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·Review·

Role of gap junctions in epilepsy

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Abstract: Epilepsy is a common neurological disorder characterized by periodic and unpredictable seizures. Gap junctions have recently been proposed to be involved in the generation, synchronization and maintenance of seizure events. The present review mainly summarizes recent reports concerning the contribution of gap junctions to the pathophysiology of epilepsy, together with the regulation of connexin after clinical and experimental seizure activity. The anticonvulsant effects of gap junction blockers both *in vitro* and *in vivo* suggest that the gap junction is a candidate target for the development of antiepileptic drugs. It is also of interest that the roles of neuronal and astrocytic gap junctions in epilepsy have been investigated independently, based on evidence from pharmacological manipulations and connexin-knockout mice. Further studies using more specific manipulations of gap junctions in different cell types and in human epileptic tissue are needed to fully uncover the role of gap junctions in epilepsy.

Keywords: epilepsy; gap junction; connexin

1 Introduction

Epilepsy, one of the most common neurological disorders with an annual incidence of 50–80 per 100 000 per year worldwide, is characterized by the occurrence of periodic and unpredictable seizures[1]. The mechanisms underlying the generation, synchronization and maintenance of seizure events are not yet fully understood. Although the development of antiepileptic drugs is increasing exponentially, ~30% of patients with epilepsy are medically refractory due to continued seizures or intolerable side-effects[2]. This thus calls for novel approaches to the treatment of epilepsy. In this regard, advances in understanding the role of gap junctions in epilepsy can potentially add new aspects to the pathophysiology of epilepsy and provide novel therapeutic targets.

The present review begins with a description of the structure, expression, distribution and function of gap junctions in the brain. Then the clinical and the experimental evidence for the regulation of different connexins, the units that compose gap junctions, in relation to seizure activity are reviewed. Finally, the functional effects of both blockers and openers of gap junctions as well as those of specific connexin peptide-knockout in epilepsy models *in vitro* and *in vivo* are discussed. The roles of neuronal networks in oscillations and synchronization and those of astrocytic networks in epileptic activity are also reviewed.

2 Gap junctions in the brain

Gap junctions are intercellular membrane channels

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that provide direct cytoplasmic continuity between adjacent cells. They are formed by the end-to-end docking of two hemi-channels, also referred to as "connexons", each of which is composed of six connexin subunits surrounding a central pore[3,4]. All connexins share a similar topology, with four transmembrane domains (M1–M4), intracellular N- and C-termini, two extracellular loops (E1, E2), and a cytoplasmic loop (CL)[5-7] (Fig. 1). Gap junctions occur in the form of homocellular junctions, such as between neurons, astrocytes, oligodendrocytes, microglial cells, ependymal cells and meningeal cells[8-12], in the form of heterocellular junctions, such as neuron-astrocyte[13] and astrocyte-oligodendrocyte[9], and even in the form of autocellular junctions, mainly in single astrocytes[14]. Gap junctions allow the propagation of electrical impulses and the exchange of small molecules (1–1.2 kDa) including ions, second messengers and metabolites, such as Ca^{2+}, inositol 1,4,5-trisphosphate, glutamate, glutathione, ADP, and ATP[15,16]. The intercellular coupling is regulated by either the number of channels or by the open or closed status of the hemi-channels, as well as the single-channel conductance. It is proposed that phosphorylation is involved in the mechanisms of regulating the function and rapid turn-over of connexins by influencing their trafficking, assembly, disassembly, degradation and control of gating[16,17]. Moreover, changes in cytoplasmic pH and Ca^{2+} concentration also allow the opening or closing of hemi-channels and hence regulate the function of the gap junction[16].

The family of connexin genes consists of at least 20 members in mouse and 21 in humans[18]. Connexins (Cxs) 26, 29, 30, 32, 36, 37, 40, 43, 45, 46 and 47 are synthesized and function in the brain, and each is expressed in specific cell types, brain regions and developmental stages[10,19] (Table 1). Cx43 and Cx30 are the major gap junction proteins in astrocytes[20-23] that are proposed to be organized as networks and communicate through gap junctions to regulate neuronal network activity under normal and pathophysiological conditions[24,25]. On the other hand, neurons, especially GABAergic interneurons, are electrically coupled via gap junctions predominantly composed of Cx36 in many brain regions[26,27]. These gap junction-

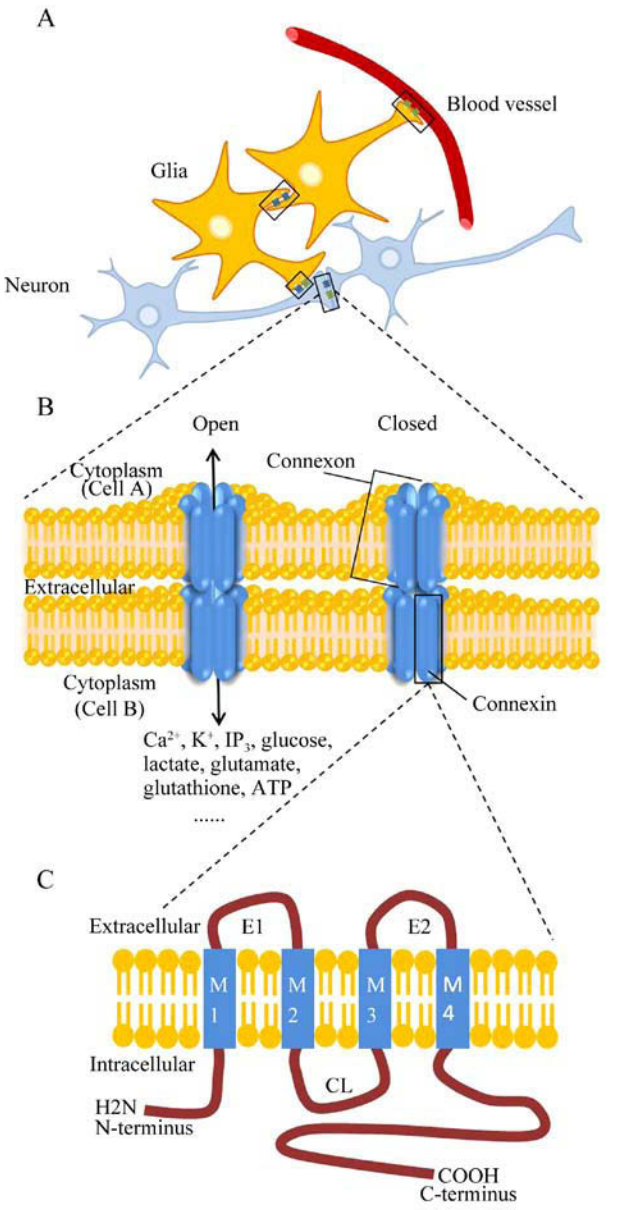

Fig. 1 Schematic diagram illustrating gap junctions between different cells in the mammalian brain. A: Gap junctions between glial cells, between neurons, between glial cells and blood vessel cells, as well as between glial cells and neurons. B: Connexons traverse the opposed phospholipid bilayers and dock with other connexons on the neighboring cell to form a gap junction channel. They allow the passage of ions, second messengers and metabolites. Each connexon consists of six connexins. Several conditions regulate the function of a gap junction and allow the opening (left connexon) or closing (right connexon) of the hemichannel. C: Each connexin has four transmembrane domains (M1–M4), two extracellular loops (E1, E2), and one cytoplasmic loop (CL), together with intracellular N- and C-termini. (Modified from Rackauskas *et al.*, 2010[16] and Talhouk *et al.*, 2008[19]).

Table 1. Cellular expression and distribution of connexin subtypes in brain

Connexin subtypes	Cell types	Distribution
Cx26	Neuron	Cerebral cortex[36]; hypothalamus, inferior hippocampus, locus coeruleus, thalamus, superior colliculi[37]
	Astrocyte	Locus coeruleus[38]; perivascular, sub-pial, subependymal areas and brain parenchyma[39]; subcortical areas[37]
Cx29	Oligodendrocyte	Oligodendrocytes, Schwann cells, paranodes and juxtaparanodes[38, 40]
Cx30	Astrocyte	Mature grey matter[23]
Cx32	Neuron	Neuronal population in brainstem, cerebral cortical layers, substantia nigra[41]
	Oligodendrocyte	Soma and processes of myelinated fibers[42]
Cx36	Neuron	Inferior olivary complex and other brainstem nuclei, cerebellum, mesencephalon, hypothalamus, thalamus, habe nular nuclei, pineal gland, Basal ganglia, septum, basal forebrain, amygdala and piriform cortex, hippocampal formation, cerebral cortex, olfactory bulb[43]; locus coeruleus[44]
	Oligodendrocyte	Primary cultures of rat brain oligodendrocytes[45]
	Microglia	Microglial cultures from human and mouse[46]
Cx37	Neuron	Developing cortex of mice[47]
Cx40	Astrocyte	Temporal cortex[48]
Cx43	Neuron	Cerebral cortex[36]; hippocampal neuronal subpopulation[49]
	Astrocyte	Brain parenchyma[27]; cortical[50] and subcortical regions[41]
	Microglia	Diffuse cytoplasmic localization, and at interfaces between activated microglial cells[8]; brain stab wounds[8]
Cx45	Neuron	Cerebral cortex, hippocampus and thalamus[51,52]; olfactory nerves[53]
	Astrocyte	Temporal cortex[48]
	Oligodendrocyte	Soma and proximal processes of oligodendrocytes[54,55]
Cx46	Astrocyte	Cultured mouse astrocytes[48]
Cx47	Neuron	Cerebellum[56]
	Astrocyte	In and around demyelinated areas[57]
	Oligodendrocyte	Highly myelinated CNS tissues and few calcium-binding proteins S100β subunit-positive cells[58]; corpus callosum, striatum, cerebellum[57, 59]

CNS: central nervous system.

mediated connections between neurons, also known as electrical synapses, are reciprocal pathways for ionic currents and small organic molecules[28] and are involved in developmental events such as neuronal differentiation, cell death, cell migration, synaptogenesis, and neural circuit formation[29-31]. It is also known that neurotransmission through electrical synapses plays an important role in spike synchrony among neurons and oscillations in neuronal networks[26,32,33]. Moreover, the confirmed association of the Cx36 gene with human juvenile myoclonic epilepsy[34,35] makes Cx36 a strong candidate for epilepsy research.

