

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.

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Abbreviations: AC₅₀, toxin concentration for activation to 50%; Cav, voltage-gated calcium channel; EC₅₀, half maximal effective concentration; ED₅₀, median effective dose; ER, endoplasmic reticulum; IC₅₀, 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 Ca²⁺ 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 thorough alternative splicing and RNA editing (Zakon, 2012;Dong et al., 2014). Mammalian Nav channels are comprised of 1 pore-forming α -subunit associated with 1–2 β subunits (β 1– β 4 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,

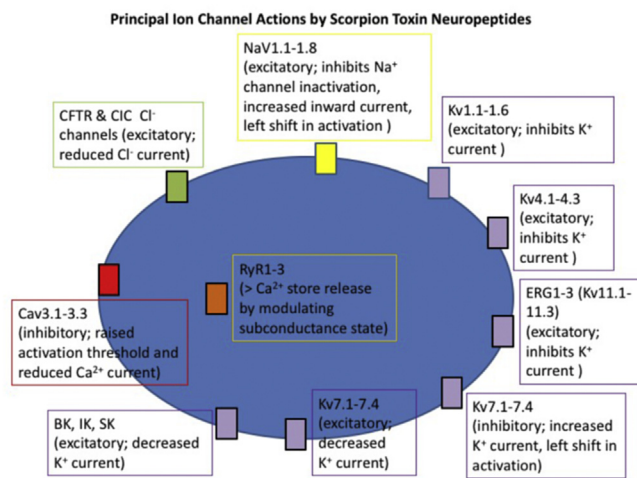


Fig. 1. Summary of major classes of ion channels targeted by scorpion toxin neuropeptides. Details of channel subclasses and specific SCTX peptide actions are provided in Table 1–5.

2010). Kv channels also encompass several subfamilies, such as the Ether-à-go-go-Related Gene (ERG) channels, as part of the ether-à-go-go gene (EAG) group (Jimenez-Vargas et al., 2012a). Potassium channels typically have inhibitory effects and act to reduce cellular excitability, such as promoting cell repolarisation after action potential firing (Martin-Eauclaire and Bougis, 2012). K⁺ channel toxins (KTx), usually short-chain peptides, can broadly influence physiological function, including modulation of neuronal activity, neurotransmitter release and hormonal secretion, lymphocyte activation, muscle contractility, and the cardiac cycle (du Plessis et al., 2008). They have been systematically organised into α , β , γ , and κ -KTx families, classified based on primary amino acid sequences and the cysteine pairing (Quintero-Hernandez et al., 2013). Of these the α -KTx family is the largest, consisting of 30 subfamilies, and can either block ion conduction in Kv1, KCa2, and KCa3 channels via intrusion of a conserved essential dyad, a paired lysine and aromatic residue, into the channel selectivity filter, or by binding to the negatively charged extracellular loop of the KCa2 channel (Tytgat et al., 1999; Quintero-Hernandez et al., 2013; Dutertre and Lewis, 2010; Nirthanan et al., 2005; Rodriguez de la Vega and Possani, 2004). Peptides of the β -family can be further divided into three subgroups, with the third group containing Scorpine-like peptides with prominent antimicrobial effects. Ergotoxins of the γ -family block ERG-K⁺ channels, while κ -peptides are known as hefutoxins and lack the conserved C α β motif found across the other families (Santibanez-Lopez and Possani, 2015; Quintero-Hernandez et al., 2013).

1.3. Overview of SCTX actions on calcium channels

Calcium channels are widely distributed in many tissue types and have been characterised in cardiac myocytes, smooth and skeletal muscle, neuronal tissue, and endocrine cells (Catterall et al., 2005b). Calcium channels can be divided into voltage-gated, voltage-independent, and ligand-gated channels (Quintero-Hernandez et al., 2013; du Plessis et al., 2008). Voltage-gated calcium channels form hetero-oligomeric complexes within the plasma membranes of all excitable cells, and underlie a number of pathological processes including epilepsy, chronic pain, heart failure and hypertension (Lee et al., 2011). These channels are comprised of a pore-forming transmembrane α -subunit, of which there are 10 known mammalian variants (Alexander et al., 2015a). SCTX peptides predominantly bind to the α -subunit (Alexander et al., 2015a). Voltage-gated calcium channels are grouped into three families: High-voltage activated dihydropyridine-sensitive (L-type, Cav1. x) channels; High-voltage activated dihydropyridine-insensitive (Cav2. x) channels; Low-voltage-activated (T-type, Cav3. x) channels (Alexander et al., 2015a). For at least the high-voltage activated calcium channel family, it is likely that the α -subunit coassembles with β , $\alpha 2$ - δ subunits that modulate channel properties, with γ ancillary subunits only proven to associate with $\alpha 1$ s skeletal muscle Cav1.1 channel (Alexander et al., 2015a; Norton and McDonough, 2008). Kurtoxin (*Parabuthus transvaalicus*) is one of the few SCTX peptides identified to inhibit voltage-gated calcium channels, initially demonstrating high affinity for low-voltage-activated calcium channels (Chuang et al., 1998), and then also showing action on high-voltage calcium channels (Sidach and Mintz, 2002), as well a range of Nav channels.

Ryanodine receptors (RyR1-3) are large channel macromolecular complexes, associated with accessory proteins and secondary messengers, that release calcium from intracellular stores located in the endo/sarcoplasmic reticulum when activated by ligands (including the plant alkaloid ryanodine), Ca²⁺, or by allosteric coupling to the L-type Ca²⁺ channel (Franzini-Armstrong and Protasi, 1997; Bers, 2004; Alexander et al., 2015b). Ryanodine

channels vary in their tissue distribution with RyR1 predominantly found in fast and slow-twitch skeletal muscle and in cerebellar Purkinje cells (Takeshima et al., 1989), RyR2 is primarily in cardiac muscle, as well as in brain and in visceral and arterial smooth muscle (Nakai et al., 1990). RyR3 is found in the diaphragm, epithelial cells, brain, and smooth muscle (Hakamata et al., 1992; Fill and Copello, 2002). SCTX peptides termed calcins can target these channels, although characterisation has been limited until recently (Quintero-Hernandez et al., 2013; Xiao et al., 2016). Calcins are able to penetrate cell membranes with high efficiency, before rapidly binding with high affinity to RyRs, increasing their activity by inducing long-lasting sub-conductance states, and thereby leading to increases in intracellular Ca²⁺ (Xiao et al., 2016; Tripathy et al., 1998; Gurrola et al., 2010; Schwartz et al., 2009). Raised intracellular Ca²⁺ serves as a second-messenger, increasing cellular excitability, neurotransmitter release, intracellular metabolism, and gene expression (du Plessis et al., 2008). Calcins are also able to carry large membrane-impermeable molecules across the membrane with them, with obvious implications for intracellular drug delivery (Boisseau et al., 2006).

1.4. Overview of SCTX actions on chloride channels

The chloride channel superfamily includes the voltage-sensitive CIC sub-family, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR), and volume-regulated channels (Alexander et al., 2015b; Jentsch et al., 2002). The mammalian CIC family contains 9 members, divided into three subgroups, incorporating plasma membrane channels and Cl⁻/H⁺ antiporters, and are thought to contribute to plasma membrane transport, lysosomal acidification, and the maintenance of cell membrane potential (Alexander et al., 2015b; Jentsch et al., 2002; Thompson et al., 2009). CFTR is a 12 transmembrane, cAMP-regulated epithelial cell membrane chloride channel involved in normal fluid transport across epithelia (Alexander et al., 2015b). Although the action of SCTX peptides on chloride channels is poorly defined, GaTx1 and GaTx2 (*Leiurus quinquestriatus herbareus*) have recently been identified to inhibit the CFTR and CIC2 channels respectively (Thompson et al., 2009; Fuller et al., 2007).

1.5. Scope of review

The characterization of SCTX peptide actions on ion channels continues to grow at a rapid pace, aided by the development of novel molecular technologies and experimental approaches. Previous reviews have focused on the structural, computational, and molecular analysis of scorpion venom components and ion channel interactions (Smith et al., 2014; Gurevitz et al., 2014), as well as functional comparison of their actions on ion channels. Although some reviews have outlined a broad overview of SCTX peptide action (Ortiz et al., 2015; Quintero-Hernandez et al., 2013; du Plessis et al., 2008), the majority have provided relatively detailed information of SCTX action within particular ion channel subfamilies, such as sodium channels (Gordon et al., 2007; Pedraza Escalona and Possani, 2013; Pucca et al., 2015a; Gilchrist and Bosmans, 2012; Gordon and Gurevitz, 2003), potassium channels (Martin-Eauclaire and Bougis, 2012; Jimenez-Vargas et al., 2012a; Bartok et al., 2015; Yu et al., 2016; Bougis and Martin-Eauclaire, 2015; Yang et al., 2015; Wang et al., 2014; Wanke and Restano-Cassulini, 2007), and to a lesser extent, calcium (Norton and McDonough, 2008; Ramos-Franco and Fill, 2016), and chloride channels (Dardevet et al., 2015). This review establishes a comprehensive comparison of the broad range of functionally-validated SCTX peptide actions across the breadth of ion channel families. We

assembled 320 of these SCTX peptides, out of potentially thousands of known molecules, based on the characterization of their selectivity within 41 functional channels. This review highlights the desirability of expanding reproducible screening of these SCTX peptides across the full breadth of known ion channels.

2. Methods

PubMed/Medline and the Scopus databases were searched to identify studies that had specifically elicited the action of a defined SCTX on particular ion channel subtypes. Publications focusing on the use of whole venom and fractions were excluded as these typically contain a multitude of individual peptides, confounding any attempt to quantify molecular effect.

Data were extracted from the primary literature to identify the scorpion peptide nomenclature, species of origin, ion channel subtype (and its species origin), expression system, the effect noted, and the necessary concentrations. This information was then synthesised and organised according to the specific effects of defined peptides on particular ion channel subtypes.

The data were arranged to highlight the action of unique and well-defined SCTX peptides on the most specific ion channel subclasses known. To this end, the positive findings from the studies have been highlighted in the body of the text and summarized within tables based on ion channel classes. Negative findings were not integrated into these tables.

