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Invited review

Scorpion toxin peptide action at the ion channel subunit level

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ABSTRACT

This review categorizes functionally validated actions of defined scorpion toxin (SCTX) neuropeptides across ion channel subclasses, highlighting key trends in this rapidly evolving field. Scorpion envenomation is a common event in many tropical and subtropical countries, with neuropharmacological actions, particularly autonomic nervous system modulation, causing significant mortality. The primary active agents within scorpion venoms are a diverse group of small neuropeptides that elicit specific potent actions across a wide range of ion channel classes. The identification and functional characterisation of these SCTX peptides has tremendous potential for development of novel pharmaceuticals that advance knowledge of ion channels and establish lead compounds for treatment of excitable tissue disorders. This review delineates the unique specificities of 320 individual SCTX peptides that collectively act on 41 ion channel subclasses. Thus the SCTX research field has significant translational implications for pathophysiology spanning neurotransmission, neurohumoral signalling, sensori-motor systems and excitation-contraction coupling.

Contents

Abbreviations: AC_{50}, toxin concentration for activation to 50%; Cav, voltage-gated calcium channel; EC_{50}, half maximal effective concentration; ED_{50}, median effective dose; ER, endoplasmic reticulum; IC_{50}, half maximal inhibitory concentration; K_{Ca}, calcium-activated potassium channel; K_D, dissociation constant; K_i, inhibition constant; K_{ir}, inwardly rectifying potassium channel; KTx, scorpion potassium toxin; Kv channel, voltage-gated potassium channel; K_{2p}, two-pore potassium channel; Nav channel, voltage-gated sodium channel; RyR, ryanodine receptor; SCTX, scorpion toxin; SR, sarcoplasmic reticulum.

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1. Introduction

Scorpion envenomation is a relatively common event in many subtropical and tropical countries with about 1 million stings annually, resulting in approximately 2600 fatalities, largely in children (Chippaux and Goyffon, 2008). Stings from the Moroccan black scorpion *Androctonus mauretanicus mauretanicus* for example, have an 8% mortality rate in children under 10 years old (Martin-Eauclaire and Bougis, 2012). With envenomation, pain and swelling at the site is often followed by paraesthesia and hyperalgesia lasting hours, with possible numbness and tingling lasting days. Systemic effects, such as nausea, vomiting, malaise, tachycardia, and seizures, are seen in about 10% of cases and are thought to be the result of autonomic nervous system dysregulation (Nicholson et al., 2006). Scorpion venom typically contains a complex mixture of small peptides, proteins (enzymes, phospholipases, and proteases), amino acids, biogenic amines, lipids, carbohydrates, and inorganic salts (Ortiz et al., 2015). The physiological effects of scorpion envenomation, such as modulation of central and peripheral nervous system excitability, altered smooth and skeletal muscle activity, and membrane destabilisation, are primarily mediated through the action of small neuropeptides on various ion channels in excitable membranes, a process thought to have developed in response to extended positive selection pressure via predator-prey interactions (Ménez et al., 1992;Goudet et al., 2002;Tytgat et al., 1999). These peptides can be characterised generically (disulfide bridge-containing peptides and non-disulfide bridge-containing peptides) (Zeng et al., 2005), or by the size of the peptide chain (short chain peptides, usually potassium channel blockers, or long-chain peptides, usually sodium channel modulators) (Quintero-Hernandez et al., 2015;Santibanez-Lopez and Possani, 2015).

This review comprehensively synthesises the available functional data regarding the actions of individually identified SCTX peptides on specific ion channel targets across the main classes of ion channel superfamilies, including voltage-gated sodium channels (Nav), voltage-gated potassium channels (Kv), calcium-activated potassium channels (K_{Ca}), as well as chloride channels and Ca^{2+} channels. The breadth of SCTX actions on ion channels are summarized schematically in Fig. 1.

