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GABAergic Transmission in Temporal Lobe Epilepsy: the Role of Neurosteroids

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Abstract

Modification of GABAergic inhibition is an intensely investigated hypothesis guiding research into mechanisms underlying temporal lobe epilepsy (TLE). Seizures can be initiated by blocking γ amino butyric acid type A (GABA_A receptors, GABARs), which mediate fast synaptic inhibition in the brain, and controlled by drugs that enhance their function. Derivatives of steroid hormones called neurosteroids are natural substances that physiologically enhance GABAR function and suppress seizures. GABAR structure, function, expression, assembly, and pharmacological properties are changed in the hippocampus of epileptic animals. These alterations render GABARs less sensitive to neurosteroid modulation, which may contribute to seizure susceptibility. Plasticity of GABARs could play a role in periodic exacerbation of seizures experienced by women with epilepsy, commonly referred to as catamenial epilepsy.

Introduction

Temporal lobe epilepsy (TLE) is characterized by recurrent unprovoked seizures arising from the mesial temporal lobe structures (Engel, Jr., 1996; Engel J Jr., 1997; Williamson et al., 1993). Many patients with TLE remain refractory to medical management and may require resective surgery. γ amino butyric acid type A (GABA_A) receptors (GABARs) mediate fast inhibitory neurotransmission in the brain. *In vivo* studies demonstrated that many drugs known to cause seizures in the experimental animals and humans, such as penicillin (Gloor et al., 1979; Schwartzkroin and Prince, 1980), pentylenetetrazol, picrotoxin and bicuculline are GABAR antagonists (Gale, 1992; Gloor et al., 1967; Klitgaard et al., 1998). On the other hand, drugs that potentiate GABAR-mediated inhibition, including diazepam (Choi et al., 1977; Choi et al., 1981; MacDonald and Barker, 1978), Phenobarbital (MacDonald and Barker, 1979; MacDonald et al., 1989a; MacDonald et al., 1989b; Nicoll, 1972; Schmidt, 1963; Twyman et al., 1989) have an anticonvulsant action. These early observations suggested the hypothesis that compromised GABAergic inhibition could lead to the development of epilepsy.

Much of our current understanding of the role of GABARs in the pathogenesis of TLE comes from studies performed on the hippocampal formation. Patients with TLE have characteristic hippocampal pathology, which includes loss of CA1 and CA3 pyramidal

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neurons and hilar interneurons, with gliosis and sprouting of mossy fiber axons. There is similar hippocampal pathology in animal models of TLE (Buckmaster and Dudek, 1997a; Buckmaster and Jongen-Rêlo, 1999; Houser and Esclapez, 1996; Obenaus et al., 1993; Sloviter, 1987; Sun et al., 2007a). The hippocampal formation has a low threshold for seizures (Traub et al., 1989), and seizures originate in or propagate through the hippocampus in different epilepsy models (Bragin et al., 1999; Bragin et al., 2009). In this review we will discuss TLE-associated changes in GABARs in the hippocampus, with particular focus on the dentate gyrus granule cells (DGCs).

GABAR structure and plasticity in the hippocampus

The heteropentameric GABARs are formed from a family of 19 subunits, namely α (1–6), β (1–3), γ (1–3), δ , ϵ , π , and ρ (1–3) (Whiting et al., 1999). The subunit composition of GABARs determines their kinetic and pharmacological properties, as well as membrane localization (Olsen and Sieghart, 2009). The α_1 , α_2 , α_4 , α_5 , β_1 , β_3 , γ_2 and δ subunit mRNA and peptide are highly expressed in the hippocampus (Sperk et al., 1997). The dentate granule cells (DGCs) and CA1 pyramidal neurons express $\alpha_1\beta_x\gamma_2$ and $\alpha_2\beta_x\gamma_2$ subunit-containing receptors; which mainly mediate fast synaptic inhibition (Prenosil et al., 2006; Sun et al., 2007b; Zhang et al., 2007). In addition, $\alpha_4\beta_x\delta$ subunit-containing receptors are highly expressed on the DGCs (Wei et al., 2003; Zhang et al., 2007), whereas $\alpha_5\beta_x\gamma_2$ subunit-containing receptors are expressed on the CA1 neurons. These receptor types mediate a steady state background inhibition called tonic inhibition, in response to GABA spilled over from synaptic cleft, or released from neurons or glia via reverse transport (Caraiscos et al., 2004; Farrant and Nusser, 2005; Glykys et al., 2008; Mtchedlishvili and Kapur, 2006; Prenosil et al., 2006).

