Prospects for Using Bacteriocins of Normal Microbiota in Antibacterial Therapy (Review)

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Increasing resistance of microorganisms to antibiotics has encouraged researchers to seek alternative antimicrobial therapy. The review studies the prospects for using bacteriocins as antibacterial drugs. The definition of bacteriocins is given and their difference from traditional antibiotics is explained. The modern classification of bacteriocins, their properties and mechanisms of action are presented. Examples of the main bacteriocin-producing bacteria representing normal human microbiota are given. The authors investigate the role of bacteriocins produced by microbiota in maintaining mucosal resistance and stabilizing the human microbiome as well as the possibility of their application in creating probiotic drugs. The advantages and disadvantages of bacteriocins as alternative antibacterial drugs are described. The applications of bacteriocins in antimicrobial therapy, as well as methods for their industrial manufacturing, are discussed.

Key words: bacteriocins; antimicrobial therapy; normal human microbiota.

Introduction

A sharp increase in bacterial resistance to antibiotics [1, 2] poses difficulty in conducting effective antimicrobial therapy. Besides, side effects of antibiotics, such as cytotoxicity, suppression of normal human microbiota, the likelihood of allergic and autoimmune diseases can also impose restrictions on the use of these drugs [3, 4]. All this necessitates the search for new approaches and treatment regimens for infectious diseases [2, 5]. The use of bacteriocins in alternative or combined antimicrobial therapy seems to be a possible solution to this problem [6, 7].

Classification of bacteriocins and their mechanisms of action

Bacteriocins are a large group of peptides secreted by individual bacteria with antimicrobial activity. In contrast of antibiotics acting as antimetabolites, bacteriocins cause damage to bacterial cell structures and subsequent cell death [7–13]. Such peptides are produced by most species of bacteria, though this ability is strain-dependent [7]. The biocidal effect of these peptides is likely to manifest itself not only in strains of the same species, but also in representatives of other species and genera. The range of antimicrobial activity of bacteriocins is somewhat narrower than that of antibiotics as it is determined by presence of receptors for their adsorption in target bacteria [14].

Bacteriocins are classified based on several characteristics: the primary molecular structure, molecular weight, the presence of post-translational modifications, physical and chemical properties, the range of antimicrobial activity, the mechanism of antimicrobial action, receptors of target cells and genetic characteristics [7, 8, 13–17]. There are three main classes of bacteriocins (Table 1). Notably, bacteria of the same strain are able to secrete bacteriocins belonging to different classes.

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Table 1

Functional classification of bacteriocins and their possible mechanisms of action

Bacteriocins	Receptor variants	Possible action on the target cell
Class I — post-translationally modified Subclasses: *lantibiotics* *sactibiotics, etc.* These are heat-resistant peptides with molecular weight less than 10 kDa	In some cases, the receptor is a precursor of peptidoglycan, lipid II	Formation of pores in the bacterial membrane, inhibition of bacterial enzyme activity
Class II — unmodified, or cyclic Subclasses: *IIa–IIe* These are heat-resistant peptides with molecular weight less than 10 kDa	Class IIa bacteriocins bind with the receptor of mannose phosphotransferase	Increased membrane permeability due to formation of ion-selective pores
Class III Subclasses: *IIIa, IIIb* These are thermolabile proteins with molecular weight more than 30 kDa	Underexplored	Cleavage of bacterial cell wall peptidoglycan, ATP release from cells

Among class I bacteriocins, lantibiotics are the most well studied group. They are post-translational modified antimicrobial peptides of small size (<5 kDa) characterized by unusual amino acids: lanthionine (Lan), α-methillothionine (MeLan), dehydroalanine, and dehydroretinol [18]. When intramolecular bonds are formed, their serine and threonine residues dehydrate to dehydroalanine and dihydrobetulin respectively [7].

Class I molecules can be grouped as type A or B according to their chemical structure and antimicrobial action [18]. Type A lantibiotics are positively charged elongated screw-shaped peptides with the average molecular weight of 2–4 kDa. The shape and charge of type A molecules facilitate formation of pores in membranes and depolarization of the latter in sensitive bacterial cell species, which leads to their lysis [16]. Type B lantibiotics (2–3 kDa) are globular peptides with negative or neutral charge. These peptides exhibit antimicrobial activity through cell lysis and inhibition of major bacterial enzymes [19–23]. Type B lantibiotics increase membrane permeability and reduce ATP-dependent transport of proteins and ATP-dependent calcium absorption in sensitive bacterial cells, which results in cytolysis [24].

