Neurobiology of Disease 125 (2019) 190–197

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

$GABA_A$ receptor-mediated networks during focal seizure onset and progression *in vitro*

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A B S T R A C T

Focal seizures are triggered by the pathological synchronization of a functionally altered group of neurons. *In vivo* and *in vitro* results in rodents and single unit studies in humans suggest that seizure can be initiated by increased activity in interneuronal networks. We review here the data derived from *in vitro* perparations to describe the function of GABAergic network in different phases of focal seizures. The data demonstrate that GABA-mediated synchronization of interneuronal activity has an active role in shaping focal seizure dynamics.

Focal seizures are the expression of perturbed excitability triggered by the pathological synchronization of a functionally altered group of neurons. It is often stated that seizures are due to the disruption of the balance between excitation and inhibition that contributes to maintain the normal cortical excitability. It is also commonly assumed that this balance is altered when (glutamatergic) synaptic excitation is enhanced or when (GABAergic) inhibitory transmission is dampened or reduced. This postulation is attractive but simplistic, and does not consider alternative hypotheses, such as the synchronizing role of GABAergic networks or the control of brain excitability by extracellular ion changes.

With respect to the synchronizing action of GABAergic activity, two main elements should be considered. The synchronous activation of specific subtypes of GABAergic inhibitory interneurons controls the output of a very large number of principal cortical neurons, as well as of other interneurons (Pelkey et al., 2017; Tremblay et al., 2016). It has been demonstrated that individual GABAergic interneurons can effectively synchronize the activity of excitatory cells by imposing a rebound firing in principal neurons after a transient and synchronous hyperpolarizing synaptic potential (Chang et al., 2018; Cobb et al., 1995). Through this rebound mechanism, a single inhibitory GABAergic cell can promote synchronization of a large populations of neurons. It is also very important to recognize that synaptic GABA function sustains spontaneous and event-driven synchronous activity in the normal brain, mainly through the generation of oscillations in the *beta-gamma* frequency band (> 20 Hz). The role of $GABA_A$ receptor-mediated network activity in physiological rhythmogenesis has been the focus of several reviews that examined *in vitro* and *in vivo* studies performed in different experimental settings. For an update on this topic, we refer the reader to these reports (Bartos et al., 2007; Mann and Paulsen, 2007) and to the contributions by Avoli et al., Peyrache et al. and Williams et al. in the present Special Issue. Interestingly, one line of evidence suggests that GABA-receptor dependent fast activity can be evoked both by sensory stimulation (Pritchett et al., 2015) and by performing cognitive tasks (Fries et al., 2007; Lachaux et al., 2012). The relevance of internal or external stimuli in generating physiological GABA-dependent oscillatory activity and also pathological synchronization is intriguing and may be invoked to explain why certain types of seizures are triggered by sensory stimulations (*i.e.*, reflex seizures, music-induced seizures, reading seizures, *etc.*). These aspects have not been thoroughly explored and require proper experimental assessment. Cortical high frequency fast activities, such as pathological “epileptic” high-frequency oscillations (HFOs), are also in some cases reported to be sustained by GABAergic networks (as reviewed in (Jiruska et al., 2017; Ylinen et al., 1995; Levesque et al. in this Special Issue), further strengthening the concept that altered GABAergic activity likely sustains interictal and possibly also ictal epileptiform discharges.

The evidence mentioned in the previous paragraphs supports the notion that GABAergic networks play a role not only in physiological synchronization, but also in pathological epileptiform synchronization. Based on the premises that GABAergic network activity does not dampen excitation exclusively, we will review the data on GABAergic network function mediated by $GABA_A$ receptors during the initiation, the progression and the termination of focal seizures analyzed on brain slices and other *in vitro* preparations. Previous reports reviewed GABA involvement in the generation of epileptiform activity (Avoli and de Curtis, 2011; de Curtis and Avoli, 2016) and recent additional evidence prompted its reexamination.

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https://doi.org/10.1016/j.nbd.2019.02.007
Received 19 November 2018; Received in revised form 8 January 2019; Accepted 7 February 2019
Available online 08 February 2019
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1. Epileptiform activity *in vitro*

A relevant issue to consider in the context of *in vitro* experiments is the notion that seizure-like events (*SLEs*) do not occur spontaneously *in vitro* (see Dulla et al., 2018). With the exception of long-term organotypic hippocampal slice cultures maintained *in vitro* for at least 1 week (Berdichevsky et al., 2012), *in vitro* studies of epileptic seizure-genesis are based on SLEs induced by a precipitating condition. This applies also to studies performed on brain slices obtained from chronically epileptic animals and in cortical and hippocampal slices obtained from human tissue from therapeutic surgical resections performed in patients with focal epilepsy resistant to pharmacological treatment (for review see Jones et al., 2016; Raimondo et al., 2017; Dulla et al., 2018). SLEs can be reliably induced *in vitro* by pharmacological manipulations: $GABA_A$ receptor blockers and 4-aminopyridine (4AP) are the most commonly utilized pro-epileptic drugs (Hablitz, 1984; Macdonald and Barker, 1977; Perrault and Avoli, 1992; Perreault and Avoli, 1991). SLEs can be induced *in vitro* also by increasing potassium (K^+) or by lowering magnesium (Mg^{2+}) and/or calcium (Ca^{2+}) concentration in the composition of the extracellular solution utilized to incubate the brain tissue (Anderson et al., 1986; Mody et al., 1987; Tancredi et al., 1990; Taylor and Dudek, 1982; Yaari et al., 1986). Moreover, seizure-like activities are obtained on *in vitro* slices by delivering electrical stimulation at high frequency directly on brain tissue (Fujiwara-Tsukamoto et al., 2003; Stasheff et al., 1989). These experimental conditions have been utilized in slices of different cortical brain areas and in more extensive brain preparations, such as the immature *in toto* hippocampus (Derchansky et al., 2004; Khalilov et al., 1997) and in the *in vitro* isolated adult guinea pig brain preparation (de Curtis et al., 2016; de Curtis et al., 2017), to induce both interictal epileptiform discharges (interictal spikes and/or HFOs) and SLEs that mimic seizure patterns observed in human focal epilepsies. The two most frequent and more thoroughly analyzed *in vitro* SLE onsets are characterized by the hypersynchronous and the low-voltage fast activity pattern (Avoli et al., 2016; Boido et al., 2014b; Devinsky et al., 2018; Jiruska et al., 2013; see also Weiss et al., in this issue). As discussed in the next paragraphs, the role of GABAergic networks in the initiation of these two different patterns of focal seizures can be very different.

Finally, it has to be pointed out that the read-out of network interactions with neurophysiological techniques contributes to understand the mechanistic dynamics in different phases of a seizure, including its onset, but do not provide information on why and how a seizure is initiated. The large amount of data currently available on seizure onset patterns does not consent to identify the first prime mover (or movers, if we accept that more factors can ignite seizures) of a focal seizure. The next paragraph indicates that both GABAergic and excitatory networks can be prominently activated at the very onset of a focal seizure, but does not clarify why this happens. This is a crucial question that still remains unanswered.

2. GABAergic networks at SLE onset *in vitro*

GABAergic network involvement during the interictal and preictal state may be different. Most interictal spikes induced by pharmacological manipulations are sustained by a prominent contribution of glutamatergic networks and are abolished by glutamate receptor antagonists (de Curtis and Avanzini, 2001). The group of Massimo Avoli first demonstrated the existence of *in vitro* epileptiform population spike events that resist glutamate receptor blockers and are abolished by $GABA_A$ receptor antagonists, such as bicuculline methiodide (Avoli, 1996; Kohling et al., 2000; Lopantsev and Avoli, 1998); for review see (Avoli et al., 2016). Spikes sustained by GABAergic networks were observed mainly, but not exclusively, in the 4AP model, both in slices and in the isolated guinea pig brain (for review, see (Avoli and de Curtis, 2011; de Curtis and Avoli, 2016)). GABAergic spikes were also identified as pre-seizure (or pro-seizure) events during brief perfusions of bicuculline and in the 4AP models developed in the isolated guinea pig brain (Uva et al., 2015, 2009); see below.

