Striatal systems and mechanisms regulating L-dopa-induced dyskinesias in Parkinsons disease

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Research Abstract
PROJECT SUMMARY / ABSTRACT Our overall aim is to understand the striatal systems and mechanisms through which nicotine treatment reduces L-dopa-induced dyskinesias (LIDs). This is important because few treatments are available to reduce these disabling abnormal involuntary movements that develop in most Parkinson’s disease patients with long- term L-

dopa. Our recent studies show that nicotine decreases LIDs up to 60% in mouse, rat and monkey models of Parkinson’s disease. However, the mechanisms and pathways remain to be identified. A better understanding is critical for the development of the best therapeutics to reduce LIDs. Since abnormal striatal activity is linked to LIDs, our goal is to determine if nicotine reduces LIDs by restoring aberrant striatal signaling mechanisms. This will be done using optogenetics because it allows for the selective manipulation in real time of the pathways that contribute to LIDs. We will focus on several major neuronal cell types in the striatum, including cholinergic interneurons and GABAergic medium spiny neurons (MSNs) of the D1 direct and D2 indirect pathways. Our preliminary data using 6-hydroxydopamine-lesioned cholineacetyl transferase (ChAT)- Cre mice expressing ChR2 (a stimulatory opsin) in striatal cholinergic neurons show that short periods of light activation increase LIDs, while longer activation decreases LIDs. These data indicate a key role for cholinergic interneurons in LIDs and suggest that the decrease in LIDs is due to nicotinic acetylcholine receptor (nAChR) desensitization. We propose to continue this work, and examine other striatal systems involved in LIDs and the nicotine-mediated antidyskinetic effect. In Aim 1 we will investigate the mechanisms whereby optical stimulation of striatal cholinergic interneurons modulates LIDs using electrophysiology and cyclic voltammetry in striatal slices. We will also examine molecular changes linked to LIDs including intracellular signaling steps such as c-Fos, ERK and DARPP-32. In Aim 2 we will determine if nicotine decreases LIDs by dampening the function of striatal cholinergic interneurons. Behavioral assessments as well as electrophysiology, cyclic voltammetry and molecular studies will be done to examine the mechanisms by which nicotine reduces LIDs. In AIMs 3 and 4 we will test the hypothesis that nicotine decreases LIDs by reducing activity of GABAergic MSNs of the D1 and D2 direct and indirect pathways. D1-Cre and Adora2a-Cre mice will be lesioned, injected with virus to allow for expression of ChR2, implanted with optical fibers and treated with vehicle or L-dopa. The effect of varying light stimulation will then be examined on LIDs in vehicle and nicotine-treated mice. Mechanisms will be investigated using a combination of in vitro optogenetics with voltammetry, electrophysiology and molecular approaches. The above studies are the first to use optogenetics to investigate the striatal systems and mechanisms that underlie LIDs, as well as elucidate how nicotine exerts its antidyskinetic effect. A better understanding of the action of nicotine on specific striatal systems will help design optimal strategies to treat LIDs.

Further information available at:

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