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Effects of Brazilian scorpion venoms on the central nervous system

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Abstract

In Brazil, the scorpion species responsible for most severe incidents belong to the *Tityus* genus and, among this group, *T. serrulatus*, *T. bahiensis*, *T. stigmurus* and *T. obscurus* are the most dangerous ones. Other species such as *T. metuendus*, *T. silvestres, T. brazilae*, *T. confluens*, *T. costatus*, *T. fasciolatus and T. neglectus* are also found in the country, but the incidence and severity of accidents caused by them are lower. The main effects caused by scorpion venoms – such as myocardial damage, cardiac arrhythmias, pulmonary edema and shock – are mainly due to the release of mediators from the autonomic nervous system. On the other hand, some evidence show the participation of the central nervous system and inflammatory response in the process. The participation of the central nervous system in envenoming has always been questioned. Some authors claim that the central effects would be a consequence of peripheral stimulation and would be the result, not the cause, of the envenoming process. Because, they say, at least in adult individuals, the venom would be unable to cross the blood-brain barrier. In contrast, there is some evidence showing the direct participation of the central nervous system in the envenoming process. This review summarizes the major findings on the effects of Brazilian scorpion venoms on the central nervous system, both clinically and experimentally. Most of the studies have been performed with *T. serrulatus* and *T. bahiensis*. Little information is available regarding the other Brazilian *Tityus* species.

Keywords: Brazilian scorpions, Central nervous system, Scorpion venom, Scorpion toxins

Background

Approximately 1500 scorpion species, distributed among 18 families, are described worldwide [1]. From these species, only nearly 30, belonging to the Buthidae family, are dangerous for humans and are responsible for serious envenoming or death [2–5].

In Brazil, from about 160 scorpion species that occur in the country, those belonging to *Tityus* genus are responsible for severe incidents. *T. serrulatus, T. bahiensis, T. stigmurus and T. obscurus* are the most dangerous ones found in the country. Other species, such as *T. metuendus, T. silvestres, T. brazilae, T. confluens, T. costatus, T. fasciolatus, T. neglectus, T. aba, T. anneae, T. carvalhoi, T. cylindricus, T. kuryi, T. maranhensis, T. martinpaechi, T. mattogrossensis, T. melici, T. pusillus, and T. trivittatus*, also occur, but the incidence and severity of accidents caused by them are lower [6–10].

Tityus serrulatus is the Brazilian scorpion that is responsible for the most severe accidents, with mortality rates of approximately 1% among children and elderly people [11]. This species is widely distributed throughout the country, reaching the states of São Paulo, Minas Gerais, Bahia, Espírito Santo, Goiás, Paraná and Rio de Janeiro [4, 12]. Similarly, *T. bahiensis* is widely distributed throughout the country, except for northern regions, and it is responsible for most of the accidents in the Southeast region [2, 4]. *T. stigmurus* is distributed predominantly in the Northeastern region of the country, where it is the main cause of accidents [4]. In the Brazilian Amazon, the main species with medical interest are *T. obscurus*, *T. metuendus* and *T. silvestris* [11, 13].

The main effects caused by scorpion venoms – such as myocardial damage, cardiac arrhythmias, pulmonary edema and shock – are mainly due to the release of mediators from the autonomic nervous system [13]. On the

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other hand, some evidence show the participation of the central nervous system and of the inflammatory system in the process [14–30].

The participation of the central nervous system in the envenoming process has always been questioned. According to Freire-Maia and Campos [31], the central effects would be the result and not the cause of the envenoming process, since the venom would be unable to cross the blood-brain barrier. On the other hand, Ismail et al. [32, 33] believe in the direct participation of the central nervous system in the process, especially in very young individuals, where the blood brain barrier would not be fully formed.

