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REVIEW ARTICLE

$GABA_B$ Receptors: are they Missing in Action in Focal Epilepsy Research?

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Abstract: GABA, the key inhibitory neurotransmitter in the adult forebrain, activates pre- and postsynaptic receptors that have been categorized as $GABA_A$, which directly open ligand-gated (or receptor-operated) ion-channels, and $GABA_B$, which are metabotropic since they operate through second messengers. Over the last three decades, several studies have addressed the role of $GABA_B$ receptors in the pathophysiology of generalized and focal epileptic disorders. Here, we will address their involvement in focal epileptic disorders by mainly reviewing *in vitro* studies that have shown: (i) how either enhancing or decreasing $GABA_B$ receptor function can favour epileptiform synchronization and thus ictogenesis, although with different features; (ii) the surprising ability of $GABA_B$ receptor antagonism to disclose ictal-like activity when the excitatory ionotropic transmission is abolished; and (iii) their contribution to controlling seizure-like discharges during repetitive electrical stimuli delivered in limbic structures. In spite of this evidence, the role of $GABA_B$ receptor function in focal epileptic disorders has been attracting less interest when compared to the numerous studies that have addressed $GABA_A$ receptor signaling. Therefore, the main aim of our mini-review is to revive interest in the function of $GABA_B$ receptors in focal epilepsy research.

Keywords: $GABA_B$ receptor signaling, focal epileptic disorders, *in vitro* epileptiform synchronization, ictal discharges, interictal discharges, limbic structures.

1. INTRODUCTION

More than seventy years of neuroscience research has firmly established that GABA represents the main inhibitory neurotransmitter in adult forebrain structures [1]. Once released from interneuron terminals, GABA activates synaptic GABA receptors that can be categorized as type A and type B [2-5]. $GABA_A$ receptors are receptor-operated ionotropic channels while $GABA_B$ receptors are metabotropic, G protein-coupled receptors [2, 6-8].

A link between seizures and GABA was first found in infants who had been fed with a formula that was accidentally deficient in pyridoxine, which is the coenzyme for the synthesis of GABA from glutamic acid; indeed, these infants developed seizures [9]. Several studies during the following decades have found that antagonizing $GABA_A$ receptor signaling leads to epileptiform activity (Avoli and Krnjević [10] and Krnjević [11]), while loss of interneurons and a consequent decrease in hippocampal inhibition was reported in experimental models of epilepsy [10, 12, 13]. However, this view has been challenged by evidence showing that: (i) inhibitory interneurons actively participate in focal seizure generation [14-17], and (ii) $GABA_A$ receptor-mediated inhibition remains preserved in some animal models of focal epilepsy [18-20], as well as in patients presenting with mesial temporal lobe epilepsy (MTLE) [21-23]. Moreover, paradoxically, $GABA_A$ signaling can lead to epileptiform synchrony in limbic and olfactory cortices (Avoli and Krnjević [10] and Avoli and de Curtis [24]). Interest in the function of $GABA_A$ receptor in epileptic disorders has continued in recent studies that employed optogenetic or chemogenetic approaches [25-28] or addressed the role of KCC2 in modulating epileptiform synchronization (Di Cristo *et al.* [29] and Kaila *et al.* [30]). Also, in these experiments, distinct and often opposite effects were exerted by modulating $GABA_A$ receptor function.

$GABA_B$ receptors also play relevant roles in physiological and pathological brain activity [6, 31-33]. It is well established that post-synaptic activation of $GABA_B$ receptors located in neuronal somato-dendritic compartments opens K^+ channels, thus causing a hyperpolarizing current in both principal glutamatergic neurons and inhibitory interneurons [34-36], while pre-synaptic activation of $GABA_B$ receptors on axon terminals of excitatory (heteroreceptors) and inhibitory cells (autoreceptors) decreases Ca^{2+} influx, thus reducing neurotransmitter release [6, 37-40]. Two $GABA_B$ receptor subunits (termed $GABA_B1$ and $GABA_B2$) were cloned in the late 1990s [41-43], and shortly after, epileptiform activity

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was identified in the $GABA_B1$ receptor subunit knockout mice. This subunit is essential for all $GABA_B$ receptor functions [44, 45].

Several studies have later shown that $GABA_B$ receptor dysfunction can play a role in the pathophysiology of generalized absence seizures [31, 46-48] and focal epileptic disorders [45, 49, 50]. Here, we will address the latter topic by focusing mainly on studies in which the contribution of $GABA_B$ receptor signaling to focal epileptiform synchronization was established in *in vitro* brain preparations that are relevant for understanding the neuronal processes that can either lead to or control focal ictogenesis. In addition, we will summarize findings obtained by analysing $GABA_B$ receptor function in human MTLE and in animals mimicking this epileptic disorder. The original findings published by our laboratory and reviewed here were obtained from experiments that were carried out between 1996 and 2004.

2. $GABA_B$ RECEPTOR AGONISM AND EPILEPTIFORM SYNCHRONIZATION

Swartzwelder *et al.* [51] were presumably the first investigators to report that in the presence of medium containing zero Mg^{2+}, activation of $GABA_B$ receptor by bath application of 4-amino-3-[4- chlorophenyl]-butanoic acid (baclofen; *cf.*, Misgeld *et al.* [52]) blocks interictal spikes and discloses ictal discharges in isolated hippocampal slices. These results were not confirmed by Jones [53], who identified depression of both interictal and ictal activities recorded in rat entorhinal cortex (EC) slices treated with zero Mg^{2+} medium following baclofen treatment. However, shortly after, two studies reported that baclofen application (i) converted the dentate gyrus responses to perforant path electrical stimuli into prolonged epileptiform discharges [54], and (ii) made ictal discharges appear while blocking interictal spikes in the CA3 subfield of hippocampal slices that were treated with the K^+ blocker 4-aminopyridine (4AP) [55]. Similar findings were later obtained by Motalli *et al.* [56], who analyzed the effects induced by baclofen (10-50 μM) on the epileptiform activity recorded in the CA3 area of juvenile (12- to 25-day-old) rat hippocampal slices during 4AP application.

