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Goldilocks Zone of Ictal Onset: Partially Recovered Synapses Provide the Kindling to Fuel Ictal Activity

A Proposed Mechanism for Spontaneous Transitions Between Interictal and Ictal Activity

Jacob T, Lillis KP, Wang Z, Swiercz W, Rahmati N, Staley KJ. *J Neurosci*. 2019;39(3):557-575. doi:10.1523/JNEUROSCI.0719-17.2018. Epub 2018 Nov 16. PMID: 30446533

Epileptic networks are characterized by 2 outputs: brief interictal spikes and rarer, more prolonged seizures. Although either output state is readily modeled in silico and induced experimentally, the transition mechanisms are unknown, in part because no models exhibit both output states spontaneously. In silico, small-world neural networks were built using single-compartment neurons whose physiological parameters were derived from dual whole-cell recordings of pyramidal cells in organotypic hippocampal slice cultures that were generating spontaneous seizure-like activity. In silico, neurons were connected by abundant local synapses and rare long-distance synapses. Activity-dependent synaptic depression and gradual recovery delimited synchronous activity. Full synaptic recovery engendered interictal population spikes that spread via long-distance synapses. When synaptic recovery was incomplete, postsynaptic neurons required coincident activation of multiple presynaptic terminals to reach firing threshold. Only local connections were sufficiently dense to spread activity under these conditions. This coalesced network activity into traveling waves whose velocity varied with synaptic recovery. Seizures were comprised of sustained traveling waves that were similar to those recorded during experimental and human neocortical seizures. Sustained traveling waves occurred only when wave velocity, network dimensions, and the rate of synaptic recovery enabled wave reentry into previously depressed areas at precisely ictogenic levels of synaptic recovery. Wide-field, cellular resolution GCamP7b calcium imaging demonstrated similar initial patterns of activation in the hippocampus, although the anatomical distribution of traveling waves of synaptic activation was altered by the pattern of synaptic connectivity in the organotypic hippocampal cultures.

Commentary

Conditions that trigger the abrupt transition of normal network activity into ictal seizures remain poorly defined. Understanding the mechanisms of ictal onset could enable seizure prediction and timely intervention. However, the unpredictable nature of seizures poses a major impediment to experimental analysis of ictal transitions. Interictal spikes, the brief sharp electroencephalographic transients that occur between seizures, often precede seizures in epileptic patients and animal models.[1] Yet, their role in initiating seizures has remained controversial.[2] To overcome the limitations of experimental analysis, Jacobs and colleagues adopt a network model, capable of generating spontaneous interictal and ictal activity to manipulate and analyze the conditions leading to ictal state transitions. Using a simplified neural network model, the study examines the structural features that make a network permissive to ictal onset and the synaptic physiological features that promote ictal transition.

The large-scale network model of 9600 glutamatergic and 400 GABAergic neurons was developed based on cellular parameters and synaptic connection probabilities from organotypic hippocampal slice cultures which generate both spontaneous interictal and ictal epileptiform activity.[3] Network activity was driven by spontaneous and activity-dependent glutamate release and regulated by activity-dependent depression and recovery of glutamatergic synapses. Inhibitory connections in the network were sparse and adopted the connectivity features of excitatory neurons instead of interneuronal populations. To address whether specific structural features permit seizure onset, the models were simulated with 3 different network connectivity motifs, "uniform/regular connectivity" in which all connections are local, "small-world" connectivity with mostly local connections and a fraction of long-range connections, and "scale-free" networks in which a majority of neurons have few connections while a few neurons are highly connected. Simulation in networks with different connectivity patterns revealed that while most configurations supported

generation of spontaneous interictal activity, ictal transitions occurred exclusively in "small-world" networks. These findings are consistent with earlier reports that the small-world network structure of the dentate gyrus make them susceptible to seizure generation.[4,5] Importantly, altering the density of long-range connections impacted interictal spikes and ictal seizures differently. Although the frequency of interictal spikes were proportional to the percentage of long-range connections, increasing or decreasing long-range connections from the range of 20% to 25% connectivity rendered the network incapable of sustaining seizures lasting over 10 seconds.

