SPECT Imaging of Dopamine Transporter with [^{123}I]β-CIT: A Potential Clinical Tool in Parkinson's Disease

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파킨슨병에서 [^{123}I]β-CIT SPECT를 이용한 도파민 운반체 영상

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[^{123}I]β-CIT [2β-carbomethoxy-3β-(4-iodophenyl)tropane]는 도파민 운반체(dopamine transporter)에 특이결합하며 [^{123}I]β-CIT의 도파민 운반체 결합정도는 파킨슨병에서 도파민 뉴우런의 변성정도를 반영하는 것으로 제안되어 왔다. 이 연구의 주요 목적은 파킨슨병 환자에서 [^{123}I]β-CIT SPECT를 이용하여 측정된 [^{123}I]β-CIT의 선조체 결합지표들이 질병의 임상적 진행정도를 반영하는지를 검토하고, 간편화된 조직방사능비가 [^{123}I]β-CIT의 결합정도를 나타내는 정량적 지표로 이용될 수 있는지를 검증하는 것이었다. 파킨슨병 환자 30명(59±9세, 평균±표준편차; Hoehn-Yahr stage 1-3)과 정상인 6명 (58±5세)을 대상으로 [^{123}I]β-CIT SPECT 영상을 얻었다. [^{123}I]β-CIT 선조체 결합의 정량적 지표로서 (선조체 방사능-소뇌방사능)/소뇌방사능 비(specific binding ratio, SBR)와 추적자역학모델을 이용하여 측정한 선조체 결합능(binding potential)(k_3/k_4)을 구하였다. 파킨슨병 환자에서 [^{123}I]β-CIT의 선조체 결합역학은 정상인에 비하여 현저하게 느렸으며 그 결합지표들은 정상인에 비하여 뚜렷하게 낮았다. 한편, 편측파킨슨병 환자에서 [^{123}I]β-CIT 결합은 증상 반대쪽 선조체 뿐만 아니라 같은 쪽 선조체에서도 정상인에 비해 유의하게 감소되어 있었다. 파킨슨병 환자에서 [^{123}I]β-CIT 투여 후 24시간의 선조체 SBR 및 최대 SBR, 선조체 결합능은 모두, 유병기간, Hoehn-Yahr stage, UPDRS(Unified Parkinson's Disease Rating Scale) 총점, UPDRS 운동점수, UPDRS 일상활동점수와 유의한 상관관계를 나타내었다. 24시간 선조체 SBR과 최대 SBR은 선조체 결합능과 우수한 상관관계를 보였다. 이상의 결과로 부터 [^{123}I]β-CIT의 선조체 결합은 파킨슨병의 진행정도를 나타내는 지표로 이용될 수 있다. 또 [^{123}I]β-CIT 투여 후 24시간 영상으로 부터 얻은 간편화된 조직방사능 비는 [^{123}I]β-CIT의 결합정도를 정량적으로 반영한다. [^{123}I]β-CIT SPECT는 파킨슨병의 조기진단 및 진행 추적에 임상적으로 유용할 것으로 판단된다.

Key Words : [^{123}I]β-CIT; Dopamine transporter; Parkinson's disease; SPECT

INTRODUCTION

Parkinson's disease(PD) is a common movement disorder associated with degeneration of dopaminergic neurons in the substantia nigra and a corresponding loss of dopamine(DA)-containing nerve terminals in the basal ganglia[1-5]. Dege-

neration of the nigrostriatal pathway is accompanied by large decreases in a number of corresponding biochemical markers, including DA[1-3, 6-10], dopa decarboxylase[2, 11, 12], tyrosine hydroxylase[2, 10, 13], DA metabotites[1, 2, 6, 8, 9], and the DA transporter [7, 14-17].

Noninvasive imaging and quantitation of the loss of dopaminergic nerve terminals in PD have evolved over the last decade by the use of 6-L-[^{18}F]fluoro-DOPA([^{18}F]FDOPA) and positron emission tomography(PET)[18-28]. This method has permitted several studies of the reduction in DA synthesis in PD, its relationship to neurological parameters of disease[22, 23, 25], and comparison of PD with other movement disorders[19, 23, 24, 27, 29].

The DA reuptake site that mediates reuptake of DA into presynaptic nerve terminals following its release is an active, sodium gradient-driven membrane transporter spanning the plasma membrane of dopaminergic terminals. It is the function of the transporter to rapidly deplete the intrasynaptic DA during a DA surge and to maintain normal DA concentrations in the intra- and extracellular spaces at other times. Cocaine blocks the DA transporter, thus increasing the levels of intrasynaptic doapmine, which may account for the central nervous system stimulant actions of the drug[30-32]. Recently, a series of cocaine analogues, including CFT [2β-carbomethoxy-3β-(4-fluorophenyl)tropane; also designated WIN 35,428], β-CIT [2β-carbomethoxy-3β(4-iodophenyl)tropane; also designated RTI-55] and isopropyl-β-CIT(also designated RTI-121), have been developed with high affinity for the DA transporter[33-43], and some have been labeled with positron emitting and single-photon emitting isotopes to permit imaging by PET and single-photon emission computed tomography(SPECT) [42-46].