As illustrated in Fig. (**1A**) (Control), 4AP induces in isolated hippocampal slices two distinct types of interictal spikes: the first, which occurs at 0.5-1 Hz (arrows), and hereafter will be termed "fast," is initiated by the synchronous discharge of CA3 pyramidal cells that is mainly contributed by ionotropic glutamatergic mechanisms; the second (asterisks), which is mostly due to GABAergic currents caused by the synchronous firing generated by interneurons located in any hippocampal area, occurs at longer intervals (hence, hereafter termed "slow") and continues to be recorded during pharmacological blockade of glutamatergic ionotropic receptors [57] (Avoli and de Curtis [24]). In addition, in juvenile hippocampal slices, prolonged ictal discharges can be observed in several experiments (thick line in Fig. **1Ab**), and they are shortly preceded (and thus presumably initiated) by the "slow" GABAergic spike [58]. Motalli *et al.* [56] found that baclofen abolishes the "fast," CA3-driven interictal activity and either discloses (Fig. **1Aa** and **1C**) or prolongs ictal discharges (Fig. **1Ab**) with concentration-dependent features (Fig. **1B**). Moreover, baclofen hyperpolarized CA3 pyramidal cells and made spontaneous, asynchronous hyperpolarizing and depolarizing potentials virtually disappear (Fig. **1D**). As illustrated in Fig. (**1E** and **F**), during application of 4AP and glutamatergic ionotropic receptor antagonists, activation of $GABA_B$ receptors abolished the spontaneous asynchronous postsynaptic potentials (PSPs) but only reduced the rate of occurrence of the synchronous PSPs (arrows in Fig. **1E**) that mirror the "slow" GABAergic spike, although their amplitude was reduced [56]. Therefore, these findings demonstrated that $GABA_B$ receptor activation leads to decreased neurotransmitter release causing the disappearance of "fast" interictal activity and of asynchronous excitatory and inhibitory potentials; in contrast, GABA-mediated synchronous PSPs are not abolished while ictal events are disclosed or potentiated by baclofen. It should be emphasized that, although not abolished by baclofen, the "slow" interictal spikes (which are the field counterpart of the synchronous GABA-mediated PSPs) and the associated increases in $[K^+]_o$ occurring during application of 4AP and glutamatergic ionotropic receptor antagonists were significantly reduced by baclofen activation. This piece of evidence indicates that $GABA_B$ receptor activation decreases GABA release from inhibitory interneurons in the CA3 subfield of isolated hippocampal slices (Fig. **2A** and **B**).

Overall, these findings are in line with what was originally proposed by Mott *et al.* [54] and Watts and Jefferys [55], who have suggested that the pro-seizure effects induced by baclofen mirror an increased $GABA_B$ receptor-mediated presynaptic inhibition of GABA release from inhibitory interneurons leading to disinhibition. A similar conclusion was reached by Dugladze *et al.* [49], who found that a low dose of baclofen (1 mg/kg, i.p.) increases the EEG gamma power along with the occurrence of interictal spikes in kainic acid-treated epileptic mice. These investigators also reported that low concentrations (0.5 μM) of baclofen cause depolarization and increased action potential firing in CA3 pyramidal cells recorded from hippocampal slices obtained from epileptic mice and that these effects are accompanied by suppression of the output (inhibitory) activity generated by cholecystokinin-positive basket interneurons. In these experiments, opposite effects were induced both *in vivo* (*i.e.*, a decrease of EEG gamma power and interictal spikes) and *in vitro* (*i.e.*, CA3 pyramidal cell hyperpolarization) when high concentrations of baclofen were employed [49]. Results supporting the $GABA_B$ receptor-mediated disinhibition hypothesis have been identified *in vivo* in the piriform cortex by Gerrard *et al.* [59] as well; these investigators monitored the activity of layer 2 neurons with 2-photon Ca^{2+} imaging and found that superfusion with medium containing baclofen (500 μM) reduced spontaneous random firing of principal cells while promoting synchronous, presumed, epileptiform activity [59]. Their findings suggested that activation of $GABA_B$ receptors in the piriform cortex reduces network excitability by involving pre-synaptic heteroreceptors and post-synaptic receptors located on glutamatergic neurons while disinhibiting glutamatergic neurons through the activation of presynaptic $GABA_B$ autoreceptors that are located on interneurons.

However, since ictal discharges generated during application of 4AP+baclofen are blocked by repetitive stimuli delivered at approx. 1 Hz (*i.e.*, a value that is similar to the

