

Extrasynaptic GABA_A Receptors: Their Function in the CNS and Implications for Disease

Stephen G. Brickley^{1,*} and Istvan Mody²

¹Division of Cell & Molecular Biology, South Kensington Campus, Imperial College, London SW7 2AZ, UK

²Departments of Neurology and Physiology, The David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

*Correspondence: s.brickley@imperial.ac.uk

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Over the past two decades, research has identified extrasynaptic GABA_A receptor populations that enable neurons to sense the low ambient GABA concentrations present in the extracellular space in order to generate a form of tonic inhibition not previously considered in studies of neuronal excitability. The importance of this tonic inhibition in regulating states of consciousness is highlighted by the fact that extrasynaptic GABA_A receptors (GABA_ARs) are believed to be key targets for anesthetics, sleep-promoting drugs, neurosteroids, and alcohol. The neurosteroid sensitivity of these extrasynaptic GABA_ARs may explain their importance in stress-, ovarian cycle-, and pregnancy-related mood disorders. Moreover, disruptions in network dynamics associated with schizophrenia, epilepsy, and Parkinson's disease may well involve alterations in the tonic GABA_AR-mediated conductance. Extrasynaptic GABA_ARs may therefore present a therapeutic target for treatment of these diseases, with the potential to enhance cognition and aid post-stroke functional recovery.

The GABAergic system of the mammalian brain consists of GABA-releasing cells and receptors that bind GABA. GABA-releasing cells are extraordinarily diverse and highly specialized (Freund and Buzsáki, 1996; Klausberger and Somogyi, 2008), both controlling the activity of local networks (e.g., interneurons) and forming the output of some brain areas and nuclei (e.g., striatal medium spiny neurons and cerebellar Purkinje cells). Receptors that bind GABA are present on virtually every neuron in the brain and represent a diverse array of receptor types (Mody and Pearce, 2004). This review focuses on GABA_A receptors (GABA_ARs) that are excluded from synapses (see Figure 1). It has long been appreciated that ligand-gated ion channels that bind glutamate and GABA are found outside synapses in the somatic, dendritic, and even axonal membranes of mammalian neurons (Brown et al., 1979; Soltesz et al., 1990). The first indication that a persistent, tonic conductance could result from activation of extrasynaptic GABA_AR populations came from whole-cell voltage-clamp recordings made from developing neurons when synapses are being formed (Ben-Ari et al., 1994; Kaneda et al., 1995; Valeyev et al., 1993). In these experiments, the addition of GABA_AR blockers reduced the standing holding current indicating that a tonic GABA_AR-mediated conductance had to be present that was not associated with conventional IPSCs (Otis et al., 1991). It is believed that these early developmental forms of GABA signaling may play a role in controlling neuronal differentiation (LoTurco et al., 1995; Markwardt et al., 2011; Owens et al., 1999). This type of intercellular communication is fundamentally different from the "point-to-point" communication that underlies both synaptic transmission and gap-junction-mediated electrical coupling. It is more similar to the volume and paracrine transmission associated with the actions of neuromodulators such as serotonin, histamine, dopamine, acetylcholine, and peptides in the brain (Agnati et al., 2010). Attention has subsequently focused on the molecular identity

of the extrasynaptic GABA_ARs that generate the tonic conductance and on exploring their physiological relevance for the adult brain (Farrant and Nusser, 2005).

GABA_ARs are pentameric assemblies usually made up from at least three different proteins selected from 19 different subunits (Olsen and Sieghart, 2008). These include α 1-6, β 1-3, γ 1-3, δ , ϵ , θ , π , and ρ 1-3 (Olsen and Sieghart, 2008, 2009; Whiting, 2003). A receptor's regional and developmental expression pattern, as well as its physiological and pharmacological properties, are determined by differences in subunit gene expression and composition (Hevers and Lüddens, 1998; Mody and Pearce, 2004) and the rules governing these relationships have received a great deal of attention in the search for highly specific drug targets in the CNS (Olsen and Sieghart, 2009; Whiting, 2003). The subunit identity of the final assembly also determines the synaptic or extrasynaptic localization of GABA_ARs within a neuron (Pirker et al., 2000), reflecting the existence of various subunit assembly rules and anchoring/trafficking mechanisms (Luscher et al., 2011; Vithlani et al., 2011). Following the original description of the GABA_AR δ -subunit (Shivers et al., 1989) and its expression patterns in the brain (Wisden et al., 1992), it was first shown for mature cerebellar granule cells that extrasynaptic α 6 β δ subunit-containing GABA_ARs mediate a tonic form of inhibition both in vitro (Brickley et al., 2001; Hamann et al., 2002) and in vivo (Chadderton et al., 2004), while conventional synaptic γ 2 subunit-containing GABA_ARs are involved in direct synaptic transmission (Farrant and Nusser, 2005). A tonic conductance mediated by α 4 β δ subunit-containing GABA_ARs has now also been reported in dentate gyrus granule cells, thalamic relay neurons, neocortical layer 2/3 pyramidal cells, and medium spiny neurons of the striatum (Ade et al., 2008; Drasbek and Jensen, 2006; Kirmse et al., 2008; Porcello et al., 2003; Salin and Prince, 1996; Santhakumar et al., 2010; Stell et al., 2003). Additionally, a tonic conductance present in

