REVIEW ARTICLE

Gap Junction Blockers: An Overview of their Effects on Induced Seizures in Animal Models

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Abstract: ***Background***: Gap junctions are clusters of intercellular channels allowing the bidirectional pass of ions directly into the cytoplasm of adjacent cells. Electrical coupling mediated by gap junctions plays a role in the generation of highly synchronized electrical activity. The hypersynchronous neuronal activity is a distinctive characteristic of convulsive events. Therefore, it has been postulated that enhanced gap junctional communication is an underlying mechanism involved in the generation and maintenance of seizures. There are some chemical compounds characterized as gap junction blockers because of their ability to disrupt the gap junctional intercellular communication.

Objective: Hence, the aim of this review is to analyze the available data concerning the effects of gap junction blockers specifically in seizure models.

Results: Carbenoxolone, quinine, mefloquine, quinidine, anandamide, oleamide, heptanol, octanol, meclofenamic acid, niflumic acid, flufenamic acid, glycyrrhetinic acid and retinoic acid have all been evaluated on animal seizure models. *In vitro*, these compounds share anticonvulsant effects typically characterized by the reduction of both amplitude and frequency of the epileptiform activity induced in brain slices. *In vivo*, gap junction blockers modify the behavioral parameters related to seizures induced by 4-aminopyridine, pentylenetetrazole, pilocarpine, penicillin and maximal electroshock.

Conclusion: Although more studies are still required, these molecules could be a promising avenue in the search for new pharmaceutical alternatives for the treatment of epilepsy.

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1. INTRODUCTION

The term "synapse" has been defined as a specialized structure allowing the functional interaction between neurons. This structure has morphologic and functional characteristics capable of directing and modulating neuronal signals. Following the classical studies of Furshpan and Potter [1], it was recognized that beside the chemical synapses, there was another type of neurotransmission in the nervous system denominated as "electrical synapses."

In the well-known chemical synapses, the communication is carried out through the release of neurotransmitters from the presynaptic neuron that bind to specific receptors, causing changes in the ionic permeability of the postsynaptic membrane. By contrast, in the electrical synapses, the communication is done by Gap Junctions (GJ) that are clusters of intercellular channels allowing the bidirectional

transit of ions directly into the cytoplasm of adjacent cells [2, 3].

GJ are formed by two assembled hemichannels, each one located in the neighboring membranes and constituted by six subunits of integral membrane proteins called connexins (Cx). The Cx gene family is represented by 21 members expressed in human and 20 in the mouse genome, and the proteins encoded by these genes have been classified and named by its molecular weight [4, 5].

The localization of electrical synapses in the brain has been extrapolated from the expression patterns of Cx. Therefore, it has been determined that approximately half of the Cx isoforms are present in the mammalian brain. Astrocytes are characterized by the high levels of the subunits Cx30 and Cx43 [6], which change their expression in an age dependent manner [7]. It has been established that Cx30 and Cx43 are necessary for different cellular processes including neurogenesis [8] and long-term synaptic plasticity [9].

Astrocytes have GJ interconnections not only with other astrocytes but also with oligodendrocytes. Recent evidence indicates that the presence of Cx32 and Cx47 in

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oligodendrocytes is related to the gap junctional coupling with astrocytes and also directly with other oligodendrocytes [10, 11]. Because oligodendrocytes are crucial for the myelination process, several human demyelinating disorders have been described which are caused by mutations in the genes that encode for Cx32 and Cx47 [12].

The first studies related to GJ located in neuronal cells revealed that Cx36 is highly expressed in neurons during the early postnatal stages, however, the abundant immuno-reactivity decreases in the adult brain [13, 14]. Subsequent studies about the expression patterns of Cx in neuronal cells showed that Cx45 is relatively abundant in both neonatal and adult mouse neurons [15]. Moreover, it has been described recently that neurons in the spinal dorsal horn express Cx45 [16]. Due to its extensive expression in the nervous system, both GJ and Cx seem to be essential elements in the development and physiology of the brain.

2. GJ AND SEIZURES

Several studies have proposed that GJ and Cx participate in several brain processes. In this regard, one hypothesis indicates that electrical coupling mediated by GJ plays a role in the generation of highly synchronized electrical activity [17, 18]. Because the hypersynchronous neuronal activity is a distinctive characteristic of convulsive events, it has been postulated that enhanced gap junctional communication is an underlying mechanism involved in the generation and maintenance of seizures [19, 20].

The electrical synapses allow the bidirectional transit of ionic currents and, therefore, can produce changes in the membrane potential of neighboring neurons. These features provide velocity and reciprocity to the communication allowing the synchronization of neuronal networks [21]. Although excitatory and inhibitory chemical transmission could be enough to synchronize neuronal activity, it has been observed that such activity is modified in the absence of GJ. Specifically, the elimination of electrical coupling in interneurons and pyramidal cells in the CA3 area and dentate gyrus of Cx36 knockout mice has been explored, and these Cx36-deficient mice showed a decrease of gamma frequency oscillations induced by kainate and carbachol in the CA3 region of the hippocampus [22].

