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REVIEW ARTICLE

Animal Venom Peptides Cause Antinociceptive Effects by Voltage-gated Calcium Channels Activity Blockage

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Abstract: Pain is a complex phenomenon that is usually unpleasant and aversive. It can range widely in intensity, quality, and duration and has diverse pathophysiologic mechanisms and meanings. Voltage-gated sodium and calcium channels are essential to transmitting painful stimuli from the periphery until the dorsal horn of the spinal cord. Thus, blocking voltage-gated calcium channels (VGCCs) can effectively control pain refractory to treatments currently used in the clinic, such as cancer and neuropathic pain. VGCCs blockers isolated of cobra *Naja naja kaouthia* (α-cobratoxin), spider *Agelenopsis aperta* (ω-Agatoxin IVA), spider *Phoneutria nigriventer* (PhTx3.3, PhTx3.4, PhTx3.5, PhTx3.6), spider *Hysterocrates gigas* (SNX-482), cone snails *Conus geographus* (GVIA), *Conus magus* (MVIIA or ziconotide), *Conus catus* (CVID, CVIE and CVIF), *Conus striatus* (SO-3), *Conus fulmen* (FVIA), *Conus moncuri* (MoVIA and MoVIB), *Conus regularis* (RsXXIVA), *Conus eburneus* (Eu1.6), *Conus victoriae* (Vc1.1.), *Conus regius* (RgIA), and spider *Ornithoctonus huwena* (huwentoxin-I and huwentoxin-XVI) venoms caused antinociceptive effects in different acute and chronic pain models. Currently, ziconotide is the only clinical used N-type VGCCs blocker peptide for chronic intractable pain. However, ziconotide causes different adverse effects, and the intrathecal route of administration also impairs its use in a more significant number of patients. In this sense, peptides isolated from animal venoms or their synthetic forms that act by modulating or blocking VGCCs channels seem to be a relevant prototype for developing new analgesics efficacious and well tolerated by patients.

Keywords: Chronic pain, nociception, ion channels, toxin, spider, cone snail.

1. INTRODUCTION

Pain is a common reason for seeking medical treatment and substantially impacts individuals' quality of life. Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Thus, it is relevant to assume that pain perception is affected by personal experience as we learn to use the definition of pain during our life experiences. Also, nociception and pain are different events once nociception is considered "the neural process of encoding noxious stimuli" by the IASP. Besides, the activation of nociceptive neurons after the threatening or actual injury to non-neural tissue causes nociceptive pain [1-5].

Nociceptive pain is a type of acute pain that is relevant to the individual's survival. Thus, the congenital insensitivity to pain induced by mutations in SCN9A (which encodes voltage-gated sodium ion channel Nav1.7) causes the inability to feel pain. This mutation results in self-induced injuries, including bruises, burns, scalds, progressive accumulation of orthopedic fractures, and breaks; although painless, it might eventually be disabling. Hence, excessive risk-taking and resultant painless physical injuries lead to higher mortality in early life. This example shows the relevance of nociceptive pain for normal sensory processing. Another painful condition caused by different mutations, including in the CACNL1A4 gene, is a familial hemiplegic migraine, a rare autosomal dominant disease, which induced migraine with aura accompanied by ataxia, seizures, and motor alterations (hemiplegia). The CACNL1A4 gene is found in chromosome 19p3 and encodes the α1 subunit of VGCC $Ca_V2.1$. This channel is expressed in the somatodendritic and presynaptic neuron membrane, where it causes calcium influx mediating neurotransmitter release. Besides, in mouse models of familial hemiplegic migraine 1, it was described that these mutations are responsible for the reduced threshold for cortical spreading depression and increased progression along the

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cortex. Also, nociceptive pain should be intact after analgesic administration to avoid tissue damage, as observed when a transient receptor potential vanilloid 1 (TRPV1) antagonist was used for pain control in humans, the blockage of this thermoreceptor impaired the perception of noxious heat, causing the withdrawal of the study [1-4].

The nociception processing is caused by the activation of high-threshold sensory receptors in the peripheral sensory neurons by diverse noxious stimuli. The nociceptive neuron expresses different ion channels in the free endings in peripheral tissues, then the activation by noxious stimuli causes the opening of these ion channels (*e.g.*, TRP channels) and may lead to the initiation of action potentials. Also, G protein-coupled receptors (GPCRs) could be found in the nociceptive neurons in the periphery and function as noxious transducers. The noxious stimuli capable of causing nociceptor activation are pressure, extremes of temperature, and diverse chemical substances (acid, adenosine triphosphate, and prostaglandins) [1-4].

In the dorsal root ganglia (DRG) and trigeminal ganglia, we can find the small and medium-size cell bodies of nociceptors, which have a pseudo-unipolar morphology. Voltage-gated sodium channels cause the generation of an action potential in the periphery; this signal is then propagated through the axon by these ionic channels to the presynaptic terminal synapses. After that, action potentials were transmitted to the dorsal horn of the spinal cord by using C (unmyelinated axons) or A δ (small-diameter myelinated axons) fibers. Then, the opening of VGCCs causes VGCCs-mediated calcium influx in the presynaptic terminals of the dorsal horn of the spinal cord leading to the release of different excitatory neurotransmitters and peptides into the synaptic cleft, including glutamate, substance P, and calcitonin gene-related peptide (CGRP) (Fig. **1**). Finally, the activation of neurotransmitter receptors in the second-order nociceptive projection neurons and interneurons (postsynaptic terminals) in the dorsal horn of the spinal cord triggers the conduction of nociceptive information to pain-related brain areas using ascending pathways (spinothalamic or spinoparabrachial pathways). Then, from the periphery (skin) or viscera, the nociceptive signal is transmitted to the central nervous system (CNS) to cause pain perception [1-3].

Nociceptor function is significantly modified in response to tissue damage, inflammation, or injury of the nervous system. Post-translational and transcriptional changes can massively alter the threshold, excitability, and transmission properties of nociceptors, contributing to pain hypersensitivity and spontaneous pain. Changes can be localized to the peripheral terminals or the central synapses. Peripheral alterations cause an increased response and a reduced threshold of nociceptive neurons resulting in peripheral sensitization. Further, increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input is named central sensitization. It occurs in response to altered synapses in the spinal cord dorsal horn. Sensitization of nociceptor fields may lead to different clinical symptoms, such as allodynia (pain to a previous non-noxious stimulus) or hyperalgesia (increase pain responsivity to a stimulus already described as painful) [5-7]. Moreover, the expression and function of specific types of VGCCs can change in pathological pain conditions. Thus different studies associated the altered VGCCs activity with pain hypersensitivity and chronic pain induction [8-10].

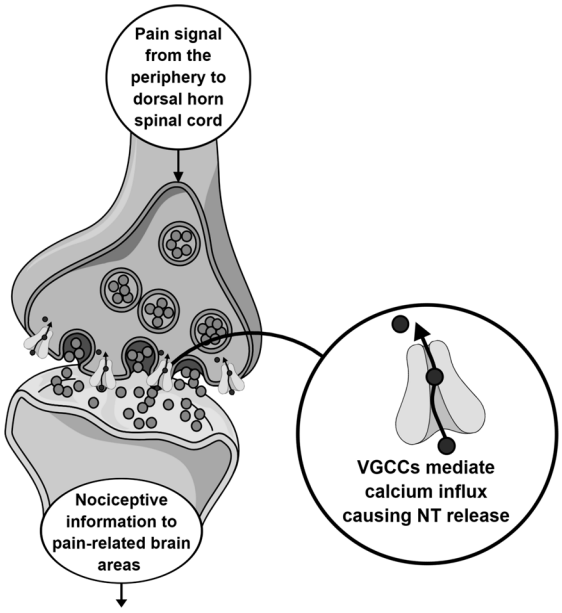

Fig. (1). A noxious signal conducted by nociceptors to the dorsal horn of the spinal cord leads to the opening of voltage-gated calcium channels (VGCCs). Then VGCCs-mediated calcium influx into the presynaptic terminals of the dorsal horn of the spinal cord causes the release of different excitatory neurotransmitters. The activation of neurotransmitter receptors in the second-order nociceptive projection neurons and interneurons (postsynaptic terminals) in the dorsal horn of the spinal cord triggers the conduction of nociceptive information to pain-related brain areas using ascending pathways. Neurotransmitters were labeled as red points, and calcium ions as green signals in the Figure.

Acute pain has a brief duration and is often related to a known cause. However, chronic pain is a complex and burdensome phenomenon usually unpleasant and aversive, where pain lasts or recurs for more than three months. Chronic pain can be classified as neuropathic pain when pain arises from an abnormal function of the somatosensory nervous system induced by a lesion or disease. Besides, another type is nociplastic pain, defined by IASP as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". Nociplastic pain is observed in fibromyalgia and complex regional pain syndrome (CRPS) type 1, also considered primary chronic pain conditions [2, 11].

