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STUDY OF BIOCHEMICAL AND IMMUNOLOGICAL FEATURES OF ANTIMICROBIAL PEPTIDES

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Abstract*: The oral cavity is the main gateway for infection to enter the human body. With inhaled air and food, a huge number of different microorganisms, including pathogens, are deposited on the mucous membrane. Most currently known AMPs have a broad spectrum of antimicrobial activity, acting against Gram-positive and Gram-negative bacteria, as well as yeast and some viruses. In addition, convincing evidence has been obtained that a number of AMPs have anticarcinogenic activity, as well as immunomodulators. The article examines in detail the biochemical and immunological features of antimicrobial peptides in the oral cavity. Due to the fact that oral AMPs are diverse and act on microorganisms very quickly, the likelihood of developing resistance to them is quite small. This gives hope that AMPs can be used to produce antimicrobials, resistance to which develops very slowly. Therefore, it is proposed to use AMPs with antiviral and antifungal activity in immunocompromised individuals, including AIDS patients, for the prevention and treatment of candidiasis and herpetic gingivostomatitis. The use of AMP for the prevention and treatment of gingivitis and periodontitis seems promising.*

Key words: *AMP, mucous membrane, immunological and biochemical functions, α- and β-defensins, cathelicidins, salivary glands.*

RELEVANCE OF THE TOPIC

The oral cavity is the main gateway for infection to enter the human body. With inhaled air and food, a huge number of different microorganisms, including pathogens, are deposited on the mucous membrane. At the same time, the vast majority of pathogens are successfully and very quickly neutralized already at the time of penetration, which indicates a powerful system of antibacterial protection in the human oral cavity. This protection is multifactorial and multi-component. First, the oral mucosa creates a physical barrier to the introduction of microorganisms. Secondly, when microbes enter, epithelial cells secrete cytokines and secretory immunoglobulin A, which activates the influx of neutrophils into the gingival sulcus. Thirdly, the most important antimicrobial functions are performed by the salivary glands. Many factors of nonspecific and specific protection against pathogens have been found in saliva: mucins, antibacterial peptides, enzymes, antibodies, proteins of the complement system, etc. These are small molecules containing 12 to 50 amino acid residues that can kill microbial cells. Most currently known AMPs have a broad spectrum antimicrobial activity, acting against gram-positive and gram-negative bacteria, as well as yeast and some viruses. In addition, convincing evidence has been obtained that a number of AMPs have anticarcinogenic activity, as well as immunomodulators.

THE PURPOSE AND OBJECTIVES OF THE RESEARCH

The aim of the study was to study the biochemical and immunological features of antimicrobial peptides.

The objectives of the study were:

1. Determine the AMP in the oral cavity
2. To study the general characteristics of AMP

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3. To study the role of AMP in oral pathology

MATERIALS AND METHODS OF RESEARCH

Volunteer work was carried out to study the oral mucosa and identify the biochemical and immunological features of AMP. The object of the study was students of the 7th-8th-9th grades of secondary schools № 4 and 37. 87 students were selected for the study, including 42 boys and 45 girls. Within 1 month, research work was carried out to determine the dynamics of the biochemical and immunological functions of AMP. The medical histories of each student were studied, and the diet, conditions and lifestyle were also taken into account. When conducting the study, we focused on each student, paying attention to the growth and decline of biochemical, immunological functions. The study was conducted daily 2 times a day - in the morning and in the evening.

In the process of research, a survey and a full examination of the oral cavity (also external), examination of teeth, as well as perimaxillary soft tissues, probing, percussion and palpation were conducted. Every two days, a bacterial study of smears from the oral mucosa was performed.

RESULTS

The following types of AMP were found in the oral cavity: α- and β-defensins, human cathelicidins, the sources of which are the oral mucosa, salivary glands and neutrophils. In the oral cavity, AMPs not only destroy pathogenic microorganisms, but also participate in maintaining normal microflora. Despite the differences in the primary structure, all AMPs share a number of common characteristics. Most AMPs are amphiphilic molecules: they contain positively charged amino acid residues of arginine, lysine or histidine, as well as more than 50% of non-polar amino acids. Their presence allows AMP to interact with the lipid bilayer of the plasma membrane of pathogens and disrupt its structure and integrity. In addition, many AMPs affect various intracellular processes. The greatest amount of AMP is produced in the oral mucosa, since the epithelium actively responds to signals from the environment, to infection, integrating innate and acquired immune responses. The β-defensins, cathelicidins, adrenomedullin, as well as the antimicrobial protein calprotectin secreted by the mucous membrane complement the protective function of the antimicrobial factors of the salivary glands, lysozyme and immunoglobulins.