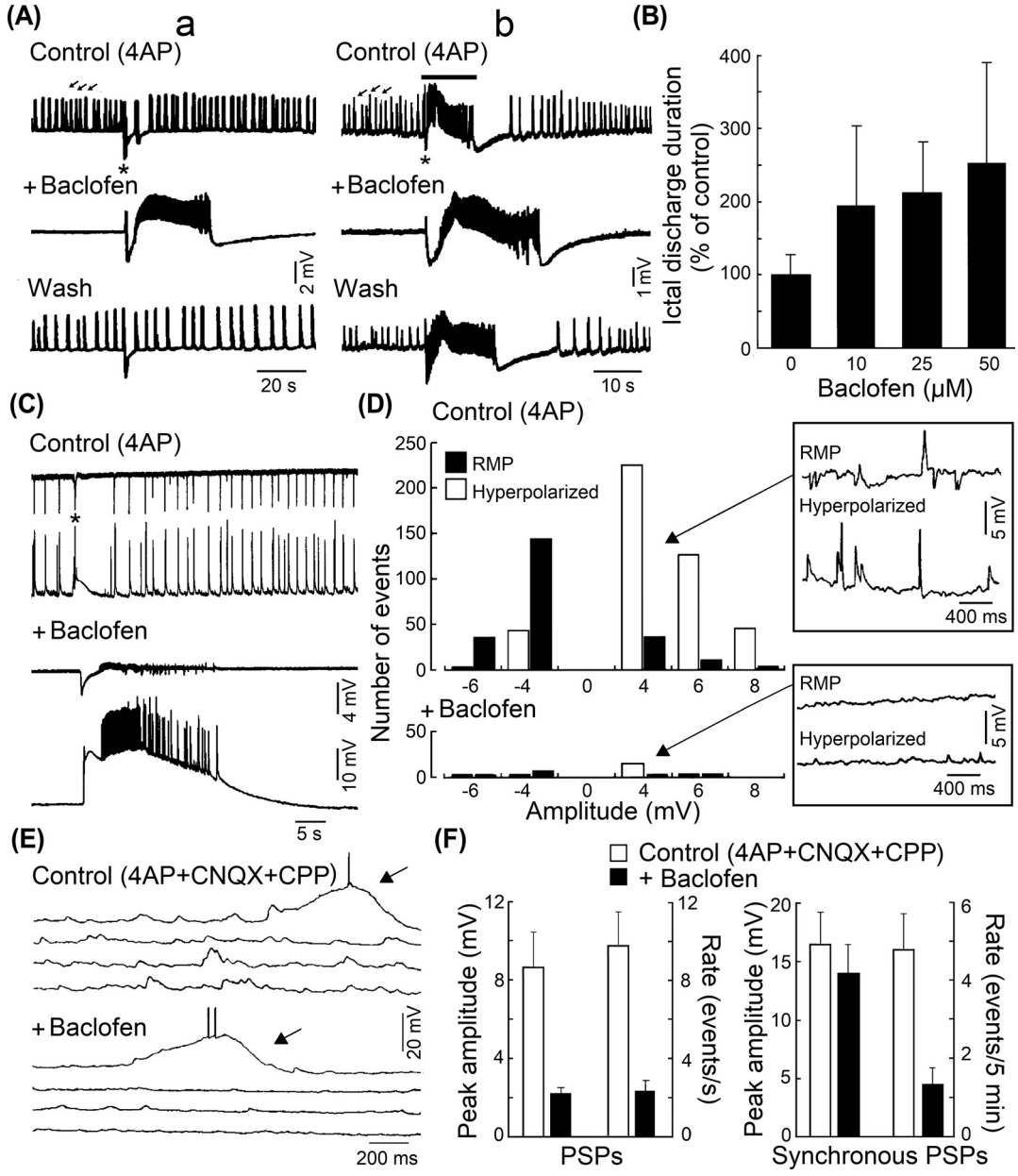

Fig. (1). Effects induced by baclofen on the epileptiform activity induced by 4AP in isolated rat hippocampal slices. (**Aa**): Field recordings obtained from the CA3 stratum radiatum show that baclofen abolishes "fast" interictal discharges (arrows) while promoting the occurrence of ictal discharges (thick line) that appear to be initiated by the negative-going, GABA-mediated event (asterisk). (**Ab**): When interictal and ictal discharges occur under control conditions (4AP), baclofen (50 μM) abolishes interictal discharges while increasing the duration of ictal discharges. In both **a** and **b** panels, the wash samples were obtained 100 min after perfusion with the control medium. (**B**)**:** Dose-dependent effects of baclofen on the duration of ictal discharges. (**C**): Simultaneous extracellular (top trace) and intracellular (bottom trace, K-acetate-filled electrode) recordings from the CA3 region in the presence of 4AP (Control) and during application of baclofen (25 μM). Under control conditions, "fast" interictal discharges and one "slow" interictal, GABA-mediated synchronous potential (asterisk) are observed. Baclofen induces a steady, Q6 mV, hyperpolarization of the resting membrane potential, makes interictal events disappear, and triggers ictal discharges that are initiated by the "slow" GABA-mediated potentials. Note that the long-lasting depolarization associated with the "slow" GABA-mediated event in this neuron increases in amplitude under baclofen application. (**D**)**:** Bar graph showing the rate of occurrence of presumptive, action potential-dependent PSPs (segregated according to their amplitude) recorded at -58 mV (resting membrane potential) and -75 mV (hyperpolarized level) under control and baclofen (25 μM) application. Insets show representative recordings under control and baclofen conditions. (**E**): Intracellular recordings obtained with a KCl-filled microelectrode under control conditions (4AP + CNQX + CPP) and during baclofen application. Under control conditions, the spontaneous activity generated by this neuron consists of asynchronous PSPs and a long-lasting depolarization presumably associated with a "slow" interictal event. Under baclofen, the asynchronous PSPs are virtually abolished while the long-lasting depolarization continues to occur. (**F**): Bar graph showing the peak amplitudes and rate of occurrence of the asynchronous PSPs and of the long-lasting depolarizations (synchronous PSPs) intracellularly recorded with KCl-filled microelectrodes from 5 neurons under control conditions (4AP + CNQX + CPP) and during baclofen application. Data were adapted from Motalli *et al.* [56].

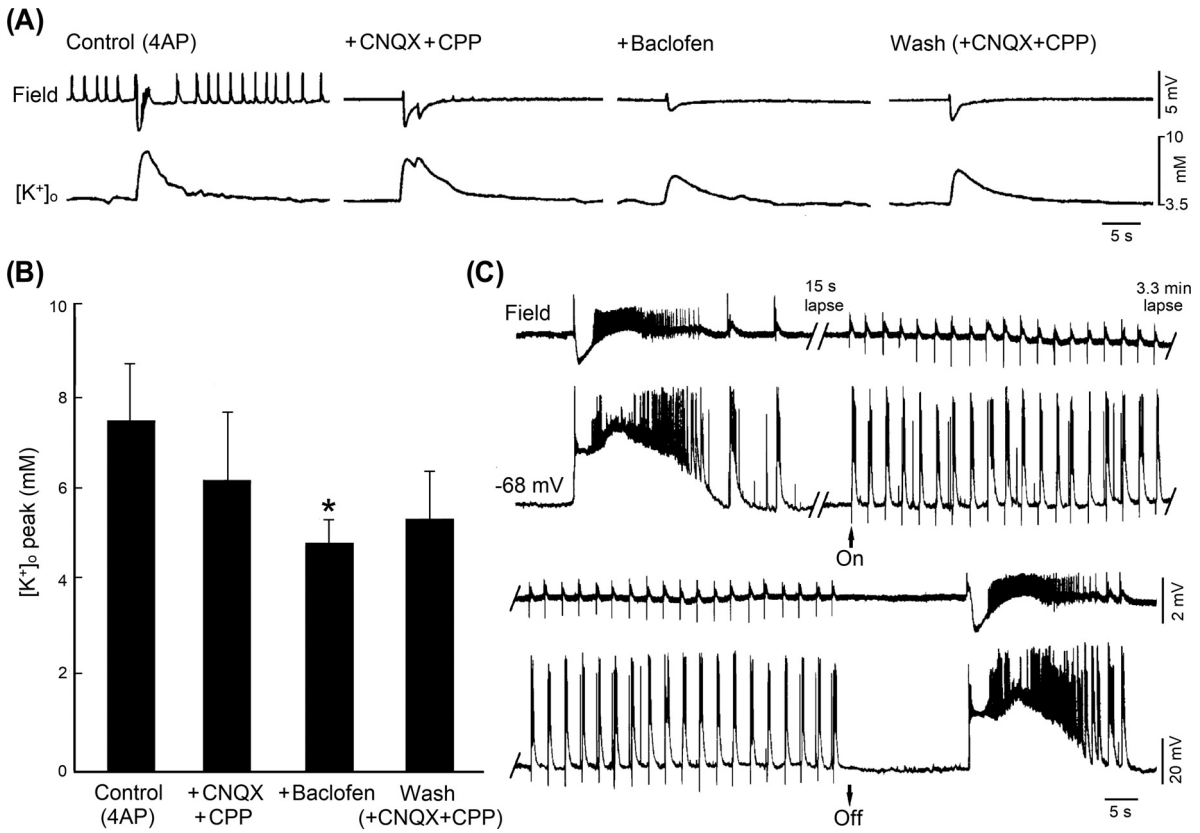

Fig. (2). Effects induced by baclofen on the pharmacologically isolated GABAergic spikes and ability of repetitive electrical stimulation to abate ictal discharges in the presence of baclofen. A: Field potential and $[K^+]_o$ recordings during control conditions and after successive applications of CPP + CNQX, and of baclofen (25 μM); note that the elevation in $[K^+]_o$ associated with the slow GABAergic spike decreases during baclofen application and that this effect was reversed during wash out. B: Plot of the peak values in $[K^+]_o$ measured in 5 experiments under these different pharmacological conditions; note that significant difference was seen between the values obtained under CPP + CNQX and those recorded after baclofen application (asterisk: $P < 0.01$). C: Field potential and intracellular (K-acetate-filled electrode) recordings obtained from the CA3 subfield during application of 4AP + baclofen (25 μM); note that ictal discharges are abolished during extracellular electrical stimuli delivered in the dentate hilus at 0.4 Hz. Data were adapted from Motalli *et al.* [56].

