Serotonin Transporters in the Midbrain of Parkinson's Disease Patients: A Study with ^{123}I-β-CIT SPECT

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In Parkinson's disease (PD), both neuropathologic and biochemical studies suggest that serotonin (5-hydroxytryptamine [5-HT]) neurons are affected by the disease process. The integrity of 5-HT transporters was assessed in PD patients with SPECT using 2β-carbomethoxy-3β-(4-^{123}I-iodophenyl)tropane (^{123}I-β-CIT), which binds with high affinity to both dopamine (DA) and 5-HT transporters. **Methods:** Forty-five PD patients at relatively early stages (mean Hoehn–Yahr stage, 2.0 ± 0.7; range, 1–3) and 7 age-matched healthy control subjects had 15 scans over a 24-h period after injection of ^{123}I-β-CIT using a 3-head SPECT system. In the midbrain, the 5-HT transporter parameter k_3/k_4 was estimated by 3 noninvasive methods: pseudoequilibrium ratio (R_{PE}) method, area ratio (R_A) method, and a modified graphic method that derives the ratio of ligand distribution volumes (R_V). Striatal V_3'', the DA transporter parameter that is equivalent to k_3/k_4, was measured using the images acquired at 24 h after tracer injection. All measures were derived using the cerebellum as the reference region. **Results:** In control subjects, the ^{123}I-β-CIT activity in the midbrain reached a peak at 91 ± 21 min after injection and then washed out at a slow rate (1.1%/h ± 0.5%/h). The peak specific uptake in the midbrain occurred at 315 ± 46 min. In PD patients, the temporal patterns of the midbrain and cerebellar activity were not significantly different from those in control subjects. None of midbrain R_{PE}, R_A, and R_V was significantly different between control subjects and PD patients, whereas striatal V_3'' was bilaterally reduced in all patients, being 32% lower than that of the control subjects (P = 0.002). In PD patients, none of the midbrain outcome measures was significantly correlated with either striatal V_3'' or motor or nonmotor symptom ratings, including the Hoehn–Yahr stage and the Unified Parkinson's Disease Rating Scale scores. When the studies of 7 PD patients with depression were analyzed separately, none of the midbrain outcome measures in these patients either was different significantly from control values or correlated with the Hamilton Depression Rating Scale score. **Conclusion:** These results suggest that DA and 5-HT transporters are differentially affected in PD, and 5-HT transporters in the midbrain region may not be affected in relatively early stages of PD. Alternatively, 5-HT transporters in the remaining neurons may be upregulated, thus raising the midbrain 5-HT transporter density to almost normal levels.

Key Words: Parkinson's disease; midbrain; serotonin transporter; dopamine transporter; 2β-carbomethoxy-3β-(4-^{123}I-iodophenyl)tropane; SPECT

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In Parkinson's disease (PD), the central pathologic process is a rather selective degeneration of the dopaminergic neurons in the pars compacta of the substantia nigra, leading to anterograde loss of the ascending nigrostriatal projections and their nerve endings. It is believed that the resultant depletion of dopamine (DA) in the caudate and putamen nuclei is the major substrate for the clinical signs and symptoms of PD (*1,2*). However, it is becoming increasingly evident that many of the basic nonmotor phenomena (e.g., psychiatric, cognitive, and autonomic) may be caused by involvement of nondopaminergic neurotransmitters, including serotonin (5-hydroxytryptamine [5-HT]), norepinephrine, and acetylcholine (*3*). Postmortem studies have shown loss of serotonergic neurons in the median (*4*) and dorsal (*5*) raphe nuclei of PD patients, accompanied by decreases in several corresponding biochemical markers, including 5-HT and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) (*3,6–8*) and the 5-HT transporters (*9–12*). Few studies, however, have sought to examine the changes of 5-HT system in the living brains of PD patients.

The 5-HT transporters located on presynaptic nerve endings play a key role in the regulation of 5-HT levels in the synaptic cleft. Over the past several years, several radioligands that bind with high affinity to 5-HT transporters have been developed and used to visualize and quantify these sites in the living human brain by SPECT or PET (*13*). The potent cocaine analog 2β-carbomethoxy-3β-(4-iodophenyl) tropane (β-CIT; also designated RTI-55) binds with high affinity to both DA and 5-HT transporters (*14,15*). SPECT brain imaging with ^{123}I-β-CIT in humans and nonhuman

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primates has shown that the tracer concentrates in striatal and midbrain regions (*16–18*). It has been demonstrated that the midbrain activity is associated with 5-HT transporters, whereas the striatal activity is associated with DA transporters (*16,19*). Therefore, ^{123}I-β-CIT can be used to label the 5-HT transporters in the human brain in vivo and should be useful for studying serotonergic neuronal integrity in cerebral degenerative processes.

