Iodine-123-N-ω-Fluoropropyl-2β-Carbomethoxy-3β-(4-Iodophenyl)Tropane SPECT in Healthy Controls and Early-Stage, Drug-Naive Parkinson's Disease

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The aims of this study were to investigate whether the loss of striatal dopamine transporters in early and drug-naive patients with Parkinson's disease could be demonstrated by means of ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane (^{123}I-FP-CIT) SPECT in a 1-day protocol and whether the SPECT measures were correlated with disease severity. **Methods:** Twenty-one early-stage and drug-naive Parkinson's disease patients (age range 42–73 yr; mean age 55.5 yr) and 14 healthy controls (age range 28–83 yr; mean age 53.6 yr) were examined. SPECT image acquisition was always performed at 3 hr postinjection. The ratio of specific to nonspecific striatal ^{123}I-FP-CIT binding was used as the outcome measure. **Results:** All striatal ^{123}I-FP-CIT ratios were significantly lower in the Parkinson's disease group compared to those in the control group. The mean reduction in the putamen was 57% of the control mean, and that in the caudate nucleus was 29% of the control mean. Patients with unilateral Parkinson's disease showed a bilateral loss of striatal ^{123}I-FP-CIT binding. Discriminant function analysis, using the ^{123}I-FP-CIT SPECT data of the ipsilateral and contralateral putamen, predicted group membership in all cases; the contralateral putamen accounted for the greatest difference between the Parkinson's disease patients and the controls. In the control group, a clear decline in ^{123}I-FP-CIT binding was found with aging, amounting to 9.6%/decade. Unexpectedly, in the Parkinson's disease group, regression analysis revealed that neither severity of disease nor age accounted for a significant part of the variance in striatal SPECT measures. **Conclusion:** Our findings indicate that ^{123}I-FP-CIT SPECT is a reliable method to discriminate between early, drug-naive Parkinson's disease patients and healthy controls and to identify patients in the preclinical phase of Parkinson's disease. Possibly due to the relatively homogeneous group of Parkinson's disease patients and the use of a suboptimal outcome measure, no significant correlations were found between striatal ^{123}I-FP-CIT binding ratios and disease severity, such as were established earlier with ^{123}I-β-CIT. Further research is necessary to interpret these findings.

Key Words: Parkinson's disease; SPECT; dopamine transporter imaging; cocaine analogs

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Parkinson's disease is a progressive neurodegenerative disease characterized by an insidious onset. Bradykinesia, tremor, rigidity and postural instability are the main motor signs. Neuropathologically, Parkinson's disease is characterized by loss of dopaminergic cells in the substantia nigra. This results in a marked deficiency of dopamine (DA) in the main output region of the substantia nigra, the striatum (*1*). Postmortem studies have also shown that the loss of DA cells in Parkinson's disease is accompanied by a decline in the striatal presynaptic DA transporter located on the nerve terminals of DA neurons (*2*).

PET and SPECT allow examination of the presynaptic nigrostriatal dopaminergic system in the human brain in vivo. Various ligands for imaging the DA transporter by PET and SPECT have been introduced successfully. Using ^{11}C-nomifensine and PET, it has been shown that Parkinson's disease patients can be distinguished from healthy controls (*3,4*). Recently, radiolabeled cocainelike ligands have become available. Frost et al. (*5*) and Rinne et al. (*6*) showed a clear loss of DA transporters in Parkinson's disease by means of ^{11}C-WIN 35,428 [or 2β-carbomethoxy-3β-(4-fluorophenyl)tropane] and PET.

Iodine-123-β-carbomethoxy-3β-(4-iodophenyl)tropane SPECT studies also showed a severe loss of striatal DA transporters in Parkinson's disease, more pronounced in the putamen than in the caudate nucleus, compared with healthy human subjects (*7–13*). However, the slow kinetics of ^{123}I-β-CIT are a serious drawback, as striatal radioactivity increases for 20 hr after injection and stabilizes thereafter up to 30 hr. The stable level of radioactivity between 20 and 30 hr postinjection satisfies conditions of prolonged equilibrium (*14*), indicating that an adequate image acquisition should be performed about 24 hr after injection, which is highly inconvenient for outpatient evaluations and is not optimal from the point of view of counting statistics because the half-life of ^{123}I is ~13 hr.

