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Short hairpin RNA targeting endogenous alpha-synuclein prevents degeneration of dopaminergic neurons in the rat rotenone model of Parkinson's disease (S7.007)

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Abstract

ABSTRACT

OBJECTIVE: The long term aim of our work is to develop effective neuroprotective treatments for Parkinson's disease (PD). The objective of this study was to test whether reducing endogenous alpha-synuclein expression in the substantia nigra prevented degeneration of dopamine neurons in the rat rotenone model of PD. **BACKGROUND:** Convergent evidence implicates both alpha-synuclein and mitochondrial dysfunction in the pathogenesis of sporadic Parkinson's disease (PD). Rats exposed chronically to rotenone, a pesticide linked epidemiologically to PD, show systemic partial mitochondrial complex I inhibition, but develop motor abnormalities that respond to dopaminergic medications and specific PD-like neuropathology, including degeneration of substantia nigra dopaminergic neurons and alpha-synuclein aggregation reminiscent of Lewy body pathology. **METHODS:** We inhibited expression of endogenous alpha-synuclein in the adult rat substantia nigra using a viral vector encoding a short hairpin RNA (shRNA) targeting the SNCA transcript. An isogenic control vector expressed a non-targeting shRNA. After vector transduction, we analyzed motor function, neurochemistry, and nigrostriatal histology at baseline and following chronic rotenone exposure. **RESULTS:** Significant knockdown of alpha synuclein in vivo did not provoke behavioral abnormalities, loss of nigral dopamine neurons or changes in the number of dendrites or density of striatal terminals, but protected nigral dopaminergic neurons from degeneration following chronic rotenone exposure. Compared with animals transduced with control vector, SNCA knockdown rescued contralateral motor function, and preserved dopaminergic neuron numbers and morphology following rotenone exposure. **CONCLUSIONS:** Alpha-synuclein is a critical factor in the specific vulnerability of dopaminergic neurons to systemic mitochondrial dysfunction, supporting a model in which genetic modulation of SNCA expression can determine whether environmental exposures trigger PD pathogenesis. shRNA targeting the SNCA transcript should be further evaluated as a possible neuroprotective therapy in PD. **Study Supported by:** Department of Veterans' Affairs; NIEHS