The purpose of this study was to assess the integrity of 5-HT transporters in PD using ^{123}I-β-CIT and SPECT. From SPECT kinetic data, the 5-HT transporter parameter k_3/k_4 in the midbrain was estimated. k_3/k_4, the ratio of the transfer constants between the nondisplaceable and specifically bound receptor compartments, indicates a measure of the transporter density (*20*). We also compared the midbrain 5-HT transporter measures with the striatal DA transporter measure and the severity of motor as well as nonmotor symptoms in patients with PD.

MATERIALS AND METHODS

Radiolabeling

^{123}I-β-CIT was prepared from the corresponding tributylstannyl precursor (Research Biochemicals International) and high radionuclidic purity ^{123}I-NaI as described (*21*). ^{123}I-β-CIT was obtained with an average radiochemical yield of 64% ± 12% (n = 21). The radiochemical purity was >95%, and the specific activity was estimated to be >185 TBq/mmol.

Subjects

The study was approved by the medical ethics committee of the hospital. Forty-five patients with idiopathic PD (18 men, 27 women; mean age, 59 ± 8 y) at relatively early stages (mean Hoehn–Yahr stage, 2.0 ± 0.7; range, 1–3) and 7 age-matched healthy control subjects (2 men, 5 women; mean age, 57 ± 6 y) were enrolled in the study after the provision of informed consent. All patients had symptoms that were responsive to L-dopa and had at least 3 of the following symptoms: resting tremor, bradykinesia, rigidity, and postural instability. Twenty-four of the patients were not receiving any antiparkinsonian medication before the SPECT scan. The rest of the patients were on treatment with L-dopa, DA agonist, L-deprenyl, amantadine, and anticholinergic drugs in various combinations. Patients were evaluated at the drug-off state using the Hoehn–Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS) (*22*). Seven of the patients had depressive symptoms and their severity was evaluated by the Hamilton Depression Rating Scale (*23*). The patients were not receiving antidepressant medication. The clinical characteristics of patients are described in Table 1.

Healthy control subjects underwent a thorough history, physical examination, and laboratory evaluation before study enrollment. Subjects with first-degree family members with psychiatric or neurologic illness were excluded. All subjects had no history of neuropsychiatric disorders and were taking no medication.

SPECT Data Acquisition

SPECT studies were performed using a 3-head system equipped with medium-energy collimators and interfaced to a dedicated computer system. Images were acquired with each head rotating 120° in 3° steps, creating 120 raw image sets. Antiparkinsonian medications were discontinued for 48 h before scanning. To minimize radioiodine uptake in the thyroid gland, each patient was given oral Lugol's solution, 1 drop 3 times daily, for 1 d before and for 3 d after intravenous administration of ^{123}I-β-CIT. Fiducial markers containing ~0.259 MBq ^{123}I were attached to the skin along the canthomeatal plane for identification during image analysis. Each subject received an intravenous bolus injection of 204 ± 67 MBq ^{123}I-β-CIT, and 15 SPECT scans were obtained over a 24-h period after injection: 10 sequential scans of 10 min starting immediately after injection, followed by scans of 20–30 min at 3, 4, 6, 12, and 24 h after injection. Images were acquired with a 10% symmetric window centered at 159 keV, reconstructed with a Butterworth filter (cutoff, 0.4 cycle/cm; power, 7) and displayed in a 128 × 128 matrix (pixel size, 3.56 × 3.56 mm with a slice thickness of 3.56 mm). Transaxial images were reoriented parallel to the canthomeatal plane as identified by the fiducial markers. Attenuation correction was performed using Chang's method (attenuation coefficient μ = 0.11/cm) (*24*). No attempts were made to correct for partial-volume effects or for the scatter fraction of the photopeak window.

