Comparative Nigrostriatal Dopaminergic Imaging with Iodine-123-βCIT-FP/SPECT and Fluorine-18-FDOPA/PET

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SPECT imaging of the dopamine transporter is now an alternative to PET in the quantification of nigrostriatal dopaminergic function. We compared [^{123}I]βCIT-FP/SPECT and [^{18}F]FDOPA/PET in the assessment of nigrostriatal dopaminergic function in Parkinson's disease (PD) and normal aging. **Methods:** We studied 12 mildly affected PD patients (mean age: 61.0 ± 13.2 yr; H&Y Stage I-II) with both [^{123}I]βCIT-FP and [^{18}F]FDOPA. Fifteen normal volunteers (mean age: 45.5 ± 22.1 yr) served as controls for both tracers. We measured the striato-occipital ratio (SOR) for both tracers at approximately 100 min postinjection. **Results:** We found a highly significant correlation between SOR measures obtained for both tracers ($r = 0.79$, $p < 0.0001$). In normal volunteers a significant age-related decline in striatal uptake was noted with [^{123}I]βCIT-FP ($r = -0.56$, $p < 0.04$) but not with [^{18}F]FDOPA. SOR values for both tracers discriminated PD patients from controls with comparable accuracy ($F[1,25] = 52.1$ and 53.0, $p < 0.0001$ for [^{123}I]βCIT-FP and [^{18}F]FDOPA, respectively). UPDRS motor ratings correlated with SOR values obtained by both imaging techniques ($r = -0.69$ and -0.60, $p < 0.04$ for [^{123}I]βCIT-FP and [^{18}F]FDOPA, respectively). **Conclusion:** These results indicate that [^{123}I]βCIT-FP/SPECT can provide quantitative descriptors of presynaptic dopaminergic function comparable to those obtained with [^{18}F]FDOPA/PET.

Key Words: dopamine transporter; SPECT; PET; Parkinson's disease

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6-[^{18}F]fluoro-L-dopa (FDOPA) has been used with PET for the quantitative assessment of presynaptic nigrostriatal dopaminergic function in life. Specifically, FDOPA/PET has become a useful diagnostic imaging tool for the early diagnosis of Parkinson's disease (PD) (*1–5*) and for the objective assessment of disease severity in this condition (*3–5*). Although simple noninvasive data analytical strategies have been developed, the widespread application of FDOPA/PET in clinical assessment has been limited by the availability of PET instruments and the radiochemical demands of FDOPA synthesis (*1,3*).

The cocaine analog, 2β-carbomethyl-3β-(4-idophenyl)tropane (βCIT), has a high affinity for the dopamine (DA) transporter. When labeled with ^{123}I, βCIT is a useful radiotracer for imaging the striatal DA transporter with SPECT (*6,7*). This compound is characterized by high striatal uptake with slow binding kinetics, reaching equilibrium between 20 and 30 hr after injection (*8*). Striatal [^{123}I]βCIT binding has been found to correlate with subject age in normal volunteers scanned with this tracer (*9*). Moreover, PD patients were found to have significantly lower striatal binding than normal controls (*6*) which also correlated with quantitative measures of disease severity (*10*).

In spite of these attributes, [^{123}I]βCIT/SPECT imaging has the disadvantage of requiring a second day for imaging and potentially prolonged dynamic acquisitions for kinetic analysis (*6,7*). By contrast, the N-ω-fluoroalkyl analogs of βCIT (*11,12*), particularly the fluoropropyl methyl ester (βCIT-FP), has faster uptake than βCIT. After injection of [^{123}I]βCIT-FP, the striatal-to-occipital ratio counts plateaus at approximately 100 min (*13*). Given the comparable kinetics of this compound, βCIT-FP/SPECT may provide a simple quantitative imaging alternative to FDOPA/PET in the study of the nigrostriatal dopaminergic system in PD and normal aging. To examine this possibility, we studied 15 normal subjects and 12 PD patients with both FDOPA/PET and βCIT-FP/SPECT. We assessed the comparative power of both imaging techniques in the early stage diagnosis of PD and in the correlation of dopaminergic function with clinical severity and subject age.

