pH and aggregation effects in the conversion of human prion into scrapie form: a study using Molecular Dynamics with excited Normal Modes.

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INTRODUCTION AND OBJECTIVES

Prions adopt two different forms: i) the cellular natural form (PrP^C) and ii) an infectious form called scrapie (PrP^{Sc}) having the propensity to aggregate under certain conditions. PrP^{Sc} and PrP^C are widely different regarding secondary and tertiary structures. PrP^{Sc} contains longer and a larger number of β-strands comparatively to PrP^C. The lack of solved PrP^{Sc} structures precludes a proper understanding of the mechanisms related to the transition between cellular and scrapie forms, and of the aggregation process.

We investigate the pH and aggregate effect in the conversion human prion into scrapie form, analyzing the molecular interaction involved. We are trying to help understand the aggregation mechanism.

MATERIAL E METHODS

We used a recently developed simulation method that allowed us to study the conformational transition between PrP^C and PrP^{Sc}. This approach is based on the excitation of low frequency normal modes during molecular dynamics simulations (MDeNM), promoting large conformational changes that are rarely obtained by standard MD simulations unless extremely long simulations are carried out. MDeNM simulations showed an increase in the β-sheet content, likely to correspond to an intermediate state of PrP^{Sc}.

DISCUSSION, RESULTS AND CONCLUSIONS

In order to better analyze the thermodynamic aspects of the transition state, the structure-based model (SBM) simulations at C_α atom resolution was applied to calculate the free energy surface and the energetic barrier related to the conversion of normal prion towards PrP^{Sc}. It was shown that the MDeNM structures with elongated β-strands are located near the energy barrier as given by the SBM simulations

Our results show that acidic pH, a condition often observed in the endosomes, plays a key role in the conversion, thus being in agreement with hydrogen exchange data. A second finding arising from our simulations is that the aggregation such as trimer formation, and larger assembly formation influence the increase of β-sheet formation under acidic pH.

Key Words: Molecular Dynamics, Normal Modes, Aggregation

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