Reduced neurosteroid sensitivity of GABARs in epileptic animals

Reduced neurosteroid sensitivity of GABARs is a physiologically important alteration associated with epilepsy. Inhibitory neurosteroids have an anticonvulsant action (Belelli et al., 1989; Frye, 1995; Frye and Scalise, 2000; Herzog, 1999; Herzog and Frye, 2003; Kokate et al., 1996; Kokate et al., 1999). Neurosteroids interact with GABARs via two distinct sites (Hosie et al., 2006), such that at lower concentrations they allosterically activate the receptors, and at higher concentrations act like an agonist (Bianchi and MacDonald, 2003). However, neurosteroid sensitivity of GABARs expressed on the DGCs of epileptic animals is diminished. Allopregnanolone modulation of whole cell GABAR currents recorded from DGCs of epileptic animals was much lower than of those recorded from controls (Mtchedlishvili et al., 2001). This diminution was because of reduced neurosteroid sensitivity of both synaptic and tonic GABAR-mediated inhibition. Physiological concentrations of allopregnanolone failed to prolong the decay of mIPSCs in DGCs of epileptic animals (Sun et al., 2007b). Similarly, neurosteroids did not enhance tonic inhibition of DGCs from epileptic animals (Rajasekaran et al., 2010; Zhang et al., 2007). In addition, neurosteroid modulation of mIPSCs recorded from pyramidal and non-pyramidal neurons of piriform cortex of kindled animals was also diminished (Gavrilovici et al., 2006; Kia et al., 2011). Whether neurosteroid modulation of GABARs expressed in other regions such as CA1 pyramidal neurons, thalamic neurons, and cortical neurons is also decreased in epileptic animals is not known. However, an overall reduction in neurosteroid sensitivity of GABARs in epileptic animals may underlie increased susceptibility to seizures.

Factors underlying reduced neurosteroid sensitivity of synaptic and tonic inhibition appear to be complex. Expression, trafficking, and assembly of subunits composing synaptic GABARs is altered in epileptic animals. Immunohistochemical studies revealed higher expression of the α_4 and γ_2 subunits, mainly in the molecular layer of DGCs, in epileptic

animals (Peng et al, 2004). Single-cell PCR amplification from DGCs of epileptic animals demonstrated increased α_4 subunit mRNA expression and diminished α_1 subunit expression compared to controls (Brooks-Kayal et al, 1998). Furthermore, in epileptic animals the α_4 subunit surface expression was increased and also its association with γ_2 subunit (Rajasekaran et al., 2010). Increased co-localization of the α_4 and γ_2 subunits (Zhang et al., 2007) could explain synaptic expression of the $\alpha_4\gamma_2$ subunit-containing receptors (Sun et al., 2007b). The intrusion of novel $\alpha_4\gamma_2$ subunit-containing GABAR into synapses could contribute to diminished neurosteroid sensitivity of synaptic inhibition of DGCs. In addition, a recent study also demonstrated that increased β_3 subunit phosphorylation was associated with reduced neurosteroid modulation of mIPSCs in the pyramidal neurons of piriform cortex from kindled animals (Kia et al., 2011).