Despite the fact that synchronization in seizures is a very complex phenomenon that depends on several factors [23], there is some consensus about the importance of the participation of GJ. Therefore, several studies have shown alterations of Cx expression in both animal seizure models and epileptic patients. Recently, Akbarpour and colleagues [24] evaluated the expression levels of Cx, in astrocytes and oligodendrocytes, during kindling epileptogenesis. They found that Cx30 was upregulated in the hippocampus after the first amygdaline electrical stimulation. With the same seizure experimental model, other authors investigated mRNA and protein levels of Cx in neurons, and described that Cx36 was upregulated in the hippocampus of rats with partial seizures [25]. Also, it has been described that after repeated seizures the levels of mRNA of Cx32, Cx36 and Cx43 significantly increased at the epileptic foci located in the somatosensory cortex [26]. Contrariwise, another study

demonstrated that injection of 4-aminopyridine induced systemic seizures related to decreased Cx36 expression levels in the hippocampus of mice [27].

The relation between seizures and Cx expression has also been explored in humans, and the most common result has been the increase of Cx43 in the hippocampus obtained from epileptic patients [28, 29]. These results not only support the hypothesis about the participation of gap junctional communication on seizures, but also show that the expression pattern of Cx strongly depends on the animal model, brain region, and seizure duration.

3. GJ BLOCKERS AND ANIMAL SEIZURE MODELS

In the literature, there is a variety of chemical compounds characterized as GJ blockers. Although the mechanisms are not well defined, the efficacy of the GJ blockers has been principally evaluated using techniques to measure dye transfer and electrical conductance [30]. After such characterization, the designation as GJ blocker has been given to some chemical compounds that have shown the ability to disrupt the gap junctional intercellular communication.

In comparison to *in vivo* experiments, GJ blockers have been used in a broader variety of *in vitro* studies. However, although the data are limited, the behavioral, cognitive and electrophysiological effects of many GJ blockers have been reviewed in the past [31]. There is the postulate of the enhanced gap junctional intercellular communication as an underlying mechanism involved in the generation and maintenance of seizures [19, 20]. For this reason, this review has focused in analyzing the available data concerning the effects of GJ blockers specifically in animal seizure models.

3.1 Carbenoxolone (CBX)

CBX is a semisynthetic derivative of glycyrrhetinic acid. This molecule was developed since the 1960´s for the treatment of peptic ulcer disease [32]. Unfortunately, the medical use of CBX has been limited because of the several side effects associated with the mineralocorticoid-like actions [33]. Interestingly, it was demonstrated that CBX produced inhibition of the gap junctional intercellular communication but without a clear selectivity for particular subtypes of Cx [34, 35]. After this discovery, many studies focused on evaluating CBX in diverse models of processes related to the gap junctional intercellular communication in the brain [36, 37].

The first reports that studied the relationship between CBX and epileptiform activity were carried out in hippocampal slices. Some studies described that CBX delayed the induction and reduced the well-established epileptiform activity induced by adding 4-amynopiridine or omitting Mg^{2+} from the slices perfusate [38, 39]. Also, Kaglund *et al*. [40] confirmed that CBX also reduced both the frequency and amplitude of epileptic field bursts induced by cesium or low calcium in hippocampal slices. More recently, two studies using genetic and pharmacological models of seizures determined that CBX significantly decreased the amplitude and duration of seizure-like activity in thalamocortical slices [41, 42]. These *in vitro* reports established the basis for the subsequent evaluation of CBX in *in vivo* models.

Anticonvulsant effects have been described in rodents administered systemically with several doses of CBX. It has been reported that intraperitoneal (i.p.) administration of CBX (40-300 mg/ kg) delayed the onset of seizures and reduced the duration of clonic seizures induced by pentylenetetrazole (PTZ) [43, 44]. Similar results but with low doses of CBX (5-30 mg/kg), were observed in audiogenic seizures in a genetic model of epilepsy-prone rats [45]. Conversely, the same research group reported that neither intravenous nor i.p. administration of CBX had any effect on the number nor duration of spike-wave discharges in a genetic animal model of absence epilepsy [46]. By contrast, Gigout *et al.* [47] using a similar genetic animal model, described that systemic doses of CBX (100 mg/kg) significantly decreased the duration of spike-wave discharges. Interestingly, results obtained in our laboratory have showed that i.p. administration of CBX protects against tonic seizures induced by maximal electroshock reducing both the incidence of tonic hindlimb extension (THLE) and the duration of the THLE (Fig. **1A**, **E**).

On the other hand, some studies have tested the application of CBX directly into the brain to identify specific anatomical substrates where CBX could be exerting its anticonvulsant effects. In this regard, some authors evaluated the effects of CBX directly in the epileptic focus induced by the application of 4-aminopyridine or tetanus toxin on the somatosensory or entorhinal cortex. They found that the direct blockage of GJ with CBX in the epileptic focus decreased both the duration of seizures and the amplitude of seizures discharges [26,48-50]. Interestingly, several studies have revealed that microinjection of CBX into the inferior colliculus, substantia nigra, inferior olivary complex [45], basolateral amygdala [51] and hippocampus [52] reduced the duration and severity of seizures. Additionally, it has been reported that bilateral microinjection into ventro-posteromedial thalamic nucleus did not produce any significant effect [46]. By contrast, in a model of absence seizures, CBX microinjected into the reticular nucleus of the thalamus decreased the duration of seizures [52]. Likewise, results recently obtained in our laboratory have showed that CBX microinjected into the reticular formation reduces the incidence of generalized tonic-clonic seizures and prevented the epileptiform activity induced by PTZ [53]. In conclusion, all of these data have showed that CBX has anticonvulsant effects when administered in different seizure experimental models.

