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Extrasynaptic $GABA_A$ receptors: Their function in the CNS and implications for disease

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Abstract

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 ($GABA_A$Rs) are believed to be key targets for anaesthetics, sleep-promoting drugs, neurosteroids, and alcohol. The neurosteroid sensitivity of these extrasynaptic $GABA_A$Rs 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 $GABA_A$R-mediated conductance. Extrasynaptic $GABA_A$Rs may therefore present a potential therapeutic target for treatment of these diseases, but also 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 Buzsaki, 1996; Klausberger and Somogyi, 2008), controlling both 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 ($GABA_A$Rs) 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 $GABA_A$R 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 $GABA_A$R blockers reduced the standing holding current indicating that a tonic $GABA_A$R-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 signalling 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, acetycholine and peptides in the brain (Agnati et al., 2010). Attention has subsequently focused on the molecular identity of the extrasynaptic $GABA_A$Rs that generate the tonic conductance and on exploring their physiological relevance for the adult brain (Farrant and Nusser, 2005).

$GABA_A$Rs are pentameric assemblies usually made up from at least three different proteins selected from 19 different subunits (Olsen and Sieghart, 2008). These include α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1–3 (Olsen and Sieghart, 2008, 2009; Whiting, 2003). A receptors’ regional and developmental expression pattern, as well as their physiological and pharmacological properties are determined by differences in subunit gene expression and composition (Hevers and Luddens, 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 $GABA_A$Rs 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 $GABA_A$R 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 α6βδ subunit-containing $GABA_A$Rs 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 γ2 subunit–containing $GABA_A$Rs are involved in direct synaptic transmission (Farrant and Nusser, 2005). A tonic conductance mediated by α4βδ subunit-containing $GABA_A$Rs 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.; Stell et al., 2003). Additionally, a tonic conductance present in Ivy/neuorgliaform cells (Capogna and Pearce, 2010; Szabadics et al., 2007) is probably generated by the persistent activation of extrasynaptic α1βδ subunit-containing extrasynaptic $GABA_A$Rs (Olah et al., 2009).

Given that persistently active δ-$GABA_A$R 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-$GABA_A$Rs 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 $GABA_A$Rs (Kasugai et al., 2010; Nusser et al., 1995) indicating that receptor occupancy is low and/or a large number of receptors are heavily desensitized. The δ-$GABA_A$Rs recorded at room (Mortensen et al., 2010) and physiological temperatures (Bright et al., 2011) 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 $GABA_A$Rs 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/neuorgliaform cells (Capogna and Pearce, 2010; Szabadics et al., 2007) and has been reported in hippocampal neurons (Vargas-Caballero et al., 2009; Zarnowska et al., 2009). One challenge for the future is to establish whether the spillover currents observed in these and other cell types, reflects activation of distinct extrasynaptic $GABA_A$R populations separate from those responsible for generating tonic inhibition (Farrant and Nusser, 2005).

It is now appreciated that in addition to δ-$GABA_A$Rs, other $GABA_A$R types are also capable of generating a tonic conductance in a number of adult brain regions. Most notably, α5βγ2 subunit-containing $GABA_A$Rs (α5-$GABA_A$Rs) 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 $GABA_A$Rs made up of only αβ subunits are also a possibility (Mortensen and Smart, 2006), as are $GABA_A$Rs 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 γ2-$GABA_A$Rs 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 $GABA_A$Rs 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 $GABA_A$R populations, such as δ-$GABA_A$Rs and α5-$GABA_A$Rs, are predominantly responsible for generating the tonic conductance found in many brain regions under normal physiological conditions. The study of these extrasynaptic $GABA_A$R 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, 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 dissapointing 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). $GABA_A$Rs play a pivotal role in the control of our sleep rhythms, and for many decades benzodiazepines and zolpidem, known for their ability to potentiate $GABA_A$R 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-$GABA_A$Rs (Brown et al., 2002). At concentrations of around 500 nM, this drug activates δ-$GABA_A$Rs with little action on synaptic $GABA_A$R types. This selectivity arises from gaboxadol's lower apparent affinity at γ2-$GABA_A$Rs compared to δ-$GABA_A$Rs (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-$GABA_A$Rs are removed by genetic manipulations in mice, gaboxadol-induced slow oscillations are absent from the EEG (Winsky-Sommerer et al., 2007) and the anaesthetic 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 likely 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 (Kekesi 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. However, neocortical circuits switch between periods of high activity and quiescence (Steriade et al., 1993). In Parkinson's disease, sleep abnormalities are among the frequent non-motor 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 α4βδ 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 characterises 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 which modulate sleep and anaesthesia share common molecular targets (Franks, 2008). Raising ambient GABA levels alone, with GABA uptake blockers, will induce an anaesthesia-like state (Katayama et al., 2007) and neurosteroids (which are brain-synthesized metabolites of ovarian and adrenal cortical steroid hormones) act as anaesthetics 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 anaesthesia (Mihalek et al., 1999). Other important general anaesthetics 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 anaesthetic potency of isoflurane, is altered in α4 knockout mice which also lack δ- $GABA_ARs$ on the cell surface (Rau et al., 2009) indicating that extrasynaptic $GABA_ARs$ are not a primary site of action for all anaesthetics.

