Imaging of the dopaminergic neurotransmission system using single-photon emission tomography and positron emission tomography in patients with parkinsonism

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Abstract. Parkinsonism is a feature of a number of neurodegenerative diseases, including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The results of post-mortem studies point to dysfunction of the dopaminergic neurotransmitter system in patients with parkinsonism. Nowadays, by using single-photon emission tomography (SPET) and positron emission tomography (PET) it is possible to visualise both the nigrostriatal dopaminergic neurons and the striatal dopamine D_2 receptors in vivo. Consequently, SPET and PET imaging of elements of the dopaminergic system can play an important role in the diagnosis of several parkinsonian syndromes. This review concentrates on findings of SPET and PET studies of the dopaminergic neurotransmitter system in various parkinsonian syndromes.

Key words: Single-photon emission tomography – Positron emission tomography – Parkinsonism – Dopamine transporter imaging – Dopamine D_2 receptor imaging

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Introduction

Parkinsonism is characterised clinically by deficits in motor function such as tremor, rigidity, bradykinesia (slowness of movement), hypokinesia (reduced movement), akinesia (loss of movement) and postural abnormalities [1]. Parkinsonism is a feature of a number of neurodegenerative diseases, including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Dopa-responsive dystonia, severe or cumulative head trauma, as well as toxins such as manganese, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and *n*-hexane, can also lead to parkinsonism. Separating these various parkinsonian syndromes using clinical criteria alone can be difficult. For example, Parkinson's disease is characterised by a good, sustained response to levo-dopa [1], but this is also found in dopa-responsive dystonia and in some patients with multiple system atrophy and progressive supranuclear palsy [2]. Tremor is present in most patients with Parkinson's disease [1], but can also be seen in patients with multiple system atrophy and progressive supranuclear palsy [2]. Discrimination of these various disorders is important in view of differences in prognosis and therapy. Structural imaging, such as computed tomography and magnetic resonance imaging, is of limited value for differentiating parkinsonian syndromes since structural changes are often only evident by the time the disease is far advanced [3].

The results of post-mortem studies, and the good or partial response to dopaminergic medication (such as levo-dopa) in most patients with parkinsonism, point to dysfunction of the dopaminergic neurotransmitter system in parkinsonism. Parkinsonian syndromes can be differentiated partially on the basis of the involvement of different components of the dopaminergic system. Single-photon emission tomography (SPET) and positron emission tomography (PET) can reveal patterns of disruption of components of the dopaminergic neurotransmitter system in vivo and can, consequently, play a role in differentiating parkinsonian syndromes. Over recent decades many reports have been dedicated to SPET and PET studies of the dopaminergic neurotransmitter system in patients with parkinsonism. This review will concentrate on the promising findings of these studies, with a special focus on results relevant for clinical practice.

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Imaging of the presynaptic nigrostriatal dopaminergic neurons

The neurotransmitter dopamine plays an important role in the regulation and control of movement, motivation and cognition [4]. Dopamine neurons reside predominantly in the mesencephalon, which is a part of the brain stem, and project predominantly to the striatum (presynaptic nigrostriatal dopaminergic projection); they are mainly concerned with the initiation and execution of movements. During recent decades, the introduction of SPET and PET has dramatically increased our knowledge of the dopaminergic neurotransmission system. In the late 1970s, Garnett and co-workers reported on the successful application of 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]DOPA) for PET studies of nigrostriatal dopaminergic neurons [5, 6]. [^{18}F]DOPA PET provides a measure of the structural as well as the biochemical integrity of the dopaminergic neurons: the uptake rate constant of [^{18}F]DOPA is determined by the transfer of DOPA across the blood-brain barrier, its decarboxylation to fluorodopamine by l-aromatic acid decarboxylase and its retention in nerve terminals.