In an effort to produce ligands with faster kinetics, N-ω-fluoroalkyl analogs of β-CIT have been synthesized recently (*15–17*). One of these new compounds, N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane (FP-CIT), has been labeled with ^{123}I for SPECT (*15*) and with ^{11}C (*18*) or ^{18}F (*19*) for PET. In baboons and humans, ^{123}I-FP-CIT (or β-CIT-FP) has been tested successfully as a tracer for the DA transporter (*15,16,20–22*). These studies showed not only high brain uptake and high striatal-to-occipital-cortex ratios (i.e., high target-to-nontarget ratios) but also faster kinetics than β-CIT and an early peak in striatal specific activity. In addition, in vivo displacement studies in nonhuman primates demonstrated that striatal uptake of ^{11}C-FP-CIT was primarily due to DA transporter labeling (*18*).

Recently, we reported a dramatic loss of striatal ^{123}I-FP-CIT binding in Parkinson's disease patients with varying disease stages compared with that in controls as early as 3 hr postin-

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TABLE 1
Demographic and Clinical Data of 21 Drug-Naive Patients with Parkinson's Disease and 14 Healthy Controls

	Parkinson's disease patients (n = 21)	Controls (n = 14)
Men/women	15/6	7/7
Age (yr)*	55.5 (42–73, 9.7)	53.6 (28–83, 14.8)
PD (yr)†	2.3 (0.5–5, 1.3)	
H&Y	1.8 (1–3, 0.7)	
UPDRS	29.1 (14–57, 12.0)	
UPDRS-motor	18.2 (8–43, 8.7)	

*Data are expressed as mean (minimum–maximum, s.d.).
†Duration of Parkinson's disease
PD = Parkinson's disease; H&Y = Hoehn and Yahr Staging Scale; UPDRS = Unified Parkinson's Disease Rating Scale; UPDRS-motor = motor section of UPDRS.

jection (*23*). The aim of this study was to investigate whether the loss of striatal DA transporters in early and drug-naive Parkinson's disease patients could also be demonstrated by means of ^{123}I-FP-CIT SPECT in a 1-day protocol and whether the SPECT measures were correlated with the severity of the disease.

MATERIALS AND METHODS

Subjects

Twenty-one early and drug-naive Parkinson's disease patients (age range 42–73 yr; mean age 55.5 yr) and 14 healthy controls (age range 28–83 yr; mean 53.6 yr) were examined (Table 1). Parkinson's disease was diagnosed according to the criteria of the United Kingdom Parkinson's Disease Society Brain Bank (*24*). The severity of the motor symptoms and signs was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (*25*). The stage of illness was determined according to the Hoehn and Yahr (H&Y) Staging Scale (*26*). All patients showed a positive apomorphine challenge test, which was defined as a 20% reduction or more in the UPDRS motor score. A good response to subcutaneous apomorphine supports the diagnosis of Parkinson's disease (*27*).

The healthy volunteers were free from any neurological or psychiatric disease and were not taking drugs known to affect the dopaminergic system.

All subjects gave written informed consent for the study, which was approved by the medical ethics committee of the hospital.

SPECT Procedure

For the SPECT, a brain-dedicated SPECT system, the Strichman Medical Equipment 810X system (Strichman Medical Equipment, Inc., Medfield, MA) linked to a Macintosh II computer was used. The Strichman camera consists of 12 individual crystals each equipped with a focusing collimator. The transaxial resolution of this camera is 7.6 mm FWHM of a line source in air, and the axial resolution is 13.5 mm FWHM. The energy window was set at 135–190 keV.

The subjects received potassium iodide orally to block thyroid uptake of free radioactive iodine. Iodine-123-FP-CIT (specific activity of >185 MBq/nmol; radiochemical purity of >99%) was injected intravenously at an approximate dose of 110 MBq. Iodine-123 labeling of FP-CIT was performed by Amersham Cygne BV (Technical University Eindhoven, The Netherlands), using the trimethylstannyl precursor of FP-CIT obtained from Research Biochemicals International (Natick, MA).

SPECT image acquisition was always performed at 3 hr postinjection (*23*). Slices were acquired during 300-sec periods from the orbitomeatal line to the vertex using an interslice distance of 10 mm. Data acquisition took place in a 128 × 128 matrix.

Attenuation correction and reconstruction of the images were performed as described previously (*23*). The measured concentration of radioactivity was expressed as Strichman medical units (1 Strichman medical unit = 100 Bq/ml, as specified by Strichman Medical Equipment).

