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$GABA_A$ receptors and their associated proteins: implications in the etiology and treatment of schizophrenia and related disorders

Erik I. Charych[1,*], **Feng Liu**[1,*], **Stephen J. Moss**[2,3], and **Nicholas J. Brandon**[1]

[1] Wyeth Research, Neuroscience Discovery, Princeton NJ 08852

[2] Dept of Neuroscience, Tufts University School of Medicine, Boston, MA 02111

[3] Dept of Pharmacology, University College, London WC1E 6BT

Abstract

γ-amino butyric acid type A ($GABA_A$) receptors play an important role in mediating fast synaptic inhibition in the brain. They are ubiquitously expressed in the CNS and also represent a major site of action for clinically relevant drugs. Recent technological advances have greatly clarified the molecular and cellular roles played by distinct $GABA_A$ receptor subunit classes and isoforms in normal brain function. At the same time, postmortem and genetic studies have linked neuropsychiatric disorders including schizophrenia and bipolar disorder with GABAergic neurotransmission and various specific $GABA_A$ receptor subunits, while evidence implicating $GABA_A$R-associated proteins is beginning to emerge. In this review we discuss the mounting genetic, molecular, and cellular evidence pointing toward a role for $GABA_A$ receptor heterogeneity in both schizophrenia etiology and therapeutic development. Finally, we speculate on the relationship between schizophrenia-related disorders and selected $GABA_A$ receptor associated proteins, key regulators of $GABA_A$ receptor trafficking, targeting, clustering, and anchoring that often carry out these functions in a subtype-specific manner.

Keywords

Schizophrenia; Psychiatric Disorders; Bipolar Disorder; GABA; $GABA_A$-receptor

Introduction

Schizophrenia is a complex psychiatric disorder with a strong genetic component, affecting approximately 1% of the world population (Perala et al., 2007; Tsuang, 2000). To date, diagnosis relies solely on the presentation of clinical symptoms, which have been framed into a reliable set of diagnostic criteria that encompass the positive (delusions, hallucinations, thought disorder), negative (anhedonia, alogia, asociality), and cognitive (deficits in attention, executive function, and memory) features of schizophrenia (Lewis et al., 2008). Until recently, schizophrenia had limited prospective therapeutic targets, namely monoamine neurotransmitter receptors such as the dopamine D2 and serotonin $5HT_{2A}$ receptors through the action of typical and atypical antipsychotics (Conn et al., 2008). While these compounds

Correspondence should be addressed to: EIC (charyce@wyeth.com).
*Authors contributed equally to this work

do not adequately address the negative and cognitive components of the syndrome, their efficacy in attenuating psychotic symptoms has led to the suggestion and subsequent demonstration that an excess in striatal dopamine release underlies the positive symptoms of schizophrenia (Morrison and Murray, 2005).

In addition to dopamine hyperfunction, a dysfunctional glutamate signaling hypothesis has also emerged, initially supported by findings that subanesthetic doses of noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonists such as ketamine recapitulate schizophrenia symptoms in healthy human subjects (Krystal et al., 1994; Malhotra et al., 1996) and exacerbate symptoms in schizophrenic patients (Lahti et al., 1995). Reinforcing this idea, it has become increasingly apparent, through advances in our understanding of the underlying biology, that a significant number of emerging candidate risk genes for schizophrenia are implicated in various aspects of glutamatergic neurotransmission, such as synaptic architecture (DISC1, Neuregulin-1, Dystrophin/Dysbindin), NMDAR function (DAAO, D-Serine Racemase), the interaction of glutamatergic and dopaminergic systems (RSG4, COMT), as well as the function of other glutamate receptors (mGluR3) (Camargo et al., 2007; Carter, 2006; Harrison and Weinberger, 2005). There is also strong evidence implicating impairments of γ-aminobutyric acid (GABA) signaling in the pathophysiology of schizophrenia. This notion, initially based on early findings that GABA has a profound influence on dopamine activity (Roberts, 1972; Stevens et al., 1974; Van Kammen, 1977), was ultimately demonstrated through postmortem studies finding reductions in cortical GABA in schizophrenic patients (Perry et al., 1979). This hypofunctional GABA hypothesis is now gaining wide acceptance as genetic, molecular, and circuit-based studies clarify the contribution of GABA signaling abnormalities to the disease, as well as shed light on the relationship between GABAergic dysfunction and other affected signaling systems. From a therapeutic standpoint, $GABA_A$ receptors ($GABA_A$Rs) hold enormous potential for pharmacological modulation and specificity, owing to the high degree of receptor subtype heterogeneity combined with differential regional, cellular, and subcellular distributions of receptor subtypes within the brain. Along these lines, $GABA_A$R functional expression and distribution are under a high degree of subtype-specific regulation, mediated in part by the interaction of these postsynaptic receptors with a number of accessory proteins (Fig. 2; Table 2). As will be discussed, cognitive deficits are considered to be core features of schizophrenia (Elvevag and Goldberg, 2000) and there is strong evidence that disturbances in GABA signaling may contribute to these deficits. Therefore, in this review, we explore the current clinical, genetic and molecular evidence implicating components of GABA signaling systems, including $GABA_A$R subunits and some associated proteins, both as they relate to the etiology of schizophrenia as well as how they may serve as entry points for therapeutic intervention.

Implications of $GABA_A$ receptor structural heterogeneity

The ionotropic GABA type A receptors ($GABA_A$Rs) mediate the majority of fast synaptic inhibition in the mammalian brain. These postsynaptic receptors are heteropentamers that allow the inward flux of Cl^- in response to binding of presynaptically released GABA, resulting in inward, anionic currents that transiently decrease local membrane excitability (Olsen and Sieghart, 2009). A remarkable feature of the brain $GABA_A$Rs is the diversity of subunit isoforms available for assembly into the receptor heteropentamer. At present, 16 subunits, each encoded by separate genes, have been cloned (α1–6, β1–3, γ1, γ2 [short and long splice forms], γ3, δ, ε, π and θ) (Barnard et al., 1998; Bonnert et al., 1999; Jacob et al., 2008; McKernan and Whiting, 1996; Sieghart, 1995; Whiting et al., 1995). Sequence homology places the $GABA_A$R in the superfamily of ligand-gated ion channels that include the nicotinic acetylcholine receptor (nAChR), the strychnine-sensitive glycine receptor (GlyR) and the serotonin type-3 receptor ($5HT_3$R) (Grenningloh et al., 1987; Julius, 1991; Maricq et al., 1991; Schofield et al., 1987). Subunits of all superfamily members share the same predicted

transmembrane topology (Fig. 1). These subunit polypeptides contain four transmembrane domains with a large extracellular N-terminal region, a large intracellular loop between transmembrane domains 3 and 4 (TM 3 and 4), and a small, extracellular C-terminal domain (Fig. 1) (MacDonald et al., 2005). When assembled, the native $GABA_AR$ subunits are arranged in a pentameric array such that the second transmembrane region (TM2) of each subunit contributes to the lining of the chloride channel pore (Fig. 1) (Imoto et al., 1986; Tierney et al., 1998).

Studies employing recombinant receptor expression as well as immunoprecipitation of native receptors have demonstrated that, despite an immense number of possible permutations of the 16 $GABA_AR$ subunit isoforms that could be combined to form the heteropentamer, native $GABA_AR$ stoichiometry is guided and limited by general rules of assembly. Heterologous expression studies using various subunit combinations have demonstrated the requirement for the coassembly of α, β and γ subunits in order to replicate the major electrophysiological and pharmacological properties of the native $GABA_AR$ (Pritchett et al., 1988; Pritchett et al., 1989). In the brain, the majority of $GABA_AR$ subtypes are assemblages of two α, two β and one γ subunit (Fig. 1) (Chang et al., 1996; Khan et al., 1996; Klausberger et al., 2000). The most abundant of these, comprising about 40% of the total $GABA_AR$ pool in the brain, consists of two α1, two β2 and one γ2 subunit (McKernan and Whiting, 1996).

$GABA_ARs$ are sensitive to a considerable number of pharmacological agents (benzodiazepines, barbiturates, neurosteroids, and ethanol) and different $GABA_AR$ subtypes have been shown to exhibit unique pharmacological profiles (Costa, 1998; Vicini, 1991). The benzodiazepine-binding site is formed between α and γ subunits (Fig. 1) (Amin and Weiss, 1993; Smith and Olsen, 1995), and the α subunit influences the sensitivity of a given subtype to different benzodiazepine site ligands (Hadingham et al., 1993). In addition, different subunit compositions confer different affinities for GABA and determine the desensitization kinetics and channel properties (Gingrich et al., 1995; Lavoie and Twyman, 1996; Verdoorn, 1994; Wafford et al., 1993).

