Parkinsonism and Related Disorders 22 (2016) S47–S51

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Optimizing diagnosis in Parkinson's disease: Radionuclide imaging

Julieta E. Arena, A. Jon Stoessl*

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

ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form
11 September 2015
Accepted 14 September 2015

Keywords:
α-synuclein
Dopamine
5-hydroxytryptamine
Neuroinflammation
Positron emission tomography
Single photon emission computed tomography
Tau

ABSTRACT

Parkinson's disease (PD) and other disorders characterized by basal ganglia dysfunction are often associated with limited structural imaging changes that might assist in the clinical or research setting. Radionuclide imaging has been used to assess characteristic functional changes. Presynaptic dopaminergic dysfunction in PD can be revealed through the imaging of different steps in the process of dopamine synthesis and storage: L-aromatic amino acid decarboxylase (AADC) activity, Vesicular Monoamine Transporter type 2 (VMAT2) binding or its reuptake via the dopamine transporter (DAT). Postsynaptic dopamine dysfunction can also be studied with a variety of different tracers that primarily assess D2-like dopamine receptor availability.

The function of other neurotransmitters such as norepinephrine, serotonin and acetylcholine can be imaged as well, giving important information about the underlying pathophysiologic process of PD and its complications. The imaging of metabolic activity and pathologic changes has also provided great advances in the field.

Together, these techniques have allowed for a better understanding of PD, may be of aid for differentiating PD from other forms of parkinsonism and will undoubtedly be useful for the establishment of new therapeutic targets.

1. Introduction

Several neurologic conditions can be successfully diagnosed non-invasively through structural imaging techniques. Unfortunately, this has for the most part not been the case for Parkinson's disease (PD) and other disorders which arise from basal ganglia dysfunction, where structural changes are subtle and cannot be used to make reliable diagnoses. In turn, several functional imaging techniques have been developed to assess dopaminergic function or provide evidence of pathologic changes. The use of radionuclide imaging has allowed the study in vivo of neurotransmitters, metabolic activity and abnormal protein deposition; not yet in order to establish diagnostic certainty, but allowing for a better understanding of disease pathophysiology and progression, sometimes helping in differential diagnosis, and probably in the future help make earlier diagnosis and develop new therapeutic targets.

2. Dopaminergic imaging in Parkinson's disease

Dopamine (DA) synthesis occurs as a result of tyrosine hydroxylation into L-3,4-dihydroxyphenylalanine (levodopa), which is in turn decarboxylated by L-aromatic amino acid decarboxylase (AADC). Both newly synthesized and recycled DA is then pumped into synaptic vesicles by the Vesicular Monoamine Transporter type 2 (VMAT2). DA is released into the extracellular space after cell depolarization, to interact with pre and post-synaptic receptors. Termination of such signalling is predominantly accomplished in the normal brain by DA reuptake from the synaptic cleft via the dopamine transporter (DAT). Several steps in this process can be studied using radio ligands, providing a direct measure of DA activity, and indirectly measuring the integrity of dopaminergic structures.

2.1. Assessment of presynaptic dopaminergic function (Fig. 1)

Presynaptic dopaminergic integrity can be measured in several ways:

- AADC activity by measuring 6-[18F]-fluoro-L-dopa (FD) uptake and decarboxylation: FD is transported across the blood brain

* Corresponding author. Pacific Parkinson's Research Centre & National Parkinson Foundation Centre of Excellence Djavad Mowafaghian Centre for Brain Health, University of British Columbia & Vancouver Coastal Health. 2221 Wesbrook Mall, Vancouver BC V6T 2B5, Canada.
E-mail addresses: jstoessl@mail.ubc.ca, jstoessl@interchange.ubc.ca (A.J. Stoessl).

http://dx.doi.org/10.1016/j.parkreldis.2015.09.029
1353-8020/

barrier, undergoes uptake by striatal dopaminergic terminals, is decarboxylated by AADC to fluorodopamine (FDA) and stored in synaptic vesicles. FD uptake correlates well with dopaminergic cell counts. Relative to VMAT2 binding, FD uptake in PD is preserved, possibly due to compensatory up-regulation of AADC in early disease. By conducting longer scans that extend beyond the time of predominantly unidirectional trapping, FD uptake can also be used to assess DA turnover.

- VMAT2 density: VMAT2 is responsible for the storage of monoamines into synaptic vesicles. Its activity can be measured with ^{11}C-dihydrotetrabenazine (DTBZ) or ^{18}F-9-fluoropropyl-(1)-dihydrotetrabenzazine (^{18}F-DTBZ) [1]. Studies in rats have demonstrated a good correlation with substantia nigra-pars compacta cell counts. VMAT2 activity is proposed to be less prone to changes induced by medication or compensatory mechanisms compared to AADC activity or DAT binding. Nonetheless, VMAT2 activity can be influenced by the level of vesicular DA, competing at the recognition site. Thus, the level of VMAT2 binding may decrease with levodopa administration [2].
- Availability of DAT: A variety of ligands can be used to assess the availability of presynaptic DAT, either with SPECT imaging, labelled with ^{123}I such as ^{123}I-fluoro-propyl-CIT (^{123}I-FP-CIT) [DaTScan], ^{123}I-β-CIT, or ^{123}I-altopane; or labelled with ^{99m}Tc such as ^{99m}Tc-TRODAT-1. DAT activity can also be imaged using PET, labelled with ^{11}C, as ^{11}C-CFT, ^{11}C-RTI-32 or ^{11}C-methylphenidate (MP); or labelled with ^{18}F, as ^{18}F-FP-CIT. DAT binding correlates well with striatal dopaminergic neuron cell counts, and with disease severity in PD. It is important to keep in mind though that DAT binding is subject to changes in response to DA levels; it has been suggested that downregulation of the DAT is expected in response to decreasing DA levels, to ensure higher levels in the synaptic cleft [3].

