Erythromelalgia: a hereditary pain syndrome enters the molecular era.

Stephen G. Waxman, MD, PhD 1 2 3 *, Sulayman D. Dib-Hajj, PhD 1 2 3
1Department of Neurology, Yale University School of Medicine, New Haven
2Center for Neuroscience and Regeneration Research, Yale University School of medicine, New Haven
3Rehabilitation Research Center, VA Connecticut Healthcare System, West Haven, CT

Published in The Annals of Neurology, June 2005

email: Stephen G. Waxman (stephen.waxman@yale.edu)

*Correspondence to Stephen G. Waxman, Department of Neurology, LCI 707, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

Funded by: Medical Research Service and Rehabilitation Research Service, Department of Veterans Affairs

National Multiple Sclerosis Society; Grant Number: RG 1912

The Erythromelalgia Association

ABSTRACT

In contrast with acquired pain syndromes, molecular substrates for hereditary pain disorders have been poorly understood. Familial erythromelalgia (Weir Mitchell's disease), also known as primary erythermalgia, is an autosomal dominant disorder characterized by burning pain in the extremities in response to warm stimuli or moderate exercise. The cause of this disorder has been enigmatic, and treatment has been empirical and not very effective. Recent studies, however, have shown that familial erythromelalgia is a channelopathy caused by mutations in the gene encoding the Nav1.7 sodium channel which lead to altered channel function. Selective expression of Nav1.7 within dorsal root ganglion neurons including nociceptors (in which this channel is targeted to sensory terminals, close to impulse trigger zones) and within sympathetic ganglion neurons explains why patients experience pain but do not suffer from seizures or other manifestations of altered excitability within central nervous system neurons. Erythromelalgia is the first human disorder in which it has been possible to associate an ion channel mutation with chronic neuropathic pain. Identification of mutations within a peripheral neuron-specific sodium channel suggests the possibility of rational therapies that target the affected channel. Moreover, because some other pain syndromes, including acquired disorders, involve altered sodium channel function, erythromelalgia may emerge

as a model disease that holds more general lessons about the molecular neurobiology of chronic pain. Ann Neurol 2005;57:785-788

ARTICLE TEXT

Chronic pain is often refractory to treatment and represents a major medical challenge. Research over the past decade has yielded important lessons about the molecular basis for acquired neuropathic and inflammatory pain,[1-3] but less is known about the molecular basis for inherited painful syndromes. Erythromelalgia was described and named (erythros = redness; melos = extremity; algos = pain) by the neurologist S. Weir Mitchell in 1878.[4] Sometimes termed erythermalgia, its characteristics include intermittent burning pain in the distal extremities, especially the hands and feet, in response to warm stimuli or exercise.[5] Primary and secondary forms have been described (the latter associated with myeloproliferative and collagen vascular disorders).[6] Primary erythromelalgia is often familial and is inherited in an autosomal dominant manner.[7][8] Although a neuropathic cause has been proposed,[9-11] a primary vasculopathy affecting skin perfusion or a disorder of cellular metabolism in affected tissues[10] also have been championed, and many patients with erythromelalgia have sought treatment from, and been followed up by, dermatologists or vascular medicine or surgery specialists.

Recently, it has become apparent that primary erythromelalgia, at least in some families, is caused by a molecular abnormality in neurons and is a member of the group of disorders resulting from mutations in voltage-gated ion channels, the hereditary channelopathies, which are known to cause epilepsy, periodic paralysis, and cardiac arrhythmias (reviews have been published[12-14]).

Three discoveries have contributed to elucidation of the molecular basis for erythromelalgia. Linkage analysis established that a primary erythromelalgia-susceptibility gene is located on chromosome 2q31-32.[7] More recently, two mutations within this locus leading to single amino acid substitutions in SCN9A, the gene for the human Nav1.7 sodium channel (Fig, A), were reported from patients with familial erythromelalgia.[15] Functional analysis using patch clamp recording showed that these Nav1.7 mutations cause a hyperpolarizing shift in activation of the channel and a slowing of deactivation which are accompanied by an enhanced response to small depolarizing stimuli (see Fig, B), changes that should confer hyperexcitability on cells which express the mutant channels.[16] In addition, the physiological observations suggest that activity of the mutant Nav1.7 channels close to resting potential may depolarize the neuronal cell membrane even when not stimulated, bringing it closer to threshold for activation of other sodium channels that contribute to the upstroke of the action potential within these cells.[16] Interestingly, one of the Nav1.7 mutations in erythromelalgia (I848T) is exactly orthologous to the I693T mutation in the Nav1.4 muscle sodium channel in hyperkalemic periodic paralysis,[13] and the mutations in both channels produce similar biophysical abnormalities.

