

---

# Is Plasticity of GABAergic Mechanisms Relevant to Epileptogenesis?

11

Helen E. Scharfman and Amy R. Brooks-Kayal

---

## Abstract

Numerous changes in GABAergic neurons, receptors, and inhibitory mechanisms have been described in temporal lobe epilepsy (TLE), either in humans or in animal models. Nevertheless, there remains a common assumption that epilepsy can be explained by simply an insufficiency of GABAergic inhibition. Alternatively, investigators have suggested that there is hyperinhibition that masks an underlying hyperexcitability. Here we examine the status epilepticus (SE) models of TLE and focus on the dentate gyrus of the hippocampus, where a great deal of data have been collected. The types of GABAergic neurons and GABA<sub>A</sub> receptors are summarized under normal conditions and after SE. The role of GABA in development and in adult neurogenesis is discussed. We suggest that instead of “too little or too much” GABA there is a complexity of changes after SE that makes the emergence of chronic seizures (epileptogenesis) difficult to understand mechanistically, and difficult to treat. We also suggest that this complexity arises, at least in part, because of the remarkable plasticity of GABAergic neurons and GABA<sub>A</sub> receptors in response to insult or injury.

---

## Keywords

GABA • GABA<sub>A</sub> receptor • Interneuron •  $\alpha$ 1 subunit • Chloride channel • Granule cell • Adult neurogenesis • Status epilepticus • Febrile seizures • Aberrant neurogenesis • Ectopic granule cell

---

H.E. Scharfman (✉)  
The Nathan S. Kline Institute for Psychiatric  
Research, Orangeburg, NY, USA

Departments of Child & Adolescent Psychiatry,  
Physiology & Neuroscience, and Psychiatry,  
New York University Langone Medical Center,  
New York, NY, USA  
e-mail: [hscharfman@nki.rfmh.org](mailto:hscharfman@nki.rfmh.org)

---

A.R. Brooks-Kayal  
Departments of Pediatrics, Neurology and  
Pharmaceutical Sciences, University of Colorado  
School of Medicine, Aurora, CO 80045, USA

Skaggs School of Pharmacy and Pharmaceutical  
Sciences, Aurora, CO 80045, USA

Children's Hospital Colorado,  
Aurora, CO 80045, USA

## 11.1 Introduction

In the nineteenth century, the idea that epilepsy was a brain disorder arose as a consequence of the relatively new discipline of neurology. In the latter half of the twentieth century, many studies showed that chemicals such as penicillin, a GABA<sub>A</sub> receptor (GABA<sub>A</sub>R) antagonist, caused experimental seizures or epileptiform activity when applied to the neocortex of animals. Philip Schwartzkroin played a major role in the development and refinement of these ideas by the use of the hippocampal slice preparation [131, 132, 152]. One view that emerged was that epilepsy might be caused by defects in inhibition, which was supported by pharmacological experiments showing that several anticonvulsants, such as the barbiturates and benzodiazepines, exerted their actions by facilitating the actions of GABA at GABA<sub>A</sub>Rs [88, 109].

The idea that epilepsy is caused by insufficient GABAergic inhibition has developed more support as it has become clear that some types of GABAergic neurons are vulnerable in animal models of epilepsy, or lost in tissue resected surgically from patients with intractable epilepsy [78, 126, 127]. In addition, mutations in the subunits of the GABA<sub>A</sub> receptor have been identified as a basis of some genetic epilepsy syndromes, such as Genetic Epilepsy with Febrile Seizures+ (GEFS+) which can be caused by a point mutation in the *GABRG<sub>2</sub>* gene which normally encodes the  $\gamma$  subunit of the GABA<sub>A</sub>R [4, 159]. However, many arguments have also been made that epilepsy cannot be explained solely by a defect in GABAR-mediated inhibition. Some of the opposing views have come from studies of GABAergic agonists, which exacerbate some types of seizures instead of inhibiting them. For example, drugs that enhance GABAergic inhibition increase absence seizures instead of suppressing them. The explanation is related to the actions of GABA at GABA<sub>B</sub> receptors on thalamocortical relay cells. By enhancing the actions of GABA to hyperpolarize relay cells, T-type Ca<sup>2+</sup> current in relay cells are strongly deactivated, leading to more robust bursts of

action potentials in relay cells when the hyperpolarizations end; these rebound bursts drive the thalamocortical oscillation [58, 141].

In the last 20 years, a wealth of new information about GABA and GABA<sub>A</sub>Rs has been published using animal models of epilepsy and clinical research. One of the complexities that has emerged is the plasticity of GABAergic mechanisms. This plasticity is remarkable because it involves many aspects of GABAergic transmission: the numbers of GABAergic neurons and the locations of their axons; the synthesis, release and uptake of GABA; and alterations in GABA receptors. Although the contribution of GABAergic mechanisms, and their plasticity, to epilepsy is still an area of active research, it seems unlikely that there is simply too little GABA in epilepsy – or too much. Instead, GABAergic transmission is very different in epilepsy compared to the normal brain. This concept, that GABAergic inhibition is not simply deficient in epilepsy, is consistent with the relatively normal function of individuals with epilepsy during the interictal state.

We discuss below the basic characteristics of GABAergic transmission in the normal and epileptic condition to clarify this idea. For the epileptic condition, we focus on temporal lobe epilepsy (TLE) where this concept appears to be particularly relevant. We also focus on the dentate gyrus (DG) in animal models where status epilepticus (SE) is used to produce spontaneous recurrent seizures and simulate acquired TLE. The reason for this focus is that the data that are available for this context are extensive. However, these models have been criticized because they do not simulate all aspects of TLE.

Most of the discussion below addresses the ways that GABAergic circuitry are changed by SE and alterations in GABA<sub>A</sub>Rs in DG granule cells (GCs). Presynaptic GABA<sub>A</sub>Rs and effects of GABA<sub>A</sub>Rs on other cell types are also important to consider in the context of the DG and epilepsy, and are reviewed elsewhere [70]. Regulation of GABA<sub>A</sub>Rs by phosphorylation also has implications for the dynamics of GABAergic transmission in epilepsy; effects relevant to the DG are discussed below and

additional issues are described elsewhere [83, 155]. Finally, GABA<sub>B</sub>Rs clearly have a role in epilepsy, but are outside the scope of this discussion and readers are referred to excellent reviews published previously [14, 84].

## 11.2 GABAergic Transmission in the Normal Adult Dentate Gyrus (DG)

### 11.2.1 GABAergic Neurons in the DG of the Adult Rodent

Figure 11.1 illustrates the fundamental circuitry of the DG in the normal adult rodent [2]. The principal cell of the DG is the granule cell (GC), which uses glutamate as its primary neurotransmitter, but also has the capacity to synthesize GABA, especially after seizures (discussed further below). GCs also synthesize numerous peptides that are packaged in dense core vesicles and behave as co-transmitters [55]. The peptides are numerous: dynorphin [25], leu-enkephalin [153], brain-derived neurotrophic factor [125], and others. The major afferent input to the GCs is the perforant path projection from entorhinal cortical neurons in layer II [161]. The GCs form the major output from the DG, the “mossy fiber” pathway, which innervates neurons in the hilus and area CA3 [2]. There is another glutamatergic neuron in the DG, located in the hilus, which is called a mossy cell (for reviews see [53, 126]). The major afferent input to mossy cells comes from the GCs, and mossy cells project to GCs and GABAergic neurons within the DG [126].

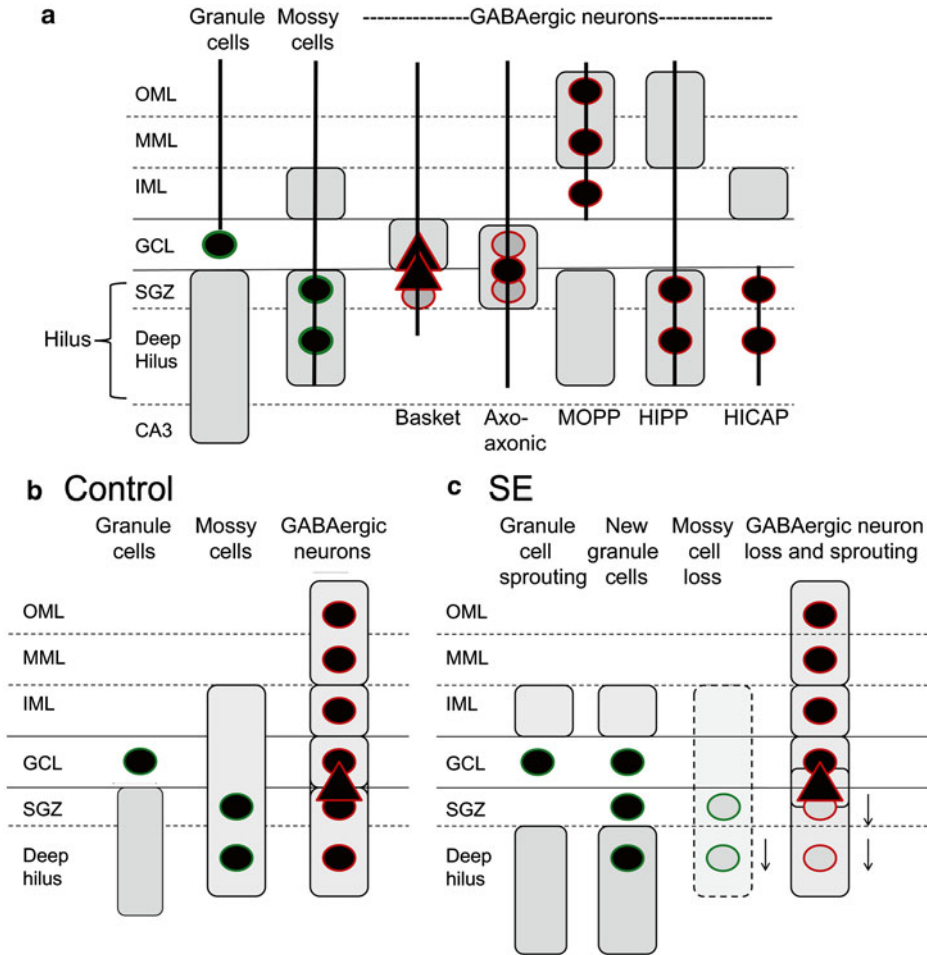
There are many other types of neurons in the DG, and they use GABA as a neurotransmitter. Most of the GABAergic neurons have an axon that projects primarily in the area surrounding the cell body, similar to other cortical circuits where most of the GABAergic neurons are local interneurons. However, there are several subtypes of DG interneurons that also have axons that project to distant areas of the DG, such as the contralateral DG [34, 49]. Like GCs, GABAergic neurons of the DG also use peptides as co-transmitters [55, 138], and after seizures, some of the peptides in

GCs are the same peptides as those in GABAergic neurons (e.g., neuropeptide Y; NPY; [120]).

