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Is Plasticity of GABAergic Mechanisms Relavant to Epileptogenesis?

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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 $GABA_A$ 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 $GABA_A$ receptors in response to insult or injury.

Keywords

GABA; $GABA_A$ receptor; Interneuron; α subunit; Chloride channel; Granule cell; Adult neurogenesis; Status epilepticus; Febrile seizures; Aberrant neurogenesis; Ectopic granule cell

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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 $GABA_A$ receptor ($GABA_AR$) 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 $GABA_ARs$ [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 $GABA_A$ 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 $GABRG_2$ gene which normally encodes the γ subunit of the $GABA_AR$ [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 $GABA_B$ receptors on thalamocortical relay cells. By enhancing the actions of GABA to hyperpolarize relay cells, T-type Ca^{2+} current in relay cells are strongly deinactivated, 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 GABARs 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 $GABA_A$Rs in DG granule cells (GCs). Presynaptic $GABA_A$Rs and effects of $GABA_A$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 $GABA_A$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, $GABA_B$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 basketlike 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 paravalbumin, 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 $GABA_A$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 ***Hi***lar 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 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 $p75^{NTR}$ 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 inter-neurons 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 serotoninergic, 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 $GABA_AR$s mediate most fast synaptic inhibition in the forebrain (Fig. 11.2). $GABA_AR$s 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 $GABA_AR$ subunit families and multiple subtypes exist within each of these subtypes (α1–6, β1–4, γ1–3, δ, ε, π, Φ). The most common $GABA_AR$ is the α1β2γ2 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 $GABA_AR$s 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 α-subtype results in differences in receptor kinetics, membrane localization and $GABA_AR$ modulation by benzodiazepines and zinc [87, 97, 140, 154]. In the GC, $GABA_AR$s that contain α1 subunits paired with γ2 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. $GABA_AR$s that contain α4 subunits have unique pharmacological properties, such as insensitivity to benzodiazepines and increased sensitivity to zinc blockade. Receptors containing α4 subunits are most often found with the δ rather than the γ subunit in combination with αβ. These α4βδ $GABA_AR$s 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 α4βγ2$GABA_AR$s are found at synapses of GABAergic neurons on GCs, where they are proposed to affect both the rise time and decay of synaptic currents [71].

11.2.3 Regulation of $[Cl]_i$ in Early Development and Its Relevance to TLE

One of the characteristics of GABAergic inhibition at $GABA_AR$s that has implications for epilepsy – and has been studied extensively in the hippocampus in TLE – is the regulation of chloride flux through the $GABA_AR$. 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^+-Cl^- 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 $GABA_AR$, leading to a depolarization [8, 27]. After maturation, KCC2

expression increases and this leads to a lower $[Cl^-]_i$ and chloride influx when GABA binds to $GABA_A$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_{Cl^-}. 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 $GABA_A$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 mismigrate (discussed further below). It has been suggested that these mismigrated 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 $GABA_AR$-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 $GABA_AR$-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 $GABA_AR$ 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 $GABA_AR$-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 $GABA_A$Rs per GC decreases [26, 47, 86] via enhanced clathrin-dependent $GABA_A$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 $GABA_A$Rs [13, 48]. In vivo studies using chemoconvulsants have shown that SE promotes a rapid reduction in the number of physiologically active $GABA_A$Rs in GCs that correlated with a reduction in the level of β2/β3 and γ2 immunoreactivity present in the vicinity of a presynaptic marker [86]. In fact, SE appears to trigger subunit specific events to regulate the trafficking of $GABA_A$Rs by promoting the dephosphorylation of β3 subunits [47, 150]. Decreased phosphorylation of β3 increases the interaction of $GABA_A$Rs with the clathrin-adaptor protein 2 (AP2), facilitating the recruitment of $GABA_A$Rs into clathrin-coated pits and promoting their removal from the plasma membrane [47, 150]. In hippocampal slices obtained from mice after SE, increased $GABA_A$R phosphorylation or blockade of normal AP2 function resulted in $GABA_A$R accumulation at the plasma membrane and increased synaptic inhibition [150].