Data Analysis

Regions of interest (ROIs) were placed on the midbrain and striatum where the binding of ^{123}I-β-CIT is associated primarily with 5-HT and DA transporters, respectively, and the cerebellum, which was assumed to include only nondisplaceable activity. From each set of transaxial images, 3 consecutive slices with highest midbrain activities were summed to construct a 10.68-mm-thick slice. A standard ROI with preset size and shape (10.68 × 10.68 mm rectangle) was positioned on the midbrain. Because of the finite spatial resolution of the scanner, we used a regional positioning technique that minimized underestimation of the true radioactivity concentration by partial-volume effects. The regions were first manually positioned on the center of the structure, using a brain atlas and the SPECT image itself as a guide. The regions were then moved 1 pixel in each of the 8 compass directions, and the location that produced the maximum value of the average counts per pixel within the region was used for quantification. The same procedures were performed for ROI placement on the striatum. Three consecutive slices representing the cerebellum were also added, and a standard ROI (14.24 × 24.92 mm rectangle) was placed on the cerebellum. Right and left cerebellar values were averaged for subsequent analysis. Average counts per pixel from each region were decay-corrected to the time of injection and divided by the scan duration to generate ROI activity in counts per minute per pixel.

At the midbrain 5-HT transporter sites, ^{123}I-β-CIT displayed a kinetic profile falling between the categories of slowly and rapidly equilibrating neuroreceptor probes (see Results). On the basis of this finding, k_3/k_4 in the midbrain was estimated from ^{123}I-β-CIT SPECT data with 3 noninvasive methods of analyzing reversible radioligand binding based on kinetic compartment models. The k_3/k_4 equivalent outcome measures were as follows: (a) pseudo-equilibrium ratio (R_{PE}), the ratio of specific (midbrain − cerebellar activity) to nondisplaceable (cerebellar) uptake at peak specific uptake (*25*); (b) area ratio (R_A), the ratio of the areas under the specific binding and nondisplaceable activity curves (*26*); and (c) the ratio of ligand distribution volumes (R_V) of specifically bound and nondisplaceable compartments, which was derived by a modified graphic method (*27*), a variation of the graphic method of

TABLE 1
Clinical Characteristics of Patients

Patient no.	Sex	Age (y)	Disease duration (mo)	Medication	H–Y	UPDRS score				HAM-D
						Total	Motor	ADL	Affection*	
1	F	80	96	Mado, BC, Aman	3	61	39	18	4	21
2	F	59	51	Drug-naive	1.5	52	34	14	4	24
3	F	60	48	Mado-HBS, BC, Aman	1	20	14	4	2	
4	F	60	51	Sin, BC	2	30	24	6	0	
5	M	40	5	Mado-HBS, BC	2	20	14	4	2	
6	F	61	27	Drug-naive	1	17	8	9	0	
7	F	57	36	Mado, BC	2	27	23	4	0	
8	M	51	8	Mado	2	37	28	9	0	
9	M	60	2	Drug-naive	2	31	23	7	1	
10	F	57	17	Mado-HBS, BC	3	59	43	15	1	
11	F	55	55	Mado, BC, Aman	1.5	23	19	4	0	
12	F	57	12	Sin, Aman	2	15	11	4	0	
13	M	55	30	Mado, BC, Aman	2.5	41	34	5	2	
14	F	77	65	Sin, Aman	2.5	51	40	10	1	
15	M	50	29	Drug-naive	2	27	22	4	1	
16	M	53	58	Sin, Lisu	2.5	55	43	10	2	
17	M	57	10	Drug-naive	2	36	30	6	0	
18	F	58	42	Drug-naive	2.5	49	35	12	2	
19	F	56	24	Drug-naive	2	50	38	9	3	14
20	M	71	13	Drug-naive	2.5	47	35	10	2	
21	M	69	12	Drug-naive	2	31	23	7	1	
22	F	42	67	Drug-naive	2.5	34	28	4	2	
23	F	56	22	Mado-HBS, Aman	3	67	54	8	5	32
24	F	55	65	Mado, BC, Seleg	2.5	52	39	9	4	21
25	F	61	41	Drug-naive	1	19	13	4	2	
26	F	60	11	Drug-naive	1	20	16	4	0	
27	F	56	66	Sin, Aman	1	11	7	3	1	
28	M	71	8	Drug-naive	3	53	45	7	1	
29	F	66	68	Drug-naive	2	37	27	9	1	
30	M	62	6	Sin, BC, Aman	2.5	52	42	6	4	18
31	F	47	14	Drug-naive	1.5	16	14	2	0	
32	F	68	22	Mado, Aman	2.5	56	41	10	5	37
33	M	57	8	Drug-naive	1	5	3	2	0	
34	F	54	104	Drug-naive	2.5	40	32	8	0	
35	F	62	13	Drug-naive	2.5	45	32	12	1	
36	F	56	8	Drug-naive	2.5	31	26	4	1	
37	M	55	50	Sin, Aman	2	29	22	5	2	
38	M	74	12	Drug-naive	1	6	6	0	0	
39	F	54	44	Sin, THP	1	18	14	4	0	
40	M	67	33	Drug-naive	2	32	26	4	2	
41	F	57	32	Sin, BC, Aman	3	38	27	9	0	
42	F	63	24	Drug-naive	1	18	14	2	2	
43	M	67	10	Drug-naive	3	47	34	12	1	
44	M	55	72	Drug-naive	1	22	15	7	0	
45	M	59	34	Sin	2.5	34	20	13	1	
Mean ± SD		59.3 ± 8.0	33.9 ± 25.4		2.0 ± 0.7	34.7 ± 15.8	26.2 ± 12.1	7.1 ± 3.9	1.4 ± 1.4	

