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CRITICAL REVIEW AND INVITED COMMENTARY

GABAergic networks jump-start focal seizures

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Summary

Abnormally enhanced glutamatergic excitation is commonly believed to mark the onset of a focal seizure. This notion, however, is not supported by firm evidence, and it will be challenged here. A general reduction of unit firing has been indeed observed in association with low-voltage fast activity at the onset of seizures recorded during presurgical intracranial monitoring in patients with focal, drug-resistant epilepsies. Moreover, focal seizures in animal models start with increased γ-aminobutyric acid (GABA)ergic interneuronal activity that silences principal cells. In vitro studies have shown that synchronous activation of $GABA_A$ receptors occurs at seizure onset and causes sizeable elevations in extracellular potassium, thus facilitating neuronal recruitment and seizure progression. A paradoxical involvement of GABAergic networks is required for the initiation of focal seizures characterized by low-voltage fast activity, which represents the most common seizure-onset pattern in focal epilepsies.

KEY WORDS: **Focal seizures, Inhibitory networks, GABA, Ictogenesis.**

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Key Points

- Enhanced glutamatergic excitation at the onset of a focal seizure is not supported by firm evidence
- A reduction of unit firing is observed in association with low-voltage fast activity at the onset of seizures in patients and animal models
- Synchronous activation of $GABA_A$ receptors occurs at seizure onset is typical of low-voltage fast activity focal seizure.

The understanding of the transition from the interictal condition into seizure generation (ictogenesis) is crucial in epileptology. Neurology textbooks as well as most reviews and original papers regard focal seizures as the expression of excessive synchronization of excitatory neuronal networks. This statement rests on the observation of large amplitude electroencephalography (EEG) transients during seizure activity both in patients presenting with focal epilepsy and in animal models of epilepsy. However, the presence of large, synchronous (and presumably excitatory) EEG events *during* a seizure does not necessarily imply that analogous mechanisms are responsible for its initiation. The events occurring at seizure onset may, therefore, be different from those involved in maintaining seizure activity. Moreover, the network and cellular mechanisms responsible for seizure generation are likely diverse in different forms of focal epilepsies.

Large amplitude EEG transients represent the most evident pattern associated with interictal activity in several forms of focal epilepsy. In patients as well as in experimental models of focal epilepsy, interictal spikes (i.e., short-lasting, large-amplitude EEG events occurring between seizures) correlate with brief increases in neuronal firing and are followed by a profound depression in excitability associated with a slow-wave component.[1] Based on in vivo intracellular recordings obtained from acute models of epileptiform synchronization, it was proposed >40 years ago that the transition from interictal to ictal activity results from weakening of the postspike "inhibitory" processes leading to an uncontrolled increase in excitation.[2] According to this hypothesis, *seizures* occur when excitatory glutamatergic transmission overcomes inhibition, thus transforming the short-lasting interictal event into a prolonged, large-amplitude epileptiform discharge. However, this scenario has been never confirmed. Rather, clinical evidence suggests that focal seizure onset is often characterized by decreased amplitude and "flattening" of the scalp EEG that correlates with low amplitude activity recorded with intracranial electrodes routinely utilized to identify the boundaries of the epileptogenic zone in patients with drug-resistant epilepsy candidate for epilepsy surgery.

Intracranial human data[3] and experimental evidence in animal models in vivo[4,5] and in vitro[6,7] have demonstrated that the most common EEG-onset pattern observed in focal seizures/epilepsies is characterized by low voltage fast activity (*preceded by ictal spikes or not*), whereas large amplitude discharges represent the established seizure core. As illustrated in Figure 1, human intracerebral recordings have demonstrated that seizure onset correlates with (1) waning of background activity, (2) the appearance of low-voltage fast activity in the beta-gamma range (30–100 Hz), and (3) a very slow field potential shift.[8–11] Such low-voltage fast focal-onset pattern gradually evolves within seconds into large-amplitude EEG discharges that are unmistakably recognizable as seizure activity. Of interest, the low-voltage fast seizure onset observed both in temporal lobe structures and in neocortical regions can be heralded by one or more large-amplitude synchronous potentials,[8,11,12] designated as preictal spikes (see subsequent text).

