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Upregulation of Putaminal Dopamine D_2 Receptors in Early Parkinson's Disease: A Comparative PET Study with [^{11}C]Raclopride and [^{11}C]*N*-Methylspiperone

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Dopamine D_2 receptor function was assessed in a PET study with 2 dopamine D_2 receptor PET ligands, [^{11}C]raclopride (RAC) and [^{11}C]*N*-methylspiperone (NMSP), in early Parkinson's disease. **Methods:** Seven patients with early Parkinson's disease and 5 healthy volunteers were studied. Each underwent PET both with reversible [^{11}C]RAC and with irreversible [^{11}C]NMSP. **Results:** Upregulation of dopamine D_2 receptors in the putamen contralateral to the predominant symptoms of Parkinson's disease was confirmed using both [^{11}C]RAC and [^{11}C]NMSP. Uptake of [^{11}C]RAC in the contralateral putamen was 105% of uptake in the opposite putamen ($P = 0.020$). For [^{11}C]NMSP, uptake in the contralateral putamen was 105% of uptake in the ipsilateral putamen ($P = 0.011$). No significant differences between Parkinson's disease patients and healthy volunteers were detected in any of the studied brain regions using either [^{11}C]RAC or [^{11}C]NMSP. No significant differences between [^{11}C]RAC and [^{11}C]NMSP uptake were detected in the striatum, whereas in the extrastriatal regions, [^{11}C]NMSP showed significantly higher uptake than [^{11}C]RAC both in healthy volunteers and in Parkinson's disease patients. **Conclusion:** This study confirms an increase in dopamine D_2 receptors in the putamen contralateral to the predominant symptoms, compared with the ipsilateral putamen, in early Parkinson's disease. This increase was seen both with reversible ligand [^{11}C]RAC and with irreversible ligand [^{11}C]NMSP and thus does not seem a consequence of depleted endogenous dopamine.

Key Words: Parkinson's disease; dopamine D_2 receptor; raclopride; *N*-methylspiperone; PET

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The predominant pathology in Parkinson's disease is degeneration of the nigrostriatal dopaminergic pathway, leading to a deficiency of endogenous dopamine in the striatum. In addition to presynaptic changes in the nigrostriatal neurons, the striatal dopamine receptors alter. For instance, in early Parkinson's disease, uptake of [^{11}C]raclopride (RAC), which is a selective dopamine D_2 receptor ligand, increases in the striatum contralateral to the predominant symptoms of Parkinson's disease, compared with uptake in the opposite hemisphere (*1–7*).

In vitro studies indicate, however, that lack of dopamine may itself produce an increase in [^{11}C]RAC uptake (*8,9*), possibly without a change in dopamine receptors. Young et al. (*9*) depleted dopamine stores with reserpine and showed an increase of more than 50% in striatal [^{3}H]RAC binding in rats. Hall et al. (*10*) investigated the interaction of dopamine and dopamine D_2 receptors labeled with [^{3}H]RAC in a human postmortem study and found that endogenous dopamine interacted potently with dopamine D_2 receptors in the caudate nucleus. Increasing the dopamine concentration decreased the amount of [^{3}H]RAC bound to the dopamine D_2 receptors (*10*). Dewey et al. (*11*) investigated baboons in a PET study and reported a similar decrease in [^{11}C]RAC binding after administration of *d*-amphetamine, which increases synaptic dopamine. In contrast to in vitro studies, the study of Dewey et al. also showed a significant decrease in striatal [^{11}C]RAC binding after administration of tetrabenazine (a dopamine-depleting drug). As Dewey et al. point out, however, tetrabenazine has been shown not only to deplete biogenic amines, such as dopamine, but also to bind to dopamine D_2 receptors and thus compete with other dopaminergic antagonists such as [^{11}C]RAC.