As described above, $GABA_AR$ subunit heterogeneity leads to pharmacological and functional diversity, which is paralleled by the differential regional distribution of $GABA_AR$ subtypes throughout the brain as well as at the subcellular level (Fritschy and Brunig, 2003). The combined efforts of many groups have characterized the differential mRNA and protein distributions of the $GABA_AR$ subunits throughout the brain (reviewed by Olsen and Sieghart, 2009). With respect to $GABA_AR$ subcellular distribution, it has been reported for example that in cerebellar granule cells, $GABA_ARs$ containing the γ2 subunit are synaptically localized while those containing the δ subunit in place of the γ2 subunit are localized extrasynaptically (Fig. 1) (Nusser et al., 1998). In forebrain pyramidal neurons, $GABA_ARs$ containing the α1 subunit are expressed throughout the somatodendritic region while those containing the α2 subunit are concentrated preferentially at the axon initial segment (Loup et al., 1998; Nusser et al., 1996). Taken together, subunit structural heterogeneity is the major determinant of pharmacological profile, channel kinetics, and subcellular localization of distinct $GABA_AR$ subtypes. That these subunits are expressed at varying levels in different cell types throughout the brain suggests that distinct $GABA_AR$ subtypes are regionally distributed in a manner that is specific for the neural circuits in which they participate. Since the pathological entity of schizophrenia and related disorders in the adult brain is ultimately characterized by deficits in neural circuitry (Carlsson, 2006; Lisman et al., 2008), $GABA_ARs$ are ideal therapeutic targets because of their putative role in circuit dysfunction (as described below) combined with circuit-specific expression of subtypes exhibiting unique pharmacological properties.

Modified $GABA_AR$ expression in schizophrenia

The role of DLPFC GABAergic dysfunction in schizophrenia

Studies using functional magnetic resonance imaging (fMRI) during working memory tasks in schizophrenic subjects indicate that deficits in working memory, the cognitive processes involved in maintaining and manipulating information, is correlated with disturbances in dorsolateral prefrontal cortical (DLPFC) activity (Lewis et al., 2004). Furthermore, working memory deficits as well as disturbances in DLPFC activity are predictive of the severity of cognitive disorganization in patients with schizophrenia (Perlstein et al., 2001). These deficits appear to be specific for schizophrenia, as they are not present in individuals with major depression (Barch et al., 2003) or nonschizophrenia-related psychosis (MacDonald et al., 2005). At the same time, studies have also revealed that GABAergic interneuron activity is essential for spatial tuning in the DLPFC during working memory tasks (Rao et al., 1999) and that local injection of $GABA_AR$ antagonists to the DLPFC disrupts working memory performance in macaque monkeys (Sawaguchi et al., 1989). Thus, in the DLPFC, GABAergic inhibition controls the timing of principal neuron activities and, in doing so, controls the temporal flow of information during working memory tasks (Constantinidis et al., 2002).

Alterations in the expression of DLPFC GABAergic signaling components in schizophrenia

Numerous postmortem studies have indicated that mRNA expression of the GABA-synthesizing enzyme, glutamic acid decarboxylase of 67 kD (GAD67), is reduced in a subset of GABAergic interneurons in schizophrenic patients (Fig. 2) (Akbarian et al., 1995;Guidotti et al., 2000;Hashimoto et al., 2008a;Hashimoto et al., 2008b;Hashimoto et al., 2005;Mirnics et al., 2000;Straub et al., 2007;Vawter et al., 2002;Volk et al., 2002). Although corresponding decreases in GAD67 protein has only been demonstrated in one of these studies (Guidotti et al., 2000), these data are likely related to the observed deficits in cortical GABA reported in early postmortem studies of schizophrenic patients (Perry et al., 1979) as well as a more recent study in living patients using 2D proton magnetic resonance (Rosso et al., 2006). Interestingly, these losses in GAD67 were largely confined to parvalbumin (PV)-expressing chandelier and wide-arbor basket interneurons located in the middle layers of the cortex. PV is a Ca^{2+}-binding protein that is thought to reduce residual Ca^{2+} levels in axon terminals during repetitive firing, but is also postulated to prolong neurotransmitter release by maintaining elevated Ca^{2+} levels (Collin et al., 2005;Lisman et al., 2008). These fast-spiking PV-expressing interneurons target the perisomatic regions (basket interneurons) and the axon initial segments (chandelier interneurons) of multiple pyramidal neurons simultaneously (Fig. 2) (Conde et al., 1994;Lewis and Lund, 1990;Peters et al., 1982;Somogyi, 1977) and can thus synchronize the activity of local pyramidal cell populations (McBain and Fisahn, 2001). Such synchronized networks give rise to oscillatory activity in the gamma band frequency range (30-80 Hz), which has been correlated with working memory load in healthy human subjects (Howard et al., 2003;Tamas et al., 2000) but is impaired in schizophrenic patients (Cho et al., 2006). Thus, disturbances in executive function of schizophrenic patients, such as working memory, might result from disruptions in the synchronized firing activity of cortical networks normally coordinated by PV-interneurons, the latter of which are deficient in GABA release due to a selective loss in GAD67 expression.

In addition to reductions in GAD67 mRNA expression in PV-interneurons, concurrent reductions in mRNA levels for GAT1 (the high-affinity GABA transporter; Fig. 2) and PV have also been observed in these interneurons (Lewis et al., 2005;Woo et al., 1998). Moreover, decreases in GAT1 immunoreactivity (IR) at chandelier cell axon terminals, as well as increases in the IR of $GABA_AR$ α2 subunit at the AIS of pyramidal neurons, which are contacted by chandelier terminals, have also been described (Fig. 2) (Lewis et al., 2005). As noted in the previous section, $GABA_ARs$ containing the α2 subunit are selectively localized to the AIS of

forebrain pyramidal neurons (Nusser et al., 1996). While the $GABA_AR$ α2 is not expressed only on the AIS of pyramidal neurons, it is worth noting that, when measured in hippocampal pyramidal neurons, the $GABA_AR$ α2 subunit was found to be present in greater than 80% of all pyramidal cell AIS synapses (Nusser et al., 1996;Nyiri et al., 2001) whereas it is thought that only 15% of all $GABA_ARs$ contain the α2 subunit (Fritschy and Mohler, 1995). This is a significant point since this upregulation of α2 subunit IR is thought to indicate a compensatory attempt to increase GABAergic synaptic strength precisely at the chandelier-AIS synapse. In fact, the alterations in GAT1, $GABA_AR$ α2 subunit, and PV expression are thought to reflect compensatory changes that arise in response to the primary pathology of GAD67 loss in these interneurons (Lewis et al., 2005), which itself is thought to result from altered methylation of GAD1, the gene encoding GAD67 (Benes et al., 2007;Costa et al., 2003;Huang and Akbarian, 2007;Ruzicka et al., 2007;Tochigi et al., 2008;Veldic et al., 2007). Recently, it has been reported that in addition to those associated with GABAergic transmission at the chandelier-pyramidal cell synapse, mRNA expression of $GABA_AR$ subunits associated with other interneurons in the DLPFC is also altered (Hashimoto et al., 2008a). For example, significant reductions in $GABA_AR$ α1, α4, γ2, and δ subunit expression was detected in the distal dendrites of pyramidal cells, contacted by somatostatin/neuropeptide Y-expressing neurons, in the DLPFC of schizophrenic subjects (Fig. 2) (Hashimoto et al., 2008a). The reduction in γ2 subunit expression reinforces an earlier study which found a significant reduction in the short isoform of the $GABA_AR$ γ2 subunit ($\gamma2_S$) over the long isoform ($\gamma2_L$) in the DLPFC of schizophrenic patients compared to control subjects (Huntsman et al., 1998). The $\gamma2_S$ isoform is identical to the $\gamma2_L$ isoform except that the $\gamma2_S$ form lacks an 8 amino acid insert in the large intracellular loop containing a protein kinase C (PKC) phosphorylation site that, when phosphorylated, causes a reduction in GABA-mediated current amplitudes (Krishek et al., 1994). Whether these alterations in γ2 expression reflect cause or consequence of the disease is not known, however it stands to reason that a preferential reduction in the $\gamma2_S$ isoform might lead to significant reductions in GABAergic inhibition in the DLPFC since 1) this change would result in an overrepresentation of $GABA_AR$ subtypes containing the $\gamma2_L$ subunit isoform, 2) observations with recombinant $GABA_ARs$ containing $\gamma2_L$ suggest the remaining $\gamma2_L$-containing subtypes in the DLPFC will exhibit a diminished response to GABA, and 3) the γ2 subunit is the most ubiquitous synaptic $GABA_AR$ subunit in the brain (Olsen and Sieghart, 2009).

Alterations in GABA signaling components associated with schizophrenia are not restricted to the DLPFC. Within the granule cell layer of the cerebellum, reductions in the mRNA levels of GAD65/67, with elevations in the mRNA levels of $GABA_AR$ α6 and δ subunits have been reported (Bullock et al., 2008). In the hippocampus, mRNA levels of GAD65/67 were reduced in all layers of CA2/3 as well as in the stratum oriens of CA1, as determined by laser-capture microdissection in postmortem tissue (Benes et al., 2007). Moreover, cortical regions outside the DLPFC such as the primary visual cortex, primary motor cortex, and anterior cingulate cortex have also been shown to exhibit reductions in the mRNA levels of GAD67, GAT1, and $GABA_AR$ α1 and δ subunits (Hashimoto et al., 2008b).

