Behavior of ion channels controlled by electric potential difference and of Toll-type receptors in neuropathic pain pathophysiology

O comportamento dos canais iônicos controlados por diferença de potencial elétrico e dos receptores do tipo Toll na fisiopatologia da dor neuropática

André Prato Schmidt*, Sérgio Renato Guimarães Schmidt

ABSTRACT

BACKGROUND AND OBJECTIVES: Neuropathic pain is a severe and refractory medical condition, for which only partially effective treatments are currently available. Recent experimental data on the role of voltage-gated ion channels, particularly sodium and potassium channels, have been described. In this brief review, we aimed at addressing the role of sodium and potassium channels in the pathophysiology of neuropathic pain and recent evidences about their role as a new therapeutic target in painful conditions.

CONTENTS: Pharmacological and biophysical studies have shown that voltage-gated sodium channels, particularly Na\textsubscript{v}1.7, Na\textsubscript{v}1.8, and Na\textsubscript{v}1.9 isoforms are important in the pathophysiology of neuropathic pain. Similarly, the involvement of voltage-gated potassium channels, especially K\textsubscript{v}1.1 and K\textsubscript{v}7 isoforms, has been clearly shown in the establishment of chronic painful conditions. Recent evidences that ion sodium and potassium channels dysfunction is involved in the development of chronic painful conditions corroborate the possibility of pharmacologically modulate them as a new therapeutic strategies.

CONCLUSION: Recent evidences suggest that selective sodium channel blockers and potassium channels activating of modulating drugs are important and promising targets in the search for new options to treat neuropathic pain.

Keywords: Chronic pain, Ion channels, Neuropathic pain, Potassium channels, Sodium channels.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor neuropática constitui-se em uma condição clínica grave e refratária, para a qual apenas tratamentos com eficácia parcial estão disponíveis. Estudos experimentais recentes sobre o papel relevante de canais iônicos controlados por diferença de potencial elétrico ou voltagem, especialmente canais de sódio e potássio, tem sido descritos. Nesta breve revisão, objetivou-se abordar o papel dos canais de sódio e potássio na fisiopatologia da dor neuropática e as recentes evidências a respeito do seu papel como novo alvo terapêutico em quadros dolorosos.

CONTEÚDO: Estudos farmacológico e biofísico têm demonstrado que os canais de sódio dependentes de voltagem, particularmente as isoformas Na\textsubscript{v}1.3, Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 e Na\textsubscript{v}1.9 são relevantes na fisiopatologia da dor neuropática. De forma similar, o envolvimento dos canais de potássio dependentes de voltagem, especialmente as isoformas K\textsubscript{v}1.1 e K\textsubscript{v}7, tem sido claramente demonstrado no estabelecimento de quadros dolorosos crônicos. As evidências recentes de que a disfunção de canais iônicos de sódio e potássio está envolvida no desenvolvimento de quadros dolorosos crônicos evidenciam a capacidade de modulá-los farmacologicamente em novas estratégias terapêuticas.

CONCLUSÃO: Evidências recentes sugerem que bloqueadores seletivos de canais de sódio e fármacos ativadores ou moduladores dos canais de potássio representam um alvo relevante e promissor na busca por novas opções no tratamento da dor neuropática.

Descritores: Canais iônicos, Canais de potássio, Canais de sódio, Dor crônica, Dor neuropática.

INTRODUCTION

Neuropathic pain (NP) is a multifactorial event involving different central and peripheral nervous system (CNS, PNS) components. However, in spite of its perception usually being complex, NP is often related to peripheral origin dependent on the electric activity present in sensory neurons responsible for tissue and viscera innervation\textsuperscript{1}. Among such structures, the role of electric potential-gated or voltage-gated ion channels is to be highlighted. In PNS, these sensory neurons are essentially located in dorsal roots ganglia where distal axons in peripheral nerves responsible for the innervation of distant targets such as skin emerge. In peripheral nerve trauma, these neuronal structures have the ability to develop adaptive neuroplastic phenomena, promoting axonal remyelination and regeneration.

