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Inherited Pain Syndromes and Ion Channels

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Individuals rely on the perception of pain to avoid injury, to signal disease, and to warn about tissue inflammation and damage. However, the inheritance of inappropriate, extreme, or inadequate pain production is a source of significant human suffering. Substantial progress has been made in our understanding of the genetics and pathophysiology of pain through the study of individuals and families with several specific inherited pain syndromes. These studies have led to the discovery of a number of gene mutations associated with specific ion channel disturbances that produce familial inherited pain sensitivity and insensitivity syndromes. The sodium channel has been identified as the primary determinant of most of these syndromes. This article focuses on the inherited pain syndromes and their corresponding ion channel mutations. There is hope that through continued research into these ion channels and pain syndromes, targeted drug therapy would be fruitful and beneficial to those afflicted.
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Introduction

Pain is something recognizable when seen but can be only understood through experience. Comprehended as an unpleasant sensory and emotional experience, pain serves an important protective mechanism. Individuals rely on this sensory modality to avoid injury, to signal disease, and to warn about tissue inflammation and damage. The genesis of pain incorporates both physiological mechanism and perceptual experience; both are required. Understanding these components results in improved approaches to treatment.

Substantial progress has been made in determining the genetics and corresponding pathophysiology of pain.[1] This has been possible in part by the identification and study of individuals and families with several specific inherited pain syndromes.[2,3] These studies have led to the discovery of a number of specific gene mutations that produce clinically delineated patterns of inherited pain sensitivity and insensitivity.[2,3] The identified genetic variations encode differences in the kinetics and ion flow through sodium and other ion channels.[2-4] These variations in ion flow modify nociceptor excitability and response, which results in faulty or persistent propagation of electrical current from sensory nociceptive neurons. The summation of these currents ultimately produces pain sensory signals.[4,5] This article focuses on the sodium ion channel and associated inherited pain syndromes.

Ion Channel Function

Primary nociceptors serve as the initial pain signaling sensory neurons. These are unmyelinated or small-diameter myelinated axons whose distal ends contain receptors that reside in an end organ such as the skin. Their axons extend from the periphery to cell bodies located within the dorsal root ganglia (DRG) or trigeminal nerve ganglia. Distal stimuli travel along axons through these ganglia en route to the dorsal horn of the spinal cord passing pain signals into the central nervous system for conscious perception. These pain signals are generated by a series of action potentials induced by the summation of ion flux through ion channels that result in neuronal depolarization.[4,5] Both ligand and voltage-gated ion channels play a role in nociceptor function. These channels are expressed within the axonal membranes in complex and uniformly exclusive patterns along different nociceptor neurons.[4,5] These patterns of expressed channels generate the distinctive abnormal firing related to nociceptor excitability.

Among the channels involved in nociceptive signaling are the transient receptor potential cation channel (TRP) family of ion channels and the voltage-gated sodium channels (Nav). Each TRP channel is adapted to detect specific chemical or mechanical stimuli and is activated by environmental irritants

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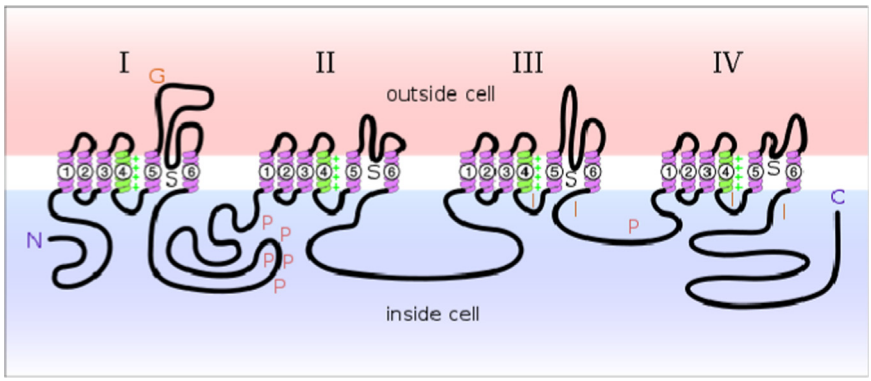