$GABA_AR$ as a therapeutic target for schizophrenia

Given that cognitive deficits are considered to be core features of schizophrenia (Elvevag and Goldberg, 2000), and given the strong evidence implicating disturbances in GABA signaling as contributing to these deficits, it is not surprising that the effects of GABA-modulating drugs on clinical measures related to schizophrenia, including cognitive and positive symptoms, have been investigated. One early study investigated bretazenil (Ro 16-6028), a short-acting partial benzodiazepine agonist, on clinical outcome measures predictive of antipsychotic efficacy in schizophrenic patients (Delini-Stula and Berdah-Tordjman, 1996; Delini-Stula et al., 1992). Using semi-quantitative measures of psychosis, results of these studies indicated that

approximately half of the subjects responded favorably to treatment compared to placebo control. Other studies have demonstrated the efficacy of diazepam, a classical benzodiazepine agonist, in preventing psychotic symptom progression in schizophrenic patients (Carpenter et al., 1999; Kirkpatrick et al., 1989).

Recently, a clinical study was carried out to test the effect of benzodiazepines on working memory performance in schizophrenic subjects. Curiously, this study concluded that lorazepam, a relatively non-selective $GABA_AR$ positive allosteric modulator, exacerbated working memory deficits in schizophrenic patients, while flumazenil, a $GABA_AR$ partial inverse agonist, ameliorated working memory deficits in these patients (Menzies et al., 2007). While the efficacy of a partial inverse agonist in improving working memory does not appear to be in line with the hypothesis that GABA deficiencies contribute to deficits in working memory, flumazenil has been reported to enhance learning and memory in rodents, presumably by increasing arousal and anxiety (Lal et al., 1988). This arousal- or anxiety-related effect may reflect the broad binding profile of flumazenil, however it has also been reported that α5 subunit-selective inverse agonists, such as alpha5IA, improve working memory in rodents (Chambers et al., 2004; Dawson et al., 2006; Sternfeld et al., 2004). This is consistent with studies showing that the $GABA_AR$ α5 subunit is highly enriched in the hippocampus over other brain regions (Fritschy and Mohler, 1995) and that α5 null mutant mice exhibit enhanced cognition (Collinson et al., 2002). While these studies point toward the α5-selective alpha5IA as a candidate for overcoming cognitive deficits associated with schizophrenia, prolonged clinical studies have been excluded since a metabolite of this compound was shown to be highly insoluble leading to renal toxicity in preclinical studies (Atack, 2008). Moreover, α5-selective compounds, such as alpha5IA, have not been tested in rodent models of schizophrenia. Since it is postulated that hippocampal hyperactivity may underlie the excessive dopamine release associated with psychosis (Lodge et al., 2009; Lodge and Grace, 2008), antagonizing a $GABA_AR$ subtype highly enriched in the hippocampus might be expected to exacerbate psychotic symptoms. Nevertheless, these studies underscore the potential utility of $GABA_AR$ subtype-selective compounds in addressing the cognitive deficiencies central to schizophrenia psychopathology.

A similar approach in targeting specific $GABA_AR$ subtypes for improving working memory in schizophrenia has exploited the restricted localization of α2 subunit-containing $GABA_ARs$ to the pyramidal neuron AIS, combined with the putative role chandelier neuron inhibition plays in generating pyramidal cell network oscillations (Lewis et al., 2005; Lewis et al., 2004). Moreover, the compensatory upregulation of α2-containing receptors in schizophrenia suggests that further agonism at this receptor subtype might be beneficial. Thus, treatment with a α2-selective benzodiazepine site agonist would be predicted to selectively potentiate GABA responses predominately at chandelier interneuron synapses onto pyramidal cell AIS, raising the possibility of enhancing DLPFC pyramidal cell network oscillations at the gamma band frequency. The development of the α2/3-selective compound, TPA023, suggests that this is indeed a feasible and attractive pharmacological approach, since this compound exhibits minimal liabilities normally associated with benzodiazepines such as sedation, ethanol interaction, dependence, and withdrawal effects (Atack et al., 2006). Moreover, a small proof-of-concept clinical trial conducted by David Lewis et al. (University of Pittsburgh) has tested this hypothesis with the Merck compound MK-0777, a $GABA_AR$ α2/3-selective benzodiazepine-like compound, on 15 male subjects with chronic schizophrenia (Fig. 2). The authors found that, compared to placebo control, MK-0777, administered over four weeks, improved subject performance in three tasks for working memory and/or cognitive control, as well as increased gamma band power during one of these tasks (Lewis et al., 2008). This study provides preliminary evidence that selectively potentiating the postsynaptic response of α2 subunit-containing $GABA_ARs$ results in cognitive improvement in schizophrenia, providing a potential new adjunctive therapy that could ameliorate the cognitive deficits of this disorder.

In addition to benzodiazepines, $GABA_AR$s are also sites for endogenous neuroactive steroids such as allopregnanolone, which potentiate the response to GABA with greater potency than benzodiazepine binding (Majewska et al., 1986; Morrow et al., 1990; Morrow et al., 1987). Interestingly, it has been shown that the atypical antipsychotics olanzapine (Marx et al., 2000; Marx et al., 2003) and clozapine (Barbaccia et al., 2001; Marx et al., 2003) elevate endogenous allopregnanolone to levels that are sufficient to modulate $GABA_AR$-mediated neuronal activity. Furthermore, it was shown that administration of allopregnanolone significantly potentiated olanzapine-induced, but not risperidone- or haloperidol-induced, inhibition of the conditioned avoidance response and apomorphine-induced climbing, two rodent models used to predict antispsychotic efficacy (Ugale et al., 2004). These studies support a hypothesis in which atypical antipsychotics such as olanzapine may ameliorate psychotic symptoms, in part, through the action of elevating allopregnanolone levels. The role it may play in the pathophysiology of schizophrenia and its therapeutic potential in humans is not yet clear, however it has recently been shown in postmortem studies that allopregnanolone levels are reduced in the parietal cortex of schizophrenic subjects compared to controls (Marx et al., 2006). Moreover, a recent proof-of-concept pilot trial of another neuroactive steroid, pregnenolone, demonstrated clinical efficacy in improving cognitive and negative symptoms in schizophrenic subjects (Marx et al., 2009). Pregnenolone and its derivative pregnenolone sulfate have been shown to enhance learning and memory in rodents (Akwa et al., 2001; Darnaudery et al., 2002; Flood et al., 1992, 1995; Ladurelle et al., 2000; Mayo et al., 1993; Meziane et al., 1996; Pallares et al., 1998; Vallee et al., 1997; Vallee et al., 2001), likely due in part to the ability of pregnenolone sulfate to act as a positive allosteric modulator at the NMDA receptor (Bowlby, 1993; Irwin et al., 1994; Wu et al., 1991). Interestingly, pregnenolone is the biosynthetic precursor to allopregnanolone and administration of pregnenolone resulted in serum increases in allopregnanolone in this trial (Marx et al., 2009). Furthermore, the levels of serum allopreganaolone were strongly correlated with cognitive improvement as measured by composite Brief Assessment of Cognition in Schizophrenia (BACS) score (Marx et al., 2009). Thus, it is conceivable that metabolism of pregnenolone to allopregnanolone contributed to its efficacy in this study. To date, however, it is unclear why neurosteroids such as allopregnanolone might enhance cognition or atypical antipsychotic efficacy when these molecules are thought to be more potent than benzodiazepines and barbiturates in potentiating $GABA_AR$ activity. This is especially puzzling in light of the above studies showing that lorazepam, a relatively non-selective $GABA_AR$ positive allosteric modulator, exacerbated working memory deficits in schizophrenic patients, while flumazenil, a $GABA_AR$ partial inverse agonist, ameliorated working memory deficits in these patients (Menzies et al., 2007). The answer might be related to the increased sensitivity to allopregnanolone of $GABA_AR$s containing a δ subunit in place of a γ subunit (Belelli et al., 2002; Bianchi et al., 2002; Wohlfarth et al., 2002) combined with the notion that these δ-containing receptors are localized extrasynaptically (Nusser et al., 1998) and mediate tonic rather than phasic inhibition, the former of which can be enhanced by neuroactive steroids (Stell et al., 2003). Thus, treatment with allopregnanolone might represent yet another approach to selectively targeting specific $GABA_AR$ subtypes, though the consequences of targeting these extrasynaptic receptors are not fully understood in the context of schizophrenia.

Experimental genetics studies linking GABA hypofunction and schizophrenia

At present, few experimental genetics studies have specifically addressed the role of GABA hypofunction in the etiology of schizophrenia and related psychiatric disorders. One notable study that has begun to address this issue, conducted by Heldt et al.(Heldt et al., 2004), generated mutant mice in which the 65 kD isoform of GAD was deleted. These mice exhibited robust deficits in prepulse inhibition (PPI) of the acoustic startle response, a behavioral

phenomenon in which the response to a startling acoustic stimulus is suppressed when the startling stimulus is preceded by a weaker one. PPI is used as a measure of intact sensorimotor gating, a mechanism that 1) results in the attribution of salience to behaviorally relevant sensory stimuli at the expense of irrelevant stimuli, 2) is largely influenced by mesolimbic dopaminergic neuron activity, and 3) is deficient in untreated schizophrenic patients as well as in a variety of other psychiatric disorders, including bipolar disorder. Interestingly, the PPI deficits exhibited by these GAD65$^{-/-}$ mice were reversed by the atypical antipsychotic clozapine.

