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Epilepsy, E/I balance and $GABA_A$ receptor plasticity

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$GABA_A$ receptors mediate most of the fast inhibitory transmission in the CNS. They form heteromeric complexes assembled from a large family of subunit genes. The existence of multiple $GABA_A$ receptor subtypes differing in subunit composition, localization and functional properties underlies their role for fine-tuning of neuronal circuits and genesis of network oscillations. The differential regulation of $GABA_A$ receptor subtypes represents a major facet of homeostatic synaptic plasticity and contributes to the excitation/inhibition (E/I) balance under physiological conditions and upon pathological challenges. The purpose of this review is to discuss recent findings highlighting the significance of $GABA_A$ receptor heterogeneity for the concept of E/I balance and its relevance for epilepsy. Specifically, we address the following issues: (1) role for tonic inhibition, mediated by extrasynaptic $GABA_A$ receptors, for controlling neuronal excitability; (2) significance of chloride ion transport for maintenance of the E/I balance in adult brain; and (3) molecular mechanisms underlying $GABA_A$ receptor regulation (trafficking, posttranslational modification, gene transcription) that are important for homoeostatic plasticity. Finally, the relevance of these findings is discussed in light of the involvement of $GABA_A$ receptors in epileptic disorders, based on recent experimental studies of temporal lobe epilepsy (TLE) and absence seizures and on the identification of mutations in $GABA_A$ receptor subunit genes underlying familial forms of epilepsy.

Keywords: temporal lobe epilepsy, absence epilepsy, homeostatic plasticity, tonic inhibition, synaptic plasticity

INTRODUCTION

The convulsant effects of GABA and glycine receptor antagonists, and conversely the clinically relevant antiepileptic action of classical benzodiazepines, such as diazepam, led to the concept that epileptic seizures reflect an imbalance between excitatory and inhibitory transmission in the brain (Bradford, 1995; Gale, 1992; Olsen and Avoli, 1997). This view was further supported by the strong epileptogenic effects of glutamate receptor agonists, in particular kainic acid (Ben-Ari et al., 1980; Sperk, 1994). Unlike acute drug effects, which occur in an intact system, epileptogenesis and recurrent seizures in chronic epilepsy likely reflect pathological disturbances of neuronal circuits that may have multiple origins. Furthermore, the simple view that GABAergic transmission acts like a break preventing overexcitation of neuronal circuits has been challenged by the highly sophisticated anatomical and functional organization of GABAergic interneurons in cerebral cortex (Blatow et al., 2005; Markram et al., 2004). Rather, GABAergic function is required for fine-tuning of neuronal circuits and its influence on cell firing and network oscillations is constrained spatially and temporally (Mann and Paulsen, 2007; Tukker et al., 2007). Furthermore, GABAergic transmission, while typically qualified as being inhibitory, can also be depolarizing, even under physiological conditions, in the adult brain (Gulledge and Stuart, 2003; Szabadics et al., 2006). Finally, in epileptic tissue neuronal network undergo extensive rewiring that considerably changes the function of interneurons and their control over pyramidal cells (Cossart et al., 2005; Ratte and Lacaille, 2006). Therefore, the classical dichotomy between inhibitory and excitatory GABAergic/glutamatergic transmission has to be revised and the role of GABAergic transmission in epilepsy is much more complex than suggested by simple pharmacological experiments.

The purpose of this review is to summarize recent advances on the concept of E/I balance and its relevance for epilepsy and to discuss the significance of $GABA_A$ receptor heterogeneity for the pathophysiology of epileptic disorders.

EPILEPSY

Epilepsy is a generic term encompassing multiple syndromes, with distinct symptoms, etiology, prognosis, and treatments. The role of $GABA_A$ receptors in the pathophysiology of epilepsy has been examined experimentally in most detail in two major diseases, namely absence epilepsy and temporal lobe epilepsy (TLE). In addition, the functional consequences of mutations associated with familial forms of epilepsies are now being analyzed in recombinant expression system and *in vivo* using transgenic mouse models carrying these mutations (Noebels, 2003).