Figure Diagram of a voltage-sensitive sodium channel α-subunit. G, glycosylation; P, phosphorylation; S, ion selectivity; I, inactivation. Positive (+) charges in S4 are important for transmembrane voltage sensing. (Adapted with permission from Yu and Catterall[5]). (Color version of figure is available online.)

such as temperature, mustard, cinnamon, capsaicin, and wasabi, for example.[2] However, the voltage-gated sodium channels are primary to nociceptor excitability. All ion channels share similar basic structure (Fig.). They are hetero-multimers composed of a single α-subunit and several β-subunits, which traverse the cell membrane to form a pore for ion flow between internal and external compartments.[4-6] The α-subunit creates the ion selective pore, and the β-subunits provide an anchor to the membrane, modify channel gating, and regulate trafficking. Each subunit consists of 4 domains (DI-DIV) and 6 transmembrane segments (S1-S6). The S1-S4 segments are voltage-sensing segments, and S5-S6 contribute to the formation of the channel pore[5] (Fig.).

With the onset of membrane depolarization, sodium channels change structure and conformation shifting from a closed and inactive rest state to an open and activated one that allows ions to flow inward down their concentration gradient, further depolarizing the neuron.[4,6] The channel rapidly converts back to a repriming state, then an inactive rest state again, ready to recycle.[4,6] Nine sodium channel isoforms have been identified but only 7 are found within the nervous system (Table 1). Importantly, Nav1.7, Nav1.8, and Nav1.9 are predominantly found in the peripheral nervous system, and Nav1.7 and Nav1.9 have been specifically linked to human-inherited pain syndromes.[2,6] Each sodium channel isoform has a similar basic structure with differing amino acid sequences that impart differing kinetics and voltage-dependent properties[4,6] (Table 2).

Most neurons exhibit multiple sodium channel isoforms. The pattern of sodium channel isoform expression is directly induced by the neuron's particular pattern of gene transcription. Under certain circumstances, the gene transcription pattern may be altered such that particular isoforms would predominate. For example, in rat models of nerve injury, Nav1.3 is upregulated; Nav1.8 and Nav1.9 are significantly downregulated in the injured nerve whereas Nav1.1, Nav1.6, and Nav1.7 are reduced in the DRG.[6] However, in human nerve ligation that results in neuroma formation, there is an upregulation of Nav1.7 and Nav1.8 channels.[4] Chronic compression injury, on the contrary, induces a shift in the firing threshold of the neuron toward hyperpolarization without a specific pattern of gene upregulation or downregulation

Table 1 Ion Channels Associated With Pain Signaling

Gene	Channel	Location	TTX	Channel Attributes
SCN1A	Nav1.1	CNS/DRG	S	–
SCN2A	Nav1.2	CNS	S	–
SCN3A	Nav1.3	CNS/DRG*/SN	S	Rapid repriming, persistent current, amplifies small depolarizing inputs, produces large ramp current
SCN4A	Nav1.4	Skeletal muscle	–	–
SCN5A	Nav1.5	Cardiac muscle	R	–
SCN8A	Nav1.6	CNS/DRG/PN	–	–
SCN9A	Nav1.7	DRG/SN/PN/TG	S	Slow repriming, amplifies small depolarizing inputs, produces large ramp current
SCN10A	Nav1.8	DRG/TG	R	Rapid repriming, depolarized voltage dependence for activation & reactivation
SCN11A	Nav1.9	DRG/TG	R	Hyperpolarized voltage dependency of activation, slow activation, very slow inactivation, amplifies and prolongs small depolarizing inputs
TRPA1	TRP1	DRG/PN	–	–

CNS, central nervous system; PN, peripheral nerves; S, sensitive; SN, sympathetic nerves; TG-trigeminal nerve ganglia; TTX, response to tetrodotoxin (TTX); R, resistant.

*Upregulated in DRG after injury.