Schematic showing the secondary structure of voltage-gated sodium channels, which consist of 24 membrane-spanning sequences organized into four domains. Nav1.7 is

unique in being selectively expressed within dorsal root ganglia neurons and their sensory terminals, and within sympathetic ganglia neurons, where it controls excitability by amplifying small depolarizing inputs. Two mutations, which produce single amino acid substitutions at the sites shown in Nav1.7, have been found in two different families with erythromelalgia. As shown in the aligned sequences below the schematic channel, each of the two mutations (Nav1.7I848T and Nav1.7L858H) changes the identity of a single amino acid residue which is invariant in all known sodium channels. (B) Enhanced response of mutant Nav1.7 channels to small stimuli. Note the larger response of mutant (I848T; L858H) Nav1.7 channels to a slow (500-millisecond duration) depolarizing ramp stimulus from -100 to 0mV, compared with wild-type hNav1.7 channels (Fig. B reprinted with permission from the Society for Neuroscience © 2004, from Cummins and colleagues).[16]

The physiological abnormalities in the mutant Nav1.7 channels are especially notable in the context of two earlier findings which had demonstrated a unique distribution and function of Nav1.7 within the nervous system. First, Nav1.7 channels are not globally present within all neurons but, on the contrary, are selectively expressed (as part of an ion channel repertoire that includes several sodium channel isoforms) within peripheral sensory neurons in dorsal root ganglia (DRG) and in sympathetic ganglia.[17][18] The level of expression of Nav1.7 is especially high in small-diameter DRG neurons which include nociceptors.[19][20] Second, a pivotal role of Nav1.7 channels in signaling by these neurons arises from the ability of these channels to respond to small, slow stimuli such as generator potentials, by opening and producing their own depolarization, thus amplifying weak signals, to recruit other sodium channels to produce an action potential.[21][22] Consistent with a role of Nav1.7 in amplifying generator potentials, this channel is targeted to the distal neurites of DRG neurons, close to impulse trigger zones.[18]

These Nav1.7 mutations would be expected to increase the excitability of peripheral sensory neurons that include nociceptors and sympathetic ganglion neurons. The gain-of-function changes in the properties of the channel are consistent with the dominant mode of inheritance of erythromelalgia. The absence of Nav1.7 channels within central neurons, moreover, explains why patients with erythromelalgia experience peripheral pain but do not suffer from seizures or other manifestations of hyperexcitability of neurons within the central nervous system.

Treatment of erythromelalgia has been empirical and largely unsuccessful. Aspirin, nonsteroidal antiinflammatory drugs, vasodilators, vasoconstrictors, antihistamines, capsaicin, adrenergic blockers, antimitotic agents, calcium channel blockers, phenytoin, carbamazepine, plasma exchange, sympathetic block, and many other therapeutic approaches have been tried, usually without success or with inconsistent or only partial success.[10] More drastic attempts at treatment have included bilateral sympathectomy.[23] Interestingly, anecdotal reports have described pain reduction in patients with erythromelalgia who were treated with two sodium channel blockers, lidocaine and mexilitine,[24][25] and a study on four family members with erythromelalgia reported relief for as long as 2 years with oral mexilitine.[26] A more

definitive evaluation of these and related medications is clearly needed. Identification of Nav1.7 as a major molecular player in erythromelalgia raises the exciting possibility of rational treatment, either with existing sodium channel blocking drugs (which are relatively nonselective) or possibly with an isoform-specific blocker that targets Nav1.7.

Recent advances in the understanding of erythromelalgia open new opportunities and challenges. Spontaneously occurring rodent models of chronic pain have not been available (in contrast with studies of epilepsy in which mouse mutants have been recognized and have provided important insights[27]), possibly because of the difficult challenges of recognizing and quantitating spontaneous pain in subhuman species, but it now may be possible to create a transgenic model. Importantly, thresholds for acute and inflammatory pain are elevated in knockout mice lacking Nav1.7[28], pointing to a role for Nav1.7 in rendering sensory neurons hyperexcitable in some acquired pain syndromes. Also suggesting a role of Nav1.7 in inflammatory pain, experimentally induced inflammation within the peripheral projection fields of DRG neurons triggers upregulated gene transcription that results in increased expression of Nav1.7 channels and a concomitant increase in the amplitude of the tetrodoxin-sensitive sodium current (which includes the current produced by Nav1.7 channels) within these cells.[29] Thus, erythromelalgia may be able to teach us about the pathobiology of some acquired pain syndromes.