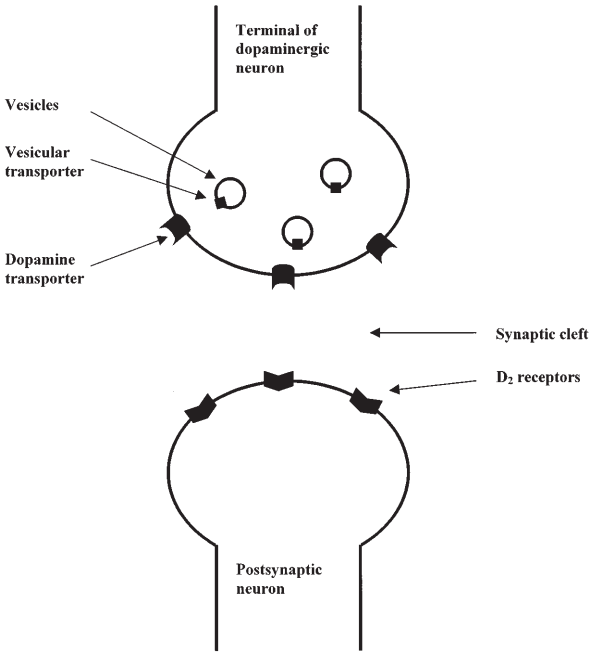

Fig. 1. Simplified diagram of a terminal of a nigrostriatal dopaminergic cell and a postsynaptic cell in the striatum. Dopamine transporters are situated in the membrane of the terminal, whereas vesicular transporters are situated in the membrane of the vesicles. For convenience, dopamine D_2 receptors are shown only on the postsynaptic cell, whereas they are almost certainly also localised in low concentrations on presynaptic terminals

Another approach to the visualisation of dopaminergic neurons is the use of radiotracers for the dopamine transporter. Since the late 1980 s, studies have shown the possibility of quantifying nigrostriatal dopaminergic neurons in vivo by means of SPET and PET using the dopamine transporter as a neurochemical marker [7–12]. Radiotracers for the vesicular monoamine transporter have recently been introduced to visualise dopaminergic neurons [13].

The dopamine transporter and vesicular monoamine transporter

Dopamine is synthesised in dopaminergic neurons where it is stored in vesicles which protect it from oxidation by monoamine oxidase. In response to an action potential, dopamine is released in the synaptic cleft and interacts with dopamine receptors. To terminate the interaction with these receptors, the extracellular dopamine is actively pumped back into the dopaminergic terminal by the dopamine transporter (Fig. 1). The dopamine transporter, or reuptake site, is presumably a unique constituent of dopaminergic nerve terminals [14–16]. Following reuptake, the dopamine molecules present in the neuronal cytosol are either catabolized or actively transported via the vesicular monoamine transporter into the vesicles to be stored (Fig. 1). Until now, successful radiotracers for the vesicular transporter have been derivatives from tetrabenazine [13].

In summary, the integrity of the presynaptic nigrostriatal dopaminergic projection can now be studied in vivo with radiotracers whose striatal uptake reflects a measure of the structural as well as the biochemical integrity of the dopaminergic nerve terminals (e.g. [^{18}F]DOPA [6]; Table 1) or dopamine transporter density (e.g. the ^{123}I- or ^{18}F-labelled cocaine analogue FP-CIT (*N*-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}tropane) [17, 18], ^{123}I- or ^{11}C-labelled β-CIT (2β-carbomethoxy-3β-{4-iodophenyl}tropane) [19], ^{123}I-labelled IPT (N-{3-iodopropen-2-yl}-2β-carbomethoxy-3β-{4-chlorophenyl}tropane) [20] and its 4-fluorophenyl analogue

Table 1. Commonly used radiolabelled ligands for SPET and PET imaging of dopamine transporters, vesicular transporters and dopamine D_2 receptors

Dopamine transporter	Vesicular transporter	Dopamine D_2 receptor
FP-CIT	Derivatives from tetrabenazine	IBZM
β-CIT		Epidepride
IPT		IBF
CFT (WIN 35 428)		Raclopride
Altropane		*N*-Methylspiroperidol
Cocaine		
Methylphenidate		

[^{123}I]altropane [21], [^{11}C]cocaine [8], ^{11}C-labelled CFT (2β-carbomethoxy-3β-{4-fluorophenyl}tropane) [22], [^{11}C]*d-threo*-methylphenidate [23]; Table 1) or density of monoaminergic vesicles (e.g. [^{11}C]tetrabenazine [13]; Table 1).

Imaging of D_2 dopamine receptors

Dopamine exerts its effects in the central nervous system through activation of dopamine receptors. Dopamine receptors are present both pre- and postsynaptically at dopaminergic synapses. Receptors which are located presynaptically modulate the release and synthesis of dopamine. Receptors at the postsynaptic side function in cell-to-cell communication (Fig. 1). Dopamine receptors play a primary role in modulating locomotor function and are an important target for dopaminergic medication [24]. At least five different subtypes of dopamine receptors have now been described [25], but broadly they fall into two classes: D_1 type (D_1, D_5) and D_2 type (D_2, D_3, D_4). The concentration of dopamine D_1 and D_2 receptors is higher than that of other dopamine receptors. The highest concentrations for dopamine D_1 and D_2 receptors are in the striatum [25]. Radiotracers for imaging of the dopamine D_1 and D_2 receptors have been developed. In this review, attention will be paid only to radiotracers for the dopamine D_2 receptor, since specific imaging studies of the D_2 receptor have been shown to be of value for the differential diagnosis of parkinsonism.

