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REVIEW ARTICLE

Evolving Mechanistic Concepts of Epileptiform Synchronization and their Relevance in Curing Focal Epileptic Disorders

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Abstract: The synchronized activity of neuronal networks under physiological conditions is mirrored by specific oscillatory patterns of the EEG that are associated with different behavioral states and cognitive functions. Excessive synchronization can, however, lead to focal epileptiform activity characterized by interictal and ictal discharges in epileptic patients and animal models. This review focusses on studies that have addressed epileptiform synchronization in temporal lobe regions by employing *in vitro* and *in vivo* recording techniques. First, we consider the role of ionotropic and metabotropic excitatory glutamatergic transmission in seizure generation as well as the paradoxical role of $GABA_A$ signaling in initiating and perhaps maintaining focal seizure activity. Second, we address non-synaptic mechanisms (which include voltage-gated ionic currents and gap junctions) in the generation of epileptiform synchronization. For each mechanism, we discuss the actions of anti-epileptic drugs that are presumably modulating excitatory or inhibitory signaling and voltage-gated currents to prevent seizures in epileptic patients. These findings provide insights into the mechanisms of seizure initiation and maintenance, thus leading to the development of specific pharmacological treatments for focal epileptic disorders.

Keywords: Epileptiform synchronization, mesial temporal lobe epilepsy, interictal spikes, seizures, anti-epileptic drugs, excitatory transmission, inhibitory transmission, voltage-gated channels.

1. INTRODUCTION

Neuronal synchronization represents the integrated activity occurring over time among neuronal networks that are located in one or more interconnected brain structures [1]. Under normal conditions, neuronal synchronization makes the brain generate specific EEG rhythms that are associated with different physiological states extending from cognitive functions (such as perception, formation and recall of memories) to specific sleep states; these EEG patterns include the theta rhythm, beta and gamma oscillations, sharp-wave ripples and sleep spindles [2, 3]. However, excessive and thus abnormal neuronal synchronization can cause the occurrence of both focal [4, 5] and generalized epileptic discharges [6-9].

Here, we will review the evolving concepts regarding the cellular and pharmacological mechanisms that cause the generation of focal epileptiform discharges; these studies encompass over fifty years of neuroscience research paralleling many of our advancements in understanding the processes that regulate neuronal excitability and thus brain function. We will review data obtained from *in vivo* and *in vitro* animal models of focal epilepsy as well as from epileptic patients not responding to antiepileptic drugs and thus investigated with invasive electrophysiological recordings (including detection of single unit activity) before undergoing brain surgery. Most of these studies were performed in limbic brain structures that include the hippocampus, the rhinal cortices and the amygdala, which are known to play a role in mesial temporal lobe epilepsy (MTLE) [10-12].

An epileptic brain generates interictal discharges (*i.e.*, short lasting electrographic events lasting less than one second that are not accompanied by any detectable clinical symptom) (Fig. **1A**) as well as ictal discharges (*i.e.*, periods of abnormal, hypersynchronous activity lasting between a few tens of seconds and several minutes thus disrupting normal brain function) (Fig. **1B**). Moreover, during the last few years, it has been shown that epileptiform synchronization is associated with the occurrence of high-frequency oscillations (HFOs) in the EEG (field) recordings (Fig. **1C**). These HFOs - which are not visible in standard EEG recordings and can only be extracted by amplifying the appropriately filtered signal - have been categorised into two groups, based on their frequency content: (i) ripples, which include

