MODE OF ACTION OF ANTIMICROBIAL PEPTIDES: LONG AND SHORT AMPHIPATHIC ALPHA-HELIXES USE DIFFERENT MECHANISMS

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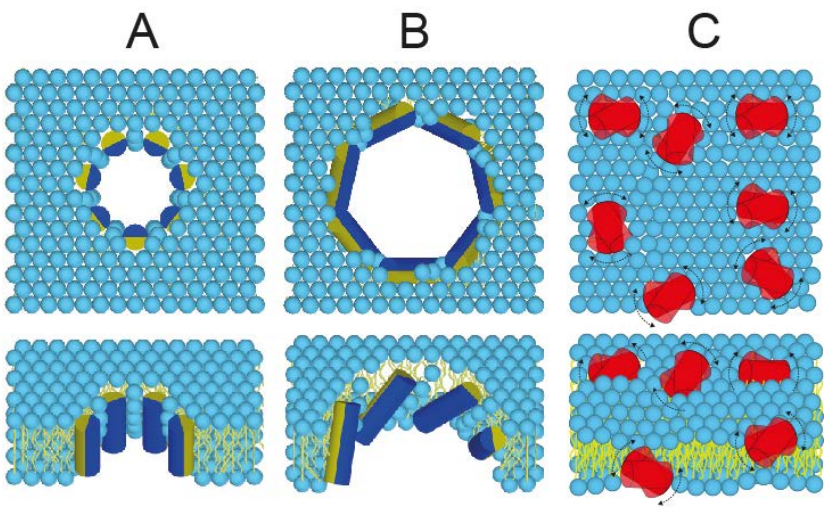
We have studied the membrane structure and orientation of cationic amphipathic α-helical antimicrobial peptides (AMPs) using circular dichroism and solid-state NMR, combined with activity studies. For a series of model peptides, called KIA peptides, a clear length-dependent activity is found, and only peptides with 17 or more amino acids are able to kill bacteria or induce leakage in POPC/POPG vesicles. In membrane systems with a positive spontaneous curvature the peptides are inserted into the membrane in a transmembrane orientation. All results indicate that these peptides act by forming pores through the membrane (Figs. A and B) [1,2]. If the peptide is just long enough to span the membrane, it is upright in the pore (Fig. A) but longer peptides can tilt in the pore (Fig. B). 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. This peptide is found to dip into the membrane and to be very mobile inside the membrane, and it most likely disturbs the membrane order and thereby induces permeability in the membrane, which indicate a carpet-like mechanism of action (Fig. C) [3]. The results show that peptides with similar structural characteristics can act by very different mechanisms.



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