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 alphaxalone (5α-pregnan-3α-ol-11,20 dione). Shortly after, it was demonstrated that a metabolite of the ovarian steroid hormone progesterone (allopregnanolone, also called 3α-hydroxy-5α-pregnan-20-one, or 3α,5α-tetrahydroprogesterone, or 5α-pregnan-3α-ol-20-one, or 5α3α-THPROG) and a metabolite of the stress steroid deoxycorticosterone (aka 5α3α-THDOC) are potent barbiturate-like ligands of $GABA_ARs$ (Majewska et al., 1986). Our first collaborative research (Stell et al., 2003) demonstrated δ-$GABA_ARs$ are a preferred site of action for neurosteroids at low (nanomolar) concentrations. This preferred action likely reflects a simple property of these receptors: GABA is not an efficacious agonist at δ-$GABA_A$Rs (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-$GABA_A$Rs and thus modulate receptor activity, while this is less likely at other $GABA_A$Rs where GABA is already an efficacious agonist. Perhaps δ-$GABA_A$Rs 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-$GABA_A$Rs. 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 $GABA_A$R number and post-partum levels of the progesterone metabolite allopregnanolone has been linked to post-partum 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-$GABA_A$Rs, are elevated accordingly. High neurosteroid levels in the brain are dangerous because, they might produce an anaesthetic-like effect by sedating expectant mothers. Most likely as a compensatory mechanism, the number of neurosteroid-sensitive δ-$GABA_A$Rs decrease during pregnancy, so that the high levels of neurosteroids are offset by fewer δ-$GABA_A$Rs. However, this balance in the mother's brain recalibrates just after delivery, when progesterone and neurosteroid levels are restored. With the post-partum drop in neurosteroid levels, the reduced numbers of δ-$GABA_A$Rs 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-$GABA_A$Rs is restored to pre-pregnancy levels. In our experiments, we found that delays in the process δ-$GABA_A$R recovery, severe depression-like behavior ensues in mice, which results in mothers cannibalizing their offspring. This behavior is reduced by administering gaboxadol to activate the δ-$GABA_A$Rs. The recently identified selective δ-$GABA_A$R agonist (DS-1) and an allosteric enhancer (DS-2) of δ-$GABA_A$R function (Wafford et al., 2009) may aid the design of specific treatments for post-partum depression. Analogous changes in δ-$GABA_A$R 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-$GABA_A$Rs 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-$GABA_A$R mRNA have been reported in post-mortem brains of patients with schizophrenia (Maldonado-Aviles 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 behaviour described in such disorders. Interestingly, in humans the $GABA_AR$ α5 subunit gene has also been identified as a susceptibility locus for schizophrenia (Maldonado-Aviles 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 signalling pathways, including alterations in the expression of α5-$GABA_A$Rs and δ-$GABA_A$Rs (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 α5 and δ containing $GABA_A$Rs 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 importance of maintaining appropriate levels of tonic inhibition for the control of neuronal network behaviour (Vida et al., 2006) it is not surprising that δ-$GABA_A$Rs are targets in the treatment of specific forms of epilepsy. Several of the drugs listed in Table I, 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 analogue 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-$GABA_A$Rs 