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Review

The role of spontaneous lipid curvature in the interaction of interfacially active peptides with membranes ☆

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ABSTRACT

Research on antimicrobial peptides is in part driven by urgent medical needs such as the steady increase in pathogens being resistant to antibiotics. Despite the wealth of information compelling structure–function relationships are still scarce and thus the interfacial activity model has been proposed to bridge this gap. This model also applies to other interfacially active (membrane active) peptides such as cytolytic, cell penetrating or antitumor peptides. One parameter that is strongly linked to interfacial activity is the spontaneous lipid curvature, which is experimentally directly accessible. We discuss different parameters such as H-bonding, electrostatic repulsion, changes in monolayer surface area and lateral pressure that affect induction of membrane curvature, but also vice versa how membrane curvature triggers peptide response. In addition, the impact of membrane lipid composition on the formation of curved membrane structures and its relevance for diverse mode of action of interfacially active peptides and in turn biological activity are described. This article is part of a Special Issue entitled: Interfacially Active Peptides and Proteins. Guest Editors: William C. Wimley and Kalina Hristova.

Contents

Abbreviations: AMPs, antimicrobial peptides; DPPC, dipalmitoyl phosphatidylcholine; DPPG, dipalmitoyl phosphatidylglycerol; DOPC, dioleoyl phosphatidylcholine; DSPC, distearoyl phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; SUVs, small unilamellar vesicles; GUVs, giant unilamellar vesicles; LUVs, large unilamellar vesicles; BSM, brain sphingomyelin; MPER, glycoprotein 41 membrane-proximal external region; TP-1, tachyplesin-1; PG-1, protegrin-1; CB3, cecropin B3; Beta-17, 17 β-amino acid oligomer; CCT, CTP:phosphocholine cytidylyltransferase

☆ This article is part of a Special Issue entitled: Interfacially Active Peptides and Proteins. Guest Editors: William C. Wimley and Kalina Hristova.

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1. Introduction

Research on antimicrobial peptides (AMPs), effector molecules of innate immunity that provide a first line of defense against a substantial array of pathogenic microorganisms [1,2], is in part driven by the medical need to find alternative agents to conventional antibiotics [3,4]. The development of novel antibiotics is a pressing need in light of the rapid increase of multidrug resistant bacteria and the steady decline of

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approval of novel compounds since the early 1980s. Thus considerable efforts have been made to elucidate the molecular mechanism(s) of action of AMPs in model and in vitro studies, in order to provide both, a sound basis for rationale peptide design and parameters for high-throughput screening approaches [4–10]. Thereby, numerous studies have demonstrated that AMPs interfere with the integrity of bacterial membranes via diverse mechanisms (for reviews see e.g. [3,11–13]). In one of his recent reviews Wimley [14] pointed out that despite the large volume of data available, compelling structure–function relationships are still very rare and further described a paradigm to bridge the gap between biophysical and biological activity: the interfacial activity model. Thereby, "interfacial activity" was described as "the ability of a molecule to bind to a membrane, partition into the membrane–water interface, and to alter the packing and organization of the lipids" ([6], and contribution in this special issue), which depends mainly on the appropriate balance of hydrophobic and electrostatic interactions between peptides, water, and lipids. In fact, a number of publications suggest that antimicrobial activity is not dependent on specific amino acid sequences or on specific peptide structures [15–18], but rather depends on the physical chemical properties of AMPs [19]. Thereby the variety and distribution of amino acids determine the peptide properties in respect to charge, amphiphilicity, hydrophobicity, flexibility, H-bonding capacity and secondary structure, to mention some. However, there is consensus that the positive charge of the peptide is essential for initial binding to the negatively charged bacterial membrane surface, which allows discrimination between bacterial and host cell membrane, and that hydrophobicity is needed for insertion into and disruption of the membrane (e.g. [20,21]). Although most of the examples given in this review refer to antimicrobial peptides, these features are not only related to their activity, but are also of importance for other membrane active peptides, such as cytolytic peptides with melittin from bee venom being the most prominent representative, or antitumor peptides [22–24]. Furthermore, cell penetrating peptides share also some properties with antimicrobial peptides. They are typically composed of 5–30 amino acids and mostly cationic, have in general no sequence homology, but can exhibit an amphipathic character and frequently show structural plasticity. Therefore, it is not surprising that one may find cell penetrating peptides that exhibit antimicrobial activity and vice versa antimicrobial peptides that translocate through cell membranes [25,26].

2. The role of spatial arrangement of amino acids within a peptide

The importance of spatial arrangement of polar, charged and hydrophobic amino acids on membrane interaction and its correlation with antimicrobial as well as hemolytic activity has been addressed in a number of studies. Within this review only few examples will be described to emphasize the complexity of this topic. A systematic study in White's laboratory challenged the impact of peptide amphiphilicity compared to hydrophobicity for the interaction with zwitterionic and anionic lipid model systems [27]. For this purpose six different peptides with a length of seventeen residues, composed only of Ala, Leu and Gln flanked with Trp at the C-terminus to facilitate measurements of partitioning free energy, were synthesized. The peptides were all uncharged and differed only in amphiphilicity, but not in total hydrophobicity. The study revealed that helicity in water and interface was higher for amphiphilic peptides, which affects the partitioning of peptides to the membrane interface [27]. However, the free energy reduction per residue (ΔG_{res}) turned out to be independent from the hydrophobic moment (amphiphilicity) of peptides, which only influences the α-helical content but not the energy gain of folding per residue [28]. As first noted by Wimley et al., ΔG_{res} is driven by hydrogen bonding of the peptide backbone [29]. Therefore the spatial arrangement of hydrophilic, charged and hydrophobic residues within a peptide may represent an important factor, apart from others affecting the electrostatic or hydrophobic interactions of peptides with lipid membranes.

