Iodine-123-Iodo-Lisuride SPECT in Parkinson's Disease

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Recently, [^{123}I]iodo-lisuride was synthesized for possible applications in SPECT studies. The purpose of this investigation was to compare the striatal binding and kinetics of this radioligand in patients with Parkinson's disease and normal controls. **Methods:** Six patients with Parkinson's disease and three normal controls were examined. After intravenous injection of 111 MBq [^{123}I]iodo-lisuride, sequential SPECT examinations at 20, 40, 80 and 120 min were performed. For each SPECT series the basal ganglia-to-cerebellum ratio of tracer accumulation was calculated. In one patient a repeat SPECT examination was undertaken under identical conditions to test the reproducibility of the procedure. In two other patients a second SPECT examination was performed after injection of cold lisuride as a receptor saturation study. In addition, the time course of the radioactivity was measured in the plasma and red blood cells in each individual. **Results:** In both patients and controls, the highest tracer accumulation was found within the striatum. The basal ganglia-to-cerebellum ratio was 1.182 and 1.303 at 20 min, 1.353 and 1.450 at 40 min, 1.490 and 1.533 at 80 min, 1.550 and 1.583 at 120 min for patients and controls, respectively, which was not statistically different. In the saturation study, 50 μg and 100 μg cold lisuride led to a 28% and 33% reduction, respectively, of the basal ganglia-to-cerebellum ratio at 120 min. The ligand showed a rapid decline in plasma and red blood cells. The percent injected dose per liter was calculated to be 1.6 and 0.9, respectively, for plasma and red blood cells at 20 min. **Conclusion:** Iodine-123-iodo-lisuride SPECT seems useful for imaging intact striatal dopamine D2 receptors in patients with Parkinson's disease and may provide clinically relevant information for quantitative assessment of the availability and integrity of dopamine D2 receptors.

Key words: iodine-123-iodo-lisuride; Parkinson's disease; dopamine D2 receptors; SPECT

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A striatal dopamine deficiency represents the major pathophysiological mechanism in Parkinson's disease (*1*). Neuropathologic examinations of patients with Parkinson's disease have revealed that more than 60% of the dopaminergic neurons of the substantia nigra can be degenerated (*2*). PET studies have demonstrated that the presynaptic decarboxylation and storage of [^{18}F]fluorodopa may be severely disturbed in this central nervous system disorder (*3*). PET examinations with different receptor ligands, however, have shown that the postsynaptic dopamine D2 receptors are unaffected in Parkinson's disease (*4–6*).

Postsynaptic dopamine D2 receptors have also been studied by SPECT in akinetic-rigid disorders (*7,8*). SPECT with [^{123}I]IBZM as a dopamine D2 receptor ligand have demonstrated intact dopamine D2 receptors in Parkinson's disease (*9*). In contrast, patients with Parkinsonism plus syndromes have revealed decreased striatal dopamine D2 receptors (*10*).

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Dopamine agonists such as lisuride have been used clinically for the treatment of Parkinson's disease. Recently, lisuride has been successfully labeled by ^{123}I (*11*). It has been assumed that this compound might be suitable for SPECT examinations because of its high affinity and specificity to dopamine D2 receptors. Until today, SPECT examinations using this compound have been performed in patients with progressive supranuclear palsy (*12*) and Rett's syndrome (*13*).

In animal studies, it has been shown that after labeling [^{123}I]-iodo-lisuride is able to pass the blood-brain barrier and acts as a dopamine antagonist (*14*). Radiolabeled lisuride is relatively stable metabolically. For [^{76}Br]bromo-lisuride, 83% of radioactivity in the striatum represents metabolically unchanged radioligand after 180 min (*14*).

The purpose of this study was to compare striatal binding and [^{123}I]iodo-lisuride kinetics. In patients with Parkinson's disease and in healthy controls, sequential SPECT measurements were performed to detect the time course of specific and nonspecific binding of this compound. In addition, receptor displacement studies were carried out after administration of cold lisuride. Furthermore, the time course of [^{123}I]iodo-lisuride was measured in the plasma and red blood cells in both patients and controls.