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 for 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 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-imparing. In the US, 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-$GABA_A$Rs containing the α4, α6, α1, and β2 or β3 subunits, are all potentiated by ethanol at intoxicating concentrations (Sundstrom-Poromaa et al., 2002). Moreover, ethanol's action on δ-$GABA_A$Rs was demonstrated in native neurons (Fleming et al., 2007; Hanchar 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-$GABA_A$Rs as a molecular target for intoxicating ethanol concentrations. Indeed, antagonism of the putative alcohol binding site on the δ-$GABA_A$R does not alter alcohol-related behavioural responses *in vivo* (Linden et al., 2011). It is of course possible that acute effects are due to indirect actions of alcohol on δ-$GABA_A$Rs (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 path physiology in alcohol dependence, δ-$GABA_A$Rs 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 α4 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-$GABA_A$Rs 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 $GABA_A$R expression patterns in both animal models and postmortem brain tissue(Kumar et al., 2009). Understanding how changes in extrasynaptic $GABA_A$R function may impact upon addictive behaviour 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 (Wigstrom and Gustafsson, 1983). Low doses of picrotoxin, a non-competitive antagonist that blocks synaptic and extrasynaptic $GABA_A$Rs, 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 α5-$GABA_A$Rs and knockout mice for the α5-$GABA_A$Rs 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 α5-$GABA_A$Rs 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 α5-$GABA_A$Rs, such as α5IA, 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 α5IA to healthy volunteers (Nutt et al., 2007). In hippocampal pyramidal cells, the elevated numbers of δ-$GABA_A$Rs 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-$GABA_A$Rs. The continuing development and refinement of negative allosteric modulators specific for α5-$GABA_A$Rs (Knust et al., 2009), and other drugs that modulate tonic inhibition mediated by δ-$GABA_A$Rs, holds 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-$GABA_A$Rs 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-$GABA_A$Rs, 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 $GABA_A$Rs 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 α5-$GABA_A$Rs or animals treated with a negative allosteric modulator of α5-$GABA_A$R, might also be operational during post stroke recovery. Therefore, α5-$GABA_A$R 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 $GABA_A$Rs in the adult brain and how the tonic conductance they generate can alter network behaviour in a number of ways. Manipulating ambient GABA levels and/or altering extrasynaptic $GABA_A$R function may offer novel strategies for the treatment of a diverse array of neurological and psychiatric disorders. Nonetheless, the development of drugs to alter the function of extrasynaptic $GABA_A$Rs has seen remarkable progress (see Figure 2). A number of drugs designed to modulate α5-$GABA_A$Rs 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-$GABA_A$Rs, but the discovery of compounds that are able to specifically antagonize tonic inhibition mediated by δ-$GABA_A$Rs is still needed. The diversity of the GABAergic system in general, and of $GABA_A$Rs 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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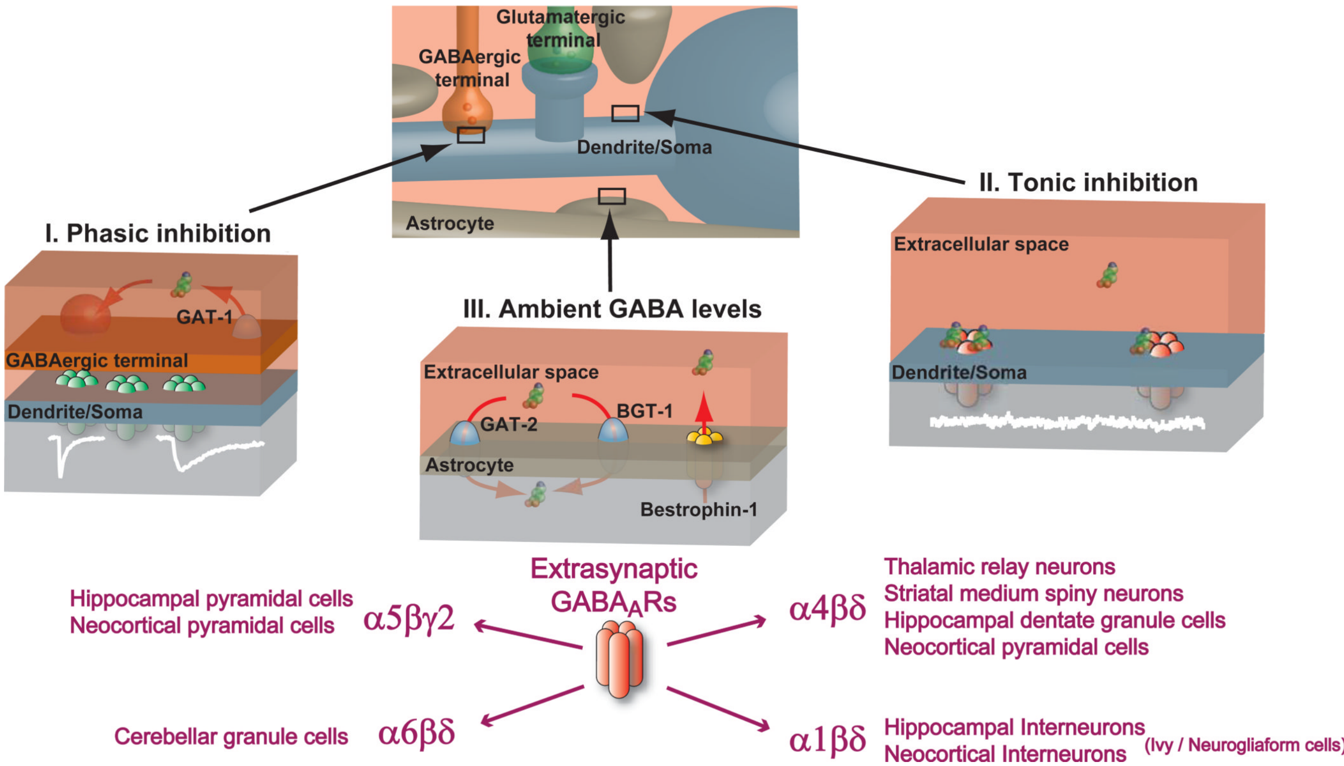

