EPILEPSY CURRENTS

Current Literature

In Basic Science

Interneurons and the Ictal Orchestra

Involvement of Fast-Spiking Cells in Ictal Sequences During Spontaneous Seizures in Rats With Chronic Temporal Lobe Epilepsy.

Neumann AR, Raedt R, Steenland HW, Sprengers M, Bzymek K, Navratilova Z, Mesina L, Xie J, Lapointe V, Kloosterman F, Vonck K, Boon PAJM, Soltesz I, McNaughton BL, Luczak A. *Brain* 2017;140:2355–2369.

Epileptic seizures represent altered neuronal network dynamics, but the temporal evolution and cellular substrates of the neuronal activity patterns associated with spontaneous seizures are not fully understood. We used simultaneous recordings from multiple neurons in the hippocampus and neocortex of rats with chronic temporal lobe epilepsy to demonstrate that subsets of cells discharge in a highly stereotypical sequential pattern during ictal events, and that these stereotypical patterns were reproducible across consecutive seizures. In contrast to the canonical view that principal cell discharges dominate ictal events, the ictal sequences were predominantly composed of fast-spiking, putative inhibitory neurons, which displayed unusually strong coupling to local field potential even before seizures. The temporal evolution of activity was characterized by unique dynamics where the most correlated neuronal pairs before seizure onset displayed the largest increases in correlation strength during the seizures. These results demonstrate the selective involvement of fast spiking interneurons in structured temporal sequences during spontaneous ictal events in hippocampal and neocortical circuits in experimental models of chronic temporal lobe epilepsy.

Commentary

There exists a classic line of thought that seizures are generated by the abnormal, hypersynchronous activity of neurons and that this dysfunctional, epileptiform network is repeatedly engaged during recurrent seizure activity. This idea exists, in part, due to interpretations of EEG recordings in which seizure activity is characterized as paroxysmal activity of a population of neurons reflected in the EEG. Although at the macroscopic level of the EEG, the population hyperexcitability is apparent, less is known about the activity of the individual neurons or even subtypes of neurons that underlie this activity at the microcircuit level. A good example of our lack of understanding at this level is the evidence that GABAergic neurons can play a role in both seizure prevention and seizure generation. GABA is known to exert inhibitory control on over principal neurons, acting as the "brakes" on the local network, limiting neuronal excitability, seizure generation and propagation. However, recent evidence also suggests that GABAergic neurons can play a role in the abnormal synchronization of the network—that through a collapse in the chloride gradient, GABA can exert excitatory actions, directly contributing to the generation of epileptiform activity. Thus, a closer look at the activity of neurons within epileptic microcircuits is necessary to fully understand the network dynamics of both interneurons and principal neurons in the generation of ictal activity.

The role of microcircuits in epilepsy has been beautifully discussed elsewhere (1), and the readers are encouraged to refer to this review since this complex topic cannot be comprehensively addressed here. The development of more precise imaging and recording techniques has enabled investigators to begin to explore microcircuit dynamics associated with epileptiform activity. Initially, studies examining the activity of microcircuits in chronically epileptic mice focused on interictal epileptiform activity (such as interictal spikes) due to the difficulty in assessing microcircuit activity during seizures; these events can be somewhat infrequent and difficult to predict, and technical limitations make spike analysis challenging. Large-scale evaluation of populations of individual neurons during epileptiform activity have demonstrated that, in contrast to previous thought, interictal activity is not generated by the repetitive, hypersynchronous activation of a homogeneous population of neurons; rather, it is a well-orchestrated but variable sequence of neuronal activity involving a heterogeneous population of neurons (2, 3). Somewhat unexpectedly, these studies also identified that GABAergic neurons are preferentially recruited during spontaneous interictal activity in the hippocampus of chronically epileptic mice (4), contributing to the accumulating evidence redefining the role of GABAergic neurons in epilepsy.