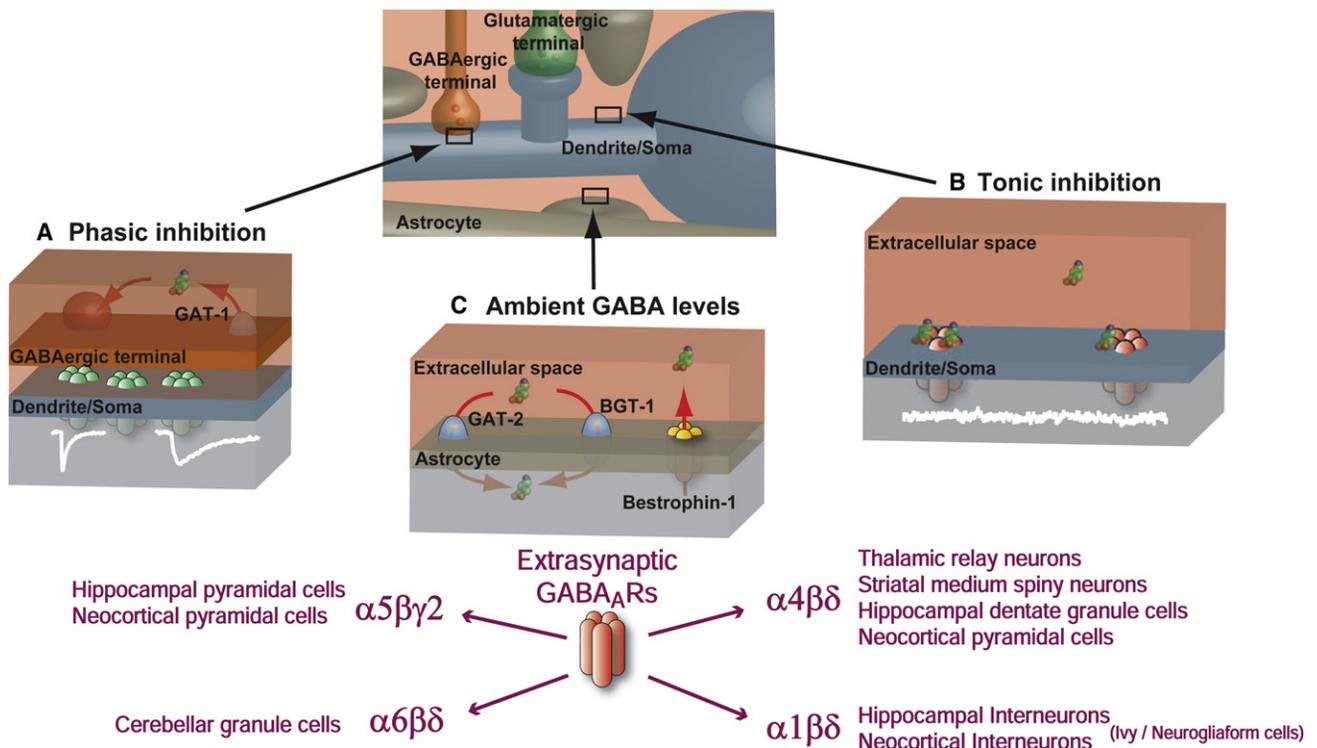


Figure 1. Tonic Inhibition Mediated by Extrasynaptic GABA_A Receptors

The dendrite/soma of a neuron receives a constant barrage of synaptic drive from glutamatergic and GABAergic terminals. The astrocytes that closely intermingle with these structures sense the release of these neurotransmitters as well as modulating their levels within the extracellular space. Vesicular GABA release from GABAergic terminals as well as nonvesicular GABA release from other sources interacts with GABA uptake mechanisms to set the ambient GABA levels within the extracellular space.

(A) Phasic inhibition. GABA molecules are packaged into synaptic vesicles within the GABAergic terminal. Once released, GABA rapidly diffuses across the synaptic cleft to occupy synaptic GABA_ARs that can exist in various subunit compositions. The low affinity of synaptic receptors means that although the synaptic cleft concentration is high (1–10 mM) the GABA molecules only occupy the receptors for a very short duration. Brief GABA_AR occupancy is further ensured by the rapid removal of GABA from the synaptic cleft (<1 ms) due to diffusion and active binding and uptake by GABA transporter proteins (GAT-1) located in the presynaptic axon terminal. The resulting brief postsynaptic conductance change (white trace) is characterized by a fast rising and slow decaying waveform that can vary in duration depending upon the subunit composition of the synaptic GABA_ARs and the transmitter profile within the cleft.

(B) Tonic inhibition. The low resting ambient GABA levels present in the extracellular space are able to activate high-affinity extrasynaptic GABA_ARs to generate a persistent conductance (Cl⁻ and to a lesser extent HCO₃⁻) that is responsible for generating tonic inhibition (noisy white trace) in a number of neuronal types. (C) Ambient GABA levels. The precise mechanisms for regulating ambient GABA levels within the brain's extracellular space is beginning to be elucidated and involves an interplay between the level of vesicular GABA release, the stoichiometry of the GABA transporters (GAT-2 and BGT-1 in astrocytes and GAT-1 in axon terminals), and other forms of nonvesicular GABA release such as GABA permeation through bestrophin channels. Ultimately, it is the level of ambient GABA that leads to the activation of extrasynaptic GABA_ARs in the soma/dendrite and even axonal membrane to generate tonic inhibition.

Ivy/neurogliaform cells (Capogna and Pearce, 2011; Szabadics et al., 2007) is probably generated by the persistent activation of extrasynaptic $\alpha 1\beta\delta$ subunit-containing extrasynaptic GABA_ARs (Oláh et al., 2009).

