The dopamine D_2 receptor ligand ^{18}F-desmethoxyfallypride: an appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism

Mathias Schreckenberger[1], Stefan Hägele[2], Thomas Siessmeier[1], Hans-Georg Buchholz[1], Heike Armbrust-Henrich[1], Frank Rösch[3], Gerhard Gründer[4], Peter Bartenstein[1], Thomas Vogt[2]

[1] Department of Nuclear Medicine, Johannes Gutenberg-University Mainz, Mainz, Germany
[2] Department of Neurology, Johannes Gutenberg-University Mainz, Germany
[3] Institute of Nuclear Chemistry, Johannes Gutenberg-University Mainz, Germany
[4] Department of Psychiatry, Johannes Gutenberg-University Mainz, Germany

Received: 8 October 2003 / Accepted: 30 December 2003 / Published online: 23 March 2004

Abstract. For therapeutic and prognostic reasons it is important to differentiate between idiopathic parkinsonian syndrome (IPS, Parkinson's disease) and atypical parkinsonian syndromes (APS) like multiple system atrophy or progressive supranuclear palsy. Whereas IPS patients usually show a normal or upregulated postsynaptic dopamine D_2 receptor profile, APS patients present decreased postsynaptic tracer binding. The aim of this prospective study was to evaluate the D_2 receptor antagonist fluorine-18 desmethoxyfallypride (^{18}F-DMFP), a recently developed positron emission tomography (PET) tracer with better clinical availability than carbon-11 raclopride, for the differential diagnosis of IPS versus APS. The study included 16 healthy control subjects and 35 patients with clinically diagnosed parkinsonism (16 IPS patients, 19 APS patients). All patients underwent PET imaging after injection of 180–200 MBq ^{18}F-DMFP. Receiver operating characteristic (ROC) analyses were performed in order to assess the diagnostic performance of ^{18}F-DMFP PET. We found the striatal ^{18}F-DMFP uptake ratio to be significantly (P<0.01) reduced in the APS patients (2.44±0.42) compared with the healthy control subjects (3.61±0.43) and the IPS patients (3.21±0.78), whereas the uptake ratios of the IPS patients and the control subjects did not differ significantly. For the differential diagnosis of APS versus IPS, the ROC analysis of caudate ^{18}F-DMFP binding showed a specificity, sensitivity and accuracy of 100%, 74% and 86%, respectively, as well as positive and negative predictive values of 100% and 76%, respectively. Based on these first clinical results, we consider ^{18}F-DMFP to be an appropriate PET tracer for the differential diagnosis of parkinsonian syndromes, with the advantage of better clinical availability than ^{11}C-labelled D_2 radioligands.

Keywords: Parkinsonism – Dopamine receptor – PET – ^{18}F-desmethoxyfallypride – ROC analysis

Eur J Nucl Med Mol Imaging (2004) 31:1128–1135
DOI 10.1007/s00259-004-1465-5

Mathias Schreckenberger (✉)
Department of Nuclear Medicine,
Johannes Gutenberg-University Mainz, 55101 Mainz, Germany
e-mail: schreckenberger@nuklear.klinik.uni-mainz.de
Tel.: +49-6131-172901, Fax: +49-6131-172386

Introduction

Parkinsonism is characterised by a pathological dopaminergic transmission in the striatum that can be examined in vivo by means of functional imaging using pre- and postsynaptic radiotracers [1]. The typical finding of a reduced striatal uptake of fluorine-18 DOPA or labelled cocaine derivatives is a reliable criterion to distinguish patients with parkinsonism from healthy subjects or patients with essential tremor [2, 3] or from other forms of parkinsonism not characterised by the loss of pre-synaptic dopaminergic cells (e.g. psychogenic parkinsonism or drug-induced postsynaptic parkinsonism [4]). For therapeutic and prognostic reasons it seems necessary to differentiate between idiopathic parkinsonian syndrome (Parkinson's disease) and atypical parkinsonian syndromes due to other neurodegenerative diseases such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or corticobasal degeneration [5, 6]. Although clinical criteria have been defined for the purpose of differential diagnosis, neuropathological post-mortem studies have shown that approximately 20% of clinically diagnosed Parkinson's disease patients have had an atypical parkinsonian syndrome due to another neurodegenerative disease [7].

Whereas functional imaging of the presynaptic striatal neuron using ^{18}F-DOPA or cocaine derivatives does not

Table 1. Pre- and postsynaptic PET and SPECT tracers for investigation of the dopaminergic system