Class II bacteriocins are small (<10 kDa), heat-stable peptides containing no lanthionine. They can be subdivided into subgroups a, b, c, d, e based on amino acid sequences and functions. Subclass IIa bacteriocins kill target cells by increasing the cell membrane permeability, which causes release of cytoplasmic components through the membrane and cell death. Subclass IIb bacteriocins act as pore-forming peptides [25]. Subclass IIc peptides have different mechanisms of action on membrane permeability and cell wall formation in bacteria [26], while subclass IId bacteriocins are linear, single-peptide molecules with similar antimicrobial activity.

Class III bacteriocins consist of proteins with high molecular weight (>30 kDa). This class is subdivided into subclasses IIIa and IIIb. Subclass IIIa (bacteriolysins) includes peptides destroying bacterial cell membranes, thus causing lysis and subsequent cell death [27]. Subclass IIIb comprises peptides that do not damage the potential of target cell membrane. Target cell death occurs not by cytolysis, but due to ATP outflow [16].

Bacteriocins can be identified according to the specific name of bacteria producing them: e.g., *Escherichia coli* synthesizes colicins, enterocins are produced by *Enterococcus spp*., etc. However, many of the molecules have their own original names: nisin, mersacidin, etc.

Bacteriocins of normal microbiota and their significance for the human microbiome

Bacteria of normal microbiota, representatives of the microbiome, are a permanent source of bacteriocin production, playing a significant role in human life. Microbiota forms colonization resistance barrier limiting contamination of the mucous membranes by pathogenic and non-resident opportunistic microorganisms, it is involved in stimulation of lymphoid tissue, vitamin formation, etc. [28].

In recent years, the concept of “co-immunity” has gained popularity. It suggests that a macroorganism can be protected by both its own immune system and components of its normal microbiota [29]. Representatives of the human microbiome producing bacteriocins have an ecological advantage over other strains *in vivo*, which indicates the significant role of these antimicrobial peptides in formation of an ecological niche [30]. Differences in specific composition of biotopes affect the density of secretion and the types of bacteriocins found in different parts of the human

Table 2

Examples of bacteriocins produced by enterococci, lactobacilli, and bifidobacteria

Groups of bacteriocins	Enterococci	Lactobacilli	Bifidobacteria
		Class I	
Lantibiotics	Cytolysin Enterocin W	Lactocin S Carnocin U149 Plantaricin W Lacticin 3147 Lactocin B Amylovarin Thermophylin A	Bisin Thermophilicin B67 Bifilong
		Class II	
Subclass IIa	Enterocin A Enterocin SE-K4 Enterocin CRL-35	Sakacin A Sakacin 674 Curvacin A Plantarcin 423 Sakacin G	Bifidin Bifidin 1 Bifidocin B Bificin C6165
Subclass IIb	Enterocin 1071 Enterocins L50 Enterocins C	Plantaricin E/F Plantaricin J/K Plantaricin NC8	
Subclass IIc	Enterocin B Enterocin P		
Subclass IId	Bacteriocin 31 Enterocin I Bacteriocin AS-48		
		Class III	
Subclasses IIIa, IIIb	Enterolisin A	Helviticin J	Bifilong Bb-46 Bifilact Bb-12

body. The highest concentration of bacteriocins was revealed in samples from the vagina, the respiratory tract, and the oral cavity, while intestinal samples showed the lowest concentration [31]. Bacteriocins are believed to allow indigenous commensal bacteria to occupy several ecological niches as well as establish long-term relationships with other representatives of the biocenosis and commensal relationships with the host [31]. Regulation of a bacteriocin production system may be pheromone-dependent [16, 32]. A bacteriocin peptide can function as a pheromone inducing its own production. When bacterial cell density becomes high, the auto-induction loop is activated and bacteriocins are produced in high concentrations [16]. Thus, these peptides are synthesized intensively to affect similar species only when the bacterial density in the biotope is high enough to inhibit the growth of competitive strains. Production of bacteriocins in biofilms also suggests balanced competition and coexistence of organisms in a microbial community [33].

Bacteriocin synthesis by representatives of normal microbiota is considered to be one of the mechanisms of *quorum sensing*, which allows bacteria to communicate, coordinate their actions and synchronize group behavior through secretion of diffusing signal molecules [34]. In the process, strains producing "weak" bacteriocins have greater chances of survival in the biotope: they are less toxic to competitors, cause mild expression of bacteriocins on the part of the latter, which results in controlled competition and development of dynamic equilibrium in the population [35–38]. This fact may also explain the predominance of weak bacteriocin producers in nature [35].