Several studies reported *in vitro* SLEs recorded on cortical slices from naïve non-epileptic rodents. The large majority of early *in vitro* studies utilized blockers of $GABA_A$ receptor mediated inhibition to induce epileptiform discharges; the application of these convulsants (penicillin, bicuculline and picrotoxin) prevented the possibility to analyze GABAergic function during epileptiform activities. Interestingly, protracted *in vitro* perfusions with GABA receptor blockers prominently induced interictal spikes and brief poly-spike discharges in both hippocampus and neocortex (de Curtis and Avanzini, 2001; Wong et al., 1986), whereas proper SLEs were observed only occasionally. Recurrent SLEs were consistently generated in cortical slices (olfactory-, entorhinal-, neocortex, hippocampus) bathed either in 4AP or in low-Mg^{2+}/high-K^+ solutions; these models were introduced in the '90s and became widely utilized, replacing the GABA-blockers models. It became clear since the introduction of these models that GABAergic neurons are active at the very onset of SLEs. As mentioned above, hippocampal and hippocampal-entorhinal slices perfused with 50 μM 4AP showed two types of interictal extracellular spikes: sharp spikes blocked by AMPA receptor antagonists, and broad spikes abolished by $GABA_A$ receptor antagonists (Avoli et al., 1996a, 1993). A later report on entorhinal cortex slices (Lopantsev and Avoli, 1998) demonstrated that $GABA_A$-dependent potentials were activated at the transition into a SLE during 4AP application.

GABAergic interneuronal synchronization was confirmed to be prominent during SLEs induced by different stimuli in hippocampal slices (Lasztoczi et al., 2009; Panuccio et al., 2009; Velazquez and Carlen, 1999; Žiburkus et al., 2006). These findings were confirmed in the isolated whole brain of the adult guinea pig arterially perfused with a bolus of bicuculline or with 4AP (Gnatkovsky et al., 2008; Uva et al., 2015, 2009). The activity of GABAergic interneurons was also analyzed in a series of collaborative studies between the Tokyo Metropolitan Institute for Neuroscience and the RIKEN Brain Science Institute, performed on hippocampal slices after intense electrical stimulation (*tetanic* stimulation) of CA1 Schaffer collaterals, utilized as a model of SLE precipitation. In these experiments, neuronal synchronization during the epileptiform afterdischarge induced by tetanic stimuli was proposed to be generated by a positive feedback circuit initiated by activity in interneurons, that impose a depolarizing GABAergic input on principal pyramidal cells in the CA1 area and facilitate their oscillatory synchronization (Fujiwara-Tsukamoto et al., 2010, 2004, 2003). Other *in vitro* neurophysiological studies performed on the immature hippocampus *in toto* (Derchansky et al., 2008) and on limbic and neocortical slices *in vitro* (Cammarota et al., 2013; Schevon et al., 2012; Trevelyan et al., 2006) confirmed that interneurons are active at the very beginning of a seizure. Based on the authors assumption that inhibitory interneurons should not be expected to initiate seizure activity, these studies proposed that the interneuronal discharge represents a last attempt of the cortical network to prevent seizure precipitation, mediated by a powerful feed-forward inhibition that ultimately fails and surrenders to a wave of excessive excitation. This hypothesis was more recently challenged by optogenetic and dual intracellular recordings. The generation of large IPSPs in principal cells coupled with burst firing in interneurons was demonstrated in the 4AP model during double patch recordings in the EC (Librizzi et al., 2017). The study demonstrated that in the 4AP model *circa* 90% of SLEs are preceded by GABAergic synaptic potentials. The modifications of the extracellular K^+ associated with these inhibitory events (Fig. 1) were proposed to be responsible for the recruitment of excitatory principal neurons and for the transition into SLE. These findings strongly support the conclusion that, at least in this model, interneuronal activity and the associated changes in extracellular K^+ is the most common network pattern responsible for promoting seizures. These data confirmed the hypothesis originally formulated twenty years before by the experiments performed on hippocampal slices by the team of Massimo Avoli (Avoli et al., 1996b).

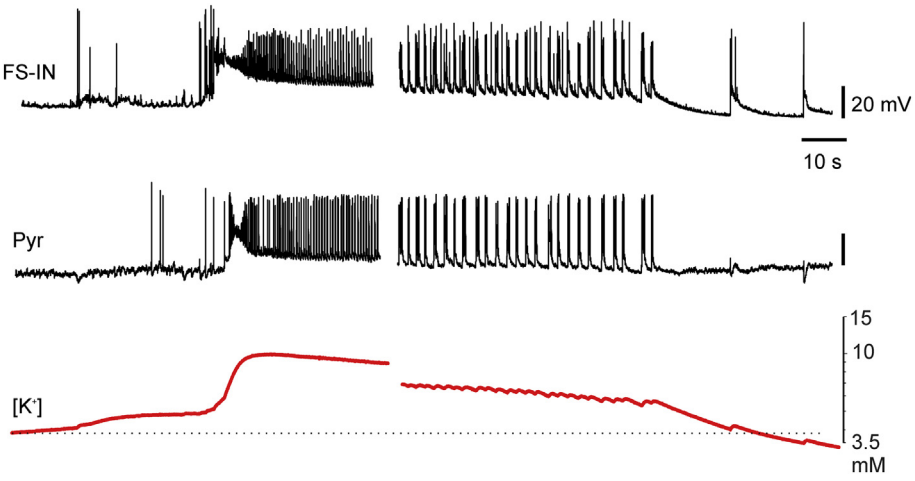

Fig. 1. Simultaneous intracellular double-cell recording of a fast-spiking interneuron (FS-IN) and a pyramidal neuron (Pyr) and the associated changes in extracellular potassium [K^+] measured with an ion-selective electrode in the entorhinal mouse cortex slice. Seizure-like activity was induced by slice perfusion with 100 μM 4-aminopyridine and low-magnesium solution. SLE initiate in the FS-IN and generates [K^+] rise that is further increased when the Pyr neuron is entrained. Note the simultaneous burst firing of FS-IN and Pyr cells at the end of the SLE (Librizzi, Losi, Carmignoto and de Curtis, unpublished data).

More recently, optogenetic stimulation of GABAergic networks proved sufficient to induce SLEs in limbic cortex slices perfused with 4AP. Selective activation of parvalbumin- or somatostatin-expressing GABAergic neurons in the mouse entorhinal cortex precipitates SLEs (Sessolo et al., 2015; Yekhlef et al., 2015) with a LVFA onset pattern (Shiri et al., 2016, 2015) typical of human mesial TLE. Finally, both optogenetic stimulation of GABAergic interneurons and local GABA applications during 4AP and low-Mg^{2+} perfusions both in mouse neocortical tissue and in cortex resected from epilepsy patients maintained *in vitro* demonstrated that the synchronous activation of GABAergic interneurons is a robust trigger for SLE onset through a mechanism of post-inhibitory rebound spiking (Chang et al., 2018). Interestingly, a study performed on a model of focal NMDA-induced SLEs in mouse cortical slices revealed that activation of GABAergic parvalbumin-containing interneurons in the same area of NMDA application fails to block SLEs generation, and induced post-inhibitory rebound spiking in pyramidal neurons, enhancing neuronal synchrony and promoting ictal generation. In contrast, the activation of the same interneurons was able to block the propagation of SLE out of the area of SLE generation (Sessolo et al., 2015). In line with these *in vitro* findings, pre-surgical intracerebral studies that utilized microelectrodes to analyze single unit recordings confirmed that the majority of neurons are silenced during a focal seizure (Truccolo et al., 2011), whereas putative interneurons are active at the very beginning of focal seizures that show a low-voltage fast activity onset ((Elahian et al., 2018; Weiss et al., 2016); see also Weiss et al. and in the present Special Issue). More recently, a computational model of cortical networks Dravet syndrome (Kurbatova et al., 2016) suggested that sub-populations of interacting interneurons, such as perisomatic-projecting interneurons (basket-like)and dendritic-projecting interneurons with fast and slow $GABA_A$ synaptic kinetics, respectively, may differently contribute to seizure control and ictogenesis.

