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Neuroimaging in Parkinson's Disease

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Neuroimaging has provided insight into the pathophysiology and natural history of Parkinson's disease (PD) and has emerged as a tool to monitor disease progression and to assess new potentially neuroprotective or neurorestorative therapies for PD. Diverse imaging methods have been successfully applied to neurological disorders. While technology like functional magnetic resonance imaging or magnetic resonance spectroscopy has been especially useful in assessing stroke, multiple sclerosis and epilepsy (1 3), in vivo neuroreceptor imaging using single photon emission tomography (SPECT) and positron emission tomogrpahy (PET) have so far been most valuable in assessing PD. SPECT and PET use specific radioactively labeled ligands to neurochemically tag or mark normal or abnormal brain chemistry. Recent advances in radiopharmaceutical development, imaging detector technologies, and image analysis software have expanded and accelerated the role of imaging in clinical research in PD, in general, and neurotherapeutics, in particular. In this overview we will focus on developments in neuroreceptor imaging in PD.

IMAGING TECHNOLOGY

Both PET, also called dual photon emission tomography, and SPECT are sensitive methods of measuring in vivo neurochemistry (4,5). The choice of imaging modality is ultimately determined by the specific study questions and study design. While, generally PET cameras have better resolution than SPECT cameras, SPECT studies may be technologically and clinically more feasible, particularly for large clinical studies and in clinical practice. PET studies may benefit from greater flexibility in the range of radiopharmaceuticals that can be tested, but SPECT studies have the advantage of longer half-life radiopharmaceuticals necessary for some studies.

The strengths and limitations of in vivo neuroreceptor imaging studies depend on the imaging technology utilized to measure brain neurochemistry and the ligand or biochemical marker used to tag a specific brain neurochemical system. The properties of the radiopharmaceutical are the most crucial issue in developing a useful imaging tool for PD. Some of the key steps in development of a potential radioligand include assessment of the brain penetration of the radioligand, the selectivity of the radioligand for the target site, the binding properties of the radioligand to the site, and the metabolic fate of the radioligand. These properties help to determine the signal-to-noise ratio of the ligand and the ease of quantitation of the imaging signal. While ligands targeting neuronal metabolism have been used successfully to study PD patients, this review will focus on dopaminergic ligands (6). Specific markers for the dopaminergic system including ^{18}F-DOPA (7 12), ^{11}C-VMAT2 (13 15), and dopamine transporter (DAT) ligands (16 22) (Fig. 1) have been widely used to evaluate patients with PD.

Dopamine ligands are useful to assess PD in so far as they reflect the ongoing dopaminergic degeneration in PD. In the study most directly correlating changes in dopamine neuronal numbers and imaging outcomes there is good correlation between dopamine neuron loss and ^{18}F-DOPA uptake, although conclusions are limited by a small sample size of five subjects (12). Numerous other studies have shown that the vesicular transporter and dopamine transporter are reduced in striatum in postmortem brain from PD patients (23 25). In turn numerous clinical imaging studies have shown reductions in ^{18}F-DOPA, ^{11}C-VMAT2, and DAT ligands uptake in PD patients and aging healthy subjects consistent with the expected pathology of PD and of normal aging. Specifically these imaging studies demonstrate asymmetric, putamen greater than caudate loss of dopaminergic uptake that is progressive (26 28) (Table 1). In addition both ^{11}C-VMAT2 and DAT ligands demonstrate reductions in activity with normal aging (13,29).

