Usefulness of a dopamine transporter PET ligand [^{18}F] β -CFT in assessing disability in Parkinson's disease

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Abstract

Objectives—The usefulness of a novel dopamine transporter PET ligand, [^{18}F] β -CFT in assessing disability in Parkinson's disease was studied.

Methods—Twenty seven patients with Parkinson's disease in different disability stages (of which nine were patients with early disease) and nine healthy controls were studied. The regions of interest were drawn on a magnetic resonance image resliced according to the PET image.

Results—There was a significant reduction in [^{18}F] β -CFT uptake in the posterior putamen (to 18% of the control mean, $p<0.00001$), anterior putamen (28%, $p<0.00001$), and caudate nucleus (51%, $p<0.00001$) in the total population of patients with Parkinson's disease. The reduction in [^{18}F] β -CFT uptake was more pronounced with more severe disability of the patients, the correlations between the total motor score of the unified Parkinson's disease rating scale (UPDRS) and [^{18}F] β -CFT uptake being significant in the posterior putamen ($r=-0.62$, $p=0.0005$), anterior putamen ($r=-0.64$, $p=0.0003$), and the caudate nucleus ($r=-0.62$, $p=0.0006$). There was a significant negative correlation with putaminal [^{18}F] β -CFT uptake and the hypokinesia and rigidity scores, but not with the tremor score of the UPDRS motor part. In nine patients with early disease and without any antiparkinsonian medication the reduction in the [^{18}F] β -CFT uptake (average of ipsilateral and contralateral side) was reduced in the total putamen to 34% of the mean control value ($p<0.00001$). The corresponding figures in the other brain areas were: posterior putamen 21% ($p<0.00001$), anterior putamen 43% ($p<0.00001$), and caudate nucleus 76% ($p<0.01$). The reductions in [^{18}F] β -CFT uptake were more severe in the contralateral than in the ipsilateral side. Individually, [^{18}F] β -CFT uptake in the putamen in all patients was below 3 SD from the control mean.

Conclusions—[^{18}F] β -CFT is a sensitive marker of nigrostriatal dopaminergic dysfunction in Parkinson's disease and can be used in the diagnosis, assessment of disease severity, and follow up of patients.

Keywords: dopamine transporter; dopamine reuptake, Parkinson's disease; positron emission tomography

Loss of dopaminergic neurons in the substantia nigra is a characteristic feature of Parkinson's disease. This neuronal loss is most severe in the ventrolateral nigra,¹⁻⁵ projecting mainly to the posterior putamen. Impaired dopaminergic function in Parkinson's disease has been demonstrated in vivo with positron emission tomography (PET)⁶⁻¹⁰ and single photon emission computed tomography (SPECT),¹¹⁻¹⁴ using various tracers.

Dopamine transporter is a protein situated in the presynaptic dopaminergic terminal, regulating the synaptic concentration of dopamine. [^{18}F] β -CFT ([^{18}F]WIN 35,428) is a novel PET ligand for these dopamine reuptake sites.¹⁵⁻¹⁷ The uptake of [^{18}F] β -CFT reflects the integrity of nigrostriatal dopamine terminals, and [^3H]-labelled WIN 35,428 binding in Parkinson's disease was related to dopamine and dopamine transporter protein concentrations.¹⁸ CFT is more selective for dopamine transporter (compared with noradrenaline (norepinephrine) and serotonin transporter, and dopamine is four and 16 times more potent in inhibiting CFT binding than noradrenaline or serotonin, respectively.^{19, 20} Thus [^{18}F] β -CFT might be a useful ligand to assess disability and disease progression in Parkinson's disease. We have previously shown that [^{18}F] β -CFT is sensitive in detecting presynaptic dopaminergic defects in early Parkinson's disease.¹⁷

The aim of the present study was to investigate the usefulness of dopamine transporter ligands, such as [^{18}F] β -CFT, to assess disability in Parkinson's disease.

Patients and methods

PATIENTS

We studied 27 patients (nine women, 18 men) with various disability stages of Parkinson's disease. The mean age of the patients was 61.4 years (SD 8.6, range 54-73).

