Neurobiology of Disease 43 (2011) 609–615

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Serotonergic mediated body mass index changes in Parkinson's disease

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ARTICLE INFO

Article history:
Received 16 March 2011
Revised 12 May 2011
Accepted 14 May 2011
Available online 23 May 2011

Keywords:
Parkinson's disease/Parkinsonism
BMI
Serotonin
PET
DASB

ABSTRACT

More than 50% of patients with Parkinson's disease (PD) are expected to show abnormalities with their weight in a process that starts several years before the diagnosis. The serotonergic (5-HT) system has been proposed to regulate appetite and the 5-HT transporter (SERT) is a key modulator of 5-HT metabolism. Here, we hypothesized that a dysfunctional 5-HT system could be responsible for alterations of weight in PD and we sought to investigate this in vivo. Thirty four PD patients had Body Mass Index (BMI) changes monitored over a 12-month period and one positron emission tomography (PET) brain scan with ^{11}C-DASB, a selective marker of SERT availability, during their second clinical assessment. Results were compared with those of a group of 10 normal controls.

Half (17) of the PD patients showed abnormal BMI changes over the 12-month period; 12 lost while 5 gained weight. PD patients with abnormal BMI changes showed significantly raised ^{11}C-DASB binding in rostral raphe nuclei, hypothalamus, caudate nucleus and ventral striatum compared to cases with no significant BMI changes. ^{11}C-DASB binding in other regions was similarly decreased in the PD BMI subgroups compared to normal controls. BMI gainers showed significantly raised ^{11}C-DASB binding in anterior cingulate cortex (ACC) compared to BMI losers. Our findings suggest that abnormal BMI changes over a 12-month period are linked with relatively raised SERT availability in PD on an overall background of decreased 5-HT function. The regions implicated are the rostral raphe nuclei and its connections to limbic and cognitive areas. It is conceivable that 5-HT agents could help alleviate abnormal changes in BMI in PD.

Introduction

The clinical course of Parkinson's disease (PD) is commonly complicated by the occurrence of non-motor symptoms (Chaudhuri and Healy, 2006). PD patients characteristically lose weight (Abbott et al., 1992; Chen et al., 2003) evidenced as a decrease in their body mass index (BMI) (Beyer et al., 1995) compared to age matched controls. The frequency of BMI loss among PD patients has been reported between 52% and 65% (Abbott et al., 1992; Moroo et al., 1994). Weight loss in PD patients appears to be a continuous process that starts several years before the diagnosis and is not associated with reduced energy intake (Chen et al., 2003). Symptoms of the disease, medication side effects, and depression have all been proposed as contributors to BMI loss in PD patients (Beyer et al., 1995; McDonald et al., 2003).

In contrast, weight gain has been observed in PD patients on L-DOPA possibly *via* a pharmacological action in the hypothalamus (Gasparini and Spinnler, 1975), a region associated with appetite regulation (Morton et al., 2006). BMI gain has been demonstrated in patients following pallidotomy (Ondo et al., 2000) and stimulation of the subthalamic nucleus (Macia et al., 2004) probably secondary to amelioration of dyskinesias.

The serotonergic (5-HT) system has been proposed to regulate appetite (Leibowitz and Alexander, 1998) and the 5-HT transporter (SERT) is a key modulator of 5-HT metabolism by maintaining its levels in the extracellular space (Lesch and Gutknecht, 2005). Previous ^{18}F-altanserin positron emission tomography (PET) studies in healthy humans have shown positive correlations between BMI levels and brain 5-HT$_{2A}$ receptor availability (Adams et al., 2004; Erritzoe et al., 2009). ^{11}C-DASB PET studies in healthy humans have demonstrated decreased cerebral SERT binding levels in individuals with high BMI (Matsumoto et al., 2008; Erritzoe et al., 2010). These findings are compatible with either a direct role of SERT on BMI regulation, or more likely, reflect compensatory mechanism due to altered extracellular 5-HT levels.