Data Processing

For analysis of striatal ^{123}I-FP-CIT binding, the ratio of specific to nonspecific binding was calculated by summing up two transversal slices representing the most intense striatal binding. Analyses were performed blind to the clinical data. A standard region of interest (ROI) template (constructed according to a stereotactic atlas and including regions for putamen, caudate nucleus and occipital cortex) and additional ROIs for the entire striatum were placed bilaterally on the acquired image as described previously (*23*). Estimates of specific striatal binding were made by subtracting occipital counts from striatal counts. The ratio of specific to nonspecific striatal ^{123}I-FP-CIT binding was then calculated by dividing the specific striatal uptake by the occipital binding (*10*).

The binding measures were used:

1. To calculate ipsilateral to contralateral asymmetry of ^{123}I-FP-CIT binding: asymmetry index = (ipsilateral − contralateral)/(ipsilateral + contralateral); and
2. To express the relation between ^{123}I-FP-CIT binding in putamen and caudate nucleus based on the following formula: putamen-caudate index = (putamen − caudate)/(putamen + caudate).

Contralateral is the side opposite that of the initial presentation of motor signs.

Statistics

Relationships between variables were measured using Spearman's rho. Analysis of variance, with age as a covariate, was used to compare the regional SPECT data in the Parkinson's disease patients and healthy controls. For healthy subjects, the mean binding of the left and right sides was used for the analyses. Multiple regression analysis was used to examine the relationship between the ^{123}I-FP-CIT binding measures and age and UPDRS ratings.

The discriminative power of the binding measures was analyzed using discriminant function analysis. All analyses were performed with statistical software (SPSS version 5.0, Chicago, IL). Significance was assessed at the $p < 0.05$ level.

RESULTS

No significant differences in age and gender could be detected between the patient and control groups. For both groups, the ratios of specific to nonspecific striatal ^{123}I-FP-CIT binding in all studied brain regions are shown in Table 2. All ratios were significantly lower in the patient group than in the control group (all $p < 0.01$) and were consistently lower at the contralateral side ($p < 0.01$, by Wilcoxon's signed rank test; Fig. 1). The reduction of the ^{123}I-FP-CIT ratio in the putamen in the Parkinson's disease group was ipsilateral 50% and contralateral 64% of the control mean, whereas the decreases in the caudate nucleus were much lower, 23 and 35%, respectively. Consequently, the putamen-caudate indices were ipsi- as well as contralaterally lower in the Parkinson's disease patients ($p < 0.001$, $r^2 = 0.72$ and 0.77, respectively). The asymmetry indices for putamen, caudate and entire striatum were significantly higher in the patient compared to the control group (putamen: $p < 0.001$, $r^2 = 0.61$; caudate: $p < 0.001$, $r^2 = 0.35$; striatum: $p < 0.001$, $r^2 = 0.51$).

TABLE 2
Iodine-123-FP-CIT SPECT Measurements of 21 Drug-Naive Patients with Parkinson's Disease and 14 Healthy Controls

	Controls (n = 14)	Parkinson's disease patients (n = 21)
Putamen		
Ipsi*	2.36 (1.60–3.93, 0.69)†	1.18 (0.63–2.37, 0.43)‡
Contra	2.24 (1.27–4.00, 0.71)	0.80 (0.52–1.59, 0.27)‡
AI	0.03 (−0.06 to 0.14, 0.05)	0.18 (−0.02 to 0.27, 0.07)‡
Caudate		
Ipsi	2.70 (1.67–5.13, 0.89)	2.07 (1.19–3.31, 0.63)‡
Contra	2.75 (1.80–5.00, 0.80)	1.79 (0.95–3.24, 0.65)‡
AI	−0.01 (−0.05 to 0.04, 0.03)	0.08 (−0.06 to 0.25, 0.08)‡
Striatum		
Ipsi	2.48 (1.53–5.00, 0.88)	1.45 (0.85–2.51, 0.47)‡
Contra	2.38 (1.40–4.20, 0.70)	1.14 (0.68–1.88, 0.36)‡
AI	0.02 (−0.05 to 0.09, 0.03)	0.12 (0.00–0.21, 0.06)‡
Pcidx		
Ipsi	−0.06 (−0.17 to 0.00, 0.05)	−0.28 (−0.43 to 0.11, 0.08)‡
Contra	−0.11 (−0.18 to 0.03, 0.05)	−0.37 (−0.47–0.20, 0.09)‡

*Ipsilateral is arbitratily assigned to the left region.

