Monomer adds to preformed structured oligomers of Aβ-peptides by a two-stage dock-lock mechanism

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Abstract

Nonfibrillar soluble oligomers, which are likely to be transient intermediates in the cascade of steps in the transitions from monomers to amyloid fibrils, may be the toxic species in Alzheimer's disease. In order to monitor the early events that direct assembly of amyloidogenic peptides we probe the dynamics of formation of $(A\beta_{16-22})_n$ by adding a monomer to a preformed $(A\beta_{16-22})_{n-1}$ $(n = 4 - 6)$ oligomer in which the peptides are arranged in an antiparallel β-sheet conformation. Using all atom molecular dynamics simulations in explicit water and multiple long trajectories, for a cumulative time of $6.9\mu s$, we find that the oligomer grows by a two-stage dock-lock mechanism. The largest conformational change in the added disordered monomer occurs during the rapid ($\approx 50ns$) first dock stage in which the β-strand content of the monomer increases substantially from a low initial value. In the second slow lock phase the added monomer rearranges to form in register antiparallel structures. Surprisingly, we find that the mobile structured oligomers undergo large conformational changes in order to accommodate the added monomer. The time needed to incorporate the added monomer into the fluid-like oligomer grows even when $n = 6$ which suggests that, for Aβ_{16-22}, the critical nucleus size must exceed six. For all n the time to form the stable antiparallel structure exceeds hundreds of nanoseconds even though frequent inter-peptide collisions occur at elevated monomer concentrations used in the simulations. The dock-lock mechanism, which was previously proposed to explain the kinetics of fibril elongation of full length Aβ-peptides, should be a generic mechanism for growth of oligomers of amyloidogenic peptides.