Chronic pain affects many individuals worldwide, with a prevalence of nearly 20% in the general population. Chronic primary and secondary pain conditions are now described in the International Classification of Diseases 11 (ICD-11). Chronic primary pain syndromes, such as nonspecific low-back pain and temporomandibular disorder, are recognized as disease conditions that cause emotional suffering or functional disability and are not associated with another type of chronic pain. However, in secondary pain syndromes, pain is

primarily a symptom of another disorder, such as cancer or neuropathy [1, 12].

Also, chronic pain is frequently accompanied by depression and anxiety disorders and often causes a significant social and economic burden globally [13, 14]. The Global Burden of Disease (GBD) Study 2017 showed that low back pain, headache disorders, and depressive disorders are the three leading causes of years lived with disability. Also, headache disorders are included in the most common causes of all ages and both sexes. Thus, the GBD study confirmed that chronic pain is one of the important causes of disability and disease burden globally [15].

The compounds frequently used for pain control are nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, antidepressants, skeletal muscle relaxants, and topical agents (*e.g.*, lidocaine and capsaicin) [16-19]. However, pain treatment should be improved because the analgesics available frequently induce dose-limiting adverse effects and have low efficacy. Consequently, the study of the VGGCs channels involved in pain transduction and transmission are relevant to understanding the pathophysiology of chronic pain [8, 20]. Moreover, a better understanding of the functioning of VGCCs may lead to the discovery and development of better analgesic compounds.

2. VOLTAGE-GATED CALCIUM CHANNELS (VGCC)

There is a great diversity of native calcium channel subtypes classified according to their voltage-dependent and kinetic biophysical properties combined with their sensitivities to pharmacological agents. Calcium channels are defined according to their primary α1 subunit type ($Ca_V\alpha1$). CaVα1 is a membrane protein (~200-260 kDa) that contains the structural and functional machinery and is submitted to regulation by second messengers, drugs, and animal venom peptides [21-23].

The VGCCs are classified into high voltage-activated (HVA) or low voltage-activated (LVA) calcium channels. Based on biochemical and molecular analyses, the HVA calcium channels are heteromultimeric protein complexes comprised of a pore-forming $Ca_V\alpha1$ subunit that coassembles with ancillary $Ca_V\beta$, $Ca_V\alpha2\delta$ and possibly $Ca_V\gamma$ subunits, plus calmodulin (CaM). On the other hand, the LVA calcium channels lack these ancillary subunits and function as $Ca_V\alpha1$ subunit monomers [22, 24]. The ten major genes encoding α1 subunits have been subdivided by sequence homology into three families; Ca_V1, Ca_V2, and Ca_V3 [21, 25].

The HVA calcium channels are open in response to large membrane depolarizations and have a positive membrane potential threshold for opening, and are further classified as L-type ($Ca_{V1.1}$, which is a skeletal muscle-specific isoform, $Ca_{V1.2}$, $Ca_{V1.3}$, $Ca_{V1.4}$), P/Q-type ($Ca_{V2.1}$), N-type ($Ca_{V2.2}$), and R-type ($Ca_{V2.3}$) based upon distinct pharmacological sensitivities [21, 22, 24, 26]. The LVA calcium channels, also called the T-type calcium channel, are activated by lower voltage changes and open transiently, exhibit a relatively negative membrane potential threshold for activation, and are molecularly classified into three types: $Ca_{V3.1}$, $Ca_{V3.2}$, and $Ca_{V3.3}$ [20, 22, 24].

All ten α1 subunits of VGCCs ($Ca_V\alpha1$) share a typical topology of four homologous transmembrane domains (I-IV) connected by cytoplasmic linkers. These domains contain six transmembrane segments in helices (termed S1-S6), plus a re-entrant pore loop. The fourth transmembrane segment (S4 segment) in each domain, which contains positively charged amino acids in every third position, forms the voltage sensor controlling the voltage-dependent activation [27]. In contrast, the pore loop between transmembrane segments S5 and S6 in each domain (I-IV) determines ion conductance and selectivity. Each of the pore loop regions contains highly conserved negatively charged amino acid residues, as glutamic acids in the case of HVA channels, which cooperate to form a highly selective pore for permeant cations calcium [28-30]. Moreover, each of the different calcium channels shows different single-channel conductance variations in one order of magnitude [31-33]. The primary membrane domains are connected by sizable cytoplasmic linker regions and are bracketed by cytoplasmic N and C termini [22].

These cytoplasmic regions are essential for the second messenger regulation of channel function. They contain relevant sites for protein-protein interactions with regulatory elements, such as G proteins and protein kinases [34-37]. Moreover, four known genes encode $Ca_V\beta$ subunits ($Ca_V\beta1$-$Ca_V\beta4$), which are cytoplasmic proteins that associate with the $Ca_V\alpha1$ subunit resulting in alterations of the gating properties of the $Ca_V\alpha1$ subunit, and perhaps more importantly, in increased cell surface trafficking [24]. Further, there are also four different types of $Ca_V\alpha2\delta$ subunits ($Ca_V\alpha2\delta1$- $Ca_V\alpha2\delta4$) that are each transcribed and translated as a single protein, posttranslationally cleaved, and then reconnected by a disulfide bond [24,38]. The $Ca_V\alpha2\delta$ coexpression typically results in augmented channel cell surface density, and its increased expression in neurons results in improved synaptic targeting of VGCCs [39].

VGCCs constitute the predominant pathway for depolarization-mediated calcium entry into neurons. Thus they play a crucial role in painful processes such as inflammatory and neuropathic pain [10]. The calcium channels must be localized within the active zones of presynaptic nerve terminals to assure efficient coupling of calcium influx to rapid vesicle release containing neurotransmitters (glutamate, and neuropeptides SP and CGRP) or other pro-inflammatory mediators [24, 40-42]. However, the distributions of each channel subtype and its exact roles are dependent on the neuron subtype, so that most types of the calcium channels are expressed at various subcellular loci [10]. For example, both N-type and L-type channels can be expressed in dendrites [43], supporting a more comprehensive range of functions of these channels. These diverse functional roles ultimately pose a challenge when designing new calcium channel therapeutics with a low risk of adverse effects [10].

Their sensitivities can also distinguish the different calcium channel subtypes from specific antagonists. L-type ($Ca_{V1.1}$, $Ca_{V1.2}$, $Ca_{V1.3}$, $Ca_{V1.4}$) calcium channels belong Ca_{V1} family, display slow voltage-dependent gating characteristics, and are sensitive to many different dihydropyridine antagonists and agonists [44]. P- and Q-type ($Ca_{V2.1}$) calcium channels, belong to the Ca_{V2} family, [45,46], are both blocked with different affinities by ω-agatoxin IVA, a pep-

tide isolated from American funnel-web spider venom (*Agelenopsis aperta*) [47]. N-type ($Ca_{V2.2}$) calcium channels, also belong Ca_{V2} family, are selectively inhibited by ω-conotoxins GVIA and MVIIA, toxins isolated from the venom of marine fish-hunting mollusks *Conus geographus* and *Conus magus*, respectively [48, 49]. R-type ($Ca_{V2.3}$) calcium channels [50], also belong Ca_{V2} family, can be inhibited by SNX-482, a peptide from *Hyristocrates gigas* Tarantula venom [51, 52]. However, SNX-482-insensitive R-type channels have also been identified in certain types of neurons [10, 53]. T-type ($Ca_{V3.1}$, $Ca_{V3.2}$, and $Ca_{V3.3}$) calcium channels belong to the Ca_{V3} family can be distinguished by their sensitivity to nickel and relative resistance to block by cadmium ions [54].

The Ca_Vα2δ subunit is a relevant accessory subunit for all HVA calcium channels, as mentioned above, and typically promotes the trafficking of HVA α1 subunits to the plasma membrane. The overexpression of Ca_Vα2δ1 in transgenic animals is related to hyperexcitability in the trigeminal sensory neurons (Li *et al.*, 2006). In neuropathic pain, the Ca_Vα2δ1 expression is upregulated similarly to those models triggered by mechanical nerve injury or diabetes [55, 56]. The increase in the Ca_Vα2δ1 expression is related to the development of tactile allodynia [56, 57]. Although the Ca_Vα2δ1 subunit is an accessory subunit for HVA calcium channels, it is an important pharmacological target for gabapentinoids such as gabapentin and pregabalin [58]. Both gabapentin and pregabalin are highly effective treatments for neuropathic pain [59].

