In vivo imaging of levodopa-induced angiogenesis and its relevance to tardive dyskinesia in a parkinsonian rat model

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In vivo imaging of levodopa-induced angiogenesis and its relevance to tardive dyskinesia in a parkinsonian rat model

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Research Abstract
As baby boomers are aging (by 2031, all baby boomers will be over 65 years old), more health care needs are anticipated for aging-related neurodegenerative disorders. After Alzheimer's Disease, PD is the second most common neurodegenerative disorder and it affects more than 1% of people over 65 years of age. In Canada, nearly 100,000 people are estimated to have PD. With an aging population, the financial burden on society is expected to be greatly

increased. The dopamine precursor levodopa is the most effective medication available for the treatment of PD, but it causes a particularly disruptive motor side effect: levodopa-induced dyskinesia (LID). LID refers to involuntary muscle movement and it is one of the most critical factors that deteriorates a patient's quality of life in the later disease stage. More than 50% of PD patients develop LID in the course of long term levodopa treatment. Despite these side effects, levodopa has been the first-line anti-parkinsonian therapy since its introduction in the 1960's, thanks to its superior efficacy.

In clinics the most common strategy to address LID is to delay or to minimize levodopa treatment, lower the individual levodopa doses and increase the dosing frequency or, where possible, by administering dopamine receptor agonists. Symmetryl (amantadine) can also be used to ameliorate dyskinesia, but its effect is relatively short-lived ranging from several months to a few years, and its specific underlying mechanisms in suppressing LID is still unknown. Subthalamic deep brain stimulation (DBS) is commonly advised to allow substantial reduction of levodopa dosage, which significantly ameliorates LID for long-term. However only 20% of PD patients are qualified for DBS due to old age, cognitive impairment or other health-related problems. Therefore significant effort has been undertaken to determine how to minimize the incidence of LID, and thus to avoid its disabling effects. Clinical studies utilizing the LID incidence rate alone as a final outcome require a very large number of test subjects, making it difficult to evaluate possible promising treatment strategies. Therefore, an objective biomarker for LID with predictive capacity is required. The overarching aim of the current project is to establish an imaging-based biomarker for LID and explore its underlying mechanisms. Here, we propose to use the hybrid of positron emission tomography (PET) and magnetic resonance imaging (MRI), which has only become recently available. To our knowledge, we are the only centre in Canada that has hybrid PET-MRI for small animals.

Acutely, LID is triggered by large, transient increases in striatal levels of dopamine following peripheral levodopa administration. Chronically, both the severity of dopaminergic denervation and malfunction of preserved serotonergic terminals (e.g., un-regulated release of dopamine by serotonergic neurons) play important roles in LID. PET with appropriate radiotracers can estimate how much dopamine is released in response to levodopa or how much serotoninergic terminal is preserved, but the poor test-retest variability and tracer-unavailability in most PET centers discourage their uses as a LID-related biomarkers. On the other hand, recent functional MRI (fMRI) studies suggested that LID is associated with hyperactivity in the thalamo-cortical motor circuits. As increased neuronal activity increases both metabolism and blood flow (i.e., neurovascular coupling hypothesis), the increased fMRI-measured activity in patients with LID was interpreted as increased neuronal activity in response to levodopa. However, our recent data challenge this interpretation.

A recent observation that striatal glucose metabolism was slightly decreased in response to levodopa infusion suggested that the increased blood flow is not driven by the increased oxygen demand as in normal neurovascular interaction, but it may stem from a direct vasodilation effect of levodopa. This increase of cerebral blood flow induced by acute levodopa is exaggerated in LID patients due to angiogenesis induced by chronic levodopa exposure. Emerging evidence of angiogenesis has been reported in the striatum in the rat model of LID, which is also confirmed post-mortem in PD patients. Chronic levodopa exposure increases microvasculature, which may result in dopaminergic overshoot by acute oral levodopa intake in the dopamine-abundant regions, and this may play the key roles in developing LID.

Using this phenomenon of “non-neuronal hyper-perfusion” (a term coined to emphasize that the increased blood flow is not mediated by increased neuronal activity as described in the neurovascular coupling hypothesis), we proposed a novel brain imaging-based biomarker for LID-related angiogenesis in PD, i.e., the non-neuronal hyper-perfusion index (NNHI). The NNHI reflects increased blood flow (measured by MRI) in selective regions (i.e., striatum, thalamus and pons) bearing unchanged or decreased glucose metabolism (measured by PET). In our preliminary study, we showed that patients with LID have a significantly increased NNHI score compared to patients without LID. With a low dose daily levodopa regimen, about half of parkinsonian rats develop LID and the rest do not, which is similar to what happens in PD patients. It has been reported that the LID rats’ regional cerebral blood flow was increased in response to levodopa compared to non-LID rats while glucose metabolism was relatively unchanged.

In the current project, we propose a preclinical brain imaging study with a parkinsonian rat model to establish the suggested PET-MR imaging-based biomarker. Thirty 6-OHDA-lesioned parkinsonian rats will receive daily levodopa treatment. It is anticipated that fifteen rats will develop LID and the other fifteen will not. Nine additional parkinsonian rats will receive saline instead of levodopa (control group). All rats will be scanned with PET-MRI six times longitudinally; 1) baseline-OFF (before levodopa treatment initiation), 2) early-ON (1st day of levodopa treatment), 3) mid-ON (12th day), 4) late-ON-1 (21st day), 5) late-ON-2 (22nd day), 6) late-OFF (23rd day). Aim 1) Optimizing the brain imaging analytic protocol for non-neuronal hyper-perfusion detection. The NNHI method will be compared with other analytic methods (principal component analysis and support vector machine) that is designed to minimize test-retest variability (late-ON-1 vs. late-ON-2) and maximize the group differentiation (LID-rats vs. non-LID-rats), and the best method will be selected as a LID-related imaging-based biomarker. Aim 2) Confirming the acute effect of levodopa on non-neuronal hyper-perfusion. We will examine if acute vasodilation induced by levodopa increases NNHI (or other selected method outcome) replicating the human study. This will examine if the affected site of the acute vasodilation and chronic angiogenesis are spatially overlapping. Aim 3) Estimating the risk of developing LID before its emergence. We will test if NNHI (or other selected method outcome) predicts future emergence of LID at baseline, early or mid-point of levodopa treatment schedule. If successful, this study will strengthen the hypothesis that the proposed method can be used as a prognostic tool for LID in human. Aim 4) Post-mortem validation and underlying mechanisms of levodopa-induced angiogenesis. We will investigate newly proliferated endothelial cell count (BrdU+RECA co-localization) in the key anatomical regions that showed non-neuronal hyper-perfusion is correlated with NNHI (or other selected outcome). We will also explore how astrocytes (GFAP), dopaminergic (TH) and serotonergic (Serotonin) neurons are co-localized

with the newly proliferated endothelial cells and how they differ between LID-rats vs. non-LID-rats.

The ultimate goal of the proposed research is to establish an imaging-based biomarker for levodopa-induced angiogenesis which may precede and be responsible for LID emergence. If successful, follow-up studies will be conceived testing the effect of existing and experimental LID treatment strategies, e.g., amantadine and eltoprazine. In the midst of rapidly rising popularity of hybrid PET-MRI (clinical), as the only imaging center equipped with small animal hybrid PET-MRI in Canada (as of February 8th, 2016), we expect that our subsequent research proposals based on the prospective finding (sponsored by Research Manitoba) will be strong candidates for national research fund competitions such as CIHR.

Further information available at:

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