At odds with a prominent role of GABAergic networks in focal seizure initiation, experiments performed in rodent slices (Derchansky et al., 2008; Žiburkus et al., 2006) and in the *in vitro* post-surgical human subiculum (Huberfeld et al., 2011) demonstrated that the enhanced $GABA_A$ receptor-mediated inhibitory mechanisms observed during the interictal period fades away as the ictal discharge approaches. Whether these results are due to differences in drug treatment or brain structure analyzed compared to the studies mentioned in the previous paragraphs or to the developmental stage of the analyzed tissue remains a matter of discussion. More recent studies demonstrated that glutamatergic activity is prominent at the onset of focal limbic seizures characterized by an hypersynchronous onset (Avoli et al., 2016; Köhling et al., 2016). This pattern is most frequently observed in limbic SLEs during *in vitro* slices perfused with low-Mg^{2+} and low Mg^{2+}/high-K^+ solutions (Derchansky et al., 2008, 2006; Zhang et al., 2012) in association with 4AP (Huberfeld et al., 2011; Köhling et al., 2016). Therefore, the possibility that these *in vitro* models are more representative of the hypersynchronous focal seizure pattern typical of limbic cortices should be considered.

A different mechanism that explains the pro-epileptic action of GABAergic activity has been proposed: the abnormal depolarization of principal neurons mediated by $GABA_A$ receptors. Depolarizing GABA responses were first demonstrated in immature hippocampus *in vitro* ((Ben-Ari et al., 2012; Khalilov et al., 1999; Khazipov et al., 2004; Lamsa et al., 2000) and were later confirmed in mature hippocampal neurons (Kaila et al., 1997; Staley et al., 1995). Different mechanisms were proposed to explain the paradox GABA-mediated depolarization (Kaila et al., 1997; Lamsa and Kaila, 1997; Lillis et al., 2012; Viitanen et al., 2010); according to one hypothesis, recurrent network (synaptic) activity results in extracellular K^+ accumulation that promotes a direct depolarizing effect on the postsynaptic cell membrane potential. A mixture of postsynaptic currents (*i.e.* Na^+, K^+, Cl^- and $HCO3^-$) were also invoked for the generation of the slow GABA-mediated depolarization. Notably, depolarizing GABA responses were observed in a minority of *in vitro* studies, including a report on postsurgical subiculum slices obtained in adult patients with mesial temporal epilepsy associated with hippocampal sclerosis (Huberfeld et al., 2007), but not in slices of the hippocampal Cornu Ammonis 2 (CA2) region (Wittner et al., 2009). In the study by Huberfeld, a defect in GABAergic signaling associated with altered chloride homeostasis was described, characterized by an increase in NKCC1 ion co-transport and a down-regulation of KCC2 transporter that promoted elevated levels of intracellular Cl^- and the consequent depolarization of neuronal membranes during $GABA_A$ receptor activation. Whether GABA-dependent depolarization due to altered Cl^- homeostasis is sufficient to generate epileptiform activity is still not experimentally demonstrated. Interestingly, a biophysically realistic network model of ictogenesis proposed that gradual accumulation of the extracellular K^+ coupled to the increase in the intracellular Cl^- concentration associated to a normal activation of KCC2 co-transporter is indeed sufficient to promote epileptiform ictal activity (González et al., 2018). Moreover, a recent study showed how epilepsy itself could be responsible for KCC2 expression and activity alterations by increasing BDNF levels and/or mTOR activation (Di Cristo et al., 2018). The role of Cl^- accumulation in principal cells in the transition from the pre-ictal condition to the SLE was also confirmed using the Cl^- indicator, Clomeleon (Lillis et al., 2012). The Cl^- influx at seizure onset has been proposed to shift the equilibrium potential of GABA-mediated Cl^- conductance to produce a positive feedback loop that contributes to SLE progression. Finally, Cl^- loading inside pyramidal cells has been demonstrated to cause inhibitory postsynaptic currents to become depolarizing in the mature hippocampal CA1 region, suggesting that GABAergic inhibitory-to-

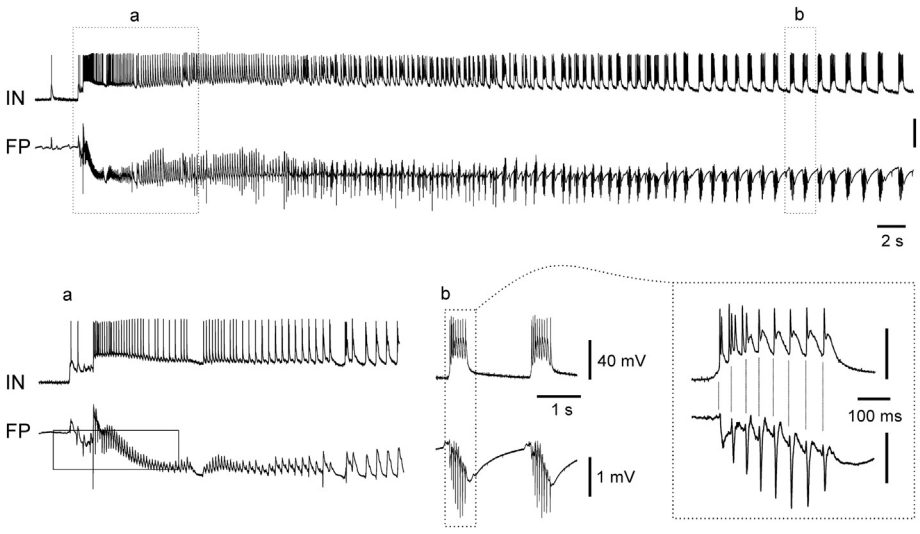

Fig. 2. Simultaneous intracellular recording of a putative interneuron (IN) and the extracellular field potential (FP) in the entorhinal cortex of the *in vitro* isolated guinea pig brain during a SLE induced by 3-min arterial perfusion with 50 μM bicuculline methiodide. The fast activity at the onset of the SLE is illustrated in the expanded trace (a); late bursts are illustrated in (b). The time-locked correlation between the interneuronal firing and the extracellular spikes within a burst is illustrated in the rightmost bottom panel (Gnatkovsky, Uva, Librizzi and de Curtis, unpublished data).