	Parameter	PET	SPECT
Presynaptic	Dopamine storage (dopamine decarboxylase activity)	^{18}F-DOPA	–
	Dopamine re-uptake	^{11}C-nomifensine	^{123}I–FP–CIT
		^{11}C-WIN	^{123}I-β-CIT
			^{99m}Tc-TRODAT
Postsynaptic	D_1 receptor density	^{11}C-SCH23390	–
	D_2 receptor density	^{11}C-raclopride	^{123}I–benzamide (IBZM)
		^{11}C-methylspiperone	
		^{18}F-ethylspiperone	
		^{18}F-desmethoxyfallypride	
		^{18}F-fallypride	

allow reliable differentiation between Parkinson's disease and atypical parkinsonian syndromes [8], imaging of the postsynaptic neuron can help in this differential diagnosis. Patients with Parkinson's disease show a normal or (in the early stage) even an upregulated postsynaptic dopamine D_2 receptor binding profile in positron emission tomography (PET) studies with the ligand carbon-11 raclopride, which binds selectively to D_2-like receptors (D_2 and D_3) [9, 10], or in single-photon emission computerised tomography (SPECT) studies using the selective D_2 receptor radioligand iodine-123 iodobenzamide (IBZM) [11, 12]. In contrast, patients with atypical parkinsonian syndromes typically show reduced striatal ^{11}C-raclopride binding, indicating a decreased postsynaptic D_2 receptor density [10]. Table 1 shows a short survey on the most relevant PET and SPECT tracers for the investigation of the dopaminergic system.

Compared with IBZM SPECT imaging, PET using ^{11}C-raclopride has the significant advantages of depicting striatal structures with considerably better spatial resolution and providing a superior specific to non-specific binding ratio, which enables more precise quantification of postsynaptic D_2 receptors. Because of the short half-life of ^{11}C (20.4 min), the benzamide ^{11}C-raclopride is exclusively available in a few medical centres with an on-site cyclotron. ^{18}F-labelled substituted benzamides offer the advantage of a considerably longer half-life (109.8 min), making them more suitable for PET examinations at greater distances from the centre of tracer synthesis.

First human investigations on the recently developed ^{18}F-fluorinated benzamide ^{18}F-desmethoxyfallypride [((*S*)-*N*[(1-allyl)-2-pyrrolidinyl)methyl]-5-[(3-^{18}F-fluoropropyl)-2-methoxybenzamide: ^{18}F-DMFP] demonstrated that ^{18}F-DMFP is a highly reliable tracer for the PET imaging of dopamine D_2-like receptors, showing a comparable receptor affinity and very similar selectivity to ^{11}C-raclopride [13]. Since there have as yet been no clinical experiences with ^{18}F-DMFP, it was the purpose of this prospective study to investigate the clinical suitability of this PET tracer in the differential diagnosis of patients with parkinsonism.

Materials and methods

Patients. We studied 35 patients with parkinsonism (18 women, 17 men, mean age 64.9±9.1 years, range 43–77 years, median 65 years) and 16 healthy male control subjects (mean age 38.5±9.5 years, range 26–64 years). Ethical approval was obtained for all volunteers and the subjects gave informed written consent.

The patients were recruited by our neurological outpatient department for movement disorders that were diagnosed clinically as either idiopathic parkinsonian syndrome (IPS, Parkinson' s disease; *n*=16) or atypical parkinsonian syndromes (APS, *n*=19). The APS group comprised 15 patients with MSA and four with PSP. The mean value on the UPDRS part III was 31.3 (minimum 1, maximum 81, median 34) and the mean value on the Hoehn & Yahr scale was 2.3 (minimum 0, maximum 5, median 2). The mean value of the duration of disease was 4.0 years (minimum 1, maximum 20, median 2). The clinical diagnosis of IPS was based on the criteria of the Parkinson's Disease Society Brain Bank. In making the clinical diagnosis of MSA or PSP we followed the proposed diagnostic criteria of Gilman et al. for MSA [14] and Litvan et al. [6] for PSP. The patients stopped taking dopaminergic medication at least 48 h before PET imaging in order to avoid postsynaptic receptor blocking by the medication. Patients taking dopamine agonists with a long pharmacological half-life, such as cabergoline, discontinued the medication for at least 5 days before the PET examination.

Tracer synthesis. ^{18}F-DMFP was synthesised via direct fluorination of a tosylated precursor, ((*S*)-*N*-[(1-allyl)-2-pyrrolidinyl)methyl]-5-(3-toluenesulfonyloxy-propyl)-2-methoxybenzamide. The synthesis of the labelling precursor was performed according to a method described in the literature [15, 16]. Modifications of the published method led to a fourfold increase in the yield of the labelling precursor and simultaneously simplified the purification [17]. For routine synthesis, the ^{18}F-fluoride was delivered from other cyclotron centres with transport periods ranging from 2 to 4 h. The reaction mixture was heated for 20 min at 85°C, diluted with 1 ml phosphoric acid (10%) and separated using high-performance liquid chromatography (HPLC) (250×10, RP8, CH_3CN: 0.25 mol/l ammonium acetate buffer + 5 ml acetic acid/l 30:70, 5 ml/min) using an automatic synthesis module. The fraction containing ^{18}F-DMFP was isolated, diluted with 0.15 mol/l disodium hydrogen phosphate buffer and adsorbed on a C18 cartridge to remove the HPLC solvent. The column was washed with 2 ml water and eluted with 1 ml ethanol. The eluate was diluted with 9 ml of an isotonic NaCl solution and sterilised by filtration.

