Dopamine D1 receptors in Parkinson's disease and striatonigral degeneration: a positron emission tomography study

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Abstract

Striatal dopamine D1 receptors were investigated in 11 patients with Parkinson's disease (PD), five patients with striatonigral degeneration (SND) and six age-matched controls by positron emission tomography and carbon-11 labelled SCH23390. The SND patients showed mean 12%, 21%, and 31% declines in the ratios of radioactivity in the caudate, anterior putamen, and posterior putamen compared with that in the occipital cortex. These ratios were not significantly altered in the PD patients. The results may explain the different therapeutic responses to levadopa between SND and PD patients, and this technique might prove useful for their differentiation.

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Dopamine receptors were initially divided into D1 and D2 receptors.[1] The D1 receptors stimulate the dopamine dependent adenylate cyclase system, whereas the D2 receptors are independent of adenylate cyclase or inhibit adenylate cyclase.[1][2] The influence of D1 receptors in Parkinson's disease (PD) has been repeatedly investigated in vitro but there is no consensus on the type of alteration in striatal D1 receptors. Striatal D1 receptors in PD have been reported to be either unchanged or upregulated.[3-9] Positron emission tomography (PET) provides a unique opportunity to assess neuroreceptors in vivo in humans, but there are few investigations to date on the status of striatal D1 receptors in patients with PD using PET.[10]

Striatonigral degeneration (SND) presents Parkinsonian symptoms; the incidence of SND has been estimated as between 4 and 8% of Parkinsonian patients.[11] Patients with SND usually fail to respond to levadopa therapy, whereas most patients with PD respond well to it.[12] This poor response or lack of response in SND might be attributed to a loss of striatal dopamine receptors but there have been few studies which report the status of dopamine receptors either in vitro or in vivo.[13-16]

We investigated 11 patients with PD, five patients with SND and six age-matched controls, using PET with carbon-11 labelled SCH23390.

Materials and methods

PATIENTS

The patients were clinically assessed and details are given in table 1. Eleven patients with PD (patients 1–11), including two patients (patients 3 and 9) with young onset PD,[17] were investigated. All PD patients except two (patients 9 and 10) presented typical Parkinsonian rest· tremor in addition to akinetic rigid syndrome. All of the treated PD patients (patients 6–11) responded well to levadopa. Patient 9 had been treated for five years with levadopa and presented levadopa induced dyskinesia (right foot dystonia). The untreated PD patients (patients 1–5) received levadopa after the PET study and showed a good response to the therapy. Brain CT scans of all PD patients showed no abnormal findings except mild cortical atrophy in three patients. The clinical features of all PD patients met the research diagnostic criteria for Parkinson's disease.[18]

Five patients (patients 12–16) were diagnosed as SND based on the following findings: (1) the predominance of rigidity and akinesia with no or minimal tremor at rest; (2) no or poor response to levadopa therapy; (3) rapidly progressive disability compared with PD patients, and (4) mild to moderate cerebellar atrophy on CT scan and MRI (except in one patient, no 12). In addition to the above features, two showed slight cerebellar ataxia, two had positive Babinski's sign, and four had impairment of autonomic function. Since the initial and primary finding was Parkinsonian syndrome, the specific diagnosis of SND was made rather than that of multiple system atrophies (MSA) which encompass SND, Shy-Drager syndrome, and olivopontocerebellar atrophy.[19-21]

Administration of all anti-Parkinsonian drugs was discontinued at least 48 hours before the PET study. Locomotor disability was assessed based on the Hoehn and Yahr stage at the time of the PET study.[22] Six healthy, age-matched subjects (three men and three women; mean age (SD) 65 (6) years, ranging from 56 to 73 years) served as controls. None of them showed neurological abnormalities, and they were not taking any medication at the time of the PET study. These studies were approved by the Inquiry Council of Medical and Research Morals on Medical Uses of Short-lived and Positron Radioisotopes of the National Institute of Radiological Sciences (NIRS), Japan.

