Altered slow inactivation of sodium channels carrying an epilepsy mutation promotes depolarization block | Louisiane Lemaire

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Dravet syndrome is a developmental and epileptic encephalopathy (DEE) that typically begins in the first year of life. This complex pathology is characterized by drug-resistant seizures, various comorbidities such as cognitive delay, and a risk of early death. Most cases are due to mutations of NaV1.1, a voltage-gated sodium channel expressed in fast-spiking (FS) inhibitory neurons. The pathological mechanism in the initial stage of the disease involves impaired function of those neurons, leading to network hyperexcitability. However, the details remain unclear.

Mutations of NaV1.1 may result in non-functional channels or channels with altered gating properties. We focus on the less studied case of altered gating, by investigating how it impairs neuronal activity in the case of a specific mutation (A1783V). Using recordings in cell lines, Layer et al. (2021) showed that A1783V alters the voltage dependence of channel activation, as well as the voltage dependence and kinetics of slow inactivation. Slow inactivation is a mechanism distinct from the fast inactivation of sodium channels at each spike, developing much more slowly, during prolonged trains of depolarization. Implementing the three effects of the mutation in a conductance-based model, Layer et al. predict that altered activation has the largest impact on channel function, as it causes the most severe reduction in firing rate.

Using conductance-based models tailored to the dynamics of FS inhibitory neurons, we examine how the three alterations affect susceptibility to depolarization block, another firing deficit aside from frequency reduction. We look deeper into slow inactivation, exploiting the timescale difference with the rest of the system. We find that slow inactivation of mutant channels at lower voltage values than wild type channels favors depolarization block upon sustained stimulation. More precisely, shifting the steady-state voltage dependence of slow inactivation destroys the stable limit cycle of the full system corresponding to tonic spiking, and creates a stable equilibrium corresponding to depolarization block (Figure 1). The accelerated kinetics of slow inactivation in mutant channels hastens the transition from tonic spiking to depolarization block. These findings suggest that alterations of NaV1.1 slow inactivation should not be neglected as they might play an important pathological role, adding to the conclusions of Layer et al. on the consequences of altered NaV1.1 activation. We test our predictions with classical ramped electrophysiology protocols.