Gabapentin directly binds to the Ca_Vα2δ1 subunit [60]. Mutants mice in the Ca_Vα2δ1 subunit, the primary *in vivo* target of pregabalin, are insensitive to the analgesic actions of pregabalin [58]. Moreover, pregabalin inhibits the synaptic targeting of Ca_Vα2δ [61] and abolishes the increased membrane expression of Ca_Vα2δ in DRG neurons from rodents under neuropathic pain conditions [62]. Together, these findings suggest that upregulation of Ca_Vα2δ subunits in afferent pain fibers trigger enhanced expression of synaptic N-type calcium channels facilitating the transmission of pain signals. Since gabapentinoids interfere with Ca_Vα2δ subunit trafficking, they promote regular N-type channel trafficking activity and synaptic transmission to produce analgesia [63]. Gabapentin can also decrease P/Q-type calcium channel activity in dorsal horn synapses, and this fact potentially contributes to its analgesic properties [64].

Peripheral T-type VGCCs are also crucial to the nociceptive information processing, and blockers of these channels present analgesic effects in diverse pain models. Ethosuximide (Zarontin®, Pfizer) in the rat spinal cord inhibits electrically, mechanically, and thermally evoked neuronal responses in normal and neuropathic animals [65, 66]. Ethosuximide also exerts antiallodynic and antihyperalgesic actions in animal models of neuropathic and inflammatory pain [66-69]. On the other hand, it showed that ethosuximide is not effective in treating non-diabetic peripheral neuropathic pain in a randomized, double-blind, and controlled trial in humans. Zonisamide (Zonegran®, Eisai) causes antihyperalgesic actions after sciatic nerve injury in rats and presents analgesic activity in the clinic [70-73]. Mibefradil (Posicor®, Roche) is a relatively potent and somewhat selective blocker of T-type VGCCs and presented antinociceptive action in animal models of pain after intraperitoneal or local administration [67, 74]. However, Roche Laboratories withdrew Posicor (mibefradil) from the market due to potentially harmful interactions with other drugs [75].

L-type VGCCs blockers also present analgesic effects in pre-clinical and clinical pain models. Nifedipine, nimodipine, and verapamil enhanced the analgesic action of morphine and prevented the development of the naloxone-precipitated withdrawal syndrome. Moreover, nifedipine and verapamil effectively blocked the development of tolerance. On the other hand, only the nifedipine plus morphine in a chronic experiment alleviates the tolerance. This treatment also prevents the development of dependence, as shown by the reduction of the ability of naloxone to precipitate the behavioral and biochemical signs of abstinence syndrome. Besides, the block of L-type VGCCs increased the analgesic effect of opioids and interfered with morphine hyperalgesia and morphine tolerance (for review, see [10, 76, 77]). Additionally, diltiazem and nifedipine can prevent oxaliplatin-induced cold hyperalgesia in rats [78]. In a clinical study, the oral nimodipine was also able to reduce the daily requirement of morphine in patients already treated with morphine for some time [79].

Cilnidipine, a dihydropyridine derivative that inhibits N-type and L-type channels, alleviated the hyperalgesia and allodynia associated with neuropathic pain in mice. The spinal administration of cilnidipine in rats inhibited the induction and maintenance of high-frequency stimulation-induced spinal long-term potentiation of C-fiber-evoked field potentials. The basal C-fiber-evoked field potentials in nerve-injured rats were strongly inhibited by cilnidipine. Nicardipine, another L-type VGCC blocker, attenuated the mechanical hyperalgesia but not mechanical allodynia in nerve-injured mice and attenuated the established long-term potentiation C-fiber-evoked field potentials in rats [80].

Different highly selective N-type VGCC inhibitors derived from cone snail venom were described to have antinociceptive effects. However, the synthetic ω-conotoxin MVIIA form (Ziconotide) is the only N-type VGCC blocker approved for pain control in patients. Although this compound is administered by the intrathecal (i.t.) route, and its analgesic effect is accompanied by substantial adverse effects [81, 82].

Thus, we described the diverse VGCCs peptide inhibitors found in animal venoms with antinociceptive properties already tested in this review (Table **1**). These peptides could be helpful to control chronic pain; however, the development of adverse effects is still a problem to be solved.

3. N-TYPE VGCCS BLOCKERS DERIVED FROM ANIMAL VENOMS

The N-type VGCC subtype is found mainly at presynaptic neuronal terminals in the CNS and PNS, and this ion channel has meaningful participation for neurotransmitter release. This VGCC subtype is also commonly found along the lengths of dendrites. N-type VGCC was studied for nociceptive transmission because by controlling synaptic vesicle neurotransmitters release at presynaptic terminals in the superficial laminae I and II; this calcium channel can modulate nociception in the dorsal horn of the spinal cord. Thus, the

Table 1. Animal venom peptides with antinociceptive action by voltage-gated calcium channels (VGCC) blockage effect.

Peptide	Organism	Blockage Activity	Pain Models Used to Test the Antinociceptive Effect	References
ω-conotoxin GVIA (SNX-124)	*Conus geographus* (cone snail)	N-type VGCC	Inflammatory and neuropathic pain models.	[91-93]
ω-conotoxin MVIIA (SNX-111, ziconotide, or Prialt)	*Conus magus* (cone snail)	N-type VGCC	Acute, inflammatory, postoperative, and neuropathic pain models.	[93, 96-98]
ω-conotoxin CVID (AM336, leconotide, or CNSB004)	*Conus catus* (cone snail)	N-type VGCC	Acute, neuropathic, inflammatory, bone cancer pain models.	[93, 109-111]
ω-conotoxin SO-3	*Conus striatus* (cone snail)	N-type VGCC	Acute pain models.	[115, 116]
ω-conotoxin FVIA	*Conus fulmen* (cone snail)	N-type VGCC	Acute and neuropathic pain models.	[117]
ω-conotoxins CVIE and CVIF	*Conus catus* (cone snail)	N-type VGCC	Neuropathic pain model.	[118]
MoVIA and MoVIB ω-conotoxins	*Conus moncuri* (cone snail)	N-type VGCC	Neuropathic pain model.	[119]
RsXXIVA	*Conus regularis* (cone snail)	N-type VGCC	Acute pain models.	[120]
α-conopeptide Eu1.6	*Conus eburneus* (cone snail)	N-type VGCC	Neuropathic pain models	[121]
Huwentoxin-I (HWTX-I or HWAP-I)	*Ornithoctonus huwena* (spider)	N-type VGCC	Acute and inflammatory pain models.	[127, 128]
Huwentoxin-XVI (HWTX-XVI)	*Ornithoctonus huwena* (spider)	N-type VGCC	Acute and postoperative pain models.	[129]
Phα1β (PnTx3.6 or CTK 01512-2)	*Phoneutria nigriventer* (spider)	N-type VGCC and TRPA1 antagonist	Acute, neuropathic, inflammatory, postoperative, visceral, cancer, and facial pain models.	[134, 144-153, 135, 154-158, 136-140, 142, 143]
α-cobratoxin	*Naja naja kaouthia* (cobra)	T-type VGCC	Acute and Inflammatory pain models.	[180]
ω-Agatoxin IVA	*Agelenopsis aperta* (spider)	P-type VGCC	Inflammatory pain models.	[219]
PhTx3.3	*Phoneutria nigriventer* (spider)	R- and P/Q- VGCC	Neuropathic and inflammatory pain models.	[221]
PhTx3.4	*Phoneutria nigriventer* (spider)	L-type VGCC	Postoperative and acute pain models.	[211, 212]
PhTx3.5	*Phoneutria nigriventer* (spider)	L-type VGCC	Postoperative, neuropathic, cancer-related pain models.	[195]
SNX-482	*Hysterocrates gigas* (spider)	L-type VGCC	Neuropathic pain models.	[25, 45]

block of N-type VGCC interrupts the signaling between the primary nociceptive neuron and the projecting neuron to brain areas related to pain perception. So, in situations related to increasing excitation of nociceptive neurons, the block of N-type VGCC inhibits the pain [9, 83-86].

Moreover, the genetic deletion of $Ca_V2.2$ generates mice with functioning CNS, without alterations in locomotor activity, and with reduced anxiety-like behaviors. $Ca_V2.2$ mutant mice demonstrated nearly normal latency/threshold to acute nociceptive stimuli when compared with $Ca_V2.2^{+/+}$. Besides, the spinal nerve ligation caused mechanical allodynia and thermal hyperalgesia in $Ca_V2.2^{+/+}$ mice but reduced nociception in $Ca_V2.2^{-/-}$ mice [87]. A different study detected that in mice lacking the α_{1B} subunit of N-type VGCC channels, the nociceptive response is reduced in the formalin test (phase 2). No difference was detected in the mechanical threshold (tail pinch test) in α_{1B}-deficient mice. However, it was verified an increased response to the latency in the hot plate test at 55ºC without locomotor dysfunction [84].

It was detected an altered response to acute nociceptive tests (von Frey stimulation and tail-flick tests) in α_{1B}-

deficient mice, with no motor alteration. Besides, α1B-deficient mice presented a reduced nociceptive response in formalin and acetic acid-induced visceral nociception tests [87]. These studies using mutant mice were relevant for understanding the role of N-type VGCC channels in pain development and neurotransmitter release. However, the results detected for acute pain are not conclusive and showed some discrepancies.