The δ subunit-containing receptors, which mediate tonic inhibition of DGCs, have higher neurosteroid sensitivity (Mihalek et al., 1999; Wohlfarth et al., 2002). However, in the epileptic animals, total and surface expression of the δ subunit was reduced (Peng et al., 2004; Rajasekaran et al., 2010; Zhang et al., 2007). A larger fraction of δ subunit was retained in the endoplasmic reticulum in the hippocampus of epileptic animals (Rajasekaran et al., 2010), suggesting that impaired membrane insertion could underlie observed reduction in surface expression of the δ subunit-containing receptors. Proteins regulating trafficking of the δ subunit-containing receptors are not well understood. Brain derived neurotrophic factor (BDNF) and activation of calcium dependent protein kinase C (PKC) regulate surface expression of the δ subunit by reducing receptor internalization (Joshi and Kapur, 2009), and whether they play a role in epileptic animals is not known. Proteins chaperoning insertion of the δ subunit-containing receptors at the surface membrane once identified may reveal mechanisms of its reduced surface expression.

Reduced neurosteroid sensitivity contributes to seizure susceptibility

Reduced neurosteroid sensitivity of GABARs in the epileptic hippocampus has important physiological implications. Neurosteroids can be synthesized from circulating steroid hormones or de novo from cholesterol by neurons and glia [see review (Papadopoulos et al., 2006)]. Steroidogenic acute regulatory protein (StAR) transports cholesterol from cytoplasm to the outer mitochondrial membrane, where translocator proteins, also called as peripheral benzodiazepine receptors, carries it to the inner mitochondrial membrane (Rone et al., 2009). The enzyme cytochrome P450 side chain cleavage (P450_{ssc}) then converts cholesterol to pregnanolone (Kimoto et al., 2001). Subsequent biosynthetic steps occur in the endoplasmic reticulum, and involve conversion of pregnanolone to progesterone by the enzyme 3β hydroxysteroid dehydrogenase (Ibanez et al., 2003). Next, progesterone is converted to allopregnanolone by a two step conversion process involving intermediate 5α dihydro progesterone. These reactions are catalyzed by sequential action of enzymes 5α reductase and 3α hydroxysteroid oxido-reductase (Georges, 2010). 5α reductase is the rate limiting enzyme in this pathway, whereas enzyme 3α hydroxysteroid oxido-reductase has bidirectional activity, and depending on availability of the substrate can convert 5α dihydro progesterone to allopregnanolone or vice a versa.

These biosynthetic enzymes are expressed in the hippocampus (Kimoto et al, 2001; Ibanez et al, 2003). Their immunoreactivity is predominately found in DGCs, pyramidal neurons, glia, and glutamatergic interneurons (Agis-Balboa et al, 2006). In contrast, neurosteroidogenic enzymes are not expressed in GABAergic interneurons. Endogenous neurosteroids appear to regulate kinetic properties of synaptic GABAR currents. Inhibition of enzyme 5α reductase by finasteride accelerates the decay of mIPSCs in lamina II neurons, presumably by reduced neurosteroid synthesis (Keller et al., 2004). In addition, progesterone and its neurosteroid derivatives also influence mRNA, protein, and surface

expression of different GABAR subunits (Concas et al., 1998; Maguire et al., 2005; Maguire and Mody, 2007; Michael Foley et al., 2003; Sanna et al., 2009).

Women with epilepsy often experience menstrual cycle-associated seizure exacerbation commonly referred to as catamenial epilepsy (Reddy and Rogawski, 2000; Reddy and Rogawski, 2009). Cyclic fluctuations in progesterone and neurosteroid levels form high (during diestrus) to low (during estrus) associated with female reproductive cycle, are thought to create a seizure susceptibility window. We recently demonstrated regulation of seizure activity by endogenous neurosteroids (Lawrence et al., 2010). In the female epileptic animals, finasteride blockade of enzyme 5 α reductase increased seizure frequency hundred folds when progesterone levels were higher. This was in accordance with the hypothesis that a withdrawal from higher progesterone and neurosteroid levels lowers the seizure threshold. Interestingly, finasteride also caused seizure exacerbation at physiological levels of progesterone, or in the animals with fixed progesterone levels. These studies revealed that a sudden decline in neurosteroid levels increased seizure frequency in epileptic animals, and the extent of seizure exacerbation was proportional to pre-finasteride neurosteroid levels. Increased seizure frequency under basal progesterone levels was most likely due to removal of control by endogenous neurosteroids, which could be synthesized locally from cholesterol.

