



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



Ruben Smith^{a,b}, Kit Wu^b, Thomas Hart^b, Clare Loane^b, David J. Brooks^{b,c}, Anders Björklund^d, Per Odin^{a,e}, Paola Piccini^b, Marios Politis^{b,f,*}

^a Department of Clinical Sciences, Section for Neurology, Skåne University Hospital, Lund University, Lund, Sweden

^b Division of Brain Sciences, Department of Medicine, Imperial College London, London, UK

^c Positron Emission Tomography Center, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

^d Department of Experimental Medical Sciences, Wallenberg Neuroscience Center, Lund University, Lund, Sweden

^e Department of Neurology, Central Hospital, Bremerhaven, Germany

^f Neurodegeneration Imaging Group, Department of Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, UK

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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 neurones 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 intra-striatal 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

* Corresponding author at: Neurodegeneration Imaging Group, Department of Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London SE5 8AF, UK. Tel.: +44 (0)207 848 5682; fax: +44 (0) 207 848 0988.

E-mail address: marios.politis@kcl.ac.uk (M. Politis).

(Albin et al., 1989; DeLong and Wichmann, 2009). 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 ³H-citalopram has shown increased levels of serotonin transporters (SERT) in the putamen and GP of PD patients with dyskinesias compared with PD patients without a history of dyskinesias (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 with 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 ¹¹C-DASB PET, a marker of SERT binding, and ¹¹C-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 nondemented 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. We obtained approval from the local ethics committees, and written 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 1

Characteristics for normal control subjects, Parkinson's disease patients with stable response to levodopa (PD stable) and with levodopa-induced dyskinesias (PD LIDs)

	Normal control subjects	PD stable	PD LIDs
Number of subjects	12	12	12
Sex (M/F)	10/2	9/3	10/2
Age (y)	63.3 ± 7.0	65.6 ± 6.9	65.2 ± 8.2
Disease duration (y) ^a	—	5 ± 1.6	12.0 ± 4.0***
UPDRS-III—OFF medication	—	23.9 ± 13.1	44.7 ± 7.5***
Daily LED (mg)	—	444 ± 105	1080 ± 735**
Lifetime LED (g)	—	295 ± 174	2184 ± 1372***
MMSE	29.4 ± 0.7	29.3 ± 1.2	29.6 ± 0.8
Hoehn and Yahr-stage	—	2.3 ± 0.7	3.4 ± 0.8**

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

Key: LED, levodopa equivalent dose; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's disease rating scale.

^a 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 dyskinesias) 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 ¹¹C-DASB PET scan or the 2 ¹¹C-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 ¹¹C-raclopride and ¹¹C-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 ¹¹C-raclopride and ¹¹C-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 ¹¹C-raclopride or 450 MBq of ¹¹C-DASB. We obtained images as 20 dynamic time frames over a period of 60 minutes for ¹¹C-raclopride and as 28 time frames over 90 minutes for ¹¹C-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 dyskinesias 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 ¹¹C-raclopride nondisplaceable binding potential (BP_{ND}) from the dynamic ¹¹C-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 ¹¹C-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 ¹¹C-DASB PET to correct for any confounding factors of weather and seasonal changes on ¹¹C-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

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