Furthermore, the activation of diverse receptors can reduce the functioning of N-type calcium channels through Gβγ-mediated pathway. The activation of Gi/Go causes this indirect inhibition of the ion channels coupled GPCRs by α2-adrenergic agonists (such as clonidine) and μ-opioid receptor agonists (including morphine) [9, 10]. Moreover, the role of N-type VGCCs channels was highlighted in various studies using models of inflammatory or neuropathic pain. In this view, different N-type VGCCs direct blockers, including ω-conopeptides, were tested in pain models and showed antinociceptive activity [85, 88].

Initially, ω-conotoxin GVIA and ω-conotoxin MVIIA (named SNX-111, Prialt, or Ziconotide) were used as pharmacological tools to understand the role of N-type VGCCs in nociception. The ω-conotoxins are included in the O-superfamily that is also composed of μO-conotoxins (voltage-gated sodium currents inhibitors), δ-conotoxins (block fast inactivation of the voltage-gated sodium channels), and κ-conotoxins (potassium channels modulators). The ω-conotoxins are small disulfide-bonded peptides usually isolated from fish hunter cone snails and are formed by 13-30 amino acid residues. The cone snail peptides are not orally administered because proteases rapidly degrade them. Thus, these peptides need to be injected into the CNS by i.t. route to cause N-type VGCCs inhibition and consequently cause antinociceptive effect [82, 89, 90].

The ω-conotoxin-GVIA (SNX-124) is a peptide composed of 27 amino acids and three disulfide bonds. It was the first found in the venom of *Conus geographus*. This conopeptide is a selective, potent (nanomolar affinity) and irreversible blocker of N-type VGCCs channels. Besides, by effective inhibition of N-type VGCCs ω-conotoxin-GVIA decreased the release of neurotransmitters in the spinal cord, contributing to understanding the physiological role of N-type channels to nociception transmission [82, 89, 90]. The i.t. delivery of ω-conotoxin-GVIA reduced the secondary mechanical allodynia and hyperalgesia caused by capsaicin intraplantar (i.pl.) injection in rats. These results are similar to those found to nifedipine (an L-type VGCC blocker) and ω-agatoxin IVA (a P-type VGCC blocker) [91]. Likewise, ω-conotoxin-GVIA reduced the nociception caused by mustard oil injection into the knee. These results showed the relevant role of N-type VGCCs in the induction of hyperexcitability of spinal cord neurons caused by peripheral inflammation [92].

ω-Conotoxin GVIA i.t. also caused antinociceptive action in a neuropathic pain model (spinal nerve ligation) in rats. In this study, authors compared the antiallodynic effect of ω-conotoxins GVIA (SNX-124), MVIIA (SNX-111), CVID (AM-336) in this neuropathic pain model by i.t. administration. The ω-conotoxin GVIA was more potent than ω-conotoxins MVIIA and CVID (3-4 times) or morphine (nearly 40 times). Besides, the injection of the ω-conopeptides did not alter the perception of acute nociception. Also, CVID showed a better therapeutic margin than ω-conotoxins GVIA and MVIIA [93]. However, ω-conotoxin GVIA showed a slow onset/offset kinetics, and these characteristics difficulties the dose-titration in the clinical setting [82].

The ω-Conotoxin MVIIA is a peptide present in the venom of the fish-hunting marine snail *Conus magus*, also named Magician's Snail. This marine snail is observed in the Pacific Ocean (Philippines) and diverse potent nerve toxins are found in its venom. ω-Conotoxin MVIIA is capable of selectively and reversibly blocking N-type VGCCs, reducing neurotransmission and neuronal excitability. Ziconotide (previously called SNX-111) is the synthetic form of this peptide and is formed by 25-amino acids connected by three disulfide bridges [88, 94, 95]. Different research papers were published showing the antinociceptive action of ziconotide using models of acute and inflammatory pain [96-98]. Also, the antinociceptive activity of this peptide was tested using neuropathic and postoperative pain models. Thus, the analgesic effect of ziconotide occurs by blocking calcium influx mediated by N-type VGCCs. The block of this channel inhibits the release of neurotransmitters from the primary afferent nerve terminals to the synaptic cleft in the spinal cord and, thus, inhibits pain transmission [98-103].

Currently, ziconotide (Prialt) is the single selective N-type VGCCs blocking drug approved for clinical control of pain. This peptide was approved by the European Medicines Agency and the US Food and Drug Administration to control chronic intractable pain as an intraspinal agent. Thus, ziconotide is inserted in polyanalgesic guidelines only by i.t. infusion, and the long-term therapy is done by utilizing specific i.t. implanted drug delivery systems. The i.t. drug administration is considered an invasive method for the control of refractory pain. It is well known that i.t. drug delivery systems can cause various complications, including ziconotide overdose and meningitis. Once this peptide is hydrophilic and formed by a large chain of amino acid, after the i.t. injection, there is a slow propagation of the peptide within the cerebral spinal fluid (CSF) to the site of action in the dorsal horn of the spinal cord, causing a slow onset of the analgesic effect. The initial doses of ziconotide used should be low, and a gradual increase in the dose is recommended to reduce the incidence and severity of adverse effects. Thus, the ziconotide analgesic effect has a lag time for the onset and offset of analgesia induction and adverse effects. Also, the potent analgesia detected for this compound occurred in cancer- and non-cancer-related chronic pain [94, 100, 104-106].

Once ziconotide did not interact with opioid receptors, it did not cause analgesic tolerance, addiction, withdrawal syndrome, hyperalgesia, or other opioid-induced systemic effects. However, ziconotide injection causes different CNS adverse effects, such as dizziness, confusion, memory impairment, ataxia, nausea, vomiting, and nystagmus. Additionally, another problem is the risk of suicidal ideation and psychosis caused by ziconotide. Thus, patients with psychiatric symptoms are not suitable for this type of analgesia. Once the adverse effects of ziconotide are reversible, the clinician can reduce the dosage, if necessary, or discontinue the treat-

ment. The adverse effects will usually disappear in some days to two weeks. Nevertheless, the clinical acceptance of this drug has been reduced due to concern about the limited trialing options, adverse effects, and the cost of ziconotide. Thus, it is still necessary to search for novel N-type VGCCs for pain control without a narrow therapeutic window [94, 100, 104-106].

Moreover, the i.t. route of administration limits the administration of ziconotide to a small group of patients with chronic pain. Thus, the search for small compounds that can block N-type VGCCs and could be used by oral administration for pain control is relevant. Besides, the injection of ziconotide by the intravenous (i.v.) route is not used because this peptide has a limited capacity to cross the blood-brain barrier. Moreover, systemic delivery of ziconotide causes different adverse effects, such as dizziness, sinus bradycardia, and nausea. Also, orthostatic hypotension could be induced by the altered function of N-type VGCCs in the sympathetic nervous system [94, 95, 100].

Thus, there is still the search for a noninvasive administration for ziconotide that will increase its bioavailability to CSF, as the intranasal route causes a direct pathway to CSF. One study showed that ziconotide intranasal administration in rats could deliver this peptide to the CSF. So, this could be a beneficial route of administration to the control of chronic pain [107]. In a different study, the authors used a fusion protein strategy. The MVIIA-TAT (transactivator of transcription domain) fusion peptide was able to cross the biomembranes. Also, the administration of MVIIA-TAT by i.v. and intranasal routes caused an antinociceptive effect. Thus, this could be a strategy to increase the accessibility of this peptide to CNS [108].

Moreover, CVID (named AM336, leconotide, or CNSB004) was isolated *Conus catus* venom, a type of cone snail described in Australia in the Great Barrier Reef. This peptide is formed by 27 amino acids and can block the N-type VGCCs with a better selectivity than MVIIA for N-type compared to P/Q-calcium channels. It is considered the most potent inhibitor of all peptide blockers. AM336 and MVIIA ω-conotoxins i.t. administration dose-dependently reduced the mechanical allodynia in a model of inflammatory pain (i.pl. injection of complete Freund's adjuvant) in rats. The ω-conotoxin MVIIA showed a better antinociceptive potency, while AM336 presented a more significant therapeutic window. Also, both peptides reduced the release of SP from rat spinal cord slices [109].

AM336, when administered intravenously, showed a slight antihyperalgesic effect to noxious heat in a bone cancer model in rats. When this peptide was coinjected with morphine, it enhanced the antinociceptive effect of morphine. The coadministration of the drugs or AM336 did not cause adverse effects. The i.v. administration of a conopeptide was possible because AM336 can penetrate the CNS after systemic route injection [110].

