

Interictal Spikes and Epileptogenesis

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Interictal spikes are widely accepted diagnostically as a sign of epilepsy, but reasons for the presence of interictal activity in the epileptic brain are unknown. Interictal spikes are easily generated in normal brain by pharmacologically reducing inhibition, and experimental studies of acquired epilepsy indicate that spikes precede seizures. These data lead to the hypothesis that interictal spikes are correlated with epilepsy because they play a fundamental role in epileptogenesis following brain injury. Spikes may guide sprouting axons back to their network of origin, increase and sustain the strength of the synapses formed by sprouted axons, and alter the balance of ion channels in the epileptic focus, such that seizures become possible. This hypothesis has implications that are testable: altering spiking or the calcium signals generated by spikes should alter epileptogenesis and spikes should precede seizures in brain-injured human patients.

Interictal spikes are brief (< 250 millisecond), morphologically defined events observed in the EEGs of patients predisposed to spontaneous seizures of focal onset. The spikes are generated by the synchronous discharges of a group of neurons in a region referred to as the epileptic focus. While some would argue that the neural network that generates spikes is not always identical to the network that generates seizures, interictal spikes are so highly correlated with spontaneous seizures that their presence is used to support the diagnosis of epilepsy (1). This article addresses the hypothesis that interictal spikes are highly correlated with epilepsy because they are a fundamental component contributing to epileptogenesis (2).

In acquired epilepsy, a previously normal brain responds to injury by slowly (i.e., over a period of months to years) developing a propensity to generate spontaneous seizures (3,4). EEG recordings usually demonstrate interictal spikes once a patient with new-onset epilepsy has experienced a spontaneous

seizure. The EEGs of patients who have not yet experienced seizures following brain injury have not been extensively studied (5,6); however, the recent development of continuous behavioral monitoring and recording techniques for mechanistic studies of experimental epilepsy (7,8) makes possible more rigorous analyses of possible interictal activity at the earliest stages of epileptogenesis.

In the kainate model of acquired epilepsy, repeated low-dose systemic injections of kainate result in a single, prolonged episode of status epilepticus. After recovering from prolonged seizures, the experimental animals develop spontaneous seizures about 2 weeks later (9), with interictal spikes actually preceding the first spontaneous seizures (10). The kainate model incorporates several key features of intractable temporal lobe epilepsy in humans, including loss of inhibitory neurons in the hilus and elsewhere in the hippocampus; axonal sprouting, such that principal cells provide increased recurrent excitatory drive to their neighbors; a slow and progressive development of spontaneous seizures (9,10); and an incomplete therapeutic response to anti-convulsant medications (11). Thus, the observation that spikes precede spontaneous seizures in this model may be relevant to human brain injury.

Why Would Interictal Spikes Precede Seizures?

Reductions in GABA-mediated synaptic inhibition can trigger interictal spikes in experimental preparations (12,13), and such reductions also can be produced by the immediate interneuron loss that is known to occur as a consequence of traumatic brain injury (14) as well as of prolonged seizures (15). Once regular interictal spiking has been initiated, the synchronous activity of neurons in the epileptic focus could guide axon growth (16) in a similar manner to what occurs with the wiring of neural circuits during development (17). However, axon growth that leads to epilepsy after brain injury differs in two respects from growth during development: first, axon growth following injury is thought to be initiated by loss of the normal downstream axon targets (18). Second, axon growth during epileptogenesis is characterized by excessive return of glutamatergic fibers to their network of origin, where they provide positive feedback that leads to pathologically synchronized activity (i.e., seizures). For example, axons from the dentate gyrus normally innervate the hilus and area CA3 of the hippocampus. Loss of neurons in the hilus and area CA3 as a result of pilocarpine- or kainate-induced status epilepticus would leave the mossy fibers of the dentate gyrus with fewer postsynaptic targets. Dentate neurons may fire synchronously as a consequence of the loss

of feedback interneurons in the hilus (14,15) or from synchronous driving from the entorhinal cortex (1). Such firing might comprise a sufficient signal to guide axon growth back into the dentate, perhaps by controlling the secretion of axon guidance molecules (17,20). Growth of dentate granule cell axons back into the input layer of the dentate gyrus (i.e., mossy fiber sprouting) is a robustly verified phenomenon that is highly correlated with epilepsy (21). It should be possible, at least in theory, to test whether interictal spikes guide sprouting. For example, blockade of spikes or perhaps periodic stimulation in other hippocampal areas may alter mossy fiber sprouting and possibly interfere with the development of epilepsy.

Neurons in the epileptic focus undergo a paroxysmal depolarizing shift (PDS) in membrane potential during interictal spikes (22). The activation of excitatory glutamate receptors leads to the opening of voltage-dependent conductances that trigger action potentials and intracellular calcium transients that underlie the PDS. The synchronous release of glutamate from other neurons in the epileptic focus activates additional glutamate receptors via the recurrent collateral synapses that link the neurons in the network (23). The PDSs generated in the neurons of the epileptic focus drive repetitive action potentials down the axons of these neurons, sustaining the glutamate release. The membrane depolarization during the PDS is sufficient to remove the voltage-dependent magnesium block of *N*-methyl-D-aspartate (NMDA) receptors, a glutamate receptor subtype (24). NMDA receptors are permeable to calcium, so activation of these receptors during the interictal spike results in calcium transients in the postsynaptic spines that are sufficient to induce long-term increases in the strength of the synapses activated during the spike (25,26,27). Thus, in addition to guiding sprouting axon fibers back to their network of origin, another mechanism through which interictal spikes may contribute to epileptogenesis is by strengthening the recurrent collateral synapses that link the neurons in the epileptic focus, which increases the probability of subsequent interictal spikes (25,27,28). This cycle of spikes, synaptic strengthening, and increased spike probability may sustain the epileptic focus, thereby maintaining the propensity for seizures.

