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Does Epilepsy Cause a Reversion to Immature Function?

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Abstract

Seizures have variable effects on brain. Numerous studies have examined the consequences of seizures, in light of the way that these may alter the susceptibility of the brain to seizures, promote epileptogenesis, or functionally alter brain leading to seizure-related comorbidities. In many –but not all- situations, seizures shift brain function towards a more immature state, promoting the birth of newborn neurons, altering the dendritic structure and neuronal connectivity, or changing neurotransmitter signaling towards more immature patterns. These effects depend upon many factors, including the seizure type, age of seizure occurrence, sex, and brain region studied. Here we discuss some of these findings proposing that these seizure-induced immature features do not simply represent rejuvenation of the brain but rather a de-synchronization of the homeostatic mechanisms that were in place to maintain normal physiology, which may contribute to epileptogenesis or the cognitive comorbidities.

Keywords

GABA receptor; Chloride cotransporter; Neurogenesis; mTOR; Dysplasia; Epileptogenesis

16.1 Introduction

Epilepsies have multiple causes and phenotypes, leading to different seizure and epilepsy syndromes. A variety of genetic, toxic/metabolic, or structural abnormalities have been causally associated with epilepsies. Epilepsy may occur as a “system disorder”, attributed to dysfunction –but no overt structural pathology – of specific neuronal networks, as typically occurs in genetic generalized epilepsies, like absence epilepsy [4]. In other cases, specific

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pathologies, e.g., cortical malformations or hippocampal sclerosis, may lead to the generation of an epileptogenic focus.

Seizures and epilepsies may disrupt brain development. Often, these maldevelopmental consequences of seizures may manifest as age- inappropriate reversal to immature functions and developmental processes. For example, seizures may trigger the aberrant re-emergence of immature features of $GABA_A$ receptor ($GABA_AR$) signaling in neurons from adult animals or may cause morphological changes reminiscent of immature neurons. Immature features include the generation of new neuronal progenitor cells, functional alteration of selected signaling pathways or morphological changes. Many of these immature features have been documented in surgically resected epileptic tissues from individuals with drug-resistant epilepsies, like temporal lobe epilepsy (TLE), hypothalamic hamartomas, cortical dysplasias, or peritumoral epileptic tissue. Comparisons with nonepileptic post-mortem or surgically resected tissues have indicated that some of these changes are specific for the epileptic tissue [46, 47]. Yet, the appearance of these changes after seizures in animal models often depends upon a variety of factors. Here we will discuss the animal studies that have supported these observations and have provided insights on the complex interactions between the immature features of the epileptic focus and epilepsies, their etiologies and treatments and how these can be modified by age, sex, region-specific or other factors.

16.2 Neurogenesis in TLE

Perhaps the most classic argument for a reversal of normal age-specific functions with a reemergence of patterns observed during development is the observation that there is an increased number of newborn cells in the dentate gyrus, in response to seizures or during the epileptic state [101]. Increased neurogenesis in the dentate gyrus of adult rats has been shown using post-SE models of epilepsy [48, 86, 100] or kindling [84, 105] or hyperthermic seizures [[61] and reviewed in [85, 101]] (Table 16.1). Newborn cells manifest many of the electrophysiological and morphological features of the granule cells, but also some distinctive characteristics. For example, they may be more dispersed [48, 100], have bipolar rather than polarized dendrites and they do not stain for Neuropeptide Y (NPY) or glutamic acid decarboxylase (GAD) immunoreactivity [100]. Furthermore, newborn cells may integrate abnormally into the hippocampus after seizures. Newborn neurons that migrate towards the CA3 pyramidal region may synchronize with CA3 neurons into epileptiform bursts [100]. Doublecortin-positive newborn neurons in the hilar dentate of epileptic rats exhibit long and recurrent basal dendrites directed towards the granule cell layer and also receive excitatory synaptic input which is unusual in seizure-naive rats [95]. These seizure-induced changes may contribute to the excitability of the hippocampus. It has also been proposed that newborn neurons may not be capable to integrate normally in processes controlling cognitive processes, contributing therefore to cognitive deficits [30, 88].