3. Analysis of isolated SCTX neuropeptides on ion channel targets

3.1. Scorpion venom peptide actions on voltage-gated sodium channels

63 unique SCTX peptides with specific action on voltage-gated sodium channels are described in Table 1. These peptides acted by three main mechanisms: Direct inhibition of current flow; hyperpolarisation of the channel activation threshold, or by delaying or inhibiting channel inactivation. These actions occurred over a wide range of SCTX peptide concentrations, from 100 pM (Meng et al., 2015), to greater than 30 μ M (Dai et al., 2012), suggesting that there was significant variability in peptide affinity for these channels. Table 1 also highlights the significant distinction in the selectivity of SCTX peptides. 19 peptides appeared to be highly selective, with action only characterised on one particular subtype of ion channel in a multi-channel screen. In contrast, other SCTX peptides, such as MeuNaTx α -5 (*Mesobuthus eupeus*), and OD1 (*Odonthobuthus doriae*), appeared to have much broader action, each modulating 6 different channel subtypes. However, it is important to note that many of the studies were restricted in the breath of their target screening. Some identified peptides demonstrated the ability to discriminate between mammalian and non-mammalian channel subtypes. For example, AaHIT (*Androctonus australis* Hector) (Bosmans et al., 2007) and BjaIT (*Buthotus judaicus*) (Arnon et al., 2005) were highly selective against insect channel orthologues. In contrast C α VI (*Centruroides suffusus suffusus*) affected rat Nav1.2 at 5 μ M, but did not affect DMNaV1 (Bosmans et al., 2007). Such differences are likely to be due to differences in ion channel amino acid sequence affecting the site of toxin action.

MeuNaTx α -12 (*Mesobuthus eupeus*) was one of the most specific inhibitors of the DMNaV1 channel with an EC₅₀ of 20 nM, 45 fold higher affinity than for rat Nav1.1 and significantly higher affinities than for the rest of the Nav1 subfamily (Zhu et al., 2013). Cn8 (*Centruroides noxius*) had the greatest affinity for Nav1.1 (K_d = 140 nM), although it was found to also have action on Nav1.2

and Nav1.6 at similar concentrations (Schiavon et al., 2012). Amm VIII (*Androctonus mauretanicus mauretanicus*) and AaH2 (*Androctonus australis* Hector) are both potent Nav1.2 inhibitory peptides; EC₅₀ = 29 nM and 2.6 nM respectively. However AmmVIII has subsequently been shown to be significantly more selective for Nav1.2 over Nav1.4 with a EC₅₀ of 416 nM compared to 2.2 nM for AaH2 (Alami et al., 2003). Tf2 (*Tityus fasciolatus*) was the only Nav1.3 selective activator identified, with no action on Nav1.1–1.2, or Nav1.4–1.8 channels expressed in *Xenopus oocytes* following 1 μ M application (Camargos et al., 2015). Bmk AGP-SYPU1 (*Buthus martensii* Karsch) had high affinity for Nav1.4 and Nav1.5, acting in picomolar concentrations (Meng et al., 2015). However it has similar preference for both channels, causing inhibition at 100 pM, and has not been further characterised in other ion channel subclasses. The most selective inhibitor of Nav1.4 was the peptide Cell9 (*Centruroides elegans*). This toxin specifically targeted Nav1.4 when applied at 700 nM, while leaving Nav1.2, Nav1.5 and Nav1.7 unaffected (Vandendriessche et al., 2010).

Of the toxins showing a degree of preference to Nav1.5, Bmk1 (*Buthus martensii* Karsch), Lqh III (*Leiurus quinquestriatus hebraeus*) and Ts1 (*Tityus serrulatus*) are the best characterised. Nav1.6 was selectively inhibited by peptide Cn2 (*Centruroides noxius*) with an ED₅₀ of 39.2 nM after screening on channels Nav1.1–Nav1.7, demonstrating unique selectivity. Nav1.7 was found to be potently inhibited by peptide OD1 (*Odonthobuthus doriae*) with an EC₅₀ of 4.5 nM, however it was not particularly selective, affecting Nav1.4 and Nav1.6 at similar concentrations (Maertens et al., 2006). However a triple mutant of this peptide was engineered and found to increase selectivity by up to 40 fold (Maertens et al., 2006), indicating the great scope to tailor SCTX to specific molecular targets. Scorpion action on channels Nav1.8 and 1.9 is relatively poorly defined. The sole peptide definitively found to affect Nav1.8 was Bmk I (*Buthus martensii* Karsch) with an EC₅₀ of 302.95 nM (Ye et al., 2015). However this peptide is not selective and affects other Nav1 family channels at similar concentrations. AmmVIII and AaH1 were found not to alter the Nav1.9 current in DRG neurons (Abbas et al., 2013). Recent publications have suggested that *Tityus bahiensis* scorpion venom (TbScV) (Morales et al., 2011) and TsVII (*Tityus serrulatus*) (Gilchrist and Bosmans, 2012) have potential action on Nav1.8 and Nav1.9 channels, although this requires further assessment and characterization.

3.2. Scorpion toxin peptide actions on voltage-gated potassium channels

All peptide toxins acting on voltage-gated potassium channels described in Tables 2 and 3 were inhibitory with the exception of the excitatory peptide AaTXKb2–64 (*Androctonus australis*) (Zhu et al., 2009c). There was marked variation in peptide selectivity for ion channel subclasses. We found 43 SCTX peptides with identified action restricted to a particular Kv subclass, however not all of these have been subjected to comprehensive testing across ion channel subfamilies. In contrast, 36 SCTX peptides were more promiscuous, acting on 3 or more Kv subclasses. Some peptides were selective between mammalian and non-mammalian channels. For example 9 SCTX peptides have been shown to be highly selective at blocking the non-mammalian Shaker potassium channels in invertebrates. Of these Agitoxin 1 (*Leiurus quinquestriatus hebraeus*) is among the most potent SCTXs, with a K_i of 160 pM (Garcia et al., 1994).

Table 2 shows peptides with action on the Kv1 and Kv4 families. Channel subclasses have only been included where a peptide has been demonstrated to cause a functional effect. SCTX action on Kv1.1–1.3 has been highly researched, with 74 peptides currently identified as having blocking effects with wide variation in their

Bactridine 4	<i>Tityus discrepans</i>		Hyperpolarisation of activation and reduction of peak current (11%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)	Hyperpolarisation of activation and reduction of peak current (64%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)	Hyperpolarisation of activation, Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)
Bactridine 5	<i>Tityus discrepans</i>		Hyperpolarisation of activation and reduction of peak current (45%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)	Hyperpolarisation of activation and reduction of peak current (21%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)	Hyperpolarisation of activation, Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)
Bactridine 6	<i>Tityus discrepans</i>		Hyperpolarisation of activation and reduction of peak current (34%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)		Reduction of peak current (10%), Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012) Slowed inactivation, Rat, <i>Xenopus</i> oocytes, 100 nM, (Peigneur et al., 2012)
BjzIT	<i>Buthotus judaicus</i>	Complete inhibition of inactivation, <i>Xenopus</i> oocytes, 100 nM, (Arnon et al., 2005)			
BmK 11(2)	<i>Buthus martensii</i> Karsch			Hyperpolarisation of activation threshold, Increased current (40%), slowed inactivation, Rat, HEK293, 100 nM, (Kondratiev et al., 2003)	Reduced current (15%) and slowed inactivation, Human, HEK293, 100 nM, (Kondratiev et al., 2003)
Bmk AGP-SYPU1	<i>Buthus martensii</i> Karsch			Increased current, Human, CHO cells, 100 pM, (Meng et al., 2015)	Increased current, Human, CHO, 100 pM, (Meng et al., 2015)
BmK AS	<i>Buthus martensii</i> Karsch		Hyperpolarisation of activation threshold and depolarisation of inactivation, Rat, <i>Xenopus</i> oocytes, 500 nM, (Tan et al., 2008); U-shaped modulation of activation by dose, Rat, <i>Xenopus</i> oocytes, nM, (Zhu et al., 2009a)	Inhibits slow inactivation and facilitates steady-state activation, Rat, <i>Xenopus</i> oocytes, 100 nmol/L, (Liu et al., 2012)	

Table 1 (continued)

Peptide	Species	DmNav1 (Para)	Nav1.1	Nav1.2	Nav1.3	Nav1.4	Nav1.5	Nav1.6	Nav1.7	Nav1.8
BmK I	<i>Buthus martensii</i> Karsch			Inhibit inactivation and increased current, Rat, <i>Xenopus</i> oocytes, 500 nM, (Zhu et al., 2009b)			Inhibit inactivation and increasing peak current, Rat, HEK293, EC ₅₀ = 99.4 nM, (Feng et al., 2008)	Inhibit fast inactivation and increases current, Mouse, <i>Xenopus</i> oocytes, EC ₅₀ = 214 nM, (He et al., 2010)		Inhibit inactivation and hyperpolarisation of activation threshold, DRG neurons, EC ₅₀ = 302.95 nM, (Ye et al., 2015)
BmK IT2	<i>Buthus martensii</i> Karsch	Hyperpolarised activation threshold and inhibit current, <i>Xenopus</i> oocytes, EC ₅₀ = 2.9 μM, (He et al., 2011)								
BmK M1	<i>Buthus martensii</i> Karsch						Slow inactivation and hyperpolarise steady state inactivation, Human, <i>Xenopus</i> oocytes, EC ₅₀ = 195 nM, (Goudet et al., 2001)		Inhibit fast inactivation and increased current, Rat - <i>Xenopus</i> oocytes, 50 nM, (Maertens et al., 2006)	
BmK αIV	<i>Buthus martensii</i> Karsch			Prolonged inactivation and increased current, Rat, <i>Xenopus</i> oocytes, 100 nM, (Chai et al., 2006)						
BmKITc	<i>Buthus martensii</i> Karsch	Inhibit slow inactivation, <i>Xenopus</i> oocytes, 3 μM, (Yuan et al., 2010)								
BmKITc2	<i>Buthus martensii</i> Karsch	Inhibit slow inactivation, <i>Xenopus</i> oocytes, 3 μM, (Yuan et al., 2010)								
BmαTX14	<i>Buthus martensii</i> Karsch			Inhibit fast inactivation, Rat, HEK293 cells, EC ₅₀ = >30 μM, (Dai et al., 2012)			Inhibit fast inactivation, Mouse, HEK293 cells, EC ₅₀ = 82.3 nM, (Dai et al., 2012)			
BmαTX47	<i>Buthus martensii</i> Karsch			Inhibit fast inactivation, Rat, HEK293, EC ₅₀ = 7.26 μM, (Li et al., 2014)			Inhibit fast inactivation, Mouse, HEK293, 10 μM, (Li et al., 2014)	Inhibit fast inactivation, Human, HEK293, EC ₅₀ = 1 μM, (Li et al., 2014)		
Cell8	<i>Centruroides elegans</i>									Hyperpolarisation of activation threshold and inhibit current, Rat, <i>Xenopus</i>