The vast majority of striatal dopamine D_2 receptors are localised postsynaptically; therefore, imaging of dopamine D_2 receptors is frequently referred to as imaging of postsynaptic D_2 receptors. The most widely used radiotracers for imaging of these receptors with SPET are the dopamine receptor antagonists ^{123}I-labelled IBZM ([^{123}I]iolopride) [26, 27], ^{123}I-labelled epidepride [28, 29] and ^{123}I-labelled IBF ([^{123}I](*S*)-5-iodo-7-*N*-{(1-ethyl-2-pyrrolidinyl)methyl}carboxamido-2, 3-dihydrobenzofuran) [30, 31]. For dopamine D_2 receptor imaging with PET, [^{11}C]raclopride [32] and ^{11}C- or ^{18}F-labelled *N*-methylspiroperidol [33, 34] are most widely used (Table 1).

Parkinson's disease

Imaging of the presynaptic nigrostriatal dopaminergic neurons

The major cause of parkinsonism is Parkinson's disease, accounting for approximately 60%–85% of all cases [35, 36]. Parkinson's disease is characterised neuropathologically by degeneration of brain stem nuclei, particularly the substantia nigra pars compacta, in association with the formation of neuronal Lewy bodies. Nigral dopaminergic projections to the striatum are targeted in Parkinson's disease, especially those to the putamen, while those to the caudate nucleus are relatively spared. Degeneration of the nigrostriatal dopaminergic projection leads to loss of dopamine transporters and dopamine in the striatum [37–39]. The lack of dopamine innervation to the striatum is believed to be responsible for the deficits in motor function.

Until recently, most research on the dopaminergic deficit in Parkinson's disease has been performed with [^{18}F]DOPA PET scanning [40–45]. These studies showed a more pronounced reduction of striatal uptake in the putamen than in the caudate nucleus (Table 2). This finding is in agreement with results from necropsy studies, which disclosed a more severe depletion of dopamine in the putamen than in the caudate nucleus [37, 38]. Moreover, striatal uptake of the radiotracer was asymmetric (in nearly all patients with Parkinson's disease symptomatology starts unilaterally) and correlated with disease severity.

The results of SPET and PET studies, using tracers for the dopamine transporter, are consistent with the results of [^{18}F]DOPA PET studies. These studies also showed a more pronounced reduction of striatal binding in the putamen than in the caudate nucleus, asymmetric loss of striatal dopamine transporters, and a correlation with disease severity [11, 12, 46–50].

Table 2. Results of SPET and PET studies of the dopaminergic system in relatively common syndromes which may be relevant in the differential diagnostic considerations in parkinsonism

Syndromes	Integrity of the dopaminergic nigrostriatal pathway	Binding to striatal D_2 receptors
Parkinson's disease	Loss	Normal[a]
Multiple system atrophy	Loss	Reduced
Progressive supranuclear palsy	Loss	Reduced
Dopa-responsive dystonia[b]	No loss	Increased
Essential tremor	No loss	?

[a] The striatal binding of radioligands for dopamine D_2 receptors can be increased in the onset of Parkinson's disease

[b] Although dopa-responsive dystonia is a rare disorder, SPET or PET studies of the dopaminergic nigrostriatal pathway may be of value to differentiate dopa-responsive dystonia from juvenile- or young-onset Parkinson's disease

Early Parkinson's disease and [^{18}F]DOPA PET

For clinical practice, results obtained in patients at an early phase of Parkinson's disease are of special interest. Recently, Morrish and co-workers [43] showed a decline in [^{18}F]DOPA uptake in early Parkinson's disease. In this study most contralateral putamen K_i values (contralateral is the side opposite to the side of initial motor signs) of 11 patients with hemi-Parkinson's disease of recent onset fell outside the range of normal values, while most ipsilateral putamen [^{18}F]DOPA uptake values fell within the normal range. Interestingly, a recent [^{18}F]DOPA PET study showed the presence of bilateral dopaminergic dysfunction in hemiparkinsonian patients using three-dimensional [^{18}F]DOPA PET coupled with statistical parametric mapping [51]. Consequently, the [^{18}F]DOPA PET technique may be sensitive enough to detect patients in the preclinical period of Parkinson's disease, which may last several years. Moreover, by using three-dimensional models, one is also able to study extrastriatal dopaminergic projections.

