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NLM Citation: Brooks-Kayal AR, Russek SJ. Regulation of $GABA_A$ Receptor Gene Expression and Epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Regulation of $GABA_A$ Receptor Gene Expression and Epilepsy

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Epileptogenesis, is associated with changes in the expression of a multitude of genes, including those related to inhibitory neurotransmission, and alterations in many of these genes and their gene products may be critical contributors to hyperexcitability. The $GABA_A$ receptor (GABAR) mediates most fast synaptic inhibition in brain, and changes in GABAR subunit expression and function appear to directly contribute to epileptogenesis. Results of our studies indicate that GABAR regulation after SE occurs in response to 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). Transcriptional sensors for pathway activation, such as cAMP response element binding protein (CREB), inducible cAMP response element repressor, and early growth response factor 3 (Egr3) regulate α1 and α4 subunit gene expression in parallel resulting in specific changes in GABAR populations that may contribute to hyperexcitability. In this chapter, we will discuss the results of our studies in the context of how they may provide novel therapeutic approaches for preventing or inhibiting development and progression of epilepsy after a precipitating insult.

Results of research in animal models as well as from human retrospective studies suggest that an initial precipitating event such as status epilepticus (SE), stroke or traumatic brain injury can increase the risk of later development of recurrent spontaneous seizures which define epilepsy. The process by which a normal brain transforms into one capable of producing recurrent spontaneous seizures, known as epileptogenesis, is likely to be complex and multifactorial. Among the many changes that occur during epileptogenesis are alterations in expression of a wide variety of genes. Determining what molecular pathways regulate these changes in gene expression and which of them are consequential or causative of disease are two of the major challenges of research in this area, and are critical to effectively utilizing this information to develop new therapies for the prevention and treatment of epilepsy.

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Role of $GABA_A$ receptors in epilepsy

Many laboratories, including our own, have focused on the role of gene regulation in determining changes in γ-aminobutyric acid (GABA) receptor plasticity that begin during the latent period after brain insult and persist after the development of the epileptic state. GABA is the major inhibitory neurotransmitter in the mature brain, and several drugs that enhance GABAergic inhibition are commonly used as antiepileptic medications. Conversely, drugs that block GABAergic inhibition can induce seizures in animals, further supporting the potential importance of alterations in GABAergic transmission in the etiology of epilepsy.

Three types of GABA receptors, $GABA_A$, $GABA_B$ and $GABA_C$, are found in the mature central nervous system. $GABA_A$ and $GABA_C$ are ionotropic receptors, whereas, $GABA_B$ is a metabotropic receptor. Most fast synaptic inhibition in the mature brain is mediated by $GABA_A$ receptors (GABARs), whereas slow inhibition is mediated by $GABA_B$ receptors. GABARs are composed of multiple subunits from a variety of subtypes (α1-6, β1-3, γ1-3, δ, ε, π, θ and ρ1-3) that form a pentameric anion-selective channel[1]. GABAR subunit composition determines the intrinsic properties of each channel including GABA affinity, kinetics, conductance, allosteric modulation, probability of channel opening, interaction with modulatory proteins and subcellular distribution[2]. The typical *in vivo* subunit composition is two α, two β and one γ or δ subunit. Synaptic GABARs in cortex and hippocampus most commonly contain a γ subunit in combination with an α1 or α2 and β_x- subunit whereas those located at perisynaptic and extrasynaptic sites contain predominantly a δ subunit in combination with an α4 and β_x subunit, or a γ subunit in combination with an α5 and β_x subunit[3]. There is remarkable receptor heterogeneity, with subtype combinations varying in different brain regions, cell types, membrane locations and during different times in ontogeny[2,4–6].