†Data are shown as mean (minimum–maximum, s.d.).

‡Significant difference compared to the controls ($p < 0.001$, except the ipsilateral caudate: $p < 0.01$). Bonferroni correction was used to allow for multiple testing.

SPECT data are expressed as follows: (binding in region of interest − binding in occipital cortex)/(binding in occipital cortex). ipsi = ipsilateral; contra = contralateral (side opposite that of initial presentation of motor signs); AI = asymmetry-index; Pcidx = Putamen-caudate index.

Comparing the patients with unilateral Parkinson's disease (H&Y = 1, n = 8) with the healthy controls, the striatal binding measures were bilaterally significantly reduced (ipsilateral: $p < 0.01$, $r^2 = 0.47$; contralateral: $p < 0.001$, $r^2 = 0.61$).

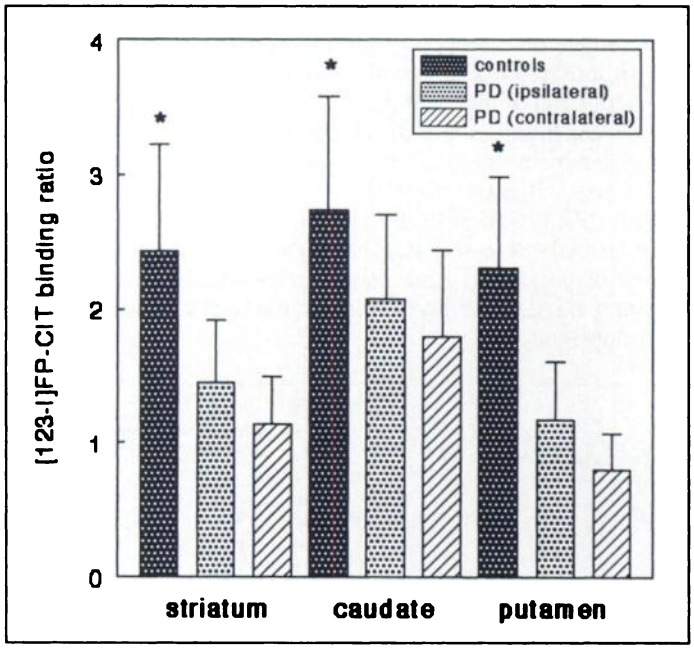

FIGURE 1. Mean striatal ^{123}I-FP-CIT SPECT binding ratios of 21 drug-naive patients with Parkinson's disease and 14 healthy controls. Contralateral is opposite side of initial presentation of motor signs. Asterisk indicates significantly higher ratios in control compared to Parkinson's disease group ($p < 0.01$).

TABLE 3
Results of Discriminant Function Analyses in 21 Drug-Naive Patients with Parkinson's Disease and 14 Healthy Controls

Predictors	λ	F ratio	p value	Correctly classified (%)
Putamen contra	0.29	82.1	<0.0001	94
Putamen ipsi	0.48	35.2	<0.0001	100
Putamen contra	0.29	82.1	<0.0001	
Caudate contra	0.71	13.5	<0.001	69
Caudate ipsi	0.83	7.0	<0.05	89
Caudate contra	0.71	13.5	<0.001	
Striatum contra	0.43	43.5	<0.0001	94
Striatum ipsi	0.61	21.1	<0.001	100
Striatum contra	0.43	43.5	<0.0001	
Putamen contra	0.29	82.1	<0.0001	100
Caudate contra	0.71	13.5	<0.001	
Pcidx ipsi	0.28	84.0	<0.0001	94
Pcidx contra	0.24	107.1	<0.0001	

ipsi = ipsilateral; contra = contralateral (opposite the side of initial presentation of motor signs); Pcidx = putamen-caudate index.

Discriminant Analysis

Discriminant function analysis, using the ^{123}I-FP-CIT SPECT data of the ipsi- and contralateral putamens, predicted group membership in all cases; the contralateral putamen accounted for the greatest difference between the Parkinson's disease patients and the healthy controls (Table 3 and Fig. 2). Correct classification was also reached in 100% of the cases using the contralateral putamen and caudate nucleus (the latter showed the least discrimination between the groups), whereas 94% was assigned correctly using the ipsi- and contralateral putamen–caudate index.

