The Impact of Oxidative Stress on GAD67 Levels and Parvalbumin-Positive Neurons

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Abbreviations

BA	Brodmann area
EEG	Electroencephalographic
GAD	Glutamic acid decarboxylase
LPS	Lipopolysaccharide
MAM	Methylazoxymethanol acetate
NOX	NADPH oxidase
poly IC	Polyinosinic: polycytidylic acid
PV	Parvalbumin
RT-qPCR	Reverse transcriptase-quantitative polymerase chain reaction
TLR3	Toll-like receptor 3
TLR4	Toll-like receptor 4

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1 Introduction

There is substantial evidence for dysregulation of GABA neurotransmission in the cortex of patients with schizophrenia. The most replicated finding concerns the decrease in expression levels of the rate-limiting enzyme glutamic acid decarboxylase (GAD). From a functional perspective, these abnormalities have been linked to electrophysiological and cognitive dysfunctions. From a mechanistic point of view, recent evidence has been provided linking GAD abnormalities to glutamatergic dysregulation and suggesting that oxidative status is a key player between glutamatergic phenomena (namely, NMDA hypofunction) and GAD downregulation. Therefore, in parallel with other neurochemical systems, GABA, and more specifically GAD, abnormalities, provide an interesting framework to understand the potential role of oxidative phenomena in the pathogenesis of psychiatric disorders.

2 Overview of GABA Neurotransmission

In GABAergic neurons, the synthesis of GABA (see section "Glutamic acid decarboxylases"), an inhibitory neurotransmitter, occurs in the cytosol, and GABA is transported in the synaptic vesicles by the vesicular GABA transporter (vGAT). At the nerve terminal, an action potential triggers, in a Ca^{2+}-dependent manner, vesicular GABA release (see section "GABA interneurons") (Gonzalez-Burgos et al. 2011). In cortical GABA neurons, released GABA induces effects that are mediated by ionotropic ($GABA_{A/C}$) or metabotropic receptors. The $GABA_A$ receptors are heteropentameric structures composed from a repertoire of 19 subunits that have distinct affinities for GABA and that determine functional properties of the GABA receptor (Uusi-Oukari and Korpi 2010). $GABA_B$ receptors, which are metabotropic receptors coupled to $G_{i/o}$ GTP-binding protein, play a role in the postsynaptic effects of GABA in GABAergic neurons (Olah et al. 2009). Finally, plasma membrane GABA transporters (GATs) reuptake GABA to terminate the effect of GABA. In the central nervous system (CNS), GABA uptake is mainly mediated by GAT1. GAT1 translocates GABA from neuronal cells to glial cells. Other transporters, GAT2 and GAT3, are also found in the brain (Fig. 1) (Gonzalez-Burgos et al. 2011).

2.1 Glutamic Acid Decarboxylases

GABA synthesis, from glutamate, is regulated by the enzyme glutamic acid decarboxylase (GAD). GABA plays a crucial role in the maintenance of excitatory-inhibitory balance of the CNS (Li et al. 2008). GABA is the only neurotransmitter being synthesized by two different enzymes, namely, the two molecular forms of glutamic acid decarboxylase, the 67 kDa (GAD67) and 65 kDa forms of GAD (GAD65).

