Abstract

Neonatal infection is a significant cause of mortality and morbidity in infants. Globally, neonatal pathogens are increasingly becoming multi-drug resistant, indicating the need to discover novel alternative treatment strategies. Nisin is an antimicrobial peptide that exhibits broad-spectrum activity against Gram-positive and Gram-negative bacteria including a wide variety of clinical pathogens. Nisin can be used in combination with antibiotics to improve their efficacy. This study examined the activity of nisin and bioengineered derivatives against multi-drug resistant *Streptococcus agalactiae* and *Staphylococcus capitis* isolates and investigated the potential synergy between nisin peptides and selected antibiotics. Whole genome sequence analysis of the strains revealed the presence of multi-drug resistant determinants in all strains, e.g., macrolide, tetracycline, β-lactam, aminoglycoside. The *S. agalactiae* strains all possessed both *nsr* and *nsr*FP genes and the *S. capitis* strains were found to encode the *nsr* gene alone. Deferred antagonism assays demonstrated that nisin PV had improved antimicrobial activity against all strains tested (n = 10). The enhanced specific activity of this peptide was confirmed using minimum inhibitory concentrations (MIC) (0–4-fold lower MIC for nisin PV). Combinations of nisin peptides with antibiotics were assessed for enhanced antimicrobial activity using growth and time-kill assays and revealed a more effective nisin PV/ampicillin combination against one *S. capitis* strain while a nisin A/erythromycin combination displayed a synergistic effect against one *S. agalactiae* strain. The findings of this study suggest that nisin derivatives alone and in combination with antibiotics have potential as alternative antimicrobial strategies to target neonatal pathogens.