Cell9	<i>Centruroides elegans</i>			Hyperpolarisation of activation threshold and inhibit current, Rat, <i>Xenopus</i> oocytes, 700 nM, (Vandendriessche et al., 2010)	oocytes, 300 nM, (Vandendriessche et al., 2010)
Cii1	<i>Centruroides infamatus infamatus</i>			Inhibit current, Rat, <i>Xenopus</i> oocytes, 1.7 μ M, (Dehesa-Davila et al., 1996)	
CII1	<i>Centruroides limpidus limpidus</i>	Hyperpolarisation of activation threshold and inhibit current, HEK293, 560 nM, (Schiavon et al., 2012)	Hyperpolarisation of activation threshold and inhibit current, HEK293, 560 nM, (Schiavon et al., 2012)		Hyperpolarisation of activation threshold and inhibit current, HEK293, $K_d = 44.9$ nM, (Schiavon et al., 2012)
CII2	<i>Centruroides limpidus limpidus</i>	Hyperpolarisation of activation threshold and inhibit current, HEK293, 460 nM, (Schiavon et al., 2012)	Hyperpolarisation of activation threshold and inhibit current, HEK293, 460 nM, (Schiavon et al., 2012)	Inhibit current Rat, <i>Xenopus</i> oocytes, 1.2 μ M, (Dehesa-Davila et al., 1996)	Hyperpolarisation of activation threshold and inhibit current, HEK293, $K_d = 172$ nM, (Schiavon et al., 2012)
Cn2	<i>Centruroides noxius</i>			Inhibition of current, Rat, <i>Xenopus</i> oocytes, 0.5 μ M, (Dehesa-Davila et al., 1996)	Hyperpolarisation of activation threshold, Human, HEK293ED ₅₀ = 39.2 nM, (Schiavon et al., 2006)
Cn8	<i>Centruroides noxius</i>	Hyperpolarisation of activation threshold and inhibit current, HEK293, 140 nM, (Schiavon et al., 2012)	Hyperpolarisation of activation threshold and inhibit current, HEK293, 140 nM, (Schiavon et al., 2012)		Hyperpolarisation of activation threshold and inhibit current, HEK293, $K_d = 67.7$ nM, (Schiavon et al., 2012)
Css II	<i>Centruroides suffusus suffusus</i>	Hyperpolarisation of activation threshold and inhibit current, HEK293, 280 nM, (Schiavon et al., 2012)	Hyperpolarisation of activation threshold and inhibit current, HEK293, 280 nM, (Schiavon et al., 2012); Hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes, 5 μ M, (Bosmans et al., 2007)		Hyperpolarisation of activation threshold and inhibit current, HEK293, $K_d = 307$ nM, (Schiavon et al., 2012)
Css IV	<i>Centruroides suffusus suffusus</i>	Hyperpolarisation of activation threshold, <i>Xenopus</i> oocytes,	Hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes,		

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Table 1 (continued)

Peptide	Species	DmNav1 (Para)	Nav1.1	Nav1.2	Nav1.3	Nav1.4	Nav1.5	Nav1.6	Nav1.7	Nav1.8
Css VI	<i>Centruroides suffusus suffusus</i>	5 μ M, (Bosmans et al., 2007)		5 μ M, (Bosmans et al., 2007) Hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes, 5 μ M, (Bosmans et al., 2007)						
CvIV4	<i>Centruroides vittatus</i>			Inhibit fast inactivation, Rat, HEK293, 1 μ M, (Rowe et al., 2011)	Inhibit fast inactivation, Rat, HEK293, 1 μ M, (Rowe et al., 2011)	Inhibit fast inactivation, Rat, HEK293, 1 μ M, (Rowe et al., 2011)			Inhibit fast inactivation, Human, HEK293, 1 μ M, (Rowe et al., 2011)	
Kbot55 α -Ktx31.1	<i>Buthus occitanus tunetanus</i>		Inhibit current (32%), Rat, <i>Xenopus</i> oocytes, 1 μ M, (ElFessi-Magouri et al., 2015)	Full Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μ M, (ElFessi-Magouri et al., 2015)	Inhibition of current (83%), Human, <i>Xenopus</i> oocytes, 1 μ M, (ElFessi-Magouri et al., 2015)			Inhibit current (21%), Rat – <i>Xenopus</i> oocytes, 1 μ M, (ElFessi-Magouri et al., 2015)		
Kurtoxin-Like II (Identical)	<i>Parabuthus transvaalicus</i> <i>Parabuthus granulatus</i>			Slows activation and inactivation, Rat, <i>Xenopus</i> oocytes, 500 nM, (Chuang et al., 1998)			Delays inactivation, Human, <i>Xenopus</i> oocytes, 700 nM, (Olamendi-Portugal et al., 2002)	Voltage-dependent modulator, Mouse, Smooth muscle, EC ₅₀ = 365.1 nM, (Zhu et al., 2009c)		
Lm α TX3	<i>Lychas mucronatus</i>					Inhibit fast inactivation, Mouse, HEK293, EC ₅₀ = 4.98 μ M, (Xu et al., 2014)	Inhibit fast inactivation, Human, HEK293, EC ₅₀ = 1.23 μ M, (Xu et al., 2014)		Inhibit fast inactivation, Human, HEK293, EC ₅₀ = 31.46 μ M, (Xu et al., 2014)	
Lm α TX5	<i>Lychas mucronatus</i>					Inhibit fast inactivation, Mouse, HEK293, EC ₅₀ = 4.53 μ M, (Xu et al., 2014)	Inhibit fast inactivation, Human, HEK293, EC ₅₀ = 1.03 μ M, (Xu et al., 2014)		Inhibit fast inactivation, Human, HEK293, EC ₅₀ = 67.62 μ M, (Xu et al., 2014)	
Lqh II	<i>Leiurus quinquestriatus hebraeus</i>			Inhibit inactivation, Rat - HEK293, EC ₅₀ = 1.8 nM, (Chen et al., 2002); Inhibit inactivation (strong), Rat, HEK293, 5 nM, (Gilles et al., 2000)		Delay inactivation and speeds recovery, Rat, HEK293, EC ₅₀ = 1.4 nM, (Chen et al., 2000); Slow inactivation and increased current, Rat, HEK293, 5 nM, (Gilles et al., 2000)	Inhibit fast inactivation and enhanced slow inactivation, Human, HEK293, EC ₅₀ = 12 nM, (Chen and Heinemann, 2001)		Inhibit inactivation, Human, HEK293, EC ₅₀ = 32 nM, (Chen et al., 2002)	
Lqh III	<i>Leiurus quinquestriatus hebraeus</i>			Inhibit inactivation, Rat, HEK293, EC ₅₀ = 342 nM, (Chen et al., 2002); Inhibit inactivation (weak), Rat, HEK293, 2 μ M, (Gilles et al., 2000)		Delays inactivation and speeds recovery, Rat, HEK293, EC ₅₀ = 5.4 nM, (Chen et al., 2000); Inhibit inactivation and increased current, Rat, HEK293,	Inhibit fast inactivation and enhanced slow inactivation, Human, HEK293, EC ₅₀ < 2.5 nM, (Chen and Heinemann, 2001)		Inhibit inactivation, Human, HEK293, EC ₅₀ = 13.6 nM, (Chen et al., 2002)	

Lqh α IT	<i>Leiurus quinquestriatus hebraeus</i>			5 nM, (Gilles et al., 2000)	Delays inhibition and speeds recovery, Rat, HEK293, EC ₅₀ = 0.5 nM, (Chen et al., 2000)	Inhibition of fast inactivation, Human, HEK293, EC ₅₀ = 33 nM, (Chen and Heinemann, 2001)
Lqh6	<i>Leiurus quinquestriatus hebraeus</i>			Delays inhibition and increased current, Rat, <i>Xenopus</i> oocytes, 1 μ M, (Hamon et al., 2002)	Delays inhibition and increased current, Rat, <i>Xenopus</i> oocytes, 1 μ M, (Hamon et al., 2002)	Delays inhibition, Human, <i>Xenopus</i> oocytes, 0.2 μ M, (Hamon et al., 2002)
Lqh7	<i>Leiurus quinquestriatus hebraeus</i>		Delays inhibition, Rat, <i>Xenopus</i> oocytes, 10 μ M, (Hamon et al., 2002)	Delays inhibition and increased current, Rat, <i>Xenopus</i> oocytes, 1 μ M, (Hamon et al., 2002)	Delays inhibition and increased current, Rat, <i>Xenopus</i> oocytes, 1 μ M, (Hamon et al., 2002)	Delays inhibition, Human, <i>Xenopus</i> oocytes, 0.2 μ M, (Hamon et al., 2002)
Lqh β 1	<i>Leiurus quinquestriatus hebraeus</i>	Hyperpolarisation of activation threshold and inhibits current, <i>Xenopus</i> oocytes, 2.5 μ M, (Gordon et al., 2003)	Hyperpolarisation of activation threshold and inhibits current, Rat, <i>Xenopus</i> oocytes, 2.5 μ M, (Gordon et al., 2003)	Hyperpolarisation of activation threshold and inhibits current, Rat, <i>Xenopus</i> oocytes, 2.5 μ M, (Gordon et al., 2003)	Hyperpolarisation of activation threshold and inhibits current, Rat, <i>Xenopus</i> oocytes, 2.5 μ M, (Gordon et al., 2003)	Inhibition of current (minor), Human, <i>Xenopus</i> oocytes, 2.5 μ M, (Gordon et al., 2003)
LqqIT2	<i>Leiurus quinquestriatus quinquestriatus</i>	Hyperpolarisation of activation threshold and inhibits current, <i>Xenopus</i> oocytes, 1 μ M, (Bosmans et al., 2005)				
MeuNaTx α -1	<i>Mesobuthus eupeus</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 1.17 μ M, (Zhu et al., 2012a)	Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 1 μ M, (Zhu et al., 2012a)	Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 1 μ M, (Zhu et al., 2012a)		Inhibit inactivation, Mouse, <i>Xenopus</i> oocytes, EC ₅₀ = 3.1 μ M, (Zhu et al., 2012a)
MeuNaTx α -2	<i>Mesobuthus eupeus</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 1.22 μ M, (Zhu et al., 2012a)			Inhibit inactivation, Rat, <i>Xenopus</i> oocytes, EC ₅₀ = 2.23 μ M, (Zhu et al., 2012a)	
MeuNaTx α -4	<i>Mesobuthus eupeus</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 0.13 μ M, (Zhu et al., 2012a)				
MeuNaTx α -5	<i>Mesobuthus eupeus</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 0.28 μ M, (Zhu et al., 2012a)		Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 1 μ M, (Zhu et al., 2012a)	Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 1 μ M, (Zhu et al., 2012a)	Inhibit inactivation, Human, <i>Xenopus</i> oocytes, 1 μ M, (Zhu et al., 2012a)
	<i>Mesobuthus eupeus</i>					Inhibit inactivation, Mouse, <i>Xenopus</i> oocytes, EC ₅₀ = 0.79 μ M, (Zhu et al., 2012a)

Table 1 (continued)

