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Elevated [^{18}F]FDOPA utilization in the periaqueductal gray and medial nucleus accumbens of patients with early Parkinson's disease

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ABSTRACT

PET studies with the DOPA decarboxylase substrate 6-[^{18}F]fluoro-L-DOPA (FDOPA) reveal the storage of [^{18}F]-fluorodopamine within synaptic vesicles, mainly of dopamine fibres. As such, FDOPA PET is a sensitive indicator of the integrity of the nigrostriatal dopamine innervation. Nonetheless, there have been several reports of focal elevations of FDOPA utilization in brain of patients with Parkinson's disease (PD), all based on reference tissue methods. To investigate this phenomenon further, we used voxel-wise steady-state kinetic analysis to search for regions of elevated FDOPA utilization (K; ml g^{-1} min^{-1}) and steady-state trapping (V_d; ml g^{-1}) in a group of well-characterized patients with early, asymmetric PD, who were contrasted with an age-matched control group. Subtraction of the population mean parametric maps revealed foci of increased FDOPA utilization K (+25%) in the bilateral medial nucleus accumbens, whereas the expected declines in the trapping of FDOPA were seen in the caudate and putamen. This observation suggests hyperfunction of catecholamine fibres innervating specifically the limbic striatum, which could guide the design of future prospective FDOPA-PET studies of the impulse control disorders occurring in some PD patients under treatment with dopamine agonists. A focus of increased FDOPA influx and also V_d was detected in the periaqueductal grey, consistent with some earlier reports based on reference tissue analysis. Increased FDOPA trapping in the periaqueductal grey of PD patients seems consistent with recent reports of increased activity of serotonin neurons in a rat model of parkinsonism.

Introduction

The insidious onset of Parkinson's disease (PD) implies the occurrence of a pre-clinical pathophysiological process of some duration. A longitudinal positron emission tomography (PET) study with the DOPA decarboxylase substrate [^{18}F]fluoro-L-DOPA (FDOPA) suggests a pre-clinical interval of nigrostriatal degeneration lasting 5 years (Hilker et al., 2005), although we have argued that the initiation may occur as much as two decades prior to the emergence of frank motor symptoms (Borghammer et al., 2005). It is, however, generally accepted that early, unilateral PD is associated with a 25% decline in FDOPA utilization in the putamen of the hemisphere contralateral to the first symptoms (Morrish et al., 1995; Rinne et al., 2001). In contrast, FDOPA uptake in the caudate nucleus is generally preserved until considerable disease progression has occurred; late decreases in caudate may have a particular association with declining cognitive function (Holthoff-Detto et al., 1997; Koerts et al., 2007). Whereas FDOPA is an accepted tracer for nigrostriatal degeneration, there is an isolated report that FDOPA uptake may be elevated in the pineal gland in patients with advanced PD (Ghaemi et al., 2001). Furthermore, focally increased FDOPA utilization has been described in the anterior cingulate cortex and in the dorsal midbrain of patients with early, asymmetric PD (Rakshi et al., 1999). Similarly, FDOPA utilization was elevated in the right dorsolateral prefrontal cortex of patients with early PD, most especially in women (Kaasinen et al., 2001); this cortical increase correlated negatively with performance of a "frontal" cognitive task (Bruck et al., 2005). Recently, the earlier finding of increased FDOPA uptake in the dorsal mesencephalon (but not in cortex) has been replicated in an independent group of patients with early PD (Moore et al., 2008).

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The utilization of FDOPA in living striatum is indicative of the activity of DOPA decarboxylase (Cumming et al., 1994), but the late washout phase of prolonged PET recordings reflects catabolism of the enzymatic product [^{18}F]fluorodopamine (Huang et al., 1991; Kuwabara et al., 1993; Holden et al., 1997; Sossi et al., 2001; Cumming et al., 2001). The previous reports of increased FDOPA utilization have all employed a reference tissue method for quantitation of the PET recordings. We have developed an improved kinetic analysis (inlet and outlet model), which allows stable voxel-wise calculation of steady state FDOPA kinetics, based upon the metabolite-corrected arterial input (Kumakura et al., 2005, 2006, 2007 and 2008). Results of this analysis have shown that the rate constant for the turnover of [^{18}F]fluorodopamine formed in brain (k_{loss}; min^{-1}) and the steady state storage of FDOPA together with its decarboxylated metabolites (V_d; ml g^{-1}) are more sensitive indicators of nigrostriatal degeneration than is the conventional index of initial blood–brain net clearance (K_{in}^{app}; ml g^{-1} min^{-1}), or the reference tissue method. Furthermore, steady-state methods have greater process specificity, in that FDOPA trapping (V_d) and washout of the trapped metabolites (k_{loss}) can be calculated separately. In the present study, we test the hypothesis that our new method for parametric mapping of the steady-state kinetics can detect foci of increased FDOPA trapping in a group of patients with early PD.