The antinociceptive action of AM336 was also compared to that detected for ziconotide in a diabetic neuropathic pain model using an i.v. injection in rats. AM336 treatment reduced the nociception observed in this model (thermal test using noxious heat). Besides, sub-effective doses of AM336 plus flupirtine (a potassium channel modulator) induced an antihyperalgesic effect. However, ziconotide used in doses that do not induce sedation did not cause an antihyperalgesic effect, even when associated with flupirtine [111]. Nevertheless, leconotide failed in clinical trials because of severe adverse effects induction after i.t. injection in patients, and the peptide was not tested again for i.v. injection [112].

Another conopeptide with antinociceptive action described in the literature is SO-3, which has 25 amino and contains 3 disulfide bridges. This ω-conotoxin was first observed in the venom of the fish-eating snail Conus striatus found in the sea of South China. SO-3 is a selective and reversible N-type VGCC blocker with 72% sequence identity with ω-conotoxin MVIIA [113,114]. The synthetic form of SO-3 showed antinociceptive action in two assays of noxious heat (hot-plate test and light radiation method). The effect observed was similar to that described for MVIIA in mice after intracerebral injection. Besides, SO-3 intracerebral injection in mice also reduced the nociception caused by acetic acid intraperitoneal (i.p.) injection. The intracerebral administration of higher doses of SO-3 than those used in the antinociceptive assays caused adverse effects in mice, described as tremors. This sign was slightly lower when compared to the same doses used of MVIIA. These peptides also caused similar antinociceptive effects after i.t. injection in rats in the tail immersion model in hot water (55 °C) [115].

Moreover, in another study, the antinociceptive effect of synthetic SO-3 was compared to those of morphine and MVIIA. In the acetic acid writhing test in mice, all the i.t. treatments showed antinociceptive action. SO-3 caused an antinociceptive effect similar to MVIIA until 4 hours of administration, while morphine showed a lower median effective dose (ED_{50}) and only caused antinociceptive action 30 minutes after injection. Also, after 30 minutes of i.t. injection, SO-3, MVIIA, and morphine reduced the nociception in both phases of the formalin test in rats. Also, in this test in rats, the antinociceptive effect detected for SO-3 was similar to MVIIA, and both were more effective in reducing phase 2 of the formalin test. Higher doses of MVIIA caused motor alterations. However, the same doses of SO-3 did not induce these dysfunctions. SO-3, when co-injected with morphine, was able to potentiate morphine antinociceptive action in the acetic acid writhing test in mice and the formalin test in rats. The repeated i.t. injection for 5 days of SO-3 did not induce analgesic tolerance, but morphine repeated i.t. administration caused analgesic tolerance. There is also no detection of cross-tolerance to antinociceptive effect between morphine and SO-3. While antinociceptive doses of SO-3 did not cause any locomotor alterations in rats, they promoted locomotor alterations in mice. Thus, SO-3 is an N-type VGCC blocker with antinociceptive action after spinal or intracerebral injection that did not cause analgesic tolerance or cross-tolerance to morphine. Also, the antinociception detection is very potent and long-lasting without significant locomotor alterations induction [116].

The ω-conotoxin FVIA was isolated from the venom of the Korean *Conus fulmen.* It is a high sequence similarity with ω-conotoxins MVIIA (76%), SO3 (88%), CVID (56%), and GVIA (52%). Also, this conopeptide is an N-type VGCCs blocker, and its binding to the channel is more re-

versible compared to ω-conotoxin MVIIA action. The i.t. administration of ω-conotoxin FVIA reduced the nociceptive response caused by the formalin test and the acetic acid-induced writhing response in mice. Also, this peptide showed antinociception after SP, glutamate, TNF-α, and IL-1β i.pl. injection in mice. The injection of ω-conotoxin FVIA reduced the mechanical, cold, and warm allodynia observed in a tail nerve injury in rats. When injected intravenously, both ω-conotoxins FVIA and MVIIA reduced the arterial blood pressure instantly after treatment, with a quicker pressure recovery for ω-conotoxin FVIA injection [117].

Moreover, ω-conotoxins CVIE and CVIF were isolated from the fish-hunting cone snail *Conus catus*. These conopeptides blocked N-type VGCCs potently and selectively and reversibly inhibited the excitatory synaptic transmission. Also, the recovery of the calcium channel from peptide blocking may depend on the β-subunit isoform type. These conopeptides exert greater affinity for N-type VGCCs in the inactivated state. Still, the i.t. injection of ω-conotoxins CVIE and CVI exhibited antiallodynic action in a model of neuropathic pain (partial nerve ligation model) in rats [118].

In another study, MoVIA and MoVIB ω-conotoxins were isolated from a western Pacific worm-hunting cone snail venom, *Conus moncuri*. These conopeptides with three disulfide bonds have 31 and 30 amino acids in length for MoVIA and MoVIB, respectively. These conopeptides interact with N-type VGCC of distinct species (human, fish, and rat) and induce selective blockage of human VGCCs in functional assays. Besides, MoVIB i.t. injection reduced the mechanical allodynia observed in a neuropathic pain model in rats (partial nerve ligation model). When authors assessed the adverse effects after MoVIB i.t. administration using a visual scoring method, they detect alterations in the higher dose tested for up to 4 hours of evaluation. Then, this conopeptide displayed a narrow safety window, but it is higher when compared to the ω-MVIIA already published data [119].

The RsXXIVA peptide contains 40 amino acids, and it is composed of a unique four disulfide bond composition, which is a different pattern for the cysteine family framework observed in ω-conotoxins. Also, a portion of the primary structure of RsXXIVA is very similar to the amino acid residues forming two loops of conopeptide ω-MVIIA. This peptide was found in the venom of *Conus regularis*, which is a vermivorous cone snail of the Sea of Cortez (México). RsXXIVA is a partially reversible N-type VGCC blocker when tested in rat superior cervical ganglion (SCG) neurons. Moreover, the i.p. injection of RsXXIVA increased the latency to the hot plate test at 55 ºC in mice. This peptide also showed an antinociceptive effect in both phases of the formalin test in mice after i.p. administration. However, other studies should explore the use of this peptide for pain control and investigate related adverse effects [120].

Besides, the α-conopeptide named Eu1.6 also blocks N-type VGCCs of DRG neurons of mice with high affinity. This peptide has a weak capacity to inhibit α3β4 and α7 nicotinic acetylcholine receptors (nAChRs) subtypes. Eu1.6 peptide was first isolated from the venom of the *Conus eburneus* (South China sea). The intramuscular (i.m.; near to the injury site) or i.v. injection of Eu1.6 reduced the mechanical allodynia caused by different neuropathic pain models in rats (partial nerve ligation and chronic constriction injury). The antinociceptive effects of peptide were compared to those observed for morphine plus gabapentin (subcutaneous or oral injection) or Vc1.1 (i.m. administration). These compounds also showed antinociceptive activity in neuropathic pain models used. Also, this peptide did not cause locomotor alterations in mice (i.m. administration) or any cardiac and respiratory function disfunction in dogs (i.v. administration). After repeated i.m. administration of Eu1.6 in mice for 8 days it was not detected weight loss or morphine-like dependence behavior after naloxone injection. Thus, the authors propose that this α-conopeptide Eu1.6 could be an interesting novel analgesic for neuropathic pain treatment [121].

Usually, α-conopeptides (such as PeIA, AuIB, Vc1.1, and Rg1A) derived from cone snails modulate the nAChR. α-Conotoxin Vc1.1 (16 amino acid peptide) was first detected from the venom of *Conus victoriae,* and RgIA (13 amino acid peptides) was found in the venom of *Conus regius*. RgIA and Vc1.1 caused antinociceptive activity in different animal pain models, an effect that initially was described to be caused by the antagonism of the neuronal α9α10 nAChR. Furthermore, these α-conopeptides (Vc1.1 and Rg1A) could reduce nociception observed in pain models by blocking N-type VGCCs via an indirect mechanism involving $GABA_B$ receptor activation (G protein-coupled pathway). Also, a study showed that the Vc1.1 and RgIA blockage of N-type VGCCs is not dependent on the expression of α9α10 nAChRs in DRG [122-124]. The α-conotoxin Vc1.1 (ACV1) failed in the clinical trial for pain control because of a lack of efficacy [112]. An analog of α-conotoxin RgIA, named RgIA4, has a high affinity for α9α10 nAChRs without activity on the $GABA_B$ receptor. This peptide, also described as KCP-400, showed antinociceptive effects in pain models and is currently under testing in clinical trials conducted by Kineta Inc. [125, 126].

Spider venoms are also a source for bioactive peptides targeting N-type VGCCs, such as huwentoxin-I (HWTX-I or HWAP-I). This peptide composed of 33 amino acid residues with three disulfide bonds was found in the venom of the *Ornithoctonus huwena* (Chinese bird spider). The i.t. administration of HWTX-I reduced the nociceptive behavior induced by injection of formalin i.pl. in rats, with similar potency of conopeptide ω-MVIIA, but without the detection of adverse effects [127]. This peptide showed antinociceptive and antiedematogenic action in a model of arthritic pain caused by Complete Freund's Adjuvant (CFA) injection into ankle joints in rats. Also, HWTX-I injection reduced the levels of TNF-α and increased the concentration of IL-4 and IL-10 in rat serum. Similarly, there is a reduction of IL-1β, IL-6, and TNF-α mRNA expression in the synovium and chondrocytes [128].