3.2 Quinine (QUIN)

QUIN is an alkaloid produced in the bark of *Chinchona* trees. Some historical records suggest that QUIN has been used for the treatment of malaria since almost 400 years ago [54, 55]. However, due to some adverse effects, the World Health Organization recommended avoiding the use of QUIN as a first-line treatment reducing its use only to cases of severe malaria [56].

The first studies concerning QUIN and excitable cells revealed that this antimalarial drug could block ionic channels and, therefore, suppress some ionic conductances [57, 58]. Also, it was showed that QUIN modulated the activity of hemichannels in neurons from the vertebrate retina, and also in oocytes expressing some isoforms of Cx [59, 60]. Subsequently, Srinivas *et al.* [61] demonstrated for the first time that QUIN blocked GJ formed by Cx36 and Cx50 in a reversible and dose-dependent way. Since Cx36 is expressed in mammalian neurons [13-14], several studies emphasized the effects of QUIN on processes related to neuronal synchronization.

Few studies have explored the possible effects of QUIN on *in vitro* and *in vivo* experimental models of seizures. The first report in this subject described that QUIN blocked the excitability of CA3 pyramidal neurons in hippocampal slices, through the modification of the properties of the membrane resting potential, and the duration and amplitude of spikes [62]. Also using hippocampal slices, Uusisaari *et al.* [63] induced synchronous bursting in pyramidal neurons exposing slices to GABA$_B$ receptor antagonists and discovered that QUIN reversibly blocked the denominated GABAergic ictal-like events. Interestingly, another study tested the *in vitro* effects induced by QUIN in the neocortex of patients with temporal lobe epilepsy. This study showed that QUIN decreased irreversibly the occurrence of synchronous field potential activity produced by the application of 4-aminopyridine [64]. Paradoxically, there is a report that describes excitatory effects of this GJ blocker in rat slices. Specifically, it was found that QUIN increased the frequency and amplitude of seizure-like activity induced by low magnesium in neocortical slices. However, it was also described that at high doses, QUIN caused a biphasic effect characterized by an initial excitatory phase followed by an apparent reduction in seizure-like activity [65].

Some *in vivo* reports have established that QUIN could have effects on seizure experimental models. Wambebe *et al.* [66] and Nassiri-Asl *et al.* [67] described that i.p. administration of QUIN (25-100 mg/kg), reduced both the incidence and duration of seizures and modified the latency to the tonic and myoclonic phases in mice administered with PTZ. However, they did not find significant effects when analyzed the effects of QUIN on maximal electroshock seizures. Similar to these last results, we have observed that i.p. administration of QUIN (60-240 mg/kg) only elicited a slight protection against the incidence and duration of THLE induced by maximal electroshock (Fig. **1B**, **F**). The administration of QUIN directly to the brain ventricles has also been evaluated. Thus, in rats, QUIN (200, 400 and 1000 nmol) significantly decreased the frequency and amplitude of the epileptiform activity induced by the intracerebro-ventricular (icv) injection of penicillin [68]. Likewise, another study reported that icv administration of QUIN (0.5 and 1 mM) significantly increased the latency and decreased the duration of the generalized tonic-clonic seizures induced by PTZ [69].

