Scorpion venom as antimicrobial peptides (AMPs): A review article

Abstract

The high level of reported multidrug resistant pathogens with the failure of most conventional antibiotic to kill many of them arise the global concern in the last decade to find alternatives urgently. Many researches have been conducted on scorpion venom biological characteristics, and its different antimicrobial peptides had been reported in literature since the last decade. Here short overview of all scorpion AMPs with antibacterial activity, their structural determinants, classification types and their mode of action, in addition to their resistance mechanism and finally their therapeutics potential.

Keywords: Antimicrobial peptides (AMPs), Scorpion venom, Antibacterial activity, therapeutics potential.

Introduction

Scorpions are one of the most ancient animals living on planet earth, having survived over 400 million years, a time span that would impose several environmental pressures on the scorpions to evolve anatomically, conversely scorpions have conserved their morphology almost unaltered[1] which is mainly attributed to their development of a set of an efficient venom weapon to support their needs for prey and defense they are widely distributed all over the world and are represented by over 1500 species[2].

Scorpions venomous glands contains a wide range of biological active molecules like enzymes, lipids, nucleotides, biogenic amines and other unknown molecules[3,4], also contains a large number of diverse peptides with different biological activities that are believed to be an integral component of an innate immune system that serves to protect the scorpion and its gland against variety of pathogen [5,6]. One of the most comprehensive methods to classify scorpion toxins is based upon their structural and biological features and by applying this method they can be classified into two major groups the disulfide bridged peptides (DBPs) reported to block the ion channels, including four types of toxins: K-, Cl-, Ca$^{2+}$ and Na$^{+}$ channels blockers[7,8] and thenon-disulfide bridged peptides (NDBPs) is a less abundant group of peptides without disulfide bridges gain interest recently, they represent a wide range of biological activities like bradykinin potentiating,
Anticancer, hemolytic, anti-inflammatory, immune-modulatory and antimicrobial activities[9,10,11].

Many scorpion anti-microbial peptides had been functionally characterized in the last decade. Here quick overview of all scorpion AMPs with antibacterial activity, Structural Determinants, classification, mode of action, resistance and therapeutics potential.

**Antimicrobial peptides (AMPs)**

Antimicrobial peptides are one of the innate immune system components in a wide range of eukaryotic organisms like human, plant and insects; they play a vital role in early immune defense mechanisms against pathogens [12]. Defensins a peptides found inside human neutrophils consist of 18-45 amino acid residues long, play a role in killing phagocytosed bacteria by membrane destruction and pore formation were the first antimicrobial peptides discovered on 1966 [13]. Since that time till now many AMPs with antibacterial activity have been isolated and functionally characterized from different scorpions species venoms (Table 1) [14].

These groups of peptides have been named host defense peptides after the discovery of additional immunological activities of it or in other way called HDPs to assess its multiple functions in innate immune system, also when these peptides have reported to have a direct antimicrobial activity they refer to it as cationic antimicrobial peptides [15].

Antimicrobial peptides are short in length consist of amino acids ranging from 10 to 50 residues[16], with a net positive charge ranging from +2 to +9 and the proportion of hydrophobic residues are equal or more than 30% of total amino acids residues[17], the positive amino acid residues are separated by patches of hydrophobic amino acids by this arrangement AMPs prevented to fold into amphipathic or amphiphilic structure usually at the contact with membranes or membranes mimics [15].

Because of AMPs sequences are highly diverse and there are many sequence similarities so classify AMPs according to sequence a rise many difficulties specially when trying to put peptide in different and specific classes. One of the most used techniques for classification is based on structural motifs homology [19]. Based on structural motifs homology, AMPs are classified into four main groups: more common groups α-helical peptides and β-sheet peptides, less common groups extended peptides and loops peptides among these α-helical peptides are the most studied group till now [20].

Scorpion AMPs with antibacterial activity against gram positive and gram negative bacterial strains had been documented by measuring the minimal inhibitory concentrations. Also some of these peptides have potent antibacterial activity while others have mild activity can be easy concluded from higher MIC values (Table 1) [14].