In this review we challenge the common belief that enhancement of glutamatergic transmission underlies the transition from interictal to ictal activity in focal seizures with low-voltage fast onset. We review clinical and experimental evidence that underscores the paradoxical and unexpected role played by γ-aminobutyric acid (GABA)ergic networks in seizure initiation. The preservation of GABAergic neurons in humans and in animal models of focal epilepsies, albeit controversial, is supported by numerous reports.[8,13] First, we address the results obtained in vivo by analyzing single unit activity in patients with epilepsy and in chronic animal models. Then, we discuss the role played by $GABA_A$ receptor signaling in seizure initiation. Finally, we propose a mechanistic model of ictogenesis that highlights the concept that synchronization of interneuron networks leads to increases in extracellular potassium that support seizure progression. Our hypothesis is specifically proposed for focal seizures that initiate with low-voltage fast activity and represent the most common seizure-onset pattern in focal epilepsies.[8,14]

Interneuron Activity Marks the Initiation of Focal Seizures

Early work performed in patients with drug-resistant epilepsy during presurgical EEG monitoring casted doubt on the experimental view that transition from interictal to ictal activity could result from increased excitation, as proposed

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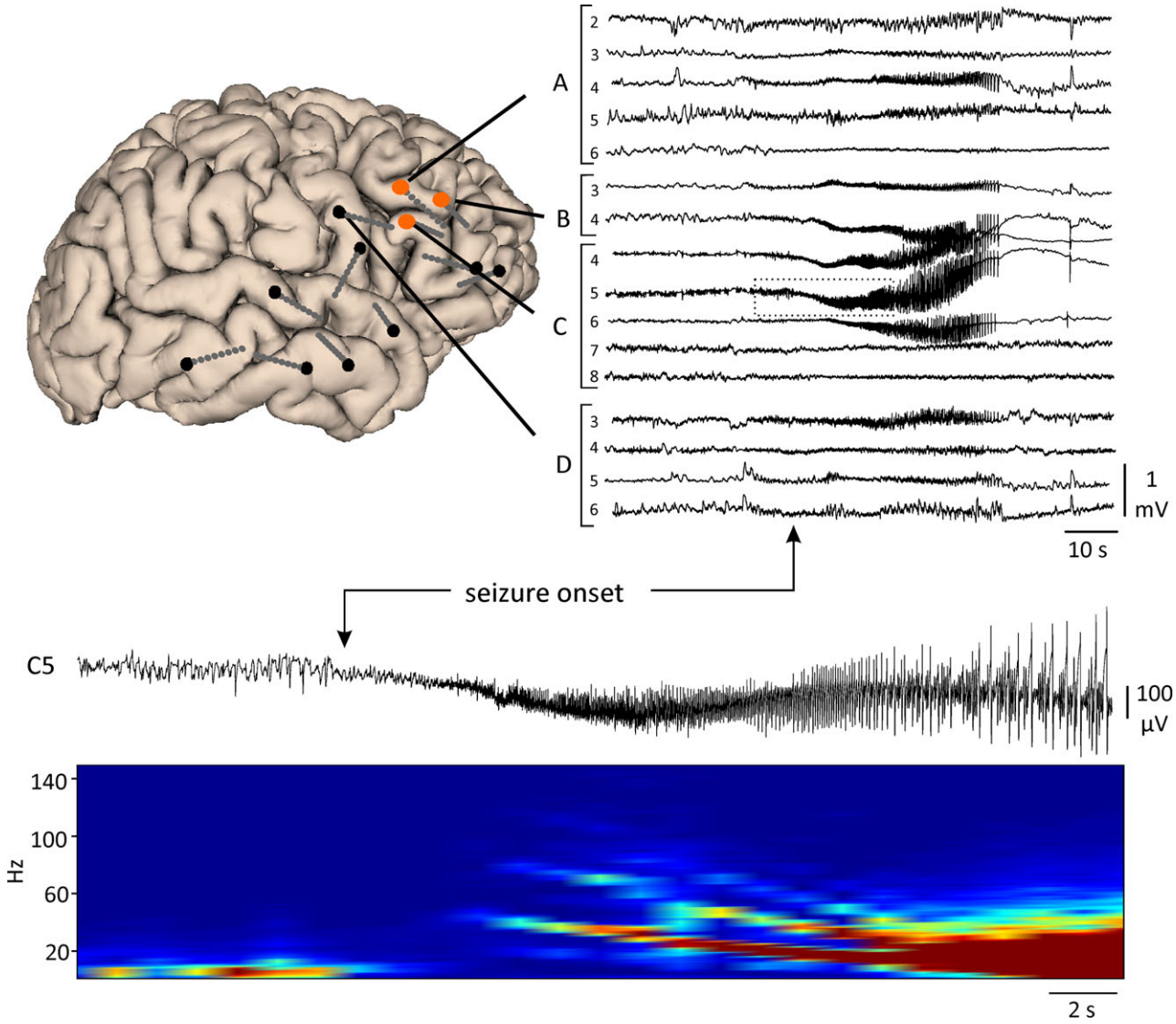

