Zwitterionic Detergents Promote the Formation of Atypical \( \beta \text{-40} \) Fibrils


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Alzheimer’s disease is characterized by the presence in the brain of distinctive extracellular amyloid plaques. The major constituent of these deposits is the beta amyloid (A\( \beta \)) peptide, which self-associates \textit{in vitro} to form amyloid-like fibrils [1]. The mechanism of fibrillization has been extensively studied in hopes of developing anti-amyloid therapeutic agents [2]. We have studied a family of compounds that promote A\( \beta_{40} \) assembly as a means to explore the process of fibril formation. Using circular dichroism (CD) to test their effect on A\( \beta_{40} \) assembly, zwitterionic detergents with 14 or 16 carbon chain lengths, 3-(N, N-dimethyltetradecylammonio)propanesulfonate (\( \text{III} \)) and 3-(N, N-dimethylhexadecylammonio)propanesulfonate (\( \text{IV} \)) were identified as promoters of A\( \beta_{40} \) fibrillogenesis based on their induction of \( \beta \)-sheet structure. Interestingly, two related compounds with chain lengths of 10 and 12 carbons respectively, 3-(N, N-dimethyldecylammonio)propanesulfonate (\( \text{I} \)) and 3-(N, N-dimethyldodecylammonio)propanesulfonate (\( \text{II} \)) were found not to have this effect. CD only indirectly infers the assembly state of A\( \beta \), based on the appearance of \( \beta \)-structure [3]. Transmission electron microscopy (TEM) was therefore used to directly visualize the appearance of the A\( \beta_{40} \) fibrils in the presence of these compounds. EM confirmed the CD findings and revealed the presence of a unique fibril morphology [4, 5]. TEM images of high-resolution platinum/carbon replicas showed that the A\( \beta_{40} \) in the presence of compounds \( \text{III} \) and \( \text{IV} \) assembled into a network of highly bundled and cross-linked fibrils not observed with A\( \beta_{40} \) alone. Compounds \( \text{I} \) and \( \text{II} \) did not have this effect, indicating that the promotion and morphological changes are dependent on the length of the hydrophobic chain. Preliminary 2-D-NOESY experiments clearly indicate that these detergents interact with the A\( \beta \) molecules. Studies are currently ongoing to better characterize the interactions between A\( \beta_{40} \) and \( \text{III} \) and \( \text{IV} \).

REFERENCES

Figure 1. Electron micrographs of platinum/carbon replicas showing Aβ fibril structures in the presence of compounds I, II, III, and IV compared to control. Magnification = X 21 000. Typical amyloid fibrils are formed by Aβ control (C). Identical fibril morphology is visualized in the presence of compounds I and II. A network of cross-linked fibrils is visualized in the presence of compounds III and IV.

Figure 2. Circular dichroism analysis of compounds I, II, III, IV, and control after a 4-h incubation. Compounds III and IV are potent promoters of β-sheet formation.