The complexity to predict the consequences of amino acid rearrangement is also outlined by a recent study from the laboratory of Vogel [30]. This group designed three different variants of Trp-rich peptides derived from the HIV glycoprotein, gp41, with the purpose to increase the antimicrobial activity owing to an increase of the net positive charge and amphiphilicity of the helical peptide. The parent peptide interacted with dipalmitoyl-PC and -PG (DPPC, DPPG) model systems, whereas it was inactive against bacteria, which was attributed to oligomerization in aqueous solution. In the variant gp41w-4R four polar residues were replaced by cationic Arg. While the antimicrobial activity of the peptide was not increased, the peptide elicited extremely high hemolytic activity. Haney et al. [30] related this observation to the even distribution of the positively charged residues along the α-helix. Therefore, in case of negatively charged lipid head groups, as found in bacterial membranes, the peptide stays bound to the surface due to strong electrostatic interactions. In contrast, in neutral or zwitterionic lipid systems, as found in erythrocytes, Van der Waals interaction between the hydrophobic residues and the hydrophobic core of the lipid bilayer are strong enough to promote the insertion of the peptide into the bilayer, causing severe membrane destabilization. Using the variants gp41w-KA and gp41w-FKA, where the positively charged residues were located on one side of the helix, the hemolytic activity was reduced, most likely because deeper insertion was prevented by the concentration of the charged amino acid residues on one side of the peptide. Finally, three Trp residues were replaced by Phe in case of gp41w-FKA, which resulted in reasonable antimicrobial activity. This was not expected, because Trp due to its bulky, uncharged side chain is considered to be important for the activity of AMPs [31–34]. In contrast to Phe Trp does not reside deeply in the hydrocarbon chain region, but preferentially locates at the polar/apolar interface. This ambivalence is attributed to the π-electron system of Trp, which facilitates cation–π interactions of the Trp electron cloud with any positively charged species (ions, positively charged amino acids, etc.) [32,35]. The importance of the vectorial arrangement of tryptophan, i.e. the arrangement on the same face of the α-helix, as well as the importance of the positioning of the aromatic residues, i.e. flanking one or both termini of the peptide, for antimicrobial activity were recently shown [36]. This study demonstrated that orientation of Trp on the same side of the α-helix facilitated their concomitant insertion and thereby alleviated the adoption of the α-helical structure, which is diminished in a peptide that excluded a simultaneous arrangement of the Trp residues at one side of the α-helix. Moreover, Trp residues flanking both termini of the peptide rigidly anchored the peptide in the interfacial region, thereby impeding insertion into the hydrophobic region [36].

To conclude, small differences in the spatial arrangement of amino acids can cause big changes in the interaction of peptides with lipid membranes mostly affecting peptide orientation and/or depth of membrane insertion. The orientation of a peptide in the membrane is considered to be a key parameter determining the mechanism of action, as for example the toroidal pore mechanism presumes vertical orientation [37,38] and the carpet mechanism initially presumes horizontal orientation [39]. Also, the depth of insertion is a critical parameter, as it is correlated with the insertion of a certain peptide volume in a certain region of the bilayer, which can induce different "voids" and in turn may give rise to local membrane curvature or at high peptide concentration to interdigitated lipid structures [3]. Insertion of a volume in the membrane interface may cause lateral pressure in this region facilitating positive membrane curvature, while insertion of a volume in the hydrophobic core region may cause lateral pressure in the acyl chain region facilitating negative membrane curvature (see Fig. 2). The few examples mentioned above emphasize that the concerted sum of all properties determines the interaction with lipid systems, which in turn also comprise crucial differences depending on the lipid species as for example demonstrated for the human cathelicidin LL-37 [40,41].

3. Membrane interface and its relation to membrane curvature

The balance of entropy and shielding of the hydrophobic entities leads to an optimized packing of the lipid molecules, i.e. the free energy with respect to the lipid area/molecule is minimized [42]. Owing to the variation of lateral intramolecular interactions along the bilayer normal, a lateral pressure field emerges, known as the lateral pressure profile, which strongly depends on the nature of lipids [43,44]. It is composed essentially of three regimes: (i) headgroup, (ii) polar/apolar interface and (iii) hydrocarbon chain region [43]. Repulsion exists in the lipid headgroup region resulting from electrostatic interactions and entropic effects as well as in the hydrocarbon chain region of the membrane, where mutual repulsion of the hydrocarbon chains dominates. At the polar/apolar interface, the hydrophobic free energy density (or interfacial tension) associated with the exposure of the apolar hydrocarbon regime leads to a significant lateral attraction, i.e. to a minimization of the interaction of the lipid chains with water. The components of the internal lateral pressure in a membrane and their transmembrane profiles are not accessible to direct measurement, because the net lateral pressure in a membrane at equilibrium is zero. In order to relate the effects of the lateral pressure profile e.g. on membrane protein conformational equilibria or interaction with membrane active compounds to experimentally accessible quantities it is necessary to introduce the elastic constants for membrane bending. This includes especially the spontaneous (or intrinsic) lipid curvature, c_0 [43,45–47], which for a tubular/cylindrical system like the inverse hexagonal phase, H_{II}, is directly related to the spontaneous radius of curvature. Usually, this parameter is measured in fully hydrated H_{II} phases in the presence of excess hydrocarbons using X-ray diffraction [43,48,49], where outward curvatures, i.e. bending of the membrane surface away from the aqueous phase (oil-in-water), are defined as positive and inward curvatures, i.e. bending of the membrane surface towards the aqueous phase (water-in-oil), as negative curvatures (see Fig. 1). The spontaneous curvature of a planar configuration is always zero.