Demographic and Disease Variables Versus SPECT Measures

Age was significantly and negatively correlated with ^{123}I-FP-CIT binding in the studied brain areas in the control group (putamen: $r = -0.81$; caudate: $r = -0.65$; striatum: $r = -0.70$) as well as in the patient group (putamen: $r = -0.55$; caudate: $r = -0.51$; striatum: $r = -0.53$), whereas disease duration was not correlated (Fig. 3). Unexpectedly, stage and severity of Parkinson's disease were not correlated significantly with the SPECT measures (H&Y: putamen, $r = -0.18$; caudate, $r = -0.13$; striatum, $r = -0.14$; UPDRS motor score: putamen, $r = -0.22$; caudate, $r = -0.09$; striatum, $r = -0.13$; Fig. 3).

Multiple regression analysis was performed with the ^{123}I-FP-CIT binding measures of the entire putamen, the caudate nucleus and the striatum as dependent variables and with age and UPDRS motor score (only in Parkinson's disease group) as independent variables (Table 4). Within the control group, age accounted for a significant part of the variance in the putamen and striatum but not in the caudate nucleus. A significant age-dependent decline in striatal ^{123}I-FP-CIT binding of 9.6%/decade was found (regression equation, $3.96 - 0.03 \times$ age). One outlier was seen in the control group (high binding ratio relative to age). When this outlier was excluded, regression analysis revealed that age accounted for a significant and greater part of the variance in all three studied regions (putamen: $r^2 = 0.73$, $p < 0.001$; caudate nucleus: $r^2 = 0.58$, $p < 0.01$; striatum: $r^2 = 0.65$, $p < 0.001$).

In the Parkinson's disease group, the proportion of the total variation in ^{123}I-FP-CIT binding explained by age and disease severity (r^2) was low, and the F statistic was not significant. Therefore, age and severity of motor signs did not account for

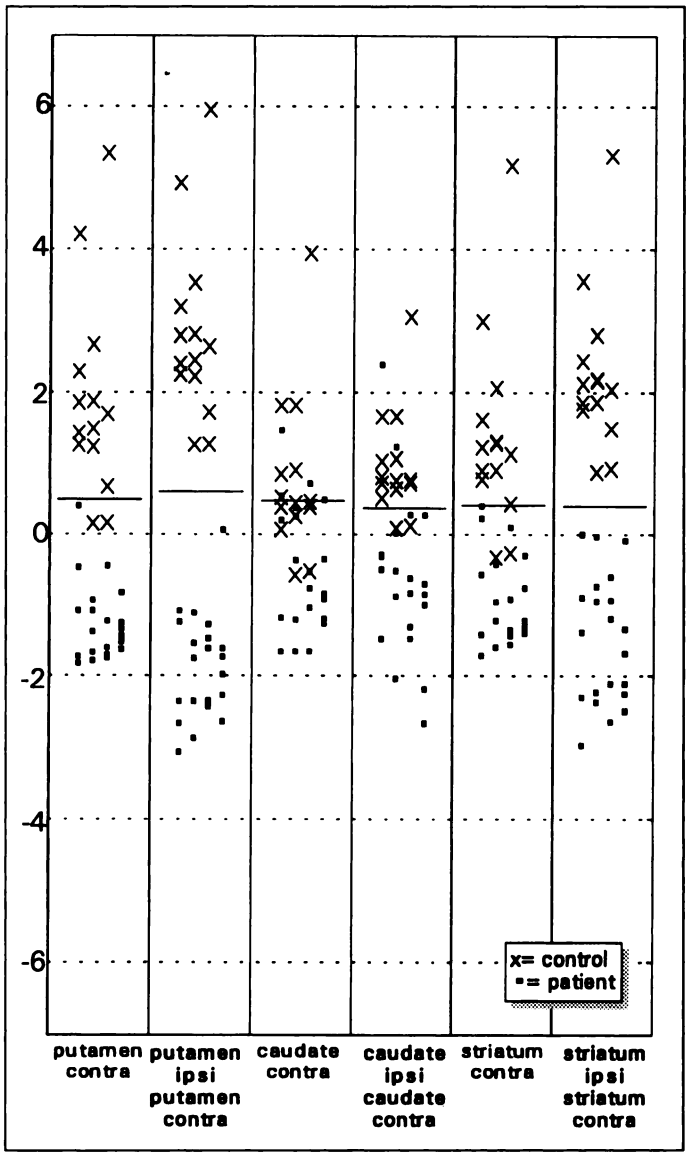

FIGURE 2. Application of discriminant analyses to 21 drug-naive patients with Parkinson's disease and 14 healthy controls using different predictors. Individual discriminant scores are shown.

a significant part of the variance in ^{123}I-FP-CIT binding in the studied brain regions.