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Table 1 Clinical features of patients with Parkinson's disease (PD), and striatonigral degeneration (SND)

Patient No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age/sex (year)	56/M	62/F	30/M	56/F	72/F	48/F	69/F	72/M	41/M	62/M	73/M	42/F	51/F	69/F	61/M	69/M
Duration of illness (year)	6 mo	2	1	3	2	3	1	3	10	10	5	9 mo	2	4	5	5
Hoehn and Yahr stage	I	I	II	II	III	II	III	III	III	III	IV	II	II	IV	IV	IV
Tremor	+ +	+	+ +	+	+	+ +	+	+	–	–	+	+*	–	+*	–	–
Rigidity	+ +	+	+ +	+	+ +	+ +	+ +	+	+ +	+	+ +	+	+ +	+ + +	+ + +	+ +
Akinesia	+	+	+	+	+	+	+ +	+	+	+ +	+ + +	+	+	+ + +	+ +	+
Initial symptom	Tremor	Tremor	Tremor	Tremor	Clumsiness	Tremor	Gait dist	Tremor	Writing diff	Gait dist	Gait dist	Tremor	Gait dist	Clumsiness	Gait dist	Writing diff
Asymmetry at onset	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Asymmetry of signs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dominant side	R	R	L	L	L	R	L	R	R	L	R	R	L	L	L	R
Cerebellar signs	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–
Pyramidal signs	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Postural hypotension	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+
Urinary disturbance	–	–	–	–	–	–	+	–	–	–	–	+	+	–	+	+
Decreased sweating	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–
MRI/CT scan																
Cortical atrophy	–	–	–	–	–	–	+	+	–	–	+	–	–	+	+	+
Cerebellar atrophy	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+ +	+ +
MRI																
Putaminal hypointensity	NE	–	–	–	NE	–	–	NE	–	–	NE	–	+	–	–	+ + +
Pars compacta width (mm)	NE	2·8	3·5	2·0	NE	2·7	2·8	NE	2·0	2·9	NE	3·2	2·7	2·8	2·9	3·3
Response to levadopa	Good[b]	Good[b]	Good[b]	Good[b]	Good[b]	Good	Good	Good	Good	Good	Good	Poor[b]	Poor[b]	Poor	Poor	Poor
Duration of levadopa (year)	0	0	0	0	0	2 mo	6 mo	2	5	5	2 mo	0	0	3	3	1[c]
Treatment	Nil	Nil	Nil	Nil	Nil	levadopa	levadopa	levadopa A	levadopa B	levadopa	levadopa	Nil	Nil	levadopa M	levadopa B	B L-dops
Clinical diagnosis	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	SND	SND	SND	SND	SND

–, absent; +, mild; + +, moderate; + + +, severe; NE, not examined; B, bromocriptine; A, anticholinergic; M, amantadine; L-dops, L-threo-3, 4-dihydroxyphenylserine; *postural tremor; [b]treated after the PET study; [c]discontinued owing to postural hypotension; Gait dist, gait disturbance; Writing diff, writing difficulty.

Informed written consent was obtained from all the subjects.

MRI

All the patients except four PD patients underwent MRI with a Philips 1·5 tesla Gyroscan using SE pulse sequence (TR/TE: 2500/40, 80 milliseconds) at NIRS. Fourteen 5 mm thick sections with a scan plane orientation of 100 degrees positive to the axis of the brainstem (roughly parallel with the orbitomeatal line) and a 0·5 mm interval were analysed. The width of the pars compacta signal with an echo time of 40 milliseconds was measured according to the method of Dugid et al,[23] and the average width of the right and left pars compacta signal was calculated. The width of the pars compacta signals of 10 healthy volunteers (six men and four women, ranging in age 40 years to 72 years) were used as the control values.

PET

The PET study was performed at NIRS. [11C]SCH23390 was prepared by N-alkylation of SCH24518 with carbon-11 labelled methyliodide by analogy with the preparation of [11C]Ro15–1788.[24] The total synthesis time was 35 to 40 minutes with a radiochemical purity of more than 99%, and the specific activity ranged from 13·4 to 57·5 GBq/μ mol at the time of injection.

A five ring, high resolution PET system was used to follow the radioactivity in nine sections of the brain covering an axial distance of 76 mm with an axial full width half maximum resolution of 5·7 mm and an inplane resolution of 3·5 mm times 3·5 mm (Hamamatsu Photonics, KK, Japan).[25] The subjects were carefully positioned by using crossed laser beams, and nine sections (13, 21, 29, 37, 45, 53, 61, 69, and 77 mm above and parallel to the orbitomeatal plane) were scanned. Correction for tissue attenuation of

511 keV γ radiation was measured with an external [68]Ge ring.

A mean dose of 629 pmol/kg [range from 290 to 1000 pmol/kg (450 to 945 MBq)] of [11C]SCH23390 in 2 to 5 ml of normal saline solution was infused intravenously for 30 seconds in each subject. Scanning began between 20 and 30 seconds following the start of the injection when PET first detected the radioactivity. Serial 2 minute scans were performed during the initial 10 minutes and then serial 5 minute scans were performed during the subsequent 50 minutes, yielding 15 frames over the 60 minutes period.