In vitro binding study showed that β-CIT, the iodo analog of CFT, has a high affinity for the DA and serotonin(5-hydroxytryptamine: 5-HT) transporters from baboon brain, with an IC50 of 1.6 nM against [^{3}H]CFT and 3.8 nM against [^{3}H]paroxetine[37]. ^{123}I-Labeled β-CIT has been used in SPECT imaging for visualization of binding to DA and 5-HT transporters in the baboon brain in vivo[36, 43, 47]. In vivo displacement studies in the monkey demonstrated that striatal uptake of [^{123}I] β-CIT was primarily due to DA transporters while uptake in hypothalamus-midbrain areas was mainly associated with 5-HT transporters[36, 37]. Initial studies in human subjects confirmed the high and prolonged levels of activity in striatum and demonstrated significant reductions of tracer uptake in patients with PD[47-49]. These studies suggest that [^{123}I]β-CIT SPECT imaging is a promising technique for the diagnosis and evaluation of PD.

Attempts to estimate receptor binding characteristics in vivo using PET and SPECT have followed a variety of approaches. One method is to assume a particular model in which a measured plasma input function governs the uptake of the labeled ligand. Model parameters can then be determined by a nonlinear least-square fit to the experimental data[50]. Graphical method of analysis applicable to ligands that are trapped in tissue for the duration of the experiment have been developed and applied by several investigators[51-56]. These model-based methods usually require arterial sampling and repeated scans, procedures that are not easily implemented in the clinical setting. The simplest procedure is using the ratio among different regions(i.e., receptor-rich versus receptor-poor region) or the slope of the ratio over scanning time, which is a measure of the specific binding or the rate of binding of the ligand in limited conditions[57].

The aim of the present study was: 1) to characterize the pharmacokinetics and regional distribution of [^{123}I]β-CIT in healthy subjects and

PD patients, 2) to evaluate the correlation between SPECT measures of [^{123}I]β-CIT binding and motor symptoms in patients with PD, and 3) to validate the use of simplified ratio method for the assessment of [^{123}I]β-CIT binding by comparing with a more complete tracer kinetic approach.

METHODS

1. Synthesis of [^{123}I]β-CIT

[^{123}I]β-CIT was prepared from the corresponding tributylstannyl precursor(Research Biochemicals International, Natick, MA) and high radionuclidic purity [^{123}I]NaI (Korea Atomic Energy Research Institute, Seoul, Korea), using the method described by Zea-Ponce et al.(1995) with minor modification. [^{123}I]β-CIT was obtained in an average radiochemical yield of 64%±12%(n=21, mean±s.d.) and a radiochemical purity of 96%± 4%. Although specific activity of the radiotracer could not be measured because of limit of UV detection with our HPLC system, it might be higher than 67,000 Ci/mmol based on the literature[58].

2. Subjects

Thirty patients [13 males and 17 females; age 59±9 yr(mean±s.d.)] with idiopathic PD(Hoehn-Yahr stages 1-3) and 6 age-matched healthy controls (4 males and 2 females; age 58±5 yr) were enrolled in the study following the provision of informed consent. All patients had symptoms that were responsive to L-dopa and had at least three of the following symptoms: resting tremor, bradykinesia, rigidity, and postural instability. Fourteen of the patients were recent-onset patients and were not receiving any dopaminergic medication before the SPECT scan. The rest of the patients were at an advanced stage of PD and were on treatment with L-dopa, DA agonist, L-deprenyl, amantadine and anticholinergic drugs in various combinations. Each patient was evaluated at drug-off state using the Hoehn-Yahr stage and the Unified Parkinson's Disease Rating Scale(UPDRS)[59]. The clinical characteristics of the patients are summarized in Table 1. The healthy controls were taking no medications and were free of serious medical illnesses by physical examination and laboratory testing.

3. Data Acquisition

SPECT studies were performed using a three-headed Triad XLT system(Trionix Research Laboratory, Twinsburg, OH) equipped with medium-energy collimators. Images were acquired with each head rotating 120° in 3° steps, creating 120 raw image sets. Antiparkinsonian medications were discontinued for 2 days prior to the scanning. In order to minimize radioiodine uptake in the thyroid gland, each patient was given oral Lugol's solution, 1 drop tid, for 1 day prior and for 3 days after intravenous administration of [^{123}I]β-CIT. Fiducial markers containing ~7 μCi of ^{123}I were attached to the skin along the canthomeatal line for realignment of all images from each subject in a plane parallel to the canthomeatal line. Each subject received an intravenous bolus injection of 185-370 MBq [^{123}I]β-CIT. In all of the healthy controls and 14 of the patients, a total of 15 SPECT scans was obtained for each subject over a 24 hr period following injection: ten sequential scans of 10 min starting immediately after injection, followed by scans of 20-30 min at 3 hr, 4 hr, 6 hr, 12 hr, and 24 hr postinjection. Based on the time-activity curve from serial scans, the rest of the patients were scanned at 12 hr and 24 hr postinjection. Images were acquired with a 10% symmetric window centered at 159 keV, reconstructed with a Butterworth filter(power=7; cutoff=0.4 cyc/cm) and displayed in 128×128 matrix(pixel size = 3.56× 3.56 mm with a slice thickness of 3.56 mm).

