Dysregulation of Glutathione Synthesis in Psychiatric Disorders

Elżbieta Lorenc-Koci

1 Introduction

There is a growing body of evidence implicating oxidative stress mechanisms and the impaired redox regulation in the pathophysiology of diverse psychiatric disorders (Do et al. 2009; Steckert et al. 2010; Bitanihirwe and Woo 2011; Yao and Keshavan 2011). Oxidative stress defined in accordance with the free radical hypothesis refers to the cytopathological consequences of an imbalance between free radical production on the one side and deficiency of the antioxidant defense system on the other side. Brain cells are particularly vulnerable to oxidative damage due to relatively low to moderate activity of antioxidant enzymes (superoxide dismutase, SOD; catalase, CAT; glutathione peroxidase, GPx) when compared to the liver or kidney, high levels of lipids and polyunsaturated fatty acids, high metal content, and high oxygen utilization (Dringen 2000; Valko et al. 2007). Hence, the free radical-mediated damage of important cellular molecules, like lipids, proteins, and DNA, leading to the impairment of cell function and vitality is currently considered as one of the main mechanisms in the pathophysiology of both neurodegenerative and psychiatric disorders (Bains and Shaw 1997; Valko et al. 2007; Ng et al. 2008; Steckert et al. 2010; Bitanihirwe and Woo 2011).

On the other hand, as the clinical trials with supplementation of free radical scavenging antioxidants show little benefit in humans, a complementary hypothesis for oxidative stress has been postulated (Jones 2006, 2008). This hypothesis, which is termed the "redox hypothesis" to facilitate its distinction from the "free radical hypothesis," assumes that disruption of the redox states of thiol systems which

E. Lorenc-Koci (✉)
Department of Neuro-Psychopharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna St., PL-31-343 Krakow, Poland
e-mail: lorenc@if-pan.krakow.pl

A. Dietrich-Muszalska et al. (eds.), *Studies on Psychiatric Disorders*, Oxidative Stress in Applied Basic Research and Clinical Practice,
DOI 10.1007/978-1-4939-0440-2_14

normally function in cell signaling and physiological regulations is the most central feature of oxidative stress. Three main thiol systems represented by thiol/disulfide redox couples exist in biological systems: (i) reduced glutathione (GSH) and its disulfide (GSSG), GSH/GSSG couple; (ii) cysteine (Cys) and its disulfide, cystine (CySS), Cys/CySS couple; and (iii) reduced and oxidized thioredoxins (Trx), Trx^{red}/Trx^{ox} couple (Kemp et al. 2008). All these systems are responsible for the maintenance of the appropriate redox potential in different cellular compartments (Jones 2006, 2008). The "redox hypothesis" draws attention to non-radical mechanisms of oxidative stress. It has been demonstrated that biological systems generate significantly more non-radical oxidants than free radicals (Jones 2008). Hydrogen peroxide (H_2O_2), the most abundant non-radical oxidant, is formed in many enzymatic reactions. For instance, H_2O_2 is the predominant product in the reaction catalyzed by xanthine oxidase although the superoxide radical anion ($O_2^{-\bullet}$) is also produced. Moreover, $O_2^{-\bullet}$ is converted into oxidant H_2O_2 in the reaction catalyzed by the antioxidant enzyme SOD. The free radicals $NO^{\bullet}$ and $O_2^{-\bullet}$ react to generate peroxynitrite ($ONOO^-$) that is a powerful oxidizing and nitrating non-radical intermediate (Thomas et al. 2006). Apart from the abovementioned oxidants, biological systems produce other oxidants, such as hydroperoxyfatty acids, aldehydes, quinones, epoxides, and disulfides. All these oxidants, albeit not free radicals, contribute importantly to the regulation of cellular redox state by modulation of the thiol-containing proteins that play important roles in cell-to-cell signaling, macromolecular trafficking, and physiological regulation (Jones 2008). Redox elements represented by sulfhydryl (–SH) residues of cysteine and thioether groups of methionine, found in the active site of many proteins, are susceptible to two-electron oxidants. Hence, the two-electron oxidation can be considered to be a component of oxidative stress that is distinct from free radical-mediated macromolecular damage. The function of these thiol-containing proteins is controlled by thiol antioxidants, GSH, Cys, and Trx^{red}, which are able to prevent the two-electron oxidation. Therefore, the appropriate levels of these antioxidants are of great importance for the maintenance and regulation of the thiol redox status of the cells.

