The possible role of GABA<sub>A</sub> receptors and gephyrin in epileptogenesis

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This review centers on the possible role of GABA<sub>A</sub> receptors (GABA<sub>A</sub>R) and the scaffolding protein gephyrin in epileptogenesis. The basic premise is that disruption of the network of proteins involved in the trafficking and anchoring of GABA<sub>A</sub>R might result in decreased inhibitory drive, which may promote the development of spontaneous seizures. A brief introduction to epilepsy and epileptogenesis is provided along with some of the fundamental aspects of the regulation of GABA<sub>A</sub>R by gephyrin. Finally, an overview of the alterations in gephyrin and GABA<sub>A</sub>R function observed during epileptogenesis is included.

EPILEPTOGENESIS AND EPILEPSY

In the majority of patients, temporal lobe epilepsy (TLE) appears to be the result of an injury to the brain caused by trauma, febrile seizures, encephalitis, or status epilepticus (Duncan et al., 2006; Loscher and Brandt, 2010). Induction of SE in rodents by systemic or local administration of a chemoconvulsant is usually followed by a silent (latent) period lasting days or weeks when no obvious seizure activity is observed. During the latent period brain abnormalities develop and interictal activity becomes more frequent, and then suddenly with no apparent cause overt spontaneous seizures manifest (Curia et al., 2008; Scozza et al., 2009). To capitalize the methodological advantages provided by the experimental models, several laboratories have attempted to characterize and establish the duration of the latent (silent) period, unfortunately these attempts have yielded a wide range of measures (Williams et al., 2007). It appears that despite the advantages provided by a well-controlled experimental setting, the animals used in the experiments and the type and severity of injury being tested might impact the length of the latent period. More importantly, some methodological limitations (i.e., accuracy of seizure detection, continuous vs. intermittent monitoring, authentication of when the first seizure occurred, etc.) directly impact the accuracy of the measurements and need to be overcome in order to obtain a definitive characterization of the latent period (Williams et al., 2007).

The term epileptogenesis refers to a dynamic alteration in neuronal excitability that promotes the appearance of spontaneous seizures. Temporal lobe epilepsy, the most common type of acquired epilepsy, often develops after an insult to the brain such as trauma, febrile seizures, encephalitis, or status epilepticus. During the pre-epileptic state (also referred as latent or silent period) there is a plethora of molecular, biochemical, and structural changes that lead to the generation of recurrent spontaneous seizures (or epilepsy). The specific contribution of these alterations to epilepsy development is unclear, but a loss of inhibition has been associated with the increased excitability detected in the latent period. A rapid increase in neuronal hyperexcitability could be due, at least in part, to a decline in the number of physiologically active GABA<sub>A</sub> receptors (GABA<sub>A</sub>R). Altered expression of scaffolding proteins involved in the trafficking and anchoring of GABA<sub>A</sub>R could directly impact the stability of GABAergic synapses and promote a deficiency in inhibitory neurotransmission. Uncovering the molecular mechanisms operating during epileptogenesis and its possible impact on the regulation of GABA<sub>A</sub>R and scaffolding proteins may offer new targets to prevent the development of epilepsy.

Keywords: epilepsy, epileptogenesis, GABA receptors, gephyrin, status epilepticus
The dynamic process characterized by progressive alterations in neuronal excitability that promotes appearance of spontaneous seizures and its associated structural lesions is known as epileptogenesis (Pitkanen and Lukasiuk, 2011). Currently, the terms epileptogenesis and latent (or silent) period are used interchangeably to describe the period that encompasses the occurrence of an insult to the brain and the appearance epileptic seizures. However, recent findings in patients and experimental models suggest that the alterations resulting from an injury to the brain might progress beyond the appearance of the first spontaneous seizure. Accordingly, it has been suggested that during the natural evolution of epilepsy, each new episode of spontaneous seizures (an insult itself) produces new damage that compounds the damage produced by the original brain injury (Williams et al., 2007; Slivoter, 2008; Pitkanen and Lukasiuk, 2009; O’Dell et al., 2012). Many cellular and molecular alterations in both neuronal and non-neuronal cells have been observed during epileptogenesis. Neuronal alterations include neurodegeneration, neurogenesis, and axonal damage in addition to the architectural reorganization of neuronal processes that result from abnormal sprouting and altered dendritic plasticity. Astrocytes become hypertrophic, develop longer and thicker processes and increase the expression of glial fibrillary acidic protein all as part of a process known as reactive astrogliosis (Gibbons et al., 2012; Heinemann et al., 2012; Kovács et al., 2012). During epileptogenesis there are many pathological processes that affect brain excitability including the breakdown of the blood-brain barrier (BBB) and inflammation. Ultrastructural analysis of epileptic tissue revealed significant abnormalities in the BBB components and focal opening of the BBB by direct application of albumin can lead to the generation of an epileptic focus (Ivens et al., 2007; Vezzani et al., 2011; Heinemann et al., 2012). Further, the magnitude of BBB leakage occurring during epileptogenesis has been shown to directly correlate with the seizure frequency detected during the chronic period (Van Vliet et al., 2007; Vezzani et al., 2013). Inflammatory response due to activation of microglia and astrocytes is associated with brain damage and increased BBB permeability in the tissue adjacent to the region of injury (Vezzani et al., 2011; Marchi et al., 2012). SE-induced inflammation is observed during the epileptogenic period and appears to be reactivated by the occurrence of spontaneous seizures, suggesting that inflammation might have a role in epileptogenesis and promote epileptic activity during the chronic period due to the continuous presence of inflammation intermediaries (Vezzani et al., 2011, 2013).