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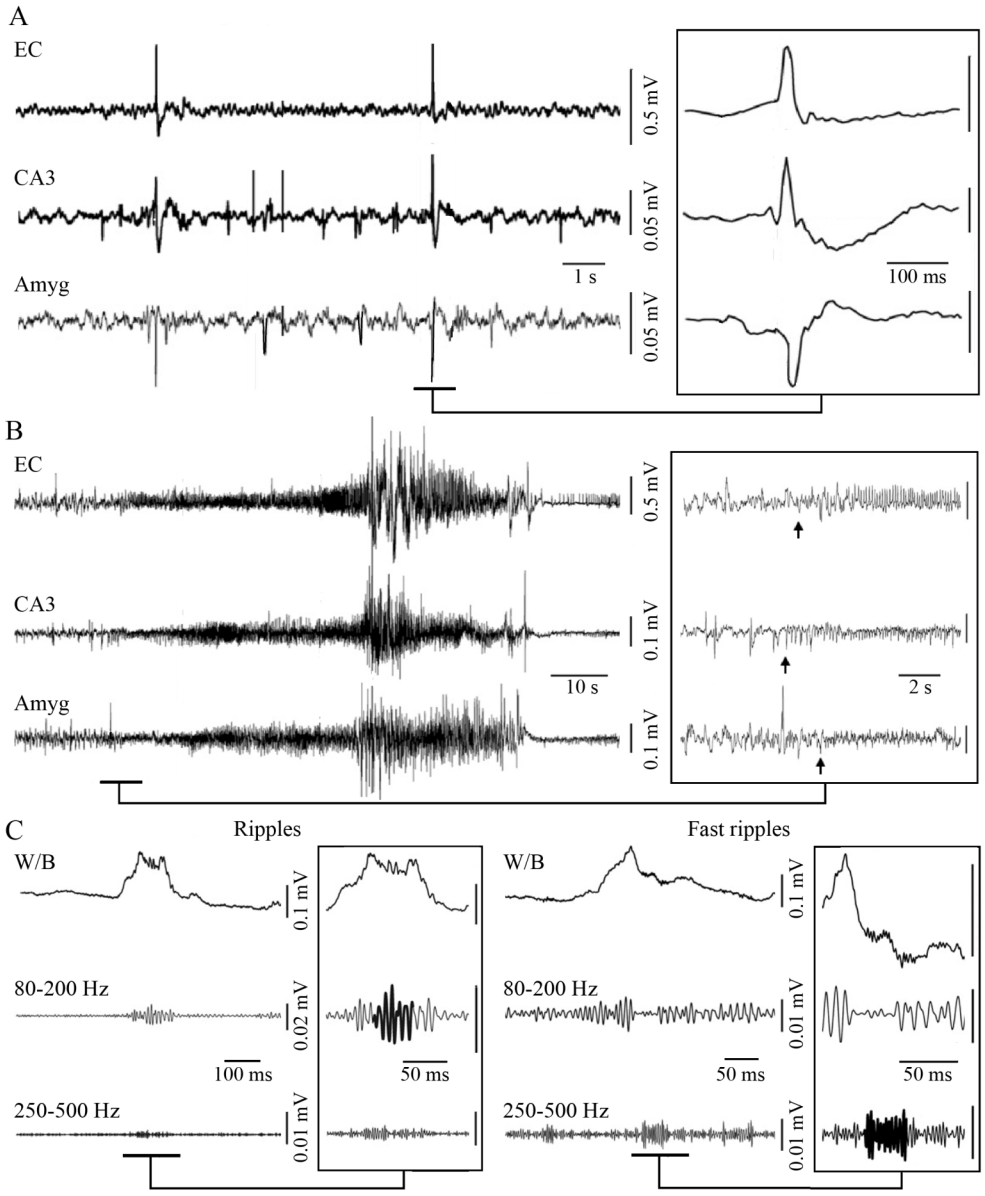

Fig. (1). A: Interictal discharges recorded in the entorhinal cortex (EC), CA3 region of the hippocampus and amygdala (Amy) of a pilocarpine-treated epileptic rat. Note that some interictal spikes are only observed in some regions whereas other tend to propagate. **B**: Representative spontaneous seizure recorded in a pilocarpine-treated epileptic rat from the EC, CA3 region and amygdala. Low-voltage fast activity (arrows) marks the onset of the seizure, which is in this case first observed in the CA3 region. **C**: High-frequency activity (80-500 Hz) recorded in association with an interictal spike, from a pilocarpine-treated epileptic animal. The interictal spike is visible on the wideband signal (W/B) whereas high-frequency activity is only visible after the signal has been filtered between 80-200 Hz and between 250-500 Hz. Ripples include oscillatory events that are only visible in the 80-200 Hz frequency band (left panel) whereas fast ripples include events that are only visible in the 250-500 Hz frequency band (right panel).

oscillatory events between 80 and 200 Hz [13] and (ii) fast ripples, namely oscillatory events between 250-500 Hz [14]. Both ripples and fast ripples have been observed in the epileptic tissue of animals and humans, in association with interictal spikes or seizures; moreover, fast ripples have been reported to occur more frequently in seizure onset zones [14-21]. Interictal and ictal discharges as well as HFOs may share some common synchronizing mechanisms [5].

This review will specifically focus on the role of (i) excitatory and (ii) inhibitory signaling as well as (iii) non-synaptic mechanisms (which include voltage-gated ionic currents and gap junctions) in epileptiform synchronization. In each of these sections, we will also take into consideration which of the current antiepileptic drugs are thought to target these mechanisms thus leading to reduction or prevention of seizures in patients (and animal models).

2. EXCITATORY SIGNALING

Interictal discharges represent the first epileptic phenomenon to be experimentally reproduced. Several studies

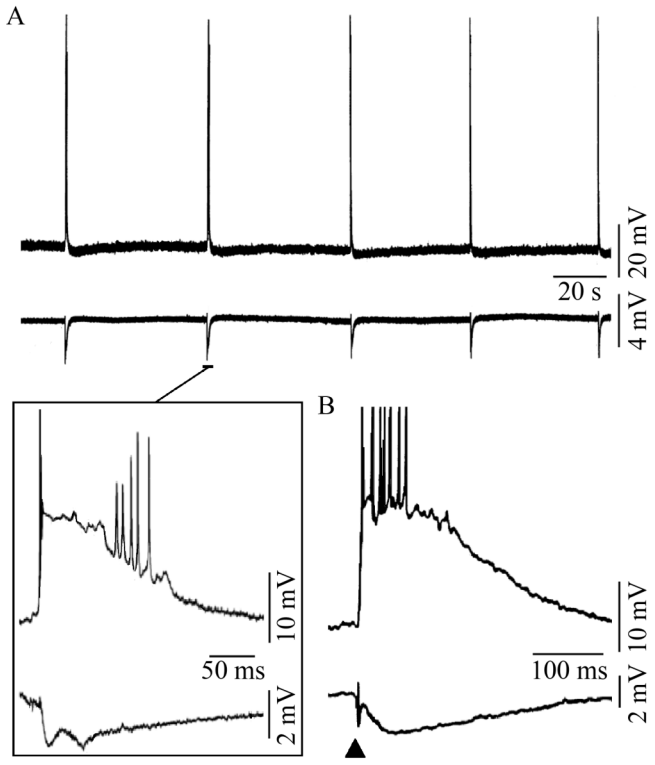

Fig. (2). **A**: Spontaneous interictal-like events recorded in the perirhinal cortex in a rat brain slice maintained *in vitro* during application of picrotoxin. **B**: Interictal discharge recorded from the human neocortex in an *in vitro* brain slice preparation following a single-shock electrical stimulus (triangle) that was delivered through a stimulating electrode close to recording micropipettes. Upper and lower traces, in both **A** and **B**, correspond to intracellular and field potential recordings.