Early Parkinson's disease and SPET and PET imaging studies of the dopamine transporter

SPET imaging with ^{123}I-labelled cocaine analogues [52] such as FP-CIT, β-CIT, IPT and altropane showed a dramatic loss of striatal dopamine transporters in patients with Parkinson's disease (Table 2) with high signal-to-noise ratios [45, 47, 48, 50, 53, 54, 56]. Of these cocaine analogues for SPET imaging, most experience has been gained with the tracers [^{123}I]FP-CIT and [^{123}I]β-CIT. Importantly, both [^{123}I]FP-CIT and [^{123}I]β-CIT SPET studies showed loss of striatal dopamine transporters in patients with early Parkinson's disease (Fig. 2) [55–60]. Moreover, these techniques were able to show bilateral loss of striatal dopamine transporters in patients with hemi-Parkinson's disease [50, 55, 56, 59]. Therefore, these techniques may also be sensitive enough to detect preclinical Parkinson's disease. Furthermore, both the [^{123}I]FP-CIT and [^{123}I]β-CIT SPET techniques were able to discriminate completely groups of patients with Parkinson's disease from groups of healthy controls, using ratios of specific striatal to non-specific binding as the outcome measure and manual placement of regions of interest [47, 59]. These results indicate that both [^{123}I]FP-CIT and [^{123}I]β-CIT SPET are sensitive means of detecting degeneration of nigrostriatal dopaminergic neurons. However, there are clear differences in the kinetics of [^{123}I]FP-CIT and [^{123}I]β-CIT. Binding of [^{123}I]β-CIT in the human striatum is characterised by very slow kinetics, which is a serious drawback for routine clinical studies [61]. This indicates that an image acquisition should be performed on the day after injection, which is not convenient for out-patient evaluation. The kinetics of [^{123}I]FP-CIT are faster than that of [^{123}I]β-CIT, which permits image acquisition several hours after injection [45, 49, 62, 63]. Using such a 1-day protocol will be to great advantage in out-patient evaluations [49].

PET in Parkinson's disease, using the ^{11}C-labelled cocaine analogue β-CFT (or WIN 35 428) as a radiotracer for the dopamine transporter, showed relatively low signal-to-noise ratios, although patients with early Parkinson's disease could be clearly discriminated from controls [46, 64]. The use of [^{11}C]β-CIT in PET imaging failed to discriminate significantly between small groups of patients with early Parkinson's disease and healthy controls [64]. PET measurements with [^{11}C]β-CIT and [^{11}C]CFT must be performed far from equilibrium due to the short half-life of ^{11}C and the slow kinetics of β-CIT and CFT, respectively. Therefore, the sensitivity of the [^{11}C]β-CIT and [^{11}C]CFT PET techniques is not optimal to detect small decreases in dopamine transporters [23]. The fast kinetics of FP-CIT offers the potential for it to be a useful radiotracer, not only for SPET imaging of the dopamine transporter but also for PET imaging [17, 18, 65]. Interestingly, the results of recent imaging studies showed that [^{11}C]FP-CIT and [^{18}F]FP-CIT binding to striatal dopamine transporters reaches binding pseudo-equilibrium within the time course of a typical PET experiment [18, 66]. Moreover, the signal-to-noise ratios were very high.

The results of recent studies showed the potential of PET and radiolabelled tetrabenazine derivatives to demonstrate the loss of striatal monoaminergic vesicles in patients with early Parkinson's disease [67, 68].

The results of the above-mentioned studies indicate that imaging of the dopamine transporter using SPET or PET is a very sensitive means of detecting disturbances of the nigrostriatal dopaminergic pathway in patients with Parkinson's disease, even at an early stage of the disease. Both the widespread availability and the lower operating costs of SPET compared with PET suggest that SPET imaging of the nigrostriatal pathway may become an important diagnostic tool in clinical practice.

Imaging of dopamine D_2 receptors

Several post-mortem studies have shown small increases or no change in numbers of striatal dopamine D_2 receptors in Parkinson's disease [69]. In agreement with these post-mortem findings, dopamine D_2 receptors imaging with SPET and PET showed normal or increased dopamine D_2 receptor binding in patients with Parkinson's disease [58, 70–72] (Table 2). This is in agreement with the, generally speaking, good clinical response to dopaminomimetics (e.g. levo-dopa or dopamine receptor agonists) in patients with Parkinson's disease.

Recently, Schwarz and co-workers [58] reported results from a study of patients with de novo parkinsonism in whom imaging of dopamine D_2 receptors with [^{123}I]IBZM SPET was performed before the initiation of dopaminergic medication. During clinical follow-up

