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Antimicrobial peptides characteristics and their applications as feed additives in domestic animals

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ABSTRACT

Antimicrobial peptides (AMP) , also termed Host defense peptides, are important innate immune effectors. AMPs contain a broad spectrum of antimicrobial activities against Gram-positive and Gram-negative bacteria, mycobacteria, fungi, and viruses. They are widely expressed at specific cells or tissues in various animals. Recently, their immunoregulatory activities have been demonstrated, including chemotaxis, neutralization of pro-inflammatory cytokines, anti-endotoxin activity, promotion of wound healing, and initiation of adaptive immune responses. Therefore, the multifunctional roles of AMPs could potentially provide a foundation for the development of novel feed additives. The purpose of this review is to give an overview of AMPs, and their potentials as alternatives to conventional antibiotics used in domestic animal farming.

(Key Words: Antimicrobial peptides, Domestic animals, Feed additives)

INTRODUCTION

Why animals are able to stay healthy in the environment full of dangerous microorganisms? The answer is in the host's immune systems, which have outstanding defense mechanism that can protect the animals from invading pathogenic microbes. In higher vertebrates such as mammals, there are two types of defense mechanism: innate (nonspecific) immunity and adaptive (specific) immunity (Thomas et al., 2007). The innate immunity provides organisms with a rapid and non-specific first line of defense against pathogens. Those include physical, chemical, and cellular barriers. The main physical barriers are skin and mucous membranes. Chemical barriers include the high acidity of gastric juice, and specialized soluble molecules that posse ss antimicrobial activity.

The cellular defense comprises an array of cells with sensitive receptors that can detect foreign microbial components and instigate a counterattack. There is no memory component involved in innate immunity. The response to invasion by a microbial agent that overcomes the initial barriers of skin and mucous membranes is rapid, typically within minutes.

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Adaptive immunity or acquired immunity refers to defenses that involve the specific recognition of a microbe, once it has breached the innate immunity defenses, and the activation of B and T lymphocytes to destroy the invading microbes. This takes a week or two to become fully active, involving the immunological memory. It will elicit quicker and often more vigorous responses in next contact with that particular pathogen (Gerard et al., 2007).

1. AMPs play a role in innate immunity

One of the well-known innate immunity defenses is the production of antimicrobial substances by specific cells or tissues of the organisms. These natural substances with antimicrobial activities consist of three major groups (Linde et al., 2008):

(1) Digestive enzymes that destroy the ingested microbe (e.g. lysosomal enzymes)

(2) Peptides that bind essential elements like zinc or iron (e.g. calprotectin and lactoferrin, respectively)

(3) AMPs that possess the capacity to directly kill or inhibit the growth of microbes (e.g. cathelicidins and defensins).

AMPs are innate immune effectors, existing ubiquitously in both plant and animal kingdoms (Zasloff, 2002; Chou et al., 2010). These peptides provide primary immune protection in plants, fungi, and invertebrates and are usually termed antimicrobial peptides (AMPs). In higher vertebrates, some AMPs were found to also have immunoregulatory activities, besides the antimicrobial activities. Genes encoding these peptides are expressed in a variety of cells in the host, including circulating phagocytic cells and mucosal epithelial cells. Recently, close to 900 different AMP sequences have been identified (Kang et al., 2012).

2. AMPs share common characteristics and bioactivities

Most of these peptides share certain common features (Lai et al., 2009). For example, they are small in size (consist of 6 to 59 amino acids in length), with positive charge and amphipathic feature, i.e. molecular conformations with both hydrophilic and hydrophobic domains. AMPs are capable of targeting any organism with a cholesterol-free, negatively charged membrane. Thus, AMPs contain a broad spectrum of antimicrobial activities against Gram-positive and Gram-negative bacteria (Brogden, 2005; Shen et al., 2010), mycobacteria (Méndez-Samperio, 2008), fungi (Hancock et al., 2000), and enveloped viruses (Klotman et al., 2006). However, some microbes have evolved mechanisms to inactivate or avoid AMPs and subsequently become AMP-resistant (Diamond et al., 2009). This potentially put some limitation on AMP's practical application. Interestingly, some AMPs are also able to kill cancerous cells (Bullard et al., 2008), and many studies have shown that AMPs can act by mechanisms that extend beyond their capacity to serve as natural antibiotics.