The effects of seizures on neurogenesis at the dentate is age, sex, region, model specific and may depend on the number and type of seizures that the animal experiences (reviewed in Table 16.1). In brief, neonatal rats may respond instead with reduced or unaltered neurogenesis. Furthermore, aged rats may not respond as robustly with neurogenesis following seizures as younger adults do. Longitudinal studies may reveal time-dependent

changes in neurogenesis, which may be influenced also by the ability of these newborn cells to survive. For example, hyperthermic seizures caused the newborn neurons to survive longer in males than in females till adulthood, suggesting sex-specific factors controlling their function [61]. Few brief seizures may not be as sufficient to affect neurogenesis, as frequent or prolonged seizures do.

Investigations into whether aberrant neurogenesis may contribute to epileptogenesis have yielded variable results. Administration of anti-mitotics that prevent neurogenesis may decrease the frequency of spontaneous seizures in post-SE animals [51]. However, other treatments that reduce seizure-induced neurogenesis have resulted in either reduction [109] or no effect [88] on the frequency of spontaneous seizures. The developmental studies on the effects of SE in 2–3 week old rats which show increased SE-induced neurogenesis, even though neither cell loss nor epileptogenesis always ensue have also failed to associate the increase seizure-induced neurogenesis with either of these consequences of SE [98]. Seizure-induced neurogenesis appears therefore to contribute to the excitability of the epileptic hippocampus and possibly to the associated cognitive dysfunction, but there is no definite evidence that it is required for or mediates the ensuing epileptogenesis. Future research into deciphering the mechanisms leading to seizure-induced neurogenesis and how these are modified by age or sex or seizure-specific factors would be needed.

16.3 Evidence for Immaturity of $GABA_A$ Receptor ($GABA_AR$) Signaling in Epilepsies

$GABA_AR$ signaling is well known to undergo structural and functional changes through development. The subunit composition of the $GABA_AR$ complexes changes to include subunits that will provide electrophysiologic and pharmacological properties more akin to mature neurons. A typical example is the developmental shift from alpha 2 or 3 (GABRA2 or GABRA3) to alpha 1 (GABRA1) subunits, which attribute faster kinetics of the inhibitory post-synaptic currents (IPSCs) and higher sensitivity to benzodiazepines [17, 47, 60]. In addition, $GABA_AR$ signaling changes from depolarizing early in development to hyperpolarizing in more mature neurons, rendering $GABA_AR$-mediated inhibition more effective in older animals [70]. This is thought to be due to the developmental shift in the balance of the activity of cation/Cl^- cotransporters (CCCs) that control the intracellular Cl^- concentration to favor cotransporters that maintain high intracellular Cl^- (i.e., NKCC1) in immature neurons and low intracellular Cl^- in mature neurons (i.e., KCC2) [6, 26, 33, 90, 97]. The developmental increase in the expression and activity of KCC2, a Cl^- exporting transporter, and the parallel decrease in NKCC1 eventually reduce intracellular Cl-, permitting the appearance of hyperpolarizing $GABA_AR$ signaling in more mature neurons.

The presence of depolarizing $GABA_AR$ signaling is critical for normal development, as it promotes neuronal growth, differentiation and synaptogenesis, by controlling calcium-sensitive signaling processes. In parallel, KCC2 may also modify the development of glutamatergic synapses in dendritic spines via interactions with cytoskeletal proteins, like 4.1 N, independently of any effects on $GABA_AR$ regulation [62]. The absence of depolarizing $GABA_AR$ signaling early in life can either be incompatible with life or disrupt

neuronal differentiation and communication [6, 16, 26, 33, 43, 118, 119]. Considering the neurotrophic effects of depolarizing $GABA_AR$ signaling, it is not entirely surprising that depolarizing $GABA_ARs$ are also found in pathologic conditions that favor neuritic growth and differentiation so as to promote aberrant synaptogenesis, connectivity and re-wiring, as occurs in various forms of acquired, focal-onset epilepsies (Table 16.2). Indeed, depolarizing $GABA_AR$ signaling can be facilitated by neurotrophins, like brain-derived neurotrophic growth factor (BDNF), which are released after seizures [96].