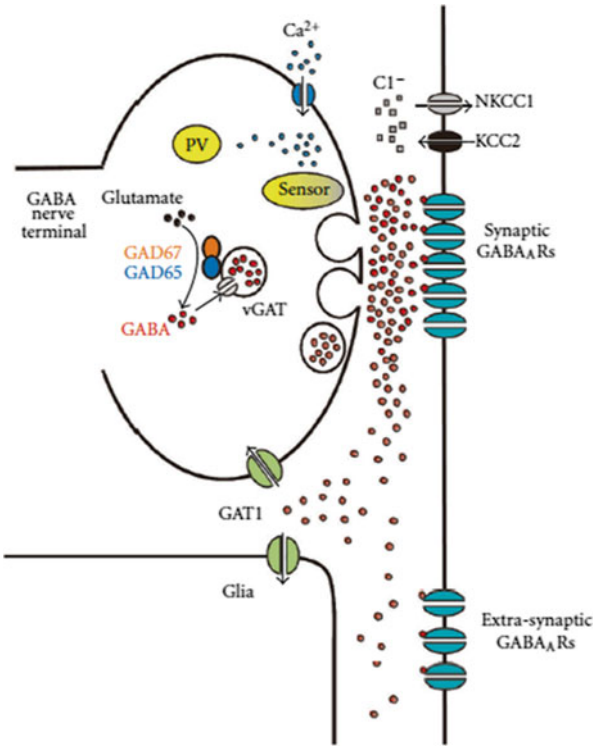

Fig. 1 Scheme of a parvalbumin (PV)-positive GABA neuron after Ca^{2+}-dependent GABA release. GAD65 and GAD67 promote GABA synthesis in the cytosol and synaptic vesicules uptake newly synthesized GABA via vesicular GABA transporter (vGAT). Vesicule fusion with the presynaptic membrane releases GABA and increases GABA concentration in the synaptic cleft. Thus, GABA links and activates postsynaptic $GABA_A$ receptors. Presynaptic GAT1, localized in neuronal and glial membranes, reuptakes GABA, regulating GABA concentration in the synaptic cleft. The transporters KCC2 and NKCC1 uptake and extrude chloride, regulating the chloride current produced by $GABA_A$ receptor activation (Figure from Gonzalez-Burgos et al. 2011)

GAD67 is the main enzyme responsible for most (>90 %) GABA synthesis from glutamate in the central nervous system (Lewis et al. 2005) and is used as a marker for GABA neurons. GAD67 is the product of the GAD1 gene, located on 2q31.1. Knock out of GAD67 provokes, besides a drastic reduction in GABA levels, a cleft palate (which suggests a role in developmental processes besides conventional neurotransmission (Maddox and Condie 2001)) and neonatal lethality.

GAD67 can exist in its native soluble form or bound to membranes, possibly through possible heterodimerization with GAD65 or through other anchoring mechanisms (Kanaani et al. 2010). Cytoplasmic GABA is involved in functions not directly related to neurotransmission, and the different pools of GABA are differentially regulated during resting state, exocytosis, or reversal of membrane uptake processes (Waagepetersen et al. 2001).

Conversely, GAD65 is activity dependent, tightly associated to synaptic vesicles, and synthesizes GABA for exocytotic release (Fukuda et al. 1998; Soghomonian and Martin 1998).

It has been demonstrated that GAD67 mRNA expression increases with the development of CNS (Greif et al. 1991; Thuesen and Lohmann 1992; Lundgren et al. 1997; Hyde et al. 2011) and decreases with aging (Duncan and Wheeler 1999; Gutierrez et al. 1994; Shetty and Turner 1998).

2.2 GABA Interneurons

GABAergic synapses are the key inhibitory synapses within the brain. GABA interneurons are associated with information processing in the cerebral cortex and regulate pyramidal neuron firing rates (McBain and Fisahn 2001). GABA interneurons coexpress different proteins and can be distinguished by expression of these proteins: reelin, parvalbumin (PV), and calretinin (Lieberman et al. 2008), as well as by other morphologic and functional criteria, which have been recently reviewed in the context of neurodevelopmental disorders (Rossignol 2011).

PV-positive basket cells synapse on the perisomatic and proximal dendrite region of their target pyramidal cells. Their electrophysiological properties and divergent projections enable them to provide high-frequency inhibition to their target pyramidal cells. They contribute significantly to the generation of the functionally important fast cortical gamma frequencies.

Chandelier cells are also PV-positive GABA interneurons, able to sustain high-frequency inhibition. They target the axon initial segment, with axoaxonic synapses displaying a characteristic morphology of vertically arranged cartridges. Intriguingly, because of locally high concentration of chloride at the axon initial segment on which they synapse, they have been suggested to trigger depolarization in some, but not all contexts (Woodruff et al. 2010).

Somatostatin-positive interneurons include Martinotti and non-Martinotti cells. They are diversely co-labelled for calretinin and calbindin and have variable morphology and targets. Martinotti cells contact multiple pyramidal cells at the distal dendritic level (a feature they share with the reelin-/calbindin-positive, somatostatin/vasoactive intestinal peptide-negative neurogliaform cells) in adjacent cortical columns, thereby exerting control over dendritic summation (Rossignol 2011).

