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# A rational nomenclature for naming peptide toxins from spiders and other venomous animals

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ABSTRACT

Molecular toxinology research was initially driven by an interest in the small subset of animal toxins that are lethal to humans. However, the realization that many venomous creatures possess a complex repertoire of bioactive peptide toxins with potential pharmaceutical and agrochemical applications has led to an explosion in the number of new peptide toxins being discovered and characterized. Unfortunately, this increased awareness of peptide-toxin diversity has not been matched by the development of a generic nomenclature that enables these toxins to be rationally classified, catalogued, and compared. In this article, we introduce a rational nomenclature that can be applied to the naming of peptide toxins from spiders and other venomous animals.



## 1. Introduction

Scientists and lay public alike have been interested in the secretions from venomous animals for many centuries. However, the modern era of molecular toxinology did not begin until the 1960s and it was driven primarily by a desire to purify and understand the mechanism of action of lethal components from medically important animals such as marine cone snails (Whysner and Saunders, 1966), stonefish (Deakins and Saunders, 1967), and snakes (Sato et al., 1969).

The pioneering work of Baldomero Olivera, Michael Adams, Lourival Possani and others in the late 1980s and early 1990s led to the realization that most animal venoms comprise a complex cocktail of peptide and protein components of which the lethal toxin often represents only a minor proportion (Olivera, 1997; Possani et al., 2000; Adams, 2004). Moreover, it gradually became clear that many of the non-lethal venom components have useful bioactivities that enable them to be deployed as research tools, such as in the characterization of ion channels (Adams et al., 1993; McIntosh et al., 1999a; King, 2007; King et al., 2008), or as leads for the development of pharmaceutical agents (Harvey, 2002; Lewis and Garcia, 2003) and insecticides (Tedford et al., 2004b; Bosmans and Tytgat, 2007). This realization, combined with the development of more sophisticated venom fractionation techniques, advances in mass spectrometry (Escoubas, 2006; Favreau et al., 2006; Escoubas et al., 2008), and the ability to directly analyze toxin transcripts from venom-gland cDNA libraries (Kozlov et al., 2005; Sollod et al., 2005), has led to a rapid increase in rate of peptide-toxin discovery during the past decade.

Unfortunately, this rapid expansion of the peptide-toxin database has not been matched by the development of a rational nomenclature for naming these toxins. In this article, we demonstrate that the number of peptide-toxin sequences being deposited in the protein and nucleic acid

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databases is growing exponentially, with the result that continued use of *ad hoc* naming schemes will introduce confusion and make it difficult to compare toxins and establish evolutionary relationships. We have therefore developed a rational nomenclature that imparts each toxin name with information about its origin and biological activity. We suggest that this nomenclature can be applied to the naming of peptide toxins from spiders and other venomous animals.

## 2. Results and discussion

### 2.1. Growth of the peptide-toxin database

We define peptide toxins as venom peptides with a molecular mass less than 10 kDa, which includes the vast majority of proteinaceous toxins from spiders, hymenopterans, cone snails, and scorpions (and a significant proportion of sea anemone and snake toxins). This cut-off value provides a clear distinction between the peptide toxins that dominate most animal venoms and larger enzymes and haemostatic factors from snakes, for which an established nomenclature already exists (Meier and Stocker, 1992).

We have used the Tox-Prot database (Jungo and Bairoch, 2005) in order to examine the rate of discovery of peptide toxins. While there are more comprehensive sequence databases available for peptide toxins from scorpions (Tan et al., 2006) and cone snails (Haas et al., 2008), the Tox-Prot database allows an objective historical comparison of the rate of discovery of peptide toxins from different venomous animals. Fig. 1 shows the growth in peptide-toxin discovery during the period 1967–2006. We have defined the year of discovery as the date in which a particular peptide sequence was first published, patented, or deposited in Swiss-Prot (Boeckmann et al., 2003). The number of peptide-toxin sequences isolated from sea anemones, cone snails, scorpions, and spiders has grown exponentially over the past decade (Fig. 1A–D), whereas the number of peptide toxins isolated from snakes has grown only linearly since 1970 (Fig. 1E).

If one considers only peptide toxins from sea anemones, cone snails, scorpions, and spiders, the cumulative total number of sequences has been growing exponentially since 1985 (Fig. 1F). Based on an extrapolation of this exponential rate of increase, the number of the peptide toxins isolated from these animals alone is expected to grow from 1111 in 2006 to ~4500 by 2015 and ~24,000 by 2025 (Fig. 2). However, these projections are likely to be underestimates and they fall well short of the millions of unique sequences projected to be present in the venoms of these animals (Table 1). The ability to sequence toxins directly from mass spectrometric analysis of venoms (Escoubas et al., 2008), as well as initiatives to sequence the genomes of venomous animals (Menez et al., 2006; Putnam et al., 2007), will further accelerate the rate of peptide toxin discovery over the next decade. Thus, in order to facilitate future cataloguing and analysis, it is imperative that a rational nomenclature be developed for naming these peptide toxins.

### 2.2. Extant schemes for naming peptide toxins

Several attempts have been made previously to develop a rational nomenclature for naming venom proteins. For example, in 1991, the International Society for Toxinology (IST) established a Nomenclature Committee to develop a standardized nomenclature for naming toxins from plants, bacteria, and venomous animals (Meier and Stocker, 1992). A survey of IST members carried out by this committee (Meier and Stocker, 1992) indicated that 98% of respondents favoured development of a standardized toxin nomenclature but, almost two decades later, no such system has been formulated. As a result, numerous different methods have been employed to name peptide toxins. As outlined in the following sections, these range from *ad hoc* schemes that contain no information about function or species of origin to more rational nomenclatures based on toxin origin, function, molecular scaffold, or some combination of these parameters.

#### 2.2.1. Ad hoc *naming schemes*

The relatively small number of lethal proteinaceous toxins purified from venomous animals in the earliest period of molecular toxinology research were typically named in an *ad hoc* fashion, usually by concatenating some derivative of the genus or species name with the word "toxin". For example, the lethal peptide toxin from the Sydney funnel-web spider *Atrax robustus* was named robustoxin (Sheumack et al., 1985), whereas the toxic protein from the black widow spider *Latrodectus tredecimguttatus* was named α-latrotoxin (Tzeng and Siekevitz, 1978). While this *ad hoc* approach to naming toxins provides information about the biological origin of the peptide, it has the potential to cause confusion. For example, the lethal toxin from the Blue Mountains funnel-web spider *Hadronyche versuta* was named versutoxin (Brown et al., 1988), even though this peptide is an ortholog of robustoxin from *A. robustus* (34/42 residues are identical). Not surprisingly, these toxins have the same three-dimensional (3D) fold (Fletcher et al., 1997a; Pallaghy et al., 1997) and biological activity (Nicholson et al., 1994, 1998).

