

Morphological and Kinetic studies of the Alzheimer's β -amyloid, residues 22-35, uncovered the secondary structural transformation of soluble β -sheet intermediate species.

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Synaptic malfunctions and neural death resulting from accumulations of misfolding amyloid proteins is characteristic of neurodegenerative diseases. The beta-amyloid peptide 1-40 and 1-42, associated with the cause of Alzheimer's disease, undergoes various transformation processes resulting in structural changes. Although, the cause of neurodegeneration in Alzheimer's is often attributed to toxic beta-sheet filaments, research conducted by Dr. Chimon Peszek found diffusible beta-sheet intermediates presenting toxicity comparable to fibrils. These highly unstable morphologies may play an important role in neurodegeneration. Moreover, they provide potential information about the irregular folding process and rate of fibril formation. Many studies contribute neurotoxicity to the "KLVFFA" region, from residues 16-21; however, we chose to concentrate on a shorter sequence, 22-35, in order to study the effect on fibril formation without "KLVFFA". Instead, our research focuses on the role of the hair-pin turn and the salt-bridge attraction between Asp-23 and Lys-28 to the rate of beta-sheet formation.

Our research utilizes Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR) to identify beta-sheet formation and the secondary conformations of beta-sheet intermediates. Ultraviolet Visible Spectroscopy (UV-Vis) and Transmission Electron Microscopy (TEM) also provided data on the kinetics and morphology of these intermediate forms.

ATR-IR, UV-Vis, and TEM of the beta-amyloid 22-35 confirmed the formation of toxic beta-sheets from within the hair-pin region of the peptide. Nuclear Magnetic Resonance Spectroscopy (NMR) may help to identify intermediate variants and the structural contribution of these soluble sub-fibrillar species to the rate of beta-sheet formation. Discovering more knowledge about the transition of soluble intermediates to insoluble beta-sheet fibrils will provide an important baseline for comparison to the various mutations of beta-amyloid 1-40. These new discoveries could significantly impact future therapeutic treatments.