Worldwide, some clinical reports have indicated the involvement of the central nervous system in the effects of the venom. Nagaraja et al. [34], in a study carried out in India, reported two cases of stroke after a scorpion sting. Barthwal et al. [35] also reported a case of brain infarct after myocarditis and pulmonary edema, after a scorpion sting. Fernandez-Bouzas et al. [36] reported two children with severe neurological complications after scorpion stings. Tracker et al. [37] reported a case of multiple cerebral infarcts, limb ischemia and bilateral optic neuropathy due to scorpion (possibly a *Buthus tumulus*) envenoming. Gadwalkar et al. [38] demonstrated a rare case of extensive cerebellar infarction following a scorpion sting caused by the vasculotoxic action of the scorpion venom. Prasad et al. [39] reported a case of ischemic infarction of the cerebral cortex in a child suffering from scorpion envenoming. Sigirci et al. [40] demonstrated cerebellar and cerebral infarctions with corpus callosum involvement and bilateral cerebral atrophy with subdural hemorrhage in an 8-month-old girl stung by a *Leiurus quinquestriatus.* Unfortunately, most of the scorpions that caused the accidents were not identified.

In Brazil, cerebrovascular complications after scorpion stings are rare. Few cases have been described in the literature. Bonilha et al. [41] reported a case of a child who developed epilepsy due to a destructive brain lesion after a sting by *T. serrulatus*. Oliveira et al. [42] reported neurological alterations such as hemiplegia, paralysis of the facial nerve and cerebral edema in a 10-year-old girl who was stung by an unidentified scorpion. Seizures and hemorrhagic stroke on the frontal lobe were described in a woman stung by *T. serrulatus* [43]. Marrone et al. [44] described the first case of posterior reversible encephalopathy syndrome in a 13-year-old boy stung by *T. bahiensis*. Bucaretchi et al. [45] reported a fatal envenoming involving multiple, extensive brain infarcts in a patient with a previous diagnosis of essential thrombocythemia who was stung by *T. serrulatus*.

Moreover, experimental studies performed mainly with *T. serrulatus* and *T. bahiensis* have demonstrated the central effects of the scorpion venoms and toxins [17–19, 46].

This review aims to provide an update of clinical and experimental findings on the effects of Brazilian scorpion venoms on the central nervous system.

Tityus serrulatus

T. serrulatus is the most known Brazilian scorpion (Fig. 1) and its venom has been extensively studied. Lutz and Mello described this species for the first time in Brazil in 1922. Its reproduction is parthenogenetic [5].

Clinically, it is responsible for the majority of the accidents in the country [12, 20]. Local pain is the primary local manifestation, and this type of accident is classified as mild [47, 48]. In moderate cases, cardiac effects, vomiting, abdominal pain, agitation, hypersalivation, fever, priapism, and hyperglycemia occur, whereas in severe cases, cardiovascular, pulmonary, gastrointestinal and metabolic complications appear, in addition to neurological symptoms [47, 48]. Central effects such as coma and convulsion rarely appear, therefore there are only few cases described in the literature [41, 43, 45].

Experimentally, studies on *T. serrulatus* venom started in the 1960s by Gomez and Diniz, when they reported the first fractionation process and the first fraction obtained was named "tityustoxin" [49]. For a long time, this component was considered a purified toxin. However, the improvement of the purification methodology showed it is a "pool" constituted of several peptides [50]. Since then, this pool has been designed as "tityustoxin" (in quotation marks) in order to differentiate it from the purified tityustoxin (without quotation marks) described later [51–53]. One of the first studies performed with

Fig. 1 *Tityus serrulatus*. Known as the yellow scorpion, *T. serrulatus* is 5 to 7 cm long, with the third and fourth segments of the metasoma serrated, and parthenogenetic reproduction. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

"tityustoxin" showed cardiovascular and respiratory effects after intravenous injection [54]. The intracerebral injection induced similar cardiorespiratory alterations, in addition to neurological alterations, such as tremors, hyper-reactivity, extensor rigidity and convulsions [54].

Since the first purification processes, several toxins have been isolated and sequenced and some of their biological effects have been characterized [15, 52, 53, 55–64].

Throughout more than 50 years, many studies have tried to explain the action of this venom and its components on the central nervous system. Although Revelo and collaborators [65] have not detected *T. serrulatus* venom in the central nervous system after subcutaneous injection in an immunoenzymatic assay, a number of studies have demonstrated the ability of this venom, or part of it, to cross the blood-brain barrier and to reach the central nervous system [66–69].