However, this physiologic response to trauma might be associated to pathologic phenomena, inducing nociceptive sensory neurons sensitization and, subsequently, chronic stimulation of peripheral painful transmission pathways generating a painful chronicity process\textsuperscript{1-3}. Physiologic nociceptive response is essentially maintained by a frequency of action potentials mediated by ion channels present in afferent fibers. So, one may infer that in chronic pain there is increase and maintenance of transmission of action potential coming from the periphery and responsible for central interpretation of noxious stimuli. In this process, several components are involved, including increased neural excitability, decreased threshold for action potential onset, action potentials amplification, spontaneous discharges, among other alterations, all involving electric potential difference-gated ion channels\textsuperscript{4-6}.

This study aimed at briefly addressing aspects involved in pathophysiology and pharmacology of major electric potential difference-gated or voltage-gated ion channels present in axonal membrane of dorsal root ganglion neurons represented by voltage-gated sodium channels (Na\textsubscript{v}) and voltage-gated potassium channels (K\textsubscript{v}).

ELECTRIC POTENTIAL DIFFERENCE-GATED SODIUM CHANNELS (Na\textsubscript{v})

Electric activity of peripheral sensory neurons is closely related to their ability to generate and transport action potential promoted by voltage-gated ion channels (or ionophores) (Na\textsubscript{v}) located along axonal membrane. This essential Na\textsubscript{v} role in neural electrogensis has brought to light a new important target for new therapeutic approaches aiming at attenuating neural firing resulting in painful response\textsuperscript{7-11}. Na\textsubscript{v} remain inactive and closed at rest, but develop conformational and structural changes in response to initial membrane depolarization, causing a cyclic phenomenon of channels opening and closing during physiologic sensory transmission process. Transient Na\textsubscript{v} opening allows the flow of sodium ions toward the concentration gradient, promoting a neuronal depolarization transmembrane current leading closest axonal membrane to

the threshold to generate action potential. Most Na+ are rapidly inactivated opening, then suffering conformational changes for a new activation cycle. Na+ are heteromultimer made up of a larger subunit called alpha (α) and of smaller auxiliary subunits called beta (β). Subunit α is needed to form essential functional structure of Na+ and subunits β modulate channel biophysical properties, in addition to regulating channels transport and fixation next to the axonal membrane. Each domain has 6 potential segments in α-helix (S1 to S6) actively participating in Na+ activation and closing process. Nine mammal genes have been described with significant consequence on central nervous system and cardiovas-

cular system, respectively12,13. Dorsal root ganglion neurons express many different subtypes of voltage-gated sodium channels, especially Na+1.1, Na+1.2, Na+1.3 and Na+1.7 are similar to each other. These channels are broadly distributed and expressed in neurons and are sensitive to tetrodotoxin block (TTX)12,13. Na+1.5, Na+1.8 and Na+1.9 are also similar to each other and are highly expressed in heart and dorsal root ganglion neurons, being however resistant to low TTX concentrations. Na+1.4 and Na+1.6 are significantly different from the others and are TTX-sensitive, being essentially expressed in skeletal muscle and nervous system, respectively12,13.

Dorsal root ganglion neurons express many different subtypes of voltage-gated sodium channels, especially Na+1.1, Na+1.6, Na+1.7, Na+1.8 and Na+1.9, in addition to Na+1.5 isoform in low levels. Na+1.6 isoform is expressed in different neurons, while Na+1.1 is expressed in sensory neurons. Na+1.8 is essentially present in nociceptive sensory neurons. Most neurons express multiple Na+ isoforms, being that Na+1.7, Na+1.8 and Na+1.9 are preferably expressed in peripheral neurons such as dorsal root ganglion neurons, being targets for the development of pharmacological modulation without significant consequence on central nervous system and cardiovascular system, where such structures are less prevalent12. Sodium inflow in peripheral axons is essential for the generation and propagation of action potentials which transmit painful information to central nervous system. Total blockade of Na+ present in peripheral sensory fibers is possible with high concentrations of local anesthetics. However, such concentrations cannot be systemically reached due to high toxicity, especially related to the broad distribution of sodium channels in heart and central nervous system14,15.

