Probing the disparate effects of arginine and lysine residues on antimicrobial peptide/bilayer association

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Probing the disparate effects of arginine and lysine residues on antimicrobial peptide/bilayer association

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Abstract

Antimicrobial peptides (AMPs) are key components of the innate immune response and represent promising templates for the development of broad-spectrum alternatives to conventional antibiotics. Most AMPs are short, cationic peptides that interact more strongly with negatively charged prokaryotic membranes than net neutral eukaryotic ones. Both AMPs and synthetic analogues with arginine-like side chains are more active against bacteria than those with lysine-like amine groups, though the atomistic mechanism for this increase in potency remains unclear. To examine this, we conducted comparative molecular dynamics simulations of a model negatively-charged membrane system interacting with two mutants of the AMP KR-12: one with lysine residues mutated to arginines (R-KR12) and one with arginine residues mutated to lysine (K-KR12). Simulations show that both partition analogously to the bilayer and display similar preferences for hydrogen bonding with the anionic POPGs. However, R-KR12 binds stronger to the bilayer than K-KR12 and forms significantly more hydrogen bonds, leading to considerably longer interaction times. Additional simulations with methylated R-KR12 and charge-modified K-KR12 mutants show that the extensive interaction seen in the R-KR12 system is partly due to arginines strong atomic charge distribution, rather than being purely an effect of the greater number of hydrogen bond donors. Finally, free energy simulations reveal that both peptides are disordered in solution but form an amphipathic α-helix when inserted into the bilayer headgroup region. Overall, these results highlight the role of charge and hydrogen bond strength in peptide bilayer insertion, and offer potential insights for designing more potent analogues in the future.

Keywords: `Molecular dynamics simulations, antimicrobial peptides, peptide-bilayer interactions, KR-12`

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