Table 1. Clinical Characteristics of Patients

Patient	Sex	Age (yr)	Disease duration(mo)	UPDRS					
				H-Y	Total	Motor	ADL	Motor subscales*, Right	Motor subscales*, Left
1	F	80	96	3	61	39	18	13	12
2	F	59	51	1.5	52	34	14	0	21
3	F	60	48	1	20	14	4	12	0
4	F	60	51	2	30	24	6	2	14
5	M	40	5	2	20	14	4	3	10
6	F	61	27	1	17	8	9	0	7
7	F	57	36	2	27	23	4	10	11
8	M	51	8	2	37	28	9	17	7
9	M	60	2	2	31	23	7	3	14
10	F	73	12	1.5	30	21	5	0	15
11	F	63	17	3	59	43	15	11	16
12	F	55	55	1.5	23	19	4	0	15
13	F	59	48	2.5	42	32	9	14	9
14	F	55	12	2	15	11	4	3	6
15	M	55	30	2.5	41	34	5	6	12
16	F	77	65	2.5	51	40	10	11	18
17	M	50	29	2	27	22	4	1	14
18	M	58	28	NA	NA	NA	NA	14	8
19	M	54	26	NA	NA	NA	NA	0	3
20	M	69	16	NA	NA	NA	NA	9	3
21	F	39	18	NA	NA	NA	NA	7	0
22	M	53	58	2.5	55	43	10	19	12
23	M	45	NA	NA	NA	NA	NA	NA	NA
24	M	57	10	2	36	30	6	17	5
25	F	63	24	NA	NA	NA	NA	NA	NA
26	F	58	42	2.5	49	35	12	11	11
27	F	56	24	2	50	38	9	18	11
28	M	71	13	2.5	47	35	10	16	7
29	F	57	48	3	65	49	14	22	10
30	M	69	12	2	31	23	7	16	3
Mean±s.d.		59±9	31.4±21.7	2.1±0.6	38.2±14.8	28.4±11.0	8.3±4.0	9.1±6.9	9.8±5.3

* Sum of lateralizing motor UPDRS subscales(tremor, rigidity, bradykinesia)
UPDRS=Unified Parkinson's Disease Rating Scale; H-Y=Hoehn-Yahr stage; ADL=activities of daily living; NA=data not available

Attenuation correction was performed using Chang's method(μ=0.11/cm)[60], and SPECT activity (cpm) was converted to absolute units of radioactivity(μCi) based upon a calibration factor determined from a cylindrical phantom of 20 cm diameter filled with an ^{123}I solution.

4. Data Analysis

Three consecutive slices with highest striatal activities were summed to construct a 10.68 mm thick slice, and standardized size and shape region of interest(ROI) (10.68 mm×10.68 mm rectangle) was visually positioned on each striatum. The same procedures were performed for

the ROI placement on hypothalamus-midbrain regions. Three consecutive slices representing the cerebellum were also added and ROI(14.24 mm x 24.92 mm) was placed on each cerebellar hemisphere. Right and left cerebellar values were averaged for subsequent analysis.

[^{123}I]β-CIT binding in the striatum was estimated using two quantitative indices: 1) the simplified ratio of specific to nonspecific binding, or the radioactivity ratio of striatum(an area rich in DA transporter) to cerebellum [an area containing few or no DA transporter[61]] minus 1 (specific binding ratio: SBR) and 2) the binding potential, or the ratio of the rate constant of binding to the DA transporter(k_3) to that of dissociation from the DA transporter(k_4), as calculated based on a kinetic two-compartment analysis of radioligand binding.

5. Kinetic Analysis of [^{123}I]β-CIT Binding

By using a two-compartment kinetic model, the rate constants k_3 and k_4 were determined in the striata of healthy subjects and PD patients. Since the number of DA transporter is negligible in the cerebellum, the assumption was made that the concentration and kinetics of [^{123}I]β-CIT in the cerebellum is the same as in the free plus nonspecifically bound space in the striatum[62, 63]. Therefore, the time-activity curve of the cerebellum was used as an input function for the two-compartment model. The concentration of specifically bound radioligand in the striatum was determined by subtracting the radioactivity concentration in the cerebellum from that in the striatum. The optimum values of k_3 and k_4 were obtained using a nonlinear least square fitting procedure. The binding of [^{123}I]β-CIT to the DA transporter in the striatum was evaluated using the binding potential, defined as k_3/k_4 ratio[64].

6. Statistical Analysis

Results are expressed as the mean±s.d. Comparisons of the SPECT measures of [^{123}I]β-CIT binding between patients and controls were made with the Mann-Whitney U-test; comparisons between contralateral and ipsilateral striatum were performed using the Wilcoxon signed rank test.

