Do Interictal Spikes Sustain Seizures and Epileptogenesis?

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Interictal spiking is seen in the EEG of epileptic patients between seizures. To date, the roles played by interictal events in seizure occurrence and in epileptogenesis remain elusive. While interictal spikes may herald the onset of electrographic seizures, experimental data indicate that hippocampus-driven interictal events prevent seizure precipitation. Even less clear than the role of interictal events in seizure occurrence is whether and how interictal spikes contribute to epileptogenesis. Thus, while plastic changes within limbic neuronal networks may result from ongoing interictal activity, experimental evidence supports the view that epileptogenesis is accompanied by a decrease in hippocampus-driven interictal activity.

The EEG of patients presenting with partial seizures is characterized by brief, epileptic spikes that are not associated with evident clinical symptoms. The interictal spiking is valuable for diagnosing the epileptic condition, and when required, for localizing the epileptogenic area. Intercal and ictal discharges in animal models of epileptiform activity consist of similar (but for duration) neuronal depolarizations, leading to sustained action potential firing (1–4), suggesting that intercal and ictal events may reflect similar neuronal mechanisms. Moreover, interictal spikes may herald the onset of electrographic seizures. However, the precise relationship between interictal and ictal activity remains ambiguous, as careful studies performed in patients with temporal lobe epilepsy (TLE) and in animal models mimicking this condition indicate that the interictal spike rate does not change before seizure onset (5–7). Finally, it has been proposed that interictal spiking prevents seizure precipitation in some animal models (8–11).

Even more elusive than interictal–ictal relationship is the role played by interictal spikes in epileptogenesis, which is the process leading to the development of an epileptic condition (12). While it is indisputable that plasticity is a fundamental characteristic of neuronal networks, as epitomized by the kindling phenomenon (13), it is unclear whether changes in synaptic efficacy or formation of new connections result from ongoing interictal activity. Here, we review data indicating that interictal spikes can have both anti- and pro-seizure actions. In addition, experimental evidence supporting the view that a decrease in hippocampal-driven interictal activity contributes to epileptogenesis in the pilocarpine model of TLE is summarized. The hippocampus (and in particular its CA3 subfield) is the limbic area that is most prone to generate interictal events, at least with in vitro preparations (4).

Antiseizure and Proseizure Actions of Intercal Spikes

Because TLE patients present with seizure discharges in limbic structures, such as the entorhinal cortex (EC) and the hippocampus proper, several electrophysiological studies have been carried out on rodent brain slices that contain reciprocally interconnected portions of hippocampal and parahippocampal areas (4) or with isolated brain preparations (11,14,15). As illustrated in Figure 1A, under appropriate conditions (e.g., when treated with 4-aminopyridine), combined EC–hippocampus slices generate epileptiform discharges resembling interictal and ictal events (4). Intercal activity, which is caused by non-N-methyl-D-aspartate (NMDA) glutamatergic mechanisms, originates in the CA3 subfield of the hippocampus, spreads via the CA1/subiculum areas to the EC, and returns to CA3 via the perforant path/dentate gyrus (Figure 1Ba). In contrast, ictal events—dependent on the activation of both NMDA and non-NMDA glutamatergic and GABA_A receptors—initiate in the EC and propagate to the hippocampus (Figure 1Bb). The EC is known to be prone to generate seizures in TLE patients (16–18). In vitro studies also have shown that ictal discharges disappear within 1–2 hours, while the CA3-driven interictal activity occurs throughout the experiment (Figure 1A). Moreover, cutting the Schaffer collaterals, which connect CA3 to CA1, abolishes interictal spikes in the EC and allows ictal

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discharges to be reestablished in this area (Figure 1C). Therefore, CA3-driven interictal activity can reduce, rather than sustain, the ability of the EC to generate ictal events (10).

The antiseizure action exerted by interictal activity (9, 19) can be mimicked by electrical stimuli at rates that are similar to those of the CA3-driven interictal activity (i.e., approximately 1 Hz). In addition, an inverse relationship between ictal and interictal discharges occurs in hippocampal slices when using drugs (e.g., baclofen) that depress interictal spikes (20, 21). Evidence from the in vitro isolated guinea pig brain, indicates that periodic interictal spiking in the piriform cortex prevents involvement of this region by seizure-like activity generated in the EC–hippocampus during transient GABAergic impairment (11). Finally, interictal spikes are known to be followed by a prolonged period of inhibition (22) in which the threshold for the generation of an epileptic discharge is increased—an effect found both in models of epileptiform activity (23) and in patients with neocortical epilepsy (24).