In the case of Parkinson's disease, in which the deficiency of dopamine is a key phenomenon and in which [^{11}C]RAC has been used in PET studies to show changes in the dopamine D_2 receptor, this issue is crucial. If increased uptake of [^{11}C]RAC to the contralateral putamen in PET studies is merely an indication of dopamine deficiency in that brain region, rather than a sign of altered receptor density, re-evaluation of the studies already concluded is necessary.

To show a possible change in kinetic properties of [^{11}C]RAC, another dopamine D_2 receptor ligand, which is preferably stable in response to changes in endogenous dopamine, is needed. [^{3}H]NMSP has a 10-fold higher

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affinity (K_d = 0.2 nmol/L versus K_d = 3.9 nmol/L) for putaminal dopamine D_2 receptors than does [^{3}H]RAC in the human brain (*12*). Depletion of brain dopamine has no significant effect on [^{3}H]NMSP striatal binding (*9*).

Our study was designed primarily to determine whether striatal uptake of these 2 dopamine D_2 receptor PET ligands differs in vivo in patients with early Parkinson's disease. Finding no difference in striatal binding would indicate that endogenous dopamine may not be the explanation for the increase seen in [^{11}C]RAC binding in early Parkinson's disease. For this purpose, the results obtained using both radioligands were intraindividually compared.

MATERIALS AND METHODS

Patients

Seven patients with idiopathic, early Parkinson's disease and 5 healthy age-matched volunteers were studied. The patients had predominantly unilateral symptoms, and no patient had received antiparkinsonian medication. Four patients were receiving antihypertensive medication, and 1 patient was receiving anticholinergic medication. The alcohol consumption of all subjects was occasional and moderate, and all subjects were nonsmokers. The severity of Parkinson's disease was assessed according to the motor part of the Unified Parkinson's Disease Rating Scale (*13*). Table 1 shows the main clinical characteristics of the patients. All gave informed consent. The study was approved by the ethical committee of Turku University Central Hospital.

Radiochemistry

[^{11}C]RAC was prepared as previously described (*14*), and the quality control of the product was performed using the method of Rinne et al. (*15*). [^{11}C]NMSP was prepared from [^{11}C]methyl triflate (*16*). A 1-pot procedure from [^{11}C]carbon dioxide was used in the preparation of [^{11}C]methyl iodide (*17*), which was converted on-line to [^{11}C]methyl triflate by passage through a silver triflate–graphitized carbon column at 150°C–200°C (*18,19*). [^{11}C]NMSP was prepared by reaction of [^{11}C]methyl triflate with the *N*-desmethyl precursor (spiperone; Sigma Chemical Company, St. Louis, MO), and the reaction solution was purified with a 7.8 × 300 mm high-performance liquid chromatography column (μ-Bondapak C_{18}; Waters, Milford, MA) using a mixture of 10 mmol/L phosphoric acid:acetonitrile, 65:35, at a flow rate of 6 mL/min. The volume of the formulated (physiologic 0.1 mol/L phosphate buffer) [^{11}C]NMSP solution was determined by weight before and after sterile filtration. The concentration of [^{11}C]NMSP in the formulated solution was determined by reversed-phase high-performance liquid chromatography using a mixture of 10 mmol/L phosphoric acid:acetonitrile, 65:35, at a flow rate of 2 mL/min. Ultraviolet absorbance was measured at 250 nm. Samples of [^{11}C]NMSP were analyzed in triplicate, and concentrations were determined from calibration curves made by injection of 3 known concentrations of NMSP (Research Biochemicals International, Natick, MA) on the same day as the ^{11}C synthesis, with an SD of less than 2%.

PET

Each subject was scanned with [^{11}C]RAC and [^{11}C]NMSP in random order on the same day using the same scanner and patient positioning principles.