MATERIALS AND METHODS

Subjects

We recruited 12 classical PD patients without dementia (9 men, 3 women; mean age 61.0 ± 13.2 yr) from the Movement Disorders Services of North Shore University Hospital and New York Hospital-Cornell Medical Center. A diagnosis of PD was made if the patient had "pure" parkinsonism without a history of known causative factors such as encephalitis or neuroleptic treatment; did not have early dementia, supranuclear gaze palsy or ataxia and did have a convincing response to levodopa. In all patients, family history was negative for neurodegenerative illnesses. This group was selected with mild clinical involvement [Hoehn and Yahr Stages I and II (*14*) see Table 1]. Permission was obtained from the Institutional Review Board of North Shore University Hospital to perform the studies. Written consent for all subjects was obtained after a detailed explanation of the scanning procedures.

We also recruited 15 normal subjects (11 men, 4 women; mean age 45.5 ± 22.1 yr) by soliciting hospital personnel of North Shore University Hospital and the spouses of the PD patients in local support groups. The following exclusion criteria were used: (a) past history of neurological or psychiatric illness, (b) prior exposure to neuroleptic agents or drug use, (c) past medical history of hypertension, cardiovascular disease and diabetes mellitus and (d) abnormal neurological examination.

FDOPA/PET Imaging

All patients and normal volunteers fasted overnight before PET scanning. All antiparkinsonian medications were discontinued at least 12 hr before the PET studies. At the time of the PET study, all PD patients were rated quantitatively according to the Hoehn and Yahr (H&R) Scale (*14*) and the Unified Parkinson Disease Rating

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Scale (UPDRS 3.0) (*15*). PET studies were performed using a whole-body, high-resolution PET scanner (Advance, General Electric Medical Systems, Milwaukee, WI). This 18-ring bismuth germanate tomograph produces 35 slices with 4.2 mm resolution in all directions (FWHM). The performance characteristics of this instrument have been described elsewhere (*16*).

Subjects were positioned in the scanner in a Laitinen steroadaptor with three- dimensional laser alignment (*17*). The gantry angle of the tomograph was adjusted to be parallel to the orbitomeatal line. All studies were performed with eyes open in a dimly-lit room and minimal auditory stimulation. FDOPA was produced according to the radiochemical synthesis of Luxen et al. (*18*) and was >95% radiochemically pure (specific activity approximately 400 mCi/mmole). All subjects received 200 mg carbidopa 1.5 hr before the study to inhibit decarboxylation. 185–370 MBq (5–10 mCi) of FDOPA in 25 ml saline was injected into an antecubital vein over 45 sec with an automated infusion pump. Emission scan data were acquired between 40 and 100 min postinjection. PET reconstructions were also corrected for random coincidences, electronic deadtime and scatter effects. Attenuation correction was made using orbiting ^{68}Ge rod sources. The plasma FDOPA time-activity curve was determined by radial arterial blood sampling with a population-derived metabolite correction (*3*).

Region of interest (ROI) analysis was performed on 256 × 256 PET reconstructions. ROIs were identified in the striatum and occipital cortex by visual inspection with reference to coplanar MR images. Elliptical ROIs were placed interactively on composite (40–100 min) PET brain slices (slice thickness 15.2 mm) to outline the whole striatum (mean 3.7 cm^2). Irregular occipital ROIs (12–18 cm^2) were also defined on the same composite slices. Occipital counting rates were assumed to represent background activity referable to nonspecific FDOPA uptake in extrastriatal tissues and to untrapped metabolites. Occipital activity concentrations were subtracted from striatal ^{18}F-activity concentrations measured in each of seven 8-min scans, acquired approximately between 40 and 100 min postinjection to obtain the time profile for specific striatal activity for FDOPA.

Kinetic measures for striatal FDOPA uptake were calculated graphically by the multiple time graphical approach (MTGA) (*19*) using the time course of radioactivity in the whole striatum and the plasma FDOPA input function (*3*). The time course of specific (background subtracted) striatal concentration divided by plasma FDOPA activity was plotted against the ratio of the plasma time-integral to the plasma FDOPA concentration. In the MTGA, the slope of the this line represents the rate constant of FDOPA uptake into the striatum (K_i^{FD}). In all patient and control scans, we additionally calculated the ratio of target to occipital activity (SOR^{FD}) by dividing counting rates in each ROI by occipital counting rate measured in the last 8 min scan (approximately 90–100 min postinjection).

