



THERAPEUTIC PERSPECTIVE VIEW OF ANTIMICROBIAL PEPTIDES

PRITI BALA*, JAINENDRA KUMAR AND NAVIN KUMAR

College of Commerce, Magadh University, Bodh Gaya, India

ABSTRACT

Due to increasing antibiotic resistance by pathogenic bacteria, it has become necessary to develop new antimicrobial molecules as therapeutic agents to overcome this problem. Antimicrobial peptides from different organisms can serve as the natural defense molecules to combat these pathogenic microorganisms. These are small cationic peptides with diverse range of antimicrobial activity that thwart resistance by bacteria.

KEYWORDS: Antimicrobial peptides, Mode of actions, Therapeutic agents.



PRITI BALA

College of Commerce, Magadh University, Bodh Gaya, India

1. INTRODUCTION

The discovery of antibiotics has definitely been the major achievement in the treatment of infectious agents but in recent decades, it has been found that there is decrease in the effectiveness of a large number of antibiotics against several types of bacterial infections. Due to favourable adaptive mutations in bacteria facilitated by exposure to antibiotics and development of multidrug resistant bacterial strains, it is important to identify different classes of natural compounds with antibacterial therapeutic potentiality to control the infectious diseases. This has led to development of a new class of antimicrobial agents called antimicrobial peptides which have shown to be promising drugs for overcoming the problems of antibiotic resistance¹. At present, more than 1000 antimicrobial peptides have been reported from different organisms. Their structural and sequence details can be retrieved from antimicrobial peptide database² (<http://aps.unmc.edu/AP/main.php>).

2. SOURCES AND MODE OF ACTIONS

Natural antimicrobial peptides or the host defenses peptide are short polypeptides ranging upto 100 amino-acid residues in length with a net positive charge from +2 to +9. These peptides are conserved during evolutionary process in response to their innate immunity and serve as a first line of defense system³⁻⁷. These peptides have been identified in all kinds of organisms from bacteria and animals to plants. The peptides have been classified into four groups on the basis of their structure: (i) α -helical (ii) β -sheet (iii) AMPs rich in specific amino-acids (iv) Loop structures. It has been found that they possess approximately 50% hydrophobic residues and exhibit spatially separated hydrophobic and hydrophilic regions with amphipathic properties during interaction with biological membranes⁸. Although the exact mechanism of action of AMPs is not very clear but they are generally dependent on the interaction with bacterial membranes^{9,10}. They initially interact with bacterial cell membrane through electrostatic bond. The binding occurs between cationic peptides and the anionic components of outer bacterial envelop. This binding leads to membrane disorganization,

taking seconds to minutes or when it binds to intracellular targets, taking 3-5 hours. One important character of these peptides is that their action is not mediated by receptors, thus they can be used to overcome the resistance resulting by the bacterial mutations¹¹. Different models, like toroidal pore (magainins) and barrel stave (alamethicin) models, depicting the formation of pores or the formation of carpet like model (cecropins) in which the cell membrane is micellized, have been proposed to describe the structure formed as a result of interaction between peptides and membrane phospholipids^{1,11,12}.

3. THERAPEUTIC VIEW

The activity of antimicrobial peptides is diverse. Gram negative and Gram positive bacteria, viruses, fungi and protozoa are susceptible to antimicrobial peptides at very low concentration (in micromolar concentration or below). Due to their high effectiveness against the disease causing organisms, these antimicrobial peptide products are going to be introduced into the market by many companies^{13,14}. These peptides are under different developmental phases. The well known first commercially developed peptide was pexiganan acetate (MSI-78) from magainin²¹⁵. This peptide expressed broad spectrum activity *in vitro* and is under trial phase III while the peptide in most advanced phase of trial is omiganan (MBI- 226). This peptide is analogous to indolicidin purified from bovine neutrophils. On the other hand, on the basis of structure-function relationship between bactericidal and hemolytic activities, king cobra cathelicidin (OH-CATH) has been used as molecular template to develop some analogs. One of its analog OH-CATH(5-34) has the lowest hemolytic activity but has highest antimicrobial activity by its bactericidal activity against different species of bacteria like *E.coli*, *P aeruginosa*, *S. aureus*, *E.aerogenes* and *E. cloace*. It is 2-4 times stronger than pexiganan. Thus OH-CATH(5-34) can be considered as an emerging peptide for therapeutic purposes¹⁶. In the same ecological niche, bacteria have combat to their closely related microorganisms for the limited food resources. In this regard, they release some antimicrobial agents called

bacteriocins for inter-strain or intra-specific killing activity^{17,18}. Bacteriocins are grouped into two classes. Class I bacteriocins are produced by lactic acid bacteria. They are small, heat stable, post translationally modified peptides called lantibiotic. Some of them such as nisin and lactin are used as food preservatives by food and agriculture industries^{19,20}. Class II bacteriocins include Class IIa and Class IIb (22). Similar other peptides from different origin are under trial of different phase. The Class IIb bacteriocins are also in the characterization phases to make it useful for medical and biotechnological purposes such as for treatment of infections and preservation of food respectively²¹.

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CONCLUSION

From the above studies it is clear that AMPs are an important part of innate immune system with wide range of activity towards infectious bacterial, viral, fungal and parasitic pathogens. The peptides exert their effects on cells by interacting with membrane lipids. Being cationic in nature they facilitate their binding with negatively charged membranes. Diverse immunomodulatory activities of such host defense peptides are the most recent characterized property and will provide an additional stimulus to consideration of these molecules as a new class of therapeutic agents.

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