A different peptide isolated from the venom of the Chinese tarantula (*Ornithoctonus huwena*) was Huwentoxin-XVI (HWTX-XVI), containing 39 amino acid residues and three disulfide bonds. This peptide is also a reversible N-type VGCCs blocker, which causes antinociceptive activity in the formalin test in rats. Also, the i.m. injection of HWTX-XVI reduced the mechanical allodynia in a postoperative pain model (plantar incision) in rats. In the hot plate test, the i.m.

administration of this peptide increased the latency to the noxious heat but did not cause motor alteration [129].

The spiders from the Phoneutria genus are found in Central and South America. Different toxins were observed in the venom of the *Phoneutria nigriventer* spider, which is commonly identified as the Brazilian "armed" or "wandering" spider. Besides, it is well described that the accidental armed spider bite causes intense local pain, as the majority symptom, and induces local edema and different systemic reactions [130]. Various purified fractions of *Phoneutria nigriventer* venom were studied, including PhTx3, where six neurotoxic peptides can be found, named PnTx3.1 to 6. These peptides cause many biological activities, such as the inhibition of potassium and calcium channels or the activation of sodium channels [131]. The PnTx3.6, usually called Phα1β, is one of the most studied for the induction of antinociceptive activity.

Previously, Viera *et al.* (2003) showed that Phα1β reduced the glutamate release dependent on calcium from rat brain cortical synaptosomes [132]. This neurotoxin can block high VGCCs, including L-($Ca_V1.2$), N-($Ca_V2.2$), P/Q-($Ca_V2.1$), and R-($Ca_V2.3$) type, with differing potency (N > R > P/Q > L) and in a reversibly way [133]. Thus, the action of this peptide was often compared to ω-conotoxin MVIIA or ziconotide (a synthetic form of the ω-conotoxin peptide) in various studies because Phα1β seems to act as a VGCCs blocker with more selectivity for N-type. The first study that described the antinociceptive effect of Phα1β using rodent models was published in 2008 [134]. This study showed that Phα1β intrathecally administered caused long-lasting antinociception in the hot-plate test (an acute model of thermal pain) in mice. This treatment also produced an antinociceptive effect in the formalin test (both phases). It reduced the increased levels of glutamate in CSF caused by formalin injection in rats. Also, the recombinant Phα1β caused an antinociceptive effect in the formalin test. Phα1β reduced the glutamate release stimulated by capsaicin on rat spinal cord synaptosomes. Phα1β also reduced the intracellular calcium increase mediated by capsaicin observed on rat spinal cord synaptosomes. Also, the Phα1β showed an anti-allodynic effect in a neuropathic pain model caused by partial nerve sciatic lesion in mice. Moreover, Phα1β showed similar antinociceptive efficacy of ω-conotoxin MVIIA. However, Phα1β has a higher therapeutic index without causing motor alteration in animals in the doses tested in these nociceptive tests [135].

Moreover, the antinociceptive effect of Phα1β and ω-conotoxin MVIIA was also detected in inflammatory (Complete Freund's adjuvant - CFA - i.pl. injection) and neuropathic (chronic constrictive injury of the sciatic nerve) pain models in rats. In this study, the authors also showed that Phα1β and ω-conotoxin MVIIA reduced the capsaicin-induced calcium influx in dorsal root ganglion (DRG) culture extracted from CFA or CCI models in rats [136].

In a different study, authors evaluate the action of Phα1β on the transient receptor potential vanilloid 1 (TRPV1), because as described above, Phα1β was able to reduce capsaicin-evoked glutamate release and calcium influx in spinal cord synaptosomes of rats. The TRPV1 is activated by noxious heat (≥43ºC), capsaicin (the pungent ingredient in hot chili peppers), and other painful stimuli. This receptor is expressed in sensory neurons and has been investigated to develop novel analgesics [4, 137]. Intrathecal or i.pl., Phα1β or SB366791 (a TRPV1 antagonist) reduced the nociceptive response induced by capsaicin in rats. However, i.t. ω-conotoxin MVIIA, but not i.pl., reduced the capsaicin-induced nociception and mechanical allodynia. Phα1β, SB366791, and ω-conotoxin MVIIA decreased the calcium influx mediated by capsaicin in cultured DRG neurons. Nevertheless, Phα1β did not affect the TRPV1 currents verified in patch-clamp recordings in the rTRPV1 transfected HEK293 cell. Thus, the authors suggested that the peripheral antinociceptive activity of Phα1β is mediated by different voltage-gated calcium channels (T- and L-type) [138].

Besides, Phα1β plus SB366791 induced a synergistic antinociceptive action in the capsaicin-induced nociception test in mice. Also, these peptides did not cause a body temperature increase in mice [139], which is a common adverse effect observed for TRPV1 antagonist administration [4,137]. Also, Phα1β and ω-conotoxin MVIIA i.t. reduced the nociception caused by an intracolonic administration of capsaicin and intraperitoneal injection of acetic acid, which were used as models of visceral nociception. Also, these treatments reduced the content of CSF glutamate that was increased by these visceral models in mice [140].

Phα1β and its recombinant form (CTK 01512-2) may act as TRPA1 antagonists but did not interact with TRPV1 or TRPV4 channels. The TRP ankyrin 1 (TRPA1) is a cation ion channel usually co-expressed with TRPV1 in sensory neurons. This receptor is gated by natural irritant compounds, such as allyl isothiocyanate (AITC, found in mustard oil and wasabi) and cinnamaldehyde (present in cinnamon) [141]. It was also showed that Phα1β and CTK 01512-2 reduced the AITC-induced spontaneous nociception, mechanical and cold allodynia in mice. Also, Phα1β and CTK 01512-2 induced anti-allodynic action in a neuropathic pain model caused by the chemotherapy bortezomib in mice. However, ω-conotoxin MVIIA treatment did not reduce capsaicin and hypotonic saline injection-induced nociception. Thus, the TRPA1 blockage seems to be a relevant mechanism involved in Phα1β and CTK 01512-2 antinociceptive activity [142].

Moreover, the recombinant version of Phα1β (CTK 01512-2) also produced antinociceptive action in diverse models of pain by i.t. administration, including the CCI model of neuropathic pain, capsaicin i.pl. test, formalin test, a cancer pain model caused by melanoma cells inoculation in rodents. The antinociceptive effect observed for CTK 01512-2 i.t. injection was similar to that detected by Phα1β i.t. administration, also without the induction of adverse effects [143]. CTK 01512-2 i.t. induced antinociceptive effect in a rat model of neuropathic pain caused by nerve deafferentation, without causing motor alteration or genotoxicity in rats. Also, this peptide decreases the CSF levels of glutamate and the lipid peroxidation in the spinal cord induced by this pain model [144]. CTK 01512-2 i.v. caused antinociception in models of neuropathic pain caused by CCI of the sciatic nerve or paclitaxel injection in rats. Therefore, CTK 01512-2 i.v. did not induce motor alteration or alter cardiac parameters and biochemical markers in mice [145].

The pre- or post-treatment with Phα1β i.t. caused an anti-allodynic effect in a surgical pain model in mice. The antinociceptive effect observed for Phα1β was similar to that detected for ω-conotoxin MVIIA and morphine but with a long-lasting effect. Also, Phα1β, ω-conotoxin MVIIA, and morphine i.t. neither changed the neurological or locomotor performance in mice nor induced the release of cytokines in human CD14 monocytes. The injection of Phα1β or morphine did not cause cardiovascular function alteration, but ω-conotoxin MVIIA administration increased the heart rate of rats [146].

Phα1β i.t. potentiates the morphine antinociceptive effect in a postoperative pain model in mice. Phα1β i.t. also decreased the induction of opioid-limiting adverse effects, including hyperalgesia, withdrawal syndrome, and tolerance in mice treated with repeated doses of morphine. On the other hand, Phα1β i.t. does not affect the induction of constipation caused by repeated morphine administration using this model of postoperative pain [147]. Phα1β i.t. slightly improved the antinociception action caused by morphine systemic administration in a thermal test in naïve mice. Furthermore, the repeated treatment with morphine caused mechanical and thermal hyperalgesia, tolerance, withdrawal syndrome, and constipation. The i.t. injection of Phα1β or CTK 01512-2 reduced these adverse effects but had a partial impact on constipation induced by morphine. Thus, these peptides could be used as an adjuvant drug combined with opioids to control pain [148].

