EDITORIAL

Dyskinesia in Parkinson Disease – An Unmet Therapeutic Challenge

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Levodopa remains the most effective therapy for the treatment of motor symptoms in Parkinson Disease (PD)[1]. However, complications, such as motor fluctuations and dyskinesias, arise with chronic treatment. Levodopa-induced dyskinesias (LID) are involuntary movements including chorea, dystonia, myoclonus or ballism, which can occur at peak drug effect, at the onset and offset of drug effect, as the drug effect is decreasing or throughout the dose period[2]. Levodopa-induced dyskinesias occur in up to 50% of patients within five years of therapy initiation and up to 90% in patients treated for more than ten years[3]. Although some patients may not consider these dyskinetic movements as bothersome, the presence of these movements may significantly interfere with the ability to perform daily tasks. Once dyskinetic movements are induced, the treatment of PD often becomes a difficult and delicate balance between treating bradykinesia (i.e., keeping patients in a functional "on" state) without producing excessive dyskinesia.

Levodopa-induced dyskinesias is thought to be induced through biochemical mechanisms in striatal neurons resulting from rapidly fluctuating exposure to dopamine[4,5]. As dopaminergic cells are lost with disease progression, there are fewer presynaptic terminals to store dopamine and to buffer the pulsatile pharmacokinetics associated with the typical oral dosing regimens of levodopa. This effectively narrows the therapeutic window and shortens the duration of effect as post-synaptic dopamine receptors are subjected to levels of dopamine that more closely resemble the fluctuating levels found in plasma[5]. The loss of continuous dopamine receptor stimulation is thought to induce a change in the differential expression of dopamine receptors (in particular D1, D2 and D3 receptors) and their second messenger pathways, a priming process resulting in the expression of dyskinesia with subsequent administration of levodopa or other dopamine agonists[4,5].

In addition to changes observed in dopamine receptors and associated signaling cascades, priming of LID is associated with alterations in corticostriatal connectivity through changes in the functional activity of N-Methyl-D-Aspartate (NMDA) glutamate receptors[4,5]. For example, a recent *in vivo* human study demonstrated an increase in NMDA receptor activity through changes in receptor phosphorylation in response to levodopa in LID patients[5,6]. This leads to abnormal sensitization and responsiveness to glutamatergic cortical input[4], and may reflect functional interactions between NMDA and dopamine receptors on medium spiny neurons in the striatum[7]. Changes in NMDA receptor signaling is consistent with the observed clinical benefit of NMDA receptor antagonists, such as amantadine, as adjuvant therapy in LID[1,3,5,8,9]. However, to date, assessment of the antidyskinetic efficacy of amantadine, and other NMDA receptor antagonists, has been limited to reports of small trials (e.g.,[9]).

The purpose of the meta-analysis by Elahi et al in the current issue of the Canadian Journal of Neurological Sciences was to examine the efficacy of NMDA receptor antagonists, including amantadine, in the treatment of LID in patients with PD[10]. Overall, the results suggest that amantadine can be effective in treating LID, which is consistent with the theory that NMDA receptor plasticity plays a significant role in the ongoing expression of LID[4,5]. However, limitations of the study highlight the need for further investigation to evaluate the long-term effects of amantadine and the efficacy of other NMDA receptor antagonists in reducing LID.

Since the Practice Parameter from the American Academy of Neurology on the treatment of PD with motor fluctuations and dyskinesia[9], many novel therapeutic agents have been investigated including those targeting serotonergic, GABAergic, and nicotinergic pathways[3,5] as well as the use of antiseizure medications like levetiracetam[3,5,11]. In addition to advances in deep brain stimulation[3,9], other non-pharmacologic therapies such as transcranial magnetic stimulation have also been studied[3]. Much of the development of these therapies comes from studies using animal models of PD and LID. The two most established of these are the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non human primate and the 6-hydroxydopamine (6-OHDA)-lesioned rat[4,5,12]. Although not without their limitations, these and other animal models remain instrumental in advancing the understanding the patho-physiology of PD and LID.

The prevention and treatment of LID in PD remains a clinical challenge. As new agents are translated from animal models to clinical applications, it will be necessary to continue to amalgamate the results of small trials to help guide clinical utility until larger and more formal clinical trials can be organized.

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