Figure 1. Tonic inhibition is mediated by extrasynaptic $GABA_A$ receptors

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 non-vesicular GABA release from other sources interacts with GABA uptake mechanisms to set the ambient GABA levels within the extracellular space. **I. 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 $GABA_A$Rs 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 $GABA_A$R occupancy is further ensured by the rapid removal of GABA from the synaptic cleft (<1ms) 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 characterised by a fast rising and slow decaying waveform that can vary in duration depending upon the subunit composition of the synaptic $GABA_A$Rs and the transmitter profile within the cleft. **II. Tonic inhibition:** The low resting ambient GABA levels present in the extracellular space are able to activate high-affinity extrasynaptic $GABA_A$Rs to generate a persistent conductance (Cl- and to a lesser extent HCO_3^-) that is responsible for generating tonic inhibition (noisy white trace) in a number of neuronal types. **III. Ambient GABA levels:** The precise mechanisms for regulating ambient GABA levels within the brains 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 non-vesicular GABA release such as GABA permeation through bestrophin channels. Ultimately, it is the level of ambient GABA that leads to the activation of extrasynaptic $GABA_A$Rs in the soma/dendrite and even axonal membrane that generate the tonic inhibition.

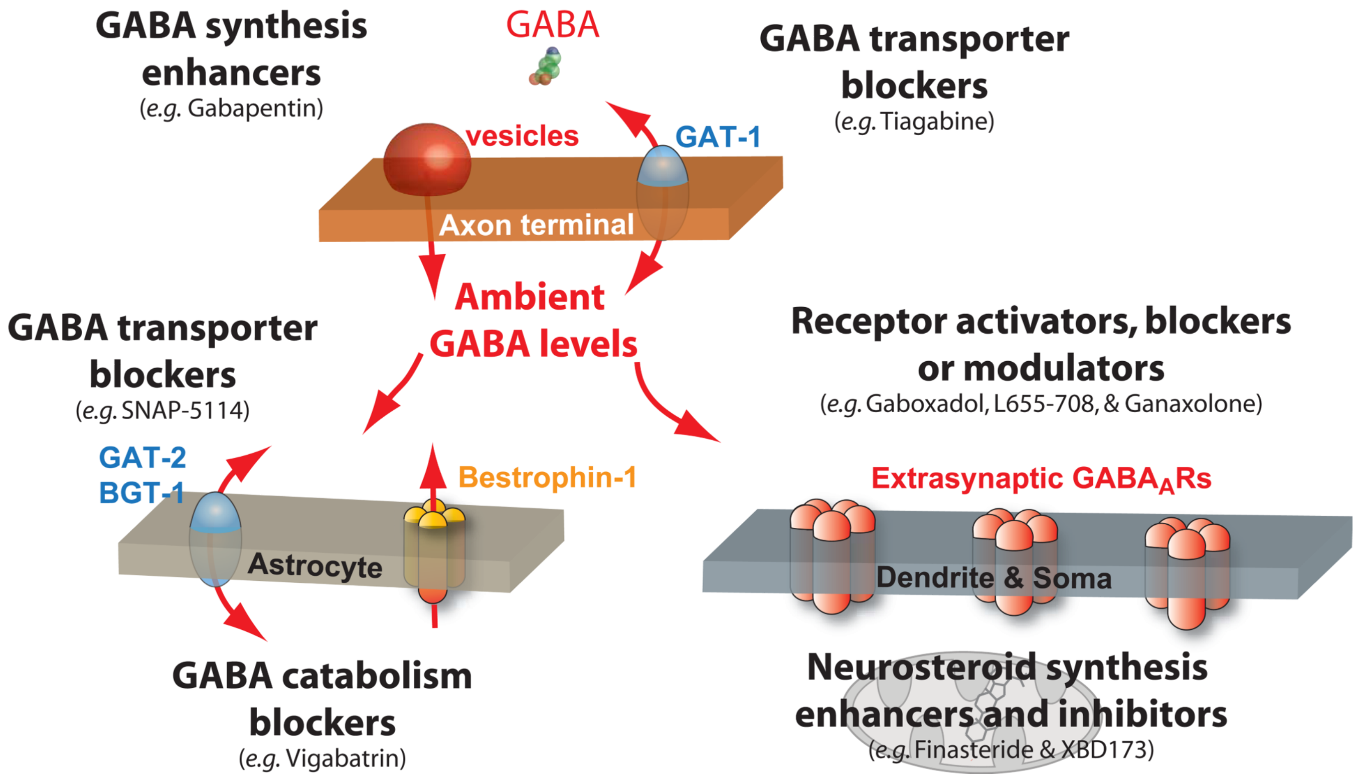

Figure 2. Pharmacological strategies for altering the tonic conductance

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 non-neuronal 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 drugs 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 favoured due to visual field loss in some adults and children. More direct mechanisms for altering tonic inhibition involve orthosteric and allosteric interactions with extrasynaptic $GABA_A$Rs. For example, the orthosteric agonist THIP or gaboxadol will selectively activate δ-$GABA_A$Rs and, therefore, promote non-REM sleep. DS-1 is a newly developed agonist that has greater selectivity for δ-$GABA_A$Rs 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 α5-$GABA_A$Rs with the general objective to being 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 β2 subunit (Belelli and Lambert, 2005; Belelli et al., 2005; Herd et al., 2008) for α4βδ subunit-containing GABARs in the thalamus and dentate gyrus of the hippocampus. Any future development of β-subunit-dependent phosphorylation drugs could be useful in this regard.