The [^{11}C]NMSP scans were obtained with an ECAT 931/08-12 PET scanner (CTI/Siemens, Knoxville, TN) with an average in-plane spatial resolution of 6.5 mm (full width at half maximum) and an average axial resolution of 6.7 mm. [^{11}C]NMSP scans consisted of 27 consecutive frames (2 × 120 s, 6 × 60 s, 5 × 120 s, and 14 × 300 s). The total duration of [^{11}C]NMSP studies was 90 min. The injected dose of [^{11}C]NMSP was 380 ± 18.9 MBq (mean ± SD) (range, 360–417 MBq), with a specific radioactivity of 39.0 ± 10.9 GBq/μmol (range, 22.6–59.3 GBq/μmol). The weight of the injected dose of [^{11}C]NMSP was 4.31 ± 1.31 μg (range, 2.42–6.73 μg).

The [^{11}C]RAC scans were obtained using a method described earlier (*1,7*). The injected dose of [^{11}C]RAC was 200 ± 15.2 MBq (range, 178–232 MBq), with a specific radioactivity of 36.0 ± 9.9 GBq/μmol (range, 17.6–49.1 GBq/μmol). The weight of the injected dose of [^{11}C]RAC was 2.09 ± 0.80 μg (range, 1.34–4.16 μg).

The region-of-interest analysis was performed by taking frontal, lateral temporal, occipital, and cerebellar cortices in each hemisphere as separate regions of interest. Moreover, regions of interest were drawn on the caudate nucleus, putamen, amygdala, cingulate gyrus, and thalamus in each hemisphere. To exclude structural lesions and to create an anatomic reference, each individual underwent brain MRI with a 1.5-T superconducting unit (Magnetom; Siemens, Erlangen, Germany). PET and MRI planes were realigned with a surface-fit computer program (*20*) so that the planes corresponded in axial and transaxial positions. Regions of interest were delineated on the basis of the anatomic boundaries in the horizontal MR images and transferred to the corresponding PET images. The distribution volume ratios, which are linear functions of receptor availability, were calculated using a graphic method described by Logan et al. (*21*) (Logan plot). Because of the comparative nature of the study, the Logan plot was also used with [^{11}C]NMSP data. [^{11}C]NMSP results calculated with a reference tissue model for irreversible ligands by Patlak and Blasberg (*22*)

TABLE 1
Clinical Characteristics of Parkinson's Disease Patients and Healthy Volunteers

Subject	n	Age (y)		Sex		Side of predominant symptoms		Duration of disease (mean ± SD) (mo)	UPDRS* (mean ± SD)
		Mean ± SD	Range	F	M	R	L		
Parkinson's disease patients	7	59.0 ± 10.9	45–75	4	3	3	4	14.7 ± 5.0	14.1 ± 6.9
Healthy volunteers	5	57.2 ± 9.5	52–74	4	1	—		—	—

*Total points scored in motor part of Unified Parkinson's Disease Rating Scale.

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had a significant positive correlation with the results of the Logan plot. The linear stage of the Logan plot was achieved 15 min after injection of [^{11}C]RAC and 20 min after injection of [^{11}C]NMSP (*21*).

Statistics

The differences in distribution volume ratios between healthy volunteers and Parkinson's disease patients were estimated by the Mann-Whitney test. The distribution volume ratios in the regions of interest between opposite hemispheres (contra- and ipsilateral to the predominant symptoms) in Parkinson's disease patients were calculated and tested against a null hypothesis of 0 (namely, no difference between the hemispheres) using the paired *t* test.

RESULTS

Uptake of [^{11}C]RAC in the putamen contralateral to the symptoms was, on average, 105% of uptake in the opposite putamen (P = 0.020). For [^{11}C]NMSP, uptake in the contralateral putamen was 105% of uptake in the ipsilateral putamen (P = 0.011) (Fig. 1; Table 2). No significant asymmetry of uptake was detected in any other brain region (e.g., in the contralateral caudate versus the ipsilateral caudate) in Parkinson's disease patients or healthy volunteers.