In another study, ω-conotoxin MVIIA or Phα1β i.t. reduced the mechanical allodynia caused by paclitaxel acute or repeated injection in rats. In this neuropathic pain model, the chemotherapy paclitaxel is commonly used to treat solid tumors induced by mechanical allodynia. Moreover, ω-conotoxin MVIIA and Phα1β i.t., in the acute phase after paclitaxel administration, were able to block the aggravation of mechanical allodynia observed in the chronic phase after paclitaxel repeated administration. ω-conotoxin MVIIA induced different adverse effects, including serpentine tail movements, dynamic allodynia, and body shaking in all doses tested. On the other hand, Phα1β only induced dynamic allodynia in the highest dose used [149].

Similarly, the i.t. injection of Phα1β and ω-conotoxin MVIIA caused an antinociceptive effect in a cancer pain model caused by the inoculation of melanoma (B16-F10 cells) i.pl. in mice. Phα1β only induced minor adverse effects, but ω-conotoxin MVIIA administration caused dose-related adverse effects at tested doses (serpentine tail, dynamic allodynia, and sedation). The antinociceptive effect of Phα1β was also observed in mice tolerant to morphine in this cancer pain model, and it partially reestablishes morphine-induced nociception in this model. This is an important feature of Phα1β treatment since cancer-induced pain is often treated using opioids, but these compounds caused diverse dose-limiting adverse effects, including analgesic tolerance [150].

Besides, Phα1β also reduced the mechanical allodynia and thermal hyperalgesia in a reserpine-induced fibromyalgia model. The Phα1β effectively reverses the increase of the immobility time caused by reserpine in the forced swim test (an indicative of depressive-like behavior). However, Phα1β i.t. did not alter the reduction of brain dopamine and serotonin content after reserpine administration [151].

All the studies performed before described the antinociceptive action of Phα1β after acute i.t. injection. Using a model of neuropathic pain (CCI), it was tested the antinociceptive effect of Phα1β after continuous i.t. injection in rats. It was observed that Phα1β after single or continuous i.t. administration caused an anti-allodynic effect in this model. Also, the antinociceptive effect caused by Phα1β did not induce behavioral adverse effects or histopathological changes in the spinal cord, brainstem, and encephalon samples [152].

The repeated i.t. administration of CTK 01512-2 caused diverse valuable effects in a model of experimental autoimmune encephalomyelitis (EAE) in mice. The effects of CTK 01512-2 in this model of multiple sclerosis were compared to ziconotide and fingolimod (a commonly used treatment for multiple sclerosis). The use of these compounds reduced the nociception, diverse EAE-induced effects, memory loss, and markers of neuroinflammation caused by this model [153].

In a different study, the CFA i.pl. injection in rats caused nociception, glial reactivity, and astrocyte proliferation in the spinal cord. Also, the i.t. injection of Phα1β and ω-conotoxin MVIIA produced an antinociceptive effect accompanied by the reduction in glial pathological features caused by peripheral inflammation. The Phα1β also reduced the astrocyte proliferation induced by CFA administration. Thus, Phα1β exerted a more effective effect to reduce glial reactivity and proliferation compared to ω-conotoxin MVIIA administration [154].

The Phα1β and ω-conotoxin MVIIA i.t. also induced an antinociceptive effect in a model diabetic neuropathic. Phα1β i.t. also reduced the levels of IL-6 in the spinal cord of diabetic rats. Also, the authors suggested that this peptide may induce the antagonism of the receptor CXCR4, as Phα1β was able to reduce chemokine stromal cell-derived factor 1 (SDF-1) induced hypersensitive after i.t. injection in rats. Still, ω-conotoxin MVIIA administration did not cause an antinociceptive effect [155].

Besides, using a model of complex regional pain syndrome I caused by chronic post-ischemia pain in mice, it was detected that i.t. injection of CTK 01512-2 exerted an antinociceptive effect. The administration of CTK 01512-2 reduced the mechanical and cold allodynia observed after 1 and 17 days of chronic post-ischemia pain induction [156].

CTK 01512-2 and ω-conotoxin MVIIA i.t. also reduce the orofacial pain caused by the intraarticular injection of CFA in the temporomandibular joint infraorbital nerve constriction model of trigeminal neuralgia. CTK 01512-2 and ω-conotoxin MVIIA reduced the CSF content of glutamate in the trigeminal neuropathic pain model. However, only CTK 01512-2 administration reduced the nociception observed after the formalin injection in the upper lip test of rats [157].

Recently, Phα1β, CTK 01512-2, and ω-conotoxin MVIIA induced antinociceptive and anti-inflammatory effects in a model of acute pancreatitis caused by cerulein injection in rats. The Phα1β and CTK 01512-2 treatments also reduced the amylase and lipase secretion observed in this model. Also, the administration of these compounds did not induce any locomotor alteration in the animals [158].

Finally, Phα1β and its recombinant form CTK 01512-2 effectively reduce the nociception caused by an inflammatory or neuropathic pain model. Also, when compared to ω-conotoxin MVIIA, this spider toxin seems to have a better therapeutic index. Regarding the action mechanism observed for the antinociceptive action elicited by Phα1β and CTK 01512-2, the block of N-type VGCCs and the antagonism of the TRPA1 channel had been studied. Then, this peptide has been described as a potential analgesic to control pain in different pathologies.

4. T-TYPE VGCCS BLOCKERS FOUND IN ANIMAL VENOMS

T-type ($Ca_V3.1$, 3.2, 3.3 isoforms) VGCCs are ideally suited for supporting low-threshold exocytosis because of their biophysical characteristics (low voltage of activation and inactivation), which give rise to a small window current near resting neuronal membrane potentials [10, 159, 160]. In neurons, the T-type calcium channels are concentrated on the cell body and dendrites. They are important in regulating neuronal excitability, although rise to T-type calcium currents in non-excitable cells [66, 161]. They are implicated in the spontaneous synaptic release in the dorsal horn of the spinal cord [162] and transglial chemical communication between dorsal root ganglion neurons [163]. Small voltage changes allow calcium entry via these channels, permitting the synaptic vesicle release machinery and also support secretion from neuroendocrine cells [24, 164].

All three T-type calcium channel isoforms are present in peripheral and central neurons of the pain pathway and act as regulators of nociceptive information processing [66, 161]. T-type channels were first described functionally in primary sensory neurons. T-type calcium currents were detected in small and medium-sized DRG neurons, being the cells with the highest expressers followed by small putative nociceptors [66, 164, 165]. In addition, kinetics differences suggested two distinct T-type channels in these neurons. The relatively fast calcium-current kinetics and high sensitivity to nickel implicate isoform $Ca_V3.2$ as the predominant subtype in these neurons besides being the major subunit identified by in situ hybridization studies [166, 167]. Since $Ca_V3.2$ calcium channels are expressed in various subpopulations of primary afferent neurons, it is probable that these channels are involved in pain processing, as demonstrated in previous studies and cited below.

Data of literature demonstrated that T-type VGCCs activity is increased in afferent pain fibers in several chronic pain conditions such as traumatic and diabetic neuropathy or chemotherapy-induced neuropathy [69, 168-172]. Recently, it was demonstrated that monosodium iodoacetate-induced knee osteoarthritis increases the T-type ($Ca_V3.2$) calcium channel activity, contributing to neuropathic-like pain [173]. According to evidence, antisense oligonucleotides or siRNA i.t. administration to $Ca_V3.2$ T-type VGCC isoform, leads to antinociceptive, antiallodynic, and antihyperalgesic effects in models of acute and neuropathic pain in experimental animals. These results implicate $Ca_V3.2$ calcium channels as important regulators of nociceptive processing in peripheral sensory neurons [66, 174-176].

Alpha-cobratoxin is a long-chain postsynaptic α-neurotoxin of 71 amino acid residues isolated from Thailand cobra *Naja naja kaouthia* venom [177, 178]. It was demonstrated that alpha-cobratoxin inhibited T-type calcium currents in DRG neurons through muscarinic M4 receptor and Go-protein βγ subunits-dependent protein kinase A pathway [179]. Alpha-cobratoxin also exhibited an analgesic action in mice in the hot-plate and acetic acid writhing tests in a manner independent of the opioid system [180]. Although not tested in this study, it can be suggested that this effect occurred by blocking T-type VGCCs.

Recently, it was also demonstrated that a novel blocker of T-type calcium channels, the neuroactive steroid (3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile (3β-OH), reduced the T-channel-dependent excitability of peripheral sensory neurons. 3β-OH, intrathecally administered, reduced the mechanical hyperalgesia while repeated i.pl. application alleviated both thermal and mechanical hyperalgesia in a postoperative pain model in rats [181].