Peptide	Species	DmNav1 (Para)	Nav1.1	Nav1.2	Nav1.3	Nav1.4	Nav1.5	Nav1.6	Nav1.7	Nav1.8
MeuNaTx α -12		Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 19.95 nM, (Zhu et al., 2013)	Inhibit inactivation, Rat, <i>Xenopus</i> oocytes, EC ₅₀ = 0.91 μ M, (Zhu et al., 2013)	Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		Inhibit inactivation (weak), Mouse, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		
MeuNaTx α -13	<i>Mesobuthus eupeus</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 65.5 nM, (Zhu et al., 2013)	Inhibit inactivation, Rat, <i>Xenopus</i> oocytes, EC ₅₀ = 2.5 μ M, (Zhu et al., 2013)	Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		Inhibit inactivation (weak), Rat, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		Inhibit inactivation (weak), Mouse, <i>Xenopus</i> oocytes, 10 μ M, (Zhu et al., 2013)		
OD1	<i>Odonthobuthus doriae</i>	Inhibit inactivation, <i>Xenopus</i> oocytes, EC ₅₀ = 80 nM, (Jalali et al., 2005)			Inhibit inactivation, Rat, <i>Xenopus</i> oocytes, 100 nM, (Maertens et al., 2006)	Inhibit fast inactivation and hyperpolarise activation threshold, Human, CHO cells, EC ₅₀ = 9.6 nM, (Durek et al., 2013)	Inhibit inactivation, Human, <i>Xenopus</i> oocytes, 2 μ M, (Jalali et al., 2005)	Inhibit fast inactivation and hyperpolarise activation threshold, Human, CHO cells, EC ₅₀ = 30 nM, (Durek et al., 2013)	Inhibit fast inactivation and increases current, Rat, <i>Xenopus</i> oocytes, EC ₅₀ = 4.5 nM, (Maertens et al., 2006); Inhibit fast inactivation, Human, CHO cells, EC ₅₀ = 8 nM, (Durek et al., 2013)	
Phaiodotoxin	<i>Anuroctonus phaiodactylus</i>		Hyperpolarisation of activation threshold, depolarisation of inactivation, more current, <i>Xenopus</i> oocytes, 2 μ M, (Valdez-Cruz et al., 2004)							
TdVIII	<i>Tityus discrepans</i>					Hyperpolarisation of activation threshold and inhibit current, Rat, <i>Xenopus</i> oocytes, 100 nM, (Tsushima et al., 1999)				
Tf2	<i>Tityus fasciolatus</i>				Hyperpolarisation of activation threshold, Human, <i>Xenopus</i> oocytes, 1 μ M, (Camargos et al., 2015)					
TiTx gamma	<i>Tityus serrulatus</i>					Hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes, 50 nM, (Marcotte et al., 1997)				
Ts1	<i>Tityus serrulatus</i>	Bell-shaping gating modulator, HEK293, 100 nM-1		Hyperpolarisation of activation threshold, Rat,	Hyperpolarisation of activation threshold, Rat,	Hyperpolarisation of activation threshold and	Inhibit current, Human, HEK293, EC ₅₀ = 55 nM,	Hyperpolarisation of activation threshold and inhibit current, Mouse,		

		μM , (Peigneur et al., 2015)	HEK293, 100 nM, (Peigneur et al., 2015)	HEK293, 100 nM, (Peigneur et al., 2015)	inhibit current, Rat, HEK293, 100 nM, (Peigneur et al., 2015)	(Peigneur et al., 2015)	HEK293, 100 nM, (Peigneur et al., 2015)
Ts2	<i>Tityus serrulatus</i>		Inhibit rapid inactivation, Rat, <i>Xenopus</i> oocytes, 1 μM , (Cologna et al., 2012)	Inhibit rapid inactivation and hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes, 1 μM , (Cologna et al., 2012)		Inhibit rapid inactivation, Human, <i>Xenopus</i> oocytes, 1 μM , (Cologna et al., 2012)	Inhibit rapid inactivation, Mouse, <i>Xenopus</i> oocytes, 1 μM , (Cologna et al., 2012)
Ts4	<i>Tityus serrulatus</i>						Inhibit fast inactivation, <i>Xenopus</i> oocytes, $\text{EC}_{50} = 1.19 \mu\text{M}$, (Pucca et al., 2015b)
TsVII	<i>Tityus serrulatus</i>	Hyperpolarisation of activation threshold, <i>Xenopus</i> oocytes, 5 μM , (Bosmans et al., 2007)	Hyperpolarisation of activation threshold, Rat, <i>Xenopus</i> oocytes, 5 μM , (Bosmans et al., 2007)				
Tt1g	<i>Tityus trivittatus</i>		Hyperpolarisation of activation threshold, Human, HEK293, 500 nM, (Coronas et al., 2015)	Hyperpolarisation of activation threshold, Human, HEK293, 500 nM, (Coronas et al., 2015)	Inhibit current, Human, HEK293, 500 nM, (Coronas et al., 2015)	Inhibit current, Human, HEK293, 500 nM, (Coronas et al., 2015)	
Tz1	<i>Tityus zulianus</i>		Hyperpolarisation of activation threshold, HEK293, 10 μM , (Leipold et al., 2006)		Hyperpolarisation of activation threshold, HEK293, $K_d = 3.5 \mu\text{M}$, (Leipold et al., 2006); Hyperpolarisation of activation threshold, Rat, HEK293, $\text{EC}_{50} = 3.5 \mu\text{M}$, (Borges et al., 2004)		Hyperpolarisation of activation threshold, HEK293, 10 μM , (Leipold et al., 2006)

Note: Data represented sequentially as: Action, channel species origin for recombinant expression (if reported), expression system, concentration, reference.

BmTX2	<i>Buthus martensii</i> Karsch				Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 1.5 nM, (Romi-Lebrun et al., 1997)			
BmTX3	<i>Buthus martensii</i> Karsch				Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 1.6 nM, (Romi-Lebrun et al., 1997)			Inhibit current, COS-7, IC50 = 105 nM, (Vacher et al., 2006)
								Inhibit current, COS-7, 300 nM, (Vacher et al., 2006)
BoiTx1 α -KTx3.10	<i>Buthus occitanus israelis</i>				Inhibit current, ShH4, <i>Xenopus</i> oocytes, IC50 = 3.5 nM, (Kozminsky-Atias et al., 2007)			
Bs6 α -KTx3.8	<i>Buthus indicus</i>				Inhibit current, Human, <i>Xenopus</i> oocytes, IC50 = 0.89 nM, (Kohl et al., 2015)			
Bs-KTx6	<i>Buthus indicus</i>				Inhibit current, Rat, HEK293, IC50 = 7.7 pM, (Ali et al., 2014)			
BTK-2	<i>Buthus tamulus</i>				Inhibit current, Human, <i>Xenopus</i> oocytes, IC50 = 4.6 μ M, (Dhawan et al., 2003)			
Butantoxin α -KTx12.2	<i>Tityus trivittatus</i>				Inhibit current, ShB, Sf9, Kd = 660 nM, (Coronas et al., 2003)			
Ce1 α -KTx 2.8	<i>Centruroides elegans</i> Thorell				Inhibit current, Human T lymphocytes, ED50 = 0.7 nM, (Olamendi-Portugal et al., 2005)			
Ce2 α -KTx 2.9	<i>Centruroides elegans</i> Thorell				Inhibit current, Human T lymphocytes, ED50 = 0.25 nM, (Olamendi-Portugal et al., 2005)			
Ce3 α -KTx 2.10	<i>Centruroides elegans</i> Thorell				Inhibit current, Human T lymphocytes, ED50 = 366 nM, (Olamendi-Portugal et al., 2005)			
Ce4 α -KTx 2.11	<i>Centruroides elegans</i> Thorell				Inhibit current, Human T lymphocytes, ED50 = 0.98 nM, (Olamendi-Portugal et al., 2005)			
Ce5 α -KTx 2.12	<i>Centruroides elegans</i> Thorell				Inhibit current, Human T lymphocytes, ED50 = 69 nM, (Olamendi-Portugal et al., 2005)			
Charbydotoxin (ChTX)	<i>Leiurus quinquestriatus hebraeus</i>	Inhibit current, ShH4, <i>Xenopus</i> oocyte, Kd = 3.6 nM,	Inhibit current, <i>Xenopus</i> oocyte, Kd = 1.5 μ M, (Garcia et al., 1994); Inhibit	Inhibit current, B82, Kd = 1.7 nM (Werkman et al., 1992); Inhibit	Inhibit current, Human, CHO, 10 nM, (Nikouee et al., 2012); Inhibit current, Mouse, L929, Kd = 2.6 nM, (Grissmer et al.,			Inhibit current, Human, MEL, Kd > 100 nM,
								Inhibit current, <i>Xenopus</i> oocytes, Ki = 22 nM,

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	<i>Heterometrus spinnifer</i>			Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 12 pM, (Lebrun et al., 1997)			
ImKTx1	<i>Isometrus maculatus</i>	Inhibit current, Mouse, HEK293, 10 μM, (Chen et al., 2011)	Inhibit current, Human, HEK293, 10 μM, (Chen et al., 2011)	Inhibit current, Mouse, HEK293, IC ₅₀ = 1.7 μM, (Chen et al., 2011)			
ImKTx88	<i>Isometrus maculates</i>			Inhibit current, HEK293, IC ₅₀ = 91 pM, (Han et al., 2011)			
J123	<i>Buthus martensii</i> Karsch	Inhibit current (20%), Human, HEK293, 1 μM, (Shijin et al., 2008)	Inhibit current, Human, HEK293, IC ₅₀ = 26.4 nM, (Shijin et al., 2008)	Inhibit current, Rat, HEK293, IC ₅₀ = 0.79 nM (Shijin et al., 2008)			
KAaH1	<i>Androctonus australis</i> Hector	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 5 nM, (Srairi-Abid et al., 2005)			Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 50 nm, (Srairi-Abid et al., 2005)		
Kaliotoxin α-KTx3.1	<i>Androctonus mauretanicus mauretanicus</i>	Inhibit current, Mouse, L929, Kd = 41 nM, (Grissmer et al., 1994)	Inhibit current, Rat, B82 fibroblast, Kd > 1 μM, (Grissmer et al., 1994)	Inhibit current, Mouse, L929, Kd = 0.65 nM, (Grissmer et al., 1994)	Inhibit current, Human, MEL, Kd > 1 μM, (Grissmer et al., 1994)		
K-KTx 2.5	<i>Opisthacanthus cayaporum</i>	Inhibit current, Human, CHO, IC ₅₀ = 217 μM, (Camargos et al., 2011)			Inhibit current, Human, CHO, IC ₅₀ = 71 μM, (Camargos et al., 2011)		
Kbot1	<i>Buthus occitanus tunetanus</i>	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 145 nM, (Mahjoubi-Boubaker et al., 2004)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 2.5 nM, (Mahjoubi-Boubaker et al., 2004)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 15 nM, (Mahjoubi-Boubaker et al., 2004)			
Kbot55 α-Ktx31.1	<i>Buthus occitanus tunetanus</i>	Inhibit current, Shaker IR, <i>Xenopus</i> oocytes, 1 μM, (ElFessi-Magouri et al., 2015)					
LmKTx10	<i>Lychas mucronatus</i>	Inhibit current, Mouse, HEK293, IC ₅₀ = 1.73 μM, (Liu et al., 2009)	Inhibit current, Human, HEK293, IC ₅₀ = 12.63 μM, (Liu et al., 2009)	Inhibit current, Mouse, HEK293, IC ₅₀ = 28 nM, (Liu et al., 2009)			
LmKTx8	<i>Lychas mucronatus</i>			Inhibit current, Mouse, COS7, IC ₅₀ = 26.4 nM, (Wu et al., 2007)			
Margatoxin (MgTx)	<i>Centruroides margaritatus</i>	Inhibit current, ShH4, IC ₅₀ = 150 nM,	Inhibit current, Human, tsA201 cells, Kd = 4.2 nM, (Bartok	Human, tsA201 cells, Kd = 6.4 pM,	Inhibit current, Human, tsA201 cells, Kd = 11.7 pM, (Bartok et al., 2014); Inhibit	Inhibit current, Rat, IC ₅₀ > 200 nM,	Inhibit current, Rat, IC ₅₀ = 5 nM,