Figure 1.
Intracerebral signals recorded with multichannel stereo-EEG recording electrodes in a patient with a right frontal cortical dysplasia during presurgical monitoring. The onset of the seizure (arrows) correlates with low-voltage fast activity in the epileptogenic zone (contacts A3, B3, B4, C4, C5, C6, and D3 recorded with multichannel depth electrodes). The activity recorded at C5 is magnified below. The C5 signal frequency content at ictal onset illustrated in the power density graph demonstrates the presence of fast activity at 30–40 Hz (courtesy of Stefano Francione).

by Ayala et al.[2] Specifically, it reported a widespread reduction of neuronal firing at seizure onset, possibly due to inhibition of principal cells.[15] More recently, intracranial presurgical recordings with microelectrode arrays in patients with focal epilepsy have confirmed a reduction of firing in a large population of single neurons at seizure onset[16] (Fig. 2A). These data suggest that the low-voltage fast activity seen in the EEG at the beginning of focal seizures correlates with an arrest of principal cell firing possibly reflecting enhanced inhibition in the epileptogenic region. In addition, Schevon et al.[17] have demonstrated irregular and relatively low level of unit firing at the onset of ictal activity in patients with focal epilepsy; this phenomenon was interpreted by these authors as an inhibitory restraint that prevents the spread of the ictal discharge (see subsequent text).

The decreased firing of principal, glutamatergic neurons along with the enhanced activity of presumptive inhibitory cells has been documented in vivo with single-unit recordings performed in the hippocampus of pilocarpine-treated epileptic animals, which represent an established model of temporal lobe epilepsy.[18–20] These studies have shown that the initial 5–10 s of a seizure correlate with a virtual cease of principal neuron activity along with interneuron firing

