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NMR structure of the Arctic mutation of the Alzheimer's Aβ(1–40) peptide docked to SDS micelles

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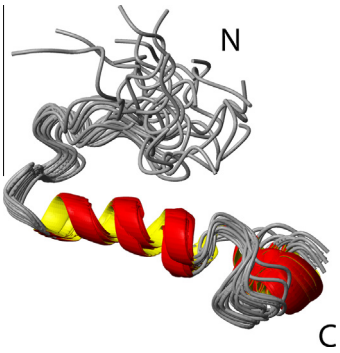
HIGHLIGHTS

- Solution structure of "Arctic" mutant of Aβ1–40 amyloid peptide in SDS micelles.
- Both mutant and wild-type interactions are hydrophobic in nature.
- Peptide conformation is very sensitive to single amino acid substitutions.
- Peptide-to-membrane binding is very sensitive to single amino acid substitutions.

GRAPHICAL ABSTRACT



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ABSTRACT

The "Arctic" point mutation of the Alzheimer's amyloid β-peptide is a rare mutation leading to an early onset of Alzheimer's disease. The peptide may interact with neuronal membranes, where it can provide its toxic effects. We used 2D NMR spectroscopy to investigate the conformation of the "Arctic" mutant of Aβ1–40 Alzheimer's amyloid peptide in sodium dodecyl sulfate micelle solutions, which are the type of amphiphilic structures mimicking some properties of biomembranes. The study showed that the Arctic mutant of Aβ1–40 interacts with the surface of SDS micelles mainly through the Leu17–Asn27 3_{10}-helical region, while the Ile31–Val40 region is buried in the hydrophobic interior of the micelle. In contrast, wild-type Aβ1–40 interacts with SDS micelles through the Lys16–Asp23 α-helical region and Gly29–Met35. Both the Arctic mutant and the wild-type Aβ1–40 peptides interactions with SDS micelles are hydrophobic in nature. Aβ peptides are thought to be capable of forming pores in biomembranes that can cause changes in neuronal and endothelial cell membrane permeability. It has also been shown that Aβ peptides containing the "Arctic" mutation are more neurotoxic and aggregate more readily than the wild-type Aβ peptides at physiological conditions. Here, we propose that the extension of the helical structure of Leu17–Asn27 and a high aliphaticity (neutrality) of the C-terminal region in the Arctic Aβ peptides are consistent with the idea that formation of ion-permeable pores by Aβ oligomers may be one of prevailing mechanisms of a larger neuronal toxicity of the Arctic Aβ compared to the wild-type Aβ peptides, independent of oxidative damage and lipid peroxidation.

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