The mean duration of disease was 5.8 years (SD 5.2, range 1.5-15). The disability of the patients was distributed according to the modified Hoehn and Yahr stage²¹ as follows: stage 1 one patient, stage 1.5 one patient, stage 2 17 patients, stage 2.5 three patients, stage 3 three patients, and stage 4 two patients. The severity of the motor symptoms of the patients with Parkinson's disease was evaluated using the motor part of the unified Parkinson's disease rating scale (UPDRS).²¹ The score of

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the motor part of the UPDRS varied from 9 to 61. Nine out of the 27 patients were new, without any antiparkinsonian medication. All the rest were receiving levodopa. In addition, eight patients were receiving a dopamine agonist; five had selegiline, and three had both. All patients who were on treatment had a favourable response to levodopa therapy. Dopamine agonists and selegiline were stopped 3 days before the PET and levodopa was discontinued at least 6 hours before the scan. The UPDRS evaluation was done just before PET, the patients being “off medication”. The PET data of the nine patients with early Parkinson’s disease has been published earlier,¹⁷ but in the present report a subregional analysis of putamen is performed.

Nine healthy volunteers (four women, five men) served as controls. They had no history or evidence of neurological or psychiatric disease. The mean age of the controls was 59.1 years (SD 8.6, range 53–70).

The study was approved by the joint ethics committee of Turku University and Turku University Hospital. A written informed consent was obtained from each study subject.

RADIOCHEMISTRY

[¹⁸F]β-CFT([¹⁸F]WIN 35,428) was synthesised by electrophilic fluorination of 2-β-carbomethoxy-3-β-(4-trimethyl-stannyl-phenyl) tropane.¹⁵ High specific radioactivity elec-

trophilic fluorine ([¹⁸F]F₂, >40 GBq/μmol) was made by a method developed at our laboratory.²² The precursor was dissolved in a solution of 700 μl Freon11 and 100 μl glacial acetic acid.²³ [¹⁸F]F₂ in neon was bubbled through the solution, whereafter preparative separation was made with high performance liquid chromatography. The fraction containing the product was evaporated to dryness, the residues dissolved in phosphate buffered saline (pH 7), and sterile filtrated. The radiochemical purity was better than 99%. The specific radioactivity at the end of synthesis was 15.8 (SD 3.9) GBq/μmol.

PET IMAGING

A whole body PET scanner (ECAT 931/08–12) was used. Attenuation was corrected individually with a transmission scan of 10 minutes using a removable ⁶⁸Ge ring source (about 13×10⁶ counts per plane). On average 148 MBq (4.0 mCi) of [¹⁸F]β-CFT was injected intravenously. The specific radioactivity at the time of injection was 10.1 (SD 3.3) GBq/μmol and the injected amount of [¹⁸F]β-CFT was 4.0 (SD 0.9) μg. A 60 minute dynamic scan starting from 150 minutes after injection was performed. The data were acquired in 2D mode. The regions of interest were drawn on the head of the caudate, putamen, and cerebellum in each hemisphere on an MR image (1.5 T) realigned according to the PET image¹⁷ using the Pellizari method.²⁴ The putamen was divided into anterior and posterior halves along its longitudinal axis. The regions of interest (ROIs) were copied on the PET image and the uptake of [¹⁸F]β-CFT was calculated as a (region-cerebellum)/cerebellum ratio at 180 to 210 minutes after injection. This uptake ratio does not necessarily represent true dopamine transporter binding potential, although there is little variation in this ratio with time at these late stages of the scan.¹⁷ The other details of the PET imaging have been published earlier.¹⁷

STATISTICS

The difference in [¹⁸F]β-CFT uptake between patients with Parkinson’s disease and controls was analysed using Student’s *t* test with Bonferroni correction for multiple comparisons. The correlation between [¹⁸F]β-CFT uptake and clinical variables of patients with Parkinson’s disease was evaluated by calculating Pearson’s regression coefficient. In these correlations the mean [¹⁸F]β-CFT uptake of left and right hemispheric structures were used.

