Scorpine-Like Peptides

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Abstract

Scorpine-like peptides are intriguing and unique compounds of scorpion venom. They possess two well-defined regions that confer them bi-functionality. The N-terminal region is similar to scorpion antimicrobial peptides lacking disulfide bridges, whereas the C-terminal region contains six cysteines forming three disulfide bridges that tightly bind the peptide. Scorpine-like peptides have shown activity against bacteria (i.e. B. subtilis, K. pneumoniae, P. aeruginosa), fungi and also as potassium channel blockers. Additionally, they have been successful in controlling malaria and some types of viruses.

Keywords: Scorpion venom; Peptides; Amino acids; Antimalarial activity

Introduction

Scorpion venoms are complex mixture of peptides with a variety of pharmacological functions, specially targeting membrane proteins and interfering with the membrane permeability for Na+, K+, Ca2+ and Cl in excitable and non-excitable cells [1,2]. Scorpion venoms also contain enzymatic and cytolytic compounds. In general, scorpion venom compounds can be classified in two groups: disulfide-bridged peptides (DBP) that represent neurotoxins [3] and non-disulfide-bridged peptides (NDBP) [4]. Interestingly, scorpion, a compound isolated from Pandinus imperator venom [5], contains a region belonging to the DBP and another belonging to the NDBP. Scorpine was shown to display antibacterial and anti-parasitic activities, but also to modify normal function of potassium ion channels. Scorpine-like peptides have been discovered in other species of scorpions, for example in Hadrurus gertschi [6,7], Tityus costatus [8], Opisthacanthus cayaporum [9], Pandinus cavimanus [10], Euscorpiops validus [11], Urodacus yaschenkoi [12], Opistophthalmus carinatus [13], Heterometrus laoticus [14] and Vaejovis species [15].

Structural Properties and Bioactivity of Scorpion-Like Peptides

The scorpine-like peptides belong to the third group of β-K+ channel specific toxins (β-KTxs) and were first called ‘orphan peptides’ because they showed contrasting pharmacological activity due to their bi-functionality [6,13,16]. The N-terminal region of scorpine-like peptides have cytolytic or antimicrobial activity like the insect cecropins [6,13,16], while the C-terminal region has K+ channel blocking activity and it is tightly folded by three disulfide bridges exhibiting a “cysteine stabilized α/β motif” (CS-α/β) [18]. The C-terminal domain is characterized by a conserved sequence: (x)GxΔx(x)GxxCHC(x)ExKxGxCxCHGKCKC GxPLSY(x) in contains 3 disulfide bridges and following completely the typical Cys pattern of invertebrate defensins discussed by Froy and Gurevitz [17] (Figure 1). This segment is responsible for the activity on potassium channels (Table 1). The biological activity of some of these peptides have been investigated (Table 1).

Antimicrobial and antiviral activity

Other examples of antimicrobial effect were reported. For instance, Opisciopine showed anti-fungal activity against Fusarium oxysporum, a pathogen causing Fusarium wilt in many plants [13]. HgsScplp1 shows cytolytic activity at 200 nM in oocytes and erythrocytes and also inhibit the growth of B. subtilis at 2 µM [16]. In contrast, the recombinant version of the scorpine-like Ev37 did not show any antimicrobial or hemolytic activity at 20 and 10 µM concentrations [11]. It remains to...
be shown whether the folding of the recombinant peptide is the correct one, necessary for activity. Scorpine was also demonstrated to affect viral replication in cell culture containing Dengue virus [19].

**Antimalarial activity**

Scorpine-like peptides have been used to control malaria, in special Scorpine, which has been recombinantly expressed in Anopheles gambiae cells showing antibacterial activity against B. subtilis and K. pneumonia, at 5 and 10 µM, respectively. It also produced 98% mortality in sexual stages of A. gambiae arabiensis, A. can be shown whether the folding of the recombinant peptide is the correct one, necessary for activity. Scorpine was also demonstrated to affect viral replication in cell culture containing Dengue virus [19].

**Modulation of activity of potassium channels**

The C-terminal region of HgeScplp1 blocks Kv1.1 channel currents (IC50 88 nM) [16] while the recombinant version Ev37 is able of inhibit the Kv1.3 channel current showing an IC50 value of 1 µM [11].

**Mechanism of Action**

The mechanism of action of scorpine-like peptides on microbes probably is similar to that described for the scorpion-AMPs. The latest are generally defined by containing 2-9 positively charged lysine or arginine residues plus hydrophobic amino acids. These residues confer physicochemical properties permitting interactions with microbial membranes and enabling their typically broad-spectrum antimicrobial activity by directly disrupting the membrane [21]. The membrane is disrupted in several stages; first the electrostatic interaction of AMPs with the polyanionic surface of lipopolysaccharide on the bacterial membrane causes an increase in surface area that weakens the bilayer. This alteration leads to pore formation causing the cell lyses. The disruption can be explained by diverse models (barrel stave, carpet model or torodial model) but merely forming a pore that creates an aqueous channel in the microbe membrane that leads to the loss of membrane function from lipid redistribution and finally death [21,22].

In the antimalarial activity both domains may be involved, the N-terminal and the blocking effect of the C-terminal on potassium channels, although there are few studies on the subject but the mechanism of action has not been elucidated [20,23].
Concluding Remarks

Scorpine-like peptides are interesting compounds of scorpion venom that might aid against the fight towards multi-resistant drug bacteria, contribute to the understanding of potassium ion channels, control viral replication and help in combating malaria. The N-terminal region of scorpine-like peptides might provide antimicrobial and antifungal activities, whereas the C-terminal region might provide novel potassium channel modulators. The critical aspect would be to cleave the peptide in such a way to create (1) a potent AMP with the linear region of scorpine-like peptides and on the other hand, (2) a specific ion channel modulator that contains the motifs that provide the bioactivity.

Scorpines have shown promising antimalarial activity. By producing transgenic mosquitoes that express recombinant scorpines, the malaria parasite transmission can be interrupted. This effect is due to the bi-functionality of scorpine-like peptides. However, our understanding of the mechanism of action of scorpine-like peptides towards parasites and viruses remains unclear. All these evidences make scorpine-like peptides attractive compounds for further research and development into drug leads.

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References