Prolonged seizures (status epilepticus or SE) result in alterations in the expression and membrane localization of several GABAR subunits (α1, α4, γ2, δ) in hippocampal dentate granule neurons[7–9]. These alterations, which are associated with changes in phasic and tonic GABAR-mediated inhibition, decreased GABAR modulation by benzodiazepines and neurosteroids, and increased inhibition by zinc, begin soon after SE and continue after animals become epileptic[7–13]. In the pilocarpine model of SE in adult rats, GABAR α1 subunit mRNA expression decreases and α4 subunit mRNA expression increases in dentate granule cells of the hippocampus, and animals uniformly go on to develop epilepsy. These changes in subunit mRNA expression correlate with decreased presence of α1γ2 containing receptors[14] and increased presence of α4γ2 containing receptors[14,11], as well as an increase in perisynaptic localization of γ2 subunits, likely partnering with α4[9]. GABAR functional and subunit expression changes have also been observed in neurons from surgically resected hippocampus from patients with intractable TLE[15–17]. The changes in GABAR subunit expression and function in dentate granule cells of epileptic animals precede the development of epilepsy, suggesting that these changes contribute to the epileptogenic process. In contrast, neonatal SE (postnatal day 10) in rats results in increased GABAR α1 subunit expression and does not lead to the subsequent development of epilepsy[18].

These studies suggest that GABAR subunit alterations may be critical contributors to epileptogenesis. To more directly determine this, we utilized gene transfer to mitigate GABAR subunit changes and examined the effect on epilepsy development. Specifically, we tested the hypothesis that the expression of higher α1 subunit levels would inhibit development of epilepsy after SE by using an adeno-associated virus (AAV) gene transfer vector (AAV2)-serotype 5 designed to express a bicistronic RNA that codes for both the GABAR α1 subunit as well as the reporter, enhanced yellow fluorescent protein (eYFP)[19]. Expression of this RNA was placed under control of the GABAR α4 subunit gene (GABRA4) core promoter region, because it had been previously shown to be markedly activated in dentate gyrus following SE[20]. Thus following SE, activity of the α4 promoter was upregulated, resulting in enhanced α1 transgene expression. AAV-vectors containing either the α1/eYFP fused cDNA (AAV-α1) or the eYFP-reporter only (AAV-eYFP) were injected into dentate gyrus of adult rats, and SE was induced two weeks later by intraperitoneal injection of pilocarpine (385 mg/kg)[19]. Rats injected with AAV-α1 showed 3-fold higher levels of α1 subunits in dentate gyrus by 2 weeks after SE compared to the control

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groups. Rats were continuously video-EEG monitored to determine the latency for the development of spontaneous seizures. AAV-α1 injection resulted in a 3-fold increase in the mean time to the first spontaneous seizure following SE, and only 39% of AAV-α1 injected rats were observed to develop spontaneous seizures in the first 4 weeks after SE, as compared to 100% of rats receiving sham-injections. Because all groups of rats experienced similar SE after pilocarpine injection, these findings provide the first direct evidence that increasing the levels of a single GABAR subunit in dentate gyrus can inhibit the development of spontaneous seizures after SE. Together, these data support a role for GABAR α-subunit changes in the process of epileptogenesis.

Mechanisms regulating $GABA_A$ receptor subunit expression

α1 subunit regulation

Although viral gene transfer is a promising therapeutic avenue to modify aberrant gene expression associated with epileptogenesis, producing the optimal level of expression over a prolonged period can be challenging. Another potential approach is to modify the mechanisms regulating gene expression. Recent work in our laboratories has established cAMP response element binding protein (CREB) and inducible cAMP early repressor[14,21] as transcriptional regulators responsible for decreased GABAR α1 subunit mRNA and protein levels occurring after SE in the dentate gyrus. CREB is a stimulus-induced bZIP transcription factor that is activated by phosphorylation at its Ser 133 site. Phosphorylated CREB (pCREB) dimerizes, or forms heterodimers with CREB family members, and binds to cAMP response element (CRE) motifs on promoters that contain the consensus sequence TGACGTCA[22]. Along with the chromatin modifier, CREB binding protein (CBP), pCREB serves as an activator to increase transcription of its target genes. Transcriptional regulation through CREB has been implicated in mechanisms of cell survival, plasticity, and learning and memory[22]. Target genes of pCREB include CREB family members, which consist of cAMP response element modulator (CREM) and activating transcription factor. These para- and homologs of CREB also bind CRE elements to modulate the transcription of particular genes, often as heterodimers with CREB. The CREM gene produces many gene products, including truncated forms that are missing the activation domain, and hence, function as transcriptional repressors. A collection of such repressors, produced by the alternative use of an internal promoter region in a downstream intron of CREM, is inducible cAMP early repressor (ICER), a group of 4 proteins (α, β, γ, and δ)[23, 24]. The γ form is most prevalent and acts as a homodimer at the CRE site or heterodimerizes with CREB to directly block CREB-induced transcription.