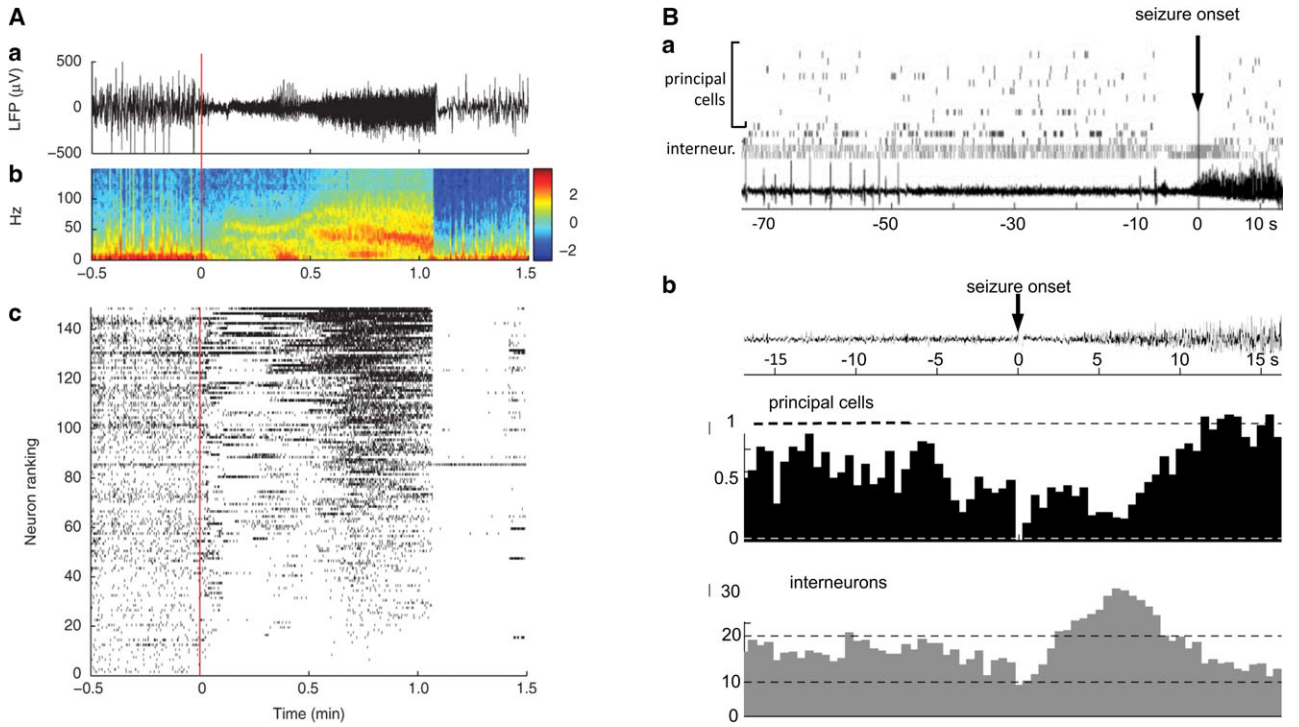

Figure 2.
Seizure-onset patterns in a patient (**A**) and in a rat (**B**) with focal epilepsy. (**A**) Focal seizure recorded in the temporal cortex with a subdural electrocorticographic electrode and a 10 × 10 multielectrode array in a patient with extensive focal lesion. Seizure onset is marked by the vertical line at time 0. Local field potential (LFP in **a**) and the corresponding spectrogram (**b**) are shown. In **c**, neuronal spike raster plot is shown including the activity of 149 neurons. Each dot represents the occurrence of an action potential. At seizure onset, most neurons either reduced or ceased firing; activity across the population became more homogenous as seizure progressed until spiking was abruptly interrupted in all neurons at seizure end. With the exception of a few neurons, spiking in the recorded population remained suppressed for about 20 s. From Truccolo et al., 2011,[16] with permission. (**B**) Firing of hippocampal neurons during a spontaneous seizure recorded in a pilocarpine-treated rat that developed temporal lobe epilepsy. Seizure onset is marked by the vertical arrows. In **Ba**, raster plots of interneurons (gray dots) and principal neurons (black dots) are illustrated. The local field potential is shown in the bottom trace. Interneurons increased the firing and principal cells reduced spiking just ahead and at seizure onset (time 0). In **Bb**, peri-event time histograms for average firing rates of pyramidal cells (in black) and interneurons (in gray) relative to the initial fast seizure activity. Data were averaged over 17 seizures and represent the activity of 154 pyramidal cells and 47 interneurons. Arrow indicates the average time of the onset of rhythmic ictal spiking. Bin size, 500 msec. Significance thresholds (dashed lines) are set at the mean ± 3 times the standard deviation from the 2 min prior to seizure onset. Kindly provided by Dr. Karen Moxon.

enhancement (Fig. 2Ba); such a pattern could be identified in >150 principal cells and about 50 interneurons recorded during several focal seizures[18] (Fig. 2Bb). Of interest, desynchronization of principal neuron firing[21] along with an increased activity of putative interneurons[22] was also identified at the transition from interictal to ictal activity in acute models of focal ictogenesis in vivo.

Overall these studies indicate that principal neurons are not hyperactive at seizure onset, presumably as the result of the increased firing of interneurons. However, a causal relation between increased interneuron activity and seizure initiation has not been identified in vivo. In the following section we address studies that have revealed the presence of synchronous GABAergic events at the start of focal seizure activity in vitro, and have provided evidence for a mechanism implicating $GABA_A$ receptor signaling in interictal to ictal transition.

$GABA_A$ Receptor Signaling Sparks Focal Seizures

As shown in Figure 3A, ictal discharges recorded in vitro from principal neurons in several limbic structures during application of the potassium channel blocker 4-aminopyridine start with an intracellular depolarization that is associated with few if any action potentials.[23] Paradoxically, this initial depolarizing component—which is mirrored by field activity—becomes hyperpolarizing when the neuron membrane potential is brought to values less negative than −60 mV with steady injection of depolarizing current (right