performed *in vivo* in the 1950s and 1960s revealed that epileptic cortical foci, acutely induced by the topical application of convulsants (such as penicillin or strychnine) or local freezing, generate spikes in the EEG of animals that share features with those recorded from patients presenting with focal epileptic disorders (see for review Ayala *et al*., 1973 [22]). Intracellular recordings from neurons located in these foci demonstrated that interictal events were associated with *paroxysmal depolarizing shifts* (PDSs) of the neuron membrane potential causing bursts of action potential firing followed by a hyperpolarization [23-28].

These findings were later confirmed in experiments performed in brain slices maintained *in vitro* during bath application of drugs interfering with $GABA_A$ receptor signaling (Fig. **2**). These studies demonstrated that interictal spikes: (i) reflect the enhancement of synaptic excitation that results from the weakening of inhibition, and (ii) rest on recurrent excitation and regenerative Ca^{2+} currents that make cortical principal cells fire synchronously [29-31]. Shortly after, Daniel Johnston and his collaborators firmly demonstrated that the PDSs associated with interictal spikes represent network-driven giant synaptic potentials [32]; moreover, results obtained in further experiments performed in this laboratory showed that the relative contribution of excitatory (glutamatergic) and inhibitory (GABAergic) currents to the PDS (and thus to the interictal spike) generation depends on the specific pharmacological manipulations employed to induce them [33-35] (see also section 3).

Ictal discharges, which are characterized by prolonged depolarizations of the neuronal membrane leading to the sustained firing of action potentials, were also reported to occur, but less frequently, in some of the original *in vivo* acute studies (*cf*., [25]). Moreover, ictal activity was recorded *in vitro* during the blockade of $GABA_A$ receptor signaling but only when immature brain slices (postnatal days 9 to 19) were employed [36]. As discussed below (section 3), ictal activity is often observed in adult brain tissue maintained *in vitro* during pharmacological procedures that do not solely interfere with $GABA_A$ receptor-mediated inhibition [5, 37]. In principle, this evidence suggests the contribution of ionotropic glutamatergic receptor-mediated inward (depolarizing) currents to both interictal and ictal discharge generation. Moreover, several studies have demonstrated the involvement of synaptic excitatory interactions in the generation of HFOs, and in particular those occurring at frequency higher than 200 Hz (the so called *fast ripples*) [38].

The availability of selective antagonists of ionotropic glutamate receptors in the 1980s led to the identification of the involvement of NMDA and non-NMDA - *i.e*., α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate - ionotropic glutamatergic receptor subtypes [39, 40] in both interictal and ictal discharges recorded from several cortical areas including the hippocampus, the subiculum, the rhinal, cingulate and insular cortices, the amygdala, and the neocortex [41-49] (Fig. **3C**-**E**). However, since ionotropic glutamate receptors are essential for normal brain activity and synaptic plasticity (*i.e*., in processes that underlie learning and memory) they cannot just be antagonized to achieve seizure control in epileptic patients. For instance, perampanel- which is the only approved antiepileptic drug with AMPA antagonism properties [50] - induces dizziness and motor impairment, perhaps due to inhibition of cerebellar AMPA receptors [51-53]. Therefore, recent attempts have been made to develop drugs that can block forebrain but not cerebellar AMPA receptors [54]. In addition, Olney *et al*. [55] have shown that NMDA receptor antagonism MK-801 could cause psychotomimetic and memory-impairing side effects, as well as neurotoxicity.

In spite of these limitations, several antiepileptic drugs can interfere with ionotropic glutamatergic functions. For instance, topiramate selectively inhibits kainate receptor-mediated excitatory postsynaptic responses in principal neurons of the rat basolateral amygdala [56], while protecting against seizures induced *in vivo* by 2-amino-3-(5-tert-butyl-3-hydroxy-4-isoxazolyl) propionic acid, which is a selective agonist of the GluR5 kainate receptor [57]. Braga *et al*. [58] reported that topiramate, by blocking presynaptic GluK1 kainate receptors, inhibits glutamate-mediated suppression of GABA release from interneurons, thus indirectly enhancing $GABA_A$ receptor-mediated inhibition. It has also been reported that the antiepileptic drug felbamate interacts with NMDA receptors in cultured rat hippocampal neurons [59]. Such action should reduce glutamate release by blocking

