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BRAIN RESEARCH REVIEWS

Review

Voltage-gated sodium channels in pain states: Role in pathophysiology and targets for treatment

Sulayman D. Dib-Hajj[a,b,*], *Alexander M. Binshtok*[c], *Theodore R. Cummins*[d], *Michael F. Jarvis*[e], *Tarek Samad*[f], *Katharina Zimmermann*[g,h]

[a]*Department of Neurology and Center for Neuroscience and Regeneration Research Yale University School of Medicine, New Haven, CT 06510, USA*
[b]*Rehabilitation Research Center, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA*
[c]*Neural Plasticity Research Group, Harvard Medical School, Charlestown, MA 02129, USA*
[d]*Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis , IN 46202, USA*
[e]*Neuroscience Research, Abbott Laboratories, Abbott Park, IL 60064, USA*
[f]*Wyeth Research, Monmouth Junction, NJ 08852, USA*
[g]*Department of Cardiology, Children's Hospital, Boston, MA 02115, USA*
[h]*Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA*

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ABSTRACT

Pain is a major unmet medical need which has been causally linked to changes in sodium channel expression, modulation, or mutations that alter channel gating properties or current density in nociceptor neurons. Voltage-gated sodium channels activate (open) then rapidly inactivate in response to a depolarization of the plasma membrane of excitable cells allowing the transient flow of sodium ions thus generating an inward current which underlies the generation and conduction of action potentials (AP) in these cells. Activation and inactivation, as well as other gating properties, of sodium channel isoforms have different kinetics and voltage-dependent properties, so that the ensemble of channels that are present determine the electrogenic properties of specific neurons. Biophysical and pharmacological studies have identified the peripheral-specific sodium channels $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ as particularly important in the pathophysiology of different pain syndromes, and isoform-specific blockers of these channels or targeting their modulators hold the promise of a future effective therapy for treatment of pain.

Contents

* *Corresponding author*. Center for Neuroscience and Regeneration Research 127A, Building 34 VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA. Fax: +1 203 937 3801.
E-mail address: sulayman.dib-hajj@yale.edu (S.D. Dib-Hajj).

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1. Introduction

Voltage-gated sodium channels are heteromultimers of a large pore-forming α-subunit and smaller auxiliary β-subunits (Catterall, 2000). The α-subunit (will be referred to as channel hereafter) is organized into four domains (DI–DIV), each consisting of six transmembrane segments that are connected by intra- and extracellular linkers (Fig. 1), whereas the β-subunits are type I membrane proteins, each with a single transmembrane segment and a larger extracellular domain that has an immunoglobulin fold (Catterall, 2000). Nine distinct genes (*SCN1A–5A*, *SCN8A–11A*) encode the $Na_v1.1$–$Na_v1.9$ channels, and several of their cognates have been identified in mammals and lower vertebrates, with many of them expressed in tissue- and developmentally-controlled manner (Catterall et al., 2005; Goldin, 2002; Goldin et al., 2000). Three of these channels ($Na_v1.7$, $Na_v1.8$ and $Na_v1.9$) are expressed only in peripheral neurons with $Na_v1.8$ and $Na_v1.9$ limited to sensory and myenteric neurons and $Na_v1.7$ is expressed in sensory, sympathetic and myenteric neurons (Catterall et al., 2005).

Sodium channels are responsible for the generation and propagation of action potentials in excitable cells in response to membrane depolarization. In a simplified scheme, sodium channels have these distinct states: resting (closed), activated (open), inactivated (closed) which itself exists as fast-inactivated (within milliseconds) and slow-inactivated (seconds), and recovering from inactivation (repriming) which is a period in which the channel is not available to open in response to a depolarization. Sodium channels can be distinguished by the voltage-dependence and kinetics of its transition between these states, and pharmacologically according to their sensitivity to the toxin tetrodotoxin (TTX). Most of the neuronal channels are sensitive to nanomolar concentrations of TTX (TTX-S), while the cardiac channel $Na_v1.5$ and the sensory neuron-specific channels $Na_v1.8$ and $Na_v1.9$ are resistant to 100–1000 fold higher concentrations of TTX (TTX-R) (Catterall et al., 2005). The peripheral sodium channels $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ channels produce sodium currents with distinct biophysical properties which enable them to make specific contributions to the electrogenic properties of neurons under

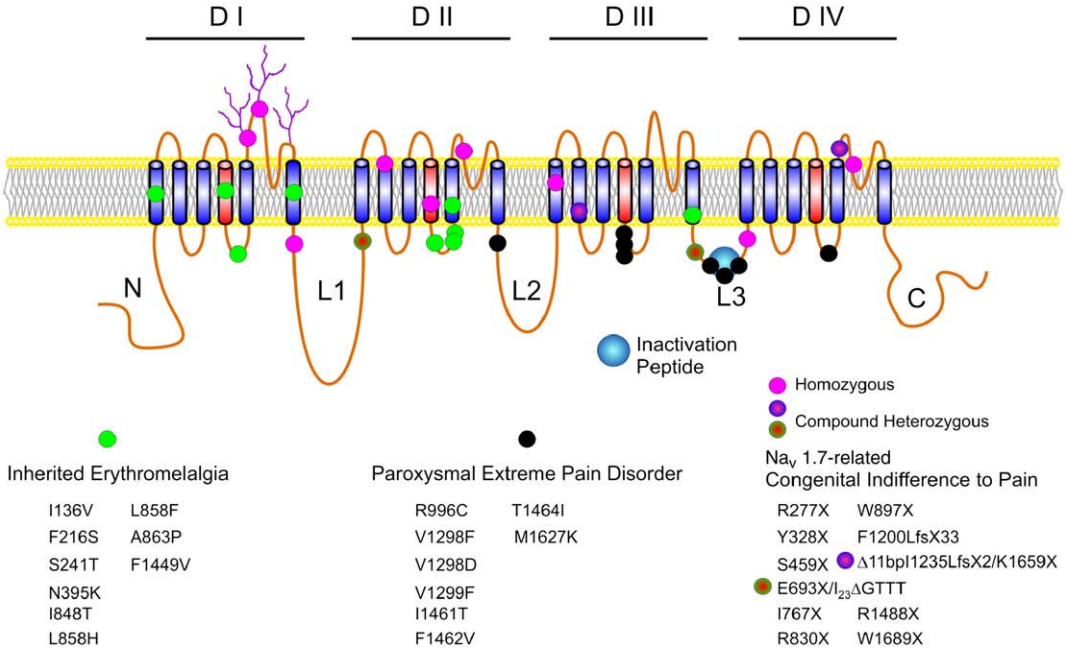

Fig. 1 – Schematic of voltage-gated sodium channel showing locations of the known mutations in $Na_v1.7$-related inherited pain disorders. Gain-of-function mutations in inherited erythromelalgia (green symbols) and paroxysmal extreme pain disorder (PEPD, black symbols) are inherited as dominant trait. $Na_v1.7$-related congenital indifference to pain (CIP) is caused by loss-of-function mutations which are inherited as a recessive trait. Homozygous $Na_v1.7$-related CIP mutations carry the same nonsense mutation on both alleles of *SCN9A* (solid magenta), whereas two pairs of compound heterozygous mutations (blue-magenta and red-green) carry different mutations which produce non-functional channels on the two alleles. Reproduced with permission from Dib-Hajj et al. (2007).