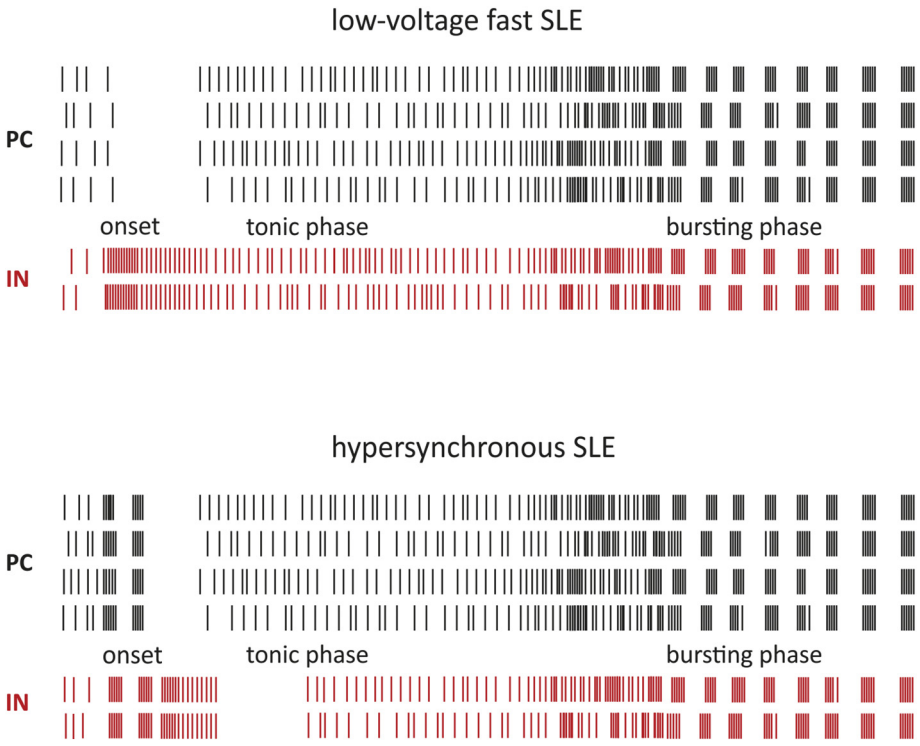

Fig. 3. Schematic model of focal ictogenesis during two focal SLE that initiate with a low-voltage fast activity (upper panel) and an hypersynchronous pattern (lower panel). Action potential firing of 4 principal cells (PC) and 2 interneurons (IN) is simulated by black and red vertical bars, respectively. Low-voltage fast SLEs start with an increase in interneuronal firing coupled with a blockade of PC activity. IN spiking slows down during the transition into the tonic SLE phase, when PC resume their firing, possibly due to PC depolarization mediated by the changes in extracellular potassium induced by the intense IN firing. Neuronal activity in both PCs and INs progressively synchronizes as SLE progress toward the bursting phase. This transition is likely due to recurrent excitation between PCs that entrain INs. During the late SLE phase burst become more synchronous and the inter-burst interval becomes progressively longer before SLE end. The tonic-to-bursting transition is similar in the hypersynchronous SLE (lower panel), that initiates with a prominent synchronous burst firing of PCs (reinforcement of interictal spiking). Each PC burst is followed by IN firing that gradually becomes prominent until IN–mediated inhibitory potentials became progressively weaker and PC neurons are re-engaged into firing by membrane depolarization, possibly because of the extracellular potassium increase. For details, see also (Avoli et al., 2016; de Curtis and Avoli, 2016; Devinsky et al., 2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

excitatory switch participates in the expression of SLE synchronization (Fujiwara-Tsukamoto et al., 2004).

3. *In vitro* GABAergic networks during seizure progression and termination

It has been largely demonstrated that synchronization of excitation is predominant at the peak and in the late phase of *in vitro* focal seizures. In the transition phase between seizure onset and the final bursting (also described as “clonic”) phase, a tonic firing phase is always present in SLEs induced by different *in vitro* challenges. During this SLE phase, defined in several manuscripts as irregular firing phase (Aracri et al., 2018; Boido et al., 2014b; Uva et al., 2005), principal neurons depolarize and generate action potentials with an irregular occurrence (Trombin et al., 2011). This sparse firing progressively synchronizes into small amplitude burst that progressively becomes larger and more synchronized as neurons repolarize and as seizure progresses into the late bursting phase. We proposed that this transition is crucial for the progression in a condition characterized by sequences of high synchronous burst excitation followed by post-burst depression (Boido et al., 2014a); reviewed in (Devinsky et al., 2018). Tonic and bursting phases of SLEs are consistently reproduced in cortical slices maintained *in vitro* exposed to different SLE-inducing protocols (Haas and Jefferys, 1984; Jefferys, 1995, 1990; Jones and Heinemann, 1988). These three phases are also common in focal seizures recorded *in vivo* both in animal epilepsy models and in patients with focal epilepsy.

It is well established that excitatory networks synchronize neuronal activity during the full-blown phase of a seizure (Žiburkus et al., 2013);

how GABAergic interneuron activity organizes in this crucial transition period is not well understood. GABAergic interneurons could be synchronized during fast oscillations discharges by several mechanisms that include muscarinic and metabotropic glutamate receptors involvement (Pálhalmi et al., 2004; Arai and Natsume, 2006). Electrical coupling through gap junctions among interneurons may also play a role in GABAergic network synchronization and may influence ictogenesis (Carlen et al., 2000), even though this is controversial. Paired recordings in slices have shown that coupling between interneurons promotes synchronous GABAergic excitatory potentials within interneuronal networks (Zsiros et al., 2007) and gap junction blockers, such as carbenoxolone, reduce 4-AP-dependent synchronization *in vitro* (Traub et al., 2001; Gigout et al., 2006; Zsiros et al., 2007). On the other hand, blockade of electrical coupling with carbenoxolone suppressed epileptiform currents in connexin36 knockout mice hippocampal slices treated with 4-AP, suggesting that gap junctions are not critical for the generation of epileptiform discharges in GABAergic networks (Beaumont and Maccaferri, 2011). Ellender et al. (2014) demonstrated that Cl^- gradients are preserved in the 4-AP model just prior to the onset and during the late phase of an ictal event, suggesting that $GABA_A$-mediated synapses remain functional throughout a SLE. A study on hippocampal slices bathed in 4AP and low extracellular Mg^{2+} demonstrated that the initial stage of the SLEs inhibition in CA1 principal cells prevails; during the central phase of the SLEs inhibition is reduced and a prevalent excitatory activity is observed; when the bursting phase approaches toward SLE end, principal cells were again controlled by inhibition and GABAergic interneurons experienced persistent excitatory synaptic barrage (Žiburkus et al., 2013) suggesting that increased excitability of interneurons may play roles in both seizure initiation and in their termination (see below). Several *in vitro* studies performed in hippocampus and in other cortical regions reported that interneurons depolarize and generate sustained bursting discharges at seizure onset, and undergo a period of firing blockade during maximal depolarization (Cammarota et al., 2013; Žiburkus et al., 2006). Depolarizing block is defined as a stop of neuronal firing due to membrane potential depolarization above action potential threshold. Membrane potential depolarization is believed to be due to the depolarizing effect of extracellular K^+ increase mediated by the intense neuronal firing observed at the very onset of a seizure (Bikson et al., 2003; Jensen and Yaari, 1997; Lux et al., 1986; Trombin et al., 2011). It is now established that activity of both interneurons and principal cells contributes to this extracellular K^+ rise (for review see (de Curtis and Avoli, 2016; Devinsky et al., 2018). Interestingly, in the low-calcium model (Bikson et al., 2003), seizures also start by low-amplitude fast activity in *gamma* band range associated to intense pyramidal and interneuronal firing, contributing additional evidence on the role of intense interneuronal activity and increased extracellular K^+ in seizure initiation. Blockade of action potential firing due to such a rapid and pronounced membrane depolarization occurs in both principal cells (Žiburkus et al., 2006) and in GABAergic interneurons (Cammarota et al., 2013; Fujiwara-Tsukamoto et al., 2006; Shin et al., 2010). Interestingly, depolarizing block of principal cells is not commonly observed during *in vitro* SLEs and it is not consistently shown in studies that report simultaneous pair recordings from interneurons and principal cells. The continuous activity of putative interneurons without depolarizing block was demonstrated in the whole brain *in vitro* preparation during low-voltage fast activity onset SLEs (Gnatkovsky et al., 2008; Uva et al., 2015) see Fig. 2).

The mechanisms that promote seizure termination are still unresolved (Lado and Moshe, 2008; Loscher and Kohling, 2010). One of the possible mechanism is the recovery of interneurons from the depolarization block phenomenon described above; interneurons repolarization re-activates action potential firing and restores GABAergic network activity that contributes to reestablish the physiological excitability conditions by promoting active inhibition of principal cells. The revision of the data available in literature demonstrates, indeed, that GABAergic (and putative GABAergic) interneurons resume firing during the tonic phase of a SLE and maintain an intense action potential bursting discharge during the late bursting phase (Figs. 1 and 2). Most *in vitro* studies show intense interneuron bursting discharges during late SLEs. In the bicuculline model interneuronal bursting is synchronous to extracellular bursting potentials (left bottom panel in Fig. 2); moreover, simultaneous double recordings from interneurons and principal cells performed in entorhinal cortex slices demonstrate that interneurons and principal neurons fire simultaneously during late seizure bursting and are silent together during the interburst period (Fig. 1; Librizzi, Losi, Carmignoto, de Curtis unpublished observations). Depolarization block has been described also in interneurons during SLEs *in vitro* (Cammarota et al., 2013). The role of this phenomenon on seizure onset and progression is not clear; it has been proposed that firing impairment of parvalbumin interneurons during membrane depolarization recruits neighboring pyramidal neurons into SLE propagation. Interestingly, *in vivo* data suggest that $GABA_A$ receptor blockade may enhance and enlarge cortical areas that generate fast oscillations, thus recruiting a larger volume of principal neurons at the transition to seizure (Bragin et al., 2002). These findings support the hypothesized that clusters of highly interconnected neurons are capable of overcoming interneuron feedback inhibition, leading to seizure activity.

