Studying the intrinsic structural properties of three human prion helices

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Motivation

The cellular prion protein (PrP) is a synaptic glycoprotein expressed in the central nervous system, in lymphatic tissue and at neuromuscular junctions. Although its physiological function is still largely unknown, PrP is unequivocally associated to the onset of a family of diseases named Transmissible Spongiform Encephalopathies (TSE) by a mechanism involving the conversion of a soluble (cellular) form, PrPC, into an insoluble (scrapie) variant, PrPSc, which is deemed to also retain an intrinsic infectivity. These two isomers of PrP, while indistinguishable from a chemical point of view, substantially differ in their secondary structures. In fact, PrPC is predominantly alpha-helical with little beta-sheet contribution, whereas PrPSc has a considerably higher beta-sheet and lower alpha-helix content, suggesting that conversion between the isoforms is driven by a major misfolding event leading to more extensive beta-sheet conformation. It is reported that several factors can affect PrP stability, including altered cellular environments like temperature, pH and presence of metals. In order to further shed light on the structural properties of the three PrP helices and investigate their stability, we have conducted a molecular dynamics study at different pH values on these three helices, applied helix propensity predictions and evaluated the energetic contribution of the helical regions to the protein prion stability.

Methods

MD simulations were performed with GROMACS software package. Models of helix segments extracted from the structure of human prion protein fragment 121-230 [PDB code:1QM2] were put in cubic boxes filled with water molecules and GROMOS43a1 was selected as force-field. In order to optimize the system, the models were previously subjected to energy minimization and position restraints cycles. The simulations were carried out with periodic boundary conditions by adding sodium ions in order to the net electrostatic charge of the system is zero.

Results

MD simulations on the helix 1 evidenced that the global architecture of its N-terminal region was kept during two whole simulations at neutral and acidic pH, respectively, but more flexible regions were observed in the C-terminal zone where some residues lost the helical conformation. The observed stability of the N terminus of helix 1 is in good agreement with the known stabilizing effects of the negatively charged residues located at the N-cap and N2 positions of the helix 1. For the helix 2 MD simulations, some flexible regions were observed expecially in the simulation conducted at neutral pH, as expected, because the analysis of helix capping motifs in helix 2 showed that only the C-cap position was occupied by a stabilizing residue (i.e. Lys). Moreover for the helix 3 the global architecture is kept during the neutral pH simulation but at the acidic pH this long helix was broken in two helices after only 3 ns. Finally, helix propensity predictions indicated that helix2 had the lowest while helix1 the highest helix propensity and this was in agreement with the calculation of the energetic contribution of alpha helices to the global energy of the structure.

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