Among the representatives of the human obligate microbiota, the range of bacteriocins from lactic acid bacteria of *Lactobacillus*, *Bifidobacterium,* and *Enterococcus* genera (lactobacilli, bifidobacteria, enterococci) [10, 15, 39–43] and from *Escherichia coli* [44] have been quite well-studied so far (Table 2).

Lactic acid bacteria of normal microbiota are most often the basis for the selection of strains in production of various probiotics [45–50]. Recently, metabiotics (preparations developed on the basis of the structural components of microbial cells, metabolites and signal molecules of probiotic strains and devoid of potential pathogenicity and other imperfections inherent in living bacteria) have been actively introduced into medical practice [51]. In production of various probiotic drugs and functional food products, it is considered preferable to use strains with a good ability to synthesize bacteriocins. These inhibit pathogens directly, they are able to modulate the composition of the microbiota positively and stimulate the host immune system [52, 53].

Advantages and disadvantages of bacteriocins as antibacterial agents

Bacteriocins have a number of advantages as antimicrobial substances. Unlike antibiotics suppressing metabolism and synthesis processes in bacteria, the action of bacteriocins is often accompanied by damage to the structures and death of the target cell, which reduces the possibility of microbial resistance. Besides, using bacteriocins is potentially advantageous due to their high biological activity (bacteriocins are efficacious in the nanomolar range) as well as low toxicity (except cytolysin) [54]. Unlike antibiotics, bacteriocins are completely metabolized in the human body, which determines their low toxicity. All this makes the use of these peptides more preferable than antibiotics in some cases [55, 56].

The advantages of bacteriocins also include their protein nature, which allows obtaining these peptides through bioengineering [57]. Bioengineering products are likely to have increased biological activity against

certain pathogens as well as improved physical and chemical properties (solubility, resistance to protease and pH changes), which further increases their value and efficacy as antimicrobials.

However, bacteriocins, despite great potential for use in clinical practice, have a number of disadvantages. It should be remembered that bacteriocins undergo proteolytic degradation when administered orally. Nevertheless, it is possible to eliminate this defect by using encapsulation technology or parenteral administration of the drug [57]. In addition, efficacy of some lantibiotics is likely to decrease due to their instability in conditions of fluctuating neutral and alkaline pH values, but the way to solve the problem is obtaining substances with increased stability by means of bioengineering [58].

It should be noted that bacteria are able to develop resistance to bacteriocins [59, 60]. Several mechanisms of bacterial resistance to lantibiotics have been described [61–66]. There are data on development of resistance to class II bacteriocins in laboratory setting [67].

Rather narrow spectrum of antimicrobial action is also able to limit the use of bacteriocins in clinical practice. It is possible to compensate for this disadvantage partially or completely when using bacteriocins in combination with other existing antimicrobials such as antibiotics.

Possibilities of using bacteriocins in antimicrobial therapy

Bacteriocins can be used to inhibit both exogenous microorganisms and the indigenous human microbiota. In particular, the possibility is considered of using bacteriocins in targeted (molecularly targeted) therapy for selective inhibition of polyresistant endogenous (auto) strains of microbiota in order to prevent antibiotic-resistant opportunistic infections difficult or impossible to treat [68].

Bacteriocins have their own antimicrobial potential that can be realized in treatment of infectious diseases [69]. However, combining these peptides with other existing antimicrobials is believed to be optimal in their clinical use [57]. The use of “bacteriocin-antimicrobial” combinations is expected to help enhance the microbicidal effect and thereby reduce the likelihood of developing resistance to both bacteriocin and antibiotic [57]. Notably, the antimicrobial effect of the combined medication is achieved owing to the fact that the subcomponents may have different mechanisms of antimicrobial action aimed at the same or different targets. Combinatorial therapy with bacteriocins can both broaden the antimicrobial spectra (which may be useful in treating infections of unknown etiology) and diminish or eliminate adverse side effects completely by reducing the concentration of antibiotic [70, 71]. In the latter case, synergistic combinations of bacteriocins and antibiotics will also help to reduce costs associated with the use of expensive antibiotics.

