



Review

Altered GABA_A receptor expression during epileptogenesisMarco I. González^{a,*}, Amy Brooks-Kayal^{a,b}^a Department of Pediatrics, Division of Neurology, School of Medicine, University of Colorado Denver, Aurora, CO 80045, United States^b The Children's Hospital, Aurora, CO 80045, United States

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ABSTRACT

γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. GABA_A receptors are heteropentamers formed by assembly of multiple subunits that generate a wide array of receptors with particular distribution and pharmacological profiles. Malfunction of these receptors has been associated with the pathophysiology of epilepsy and contribute to an imbalance of excitatory and inhibitory neurotransmission. The process of epilepsy development (epileptogenesis) is associated with changes in the expression and function of a large number of gene products. One of the major challenges is to effectively determine which changes directly contribute to epilepsy development versus those that are compensatory or not involved in the pathology. Substantial evidence suggests that changes in the expression and function of GABA_A receptors are involved in the pathogenesis of epilepsy. Identification of the mechanisms involved in GABA_A receptor malfunction during epileptogenesis and the ability to reverse this malfunction are crucial steps towards definitively answering this question and developing specific and effective therapies.

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Epilepsy

Epilepsy is one of the oldest conditions known to mankind and is still the most common neurological condition affecting individuals of all ages. At any given time approximately 50 million people world wide have epilepsy [2]. Epilepsies are characterized by spontaneous recurrent unprovoked seizures (2 or more) caused by focal or generalized paroxysmal changes in neurological function triggered by abnormal synchronized electrical activity [2,15,19,23,47]. Temporal lobe epilepsy (TLE) is the most common form of epilepsy

and is often associated with a pathology termed mesial temporal sclerosis characterized by neuronal loss and synaptic reorganization. The most common risk factors for epilepsy are cerebrovascular disease, brain tumors, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance and infections of the central nervous system (CNS) [47].

GABA receptors and epilepsy

Most fast synaptic inhibition in the mature brain is mediated by pentameric anion-selective GABA_A receptors assembled from multiple subunit subtypes (α 1–2, β 1–3, γ 1–3, δ , ϵ , π , θ , and σ 1–3). GABA_A receptors subunit composition dictates the intrinsic properties of each channel in terms of GABA affinity, kinetics, conductance, allosteric modulation, probability of channel opening and

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interaction with modulatory proteins and subcellular distribution [12,19,26]. Synaptic GABA_A receptors contain γ subunits whereas those located at perisynaptic or extrasynaptic sites contain predominantly δ subunits, electrophysiologically these receptors are responsible for phasic and tonic inhibition, respectively [19,26]. Alterations in the expression and function of GABA_A receptor subunits have been documented in animal models and human cases of TLE [25,31,48]. The general observation from these studies is that GABA_A receptor function is augmented, but despite increased inhibition there is significant alterations in the subunit composition and function of GABA_A receptors [5,8,18,31,37–39,54]. In dentate gyrus neurons (DGN) from the hippocampus, an increase in GABA_A receptor current density, zinc blockade and clonazepam augmentation is observed, while neurons from the CA1 region have reduced GABA currents and clonazepam augmentation [20,30]. These changes appear to be directly correlated with changes in the gene expression and subcellular distribution of receptors within individual pyramidal neurons that result in increased somatic but reduced dendritic inhibition [8,13].

Epileptogenesis

The term “epileptogenesis” describes the process by which a brain develops spontaneous seizures or epilepsy, and is often divided into three stages: acute injury, latent period, and spontaneous seizures [7,40,42,49]. In humans, the development of spontaneous seizures is preceded by a latent period lasting months or years after an initial precipitating event like head injury, prolonged febrile seizures, stroke, or status epilepticus (SE) [7,40,42]. Studies in animal models have shown that the latent period is characterized by a diverse array of cellular and molecular changes. Continuous monitoring of animal models has been used to define the time needed for the development of spontaneous seizures, and some studies have found that spontaneous seizures may appear in as few as 3 days after SE [9,27,43,55]. Despite intense investigation, it is still unclear whether all epileptogenic events are restricted to the latent period, or whether the end of the latent period is not a terminal milestone but just another step in a continuous chain of events that extends beyond the first spontaneous seizure [49,55]. Several laboratories, including our own, have focused on the study of diverse mechanisms involved in gene regulation and plasticity of GABA receptors during this period. Clarification of the cause-effect relationship of the changes in ion channel expression during the epileptogenic period is a major goal in this area of research.