DISCUSSION

Because direct or indirect effects of dopaminergic drugs on the DA transporter cannot be excluded, only drug-naive patients were examined in our study using ^{123}I-FP-CIT SPECT in 21 early Parkinson's disease patients and 14 healthy control subjects. For example, Ikawa et al. (*28*) reported an up-regulation of ^{3}H-mazindol-binding sites in rat striatum after chronic levodopa treatment. Others (*29*) found an inhibitory effect on acute administration of selegiline on ^{3}H-GBR 12935 binding in rat striatal slices.

TABLE 4
Data of Multiple Regression Analysis in Controls and Parkinson's Disease Patients

Dependent variable	Independent variables	Adjusted r^2	Sign F p	β	Sign T p
Controls					
Putamen	Age	0.37	<0.05	−0.65	<0.05
Caudate	Age	0.19	NS	−0.50	NS
Striatum	Age	0.23	0.05	−0.53	<0.05
Patients					
Putamen	Age	0.16	NS	−0.44	<0.05
	UPDRS*			−0.21	NS
Caudate	Age	0.16	NS	−0.48	<0.05
	UPDRS			−0.08	NS
Striatum	Age	0.17	NS	−0.47	<0.05
	UPDRS			−0.16	NS

*Motor section of UPDRS.
Sign = significance; UPDRS = Unified Parkinson's Disease Rating Scale; NS = not significant.

We found significantly lower striatal ^{123}I-FP-CIT binding ratios in Parkinson's disease patients compared to controls, especially contralateral to the side of onset of motor signs. In the Parkinson's disease group, a preferential loss of DA transporter binding was found in the putamen. These findings confirm the results of recent SPECT and PET studies in Parkinson's disease using radioligands for the DA transporter (*5,6,8,10,13,23,30*) and autopsy studies revealing a more severe depletion of DA in the putamen than in the caudate nucleus (*31*). The greater loss in the putamen is probably due to the more extensive degeneration of subpopulations of DA neurons that project primarily to the putamen (*1,31–33*).

Interestingly, the striatal binding measures of the patients with unilateral Parkinson's disease (H&Y = 1) were also significantly reduced bilaterally (contralateral, 53%; ipsilateral, 38% reduction of the control mean), indicating that ^{123}I-FP-CIT SPECT constitutes a tool for identifying patients in the preclinical phase of the disease. This was supported by Marek et al. (*12*) using ^{123}I-β-CIT SPECT.

Our ^{123}I-FP-CIT SPECT data show that, using discriminant function analysis, early, drug-naive Parkinson's disease patients can be distinguished from controls. Ipsilateral striatal regions proved to be the least discriminative; the caudate nucleus values were nonsignificant.