METHODS

Patients

Six patients (5 men, 1 woman, aged 42–72 yr) were studied. In all patients, Parkinson's disease was diagnosed according to criteria of the United Kingdom Brain Bank London. The severity of the disease was classified according to the Hoehn and Yahr scale in all patients (Table 1). One patient had never received dopaminergic therapy (de novo), one patient responded to dopaminergic treatment and four patients showed fluctuations during the course of treatment. In addition, three healthy individuals (1 man, 2 women, aged 68–78 yr) were examined as controls. Written informed consent was obtained from all subjects. The investigation was approved by the ethical committee of the Rudolf Virchow University Clinic of the Free University and the Bundesamt für Strahlenschutz.

Any dopaminergic treatment, if applicable, was withdrawn 12 hr before the examination was started. All individuals received 300 mg sodium perchlorate as a thyroid blocking agent 30 min before tracer administration.

Radiotracer

All patients and controls received 111 MBq [^{123}I]iodo-lisuride [(3-(9,10-didehydro-2-iodo-6-methyl-8a-ergolinyl)-1,1-diethyl-urea] intravenously (*11*). Specific activity of [^{123}I]iodo-lisuride was determined to be >500 MBq/nmole and the radiochemical purity was greater than 95% with a contamination of [^{125}I]iodo-lisuride of less than 2.5×10^{-4} nmole.

TABLE 1
Biographical and Clinical Data for Patients and Controls

Subject no.	Age (yr)	Sex	Disease duration (yr)	Intensity of symptoms (Hoehn/Yahr Scale)	On-Off phases (hr/day)	Diagnosis
				on/off	on/off	
1	72	M	10	2/4	10/2	PD
2	57	M	8	2/4	10/5	PD
3	55	M	11	2/2	na	PD
4	42	F	6	na	na	PD
5	67	M	2.5	3/4	na	PD
6	59	M	14	3/5	3/11	PD
7	77	F	na	na	na	Control
8	78	F	na	na	na	Control
9	68	M	na	na	na	Control

na = not applicable; PD = Parkinson's disease.

Repeat Studies

Three patients were examined twice. The first examination served as a baseline study and the second examination was performed 1 wk later. In the second examination, one patient received 50 μg and one patient received 100 μg cold lisuride intravenously 20 min before tracer administration to measure saturation of striatal receptors. Another patient underwent a repeat study 1 wk after the baseline study to measure the reproducibility of the scanning procedure.

SPECT

Sequential SPECT scans were obtained 20 min (Series I), 40 min (Series II), 80 min (Series III) and 120 min (Series IV) postinjection. The acquisition time was 15 min for Series I to III and 45 min for Series IV. All SPECT examinations were performed on a single-head gamma camera with a low-energy, all-purpose collimator. The acquisition protocol, image resconstruction techniques and image evaluation have been described elsewhere (*15*).

All SPECT examinations were evaluated by using regions of interest; for quantitative evaluation of individual radiotracer uptake, a basal ganglia-to-cerebellum ratio was calculated for each SPECT series.

Blood Analysis

During each SPECT examination, 5-ml blood samples were collected with heparinized syringes. The blood samples were immediately centrifuged, and the plasma and red blood cells were separated. The radioactivity of both the plasma and the red blood cells were measured in a gamma counter. The measured radioactivity was expressed as the percent of injected dose per liter [%ID/liter].

Statistical Analysis

Statistical analysis was performed using a computer program (Systat, Systat Inc., Evanston, IL).

RESULTS

SPECT

Visual analysis of all SPECT sequences showed highest tracer accumulation within the striatum in both patients and controls. In both groups, the extrastriatal regions of the brain revealed only nonspecific tracer binding. The sequential SPECT measurements demonstrated an initially steep increase of the basal ganglia-to-cerebellum ratio, which was followed by a slow incline from Series I to Series IV in patients and controls

