UCF Biophysics Group Virtual Seminar

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Biophysical Analysis of the Structure and Aggregation of Amyloid β Peptide

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ABSTRACT

Amyloid β (Aβ) peptide aggregates are linked to Alzheimer's disease (AD). Post-translationally pyroglutamylated Aβ (pEAβ) occurs in AD brains in significant quantities and is hypertoxic, but the underlying structural and aggregation properties remain poorly understood. Here, the structure and aggregation of Aβ1-40 and pEAβ3-40 are analyzed separately and in equimolar combination. Circular dichroism data show that Aβ1-40, pEAβ3-40, and their combination assume α-helical structure in dry state and transition to unordered structure in aqueous buffer. Aβ1-40 and the 1:1 combination gradually acquire β-sheet structure while pEAβ3-40 adopts an α-helix/β-sheet conformation. Thioflavin-T fluorescence studies suggest that the two peptides mutually inhibit fibrillogenesis. Fourier transform infrared (FTIR) spectroscopy identifies the presence of β-turn and α-helical structures in addition to β-sheet structure in peptides in aqueous buffer. The kinetics of transitions from the initial α-helical structure to β-sheet structure were resolved by slow hydration of dry peptides by D2O vapor, coupled with isotope-edited FTIR. These data confirmed the mutual suppression of β-sheet formation by the two peptides. Remarkably, pEAβ3-40 maintained a significant fraction of α-helical structure in the combined sample, implying a reduced β-sheet propensity of pEAβ3-40. Altogether, the data imply that the combination of unmodified and pyroglutamylated Aβ peptides resists fibrillogenesis and favors the prefibrillar state, which may underlie hypertoxicity of pEAβ. The other work has been done a) to identify the region(s) of Aβ responsible for aggregation and fibrillogenesis and b) to use those fragments to inhibit Aβ aggregation. Structural and aggregation properties of the parent Aβ1-42 peptide and seven overlapping peptide fragments have been studied, i. e. Aβ1-10 (P1), Aβ6-15 (P2), Aβ11-20 (P3), Aβ16-25 (P4), Aβ21-30 (P5), Aβ26-36 (P6), and Aβ31-42 (P7). It is proposed that P3 and P6 intercalate between Aβ1-42 molecules, owing to their high affinity for their respective regions, and thereby inhibit Aβ1-42 aggregation. This finding may lead to a novel way of inhibition of Aβ fibrillogenesis by Aβ-derived peptide fragments.