

Continuous Dopaminergic Stimulation in Parkinson's Disease— What Have We Learned from Positron-emission Tomography?

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Abstract

The hypothesis that pulsatile stimulation of striatal dopamine receptors in Parkinson's disease (PD) induces molecular and physiologic changes in basal ganglia neurons and may contribute to the development of motor complications has led to the design of therapeutic strategies that provide more continuous dopaminergic stimulation. Newer agents and drug-delivery systems such as slow-release preparations, catechol-O-methyltransferase, and monoamine oxidase inhibitor agents, apomorphine, and Duodopa™ infusions represent a significant step towards less pulsatile dopaminergic administration. However, their efficacy in providing steady brain levels of dopaminergic stimulation in the short and longer term has not yet been proved in patients. This article briefly reviews and discusses the findings of published positron emission tomography (PET) studies that support or oppose the value of continuous dopaminergic stimulation in PD. The potential future value of PET for proof of mechanism in this area is also debated.

Keywords

Parkinson's disease (PD), positron emission tomography (PET), dopamine release, levodopa, continuous dopaminergic stimulation

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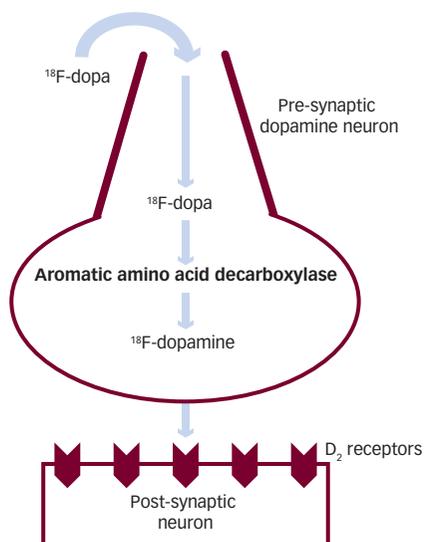
Oral levodopa remains the most effective symptomatic drug for Parkinson's disease (PD); however, its long-term use is limited by the emergence of motor fluctuations and involuntary movements, particularly in young-onset patients. A growing number of pre-clinical and clinical studies suggest that non-physiological pulsatile stimulation of striatal dopamine (DA) receptors induced by the use of short-acting oral levodopa preparations, which produce swinging levels of synaptic DA, may contribute to the onset of motor fluctuations and dyskinesias. By contrast, more continuous and less pulsatile forms of dopaminergic stimulation delivered by longer-acting oral DA agonists result in a more stable clinical response and delay the development of motor complications, while steady infusions of apomorphine and levodopa can abolish motor fluctuations and dyskinesias.^{1–3}

Based on these observations, new levodopa formulations and alternative routes of administration for both levodopa and DA agonists have been introduced in the treatment of PD during the last decade, including slow-release preparations, addition of a catechol-O-methyltransferase (COMT) (entacapone or tolcapone) or monoamine oxidase B (MAOB) inhibitor (rasagaline), intravenous and enteral (duodenal) infusions of levodopa, and transdermal administration and subcutaneous infusion of DA-receptor agonists. All of these strategies aim to optimize the clinical response by achieving stable and prolonged levels of synaptic DA. However, whether these strategies truly provide continuous dopaminergic stimulation has not yet been ascertained.

Positron-emission tomography (PET) is a neuroimaging technique that tags short-lived positron-emitting radioisotopes to chemical compounds of biological interest to produce 3D images of functional processes and drug-receptor occupancy in the body. In patients with PD, PET has been extensively used to investigate the function of brain dopaminergic nerve terminals, providing useful information on the density of functioning nerve terminals in the striatum and DA storage capacity, the availability of post-synaptic dopaminergic receptors, and changes in synaptic DA levels following behavioral and pharmacological challenges. This article will review the findings of published PET studies that support or oppose the value of continuous dopaminergic stimulation in PD.

Dopamine-replacement Treatment and Pre-synaptic Dopaminergic Function

The COMT inhibitors entacapone and tolcapone increase levodopa bioavailability in the plasma and increase its transport into the brain by blocking the peripheral 3-O-methylation of levodopa. Like levodopa, 3-O-methyldopa (3-OMD) is transported into the brain by the large neutral amino acid (LNAA) carrier, but it is not decarboxylated. The effect of COMT inhibitors on striatal levodopa kinetics has been extensively investigated with ¹⁸F-dopamine PET in both PD patients and healthy controls.^{4–8} Striatal ¹⁸F-dopa uptake, as measured by the influx constant K_i, reflects four sequential processes: transport by LNAA through the blood-brain barrier, uptake into dopaminergic neurons, metabolism to ¹⁸F-dopamine by aromatic amino acid decarboxylase (AADC), and