The primary type of GABAergic neuron in the DG is the basket cell, which makes basket-like endings around GC somata. It initially was described as a pyramidal-shaped neuron with somata at the base of the GC layer (on the border of the GC layer and the hilus) but the location, somatic morphology and other characteristics are actually diverse [115]. Furthermore, some of the basket cells with pyramidal shaped somata have axons that project to the contralateral DG [49]. There also is variation in neuropeptide content in pyramidal-shaped GABAergic neurons, ranging from parvalbumin, cholecystokinin, to substance P [55, 81, 139]. Electrophysiologically, these cells also vary, although they fit the general characteristics of interneurons because they have a very large afterhyperpolarization following single action potentials [115]. They inhibit their postsynaptic targets by opening chloride channels of GABA<sub>A</sub>Rs at the soma. Because the resting potential of GCs is close to the reversal potential for chloride or hyperpolarized to it, chloride entry depolarizes the GC rather than hyperpolarizing it, shunting currents that would otherwise reach threshold for action potential (AP) generation; for this reason, “shunting inhibition” is probably the main inhibitory effect of basket cells, rather than hyperpolarization.

Another very important inhibitory cell type also inhibits AP generation of GCs, but is slightly different because it primarily innervates the axon hillock, rather than the somata of GCs. This cell type, the axo-axonic cell, is similar to chandelier cells in neocortex [142] in that chandelier-type endings envelope the axon hillock of GCs. The cell bodies of axo-axonic cells are variable and many types of neuropeptides are co-localized with GABA. The intrinsic electrophysiology of axo-axonic cells is consistent with fast-spiking interneurons [22].

Another type of DG interneuron is the so-called HIPP cell, named because it has a *H*ilar cell body and projects to the outer 2/3 of the molecular layer, where the *p*erforant *p*ath projection terminates. This neuronal subtype usually expresses somatostatin and NPY [145] and has



**Fig. 11.1 DG circuitry in the normal adult rodent and following status epilepticus (SE).** (a) Circuitry of the normal rodent DG is shown schematically. Cell bodies outlined in *green* are glutamatergic; those cells outlined in *red* are GABAergic. *Black circles* indicate the primary location of the somata; *grey circles* are secondary locations. *Grey rectangles* indicate the location of the axon terminals. Abbreviations of the lamina of the DG are as follows: *OML* outer molecular layer, *MML* middle molecular layer, *IML* inner molecular layer, *GCL* granule cell layer, *SGZ* subgranular zone. MOPP, molecular layer cell body, axon in the terminal field of the perforant

path; HIPP, hilar cell body, axon in the terminal field of the perforant path. HICAP, hilar cell body, axon in the terminal field of the commissural/associational projection (Adapted from Freund and Buzsaki [42]). (b) A summary of a. (c) Changes in the DG circuitry following SE are diagrammed. After SE, changes are as follows: GC axons sprout into the IML; newborn GCs are born and some migrate into the hilus and GCL; many mossy cells are lost (indicated by the *arrow*, *light cell body color* and *dotted line* around the axon plexus); some GABAergic neurons are lost and others sprout into several layers (For references, see text)

axon collaterals primarily in the molecular layer [52], with a less dense projection in the hilus [35]. It has been suggested that it inhibits the EPSPs produced by the perforant path input, presumably by innervating GC dendrites and shunting EPSPs traveling to the GC soma. HIPP cells may

also inhibit glutamate release from perforant path terminals because they make synapses on the terminals [80]. The electrophysiology of HIPP cells is characteristic of interneurons generally [44], but it has been noted that they are relatively slow spiking [2, 115] and have a pronounced

'sag' in response to hyperpolarizing current commands [89]. This cell type has attracted a lot of attention in epilepsy research because these cells are relatively vulnerable to insults or injury [116, 126]. Several mechanisms have been proposed for their vulnerability, such as STAT3 expression [29]. It has also been shown that p75<sup>NTR</sup> receptors are present on the septocholinergic terminals that innervate the HIPP cells, and can cause their death when the septocholinergic pathway is lesioned [37, 38].

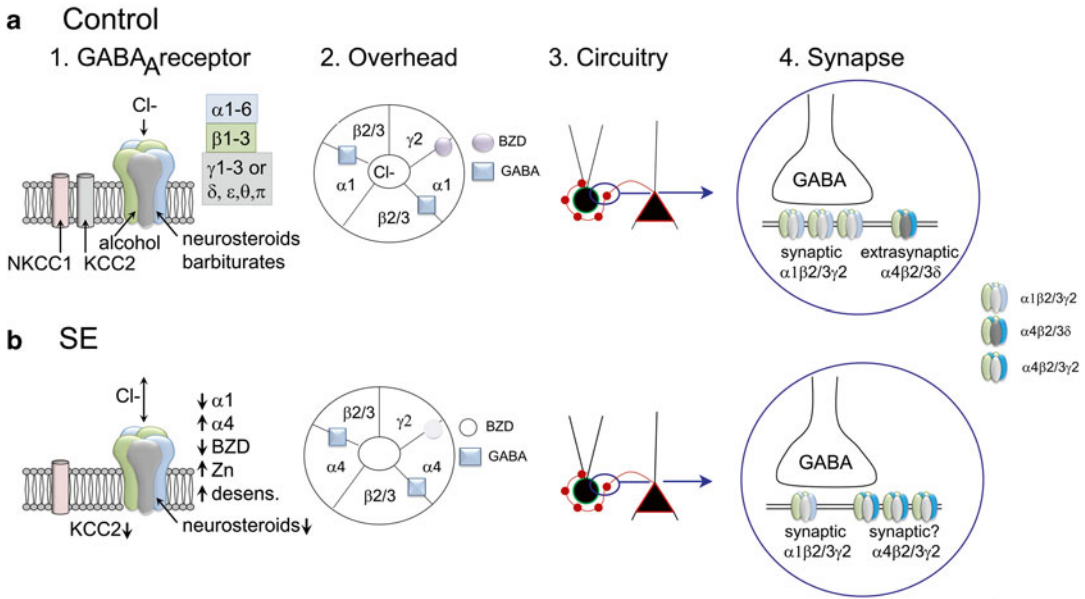
Analysis of the numbers of GABAergic neurons using immunocytochemical markers and stereological techniques has led to estimations that the majority of DG interneurons are basket cells or axo-axonic cells, which express parvalbumin or CCK. The other major subtype of DG interneuron is hilar HIPP cells, which co-express GABA and NPY or somatostatin (for reviews see [55, 81]). However, many other types of DG interneurons exist: MOPP cells [28], ivy cells and neurogliaform cells [3] and hilar neurons that innervate the inner molecular layer (HICAP cells; [51, 52]).

The major afferents to DG interneurons are the perforant path, GCs, and mossy cells. In addition, there is extrinsic input from the ascending serotonergic, cholinergic, and noradrenergic nuclei. The primary effects appear to be inhibitory [41]. In addition, there are additional inputs to the DG from areas outside the hippocampus that are not well understood functionally, such as the supramammillary input [74]. Many neuromodulators, such as endocannabinoids, have been shown to exert striking effects in the DG [40], but how all the neuromodulators act in concert in the awake behaving animal is still unclear.

### 11.2.2 GABA Receptors in the Normal Adult GC

Post-synaptic GABA<sub>A</sub>Rs mediate most fast synaptic inhibition in the forebrain (Fig. 11.2). GABA<sub>A</sub>Rs are heteromeric protein complexes composed of multiple subunits that form ligand-gated, anion-selective channels whose properties

are modulated by barbiturates, benzodiazepines, zinc, ethanol, anesthetics and neurosteroids. There are several different GABA<sub>A</sub>R subunit families and multiple subtypes exist within each of these subtypes ( $\alpha$ 1-6,  $\beta$ 1-4,  $\gamma$ 1-3,  $\delta$ ,  $\epsilon$ ,  $\pi$ ,  $\Phi$ ). The most common GABA<sub>A</sub>R is the  $\alpha$ 1 $\beta$ 2 $\gamma$ 2 subtype, but multiple subtype combinations exist and they vary in different brain regions and cell types, and during different times in development [73, 111, 134]. Subunit composition of GABA<sub>A</sub>Rs plays a major role in determining the intrinsic properties of each channel, including affinity for GABA, kinetics, conductance, allosteric modulation, probability of channel opening, interaction with modulatory proteins, and subcellular distribution [77, 97, 134]. For example, alterations in the  $\alpha$ -subtype results in differences in receptor kinetics, membrane localization and GABA<sub>A</sub>R modulation by benzodiazepines and zinc [87, 97, 140, 154]. In the GC, GABA<sub>A</sub>Rs that contain  $\alpha$ 1 subunits paired with  $\gamma$ 2 subunits are sensitive to benzodiazepines and generally located at the synapse, contributing to phasic inhibition, a term that refers to the effects of GABA released at GABAergic synapses that binds to postsynaptic receptors located at the synaptic cleft. These effects are primarily related to increased conductance when chloride channels open, and hyperpolarization of postsynaptic membrane potential when chloride influx occurs. However, as mentioned above, when the postsynaptic membrane potential is hyperpolarized relative to  $E_{Cl^-}$ , which may occur in GCs, there is a depolarization. GABA<sub>A</sub>Rs that contain  $\alpha$ 4 subunits have unique pharmacological properties, such as insensitivity to benzodiazepines and increased sensitivity to zinc blockade. Receptors containing  $\alpha$ 4 subunits are most often found with the  $\delta$  rather than the  $\gamma$  subunit in combination with  $\alpha\beta$ . These  $\alpha$ 4 $\beta\delta$  GABA<sub>A</sub>Rs are localized to extrasynaptic sites and contribute to tonic inhibition, which refers to the basal inhibitory current produced by low concentrations of extracellular GABA that are present outside of the synapse (resulting from diffusion from synaptic to extrasynaptic space). Under physiological conditions, only a minor population of  $\alpha$ 4 $\beta\gamma$ 2 GABA<sub>A</sub>Rs are found at synapses of GABAergic neurons on



