Initiation, Propagation, and Termination of Partial (Focal) Seizures

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The neurophysiological patterns that correlate with partial (focal) seizures are well defined in humans by standard electroencephalogram (EEG) and presurgical depth electrode recordings. Seizure patterns with similar features are reproduced in animal models of partial seizures and epilepsy. However, the network determinants that support interictal spikes, as well as the initiation, progression, and termination of seizures, are still elusive. Recent findings show that inhibitory networks are prominently involved at the onset of these seizures, and that extracellular changes in potassium contribute to initiate and sustain seizure progression. The end of a partial seizure correlates with an increase in network synchronization, which possibly involves both excitatory and inhibitory mechanisms.

Partial (focal) seizures are transient events that occur without warning as the result of the pathological activation of cortical areas with dysregulated excitability. The pathogenic background of partial seizures is sustained by complex structural and functional alterations of neurons and glia, and may also involve changes in the extracellular matrix (Dityatev et al. 2010), neuro–glio–vascular interactions, and blood–brain barrier function (Wetherington et al. 2008; Seifert et al. 2010; Marchi et al. 2014). These modifications presumably result from an epileptogenic process triggered by the excitotoxic damage associated with the primary insult (trauma, anoxia, inflammation, etc.).

Because of their dependence on an initial pathogenic trigger, focal symptomatic epilepsies have been classified in the most recent proposal of the International League Against Epilepsy (ILAE) as epilepsies caused by structural–metabolic etiology (Berg et al. 2010; Berg and Scheffer 2011).

The electrographic epileptiform patterns expressed during a partial seizure are distinctive for the structures and networks entrained by the seizure discharge and, with some exceptions (see below), they are thought to be independent of the original primary insult (Pelliccia et al. 2013; Perucca et al. 2014). The existence of system-specific susceptibility to seizures and epi-

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lepsy is supported by the demonstration that arterial perfusion of proconvulsive drugs induce acute interictal and ictal epileptiform patterns, which are segregated to specific cortical systems (Librizzi and de Curtis 2003; Boido et al. 2014a). Moreover, it is well known in animal models that focal chronic alterations that mimic temporal lobe epilepsy (TLE) can arise from a generalized “status epilepticus” induced by intraperitoneal treatment with convulsants, such as pilocarpine or kainic acid. This evidence suggests, therefore, a specific vulnerability of the temporal lobe system to systemic treatments (see Avanzini et al. 2012). This experimental evidence also supports the concept that specific and restricted cortical networks/systems are prone to generate seizures (Avanzini et al. 2012). In line with this view, the concept of “epileptic network” is more appropriate than the term “epileptic focus” to describe the brain area of altered tissue involved in a focal seizure. In this review, we will, therefore, use “epileptic network” as a replacement for “epileptic focus,” but we will retain the term “partial” to describe seizures attributable to localized epileptic network activation.

The notion of epileptogenic or ictogenic network is also supported by the analysis of seizure patterns and activity distribution observed during presurgical electroencephalogram (EEG) monitoring, with intracranial and intracerebral electrodes in patients with partial epilepsies submitted to epilepsy surgery. These studies have shown that the epileptogenic region (i.e., the area to be surgically removed to cure the patient) is larger than both the epileptogenic lesion and the seizure-onset area (Rosenow and Lüders 2001; Kahane et al. 2006). In the case of human mesial TLE, for instance, seizure activity propagates to extrahippocampal regions, suggesting that the entire temporal lobe is involved (Spencer and Spencer 1994; Bartolomei et al. 2001). These functional data are supported by the demonstration that the histopathological damage in mesial TLE cannot be considered “focal,” because it includes different hippocampal and parahippocampal structures with variable rostrocaudal extension (Moran et al. 2001; Ögren et al. 2009; Tassi et al. 2010). Finally, in-

tracranial microelectrode recordings in humans have shown that partial seizure may initiate in different areas or microregions within the epileptogenic zone (Stead et al. 2010), suggesting that the paroxysmal activity generated at distant sites within an epileptogenic network contributes to ictal onset patterns observed with the diagnostic macroelectrodes (Bartolomei et al. 2001; Wendling et al. 2003).

