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Research Progress on the Structure and Function of Antioxidant Peptides Derived from Amphibians: A Review

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***Abstract.*—The amphibian skin is not only a coating; it consists of a system of activities related to respiration, osmosis, and thermoregulation and, because of that, enables the creature to survive on land. Besides that, the skin synthesises a broad array of bioactive compounds that act as defences against the environment and pathogenic agents. Still, they also play a wide range of other biological roles. Antioxidant peptides in the amphibian system can hinder lipid peroxidation and defend the body against free radical attacks. Thus, when the normal balance of oxidative stress is broken by excessive production of free radicals, the intake of sufficient amounts of antioxidant peptides may reinstate the imbalance, and, therefore, minimise the risk of developing a disease. However, this is the least developed field and the research on antioxidant amphibian peptides is particularly underrepresented in the literature. The current paper provides an overview of the structure and function of antioxidant peptides in amphibian skin, aiding in a better understanding of how particular species have evolved defences against environmental assault and the future development and utilisation of amphibian antioxidant peptides.**

Keywords. Amphibians; Antioxidant peptides; Structure and function

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Introduction

Amphibians are diverse and may be found almost anywhere on Earth, such as the southern end of the Arctic Circle. Throughout the lengthy evolutionary history of amphibians, amphibian skin has played an essential role in safeguarding against environmental dangers and ecological sensitivity. Certain functions of the skin involve: breathing, moisture retention, microbial invasion prevention and excretion (Clarke, 1997). The amphibian skin of the face is easily distinguished by the absence of any perceptible scales or hair, in comparison with the skin of other parts. It is richly endowed in glands, primarily of various mucous or granular character. The primary role of these mucous glands is to provide biochemical metabolic components to the amphibians via their secretions (Kang et al., 2022). Active peptides and biogenic amines are the most common of these. In addition, the active peptides in amphibian skin are much more diverse than the active peptides in mammals (Clarke, 1997; Li et al., 2007), and here the research of active peptides has an enormous potential, which has received significant attention in the last few years in physiology, chemistry and pharmaceutics.

The Sebaceous Glands of Amphibians

The amphibian's dermal region is located beneath the epidermal region, and it consists of two strata: loosely organised spongy and densely organised compact. These are anatomically associated with the structures of the human skin known as the papillary and reticular layers (Felsemburgh et al., 2009).

Mucous and granular dermal glands are abundant on the amphibian dermis (Hoogmoed, 1988; Wells, 2010). These glands secrete glycosylated mucus and

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mucopolysaccharides that are significant in preventing dehydration through skin hydration (Schumacher et al., 1994). The poison or serous glands, also known as granular glands, produce different types of poisonous materials to defend themselves against predators. They contribute to the synthesis of numerous bioactive molecules too, including immunoglobulins, lysozymes, neuropeptides and antimicrobial peptides (Ramsey et al., 2010; Rollins-Smith & Conlon, 2005; Rollins-Smith et al., 2011). The adrenergic receptors are enclosed by myoepithelial cells covering the glandular structures. Myoepithelial cell contraction in response to adrenaline or Noradrenaline secretion causes glandular contents at the skin surface to be released in times of stress. It is a very crucial stress-protective amphibian secretory mechanism (Gammill et al., 2012; Smith et al., 2018; Woodhams et al., 2014). By 2015 over 2,000 amphibian skin peptides were known (Xu & Lai, 2015). Besides antimicrobial and antifungal action, there are many other biological activities of skin peptides. They can be classified into different categories, depending on their activity: opioids and others, bradykinins (Bevins & Zasloff, 1990; Laux-Biehlmann et al., 2013; You et al., 2009).

Bioactive Peptides and Peptide Diversification

Furthermore, their regulatory functions span nearly every aspect of human physiological processes, including the nervous system, circulatory system, digestive system, endocrine system, and other vital systems. However, with the onset of the 21st century and the continued advancement of modern medical and health technologies, some medical researchers have discovered that the hydrolysis of peptide proteins in the digestive tract is a consequence of a pro-oxidative reaction of lysosomes in the intestine (Bhat et al., 2015; Jin et al., 2009). Most peptides are taken up and utilized in the form of oligopeptides (formed in 2-6 amino acids) rather than as free amino acids by the body. Through scientific experimentation and research over the years, scientists have arrived at several discoveries about the new physiological and biochemical regulatory functions, such as antioxidant activity, regulation of blood pressure, antimicrobial effects, immune and central nervous system regulation, digestion and absorption of macro- and micro-nutrients, and regulation of calcium and mineral metabolism in the digestive process (Chen & Lin, 2005; Gill et al., 1996; Toldrá et al., 2018) Ambibians contain skin-active peptides, the discovery of which has been a hot research in recent years.