Studies performed with the whole venom have demonstrated its inhibitory effect on the sodium-dependent amino acid uptake in synaptosomes and synaptic membrane vesicles, thus affecting the absorption capacity of these amino acids [70]. Pre-treatment with the venom alters the threshold and intensity of seizures in different animal models of epilepsy. The intrahippocampal injection in rats is able to promote behavioral changes and epileptiform activity [71]. Intravenous or intracerebral injection alters the level of neurotransmitters in different regions of the brain, revealing a connection between the action of this venom and GABA and dopamine [14]. Intraperitoneal injection induces electrographic and behavioral alterations in rats [17]. In studies with isolated preparations of rat brain synaptosomes, it has been shown that this venom is not able to alter the glutamate uptake; however, it promotes an inhibition of the GABA and dopamine uptake caused by the action of the venom on the Na^+ channels [72].

Its actions on the central nervous system have generated great interest in the identification of isolated components to better elucidate the action of *T. serrulatus* venom on the central nervous system. Several toxins have already been isolated and their central effects have been described.

Some of the major toxins that affect the central nervous system are:

- Ts1, also known as TsTX-I, Ts VII or toxin γ, is the most abundant and the most toxic component isolated from *T. serrulatus* venom, corresponding to about 16% of the soluble fraction of the venom [73–75]. It acts as a classical β-toxin [75], modulating the activation process of sodium channels Nav1.6 and Nav1.3 in the negative potential direction, causing the opening of the channels at the resting potential. However, electrophysiological studies of Ts1 in Nav channels of insects resemble the effect of a typical site 3 toxin following a bell-shaped voltage dependence that does not occur with other β toxins. Additionally, Ts1 inhibits the sodium current through Nav 1.5 channels without altering the activation or steady-state inactivation curves [76]. The intracerebral injection of Ts1 in rats causes epileptiform discharges and wet dog shake behavior, and it is also able to cause paralysis of the hind limbs and severe respiratory distress followed by death [46], without altering the intrahippocampal concentration of glutamate [77]. The injection of Ts1 affects the neuroimmunological system, increasing the level of tumor necrosis factor α (TNF-α) and interferon gamma (IFN-γ) in the rat brain [77, 78].
- Ts3, also known as TsTX, toxin IV-5, TS-8F or tityustoxin, is considered the most lethal α-toxin, component of the *T. serrulatus* venom [79, 80]. Even small doses of this toxin may have a lethal effect in adult rats when injected directly into the brain [81, 82]. According to Guidine et al. [68], the toxin affects brainstem structures involved in neurovegetative control, such as cardiovascular and respiratory functions. When subcutaneously injected, the toxin crosses the blood-brain barrier and reaches these centers [69]. The basic action of this toxin is to delay the inactivation of voltage-dependent sodium channels, which increases the permeability of the cell membrane to sodium, thereby, increasing the release of the neurotransmitters [14, 83–85]. After intrahipocampal injection, Ts3 promotes the release of glutamate, causing epileptic-like discharges and neuronal loss in CA1, CA3 and CA4 hippocampal areas [15, 86, 87]. Four months after the injection, neuronal loss and mossy fiber sprouting were still observed in the supragranular layer of the dentate gyrus in rats [88]. TsTX also evokes glutamate release from cortical synaptosomes, and calcium is involved in this release [85, 89]. According to Silva et al. [90], the epileptiform discharges caused by TsTX are correlated with cardiac arrhythmias. Intracerebral injections of Ts3 can still produce severe lung edema, lead to a cerebral inflammatory process with higher levels of TNF-α and induce an increase in the microvascular leukocyte recruitment [78, 91].
- Ts4, also known as TsTX-VI, was described as a less toxic toxin, but it can cause allergic reaction (lachrymation, spasm in mouse hind paws) and it is capable of causing the release of neurotransmitters such as glutamic acid and GABA from rat brain synaptosomes [92]. This toxin specifically inhibits the rapid inactivation of the Nav1.6 channel [63].

- Ts5 is an α-neurotoxin capable of delaying the inactivation of voltage-dependent sodium channels [57, 58, 72]. It shows high toxicity and constitutes about 2% of the soluble fraction of the venom [74]. It acts specifically on channels Nav1.2, Nav1.3, Nav1.4, Nav1.5, Nav1.6 and Nav1.7, inhibiting rapid inactivation [62]. It is capable of causing the release of catecholamines and the reduction of GABA and dopamine in vitro, because of the depolarization, involving voltage-dependent sodium channels [72, 74]. Ts5 also acts as a proinflammatory toxin, inducing the production of TNF-α and IL-6 [62].