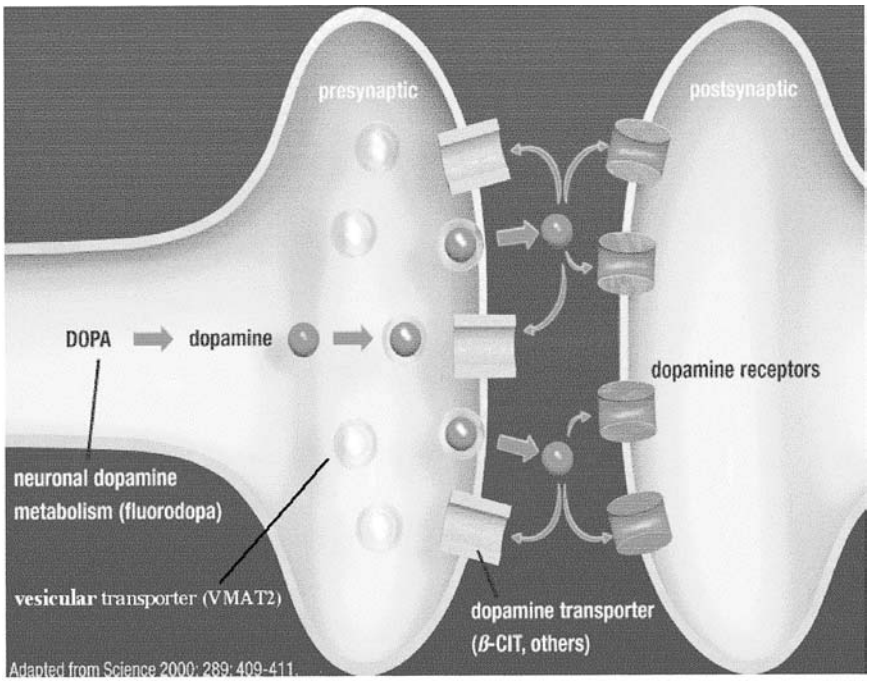

FIGURE 1 Idealized dopamine synapse showing targets for radiopharmaceutical in PD. (See color insert.)

TABLE 1 Comparison of Dopamine Presynaptic Ligands in PD Studies

	[^{123}I]β-CIT	^{11}C-VMAT2	^{18}F-DOPA
Target	DA transporter	Vesicular transporter	DA turnover
Bilateral reduction in hemi-PD	Yes	Yes	Yes
Correlates with UPDRS in cross section	Yes	Yes	Yes
Annual reduction change with aging (% loss from baseline)	0.8–1.4%	0.5%	No
Annual progression (% loss from baseline)	6–13%	10%	7–12%

Imaging with ^{18}F-DOPA, ^{11}C-VMAT2, and DAT ligands target different components of the presynaptic nigrostriatal neuron. The mechanism of each of these ligands has been elucidated in preclinical studies. Imaging with ^{18}F-DOPA depends on conversion of ^{18}F-DOPA by aromatic amino acid decarboxylase and uptake and trapping of ^{18}F-dopamine into synaptic vesicles. Studies in 1-methyl-4-Phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys have shown a correlation between the ^{18}F-DOPA uptake and both dopaminergic neuron number in the substantia nigra and dopamine levels in the striatum (30). The vesicular monoamine transporter acts to sequester newly synthesized or recovered monoamines (dopamine, serotonin, norepinephrine, and histamine) from the cytosol into the synaptic vesicles, thereby protecting the neurotransmitters from catabolism by cytosolic enzymes and packaging them for subsequent exocytotic release (31). VMAT2 ligand uptake is reduced in two commonly used rodent models of PD the 6-hydroxydopamine treated rat and the MPTP-treated mouse (32,33). DAT, a protein on the nerve terminal, is responsible for reuptake of dopamine from the synaptic cleft. In MPTP-treated monkeys the loss of DAT paralleled that of dopamine in the striatum, and in MPTP monkeys treated with nigral implants recovery of behavioral function was correlated with changes in DAT imaging (34,35).

During the past decade, several DAT ligands have been developed and used to assess PD and related disorders. Table 2 provides a more detailed comparison of the properties of these ligands. This comparison both illustrates the increasing choice of radioligands available and underscores the distinction of those ligands that enable easy quantification of the imaging signal. DAT imaging agents are cocaine analogs with nanomolar affinity at the DAT (36–41). These ligands are chemically modified to alter

TABLE 2 Characteristics of SPECT Dopamine Transporter Radioligands

SPECT tracer	[^{123}I]β-CIT	[^{123}I]FP-CIT	^{99m}Tc-TRODAT	[^{123}I]Altropane
Time to peak uptake	Protracted, 8–18 h	Rapid, 2–3 h	Rapid, 2–3 h	Rapid, 0.5–1 h
Washout phase	Prolonged	Prolonged	Intermediate	Rapid
DAT binding affinity	1.4 nM Ki	3.5 nM Ki	9.7 nm Ki	6.62 nM IC50
DAT:SERT selectivity	1.7:1	2.8:1	26:1	28:1
SPECT target:background tissue ratio	High	High	Low	Low

the rapid metabolism of cocaine at the ester linkage to provide more in vivo stability of the parent compound. Nonetheless, the kinetic properties of DAT radiotracers are quite different with regard to plasma protein binding, permeability across the blood-brain barrier, binding affinity, selectivity for the dopamine transporter, and elimination. These differences are crucial to the applications of the DAT ligand for imaging (42). For example, while a given DAT tracer may distinguish PD from healthy controls based on the qualitative appearance of striatal uptake, the ability to distinguish the longitudinal changes in severity of PD may be more difficult for tracers with relatively poorer signal-to-noise properties (lower specific to nonspecific brain uptake) (Table 2). The quantitative properties of the radiotracer must be well understood to assess disease progression. Specifically, does the imaging signal provide a measure that is related to Bmax, the density of DAT, and/or the integrity of dopamine neurons? For some tracers absolute quantitation of the DAT signal may require invasive methods involving full kinetic modeling, while other DAT tracers have a pharmacokinetic profile, which simplifies the methods for signal quantification. For example, the unusual binding kinetics of [^{123}I]β-CIT, with a protracted period of stable specific radiotracer uptake in the brain and extremely slow elimination from the DAT sites in striatum, permit reproducible quantitative determination of DAT density using a simple tissue ratio method (19,43). For DAT tracers with faster washout from specific binding sites, this simple ratio technique will overestimate the density of binding sites in healthy striatum relative to PD (44), although these tracers may permit better visual discrimination of diseased from control cases.

