GAD67 Deficiency in Parvalbumin Interneurons Produces Deficits in Inhibitory Transmission and Network Disinhibition in Mouse Prefrontal Cortex

Matthew S. Lazarus, Keerthi Krishnan and Z. Josh Huang

1Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA, 2Medical Scientist Training Program, 3Program in Neuroscience, Stony Brook University, Stony Brook, NY 11790, USA

Address correspondence to Z. Josh Huang; Email: huangj@cshl.edu

In mammalian neocortex, the delicate balance of neural circuits is regulated by a rich repertoire of inhibitory control mechanisms mediated by diverse classes of GABAergic interneurons. A key step common to all GABAergic neurons is the synthesis of GABA, catalyzed by 2 isoforms of glutamic acid decarboxylase (GAD). Among these, GAD67 is the rate-limiting enzyme. GAD67 level is regulated by neural activity and is altered in multiple neuropsychiatric disorders. The significance of altered GAD67 levels on inhibitory transmission, however, remains unclear. The presence of GAD65, postsynaptic GABA receptor regulation, and the diversity of cortical interneurons make the link from GAD67 levels to GABA transmission less than straightforward. Here, we selectively removed one allele of the GAD67 gene, Gad1, in PV interneurons in juvenile mice. We found substantial deficits in transmission from PV to pyramidal neurons in prefrontal cortex, along with increases of pyramidal cell excitability and excitation/inhibition balance in PV cells. Synaptic deficits recovered in adult mice, suggesting engagement of homeostatic and compensatory mechanisms. These results demonstrate that GAD67 levels directly influence synaptic inhibition. Thus, GAD67 deficiency in PV cells likely contributes to cortical dysfunction in disease states; the reversibility of synaptic deficits suggests nonpermanent damage to inhibitory circuitry.

Keywords: GABA, GAD67, neocortex, parvalbumin

Introduction

In the mammalian brain, the inhibitory neurotransmitter GABA is synthesized by 2 isoforms of glutamic acid decarboxylase (GAD; Soghomonian and Martin 1998). Although GAD67 and GAD65 show largely overlapping cellular expression, they differ in their subcellular localization, biochemistry, and regulation of gene transcription and enzyme activity, suggesting that they play different roles in GABAergic transmission and plasticity (Pinal and Tobin 1998). Whereas GAD67 is the rate limiting enzyme, responsible for over 90% of GABA production (Asada et al. 1997), and is found throughout the cell, GAD65 is specifically localized to synaptic terminals and appears to play a significant role mainly under conditions of heightened synaptic activity (Tian et al. 1999). Following its synthesis, GABA is released into vesicles by the vesicular GABA transporter vGAT for synaptic release. As vGAT has low affinity for GABA (McIntire et al. 1997), the cytosolic GABA concentration might significantly influence vesicle loading and synaptic transmission. Mice lacking GAD65 are largely normal in their spontaneous IPSC (sIPSC) amplitudes (Tian et al. 1999) and show subtle phenotypes such as susceptibility to seizures (Kash et al. 1997; Stork et al. 2000) and impaired visual cortical plasticity (Hensch et al. 1998). On the other hand, germline GAD67 knockout mice exhibit a 93% reduction in cerebral GABA levels and die perinatally due to developmental deficits (Asada et al. 1997); this has precluded a straightforward assessment of its role in GABA transmission in the postnatal brain. Importantly, neural activity significantly regulates the transcription and protein levels of GAD67, which impact cellular, and likely vesicular, GABA contents (Eskapez and Houser 1999; Ramirez and Gutierrez 2001; Patz et al. 2003; Lau and Murthy 2012). Furthermore, GAD67 level is profoundly altered in multiple brain regions in a variety of neuropsychiatric disorders (Torrey et al. 2005), and this molecular pathology is thought to contribute to pathophysiology and/or pathogenesis. For example, GAD67 deficiency in a subset of GABAergic interneurons in the prefrontal cortex is a highly replicated molecular pathology in schizophrenia (Lewis et al. 2005). In particular, GAD67 is reduced in ∼50% of parvalbumin (PV) interneurons in layer 2/3 of PFC (Hashimoto et al. 2003). Fast-spiking PV interneurons innervate the soma and proximal dendrites of pyramidal neurons; they regulate γ-range network oscillations that likely contribute to cognitive functions including working memory (Isaacson and Scanziani 2011). It is thus plausible that reduced GAD67 in PV interneurons might impaire perisomatic inhibition and network operations, contributing to cognitive deficits—a core feature of schizophrenia (Lewis et al. 2005). However, to date, the physiological impact of GAD67 deficiency on PV cell-mediated inhibitory transmission has not been rigorously examined. Although homozygous deletion of the GAD67 gene (Gad1−/−) results in impaired miniature inhibitory postsynaptic current (mIPSC) in cultured hippocampal neurons (Lau and Murthy 2012), whether and how altered levels of GAD67 impact synaptic transmission in developing and mature cortex has remained unclear.