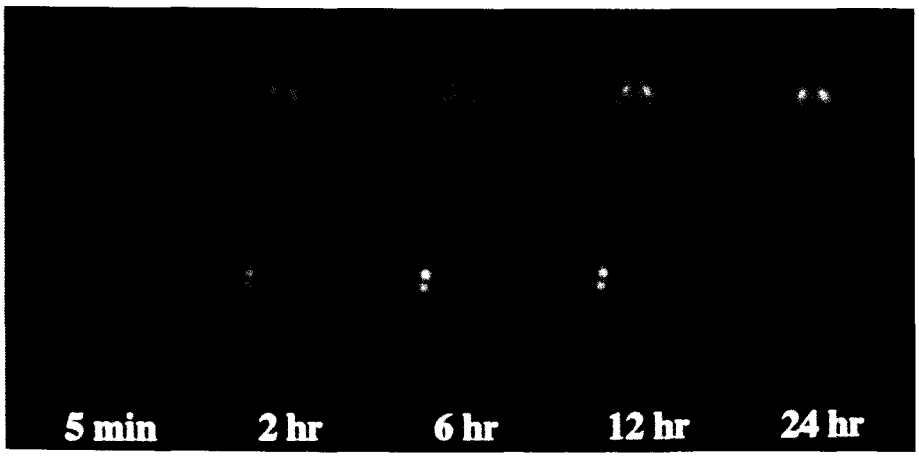

Fig. 1. Brain images obtained with [^{123}I]β-CIT in a healthy subject. The images illustrate a plane of scanning through the basal ganglia and cerebellum. With increasing time after injection [^{123}I]β-CIT concentrates highly in the striatum, an area rich in dopamine transporter; low activity is observed in the cerebral cortex and cerebellar regions, which contain few or no dopamine transporters.

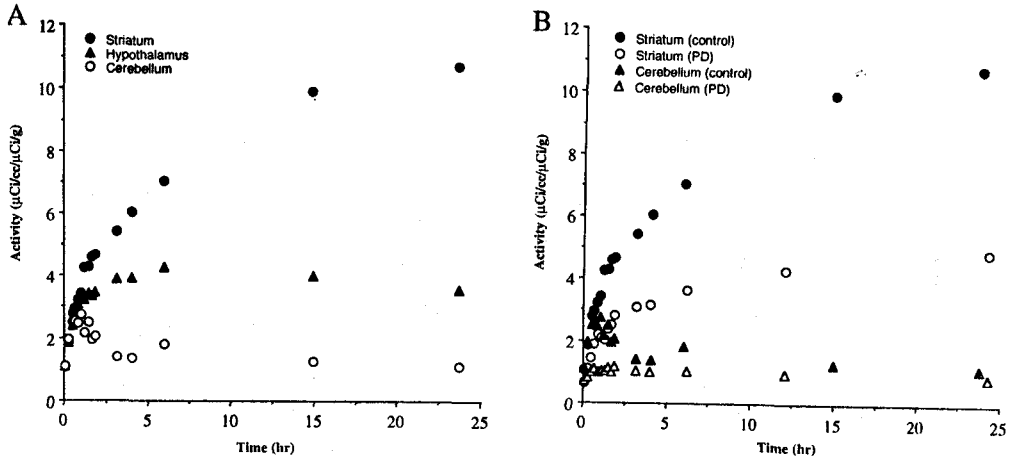

Fig. 2. Change in the level of activity in different regions of the brain with time in a healthy control (A) and in a patient with Parkinson's disease (PD) (B). Activity is expressed as μCi/cc/μCi injected/g body weight.

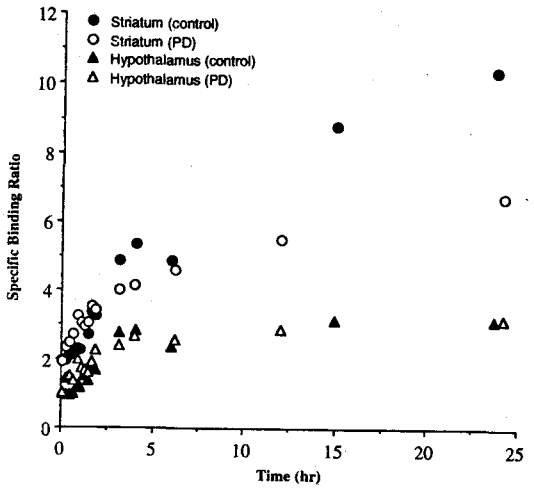

Fig. 3. Change of the specific binding ratio in the striatum and hypothalamus with time in a healthy control and in a patient with Parkinson's disease(PD).

Linear regression analysis by the least squares method was used to assess the relationship between the SPECT measures of [^{123}I]β-CIT binding and between the SPECT measures and motor ratings(Hoehn-Yahr stage and UPDRS scores). Probability values of less than 0.05 were considered significant.

