Is conformational instability related to asymmetric distribution of hydrophobic residues ?

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In prion and Alzheimer's diseases, PrP and Aβ proteins, which are involved in neurotoxicity, undergo transconformation. The protein, which is in a "normal" conformation changes to a "pathogenic" conformation (1). Recently, the existence of a tilted peptide in the sequence of those two proteins have been demonstrated. Tilted peptides are short protein segments, presenting an asymmetric distribution of hydrophobic residues, that are able to destabilize an organized system presenting a hydrophilic/hydrophobic interface (2). We hypothesise that these peptides should be related to transconformation either by their own structural lability or by their ability to destabilize the interface existing between the hydrophobic core and the hydrophilic envelope of soluble proteins.

De novo peptides were used to study the transconformation mechanisms. One of them, called "chameleon", designed by Minor and Kim was shown to be helical or in β conformation depending on its position in the same GB1 protein (3).

Since the sequence of chameleon presents characteristics of so-called tilted peptides, the destabilizing properties of the chameleon peptide were investigated. Molecular modelling showed that the chameleon peptide adopts a tilted position with respect to the membrane plane, when it is α helical. Experimentally, the chameleon peptide is able to induce lipid-mixing, permeability and core-mixing of liposomes, suggesting that this peptide is able to destabilizing a hydrophilic/hydrophobic interface. The insertion of chameleon peptide into liposomes was determined experimentally, with the ATR-FTIR method (4). The peptide inserts at an angle of 50° (± 10°) with respect to the surface of membrane. This result is in agreement with the predictions.

The conformation of the chameleon peptide has been studied in different solvents, and in presence of lipids using ATR-FTIR (4). Chameleon peptide is mainly in β conformation in organic solutions but folds in α helix when lipids are present in agreement with the results of Kim and Minor.

Theses results suggest that the chameleon peptide, originally designed as a "transconformational" peptide, has properties close to those of the tilted peptide class (5).

This study contributes to the concept that there could be a relationship between tilted fragments and transconformation. This should be important regarding our comprehensive approach towards these phenomena.

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