By analogy to other sodium channelopathies in which different mutations of a single gene can produce the disease in different families, for example, muscular disorders,[13] cardiac arrhythmias,[12] and epilepsy,[30] it is very likely that additional mutations in SCN9A will be identified in familial erythromelalgia. Additional mutations in Nav1.7, when identified, may hold lessons about the roles of various regions of the channel in endowing the Nav1.7 channel with its unique physiological characteristics. It will be informative, when different mutations are reported, to see whether they endow families with subtly different phenotypes. It is also possible that mutations in other sodium channels that are selectively expressed in DRG neurons, such as Nav1.8[31][32] or Nav1.9,[33] may be identified in erythromelalgia. In addition, it is possible that mutations of other types of channels, for example, potassium channels[34][35] or calcium channels,[36-38] which can contribute to DRG neuron hyperexcitability underlying acquired neuropathic pain, may be found in some cases of primary erythromelalgia. Identification of these mutations is important as a prelude to selective (possibly isoform-selective) targeting of ion channels with medications for treatment of this disorder. Carefully designed clinical studies testing the efficacy of existing sodium channel blockers are also indicated.

Now that erythromelalgia has entered the molecular era, there will almost certainly be rapid progress in our understanding of this disorder. Antenatal diagnosis of erythromelalgia mutations may soon, at least in principle, be feasible. We hope that effective treatments will become available for erythromelalgia as its molecular basis is even better understood. However, in addition, erythromelalgia may serve as an important model disease. As the first inherited painful neuropathy with a well-defined molecular

basis, it will probably provide lessons that will help us to understand other hereditary and acquired pain syndromes.

Acknowledgements

This work was supported by the Medical Research Service and Rehabilitation Research Service, Department of Veterans Affairs and by grants from the National Multiple Sclerosis Society (RG 1912, S.G.W.)and the Erythromelalgia Association. The Center for Neuroscience and Regeneration Research is a Collaboration of the Paralyzed Veterans of America and the United Spinal Association with Yale University.

REFERENCES

1 Lewin GR, Lu Y, Park TJ. A plethora of painful molecules. Curr Opin Neurobiol 2004; 14: 443-449. Links

2 Black JA, Cummins TR, Dib-Hajj SD, Waxman SG. Sodium channels and the molecular basis for pain. In: Malemberg AB , Chaplan SR , eds. Mechanisms and mediators of neuropathic pain. Basel, Switzerland: Birkhauser Verlag, 2002: 23-50.

3 Wood JN, Waxman SG. New molecular targets for the treatment of neuropathic pain. In: Waxman SG , ed. from neuroscience to neurology: neuroscience, molecular medicine and the therapeutic transformation of neurology. Amsterdam: Elsevier Academic Press. 2005: 339-355.

4 Mitchell SW. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. Am J Med Sci 1878; 76. Links

5 van Genderen PJ, Michiels JJ, Drenth JP. Hereditary erythermalgia and acquired erythromelalgia. Am J Med Genet 1993; 45: 530-532. Links

6 Drenth JP, Michiels JJ. Erythromelalgia and erythermalgia: diagnostic differentiation. Int J Dermatol 1994; 33: 393-397. Links

7 Drenth JP, Finley WH, Breedveld GJ, et al. The primary erythermalgia-susceptibility gene is located on chromosome 2q31-32. Am J Hum Genet 2001; 68: 1277-1282. Links

8 Finley WH, Lindsey JR Jr, Fine JD, et al. Autosomal dominant erythromelalgia. Am J Med Genet 1992; 42: 310-315. Links

9 Layzer RB. Hot feet: erythromelalgia and related disorders. J Child Neurol 2001; 16: 199-202. Links

10 Davis MD, Sandroni P, Rooke TW, Low PA. Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia. Arch Dermatol 2003; 139: 1337-1343. Links

11 Orstavik K, Mork C, Kvernebo K, Jorum E. Pain in primary erythromelalgia - a neuropathic component? Pain 2004; 110: 531-538. Links

12 Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell 2001; 104: 569-580. Links

13 Cannon SC. An expanding view for the molecular basis of familial periodic paralysis. Neuromuscul Disord 2002; 12: 533-543. Links

14 Kullmann DM, Hanna MG. Neurological disorders caused by inherited ion-channel mutations. Lancet Neurol 2002; 1: 157-166. Links