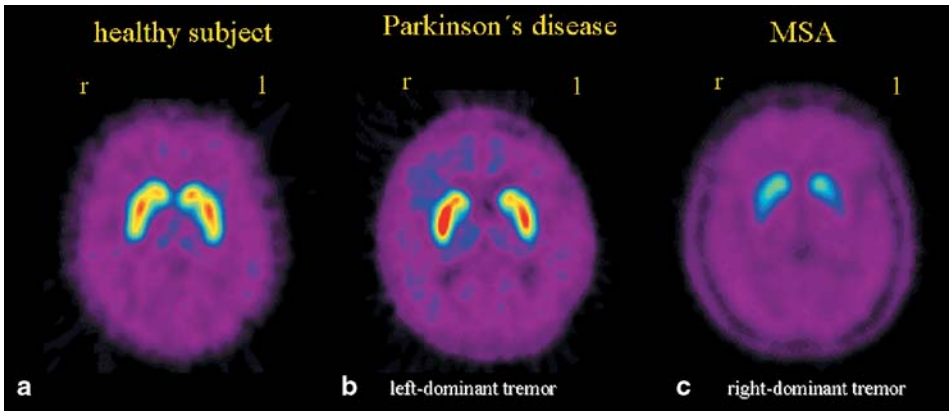

Fig. 1. The *left-hand image* shows normal striatal ^{18}F-DMFP binding in a healthy control subject. In the *middle image* of a dopanaïve IPS patient with clinically left-dominant tremor, there is slight (compensatory) increase in striatal tracer uptake, which is dominant in the right striatum. The *right-hand image* is of a patient suffering from MSA with clinically right-dominant tremor. The striatal tracer uptake is considerably decreased, with the lowest uptake in the left striatum

Average effective overall yields of the synthesis are 32%±4% (uncorrected for radioactive decay), corresponding to an average decay-corrected yield of 60%.

Before injection, quality was controlled, which included determination of chemical and radiochemical purity, specific activity, pH and absence of pyrogens. The specific activity ranged between 100 and 800 GBq/μmol. The volume of ^{18}F-DMFP injected as an ethanol:water mixture (1:9) was 5±1 ml. For the injected activity of 190±10 MBq ^{18}F-DMFP, the injected tracer mass for all studies was <1 μg. Therefore, it can be assumed that there was no relevant receptor occupation in any of the studies.

Data acquisition. Images were acquired on a Siemens ECAT EXACT PET scanner. The camera has a field of view of 16.2 cm in 47 planes with a plane spacing of 3.375 mm, an axial resolution of 4.6 mm full-width at half-maximum and an in-plane resolution of 6.0 mm (resolution in centre with scanner in three-dimensional mode). A mean of 190±10 MBq ^{18}F-DMFP was injected intravenously as a bolus into a cubital vein over approximately 30 s. The acquisition started 60 min after the tracer injection and comprised a series of 3×10-min frames in three-dimensional acquisition mode. Image data reconstruction was performed using filtered back-projection with a 4.0-mm Hamming filter in 128×128 matrix. After mathematical attenuation correction, transverse sections were resliced parallel to the canthomeatal line.

PET data analysis. Three experienced nuclear medicine physicians, who were blinded to the clinical-neurological diagnosis of the patients, evaluated the PET data visually and quantitatively by means of region of interest (ROI) analysis. Bilateral ROIs were defined in those planes where the respective regions (total striatum and caudate nucleus and putamen separately) have maximal areas. An additional cerebellar ROI was defined and designated as a reference region, because it is generally considered to be nearly free of dopamine receptors [13]. ROI templates based on the transverse PET slices of the normal control subjects were adapted to the patient PET data. With a pixel size of 2.0 mm, the caudate ROI had 21 pixels, the putamen ROI, 59 pixels and the cerebellar ROI, 3×250 pixels. Caudate/cerebellum, putamen/cerebellum and striatum/cerebellum uptake ratios were calculated to assess semi-quantitatively the specific binding of the tracer to striatal D_2 receptors.

Statistical analysis. Statistical analysis was performed using the SPSS software package. The differences in the striatum/cerebellum uptake ratio were calculated using the unpaired *t* test for the comparisons between normal controls and IPS patients, normal controls and APS patients, and IPS patients and APS patients. For the correlations between the ^{18}F-DMFP uptake ratios in the caudate nucleus and the putamen in IPS and APS patients, the correlation coefficients according to Spearman were calculated. In order to determine the differential diagnostic performance of ^{18}F-DMFP PET, a receiver operating characteristic (ROC) curve analysis [18, 19] was performed to assess specificity, sensitivity and accuracy of caudate and putaminal ^{18}F-DMFP uptake ratios for the diagnosis of APS. Based on the results of the ROC analysis, the positive and negative predictive values of ^{18}F-DMFP PET were calculated for the threshold point of 100% specificity.

Results

Visual image analysis of the striatal ^{18}F-DMFP uptake showed good spatial discrimination between caudate nucleus and putamen, and striatal tracer uptake was clearly reduced in the APS patients compared with the normal controls and the IPS patients. There were no visually detectable differences in striatal tracer binding between IPS patients and the normal control subjects. Typical examples for the different striatal tracer uptake in healthy subjects, IPS and APS patients are shown in Fig. 1.