The network mechanisms that contribute both to the generation of interictal discharges recorded between seizures and to the onset, progression, and end of partial seizures are still largely unexplained. In the first part of this report, we will review the processes that presumably initiate, sustain, and terminate a partial seizure. In the second part, we will analyze the correlation between interictal events and ictal discharges (de Curtis and Avanzini 2001; de Curtis et al. 2012; Avoli et al. 2013a).

SEIZURE PATTERNS

Partial seizures are self-terminating events, which typically last 2–6 min (Jenssen et al. 2006). In humans, their electrographic patterns can be characterized with different levels of detail, depending on the recording approach. Scalp EEG recordings are valuable to detect seizure propagation on the entire cortical mantle, ipsi-, and contralateral to the epileptogenic region, but they are not ideal to identify the onset patterns and area of seizure initiation (Pacia and Ebersole 1997). Scalp EEG recording is technically undemanding and shows that partial seizures correlate with large amplitude, rhythmic activity. Focal postictal slowing characterized by large amplitude activity in the “ δ ” frequency range is often seen at the end of the seizure. The onset of partial seizures recorded on the scalp is marked by a “flattening” of EEG signal and by the appearance of low amplitude and fast rhythms (Gloor 1975; Fariello et al. 1979).

Long-term intracranial recordings performed in surgical cases to locate the epileptogenic region are more accurate than scalp EEG to describe seizure patterns in proximity to the generators of the ictal discharge. With some exceptions, seizure patterns recorded in different

lobes and cortical areas do not differ substantially. In a recent report, among seven types of intracranial EEG seizure patterns identified in a population of patients with partial epilepsies caused by different etiologies (Perucca et al. 2014), two were the most commonly observed (see below). Ictal patterns specific for the underlying epileptogenic lesion have been described in type IIb focal cortical dysplasias (Tassi et al. 2002), periventricular heterotopias (Tassi et al. 2005), and mesial TLE with massive cell loss and gliosis (Spencer and Pappas 1992; Ogren et al. 2009).

Unlike seizure patterns in generalized idiopathic epilepsies, which present with sequences of large amplitude EEG oscillations (e.g., spike and wave complexes) virtually unmodified from the beginning to the end of the seizure, human “partial seizures show an evolving pattern that changes over time.” A typical partial seizure recorded with depth electrodes initiates either with low-voltage fast activity or “hypersynchro-

nous” potentials. This initial phase is followed by an irregular large amplitude activity, often defined as tonic discharge that evolves into phasic (clonic) activity characterized by rhythmic bursting followed by periods of electrical depression (Fig. 1) (de Curtis and Gnatkovsky 2009).

Long-term in vivo EEG monitoring in animal models of partial epilepsies show seizure patterns similar to those identified in human partial epilepsies. Evolving patterns are commonly observed in posttraumatic and poststroke epilepsy models (Pitkänen et al. 2006; Kadam et al. 2010), in models of mesial TLE either secondary to pharmacologically induced status epilepticus (Williams et al. 2009; Bortel et al. 2010; Levesque et al. 2012), or induced by kindling (Michalakis et al. 1998). As in humans, seizures in experimental animals with partial epilepsy occur randomly, often in clusters (Grabenstatter et al. 2005; Goffin et al. 2007; Williams et al. 2009).

Figure 1. Focal (partial) seizure patterns recorded with depth electrodes in the hippocampus of a patient suffering from human temporal lobe epilepsy (TLE) during presurgical stereo electroencephalogram (EEG) monitoring (*upper trace*: magnetic resonance image on the *left*, kindly provided by Stefano Francione), in the CA1 hippocampal region of the in vitro isolated guinea pig brain during bicuculline perfusion (*middle panel*: picture of the in vitro brain on the *left*), and in a temporal lobe slice maintained in vitro after perfusion with 4-aminopyridine (4AP) (*bottom panel*: picture of the slice on the *left*).

