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Chronic subthalamic nucleus deep brain stimulation reduces pathological TrkB aggregates in a PD rat model.

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Subthalamic nucleus deep brain stimulation (STN-DBS) is a highly effective treatment for motor fluctuations, tremors, and dyskinesia in Parkinson's disease (PD). While its immediate impact on motor symptom networks is well established, ongoing discussions explore the potential disease-modifying neuroplastic or neuroprotective effects of chronic STN-DBS. However, the molecular and cellular mechanisms underlying STN-DBS in PD remain largely elusive. Factors linked to neural plasticity, such as brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB), are thought to contribute to the reorganization of neural networks.

This study investigated the AAV-A53T α-synuclein (αSYN) PD rat model to assess pathological changes in striatal TrkB expression and evaluate the therapeutic potential of STN-DBS. Using immunofluorescence labeling and confocal microscopy, we analyzed TrkB expression in striatal medium spiny neurons (MSNs). Furthermore, we used high pressure liquid chromatography to measure net dopamine turnover in the striatum. Results revealed AAV dose-dependent intracellular accumulations of TrkB in MSNs of hemiparkinsonian rats. Interestingly, therapeutic STN-DBS effectively reduced the number of these pathological TrkB clusters. Furthermore, the number of TrkB clusters showed a negative correlation with dopaminergic projections, which are preserved by STN-DBS. On the other hand, no correlation between striatal αSYN level and cluster formations was found. Furthermore, the protective effect of STN-DBS seems to be independent of striatal αSYN levels.

Since abnormally high neuronal activity can result in excitotoxicity and subsequent cell death, it appears likely that early STN-DBS modulates neural activity within the nigrostriatal tract and the cortico-striatal circuit, and that the altered activity preserves dopaminergic terminals from SN afferents. Thus, changes in neural activity could play a role in the neuroprotective effects of STN-DBS, and the preservation of TrkB cell surface expression in dMSNs could maintain the capacity for plasticity at this synapse which appears essential for motor learning.

By characterizing plasticity-related changes in the PD disease state, this study offers valuable insights into the therapeutic effects of STN-DBS and its influence on neural network dynamics. Identifying this biomarker could help determine the optimal time window for STN-DBS intervention in mitigating neuronal network-induced pathoplasticity in PD.

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