Polypeptide Aggregation in the Vicinity of a Lipid Membrane: Insights from Simulations

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Abstract

Polypeptide and protein aggregates are known to form insoluble fibrillar deposits (amyloids) in the extracellular fluid, and are, therefore, considered one of the main candidates for producing toxic effects on the cell membranes. Being insoluble, amyloids have been found to strongly interact with bilayers, penetrate through those, and provoke formation of pores which, ultimately, results in rupture of the membrane. The same general phenomenon is thought to be linked with both neurodegenerative diseases, such as Alzheimer's and Parkinson's, and the mechanisms of action of antimicrobial peptides which kill bacterial or pathogenic cells by permeabilizing their membranes.

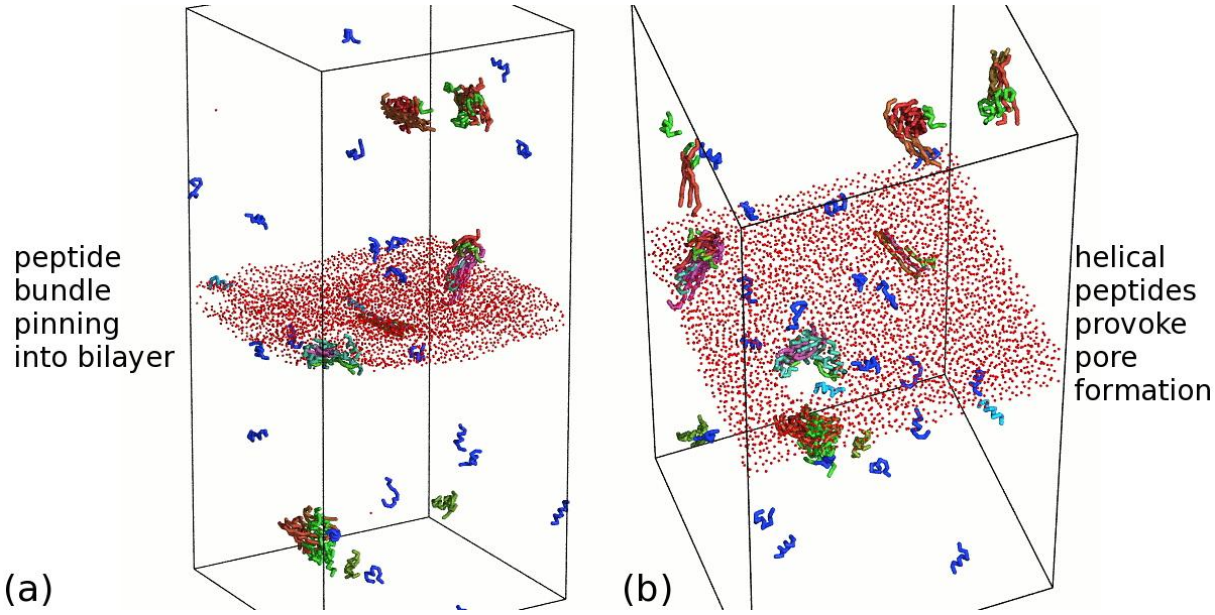
We report on discontinuous molecular dynamics simulations of polypeptides in the vicinity of a phospholipid bilayer. Aggregation of peptides and their influence on the membrane, and vice versa, are under study. A coarse-grained peptide model is used, based on a so-called tube polymer capable of folding into alpha-helical motives and aggregating into beta-strands and bundles [1]. A similar three-bead model of a lipid is employed [2].

We find that the conditions for templated peptide aggregation on the membrane comprise a very narrow window in terms of temperature and peptide-peptide and peptide-lipid interactions. We observe three main scenarios are possible:

(i) adsorption and dissolution of separate peptides within the membrane, where no polypeptide complexes are formed;

(ii) adsorption and aggregation of peptides on the membrane surface, possibly followed by insertion of small aggregates into the bilayer environment leading to pore formation;

(iii) aggregation of polypeptides in the bulk followed by incorporation of the preformed structured complexes into the membrane while pores do not emerge.



1. S. Auer, C.M. Dobson, M. Vendruscolo, HFSP J. 1, 137 (2007)
2. Charles H. Davis, Huifen Nie, M. Dokholyan, Phys. Rev. E 75, 051921 (2007)