Figure 2 demonstrates the PET findings of a patient with right-sided rigor and considerably reduced ^{18}F-DOPA uptake in the left striatum. Based on these presynaptic findings and the equivocal results of the apomorphine test, definite diagnosis of IPS or APS was not possible. ^{18}F-DMFP PET examination of the postsynaptic neuron revealed slightly increased tracer uptake in the left striatum and normal uptake in the right striatum, indicating a (compensatory) receptor upregulation on the side of reduced synaptic dopamine concentration. The result of the ^{18}F-DMFP PET examination led to the diagnosis of IPS, which was clinically confirmed by the further course of the disease.

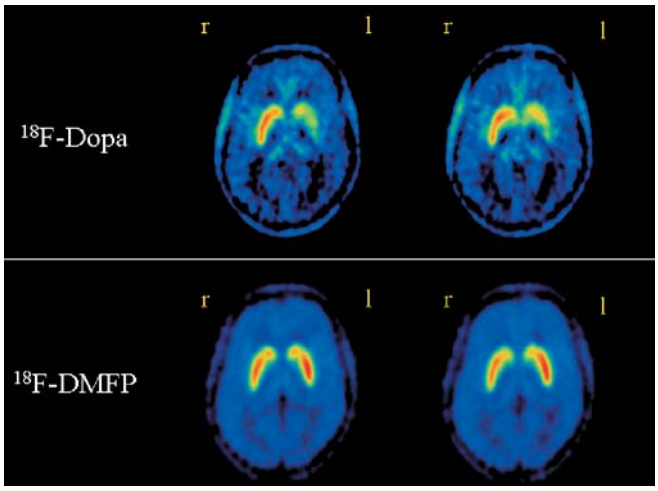

Fig. 2. Combined pre- (*upper row*) and postsynaptic (*lower row*) PET examination of a patient with suspected parkinsonism suffering from a right-dominant rigor. The ^{18}F-DOPA scan reveals considerably reduced tracer uptake in the left striatum (particularly in the putamen) and normal uptake in the right putamen, whereas the ^{18}F-DMFP scan shows normal tracer uptake in the right putamen and slightly increased uptake in the left putamen as typical findings for dopa-naïve IPS (Parkinson's disease) patient

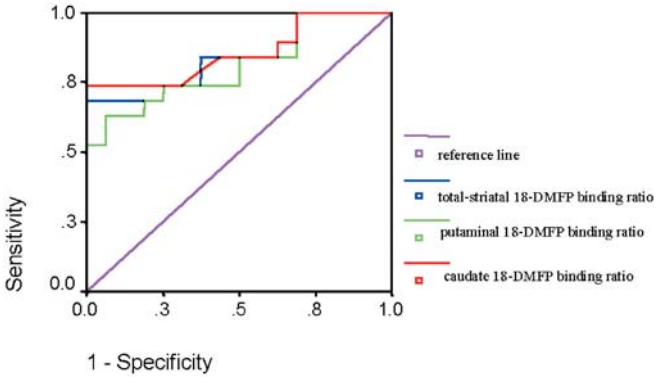

Fig. 3. ROC curves for the ^{18}F-DMFP binding ratios in the total striatum, the caudate nucleus and the putamen. The *left-hand part* of the curves (representing high sensitivity and specificity) is highest for the caudate tracer binding ratio (*red curve*)

Quantitative analysis of the ^{18}F-DMFP uptake ratios revealed significantly (P<0.01) reduced ratios in the APS patients compared with the normal subjects and the IPS patients for the total striatum, as well as separately for the caudate nucleus and the putamen. Although the mean ^{18}F-DMFP binding in the caudate nucleus, putamen and total striatum was slightly higher in the controls than in the IPS patients, the difference was not significant.

The mean caudate uptake ratio in APS patients was 2.32±0.38 (range 1.81–3.01), compared with 3.46±0.42 (range 2.86–4.25) in control subjects and 3.07±0.70 (range 2.53–5.21) in IPS patients. The mean uptake ratio in the putamen in APS patients was 2.53±0.53 (range 1.46–3.39) compared with 3.70±0.47 (range 3.10–4.72) in normal controls and 3.29±0.86 (range 2.58–6.01) in IPS patients. The mean uptake ratio in the total striatum in APS patients was 2.44±0.42 (range 1.83–3.19), compared with 3.61±0.43 (range 2.98–4.50) in normal controls and 3.21±0.78 (range 2.63–5.61) in IPS patients. Table 2 shows the mean uptake ratios and the corresponding clinical diagnosis for each of the 35 patients.

The correlation analysis of the caudate to the putaminal ^{18}F-DMFP uptake within the normal controls and within the IPS group and the APS group revealed significant (P<0.001) correlations between the two striatal structures for each group (normal controls: r=0.944; IPS patients: r=0.82; APS patients: r=0.81).

