Characterizing Effect of Glutamine Position on A[Beta] Fiber Structure

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Amyloids are misfolded proteins that have been correlated with numerous human neurodegenerative diseases including Alzheimer's (AD), but the nature of the misfolded structure that leads to disease is not known. Amyloid Beta (Aß) peptide, the primary component of the amyloid plaques in the brains of Alzheimer’s patients and the region of the protein that initiates misfolding, was used for the study. This study focuses on the nucleating core of Aß Dutch mutant, Ac-16KLVFFA22Q-NH2 or Aß(16-22)E22Q, or most simply E22Q. E22Q is known to form parallel ß sheets due to the hydrogen bonds formed between glutamine (Q). We were interested in the positional dependence of Q in amyloid assembly. Three separate substitutions for Q were designed: L17Q (KQVFFAE), V18Q (KLQFFAE), and A21Q (KLVFFQE). Isotope-edited infrared spectroscopy (IE-IR), which probes molecular vibrations within the amyloid assembly, required us to synthetically incorporate a 1-13C-enrichment at the F19 (phenylalanine) residue. Transmission electron microscopy (TEM) was optimized to visualize the overall morphology of the amyloids. The results showed that all three mutants form parallel ß sheets. However, the IE-IR spectra of the samples were significantly different despite the enrichment being on the same position, suggesting that the tertiary and quaternary structure of the fibers might be differed. This hypothesis was further confirmed by TEM which showed different bundling and twisting of the fibers. Thus, the combination of IE-IR and TEM data have now proven that the position of Q is critical to the assembled structures. This finding now allows us to define how the position of a single amino acid impacts the folding and ultimate structure of the more disease relevant amyloids.

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