Given that persistently active δ -GABA_AR openings make such a major contribution to the total charge that flows across the membrane (Belelli et al., 2005; Brickley et al., 1996; Nusser and Mody, 2002), it is not surprising that this type of conductance is capable of modulating both cell and network behavior (Farrant and Nusser, 2005). In thalamic relay neurons, for example, the membrane hyperpolarization associated with the persistent chloride flux through δ -GABA_ARs leads to burst firing (Cope et al., 2005) and slow thalamo-cortical oscillations (Winsky-Sommerer et al., 2007). However, the tonic conductance may not always result in membrane hyperpolarization. In cerebellar granule cells, the membrane shunt associated with tonic

inhibition attenuates excitatory drive with little impact on the membrane potential (Brickley et al., 2001). It is also worth noting that a shunting inhibition associated with a tonic conductance could result in a small but persistent membrane depolarization (Farrant and Kaila, 2007). Another striking feature of the tonic conductance measured in adult neurons is that it represents the simultaneous opening of only a very small fraction of the available extrasynaptic GABA_ARs (Kasugai et al., 2010; Nusser et al., 1995), indicating that receptor occupancy is low and/or a large number of receptors are heavily desensitized. δ -GABA_ARs recorded at room (Mortensen et al., 2010) and physiological (Bright et al., 2011) temperatures are predicted to be profoundly desensitized. Although tonic inhibition can be generated by a desensitized receptor population as long as receptor number is high, this feature could limit the ability of these receptors to operate as spillover detectors and other less

desensitized extrasynaptic GABA_ARs could be better suited to this role. Slow-rising and slow-decaying IPSCs generated by GABA spillover is a significant feature of GABA release from Ivy/neurogliaform cells (Capogna and Pearce, 2011; Szabadics et al., 2007) and has been reported in hippocampal neurons (Vargas-Caballero et al., 2010; Zarnowska et al., 2009). One challenge for the future is to establish whether the spillover currents observed in these and other cell types reflect activation of distinct extrasynaptic GABA_AR populations separate from those responsible for generating tonic inhibition (Farrant and Nusser, 2005).

It is now appreciated that in addition to δ -GABA_ARs, other GABA_AR types are also capable of generating a tonic conductance in a number of adult brain regions. Most notably, $\alpha 5\beta\gamma 2$ subunit-containing GABA_ARs ($\alpha 5$ -GABA_ARs) generate a tonic conductance that regulates the excitability of pyramidal neurons in CA1 and CA3 regions of the hippocampus (Caraiscos et al., 2004; Glykys and Mody, 2006, 2007; Pavlov et al., 2009; Prenosil et al., 2006; Semyanov et al., 2004) and layer 5 cortical neurons (Yamada et al., 2007). High-affinity GABA_ARs made up of only $\alpha\beta$ subunits are also a possibility (Mortensen and Smart, 2006), as are GABA_ARs that can open even in the absence of an agonist (Hadley and Amin, 2007), as reported in some immature neurons (Birnir et al., 2000). It is also possible, given the large number of $\gamma 2$ -GABA_ARs present in both the synaptic and extrasynaptic membrane (Kasugai et al., 2010; Nusser et al., 1995; Soltesz et al., 1990), that more conventional low-affinity GABA_ARs make a contribution to the steady-state conductance when ambient GABA concentrations are high (Farrant and Kaila, 2007). Nevertheless, it is now appreciated that specific high-affinity GABA_AR populations, such as δ -GABA_ARs and $\alpha 5$ -GABA_ARs, are predominantly responsible for generating the tonic conductance found in many brain regions under normal physiological conditions. The study of these extrasynaptic GABA_AR populations is now entering a defining stage and this review focuses on new insights into the potential involvement of these receptors in the cellular and molecular abnormalities underlying neurological and psychiatric disorders including sleep disturbances, stress-related psychiatric conditions, and epilepsy. We also further discuss the potential role of these receptors in cognition, in recovery from stroke, and in mediating the effects of alcohol.

Sleep Disorders

Adequate sleep is essential for our well being, and many neuropsychiatric conditions, such as depression and schizophrenia, are associated with severe disruptions in sleep patterns. It is thus disappointing that we understand little about the mechanisms that control sleep and rely on limited repertoires of clinical interventions to treat sleep disorders (Wafford and Ebert, 2008). GABA_ARs play a pivotal role in the control of our sleep rhythms, and for many decades benzodiazepines and zolpidem, known for their ability to potentiate GABA_AR currents, have remained the most widely prescribed treatment for insomnia, in spite of producing tolerance, addiction, and withdrawal problems. In a search for more refined drug interventions, it has become clear that the hypnotic actions of the sleep promoting drug gaboxadol (Wafford and Ebert, 2006) (4,5,6,7-tetrahydroisothiazolo-[5,4-c]

pyridin-3-ol; THIP) can be attributed to this drug's selective action on δ -GABA_ARs (Brown et al., 2002). At concentrations of around 500 nM, this drug activates δ -GABA_ARs with little action on synaptic GABA_AR types. This selectivity arises from gaboxadol's lower apparent affinity at $\gamma 2$ -GABA_ARs compared to δ -GABA_ARs (Mortensen et al., 2010). Gaboxadol acts as a hypnotic in humans to increase sleep duration by promoting slow-wave or non-rapid eye movement (non-REM) sleep (Faulhaber et al., 1997). When δ -GABA_ARs are removed by genetic manipulations in mice, gaboxadol-induced slow oscillations are absent from the EEG (Winsky-Sommerer et al., 2007) and the anesthetic potency of gaboxadol is reduced (Boehm et al., 2006). Unfortunately, due to side-effects such as hallucinations and disorientation in a subset of patients, gaboxadol failed phase III clinical trials as an alternative to benzodiazepines, but more potent δ -GABA_AR selective agonists are being developed (Wafford et al., 2009).

