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Mini-review

Painful peripheral neuropathy and sodium channel mutations

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HIGHLIGHTS

- Mutations in voltage-gated sodium channels are associated with several pain syndromes.
- $Na_V1.7$–$Na_V1.9$ mutations can underlie painful peripheral neuropathy.
- Mutations of $Na_V1.7$–$Na_V1.9$ can result in dorsal root ganglion hyperexcitability.
- Sodium channel mutations appear to contribute to axonal degeneration.
- The finding of sodium channel mutations offers possibilities for targeted treatment.

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ABSTRACT

Peripheral neuropathy can lead to neuropathic pain in a subset of patients. Painful peripheral neuropathy is a debilitating disorder, reflected by a reduced quality of life. Therapeutic strategies are limited and often disappointing, as in most cases targeted treatment is not available. Elucidating pathogenetic factors for pain might provide a target for optimal treatment. Voltage-gated sodium channels $Na_V1.7$–$Na_V1.9$ are expressed in the small-diameter dorsal root ganglion neurons and their axons. By a targeted gene approach, missense gain-of-function mutations of $Na_V1.7$–$Na_V1.9$ have been demonstrated in painful peripheral neuropathy. Functional analyses have shown that these mutations produce a spectrum of pro-excitatory changes in channel biophysics, with the shared outcome at the cellular level of dorsal root ganglion hyperexcitability. Reduced neurite outgrowth may be another consequence of sodium channel mutations, and possible therapeutic strategies include blockade of sodium channels or block of reverse operation of the sodium–calcium exchanger. Increased understanding of the pathophysiology of painful peripheral neuropathy offers new targets that may provide a basis for more effective treatment.

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1. Painful peripheral neuropathy

Peripheral neuropathy is a general term indicating a disorder of the peripheral nervous system. In polyneuropathy multiple peripheral nerves are involved. Although polyneuropathy is a subtype of peripheral neuropathy, frequently both terms are used interchangeably. Depending on the affected nerve types, the condition is characterized by abnormal primary sensory modalities (neuropathic pain, abnormal proprioception, touch-, temperature- and vibration-sense), motor system impairment (muscle weakness and atrophy), depressed or absent muscle tendon reflexes, and/or autonomic dysfunction [1,2]. Various disorders are associated with polyneuropathy and sometimes result in specific clinical features and abnormalities [2]. In painful small-fiber neuropathies, the thin myelinated Aδ-fibers and unmyelinated C-fibers are predominantly damaged [2,3]. These small nerve fibers arise in the skin where they serve for the detection of cold, heat and, as nociceptors, for detection of painful stimuli [4–6]. In addition, they fulfill an efferent function as part of the peripheral autonomic nervous system [3,7]. Generally, nociceptors are electrically silent; after activation by noxious stimuli an action potential is initiated and transported via peripheral axons to cell bodies located in the trigeminal- and dorsal-root ganglia (DRG) alongside the medulla and spinal column. Via central axons the signal is transmitted onward to synapse on second order neurons in the central nervous system [4,6]. Animal models and human studies have shown that nerve damage, such as in painful peripheral neuropathy, can result in pathologic sensitization and ectopic impulse generation in primary afferent nociceptors with subsequent secondary changes in central processing [8]. However, not all patients with peripheral neuropathy and a similar underlying cause develop pain. Therefore, it is likely that additional factors play a role in the pathogenesis of painful peripheral neuropathy. Voltage-gated sodium-, potassium- and calcium-channels, transient receptor potential (TRP) channels and acid-sensing ion channels (ASIC) all contribute to the regulation of nociceptor excitability [4,6,9–11]. Dysregulated expression of these channels can cause neuronal hyperexcitability and may result in a clinical picture with hypersensibility and allodynia. Channel dysfunction due to mutations in their encoding genes may cause a hyperexcitable neuronal state, and various human pain disorders have been attributed to channelopathies [12–19]. Recently, painful peripheral neuropathy has been linked to three different types of voltage-gated sodium channel (VGSC) mutations [20–22]. Studies relating peripheral neuropathy to sodium channelopathies will be discussed here, with a focus on the effect of the mutations on sodium channel gating.