Another key study, conducted by Yee et al. (Yee et al., 2005), generated mutant mice lacking the $GABA_AR$ α3 subunit (α3KO). The authors also demonstrated that these α3KO mice exhibit deficits in PPI and, further, the PPI deficits were reversed by administration of the dopamine D2 receptor antagonist haloperidol. Since the $GABA_AR$ α3 subunit is a major isoform expressed in dopaminergic neurons of the ventral tegmental area (Okada et al., 2004), a likely scenario is one in which the loss of function of a major $GABA_AR$ subtype leads to disinhibition of these dopaminergic neurons, resulting in an excess in striatal dopamine, which is thought to underlie deficits in PPI (Lisman and Grace, 2005). Thus, distinct $GABA_AR$ subtypes may play a prominent role not only in regions involved in cognitive disturbances such as the DLPFC, but also within the dopaminergic mesolimbic system, which is heavily implicated in the positive symptoms of schizophrenia. While this last point has not been directly tested, it would be interesting to determine whether the α2/3-selective compound MK-0777 (described above) might also influence dopamine release as well as dopamine-related behavioral phenotypes in animal models of schizophrenia. One such model is based on methylazoxymethanol (MAM)-administration to pregnant rats during a narrow gestational window (gestational day 17), resulting in preferentially reduced GABAergic interneurons and elevated VTA activity, resulting in excessive dopamine release in response to amphetamine challenge in adult offspring (Lisman et al., 2008). These studies raise the interesting possibility that attenuation of GABAergic inhibition may be related to the hyperdopaminergic state, a major neurochemical hallmark of schizophrenia pathology. This concept has been reviewed extensively (Grace et al., 2007).

Human genetics studies linking $GABA_AR$ subunits to schizophrenia and related disorders

The chromosome 5q $GABA_AR$ gene cluster and schizophrenia

The genes encoding the $GABA_AR$ α1 (GABRA1), α6 (GABRA6), β2 (GABRB2), γ2 (GABRG2), and π (GABRP) subunits form a cluster in human chromosome 5q34-q35, a region that in a meta-analysis had been shown to be the second most compelling schizophrenia susceptibility locus in the genome (Lewis et al., 2003). A genome-wide linkage scan in Portuguese Island families identified 5q31-5q35 as a susceptibility locus for both schizophrenia and psychosis (Sklar et al., 2004). A further association study of this $GABA_AR$ gene cluster identified SNPs and haplotypes in GABRA1, GABRA6 and GABRP associated with schizophrenia in a Portuguese sample (Petryshen et al., 2005). In the same study, Petryshen and colleagues also looked for effects of disease-related haplotypes on microarray mRNA expression of $GABA_AR$ subunits and found that a haplotype within GABRA1 was associated with reduced expression of $GABA_AR$ α6 subunit mRNA in schizophrenia patients. An additional haplotype in GABRA1 was associated with increased expression of a set of genes functionally related to $GABA_AR$ function (a group of pre-synaptic proteins and a group of neurotransmitter receptors). Together, this not only implicates the α1 subunit risk alleles in $GABA_AR$-specific alterations in expression but also suggests that this subunit can influence the expression of other relevant proteins, further highlighting the crucial role the $GABA_ARs$ may play in the etiology of this disease.

The $GABA_AR$ β2 subunit and schizophrenia

In an initial Chinese population-based study, positive associations were identified between intronic SNPs and haplotypes in the $GABA_AR$ β2 subunit gene (*GABRB2*) and schizophrenia (Lo et al., 2004). This initial finding was later replicated with other samples in multiple independent linkage and association studies (Liu et al., 2005; Lo et al., 2007a; Lo et al., 2007b; Petryshen et al., 2005; Yu et al., 2006). In fact, in a recent meta analysis of 12 candidate genes associated with schizophrenia, only the *GABRB2* association survived corrections for multiple testing for all the meta analyses performed in the study (Shi et al., 2008). Interestingly, a postmortem study exploring the validity of these genomic associations using real-time PCR found that mRNA expression for the long isoform of the β2 $GABA_AR$ subunit ($\beta2_L$) was decreased to a greater extent than that for short isoform ($\beta2_S$) in the DLPFC of schizophrenic patients (Zhao et al., 2006). Thus, the expression of alternative splice forms of the $GABA_AR$ β2 subunit might be differentially affected in schizophrenia. Although the functional consequences of this is not fully understood, a putative calcium-calmodulin dependent kinase II (CaMKII) phosphorylation site is present within the large intracellular loop of the $\beta2_L$ isoform but not in the $\beta2_S$ isoform (McKinley et al., 1995). Moreover, it was demonstrated that recombinant $\beta2_L$-containing $GABA_ARs$ exhibit greater GABA-mediated current rundown compared to $\beta2_S$-containing receptors, and it has been suggested that differential phosphorylation may account for these distinct electrophysiological properties (Zhao et al., 2006). Taken together, *GABRB2* is the strongest candidate $GABA_AR$ subunit gene associated with schizophrenia, implicated by several independent reports including a follow-up validation study and two independent meta-analyses (Allen et al., 2008; Liu et al., 2005; Lo et al., 2007a; Lo et al., 2004; Lo et al., 2007b; Petryshen et al., 2005; Shi et al., 2008; Yu et al., 2006; Zhao et al., 2006; Zhao et al., 2007). While β2 subunit-containing $GABA_ARs$ are the most abundant in the brain (McKernan and Whiting, 1996), it is worth noting that β2-containing $GABA_ARs$ are highly enriched over β1- and β3-containing $GABA_ARs$ in the globus pallidus of the rat (Schwarzer et al., 2001), the major target for GABAergic medium spiny output neurons of the striatum. These medium spiny neurons receive dopaminergic inputs from both the substantia nigra and ventral tegmental area and are thought to be critical components of the circuitry underlying psychosis associated with excess dopamine release. This, combined with the importance of the β subunits in $GABA_AR$ trafficking (Jacob et al., 2008) may prove critical in understanding the genetic basis for hypofunctional GABA systems in schizophrenia.

The $GABA_AR$ β1 subunit and bipolar disorder

A growing number of genetic variants that confer risk for psychiatric disorders such as schizophrenia and bipolar disorder are beginning to emerge by whole genome association scans (GWAS), an unbiased approach to detect correlations between genetic variation and disease susceptibility (Hirschhorn and Daly, 2005). This approach employs microarray platform technologies to examine hundreds of thousands of individual single-nucleotide polymorphisms (SNPs) across genomes of large cohorts of cases and healthy controls (Hirschhorn and Daly, 2005). Recently, the Wellcome Trust Case Control Consortium (WTCCC) undertook a GWAS study of ~3000 shared controls and ~2000 cases for each of seven human diseases including bipolar disorder (WTCCC, 2007). While this study did not include cases formally diagnosed with schizophrenia, there is increasing evidence pointing to an overlap in genetic susceptibility for schizophrenia and bipolar disorder (Craddock and Owen, 2005). Among the highest ranked GWAS signals in the bipolar disorder dataset of the Wellcome Trust study, which was derived from 1868 cases, was the *GABRB1* gene encoding the $GABA_AR$ β1 subunit (WTCCC, 2007). In a follow-up study, the *GABRB1* risk allele identified in the Wellcome Trust study was found to be strongly associated with a subset of cases (279 of the 1868 bipolar cases) that met the criteria for schizoaffective bipolar type, a phenotype characterized by psychotic symptoms (delusions and/or hallucinations) (Craddock et al., 2008). Moreover, when only these 279 schizoaffective bipolar cases were tested for association at other $GABA_AR$ genes,

additional significant associations for $GABA_AR$ α4, α5, and β3 were revealed (Craddock et al., 2008). Interestingly, no association to $GABA_AR$ genes were found when those 1589 cases that did not meet the criteria for schizoaffective bipolar type were compared to control subjects (Craddock et al., 2008).

Specificity of $GABA_AR$ modification to schizophrenia etiology

While the above studies relate schizophrenia and similar disorders to altered $GABA_AR$ subunit expression and genetic variation, it remains to be firmly established whether these alterations 1) are in fact etiological rather than compensatory or in some other way a response to the disease process, particularly with respect to $GABA_AR$ subunit expression, and 2) are specific to schizophrenia and related disorders rather than common features of psychiatric disorders. Indeed, the increase in $GABA_AR_AR$ α2 subunit immunoreactivity in the axon initial segment of cortical pyramidal neurons of subjects with schizophrenia is thought to play a compensatory role in response to reduced GABA release by PV-containing interneurons (Volk et al., 2002). This, however, does not preclude the value of α2-containing $GABA_ARs$ as therapeutic targets for schizophrenia, as has recently been demonstrated (Lewis et al., 2008). Moreover, this increase appeared to be specific for schizophrenia since it was shown that the increase in α2 immunoreactivity was not detected in matched subjects with major depressive disorder, even when this disorder was accompanied by psychotic symptoms (Volk et al., 2002). Thus, the increase in α2 subunit immunoreactivity at cortical pyramidal neuron axon initial segment does not appear to be characteristic of psychosis in general.