Status epilepticus

Status epilepticus was initially defined by Gastaut as ‘a term used whenever a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition’ [10]. There is clinical and experimental evidence that status epilepticus becomes self-sustaining after 30 min of continuous seizures promoting evident tissue damage and pharmacoresistance [10]. Clinically, this period of time has been limited to 5–15 min mostly to avoid a delay in therapeutic intervention. The fundamental pathophysiology of SE involves a failure of mechanisms that would normally abort an isolated seizure resulting in neuronal hyperexcitability and compromised GABAergic neurotransmission [17,32,50]. Mechanistic information suggests that reduced presence of GABA_A receptors at the plasma membrane may be responsible for the loss of GABAergic responses and the resistance to benzodiazepines [21,28,35]. In support of this, pharmacological blockade of GABA receptors with allosteric modulators is only effective shortly after SE initiation because at later time

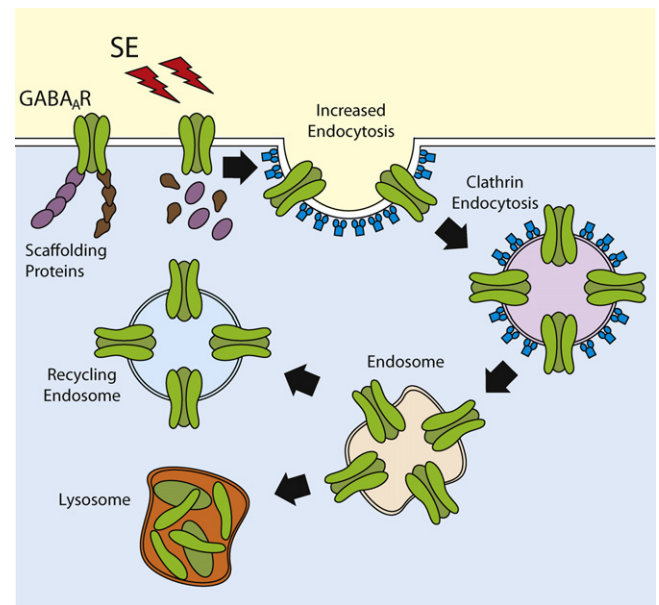


Fig. 1. Regulation of GABA_A receptor trafficking during SE. After SE induction GABA_A receptors are internalized via a clathrin-dependent mechanism. Following endocytosis, receptors can be recycled back to the plasma membrane or sorted to the lysosomes for degradation.

points (>1 h) pharmacoresistance develops and GABAergic drugs become ineffective [21,28,52].

Receptor regulation during SE

During status epilepticus there is increased neuronal hyperexcitability and inhibitory GABAergic synaptic transmission becomes compromised, miniature inhibitory post-synaptic currents (mIPSCs) are reduced and the number of active GABA_A receptors per dentate granule cell is also decreased [10,22,35]. Enhanced clathrin-dependent GABA_A receptor internalization has emerged as one of the rapid mechanisms to explain the self-sustaining nature of seizures during SE [22,26]. *In vitro* studies using hippocampal neurons stimulated with low-magnesium to promote spontaneous recurrent epileptiform discharges showed a large decrease in GABA-gated chloride currents that correlates with reduced cell surface expression and intracellular accumulation of GABA_A receptors [4,22]. *In vivo* studies using chemoconvulsants have shown that SE promotes a rapid reduction in the number of physiologically active GABA receptors in granule cells that correlates with a reduction in the level of $\beta 2/\beta 3$ and $\gamma 2$ immunoreactivity present in the vicinity of a presynaptic marker [35]. In fact, SE appears to trigger subunit specific events to regulate the trafficking of GABA_A receptors by promoting the dephosphorylation of $\beta 3$ subunits [21,52]. Decreased phosphorylation of $\beta 3$ increases the interaction of GABA receptors with the clathrin-adaptor protein 2 (AP2), facilitating the recruitment of GABA receptors into clathrin-coated pits and promoting its removal from the plasma membrane [21,52] (Fig. 1). Increased GABA receptor phosphorylation or the blockade AP2 normal function results in GABA receptor accumulation at the plasma membrane and improved synaptic inhibition in hippocampal slices obtained from mice after SE [52]. Although internalization and intracellular accumulation of different GABA receptor subunits has been documented immediately after SE induction, the fate of internalized receptors has not been detailed. Internalized receptors can be recycled back to the plasma membrane or transported to the lysosomes for degradation [10], but the details of this step of the regulation remain to be investigated.