AMPs can boost specific innate immune responses and exert selective immunoregulatory effects on

the host, including chemotaxis, neutralization of pro-inflammatory cytokines, anti-endotoxin activity, initiation of adaptive immune responses and wound healing (Yang et al., 2002; Sang and Blecha, 2009). Hancock and Diamond (2000) summarized a series of AMPs, focusing specially on defensins and cathelicidins, and their potential application as feed additives. Examples of AMPs and their activities are shown in Table 1.

Table 1 Examples of AMPs and their activities (Hancock and Diamond, 2000)

Activity	Examples
Broad-spectrum antibacterial	Defensins, indolicidin, protegrin and LL-37
Synergy with other peptides	Defensins NP-1 and NP-5
Antifungal	Protegrin, indolicidin and histatins
Anti-endotoxin	LL-37
Anti-enveloped virus (HIV,HSV,VSV)	Indolicidin, protegrin and defensins
Anticancer	Indolicidin and defensins
Wound healing	PR39 and defensins
Antiparasite	Indolicidin and defensins

3. Structure of AMPs

As described earlier, AMPs share some common features, such as a length of less than 60 amino acids and an overall positive charge. They all have broad-spectrum antimicrobial activity at physiological conditions, and are amphipathic, containing both hydrophilic and hydrophobic domains (Zasloff, 2002). AMPs can be divided into five subgroups based on their amino acid composition and structure. They are anionic peptides, linear amphipathic α-helical, cationic peptides rich in specific amino acids, peptide fragments, and peptides with cysteine that form intramolecular disufide bonds. Some examples of these classes are shown in Table 2 (Diamond et al., 2009).

Table 2 Classification by class, structure, and sources of AMPs (Diamond et al., 2009)

Class	Structure properties	Examples	Source(s)	Physiological location
Anionic	Negative charged	Maximin, Dermicidin	Amphibians, humans	Airway epithelia
Linear, α-helical	Positive charged,	Cecropin, magainin pluerocidin	Amphibians, mammals, insects	Skin
Linear, Cationic,	Cationic amino acid enriched	Abaecin, Indolicidin, Histatins	Insects ,mammals	Skin, intestinal Epithelia
Peptide fragments	Cationic, β-turm	Lactoferrin, Cathelicidins	Humans	Blood
Charged peptide with cysteine	Cationic, anionic, form disulfide bonds	α-, β-, and θ-defensins, protegin	Birds, reptiles, mammals, plants	Ubiquitous

(1) Cathelicidins

Cathelicidins are composed of a N-terminal putative signal peptide (preregion), a highly conserved cathelin-like domain (proregion), and a highly heterogenous C-terminal microbicidal domain (Figure 1) . Cathelicidins derive its name from the highly conserved N-terminal region known as the cathelin-like domain. Number of cathelicidins varies among species, including pigs, humans, dogs, and chickens. The number of cathelicidins and their primary cell distribution are compared in Table 3 (Sang and Blecha, 2009).

Table 3 The number of AMP and their primary expression site in pigs, humans, dogs, and chickens (Sang and Blecha, 2009)

Genus	Cathelicidin gene / isoform number	Primary tissue of expression
Sus	11	Leukocytes
Homo	1	Leukocytes, Epithelia
Canis	1	Leukocytes
Gallus	3	heterophiles

