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Developments in neuroimaging: positron emission tomography

A. Jon Stoessl *

Pacific Parkinson's Research Centre, University of British Columbia & Vancouver Coastal Health. Vancouver, Canada

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SUMMARY

Positron emission tomography (PET) is a powerful technique to quantitatively assess brain function in vivo. In Parkinson's disease (PD), PET can assist in the identification of dopamine deficiency, the characterization of dopamine and other neurotransmitter receptors and transporters, serve as a biomarker and provide insights into motor and non-motor complications of PD. PET can also shed light on mechanisms that underlie disease, such as aberrant protein deposition and neuroinflammation. Emerging developments in multimodal imaging offer the opportunity to study multiple questions concurrently and offer great promise for the future.

1. Introduction

Positron emission tomography (PET) has a well-established history in the assessment and investigation of Parkinson's disease (PD), primarily as a means to assess dopaminergic function. The assessment of presynaptic dopaminergic integrity remains an important application of this technique. PET studies of glucose metabolism or cerebral blood flow have been used to study regional activation in response to a variety of stimuli, as well as patterns of regional connectivity. Regional activation and connectivity can also be well addressed by functional MRI. PET can also be used to assess the function of neurotransmitters other than dopamine (DA) and shows increasing promise as a means to investigate mechanisms that contribute to disease. The increasing number of functional imaging techniques now available should be seen as complementary rather than competitive, as many questions are best addressed by a combination of approaches.

2. Clinical and research applications

2.1. Diagnosis

PD is typically associated with loss of presynaptic DA markers (dopamine transporter – DAT, vesicular monoamine transporter type 2 – VMAT2, or 6-[^{18}F]fluoro-L-dopa – F-dopa) which is asymmetric, and with a rostral–caudal gradient, in which the posterior striatum is maximally affected. The same pattern is seen using SPECT with a variety of markers for the DAT. However, while this reliably identifies DA deficiency (and may therefore distinguish between PD and essential or dystonic tremor), the pattern is not specific for PD and may be seen in other akinetic–rigid syndromes, in particular multiple system atrophy (MSA). The additional use of a marker for DA receptors, which are typically lost in MSA or progressive supranuclear palsy (PSP) but preserved in PD, may help, but this approach has not found widespread use. In contrast, PD is associated with a typical pattern of glucose metabolism or cerebral blood flow, while MSA, PSP and corticobasal syndrome all have distinct patterns that can be visually identified and quantified using a form of principal components analysis [1].

2.2. Preclinical detection and disease biomarker

All markers of presynaptic DA integrity decline according to an exponential function that is estimated to start deviating from normal age-related changes several years prior to onset of clinical disease. Based on extrapolation of our exponential model, we have found that VMAT2 binding declines first (approximately 17 years prior to disease onset), followed by decline in DAT binding (13 years prior) and then by F-dopa uptake (6 years prior) [2]. The latency between decline in DA function and clinical disease onset varies as a function of age. Patients with younger age of onset have a greater degree of DA dysfunction at disease onset (and longer duration of preclinical DA dysfunction). It should also be noted that in the posterior putamen, most of the damage has been done by the time of clinical disease onset, and even in the anterior putamen there is relatively little further decline beyond 10 years disease duration. By the time disease becomes

* Correspondence: 2221 Wesbrook Mall, Vancouver, BC Canada V6T 2B5. Tel.: +1 604 822 7967; fax: +1 604 822 7866.
E-mail address: jstoessl@mail.ubc.ca (J.A. Stoessl).

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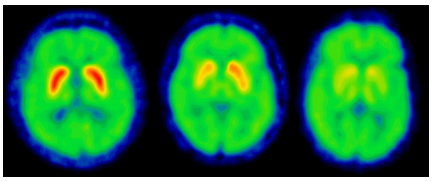

Fig. 1. VMAT2 binding assessed with [^{11}C]dihydrotetrabenazine PET in a healthy control subject (left), an asymptomatic LRRK2 mutation carrier (middle) and a patient with PD due to LRRK2 mutation (right).

manifest, DAT binding is reduced relative to VMAT2 binding, while F-dopa uptake is relatively increased. A recent post-mortem study found that tyrosine hydroxylase (TH) and DAT immunocytochemical staining is virtually absent in the dorsal putamen by 4 years disease duration [3]. Taken together, these findings highlight the importance of compensatory mechanisms in maintaining motor function in the face of severe loss of striatal DA innervation.

F-dopa uptake is decreased in subjects who are at risk of developing PD, including monozygotic twins of PD patients and subjects exposed to the nigral toxin MPTP. DAT and VMAT2 binding are decreased in asymptomatic carriers of LRRK2 mutations, although symptoms do not become apparent until F-dopa uptake is also reduced (Fig. 1). In LRRK2 mutation carriers, one of the earliest imaging abnormalities appears to be an increase in DA turnover [4], measured with F-dopa and long scan times (4 hours, as opposed to the routine 90-minute scan time, which predominantly reflects tracer uptake). This suggests that the mutation itself may result in abnormal vesicular dynamics, even prior to DA neuronal degeneration. Our findings to date suggest that the progression of DA degeneration in asymptomatic LRRK2 mutation carriers is in keeping with the preclinical trajectory predicted from extrapolation of the exponential function derived in patients with sporadic PD.

