The effect of methylation at different lysine residues on the structure of antimicrobial peptide CA(1-7)M(2-9), a cecropin-melittin hybrid peptide

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Antimicrobial peptides (AMPs) are peptides used by the immune system to fight bacterial infection in multicellular eukaryotes[1]. As bacterial resistance to standard antibiotics is increasing, the synthesis of AMPs constitutes an emerging field of interest due to their potential to form a new class of therapeutic agents.

One strategy for the design of new AMPs is the synthesis of hybrid peptides containing portions of two peptides with different antibiotic properties. CA(1-7)M(2-9)NH_2, is a hybrid peptide amide derived from cecropin A and melittin and exhibits substantial antibacterial, antiparasitic and antifungal activities.[2] To enhance the antimicrobial properties of CA(1-7)M(2-9)NH_2, several modifications on the sequence have been proposed[3] and, among them, the methylation of one or more lysine residues of CA(1-7)M(2-9)NH_2 have been demonstrated to change both its antimicrobial and its antihaemolytic properties.[4]

In order to characterize the molecular mechanism by which lysine methylated analogues of the hybrid peptide CA(1-7)M(2-9)NH2 vary their antibacterial activity, it is important to determine their three-dimensional structure. Herein we report our investigations on the effects of lysine methylation on the structure of the CA(1-7)M(2-9)NH2 derivatives in aqueous trifluoroethanol solution by NMR spectroscopy in conjunction with MD calculations. From the data obtained from NMR spectra of CA(1-7)M(2-9)NH2 analogues, multiple conformations of the peptides in membrane-mimicking environments have been derived indicating that methylation of lysine residues introduces significant changes to the most favourable conformations of the peptides. Therefore, the result of lysine methylation on the biological activity of CA(1-7)M(2-9)NH2 can be explained as consequence of structural changes associated to the presence of methylated lysines.

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