Abnormal shifts in the CCC activity towards an NKCC1-dominant state or depolarizing $GABA_AR$ signaling have also been found in a number of pathological conditions predisposing to or leading to epilepsy, like trauma [11, 74], ischemia [45, 83], anoxia/glucose deprivation [36] as well as after kindling [80, 96] or during the latent or epileptic state in post-status epilepticus (SE) rodent models of epilepsy [7, 12, 13, 22, 87] (Table 16.2). Under such pathological conditions, the role of $GABA_AR$ signaling is not just to promote the healing and re-wiring of the brain but may acquire a pathogenic role, by promoting neuronal excitability, due to the impairment in inhibition. In further support, KCC2 deficient mice manifest early life epilepsy and histopathologic alterations reminiscent of hippocampal sclerosis [122]. Pharmacologic inhibition of depolarizing $GABA_AR$ signaling using the NKCC1 inhibitor bumetanide in combination with $GABA_AR$ agonists has shown antiseizure effects in certain seizure models [18, 25, 65, 68, 75, 94, 103], although model-, region-, age-, or time-dependent differences have been reported [65, 66, 68, 117, 127]. Administration of bumetanide with phenobarbital prior to seizure onset in the kainic acid induced SE model significantly enhanced the antiseizure effect of phenobarbital, in an age-dependent manner, that was attributed to the developmental decrease in NKCC1 expression [25]. Similarly, bumetanide inhibited rapid kindling of PN11 Wistar rats when it was administered prior to kindling stimuli [68] or hypoxic seizures when given prior to hypoxia in PN10 rats, even though the brain levels of bumetanide are significantly low [18]. On the other hand, in vitro studies demonstrated variable results of bumetanide when given after seizure onset that followed model, age, and region dependent patterns [54, 117]. In addition, NKCC1-knockout mice show greater susceptibility to 4-aminopyridine than wild type animals [127]. It is therefore possible that bumetanide administration prior to seizure onset and younger ages may facilitate its ability to enhance the antiseizure effects of $GABA_AR$ agonists. However it is also evident that model and region specific factors or other competing mechanisms may modify its effect.

Bumetanide has also been proposed to alleviate the febrile seizure-induced neurogenesis [56] and the post-SE epilepsy-associated behavioral deficits [14], but has not been shown to have antiepileptogenic effects in post-SE epilepsy or an in vitro model [14, 75]. Depolarizing $GABA_AR$ signaling also renders the injured neurons dependent upon neurotrophic factors, like BDNF, for survival, by augmenting the expression of the pan-neurotrophin receptor $p75^{NTR}$ [108]. Neurons with depolarizing GABA signaling are therefore more amenable to dying in injured areas, which are deprived of BDNF.

Epilepsy and seizures have also been associated with disruption in the normal developmental patterns of expression of the subunits of GABAARs (see Table 16.3). In certain – but not all – cases these reflect a return to a more immature type of $GABA_AR$ subunit composition, as

in studies demonstrating a reduction in the α1 subunit, whereas in others they indicate disrupted development [47]. Changes in GABAAR subunits may contribute to either drug refractoriness [15] or epileptogenesis [93] or the development of comorbidities.

Most of the above studies have been done in either adult animals or are derived from individuals with drug-resistant epilepsy that underwent surgical resection of the epileptogenic focus at ages when the brain is relatively more mature. Age-specific patterns of regulation by seizures have been extensively shown for the seizure-induced changes in $GABA_AR$ subunits [126].

