Copper And Zinc Interaction with Alzheimer's Disease β-Amyloid

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Aβ is the principal component of amyloid plaque which is the hallmark of Alzheimer's disease (AD) neuropathology. We have characterized Aβ as a metalloprotein, with selective high-affinity binding sites for zinc (Ka≈ 100 nM) and copper (Ka≈ 10 attoM). Genetic ablation of the ZnT3 transporter, which loads zinc into the glutamatergic synapse, abolishes amyloid deposition in a mouse model for AD.

Aβ binds Cu and Zn through a site that involves oligomeric peptide assembly, and imidazole bridging. When synthetic Aβ binds copper, it is highly redox-active. Biological reducing agents such as dopamine, cholesterol and vitamin C are recruited for electron donation, so that the Aβ/Cu complex acts as a catalyst generating H_2O_2 (Km= 5 μM, Vmax= 30 nM/min). The toxicity of Aβ species is proportional to the peptide's ability to reduce Cu or Fe and generate H_2O_2 (Aβ42> Aβ40 >rat Aβ). H_2O_2 is a freely permeable pro-oxidant and is the chemical source of much of the oxidation damage that is abundantly evident in AD brain. Where cholesterol is the substrate for H_2O_2 production, it is specifically oxidized by Aβ:Cu complexes into forms that are markedly increased in AD post-mortem brain tissue compared to age-matched normal and neurological disease control tissue.

Chelators of copper and zinc both disaggreagate Aβ deposits from post-mortem human brain and also inhibit redox activity and H_2O_2 production. We have found that one such orally bioavailable chelator, clioquinol, markedly inhibits brain amyloid pathology in transgenic mice. This compound recently completed a successful pilot phase 2 clinical trial in AD, where cognitive decline significantly arrested.

The interactions described for Aβ, may be applicable to other protein targets implicated in other age-related degenerative diseases such as cataracts, Parkinson's disease, and amyotrophic lateral sclerosis.