As mentioned in previous paragraphs, bursting activity in late SLEs becomes larger as seizure end approaches. It has been proposed that bursting activity in the late SLE phase promotes a post-burst depression that becomes longer and larger as the amplitude and synchronization of bursting activity increases; seizure terminates when post-burst depression is large enough to hinder further burst reactivation (Boido et al., 2014a; Schindler et al., 2007). This sequence of events could represent an intrinsic control mechanism that contributes to seizure termination. In the double intracellular recordings performed in slices, IPSPs are not generated in principal cells during the late seizure inter-burst period and a shunting effect mediated by $GABA_A$ conductances should be postulated to explain the firing depression that follows each burst. Moreover, the inter-burst silent period increases to several seconds as seizure progresses (Boido et al., 2014a); these inter-burst depression periods are much longer than GABA-mediated synaptic events. These findings suggest that restored interneuronal firing (and the probable associated re-establishment of GABA function) occurs during bursting activity in late seizure phase and may contribute to seizure termination. Other non-GABAergic mechanisms promoted by bursting activity should be considered to explain the long post-burst inhibition and the post-ictal depression that lasts several seconds.

4. Conclusions

Despite the intrinsic limitation of the study on ictogenesis performed *in vitro*, interictal and SLEs recordings in cortical slices and *in toto* preparations demonstrate that GABAergic activity is constantly present during SLEs and may have an unexpected and relevant role in their initiation, progression and termination. The different involvement of interneurons and principal cells during the two most commonly observed *in vitro* SLE patterns with either low-voltage fast or an hypersynchronous onsets are summarized in the scheme reported in Fig. 3. In line with these findings, the role of GABAergic networks in human and experimental temporal lobe seizures should be re-evaluated. Specific loss of GABAergic interneurons in different brain regions has been described in human (Robbins et al., 1991; Sundstrom et al., 2001) and experimental epilepsy (Buckmaster and Dudek, 1997; Dinocourt et al., 2003; Kumar and Buckmaster, 2006; Morin et al., 1998; Sloviter, 1987). Despite these observations, more studies reported that entorhinal and hippocampal interneurons are largely preserved in rat models of temporal lobe epilepsy (Du et al., 1995; Eid et al., 1999; Esclapez et al., 1997; Rempe et al., 1997). These findings were confirmed in human specimens of hippocampus (Isokawa-Akesson et al., 1989; Lieb et al., 1989) and by functional studies of GABAergic

activity in human tissue (Cohen et al., 2002; Kohling et al., 1998). These findings set the condition for single unit analysis of interneuronal firing in animal epilepsy models and in humans. Recent studies demonstrated an increase in interneuronal unit discharges during the low-voltage fast seizures in patients with mesial temporal lobe epilepsy; this enhanced interneuronal firing parallels a decrease in principal neuron activity. These data are reviewed by Weiss et al. in the present Special Issue.

Acknowledgements

The work has been supported by the 2010-2018 *Ricerca Corrente* funding by the Italian Ministry of Health and the Regione Lombardia, by EPICARE project of the Associazione Paolo Zorzi per le Neuroscienze and by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement N. 722053 (EUGliaPhD).