**GABA<sub>A</sub> RECEPTORS AND ITS ASSOCIATED PROTEINS**

The majority of fast inhibitory neurotransmission in the mature brain is mediated by anion-selective GABA<sub>A</sub>R that are assembled as pentamers from an array of multiple subunit subtypes including α1–2, β1–3, γ1–3, δ, ε, θ, ρ, and σ1–3 (Fritschy, 2008; Jacob et al., 2008; Luscher et al., 2011; Brickley and Mody, 2012). The subunit composition of GABA<sub>A</sub>R governs the intrinsic properties of the channel such as affinity for GABA, receptor kinetics, conductance, and allosteric modulation. In addition, intracellular loops of each subunit have the potential to interact with scaffolding proteins and affect the cellular distribution and clustering (synaptic or extrasynaptic) of the channels (Jacob et al., 2008; Luscher et al., 2011; Brickley and Mody, 2012). GABA<sub>A</sub>R assembled by combining γ2 and α1–3 subunits (α1–3γ2δεθ) are more commonly located at synaptic sites and mostly responsible for phasic inhibition, whereas receptors located at perisynaptic or extrasynaptic sites are primarily composed of α4 or α6 subunits combined with ε subunits (α4ε6δθγ) and mediate most tonic inhibition (Fritschy, 2008; Jacob et al., 2008; Luscher et al., 2011; Hines et al., 2012). Notably, tonic currents in pyramidal neurons of the hippocampus can also be generated by receptors containing α5 subunits (α5β2γ2) that are located at extrasynaptic locations (Brickley and Mody, 2012; Hines et al., 2012).

Typically, following synthesis in the endoplasmic reticulum, GABA<sub>A</sub>R are delivered to extrasynaptic compartments within the plasma membrane and then diffuse toward its final destination in either synaptic or extrasynaptic locations. GABA<sub>A</sub>R located at the plasma membrane also transit among different cellular compartments due to internalization and recycling events. Thus, the final number of receptors located at the cell surface is determined by continuous insertion of de novo synthesized and recycled receptors (Michels and Moss, 2007; Leidenheimer, 2008). There are a number of accessory proteins that facilitate the transit of GABA<sub>A</sub>R along the biosynthetic pathway and the different recycling compartments within the cell (Chen and Olsen, 2007; Jacob et al., 2008; Leidenheimer, 2008). Early on, during GABA<sub>A</sub>R oligomerization, accessory proteins like BIP (heavy chain binding protein), calnexin and B0g2 (Brefeldin-A-inhibited GDP/GTP exchange factor 2) form interactions with the nascent receptors within the membranous compartments of the endoplasmic reticulum and help with the translocation of the receptors into the Golgi apparatus. During the vesicular trafficking of receptors toward the plasma membrane, GABA<sub>A</sub>R containing γ subunits are linked to tubulin and the microtubules by GABARAP (GABA<sub>A</sub>R-associated protein) that acts as a bridge between vesicles containing GABA<sub>A</sub>R and the machinery that moves those vesicles toward the plasma membrane. GABARAP can also bind to NSF (N-ethylmaleimide-sensitive factor), PRIPs (phospholipase-C-related catalytically inactive proteins) and GRIK (GABA<sub>A</sub>R-interacting factors also known as TRAK), and together these proteins promote the interaction of intracellular vesicles containing GABA<sub>A</sub>R with the cytoskeleton and facilitate the motor-dependent transport of receptors toward the plasma membrane (Krousel et al., 2000; Wang and Olsen, 2000; Charych et al., 2004). The final destination of GABA<sub>A</sub>R into synaptic or extrasynaptic sites is intrinsically determined by the subunits forming the channels and extrasynaptic by protein-protein interactions with scaffolding proteins (Luscher and Keller, 2004; Chen and Olsen, 2007; Jacob et al., 2008; Leidenheimer, 2008).