**Fig. 11.2 GABA<sub>A</sub> receptor subunits in dentate gyrus (DG) granule cells (GCs) in the normal adult rodent and following SE.** (a) Control conditions. (1) The subunits of the GABA<sub>A</sub> receptor (GABA<sub>A</sub>R) are diagrammed, with sites of modulation noted. The location of the K<sup>+</sup>Cl<sup>-</sup> cotransporters NKCC1 and KCC2 are depicted schematically. (2) An overhead view of a typical GABA<sub>A</sub>R in a normal adult GC. It has  $\alpha 1$ ,  $\beta 2/3$  and  $\gamma 2$  subunits with two sites for GABA and a benzodiazepine (BZD) site for modulation. (3) The prototypical GABAergic neuron in the DG is the basket cell (triangle) which has an axon that encircles GC somata, making periodic GABAergic synapses. (4) A schematic of the GABAergic synapse in control conditions has synaptic  $\alpha 1\beta 2/3\gamma 2$  receptors and extrasynaptic

receptors that contain different subunits ( $\alpha 4\beta 2/3\delta$ ). (b) After SE, KCC2 expression decreases and the direction of chloride flux may change as a result. The expression of  $\alpha 1$  subunits decrease and  $\alpha 4$  subunits increase. Other changes are altered sensitivity to modulators. (2) One of the changes in the GABA<sub>A</sub>Rs in the DG after SE is loss of benzodiazepine sensitivity. (3) The pyramidal basket cell and its basket plexus appears to be similar after SE, although other GABAergic neurons are altered, and there may be changes in expression of various peptides. (4) The GABAergic synapse after SE has fewer  $\alpha 1$  subunits and increased  $\alpha 4$  subunits, which may become perisynaptic (indicated by a ?) (References are listed in the text. Parts 1–2 of this figure were adapted from Jacob et al. [59])

GCs, where they are proposed to affect both the rise time and decay of synaptic currents [71].

### 11.2.3 Regulation of [Cl]<sub>i</sub> in Early Development and Its Relevance to TLE

One of the characteristics of GABAergic inhibition at GABA<sub>A</sub>Rs that has implications for epilepsy – and has been studied extensively in the hippocampus in TLE – is the regulation of chloride flux through the GABA<sub>A</sub>R. The direction of chloride flux is regulated by many factors, and one source of regulation that has attracted a great deal of attention is the K<sup>+</sup>-Cl<sup>-</sup> cotransporters

KCC2 and NKCC1. KCC2 extrudes chloride normally, and NKCC1 transports chloride into the cell [7]. In early life, KCC2 expression is low and there is a relatively high concentration of intracellular chloride; chloride efflux occurs when GABA binds to the GABA<sub>A</sub>R, leading to a depolarization [8, 27]. After maturation, KCC2 expression increases and this leads to a lower [Cl]<sub>i</sub> and chloride influx when GABA binds to GABA<sub>A</sub>Rs, leading to a hyperpolarization [106]. As mentioned above, an exception is the GC, which has a resting potential (–70 to –80 mV) that is usually negative to E<sub>Cl<sup>-</sup></sub>. Therefore, in early life, a strong depolarization of GCs by GABA is predicted, and a smaller depolarization in adulthood compared to adulthood.



The idea that GABA is depolarizing in early postnatal life has recently been contested because most data that led to the idea were collected in slices where truncation of neuronal processes leads to elevated  $[Cl^-]_i$  [15]. However, *in vivo* studies have been conducted that are consistent with a depolarizing action of GABA in pyramidal neurons in neonatal life [9]. It remains to be determined exactly at what age these depolarizing effects end; in rodents it seems likely to be the first or second postnatal week [9, 15].

In the DG, one might expect that the switch from depolarizing to hyperpolarizing effects of GABA would not be as important because GABA typically has a depolarizing effect on GCs regardless. However, the size of the depolarization will be substantially greater if KCC2 expression is low, and moreover, there are many cells besides GCs in the DG that will be affected; only the GC has a very high resting potential. There are also many types of GABAergic inhibition, not only postsynaptic. If the GABA<sub>A</sub>R is presynaptic, for example, the net effect could very different if the terminal is depolarized or hyperpolarized by GABA.

There is also another process in the DG that is likely to be affected if the effects of GABA “switch” from depolarizing to hyperpolarizing – the maturation of GCs that are born postnatally, i.e., postnatal or “adult” neurogenesis [67]. GABA is a critical regulator of the maturation and migration of immature neurons in early life [24, 160]. GABA also influences maturation and migration of adult-born GCs [36]. In acquired TLE this is potentially important because animal models of TLE have shown that there is a large increase in proliferation of adult-born GCs after seizures [90], and the young GCs often mis-migrate (discussed further below). It has been suggested that these mis-migrated GCs contribute to chronic seizures (discussed further below).

---

### 11.3 Alterations in GABAergic Transmission in Animal Models of TLE

There are many types of TLE, and one of the ways to classify the types is based on whether the epilepsy appears to have been “acquired.”

The term ‘acquired’ indicates that an insult or injury occurred prior to seizures and is likely to have caused the epilepsy. Acquired TLE has been simulated in laboratory animals by various insults or injuries that lead to a pattern of brain damage that is typical of TLE, called mesial temporal sclerosis (MTS; [127]). In general, MTS involves loss of a large number of CA1 and CA3 pyramidal cells, with sparing of CA2 and GCs. Many hilar neurons are lost, and these include both mossy cells and HIPP cells [116]. Notably, there are individuals with acquired TLE that do not have this classic description of MTS, and animal models vary in the extent they simulate MTS [127]. However, the pattern has been the focus of the most research in TLE, based on the assumption that this general pattern of neuropathology causes TLE or is very important to TLE.

One method that leads to a MTS-like pattern of neuropathology in adult rodents is induction of SE, either by injection of a chemoconvulsant such as kainic acid or pilocarpine, or electrical stimulation of hippocampus [31, 85, 95]. Here we will focus primarily on the SE models to study TLE in adult rodents, and use the data from SE models to address changes in GABAergic inhibition. We suggest that these changes involve plasticity of GABAergic mechanisms rather than simply an erosion or increase in the effects of GABA.

#### 11.3.1 Alterations in GABAergic Neurons After SE

Early observations that GABAergic neurons were decreased in neocortical epileptic foci produced by alumina gel in monkeys supported ideas that disinhibition may be the cause of epilepsy [100–102], particularly because the reduction in GABAergic neurons preceded epilepsy [56, 103]. Chandelier cells appeared to be one of the subtypes that was affected, and it was suggested that loss of the chandelier subtype of GABAergic neuron would be most likely to cause disinhibition of cortical pyramidal cells because loss of only a few axo-axonic cells would substantially change the number of GABAergic terminals at the axon hillock [33].

However, as more animal models were examined, there was less enthusiasm for the idea that disinhibition was the fundamental cause of seizures. In seizure-sensitive gerbils [93], the audiogenic seizure model [110], and kainic acid model [32], GABAergic neurons were not always decreased [54]. In fact, some GABAergic neurons increased their axon arbors, exhibiting axon sprouting (discussed further below). When GABA<sub>A</sub>R-mediated inhibition was examined, it was often strong rather than weak [11]. Therefore, even if some changes in these animal models involve disinhibition acutely, GABAergic neurons and GABA<sub>A</sub>R-dependent inhibition often show recovery and plasticity.

In the DG, an alternative hypothesis to disinhibition was suggested to address an animal model of TLE in which the perforant path of adult rats was stimulated electrically to simulate the precipitating insult in TLE. In this animal model, a 24 h period of intermittent perforant path stimulation in urethane-anesthetized rats led to a loss of 'paired-pulse' inhibition. Based on the results from these experiments, investigators suggested that the basket cells, (defined by parvalbumin expression) were spared but there was loss of HIPP cells (defined by somatostatin expression) and mossy cells [135]. Because mossy cells appeared to be decreased in numbers, and there were suggestions in the literature that they innervated basket cells, it was hypothesized that the parvalbumin-expressing basket cells lost afferent input from mossy cells and became 'dormant' and this led to disinhibition of GCs [136]. The hypothesis became known as 'the dormant basket cell hypothesis.' It was suggested that the hypothesis explained epileptogenesis in acquired TLE: if an early insult or injury led to loss of vulnerable mossy cells and HIPP cells, but GCs and basket cells were spared, the result would be disinhibition of GCs [6, 75].

However, later studies led to some doubt that this hypothesis could explain acquired TLE [12]. An alternative hypothesis – the 'irritable mossy cell hypothesis' – suggested that mossy cells could cause GC hyperexcitability because the mossy cells, which project directly to GCs, developed increased excitability. This hypothesis was

developed on the basis of recordings from mossy cells in slices after post-traumatic injury [113, 114], another type of precipitating insult that leads to TLE. In addition, mossy cell hyperexcitability was shown subsequently in slices from epileptic rats after SE [128].

A result that argued against these two hypotheses came from studies of animals with chronic epilepsy after kainic acid-induced SE. These experiments showed that there was an increase in paired-pulse inhibition of GCs, not a decrease [139]. In addition, slices from animals after SE did not exhibit spontaneous seizure-like activity, suggesting they had intact inhibition rather than weak inhibition. This was unlikely to be due to the differences in the SE model since 'irritable mossy cells' were observed, at least in one study of SE [128]. In slices, exposure of slices to GABA<sub>A</sub>R antagonists led to seizure-like activity that was more prolonged in slices from animals that had SE than slices from control rats. From these experiments, it was suggested that slices from animals with SE were hyperexcitable but it was normally masked by GABA<sub>A</sub>R-mediated inhibition [129, 147]. In slices from humans with intractable TLE, there was enhanced sensitivity to bicuculline [39]. These observations and others led to the idea that increased inhibition was present to compensate for underlying hyperexcitability [147, 162]. Although in some cases the studies of animals with SE and intractable TLE reflect differences in the models or the subtypes of TLE, here the data from different models and humans was consistent, making the observations compelling.