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Table 2 (continued)

Peptide	Species	Drosophila Shaker K ⁺	Kv1.1	Kv1.2	Kv1.3	Kv1.4	K1.5	Kv1.6	Kv4.1	Kv4.2	Kv4.3
		(Garcia-Calvo et al., 1993)	et al., 2014); Inhibit current, Mouse, L929 cells, Kd = 1.7 nM, (Bartok et al., 2014)	(Bartok et al., 2014)	current, Human T lymphocyte, Kd = 10.1 pM, (Bartok et al., 2014); Inhibit current, IC50 = 30 pM, (Garcia-Calvo et al., 1993); Inhibit current, Human, CHO, 10 nM, (Nikouee et al., 2012)		(Garcia-Calvo et al., 1993)	(Garcia-Calvo et al., 1993)			
Martentoxin	<i>Buthus martensi</i> Karsch										
Maurotoxin α -KTx6.2	<i>Scorpio maurus palmatus</i>	Inhibit current, ShB, <i>Xenopus</i> oocytes, IC50 = 2.4 nM, (di Luccio et al., 2002); Inhibit current, ShB, <i>Xenopus</i> oocytes, IC50 = 2 nM, (Carlier et al., 2000)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 45 nM, (Kharrat et al., 1997); Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 37 nM, (Kharrat et al., 1996)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 0.8 nM, (Kharrat et al., 1997); Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 0.8 nM, (Kharrat et al., 1996); Inhibit current, Mouse, B82, IC50 = 120 pM, (Castle et al., 2003)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 180 nM, (Kharrat et al., 1997); Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 150 nM, (Kharrat et al., 1996)						
Mesomartoxin	<i>Mesobuthus martensii</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, IC50 = 54 pM, (Wang et al., 2015)		Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 15.6 nM, (Wang et al., 2015)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 12.5 μ M, (Wang et al., 2015)						
MeuKTx α -KTx3.13	<i>Mesobuthus eupeus</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, 2 μ M, (Gao et al., 2010)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 203.15 pM, (Gao et al., 2010)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 8.92 nM, (Gao et al., 2010)	Inhibit current, Human, <i>Xenopus</i> oocytes, IC50 = 171 pM, (Gao et al., 2010)			Inhibit current, Rat, <i>Xenopus</i> oocytes, 2 μ M, (Gao et al., 2010)			
MeuTx3B	<i>Mesobuthus eupeus</i>				Inhibit current, Human, <i>Xenopus</i> oocytes, 2 μ M, (Gao et al., 2011)						
Noxiustoxin α -KTx2.1	<i>Centruroides noxius</i>		Inhibit current, Mouse, L929, Kd > 25 nM, (Grissmer et al., 1994)	Inhibit current, Rat, B82 fibroblast, Kd = 2 nM, (Grissmer et al., 1994)	Inhibit current, Mouse, L929, Kd = 1 nM, (Grissmer et al., 1994)			Inhibit current, Human, MEL, Kd > 25 nM, (Grissmer et al., 1994)			
OcyKTx2 α -KTx6.17	<i>Opisthacanthus cayaporum</i>	Inhibit current, ShB, Sf9, Kd = 82 nM, (Schwartz et al., 2013)				Inhibit current, Human T lymphocytes, Kd = 18 nM, (Schwartz et al., 2013)					
OdK1 α -KTx 8.5	<i>Odonthobuthus doriae</i>			Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 183 nM, (Abdel-Mottaleb et al., 2006a)							

OdK2 α -KTX3.11	<i>Odonthobuthus doriae</i>			Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 7.2 nM, (Abdel-Mottaleb et al., 2008a)
OSK1 α -KTX3.7	<i>Orthochirus scrobiculosus</i>	Inhibit current, Mouse, COS7, IC ₅₀ = 0.6 nM, (Mouhat et al., 2005)	Inhibit current, Human, COS7, IC ₅₀ = 5.4 nM, (Mouhat et al., 2005)	Inhibit current, Mouse, L929, IC ₅₀ = 14 pM, (Mouhat et al., 2005)
OSK2 α -KTX 13.2	<i>Orthochirus scrobiculosus</i>		Inhibit current, <i>Xenopus</i> oocyte, Kd = 97 nM, (Dudina et al., 2001)	
PBTx1	<i>Parabuthus transvaalicus</i>	Inhibit current, <i>Xenopus</i> oocyte, Kd = 21.1 μ M, (Huys et al., 2004b)	Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 1.0 μ M, (Huys et al., 2004b)	Inhibit current, <i>Xenopus</i> oocyte, Kd = 0.8 μ M (Huys et al., 2004b)
PBTx3 α -KTx1.10	<i>Parabuthus transvaalicus</i>	Inhibit current, <i>Xenopus</i> oocytes, Kd = 79 μ M, (Huys et al., 2002)	Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 547 nM, (Huys et al., 2002)	Inhibit current, <i>Xenopus</i> oocytes, Kd = 492 nM, (Huys et al., 2002)
Pi1	<i>Pandinus imperator</i>	Inhibit current, ShB, <i>Xenopus</i> oocytes, IC ₅₀ = 23 nM, (Fajloun et al., 2000a); Inhibit current, ShB, Sf9, Kd = 32 nM, (Gomez-Lagunas et al., 1997)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 0.44 nM, (Fajloun et al., 2000a)	Inhibit current, Human T lymphocytes, Kd = 11.4 nM, (Peter et al., 2000); Inhibit current, Human T lymphocytes, Kd = 9.7 nM, (Peter et al., 1998)
Pi2 (PiTX-K α)	<i>Pandinus imperator</i>	Inhibit current, ShB, Sf9, Kd = 8.2 nM, (Gomez-Lagunas et al., 1996)	Inhibit current, B82, IC ₅₀ = 32 pM, (Rogowski et al., 1996)	Inhibit current, Human T lymphocytes, Kd = 50 pM, (Peter et al., 2000; Peter et al., 1998)
Pi3 (PiTX-K β)	<i>Pandinus imperator</i>	Inhibit current, ShB, Sf9, Kd = 140 nM, (Gomez-Lagunas et al., 1996)		Inhibit current, Human T lymphocytes, Kd = 0.5 nM, (Peter et al., 2000; Peter et al., 1998)
Pi4	<i>Pandinus imperator</i>	Inhibit current, ShB, <i>Xenopus</i> oocytes, IC ₅₀ = 3 nM, (M'Barek et al., 2003); Inhibit current, ShB, Sf9, Kd = 8 nM, (Olamendi-Portugal et al., 1998)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC ₅₀ = 8 pM, (M'Barek et al., 2003)	
SjAPI-2	<i>Scorpiops jendeki</i>	Inhibit current, Mouse, HEK293, 1 μ M, (Chen et al., 2015)	Inhibit current, HEK293, 1 μ M, (Chen et al., 2015)	Inhibit current, Mouse, HEK293, 1 μ M, (Chen et al., 2015)
StKTx23	<i>Scorpiops jendeki</i>			Inhibit current, HEK293, 1 μ M, (Chen et al., 2012)
Tamulustoxin				

Table 2 (continued)

Peptide	Species	Drosophila Shaker K+	Kv1.1	Kv1.2	Kv1.3	Kv1.4	K1.5	Kv1.6	Kv4.1	Kv4.2	Kv4.3
	<i>Mesobuthus tamulus</i>							Inhibit current, Human, CHO, 500 nM, (Strong et al., 2001)			
Tc1	<i>Tityus cambridgei</i>	Inhibit current, ShB, SF9, Kd = 65 nM, (Batista et al., 2000)									
Tc	<i>Tityus cambridgei</i>	Inhibit current, ShB, SF9, Kd = 4.7 μM, (Batista et al., 2002)			Inhibit current, Human T lymphocyte, Kd = 16 nM, (Batista et al., 2002);						
Tc32	<i>Tityus cambridgei</i>	Inhibit current, ShB, SF9, Kd = 74 nM, (Batista et al., 2002)			Inhibit current, Human T lymphocyte, Kd = 10 nM, (Batista et al., 2002); Inhibit current, Mouse olfactory bulb and peri-glomerular cells, 1 μM, (Stehling et al., 2012)						
TdK1 α-KTx4.3	<i>Tityus discrepans</i>	Inhibit current, ShB, SF9, Kd = 280 nM, (D'Suze et al., 1999)									
Ts15α-Ktx21.1	<i>Tityus serrulatus</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, 0.5 μM, (Cologna et al., 2011)		Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 196 nM, (Cologna et al., 2011)	Inhibit current, Human, <i>Xenopus</i> oocytes, IC50 = 508 nM, (Cologna et al., 2011)			Inhibit current, Rat, <i>Xenopus</i> oocytes, 0.5 μM, (Cologna et al., 2011)			
Ts19 Frag-II	<i>Tityus serrulatus</i>			Inhibit current, <i>Xenopus</i> oocytes, IC50 = 544 nM, (Cerni et al., 2015)							
Ts6 (TSCTX-IV) α-KTx12.1	<i>Tityus serrulatus</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 6.19 nM, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocytes, IC50 = 0.55 nM, (Cerni et al., 2014)		Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)			Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)
Ts7 (TSCTX-Kα) α-KTx4.1	<i>Tityus serrulatus</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, CL1023, Kd = 0.21 nM, (Werkman et al., 1993); Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)	Inhibit current, Mouse, <i>Xenopus</i> oocytes, Kd = 3.9 nM, (Rodrigues et al., 2003); Inhibit current, Mouse, L929, Kd = 198 nM, (Rodrigues et al., 2003); Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)			Inhibit current, Rat, <i>Xenopus</i> oocytes, 1 μM, (Cerni et al., 2014)			
Tst26 α-KTx 4.6	<i>Tityus stigmurus</i>			Inhibit current, Human, COS7, Kd = 1.9 nM, (Papp et al., 2009)	Inhibit current, Human T lymphocyte, Kd = 10.7 nM, (Papp et al., 2009)						
TstβKTx	<i>Tityus stigmurus</i>		Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 96 nM, (Diego-Garcia et al., 2008)	Inhibit current, Rat, <i>Xenopus</i> oocytes, 300 nM, (Diego-Garcia et al., 2008)	Inhibit current, Rat, <i>Xenopus</i> oocytes, 300 nM, (Diego-Garcia et al., 2008)						

