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Editorial Open Access

GABR genes, Autism Spectrum Disorder, and Epilepsy

Ciria C Hernandez[1*] **and Luis E Gimenez**[2]

[1]*Departments of Neurology, Vanderbilt University, Nashville, TN, USA*
[2]*Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN,USA*

***Corresponding author:** Hernandez Ciria C, Departments of Neurology, Vanderbilt University, Nashville, TN, USA, Tel: 615-936-3326; Fax; 615-322-5517; E-mail: ciria.hernandez@vanderbilt.edu

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Editorial

Is there any link between autism and epilepsy? We can shed light on this question by taking a look at which genes are usually associated with both neurological disorders, and asking: are there genes commonly deregulated between them? An interesting fact is that, in general, children with autism are also at higher risk of suffering from certain types of seizures. The role of $GABA_A$ receptors ($GABA_A$Rs) in epilepsy is widely recognized, but the link is not as clear for autism.

GABAARs are heteropentameric ligand-gated chloride channels essential in maintaining inhibitory tone [1]. Seven subunit families have been identified, each composed of one or more subtypes (α1-α6, β1-β3, γ1-γ3,δ,ε,θ, andπ). In the adult brain (Fig. 1), when activated by γ-amino butyric acid (GABA), $GABA_A$Rs produce hyperpolarization. This results in inhibition of neurotransmission on target neurons by decreasing the chances of evoking action potentials. However, early in development, GABAergic synaptic transmission is excitatory [2]. The nature of GABAergic transmission depends on the intra- and extracellular concentration of Cl-, which sets the reversal potential for GABAergic currents. The shift from excitatory to inhibitory transmission is coupled to a developmental induction of the expression of the neuronal Cl--extruding K+/Cl- co-transporter (KCC2), which cause a significant drop of intracellular Cl-. This scenario creates a complex and dynamic excitatory/inhibitory balance regulated by GABAAR-activation (Fig. 1).

Mutations in GABAAR genes (GABRA1-A6, GABRB1-B3, GABRG1-G3, GABRD) that alter GABAergic functions are associated with epilepsy [3,4]. These mutations tend to disrupt GABAAR function by two general mechanisms: impairment of channel assembly or trafficking, such that normal receptor surface expression is reduced; or changing receptor function (kinetics, binding, or gating).

However, in Autism spectrum disorder (ASD), the contribution of GABR genes is not fully understood. ASD is considered a neurodevelopmental disorder encompassing severe deficits in socialization, communication, and the onset of repetitive or unusual behaviors [5]. An increasing number of studies have described several GABR gene single nucleotide polymorphisms (SNPs) associated with the occurrence of ASD by genetic linkage, genome-wide association studies, and assessment of chromosomal variations. Up to now, five GABR genes were linked to any form of ASD. GABRB3 was the first shown to be associated with Angelman syndrome by linkage-disequilibrium mapping across chromosome 15q11-13 [6]. Moreover, SNPs were identified in all three GABR genes (GABRB3, GABRG3 and GABRA5) with loci on this chromosome [7,8]. In particular, one study showed an interactive effect between GABRB3 and GABRG3, while another group described the association of one or more risk alleles in both GABRB3 and GABRA5. Later work identified a novel allelic and genotypic interaction on chromosome 4, between SNPs in the GABRA4 gene by independent association and interactions with GABRB1 [9]. Delahanty and coworkers reported that GABRB3 (P11S), a signal peptide variant linked to both autism and childhood absence epilepsy, reduced whole-cell current and decreased β3 subunit protein on the cell surface due to impaired intracellular β3 subunit processing [10].

These findings bring us back to our initial question: are there genes commonly deregulated between autism and epilepsy? It is remarkable that among the GABR genes associated with ASD, only GABRB3 is well known to be associated with epilepsy [3], whereas GABRA4, GABRA5, GABRB1 and GABRG3 are thought to confer susceptibility to epilepsy [4,11]. In line with these findings, it seems that there is a novel distinction between GABR genes that are associated to or directly drive epilepsy (GABRA1, GABRB3, GABRG2) [3], and the genes associated with ASD [6,10]. From a patho-physiological standpoint, it would be interesting to explore the molecular basis of this paradigm to reconcile other unavoidable questions: Why is GABRB3 common to both disorders? Is this commonality related to the fact that GABRB3 displays a dynamic expression pattern during brain development and to its involvement in homeostatic or "switch-like" events during various phases of GABAergic synaptic plasticity? Could this "multi-step" regulated process put in place during development account for an excitatory/inhibitory imbalance that differently affects neuronal circuitry during development? Does GABAergic impairment/imbalance lead to the development of autistic and/or epileptogenic phenotypes depending on the availability of different GABAAR subunits and receptor sub-types? Due to the important role that $GABA_A$R-activation plays at early stages of brain development, it seems that $GABA_A$Rs dictate the "tone" between these two neurological disorders (Fig. 1). Certainly further research will be necessary in order to address these questions.

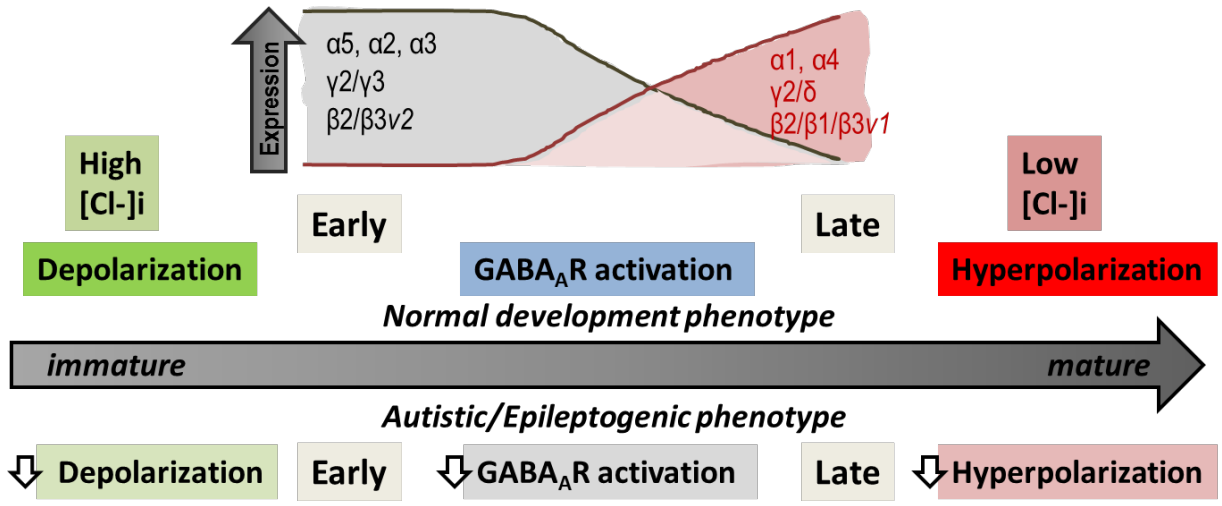

Figure 1. Defects on GABAA receptor function during brain development can lead to autistic/epileptogenic phenotype.

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