Circular regions of interest (ROIs) were placed on an integrated image representing the activity collected from 0 to 60 minutes following [11C]SCH23390 injection. Two sections optimum for striatum were selected and ROIs were defined in a standard arrangement: one circular ROI with a diameter of 8
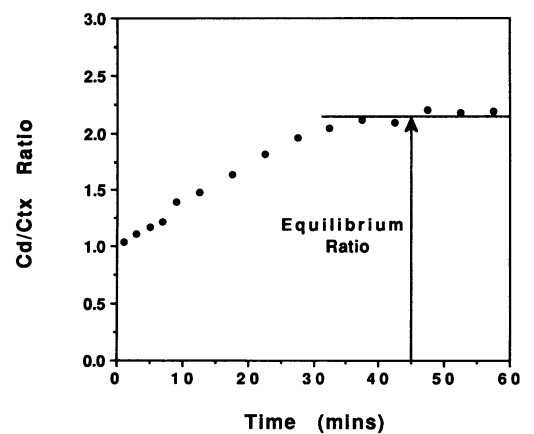

Figure 1 A plot of caudate:occipital cortex [11C]SCH23390 uptake ratio against mid scan time for a patient with Parkinson's disease (woman aged 62). The ratio approach a plateau 30 minutes after the [11C]SCH23390 injection. The average value of the ratios during the time interval of 30 to 60 minutes was used as an index of D1 receptor binding.

pixels (12·0 mm) was placed on the head of the caudate, and two circular ROI with a diameter of 8 pixels were aligned along the axis of the putamen for each hemisphere. One circular ROI with a diameter of 14 pixels (21·0 mm) was placed over the occipital cortex of each hemisphere. Two sections optimum for cerebellum were selected and one circular ROI with a diameter of 14 pixels was placed over each cerebellar hemisphere in each section. ROIs were determined by inspection with reference to the corresponding brain CT scan and the brain atlas of Matsui and Hirano.[26] Average values for each
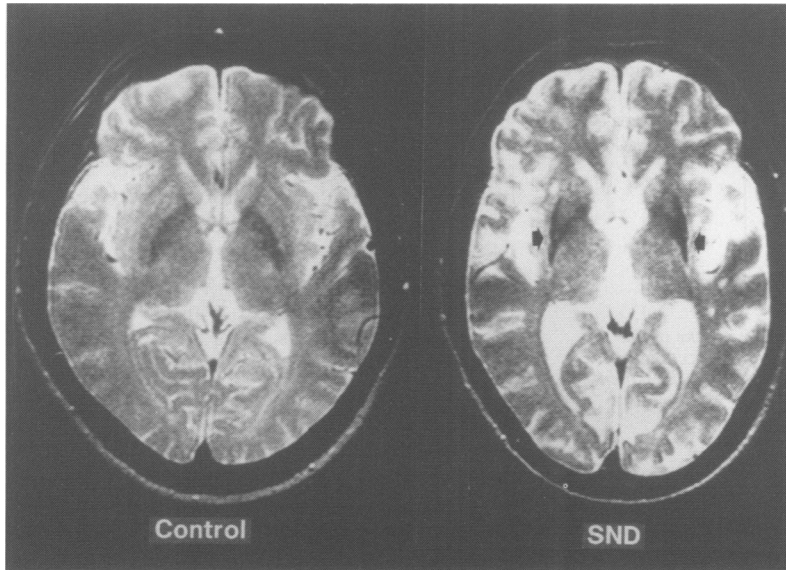