The results of the ROC analysis performed to assess the diagnostic accuracy of ^{18}F-DMFP imaging for the differential diagnosis of APS versus IPS are shown in Tables 3, 4 and 5 and in Fig. 3. The areas under the curve for

Table 2. ^{18}F-DMFP uptake ratios for the caudate nucleus, the putamen and the total striatum in IPS (n=16) and APS (n=19) patients

Patient no.	Caudate nucleus	Putamen	Total striatum	Clinical diagnosis
1	2.75	3.09	2.92	IPS
2	2.72	2.90	2.85	IPS
3	3.40	3.66	3.76	IPS
4	3.55	3.66	3.69	IPS
5	2.53	2.81	2.67	IPS
6	2.58	2.68	2.63	IPS
7	2.80	2.85	2.86	IPS
8	2.64	2.76	2.75	IPS
9	2.55	2.72	2.65	IPS
10	3.47	3.93	3.70	IPS
11	2.54	2.87	2.72	IPS
12	2.77	2.58	2.69	IPS
13	2.83	3.01	2.93	IPS
14	5.21	6.01	5.61	IPS
15	3.82	4.05	3.93	IPS
16	2.90	3.13	3.04	IPS
17	2.00	2.01	2.05	APS
18	2.27	2.63	2.47	APS
19	2.75	2.80	2.81	APS
20	2.21	2.73	2.49	APS
21	1.89	2.19	2.06	APS
22	2.94	3.39	3.19	APS
23	2.11	1.65	1.98	APS
24	2.11	2.43	2.33	APS
25	1.90	2.37	2.15	APS
26	2.46	2.96	2.71	APS
27	1.93	2.59	2.29	APS
28	2.72	2.94	2.83	APS
29	2.23	2.19	2.23	APS
30	3.01	3.35	3.19	APS
31	2.26	2.48	2.37	APS
32	2.33	2.55	2.46	APS
33	2.88	3.22	3.05	APS
34	1.81	2.03	1.95	APS
35	2.20	1.46	1.83	APS

Table 3. ROC analysis of the ^{18}F-DMFP uptake ratios of the caudate nucleus for the diagnosis of APS

Threshold value	Sensitivity	1–Specificity
0.810	0.000	0.000
1.850	0.053	0.000
1.895	0.105	0.000
1.915	0.158	0.000
1.965	0.211	0.000
2.055	0.263	0.000
2.155	0.368	0.000
2.205	0.421	0.000
2.220	0.474	0.000
2.245	0.526	0.000
2.265	0.579	0.000
2.300	0.632	0.000
2.395	0.684	0.000
2.495	0.737	0.000
2.535	0.737	0.063
2.545	0.737	0.125
2.565	0.737	0.188
2.610	0.737	0.250
2.680	0.737	0.313
2.735	0.789	0.375
2.760	0.842	0.438
2.785	0.842	0.500
2.815	0.842	0.563
2.855	0.842	0.625
2.890	0.895	0.625
2.920	0.895	0.688
2.975	0.947	0.688
3.205	1.000	0.688
3.435	1.000	0.750
3.510	1.000	0.813
3.685	1.000	0.875
4.515	1.000	0.938
6.210	1.000	1.000

Table 4. ROC analysis of the ^{18}F-DMFP uptake ratios of the putamen for the diagnosis of APS

Threshold value	Sensitivity	1–Specificity
0.460	0.000	0.000
1.555	0.053	0.000
1.830	0.105	0.000
2.020	0.158	0.000
2.110	0.211	0.000
2.280	0.316	0.000
2.400	0.368	0.000
2.455	0.421	0.000
2.515	0.474	0.000
2.565	0.526	0.000
2.585	0.526	0.063
2.610	0.579	0.063
2.655	0.632	0.063
2.700	0.632	0.125
2.725	0.632	0.188
2.745	0.684	0.188
2.780	0.684	0.250
2.805	0.737	0.250
2.830	0.737	0.313
2.860	0.737	0.375
2.885	0.737	0.438
2.920	0.737	0.500
2.950	0.789	0.500
2.985	0.842	0.500
3.050	0.842	0.563
3.110	0.842	0.625
3.175	0.842	0.688
3.285	0.895	0.688
3.370	0.947	0.688
3.525	1.000	0.688
3.795	1.000	0.813
3.990	1.000	0.875
5.030	1.000	0.938
7.010	1.000	1.000

the caudate, the putaminal and the total striatal uptake ratios were 0.86±0.07, 0.81±0.07 and 0.84±0.07, respectively. The difference between the areas for the caudate and the putaminal ^{18}F-DMFP uptake ratio were significant (P<0.05). Based on these results, we found for a threshold value of 2.495 (caudate uptake ratio) a specificity, sensitivity and accuracy of 100%, 74% and 86%, respectively. Using this threshold, the positive and negative predictive values for the diagnosis of APS were 100% and 76%.

Discussion

The differential diagnosis of Parkinson's disease (IPS) versus atypical parkinsonian syndromes (APS) is clinically important for therapeutic and particularly prognostic reasons. In contrast to IPS patients, APS patients do not benefit significantly from L-DOPA therapy, and they usually have a worse prognosis [20, 21]. Since there remains uncertainty over this differential diagnosis, especially in the cases of "possible" MSA [5], functional imaging of the postsynaptic neuronal integrity could support the selection of suitable patients for experimental (neuroprotective) therapies or stereotaxic surgery [8].