Many peptide toxins have been given trivial names based on their order of elution during a chromatographic separation procedure, such as DW13.3 (Sutton et al., 1998) and Tx4(6-1) (de Figueiredo et al., 1995). This type of naming scheme provides minimal information content with no clues about the animal from which the toxins were isolated nor their mode of action. In some cases, initials identifying the source genus and species have been attached to the toxin name, such as in the case of the ASIC1a blocker PcTx1 from the tarantula *Psalmopoeus cambridgei* (Escoubas et al., 2000). While this type of naming scheme helps with source identification, it provides no information about the molecular target of the toxin and begs the question of what name to use for other toxins isolated from the same animal, including possible paralogs.

#### 2.2.2. Nomenclature based on primary structure and molecular target

The most comprehensive *sequence*-based toxin nomenclature is that developed by Tytgat et al. (1999), which is

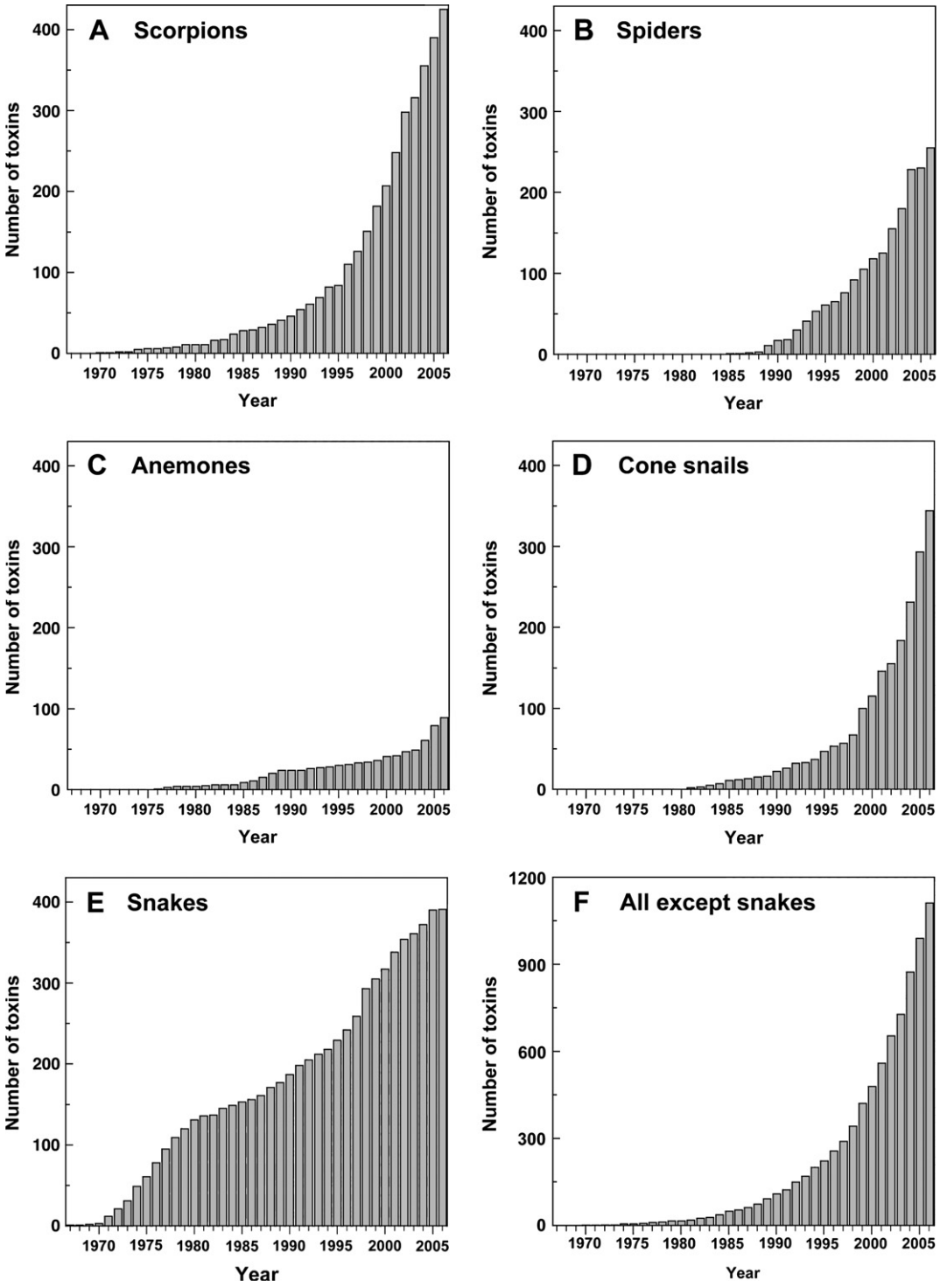


**Fig. 1.** Cumulative total number of peptide-toxin sequences reported for (A) scorpions, (B) spiders, (C) sea anemones, (D) marine cone snails, and (E) snakes for the period 1967–2006. The Tox-Prot database (Jungo and Bairoch, 2005) was used to determine the year in which a particular peptide sequence was first published, patented, or submitted to the Swiss-Prot database. Fragments and incomplete sequences were excluded from the analysis. (F) The data shown in panels (A)–(D) were used to determine the combined total number of peptide-toxin sequences discovered from anemones, cone snails, scorpions, and spiders during the period 1967–2006.

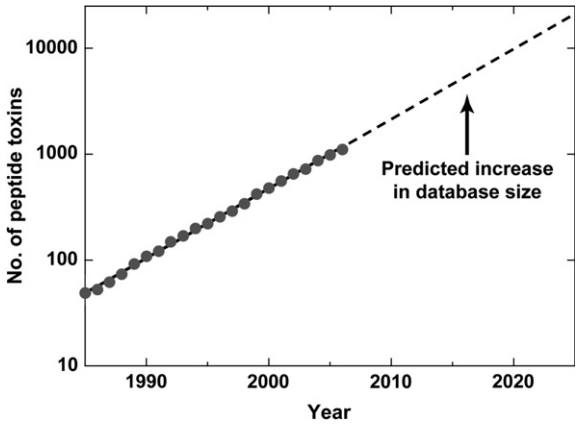


**Fig. 2.** Exponential fit (solid line) to the cumulative total number of peptide-toxin sequences discovered from anemones, cone snails, scorpions, and spiders during the period 1985–2006. Extrapolation of the fitted curve (dotted line) yields projections for the total number of peptide-toxin sequences likely to be deposited in electronic databases in future years. Note the log scale on the ordinate axis.

derived from an earlier scheme developed by Miller (1995), for naming scorpion peptides that modulate the activity of voltage-activated potassium ($K_V$) channels. In this scheme, scorpion peptides active on $K_V$ channels are grouped into one of 20 families (designated α-KTx1 through α-KTx20) based on amino acid sequence motifs plus the location of the cysteine residues that establish the 3D fold of the toxins (Tytgat et al., 1999; Rodriguez de la Vega and Possani, 2004; Abdel-Mottaleb et al., 2006). Toxins within the same family are distinguished by additional numerical descriptors. For example, within the α-KTx1 family, charybdotoxin and iberiotoxin are named α-KTx1.1 and α-KTx1.3, respectively.