The presence of GAD65, as well as the activity regulation of postsynaptic GABA4 receptor clustering and kinetics (Kilman et al. 2002; Saliba et al. 2007; Rannalls and Kapur 2011), makes the impact of GAD67 reduction on GABA transmission less than straightforward to predict without direct experimental measurement. Two additional factors may have contributed to the difficulties in assessing the physiological consequence of GAD67 levels in GABAergic neurons. First, although Gad1−/− mice are viable and show no overt phenotypes, developmental compensation at multiple levels in such germline heterozygote (e.g., transcription of the intact Gad1 allele, postsynaptic mechanisms) could mask or ameliorate the physiological deficits. Second, the diversity of interneurons and inhibitory mechanisms requires the assessment of the consequence of GAD67 reduction with cell-type resolution.

Using a genetic strategy, here, we selectively removed one allele of the gene for GAD67, Gad1, in PV interneurons in juvenile mice. By targeted recording of synaptically connected PV and pyramidal neurons in prefrontal cortex, we found...
substantial deficits in inhibitory synaptic transmission, which is correlated with a concurrent disinhibition of pyramidal neuron spiking, and increased excitation/inhibition balance in PV cells. These results unequivocally demonstrate that GAD67 levels directly contribute to the strength of synaptic inhibition; thus, GAD67 deficiency likely contributes to cortical network dysfunction in disease states. Interestingly, synaptic deficits recovered in adult mice, possibly through a homeostatic response to increased feedback excitation of the PV cells.

Materials and Methods

Animals
Experiments were performed in juvenile (P23–30) or adult mice (P50–60), in both males and females. All experiments were performed in mPFC, and generally restricted to layer 2/3 of prelimbic area. PV-Cre mice (Hippenmeyer et al. 2005) were crossed with Gad1 floxed mice (Gad1+/−; Chattopadhyaya et al. 2007) to generate mutant mice that are Gad1 heterozygous in PV cells (PVCre::Gad1−/−) and control mice (PVCre::Gad1+/−). Mice were treated in accordance with Cold Spring Harbor Laboratory guidelines on animal husbandry and care/welfare.

Immunostaining
Mice were anesthetized with avertin (tribromoethanol in amyl hydrate, intraperitoneal injection, 0.13, 0.01 mg/g), then transferred to a recording chamber continuously perfused with fluid (ACSF) for 30 min at 32 °C. Slices were recovered in ACSF with 3.5 KCl, 0.5 NaHCO3, 0.2 EGTA. For sPSC recordings (Maffei et al. 2004), slices were perfused in ACSF with 2 mM GABA, and recorded in modified ACSF with 3.5 KCl, 0.5 MgSO4, and 1 NaCl. Internal solution for paired recordings was 110 mM choline chloride, 2.5 KCl, 1.25 NaH2PO4, 0.5 CaCl2, 7 MgCl2, 25 glucose, 11.6 ascorbic acid, and 3.1 pyruvic acid. Standard ACSF was 126 NaCl, 2.5 KCl, 25 NaHCO3, 14 glucose, 1.25 NaH2PO4, 1 MgSO4, and 2 CaCl2. For sPSC recordings (Maffei et al. 2004), slices were perfused in ACSF with 2 MgSO4, and recorded in modified ACSF with 3.5 KCl, 0.5 MgSO4, and 1 NaCl. Internal solution for paired recordings was 110 K-gluconate, 30 KCl, 0.5 EGTA, 10 HEPES, 0.3 NaGTP, 10 Na-phosphocreatine, pH 7.3, and 295 mOsM. Internal solution for F/I curves was 130 K-glucuronate, 6 KCl, 0.2 EGTA, 10 HEPES, 2.5 Na-ATP, 0.5 Na-GTP, 10 Na-phosphocreatine, pH 7.3, and 250 mOsM. Internal solution for sPSC recordings was 100 CaMeSO4, 20 KCl, 10 HEPES, 0.2 EGTA, 4 Mg-ATP, 0.3 Na-GTP, 10 Na-phosphocreatine, 3 QX-314, pH 7.25, and 250 mOsM.