Alterations in the dynamics of the thalamo-striatal-cortical network probably underlie the sleep disturbances common to many neurological disorders and this may involve alterations in extrasynaptic GABA_AR function. In the thalamus a tonic GABA conductance promotes burst firing of thalamic relay neurons (Bright et al., 2007; Cope et al., 2005), a key requirement in the generation of slow 1–4 Hz EEG rhythms during non-REM sleep. During non-REM sleep, ambient GABA levels are higher in the thalamus than during REM or waking states (Kékesi et al., 1997). δ -GABA_ARs are also found in the superficial neocortical layers 2/3 but there is currently little evidence to suggest that these neocortical δ -GABA_ARs contribute to the slow thalamo-cortical rhythms observed during sleep (Steriade et al., 1993). In Parkinson's disease, sleep abnormalities are among the frequent nonmotor symptoms that present during its early evolution prior to drug treatment (Chaudhuri and Naidu, 2008). The caudate-putamen of the striatum is a brain region that regulates motor planning and is, therefore, critically linked to Parkinson's disease. This brain region also expresses high levels of extrasynaptic $\alpha 4\beta\delta$ subunit-containing GABA_ARs and dopamine D1 receptor-expressing medium spiny neurons display a tonic conductance-mediated by δ -GABA_AR populations (Ade et al., 2008; Kirmse et al., 2008). The loss of dopaminergic drive that characterizes Parkinson's disease explains the enhanced GABA concentrations found in the striatum (Kish et al., 1986) and it is intriguing to speculate that this change may underlie the sleep disruptions associated with Parkinson's and alterations in ambient GABA levels may contribute to the sleep disturbances commonly associated with a number of neurological disorders including depression.

Drugs that modulate sleep and induce anesthesia share common molecular targets (Franks, 2008). Raising ambient GABA levels alone, with GABA uptake blockers, will induce an anesthesia-like state (Katayama et al., 2007) and neurosteroids (which are brain-synthesized metabolites of ovarian and adrenal cortical steroid hormones) act as anesthetics through an action on δ -GABA_ARs (Stell et al., 2003). Indeed, the loss of δ -GABA_ARs is associated with an attenuated response to neurosteroid-induced anesthesia (Mihalek et al., 1999). Other important general anesthetics such as propofol and isoflurane enhance tonic inhibition in hippocampal neurons (Bai et al., 2001),

thalamic relay neurons (Jia et al., 2008b), and neocortical neurons (Drasbek et al., 2007). However, the amnesia-inducing effect, but not the anesthetic potency of isoflurane, is altered in $\alpha 4$ knockout mice, which also lack δ -GABA_ARs on the cell surface (Rau et al., 2009), demonstrating that extrasynaptic GABA_ARs are not a primary site of action for all anesthetics.

Stress and Psychiatric Disorders

Neurosteroids are among the most powerful regulators of GABA_AR function in the CNS (Belelli and Lambert, 2005; Chisari et al., 2010; Mitchell et al., 2008; Reddy, 2010). The first example of this robust modulatory effect was discovered nearly 30 years ago (Harrison and Simmonds, 1984) for the synthetic steroid alfaxalone (5 α -pregnan-3 α -ol-11,20 dione). Shortly after, it was demonstrated that a metabolite of the ovarian steroid hormone progesterone (allopregnanolone, also called 3 α -hydroxy-5 α -pregnan-20-one, or 3 α ,5 α -tetrahydroprogesterone, or 5 α -pregnan-3 α -ol-20-one, or 5 α 3 α -THPROG) and a metabolite of the stress steroid deoxycorticosterone (aka 5 α 3 α -THDOC) are potent barbiturate-like ligands of GABA_ARs (Majewska et al., 1986). Our first collaborative research (Stell et al., 2003) demonstrated that δ -GABA_ARs are a preferred site of action for neurosteroids at low (nanomolar) concentrations. This preferred action probably reflects a simple property of these receptors: GABA is not an efficacious agonist at δ -GABA_ARs (Chisari et al., 2010), which means that the coupling of GABA binding to channel opening is not efficient. Because neurosteroids increase the likelihood that GABA will open the channel (Chisari et al., 2010), they can enhance the efficacy of GABA at δ -GABA_ARs and thus modulate receptor activity, while this is less likely at other GABA_ARs where GABA is already an efficacious agonist. Perhaps δ -GABA_ARs are the preferred site of action for paracrine neurosteroid signaling where the neurosteroids synthesized in another cell (e.g., astrocyte) must travel through the extracellular space to act on extrasynaptic δ -GABA_ARs. Neurosteroid synthesis in astrocytes is regulated by the mitochondrial 18 kD translocator protein TSPO (the peripheral benzodiazepine receptor by its former name) for which the drug XBD173 is an excellent non-sedative anxiolytic and antipanic agent (Rupprecht et al., 2009). The mitochondrial TSPO is also in CNS neurons where it may mediate autologous effects of neurosteroids on neuronal excitability in brain slices following benzodiazepine (Tokuda et al., 2010) or ethanol (Tokuda et al., 2011) administration.