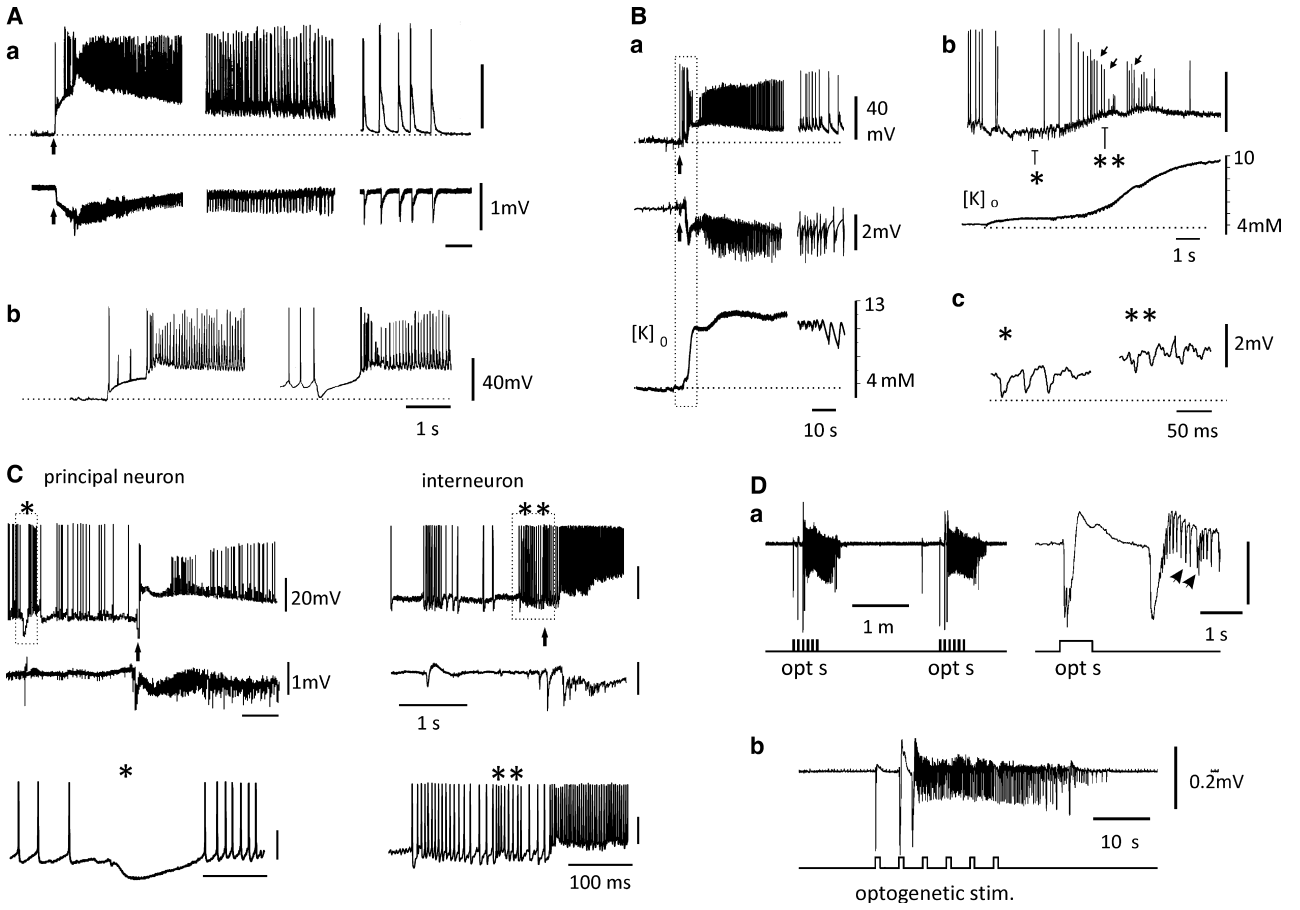

Figure 3.

Focal seizure patterns in different in vitro models of focal seizures. (**A**) Seizure-like activity in a slice of the rat entorhinal region induced by 4-aminopyridine. In **Aa**, intracellular (upper traces) and extracellular field recordings (lower traces) are illustrated. Seizure onset is marked by the vertical arrows. Spaces between the traces indicate time lapses of about 20 s. In **Ab**, intracellular recording during a different seizure-like event; note that depolarizing the membrane potential with intracellular injection of positive current (right trace) reveals a robust hyperpolarizing inhibitory potential at the onset of the seizure. Resting membrane potentials marked by the dotted line: a: −76 mV; b = −78 mV. In both **a** and **b**, the intracellular recording was obtained from a principal cell. (**B**) Acute seizure induced by arterial perfusion of 50 μM bicuculline in the entorhinal cortex of the in vitro isolated guinea pig brain (modified from Gnatkovsky et al. 2008[31]). Intracellular recording from a principal neuron, extracellular field response, and changes in the extracellular potassium ($[K^+]_o$) are shown in **Ba** at the onset of a seizure (arrow). In **Bb**, the intracellular potential and the potassium changes outlined in the dotted box in **Ba** are expanded. Small-amplitude, possibly ectopic spikes during the rising phase of $[K^+]_o$ are marked by the small arrows. Traces of low-voltage fast activity recorded intracellularly marked by the asterisks in **Bb** are further expanded in **Bc**. During the initial phase of the seizure, the membrane potential depolarizes and the amplitude of the fast inhibitory potentials decreases, suggesting a change in GABA chloride reversal potential. Resting membrane potential marked by the dotted line in **a** and **c** = −59 mV. (**C**) Seizure-like event recorded in the entorhinal cortex of the isolated guinea pig model during arterial perfusion of 50 μM 4-aminopyridine. On the left, extracellular (lower traces) and intracellular recordings from a principal neuron (upper traces) show that the ictal discharge is preceded by preictal population spikes associated with a hyperpolarizing potential (marked by the dotted outline and expanded in the lower trace). The inhibitory potentials associated with the preictal spikes show the typical reversal of inhibitory postsynaptic potential. Traces shown in the right panel are courtesy of Gianluca Breschi. Increased activity of an entorhinal cortex interneuron at seizure onset are shown in the right panels. (**D**) In the presence of 4-aminopyridine optogenetic activation of GABA-releasing parvalbumin-positive interneurons in a mouse entorhinal cortex slice induces ictal discharges; note that these extracellular field potential recordings are similar to those occurring spontaneously in the rat brain slice. Courtesy of Zahra Shri, Fred Manseau, Maxime Lévesque and Sylvain Williams.

