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Insights on the Role of Thalamocortical HCN Channels in Absence Epilepsy

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Review of David et al.

Absence epilepsy is the most common type of epilepsy in childhood (Glauser et al., 2010). It is characterized by sudden, transient loss of consciousness, behavioral arrest, and an EEG pattern dominated by spike-and-wave discharges (Crunelli and Leresche, 2002). Through studies performed on brain slices and anesthetized animals (Steriade et al., 1993; McCormick and Contreras, 2001; Timofeev and Steriade, 2004), as well as recent investigations of local circuits in awake animals (Makinson et al., 2017; Sorokin et al., 2017; McCafferty et al., 2018), many aspects of the basic mechanisms of absence epilepsy have been elucidated. This type of seizure emerges as a result of promptly generalizing, highly synchronous interaction among neurons within the thalamocortical loop. In these loops, cortical pyramidal cells excite thalamocortical (TC) cells of the relay nuclei and the nucleus reticularis thalami (NRT); this excitation drives NRT cells to periodically impose bursts of inhibition on TC cells, which in turn send synchronous excitatory feedback to cortex and NRT (Steriade et al., 1993; McCormick and Contreras, 2001). Selective optogenetic intervention at any point of the thalamocortical loop can reduce seizure activity (Berényi et al., 2012; Paz et al., 2013; Sorokin et al., 2017) and hyperexcitation at any point can result in absence-like seizures (Meeren et al., 2002; Makinson et al., 2017; Sorokin et al., 2017). Therefore, the relative contribution of the different structures to seizure activity still remains elusive (Blumenfeld, 2005).

Deficiencies in several ion channels and receptors have been identified as possible causes or contributors to absence epilepsy both in humans and in animal models (van Luijtelaar et al., 2000; Crunelli and Leresche, 2002; Blumenfeld, 2005; Reid et al., 2012), but contradictory results have complicated efforts to understand seizure activity. Some contradictions might be rooted in the fact that particular ion channels have different roles in seizure dynamics depending on which cells one examines. For example, Makinson et al. (2017) showed that the loss of a particular type of voltage-gated sodium channel, Scn8a, promotes seizures when deleted in reticular nucleus of the thalamus, but its deletion from cortical neurons inhibits seizures. Contradictions might also arise when comparing studies conducted in awake and anesthetized animal, because thalamic and cortical activity, as well as the susceptibility to seizures are highly brain-state-dependent (Steriade et al., 1993; McCormick and Bal, 1997). Together, these results show the necessity of cautious approaches, such as investigating particular ion channels in a spatially and temporally constrained manner in absence epilepsy.

David et al. (2018) addressed some of these challenges in a recent study. They investigated hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which, under normal circumstances, regulate neuronal excitability and shape network-level activity mostly by attenuating the effect of synaptic inputs on membrane potential. Importantly, in thalamus the current produced by HCN channels also contributes to burst firing (McCormick and Bal, 1997). Although HCN channels have been linked to epilepsy (Reid et al., 2012), their exact contribution remains to be elucidated. In epileptic mice HCN expression was decreased (Kase et al., 2012) and genetic deletion of HCN in mice caused absence epilepsy with increased thalamic burst activity (Ludwig et al., 2003), but in a genetic rat model of epilepsy, HCN channels were upregulated in the thalamus and that was accompanied with reduced burst firing (Cain et al., 2015).

To clarify the role of HCN channels in absence seizures, David et al. (2018) selectively blocked these channels in the ventrobasal (VB) nucleus of the thalamus in freely moving rodents, using one of two methods in three models of absence epilepsy. Specifically, they blocked HCN

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pharmacologically both in rats in which seizures were induced with gamma-hydroxybutyric acid (GHB) and in genetically absence epileptic rats from Strasbourg (GAERS), and they knocked down HCN in stargazer mice.

Blocking HCN channels in GAERS reduced tonic firing and the total firing rate of thalamocortical cells both during and between seizures. The decrease in spiking likely resulted from hyperpolarization of the resting membrane potential, because patch-clamp recordings of thalamocortical cells in brain slices taken after HCN channels were knocked down in mice confirmed previous work showing that these channels primarily contribute to setting the resting membrane potential, without affecting action potential threshold and amplitude. Although most of the TC cells are already hyperpolarized (Steriade and Contreras, 1995) and fire sparsely during ictal events (McCafferty et al., 2018), blocking HCN might eliminate the remaining firing and thus radically decrease the output of VB during seizures. Importantly, however, David et al. (2018) found no alteration of burst firing after HCN function was reduced. Considering the non-uniform expression of HCN channels along the dendrites of the TC cells, a possible explanation is that HCN blockade might differentially influence membrane resistance at different input sites, which might compensate for the expected burst activity induced by the hyperpolarization and might result in no net change of burst firing. As tonic firing accounts for most of the firing of TC cells during seizures (McCafferty et al., 2018), the decrease of solely the tonic components may already cause an anti-seizure effect.

In all models, blocking HCN channels decreased total time spent in seizure. However, the different seizure models showed different response dynamics. In GAERS, the anti-seizure effect was reached through a decrease of seizure incidence, but once a seizure was established, its length was close to the control duration. The reduction in seizure occurrence rate is somewhat surprising, given that according to the cortical focus theory (Meeren et al., 2002) a hyperexcitable initiating zone located in the cortex (which is reciprocally connected to the VB) drives the thalamocortical loop into seizure activity in polygenic rodent epilepsy models like GAERS. One possible explanation of the reduced frequency of seizures after HCN inhibition in these animals is that after seizure-inducing activity emerges in the cortex, it requires prompt thalamic feedback to become a full-blown seizure with self-sustaining oscillations. When TC cells are hyperpolarized by HCN inhibition, this strictly timed feedback may be disrupted because too few TC cells are activated. Nonetheless, the relatively small effect on seizure duration suggests that even a radically decreased thalamocortical contribution can provide sufficient feedback to maintain ongoing seizure activity in this model. This suggests that thalamocortical cells may not be the best target for therapeutical approaches.

In both the GHB model and stargazer mice, the seizure occurrence rate did not decrease significantly, unlike in GAERS, probably because of different underlying mechanisms of seizure generation. Indeed, the seizure initiation of GHB application and of stargazer mice is not confined to a single onset region, according to current understanding (Letts, 2005; Venzi et al., 2015). In fact, the results from these models suggest that initiation of seizures might require little contribution from thalamocortical cells of the VB nucleus in these models, as seizure generation was intact despite the significantly decreased firing of TC cells by HCN blockade. Importantly, VB serves as an important hub for ongoing ictal activity in these models, because selective manipulation of the VB shortened seizures.

The work by David et al. (2018) is based on findings from three different animal models of absence epilepsy in two species with various backgrounds suggests that blocking HCN channels in the thalamus may limit seizure activity by substantially decreasing firing of thalamocortical cells. As in the case of spatially nonselective HCN channel silencing, inconsistent seizure-related effects were reported, therefore, further investigations of the corticothalamic dialogue at the network level and the relative contribution of cortical and thalamic HCN channels to seizure dynamics would be beneficial. Using a combination of tools to investigate subcellular- to network-level effects is essential in studying absence epilepsy. Beyond giving mechanistic insight into seizure generation, these approaches can help to identify possible nodes of the epileptic circuitry as potential pharmacological targets for new treatments.

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