This nomenclature has the advantage of being inherently simple and the grouping into 20 toxin families recapitulates the phylogeny of the toxins (Tytgat et al., 1999; Rodriguez de la Vega and Possani, 2004). However, it has several drawbacks as a generic naming scheme. First, the toxin name contains no information about its biological origin. Second, because the secondary within-family descriptor is largely arbitrary and based on order of discovery, paralogs and orthologs that differ by only one or two amino acid residues might be given names that disguise their close evolutionary relationship. For example, it would not be immediately obvious that a charybdotoxin paralog named α-KTx1.25 was a close relative of α-KTx1.1 (charybdotoxin). Finally, the activity prefixes (e.g., α for $K_V$ blockers) might cause confusion since they have been assigned without reference to previous use in other groups of venomous animals. Thus, while this scheme is very useful for *classifying* peptide toxins, it has disadvantages as a generic naming scheme.

**Table 1**
Estimated number of unique peptide toxins in venomous animals

| Animal Group | No. of peptides | References |
|---|---|---|
| Cone snails | 50,000 | Olivera and Cruz (2001) and Norton and Olivera (2006) |
| Scorpions | 100,000 | Possani et al. (1999) |
| Spiders | 1.5–16 million | Escoubas and Rash (2004), Tedford et al. (2004b) and Escoubas et al. (2006) |

The problem with arbitrary assignment of activity descriptors (and this is a widespread problem in the field) is that they conflict with use of identical descriptors with different biological inference that are used for naming toxins from other venomous animals. For example, scorpion α-toxins target voltage-activated sodium ($Na_V$) channels (Possani et al., 1999), α-conotoxins target nicotinic acetylcholine receptors (McIntosh et al., 1999b), scorpion α-KTx toxins target $K_V$ channels (Tytgat et al., 1999), and α-agatoxins are polyamines that block mammalian glutamate receptors (Adams, 2004). The non-uniform (and up until now largely arbitrary) use of activity descriptors highlights why it is important to develop a rational nomenclature before the database becomes too large to allow systematic revision of toxin names.

### 2.2.3. *Nomenclature based on species of origin, cystine scaffold, and molecular target*

The most comprehensive toxin nomenclature is that developed by Olivera and others for naming cystine-rich peptide toxins from marine cone snails (*Conus* spp.) (McIntosh et al., 1999b). This scheme has the advantage of providing information about the toxin's biological origin, cystine framework (which determines its 3D fold), and molecular target. In this nomenclature, the toxin name begins with a Greek symbol that identifies its molecular target (if known). For example, **ω** and **κ** are used to identify peptides that block voltage-activated calcium ($Ca_V$) and $K_V$ channels, respectively. This symbol is followed an uppercase letter identifying the species of origin. Because cone snails constitute a single genus (*Conus*), this is often sufficient to identify the species. Thus, **P** and **G** denote *Conus purpurascens* and *Conus geographus*, respectively. In cases where two distinct *Conus* species names begin with the same letter, additional lowercase letters are added to avoid confusion. Thus, **Gm** is used to distinguish *Conus gloriamaris* from *C. geographus*.

The species identifier is followed by a Roman numeral that identifies the cystine framework of the toxin. Framework definitions are based on the number of Cys residues, intercystine spacing, and the pattern of disulfide connectivities. For example, framework IV defines the six-cysteine pattern $C_1C_2$–$C_3$–$C_4$–$C_5$–$C_6$ with disulfide connectivity $C_1$–$C_5$, $C_2$–$C_3$, and $C_4$–$C_6$, where the dash indicates a variable number of residues in the intercystine loops. Toxin paralogs with the same cystine framework are discriminated by an uppercase letter following the framework identifier. Thus, ω-conotoxin MVII**A**, MVII**B**, MVII**C**, and MVII**D** are paralogous $Ca_V$ channel blockers from *Conus magus* that have framework VII and very similar sequences. The framework identifiers have evolved in an *ad hoc* fashion and they do not provide information *per se* about the number of cystines, nor their connectivity. Moreover, this *ad hoc* method of defining cystine frameworks has in some cases introduced confusion since some frameworks that were initially thought to be different and hence given different names (e.g., I and II) were later shown to be identical. Alternative methods of defining conotoxin frameworks have been suggested (Olivera, 2002).

Unfortunately, this rational conotoxin nomenclature has not been applied to *Conus* peptides that have only one or no disulfide bonds. For historical reasons, these peptides are generally referred to as conopeptides rather than conotoxins and they have been named in an *ad hoc* manner (e.g., contulakin, conopressin, and conantokin). In theory, however, there is no reason why a unified nomenclature could not be systematically applied to both linear and disulfide-rich peptide toxins.

#### 2.2.4. Nomenclature based on species of origin and molecular target

The realization over a decade ago that there are likely to be well over one million unique spider toxins led us to develop a rational nomenclature for naming these peptides (Fletcher et al., 1997b; King et al., 2002). This nomenclature was derived from the scheme described above for naming conotoxins, except that information about cystine framework was excluded because of the paucity of information about spider-toxin scaffolds at that point in time.

This nomenclature begins with a Greek symbol, which is based on those previously used for naming conotoxins, that identifies the molecular target of the toxin (if known). This is followed by a generic toxin name based on the genus, subfamily, or family name of the spider or group of spiders. For example, toxins from Australian mouse spiders (*Missulena* spp.) are known generically as missulenatoxins (MSTXs) (Gunning et al., 2003). This part of the toxin name is more important for spider toxins than those from cone snails since cone snails comprise a single genus whereas spiders comprise >40,000 species in more than 3600 genera (Platnick, 1997). Moreover, spider taxonomy is in considerable flux and one has to be cautious in choosing the generic toxin name. For example, Australian funnel-web spiders currently comprise two separate genera (*Atrax* and *Hadronyche*) within the subfamily Atracinae (Gray, 1988). Thus, in order to avoid confusion as a result of future taxonomic revisions, these peptides were named atracotoxins (ACTXs) based on the subfamily name rather than one of the genera (Fletcher et al., 1997b).