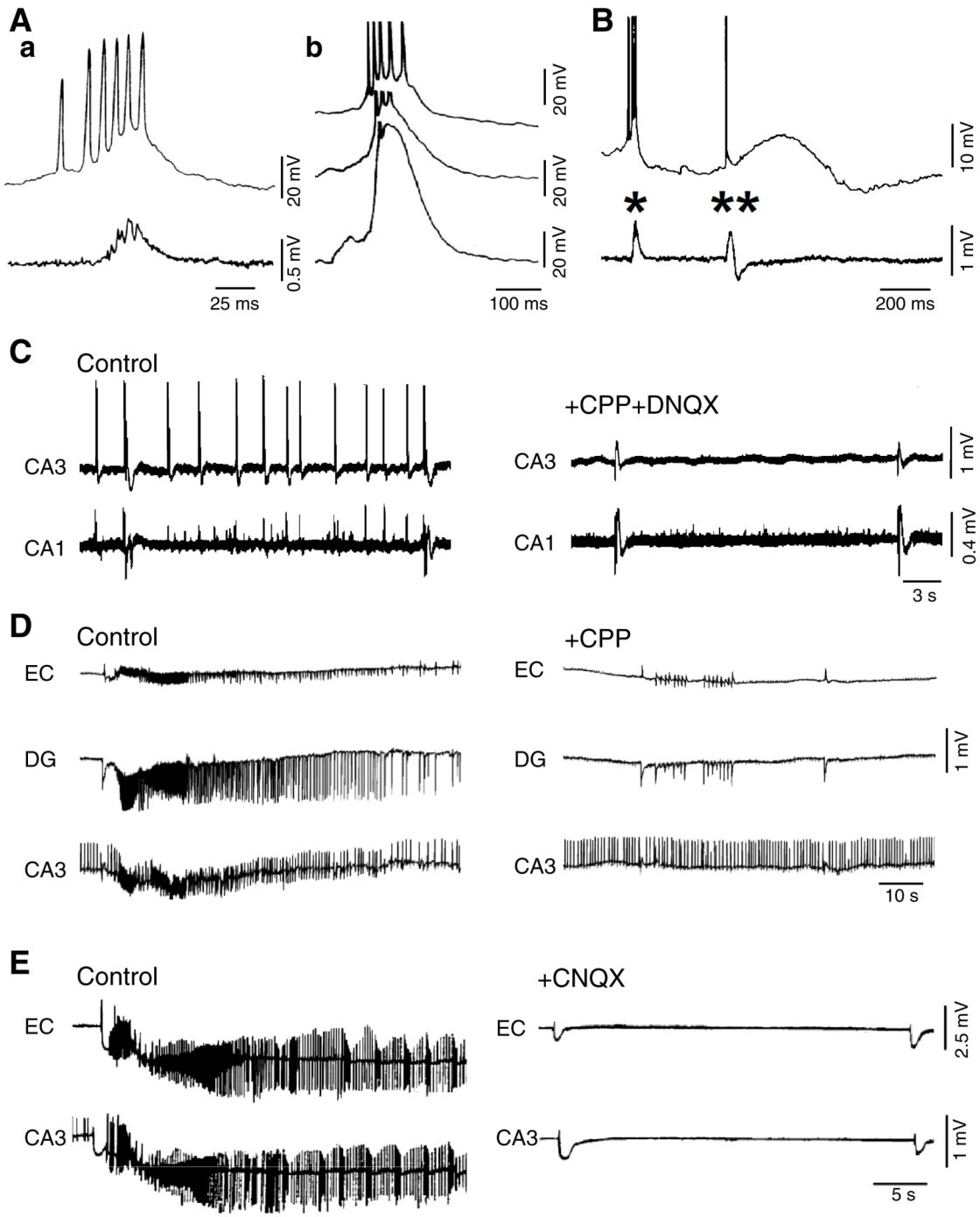

Fig. (3). A: Spontaneous interictal-like epileptiform activity recorded *in vitro* from the CA3 area of a rat hippocampal slice during application of 4-aminopyridine. Simultaneous intracellular (upper trace) and field potential (lower trace) recordings are shown in **a**, while intracellular recordings performed at different membrane potential values (obtained by injecting steady intracellular current) are illustrated in **b**. **B**: Simultaneous intracellular (upper trace) and field potential (lower trace) recordings obtained from the CA3 area of a rat hippocampal slice during application of 4-aminopyridine; note that two types of interictal-like events occur: single asterisk identifies the 'fast' interictal spike (also depicted in panels Aa and Ab) while double asterisks point to the 'slow' interictal event that is characterized by a long-lasting depolarization. **C**: Effects induced by the ionotropic glutamate receptor antagonists (CPP and DNQX) on the spontaneous interictal-like epileptiform activity induced by 4-aminopyridine in a hippocampal brain slice during 4-aminopyridine application; note that blockade of glutamatergic ionotropic transmission abolishes only the "fast" interictal spikes. **D** and **E**: Effects induced by NMDA (CPP) and non-NMDA (CNQX) receptor antagonism on the ictal discharges recorded in an extended brain slice during application of 4-aminopyridine. Note that CPP abolishes the ictal activity without modifying the interictal discharges; in contrast, CNQX blocks both ictal and fast interictal discharges while the slow spikes continue to occur.

presynaptic NMDA receptors in the entorhinal cortex; this specific effect did not occur when phenytoin or gabapentin was used [60].