Tt28 α -KTx20.1	<i>Tityus trivittatus</i>		(Diego-Garcia et al., 2008) Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 102.76 nM, (Abdel-Mottaleb et al., 2006b)	Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 7.9 nM, (Abdel-Mottaleb et al., 2006b)
Urotoxin α -KTx-6.21	<i>Urodacus yaschenko</i>	Inhibit current, Human, CHO, IC50 = 253 nM, (Luna-Ramirez et al., 2014)	Inhibit current, Human, CHO, IC50 = 160 pM, (Luna-Ramirez et al., 2014)	Inhibit current, Human, CHO, IC50 = 91 nM, (Luna-Ramirez et al., 2014)
Vm24 α -KTx 23.1	<i>Vaejovis mexicanus smithi</i>	Inhibit current, Mouse, L929 cells, Kd = 30–40 nM, (Varga et al., 2012)	Inhibit current, Human, COS7, Kd = 5–10 nM, (Varga et al., 2012)	Inhibit current, Human T lymphocytes, Kd = 3 pM, (Gurrola et al., 2012); Inhibit current, Human T lymphocytes, Kd = 2.9 pM, (Varga et al., 2012)
α -KTx 2.14	<i>Rhopalurus garridoi</i>	Inhibit current, Human, CHO, IC50 = 1 μ M, (Rodriguez-Ravelo et al., 2014)		
κ -Hefutoxin 1	<i>Heterometrus fulvipes</i>		Inhibit current, Rat, <i>Xenopus</i> oocytes, Kd = 150 μ M, (Srinivasan et al., 2002)	Inhibit current and delay activation, Rat, <i>Xenopus</i> oocytes, Kd = 40 μ M, (Srinivasan et al., 2002)
λ -MeuKTx-1	<i>Mesobuthus eupeus</i>	Inhibit current, ShIR, <i>Xenopus</i> oocytes, IC50 = 12.3 μ M, (Gao et al., 2013)		
α -KTx 10.4 (II-10.4)	<i>Centruroides tecomanus</i>		Inhibit current, Human, tsA201, IC50 = 3.6 nM, (Olamendi-Portugal et al., 2016)	Inhibit current, Human T lymphocytes, IC50 = 72 nM, (Olamendi-Portugal et al., 2016)
α -KTx 2.15 (II-10.5)	<i>Centruroides tecomanus</i>	Inhibit current, ShIR, tsA201, IC50 = 8.3 nM, (Olamendi-Portugal et al., 2016)	Inhibit current, Human, tsA201, IC50 = 0.3 nM, (Olamendi-Portugal et al., 2016)	Inhibit current, Human T lymphocytes, IC50 = 8.3 nM, (Olamendi-Portugal et al., 2016)
α -KTx 2.16 (II-12.5)	<i>Centruroides tecomanus</i>		Inhibit current, Human, tsA201, IC50 = 0.7 nM, (Olamendi-Portugal et al., 2016)	Inhibit current, Human T lymphocytes, IC50 = 26.2 nM, (Olamendi-Portugal et al., 2016)
α -KTx 2.17 (II-12.8)	<i>Centruroides tecomanus</i>	Inhibit current, Human, tsA201, IC50 = 4.8 nM, (Olamendi-Portugal et al., 2016)	Inhibit current, Human, tsA201, IC50 = 2.9 nM, (Olamendi-Portugal et al., 2016)	

Note: Data represented sequentially as: Action, channel species origin for recombinant expression (if reported), expression system, concentration, reference.

	<i>Centruroides noxius</i>	Inhibit current, Human, CHO, $K_d = 4.5$ nM, (Restano-Cassulini et al., 2006); Inhibit current, Rat, CHO, $K_d = 6.8$ nM, (Restano-Cassulini et al., 2006)	Inhibit current, Rat, CHO, $K_d = 2.8$ nM, (Restano-Cassulini et al., 2006)	Inhibit current, Human, CHO, $K_d = 4.05$ nM, (Restano-Cassulini et al., 2006); Inhibit current, Rat, CHO, $K_d = 38.1$ nM, (Restano-Cassulini et al., 2006)	
HeTx204	<i>Heterometrus petersii</i>			Inhibit current, HEK293, 10 μ M, (Chen et al., 2012)	
ImKTx104	<i>Isometrus maculatus</i>			Inhibit current, HEK293, $K_d = 11.69$ μ M, (Chen et al., 2012)	
Lq2	<i>Leiurus quinquestriatus</i> var. <i>Hebraeus</i>				Inhibit current, <i>Xenopus</i> oocytes, $K_i = 0.41$ μ M, (Lu and MacKinnon, 1997)
SjAPI-2	<i>Scorpiops jendeki</i>			Inhibit current, HEK293, $IC_{50} = 771.5$ nM, (Chen et al., 2015)	
Ts6 (TSCTX-IV) α -KTx12.1	<i>Tityus serrulatus</i>	Inhibit current, Human, <i>Xenopus</i> oocyte, 1 μ M, (Cerni et al., 2014)		Inhibit current, Rat, <i>Xenopus</i> oocyte, 1 μ M, (Cerni et al., 2014)	Inhibit current, Rat, <i>Xenopus</i> oocyte, 1 μ M, (Cerni et al., 2014)
γ -KTx 1.9 (II-10.9)	<i>Centruroides tecomanus</i>	Inhibit Current, Human, tsA201, $IC_{50} = 16.9$ nM			

Note: Data represented sequentially as: Action, channel species origin for recombinant expression (if reported), expression system, concentration, reference.

Table 4
Action of scorpion toxin peptides on calcium-activated potassium channels.

Peptide	Species	BK Channels	IK (KCa3·1/KCNN4) Channel	SK1	SKCa2	SKCa3
BmBKTx1	<i>Buthus martensii</i> Karsch	Inhibit current, Cockroach pSlo, HEK293, $K_d = 82$ nM, (Xu et al., 2004); Inhibit current, Fruit-fly dSlo, HEK293, $K_d = 194$ nM, (Xu et al., 2004)				
BmP09	<i>Buthus martensii</i> Karsch	Inhibit current, Mouse mSlo1, <i>Xenopus</i> oocytes, $EC_{50} = 27$ nM, (Yao et al., 2005)				
Charbydotoxin (ChTX)	<i>Leiurus quinquestriatus hebraeus</i>	Inhibit current, Rat, Phospholipid bilayers, $K_d = 10$ nM, (Miller et al., 1985); Inhibit current, Rabbit PCT, $IC_{50} = 7.3$ nM, (Tauc et al., 1993); Inhibit current, Snail ganglion, $K_d = 20$ nM, (Crest et al., 1992); Inhibit current, hSlo(α) Human, <i>Xenopus</i> oocytes, $EC_{50} = 30.8$ nM, (Gribkoff et al., 1996)	Inhibit current, Human RBC, $ID_{50} = 4.2$ nM, (Brugnara et al., 1993); Inhibit current, HEK293, $IC_{50} = 28$ nM, (Jensen et al., 1998); Inhibit current, Bovine BAEC, $IC_{50} = 3.3$ nM, (Cai et al., 1998), Inhibit current, Bovine BAEC, $IC_{50} = 3.3$ nM, (Cai et al., 1998)			
Iberiotoxin (IbTX)	<i>Buthus tamulus</i>	Inhibit current, Rabbit PCT, $K_d = 0.5$ μ M, (Tauc et al., 1993); Inhibit current, Bovine aortic smooth muscle, $IC_{50} = 250$ pM, (Galvez et al., 1990); Inhibit current, Mouse mSlo1, <i>Xenopus</i> oocytes, $EC_{50} = 9.1$ nM, (Gribkoff et al., 1996); Inhibit current, Human gBK, U251 glioma cells, 100 nM, (Tao et al., 2011); Inhibit current, Human hSlo(α), <i>Xenopus</i> oocytes, $EC_{50} = 7.9$ nM, (Gribkoff et al., 1996)				
Kaliootoxin (KTX)	<i>Androctonus mauretanicus mauretanicus</i>	Inhibit current, Rabbit PCT, $IC_{50} = 0.48$ μ M, (Tauc et al., 1993); Inhibit current, Snail ganglion, $K_d = 20$ nM, (Crest et al., 1992)				
Margatoxin (MgTx)	<i>Centruroides margaritatus</i>		Inhibit current, Human, HEK293, $IC_{50} = 459$ nM, (Jensen et al., 1998); Inhibit current, Bovine BAEC, 100 nM, (Cai et al., 1998)			
Martentoxin	<i>Buthus martensii</i> Karsch	Inhibit current, Rat, Adrenal medulla chromafin cells, $IC_{50} = 21$ nM, (Ji et al., 2003); Enhanced current, Human gBK, U251 glioma, $EC_{50} = 46.7$ nM, (Tao et al., 2011); Enhanced current, Human BK (hSlo α + β 1), <i>Xenopus</i> oocytes, $EC_{50} = 495$ nM, (Tao et al., 2011); Inhibit current, Human BK (hSlo α + β 4), $IC_{50} = 80$ nM, (Shi et al., 2008); Inhibit current, Human BK (hSlo α + β 4), HEK293, $IC_{50} = 186$ nM, (Tao et al., 2014)				
Maurotoxin α -KTx6.2	<i>Scorpio maurus palmatus</i>		Inhibit current, Human RBC, $IC_{50} = 50$ nM, (Castle et al., 2003); Inhibit current, Human, CHO, $IC_{50} = 1.1$ nM, (Castle et al., 2003)		Inhibit current, Human, Jurkat, $K_d = 1$ μ M, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, $K_d = >1$ μ M, (Shakkottai et al., 2001)
OSK1 α -KTx3.7	<i>Orthochirus scrobiculosus</i>					

