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Review

Scorpion venom peptides with no disulfide bridges: A review

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ABSTRACT

Scorpion venoms are rich sources of biologically active peptides that are classified into disulfide-bridged peptides (DBPs) and non-disulfide-bridged peptides (NDBPs). DBPs are the main scorpion venom components responsible for the neurotoxic effects observed during scorpion envenomation as they usually target membrane bound ion channels of excitable and non-excitable cells. Several hundred DBPs have been identified and functionally characterized in the past two decades. The NDBPs represent a novel group of molecules that have gained great interest only recently due to their high diversity both in their primary structures and bioactivities. This review provides an overview of scorpion NDBPs focusing on their therapeutic applications, modes of discovery, mechanisms of NDBPs genetic diversity and structural properties. It also provides a simple classification for NDBPs that could be adopted and applied to other NDBPs identified in future studies.

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1. Introduction

Scorpions are considered to be one of the oldest animals living on the planet and their existence dates back to more than 400 million years ago [32]. Scorpions are represented by around 1500 species and they are distributed geographically all over the world [46]. Scorpions have acquired the ability to defend themselves against predators and capture prey through the production of toxin loaded venoms that are secreted through specialized venom glands found at the end of the scorpion telson [57]. During their long evolutionary existence on this planet accompanied by the selective pressure applied on these organisms, scorpions managed to develop series of venom peptides that display diverse biological activities and pharmacological functions [52]. The scorpion venom peptides are generally classified into two main groups: the disulfide-bridged peptides (DBPs) which usually target membrane bound ion channels [9,10,54] and the non-disulfide-bridged peptides (NDBPs), a smaller group within the scorpion venom peptide

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arsenal that display multifunctional activities [68,69]. Most scorpion DBPs contain three to four disulfide bridges and are further sub-classified into four different families according the type of membrane channels they interact with. The membrane bound ion channels targeted by the DBPs family of scorpion peptides include the Na^+, K^+, Ca^{2+} and Cl^- channels [46]. These channels play major roles in regulating the normal cellular physiology within many mammalian organisms and disrupting the function of these channels by interacting with scorpion venom peptides can result in significant alterations in their normal function leading to the several symptoms developed in mammals during scorpion envenomation [61]. The NDBPs represent a different group within the scorpion venom assembly of peptides that have gained interest only recently, several peptides belonging to this group have been identified and functionally characterized only in the last decade. The great interest in NDBPs was generated due to the fact that these peptides display diverse biological functions and exhibit multifunctional activities. Some of the biological functions NDBPs display includes antimicrobial, anticancer, hemolytic, anti-inflammatory, immune-modulatory and bradykinin potentiating activities. Unlike the DBPs that display conserved structure-function relationships, the scorpions NDBPs are structurally diverse and display their activity against numerous biological targets when compared to DBPs.

2. General methods of scorpion NDBPs discovery

The scorpion group of NDBPs represents a significant component of the total scorpion peptide venom assembly [62,76]. Mass fingerprinting studies have revealed that NDBPs account for more than one third of all peptides present within scorpion venoms [42,52]. Despite representing a significant proportion of the total venom peptides, this group has the lowest number of functionally characterized peptides when compared with the membrane ion targeting DBPs that constitute the majority of functionally characterized scorpion venom peptides reported in the literature. This is attributed not least in part to the interest generated in this group as a result of their activity on membrane-associated ion channels and their often lethal effects on humans [76]. The importance of studying NDBPs lies in their biological and structural diversity. Several methods have been employed for the identification and discovery of novel NDBPs within scorpion venoms. Early methods for the identification of NDBPs depended on chromatographic separation techniques combined with mass spectrometry for the purification and identification of venom peptide components. These techniques were later followed by biological assays for the determination of the activities of the identified peptides [20].