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In *in vitro* preparations (brain slices and *in toto* preparations) isolated from chronically epileptic animals, interictal activity can be seen, but seizures do not occur spontaneously and are usually evoked by either pharmacological manipulations or patterned stimulations. The absence of spontaneous seizures in *in vitro* preparations is presumably a result of the restricted network preserved following the slicing procedure, as well as other factors (e.g., fragmentation of neuro–glio–vascular interactions, release of factors during the slicing procedure, etc.). In most *in vitro* neocortical or hippocampal slices treated with convulsants (but not all; see Avoli and Williamson 1996; Avoli et al. 2002), seizure patterns do not show the typical progression of partial seizures observed *in vivo*. This is possibly a result of the factors mentioned above and should be carefully considered when *in vitro* preparations are used to study focal ictogenesis. However, when brain slices containing broader networks are used (e.g., slices comprising the entorhinal and hippocampus), seizures with an evolving pattern similar to the *in vivo* condition are induced by pharmacological manipulations (Avoli and Williamson 1996; Avoli et al. 2002; Avoli and de Curtis 2011).

SEIZURE ONSET

Scalp EEG recordings in humans show that the most frequent marker of seizure onset is a reduction in the amplitude of background activity coupled with the appearance of fast activity in the β – γ range (so-called EEG flattening; Gloor 1975; Fariello et al. 1979; de Curtis and Gnatkovsky 2009). Clinical studies based on long-term intracranial depth recordings from the epileptogenic zone during presurgical stereo-EEG monitoring confirmed that the most common pattern at seizure onset is characterized by the abolition of background activity that is replaced by low-voltage fast activity at 20–100 Hz (“ β – γ ” range) (Allen et al. 1992; Fisher et al. 1992; Gotman et al. 1995; Gnatkovsky et al. 2011), which is often superimposed to a very slow potential (Ikeda et al. 1999; Bragin et al. 2007; Gnatkovsky et al. 2014; Wu et al. 2014). Low-voltage fast activity has a critical localizing/

lateralizing value, and is detected in the large majority of intracranially explored partial epilepsies, such as TLEs, focal cortical dysplasias, and postanoxic lesions (Gotman et al. 1995; Pelliccia et al. 2013). This EEG pattern is observed in the majority of intracranially explored partial epilepsies, such as TLEs, focal cortical dysplasias, and postanoxic lesions. Another common seizure-onset pattern, defined as hypersynchronous, is characterized by large-amplitude spike potentials (Engel et al. 1990; Maillard et al. 2004). The hypersynchronous pattern is most often seen in TLEs with hippocampal sclerosis (Spencer et al. 1992; Ogren et al. 2009) and was never reported in neocortical focal epilepsies. Other less frequent patterns of seizure initiation have been described (Perucca et al. 2014) and are interpreted as either propagated activity or “far fields,” which are volume-conducted from the cortical generators. These patterns, therefore, do not localize the epileptogenic network.

Both low-voltage fast activity and hypersynchronous seizure-onset patterns are typically observed in animal models of mesial TLE (Engel et al. 1990; Bragin et al. 1999; Levesque et al. 2012) and in models of acute temporal seizures (Bragin et al. 1999; Zhang et al. 2012; Levesque et al. 2013; Boido et al. 2014a). These two patterns may be the expression of the activation of the same networks, because the large-amplitude spikes typically detected in the hypersynchronous pattern are often followed by short runs of low-voltage fast activity (Perucca et al. 2014). In line with the concept of the epileptic network, experimental work has shown that both patterns are generated by the limbic system *in vivo* in the pilocarpine model of mesial TLE (Levesque et al. 2012), and in the *in vitro* whole guinea pig brain treated with different convulsant drugs, such as bicuculline or 4-aminopyridine (4AP) (Uva et al. 2005; Carriero et al. 2010; Boido et al. 2014a).