The generic toxin name is followed by an *uppercase* letter that identifies the genus of origin and a *lowercase* letter that identifies the species. Both genus and species designators are required to avoid confusion because of the vast number of spider species and the complications caused by the same group of spiders being assigned to more than one genus. The genus/species designators are followed by a number that designates a particular family of paralogous toxins with the biological function indicated by the activity descriptor. This designator was introduced because often there is more than one group of toxins from the same species that act on the same molecular target. This designator is simply incremented as new groups of toxins are discovered. For example, the first group of $Ca_V$ channel blockers isolated from the venom of the Blue Mountains funnel-web spider *H. versuta* were named ω-ACTX-Hv1 toxins whereas a subsequent group of $Ca_V$ blockers isolated from the same spider, which have evolved from a different gene and which have a substantially different 3D structure, were named ω-ACTX-Hv2 toxins (Wang et al., 2001).

The toxin-family designator is followed by a lowercase letter that is used to distinguish homologs (also called isoforms). This designator is critical because of the combinatorial library strategy that spiders and other venomous animals have employed to diversify their toxin repertoire (Sollod et al., 2005). That is, rather than producing "one-off" versions of each toxin, spiders typically express a small family of 3–6 homologs that can differ by as little as one or a few amino acid residues (Tedford et al., 2004b). Hence, from an evolutionary perspective, it is helpful if the toxin name conveys the relationship between homologous toxins in a facile manner. For example, six ω-ACTX-Hv1 homologs have been isolated thus far from *H. versuta* and they were named ω-ACTX-Hv1**a** through ω-ACTX-Hv1**f** based on this nomenclature (Wang et al., 1999).

This rational but simple nomenclature solved the confusion that was caused by use of the names versutoxin and robustoxin for the very similar orthologous lethal toxins from *H. versuta* and *A. robustus*, respectively. These toxins were renamed δ-ACTX-Hv1a and δ-ACTX-Ar1a (Fletcher et al., 1997a), which rapidly conveys the knowledge that these toxins are orthologs and that they both target $Na_V$ channels (Nicholson et al., 2004).

### 2.3. Development of a rational nomenclature for naming peptide toxins

#### 2.3.1. Key criteria for development of a generic toxin nomenclature

In developing a rational nomenclature for naming peptide toxins one has to consider the diverse groups of researchers who study or use toxins. While most toxinologists have a broad interest in the structure, function, and evolution of toxins, physiologists and pharmacologists are primarily interested in the molecular target of the toxin while molecular geneticists may be more concerned with phylogenetic relationships and the genetic mechanisms for evolving toxin diversity. Thus, in any rational nomenclature for naming peptide toxins, the toxin name should, at minimum, include information about the biological origin of the peptide as well as its molecular target and/or biological function (if known). In addition, the name should facilitate rapid searching of electronic databases for toxins from different venomous animals that act on the same or similar molecular target, and it should allow inferences to be drawn about possible evolutionary relationships (e.g., paralogs and orthologs).

Structural biologists are also interested in peptide toxins as they often present novel 3D folds not found outside of venomous animals. In addition, they can serve as structural templates for medicinal chemists for the rational design of drugs (Lewis and Garcia, 2003; Clark et al., 2005; Armishaw et al., 2006) and insecticides (Froy et al., 1999b; Maggio and King, 2002; Cohen et al., 2004; Tedford et al., 2004a). However, classifying toxins on the basis of 3D structure is very difficult, largely because structures have not been determined for the vast majority of peptide toxins. Thus, it will be many years before we have even a rudimentary understanding of the complete range of 3D scaffolds that have been recruited into venom peptidomes. Hence, while it might be desirable for a toxin's name to provide

information about its 3D fold, or even simply its disulfide architecture, this is a difficult task and should only be done if it provides useful information without introducing confusion.

*2.3.2. Proposed nomenclature for naming peptide toxins*

The nomenclature we propose for naming peptide toxins, *regardless of whether they contain disulfide bonds or not*, is outlined in Fig. 3. It is a simple extension of the nomenclature we developed earlier for naming spider toxins (Fletcher et al., 1997b), as described in Section 2.2.4.

*2.3.2.1. Broad activity descriptor.* The toxin name should begin with a Greek letter or other symbol denoting its biological activity or molecular target. These activity descriptors, which are summarized in Table 2, were chosen to be as parsimonious as possible. Wherever a conflict existed between extant activity descriptors, we gave precedence to the descriptor used for naming conotoxins, since this is the most widely used rational nomenclature. Thus, for example, we propose that scorpion α-toxins, which target $Na_V$ channels, should be renamed δ or μ toxins since these Greek symbols have been widely used to describe both spider and cone snail toxins that modify the activity of $Na_V$ channels (see Table 2). In Table 2, we introduce a number of new activity descriptors to account for recently discovered toxins with novel activities. For example, we propose

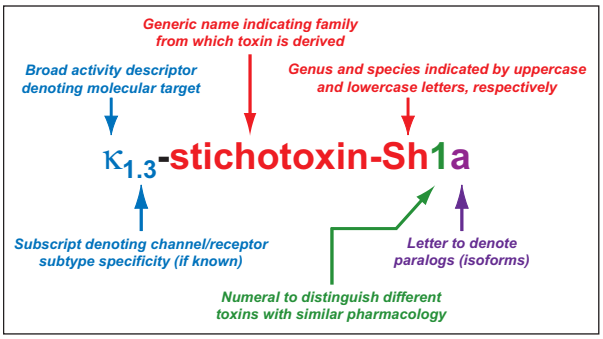


**Fig. 3.** Schematic of the proposed nomenclature for naming peptide toxins. The toxin name can be broadly divided into three parts that describe the toxin's activity (blue), biological source (red), and relationship to other toxins (green/purple). The example given is for a sea anemone toxin, commonly known as ShK, that specifically targets $K_V1.3$ channels. The subtype descriptor should be based on IUPHAR-recommended nomenclature for channels and receptors (Alexander et al., 2007).

the use of π to designate toxins such as PcTx1 (Escoubas et al., 2000) and APETx2 (Diochot et al., 2004) that target acid-sensing ion channels (ASICs) and φ to denote toxins such as maurocalcine (Fajloun et al., 2000) that target ryanodine receptors. In addition, we have introduced activity descriptors for a variety of 7TM receptors such as the