Similarly, the effects of neonatal seizures on $GABA_AR$ signaling and CCCs are not only age [32, 53] but sex-specific as well [32]. Kainic acid induced SE in PN4–6 rats accelerated the switch to hyperpolarizing $GABA_AR$ signaling in the CA1 pyramidal neurons of males, due to an increase in KCC2 expression and decrease in NKCC1 activity [32]. In contrast, kainic acid induced SE in PN4–6 female rats, in which $GABA_AR$ signaling is not depolarizing, causes a transient return to the depolarizing signaling mode due to an increase in NKCC1 activity [32]. In this study, the sexually dimorphic response to neonatal seizures seemed to depend upon the earlier maturation of $GABA_AR$ signaling in the female hippocampus, attributed to a higher expression of KCC2 and lower NKCC1 activity in females [32]. Sex differences in the expression of KCC2 and NKCC1 or GABAAR signaling in the hippocampus have also been confirmed in other studies [73, 79]. In addition, brief kainic acid seizures augment the activity of KCC2 shortly after induction of seizures in neonatal male rats [53]. It should be noted however that these studies relate to the postictal – acute or subacute – stages of neonatal SE. During the acute ictal phase of the SE, there is plenty of evidence to support that GABAAR signaling becomes depolarizing [25, 52].

The consequences of these seizure effects on the direction of GABAAR signaling could impact upon the subsequent susceptibility of the animal to seizures, affect its ability to stop seizure propagation, or alter cognitive abilities. For example, activation of GABAAR signaling in the anterior substantia nigra pars reticulata (SNR) in rats has important age and sex specific role in controlling seizure propagation in the flurothyl model [114, 115]. Exposure of male and female PN4–6 rats to kainic acid induced SE, at the time when $GABA_AR$ signaling is depolarizing, causes a precocious appearance of hyperpolarizing $GABA_AR$ signaling due to increase in KCC2 expression [35] and disrupts the $GABA_AR$-sensitive anticonvulsant function of the anterior SNR in the flurothyl seizure model (unpublished data). It is possible that the early deprivation of the SNR of the neurotrophic effects of the depolarizing GABAAR signaling effects may impair its development, leading to these long-lasting deficits.

16.4 Other Immature or Dysmature Features Associated with Epilepsies

Seizures may cause long-lasting changes in other signaling pathways involved in neurodevelopmental plasticity. The mTOR pathway has attracted a lot of research interest recently because it is central to cellular differentiation and growth. The mTOR pathway may become dysregulated in several seizure and epilepsy models [34, 92, 111, 121, 125] even if not necessarily caused by genetic disruption of components of the mTOR pathway. The

ability of rapamycin, an mTOR inhibitor, to suppress epilepsy in these models as well as prevent or reverse certain of the histopathological or cognitive abnormalities has supported its role as a potential epileptostatic and potentially disease-modifying treatment. We use the term “epileptostatic” (i.e., epilepsy is on hold) to indicate that inhibition of the expression of epilepsy and associated histopathological abnormalities occur only in the presence of mTOR inhibition but re-appear after the mTOR inhibitor is withdrawn. Other neurodevelopmental processes may also be affected, such as excitatory signaling or myelination. A neonatal brief kainic acid seizure may reduce the surface expression of the NMDA receptor (NR) subunit that normally emerges through developmental maturation, NR2A [21]. Seizures during the period of myelination can halt or impair myelination in both animal and human studies [24, 50, 91].

Loss of dendritic spines and less frequently shortening of dendritic length or abnormal dendritic branching patterns may be seen in patients with TLE or focal epilepsies [5, 10, 31, 44, 71, 102, 116]. Whether dendritic pathologies cause epilepsy is a matter open for investigation. Certainly many known etiologies of epilepsies demonstrate similar dendritic pathologies, including Rett syndrome [2] and tuberous sclerosis (TSC) [112] implicating the affected pathways (MeCP2, mTOR) in their pathogenesis. However the evidence that dendritic pathology causes epilepsy is currently lacking. Animal studies of seizures or epilepsy, in models like kindling, iron-induced cortical epilepsy, tetanus toxin model, or post-SE models of epilepsy have demonstrated similar dendritic abnormalities suggesting that seizures may impair dendritic architecture and spine development [1, 39, 49, 57, 77, 120, 125]. The lack of selectivity of the dendritic abnormalities for the epileptogenic focus, rather poses this feature as contributory to the overall neuronal dysfunction and seizure-associated comorbidities and to a lesser degree as causative of epilepsy.