5. L-, R- AND P/Q-TYPE VGCCS BLOCKERS DERIVED FROM ANIMAL VENOMS

In addition to N- and T-type voltage-gated calcium channels, the L-, R- and P/Q-type calcium channels are also involved in nociceptive processing. L-type VGCCs, also known as Ca_V1, are divided into $Ca_V1.1$, 1.2, 1.3, and 1.4 subtypes, as described above. They are activated by medium to high voltages and are sensitive to 1,4 dihydropyridine agonists and antagonists [182]. It is known that L-type VGCCs are involved in signaling to the nucleus and excitation-transcription coupling (a process that converts a rise in intracellular Ca^{2+}, resulting from depolarization, into a change in transcription in the nucleus in neurons and muscle cells), which results in the transcription of immediate early genes, such as *c-fos* [183-187]. L-type VGCCs have been shown to be critically responsible for mediating wind-up, a form of short-term plasticity in nociceptive neurons, which results from repetitive activity in pain transmitting neurons. Possibly, blockade of L-type VGCCs might attenuate this process of wind-up and central sensitization and facilitate the analgesic effect of opioids [79, 188].

Among the Ca_V1 channels, $Ca_V1.2$ $Ca_V1.3$ subtypes are expressed in the dorsal and ventral horn of the spinal cord, where Ca_V 1.2 channels are localized mostly in the soma and proximal dendritic shafts, and Ca_V 1.3 channels are more distally located in the somatodendritic compartment [189]. The $Ca_V1.2$ subtype is predominantly expressed by neurons and is believed to regulate synaptic plasticity and gene expression [190, 191]. Moreover, there is evidence of L-type VGCCs in the afferent pain pathway once $Ca_V1.2$ channels are upregulated in spinal cord neurons in chronic pain conditions. The Ca_V 1.2 channels also support calcium influx crucial for the excitation-transcription coupling underlying nerve injury-induced dorsal horn hyperexcitability [189]. In this sense, it was showed that L-type VGCCs in the spinal dorsal horn play an essential role in pain processing. Moreover, the maintenance of chronic neuropathic pain depends specifically on $Ca_V1.2$ channels once $Ca_V1.2$ knockdown mice reversed the neuropathy-associated mechanical hypersensitivity and the hyperexcitability and increased responsiveness of dorsal horn neurons [192].

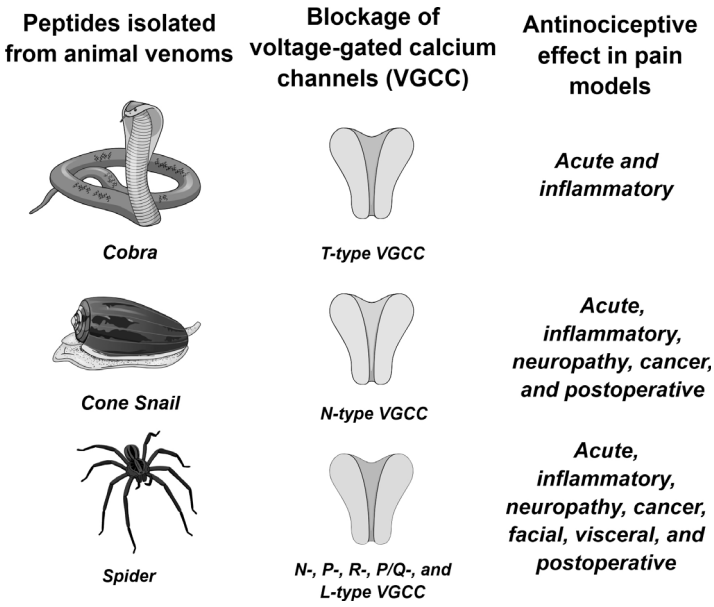

Fig. (2). Peptides isolated from animal venom can modulate or block voltage-gated calcium channels (VGCC) causing antinociceptive effect in diverse pain models.

Ca_V 1.3 channels sustain the expression of plateau potentials, an input/output amplification phenomenon that contributes to short-term sensitization to pain such as prolonged after-discharges, dynamic receptive fields, and wind-up [189]. However, its role in persistent pain is controversial once it was demonstrated mice lacking $Ca_V1.3$ subunit display a normal pain phenotype presenting unmodified mechanical and thermal nociceptive sensitivity [193, 194].

Relevantly, our research group demonstrated that the PhTx3.5 i.t. peptide, purified from Phoneutria nigriventer spider venom, presented antinociceptive effects in postoperative (plantar incision) and neuropathic (partial sciatic nerve ligation) pain models. Further, PhTx3.5 i.t. peptide reduced the cancer-related pain (inoculation with melanoma cells) in animals that were either sensitive or tolerant to morphine. These antinociceptive effects caused by PhTx3.5 occurred without altering the normal mechanical or thermal sensitivity of the animals or causing immunogenicity [195]. Our study is in accordance with others which show the involvement of the L-type VGCCs in different models of pain, such as inflammatory [96, 196, 197], neuropathic [192, 198], and cancer [199, 200] pain models, in addition to being able to block the development of tolerance caused by opioids in experimental animals [77, 201-204].

The R-type ($Ca_V2.3$) VGCCs are similar to T-type voltage-sensitive calcium channels at the functional level, including a hyperpolarized activation and inactivation range and rapid inactivation kinetics [50]. R-type calcium channels are distributed throughout the central and peripheral nervous system, including nociceptive spinal cord pathways and DRG neurons [40, 87, 205, 206]. Thus, R-type calcium channels are implicated in pain transmission. Further, previous reports showed that R-type calcium channels contribute to neurotransmitter release at specific synapses [207, 208]. Mice lacking R-type channels present a complex nociception phenotype, regulating both nociceptive and antinociceptive behaviour by spinal and supraspinal mechanisms since its demonstrated hyposensitivity to inflammatory pain through alterations in both ascending and descending pathways [25, 87, 209]. R-type channels are also up-regulated during spinal nerve ligation [210].

Matthews *et al.* (2007) demonstrated that i.t. SNX-482, a peptide isolated from the venom of the Tarantula *Hysterocrates gigas* and R-type channel selective blocker, causes antinociception in neuropathic pain models [25, 45]. Importantly, it was demonstrated that the PhTx3.4 peptide, also purified from *Phoneutria nigriventer* spider venom, blocks R-type currents. Moreover, PhTx3.4 i.t. reversed the nociceptive behavior in inflammatory persistent (formalin test) and postoperative pain models in mice [211, 212].

P/Q-type VGCCs ($Ca_V2.1$) were found to be expressed in Purkinje cells and cerebellar granule neurons [213, 214]. They are also expressed in presynaptic nerve terminals and play an essential role in neurotransmitter release, contributing to nociceptive signaling in the afferent pain pathway. The P/Q-type channel is preferably expressed in neurons of the CNS. Thus most CNS synapses depend on P/Q-type and N-type VGCCs for fast synaptic transmission [10, 42]. Along these lines, it was demonstrated the involvement of P/Q-type VGCCs in familiar hemiplegic migraine that occurs due to different mutations in the CACNA1A gene that codifies the P/Q channel and lead to altered calcium influx [215, 216]. However, once P/Q channel blockade in the CNS reduced the neurotransmission and thus decreased the cortical excitability, P/Q-type channel blockers could act as a therapeutic strategy for the prophylactic migraine treatment [217]. Furthermore, the topical application of the P-type blocker ω-Agatoxin IVA from funnel-web spider venom appears to inhibit inflammatory pain processing in neurons innervating the knee joint [218].

Moreover, P-type VGCCs are involved in the generation and maintenance of inflammation-evoked hyperexcitability of spinal cord neurons. However, once ω-Agatoxin IVA pre-

sented limited effectiveness to reduces this hyperexcitability, it is unlikely that the blockade of P-type VGCCs alone will be sufficient to reduce the inflammation-evoked hyperalgesia and pain [219]. P/Q-type channels are also involved in peripheral nerve repair, and they are fundamental for the proper regeneration of injured nerve [220].

Further, the mixed R-type and P/Q-type channel blocker PhTx3.3 (also isolated from the venom of an armed Brazilian spider) produces antinociception in neuropathic pain and inflammatory models. PhTx3.3 was also able to inhibit the electrical-evoked neuronal response of spinal nerve ligation rats, inhibiting nociceptive C-fibre and Aδ-fibre responses [221]. Additionally to these data, mice lacking P/Q-type calcium channels exhibit hyposensitivity to inflammatory and neuropathic pain. Also, mutant mice with function loss in P/Q-type calcium channels display reduced inflammatory pain [222-224].

CONCLUSION

Multiple VGCCs are involved in primary afferent pain signaling implicating these channels as a potential target for new analgesics. Moreover, in this review, we highlight peptides isolated from animal venom that modulate or block VGCCs channels (Fig. **2**). The action of these peptides on VGCCs ion channels promote significant antinociceptive effects in different pain models when tested in pain models, including clinically relevant pathological pain models such as neuropathic pain. Thus, toxins isolated from animal venom or their synthetic forms, if any, seem to be an interesting prototype for the development of new analgesics to treat various types of pain, including those that are refractory to medications available at the clinic.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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