Gephyrin is the main structural scaffold that links proteins located at the synaptotagm compartment with the cytoskeleton and it is required for the organization and clustering of GABA<sub>A</sub>R at inhibitory synapses (Michels and Moss, 2007; Fritschy et al., 2008). During development, increased concentration of gephyrin precedes the accumulation of GABA<sub>A</sub>R at synaptic sites and facilitates the formation and stabilization of inhibitory synapses (Christie et al., 2011).
ALTERATIONS IN GABAAR AND SCAFFOLDING PROTEINS DURING EPILEPTOGENESIS

The belief that following a brain injury there is a quiescent, pre-epileptic state in which there is gradual changes at the molecular, cellular, and circuit levels that ultimately results in the manifestation of spontaneous seizures, has led to the search for mechanisms underlying epileptogenesis. Induction of SE using the chemoconvulsant pilocarpine produces a transient decrease in GABAergic drive readily detectable during the latent period. Abnormal electroencephalogram (EEG) patterns, such as large amplitude spikes and sharp waves can be detected as early as 3–5 days following SE, which overtime culminate with the appearance of full-blown electrophysic seizures (El-Hassar et al., 2007). During SE there is a rapid increase in neuronal hyperexcitability due to a quick decline in the number of physiologically active GABAAR at the plasma membrane (Goodkin et al., 2005; Nayler et al., 2003). SE triggers a rapid loss of synaptic GABAAR containing β and γ subunits while extrasynaptic receptors containing α5 and β3 subunits remain unaffected (Goodkin et al., 2008; Terunuma et al., 2008). A decrease in the phosphorylation of β3 subunits allows the interaction of β3-containing GABAAR with the clathrin-adaptor protein 2 and the recruitment of GABAAR into clathrin-coated pits promotes a faster removal of these receptors from the cell surface, suggesting that a decrease in the phosphorylation of β3 subunits may account for the selective loss of synaptic GABAAR observed following SE (Goodkin et al., 2008; Terunuma et al., 2008). These biochemical observations directly link the decrease in miniature inhibitory post-synaptic currents observed after induction of SE with the selective internalization of synaptic GABAAR containing β and γ subunits and explain why the currents mediated by extrasynaptic receptors are spared (Goodkin et al., 2005; Nayler et al., 2003).

The fate of internalized receptors following induction of SE is more likely to be determined by the cellular compartment where they are transiently stored (Figure 1). Receptors present in endosomal compartments can be reincorporated into the active pool of receptors at the plasma membrane or they can be relocated to the lysosomes for degradation (Chen et al., 2007; Wasterlain and Chen, 2003; Peng et al., 2004). Our recent characterization of the network of proteins required for the proper trafficking and anchoring of GABAAR might be disrupted following SE. During the latent period there is a reduction in the total expression of gephyrin that appears to translate into a reduction in the number of gephyrin clusters (Knuesel et al., 2008; Fang et al., 2011; González et al., 2013). The pattern of gephyrin loss observed during the silent period parallels the changes in excitability previously observed, and suggests that the loss of scaffolding proteins directly impact the function of GABAAR during epileptogenesis. Intriguingly, during the chronic period there is an increase in both the total expression and the number of gephyrin clusters (Thind et al., 2010; Fang et al., 2011), but it is unclear if this rebound in gephyrin expression results in fully functional inhibitory synapses.

Alterations in the expression of GABAAR during the epileptogenic period include rapid down-regulation of α4, β2/3, γ2, and δ subunits (Schwarzer et al., 1997; Houser and Esclapez, 2003; Peng et al., 2004). Our recent characterization of the expression of several GABAAR subunits in microdissected CA1
FIGURE 1 | Altered stability of GABAAR and scaffolding proteins during epileptogenesis. Induction of status epilepticus produces alterations in the expression of gephyrin and might disrupt GABAAR anchoring. Decreased expression of gephyrin might compromise the recycling of GABAAR and reduce the stability of receptors present at the plasma membrane. Reduced expression of GABAAR at the plasma membrane may contribute to the increased excitability observed during epileptogenesis.