The spontaneous lipid curvature c_o also appears in the Helfrich description of membrane elasticity [50], where the free energy per unit area, g_C is

$$g_C = \frac{\kappa_m}{2}(H - c_0)^2 + \kappa_g K \quad (1)$$

where κ_m is the bending rigidity, κ_g is the Gaussian modulus of the curvatures of the lipid monolayers (because the integral is over half of the bilayer); H is the mean curvature and K is the total or Gaussian curvature (see, e.g. [51]). The latter are related to the planes of principal curvatures c_1 and c_2 at a given point P (Fig. 1) on the surface by:

$$H = (c_1 + c_2)/2 \quad (2)$$

$$K = c_1 * c_2 \quad (3)$$

where the mean curvature, H, is the average of the principal curvatures and the total or Gaussian curvature, K, is the product of the principal curvatures. The two principal curvatures determine the local shape of a point on a surface, c_1 characterizing the rate of maximum bending of the surface and the tangent direction in which it occurs, while c_2 characterizes the rate and tangent direction of minimum bending. The mean curvatures $H > 0$ denote curvature towards the chain region, whereas $H < 0$ denotes curvature towards the water region. The Gaussian curvature is a more fundamental property of the interface than the mean curvature since it determines the qualitative nature of the membrane surface. For example, surfaces for which K is positive describe a micelle or an inverted micelle, whereas K is zero, when either one or both of the principal curvatures are zero, which is the case for cylindrical/tubular (e.g. H_{II}) and planar structures (e.g. lamellar phases). When the principal curvatures c_1 and c_2 are of opposite sign K is negative as observed for the saddle-shaped surface of cubic phases [52,53].

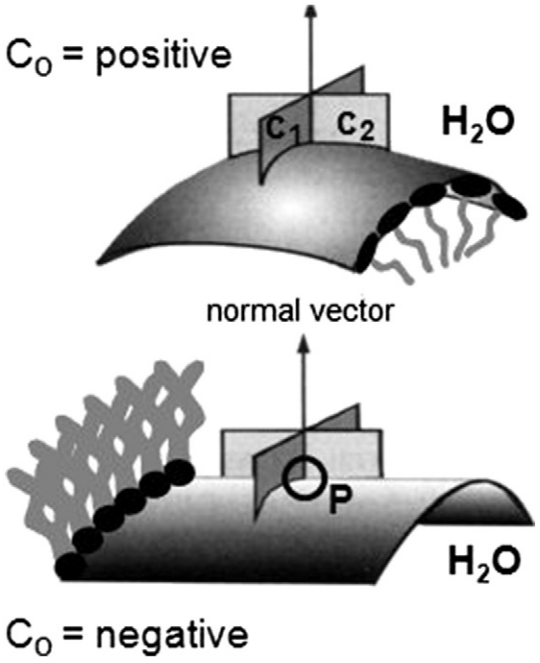

Fig. 1. Schematic representation of the planes of principal curvatures c_1 and c_2 for a micelle (top) or tubular structure such as the inverse hexagonal phase (bottom). The Gaussian curvature, K, is positive for the former and zero for the latter. Note, the spontaneous curvature, c_0, is also positive for a micelle, but negative for the H_{II} phase.

4. Modulation of membrane curvature

In general, the action of interfacially active peptides is often accompanied by membrane deformations as a result in changes of local and global membrane curvature. In a recent review, Haney et al. [54] gave a comprehensive overview on peptides inducing membrane curvature, whereby positive curvature was largely associated with toroidal pore formation or micellization and negative curvature with the peptide aggregation model and peptide translocation via non-bilayer intermediate structures. In this section we want to discuss the following aspects related to membrane curvature: (i) intrinsic properties of lipids to adopt planar or curved lipid structures (lipid molecular shape), (ii) differences in inner and outer membrane leaflet leading to membrane curvature and (iii) physical chemical parameters facilitating the formation of membrane curvature. These parameters are very often interrelated. For example, one may envision that induction of curvature by a peptide in a lipid membrane of complex composition could concomitantly induce phase separation and enrichment of lipid species fitting the local steric requirements best. Further binding of interfacially active peptides at the outer leaflet of a lipid membrane may induce a difference in inner and outer bilayer area and thereby induce curvature.

4.1. Molecular shape of lipids and curvature

The nature of lipids determines the intrinsic tendency to form distinct phases in relaxed systems mostly explained by the molecular shape of the lipids [55,56,57]. Op den Kamp demonstrated that a mixture of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) when sonicated forms small unilamellar vesicles (SUVs) with an asymmetrical lipid distribution [55]. Most of PE was located in the inner monolayer and PC in the outer monolayer. This observation suggested a physical parameter that enables PE and PC to adapt to different membrane curvatures to a different extent. Cullis and de Kruijff suggested that the shape of the lipid molecules determines the morphology of lipid aggregates [56]. PC is

characterized by a cylindrical molecular shape, while PE is characterized by a truncated cone shape because of its small head group area as compared to the cross-section of its hydrocarbon chains [56]. Thus PC is prone to form bilayers and PE an inverse hexagonal phase. A dimensionless packing parameter to describe the molecular shape of lipids and in turn the preferred lipid phase was introduced by Israelachvili [57] and Cevc pointed out that the effective area per lipid chain correlates with the ease of bilayer vesicle formation and bilayer deformability [92] emphasizing that the lipid composition of a biological membrane is of importance for its interaction with membrane active peptides.

The implication of the different lipid molecular shapes is also of interest for the biological activity of AMPs [20,58]. In microorganisms like *Escherichia coli* or *Acholeplasma laidlawii* the amount of lamellar to non-lamellar phase preferring lipids is strictly regulated [59–61]. The presence of cone-shaped lipids such as PE, a predominant component of the cytoplasmic bacterial membrane, increases the lateral hydrocarbon chain pressure in the center of the bilayer. In contrast, lamellar phase forming lipids such as PG or PC with a cylindrical shape exhibit a more uniform lateral pressure throughout the hydrocarbon chain region. These differences in packing properties may also affect membrane functions. For example, it has been suggested that the lateral hydrocarbon chain pressure regulates the functionality of integral membrane proteins [62], which is in line with the observations that non-lamellar lipids are often required for functional reconstitution of membrane proteins [63] and that PE is found in protein rich domains [64]. One may speculate that AMPs could induce membrane rupture by lowering the lamellar to non-lamellar phase boundary, as demonstrated with lipid extracts of *E. coli* and *A. laidlawii* treated with gramicidin S [65]. It was proposed that the limited flexibility of the β-turn of the peptide as well as the clustered location of the ornithine side chains confer the peptide a molecular shape similar to PE. Thus, incorporation of this peptide in the lipid membrane promotes formation of negative curvature. Implication on lipid morphology was also shown for other AMPs in PE model systems ([54] and see also Table 1). In sum, an increasing number of studies outline the relevance of the lipid matrix and the physical properties of different lipid species for the mode of action of AMPs [20].