A few studies have assessed microcircuit activity during ictal events, including the currently highlighted manuscript. Population recordings were performed in two different rat

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models of temporal lobe epilepsy (TLE)—perforant path stimulation and intrahippocampal kainic acid—enabling the authors to examine the patterns of neuronal activity that emerged across spontaneous recurrent seizures. The authors observed a sequential pattern of neuronal activity that is stereotyped across ictal events, similar to the observations for interictal events (2, 3), and that the increased synchrony during seizure activity was due to an increase in overall spike rate rather than true synchronization of the network (5). Further, these data suggested that neurons whose activities are highly correlated with the local field potential during the preictal period were the same neurons that participated in the sequential neuronal activity underlying ictal activity. This data was consistent with previous studies demonstrating that while there is a heterogeneity in the recruitment of neurons (i.e., not all neurons recruited are the same type and not all are recruited simultaneously), there is a conserved, sequential pattern of activity at least between consecutive seizure events (3, 6). One caveat of the currently highlighted study by Neumann et al. and others is that the analysis involved consecutive seizure activity, which may not be representative of overall ictal activity and is unable to address how this pattern of neuronal activity evolves during seizure progression. The authors noted that this approach was taken to prevent drift in the positioning of the tetrodes over time. While this is understandable, it limits our understanding of how this sequential pattern of activity holds up over time or whether new or more robust ensembles emerge.

The authors also stated that the sequential pattern of neuronal activity was observed in both the hippocampus and parietal cortex. However, the entrainment of the neurons in the parietal cortex to ictal activity was more apparent in the kainic acid model (Neumann et al., see Figure 2) versus the perforant path stimulation model (Neumann et al., see Figure 1), although this direct comparison was not made in this study, likely due to the lownumbers in these experimental groups. The conserved, sequential pattern of activity over the larger network (hippocampus and parietal cortex) suggests that specific neuronal ensembles distributed throughout large networks may play a role in ictal activity, shifting our current understanding of seizure propagation involving breakdown of the "brakes" on the network. Rather, propagation of ictal activity may involve the engagement of a heterogeneous population of neurons throughout a distributed network, generating ictal activity and facilitating variability in the propagation through the larger network. In fact, the propagation of interictal activity has been shown to be remarkably variable, a phenomenon shown to involve GABAergic inhibition (7).

Interestingly, the highlighted manuscript established that interneurons were the predominant cell type participating in the stereotypical sequential pattern of neuronal activity associated with ictal events, consistent with the findings presented in previous studies (5, 6). Putative interneurons exhibited higher entrainment values with ictal activity than did principal neurons. Interneurons showed a higher degree of entrainment during both the early and late phases of ictal activity, which is important since interneurons have been suggested to play different roles in the generation of epileptiform activity at different stages of ictal-like events (8). Although these data demonstrate a contribution of interneurons throughout the ictal period, it still is not clear what the nature of this contribution is to the ictal activity. More information regarding the pattern of interneuron activity relative to principal neuron activity is required to start to deconstruct the ictal activity measured at the levels of the local field potential or EEG.

The evidence that the same neurons that are highly correlated with the local field potential during the preictal period are also the ones that contribute to the sequential pattern of activity associated with ictal activity is an important observation. These data suggest that ictal activity may represent a pathological strengthening of the existing network, a concept put forth previously suggesting a relationship between epilepsy and neural plasticity (9). These findings hold the promise that it may be possible to predict the sequential activation of neurons and propagation of ictal activity from examining preictal activity alone.

As technical advances allow us a closer glimpse into the activity of both the healthy and diseased network, it is becoming increasingly apparent that ensembles of neurons communicating through orchestrated patterns of activity are involved in a multitude of normal and pathological processes. These findings force us to shift our thinking away from the canonical view of seizures as hypersynchronous activity of a population of neurons to the idea that ictal activity is driven by a heterogeneous population of neurons playing out an orchestrated pattern of activity and that synchrony results from an overall increase in spiking rates rather than synchronization of a specific population (5). In particular, GABAergic neurons play an important role in neuronal computation and network communication. The expanse of interneuron connections onto principal neurons endows them with the capability of coordinating network activity. As we consider the role of the microcircuit in the large-scale coordination of activity associated with epilepsy, it is useful to think of biological networks as including nodes that mediate information flow. In fact, network theory has been utilized to describe the role of microcircuits in more expansive network communication (again, readers are referred to [1]). Interestingly, GABAergic neurons have been identified as "operational hubs" critical for coordinating network dynamics (10). Thus, it appears that GABAergic neurons may have yet another role to play in epilepsy, not only orchestrating the microcircuit but also coordinating communication between larger networks.

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