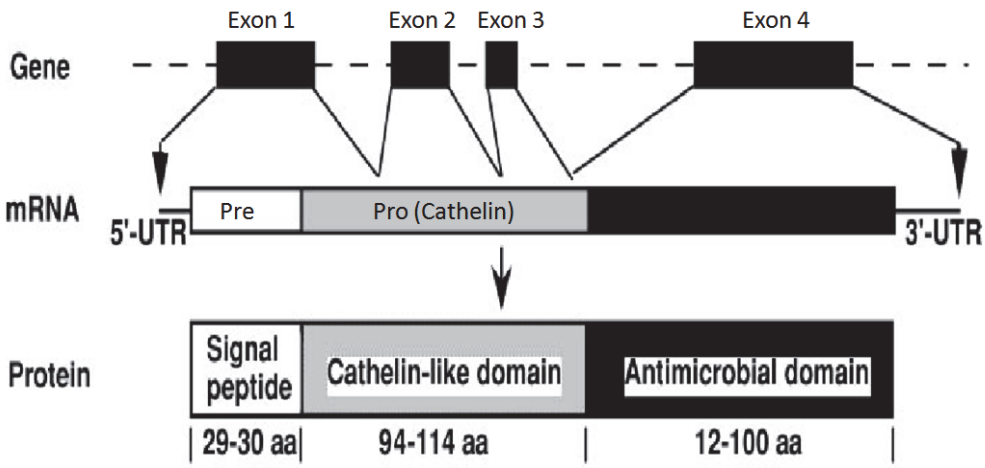

Figure 1 Structural organization of cathelicidin genes and the encoded poly- peptides. Each cathelicidin gene contains four exons separated by three introns. The prepro-peptide is composed of a conserved signal sequence and a proregion, followed by highly heterogeneous mature peptide with antibacterial activity. Exons 1-3 encode the 5'-untranslated region (UTR) and the prepro-sequence, and exon 4 encodes several final residues of the proregion and the mature peptide sequence as well as 3'-UTR. The map is drawn to scale (Yang et al., 2004)

(2) Defensins

All defensins are cationic, lacking glycosyl- or acyl- side-chain modifications, and contain six highly conserved cysteine residues which form three pairs of intramolecular disulfide bonds (Kloman and Chang, 2006). On the basis of their size and pattern of disulfide bonds, mammalian defensins can be categorized into three subfamilies: α-, β- and θ-defensins (Yang et al., 2002 ; Yang et al., 2004). α- and β-defensins are differentiated based on cysteine pairs (C1–C6, C2–C4, and C3–C5 for α-defensins and C1–C5, C2–C4, and C3–C6 for β-defensins) and the conserved spacing pattern of their canonical six cysteine residues. θ-Defensins are small (18 amino acids) circular peptides without a free N- or C-terminus. The disulfide paring of θ-defensins is different from α- and β-defensins, because θ-defensins are formed by two hemi-α-defensins with each contributing three cysteines. Several structures that are representative of the three families have been solved (Ganz, 2003).

4. Antimicrobial activity and action mechanism of AMPs

AMPs contain broad-spectrum antimicrobial activities against Gram-positive and Gram-negative bacteria, mycobacteria, fungi, and enveloped viruses. How do AMPs exert their antimicrobial activity? The antimicrobial and cytotoxic properties of the AMPs are believed to be associated with their pore-forming activities, as multimers, in the target membrane, leading to the loss of cellular function and cell-death. The structure-function models of Shai-Matsuzaki-Huang (SMH) provide a reasonable

explanation for the antimicrobial activity of most of these compounds (Linde et al., 2008).

Since cationic AMP's activity is based on its interaction with the microbial membrane to induce membrane destabilization, how can they avoid causing toxicity to the host cells? To address this point, several hypotheses have been proposed. One explanation is that AMPs produced by mammals do not act on eukaryotic cells because of the presence cholesterol in eukaryotic membranes. The outer layer of the membranes of eukaryotic cells is composed mainly of lipid molecules without charged group; and most of the lipid molecules with negatively charged groups are segregated into the inner layer with the charged group facing the cytoplasm (Zasloff, 2002). This is different from the bacterial membranes, which have the negatively charged lipid molecules existed both on the outer and inner membrane layers (Bolinteneanu et al., 2009).

5.Immuno-regulatory activity

The minimal inhibitory concentrations (MIC) of AMPs against microbes *in vitro* are typically much higher than the physiological concentrations of AMP peptides found *in vivo* under resting conditions (Lai et al., 2009). For instance, the concentration of cathelicidin LL37 in human is less than 2 μg ml^{-1} at mucosal sites, whereas the MIC of LL37 *in vitro* for *E.coli* is more than 32 μg ml^{-1}. Thus, the question arises; how do AMPs exert their antimicrobial function *in vivo* if the effective concentration is too low? One plausible explanation is that they act synergistically with other classes of AMPs to enhance their desired cytotoxic effect. For example, LL37 can act with β-defensin 2, lysozyme and lactoferrin to exert optimal killing. Another plausible explanation is that, in situations of inflammation, AMPs often accumulate at a high local concentration above the MIC, thus can acting alone as a classic AMP. However, increasing evidence indicates that some AMPs can confer protection by an indirect mechanism and not simply by killing microbes. They can function as potent immune regulators, altering host gene expression, acting as chemokines and/or inducing chemokine production, inhibiting LPS- or hyaluronan-induced pro-inflammatory cytokine production, promoting wound healing and modulating the responses of dendritic cells or T cells of the immune system.