*Mentation, behavior, and mood.

H–Y = Hoehn–Yahr stage; ADL = activities of daily living; HAM-D = Hamilton Depression Rating Scale score; Mado = L-dopa as Madopar; BC = bromocriptine; Aman = amantadine; Mado-HBS = L-dopa as Madopar Hemodynamically Balanced System; Sin = L-dopa as Sinemet; Lisu = lisuride; Seleg = selegiline; THP = trihexyphenidyl.

Logan et al. (*28*). R_{PE} was calculated according to the method of Farde et al. (*25*,*29*,*30*): a Levenberg–Marquardt least-squares minimization technique (*31*) was used for curve fitting, implemented in GraphPad PRISM (GraphPad Software, Inc.). R_A, based on the steady-state principle of reversible ligand binding (*32*), was calculated using all 24-h data. R_V was derived by multilinear regression procedures of Ichise et al. (*27*).

Striatal V_3'', the DA transporter parameter that is equivalent to k_3/k_4 (*33*), was calculated as (striatal − cerebellar)/cerebellar uptake using the images acquired at 24 h after ^{123}I-β-CIT injection.

Statistical Analysis

Values are expressed as mean ± SD. ^{123}I-β-CIT uptake in the midbrain and cerebellum and midbrain-specific uptake were compared between control subjects and PD patients for each SPECT acquisition using repeated-measures ANOVA. A 2-tailed unpaired Student *t* test was used to assess the differences in SPECT outcome measures between the control and PD patient groups. The differences among the control group and PD subgroups classified according to the Hoehn–Yahr scale or medication status were evaluated using a 1-way ANOVA. Correlations of midbrain outcome measures with striatal V_3'' and symptom ratings (Hoehn–Yahr stage, UPDRS scores, Hamilton Depression Rating Scale score) were evaluated by calculating either the Pearson linear correlation coefficient or the Spearman rank correlation coefficient (for correlation with Hamilton Depression Rating Scale score). A *P* value of <0.05 was considered significant.

RESULTS

Brain activity was concentrated in the midbrain and hypothalamus as well as in the striatum. Regional ^{123}I-β-CIT time–activity curves in healthy control subjects and PD patients are shown in Figure 1. In control subjects, the activity in the midbrain reached a peak at 91 ± 21 min after injection and then washed out at a slow rate (1.1%/h ± 0.5%/h). The cerebellar activity exhibited an early peak at 30–60 min, then washed out rapidly, and stabilized by 255 min. The peak specific uptake in the midbrain occurred at 315 ± 46 min. Similar patterns were observed in PD patients: the peak midbrain activity at 107 ± 34 min followed by a slow washout (1.3%/h ± 0.7%/h), an early cerebellar peak within the first 60 min with a rapid washout until stabilization, and the peak midbrain specific uptake at 327 ± 55 min. ^{123}I-β-CIT uptake in the midbrain and cerebellum and midbrain-specific uptake were not significantly different between control subjects and PD patients at each acquisition time. Selected ^{123}I-β-CIT SPECT images of a healthy control subject and PD patients are shown in Figure 2.