Recent studies have also focussed on the role of metabotropic glutamate receptors in seizure generation and epileptogenesis [61]. Activation of metabotropic group II and III receptors exerts anticonvulsant effects [62, 63]. In contrast, stimulation of metabotropic group 1 receptors in brain slices that were not generating spontaneous epileptiform activity under control conditions, elicits seizure-like discharges that continue to occur after washout of the agonist, and result from the activation of voltage-dependent cationic currents along with concomitant suppression of afterhyperpolarization [64-66]. These effects are similar to those reported to occur during activation of muscarinic receptors by the muscarinic agonist carbachol in subiculum and entorhinal cortex [67-69]. It has been indeed shown that the antiepileptic drug topiramate can reduce these carbachol-induced excitatory effects [70]. To date, however, in spite of this evidence, little is known about the precise ability of antiepileptic drugs to target metabotropic glutamate receptors.

3. INHIBITORY SIGNALING

Inhibition in the brain results mainly from the activation of $GABA_A$ and $GABA_B$ receptors that are located pre-, post- and extra-synaptically on the membrane of principal cells and interneurons. $GABA_A$ receptors activate ionotropic anionic channels that are permeable to Cl^- and HCO_3^{--} while $GABA_B$ receptors act through second messengers leading to a K^+ hyperpolarizing current [37, 71]. Early studies reported that interfering with GABA synthesis leads to convulsions [72] while treatment with exogenous GABA prevents seizures [73]. In addition, as mentioned in section 2, several convulsive drugs are $GABA_A$ receptor antagonists [29, 30], and inhibition is markedly reduced at the onset of electrographic seizures recorded in the hippocampus [74] or neocortex [75]. As originally reported by Sloviter [76], several studies have also suggested that decreased inhibition in an epileptic brain results from functional disconnection of interneurons from excitatory inputs (a.k.a., dormant interneuron hypothesis). In addition, decreased inhibition has been documented in mesial temporal lobe epilepsy and attributed to deficits in GABA transporter function [77] and/or alterations in $GABA_A$ receptor subunit composition [78-82]. Therefore, in the early 1990s, weakening of inhibition was considered by the majority of epilepsy researchers as the main mechanism leading to focal seizures and thus to epileptic disorders.

This view has been challenged by successive studies in which epileptiform activity was found to occur during pharmacological manipulations that do not interfere with $GABA_A$ receptor function and at times, paradoxically, enhance it. First, it was shown that epileptiform discharges induced by application of Mg^{2+} free-medium, were accompanied by preservation of inhibition [83, 84]. Second, it was found that cortical networks made hyperexcitable by blocking specific K^+ currents generate two types of synchronous interictal spikes (Fig. **3A**, **B**) and that one of them continues to be generated even when AMPA and NMDA glutamatergic receptors were antagonized [85-87] (Fig. **3C**-**E**). These interictal spikes were abolished by $GABA_A$ receptor antagonists and were associated with elevations in extracellular $[K^+]$ that depend on $GABA_A$ receptor activation [88-91]. $GABA_A$ receptor activation can indeed lead to accumulation of Cl^- inside the postsynaptic neurons thus activating the co-transporter KCC2 that extrudes K^+ and Cl^- [92, 93]. In addition, $GABA_A$ receptor-mediated depolarizations in cortical neurons are contributed by HCO_3^-, an anion that goes through the activated $GABA_A$ receptor and has an equilibrium potential more positive than Cl^- [94-96].

Around this time, several studies demonstrated that $GABA_A$ receptor activation can play a paradoxical role in initiating and maintaining focal seizure-like activity [88, 89, 97-105]. As illustrated in Fig. **4A**-**C**, pharmacological procedures that interfere with $GABA_A$ signaling, can abolish prolonged periods of epileptiform synchronization (which resemble ictal events) and replace them with a pattern of recurring, short-lasting interictal spikes. In addition, such ictal activity was potentiated by low doses of phenobarbital, a drug that enhances $GABA_A$ receptor function (Fig. **4D**). The unexpected role played by $GABA_A$ receptors in initiating and maintaining focal seizures has been confirmed over the last two decades by several studies including those in which optogenetic activation of parvalbumin- or somatostatin-positive interneurons was reported to initiate ictal events similar to those occurring spontaneously [106, 107]. Interestingly, the role of $GABA_A$ signaling in promoting epileptiform synchronization is underscored by the ability of CA1 hippocampal networks to generate prolonged discharges following pharmacological blockade of both $GABA_B$ and ionotropic glutamatergic receptors [108]. Data obtained from models of mesial temporal lobe epilepsy also indicate that the onset of focal seizures is associated with increased activity of interneurons that release GABA thus silencing principal neurons [109-111]. In line with this evidence, the onset of seizures in epileptic patients undergoing presurgical electrophysiological investigations, is associated with marked reduction of unit firing [112, 113].

The evidence that increasing $GABA_A$ receptor function promotes epileptiform synchronization and thus focal seizure activity may explain the disappointingly limited efficacy of several antiepileptic drugs that were developed in the 1990s to potentiate $GABA_A$ signaling, to control seizures in epileptic patients. These compounds include γ-vinyl-GABA (which inhibits the breakdown of GABA by the enzyme GABA transaminase) [114], tiagabine (which increases GABA levels by inhibiting GABA reuptake) [115, 116] and progabide [117, 118]. Gabapentin, which is similar in structure to GABA but does not interact with GABA receptors [119], has also shown limited efficacy in controlling seizures. On the other hand, benzodiazepines can halt seizure activity and stop *status epilepticus* [120]. These compounds increase $GABA_A$ receptor function in the central nervous system by acting on an allosteric 'benzodiazepine site' located on most α subunit-containing $GABA_A$ receptors [121-123].