Clearly, nerve submitted to traumatic injury are more susceptible to the anesthetic effect of Na+ blockers, which is related to their building up in injured nervous region16. In addition, non-selective sodium channel blockers, such as lidocaine, more rapidly and intensively bind to active receptors, being more effective in more active fibers. Some isoforms with altered expression in pathological states are more susceptible to lidocaine effects. Intriguingly, lidocaine and other local anesthetics used to treat NP may have a significantly longer effect than direct pharmacological effects based on their short half-lives, effect which seems to be related to long-lasting blockade of peripheral Na+, but which is still poorly understood17. As a consequence of peripheral neural injury, there is disturbance in the expression of genes responsible from sodium channels transcription, causing decrease in slow sodium currents (inactivation) and increase in inactivated channels depolarization and recovery currents, converging to significant increase in excitability of sensory neurons responsible for painful transmission18. During this process, there is increased Na+1.3 sodium channels expression, characteristic channel of embryonic neurons, but with relatively low expression in dorsal root ganglion neurons of adults19. Other studies have also shown that voltage-gated ion channels 1.6, responsible for salutatory conduction in thick myelinated fibers are also increased in pathological states in situations of nervous injury and regeneration17. Additionally, multiple inflammatory mediators have been described as potential modulators of the expression and activity of some Na+ isoforms, especially Na+1.818. markedly, a selective Na+1.8 blocker (A-803467) was antinociceptive in animal models with inflammatory pain19 and NP20. Animal studies have shown that neuromas formed after nervous injury may induce ectopic generation of spontaneous potential impulses and firings, closely related to increased Na+1.3 expression21. Studies with human neuromas have also shown significant increase in the expression of Na+1.7 and Na+1.8 isoforms and of axonal biochemical mediators (p38 and protein kinase activated by mitogen ERK1/2). Previous studies have shown significant genetic relation of hereditary painful syndromes related to Na+ disorders in humans and animal models22,24. SCN9A gene mutations, responsible for Na+1.7 channel transcription, were identified in two severe painful syndromes (hereditary erythromelalgia and paroxysmal extreme painful disorder)23,25. Mutations with loss of Na+1.7 gene function were also identified in patients with congenital insensitivity to pain26.

Additionally, there is significant and abundant information in the literature about the role of voltage-gated Na+ ionophores in painful transmission, in addition to the specific role of each subunit in the generation and maintenance of chronic pain. To date, unspecified Na+ blockers, such as lidocaine and carbamazepine have been significantly effective in different clinical protocols to treat chronic pain, especially NP. However, their partial efficacy, adverse effects profile and multifactorial aspects of pain mechanisms show the need for identification and development of safer, more selective and effective pharmacological therapies to address Na+ located in peripheral neuronal membrane. In this context, the identification and the study of different Na+ isoforms preferably or exclusively expressed in primary sensory neurons open a possibility for new therapies focused on decreasing neural hyperexcitability without significant cardiovascular effects or central nervous system toxicity. Considering multiple recent studies focused on Na+, the clinical use of effective drugs to treat painful presentations and which are more selective for some Na+ isoforms seems to be promising and may be soon available.