However, all these studies have mainly focused on role of neurosteroids in regulating seizure activity in female animals (Lawrence et al, 2010; Reddy and Rogawski 2000; Reddy and Rogawski, 2001; Reddy et al, 2001). Since neurons and glia can synthesize neurosteroids de novo from cholesterol, endogenous neurosteroids are likely to regulate seizure frequency in male animals. We tested whether endogenous neurosteroids also regulate seizure activity in male epileptic animals. Following lithium pilocarpine induced status epilepticus (SE); male animals which developed spontaneous seizures were used 8–12 after SE. Hippocampal and cortical electrodes were implanted and following a week of recovery, basal seizure frequency was determined for 10 days. On the morning of 11th day, finasteride (100 mg/kg) was administered. Seizure frequency increased within an hour of finasteride administration and lasted for approximately 3 hours (Figure 1). In each of the animals (n=4), seizure frequency on the day of finasteride administration was higher than the average daily seizure frequency recorded for previous 10 days. Mean seizure frequency during the basal recording period was 0.5 ± 0.11 and increased to 16 ± 4 on the day of finasteride administration ($p < 0.05$, chi square test). This pattern of seizure exacerbation was slightly different from that in the female epileptic animals. For example extent of increase in seizure frequency observed in male animals was not as much as in female animals, and seizure activity returned to the baseline comparatively faster. Some of these differences could be due to endogenous neurosteroid levels as well as time required to replenish them following finasteride treatment. However, despite these differences, the results demonstrate that endogenous neurosteroids regulate seizure activity in both male and female epileptic animals. We propose that finasteride administration precipitates seizures by reducing the neurosteroid levels below a critical threshold needed to activate the relatively neurosteroids insensitive GABARs expressed in the epileptic animals (Figure 2).

Reduced neurosteroid sensitivity of GABARs in the DGCs of epileptic animals may also contribute to the breakdown of dentate gating function, hypothesized to underlie seizure spread in the hippocampus (Lothman et al., 1992). However, the gating function of DGCs is only transiently impaired during the course of seizure development (Pathak et al., 2007). Whether neurosteroid sensitivity of GABARs is also diminished during epileptogenesis is currently unknown. Two recent studies suggested an association between reduced neurosteroid sensitivity and epileptogenesis (Biagini et al., 2006; Biagini et al., 2009), which needs to be probed further.

Increased expression of synaptic GABAR in TLE

Another epilepsy associated alteration is augmentation of synaptic GABAR mediated inhibition. Early studies using electrophysiological, biochemical, and electron microscopic techniques revealed increased paired pulse inhibition (de Jonge and Racine, 1987; Tuff et al., 1983), higher ligand binding (Shin et al., 1985; Titulaer et al., 1995; Valdes et al., 1982; Fanelli and McNamara, 1983; McNamara et al., 1980), and greater synaptic expression of the $\beta 2/3$ subunits (Nusser et al., 1998). Whole cell GABAR currents were larger in DGCs from epileptic animals compared to controls (Gibbs, III et al., 1997; Mtchedlishvili et al., 2001). Subsequent studies revealed increased synaptic transmission; amplitude of sIPSCs (spontaneous inhibitory post synaptic currents) and mIPSCs (miniature inhibitory post synaptic currents) recorded from DGCs of epileptic animals was larger than that from controls (Cohen et al., 2003; Kobayashi and Buckmaster, 2003; Leroy et al., 2004; Otis et al., 1994; Sun et al., 2007b). Increased expression of GABARs in synapses may be a homeostatic response (Swanwick et al., 2006) to increased activity of recurrent seizures. On the other hand tonic inhibition of DGCs remained unaltered (Rajasekaran et al., 2010; Scimemi et al., 2005; Zhang et al., 2007). Reduced expression of the δ subunit-containing receptors appears to be compensated by increased expression of $\alpha_4\gamma_2$ or $\alpha_5\gamma_2$ subunit-containing GABARs, which maintains tonic inhibition (Rajasekaran et al., 2010; Zhan and Nadler, 2009). In addition to these changes in the DGCs, GABAR function in CA1 pyramidal neurons, thalamic neurons, piriform cortex and subiculum is also modified in epileptic animals (Gavrilovici et al., 2006; Knopp et al., 2008; Rajasekaran et al., 2007).

