The Pathogenic A2V Mutant Exhibits Distinct Aggregation Kinetics, Metal Site Structure, and Metal Exchange of the Cu^{2+} -Aβ Complex - DTU Orbit (19/05/2018)

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A prominent current hypothesis is that impaired metal ion homeostasis may contribute to Alzheimer's disease (AD). We elucidate the interaction of Cu^{2+} with wild-type (WT) Aβ_{1-40} and the genetic variants A2T and A2V which display increasing pathogenicity as A2T<WT<A2V. Cu^{2+} significantly extends the lag phase in aggregation kinetics, in particular for the pathogenic A2V variant. Additionally, a rapid, initial, low intensity ThT response is observed, possibly reflecting formation of Cu^{2+} induced amorphous aggregates, as supported by atomic force microscopy (AFM) and circular dichroism (CD) spectroscopy, again most notably for the A2V variant. Electron paramagnetic resonance (EPR) spectroscopy gives pK_a values for transition between two Cu^{2+} coordination geometries (component I and II) of 7.4 (A2T), 7.9 (WT), and 8.4 (A2V), that is, component I is stabilized at physiological pH in the order A2T<WT<A2V. 1H NMR relaxation exhibits the same trend for the non-coordinating aromatic residues (A2T<WT<A2V), and implies markedly faster inter-peptide Cu^{2+} exchange for the A2V variant than for WT and A2T. We therefore hypothesize that component I of the Cu–Aβ complex is related to pathogenicity, accounting for both the pathogenic nature of the A2V variant and the protective nature of the A2T variant.

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