C-terminal fragments inhibit amyloid β-protein oligomerization and neurotoxicity

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Abstract: Self-association of amyloid β-protein (Aβ) into toxic oligomers is a seminal event in Alzheimer’s disease (AD). Aβ exists in two predominant forms, Aβ40 and Aβ42. The oligomers formed by Aβ42 are significantly more toxic than those formed by Aβ40. Previously, it was shown that the C-terminus of Aβ42 is critical for the formation of higher order oligomers. We hypothesized that molecules with a high affinity for the C-terminus of Aβ42 may inhibit Aβ42-induced neurotoxicity. We prepared a series of Aβ(x-42) C-terminal fragments (CTFs) and tested their ability to inhibit Aβ42 oligomerization and neurotoxicity. The formation of neurotoxic Aβ42 hexamers was attenuated by CTFs and correlated roughly with peptide length. Aβ(29-42) inhibited hexamer formation at submicromolar concentrations. Surprisingly, inhibition of toxicity did not correlate with inhibition of oligomerization. Aβ(31-42) was the strongest inhibitor of toxicity and significant inhibition was found for Aβ(39-42). Aβ(31-42) inhibited Aβ42 induced neurotoxicity completely and fully rescued cells from Aβ42-induced inhibition of mini excitatory postsynaptic currents. Additionally, dynamic light scattering revealed that Aβ(31-42) significantly decreased the rate of Aβ42 aggregation. The ability of both short and long CTFs to inhibit Aβ42 toxicity suggests the existence of two classes of CTFs that act through different mechanisms. Preliminary data suggest that Aβ(31-42) interacts with Aβ42 to form large heterooligomers that precipitate out of solution, whereas, Aβ(39-42) may interact with the N-terminus of Aβ42 modifying the biological properties of the oligomers.

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