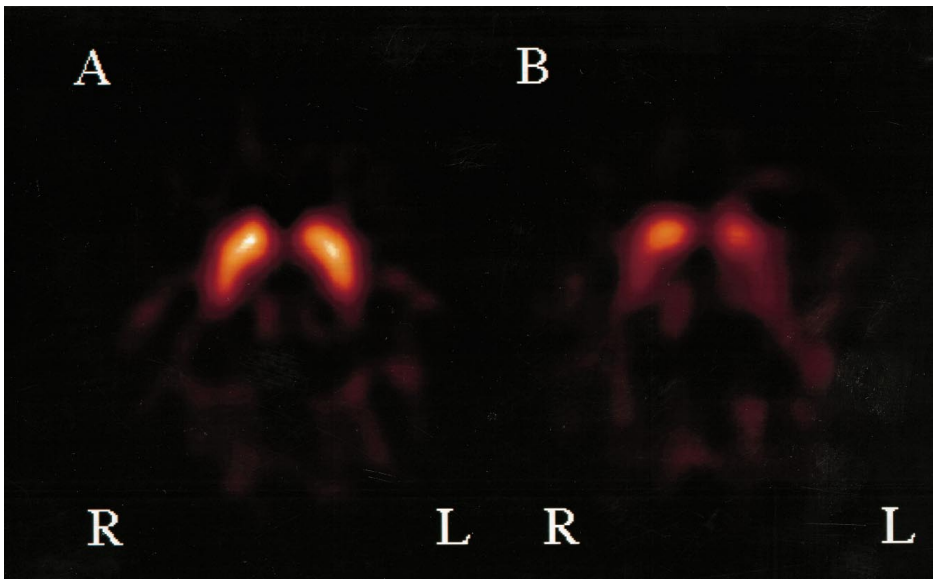

Fig. 2. [^{123}I]FP-CIT SPET images, obtained 3 h after injection of the radiotracer, of a healthy volunteer (**A**) and a patient with hemi-Parkinson's disease (**B**). Transverse slices from the brain at the level of the striatum (*L*, left side; *R*, right side). In both images the level of activity is colour encoded from low (*black*) via medium (*yellow*) to high (*white*) and scaled to the maximum in the slice of the control person. **A** 65-year-old healthy woman; **B** 59-year-old woman with hemi-Parkinson's disease (Hoehn and Yahr stage I). Note that the overall striatal binding is lower in the patient than in the control person. In the patient the binding is asymmetric, with lower binding in left than in the right striatum (at the time of imaging, motor signs were present only in the right side of the body of the patient). So, although clinical signs are only present unilaterally, bilateral loss of striatal dopamine transporters is already detectable at a very early stage of the disease. Finally, note that, in the patient, the binding is lower in the putamen than in the caudate nucleus

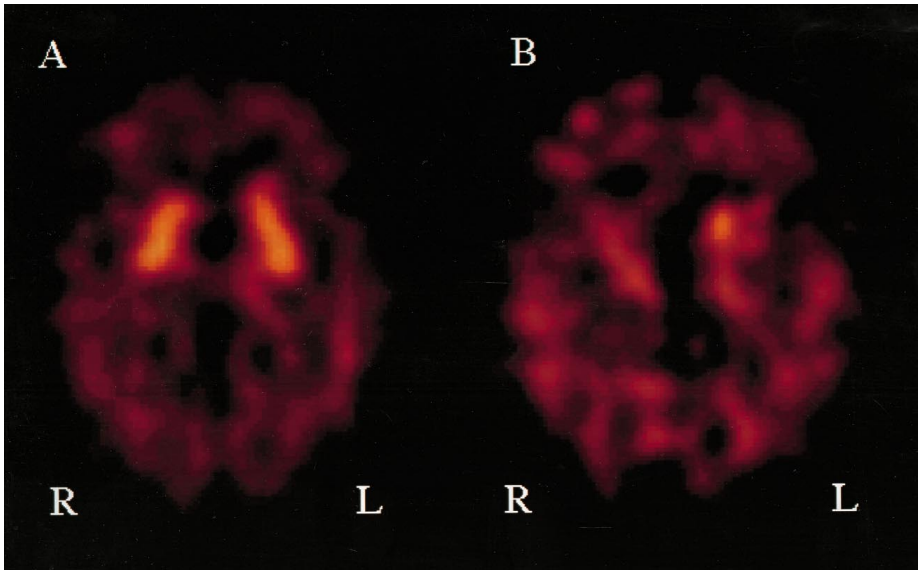

Fig. 3. [^{123}I]IBZM SPET images, obtained 2 h after injection of the radiotracer, of a healthy volunteer (**A**) and a patient with multiple system atrophy (**B**). Transverse slices from the brain at the level of the striatum (*L*, left side; *R*, right side). In both images the level of activity is colour encoded from low (*black*) via medium (*yellow*) to high (*white*) and scaled to the maximum in the slice of the control person. **A** 63-year-old healthy woman; **B** 71-year-old woman with multiple system atrophy. Note that the overall striatal binding is lower in the patient than in the control person

none of the patients with reduced [^{123}I]IBZM binding showed a positive response to dopaminergic medication. Therefore reduced striatal [^{123}I]IBZM binding is likely to exclude a diagnosis of Parkinson's disease early in the course of the disease.