Figure 1: Scheme Showing the Metabolic Pathway of ^{18}F -dopa

vesicular storage of ^{18}F -dopamine (see *Figure 1*). As ^{18}F -dopa and non-fluorinated levodopa follow the same metabolic pathway, peripheral COMT inhibition boosts ^{18}F -dopa bioavailability to the brain and increases its striatal uptake and subsequent metabolism in PD patients. Several PET studies have been performed to measure the effect of peripheral COMT inhibitor entacapone on striatal uptake of ^{18}F -dopa.⁴⁻⁷ Striatal K_i values can be computed by graphical analysis in two main ways. If a plasma input reference function is used, corrected for levels of ^{18}F -3-OMD, the striatal K_i value primarily reflects the rate constant for dopa decarboxylation. Alternatively, if an occipital cortex reference input function is used, the ^{18}F reference signal reflects occipital levels of both ^{18}F -dopa and ^{18}F -3-OMD in equilibrium with plasma. The striatal K_i then reflects the product of the rate constant for dopa decarboxylation and the striatal volume of distribution (VD) of ^{18}F -dopa.

Sawle et al.⁴ performed ^{18}F -dopa PET in four early parkinsonian patients and six age-matched normal controls both before and after taking entecapone 400mg. Using a plasma input function they found no change in striatal K_i after entecapone, implying that this agent does not influence dopa decarboxylation. However, they found a 45% increase in the striatal ^{18}F -dopa influx constant K_i after entecapone when computed with an occipital reference input function. As the effect of entecapone was to increase the fraction of unmetabolised ^{18}F -dopa in plasma from 22 to 56% 90 minutes after injection; this 45% increase in K_i represents a corresponding increase in striatal ^{18}F -dopa VD.

In a similar study in PD patients,⁵ entecapone enhanced the striatal ^{18}F -dopa K_i (computed with an occipital reference input function) by 53.5% compared with placebo. However, changes in striatal ^{18}F -dopa uptake induced by entecapone are smaller in patients with advanced PD. This probably reflects a more severe loss of dopaminergic terminals, leading to impaired DA storage capacity in these patients.^{6,7} From these studies it can be concluded that entecapone has little effect on ^{18}F -dopa decarboxylation in the striatum and that its main pharmacologic

effect is related to reduced peripheral 3-O-methylation and increased availability of plasma ^{18}F -dopa to the brain.

Unlike entecapone, which is purely a peripheral COMT inhibitor, tolcapone is a mixed peripheral and central COMT inhibitor.^{9,10} The effect of tolcapone on COMT activity has been investigated in 12 PD patients with ^{18}F -dopa PET.⁸ The study design comprised two PET scans on two separate days. Each patient received levodopa/carbidopa (100/125mg) with either tolcapone (200mg) or placebo one hour before an ^{18}F -dopa injection and was scanned for 240 minutes after tracer injection. ^{18}F -dopa K_i values were computed using a graphical approach with a plasma input function corrected for the presence of ^{18}F -3-OMD. Mean putamenal ^{18}F -dopa K_i values for the first 30–90 minutes, reflecting central AADC activity, were not modified by tolcapone pre-treatment in PD. Mean putamen K_i values calculated 180–240 minutes after tracer injection, which reflect dopa metabolism by both central AADC and COMT, fell with placebo but were unchanged with tolcapone, implying that this agent was successfully blocking central COMT.

