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Antimicrobial peptides and their therapeutic potential as anti-infective drugs: A review

Azhen Fatih Muhammad[1]

[1]*Directorate of veterinary Hospital, Sulaimani City, Republic of Iraq*
E.mail: azhinfatih1993@gmail.com

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Abstract

Antimicrobial peptides (AMPs), also referred to as host defense peptides, are small molecular weight proteins with broad spectrum antimicrobial activity against bacteria viruses, fungi, and parasites. The AMPs are important components of innate immune systems. They are believed to be existed more than 2.6 billion years ago as part of the innate immunity in primitive organisms. The antimicrobial activity of these natural peptides makes them possible candidates in the development of new drugs against the multidrug resistant bacterial strains that have emerged recently. However, development of new therapeutics from the natural source *Anti-infective drugs* (AMPs) seems to be faced with many problems, such as toxicity, rapid, degradation and inability to maintain required concentrations in the target tissues. This review focuses on the therapeutic possibility of the natural antimicrobial peptides, the advantages and disadvantages of these compounds when used for topical and systemic applications, as well as their possible utilization in the development of new anti- infective drugs.

Introduction

Animals and human are susceptible to infective diseases. Patients take large and excessive amounts of antimicrobial compounds, particularly in critical care settings, which has resulted in the emergence of some pathogens resistant to all the available antimicrobial agents. Therefore, the development of new anti-infective drug is a necessary. Antimicrobial peptides (AMPs) are small molecular weight proteins with broad spectrum antimicrobial activity against viruses, bacteria, parasites and fungi. They are important components of innate immune systems. This subject field is presently moving quickly because of the impressing demand for novel antimicrobial compounds due to the current reduction in the strength of commonly used antibiotics.

An unbalanced expression of antimicrobial compound has been concerned in human disease [1,2,3,4,5]. Historically, the AMPs have been referred to as cationic host defense peptides [6], anionic antimicrobial peptides/proteins [7], cationic amphipathic peptides [8], cationic AMPs [9], host defense peptides [10], and α-helical antimicrobial peptides [11]. The AMPs were first found by Dubos during extraction of an antimicrobial agent from a soil *Bacillus* strain in 1939 [12] that was reported to protect mice against pneumococci infection. A year later, Dubos and Hotchkiss fractionated this extract and found a new AMP known as gramicidin [13]. Gramicidin is reported to have some degree of toxicity after intraperitoneal injection, but can be used as an effective treatment for topical ulcers and wounds [14]. A couple of years later, tyrocidine was identified to be efficacious against both Gram-positive and Gram-negative bacteria [15]. Later on, scientists found that Triticum aestivum contains AMP named purothionin that was effective against some pathogenic bacteria and fungi [16,17]. These antimicrobial compounds have a broad-spectrum antibacterial, antifungal, and antiviral activities, as well as a rapid action of killing with potentially low degree of get resistance [18]. The AMPs are evolved in most living

organisms to combat microbial challenge. These small cationic peptides play an important role as effectors of innate immunity on mucosal surfaces and skin, and they exhibit direct antimicrobial activity against different viruses, bacteria, parasites, and fungi [19]. Marine organisms are of import origin of bioactive molecules that have been used to treat assorted diseases. Marine context are associated with chemical variety, leading to a resource of new active agents for the evolution of bioactive products [20,21,22]. This review article deals with the therapeutic probability of the AMPs as topical and systemic antimicrobial agents and their possible development to become promising replacements to the currently available conventional anti-infective agents.

The Need for New Chemotherapeutic Agents

The widespread use of antibiotics in veterinary clinic and animal agriculture resulted in an increased pace of antimicrobial resistance among infective bacteria [23]. The appearance of bacterial resistance to the currently available antibiotics is the driving force for the evolution of newer anti-infective drugs. The pharmaceutical industry has continuously met the needful of novel anti-pathogenic by modifying existent antibiotics and developing newer antibiotics, in a timely manner, giving rise to development of many newer antibiotics such as beta-lactams (carbapen ems, penicillins, cephalosporins), macrolides, glycopeptides, ketolides, fluoroquinolones, aminoglycosides, and oxazolidinones [18]. Although a huge success in the development of antimicrobial agents has been done up to date, but ongoing emergence of antibiotic resistance worldwide continues to motivate the search for novel anti-infective therapies to replace and/or supplement conventional antibiotics [18]. A continuous supply of the antibiotic generations is an important requirement to deal with the choice of resistant pathogenic substances that emerge as therapeutic application of an antibiotic get widespread [24].

