Amyloid-β Tetramer: Structural Stability of a New Fold

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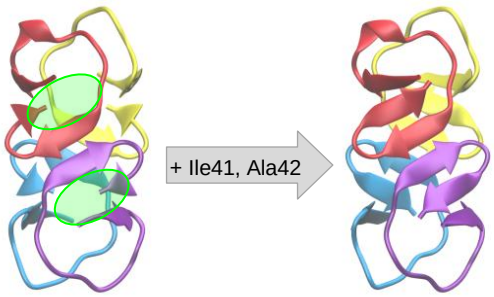
Worldwide, more than 35 million people are living with dementia.[1] The most common type of dementia is Alzheimer's disease (AD),[1] which is also the most common neurodegenerative disorder.[2] One of the key molecules in the pathogenesis of AD is the amyloid-β peptide (Aβ), which occurs in two major forms: 40 ($A\beta_{40}$) or 42 ($A\beta_{42}$) residues long. Thereby, $A\beta_{40}$ is produced at higher levels, whereas the more hydrophobic $A\beta_{42}$ is more neurotoxic.

The neuritic plaques, which are a major pathological hallmark in the brain of AD patients, are mainly composed of Aβ fibrils.[3] However, recent studies showed that not the insoluble Aβ fibrils seem to be the neurotoxic agents: the small Aβ oligomers, as a preliminary stage of the fibrils, exhibited much higher cytotoxicity.[4] Despite the fact that newer studies on AD have focused on the small Aβ oligomers, the structural information on the Aβ oligomers is restricted, because of their noncrystalline and unstable nature.

Lately, Streltsov et al. have described a crystal structure of the amyloidogenic residues 18-41 of the Aβ peptide genetically engineered into the CDR3 loop region of a shark Ig new antigen receptor (IgNAR) single variable domain.[5] They suggested this structure as a potential model system for nonfibrillar oligomer formation in AD, because the Aβ-IgNARs formed a tight homo-tetramer as a dimer of dimers through interactions mediated by the Aβ-peptide component. In our study, we extracted the Aβ-peptide component from the crystal structure and investigated it in two lengths ($A\beta_{17\text{-}40}$ and $A\beta_{17\text{-}42}$) to study the structural stability in explicit solvent by means of all-atom molecular dynamics simulations. In addition to the simulations of the tetramers, we examined the derived dimer and monomer structures.

In summary, the results suggest that the novel tetramer topology is a stable conformation for $A\beta_{17\text{-}42}$, but not for the $A\beta_{17\text{-}40}$ variant. Generally, the dimer and monomer simulations revealed the same trend: the structures of the $A\beta_{17\text{-}42}$ variant were more stable than the $A\beta_{17\text{-}40}$ variants. The increased stability of the $A\beta_{17\text{-}42}$ variants can be explained by the C-terminal extension of the middle strand in a 3-stranded antiparallel β-sheet.



$A\beta_{17\text{-}40}$ tetramer $A\beta_{17\text{-}42}$ tetramer

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