Figure 2   T2-weighted MRI (TR/TE 2500/80 ms, 1·5 tesla, 5 mm thickness) of a healthy volunteer (man aged 58, the left image) and of a patient with striatonigral degeneration (patient 16, the right image). Arrows indicate an abnormal decrease in signal intensity in the putamen of the SND patient. The right side of the head is on the left.
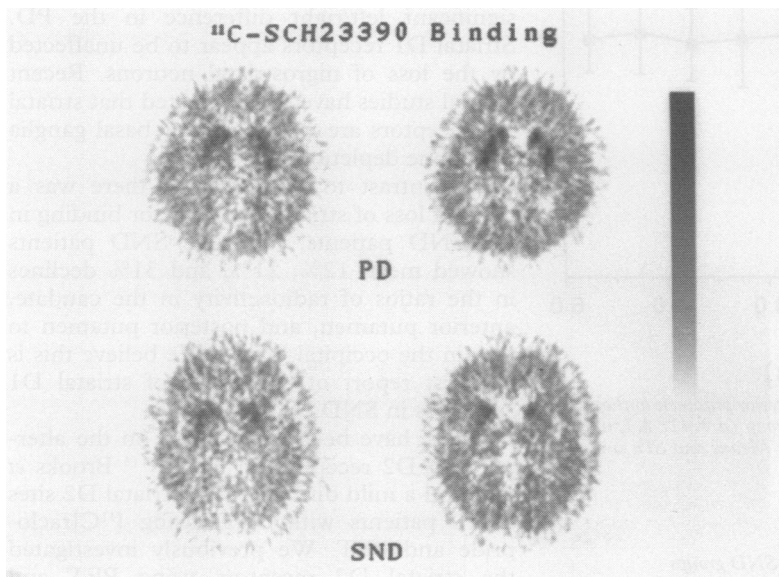

Figure 3   Integrated PET images of striatal [¹¹C]SCH23390 binding at two axial levels, 45 and 53 mm above and parallel to the orbitomeatal line, in a patient with PD (patient 5), and a patient with SND (patient 16), obtained 30 to 60 minutes after [¹¹C]SCH23390 injection. There is a high accumulation of ¹¹C in the caudate and putamen of the PD patient, but a marked decrease in ¹¹C in the striatum of the SND patient, especially in the dorsal and posterior putamen. These images are normalised to the radioactivity in the occipital cortex. The right side of the head is on the left.

anatomical structure over the two optimum sections were then calculated from the individual ROI data.

A regional time activity curve was obtained following correction for carbon-11 decay, and the ratios of radioactivity in each striatal ROI to that in the cerebellum (St/Cbl) and to that in the occipital cortex (St/Ctx) were calculated. Since both the St/Cbl ratio and the St/Ctx ratio reached a plateau 30 minutes after the injection, suggesting that a pseudoequilibrium of D1 receptor binding was achieved, the average values of the St/Cbl ratio and St/Ctx ratio during the time interval of 30 to 60 minutes were used as indices of D1 receptor binding (fig 1). The St/Ctx ratios were 11% to 19% lower than the St/Cbl ratios in the controls owing to the small amount of specific binding of [¹¹C]SCH23390 in the cerebral cortex.[27]

The cerebellum has virtually no dopamine D1 receptors[27] and is an ideal tissue to estimate non-specific striatal tracer binding. However, in this study there was mild to moderate cerebellar atrophy in SND patients, which might be considered to affect the uptake of carbon-11 in the cerebellum of those patients. Therefore, only the St/Ctx ratios are shown below.

The St/Ctx ratios for the patients with SND were compared with those from patients with PD and normal controls by using Mann-Whitney U tests, with the Bonferroni correction for multiple comparison.[28] A correlation analysis of the duration of illness, the locomotor disability, and the abnormal MRI findings with the St/Ctx ratios was performed.

Results

MRI

The measured width of the pars compacta signal in all PD and SND patients was narrower than 1 SD of the mean control values (n = 10, mean (SD) 4·3 (0·6) mm) (table 1).[29] T2-weighted MRI showed an abnormal prominence of signal hypointensity in the bilateral putamen in two of the five SND patients (fig 2), but no obvious atrophy of the striatum was noted in the SND patients. No abnormal findings were noted in the putamen of the PD patients.

PET

There was rather uniform distribution of carbon-11 in the caudate head, and putamen in the controls and PD patients following [¹¹C]SCH23390 injection (fig 3).

The mean ratios of radioactivity of the caudate, anterior putamen, and posterior putamen to that of the occipital cortex in the PD group were similar to the control values (figs 4, 5, table 2). No significant left/right difference was noted in the PD, when carbon-11 accumulation in the striatum contralateral to the predominant side of the Parkinsonian symptoms was compared with that in the opposite striatum. The St/Ctx ratios between the untreated (patients 1—5) and the treated

PD patients (patients 6—11) were similar (fig 4). In the PD patients there was no significant correlation between these ratios and the locomotor disability, between the ratios and the duration of illness, or between the ratios and the measured width of pars compacta by MRI.