Materials and methods

Subject recruitment

13 healthy volunteers (9 men and 4 women) aged 43–73 years (Mean 56.2 ± 8.0 years) were selected from normal cohorts in previously-published FDOPA PET studies (Kumakura et al., 2004; Siessmeier et al., 2006; Vernaleken et al., 2006), which had been approved by the Research and Ethics Committees of the Universities of Mainz and Aarhus. All subjects had provided written informed consent for the earlier studies. Eight patients with early Parkinson's disease (3 men and 5 women) aged 45–73 years (Mean 58.6 ± 10.2 years) were the patient cohort in the previously-published FDOPA PET studies (Kumakura et al., 2004 and 2006). The patients were recruited from the Aarhus University Movement Disorders clinic, and were under treatment with levodopa monotherapy (six patients; 675 ± 150 mg levodopa/day) or no prior medication (two patients). The patients had never been exposed to COMT inhibitors, MAO inhibitors, or dopamine direct agonists, and had a pause of routine medication for 3 days before the PET examination. At the time of scanning, the patients were assessed by the Hoehn and Yahr scale (mean score of 2.4 ± 0.2; range 2 to 3); all patients had either unilateral or asymmetric motor symptoms. The mean disease duration was 3.1 ± 1.5 years. Impulse control disorders, mood disorders or levodopa abuse were not noted in any of the patients. Exclusion criteria for PD patients included systemic disease, any medication CNS-acting medication other than levodopa, on–off motor symptoms, and fluctuating symptoms.

PET scanning and plasma sampling procedure

Subjects fasted overnight, and received carbidopa (Merck Sharpe and Dohme; 2 mg/kg, p.o.) 1 h prior to the PET scanning in order to minimize the decarboxylation of FDOPA in peripheral tissues (Cumming et al., 1993). Subjects reclined on the scanning bed of the ECAT EXACT 47 whole body PET scanner (CTI/Siemens, Knoxville, TN), with their heads comfortably immobilized using a custom-made head-holder. After a brief ^{68}Ge transmission scan for attenuation correction, a 3D dynamic emission recording lasting 120 min was initiated upon intravenous injection of FDOPA (200 MBq). Total radioactivity concentration was measured in serial arterial blood, and the fractions of untransformed FDOPA and its major plasma metabolite OMFD were determined in nine selected plasma samples (5, 10, 15, 20, 30, 45, 60, 90 and 120 min) by reverse-phase HPLC (Cumming et al., 1993). Continuous input functions for FDOPA and OMFD were calculated by fitting bi-exponential functions to the measured fractions (Gillings et al., 2001).

The dynamic PET sequences were realigned and corrected frame-wise for head motion as described previously (Kumakura et al., 2004). Time–radioactivity curves (TACs) were then extracted by masking template VOIs for eight structures, i.e. left and right caudate nucleus (left 4.2 cm^3; right 4.3 cm^3), putamen (left 5.0 cm^3; right 4.7 cm^3), medial nucleus accumbens (NAc; left 0.6 cm^3; right 0.6 cm^3), anterior cingulate cortex (ACC; 2.5 cm^3) and the periaqueductal gray (PAG; 0.4 cm^3) (Fig. 1). The cerebellum (48.3 cm^3) served as a reference region nearly devoid of dopamine innervation. In the conventional

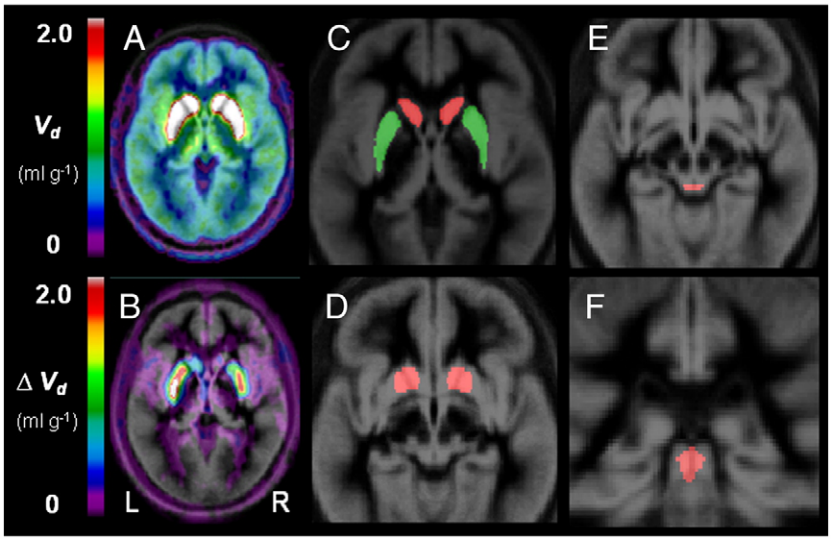

Fig. 1. An example of PET image registration to the MNI stereotaxic brain, displayed together with the template VOIs. A spatially normalized map of (A) the total distribution volume of FDOPA (V_d, ml g^{-1}) from a 58-year-old healthy subject is superimposed onto the MRI gray matter template of the MNI stereotaxic brain. The parametric subtraction map (B) showing voxels in which the steady-state storage capacity for FDOPA (V_d; ml g^{-1}) was lower in patients with early Parkinson's disease than in a group of age-matched control subjects. The difference map (B) calculated from the same groups as Fig. 3 displays the greatest V_d-reduction in left putamen, because the individual parametric maps of the patients were flipped so that the most affected cerebral hemisphere is on the left. Template VOIs are shown for (C) caudate and putamen, (D) medial nucleus accumbens (medial NAc), and (E, F) periaqueductal gray (PAG), all projected on the MNI stereotaxic brain.