There are also examples emphasizing the role of membrane curvature for biological processes, e.g. in lipid sorting and fission of membrane tubules. Roux et al. [66] demonstrated that different lipid species respond differently to membrane curvature strain. The group performed experiments with fluorescence labeled giant unilamellar vesicles (GUVs), which consisted of an equimolar mixture of brain sphingomyelin (BSM), cholesterol and dioleoyl-PC (DOPC). GM1 served as fluorescence label for a liquid ordered phase enriched in BSM and BODIPY$_{FL}$-C$_5$-HPC served as a label for a liquid disordered phase enriched in DOPC. Both labels were distributed homogenously within the bilayer of the GUVs. However, when tubular structures were pulled out of the GUVs, and thereby regions of high curvature were created, an increase of BODIPY$_{FL}$-C$_5$-HPC in the tubes as compared to GUVs was observed. Therefore, the authors concluded that these tubes were enriched in DOPC but were depleted of both cholesterol and BSM. These results demonstrate that induction of membrane curvature may lead to an enrichment of lipid species that fit the curvature requirements best. Furthermore, it was suggested that these processes are of importance for biological systems like the Golgi apparatus [66].

Table 1
Selection of peptides inducing membrane curvature in different lipid model systems.

Peptide	Lipid system/observation	Proposed mechanism	Ref.
Induction of positive mean curvature			
Surfactin	DMPC:DMPS/vesicularization	Electrostatic repulsion	[80]
Temporins B and L	POPC:POPG/tubule formation	–	[123]
TRP3	DPPA, DPPG/vesicularization	Increased surface pressure	[124]
M2 pep.	DMPC; VM-vesicles/isotropic phase	Increased surface pressure	[96]
Duramycin, cinnamycin	PE/tubule formation	Increased surface pressure	[97]
MPER	DPPC:Chol	Surface area increase	[68]
Acylated/nonacylated-LF11 variants	POPE/T_{HII} increase	–	[125,126]
PG-1	PC:PG/micellization	Increased surface pressure	[84],
	POPC, DLPC, DPPC/micellization	Hydrophobic mismatch	[127]
MSI-367	DiPoPE/T_{HII} increase	Increase interface pressure	[128]
MSI-843	DiPoPE/T_{HII} increase	–	[129]
MSI-594, MSI-78	POPC: H_I phase formation	–	[130]
	POPG: H_I phase formation		
RL16	DiPoPE/T_{HII} increase	–	[131]
Oxki1	DEPE/T_{HII} increase	–	[132]
Oxki2	DEPE/T_{HII} increase	–	[132]
	DMPC/micellization		
Melittin	POPE/T_{HII} increase		[133]
Induction of negative mean curvature			
Phenylene ethylene AMOs	PE/T_{HII} shift	–	[134]
TP-1	POPG:POPE/isotrop. NMR sig.	Increased hyd. core pressure	[84]
Oritavancin	CL:POPE/T_{HII} decrease	Red. of electrostat. repulsion	[135]
Penetratin	DiPoPE/T_{HII} decrease	–	[131]
Polyphemusin I	PE/T_{HII} decrease	Steric mechanism	[136]
RMAF4; R/K-RMAD4	DOPS:DOPE:DOPC/T_{HII} decrease	Arg/Lys H-bonding	[75]
Crp4	DOPS:DOPE:DOPC/T_{HII} decrease	Arg H-bonding	[75]
NK-2	POPE/T_{HII} decrease	Steric mechanism	[137]
Nisin	DOPE, POPE/H_{II} phase formation	Increased hyd. core pressure	[88]
Beta-17	PE/T_{HII} decrease	Increased hyd. core pressure	[90]
Induction of negative Gaussian curvature			
R/K-Crp4	DOPS:DOPE:DOPC/T_{QII} shift	Lys H-bonding	[75]
SMAMPs	PE/Q_{II} phase formation	–	[138]
Alamethicin	PE/Q_{II} phase formation	–	[139,103,140]
Gramicidin S	POPE, *E. coli*, *A. laidlawii* lipid extract/Q_{II} phase formation	–	[65,133]
PGLa, PG-1	POPE/Q_{II} phase formation	–	[133]
LF-11 variants	*E. coli*-lipid extract/Q_{II} phase formation	–	[125,126]

4.2. Membrane curvature through differences in inner and outer membrane leaflet area

A more general, physical approach to membrane curvature is described by Zimmerberg and Kozlov [52] and is based on the work of Helfrich on the elastic properties of lipid bilayers [50]. The radius of a membrane curvature is described as a function of the lateral tension γ and the membrane bending rigidity κ_B and thereby depends on the monolayer asymmetry. This model describes how changes in the area of the inner or outer bilayer leaflet results in lateral tension and membrane curvature. This mechanism was in particular used to describe the influence of flippases on the curvature of biological membranes [67] and may be of special interest to describe long range curvatures like cell shapes but also to describe the effects of interfacially active peptides in some cases [68]. A chemo-mechanical view on lipid membranes with certain similarities was presented as "balanced-spring model", where a planar lipid membrane was described as plane structure comprising frustrated monolayer curvatures. It was hypothesized that insertion of a peptide in one monolayer could release intrinsic tension and thereby induce formation of membrane curvature [69].