3 Changes of connexins in epilepsy

Studies of connexin expression in human epileptic tissue confirm that the astrocytic gap junction protein Cx43 and its mRNA are up-regulated in various human brain regions including temporal lobe neocortex[60], hippocampus[61,62] and cortex[63], while the absence of up-regulation of Cx43 mRNA or protein in the hippocampus has also been reported[64] (Table 2). The mRNA level of Cx32 increases in epileptic temporal lobe neocortex[60] and decreases in the hippocampus[61]. These changes in connexins imply their involvement in epilepsy. It is also possible that epileptogenicity is associated with functional changes in the dynamic states of connexins (open *vs*. closed), from the evidence that chronic epileptic activity promotes gap junction dye-coupling both in chronic experimental models[65] and in clinical epilepsy[66].

Table 2. Changes of connexin mRNA or protein in human epileptic brain tissue

Clinical seizure types	Brain regions	Changes of connexin mRNA or protein
Epilepsy secondary to FCD	Cortex	Cx43 mRNA↑; large aggregates of Cx43-immunopositivity clustered around subsets of balloon cells and astrocytes in FCD type IIB[63]
Mesial temporal lobe epilepsy	Hippocampus	Cx43↑, Cx32↓ and preservation of Cx36 expression[61] Cx43↑ in CA1 and CA4[62]
Intractable complex partial seizure disorder	Hippocampus	Cx43 mRNA↓; no significant difference in Cx43 protein expression[64]
Intractable seizure disorder	Temporal lobe neocortex	Cx43 mRNA↑ and Cx32 mRNA↑[60]

"↑": increase, "↓": decrease. FCD: focal cortical dysplasia.

The results of studies on changes of connexins in animal models of epilepsy are currently controversial (Table 3). In a rat model with amygdala kindling, Beheshti *et al.* found that hippocampal Cx36 mRNA and protein are up-regulated during the acquisition of focal seizures but return to basal levels after the acquisition of secondarily-generalized seizures[67]. Sohl *et al.* reported reductions of both Cx36 mRNA and protein levels in the hippocampus of fully-kindled rats[68]. Similarly, in a rat hippocampal kindling model of epilepsy, McCracken and Roberts found that Cx36 protein levels significantly decrease in the dorsal hippocampus 3 h after a single brief evoked after-discharge, and then return to control levels by 24 h[69]. These studies strongly suggest that Cx36 expression is regulated specifically at different stages of epilepsy in kindling models. Although early in 1997 Elisevich *et al.* found reductions of Cx43 mRNA and protein in the amygdala with a trend toward normalizing levels with increasing kindling stimulation number[70], recent studies showed no change in hippocampal Cx43 mRNA or protein after a brief after-discharge evoked[69], during kindling epileptogenesis[67] or weeks after acquisition of secondarily-generalized seizures[68]. Using a neocortical epilepsy model involving local application of the K^+ channel antagonist 4-aminopyridine (4-AP), Szente and colleagues found that the mRNA levels of Cx32, Cx43, and Cx36 increased significantly at both the primary site and the mirror focus[71,72]. Several studies reported the expression of different connexins, especially Cx30, Cx36 and Cx43, in kainic-acid (KA)-induced epilepsy. In rat hippocampus, Cx36 mRNA and protein are reduced 4 weeks after KA application[68]. Condorelli *et al.* found a dramatic reduction in Cx43 mRNA levels in the CA3–CA4 pyramidal layers, and a marked up-regulation of Cx43 expression in other hippocampal regions starting at 24 h, reaching maximum levels at 48 h, and persisting at 72 h after KA application[73]. However, Sohl *et al.* found only slight decreases of hippocampal Cx43 mRNA and protein 4 weeks after KA treatment[68]. For Cx30, Condorelli *et al.* revealed a region-specific regulation of expression after KA-induced epilepsy[74]: Cx30 mRNA and protein are up-regulated within 6 h and Cx30 mRNA decreases 12 h and 24 h after KA treatment in the cerebral cortex, laterodorsal and mediodorsal nuclei of the thalamus and medial amygdaloid nucleus, while in the hippocampus, Cx30 expression declines within 12 h and 24 h and Cx30 mRNA is up-regulated from 6 h to 48 h in the CA3–CA4 pyramidal layers. However, other studies showed that Cx30 expression in the hippocampus is either slightly reduced[75] or unchanged[68]. In lithium pilocarpine-induced epilepsy, Su and Tong found that Cx43 protein is increased in CA1, CA3 and the dentate gyrus 2 h to 7 d after status epilepticus[76]. These discrepancies among studies may be due to variations in the preparation, method of seizure induction, duration of seizure activity[77], and time points as well as the brain regions examined after seizure activity.

Apart from the above studies of *in vivo* epilepsy models, *in vitro* studies shed further light on the regulation of connexins by seizure activity. Using repetitive tetanization of the Schaffer collaterals in rat hippocampal-parahippocampal slices, Jahromi *et al.* found that Cx26, Cx32,

Table 3. Changes in mRNA and protein expression of different connexins in experimental epilepsy models

Experimental epilepsy models	Brain regions	Animals	Changes
in vivo			
Amygdala kindling	Amygdala	Rats	Cx43 mRNA and protein↓ with a trend toward normalizing levels with increasing numbers of stimulations[70]
	Hippocampus	Male Sprague-Dawley rats	Cx36 mRNA and protein↓ in fully-kindled rats 2–3 weeks after the last kindled seizure; no changes of Cx43, Cx32 and Cx30 mRNA and proteins[68]
	Hippocampus	Male Wistar rats	Cx36 mRNA and protein↑ during acquisition of focal seizures but return to basal levels after acquisition of secondarily-generalized seizures; no change in Cx43 mRNA and protein during kindling epileptogenesis[67]
Hippocampus kindling	Dorsal hippocampus	Male Sprague-Dawley rats	Cx36 expression↓ at 3 h after brief evoked after-discharge, and return to control levels by 24 h; no changes in Cx26, Cx32, and Cx43[69]
4-Aminopyridine-induced	Neocortex	Wistar rats	Cx32 and Cx43 mRNA↑ at primary focus as well as at mirror focus, after 60 min of repeated ictal discharges[72]
	Neocortex	Wistar rats	Cx32, Cx43, and Cx36 mRNA↑ at epileptic foci[71]
Kainic-acid (KA)-induced	Hippocampus	Male Sprague-Dawley rats	Cx36 mRNA and protein↓ 4 weeks after KA application; Cx43 and Cx30 mRNA or protein slightly decrease or remain unchanged[68]
	Hippocampus	Adult male rats	Cx30 expression↓ within 12 h and 24 h; in CA3–CA4 pyramidal layers Cx30 mRNA↑ from 6 to 48 h[74]
	Cerebral cortex; Laterodorsal and mediodorsal nuclei of thalamus; Medial amygdaloid nucleus	Adult male rats	Cx30 mRNA and protein↑ within 6 h of KA injection and Cx30 mRNA↓ 12 h and 24 h after KA[74]
	Hippocampus	Male Wistar rats	Cx43 mRNA↓ in CA3–CA4 pyramidal layers involved in KA-induced lesion; Cx43 expression↑ in molecular layer, strata radiatum and oriens, and hilus, starting at 24 h, reaching maximum at 48 h and persisting at 72 h after KA[73]
	Hippocampus	Male Sprague-Dawley rats	Cx43↑ and Cx30↓ at 7 d after KA[75]
Lithium pilocarpine-induced	Hippocampus	Male Sprague-Dawley rats	Cx43↑ in CA1, CA3 and dentate gyrus 2 h to 7 d after status epilepticus (SE), most prominent at 24 h after SE and absent 30 d and 60 d after SE[76]
in vitro			
Repetitive tetanization of Schaffer collaterals	Hippocampal-parahippocampal slices	Wistar Rats	Cx26, Cx32, Cx36 and Cx43 unchanged after robust seizure-like primary after-discharges; level of dephosphorylated Cx43↓[78]
Co^{2+}-induced epileptiform discharges	Whole hippocampus	C57BL/6 male mice	Cx43 mRNA and protein↑; mRNAs of Cx26, Cx30, Cx32, Cx36, Cx40, Cx45 and Cx47 unchanged[79]
Bicuculline-induced epileptiform activity	Whole hippocampus	Male C57BL/6 mice (15-day-old)	After 2–10-h exposure to bicuculline, Cx32 mRNA and protein↑; protein and mRNA of Cx43 and Cx26 unchanged[80]
	Hippocampal slices	Wistar rats (7-day-old male)	mRNAs and proteins of both Cx43 and Cx32↑ with chronic (18 h) exposure to bicuculline; Cx26 and Cx36 unchanged[81]

"↑": increase, "↓": decrease.