The scope of this chapter is to review the available literature referring to GSH synthesis and its multiple functions in the central nervous system. Particular attention will be focused on GSH deficit and dysregulation of redox state in psychiatric disorders such as schizophrenia and bipolar disorder. Oxidative stress-mediated alterations in psychiatric patients will be compared to those observed in animal models of GSH deficiency. Finally, a treatment restoring the redox balance will be discussed in the context of therapy of psychiatric disorders.

2 Functions of Glutathione

Glutathione (γ-glutamyl-L-cysteinylglycine, GSH), a cysteine-containing tripeptide and the most abundant nonprotein thiol, is present in the mammalian brain with an average concentration of 2–3 mM, but there are marked differences in its content between particular cell types (Dringen 2000). Neurons have much less GSH than

glial cells. Among glial cells, microglia contains the highest amount of GSH, while oligodendrocytes, which are affected in schizophrenia, the lowest level. Astrocytes, like microglial cells, are characterized by a relatively high level of GSH (Dringen 2000). Glutathione exists predominantly in the thiol, i.e., reduced (GSH) form (99 %), while the disulfide, i.e., oxidized form (GSSG), represents less than 1 % of the total glutathione pool under physiological conditions.

2.1 The Main Functions of Glutathione

In the mammalian cells, GSH plays a lot of diverse functions including (1) scavenging of free radicals; (2) detoxification of xenobiotics; (3) maintenance of the redox state of proteins; (4) providing a nontoxic storage form of cysteine; (5) modulation of critical cellular processes, such as DNA synthesis and repair, cell proliferation, and redox signaling; (6) regulation of nitric oxide homeostasis; and (7) modulation of the activity of glutamate receptors in the central nervous system (Jánaky et al. 1998, 1999; Oja et al. 2000). GSH serves as an endogenous NO reservoir to form S-nitrosoglutathione (GSNO) (Hogg 2002). In the brain, GSNO can also elicit neuroprotective effect under oxidative stress conditions (Rauhala et al. 1998).

Thus, given many critical processes that are affected by GSH, it is not surprising that disturbances in its homeostasis have been implicated in the etiology and/or progression of a number of human diseases, including neurodegenerative and neuropsychiatric diseases (Ballatori et al. 2009; Do et al. 2009).

2.2 Antioxidant Activity of Glutathione

As an antioxidant, GSH scavenges reactive oxygen species (ROS) generated during electron transport and cellular metabolism of endo- and exogenous compounds. GSH is also involved in the disposal of hydrogen peroxide (H_2O_2) and hydroperoxides, which are non-radical oxidants produced during different cellular processes, strongly affecting redox state of cells. The detoxification of ROS and peroxides is associated with two types of reaction. Firstly, GSH reacts directly and nonenzymatically with such radicals as superoxide radical anion ($O_2^{-\bullet}$), nitric oxide ($NO^{\bullet}$), or hydroxyl radical ($HO^{\bullet}$) (Hogg 2002; Winterbourn and Metodiewa 1994). The removal of $HO^{\bullet}$ via this route is one of the most important functions of GSH in the nervous system:

$$2\,GSH + 2\,HO^{\bullet} \longrightarrow GSSG + 2\,H_2O$$

Secondly, GSH is an electron donor in the reduction of peroxides, mainly H_2O_2 in the reaction catalyzed by glutathione peroxidase (GPx):