2.2. Assessment of postsynaptic dopaminergic function

Most studies have focused on availability of D2-like dopamine receptors. The most widely used tracer in PET is ^{11}C-raclopride (RAC) which is subject to competition from endogenous DA. RAC binding is increased in the PD striatum, reflecting a combination of receptor upregulation and reduced occupancy by endogenous DA. Dopaminergic medication or disease progression may result in decreased uptake with time. ^{11}C—PHNO is a D2-like agonist which binds preferentially to D3 receptors, particularly in the substantia nigra and globus pallidus. Its binding is also highly sensitive to the effects of synaptic dopamine [4].

3. Imaging of other neurotransmitters

A number of non-DA pathways are affected in PD. Both the locus coeruleus (LC; noradrenergic), and the median raphe nucleus (serotonergic), also take up ^{18}F-FDOPA, showing an increased uptake in early PD, probably reflecting compensatory upregulation of AADC. Decline to subnormal levels with advanced disease is ultimately seen [5]. The norepinephrine transporter can be evaluated using the non-selective tracer ^{11}C-RTI-32; decreased uptake has been found in the LC, thalamus and limbic system in patients with PD and associated depression [6].

The selective 5HT transporter ligand ^{11}C-DASB can be used to estimate the density of serotonergic nerve terminals (Fig. 1). DASB binding is reduced in the cerebral cortex, striatum and brain stem in PD, suggesting a progressive dysfunction, unaffected by disease duration, severity, or exposure to dopaminergic drugs [7].

The study of cholinergic activity using tracers for acetylcholinesterase such as ^{11}C-Methylpiperidin-4-yl propionate (PMP) showed it to be reduced in cortical regions in patients with PD, especially in patients with PD dementia or dementia with Lewy bodies. With the exception of lateral temporal cortex, PD and PD-dementia patients showed less cholinergic activity than Alzheimer's disease patients [8]. Given the limited response of parkinsonian gait disturbances to levodopa, it is reasonable to think that other networks are affected. With comparable dopaminergic activity, PD patients with frequent falls were found to have reduced cortical and thalamic cholinergic activity, as measured by ^{11}C-PMP PET [9]. This supports the importance for gait of the pedunculopontine nucleus, the principal cholinergic input to the thalamus.

Studies with ^{11}C-PMP have also shown a direct relation between cholinergic activity in the hippocampal formation, amygdala and neocortex, and olfactory function [10]. Subjects with PD and REM sleep behaviour disorder (RBD) were found to have greater degrees of neocortical, limbic cortical and thalamic cholinergic denervation [11].

It has been proposed that deposits of α-synuclein may originate in autonomic nerve endings of the gastrointestinal tract and follow a retrograde transmission to the caudal brainstem via the vagus. A recent study used ^{11}C-donepezil PET to demonstrate parasympathetic denervation of the GI tract in PD [12]. The role of GI imaging for differential diagnosis is uncertain. However, the demonstration of parasympathetic dysfunction in the gastrointestinal system provides further evidence to support Braak's theory.

4. Metabolic activity measurement

Energy metabolism can be studied using ^{18}F-2-fluorodeoxyglucose (FDG) PET, which reflects neuronal and synaptic activity. By applying a form of principal components analysis, it is possible to identify networks of linked increases and decreases in activity. PD exhibits a characteristic network of altered metabolism, coined the PD related pattern (PDRP). The most prominent abnormality is increased pallidothalamic, pontine and cerebellar metabolic activity, and decrease in premotor cortex and parietal association regions in later stages. This pattern is useful for the differential diagnosis from other causes of parkinsonism, such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration, each of which has its own defining features. The PDRP correlates with motor ratings, and is reduced by L-dopa treatment or deep brain stimulation [13].

Increased metabolic activity in the cerebellum, dentate nucleus, primary motor cortex and caudate/putamen to a lesser extent has been related to parkinsonian tremor; while reduced activity in the medial prefrontal, premotor and parietal association areas, accompanied by increased activity in the cerebellar vermis and dentate nucleus has been associated with cognitive dysfunction in PD [13].

5. Imaging pathology (Figure)

As is the case for the measurement of β-amyloid or tau in Alzheimer's disease, the optimal scenario would the capacity to measure a marker of disease burden in PD. This would provide an earlier diagnosis, even before dopaminergic dysfunction. Earlier diagnosis will be of particular importance as neuroprotective therapies become available. The ability to localize α-synuclein aggregation might additionally assist in differential diagnosis.

Attempts to image α-synuclein have been hampered by limited tracer specificity and intraneuronal localization of such deposits [14]. Several markers such as ^{11}C- and ^{18}F-labelled benzoxazole compounds have been developed to label α-synuclein, but they also