4.3. Membrane curvature induced by interfacially active peptides

The action of AMPs or more generally interfacially active peptides on lipid membranes is often accompanied by the induction of membrane curvature, as revealed by a number of studies on model systems (see Table 1). Incorporation of such molecules in a bilayer can induce a curvature strain, which under certain experimental conditions such as high peptide concentrations or elevated temperatures may lead to induction of membrane curvature (see Fig. 2). Experimentally this was shown mostly on the basis of changes in the transition temperature from the fluid L_α phase to inverse hexagonal phase of PE lipid systems. Changes in H_{II} phase transition temperature are technically easily accessible through differential scanning calorimetry and present the most common parameter describing the curvature behavior of interfacially active peptides [70]. As outlined above PE comprises a conical shape and therefore undergoes the transition of L_α to H_{II} at characteristic temperatures depending on the nature of the hydrocarbon chain [71]. Incorporation of AMPs that lead to an increase of H_{II} phase transition temperature indicates promotion of positive spontaneous curvature and a decrease of H_{II} phase transition temperature indicates promotion of negative spontaneous curvature [72]. One has to emphasize that induction of curvature in PE lipid systems by a peptide cannot be generalized for other lipid systems. For example, PE comprises the possibility of H-bonding, which can largely influence the behavior of a peptide in respect to curvature induction. Especially Arg and Lys residues can lead to negative mean or Gaussian curvature through H-bonding with the PE head group [73]. As different lipid head groups differ in the ability of H-bonding or charge, the curvature induction by a peptide may differ for different lipid systems. Several factors were proposed to be important for peptides inducing curvature such as (i) H-bonding, (ii) electrostatic repulsion, (iii) monolayer surface area and (iv) lateral pressure, which will be discussed below.

4.3.1. H-bonding

PE and phosphatidylserine (PS) are capable of both, serving as H-bond donors with their amino group and serving as H-bond acceptors with their phosphate and carboxyl groups. This distinguishes them from other lipids like PC or PG, which can only serve as H-bond acceptors. For this reason, H-bonding with the hydroxyl-, thiol-, amido-, amino-, and guanidinium groups of polar and basic amino acids like Arg, Lys, Asn and Gln is more pronounced with PE and PS compared to other lipids [74]. In addition, the chemical structure of the amino acids and thereby their ability to act as multiple or single donors or acceptors can affect the morphology of PE or PS bilayers. The impact of the different H-bonding capacity of Arg compared to Lys and consequences on non-lamellar phase induction has been most systematically studied by the group of Wong (see also contribution of Wong in this special issue). Here, we only refer to one of their recent studies, where all Arg residues of the peptides Crp4 and RMAD4 were replaced by Lys residues [75]. Arg is capable to maintain H-bonds with multiple lipid headgroups through its guanidinium group, whereas Lys can only interact with one PE headgroup, Schmidt et al. [75] claimed that Arg can induce a negative Gaussian curvature (saddle shaped structures), while Lys is limited to a negative mean curvature. Thus Arg residues should promote bicontinuous cubic (Q_{II}) phase formation and Lys H_{II} phase formation, respectively. Interestingly, the lysine variant of RMAD4 showed no difference in non-lamellar phase induction compared to the parent peptide. The authors attributed this observation to the relatively dense spatial arrangement of Lys on RMAD4 and hypothesized that a clustering of lysine residues may be able to mimic the multi-dentate H-bonding of Arg and therefore may also be capable of inducing negative Gaussian curvature as required for cubic lipid phases [75].

The hypothesis that Arg-to-Lys substitution would shift the ability of a peptide to induce Q_{II} phase formation was also not fully reflected in the phase diagram of R/K-Crp4, as the lysine variant was capable to

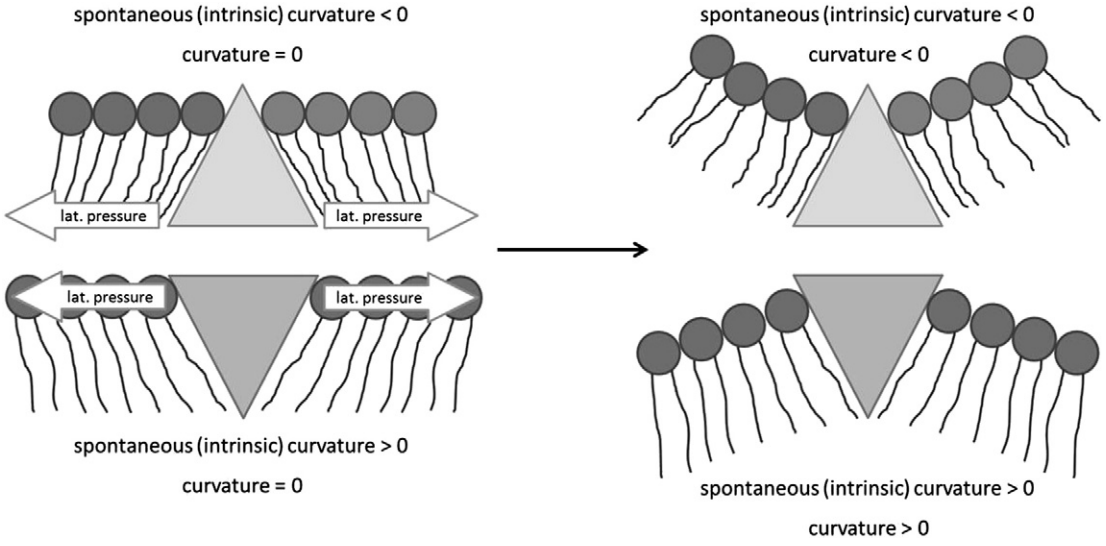

Fig. 2. Sketch of a molecule preferentially inserting in the hydrocarbon chain region (top) and headgroup region (bottom), respectively, inducing changes in lateral pressure and hence curvature strain, which can lead to induction of negative or positive membrane curvature.

induce a Q_{II} phase already at lower PE content. This observation may be related to the fact that the $L\alpha$–H_{II} phase transition can be accompanied by the formation of cubic phases [76–78]. In addition, the evolution of a bicontinuous cubic lattice can proceed very slowly [79]. These circumstances may impede a clear distinction of the peptide induction of Q_{II} versus H_{II} phase formation under certain conditions. In terms of biological activity big differences were detected between Crp4 and R/K-Crp4, whereby the parent peptide was more toxic against *E. coli ML35* than the variant. The authors assumed that the ability of peptides to promote negative Gaussian curvature is evolutionarily adapted to the lipid composition of bacterial membranes and disposition of Arg by Lys could shift the peptide activity out of the optimal range [75].