Alterations in $GABA_A$R subunit composition occur subsequent to SE in a number of animal models, and there is evidence that these changes my 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 $GABA_A$R subunits (e.g., α1, α4, γ2, and δ) 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 $GABA_A$R-mediated inhibition, and in $GABA_A$R pharmacology [21, 30, 45]. After pilocarpine-induced SE, $GABA_A$R α1 subunit mRNA expression decreases, and $GABA_A$R α4 subunit mRNA expression increases [18]. Changes in $GABA_A$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 α4γ2 containing receptors, a reduction in α1γ2 containing receptors in the DG [76], and shift of α4-containing receptors from extrasynaptic to synaptic and perisynaptic locations, which is likely to be related to the appearance of α4βγ2 receptors [146, 166]. Changes in expression and localization of α-subunits associated with changes in synaptic $GABA_A$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 $GABA_AR$ subunit α1 expression after SE via viral-mediated transfer of an α1 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-α1-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 $GABA_AR$ α-subunit changes in the process of epileptogenesis.

Receptors containing α4 subunits are most often found with the δ rather than the γ subunit in combination with αβ. These α4βδ $GABA_ARs$ are localized to extrasynaptic sites and contribute to tonic inhibition. Under physiological conditions, only a minor population of α4βγ2 GABARs 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 α1 subunit expression in GCs after SE, there is a marked increase in α4 subunit expression that results in an increase in the abundance of α4γ2-containing receptors in synaptic and perisynaptic locations [146, 166] (see Fig. 11.2), along with the reduction in α1γ2-containing receptors [76]. The α4βγ2 receptors may contribute to epileptogenesis, as α4-containing $GABA_ARs$ have been shown to desensitize rapidly, especially when assembled with β3 subunits [71]. In addition, $GABA_ARs$ containing the α4 subunit are very sensitive to zinc blockade, as are $GABA_ARs$ 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 α4βγ2 receptors causing a decreased response to GABA. Collectively these alterations may contribute to epilepsy development, phar macoresistance and further epilepsy progression.

$GABA_AR$ 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 GABARα1 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 α1 subunit levels following SE and may contribute to epileptogenesis. Increases in GABARα4 subunit are transcriptionally regulated by BDNF activation of the TrkB

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 stimulusevoked 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 mismigrate 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 $GABA_A$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 $GABA_A$Rs; more $GABA_A$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 β2/3subunits

occurred in newborn GCs after febrile seizures [149]. Changes in α3 subunits were also noted by Swijsen et al. [148]. The results suggest that febrile seizures lead to long-lasting changes in the expression of $GABA_A$Rs in the DG, and in the GCs that were born after febrile seizures. These effects could lead to lifelong 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, mismigrate 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 $GABA_A$ 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.

