CURRENT LITERATURE

EPILEPTOGENESIS BEYOND THE HIPPOCAMPUS

On the Origin of Interictal Activity in Human Temporal Lobe Epilepsy In Vitro

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The origin and mechanisms of human interictal epileptic discharges remain unclear. Here we describe a spontaneous, rhythmic activity initiated in the subiculum of slices from patients with temporal lobe epilepsy. Synchronous events were similar to interictal discharges of patient electroencephalograms. They were suppressed by antagonists of either glutamatergic or γ-aminobutyric acid (GABA)ergic signaling. The network of neurons discharging during population events comprises both subicular interneurons and a subgroup of pyramidal cells. In these pyramidal cells, GABAergic synaptic events reversed at depolarized potentials. Depolarizing GABAergic responses in neurons downstream to the sclerotic CA1 region contribute to human interictal activity.

COMMENTARY

Efforts to unravel the mechanisms of temporal lobe epilepsy (TLE) often use animal models. Over the past several decades, epilepsy induced by kainic acid, pilocarpine, or kindling has advanced our knowledge about the clinical characteristics, time course, and histopathology of the epileptogenic process. However, truly to understand the intricacies of the human disorder, the use of human epileptic tissue would be optimal. Despite methodologic difficulties in using brain tissue resected from patients with TLE, such as the adequacy of control tissue and disruption of normal laminar architecture (6), data from human patients can yield important pathophysiological insights.

One of the vexing questions is the site of origin of interictal discharges in TLE. The typical pathologic picture of TLE is mesial temporal sclerosis, with atrophy and gliosis of the hippocampus, particularly the dentate hilus and the CA1 and CA3 subfields. In severe cases, the majority of neurons in these regions die, and perhaps not surprisingly, many recordings from epileptic CA1 or CA3 regions have shown little or no spontaneous epileptiform activity. This lack of epileptiform activity might be owing to the severe damage to these areas, or alternatively, the abnormal synchronous activity might arise elsewhere. A logical possibility would be an upstream site such as the subiculum, which receives afferent information from CA1 and has widespread projections beyond the hippocampus. Because of its location and ability of local neuronal circuits to generate paroxysmal activity, the subiculum is well placed to synchronize widespread neuronal networks (e.g., distant temporal and extratemporal regions).

Until recently, epilepsy was conceptualized as a simple imbalance of excitation and inhibition. By restoring that balance (i.e., by increasing inhibitory or decreasing excitatory neurotransmission or by reducing the activity of neurons with hyperexcitable intrinsic membrane properties), seizures could be suppressed. Indeed, many anticonvulsant drugs (AEDs) are based on this formulation. It is now apparent that the cellular and functional alterations leading to seizures are considerably more complex: neuromodulators (e.g., norepinephrine, brain-derived neurotrophic factor) can enhance excitation or inhibition depending on the location or circumstance; some "anti-epileptic" drugs can actually cause or worsen seizures; and γ-aminobutyric acid (GABA) can exert inhibitory or excitatory effects depending on age and, as suggested by this report, pathologic state. Therefore it is critical to determine if specific neuronal populations or synapses can initiate, coordinate, or propagate epileptic discharges (3).

Cohen et al. investigated the resected mesial temporal tissue of 21 adult patients with medically refractory TLE. The epilepsy in these patients was particularly severe: the patients averaged 11 seizures per month, and their average duration of refractory partial seizures was 25 years! The EEG of each patient showed interictal discharges (from the scalp and/or intracranially) from the temporal region, and each patient had MRI evidence of hippocampal atrophy and sclerosis. Therefore this patient cohort represents very advanced cases of TLE, of the kind that often responds well to surgical intervention. Surprisingly, electrophysiologic recording from the combined hippocampal-subicular-entorhinal slices from these patients showed little or no spontaneous synchronous activity in CA1 or CA3. However, rhythmic discharges were recorded from

several distinct sites in the subiculum, and these discharges had a duration, frequency, and morphology that matched scalp-recorded interictal EEG spikes from the same patients. The discharges persisted in isolated subicular slices, showing that they originated in this structure. These findings imply that multiple potential pacemaker sites exist within the epileptic subiculum that can generate hypersynchrony, and by extension, could potentially recruit other, connected cortical regions (e.g., entorhinal and extratemporal cortex) into an epileptic firing mode.

The authors then used pharmacologic blockers to investigate the mechanism of the paroxysmal firing in the subiculum. Unexpectedly, antagonists of both excitatory *and* inhibitory neurotransmission blocked the interictal discharges, suggesting that both excitation and inhibition participate in generation of the hypersynchronous activity. The existence of a single pacemaker region with an inhibitory surround was excluded by the finding of multiple independent sites of discharge generation. Instead, they found that inhibitory interneurons fired just before the synchronous bursts in pyramidal neurons, and that a subpopulation (22%) of pyramidal neurons in the subiculum were *excited* by stimulation of GABA-containing interneurons. These results suggest that GABA-releasing interneurons could elicit either excitation or inhibition of pyramidal neurons within epileptic subiculum. In the more common inhibitory mode, hyperexcitability might be constrained by an "inhibitory surround," whereas GABA-induced excitation of the aberrant subpopulation of subicular pyramidal neurons could lead to pathologic, interictal firing, or even to an ictal event.

It is now well established that GABA can exert a depolarizing action, especially in the neonatal brain. This excitatory effect is due to a reversal of the usual chloride gradient, with the chloride-reversal potential positive to resting potential early in life (2). Therefore, when GABA activates its receptor, chloride flows out of the cell, causing a depolarization of membrane potential. Later in development, as the KCC2 K^+/Cl^- cotransporter matures, Cl^- accumulates extracellularly, and GABA receptor activation causes inward flux of Cl^- and hence hyperpolarization (5). Cohen et al. hypothesize that the existence of depolarizing GABA responses in epileptic subicular neurons might be explained by a regression to the earlier developmental stage. This would certainly constitute a novel epilepsy mechanism in the adult brain and might open up opportunities for selective pharmacologic intervention.

Several critical questions remain. First, is the expression of KCC2 reduced in these subicular neurons, as would be expected if the early developmental pattern were reactivated? Second, would the same results have been seen in less damaged hippocampus (e.g., early in epileptogenesis, when CA1 and CA3 are more intact)? The lack of availability of control tissue limits the determination as to whether subicular interneurons or pyramidal neurons are morphologically or physiologically altered. Similarly, it is presently unknown whether extensive synaptic reorganization akin to mossy fiber sprouting is present in the human epileptic subiculum (4). Perhaps ironically, returning to animal models might be helpful in this regard. Third, what is the relation between this interictal firing and actual seizure generation? Much controversy exists about the relation between interictal spikes and the ictal state, and even whether interictal discharges lead to seizures (1). Nevertheless, these fascinating results, obtained in human epileptic tissue, urge us to cast our net further afield—out of the hippocampus and into nearby parahippocampal structures that may also be critical for ictogenesis. The subiculum may harbor novel and unexpected forms of neural plasticity in TLE.

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