On the other hand, some studies have tested the effects of QUIN applied directly to cortical areas, and the results have been consistent. Gadja *et al.* [70] demonstrated that pretreatment with QUIN on the somatosensory cortex slightly reduced the epileptogenesis induced by 4-aminopyridine. However, when QUIN was applied to contralateral and ipsilateral cortical areas after the constant expression of seizures, the duration and propagation of seizures decreased significantly. Similarly, two reports have established that
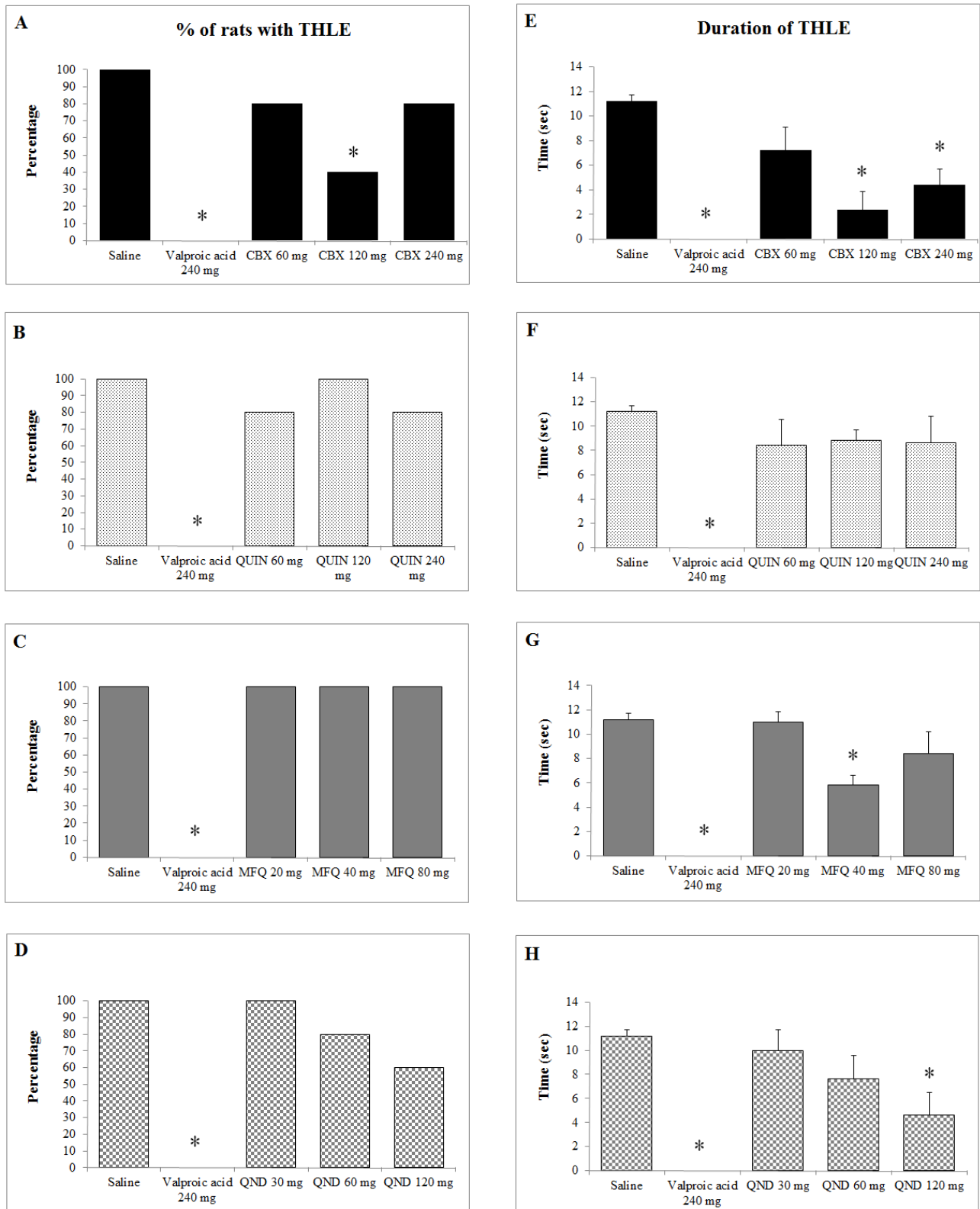
Fig. (1). Percentage of rats with Tonic Hindlimb Extension (THLE) and duration of THLE after the application of maximal electroshock in rats previously administered with saline solution (negative control), valproic acid (positive control) and with different doses of Carbenoxolone (CBX) (1A, 1E), Quinine (QUIN) (1B, 1F), Mefloquine (MFQ) (1C, 1G) and Quinidine (QND) (1D, 1H). Values are expressed as a percentage and in seconds (mean ± SEM). The level of significance for percentage of rats with THLE was determined by independent Fisher´s exact probability tests comparing each experimental group versus saline group The level of significance for duration of THLE was determined by a Kruskal-Wallis one-way analysis of variance on ranks (*p<0.05).

microinjection of QUIN into the entorhinal cortex modified the characteristics of the hippocampal epileptiform activity induced by both 4-aminopiridyne and pilocarpine [71, 72].

3.3. Mefloquine (MFQ)

MFQ is a synthetic compound structurally analog to QUIN. The Walter Reed Army Institute of Research in the USA developed it in the early 1970′s. Initially, MFQ was indicated for the treatment and prophylaxis of malaria; however, currently it is no longer considered by the World Health Organization as a first-line drug to eliminate the parasite causing malaria [73].

Before its proposal as GJ blocker, some studies had reported that MFQ has the capability to shorten action potential duration, decreasing currents through L-type calcium channels [74]. Later, it was demonstrated that MFQ reduced, in a concentration-dependent manner, the intercellular gap junctional currents in N2A cells selectively expressing Cx36 and Cx50 [75]. Consequently, MFQ was evaluated on the brain due to the expression of Cx36 in neuronal cells [14]. Therefore, it was determined that MFQ reduced, in a time and concentration-dependent manner, the electrical coupling of interneurons in neocortex slices [75].

There is a significant decrease in the excitatory activity of the hippocampus after the application of MFQ [75]. However, another report described that MFQ induced increases in both the amplitude and frequency of seizure-like events in cortical slices of rats [65]. Although this is a still unexplored issue, it has been proposed that the opposing effects observed could be related to the doses of MFQ used. This controversy has been a constant in the *in vitro* studies. Voss *et al.* [76] reported that, in mouse neocortical slices, MFQ (25 μM) has no effects on the seizure-like activity induced by perfusion with low concentrations of magnesium. On the other hand, more recently it was described that MFQ (10 μM) significantly decreased the amplitude and frequency of seizure-like activity induced by the coadministration of 4-aminipyridine and bicuculline in thalamocingulate mice slices [42].