Multiple system atrophy

Imaging of the presynaptic nigrostriatal dopaminergic neurons

Multiple system atrophy is a neurodegenerative disease that may account for up to 10% of patients with parkinsonism [2]. It may present with any combination of extrapyramidal, pyramidal, autonomic and cerebellar fea-

tures and is poorly responsive to dopaminergic medication [2]. Multiple system atrophy is neuropathologically characterised by neuronal degeneration and gliosis in the caudate and putamen, globus pallidus, brain stem, cerebellum and spinal cord [73, 74]. As in Parkinson's disease, degeneration of the nigrostriatal dopaminergic pathway has been reported [73, 75].

Brooks and co-workers [42] have shown with [^{18}F]DOPA and PET that patients with multiple system atrophy may present with relatively more impairment of the nigrostriatal dopaminergic projections to the caudate nucleus than patients with Parkinson's disease. Consequently, they suggested that putamen-to-caudate nucleus ratios could be used in the differential diagnosis among different forms of parkinsonism. However, the results from more recent [^{18}F]DOPA PET studies [44, 76, 77] and from a recent SPET study, using [^{123}I]β-CIT [78], showed that the pattern of presynaptic dopaminergic degeneration is comparable in patients with multiple system atrophy and patients with Parkinson's disease (Table 2).

Imaging of dopamine D_2 receptors

Loss of striatal dopamine D_2 receptors in patients with multiple system atrophy has been reported in a post-mortem study [79]. In agreement with this finding, SPET and PET studies showed a reduced postsynaptic dopamine D_2 receptors density in patients with multiple system atrophy in vivo (Fig. 3; Table 2) [77, 80–82].

Progressive supranuclear palsy

Imaging of presynaptic nigrostriatal dopaminergic neurons

Progressive supranuclear palsy is another akinetic-rigid syndrome characterised by an increased axial tone, bulbar palsy, rigidity of the extensors of the neck and supranuclear palsy. Neuropathologically, degeneration is found of the basal ganglia and the brain stem nuclei without Lewy bodies but, unlike in multiple system atrophy, with neurofibrillary tangles. Degeneration of the nigrostriatal dopaminergic pathway has been reported in progressive supranuclear palsy. In contrast to findings in Parkinson's disease, a similar degree of depletion of dopamine was found in the caudate nucleus and putamen [83, 84]. In agreement with the post-mortem finding, striatal [^{18}F]DOPA uptake is reduced in patients with progressive supranuclear palsy (Table 2) [42], putamen and caudate nucleus tracer uptake being similarly affected. This finding contrasted with findings in patients with Parkinson's disease, in whom caudate uptake is relatively spared [42]. However, a recent SPET study showed that the pattern of loss of striatal dopamine transporters in patients with progressive supranuclear palsy is comparable to that pattern in Parkinson's disease [78]. Although it is possible that a pattern different from Parkinson's disease might be found in a larger sample of patients with supranuclear palsy, it does not seem possible to make a distinction in individual cases on the basis of the results of imaging studies of the striatal dopamine transporter density alone [78].

Imaging of dopamine D_2 receptors

Loss of striatal dopamine D_2 receptors in progressive supranuclear palsy has been supported by the findings of necropsy studies [85, 86]. Both SPET and PET studies reported reduced striatal D_2 receptor binding in groups of patients with progressive supranuclear palsy, although individual data showed overlap between patients and controls (Table 2) [3, 80, 81].

Dopa-responsive dystonia

Imaging of presynaptic nigrostriatal dopaminergic neurons

Dopa-responsive dystonia is a rare familial disorder that generally presents in childhood, with dystonic posturing of the legs, with concurrent or subsequent parkinsonism [87]. Sometimes, dopa-responsive dystonia presents as a dopa-responsive parkinsonian syndrome in late adulthood superficially indistinguishable from Parkinson's disease [88]. Consequently, it may be hard to differentiate patients with dopa-responsive dystonia from patients with juvenile- or young-onset Parkinson's disease on clinical examination alone.

Dopa-responsive dystonia has an autosomal dominant pattern of inheritance with incomplete penetrance and variable expression. In dopa-responsive dystonia, mutations in the gene for GTP cyclohydrolase I have been found [89]. (GTP cyclohydrolase I is the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterine, which is the essential co-factor for tyrosine hydroxylase. Tyrosine hydroxylase converts tyrosine to levo-dopa, and levo-dopa is consequently converted to dopamine by the enzyme dopa decarboxylase.) The defect in this enzyme leads to a unique dopaminergic deficiency state, with a biochemical deficit in the presynaptic dopaminergic neurons. Post-mortem findings in a single case of dopa-responsive dystonia showed loss of dopamine concentration in the striatum but no structural loss of dopaminergic cells in the substantia nigra [90]. Since there is no structural loss of dopamine cells, and no biochemical deficit in the enzyme dopa decarboxylase, patients with dopa-responsive dystonia respond dramatically to levo-dopa.