There were excellent correlations among midbrain R_{PE}, R_A, and R_V (R_{PE} vs. R_A, $r = 0.79$, $P < 0.0001$; R_{PE} vs. R_V, $r = 0.84$, $P < 0.0001$; R_A vs. R_V, $r = 0.96$, $P < 0.0001$). Comparisons of the midbrain outcome measures between PD patients and control subjects are summarized in Table 2. None of midbrain R_{PE}, R_A, and R_V was significantly different between control subjects and PD patients as a whole, whereas striatal V_3'' was bilaterally reduced in all patients, with total striatal V_3'' being 32% lower than that of the control subjects (4.22 ± 1.45 vs. 6.20 ± 0.74; $P = 0.002$). Also, there were no significant differences in the midbrain outcome measures among control subjects and patients with Hoehn–Yahr stages 1–1.5, stages 2–2.5, and stage 3. In PD patients, none of the midbrain outcome measures was significantly correlated with either striatal V_3'', Hoehn–Yahr stage, or UPDRS scores including total; motor; activities of daily living; and mentation, behavior, and mood scores of UPDRS (Table 3). When the studies of 24 drug-naive PD patients were analyzed separately, none of the midbrain outcome measures in these patients was either different significantly from those in control subjects or drug-treated PD patients (Table 2) or correlated with striatal V_3'', Hoehn–Yahr stage, or UPDRS scores (Table 3). Also, when the studies of 7 PD patients with depression were analyzed separately, none of the midbrain outcome measures in these patients was either different significantly from control values (Table 2) or correlated with the Hamilton Depression Rating Scale score (R_{PE}, $\rho = -0.33$, $P = 0.418$; R_A, $\rho = -0.45$, $P = 0.197$; R_V, $\rho = -0.38$, $P = 0.306$).

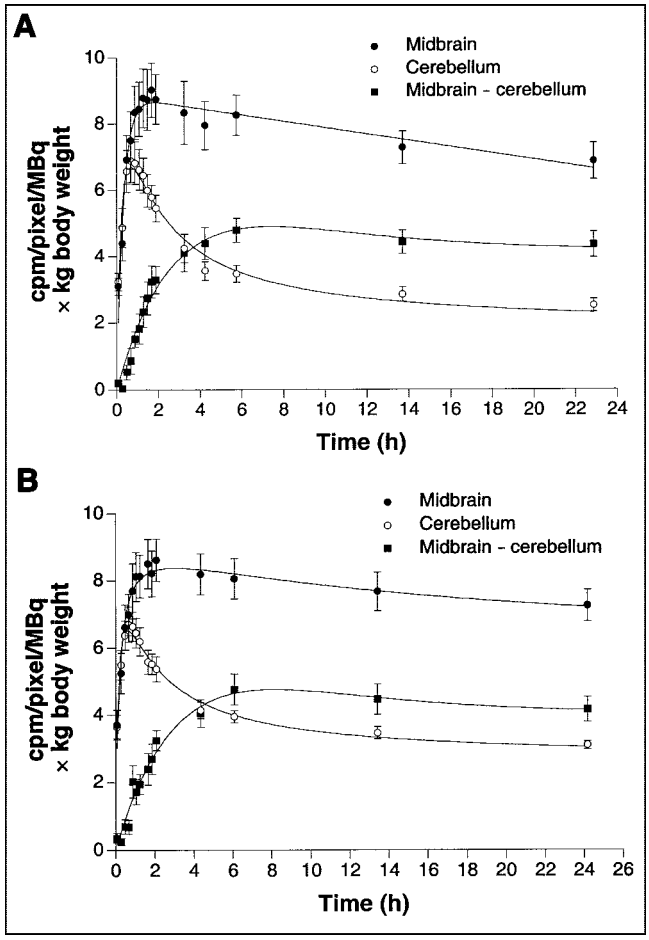

FIGURE 1. Regional ^{123}I-β-CIT activity curves in healthy control subjects (A) and PD patients (B) including midbrain and cerebellar activities and specific uptake in midbrain. Data are mean radioactivities (cpm/pixel/MBq injected × kg body weight) ± SD. Difference between midbrain and cerebellum was defined as specific uptake.