Of the DAT SPECT tracers in development, [^{123}I]β-CIT, [^{123}I]FP-CIT, [^{123}I]-altropane, and [^{99m}Tc]-TRODAT have been the most widely evaluated dopamine transporter agents for SPECT imaging (18,20,45) and ^{18}F-CFT (WIN 35,428) for PET (46,47). None of these tracers is commercially available as yet in North America, although one tropane derivative of cocaine (FP-CIT, DATSCAN®) is available as a [^{123}I]-labeled tracer in Europe.

PD DIAGNOSIS ACCURACY

The diagnosis of PD is currently based primarily on clinical judgment. However, the variability of disease presentation, progression, and response to medications often makes diagnosis uncertain. Prevalence studies of parkinsonism suggest a diagnostic accuracy of 80% after examination and application of clinical diagnostic criteria (48–50). Long-term clinicopathological studies evaluating the diagnostic accuracy of PD demonstrate that the diagnoses most commonly mistaken for PD are progressive supranuclear

palsy (PSP) and multisystem atrophy (MSA) (51,52). However, early in the course of PD the diagnoses most commonly mistaken for PD include essential tremor, vascular parkinsonism, drug-induced parkinsonism, and Alzheimer's disease (53,54). It is estimated that diagnosis is incorrect in as many as 35% of those initially diagnosed as PD by generalists (55). In addition, symptoms of parkinsonism are relatively common in elderly subjects, making the diagnosis most challenging in this population. Subtle extrapyramidal signs on neurological evaluation are common in the elderly, with recorded prevalences of 32% (56) and 35% (57). Prevalence estimates for clinically evident parkinsonism in similarly aged subjects are much lower at around 3%. Neurologists with specialized training in parkinsonism are able to make the diagnosis of PD with higher accuracy than generalists as demonstrated by a follow-up study of the DATATOP cohort in which the diagnosis of PD was changed in only 8.1% of subjects at 6-year follow-up and by a study of movement disorder specialists in the United Kingdom demonstrating sensitivity of 91.1% for diagnosis of PD compared to the diagnosis based on pathology (58,59).

In vivo imaging holds the promise of improving diagnostic accuracy by providing an in vivo assessment of the nigrostriatal dopaminergic system early in disease. While comparison of imaging and pathology helps to confirm the validity of the imaging studies, it also highlights questions for which imaging studies may provide unique and otherwise unobtainable data. For example, in vivo imaging studies with either ^{18}F-DOPA/PET or [^{123}I]β-CIT/SPECT demonstrate a reduction in ligand uptake of approximately 50 70% in the putamen in PD subjects (20,60). The reduction in dopamine terminal function or DAT density and the pattern of striatal degeneration is consistent with the reduction in substantia nigra pars compacta neurons of greater than 80% and of putamenal dopamine content of 95% in PD brains (61 63). However, these imaging studies have shown at or near the threshold of diagnosis of PD a reduction in putamenal ^{18}F-DOPA or DAT activity of 40 60% rather than 80 90% as suggested by pathology studies (64 66). These imaging data acquired from early PD patients have clarified the natural history of disease, led to longitudinal studies on the rate of disease progression (as indicated below), and provide further impetus to develop therapies to protect the remaining 50% of dopaminergic neurons not yet affected at disease onset.

PD DIFFERENTIAL DIAGNOSIS AND SEVERITY

The first questions of an imaging ligand is whether it reliably distinguishes between subjects with and without known pathology (a marker for disease trait) and whether the changes in the imaging outcomes correlate with

disease severity (a marker for disease state). In several studies both dopamine and vesicular transporter ligands and ^{18}F-DOPA discriminated between individuals with PD and healthy subjects with a sensitivity of >95% (11,13,20,67 69). These studies take advantage of the relatively greater dopaminergic loss in the putamen to enhance the discriminant function. Furthermore, the reduction in both dopamine and vesicular transporter and ^{18}F-DOPA imaging activity correlated with well-defined clinical rating scales of PD severity (16,20,28,70). Interestingly when specific PD symptoms are compared, the loss of dopaminergic activity measured by imaging correlated with bradykinesia but not with tremor (20,71). Cross-sectional studies show that severity of bradykinesia measured by clinical scales reflects the severity of the nigrostriatal dopamine neuron loss. Therefore, in vivo dopaminergic imaging provides a biomarker both for the presence of disease and for the severity of the pathological process.