It might also be argued that these changes in α2 subunit expression are related to comorbid substance abuse since 1) numerous reports have demonstrated that genetic variation in the gene encoding the α2 subunit is strongly associated with risk for alcoholism (Covault et al., 2004; Covault et al., 2008; Dick et al., 2006; Edenberg et al., 2004; Fehr et al., 2006; Lappalainen et al., 2005; Soyka et al., 2008) and drug abuse (Agrawal et al., 2006; Drgon et al., 2006), and 2) substance abuse, including that of alcohol and cannabis, is the most common psychiatric comorbidity among patients with schizophrenia (Cantor-Graae et al., 2001; Mueser et al., 1990). However, the increase in α2 subunit expression does not appear to result from mutation within the α2 subunit gene, since alleles associated with increased risk for schizophrenia have not been identified within the $GABA_AR$ α2 subunit gene. In addition, studies have demonstrated that $GABA_AR$ α2 subunit mRNA is decreased rather than increased when rats were subjected to prolonged ethanol exposure (Mhatre et al., 1993; Montpied et al., 1991), while human postmortem studies found that $GABA_AR$ α2 subunit mRNA levels were unchanged in the cerebral cortex of alcoholic cases compared to that of control subjects (Thomas et al., 1998).

Reductions in $GABA_AR$ α1 and δ subunit mRNA in the DLPFC, as well as other cortical regions, of schizophrenic subjects were recently reported (Hashimoto et al., 2008a; Hashimoto et al., 2008b). At the same time, reductions in α1 and δ subunit mRNA have been detected in the frontopolar region of postmortem samples obtained from suicide victims (Merali et al., 2004), which may confound interpretation of results from schizophrenic subjects where the cause of death was suicide. However, in the studies cited, the reduced levels of α1 and δ subunit mRNA in schizophrenic subjects compared to controls could not be attributed solely to samples obtained from subjects whose cause of death was suicide (Hashimoto et al., 2008a).

The extent to which SNPs and haplotypes within the 5q34 $GABA_AR$ gene cluster are specific for schizophrenia risk is confounded by recent reports showing that this region is also associated with mood disorders in female patients (Yamada et al., 2003). Approximately half of the mood disorder cases in this study were formally diagnosed with bipolar disorder, with which 5q34 SNPs were significantly associated, consistent with a previous study (Horiuchi et

al., 2004). This might be consistent with recent studies highlighting the increasingly recognized overlap in genetic vulnerability between schizophrenia and bipolar disorder (Badner and Gershon, 2002; Berrettini, 2003; Cardno et al., 2002; Fallin et al., 2005; Lichtenstein et al., 2009). However, these SNPs were also significantly associated with unipolar mood disorder (Yamada et al., 2003), a finding less easily reconciled. It should be noted, however, that the functional consequences of these SNPs in mood disorder patients have yet to be elucidated. This may be important, since different risk alleles, even within the same gene, may be associated with distinct functional consequences. For example, Petryshen and colleagues (2005) have shown that the haplotype within the $GABA_AR$ α1 gene that was overrepresented in schizophrenic patients was correlated with reductions in $GABA_AR$ α6 mRNA expression (Petryshen et al., 2005). Similar explorations into the specific effects of genetic variation are necessary in order to reconcile the apparent overlap in susceptibility loci between schizophrenia and other neuropsychiatric disorders.

$GABA_A$ receptor associated proteins and psychiatric disease

Much of the sequence diversity among the $GABA_AR$ subunits is attributed to the intracellular loop between TM3 and TM4, which represents the largest intracellular domain with the highest amino acid sequence variability among the $GABA_AR$ subunit isoforms (Olsen and Tobin, 1990). The specific interaction of defined amino acids in the $GABA_AR$ intracellular loops with intracellular interacting proteins is thought to mediate key regulatory processes such as intracellular vesicular trafficking, plasma membrane insertion, synaptic clustering, turnover, and functional modulation by protein phosphorylation, palmitoylation and ubiquitination. These $GABA_AR$-interacting proteins have been identified over the last 10 years by a combination of biochemical, cell biological, and physiological assays (for further detail, see reviews by (Arancibia-Carcamo and Moss, 2006; Chen and Olsen, 2006). Given the emerging roles for these proteins in regulating the functional expression of $GABA_ARs$, we have evaluated their possible roles in the etiology of psychiatric disorders.

$GABA_AR$ associated proteins implicated by whole genome homozygosity association

While the GWAS approach has revolutionized the search for rare disease-related genetic variants, it has been argued that GWAS requires especially conservative statistical thresholds, which might lead to false negative results (Lencz et al., 2007). An extension of this approach, termed whole genome homozygosity association (WGHA), addresses this potential limitation, by first identifying regions of SNPs that exhibit extended homozygosity, called runs of homozygosity (ROH), followed by association analysis of these regions to identify susceptibility loci. This approach is based on the notion that large regions of homozygous SNPs can be found in common between groups of individuals without direct common lineage, reflecting loci with low recombination rates (Lencz et al., 2007). In the first study to employ this technique, Lencz et al. (2007) found that genes encoding two $GABA_AR$-associated proteins, gephyrin (*GPHN*) and N-ethylmaleimide sensitive factor (*NSF*) were located within ROHs identified as susceptibility loci for schizophrenia.

Gephyrin (Fig. 2) was originally identified as a 93 kD protein that co-purified with the glycine receptor (GlyR) (Schmitt et al., 1987) and was found to interact with an 18 amino acid region of the large intracellular loop of the GlyR β subunit (Meyer et al., 1995). In addition to its association with the GlyR, colocalization of gephyrin and $GABA_AR$ clusters has been demonstrated both in the rat brain and in cultured neurons (Christie and de Blas, 2002;Christie et al., 2002;Craig et al., 1996;Danglot et al., 2003;Essrich et al., 1998;Giustetto et al., 1998;Sassoe-Pognetto et al., 2000). Although convincing evidence for direct binding of gephyrin to any $GABA_AR$ subunit has eluded investigators for more than 10 years, gephyrin was recently reported to interact with a 10 amino acid hydrophobic motif within the large intracellular loop of the $GABA_AR$ α2 subunit and, further, this domain was shown to regulate

$GABA_AR$ synaptic accumulation in a gephyrin-dependent manner (Tretter et al., 2008). Earlier studies using gephyrin and $GABA_AR$ γ2 subunit knockout mutant mice revealed the mutual dependence of gephyrin and the γ2 subunit in the clustering and maintenance of α2/γ2-containing $GABA_ARs$ at GABAergic synapses (Essrich et al., 1998;Kneussel et al., 1999;Schweizer et al., 2003). For example, the loss of $GABA_AR$ clustering in γ2 knockout mice was paralleled by a loss of synaptic gephyrin clusters (Essrich et al., 1998). Studies using hippocampal pyramidal cells derived from gephyrin-deficient mice suggested that gephyrin is essential for postsynaptic localization of α2/γ2-containing $GABA_ARs$ (Kneussel et al., 1999). Furthermore, gephyrin might be important for $GABA_AR$ insertion or stabilization at the synaptic membrane, since the loss of synaptic α2 and γ2 immunoreactive puncta was paralleled by an increase in intracellular α2 and γ2 microclusters in gephyrin-deficient neurons, but not accompanied by a change in overall levels of α2 or γ2 subunits (Kneussel et al., 1999). However, studies with spinal chord sections of gephyrin-deficient mutant mice provided evidence for the existence of gephyrin-independent clustering mechanisms for the α1 and α5 subunit-containing $GABA_ARs$, the synaptic clusters of which were not abolished in the spinal cord sections of gephyrin-deficient mutants (Kneussel et al., 2001). Moreover, contrary to earlier findings, another study using cultured hippocampal neurons derived from gephyrin-deficient mice showed only a partial decrease in the number of synaptic $GABA_AR$ α2/γ2-containing $GABA_AR$ clusters (Levi et al., 2004). Thus, gephyrin alone might not be sufficient for synaptic clustering of α2/γ2-containing $GABA_ARs$, but may instead participate in a complex mechanism whereby it acts to reduce the lateral mobility of $GABA_ARs$, facilitating the accumulation of α2/γ2-containing $GABA_ARs$ at sites apposed to GABAergic terminals (Jacob et al., 2005). Although the functional implications of the occurrence of the *GEPHN* gene within a schizophrenia-associated ROH have not been investigated, it is tempting to speculate on the relationship between gephyrin-mediated synaptic accumulation of α2/γ2-containing $GABA_ARs$, the importance of α2/γ2-containing $GABA_ARs$ concentrated in the AIS of DLPFC pyramidal neurons, and the role of chandelier-AIS synapses in the generation of γ-oscillatory network activity, that latter of which may underlie cognitive deficits in schizophrenia (Lewis et al., 2005).