It is well known from autoradiographic findings [22], as well as PET [23] and SPECT [24] studies using dopamine D_2 receptor ligands, that, compared with IPS patients and healthy controls, APS patients show reduced postsynaptic tracer binding, indicating a decreased receptor density due to neuronal cell loss. For the functional imaging of postsynaptic D_2 receptors, the iodinated benzamide (*S*)-2-hydroxy-3-[^{123}I]iodo-6-methoxy-*N*-[(1-ethyl-2-pyrrolidonyl)-methyl]benzamide (IBZM) was first presented by Kung et al. [25, 26] as a new radioligand for SPECT imaging. In the following years, the clinical use of IBZM SPECT in patients with parkinsonism was well documented by numerous prospective studies [11, 12, 27].

Table 5. ROC analysis of the ^{18}F-DMFP uptake ratios of the total striatum for the diagnosis of APS

Threshold value	Sensitivity	1–Specificity
0.830	0.000	0.000
1.890	0.053	0.000
1.965	0.105	0.000
2.015	0.158	0.000
2.055	0.211	0.000
2.105	0.263	0.000
2.190	0.316	0.000
2.260	0.368	0.000
2.310	0.421	0.000
2.350	0.474	0.000
2.415	0.526	0.000
2.465	0.579	0.000
2.480	0.632	0.000
2.560	0.684	0.000
2.640	0.684	0.063
2.660	0.684	0.125
2.680	0.684	0.188
2.700	0.684	0.250
2.715	0.737	0.250
2.735	0.737	0.313
2.780	0.737	0.375
2.820	0.789	0.375
2.840	0.842	0.375
2.855	0.842	0.438
2.890	0.842	0.500
2.925	0.842	0.563
2.985	0.842	0.625
3.045	0.842	0.688
3.120	0.895	0.688
3.440	1.000	0.688
3.695	1.000	0.750
3.730	1.000	0.813
3.845	1.000	0.875
4.770	1.000	0.938
6.610	1.000	1.000

Since PET imaging provides a more precise quantification of striatal receptor binding owing to its superior imaging properties, the use of positron-emitting radionuclides labelled to appropriate ligands should enable better diagnostic discrimination between IPS and APS patients and should facilitate the diagnosis of early APS stages, especially when ligands are used with higher affinity to D_2-like receptors and with lower unspecific binding. Nevertheless, in a clinical setting, the benzamide SPECT tracer IBZM has been well established compared with PET tracers such as ^{11}C-raclopride or ^{11}C-methylspiperone and is much more widely available clinically owing to the more "appropriate" ^{123}I half-life of 13 h.

In this context, an ^{18}F-fluorinated dopamine D_2 receptor ligand with binding properties similar to those of ^{11}C-raclopride could be very attractive for the differential diagnosis of parkinsonism. The advantages of PET imaging are combined with an isotope half-life that permits distribution from a central cyclotron to satellite hospitals, as exemplified by the use of ^{18}F-fluorodeoxyglucose over a period of many years. Benzamide derivatives are preferable to fluorinated spiperone derivatives like ^{18}F-spiperone, because spiperone derivatives generally show a relatively non-selective binding profile [28]. It has been previously demonstrated in non-human primate studies that 74% of putaminal ^{18}F-spiperone binding is to dopamine D_2-like receptors and 26% to serotonergic S2 receptors [29].

First investigations into the quantification of human dopamine receptors with the new radioligand ^{18}F-DMFP [13], the use of which was initially described in monkeys by Mukherjee et al. [30], revealed that ^{18}F-DMFP has a very similar binding profile to ^{11}C-raclopride. Therefore, ^{18}F-DMFP could be an ideal tracer for the examination of movement disorders, especially given that it shows a considerably higher signal to noise ratio than IBZM. Gründer et al. [13] demonstrated by means of invasive and non-invasive analytic methods that striatal dopamine D_2 receptor quantification with ^{18}F-DMFP can be performed using non-invasive approaches with reference regions in the cerebellum. For diagnostic purposes ^{18}F-DMFP is also preferable to ^{18}F-labelled fallypride, a D_2 receptor ligand with higher affinity, which is suitable for imaging extrastriatal dopamine receptors [31]. Because of the slow pharmacokinetics of ^{18}F-fallypride, imaging has to be extended to 3–4 h, which is not practical in a clinical setting.

Since there are still no data on the suitability of ^{18}F-DMFP in the diagnosis of parkinsonism, it was the purpose of this prospective study to investigate the diagnostic performance of ^{18}F-DMFP in patients with different forms of parkinsonism (IPS and APS) compared with healthy subjects. As shown in Fig. 1, the striatal ^{18}F-DMFP uptake 60 min post injection shows a high specific to non-specific binding ratio (of approximately 3.6 in normals, compared with approximately 1.5–1.8 reported for IBZM), enabling definite discrimination between the caudate nucleus and putamen, which is usually difficult using IBZM SPECT imaging. The better spatial resolution and higher specific to non-specific binding ratio might allow assessment of subtle changes, such as the upregulation of putaminal receptor binding in IPS, as shown in Fig. 1. Although the normal control subjects were somewhat younger than the patients, they showed no visual or quantitatively significant differences in striatal tracer binding compared with the IPS patients. In contrast, in most of the APS patients the visual image analysis revealed an unequivocal reduction in striatal tracer uptake.