Further insight to the cellular mechanisms underlying low-voltage fast activity and hypersynchronous seizure onsets, rests on *in vivo* data obtained by analyzing the high-frequency oscillations (HFOs) occurring during the preictal and ictal periods in pilocarpine-treated epi-

leptic rats. HFOs are categorized as ripples (80–200 Hz) and fast ripples (250–500 Hz) (Jefferys et al. 2012a), and it has been proposed that ripples represent inhibitory postsynaptic potentials (IPSPs) generated by principal neurons entrained by synchronously active interneuron networks (Ylinen et al. 1995), whereas fast ripples reflect synchronous in-phase or out-of-phase firing of abnormally active (Jefferys et al. 2012) principal cells, thus being independent of inhibitory neurotransmission (Dzhala and Staley 2004; Foffani et al. 2007; Engel et al. 2009; Ibarz et al. 2010; Bragin et al. 2011). According to the findings reported by Avoli and colleagues (Levesque et al. 2012), low-voltage fast activity seizures are mainly associated with increased ripple rates, whereas hypersynchronous seizures are mostly accompanied by fast ripples. Moreover, the increases in occurrence of fast ripples during hypersynchronous seizures and ripples during low-voltage fast activity seizures are mostly occurring in seizure-onset zones, suggesting that they could reflect distinct, as well as specific, mechanisms of ictogenesis (Levesque et al. 2012).

Low-voltage fast activity and hypersynchronous onset patterns can also be reproduced in a combined hippocampus–entorhinal cortex, or hippocampus amygdala slices perfused in vitro with either 4AP (Lopantsev and Avoli 1998; Avoli et al. 2013b), low-magnesium and high-potassium solution (Derchansky et al. 2006; Zhang et al. 2012), as well as following high-frequency tetanic stimulation (Isomura et al. 2008; Fujiwara-Tsukamoto et al. 2010). In these in vitro models, low-voltage fast activity onset is characterized at the start by a prominent activation of inhibitory interneurons (Velazquez and Carlen 1999; Kohling et al. 2000; Ziburkus et al. 2006; Lasztocki et al. 2009; Fujiwara-Tsukamoto et al. 2010), which transiently shut off principal cells (Fig. 2A) (Gnatkovsky et al. 2008). In the in vitro isolated guinea pig brain preparation, enhanced activity of inhibitory neurons in the entorhinal cortex lasting several seconds was consistently observed in correspondence with low-voltage fast activity induced by either low concentrations of bicuculline or 4AP (Gnatkovsky et al. 2008; Uva et al. 2009). During this

initial period, principal neurons of superficial and deep layers of the entorhinal cortex were silent and resumed firing when inhibition was presumably neutralized by the changes in extracellular potassium associated with interneuronal firing (see below) (Gnatkovsky et al. 2008; Trombin et al. 2011). The enhanced activation of the potassium-chloride cotransporter KCC2 in principal neurons during synchronous inhibitory GABAergic activation has been proposed as a potential mechanism of the potassium elevations that are associated with the onset of the ictal discharge (see Figs. 2B and 4A, as well as the next paragraph) (Lopantsev and Avoli 1996; Viitanen et al. 2010). The role of large amplitude preictal GABAergic potential in driving the epileptogenic network into seizure will be discussed in the last paragraph (see below).