Electrophysiology
Animals were anesthetized with avertin or choline-based cutting solution on a Microm HM650V (Walldorf, Germany), and recovered in artificial cerebrospinal fluid (ACSF) for 30 min at 32–34 °C. Slices were then transferred to a recording chamber continuously perfused with oxygenated ACSF, maintained at 32–34 °C. Patch pipettes were pulled from borosilicate glass on a Flaming-Brown micropipette puller (Sutter Instruments, Novato, CA, USA), and generally had a resistance of 2–4 MΩ. Paired recordings were performed on PV cells, identified by GFP expression, and nearby pyramidal neurons, identified by large apical dendrites oriented toward the pia, and held in voltage clamp at −75 mV. Frequency–current (F/I) relationships of pyramidal neurons were generated by injecting a series of 1-s-long current steps increasing by 20 pA. Paired recordings and F/I relationships were analyzed in ClampFit 9.0 (Molecular Devices, Sunnyvale, CA, USA). Spontaneous post-synaptic currents (sPSCs) were recorded in PV cells, and analyzed in MiniAnalysis (Synaptosoft, Decatur, GA, USA). All events in 3 min were averaged to determine sPSC area. Excitation and inhibition charge transfers were then assessed by multiplying sPSC area by the number of recorded events; excitation and inhibition charge transfers were compared to determine E/I ratio.

Solutions
Choline-based cutting solution consisted of 110 mM choline chloride, 2.5 KCl, 25 NaHCO3, 1.25 NaH2PO4, 0.5 CaCl2, 7 MgCl2, 25 glucose, 11.6 ascorbic acid, and 3.1 pyruvic acid. Standard ACSF was 126 NaCl, 2.5 KCl, 25 NaHCO3, 14 glucose, 1.25 NaH2PO4, 1 MgSO4, and 2 CaCl2. For sPSC recordings (Maffei et al. 2004), slices were perfused in ACSF with 2 MgSO4, and recorded in modified ACSF with 3.5 KCl, 0.5 MgSO4, and 1 NaCl. Internal solution for F/I curves was 130 K-glucuronate, 6 KCl, 0.2 EGTA, 10 HEPES, 2.5 Na-ATP, 0.5 Na-GTP, 10 Na-phosphocreatine, pH 7.3, and 250 mOsM. Internal solution for sPSC recordings was 100 CaMeSO4, 20 KCl, 10 HEPES, 0.2 EGTA, 4 Mg-ATP, 0.3 Na-GTP, 10 Na-phosphocreatine, 3 QX-314, pH 7.25, and 250 mOsM.

Statistics
All data are reported as mean ± standard error of the mean (SEM). Significance level for statistical analysis was set at P < 0.05.

Results
Reduced GAD67 Leads to Synaptic Deficit in Juvenile Mice
We and others have shown that Cre activity patterns in the PV-ires-Cre knockin line precisely recapitulate endogenous PV expression (e.g., Kuhlman and Huang 2008). PV expression in rodent cortex starts by the end of the second postnatal week, with increased levels thereafter (Huang et al. 1999). In PV-ires-Cre mice, Cre activity in cortex is detected by P12 (K.K and Z.J.H., unpublished data). In PVCre::Gad1+/− mice (referred to as “heterozygote” or “Het” hereafter), immunostaining for PV and GAD67 in frontal cortex of juvenile mice (age P29–30) demonstrated that GAD67 reduction was effective and specific (Fig. 1). Cell-body staining intensity for GAD67, quantified in all layers of medial prefrontal cortex, was decreased by 28% in PV cells in Het mice (WT, 1947 ± 96, n = 30; Het, 1407 ± 68, n = 30; P < 0.001, unpaired Student’s t-test), while GAD67 staining in non-PV cells was largely unaffected (WT, 1740 ± 100, n = 30; Het, 1597 ± 93, n = 30; P = 0.298, unpaired Student’s t-test). Furthermore, the ratio of GAD67 maximum staining intensity in PV cells versus non-PV cells was reduced in knockdown heterozygote mice by 21% (WT, 1.13 ± 0.05; Het, 0.90 ± 0.08; P < 0.05, paired Student’s t-test, n = 5 pairs).