2. Voltage-gated sodium channels

The kinetics of VGSCs were first described more than half a century ago [23], and the detailed mechanisms of the kinetics and gating of VGSCs are being increasingly clarified. In mammals, VGSCs are responsible for the generation and conduction of action potentials in various excitable cells, including cardiac myocytes, skeletal muscle cells and neurons in the central and peripheral nervous system [24,25]. In response to membrane potential changes, the channel passes through states of activation, deactivation and inactivation. Abnormal VGSC functioning can result in disorders that manifest with cardiac arrhythmias, disturbed skeletal muscle contraction or relaxation, epilepsy, migraine or neuropathic pain.

VGSCs are integral membrane polypeptides, which consist of a large α-subunit, serving as a voltage sensor, and one or more smaller auxiliary β-subunits, responsible for modulation of the gating properties and for anchoring in the plasma membrane [24,26]. The α-subunit is constructed of four homologous domains (DI–IV), each composed of six transmembrane segments (S1–S6) (Fig. 1). The first four transmembrane segments form the voltage-sensing domain of the channel, followed by the pore domain, consisting of segments 5 and 6. An extracellular linker (P-loop) connects S5 and S6 [27]. Amino acid residues located within the P-loops provide the ion-selectivity [28]. The positive charged S4 segment is involved in the activation and deactivation process. In response to a depolarizing stimulus, membrane depolarization triggers the S4 segment to move outward, resulting in opening the pore. At the end of depolarization the S4 segment returns to the resting position and the channel transits to the closed state [26,27,29].

There are two mechanisms of active channel inactivation. Within a few milliseconds after depolarization, an intracellular loop between domain III and IV constructed of four amino acids, inactivates the channel by binding to the intracellular side of the channel as a hinged lid. This process is called fast inactivation [26,30,31]. The mechanism of slow inactivation is less clear. It follows after prolonged or repetitive depolarization and appears to be related with rearrangement of the channel. Again, the S4 segment in domain IV seems to play a role [32]. Also DIIS5–S6 and DIIS6 may influence the channel configuration [26,31]. After inactivation, the channel has to refold and is temporarily refractory. Recovery from this refractory state is called repriming [33].

In humans, nine distinct α-subunit isoforms have been identified: $Na_V1.1$–$Na_V1.9$, encoded respectively, by genes *SCN1A*–*SCN5A* and *SCN8A*–*SCN11A*. The nine channel isoforms differ in terms of kinetics and voltage dependence and in sensitivity to the sodium-channel pore blocker tetrodotoxin (TTX) [24]. In DRG neurons, trigeminal neurons and their small diameter peripheral axons, $Na_V1.7$–$Na_V1.9$ are preferentially expressed. These channels are involved in normal and pathological pain [34]. $Na_V1.6$ is expressed both in the central and peripheral nervous system. The channel has been demonstrated in large- and small-size DRG neurons, but also in the nodes of Ranvier of small myelinated sensory axons and in unmyelinated C-fibers [35–37]. In addition, $Na_V1.3$ seems to be relevant in the peripheral sensory system. Initially, the channel was thought to be present only in embryonic DRG neurons, but in adults a re-expression of $Na_V1.3$ after axotomy has been demonstrated [38] and a role in neuropathic pain seems likely [39].

3. Voltage-gated sodium channel mutations in human pain disorders

Initially, VGSC mutations were identified in three rare human pain disorders [40]. The first disorder is primary erythromelalgia (IEM) [13]. Gain-of-function $Na_V1.7$ mutations, particularly characterized by enhanced channel activation, cause a clinical picture dominated by burning pain and red discoloration of the extremities, aggravated by warmth and exercise. Second, paroxysmal extreme pain disorder (PEPD) is an autosomal-dominant condition leading to episodic perirectal, periorbital and perimandibular pain. PEPD is caused by gain-of-function $Na_V1.7$ mutations that mostly result in impaired fast-inactivation [14].

In a third disorder, congenital channelopathy-associated insensitivity to pain (CIP), patients are completely indifferent for pain.