**Table 2**
Activity descriptors for naming peptide toxins

| Descriptor | Biological function associated with descriptor | Example | Reference |
|---|---|---|---|
| α (alpha) | Targets acetylcholine receptor | α-Bungarotoxin (snake) | Changeux et al. (1970) |
| β (beta) | Shifts voltage-dependence of $Na_V$ channel activation | Bj-xtrIT (scorpion) | Froy et al. (1999b) |
| γ (gamma) | Targets HCN[a] nonspecific cation channels | γ-Ctx PnVIIA (cone snail) | Fainzilber et al. (1998) |
| δ (delta) | Delays inactivation of voltage-activated $Na_V$ channels | δ-ACTX-Hv1a (spider) | Fletcher et al. (1997a) |
| ε (epsilon) | Targets ClC chloride channels | –[b] | – |
| ζ (zeta) | Targets cyclic nucleotide-gated channels | Pseudechetoxin (snake)[c] | Brown et al. (1999) |
| η (eta) | Targets inward-rectifier potassium ($K_{IR}$) channels | Tertiapin (honey bee) | Jin and Lu (1998) |
| θ (theta) | Targets two-pore domain potassium ($K_{2P}$) channels | – | – |
| ι (iota) | $Na_V$ channel agonist | ι-Ctx RXIA (cone snail) | Buczek et al. (2007) |
| κ (kappa) | Inhibits voltage-activated potassium ($K_V$) channels | κ-Ctx PVIIA (cone snail) | Terlau et al. (1996) |
| λ (lambda) | Inhibits calcium-activated potassium ($K_{Ca}$) channels | Charybdotoxin (scorpion) | Miller et al. (1985) |
| μ (mu) | Inhibits voltage-activated sodium ($Na_V$) channels | μ-Aga-I (spider) | Skinner et al. (1989) |
| ν (nu) | Targets neurotensin receptor | Contulakin-G (cone snail) | Craig et al. (1999) |
| ξ (xi) | Targets endothelin receptor | Sarafotoxin S6c (snake) | Ambar et al. (1988) |
| ο (omicron) | Targets octopamine receptor | – | – |
| π (pi) | Targets acid-sensing ion channels (ASICs) | PcTx1 (spider) | Escoubas et al. (2000) |
| ρ (rho) | Targets adrenoceptor | ρ-Ctx TIA (cone snail) | Sharpe et al. (2001) |
| σ (sigma) | Targets 5-HT receptor | σ-Ctx GVIIIA (cone snail) | England et al. (1998) |
| τ (tau) | Targets transient receptor potential (TRP) channel | VaTx1 (spider) | Siemens et al. (2006) |
| υ (upsilon) | Targets vasopressin/oxytocin receptor | Conopressin-G (cone snail) | Cruz et al. (1987) |
| φ (phi) | Targets ryanodine receptor | Maurocalcine (scorpion) | Fajloun et al. (2000) |
| χ (chi) | Targets noradrenalin transporter | χ-Ctx MrIA (cone snail) | Sharpe et al. (2001) |
| ψ (psi) | Noncompetitive antagonist of acetylcholine receptor | ψ-Ctx PIIIE (cone snail) | Shon et al. (1997) |
| ω (omega) | Inhibits voltage-gated calcium ($Ca_V$) channels | ω-Aga-IVA (spider) | Mintz et al. (1992) |
| Γ (Gamma) | Targets glutamate receptor | Conantokin-G (cone snail) | Mena et al. (1990) |
| Λ (Lambda) | Targets GABA receptor | – | – |
| Ξ (Omicron) | Targets P2X receptor | – | – |
| Σ (Sigma) | Targets CFTR channel | GaTx1 (scorpion) | Fuller et al. (2007) |
| Ω (Omega) | Targets epidermal growth factor receptor | Gigantoxin I (sea anemone) | Shiomi et al. (2003) |
| Δ (Delta) | Cytolytic activity | Cupiennin 1a (spider) | Kuhn-Nentwig et al. (2004) |
| U | Unknown activity | ACTX-Hvf17 (spider) | Szeto et al. (2000) |

[a] Abbreviations used: CFTR, cystic fibrosis transmembrane conductance regulator; HCN, hyperpolarization-activated, cyclic nucleotide-gated.
[b] A dash indicates that no toxins have yet been isolated with this pharmacology.
[c] Pseudechetoxin (24 kDa) is not a peptide toxin by the definition employed here but is included to indicate that this pharmacology exists in venom proteomes.

endothelin, neurotensin, octopamine, and vasopressin receptors (see Table 2).

Rather than targeting a specific receptor or ion channel, many peptide toxins (primarily those without disulfide bonds) have nonspecific cytolytic activity via their ability to interact with, and disrupt, lipid membranes (Anderluh and Macek, 2002; Kuhn-Nentwig, 2003). In order to develop a unified nomenclature that includes all peptide toxins, we have introduced a new activity descriptor (**Δ**) for this group of cytolytic peptides. In addition, we propose that the activity descriptor **U** be used for toxins for which the primary biological activity has not yet been identified. Although seemingly trivial, this is an important descriptor since many toxins identified from sequencing cDNA/EST libraries will initially not have an identified biological activity. Where there is more than one family of toxins with unknown activity from a single species, then these can be discriminated by adding a subscript to the activity indicator (i.e., $U_1$, $U_2$, $U_3$, etc.).

It is likely that new activity indicators will have to be introduced in future as new toxins are discovered with novel activities. However, the comprehensive list of activity indicators in Table 2 should suffice for the vast majority of peptide toxins.

*2.3.2.2. Descriptor for receptor and ion channel subtypes.* Many peptide toxins have become useful pharmacological probes because of their ability to discriminate between different ion channel and receptor subtypes. Unfortunately, however, information about the subtype specificity of toxins is rarely incorporated into their names. We propose that this can be readily accomplished by incorporating a subscript after the broad activity descriptor that refers to the primary receptor or ion channel subtype that is targeted by the toxin. Whenever possible, these subscripts should follow the International Union of Pharmacology (IUPHAR) recommendations for vertebrate receptor and ion channel subtypes as outlined in the 2007 Guide to Receptors and Channels (Alexander et al., 2007). Thus, for example, a toxin that specifically targeted $K_V1.3$ channels (e.g., ShK) would be given the prefix $\kappa_{1.3}$, whereas a toxin that targeted endothelin receptor B (e.g., sarafotoxin S6c) would be given the prefix $\xi_B$. If the subtype specificity of a toxin is not known, or if it is broadly active against all subtypes of the molecular target, then only the broad activity descriptor should be used, without the subscript denoting subtype specificity.

