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Mechanisms of axonal degeneration induced by alpha-synuclein

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the midbrain. One of the earliest pathological signs of PD is the degeneration of axonal processes starting at the striatal presynaptic terminals and then progressing towards the cell body. Affected neurons typically exhibit aggregates known as Lewy bodies, which contain the protein alpha-synuclein. The physiological functions of alpha-synuclein as well as the mechanisms through which it contributes to axonal degeneration remain poorly understood.

In this study, we aimed at investigating the cellular targets of alpha-synuclein involved in axonal degeneration. We used a rat in vivo optic nerve crush model, where alpha-synuclein has been shown to enhance axonal degeneration, and rat primary midbrain dopaminergic neurons, where it impairs axonal transport. In both models alpha-synuclein wild type and its A30P mutant were overexpressed using adeno-associated viral vectors. We employed immunofluorescence, Western Blot and ELISA to examine alteration of cytoskeletal proteins, autophagy and proteins involved in axonal transport such as kinesin and GAPDH. GAPDH activity has been shown to be essential for energy supply of axonal transport.

We found that alpha-synuclein overexpression resulted in a smaller amount of polymerized tubulin by trend and a significant decrease of glycolytic GAPDH activity, while the other putative targets analysed were not altered. These findings offer a possible explanation for the pathological effects of alpha-synuclein on axonal transport and axonal degeneration and contribute to the understanding of PD pathophysiology.

Keywords topics: Parkinson’s disease, alpha-synuclein, axonal degeneration, axonal transport, GAPDH, midbrain dopaminergic neurons

Keywords methods: immunocytochemistry, immunohistochemistry, Western Blot, ELISA, cell culture, AAV transduction.