6. Potential application and limitation of AMP as an alternative to antibiotics

Since the discovery of penicillin, an enormous number of antibiotic compounds have been isolated. Antibiotics have been used in treating microbial infections in human, animals and plants. It is also widely used in animal feed additives. The use of low level antibiotics in livestock feeds to promote growth could have undesired consequences. The fear is the developing of antibiotics-resistant bacteria in animals, which can pass on to human, and thus reducing antibiotics' effectiveness in treating human diseases.

Because many AMPs kill bacteria by disrupting their membrane integrity and are thus thought to be less likely to induce resistance, AMPs are being extensively evaluated as novel antimicrobial drugs in the feed additives.

Currently, addition of antibiotics in animal feed is discouraged or forbidden. Animal feeds containing antibiotics may lead to public health problems, such as the appearance of antibiotics-resistant bacteria and existence of antibiotic residues in the meat (Vaara, 2009). In addition, the recent trend of animal farming involves the use of green and safe production of animal feed. The development of high-efficiency, antibiotics-free and environment-friendly feed additive is an important field of research. For example, several reports have shown beneficial results of incorporating different source of AMPs in the feed or as water additives. These include the increased protection against a variety of bacterial pathogen during the first week of hatched chicks (Michael et al., 2010), improved growth performance and intestinal mucosal immunity (Bao et al., 2009; Kogutm et al., 2010), and inhibited replication of infectious bursa disease virus in chicks embryo (Sun et al., 2010).

Animal production facility in Taiwan has been employing the high-density feeding system for many years. To gain better growth performance, most of the feeders rely on feeds containing antibiotics to protect animals from diseases. The incidence of antibiotic-resistant bacteria is higher in Taiwan than other countries in the world (Lauderdale et al., 2004). For instance, *Salmonella* in livestock was reported to resist a variety of antibiotics. How do we improve the immunocompetence of animals in an environment full of antibiotics-resistant microorganisms? The unique and novel feed additive, AMPs, could plays an important role in reducing animal mortality and enhancing animal welfare for the next generation of animal farming strategies.

There are limitations to be solved when applied in domestic animal, because AMPs are peptide. Firstly, AMPs may be labile when incorporated in feeds, some harsh processing conditions, such as pelleting, dietary salt content, and storage temperature may inactivate AMPs. Secondly, low pH value of gastric acid and degradation by endogenous enzymes, pepsin and trypsin , may also inactivate AMPs. Thirdly, the most critical point of AMPs production is cost for gene cloning, fermentation and purification steps, which will be the limiting step in large scale application in farm animals.

7. Examples of practical use of AMP: β-defensins

A series of references which focus on practical application of β-defensins are listed in Table 4.

Table 4 Efficacy of β-defensins during practical application

Species	Testing system	Effects	References
Chicken			
β- defensin 1 β- defensin 2 β- defensin 7	In vitro	Showed antibacterial to Gram positive and negative strain.	Derache et al., 2009
Quail, Chicken			
β- defensin 10	In vitro	Anti-Gram positive and negative bacterial, but no significant effect on *Salmonella cholerasui s*and *Proteus mirabilis*	Ma et al., 2012
Duck			
β- defensin 7 β- defensin 10	In vitro	Anti-*Staphylococcus aureus* under a range of different temperature and pH value	Ma et al., 2009
β- defensins	In vitro	Against *Micrococcus luteus* and *Escherichia coli* at MIC 3.7μM, and anti-*Reimerella anatipestifer* at 2.3μM	Soman et al., 2009
Piglets			
β- defensin 1	In vitro	Showed strong anti-*Bordetella pertussis* at 500 μg, but no effect on *B. brochispetica* bactericidal activity	Elahi et al., 2006
AMP-p5	In vivo	Improved growth performance at 60 μg/kg in diets, and apparent total tract digestibility, reduce coliform in intestine	Yoon et al., 2012
Pig			
β- defensin 2	In vitro and in vivo	Killed *Salmonella*, *Listeria* and *Erysipeloidrix* at 4-8μM, complete killing *Salmonella typhimurium* in 90 minute	Veldhuizen *et al*., 2008
β- defensin 3 β- defensin 4	In vitro	Inhibit PRRS viral infectivity in MARC-145 cells, and suppressed PRRSV titer in areolar macrophage at 5-40 μg/ml	Sang et al., 2009