RESULTS

1. Pharmacokinetics of [^{123}I]β-CIT

With increasing time after injection [^{123}I]β-CIT concentrated highly in the striatum, an area rich in DA transporter, followed by hypothalamus and midbrain, regions rich in 5-HT transporters(Fig. 1-3). Low activity was observed in the cerebral cortex and cerebellar regions, which contain few or no DA transporters. Fig. 2 and 3 show representative regional time-activity curves for the binding of [^{123}I]β-CIT. The striatal activity in all healthy subjects increased over time during the 24 hr scanning period. In the patients with PD, [^{123}I]β-CIT accumulated more slowly and the peak striatal activity was clearly lower than in the healthy subjects. In the healthy subjects, the cerebellar activity reached a peak by 1 hr postinjection with a rapid washout thereafter; a similar uptake and washout was shown in the patients with PD. As a consequence, the striatal SBR in the healthy subjects increased steadily over time, while it peaked earlier at 12-24 hr postinjection and attained lower peak levels in the

Parkinsonian patients.

2. Striatal Binding of [^{123}I]β-CIT in PD

In the patients with PD, the binding of [^{123}I]β-CIT in the striatum was markedly reduced; a greater reduction occurred in the putamen than in the caudate(Fig. 4). The results of SPECT measurement of [^{123}I]β-CIT binding in the Parkinsonian patients and healthy controls are shown in Table 2 and Fig. 5. The mean of right and left SBR at 24 hr postinjection and the mean peak SBR in the striatum were reduced to 48% and

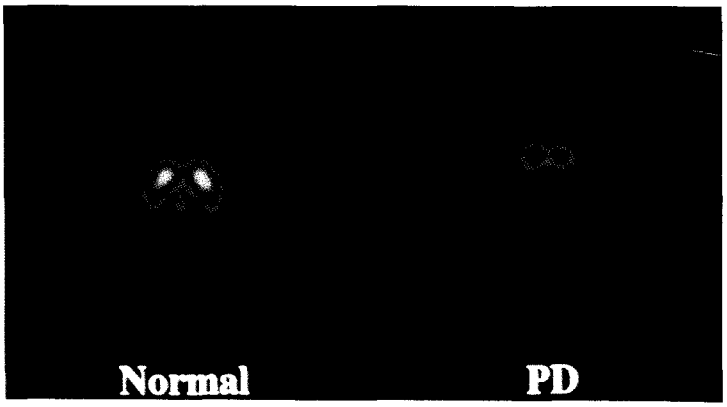

Fig. 4. [^{123}I]β-CIT SPECT images of a healthy subject and of a Parkinson's disease (PD) patient. In the patient with PD, [^{123}I]β-CIT binding in the striatum is markedly reduced; a greater reduction occurred in the putamen than in the caudate.

Table 2. [^{123}I]β-CIT SPECT Measures in Parkinson's Disease Patients and Healthy Controls

	Controls			PD patients			Symptomatic striatum*		
	24hr SBR†	Peak SBR†	BP†	24hr SBR†	Peak SBR†	BP†	24hr SBR†	Peak SBR†	BP†
Mean±s.d.	8.0±0.7	8.0±0.7	7.9±0.6	3.9±1.3	4.0±1.1	3.7±1.1	3.7±1.2	3.9±1.1	3.6±1.2
p	-	-	-	0.0001	0.0001	0.0005	<0.0001	<0.0001	0.0002
% of control mean	-	-	-	48%	50%	47%	46%	48%	46%

	Patients with hemiparkinsonism					
	Contralateral striatum			Ipsilateral striatum		
	24hr SBR	Peak SBR	BP	24hr SBR	Peak SBR	BP
Mean±s.d.	3.4±1.2	3.8±1.0	3.7±1.1	4.0±1.2	4.4±1.0	4.5±0.8
p	0.0027	0.0039	0.0105	0.0027	0.0039	0.0105
% of control mean	42%	48%	47%	50%	56%	57%

* Striatum contralateral to symptoms
† Mean of right and left striatal values
SBR=specific binding ratio calculated as the specific(striatal minus cerebellar activity) to cerebellar activity ratio; BP=binding potential(k_3/k_4) measured using the two-compartment model; p=probability, Parkinson's disease patients vs controls, according to the Mann-Whitney U-test