In addition, dysplastic lesions may be encountered in pathological specimens from patients with TLE [9]. These can be found as clusters of granular neurons in layer 2 of the neocortex, nodular heterotopias in the temporal lobe, or heterotopic isolated neurons in the gray-white matter junction or deep subcortical white matter. It is currently unclear whether these dysplastic lesions are causative of or secondary to TLE. However, the possibility that such lesions may predispose to the development of TLE is supported by studies that demonstrate epileptogenic potential of these dysplastic lesions [27] as well as the animal studies demonstrating the pro-epileptogenic potential of pre-existing dysplastic lesions in two-hit seizure models [37, 99].

16.5 Conclusions

Seizures and several pathologies predisposing to focal-onset epilepsies may trigger the reacquisition of immature features in mature neurons that are integrated in the epileptogenic focus. The appearance of these immature features is influenced by age and sex-specific factors, at least for certain of the events that precipitate epilepsies. We propose that this untimely re-acquisition of the immature features is not equivalent to rejuvenation of the brain but may rather represent a de-synchronization of the homeostatic mechanisms that were in place to maintain normal physiology. In other words the maladaptive interactions and integration of these immature components with otherwise appropriately functioning

brain regions may contribute to the increased excitability and underlying pathological changes seen in the epileptic focus. Furthermore, such effects may disrupt normal brain development, leading to long-lasting impairments in networks that are critical for either seizure control, like the SNR, or for information processing leading to cognitive dysfunction.

A number of important unresolved questions arise. Under which conditions does the untimely presence of immature features and functions in the seizure-exposed brain promote epileptogenesis or cognitive decline? Conversely, what are the factors that can compensate and prevent disease progression? Are these functional changes different in epileptogenic foci than in regions that are secondarily affected by propagated seizures and why? What are the mechanisms leading to seizure-induced neurogenesis and how are these modified by age or sex or seizure-specific factors? Under which conditions might aberrant neurogenesis or abnormal GABAAR signaling have a pathogenic role in epileptogenesis or cognitive processes? What is the key switch mechanism that shifts depolarizing $GABA_AR$ signaling from promoting neurotrophic and healing processes in seizure-exposed or injured brains to facilitating excitability, seizure maintenance, and potentially epileptogenesis? Does the altered expression of $GABA_AR$ subunits in post-seizure or epileptic brain impair inhibition or could it, in certain situations, protect from the potentially excitatory effects of depolarizing GABA? It is evident from the examples presented in Tables 16.1, 16.2 and 16.3, that there is significant variability across studies, animal models, disease states, and regions suggesting that the answer may not be ubiquitous. Therefore, even if certain answers may be obtained in specific experimental paradigms, it is critical to be able to translate them into the human situation and, most specifically, to a specific individual in need of specific prognosis or treatment after a specific insult. Identifying markers that will enable us to detect and follow longitudinally, in vivo, the evolution of these changes and their functional alterations would be critical in both validating their significance and implementing individualized targeted treatments to prevent disease progression.