The human α1 promoter *(GABRA1-p)* contains a functional CRE site[25], and several studies using adult animal models of epilepsy suggest that seizures increase levels of the activated form of CREB (pCREB) and CREM/ICER activity[26,27]. Our laboratories have found sustained increases in levels of both pCREB and ICER in the dentate gyrus of the hippocampus, at 1–48 hours after pilocarpine induced SE[14]. Using chromatin immunoprecipitation (ChIP) and DNA pulldown studies, it was determined that there was also increased binding of pCREB and ICER to the endogenous *GABRA1-p* in dentate gyrus after SE[14]. Further, results of *GABRA1-p*/luciferase reporter assays in transfected primary hippocampal neurons show that overexpression of CREB and ICER produce robust decreases in *GABRA1-p* activity, and overexpression of ICER alone produces a marked decrease in the levels of endogenous α1 subunits at the cell surface[21]. These findings suggest that CREB and ICER are important regulators of seizure-induced changes in α1 subunit expression.

The excessive neuronal activity associated with SE stimulates many different signaling pathways that could lead to enhanced phosphorylation of CREB and expression of ICER[28]. We focused our studies on Brain Derived Neurotrophic Factor (BDNF) as a potential regulator of ICER because BDNF expression increases markedly after SE[29–33], and because BDNF differentially regulates the abundance of both α1 and α4 subunits in cultured neurons[32]. Our results demonstrated that BDNF treatment of primary hippocampal neurons in culture produces similar changes in α subunit levels as observed after SE. 24 hours after BDNF treatment, α1 levels decrease 42% and α4 levels increase 120%[32]. We further found that BDNF regulates α1 subunit levels via

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activation of the Janus kinase (JAK)/Signal Transducer and Activators of Transcription (STAT) pathway that in turn controls the synthesis of ICER which then represses *GABRA1* transcription.

The JAK-STAT pathway can be activated by a variety of methods, including cytokines binding to their specific receptors, resulting in transphosphorylation of Janus kinases (JAKs) that then lead to phosphorylation of STAT proteins[34–38]. Phosphorylation of STATs on tyrosine residues leads to STAT homo- or heterodimerization, translocation from the cytoplasm to the nucleus and binding to specific DNA elements (STAT-recognition sites) to regulate target gene expression[37, 38]. There is a STAT-recognition element in the ICER promoter and using chromatin immunoprecipitation (ChIP), we have shown that pSTAT3 association with this site is enhanced after SE in dentate gyrus[14]. Furthermore, siRNA knockdown of STAT3 inhibits BDNF-induced ICER increases, as does blockade of JAK/STAT signaling pathway with pyridone 6 (P6) in primary hippocampal cultures[14]. Most importantly, P6 administration *in vivo* into rat dentate gyrus prior to SE blocks both ICER induction and decreased transcription of *GABRA1*[14]. These findings suggest that the interplay of the CREB, JAK/STAT, and BDNF signaling pathways are critical for the decrease in α1 subunit levels that occurs in response to SE and that these pathways may provide novel therapeutic targets for epilepsy. In fact, several drugs that specifically inhibit the activity of JAK2 or block downstream STAT activation[39–42], have already been identified as potential agents in cancer chemotherapy and are in clinical trials. We are currently testing these agents to determine whether they may also provide alternative therapy for the future prevention or treatment of epilepsy.