Epileptogenic period

Epileptogenesis is accompanied by many changes in synaptic plasticity and in passive and active membrane properties of neurons [3,29,34]. Hippocampal networks are hyperexcitable during the latent period and EEG measurements display interictal-like activity [16]. Hippocampal pyramidal neurons change from a normal regular firing pattern to burst firing in response to depolarization or even spontaneously a few days after SE [46]. This abnormal activity acts as a pacemaker synchronizing entire cell populations [46]. During this period, there appears to be an overall reorganization of glutamatergic and GABAergic networks. A loss of interneurons and mossy cells reduces the number of GABAergic and glutamatergic synapses [6,53].

Gene regulation during the latent period

Repeated or prolonged seizures produce a broad and complex cascade of pathophysiological and biochemical changes in the brain. In the minutes to hours after SE, activation of plasma membrane receptors result in changes in the intracellular signal transduction pathways involved in the maintenance of vital cellular functions [10,34]. In the following hours and days, long-term changes in gene expression result from the combined effects of repeated seizures, seizure-induced cell death, and subsequent neuronal reorganization [10]. In DGC of adult rodents, pilocarpine-induced SE reduces the expression of the $\alpha 1$ [8] and γ [37] subunits of GABA_A receptors and increases the expression of $\alpha 4$ subunits [8,37]. This is associated with an increased abundance of $\alpha 4\gamma 2$ containing receptors, a reduction in $\alpha 1\gamma 2$ containing receptors in dentate gyrus [33] and shift of $\gamma 2$ -containing receptors from synaptic to perisynaptic locations, likely as part of $\alpha 4\beta\gamma 2$ receptors [57]. In contrast, when neonatal rodents (at postnatal day 10) are subject to SE, mRNA of the $\alpha 1$ subunit increases over-time [56]. Adult rats uniformly develop the recurrent spontaneous seizures that define epilepsy, but neonatal rats do not [56]. The changes in GABA_A receptor subunit expression observed in adult animals precede the development of spontaneous seizures, suggesting a possible correlation between the changes in GABA_A receptor expression and the epileptogenic process.

More direct evidence for a role of GABA receptor subunit expression in epileptogenesis was obtained by over-expression of $\alpha 1$ subunits using an adeno-associated virus for gene transfer [43]. Expression of a bicistronic RNA containing the coding information for the $\alpha 1$ subunit and the yellow enhanced fluorescent protein was placed under control of the $\alpha 4$ subunit promoter, a promoter that is markedly activated in the dentate gyrus after SE [43]. Rats injected with the virus showed increased expression of $\alpha 1$ subunits in the dentate gyrus two weeks after SE and had a 3-fold increase in the mean time to the first spontaneous seizure. More importantly, in the first 4 weeks after SE, only ~40% of the virus injected rats develop spontaneous seizures while a 100% of the rats receiving sham-injections became epileptic, providing direct evidence that increasing the levels of a single GABA receptor subunit in DG can inhibit the development of spontaneous seizures after SE [43].

SE is associated with excessive neuronal activity that stimulates many different signaling pathways. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is activated during seizures and ischemia as well as by stress and inflammation [11,14,24,41,51]. Typically, cytokine receptors activate JAK/STAT by first promoting JAK phosphorylation that in turn phosphorylates STATs [14,24,58,59]. Tyrosine phosphorylation of STATs promotes its homo- or hetero-dimerization followed by translocation to the nucleus where they bind to specific DNA elements (STAT-recognition sites) to regulate gene expression [1,58]. One of the transcriptional elements regulated by STAT binding is