Between the Parkinson's disease patients and the healthy volunteers, no significant differences were detected in any of the brain regions studied, using either [^{11}C]RAC or [^{11}C]NMSP. No significant difference was detected between the Parkinson's disease patients and the healthy volunteers in pooled average values of the 2 hemispheres or in the comparison of contra- or ipsilateral putamen in Parkinson's disease patients versus the average value in healthy volunteers.

In the striatum, no significant differences were seen between uptake of [^{11}C]RAC and uptake of [^{11}C]NMSP. However, in the extrastriatal regions, uptake was significantly lower for [^{11}C]RAC than for [^{11}C]NMSP in both the Parkinson's disease patients and the healthy volunteers (Table 3). In the extrastriatal regions, the difference in the healthy volunteers was statistically significant in the frontal cortex, thalamus, occipital cortex, and temporal cortex. In the cingulate gyrus, the difference did not reach statistical significance. In the Parkinson's disease patients, all extrastriatal regions studied differed significantly between [^{11}C]RAC and [^{11}C]NMSP, and the difference was also significant in the ventral striatum.

DISCUSSION

Our results show that in early Parkinson's disease, the increase in uptake to dopamine D_2 receptors in the putamen contralateral to predominant symptoms, compared with the opposite putamen, is similar for [^{11}C]NMSP and [^{11}C]RAC. This finding suggests that the deficiency of endogenous dopamine does not explain the increased uptake of [^{11}C]RAC in PET studies of early Parkinson's disease (*1–7*).

In a PET study by Hägglund et al. (*23*) that used [^{11}C]NMSP in 6 patients with different stages of Parkinson's disease, dopamine receptor densities of striatal structures tended to vary with the stage of disease. Uptake of [^{11}C]NMSP was increased in patients whose disease was in Hoehn and Yahr (*24*) stage 1 but was reduced in later stages to a level lower than in healthy volunteers. Hägglund et al. did not, however, find any evidence supporting side-to-side differences in the striatum, possibly because of the limited number of suitable patients in their study. Only 3 of the 6 patients had unilateral symptoms and only 1 of those 3 was not treated with dopaminergic medication. In our patients, all of whom were not receiving medication and had strictly unilateral symptoms indicating Hoehn and Yahr stage 1 or 1.5, uptake of [^{11}C]NMSP was higher in the contralateral putamen than in the ipsilateral putamen.

The relative increase in [^{11}C]RAC uptake in early Parkinson's disease persists at least 6 mo after diagnosis (*4*). This upregulation disappears later, and when the disease is advanced the [^{11}C]RAC uptake is reduced (*25*). This finding

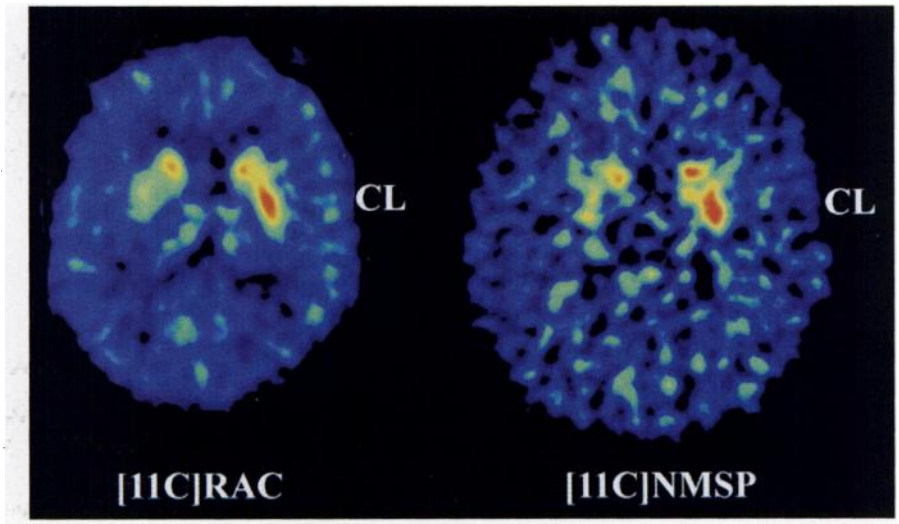

FIGURE 1. Striatal [^{11}C]RAC and [^{11}C]NMSP PET images of patient with early Parkinson's disease. Uptake of both radioligands to contralateral putamen is asymmetric, compared with opposite putamen. CL = side contralateral to predominant symptoms of Parkinson's disease.