Porcine defensin pBD-2A from intestine was found to possess anti-microbial activity (Veldhuizen et al., 2008). The synthetic peptide corresponding to the mature protein showed a high antimicrobial activity against a broad range of pathogenic bacteria, while it only showed limited hemolytic activity against porcine red blood cells. Highest activity was observed against *Salmonella typhimurium*, *Listeria*

monocytogenes and *Erysipelothrix rhusiopathiae* (Veldhuizen et al., 2008). pBD-2 at 4 to 8 μM killed these pathogens within 3 h. The activity of pBD-2 against *S. typhimurium* was studied in more detail. At the minimum bactericidal concentration of pBD-2, complete killing of *S. typhimurium* was relatively fast with no viable bacteria left after 90 min. However, antimicrobial activity of pBD-2 was decreased at higher ionic strengths with no residual activity at 150 mM NaCl (Zhang et al., 2000). Transmission electron microscopy of pBD-2 treated *S. typhimurium* indicated that relatively low doses of pBD-2 caused a retraction of the cytoplasmic membrane, while pBD-2 concentrations close to the MBC led to cytoplasm leakage and complete lysis of bacterial cells.

Avian antimicrobial peptides, classified as β-defensins, have been identified from bloods of chicken, turkey and ostrich, epithelial cells of chicken and turkey, and stomach contents of king penguin. Avian β-defensins play an important role in the innate defense system because avian heterophil lacks oxidative mechanisms. Oxidative mechanism consists of superoxide ion, hydrogen peroxide, and myeloperoxidase and non-oxidative mechanism consists of a few enzymes, cationic proteins, and peptides. Avian heterophils lack of superoxide ion and myeloperoxidase, therefore, they rely more on the non-oxidative mechanisms that include lysozyme and microbial peptides (Harmon, 1998).

The study by Meade et al. (2009) on avian heterophil β-defensins has shown activities against a number of microorganisms. Sugiarto et al. (2004) have demonstrated that avian heterophil β-defensins have antimicrobial activity against Gram-positive, *Staphylococcus aureus*, and Gram-negative bacteria, *E. coli.* However, only some peptides, such as the chicken and turkey heterophil peptides, have antimicrobial activity against *C. albicans.*

CONCLUSIONS

AMPs are the important effectors of the innate immune system. They are major participants in the host defense against microbial infection, such as bacteria, mycobacteria, fungi, and viruses. New research has also focused on the multifunctional role of AMPs, including the immuno-regulatory activity. This activity is related to chemotactic activity, neutralization of pro-inflammatory cytokines, anti-endotoxin activity, and wound healing. These functions complement their antimicrobial action and favor resolution of infection and repair of damaged epithelia. As a result, AMPs have a great potential for application in animal feeding and provide the basis for the design of novel feed additive in domestic animals. However, the cost of AMPs production is a main concern now, as chemical synthesis is costly. Gene cloning and expression approaches using microorganism, tissue culture, transgenic animals or plant as the expression host, might be a competitive and efficient way of producing AMPs. Lastly, the optimal dosage and treatment duration of different AMP to replace antibiotics in domestic animals diet or drinking water remain to be elucidated.

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抗菌胜肽特性及其作為飼料添加物之應用

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摘要:抗菌胜肽爲重要之先天性免疫作用者，抗菌胜肽含有廣泛的抗菌範譜，可對抗革蘭氏陽性菌、陰性菌、分枝桿菌、真菌及病毒。 其普遍表現在各種家畜禽特異性細胞或組織。近年來，抗菌胜肽之免疫調節特性被廣泛研究，包括趨化作用、中和促發炎細胞激素、抗內毒素活性、促進傷口癒合及啓動後天性免疫反應等。因此抗菌胜肽所扮演之多功能角色，可開發作爲新穎性飼料添加物之基礎，本文針對宿主防禦性胜肽進行文獻回顧並探討其應用於家畜禽飼養時替代傳統抗生素之潛力。

(關鍵語: 抗菌胜肽、家畜禽、飼料添加物)

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