Electric potential difference-gated potassium channels Voltage-gated potassium channels (K+) have received significantly less attention as compared to other ion channels (sodium and calcium) in terms of investigating their physiologic and pathologic role in pain transmission mechanisms. In spite of their minor representation in scientific literature, recent studies have shown that K+ are important in pain processing and in pathologic processes such as chronic pain of neuropathic origin26,31. K+ super-family has more than 80 different genes related to different subunits forming the ion channel, followed by the family of the gene responsible for their transcription and of their isoforms26, but different names have been described and used. Among different K+ subtypes, channels regulating neural membrane potential, as well as the shape and adaptation of neural action potential are the most closely related to axonal excitability modulation in painful transmission26. K+ from 1 to 12 are tetramers of α subunits associated to up to four auxiliary β subunits, able to change their binding properties24. Electrophysiological studies have shown that many different K+ types are present in neurons of mammals, being briefly divided in fast activation K+ (mediated by the family of K+1 channels) and slow activation K+ (mediated by the family of K+7 channels), being the latter the most widely studied K+ in painful transmission26. Several non-selective blockers have been used in experimental pharmacologic models, such as tetramethylammonium ions (TEA) and 4-aminopyridine (4-AP), being that TEA is able to block K+1 and K+7, while 4-AP is more selective for K+1 family ion channels, especially those related to fast current type (K+1a). Interestingly, many natural toxins are K+ blockers, such as some spider poisons (margatoxin, agitoxin) or snake poisons (α-dendrotoxin) being that the latter helps discriminating different isoforms of the K+1 family, being more selective for K+1 and K+2 than for K+4-7. In contrast to K+1 channels, K+7 channels may be more specifically modulated by drugs able to open such potassium ion channels (retigabine) or to block them (linopirdine)26,32. Some classes of dorsal root ganglion neurons express combinations of different voltage-gated K+ subunits. Neurons with larger axonal diameter have higher levels of K+1.1 and K+1.2 channels (modulators of action potential propagation) and of K+7.2 (related to slow potassium currents which regulate neuronal excitability threshold), while smaller diameter fibers predominantly express K+1.4 and K+7.3 isoforms, also related to fast and slow potassium currents, respectively26,32. Studies have shown that K+ block in neuromas after nervous injury is associated to spontaneous discharges amplification, emphasizing the stabilizing role of K+ in neuronal membrane, compensating increased excitability related to Ca2+. Additionally, there is significant decrease in the number
of K<sub>i</sub> in dorsal root ganglion neurons, essentially attributed to decreased K<sub>1</sub> channel expression.<sup>26</sup> Decrease of voltage-gated potassium channels in neurons submitted to traumatic stabilization during pain transmission process, may one infer that the investigation of drugs potentially able to promote the activation of such channels is a relevant target in the search for new pharmacological options, especially to treat NP. Recently, experimental results have shown that drugs responsible for opening or activating K<sub>i</sub> may represent a new class of analgesics to treat NP and other pathologies.<sup>27-30</sup> In spite of the modest recent advance in the development of drugs able to positively modulate K<sub>i</sub> channels, modulators of K<sub>7</sub> channels activity are good alternatives in this context.<sup>31-35</sup> K<sub>i</sub> activator retigabine, developed as anticonvulsant, has shown significant analgesic properties<sup>36</sup>, effect potentially related to the opening of K<sub>7</sub> potassium channels, since it had its effect reverted by selective K<sub>7</sub> channel antagonists<sup>37</sup>.

**CONCLUSION**

This brief review has shown that recent evidences are emerging about electric potential difference-gated Ca<sup>2+</sup> and K<sup>+</sup> as essential for physiologic pain transmission mechanisms and NP mechanisms, being considered relevant new targets for the development of therapeutic alternatives. Selective Ca<sup>2+</sup> block and K<sup>+</sup> (K<sub>7</sub>) activation and modulation are able to produce effective analgesia in experimental models. Clearly, these results although preliminary suggest that drugs able to modulate these Ca<sup>2+</sup> may be a new class of analgesics to treat chronic pain and other pathological states. However, regardless of increased availability of selective Ca<sup>2+</sup> blockers or K<sup>+</sup> activators, one should be aware that painful presentations are hardly related to a disorder exclusively focused on an ion channel isoform. So, the combination of drugs and the tailoring of treatments based on pain mechanisms should remain as major therapeutic approach.

**REFERENCES**