

Summary

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Voltage-gated sodium channels and pain associated with nerve injury and neuropathies

Injury to peripheral nerves and peripheral neuropathies produce pathophysiological changes within sensory neurons that often leads to the development of neuropathic pain. Sensory neurons express multiple, distinct voltage-gated sodium channel isoforms, and the altered expression and distribution of specific sodium channels within sensory neurons following nerve injury have been implicated as important contributors to the pathogenesis and persistence of neuropathic pain. In this chapter, we will review findings that describe changes in the expression of sodium channels $Na_v1.3$, $Na_v1.8$ and $Na_v1.9$ in three experimental models of neuropathic pain: nerve transection (neuroma), chronic constriction injury (CCI) and diabetic neuropathy. The available literature strongly suggests that these three sodium channels play important, although different, roles in the development.

Key words: axon, axotomy, chronic constriction injury, dorsal root ganglion, ectopic discharge, nerve injury, neuroma, neuropathic pain, peripheral neuropathy, sodium channel, tetrodotoxin

Summary

Jeffrey J. Clare

Current approaches for the discovery of novel NaV channel inhibitors for the treatment of brain disorders

Recent advances in methods for assaying brain NaV channels have greatly increased their tractability for drug development. As a result, the way has been opened for the discovery of a new generation of NaV inhibitors with improved potency and use-dependence. There is also growing evidence that selectivity over other types of channel, and indeed over individual NaV subtypes, are more achievable hurdles than previously predicted. In parallel with this, the cloning and expression of the human NaV channel family is enabling a better understanding of their properties as well as of their roles in normal physiology and in various disease settings. Armed with this increased knowledge, it is anticipated that better selectivity, potency and use-dependence will lead to improved therapeutic efficacy of NaV inhibitors, although a clearer understanding of the in vivo consequences of these refinements still awaits the emergence of this new generation of NaV inhibitors.

Key words: brain NaV channels, epilepsy, bipolar disorder, cerebral ischaemia, cloning, expression, high-throughput assays, automated electrophysiology, drug discovery

Summary

Jennifer M.A Laird and Fernando Cervero

Voltage-gated sodium channels and visceral pain

Visceral pain is a problem of substantial clinical relevance and its neurobiological mechanisms differ from those of somatic nociceptive or neuropathic pain. Considerable progress has been

made in recent years in understanding the functional properties of the visceral nociceptors that trigger pain states, their molecular mechanisms of activation and sensitization and their central actions. Voltage-gated sodium channels have been identified as key players in the sensitization of visceral nociceptors. This chapter reviews current evidence on the role of voltage-gated sodium channels in the activation and sensitization of visceral nociceptive afferents, and in the triggering and maintenance of clinically relevant visceral pain states.

Key words: visceral nociceptors, bladder, colon, ileum, stomach, sensitization, NaV1.7, NaV1.8, NaV1.9, dorsal root ganglia, knockout mice, antisense oligonucleotides

Summary

Kenji Okuse and Mark D. Baker

The functional interaction of accessory proteins and voltage-gated sodium channels

Voltage-gated sodium channels confer excitability on axons including those known to be involved in nociception. The tetrodotoxin-resistant Na_v1.8 sub-type is known to play an important role in transduction and transmission of pain. Evidence also exists that changes in the expression and function of other sodium channels play a role in pain states. This chapter considers the role of sodium channel accessory proteins in pain pathways, that may modify channel function, the amount of channel protein expressed, and the interactions of sodium channels with proteins involved in cytoskeletal tethering.

In addition to single transmembrane auxiliary β -subunits, there have been numerous other associating partners reported for sodium channel α -subunits. The role of accessory proteins in the functional expression of Na_v1.8 has recently become clearer through the development of a yeast two-hybrid screen utilizing parts of the channel as baits for interactor proteins. As some of these accessory proteins have the ability to regulate α -subunits, they may be attractive therapeutic drug targets for inflammatory and neuropathic pain.

Key words: sodium channel, Na channel α -subunit, Na channel β -subunit, yeast two-hybrid, DRG, pain, gene knockout, p11, annexin II light chain, membrane trafficking, excitability, voltage-clamp, nerve, nociception

Summary

James A. Brock

Sodium channels and nociceptive endings

Recent studies have demonstrated that sensory neurones possess multiple subtypes of voltage-gated Na⁺ channels and that the expression of these ion channels differs depending on their sensory modality. This chapter concentrates on the Na⁺ channels expressed in nociceptive neurons in dorsal root and trigeminal ganglia. Studies on the cell bodies of these neurones have revealed that they express both tetrodotoxin (TTX)-sensitive and TTX-resistant Na⁺ channels. Recent evidence indicates that both TTX-sensitive and TTX-resistant Na⁺ channels are also present in the receptive nerve endings of nociceptive neurones and that their biophysical properties contribute to determining the normal behaviour of these sensory receptors. Furthermore, alterations in the function and / or expression of particular Na⁺ channel subtypes induced by inflammatory mediators are likely to contribute to hyperexcitability of these sensory

receptors in inflamed tissues. Drugs targeted at specific Na⁺ channel subtypes may provide a novel means to manage pain arising in inflamed tissue without interfering with other neural functions.