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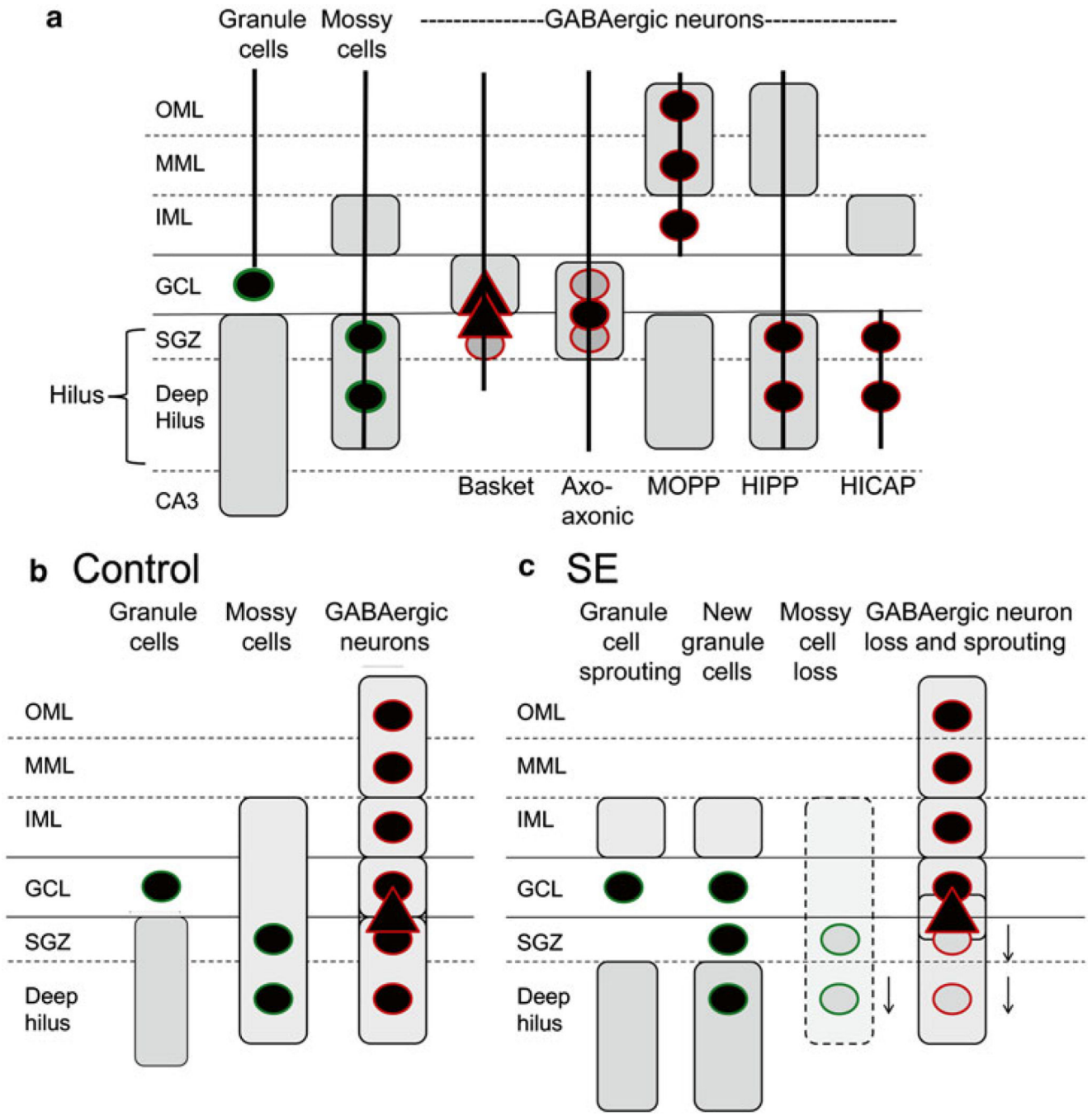

Fig. 11.1. DG circuitry in the normal adult rodent and following status epilepticus (SE)

(**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. *Gray 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)

