Effect of N-terminal Truncation of Latarcin Ltc2a on Its Cytotoxic Properties and Interactions with Membranes

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Ltc2a isolated from the venom of the spider *Lachesana tarabaevi* is a linear cationic peptide that exhibits bactericidal activity at micromolar and sub-micromolar concentrations *in vitro* [1]. Plasma membrane damage is the most probable mechanism of its antibacterial action. We have studied the influence of the N-terminal cluster of hydrophobic aminoacid residues on biological activity of Ltc2a. The deletion of four N-terminal residues one by one resulted in a gradual decrease in haemolytic activity and bactericidal effect against *Staphylococcus aureus,* whereas activity against Gram-negative bacteria was affected weakly.

In order to clarify structure-function relationships we have performed conformational analysis of the peptides bound at zwitterionic and anionic membranes using circular dichroism spectroscopy. All the peptides exhibit high propensity to α-helix formation in 50% trifluoroethanol. Binding of Ltc2a and its derivatives at zwitterionic membranes is accompanied with a conformational transition from a random coil to an α-helical structure. The truncation leads to a decrease in binding affinity at zwitterionic membranes that correlates strongly with a decrease in haemolytic activity. Ltc2a forms a β-sheet structure at anionic membranes. The truncation of N-terminal residues results in gradual conformational changes from β-sheet to α-helix.

In this report we discuss how the shortening of the hydrophobic motif of Ltc2a modulates its biological activity via the balance of electrostatic and hydrophobic interactions with lipid membranes. Fine correction of haemolytic *vs.* antibacterial activity seems to be a useful way to design antimicrobial peptides with increased therapeutic potential.

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[1] *Kozlov S.A., Vassilevski A.A., Feofanov A.V. et al.* Latarcins, antimicrobial and cytolytic peptides from the venom of the spider *Lachesana tarabaevi* (*Zodariidae*) that exemplify biomolecular diversity// *J. Biol .Chem.* **281**, 30(2006). Pp. 20983–92.