trace in Fig. 3Ab). Therefore, in this in vitro model of epileptiform synchronization, ictal-discharge onset is associated with a powerful GABAergic event. In line with these data, Ziburkus et al.[24] have reported increased activity of interneurons at the onset of ictal discharges induced in vitro by 4-aminopyridine. Moreover, pharmacologic manipulations that antagonize $GABA_A$ receptors or decrease presynaptic release of GABA from interneurons, abolish

this initial synchronous event and prevent ictal discharge occurrence.[6] In vitro data supporting the participation of GABAergic inhibition in the initiation of seizure activity are not specific to the 4-aminopyridine model; similar findings have also been obtained in other models of focal seizures induced in brain slices by high-frequency tetanic stimulation,[25–28] in the isolated immature hippocampus by application of low magnesium medium,[29,30] and in the in vitro isolated guinea pig whole brain following proconvulsive drug treatment.[31–33] As illustrated in Figure 3B, fast beta-gamma activity observed at the start of an ictal discharge in the entorhinal cortex of the isolated guinea pig brain is paralleled by intracellular hyperpolarizing potentials that become smaller in amplitude as seizure progresses, suggesting a dynamic positive shift of the $GABA_A$-mediated inhibitory post-synaptic potential (IPSP) reversal potential.[29,34]

It should be remarked that fast-onset activity in seizures studied in vitro is usually preceded by one or more preictal spikes that correlated with bursting activity of GABAergic interneurons (Fig. 3C, right traces) and with inhibitory potentials in principal neurons (Fig. 3C, left traces[31]). Synchronous GABAergic potentials during the interictal period and just ahead of a focal seizure have been observed in brain slices obtained from different cortical areas and in the isolated guinea pig brain preparation.[23,32–34] As mentioned earlier, sequences of large amplitude spikes were observed at seizure onset in both humans and animal models in vivo.[11,35–37] Such preictal spikes are different from interictal spikes and should be considered as proper ictal events, since they occur exclusively at seizure onset. Of interest, seizure onset in human partial epilepsy has been hypothesized to be due to a reduction of GABAergic dendritic inhibition releasing an enhancement of somatic inhibitory interneurons generating fast IPSPs on pyramidal cells.[38]

The slow negative shift of the local field potential observed in association with preictal spikes and the ensuing low-voltage fast activity (lower extracellular traces in Fig. 3A–C) correlates with elevations in extracellular potassium (Fig. 3B)[31] that are known to accompany synchronous neuronal activity.[39–42] However, and even more important in the context of our hypothesis stating that seizure onset rests on "excessive GABAergic signaling," increases in extracellular potassium are induced by activation of $GABA_A$ receptors following application of GABA[39] or sustained interneuron activity, such as that occurring at seizure onset in rodent brain slices and in slices of human dysplastic cortex maintained in vitro.[23,25,43–46]

An explanation for these $GABA_A$ receptor–dependent elevations in extracellular potassium rests on the intracellular chloride accumulation that is known to occur in neurons once postsynaptic $GABA_A$ receptors are activated; this process increases the activity of the potassium-chloride cotransporter (KCC2), thus causing the efflux in the extracellular space of both potassium and chloride ions.[47] In addition, $GABA_A$ receptor–dependent elevations in extracellular potassium can also be contributed by network-driven, bicarbonate currents.[45,46] These mechanisms of extracellular potassium elevation mediated by GABA release are expected to involve an extensive population of mutually interconnected and electrically coupled interneurons that innervate a large number of principal cells.