Cx36 and Cx43 levels remain unchanged while the level of dephosphorylated Cx43 decreases after robust seizure-like primary after-discharges in the hippocampus[78]. In Co^{2+}-induced epileptiform discharges, Cx43 mRNA and protein are up-regulated, while the mRNA levels of Cx26, Cx30, Cx32, Cx36, Cx40, Cx45, and Cx47 do not change in the hippocampus[79]. In mouse hippocampal slices, 2- to 10-hour exposure to bicuculline induces marked increases in Cx32 mRNA and protein, with no changes in the protein and mRNA levels of Cx26 and Cx43[80]. Moreover, the protein and mRNA levels of Cx32 and Cx43 increase after chronic (18 h) exposure of rat hippocampal slices to bicuculline[81].

4 Effects of gap junction blockers and openers on seizures

Agents that are known to regulate the open/closed state of gap junction channels include general blockers, such as acids that cause intracellular acidification (e.g., propionic acid/sodium propionate), long-chain alcohols (e.g., heptanol and octanol), anesthetics (e.g., halothane and ethrane) and glycyrrhetinic acid derivatives (e.g., carbenoxolone); astrocytic (mainly Cx43) blockers such as meclofenamic acid, niflumic acid and flufenamic acid; neuronal (mainly Cx36) blockers, namely quinine, quinidine and mefloquine; and general openers such as alkalis that cause intracellular alkalization (e.g., trimethylamine and ammonium chloride) (Table 4). However, all these compounds have limited specificity for connexin channels over other membrane channels or other cellular targets[82]. Thus, their effects on gap junctional communication are likely to be indirect. With this limited selectivity of pharmacological manipulation, researchers need to use multiple blockers

Table 4. Pharmacological agents that interfere with gap junction coupling

Classes	Proposed mechanisms	Agents
General gap junction blockers		
Long-chain alcohols	Limit junctional communication by dissolving in membrane lipids and inducing changes in membrane fluidity	Heptanol[85, 86], Octanol[85-87]
Anesthetics	Limit junctional communication by dissolving in membrane lipids and changing membrane fluidity	Halothane[78, 88], Ethrane[88]
Glycyrrhetinic acid derivatives	Act indirectly via activation of protein kinases, G proteins, transport ATPases and gap junction phosphorylation states to inhibit junctional conductance	Carbenoxolone[78, 89], 18α-glycyrrhetinic acid[85, 87, 89]
Acids	Intracellular acidification	Propionic acid/sodium propionate[78]
General gap junction openers		
Alkalis	Intracellular alkalization	Ammonium chloride[78, 90], Trimethylamine[91]
Neuronal gap junction blockers		
Antimalarial drugs	Specifically block Cx36, while other Cxs unaffected; binding site intracellular, possibly within the pore	Quinine[92], Quinidine[92], Mefloquine[93]
Astrocytic gap junction blockers		
Fenamates	Potent blockers of Cx43-mediated intercellular communication. The effect does not involve changes in intracellular Ca^{2+} or pH, and is unrelated to protein kinase C activity or inhibition of cyclooxygenase activity	Meclofenamic acid[94, 95], Niflumic acid[94], Flufenamic acid[94]
Mimetic peptides as gap junction blockers		
Connexin-mimetic peptides	Interact with two highly-conserved extracellular loops of Cx43 to inhibit gap junctions mainly constructed of Cx43, but also of Cx32, 40 and 37 in a wide range of cells and tissues	Gap 26[83, 84], Gap 27[83, 84], Gap 36[83]

together with openers to safely determine relationships between gap junctions and epilepsy. Fortunately, connexin-mimetic peptides, short synthetic peptides corresponding to selected sequences in each of the two well-conserved extracellular loops of the connexins, are promising pharmacological tools for studying specific connexin-related cellular functions[83,84]. It is worth mentioning that specific connexin-knockout mice are now available to further confirm the respective roles of neuronal and astrocytic networks connected by gap junctions in epilepsy. Studies in knockout mice are reviewed separately below.

4.1 *In vitro* studies using gap junction blockers and openers Since the last 20 years, the effects of gap junction blockers and openers have been tested in various *in vitro* models of epilepsy (Table 5). Jahromi *et al.* found that the junction blockers octanol, carbenoxolone, and propionic acid reduce the duration of seizure-like primary after-discharges evoked by repetitive tetanization of the Schaffer collaterals in rat hippocampal slices. Conversely, ammonium chloride, which causes intracellular alkalization and opens junctional coupling, initially evokes spontaneous secondary after-discharges[78]. Carbenoxolone inhibits both spontaneous and seizure-like events evoked by a single stimulus and brief titanic stimulation of the Schaffer collaterals, while a connexin-mimetic peptide (Gap 27) attenuates spontaneous recurrent epileptiform activity[96]. In addition, the Cx36-selective blocker quinine markedly reduces the number of spikes in the after-discharges evoked by alvear stimulation in low-Ca^{2+} solution[97].

In other models of epilepsy without electrical stimulation, the anti-seizure effects of gap junction blockers and pro-seizure effects of gap junction openers are also reported.

Table 5. Effects of gap junction blockers (in black) and openers (in *italic*) in *in vitro* models of epilepsy

Models and experiments	Animals and slices	Results
Repetitive tetanization of Schaffer collaterals-evoked seizure-like primary after-discharges (PADs)	Wistar rats Hippocampal-parahippocampal slice	In the CA1 pyramidal region, **octanol** reversibly blocks the duration of PADs and **carbenoxolone** reduces the duration of PADs but this effect is not reversible[78]. **Propionic acid** reversibly reduces the duration of PADs, while *ammonium chloride* initially evokes spontaneous secondary after-discharges[78].
Single stimulus and brief tetanic stimulation of Schaffer collaterals-induced spontaneous recurrent seizure-like events (SLEs) and PADs respectively	Wistar rats (7-day-old) Organotypic hippocampal slice	In CA1, while **carbenoxolone** inhibits both spontaneous and evoked SLEs, **connexin-mimetic peptide (Gap 27)** selectively attenuates spontaneous recurrent epileptiform activity[96].
Alvear stimulation-evoked ADs in pyramidal cell layer in low-Ca^{2+} solution	Male Sprague-Dawley rats Hippocampal slice	In CA1, **quinine** increases the duration of individual population spikes and markedly reduces the number of spikes in the AD[97].
Mg^{2+}-free induction of epileptiform activity	Male Sprague-Dawley rats Hippocampal slice	**Halothane**, **octanol** and **carbenoxolone** abolish secondary discharges, but leave primary bursts intact[91]. *Trimethylamine* reversibly induces secondary and tertiary discharges[91].
	Sprague-Dawley rats (5- to 8-week-old) Neocortical slice	**Quinine** and **carbenoxolone** increase both the frequency and the amplitude of SLEs[104].
	C57/BL6 wild-type and Cx36-knockout mice (4-month-old) Neocortical slice	**Mefloquine** increases SLE frequency and amplitude in WT mice and these effects are absent in slices from Cx36-knockout mice[104].

Continued

Table 5. Continued

Ca^{2+}-free induction of field burst activity	Young Wistar rats Hippocampal slice	**Octanol** suppresses spontaneous field activity[90]. **Sodium propionate** blocks all spontaneous activity, while *ammonium chloride* increases the frequency and duration of spontaneous field activity[90].
	Male Sprague-Dawley rats Hippocampal slice	After ~25-min **quinine**, low-Ca^{2+} bursts occur more frequently but are dramatically shortened in amplitude and duration. After 60 min, **quinine** either completely suppresses bursting or reduces the amplitude and duration of spontaneous activity[97].
High-K^+ induction of spontaneous ictal activity and inter-ictal activity in CA1	Male Sprague-Dawley rats Hippocampal slice	After 20 min in **quinine**, spontaneous interictal burst amplitude and duration are attenuated and the frequency of ictal activity in CA1 increases. After >40 min in **quinine**, interictal activity in CA3 is abolished, however, very high-frequency 'mini-population spikes' persist[97].
High-K^+/low-Ca^{2+} induction of evoked and spontaneous epileptiform field potentials	Male Sprague-Dawley rats Hippocampal slice	In CA3, **octanol** and **heptanol** gradually reduce spontaneous field bursting and even stop it within 1 h and depress all the epileptiform markers of the evoked responses[98]. In CA3, carbenoxolone shows dose-dependent anti-bursting activity, but does not reduce the number of repetitive population spikes evoked by single stimuli[98].
	Adult male Sprague-Dawley rats Hippocampal slice	In dentate gyrus, **octanol**, **oleamide**, and **carbenoxolone** block prolonged field bursts[99].
4-AP/Mg^{2+}-free induction of spontaneous bursts of population spikes	Female Sprague-Dawley rats Hippocampal slice	**Carbenoxolone** post-perfused reduces the frequency of spontaneous burst activity, while incubation prior to recording increases the time taken for the spontaneous activity to start and decreases the total number of spontaneous bursts over the first 60 min[100]. **Octanol** reduces interictal burst rate and increases negative activity burst rate[100].
4-AP induction of spontaneous large inhibitory postsynaptic currents (IPSCs) and ectopic spikes	3- to 5-week-old Wistar rats Hippocampal slice	**Carbenoxolone** suppresses spontaneous large IPSCs and ectopic spikes[101].
4-AP induction of spontaneous ictal-like activity (ILA)	Adult genetic absence epilepsy rats from Strasbourg (GAERs) or non-epileptic Wistar rats Thalamocortical slice	After bath application of **carbenoxolone**, the frequency and cumulative duration of ILA decreases but less rapidly in GAERS than in NER slices[102]. After applying **quinidine**, ILA vanishes[102].
Bicuculline-induced epileptiform activity	Male Wistar rats (7-day-old) Organotypic hippocampal slice	Spontaneous epileptiform discharges are blocked reversibly by ap plication of **carbenoxolone** for 20 min[81].
	Male C57BL/6 mice (15-day-old) Whole hippocampus	Spontaneous epileptiform activity is depressed by 10-min perfusion with **carbenoxolone**[80].
	Young adult guinea pigs Isolated brain preparation	**Octanol** transiently blocks spontaneous interictal spikes (sISs)[103]. **18α-Glycyrrhetinic acid** reversibly abolishes sISs[103].
Co^{2+}-induced epileptiform discharges	C57BL/6 male mice Whole hippocampus	In the presence of **octanol**, no ictal or interictal discharges recorded but basal rhythmic activity is evident[79].