*2.3.2.3. Toxin name.* The activity descriptor should be followed by a name that is common to all toxins from a single venomous family, regardless of the species, so that taxonomic relationships between toxins can be quickly established. Surprisingly, with several notable exceptions such as the conotoxins (Gray et al., 1981) and atracotoxins (Fletcher et al., 1997b), this has not been common practice. For example, toxins from the scorpion *Leiurus quinquestriatus* have been given a variety of trivial names such as charybdotoxin (Miller et al., 1985), 18-2 (Marshall et al., 1994), and Lq2 (Lu and MacKinnon, 1997), which makes it impossible without consulting the literature to establish that these toxins all derive from the same source.

Since cone snails comprise a single genus, *Conus*, it makes sense to continue to use the generic term conotoxin (abbreviated CTX) to describe peptide toxins from marine cone snails. However, the situation is considerably more complex for scorpions, sea anemones, snakes, and spiders which comprise ~175, 68, 328, and >3600 genera, respectively [see (Platnick, 1997) and the Integrated Taxonomic Information System at http://www.itis.gov/index.html]. For these animals, using toxin names based on genus would cause confusion (since it would be exceedingly difficult to keep track of more than 4000 generic toxin names!) and it would disguise the evolutionary relationship between orthologous toxins. Moreover, since taxonomy is generally more stable at the family level as opposed to the genus level, a nomenclature based on family rather than genus should be less susceptible to future taxonomic revisions. Thus, for venomous animals other than marine cone snails, we propose that the toxin name should be based on the taxonomic *family* rather than the *genus*. This considerably simplifies the naming scheme since snakes, scorpions, sea anemones, and spiders comprise only 18, 18, 48, and 108 families, respectively.

Devising generic names based on taxonomic family rather than genus has the additional advantage of highlighting evolutionary relationships between toxins. To give an example, toxins from the spider genera *Macrothele* and *Hadronyche* have been named Magi toxins and atracotoxins (ACTXs), respectively. However, these hexathelid spiders are closely related, and it is clear that many of the toxins isolated from these spiders are orthologs, a fact completely disguised by their very different names. For example, as illustrated in Fig. 4, Magi-14 (Satake et al., 2004) and δ-ACTX-Hv1a (Fletcher et al., 1997a) are 70% identical and have the same cystine framework; they are clearly derived from the same ancestral gene. Thus, we propose that toxins derived from these two genera, as well as all other genera within the taxonomic family Hexathelidae, be named hexatoxins (HXTXs). Thus, δ-ACTX-Hv1a from *H. versuta* and Magi-14 from *Macrothele gigas* would be renamed δ-HXTX-Hv1a and δ-HXTX-Mg1a, respectively. The revised names immediately reveal that these toxins are orthologs and that they both target $Na_V$ channels.

We have developed a complete list of generic toxin names (and corresponding abbreviations) for all extant families of snakes, spiders, scorpions, and sea anemones. These names were developed based on the following criteria.

(i) The generic toxin name should be as short as possible.
(ii) Generic toxin names should all be sufficiently different to avoid potential confusion.
(iii) The abbreviations for these toxin names should comprise no more than five letters and, in accordance with longstanding convention, they should end with the letters "TX".
(iv) Toxin abbreviations must be unique, with no overlap between groups of venomous animals.
(v) To avoid confusion, names and abbreviations in current use should be avoided.

Criterion (v) is important, and it required exhaustive literature searches to fulfill. For example, although exotoxin and lipotoxin would appear to be suitable names for toxins

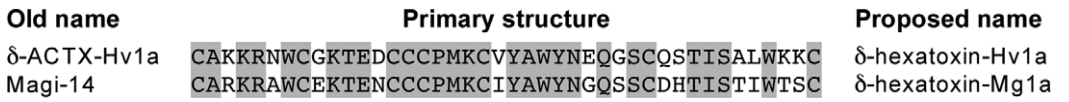


**Fig. 4.** Alignment of the primary structure of orthologous peptide toxins from the spiders *Hadronyche versuta* (δ-ACTX-Hv1a) and *Macrothele gigas* (Magi-14), along with revised names based on the nomenclature proposed herein. Identical residues are shaded grey.

from the sea anemone families Exocoelactiidae and Liponematidae, respectively, these names are currently used for bacterial toxins and thus should be avoided. We therefore chose the generic names coelatoxin and liponetoxin, respectively, for toxins from these two families of sea anemones. We have also avoided names that might invoke a broader meaning, such as isotoxin, microtoxin, megatoxin, and pseudotoxin, as well as toxin abbreviations in common use such as SRTX (sarafotoxin), ACTX (atracotoxin), and MSTX (missulenatoxin). We purposefully avoid three-letter abbreviations for generic toxin names in order to avoid confusion with extant abbreviations such as BTX (batrachotoxin), CTX (conotoxin and ciguatoxin), DTX (dendrotoxin), LTX (latrotoxin), and STX (saxitoxin).

In order to minimize the extent of name revisions required by the proposed nomenclature, we were able in several cases to chose generic toxin names that were initially developed to describe toxins from certain genera, but for which the definition can be readily expanded to include toxins from all species *within the same taxonomic family*. For example, the name agatoxin has been used for almost 20 years to describe peptide toxins from the spider genus *Agelenopsis* (Bindokas and Adams, 1989; Adams, 2004), which is a member of the family Agelenidae. Thus, we propose that all toxins derived from species within Agelenidae be named agatoxins in order to avoid major revision of the names of the widely used and studied agatoxins. Similarly, the definition of lycotoxin, which was originally used to describe toxins from spider genus *Lycosa* (Yan and Adams, 1998), can be extended to include all toxins derived from the spider family Lycosidae, in which *Lycosa* resides. We have also extended the definition of the name plectoxin (abbreviated PLTX), which is commonly used to describe toxins from the spider genus *Plectreurys*, to include all toxins from the spider family Plectreuridae.

The proposed generic names for peptide toxins from snakes, scorpions, sea anemones, and spiders are given in Supplementary Tables 1–4 and they are reproduced for convenience at http://www.venomics.org/nomenclature. Using iterative rounds of naming and revision, we were able to devise a unique set of abbreviations that comprise only four letters for 94% of these 192 taxonomic families (including all scorpion, sea anemone, and snake families).

*2.3.2.4. Genus and species descriptors.* While the toxin name alone should be sufficient to identify the family from which a toxin derives, an additional descriptor is necessary to distinguish different species within each family. This descriptor is important for source identification since, in many cases, there will be tens or even hundreds of different species within each family. The most extreme case is the spider family Linyphiidae, which comprises 4329 species in 571 genera (see http://research.amnh.org/entomology/spiders/catalog/counts.html for an up-to-date list of all spider families, genera, and species).