Results

In the putamen (average of ipsilateral and contralateral side) of all 27 patients with Parkinson’s disease the mean uptake value of [¹⁸F]β-CFT was reduced to 25% of the control mean (0.80 (SD 0.56) for patients with Parkinson’s disease, 3.24 (SD 0.58) for controls, *p*<0.0001). When the putamen was divided into the anterior and posterior putamen, there was a slightly greater reduction in [¹⁸F]β-CFT uptake in the posterior putamen (to 18% of the control mean, *p*<0.00001) than

Table 1 [¹⁸F]β-CFT uptake as (region-cerebellum)/cerebellum ratio in the putamen and the caudate nucleus in patients with Parkinson’s disease and controls

Group	n	Posterior putamen	Anterior putamen	Caudate	Put/Cau†
Control	9	2.91; 0.66	3.44; 0.60	3.28; 0.49	0.89; 0.08
Parkinson	27	0.51; 0.22*	0.97; 0.46*	1.67; 0.72*	0.30; 0.11*
% of control	18		28	51	34

Values are means of ipsilateral and contralateral sides (SD).
**p*<0.00001 v controls.
†Posterior putamen to caudate ratio.

Figure 1 Scatterplot of individual [¹⁸F]β-CFT uptake values (average of ipsilateral and contralateral side) in patients with Parkinson’s disease (PD) and controls. Each dot denotes an individual subject (n=27 for Parkinson’s disease and n=9 for controls). Dashed line=mean. Note that there is no overlap between Parkinson’s disease and control values either in the posterior putamen or in the anterior putamen.

Figure 2 Correlation between the scores of the motor part of the unified Parkinson's disease rating scale (UPDRS) and [^{18}F] β -CFT uptake (average of ipsilateral and contralateral side) and in the posterior putamen (A, $r=-0.62$, $p=0.0005$), anterior putamen (B, $r=-0.64$, $p=0.0003$) and the caudate nucleus (C, $r=-0.62$, $p=0.0006$). $n=27$.

in the anterior putamen (28%, $p<0.00001$, table 1). In the caudate nucleus region-to-cerebellum/cerebellum ratio was 1.67 (SD 0.72), which was 51% of the control mean (3.28 (SD 0.49), $p<0.0001$). Figure 1 shows a scatterplot of individual [^{18}F] β -CFT uptake values. The posterior putamen to caudate nucleus ratio of [^{18}F] β -CFT uptake was significantly smaller in patients with Parkinson's disease than in controls (table 1) indicating a predominantly putaminal defect.

Table 2 Correlation between [^{18}F] β -CFT uptake and the scores of the motor part of the unified Parkinson's disease rating scale (UPDRS) in patients with Parkinson's disease ($n=27$)

Brain area	UPDRS		Hypokinesia		Rigidity		Tremor	
	<i>r</i>	<i>p</i> Value	<i>r</i>	<i>p</i> Value	<i>r</i>	<i>p</i> Value	<i>r</i>	<i>p</i> Value
Putamen	-0.68	0.0001	-0.62	0.0005	-0.61	0.0006	-0.04	0.84
Putamen (posterior)	-0.62	0.0005	-0.56	0.002	-0.60	0.001	-0.20	0.33
Putamen (anterior)	-0.64	0.0003	-0.51	0.001	-0.55	0.003	-0.02	0.94
Caudate	-0.62	0.0006	-0.55	0.003	-0.26	0.19	-0.13	0.51