NSF (N-ethyl maleimide-sensitive factor) is known for its role in transport vesicle fusion to acceptor membranes and was previously demonstrated to be involved in the trafficking of AMPA receptors (Nishimune et al., 1998; Noel et al., 1999). It was reported that another $GABA_AR$-associated protein, GABARAP, interacts with NSF and that these two proteins colocalize in cultured hippocampal neurons (Kittler et al., 2001). GABARAP has been postulated to play a role in the intracellular trafficking of $GABA_ARs$, because of its association with NSF combined with its localization predominantly at cisternae of endoplasmic reticulum and Golgi apparatus (Fig. 2), consistent with a role in protein transport (Moss and Smart, 2001). More recently, NSF itself was shown to interact directly with the β subunits of the $GABA_ARs$, and that overexpression of NSF with recombinant $GABA_ARs$ decreased receptor expression at the cell surface of transfected COS7 cells (Goto et al., 2005), consistent with an important role in the exocytosis of assembled $GABA_ARs$. While the functional significance of the *NSF* gene within a schizophrenia-associated ROH has not been investigated, its interaction with the $GABA_AR$ β subunits (see previous discussion of *GABRB2*) combined with a role in $GABA_AR$ trafficking implies a critical role in the functional expression of $GABA_ARs$, a process which mounting evidence suggests is impaired in schizophrenia.

PKC and RACK1

$GABA_ARs$ are regulated by direct phosphorylation by protein kinase C (PKC) on conserved serine residues within the large intracellular loop of all β subunits (Moss and Smart, 2001) via direct interaction with the βII isoform of PKC (Brandon et al., 1999). Moreover, the receptor for activated C kinase (RACK1), a PKC interacting protein involved in the subcellular targeting

of PKC, also interacts independently with the intracellular loops of the $GABA_AR$ β subunits (Brandon et al., 1999). Functional analysis of these interactions suggest that enhancing PKC activity results in a reduction in $GABA_AR$ channel activity (Brandon et al., 2000) and that the direct, independent binding of RACK1 to $GABA_AR$ β subunits serves to potentiate the catalytic activity of $GABA_AR$-bound PKC (Brandon et al., 2002). Thus, regulation of the stoichiometry of $GABA_AR$ β subunit phosphorylation plays a key regulatory role in $GABA_AR$ function.

It has been shown that PKC activity is increased in frontal cortex from postmortem brains of subjects with bipolar affective disorder (Wang and Friedman, 1996), raising the possibility that $GABA_AR$ channel activity may be reduced under these conditions by virtue of the role played by PKC phosphorylation on $GABA_AR$ channel activity (Brandon et al., 2000). Consistent with this hypothesis, it has also been shown that the association of RACK1 and PKC is increased in the frontal cortex of postmortem brains of subjects with bipolar affective disorder (Wang and Friedman, 2001), which may explain the increase in PKC activity in these subjects and lends further support to the notion that PKC phosphorylation of $GABA_AR$ β subunits may be enhanced in bipolar disorder, leading to reductions in $GABA_AR$ channel activity in this region, an emerging feature of psychiatric disease.

Septin 11

Septins are a family of GTPases that form polymeric filaments and ring-like structures, are expressed in various tissues, including brain, and are thought to act as diffusion barriers and scaffolds in a range of cellular processes (Barral and Kinoshita, 2008). It was recently reported that one septin family member, Septin 11, was identified by mass-spectrometry analysis in a brain fraction enriched in the GABAergic postsynaptic complex (Li et al., 2009). Furthermore, it was demonstrated in cultured hippocampal neurons that RNAi-mediated knockdown of septin 11 resulted in a decrease in the density of γ2 subunit-containing $GABA_ARs$ as well as a reduction in the number of GABAergic synaptic contacts to those neurons where septin 11 expression was attenuated (Li et al., 2009). Interestingly, a recent postmortem study concluded that protein and mRNA expression of septin 11, in addition to other septin family members, is significantly elevated in the DLPFC of both schizophrenic and bipolar cases compared to controls (Pennington et al., 2008). Given the findings that septin 11 appears to positively regulate $GABA_AR$ localization and GABAergic synapse formation, the upregulation of septin 11 might reflect a compensatory response to the loss of GABAergic signaling in schizophrenia and bipolar disorder.

$GABA_AR$-associated proteins indirectly associated with schizophrenia

Segments of a large run of homozygosity (ROH) associated with schizophrenia was found to occur directly in the coding region of *SNTG1* (Lencz et al., 2007), a gene encoding γ-syntrophin, a brain-enriched PDZ domain-containing scaffolding protein that binds to dystrophin and is part of the dystrophin protein complex (Alessi et al., 2006). In addition to γ-syntrophin, a number of reports have linked dysbindin (*DTNBP1*), another member of the dystrophin complex thought to play a role in trafficking and tethering postsynaptic receptors including $GABA_ARs$, to schizophrenia (Straub et al., 2002). Dystrophin is found colocalized with α2 and γ2 $GABA_AR$ subunit clusters in pyramidal cells as well as in α1 and γ2 clusters in Purkinje cells of the cerebellum (Knuesel et al., 1999). The dystrophin gene plays an important role in Duchenne muscular dystrophy (DMD), the second most commonly occurring genetically inherited disease in humans. Studies of mdx mice (dystrophin mutant), a model of Duchenne muscular dystrophy, have shown neural shrinkage as well as a 50% decrease in neuron number in regions of the cerebral cortex and brainstem. Histological evidence shows a reduction in the density of $GABA_A$ channel clusters in mdx Purkinje cells and hippocampal CA1 neurons, and in particular a marked reduction in the number of clusters immunoreactive for the $GABA_ARs$ α1 and α2, indicating that dystrophin may play an important role in the clustering or

stabilization of $GABA_A$Rs. Interestingly, dystrophin has also been identified as a component of the so-called DISC1-interactome, a network of protein-protein interactions around the key schizophrenia risk gene DISC1 (Camargo et al., 2007). To date, DISC1 has not been associated with inhibitory synapses but it may be worth examining such a link in the future. DISC1 has been associated genetically not only to schizophrenia but also to bipolar disorder, Asperger syndrome, and Autism (Hennah et al., 2008; Kilpinen et al., 2008).

mRNA expression of the PDZ domain-containing Ezrin/Radixin/Moesin (ERM)-binding phosphoprotein 50 (EBP50), a protein required for the maintenance of active, phosphorylated ERM proteins at the cell surface (Morales et al., 2004), is significantly reduced in peripheral blood lymphocytes derived from schizophrenic patients (Bowden et al., 2006). The actin-binding protein radixin, a member of the ERM family, directly binds to the large intracellular loop of the $GABA_A$R α5 subunit (Loebrich et al., 2006). This interaction requires the activation of radixin by phosphorylation at a C-terminal threonine residue, resulting in a shift from an inactive, closed conformation to an active open conformation. The binding of activated radixin with the $GABA_A$R α5 subunit was demonstrated to be essential for clustering and localization of extrasynaptic α5-containing $GABA_A$Rs (Loebrich et al., 2006). Conceivably, a reduction in EBP50 protein could result in a loss of active radixin at the cell surface and, consequently, compromised extrasynaptic clustering and localization of α5-containing $GABA_A$Rs. Recently, an α5-specific benzodiazepine site radioligand ($[^{11}C]$Ro15-4513), was used in a positron emission tomography (PET) study, which found that $[^{11}C]$Ro15-4513 binding in the prefrontal cortex and hippocampus was negatively correlated with PANSS negative symptoms scores in patients with schizophrenia (Asai et al., 2008). These data are consistent with a loss of extrasynaptic α5-containing $GABA_A$R localization, without a concurrent loss in α5 subunit mRNA or protein levels, which might be expected if α5-specific clustering mechanisms, such as that mediated by radixin binding, were compromised.

General Conclusions

Modern genetics has allowed us to make great progress in cataloging the genetic links between $GABA_A$R function in inhibitory neurotransmission and psychiatric disorders. However, until now most of the genetic polymorphisms have been found in non-coding regions, such as introns and other untranslated regions. One can only speculate that these non-coding regions may affect gene transcription which, in turn, may affect subunit protein levels, observations which, in some cases, have been substantiated in post-mortem tissue. By combining the ever-increasing power of genetic association with invaluable insights gained from sound biological validation, a deeper understanding of the underlying mechanisms that give rise to these disorders are beginning to take shape. A growing body of evidence suggests that a malfunction in cortical GABAergic transmission resulting in a disturbance in cortical network activity is a critical factor underlying such psychiatric disorders as schizophrenia and bipolar disorder. Therefore the development of novel and innovative pharmacological agents that target individual $GABA_A$R subtypes hold enormous potential for a novel, highly specific therapeutic approach to schizophrenia and other psychiatric conditions.