Thus, we propose that the generic toxin name should be followed by an *uppercase* letter that identifies the genus of origin and a *lowercase* letter that identifies the species. Thus, *Phoneutria nigriventer* would be identified as **Pn**. In some cases, additional lowercase letters will be required to distinguish species that begin with the same letter. For example, *Phoneutria bahiensis* and *Phoneutria boliviensis* could be denoted **Pbh** and **Pbv**, respectively. In special cases where the species has not yet been identified, we propose use of the lowercase identifier "spp". Thus, an unidentified *Phoneutria* species would be given the genus/species designation **Pspp**.

*2.3.2.5. Discriminating between different toxins with the same activity and species of origin.* In some cases, distinctly different toxins (i.e., not paralogs) from the same species might have activity against the same molecular target. Examples include the ω-ACTX-Hv1 and ω-ACTX-Hv2 toxin families from *H. versuta* that both have activity against invertebrate $Ca_V$ channels (King et al., 2002), as well as the numerous different families of ω-agatoxins that target vertebrate $Ca_V$ channels (Adams, 2004). In order to discriminate between these toxins, we propose that the genus/species descriptor be followed by a numerical descriptor that is simply incremented as new families of toxins are discovered with similar activity. Thus, if four families of ω-atracotoxins had already been discovered, then the next family of toxins from these spiders with activity against $Ca_V$ channels would be denoted the ω-atracotoxin-Xx5 family, where the Xx refers to the genus/species descriptor.

*2.3.2.6. Discriminating between closely related homologs.* Spiders, cone snails, and scorpions (and probably other venomous animals) have used a combinatorial library strategy to diversify their toxin repertoire (Sollod et al., 2005) and they often express a number of closely related homologous toxins (often referred to as isoforms) that can differ by as little as a single amino acid residue. In order to distinguish between these homologs in a manner that readily indicates their close evolutionary relationship, we propose that the numerical descriptor indicating the toxin family be followed by a lowercase letter. Thus, the six known homologs of ω-ACTX-Hv1 were formerly denoted ω-ACTX-Hv1**a** through ω-ACTX-Hv1**f** (Wang et al., 1999).

*2.3.2.7. Structural information.* While it would be helpful in some instances to provide information about toxin structure or even just the disulfide framework within the toxin name, this is currently very difficult because of the limited range of toxin structures that are available. For example, although there are 105 potential disulfide isomers for toxins

with four disulfide bonds and 945 possible disulfide isomers for toxins with five disulfide bridges, it is unclear how many of these frameworks have been utilized by venomous animals. It seems likely that venom peptidomes include only a small number of privileged disulfide scaffolds, but the extent of these is uncertain at the present time. Thus, with the exception of the conotoxins, for which a framework definition has been developed (Terlau and Olivera, 2004), it seems premature to include structural information in the toxin name. This does not imply, however, that cysteine motifs cannot be used for toxin *classification* (e.g., Tytgat et al., 1999; Kozlov and Grishin, 2005).

### 2.3.3. Examples of the proposed toxin nomenclature

Although the nomenclature we have proposed is, by design, relatively simple, it is perhaps best understood by considering several examples (summarized in Table 3).

*2.3.3.1. Example 1.* We first consider peptide toxins from the sea anemone genus *Stichodactyla*, which have previously been given trivial names such as ShK, Sh I, and gigantoxin. These names provide no information about molecular target and they disguise close evolutionary relationships, including the fact that Sh I and gigantoxin III are orthologs. We propose that all of these toxins be referred to generically as stichotoxins (SHTXs) based on the taxonomic family (Stichodactylidae) in which the genus *Stichodactyla* resides (see Table 2 in Supplementary data). Thus, ShK from *Stichodactyla helianthus*, which is a specific blocker of $K_V$1.3 channels, would be renamed $\kappa_{1.3}$-stichotoxin-Sh1a ($\kappa_{1.3}$-SHTX-Sh1a) whereas Sh I, which delays $Na_V$ channel inactivation, would be renamed δ-SHTX-Sh1a. Gigantoxin III, an ortholog of Sh I from *S. gigantea* (the two toxins are 79% identical), would be renamed δ-SHTX-Sg1a, which immediately reveals its similarity to δ-SHTX-Sh1a. Gigantoxin I, which has very different pharmacology to the unrelated gigantoxins II and III, would be renamed Ω-SHTX-Sg1a based on its activity against the EGF receptor.

*2.3.3.2. Example 2.* The Brazilian armed spider *P. nigriventer* is one of the few spiders that are potentially deadly to humans, and hence its venom has been the subject of intensive study (reviewed in Gomez et al., 2002). Peptide toxins from this spider have typically been given trivial names such as Tx2-1, Pn2-1A, and Pn4B, mostly based on order of elution during a chromatographic separation procedure. These names have minimal information content and they disguise the fact that many of the isolated toxins, such as Tx2-1, Pn2-1A, Tx2-5, Pn2-5A, and Tx2-6, are closely related paralogs. Thus, we propose that *all* peptide toxins from the genus *Phoneutria* be described using the generic term ctenitoxin (CNTX), based on the taxonomic family (Ctenidae) in which *Phoneutria* resides (see Table 4 in Supplementary data).

Members of the Tx2-1 family of *Phoneutria* toxins have complex effects on $Na_V$ channels (Matavel et al., 2002) but their primary effect appears to be an inhibition of channel inactivation, a pharmacology similar to that of the δ-atracotoxins (Nicholson et al., 2004) and δ-conotoxins (Ekberg et al., 2008). Hence, we propose that Tx2-1 be renamed δ-CNTX-Pn1a to indicate this pharmacology, and that the paralogs Tx2-5, Tx2-6, Pn2-1A and Pn2-5A be named δ-CNTX-Pn1b through δ-CNTX-Pn1e, respectively. This nomenclature immediately conveys the information