Effect of Dopamine-replacement Treatment on Post-synaptic Dopamine Function

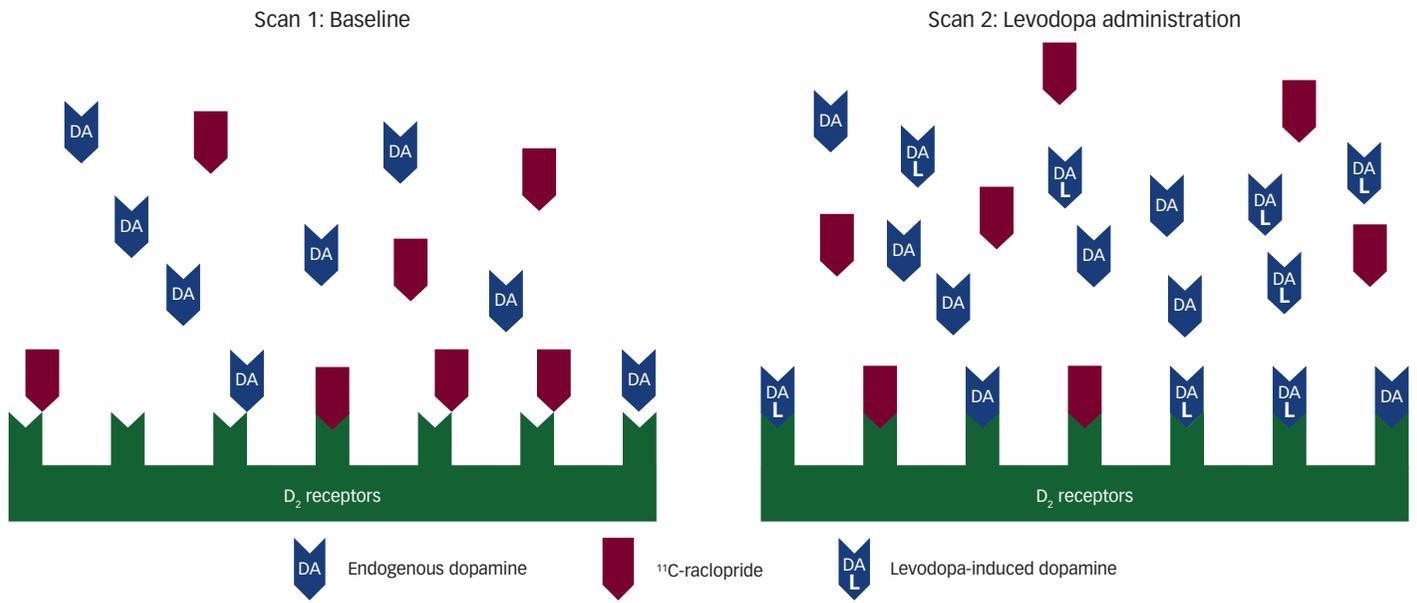
^{11}C -raclopride, a reversibly binding DA D_2/D_3 receptor ligand, is often used to assess post-synaptic dopaminergic receptor availability with PET. Its uptake is influenced by the synaptic level of DA, which competes for the same receptors, so ^{11}C -raclopride PET can potentially be used to monitor dopaminergic transmission.¹¹

Studies in untreated PD patients have reported 10–20% increases in putamenal ^{11}C -raclopride binding, suggesting increased DA D_2 receptor availability is present.^{12–14} This increase could simply reflect lower synaptic DA levels competing for DA D_2 sites or, conversely, could represent compensatory receptor upregulation to loss of nigrostriatal input. In PD patients treated long-term with levodopa, putamenal ^{11}C -raclopride binding returns to the normal range as synaptic DA levels are restored and adaptive upregulation reverses.^{14–18}

Uitti et al.¹⁹ scanned 10 untreated PD patients with ^{11}C -raclopride PET who were subsequently treated with either Sinemet® (300mg of levodopa daily) or Sinemet® CR (400mg of levodopa controlled-release daily) for six months and then crossed over to the other levodopa preparation for a further six months. At baseline, these workers found striatal ^{11}C -raclopride binding to be increased in the untreated PD patients. When the patients were re-scanned after six months of levodopa treatment, there were no significant differences in striatal ^{11}C -raclopride binding in either group from baseline. After the second six-month period of levodopa treatment, again no differences in ^{11}C -raclopride binding were seen compared with baseline or between type of levodopa preparation. Clinically, both groups received similar symptomatic benefit following treatment, and none developed motor fluctuations. These workers concluded that striatal DA D_2 normalization via downregulation in PD following levodopa exposure must take longer than 12 months.

Striatal DA D_1 receptor availability can be assessed with ^{11}C -SCH23390 PET and is preserved in untreated PD patients, but reduced by 20% in patients chronically exposed to levodopa.^{14,20}

Figure 2: Schematic Representation of the ¹¹C-raclopride Displacement Paradigm



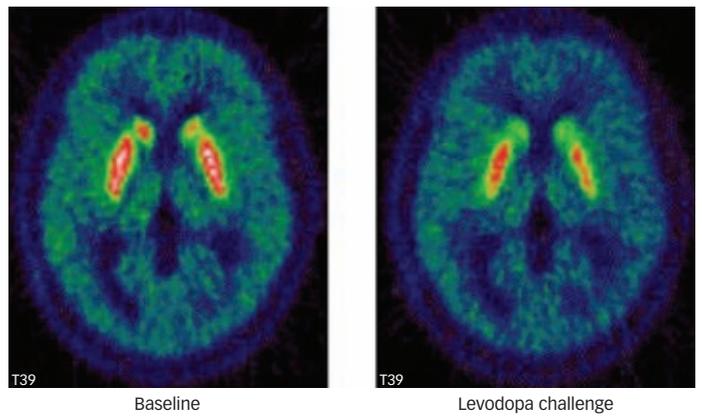
Changes in ¹¹C-raclopride binding between baseline and post-treatment states (in this case administration of oral levodopa/carbidopa) represent a change in synaptic dopamine levels, reflecting the release of dopamine induced by levodopa administration. DA = dopamine.