Due to the lack of *in vivo* studies, we have worked on clarifying the controversy about MFQ and seizures. Our results indicated that MFQ (40 mg/kg, i.p.) significantly decreased the incidence of seizures and the total spectral power of the epileptiform activity induced by PTZ [77]. We have also observed a significant reduction of the duration of THLE induced by maximal electroshock (Fig. **1C**, **G**). Most likely, the lack of *in vivo* studies is because some reports have suggested that MFQ could cause undesired neurological effects at doses around 187 mg/kg [78]. We have observed that MFQ (40 mg/kg) elicited some protection against the seizures induced by two acute models of seizures (Fig. **2**). Therefore, it seems reasonable to propose that MFQ acts in a dose-dependent manner, showing anticonvulsant effects at small doses and neurotoxic effects at high doses.

3.4. Quinidine (QND)

QND is another compound derived from the *Chinchona* tree bark and chemically related to QUIN. The use of QND

dates since 1914 when it was demonstrated that this compound could be beneficial in the treatment of cardiac arrhythmias [79]. In addition to its antiarrhythmic effect, the Center for Disease Control and Prevention has established that QND gluconate is the only antimalarial agent available for parental administration in the United States [80].

Some classical studies reported that the application of QND to neurons provoked a clear block of ionic conductances though Na+, K+ and Ca+ channels, and consequently caused modifications of action potentials properties [81-83]. However, after a meticulous analysis, Malchow *et al.* [83] proposed for the first time that QND could modify the gap junctional communication between neurons. More recently, this hypothesis was explored using N2A cells transfected with Cx50 channels, and it was demonstrated that QND (300 μM) significantly inhibited the currents in GJ formed by Cx50 [75].

Very few studies have evaluated the effect of QND on seizure experimental models. One study has reported that QND induces an increase in the frequency of seizure-like events caused by the addition of low concentrations of magnesium to rat cortical slices [65]. By contrast, it has been showed that QND abolishes the ictal-like activities induced by 4-aminopyridine in rat thalamocortical slices [47]. Similarly, Gigout, *et al.* [64] evaluated the effects of QND but in slices obtained from the neocortex of temporal lobe epileptic patients; they found that QND decreases irreversibly the frequency of occurrence of the synchronous field potential activity induced by 4-aminopyridine. Using *in vivo* models, Steriade and Stoica [84] performed well-designed experiments and reported that QND (4-30 mg/kg) caused significant anticonvulsant effects in experimental models such as electroshock and cortical application of penicillin. In contrast, we have observed that higher doses of QND (120 mg/kg) are necessary to generate some protection against the THLE induced by maximal electroshock (Fig. **1D**, **H**). These previous information has led us to suggest that the relation between QND and seizure experimental models is nowadays underrepresented, and that it is necessary more *in vivo* studies to explore more in depth this topic.

3.5. Anandamide (ANA) and Oleamide (OLE)

ANA and OLE are fatty acid amides. These molecules are related to a wide range of biological functions [85]. ANA and OLE are members of the cannabinoid family and these endogenous molecules bind and activate the cannabinoid receptor 1 [86]. Some reports have demonstrated that these endocannabinoids have effects on Ca+ channels and significantly increase the intracellular concentration of Ca^{2+} in different cell types [87, 88]. Interestingly, it has been described that both, ANA and OLE, are potent inhibitors of intercellular gap junctional communication in glial cells, and ANA also blocked calcium wave propagation in striatal astrocytes [89, 90].

Following the effects of ANA and OLE on gap junctional communication, some authors have evaluated their effects on animal seizure models, including two reports that have

Motor cortex activity after pentylenetetrazole administration

Pentylenetetrazole 70 mg/kg

Mefloquine (40 mg/kg) +
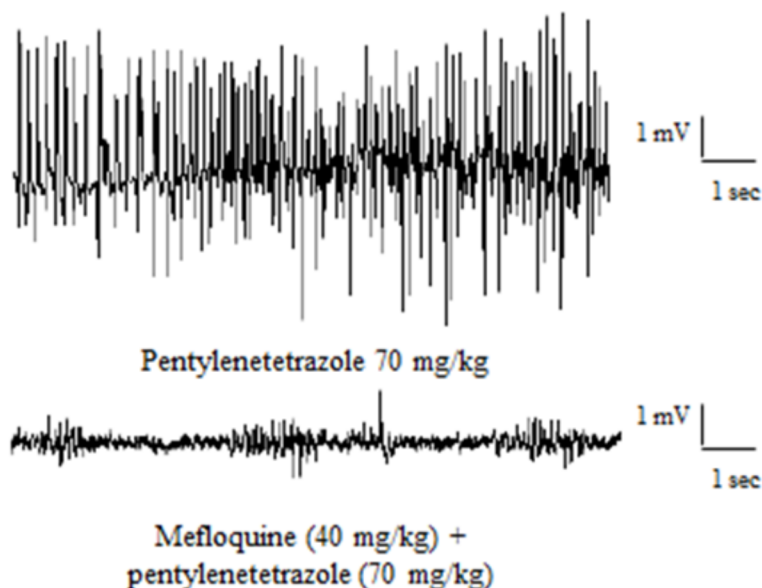pentylenetetrazole (70 mg/kg)