Having identified the optimal connectivity for generating ictal activity, the authors use small-world networks with 25% long-range connections to examine the effect of glutamatergic synaptic release and recovery dynamics in generation and propagation of interictal and ictal activity. Altering the available glutamate, kinetics of activity-dependent synaptic depression and recovery profoundly influenced the velocity of interictal spike propagation. Surprisingly, even though the mean glutamate release was not different during onset of interictal and ictal activity, ictal onset occurred only when the network was in a partially depressed state resulting from prior interictal activity. This finding demonstrates that ictal transitions need a conditional sweet spot—"the Goldilocks zone," where synapses are neither fully recovered (too hot) nor totally depressed (too cold) but "just right" with partial depression. This sweet spot resulted from the ability of synaptic parameters to shape activity propagation. When synapses are "hot," interictal spikes spread rapidly through the network and sparse long-range connections are sufficient to spawn interictal spikes in distant sites. When synapses are "cold" (activity-dependent depression and vesicle depletion), propagation fails due to lack of glutamate release. However, when the network recovery was "just right," concerted spontaneous release from local neurons recruits sequential activation of neighboring neurons forming a slowly expanding self-similar spiral ictal wave front reminiscent of ictal propagation in the cortex. Ictal propagation was disrupted and activity ceased prematurely when long-range connections were increased. Increasing glutamate release led to rapid synaptic depression and failure of propagation, while blocking inhibition failed to impact network activity. When the spatial distribution of neurons was reorganized without changing connectivity, the visually striking logarithmic spiral wave front was lost with little change in electrical activity. Furthermore, spiral wave fronts were not observed in calcium imaging data from organotypic hippocampal cultures suggesting that the spiral wave fronts, which occur in networks with certain structural organization, are not essential for electrical ictal activity. Together the simulations identify that onset and maintenance of ictal activity requires a permissive network structure coupled with optimal synaptic depression.

The relative paucity of networks capable of supporting seizures is evident from the extensive parameter search that the authors had to undertake to find networks with ictal transitions. This raises an interesting question of whether ictal transitions are restricted to a subset of networks implemented with the same average local and long-range connections, as observed in dentate network models of epileptogenesis.[5] The presence of microcircuit connectivity motifs[6] within global network structure may explain why only a subset of networks, even among those with similar average connectivity, support ictal transition. The requirement for sparse long-range connections is intriguing in the context of the dentate circuit changes in epilepsy, where long-range mossy cell connections are decreased and local-sprouted connections are enhanced.[4] Since experimental data suggest that network dimensions may influence the "ictogenic" conditions, future studies should explore how the requirement for sparse long-range connectivity scales with network size and aberrant network reorganizations in disease. Although the model was developed based on experimental data, the limitations posed by the monolayer organotypic culture system and model simplifications need to be considered while interpreting the findings, as acknowledged by the authors. Specifically, since the network implementation does not adequately capture inhibitory circuits or include extracellular ionic mechanisms, the specific parameters defining the goldilocks zone may change when effects of inhibitory and ionic mediators on ictal onset are considered.[7,8] An interesting conundrum in the findings is that while absence of long-range connections precludes ictal transitions, long-range connections do not appear to seed or drive ictal onset. Analyzing the velocities of ictal and interictal spread as a function of the density of long-range connections could shed light on whether sparse long-range connections aid development of partially depressed network spaces by hastening interictal propagation. If so, it would be interesting to explore whether specific combinations of network dimension and synaptic parameters could precipitate seizures in networks with different structural motifs.

In conclusion, the study highlights the narrow structural framework and synaptic milieu required to make or break ictal seizures. The findings that sustained ictal traveling waves occur only when wave velocity and the rate of synaptic recovery were precisely matched to enable wave reentry into previously depressed areas provides novel insights into the improbable nature of seizures. Implementing connection parameters derived from in vivo systems and further evaluation of how these concepts scale with network size and apply to 3-dimensional networks will certainly improve our understanding of the complex processes involved in ictal onset. Overall, the findings from this study provide an exciting framework that can be leveraged to develop novel therapeutic strategies to nudge the network out of the Goldilocks zone.

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