Paired recordings from PV to pyramidal neurons revealed substantial deficits in synaptic transmission following reduction of GAD67 (Fig. 2). Analysis of individual pairs demonstrated reduction of inhibitory postsynaptic current (IPSC) amplitude by 55% (WT, 82 ± 21 pA, n = 14; Het, 37 ± 7 pA, n = 17; P < 0.05, unpaired Student’s t-test) and nonsignificant reduction of IPSC decay time by 14% (WT, 5.92 ± 0.31 ms, n = 14; Het, 5.07 ± 0.42 ms, n = 17; P = 0.12, unpaired Student’s t-test). These 2 features, reduced amplitude and faster decay, combined to produce a supralinear impact on synaptic transmission in GAD67 heterozygote mice, reflected by a 63% reduction in IPSC charge transfer (WT, 629 ± 161 nC, n = 14;
Het, 233 ± 44 fC, n = 17; P < 0.05, unpaired Student’s t-test). Owing to high variability in synaptic parameters, analysis was also performed on the average of IPSC features for each tested heterozygote animal, and compared with an age- (within 1 day) and sex-matched control. Significant reductions were observed in both IPSC amplitude (57% reduction; WT, 84 ± 13 pA; Het, 36 ± 6 pA; P < 0.01; for all parameters, paired Student’s t-test, n = 4 pairs) and IPSC decay time (16% reduction; WT, 5.98 ± 0.39 ms; Het, 5.03 ± 0.42 ms; P < 0.05), combining to produce a 65% reduction of IPSC charge transfer (WT, 648 ± 115 fC; Het, 228 ± 31 fC; P < 0.05). Connection probability, assessed in 3 matched pairs of mice, did not differ between WT and Het mice (WT, 11 of 27 paired recordings connected, 41%; Het, 12 of 25 paired recordings connected, 48%; Fisher’s exact test, P = 0.78).

Pyramidal Cell Hyperactivity and Increased Excitation-Inhibition Balance in PV Cell Network

Engagement of PV cells regulates spiking activity in local pyramidal neurons (Wen et al. 2010). Therefore, we tested spiking properties of pyramidal neurons to determine the functional impact of GAD67 reduction in PV cells, and the subsequent reduction of synaptic output (Fig. 3). In heterozygote mice, the frequency–current relationship steepened by 14% (WT, 0.106 ± 0.003 Hz/pA, n = 25; Het, 0.121 ± 0.005 Hz/pA, n = 23; P < 0.05, unpaired Student’s t-test; Fig. 3B), indicating a disinhibition of local network activity in response to reduced output from PV cells. This effect disappeared in the presence of 20 μM bicuculline (WT, 0.139 ± 0.007 Hz/pA, n = 16; Het, 0.132 ± 0.007 Hz/pA, n = 14; P = 0.5, unpaired Student’s t-test; Fig. 3B), demonstrating that the increased activity of pyramidal
neurons in the heterozygote mice is acutely dependent on altered activation of GABA_ receptors, as opposed to chronic changes in pyramidal cell properties.

As GAD67 expression is a potential homeostatic mechanism, functioning as a negative feedback response to control cortical excitation, we returned to targeted recordings of PV cells to assess the impact of pyramidal cell hyperactivity on the PV network itself. Excitation–inhibition (E/I) balance was quantified in PV cells. In individual cells, spontaneous excitatory and inhibitory post-synaptic currents were measured and compared to determine E/I ratio for each individual cell (Fig. 4). In heterozygote mice, E/I ratio in PV cells increased 71% (WT, 0.83 ± 0.28, n = 18; Het, 1.42 ± 0.26, n = 18; P < 0.01, Kolmogorov–Smirnov test).