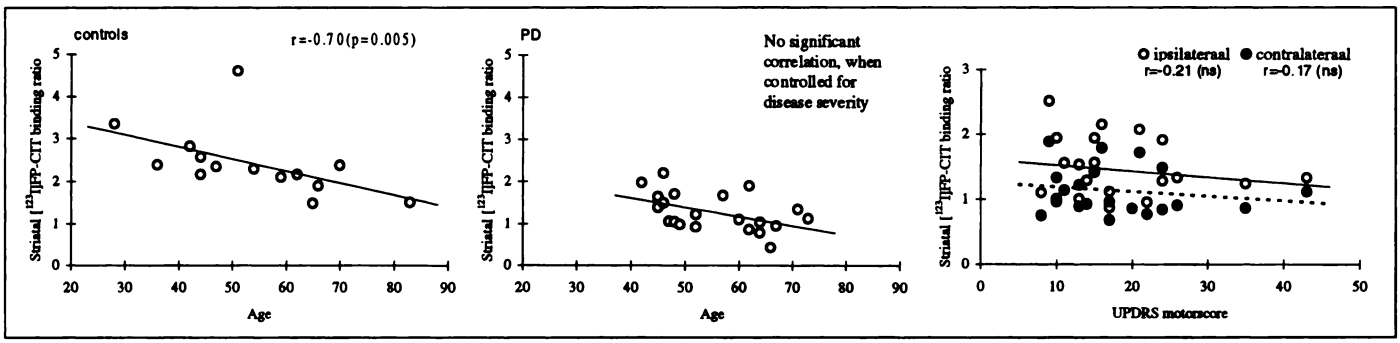

FIGURE 3. Striatal ^{123}I-FP-CIT binding versus age in 14 healthy controls (left) and 21 drug-naive patients with early Parkinson's disease (center). Striatal ^{123}I-FP-CIT binding in 21 drug-naive patients with Parkinson's disease (right) versus disease severity. Each symbol represents an individual subject.

Recently, Ishikawa et al. (*30*) reported that ^{123}I-FP-CIT SPECT discriminated mildly affected Parkinson's disease patients with dopaminergic therapy from healthy controls. Their results obtained with ^{123}I-FP-CIT SPECT correlated highly significantly with ^{18}F-dopa PET.

In our control group, a clear decline in ^{123}I-FP-CIT binding with aging was found, amounting to 9.6%/decade, which is in agreement with the results of earlier imaging studies with ^{123}I-β-CIT (8%) (*34*) and ^{11}C-D-threo-methylphenidate (6.6%) (*35*). Ishikawa et al. (*30*), also using ^{123}I-FP-CIT SPECT, found a somewhat smaller decline (3.3%) probably due to differences between the control groups and the methodologies.

Unexpectedly, in the Parkinson's disease group, regression analysis revealed that neither age nor severity of disease was significantly correlated with the striatal SPECT measures. This result confirms our earlier ^{123}I-FP-CIT study in a heterogeneous group of Parkinson's disease patients (three patients of this current study had already been reported in that study), in which we were also not able to establish correlations between motor UPDRS scores and ^{123}I-FP-CIT binding (*23*) but is in contrast to the findings by others (*30*). In our opinion, however, in the case of a significant correlation between severity of disease and disease duration, one has to control for the latter variable when correlating disease severity and ^{123}I-FP-CIT SPECT measures. This may explain the reported correlation between disease severity and ^{123}I-FP-CIT SPECT (*36*).

Methodological differences regarding the SPECT camera and procedure, for example, attenuation correction and reconstruction of the images, and data analyses, as well as differences in the time period postinjection, after which scans were acquired, might also underlie the discrepancy between our findings and those reported by Ishikawa et al. (*30*). Nevertheless, several authors suggested that stable striatal ^{123}I-FP-CIT ratios can be obtained beginning after 70 min until ~4 hr postinjection (*21,23,30*), which makes it most unlikely that the difference in acquisition time frame is an important explanatory variable. Moreover, applying the same SPECT procedure and ^{123}I-β-CIT as a ligand to a comparable group of drug-naive Parkinson's disease patients, we found a clear and significant negative correlation between UPDRS ratings and striatal ^{123}I-β-CIT binding measures obtained 24 hr postinjection (*37*), which is in agreement with the findings by others (*10,13*). So, it is also unlikely that the SPECT procedure is the underlying cause of the observed discrepancy.

A critical issue of this study is the relatively homogeneous composition of the Parkinson's disease group. We examined mainly early Parkinson's disease patients with mild symptoms and signs not yet using medication. Possibly, this might have biased our results. A more heterogeneous group of Parkinson's disease patients needs to be examined to measure more accurately the correlation between disease severity and ^{123}I-FP-CIT SPECT measures.

The reason for the difference between our ^{123}I-FP-CIT and ^{123}I-β-CIT findings regarding the correlation with disease severity is unclear. For ^{123}I-β-CIT, it has been reported that the specific to nonspecific striatal binding ratio, measured 24 hr postinjection, adequately reflects the density of DA transporters (*14*). Although it has been shown that dopaminergic neuronal loss can be detected by means of ^{123}I-FP-CIT SPECT, no extensive kinetic studies have been performed. Recently, Seibyl et al. (*38*) found faster specific striatal washout rates for FP-CIT than those previously reported for β-CIT. Thus, to date it is still unclear which outcome measure (e.g., the specific-to-nonspecific striatal binding ratio, the striatal activity or the striatal to plasma activity) provides an accurate assessment of the DA transporter density. This might underlie the lack of correlation between disease severity and ^{123}I-FP-CIT binding measures. Kinetic analyses of ^{123}I-FP-CIT have to be performed to define an optimal outcome measure.