4.3.2. Electrostatic repulsion

Antimicrobial peptides mostly comprise positive charges and thereby exhibit higher affinity to negatively charged lipid membranes. Binding of cationic peptides thereby decreases the electrostatic field of negatively charged headgroups and diminishes the electrostatic repulsion. In turn, peptides may induce negative spontaneous curvature through a decrease in the mean headgroup area. In contrast, Buchoux et al. report on a relatively rare case of a peptide inducing electrostatic repulsion in the headgroup region [80]. Surfactin, a negatively charged lipopeptide secreted by *Bacillus subtilis*, contains a β-hydroxy fatty acid with a chain length varying from 12 to 14 carbon atoms. Obvious, favorable Van der Waals interactions of the fatty acid chain with the hydrophobic core of lipid membranes enable the insertion of the peptide even into negatively charged lipid systems. The electrostatic repulsion of peptide molecules and lipid headgroups induces positive curvature strain resulting in membrane vesicularization, which was not observed in zwitterionic lipid systems emphasizing that membranolysis is due to electrostatic repulsion between peptides and lipids [80].

4.3.3. Increase of monolayer surface area

Ivankin et al. [68] investigated the interaction of the glycoprotein 41 membrane-proximal external region (MPER) on POPC/cholesterol membranes. Grazing incidence X-ray diffraction experiments showed that the peptide was located deeply into the acyl-chain region below the membrane surface at low cholesterol content, whereas it was located in the interface at high cholesterol content. Location at the interface was accompanied by an increase of the area occupied by the peptide and a reduction of monolayer thickness due to void compensation. The authors assume that the asymmetric increase in monolayer surface generates elastic stress and curvature, according to the model of Kozlov and Zimmerberg [52]. Induction of "free volume" (void) by incorporation of peptides aligned parallel at the membrane interface and various modes of compensation was also suggested to represent one mode of action of AMPs [3].

4.3.4. Increase of lateral pressure in headgroup and hydrocarbon chain region, respectively

Curvature induction of interfacially active peptides is often referred to changes in lateral pressure (see above). Thereby, insertion of a peptide into the headgroup region of a membrane may enhance positive spontaneous curvature whereas insertion into the hydrophobic core may enhance negative spontaneous curvature (see Fig. 2). In this model, the membrane compensates the curvature strain induced by a peptide through the formation of curvature. In this context, it is of interest to note the coupling between membrane lateral pressure and membrane protein function that is often strongly influenced by the molecular composition of the bilayer in which the protein is embedded [81,82]. Cantor suggested that a shift of the lateral pressure in a bilayer due to changes in lipid composition alters the amount of mechanical work of a protein conformational transition. Furthermore, he predicted that besides variations in lipid chain length, degree and position of chain unsaturation as well as headgroup repulsion incorporation of interfacially active molecules can result in large redistributions of lateral pressure [83]. A study of Doherty et al. [84] addresses the effect of lateral pressure at different regions of the bilayer in the presence of peptides. In this study the β-hairpin AMPs tachyplesin-1 (TP-1) inducing negative spontaneous curvature, and protegrin-1 (PG-1) inducing positive spontaneous curvature, are discussed. PG-1 was shown to insert into the lipid bilayer near the membrane surface [85,86] and thereby expands the surface area. In contrast, the conformation of TP-1 displays an increased hydrophobic accessible surface area [87] and thereby may increase the peptide volume in the hydrophobic region of the bilayer. A similar behavior like TP-1 was reported for nisin, lowering the $L\alpha$ to H_{II} phase transition in POPE [88]. Insertion of its large hydrophobic volume in the bilayer interior would promote negative spontaneous curvature, hence the formation of inverted non-lamellar structures. The same mechanism of action can also be deduced from studies on a cecropin B analog (CB3) [89] and a 17 β-amino acid oligomer (beta-17) [90]. Nevertheless, this mechanism of curvature induction emphasizes the importance of the location of peptides within the bilayer, and change of lateral pressure in the corresponding membrane region. These parameters are not always easily accessible and more detailed information on this topic will be necessary.

5. Membrane curvature triggering peptide response

Effects of membrane curvature and hence interfacial properties on peptide binding and secondary structure formation were investigated recently. For example, Bozelli et al. [91] reported that the conformation of TRP3 is highly independent from the membrane lipid composition, but differs strongly between large unilamellar vesicles (LUVs) and micelles. Furthermore, TRP3 bound preferentially to LUVs containing negatively charged lipids, whereas it bound to micelles irrespective of headgroup charge. This observation suggests that in highly positively curved membranes such as micelles other intermolecular interactions, presumably Van der Waals forces, than electrostatic interactions become predominant. In this view, the authors attributed the different peptide behavior to the looser molecular packing of micelles and proposed implications for toroidal pore formation by TRP3 [91]. Membrane curvature dependent binding was also observed for the antimicrobial peptides duramycin and cinnamycin [97], which bound to PE-containing liposomes with about 40 nm in size, but not 700 nm in size. Further, Tabaei et al. [95] described that an antiviral amphipathic α-helical peptide, derived from the NS5A protein N-terminus of the hepatitis C virus, induced pore formation in vesicles of 70 nm size 10 times faster than in vesicles of 200 nm in size. The authors suggested that this difference in kinetics may be due to curvature dependent binding affinities.