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are compounds that represent an important part of the innate immunity [18]. They are effective enough to kill or reduce the number of viruses, bacteria, parasites, and fungi [25]. Nature is a generous origin of AMPs (Table 1); they are found in almost everything from primitive microorganisms to the innate part of human immune response [18]. The AMPs are either synthesized in the ribosome of eukaryotic cells through gene transcription or synthesized in the cytosol of fungi and bacteria with the action of peptide synthetases [26]. Polymyxin B [27], bacitracin [28], vancomycin [29], and gramicidin A [18] are models of non-ribosomally synthesized peptides. Some organisms synthesize AMPs since they act as a host's natural defenses against the daily exposure to millions of infective pathogens [30]. The AMPs may have antiparasitic, antiviral, anticancer, and immunomodulatory action (Table 2). In mammals, the AMPs that represent part of the innate immune system for protection against infection are called defensins [31]. In this regard, down regulation of enteric cathelicidin and β-defensin-1 expression was correlated with Shigella infections in humans [32], and overexpression of a human AMP gene improves lung clearance of Pseudomonas aeruginosa [33].

Table 1. Some Antimicrobial Peptides and Their Natural Sources.

Peptide	Source	Reference
DermaseptinB-2	South American giant leaf frog (*Phyllomedusabicolor*)	[34]
Andropin	Fruit fly (*Drosophila melanogaster*)	[35]
Alloferon 2	Blow fly (*Calliphoravicina*)	[36]
Lactoferricin B	Cattle (*Bos Taurus*)	[37]
Heliomicin	Tobacco budworm (*Heliothisvirescens*)	[38]
Aurein 2.3	Southern green and golden bell frog (*Litoriaaurea*)	[39]
Temporin A	European common frog (*Ranatemporaria*)	[40]
Magainin 2	Skin and stomach of African clawed frog (*Xenopuslaevis*)	[41]

Role of Antimicrobial Peptides in Innate Immunity

The immune response in vertebrates is divided into the innate and acquired immune responses. The innate part of immunity is not specific against the microorganisms and includes phagocytic cells (neutrophils and macrophages), tear, sweat, nasal discharge, stomach acid, etc. The acquired immunity is specific within the body's organs which results in the activation of cytotoxic T-lymphocytes and production of antibodies against the organism by B-lymphocytes [42]. The small cationic peptides with strong antimicrobial activity against Gram-negative and Gram-positive bacteria, parasites, fungi, and several viruses are stimulated by antimicrobial function of innate immunity [43,44]. The perturbation of the microbial cell membrane is considered as the main mechanism of rapid killing of the microbial pathogens [45]. The AMPs also take part in immune activation, inflammation, and wound healing [46,47].

Drug development from Antimicrobial Peptides

The microbial resistance to drugs in human, pigs, chickens, and feedlot cattle has increased in range and pace [48,23]. The best example is the human immunodeficiency virus (HIV), where the rapid growth of resistance to a single drug posed threatening clinical problems. The only efficient solution to this trouble was to develop combining therapy involving some antiviral drugs with different chemical mechanisms of inhibitory action. The need to the development of newer anti-infective therapies is always inevitable [49].

Table 2. Activities and Sources of Some Antimicrobial Peptides.

Peptide	Source	Activity	Reference
Magainin 2	Skin and stomach of African clawed frog	Anti G+ & G-, antiviral	[53]
Cecropin A	Giant silk moth (*Hyalophora cecropia*)	Anti G+ & G-, anti-HIV, antiparasitic, cancer cell	[54]
Brevinin-1	*Ranabrevipoda porsa*, Japan	Anti G+ & G-, antiviral	[55]
Tricyclic peptide RP 71955	*Streptomyces* strainAA3891	Antiviral, anti-HIV	[56]
Lactoferricin B	*Bos Taurus*	Anti G+ &G-, antiviral, antifungal, cancer cells	[57]
Heliomicin	Tobacco budworm	Antifungal	[38]
Aurein 1.1	Green and Golden Bell Frogs (*Litoria aurea* and *Litoria raniformis*), Australia	Anti-Gram+, antifungal, cancer cells	[39]
Aurein 2.1	*Litoria aurea* or *Litoria raniformis*, Australia	Anti G+ & G-, antifungal, cancer cells	[39]
Caerin 1.1	Australian green tree Frog (*Litoria splendida*)	Antiparasitic, anti G-, G+, anti –HIV, cancer cell	[58]
Caerin 1.8	Blue thighed frog (*s*)	Anti G+, G- antifungal, antiparasitic	[59]
Human neutrophil peptide-1	Neutrophils, natural killer cells, monocytes, saliva of human (*Homo sapiens*)	Anti G+ & G-, antiviral, antifungal, antiparasitic, anti-HIV, Chemotactic, Enzyme inhibitor, wound healing, cancer cells	[60]
Dermaseptin-S5	(*Phyllomedusa sauvagii*), South America	Anti G+ & G-, antifungal, antiparasitic	[61]
Dermaseptin- B2	Giant leaf frog (*Phyllomedusa bicolor* South America	Anti G+ & G-, antifungal, cancer cells	[61]
Bactenecin 5	Bovine neutrophils (*Bos(taurus*)	Anti G-	[62]
Apidaecin IA	Honeybee (*Apis mellifera L.*)	Anti G-& G+	[62]
Andropin	Fruit fly (*Drosophila melanogaster*)	Anti G+	[63]

G+ = Gram-positive bacteria; G- = Gram-negative bacteria; HIV = human immunodeficiency virus.

