Blame it on the Inputs: Overexcited Entorhinal Inputs Drive Dentate Gyrus Hyperexcitability in a Mouse Model of Dravet Syndrome

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Corticohippocampal Circuit Dysfunction in a Mouse Model of Dravet Syndrome
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Dravet syndrome (DS) is a neurodevelopmental disorder due to pathogenic variants in SCN1A encoding the Nav1.1 sodium channel subunit, characterized by treatment-resistant epilepsy, temperature-sensitive seizures, developmental delay/intellectual disability with features of autism spectrum disorder, and increased risk of sudden death. Convergent data suggest hippocampal dentate gyrus (DG) pathology in DS (Scn1a+/-) mice. We performed two-photon calcium imaging in brain slice to uncover a profound dysfunction of filtering of perforant path input by DG in young adult Scn1a+/- mice. This was not due to dysfunction of DG parvalbumin inhibitory interneurons (PV-INs), which were only mildly impaired at this timepoint; however, we identified enhanced excitatory input to granule cells, suggesting that circuit dysfunction is due to excessive excitation rather than impaired inhibition. We confirmed that both optogenetic stimulation of entorhinal cortex and selective chemogenetic inhibition of DG PV-INs lowered seizure threshold in vivo in young adult Scn1a+/- mice. Optogenetic activation of PV-INs, on the other hand, normalized evoked responses in granule cells in vitro. These results establish the corticohippocampal circuit as a key locus of pathology in Scn1a+/- mice and suggest that PV-INs retain powerful inhibitory function and may be harnessed as a potential therapeutic approach toward seizure modulation.

Commentary
Epilepsy has long been considered an interneuron disorder due to the extensive changes observed in inhibitory signaling (cell death, abnormal firing, etc.) across epilepsy models. For instance, in Dravet syndrome, a debilitating genetic epilepsy, the predominant hypothesis has been that chronic seizures are caused by reduced interneuron signaling within the hippocampus,1 the so-called “interneuron hypothesis.” However, in their recent paper, Mattis and colleagues2 challenge this notion and demonstrate that in a mouse model of Dravet syndrome, hippocampal inhibition is primarily intact during the chronic seizure phase, and that the increased excitatory inputs into the dentate gyrus (DG) may drive seizures. This work highlights the need to consider seizures as an output of an extended network of circuits beyond just the hippocampus with highly dynamic and complex interactions.

Dravet syndrome is a debilitating early onset genetic epilepsy characterized by prolonged seizures, intellectual disability, motor dysfunction, and high mortality. The disorder is primarily caused by mutations of the SCN1A gene, which encodes for the voltage-gated sodium channel Nav1.1 subunit. It can be modeled in rodents by removing one copy of this gene (Scn1a±), resulting in chronic seizures and early mortality. Importantly, this gene mediates an excitatory sodium channel and is preferentially expressed in interneurons, particularly in GABAergic parvalbumin-positive (PV+) interneurons.1,3 This has led many to speculate that seizures and hyperexcitability in Dravet syndrome are triggered by a failure of inhibition. Supporting this notion, restricting the Scn1a± transgenic manipulation to only interneurons is still sufficient to induce seizures and early mortality.4 In addition, several studies have shown abnormal interneuron properties in Scn1a± mice and induced pluripotent stem cell recordings from patients with Dravet syndrome.5 However, several studies (including the current study by Mattis and colleagues)2,6 have now demonstrated that interneuron deficits in Scn1a± mice are transient and...
mostly normalized by early adulthood, despite ongoing chronic seizures and hyperexcitability of the DG circuit in late adulthood. Therefore, another mechanism appears to be responsible for ongoing chronic seizures in Scn1a+/− mice. This led Mattis and colleagues to investigate the excitatory and inhibitory signaling in the DG of Scn1a+/− mice, where they found massively increased entorhinal inputs to the DG that likely contribute to chronic seizures.

Many studies have suggested that DG is the primary focus of pathology and seizure initiation in Dravet syndrome. Yet, DG primarily receives excitatory input from the upstream entorhinal cortex (EC), suggesting that this upstream region could also contribute to seizures. In this study, Mattis and colleagues demonstrated profound hyperexcitability of this cortico-hippocampal circuit in young adult Scn1a+/− mice utilizing two-photon calcium imaging, cellular and synaptic slice electrophysiology, and in vivo chemogenetic and optogenetic manipulations. The authors first electrically stimulated EC inputs and found that the DG of young adult Scn1a+/− mice had a much larger response than in controls suggesting strong hyperexcitability in the DG. The authors initially hypothesized that this could be due to abnormal PV+ interneuron signaling, but found that these neurons were primarily intact in young adulthood and were unlikely to be the primary source of DG hyperexcitability. They then patched onto dentate granule cells and found dramatically higher evoked excitatory inputs and a higher excitation-to-inhibition ratio of inputs onto these cells. This strongly indicated that DG hyperexcitability in adult Scn1a+/− mice is primarily driven by increased inputs rather than damaged local inhibition. If pathologically increased excitatory input from EC to GCs is truly the key contributor to seizures in aged local inhibition. Therefore, another mechanism appears to be responsible mostly normalized by early adulthood, despite ongoing chronic deficits across epilepsy models. Understanding how abnormal entorhinal cortex signaling can be produced by direct or compensatory mechanisms. For instance, it is somewhat counterintuitive that reducing the expression of an excitatory sodium channel subunit can drive neuronal hyperexcitability, but the brain has many compensatory mechanisms that maintain homeostasis and can often lead to counterintuitive changes in neural activity. This makes it challenging to determine which neuronal changes that occur are actually driving seizures and which might simply be secondary homeostatic responses. In this case, selective manipulations restricted to individual brain regions or cell types may help parse the specific roles of each population.

Interestingly, entorhinal-hippocampal circuit dysfunction has been implicated in other forms of epilepsy like temporal lobe epilepsy (TLE), suggesting that this may be a convergent circuit-level deficit contributing to seizures. The entorhinal cortex is also a critical region for memory processing and abnormal processing in this circuit may be a primary driver of cognitive deficits across epilepsy models. Understanding how abnormal entorhinal cortex signaling may influence seizures and cognition in epilepsy is an important area of the ongoing investigation and holds promise for new insight into the mechanisms of epilepsy symptoms and new avenues for therapeutic development.

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