Reelin, which is a secretory glycoprotein, regulates neural migration and is implicated in synaptic plasticity via its release from GABAergic terminals and binding to integrin receptors. During postnatal development and adulthood, reelin is located in GABAergic interneurons, where it modulates N-methyl-D-aspartate receptor (NMDAR) activity and synaptic plasticity (Beffert et al. 2005). PV and calretinin are calcium-binding proteins that contribute to intracellular calcium-signaling signaling pathways. PV interneurons are implicated in the generation of gamma oscillations, which regulate recall of information for working memory (Bartos et al. 2007). The glutamatergic input from all GABA-releasing neurons in cortex projects to PV interneurons (Lewis et al. 2005; Gulyas et al. 1999). During GABA release (see section “Overview of GABA neurotransmission”), PV (and, for

that matter, other calcium-binding proteins) acts as a Ca^{2+} buffer: it binds residual Ca^{2+} after its entry and activation of the Ca^{2+} sensor (Gonzalez-Burgos et al. 2011), thereby limiting the duration of the exocytotic phase and enabling the fast inhibition typical of PV-containing interneurons, basket, and chandelier cells.

3 GABA Neurotransmission in Neuropathological Conditions

3.1 Postmortem Studies

In 1995, Akbarian et al. published the first report of decreased GAD67 mRNA in the cortex of patients with schizophrenia, with a consistent decrease of ≈30 % across cortical layers III–VI peaking at – 40–50 % in layers I–II (Scottish Schizophrenia Research Group 2000). As of 2006, there were 13 published reports on GAD65/67 levels in schizophrenia or bipolar disorder, 11 of which showed decreased mRNA or protein levels (Akbarian and Huang 2006). Subsequent work has further validated and expanded these observations (Veldic et al. 2005; Bernstein et al. 2007; Woo et al. 2007, 2008; Bullock et al. 2008; Eggan et al. 2008; Hashimoto et al. 2008a, b; Thompson et al. 2009; Curley et al. 2011; Konradi et al. 2011; Thompson Ray et al. 2011; Benes et al. 2007; Huang and Akbarian 2007; Moyer et al. 2012).

There was one report of increased GAD immunoreactive levels in parahippocampal regions (subiculum and parahippocampal gyrus), which correlated with disease duration (Schreiber et al. 2011).

Anatomically, decreased transcript levels have been reported in different cortical regions (prefrontal dorsolateral cortex (Brodmann area (BA) 9) (Guidotti et al. 2000), anterior cingulate cortex, primary motor and visual cortices (Hashimoto et al. 2008b), orbitofrontal cortex (Thompson et al. 2009), primary auditory cortex (Woo et al. 2007), caudate and accumbens nuclei (Thompson et al. 2009), and cerebellum (Guidotti et al. 2000).

Different techniques have provided convergent results: Hashimoto et al. used a combined microarray/reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) approach which yielded convergent (and correlated) decreases of –10 % transcript levels (RT-qPCR), confirming a similar result of the same group, and 1.33-fold decrease (microarray) (Hashimoto et al. 2008a).

In another paper, the same group studied the decrease pattern across four different cortical regions (dorsolateral prefrontal cortex, anterior cingulate cortex, primary motor cortex, and primary visual cortex) and reported a homogeneous decrease in the 20–30 % range (Hashimoto et al. 2008b).

The use of microarrays has provided a much more detailed insight on the signaling network associated with GAD67 transcriptional decrease, e.g., GABA-A receptor subunits, GAT, NMDA receptor subunits, to name a few. In an influential article, Benes et al. combined laser microdissection of hippocampal circonvolutions to provide a comparative analysis of transcription factors and cell cycle molecules in the

stratum oriens of CA2/3 in patients with schizophrenia and bipolar disorder. Indeed, while GAD67 mRNA was decreased in the two conditions, the cell signaling/transcriptional pathways appeared strikingly dissimilar, with an increase in cyclin D2 levels in schizophrenia and a decrease in bipolar disorder, for instance. Although published data often report on mRNA levels (microarray, in situ hybridization, RT-qPCR), decreased protein levels have also been published. Guidotti et al. showed a 40–50 % decrease in GAD67 protein levels (prefrontal cortex Brodmann area 9 and cerebellar hemisphere), with a much more pronounced mRNA decrease in the same cohort. While there was a robust positive correlation between reelin and GAD67 mRNA levels in controls, this correlation was lost in patients with schizophrenia (Guidotti et al. 2000). The results are not always concordant between the two techniques, as exemplified in an earlier report of increased GAD65/67 mRNA levels in the dorsolateral prefrontal and occipital cortices, contrasting with normal protein levels in the same regions (Dracheva et al. 2004).