These early peptide separation and proteomic techniques were later followed by peptide sequence determination employing Edman degradation, a technique that proved to be crucial in determining the full amino acid sequence of the peptides studied but posed technical limitations in identifying long chain peptides in addition to the technical challenges associated with the N-terminal modifications reported in some peptides [39,60]. One of the major breakthroughs in the study of scorpion venom peptidomics was the integration of molecular cloning techniques combined with HPLC fractionation and mass spectrometry for the characterization of venom peptide components. In this novel approach, even limited N-terminal peptide sequence information obtained through Edman degradation permits the design of degenerate primers suitable for the cloning of full-length cDNA sequences of the toxin precursor peptides [13]. Additionally, construction of scorpion mRNA derived cDNA libraries allowed the screening of several random cDNA generated clones that proved to be a successful strategy for the identification of several putative NDBPs reported in several studies [72]. The study of the transcriptomic profile of NDBPs managed to provide additional information about the post-translational processing and the evolutionary diversity of such peptides, factors which are proving to be important tools in the field of taxonomy as well [52].

3. Structural properties of scorpion NDBPs

The scorpion NDBPs are composed of 13–56 amino acid residues and exhibit marked diversity in their sequences. To date more than 40 peptides have been identified and functionally characterized from scorpion venoms so far. Table 1 lists all of these peptides with their corresponding number of amino acids, isoelectric point, charge, biological function and scorpion species. Regarding the secondary structure of NDBPs, the majority of NDBPs with the exception of Peptide T and peptide K-12 display a cationic amphipathic α-helical structure [20,37]. The information regarding the conformation of NDBPs was either generated from Circular dichroism studies or from the use of bioinformatics for the prediction of the secondary structure of peptides. The majority of NDBPs display an α-helical structure and fall in to three different classes regarding the organization of their α-helical regions within the major body of the mature peptide. The first family consists of a single α-helix domain and two random coiled regions at both C and T termini. This organization has been observed with Pandinin 2, BmKb1, BmKn2, IsCT, IsCT2, Meucin-24, Im-1, AamAP1, AamAP2, HsAP and Mauriporin [1,2,11,12,14,21,38,43,72]. The second class of helical organization for NDBPs suggests the presence of two alpha-helical regions within the major peptide body separated in the middle by a random coiled region and this orientation has been observed in Hadrurin, Pandinin 1, Opistoporin 1, Parabutoporin and BmKbpp [11,39,60,71]. The last class described is for peptides that display 100% helicity and this has been observed in a fewer number of NDBPs such as Imcroporin and StCT2 [8,74]. One of the characteristic features of NDBPs regarding their conformation is that all these peptides are present in an unordered random coil conformation when present in benign conditions such as aqueous solutions and only when these peptides are shifted to membrane mimicking solutions such as 50–60% aqueous trifluoroethanol (TFE) or in the presence of dodecylphosphocholine (*DPC*) micelles that the peptides dramatically change their conformation adopting an α-helical structure. This behavior and conformational transition which is observed with all studied NDBPs when exposed to membrane mimicking solvents reflects the potential ability and structural flexibility of this group of peptides to interact with anionic membranes of target cells as these solvents mimic the membrane environment of the cells and are responsible for stabilizing the hydrogen bonds within the peptide and its surrounding solutes which ultimately leads to the induction of an α-helical structure only in peptides that have the propensity to adopt such a conformation. Additionally, the majority of NDBPs carry a net positive charge in the range of (1–7), a feature that allows theses peptides to be attracted toward the negatively charged phospholipid head groups of the lipid membranes of target cells, a force that is mainly driven by electrostatic interactions.

4. Therapeutic applications of NDBPs

The NDBPs group of scorpion peptides displays their activity against a wide range of biological targets leading to significant variation in their biological activity. Unlike the scorpion DBPs that target membrane bound ion channels with their function being predicted through sequence analysis of their mature peptides, the NDBPs do not seem to display conserved sequence–function relationships and some of these peptides even exhibit multifunctional activities without regard to their biological target. To date,