Absence seizures can be genetically determined (GAERS, WAG/Rij rats) (van Luijtelaar and Sitnikova, 2006) or pharmacologically-induced, for example by treatment with a cholesterol biosynthesis inhibitor, AY-9944 (Snead, 1992). They are characterized by low frequency spike-and-wave discharges reflecting impaired thalamo-cortical function. Typically, they are aggravated by benzodiazepine agonists. TLE is mimicked by induction of a prolonged status epilepticus (either upon repetitive electrical stimulation of sensitive regions of the temporal lobe or by injection of a convulsant, such as kainic acid or pilocarpine), which is followed in most cases by the occurrence of spontaneous recurrent seizures (reviewed in Coulter et al., 2002). Kindling, either electrical or chemical, is also used to model TLE, with the major difference that the animals do not present with recurrent seizures. In both TLE and absence epilepsy, alterations of $GABA_A$ receptor expression, pharmacology, and functional properties

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have been studied in detail over many years. Recent results highlighting novel features will be discussed in more detail in the sections "Phasic/tonic inhibition" and "$GABA_A$ receptor plasticity in epilepsy". Importantly, changes observed in experimental models need to be compared to alterations taking place in the brain of TLE patients. The availability of tissue resected at surgery from patients with intractable epilepsy represents an invaluable source for understanding the pathophysiology of the disorder (Loup et al., 2006; Magloczky and Freund, 2005).

$GABA_A$ RECEPTORS AND EXCITATORY/INHIBITORY (E/I) BALANCE

The concept of E/I balance has gained much weight following the discovery of homeostatic synaptic plasticity, through which the level of activity of neuronal networks is maintained within a narrow window by locally adapting the strength and weight of synaptic transmission in response to external stimuli (Marder and Goaillard, 2006; Rich and Wenner, 2007; Turrigiano, 2007). Major factors contributing to homeostatic synaptic plasticity include intrinsic membrane properties of pre- and postsynaptic neurons, patterns of synaptic inputs, non-synaptic interactions with neighboring cells, including glial cells, ionic composition of the extracellular fluid, and hormonal influences. Implicitly, an altered E/I balance, frequently postulated as mechanism underlying epileptogenesis and seizure generation, postulates a disturbance in homeostatic plasticity resulting from either insufficient or excessive compensatory mechanisms in response to a change in network activity.

In this review, we focus on three main factors underlying the contribution of $GABA_A$ receptors for homeostatic synaptic plasticity (Mody, 2005). The first of these factors is tonic inhibition, mediated primarily by extra- or perisynaptic receptors. Although tonic inhibition typically is evidenced in patch clamp recordings by a reduction in holding current (typically 10–100 pA) upon application of a $GABA_A$ receptor antagonist, it represents a significant fraction of GABA-mediated charge transfer and is therefore likely to have a strong impact on neuronal excitability. The second factor is the regulation of Cl^- ion fluxes upon opening of $GABA_A$ receptors, which are determined by specific potassium-chloride co-transporters such as NKCC1 and KCC2. In addition of being developmentally regulated (Rivera et al., 2005), these co-transporters undergo rapid changes in expression and function under pathological conditions, leading to chronic dysregulation of GABAergic inhibition (Price et al., 2005). The third factor is the activity-dependent regulation of GABAergic and glutamatergic synapse function, recently brought to light by systematic analyses of the effects of chronic epileptiform activity or axon potential blockade *in vitro* (Costantin et al., 2005; Marty et al., 2004; Rutherford et al., 1997).

Phasic/tonic inhibition

Phasic and tonic neurotransmission are used to discriminate between the short, spatially restricted action of transmitters activating postsynaptic receptors, and the continuous activation of receptors localized peri- or extrasynaptically by transmitter spillover into the extracellular space. Given the prolonged duration of tonic transmission compared to the short openings of ion channels, most of the total charge transported by ligand-gated ion channels occurs via tonic transmission, suggesting a major role in modulating neuronal activity (Farrant and Nusser, 2005; Mody and Pearce, 2004; Semyanov et al., 2004).