Development of Antimicrobial Peptides for Ophthalmic Uses

Since 1987, when the interest in commercial of AMPs had been started with the discovery of magainins [50], there has not been any apparent progress in the ophthalmic field. Ophthalmic pharmaceutical industry has expressed intermittent interest in AMPs as an important new family of drugs and has supported contract researches for exploration of in vitro and animal studies. The continuous development of newer, very successful, conventional antibiotics to exchange the previously developed antibiotics, with lower effect due to increasing bacterial resistance, makes a major discouragement to the exploration of newer ophthalmic drugs of AMPs origin. However, the recent introduction of moxifloxacin for topical ophthalmic treatments and gatifloxacin for treatment of ocular infections has again provided a change from the older drugs, ofloxacin and ciprofloxacin, to the newer ones [51,52]. Specifically, the emergence of increasing resistance among importance ocular pathogens such as Pseudomonas aeruginosa and Staphylococcus aureus taken together with the expiration of patent protection on the older fluoroquinolones have led ophthalmic pharmaceutical companies to place marketing emphasis on the newer, more effective fluoroquinolones [18].

The development of topical AMPs agents for the treatment of ophthalmic infections have some attractive features including direct delivery to the infected site and possible combination therapy with conventional antibiotics to reach a synergistic or additive antibacterial effect at nontoxic AMP concentrations [64, 65]. Moreover, the broad-spectrum antimicrobial effect of AMPs against both viral and bacterial ocular pathogens may lead to better empirical treatment formula for superficial ocular infections by generalists [66]. The use of AMPs as a cure for ophthalmic infections has several disadvantages such as extreme toxicity to the delicate conjunctival epithelium and the highly innervated, fine sensitive corneal epithelium. Additionally, the application of AMPs to the eye will affect in infection clearance, but the damage paid may be a scarred cornea, with increased vascularization, and the AMPs undergo proteolysis at time application to the ocular surface, leading to reduced efficacy of these antimicrobial compounds [18]. Furthermore, the concentration of the AMPs may be decreased following ophthalmic application due to chemical interaction with components of tear [67].

Most probably, the AMPs toxicity is controlled in vivo by several crucial mechanisms such as epithelial synthesis as nontoxic, inactive propeptides requiring enzymatic activation for biological function (cathelicidin), protected storage in granules (leucocyte defensins and cathelicidins), programmed, on site neutralizing mechanisms to limit damage, and smallest concentration because of the additive and synergistic effects achieved in combination with other effector molecules with overlapping antimicrobial activity [64].

Parenteral Application of Antimicrobial Peptides

The systemic application of AMPs appears to be more difficult than the ophthalmic application of these compounds; e.g., the N-terminal fragments of BPI (rBPI 21)(bactericidal permeability-increasing protein), of AMPs origin, had reported to bind and neutralize endotoxin and exert potent bactericidal effects against Neisseria meningitidis [18]. However, in a clinical trial conducted on 393 children suffering from severe meningococcemia, the $rBPI_{21}$ failed to reduce the mortality rate when administered as a supporting treatment to conventional antibiotic therapy.

Current Status and Future Prospects of AMPs as Local and Systemic Anti-infective Drugs

From the year 2000 until 2014, approximately 100 new antimicrobial compounds were into the Antimicrobial Peptide Database (APD) every year [67]. On May 28 2018, the APD involved 2707 antimicrobial peptides (269 bacteriocins from bacteria, 8 from 4 from archaea, 33 from plants, 13 from and 2034 from animals). The discovered AMPs were reported to have antiviral (Anti-HIV), antibacterial (antibiofilms), antiparasitic (antimalaria) antifungal, anti-protist, anticancer, insecticidal, spermicidal, chemotactic, antioxidant, wound healing, and protease inhibiting activities. It is that the isolation and identification of new antimicrobial peptides will go on.

Conclusion

Antimicrobial peptides are molecules produced by many organisms, from bacteria to the higher mammals including human. They promote numerous activities inside the living body such as assisting the innate immunity, antiprotozoal, antiviral, antibacterial, anticancer and antifungal effects. The antimicrobial activity of these peptides has motivated the pharmaceutical industry to consider these compounds as possible alternatives to the currently available antimicrobial drugs. This is particularly essential because of the rapidly increasing emergence of antibiotic-resistant bacterial strains. However, it seems that the discovery and improvement of AMPs for local ophthalmic and systemic applications are not easy and encounter many obstacles, such as toxicity, rapid degradation by lytic enzymes and difficulty in maintaining sufficient concentration in the target sites.

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