The junction blockers halothane, octanol and carbenoxolone abolish the secondary discharges induced by Mg^{2+}-free solution, while the junction opener trimethylamine reversibly induces secondary and tertiary discharges[91]. In a Ca^{2+}-free model of epilepsy, octanol and sodium propionate suppress spontaneous field activity, while ammonium chloride increases its frequency and duration[90]. However, the effect of the Cx36-selective blocker quinine is difficult to interpret in this model. Bikson *et al.* found that low-Ca^{2+} bursts are increased in frequency by 25-min exposure to quinine, but are completely suppressed by 60 min of exposure. The amplitude and duration of bursts are dramatically and consistently reduced[97]. In a high-K^+ model of epilepsy, quinine has similar effects: a 20-min exposure to quinine attenuates the amplitude and duration but increases the frequency of spontaneous interictal bursts in the CA1 region. After 40 min in quinine, interictal activity in CA3 is abolished, while very high-frequency "mini-population spikes" persist[97]. In a high-K^+/low-Ca^{2+} model, octanol, heptanol and carbenoxolone inhibit spontaneous field bursts in CA3[98] and the dentate gyrus[99]. Carbenoxolone reduces spontaneous burst activity in a 4-AP/Mg^{2+}-free model in hippocampal slices[100]. In a 4-AP model of epilepsy, carbenoxolone suppresses spontaneous large inhibitory postsynaptic currents and ectopic spikes[101], and reduces the frequency and cumulative duration of spontaneous ictal-like activity, while the Cx36-selective blocker quinidine diminishes this activity[102]. Carbenoxolone[80,81], octanol and 18α-glycyrrhetinic acid[103] also depress the spontaneous epileptiform discharges induced by bicuculline. In a Co^{2+} epilepsy model, Mylvaganam *et al.* demonstrated that octanol diminishes ictal and interictal discharges[79]. However, paradoxical excitatory effects of gap junction blockers on seizure-like activity induced by low Mg^{2+} in rat cortical slices were recently reported by Voss *et al.* They found that quinine and carbenoxolone increase both the frequency and the the amplitude and quinidine increases the frequency of seizure-like events[104]. They also found similar excitatory effects in adult wild-type mouse cortical slices perfused with mefloquine, but not in slices from Cx36-deficient mice. Thus they proposed that this effect is due to disruption of inhibitory interneuron-coupling secondary to Cx36 blockade.

4.2 *In vivo* studies using gap junction blockers and openers Accumulating evidence from *in vivo* experimental studies reveals the involvement of gap junctions in epileptiform activity (Table 6). The broad-spectrum junction blocker carbenoxolone has anti-seizure properties in epilepsy models induced by amygdala kindling[105], maximal electroshock[106], 4-AP[71,72,107], penicillin[108] and tetanus toxin[109], as well as in the pentylenetetrazole model of seizures[106], absence seizure models[102,110,111] and audiogenic seizure models[112,113]. The Cx43-selective junction blocker meclofenamic acid has anticonvulsant effects both in the maximal electroshock model[114] and in tetanus toxin-induced refractory focal cortical epilepsy[109]. The anticonvulsant effect of quinine, a Cx36-selective junction blocker, has also been demonstrated in models *in vivo*, such as 4-AP-induced epilepsy[107,115,116], penicillin-induced epileptiform activity[117] and the pentylenetetrazole model of seizures[118,119]. Pretreatment with the junction opener trimethylamine reverses the inhibitory effects of quinine on the latency and the duration of generalized tonic-clonic seizures induced by pentylenetetrazole[119]. In the amygdala-kindled epilepsy model[105], 4-AP-induced epilepsy[71,107,116] and a rodent model of atypical absence seizures[111], the junction opener trimethylamine has a pro-convulsant effect.

Taken together, these studies suggest that gap junction blockers diminish seizures, while openers promote them, both *in vitro* and *in vivo*. However, the drawbacks of manipulation with pharmacological agents are their low selectivity, off-target effects, and even activation of independent mechanisms that interfere with seizure susceptibility rather than the gap junction itself. Therefore, the interpretation of these results is currently problematic.

5 Connexin knockout studies

Currently, many knockout mouse models lacking specific connexin proteins have been generated, however, due to the resulting deficits, only few have been tested in established seizure models. Maier *et al.* found that epileptiform discharges elicited by 4-AP are attenuated in slices from Cx36-knockout (Cx36KO) mice[121], while Jacobson

Table 6. Effects of gap junction blockers (in black) and openers (in *italic*) in various *in vivo* models of epilepsy

Models and experiments	Animals	Results
Amygdala-kindled seizures	Male Wistar rats	Intra-basolateral amygdala infusion of **carbenoxolone** shortens duration of afterdischarge (AD) and generalized seizures, while *trimethylamine* enhances seizure susceptibility by prolonging AD duration and generalized behavioral seizures[105].
Maximal electroshock	Male BALB/c mice	**Carbenoxolone** (i.p.) decreases duration of seizure[106].
	ICR mice	**Meclofenamic acid** (i.p.) protects mice from hindlimb extension[114].
4-AP-induced cortical epileptiform activity at both the primary focus (Pf) and the mirror focus (Mf) in neocortex of anesthetized rats	Adult Wistar rats	**Carbenoxolone** applied locally at the Pf or Mf, decreases the intensity of seizure activity of already active epileptic foci[72].
		Blockade with **carbenoxolone** at the already active Pf shortens the duration of seizures and decreases the amplitude of seizure discharges, whereas opening with *trimethylamine* lengthens the duration and increases the amplitude[71].
		Blockade of neuronal Cx36 channels by **quinine** at the already active epileptic focus has an anticonvulsive effect and modifies the manifestation of 1–18 Hz seizure discharges[115].
4-AP adminstration in entorhinal cortex (EC) induces epileptiform acitivity in vigilant rats	Adult male Wistar rats	Injection of **carbenoxolone** into the EC decreases the amplitude and frequency of 4-AP-induced epileptiform discharges, and completely blocks seizure activity both in the injected EC and in the propagated CA1[107].
		In the presence of *trimethylamine*, 4-AP produces distinct epileptiform patterns with continuous, long epileptiform discharges of higher amplitude and lower frequency than 4-AP injection alone during the first 30 min post-drug administration[116].
		Quinine injection into the EC decreases amplitude and frequency of discharge trains in EC and CA1, which are completely blocked after 34 min. Seizure behavior is completely blocked in 5 of 6 rats 53.2 s after quinine administration[116].
Penicillin-induced epileptiform activity in fully conscious rats	4-month-old male Wistar rats	Application of **octanol** (i.c.v.) reduces epileptiform activity in spike frequency, amplitude and behavioral scores[120].
		Carbenoxolone (i.c.v.) suppresses epileptiform activity by decreasing the amplitude and frequency of epileptiform spikes and attenuating epileptiform behavior[108].
		Quinine (i.c.v.) suppresses epileptiform activity by decreasing the amplitude and frequency of epileptiform spikes and attenuating epileptiform behavior[117].
Tetanus toxin-induced refractory focal cortical epilepsy in fully conscious rats	Sprague-Dawley rats	Both **carbenoxolone** and **meclofenamic acid** applied focally reduce percentage of seizure time[109].
Pentylenetetrazole (PTZ) model of seizure	Male BALB/c mice	**Carbenoxolone** (i.p.) prolongs onset time of seizures and decreases duration of seizures[106].
		Quinine (i.p.) increases latency and decreases duration of seizures[118].
	Male Wistar rats	i.c.v. injection of **quinine** affects generalized tonic-clonic seizures (GTCS) induced by PTZ by increments in seizure onset and reduced seizure duration; pretreatment with *trimethylamine* (i.c.v.) reverses the anticonvulsant effects of **quinine** on latency and duration of GTCS[119].
A rodent model of atypical absence seizures	Long-Evans rat pups given subcutaneous cholesterol synthesis inhibitor AY9944 every 6 d from postnatal day (P)2 to P22	**Carbenoxolone** and **18*α*-glycyrrhetinic acid** injected into the reticular nucleus of the thalamus (NRT) decreases duration of seizures; **carbenoxolone** injections into the hippocampus result in diminished seizure activity; NRT injections of *trimethylamine* enhance seizures and spindle activity[111].