Although less generally studied, GAD65 signal has also been reported, with a general trend for GAD67 correlation and decreased levels (Bullock et al. 2008; Benes et al. 2007; Fatemi et al. 2005).

Generally, larger decreases are reported when GAD levels are assayed in a more restricted fashion, whether at the anatomical or cellular level. For instance, hippocampal GAD67 levels were found to be severely decreased (ranges −2.8/−9.5-fold) compared to controls when measured on laser microdissected strata, whereas more modest decreases were reported on homogenates of the same region (Benes et al. 2007). Similarly, more pronounced effects were reported in neurons co-expressing PV (Curley et al. 2011) or the NMDA subunit NR2A (Woo et al. 2004, 2008).

Interestingly, complementing previous results showing decreased GAD67 neuronal density in orbitofrontal cortex, it has been recently reported that the density of interstitial white matter neurons expressing GAD65/67 mRNA was indeed increased in adjacent white matter, adding migration abnormalities to the potential mechanisms of altered GAD expression (Joshi et al. 2012).

3.2 Preclinical Models

A significant number of studies have assessed the same neurochemical pathways in preclinical models of schizophrenia or have directly examined more specific mechanistic aspects such as the impact of DNA methylation (or more broadly epigenetic aspects).

One of the first neurodevelopmental models of schizophrenia was obtained after neonatal ventral hippocampus lesion, and, as expected, it gave rise to decreased (50 %) GAD67 mRNA levels (Lipska et al. 2003).

Using the methylazoxymethanol acetate (MAM) gestational injection model, also intended to mimic neurodevelopmental aspects of schizophrenia, a significant decrease in the density of PV-positive neurons has been reported, while GAD67 decreases did not reach statistical significance; interestingly, there was a loss of medial prefrontal cortex theta and gamma frequencies elicited by fear conditioning in the MAM group (Lodge et al. 2009).

A large "family" of animal schizophrenia models relies on the induction of gestational or early postnatal inflammation designed to mimic some well-known epidemiological aspects of the disease such as an excess of winter/spring births, increased prevalence after influenza epidemics, and increased gestational antibody titers retrospectively documented in mothers of future schizophrenic patients. Currently two such models are in wide use and rely, respectively, on the injection of a gram-negative bacterial wall component, lipopolysaccharide (LPS), and polyinosinic:polycytidylic acid (poly IC), a synthetic ribonucleic. Both molecules engage innate immunity: poly IC is a Toll-like receptor 3 (TLR3) and LPS a Toll-like receptor 4 (TLR4) ligand.

Prenatal injection of pregnant female Sprague Dawley rats with LPS induced a decrease of GAD67 immunoreactive cells in the dentate gyrus of the hippocampus at postnatal days 14 and 28 (Nouel et al. 2012). In one of the rare direct comparisons of the two protocols, Harvey and Boksa showed an increase in GAD67 cell number in the ventral stratum oriens of the hippocampal circonvolution CA1 in PD28 male mice prenatally (gestational day 9) treated with LPS and in PD28 female mice prenatally treated with poly IC (Harvey and Boksa 2012).

GAD67 immunoreactivity was, however, decreased by some 40 % by early prenatal (9.5 gestational days) (Soumiya et al. 2011). Other reports have pointed to a decrease in PV levels in the prefrontal cortex in a double hit model of schizophrenia (dominant-negative DISC1 transgenic mice x poly IC) (Ibi et al. 2010) or in hippocampal CA1 region (Ducharme et al. 2012); interestingly, the latter paper also demonstrated a strong reduction in hippocampal theta rhythms. Overall, in spite of somewhat conflicting results, it seems that a number of GABAergic abnormalities can be elicited by the prenatal inflammatory models currently validated and in wide use.

In another perspective, a number of authors have used the GAD67 response, and its robust reproducibility in humans, to directly test the glutamatergic, and more specifically the NMDA hypofunction, hypothesis of schizophrenia.