References

Anderson, W.W., Lewis, D.V., Swartzwelder, H.S., 1986. Magnesium free medium activates seizure-like events in the rat hippocampal slices. Brain Res. 398, 215–219.
Aracri, P., de Curtis, M., Forcaia, G., Uva, L., 2018. Enhanced thalamo-hippocampal synchronization during focal limbic seizures. Epilepsia 59, 1774–1784.
Arai, J., Natsume, K., 2006. The properties of carbachol-induced beta oscillation in rat hippocampal slices. Neurosci. Res. 54, 95–103.
Avoli, M., 1996. GABA-mediated synchronous potentials and seizure generation. Epilepsia 37, 1035–1042.
Avoli, M., de Curtis, M., 2011. GABAergic synchronization in the limbic system and its role in the generation of epileptiform activity. Prog. Neurobiol. 95, 104–132.
Avoli, M., Psarropoulou, C., Tancredi, V., Fueta, Y., 1993. On the synchronous activity induced by 4-aminopyridine in the CA3 subfield of juvenile rat hippocampus. J. Neurophysiol. 70, 1018–1029.
Avoli, M., Barbarosie, M., Lücke, A., Nagao, T., Lopantsev, V., Köhling, R., 1996a. Synchronous GABA-mediated potentials and epileptiform discharges in the rat limbic system in vitro. J. Neurosci. 16, 3912–3924.
Avoli, M., Nagao, T., Köhling, R., Lücke, A., Mattia, D., 1996b. Synchronization of rat hippocampal neurons in the absence of excitatory amino acid-mediated transmission. Brain Res. 735, 188–196.
Avoli, M., de Curtis, M., Gnatkovsky, V., Gotman, J., Köhling, R., Lévesque, M., Manseau, F., Shiri, Z., Williams, S., 2016. Specific imbalance of excitatory/inhibitory signaling establishes seizure onset pattern in temporal lobe epilepsy. J. Neurophysiol. 115.
Bartos, M., Vida, I., Jonas, P., 2007. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat. Rev. Neurosci. 8, 45–56.
Beaumont, M., Maccaferri, G., 2011 Apr 1. Is connexin36 critical for GABAergic hypersynchronization in the hippocampus? J. Physiol. 589(Pt 7), 1663–1680. https://doi.org/10.1113/jphysiol.2010.201491.
Ben-Ari, Y., Khalilov, I., Kahle, K.T., Cherubini, E., 2012. The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. Neuroscience 18, 467–486.
Berdichevsky, Y., Dzhala, V., Mail, M., Staley, K.J., 2012. Interictal spikes, seizures and ictal cell death are not necessary for post-traumatic epileptogenesis in vitro. Neurobiol. Dis. 45, 774–785.
Bikson, M., Hahn, P.J., Fox, J.E., Jefferys, J.G., 2003. Depolarization block of neurons during maintenance of electrographic seizures. J. Neurophysiol. 90, 2402–2408.
Boido, D., Gnatkovsky, V., Uva, L., Francione, S., de Curtis, M., 2014a. Simultaneous enhancement of excitation and postburst inhibition at the end of focal seizures. Ann. Neurol. 76, 826–836.
Boido, D., Jesuthasan, N., de Curtis, M., Uva, L., 2014b. Network dynamics during the progression of seizure-like events in the hippocampal-parahippocampal regions. Cereb. Cortex 24, 163–173.
Bragin, A., Mody, I., Wilson, C.L., Engel Jr., J., 2002. Local generation of fast ripples in epileptic brain. J. Neurosci. 22, 2012–2021.
Buckmaster, P.S., Dudek, F.E., 1997. Neuron loss, granule cell axon reorganization, and functional changes in the dentate gyrus of epileptic kainate-treated rats. J. Comp. Neurol. 385, 385–404.
Cammarota, M., Losi, G., Chiavegato, A., Zonta, M., Carmignoto, G., 2013. Fast spiking interneuron control of seizure propagation in a cortical slice model of focal epilepsy. J. Physiol. 591, 807–822.
Carlen, P.L., Skinner, F., Zhang, L., Naus, C., Kushnir, M., Perez Velazquez, J.L., 2000. The role of gap junctions in seizures. Brain Res. Rev. 32, 235–241.
Chang, M., Dian, J.A., Dufour, S., Wang, L., Moradi Chameh, H., Ramani, M., Zhang, L., Carlen, P.L., Womelsdorf, T., Valiante, T.A., 2018. Brief activation of GABAergic interneurons initiates the transition to ictal events through post-inhibitory rebound excitation. Neurobiol. Dis. 109, 102–116.
Cobb, S.R., Buhl, E.H., Halasy, K., Paulsen, O., Somogyi, P., 1995. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 378, 75–78.
Cohen, I., Navarro, V., Clemenceau, S., Baulac, M., Miles, R., 2002. On the origin of interictal activity in human temporal lobe epilepsy in vitro. Science 80 (298), 1418–1421.
de Curtis, M., Avanzini, G., 2001. Interictal spikes in focal epileptogenesis. Prog. Neurobiol. 63, 541–567.
de Curtis, M., Avoli, M., 2016. GABAergic networks jump-start focal seizures. Epilepsia 57, 679–687.
de Curtis, M., Librizzi, L., Uva, L., 2016. The in vitro isolated whole guinea pig brain as a model to study epileptiform activity patterns. J. Neurosci. Methods 260, 83–90.
de Curtis, M., Gnatkovsky, V., Uva, L., Librizzi, L., 2017. The in vitro isolated guinea pig brain in the study of ictogenesis. In: Models of Seizures and Epilepsy, Second Edition. .
Derchansky, M., Shahar, E., Wennberg, R.A., Samoilova, M., Jahromi, S.S., Abdelmalik, P.A., Zhang, L., Carlen, P.L., 2004. Model of frequent, recurrent, and spontaneous seizures in the intact mouse hippocampus. Hippocampus 14, 935–947.
Derchansky, M., Rokni, D., Rick, J.T., Wennberg, R., Bardakjian, B.L., Zhang, L., Yarom, Y., Carlen, P.L., 2006. Bidirectional multisite seizure propagation in the intact isolated hippocampus: the multifocality of the seizure "focus". Neurobiol. Dis. 23, 312–328.
Derchansky, M., Jahromi, S.S., Mamani, M., Shin, D.S., Sik, A., Carlen, P.L., 2008. Transition to seizures in the isolated immature mouse hippocampus: a switch from dominant phasic inhibition to dominant phasic excitation. J. Physiol. 586, 477–494.
Devinsky, O., Vezzani, A., O'Brien, T.J., Jette, N., Scheffer, I.E., de Curtis, M., Perucca, P., 2018. Epilepsy. Nat. Rev. Dis. Prim. 4, 18024.
Di Cristo, G., Awad, P.N., Hamidi, S., Avoli, M., 2018. KCC2, epileptiform synchronization, and epileptic disorders. Prog. Neurobiol. 162, 1–16.
Dinocourt, C., Petanjek, Z., Freund, T.F., Ben-Ari, Y., Esclapez, M., 2003. Loss of interneurons innervating pyramidal cell dendrites and axon initial segments in the CA1 region of the hippocampus following pilocarpine-induced seizures. J. Comp. Neurol. 459, 407–425.
Du, F., Tore, E., Kohler, C., Lothman, E.W., Schwarcz, R., 1995. Preferential neuronal loss in layer III of the medial entorhinal cortex in rat models of temporal lobe epilepsy. J. Neurosci. 15, 8301–8313.
Dulla, C.G., Janigro, D., Jiruska, P., Raimondo, J.V., Ikeda, A., Lin, C.-C.K., Goodkin, H.P., Galanopoulou, A.S., Bernard, C., de Curtis, M., 2018. How do we use in vitro models to understand epileptiform and ictal activity? A report of the TASK1-WG4 group of the ILAE/AES Joint Translational Task Force. Epilepsia Open 3, 460–473.
Eid, T., Schwarcz, R., Ottersen, O.P., 1999. Ultrastructure and immunocytochemical distribution of GABA in layer III of the rat medial entorhinal cortex following aminooxyacetic acid-induced seizures. Exp. Brain Res. 125, 463–475.
Elahian, B., Lado, N.E., Mankin, E., Vangala, S., Misra, A., Moxon, K., Fried, I., Sharan, A., Yeasin, M., Staba, R., Bragin, A., Avoli, M., Sperling, M.R., Engel, J., Weiss, S.A., 2018. Low-voltage fast seizures in humans begin with increased interneuron firing. Ann. Neurol. 84, 588–600.
Ellender, T.J., Raimondo, J.V., Irkle, A., Lamsa, K.P., Akerman, C.J., 2014. Excitatory effects of parvalbumin-expressing interneurons maintain hippocampal epileptiform activity via synchronous afterdischarges. J. Neurosci. 34, 15208–15222.
Esclapez, M., Hirsch, J.C., Khazipov, R., Ben-Ari, Y., Bernard, C., 1997. Operative GABAergic inhibition in hippocampal CA1 pyramidal neurons in experimental epilepsy. Proc. Natl. Acad. Sci. U. S. A. 94, 12151–12156.
Fries, P., Nikolic, D., Singer, W., 2007. The gamma cycle. Trends Neurosci. 30, 309–316.
Fujiwara-Tsukamoto, Y., Isomura, Y., Nambu, A., Takada, M., 2003. Excitatory GABA input directly drives seizure-like rhythmic synchronization in mature hippocampal CA1 pyramidal cells. Neuroscience 119, 265–275.
Fujiwara-Tsukamoto, Y., Isomura, Y., Kaneda, K., Takada, M., 2004. Synaptic interactions between pyramidal cells and interneurone subtypes during seizure-like activity in the rat hippocampus. J. Physiol. 557, 961–979.
Fujiwara-Tsukamoto, Y., Isomura, Y., Takada, M., 2006. Comparable GABAergic mechanisms of hippocampal seizurelike activity in posttetanic and low-Mg2+ conditions. J. Neurophysiol. 95, 2013–2019.
Fujiwara-Tsukamoto, Y., Isomura, Y., Imanishi, M., Ninomiya, T., Tsukada, M., Yanagawa, Y., Fukai, T., Takada, M., 2010. Prototypic seizure activity driven by mature hippocampal fast-spiking interneurons. J. Neurosci. 30, 13679–13689.
Gigout, S., Louvel, J., Kawasaki, H., D'Antuono, M., Armand, V., Kurcewicz, I., Olivier, A., Laschet, J., Turak, B., Devaux, B., Pumain, R., Avoli, M., 2006. Effects of gap junction blockers on human neocortical synchronization. Neurobiol. Dis. 22, 496–508.
Gnatkovsky, V., Librizzi, L., Trombin, F., de Curtis, M., 2008. Fast activity at seizure onset is mediated by inhibitory circuits in the entorhinal cortex in vitro. Ann. Neurol. 64, 674–686.
González, O.C., Shiri, Z., Krishnan, G.P., Myers, T.L., Williams, S., Avoli, M., Bazhenov, M., 2018. Role of KCC2-dependent potassium efflux in 4-Aminopyridine-induced Epileptiform synchronization. Neurobiol. Dis. 109, 137–147.
Haas, H.L., Jefferys, J.G., 1984. Low-calcium field burst discharges of CA1 pyramidal neurones in rat hippocampal slices. J. Physiol. 354, 185–201.
Hablitz, J.J., 1984. Picrotoxin-induced epileptiform activity in hippocampus: role of endogenous versus synaptic factors. J. Neurophysiol. 51, 1011–1027.
Huberfeld, G., Wittner, L., Clemenceau, S., Baulac, M., Kaila, K., Miles, R., Rivera, C., 2007. Perturbed chloride homeostasis and GABAergic signaling in human temporal lobe epilepsy. J. Neurosci. 27, 9866–9873.
Huberfeld, G., Menendez de la Prida, L., Pallud, J., Cohen, I., Le Van Quyen, M., Adam, C., Clemenceau, S., Baulac, M., Miles, R., 2011. Glutamatergic pre-ictal discharges emerge at the transition to seizure in human epilepsy. Nat. Neurosci. 14, 627–634.
Isokawa-Akesson, M., Wilson, C.L., Babb, T.L., 1989. Inhibition in synchronously firing human hippocampal neurons. Epilepsy Res. 3, 236–247.
Jefferys, J.G., 1990. Basic mechanisms of focal epilepsies. Exp. Physiol. 75, 127–162.
Jefferys, J.G., 1995. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. Physiol. Rev. 75, 689–723.
Jensen, M.S., Yaari, Y., 1997. Role of intrinsic burst firing, potassium accumulation, and electrical coupling in the elevated potassium model of hippocampal epilepsy. J.