Continued

Table 6. Continued

Genetic animal models of absence epilepsy	WAG/Rij rats	Bilateral microinjection of **carbenoxolone** into NRT and ventral posterolateral nucleus of the thalamus decreases duration and number of spike-wave discharges (SWDs)[110].
	lh/*lh* mice	i.p. or i.c.v. administration of **carbenoxolone** induces marked decreases in number and duration of SWDs[110].
	Genetic absence epilepsy rats from Strasbourg (GAERS)	i.p. injection of **carbenoxolone** decreases cumulative duration of cortical SWDs without reduction in the SW amplitude or frequency[102].
Audiogenic seizure models	Genetically epilepsy-prone rats (GEPRs), a strain derived from Sprague-Dawley rats	Intravenous or i.p. administration of **carbenoxolone** reduces clonic and tonic phases of audiogenic seizures in GEPRs; bilateral microinjection of **carbenoxolone** into the inferior colliculi, substantia nigra and inferior olivary complex reduces seizure severity score[113].
	DBA/2 mice	i.p. injection of **carbenoxolone** decreases DBA/2 audiogenic seizure severity score[112].

et al. showed an increased sensitivity of Cx36KO animals to pentylenetetrazole-induced seizures[122]. Importantly, Cx36KO mice have visual deficits[123] as well as deficient synchronous activity of inhibitory interneuronal networks in neocortex[32]. Knockout of Cx43, the major astrocytic connexin, is neonatal-lethal[124] and causes neural crest migration deficits[125]. Deletion of Cx26[126] or Cx45[127] is also embryonic-lethal. With the application of conditional gene knockout techniques, especially the Cre-Lox recombination system, the roles of these connexin proteins in different brain cell types in epilepsy can be widely tested in the near future, and the functions of neuronal networks and astrocytic networks linked by their specific connexins can be distinguished under epileptic conditions.

6 Role of neuronal networks in oscillations and seizure synchronization

In 1982, Taylor and Dudek proposed that the interconnections between neurons through electrical synapses, or gap junctions, play an important role in neuronal synchronization and epileptogenesis[128]. High-frequency oscillations (HFOs), also called ripples, at 80–200 Hz or even higher frequencies (250–600 Hz), are ensembles of repeated and synchronous firing in many neurons. Because they have been recorded immediately preceding seizure onset *in vivo*[129,130], *in vitro*[101,131] and in human clinical electroencephalograms (EEGs)[132-136], HFOs are thought to be an indication of an epileptiform network mechanism in seizure initiation[137-143]. An increasing number of studies suggests that gap junctions interconnecting neurons, rather than chemical synapses, are important in the generation of these synchronous oscillations. Draguhn *et al.* found that the very fast oscillations (VFOs, 140–200 Hz) recorded in rat hippocampal slices are not dependent on chemical synaptic transmission, and are abolished by the gap junction inhibitor carbenoxolone[144]. Coincidently, Maier *et al.* found that spontaneous sharp waves and ripples are less frequent in hippocampal slices from Cx36KO mice[121]. However, in another study, VFOs and ultrafast (200–600 Hz) oscillations in the hippocampus are described in Cx36KO mice[145]. Future studies are needed to verify the role of synchronous neuronal networks connected by gap junctions in the generation of epilepsy.

7 Astrocytic networks and epilepsy

Although isolated cellular and molecular changes in individual astrocytes are involved in epileptogenesis under pathological conditions[146,147], the physiological and pathological implications of astrocytic networks connected by gap junctions have recently attracted increasing attention[24]. On one hand, neuronal activity shapes astroglial networks by affecting the permeability of astrocytic gap junctions[148,149]. On the other hand, astrocytic networks regulate neuronal function[150,151]. Despite the accumulating evidence of the interplay between neuronal activity and astrocytic networks, there are only limited studies of the role of astrocytic

networks in epilepsy. Wallraff *et al.* found that astrocytic network deficiency due to conditional knockout of both Cx43 and Cx30 leads to the generation of spontaneous epileptiform activity and a decreased threshold for Mg^{2+}-free-evoked seizure activity by interfering with K^+ buffering in the mouse[151]. However, Rouach *et al.* showed that glutamate released during epileptiform activity increases astrocyte glucose trafficking, and that glucose delivery through the astrocytic network is, in turn, needed to sustain epileptiform activity[149]. These two studies indicate that a decrease in gap junction permeability seems to exert opposite effects on neuronal excitability: a pro-convulsive effect through impairing K^+ redistribution or buffering, and an antiepileptic effect through disrupting the neuronal energy supply. Hence, the ambiguous roles of gap junctions in epilepsy reveal an urgent need for further efforts to study the mechanisms of epileptogenesis involving astrocytic networks.

8 Conclusion

Although gap junctions in the brain were found several decades ago, the exploration of their roles in different cell types, especially neurons and astrocytes, in epilepsy is just at the preliminary stage. Converging evidence from both clinical and experimental studies suggest that seizure activity affects connexin expression and gap junction permeability. However, further studies are needed to investigate possible downstream and parallel cell-signaling events associated with seizure activity induced by changes in connexin expression. Besides, carefully ruling out connexin alteration by other processes such as cell death instead of epilepsy is also greatly needed. As demonstrated by current data both *in vivo* and *in vitro*, gap junctions represent a potential novel target for anticonvulsant therapy, although gap junction inhibitors have not been used clinically to treat seizure disorders. Among the limitations of gap junction blockers for clinical application, lack of specificity is of great importance, which may lead to various side-effects instead of anticonvulsant effects.

The role of neuronal gap junctions and astrocytic gap junctions in the generation, synchronization and maintenance of seizure events should be separately evaluated. Neuronal gap junctions play an important role in the generation of synchronous high-frequency oscillations, and astrocytic gap junctions affect seizure activity through at least two contradictory mechanisms: one allows K^+ buffering to tune down the neuronal activity, and the other delivers energy to neurons to sustain neuronal excitability. However, further evidence is needed to get the whole profile of the respective roles of neuronal and astrocytic networks in epilepsy, where many questions are still unanswered.

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References:

[1] Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol 2003, 16: 165–170.

[2] Rudzinski LA, Meador KJ. Epilepsy: five new things. Neurology 2011, 76: S20–25.

[3] Bennett MV, Goodenough DA. Gap junctions, electrotonic coupling, and intercellular communication. Neurosci Res Program Bull 1978, 16: 1–486.

[4] Simon AM, Goodenough DA. Diverse functions of vertebrate gap junctions. Trends Cell Biol 1998, 8: 477–483.

[5] El-Sabban ME, Abi-Mosleh LF, Talhouk RS. Developmental regulation of gap junctions and their role in mammary epithelial cell differentiation. J Mammary Gland Biol Neoplasia 2003, 8: 463–473.

[6] Kumar NM, Gilula NB. The gap junction communication channel. Cell 1996, 84: 381–388.

[7] Yeager M, Unger VM, Falk MM. Synthesis, assembly and structure of gap junction intercellular channels. Curr Opin Struct Biol 1998, 8: 517–524.

[8] Eugenin EA, Eckardt D, Theis M, Willecke K, Bennett MV, Saez JC. Microglia at brain stab wounds express connexin 43 and *in vitro* form functional gap junctions after treatment with interferon–gamma and tumor necrosis factor-alpha. Proc Natl Acad Sci U S A 2001, 98: 4190–4195.

[9] Nagy JI, Rash JE. Connexins and gap junctions of astrocytes and oligodendrocytes in the CNS. Brain Res Brain Res Rev 2000, 32: 29–44.

[10] Nakase T, Naus CC. Gap junctions and neurological disorders of

the central nervous system. Biochim Biophys Acta 2004, 1662: 149–158.

[11] Rouach N, Avignone E, Meme W, Koulakoff A, Venance L, Blomstrand F, *et al.* Gap junctions and connexin expression in the normal and pathological central nervous system. Biol Cell 2002, 94: 457–475.

[12] Rozental R, Giaume C, Spray DC. Gap junctions in the nervous system. Brain Res Brain Res Rev 2000, 32: 11–15.

[13] Nedergaard M. Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. Science 1994, 263: 1768–1771.

[14] Wolff JR, Stuke K, Missler M, Tytko H, Schwarz P, Rohlmann A, *et al.* Autocellular coupling by gap junctions in cultured astrocytes: a new view on cellular autoregulation during process formation. Glia 1998, 24: 121–140.

[15] Naus CC, Bani-Yaghoub M. Gap junctional communication in the developing central nervous system. Cell Biol Int 1998, 22: 751–763.

[16] Rackauskas M, Neverauskas V, Skeberdis VA. Diversity and properties of connexin gap junction channels. Medicina (Kaunas) 2010, 46: 1–12.

[17] Lampe PD, Lau AF. Regulation of gap junctions by phosphorylation of connexins. Arch Biochem Biophys 2000, 384: 205–215.

[18] Sohl G, Willecke K. Gap junctions and the connexin protein family. Cardiovasc Res 2004, 62: 228–232.

[19] Talhouk RS, Zeinieh MP, Mikati MA, El-Sabban ME. Gap junctional intercellular communication in hypoxia-ischemia-induced neuronal injury. Prog Neurobiol 2008, 84: 57–76.

[20] Dermietzel R, Hertberg EL, Kessler JA, Spray DC. Gap junctions between cultured astrocytes: immunocytochemical, molecular, and electrophysiological analysis. J Neurosci 1991, 11: 1421–1432.

[21] Giaume C, Fromaget C, el Aoumari A, Cordier J, Glowinski J, Gros D. Gap junctions in cultured astrocytes: single-channel currents and characterization of channel-forming protein. Neuron 1991, 6: 133–143.

[22] Kunzelmann P, Schroder W, Traub O, Steinhauser C, Dermietzel R, Willecke K. Late onset and increasing expression of the gap junction protein connexin30 in adult murine brain and long-term cultured astrocytes. Glia 1999, 25: 111–119.

[23] Nagy JI, Patel D, Ochalski PA, Stelmack GL. Connexin30 in rodent, cat and human brain: selective expression in gray matter astrocytes, co-localization with connexin43 at gap junctions and late developmental appearance. Neuroscience 1999, 88: 447–468.

[24] Giaume C, Koulakoff A, Roux L, Holcman D, Rouach N. Astroglial networks: a step further in neuroglial and gliovascular interactions. Nat Rev Neurosci 2010, 11: 87–99.

