Interneuron Dysfunction in a New Mouse Model of SCN1A GEFS.

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Public Summary:
Advances in genome sequencing have identified over 1300 mutations in the SCN1A sodium channel gene that result in genetic epilepsies. However, it still remains unclear how most individual mutations within SCN1A result in seizures. A previous study has shown that the K1270T (KT) mutation, linked to genetic epilepsy with febrile seizure plus (GEFS+) in humans, causes heat-induced seizure activity associated with a temperature-dependent decrease in GABAergic neuron excitability in a Drosophila knock-in model. To examine the behavioral and cellular effects of this mutation in mammals, we introduced the equivalent KT mutation into the mouse (Mus musculus) Scn1a (Scn1a(KT)) gene using CRISPR/Cas9 and generated mutant lines in two widely used genetic backgrounds: C57BL/6NJ and 129X1/SvJ. In both backgrounds, mice homozygous for the KT mutation had spontaneous seizures and died by postnatal day (P)23. There was no difference in mortality of heterozygous KT mice compared with wild-type littermates up to six months old. Heterozygous mutants exhibited heat-induced seizures at approximately 42 degrees C, a temperature that did not induce seizures in wild-type littermates. In acute hippocampal slices at permissive temperatures, current-clamp recordings revealed a significantly depolarized shift in action potential threshold and reduced action potential amplitude in parvalbumin (PV)-expressing inhibitory CA1 interneurons in Scn1a(KT/+) mice. There was no change in the firing properties of excitatory CA1 pyramidal neurons. These results suggest that a constitutive decrease in inhibitory interneuron excitability contributes to the seizure phenotype in the mouse model.

Scientific Abstract:
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