Increased extracellular potassium concentration is well known to cause hyperexcitability and epileptiform synchronization[48] by (1) depolarizing neuronal membranes, (2) promoting the generation of small amplitude, possibly ectopic spikes[49] (arrows in Fig. 3A,B), (3) releasing the resonance of local networks to generate oscillatory patterns in the beta-gamma range,[50] and (4) causing a positive shift of the membrane reversal of $GABA_A$ receptor–mediated inhibitory postsynaptic potential that weakens inhibition and releases intrinsic excitatory mechanisms.[11]

The pivotal role played by interneurons in ictal discharge initiation has recently been confirmed with optogenetic techniques in the entorhinal cortex during 4-aminopyridine treatment.[51,52] In these studies, optogenetic stimulation of parvalbumin- or somatostatin-positive interneurons initiated ictal events similar to those occurring spontaneously (Fig. 3D); when the onset of an optically induced ictal discharge was expanded, the typical pattern characterized by one or two interictal spikes leading to the fast beta-gamma ictal activity could be identified (arrowheads in Fig. 3D). We should also mention that optogenetic studies have demonstrated that activation of GABAergic cells contributes to seizure maintenance[53] and can play a more conventional inhibitory role by contributing to the termination of ictal discharges.[54,55]

A New Model for Focal Ictogenesis

Taking into consideration the clinical and experimental evidence reviewed here, we propose a model of focal ictogenesis whereby GABAergic network activity initiates (and presumably maintains) seizures through the activation of $GABA_A$ receptors that are postsynaptically located mainly on principal glutamatergic cells. As mentioned earlier, we propose that "preictal" spikes reflect interneuronal network synchronization at seizure onset and thus belong to the ictal condition.

As summarized in Figure 4, interictal spikes are largely contributed by short-lasting synchronous discharges of action potentials generated by principal cells. Such activity is restrained by several mechanisms, including recurrent synaptic inhibition, that limit excitation both spatially and temporally, and hinder seizure occurrence. EEG spikes subsidized by interneuronal firing herald the period that immediately precedes seizure onset. The intense and possibly synchronous discharge of action