Other important toxins, whose effects on the central nervous system have not been directly demonstrated yet, should not be ruled out due to their action on ion channels, essential elements for the functioning of the central nervous system.

Among the toxins acting on sodium channels is Ts2, also known as TsTX-III or III-8, which has been classified as both an α- and β-toxin [53, 56]. Ts2 inhibits the rapid inactivation of some sodium channels, but does not affect others [93]. It represents the newest member of a small group of toxins with the structural features of β-toxins but displaying α-like activity [94]. Ts17 and Ts18 toxins have been described based on transcriptomic studies from venom glands, and neurotoxic activities were attributed to these toxins [95]. Ts17 was classified as a toxin that acts on sodium channels, since its sequence has about 86% of identity with the Ts5 toxin [95]. Ts18 is also classified as a toxin that acts on sodium channels, due to the high degree of identity (63%) with the U1-buthitoxina-Hj1a toxin, a sodium channel toxin isolated from the venom of the black scorpion *Hottentotta judaicus* [95, 96].

Among the toxins that act on potassium channels is Ts6, also known as TsTX-IV, which is able to block calcium activated potassium channels of high conductance. Ts6 showed a high blocking effect on Kv1.2, Kv1.3 and Shaker IR channels and was capable of blocking, with low efficiency, the channels Kv1.1, Kv1.5, Kv1.6, Kv4.3, Kv7.1, Kv7.2, Kv7.4 and hERG [97, 98]. It has a high capacity to interact with different subtypes of K^+ channels with different affinities [99]. According to Arantes et al. [52], this toxin induces a release of noradrenaline.

Ts7, also known as TsTX-Kα or tityustoxin K-α, has been classified as a potent and selective potassium channel blocker toxin [100, 101], which partially inactivates K^+ currents in dorsal root ganglion neurons of rats [102]. Ts7 showed a high and significant blocking effect on Kv1.1, Kv1.2, Kv1.3, Kv1.6 and Shaker [98]. Some years ago, studies have classified this toxin as a simple blocker of Kv1.3 channels [103].

Ts8, also known as tityustoxin K-β or TsTX-K β, is a 60-amino-acid-residue peptide and can be classified as β-KTX (toxins acting on potassium channels) [64], which means that it selectively blocks voltage-gated noninactivating K^+ channels in synaptosomes [104]. Since it shows a very different sequence from the standard observed for toxins that act on K^+ channels (toxins that have between 23 and 42 amino acid residues), it was classified as the first toxin from the β-KTx subfamily [94].

Ts8 presents a specific inhibiting effect on Kv4.2, showing a reversible inhibition [105]. Ts9, also known as TsKappa, has been described as an active toxin on calcium-activated small conductance potassium channels [59]. Cologna et al. [75] classified the peptides TsPep1, TsPep2 and TsPep3 described by Pimenta et al. [106] as Ts11, Ts12 and Ts13, respectively. These peptides are formed by four disulfide bridges, and their structural characteristics point out that they are active on K^+ channels, on the basis of a functional analysis evidencing these toxins as preferential Kv blockers. Due to the poor percentage of identity with the other KTxs, Cremonez et al. [107] suggested that they can be regarded as the first members of a new subfamily of KTxs, called ε-KTx.

Ts15, also known as α-KTx21, is capable of blocking potassium channels in a nanomolar range [60, 108]. In 2013, Verano-Braga et al. [109] described a post-translational modification in the structure of Ts15 that presented an N-glycosylation; this was the first toxin in the *T. serrulatus* venom to have this modification described.

Ts16 toxin shows high selectivity towards blocking the Kv1.2 subtype of potassium channels, and this selectivity is demonstrated by means of two-electrode voltage-clamp technique [94]. This toxin demonstrated 62% of identity with Tt28, a component from the *T. trivittatus* venom, belonging to α-KTx20.1 [110].