DISCUSSION

As reported previously (*34*), we found an earlier peak of ^{123}I-β-CIT uptake and a faster washout of the tracer in the midbrain than in the striatum, where the uptake of ^{123}I-β-CIT increases for 15–20 h after injection, followed by stable levels with no significant washout up to 30 h after injection (*33*). This indicates that ^{123}I-β-CIT has higher reversibility

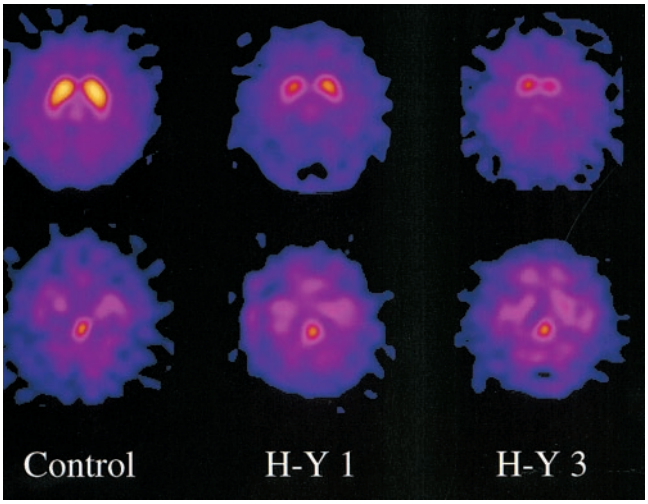

FIGURE 2. Transaxial SPECT images at levels of striatum (top row) and midbrain (bottom row) obtained 24 and 6 h, respectively, after injection of ^{123}I-β-CIT in healthy control subject and PD patients with Hoehn–Yahr stage 1 (H-Y 1) and stage 3 (H-Y 3). In contrast to striatal uptake, uptake in midbrain is not significantly different among control and PD subjects.

at the midbrain 5-HT transporter sites than at the DA transporters.

Postmortem studies in PD patients have shown various degrees of reduced concentrations of 5-HT in various brain regions (*3,6–8*), loss of 5-HT neuronal perikarya in the median (*4*) and dorsal (*5*) raphe nuclei, and decreases in 5-HT transporters in the striatum (*9,10,12*) and cortex (*9,11,12*). More recently, a PET study, performed in a small number of PD patients, with 5-HT transporter ligand ^{11}C-(+)-McN5652 has shown reduced binding of the ligand to 5-HT transporters in subcortical regions of PD patients (*35*). On the contrary, there was no significant difference in midbrain uptake ratios between PD patients and healthy control subjects in a study with ^{123}I-β-CIT SPECT (*36*).

In our study, ^{123}I-β-CIT SPECT measures of 5-HT transporter density (R_{PE}, R_A, R_V) in the midbrain of PD patients were not significantly different from control values. One possibility is that our patients are at relatively early stages of the disease (mean Hoehn–Yahr stage, 2.0 ± 0.7; range, 1–3), so that their 5-HT systems may remain intact. At present, there is a lack of chronologic studies in PD that would allow correlation of alterations in the 5-HT system and disease progression. An alternative explanation is that 5-HT transporters may be differentially affected in PD. Supporting our in vivo SPECT finding, Chinaglia et al. found that the density of ^{3}H-citalopram binding sites in the raphe nuclei of PD patients was comparable with control values, whereas it was significantly reduced in the basal ganglia of the same patients (*12*). They proposed that the 5-HT transporter system in PD may be less compromised at the origin of the 5-HT projection system than at its target areas. Nevertheless, normal densities of 5-HT transporters in the midbrain stand in contrast with the reported decrease of neuronal numbers within this region (*4,5*). It might be that the remaining 5-HT neurons compensate for a moderate loss of 5-HT neurons and overexpress 5-HT transporters, thus raising the regional density of 5-HT transporter binding sites to almost normal levels. Alternatively, it cannot be excluded that 5-HT transporters in the midbrain are also expressed by nonneuronal cells that might increase in number in PD. It has been shown that the total 5-HT concentration in the cerebrospinal fluid of PD patients was significantly correlated with the severity of motor symptoms (*37*). However, we did not find significant correlations of SPECT measures of 5-HT transporter density in the midbrain with either motor or nonmotor symptom ratings or a measure of striatal DA transporter density in PD patients. The discrepancy may support the regulation of the midbrain 5-HT transporters in PD.

