

PAIN WITHOUT GAIN (OF FUNCTION): SODIUM CHANNEL DYSFUNCTION IN EPILEPSY

Increased Neuronal Firing in Computer Simulations of Sodium Channel Mutations That Cause Generalized Epilepsy with Febrile Seizures Plus

Spampanato J, Aradi I, Soltesz I, Goldin AL

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Generalized epilepsy with febrile seizures plus (GEFS+) is an autosomal dominant familial syndrome with a complex seizure phenotype. It is caused by mutations in one of three voltage-gated sodium channel subunit genes (*SCN1B*, *SCN1A*, and *SCN2A*) and the γ -aminobutyric acid (GABA)_A receptor 2 subunit gene (*GABRG2*). The biophysical characterization of three mutations (T875M, W1204R, and R1648H) in *SCN1A*, the gene encoding the CNS voltage-gated sodium channel subunit Nav1.1, demonstrated a variety of functional effects. The T875M mutation enhanced slow inactivation, the W1204R mutation shifted the voltage dependence of activation and inactivation in the negative direction, and the R1648H mutation accelerated recovery from inactivation. To determine how these changes affect neuronal firing, we used the NEURON simulation software to design a computational model based on the experimentally determined properties of each GEFS+ mutant sodium channel and a delayed rectifier potassium channel. The model predicted that W1204R decreased the threshold, T875M increased the threshold, and R1648H did not affect the threshold for firing a single action potential. Despite the different effects on the threshold for firing a single action potential, all of the mutations resulted in an increased propensity to fire repetitive action potentials. In addition, each mutation was capable of driving repetitive firing in a mixed population of mutant and wild-type channels, consistent with the dominant nature of these mutations. These results suggest a common physiological mechanism for epileptogenesis resulting from sodium channel mutations that cause GEFS+.

Epilepsy-associated Dysfunction in the Voltage-gated Neuronal Sodium Channel *SCN1A*

Lossin C, Rhodes TH, Desai RR, Vanoye CG, Wang D, Carniciu S, Devinsky O, George AL Jr

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Mutations in *SCN1A*, the gene encoding the brain voltage-gated sodium channel 1 subunit (Nav1.1), are associated with at least two forms of epilepsy, generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). We examined the functional properties of four GEFS+ alleles and one SMEI allele by using whole-cell patch-clamp analysis of heterologously expressed recombinant human *SCN1A*. One previously reported GEFS+ mutation (I1656M) and an additional novel allele (R1657C), both affecting residues in a voltage-sensing S4 segment, exhibited a similar depolarizing shift in the voltage dependence of activation. Additionally, R1657C showed a 50% reduction in current density and accelerated recovery from slow inactivation. Unlike three other GEFS+ alleles that we recently characterized, neither R1657C nor I1656M gave rise to a persistent, noninactivating current. In contrast, two other GEFS+ mutations (A1685V and V1353L) and L986F, an SMEI-associated allele, exhibited complete loss of function. In conclusion, our data provide evidence for a wide spectrum of sodium channel dysfunction in familial epilepsy and demonstrate that both GEFS+ and SMEI can be associated with nonfunctional *SCN1A* alleles.

COMMENTARY

Sodium (Na⁺) channels carry inward depolarizing currents of propagated action potentials in mammalian neurons. Channel proteins are heterotrimers composed of single, large α subunits, which form the transmembrane pore and voltage-sensitive gates, and two smaller β subunits, which enhance channel surface expression and modulate gating properties.

Frequency or use-dependent block of neuronal Na⁺ channels is a prominent short-term effect of several commonly used antiepileptic drugs (AEDs; e.g., phenytoin, carbamazepine, valproate, and lamotrigine). Hyperexcitability disorders of cardiac and skeletal muscle, such as hyperkalemic periodic paralysis, paramyotonia congenita, and long QT syndrome, have been associated with Na⁺ channel mutations that result in increased, persistent Na⁺ currents (1). One might suppose, therefore, (a) that mutations in genes for neuronal Na⁺ channels would be strong candidates for Mendelian forms of epilepsy and (b) that the involved mutations would exhibit “gain of function” in the form of excessive or persistent channel activity.

Although Na⁺ channel–subunit mutations have been linked to epilepsy in a large number of pedigrees, the patterns of electrical activity exhibited by pathogenic neuronal channels have proved far more diverse than might have been initially predicted. The studies on *SCN1A* mutant channels reviewed here illustrate both the state of current knowledge and uncertainties remaining for future exploration. In earlier studies by Lossin et al., it was determined that *SCN1A* mutations from families with generalized epilepsy with febrile seizures plus (GEFS+) result in channels with increased, persistent sodium current (2). The same authors now report results of experiments with five additional *SCN1A* mutations: four from families with GEFS+ and one from a patient with severe myoclonic epilepsy of infancy (SMEI). The function of the mutant channels was studied by using patch-clamp electrophysiology techniques in transfected cell lines. Quite surprisingly, none of these mutations exhibits increases in persistent current. Instead, two of the GEFS+ mutants exhibited changes that might *reduce* sodium current, and the other three mutants produced nonfunctional Na⁺ channels. Although surprising, such dysfunctional channel heterogeneity was anticipated by earlier studies (3,4).

How could mutations that cause distinctive and, in some instances, opposing effects on Na⁺ channel biophysical properties result in similar epileptic phenotypes? With a computational model of a neuronal cell soma, Spampanato et al. suggest a common cellular mechanism to explain the neuronal hyperexcitability associated with *SCN1A* mutations. They report that although three biophysically distinctive mutations exert varied effects on gating and on the threshold for firing an individual action potential, all three mutations result in an *increased* propensity for repetitive firing. This model, admittedly a highly simplified one of a single region of the neuron (the soma), demonstrates the advisability of placing the mutant channels back in their subcellular, cellular, and neuronal network contexts to understand how channel gene mutations lead to epilepsy. Ultimately, additional clues will be provided by *in vivo* studies and patch-clamp recordings of neuronal Na⁺ currents from animals or mice with channel mutations.

by Edward C. Cooper, M.D., Ph.D.,
and Scott C. Baraban, Ph.D.

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