In contrast to the PD patients, in the SND patients a significant decrease in carbon-11 accumulation in the striatum, especially in
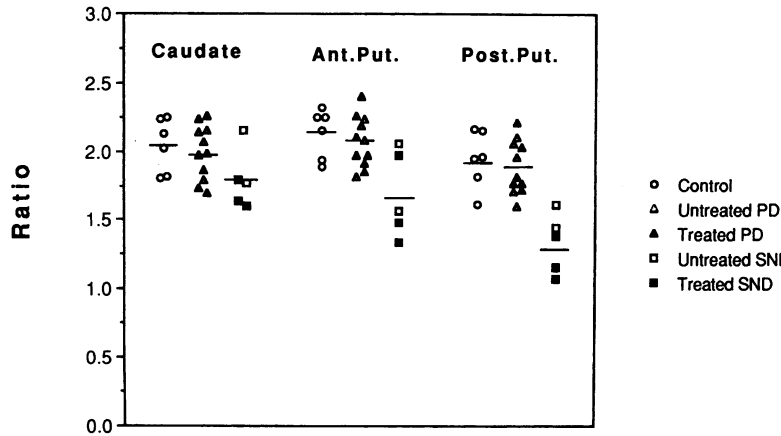

Figure 4   Scattergram showing individual ratios of [¹¹C]SCH23390 uptake in the caudate to that in the occipital cortex, the anterior putamen to that in the occipital cortex, and the posterior putamen to that in the occipital cortex for the normal controls, patients with PD, patients with SND.
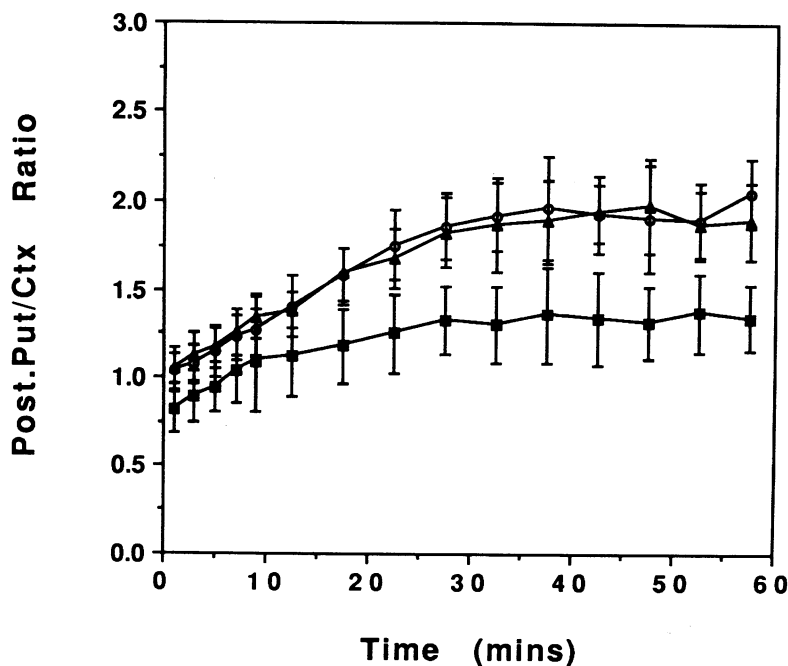

Time (mins)

Figure 5   Time course of the ratio of the radioactivity in the posterior putamen to that in the occipital cortex in the control group (n = 6; O), in the PD group (n = 11; ▲), and the SND group (n = 5; ■) following [¹¹C]SCH23390 injection. Means and SDs are shown.

Table 2   [¹¹C]SCH23390 uptake ratios in the control, PD and SND groups

Group (n)	Caudate/Cortex Mean (SD)	Ant putamen/cortex Mean (SD)	Post putamen/cortex Mean (SD)
Controls (6)	2·04 (0·20)	2·13 (0·18)	1·94 (0·21)
PD (11)	1·99 (0·20)	2·07 (0·18)	1·89 (0·19)
SND (5)	1·82 (0·29)	1·72 (0·38)	1·36 (0·25)ᵃᵇ

ᵃp < 0·05 compared with normal control (Bonferroni statistics, n = 3).
ᵇp < 0·01 compared with PD (Bonferroni statistics, n = 3).

the dorsal posterior putamen was noted (fig 3). The St/Ctx ratios in the SND group were lower than those in the control and PD groups. These ratios were the lowest in the posterior putamen among the three regions in the striatum of the SND patients (figs 4, 5, table 2). There was a trend for the ratios in the posterior putamen to decrease in the SND patients with the advance in locomotor disability. In the SND patients there was no correlation between the St/Ctx ratios and the measured width of pars compacta or between the ratios and the abnormal hypointensity of putamen in MRI.