Neurophysiol. 77, 1224–1233.
Jiruska, P., de Curtis, M., Jefferys, J.G.R., Schevon, C.A., Schiff, S.J., Schindler, K., 2013. Synchronization and desynchronization in epilepsy: controversies and hypotheses. J. Physiol. 591, 787–797.
Jiruska, P., Alvarado-Rojas, C., Schevon, C.A., Staba, R., Stacey, W., Wendling, F., Avoli, M., 2017. Update on the mechanisms and roles of high-frequency oscillations in seizures and epileptic disorders. Epilepsia 58, 1330–1339.
Jones, R.S.G., Heinemann, V., 1988. Synaptic and intrinsic responses of medial entorhinal cortical cells in normal and magnesium-free medium "in vitro". J. Neurophysiol. 59, 1476–1496.
Jones, R.S.G., da Silva, A.B., Whittaker, R.G., Woodhall, G.L., Cunningham, M.O., 2016. Human brain slices for epilepsy research: pitfalls, solutions and future challenges. J. Neurosci. Methods 260, 221–232.
Kaila, K., Lamsa, K., Smirnov, S., Taira, T., Voipio, J., 1997. Long-lasting GABA-mediated depolarization evoked by high-frequency stimulation in pyramidal neurons of rat hippocampal slice is attributable to a network-driven, bicarbonate-dependent K+ transient. J. Neurosci. 17, 7662–7672.
Khalilov, I., Esclapez, M., Medina, I., Aggoun, D., Lamsa, K., Leinekugel, X., Khazipov, R., Ben-Ari, Y., 1997. A novel in vitro preparation: the intact hippocampal formation. Neuron 19, 743–749.
Khalilov, I., Dzhala, V., Ben-Ari, Y., Khazipov, R., 1999. Dual role of GABA in the neonatal rat hippocampus. Dev. Neurosci. 21, 310–319.
Khazipov, R., Khalilov, I., Tyzio, R., Morozova, E., Ben-Ari, Y., Holmes, G.L., 2004. Developmental changes in GABAergic actions and seizure susceptibility in the rat hippocampus. Eur. J. Neurosci. 19, 590–600.
Kohling, R., Lucke, A., Straub, H., Speckmann, E.J., Tuxhorn, I., Wolf, P., Pannek, H., Oppel, F., 1998. Spontaneous sharp waves in human neocortical slices excised from epileptic patients. Brain 121 (Pt 6), 1073–1087.
Kohling, R., Vreugdenhil, M., Bracci, E., Jefferys, J.G., 2000. Ictal epileptiform activity is facilitated by hippocampal GABAA receptor-mediated oscillations. J. Neurosci. 20, 6820–6829.
Köhling, R., D'Antuono, M., Benini, R., de Guzman, P., Avoli, M., 2016. Hypersynchronous ictal onset in the perirhinal cortex results from dynamic weakening in inhibition. Neurobiol. Dis. 87, 1–10.
Kumar, S.S., Buckmaster, P.S., 2006. Hyperexcitability, interneurons, and loss of GABAergic synapses in entorhinal cortex in a model of temporal lobe epilepsy. J. Neurosci. 26, 4613–4623.
Kurbatova, P., Wendling, F., Kaminska, A., Rosati, A., Nabbout, R., Guerrini, R., Dulac, O., Pons, G., Cornu, C., Nony, P., CRESIM/EpiCRESIM Study Group, Chiron, C., Benquet, P., 2016 Sep. Dynamic changes of depolarizing GABA in a computational model of epileptogenic brain: Insight for Dravet syndrome. Exp. Neurol. 283 (Pt A), 57–72. https://doi.org/10.1016/j.expneurol.2016.05.037.
Lachaux, J.P., Axmacher, N., Mormann, F., Halgren, E., Crone, N.E., 2012. High-frequency neural activity and human cognition: past, present and possible future of intracranial EEG research. Prog. Neurobiol. 98, 279–301.
Lado, F.A., Moshe, S.L., 2008. How do seizures stop? Epilepsia 49, 1651–1664.
Lamsa, K., Kaila, K., 1997. Ionic mechanisms of spontaneous GABAergic events in rat hippocampal slices exposed to 4-aminopyridine. J. Neurophysiol. 78, 2582–2591.
Lamsa, K., Palva, J.M., Ruusuvuori, E., Kaila, K., Taira, T., 2000. Synaptic GABA $_A$ activation inhibits AMPA-kainate receptor–mediated bursting in the newborn (*P0–P2*) rat hippocampus. J. Neurophysiol. 83, 359–366.
Lasztoczi, B., Nyitrai, G., Heja, L., Kardos, J., 2009. Synchronization of GABAergic inputs to CA3 pyramidal cells precedes seizure-like event onset in juvenile rat hippocampal slices. J. Neurophysiol. 102, 2538–2553.
Librizzi, L., Losi, G., Marcon, I., Sessolo, M., Scalmani, P., Carmignoto, G., de Curtis, M., 2017. Interneuronal network activity at the onset of seizure-like events in entorhinal cortex slices. J. Neurosci. 37, 10398–10407.
Lieb, J.P., Babb, T.L., Engel, J., 1989. Quantitative comparison of cell loss and thiopental-induced EEG changes in human epileptic hippocampus. Epilepsia 30, 147–156.
Lillis, K.P., Kramer, M.A., Mertz, J., Staley, K.J., White, J.A., 2012. Pyramidal cells accumulate chloride at seizure onset. Neurobiol. Dis. 47, 358–366.
Lopantsev, V., Avoli, M., 1998. Participation of GABAA-mediated inhibition in ictallike discharges in the rat entorhinal cortex. J. Neurophysiol. 79, 352–360.
Loscher, W., Kohling, R., 2010. Functional, metabolic, and synaptic changes after seizures as potential targets for antiepileptic therapy. Epilepsy Behav. 19, 105–113.
Lux, H.D., Heinemann, U., Dietzel, I., 1986. Ionic changes and alterations in the size of the extracellular space during epileptic activity. Adv. Neurol. 44, 619–639.
Macdonald, R.L., Barker, J.L., 1977. Pentylenetetrazol and penicillin are selective antagonists of GABA-mediated post-synaptic inhibition in cultured mammalian neurones. Nature 267, 720–721.
Mann, E.O., Paulsen, O., 2007. Role of GABAergic inhibition in hippocampal network oscillations. Trends Neurosci. 30, 343–349.
Mody, I., Lambert, J.D., Heinemann, U., 1987. Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. J. Neurophysiol. 57, 869–888.
Morin, F., Beaulieu, C., Lacaille, J.C., 1998. Cell-specific alterations in synaptic properties of hippocampal CA1 interneurons after kainate treatment. J. Neurophysiol. 80, 2836–2847.
Pálhalmi, J., Paulsen, O., Freund, T.F., Hájos, N., 2004. Distinct properties of carbachol- and DHPG-induced network oscillations in hippocampal slices. Neuropharmacology 47, 381–389.
Panuccio, G., Curia, G., Colosimo, A., Cruccu, G., Avoli, M., 2009. Epileptiform synchronization in the cingulate cortex. Epilepsia 50, 521–536.
Pelkey, K.A., Chittajallu, R., Craig, M.T., Tricoire, L., Wester, J.C., McBain, C.J., 2017. Hippocampal GABAergic inhibitory interneurons. Physiol. Rev. 97, 1619–1747.
Perrault, P., Avoli, M., 1992. 4-Aminopyridine-induced activity in hilar neurons in the Guinea pig hippocampal slice. J. Neurosci. 12, 104–115.
Perreault, P., Avoli, M., 1991. Physiology and pharmacology of epileptiform activity induced by 4-aminopyridine in rat hippocampal slices. J. Neurophysiol. 65, 771–785.
Pritchett, D.L., Siegle, J.H., Deister, C.A., Moore, C.I., 2015. For things needing your attention: the role of neocortical gamma in sensory perception. Curr. Opin. Neurobiol. 31, 254–263.
Raimondo, J.V., Heinemann, U., de Curtis, M., Goodkin, H.P., Dulla, C.G., Janigro, D., Ikeda, A., Lin, C.-C.K., Jiruska, P., Galanopoulou, A.S., Bernard, C., 2017. Methodological standards for in vitro models of epilepsy and epileptic seizures. A TASK1-WG4 report of the AES/ILAE Translational Task Force of the ILAE. Epilepsia 58 (Suppl. 4), 40–52.
Rempe, D.A., Bertram, E.H., Williamson, J.M., Lothman, E.W., 1997. Interneurons in area CA1 stratum radiatum and stratum oriens remain functionally connected to excitatory synaptic input in chronically epileptic animals. J. Neurophysiol. 78, 1504–1515.
Robbins, R.J., Brines, M.L., Kim, J.H., Adrian, T., De Lanerolle, N., Welsh, S., Spencer, D.D., 1991. A selective loss of somatostatin in the hippocampus of patients with temporal lobe epilepsy. Ann. Neurol. 29, 325–332.
Schevon, C.A., Weiss, S.A., McKhann Jr., G., Goodman, R.R., Yuste, R., Emerson, R.G., Trevelyan, A.J., 2012. Evidence of an inhibitory restraint of seizure activity in humans. Nat. Commun. 3, 1060.
Schindler, K., Leung, H., Elger, C.E., Lehnertz, K., 2007. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. Brain 130, 65–77.
Sessolo, M., Marcon, I., Bovetti, S., Losi, G., Cammarota, M., Ratto, G.M., Fellin, T., Carmignoto, G., 2015. Parvalbumin-positive inhibitory interneurons oppose propagation but favor generation of focal epileptiform activity. J. Neurosci. 35, 9544–9557.
Shin, D.S.-H., Yu, W., Fawcett, A., Carlen, P.L., 2010. Characterizing the persistent CA3 interneuronal spiking activity in elevated extracellular potassium in the young rat hippocampus. Brain Res. 1331, 39–50.
Shiri, Z., Manseau, F., Levesque, M., Williams, S., Avoli, M., 2015. Interneuron activity leads to initiation of low-voltage fast-onset seizures. Ann. Neurol. 77, 541–546.
Shiri, Z., Manseau, F., Lévesque, M., Williams, S., Avoli, M., 2016. Activation of specific neuronal networks leads to different seizure onset types. Ann. Neurol. 79, 354–365.
Sloviter, R.S., 1987. Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. Science 235 (80), 73–76.
Staley, K.J., Soldo, B.L., Proctor, W.R., 1995. Ionic mechanisms of neuronal excitation by inhibitory GABAA receptors. Science 269 (80), 977–981.
Stasheff, S.F., Anderson, W.W., Clark, S., Wilson, W.A., 1989. NMDA antagonists differentiate epileptogenesis from seizure expression in an in vitro model. Science 245, 648–651.
Sundstrom, L.E., Brana, C., Gatherer, M., Mepham, J., Rougier, A., 2001. Somatostatin- and neuropeptide Y-synthesizing neurones in the fascia dentata of humans with temporal lobe epilepsy. Brain 124, 688–697.
Tancredi, V., Hwa, G.G., Zona, C., Brancati, A., Avoli, M., 1990. Low magnesium epileptogenesis in the rat hippocampal slice: electrophysiological and pharmacological features. Brain Res. 511, 280–290.
Taylor, C.P., Dudek, F.E., 1982. Synchronous neural afterdischarges in rat hippocampal slices without active chemical synapses. Science 218, 810–812.
Traub, R.D., Bibbig, R., Piechotta, A., Draguhn, R., Schmitz, D., 2001. Synaptic and nonsynaptic contributions to giant IPSPs and ectopic spikes induced by 4-aminopyridine in the hippocampus in vitro. J. Neurophysiol. 85, 1246–1256.
Tremblay, R., Lee, S., Rudy, B., 2016. GABAergic interneurons in the neocortex: from cellular properties to circuits. Neuron 91, 260–292.
Trevelyan, A.J., Sussillo, D., Watson, B.O., Yuste, R., 2006. Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. J. Neurosci. 26, 12447–12455.
Trombin, F., Gnatkovsky, V., de Curtis, M., 2011. Changes in action potential features during focal seizure discharges in the entorhinal cortex of the in vitro isolated guinea pig brain. J. Neurophysiol. 106, 1411–1423.
Truccolo, W., Donoghue, J.A., Hochberg, L.R., Eskandar, E.N., Madsen, J.R., Anderson, W.S., Brown, E.N., Halgren, E., Cash, S.S., 2011. Single-neuron dynamics in human focal epilepsy. Nat. Neurosci. 14, 635–641.
Uva, L., Librizzi, L., Wendling, F., de Curtis, M., 2005. Propagation dynamics of epileptiform activity acutely induced by bicuculline in the hippocampal-parahippocampal region of the isolated Guinea pig brain. Epilepsia 46, 1914–1925.
Uva, L., Avoli, M., de Curtis, M., 2009. Synchronous GABA-receptor-dependent potentials in limbic areas of the in-vitro isolated adult guinea pig brain. Eur. J. Neurosci. 29, 911–920.
Uva, L., Breschi, G.L., Gnatkovsky, V., Taverna, S., de Curtis, M., 2015. Synchronous inhibitory potentials precede seizure-like events in acute models of focal limbic seizures. J. Neurosci. 35, 3048–3055.
Velazquez, J.L.P., Carlen, P.L., 1999. Synchronization of GABAergic interneuronal networks during seizure-like actvity in the rat horizontal hippocampal slice. Eur. J. Neurosci. 11, 4110–4118.
Viitanen, T., Ruusuvuori, E., Kaila, K., Voipio, J., 2010. The K+-Cl cotransporter KCC2 promotes GABAergic excitation in the mature rat hippocampus. J. Physiol. 588, 1527–1540.
Weiss, S.A., Alvarado-Rojas, C., Bragin, A., Behnke, E., Fields, T., Fried, I., Engel, J., Staba, R., 2016. Ictal onset patterns of local field potentials, high frequency oscillations, and unit activity in human mesial temporal lobe epilepsy. Epilepsia 57, 111–121.
Wittner, L., Huberfeld, G., Clemenceau, S., Eross, L., Dezamis, E., Entz, L., Ulbert, I., Baulac, M., Freund, T.F., Magloczky, Z., Miles, R., 2009. The epileptic human hippocampal cornu ammonis 2 region generates spontaneous interictal-like activity in