The roles played by metabotropic $GABA_B$ receptors remain to some extent unclear. Their activation, obtained by bath applying baclofen, promotes ictal-like discharges in

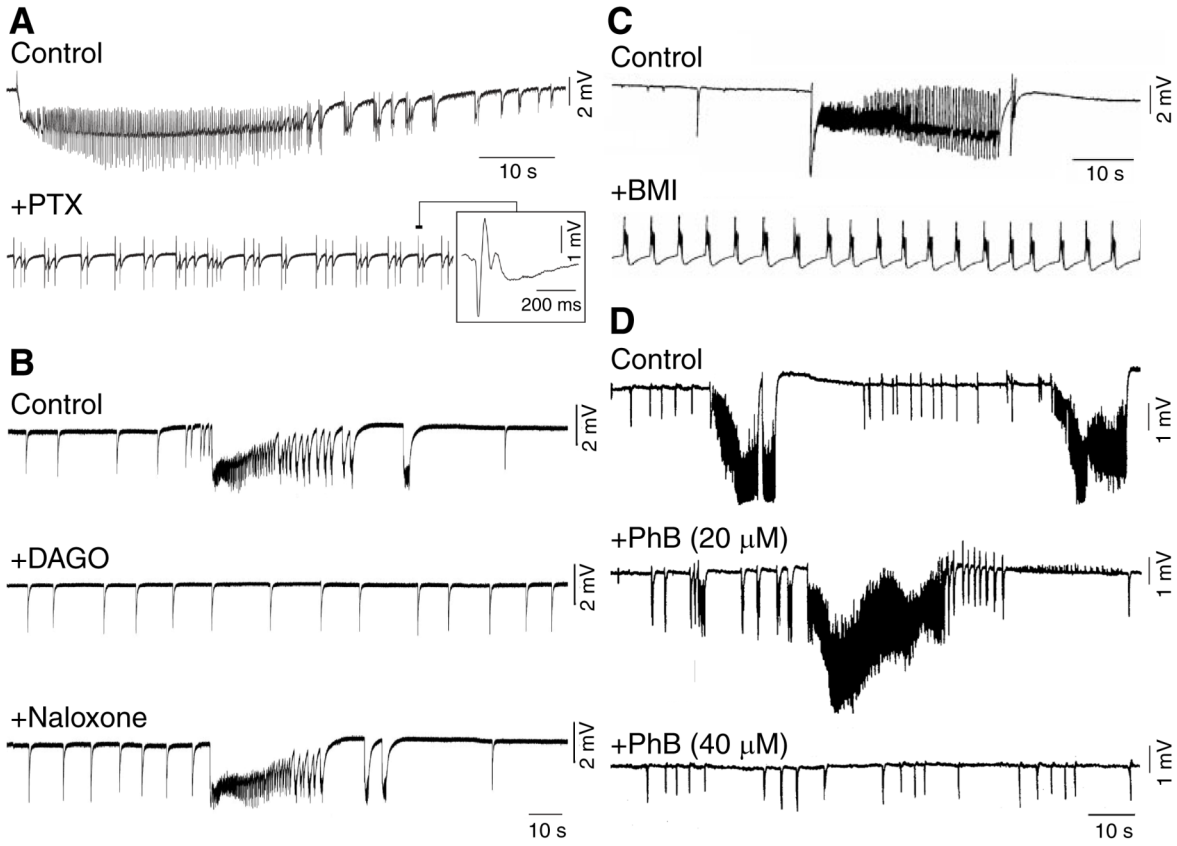

Fig. (4). A and **B**: Effects induced by interfering with GABA receptor function on the epileptiform synchronization induced *in vitro* by 4-aminopyridine in the rodent piriform (**A**) or anterior cingulate cortex (**B**). Note that both antagonizing $GABA_A$ receptors with picrotoxin (PTX) or decreasing GABA release with the mu-opioid receptor agonist [d-Ala^2,N-$MePhe^4$-,Gly-ol^5] enkephalin (DAGO) abolish ictal discharges; note also that the effects induced by DAGO are abolished by successive application of naloxone. **C**: Antagonizing $GABA_A$ receptors with bicuculline methiodide (BMI) blocks the occurrence of ictal discharges induced by 4-aminopyridine in slices of the human neocortex presenting with focal dysplasia. **D**: In these *in vitro* experiments, ictal discharges are increased in duration by low doses of phenobarbital (PhB, 20 μM), but abolished by higher concentrations of this barbiturate (PhB, 40 μM).

hippocampal slices during exposure to 4-aminopyridine [124, 125]; but see also Mott *et al* [126]. Presumably, these effects depend on activity-dependent changes in hippocampal network excitability along with the weakening of $GABA_A$ receptor signaling [125, 126]. However, successive experiments demonstrated that blocking $GABA_B$ receptors, at least in the 4-aminopyridine model, did not consistently reduce epileptiform synchronization [127].

4. NON-SYNAPTIC MECHANISMS

Voltage-gated Na^+ currents, which play a role in action potential firing and in generating persistent depolarizing currents, are by definition non-synaptic although they are triggered and sustained by synaptic depolarizations [128-130]. The repetitive firing of action potentials is a consistent feature of epileptiform discharges (Fig. **5A**), and therefore the activity of voltage-gated Na^+ channel is relevant in the pathophysiology of both generalized and focal epileptic disorders [131, 132]. A significant increase in persistent Na^+ currents occurs in models of mesial temporal lobe epilepsy [133, 134] and in neurons recorded from tissue resected from temporal lobe epileptic patients [135]. Findings obtained from transgenic mice have also indicated that an increase in persistent Na^+ current is sufficient to cause chronic seizures [133, 135-137].