Antioxidant Peptides Derived from Amphibians

Amphibians have also undergone an evolution process between water and terrestrial life and hence their skin is exposed to the outside environment and harmful UV rays. The way in which they prevent oxidative risks and reverse the damage done by the free radicals concerns different researchers. In previous studies, bioactive peptide antioxidant compounds have been shown to scavenge free radicals effectively, maintain regular cell organelle activity and help the organism to maintain homeostasis (Karadag et al., 2009). It has been suggested that such antioxidant peptides constitute the third line of defense alongside numerous antioxidant enzymes and low-molecular-weight antioxidants. However, the details of this new defense system remain unclear; and hence, they must be examined further (Yang et al., 2009). Only 11 antioxidant peptides have been isolated in amphibian skin secretions by others. These antioxidant peptide groups belong to various families, and the comparison of the primary structures revealed that these groups are comparable in the signal peptide regions. In the meantime, the significant differences were in the mature peptide sequences that led researchers to suggest that these antioxidant peptides may be of a common origin (Liu et al., 2010). Additionally, previous researchers have found that some antioxidant peptides of multiple family types are formed primarily by the skin and secretions of giant green frogs and wood frogs (Zhang et al., 2016). These antioxidant peptides can effectively scavenge most of the free radicals. The discovery of antioxidant peptides within the skin and secretion of amphibians has led to new applications in pharmaceuticals and medical research.

The Structure of Antioxidant Peptides Derived from Amphibians

Even at this stage there are very few reports as to the close relationship between active peptides and their molecular structures. However, some peptides are strongly correlated with the molecular weight.

Molecular Weight

The antioxidant properties of the oligopeptides are higher than those of their parent protein and the polypeptides containing 10-50 amino acids, primarily because the oligopeptides consist of 2-10 amino acids. The lipid radical scavenging activity of low-molecular-weight bioactive peptides is significantly higher in comparison to that of high-molecular-weight bioactive peptides. As an example, Lee et al. (2012) explored the peptides secreted by the skin of the Chinese toad (Bufo gargarizans) using LC-MS/MS and RNA sequencing and bioinformatics. Their results indicated the enhanced cell-killing, antioxidant and antibacterial potential of bioactive peptides in the mass range of 0.7 to 4 kDa.

Amino Acids

The antioxidant capacity of bioactive peptides also depends on the types and composition of amino acids. This is a better known influencing factor. Additionally, each of these differences in peptide sources, hydrolytic

enzymes, and hydrolysis methodologies lead to a large spectrum of variations in the molecular makeup, structure, and organization of amino acids to create peptidic antioxidants. Furthermore, cysteine contains a functional group, the thiol group, which can react directly with the free radicals and demonstrate specific antioxidant activity (Nagasawa et al., 2001; Qian et al., 2008; Rajapakse et al., 2005; Wang & de Mejia, 2005).

The arrangement of amino acids, along with the presence of specific amino acids, influences the antioxidant power. An example is the Yunnan pond frog proteins (pleurain), 10-member antioxidant proteins, some of which may also be antibacterial and anti-inflammatory, found in the Yunnan pond frogs, *Amolops wuyiensis*. The strongest antioxidant peptide RP1 in Yunnan pond frog contains most antioxidant amino acids. There are also two tyrosine residues present in RP1 (Tyr6 and Tyr12), which support antioxidant activity. Therefore, it is arguable that the chemical properties of the tyrosine residues, besides their position, impart different antioxidant properties (Nagasawa et al., 2001; Yang et al., 2009).

N-terminal peptides of histidine also possess greater metal ion chelation capacities than C-terminal peptides of histidine. It has been discovered that the addition of specific amino acids to dipeptides has a positive influence on their antioxidant activities (Nagasawa et al., 2001). Conversely, other researchers find that the antioxidant properties of amino acids may also decrease depending on the variation in the peptide bonds and peptide structures. Accordingly, it is a two-sided sword since, on the one hand, the structures of the bioactive peptides can change under antioxidant conditions, and, on the other hand, they can act in a synergistic or antagonistic manner (Hernández-Ledesma et al., 2005).

Hydrophobicity

The antioxidant peptides of different origins exhibit considerable differences in hydrophobicity, and this leads to a range of antioxidant effects. These non-polar side chains augment the association with the hydrophobic unsaturated fatty acids and, thus, prevent the liberation of lipid hydroperoxides and the chain reaction of lipid peroxidation.