Fig. (2). The intraperitoneal administration of mefloquine (40 mg/kg) inhibits the epileptiform activity induced by the application of pentylenetetrazole (70 mg/kg) in rats.

described ANA role in the modulation of seizures induced by maximal electroshock [91, 92]. Specifically, one report described a modest anticonvulsant activity with ANA alone (50 mg/kg) [91]. However, the combination of ANA (300 mg/kg) with an inhibitor of amidohydrolase, which rapidly metabolize ANA, generated a complete protection against seizures induced by electroshock [92]. Similar studies have demonstrated that inhibition of amidohydrolase increased the levels of ANA in the brain, and reduced the severity of seizures induced by application of kainic acid [93, 94]. ANA has also been evaluated in other animal seizure models such as PTZ and a genetic model of absence epilepsy. Interestingly, Mannea and Umathe [95] have reported that icv administration of ANA showed dose-dependent effects; namely, at small doses (10-40 µg) ANA produced anticonvulsant effects, while at high doses (80-160 µg) ANA increased the percentage of animals with seizures induced by application of PTZ. More recently, it has been reported that icv administration of ANA significantly decreases in a dose-dependent manner, the presence and duration of spike-wave discharges related to absence seizures [96].

There are few studies relating OLE and seizures; however, they are consistent with those using ANA. Hence, it has been showed that OLE (43-700 mg/kg, i.p.) inhibited the seizures induced by PTZ but not those induced by picrotoxin or strychnine [97, 98].

3.6. Other GJ blockers

In addition to the substances previously mentioned, more compounds have been characterized as GJ blockers [31]. Some of these compounds include meclofenamic acid, niflumic acid, flufenamic acid, heptanol, octanol, glycyrrhetinic acid and retinoic acid. These chemicals have shown ability to

block hemichannels and GJ composed of Cx26, Cx32, Cx36, Cx40, Cx43, Cx46 and Cx50 [99-105] (Table **1**).

The meclofenamic, niflumic and flufenamic acids are grouped in the fenamates family, which is a group of drugs used as anti-inflammatories and analgesics. Of these three compounds, both meclofenamic and flufenamic acids have been evaluated in relation to seizures, and it has been shown that i.p. administration of meclofenamic acid increases the latency to the onset of seizures induced by PTZ [106]. Additionally, in rats with epileptic focus caused by tetanus toxin, a significant reduction in seizure duration was observed when meclofenamic acid was applied directly to the cortex [107]. Similarly, Schiller [108] stimulated neocortical slices with a GABA$_A$ receptor blocker to evoke seizure-like events, and observed that addition of flufenamic acid (100-200 µM) reversibly eliminated the seizure-like events.

Heptanol and octanol are long carbon chain n-alkanols capable of modifying the gap junctional intercellular communication [102, 103]. Therefore, it was demonstrated that perfusion of entorhinal/hippocampal slices with octanol blocked the primary afterdischarges produced by the tetanic stimulation of Schaffer´s collaterals [109]. Using the same model, D´Antuono *et al.* [110] showed that octanol blocked theta activity of the epileptiform afterdischarges induced by the application of picrotoxin. Heptanol has also been evaluated in hippocampal slices with similar results to those exhibited by octanol. Namely, heptanol significantly depressed the spontaneous field burst and the repetitive population spikes evoked by fimbrial stimulation [111]. To date, there are few studies reporting data about the use of octanol on *in vivo* seizure experimental models. Relatedly, it was showed that octanol reduced seizure induction and

Table 1.   Characteristics of some Gap Junction blockers.

GJ Blocker	Affinity	Selectivity for Cx Isoforms	Efficacy	Specificity (Other Targets Outside GJ)
Carbenoxolone	GJ, Cx and Panx hemichannels	Non-selective	5-100 µM	Voltage-gated Ca^{2+} channels; p2x7 receptors; NMDA-evoked currents
Quinine	GJ and Cx hemichannels	36, 45, 50	30-300 µM	Voltage-dependent K^+ channels; nicotinic and cholinergic receptors; Na^+ currents; inhibitor of P-glycoprotein
Mefloquine	GJ, Cx and Panx hemichannels	36, 43, 50	3-30 µM	Adenosine and p2x7 receptors; ATP-sensitive K^+ channels; inhibitor of P-glycoprotein
Quinidine	GJ and Cx hemichannels	50	300 µM	K^+ and Na^+ channels; muscarinic and nicotinic receptors; inhibitor of P-glycoprotein
Anandamide	GJ	32, 43	5-50 µM	CB1, GABA, glycine and 5-HT receptors; Na^+ and Ca^{2+} channels
Oleamide	GJ and Cx hemichannels	32, 43	20-50 µM	CB1,5-HT, GABA and glycine receptors
Meclofenamic acid	GJ and Cx hemichannels	36, 43, 50	25-100 µM	Voltage-gated K^+ channels; GABA receptors
Niflumic acid	GJ and Cx hemichannels	43, 46, 50	10-1000 µM	Voltage-gated K^+ channels; Cl^-, Ca^{2+} and Na^+ channels; GABA and NMDA receptors
Flufenamic acid	GJ, Cx and Panx hemichannels	26, 32, 40, 43, 46, 50	40-250 µM	p2x7, GABA and NMDA receptors; Cl^- and K^+ channels; voltage-gated K^+ channels
Heptanol	GJ and Cx hemichannels	32, 43, 45	1-3 mM	p2x7 and kainate receptors; Ca^{2+} and K^+ channels
Octanol	GJ and Cx hemichannels	43, 46, 50	0.5-1 mM	GABA, glycine, AMPA, NMDA, kainate and p2x7 receptors; T-type Ca^{2+} channels
Glycyrrhetinic acid	GJ, Cx and Panx hemichannels	Non-selective	2-250 µM	Ca^{2+} channels; glutamate transporters
Retinoic acid	GJ and Cx hemichannels	38	2-100 µM	Retinoids, dopamine and 5-HT receptors; noradrenaline, GABA and acetylcholine transporters; L and N-type Ca^{2+} channels
Mimetic peptides (Gap24, Gap26, Gap27)	GJ, Cx and Panx hemichannels	32, 37, 40, 43	300-600 µM	

