Out of (Dis)order? The Dynamics of Seizure Initiation

Network Dynamics During Development of Pharmacologically Induced Epileptic Seizures in Rats *in Vivo*. Cymerblit-Sabba A, Schiller Y. *J Neurosci* 2010;30(5):1619–1630. In epilepsy, the cortical network fluctuates between the asymptomatic interictal state and the symptomatic ictal state of seizures. Despite their importance, the network dynamics responsible for the transition between the interictal and ictal states are largely unknown. Here we used multielectrode single-unit recordings from the hippocampus to investigate the network dynamics during the development of seizures evoked by various chemoconvulsants *in vivo*. In these experiments, we detected a typical network dynamics signature that preceded seizure initiation. The preictal state preceding pilocarpine-, kainate-, and picrotoxin-induced seizures was characterized by biphasic network dynamics composed of an early desynchronization phase in which the tendency of neurons to fire correlated action potentials decreased, followed by a late resynchronization phase in which the activity and synchronization of the network gradually increased. This biphasic network dynamics preceded the initiation both of the initial seizure and of recurrent spontaneous seizures that followed. During seizures, firing of individual neurons and interneuronal synchronization further increased. These findings advance our understanding of the network dynamics leading to seizure initiation and may in future help in the development of novel seizure prediction algorithms.

COMMENTARY

Epileptic seizures arise from a variety of pathological conditions, such as cortical injuries, malformations, and dysplasias, as well as from genetic alterations in ion channel function. Somehow, diverse abnormalities in neuronal network structure and function share the predisposition toward hyperexcitability and hypersynchrony that defines epilepsy. Seizure generation cannot be explained entirely on the level of individual neurons, but rather requires an understanding of the complex interactions between interconnected groups of neurons—the so-called epileptic network. Because of the complexity of these networks, much research in the area of seizure initiation and termination has been based on theoretical models and is driven by two main goals. The first goal is to know how and why seizures start and stop, which will help in designing novel methods, pharmacological and otherwise, to prevent or stop them. The second research objective concerns the transitions between the interictal and ictal states. It is expected that some, or perhaps all, epileptic networks undergo transitions from interictal to ictal behavior, which may happen before the clinical seizure begins. Several lines of evidence suggest that changes occur in epileptic brain before an electrographic ictal discharge can be detected. If these transitions can be detected accurately, then it is possible that seizures can be aborted before they start. For example, novel devices under development aim to prevent or terminate seizures by reverting epileptic neuronal networks back to a more normal state. However, seizure anticipation has remained an elusive goal despite many years of research. The use of animal models of epilepsy one day will provide the crucial data needed to understand how seizures initiate and terminate. With animal models, investigators will be able to recognize the features of the network that change prior to the seizure and test how to apply feedback to the network to alter its behavior favorably.

Seizure activity in model systems have been evaluated in several ways. At one end of the spectrum, ictal-like activity can be induced in brain slices, usually from the hippocampus, and either single cell activity or extracellular field potentials can be recorded. On the other end of the spectrum, EEG can be recorded from the intact brain. The first method enables the determination of the synaptic and intrinsic neuronal elements that are involved in generating ictal activity, while the second method enables viewing the patterns of electrical activity generated by large epileptic networks. In the present study, Cymerblit-Sabba and Schiller used a third method to measure the interictal and ictal activity within the intact brain of rats that enabled them to correlate the activity of individual neurons within groups and then measure the synchronization of action potential firing within and between these distinct units of the seizure network.

The authors implanted bundles of electrodes, which covered an area of approximately 0.25 to 0.75 mm^2, into area CA1 of the hippocampus. With this electrode array, they could detect the firing of up to 10 individual neurons simultaneously. They used cross-correlation analysis to determine the probability that any pair of neurons was firing action potentials in synchrony. They recorded the activity of neurons after inducing seizures with a variety of different convulsant agents in both anesthetized and awake rats. This study revealed several interesting findings. First, when a convulsant agent was administered, the firing rate of individual neurons gradually increased until the onset of the seizure. This outcome demonstrates that, at least in terms of the frequency of firing, the onset of a seizure does not represent an abrupt change, but rather the culmination of a gradual build

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up of activity. Second, they determined that prior to the administration of any convulsant agent, there was a high degree of correlated firing, or synchrony. That is, almost 100% of neuron pairs fired in a correlated manner with a probability of more than twice that would be expected by chance (although there was less correlation in awake than anesthetized rats). This finding suggests that the neurons that were being recorded were in fact functioning as a network. The third, and perhaps the most interesting finding, pertained to the changes in this synchrony within the network as the transition from normal activity to seizure onset occurred. The investigators found that in the early preictal phase (i.e., within the first few minutes after the convulsant was administered) the degree of synchrony within the network dramatically decreased almost to levels seen by chance, even as neuronal firing frequency was increasing. The authors suggest that this desynchronization represents a functional disconnection of the epileptic network that originates from the more distant parts of the network. In the late preictal phase (i.e., several minutes before the seizure started), synchrony increased (although it continued to be less than during the control period) until there was a final abrupt increase in synchrony at seizure onset.

Because this study utilized pharmacologically induced seizures, the authors considered that they could have observed a pattern of network dynamics that was unique to the effects of the convulsant agent. Therefore, they performed the same analysis in rats treated with systemic pilocarpine and picrotoxin, which have different mechanisms of action. By administering either pilocarpine or kainate directly into the hippocampus of anesthetized rats, they also attempted to rule out that the possibility that systemic administration of the drug drove the network activity from outside the hippocampus networks. In all of these conditions, the authors found remarkably similar results. Moreover, because administration of pilocarpine induces a period of repetitive seizures (and is often used to induce status epilepticus), they were able to determine that the network dynamics of recurrent seizures were similar to those of the initial seizure. For these experiments, the seizures occurred minutes apart, so care was taken to differentiate the postictal period (during which neuronal firing was dramatically reduced) from the preictal period. Moreover, although the pattern of desynchronization followed by resynchronization was seen in recurrent as well as initial seizures, the gradual build up of neuronal firing frequency was not observed prior to recurrent seizures.

Clearly, there are many limitations to the interpretation of this study, the most obvious one being that these seizures were induced and not generated intrinsically, as in a true epileptic network. In addition, the generation of seizures in hippocampal area CA1 may be different from that in the cortex or in lesions, such as dysplasias. Considering these caveats, though, it is remarkable that the desynchronization–synchronization pattern occurred in multiple conditions and argues for the possibility that there is one underlying mechanism that begins the genesis of the seizure, long before it is recognized as a seizure. If so, detection of network desynchronization could provide the elusive marker that can reliably anticipate seizures. Moreover, use of such animal models may allow determination of the best methods to abort seizures before they start. For example, closed loop stimulators, drug applicators, and cooling devices are technically feasible, but determining when and how to trigger them is still a challenge. So, although it remains to be seen if these findings are relevant to human epilepsy, at least there is another window into the complexity of seizures and more hope for better treatments.

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