[25] Seifert G, Steinhauser C. Neuron-astrocyte signaling and epilepsy. Exp Neurol 2011. [Epub ahead of print]

[26] Bennett MV, Zukin RS. Electrical coupling and neuronal synchronization in the Mammalian brain. Neuron 2004, 41: 495–511.

[27] Rash JE, Yasumura T, Dudek FE, Nagy JI. Cell-pecific expression of connexins and evidence of restricted gap junctional coupling between glial cells and between neurons. J Neurosci 2001, 21: 1983–2000.

[28] Connors BW, Long MA. Electrical synapses in the mammalian brain. Annu Rev Neurosci 2004, 27: 393–418.

[29] Bani-Yaghoub M, Underhill TM, Naus CC. Gap junction blockage interferes with neuronal and astroglial differentiation of mouse P19 embryonal carcinoma cells. Dev Genet 1999, 24: 69–81.

[30] de Rivero Vaccari JC, Corriveau RA, Belousov AB. Gap junctions are required for NMDA receptor dependent cell death in developing neurons. J Neurophysiol 2007, 98: 2878–2886.

[31] Personius K, Chang Q, Bittman K, Panzer J, Balice-Gordon R. Gap junctional communication among motor and other neurons shapes patterns of neural activity and synaptic connectivity during development. Cell Commun Adhes 2001, 8: 329–333.

[32] Deans MR, Gibson JR, Sellitto C, Connors BW, Paul DL. Synchronous activity of inhibitory networks in neocortex requires electrical synapses containing connexin36. Neuron 2001, 31: 477–485.

[33] Randall FE, Whittington MA, Cunningham MO. Fast oscillatory activity induced by kainate receptor activation in the rat basolateral amygdala *in vitro*. Eur J Neurosci 2011, 33: 914–922.

[34] Mas C, Taske N, Deutsch S, Guipponi M, Thomas P, Covanis A, *et al.* Association of the connexin36 gene with juvenile myoclonic epilepsy. J Med Genet 2004, 41(7): e93.

[35] Hempelmann A, Heils A, Sander T. Confirmatory evidence for an association of the connexin-36 gene with juvenile myoclonic epilepsy. Epilepsy Res 2006, 71: 223–228.

[36] Bittman KS, LoTurco JJ. Differential regulation of connexin 26 and 43 in murine neocortical precursors. Cereb Cortex 1999, 9: 188–195.

[37] Nagy JI, Li X, Rempel J, Stelmack G, Patel D, Staines WA, *et al.* Connexin26 in adult rodent central nervous system: demonstration at astrocytic gap junctions and colocalization with connexin30 and connexin43. J Comp Neurol 2001, 441: 302–323.

[38] Alvarez-Maubecin V, Garcia-Hernandez F, Williams JT, Van Bockstaele EJ. Functional coupling between neurons and glia. J Neurosci 2000, 20: 4091–4098.

[39] Mercier F, Hatton GI. Connexin 26 and basic fibroblast growth factor are expressed primarily in the subpial and subependymal layers in adult brain parenchyma: roles in stem cell proliferation and morphological plasticity? J Comp Neurol 2001, 431: 88–104.

[40] Altevogt BM, Kleopa KA, Postma FR, Scherer SS, Paul DL. Connexin29 is uniquely distributed within myelinating glial cells of the central and peripheral nervous systems. J Neurosci 2002, 22: 6458–6470.

[41] Dermietzel R, Traub O, Hwang TK, Beyer E, Bennett MV, Spray

DC, *et al*. Differential expression of three gap junction proteins in developing and mature brain tissues. Proc Natl Acad Sci U S A 1989, 86: 10148–10152.

[42] Li J, Hertzberg EL, Nagy JI. Connexin32 in oligodendrocytes and association with myelinated fibers in mouse and rat brain. J Comp Neurol 1997, 379: 571–591.

[43] Condorelli DF, Belluardo N, Trovato-Salinaro A, Mudo G. Expression of Cx36 in mammalian neurons. Brain Res Brain Res Rev 2000, 32: 72–85.

[44] Rash JE, Olson CO, Davidson KG, Yasumura T, Kamasawa N, Nagy JI. Identification of connexin36 in gap junctions between neurons in rodent locus coeruleus. Neuroscience 2007, 147: 938–956.

[45] Parenti R, Campisi A, Vanella A, Cicirata F. Immunocytochemical and RT-PCR analysis of connexin36 in cultures of mammalian glial cells. Arch Ital Biol 2002, 140: 101–108.

[46] Dobrenis K, Chang HY, Pina-Benabou MH, Woodroffe A, Lee SC, Rozental R, *et al.* Human and mouse microglia express connexin36, and functional gap junctions are formed between rodent microglia and neurons. J Neurosci Res 2005, 82: 306–315.

[47] Cina C, Bechberger JF, Ozog MA, Naus CC. Expression of connexins in embryonic mouse neocortical development. J Comp Neurol 2007, 504: 298–313.

[48] Dermietzel R, Gao Y, Scemes E, Vieira D, Urban M, Kremer M, *et al.* Connexin43 null mice reveal that astrocytes express multiple connexins. Brain Res Brain Res Rev 2000, 32: 45–56.

[49] Venance L, Rozov A, Blatow M, Burnashev N, Feldmeyer D, Monyer H. Connexin expression in electrically coupled postnatal rat brain neurons. Proc Natl Acad Sci U S A 2000, 97: 10260–10265.

[50] Nadarajah B, Thomaidou D, Evans WH, Parnavelas JG. Gap junctions in the adult cerebral cortex: regional differences in their distribution and cellular expression of connexins. J Comp Neurol 1996, 376: 326–342.

[51] Zlomuzica A, Reichinnek S, Maxeiner S, Both M, May E, Worsdorfer P, *et al.* Deletion of connexin45 in mouse neurons disrupts one-trial object recognition and alters kainate-induced gamma-oscillations in the hippocampus. Physiol Behav 2010, 101: 245–253.

[52] Maxeiner S, Kruger O, Schilling K, Traub O, Urschel S, Willecke K. Spatiotemporal transcription of connexin45 during brain development results in neuronal expression in adult mice. Neuroscience 2003, 119: 689–700.

[53] Zhang C, Restrepo D. Expression of connexin 45 in the olfactory system. Brain Res 2002, 929: 37–47.

[54] Kunzelmann P, Blumcke I, Traub O, Dermietzel R, Willecke K. Coexpression of connexin45 and -32 in oligodendrocytes of rat brain. J Neurocytol 1997, 26: 17–22.

[55] Dermietzel R, Farooq M, Kessler JA, Althaus H, Hertzberg EL, Spray DC. Oligodendrocytes express gap junction proteins connexin32 and connexin45. Glia 1997, 20: 101–114.

[56] Teubner B, Odermatt B, Guldenagel M, Sohl G, Degen J, Bukauskas F, *et al.* Functional expression of the new gap junction gene connexin47 transcribed in mouse brain and spinal cord neurons. J Neurosci 2001, 21: 1117–1126.

[57] Parenti R, Cicirata F, Zappala A, Catania A, La Delia F, Cicirata V, *et al.* Dynamic expression of Cx47 in mouse brain development and in the cuprizone model of myelin plasticity. Glia 2010, 58: 1594–1609.

[58] Odermatt B, Wellershaus K, Wallraff A, Seifert G, Degen J, Euwens C, *et al.* Connexin 47 (Cx47)-deficient mice with enhanced green fluorescent protein reporter gene reveal predominant oligodendrocytic expression of Cx47 and display vacuolized myelin in the CNS. J Neurosci 2003, 23: 4549–4559.

[59] Orthmann-Murphy JL, Enriquez AD, Abrams CK, Scherer SS. Loss-of-function GJA12/Connexin47 mutations cause Pelizaeus-Merzbacher-like disease. Mol Cell Neurosci 2007, 34: 629–641.

[60] Naus CC, Bechberger JF, Paul DL. Gap junction gene expression in human seizure disorder. Exp Neurol 1991, 111: 198–203.

[61] Collignon F, Wetjen NM, Cohen-Gadol AA, Cascino GD, Parisi J, Meyer FB, *et al.* Altered expression of connexin subtypes in mesial temporal lobe epilepsy in humans. J Neurosurg 2006, 105: 77–87.

[62] Fonseca CG, Green CR, Nicholson LF. Upregulation in astrocytic connexin 43 gap junction levels may exacerbate generalized seizures in mesial temporal lobe epilepsy. Brain Res 2002, 929: 105–116.

[63] Garbelli R, Frassoni C, Condorelli DF, Trovato Salinaro A, Musso N, Medici V, *et al.* Expression of connexin 43 in the human epileptic and drug-resistant cerebral cortex. Neurology 2011, 76: 895–902.

[64] Elisevich K, Rempel SA, Smith BJ, Edvardsen K. Hippocampal connexin 43 expression in human complex partial seizure disorder. Exp Neurol 1997, 145: 154–164.

[65] Colling SB, Man WD, Draguhn A, Jefferys JG. Dendritic shrinkage and dye-coupling between rat hippocampal CA1 pyramidal cells in the tetanus toxin model of epilepsy. Brain Res 1996, 741: 38–43.

[66] Cepeda C, Walsh JP, Peacock W, Buchwald NA, Levine MS. Dye-coupling in human neocortical tissue resected from children with intractable epilepsy. Cereb Cortex 1993, 3: 95–107.

[67] Beheshti S, Sayyah M, Golkar M, Sepehri H, Babaie J, Vaziri B. Changes in hippocampal connexin 36 mRNA and protein levels during epileptogenesis in the kindling model of epilepsy. Prog Neuropsychopharmacol Biol Psychiatry 2010, 34: 510–515.

