Molecular dynamics analyses of peptides forming amyloid-like fibrils

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Motivation

The insurgence of severe neurodegenerative disease is frequently associated with insoluble amyloid-like fibrils . The structural characterization of these fibrils has long been hampered by the very low solubility and by the non-crystalline nature of these aggregates. Major advances in this field have been recently accomplished by the use of model peptides, whose solid aggregates exhibit most of the features of amyloid fibrils. Particularly impressive are the results achieved in the structural characterization of the peptide GNNQQNY derived from the prion-determining domain of the yeast protein Sup35. The high resolution structure of the peptide offered an atomic detailed model, denoted as cross-beta spine steric zipper, for amyloid-like fibrils (Nelson, R., Sawaya, M.R., Balbirnie, M., Madsen, A.O., Riekel, C., Grothe, R., Eisenberg, D. (2005) Nature 435, 773-8). In order to obtain further insights into the structure determinants of amyloid fiber structure and formation, we have undertaken molecular dynamics (MD) simulations on a variety of different models arranged in a cross-beta spine structure

Methods

The starting coordinates for the MD simulations were derived from the crystal structure of the peptide GNNQQNY. For simulation on polyglutamine systems, the starting models were generated by molecular modelling using the structure of GNNQQNY as template. MD simulations were performed with the GROMACS software package. Models were immersed in rectangular or cubic boxes filled with water molecules. An extensive analysis of GNNQQNY dynamics was performed by using replica exchange MD (REMD), an advanced methodology for enhancing conformational sampling.

Results

The MD simulations of several GNNQQNY assemblies of different sizes indicate that the aggregates are endowed with a remarkable stability. Our data also indicate that these assemblies can assume twisted beta-sheeted structures. As a consequence, the occurrence of steric zipper interactions is compatible with both flat and twisted beta-sheets. This result is in line with several literature reports suggesting twisted beta-sheet structures as a basic motif of amyloid fibrils. The evolution of pairs of sheets separated by a wet interface during the simulation has additionally provided interesting information on the structure of larger aggregates (Esposito, L, Pedone, C & Vitagliano, L. (2006). Proc. Natl. Acad. Sci. USA 103, 11533-8). Further studies carried out by using REMD approaches have provided interesting clues on the structural properties of the intermediate states along the fiber formation pathway.

Our findings are in line with the concentration dependent lag phase growth of GNNQQNY fibers experimentally observed.

Finally, MD simulations were also used to investigate the structural compatibility of polyglutamine fragments, associated with the occurrence of several neurodegenerative diseases, with the steric zipper model. MD simulations have been carried out on a variety of models (parallel and antiparallel pairs of sheets) with different sizes and various aggregation levels. Our simulations, carried out over a wide range of temperatures, clearly indicate that these assemblies are very stable. Glutamine side chains strongly contribute to the overall stability of the models by perfectly fitting within the zipper. In contrast to GNNQQNY zipper motifs, hydrogen bonding interactions provide a significant contribution to the overall stability of polyglutamine models. Simulations carried out at high temperatures (450-500 K) also show that the steric zipper motif is reversibly destroyed. This provides a clear indication on the structural determinants that regulate its formation. On this basis, a mechanism that explains the nucleation-dependent process of polyglutamine fiber formation is proposed.

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