The analysis of the St/Cbl ratios produced similar results to that of the St/Ctx ratios (data not shown).

Discussion

The present PET findings suggest that there is no significant alteration of striatal D1 receptor binding in the PD patients. No significant difference was found between the St/Ctx ratios in the untreated and the treated PD patients. These results indicated that striatal D1 receptor binding is not upregulated in the untreated PD, and it is not downregulated by the treatment with anti-Parkinsonian drugs including levadopa in the PD patients.

In in vitro studies, some reports have proposed the upregulation of D1 receptors in PD,[3 7] especially in untreated PD,[4] while other reports claim that there is no alteration of D1 receptors in PD.[5 6 8] Rinne and co-workers investigated D1 receptors in five untreated, early PD patients using PET and [¹¹C]SCH23390.[10] They found no left/right difference in D1 receptor binding in spite of asymmetrical symptoms in these patients, suggesting that there is no denervation hypersensitivity of D1 receptors in these patients. Likewise, in the present study there was no significant left/right difference in the PD. Striatal D1 receptors appear to be unaffected by the loss of nigrostriatal neurons. Recent animal studies have demonstrated that striatal D1 receptors are not altered by basal ganglia dopamine depletion.[30 31]

In contrast to PD patients, there was a marked loss of striatal D1 receptor binding in the SND patients. The five SND patients showed mean 12%, 21%, and 31% declines in the ratios of radioactivity in the caudate, anterior putamen, and posterior putamen to that in the occipital cortex. We believe this is the first report of the status of striatal D1 receptors in SND.

There have been few reports on the alteration of D2 receptors in SND.[13-16] Brooks et al found a mild diffuse loss of striatal D2 sites in 10 patients with SND using [¹¹C]raclopride and PET. We previously investigated the striatal D2 receptors using PET and [¹¹C]N-methylspiperone, and found that there is a marked loss of striatal D2 receptors, especially in the posterior putamen in SND patients.[13] The present study demonstrated that the distribution of the loss of D1 receptors was similar to the pattern of D2 receptor

loss in SND in our previous study. Based on a pathological study of SND it was proposed that striatal involvement starts dorsally in the posterior two thirds and as it progresses, it spreads ventrally and anteriorly in a dorsolateral manner.[32] The distribution of the loss of dopamine receptors in the present study corresponded to the pattern of striatal involvement in SND. Thus we can conclude that the striatal D1 receptors are located on the striatal neurons which degenerate in SND. It has been reported that striatal D1 receptors are not modified in progressive supranuclear palsy (PSP) patients despite the loss of striatal D2 receptors.[8] The subpopulation of striatal neurons affected must differ between SND and PSP.

Although the precise functional roles of D1 receptors remain unknown, it has been postulated that D1 receptor activation is required for postsynaptic expression of D2 agonist effects.[33] Therefore, the inefficiency of levadopa in SND might be due to the loss of striatal D1 receptors as well as to the loss of striatal D2 receptors.

It is difficult to diagnose SND with certainty, especially when SND is not associated with pontocerebellar atrophy. MRI may disclose the abnormal hypointensity in the putamen,[34] but only half of the present SND patients showed this abnormality. The width of the pars compacta signal was narrow in the SND patients as well as in the PD patients in this study. These results suggest that it is not possible to differentiate all SND patients from PD patients by MRI.

PET shows a uniform decrease of [18F]fluorodopa uptake in the striatum in multiple system atrophy (MSA) patients, whereas a prominent decrease of [18F] fluorodopa in the putamen with relative sparing of caudate function has been observed by PET in PD patients.[35 36] But it was also reported that some MSA patients show a pattern similar to that in PD patients;[35] thus this technique could not differentiate all SND patients from PD patients.

PET discloses a considerably decreased glucose utilisation (20·5%) in the striatum of SND patients,[37] whereas glucose utilisation in the striatum of PD patients is normal.[36] Thus PET with [18F]fluorodeoxyglucose (FDG) is a useful tool for the differential diagnosis between SND and PD. However, imaging of dopamine receptors with PET seems superior to PET/FDG for the differential diagnosis of SND and PD, because the radioligand selectively accumulates in the striatum and even the early SND patients (patients 12 and 13) showed a significant decrease of [11C]SCH23390 binding in the posterior putamen. Although further studies are required to determine the selectivity of these abnormal findings in SND using PET, this technique might prove useful for the differential diagnosis of PD and SND.

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