Trifluoperazine rescues human dopaminergic cells from wild-type ?-synuclein-induced toxicity.

Parkinson's disease (PD) is the most frequent neurodegenerative movement disorder. Presently, there is no causal therapy available to slow down or halt disease progression. The presynaptic protein alpha-synuclein aggregates to form intraneuronal Lewy bodies in PD. It is generally believed that intermediates on the way from monomers to the large aggregates would mediate neurotoxicity, but the precise species and mechanism responsible for neuronal death are controversially debated. To study alpha-synuclein-mediated toxicity, we developed a new model in which moderate overexpression of wild-type alpha-synuclein led to gradual death of human postmitotic dopaminergic neurons. In accordance with findings in postmortem PD brains, small oligomeric species occurred and the autophagic flux was impaired in our model. The phenothiazine neuroleptic trifluoperazine, an activator of macroautophagy, selectively reduced one particular alpha-synuclein species and rescued cells. Inversely, blocking of autophagy led to an accumulation of this oligomeric species and increased cell death. These data show that activation of autophagy is a promising approach to protect against alpha-synuclein pathology and likely acts by targeting one specific alpha-synuclein species.