Trevelyan and colleagues (2006, 2007) proposed that the increase of inhibitory network activity just ahead of a seizure may reflect the attempt of the network to impede seizure precipitation by imposing a feedforward inhibition on excitatory networks. When such inhibition fails, seizure activity characterized by hyperactivity of principal neurons ensues (Trevelyan et al. 2006, 2007). This interpretation was also suggested by Cammarota et al. (2013), who analyzed the propagation of seizures induced by local application of *N*-methyl-D-aspartate (NMDA) in the entorhinal and temporal cortex in a brain slice preparation. The failure of inhibition to control seizure activity in this model is caused by a depolarizing block of interneurons (Cammarota et al. 2013), a phenomenon that was never shown in vivo. A depolarizing block of the firing generated by inhibitory cells was also proposed as a seizure-initiation event in another model of acute seizures in the immature hippocampus in vitro (Derchansky et al. 2006; Ziburkus et al. 2006; Holler et al. 2011). However, the reduction of interneuron activity as responsible for the recruitment of principal cells has not been shown in these models. Interestingly, a prominent bursting activity of interneurons is observed at the very onset of the seizure in these studies. The hypersynchronous seizure onset detected in these models is differ-

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Figure 2. Focal seizure onset in vitro. (A) Simultaneous intracellular (*upper trace*) and extracellular (*lower trace*) recordings from the entorhinal cortex of the isolated guinea pig brain during a seizure induced by 4-aminopyridine (4AP). Seizure onset (marked by the arrow) correlates with a hyperpolarizing transient followed by neuronal depolarization. (B) Simultaneous recording of field potentials and changes in the extracellular concentration of potassium ($[K^+]_o$) during a seizure induced by bicuculline in the entorhinal cortex of the isolated guinea pig brain.

ent from the low-voltage fast activity pattern seen during partial seizures in chronic epilepsy models and in humans.

Hypersynchronous pattern at seizure onset is most consistently observed when cortical excitability is enhanced in brain slices by a solution containing low magnesium and high potassium (Derchansky et al. 2006; Lasztoczi et al. 2009; Zhang et al. 2012). In these conditions, a gradual recruitment of both inhibitory and excitatory networks occurs (Derchansky et al. 2008). Zhang and colleagues (2012) confirmed that, also during the hypersynchronous seizure onset, the interictal and early preictal states are dominated by GABAergic activity, and that seizure onset coincides with (or is, perhaps, heralded by) exhaustion of presynaptic release of GABA, associated with unopposed increased glutamatergic events. A buildup of glutamatergic synaptic excitation with progressive recruit-

ment of neurons was suggested to be responsible for the hyperexcitable state during transition to seizure in both experimental in vitro preparations (Cossart et al. 2001; Trotter et al. 2006; Derchansky et al. 2008), and postsurgical human tissue studied in vitro (Huberfeld et al. 2011). According to what is discussed above, an increase of inhibitory network activity is consistently observed at seizure onset. However, whether this process represents the very onset of a seizure, or the ultimate attempt to impede seizure outburst in a hyperexcitable network, is still an unresolved issue.

A decrease in neuronal activity of principal cells at seizure onset was recently confirmed during partial seizures recorded in the hippocampus of epileptic rats after pilocarpine-induced “status epilepticus” (Grasse et al. 2013). In this study of unit activity performed with tetrode electrodes, the decrease in firing gener-

ated by principal neurons was preceded by an increase in the activity of units identified as inhibitory interneurons. A reduction of unit activity at seizure onset was seen also in multiunit studies performed during presurgical intracranial monitoring in drug-resistant patients with partial epilepsy (Truccolo et al. 2011; Bower et al. 2012; Schevon et al. 2012), suggesting that dampening of neuronal firing at the very beginning of a partial seizure occurs in epileptic patients as well.

As a correlate of the evidence summarized above, low-voltage fast activity in the β/γ range substitutes in humans the background rhythmic activity, suggesting that a selective synchronization in a narrow frequency band, rather than a synchronization of large amplitude discharges, occurs at seizure onset. A reduction in synchronization during the early phases of a seizure was shown in patients by intracranial multi-channel EEG signal analysis (Mormann et al. 2003; Schindler et al. 2007a), in cortical and hippocampal slices maintained in vitro (Netoff and Schiff 2002), and by unit activity recordings in models of drug-induced hippocampal seizures in vivo (Cymerblit-Sabba and Schiller 2012). Therefore, diffuse and widespread synchronization is not a typical pattern at the beginning of most partial seizures observed in humans and animals (Jiruska et al. 2013).