α4 subunit regulation

GABARs that contain α4 subunits have unique pharmacologic properties such as insensitivity to benzodiazepines and increased sensitivity to zinc blockade[43]. Receptors containing α4 subunits are most often found with the δ rather than γ subunit, in combination with αβ. These α4βδ GABARs are localized to extrasynaptic sites and contribute to tonic inhibition. A minor population of α4βγ2 GABARs are found within dentate gyrus synapses where they are proposed to affect both the rise time and decay of synaptic currents[44]. In addition to the decrease in α1 subunit expression, there is a marked increase in α4 subunit expression in dentate granule cells during epileptogenesis in TLE models[7–9] that results in an increase in the abundance of α4γ2 containing receptors[9,11,14] and a reduction in α1γ2 containing receptors[14]. The change in receptor subtype from α1βγ2 to α4βγ2 may contribute to epileptogenesis, as α4 containing GABARs have been shown to desensitize rapidly, especially when assembled with β3 subunits[45]. In addition, GABARs containing the α4 subunit are very sensitive to zinc blockade[43], as are dentate granule cells of epileptic brain[7].

Our studies have shown that the alteration in α4 levels after pilocarpine-induced SE is transcriptionally mediated via an increase in the expression of the transcription factor early growth response factor 3 (Egr3)[20]. Egrs are a family 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 consensus sequence (ERE), GCG T/GGG GCG[46]. Our laboratories have shown induction of Egr family transcription factors after SE, with increases in protein levels of Egr3 and enhanced binding of Egr3 to the promoter of the endogenous α4 subunit gene (*GABRA4*) in the DG of the hippocampus 24 hours after pilocarpine induced SE[20]. α4 subunit upregulation has also been demonstrated following withdrawal of progesterone-derived neurosteroids, such as allopregnanolone and pregnanolone[47,48], resulting in enhanced neuronal excitability, seizure susceptibility and benzodiazepine resistance. This increase in α4 subunit expression is thought to be a potential molecular basis of catamenial epilepsy, a neuroendocrine condition that occurs around the perimenstrual period and characterized by neurosteroid withdrawal-linked seizure exacerbations in women with epilepsy. Recently, neurosteroid withdrawal-induced α4-subunit upregulation was found to be mediated by Egr3 similar to the role played by this transcription factor in upregulating α4 after SE[49].

Similar to its critical role in decreased expression of α1 containing GABARs, BDNF again is the endogenous signal that induces Egr3 synthesis and overexpression of α4 subunits, however, now through different signaling pathways, protein kinase C (PKC) and mitogen activated protein kinase (MAPK)[32]. In addition to its role in

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regulation of α1 and α4 subunit gene transcription after SE (for summary see figure 1), BDNF, acting via activation of TrkB receptors, has been shown to play an important role in determining the surface expression of the α2, β2,3 γ2 and δ subunits[50–52]. In combination, these findings establish BDNF's role as a multifunctional regulator of altered inhibition during epileptogenesis.

In addition to changes in α1 and α4 expression, an increase in γ2-subunit and decrease in δ-subunit surface expression in dentate granule cells with associated diminished neurosteroid sensitivity of tonic currents has also been demonstrated in rodent models of TLE[8, 9, 53, 54]. As for the α4 subunit, studies support an important role for the neurosteriods in regulation of γ and δ–subunit expression during the ovarian cycle and in pregnancy[47, 48, 55, 56] although the specific molecular mechanisms regulating changes in expression of these subunits during epileptogenesis remain to be determined.

Conclusion

The full range of gene expression changes that are involved in epileptogenesis and the molecular mechanisms that underlie them are just beginning to be characterized. Studies in animal models suggest that modulation in the transcription of a number of these genes via viral-mediated delivery of DNA binding proteins or RNA silencers, or the manipulation of their upstream regulation via selective inhibition of signal transduction pathways, may be useful therapeutic tools for the future treatment of epilepsy.

