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Review

Scorpion venom components as potential candidates for drug development

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ABSTRACT

Scorpions are well known for their dangerous stings that can result in severe consequences for human beings, including death. Neurotoxins present in their venoms are responsible for their toxicity. Due to their medical relevance, toxins have been the driving force in the scorpion natural compounds research field. On the other hand, for thousands of years, scorpions and their venoms have been applied in traditional medicine, mainly in Asia and Africa. With the remarkable growth in the number of characterized scorpion venom components, several drug candidates have been found with the potential to tackle many of the emerging global medical threats. Scorpions have become a valuable source of biologically active molecules, from novel antibiotics to potential anticancer therapeutics. Other venom components have drawn attention as useful scaffolds for the development of drugs. This review summarizes the most promising candidates for drug development that have been isolated from scorpion venoms.

1. Introduction

Scorpions constitute a very well adapted order of predatory animals that have been living in the Earth for nearly 400 million years (Polis, 1990). They now inhabit virtually every terrestrial habitat, except Antarctica. More than 1700 species have been described to date (Stockmann and Ythier, 2010). The key to their success is the production of potent venoms that they use primarily to kill or paralyze their preys and to deter possible competitors and predators. The expansion of human civilization and the growth of human population have led to increased interaction with these arthropods, frequently resulting in accidents when people get stung (Chippaux and Goyffon, 2008). The immediate pain that the sting elicits and the devastating consequences that the envenomation can ultimately cause in human beings can be credited for the bad reputation of these animals.

The effects of a scorpion sting can vary widely, from just local pain or inflammation to severe clinical complications, including death. The severity of scorpion envenomation is related to the presence of neurotoxins in the venom (see recent review: Quintero-Hernandez et al., 2013). They can block or modify the functioning of their targeted ion channels in excitable cells, which results in autonomic excitation. Scorpion α-toxins cause massive endogenous release of catecholamines. The combination of sympathetic excitation and the release of catecholamines in plasma generates a cascade of physiological events that can progress to arterial hypertension or hypotension, tachycardia or bradycardia, arrhythmia, unconsciousness, pulmonary edema, heart failure and death (Isbister and Bawaskar, 2014). Scorpionism represents a major health problem in several countries. More than 1.2 million scorpion stings are registered globally every year. Despite the fact that only about 30 scorpion species are known to be dangerous to humans, about 3000 stings per year are fatal (Chippaux, 2012).

Scorpions, on the other side, have been used in traditional medicine since the emergence of ancient cultures, mainly in Asia and Africa (Goudet et al., 2002; Shao et al., 2007). Scorpions, their body parts, or their venoms, are claimed to be effective for the treatment of many conditions, including cancer (Das Gupta et al., 2007; Diaz-Garcia et al., 2013; Goudet et al., 2002). With the advent of novel methodologies for the massive study and characterization of venom components, it has become evident that along with toxins, many other peptides are present in the scorpion venoms. Several of these peptides are biologically active and have

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proven to be valuable tools for the development of drugs for the treatment of many important diseases.

2. Scorpion venom components

Scorpion venoms are highly complex mixtures of peptides, enzymes, mucoproteins, free amino acids, nucleotides, lipids, amines, heterocyclic components, inorganic salts and probably other unknown substances. Toxins are the most thoroughly studied scorpion venom components. This is due to their pharmacological action on ion channels and their clinical relevance as neurotoxins. They are disulfide-bridged peptides with a significantly constrained structure. Toxins that act on sodium channels are the most relevant for their effects on mammals, including humans. They can be classified into two main types: α-toxins that delay the voltage-gated Na^+-channel's inactivation, and β-toxins that trigger the opening of the channels at more negative potentials (Rodriguez de la Vega and Possani, 2005). In low doses, α-toxins provoke a strong depolarization of the cell membrane, followed by a drop in excitability. At higher doses they prolong the action potential of excitable cells and induce paralysis and cardiac arrhythmia (Bosmans and Tytgat, 2007). The action of β-toxins results in myoclonic or spastic muscular responses (Chippaux, 2012). Other characterized scorpion toxins act on potassium, chlorine and calcium channels. Though they can display synergistic actions leading to clinical manifestations, their role in human envenomation seems to be subsidiary. Toxins or toxin-related scorpion venom components are best known for their deleterious effects on cells, tissues and organisms, but paradoxically, some of them have been shown to display activities that might be relevant for the development of pharmaceutical drugs. These include antimicrobial, antimalarial, immunosuppressing and anticancer activities.