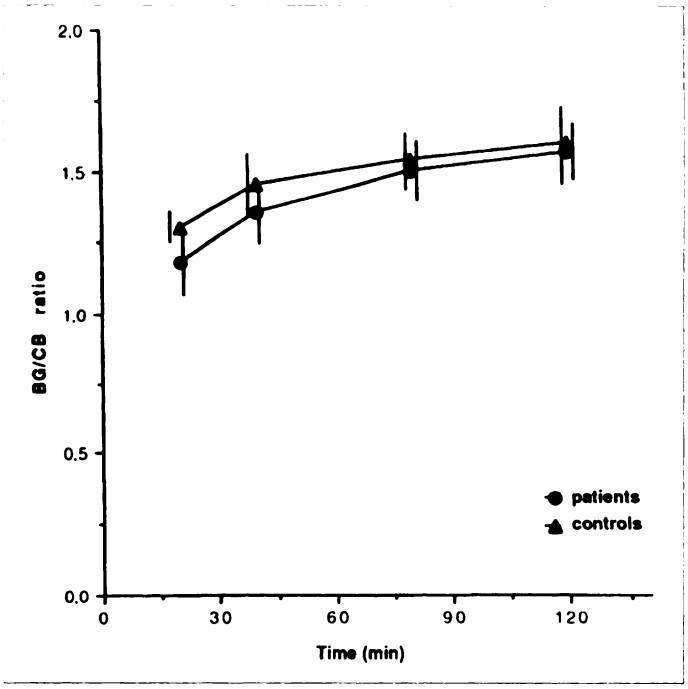

FIGURE 1. Basal ganglia-to-cerebellum (BG/CB) ratio versus time as measured by [^{123}I]iodo-lisuride SPECT (mean ± s.d.) in patients and controls.

(Fig. 1). The basal ganglia-to-cerebellum ratio was 1.182 and 1.303 at 20 min, 1.353 and 1.450 at 40 min, 1.490 and 1.533 at 80 min and 1.550 and 1.583 at 120 min for patients and controls, respectively, which was not statistically different ($p = 0.353$, ANOVA). The results of the basal ganglia-to-cerebellum ratio for all SPECT series are shown in Table 2.

Repeat Studies

The two SPECT examinations performed under the same conditions 1 wk apart revealed almost identical results for the basal ganglia-to-cerebellum ratio (Fig. 2).

The saturation study showed that 50 μg cold lisuride led to a 28% decrease of total tracer binding, which was equivalent to a decrease of approximately 80% of the specific tracer binding in SPECT Series IV (Fig. 3) and the application of 100 μg cold lisuride resulted in a 33% decrease of total tracer binding.

Blood Examinations

The radioactivity measurements in the plasma and red blood cells revealed a rapid decline in the percent injected dose per liter (1.6 and 0.9, respectively) at 20 min (Fig. 4).

General Observations

Both patients and controls tolerated the studies well. No side effects from tracer injection were observed.

TABLE 2
Basal Ganglia-to-Cerebellum (BG/CB) Ratio Results in Patients and Controls

SPECT series	Time (min)	BG/CB ratio: Patients (n = 6) Mean	Patients (n = 6) s.d.	Controls (n = 3) Mean	Controls (n = 3) s.d.	p (ANOVA)
I	20	1.182	0.136	1.303	0.055	
II	40	1.353	0.119	1.450	0.111	
III	80	1.490	0.117	1.533	0.099	
IV	120	1.550	0.103	1.583	0.138	
						0.353

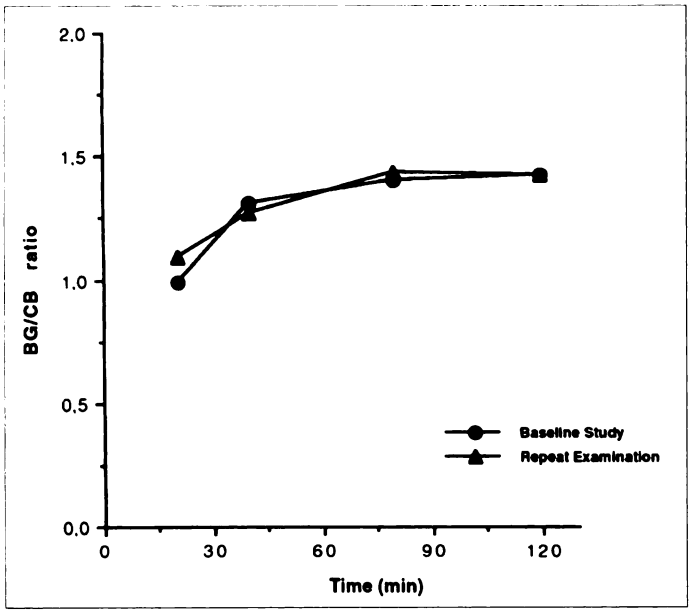

FIGURE 2. Basal ganglia-to-cerebellum (BG/CB) ratio versus time as measured by [^{123}I]iodo-lisuride SPECT in a patient with Parkinson's disease. Baseline study and repeat examination under identical conditions 1 wk apart from the baseline study.