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Table 16.1

Effects of seizures on neurogenesis in the dentate gyrus

Animal characteristics	Model of seizures	Effect on neurogenesis in the dentate gyrus	Reference
PN0–4 Sprague-Dawley rats	PN0–4 flurothyl seizures (brief, repetitive)	1–5 brief flurothyl seizures had no effect on neurogenesis	[69]
		25 flurothyl seizures over 4 days ***reduced*** neurogenesis in the dentate	
PN1–7 Wistar rats	Recurrent pilocarpine SE (PN1, PN4, PN7)	***Reduced*** neurogenesis on PN8, PN14	[124]
	BrdU (PN7, PN13, PN20, PN48)	***Increased*** neurogenesis on PN49	
PN9 rats	PN9: kainic acid SE (2–3 h)	***Reduced*** neurogenesis in the superior blade of the dentate	[59]
	BrdU: 3 h after kainic acid		
PN6–20 Sprague-Dawley rats	1–3 episodes of kainic acid SE between PN6–20	***Reduced*** number of BrdU-positive neurons in rats with 3 SEs, assessed on PN13, PN20, PN30, but not at earlier timepoints	[63]
	BrdU after each seizure and 4 h prior to sacrifice		
PN10	PN10: Hyperthermic seizures (<30 min)	Normothermia-exposed males had more BrdU-positive cells than females	[61]
Sprague-Dawley male, female rats	PN11–16: Brdu injections	Hyperthermia had ***no acute effect*** on neurogenesis (assessed at PN17)	
		Following hyperthermic seizures, newborn neurons in males ***survived better*** till PN66 than in females	
PN15 Sprague-Dawley rats	PN15: flurothyl SE	***Increased*** neurogenesis after SE	[78]
	PN17: BrdU injection	Further increased in malnourished animals	
PN21, PN35 Sprague-Dawley rats, both sexes	Lithium-pilocarpine SE	***Increased*** neurogenesis in both age groups	[98]
	BrdU 3th-6th day after SE	No association with cell loss or subsequent probability for epilepsy	
Adult	Pilocarpine-SE (3–5 h)	***Increased*** neurogenesis at 3, 6, and 13 days post-pilocarpine SE	[86]
Sprague-Dawley rats	BrdU: 1–27 days post-pilocarpine		
Adult	Pilocarpine or kainic acid induced SE (1 h)	Newborn neurons born after SE migrate into the CA3 layer, maintain many granule cell characteristics (electrophysiological, morphological). However, they are NPY or GAD negative, have bipolar dendrites, and integrate abnormally, firing synchronously to CA3 pyramidal neurons	[100]
Sprague-Dawley rats	BrdU: 4–11 or 26–30 days post SE		
Adult female mice (nestin-GFP transgenic mice)? (8 week old)	Kainic acid SE (2–3 h)	***Increased*** neurogenesis post-SE seen with the doublecortin positive neurons but not with the nestin or calretinin positive neurons	[48]
	BrdU: 8 days post SE	Increased dispersion of newborn cells was seen with both doublecortin and calretinin positive neurons after SE	
Adult male Sprague- Dawley rats	Amygdala kindling	***Increased*** neurogenesis after >9 stage 4–5 seizures but not after 4–6 seizures	[84]
	BrdU: 1 day after last kindled seizure or stimulation	Neurogenesis may not play a role in kindling development	
Adult male Wistar rats	Amygdala kindling	***Increased*** neurogenesis seen only at the BrdU late group (after stage 5 seizures)	[105]

Animal characteristics	Model of seizures	Effect on neurogenesis in the dentate gyrus	Reference
	BrdU early group: on the 2nd-4th stimulation days		
	BrdU late group: on the days of their 2nd-4th stage 5 seizure		
Adult C57BL/6J mice	Flurothyl kindling	***Increased*** neurogenesis after:	[28, 29]
	BrdU injections 0–28 days after 1 or 8 flurothyl seizures	1–3 days following 1 seizure	
		0–7 days after 8 seizures	
		Greater degree of neurogenesis in dorsal than in ventral hippocampus, but the seizure induced increase in newborn cells was greater in the ventral hippocampus	
Adult F344 rats (4 months old)	Kainic acid i.c.v. or graded kainic acid SE (<6 h) i.p.	*16 days post-SE: Increased* number of doublecortin positive neurons in the dentate	[40]
		5 months after SE: decreased numbers of doublecortin positive neurons in the dentate	
Adult F344 rats (12 month old)	Kainic acid SE (i.p.)	***Increased*** neurogenesis in the dentate, but to a less degree than in younger rats	[106]
	BrdU: day 0–12 after SE		

