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# Interaction of amphipathic $\alpha$-helical peptides with a lipid membrane: Adsorption and pore formation

Vladimir P. Zhdanov *

*Section of Biological Physics, Department of Applied Physics, Chalmers University of Technology, S-41296 Göteborg, Sweden*
*Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia*

## HIGHLIGHTS

- Peptide–peptide lateral interactions may be repulsive and attractive.
- A statistical model describing both these cases is proposed.
- Role of lateral interactions in the adsorption kinetics is discussed.
- Conditions of peptide-induced pore formation are scrutinized.

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## ABSTRACT

Amphipathic $\alpha$-helical peptides often exhibit antimicrobial or antiviral properties. Adsorption of such peptides at a lipid membrane may result in pore formation. Current phenomenological models of the latter process imply that the peptide–peptide lateral interaction is repulsive and that the conditions for pore formation depend on the difference of the peptide energies at the membrane surface and in a pore. There is, however, experimental evidence that the kinetics of peptide adsorption at small vesicles (about 100 nm diameter) may be cooperative and accordingly the peptide–peptide lateral interaction may be attractive. In addition, the experiments indicate that the peptide-induced pore formation is often observed at the conditions close to those corresponding to pore formation under externally induced tensile stress where the difference of the peptide energies at the membrane surface and in a pore is irrelevant. Here, a model describing both types of peptide–peptide lateral interactions at a membrane is proposed. In addition, a new scenario of peptide-induced pore formation naturally explaining the similarity of this process under different conditions is suggested.



## 1. Introduction

Lipid membranes play an extremely important role in cells. For example, an appreciable part of proteins and enzymes is associated with lipid membranes [1]. Kinetic processes occurring at or in such membranes are often complicated by various physical factors, e.g., by the existence of short- and/or long-range order in the arrangement of lipids and adsorbed and/or incorporated proteins, membrane strain, curvature and roughness, etc. (see [2,3] and references therein). For these reasons, membrane processes are of interest from the point of view of physics in general and biophysics and statistical physics in particular. Many aspects of the theory of such processes are still not well developed.

Herein, we focus on the interaction of antimicrobial peptides with lipid bilayers. Such peptides, ranging from 4 to about 40 amino acids in length and exhibiting various shapes (linear, cyclic, disulfide cross-linked, or acylated) with many

* Correspondence to: Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia.
*E-mail address:* zhdanov@catalysis.ru.

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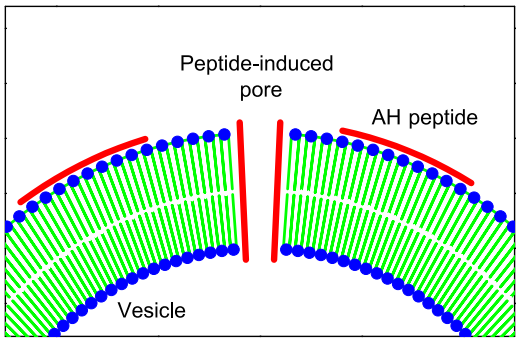


**Fig. 1.** Schematic structure of peptide-induced "barrel-stave" pores in a vesicle. Alternatively, the pores may have the "toroidal" or "carpet" shape (reviewed in [27]).

types of secondary structure (including $\alpha$-helix, $\beta$-sheet, irregular structure, or random coil), are usually amphipathic, i.e., contain hydrophobic and hydrophilic regions (the latter are partly of cationic nature) [4]. The most abundant subclass of antimicrobial peptides includes amphipathic $\alpha$-helical (AH) peptides (reviewed in [4–6]). Some of AH peptides are antiviral [7,8]. In general, AH peptides are able to attach to a lipid membrane and to form pores there with eventual membrane degradation. The understanding of mechanistic details of these processes is of considerable intrinsic interest and is also important from various perspective of molecular biology, bacteriology, virology, and applications in therapeutics, because *in vivo* the extracellular AH peptides represent an element of the defense of cells against bacteria, and potentially these peptides may form a new class of drugs aimed at bacteria [5,6] and enveloped viruses [7]. In related academic studies, the interaction of AH peptides with such pathogens can be mimicked by their interaction with small vesicles attached to a solid support [9]. This platform combined with total internal reflection fluorescence microscopy allows one to track the kinetics of peptide-induced pore formation on the level of single vesicles [10]. In another general context, the ability of AH peptides to rupture attached vesicles can be used as a basis of one of the ways of formation of supported lipid bilayers [9,11].

Experimental investigations of the interaction of AH peptides with lipid bilayers have initiated the related theoretical studies including the analytical treatments, focused on the phenomenological thermodynamics of pore formation [12,13] and various aspects of the kinetics of pore formation and growth ([10] and [14–18]), and molecular dynamics simulations [19–22]. The phenomenological treatments [12,13] articulate the role of the peptide-induced membrane strain in the pore formation (see below). The kinetic models ([10] and [14–18]) help to interpret the observed kinetics but typically do not describe the underlying physics in detail. The use of the molecular dynamics technique is limited due to a large number of atoms participating in the processes under consideration. The available simulations scrutinize the effect of induced tension and electrostatic interactions on the translocation of single peptides across a lipid bilayer [19], influence of the membrane curvature on the conformations of peptides [20], peptide-caused large perturbations in the bilayer during the pore formation [21], and buckling of the bilayer near a peptide-induced pore [22].

Despite the available experimental and theoretical studies, the understanding of the interaction between AH peptides and a lipid bilayer is still not complete. In this article, we scrutinize two related aspects including the type of the peptide–peptide lateral interaction at a lipid membrane (Sections 2 and 3) and conditions for peptide-induced pore formation and membrane rupture (Sections 2 and 4). Referring to the available experiments, we argue that the applicability of the existing models is limited. Our theoretical analysis predicts qualitatively novel features extending the ways how the experiments can be explained. To be specific, we discuss AH peptide adsorption on vesicles (Fig. 1). For briefness, the abbreviation "AH" is below often omitted, i.e., "AH peptide" is identified with "peptide".

## 2. Previous treatments

Adsorption of AH peptides (which are linear on the coarse-grained level) on a lipid membrane is usually accompanied by membrane stretching with subsequent pore formation and vesicle lysis [12,13]. In the available phenomenological treatments of these processes, the peptide-induced membrane area expansion is considered to be equivalent to that produced by the conventional tensile stress despite the fact that the peptide-induced tension does not exert force at the membrane boundary (e.g., in a pore) while the conventional tensile stress is created by such force [12]. The area increment is considered to be proportional to the numbers of peptides located at the membrane surface. The membrane elastic energy related to the area increment is assumed to be the same as in the case of the tension produced by the conventional stress. Following this line, the energy of peptides attached to a vesicle is represented as [12]

$$E = \epsilon_s N_s + \epsilon_p N_p + \frac{Kns}{2}\left(\frac{\phi N_s}{ns}\right)^2, \tag{1}$$