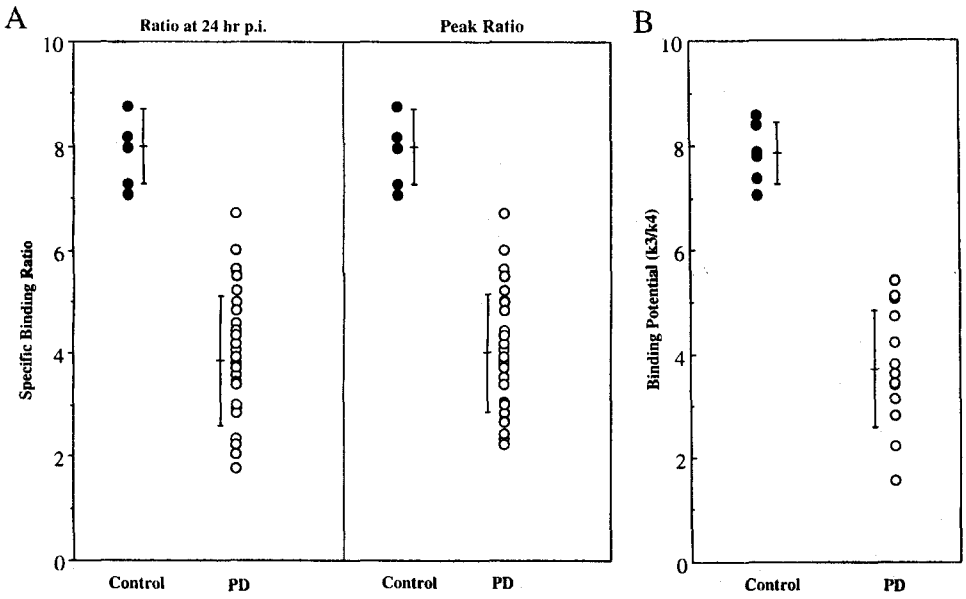

Fig. 5. Specific binding ratio(A) and binding potential(B) in healthy controls and Parkinson's disease (PD) patients.

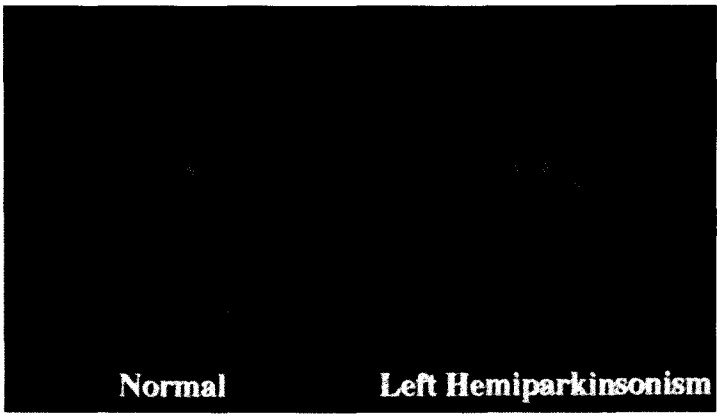

Fig. 6. [^{123}I]β-CIT SPECT images of a healthy subject and of a patient with hemiparkinsonism. In the patient with hemiparkinsonism, [^{123}I]β-CIT binding is reduced not only in the striatum contralateral to the clinical symptoms but also in the ipsilateral striatum. Note that left is on the right in the figure.

50%, respectively, of the control mean(3.9±1.3 versus 8.0±0.7, p=0.0001; 4.0±1.1 versus 8.0±0.7, p=0.0001, respectively). The mean binding potential in the striatum was also reduced to 47% of the control mean(3.7±1.1 versus 7.9±0.6, p=0.0005). The SBR at 24 hr postinjection, the peak SBR and the binding potential in the striatum corresponding to the clinical symptoms were reduced to 46%, 48%, and 46%, respectively, of the control mean(3.7±1.2 versus 8.0±0.7, p<0.0001; 3.9±1.1 versus 8.0±0.7, p<0.0001; 3.6±1.2 versus 7.9±0.6, p=0.0002). In the patients with hemiparkinsonism,

Table 3. Correlation Coefficients for SPECT Measures and Motor Ratings in Parkinson's Disease Patients

	SBR at 24hr p.i.	Peak SBR	Binding potential
Disease duration(mo)	-0.372	-0.379	-0.572
p	0.0510	0.0466	0.0325
Hoehn-Yahr stage	-0.508	-0.564	-0.453
p	0.0133	0.0050	0.1042
Total UPDRS	-0.557	-0.591	-0.697
p	0.0058	0.0030	0.0056
Motor UPDRS	-0.542	-0.568	-0.681
p	0.0075	0.0047	0.0073
ADL score of UPDRS	-0.487	-0.543	-0.599
p	0.0183	0.0075	0.0235

Note : Correlations are for means of right and left striatal values.
p = probability according to linear regression analysis; SBR = specific binding ratio calculated as the specific(striatal minus cerebellar activity) to cerebellar activity ratio; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living.

the 24 hr and peak SBR and the binding potential were reduced not only in the striatum contralateral to the clinical symptoms [42%(3.4±1.2 versus 8.0±0.7, p=0.0027), 48%(3.8±1.0 versus 8.0 ±0.7, p=0.0039), and 47%(3.7±1.1 versus 7.9±0.6, p=0.0105), respectively, of the control mean] but also in the ipsilateral striatum [50%(4.0±1.2 versus 8.0±0.7, p=0.0027), 56%(4.4±1.0 versus 8.0 ±0.7, p=0.0039), and 57%(4.5±0.8 versus 7.9±0.6, p=0.0105), respectively, of the control mean](also see Fig. 6). In the patients with hemiparkinsonism or predominantly unilateral symptoms, the reduction was greater on the side opposite to the predominant symptoms than on the ipsilateral side(24 hr SBR, 3.6±1.0 versus 4.3±1.1, p=0.0046; peak SBR, 3.9±0.8 versus 4.5±0.9, p=0.0047; binding potential, 3.5±0.8 versus 4.4±0.6, p=0.0180).