Ts19 is a toxin that has been described initially from peptide fragments identified by peptidomic analyses. These fragments are related to β-KTx, toxins that act on potassium channels [94, 111]. Subsequently, transcriptome studies were able to identify the precursor sequence of this toxin, called Ts19 [95]. Currently, in the literature, there are three fragments related to Ts19, which are Ts19 Frag-I, Ts19 Frag-II and Ts19 Frag-III [64, 94]. The Ts19 fragment Frag-I shows 58 amino acid residues and has a high level of identity with toxins that act on potassium channels (KTx) [112]. In relation to the Ts19 Frag-II, it has 49 amino acid residues and was described as a β-KTx 2 toxin, characterized by an important selective and blocking action on Kv1.2 potassium channels [64, 113].

Finally, Ts14 represents a group of four peptides classified as hypotensins, TsHpt-I to TsHpt-IV [114]. The tests

with TsHpt-I in rats in vivo demonstrated that this toxin has a bradykinin potentiating effect and a vasorelaxation effect on aortic rings dependent on nitric oxide [115].

Tityus bahiensis

Unlike *T. serrulatus*, the distribution of *T. bahiensis* (Fig. 2) depends on its biological and ecological needs, such as sexual reproduction and relationship with environmental changes (including temperature and humidity), which limits its presence to the central and southwest regions of the state of Minas Gerais, the western São Paulo and northern Paraná [116].

T. bahiensis is responsible for most of the accidents in the Southeastern region of Brazil. However, in general, these accidents are considered mild with only local pain. In the literature, there is only one case of a patient with more severe symptoms and the involvement of the central nervous system [44].

Several experimental studies have been carried out with *T. bahiensis* venom, most of them dedicated to the purification and sequencing of the toxins [79, 117, 118]. Others aimed to describe the activity of some toxins, such as anti-insect or proteolytic properties, or the effects of the venom on sodium channels [119–121]. Recently, the transcriptome was performed in order to identify the main components of the venom [122].

Regarding the action on the central nervous system, it was demonstrated that crude venom, when peripherally injected into rats, promotes behavioral alterations such as wet dog shake, chewing movements, postural loss and sometimes priapism, as well as electrographic alterations including isolated spikes in the cortex and in the hippocampus [17]. Moreover, the intracerebral levels of homovanillic acid (HVA) are increased [17]. The partially purified venom, intravenously injected in mice, causes convulsion [18].

The direct application in the central nervous system of rats causes behavioral alterations such as wet dog shake, myoclonus and immobility and clonus of limbs, and electrographic alterations characterized by moderate and intense discharges, and neuronal loss in CA1, CA3 and CA4 hippocampal areas [18]. When the study is performed with purified toxins applied directly in the hippocampus of rats, the following alterations appear: wet dog shake, myoclonus, yawning, orofacial automatisms, and isolated or grouped spikes and epileptic-like discharges, varying in intensity from short to medium or strong [19, 123]. An increase in the extracellular level of glutamate and neuronal loss in the hippocampus are also observed as a consequence of the increase in the intracellular calcium concentration [19].

Tityus stigmurus

T. stigmurus (Fig. 3) is responsible for most of the accidents in the Brazilian Northeastern region [124]. Many of these accidents are mild, and the death of only three children with less than five years of age has been reported in the period from 2006 to 2010 in the state of Pernambuco [125]. The severity of the envenoming is similar to that caused by *T. serrulatus* and is characterized by pain, edema, erythema, paresthesia, headache and vomiting [126].

T. stigmurus venom has been further studied in the last few years by means of proteomic and transcriptomic approaches in order to characterize the genic expression of the venom gland [126, 127]. Several peptides of pharmacological interest have been identified including

Fig. 2 *Tityus bahiensis*. Known as the brown scorpion, *T. bahiensis* has a dark trunk, legs and palps with dark spots and reddish brown tail. The adult measures about 7 cm and presents sexual reproduction. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

Fig. 3 *Tityus stigmurus*. The yellow scorpion of the Northeast resembles *T. serrulatus* in habits and coloration, but it shows a dark longitudinal band in the dorsal area. Adult specimens are black and can reach 9 cm. They present sexual reproduction. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

hypotensins, antimicrobial peptides and toxins active on sodium and potassium channels [126, 128, 129]. Other studies evaluated the effects of this venom on the renal function [130], analyzed the structure and toxicity of a hypotensive peptide [131], and characterized potassium channel blocker peptides [132, 133]. There are neither experimental studies nor clinical data demonstrating the central effect of this venom.