Since neurosteroid levels in the brain will also mirror ovarian or stress steroid hormone levels, the tonic inhibition regulated by the neurosteroid metabolites of these hormones may contribute to CNS disorders associated with altered hormonal states. For example, the anxiety associated with premenstrual dysphoric disorder (PMDD) has been linked to neurosteroid regulation of tonic inhibition in animals (Maguire et al., 2005; Smith et al., 1998) and the discrepancy between extrasynaptic GABA_AR number and postpartum levels of the progesterone metabolite allopregnanolone has been linked to postpartum depression (Maguire and Mody, 2008). During pregnancy, progesterone levels increase by over 100-fold, and the levels of allopregnanolone (produced in the brain from progesterone), which could potentially enhance inhibition through δ -GABA_ARs,

are elevated accordingly. High neurosteroid levels in the brain are dangerous because they might produce an anesthetic-like effect by sedating expectant mothers. Most likely as a compensatory mechanism, the number of neurosteroid-sensitive δ -GABA_ARs decrease during pregnancy, so that the high levels of neurosteroids are offset by fewer δ -GABA_ARs. However, this balance in the mother's brain recalibrates just after delivery, when progesterone and neurosteroid levels are restored. With the postpartum drop in neurosteroid levels, the reduced numbers of δ -GABA_ARs are no longer sufficient to maintain an optimal level of inhibitory tone. The result is a period of increased neuronal excitability until the number of δ -GABA_ARs is restored to pre-pregnancy levels. In our experiments, we found that delays in δ -GABA_AR recovery were associated with severe depression-like behavior in mice, which results in mothers cannibalizing their offspring. This behavior is reduced by administering gaboxadol to activate the δ -GABA_ARs. The recently identified selective δ -GABA_AR agonist (DS-1) and an allosteric enhancer (DS-2) of δ -GABA_AR function (Wafford et al., 2009) may aid the design of specific treatments for postpartum depression. Analogous changes in δ -GABA_AR expression have also been reported to occur during puberty (Shen et al., 2007), which could in part explain why this developmental period is associated with increased susceptibility to stress-related disorders.

Stress induced by social isolation in rats leads to upregulation of extrasynaptic δ -GABA_ARs and correlates with an increase in hippocampal tonic inhibition (Serra et al., 2006). Hippocampal tonic inhibition counteracts the excitation of interneurons and can regulate the frequency of gamma oscillations (Mann and Mody, 2010) that have been shown to be altered in schizophrenic patients (Uhlhaas and Singer, 2010). The observation that reductions in δ -GABA_AR mRNA have been reported in post-mortem brains of patients with schizophrenia (Maldonado-Avilés et al., 2009), and the association between two polymorphisms in the GABRD gene and childhood onset mood disorders in males (Feng et al., 2010), potentially suggests that altered tonic conductance could explain the disturbances in network behavior described in such disorders. Interestingly, in humans the GABA_AR $\alpha 5$ subunit gene has also been identified as a susceptibility locus for schizophrenia (Maldonado-Avilés et al., 2009) and depression (Kato, 2007). Autopsy studies from individuals who have suffered from major depression exhibit marked changes in a number of genes involved in both glutamate and GABA signaling pathways, including alterations in the expression of $\alpha 5$ -GABA_ARs and δ -GABA_ARs (Choudary et al., 2005; Sequeira et al., 2009). Although many genes, including those involved in synaptic GABA_AR function, can be altered in neuropsychiatric disorders an emerging theme of these and many other studies is that the $\alpha 5$ and δ containing GABA_ARs are heavily regulated by stress hormones, and this feature is likely to explain why changes in extrasynaptic GABA_A receptor expression are so often associated with stress-related disorders.

Epilepsy

Disturbances in synaptic and extrasynaptic GABA_AR function, including several point mutations (Macdonald et al., 2010), have been implicated in many forms of epilepsy. Given the

Table 1. Summary of Some Clinically Relevant Drugs that Can Alter Tonic Inhibition within the Brain

Drug (Trade Names)	Mechanism of Action	Current Drug Indications
Gabapentin (<i>Fanatrex</i> , <i>Gabarone</i> , <i>Gralise</i> , <i>Neurontin</i>)	Originally thought to be a GABA mimetic, but mechanism of action is now unclear. Possible enhancement of GABA synthesis could explain why ambient GABA levels in the brain are raised (Maneuf et al., 2003).	Partial-onset seizures in adults and the elderly (Beghi, 2010); alcohol withdrawal as a combination therapy (Anton et al., 2011); sleep disorders (Ehrenberg, 2000).
Vigabatrin (<i>Sabril</i>)	Irreversible block of GABA transaminase to interfere with GABA catabolism and, therefore, raise ambient GABA levels.	Refractory complex partial seizures and infantile spasms (Tolman and Faulkner, 2009). Not favored due to visual field loss in some adults and children (Chiron and Dulac, 2011).
Tiagabine (<i>Gabitril</i>)	Blockade of GABA transporters on nerve terminals (predominantly GAT-1) leads to raised ambient GABA levels.	Partial seizures; generalized anxiety disorders/panic disorders (Pollack et al., 2005).
Pregabalin (<i>Lyrica</i>)	Enhances the activity of glutamic acid decarboxylase (GAD) leading to increased GABA synthesis and, therefore, raised ambient GABA levels.	Partial seizures with or without secondary generalization (Tassone et al., 2007); neuropathic pain in diabetes, postherpetic neuralgia, and fibromyalgia (Tassone et al., 2007); generalized anxiety disorder (Tassone et al., 2007).
Gaboxadol	Selective orthosteric agonist at δ -GABA _A Rs leading to specific enhancement of the tonic conductance.	Sleep enhancer, but withdrawn from Phase III clinical trials due to poor risk-to-benefit ratio (Saul, 2007).
L-655,708	High-affinity negative allosteric modulator of α 5-GABA _A Rs that will reduce tonic conductances.	Cognitive enhancer but not thought to be suitable for human use due to anxiogenic properties (Navarro et al., 2002).
Ganaxolone	Positive allosteric modulator of most GABA _A Rs with greater potency at δ -GABA _A Rs leading to selective enhancement of the tonic conductance.	Catamenial epilepsy (Biagini et al., 2010).
Alphaxalone (<i>Althesin</i> , <i>Saffan</i>)	Positive allosteric modulator of most GABA _A Rs with greater potency at δ -GABA _A Rs leading to selective enhancement of the tonic conductance.	Anesthetic (Winter et al., 2003) and sedative in long-term intensive care patients (Stewart et al., 1983). Was withdrawn from clinical practice due to complications with the vehicle, Cremophor EL. Rebranded as <i>Saffan</i> and widely used as an anesthetic in veterinary surgery.
Propofol (<i>Diprivan</i>)	Positive allosteric modulator of most GABA _A Rs including α 5 and δ -GABA _A Rs leading to enhanced tonic conductance.	Widely used as an intravenous anesthetic.

