393e Influence of Anionic and Zwitterionic Membrane Interfaces on Structure of Antimicrobial Peptides and Implications on Peptide Toxicity and Activity: a Molecular Dynamics Simulation Investigation

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Molecular dynamics simulations of three related helical antimicrobial peptides have been carried out in zwitterionic diphosphocholine (DPC) micelles and anionic sodiumdodecylsulphate (SDS) micelles. These systems can be considered as model mammalian and bacterial membrane interfaces respectively. The goal of this study is to dissect the differences in peptide composition which make the mutant peptides (novispirin-G10 and novispirin-T7) less toxic than the parent peptide ovispirin (OVIS), although all three peptides have highly antibacterial properties. Each simulations was carried out for 40 ns. OVIS binds most strongly to the DPC micelle, while G10 and T7 bind only weakly. This correlates well with the lesser toxicity of G10 and T7. There is strong evidence which suggests that synergistic binding of hydrophobic residues drives binding of OVIS to the micelle. The helical content of G10 and T7 is reduced in the presence of DPC, and this leads to less amphipathic peptide structures which bind weakly to the micelle. Simulations in SDS were carried out to compare the influence of membrane electrostatics on peptide structure. All three peptides bound strongly to SDS, and retained helical form. This corresponds well with their equally potent antibacterial properties. Based on the simulations, we argue that secondary structure stability often leads to toxic properties. We also propose that G10 and T7 also operate by the carpet mechanism of cell lysis. Toxicity of peptides operating by the carpet mechanism can be attenuated by reducing the peptide helical content. The simulations successfully capture experimental binding states, and the different extents of binding of the three peptides to the two micelles correlate with their antibacterial and toxic properties.