STRUCTURAL AND DYNAMICAL ASPECTS OF FUSION PEPTIDE BINDING TO CELL MEMBRANE

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Structural studies of membrane proteins represent an intriguing challenge in modern biology. In spite of the large importance, spatial structure of only few such proteins is known at atomic resolution. This is caused by enormous difficulties in experimental analysis of the proteins in their membrane-bound state. In such a situation, application of computer simulation techniques represents a very promising alternative to solve the problem. Here we report the molecular dynamics (MD) results for membrane binding of the peptide E5 - close homolog of the fusion peptide HA from Influenza A hemagglutinin. The membrane is presented by equilibrated all-atom fully hydrated bilayer of dipalmitoylphosphatidylcholine (DPPC), obtained earlier [1]. To assess the influence of membrane on structure and dynamics of E5, MD simulations of the peptide have also been done in aqueous solution.

The starting structure of the peptide E5 (sequence: GLFEAIAFIEGGWEG LIEG) was that obtained via NMR spectroscopy in detergent micelles [2]. Before the simulations the peptide was placed in water phase and had no contacts with the polar heads of DPPC molecules. After initial stages of the system relaxation, heating to 300 K, and membrane binding, 6-ns NPT collection MD run has been performed. The results may be summarized as follows: 1) During all the dynamics run the peptide stays in contact with lipid bilayer and inserts with its N-terminal part. Strongest interactions with the membrane are observed for side chains of Leu2 and Trp14; 2) In the membrane-bound state the peptide well retains alpha-helical conformation on its N-terminus (residues 2-12), while the C-terminal part is rather flexible and adopts different conformations. 3) The helical segment lies almost parallel to the membrane plane and exposes negatively charged side chains of residues Glu4, Glu8, Glu11 to the aqueous phase. 4) MD simulations in water demonstrate rapid degradation of the peptide secondary structure due to strong competition of water molecules for hydrogen bonding with the peptide backbone amide and carbonyl groups. Therefore, presence of the lipid bilayer strongly stabilizes alpha-helical conformation of E5. 5) Analysis of order parameters for acyl chain regions of DPPC molecules reveals that in the place of E5 insertion they are significantly lower than those obtained in "pure" bilayer simulations [1]. Relevance of such local destabilization of bilayer to the mechanism of the fusion peptide action is discussed.

References.

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