Pi1	<i>Pandinus imperator</i>		Inhibit current, Human, tsA, IC ₅₀ = 225 nM, (Mouhat et al., 2005)		Inhibit current, Human, Jurkat, K _d = 100 nM, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, K _d = 250 nM, (Shakkottai et al., 2001)
PO1	<i>Androctonus mauretanicus mauretanicus</i>				Inhibit current, Human, Jurkat, K _d = >1 μM, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, K _d = >1 μM, (Shakkottai et al., 2001)
PO5	<i>Androctonus mauretanicus mauretanicus</i>				Inhibit current, Human, Jurkat, K _d = 22 nM, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, K _d = 25 nM, (Shakkottai et al., 2001)
SjAPI-2	<i>Scorpiops jendeki</i>		Inhibit current, Human, HEK293, 1 μM, (Chen et al., 2015)		Inhibit current, Rat, HEK293, 1 μM, (Chen et al., 2015)	Inhibit current, Human, HEK293, 1 μM, (Chen et al., 2015)
Slotoxinz KTx1.11	<i>Centruroides noxius Hoffmann</i>	Inhibit current, Human hSlo(α), <i>Xenopus</i> oocytes, K _d = 1.5 nM, (Garcia-Valdes et al., 2001); Inhibit current with delayed action, Human BK (hSloα + β1), <i>Xenopus</i> oocytes, 100 nM, (Garcia-Valdes et al., 2001); Inhibit current with delayed action, Human BK (hSloα + β4), 1 μM, (Garcia-Valdes et al., 2001)				
Scyllatoxin (Leiuurotoxin) αKTx5.1	<i>Leiurus quinquestriatus hebraeus</i>				Inhibit current, Human, Jurkat, K _d = 0.2 nM, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, K _d = 1.1 nM, (Shakkottai et al., 2001)
Tamapin	<i>Mesobuthus tamulus</i>			Inhibit current, Human, CHO, IC ₅₀ = 32 nM, (Pedarzani et al., 2002)	Inhibit current, Rat, HEK293, IC ₅₀ = 24 pM, (Pedarzani et al., 2002)	Inhibit current, Rat, HEK293, IC ₅₀ = 1.7 nM, (Pedarzani et al., 2002)
Ts6 (TSCTX-IV) α-KTx12.1	<i>Tityus serrulatus</i>	Inhibit current, Mouse Leydig, 50 nM, (Novello et al., 1999)				
Tsk	<i>Tityus serrulatus</i>		Inhibit current, Human, HEK293, IC ₅₀ = 70 nM, (Luna-Ramirez et al., 2014)		Inhibit current, Human, Jurkat, K _d = 80 nM, (Shakkottai et al., 2001)	Inhibit current, Human, COS7, K _d = 197 nM, (Shakkottai et al., 2001)
Urotoxinα-KTx- 6.21	<i>Urodacus yaschenkoi</i>		Inhibit current, Human, HEK293, IC ₅₀ = 70 nM, (Luna-Ramirez et al., 2014)			
Vm24α-KTx 23.1	<i>Vaejovis mexicanus smithi</i>		Inhibit current, Human, COS7, K _d = 14–30 nM, (Varga et al., 2012)			

Note: Data represented sequentially as: Action, channel species origin for recombinant expression (if reported), expression system, concentration, reference.

	<i>Parabuthus transvaalicus</i>	Depolarisation of activation threshold and inhibit current, Rat, <i>Xenopus</i> oocytes, $K_d = 15$ nM, (Chuang et al., 1998)	Depolarisation of activation threshold and inhibit current, Human, <i>Xenopus</i> oocytes, $K_d = 61$ nM, (Chuang et al., 1998)	
Kurtxin-like 1 (KLI)	<i>Parabuthus granulatus</i>		Depolarisation of activation threshold and weakly inhibits current, Rat, <i>Xenopus</i> oocytes, 700 nM, (Olamendi-Portugal et al., 2002)	
Maurocalcine (MCA)	<i>Scorpio maurus palmatus</i>			Subconductance state, Rabbit, Planar lipid bilayers, 100 nM, (Xiao et al., 2016); Subconductance state, Planar lipid bilayers, 50 nM, (Fajloun et al., 2000b)
Opicalcin 1 (OpCa1)	<i>Opisththalmus carinatus</i>			Subconductance state, Rabbit, Planar lipid bilayers, 100 nM, (Xiao et al., 2016)
Opicalcin 2 (OpCa2)	<i>Opisththalmus carinatus</i>			Subconductance state, Rabbit, Planar lipid bilayers, 100 nM, (Xiao et al., 2016)
Ryanotoxin	<i>Buthotus judiacus</i>			Subconductance state, Rabbit, Skeletal Muscle SR, $ED_{50} = 0.16$ μ M, (Morrisette et al., 1996)
Urocalcine (UrCa)	<i>Urodaeus yaschenkoi</i>			Subconductance state, Rabbit, Planar lipid bilayers, 1 μ M, (Xiao et al., 2016)
Vejocalcin (VrCa)	<i>Vaejovis mexicanus</i>			Subconductance state, Rabbit, Planar lipid bilayers, 100 nM, (Xiao et al., 2016)
ϕ -LITX-Lw1a	<i>Liocheles waigiensis</i>			Excitatory increasing opening probability and time in the open state with reduced closed time, Rabbit, lipid bilayer, $AC_{50} = 6.0$ pM, (Smith et al., 2013)
				Excitatory increasing opening probability and time in the open state with reduced closed time, Sheep, lipid bilayer, $AC_{50} = 2.0$ pM, (Smith et al., 2013)

Table 5 (continued)

Peptide	Species	Cav3.1 ($\alpha 1G$)	Cav3.2 ($\alpha 1H$)	Cav3.3 ($\alpha 1I$)	RyR1	RyR2	RyR3	CFTR Cl channel	CIC-2 Cl channel
α -KTx 2.15 (II-10.5)	<i>Centruroides tecomamus</i>	Inhibition of current, Human, tsA201, IC500 = 6.4 nM, (Olamendi-Portugal et al., 2016)							
α -KTx 2.16 (II-12.5)	<i>Centruroides tecomamus</i>	Inhibition of current, Human, tsA201, IC500 = 56 nM, (Olamendi-Portugal et al., 2016)							

Note: Data represented sequentially as: Action, channel species origin for recombinant expression (if reported), expression system, concentration, reference.

potency and specificity. The specificity of these peptides on Kv1.1 is uncertain as the majority of studies have had limited testing across subclasses. KAaH1 appears to be selective for Kv1.1, with an IC₅₀ of 5 nM compared to Kv1.4 with an IC₅₀ of 50 nM (Srairi-Abid et al., 2005). Margatoxin (*Centruroides margaritatus*) has the greatest affinity for Kv1.2 (K_d = 5.4 pM) but is not selective, also acting on Kv1.1 and Kv1.3 channels (Bartok et al., 2014). Urotoxin (*Urodacus yaschenk*) appears particularly specific for Kv1.2 (IC₅₀ = 160 pM) compared to Kv1.1 (IC₅₀ = 253 nM) or Kv1.3 (IC₅₀ = 91 nM) (Luna-Ramirez et al., 2014). The most specific inhibitor of Kv1.3 is the peptide Vm24 (*Vaejovis mexicanus smithi*), with a K_d of 2.9 pM compared to 30–40 nM and 5–10 nM for Kv1.1 and Kv1.2 respectively, and K_d 14–30 nM for KCa3.1 channels (Varga et al., 2012). Vm24 has the highest affinity of all the Kv toxins. Another highly selective Kv1.3 inhibitor is Bs-KTx6 (*Buthus sindicus*) with an IC₅₀ of 7.7 pM, whereas its action on Nav1.1 and Nav1.2 required application of micromolar concentrations. The most specific inhibitor of Kv1.4 was the peptide κ -KTx 2.5 (*Opisthacanthus cayaporum*); IC₅₀ = 71 μ M. While requiring relatively high concentrations for effect, it was screened against 12 Kv and 5 Nav channels and was found to be selective for Kv1.4, as well as having minor action on Kv1.1 (IC₅₀ = 217 μ M) (Camargos et al., 2011). In contrast no particularly specific blockers of Kv1.5 or Kv1.6 have been identified to date. Tamulostoxin (*Mesobuthus tamulus*) acts on Kv1.6 at 500 nM (Strong et al., 2001), but selectivity against other channels has not been determined. BmTx3 (*Buthus martensii* Karsch) appears to be selective for Kv4 channels, showing preference for Kv4.1 acting with an IC₅₀ of 105 nM (Vacher et al., 2006).

Table 3 summarizes SCTX peptide actions on the ERG, Kv7 and Kir voltage-gated potassium channel families. Seven of these peptides target ERG1–3 channels, of which none were particularly selective between subclasses. BmTx3 was selective for hERG (human ERG) over a number of other potassium channels, (Kv1.1, Kv1.2, Kv1.3, KCNQ1 and KCNQ1+mIsK, Kir2.1) but its selectivity between ERG subclasses has not been assessed (Huys et al., 2004a). The peptide ErgTx1 (*Centruroides noxius*) showed some preference for ERG2 channels (Restano-Cassulini et al., 2006), while peptides CeErg4 and CeErg5 (*Centruroides elegans elegans*) showed some preference for ERG3 channels (Restano-Cassulini et al., 2008). SCTX peptides were able to discriminate between human and rat ERG channel isoforms. For example, ErgTx1, CeErg4, and CeErg5 did not affect the human ERG2 isoform despite action on rat ERG2, and ErgTx1 had much lower affinity for the rERG3 than the hERG3 isoform. The Kv7 family has very limited reported sensitivity to SCTXs, where AaTXKb2-64 (*Androctonus australis*) peptide is excitatory (Landoulsi et al., 2013). This peptide was shown to be a subtype-selective activator of Kv7.2/3, Kv7.3, and Kv7.4 ion channels at a concentration of 20 μ g/ml, while not affecting Kv1.1, Kv7.1, Kv7.2 m and Kv7.5 (Landoulsi et al., 2013). The only peptide reported to block Kir1.1 is Lq2 (*Leiurus quinquestriatus* var. *Hebraeus*) with a K_i of 0.41 μ M, a concentration that did not affect IRK1 channels (Lu and MacKinnon, 1997).

3.3. Scorpion toxin peptide action on calcium-activated potassium channels

Table 4 classifies 20 identified SCTX peptides acting on K_{Ca} channels, with evident capacity to discriminate between big (BK_{Ca}), intermediate (IK_{Ca}), and small conductance (SK_{Ca}) potassium channels. Of the 7 peptides that were relatively specific for BK_{Ca}, Iberitoxin (*Buthus tamulus*) appears to be one of the most potent selective inhibitors, generally acting at nanomolar concentrations (Gribkoff et al., 1996). Slotoxin (*Centruroides noxius* Hoffmann) also has one of the highest affinities, with a K_d of 1.5 nM (hSlo α) in *Xenopus* oocytes (Garcia-Valdes et al., 2001). In addition, study of

Slotoxin indicated that the beta subunits were significant effectors, significantly delaying responses in the presence of either $\beta 1$ or $\beta 4$ subunits (Garcia-Valdes et al., 2001). Martentoxin (*Buthus martensii* Karsch) was the only peptide to show excitatory effects on human glioma and hSlo α with $\beta 1$, again showing modulation of action by the presence of β subunits (Tao et al., 2011).