To summarize, exposure to oral levodopa appears to have only mild effects on the total availability of DA D₁ and D₂ receptors in PD patients. Having said that, current PET studies with antagonist tracers are unable to separate signal from high and low agonist affinity receptor conformations and it is possible that the relative sub-populations are altered. Additionally, they do not exclude that downstream neurotransmitter changes can be induced depending on the kinetics of DA-receptor stimulation.

Effect of Dopamine-replacement Treatment on Striatal Dopamine Release

¹¹C-raclopride PET can also be used to assess fluctuations in synaptic concentrations of DA following pharmacological or behavioral challenges (see Figure 2). Rises in synaptic DA levels translate into decreases in DA D₂-receptor availability, which can be detected as reductions in ¹¹C-raclopride binding.¹¹ It has been estimated that a 10% reduction in ¹¹C-raclopride binding reflects a five-fold increase in synaptic DA levels.²¹ This paradigm has recently been employed to assess the changes in synaptic DA levels after administration of a single dose of exogenous levodopa in PD patients (see Figure 3). Results from these studies have shown that striatal reductions in ¹¹C-raclopride binding after a levodopa challenge become greater as motor disability increases and the disease progresses.²²⁻²⁵ Changes in ¹¹C-raclopride binding after oral administration of standard levodopa/carbidopa (250/25) were assessed in a group of PD patients with and without peak-dose dyskinesias.²⁴ Each patient received three ¹¹C-raclopride PET scans. The first one was performed at baseline with the patient 'off' medication and the others at one hour and four hours after levodopa. PD patients with dyskinesias had larger increases in synaptic DA levels than patients with stable response to levodopa one hour after administration, whereas there were no between-group differences at four hours. This finding suggests that peak-dose dyskinesias are associated with enhanced

Figure 3: ¹¹C-raclopride Positron-emission Tomography Images from a Parkinson's Disease Patient



Images taken at baseline and after oral administration of standard levodopa/carbidopa (250/25).

pulses of DA release induced by levodopa administration. In line with this interpretation, our group has recently reported that large putaminal ¹¹C-raclopride binding changes induced by Sinemet® 275 were directly associated with higher dyskinesias scores during the scan session.²⁵

The increased synaptic DA levels that result from levodopa administration in dyskinetic and in more advanced PD patients probably reflect the reduced DA storage capacity of the severely affected putamen. However, another explanation could be the reduction of DA transporters (DAT) available to clear the transmitter. In line with this theory, Sossi and colleagues²⁶ found a significant negative correlation between changes in synaptic DA concentration and binding of the DAT marker ¹¹C-methylphenidate. Greater reductions in ¹¹C-raclopride, indicative of lower changes in synaptic DA concentration and

lower DA turnover, were observed to be associated with lower ¹¹C-methylphenidate binding. This finding suggests that DAT may play an important functional role in maintaining synaptic DA levels when pulsatile levodopa is administered. Therefore, decreases in DAT availability/function may result in greater oscillations in synaptic DA levels, contributing to the development of motor complications as the disease progresses. Although previous studies indicate that ¹¹C-raclopride PET represents a useful tool to investigate turnover of levodopa-induced synaptic DA in PD, this paradigm has not been applied to assess the efficacy of approaches to continuous levodopa delivery. Our group is currently testing the hypothesis that enteral (duodenal) infusions of levodopa provide stable and more prolonged synaptic levels of striatal DA compared with standard levodopa administration along with a sustained motor response.

Discussion

To our knowledge there are no PET studies that have directly tested whether currently available drug approaches, which provide more sustained levodopa delivery, also provide stable and more prolonged synaptic levels of striatal DA along with a sustained motor response. However, it is clear that PET has a great potential in this specific research field and could provide valuable insight on the pharmacokinetics and pharmacodynamics of new agents and therapeutic strategies in PD. First, the entacapone and tolcapone experience clearly indicates that quantitative ¹⁸F-dopa PET may be useful in assessing pharmacological manipulations of levodopa delivery into the brain. Late imaging can be informative if central COMT inhibition needs to be demonstrated. More importantly, sequential ¹¹C-raclopride PET scans can be used to compare the effects of

intermittent and continuous dopaminergic delivery directly on striatal DA levels in PD patients. The same paradigm may also be useful to examine whether pulsatile and continuous dopaminergic stimulation have different long-term effects on pre-synaptic function and on the ability of the striatum to release DA in the synaptic cleft following an acute levodopa challenge. ■



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