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Design of copper-selective peptidic shuttles to prevent β-amyloid toxicity in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is the most common neurodegenerative disease with approximately 5% of all cases due to mutations of genes such as APP, PSEN1 and PSEN2. However, most cases are considered sporadic and are associated with numerous factors such as genetic predisposition and environmental factors. Nevertheless, one of the hallmarks of AD is the apparition, in specific parts of the brain, of extracellular Aβ aggregation, resulting from an abnormal increase in the amyloid pathway cleavage of the Amyloid precursor protein (APP). Although the nature of the main form of the Aβ aggregate responsible for the disease is still debated, an emerging model suggests that the main culprits are the Aβ oligomers in the development of AD and not extracellular plaques. However, Aβ in both soluble and aggregate conformations have been shown to bind Copper (Cu) at high concentrations as well as other trace metals such as Zinc and Iron. Intriguingly, Lower neuronal Cu levels in brain regions affected by AD is one of the phenotypes of AD and has been suggested to contribute to some of the symptoms of AD. Furthermore, complexation of Cu by extracellular Aβ has also been shown to produce reactive oxygen species (ROS), which is detrimental to the cells in proximity. This ROS production is generated through the shuttle of Cu between its two oxidation states, Cu(II) and Cu(I) , bound loosely to Aβ.

The aim of the current study is to design a molecule that would capture Cu(II) from Aβ and shuttle Cu back into neuronal cells. Thanks to the versatile nature of synthetic peptides, we have linked different cell penetrating peptides (CPP) to an ATCUN motif (XXH) for its ability to selectively bind Cu(II) with a high affinity. These novel "Shuttles" should thus simultaneously decrease extracellular Cu levels, hence attenuating ROS production, and increase intracellular Cu levels in the brain cells.

We will present the characterization of two Cu(II) shuttles, demonstrating their capability to bind Cu(II) in biological media and retrieve Cu(II) from Aβ, and thus halting ROS production. We will also present evidence showing their ability to import of copper into PC12 cells, a model of neuronal cells.