Seizures have age and model-specific effects on neurogenesis in the dentate gyrus

BrdU bromodeoxyuridine, *GAD* glutamic acid decarboxylase, *GFP* Green fluorescent protein, *i.c.v* intracerebroven- tricular, *i.p.* intraperitoneal, *NPY* neuropeptide Y, *PN* postnatal day, *SE* status epilepticus

Table 16.2

Epilepsies associated with depolarizing $GABA_AR$ signaling

Epilepsy type/animal model	Stage in epilepsy	Findings	Reference
Human epilepsies			
Human TLE	Following surgery for intractable epilepsy	*Subiculum*	[19,42]
		Depolarizing $GABA_AR$ signaling	
		Bicuculline inhibits interictal epileptic discharges in vitro	
		Higher probability for depolarizing $GABA_AR$ in KCC2-negative neurons	
		Microinjections of hippocampal/temporal lobe extracts in Xenopus oocytes yield depolarizing $GABA_AR$ and high NKCC1 and low KCC2 mRNA expression	[81]
		Lower probability for NKCC1 to colocalize with KCC2 in epileptic subiculum / CA1	[72]
Human epilepsy due to hypothalamic hamartomas	Following surgery for intractable epilepsy	Depolarizing $GABA_AR$ signaling in hypothalamic hamartomas	[55]
Human epilepsy due to cortical dysplasias	Following surgery for intractable epilepsy	Reduced KCC2 expression in focal cortical dysplasias	[107]
		TSC, FCD type IIB	[110]
		Increased NKCC1, reduced KCC2	
		TSC (single case)	
		Depolarizing $GABA_AR$ signaling	
		FCD type IIA	
		Increased NKCC1 and KCC2	
		FCD type I or II	[47]
		Abnormal developmental changes in the expression of NKCC1, KCC2	
		Increase in NKCC1, altered subcellular expression of KCC2 in cortical malformations (FCD type IIB, hemimegalencephaly, gangliogliomas)	[3]
Tumor-associated human epilepsy	Peritumoral cells	Increased NKCC1 expression	[20]
Animal models of epilepsy			
Post-SE epileptic rats, pilocarpine model, male Wister rats	Latent phase, 3 weeks post-SE	Depolarizing $GABA_AR$ signaling in layer 5 entorhinal cortex but not in entorhinal layer 3, subiculum, dentate gyrus, or perirhinal cortex.	[13]
Post-SE epileptic rats, pilocarpine model, adult male Sprague- Dawley rats	Established epilepsy, 2–5 months after SE	Depolarizing $GABA_AR$ signaling in granule cells of the dentate gyrus, insular, subicular neurons or the deep layers of the piriform cortex	[7, 12, 22, 87]

Epilepsy type/animal model	Stage in epilepsy	Findings	Reference
		Reduction of KCC2 expression in the dentate gyrus, subiculum or the deep layers of the piriform cortex	

Abnormal shift to depolarizing $GABA_AR$ signaling and/or expression of cation chloride cotransporters KCC2 and NKCC1 have been described in both human tissue derived from epileptogenic areas of patients with epilepsies, as well as in animal models of epilepsy

FCD Focal cortical dysplasia, *SE* status epilepticus

Table 16.3

Abnormalities in $GABA_AR$ subunit expression in human epilepsies and animal models of SE or epilepsies