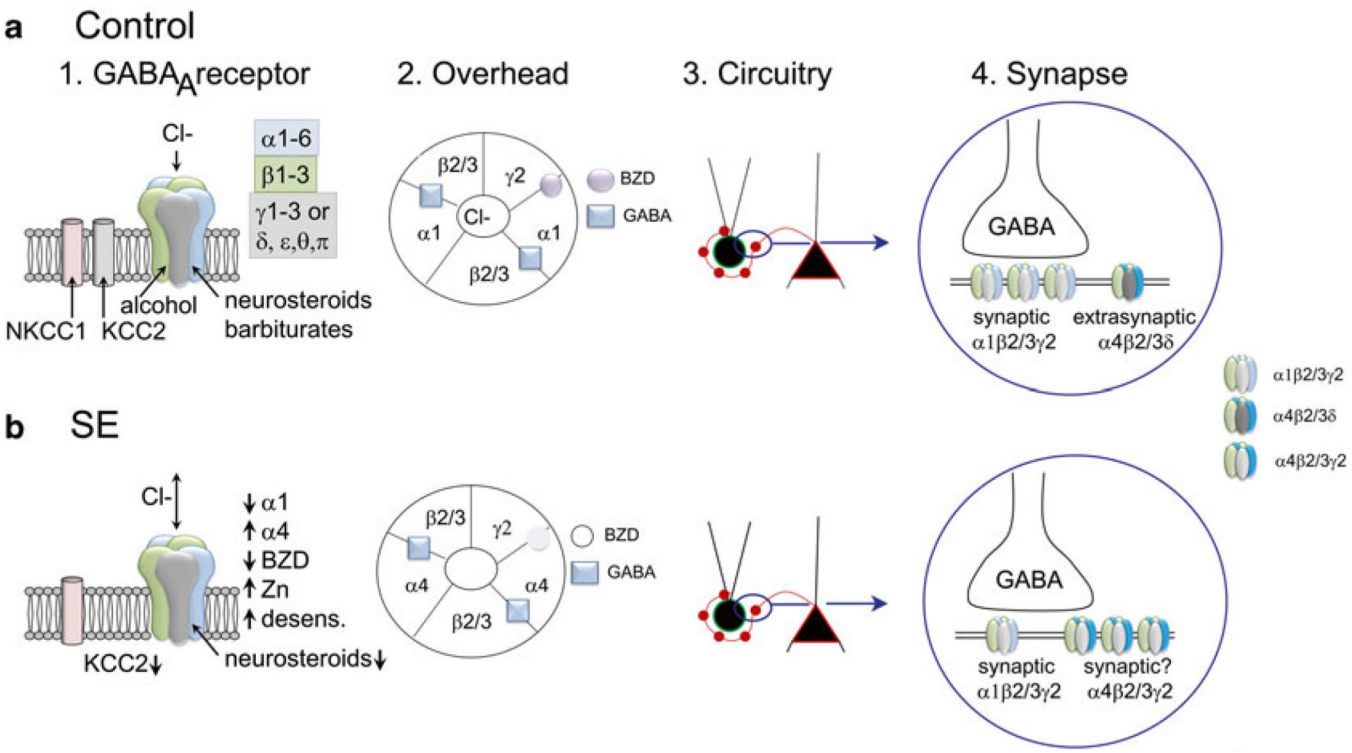

Fig. 11.2. $GABA_A$receptor subunits in dentate gyrus (DG) granule cells (GCs) in the normal adult rodent and following SE

(**a**) Control conditions. (*1*) The subunits of the $GABA_A$receptor ($GABA_AR$) are diagrammed, with sites of modulation noted. The location of the K^+Cl^- cotransporters NKCC1 and KCC2 are depicted schematically. (*2*) An overhead view of a typical $GABA_AR$ in a normal adult GC. It has α1, β2/3 and γ2 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 **α1β2/3γ2** receptors and extrasynaptic receptors that contain different subunits (α4β2/3δ). (**b**) After SE, KCC2 expression decreases and the direction of chloride flux may change as a result. The expression of **α1** subunits decrease and α4 subunits increase. Other changes are altered sensitivity to modulators. (*2*) One of the changes in the $GABA_ARs$ 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 α1 subunits and increased α4 subunits, which may become perisynaptic (indicated by a ?) (References are listed in the text. Parts 1–2 of this figures were adapted from Jacob et al. [59])

