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ION CHANNELS

Extremes of excitability

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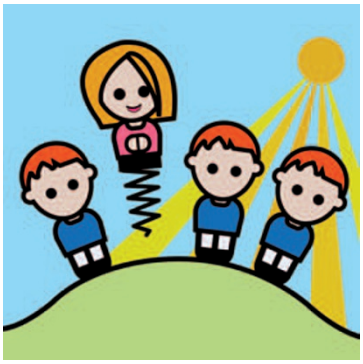

Mutations in ion channels, usually characterized as producing either hyperexcitability or hypoexcitability, are associated with various neurological disorders. Now, Stephen Waxman and colleagues report that the same mutation in the sodium channel Nav1.7 has opposing effects on excitability in dorsal root ganglion (DRG) neurons and sympathetic ganglion neurons.

Nav1.7 is expressed mainly in primary sensory neurons such as DRG neurons and sympathetic ganglion neurons such as superior cervical ganglion (SCG) neurons, each of which possesses a different suite of sodium channel isoforms. The Nav1.7 mutations characterized so far produce changes in channel physiology that augment the response of the channel to small stimuli, but the effects of cell type on these changes had not been assessed. Waxman and colleagues proposed that the same mutation might have different effects on excitability in different neurons, and that the ensemble of channels present in a cell might be an important determinant of these effects.

To test this hypothesis, the authors studied the functional effects of the Nav1.7 mutation L858H, which is associated with the neuropathic pain syndrome erythermalgia, in cultured DRG and SCG neurons. They showed that the mutation depolarized the resting membrane potential (by ~5 mV relative to wild-type Nav1.7) in both types of neuron. However, it led to opposite changes in the current threshold for firing a single action potential, which was decreased in DRG neurons but increased in SCG neurons. The firing frequency of neurons in response to prolonged stimulation was also altered in an opposing manner, being lower in DRG neurons but higher in SCG neurons.

Action potential generation in DRG neurons involves the sequential activation of Nav1.7 channels followed by Nav1.8 channels, which are relatively resistant to inactivation by depolarization. To determine the role of other sodium channel isoforms in the apparently disparate effects of Nav1.7 mutation, the authors looked for differences in the isoforms expressed by both types of neuron. Immunocytochemistry of cultured cells and adult rat neurons revealed the presence of Nav1.7 protein in both types of neuron, and the presence of Nav1.8 protein in DRG neurons, but not SCG neurons. Co-expression of Nav1.8 and Nav1.7/L858H in SCG neurons restored the action potential threshold and amplitude to near wild-type levels, despite the persistence of membrane depolarization.

These findings show that opposing functional effects can be induced by the same ion channel mutation, and provide a molecular basis for the sympathetic dysfunction observed in erythermalgia.

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ORIGINAL RESEARCH PAPER Rush, A. M. *et al.* A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc. Natl Acad. Sci. USA* **103**, 8245–8250 (2006)