3. Correlation of SPECT Measures with Motor Symptoms

Table 3 shows the correlations of SPECT measures with motor ratings in PD patients. The mean SBR at 24 hr postinjection, the mean peak SBR and the mean binding potential in the striatum were significantly correlated with disease duration, Hoehn-Yahr stage, total score of

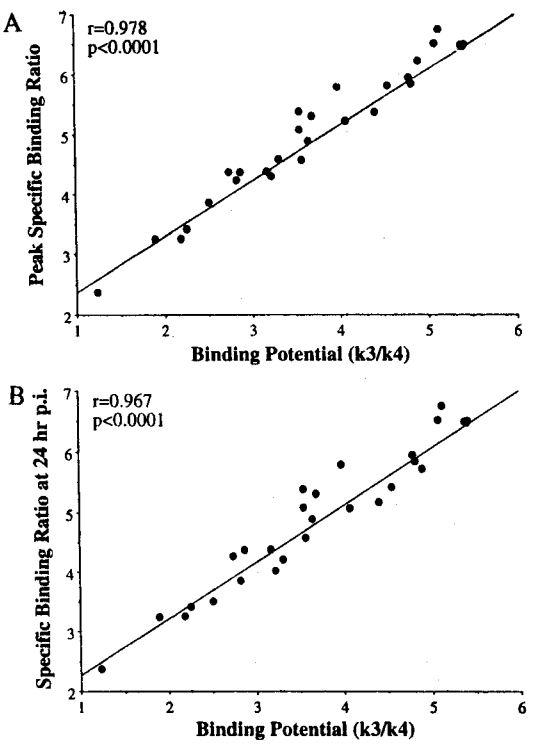

Fig. 7. Correlation of the peak specific binding ratio (A) and the specific binding ratio at 24 hr postinjection (B) with the binding potential.

UPDRS, motor score of UPDRS, and activities of daily living score of UPDRS.

4. Correlation between Simplified Ratio Index and Kinetic Parameters

There was an excellent correlation between the peak striatal SBR and the binding potential ($r=0.978$, $p<0.0001$)(Fig. 7). Correlation between the striatal SBR at 24 hr postinjection and the binding potential was also shown to be excellent ($r=0.967$, $p<0.0001$).

DISCUSSION

The present study demonstrates that SPECT measurement of [^{123}I]β-CIT binding clearly distinguishes patients with PD from healthy subjects. Between symptomatic patients and healthy subjects, the striatal SBR and binding potential values were not only significantly different but also showed a significant interval. The wide gap in the striatal [^{123}I]β-CIT binding between symptomatic patients and healthy subjects suggests that in vivo imaging may be able to identify patients before the development of definite clinical symptoms. Indeed, we found that in patients with hemiparkinsonism, the [^{123}I]β-CIT binding reduced not only in the striatum contralateral to the clinical symptoms but also in the ipsilateral striatum. The ability to identify biochemically patients with PD who have early symptoms or presymptomatic individuals at risk for PD might be helpful in light of recent studies suggesting that early treatment with L-deprenyl, a monoamine-oxidase B inhibitor, slows the progression of disability in PD[65-67]. Additionally, the measurement of [^{123}I]β-CIT binding in the striatum corresponding to the symptomatic or asymptomatic side may provide information regarding the threshold for dopaminergic terminal loss at which symptoms become clinically apparent.

The decrease of [^{123}I]β-CIT binding in the striatum contralateral to the clinical symptoms (approximately 50%) was not as great as the loss of endogenous DA and DA transporter reported in postmortem human tissue samples(>80%)[3, 68]. This may be due to difference in the patient population: the patients in the present study (Hoehn-Yahr stages 1-3) appear much less severely affected than those from postmortem examinations. Although it has been proposed that Parkinsonian symptoms develop only after 85-90% depletion of endogenous DA levels, this imaging study suggests that symptoms may begin with only a 50% decrease in striatal DA terminal innervation.

We found a clear negative correlation between [^{123}I]β-CIT binding in the striatum and the disability of the patients, assessed by the Hoehn-Yahr stage and the UPDRS scores. This finding from [^{123}I]β-CIT and SPECT is in accordance with other SPECT or PET studies using the same ligand[69, 70] or [^{18}F]FDOPA[71]. Also in vitro studies have indicated a correlation of the degree of hypokinesia and rigidity of PD patients with striatal DA deficiency[1] and nigral neuronal loss[1, 4, 72, 73].

