Molecular Dynamics simulation of Prion fragment 180-193 in water and hydrophobic medium.

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Transmissible spongiform encephalopathies (TSE) in humans and animals can be manifested as sporadic, familial and acquired disorders, and include Creuzfeldt-Jakob disease (CJD) in humans, scrapie in sheep and bovine spongiform encephalopathy in cattle. These neurodegenerative diseases are caused by the accumulation of a conformationally altered isoform of the cellular prion protein (PrP^c).

Structural analysis indicates that normal cellular PrP^c is a soluble monomeric protein rich in α-helix. In contrast, PrP^{sc} has a high content of β-sheet, insoluble and protease resistant.

The conversion of the α-helix form of PrP^c into an insoluble β-sheet and infectious form PrP^{sc} is considered the fundamental event in prion diseases. This implicates that parts of the structured domain of PrP^c must change their structure.

Peptides belonging to the structured domain of the prion protein have also been tested for a better understanding of PrP^{sc} toxicity. In particular, peptides corresponding to the three helical regions of PrP^c have been synthetized. Fragments corresponding to the second helical domain, PrP 180-193 and PrP 178-193, were the only ones that formed amyloid and promoted Cu(II) induced lipid peroxidation as well as cytotoxicity in primary neuronal cultures. Recently PrP 180-193 has been shown to interact with lipid membranes.

In the present work Molecular Dynamics simulations have been carried out on PrP 180-193 in order to evaluate its conformational stability as a function of both charges at end groups, and solvent hydrofobicity.

Two different peptides have been investigated: the zwitterionic and the neutral.

The hydrocarbon core of the membrane was simulated by using ethane as the solvent

The Simulation engine used was ORAC , with native amber/charm22 forcefield.

The simulations pointed out that the presence of charges influences greatly the stability of starting helix structure.The hydrocarbon environment destabilizes prevalently the TVTTTT region, which in ethane adopts a turn structure.

These findings might have intriguing implications in the understanding of the molecular mechanism triggering α/β conversion in Prion protein.