Although an attractive idea, GABAergic inhibition in the animal models of SE does not necessarily seem to be too strong, masking underlying hyperexcitability. For example, interneurons exhibit axonal sprouting in the DG in animal models of TLE [5, 32, 151]. It is not clear that they simply extend their output, inhibiting more glutamatergic neurons than normal, because they innervate inhibitory neurons as well [137]. Interneurons develop abnormal glutamatergic input from sprouting of the GCs into the inner molecular layer (mossy fiber sprouting; for review see [19]). The evidence for this is based on



staining of the mossy fibers with Timm stain [137]. Electron microscopy of the mossy fiber boutons in the inner molecular layer supported the idea that the sprouted mossy fibers activate GABAergic basket cells [43]. In further support of this idea, it was suggested that normal mossy fibers in the hilus and area CA3 primarily innervate GABAergic neurons and primarily have an inhibitory effect on CA3 [1]. Moreover, GCs express GABA as well as glutamate after SE [50] and GABA release from GCs can be inhibitory [158] although the latest studies suggest this may be limited to GCs at an early stage of development [23]. The vast majority of studies show that GCs in normal hippocampus excite their target cells [60, 122, 156]. In addition, when mossy fiber synapses in the epileptic rat were quantified in the inner molecular layer, the majority were located on GCs, not interneurons [19, 20].

One way to reconcile the different data is to suggest that mossy fibers have a large dynamic range, with filopodia that excite interneurons and massive boutons that excite principal cells. The outcome may depend on recent activity, which can potentially upregulate GABA expression, or alter the peptide content of the massive boutons so that they are more excitatory [123]. Other hypotheses suggest that mossy fibers can be inhibitory to area CA3 pyramidal cells depending on the firing mode of GCs – after bursts of GC action potentials, excitation of pyramidal cells is transiently suppressed [82].

As our experimental techniques improved, our understanding of the underlying changes became clearer. For example, initial assays to assess inhibition measured paired-pulse inhibition which uses extracellular recordings and is not an extremely reliable measurement, because small changes in the stimulating or recording sites can alter the extent of inhibition even in the same preparation [157]. As patch clamp recordings developed, more indices of pre- and postsynaptic GABAergic inhibition became possible, and the results have shown that the GABAergic system in the DG is changed in diverse ways after SE, not always consistent with disinhibition of GCs, and not always consistent with hyperinhibition (Fig. 11.1b, c).

### 11.3.2 Alterations in GABA Receptors in GCs After SE

During SE, inhibitory GABAergic synaptic transmission in the DG becomes compromised, presumably due to the dramatic increase in activation of GABAergic neurons. Miniature inhibitory post-synaptic currents (mIPSCs) are reduced in GCs and the number of active GABA<sub>A</sub>Rs per GC decreases [26, 47, 86] via enhanced clathrin-dependent GABA<sub>A</sub>R internalization [48, 59]. In vitro studies using hippocampal neurons, stimulated with a buffer containing low magnesium to induce spontaneous recurrent epileptiform discharges, showed a large decrease in GABA-gated chloride currents that correlated with reduced cell surface expression and intracellular accumulation of GABA<sub>A</sub>Rs [13, 48]. In vivo studies using chemoconvulsants have shown that SE promotes a rapid reduction in the number of physiologically active GABA<sub>A</sub>Rs in GCs that correlated with a reduction in the level of  $\beta 2/\beta 3$  and  $\gamma 2$  immunoreactivity present in the vicinity of a pre-synaptic marker [86]. In fact, SE appears to trigger subunit specific events to regulate the trafficking of GABA<sub>A</sub>Rs by promoting the dephosphorylation of  $\beta 3$  subunits [47, 150]. Decreased phosphorylation of  $\beta 3$  increases the interaction of GABA<sub>A</sub>Rs with the clathrin-adaptor protein 2 (AP2), facilitating the recruitment of GABA<sub>A</sub>Rs into clathrin-coated pits and promoting their removal from the plasma membrane [47, 150]. In hippocampal slices obtained from mice after SE, increased GABA<sub>A</sub>R phosphorylation or blockade of normal AP2 function resulted in GABA<sub>A</sub>R accumulation at the plasma membrane and increased synaptic inhibition [150].

Alterations in GABA<sub>A</sub>R subunit composition occur subsequent to SE in a number of animal models, and there is evidence that these changes may contribute to epileptogenesis [18, 72, 76, 92, 144, 166]. SE results in changes in the expression and membrane localization (i.e., extrasynaptic vs. synaptic) of several GABA<sub>A</sub>R subunits (e.g.,  $\alpha 1$ ,  $\alpha 4$ ,  $\gamma 2$ , and  $\delta$ ) in GCs. Beginning soon after SE and continuing until and after the animals become epileptic, these alterations are associated with changes in phasic and tonic GABA<sub>A</sub>R-

mediated inhibition, and in GABA<sub>A</sub>R pharmacology [21, 30, 45]. After pilocarpine-induced SE, GABA<sub>A</sub>R  $\alpha 1$  subunit mRNA expression decreases, and GABA<sub>A</sub>R  $\alpha 4$  subunit mRNA expression increases [18]. Changes in GABA<sub>A</sub>R function and subunit expression have also been observed in neurons from surgically resected hippocampus of patients with intractable TLE; [17, 143]. These alterations are associated with an increase in  $\alpha 4\gamma 2$  containing receptors, a reduction in  $\alpha 1\gamma 2$  containing receptors in the DG [76], and shift of  $\alpha 4$ -containing receptors from extrasynaptic to synaptic and perisynaptic locations, which is likely to be related to the appearance of  $\alpha 4\beta\gamma 2$  receptors [146, 166]. Changes in expression and localization of  $\alpha$ -subunits associated with changes in synaptic GABA<sub>A</sub>R composition result in a number of changes in synaptic inhibition in GCs, including diminished benzodiazepine sensitivity, enhanced zinc sensitivity, reduced neurosteroid modulation, and diminished phasic inhibition in dendrites [21, 30, 45, 146]. Preventing the reduction in GABA<sub>A</sub>R subunit  $\alpha 1$  expression after SE via viral-mediated transfer of an  $\alpha 1$  subunit transgene in adult rodents reduced subsequent epilepsy development, resulting in a three-fold increase in the mean time to the first spontaneous seizure, and a decrease to 39 % of AAV- $\alpha 1$ -injected rats developing spontaneous seizures in the first 4 weeks after SE compared to 100 % of rats receiving sham injections [99]. Together, these data support a role for GABA<sub>A</sub>R  $\alpha$ -subunit changes in the process of epileptogenesis.

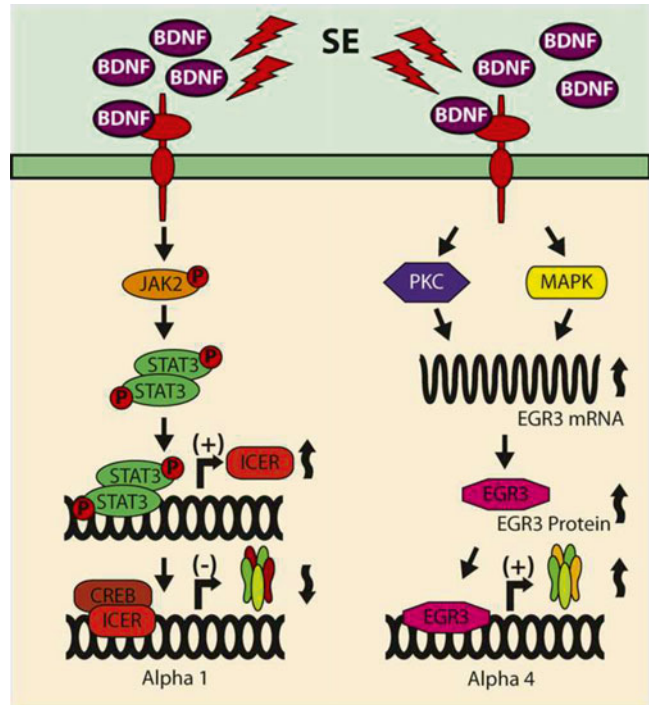
Receptors containing  $\alpha 4$  subunits are most often found with the  $\delta$  rather than the  $\gamma$  subunit in combination with  $\alpha\beta$ . These  $\alpha 4\beta\delta$  GABA<sub>A</sub>Rs are localized to extrasynaptic sites and contribute to tonic inhibition. Under physiological conditions, only a minor population of  $\alpha 4\beta\gamma 2$  GABA<sub>A</sub>Rs are found within GABAergic synapses on GCs, where they are proposed to affect both the rise time and decay of synaptic currents [71]. In parallel with the decrease in  $\alpha 1$  subunit expression in GCs after SE, there is a marked increase in  $\alpha 4$  subunit expression that results in an increase in the abundance of  $\alpha 4\gamma 2$ -containing receptors in synaptic and perisynaptic locations [146, 166] (see Fig. 11.2), along with the reduction in

$\alpha 1\gamma 2$ -containing receptors [76]. The  $\alpha 4\beta\gamma 2$  receptors may contribute to epileptogenesis, as  $\alpha 4$ -containing GABA<sub>A</sub>Rs have been shown to desensitize rapidly, especially when assembled with  $\beta 3$  subunits [71]. In addition, GABA<sub>A</sub>Rs containing the  $\alpha 4$  subunit are very sensitive to zinc blockade, as are GABA<sub>A</sub>Rs on GCs in the epileptic brain [21, 30]. Zinc containing mossy fiber terminals sprout from the granule cell layer of the hippocampus onto other GCs and into CA3, likely depositing zinc onto the newly formed  $\alpha 4\beta\gamma 2$  receptors causing a decreased response to GABA. Collectively these alterations may contribute to epilepsy development, pharmacoresistance and further epilepsy progression.

