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

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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 $Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ isoforms are important in the pathophysiology of neuropathic pain. Similarly, the involvement of voltage-gated potassium channels, especially K_V1 and K_V7 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 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 farmacológicos e biofísicos tem demonstrado que os canais de sódio dependentes de voltagem, particularmente as isoformas $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ e $Na_v1.9$ são relevantes na fisiopatologia da dor neuropática. De forma similar, o envolvimento dos canais de potássio dependentes de voltagem, especialmente as isoformas K_v1 e K_v7, 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 viscerae innervation[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 adaptative 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[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[3-6].

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_v) and voltage-gated potassium channels (K^+).

ELECTRIC POTENTIAL DIFFERENCE-GATED SODIUM CHANNELS (NA_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_v) located along axonal membrane. This essential Na_v role in neural electrogenesis has brought to light a new important target for new therapeutic approaches aiming at attenuating neural firing resulting in painful response[7-11].

Na_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_v opening allows the flow of sodium ions toward the concentration gradient, promoting a neuronal depolarization transmembrane current leading closest axonal membrane to

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the threshold to generate action potential.

Most Na_v are rapidly inactivated opening, then suffering conformational changes for a new activation cycle. Na_v 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_v 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_v activation and closing process. Nine mammal genes have been described so far (SCN1A to SCN5A; SCN8A to SCN11A) which are related at molecular level to different α subunits, causing the formation of nine different sodium channels isoforms (N a_v1.1 to Na_v1.9), all sharing similar central structure, but with different amino acids sequences and, as a consequence, different kinetics and voltage-gated properties.

Structurally, isoforms Na_v1.1, Na_v1.2, Na_v1.3 and Na_v1.7 are similar to each other. These channels are broadly distributed and expressed in neurons and are sensitive to tetrodotoxin block (TTX)[12,13]. Na_v1.5, Na_v1.8 and Na_v1.9 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_v1.4 and Na_v1.6 are significantly different from the others and are TTX-sensitive, being essentially expressed in skeletal muscle and nervous system, respectively[12,13].

Dorsal root ganglion neurons express many different subtypes of voltage-gated sodium channels, especially Na_v1.1, Na_v1.6, Na_v1.7, Na_v1.8 and Na_v1.9, in addition to Na_v1.5 isoform in low levels. Na_v1.6 isoform is expressed in different neurons, while Na_v1.1 is expressed in sensory neurons. Na_v1.8 is essentially present in nociceptive sensory neurons. Most neurons express multiple Na^+ isoforms, being that Na_v1.7, Na_v1.8 and Na_v1.9 are preferably expressed in peripheral neurons such as dorsal root ganglion neurons, being targets for the development of pharmacological modulation without significant consequences on central nervous system and cardiovascular system, where such structures are less prevalent[12].

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_v 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 system[14,15].

Clearly, nerves submitted to traumatic injury are more susceptible to the anesthetic effect of Na_v blockers, which is related to their building up in injured nervous region[16]. 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_v, but which is still poorly understood[15,16].

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 transmission[5-7].

During this process, there is increased Na_v1.3 sodium channels expression, characteristic channel of embryonic neurons, but with relatively low expression in dorsal root ganglion neurons of adults[5-7]. Other studies have also shown that voltage-gated ion channels 1.6, responsible for saltatory conduction in thick myelinated fibers are also increased in pathological states in situations of nervous injury and regeneration[17].

Additionally, multiple inflammatory mediators have been described as potential modulators of the expression and activity of some Na_v isoforms, especially Na_v1.8[18]. markedly, a selective Na_v1.8 blocker (A-803467) was antinociceptive in animal models with inflammatory pain[19] and NP[20].

Animal studies have shown that neuromas formed after nervous injury may induce ectopic generation of spontaneous potential impulses and firings[9], closely related to increased Na_v1.3 expression[21]. Studies with human neuromas have also shown significant increase in the expression of Na_v1.7 and Na_v1.8 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_v disorders in humans and animal models[23,24]. SCN9A gene mutations, responsible for Na_v1.7 channel transcription, were identified in two severe painful syndromes (hereditary erythromelalgia and paroxysmal extreme painful disorder)[23,24]. Mutations with loss of Na_v1.7 gene function were also identified in patients with congenital insensitivity to pain[25].

As presented, 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, unspecific Na_v 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_v 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_v, the clinical use of effective drugs to treat painful presentations and which are more selective for some Na_v isoforms seems to be promising and may be soon available.