The subunit composition of $GABA_A$ receptors appears to be a major determinant of phasic and tonic GABAergic transmission. The $\gamma 2$ subunit, which is present in the vast majority of $GABA_A$ receptor subtypes, is required for postsynaptic clustering of $GABA_A$ receptors and gephyrin (Essrich et al., 1998; Luscher and Fritschy, 2001; Schweizer et al., 2003), a cytoskeletal protein selectively concentrated in GABAergic and glycinergic synapses in the CNS (Sassoè-Pognetto and Fritschy, 2000; Triller et al., 1985). Multiple $GABA_A$ receptor subtypes are clustered at postsynaptic types in defined neuronal populations ($\alpha 1$-, $\alpha 2$-, $\alpha 3$-, and, in part, $\alpha 5$-$GABA_A$ receptors). A major additional property of the $\gamma 2$ subunit is to confer diazepam sensitivity to receptor complexes containing these α subunit variants. It is important to note, however, that $GABA_A$ receptors containing the $\gamma 2$ subunit are not only confined to postsynaptic sites. For instance, most $\alpha 5$-$GABA_A$ receptors are extrasynaptic (Crestani et al., 2002), contribute to tonic inhibition modulated by diazepam (Caraiscos et al., 2004; Glykys and Mody, 2006; Prenosil et al., 2006) and regulate the excitability of pyramidal cells (Bonin et al., 2007). Consequently, postsynaptic and extrasynaptic receptors formed with the $\gamma 2$ subunit are diazepam-sensitive and contribute to the pharmacological profile of classical benzodiazepine-site agonists.

Receptors containing the δ subunit, in contrast to the $\gamma 2$ subunit, appear to be excluded from postsynaptic sites, as demonstrated by immunoelectron microscopy (Nusser et al., 1998; Wei et al., 2003). The δ subunit is associated mainly with the $\alpha 4$ subunit, e.g., in thalamus and dentate gyrus (Peng et al., 2002; Sun et al., 2004), or the $\alpha 6$ subunit in cerebellar granule cells (Jones et al., 1997). These receptors are diazepam-insensitive (Kapur and Macdonald, 1996; Makela et al., 1997) but are selectively modulated by GABA agonists such as gaboxadol and muscimol (Drasbek and Jensen, 2005; Storustovu and Ebert, 2006) as well as neurosteroids (Belelli and Herd, 2003; Belelli et al., 2005; Stell et al., 2003), pointing to possible novel target for drug therapy (Krogsgaard-Larsen et al., 2004). Importantly, $GABA_A$ receptors containing the $\alpha 4$ and/or δ subunit exhibit unique functional properties that may contribute to epileptogenesis and recurrent seizures upon altered expression, as occurs in TLE (Lagrange et al., 2007). δ subunit-null mice exhibit enhanced sensitivity to pentylenetetrazol-induced seizures, but it is not established whether this reflects a reduced tonic inhibition in thalamocortical circuits or a reduced availability of binding sites for endogenous neurosteroids with anticonvulsant activity (Spigelman et al., 2002).

Ectopic expression of the $\alpha 6$ subunit under the control of the Thy-1.2 promoter has been used to assess the functional and pharmacological significance of enhanced tonic inhibition. These transgenic mice overexpress $\alpha 1/\alpha 6/\beta/\gamma 2$-$GABA_A$ receptors and exhibit a five-fold increase in tonic inhibition in CA1 pyramidal cells (Wisden et al., 2002). Behaviorally, these mice are essentially normal, but are more sensitive than wild-type to the convulsant effects of $GABA_A$ receptor antagonists (Sinkkonen et al., 2004), suggesting an imbalance between phasic and tonic inhibition, with an overall decrease in GABAergic synaptic strength.