Epilepsy type/animal model	Stage in epilepsy	Findings	Reference
Human epilepsies			
Human TLE	Following surgery for intractable epilepsy	Decreased GABRA3 protein in temporal neocortex (layers I-III), no change in GABRA1 or GABRA2	[64]
		Increased GABRA3, GABRA5, GABRB1, GABRB2, GABRB3 mRNA in subiculum compared to neocortex	[82]
		Decreased GABRG2 mRNA in subiculum compared to neocortex	
		Decreased GABRA1, GABRA3, GABRB3, GABRG2 protein expression in sclerotic but not in nonsclerotic hippocampus (CA1)	[89]
		Increased GABRB1, GABRB2, GABRB3 protein expression in both sclerotic and nonsclerotic hippocampus	
Human mesial TLE	Following surgery for intractable epilepsy	No change in GABRA1, GABRB1, GABRB2 mRNA expression in the amygdala	[23]
Human epilepsy due to hypothalamic hamartomas	Following surgery for intractable epilepsy	No change in GABAAR subunit mRNA	[123]
Human epilepsy due to cortical dysplasias	Following surgery for intractable epilepsy	*TSC, FCD type IIB*	[110]
		Decreased GABRA1 protein	
		FCD type IIA	
		Decreased GABRA4 protein	
		FCD type I or II	[47]
		Abnormal developmental changes in the expression of GABRA1, GABRA4, GABRG2 protein	
Animal models of SE or epilepsy			
Post-SE, pilocarpine model, PN10 rats	Nonepileptic (adult)	*In dentate gyrus granule cells*	[126]
		Increase in GABRA1 mRNA	
		No change in GABRA4, GABRD mRNA	
Post-SE rats, pilocarpine model, adult male Sprague- Dawley rats	1–8 days post-SE	*In CA1 pyramidal neurons*	[38]
	Decrease in GABRA4, GABRB2/3, GABRG2, gephyrin protein		
Post-SE rats, pilocarpine model, adult rats	1–5 months post-SE	*In dentate gyrus granule cells (hippocampus)*	[15]
		Decrease in GABRA1, GABRB1 mRNA	

Epilepsy type/animal model	Stage in epilepsy	Findings	Reference
		Increase in GABRA4, GABRB3, GABRD, GABRE mRNA	
Post-SE rats, kainic acid, adult male Sprague-Dawley	1 month post-SE	*In dorsal hippocampus*	[104]
		Increase in GABRA1, GABRA2, GABRA4, GABRB2, GABRB3, GABRG2 protein	
		Decrease in GABRD	
Post-SE rats, kainic acid, adult male Sprague- Dawley rats	7–30 days post SE	*In dorsal hippocampus*	[113]
		Decrease in GABRA5 and GABRD mRNA	
Post-SE, Electrically induced, adult male Sprague-Dawley rats	7–30 days post SE	*In dorsal hippocampus*	[76]
		Increase in GABRA1, GABRA4, GABRB1, GABRB2, GABRB3 mRNA	
		Decrease in GABRD mRNA	
Post-SE rats, pilocarpine, adult male Sprague- Dawley rats	3–4 months post-SE	*In CA1, CA3 pyramidal neurons*	[41]
		Decrease in GABRA5 protein	
Post-SE rats, electrical stimulation of the amygdala, adult male Sprague-Dawley rats	Epileptic rats	*In hippocampus*	[58]
		Increase in GABRB3 mRNA (all regions)	
		Decrease in GABRA2 mRNA (CA3c) and GABRA4 mRNA (CA1)	
Post-SE, pilocarpine model, adult Wistar rats	Epileptic rats	*In cerebral cortex*	[67]
		Decrease in GABRA1, GABRG3, GABRD mRNA	
		Increase in GABRA5 mRNA	
Post-SE, electrical stimulation of amygdala, adult female Sprague- Dawley rats	Epileptic rats	*In hippocampus*	[8]
		Phenobarbital non-responders are more likely to have reduced GABRA1, GABRB2/3, GABRG2 protein expression in the hippocampus than responders	

SE and epilepsies have different effects upon the expression of $GABA_AR$ subunits (GABR). Their effects depend upon the type and/or model of SE or epilepsy, age at seizure occurrence, the region and time point after seizures when the study is conducted, and the specific subunit examined