We were unable to study neocortical 5-HT transporters because neocortical regions have low densities of 5-HT transporters and, thus, neocortical uptake of ^{123}I-β-CIT is only slightly higher than that in the cerebellum, a region with a minimal density of 5-HT transporters. Ligands with picomolar affinity for 5-HT transporters would make it possible to study neocortical 5-HT transporters in vivo with SPECT or PET. Another possible limitation of this study is that our control group (n = 7) is small compared with a relatively large number of patients (n = 45), although the control subjects were carefully matched for age.

It has been suggested that decreased serotonergic transmission may be implicated in the pathophysiology of de-

TABLE 2
Comparison of Midbrain SPECT Measures Between Control Subjects and PD Patients

Measure	Control subjects (n = 7)	Total PD patients (n = 45)	PD with H–Y 1–1.5 (n = 13)	PD with H–Y 2–2.5 (n = 26)	PD with H–Y 3 (n = 6)	Drug-naive PD (n = 24)	Drug-treated PD (n = 21)	PD with depression (n = 7)
R_{PE}	1.77 ± 0.26	1.66 ± 0.38	1.72 ± 0.35	1.60 ± 0.43	1.75 ± 0.23	1.74 ± 0.41	1.56 ± 0.34	1.68 ± 0.31
R_A	1.33 ± 0.15	1.22 ± 0.20	1.19 ± 0.25	1.29 ± 0.11	1.08 ± 0.29	1.21 ± 0.21	1.25 ± 0.20	1.27 ± 0.22
R_V	1.52 ± 0.20	1.41 ± 0.24	1.38 ± 0.30	1.47 ± 0.15	1.30 ± 0.41	1.36 ± 0.24	1.44 ± 0.25	1.44 ± 0.28

H–Y = Hoehn–Yahr stage.
Values are mean ± SD.

TABLE 3
Correlation Coefficients for SPECT Measures and Symptom Ratings in PD Patients

Measure	Total PD patients			Drug-naive PD patients		
	R_{PE}	R_A	R_V	R_{PE}	R_A	R_V
Striatal V_3''	0.137	0.120	−0.008	−0.126	0.226	0.167
P	0.696	0.733	0.982	0.857	0.745	0.812
Hoehn–Yahr stage	−0.015	−0.210	−0.137	0.265	−0.023	−0.086
P	0.921	0.547	0.697	0.213	0.974	0.902
Total UPDRS	−0.083	−0.397	−0.226	0.114	−0.391	−0.273
P	0.591	0.235	0.515	0.600	0.559	0.692
Motor UPDRS	−0.047	−0.341	−0.203	0.191	−0.266	−0.154
P	0.761	0.316	0.560	0.375	0.700	0.826
ADL UPDRS	−0.183	−0.411	−0.307	−0.193	−0.398	−0.365
P	0.231	0.211	0.369	0.371	0.542	0.571
Mentation, behavior, and mood UPDRS	−0.011	−0.090	0.069	0.234	−0.131	−0.052
P	0.942	0.799	0.846	0.273	0.852	0.941

ADL = activities of daily living.

pression in PD (*38*). In this study, when the studies of 7 PD patients with depression were analyzed separately, the measures of 5-HT transporter density in the midbrain of these patients were neither different significantly from control values nor correlated with the Hamilton Depression Rating Scale score. If the densities of 5-HT transporters in the neocortex can be measured in large samples of well-characterized patients using SPECT or PET, the role of the 5-HT system in depression in PD may become clearer.

We found no significant differences in the midbrain 5-HT transporter measures among drug-naive and drug-treated PD patients and control subjects. Nevertheless, the effect of L-dopa treatment on 5-HT neurotransmission should be discussed, as many of our patients were on long-term treatment with L-dopa. Exogenous L-dopa can interact with 5-HT mechanisms in several ways. For instance, DA formed from the administered L-dopa in the striatum, but also ubiquitously in the brain, can either inhibit or enhance 5-HT release depending on the type and location of the interaction synapse (*39*). In addition, L-dopa may be taken up by 5-HT terminals and converted therein by aromatic L-amino acid decarboxylase to DA, with resultant displacement of the endogenous 5-HT from vesicular stores (*40*). However, it is not known whether and how the interactions of L-dopa with 5-HT neurotransmission influence 5-HT transporter levels.

CONCLUSION

These data suggest that DA and 5-HT transporters are differentially affected in PD, and 5-HT transporters in the midbrain region may not be affected in relatively early stages of PD. Alternatively, 5-HT transporters in the remaining neurons may be upregulated, thus raising the midbrain 5-HT transporter density to almost normal levels.

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