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Molecules in focus

Neuronal voltage-gated sodium channel subtypes: Key roles in inflammatory and neuropathic pain

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Abstract

Voltage-gated sodium channels (VGSCs) play an important role in neuronal excitability. Regulation of VGSC activity is a complex phenomenon that occurs at multiple levels in the cell, including transcriptional regulation, post-translational modification and membrane insertion and retrieval. Multiple VGSC subtypes exist that vary in their biophysical and pharmacological properties and tissue distribution. Any alteration of the VGSC subtype profile of a neuron or the mechanisms that regulate VGSC activity can cause significant changes in neuronal excitability. Inflammatory and neuropathic pain states are characterised by alterations in VGSC subtype composition and activity in sensory neurons. This review focuses on the VGSC subtypes involved in such pain states.

Keywords: Sodium channels; Intracellular binding domain; Sensory neuron; Pain; Trafficking

1. Introduction

Voltage-gated Na^+ channels (VGSCs) are large transmembrane proteins that mediate the rising phase of the action potential in excitable cells. VGSCs consist of an α-subunit which forms a Na^+-conducting pore and associated β-subunits that modulate the biophysical properties of the channel. Although it has been known since the late 1940s that movement of Na^+ across the membrane mediate action potentials in excitable cells, it was not until 1984 that the first VGSC α-subunit was cloned from the electric eel *Electrophorus electricus* (Noda et al., 1984). Since then, nine mammalian VGSC α-subunit subtypes have been identified. These vary in their tissue distribution, biophysical properties and their sensitivity to neurotoxins. VGSCs are generally classified as either tetrodotoxin (TTX)-sensitive (TTX-S) or TTX-resistant (TTX-R) (see Table 1). Four auxiliary β-subunits of approximately 35 kDa have been identified: β1 (with the variant β1A), β2, β3 and β4 (Wood, Boorman, Okuse, & Baker, 2004).

The combination of VGSC subtypes expressed in individual cells is a key determinant of the membrane excitability, conduction velocity and possibly in some tissues also the resting membrane potential. Alterations in the activity or expression of VGSCs subtypes leading to hyperexcitability are associated with several disease states such as epilepsy, stroke and pain. In particular, chronic pain states are known to involve alterations of VGSC activity and subtype composition in sensory neurons. This brief review describes the structure, function and regulation of VGSCs with the focus on VGSC subtypes involved in inflammatory and neuropathic pain.

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Table 1
Tissue distribution and tetrodotoxin sensitivity of the nine mammalian VGSC subtypes

Na_v α-subunit subtype	Former name	Distribution	TTX sensitivity (IC_{50})
$Na_v1.1$	Rat I	CNS, sensory neurons	TTX-S (6 nM)
$Na_v1.2$	Rat II	CNS, sensory neurons	TTX-S (12 nM)
$Na_v1.3$	Rat III	CNS, embryonic sensory neurons	TTX-S (4 nM)
$Na_v1.4$	μ1	Skeletal muscle	TTX-S (5 nM)
$Na_v1.5$	H1	Cardiac muscle, immature and denervated skeletal muscle	TTX-R (1–2 μM)
$Na_v1.6$	NaCh6	CNS, sensory neurons, nodes of Ranvier in both CNS and PNS	TTX-S (1 nM)
$Na_v1.7$	PN1	Sensory neurons, sympathetic neurons, Schwann cells	TTX-S (4 nM)
$Na_v1.8$	SNS/PN3	Sensory neurons	TTX-R (60 μM)
$Na_v1.9$	SNS2/NaN	Sensory neurons	TTX-R (40 μM)

CNS, central nervous system; PNS, peripheral nervous system; TTX-S, TTX-sensitive; TTX-R, TTX-resistant; IC_{50}, half-maximal inhibitory concentration.

2. Structure of VGSCs

The VGSC α-subunits of approximately 260 kDa consist of more than 1800 amino acids with four internally homologous domains, each of which contains six membrane-spanning helices (S1–S6) (Fig. 1) (Noda et al., 1984). During an action potential, the VGSC transits through at least three states; closed, open and inactivated. Activation of the VGSC is mediated by the S4 helix of each domain, whereas inactivation is mediated by a motif located on the cytoplasmic side of the channel in the intracellular loop that connects domains III and IV. The loop between segment S5 and S6, called the P-loop, is thought to mediate the cation selectivity of the open channel (Catterall, 2000). VGSC α- and β-subunits interact mainly through their extracellular domains, most likely in the configuration 1α:2β. All β-subunits adopt the immunoglobulin-like fold with an intracellular C-terminus, one membrane-spanning domain and two extracellular β-sheets. β1 and β3 are non-covalently attached to the α-subunit, whereas β2 and β4 are connected via disulfide bonds (Isom, 2001).

3. Expression, activation and turnover

Neuronal VGSC expression is modulated by growth factors such as nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF). These growth factors up-regulate VGSC mRNA levels, often in a subtype-specific manner that depends on the neuronal cell type and growth factor combination (Fjell et al., 1999). Post-translational regulation is even more complex and also varies between VGSC α-subunit subtypes. Phosphorylation and auxiliary β-subunits can modulate current amplitude as well as the kinetics of transition between the closed, open and inactivated state (Isom, 2001). Phosphorylation sites for protein kinase A (PKA) and protein kinase C (PKC) are localised in the intracellular loops of the α-subunit (see Fig. 1), and in general, phosphorylation increases the current amplitude of TTX-R VGSCs but exerts the opposite effect on TTX-S subtypes (Chahine, Ziane, Vijayaragavan, & Okamura, 2005). In addition to regulating the biophysical properties of VGSCs, β-subunits also modulate their cell surface levels by anchoring the VGSC to the cytoskeleton (Isom, 2001). In general, little is known about the regulation of trafficking and turnover of VGSCs, however, certain regulatory pathways involving membrane insertion, stabilisation and retrieval have been described (Fig. 2). Association with ankyrin, annexin II and contactin stabilise VGSCs in the membrane and may also increase their trafficking to the cell surface (Chahine et al., 2005). On the other hand, ubiquitin ligases of the Nedd4 family target VGSCs for proteasomal destruction, thus reducing their membrane density (Fotia et al., 2004).

4. Biological function of VGSCs in sensory neurons

Of the nine mammalian VGSC subtypes, six are expressed at high levels in sensory neurons (see Table 1). Sensory neurons constitute the first link in the somatosensory pathway and include dorsal root ganglion (DRG) neurons, trigeminal ganglion neurons and nodose ganglion neurons. Large DRG neurons (≥35 μm diameter) exhibit fast activating and inactivating TTX-S Na^+ current and express high levels of $Na_v1.1$, $Na_v1.2$ and $Na_v1.6$. Neurons of intermediate size exhibit both TTX-S and TTX-R Na^+ currents whereas small neurons (<20 μm diameter) exhibit primarily TTX-R Na^+ currents. $Na_v1.7$ is expressed throughout DRG neurons of all sizes (Black et al., 1996). The two TTX-R Na^+ channels, $Na_v1.8$, which produces a slowly inactivat-