Alzheimer's disease - Features and Problems

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Abstract

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by the presence of amyloid plaques. The major constituent of AD plaques is the amyloid – β peptide, which is cleaved from the membrane-bound amyloid precursor protein via β/γ – secretase enzymes. Aβ is produced in health brains in a soluble, monomeric form, which is not toxic. AD risk factors are associated with abnormal production of amyloid beta. An increased Aβ production and/or accumulation lead first to the formation of Aβ oligomers, then to protofibrils and fibrils (Fig. 1). Oligomers are supposed to be the most toxic species. On the other hand, high concentrations (~mM) of Fe^{3+}, Cu^{2+} and Zn^{2+} are observed in AD plaques, suggesting that Aβ aggregation could be mediated by some of these essential ions; These metals are involved in two key steps: 1) Cu and Zn are able to bind Aβ directly and modulate aggregation and 2) redox active Cu and Fe are crucial for the production of ROS (reactive oxygen species), though the mechanism of metal reduction and ROS production is still unclear. Therefore, elucidation of the coordination of metal ions to Aβ is important to understand their role in the aggregation of Aβ and in the production of ROS. The question is relevant to the mechanism and/or Cu^{2+} binding structure in Aβ aggregates. There are many different and sometimes controversial studies on the coordination environment of copper and zinc (iron is less studied) and different coordination modes are proposed; predominantly, copper(II) form monomeric Cu-Aβ (1:1) species and its coordination environment changes with pH and at neutral pH at least two binding modes coexist and are in fast equilibrium. The amine terminal, three histidine imidazole ring (His6, His13, His14) and carbonyl or carboxylate oxygen (from Ala2, Asp1, Asp3, Glu3 and Glu11) are most binding modes, but deprotonated peptide nitrogen is also taken into account. Thus, the 2N2O-, 3N1O- and 4N-coordination modes are mostly accepted (*e.g.* from HisHis(His), Asp and/or Glu), but still there are a lot of unanswered questions and researches intensively are carry out to make more clearance about chemical and coordination environment in Alzheimer's disease.

***Key words**: Alzheimer's disease, amyloid-beta, metal ions, aggregation*

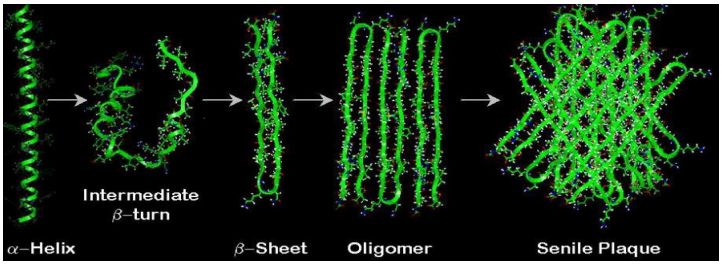

Fig. 1 Structural changes and aggregation of beta-Amyloid peptide