In clinical practice, diagnosis is often difficult at the onset of symptoms. In studies focused on early PD patients, at the threshold of their illness, in vivo imaging demonstrated a 40 60% reduction in DAT or F-DOPA activity in the putamen contralateral to the symptomatic side. PD generally presents as a unilateral motor disorder and progresses during a variable period of 3 6 years to affect both sides although frequently remaining asymmetric (72). The unilateral motor presentation reflects the asymmetric dopaminergic pathology, which is in turn demonstrated by in vivo dopaminergic imaging (11,65,66).

Imaging may also be useful in special diagnostic situations such as psychogenic, drug-induced, traumatic, or vascular parkinsonism in distinguishing these syndromes without a presynaptic dopamine deficit from PD and other related disorders (73,74). A more difficult diagnostic problem is the distinction between the more specific diagnosis of PD and other related neurodegenerative disorders categorized as Parkinsonism or Parkinson's syndrome. The more common etiologies of Parkinson's syndrome are PSP, MSA, cortical basal ganglionic degeneration, and diffuse Lewy body disease, which may account for about 15 20% of patients with apparent PD. Parkinsonism is characterized by significant nigrostriatal neuronal loss, which is demonstrated by reduction in in vivo presynaptic dopaminergic imaging. While the severity of DAT or ^{18}F-DOPA loss does not discriminate between PD and other causes of Parkinson's syndrome, the pattern of loss in Parkinson's syndrome is less region specific (putamen and caudate equally affected) and more symmetric than PD. This strategy discriminates between PD and other causes of Parkinson's syndrome with a sensitivity of about 75 80% (75 77). In addition, the more widespread pathology associated with Parkinson's syndrome may be reflected in abnormalities in post-synaptic dopamine receptor imaging and in metabolic imaging which are

not seen in PD. Therefore the pattern of presynaptic dopaminergic loss may be coupled with postsynaptic dopamine receptor imaging or metabolic imaging to distinguish PD from other related Parkinsonian syndromes (78,79).

PARKINSON'S DISEASE PROGRESSION

The rate of clinical progression of PD is highly variable and unpredictable (72). In clinical studies several clinical endpoints for progressive functional decline in PD have been used including Unified Parkinson's Disease Rating Scale (UPDRS) in the "defined off" state or after drug washout up to 2 weeks, time to need for dopaminergic therapy, or time to development of motor fluctuations (80 84). Clinical rating scales are extremely useful, but ratings may be investigator dependent and are frequently confounded by changes in symptomatic treatment. Pathological studies investigating rate of progression have been limited and rely entirely on cross-sectional data (62,63). These studies have in general considered patients with severe illness of long duration. In vivo imaging studies provide the opportunity to evaluate patients longitudinally from early to late disease using an objective biomarker for dopaminergic degeneration.

In several studies neuroreceptor imaging of the nigrostriatal dopaminergic system has been used as a research tool to monitor progressive dopaminergic neuron loss in PD. In longitudinal studies of PD progression both ^{18}F-DOPA and DAT imaging [β-CIT(2β-carboxymethoxy-3β(4-iodophenyl)tropane) and CFT] using both PET and SPECT have demonstrated an annualized rate of reduction in striatal ^{18}F-DOPA, ^{18}F-CFT, or [^{123}I]β-CIT uptake of about 6 13% in PD patients compared with 0 2.5% change in healthy controls (85 89). Similar findings have been reported for VMAT2 imaging (K. Frey, personal communication, 2002) (Fig. 2).

Evidence from studies of hemi-PD subjects provide further insight into the rate of progression of disease. In early hemi-PD there is a reduction in ^{18}F-DOPA and DAT uptake of about 50% in the affected putamen and of 25 30% in the unaffected putamen. Since most patients will progress clinically from unilateral to bilateral in 3 6 years, it is therefore likely that the loss of these in vivo imaging markers of dopaminergic degeneration in the previously unaffected putamen will progress at about 5 10% per annum (11,65).

Imaging has also been used to monitor progression of PD in patients receiving fetal substantia nigral transplants for PD. Several studies during the past several years show an increase in ^{18}F-DOPA uptake with follow-up of 6 months to 6 years posttransplant (90,91). The change in ^{18}F-DOPA