GABA<sub>A</sub>R subunit alterations after SE are regulated by increased synthesis of brain-derived neurotrophic factor (BDNF) and activation of its receptors (TrkB and p75) that control a number of down-stream pathways, including Janus kinase (JAK)/Signal Transducer and Activators of Transcription (STAT), protein kinase C, and mitogen activated protein kinase (MAPK; [76, 107, 108]). BDNF is known to enhance cAMP response element binding protein (CREB) phosphorylation through binding to TrkB receptors [105, 163], and is also a potent regulator of inducible cAMP response element repressor (ICER) synthesis [57]. Using chromatin immunoprecipitation (ChIP) and DNA pulldown studies, it has been determined that there is increased binding of pCREB and ICER to the GABA<sub>A</sub>R $\alpha 1$  gene promoter (*GABRA1-p*) in DG after SE [76]. BDNF regulation of ICER expression is mediated by JAK/STAT pathway activation, specifically activation of pJAK2 and pSTAT3 [76]. pSTAT3 association with the STAT-recognition site on the ICER promoter is enhanced after SE in DG and inhibition of JAK/STAT signaling pathway with pyridone 6 (P6) in primary hippocampal cultures and *in vivo* in DG prior to SE blocks both ICER induction and decreased transcription of *GABRA1* [76]. These findings suggest a specific signaling cascade involving BDNF, JAK/STAT, and CREB that is critical to the reported decreases in  $\alpha 1$  subunit levels following SE and may contribute to epileptogenesis. Increases in GABA<sub>A</sub>R $\alpha 4$  subunit are transcriptionally regulated by BDNF activation of the TrkB

**Fig. 11.3 Regulation of GABA<sub>A</sub> receptor expression after SE.**

BDNF regulates the final composition of GABA<sub>A</sub>Rs by differentially altering the expression of  $\alpha 1$  and  $\alpha 4$  subunits. Both in vivo and in vitro evidence suggest that increased levels of BDNF following SE activate at least two different signaling pathways: JAK/STAT and PKC/MAPK, resulting in the down-regulation of  $\alpha 1$  subunits and the up-regulation of  $\alpha 4$  subunits, respectively (Reproduced from Gonzalez and Brooks-Kayal [46])



receptor which leads to upregulation of the early growth response factor (Egr3) pathway via a PKC/MAPK-dependent pathway [107]. Egr3 association with the early-growth response-recognition (ERE) site on the *GABRA4* promoter is enhanced after SE in DG [107] (See Fig. 11.3).

### 11.3.3 Regulation of GABA in Early Development and Its Relevance to TLE

One of the themes in studies of animal models of TLE is the idea that the myriad of changes in hippocampal structure and function that have been described are associated with a recapitulation of development that is caused by the epileptogenic insult. A robust example is the dramatic increase in the rate of adult neurogenesis in the DG after epileptogenic insults like SE. First noted by Bengzon et al [10] using stimulus-evoked afterdischarges, and Parent et al. [90] after pilocarpine-induced SE, the increase in the rate of adult neurogenesis after seizures, and particularly SE (in adult rodents), has been reproduced by many laboratories in response to virtually all

epileptogenic insults: kindling, kainic acid or electrically-induced SE, or traumatic brain injury [121, 124].

Initially it was suggested that many of the neurons that are born after SE do not survive long-term [90] which has also been shown by others [96] but a substantial fraction of newborn neurons can survive in some animal models, and these migrate into the hilar region, where they are called hilar ectopic GCs (hEGCs; [119]). Other adult-born GCs migrate correctly but develop abnormal dendrites in the hilus, called hilar basal dendrites [104, 133]. These neurons also appear to survive long-term and can be generated for a long-time after SE [62]. Another subset of GC that develops after SE and is abnormal develops an enlarged cell body (hypertrophy; [98]). The abnormal GCs are potentially important because they contribute to mossy fiber sprouting, particularly hEGCs [69, 94, 119]. HEGCs participate in seizures in vivo [130] and their numbers are correlated with chronic seizure frequency [79]. Manipulations that reduce hEGC number reduce chronic seizure frequency after SE [63], although selective deletion of hEGCs is not yet possible. The hEGCs display a variety of

electrophysiological characteristics [61, 118, 164, 165] which are unlike normal GCs. For these reasons, the neurons that hypertrophy, and the hEGCs, have been suggested to contribute to seizure generation [63, 68, 98, 117, 119].

The plasticity of GABAergic mechanisms in animal models of TLE plays a potentially important role in the development of abnormal GCs, and therefore the role these GCs play in seizure generation. In a study that used experimental febrile seizures to induce epilepsy later in life, febrile seizures caused mismigration of immature GCs into the hilus by changing the normal regulation of migration by GABA acting at GABA<sub>A</sub>Rs. This study was important in showing that altering the normal effect of GABA by febrile seizures could cause aberrant circuitry that would persist long-term, potentially contributing to seizure generation. Interestingly, the way that GABA was altered was in the expression of GABA<sub>A</sub>Rs; more GABA<sub>A</sub>Rs were found by western blot after febrile seizures. In response to increased depolarization by GABA, immature GCs migrated opposite to their normal direction, into the hilus instead of the GC layer. Knockdown of NKCC1 could block the formation of hEGCs and reduce the long-term effects [68]. The studies of Koyama and colleagues and Swijsen et al. [149], who also studied febrile seizures, both found increased  $\beta$ 2/3 subunits occurred in newborn GCs after febrile seizures [149]. Changes in  $\alpha$ 3 subunits were also noted by Swijsen et al. [148]. The results suggest that febrile seizures lead to long-lasting changes in the expression of GABA<sub>A</sub>Rs in the DG, and in the GCs that were born after febrile seizures. These effects could lead to life-long reduction in limbic seizure threshold. They also may contribute to the comorbidities in TLE, such as depression [16, 66], a psychiatric condition where adult neurogenesis in the DG has been shown to play a critical role [112].

Another study of adult rodents is also relevant to the formation of aberrant GCs in TLE. This study used pilocarpine-induced SE in adult rodents to ask how KCC2 is altered immediately after SE. The investigators showed that there was a downregulation of KCC2 in the DG after

SE which would make GCs (both mature and immature GCs) depolarize more in response to GABA [91]. If the results of Koyama et al. [68] are correct, greater depolarization by GABA would be likely to foster mismigration of immature GCs. A similar phenomenon may explain why newborn neurons after SE, in the adult, mis-migrate for long distances—it has been described that they migrate from the subgranular zone to the border of the hilus and area CA3 [118]. Together the new information about  $[Cl^-]_i$  regulation are providing potential mechanisms underlying acquired epileptogenesis in the immature and mature brain. Although a great deal more information will be necessary before new treatments can be developed based on the new hypotheses, NKCC1 antagonists are already in clinical trial [64, 65].

---

## 11.4 Summary

In the DG, the robust plasticity of GCs has been of avid interest because they upregulate numerous proteins and exhibit robust sprouting of their axons after seizures. Although extensive studies of GABA in the DG have been made in TLE, the remarkable plasticity of GABAergic mechanisms is often not considered as much as development of disinhibition or hyperinhibition. Here we suggest that there are numerous pre- and postsynaptic changes in GABAergic transmission, even if one only addresses GABAergic synapses on GCs and GABA<sub>A</sub> receptors. Taken together, this plasticity leads to more complexity of GABAergic transmission in the epileptic brain, not simply an increase or decrease. The idea that GABAergic inhibition is dramatically altered, rather than increased or decreased, is consistent with the diversity of results of past studies. Therefore, this perspective helps address some of the conflicts in the past. It also provides a different and potentially more accurate perspective that will facilitate antiseizure drug development.

**Acknowledgements** This article is dedicated to Philip A. Schwartzkroin, a pioneer and leader in epilepsy research, esteemed mentor, and outstanding colleague.

*Other Acknowledgements* Supported by R01 NS-081203, R21 MH-090606 and the New York State Office of Mental Health (HES) and R01 NS-038595, R01 NS-051710, R01-NS-050393 and grants from Citizens United for Research in Epilepsy, Department of Defense and the American Epilepsy Society (ABK).

## References

1. Acsady L, Kamondi A, Sik A, Freund T, Buzsaki G (1998) GABAergic cells are the major postsynaptic targets of mossy fibers in the rat hippocampus. *J Neurosci* 18:3386–3403
2. Amaral DG, Scharfman HE, Lavenex P (2007) The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Prog Brain Res* 163:3–22
3. Armstrong C, Krook-Magnuson E, Soltesz I (2012) Neurogliaform and ivy cells: a major family of nNOS expressing GABAergic neurons. *Front Neural Circuit* 6:23
4. Baulac S, Huberfeld G, Gourfinkel-An I, Mitropoulou G, Beranger A, Prud'homme JF, Baulac M, Brice A, Bruzzone R, LeGuern E (2001) First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the  $\gamma 2$ -subunit gene. *Nat Genet* 28:46–48
5. Bausch SB (2005) Axonal sprouting of GABAergic interneurons in temporal lobe epilepsy. *Epilepsy Behav* 7:390–400
6. Bekenstein JW, Lothman EW (1993) Dormancy of inhibitory interneurons in a model of temporal lobe epilepsy. *Science* 259:97–100
7. Ben-Ari Y (2002) Excitatory actions of GABA during development: the nature of the nurture. *Nat Rev Neurosci* 3:728–739
8. Ben-Ari Y, Khalilov I, Kahle KT, Cherubini E (2012) The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. *Neuroscientist* 18:467–486
9. Ben-Ari Y, Woodin MA, Sernagor E, Cancedda L, Vinay L, Rivera C, Legendre P, Luhmann HJ, Bordey A, Wenner P, Fukuda A, van den Pol AN, Gaiarsa JL, Cherubini E (2012) Refuting the challenges of the developmental shift of polarity of GABA actions: GABA more exciting than ever! *Front Cell Neurosci* 6:35
10. Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O (1997) Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Sci U S A* 94:10432–10437
11. Bernard C, Cossart R, Hirsch JC, Esclapez M, Ben-Ari Y (2000) What is GABAergic inhibition? How is it modified in epilepsy? *Epilepsia* 41(Suppl 6):S90–S95
12. Bernard C, Esclapez M, Hirsch JC, Ben-Ari Y (1998) Interneurons are not so dormant in temporal lobe epilepsy: a critical reappraisal of the dormant basket cell hypothesis. *Epilepsy Res* 32:93–103
13. Blair RE, Sombati S, Lawrence DC, McCay BD, DeLorenzo RJ (2004) Epileptogenesis causes acute and chronic increases in GABA(A) receptor endocytosis that contributes to the induction and maintenance of seizures in the hippocampal culture model of acquired epilepsy. *J Pharmacol Exp Ther* 310:871–880
14. Bowery NG (2010) Historical perspective and emergence of the GABA<sub>B</sub> receptor. *Adv Pharmacol* 58:1–18
15. Bregestovski P, Bernard C (2012) Excitatory GABA: how a correct observation may turn out to be an experimental artifact. *Front Pharmacol* 3:65
16. Brooks-Kayal AR, Bath KG, Berg AT, Galanopoulou AS, Holmes GL, Jensen FE, Kanner AM, O'Brien TJ, Whittemore VH, Winawer MR, Patel M, Scharfman HE (2013) Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia* 54(Suppl 4):44–60
17. Brooks-Kayal AR, Shumate MD, Jin H, Lin DD, Rikhter TY, Holloway KL, Coulter DA (1999) Human neuronal  $\gamma$ -aminobutyric acid<sub>a</sub> receptors: coordinated subunit mRNA expression and functional correlates in individual dentate granule cells. *J Neurosci* 19:8312–8318
18. Brooks-Kayal AR, Shumate MD, Jin H, Rikhter TY, Coulter DA (1998) Selective changes in single cell GABA(A) receptor subunit expression and function in temporal lobe epilepsy. *Nat Med* 4:1166–1172
19. Buckmaster PS (2012) Mossy fiber sprouting in the dentate gyrus. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (eds) *Jasper's basic mechanisms of the epilepsies*, 4th edn. Oxford, New York, pp 416–431
20. Buckmaster PS, Zhang GF, Yamawaki R (2002) Axon sprouting in a model of temporal lobe epilepsy creates a predominantly excitatory feedback circuit. *J Neurosci* 22:6650–6658
21. Buhl E, Otis T, Mody I (1996) Zinc-induced collapse of augmented inhibition by GABA in a temporal lobe epilepsy model. *Science* 271:369–373
22. Buhl EH, Han ZS, Lorinczi Z, Stezhka VV, Karnup SV, Somogyi P (1994) Physiological properties of anatomically identified axo-axonic cells in the rat hippocampus. *J Neurophysiol* 71:1289–1307
23. Caiati MD (2013) Is GABA co-released with glutamate from hippocampal mossy fiber terminals? *J Neurosci* 33:1755–1756
24. Cancedda L, Fiumelli H, Chen K, Poo MM (2007) Excitatory GABA action is essential for morphological maturation of cortical neurons in vivo. *J Neurosci* 27:5224–5235
25. Chavkin C (2000) Dynorphins are endogenous opioid peptides released from granule cells to act neurohumorally and inhibit excitatory neurotransmission in the hippocampus. *Prog Brain Res* 125:363–367