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Abbreviations

AIS	axon initial segment
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid
DISC1	disrupted in schizophrenia-1
DLPFC	dorsolateral prefrontal cortex
ERM	ezrin-radixin-moesin family
GABA	γ-aminobutyric acid
$GABA_AR$	γ-aminobutyric acid type A receptor
GAD	glutamic acid decarboxylase
GAT1	GABA transporter-1
GlyR	glycine receptor

GWAS	genome-wide association scan
IR	immunoreactivity
NMDAR	N-methyl-D-aspartic acid-sensitive receptor
NSF	*N*-ethylmaleimide-sensitive factor
PET	positron emission tomography
PKC	protein kinase C
PPI	prepulse inhibition
PV	parvalbumin
RACK1	receptor for activated C kinase-1
ROH	run of homozygosity
SNP	single-nucleotide polymorphism
TM	transmembrane domain
VTA	ventral tegmental area

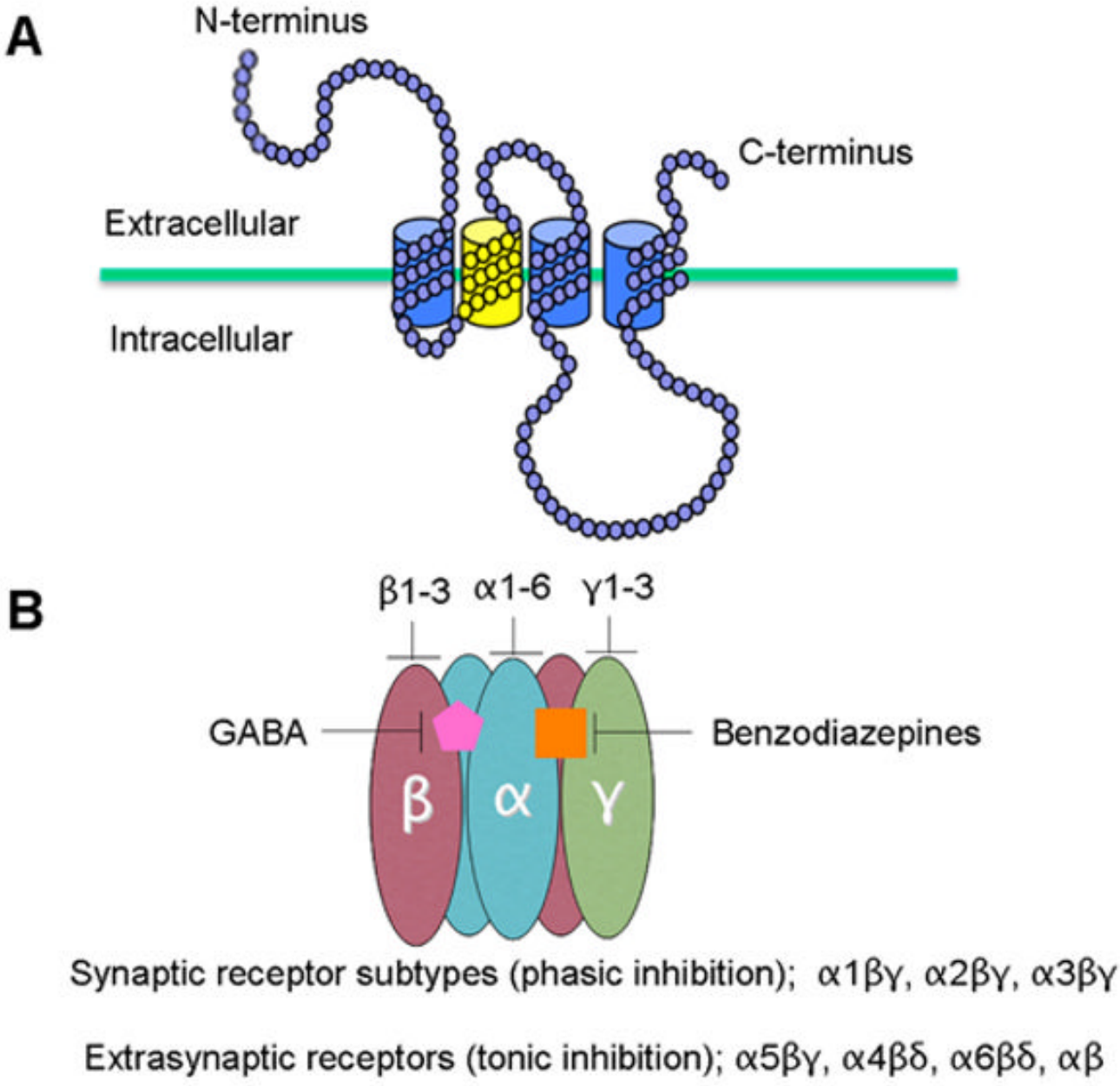

Figure 1. The Structure of $GABA_A$ Receptor Subunit

A. The membrane topology of an individual $GABA_A$ receptor subunit, TM1-3 are indicated in blue and TM2 in yellow. **B.** The tertiary structure of assembled $GABA_A$ receptors. Receptor α subunits are illustrated in blue, β subunits in pink and δ/γ in green. The benzodiazepine binding pocket is formed between α and γ subunits (orange square) and the GABA binding pocket is formed between α and β subunits (pink pentagon).

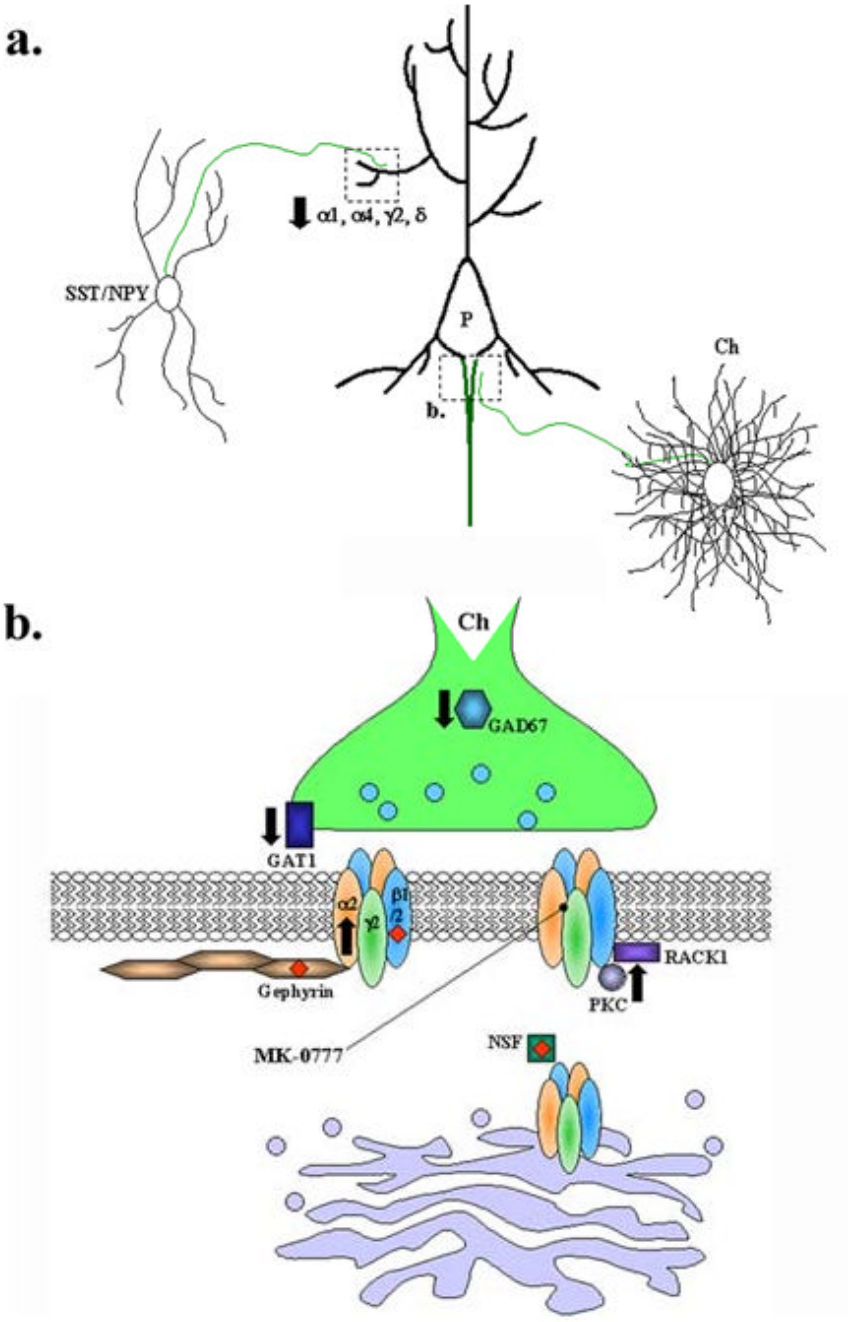

Figure 2. Summary of modified GABAergic signaling components in psychiatric disease

A. Schematic of relevant GABAergic interneuron synapses onto layer III pyramidal neurons (P) in the dorsolateral prefrontal cortex (DLPFC). Distal dendrites receive GABAergic input from Somatostatin (SST) and neuropeptide Y-expressing Interneurons (NPY) (upper left). The axon initial segment (AIS) is contacted by axons originating from chandelier neurons (Ch) located in layer IV of the DLPFC (lower right). Axons of SST/NPY, P, and Ch neurons are shown in green. **B**. Hypothetical AIS synapse highlighting some GABAergic synaptic components implicated in schizophrenia and/or bipolar affective disorder. Black arrows indicate reported reductions or elevations in mRNA or protein expression. Red diamonds indicate genetic association with schizophrenia or bipolar disorder.