importance of maintaining appropriate levels of tonic inhibition for the control of neuronal network behavior (Vida et al., 2006), it is not surprising that δ -GABA_ARs are targets in the treatment of specific forms of epilepsy. Several of the drugs listed in Table 1, which are already in clinical use as antiepileptics, modulate tonic inhibition by altering ambient GABA levels in the brain (see also Figure 2). Mutations in the δ subunit gene have also shown some degree of association with genetic forms of human epilepsy (Dibbens et al., 2004; Mulley et al., 2005) and mouse models of temporal lobe epilepsy (Peng et al., 2004) involve changes in tonic inhibition within the hippocampus (Maguire et al., 2005; Peng et al., 2004; Spigelman et al., 2002; Zhang et al., 2007). The neurosteroid analog ganaxolone is in clinical trials for the treatment of catamenial epilepsy, a form of epilepsy in women that shows cyclic variations in the frequency and intensity of seizures depending on the phases of the menstrual

cycle. δ -GABA_AR-mediated tonic inhibition has been shown to change during the ovarian cycle (Maguire et al., 2005). As extrasynaptic δ -GABA_ARs are highly sensitive to modulation by neurosteroids such as progesterone (Stell et al., 2003), the ability of ganaxolone to enhance tonic inhibition (Belelli and Herd, 2003) could explain why this drug protects against seizure during these sensitive periods of the ovarian cycle. However, enhancing tonic inhibition is not a useful strategy for the treatment of all epilepsies. For example, slow wave discharges within the thalamo-cortical network are a defining feature of absence seizures. Paradoxically, this type of seizure is triggered by enhanced δ -GABA_AR openings with the GABA agonist gaboxadol (Fariello and Golden, 1987). In rodents, a model of absence epilepsy correlates with increased levels of tonic inhibition on thalamic relay neurons (Cope et al., 2009) due to dysfunction of the GABA transporter (GAT-1) and the resulting elevated

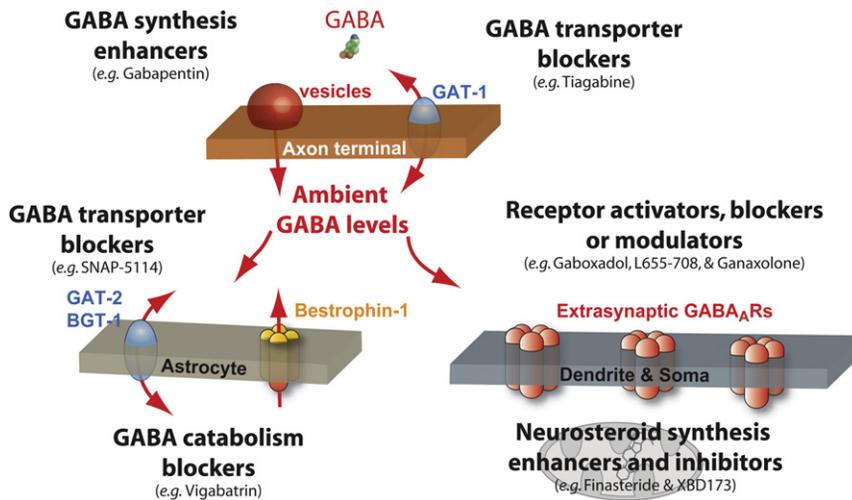


Figure 2. Pharmacological Strategies for Altering the Tonic Conductance

A number of clinically relevant drugs are available that are known to alter the tonic conductance via a variety of direct and indirect targets. Here we illustrate a number of these targets situated within the principal neuronal and nonneuronal compartments of the brain. Although it was originally thought to be a GABA mimetic, the mechanism of action for Gabapentin is currently unclear, but the drug's ability to increase ambient GABA levels in the brain could reflect an alteration in GABA synthesis or release. Gabapentin is currently prescribed for the treatment of partial-onset seizures in adults and the elderly as well as a combination therapy for alcohol withdrawal and for sleep disorders. Tiagabine is a GABA transporter blocker acting predominantly on GAT-1 in nerve terminals leading to raised ambient GABA levels. This drug is prescribed for the treatment of partial seizures as well as generalized anxiety disorders/panic disorders. Other GABA transporter blockers such as SNAP-5114 are more