Frequency of synaptic currents recorded from DGCs of epileptic animals is lower than that recorded from controls. Loss of somatostatin-containing interneurons is thought to underlie this reduction (Buckmaster and Dudek, 1997b; Buckmaster and Jongen-Rêlo, 1999; Kobayashi and Buckmaster, 2003; Sun et al., 2007a). However changes in pre-synaptic release from GABAergic interneurons may contribute to this reduction in IPSC frequency (Zhang et al., 2009).

In addition, status epilepticus (SE) used to induce TLE also triggers neurogenesis of DGCs, which brings about network reorganization and hippocampal disinhibition (Parent et al., 1997; Scharfman et al., 2000). A fraction of new born DGCs migrate to ectopic locations such as dentate hilum and GABARs expressed on these neurons have distinct properties compared to those expressed on new born DGCs that stay in the granule cell layer (normotrophic) (Zhan and Nadler, 2009). Although the amplitude of eIPSCs recorded from normotrophic DGCs were larger than controls, those recorded from ectopic DGCs which migrated to the hilum were significantly attenuated, and suggested that homeostatic alterations occurring in the DGCs were absent in these neurons.

GABARs expressed in the epileptic animals have lower benzodiazepine sensitivity

Although expression of synaptic GABARs is increased in epileptic animals, their benzodiazepine sensitivity is reduced, which could have clinical implications. Benzodiazepines are important anti-convulsants used in the treatment of epilepsy, and increase GABAR function by allosteric modulation. In the DGCs of epileptic animals, bath application of zolpidem did not enhance GABA-evoked whole cell currents (Brooks-Kayal et al., 1998), and similarly diazepam also failed to increase the amplitude or prolong the decay of synaptic currents (Leroy et al., 2004; Sun et al., 2007b). Increased expression of $\alpha_4\gamma_2$ subunit-containing receptors could explain these observations. The pharmacological properties of $\alpha_4\gamma_2$ subunit-containing receptors are distinct from those containing $\alpha_1\gamma_2$ subunits (Wafford et al., 1996). For example, flumazenil acts as a benzodiazepine antagonist

at $\alpha_1\gamma_2$ subunit-containing receptors; but has a low efficacy partial agonist-like action on $\alpha_4\gamma_2$ subunit-containing receptors. Furthermore, $\alpha_4\gamma_2$ subunit-containing receptors are also insensitive to modulation by zolpidem or diazepam whereas $\alpha_1\gamma_2$ subunit-containing receptors get potentiated (Knoflach et al., 1996). In a recent study, neurosteroid withdrawal-induced seizures in kindled animals were associated with increased expression of $\alpha_4\gamma_2$ subunit-containing receptors. Diazepam did not suppress withdrawal seizures however flumazenil was effective in preventing these seizures (Gangisetty and Reddy, 2010). This suggests that drugs that activate $\alpha_4\gamma_2$ subunit-containing receptors may be better targets for treating withdrawal seizure.