With regard to the interpretation of ROC analyses, it is important to note that the diagnostic validity of a test is generally better, the higher the area under the curve and the higher the left-hand part of the curve [18, 19]. In our patient study group, caudate ^{18}F-DMFP binding showed a higher area under the curve (0.86±0.07) com-

pared with the putamen (0.81±0.07). Furthermore, from Fig. 3 it is evident that the left-hand part of the caudate ROC curve is higher than the corresponding part of the putaminal curve. Both parameters thus indicate that the caudate ^{18}F-DMFP binding enables better diagnostic discrimination between IPS and APS patients than the putaminal tracer uptake. This finding seems surprising given that in the majority of studies the most prominent reduction in D_2 ligand binding in APS patients has been reported to occur in the putamen [23]. In contrast, different findings in PSP patients are reported. Sasaki et al. found a decreased striatal radioligand binding with an increased putamen to caudate ratio [32]. At least some of the MSA patients presented by Antonini et al. [8] showed a putamen to caudate ratio >1, indicating a predominant involvement of the caudate nucleus. Therefore, our results showing the caudate uptake ratio to be the better discriminator for the differential diagnosis of IPS versus APS might be explained by the fact that the APS patient group consisted of subgroups with MSA and PSP. Further studies regarding MSA and PSP patients as separate groups are mandatory to elucidate this aspect.

Based on the above mentioned findings, which we consider as preliminary owing to the limited number of patients (n=35), a threshold value was defined that provided the best compromise between sensitivity and specificity. For a threshold value of 2.495 for caudate to cerebellar uptake, we calculated a specificity, sensitivity and accuracy of 100%, 74% and 86%, respectively, for the differential diagnosis of APS versus IPS (Table 3). Due to the prognostic relevance of the diagnosis of APS, a diagnostic tool should have a high specificity in order to provide a 100% positive predictive value using the calculated threshold of 2.495. In this context, the considerably lower negative predictive value of 76% might be less relevant because, from the neurological-clinical viewpoint, the definite diagnosis of an APS seems clinically more important than the definite exclusion of an APS.

In conclusion, the dopamine D_2 receptor ligand ^{18}F-DMFP seems an appropriate PET tracer for the differential diagnosis of IPS versus APS. It has a very good specific to non-specific binding ratio, providing a high specificity and positive predictive value for the diagnosis of APS. Because of the better availability of this fluorinated benzamide tracer, which has properties similar to ^{11}C-raclopride, clinical PET examinations of patients with parkinsonism are possible with this tracer in centres without an on-site cyclotron. Further clinical investigations to compare ^{18}F-DMFP with the established D_2 receptor SPECT ligand IBZM are required in order to evaluate the potential additional diagnostic benefit provided by ^{18}F-DMFP.

Acknowledgements. Part of this work was supported by the Deutsche Forschungsgemeinschaft (Grant Ba 1011/2–1). The authors wish to thank Dr. M. Piel, S. Höhnemann and S. Maus (Institute of Nuclear Chemistry, Johannes Gutenberg-University Mainz) for tracer synthesis.

References

1. Sawle GV, Playford ED, Brooks DJ, Quinn N, Frackowiak RSJ. Asymmetrical pre-synaptic and post-synaptic changes in the striatal dopamine projections in dopa naïve parkinsonism. Brain 1993; 116:853–867.
2. Tatsch K, Schwarz J, Mozley PD, Linke R, Pogarell O, Oertel WH, Fieber RS, Hahn K, Kung HF. Relationship between clinical features of Parkinson's disease and presynaptic dopamine transporter binding assessed with [^{123}I]IPT and single-photon emission tomography. Eur J Nucl Med 1997; 24:415–421.
3. Brucke T, Djamshidian S, Bencsits G, Pirker W, Asenbaum S, Podreka I. SPECT and PET imaging of the dopaminergic system in Parkinson's disease. J Neurol 2000; 247: Suppl 4:IV/2–7.
4. Booij J, Speelman JD, Horstink MW, Wolters EC. The clinical benefit of imaging striatal dopamine transporters with [^{123}I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. Eur J Nucl Med 2001; 28:266–272.
5. Quinn N. Multiple system atrophy. The nature of the beast. J Neurol Neurosurg Psychiatry 1989; 52 (Suppl):78–89.
6. Litvan I, Campbell G, Mangone CA, et al. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? Brain 1997; 120:65–74.
7. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55:181–184. Comment in: J Neurol Neurosurg Psychiatry 1993; 56:939.
8. Antonini A, Leenders KL, Vontobel P, Maguire RP, Missimer J, Psylla M, Günther I. Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease. Brain 1997; 120:2187–2195.
9. Brooks DJ, Ibanez V, Sawle GV, et al. Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supraneclear palsy, measured measured with [^{11}C]raclopride and positron emission tomography. Ann Neurol 1992; 31:184–192.
10. Kaasinen V, Ruottinen HM, Nagren K, Lehikoinen P, Oikonen V, Rinne J. Upregulation of putaminal dopamine D2 receptors in early Parkinson's disease: a comparative PET study with [^{11}C]raclopride and [^{11}C]n-methylspiperone. J Nucl Med 2000; 41:65–70.
11. Schwarz J, Tatsch K, Arnold G, Gasser T, Trenkwalder C, Kirsch CM, Oertel WH.^{123}I-iodobenzamide-SPECT predicts dopaminergic responsiveness in patients with de novo parkinsonism. Neurology 1992; 42:556–561 [erratum in: Neurology 1992; 42:1028].
12. Tatsch K, Schwarz J, Oertel WH, Kirsch CM. Idiopathic Parkinson syndrome: I-123 IBZM SPECT findings in drug naive and treated patients [abstract]. Eur J Nucl Med 1992; 19:609.
13. Gründer G, Siessmeier T, Piel M, Vernaleken I, Buchholz HG, Zhou Y, Hiemke C, Wong DF, Rösch F, Bartenstein P. Quantification of D2-like dopamine receptors in the human brain with ^{18}F-desmethoxyfallypride. J Nucl Med 2003; 44:109–116 [erratum in: J Nucl Med 2003; 44:145].
14. Gilman SL, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Auton Nerv Syst 1998; 74:189–192.

