The role of striatal cholinergic interneurons in Parkinson’s disease

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1

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L-DOPA induced dyskinesia, cholinergic, Interneurons, Corpus striatum structure, Parkinson Disease

Research Abstract

? DESCRIPTION (provided by applicant): Dopaminergic therapy in Parkinson’s disease (PD) is the most successful example of rationale treatment approach addressing neurotransmitter deficit in neurodegenerative disorders. However, it is limited by motor fluctuations including dyskinesia that develops over several years of treatment. It is not clear if disease progression or treatment is the major factor in producing L- DOPA-induced dyskinesia (LID), but clinical and

experimental evidences point to contributions of age of onset, disease severity, and chronic dopaminergic drug exposure. We have recently reported that elevated cholinergic signaling may be a major contributor to LID. Repeated L- DOPA administration in parkinsonian mice produces LID, which is associated with hyperexcitability of striatal cholinergic interneuron (ChI) evidenced by extracellular signal- regulated kinase (ERK) activation and enhanced response of ChI to dopamine. Moreover, the expression of LID was partially attenuated by preventing ERK activation or a muscarinic receptor antagonist. Ablation of ChI dramatically reduces LID in a mouse model of PD created by 6-OHDA lesion. To define the role of ChI further, we will utilize a novel method of selectively activating or suppressing ChI by Designer Receptor Exclusively Activated by Designer Drug (DREADD) system using transgenic mice expressing Cre in ChI and adenovirus-mediated delivery of floxed construct of DREADD to the striatal ChI. We will determine the role of ChI in LID development and expression separately. We will characterize cellular mechanisms of ChI hyperactivity associated with LID. Finally, we will examine the effect of ChI on the excitability of the medium spiny neuron that is the major striatal output neuron.

Further information available at:

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