Some studies also report on membrane curvature influencing the secondary structure of peptides. For example, Sani et al. [94] measured a decreased α-helical fraction of maculatin 1.1 in SUVs compared to LUVs. Further, Galanth et al. [98] discussed that the observed hinge region in the α-helix of Drs B2 may be due to the high degree of positive surface curvature of SDS micelles. Such a flexible structure may allow the peptide to adapt to this unusual curvature by insertion of the hydrophobic N- and C-termini into the hydrophobic core of the micelle [98]. Finally, Hong and Tamm [99] demonstrated that urea-induced unfolding of the β-barrel outer membrane protein OmpA was reversible in small unilamellar vesicles with a mean diameter of 30 nm. Urea unfolded OmpA inserted and refolded spontaneously into SUVs composed of phosphatidylcholines independent on acyl chain length. In contrast, OmpA did not insert into large unilamellar vesicles unless the acyl chain length of the constituent lipid was twelve C-atoms or less. In SUVs, the lipids of the outer monolayer adopt a positive curvature, whereas those of the inner monolayer possess a rather strong negative curvature. Examination of the intramembranous shape of OmpA revealed that this peptide favors lipid membranes with negative curvature [99,100]. This circumstance was attributed in part to the two belts of aromatic side chains (containing especially Trp) that are located at the polar–apolar interfaces of the membrane [101].

In sum, these results suggest that both scenarios occur: peptides can induce curvature strain in lipid membranes and thereby facilitate the formation of certain curved morphologies, or curved membrane regions can facilitate the attachment of curvature-sensitive peptides or influence their structure in the bilayer.

6. Determination of membrane curvature in the presence of peptides

The importance of membrane curvature and hence the impact of the individual lipid spontaneous curvature was nicely demonstrated in studies on the ionophoric peptide alamethicin and CTP:phosphocholine cytidylyltransferase (CCT), emphasizing the importance of being able to measure the respective parameters quantitatively. Lewis and Cafiso pointed out that the Gibbs free energy of the peptide–bilayer partitioning of alamethicin, a channel forming peptide, depends linearly on the mole fraction of DOPE [102]. Upon increase of the mole fraction of DOPE in mixtures of DOPC/DOPE the binding of alamethicin decreased. Hence, the authors suggested that alamethicin is sensitive to the membrane spontaneous curvature, and that a negative spontaneous curvature (introduced by the cone shape of DOPE) counteracts the insertion of the peptide into the bilayer. EPR-experiments with site directed spin-labeling [102] together with diffraction studies [103] showed that alamethicin is spanning the lipid membrane as a vertical α-helix [104]. Thereby the hydrophobic helical segment is shorter than the normal DOPC/DOPE bilayer thickness, resulting in membrane thinning. Such a bilayer distortion requires that lipids in the vicinity of the peptide assume a positive curvature, which becomes energetically less favorable when the fraction of PE is increased [102,105]. The same results were obtained with the methyl-derivative of DOPE, which is characterized by the same spontaneous lipid curvature. This observation demonstrates that the impact of spontaneous curvature is independent from the chemical nature of the lipids [43].

The study performed on CCT, an enzyme that is involved in lipid biosynthesis and is activated through binding to lipid membranes, supports the notion that spontaneous curvature is also a controlling factor in protein/peptide–lipid interactions [106,107]. Attard et al. [106] demonstrated that lipids with spontaneous curvatures of opposite signs show different effects on protein–lipid association: increased membrane association of CCT was measured with DOPC/DOPE mixtures as compared to dimyristoyl phosphatidylcholine (DMPC)/DOPE mixtures. DOPC is characterized by a negative spontaneous curvature due to its long, unsaturated acyl chains, whereas DMPC comprises a positive spontaneous curvature. One has to mention that the bilayer thickness in the fluid phase of both PC lipids does not differ significantly.

In addition, Strandberg et al. showed that the orientation of magainin 2 and PGLa is influenced by the degree of acyl chain saturation and related this effect to the molecular shape of the lipids [93]. As mentioned above unsaturated acyl chains confer a more negative cone shape to the lipid molecule as compared to saturated acyl chains. For this reason, oriented planar PC bilayers differing in the degree of acyl chain saturation may comprise different lateral pressures in the hydrocarbon chain region, as the bilayers are not able to relax the lateral pressure by undergoing a curvature. Strandberg et al. [93] observed that magainin 2 and PGLa remained flat on the surface in oriented planar PC bilayers comprising unsaturated hydrocarbon chains, regardless of the chain length. A different behavior was observed in phospholipids with fully saturated dimyristoyl and dipalmitoyl hydrocarbon chains: PGLa alone adopted a tilted orientation but a transmembrane alignment in the presence of magainin 2, whereas magainin 2 stays only slightly tilted on the surface, either alone or in the presence of PGLa. The authors proposed that the orientation and insertion of the peptides depend on the nature of the hydrocarbon chains and thereby reflect their impact of the molecular shape of the lipids [93,108,109]. Nevertheless, one has to mention that the oriental behavior of magainin 2 and PGLa is still a matter of debate, as this system seems to be very sensitive to experimental conditions like peptide concentration, lipid species and chain length [110–112]. More detailed and quantitative information on the spontaneous curvature of the single lipid species will be helpful in understanding such processes.

