Are the Breaks Breaking Down?

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Altered Hippocampal Interneuron Activity Precedes Ictal Onset

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Although failure of GABAergic inhibition is a commonly hypothesized mechanism underlying seizure disorders, the series of events that precipitates a rapid shift from healthy to ictal activity remains unclear. Furthermore, the diversity of inhibitory interneuron populations poses a challenge for understanding local circuit interactions during seizure initiation. Using a combined optogenetic and electrophysiological approach, we examined the activity of identified mouse hippocampal interneuron classes during chemoconvulsant seizure induction in vivo. Surprisingly, synaptic inhibition from parvalbumin-(PV) and somatostatin-expressing (SST) interneurons remained intact throughout the preictal period and early ictal phase. However, these 2 sources of inhibition exhibited cell type–specific differences in their preictal firing patterns and sensitivity to input. Our findings suggest that the onset of ictal activity is not associated with loss of firing by these interneurons or a failure of synaptic inhibition but is instead linked with disruptions of the respective roles these interneurons play in the hippocampal circuit.

Commentary

One of the most omnipresent ideas in the field of epilepsy research is that seizures manifest when there is an imbalance between excitation and inhibition.[1] Specifically, it is widely believed that there is a failure or breakdown of synaptic inhibition acutely during seizures. Surprisingly, the existing data about inhibition and seizures are much more complex (and even controversial) than would be expected given the seemingly straightforward and intuitive idea that inhibition would be dysfunctional during seizures. Synaptic inhibition is mediated by GABAergic interneurons, which comprise several subtypes. Interneuron diversity makes understanding the role of inhibition in seizures challenging, as different subtypes may engage in seizures differently. Over the last decade, there have been significant technological advancements that support experiments combining cell type-specific tagging or manipulation and network-level observation, which provide insight to the role of specific classes of neurons in network activity patterns. Here, Miri et al, combine optogenetic strategies and single unit recording to probe the function and activity of specific interneuron types before and during seizures recorded in vivo.

The seizures in this study are not spontaneous, rather they are induced acutely by systemically injecting either pentylenetetrazol or pilocarpine. Therefore, this study reveals dynamics of a "normal" brain generating seizures rather than of a chronically epileptic brain. The experimenters optogenetically tag PV+ and SST+, allowing them to record from (and stimulate) classified PV+ and SST+ interneurons. The nonchronic nature of the epilepsy they are studying here is especially important to keep in mind when considering SST+ interneurons, as SST+ interneurons in the hippocampus change dramatically during disease progression.[2] Miri et al record the activity from both interneuron types during preictal and ictal periods. Both types increase firing preictally and decrease firing after ictal onset. Such increases in interneuron rates prior to seizure have been observed in acute and chronic models of epilepsy,[3,4] though for spontaneous seizures it is noteworthy that preictal increases in interneuron rate may reflect normal changes associated with brain state transitions.[5]

Increases in interneuron rate do not necessarily mean increases in inhibition. A looming question about the role of interneurons during seizures is whether they undergo depolarization block—in such cases interneurons would be functionally impotent as they would no longer fire action potentials despite being excited. It is also possible that sustained high rates would lead to synaptic rundown or postsynaptic depression of inhibitory outputs again rendering interneurons impotent (despite persisting to fire action potentials). To test whether any of this was going on, Miri et al did a smart experiment. They light-stimulated either PV+ or SST+ interneurons during baseline, preictal, and ictal periods to determine whether interneurons had a functional impact on principal cell activity during these different periods. If inhibition from either cell type

was compromised due to either mechanism described above, stimulating interneurons via light would have little effect on principal cell activity. Inhibition was intact during all periods—stimulation always caused a reduction in firing rate of principal cells. This suggests that leading up to and during early phases of seizures, inhibition from these 2 interneuron types is functioning—the breaks are on. These results are consistent with other work showing that optogenetic activation of PV+ interneurons is capable of truncating spontaneous seizures in chronic epilepsy.[6]

Even though the breaks are on—they aren't working 100% normally. In the case of PV+ interneurons, the timing of activity changes. Just prior to the preictal period, PVs fire more regularly and spike-field coherence in the low-γ range reduces. The timing of SSTs was not abnormal; however, they showed changes in input output curves that suggested that despite increasing firing during preictal periods, they may be less effectively recruited than in normal conditions. Overall, these effects are subtle and it is interesting whether these changes lead to the "initiation" of seizure or reflect early changes as a seizure (initiated elsewhere) propagates to the region they are recording from. Without multisite recording, it is nearly impossible to isolate the true initiation site of seizures—though other recordings suggest that limbic seizures in rodents often initiate in more ventral parts of hippocampus or subiculum.[7] Here, recordings were made dorsally, so it is possible that they are recording the spread of seizures—which are also known to correlate with early recruitment of inhibitory cells.[8]

Looking forward, this study suggests that several inhibitory cell types are capable of mediating inhibition during early phases of local ictal activity—and thus are a viable target for intervention. Specifically, it would be interesting to know whether normalizing preictal activity (timing for PV+ interneurons, and input/output curves for SST+ interneurons) would be sufficient to derail seizure initiation/spread.

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