Tityus obscurus

T. obscurus (Fig. 4), also known as *T. cambridgei* or *T. paraensis*, is the most dangerous found in the Amazon forest and it is responsible for several accidents in this region [134, 135].

The effects of their stings may be different according to the region of origin. Generally, a local and radiating pain is observed, as well as paresthesia, edema, erythema, sweating, piloerection and burning. Paresthesia and radiating pain predominated in patients from the western region of the state of Pará [136]. The main neurological effects are myoclonus, dysmetria and ataxia, without autonomic manifestations. Myoclonus, electric shock-like sensations in the body, dysarthria, paresthesia, ataxia and dysmetria were reported only in patients from the western region of the state of Pará [136]. It was reported that the vast majority of the patients presented symptoms compatible with acute cerebellar dysfunction and abnormal neuromuscular manifestations and, in some cases, muscle injury, which Torrez et al. [137] claim that have never been described in any other region of the world.

The composition of the venom is poorly known. The first studies characterizing its components started less the 20 years ago, when the complete description of a potassium channel blocker peptide was carried out and four new active toxins on the sodium channel were described [138, 139]. Other peptides specific for the potassium channel, particularly on the Kv1.3 channel, which is pivotal for the functioning of cells related to the immune system, were described later as well as sodium channel toxins [140–142]. Recently, the cDNA library of venom glands was built [134].

Experimentally, it was demonstrated that *T. obscurus* venom acts directly on skeletal muscle, differently from *T. serrulatus* venom [143]. It was also demonstrated that this venom causes hemorrhagic patches in the lung parenchyma, but it does not lead to pulmonary edema when intraperitoneally injected into rats, and promotes a decrease in the general activity without inducing convulsions neither hippocampal neuronal loss. In mice, it induces edematogenic and moderate nociceptive activity [144].

Other *Tityus*

T. fasciolatus scorpion (Fig. 5) is found mainly in the central region of Brazil, where it is responsible for some accidents [145]. Little information is available on the toxicity of this venom. The first pharmacological characterization of the venom was conducted in 2003, when a toxin active on the sodium channel was isolated [145]. The deleterious effect of the venom on the cardiovascular system was more recently determined, and other active toxins on the sodium channel were identified [146, 147]. Immunologically and molecularly, this venom was considered to be similar to *T. serrulatus* venom [148]. There is no information on its effect on the central nervous system.

Fig. 4 *Tityus obscurus*. Adults are black and can reach 9 cm in length. However, young animals are brown. They present sexual reproduction. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

Fig. 5 *Tityus fasciolatus*. It is generally yellowish brown with three longitudinal bands on the dorsal side of the trunk. It can measure from 4.5 to 7 cm in length. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

Fig. 6 *Tityus silvestris*. It is generally yellowish brown with spots all over the body, legs and palps. It can measure from 2.5 to 4.5 cm in length. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

Little information is available on another Amazonian scorpion, *T. silvestris* (Fig. 6). The first description of the systemic effects of its venom is recent [149]. Symptoms include nausea, vomiting, somnolence, malaise and prostration. Muscular spasms are described after the scorpion sting, classifying the case as severe envenoming [150].

Regarding *T. costatus* (Fig. 7), there is only one study identifying some components of the venom, which are considered similar to those present in the scorpions of the *Tityus* genus [151].

Fig. 7 *Tityus costatus*. This species is yellowish brown with spots on the legs and palps. It can measure from 5 to 7 cm in length. Source: Brazilian Ministry of Health [6]. Image copyright by Denise Cândido, reproduced with permission

Conclusions

There are several evidences showing the direct participation of the central nervous system in the envenoming process provoked by scorpions. Although the central effects rarely appear in patients, they can be serious and potentially fatal, requiring special attention in the treatment of envenoming cases. In addition, these scorpion toxins may be important tools for central nervous system studies.

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Ethics approval and consent to participate

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The authors declare that they have no competing interests.

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