also showed a reduction in the levels of α4, β2/3, and γ2 (but not α1) subunits as early as 4 days after SE (González et al., 2013). The loss of these subunits correlated with the down-regulation of gephyrin, suggesting that the loss of GABAAR might result from the lack of proper receptor anchoring and clustering (González et al., 2013). Accordingly, analysis of the cell surface levels of GABAAR revealed a time-dependent reduction in the plasma membrane levels of α4 and γ2 subunits that correlated with the down-regulation of gephyrin (González et al., 2013). These observations hint to the possibility that during the epileptogenic period, the stability of the GABAAR receptors that recycle back to the plasma membrane might be compromised because they cannot be properly anchored (González et al., 2013). They also suggest that the loss of inhibition and increased inter-ictal activity observed during the latent period might result from the persistent dysregulation of GABAAR and its appearance has been associated with the transition from the latent to the chronic stage of epilepsy (Mazzuferi et al., 2010). Initial exploration of the molecular mechanisms behind this phenomenon revealed a switch in the composition of GABAAR and uncovered an increase in the ratio of α4/α1 subunits incorporated into receptors. More importantly, the switch in GABAAR assembly occurs at the same time that the current run-down appears, underscoring previous findings showing alterations in the expression of α4 and α1 subunits that affect the assembly, localization, and function of GABAAR and results in the impairment of tonic and phasic inhibition (Brooks-Kayal et al., 1998; Peng et al., 2004; Mazzuferi et al., 2010).
The specific mechanisms involved in the regulation of gephyrin during epileptogenesis and epilepsy remain to be fully characterized, but some clues are starting to emerge. Analysis of samples obtained from epileptic patients show a reduction in gephyrin expression, which correlates with the appearance of protein fragments probably resulting from gephyrin degradation (Forstera et al., 2010; Tang et al., 2011). The process involved in the generation of gephyrin fragments remains unclear but a favored hypothesis is that cellular stress (alkalosis and hyperthermia) might be sufficient to induce the skipping of exons in gephyrin messenger RNA resulting in the production of abnormally spliced variants of gephyrin. These abnormal variants may then interact with normal gephyrin molecules and act as dominant-negative mutants and promote the accumulation of gephyrin in ubiquitin positive inclusions (Forstera et al., 2010). The impact abnormally spliced variants of gephyrin have been associated with oligomerization deficits and aberrant clustering of GABA<sub>R</sub> containing a2 subunits (Forstera et al., 2010). Induction of mild seizures or inflammatory events triggers the generation of adult-born hippocampal neurons and increases the expression of gephyrin, mostly in the newly generated neurons (Jakubs et al., 2006, 2008; Jackson et al., 2012). Electrophysiological recordings revealed that newborn neurons produced after these injuries have reduced excitatory and increased inhibitory drive partially associated with the increase in gephyrin expression. Together, these observations point out to the possibility that newly generated cells might increase gephyrin expression as a compensatory mechanism to ameliorate the hippocampal hyperexcitability observed after an insult to the brain (Jakubs et al., 2006; Jackson et al., 2012).

Another line of evidence implicating gephyrin dysfunction as a key element in the generation of epileptic seizures includes recent genetic evidence found in individuals affected by pathologies associated with a seizure phenotype. Rare hemizygous microdeletions in the chromosome 14q23.3 that encompass exons 3–5 in the coding region of the G-domain were found in individuals from six unrelated families presenting autism, schizophrenia, and seizures (Lionel et al., 2013). Other mutations that interfere with collybistin function have also been associated with abnormalities observed in patients with epilepsy and mental retardation (Harvey et al., 2004; Marco et al., 2008; Kalscheuer et al., 2009; Lesca et al., 2011). These mutations found in the coding sequence of collybistin interfere with the somatic and synaptic localization of gephyrin via dominant-negative mechanisms that indirectly affect the distribution and synaptic clustering of GABA<sub>R</sub> (Harvey et al., 2004; Kalscheuer et al., 2009).

The impact that disruption of gephyrin and other scaffolding proteins might have on GABA<sub>R</sub> function during epileptogenesis remains to be elucidated. If a loss of gephyrin directly impacts the number and function of GABA<sub>R</sub> at inhibitory synapses, interventions to promote the stability of gephyrin and GABA<sub>R</sub> might ameliorate the deleterious changes in excitability observed during epileptogenesis and epilepsy. Altered expression of gephyrin has been observed in several pathologies presenting symptomatic seizures, but it is unclear if changes in gephyrin are beneficial or pathologic (Jakubs et al., 2008; Thind et al., 2010; Jackson et al., 2012). Understanding the molecular mechanism(s) behind the dysregulation of scaffolding proteins involved in the regulation of GABA<sub>R</sub> might provide new insights into the pathologic events that contribute to the generation of spontaneous seizures and might offer new targets to disrupt epileptogenesis and prevent epilepsy.

ACKNOWLEDGMENT

Marco I. González is supported by the National Institutes of Health Grant K01-NS069583.

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GABA<sub>A</sub>, gephyrin, and epileptogenesis

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 23 April 2013; accepted: 26 June 2013; published: 22 July 2013.