Table I

Genetic association and modified expression patterns of $GABA_A$ receptor subunits in schizophrenia and related disorders

$GABA_AR$ Subunit; Gene Name	Chromosomal Location	Evidence for Genetic Association	Evidence for Modified Expression	References
α1; GABRA1	5q34-q35	Identified as within susceptibility locus for schizophrenia in Portuguese Island families.	Reduced mRNA expression in pyramidal neurons of DLPFC of schizophrenic patients.	Hashimoto et al., 2008a; Sklar et al., 2004
α2; GABRA2	4p12	None.	Elevated expression of $GABA_AR$ α2 subunit at chandelier-pyramidal neuron AIS synapses in schizophrenic patients.	Volk et al., 2002
α4; GABRA4	4p12	Association with schizoaffective disorder, bipolar type.	Reduced mRNA expression in DLPFC of schizophrenic patients.	Craddock et al., 2008; Hashimoto et al., 2008a
α5; GABRA5	15q11.2-q12	Association with schizoaffective disorder, bipolar type and bipolar disorder.	α5-specific PET ligand binding negatively correlated with PANSS negative symptoms scores.	Asai et al., 2008; Craddock et al., 2008; Papadimitriou et al., 2001; Papadimitriou et al., 1998
α6; GABRA6	5q34	Identified as within susceptibility locus for schizophrenia in Portuguese Island families.	Reduced mRNA expression in patients with an associated haplotype for the GABRA1 gene.	Sklar et al., 2004
β1; GABRB1	4p12	GWAS association with schizoaffective disorder, bipolar type.	None.	2007; Craddock et al., 2008
β2; GABRB2	5q34	Multiple linkage, association, and meta-analyses.	Differential mRNA expression of long versus short isoforms n the DLPFC of schizophrenic patients.	2007; Allen et al., 2008; Craddock et al., 2008; Liu et al., 2005; Lo et al.,2007a; Lo et al., 2004; Lo et al., 2007b; Petryshen et al., 2005; Shi et al., 2008; Yu et al., 2006; Zhao et al., 2006; Zhao et al., 2007
γ1; GABRG	4p12	None.	Reduced mRNA expression in DLPFC of schizophrenic patients.	Hashimoto et al., 2008a
γ2; GABRG2	5q31.1-q33.2	Identified as within susceptibility locus for schizophrenia in Portuguese Island families.	Differential mRNA expression of long versus short isoforms in schizophrenic patients. Reduced mRNA expression in pyramidal neurons of DLPFC of schizophrenic patients.	Hashimoto et al., 2008a; Huntsman et al., 1998; Sklar et al., 2004

$GABA_AR$ Subunit; Gene Name	Chromosomal Location	Evidence for Genetic Association	Evidence for Modified Expression	References
δ; GABRD	1p36.3	None.	Reduced mRNA expression in pyramidal neurons of DLPFC of schizophrenic patients.	Hashimoto et al., 2008a
π;GABRP	5q33-q34	Identified as within susceptibility locus for schizophrenia in Portuguese Island families.	None.	Sklar et al., 2004

Table II

Summary of Proteins that regulate $GABA_A$ trafficking and stability

Associated Protein; Gene Name	Interacting $GABA_AR$ Subunit(s)	Function	Chromosomal Location	Genetic Association	References
BIG2; ARFGEF2	β1-3	$GABA_AR$ trafficking from trans-Golgi network.	20q13	Linkage of 20q13 to psychotic bipolar disorder.	Becher et al., 2002; Charych et al., 2004; Park et al., 2004
CAML	γ2	$GABA_AR$ synaptic accumulation and endocytic recycling.	5q23	None.	Yuan et al., 2008
Collybistin; ARHGEF9	Indirect, gephyrin-binding	Synaptic clustering of $GABA_ARs$ and gephyrin.	Xq11.1	Associated with epilepsy, anxiety, aggression, and mental retardation.	Harvey et al., 2004; Kalscheuer et al., 2009; Kins et al., 2000; Marco et al., 2008; Papadopoulos et al., 2008; Papadopoulos et al., 2007
Dystrophin; DMD	Indirect	Receptor stabilization.	Xp21.2	DMD-deficient boys have cognitive impairment and a lower IQ. Associated proteins γ-syntrophin and dysbindin associated with schizophrenia.	Anderson et al., 2002; Kneussel et al., 1999; Lencz et al., 2007; Straub et al., 2002
GABARAP	γ1, $γ2_{S/L}$	Receptor trafficking and clustering	17p13.1	Locus associated with schizophrenia and bipolar disorder.	Kittler et al., 2000; Klei et al., 2005; Kneussel et al., 2000; Wang et al., 1999
Gephyrin; GPHN	α2	Receptor clustering and anchoring.	14q23.3	Run of homozygosity within GPHN gene associated with schizophrenia.	Craig et al., 1996; Essrich et al., 1998;Lencz et al., 2007; Levi et al., 2004; Toyota et al., 2003
GRIF-1; TRAK2	β2	Receptor trafficking, mitochondrial transport.	2q33	2q33 linkage with affective disorder in northern Swedish isolated population.	Beck et al., 2002; Brickley et al., 2005; Iyer et al., 2003; MacAskill et al., 2009; Venken et al., 2005
GODZ; ZDHHC3	γ1, $γ2_{S/L}$	Palmitoyltransferase.	3p21.31	None.	Keller et al., 2004; Uemura et al., 2002
HAP-1; HAP1	β1	Vesicular trafficking.	17q21.2-q21.3	None.	Kittler et al., 2004; Liao et al., 2005; McGuire et al., 2006
Neuroligin-2; NLGN2	Indirect	Cell adhesion, synapse formation.	17p13	Close to ALOX12 gene (17p13.1), linked to bipolar disorder.	Chih et al., 2004; Graf et al., 2004; Varoqueaux et al., 2004
NSF	β1-3	$GABA_AR$ exocytosis.	17q2	Run of homozygosity associated with schizophrenia.	Goto et al., 2005; Kittler et al., 2001; Lencz et al., 2007
Plic-1; UBQLN1	α1,α2, α3, α6 and β1–3	$GABA_AR$ recycling.	9q21.2-21.3	UBQLN1 SNPs are associated with early-onset Alzheimer's disease.	Bedford et al., 2001; Hovatta et al., 1999; Kamboh et al., 2006

Associated Protein; Gene Name	Interacting $GABA_AR$ Subunit(s)	Function	Chromosomal Location	Genetic Association	References
PRIP-1; PLCL1	β1-3 and γ2	Regulation of subunit phosphorylation.	2q33-34	2q33 linkage with affective disorder in northern Swedish isolated population.	Kanematsu and Hirata, 2003; Kanematsu et al., 2002; Terunuma et al., 2004; Uji et al., 2002; Venken et al., 2005; Yamaguchi et al., 2004
RACK1; GNB2L1	β1-3	Modulation of $GABA_AR$ channel activity.	5q35	In risk locus for schizophrenia in Portuguese island families.	Brandon et al., 2000; Brandon et al., 2002; Brandon et al., 1999; Sklar et al., 2004
Radixin; RDX	α5	Membrane-cytoskeletal crosslinking; $GABA_AR$ clustering.	11q23	No genetic association. Associated protein EBP50 reduced in peripheral blood lymphocytes of schizophrenic patients.	Bowden et al., 2006; Loebrich et al., 2006
Septin 11; SEPT11	Indirect	Synaptic structure and dendritic morphology.	4q21.1	No genetic association. Septin 11 mRNA and protein levels are elevated in DLPFC of schizophrenic and bipolar subjects.	Li et al., 2009; Pennington et al., 2008

Abbreviations: *BIG2*, Brefeldin A-inhibited GDP/GTP exchange factor 2; *ARFGEF2*, ADP-ribosylation factor GDP/GTP exchange factor 2; *CAML*, calcium-modulating cycophilin ligand; *GABARAP*, $GABA_AR$-associated protein; *GRIF-1*, $GABA_AR$-interacting factor; *GODZ*, golgi-specific DHHC zinc-finger-domain protein; *HAP-1*, Huntingtin associated protein 1; *NSF*, *N*-ethylmaleimide-sensitive factor; *Plic-1*, protein linking IAP to the cytoskeleton-1; *PRIP-1*, phosopholipase C-related catalytically inactive protein-1; *RACK1*, receptor for activated C kinase-1.