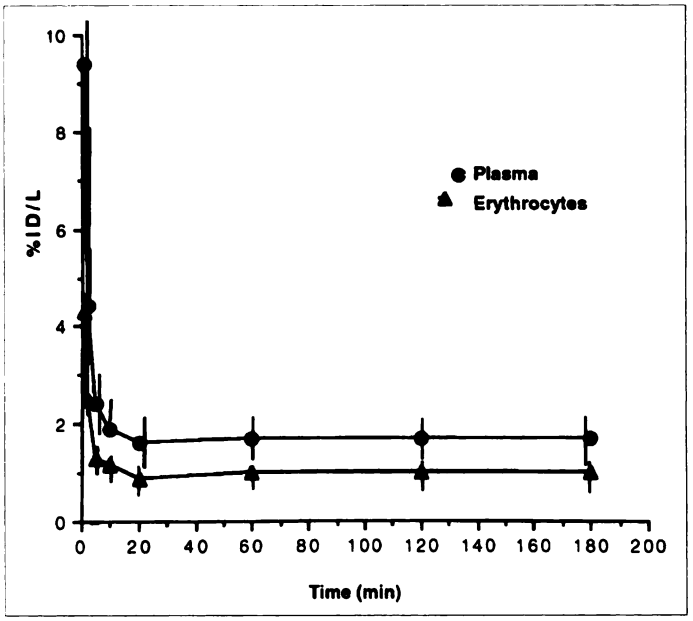

FIGURE 4. Time course of activity (%ID/liter) in plasma and red blood cells for patients and controls.

DISCUSSION

The dopamine agonist lisuride, a lysergic acid derivative, was synthesized by Zikan and Semonsky in 1968 (*16*). In 1976, direct dopaminergic action in mice was reported (*17*). Lisuride shows a high affinity to dopamine D2 receptors with only negligible binding to dopamine D1, serotonin or beta-adrenergic receptors (*17*).

After labeling with ^{123}I, lisuride reacts as a dopamine D2 receptor antagonist and becomes suitable for SPECT examinations. Therefore, for receptor displacement or saturation studies, a radioligand has become available that is a derivative of a cold pharmacologic active analog. Further comparative studies are needed to demonstrate whether [^{123}I]iodo-lisuride is more advantageous than [^{123}I]IBZM as a dopamine D2 receptor imaging agent.

We believe that the use of ^{123}I-labeled substances such as [^{123}I]iodo-lisuride or [^{123}I]IBZM might be of diagnostic value in the differential diagnosis among parkinsonian syndromes. Using [^{123}I]iodo-lisuride, Chabriat et al. (*12*) found that dopamine D2 receptors are decreased in patients with supranuclear palsy. Hierholzer et al. (*10*) also studied [^{123}I]IBZM and detected significantly lower dopamine D2 receptors in patients with Parkinsonism plus syndromes compared to patients with Parkinson's disease. Most substances that have been used for PET or SPECT examinations of dopamine D2 receptors belong to the classes of neuroleptics, butyrophenones and benzamides.

In this study, [^{123}I]iodo-lisuride had the highest accumulation in the striatum. This observation agrees with other investigators who also found the highest binding of [^{123}I]iodo-lisuride and [^{76}Br]-bromo-lisuride in the basal ganglia of the baboon and human brain (*12,18*). In their SPECT study, Chabriat et al. (*12*) found basal ganglia-to-cerebellum ratios in controls with a mean value of 1.59 ± 0.22 at 60 min postinjection. The sequential SPECT measurements in our study revealed an initially steep increase of tracer accumulation followed by a slow incline of the time-activity curves until 120 min in patients and controls. Additional data points at 3 and 4 hr would have been of value to clarify whether the basal ganglia-to-cerebellum ratio plateaus. For patients and controls, however, a total scan time of 120 min during which they were immobilized was strenuous. To avoid repositioning artifacts, we believe that a scan time of 2 hr is the maximum tolerable.

For patients and controls, there was no difference in the striatal binding of [^{123}I]iodo-lisuride in the time course of tracer accumulation or in the basal ganglia-to-cerebellum ratio. Results from PET studies demonstrated some evidence that the basal ganglia-to-cerebellum ratio is proportional to dopamine

