CHARACTERIZING α-SYNUCLEIN MEMBRANE BOUND STRUCTURE

Thesis by

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ABSTRACT

A feature of Parkinson's disease is the presence of fibrillar protein deposits composed mostly of α-synuclein and calcium ions in the brain's *substantia nigra* region. Although α-synuclein is natively unfolded, the N-terminal region of the protein is highly helical in the presence of membrane mimics, such as acidic phospholipid vesicles and SDS micelles. The C-terminal region of α-synuclein is known to bind to calcium ions and modulates aggregation. In this thesis, the structure of α-synuclein variants, incorporated with tryptophan and 3-nitrotyrosine as donor and energy acceptor pairs, have been characterized in the presence of SDS micelles, small unilammelar vesicles, and calcium ions by various techniques. Distance distributions extracted from time-resolved fluorescence energy-transfer measurements provide site-specific information on the protein conformations. In addition, similar studies using mutants linked to early onset Parkinson's disease were also performed to investigate the structural effect caused by these mutations. Furthermore, single tryptophan mutants have been designed as fluorescent reporters. The locations of these different tryptophan residues in the bilayer were probed by lipids labeled with bromine and dinitrophenol quenchers. Finally, preliminary studies of the intramolecular structure of α-synuclein aggregates have been carried out, while elucidation of intermolecular α-synuclein aggregate structures was made possible by the synthesis of new dyes that allow for long-range fluorescent energy transfer.

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