CONCLUSION

Our findings indicate that ^{123}I-FP-CIT SPECT is a reliable method to discriminate between drug-naive Parkinson's disease patients and healthy controls. Moreover, due to the rapid kinetics of ^{123}I-FP-CIT (*21,23*) compared to ^{123}I-β-CIT, the former radioligand has the practical advantage of detecting the presynaptic dopaminergic deficit as early as 1–3 hr postinjection, which also makes FP-CIT a potentially useful PET tracer (*18,19*).

Patients with unilateral Parkinson's disease showed a bilateral loss of striatal ^{123}I-FP-CIT binding. This finding indicates that when using ^{123}I-FP-CIT SPECT patients can be identified in the preclinical phase of the disease. Unexpectedly, no significant correlations were found between striatal ^{123}I-FP-CIT SPECT binding ratios and disease severity, possibly due to the relatively homogeneous group of Parkinson's disease patients and the use of a suboptimal outcome measure, i.e., the specific-to-nonspecific striatal binding ratio. Thus, although the discriminatory power of ^{123}I-FP-CIT SPECT is great and, therefore, of interest for clinical use, further research is necessary to examine which outcome measure more accurately reflects the DA transporter density.

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5-[^{125}I]Iodo-2′-Deoxyuridine in the Radiotherapy of Brain Tumors in Rats

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Glial neoplasms of the human central nervous system have defied treatment, in part because of the limited selectivity of available cytotoxic agents. The thymidine analog 5-iodo-2′-deoxyuridine radiolabeled with the Auger electron emitter ^{125}I (^{125}IUdR) is highly toxic to dividing cells when it is deoxyribonucleic acid incorporated, but it is relatively innocuous when located outside the nucleus. Previous studies have shown that ^{125}IUdR has significant antineoplastic potential against mammalian cells in vitro and direct administration of ^{125}IUdR is effective therapy for ovarian ascites tumors in mice and neoplastic meningitis in rats. Studies using external gamma imaging and autoradiography have also shown that direct intratumoral administration of ^{123}IUdR/^{125}IUdR into intracerebral 9L gliosarcomas in rats results in selective uptake of the radionuclide into tumor cells. Based on these encouraging results, we have evaluated the therapeutic potential of ^{125}IUdR in rats bearing intracerebral 9L gliosarcomas. **Methods:** Iodine-125-IUdR was infused intracerebrally over a 2-day period into rats bearing 1-day-old 9L tumors and over a 6-day period into animals with 9-day-old 9L tumors; equimolar concentrations of ^{127}IUdR were infused into control animals. Tumor growth was monitored by contrast-enhanced ^{1}H MRI and animal survival was followed over time. **Results:** Intracerebral tumors (3–7 mm) were readily detected by MRI. Tumor-bearing rats treated with ^{127}IUdR succumbed within 17–24 days, whereas tumor-bearing animals treated with ^{125}IUdR survived significantly longer, and 10%–20% of the animals were cured of tumors. **Conclusion:** These data substantiate the antineoplastic potential of 5-[^{125}I]iodo-2′-deoxyuridine and indicate that it may be a useful agent for the therapy of solid tumors that are accessible to direct radiopharmaceutical administration.

Key Words: 5-iodo-2′-deoxyuridine; Auger electrons; iodine-125; brain tumor therapy; locoregional administration

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Malignant gliomas account for approximately half of the 17,500 primary brain tumors diagnosed in patients in the U.S. each year (*1,2*). Despite treatment with surgery, radiotherapy and chemotherapy, the prognosis for these patients remains poor. Median survival is 9–12 mo for patients with glioblastomas and 24–36 mo for patients with anaplastic astrocytomas (*3*). Efforts to improve the prognosis of patients with malignant gliomas have included advances in neurosurgical techniques (*4*), novel approaches to increasing the effectiveness of radiotherapy (*3,5–7*), stereotactic brachytherapy and radiosurgery (*8*), immunotherapy (*9,10*), boron-capture therapy (*11*) and, most recently, gene therapy (*12–15*). Despite these therapeutic approaches, there has been only minimal improvement in the prognosis of patients with malignant gliomas over the past two

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