Alpha-Synuclein Oligomers and Mitochondrial Membrane Permeabilization: A Potential Cytotoxic Mechanism in Parkinson's Disease

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Parkinson’s disease (PD) is an incurable, progressive neurodegenerative disorder characterized by the intracellular accumulation of alpha-synuclein (aSyn). aSyn oligomers have been implicated in various mechanisms of cytotoxicity. Among other effects, they impair mitochondrial function and permeabilize plasma membranes. The interesting possibility that aSyn oligomers permeabilize mitochondrial membranes has not been previously investigated. Permeabilization was measured by the leakage of 4 kDa and 40 kDa fluorescein-dextran from whole mitochondria. Oligomers were applied to mitochondria at varying concentrations. After incubation, samples were centrifuged and the fluorescence in the supernatant was quantified. All oligomer-treated samples exhibited dextran leakage from mitochondria. This leakage was much more significant among 4 kDa samples (ANOVA, $p < 0.0001$) than among 40 kDa samples (ANOVA, $p = 0.0889$). In both groups, leakage was greatest at intermediate concentrations (250 nM - 1.5 μM), while at 7 μM, no significant leakage was observed. This inhibition at higher concentrations (relative to 250 nM) was significant (Tukey HSD, $p = 0.0272$). The magnitude of normalized leakage was consistently greater for 4 kDa dextran than 40 kDa. The approximate diameter of membrane pores formed by oligomers was calculated to be 21 nm. Thus, alpha synuclein oligomers likely increase the permeability of mitochondria to small proteins such as cytochrome c. This study has presented evidence indicating that aSyn oligomers permeabilize mitochondrial membranes. Because such permeabilization is associated with cyt c release and the initiation of apoptosis, it is a potentially potent and relevant cytotoxic mechanism in PD.

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