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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 (*Fanatrex, Gabarone, Gralise, Neurontin*)	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[1].	Partial-onset seizures in adults and the elderly[2] Alcohol withdrawal as a combination therapy[3] Sleep disorders[4]
Vigabatrin (*Sabril*)	Irreversible block of GABA transaminase to interfere with GABA cetabolism and, therefore, raise ambient GABA levels.	Refractory complex partial seizures and infantile spasms[5]. Not favoured due to visual field loss in some adults and children[6].
Tiagabine (*Gabitril*)	Blockade of GABA transporters on nerve terminals (predominantly GAT-1) leads to raised ambient GABA levels.	Partial seizures Generalized anxiety disorders/panic disorders[7]
Pregabalin (*Lyrica*)	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[8] Neuropathic pain in diabetese, post herpetic neuralgia and fibromyalgia[8]. Generalized anxiety disorder[8].
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[9].
L-655,708	High-affinity negative allosteric modulator of α5-$GABA_A$Rs that will reduce tonic conductances.	Cognitive enhancer but not thought to be suitable for human use due to anxiogenic properties[10].
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.	Catemenial epilepsy[11]
Alphaxalone (*Althesin, Saffan*)	Positive allosteric modulator of most $GABA_A$Rs with greater potency at δ-$GABA_A$Rs leading to selective enhancement of the tonic conductance.	Anaesthetic[12] and sedative in long-term intensive care patients[13]. Was withdrawn from clinical practice due to complications with the vehicle, Cremophor EL. Re-branded as *Saffan* and widely used as an anaesthetic in veterinary surgery.
Propofol (*Diprivan*)	Positive allosteric modulator of most $GABA_A$Rs including α5 and δ-$GABA_A$Rs leading to enhanced tonic conductance.	Widely used as an intravenous anaesthetic.

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