Exploring Polygenic Mechanisms of Pathogenesis and Treatment Resistance in Childhood Absence Epilepsy with a Multiscale Thalamocortical Model

Andrew T Knox1, Jeffrey Tenney1, Katherine Holland1, Tracy Glauser1, William W. Lytton2

1 Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital

Medical Center, Cincinnati, Ohio, USA and the University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

2 Departments of Neurology and Physiology & Pharmacology, SUNY Downstate Medical Center; Department Neurology, Kings County Hospital Center, Brooklyn, NY

Childhood Absence Epilepsy (CAE) is a genetic epilepsy syndrome with polygenic inheritance, with genes for GABA receptors and T-type calcium channels (TCC) contributing to the disorder. Previous studies have investigated the effects of genetic changes and medications on TCC function[[1](#_30j0zll)]. We hypothesized that changes in reticular nucleus TCCs and cortical excitability work in tandem to cause spike and wave oscillations. We used an established thalamocortical model[[2](#_1fob9te)] to explore how changes in channel function cause absence seizures.

On the molecular scale, the model was comprised of: TCC and other ion channels, synaptic receptors (AMPA, GABAA, GABAB); on the cellular scale: cortical pyramidal (PY), cortical inhibitory (IN), thalamic relay (TC) and thalamic reticular (RE) single compartment neurons; and on the network scale: a reduced cortical column and thalamic network. Neurons were implemented with Hodgkin-Huxley models of ion channels, including TCCs in RE neurons. We ran simulations for different combinations of 1) cortical GABAA conductance and RE TCC conductance, 2) cortical GABAA conductance and RE TCC inactivation time, and 3) cortical GABAA conductance and RE TCC steady state activation/inactivation shift. Decreasing cortical excitability (GABAA conductance) more than 75% or increasing RE TCC conductance more than 130% converted 8-10Hz spindle oscillations to a 3-5Hz spike and wave oscillation; smaller changes were required if both were changed in concert. In contrast, left shift in TCC steady state voltage activation/inactivation did not lead to spike and wave oscillations, whereas right shift reduced the network propensity for oscillations of any type. These simulations provide a window into mechanisms underlying polygenic inheritance in CAE, with increases in RE TCC conductance and inactivation time working in concert with decreased cortical GABAA conductance to change spindle oscillations to spike and wave discharges. Additionally, this model provides a possible unifying mechanism for the efficacy of medications commonly used in CAE, as well as mechanisms behind treatment failures. While the model is a vast simplification of the human thalamocortical network, it serves as a useful starting point for understanding the implications of ion channel electrophysiology in CAE, as well as a paradigm for exploring mechanisms underlying polygenic epilepsy.

**References:**

1. Glauser, T.A., et al., *Pharmacogenetics of Antiepileptic Drug Efficacy in Childhood Absence Epilepsy.* Ann Neurol, 2017.

2. Destexhe, A., *Spike-and-wave oscillations based on the properties of GABAB receptors.* J Neurosci, 1998. **18**(21): p. 9099-111.