frequency of the "fast" interictal events occurring under control conditions) (Fig. **2C**) [56], an additional, relevant mechanism underlying baclofen-induced effects may rest on activity-dependent changes in network excitability that result from the block of the "fast" interictal spikes caused by this drug. In line with this hypothesis, it has been reported that in combined hippocampal-EC slices of adult rat, during application of 4AP or Mg^{2+}-free medium, CA3-driven interictal activity can overtime control the propensity of EC networks to generate ictal discharges that depend on the activation of NMDA receptors [60-62] (Fig. **3A**, Control panels). Ictal discharges were, however, re-established by cutting the Schaffer collaterals, a procedure that abolishes CA3-driven interictal discharge propagation to the EC (Fig. **3A**, Schaffer collateral cut panel). As shown in Fig. (**3B**), application of baclofen to combined hippocampal-EC slices of adult rat, during 4AP treatment, depressed CA3-driven "fast" interictal spiking while disclosing non-NMDA glutamatergic receptor-dependent ictal discharges that initiate in the CA3 subfield and could propagate to EC [62]. These findings were intriguing since, according to the pro-ictogenic, disinhibitory action exerted by $GABA_B$ receptor agonism [54,55], baclofen treatment should have resulted in the generation of NMDA receptor ictal events initiating in the EC as well.

In an attempt to better understand these findings, the effects induced by increasing baclofen doses were analyzed in rat brain slices in which hippocampus and EC networks were surgically isolated [62]. As illustrated in Fig. (**3Ca**), baclofen abolished ictal discharges generated by the isolated EC at concentrations as low as 0.5 μM. In contrast, in isolated hippocampal slices, it decreased the occurrence of "fast" interictal discharges at low concentrations (1 μM trace) and disclosed ictal epileptiform events at high doses (10 μM trace). In this study, dose-response curves of the depression exerted by baclofen on the interictal activity generated by isolated hippocampal and EC slices identified IC_{50} of 2.5 μM and 0.6 μM, respectively (Fig. **3Cb**). In addition to being in agreement with the findings reported by Jones [53] while studying the effects of baclofen on interictal and ictal events recorded in the rat EC treated with zero Mg^{2+}, these data demonstrate that in connected hippocampus-EC slices, under control conditions, EC ictogenesis depends on NMDA receptor function and is controlled by CA3-driven output activity; in contrast, following $GABA_B$ receptor activation EC excitability is depressed to a greater extent than CA3, which leads to non-NMDA glutamatergic receptor-mediated ictal discharges initiating in the CA3 subfield and spreading to the EC. Therefore, these findings indicate that modulating $GABA_B$

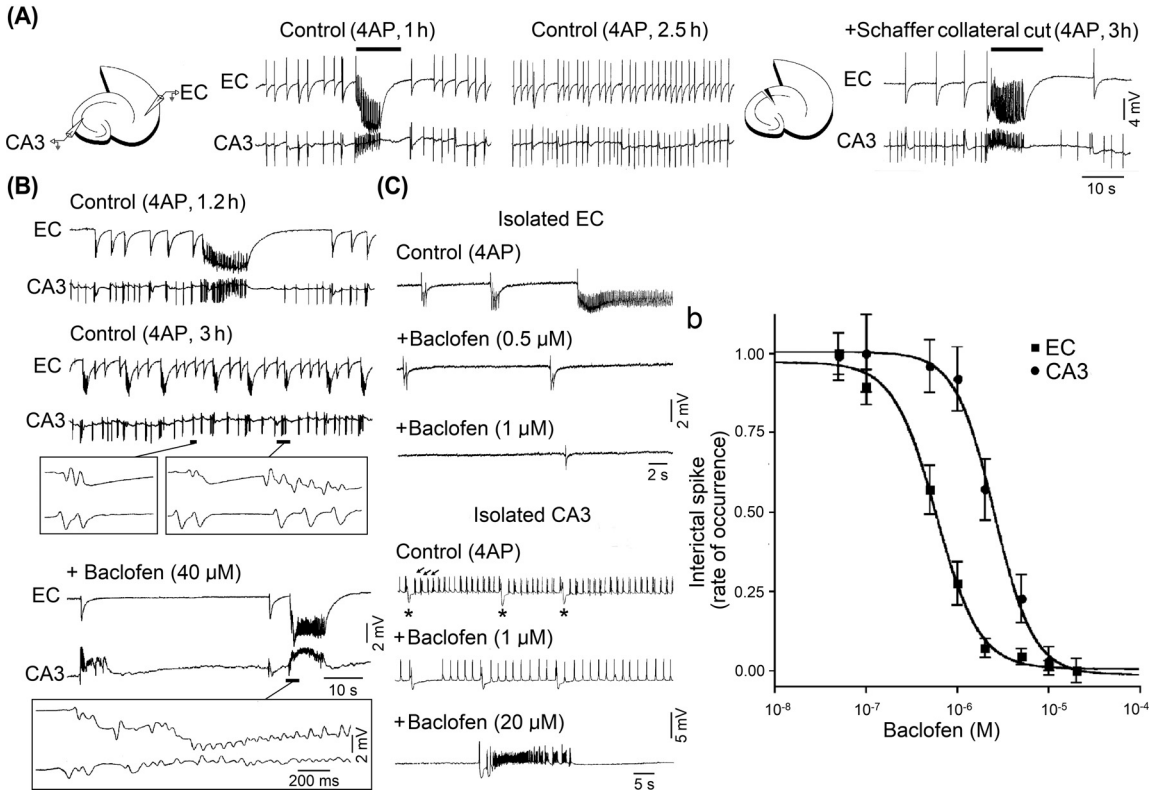

Fig. (3). Effects induced by baclofen on the epileptiform activity induced by 4AP in combined rat hippocampus-EC slices. **A**: "Fast" interictal spikes and ictal discharges were recorded from the EC and CA3 1 hr after 4AP application. After 2.5 h of 4AP application, ictal discharges disappeared while interictal discharges continued to occur in both regions. Ictal discharges reoccurred after cutting Schaffer collaterals, a procedure that blocks the propagation of CA3 output activity to EC, and disclosed "slow" interictal events that propagate from EC to CA3. **B**: In a reciprocally connected hippocampus-entorhinal cortex slice, both interictal and ictal discharges are observed after 1.2 h of 4AP application. After 3h, only interictal discharges that originate in CA3 and propagate to EC are observed. However, some interictal discharges can cause in EC an afterdischarge that re-enters CA3 (insets). Application of baclofen abolishes CA3-driven interictal discharges and reveals spontaneous ictal discharges that can propagate to EC (inset). **Ca**: Increasing concentrations of baclofen modifies epileptiform synchronization patterns recorded from isolated CA3 and EC. Application of baclofen (0.5 µM) doubles the interval of occurrence of the interictal discharges generated by the EC and abolishes ictal activity; during application of 1 µM baclofen, epileptiform activity is virtually abolished in the EC. In contrast, "fast" interictal discharges (arrows) in the isolated CA3 are decreased by less than 50 % under 1 µM baclofen while "slow" interictal events (asterisks) are not unaffected. Ictal discharges, however, appear during the application of a medium containing 20 µM baclofen, a procedure that fully blocks "fast" interictal spikes. **Cb**: Dose-response curves of the depression induced by baclofen on interictal discharges in isolated CA3 and EC. The baclofen IC_{50} of the interictal discharge reductions are 2.2 0.1 µM for the isolated CA3 and 0.1 µM for the isolated EC. Data were adapted from Avoli *et al.* [62].