It is on this basis that we can conclude that the scavenging capacity of antioxidant peptides may increase with an increase of hydrophobicity, as by so doing the peptides may approach hydrophobic lipid radicals. Some research (Bousset, 2002) indicates that the antioxidant activity of bioactive peptides is not affected by the absence of an N-terminal or C-terminal amino acid (including histidine or lysine). Synergetic or antagonistic effects on antioxidant activity of the peptides may be observed, however, depending on the presence or absence of N-terminal or C-terminal amino acids. Therefore, the impact of terminal amino acid deficiency should also be considered in the study of the antioxidant property of terminal amino acids to provide information on the relationship between the properties of the terminal amino acids in the antioxidant peptides and their antioxidant activity against different substrates.

4.4 Peptide Conformation

The antioxidant activity of bioactive peptides depends also on the spatial organization (associated studies indicate) of bioactive peptides, i.e., on the secondary and disulfide bonds and hydrophobicity. Moreover, the reduced cysteine (-SH) in the primary structure of peptides enhances the antioxidant capacity of the peptide because the thiol group (-SH) of cysteine has a high antioxidant potential compared to tyrosine, methionine, proline, and tryptophan. Chen et al. (2013) replaced histidine-histidine-proline-leucine (HHPL) or leucine-histidine-proline (HHLP) with histidine-leucine (HL), also significantly decreasing the antioxidant activity. The activity of the two peptides was greatly diminished when proline was replaced with D-histidine. The antioxidant properties of histidine-containing peptides were reduced considerably, indicating that the peptide bonds, amino acid sequence, and peptide structure influence the properties of bioactive peptides. Similar results were obtained regarding the free radical scavenging ability of carnosine and other histidine-containing dipeptides by the electron spin resonance method (Chan et al., 1994). Moreover, structure modification of amino acid residues also has an impact on the antioxidant property of bioactive peptides. Replacement of L-histidine with D-histidine reduces antioxidant activity, studies have found (Chan et al., 1994), possibly due to the position, orientation and the spatial potential of the imidazole ring.

This also provides a reason why the study of the functions and mechanisms of antioxidant peptides should be conducted in the future.

Functions of Antioxidant Peptides Derived from Amphibians

Amphibian-derived antioxidant peptides are the natural forms of antioxidant compounds, which can not only effectively scavenge excess free radicals in the body, but also prevent the formation of free radicals, minimising the damage caused by excessive free radicals. These peptides inhibit the chelation of saturated fatty acids, peroxidation, and heavy metal peroxide ions (Chen et al., 1996; Duan et al., 2014).

Direct Scavenging of Reactive Oxygen Species (ROS)

As shown in the past, antioxidant peptides have a better scavenging ability of free radicals and, since they are natural antioxidants, they are not harmful to the body, thus making them the best free radical scavenging agents. Antioxidant capacity of the peptides is determined by the ability of the peptides to donate hydrogen atoms as well as their stability. The simpler and more stable the

antioxidant peptide is, the more likely it is to act as an intermediate, trapping the free radical chain and breaking it, thereby enhancing its antioxidant activity. It has also been established that the corresponding individual amino acids, which are part of bioactive peptides, possess antioxidant action to a far lesser extent than the whole peptide and hence the overall activity of the entire peptide is significantly higher than that of the individual amino acids.

Yang et al. (2016) simulated the UV radiation inside the home of the Yunnan odorous frog by subjecting the skin of the frog to UVB radiation (1600 μW/cm²) over a period of 9 hours. Then they quantified the free radical scavenging capacity of the skin secretions through the ABTS assay and noted that the antioxidant activity of the skin secretions did indeed increase to a peak of 99% in 5 hours. Cao et al. (2018) identified a novel antioxidant peptide, Cathelicidin-OA1, which exhibits 90% ABTS radical scavenging capacity at 32 μM and 90% DPPH radical scavenging capacity at 128 μM. In addition, the antioxidant activity of 18 families of peptides was tested by Wang et al. (2017) with the assistance of the ABTS and DPPH radical scavenging procedures. They found that the different peptide families were not equally active as antioxidants, as they differed in their primary structures. Although the scavenging rate of ABTS and DPPH was low at this concentration level, even after 30 minutes, the reaction rate between ABTS and DPPH increased significantly to 30.1, 48.9, 77.1, and 20.1 per cent after 14 hours.

Inhibition of Lipid Peroxidation

In the metabolism of organisms, lipid peroxidation and oxygen-free radicals play an essential role. They possess diverse biochemical and immune reactions in the normal state of affairs. However, when the dynamic balance is disrupted, metabolic diseases and immune dysfunction could occur, and a chain reaction of free radicals called lipid peroxidation can happen.