**Structural determinants of antimicrobial activity**

There are five interdependent types of structural components that determine the AMPs activity in which change in one factor affects the others [18]

**Conformation:** There are different ways to classify AMPs based on different criteria like peptide source, peptides precursors and peptides enrichment in one or more amino acids and based on other parameters [19]. AMPs vary in primary sequences and in origins but share some common structural motifs in their three dimensional topology they classified accordingly to two large groups α helical peptides and β sheets peptides, the other are less common groups contains loop peptides and extended peptides. The three dimensional structure is one of the factors that determine the activity and toxicity of AMPs by playing a role in the pore
Table 1. List of all antimicrobial peptides with corresponding scorpion species and length as number of amino acids with MIC values for both Gram negative and Gram positive strains

<table>
<thead>
<tr>
<th>Scorpion</th>
<th>AMPs</th>
<th>Length</th>
<th>MIC (µM) Gram positive</th>
<th>MIC (µM) Gram negative</th>
<th>Reference</th>
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<tr>
<td><em>Hadrurus aztecus</em></td>
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<td>1.3–5.2</td>
<td>20.8–20.8</td>
<td>[58]</td>
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<tr>
<td><em>Pandinus imperator</em></td>
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<td>24</td>
<td>2.4–4.8</td>
<td>19.1–38.2</td>
<td>[58]</td>
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<td><em>Opistophthalmus carinatus</em></td>
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<td>44</td>
<td>12.5–50</td>
<td>1.6–50</td>
<td>[59]</td>
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<td>BmKb1</td>
<td>18</td>
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<td>18.1–90.8</td>
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<td><em>Opistocactus madagascariensis</em></td>
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<td>0.7–16.6</td>
<td>3.3–150</td>
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<td>0.25–2.9</td>
<td>6.2–50</td>
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<td>&gt;320</td>
<td>[28]</td>
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</table>
formation after the initial attachment of peptides to microorganisms membranes [23,21].

**Charge:** Positive charge of cationic AMPs play an important role in the initial electrostatic attachment to the targeted negatively charged membranes components like acidic phospholipids, LPS and teichoic or teichuronic acid of gram negative and gram positive bacteria [15]. Many of AMPs are reported to have a net positive charge ranging from +2 to +9, there is a direct relationship between peptides net positive charge and activity within limited range differ in different peptides, increase the charge up the limit or decrease it below the limit resulted in the loss of optimum activity [24].

**Amphipathicity & hydrophobic moment:** Amphipathic molecule defined as molecule structurally contains both hydrophilic and hydrophobic domains, one way to express amphipathicity quantitatively by hydrophobic moment which defined as the sum of all amino acid residues hydrophobicities [25]. With respect to the interdependent relationship between structural components that determine HDPs activity, when the hydrophobic moment increased the activity of HDPs toward pathogens negatively membranes increased with a remarkable higher activity against neutral or zwitterionic membranes [26].

**Hydrophobicity:** Defined as the percentage of hydrophobic amino acid residues compared with peptide total amino acids residues, approximately 50% of hydrophobicity needed for optimum HDPs activity toward microorganism’s membranes and any increase over this percentage resulted in loss of antimicrobial specificity of HDPs [18].

**Polar angle:** Polar angle in amphipathic helix is defined as the proportion of polar sides compared with nonpolar ones. When polar sides decreased the proportion of hydrophobic surfaces increased which leads to increase antimicrobial activity against microorganisms membranes [27].

## Antimicrobial peptides mechanisms of action

The action of antimicrobial peptides toward bacterial membranes initiated by electrostatic interactions with negatively charged components of membranes like strong interaction with LPS in the outer membrane of gram negative bacteria and acidic phospholipids in the outer cell wall of gram positive bacteria, after the initial attachment AMPs aggregated within membranes then destruction of membranes have been achieved by channels (pores) formation [28,29].

The exact mechanism of AMPs action against microorganisms membranes are not fully understood yet for all AMPs. However different models have been proposed previously to explain the process induced by AMPs such as, barrel-stave pore model, toroidal pore model (Figure 1), molecular electroporation and sinking-raft.

**Barrel-Stave pore model:** After the initial electrostatic attachment, the assembly of two or more AMPs in membranes is a critical role for membranes destruction by pores formation [30]. AMPs cross the bacterial membranes and form barrel like pores look like staves in which the hydrophobic part of AMPs is attached to inner lipid bilayer while the hydrophilic part of AMPs are facing the lumen of the pores [21,31].

**Toroidal pore model:** The mechanism of AMPs action as proposed by this model share a common features with the barrel-stave pore model although here the hydrophobic part of AMPs bind not only to the inner lipid bilayer but also to the outer layer, this conformation causing a strain on membranes leading to its destruction [32]. Before AMPs action start to destruct membranes it continuo to aggregate until reach a threshold differ in different peptides defined as the concentration of peptides in compared with membrane lipids concentration (peptides to lipids ratio) [18, 33].
Carpet model: The carpet model propose that AMPs work like detergents, after the AMPs aggregate on the surface of membranes forming carpet structure and reach its defined threshold, the destruction starts and released patched of membrane look like micelles [34,35].

Molecular electroporation: Molecular electroporation suppose that some peptides can form pores in targeted microorganisms membranes by electroporation in which AMPs creates electrostatic potential through the lipid bilayer responsible for pores generation and membrane destruction. These AMPs reported to have highly positively charged amino acids responsible for sufficient charge density to create the electrostatic potential [36].