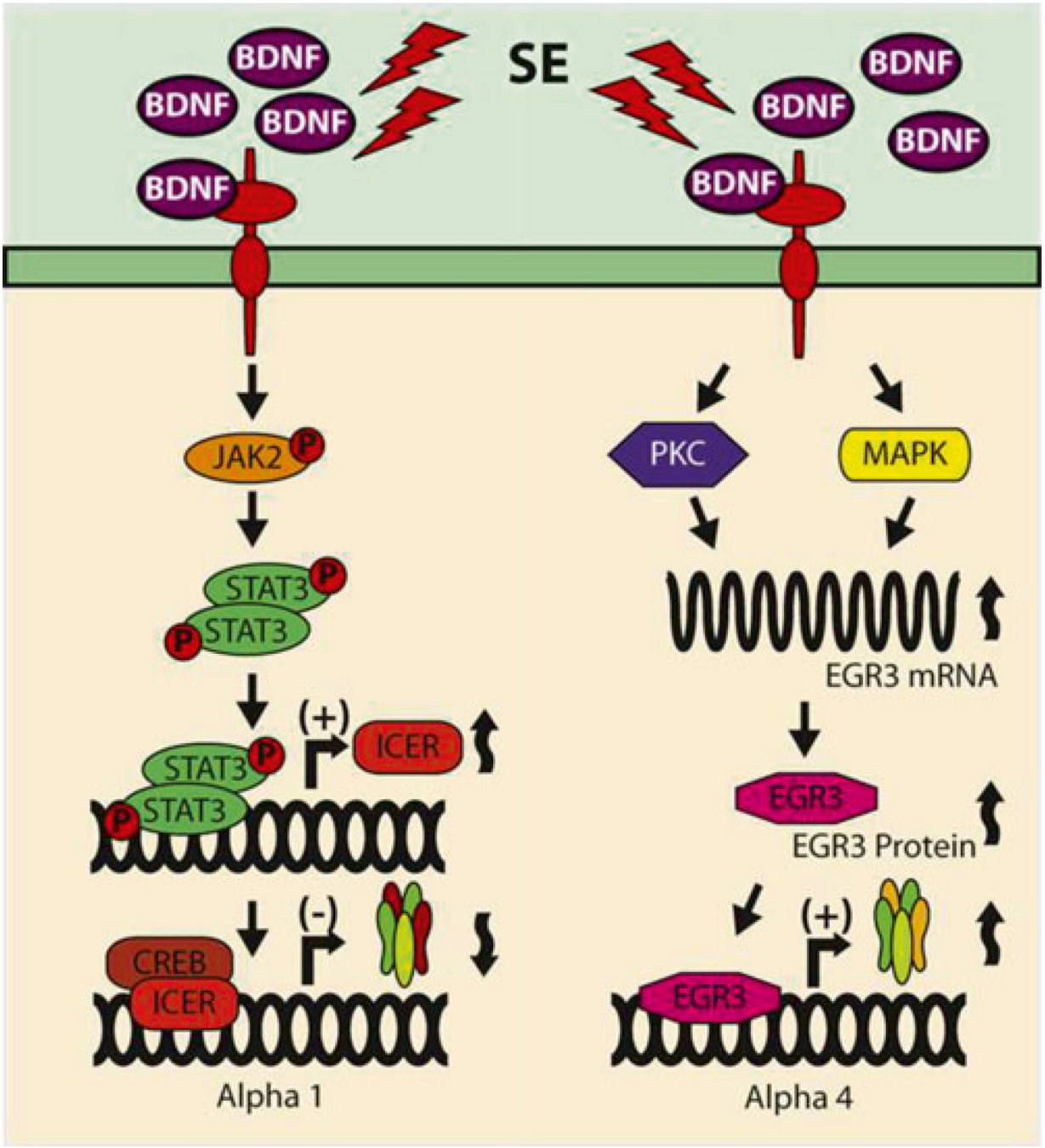

Fig. 11.3. Regulation of $GABA_A$ receptor expression after SE

BDNF regulates the final composition of $GABA_A$Rs by differentially altering the expression of α1 and α4 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 α1 subunits and the up-regulation of α4 subunits, respectively (Reproduced from Gonzalez and Brooks-Kayal [46])