For references [31,36,37,61,75,89,90,99-105].

seizure discharges when it was applied directly to the epileptic focus in the somatosensory cortex [70]. Additionally, it has been reported that icv administration of octanol significantly reduces the frequency and amplitude of epileptiform spikes, as well as the epileptic behavioral score induced by the icv administration of penicillin [112].

The glycyrrhetinic acid is a derivative compound from a genus of plants named Glycyrrhiza. Interestingly, it has been shown that this chemical displays some anti-tumoral, anti-allergic and anti-inflammatory effects [113]. The first studies concerning glycyrrhetinic acid in the context of epileptogenesis were carried out by de Curtis *et al.* [114]; they described that glycyrrhetinic acid eliminated the spontaneous interictal spikes in an *in vivo* model of focal epileptogenesis. More recently, using rats implanted with a cannula into the reticular nucleus of the thalamus, it was found that glycyrrhetinic acid significantly decreased the duration of atypical absence seizures [52]. Interestingly, despite the fact that glycyrrhetinic acid is a compound that is chemically related to CBX, its effects on animal seizure models are not yet fully explored.

Retinoic acid, a product of the metabolism of vitamin A, has also been reported as a GJ blocker. Specifically, it has been observed in retinal cells that retinoic acid was able to reduce, in a dose-dependent manner, the amplitude of the gap junctional conductance [104]. Lately, Sayyah *et al.* [51] evaluated the infusion of retinoic acid directly into the amygdala of rats, and they observed that retinoic acid significantly reduced both the afterdischarge duration and the seizures generated in rats electrically stimulated in the amygdala. Although these results seem consistent with the blockage of GJ, other recent evidence has suggested that retinoic acid not only increased the expression of Cx32 and Cx43 but also increased the gap junctional intercellular communication [115, 116].

3.7. Cx-mimetic Peptides

An alternative approach to precisely block GJ and Cx hemichannels consists of using specific antibodies or small peptide fragments corresponding to intracellular amino acid sequences of diverse Cx. Thus, the first studies done by Moore and Burt [117] described that Cx-specific antisense

oligodeoxynucleotides could reduce the frequency of unitary conductances in cells expressing Cx40 and Cx43. Later, it was established that cells incubated with a synthetic oligopeptide corresponding to a segment of the second extracellular loop of Cx43, showed decreased dye coupling and dual whole-cell voltage clamp, indicating a reduction of the cell-to-cell coupling [118]. The Cx-mimetic peptides have been proposed as specific and reversible blockers of GJ and Cx hemichannels; however, it has been reported that these short amino acid sequences have the ability to inhibit currents from channels constituted of proteins topologically similar to Cx, called pannexins (Panx) [119].

From all the synthesized peptides, Gap26 and 27 are the most widely used because they correspond to specific sequences within the extracellular loops of Cx37, 40 and 43. Although the detailed mechanism of action of the Cx-mimetic peptides is unknown, it has been suggested that they interact with the extracellular loops, disrupting the docking of the hemichannels and, therefore reducing the assembly of functional GJ [120, 121].

To evaluate the effects of Cx-mimetic peptides concerning epileptiform activity, Samoilova *et al*. [122] studied the administration of Gap27 to hippocampal slices and detected that spontaneous recurrent epileptiform activity was diminished but only after 10 hours of Gap27 treatment. On the other hand, it has been reported that application of a mimetic peptide in hippocampal slices, targeted to the extracellular loop two of Cx43, evoked a dose- and exposure time-dependent response, preventing the seizure-induced neuronal death caused by the application of an antagonist of GABA-A receptors [123]. Based on these reports, it has been suggested that blockage of GJ and hemichannels constituted by Cx43 could prevent the neuronal damage induced by the epileptiform neuronal activity.