15 Yang Y, Wang Y, Li S, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet 2004; 41: 171-174. Links

16 Cummins TR, Dib-Hajj SD, Waxman SG. Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. J Neurosci 2004; 24: 8232-8236. Links
17 Sangameswaran L, Fish LM, Koch BD, et al. A novel tetrodotoxin-sensitive, voltage-gated sodium channel expressed in rat and human dorsal root ganglia. J Biol Chem 1997; 272: 14805-14809. Links
18 Toledo-Aral JJ, Moss BL, He ZJ, et al. Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons. Proc Natl Acad Sci USA 1997; 94: 1527-1532. Links
19 Black JA, Dib-Hajj S, McNabola K, et al. Spinal sensory neurons express multiple sodium channel alpha-subunit mRNAs. Mol Brain Res 1996; 43: 117-131. Links
20 Djouhri L, Newton R, Levinson SR, et al. Sensory and electrophysiological properties of guinea-pig sensory neurones expressing Na(v)1.7 (PN1) Na(+) channel alpha subunit protein. J Physiol 2003; 546: 565-576. Links
21 Cummins TR, Howe JR, Waxman SG. Slow closed-state inactivation: a novel mechanism underlying ramp currents in cells expressing the hNE/PN1 sodium channel. J Neurosci 1998; 18: 9607-9619. Links
22 Herzog RI, Cummins TR, Ghassemi F, et al. Distinct repriming and closed-state inactivation kinetics of Nav1.6 and Nav1.7 sodium channels in mouse spinal sensory neurons. J Physiol 2003; 551: 741-750. Links
23 Nakajima Y, Koizumi K, Hirata T, et al. Successful thoracoscopic sympathectomy for primary erythromelalgia in the upper extremities. Jpn J Thorac Cardiovasc Surg 2004; 52: 524-526. Links
24 Kuhnert SM, Phillips WJ, Davis MD. Lidocaine and mexiletine therapy for erythromelalgia. Arch Dermatol 1999; 135: 1447-1449. Links
25 Davis MD, Sandroni P. Lidocaine patch for pain of erythromelalgia. Arch Dermatol 2002; 138: 17-19. Links
26 Legroux-Crespel E, Sassolas B, Guillet G, et al. Treatment of familial erythermalgia with the association of lidocaine and mexiletine. Ann Dermatol Venereol 2003; 130: 429-433. Links
27 Felix R. Insights from mouse models of absence epilepsy into Ca2+ channel physiology and disease etiology. Cell Mol Neurobiol 2002; 22: 103-120. Links
28 Nassar MA, Stirling LC, Forlani G, et al. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. Proc Natl Acad Sci USA 2004; 101: 12706-12711. Links
29 Black JA, Liu S, Tanaka M, et al. Changes in the expression of tetrodotoxin-sensitive sodium channels within dorsal root ganglia neurons in inflammatory pain. Pain 2004; 108: 237-247. Links
30 Robinson R, Gardiner M. Molecular basis of Mendelian idiopathic epilepsies. Ann Med 2004; 36: 89-97. Links
31 Akopian AN, Sivilotti L, Wood JN. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. Nature 1996; 379: 257-262. Links
32 Sangameswaran L, Delgado SG, Fish LM, et al. Structure and function of a novel voltage-gated, tetrodoxtoxin-resistant sodium channel specific to sensory neurons. J Biol Chem 1996; 271: 5953-5956. Links
33 Dib-Hajj SD, Tyrrell L, Black JA, Waxman SG. NaN, a novel voltage-gated Na

channel, is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy. Proc Natl Acad Sci USA 1998; 95: 8963-8968. Links
34 Everill B, Cummins TR, Waxman SG, Kocsis JD. Sodium currents of large (Abeta-type) adult cutaneous afferent dorsal root ganglion neurons display rapid recovery from inactivation before and after axotomy. Neuroscience 2001; 106: 161-169. Links
35 Ishikawa K, Tanaka M, Black JA, Waxman SG. Changes in expression of voltage-gated potassium channels in dorsal root ganglion neurons following axotomy. Muscle Nerve 1999; 22: 502-507. Links
36 Todorovic SM, Jevtovic-Todorovic V, Meyenburg A, et al. Redox modulation of T-type calcium channels in rat peripheral nociceptors. Neuron 2001; 31: 75-85. Links
37 Luo ZD, Chaplan SR, Higuera ES, et al. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci 2001; 21: 1868-1875. Links
38 Abdulla FA, Smith PA. Axotomy- and autotomy-induced changes in Ca2+ and K+ channel currents of rat dorsal root ganglion neurons. J Neurophysiol 2001; 85: 644-658. Links