Postnatal injection of MK-801 to rat pups induced divergent responses with decreased PV levels in the anterior cingulate and decreased GAD67 levels in the somatosensory cortex, where PV levels were unchanged (Turner et al. 2010). In adult rats, daily injections of ketamine for 2 days was sufficient to subacutely decrease GAD67- and PV-immunoreactive cells by *circa* 40 % (Zhang et al. 2008), at odds with the acute effects of MK801, which, however, induced a diffuse decrease of PV levels (Romon et al. 2011). The comparative effects of single versus repeated phencyclidine (PCP) administration was studied in detail by Amitai et al. (Amitai et al. 2012). In all experimental conditions, there was a significant decrease in GAD67 and PV levels, and chronic administration of clozapine provided a partial (GAD) or complete (PV) restoration. Apart from the pharmacological manipulations mentioned above, the most direct test of a relationship between NMDA hypofunction and GAD abnormalities has come from genetic ablation of some components of the NMDA receptor. Belforte et al. achieved selective elimination of the NR1 subunit in cortical and hippocampal interneurons (Belforte et al. 2010). This very specific model mimicked the most salient aspects of schizophrenia pathology including GAD67 and PV reduction in targeted, NR1-deficient, cells. This effect was only observed when the NR1 subunit was ablated at an early age, thereby emphasizing the neurodevelopmental aspects of "hypoglutamatergic" insults.

3.3 Interventional Studies

Most of the subjects with psychiatric diseases whose brains were used in postmortem studies were or had been receiving medication, most often antipsychotic treatment, which raised questions about the origin (endogenous vs iatrogenic) of GAD decreases. To address this problem, some authors reported on animal interventional studies in parallel with their human postmortem results. Bullock et al. (Bullock et al. 2008) showed an augmentation of GAD65/67 levels by clozapine, whereas haloperidol decreased GAD65, but increased GAD67 levels.

In parallel with their postmortem study, Hashimoto et al. (Hashimoto et al. 2008a) treated male macaque monkeys with haloperidol or olanzapine for >12 months, achieving therapeutic blood drug levels. The two drugs were devoid of any effect on GAD67 mRNA levels.

In male Sprague Dawley rats, daily injections of haloperidol or clozapine increased GAD67 mRNA with concomitant protein increase only in the haloperidol group (Chertkow et al. 2006).

Overall, these results have confirmed that GAD abnormalities are indeed related to the underlying pathological process and not to some medication effects.

3.4 Clinical Aspects

The consequences of GABAergic disturbances in schizophrenia, and more relevant to the present chapter, the functional consequences of diffuse GAD downregulation, are generally thought to relate to the well-known cognitive disturbances, which are the defining feature of the disease. A large preclinical literature has consistently shown that GAD67-/PV-expressing interneurons of the cortex were critically involved in the generation of two specific electroencephalographic (EEG) rhythms, the theta and gamma bands (4–7 and 30–80 Hz, respectively). Gamma oscillations are associated with diverse cognitive functions such as perceptual binding, attention, arousal, object recognition, language perception, and executive function, some of which are highly relevant to schizophrenia disturbances (Herrmann et al. 2004). Optogenetic data have confirmed that PV neurons where necessary and sufficient to give rise to gamma rhythms, while the situation appears more complex for the generation of theta rhythms (Royer et al. 2012). While the notion that there is a mere gamma decrease in schizophrenia appears to be an oversimplification, there is little doubt that the power and organization of this spectral band as well as others are disturbed in schizophrenia, another feature being an increase in theta frequencies and a defective theta suppression during sensory gating (Moran and Hong 2011). Overall, it can be hypothesized that GAD/PV disturbances in schizophrenia (and to some extent bipolar affective disorder) disrupt the function of basket and chandelier PV-positive interneurons giving rise to abnormalities in EEG spectra critically associated with proper cognitive functioning. In the absence of sufficiently specific pharmacological interventions, some empirical validation of this model could come from genetic association studies linking GAD polymorphisms to cognitive function

or, more convincingly, to EEG analyses. Indeed, a recent report showed a significant association of GAD1 polymorphisms with schizophrenia, epistasis with the catechol-O-methyl transferase val/met polymorphism (another significant contributor to prefrontal function in schizophrenia), and contribution of a polymorphism in the putative promoter region of the GAD1 gene to GAD67 prefrontal transcript levels (Straub et al. 2007).