There is pathological and imaging evidence suggesting that the 5-HT system is affected in PD (Scatton et al., 1983; Shannak et al., 1994; Kish et al., 2008) and a recent ^{11}C-DASB PET study reported significant

Abbreviations: ACC, anterior cingulate cortex; BMI, body mass index; BP$_{ND}$, binding potential of the specifically bound radioligand relative to the non-displaceable radioligand in tissue; DA, dopamine agonists; FOV, field of view; H&Y, Hoehn and Yahr staging; LED, Levodopa-Equivalent-Dose; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; MRI, Magnetic Resonance Imaging; PCC, posterior cingulate cortex; PD, Parkinson's disease; PET, positron emission tomography; PFC, prefrontal cortex; ROI, regions of interest; SD, standard deviation; SERT, serotonin transporter; TAC, time-activity curve; UK, United Kingdom; UPDRS, Unified Parkinson's Disease Rating Scale; VDR, Volume of Distribution Ratio.

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doi:10.1016/j.nbd.2011.05.009

SERT reductions in striatal, brainstem, and cortical regions in different stages of PD (Politis et al., 2010). However, whether dysfunction of the 5-HT system is associated with alterations of weight in PD remains unknown. Here, we have monitored BMI changes over a 12-month period in a population of PD patients. Our objective was to explore the relationship between BMI changes and SERT availability. We hypothesized that 5-HT dysfunction may influence the BMI in PD and we sought to investigate this in vivo by using ^{11}C-DASB PET, a selective marker of SERT availability.

Methods

Subjects and clinical evaluation

Thirty-four non-demented, non-depressed patients with idiopathic PD were studied. All patients underwent an assessment battery comprising of the Hoehn and Yahr (H&Y), Unified PD Rating Scale (UPDRS), Mini-Mental State Examination (MMSE), Beck Depression Inventory-II (BDI-II) and Hamilton Rating Scale for Depression (HRSD). Daily and lifetime L-DOPA-Equivalent-Dose (LED) were also calculated. All subjects included had ≤16 BDI-II and ≤13 HRSD scores and we have also excluded subjects with apathy or/and anhedonia without depression. The lifetime LED was calculated from medical notes and general practitioner letters and these data were cross-checked with the subjects. Alcohol and tobacco use was calculated. Ten healthy subjects, all in good health and with no history of neurologic or psychiatric illness and not taking medication, served as the control group. Whole blood samples from all subjects for genotyping the functional polymorphisms of SERT gene (LPR and VNTR) were also acquired. None of the total of 44 subjects studied made any dietary change, had any concurrent medical illness affecting weight or received any medication with a known action on the 5-HT system during the 12-month period of the study. In each subject, BMI, defined as the body weight divided by the squared height, was measured on two separate occasions, with a 12-month interval. All subjects underwent one ^{11}C-DASB PET scan on the day of the second BMI assessment (Table 1).

The study received ethical approval from the Hammersmith and Queen Elizabeth Charlotte's Hospital Ethics Committee and permission to administer ^{11}C-DASB was obtained from the Administration of Radioactive Substances Advisory Committee, United Kingdom. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Scanning procedures

PET scans were performed with an ECAT HR$^+$ (CTI/Siemens 962) 3D PET camera with a total axial field of view (FOV) of 15.5 cm, a mean image transaxial resolution (3D mode) over a 10 cm radius FOV (from the center) of 6.0 + 0.5 mm and an axial resolution of 5.0 + 0.8 mm. A mean ^{11}C-DASB dose of 450 MBq was administered as a bolus injection 30 s after the initiation of scanning. Twenty-eight frames were collected over a 90-min-long emission recording. All subjects underwent a T1 magnetic resonance imaging (MRI) scan with a 1.5-Tesla MRI (Picker Eclipse) scanner for co-registration and region of interest (ROI) localization purposes. Head position was aligned using a laser system ensuring the detectors and orbitomeatal line were parallel and monitored throughout the scan. All subjects discontinued medication at least 18 h prior to scanning and were scanned fasted and in a resting state. Smoking, consumption of alcohol, coffee and other caffeinated beverages were not allowed at least 12 h before scanning. Meteorological data (London Office, UK) for the periods of the assessments were also acquired in order to account for confounding factors of weather and seasonal changes on ^{11}C-DASB binding as previously described (data not shown) (Politis et al., 2010).

