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A Tango for Two: Dopamine and α -Synuclein Synergy May Explain Nigrostriatal Degeneration in Parkinson's Disease

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Dopamine (DA) and α -synuclein (α -syn) are 2 main factors linked to Parkinson's disease.¹ It is known that α -syn generates toxic oligomeric species that are stabilized by DA.² Nonetheless, α -syn transgenic mice do not display dopaminergic neuron death, leaving the question of α -syn-mediated neurotoxicity unanswered. The work presented by Mor and colleagues addresses this by manipulating DA levels in mice expressing human A53T-mutant α -syn. Ultimately, they propose a DA-mediated, α -syn-dependent neurotoxicity in PD.

To elevate DA levels in vivo, they injected a lentiviral vector carrying the mutant tyrosine hydroxylase (TH-RREE) into the substantia nigra (SN) of mice. The mutant TH was modified to be insensitive to the feedback inhibition by DA.³ Subsequently, TH-RREE induced increased TH and DA in the SN and striatum of these mice. The authors then developed a transgenic A53T TH-RREE mouse line to study the effect of elevated DA levels in α -syn mice. These mice depicted a significant loss of DA neuron terminals in the striatum preceding the time-dependent neuronal loss in the SN, concomitant with impaired ambulatory activity.

Because potentially toxic α -syn oligomers are known to be stabilized by DA,² the authors used sodium dodecyl sulfate-polyacrylamide gel electrophoresis and native size exclusion chromatography to reveal changes in quantity and conformation of oligomeric α -syn species extracted from the SN of A53T TH-RREE mice. They observed that DA directly modifies α -syn oligomers in vivo. To further link this to PD, primary neuronal cultures were exposed to recombinant α -syn oligomers generated in the presence of DA in vitro, and the viability of the cells was strongly reduced compared with those exposed to control α -syn oligomers.

To confirm results in another model system, the authors showed that overexpression of CAT-2 (a homologue of TH) in *C. elegans* also induced degeneration of DA neurons for A53T. Disrupting the interaction of DA with α -syn by using a modified form of A53T-mutant α -syn revealed it to be neuroprotective.

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This study represents an exciting step forward in understanding the selective vulnerability of DA neurons. For the first time, DA toxicity has been investigated by increasing nigrostriatal DA levels in A53T-mutant human α -syn transgenic mice, greatly improving the mouse model for PD. In addition, this is the first study to investigate the effects of DA on α -syn oligomerization in vivo, showing that DA stabilizes α -syn oligomers by mediating alterations to α -syn oligomer conformations. Importantly, this presents the possibility of treatments for PD that inhibit interactions between DA and α -syn oligomers.

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