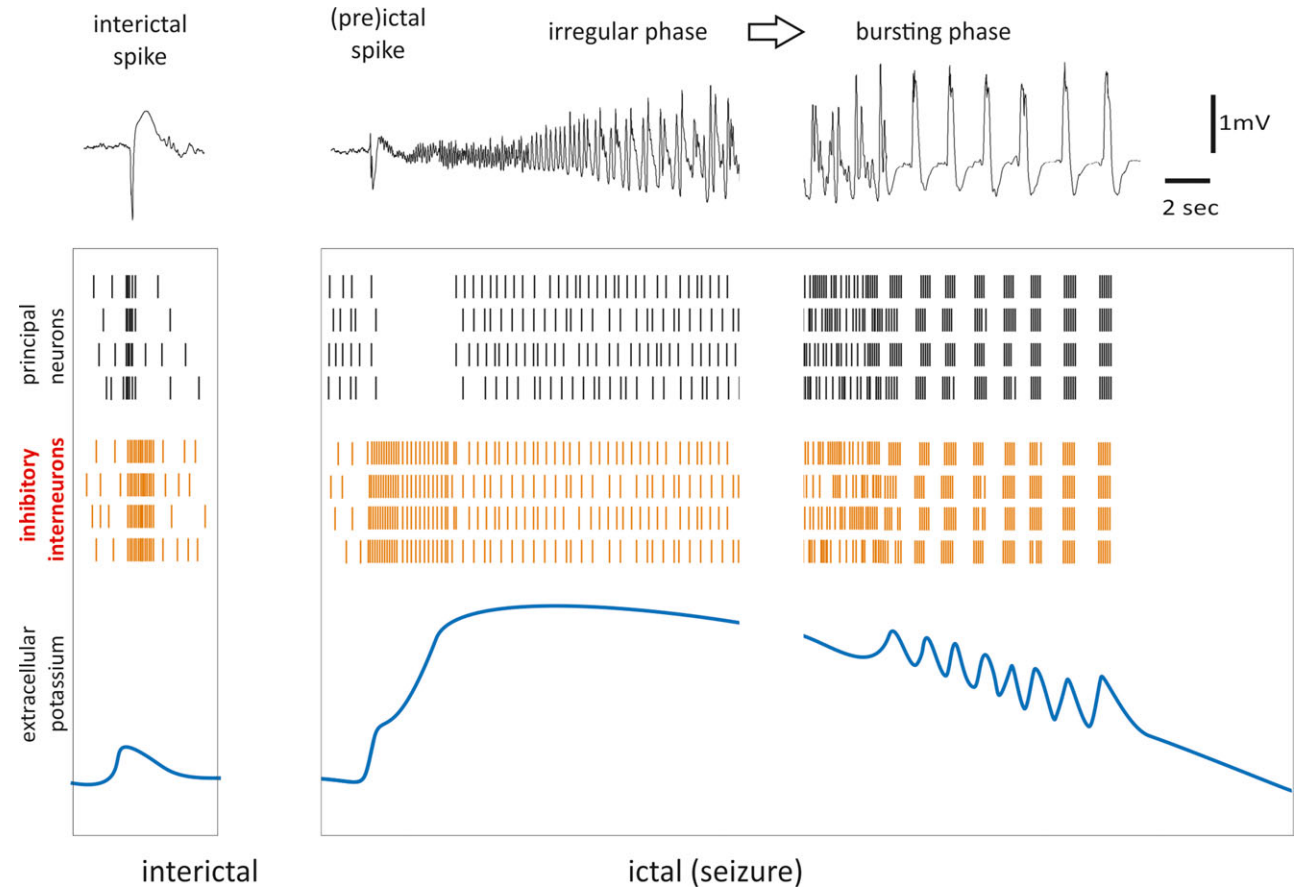

Figure 4.
Schematic model of focal ictogenesis. Representative traces of interictal and ictal discharges recorded extracellularly are shown on top. Action potential firing of principal neurons and interneurons is illustrated by black and red vertical bars, respectively. Changes in the extracellular potassium concentration are represented by the blue line. See text for the explanation.

potentials generated by interneurons during such spikes leads to a large release of GABA that inhibits and silences principal cells via activation of postsynaptic $GABA_A$ receptors. The cotransport of potassium and chloride out of principal neurons consequent to the activation of $GABA_A$ receptors will cause sizeable increases in extracellular potassium that depolarizes all neurons and contributes to the emergence of resonant low-voltage fast-network activity. Further increases in potassium also facilitate recruitment of principal cells, leading to overt seizure discharge, which is characterized by progressive, excessive, and simultaneous coactivation of glutamatergic and GABAergic networks.

Other Possible Interpretations of GABA Synchronization at Seizure Onset

Several researchers have confirmed the occurrence of GABAergic synchronization at seizure onset, but have provided different interpretations of ictogenesis. For instance, Trevelyan and colleagues[17,56] proposed that GABAergic activation represents an inhibitory restraint occurring ahead of the ictal excitatory wave and thus opposes the generation of epileptiform activity. This interpretation, however, rests on the nonverified assumption that excitatory-based ictal discharges have already started somewhere else (as in the model of focal seizures induced by local *N*-methyl-D-aspartate (NMDA) applications[57]) and on the presumption that GABA receptor signaling has a compensatory (reparative) function rather than an active role in seizure generation as reviewed earlier.

A possible interpretation of the role played by GABAergic synchronization at seizure onset is based on data obtained from immature/juvenile rodent brain tissue; specifically, it proposes that excessive interneuron activity during epileptiform discharges induces a shift of the $GABA_A$ receptor–mediated chloride reversal potential, thus transforming GABAergic signaling from inhibitory to excitatory.[58–60] However, neuronal firing during depolarizing GABA shifts was never demonstrated in adult animal models of seizures/epilepsy.

Conclusions

The clinical and experimental data reviewed herein suggest that the role of GABAergic networks in focal seizures is more complex than what was assumed in the past. The general belief that a reduction of GABAergic activity is proepileptic, whereas its increase protects against seizure precipitation, is presumably too simplistic and certainly reflects only one side of the coin. It is now well known that GABAergic networks can promote and sustain synchronous cortical fast oscillations in the beta-gamma range.[50] The observation that $GABA_A$-receptor signaling can synchronize neuronal networks and can promote seizures may explain the disappointingly limited efficacy of antiepileptic drugs designed in the 1980s to potentiate GABA receptor–mediated actions. More subtle modulations of $GABA_A$-receptor signaling should be envisioned to interpret the effects of currently available drugs and to develop new antiepileptic therapies. In line with this concept are the observation that bicarbonate efflux via $GABA_A$-receptor channels[61] is decreased by the carbonic anhydrase inhibitor topiramate and the demonstration of an antiseizure effect by the KCC2 antagonists that regulate chloride/potassium exchange. [62]

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Disclosure

The authors declare no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Additional Contributions

MdC and MA equally contributed to the design and the writing of this review.

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