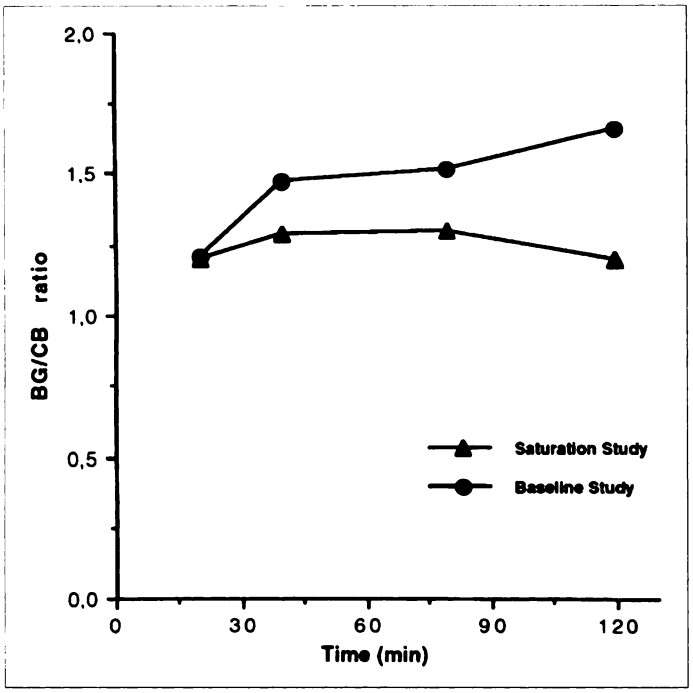

FIGURE 3. Basal ganglia-to-cerebellum (BG/CB) ratio versus time as measured by [^{123}I]iodo-lisuride SPECT in a patient with Parkinson's disease. Baseline study and receptor saturation study before application of 50 μg cold lisuride.

D2 receptor density and that this ratio can be used for clinical purposes because of its sensitivity and low variability (*6,19*). Therefore, it seems justified that undisturbed striatal accumulation of [^{123}I]iodo-lisuride indicates intact dopamine D2 receptors in Parkinson's disease (*20*).

Radioactivity measurements in the plasma and red blood cells after application of [^{123}I]iodo-lisuride showed that this radioligand is rapidly cleared from peripheral blood. Furthermore, there was no significant transport of [^{123}I]iodo-lisuride from the plasma compartment to the red blood cell compartment.

The saturation study in two patients demonstrated that 50 and 100 μg cold lisuride led to a 28% and 33% reduction, respectively, in ligand binding at 120 min. Such experiments seem promising to test the availability of dopamine D2 receptors for dopamine agonists during the treatment of patients with Parkinson's disease.

The repeat SPECT study, in one patient 1 wk after the baseline study, indicates that such measurements using SPECT yield reliable results and can be used for semiquantitative assessment of radioligand binding.

The variation of striatal dopaminergic function versus age has been the subject of some studies. There is some controversy about the decline in presynaptic dopaminergic function versus age. Although some investigators have found a correlation between striatal [^{18}F] fluorodopa uptake with age (*21*), others have not (*22*). There is consensus on the decline in striatal dopaminergic D2 receptors versus age (*23,7*) in both PET and SPECT studies. It has been shown that there is initially a steeper decline in striatal dopaminergic D2 receptors in younger subjects, which levels off in older groups (*23*). These findings agree with our own results, in which a correlation of the basal ganglia-to-cerebellum ratio of [^{123}I]iodo-lisuride versus age could not be detected ($p = 0.722$ and $p = 0.0841$, respectively) in older patients (aged 42–72 yr) or controls (aged 68–78 yr).

CONCLUSION

Iodine-123-iodo-lisuride SPECT can be utilized for imaging intact striatal dopamine D2 receptors in patients with Parkinson's disease as compared to normal controls. Iodine-123-iodo-lisuride SPECT may yield clinically relevant information about the functional status of dopamine D2 receptors by assessing the basal ganglia-to-cerebellum ratio and by receptor saturation studies.