1.1. Overview of SCTX actions on voltage-gated sodium channels

Nav channels are present in the plasma membrane of most excitable cells and are responsible for the initiation and propagation of action potentials (Catterall et al., 2005a). There is one family of mammalian Nav channels with nine functional subtypes (Nav1.1–1.9), encoded by multiple genes within species. In contrast invertebrates possess one functional Nav channel, with a number of orthologs, with functional diversity generated thorugh alternative splicing and RNA editing (Zakon, 2012;Dong et al., 2014). Mamallian Nav channels are comprised of 1 pore-forming α-subunit associated with 1–2 β subunits (β1-β4 or TipE subunits in insects) (Dong et al., 2014). The α-subunits consist of four homologous domains (I-IV) each with 6 transmembrane segments (S1–S6) and a pore-forming loop, as well as a recently identified Na^{+}-selectivity filter (Payandeh et al., 2011). The β accessory subunits have a large extracellular N-terminal domain, a single transmembrane segment, and a shorter cytoplasmic domain, and alter the kinetics and voltage-dependence of channel gating, as well as channel localization and interaction with surrounding structures (Catterall et al., 2005a;Gordon et al., 2007;Alexander et al., 2015a). Sodium channel SCTX 'long-chain' peptides are typically 6.5–8.5 kDa polypeptides containing 58–76 amino acid residues, forming a common structural core secured by four disulfide bridges (Rodriguez de la Vega and Possani, 2005;Quintero-Hernandez et al., 2013). They have been functionally divided into alpha or beta toxins according to their primary actions on these channels. Scorpion α-toxins target the Nav receptor site 3 slowing or inhibiting channel inactivation, thereby enhancing persistent activation (Catterall, 1992;du Plessis et al., 2008;Possani et al., 1999). These toxins can be further classified as the common "classical" mammalian-selective toxins, insect-specific alpha toxins, or alpha-like toxins, acting on both mammals and insects (Quintero-Hernandez et al., 2013). In contrast, β-toxins bind to receptor site 4 and hyperpolarise the Nav channel activation threshold to more negative voltages. These are divided into 4 subtypes; anti-mammalian-selective, mammalian and insect, insect-selective excitatory, or insect-select depressant toxins (Quintero-Hernandez et al., 2013;Pedraza Escalona and , 2013;de la Vega, 2007;Ortiz and Possani, 2015).

1.2. Overview of SCTX actions on potassium channels

Potassium channels are the largest and most diverse group of ion channels, represented by 70 known loci in the mammalian genome (Gutman et al., 2005). They typically consist of a primary pore-forming α-subunit, and are often associated with auxillary regulatory subunits (Alexander et al., 2015a). These channels can be divided into 2 transmembrane domain (2TM), 4TM, and 6TM groups (Alexander et al., 2015a), and contain families such as Kv, $K_{Ca,}$ inward rectifier potassium channels (Kir), and two-pore potassium channels (K_{2p}) (Gutman et al., 2005;Dutertre and Lewis, 2010). Kv channels also encompass several subfamilies, such as the Ether-à-go-go-Related Gene (ERG) channels, as part of the

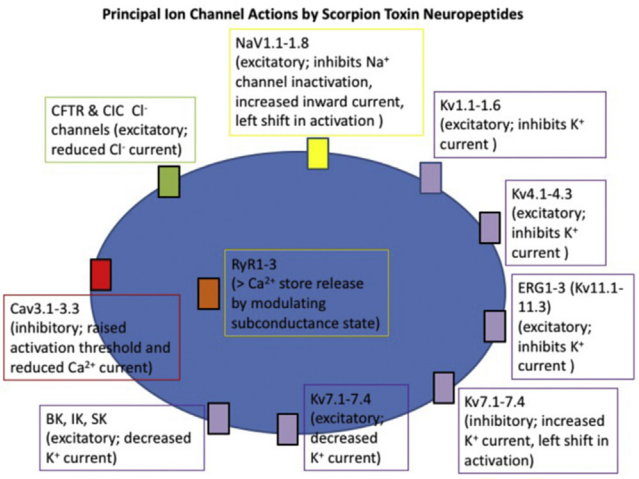

Fig. 1. Summary of major classes of ion channels targeted by scorpion toxin neuropeptides. Details of channel subclasses and specific SCTX peptide actions are provided in Table 1–5.

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