SEIZURE MAINTENANCE AND TERMINATION

After seizure onset, characterized by low-voltage fast or hypersynchronous patterns, a transition into a tonic discharge is consistently observed in partial seizures recorded intracranially in humans and animal models (Lopantsev and Avoli 1998; de Curtis and Gnatkovsky 2009). This transition may result from changes in extracellular potassium associated with the increased activity in interneurons (or in principal neurons, according to the alternative KCC2 hypothesis; see below) on network excitability. Several studies by the German school (Heinemann et al. 1977) showed that seizure onset correlates with extracellular enhancements in potassium. Later studies showed that synchronous activation of

inhibitory networks is sufficient to generate large changes in extracellular potassium concentration (Avoli et al. 1996b; Avoli and de Curtis 2011). As mentioned above, an inhibitory network-driven increase in extracellular potassium is also contributed by the neuronal KCl cotransporter, KCC2, which mediated KCl extrusion from principal neurons during GABAergic inhibition (Viitanen et al. 2010). According to this view, inhibitory network activity and the consequent release of GABA by interneurons massively activated GABA_A receptors, leading to intracellular accumulation of chloride that, in turn, forces KCC2 to extrude potassium.

The increased extracellular potassium, in turn, influences inhibition by reducing the electrochemical drive of chloride ions, and results in a reduction in the inhibitory constrain imposed by the inhibitory network activity observed at seizure onset. In the isolated guinea pig brain, transition from low-voltage fast activity into tonic firing correlated with the increases in extracellular potassium (Trombin et al. 2011). In this study, it was suggested that the elevated potassium could directly induce ectopic firing in principal neurons (but, see also Avoli et al. 1998; Avoli and de Curtis 2011). The decrease in inhibition coupled with ectopic firing may reinforce excitatory interactions between principal cells that reciprocally recruit and generate the firing typically observed during the tonic discharge.

In all partial seizures described in epileptic patients or animals, as well as in acute seizures induced by pharmacological manipulations, a transition from tonic firing into rhythmic bursting (also referred to as “clonic” phase of the seizure, an indefinite term derived from the clonic contractions observed at the end of a generalized seizure) is consistently observed. This tonic-to-bursting transition could be accounted for by the progressive synchronization of neuronal firing that occurs when principal neurons are reactivated during the tonic phase. Large amplitude activity synchronized in time and in space represented by large amplitude bursts typically develops at the end of a partial seizure, strongly suggesting that synchroniza-

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tion of excitation may be involved in seizure termination (Topolnik et al. 2003; Jiruska et al. 2013). Resynchronization of intracranial signals during the late seizure phase was shown in human partial seizures (Wendling et al. 2003; Schindler et al. 2007b), suggesting that networks are fragmented at seizure onset and merge during seizure progression, to form a single dominant component before seizure termination (Kramer et al. 2012).

Progressive enhancement of burst activity during the late phase of seizures is associated with a parallel increase of the interburst interval, suggesting that enhanced excitation (burst activity) and enhanced inhibition (postburst inhibition/depression) may develop in parallel when seizures come to an end (Fig. 3). Analysis of responses to local stimulation just supra-threshold for burst generation during focal seizures recorded in the isolated guinea pig brain preparation confirmed that interburst intervals correlated with an inhibition/depression lasting 1–2 sec (Boido et al. 2014b). These data show that conflicting enhancement of both excitation and the ensuing inhibition char-