Among the other components present in scorpion venoms are the non-disulfide-bridged peptides (NDBPs) (Zeng et al., 2005, 2002). The NDBP group represents a major component of the scorpion venoms. Mass-fingerprint studies involving whole venoms have consistently shown that low molecular weight peptides represent more than a third of all the molecular weights that are determined (Rodriguez de la Vega et al., 2010). Since the main research interest was usually shifted towards the higher molecular weight peptides in the toxic venom fractions, the discovery rate of NDBPs was lagging till the last decade, as compared to the available information on toxins. The finding that NDBPs can exhibit relevant biological activities has drawn significant attention from researchers. This, together with the availability of molecular biology techniques, as cDNA library construction, heterologous expression, and lately, RNA-Seq have resulted in the increase of the available information on these small peptides (Quintero-Hernandez et al., 2011). Still, while several hundred toxins have been isolated from the scorpion venoms and described, just a few dozen NDBPs have been characterized thus far (Almaaytah and Albalas, 2014).

The venom components belonging to de NDBP group are small 13 to 56 amino acids-long peptides, with very diverse sequences. Most of them are cationic and display a remarkable structural flexibility. They exist in random coil conformations in aqueous solutions, but readily adopt amphipathic α-helical structures when placed in membrane mimicking environments, such as 50–60% aqueous trifluoroethanol (TFE). Positively charged NDBPs can easily interact with the negatively charged lipid head groups of the biological membranes. The membrane adhesion process drives the formation of the amphipathic helix and the insertion of the hydrophobic residues into the membrane, which leads to their displayed activity (Huang et al., 2010). This mechanism, in which there is no specific molecular target, results in their broad spectrum of biological targets. Several NDBPs exhibit multifunctional activities regardless of the target cells. This stands in sharp contrast with the mechanism of toxin action, since toxins are targeted against specific receptors (ion channels) from specific biological targets.

Several relevant activities have been described for the characterized scorpion venom NDBPs, including antibacterial, antifungal, cytolytic, antiviral, antimalarial, anticancer, bradykinin potentiating and immuno-modulating activities (Almaaytah and Albalas, 2014). This discovery has put the NDBP as very interesting and promising candidates for therapeutic drugs.

Hereafter, we will describe the diverse activities reported for scorpion venom components that could be relevant for the design and development of new pharmacological drugs. The molecules that constitute the most significant and promising candidates will be particularly covered.

2.1. Antibacterial peptides

The emergence of bacteria that are resistant to available antibiotics represents a first-line problem for the world health systems. Several pathogens that were once sensible to antibiotics are now rapidly becoming multi-resistant. Diverse bacterial mechanisms are responsible for the appearance of multi-resistance, including their rapid generation rates and chromosomal mutations, the acquisition of extra-chromosomal mobile DNA elements from other bacteria in the surroundings, together with some intrinsic mechanisms conferring the capacity to expel antibiotics from the cells (Alekshun and Levy, 2007). Once a multi-resistant organism emerges, it spreads in the human population, severely compromising the treatment of infections and thus provoking public health crises. This has reduced the long-term therapeutic value of many classical antibiotics and has forced the search for new antimicrobial candidates able to cope with the bacterial mechanisms of drug resistance (Gould and Bal, 2013).

Antimicrobial peptides (AMPs) are found in a very diverse range of phyla, from bacteria to mammals, including humans (Maroti et al., 2011). More than 2000 have already been described (Wang et al., 2009). In multicellular organisms they constitute primitive and conserved components of the innate immune system, functioning as a first barrier against many pathogens. Thanks to their broad spectrum of activities and targets, rapid action, and the low potential to induce resistance, AMPs have become promising prospects for new antibiotics (Huang et al., 2010; Mookherjee and Hancock, 2007). They kill microbes mainly by membrane-targeting pore-forming mechanisms that are inherently more difficult for microbes to circumvent by developing resistance (Hancock and Sahl, 2006). A significant fraction of the functionally characterized scorpion venom NDBPs displays antimicrobial activities, so they can be considered as AMPs (Almaaytah and Albalas, 2014; Harrison et al., 2014). It is not clear why they are present in the scorpion venom. They could play a synergistic role in facilitating venom activity or be part of the antimicrobial response within the venom gland (Kuhn-Nentwig, 2003). The pair of venom glands present in the last postabdominal segment (telson) of the scorpions has open communication with the environment, which can facilitate contamination by saprophytic organisms of the soil. Thus, scorpions are expected to possess means of defending themselves from the microorganisms present in the environment.

The first AMPs found in scorpion venoms were hadrurin from *Hadrurus aztecus* (now renamed as *Hadrurus gertschi*) (Torres-Larios et al., 2000), scorpine (Conde et al., 2000) and pandinins (Corzo et al., 2001) from *Pandinus imperator*, IsCTs from *Opisthacanthus madagascariensis* (Dai et al., 2001), opistoporins from *Opistophtalmus carinatus* and parabutoporin from *Parabuthus schlechteri* (Moerman et al., 2002). The main drawback of AMPs in general, is their frequent cytotoxicity against eukaryotic cells,