**Recovery of Synaptic Deficit in Adulthood**

In adult heterozygote mice, synaptic transmission appeared to be intact (Fig. 5). IPSC amplitude was no longer decreased (WT, 104 ± 27 pA, n = 13; Het, 135 ± 47 pA, n = 17; P = 0.60, unpaired Student’s t-test); and neither IPSC decay time (WT, 6.29 ± 0.44 ms, n = 13; Het, 6.27 ± 0.38 ms, n = 17; P = 0.97, unpaired Student’s t-test) nor IPSC charge transfer decreased compared with wild-type animals (WT, 864 ± 269 fC, n = 13; Het, 1023 ± 377 fC, n = 17; P = 0.75, unpaired Student’s t-test).

**Discussion**

There is evidence that inhibitory synapses are highly sensitive to the concentration of synaptically released GABA. Several studies indicate that postsynaptic GABA_A receptors are often not saturated (Cohen et al. 2000; Perrais and Ropert 2000; Rumpel and Behrends 2000; Mathews and Diamond 2003), thereby allowing fine-tuning of quantal transmission via presynaptic changes. Modulation of GABA synthesis thus may represent a crucial way to regulate the inhibitory drive in neural networks. As the rate-limiting enzyme that influences cellular and vesicular GABA contents, a prominent property of GAD67 is the regulation of its expression by neural activity in both physiological and pathophysiological processes (Benevento et al. 1995; Maqueda et al. 2003; Patz et al. 2003). For example, GAD67 level is reduced following chronic activity suppression in cultured hippocampal neurons (Lau and Murthy 2012), and in PV cells deficient for NMDA receptors (Belforte et al. 2010).

It is therefore possible that altered GAD67 expression may reflect circuit activity levels, continuously modulating inhibitory strength in response to input and network activity—i.e., increasing inhibitory output when circuit activity is high, and decreasing output when activity is low. In a diseased state, this potential homeostatic mechanism may be a convergence point...
for multiple upstream etiologic factors that impair cortical network activity patterns.

Studies in neuronal cultures suggest that activity homeostatically regulates the quantal size of inhibition (Kilman et al. 2002; Rosato-Siri et al. 2002). There is also evidence that modulation of mIPSC amplitude by activity occurs in part via a change in the vesicular GABA content (Hartman et al. 2006). A recent study in cultured hippocampal neurons further indicates that GAD67 regulates cytosolic levels and vesicular filling of GABA in an activity-dependent manner (Lau and Murthy 2012). However, the functional significance of reduced GAD67 levels in the neocortex, more reflective of physiological or pathologic conditions, has remained unclear. Several factors have contributed to the difficulty in examining this important issue. First, homozgyous knockout of Gad1 is perinatal lethal (Asada et al. 1997), and germline heterozygosity likely allows for substantial compensation during development. Second, the presence of GAD65, as well as the activity regulation of postsynaptic GABA<sub>A</sub> receptors (Kilman et al. 2002; Saliba et al. 2007; Rannals and Kapur 2011), makes the connection between GAD67 reduction and altered GABA transmission less than straightforward to predict without direct experimental measurement. Third, the diversity of cortical GABAergic interneurons and the complex circuitry require the assessment of this issue with cell-type resolution. By removing one copy of Gad1 in PV cells during postnatal development (with the PV-ires-Cre knockin driver, conditional Gad1 deletion is likely to occur around the second postnatal week; del Rio et al. 1994; Meyer et al. 2002), we were able to examine the more acute impact of GAD67 reduction. Using PV-cell-targeted recordings, we have demonstrated for the first time that reduced GAD67 expression can have a major impact on synaptic transmission and network properties. This is in contrast to knockout of GAD65, which leads to impaired GABA transmission only under high rates of synaptic activity (Tian et al. 1999). The physiologic changes following GAD67 reduction in PV cells may reflect a combination of direct reduction of vesicular GABA content and release, as well as alteration of PV cell axon morphology, such as reduced axonal arbor complexity and persomatic synapse formation (Chattopadhya et al. 2007).