The loss of midbrain DA in PD is accompanied by a rise in the DA D_1 and D_2 receptor densities[17, 74]. This is found in the putamen and caudate tissues from unmedicated patients, and may account for the clinical supersensitivity to DA agonists in PD patients[75, 76]. However, little is known about the DA transporter regulation in residual neruons following DA neuronal loss. The density of DA transporter on the plasma membrane of dopaminergic terminals is commonly believed to be so constant that the number of terminals can be inferred from the DA transporter density[14, 77, 78], but there is very little direct evidence to support this notion. Therefore, it is not entirely certain whether alterations of the

number of dopaminergic terminals can be revealed by measurements of the density of DA transporters in such diseases as Parkinson's. Although we found a linear relationship between [^{123}I]β-CIT binding and the motor symptoms of the patients, the patients in the present study were in relatively early stages of the disease. Studies of a large series of patients with a wide range of symptom severity may clarify this issue.

While the agonist-induced down-regulation of postsynaptic DA receptors is established[17, 75], the effect of long-term treatment with L-dopa on the DA transporter density has still to be determined. In particular, the duration of the L-dopa effect in Parkinson's patients taking high doses of levodopa on a daily basis and undergoing SPECT imaging with [^{123}I]β-CIT, should be investigated further. Following chronic treatment with L-deprenyl, Wiener et al[79]. found an up-regulation of the DA transporter in vitro in the mouse brain using [^{3}H]mazindol, whereas Ursula et al. failed to find a significant change in in vivo [^{3}H]CFT accumulation in the mouse striatum (unpublished observation). It remains possible that at least some of the present findings can be related to the long-term dopaminergic treatment of the patients.

In the present study, antiparkinsonian medications were discontinued for 2 days prior to the scanning. Competetion by endogenous DA has previously been reported for the binding of the radioligand [^{11}C]raclopride to postsynaptic DA D_2 receptors, and the consequences of these findings on the interpretation of PET studies have been discussed[80-82]. Since the affinity of β-CIT for DA transporter is approximately 3 orders of magnitude greater than that of DA, it appears unlikely that the binding of this ligand is influenced by modest fluctuations in intrasynaptic DA levels. With large doses of L-dopa(50-200 mg/kg) in vivo microdialysis studies in normal rat striata showed DA concentrations to be rising either not at all[83] or only 2 to 4 times above baseline levels[84-87]. Infusion of L-dopa(50 mg/kg) failed to displace striatal [^{123}I]β-CIT binding in nonhuman primates[88], suggesting that the binding would not be affected by L-dopa administration in Parkinsonian patients. However, it has been shown that in 6-hydroxydopamine lesioned rats, L-dopa infusion(100 mg/kg) increases striatal extracellular DA 30-fold, compared with less than 2-fold in normal striatum[89]. This difference has been attributed to reduced buffering capacity in denervated striatum as a result of loss of DA terminals. Supporting this notion, Antonini et al[90]. found that several hours of continuous L-dopa infusion(60-80 mg/hr) reduced [^{11}C]raclopride binding in the putamen by 20%-27% but not in the caudate which is less severely affected than the putamen in PD. In Parkinson's patients, therefore, L-dopa therapy may have to be temporarily interrupted to avoid its potential interference with the binding of [^{123}I]β-CIT to DA transporter. In addition, L-deprenyl and its major metabolite, L-methamphetamine[91], enhance intrasynaptic DA levels[92-94]. However, it is presently unknown whether acute administration of L-deprenyl affects [^{123}I]β-CIT binding.

For [^{123}I]β-CIT SPECT to be easily applicable in the clnical setting, relatively simple methods of quantification will be required. In the present study, we found an excellent correlation between the simplified tissue ratio obtained either at peak striatal binding or 24 hr postinjection and the binding potential from kinetic analysis. This finding indicates that the simplified ratio index obtained at 24 hr postinjection may be feasible for the assessment of [^{123}I]β-CIT binding. The combination of SPECT camera availability with a simple accurate method that does not require repeated scanning or complicated modeling procedures would certainly increase the clinical use

of [^{123}I]β-CIT SPECT in the diagnosis and treatment of PD.

The diagnosis of PD remains a clinical judgment based primarily upon motor examination and the patient's response to L-dopa. A prior study correlating clinical impression with subsequent pathology showed only 75-80% agreement between clinical and pathological diagnoses[95]. Moreover, evaluation of disease progression based on clinical examination is complicated by the drug therapy of motor symptoms. Hence, an objective marker of DA neuronal loss is essential for the diagnosis and serial monitoring of the disease and for improved understanding of the pathophysiology of disease onset and progression. The results of the present study demonstrate marked differences in [^{123}I]β-CIT SPECT measures between healthy subjects and PD patients. The significant correlation of SPECT measures with motor severity suggests that [^{123}I]β-CIT may be a useful marker of disease severity in PD. Additionally, the simplified tissue ratio obtained at 24 hr postinjection may be feasible for the assessment of [^{123}I]β-CIT binding, avoiding repeated scanning and complicated modeling procedures. [^{123}I]βCIT SPECT may be clinically useful for the early diagnosis and serial monitoring of PD.

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