The role of interictal spikes, however, is not as straightforward as indicated by the results reviewed above. Early experiments performed using focal discharges induced in vivo by convulsant drugs showed that interictal discharges sometimes accelerate before the onset of seizure (1). Moreover, initial studies in the kindling model suggested that interictal spikes become more frequent as the kindling process evolves and may increase prior to the appearance of spontaneous seizures (25, 26). This evidence, however, was not confirmed by continuously monitoring of the EEG in kindled animals (27). More recently, analysis of the epileptiform activity induced by 4-aminopyridine in the EC revealed that local interictal spikes, which are largely contributed by GABA<sub>A</sub> receptor-mediated conductances, lead to electrographic seizure onset (4). As illustrated in Figure 2 (A and B panels), the onset of an ictal discharge recorded intracellularly from EC neurons is characterized by a long-lasting depolarization, resembling what is seen during an interictal event generated within the EC network. The similarity between
FIGURE 2. A and B: Field and intracellular (potassium-acetate–filled microelectrode) recordings from the EC demonstrate two types of activity during 4-AP application. Slow interictal and ictal discharges are identified with asterisks and an open circle, respectively. Note the similarities between the isolated interictal discharge (Ba) and the onset of the ictal event (Bb). Adapted with permission from J Neurophysiol. (47) Copyright 1998 American Physiological Society. C: When the neuronal membrane is depolarized by intracellular injection of steady positive current (−55 mV), the amplitude of sustained ictal depolarization decreases, while the initial long-lasting depolarization becomes hyperpolarizing as compared with the recording obtained at resting membrane potential (−70 mV). When the membrane is hyperpolarized by intracellular injection of steady negative current (−80 mV) both long-lasting depolarization and ictal depolarization increase in amplitude as compared with the samples obtained at resting membrane potential. The time occupied by this initial long-lasting depolarization is indicated by the continuous line on top of the −55 mV trace. Adapted with permission from J Neurophysiol. (47) Copyright 1998 American Physiological Society.

EC, entorhinal cortex; DG, dentate granule; 4-AP, 4-aminopyridine.

the local interictal discharge and the event recorded at seizure onset is further supported by evidence showing that ictal discharge onset consists of a hyperpolarization when the neuron is depolarized with steady current injection (Figure 2C). Thus, in this in vitro model of limbic seizures, ictal depolarizations paradoxically originate from a hyperpolarizing event. Interictal spiking also has been observed ahead of ictal discharges in the isolated guinea pig brain preparation during short-lasting bicuculline treatment (15). Hence, interictal spikes may exert either a protective or precipitating role with respect to seizure generation.

Interictal Spikes and Epileptogenesis

Interictal spiking is the first sign of an epileptic discharge appearing after status epilepticus (SE) in animals committed to develop seizures (28–30). However, it is unknown whether this activity reflects an altered neuronal network unable to impede the ongoing epileptogenic process or a sign of incipient seizure activity. Moreover, investigators ignore whether and how interictal discharges change in their occurrence, shape, and underlying mechanisms during the period that follows SE. Indeed, after pilocarpine-induced SE, CA3-driven interictal activity in unable to control ictal discharges recorded during 4-aminopyridine treatment: electrographic seizures originating in the epileptic EC occur throughout the experiment, while they disappear in slices from nonepileptic control animals (31). In contrast, the kindling phenomenon and the development of mirror foci suggest that activity-dependent changes in synaptic transmission along with formation of new synaptic connections represent potential epileptogenic factors. In this context, recurrent interictal events could play a role in epileptogenesis, perhaps through the induction of activity-dependent synaptic plasticity mechanisms.

A point that merits critical evaluation is the assessment of mechanisms underlying the impairment of hippocampal networks generating interictal activity after SE. It is known that TLE patients display mesial temporal (or Ammon’s horn) sclerosis. This condition, which is characterized by a rather selective loss of neurons in specific limbic areas (32,33), also is found in animal models of TLE (34–36). Experimental evidence suggests that in the presence of Ammon’s horn sclerosis, both cell loss and the consequent synaptic reorganization contribute to epileptogenesis (37–40). In the model of self-sustaining SE, lesions are extensive in the hippocampus and CA3 pyramidal cells numbers are reduced to approximately 50% of control values (41). However, in spite of such damage, the hippocampus is still able to generate interictal spikes (29). A decrease in hippocampal network function associated with cell damage also occurs in pilocarpine-treated epileptic animals (31,4). Recurrent limbic seizures persist in this model when mossy fiber sprouting, but not neuronal damage, is reduced by protein synthesis inhibition


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