In contrast to findings in Parkinson's disease, SPET and PET studies in dopa-responsive dystonia showed normal, or only mildly reduced, integrity of nigrostriatal

dopaminergic neurons [87, 88, 91–97]. So, imaging of the nigrostriatal dopaminergic pathway may provide a unique method to differentiate patients with dopa-responsive dystonia from patients with juvenile- or young-onset Parkinson's disease (Table 2).

Imaging of dopamine D_2 receptors

A recent study showed an increased striatal D_2 dopamine receptor binding in most patients with dopa-responsive dystonia (Table 2). The increase in receptor binding could reflect receptor up-regulation or reduced competition for the radioligand [96, 98] as a consequence of a decreased level of dopamine in the striatum [90]. Finding no loss of striatal dopamine D_2 receptors in patients with dopa-responsive dystonia is in line with the dramatic clinical response to levo-dopa.

Other rare causes of parkinsonism

Chronic manganese intoxication, from working in ferromanganese factories, is a risk factor for development of parkinsonism. This condition responds poorly to levodopa. In contrast to Parkinson's disease, multiple system atrophy and progressive supranuclear palsy, striatal [^{18}F]DOPA uptake is normal in these patients [99]. Interestingly, a recent PET study showed that striatal D_2 receptor binding is reduced in the caudate nucleus [100].

MPTP produces a relatively selective lesion of nigrostriatal dopaminergic neurons. Using PET and the tracer [^{18}F]DOPA, the integrity of the nigrostriatal dopaminergic neurons has been studied in subjects who had been exposed to MPTP [101]. These studies demonstrated reduced striatal tracer uptake in the MPTP-exposed subjects, and progression of degeneration of nigrostriatal cells faster than in normal ageing [101, 102].

The hydrocarbon *n*-hexane may have a toxic effect on dopaminergic cells. *n*-Hexane is a common component of glues, varnishes and gasoline. Neuropathological analysis of a case of parkinsonism in a worker in the leather industry who had been exposed to *n*-hexane showed loss of dopaminergic neurons in the substantia nigra, but no Lewy bodies [103]. A recent [^{18}F]DOPA PET study demonstrated regional striatal abnormalities of the nigrostriatal pathway in *n*-hexane-induced parkinsonism that was different from that found in Parkinson's disease: the uptake of radiotracer was reduced to a comparable extent in the caudate and putamen. Moreover, the dopamine D_2 receptor binding, as measured with [^{11}C]raclopride, was reduced in the caudate nucleus [103].

The striatal variant of post-traumatic encephalopathy, post-traumatic parkinsonism, is uncommon and may be difficult to distinguish from Parkinson's disease. Recently, Turjanski and co-workers [104] showed a uniform reduction of mean [^{18}F]DOPA uptake in the caudate nucleus and putamen compared with healthy controls. This suggests that imaging of the nigrostriatal pathway may help to differentiate post-traumatic parkinsonism from Parkinson's disease by demonstrating uniform nigrostriatal involvement in patients with posttraumatic parkinsonism as opposed to relative sparing of caudate nucleus uptake in patients with Parkinson's disease. However, since imaging of the dopamine transporter by SPET and PET is becoming more and more relevant in clinical practice, confirmation by dopamine transporter imaging studies of the results of the [^{18}F]DOPA PET studies is to be recommended.

Essential tremor

Classically, patients with essential tremor present with a postural tremor of approximately 7 Hz with or without a kinetic tremor, involving hands or forearms [105]. Parkinson's disease is clinically characterised by a resting tremor, rigidity, bradykinesia and postural instability. However, in addition to a rest tremor, a postural tremor similar to that in patients with essential tremor may occur in patients with Parkinson's disease [106]. On the other hand, patients with essential tremor often demonstrate a resting tremor component as well. Consequently, this may occasionally lead to difficulties in distinguishing patients with essential tremor from patients with Parkinson's disease.

SPET and PET studies have shown that there is no loss of nigrostriatal dopaminergic neurons in patients with essential tremor (Table 2) [107, 108]. Consequently, SPET or PET may be of value to discriminate essential tremor from Parkinson's disease.

Future studies

Imaging of presynaptic nigrostriatal dopaminergic neurons to examine neuroprotective properties of drugs

In vivo imaging of the presynaptic nigrostriatal dopaminergic system will be of interest not only from a diagnostic point of view. Quantification of dopaminergic neurons will also provide an "objective" tool which can be of value to monitor progression of degeneration of dopaminergic neurons or to evaluate the efficacy of neuroprotective medication in patients with Parkinson's disease [109].

