Cardiolipin-Targeted Peptides Block Alzheimer’s Beta-Amyloid Oligomer Toxicity through a Two-Hit Approach: Fibril Formation and Inhibition of Newly Characterized Oxygenase Activity

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Accumulation of beta-amyloid peptide in the brain is widely regarded as the primary pathogenic factor of Alzheimer’s disease (AD). The oligomeric form of beta-amyloid has been recently implicated as the most neurotoxic structure of the peptide. It is known to impair mitochondrial function, but the exact process by which this occurs has remained elusive. Here, a possible mechanism of beta-amyloid mitotoxicity was characterized, namely the oxygenase activity of beta-amyloid interaction with a specific form of cardiolipin (CL) and copper (II) ions. From this, two targets for treatment of AD were identified: firstly, inhibition of this mitochondrial oxygenase activity, and secondly, prevention of membrane permeation by beta-amyloid in the first place. An aladan (ald) analog of the drug Bendavia (SS31) has been discovered to be able to treat both of these targets. SS31 is a blood-brain barrier permeable peptide that exhibits numerous mito-protective and antioxidant properties through the stabilization of cardiolipin in mitochondria. Here, [ald]SS31 was shown to be able to successfully both inhibit beta-amyloid oxygenase activity and drive the beta-amyloid equilibrium from soluble, toxic oligomers to nontoxic insoluble fibrils by more than a four hundred fold increase in speed compared to the natural mechanism, thereby demonstrating its potential as a therapy for AD.

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