TITLE: A PEPTIDE DERIVED FROM *Lycosa erythrognatha* SPIDER VENOM SHOWS HIGH ACTIVITY AGAINST PNEUMONIA INDUCED BY CARBAPENEM-RESISTANT *Acinetobacter baumannii*

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ABSTRACT:

The emergence of antibiotic-resistant bacteria, especially carbapenem-resistant *Acinetobacter baumannii* (CRAB), together with relative stagnation in the development of effective antibiotics, has led to enormous health and economic problems. Antimicrobial peptides (AMPs) have shown significant promise in recent years as novel therapeutic agents for the treatment of infections caused by extensively drug-resistant (XDR) bacteria, such as CRAB. In this context, we have development the LyeTx I mnΔK that is a novel designed short peptide comprising 13 amino acids residues obtained from the *C*-terminal portion of LyeTxI native peptide. LyeTxI is a peptide derived from *Lycosa erythrognatha* spider venom that has been shown to be active against pathogenic bacteria (*Escherichia coli* and *Staphylococcus aureus*) and fungi (*Candida krusei* and *Cryptococcus neoformans*). Here, we aimed to describe the antibacterial spectrum of LyeTx I mnΔK against CRAB. LyeTx I mnΔK showed considerable antibacterial activity against extensively resistant *A. baumannii*, with minimum inhibitory and bactericidal concentrations ranging from 1 to 16 μM and 2 to 32 μM, respectively. This peptide significantly increased the release of 260 nm-absorbing intracellular material from CRAB, suggesting bacteriolysis. In addition, the peptide had a potent anti-biofilm effect and did not elicit resistance in vitro after 14 days of exposure. We suggest that the activity of LyeTx I mnΔK on the membrane ensured an increase in the uptake of conventional antibiotics, thereby generating a synergistic effect with meropenem and colistin. The cytotoxic concentration of LyeTx I mnΔK against Vero cells (CC_{50} = 55.31±5.0 μM) and its hemolytic activity (HC_{50} = 77.07±4.00 μM) were considerably low; however, its antibacterial activity was significantly reduced in the presence of human and animal serum and trypsin. Nevertheless, the inhalation of this peptide was effective in reducing pulmonary bacterial load in a mouse model of CRAB infection. In conclussion, the results of this study highlight that the peptide LyeTx mnΔK is a potential prototype for the development of new effective and safe antibacterial agents against extensively resistant pathogens of clinical relevance, especially CRAB.

Keywords: *Acinetobacter baumannii*; Antimicrobial peptide; Spider venom; Pneumonia; Antimicrobial development

Development Agency: Coordenação de Aperfeiçoamento de Pessoal do Nível Superior (CAPES); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), and Pro-Reitoria de Pesquisa of Universidade Federal de Minas Gerais (PRPq/UFMG).