receptor function influence the site of initiation, the modalities of propagation, and the ionotropic glutamatergic receptor properties of ictogenesis in the limbic system and, perhaps, in patients presenting with MTLE.

The *in vitro* ability of activation of $GABA_B$ receptors to exert pro-epileptic actions is in line with an early *in vivo* report in which baclofen injection into layers IV-V of the rat sensorimotor cortex was shown to induce focal epileptic discharges [63]. In addition, clinical studies have reported that baclofen can exert pro-convulsant effects in humans [64-67].

3. $GABA_B$ RECEPTOR ANTAGONISM AND EPILEPTIFORM SYNCHRONIZATION

Motalli *et al.* [56] also reported that most of the effects induced by baclofen on the epileptiform activity induced by 4AP in isolated hippocampal slices were reversed by the $GABA_B$ receptor antagonist CGP 35348 [68] (Fig. **4A**). Therefore, a successive study addressed the effects induced by antagonizing $GABA_B$ receptors on the 4AP-induced spontaneous discharges occurring in the CA3 subfield of rat isolated hippocampal slices [69]. These experiments demonstrated that CGP 35348 increases the rate of occurrence of interictal and ictal events (Fig. **4B**) and uncovers ictal discharges in those experiments in which only "fast" and "slow" spikes were generated under control conditions (*i.e.*, 4AP-containing medium) (Fig. **4C**). As summarized in Fig. (**4D**), all types of 4AP-induced synchronous activity occurred more frequently than under control conditions during the application of this $GABA_B$ receptor antagonist.

Intracellular recordings obtained from CA3 pyramidal cells also showed that CGP 35348 increased the frequency and, to a lesser extent, the duration of the asynchronous PSPs (Motalli *et al.* [69]). Moreover, the transient elevations in

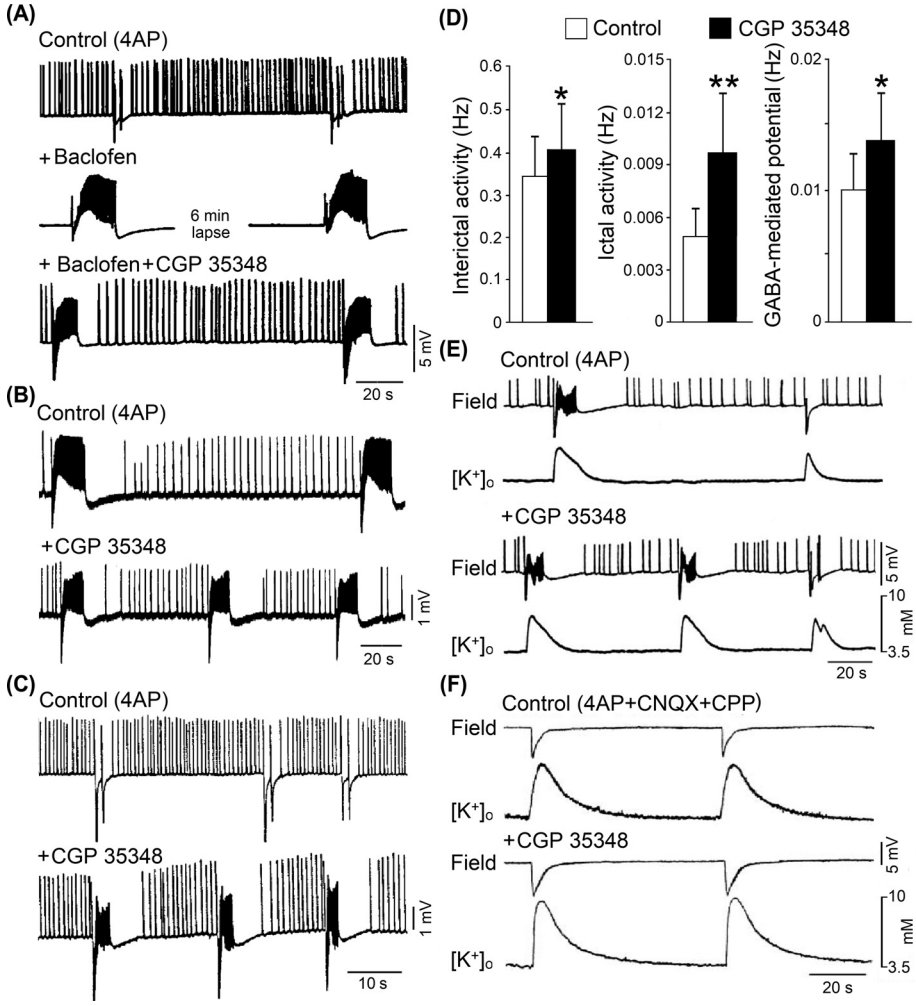

Fig. (4). Effects induced by blocking GABA$_B$ receptors on the epileptiform activity induced by 4AP in isolated rat hippocampal slices. A: Application of the GABA$_B$ receptor antagonist CGP 35348 (1 mM) to 4AP+baclofen (50 μM)-containing medium makes interictal discharges reappear while decreasing the duration of ictal discharges that, however, continue to occur. B: Field recordings showing the occurrence of "fast" interictal and ictal discharges that are initiated by negative-going GABA receptor-mediated events in control (4AP) condition. Application of CGP 35348 (1 mM) increases the rate of occurrence of ictal discharges that are shorter in duration when compared to control conditions. C: When only "fast" interictal activity and GABA receptor-mediated "slow" interictal spikes potentials occur under control conditions (4AP), CGP 35348 (1 mM) induces ictal discharges that are preceded by the GABA receptor-mediated negative-going potential. D: Bar graphs showing the effects induced by CGP 35348 (1 mM) on the rate of occurrence (Hz) of "fast" interictal and ictal discharges and of "slow" GABA-mediated spikes. CGP 35348 induces an increase in the frequency of all types of synchronous discharges. E: Under control conditions (4AP), one of the two "slow" GABA receptor-mediated spikes initiate an ictal discharge; note that the increase in $[K^+]$ associated with the "slow" spike unable to trigger an ictal discharge is smaller than what observed when an ictal discharge occurs. Application of CGP 35348 (1 mM) induces an increase of all synchronous activities and makes all negative-going field potentials trigger ictal activity. F: Field potential and $[K^+]_o$ recordings obtained from the CA3 stratum radiatum showing that the negative-going field potentials are associated with an increase in $[K^+]_o$, even when the ionotropic glutamatergic transmission is blocked. Application of CGP 35348 (1 mM) induces an increase in the amplitude of the elevations in $[K^+]_o$ but does not modify the rate of occurrence of "slow" GABA receptor-mediated events. Data in panel A are adapted from Motalli *et al.* [56], those in B to E are from Motalli *et al.* [69].