Dopaminomimetics, such as levo-dopa or dopamine receptor agonists, are initially efficacious in diminishing the clinical signs of Parkinson's disease. However, long-term therapy is usually not completely satisfactory since it frequently results in fading of the therapeutic effect, in the development of serious side-effects, especially motor disturbances, and, to a lesser extent, in psychiatric complications [110–113]. Primary or secondary prevention of degeneration of dopaminergic neurons can be consid-

ered as a theoretical strategy to delay the need for medication, and consequently, to delay the development of side-effects from long-term therapy with dopaminomimetics.

During recent decades neuroprotective qualities have been attributed to several drugs. For example, it has been suggested that the beneficial effects of the monoamine oxidase-B inhibitor selegiline in the treatment of patients with Parkinson's disease were due to the potency of selegiline in slowing down degeneration of dopaminergic neurons. However, other authors have suggested that the beneficial effects of selegiline could be explained by inhibition of dopamine breakdown and a consequent elevation of brain dopamine levels in patients with Parkinson's disease [114, 115]. By performing only clinical assessments in patients one is not able to resolve the question of whether the beneficial effect of the drug selegiline is caused by neuroprotective properties of the drug or by elevation of brain dopamine levels. Interestingly, it has also been suggested that treatment with levo-dopa, although symptomatically effective, might accelerate degeneration of dopaminergic neurons by enhanced generation of free radicals through dopamine auto-oxidation [116, 117]. Since levo-dopa diminishes parkinsonian signs, it is hard to demonstrate clinically whether levo-dopa indeed enhances degeneration of dopaminergic neurons. Therefore, quantification of dopaminergic neurons by means of in vivo imaging techniques offers an important tool to examine the efficacy of drugs in slowing down or enhancing degeneration of dopaminergic neurons [109].

Recently, both SPET and PET showed progression of degeneration of dopaminergic cells in patients with Parkinson's disease [118–121]. Since SPET and PET seem to be able to monitor progression of the disease, clinical studies have already started to use these imaging techniques to monitor the potency of several drugs (especially dopamine receptor agonists) in slowing down disease progression. In the forthcoming years, the results of these studies will be reported.

Selectivity of SPET and PET tracers for the dopamine transporter

The development of radiolabelled cocaine derivatives as SPET and PET ligands for the dopamine transporter has been successful [17, 19, 21, 22, 52, 122]. However, these analogues of cocaine appeared to label not only the dopamine but also other monoamine transporters, such as the serotonin transporter, as has been demonstrated for FP-CIT, β-CIT, IPT, CFT and altropane by in vitro and in vivo studies [21, 63, 66, 123–128]. Within these series, the selectivity of the cocaine analogues for the dopamine over the serotonin transporter is different, e.g. altropane displays higher selectivity for the dopamine transporter than β-CIT [21]. Notwithstanding the progress made in dopamine transporter imaging, future studies will focus on the development of more selective radiotracers for the dopamine transporter [129]. However, apart from a high selectivity, the in vivo binding properties, brain distribution and pharmacokinetics of a radiotracer will also influence its suitability for SPET or PET imaging of dopamine transporters.

SPET studies of the nigrostriatal pathway with ^{99m}Tc-labelled tracers

As mentioned above, several ^{123}I-labelled SPET tracers have recently been evaluated as agents for the dopamine transporter. Despite the success of ^{123}I-labelled radiotracers as SPET agents for imaging of the dopamine transporter, an agent for this transporter incorporating the radionuclide ^{99m}Tc would be more desirable for several reasons: the physical half-life of ^{99m}Tc is shorter than that of ^{123}I, ^{99m}Tc is less expensive than ^{123}I, and ^{99m}Tc is easily available. However, it is difficult to attach a chelator for ^{99m}Tc to form a stable agent while still maintaining adequate binding affinity to the dopamine transporter. Moreover, the ^{99m}Tc complexing moiety is large, which limits the brain uptake. Interestingly, despite these problems, initial studies have shown the potential of ^{99m}Tc-labelled tracers to image dopamine transporters in vivo [130–132]. In the near future, progress in the field of imaging of the dopamine transporter with ^{99m}Tc-labelled tracers is to be expected. ^{99m}Tc-labelled tracers may facilitate use of SPET imaging of the dopamine system as a cost-effective clinical tool.

Conclusion

Imaging of components of the dopaminergic neurotransmission system by SPET or PET has emerged as an exciting field in nuclear medicine. Imaging of the presynaptic dopaminergic nigrostriatal neurons and dopamine D_2 receptors has been shown to be of value in differentiating parkinsonian syndromes. There is ongoing progress in the optimisation of radioligands for components of the dopaminergic neurotransmission system. In future studies, imaging of the nigrostriatal dopaminergic integrity by SPET or PET will not only be of diagnostic value. These techniques will also be used in clinical trials to evaluate neuroprotective properties of drugs in patients with Parkinson's disease.

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