**Table 3**
Revised nomenclature for selected peptide toxins from scorpions, sea anemones, and spiders

| Animal | Genus/species | Target (if known) | Previous name(s) | Proposed new name | Reference |
|---|---|---|---|---|---|
| Sea anemone | *Stichodactyla helianthus* | $K_V$1.3 | ShK | $\kappa_{1.3}$-Stichotoxin-Sh1a ($\kappa_{1.3}$-SHTX-Sh1a) | Castaneda et al. (1995) |
| | *Stichodactyla helianthus* | $Na_V$ (inhibits inactivation) | Sh I | δ-SHTX-Sh1a | Norton (1991) |
| | *Stichodactyla gigantea* | $Na_V$ (inhibits inactivation) | Gigantoxin III | δ-SHTX-Sg1a | Shiomi et al. (2003) |
| | *Stichodactyla gigantea* | $Na_V$ (inhibits inactivation) | Gigantoxin II | δ-SHTX-Sg2a | Shiomi et al. (2003) |
| | *Stichodactyla gigantea* | EGF receptor | Gigantoxin I | Ω-SHTX-Sg1a | Shiomi et al. (2003) |
| Spider | *Phoneutria nigriventer* | $Na_V$ (inhibits inactivation) | Tx2-1/PnTx2-1 | δ-Ctenitoxin-Pn1a (δ-CNTX-Pn1a) | Cordeiro et al. (1992) |
| | *Phoneutria nigriventer* | $Na_V$ (inhibits inactivation) | Tx2-5/PnTx2-5 | δ-CNTX-Pn1b | Cordeiro et al. (1992) |
| | *Phoneutria nigriventer* | $Na_V$ (inhibits inactivation) | Tx2-6/PnTx2-6 | δ-CNTX-Pn1c | Cordeiro et al. (1992) |
| | *Phoneutria nigriventer* | $Na_V$ (inhibits inactivation) | Pn2-1A | δ-CNTX-Pn1d | Kalapothakis et al. (1998) |
| | *Phoneutria nigriventer* | $Na_V$ (inhibits inactivation) | Pn2-5A | δ-CNTX-Pn1e | Kalapothakis et al. (1998) |
| | *Phoneutria reidyi* | $Na_V$ (inhibits inactivation) | PRTx32C1 | δ-CNTX-Pr1a | Swiss-Prot P83904 |
| | *Phoneutria keyserlingi* | $Na_V$ (inhibits inactivation) | PKTx36C1 | δ-CNTX-Pk1a | Swiss-Prot P84012 |
| | *Phoneutria nigriventer* | Blocks $Ca_V$2 channels | Tx3-4/ω-PNTX-IIA | $\omega_2$-CNTX-Pn1a | Cassola et al. (1998) |
| | *Phoneutria nigriventer* | Blocks $Ca_V$2 channels | Tx3-6/PnTx3-6 | $\omega_2$-CNTX-Pn2a | Cordeiro et al. (1993) |
| Scorpion | *Leiurus quinquestriatus hebraeus* | Inhibits $K_{Ca}$ channels | Charybdotoxin-a/α-KTx1.1 | λ-Buthitoxin-Lqh1a (λ-BUTX-Lqh1a) | Gimenez-Gallego et al. (1988) |
| | *Leiurus quinquestriatus hebraeus* | Inhibits $K_{Ca}$ channels | Charybdotoxin-b/α-KTx1.12 | λ-BUTX-Lqh1b | Froy et al. (1999a) |
| | *Leiurus quinquestriatus hebraeus* | Inhibits $K_{Ca}$ channels | Charybdotoxin-c/α-KTx1.13 | λ-BUTX-Lqh1c | Froy et al. (1999a) |
| | *Leiurus quinquestriatus hebraeus* | Inhibits $K_{Ca}$ channels | Charybdotoxin-d/Lqh 18-2/ ChTx-Lq2/α-KTx 1.2 | λ-BUTX-Lqh1d | Lucchesi et al. (1989) |
| | *Mesobuthus martensii* | Inhibits $K_{Ca}$ channels | BmTX2/α-KTx1.6 | λ-BUTX-Mm1a | Romi-Lebrun et al. (1997) |
| | *Hottentotta tamulus* | Inhibits $K_{Ca}$ channels | Iberiotoxin/α-KTx1.3 | λ-BUTX-Mt1a | Galvez et al. (1990) |
| | *Centruroides noxius* | Inhibits $K_{Ca}$ channels | Slotoxin/α-KTx1.11 | λ-BUTX-Cn1a | Garcia-Valdes et al. (2001) |

that these toxins are paralogs and that they have the same molecular target. In addition, using this nomenclature, the orthologous toxins PRTx32C1 and PKTx36C1 from *Phoneutria reidyi* and *Phoneutria keyserlingi* would be named δ-CNTX-Pr1a and δ-CNTX-Pk1a, respectively, which immediately conveys the close evolutionary relationship between this family of toxins.

Since the subtype specificity of the δ-CNTXs remains to be determined, only the broad activity descriptor (δ) can be deployed at present. In contrast, Tx3-4/ω-phonetoxin-IIA and Tx3-6/PnTx3-6 from *P. nigriventer* appear to be specific blockers of vertebrate $Ca_V2$ channels (Cassola et al., 1998; Dos Santos et al., 2002; Vieira et al., 2005), and consequently we propose that these toxins (which are not paralogs) be renamed $\omega_2$-CNTX-Pn1a and $\omega_2$-CNTX-Pn2a, respectively.

*2.3.3.3. Example 3.* Charybdotoxin (α-KTx1.1) from the scorpion *Leiurus quinquestriatus hebraeus* is one of the most widely used peptide toxins due to its ability to specifically inhibit $K_{Ca}$ channels (Gimenez-Gallego et al., 1988). In addition to several homologs from *L. quinquestriatus hebraeus*, numerous orthologs such as iberiotoxin, BmTX2, and slotoxin have been discovered in the venom of related scorpions within the family Buthidae. These very different names disguise the evolutionary connection between these toxins and provide no information about their molecular target. We propose the generic name buthitoxin (BUTX) for all peptide toxins derived from species within Buthidae (see Table 1 in Supplementary data). Thus, charybdotoxin would be renamed λ-BUTX-Lqh1a, where the activity descriptor λ signifies activity against $K_{Ca}$ channels (see Table 2), and its homologs charybdotoxin b–d would be renamed λ-BUTX-Lqh1b, λ-BUTX-Lqh1c, and λ-BUTX-Lqh1d. The orthologous toxins iberiotoxin, BmTX2, and slotoxin from *Hottentotta tamulus*, *Mesobuthus martensii*, and *Centruroides noxius* would be renamed λ-BUTX-Mt1a, λ-BUTX-Mm1a, and λ-BUTX-Cn1a, respectively. These names make it immediately apparent that these toxins are orthologs and that they all target $K_{Ca}$ channels.

## 3. Conclusions

We have devised a simple, rational nomenclature for naming peptide toxins that conveys each toxin name with information about the biological origin of the peptide, its molecular target, and its relationship to known paralogs and orthologs. Although there will inevitably be some resistance to revising toxin names that have been in use for some time, it should be emphasized that systematic revision of toxin names at this point in time, with less than 1500 sequences in the Tox-Prot database, is likely to be much easier than deferring the problem to a future time when tens of thousands of peptide-toxin sequences have been determined. Moreover, the adoption of a unified nomenclature for naming peptide toxins will greatly facilitate their cataloguing and analysis using electronic databases, thus enabling their potential as drugs, insecticides, and pharmacological probes to be better exploited.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.toxicon.2008.05.020.

## Conflict of interest

The authors declare no conflict of interest.

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