$[K^+]_o$ associated with the "slow" GABA receptor-mediated potentials (and the successive ictal discharge occurring in some experiments) induced by 4AP became larger during CGP 35348 application (Fig. **4E**), and similar findings were also obtained when CGP 35348 was applied to medium containing 4AP + ionotropic glutamatergic blockers (Fig. **4F**). Hence, these data strongly suggest that GABA$_B$ receptor antagonism leads to an increased release of GABA from interneuron terminals, at least in the hippocampus CA3 subfield. However, the effects induced by CGP 35348 on 4AP-induced epileptiform activity cannot be identified as "anticonvulsant," and, to some extent, they are surprisingly similar to what was reported in this model during GABA$_B$ receptor activation. Thuault *et al.* [70] have also shown that synchronous GABA receptor-mediated potentials recorded during application of 4AP and ionotropic glutamatergic antagonists display longer duration in hippocampal slices obtained from transgenic mice presenting with complete loss of GABA$_B$ receptor function when compared to those occurring in hippocampal slices from wild-type animals.

It should be emphasized that the findings obtained from experiments in which epileptiform activity was induced by 4AP are associated with preserved (and perhaps enhanced) $GABA_A$ receptor function [24]. However, blocking $GABA_B$ receptors has also been reported to be effective in prolonging stimulus-induced epileptiform responses in rat hippocampal [71] and human neocortical [72] slices as well as in making spontaneous ictal-like discharges appear in rat hippocampal slice cultures during $GABA_A$ receptor antagonism [73]. Later, Sutor and Luhmann [74] obtained similar results by testing the effects induced by CGP 35348 on the epileptiform activity recorded in rat neocortical slices during application of the $GABA_A$ receptor antagonist bicuculline.

Uusisaari *et al.* [75] have also found in rat hippocampal slices that when the ionotropic glutamatergic transmission is blocked, $GABA_B$ receptor antagonism induces a progressive synchronization of spontaneous interneuronal activity leading in some cases to the occurrence of spontaneous, bicarbonate-dependent, $GABA_A$ receptor-mediated ictal-like events accompanied by transient elevations in $[K^+]_o$. Intracellular recordings obtained in these experiments from CA1 pyramidal cells have revealed that these ictal-like discharges are characterized by biphasic hyperpolarizing/depolarizing potentials along with synchronous bursting; in addition, they found that these ictal-like events were: (i) not reversed by wash-out of the $GABA_B$ receptor antagonists or by baclofen application; (ii) blocked by agonists acting on presynaptic μ-opioid and cannabinoid receptors; (iii) abolished by gap-junction de-couplers such as quinine/quinidine or octanol [75]. Therefore, these data demonstrated, for the first time, that the enhanced release of GABA, consequent to $GABA_B$ receptor antagonism, can induce epileptiform ictal-like discharges in the absence of ionotropic glutamatergic transmission. These effects were long-lasting, thus confirming the role of $GABA_B$ receptors in synaptic plasticity [2, 76, 77].

4. $GABA_B$ RECEPTORS AND EPILEPTIFORM SYNCHRONIZATION IN THE HUMAN CORTICAL TISSUE MAINTAINED *IN VITRO*

As already mentioned, clinical studies have reported pro-convulsant effects in patients that were treated with baclofen [64-67]. However, no pro-epileptiform action was induced, during the application of 4AP, by baclofen in neocortical slices that were obtained during neurosurgery from epileptic patients presenting with focal cortical dysplasia (FCD) or, for the purpose of comparison, with MTLE [78]. As illustrated in Fig. (**5A**), the application of 2 μM baclofen abolished the 4AP-induced ictal events that were recorded in some experiments from FCD slices, and these effects were abolished by the $GABA_B$ receptor antagonist CGP 35348. Baclofen also decreased, in a dose-dependent modality, the interictal events generated in the remaining experiments during 4AP application (Fig. **5B**). When the effects induced by baclofen were tested on the spontaneous synchronous GABAergic spikes recorded during bath application of 4AP and excitatory amino acid receptor antagonists, the baclofen concentration needed to exert similar depressant effects was consistently larger in FCD than in MTLE slices (Fig. **5C**), suggesting that $GABA_B$ receptor function is decreased in FCD tissue [78]. Nonetheless, the application of CGP 35348 to a medium containing 4AP reversibly increased the duration of the interictal discharges in those brain slices in which only interictal activity was present (Fig. **5D**). Interestingly (and perhaps surprisingly), a recent study - which was performed in human brain slices that were obtained during pediatric epilepsy surgery - has shown that ictal discharges can be recorded from cortical dysplasia and tuberous sclerosis complex tissue when the $GABA_B$ receptor antagonist phaclofen is added to medium containing 4AP and the $GABA_A$ receptor antagonist bicuculline [79].

5. $GABA_B$ RECEPTORS IN MTLE PATIENTS AND IN ANIMAL MODELS

Employing receptor autoradiography, Billinton *et al.* [80] have analyzed $GABA_B$ receptor expression in samples of the hippocampus resected from MTLE patients presenting with hippocampal sclerosis and in samples of neurologically normal, post-mortem control patients. They found that in sclerotic epileptic samples, $GABA_B$ receptor density is reduced in CA1-CA3 subfields, hilus, and dentate gyrus while it is increased in the subiculum; in addition, they reported that $GABA_B$ receptor expression in CA1 is also upregulated when the data are adjusted for neuronal loss [80]. By employing *in situ* hybridization, these investigators found similar evidence by analyzing the $GABA_B1$ receptor subunit mRNA [81]. Shortly after, Muñoz *et al.* [82] used immunocytochemistry to examine the expression of $GABA_B$ receptor 1a-b proteins in the human hippocampal formation and identified reduced immunostaining in the granule cell layer of the dentate gyrus in hippocampal sclerotic tissue. Similar evidence has been later confirmed for different $GABA_B$ isoforms and subunit mRNA expression in the hilus and dentate gyrus of the sclerotic human epileptic hippocampus [83]. A reduced function of post- and pre-synaptic $GABA_B$ receptors has also been found in slices of human cortical tissue that was surgically resected from patients presenting with a variety of focal epileptic disorders that were refractory to pharmacological treatment [84, 85].