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REFERENCES

1. Jenner P. Clues to the mechanism underlying dopamine cell death in Parkinson's disease. *J Neurol Neurosurg Psych* 1989;51(suppl):22–28.
2. McGeer PL, Itagaki S, Akiyama H, McGeer EG. Comparison of neuronal loss in Parkinson's disease and aging. In: Calne DB, ed. *Parkinsonism and aging*. New York: Raven Press; 1989:25–34.
3. Martin WRW, Palmer MR, Patlak CS, Calne DB. Nigrostriatal function in humans studied with positron emission tomography. *Ann Neurol* 1989;26:535–542.
4. Brooks DJ, Ibanez V, Sawle GV, et al. Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supranuclear palsy, measured with ^{11}C-raclopride and positron emission tomography. *Ann Neurol* 1992; 31:184–192.
5. Leenders KL, Herold S, Palmer AJ. Human cerebral dopamine system measured in vivo using PET. *J Cereb Blood Flow Metab* 1985;5:S157–S158.
6. Wienhard K, Coenen HH, Pawlik G, et al. PET studies of dopamine receptor distribution using [^{18}F]fluoroethylspiperone: findings in disorders related to the dopaminergic system. *J. Neural Trans* 1990;81:195–213.
7. Brücke T, Podreka I, Angelberger P, et al. Dopamine D2 receptor imaging with SPECT: studies in different neuropsychiatric disorders. *J Cereb Blood Flow Metab* 1991;11:220–228.
8. Schwarz J, Tatsch K, Arnold G, et al. Iodine-123-iodobenzamide SPECT predicts dopaminergic responsiveness in patients with de novo parkinsonism. *Neurology* 1992;42:556–561.
9. Cordes M, Hierholzer J, Schelosky L, et al. IBZM-SPECT imaging in Parkinson's disease. In Narabayashi T, Nagatsu T, Yanagisawa N, Mizuno Y, eds. *Advances in neurology. Parkinson's disease—from basic research in treatment*. New York: Raven Press; 1993:525–528.
10. Hierholzer J, Cordes M, Schelosky L, et al. Differentialdiagnose der Parkinson-Erkrankungen; ^{123}I-IBZM SPECT versus Apomorphin-Test. *Fortschr Röntgenstr* 1993;159:86–90.
11. Mazière B, Loc'h C, Raynaud C, et al. Iodine-123-lisuride, a new SPECT imaging ligand for brain dopamine D2 receptors [Abstract]. *J Nucl Med* 1989;30:731–732.
12. Chabriat H, Levasseur M, Vidailhet M, et al. In vivo SPECT imaging of D2 receptor with iodine-iodolisuride: results in supranuclear palsy. *J Nucl Med* 1992;33:1481–1485.
13. Chiron C, Bulteau C, Loc'h C, et al. Dopaminergic D2 receptor SPECT imaging in Rett syndrome: increase of specific binding in striatum. *J Nucl Med* 1993;34:1717–1721.
14. Loc'h C, Mazière B, Raynaud C, et al. SPECT imaging of dopaminergic D2 receptors with ^{123}I-iodolisuride [Abstract]. *Eur J Nucl Med* 1989;15:403.
15. Hierholzer J, Cordes M, Schelosky L, et al. Dopamine D2 receptor imaging with iodine-123-iodobenzamide SPECT in patients with idiopathic rotational torticollis. *J Nucl Med* 1994:35:1921–1927.
16. Zikan V, Semonsky M. Mutterkorn-Alkaloide: 31 Mitt: Ein Beitrag zur Herstellung von N-(D-6-methyl-8-isoergolenyl)-N′,N′-Diäthylharnstoff. *Pharmazie* 1968;23:147–148.
17. Horowski R, Wachtel H. Direct dopaminergic action of lisuride hydrogen maleate, an ergot derivative, in mice. *Eur J Pharmacol* 1976;36:373–383.
18. Mazière B, Loc'h C, Hantraye P, et al. PET imaging of D2 receptors in the living baboon and human brain in normal and pathological conditions using [^{76}Br]bromolisuride. In: Bunney H, ed. *Neuropsychopharmacology* Berlin: Springer; 1990:409–417.
19. Delforge J, Loc'h C, Hantraye P, et al. Kinetic analysis of central [^{76}Br]bromolisuride binding to dopamine D2 receptors studied by PET. *J Cereb Blood Flow Metab* 1991;11:914–925.
20. Jacob M, Müller T, Bier D, et al. Lisuride SPECT—a valuable tool to visualize dopaminergic degeneration in Parkinson's disease [Abstract]. *Eur J Nucl* 1994;21:728.
21. Cordes M, Snow BJ, Cooper S, et al. Age-dependent decline of nigrostriatal function: a positron emission tomographic study of grandparents and their grandchildren. *Ann Neurol* 1994;36:667–670.
22. Eidelberg D, Takikawa S, Dhawan V, et al. Striatal ^{18}F-DOPA uptake: absence of an aging effect. *J Cereb Blood Flow Metab* 1993;13:881–888.
23. Rinne JO, Hietala J, Ruotsalainen U, et al. Decrease in human striatal dopamine D2 receptor density with age: a PET study with [^{11}C]raclopride. *J Cereb Blood Flow Metab* 1993;13:310–314.