[68] Sohl G, Guldenagel M, Beck H, Teubner B, Traub O, Gutierrez R, *et al.* Expression of connexin genes in hippocampus of kainite-treated and kindled rats under conditions of experimental epilepsy. Brain Res Mol Brain Res 2000, 83: 44–51.

[69] McCracken CB, Roberts DC. A single evoked afterdischarge produces rapid time-dependent changes in connexin36 protein expression in adult rat dorsal hippocampus. Neurosci Lett 2006, 405: 84–88.

[70] Elisevich K, Rempel SA, Smith B, Allar N. Connexin 43 mRNA expression in two experimental models of epilepsy. Mol Chem Neuropathol 1997, 32: 75–88.

[71] Gajda Z, Gyengesi E, Hermesz E, Ali KS, Szente M. Involvement of gap junctions in the manifestation and control of the duration of seizures in rats in vivo. Epilepsia 2003, 44: 1596–1600.

[72] Szente M, Gajda Z, Said Ali K, Hermesz E. Involvement of electrical coupling in the *in vivo* ictal epileptiform activity induced by 4-aminopyridine in the neocortex. Neuroscience 2002, 115: 1067–1078.

[73] Condorelli DF, Trovato-Salinaro A, Mudo G, Mirone MB, Belluardo N. Cellular expression of connexins in the rat brain: neuronal localization, effects of kainite-induced seizures and expression in apoptotic neuronal cells. Eur J Neurosci 2003, 18: 1807–1827.

[74] Condorelli DF, Mudo G, Trovato-Salinaro A, Mirone MB, Amato G, Belluardo N. Connexin-30 mRNA is up-regulated in astrocytes and expressed in apoptotic neuronal cells of rat brain following kainite-induced seizures. Mol Cell Neurosci 2002, 21: 94–113.

[75] Takahashi DK, Vargas JR, Wilcox KS. Increased coupling and altered glutamate transport currents in astrocytes following kainic-acid-induced status epilepticus. Neurobiol Dis 2010, 40: 573–585.

[76] Su M, Tong XX. Astrocytic gap junction in the hippocampus of rats with lithium pilocarpine-induced epilepsy. Nan Fang Yi Ke Da Xue Xue Bao 2010, 30: 2738–2741.

[77] Volman V, Perc M, Bazhenov M. Gap junctions and epileptic seizures – two sides of the same coin? Plos One 2011, 6(5): e20572.

[78] Jahromi SS, Wentlandt K, Piran S, Carlen PL. Anticonvulsant actions of gap junctional blockers in an in vitro seizure model. J Neurophysiol 2002, 88: 1893–1902.

[79] Mylvaganam S, Zhang L, Wu C, Zhang ZJ, Samoilova M, Eubanks J, *et al.* Hippocampal seizures alter the expression of the pannexin and connexin transcriptome. J Neurochem 2010, 112: 92–102.

[80] Li J, Shen H, Naus CC, Zhang L, Carlen PL. Upregulation of gap junction connexin 32 with epileptiform activity in the isolated mouse hippocampus. Neuroscience 2001, 105: 589–598.

[81] Samoilova M, Li J, Pelletier MR, Wentlandt K, Adamchik Y, Naus CC, *et al.* Epileptiform activity in hippocampal slice cultures exposed chronically to bicuculline: increased gap junctional function and expression. J Neurochem 2003, 86: 687–699.

[82] Salameh A, Dhein S. Pharmacology of gap junctions. New pharmacological targets for treatment of arrhythmia, seizure and cancer? Biochim Biophys Acta 2005, 1719: 36–58.

[83] Boitano S, Evans WH. Connexin mimetic peptides reversibly inhibit Ca(2+) signaling through gap junctions in airway cells. Am J Physiol Lung Cell Mol Physiol 2000, 279: L623–630.

[84] Evans WH, Leybaert L. Mimetic peptides as blockers of connexin channel–facilitated intercellular communication. Cell Commun Adhes 2007, 14: 265–273.

[85] Rose CR, Ransom BR. Gap junctions equalize intracellular Na^+ concentration in astrocytes. Glia 1997, 20: 299–307.

[86] Johnston MF, Simon SA, Ramon F. Interaction of anaesthetics with electrical synapses. Nature 1980, 286: 498–500.

[87] Cotrina ML, Lin JH, Alves-Rodrigues A, Liu S, Li J, Azmi-Ghadimi H, *et al.* Connexins regulate calcium signaling by controlling ATP release. Proc Natl Acad Sci U S A 1998, 95: 15735–15740.

[88] Burt JM, Spray DC. Volatile anesthetics block intercellular communication between neonatal rat myocardial cells. Circ Res 1989, 65: 829–837.

[89] Davidson JS, Baumgarten IM, Harley EH. Reversible inhibition of intercellular junctional communication by glycyrrhetinic acid. Biochem Biophys Res Commun 1986, 134: 29–36.

[90] Perez-Velazquez JL, Valiante TA, Carlen PL. Modulation of gap junctional mechanisms during calcium-free induced field burst activity: a possible role for electrotonic coupling in epileptogenesis. J Neurosci 1994, 14: 4308–4317.

[91] Kohling R, Gladwell SJ, Bracci E, Vreugdenhil M, Jefferys JG. Prolonged epileptiform bursting induced by 0–Mg(2+) in rat hippocampal slices depends on gap junctional coupling. Neuroscience 2001, 105: 579–587.

[92] Srinivas M, Hopperstad MG, Spray DC. Quinine blocks specific gap junction channel subtypes. Proc Natl Acad Sci U S A 2001, 98: 10942–10947.

[93] Cruikshank SJ, Hopperstad M, Younger M, Connors BW, Spray DC, Srinivas M. Potent block of Cx36 and Cx50 gap junction channels by mefloquine. Proc Natl Acad Sci U S A 2004, 101: 12364–12369.

[94] Harks EG, de Roos AD, Peters PH, de Haan LH, Brouwer A, Ypey DL, *et al.* Fenamates: a novel class of reversible gap junction blockers. J Pharmacol Exp Ther 2001, 298: 1033–1041.

[95] Schools GP, Zhou M, Kimelberg HK. Development of gap junctions in hippocampal astrocytes: evidence that whole cell electrophysiological phenotype is an intrinsic property of the individual cell. J Neurophysiol 2006, 96: 1383–1392.

[96] Samoilova M, Wentlandt K, Adamchik Y, Velumian AA, Carlen PL. Connexin 43 mimetic peptides inhibit spontaneous epileptiform activity in organotypic hippocampal slice cultures. Exp Neurol 2008, 210: 762–775.

[97] Bikson M, Id Bihi R, Vreugdenhil M, Kohling R, Fox JE, Jefferys JG. Quinine suppresses extracellular potassium transients and ictal epileptiform activity without decreasing neuronal excitability in vitro. Neuroscience 2002, 115: 251–261.

[98] Margineanu DG, Klitgaard H. Can gap-junction blockade preferentially inhibit neuronal hypersynchrony vs. excitability? Neurop-

harmacology 2001, 41: 377–383.

[99] Schweitzer JS, Wang H, Xiong ZQ, Stringer JL. pH Sensitivity of non-synaptic field bursts in the dentate gyrus. J Neurophysiol 2000, 84: 927–933.

[100] Ross FM, Gwyn P, Spanswick D, Davies SN. Carbenoxolone depresses spontaneous epileptiform activity in the CA1 region of rat hippocampal slices. Neuroscience 2000, 100: 789–796.

[101] Traub RD, Bibbig R, Piechotta A, Draguhn R, Schmitz D. Synaptic and nonsynaptic contributions to giant ipsps and ectopic spikes induced by 4-aminopyridine in the hippocampus in vitro. J Neurophysiol 2001, 85: 1246–1256.

[102] Gigout S, Louvel J, Pumain R. Effects *in vitro* and *in vivo* of a gap junction blocker on epileptiform activities in a genetic model of absence epilepsy. Epilepsy Res 2006, 69: 15–29.

[103] de Curtis M, Manfridi A, Biella G. Activity-dependent pH shifts and periodic recurrence of spontaneous interictal spikes in a model of focal epileptogenesis. J Neurosci 1998, 18: 7543–7551.

[104] Voss LJ, Jacobson G, Sleigh JW, Steyn-Ross A, Steyn-Ross M. Excitatory effects of gap junction blockers on cerebral cortex seizure-like activity in rats and mice. Epilepsia 2009, 50: 1971–1978.

[105] Sayyah M, Rezaie M, Haghighi S, Amanzadeh A. Intra-amygdala all-trans retinoic acid inhibits amygdale-kindled seizures in rats. Epilepsy Res 2007, 75: 97–103.

[106] Hosseinzadeh H, Nassiri Asl M. Anticonvulsant, sedative and muscle relaxant effects of carbenoxolone in mice. BMC Pharmacol 2003, 3: 3.

[107] Medina-Ceja L, Cordero-Romero A, Morales-Villagran A. Antiepileptic effect of carbenoxolone on seizures induced by 4-aminopyridine: a study in the rat hippocampus and entorhinal cortex. Brain Res 2008, 1187: 74–81.

[108] Bostanci MO, Bagirici F. Anticonvulsive effects of carbenoxolone on penicillin-induced epileptiform activity: an *in vivo* study. Neuropharmacology 2007, 52: 362–367.

[109] Nilsen KE, Kelso AR, Cock HR. Antiepileptic effect of gap-junction blockers in a rat model of refractory focal cortical epilepsy. Epilepsia 2006, 47: 1169–1175.

