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The impact of C-terminal amidation on antimicrobial peptide behavior: insights from molecular dynamics simulations approach

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C-terminal amidation is a common modification found in wild-type antimicrobial peptides (AMPs) and is believed to increase their antimicrobial efficacy. However, the exact mechanism by which this modification works is not yet fully understood. It has been observed that C-terminal amidation changes both the net charge and helicity of the peptide and plays important roles in the mechanism of action. However, previous studies have overlooked the differences in the physicochemical properties of the carboxyl and amide moieties. U3.5 is a 17-amino-acid peptide (GVGDLIRKAVSVIKNIV-NH2) that is found in the skin of Australian toadlets *(Uperoleia mjobergii)*. It shows amyloidogenic and antimicrobial properties and exhibits cross-α/cross-β forms in different environmental conditions. While it is still unknown whether its chameleon-like properties are linked to its antimicrobial activity, it is believed that U3.5 interacts with bacterial membrane lipids to stabilize its α-helical conformation.

This study used classical MD simulations to investigate the interaction between Uperin 3.5 peptide and negatively charged phospholipid bilayers (POPE: DOPG 3:1, DOPE: DOPG 1:1). To elucidate the interaction mechanism and efficiency, two structurally correlated variables, C-terminal amidation, and non-amidated peptide were introduced. The simulation results indicated that due to an increase in positive charge, C-terminal amidation is believed to increase the antimicrobial efficacy and amyloidogenic properties of wild-type peptides and facilitated rapid adsorption on the lipid bilayer.