As illustrated in Fig. **5B**, voltage-gated Na^+ channels comprise a central α-subunit and two auxiliary β-subunits; these channels: (i) are in a closed state at hyperpolarized (around resting) membrane potentials; (ii) briefly open when the membrane is depolarized thus producing an inward Na^+ current causing the ascending component of the action potential; and then (iii) convert to a non-conducting inactivated state [128]. Attenuation of voltage-gated Na^+ current is induced, at therapeutic concentrations, by several antiepileptic drugs that are effective for treating epileptic patients presenting with focal and secondarily generalized seizures. Phenytoin and carbamazepine are the prototypic drugs exerting such an effect but several other antiepileptic compounds-which include valproate, lamotrigine, topiramate and lacosamide-may also act on this target (see for review [131, 138]).

As detailed in Fig. **5B**, these antiepileptic drugs are weak blockers of voltage-gated Na^+ channels when the neuron is at resting membrane potential but their action is greatly enhanced during sustained membrane depolarization or high-frequency channel activity, which are both occurring during seizure activity. These functional characteristics mirror the

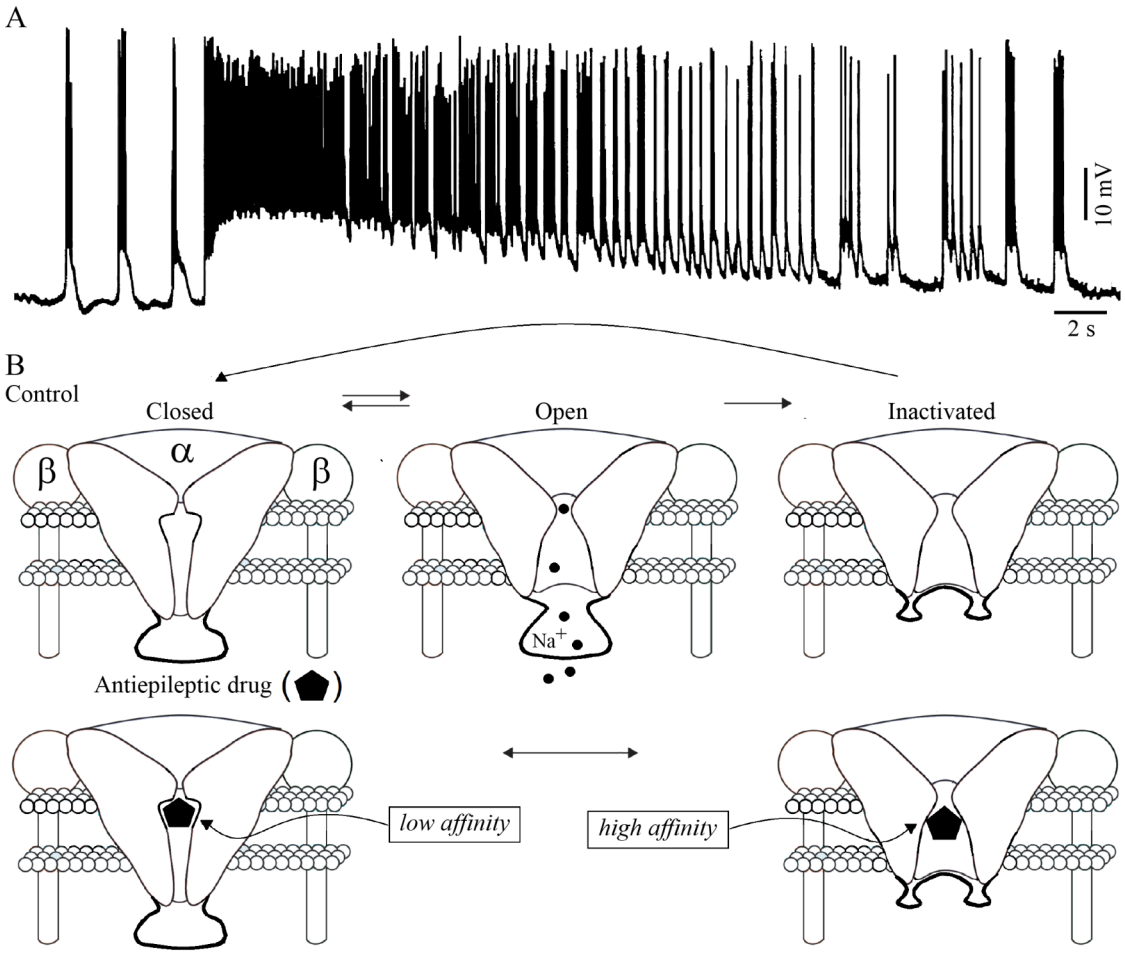

Fig. (5). A: Intracellular activity generated by a presumptive principal cell in the rodent perirhinal cortex maintained *in vitro* during application of 4-minopyridine; note that the ictal activity is associated with sustained discharge of 'fast', Na^+ dependent action potentials. **B**: Functional states of the voltage-gated Na^+ channel under control conditions and in the presence of an antiepileptic drug such as phenytoin or lamotrigine. Na^+ channels are in resting states at hyperpolarized membrane potentials. In response to membrane depolarization, they open and then inactivate. Antiepileptic Na^+ channel blockers bind with low affinity to resting states but with higher affinity to inactivated states. This state-dependent action causes the voltage and activity-dependent inhibition that enables these drugs to be effective antiepileptic agents.

modulated receptor model that was developed to describe the mechanism of action of local anesthetics [128]. According to this model, the closed channels, which predominate at resting membrane potential, have a low affinity for these antiepileptic drugs while the inactivated channels, which are predominant at depolarized potentials, bind them with high affinity [114, 128, 139]. These characteristics explain why these antiepileptic drugs suppress seizures while having minimum effects on normal brain functions, *i.e.*, when brain neuronal networks are normally functioning and thus not undergoing sustained prolonged states of depolarization.

