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Pain

Mutations in the sodium channel $Na_v1.7$ underlie inherited erythromelalgia

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Mutations in sodium channel $Na_v1.7$, which is preferentially expressed within dorsal root ganglion and sympathetic ganglion neurons, underlie inherited erythromelalgia (IEM). IEM is characterized by severe pain in the extremities evoked by mild thermal stimuli. Functional studies have demonstrated altered biophysical properties of mutant channels, which decrease the threshold for single action potential and increase high-frequency firing in DRG neurons. IEM may be a model disease that holds lessons for other painful conditions.

Introduction

SCN9A-related inherited erythromelalgia (also known as erythermalgia; IEM) is a rare, autosomal dominant disorder that until recently was of enigmatic etiology [1]. IEM is characterized by recurrent and symmetric attacks of intense burning pain, and redness and warmth in distal extremities, which are triggered by mild exercise or warm temperatures [2,3]. Life-long symptoms of IEM usually start in childhood [3] but can have onset in adulthood [4] and can vary among members of the same family [2,5]. Similar symptoms have been described in association with certain vascular diseases or as a reaction to medications [3]. Mutations in sodium channel $Na_v1.7$ (GenBank accession no. Q15858) have now been identified in SIMPLEX and FAMILIAL CASES (see Glossary) of IEM [1]. Treatment has been empirical and is often ineffective or only partially effective. The elucidation of sodium CHANNELOPATHY (see Glossary) in IEM is promising for the development of better treatments, which might be applicable to other painful neuropathies because $Na_v1.7$ plays a role in acquired inflammatory pain [6–8].

Genetic basis of IEM

Investigation of a large kindred established IEM as autosomal dominant [2] and subsequently localized the disease locus to chromosome 2 (2q31-32) [9], where a cluster of voltage-gated sodium channel genes including SCN9A, the gene that encodes $Na_v1.7$, are known to exist. Initially, mutations in SCN9A were described in two Chinese families with IEM [10]. To date, seven mutations in transmembrane segments and cytoplasmic linkers of the channel have been identified in simplex and familial cases of IEM in different ethnic groups (Fig. 1); the contribution of substitution of proline 610 by threonine (P610T) and arginine 1150 by tryptophan (R1150W) to IEM is not clear at this time. PENETRANCE

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Glossary

Channelopathy: alteration in properties of channels underlying pathological conditions.
Closed-state inactivation: transition of the channel from closed to inactive state without passing through the open state, which usually occurs following the application of a weak stimulus.
Deactivation: transition of channel from the open state to closed state without passing into an inactive state.
Familial cases: inheritance of mutation across multiple generations within the same family.
Fast-inactivation peptide: the tetrapeptide isoleucine-phenylalanine-methionine-threonine (IFMT) in L3, which blocks the inner mouth of the channel to stop the inward flow of sodium ions and inactivates the channel within milliseconds of channel opening.
Nociceptive neurons: pain-sensing neurons, which require a high stimulus threshold to fire action potentials.
Overshooting action potential: response of neurons to suprathreshold stimulation by firing an all-or-none action potential, which peaks at a voltage more positive than 0 mV.
Penetrance: percentage of patients carrying a mutant allele and showing a mutant phenotype.
Polymorphic sites: the presence in a population of more than one residue at a single site.
Ramp current: inward sodium current in response to the application of a slow depolarizing stimulus in the shape of a ramp.
Recovery from inactivation (also known as repriming): series of conformational changes in the channel following inactivation, which lead to the closed but available state. The channel is refractory to depolarizations during this period.
Simplex cases: appearance of mutation in an individual whose parents do not carry the mutation. Simplex cases are also referred to as sporadic cases.
Slow inactivation: a state of inactivation of the channel, which lasts for seconds following a prolonged depolarizing stimulus; it is distinct from fast inactivation which is caused by blocking of the channel pore by the IFMT fast-inactivation particle.
Tetrodotoxin (TTX): a small molecule neurotoxin which binds to the outer vestibule of most voltage-gated sodium channels from neurons and skeletal muscle thus blocking the inward sodium current. Sensitive channels are blocked by nanomolar (nM) concentration of TTX and are referred to as TTX-S; resistant channels require micromolar (μM) concentrations of TTX for blockage and are referred to as TTX-R.
Threshold channel: sodium channel which responds to small stimuli below the threshold for an all-or-none action potential threshold currents amplify the response to small depolarizations and recruit different types of sodium channels to fire the all-or-none action potential.
Transcriptional dysregulation: increase or decrease in the levels of mRNA due to altered transcription.
TRPV channels: transient receptor potential, Vanilloid subfamily, which are thermal receptors gated by temperature, and by ligands, which are specific for different members of this subfamily.
Window current: persistent current within a voltage-range that is defined by the overlap in graphs of the Boltzmann's fits of voltage-dependent activation and steady-state inactivation of a particular channel.

(see Glossary) of the identified mutations appears to be complete [5,10–13].

Unlike familial IEM where the mutation has been shown to segregate with the disease across multiple generations, simplex cases may not appear compelling because the substitution appears *de novo* in a patient with asymptomatic parents. However, the causative potential of the L858F mutation in a simplex case from China [13] has been validated by its presence in a multigeneration family from Canada with IEM [12]; another simplex mutation (I848T) from another Chinese patient [10] has been found in a multigeneration family from France [12]. The fact that seven mutations have been identified in nine families [5,10–13] suggests that new mutations are likely to be identified in new cases of IEM, thus increasing the repertoire of $Na_v1.7$ mutations to be studied and raising the possibility of correlating genotype and phenotype.

So far, all IEM patients with known mutations have had early onset of symptoms (as early as 1–2 years of age and generally before the age of 10 years). However, a case of familial adult-onset IEM has recently been described, and $Na_v1.7$ was excluded as the causative factor [4]. Thus, it is possible that mutations in other target genes including other peripherally expressed voltage-gated sodium channels, $Na_v1.8$ and $Na_v1.9$, might cause IEM.

Several sporadic adult-onset erythromelalgia cases have been reported that cannot be attributed to underlying vascular disorders or to side effects of medications. The adult onset of symptoms in these cases suggests that they might be caused by mutations less penetrant than those that have been identified in IEM. So far, it has been difficult to ascertain if the multiple POLYMORPHIC SITES (see Glossary) in $Na_v1.7$, which have been reported in genomic databases are benign substitutions or less penetrant causative mutations because we lack clinical information about the donor subjects. Functional analyses of channels carrying these polymorphic sites in native neurons should clarify the putative mutagenic potential of these substitutions.

Voltage-gated sodium channel $Na_v1.7$

Nine sodium channels ($Na_v1.1$–1.9) have been identified in mammalian cells, with different expression patterns and with distinct electrophysiological and pharmacological characteristics [14]. Thus, central and peripheral nervous systems (CNS and PNS, respectively), where different combinations of these channels are expressed, are endowed with specific electrogenic characteristics. TRANSCRIPTIONAL DYSREGULATION (see Glossary) of sodium channels, which alters the complement of channels under pathological conditions can lead to neuronal hyperexcitability associated with acquired neuropathic pain [15].

$Na_v1.7$ sodium channels are preferentially expressed within dorsal root ganglia (DRG) neurons and sympathetic ganglion neurons [16–18], and are not expressed at significant levels in the CNS [17]. Within DRG, $Na_v1.7$ has been identified in 85% of the NOCICEPTIVE NEURONS (see Glossary) [19]. Neurotrophic growth factor (NGF), which is upregulated by inflammation, regulates transcription levels of $Na_v1.7$ via