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Increased Rate of Recovery from Inactivation in $Ca_V3.2$ T-type Calcium Channels Promotes Robust Neuronal Burst Firing During Oscillations in a Rat Absence Epilepsy Model

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The Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model displays a well characterized absence epilepsy phenotype. We previously described an arginine to proline missense mutation at position 1584 (R1584P) in the GAERS *Cacna1h* gene encoding the $Ca_V3.2$ T-type Ca^{2+} channel, which correlates strongly with seizure expression. In $Ca_V3.2$ channels exogenously expressed in HEK cells the mutation both increases the rate of recovery from inactivation and increases charge transference during high frequency bursts in a $Ca_V3.2$ splice variant–specific manner.

Neurons from the reticular thalamic nucleus (nRT) are thought to express mixed $Ca_V3.2$ / $Ca_V3.3$ T-type calcium currents and burst firing in these neurons is implicated in the propagation of spike-and-wave discharges within the thalamocortical network. Therefore, in order to examine the impact of the R1584P mutation on neuronal firing properties, we compared burst firing in nRT neurons using acute brain slices from GAERS vs non-epileptic control (NEC) rats. Under current clamp conditions repetitive bursting was induced by applying an oscillatory cosine wave of hyperpolarizing / depolarizing current. nRT neurons from GAERS demonstrated more robust multiple bursting, which attenuated to a lesser degree over time when compared with NECs. Furthermore, this difference was found to be frequency-dependent, since it was not observed at lower frequencies (<6Hz) in neonatal or adult nRT neurons, which reflects the frequency range of absence seizure spike-and-wave discharges. These findings describe the first ion channelopathy identified in GAERS with a functional effect on neuronal burst firing properties and the potential to contribute to the absence epilepsy phenotype. *Supported by the Canadian Institutes of Health Research.*