Sinking-Raft model: As its name implies the model suppose that amphipathic peptides sink and bind to the membrane lipid bilayer, resulted in structurally imbalance. Their mechanism of action may through create temporarily pores with lethal effect on microorganisms [37].

Alternative antimicrobial peptides mechanisms: Most AMPs mechanisms of action have been identified to be pore formation and membrane destruction to the targeted microorganisms. However, other mechanisms rather than pore formation have been identified [33], for example some AMPs identified to act through inhibit either DNA synthesis or protein synthesis or both [38,39,40].

Resistance to antimicrobial peptides

Because microorganisms exposed to AMPs in different tissues of many organisms, the resistance to AMPs is difficult or somehow impossible also microorganism’s mutations to resist AMPs are rare [42]. The resistance to AMPs by human pathogen is recently accepted as one of the microorganism virulence factors, bacterial strains resistant to AMPs
also reported to be highly resistant to conventional antibiotics [43].

Microorganisms have two distant mechanisms to resist AMPs either by constitutive resistance (inherent resistance) or adaptive resistance (inducible resistance) [18], the microorganism’s strategies of resistance depend on counter the peptides mechanisms of action started with peptide electrostatic attachment with negatively charged components of microorganism’s membranes and ended mostly with pore formation led to membrane destruction [33,44].

Constitutive resistance is defined as permanent resistance of microorganisms to AMPs in the presence and the absence of peptides due to the presence of resistance factor always. Microorganisms constitutively resist the action of AMPs by using different mechanisms, for example resistance strains of Staphylococcus aureus contain high D-alanylation of lipoteichoic acid with positively charged amine groups resulted in lowering the membrane negatively charge so lack of electrostatic affinity for AMPs toward membranes [45], another mechanism by membrane energy alteration, studies reports that microorganisms with altered membrane energetic are more resistance to AMPs action than microorganisms with normal membrane energy status, such as Candida albicans a respiratory deficient mutant fungi with membrane energy altered by lowered mitochondrial ATP synthesis [46] and S. aureus with membrane energy altered by constitutively reduced transmembrane potential [47]. Electrostatic shielding mechanism used also by microorganisms to resist the action of AMPs in which membranes have been covered with highly anionic glycocalyx or special capsule resulted in shield the lipid bilayer from AMPs [19].

Inducible resistance defined as the resistance mechanisms temporarily triggered in response to AMPs exposure with greatest aid to assist the survival of microorganisms. Adaptive resistance includes many mechanisms like: extracellular structural modifications, protease mediated microorganism’s resistance, efflux dependent resistance mechanisms, and modification of intracellular targets. Inducible resistance involved two component regulatory systems in many causes for example in gram negative bacteria Pho P/ Pho Q are two components of regulatory systems involved in microorganisms adaptive resistance in which AMPs act as ligands when it bind to bacterial sensory kinase Pho Q initiation of multiple adaptive responses and virulence mechanisms have been started [18].

**Antimicrobial peptides therapeutic applications and drug development**

Pathogenic microorganisms (microbes) have been reported to resist conventional used antibiotics, approximately 70% of bacterial strains that cause nosocomial infections are found to be resistance to one or more conventional used antibiotics also some strains have been reported to be multidrug resistance and other reported to resist almost all approved antibiotics [19]. Because of the structural and chemical nature diversity of AMPs, also the probability of microbes to resist AMPs is much lower than conventional antibiotics, make them a good candidate for a novel drug with antibacterial, anti fungal and anti viral properties [48, 49] also Anti parasitic activity [50] and AMPs may used in treatment of cancer [51,52,53] and HIV infections [54].

As an example pexiganan (analog of magainin-2 peptide), it has been reported to have a very potent activity against foot ulcers of diabetic patient and 90% of treated patient with pexiganan reported to clinically cure or improve in phase III clinical trial [41].

Many pharmaceutical researches have been conducted to introduce AMPs to the market, during pharmaceutical development two main problems...
arise, first the toxicity of AMPs against normal cells are not precisely can be predicted because AMPs targeted membranes lipids bilayer and they don’t have specific targets or receptors, and secondly AMPs don’t meet their primary end points during the development of pharmaceutical research to advanced clinical trials [77]. As an example indolicidin (HDP) synthetic analogue called omiganan, a potent and a wide range in vitro antibacterial and antifungal activities of omiganan have been reported against broad spectrum of microorganisms [55], but when phase III clinical trial has been conducted omiganan failed to targeted the primary ends points [33], another difficulty face the development of clinical trials is the cost of commercial pharmaceutical production, as the one gram of HDPs cost from 100-600 US dollars [56].

References


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