15. Mukherjee J, Yang ZY, Brown T, et al. Potential anomalies of dopamine D-2 receptor: challenges for non-invasive imaging studies by positron emission tomography. Med Chem Res 1994; 5:174–192.
16. Mukherjee J, Yang ZY, Brown T, Roemer J, Cooper M. ^{18}F-desmethoxyfallypride: a fluorine-18 labeled radiotracer with properties similar to carbon-11 raclopride for PET imaging studies of dopamine D_2 receptors. Life Sci 1996; 59:669–678.
17. Piel M, Schirrmacher R, Hamkens W, Schmitt U, Hiemke C, Gründer G, Rösch F. Improved precursor synthesis and ^{18}F-fluorination of [^{18}F]desmethoxyfallypride. J Labelled Cpd Radiopharm 1999; 42 Suppl 1:381–383.
18. Swets JA. ROC analysis applied to the evaluation of medical imaging techniques. Invest Radiol 1979; 14:109–121.
19. Hanley J, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143:29–36.
20. Litvan I. Recent advances in atypical parkinsonian disorders Curr Opin Neurol 1999; 12:441–446.
21. Poewe W, Wenning G. The differential diagnosis of Parkinson's disease. Eur J Neurol 2002; 9 Suppl 3:23–30.
22. Churchyard A, Donnan GA, Hughes A. Dopa resistance in multiple system atrophy: loss of postsynaptic D2 receptors. Ann Neurol 1993; 34:219–226.
23. Ghaemi M, Hilker R, Rudolf J, Sobesky J, Heiss WD. Differentiating multiple system atrophy from Parkinson's disease: contribution of striatal and midbrain MRI volumetry and multi-tracer PET imaging. J Neurol Neurosurg Psychiatry 2002; 73:517–523.
24. Tissingh G, Booij J, Winogrodzka A, van Royen EA, Wolters EC. IBZM- and CIT-SPECT of the dopaminergic system in parkinsonism. J Neural Transm Suppl 1997; 50:31–37.
25. Kung HF, Pan S, Kung MP, Kasliwal R, Reilly J, Alavi A. In vitro and in vivo evaluation of [^{123}I]IBZM: a potential CNS D-2 dopamine receptor imaging agent. J Nucl Med 1989; 30:88–92.
26. Kung HF, Alavi A, Chang W, et al. In vivo SPECT imaging of CNS D-2 dopamine receptors: initial studies with iodine-123-IBZM in humans. J Nucl Med 1990; 31:573–579.
27. Schwarz J, Tatsch K, Gasser T, Arnold G, Pogarell O, Kunig G, Oertel WH.^{123}I-IBZM binding compared with long-term clinical follow-up in patients with de novo parkinsonism. Mov Disord 1998; 13:16–19.
28. Perlmutter JS, Stambuk MK, Markham J, Black KJ, McGee-Minnich L, Jankovic J, Moerlein SM. Decreased [^{18}F]spiperone binding in putamen in idiopathic focal dystonia. J Neurosci 1997; 17:843–850.
29. Perlmutter J, Moerlein S, Huang D-R, Todd R. Non-steady-state measurement of in vivo radioligand binding with positron emission tomography: specificity analysis and comparison with in vitro binding. J Neurosci 1991; 11:1381–1389.
30. Mukherjee J, Luh KE, Yasillo N, et al. Dopamine D-2 receptors imaged by PET in *Cebus apella* using [^{18}F]benzamide neuroleptic. Eur J Pharmacol 1990; 175:363–364 [published correction appears in Eur J Pharmacol 1990; 187:143].
31. Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, Mantil J. Brain imaging of ^{18}F-fallypride in normal volunteers: blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. Synapse 2002; 46:170–188.
32. Sasaki T, Amano T, Hashimoto J, Itoh Y, Muramatsu K, Kubo A, Fukuuchi Y. SPECT imaging using [^{123}I]beta-CIT and [^{123}I]IBF in extrapyramidal diseases. No To Shinkei 2003; 55:57–64.