[110] Gareri P, Condorelli D, Belluardo N, Citraro R, Barresi V, Trovato-Salinaro A, *et al.* Antiabsence effects of carbenoxolone in two genetic animal models of absence epilepsy (WAG/Rij rats and lh/lh mice). Neuropharmacology 2005, 49: 551–563.

[111] Proulx E, Leshchenko Y, Kokarovtseva L, Khokhotva V, El-Beheiry M, Snead OC, 3rd, *et al*. Functional contribution of specific brain areas to absence seizures: role of thalamic gap-junctional coupling. Eur J Neurosci 2006, 23: 489–496.

[112] Gareri P, Condorelli D, Belluardo N, Gratteri S, Ferreri G, Donato Di Paola E, *et al.* Influence of carbenoxolone on the anticonvulsant efficacy of conventional antiepileptic drugs against audiogenic seizures in DBA/2 mice. Eur J Pharmacol 2004, 484: 49–56.

[113] Gareri P, Condorelli D, Belluardo N, Russo E, Loiacono A, Barresi V, *et al.* Anticonvulsant effects of carbenoxolone in genetically epilepsy prone rats (GEPRs). Neuropharmacology 2004, 47: 1205–1216.

[114] Peretz A, Degani N, Nachman R, Uziyel Y, Gibor G, Shabat D, *et al.* Meclofenamic acid and diclofenac, novel templates of KCNQ2/Q3 potassium channel openers, depress cortical neuron activity and exhibit anticonvulsant properties. Mol Pharmacol 2005, 67: 1053–1066.

[115] Gajda Z, Szupera Z, Blazso G, Szente M. Quinine, a blocker of neuronal cx36 channels, suppresses seizure activity in rat neocortex *in vivo*. Epilepsia 2005, 46: 1581–1591.

[116] Medina-Ceja L, Ventura-Mejia C. Differential effects of trimethylamine and quinine on seizures induced by 4-aminopyridine administration in the entorhinal cortex of vigilant rats. Seizure 2010, 19: 507–513.

[117] Bostanci MO, Bagirici F. Anticonvulsive effects of quinine on penicillin-induced epileptiform activity: an *in vivo* study. Seizure 2007, 16: 166–172.

[118] Nassiri-Asl M, Zamansoltani F, Torabinejad B. Antiepileptic effects of quinine in the pentylenetetrazole model of seizure. Seizure 2009, 18: 129–132.

[119] Nassiri-Asl M, Zamansoltani F, Zangivand AA. The inhibitory effect of trimethylamine on the anticonvulsant activities of quinine in the pentylenetetrazole model in rats. Prog Neuropsychopharmacol Biol Psychiatry 2008, 32: 1496–1500.

[120] Bostanci MO, Bagirici F. The effects of octanol on penicillin induced epileptiform activity in rats: an *in vivo* study. Epilepsy Res 2006, 71: 188–194.

[121] Maier N, Guldenagel M, Sohl G, Siegmund H, Willecke K, Draguhn A. Reduction of high-frequency network oscillations (ripples) and pathological network discharges in hippocampal slices from connexin 36-deficient mice. J Physiol 2002, 541: 521–528.

[122] Jacobson GM, Voss LJ, Melin SM, Mason JP, Cursons RT, Steyn-Ross DA, *et al.* Connexin36 knockout mice display increased sensitivity to pentylenetetrazol-induced seizure-like behaviors. Brain Res 2010, 1360: 198–204.

[123] Guldenagel M, Ammermuller J, Feigenspan A, Teubner B, Degen J, Sohl G, *et al.* Visual transmission deficits in mice with targeted disruption of the gap junction gene connexin36. J Neurosci 2001, 21: 6036–6044.

[124] Reaume AG, de Sousa PA, Kulkarni S, Langille BL, Zhu D, Davies TC, *et al.* Cardiac malformation in neonatal mice lacking connexin43. Science 1995, 267: 1831–1834.

[125] Fushiki S, Perez Velazquez JL, Zhang L, Bechberger JF, Carlen PL, Naus CC. Changes in neuronal migration in neocortex of connexin43 null mutant mice. J Neuropathol Exp Neurol 2003, 62: 304–314.

[126] Gabriel HD, Jung D, Butzler C, Temme A, Traub O, Winterhager E, *et al.* Transplacental uptake of glucose is decreased in embryonic lethal connexin26-deficient mice. J Cell Biol 1998, 140: 1453–1461.

[127] Kruger O, Plum A, Kim JS, Winterhager E, Maxeiner S, Hallas G, *et al.* Defective vascular development in connexin 45-deficient mice. Development 2000, 127: 4179–4193.

[128] Taylor CP, Dudek FE. Synchronous neural afterdischarges in rat hippocampal slices without active chemical synapses. Science 1982, 218: 810–812.

[129] Grenier F, Timofeev I, Steriade M. Neocortical very fast oscillations (ripples, 80–200 Hz) during seizures: intracellular correlates. J Neurophysiol 2003, 89: 841–852.

[130] Rodin E. Paper recordings of ultrafast frequencies in experimental epilepsy. Clin EEG Neurosci 2005, 36: 263–270.

[131] Traub RD, Contreras D, Cunningham MO, Murray H, LeBeau FE, Roopun A, *et al.* Single-column thalamocortical network model exhibiting gamma oscillations, sleep spindles, and epileptogenic bursts. J Neurophysiol 2005, 93: 2194–2232.

[132] Bragin A, Engel J, Jr., Wilson CL, Fried I, Buzsaki G. High-frequency oscillations in human brain. Hippocampus 1999, 9: 137–142.

[133] Bragin A, Engel J, Jr., Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. Epilepsia 1999, 40: 127–137.

[134] Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain 2006, 129: 1593–1608.

[135] Staba RJ, Wilson CL, Bragin A, Fried I, Engel J, Jr. Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. J Neurophysiol 2002, 88: 1743–1752.

[136] Staba RJ, Wilson CL, Bragin A, Jhung D, Fried I, Engel J, Jr. High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann Neurol 2004, 56: 108–115.

[137] Alarcon G, Binnie CD, Elwes RD, Polkey CE. Power spectrum and intracranial EEG patterns at seizure onset in partial epilepsy. Electroencephalogr Clin Neurophysiol 1995, 94: 326–337.

[138] Allen PJ, Fish DR, Smith SJ. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1992, 82: 155–159.

[139] Bragin A, Mody I, Wilson CL, Engel J, Jr. Local generation of fast ripples in epileptic brain. J Neurosci 2002, 22: 2012–2021.

[140] Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J, Jr. Interictal high-frequency oscillations (80–500 Hz) in the human epileptic brain: entorhinal cortex. Ann Neurol 2002, 52: 407–415.

[141] Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol 1992, 9: 441–448.

[142] Traub RD, Draguhn A, Whittington MA, Baldeweg T, Bibbig A, Buhl EH, *et al.* Axonal gap junctions between principal neurons: a novel source of network oscillations, and perhaps epileptogenesis. Rev Neurosci 2002, 13: 1–30.

[143] Traub RD, Whittington MA, Buhl EH, LeBeau FE, Bibbig A, Boyd S, *et al.* A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. Epilepsia 2001, 42: 153–170.

[144] Draguhn A, Traub RD, Schmitz D, Jefferys JG. Electrical coupling underlies high-frequency oscillations in the hippocampus *in vitro*. Nature 1998, 394: 189–192.

[145] Hormuzdi SG, Pais I, LeBeau FE, Towers SK, Rozov A, Buhl EH, *et al.* Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. Neuron 2001, 31: 487–495.

[146] Binder DK, Steinhauser C. Functional changes in astroglial cells in epilepsy. Glia 2006, 54: 358–368.

[147] Wetherington J, Serrano G, Dingledine R. Astrocytes in the epileptic brain. Neuron 2008, 58: 168–178.

[148] Enkvist MO, McCarthy KD. Astroglial gap junction communication is increased by treatment with either glutamate or high K^+ concentration. J Neurochem 1994, 62: 489–495.

[149] Rouach N, Koulakoff A, Abudara V, Willecke K, Giaume C. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science 2008, 322: 1551–1555.

[150] Pannasch U, Vargova L, Reingruber J, Ezan P, Holcman D, Giaume C, *et al.* Astroglial networks scale synaptic activity and plasticity. Proc Natl Acad Sci U S A 2011, 108: 8467–8472.

[151] Wallraff A, Kohling R, Heinemann U, Theis M, Willecke K, Steinhauser C. The impact of astrocytic gap junctional coupling on potassium buffering in the hippocampus. J Neurosci 2006, 26: 5438–5447.

缝隙连接在癫痫中的作用

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摘要：癫痫是最常见的神经系统疾病之一，临床主要表现为周期性和无法预见性的癫痫样发作。目前认为，癫痫的形成、同步化以及癫痫样放电的维持与细胞间的缝隙连接有关。大量的体内外实验研究表明，缝隙连接抑制剂具有较强的抗癫痫作用，提示缝隙连接可能成为开发新型抗癫痫药物的潜在靶点。此外，选择性药理学研究和基因敲除技术研究表明，神经元间与胶质细胞间的缝隙连接在癫痫中的作用需区别看待。随着条件性基因敲除技术的成熟、高选择性的新型缝隙连接调控药物的出现以及更详细的人类癫痫脑组织样本的研究，人们将更全面地了解缝隙连接在癫痫中的作用。本综述总结了目前关于缝隙连接在癫痫发病机制中作用的研究结果，并对临床和基础研究中癫痫发作导致的缝隙连接蛋白表达的变化进行讨论。

关键词：癫痫; 缝隙连接; 缝隙连接蛋白