The synchronous release of glutamate in the epileptic focus should also be sufficient to activate perisynaptic metabotropic glutamate receptors (29). These receptors could trigger trophic second-messenger cascades that also may be important in the maintenance of the epileptic network. For example, activation of group I metabotropic glutamate receptors upregulates slowly inactivating nonselective cation channels (30). The sustained depolarizing currents admitted by these channels underlie the plateau potentials that can transform brief interictal discharges into sustained, seizure-like events (31,32). Thus, interictal spikes may not only increase the probability of more

spikes but also may produce the conditions that are permissive for seizure activity.

Clinical Implications of Preictal Spikes

The demonstration that interictal spikes precede spontaneous seizures in the kainate model of epilepsy brings up important diagnostic questions for human epilepsy. Are interictal spikes also present in brain-injured human patients who will eventually develop epilepsy? Conversely, are spikes not present in brain-injured patients who do not develop epilepsy? One could argue that if interictal spikes are demonstrated in human patients before the occurrence of epilepsy, they should be termed *preictal spikes*. The findings associated with the kainate model leave open the question of whether detection of such preictal spikes in brain-injured humans may someday be used to diagnose a predisposition for epilepsy prior to the first spontaneous seizure. The ability to diagnose which brain-injured patients will go on to develop chronic epilepsy would be an important advance that could help patients avoid potentially dangerous activities, could direct early therapy to prevent seizures, and possibly even could be used to prevent epilepsy.

Using Interictal Spikes to Treat Epilepsy

Could treatment of spikes prevent epilepsy, once axon sprouting and the other stages of epileptogenesis have already occurred, that is, after the first spontaneous seizure? Although the intracellular calcium transients that occur during spikes are sufficient to strengthen the recurrent synapses between neurons in the epileptic focus, synapses can also undergo long-term reductions in synaptic strength if calcium influx into the dendritic spine is reduced (33). Partial blockade of NMDA receptors with low-affinity competitive antagonists can reduce the calcium influx through NMDA receptors, which results in long-term weakening of the recurrent collateral synapses in experimental models of interictal spikes (25). Theoretically, this weakening process could be continued to the point that the synapses are too weak to initiate or sustain the activity needed to generate interictal spikes and, perhaps, seizures as well. Thus, by partially blocking NMDA receptors pharmacologically, the interictal spikes could be used to produce long-term reductions rather than long-term increases in the probability of spikes and seizures. It is important to note that in experimental preparations, synapses from neurons that do not participate in the spike activity are not weakened (25), so patients treated in this way would not be expected to lose any learned information encoded in the strength of synapses that are not part of the epileptic focus.

The role of preictal spikes in epileptogenesis remains speculative, in part because the study of spikes that occur before the first spontaneous seizure has just begun. In addition, anti-convulsants are not particularly effective in blocking interictal

activity (see discussion to follow); however, this effect is helpful in some clinical situations. For example, the clinical decision to begin anticonvulsant treatment prior to an EEG will not affect the diagnostic utility of the EEG, because spikes will be present regardless of anticonvulsant treatment. However, without anticonvulsants that block interictal spikes, investigators cannot test whether interictal spikes are an important component of epileptogenesis. Although no anticonvulsants block interictal activity, it may be possible to alter interictal spike frequency. Low-dose benzodiazepines have been reported to reduce interictal spiking (34), as has flumazenil, a weak partial agonist used clinically as a benzodiazepine antagonist (35). Levetiracetam also has been reported to reduce interictal spike frequency (36), and sulthiame blocks interictal activity in benign rolandic epilepsy (37,38). These agents may represent the most promising clinically available medications to test the hypothetical antiepileptogenic effects of reducing interictal spike frequency.

Interictal Spikes and Genetic Epilepsy Syndromes

The relationship between interictal activity and the natural history of seizures in the acquired epilepsies cannot be generalized to genetic epilepsy syndromes. For example, the frequency of interictal spikes does not predict the probability of regression of epilepsy in benign rolandic epilepsy (39) and the frequency of brief episodes of epileptiform activity (absence spells) does not predict the probability of eventually outgrowing childhood absence epilepsy, whereas the presence of interictal spikes is correlated with continued seizures in acquired epilepsies (40,41). Which is not to say that spikes are entirely benign in the genetic epilepsies, as frequent interictal activity is correlated with cognitive dysfunction in benign rolandic epilepsy (39). Based on the relationship between the interictal EEG activity and the evolution of epilepsy, the pathophysiology of brief epileptiform activity in the genetically determined epilepsies is heterogeneous and likely to be heavily influenced by the temporal pattern of expression of underlying genetic defects. This finding is quite different from the acquired epilepsies, which occur in the setting of injury to a brain that was previously normal (though perhaps genetically predisposed).

Conclusion

If spikes associated with acquired epilepsy function to maintain an epileptic focus between seizures by strengthening the synaptic connections that link the neurons in the epileptic focus, then reduction of spike frequency below a critical number may allow normal restorative processes to reduce seizure probability. An analogous process may be the “running down” of interictal spike frequency and seizures following successful epilepsy surgery (42). Postoperative EEGs demonstrate a gradual re-

duction in interictal spike frequency, which is correlated with eventual seizure control. As with all observations that do not involve blocking interictal spikes, “running down” only constitutes correlational evidence. Stronger evidence of the role of interictal spikes in epilepsy awaits completion of studies in which spikes are blocked or perhaps their long-term effects on synaptic strength are reversed by partial block of NMDA receptors.

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