βCIT-FP/SPECT

The mean interval between the PET and SPECT imaging sessions was 29.2 ± 25.4 days. Two days before SPECT imaging, all subjects received potassium iodide orally to block thyroid uptake of free radioactive iodine. For PD patients, deprenyl was withdrawn 2 days before the study, while other antiparkinsonian medication, including L-dopa, were continued (*7*). βCIT-FP was produced from the corresponding trimethylstannyl precursor as described previously (*11,12*) and was >95% radiochemically pure (specific activity > 500 mCi/mmole); 185–333 MBq (5–9 mCi) of this tracer were injected intravenously as described above. SPECT imaging was performed on a tomograph with a resolution of 7.7 mm FWHM measured by a point source in the air. To assume compatibility with the PET studies, SPECT scanning was conducted using the Laitinen stereoadaptor with settings identical to those used in the PET studies. Tomographic images were acquired for 60-min beginning approximately 70 min after the injection. In eight subjects, a second 60 min scan was obtained beginning approximately 220 min postinjection. Images were acquired with the energy window set at 159 keV, reconstructed with a ramp filter and displayed in 128 × 128 matrix (pixel size 2.8 × 2.8 mm with an interslice distance of 2.8 mm). Attenuation correction was performed with reslicing parallel to the orbitomeatal line. We determined striatal and occipital ROIs of size and configuration analogous to those used in the PET studies. To reduce partial volume effects, 55% of pixels with the highest counts were used to determine the striatal concentration of ^{123}I activity within each ROI (*20*). We calculated the striatal-occipital ratio ($SOR^{\beta CIT}$) in each subject by dividing striatal by occipital counting rates.

Statistical Analysis

βCIT-FP/SPECT—Scan Stability. In the eight subjects who underwent two sequential βCIT-FP/SPECT scans, we compared the $SOR^{\beta CIT}$ values for the first and second scans using Student's t-test.

Normal Aging. In the normal subjects, we correlated subject age with the mean of left and right values for each parameter (K_i^{FD}, SOR^{FD} and $SOR^{\beta CIT}$) by computing Pearson product-moment correlation coefficients.

Disease Discrimination. Discriminant analysis for PD and normal subjects was performed for each parameter (K_i^{FD}, SOR^{FD} and $SOR^{\beta CIT}$) using a stepwise procedure with the *F*-test associated with Wilk's λ (*21*). We used the mean of left and right striatal values for the normal control subjects. For the PD patients, we used striatal values for the side contralateral to the more affected limbs. Because of potential aging effects with βCIT and related tracers (*9*) we corrected $SOR^{\beta CIT}$ by dividing the measured values by normal values calculated for the subject's age (*10*). Discriminant analysis for the age-corrected values [$SOR^{\beta CIT}$(COR)] was performed in the same manner as described above.

Disease Severity Assessment. In the PD group, we independently correlated mean values for striatal K_i^{FD}, SOR^{FD}, $SOR^{\beta CIT}$ and $SOR^{\beta CIT}$(COR) with off-state UPDRS composite motor scores by computing Pearson product-moment correlation coefficients.

Correlation between FDOPA/PET and βCIT-FP/SPECT. We correlated individual left and right striatal K_i^{FD} and SOR^{FD} values with corresponding striatal $SOR^{\beta CIT}$ values for all subjects using

TABLE 1
Parkinson's Disease Patients

Patient no.	Age	Sex	Disease duration (yr)	H&Y*	UPDRS ratings† BK	T	R	Composite
1	44	F	4	1	1	0	1	2
2	46	M	3	1	1	3	1	5
3	54	M	5	1	4	1	1	8
4	71	M	5	1	1	1	2	4
5	72	M	1.5	1	2	0	1	3
6	69	M	10	1	2	1	0	3
7	72	M	1.5	1	0	0	1	2
8	59	F	8	2	5	0	1	8
9	42	F	10	2	5	1	1	9
10	80	M	9	2	1	1	4	9
11	51	M	9	2	3	4	5	15
12	70	M	12	2	7	1	2	12

*Hoehn and Yahr score in the "off" state.

†Summed United Parkinson's Disease Rating Scale scores for bradykinesia (BK), tremor (T) and rigidity (R) in the affected limbs.