeys (Breier et al., 1997). In the GPi, dopamine release seen with $^{11}$C-raclopride will have to serve as an indirect marker for dopamine release at D1 sites, because these receptors are the main mediators of dopaminergic effects in the GPi (Kliem et al., 2010). We speculate that the increased dopamine release, seen in patients with LIDs, may be a result of an increased serotonergic innervation in the striatum of rats with dyskinesias (Carta et al., 2007; Lindgren et al., 2010).

In PD patients with stable response to levodopa, the $^{11}$C-DASB reductions in the GP were comparable with those seen in the putamen and caudate. In PD patients experiencing LIDs, there were similar decreases in striatal SERT levels compared with the stable PD cases, but GP SERT binding was at the level of healthy control subjects. The basal ganglia receive a widespread serotonergic innervation, mainly from the rostral dorsal raphe nuclei in the brain stem (Wallman et al., 2011). The GP serotonergic innervation is dense, and 5-HT$_1$ receptors are abundant in both GP segments (Di Matteo, 2008; Wallman et al., 2011).

The role for dopamine as a neurotransmitter in the neostriatum is well established (for review see Rommelfanger and Wichmann, 2010). In the conventional model, dopaminergic input from substantia nigra pars compacta facilitates movement by stimulating the GABAergic neurons projecting to the internal segment of the GPi via D1 receptors and by inhibiting the indirect pathway neurons projecting to the GPe via D2 receptors (Rommelfanger and Wichmann, 2010; see Fig. 4A). The net result is an inhibition of the GPi GABA output to the thalamus and an increase in cortical activity. Interestingly, there are also parallel projections from the SNc to the GPi and GPe. The dopaminergic neurons projecting to the GPe appear to act predominately through presynaptic contacts on the striatopallidal GABA-neurons. This effect is mainly mediated via D2 receptors, although the presence of several other dopamine-receptors have been described in animal models (Rommelfanger and Wichmann, 2010). The dopaminergic neurons projecting to the GPi appear to act predominantly through presynaptic contacts on the striatopallidal GABA-neurons. This effect is mainly mediated via D2 receptors, although the presence of several other dopamine-receptors have been described in animal models (Rommelfanger and Wichmann, 2010). Both

**Fig. 4.** The basal ganglia circuitry. (A) Represents conditions in the normal brain. (B) Alterations due to PD in patients not suffering from dyskinesias. Progressive degeneration of the dopaminergic and serotonergic innervation results in increased activity in the indirect pathway and a reduced motor output. (C) Proposed model for changes leading to development of dyskinesias in patients with PD. Dopamine released from the sprouting serotonergic terminals stimulates D1 and D2 receptors resulting in an increased motor output on levodopa administration. (Blue indicates glutamate, red indicates GABA, green indicates DA; and turquoise indicates serotonin; + indicates excitation and – inhibition). Abbreviation: PD, Parkinson’s disease. (For interpretation of the references to color in this figure, the reader is referred to the Web version of this article.)
dopaminergic and serotonergic neurons can fine-tune and modulate the output from the GPi segment. As shown by Whone et al. (2003), the nigro pallidal projection neurons can compensate for the nigrostriatal degeneration in early stages of PD by upregulating dopamine turnover and storage capacity. However, this compensatory mechanism ultimately fails because of the progressive nature of the disease. Our 11C-raclopride PET studies showed that the baseline availability of D2 receptors in the GP is unaltered by PD. The post-synaptic part of the dopaminergic modulatory pathways in the GP thus seem to be intact (i.e., the striatopallidal GABAergic neurons), although the presynaptic innervation is gradually reduced because of the disease affecting dopaminergic neurons in the SNC (Fischman et al., 1998; Whone et al., 2003). We found that after levodopa administration there was a significant decrease of 11C-raclopride binding in both GP segments in patients with LIDs, but not in patients with a stable levodopa response, indicating a greater dopamine release in patients with LIDs leading to reduced D2 availability. Limitations of the method, however, do not allow us to discern other differences between the groups as discussed previously. Earlier studies in animal models of PD suggest that levodopa can be converted to dopamine in serotonergic cells and act as a false neurotransmitter (Carta et al., 2007, 2010; Lindgren et al., 2010). An increased serotonergic innervation could thus store more levodopa, resulting in increased and uncontrolled dopamine release in the GP (Fig. 4C) and possibly result in an increased motor output in the form of LIDs. The GP receives dopaminergic innervation, but to a lower extent compared with the neostriatum (Fahn et al., 1971; Hortnagl et al., 1983; Parent and Cossette, 2001). With the gradual degeneration of the GP dopaminergic neurons (Whone et al., 2003), the effect of the aberrant dopamine release from serotonergic terminals is likely to be potentiated by a reduced dopamine reuptake by dopamine terminals, failing to retrieve and buffer dopamine.

We suggest that the imbalance caused by a normalization of serotonin terminals in the dopamine-denervated striatum creates increased dopamine release on levodopa intake, resulting in an increased negative input to the GPi neurons controlling thalamic output. Mechanistically, the increase in dyskineticus could be mediated via neurotransmission alterations at presynaptic dopamine receptors located at the synapses of striatopallidal GABAergic neurons in the GP. These neurons control the projection neurons to the thalamus and thereby the thalamic output (Fig. 4C). By over-inhibition of these neurons, the dysregulated basal ganglia output then results in dyskineticus on levodopa administration. Interestingly, D1LR-agonist injection in the Gpi in monkeys results in a decreased Gpi neuronal activity (Kliem et al., 2010), and a profound suppression of Gpi output activity has been shown to be present in monkeys experiencing LIDs (Papa et al., 1999).

In conclusion, our findings support a role for an altered serotonergic innervation and modulation of GP activity in the development of LIDs. Patients developing dyskineticus have relatively increased presynaptic SERT in both the GPe and the Gpi compared with stable PD cases and show a more robust dopamine release in these structures after levodopa administration. The level of serotonergic innervation is correlated to the severity of the LIDs. By directly affecting the modulatory pathways of the basal ganglia, these alterations can directly interfere with motor output and contribute to the development of dyskineticus.

Acknowledgements

The authors thank the patients and their families for the participation and the Medical Research Council, UK for the workspace. They also thank the radiographers of Hammersmith Imanet Ltd for their help.

The funding source of this study is the Michael J. Fox Foundation for Parkinson’s Research (P14104). Dr Smith was funded by Multipark, Sweden. Dr Politis’ research is supported by Parkinson’s UK, Edmond J. Safra Foundation, Michael J. Fox Foundation for Parkinson’s Research, and NIH R01. The funding agencies had no role in the study design, data analysis, or in article drafting and submission.

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