26. Chen JW, Naylor DE, Wasterlain CG (2007) Advances in the pathophysiology of status epilepticus. *Acta Neurol Scand Suppl.* 186:7–15
27. Cherubini E, Griguoli M, Safiulina V, Lagostena L (2011) The depolarizing action of GABA controls early network activity in the developing hippocampus. *Mol Neurobiol* 43:97–106
28. Chittajallu R, Kunze A, Mangin JM, Gallo V (2007) Differential synaptic integration of interneurons in the outer and inner molecular layers of the developing dentate gyrus. *J Neurosci* 27:8219–8225
29. Choi YS, Lin SL, Lee B, Kurup P, Cho HY, Naegele JR, Lombroso PJ, Obrietan K (2007) Status epilepticus-induced somatostatinergic hilar interneuron degeneration is regulated by striatal enriched protein tyrosine phosphatase. *J Neurosci* 27:2999–3009
30. Cohen AS, Lin DD, Quirk GL, Coulter DA (2003) Dentate granule cell GABA(A) receptors in epileptic hippocampus: enhanced synaptic efficacy and altered pharmacology. *Eur J Neurosci* 17:1607–1616
31. Curia G, Longo D, Biagini G, Jones RS, Avoli M (2008) The pilocarpine model of temporal lobe epilepsy. *J Neurosci Methods* 172:143–157
32. Davenport CJ, Brown WJ, Babb TL (1990) GABAergic neurons are spared after intrahippocampal kainate in the rat. *Epilepsy Res* 5:28–42
33. DeFelipe J (1999) Chandelier cells and epilepsy. *Brain* 122(Pt 10):1807–1822
34. Deller T (1998) The anatomical organization of the rat fascia dentata: new aspects of laminar organization as revealed by anterograde tracing with phaseolus vulgaris-luecoagglutinin (PHAL). *Anat Embryol (Berl)* 197:89–103
35. Deller T, Leranthe C (1990) Synaptic connections of neuropeptide Y (NPY) immunoreactive neurons in the hilar area of the rat hippocampus. *J Comp Neurol* 300:433–447
36. Dieni CV, Chancey JH, Overstreet-Wadiche LS (2012) Dynamic functions of GABA signaling during granule cell maturation. *Front Neural Circuits* 6:113
37. Dougherty KD, Milner TA (1999) Cholinergic septal afferent terminals preferentially contact neuro-peptide Y-containing interneurons compared to parvalbumin-containing interneurons in the rat dentate gyrus. *J Neurosci* 19:10140–10152
38. Dougherty KD, Milner TA (1999) P75<sup>ntr</sup> immunoreactivity in the rat dentate gyrus is mostly within presynaptic profiles but is also found in some astrocytic and postsynaptic profiles. *J Comp Neurol* 407:77–91
39. Franck JE, Pokorny J, Kunkel DD, Schwartzkroin PA (1995) Physiologic and morphologic characteristics of granule cell circuitry in human epileptic hippocampus. *Epilepsia* 36:543–558
40. Frazier CJ (2007) Endocannabinoids in the dentate gyrus. *Prog Brain Res* 163:319–337
41. Freund TF (1992) GABAergic septal and serotonergic median raphe afferents preferentially innervate inhibitory interneurons in the hippocampus and dentate gyrus. *Epilepsy Res Suppl* 7:79–91
42. Freund TF, Buzsaki G (1996) Interneurons of the hippocampus. *Hippocampus* 6:347–470
43. Frotscher M, Jonas P, Sloviter RS (2006) Synapses formed by normal and abnormal hippocampal mossy fibers. *Cell Tissue Res* 326:361–367
44. Fu LY, van den Pol AN (2007) Gaba excitation in mouse hilar neuro-peptide Y neurons. *J Physiol* 579:445–464
45. Gibbs J, Shumate M, Coulter D (1997) Differential epilepsy-associated alterations in postsynaptic GABA<sub>A</sub> receptor function in dentate granule and cal neurons. *J Neurophysiol* 77:1924–1938
46. Gonzalez MI, Brooks-Kayal A (2011) Altered GABA(A) receptor expression during epileptogenesis. *Neurosci Lett* 497:218–222
47. Goodkin HP, Joshi S, Mtchedlishvili Z, Brar J, Kapur J (2008) Subunit-specific trafficking of GABA(A) receptors during status epilepticus. *J Neurosci* 28:2527–2538
48. Goodkin HP, Yeh JL, Kapur J (2005) Status epilepticus increases the intracellular accumulation of GABA(A) receptors. *J Neurosci* 25:5511–5520
49. Goodman JH, Sloviter RS (1992) Evidence for commissurally projecting parvalbumin-immunoreactive basket cells in the dentate gyrus of the rat. *Hippocampus* 2:13–21
50. Gutierrez R, Heinemann U (2006) Co-existence of GABA and Glu in the hippocampal granule cells: implications for epilepsy. *Curr Top Med Chem* 6:975–978
51. Halasy K, Somogyi P (1993) Subdivisions in the multiple GABAergic innervation of granule cells in the dentate gyrus of the rat hippocampus. *Eur J Neurosci* 5:411–429
52. Han ZS, Buhl EH, Lorinczi Z, Somogyi P (1993) A high degree of spatial selectivity in the axonal and dendritic domains of physiologically identified local-circuit neurons in the dentate gyrus of the rat hippocampus. *Eur J Neurosci* 5:395–410
53. Henze DA, Buzsaki G (2007) Hilar mossy cells: functional identification and activity in vivo. *Prog Brain Res* 163:199–216
54. Houser CR (1991) GABA neurons in seizure disorders: a review of immunocytochemical studies. *Neurochem Res* 16:295–308
55. Houser CR (2007) Interneurons of the dentate gyrus: an overview of cell types, terminal fields and neurochemical identity. *Prog Brain Res* 163:217–232
56. Houser CR, Harris AB, Vaughn JE (1986) Time course of the reduction of GABA terminals in a model of focal epilepsy: a glutamic acid decarboxylase immunocytochemical study. *Brain Res* 383:129–145
57. Hu Y, Russek SJ (2008) BDNF and the diseased nervous system: a delicate balance between adaptive and pathological processes of gene regulation. *J Neurochem* 105:1–17
58. Huguenard JR (1999) Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action. *Adv Neurol* 79:991–999