Recent work characterizing the functions of the BDNF, JAK/STAT, CREB/ICER and Egr3 signaling pathways in GABAR α1 and α4 subunit changes in the dentate gyrus after SE provides an important lead for the future development of molecular therapies aimed at restoring the balance of excitation and inhibition in the nervous system. However, the upstream components of these pathways, and the exact means through which they confer vulnerability to epilepsy must be further elucidated. Further, as these pathways regulate a myriad of genes with diverse functions, modulation of any of these pathways may have a multitude of downstream effects, many of which may involve cell- and region-specific responses throughout the brain. Therefore, the final impact of pathway blockade on epileptogenesis may be difficult to predict. For example, although the enhanced GABAR α1-subunit expression in dentate gyrus that results from JAK/STAT pathway blockade and subsequent ICER inhibition would be expected to have an antiepileptic effect, mutant mice lacking ICER have accelerated kindling[57] and develop more severe epilepsy following pilocarpine-induced SE[58]. Consistent with this finding, ICER overexpressing mice show retardation of kindling development[57]. Whether the effects of acute and transient blockade of ICER upregulation at the time of SE specifically in the hippocampal formation will have a similar effect on epileptogenesis as constitutive under- or over-expression of ICER globally in the brain remains to be determined. Finally, as several of these signaling pathways have been implicated in the regulation of learning, memory and cell survival, the effects of modulation of these pathways on these critical parameters will need to be closely monitored.

Acknowledgements

NIH/NINDS grants R01NS051710, R01NS050393, and R21NS042363 and grants from Citizens United for Research in Epilepsy (CURE), and the American Epilepsy Foundation supported the research from the Brooks-Kayal and Russek laboratories described in this chapter.

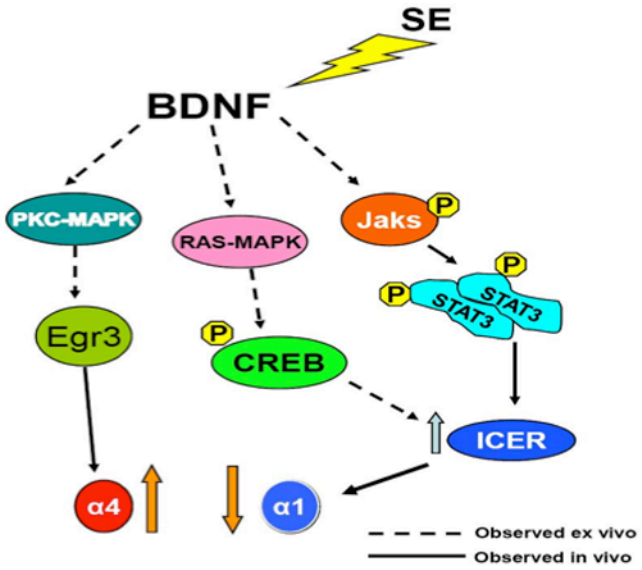

Figure 1. Differential expression of $GABA_A$ Receptor α subunits via BDNF-stimulated signal transduction pathways. Whether a $GABA_A$ receptor has an α1 or α4 subunit in its complex may have dramatic effects on brain inhibition. The results of our research show that BDNF may be responsible for flipping the switch in alpha subunit expression, with decreased α1 and increased α4, all in response to the activities of one signaling molecule, BDNF. Dramatic increases in the levels of BDNF associated with status epilepticus (SE) may drive distinct changes in gene expression through activation of at least three pathways: protein kinase C (PKC)/mitogen activated protein kinase (MAPK); RAS/MAPK; and janus kinase (JAK)/signal transducer and activator of transcription (STAT). Evidence to support this model comes from both in vitro, ex vivo, and in vivo studies. Reprinted from Brooks-Kayal AR, Raol YH, Russek SJ. Neurotherapeutics. 2009 Apr;6(2):312–8 Figure 1 with kind permission from Springer Science+Business Media B.V.

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