Chloride ion homeostasis

A major facet of GABAergic transmission is the intimate link between $GABA_A$ receptor function and ion homeostasis. Therefore, multiple ATP-dependent transport processes determine GABAergic signaling (Farrant and Kaila, 2007). $GABA_A$ receptors are primarily permeable to Cl^- and $HCO3^-$ anions. Cl^- gradients are determined by two major pumps acting in opposite fashion, NKCC1 and KCC2, whereas bicarbonate is produced by carbonic anhydrases. The relative expression level of these molecules changes markedly during development, thereby rendering the reversal potential of Cl^- more negative (Farrant and Kaila, 2007, Fiumelli and Woodin, 2007; Rivera et al., 2005). An opposite change in Cl^- reversal potential affecting $GABA_A$-mediated transmission has been suggested to occur in neurological disorders and following brain trauma (De Koninck, 2007, Huberfeld et al., 2007; Payne et al., 2003; Toyoda et al., 2003), due to reduced expression or function of KCC2. It should be emphasized, however, that it remains largely unclear, whether $GABA_A$-mediated depolarization after down-regulation of KCC2 has an excitatory effect on postsynaptic neurons, or whether shunting inhibition or deactivation of voltage-gated Na^+ channels predominate after $GABA_A$ receptor activation, resulting functionally in inhibition.

In any case, KCC2 expression and function are regulated on a short-time basis by activity-dependent mechanisms (Rivera et al., 2004), determined in particular changes in phosphorylation (Lee et al., 2007; Wake et al., 2007) and by the short half-life of this transporter. These specific properties of KCC2 provide a major tool for local and rapid adjustments of Cl^- ion fluxes, and therefore network activity, in adult brain.

Activity-dependent changes in synaptic structure and function

Pharmacological enhancement or blockade of neuronal activity *in vitro* represents a simplified model of epileptiform activity or removal of afferents (as would happen after a lesion), respectively. The effects are evident on the molecular, functional, and structural level. To mention a few examples, enhanced activity has marked effects on postsynaptic receptor mobility, reflecting diffusion within the plasma membrane. The effect is Ca^{++}-dependent and likely mediated by interactions with the actin cytoskeleton (Hanus et al., 2006). The induction of epileptiform activity *in vitro* by application of $GABA_A$ receptor antagonists regulates synaptic function in hippocampal neurons by selectively favoring the loss of synapses on spines but not on dendritic shafts, resulting in increased GABAergic inhibition (Zha et al., 2005). In contrast, activity deprivation in hippocampal slices can induce epileptiform discharges (Trasande and Ramirez, 2007) and, during development, markedly affects the balance between glutamatergic and GABAergic synapses (Marty et al., 2000). Although multiple mechanisms are involved in these changes, neurotrophins and extracellular matrix proteins, including integrins or cell-adhesion molecules, for example, play an important role in synaptic plasticity and remodeling induced by chronic changes in network activity (Gall and Lynch, 2004, Kuipers and Bramham, 2006).

$GABA_A$ RECEPTOR PLASTICITY

Several mechanisms contribute to the dynamic regulation of $GABA_A$ receptor function, which is essential for fine tuning of neuronal networks and the generation of rhythmic activities under physiological conditions:

1. Regulation of $GABA_A$ receptor trafficking, synaptic clustering, and cell-surface mobility (Kittler and Moss, 2001; Kneussel and Loebrich, 2007; Thomas et al., 2005). In particular, $GABA_A$ receptor internalization mediated by clathrin-coated vesicle endocytosis (Herring et al., 2003, van Rijnsoever et al., 2005) has emerged as a major mechanism of short- and long-term plasticity of GABAergic synapses. Unlike AMPA receptors (Man et al., 2000), $GABA_A$ receptor internalization is not triggered by agonist exposure but is regulated by phosphorylation (Kanematsu et al., 2006). In addition, several tyrosine kinase receptor ligands, such as TNF-α, insulin, or BDNF also modulate $GABA_A$ receptor cell surface expression by regulating its rate of internalization and/or membrane insertion (Brünig et al., 2001; Gilbert et al., 2006; Jovanovic et al., 2004; Wan et al., 1997). Next, synaptic clustering of $GABA_A$ receptors is largely inter-dependent on the scaffolding protein gephyrin. Thus, down-regulation of gephyrin expression by gene targeting or silencing leads to rapid disappearance of postsynaptic $GABA_A$ receptor clustering and loss of IPSCs (Essrich et al., 1998; Yu et al., 2007). Finally, cell surface mobility, reflecting membrane diffusion, represents a major mechanism for the dynamic, short-term regulation of $GABA_A$ receptors available for synaptic transmission (Thomas et al., 2005).
2. Regulation of receptor functions by chemical modification, with phosphorylation being one of the major covalent modifiers. Increasing evidence indicates that chemical modification affects receptor trafficking and cell surface expression, as well as intrinsic functions of the ligand-gated ion channel (Kittler and Moss, 2003; Hinkle and Macdonald, 2003). $GABA_A$ receptor palmitoylation, selectively of the γ2 subunit, represents an additional mechanism for regulation of trafficking, cell-surface expression and postsynaptic clustering (Keller et al., 2004; Rathenberg et al., 2004).
3. Regulation of subunit expression, at the transcriptional and translational level (Steiger and Russek, 2004); this mechanism determines the abundance and subunit composition of $GABA_A$ receptors in a given cell type or brain region and is of particular relevance for physiological alterations of network function, such as occurring upon hormonal fluctuations during the ovarian cycle (Brussaard and Herbison, 2000; Maguire et al., 2005) and during puberty (Shen et al., 2007).

$GABA_A$ RECEPTOR ALTERATION IN EPILEPSY

Changes in subunit composition

Alterations in $GABA_A$ receptor subunit expression and composition in epilepsy are well documented in human (Loup et al., 2000, 2006) and in animal models (Gilby et al., 2005; Li et al., 2006; Nishimura et al., 2005; Peng et al., 2004; Roberts et al., 2005). The latter studies extend previous work by demonstrating a major contribution of extrasynaptic $GABA_A$ receptors to the changes in inhibitory function that might underlie epileptogenesis and occurrence of chronic recurrent seizures. For example, in the mouse pilocarpine model of TLE, a profound decrease in δ subunit immunoreactivity was observed, correlating with a redistribution of the γ2 subunit from synaptic to perisynaptic sites, where it assembled with the α4 subunit, which is normally associated with the δ subunit (Zhang et al., 2007). A down-regulation of the α5 subunit also occurs in CA1 pyramidal cells of pilocarpine-treated rats (Houser and Esclapez, 2003), resulting in a loss of diazepam-sensitive tonic inhibition seen upon blockade of GABA reuptake (Scimemi et al., 2005). Despite this change, tonic inhibition is enhanced in pyramidal cells, suggesting compensatory up-regulation of other extrasynaptic $GABA_A$ receptors, possibly containing the α4 subunit.

Quite recently, region-specific changes in $GABA_A$ receptor function and expression have been reported in models of absence epilepsy (Bessaih et al., 2006; Li et al., 2006; Liu et al., 2007). In the pharmacological model of absence seizures induced by neonatal treatment with the cholesterol biosynthesis inhibitor AY-9944, a reduced expression of the α1 and γ2 subunit has been reported (Li et al., 2006), with distinct sex differences and temporal profiles, correlating with the higher incidence of absence seizures in female rats (Li et al., 2006). Electrophysiologically, in the GAERS strain, $GABA_A$ receptor-mediated currents are altered selectively in the thalamic reticular nucleus, but not in ventrobasal complex or somatosensory cortex, with mIPSCs exhibiting enhanced amplitude and reduced decay kinetics (Bessaih et al., 2006). Such changes might be accounted for by expression of the β1 subunit (Huntsman and Huguenard, 2006). Finally, in WAG/Rij rats, a loss of $GABA_A$ receptor α3 subunit-immunoreactivity has been shown to occur without alteration in mRNA expression in the reticular thalamic nucleus (Liu et al., 2007), suggesting a local and highly specific deficit in $GABA_A$ receptor function as a possible cause of absence seizures in these mutant rats.

