Marching Towards a Seizure: Spatio-Temporal Evolution of Preictal Activity

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Preictal Activity of Subicular, CA1, and Dentate Gyrus Principal Neurons in the Dorsal Hippocampus Before Spontaneous Seizures in a Rat Model of Temporal Lobe Epilepsy

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Previous studies suggest that spontaneous seizures in patients with temporal lobe epilepsy might be preceded by increased action potential firing of hippocampal neurons. Preictal activity is potentially important because it might provide new opportunities for predicting when a seizure is about to occur and insight into how spontaneous seizures are generated. We evaluated local field potentials and unit activity of single, putative excitatory neurons in the subiculum, CA1, CA3, and dentate gyrus of the dorsal hippocampus in epileptic pilocarpine-treated rats as they experienced spontaneous seizures. Average action potential firing rates of neurons in the subiculum, CA1, and dentate gyrus, but not CA3, increased significantly and progressively beginning 2–4 min before locally recorded spontaneous seizures. In the subiculum, CA1, and dentate gyrus, but not CA3, 41–57% of neurons displayed increased preictal activity with significant consistency across multiple seizures. Much of the increased preictal firing of neurons in the subiculum and CA1 correlated with preictal theta activity, whereas preictal firing of neurons in the dentate gyrus was independent of theta. In addition, some CA1 and dentate gyrus neurons displayed reduced firing rates preictally. These results reveal that different hippocampal subregions exhibit differences in the extent and potential underlying mechanisms of preictal activity. The finding of robust and significantly consistent preictal activity of subicular, CA1, and dentate neurons in the dorsal hippocampus, despite the likelihood that many seizures initiated in other brain regions, suggests the existence of a broader neuronal network whose activity changes minutes before spontaneous seizures initiate.

Commentary

The unpredictability of seizures is a major stumbling block in the treatment of epilepsy. Predicting impending seizures would enable preempting seizures before alterations in consciousness and improve patient lifestyle. Despite years of careful research, there are few reliable methods to definitively predict seizures in patients with epilepsy (1). A practical issue in evaluating the brain's electrical activity to predict focal onset seizures is "where to look?" Is it necessary to identify and analyze the seizure focus? Are the same networks and neurons activated from one seizure to the next? Answers to these questions, which could guide seizure prediction strategies, are particularly challenging in human studies.

A related issue concerns the mechanism underlying seizure initiation. Focal seizures have been proposed to initiate as circumscribed pathologic increases in excitability, which progressively recruits connected circuits. This would imply that the preictal predictor of network activity may originate at the disease focus. An alternative hypothesis has argued for the existence of a distributed brain state in which multiple brain regions exhibit abnormal activity that evolves into seizures (2). Analysis of intracranial EEGs in patients with diverse pathologies, including mesial temporal sclerosis, has shown an across-the-spectrum increase in oscillatory power in several brain regions up to 30 seconds prior to seizure onset (3). While these studies support the existence of distributed preictal network abnormalities, whether individual neurons and networks show consistent preictal changes has not been examined.

Fujita et al. examined this conceptually fundamental and technically challenging question of what happens to principal neuron firing in circuits involved in seizure activity prior to the onset of spontaneous seizures. They provide compelling evidence for the presence of a distributed network with enhanced preictal activity starting several minutes before onset of the ictal event. By combining precise long-term field and single-unit recordings obtained from eight independent movable tetrodes chronically implanted in epileptic rats with spontaneous seizures, the study tracked the evolution of preictal activity over the course of multiple seizures in each animal. While the validity of specific rodent epilepsy models to human temporal lobe epilepsy has been a subject of ongoing debate, the pilocarpine-induced status epilepticus model of epilepsy adopted by Fujita et al. was shown to replicate the focal seizure onset sites reported in patients with temporal lobe epilepsy (4). Of particular note is the remarkable single-

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unit resolution of activity in putative excitatory neurons in the subiculum, CA1, CA3, and dentate gyrus in the dorsal hippocampus. The dorsal circuits were targeted despite the prior knowledge that less than 10% of the spontaneous seizures were likely to initiate from the sampled region.

The most salient finding is that firing rates of individual neurons in the subiculum, CA1, and dentate gyrus increase minutes before seizure onset. Neurons in the subiculum, a region that contributes to epileptiform activity (4), were most likely to exhibit enhanced firing for up to 4 minutes before a seizure. Since seizures spread from the focus to distributed networks in less than a minute (5), subicular preictal activity is unlikely to reflect the spread of seizures from a remote focus. Unlike subicular neurons, which rarely showed decrease in preictal activity, CA1 and dentate neurons showed an equitable distribution of activity patterns with preictal increase in activity in a third of the units sampled, decrease in activity in half of the units, and no change in the rest. Preictal changes in individual unit activity appeared consistent from one seizure to the next. Surprisingly, in contrast to their reported role in seizure initiation (6), CA3 neurons rarely increased their activity prior to seizure onset. Similarly, theta frequency power (5–8 Hz) increased over 3 minutes prior to seizure onset in the subiculum and over a minute prior to seizure onset in the remaining regions examined. Although enhanced firing rate in preictally active neurons correlated with epochs with an increase in theta power, the preictal increase in activity of several neurons, especially in the dentate gyrus, was unrelated to theta. The observed differences in preictal unit excitability between the sampled regions indicate that network-specific mechanisms may shape preictal activity. Moreover, the presence of theta-related and unrelated activity in a given region suggests that the origin of preictal unit activity within a circuit may not be uniform. Remarkably, regular spiking, rather than bursting subicular and dentate neurons were more likely to be active preictally, and neurons tended to morph from regular spiking into bursting in the preictal period, leading to the proposed predominant involvement of bursting neurons in preictal activity.

Demonstration that over 50% of subicular excitatory neurons reliably show increased activity up to 4 minutes before each seizure indicates the theoretical feasibility of seizure prediction. However, there are considerable technical challenges to isolating single-unit activity in patients, and the variability in basal activity and preictal changes would necessitate sampling multiple units. Mechanistically, the findings provide strong support for the presence of distributed network abnormalities prior to seizure onset. While the current study targeted the more accessible dorsal circuits, it would be important for future work to examine the seizure onset zone to determine if preictal activity reflects a distributed network phenomenon or is driven by a focus. Additionally, the mechanisms underlying circuit-specific differences in preictal activity warrant further analysis. Indeed, the group recently reported circuit-specific recruitment of inhibitory neurons during preictal activity (7), which could contribute to preictally inhibited neurons. Of note, Fujita et al. do not observe preictal changes in high-frequency oscillations, which are reported to occur before spontaneous seizures (8). Whether this reflects model or circuit-specific differences or mechanistic distinctions between the evolution of spontaneous seizures and preictal activity remains to be explored. Another intriguing issue is the temporal difference in the order of a couple of minutes between the emergence of preictal activity in subicular and hippocampal circuits, while seizures spread between circuits within seconds. Further studies are needed to determine whether preictal activity is orchestrated by master regulators or emerges from autonomous units. In this context, current experimental techniques such as target closed-loop detection and suppression of the seizures (9) at the onset zone would help reveal if the distributed preictal network inevitably generates seizures. Experimental studies can be coupled with network simulation to narrow the potential mechanisms underlying preictal activity, its spatio-temporal profile, and the relation to seizure onset.

In summary, Fujita et al. provide a meticulous, high-resolution characterization of individual neuronal activity prior to seizure onset. Their interesting finding that neuronal firing increases minutes before seizures in regions that are not commonly within the seizure focus has practical importance for seizure prediction and opens avenues for future mechanistic studies to understand the generation of distributed preictal activity and its role in seizure onset.

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