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 Glauser2, William W. Lytton3.

1 Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA
2 Departments of Neurology and Physiology & Pharmacology, SUNY Downstate Medical Center, Department of Neurology, Kings County Hospital Center, Brooklyn, NY

Introduction

Childhood Absence Epilepsy (CAE) is the most common childhood epilepsy syndrome, and is clinically characterized by frequent, brief seizures with impairment of consciousness and generalized 3Hz spike and wave discharges on EEG. Ethosuximide, valproic acid, and lamotrigine are most commonly used to treat CAE, but there is significant variability in patient response to medication, with even the first line choice ethosuximide showing a 42% failure rate.

CAE exhibits polygenic inheritance, with genes for GABA receptors and T-type calcium channels (TCC) contributing to the disorder. Previous studies have used genetic testing techniques and patch-clamp electrophysiology to characterize the effects of genetic changes and medications on TCC function; however, studies have shown varied and sometimes contradictory effects, making it difficult to predict the clinical implications of electrophysiological changes.

A recent study by Glauser et al. analyzed electrophysiology of the PL450 TCC variant, which they showed linked to reduced GABA conductance, and reactivated, ethosuximide. These changes led to treatment failure. In doing so, we shed light on mechanisms that may underlie pathogenicity and medication effects of channel function in CAE.

Methods

The model spans three scales. The network scale is comprised of a simplified cortical column and thalamic network; the figure shows the arrangement of neurons (represented as dots) into pyramidal (PY) and inhibitory (IN) layers in the cortex, as well as reticular nucleus (RE) and thalamocortical (TC) layers in the thalamus, which are connected with AMPA, GABAα, and GABAβα synapses as shown. The neuron scale table lists the types of channels incorporated into single compartment neurons of the four different types. The molecular scale shows Hodgkin-Huxley functions used to represent each channel, which directly correspond to electrophysiology measurements.

Results

We began by running simulations for different combinations of 1) cortical GABAα conductance and RE TCC inactivation time, 2) cortical GABAα conductance and RE TCC steady state activation/inactivation shift, as these TCC parameters correspond directly to calcium channel electrophysiology. All oscillations following the stimulus could be characterized as one of three patterns: spindle oscillations (Fig 2A), spike and wave oscillations (Fig 2B), or transitional patterns.

An extensive search of this parameter space was conducted, with results shown in Fig 3. Decreasing cortical excitability (GABAα conductance) more than 75% or increasing RE TCC conductance more than 10% converted 3Hz spike 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, instead, it caused disorganized spontaneous bursting, decreasing network propensity for oscillations. Right shift also reduced the network’s propensity for oscillations of any type.

At a concentration of 3mM no significant change in conductance for either the wild type or the variant TCC. However, both Shift of Steady State Activation / Inactivation and the inactivation time constant (Tau) showed a statistically significant change. Applying the simulation results from Fig 3 suggest that change in Steady State Activation/inactivation will not convert seizures to spindle oscillations, while decreased inactivation time constant could change spike and wave oscillations to spindle oscillations. The region of spike and wave discharges predicted to be treated in the model is shown in Fig 5, and it is clearly larger for the wild type TCC channel than the variant TCC. This corresponds to the observation that individuals with the PL460 variant have a blunted response to ethosuximide.

Discussion

These results show useful guidelines for predicting clinical implications of changes in TCC electrophysiology. On a broader scale, this model sheds light on mechanisms behind pathogenicity and medication effects in CAE. Fig 5A highlights ways in which combinations of changes in TCC and GABAα channels may or may not lead to the common endpoint of CAE, illustrated by hypothetical individuals 1-4 compared to a baseline individual. Fig 5B illustrates how these individuals (5-7) may respond to different medications based on their underlying combination of channels.

Conclusion

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 GABAα 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 failure.

Although these simulations were used to study CAE in particular, a similar approach could be used to study other polygenic epilepsies in which several genes are implicated. An alternative (and perhaps more clinically pertinent) approach is to use a computer model to simulate a specific set of channel electrophysiology parameters, determined by an individual’s genetic profile. Computer simulations could then be used to determine whether that particular genetic profile is expected to cause epilepsy, and could also predict that individual’s response to different anti-epileptic drugs. These techniques would aid both the clinician in selecting optimal combinations anti-epileptic drugs for patients with refractory epilepsy, as well as researchers in the development of effective novel treatments.

References