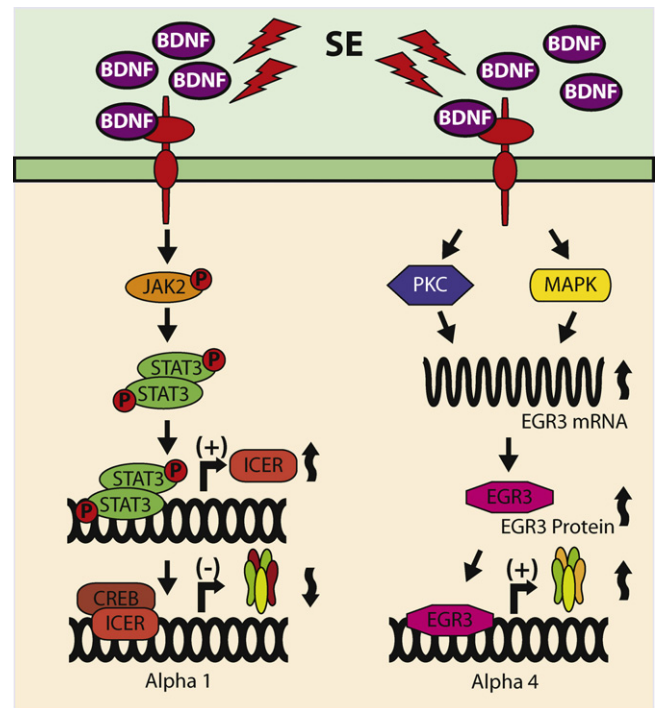


Fig. 2. BDNF-stimulated signaling pathways differentially regulate GABA_A receptor expression. BDNF may regulate the final composition of GABA_A receptors by differentially altering the expression of $\alpha 1$ and $\alpha 4$ subunits. Both *in vivo* and *in vitro* evidence suggest that increased levels of BDNF following status epilepticus (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.

found in the promoter of the inducible cAMP early repressor (ICER). *In vitro* studies using hippocampal neurons show that brain derived neurotrophic factor (BDNF) differentially regulates the expression of $\alpha 1$ and $\alpha 4$ GABA_A receptor subunits [44]. In cultured neurons, BDNF increases binding of phosphorylated STAT3 to the ICER promoter and up-regulates ICER mRNA and protein expression. Blockade of JAK/STAT signaling with pyridone 6 or by STAT3 siRNA-knockdown inhibits the effects of BDNF on ICER expression [33]. Most importantly, *in vivo* experiments show that administration of the JAK inhibitor pyridone 6 into the dentate gyrus blocks the induction of ICER and the subsequent decrease in the expression of mRNA for the $\alpha 1$ subunit [33]. These findings suggest a key interplay among signaling pathways involving BDNF, JAK/STAT, and ICER that are critical for the regulation of GABA_A receptor subunits in response to SE (Fig. 2). The potential for these signaling pathways as novel therapeutic targets for prevention and/or treatment of epilepsy are currently under investigation.

Shortly after SE induction, animal models of epilepsy show increased expression of the $\alpha 4$ subunit [45] and increased abundance of $\alpha 4\gamma 2$ containing receptors with a concomitant reduction in $\alpha 1\gamma 2$ containing receptors [33]. Strong evidence suggests that, BDNF is also responsible for triggering the endogenous signals involved in the regulation of $\alpha 4$ subunit expression. *In vitro* experiments showed that activation of PKC and MAPK by BDNF (or phorbol ester) application results in increased expression of the early growth response factor 3 (Egr3) (Fig. 2) [44]. Egr3 belongs to a family of transcription factors composed of four proteins (Egr1, 2, 3 and 4) that share nearly identical zinc finger DNA binding domains and bind to a common Egr response element (ERE) consensus sequence [36]. *In vivo* experiments showed that SE triggered increases in mRNA and protein levels of Egr3 and enhanced binding of Egr3 to the promoter of the $\alpha 4$ GABA_A receptor subunit gene in

cells from the dentate gyrus 24 h after pilocarpine-induced SE [45]. In addition, mice devoid of *Egr3* have significant lower levels of $\alpha 4$ mRNA strongly suggesting that *Egr3* may be a critical regulator of endogenous GABA_A receptors containing $\alpha 4$ subunits [45].

Conclusion

Temporal information concerning the cascade of molecular events underlying the pathophysiology of epilepsy is starting to emerge, and the time during which epilepsy slowly develops is now been more carefully studied [49,55]. At this point, there is no doubt that the epileptogenic period includes a diverse array of molecular events that contribute to increased excitability in the immediate days following SE and continue as epilepsy develops [16,27,30]. It will be necessary to identify many additional transcriptional and posttranscriptional events triggered by SE in order to build an integrated view of the myriad of molecular events taking place during epileptogenesis. A detailed characterization of the regulation of GABA_A receptors as well as that of many other individual proteins during this period is a necessary step in the process of establishing true correlations between molecules and function in order to tailor new therapeutic strategies for the prevention and treatment of epilepsy.

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