4. GJ OR HEMICHANNELS AS TARGETS OF GJ BLOCKERS

The GJ blockers show affinity not only for GJ but also for hemichannels composed of different subtypes of Cx (Table **1**). The Cx family is characterized by 20 isoforms expressed in the mouse genome; however, it has been determined that approximately half of the Cx isoforms are present in the brain. Interestingly, following previous reports, it has been observed that GJ blockers mainly modify the communication of GJ and hemichannels constituted of Cx36, Cx43 and Cx50 (Table **1**) [36, 37, 61, 75, 89, 90, 99-105]. Of all the Cx isoforms expressed in the brain, it has been proposed that Cx36 is the major neuronal isoform and consequently plays an essential role in the generation of highly synchronized electrical activity. Thus, Cx36-KO mice show a decrease of gamma frequency oscillations induced by kainate and carbachol in the CA3 region of the hippocampus [22]. On the other hand, it has been described that Cx36 levels are upregulated in the hippocampus and cortex after the expression of epileptic seizures in rodents [25, 26]. CBX, QUIN, and MFQ are GJ blockers which have certain selectivity for neuronal isoforms such as the Cx36 (Table **1**) [36, 37, 61, 75]. Therefore, it has been suggested that the effects caused by GJ blockers are related to the inhibition of assembled GJ constituted of neuronal isoforms. Similarly,

the anticonvulsant effects produced by these GJ blockers are comparable to the marked attenuation of the epileptiform discharges elicited by 4-aminopyridine in slices from Cx36-KO mice [124].

In the brain, cell-to-cell coupling mediated by GJ occurs between neurons, astrocytes, oligodendrocytes, microglia and ependymal cells. There are several Cx isoforms expressed in those cells types; however, the Cx43 isoform is expressed predominantly in astrocytes and located ubiquitously in the brain [6]. Astrocytes have been identified as key regulators of the extracellular homeostasis in the brain. Specifically, it has been proposed that astrocytes participate regulating the extracellular concentration of ions, such as potassium and calcium, and also releasing and reuptaking gliotransmitters and signaling molecules, for example glutamate and ATP [125]. Many pathological processes including seizures are characterized by reactive changes in the structure and functionality of astrocytes. Thus, some reactive changes in astrocytes comprise modifications in the ultrastructure of cytoskeletal proteins, as well as the down- or up-regulation of many proteins [126]. The role of interastrocytic coupling mediated by Cx43 in the pathophysiology associated with epileptogenesis is still unknown. However, it has been well described that Cx43 expression levels are altered in human epileptic brain and in seizure experimental models [26, 28, 127]. Cx and Panx have the ability to constitute single functional hemichannels that open to the extracellular space under physiological and pathological conditions. Cumulative evidence indicates that astrocytes release ATP and glutamate associated with intracellular calcium signaling *via* Cx43 and Panx hemichannels [128]. Consequently, it has been suggested that dysregulation of hemichannel functionality in astrocytes, could lead to increased calcium influx and calcium waves, and hence to a release of neurotoxic concentrations of glutamate and as a consequence the propagation of epileptiform activity [128-130]. As previously mentioned, most of the GJ blockers modify the communication of GJ and hemichannels constituted of Cx43 (Table **1**) [36, 37, 61, 75, 89, 90, 99-105]. Therefore, this could be an essential mechanism that explains the anticonvulsant effects evidenced by the GJ blockers.

In agreement with all of the previous studies, it can be proposed that GJ blockers have two main pharmacological mechanisms, which act together to elicit anticonvulsant effects: a) the blockage of assembled GJ constituted of neuronal Cx (Cx36) and the consequent inhibition of the neuronal synchronization, and b) the blockage of astrocytic hemichannels (Cx43), causing a reduction of calcium signaling and as a consequence a decreased release of gliotransmitters.

5. CONCLUSION

Nowadays, many substances have been described as GJ blockers. However, in some cases the blockage of gap junctional intercellular communication has been evaluated in cellular types which are different from those located in the brain. Because of the complexity of the cellular interconnections in the central nervous system, we propose that the effects of some GJ blockers in the brain should be

analyzed carefully. Of all the chemicals with "anti-gap junctional" properties, the ones that have been the most evaluated on seizure experimental models have been the CBX and QUIN. These two compounds share anticonvulsant effects typically characterized by the reduction of both amplitude and frequency of the epileptiform activity as well as by modifications of the behavioral parameters related to seizures. In accordance with these observations, another GJ blocker (MFQ) has showed anticonvulsant effects when administered at low doses. Reports have suggested that some GJ blockers could induce undesired neurological effects at high doses; however, we propose that small doses must be prudently selected to avoid neurotoxic effects.

Although the relationship between GJ and seizures is a topic which is progressively growing, it is important to note that some GJ blockers have not been evaluated in animal seizure models. Consequently, we propose that more studies are necessary to explore this issue, and to contribute to the search for new pharmaceutical alternatives for the treatment of epilepsy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

ANA	=	Anandamide
CBX	=	Carbenoxolone
Cx	=	Connexins
icv	=	Intracerebroventricular
i.p.	=	Intraperitoneal
MFQ	=	Mefloquine
OLE	=	Oleamide
Panx	=	Pannexins
PTZ	=	Pentylenetetrazole
QND	=	Quinidine
QUIN	=	Quinine
THLE	=	Tonic hindlimb extension

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