STRESZCZENIE W JĘZYKU ANGIELSKIM

Antimicrobial peptides (AMPs) play a key role in innate immunity of humans and are recognized as an important component of immunological defense first line against pathogens. AMPs are characterized by a wide range of antimicrobial activity. Due to their biological properties, chemical structure, functions and mechanism of action, AMPs have been divided into several groups, and the two main ones are: defensins and cathelicidins. In human, the presence of only one cathelicidin-derived peptide LL-37 have been identified, which is released from cathelicidin-hCAP 18 by serine protease. A compelling number of studies indicate that the human LL-37 peptide is characterized by a broad spectrum of antimicrobial, antineoplastic and immunomodulatory activity. The membrane-permeabilizing properties of endogenous peptides has become an inspiration for the design of novel antimicrobial agents with similar, nonspecific, membrane-based mechanism of action. A particularly interesting group of compounds with broad spectrum of antimicrobial activity are synthetic analogs of cationic antibacterial peptides - ceragenins (CSAs), being the cholic acid derivatives. In analogy to AMPs, they are characterized by positive surface charge, which determines their electrostatic interaction with the negatively charged surface of bacteria, viruses, fungi and protozoa. After insertion into the lipid structure, the function of the microorganisms' membrane is disturbed, which ultimately leads to cell death.

The aim of this study was to determine the bactericidal activity of cathelicidin-derived LL-37 peptide and its synthesis analogs from the ceragenins family against the laboratory and clinical isolates of *Pseudomonas aeruginosa*. The performed analyses allowed to elucidate the potential of ceragenins in combating infections caused by multi-drug resistant strains of *Pseudomonas aeruginosa.*

The research was performed using the antibacterial LL-37 peptide, conventional antibiotics, ceragenins (CSA-13, CSA-131) and polyelectrolytes released from host cells (i.e. DNA, F-actin) or produced by bacteria (i.e. bacteriophage Pf1). In the course of the research following bacteria strains were used: 1) *P. aeruginosa* isolated from the sputum of cystic fibrosis patients; 2) *P. aeruginosa* Xen 5, a bioluminescent strain that has in its chromosome a stable copy of the lux operon derived from *Photorhabdus luminescens*; 3) hypervirulent *P. aeruginosa* strain LESB58.

The antimicrobial activity of the tested compounds were evaluated against the planktonic form of the bacteria, as well as the *P. aeruginosa* biofilm. Determination of minimal inhibitory

concentration (MIC) as well as minimal bactericidal concentration (MBC) was performed. In order to more accurately assess the antibacterial activity of the test compounds, the colony counting assay (i.e. "killing assay") was carried out. The above experiments were also performed in the presence of polyelectrolytes such as DNA, F-actin and the bacteriophage Pf1. To visualize the surface of bacteria cells after incubation with tested agents, topography of bacteria with the use of an atomic force microscope was performed.

The performed studies demonstrate that ceragenins exert a significantly stronger antibacterial activity against clinical, highly resistant strains of *P. aeruginosa*, as well as against the hypervirulent LESB58 strain, than natural LL-37 peptide or conventional antibiotics. Interestingly, the significant inhibition of the bactericidal activity of the LL-37 peptide in the presence of a purified Pf1 bacteriophage, which is produced by *P. aeruginosa* LES was observed. In contrast to that, activity of CSA-13 and CSA-131 cationic antibacterial lipids has not been reduced in the presence of this polyanion virus. The effective prevention of formation of biofilm by *P. aeruginosa* LESB58 by CSA-13 and CSA-131 was also noted, despite the stimulating effect of bacteriophage Pf1 on biofilm development.

The results obtained during this research indicate the possibility to employ the synthetic analogs of AMPs from ceragenins group in the effective treatment of infections caused by multi drug resistant strains of Gram-negative bacteria and justify further research in this area.