Plasticity of bridge collaterals in Parkinonian state and treatment

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Principal Investigators

KANG, UN JUNG

Institution

COLUMBIA UNIVERSITY HEALTH SCIENCES

Contact information of lead PI
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Research Abstract

? DESCRIPTION (provided by applicant): In Parkinson’s disease (PD), degeneration of dopaminergic neurons leads to symptoms including slowness of movement, rigidity, tremor, and gait abnormality. The dopamine (DA) precursor levodopa (L-DOPA) dramatically alleviates motor symptoms, but can cause side effects such as L-DOPA-induced dyskinesia (LID) after prolonged treatment, thereby limiting its therapeutic use. A critical mediator of motor deficit in

PD and excessive movement in LID is the striatal medium spiny neurons (MSNs), which form the sole output of the striatum and receive DA input under normal conditions. The lack of DA input in PD, and the excessive, non-physiological DA input after chronic L-DOPA leads to abnormal MSN function and contribute to slowness of movement and LID respectively. The classical model of basal ganglia (BG) proposes that MSNs can be divided into two segregated pathways: i) D1-MSNs, which express dopamine D1 receptors (D1Rs) and form the “”direct pathway””, targeting only the output nuclei of BG; ii) D2-MSNs, which express D2 receptors (D2Rs) and form the “”indirect pathway””, targeting the output nuclei of BG indirectly via the external globus pallidus (GPe). However, subsequent anatomical studies found that axons from D1-MSNs form collaterals that also project to the GPe. These “”bridging collaterals”” thus allow D1-MSNs to influence the targets of both direct and indirect pathway. We recently found that the terminal density of these bridging collaterals is highly plastic and changes in response to alterations in DA signaling. D-1MSN bridging collateral is reduced by chronic D2R blockade but is almost doubled by D2R overexpression. Importantly, changes in bridging collateral density dramatically alter D1-MSN’s influence on motor output. While optogenetic stimulation of D1-MSNs normally increases locomotor behavior, increasing bridging collaterals by D2R overexpression caused the same stimulation to inhibit locomotor behavior. This motor inhibition was reversed back to motor activation by normalizing bridging collateral terminal density via chronic D2R blockade. Experiments proposed here will test the hypothesis that bridging collaterals are also altered by abnormal DA signaling in PD and LID. We will use transgenic mice that express green fluorescent protein (GFP) under the control of the Drd1a promoter, which allows the axonal projections of D1-MSNs to be visualized by immunohistochemistry against GFP. The terminal density of D1- MSN bridging collateral can therefore be determined by GFP staining intensity in the GPe. DA denervation by 6-hydroxydopamine will be used to induce hemi-parkinsonism. Limb-use bias will be used to assess akinesia, and LID will be induced by chronic L-DOPA treatment. We propose that DA depletion will progressively reduce bridging collateral terminal density, and that it would parallel the progressive ability of a D1R agonist to reverse akinesia. Furthermore, we propose that chronic L-DOPA treatment, which causes increases in LID severity, will be associated with further alterations in the terminal density of bridging collaterals. The identification of abnormal bridging collateral changes in PD will justify future development of therapy to reverse these changes.

Further information available at:

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