acterize the end of a focal seizure and suggest that long postburst depression during the late ictal phase may stop the seizure by preventing further reactivation of the network (Boido et al. 2015). Postburst inhibition/depression was also shown after interictal spikes in the cat hippocampus in vivo (Lebovitz 1979), the olfactory cortex of the isolated guinea pig brain (de Curtis et al. 2001), and human neocortex of patients with partial epilepsy (de Curtis et al. 2005). A postburst refractory period may be caused by synaptic inhibitory potentials that resume in late phase of seizures (Isomura et al. 2008), activity-dependent changes in ion concentrations (K^+ , Cl^- , Ca^{2+}) and pH (Bragin et al. 1997; Velisek 1998), or by inhibitory neuromodulators, such as adenosine (During and Spencer 1992; Boison 2013).

Interestingly, seizure termination characterized by synchronous periodic bursting involves cortical areas more diffusely than at seizure onset. These rather consistent and intriguing findings might be explained by considering the involvement of subcortical structures. After the end of a partial seizure, postictal depression is

Figure 3. Partial seizure recorded from the hippocampal region of a patient with partial epilepsy during presurgical stereo-EEG monitoring (kindly provided by Stefano Francione). The seizure is characterized by fast activity at onset, followed by tonic activation, and terminates with bursting activity that progressively slows down before seizure end. The closing phase of the seizure correlates with a progressive increase in interburst interval, measured in the shaded area outlined on the EEG trace (see Boido et al. 2014b). TLE, temporal lobe epilepsy.

evident and can be measured as a reduction of background activity in comparison with the preictal condition.

INTERICTAL EVENTS AND SEIZURES

Pathological epileptiform activity (termed interictal discharge or spike) can be recorded in the EEG between seizures. Interictal discharges assume different forms, the most common being spikes and sharp waves along with HFOs (see Gotman 1984; de Curtis and Avanzini 2001; Engel et al. 2009; Avoli and de Curtis 2011; de Curtis et al. 2012; Jefferys et al. 2012b). Early, presurgical studies, which were focused on the analysis of the distribution of interictal spikes, showed that the area of spike/sharp wave generation, defined as irritative zone (Talairach and Bancaud 1966), is usually larger than the epileptogenic/seizure-onset zone.

Overall, no coherent relationship has been found between seizure and interictal spike occurrence. For instance, pioneering animal studies on acute seizures induced by topical application of proepileptic agents, such as penicillin, to the cortex suggested that the transition to seizure is characterized by acceleration of interictal spikes (Dichter and Spencer 1969; Ayala et al. 1973). Similar findings were also reproduced in acute, drug-induced seizures in *in vitro* models (Chamberlin et al. 1990). Extensive work achieved in patients during scalp EEG and intracranial recordings (Lieb et al. 1976; Lange et al. 1983; Gotman 1984; Katz et al. 1991; de Curtis and Avanzini 2001) and in chronic animal models of epilepsy (Ralston 1958; Elazar and Blum 1974; Gotman 1984; Sherwin 1984; Leung et al. 1990) showed that the rate of interictal discharges can either increase or decrease just ahead of a seizure. Therefore, these findings suggest that although interictal spikes/sharp waves are pathological events generated by the epileptic network, they are not necessarily correlated to seizure occurrence.

Experimental and clinical data have, however, shown that sustained interictal spiking, either spontaneously occurring or promoted by low-frequency stimulation, reduces the probability to generate a seizure discharge (Fig. 4)

(Nakagawa and Durand 1991; Barbarosie and Avoli 1997; Librizzi and de Curtis 2003; Tellez Zenteno 2006; Koubeissi et al. 2013). Activity-dependent changes in excitability, pH, and gap-junction coupling should contribute to the ability of frequent interictal spiking to prevent the occurrence of seizures. In addition, *in vitro* evidence suggests that a main player in controlling ictogenesis might rest on the ability of recurring interictal spikes to decrease the transient elevations in extracellular potassium that, at least experimentally, appear to be instrumental for ictal discharge onset (Barbarosie et al. 2002; Avoli et al. 2013a).

