

Activation of the GPCR Smoothened as a treatment of L-Dopa Induced dyskinesia

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Activation of the GPCR Smoothened as a treatment of L-Dopa Induced dyskinesia

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Research Abstract

Dopamine replacement therapy, specifically L-DOPA treatment, continues to be the mainstay in Parkinson's Disease (PD) treatment. Unfortunately, with continued use patients develop debilitating side-effects of involuntary movements, L-DOPA induced dyskinesia (LIDs), which severely limit the long-term therapeutic utility of L-DOPA. Intensive research has been devoted to finding a treatment that can reduce or eliminate LIDs, but to date without success. In addition

to releasing dopamine (DA), dopamine neurons secrete a number of molecules to communicate with their targets. The concentration of all of these factors, in addition to DA, must diminish in the basal ganglia of PD patients due to the progressive degeneration of DA neurons. We previously found that all dopamine neurons produce sonic hedgehog (Shh), a cell trophic factor, throughout life and release it in the striatum. There it activates the G-protein coupled receptor (GPCR) smoothed (Smo), which is expressed by cholinergic (ACh) interneurons in the striatum. ACh neurons have recently been recognized for their potential involvement in aberrant neuronal function in the basal ganglia of PD and related diseases. Consistent, preliminary work from our laboratory demonstrates that pharmacological inhibition of Smo in a neurotoxic lesion model of PD or genetic ablation of Shh both increase vulnerability to LIDs upon L-DOPA challenge, suggesting that the loss of Shh signaling due to dopamine denervation may significantly contribute to LID. Based on our results, we hypothesize that complementation of reduced Shh signaling by Shh agonist treatment in models of PD will delay and/or reduce dyskinesia formation upon L-DOPA treatment. We have two specific aims: (A) Determine whether the systemic, pharmacological stimulation of the Shh signaling pathway (1) attenuates LIDs, and (2) decreases MAP kinase pathway activation in ACh neurons of the striatum which is associated with LIDs, in established models of LIDs. (B) Identify LID specific gene expression changes selectively in striatal ACh neurons that are mediated by Shh signaling. This proposal is a proof of principle study that offers preclinical validation of the Smo signal transduction pathway as a target for counteracting dyskinesia formation and novel insights into the regulation of cholinergic plasticity in the striatum. Although this application is focused on LIDs, results from testing our hypotheses will have broader implications for many disorders involving abnormal function of the basal ganglia. Further, we anticipate that positive results from this work will lead to an R01 application that will test the mechanisms by which Shh signaling originating from DA neurons influences circuit structure and function in the striatum.

Further information available at:

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