Defensins (from the English - defense and Latin -in (e) - a suffix denoting "similar") are a family of cationic peptides with a length of 18-45 amino acid residues and containing 6-8 cysteine residues. The spatial protein structure of defensins contains antiparallel β layers and is stabilized by three disulfide bridges. The presence of disulfide bonds increases the resistance of defensins to leukocyte and microbial proteases in the focus of inflammation. Defensins are active against gram-positive and gram-negative bacteria, fungi, as well as against many viruses. As a rule, defensins attach to the outer cell membrane of the microbe and go deep into it, forming porous breaks. Violation of the barrier function of the membrane leads to the death of the microbial cell. The target for positively charged defensins are negatively charged phosphatidylglycerol molecules, which are rich in bacterial membranes. The presence in the membranes of host cells of a large number of phosphatidylcholine molecules, which carry a significant positive charge, prevents the attachment of defensins to the cells of the microorganism. In addition to antimicrobial properties, defensins activate chemotaxis factors and immunomodulators. Some defensins are synthesized constitutively, and the formation of other molecules increases in response to infection or the active synthesis of pro-inflammatory cytokines. Based on structural differences, defensins are divided into two families: α-defensins, formed mainly in neutrophils, and β-defensins, synthesized by epithelial cells. In humans, α-defensins were first isolated from neutrophils, which is why they are also called "human neutrophil peptides" (HNP). Neutrophils, migrating through the epithelium into the gingival sulcus, protect the

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periodontal junction from pathogens. Currently, six groups of α-defensins have been characterized. Of these, four groups (HNP1-4) are formed in neutrophils, and two more are isolated from Pennet cells and are designated HD5 and HD6 (from Human Defensin). All HNPs of the human body are isolated from neutrophil granules before cell maturation and differentiation. The peptides HNP-1 and HNP-3 consist of 30 amino acid residues. They are identical to each other, except for the replacement of alanine with asparagine. HNP-2 consists of 29 amino acids and is obtained by the cleavage of the first amino acid from HNP-1 and HNP-3. In smaller quantities than other neutrophil peptides, HNP-4 is formed. Despite the similarity of the amino acid sequence, each of the α-defensins has a unique spectrum of antimicrobial activity. For example, HNP-3 is highly effective against Porphyromonas gingivalis, which cause periodontal tissue damage. α-Defensins have a pronounced antiviral activity, and it is assumed that they can interact with both viral particles and virus-infected cells. Thus, HNP-1-3 have a depressing effect on herpes, influenza, hepatitis C viruses, human immunodeficiency virus (HIV)-1, cytomegaloviruses, papillomaviruses, adenoviruses. Since HNPs form channels in the membrane and can enter the cell, they also produce a variety of intracellular effects. It has been shown that they can inhibit the synthesis of nucleic acids and protein. Scientists have shown that α-defensins, binding to plasminogen, prevent the spread of infection. In addition, α-defensins also contribute to the activation of phagocytosis. With a decrease in the production of interleukin (IL)-10 by monocytes, HNP-1-3 enhances the synthesis of tumor necrosis factor-α (TNF-α) and IL-1, which is very important for the development of a local inflammatory response.

Cathelicidins are a family of AMPs found in a variety of living organisms. The only human cathelicidin is called LL-37, as it consists of 37 amino acid residues and contains two leucine residues at the N-terminus. The synthesis of LL-37 begins with the formation of a large precursor, which then undergoes limited proteolysis by the action of elastase or proteinase-3. At neutral pH values, LL-37 peptide is positively charged, and more than half of its amino acid residues are nonpolar. In an aqueous solution, LL-37 forms a messy tangle, but forms a α helix when embedded in a double layer of lipids of biological membranes. The ability to form a α-helix, apparently, determines the antimicrobial activity of this peptide. The mechanism of antimicrobial action of human cathelicidin differs from that of defensins. It is assumed that LL-37 covers the membrane like a carpet and destroys it in a similar way to detergents with the formation of many micelles. LL-37 is expressed in epithelial cells of the respiratory tract, digestive and urogenital tracts, as well as in the oral cavity. In mixed saliva, human cathelicidin is secreted by neutrophils and, to a lesser extent, epithelial cells. It has been shown that during inflammation, the synthesis of LL-37 occurs in the epithelial cells of the gums, tongue, and mucous membrane of the cheeks. According to the results of studies, it was found that cathelicidin reduces the development of an inflammatory response in response to the introduction of P. gingivalis into the human gum. Cathelicidin LL-37 is a chemoattractant for immune cells and causes the migration of neutrophils, monocytes and T cells to the site of inflammation. Some researchers believe that human cathelicidin is an "alarm signal", and its main function is to activate antigen-presenting cells. LL-37 plays an important and complex role in carcinogenesis, and its action is characterized by tissue specificity.

INFERENCE

AMP in some hereditary pathologies is accompanied by the development of diseases of the tissues of the oral cavity. Thus, Papillon-Lefebvre syndrome, characterized by early periodontitis and multiple dental caries, occurs due to a mutation in the cathepsin C gene. Due to the fact that oral AMPs are diverse and act on microorganisms very quickly, the likelihood of developing resistance to them is quite small. This gives hope that AMPs can be used to produce antimicrobials, resistance to which develops very slowly. Therefore, it is proposed to use AMPs with antiviral and antifungal activity in immunocompromised individuals, including AIDS patients, for the prevention and

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treatment of candidiasis and herpetic gingivostomatitis. The use of AMP for the prevention and treatment of gingivitis and periodontitis seems promising. There is speculation that the use of AMP can stop the progression of these diseases. For this purpose, it is proposed to use AMP in the composition of gels, rinses or applications for topical use. Currently, on the basis of pig cathelicidin, the drug Iseganan has been created, which is successfully used in the treatment of mucositis of the oral mucosa that occurs in cancer patients during chemotherapy.

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