Zinc sensitivity of GABARs is also increased in the epileptic animals (Brooks-Kayal et al., 1998; Buhl et al., 1996; Gibbs, III et al., 1997), and was proposed to play a role in epileptogenesis [see review (Dudek, 2001)]. It was proposed that zinc released from sprouted mossy fibers would inhibit GABARs expressed on the DGCs of epileptic animals and cause collapse of inhibition. However, in slice experiments activation mossy fibers could not release sufficient zinc to inhibit IPSCs recorded from DGCs of epileptic animals (Molnar and Nadler, 2001).

Potential signaling mechanisms associated with altered expression and subunit assembly of GABARs

Activation of different second messengers underlies observed changes in GABAR expression and subunit assembly. Mitogen activated protein kinases (MAP kinases), specifically extracellular receptor kinase 1/2 (ERK1/2), as well as signal transducer and activator of transcription (STAT), which are activated during SE and spontaneous seizures (Houser et al., 2008; Choi et al., 2003), are thought to play important role in regulation of GABARs. Increased BDNF expression following SE appears to regulate reduced expression of the α_1 subunit, increased expression of the α_4 subunit and increased assembly between the $\alpha_4\gamma_2$ subunits observed in epileptic animals [see reviews (Brooks-Kayal et al., 2009; González and Brooks-Kayal, 2011)]. BDNF is proposed to increase phosphorylation CREB (cAMP-responsive element binding protein) through activation of RAS/MAP kinases, which in turn results in activation of ICER (Inducible cAMP Early Repressor) leading to decreased expression of α_1 subunit. Similarly BDNF induced activation of PKC and MAP kinases is shown to activate transcription factor Egr3 (Early growth response factor) inducing expression of α_4 subunit (Roberts et al., 2006). In addition ICER activity can also be regulated through JAK-STAT (Janus kinase/signal transducer and activator of transcription) signaling by BDNF (Lund et al., 2008). Drugs targeting these signaling mechanisms may have therapeutic potentials.

GABAR function and changes in excitability in TLE

Altered function and pharmacology of GABARs in epileptic animals may contribute to synchronization and emergence of seizures. Seizures arise, both *in vitro* and *in vivo*, due to the synchronous activation of large populations of neurons (Bragin et al., 2005; Dzhala and Staley, 2003; Khosravani et al., 2005; Miles and Wong, 1983; Traub et al., 1987a; Traub et al., 1993; Traub et al., 1996). The mechanism(s) underlying the generation of neuronal synchrony during seizures is an area of active study. GABAR activation via interneuronal activation can modulate the synchrony and firing of pyramidal neurons in a state-dependent manner (Jefferys and Haas, 1982; Lytton and Sejnowski, 1991; Miles and Wong, 1986; Traub et al., 1987c; Traub et al., 1987b; Wong et al., 1986). The loss of GABAR conductance can produce epileptic synchrony in the hippocampus by making it easier for a single CA3 pyramidal neuron to be activated by a single presynaptic counterpart (Miles and Wong, 1987a; Miles and Wong, 1987b). Thus, recurrent GABAergic inhibition onto CA3

pyramidal neurons via interneuronal input acts as a check to prevent recurrent excitation-induced bursting of CA3 pyramidal neurons. Enhancement of GABAR mediated conductance can desynchronize network synchrony in the CA3 region by significantly reducing the number of recruited pyramidal cells firing in each cycle (Traub et al., 1987a). In the neocortex, the onset of seizure activity is quickly followed by a strong interneuron-mediated feed forward ('surround') inhibition (Prince and Wilder, 1967; Trevelyan et al., 2006); however a breakdown of this GABAR mediated inhibition results in the spread of seizures (Trevelyan et al., 2007; Trevelyan, 2009).