Besides Na^+, other voltage-gated channels can be the target of antiepileptic drugs. Accordingly, it has been reported that lamotrigine increases the hyperpolarization-activated cation current, also termed I_h, that is largely present in the dendrites of pyramidal cells of the hippocampus [140] (see for review Poolos *et al.*, 2012 [141]). A similar effect has been identified with the antiepileptic drug gabapentin [142]. Lamotrigine has also been shown to inhibit N-type and P-type high-voltage-activated Ca^{2+} channels [143] that are instrumental in both excitatory and inhibitory synaptic transmission [144]. In keeping with the role of synaptic neurotransmitter release in the generation of seizure activity, a rather new and efficacious antiepileptic drug, levetiracetam, has been proposed to modulate presynaptic Ca^{2+} channel activity by acting on the synaptic vesicle glycoprotein SV2A, which interacts with synaptotagmin and results in neurotransmitter release modulation [145, 146]. Levitiracetam has anti-ictogenic effects in animal models of epilepsy such as in the amygdala kindling model [147], audiogenic kindling [148], spontaneously epileptic rats [149], the kainic acid model [150] and the pilocarpine model [151]. Since alterations in Ca^{2+} are correlated to epileptiform discharges, the antagonistic effects of levetiracetam and lamotrigine on Ca^{2+} signaling might represent the basis for their anticonvulsant efficacy. Beyond that, regulation of Ca^{2+} homeostasis could also preserve neuronal viability [152], and also lacosamide can provide protection against excitotoxicity without altering synaptic plasticity [153]. Lamotrigine as well as carbamazepine have also been reported to increase voltage-gated K^+ outward (repolarizing) currents [154, 155].

Epileptiform synchronization also depends on non-synaptic interactions such as intercellular gap junctions, ephaptic interactions, and - as discussed above - elevations in extracellular $[K^+]$ (see for review Jefferys *et al*. [4]). Indeed, non-synaptic synchronizing mechanisms may play important roles in contributing to seizure activity, which is associated with decreases in extracellular $[Ca^{2+}]$ that are incompatible with fully efficient synaptic transmission [7, 156]. Gap junctions, which are constituted by connexins and pannexins [157, 158], may play significant roles in synchronizing neuronal networks under physiological and pathological conditions including epileptic disorders [159-162]. For instance, Draguhn *et al*. [163] have reported that spontaneous high-frequency activity at approximately 200 Hz (ripples) in the CA1 region of the hippocampus *in vitro* is generated by principal cell networks that are synchronized trough gap junctions. *In vivo*, in transgenic Connexin36 deficient mice, a reduction in the frequency of occurrence of ripples and epileptiform discharges induced with 4-aminopyridine was observed by the same group [164]. Oscillations at higher frequencies (> 250 Hz) are also reduced under carbenoxolone in hippocampal slices from epileptic patients [165] and *in vivo* in pilocarpine-treated mice [166]. Pharmacological procedures that block or enhance the function of gap junctions could therefore lead to a decrease or an increase of epileptiform synchronization, respectively (see for review Mylvaganam *et al*., 2014 [162]; Carlen *et al*., 2000 [167]). It has also been established that the astrocytic connexin 43 is elevated in human epileptic tissue [168, 169] while experiments performed in human neocortical tissue from patients with focal cortical dysplasia have shown that gap junction blockers reduce ictal-like events induced by 4-aminopyridine [170]. Although gap junction blockers depress synaptic and non-synaptic currents thus producing nonspecific effects (*cf*., [171, 172]), gap junctions remain an appropriate target for the development of antiepileptic drugs.

CONCLUDING REMARKS

We have presented here a short review of the studies addressing the fundamental cellular and pharmacological mechanisms that lead to the initiation, maintenance and spread of focal epileptiform discharges. We have highlighted the fact that while excitation and voltage-gated sodium are a main components of the synchronous firing that characterize an epileptiform event, $GABA_A$ receptor signaling emerges as a surprising, paradoxical mechanism that actively contributes to the initiation and maintenance of prolonged epileptiform phenomena (*i.e*., to ictogenesis). In addition, while voltage-gated sodium channels remain the best studied target for antiepileptic drugs, recent data obtained with levetiracetam suggest that its anti-ictogenic properties might be associated with the modulation of both excitatory and inhibitory transmission trough changes in calcium dynamics. Non-synaptic mechanisms, such as the activity of gap junctions, might also underlie the generation of epileptiform synchronization. Altogether, these findings-which have been obtained *in vivo* and *in vitro* over the last six decades - reveal a complex pattern of participating mechanisms to ictogenesis.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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