Mechanistic Insight into the Inhibition of Aβ42 Neurotoxicity by Aβ42 C-terminal Fragments

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A key event in Alzheimer's disease (AD) etiology is the assembly of amyloid β-protein (Aβ) into neurotoxic oligomers. The longer form of Aβ, Aβ42 forms hexamers and dodecamers, which are not formed by the shorter Aβ40. Aβ42 oligomers are substantially more neurotoxic than Aβ40 oligomers.

We designed Aβ oligomerization inhibitors derived from C-terminal fragments (CTFs) of Aβ42. The CTF inhibitory activity is described in the abstract by Fradinger et al. Here, we present the results of biophysical studies of the CTFs using circular dichroism spectroscopy (CD) and quasielastic light scattering (QLS) spectroscopy. The CD data show initially a high ratio of unordered structure for all CTFs. An increase of β-sheet content with time is observed for all CTFs longer than Aβ(34-42). The rate of conformational change increases with peptide length. Aggregation of CTFs into particles of 10 - 200 nm is observed by QLS for all peptides longer than Aβ(34-42). QLS measurements of Aβ42 assembly in the presence of CTFs suggest that the CTFs longer than Aβ(34-42) form heterooligomers with Aβ42. Importantly, the rate of co-oligomerization correlates inversely with inhibition of Aβ42 toxicity. The data suggest that inhibition of neurotoxicity results from hindering the interaction of Aβ42 oligomers with neurons through sequestering of Aβ42 by co-oligomerization with the CTF rather then from disassembly of Aβ42 oligomers.