selective blockers of GABA uptake in astrocytes, but these also lead to enhanced ambient GABA levels. Although bestrophin-1 channels could be an alternative nonvesicular source of GABA release, blockade of these channels by NPPB [5-nitro-2-(3-phenylpropylamino) benzoic acid] has been reported to both increase (Rossi et al., 2003) and decrease tonic inhibition (Lee et al., 2010) onto cerebellar granule cells. Irreversible block of GABA transaminase with the prescription drug Vigabatrin represents another strategy for raising ambient GABA levels. Vigabatrin has been used for the treatment of refractory complex partial seizures and infantile spasms but is currently not favored due to visual field loss in some adults and children. More direct mechanisms for altering tonic inhibition involve orthosteric and allosteric interactions with extrasynaptic GABA_ARs. For example, the orthosteric agonist THIP or gaboxadol will selectively activate δ -GABA_ARs and, therefore, promote non-REM sleep. DS-1 is a newly developed agonist that has greater selectivity for δ -GABA_ARs than THIP, but its clinical benefit has yet to be established. Inverse agonists such as L-655,508 are currently being used to block the current generated by α 5-GABA_ARs with the general objective to be used as cognitive enhancers. Allosteric modulators such as neurosteroids also offer a mechanism for more directly enhancing tonic inhibition. One such drug, Ganaxolone, is currently being developed for the treatment of drug resistant forms of catamenial epilepsy. It may also be possible to enhance or reduce tonic inhibition with Finasteride that blocks neurosteroid synthesis and XBD173 that enhances neurosteroid synthesis via the mitochondrial 18 kD translocator protein TSPO. It is also possible that the β subunit isoform identity may provide a means for selectively modulating tonic inhibition as the preferred β partner is the β 2 subunit (Belelli and Lambert, 2005; Belelli et al., 2005; Herd et al., 2008) for α 4 β subunit-containing GABA_ARs in the thalamus and dentate gyrus of the hippocampus. Any future development of β -subunit-dependent phosphorylation drugs could be useful in this regard.

ambient GABA levels within the thalamus (Errington et al., 2011). The membrane hyperpolarisation that occurs following enhanced tonic conductance in thalamic relay neurons (Cope et al., 2005) alters the fine balance of the thalamo-cortical network (Bright et al., 2007), leading to slow wave discharges. These observations provide a plausible explanation why treatment of absence seizures in humans, with drugs like tiagabine and vigabatrin, exacerbates this particular form of epilepsy (Perucca et al., 1998).

Effects of Alcohol on the Brain

Unlike other addictive drugs that have well-defined targets in the CNS (e.g., cannabis and cocaine), the intoxicating actions of alcohol have poorly defined molecular targets (Kumar et al., 2009). To demonstrate measurable and consistent effects on neuronal targets, past *in vitro* studies have used higher ethanol concentrations than those considered to be performance impairing. In the U.S., for example, every state sets the legal threshold for blood alcohol concentration at 0.08%, which corresponds to ~17 mM ethanol in the blood. Thus, intoxicating alcohol concentrations within a physiologically relevant range should be used when searching for brain targets of ethanol. In expression systems, δ -GABA_ARs containing the α 4, α 6, α 1, and β 2 or β 3 subunits are all potentiated by ethanol at intoxicating concentrations (Sundstrom-Poromaa et al., 2002). Moreover, ethanol's action on δ -GABA_ARs was demonstrated in native neurons (Fleming et al., 2007; Hancher et al., 2005; Jia et al., 2008a; Liang et al., 2007; Santhakumar et al., 2007; Wei et al.,

2004). However, a number of studies have failed to replicate these findings in heterologous expression systems (Baur et al., 2009; Borghese et al., 2006; Korpi et al., 2007; Yamashita et al., 2006), calling into question extrasynaptic δ -GABA_ARs as a molecular target for intoxicating ethanol concentrations. Indeed, antagonism of the putative alcohol binding site on the δ -GABA_AR does not alter alcohol-related behavioral responses *in vivo* (Linden et al., 2011). It is of course possible that acute effects are due to indirect actions of alcohol on δ -GABA_ARs (Kumar et al., 2009), either by enhancing vesicular GABA release (Carta et al., 2004) or by enhancing neurosteroid synthesis (Sanna et al., 2004). Hopefully, it will not be too long before a consensus is reached on the acute actions of intoxicating levels of alcohol in the brain.

In the context of the underlying pathophysiology in alcohol dependence, δ -GABA_ARs may contribute to the effects of alcohol on the reward system of the brain responsible for reinforcing continued alcohol abuse. RNA interference (RNAi) to reduce the expression of α 4 subunits (Rewal et al., 2009) or of δ subunits (Nie et al., 2011) in the nucleus accumbens dorsomedial shell decreased ethanol intake and alcohol preference in rats. Since this highly circumscribed region of the nucleus accumbens is the preferred site of self-administration for alcohol and other drugs of abuse such as amphetamine, cocaine, or dopamine receptor agonists, novel mechanisms of acute and chronic ethanol actions on δ -GABA_ARs discovered over the past decade are beginning to form a cohesive picture, and constitute a first step in understanding the role of the GABAergic

system in alcohol abuse, tolerance, and dependence. Additionally, long-term alcohol abuse alters GABA_AR expression patterns in both animal models and postmortem brain tissue (Kumar et al., 2009). Understanding how changes in extrasynaptic GABA_AR function may impact upon addictive behavior could lead to more rational strategies for the treatment of alcohol dependence and abuse.