In the nine patients with early Parkinson's disease the [^{18}F] β -CFT uptake (average of ipsilateral and contralateral side) was reduced in the total putamen to 34% of the mean control value ($p<0.00001$). The corresponding figures in the other brain areas were: posterior putamen 21% ($p<0.00001$), anterior putamen 43% ($p<0.00001$), and caudate nucleus 76% ($p<0.01$). The reductions in [^{18}F] β -CFT uptake were more severe in the contralateral than in the ipsilateral side. The [^{18}F] β -CFT uptake in the posterior putamen contralateral to the predominant symptoms was most severely affected, the mean [^{18}F] β -CFT uptake value being 18% of the control mean ($p<0.00001$). In the anterior putamen the corresponding figure was 34% ($p<0.00001$) and in the caudate nucleus 67% ($p<0.001$). In the ipsilateral side the respective values were: posterior putamen 30% ($p<0.00001$), anterior putamen 47% ($p<0.001$), and caudate nucleus 78% ($p=0.01$). Individually, the uptake of [^{18}F] β -CFT in the posterior putamen contralateral to the predominant symptoms in all patients was below 3 SD of the control mean. Even in the ipsilateral posterior putamen all patients were below 2.5 SD of the control mean. The ratio of [^{18}F] β -CFT uptake in the posterior putamen to that in the caudate nucleus was 0.23 (SD 0.07) in the contralateral striatum in the patients with Parkinson's disease, which was significantly smaller than the corresponding value in the controls (0.89 (SD 0.08), $p<0.00001$). Also in the ipsilateral striatum the ratio of posterior putamen [^{18}F] β -CFT uptake to that in the caudate nucleus (0.33 (SD 0.07)) was significantly smaller than in the controls ($p<0.00001$).

The total motor UPDRS score of all 27 patients with Parkinson's disease had a negative correlation with the [^{18}F] β -CFT uptake value in the posterior putamen ($r=-0.62$, $p=0.0005$, figure 2). This is to say, the more severe the disability, the smaller the [^{18}F] β -CFT uptake. A similar correlation was seen in the anterior putamen ($r=-0.64$, $p=0.0003$, fig 2) and the caudate nucleus ($r=-0.62$, $p=0.0006$, fig 2). The UPDRS scores for rigidity ($r=-0.62$, $p=0.0006$) and hypokinesia ($r=-0.62$, $p=0.0005$) had a negative correlation with [^{18}F] β -CFT uptake in the putamen. However, the severity of tremor showed no such correlation ($r=-0.04$, $p=0.84$). In the caudate nucleus no significant correlation was seen between the [^{18}F] β -CFT uptake and the rigidity or tremor scores (table 2).

Discussion

Our results show that striatal dopamine transporter uptake declines with increasing disability in Parkinson's disease. Thus, [^{18}F] β -CFT is a useful ligand, not only in the diagnosis of Parkinson's disease, but also in the follow up of the disease.

We found the most severe reduction in [^{18}F] β -CFT uptake in the posterior putamen. This is in agreement with the results obtained with other PET ligands such as [^{18}F]-fluorodopa and [^{11}C] β -CFT.^{8,9,25} The predominant involvement of the posterior putamen is compatible with the *in vitro* findings of most severe neuronal loss in the ventrolateral part of the SN¹⁻⁶ projecting mainly to the posterior putamen.²⁶⁻²⁸ Our findings are also in agreement with the more severe depletion of dopamine in the posterior versus anterior putamen in Parkinson's disease.²⁹

In our study we drew the ROIs on the MR image realigned with the PET image. This allows determination of the anatomical boundaries of the various brain structures. This is especially important in the posterior putamen, where the uptake in Parkinson's disease is severely reduced. It would be difficult to place the ROI on such a structure simply on the basis of the distribution of radioactivity.

In our new patients the uptake of [^{18}F] β -CFT in the posterior putamen was more severely affected than in the anterior putamen or the caudate nucleus. There was no overlap between patients with Parkinson's disease and controls in the [^{18}F] β -CFT uptake in the putamen. Interestingly, although the reduction in [^{18}F] β -CFT uptake was most severe in the striatum contralateral to the predominant symptoms, even in the ipsilateral putamen there was already a significant reduction especially in the posterior putamen. A significant, although less pronounced, decline was also seen in the anterior putamen and the caudate nucleus. This indicates that there is already a considerable decline in the uptake of [^{18}F] β -CFT in the "healthy" striatum ipsilateral to the predominant symptoms, indicating presymptomatic nigrostriatal hypofunction. Similar findings have also been seen in a SPECT study with [^{123}I] β -CIT.³⁰ The posterior putamen to caudate ratio was also significantly smaller in patients with Parkinson's disease compared with controls, indicating more severe putaminal than caudate impairment in early Parkinson's disease. As the disease progresses, the caudate nucleus becomes increasingly affected and thus the ratio (posterior putamen/caudate nucleus) increases, but still remains below the control values indicating, still more severe putaminal than caudate involvement in Parkinson's disease.