4 Role of Oxidative Stress in GABA Neurotransmission

Subanesthetic doses of NMDAR antagonists, like phencyclidine and ketamine administered in adulthood, reproduce positive and negative symptoms of schizophrenia in vivo. Thus, NMDAR antagonists are used for modeling schizophrenia (Javitt 2010). It has been shown that NMDAR antagonists induce a decrease in PV expression in GABAergic interneurons in rodents and nonhuman primates (Cochran et al. 2002, 2003; Keilhoff et al. 2004; Rujescu et al. 2006; Morrow et al. 2007). Indeed, PV interneurons are highly sensitive to NMDAR antagonists (Jones and Buhl 1993), which suggests that NMDARs are implicated in the control of basal synaptic activation in PV interneurons (Goldberg et al. 2003). Specifically, NMDAR subunits NR2A are expressed at higher levels in PV interneurons than in pyramidal neurons (Kinney et al. 2006) and NR2A antagonist NVP-AAM077 reduced GAD67 expression (Kinney et al. 2006), which supports the role of NMDAR subunit NR2A in reduction of GAD67 levels. Furthermore, NMDAR antagonists increase reactive oxygen species (ROS) in vitro (Xia et al. 2002) and in vivo (Zuo et al. 2007) and, thus, induce an imbalance of redox status. Oxidative stress is implicated in the pathogenesis of schizophrenia through, among others things, a decrease in glutathione (GSH) levels (Do et al. 2009). GSH, an important radical scavenger, is crucial for NMDAR activation, a redox-sensitive process (Lipton et al. 2002). We present hereafter a review of in vitro and in vivo studies that demonstrated the crucial role of oxidative stress on GAD67 expression and on PV interneurons via NMDAR hypofunction and its relevance to schizophrenia.

4.1 In Vitro Studies

CNS oxygen toxicity has been associated with generation of ROS (Li et al. 2008), which attacks enzymes like GAD67. It has been demonstrated that primary rat hippocampus neurons, exposed to prolonged hyperbaric oxygen treatment (HBO), show a decrease in GAD67 content, GAD activity, and intracellular GABA content (Li et al. 2008). As HBO exposure increases oxygen-free radicals and, then, induces oxidative stress, it has been suggested that the decrease in GAD67 expression is provoked by the increase of oxidative stress (Li et al. 2008). In fact, it has been reported that oxygen-free radicals decrease GAD67 activity by disrupting their hydrosulfide groups (−SH), which are essential for GAD67 activity (Satyanaran et al. 1985).

In primary cortical neuronal cultures, NMDAR antagonists induced a reversible decrease in GAD67 and PV levels in PV interneurons (Kinney et al. 2006), while ketamine, a NMDAR antagonist, increased superoxide production and NADPH oxidase subunit NOX2 expression in PV interneurons (Behrens et al. 2007). Furthermore, the superoxide production and the loss of PV and GAD67 immunoreactivity were prevented by treatment with apocynin, an inhibitor of NADPH oxidase activity (Behrens et al. 2007), thereby confirming the pivotal role of oxidative stress between "PCP-like" antagonism of NMDA receptors and down-modulation of GAD67 levels.

While most of these results involve posttranscriptional functional modifications, transcriptional regulation of GAD67 also raises interesting questions. The notion of transcriptional repression in the CNS in situations of oxidative stress, if confirmed, would stand in sharp contrast to what happens in the systemic compartment where oxidative stress upregulates GAD67 in an NFkB-dependent fashion (Choi et al. 2002). Among the signaling network associated with GAD67 downregulation, Daxx is well placed to achieve transcriptional repression. One other potential mechanism, given the robust evidence of epigenetic modulation of GAD67 transcription (Kundakovic et al. 2009), would be the redox modulation of DNA methylation of histone deacetylation.

4.2 In Vivo Studies

Many studies have demonstrated that hyperoxia, in vivo, decreases GAD activity (Tunnicliff et al. 1973; Davis et al. 2001; Segerbo 1979; Hori 1982). A rise-and-fall dynamic pattern of GAD activity has been reported exposing rats to hyperbaric oxygen treatment (HBO) (Li et al. 2008). Indeed, in the hippocampus, GAD content increased gradually in the first 15 min after exposure to HBO, but decreased from 20 min onward after exposure, which correlated with the development of convulsions in rats. Furthermore, this effect on GAD content came from changes in GAD67 expression, because GAD65 remained unchanged (Li et al. 2008).

Furthermore, it has been reported, in vivo, a decrease in PV and GAD67 immunoreactivity, following treatment with ketamine, in PV interneurons from mouse prefrontal cortex and an increase in superoxide production. Pretreatment of animals with apocynin, an inhibitor of NADPH oxidase (NOX) activity, prevented the ketamine-induced effects (Behrens et al. 2007). The effects were specific for the PV-interneuronal population, because other interneurons expressing the calcium-binding proteins calbindin (CB) and calretinin (CR) were unchanged by ketamine (Behrens et al. 2008). In Nox2-deficient ($gp91^{phox-/-}$) mice, ketamine did not induce an increase of superoxide production nor a loss of phenotype of PV interneurons, which suggests that the decrease in PV and GAD67 levels in PV interneurons is dependent on NOX and, thus, on oxidative stress (Behrens et al. 2008).