Mutations affecting $GABA_A$ receptor assembly and trafficking

Several mutations in $GABA_A$ receptor subunits have been associated with familial idiopathic epilepsies, including childhood absence epilepsy (CAE), generalized epilepsy with febrile seizures plus (GEFS+) and juvenile myoclonic epilepsy (JME) (Heron et al., 2007; Noebels, 2003). Missense and frame shift mutations in the $GABA_A$ receptor α1 subunit gene (GABRA1; 5q34) are associated with JME (Cossette et al., 2002) and childhood absence epilepsy (CAE) (Maljevic et al., 2006). By contrast, missense, splice site mutations, or deletions in the γ2 subunit gene (GABRG2; 5q34) have been found in families with GEFS+ and CAE with febrile seizures (Audenaert et al., 2006; Baulac et al., 2001; Harkin et al., 2002; Kananura et al., 2002; Wallace et al., 2001). In recombinant expression systems, these missense mutations typically affect single channel gating and/or cell surface availability of $GABA_A$ receptors. The precise mechanism underlying seizure generation remains in most cases ill-defined. The $GABA_A$ receptor γ2 subunit R43Q mutation has been reported to impair assembly and cell surface expression of $GABA_A$ receptors (Baulac et al., 2001; Bowser et al., 2002). The mutation causes an increase in intracortical excitability in patients compared to unaffected relatives (Fedi et al., 2007). Intriguingly, the effect of the mutation was shown to be temperature-dependent, with cell surface expression being reduced *in vitro* at temperatures higher than 37ºC (Kang et al., 2006). However, since most GEFS+ patients do not carry this mutation, such a mechanism alone is not sufficient for explaining the onset of seizures. In fact, other studies have shown that the γ2(R43Q) mutation affects $GABA_A$ receptor cell surface trafficking and subunit composition independently of temperature (Frugier et al., 2007). The reduction of cell surface expression mainly affects extrasynaptic receptors containing the α5 subunit, without altering phasic inhibition mediated by synaptic $GABA_A$ receptors (Eugène et al., 2007). In the same study, these effects were contrasted to the γ2(K289M) mutation, which accelerates decay kinetics of miniature and evoked postsynaptic inhibitory currents, but does not affect $GABA_A$ receptor trafficking and cell surface expression. Another mutation, α1(A322D), is characterized by reduced subunit expression due to enhanced proteosomal degradation, probably due to protein misfolding (Gallagher et al., 2007). Finally, two susceptibility variants (E177A and A220H) have been found in the δ subunit gene (GABRD; present primarily in extrasynaptic $GABA_A$ receptors, see section **"Phasic/tonic inhibition"**), affecting channel kinetics and cell surface expression in recombinant systems (Dibbens et al., 2004; Feng et al., 2006). However, no segregation of A220H with epilepsy could be found in a subsequent analysis of a large family (Lenzen et al., 2005), and the significance of these mutations remains to be established.

CONCLUSIONS AND PERSPECTIVES

The heteregeneous molecular structure of $GABA_A$ receptors and their differential expression, trafficking, localization, and function underscore their complex regulation. They contribute in multiple ways to the maintenance of E/I balance and the pathophysiology of epilepsy. Consequently, much work remains to be done to conceive therapeutic applications exploiting specific facets of $GABA_A$ receptor heterogeneity. So far, data sets obtained with different methods cannot be integrated into a single coherent picture, and multidisciplinary approaches will be required to grasp the significance of $GABA_A$ receptors in homeostatic synaptic plasticity. The postulated "imbalance" between synaptic excitation and inhibition has been a motor for studying the functional properties of GABAergic and glutamatergic synapses in great detail. However, it is too simple a model for allowing conceptual advances about the pathophysiology of complex brain diseases, such as epilepsy disorders. While the present review focused solely on $GABA_A$ receptors, it is evident that other mechanisms contributing to synaptic homeostasis will have to be included in a global concept as a prerequisite for understanding and preventing epileptogenesis and ictogenesis. Yet, the central role played by GABAergic transmission in the regulation of neuronal networks justifies the current interest given to $GABA_A$ receptors in studies of epilepsy.

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.

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