Key words: nociceptor, tetrodotoxin, nerve terminal, sensory receptor, Nav1.3, Nav1.6, Nav1.7, Nav1.8, Nav1.9, nociceptor sensitization, prostaglandin E₂

Summary

Grant D. Nicol

Signalling cascades that modulate the activity of sodium channels in sensory neurons

Inflammatory mediators, such as prostaglandin E₂, can enhance the sensitivity to noxious stimulation in a variety of animal models for the perception of pain. This enhanced sensitivity results in large part from the augmented excitability of small diameter nociceptive sensory neurons. This chapter reviews the signalling cascades that are activated by inflammatory mediators and their resulting modulation of voltage-dependent sodium channels that give rise to this enhanced excitability. Small diameter sensory neurons are unique in that they express both tetrodotoxin-sensitive and -insensitive types of sodium channels and that the expression patterns appear to vary significantly amongst individual neurons. To date, studies have largely focused on the modulation of the tetrodotoxin-insensitive sodium channel, Nav1.8 by the protein kinase A and C pathways as well as the cascades activated by nerve growth factor, although more recent work has begun to explore the tetrodotoxin-sensitive subtypes. It is intriguing that the modulation of sodium channels in sensory neurons appears to be different from that observed for neurons of the central nervous system despite the molecular similarities of the channels. To determine the cellular mechanisms giving rise to the hyperalgesia that occurs with inflammation, it is critical to understand these modulatory pathways and how integration of the activities of these different channel subtypes alter the firing properties of nociceptive sensory neurons.

Key words: sodium channel, tetrodotoxin, sensitization, protein kinase A, protein kinase C, nerve growth factor, calmodulin, hyperalgesia, capsaicin-sensitive small diameter sensory neuron, neuronal excitability, phosphorylation, signalling pathways

Summary

Lodewijk V. Dekker and David Cronk

Nav1.8 as a drug target for pain

The last few years have seen significant advances in the understanding the molecular events underlying chronic pain. Genomic studies have identified genes specifically expressed in pain-transmitting neurons (nociceptors). Among these the voltage-gated sodium channel Nav1.8 is a prime target for development of analgesic drugs since (1) its restricted expression in nociceptors suggests that specific drugs would have a beneficial side-effect profile, (2) it is modulated in various ways in pain states suggesting that it may play a role in the pathophysiology of pain and (3) several interference methods suggest that Nav1.8 contributes to the pathology. Technically Nav1.8 is now a feasible drug target with cell lines being developed that allow high throughput screening of Nav1.8 in a physiological context and screening technology being available to measure sodium channel activity in high throughput functional assays. Here we discuss the

biological functions of Nav1.8 and summarize the screening technology available to identify modulators for this channel.

Summary

Michael S. Gold

Role of voltage-gated sodium channels in oral and craniofacial pain

Voltage-gated sodium channels (VGSCs) play a critical role in pain, hyperalgesia (increased pain in response to normally painful stimuli) and/or allodynia (pain in response to normally innocuous stimuli) associated with injury to somatic and visceral structures. Evidence for such a role in pain arising from oral and craniofacial structures is relatively rudimentary. However, it is important to consider a potential role for VGSCs in pain arising from these structures for several reasons. First, it is likely that many trigeminal ganglia (TG) neurons are distinct from dorsal root ganglia (DRG) neurons, and therefore that the underlying mechanisms of injury-induced changes in excitability are different. Oral and craniofacial structures are innervated by afferents arising from sensory neurons located in TG, a structure analogous to DRG, which give rise to somatic and visceral afferents. However, TG neurons are different than DRG neurons in that they are of mixed embryological origin, possess few, if any, proprioceptive afferents (which arise from the mesencephalic nucleus of the 5th cranial nerve), have some somatotopic organization, and innervate a number of unique structures. Second, there are a number of unique pain syndromes associated with oral and craniofacial structures including migraine, temporomandibular disorder (TMD) and trigeminal neuralgia. And third, while TG neurons appear to express the same VGSCs as DRG neurons and several of these appear to sub-serve similar functions, several lines of evidence suggest VGSCs play different roles in pain arising from oral and craniofacial structures than they do in that arising from visceral or other somatic structures. The implications of all these differences is that the therapeutic interventions needed to treat pain arising from oral and craniofacial structures may be different than those needed to treat pain arising from somatic or visceral structures. The purpose of this chapter is to summarize our current knowledge about VGSCs in TG neurons, detail their potential role in pain syndromes arising from these structures and highlight a number of areas where additional research is needed.

Key words: migraine, trigeminal neuralgia, temporomandibular disorder, temporomandibular joint, neuropathic pain, inflammatory pain, trigeminal ganglia, cornea, tooth

Andreas Scholz

Sodium channel gating and drug blockade

(No summary & key words available)

Summary

John N. Wood

Future directions in sodium channel research

Tissue-specific splice variants and association with cell-specific proteins vastly increase the functional diversity of sodium channel subtypes encoded by the nine different α -subunit genes. As channel trafficking, localisation and density are key determinants of neuronal excitability, a

better understanding of the regulation of sodium channel expression is likely to provide new possibilities for therapeutic intervention in pain, epilepsy and cardiac function. Genetic approaches focussing on tissue-specific null mutants provide a route to defining the functional significance of sodium channel subtypes. In particular, the use of inducible Cre-recombinase constructs in defined cell populations should enable a much more clear idea of physiological significance to be assessed in mouse models. This chapter overviews recent insights into post-transcriptional processing of sodium channels, and the use of tissue-specific inducible null mutant mice to explore sodium channel function.

Key words: splice variants, RNA editing, transcription, conotoxins, Cre-loxp, tissue specific inducible knock-outs



<http://www.springer.com/978-3-7643-7062-6>

Sodium Channels, Pain, and Analgesia

Coward, K.; Baker, M.D. (Eds.)

2005, X, 202 p., Hardcover

ISBN: 978-3-7643-7062-6

A product of Birkhäuser Basel