Our results have implications for neuropsychiatric diseases with altered GAD67 expression, such as schizophrenia (Akbarian et al. 1995; Guidotti et al. 2000; Volk et al. 2000), autism (Fatemi et al. 2002), and bipolar disorder (Guidotti et al. 2000; Heckers et al. 2002; Fatemi et al. 2005). All of these psychiatric disorders show reduction in GAD67 level, likely secondary to reduced or aberrant network activity (Akbarian and Huang 2006). Our experimental model more directly relates to the condition observed in schizophrenia, in which GAD67 is reduced particularly in PV cells (Hashimoto et al. 2003). Reduced engagement of PV cells, possibly secondary to reduced dopaminergic or glutamatergic drive (Lewis and Gonzalez-Burgos 2006), likely leads to decreased activity-dependent transcription of Gad1. Once initiated, this process may remain throughout the disease course and produce sustained reduction of GAD67 expression, leading to persistent deficits in synaptic transmission and network dysfunction through adulthood. Here, we have attempted to dissect this pathophysiologic process by directly reducing Gad1 gene dosage and GAD67 expression in PV cells. This manipulation led to substantial deficits in synaptic transmission from PV to pyramidal neurons, and a concurrent disinhibition of pyramidal cell spiking. Increased excitability of pyramidal neurons following GAD67 reduction in only one class of interneurons indicates PV cells play a major role in regulating network activity. Increased pyramidal neuron activity presumably contributes to the observed increase of PV cell excitation/inhibition ratio, which in turn may engage compensatory responses in PV circuits. Activity-dependent upregulation of the remaining Gad1 allele may be one of these mechanisms, and a full recovery in synaptic function might further include compensatory changes in neurotransmitter synthesis (e.g., GAD65) and loading (e.g., vGAT), as well as postsynaptic response (e.g., GABA<sub>A</sub> receptor trafficking and distribution).

Our results indicate that GAD67 reduction may effectively contribute to PV network dysfunction. However, GAD67 reduction (e.g., as a result of gene mutation), in and of itself, is unlikely to represent a primary etiology in schizophrenia, and our data suggest that this alone will not produce sustained dysfunction. Consistent with this notion, linkage of schizophrenia to the Gad1 gene has provided mixed results (De Luca et al. 2004; Addington et al. 2005; Lundorf et al. 2005; Zhang et al. 2005; Ikeda et al. 2007; Straub et al. 2007). It is possible that cortical circuits are able to adapt to changes in GAD67 expression, limiting the impact of allelic variations in the Gad1 gene.

Current evidence for GAD67 reduction and alterations in other GABAergic markers are from postmortem studies, making it difficult or impossible to determine the cause and

---

**Figure 5.** Synaptic transmission was normalized in adult GAD67 Het mice. (A) Overlaid example traces of IPSC recordings in WT (gray) and Het (black) show comparable amplitude in WT and Het mice (left). Amplitude-scaled overlay of these same responses reveals comparable decay time in WT and Het mice (right). Quantifications of IPSC amplitude and decay time are shown. (B) Overlaid area-filled tracings of these same responses demonstrate comparable IPSC charge transfer in WT and Het mice. Quantification of IPSC charge is shown. Scale bars in (A): for amplitude trace, 20 pA, 5 ms; for scaled trace, 5 ms. Scale bars in (B): 20 pA, 3 ms.
effect relationships in disease pathogenesis. In schizophrenia, altered GAD67 expression is likely a more downstream consequence of genetic or environmental etiological factors, which subsequently contributes to disease symptoms. Genetic manipulations in mice allow us to model GAD67 alterations in specific cell types to determine their physiological and downstream impact. Our demonstration of the reversibility of synaptic dysfunction following GAD67 deficiency suggests a lack of permanent alteration to circuits and the possibility that pharmacological intervention at specific inhibitory connections may partially restore GABAergic function in patients.

Funding
This work was supported by a National Institute of Mental Health Predoctoral Fellowship F30 MH0870362 to M.S.L. and Marie and Charles Robertson Fund at CSHL to Z.J.H.

Notes
Conflict of Interest: None declared.

References


Akkarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE Jr, Jones EG. 1995. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenia. Arch Gen Psychiatry. 52:258–266.


Fatemi SH, Stary JM, Earle JA, Araghi-Niknam M, Eagan E. 2005. GABAergic dysfunction in schizophrenia and mood disorders as reflected by decreased levels of glutamic acid decarboxylase 65 and 67 kDa and Reelin proteins in cerebellum. Schizophr Res. 72:109–122.

Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pessold C, Sharma R et al. 2000. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Arch Gen Psychiatry. 57:1061–1069.


Lewis DA, Hashimoto T, Volk DW. 2005. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 6:312–324.