59. Jacob TC, Moss SJ, Jurd R (2008) GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat Rev Neurosci* 9:331–343
60. Jaffe DB, Gutierrez R (2007) Mossy fiber synaptic transmission: communication from the dentate gyrus to area ca3. *Prog Brain Res* 163:109–132
61. Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O (2006) Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* 52:1047–1059
62. Jessberger S, Zhao C, Toni N, Clemenson GD Jr, Li Y, Gage FH (2007) Seizure-associated, aberrant neurogenesis in adult rats characterized with retrovirus-mediated cell labeling. *J Neurosci* 27:9400–9407
63. Jung KH, Chu K, Kim M, Jeong SW, Song YM, Lee ST, Kim JY, Lee SK, Roh JK (2004) Continuous cytosine-b-D-arabinofuranoside infusion reduces ectopic granule cells in adult rat hippocampus with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. *Eur J Neurosci* 19:3219–3226
64. Kahle KT, Staley KJ (2008) The bumetanide-sensitive Na-K-2Cl cotransporter NKCC1 as a potential target of a novel mechanism-based treatment strategy for neonatal seizures. *Neurosurg Focus* 25:E22
65. Kahle KT, Staley KJ (2012) Neonatal seizures and neuronal transmembrane ion transport. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (eds) *Jasper's basic mechanisms of the epilepsies*, 4th edn. Oxford, New York, pp 1066–1076
66. Kanner AM (2013) Epilepsy, depression and anxiety disorders: a complex relation with significant therapeutic implications for the three conditions. *J Neurol Neurosurg Psychiatry* 84:e1
67. Kempermann G (2006) *Adult neurogenesis*. Oxford University Press, Oxford
68. Koyama R, Tao K, Sasaki T, Ichikawa J, Miyamoto D, Muramatsu R, Matsuki N, Ikegaya Y (2012) GABAergic excitation after febrile seizures induces ectopic granule cells and adult epilepsy. *Nat Med* 18:1271–1278
69. Kron MM, Zhang H, Parent JM (2010) The developmental stage of dentate granule cells dictates their contribution to seizure-induced plasticity. *J Neurosci* 30:2051–2059
70. Kullmann DM, Ruiz A, Rusakov DM, Scott R, Semyanov A, Walker MC (2005) Presynaptic, extrasynaptic and axonal GABA<sub>A</sub> receptors in the CNS: where and why? *Prog Biophys Mol Biol* 87:33–46
71. Lagrange AH, Botzolakis EJ, Macdonald RL (2007) Enhanced macroscopic desensitization shapes the response of  $\alpha 4$  subtype-containing GABA<sub>A</sub> receptors to synaptic and extrasynaptic GABA. *J Physiol* 578:655–676
72. Lauren HB, Pitkanen A, Nissinen J, Soini SL, Korpi ER, Holopainen IE (2003) Selective changes in  $\gamma$ -aminobutyric acid type a receptor subunits in the hippocampus in spontaneously seizing rats with chronic temporal lobe epilepsy. *Neurosci Lett* 349:58–62
73. Laurie DJ, Wisden W, Seeburg PH (1992) The distribution of thirteen GABA<sub>A</sub> receptor subunit mRNAs in the rat brain. Iii. Embryonic and postnatal development. *J Neurosci* 12:4151–4172
74. Leranth C, Hajszan T (2007) Extrinsic afferent systems to the dentate gyrus. *Prog Brain Res* 163:63–84
75. Lothman EW, Bertram EH 3rd, Kapur J, Bekenstein JW (1996) Temporal lobe epilepsy: studies in a rat model showing dormancy of GABAergic inhibitory interneurons. *Epilepsy Res Suppl* 12:145–156
76. Lund IV, Hu Y, Raol YH, Benham RS, Faris R, Russek SJ, Brooks-Kayal AR (2008) BDNF selectively regulates GABA<sub>A</sub> receptor transcription by activation of the JAK/STAT pathway. *Sci Signal* 1:ra9
77. Macdonald RL, Olsen RW (1994) GABA<sub>A</sub> receptor channels. *Annu Rev Neurosci* 17:569–602
78. Magloczky Z, Freund TF (2005) Impaired and repaired inhibitory circuits in the epileptic human hippocampus. *Trends Neurosci* 28:334–340
79. McCloskey DP, Hintz TM, Pierce JP, Scharfman HE (2006) Stereological methods reveal the robust size and stability of ectopic hilar granule cells after pilocarpine-induced status epilepticus in the adult rat. *Eur J Neurosci* 24:2203–2210
80. Milner TA, Veznedaroglu E (1992) Ultrastructural localization of neuropeptide Y-like immunoreactivity in the rat hippocampal formation. *Hippocampus* 2:107–125
81. Morgan RJ, Santhakumar V, Soltesz I (2007) Modeling the dentate gyrus. *Prog Brain Res* 163:639–658
82. Mori M, Gahwiler BH, Gerber U (2007) Recruitment of an inhibitory hippocampal network after bursting in a single granule cell. *Proc Natl Acad Sci U S A* 104:7640–7645
83. Moss SJ, Smart TG (1996) Modulation of amino acid-gated ion channels by protein phosphorylation. *Int Rev Neurobiol* 39:1–52
84. Mott DD, Lewis DV (1994) The pharmacology and function of central GABA<sub>B</sub> receptors. *Int Rev Neurobiol* 36:97–223
85. Nadler JV, Perry BW, Cotman CW (1978) Intraventricular kainic acid preferentially destroys hippocampal pyramidal cells. *Nature* 271:676–677
86. Naylor DE, Liu H, Wasterlain CG (2005) Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci* 25:7724–7733
87. Nusser Z, Mody I (2002) Selective modulation of tonic and phasic inhibitions in dentate gyrus granule cells. *J Neurophysiol* 87:2624–2628
88. Olsen RW (1981) The GABA postsynaptic membrane receptor-ionophore complex. Site of action of convulsant and anticonvulsant drugs. *Mol Cell Biochem* 39:261–279
89. Paredes MF, Greenwood J, Baraban SC (2003) Neuropeptide Y modulates a g protein-coupled inwardly rectifying potassium current in the mouse hippocampus. *Neurosci Lett* 340:9–12

90. Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 17:3727–3738
91. Pathak HR, Weissinger F, Terunuma M, Carlson GC, Hsu FC, Moss SJ, Coulter DA (2007) Disrupted dentate granule cell chloride regulation enhances synaptic excitability during development of temporal lobe epilepsy. *J Neurosci* 27:14012–14022
92. Peng Z, Huang CS, Stell BM, Mody I, Houser CR (2004) Altered expression of the delta subunit of the GABA<sub>A</sub> receptor in a mouse model of temporal lobe epilepsy. *J Neurosci* 24:8629–8639
93. Peterson GM, Ribak CE (1987) Hippocampus of the seizure-sensitive gerbil is a specific site for anatomical changes in the GABAergic system. *J Comp Neurol* 261:405–422
94. Pierce JP, McCloskey DP, Scharfman HE (2011) Morphometry of hilar ectopic granule cells in the rat. *J Comp Neurol* 519:1196–1218
95. Pitkanen A, Moshe s, Schwartzkroin PA (2006) Models of seizures and epilepsy. Elsevier, New York
96. Porter BE, Maronski M, Brooks-Kayal AR (2004) Fate of newborn dentate granule cells after early life status epilepticus. *Epilepsia* 45:13–19
97. Pritchett D, Sontheimer H, Shivers B, Ymer S, Kellenmann H, Schofield P, Seeburg P (1989) Importance of a novel GABA<sub>A</sub> receptor subunit for benzodiazepine pharmacology. *Nature* 338:582–585
98. Pun RY, Rolle IJ, Lasarge CL, Hosford BE, Rosen JM, Uhl JD, Schmeltzer SN, Faulkner C, Bronson SL, Murphy BL, Richards DA, Holland KD, Danzer SC (2012) Excessive activation of mTOR in postnatally generated granule cells is sufficient to cause epilepsy. *Neuron* 75:1022–1034
99. Raol YH, Lund IV, Bandyopadhyay S, Zhang G, Roberts DS, Wolfe JH, Russek SJ, Brooks-Kayal AR (2006) Enhancing GABA(A) receptor  $\alpha$  1 subunit levels in hippocampal dentate gyrus inhibits epilepsy development in an animal model of temporal lobe epilepsy. *J Neurosci* 26:11342–11346
100. Ribak CE (1985) Axon terminals of GABAergic chandelier cells are lost at epileptic foci. *Brain Res* 326:251–260
101. Ribak CE, Harris AB, Vaughn JE, Roberts E (1979) Inhibitory, GABAergic nerve terminals decrease at sites of focal epilepsy. *Science* 205:211–214
102. Ribak CE, Hunt CA, Bakay RA, Oertel WH (1986) A decrease in the number of GABAergic somata is associated with the preferential loss of GABAergic terminals at epileptic foci. *Brain Res* 363:78–90
103. Ribak CE, Joubbran C, Kesslak JP, Bakay RA (1989) A selective decrease in the number of GABAergic somata occurs in pre-seizing monkeys with alumina gel granuloma. *Epilepsy Res* 4:126–138
104. Ribak CE, Shapiro LA, Yan XX, Dashtipour K, Nadler JV, Obenaus A, Spigelman I, Buckmaster PS (2012) Seizure-induced formation of basal dendrites on granule cells of the rodent dentate gyrus. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (eds) Jasper's basic mechanisms of the epilepsies, 4th edn. National Center for Biotechnology Information, Bethesda
105. Riccio A, Alvania RS, Lonze BE, Ramanan N, Kim T, Huang Y, Dawson TM, Snyder SH, Ginty DD (2006) A nitric oxide signaling pathway controls CREB-mediated gene expression in neurons. *Mol Cell* 21:283–294
106. Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, Pirvola U, Saarma M, Kaila K (1999) The K<sup>+</sup>/Cl<sup>-</sup> co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* 397:251–255
107. Roberts DS, Hu Y, Lund IV, Brooks-Kayal AR, Russek SJ (2006) Brain-derived neurotrophic factor (BDNF)-induced synthesis of early growth response factor 3 (Egr3) controls the levels of type A GABA receptor  $\alpha$ 4 subunits in hippocampal neurons. *J Biol Chem* 281:29431–29435
108. Roberts DS, Raol YH, Bandyopadhyay S, Lund IV, Budreck EC, Passini MA, Wolfe JH, Brooks-Kayal AR, Russek SJ (2005) Egr3 stimulation of gabra4 promoter activity as a mechanism for seizure-induced up-regulation of GABA(A) receptor  $\alpha$ 4 subunit expression. *Proc Natl Acad Sci U S A* 102:11894–11899
109. Roberts E (1986) Failure of GABAergic inhibition: a key to local and global seizures. *Adv Neurol* 44:319–341
110. Roberts RC, Ribak CE, Oertel WH (1985) Increased numbers of GABAergic neurons occur in the inferior colliculus of an audiogenic model of genetic epilepsy. *Brain Res* 361:324–338
111. Rudolph U, Mohler H (2006) GABA-based therapeutic approaches: GABA<sub>A</sub> receptor subtype functions. *Curr Opin Pharmacol* 6:18–23
112. Sahay A, Hen R (2008) Hippocampal neurogenesis and depression. *Novartis Found Symp* 289:152–160; discussion 60–64, 93–95
113. Santhakumar V, Bender R, Frotscher M, Ross ST, Hollrigel GS, Toth Z, Soltesz I (2000) Granule cell hyperexcitability in the early post-traumatic rat dentate gyrus: the 'irritable mossy cell' hypothesis. *J Physiol* 524(Pt 1):117–134
114. Santhakumar V, Ratzliff AD, Jeng J, Toth Z, Soltesz I (2001) Long-term hyperexcitability in the hippocampus after experimental head trauma. *Ann Neurol* 50:708–717
115. Scharfman HE (1995) Electrophysiological diversity of pyramidal-shaped neurons at the granule cell layer/hilus border of the rat dentate gyrus recorded in vitro. *Hippocampus* 5:287–305
116. Scharfman HE (1999) The role of nonprincipal cells in dentate gyrus excitability and its relevance to animal models of epilepsy and temporal lobe epilepsy. *Adv Neurol* 79:805–820
117. Scharfman HE (2004) Functional implications of seizure-induced neurogenesis. *Adv Exp Med Biol* 548:192–212