In regard to lipid shape as an important parameter for bilayer–peptide interaction, we want to point out a recent article from our laboratory addressing the measurement of the spontaneous lipid curvature [49]. This study presents a modification of the method to determine the spontaneous curvature of bilayer forming lipids by using DOPE liposomes as a template. The spontaneous curvature for cholesterol, egg sphingomyelin, DOPE and POPE as well as a number of PCs with di(un)saturated and mixed acyl chains of varying length were obtained using small-angle X-ray scattering. The monolayer spontaneous curvature was determined under stress-free conditions by locating the neutral plane from electron density maps of H_{II} phases. For a detailed discussion of the properties and location of the neutral plane in comparison to the pivotal plane and hence relevance in defining curvature elasticity and spontaneous curvature of lipid systems the reader is referred to an excellent recent publication of Marsh [113]. In the approach used by Kollmitzer et al. [49] the lipid of interest (guest lipid) was mixed with the H_{II} forming template lipid (DOPE; host lipid) and changes in the neutral plane, which coincide with the glycerol backbone, were determined and the monolayer spontaneous curvature was calculated (see Fig. 3). Interestingly, within the investigated lipids DPPC was the only bilayer-forming lipid with a small positive curvature, while for example distearoyl phosphatidylcholine (DSPC), a lipid with the same headgroup but longer chains, comprises a negative spontaneous curvature. For phosphatidylcholines it is known that mismatch in lateral areas of heads and chains causes chain tilt and the ripple phase in a certain range of chain lengths, which in part may be responsible for this observation [114]. It can be envisaged that this methodology can also be applied to measure quantitatively changes in membrane curvature upon incorporation of interfacially active peptides into the DOPE host matrix (see Fig. 3).

7. Concluding remarks

We discussed the mutual dependence of membrane curvature on the interaction with interfacially active peptides and vice versa how such peptides can change membrane curvature. Thus, analysis of the dependence of peptide insertion on membrane spontaneous curvature will add further information on the molecular modes of action, although not all responses of membrane proteins or peptides to lipid composition are necessarily attributable to membrane curvature strain like hydrophobic matching [115,116]. Marsh [43] suggested two features to be diagnostic for lipid curvature contributions: (i) systematic response to DOPC–DOPE mixtures, because these two lipids differ markedly in their spontaneous curvature, while diffraction results show their lipid thicknesses in H_{II}-phases to be practically identical [117] and (ii) opposite response induced by lipids, which have opposite spontaneous curvatures.

It is also of interest to study the spontaneous curvature in terms of membrane lipid composition, which differs strongly between different cell types, e.g. bacteria and mammalian plasma cell membranes [58]. Hence different modes of peptide–lipid interaction can be expected depending on the amount of non-lamellar phase forming lipids being present in the target membrane. Dymond and Attard [118] proposed that the antineoplastic properties observed in vivo for alkyl-lipids are a direct consequence of the reduction of membrane stored elastic stress, i.e. curvature strain, induced by these amphiphiles and noted that several of the cationic surfactant compounds were also potent antibacterial and antifungal agents. The similarity of structure–activity relationships for these amphiphilic molecules against microorganisms and those in eukaryotic cell lines led the authors to suggest a common mechanism of action. The authors proposed that the biological activity may be due to modulation of membrane stored elastic stress. The latter can be related to the ratio of lamellar and non-lamellar phase forming lipids present

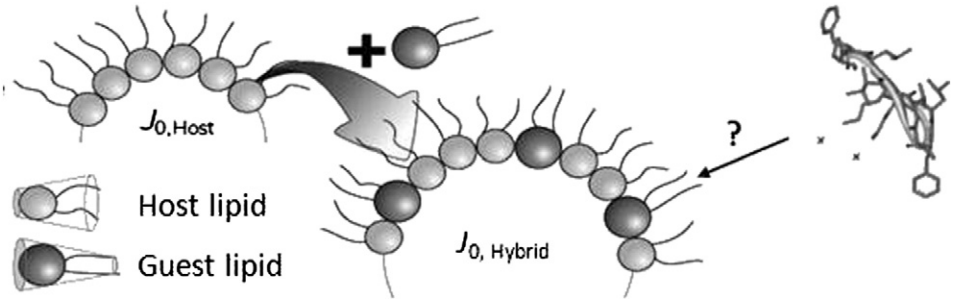

Fig. 3. Change of spontaneous curvature (J_0) upon incorporation of a guest lipid into a host lipid matrix forming a H_{II} phase. In analogy, the influence on spontaneous lipid curvature and hence preference for a given membrane curvature may be measured for interfacially active peptides (here gramicidin S) upon insertion into the host lipid matrix. Adapted and modified from [49].

in the membrane and thus governs the response towards interaction with amphiphiles such as interfacially active peptides. For example, the cytoplasmic membrane of Gram-negative bacteria is rich in lipids like PE, exhibiting a negative spontaneous curvature, and therefore may be more prone to membrane disruption by such a mechanism than mammalian plasma membranes, which contain a high amount of bilayer forming lipids.

Finally, the different packing properties of non-lamellar and bilayer stabilizing lipids may also have implications for membrane function. It was suggested that the high lateral hydrocarbon chain pressure exhibited by non-lamellar phase preferring lipids supposedly controls the conformation of integral membrane proteins [62]. In accordance with this assumption are observations that for example (i) functioning of transport proteins [119] as well as protein translocation [120] was severely impaired in *E. coli* mutants lacking PE, (ii) non-lamellar lipids are often required for functional reconstitution of membrane proteins [63] and (iii) PE is found in protein-rich membrane domains [64]. Very recently, we have shown in our laboratory that AMPs derived from human LF-11 interfere with the lipid domain organization of *E. coli* membranes preventing cell division [121]. Moreover, mechanical coupling of bulk membrane properties to the conformation of an ion channel was shown to be strongly dependent on compounds that insert into the membrane [122]. Upon insertion a change of the lateral pressure profile leads to a new conformational equilibrium of the pore protein. This will be most effective, if the compound inserts close to the polar/apolar interface, where the lateral pressure profile exhibits the largest changes. Therefore, AMPs that change the spontaneous curvature of lipid membranes will affect the lateral hydrocarbon chain pressure and in turn may lead as a secondary effect to conformational changes of integral membrane proteins and hence to impairment of membrane function. This may be an additional mechanism to – or a consequence of – the interfacial activity by which antimicrobial peptides kill bacteria.

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