Reduced presynaptic $GABA_B$ receptor function has been identified in the dentate granule cells of rodents in the kindling and kainic acid models of MTLE [86, 87]. A similar impairment was also found in glutamatergic afferents in the amygdala [88] and in the hippocampal CA1 area of kindled rats [89]. Although these studies did not identify abnormal postsynaptic $GABA_B$ receptor-mediated events, reductions in both pre- and postsynaptic $GABA_B$ receptor function have been reported in CA1 pyramidal cells in the hippocampal-kindled model [90]. More recently, it has been found that SE triggered by perforant path stimulation or pilocarpine injection leads to loss of $GABA_B$ receptor-mediated heterosynaptic depression in mossy fibers that was associated with reduced $GABA_B$ receptor binding [91]. These investigators concluded that failure of $GABA_B$ receptor function should contribute to the development of spontaneous seizures after SE, and thus to epileptogenesis [91].

6. $GABA_B$ RECEPTORS CONTRIBUTION TO THE ANTI-SEIZURE EFFECTS INDUCED BY REPETITIVE LOW-FREQUENCY STIMULATION

As discussed in section 2, some forms of interictal discharge, and in particular the "fast" CA3-driven spiking,

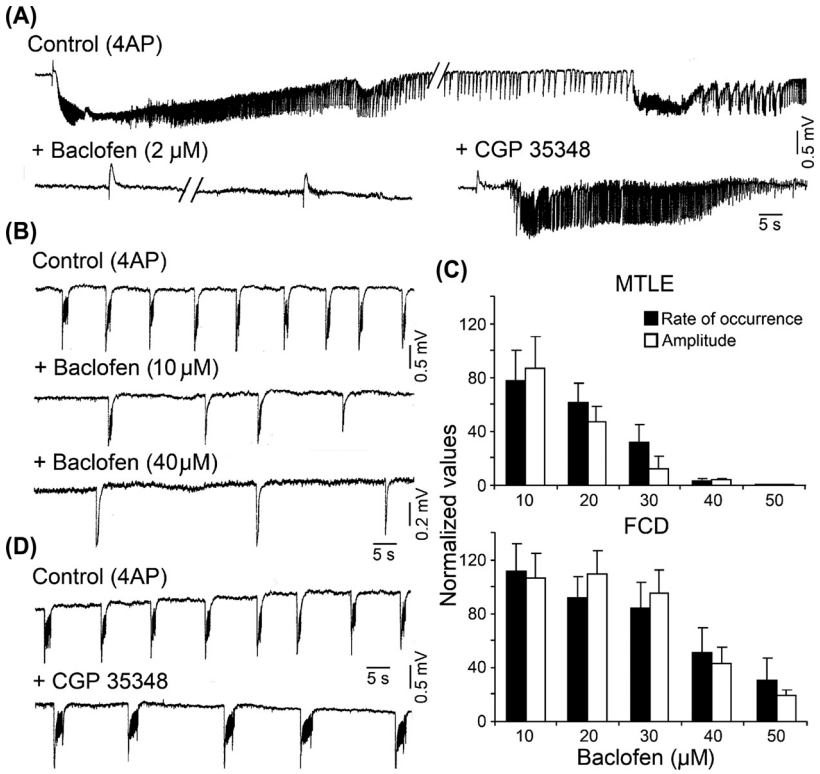

Fig. (5). Effects induced by pharmacological modulation of GABA$_B$ receptor function on the synchronous activity recorded from FCD slices during 4AP application. A: Baclofen (2 μM) abolishes the ictal activity recorded under control (4AP) conditions; note that only isolated interictal events occur during baclofen treatment and that ictal activity is restored by application of the GABA$_B$ receptor antagonist CGP 35348 (1 mM); bar breaks indicate time lapses of approx. 15 s. B: Baclofen causes a dose-dependent decrease in the duration and rate of occurrence of the synchronous epileptiform activity induced by 4AP in FCD slices that generated interictal discharge only; note the different vertical calibration in the 10 and 40 μM traces. C: Dose-response plots of the effects induced by baclofen on the rate of occurrence and amplitude of the glutamatergic-independent synchronous events generated by MTLE and FCD slices during 4AP application. Note that baclofen concentrations capable of reducing the isolated GABA receptor-mediated events by ~50% are higher in the FCD slices (~40 μM) compared with the MTLE experiments (~20 μM). Data are normalized to control values that were obtained 10 min before baclofen application. D: Effects induced by blocking the GABA$_B$ receptor with CGP 35348 (1 mM) in FCD slices that generated interictal discharges only. Note that this pharmacological procedure increases the duration of the interictal events. Data are adapted from D'Antuono *et al.* [78].

recurs at approx. 1 Hz can exert anti-ictogenic effects on the propensity of EC neuronal networks to generate this type of epileptiform activity [51, 61, 92]. In line with this evidence, ictal discharges recorded *in vitro* from the hippocampus [56], the amygdala [93], or the insular cortex [94], as well as from the neocortex [95] are depressed by repetitive stimuli delivered at 0.1-1.0 Hz. Further *in vivo* studies have confirmed these findings in rats that were acutely treated with bilateral micro-injections of 4AP into the hippocampi [96] as well as in kainic acid-treated epileptic mice [97]. Low-frequency stimulation, delivered through transcranial magnetic or deep-brain electrical procedures, has been reported to control seizures in patients presenting with epileptic disorders refractory to conventional antiepileptic therapy, including MTLE [98-100].

Toprani and Durand [101] have shown that commissural fiber tract stimulation at 1-10 Hz reduces bilateral hippocampal epileptiform discharges recorded in an *in vitro* brain slice preparation during 4AP treatment, and reported that electrical stimuli induced a long-lasting hyperpolarization that was contributed by GABA$_B$ receptor-mediated and intrinsic K^+ currents. It was found in this study that blocking GABA$_B$ receptors and intrinsic hyperpolarizing currents simultaneously abolishes the anti-ictogenic effects induced by low-frequency electrical stimulation [101]. Shortly after, Kano *et al.* [102] reported that ictal discharges induced by 4AP in the perirhinal cortex in a rat brain slice preparation are disrupted by repetitive electrical stimuli delivered at 0.1 Hz in the lateral nucleus of the amygdala and that they are abolished when the stimulus rate was brought to 1 Hz (Fig. **6A**). As shown in Fig. (**6B**), ictal activity reappeared within 2-3 minutes upon the termination of the electrical stimulation protocol; moreover, the block of ictal discharges during repetitive electrical stimulation was associated with marked jittering of the epileptiform responses following each stimulus, leading to an increased latency (Fig. **6C**, Control). Kano *et al.* [102] found that the control of 4AP-induced ictal discharges by 1 Hz stimulation and the concomitant latency jittering were significantly reduced by the GABA$_B$ receptor antagonist CGP 55845 (Fig. **6C** and **D**). Interestingly, these effects were not identified by using the GABA$_B$ receptor antagonist CGP 35348 in a previous study [60]; both binding and electrophysiological studies have shown that CGP 55845 is approx. three orders of magnitude more potent than CGP 35348 in antagonizing GABA$_B$ receptors [38].