An important factor influencing the maximum efficacy of treatment with a combination of two drugs is the way they are administered. Pharmacokinetic properties of both antimicrobials should be taken into account to optimize the delivery method of bacteriocins in combination with antibiotics. For example, it should be noted that systemically applied lantibiotics are likely to be bound by plasma proteins [72], therefore, distribution and subsequent bioavailability of bacteriocins in the area of inflammation may be significantly weakened. At the same time, localized cutaneous, intravaginal or inhaled routes of bacteriocin administration may be more effective due to the relatively low absorption rates and minimization of undesirable systemic side effects [73–75].

Data have been accumulated, concerning the effect of bacteriocins combined with various antimicrobial agents against clinical isolates (pathogens). Studies show that different combinations of bacteriocins and antimicrobials exhibit synergism [76–78], antagonism [79] or no influence on the ultimate result (indifferent effect) [80]. To predict clinical efficacy of bacteriocin-antimicrobial combinations, it is necessary to understand physical and chemical character of interactions (hydrophobic-hydrophobic or cationic-anionic interactions) between bacteriocin and antibiotic. Due attention should be paid to the molecular weight of components: perhaps a combination of two substances with the same molecular weight can be more efficacious than combining a high-molecular substance with a low-molecular one [57].

When selecting an effective combination of bacteriocin and antibiotic, it should be understood that the mechanism of antimicrobial action can be changed and clinical outcomes may appear difficult to predict when combining two antimicrobials. In this regard, finding successful synergistic interactions using genomic, proteomic and other modern research methods is likely to boost introduction of antimicrobial combinations in clinical practice, generally contributing to the development of alternative therapeutic options and solution of the global problem of antibiotic resistance [57, 81–84].

It should be noted that bacteria present in a biofilm are more resistant to antimicrobials than those present in a planktonic state. Biofilms are known to be composed of bacteria incorporated into the complex organic polymeric matrix impeding penetration of the antimicrobial into the deepest strata [85–87]. Thus, there is increased importance of seeking alternative therapeutic options and/or effective antimicrobial combinations to target microbial biofilm communities. Researchers have revealed an increase in anti-biofilm activity of enterococcal bacteriocins in combination with a number of antimicrobial drugs against Methicillin Resistant Staphylococcus Aureus (MRSA) [76, 88–91].

A potential strategy of abandoning traditional antibiotics may also involve combining bacteriocins with phages and/or endolysins. For example, a number of

researchers found a synergistic effect resulting from the combined application of these substances [92–98].

Thus, considerable information about the positive effect of combined application of bacteriocins with antimicrobial drugs is available at present. This suggests that the use of bacteriocins for treatment against antibiotic-resistant strains has real prospects [99].

Recent methods of bacteriocin production

Today, bacteriocins are most often produced by selection of producer bacteria or by chemical synthesis.

The main stages of the biological pathway (selection) are: isolation of cultures from natural sources, comparative assessment of producer activity and selection of the most promising producers, experimental enhancement of producer activity, including classical methods of mutagenesis and genetic engineering techniques [49, 100, 101]. However, large-scale commercial introduction of this method to produce bacteriocins may be limited by low output (if several purification methods are used) or low purity (with a higher output), which affects the cost or quality of the product.

Current development of peptide synthesis methods allows obtaining bacteriocins chemically [102]. Chemical synthesis is generally more appropriate and efficient in production of low molecular weight peptides (<6 kDa). Streamlined synthesis aims at obtaining various modifications of known bacteriocins with improved properties as well as creating new drugs with desired properties. The chemical method offers many advantages such as the possibility of quick amino acid replacement, the use of modifications of the main or lateral chains in the molecule, which is likely to improve efficacy and stability giving the opportunity to change bacteriocin activity spectra. Besides, steady decline in the cost of reagents for synthesis also makes the chemical method more attractive and competitive [102].

Conclusion

In view of the increasing number of antibiotic-resistant strains among pathogenic and opportunistic microorganisms, the study of bacteriocins as alternative antimicrobial substances is quite timely. Non-toxicity, biological safety and the possibility to combine bacteriocins with other antimicrobial agents (antibiotics, bacteriophages, etc.) offer the challenge of using them as mono- or combined drugs for antimicrobial therapy. Given the huge potential of bacteriocins and increasing demand for them, it is extremely timely to develop methods of selection and subsequent chemical synthesis.

Representatives of the normal human microbiota are among the safest sources of bacteriocins. These peptides are involved in the mechanisms of antagonistic activity within the microbiome to maintain it in a state of dynamic equilibrium. The capacity to produce bacteriocins is an important characteristic of probiotic strains, should be considered when creating probiotics for correction of dysbiotic conditions.

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