Electric potential difference-gated potassium channels

Voltage-gated potassium channels (K_v) 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_v are important in pain processing and in pathologic processes such as chronic pain of neuropathic orign[26-31].

K_v 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 isoforms[26], but different names have been described and used. Among different K_v 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 transmission[26].

K_v from 1 to 12 are tetramers of α subunits associated to up to four auxiliary β subunits, able to change their binding properties[4,26]. Electrophysiological studies have shown that many different K_v types are present in neurons of mammals, being briefly divided in fast activation K_v (mediated by the family of K_v1 channels) and slow activation K_v (mediated by the family of K_v7 channels), being the latter the most widely studied K_v in painful transmission[26].

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_v1 and K_v7, while 4-AP is more selective for K_v1 family ion channels, especially those related to fast current type (K_{DR})[4]. Interestingly, many natural toxins are K_v blockers, such as some spider poisons (margatoxin, agitoxin) or snake poisons (α-dendrotoxin) being that the latter helps discriminating different isoforms of the K_v1 family, being more selective for K_v1 and K_v2 than for K_v4[4,26].

In contrast to K_v1 channels, K_v7 channels may be more specifically modulated by drugs able to open such potassium ion channels (retigabine) or to block them (linopirdine)[4,26].

Specific classes of dorsal root ganglion neurons express combinations of different voltage-gated K^+ subunits. Neurons with larger axonal diameter have higher levels of K_v1.1 and K_v1.2 channels (modulators of action potential propagation) and of K_v7.2 (related to slow potassium currents which regulate neuronal excitability threshold), while smaller diameter fibers predominantly express K_v1.4 and K_v7.3 isoforms, also related to fast and slow potassium currents, respectively[28,29].

Studies have shown that K_v block in neuromas after nervous injury is associated to spontaneous discharges amplification, emphasizing the stabilizing role of K_v in neuronal membrane, compensating increased excitability related to Ca^{+}[28]. Additionally, there is significant decrease in the number

of K_v in dorsal root ganglion neurons, essentially attributed to decreased K_v1 channels expression[26]. Decrease of voltage-gated potassium channels in neurons submitted to traumatic injury seems to be related to stimuli amplification in chronic painful presentations.

Considering the role of K_v in membrane stabilization during pain transmission process, one may 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_v may represent a new class of analgesics to treat NP and other pathologies[29-34]. In spite of the modest recent advance in the development of drugs able to positively modulate K_v1 channels, modulators of K_v7 channels activity are good alternatives in this context[33-35].

K_v activator retigabine, developed as anticonvulsant, has shown significant analgesic properties[34], effect potentially related to the opening of K_v7 potassium channels, since it had its effect reverted by selective K_v7 channel antagonists[35].

CONCLUSION

This brief review has shown that recent evidences are emerging about electric potential difference-gated Ca^+ and K^+ as essential for physiologic pain transmission mechanisms and NP mechanisms, being considered relevant new targets for the development of therapeutic alternatives. Selective Ca^+ block and K^+ (K_v7) 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^+ may be a new class of analgesics to treat chronic pain and other pathological states.

However, regardless of increased availability of selective Ca^+ blockers or K^+ 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

1. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. Brain Res Rev. 2006;51(2):240-64.
2. Kuner R. Central mechanisms of pathological pain. Nat Med. 2010;16(11):1258-66.
3. Krarup C, Moldovan M. Nerve conduction and excitability studies in peripheral nerve disorders. Curr Opin Neurol 2009;22(5):460-6.
4. Moldovan M, Alvarez S, Romer Rosberg M, Krarup C. Axonal voltage-gated ion channels as pharmacological targets for pain. Eur J Pharmacol. 2013;708(1-3):105-12.
5. Waxman SG. Transcriptional channelopathies: an emerging class of disorders. Nat Rev Neurosci. 2001;2(9):652-9.
6. Waxman SG. The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. Pain. 1999; Suppl 6:S133-40.
7. Waxman SG, Dib-Hajj S, Cummins TR, Black JA. Sodium channels and pain. Proc Natl Acad Sci USA. 1999;96(14):7635-9.
8. Dib-Hajj SD, Black JA, Waxman SG. Voltage-gated sodium channels: therapeutic targets for pain. Pain Med. 2009;10(7):1260-9.
9. Devor M. Sodium channels and mechanisms of neuropathic pain. J Pain. 2006;7(Suppl 1):S3-12.
10. Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, et al. The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain. 2006;7(5 Suppl 3):S1-29.
11. Liu M, Wood JN. The roles of sodium channels in nociception: implications for mechanisms of neuropathic pain. Pain Med. 2011;12(Suppl3):S93-9.
12. Catterall WA, Goldin AL, Waxman SG. International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. Pharmacol Rev. 2005;57(4):397-409.
13. Kim CH, Oh Y, Chung JM, Chung K. The changes in expression of three subtypes of TTX sensitive sodium channels in sensory neurons after spinal nerve ligation. Brain Res Mol Brain Res. 2001;95(1-2):153-61.
14. Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, et al. The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain. 2006;7(Suppl 3):S1-29.
15. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. Pain. 2000;87(1):7-17.
16. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain. 1992;48(2):261-8.
17. Black JA, Renganathan M, Waxman SG. Sodium channel Na(v)1.6 is expressed along nonmyelinated axons and it contributes to conduction. Brain Res Mol Brain Res. 2002;105(1):19-28.
18. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annu Rev Neurosci. 2010;33:325-47.
19. Jarvis MF, Honore P, Shieh CC, Chapman M, Joshi S, Zhang XF, et al. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. Proc Nat Acad Sci USA. 2007;104(20):8520-5.
20. McGaraughty S, Chu KL, Scanio MJ, Kort ME, Faltynek CR, Jarvis MF. A selective Nav1.8 sodium channel blocker, A-803467[5-(4-chlorophenyl-N-(3,5-dimethoxyphenyl)furan-2-carboxamide], attenuates spinal neuronal activity in neuropathic rats. J Pharmacol Exp Ther. 2008;324(3):1204-11.
21. Black JA, Cummins TR, Plumpton C, Chen YH, Hormuzdiar W, Clare JJ, et al. Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. J Neurophysiol. 1999;82(5):2776-85.
22. Black JA, Nikolajsen L, Kroner K, Jensen TS, Waxman SG. Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas. Ann Neurol. 2008;64(6):644-53.
23. Dib-Hajj S, Rush A, Cummins T, Waxman S. Mutations in the sodium channel Nav1.7 underlie inherited erythromelalgia. Drug Discov Today Dis Mech. 2006;3(3):343-50.
24. Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, et al. SCN9A mutations in paroxysmal extreme pain disorder: Allelic variants underlie distinct channel defects and phenotypes. Neuron. 2006;52(5):767-74.
25. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006;444(7121):894-8.
26. Busserolles J, Tsantoulas C, Eschalier A, López García JA. Potassium channels in neuropathic pain: advances, challenges, and emerging ideas. Pain. 2016;157(Suppl 1):S7-14.
27. Bayliss DA, Barrett PQ. Emerging roles for two-pore-domain potassium channels and their potential therapeutic impact. Trends Pharmacol Sci. 2008;29(11):566-75.
28. Ishikawa K, Tanaka M, Black JA, Waxman SG. Changes in expression of voltage-gated potassium channels in dorsal root ganglion neurons following axotomy. Muscle Nerve. 1999;22(4):502-7.
29. Rasband MN, Park EW, Vanderah TW, Lai J, Porreca F, Trimmer JS. Distinct potassium channels on pain-sensing neurons. Proc Natl Acad Sci USA. 2001;98(23):13373-8.
30. Tsantoulas C. Emerging potassium channel targets for the treatment of pain. Curr Opin Support Palliat Care. 2015;9(2):147-54.
31. Tsantoulas C, McMahon SB. Opening paths to novel analgesics: the role of potassium channels in chronic pain. Trends Neurosci. 2014;37(3):146-58.
32. Hao J, Padilla F, Dandonneau M, Lavebratt C, Lesage F, Noel J, et al. Kv1.1 channels act as mechanical brake in the senses of touch and pain. Neuron. 2013;77(5):899-914.
33. Roza C, Castillejo S, Lopez-García JA. Accumulation of Kv7.2 channels in putative ectopic transduction zones of mice nerve-end neuromas. Mol Pain. 2011;7:58.
34. Blackburn-Munro G, Jensen BS. The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. Eur J Pharmacol. 2003;460(2-3):109-16.
35. Lang PM, Fleckenstein J, Passmore GM, Brown DA, Grafe P. Retigabine reduces the excitability of unmyelinated peripheral human axons. Neuropharmacology. 2008;54(8):1271-8.