Serotonin neuroplasticity in Parkinson’s disease: novel targets for the treatment of L-DOPA-induced dyskinesia


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Introduction
Since its discovery nearly 50 years ago, dopamine (DA) replacement with L-3,4-dihydroxyphenylalanine (L-DOPA) has remained the gold standard treatment for the symptomatic treatment of Parkinson’s disease (PD). Unfortunately as the disease progresses and higher doses of L-DOPA are required, exaggerated involuntary movements known as L-DOPA-induced dyskinesia (LID) develop in up to 90% of patients [1]. Several pre- and post-synaptic mechanisms likely contribute to this debilitating side effect including abnormal motor learning in corticostriatal afferents, fluctuating striatal DA levels, and supersensitive DA receptor signaling [2-4]. In recent years, research has suggested that neuroplasticity in the serotonin (5-HT) system of the parkinsonian brain may provide novel targets for the modulation of these processes and point towards innovative approaches for the treatment of LID.

Methods
To determine the utility of 5-HT modulation for the reduction of LID, our laboratory has employed the DA neurotoxin 6-hydroxydopamine (6-OHDA) to create hemi-parkinsonian rats that display movement deficits, respond to the anti-parkinsonian benefits of L-DOPA, and develop abnormal involuntary movements (AIMs), a LID proxy, with chronic L-DOPA administration [5,6]. Using multifaceted pharmacological, neurochemical and cellular approaches, we have examined how 5-HT receptors and modulators influence in vivo glutamate and DA neurotransmission in the motor circuit of actively dyskinetic rats.

Results and Discussion
While several 5-HT receptor systems appear responsive to DA loss and/or L-DOPA therapy, 5-HT1A receptors and 5-HT transporters (SERT) undergo significant gain of function, articulating neuromodulatory effects at several points within basal ganglia. First, direct stimulation 5-HT1A receptors of the dorsal raphe potently reduce LID, most likely through modulation of 5-HT neuron-derived striatal DA release [7]. Second, 5-HT1A receptors of the striatum and motor cortex modify glutamate neurotransmission and may thereby correct for aberrant plasticity pervasive in LID [8,9]. Finally, selective blockade of SERT via SSRI treatment appears reduce the expression and development of LID, perhaps by normalizing L-DOPA-mediated signaling without affecting its efficacy [10]. These collective findings indicate novel avenues of research that have important translational value for the study and treatment of LID for the improved care of the PD patient.
References