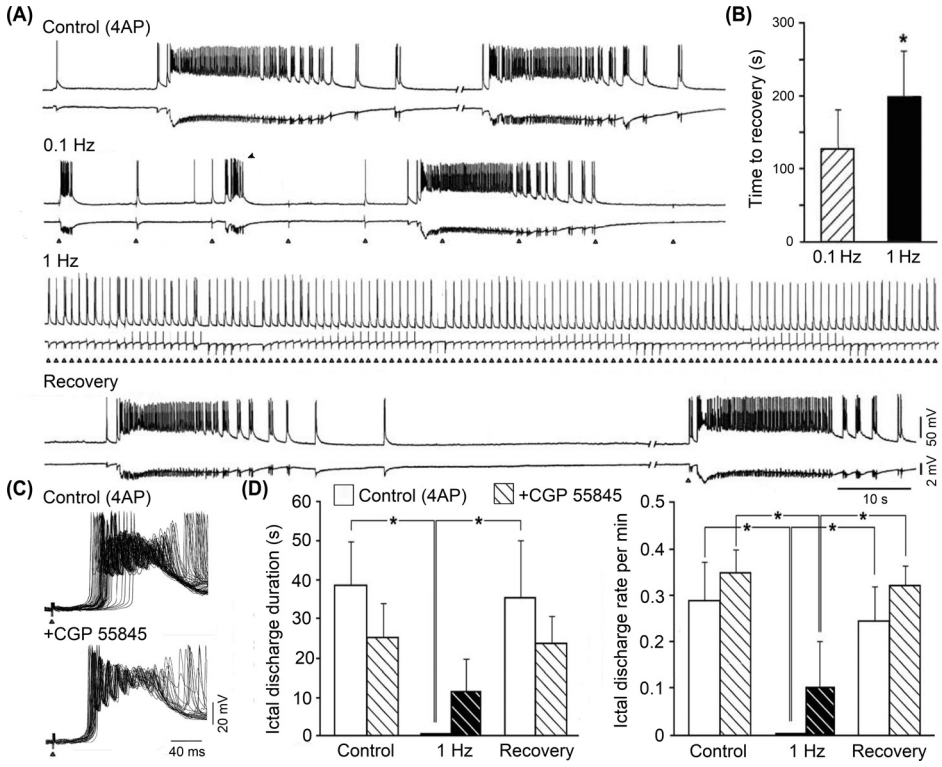

Fig. (6). Involvement of $GABA_B$ receptors in the ability of low-frequency electrical stimuli to abate ictal discharges. A: Intracellular (top trace) and field potential (bottom trace) recordings obtained from the piriform cortex under control conditions (4AP) and during continuous electrical stimulation of the lateral nucleus of the amygdala at 0.1 Hz and 1 Hz. Under control conditions, spontaneous interictal and ictal discharges regularly occur. During stimulation of the lateral nucleus of the amygdala at 0.1 Hz, some ictal discharges continue to occur spontaneously, but some of the stimulus-induced epileptiform responses resemble interictal discharges (arrowheads). Stimulation delivered at 1 Hz abolishes the generation of ictal events and induces responses that resemble the interictal-like discharges observed under control conditions. Spontaneous ictal discharges occur during the recovery period following the arrest of the 1 Hz stimulation protocol (Recovery). Bar breaks indicate time lapses of approx. 2.5 min. The resting membrane potential of this neuron was -68 mV. **B**: Bar graph showing the time between the termination of the stimulation protocols at 0.1 and 1 Hz and the reappearance of the first spontaneous ictal discharge; note that the time required for the reappearance of spontaneous ictal discharges is significantly longer following the 1 Hz stimulation protocol (*$p < 0.05$). **C**: Superimposed intracellular responses generated during repetitive stimulation at 1 Hz under control conditions (4AP) and during application of the $GABA_B$ receptor antagonist CGP 35348 (4 μM); note that the jittering of the stimulus-induced responses is greatly reduced during $GABA_B$ receptor antagonism. **D**: Bar graphs showing the duration and rate of occurrence of ictal discharges under control and during repetitive stimulation at 1 Hz during application of 4AP and after addition of CGP 55845. Note that spontaneous ictal discharges are significantly shorter in duration under 1Hz stimulation compared to control and recovery periods, while no significant differences are observed under CGP 55845. Note also that the rate of occurrence of ictal discharges is significantly lower under 1Hz stimulation protocol compared to control and recovery periods, under 4AP and CGP 55845 (*$p < 0.05$). Data are adapted from Kano *et al.* [102].

Recently Sminorva *et al.* [103] analyzed the effects induced by low-frequency electrical stimulation at 0.2 Hz on the ictal discharges induced by 4AP in the juvenile rat EC in an *in vitro* brain slice preparation. They found that the $GABA_B$ receptor antagonist SKF-97541 abolishes the blocking effects induced by low-frequency electrical stimuli on the occurrence of ictal discharges; therefore, they concluded that the anti-ictogenic effects induced by low-frequency electrical stimulation mainly depends on the activation of pre-synaptic $GABA_B$ receptors that cause the decreased probability of glutamate release from pre-synaptic terminals [103].

CONCLUSIVE REMARKS

This minireview has focused on the experimental data obtained in studies that have addressed the role of $GABA_B$ receptors in focal epileptic disorders. The findings reviewed here, which have mainly resulted from experiments performed in *in vitro* brain slice preparations, indicate that modulating $GABA_B$ receptor function causes substantial changes in several limbic structures. Surprisingly, similar pro-epileptiform synchronization effects appear to result from both the activation and the blockade of these metabotropic receptors. This contrasting evidence may be due to the localization of $GABA_B$ receptors on pre-synaptic and post-synaptic neuronal compartments as well as by their presence in both glutamatergic principal cells and inhibitory interneurons. Finally, the different sensitivity to $GABA_B$ receptor agonists and antagonists identified in some specific areas (*e.g.*, CA3 versus EC) may mirror complex changes in excitability in a whole interconnected limbic system; thus, it cannot be excluded that the different effects obtained while studying human brain tissue *in vitro* are contributed by other factors that depend on the pathological changes occurring in this type of tissue.

However, the overall picture of the research performed on $GABA_B$ receptor and focal epileptic disorders, with a few valuable exceptions (*e.g.*, Gomez *et al.* [104], Pagès *et al.* [105]), appears stagnant as few new studies have appeared during the last few years. As stated by Levinson *et al.* [79], "$GABA_B$ receptors have been largely neglected compared to $GABA_A$ receptors" in the studies aimed at identifying the mechanisms underlying focal seizures and epileptogenesis. This impasse is indeed at odds with the interest that has continued to emerge in experiments addressing the role of $GABA_B$ receptor signaling in other neurological and behavioral disorders [106-110].

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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