A decrease in GSH (glutathione) levels, which is associated with an increase of oxidative stress (Do et al. 2000), during development leads to a hypofunction of NMDARs in adulthood (Gysin et al. 2007; Tosic et al. 2006), and GABAergic neurons are highly sensitive to oxidative stress (Lipton et al. 2002; Kohr et al. 1994; Volterra et al. 1994; Mustafa et al. 2007). Catalytic (GCLC) and modifier (GCLM)

subunits of the glutamate cysteine ligase (GCL), the rate-limiting enzyme of GSH synthesis, have been associated with schizophrenia (Gysin et al. 2007; Tosic et al. 2006). It has been reported that the ventral hippocampus is vulnerable to redox dysregulation in GCLM knockout mice, which exhibit brain GSH deficits (Steullet et al. 2010), whereas no effect was observed in dorsal hippocampus. Thus, PV interneurons, but not CB or CR interneurons, were reduced in the ventral hippocampus of GCLM knockout mice, which suggests that oxidative stress-induced effects are specific to PV interneurons. The ventral hippocampus could be more vulnerable to oxidative stress because of its higher catecholamine concentration (Oleskevich et al. 1989; Gasbarri et al. 1997; Bjarkam et al. 2003), in line with the fact that reactive oxygen species (ROS) can be formed from auto-oxidation and catabolism of catecholamines (Cadet and Brannock 1998).

Thus, a redox dysregulation, through a decrease in GSH levels and/or an increase in ROS production, leads to NADPH oxidase (NOX) activation, which triggers NMDAR antagonism; for instance, the N2RA subunit of NMDAR, which is sensitive to oxidative status, maintains the function of PV interneurons (Kinney et al. 2006). As a further consequence, NMDAR hypofunction would then induce a decrease in GABAergic markers, namely, GAD67 and PV (Fig. 2) (Do et al. 2009) and downstream disruption of PV interneuron functions as well as their EEG/cognitive correlates, as discussed above.

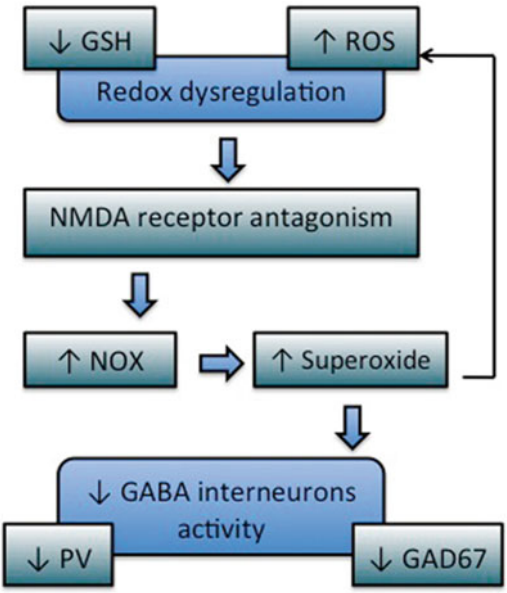

Fig. 2 Link between oxidative stress and decreased GAD67 expression. Redox regulation, induced by a decrease in glutathione (GSH) levels or an increase in reactive oxygen species (ROS) production, leads to NMDA receptor antagonism through NR2A subunit. NMDA receptor antagonism is followed by an increase in NADPH oxidase (NOX) levels, increasing superoxide production. Finally, there is a decrease in parvalbumin (PV) and the 67 kDa form of glutamic acid decarboxylase (GAD67), leading to a hypoactivity of GABA interneurons. The increase in superoxide production can also enhance ROS production through a positive feedback

5 Conclusion

GAD perturbations in severe mental disorders have been extensively replicated, making them the current neurochemical signature of these diseases. Extensive research has provided a better understanding of the upstream determinants and downstream consequences of these perturbations and suggested a prominent role of oxidative stress at the transcriptional as well as posttranscriptional level. As such, they constitute a privileged field to ascertain how oxidative status impacts the pathophysiology of psychiatric disorders.

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