All SCTX peptides shown to act on IK_{Ca} channels are inhibitory. Maurotoxin (*Scorpio maurus palmatus*) was one of the most potent and selective inhibitors, with an IC_{50} of 1.1 nM for hIK_{Ca} in CHO cells, Castle et al., (2003). At micromolar concentrations it had only minimal effects on SK_{Ca} channels, and did not affect BK_{Ca} channels. Similarly all the peptides acting on SK_{Ca} channels were inhibitory. Tamapin (*Mesobuthus tamulus*) was the most potent peptide acting on SK_{Ca} channels. It demonstrated remarkable selectivity for SK2 with an IC_{50} of 24 pM, 1750 fold more sensitive than for SK1 and 30 fold more than SK2 (Pedarzani et al., 2002). In addition it did not affect the IK_{Ca} channel. Scyllatoxin (*Leiurus quinquestratus hebraeus*), also known as Leiurotoxin, was another potent SK_{Ca} inhibitor and again showed preference for the SK2 channel with a K_d of 0.2 nM (Shakkottai et al., 2001).

3.4. Actions of scorpion peptides on calcium channels and chloride channels

Fewer SCTX peptides are able to modulate calcium or chloride channels (Table 5), with only 16 peptides affecting calcium channels, 8 of which were identified in 2016 (Xiao et al., 2016), while 2 SCTX peptides modulate chloride channels. SCTXs have inhibitory effects on Cav3.1–3.3 channels, depolarising the activation threshold and decreasing current flow.

Kurtoxin (*Parabuthus transvaalicus*) was found to selectively inhibit Cav3.1 and Cav3.2 with a K_d of 15 nM and 61 nM respectively without affecting high-voltage activated channels in *Xenopus* oocytes. Subsequently Kurtoxin has been found to modulate a variety of Nav channels (Chuang et al., 1998; Zhu et al., 2009c), as well high-voltage activated calcium channels in rats (Sidach and Mintz, 2002). The scorpion *Parabuthus granulatus* produces two similar peptides, Kurtoxin-like II (KLII), which is identical to Kurtoxin, as well as Kurtoxin-like I (KLI), that weakly blocks Cav3.3 and hNav1.5 channels at 700 nM (Olamendi-Portugal et al., 2002). RyR channels were modulated by SCTX peptides into long-lived subconductance states, as well as increasing channel opening probability and reducing closed time. The SCTX peptide ϕ -LITX-Lw1a (*Liocheles waigiensis*) was remarkably potent, affecting RyR1 and RyR2 at femtomolar concentrations, and had an AC_{50} of 6.0 pM and 2.0 pM (Smith et al., 2013). A number of calcins have recently been shown to affect RyR1, but not yet been screened against other RyR and calcium channel subtypes to determine their selectivity. Imperacalcin (*Pandinus imperator*) is the only identified scorpion RyR3 modulator, inducing a subconductance state when applied at 100 nM, but it also able to potently modulate RyR1 and RYR2 channels (Nabhani et al., 2002).

The only peptide found to modulate the CFTR chloride channel was GaTx1 (*Leiurus quinquestratus hebraeus*), which had an IC_{50} of 48 nM (Fuller et al., 2007). This peptide appears highly specific and was shown to have no effect on a panel of nine transport proteins including chloride, potassium and the ABC families (Fuller et al., 2007). GaTx2 (*Leiurus quinquestratus hebraeus*) is the only peptide discovered to inhibit CIC chloride channels. GaTx2 was found to specifically inhibit the CIC-2 channel with a K_d of 22 pM (Thompson et al., 2009). This peptide was highly specific and did not affect CIC-1, CIC3–4, CFTR, or a number of other chloride and potassium channels (Thompson et al., 2009).

4. Discussion

This review provides a comprehensive analysis of specific functionally validated SCTX peptide actions across ion channel subclasses. The information provided by the analysis is intended to be of sufficient detail to allow informed comparison of toxin effects across differing channel types and expression systems. In addition, the review provides a substantial data resource to highlight the breadth of specific SCTX peptides and also serves to draw attention to areas of SCTX research where the knowledge base is limited by the lack of comparison across ion channel types. This review will also assist to reduce redundancy of research where replication of findings is robust, and conversely, identifies areas of characterization where replication is needed to improve the validation of functionality.

Advances in molecular techniques over the last two decades have significantly revolutionised the experimental approaches used to assess SCTX action on ion channels. Early publications within the field typically examined the effects of poorly defined crude venom on net membrane current flux, and then moved to isolating and examining the function of novel peptides within this mixture. Likely ion channel targets were identified by structural comparison of these peptides to other peptides with known action, allowing more directed research, reducing the need for toxin purification, lowering costs, and saving time. However this reductionist approach likely impacted on the breadth of screening for SCTX effects, limiting identification of peptide selectivity across ion channel subfamilies. Our analysis indicates that the number of studies prioritising the identification of specific molecular targets using isolated and well-defined peptide fragments has steadily increased overtime. The development of recent techniques such as site-directed mutagenesis, production of recombinant toxin variants and chimeric ion channel constructs, together with use of improved 3D modelling, has allowed greater understanding of toxin-channel interactions and the underlying mechanisms determining the SCTX selectivity and affinity (Gilchrist and Bosmans, 2012; Zhang et al., 2011, 2012; Gur et al., 2011; Gurevitz, 2012; Ma et al., 2013). Use of cloned ion channels within expression systems has been central to study of SCTX peptide action. *Xenopus* oocytes were identified as the most commonly used expression system, with mammalian cell lines such as HEK293 and CHO also prevalent. One pertinent example involving mutagenesis was the study of SCTX ErgTx1 (*Centruroides noxius*) to analyse interactions with human ERG K^+ channels, using CHO cells (Jimenez-Vargas et al., 2012b).

The need for further research within the field is evident from the expanding library of SCTX peptides, given that venom from each of the ~1500 scorpion species is thought to have around 70 peptides, with only a minority having been functionally assessed (Possani et al., 1999). There is clear homology of the SCTX peptides across species that act on specific channel classes. For example, as noted, Kurtoxin has been isolated from both *Parabuthus transvaalicus* and *Parabuthus granulatus* with potent action on Cav3.1 and Cav3.2 (Chuang et al., 1998; Olamendi-Portugal et al., 2002).

There was significant variation within the selectivity displayed by SCTX peptides, with some appearing to be particularly specific, while others were promiscuous. Interpretation was made difficult by a common lack of comprehensive screening against a wide variety of ion channel subfamilies. However, an inverse relationship between toxin peptide concentration and selectivity was identified for several SCTX peptides, with peptides tending to have broader action on ion channel classes when applied in the micromolar, as opposed to picomolar or nanomolar concentrations. One example of this is MeuNaTx α -12 that is selective for DmNav (Para) channels with an EC_{50} of 20 nM, but when applied at micromolar

concentrations it modulates five more channels (Zhu et al., 2013). In addition, toxins such as Charbydotoxin and Maurotoxin were found to be particularly promiscuous across ion channel subfamilies. As such it is important within the literature to establish minimal effective concentrations for SCTX peptides to avoid confounding comparison of peptide selectivity. It was frequently difficult to comment on SCTX selectivity as the vast majority of peptides have only been screened against an extremely limited number of ion channel subtypes. In addition publication bias towards positive findings of peptide action may have limited the extent of channel screening reported. This impedes understanding of toxin effects, and can lead to false assumptions surrounding peptide specificity.

It is important to note the intrinsic variability of SCTX peptide channel affinity and potency highlighted by this review. A substantial contributor to this is the variation in experimental protocols between groups, including the use of different channel orthologues. One example is seen with the SCTX peptides ErgTx1, CeERG4, and CeErg5, which were found to act on rat, but not human ERG2 channel orthologues (Restano-Cassulini et al., 2006, 2008). This underlies the importance of research groups providing this critical information about their models, which is frequently not the case. However even when essentially identical experimental protocols were reported, there was variation in SCTX peptide activity on the same channels. For example, a recent publication replicating the work of four previous calcin peptide experiments found that while three calcins had similar action on RyR1 channels to what had been previously described, hemicalcin only induced approximately half the predicted subconductance (Xiao et al., 2016). This underlies the need for further replication within the field, and it is important that readers interpret the reported absolute affinity/efficacy figures as a guide.

At a broader level, it was apparent that research has focused primarily on the characterisation of SCTX peptide effects on sodium and potassium channels, potentially at the expense of furthering understanding of their actions on calcium and chloride channels. For example this review has highlighted that only recently has a SCTX peptide been determined to act on a CIC channel, and another on a CFTR channel (Thompson et al., 2009; Fuller et al., 2007). The further characterisation of these channel actions, and the identification of specific modulators has tremendous pharmacological and therapeutic potential.

The high specificity and affinity of scorpion toxin peptides has led to their use as pharmacological tools to characterize ion channel function in both normal physiology and in disease states (du Plessis et al., 2008). SCTX peptides are also a focus for agrochemical lead compounds for novel invertebrate-specific insecticides (Ortiz and Possani, 2015). Continuing SCTX peptide research has great potential for the development of novel pharmaceuticals capable of specifically modulating channel function (Kuyucak and Norton, 2014). Such development has obvious implications towards the treatment of a range of chronic medical conditions including neurodegenerative and cardiovascular disease (Fuller et al., 2007). Cancer therapy also benefits from SCTX research, where Chlorotoxin (*Leiurus quinquestriatus*), a small conductance chloride ion channel inhibitor, has been modified for use as a targeted radiotherapy agent and imaging peptide, and is currently under clinical trial for use against a range of cancers (Dardevet et al., 2015; Stroud et al., 2011). Similarly discovery and modification of SCTX peptides and compounds similar to Kurtotoxin, that selectively target voltage-gated calcium channels, present significant advances in chronic pain management (Swayne and Bourinet, 2008).

5. Conclusions

Scorpion toxins have a broad spectrum of action within

excitable cells and have become a valuable source of highly specific molecular tools for the study of ion channels. This field is advancing as molecular techniques continue to make isolation of specific peptides and expression of particular ion channel subclasses easier. This review has catalogued the unique specificities of 320 individual SCTX peptides that collectively act on 41 ion channel types. Overall the SCTX peptides have evolved over millions of years of selection to become highly selective and potent ion channel modulators. Some, such as calcins, are able to readily cross the plasma membrane to activate Ca^{2+} stores, as well as acting as co-transporters for other molecules. Research in this area is destined to provide a rich dividend in molecular discovery that will expand knowledge of ion channel function and facilitate the development of significant clinical translational opportunities.

Conflicts of interest

The authors declare no conflict of interest.

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