^{11}C-DASB PET analyses

A tissue non-specific binding reference input function was derived from ^{11}C-DASB time activity curves for the posterior part of the cerebellar gray matter cortex, avoiding inclusion of the vermis (Kish et al., 2005). Following reconstruction of the dynamic ^{11}C-DASB image volume, a summed image volume was created from the entire dynamic data set using an in-house software package. The regional concentrations of radioactivity (kBq/ml) were obtained from the full dynamic scan and decay-corrected time-activity curves (TACs) were computed and movement during the scan assessed. Motion correction was performed on all scans for frames 8 to 28 using a frame-by-frame realignment method as previously described (Montgomery et al., 2006).

Table 1
Parkinson's disease patient's and normal control's characteristics.

	All PD			Normal controls
		Normal BMI change	Abnormal BMI change	
No. of Subjects	34	17	17	10
Sex	28 M/6 F	14 M/3 F	14 M/3 F	8 M/2 F
Age (years ± SD)	64.7 ± 7.4	64.1 ± 8.9	65.3 ± 6.6	63.7 ± 7.2
SERT LPR polymorphism	11 L/L, 15 L/S, 8 S/S	6 L/L, 7 L/S, 4 S/S	5 L/L, 8 L/S, 4 S/S	3 L/L, 5 L/S, 2 S/S
SERT VNTR polymorphism	18 10/10, 16 12/12	10 10/10, 7 12/12	8 10/10, 9 12/12	6 10/10, 4 12/12
Disease duration (years ± SD)	8.8 ± 4.5	9.6 ± 5.4	8.0 ± 3.9	–
H&Y stage — "OFF" state (mean ± SD)	2.6 ± 0.7	2.5 ± 1.0	2.6 ± 0.6	–
UPDRS — "OFF" state (mean ± SD)	63.9 ± 20.2	63.9 ± 22.7	63.8 ± 17.5	–
Daily LED_{TOTAL} (mg ± SD)	762 ± 553	790 ± 651	736 ± 392	–
Lifetime LED_{TOTAL} (g ± SD)	1280 ± 1222	1446 ± 1569	1095 ± 829	–
MMSE (mean ± SD)	28.8 ± 2.4	28.8 ± 2.2	28.7 ± 2.8	29.4 ± 0.7
BDI-II (mean ± SD)	7.5 ± 4.0	6.9 ± 4.1	8.1 ± 4.9	3.5 ± 2.6 (0–7)
HRSD (mean ± SD)	5.7 ± 3.5	4.9 ± 2.0	6.2 ± 4.2	2.9 ± 2.8 (0–8)
BMI (kg/m^2) — time of PET scan (mean ± SD)	25.4 ± 3.9	24.8 ± 3.4	26.1 ± 4.4	28.1 ± 5.3
BMI (kg/m^2) — 12 months ago (mean ± SD)	26.2 ± 4.1	24.9 ± 3.2	27.5 ± 4.5	28.2 ± 5.1
BMI (kg/m^2) — Change (mean ± SD)	1.8 ± 1.2	0.8 ± 0.4	2.8 ± 1.0	0.7 ± 0.3

Disease duration has been accounted from the time of PD motor symptom initiation (not the time of diagnosis); M = male; F = female; SD = standard deviation; H&Y = Hoehn and Yahr staging; UPDRS = Unified Parkinson's Disease Rating Scale; LED = Levodopa Equivalent, The dose is calculated similarly to previous report (Politis et al., 2010), LED (mg) = (1 × Levodopa) + (0.77 × Levodopa CR) + (1.43 × Levodopa + Entacapone) + (1.11 × Levodopa CR + Entacapone) + (20 × Ropinirole) + (20 × Ropinirole ER) + (100 × Pramipexole) + (30 × Rotigotine) + (10 × Bromocriptine) + (8 × Apomorphine) + (100 × Pergolide) + (67 × Cabergoline); LED formula, In Levodopa/Carbidopa or Benserazide hydrochloride: Only Levodopa is calculated; MMSE = Mini-Mental State Examination; BDI-II = Beck Depression Inventory Second Edition; HRSD = Hamilton Rating Scale for Depression; BMI = body mass index. The clinical characteristics of 18 of these PD patients and all of normal controls are also presented in Politis et al., 2010.