Large amplitude preictal spikes are commonly observed in limbic areas just ahead of seizure onset in patients with TLE (Lange et al. 1983; Bragin et al. 2005; Wendling et al. 2005). Several experimental studies also confirmed that preictal spikes are consistently observed before seizures induced by acute pharmacological treatments (Avoli 1990; Avoli et al. 1996a; Lopantsev and Avoli 1998; Gnatkovsky et al. 2008; Carriero et al. 2010). Avoli and collaborators showed that ictal discharges induced by 4AP in brain slices of different cortical structures initiated with an inhibitory event that showed the membrane reversal of GABA_A receptor-mediated synaptic potentials (Lopantsev and Avoli 1998; Avoli and de Curtis 2011). In the isolated guinea pig brain, epileptic spikes that occur between seizures are sustained by glutamatergic transmission, whereas preictal spikes correlate with IPSPs, possibly sustained by activation of inhibitory networks and coupled with depression of neuronal firing in principal excitatory neurons (Gnatkovsky et al. 2008). These findings are at variance with data obtained from *in vitro* subiculum slices from postsurgical specimens of patients with hippocampal sclerosis. In this model, interictal spikes are abolished by the GABA_A receptor antagonist, whereas preictal spikes induced by a complex proepileptic solution are supported by glutamatergic networks (Huberfeld et al. 2007, 2011). Preictal as well as interictal spikes appear to be contributed by both GABAergic and glutamatergic mechanisms (Avoli and de Curtis 2011).

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Figure 4. Effects of low-frequency stimulation in vitro. (A) Lesioning the Schaffer collateral changes the pattern of epileptiform activity recorded from the entorhinal cortex (EC) in a combined mouse brain slice with field and potassium-selective microelectrodes. Under control conditions, EC neuronal networks generate fast interictal activity, which is driven by inputs arising in the CA3 subfield of the hippocampus. Cutting the Schaffer collateral prevents CA3-driven interictal activity from propagating the EC and uncovers slow interictal events, along with ictal discharge in this area. Note that the slow interictal spike (open arrows) is associated with an increase in extracellular potassium that is smaller than what occurs in coincidence with the spikes leading to ictal activity (black arrows). Note, also, the much larger elevation in extracellular potassium ($[K^+]_o$) occurring during the overt ictal discharge. (B) Effects induced by electrical stimuli at 1 Hz on the epileptiform activity recorded from the entorhinal cortex and the dentate gyrus during 4-aminopyridine (4AP) application. In this slice, the Schaffer collateral was cut at the beginning of the experiment. Note that ictal activity (asterisk) is abolished during the stimulation (stim) period and reappears on termination of the stimulation. DG, Dentate gyrus.

CONCLUSIONS

We have reviewed the fundamental processes that initiate, sustain, and terminate partial seizures, as well as how interictal and ictal activities correlate. We have, indeed, presented experimental evidence that clearly underscores the role of both excitatory and inhibitory synaptic transmission within neuronal networks, which include principal glutamatergic neurons, along with inhibitory interneurons. However, further mechanisms may play important roles in epileptiform synchronization. For instance, because epileptiform activity both in *in vivo* and

in vitro preparations is accompanied by decreases in extracellular Ca^{2+} that are incompatible with efficient transmitter release (Pumain et al. 1985), slow changes in extracellular ionic concentrations, which modulate intrinsic excitability, as well as ephaptic interactions, cannot be overlooked (Jefferys et al. 2012b). In addition, astrocytes perform complex tasks that go beyond the well-known function of neurotransmitter uptake/recycling and extracellular potassium buffering; these mechanisms, which are dysfunctional in the epileptic tissue, are also, presumably, involved in hyperexcitability and, thus, seizure generation in epileptic disorders

(Steinhauser and Boison 2012; Steinhauser et al. 2012; Crunelli and Carmignoto 2013).

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