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TABLE 2
Individual and Mean DVRs in Putamen and Caudate Nucleus in Parkinson's Disease Patients and Healthy Volunteers

Subject		Putamen		Caudate nucleus	
No.	Sex	Contralateral	Ipsilateral	Contralateral	Ipsilateral
[^{11}C]NMSP					
Parkinson's disease patients					
1	F	3.12	2.99	2.59	2.82
2	M	3.73	3.48	3.21	3.24
3	M	3.06	3.00	2.57	2.64
4	F	3.48	3.46	2.81	3.14
5	F	3.75	3.48	3.12	3.23
6	F	4.23	3.86	3.18	3.41
7	M	3.53	3.41	2.92	2.42
Mean ± SD		3.56 ± 0.40*	3.38 ± 0.30	2.91 ± 0.27	2.97 ± 0.36
Healthy volunteers					
1	F	3.71		3.62	
2	F	2.86		3.03	
3	F	3.42		3.01	
4	M	3.93		3.58	
5	F	4.69		3.76	
Mean ± SD		3.72 ± 0.67†		3.40 ± 0.35†	
[^{11}C]RAC					
Parkinson's disease patients					
1	F	3.20	3.17	2.36	2.61
2	M	3.32	3.25	2.73	2.82
3	M	3.93	3.47	3.14	3.01
4	F	3.10	2.87	2.76	2.32
5	F	3.96	3.71	2.80	2.92
6	F	3.66	3.61	2.09	2.60
7	M	3.96	3.79	2.89	2.78
Mean ± SD		3.59 ± 0.38‡	3.41 ± 0.33	2.68 ± 0.35	2.72 ± 0.23
Healthy volunteers					
1	F	3.20		3.05	
2	F	3.02		2.79	
3	F	3.74		3.05	
4	M	3.42		2.80	
5	F	3.48		3.07	
Mean ± SD		3.37 ± 0.28†		2.95 ± 0.14†	

*P = 0.011 compared with ipsilateral putamen.
†Mean of left and right hemisphere values.
‡P = 0.020 compared with ipsilateral putamen.

may be caused by a combination of the effect of dopaminergic medication and the disease process itself. However, in a study by Antonini et al. (*26*), 3–4 mo of oral therapy with levodopa had only a minimal effect on striatal [^{11}C]RAC uptake in untreated Parkinson's disease patients. A similar increase in receptor binding has been shown in experimental models of Parkinson's disease. Unilateral destruction of nigrostriatal projection with 6-hydroxydopamine in rats (*27*) or with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in monkeys (*28,29*) has increased striatal uptake of dopamine D_2 receptor ligands. In humans exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a similar increase in dopamine D_2 receptor binding has been reported (*30,31*). In postmortem brain studies of untreated patients with Parkinson's disease, a denervation upregulation has been found (*32–34*), and in a study comparing the results of ^{123}I-iodobenzamide SPECT and [^{11}C]RAC PET (*35*), the frequency of side-to-side differences in striatal tracer binding was similar for SPECT and PET. Furthermore, quantitative analysis has shown that increased [^{11}C]RAC binding in Parkinson's disease is caused by a relative increase in dopamine D_2 receptor density rather than dopamine D_2 receptor affinity (*7*). In summary, the results of animal, postmortem, and PET studies have suggested that the number of dopamine D_2 receptors in the denervated striatum increases in Parkinson's disease. Our study confirms the increase in dopamine D_2 receptors in the putamen contralateral to the predominant symptoms, compared with the opposite putamen.