It is important to note that even within the hippocampus; the neurons in various subfields have diverse impact on seizure generation and spread. For example, CA3 pyramidal neurons by virtue of their intrinsic bursting properties and high degree of recurrent excitatory connections can rapidly synchronize and propagate bursts, resulting in seizures (MacVicar and Dudek, 1980; Miles and Wong, 1983). In contrast, in the CA1 pyramidal neurons, where recurrent excitatory connections are minimal, synchronization occurs when inhibition maintained by GABAergic interneurons is suppressed (Jefferys and Haas, 1982; Kohling et al., 2000; Traub et al., 1993). In contrast to the pyramidal CA neurons, the DGCs typically generate single action potentials and do not generate bursts (Dzhala and Staley, 2003; Miles et al., 1984). DGCs also lack the recurrent connections necessary to synchronize and propagate bursts; therefore, unlike the pyramidal CA neurons, DGCs generally resist the spread of seizures. However, in TLE, sprouting of the mossy fibers provides a positive excitatory feedback onto the DGCs that leads to recurrent excitability of these neurons (Buckmaster et al., 2002; Dyhrfeld-Johnsen et al., 2007; Nadler, 2003; Santhakumar et al., 2005; Sutula et al., 1992). We hypothesize that loss of neurosteroid sensitivity on DGCs increase their excitability. It is proposed that tonic inhibition mediated by GABA_A receptors, primarily the δ and $\alpha 5$ subunit containing receptors, provides powerful shunting inhibition keeping neuronal excitability in check by potentially modulating the offset (threshold) of the I/O curve (Brickley et al., 1996; Semyanov et al., 2004; Bonin et al., 2007; Pavlov et al., 2009). Thus, tonic conductance mediated by these receptors increase the excitatory drive needed to induce action potential firing. The downregulation of these receptors in TLE can contribute to enhanced excitability (Mihalek et al., 2001; Glykys and Mody, 2006).

Conclusions

Studies over the past three decades have demonstrated a critical role of GABAR mediated neurotransmission in the generation of seizures, and the development of epilepsy. Subunit assembly, function, and pharmacological properties of GABAR expressed in TLE animals are distinct from those in naïve animals. Expression of synaptic receptors appears to be enhanced in the DGCs of epileptic animals; however, their neurosteroid and benzodiazepine sensitivity is diminished. Increased insertion of $\alpha 4\gamma 2$ subunit-containing receptors at the synapses and reduced expression of $\alpha 1$ subunit appears to underlie these changes. Similarly, neurosteroid sensitivity of tonic inhibition is also reduced, along with reduced surface expression of δ subunit-containing receptors. Since endogenous neurosteroids regulate seizure activity, reduced neurosteroid sensitivity of GABARs has physiological significance in epileptic animals. Further studies are needed to determine whether reduction in neurosteroid sensitivity of GABARs is widespread in the epileptic brain. Also, uncovering mechanisms regulating trafficking of the δ subunit-containing GABARs, and novel $\alpha 4\gamma 2$ subunit assembly in the epileptic hippocampus, will significantly advance our knowledge on GABAR mediated neurotransmission in the epileptic brain and its therapeutic relevance.

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Figure 1.

Finasteride increased frequency of spontaneous seizures in epileptic animals. A: Administration of 100 mg/kg finasteride, a 5 α reductase enzyme blocker, increased the frequency of spontaneous seizures in female epileptic animals (n=11). Increased seizure frequency returned to baseline 16–18 hrs after finasteride administration (inset) (modified from Lawrence et al, 2010). B: Treatment with finasteride (100 mg/kg) also increased frequency of spontaneous seizures in male epileptic animals (n=4). The seizures returned to baseline frequency 4–5 hrs after finasteride treatment (inset).

Figure 2.

A schematic showing increased synaptic expression of $\alpha_4\beta_x\gamma_2$ subunit-containing receptors, and reduced expression of $\alpha_4\beta_x\delta$ subunit-containing receptors in the DGCs of epileptic animals. Expression of receptors with lower neurosteroid sensitivity is proposed to lower seizure threshold in epileptic animals, such that finasteride administration leads to seizure exacerbation.