European Journal of Pharmacology 708 (2013) 105–112

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Axonal voltage-gated ion channels as pharmacological targets for pain

Mihai Moldovan [a,b,*], Susana Alvarez [a,b], Mette Romer Rosberg [a,b], Christian Krarup [a,b]

[a] Institute of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Denmark
[b] Department of Clinical Neurophysiology, Rigshospitalet, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 28 June 2012
Accepted 4 March 2013
Available online 13 March 2013

Keywords:
Nerve regeneration
Neuroma
Node of Ranvier
Internode
Voltage-gated ion channels
Acquired channelopathies
Subtype-selective voltage-gated ion channel blockers
Rodent pain models
Nerve excitability testing

ABSTRACT

Upon peripheral nerve injury (caused by trauma or disease process) axons of the dorsal root ganglion (DRG) somatosensory neurons have the ability to sprout and regrow/remyelinate to reinnervate distant target tissue or form a tangled scar mass called a neuroma. This regenerative response can become maladaptive leading to a persistent and debilitating pain state referred to as chronic pain corresponding to the clinical description of neuropathic/chronic inflammatory pain. There is little agreement to what causes peripheral chronic pain other than hyperactivity of the nociceptive DRG neurons which ultimately depends on the function of voltage-gated ion channels.

This review focuses on the pharmacological modulators of voltage-gated ion channels known to be present on axonal membrane which represents by far the largest surface of DRG neurons. Blockers of voltage-gated Na^+ channels, openers of voltage-gated K^+ channels and blockers of hyperpolarization-activated cyclic nucleotide-gated channels that were found to reduce neuronal activity were also found to be effective in neuropathic and inflammatory pain states. The isoforms of these channels present on nociceptive axons have limited specificity. The rationale for considering axonal voltage-gated ion channels as targets for pain treatment comes from the accumulating evidence that chronic pain states are associated with a dysregulation of these channels that could alter their specificity and make them more susceptible to pharmacological modulation. This drives the need for further development of subtype-specific voltage-gated ion channels modulators, as well as clinically available neurophysiological techniques for monitoring axonal ion channel function in peripheral nerves.

Contents

1. Introduction

Somatosensory neurons refer information about the body per se including visceral organs (rather than information about the external world). In the peripheral nervous system (PNS) they are located in the dorsal root ganglia (DRG) from where they extend a long distal axon which travels within the peripheral nerves to innervate distant targets such as the skin. Upon peripheral nerve injury (caused by trauma or disease process) DRG axons have the ability to sprout/remyelinate and regrow to reinnervate target tissue or they may form a tangled scar mass called a neuroma (Cajal, 1928).

The regenerative response to injury can become maladaptive (Navarro et al., 2007) leading to sensitization of the nociceptive somatosensory neurons (capable of encoding noxious stimuli) in the PNS and subsequently in the central nervous system (CNS) inducing a persistent and debilitating pain state referred to as "chronic" or "pathological" pain (in contrast to the "acute"/

* Corresponding author.
E-mail address: Moldovan@sund.ku.dk (M. Moldovan).

0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.03.001

nociceptive pain that has a protective function) (Kuner, 2010). These phenomena correspond to the clinical description of "neuropathic pain" which includes symptoms like hyperalgesia (increased pain from a stimulus that normally provokes pain), allodynia (pain due to a stimulus that does not normally provoke pain) and even "spontaneous pain" (if the nature of the stimulus is uncertain). When chronic pain occurs in the context of inflammation (i.e. when sensitization occurs primarily due to "inflammatory mediators") it is referred to as "inflammatory pain", although some degree of inflammation occurs also during neuropathic pain processes, and axonal damage occurs also due to inflammation.

Pain is probably the most common symptomatic reason to seek medical consultation (Loeser and Melzack, 1999). The unpleasant sensory and emotional experience (Huber et al., 2007) described as pain is ultimately made in the brain (Bingel and Tracey, 2008) under the influence of complex modulatory mechanisms such as gonadal steroid hormones (Craft et al., 2004). It is therefore not surprising that medications that interfere with CNS function (in the order of potency: secondary tricyclic antidepressants (TCAs), serotonin and norepinephrine dual reuptake inhibitors, calcium channel α(2)-δ ligands, tramadol, and opioid antagonists) (de Leon-Casasola, 2011) are also, to some extent, effective in controlling chronic pain even when considered to be of "peripheral origin". Nevertheless, mechanism-based approaches have the potential to be more effective, as indicated by the recent proof-of-concept that a humanized monoclonal antibody that inhibits nerve growth factor (NGF), known to increase and cause pain in inflamed tissue, was found to control inflammatory pain from osteoarthritis of the knee (Lane et al., 2010).