vitro. Brain 132, 3032–3046.
Wong, R.K., Traub, R.D., Miles, R., 1986. Cellular basis of neuronal synchrony in epilepsy. Adv. Neurol. 44, 583–592.
Yaari, Y., Konnerth, A., Heinemann, U., 1986. Nonsynaptic epileptogenesis in the mammalian hippocampus in vitro. II.Role of potassium. J. Neurophysiol. 56, 424–438.
Yekhlef, L., Breschi, G.L., Lagostena, L., Russo, G., Taverna, S., 2015. Selective activation of parvalbumin- or somatostatin-expressing interneurons triggers epileptic seizure-like activity in mouse medial entorhinal cortex. J. Neurophysiol. 113, 1616–1630.
Ylinen, A., Bragin, A., Nadasdy, Z., Jando, G., Szabo, I., Sik, A., Buzsaki, G., 1995. Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. J. Neurosci. 15, 30–46.
Zhang, Z.J., Koifman, J., Shin, D.S., Ye, H., Florez, C.M., Zhang, L., Valiante, T.A., Carlen, P.L., 2012. Transition to seizure: ictal discharge is preceded by exhausted presynaptic GABA release in the hippocampal CA3 region. J. Neurosci. 32, 2499–2512.
Žiburkus, J., Cressman, J.R., Barreto, E., Schiff, S.J., 2006. Interneuron and pyramidal cell interplay during in vitro seizure-like events. J. Neurophysiol. 95, 3948–3954.
Žiburkus, J., Cressman, J.R., Schiff, S.J., 2013. Seizures as imbalanced up states: excitatory and inhibitory conductances during seizure-like events. J. Neurophysiol. 109, 1296–1306.
Zsiros, V., Aradi, I., Maccaferri, G., 2007. Propagation of postsynaptic currents and potentials via gap junctions in GABAergic networks of the rat hippocampus. J. Physiol. 578, 527–544.