Not surprisingly, there is a broad correlation between markers of presynaptic DA function and clinical severity. However, most studies have failed to show a correlation between the *change* in PET markers and change in clinical function (Unified Parkinson Disease Rating Scale [UPDRS] or equivalent). There are several potential reasons for this disappointing lack of correlation between imaging and clinical measures of deterioration, including subjectivity of clinical scores, effects of medication and other symptomatic therapies, compensatory changes affecting the expression of DA markers as well as engagement of non-DA mechanisms, and the related but different problem that clinical progression may reflect degeneration of non-DA systems. This problem should not be seen as a fatal flaw in the use of functional imaging measures, but rather as a requirement for caution in interpreting the results.

2.3. Motor complications of PD

The DA D2/3 receptor ligand [^{11}C]raclopride (RAC) has a relatively weak affinity for DA receptors and its binding is accordingly subject to competition from endogenous DA. The practical significance is that by examining a change in RAC binding before and after an intervention, one can estimate the degree of DA release. Using this approach, we have found that DA release increases with increased duration of PD, and is of greater magnitude but shorter duration in patients with dyskinesias [5]. Furthermore, a similar aberrant pattern of DA release is seen in stable patients who later go on to develop motor fluctuations, compared to those patients who maintain a stable clinical response to treatment for 3 years after the scans [6]. This is in keeping with impaired storage of levodopa-derived DA in synaptic vesicles, as is also suggested by increased DA turnover as PD progresses [7]. This will presumably result in pulsatile stimulation of DA receptors, but suggests that some patients (those with greater DA turnover and a pattern of high magnitude but short duration DA release) are more prone to develop fluctuations and dyskinesias. One factor that may contribute to this is DA production by striatal serotonin (5HT) nerve terminals. While 5HT neurons are able to synthesize DA from levodopa, they do not store DA in vesicles nor is its release regulated in a physiological fashion [8]. It is therefore of great interest that PD patients who develop severe dyskinesias following fetal nigral transplantation demonstrate increased striatal binding of [^{11}C]DASB, a selective ligand for the 5HT transporter [9].

PET has shown very few changes in DA receptors related to the emergence of long-term motor complications. However, pulsatile stimulation can result in changes downstream to these receptors. It is therefore of interest that PD patients with dyskinesias have reduced opioid receptor binding, presumably reflecting occupancy secondary to increased release of endogenous opioids [10]. Cannabinoid receptor expression is decreased in the substantia nigra but increased in DA projection sites of patients with PD, but its expression is not related to the presence or absence of levodopa-induced dyskinesias [11]. In contrast, striatal adenosine A_{2A} receptor expression is no different between control and PD subjects without dyskinesias, but greatly increased in those with dyskinesia [12]. The mGluR5 receptor has attracted a great deal of interest with respect to its potential role in levodopa-induced dyskinesias. A number of radiolabelled mGluR5 ligands have been developed for PET, but there are to date no published studies on their application to the study of PD in humans.

2.4. Non-motor complications

Non-motor complications represent the greatest source of disability in PD. Cognitive impairment affects a large proportion of patients and some authors argue that the majority of patients with PD will ultimately develop dementia. Dementia in PD is associated with a pattern of glucose hypometabolism in which occipital cortex is disproportionately affected, in contrast to Alzheimer's disease (AD). Cholinergic activity is reduced throughout the cortex in PD, more so in those with cognitive impairment, in whom the abnormality is of greater magnitude than that seen in AD. There is growing interest in brainstem–thalamic cholinergic projections, which are affected to a more variable degree in PD, in association with REM behaviour disorder, olfactory dysfunction and postural instability [13–15].

Depression is another major problem in PD. Although it has long been assumed that this reflects loss of 5HT neurons, as is known to occur in PD, two imaging studies have independently demonstrated *increased* [^{11}C]DASB binding in depressed PD patients [16,17]. Another recent paper has suggested a correlation between depression in unmedicated PD patients and reduced striatal F-dopa uptake [18]. The interpretation of such studies can be confounded by the possibility that transporter binding could potentially be increased if there is reduced occupancy by endogenous ligands (i.e. DA or 5HT), although there is limited evidence to support this explanation as a basis for the imaging findings reported to date.

DA, in addition to its important role in motor function, is thought to signal the delivery of unanticipated reward, the anticipation of expected reward, and through this, incentive salience and learning. DA release can be demonstrated in response to natural rewards such as food and music, monetary rewards and placebo (expectation of therapeutic benefit). However, aberrant reward signaling may lead to addiction, and impulse control disorders (ICD) including pathological gambling, compulsive shopping, hobbyism, hypersexuality and compulsive eating affect affect some 17% or more of patients taking DA agonists [19,20]. The basis for this may represent a combination of hyperactivity in DA reward projections from ventral tegmental area (VTA) to ventral striatum (VS) and loss of normal behavioural inhibitory mechanisms. Thus, PD patients