MODE OF ACTION OF ANTIMICROBIAL PEPTIDES: LONG AND SHORT AMPHIPATHIC ALPHA-HELICES 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 transiently 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.

References: [1] Grau-Campistany et al., (2015) *Sci Rep* **5**, 9388. [2] Grau-Campistany et al., (2016) *J Phys Chem Lett* **7**, 1116-1120. [3] Zamora-Carreras et al., (2016). *Biochim Biophys Acta* **1858**, 1328-1338.