It was long recognized that in the somatosensory system the intensity of a sensation is signaled by the frequency of action potentials ("spikes") in afferent nerve fibers (Adrian and Zotterman, 1926). As such, it is reasonable to assume that in chronic pain states there is an increased spiking in DRG nociceptive neurons. There is little agreement about which neuronal compartment generates the increased spiking (i.e. the terminal receptor fields, the axon itself or the neuronal body/axonal initial segment) (Zimmermann, 2001). Typically, several events are implicated including: (i) increased excitability and lower threshold for action potential initiation, (ii) amplification of responses (i.e. "burst discharges" in response to a single stimulus) and (iii) spontaneous discharges occurring from normal (e.g. DRG) or abnormal (ectopic) sites (e.g. within a neuroma). All these events depend on the activity of voltage-dependent ion channels.

This review focuses on the pharmacological modulators of voltage-gated ion channels known to be present on axonal membrane, which represents by far the largest surface of DRG neurons: (i) the voltage-gated Na^+ channels, (ii) the voltage-gated K^+ channels and (iii) the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels.

Based on diameter, myelination and the corresponding conduction velocity (Hursh, 1939; Rushton, 1951) peripheral nerve axons were classified first by Erlanger and Gasser in three groups A–C and later by Lloyd in 4 types (I–IV) (Manzano et al., 2008). The sense of touch is conveyed by large diameter, myelinated and fast conducting Aβ (Type II) fibers from cutaneous mechanoreceptors. Slower/thinner myelinated Aδ (Type III) fibers, conduct temperature information from cold thermoceptors, pressure from free nerve endings and pain from nociceptors of the neospinothalamic tract ("sharp pain") whereas the smallest unmyelinated C (Type IV) fibers provide warm sense and pain from nociceptors (noxious chemicals) of the paleospinothalamic tract ("aching, throbbing or burning pain").

Experimental data presented hereafter come primarily from experiments on rodent models of neuropathic (Bennett et al., 2003) and inflammatory pain (Moalem and Tracey, 2006) where alterations in pain behavior could be associated with changes at the DRG level in: voltage-dependent ion channel gene mRNA (transcriptional changes), immunohistochemical antibody-detectable ion channel protein (translational changes) and electrophysiological changes (spiking behavior/membrane currents). With these methods DRG neurons are typically classified as "large neurons" having Aβ afferent fibers involved in allodynia like behavior and "small neurons" having true Aδ/C nociceptive afferents (Lloyd classification is not used). It should be noted that, in spite of their differences in myelination, Aδ and C afferents are not readily distinguished in these studies, although large and small neurons are thought to express different voltage-gated channel isoforms. Also it is implied that changes in functional ion channels at the DRGs are also extended along the axons, which in some cases could be an oversimplification.

Blockers of voltage-gated Na^+ channels and HCN channels as well as openers of voltage-gated K^+ channels that were found to reduce neuronal spiking were also found to be effective in neuropathic and inflammatory pain states. Nevertheless, it should be noted that the isoforms of these channels present on nociceptive axons are mostly non-specific and the available subtype-specific voltage-gated ion channels modulators are currently unsatisfactory (Heinzmann and McMahon, 2011). The rationale for considering these channels as nociceptive targets in pain treatment comes from the accumulating evidence that chronic pain states are associated with a dysregulation of these channels that could make them more susceptible to pharmacological modulation.

2. Voltage-dependent sodium channels

Sodium channels consist of one highly processed α subunit, associated with auxiliary β subunits. The pore-forming α subunit is sufficient for functional expression, but the kinetics and voltage dependence of channel gating are modified by the β subunits (involved primarily in channel localization and interaction with cell adhesion molecules, extracellular matrix, and intracellular cytoskeleton). The α subunits are composed of 4 homologous domains (I–IV) with the N and C termini regions located intracellularly. Each domain contains 6 probable transmembrane spanning α-helices (termed segments S1–S6) with an additional membrane-reentrant pore loop between S5 and S6. These pore loops line the outer, narrow entry to the pore, whereas the S5 and S6 segments line the inner, wider exit from the pore. The S4 in each domain contains positively charged amino-acid residues contributing to the "voltage sensor" that permits the opening of the channel when the cell is depolarized and direct Na^+ ions across the cell membrane, down the electrochemical gradient for Na^+. Additionally, a short loop connecting S3 and S4 serves as inactivation gate, blocking the pore from inside upon sustained depolarization (Catterall, 2000; Catterall et al., 2005).

Although the neurophysiologic doctrine has traditionally referred to "the" voltage-gated sodium channel, it is now clear that in mammals there are at least nine genes (SCN1A–SCN5A and SCN8A–SCN11A) that encode molecularly and physiologically distinct α subunits. The current nomenclature for these voltage-dependent Na channels (Na_V) indicates the gene family (currently only Na_V1), followed by the specific α subunit isoform assigned according to the approximate order in which the genes were identified ($Na_V1.1$–$Na_V1.9$) (Catterall et al., 2005).

By structural similarity, $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, and $Na_V1.7$ are most closely related. They are broadly expressed in neurons and they are sensitive to block by nanomolar concentration of tetrodotoxin (TTX-S) found in puffer fish and other marine and terrestrial animals (Narahashi, 2008). $Na_V1.5$, $Na_V1.8$, and $Na_V1.9$ are also closely related, are highly expressed in heart and dorsal