Qian et al. (2008). Our group could hydrolyse the skin of American frogs (Lithobates catesbeianus) with the help of alkaline proteins, neutral egg glands, papain, condensin and trypsin. The antioxidant activity of these hydrolyses was measured by inhibition of lipid peroxidation and by direct removal of the free radicals. Lipid peroxidation is inhibited by the antioxidant peptides formed during the extraction of frog skin proteins compared to the positive control group (tocopherol). These peptides also inhibit various types of radicals, including DPPH radicals (IC kid ⁻ 16.1mu), hydroxide radicals (IC kid ⁻ 12.8mu), and superoxide radicals (IC kid - 34.5mu) (IC kid - 32mu).

A strong interaction of the chelating molecules with the metal ions can lead to the incorporation of metal ions into antioxidant peptides of amphibian origin and subsequent generation of stable high-molecular-weight products. It will prevent the release of metal ions and can be used in detoxification, pollution control, and dye fixation. Carnosine and glutelin are demonstrated to be antioxidants and will inhibit the oxidation of lipids by metal ions, singlet oxygen and haemoglobin. These peptides are capable of chelating metal ions, specifically copper and iron ions, and thereby suppress non-metal ion-catalysed lipid oxidation reactions.

Prokić et al. (2016) discovered that heavy metal (Cd, Cr, Cu, Fe, Hg, Ni, Pb, Zn) does not affect the oxidative stress system in the frog Pelophylax kl. esculentus. They used two frogs of different degrees of pollution and contrasted the activity of their antioxidant defense enzymes. The results showed the activity of antioxidant enzymes in the frogs in the more polluted region to be greater, attributable to the metal ion-chelating influence of the antioxidant peptidoglomerates in their bodies.

Activation of the Endogenous Antioxidant Defense System

Antioxidant enzymes in the human body are a significant part of the body's antioxidant defence, which is inherent to the human body. These enzymes are primarily: SOD (superoxide dismutase), CAT (catalase) and GP-x (glutathione peroxidase). They discovered that the antioxidant peptides secreted in the skin of the Yunnan odorous frog (Odorrana grahami) might be helpful in the prevention of the deterioration of antioxidant enzymes under the impact of UVB radiation (Yin et al., 2019). The researchers exposed the mice to UVB radiation on their backs and subsequently measured the quantity of antioxidant enzymes in the skin tissue. Their findings also indicated that the SOD level as well as the GSH level had increased to 80 per cent and 67 per cent respectively using the antioxidant peptides. These results suggest that these peptides are capable of activating the antioxidant system within the body.

Summary

Although the mechanisms of the protective effects of skin peptides are not fully understood, it is necessary to mention that most of these molecules are antioxidants, in reference to the primary structure of reduced thiol groups (-SH) in cysteine. Notably, it is already known that oxidative stress is associated with overproduction of mitochondrial reactive oxygen species (ROS) and excitement of inflammatory cytokine generation. Therefore, localization of cysteine can specifically trigger other processes in the cell that are not necessarily associated with the oxidative stress defense. The skin peptides identified to have antioxidant and anti-inflammatory properties could be the primary defence mechanism of amphibian skin under extreme UV (ultraviolet) radiation scenarios, as the UV radiation can lead to the formation of ROS in the keratinocytes. Although significant progress has been made in researching antioxidant peptides derived from hydrolysed plant and animal proteins, both domestically and internationally, the study of their properties remains incomplete. Even though natural sources of antioxidant

peptides are abundant, given the fact that most plant and animal proteins can be hydrolysed under favourable conditions to release antioxidant peptides, the science and technology of antioxidant peptides is still in its infancy. Antioxidant studies are often performed in vitro studies to learn about the activity of antioxidant peptides, such as free radical scavenging experiments, but not in vivo experiments. In addition, there is minimal documentation concerning the structure and function of antioxidant peptides produced by amphibians. However, it is an essential point because understanding the structure-activity correlation of antioxidant peptides enables the creation and production of the most active antioxidant peptides. Therefore, it can be concluded that the research on antioxidant peptides in China is far from complete, and it is these gaps that future research and discoveries may be made in the field of antioxidant peptides.

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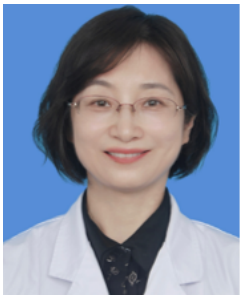

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