Optimization of the antimicrobial activity of magainin peptides by modification of charge
Authors: Margitta Dathe, Heike Nikolenko, Jana Meyer, Michael Beyermann, and Michael Bienert FEBS Letters **501**, 146-150 (2001)

Physical Basis of Membrane-Charge Selectivity of Cationic Antimicrobial Peptides
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Phys. Rev. Lett. **98**, 168101-1–16801-4 (2007)

Recommended with a commentary by Mehran Kardar, MIT

Antimicrobial peptides (AMPs) are an abundant and diverse class of molecules produced by many multicellular organisms (e.g., plants, insects, and animals) as part of their immune defense against microbes [1]. These molecules attach and insert into microbial membrane bilayers, form pores and rupture the membrane. Their amino-acid composition (charge and size) is such that they selectively attach and disrupt microbes, without harming the host cells [2]. Understanding this microbial killing mechanism is not only of fundamental interest in biology (e.g., their role in the successful evolution of multicellular organisms), but also of therapeutic value (e.g., the rational design of antibiotics). In fact, much effort has been made in developing modified AMPs as therapeutic agents to fight infective diseases [3]. Because of the alarming level of bacterial resistance to conventional antibiotics, understanding the microbial-killing action of AMPs has become increasingly important [1, 2, 3].

Experimental studies with model membranes and peptide analogues have established the importance of the amphipathic[1] character of the peptides, as well as the significance of membrane–peptide Coulomb interactions (Refs. [2, 1] and Dathe et. al.). The amphipathic design of AMPs enables them to interact simultaneously with both lipid headgroups and hydrocarbon tails. Cationic peptides in particular, can preferentially interact with microbes by taking advantage of a design feature (an 'Achilles heel' [2]) that distinguishes them from multicellular plants and animals. Bacterial membranes have an abundance of anionic lipids in their outer or outmost leaflets, while in eukaryotes charged leaflets face their cytoplasm. This allows the cationic peptides to preferentially bind to and disrupt a bacterial membrane; their asymmetrical incorporation into the outer leaflet creates a mechanical stress on the bilayer, priming it for rupture, likely through pore formation [4].

In an experimental study with cationic AMPs (magainin analogues), Dathe et al. attempt to establish relationships between peptide parameters and antimicrobial selectivity/activity, quantified by the ability of AMPs to selectively rupture microbial membranes. Their experiments suggest that antimicrobial activity increases with increasing peptide charge up to a certain value (≈ 5); beyond this, however, increasing the charge reduces the selectivity. Taheri-Araghi and Ha present a theoretical explanation of this phenomenon by considering the interactions amongst the peptides, and to the membrane. They find that a competition between the two sets of interactions leads to an optimal charge at which the selective hydrophobic

[1] Amphipatic molecules have a polar or charged end that is attracted to water and a nonpolar end that is repelled by it.

biding is optimized. The binding affinity of AMPs for the bacterial membrane is higher for larger peptide charge at low AMP concentrations on the surface. For too large peptide charge, however, the mutual repulsion between bound peptides tends to diminish the binding affinity. Thus, the competition between these opposing tendencies gives rise to the optimal charge.

Nevertheless, due caution has to be taken to draw a more definite picture. First, the binding-affinity analysis, as in the work of Taheri-Araghi and Ha, may have rather indirect implications for experimental (e.g., dye-release) measurements of antimicrobial activity/selectivity. In fact, the threshold value of peptide (in relation to membrane lipids) required for membrane rupture varies appreciably with lipid compositions [4]. This implies that other factors are also implicated in the membrane disruption process. Also, in the work of Dathe et al., reduced selectivity for too-large peptide charge is attributed to enhanced toxicity against red blood cells. It is not clear how this can be reconciled with the behavior of binding affinity, i.e., the reduced binding affinity for a neutral leaflet for larger peptide change.

In the literature, a number of different mechanisms have been employed to account for the antimicrobial actions of AMPs [1, 2]. Whichever mechanism really works, the initial step consists of their electrostatic-hydrophobic association with lipid membranes. A theoretical understanding of the underlying energetics at the molecular level is thus desired. The coarse-gained approach put forward by Taheri-Araghi and Ha may serve as a first step toward this endeavor.

References

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