Insights into the Mode of Action of the Two-Peptide Lantibiotic Haloduracin

Trent J. Oman and Wilfred A. van der Donk

Haloduracin, a recently discovered two-peptide lantibiotic comprised of the post-translationally modified peptides Halα and Halβ, is shown to have high potency against a range of Gram-positive bacteria and to inhibit spore outgrowth of Bacillus anthracis. The two peptides display optimal activity in a 1:1 stoichiometry and have similar efficacy as the commercially used lantibiotic nisin. However, haloduracin is more stable at pH 7 than nisin. Despite significant structural differences between the two peptides of haloduracin and those of the two-peptide lantibiotic lacticin 3147, these two systems show similarities in their mode of action. Like Ltnα, Halα binds to a target on the surface of Gram-positive bacteria, and like Ltnβ, the addition of Halβ results in pore formation and potassium efflux. Using Halα mutants, its B- and C-thioether rings are shown to be important but not required for bioactivity, and a similar observation was made with mutants of Glu22, a residue that is highly conserved amongst several lantibiotics. These studies provide a foundation for future characterization of the mode of action and the biosynthesis of lantibiotics.