Learning and Memory/Cognition Enhancement

After the discovery of long-term potentiation (LTP) (Bliss and Lomo, 1970) at glutamatergic synapses, a form of neuronal plasticity widely thought to underlie learning and memory, it was discovered that GABAergic inhibition obstructs this plasticity (Wigström and Gustafsson, 1983). Low doses of picrotoxin, a noncompetitive antagonist that blocks synaptic and extrasynaptic GABA_ARs, alleviates learning and memory deficits in mouse models of Alzheimer's disease (Yoshiike et al., 2008), neurofibromatosis (Cui et al., 2008), and Down syndrome (Fernandez et al., 2007). Specific blockers of tonic inhibition mediated by α 5-GABA_ARs and knockout mice for the α 5-GABA_ARs have also provided insights into how these receptors, and the tonic inhibition they mediate, impede learning and cognition (Atack, 2010; Martin et al., 2009). First, mice with a partial or full deficit of α 5-GABA_ARs show improved performance in associative learning and memory tasks (Collinson et al., 2002; Crestani et al., 2002; Yee et al., 2004), with only a minimal deficit in memory for object location (Prut et al., 2010). Second, negative allosteric modulators (or BZD-site inverse agonists) selective for α 5-GABA_ARs, such as α 5IA, L-655,708, or RO-493851, all enhance learning and cognitive performance in rodents (Ballard et al., 2009; Chambers et al., 2004; Dawson et al., 2006; Navarro et al., 2002) while having no proconvulsant effects. Data in humans are scarce, but an ethanol-induced amnesia was reduced by administering α 5IA to healthy volunteers (Nutt et al., 2007). In hippocampal pyramidal cells, the elevated numbers of δ -GABA_ARs and enhanced allopregnanolone levels during puberty reduce the probability of inducing LTP (Shen et al., 2010). Adolescent mice also exhibited deficits in an LTP-dependent spatial learning task, which are reversed in adolescent mice lacking δ -GABA_ARs. The continuing development and refinement of negative allosteric modulators specific for α 5-GABA_ARs (Knust et al., 2009), and other drugs that modulate tonic inhibition mediated by δ -GABA_ARs, hold promise as novel treatments for Alzheimer's disease or other neurological and psychiatric disorders characterized by deficits in learning, memory, or cognition.

Neuroprotection and Recovery of Function after Stroke or Other Brain Injuries

It has been suggested that recovery of function following acute injury to the sensorimotor cortex may be controlled by the availability of GABA (Levy et al., 2002). Enhanced tonic inhibition has an acute neuroprotective quality. For example, medium spiny neurons (MSNs) of the striatum are protected against quinolinic acid or NMDA receptor-mediated toxicity by tonic inhibition (Santhakumar et al., 2010). Compared to wild-type, MSNs from adult mice lacking δ -GABA_ARs had both decreased tonic GABA currents and reduced MSN survival following an

in vitro excitotoxic challenge with quinolinic acid. Furthermore, following acute exposure of MSNs to NMDA in WT, but not mice lacking δ -GABA_ARs, muscimol-induced tonic GABA currents reduced the acute swelling of the neurons. In a cortical stroke model, the increased size of the cortical lesion observed when the tonic conductance was reduced with an inverse agonist immediately after an experimental photothrombotic stroke also indicates an acute neuroprotective role for tonic inhibition in cortical neurons (Clarkson et al., 2010). These findings suggest targeting of extrasynaptic GABA_ARs that mediate tonic inhibition could potentially be developed as novel strategies to aid post stroke recovery. The adult brain possesses a remarkable structural and functional plasticity, but some barriers may impede its plasticity once a developmental window is closed (Bavelier et al., 2010). The plasticity of the brain that occurs after an injury is particularly important as it may either facilitate or hinder recovery of function. Plasticity can occur after stroke, particularly in the peri-infarct zone that is adjacent to the region devastated by the stroke (Murphy and Corbett, 2009). As our recent findings (Clarkson et al., 2010) indicate, mechanisms involving an enhanced tonic inhibition that impede the functional plasticity of the adult brain in learning and memory, such as those found in mice lacking α 5-GABA_ARs or animals treated with a negative allosteric modulator of α 5-GABA_AR, might also be operational during post stroke recovery. Therefore, α 5-GABA_AR BZD-site inverse agonists developed for treating cognitive disorders may equally be useful as the first clinical treatment to enhance functional recovery after stroke or possibly other devastating brain injuries.

Conclusions

Our motivation for this review was to highlight an emerging link between changes in tonic inhibition and pathological brain states. There has been considerable progress in understanding the functional significance of extrasynaptic GABA_ARs in the adult brain and how the tonic conductance they generate can alter network behavior in a number of ways. Manipulating ambient GABA levels and/or altering extrasynaptic GABA_AR function may offer novel strategies for the treatment of a diverse array of neurological and psychiatric disorders. The development of drugs to alter the function of extrasynaptic GABA_ARs has seen remarkable progress (see Figure 2). A number of drugs designed to modulate α 5-GABA_ARs may turn out to be useful as cognition enhancers as well as removing some of the "brakes" in the path of adult plasticity necessary for functional recovery after neuronal injury. Several classes of drugs are also becoming available to enhance the function of δ -GABA_ARs, but the discovery of compounds that are able to specifically antagonize tonic inhibition mediated by δ -GABA_ARs is still needed. The diversity of the GABAergic system in general, and of GABA_ARs in particular (Mody and Pearce, 2004), will ensure that further advances in GABA pharmacology will provide a more targeted treatment of these diseases.

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