The reductions in Parkinson's disease in striatal uptake of dopamine transporter ligand [^{123}I] β -CIT¹¹ used in SPECT studies have been reported to be slightly larger than the present reductions seen with [^{18}F] β -CFT. Differences in the severity of the disease between different patient populations is a likely explanation for this difference, given the high association

between the UPDRS score and dopamine transporter ligand uptake (present study).¹¹

We found that of the main parkinsonian symptoms, the severity of rigidity and hypokinesia had a clear association with reduced [^{18}F] β -CFT uptake in the putamen, whereas no such association was seen with tremor. Previous studies have indicated a significant association of hypokinesia with fluorodopa PET findings,³¹⁻³³ with reduced concentration of the dopamine metabolite (homovanillic acid) in the CSF,³⁴ with the degree of striatal dopamine loss,³⁵ and with nigral neuron numbers.^{1,5} Furthermore, there is an association of bradykinesia and a particular pattern of brain metabolism (decreases in the lateral frontal and paracentral areas) in fluorodeoxyglucose PET.³⁶ However, tremor did not correlate with the extent of nigrostriatal dopaminergic defect either in [^{18}F]-fluorodopa PET or in CSF or postmortem dopamine content.³¹⁻³⁶ This suggests that defects in neuronal pathways other than the nigrostriatal dopamine system are important in the genesis of tremor in Parkinson's disease. A further explanation for these correlations (association of [^{18}F] β -CFT uptake with hypokinesia and rigidity, but not with the tremor score of UPDRS) is that UPDRS is weighted towards assessment of hypokinesia.

It was also interesting that it was the total motor UPDRS score and hypokinesia score that showed a significant correlation with [^{18}F] β -CFT uptake in the caudate nucleus, whereas no such association was found with rigidity or tremor. This finding further emphasises the role of the putamen in the pathophysiology of motor manifestations in Parkinson's disease. Indeed, isolated lesions of the caudate nucleus only rarely cause parkinsonism.³⁷ However, such lesions cannot be considered to create subtle changes in connections between different basal ganglia pathways as happens in idiopathic Parkinson's disease.

A factor possibly affecting dopamine transporter uptake is medication. It is possible that dopamine transporter is down regulated by the disease or dopaminergic medication or by both. However, in baboons infusion of levodopa, even in supratherapeutic concentrations, does not displace [^{123}I] β -CIT.^{11,38} At least in experimental animals, l-deprenyl had only a weak inhibitory effect on the uptake of a dopamine transporter ligand [^3H]GBR-12935.³⁹ Thus selegiline treatment, if introduced to patients at a late stage of the disease, might "downregulate" dopamine transporter ligand uptake, falsely enhancing the association between tracer uptake and clinical severity. Eight of our patients were receiving selegiline. However, in our study selegiline treatment was stopped 3 days before the PET. The inhibitory effect of selegiline on dopamine uptake is seen after 1 hour in rats after selegiline administration, but is no longer seen after 24 hours.⁴⁰ This indicates that the "washout time" for selegiline (3 days) in our study was adequate. This inhibitory effect of selegiline on dopamine

uptake is different from its MAO-B inhibitory action, the recovery half life of which is 40 days.⁴¹

Also other dopamine transporter PET and SPECT ligands, such as [¹¹C]-nomifensine, [¹¹C]β-CFT, [¹¹C]β-CIT, [¹¹C]RTI32, [¹²³I]β-CIT, and [¹²³I]β-CIT-FP, can be used to show nigrostriatal dopaminergic hypofunction,^{9-14 42-46} and have also been shown to correlate with the severity of symptoms.^{11 13 14} The present results with [¹⁸F]β-CFT, can be most probably applied to these tracers. However, in previous studies subregional analysis of putaminal tracer uptake in Parkinson's disease has not been performed in relation to clinical severity.

In conclusion, our results show that [¹⁸F]β-CFT is a sensitive ligand to detect Parkinson's disease and to assess its severity. Thus, [¹⁸F]β-CFT can be used, not only in the diagnosis, but also in the assessment of disability and follow up of Parkinson's disease and in evaluating treatment responses.

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