

## SODIUM CHANNEL MUTATIONS IN GEFS<sup>+</sup> PRODUCE PERSISTENT INWARD CURRENT

### Molecular Basis of an Inherited Epilepsy

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*Neuron* 2002;34:877–884

Epilepsy is a common neurologic condition that reflects neuronal hyperexcitability arising from largely unknown cellular and molecular mechanisms. In generalized epilepsy with febrile seizures plus, an autosomal dominant epilepsy syndrome, mutations in three genes coding for voltage-gated sodium channel  $\alpha$  or  $\beta 1$  subunits (SCN1A, SCN2A, SCN1B) and one  $\gamma$ -aminobutyric acid (GABA)-receptor subunit gene (GABRG2) have been identified. Here we characterize the functional effects of three mutations in the human neuronal sodium channel  $\alpha$  subunit SCN1A by heterologous expression with its known accessory subunits,  $\beta 1$  and  $\beta 2$ , in cultured mammalian cells. SCN1A mutations alter channel inactivation, resulting in persistent inward sodium current. This gain-of-function abnormality will likely enhance excitability of neuronal membranes by causing prolonged membrane depolarization, a plausible underlying biophysical mechanism responsible for this inherited human epilepsy.

### COMMENTARY

Mutations in genes coding for voltage-gated ion channels and receptor-operated channels, commonly referred to as channelopathies, can result in some types of epilepsy. Generalized epilepsy with febrile seizures plus (GEFS<sup>+</sup>) is characterized by febrile seizures that persist beyond age 6 years, commonly followed by a variety of afebrile seizures such as generalized tonic-clonic, absence, myoclonic, or atonic seizures (1,2). Recently it was reported that patients with GEFS<sup>+</sup> also may develop partial seizures and temporal lobe epilepsy (3). GEFS<sup>+</sup> is inherited in an autosomal dominant fashion and is linked to mutations in genes coding for sodium channels and GABA<sub>A</sub> receptors.

The voltage-gated sodium channels in the adult mammalian brain typically consist of an  $\alpha$  subunit and associated  $\beta 1$  and  $\beta 2$  subunits. Ten different genes (SCN1A, SCN2A, etc) are known to code for the  $\alpha$  subunits. The  $\alpha$  subunit forms the ion-selective pore, inner pore, voltage sensor, inactivation gate, local anesthetic, and antiarrhythmic and anticonvulsant binding sites (4). It is a transmembrane protein that consists of four homologous domains (D I–IV), each with six transmembrane segments. The SCN1A and SCN2A gene mutations linked to GEFS<sup>+</sup> change conserved amino acids in the putative voltage-sensing fourth transmembrane segments in D II and D IV of the  $\alpha$  subunit (5).

Lossin et al. (6) examined the functional consequence of SCN1A mutations linked to GEFS<sup>+</sup> after cloning the human SCN1A gene. The biophysical behavior of human wild-type SCN1A coexpressed with human  $\beta 1$  and  $\beta 2$  subunits was compared with that of three GFS<sup>+</sup> mutants. The mutations altered inactivation of sodium channels such that a persistent, noninactivating current was evident. Sodium channels open in response to depolarization (activation), and after staying open for a brief period, they close despite persistent depolarization (inactivation). This study demonstrated that mutant sodium channels failed to close completely after opening in response to depolarization. This failure of channels to close completely is likely to cause persistent depolarization of neurons and increase seizure susceptibility. The GEFS<sup>+</sup> mutations lead to a gain of function (persistent sodium current), which also is seen in two other sodium channelopathies, hyperkalemic periodic paralysis and congenital long-QT syndrome.

Although this study clarifies the sodium-channel dysfunction associated with GEFS<sup>+</sup>, the sequence of events that leads to febrile seizures and later development of epilepsy in these patients remains unknown. The authors speculate that the mutant channels increase susceptibility to febrile seizures, which in turn lead to reorganization of neuronal circuits and recurrent afebrile seizures. There is some experimental evidence to support this hypothesis. A mutated mouse SCN2A gene that leads to gain of function and persistent sodium currents was introduced in mice by transgene technique (7). Transgenic mice carrying this mutation exhibit progressively worsening seizures that begin between ages 1 and 2 months. These mice demon-

strate several features of human temporal lobe epilepsy, seizures appear to originate in the hippocampus, there is progressive loss of CA3, CA1 pyramidal neurons, and hilar neurons and gliosis. Further studies with transgenic mice carrying the GEFS<sup>+</sup> mutations are likely to clarify the links between channel dysfunction and epileptic phenotype.

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## References

1. Abou-Khalil B, Ge Q, Desai R, Ryther R, Bazyk A, Bailey R, Haines JL, Sutcliffe JS, George AL Jr. Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation. *Neurology* 2001;57:2265–2272.
2. Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* 2000;26:13–25.
3. Kearney JA, Plummer NW, Smith MR, Kapur J, Cummins TR, Waxman SG, Goldin AL, Meisler MH. A gain-of-function mutation in the sodium channel gene *Scn2a* results in seizures and behavioral abnormalities. *Neuroscience* 2001;102:307–317.
4. Lossin C, Wang DW, Rhodes TH, Vanoye CG, George AL Jr. Molecular basis of an inherited epilepsy. *Neuron* 2002;34:877–884.
5. Meisler MH, Kearney J, Ottman R, Escayg A. Identification of epilepsy genes in human and mouse. *Annu Rev Genet* 2001;35:567–588.
6. Spanpanato J, Escayg A, Meisler MH, Goldin AL. Functional effects of two voltage-gated sodium channel mutations that cause generalized epilepsy with febrile seizures plus type 2. *J Neurosci* 2001;21:7481–7490.
7. Wallace RH, Wang DW, Singh R, Scheffer IE, George AL Jr, Phillips HA, Saar K, Reis A, Johnson EW, Sutherland GR, Berkovic SF, Mullen JC. Febrile seizures and generalized epilepsy associated with a mutation in the Na<sup>+</sup>-channel beta1 subunit gene *SCN1B*. *Nat Genet* 1998;19:366–370.