even just a collateral effect. Additionally, AMP interactions with non-lipid cell envelope components of bacteria may be important in modifying how well AMPs are able to disrupt the lipid membrane. In order to connect studies of AMPs in model lipid systems to the more complex real bacterial cell envelopes, we have deuterium-labeled the membranes of the gram-positive bacteria *Bacillus subtilis* and used ^{2}H NMR to study how lipid acyl chain order in its membranes is affected by treatment with AMPs. We have also observed ^{2}H NMR spectra from *Bacillus subtilis* in which the peptidoglycan layer has been disrupted. This has allowed us to investigate how disruption of the peptidoglycan layer affects bacterial lipid chain order and the AMP/bacteria interaction.

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Lipid Clustering by Antimicrobial Polymers and Lectins

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The current urge to understand the role of lipids in defense against pathogens is driven by two strategies: killing pathogens and protecting the cell from infection. Antimicrobial peptides and antimicrobial polymers offer a promising alternative to classical antibiotics through their action on membrane integrity. In principle, antimicrobial peptides and polymers are able to cluster lipids through lipid selection and recruitment from a mixed membrane. We show that antimicrobial polymers induce leakage in lipid vesicles by transient defects rather than defined pores. The positively charged polymers efficiently cluster negatively charged lipids from mixed model membranes. Larger domains are formed (in the order of 500 lipids). The binding of the polymers to the vesicles is exothermic. Our findings correlate with the polymers activity against bacteria. Similarly, lectins, carbohydrate binding proteins, can recognize certain glycolipids in mixed membranes, bind them and cluster them. By a yet unknown mechanism, the membrane is locally bent. Thus bacterial lectins can initiate uptake of pathogens into host cells and are promising targets for drug development.

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How Antimicrobial Peptides Permeabilize Membranes with and without Pore Formation

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One of the biggest enigmas of antimicrobial peptides (AMPs), which protect all forms of life against pathogens, is why few structures of membrane pores have been found despite clear evidence of membrane leakage and antimicrobial activity. We provide a surprisingly simple explanation: For some AMPs such as PGLa (charge +5), pores are not needed to explain both leakage and peptide translocation. Fully converged, unbiased multi-microsecond equilibrium simulations at all-atomistic level reveal that peptides spontaneously translocate across the membrane individually on a timescale of tens of microseconds, without forming pores. These findings explain why, despite vesicular leakage no channel has been identified for PGLa. However, similar simulations on other, lesser charged AMPs like maculatin clearly show pore formation. The results suggest that for some specific antimicrobial peptides, pore formation may not have to be invoked at all to explain both peptide translocation and membrane permeabilization.

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The Synergistic Effects of Lipids and Peptides on Membrane Dynamics

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There is a growing appreciation that the membrane physical properties are essential to cell and protein function. Simply altering the thickness of model membranes has been shown to influence the biological activity of several proteins, while incorporating peptides into lipid membranes also is known to affect the bilayer structural properties. Clearly there is a synergy in lipid-protein interactions in determining the membrane properties; however, the nature of these interactions are not well understood. Here we use a combination of small angle scattering techniques and neutron spin echo spectroscopy (NSE) to investigate the effects of incorporating a small peptide on both the structure and dynamics of model membrane systems. In particular, we investigated the effects of the antimicrobial peptides gramicidin and alamethecin on the lipid bilayer structure using small angle x-ray and neutron scattering. The structural studies were complemented by NSE experiments to probe the collective bending and thickness fluctuation dynamics in these model systems. Notably, the NSE results revealed enhanced thickness fluctuation dynamics in lipid bilayers containing low concentration of gramicidin that were dampened with increasing peptide concentration. An enhancement in dynamics was not seen in bilayers containing alamethicin, suggesting that the dynamics not only depend on peptide concentration, but also peptide orientation within the membrane

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Mode of Action of Antimicrobial Peptides: Long and Short Amphipathic Alpha-Helixes Use Different Mechanisms

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We have studied the membrane structure and orientation of cationic amphipathic α-helical antimicrobial peptides (AMPs) using circular dichroism and solid-state NMR, combined with activity studies. For a series of model peptides, called KIA peptides, a clear length-dependent activity is found, as only peptides long enough to span the hydrophobic thickness of the membrane could induce leakage in vesicles. There is also a clear threshold length for peptides able to kill bacteria [1]. Using another series of KIA-like peptides of different length (from 14 up to 28 residues) but with a constant charge revealed that the length, but not the charge, is the critical factor. In membrane systems with a positive spontaneous curvature, the peptides get inserted into the membrane in a transmembrane orientation. All results indicate that these peptides act by forming proper oligomeric pores in the lipid bilayer. If the peptide is just long enough to span the membrane, it is aligned perfectly upright, but longer peptides can tilt cooperatively in the pore like an iris [1,2]. On the other hand, BP100, a highly helical peptides of only 11 amino acids, is clearly too short to form a transmembrane pore, but it is still strongly active against bacteria. From solid-state ^{2}H-, ^{15}N- and ^{19}F-NMR studies, this peptide is found to dip into the membrane and to show high mobility within the amphiphilic surface layer. This way, it most likely disturbs the lipid order and thereby induces permeability, which suggests a carpet-like mechanism of action [3]. The structural results on these long and short AMPs clearly demonstrate that peptides with similar structural characteristics can act by very different mechanisms.

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Simulations of Membrane Disrupting Peptides Pores Versus Surface Binding

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Peptides that disrupt biological membranes are a source of new antibiotic and antiviral therapeutics. Here, the relationships between peptide primary sequences, membrane bound structures, and abilities to disrupt membranes are investigated using all-atom molecular dynamics simulations. First, the archetype barrel-stave alamethicin (alm) pore in a 1,2-dioleoylsn-glycero-3-phosphocholine bilayer at 313 K indicates that ~7 μs is required for equilibration of a preformed 6-peptide pore; the pore remains stable for the duration of the remaining 7 μs of the trajectory, and the structure factors agree well with experiment. A 5 μs simulation of 10 surface-bound alm peptides shows significant peptide unfolding and some unbinding, but no insertion. Simulations at 363 and 413 K with a −0.2 V electric field yield peptide insertion in 1 μs. Insertion is initiated by the folding of residues 3-11 into an α-helix, and mediated by membrane water or by previously inserted peptides. The stability of five alm pore peptides at 413 K with a −0.2 V electric field demonstrates a significant preference for a transmembrane orientation. In contrast, a hypothesis that the antimicrobial peptide piscidin 1 (p1) forms toroidal pores is tested. The