Previously reported side-to-side differences were con-

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TABLE 3
Comparison of the DVRs Obtained with [^{11}C]RAC and [^{11}C]NMSP in Parkinson's Disease Patients and Healthy Volunteers

	Parkinson's disease patients			Healthy volunteers		
Brain region	[^{11}C]RAC (mean ± SD)	[^{11}C]NMSP (mean ± SD)	Diff	[^{11}C]RAC (mean ± SD)	[^{11}C]NMSP (mean ± SD)	Diff
Frontal cortex	1.12 ± 0.07	1.40 ± 0.08	20*	1.16 ± 0.07	1.45 ± 0.08	20*
Temporal cortex	1.20 ± 0.07	1.51 ± 0.08	21*	1.23 ± 0.07	1.52 ± 0.13	19*
Occipital cortex	1.18 ± 0.08	1.38 ± 0.08	14*	1.21 ± 0.11	1.42 ± 0.09	15†
Thalamus	1.31 ± 0.04	1.45 ± 0.13	10†	1.35 ± 0.06	1.56 ± 0.14	13†
Cingulate gyrus	1.15 ± 0.07	1.39 ± 0.10	17*	1.19 ± 0.09	1.41 ± 0.20	16‡
Caudate nucleus	2.71 ± 0.26	3.04 ± 0.29	11‡	2.95 ± 0.14	3.40 ± 0.35	13‡
Putamen	3.48 ± 0.38	3.52 ± 0.37	1‡	3.37 ± 0.28	3.72 ± 0.67	9‡
Ventral striatum	2.09 ± 0.38	2.71 ± 0.34	23†	1.93 ± 0.23	2.32 ± 0.98	17‡

*$P < 0.05$.
†$P < 0.01$.
‡Not statistically significant.
Diff = percentage difference between DVRs of [^{11}C]RAC and [^{11}C]NMSP.
In caudate-putamen, no significant difference exists between [^{11}C]RAC and [^{11}C]NMSP. Values are pooled from both hemispheres.

firmed in this study using both the [^{11}C]RAC and the [^{11}C]NMSP radioligands. The Parkinson's disease patients did not, however, show the overall increased [^{11}C]RAC or [^{11}C]NMSP binding in the striatum, compared with age-matched healthy volunteers, that some studies have found (*7,23,25,26*). This inconsistency appears to be caused by the relatively small number of subjects in our study and interindividual variation. Furthermore, dopamine D_2 receptor binding characteristics generally do not seem to reliably separate Parkinson's disease patients from healthy volunteers (*7,25*).

In this study, uptake of [^{11}C]NMSP was significantly higher than uptake of [^{11}C]RAC in extrastriatal regions. Although not as selective a dopamine D_2 receptor ligand as [^{11}C]RAC, [^{11}C]NMSP is also a serotonin S_2 receptor ligand (*36*). Because of the different binding profiles, the difference in cortical uptake of [^{11}C]RAC and [^{11}C]NMSP does not reflect changes in dopamine D_2 receptors. Binding of [^{11}C]NMSP to serotonin receptors is relatively higher in extrastriatal regions, where dopamine D_2 receptor density is low, than in the striatum and may cause 10%–20% higher [^{11}C]NMSP radioactivity (Table 3). However, no differences in either [^{11}C]RAC or [^{11}C]NMSP extrastriatal uptake were found between healthy volunteers and Parkinson's disease patients. To detect differences in low-density extrastriatal dopamine D_2 receptors between diseased and healthy individuals, ligands with both high selectivity and high (picomoles per liter) affinity have to be used.

CONCLUSION

This study confirms an increase in dopamine D_2 receptors in the putamen contralateral to the predominant symptoms, compared with the ipsilateral putamen, in early Parkinson's disease. This increase does not seem to result from reduced endogenous dopamine concentrations.

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