118. Scharfman HE, Sollas AE, Berger RE, Goodman JH, Pierce JP (2003) Perforant path activation of ectopic granule cells that are born after pilocarpine-induced seizures. *Neuroscience* 121:1017–1029
119. Scharfman HE, Goodman JH, Sollas AL (2000) Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J Neurosci* 20:6144–6158
120. Scharfman HE, Gray WP (2006) Plasticity of neuro-peptide  $\gamma$  in the dentate gyrus after seizures, and its relevance to seizure-induced neurogenesis. *EXS*: 95:193–211
121. Scharfman HE, Gray WP (2007) Relevance of seizure-induced neurogenesis in animal models of epilepsy to the etiology of temporal lobe epilepsy. *Epilepsia* 48(Suppl 2):33–41
122. Scharfman HE, Kunkel DD, Schwartzkroin PA (1990) Synaptic connections of dentate granule cells and hilar neurons: results of paired intracellular recordings and intracellular horseradish peroxidase injections. *Neuroscience* 37:693–707
123. Scharfman HE, Maclusky NJ (2014) Differential regulation of BDNF, synaptic plasticity and sprouting in the hippocampal mossy fiber pathway of male and female rats. *Neuropharmacology* 76:696–708
124. Scharfman HE, McCloskey DP (2009) Postnatal neurogenesis as a therapeutic target in temporal lobe epilepsy. *Epilepsy Res* 85:150–161
125. Scharfman HE, Mercurio TC, Goodman JH, Wilson MA, MacLusky NJ (2003) Hippocampal excitability increases during the estrous cycle in the rat: a potential role for brain-derived neurotrophic factor. *J Neurosci* 23:11641–11652
126. Scharfman HE, Myers CE (2012) Hilar mossy cells of the dentate gyrus: a historical perspective. *Front Neural Circuits* 6:106
127. Scharfman HE, Pedley TA (2006) Temporal lobe epilepsy. In: Gilman S (ed) *The neurobiology of disease*. Academic, New York
128. Scharfman HE, Smith KL, Goodman JH, Sollas AL (2001) Survival of dentate hilar mossy cells after pilocarpine-induced seizures and their synchronized burst discharges with area CA3 pyramidal cells. *Neuroscience* 104:741–759
129. Scharfman HE, Sollas AL, Berger RE, Goodman JH (2003) Electrophysiological evidence of monosynaptic excitatory transmission between granule cells after seizure-induced mossy fiber sprouting. *J Neurophysiol* 90:2536–2547
130. Scharfman HE, Sollas AL, Goodman JH (2002) Spontaneous recurrent seizures after pilocarpine-induced status epilepticus activate calbindin-immunoreactive hilar cells of the rat dentate gyrus. *Neuroscience* 111:71–81
131. Schneiderman JH, Schwartzkroin PA (1982) Effects of phenytoin on normal activity and on penicillin-induced bursting in the guinea pig hippocampal slice. *Neurology* 32:730–738
132. Schwartzkroin PA, Prince DA (1977) Penicillin-induced epileptiform activity in the hippocampal in vitro preparation. *Ann Neurol* 1:463–469
133. Shapiro LA, Ribak CE, Jessberger S (2008) Structural changes for adult-born dentate granule cells after status epilepticus. *Epilepsia* 49(Suppl 5):13–18
134. Sieghart W (2006) Structure, pharmacology, and function of GABA<sub>A</sub> receptor subtypes. *Adv Pharmacol* 54:231–263
135. Sloviter RS (1987) Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. *Science* 235:73–76
136. Sloviter RS (1991) Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the “dormant basket cell” hypothesis and its possible relevance to temporal lobe epilepsy. *Hippocampus* 1:41–66
137. Sloviter RS (1992) Possible functional consequences of synaptic reorganization in the dentate gyrus of kainate-treated rats. *Neurosci Lett* 137:91–96
138. Sloviter RS, Nilaver G (1987) Immunocytochemical localization of GABA-, cholecystokinin-, vasoactive intestinal polypeptide-, and somatostatin-like immunoreactivity in the area dentata and hippocampus of the rat. *J Comp Neurol* 256:42–60
139. Sloviter RS, Zappone CA, Harvey BD, Frotscher M (2006) Kainic acid-induced recurrent mossy fiber innervation of dentate gyrus inhibitory interneurons: possible anatomical substrate of granule cell hyperinhibition in chronically epileptic rats. *J Comp Neurol* 494:944–960
140. Smith SS, Shen H, Gong QH, Zhou X (2007) Neurosteroid regulation of GABA(A) receptors: focus on the  $\alpha 4$  and delta subunits. *Pharmacol Ther* 116:58–76
141. Snead OC 3rd (1995) Basic mechanisms of generalized absence seizures. *Ann Neurol* 37:146–157
142. Somogyi P, Freund TF, Hodgson AJ, Somogyi J, Beroukas D, Chubb IW (1985) Identified axo-axonic cells are immunoreactive for GABA in the hippocampus and visual cortex of the cat. *Brain Res* 332:143–149
143. Sperk G, Drexel M, Pirker S (2009) Neuronal plasticity in animal models and the epileptic human hippocampus. *Epilepsia* 50:29–31
144. Sperk G, Furtinger S, Schwarzer C, Pirker S (2004) GABA and its receptors in epilepsy. *Adv Exp Med Biol* 548:92–103
145. Sperk G, Hamilton T, Colmers WF (2007) Neuropeptide Y in the dentate gyrus. *Prog Brain Res* 163:285–297
146. Sun C, Mtchedlishvili Z, Erisir A, Kapur J (2007) Diminished neurosteroid sensitivity of synaptic inhibition and altered location of the  $\alpha 4$  subunit of GABA(A) receptors in an animal model of epilepsy. *J Neurosci* 27:12641–12650
147. Sutula TP, Dudek FE (2007) Unmasking recurrent excitation generated by mossy fiber sprouting in the

- epileptic dentate gyrus: an emergent property of a complex system. *Prog Brain Res* 163:541–563
148. Swijssen A, Avila A, Brone B, Janssen D, Hoogland G, Rigo JM (2012) Experimental early-life febrile seizures induce changes in GABA(A)R-mediated neurotransmission in the dentate gyrus. *Epilepsia* 53:1968–1977
  149. Swijssen A, Brone B, Rigo JM, Hoogland G (2012) Long-lasting enhancement of GABA(A) receptor expression in newborn dentate granule cells after early-life febrile seizures. *Dev Neurobiol* 72:1516–1527
  150. Terunuma M, Xu J, Vithlani M, Sieghart W, Kittler J, Pangalos M, Haydon PG, Coulter DA, Moss SJ (2008) Deficits in phosphorylation of GABA(A) receptors by intimately associated protein kinase C activity underlie compromised synaptic inhibition during status epilepticus. *J Neurosci* 28:376–384
  151. Thind KK, Yamawaki R, Phanwar I, Zhang G, Wen X, Buckmaster PS (2010) Initial loss but later excess of GABAergic synapses with dentate granule cells in a rat model of temporal lobe epilepsy. *J Comp Neurol* 518:647–667
  152. Van Duijn H, Schwartzkroin PA, Prince DA (1973) Action of penicillin on inhibitory processes in the cat's cortex. *Brain Res* 53:470–476
  153. Van Kempen TA, Kahlid S, Gonzalez AD, Spencer-Segal JL, Tsuda MC, Ogawa S, McEwen BS, Waters EM, Milner TA (2013) Sex and estrogen receptor expression influence opioid peptide levels in the mouse hippocampal mossy fiber pathway. *Neurosci Lett* 552:66–70
  154. Vicini S (1991) Pharmacologic significance of the structural heterogeneity of the GABA<sub>A</sub> receptor-chloride ion channel complex. *Neuropsychopharmacology* 4:9–15
  155. Vithlani M, Moss SJ (2009) The role of GABA<sub>A</sub>R phosphorylation in the construction of inhibitory synapses and the efficacy of neuronal inhibition. *Biochem Soc Trans* 37:1355–1358
  156. von Kitzing E, Jonas P, Sakmann B (1994) Quantal analysis of excitatory postsynaptic currents at the hippocampal mossy fiber-CA3 pyramidal cell synapse. *Adv Second Messenger Phosphoprotein Res* 29:235–260
  157. Waldbaum S, Dudek FE (2009) Single and repetitive paired-pulse suppression: a parametric analysis and assessment of usefulness in epilepsy research. *Epilepsia* 50:904–916
  158. Walker MC, Ruiz A, Kullmann DM (2001) Monosynaptic GABAergic signaling from dentate to CA3 with a pharmacological and physiological profile typical of mossy fiber synapses. *Neuron* 29:703–715
  159. Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, Lerman-Sagie T, Lev D, Mazarib A, Brand N, Ben-Zeev B, Goikhman I, Singh R, Kremmidiotis G, Gardner A, Sutherland GR, George AL Jr, Mulley JC, Berkovic SF (2001) Neuronal sodium-channel  $\alpha$ 1-subunit mutations in generalized epilepsy with febrile seizures plus. *Am J Hum Genet* 68:859–865
  160. Wang DD, Kriegstein AR (2009) Defining the role of GABA in cortical development. *J Physiol* 587:1873–1879
  161. Witter MP (2007) The perforant path: projections from the entorhinal cortex to the dentate gyrus. *Prog Brain Res* 163:43–61
  162. Wu K, Leung LS (2001) Enhanced but fragile inhibition in the dentate gyrus in vivo in the kainic acid model of temporal lobe epilepsy: a study using current source density analysis. *Neuroscience* 104:379–396
  163. Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV, Bramham CR (2002) Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation of Arc synthesis. *J Neurosci* 22:1532–1540
  164. Zhan RZ, Nadler JV (2009) Enhanced tonic GABA current in normotopic and hilar ectopic dentate granule cells after pilocarpine-induced status epilepticus. *J Neurophysiol* 102:670–681
  165. Zhan RZ, Timofeeva O, Nadler JV (2010) High ratio of synaptic excitation to synaptic inhibition in hilar ectopic granule cells of pilocarpine-treated rats. *J Neurophysiol* 104:3293–3304
  166. Zhang N, Wei W, Mody I, Houser CR (2007) Altered localization of GABA(A) receptor subunits on dentate granule cell dendrites influences tonic and phasic inhibition in a mouse model of epilepsy. *J Neurosci* 27:7520–7531