Structural and dynamic properties of type A (I) lantibiotics determining their binding to lipid II

P-02.5-44

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Antibiotic resistance is one of the biggest public health challenges of our time and this is the motivation for finding new antibiotics. A class of bacteriocins — lantibiotics – are promising agents for drug discovery. Lantibiotics are ribosomally synthesized and posttranslationally modified cationic antimicrobial peptides. The specific target of type A (I) lantibiotics is the pyrophosphate moiety (PPi) of lipid II. Nisin, gallidermin, and epidermin are the main peptides in this class of bacteriocins. In binding to the lipid II the main role is played by residues 1-12. The aim of the study was to explore the structural properties of these lantibiotics' fragments in the presence of dimethyl pyrophosphate ion (DMPPi) that mimics PPi of lipid II *via* molecular dynamics (MD) simulations in water. It was shown that nisin$_{1-12}$ forms 4-5 intermolecular hydrogen bonds (H-bonds) with DMPPi, while gallidermin$_{1-12}$ and epidermin$_{1-12}$ create 6-7 H-bonds, mainly *via* backbone NH groups of the ring A. This fact correlates with experimental data on higher antimicrobial activity of gallidermin and epidermin. For the studied antibiotics, we found a similar conformation, in which the largest number of intermolecular H-bonds was formed. In this conformation, the rings A and B are placed opposite each other, thus being stabilized by two intramolecular H-bonds in the case of nisin (Dha5-Dab8 and Dha5-Pro9) and one H-bond in the case of gallidermin/epidermin (Lys4-Dab8). In nisin, gallidermin, and epidermin, the MD-derived lifetime of the aforementioned state are ≈28%, ≈85%, and ≈88%, respectively. The significant difference between nisin and gallidermin/epidermin is the position of the NH group of 5th residue, which is turned towards DMPPi in the latter case. It has been shown that lantibiotics of type A (I) are able to form stable complexes of a similar structure with the PPi mimetic of lipid II, and the residue 5 affects the binding.