$$H_2O_2 + 2\,GSH \xrightarrow{GPx} GSSG + 2H_2O$$

Final products of the GPx-mediated reduction of H_2O_2 comprise water and glutathione disulfide (GSSG). Also, catalase can reduce H_2O_2, but the brain has relatively low level of this enzyme as compared with that of GPx (Dringen and Hamprecht 1997). GSSG is then reduced back to GSH by glutathione reductase (GR):

$$\mathrm{GSSG} + \mathrm{NADPH} + \mathrm{H}^{+} \xrightarrow{\mathrm{GR}} 2\,\mathrm{GSH} + \mathrm{NADP}^{+}$$

This enzyme transfers electrons from nicotinamide adenine dinucleotide phosphate (NADPH) to GSSG, thereby regenerating GSH. Hence, the detoxification of peroxides depends on the availability and regeneration of NADPH. Organic peroxides can be reduced by GPx and glutathione S-transferase (GST). During the reactions catalyzed by GPx and GR, glutathione is not consumed but recycled. The relative ratio of the reduced to oxidized glutathione (GSH/GSSG) serves as an indicator of the cellular redox environment. The maintenance of high GSH/GSSG ratio requires energy expenditure. The adult brain relies almost exclusively on the glucose oxidation to meet its energy requirements. The pentose phosphate pathway is present in the brain, especially in astrocytes, but only 3–5 % of glucose is converted via this pathway, while the rest is oxidized via the tricarboxylic acid cycle. Nevertheless, the pentose phosphate pathway is important in the brain as a means of providing NADPH for the GSSG reduction to GSH (Dringen 2000). Consistently, it has been demonstrated that the pentose phosphate pathway was strongly activated in cultured astrocytes during the detoxification of H_2O_2 (Ben-Yoseph et al. 1996). On the other hand, glucose deprivation of astrocyte cultures significantly reduced astrocyte ability to remove H_2O_2 (Dringen and Hamprecht 1997) and prolonged regeneration time of GSH from GSSG after treatment with hydroxyperoxides (Dringen et al 1998).

The third important role of GSH is associated with the maintenance of intracellular redox homeostasis. Protein S-glutathionylation, the reversible formation of mixed disulfides between glutathione and low-pKa cysteinyl residues of proteins, is thought to be a regulatory and antioxidant mechanism (Dalle-Donne et al. 2007; Mieyal et al. 2008). The binding of glutathione molecules to proteins to form mixed disulfides protects protein –SH groups against irreversible oxidation to $–SO_2H$ and $–SO_3H$. Hence, protein S-glutathionylation is an important mechanism for a dynamic, posttranslational modification of a variety of regulatory, structural, and metabolic proteins as well as for the regulation of signaling routes and metabolic pathways (Dalle-Donne et al. 2007; Mieyal et al. 2008). This modulation of proteins is not only a cellular response to mild oxidative/nitrosative stress but also occurs under physiological conditions.

2.3 Detoxifying Function of Glutathione

GSH reacts with various endogenous compounds and xenobiotics in the reaction catalyzed by glutathione S-transferase (GST) to form glutathione S-conjugates which are exported to the outside of the cell (Commandeur et al. 1995; Salinas

and Wong 1999). There is only one enzyme, γ-glutamyl transpeptidase (γ-GT), localized on the outer side of the plasma membrane of certain cell types that is able to hydrolyze GSH conjugates to cysteinyl-glycine conjugates. The cysteinyl-glycine bond is then cleaved by dipeptidase, resulting in a cysteinyl conjugate that following N-acetylation is further metabolized to mercapturic acid.

Lipid peroxidation induced by ROS leads to the conversion of polyunsaturated fatty acids to highly reactive aldehydes, such as 4-hydroxynoneal (4-HNE), that inactivate proteins required for cell viability (Esterbauer et al. 1991). Therefore, rapid and efficient removal of these compounds is necessary to maintain cell function. GSH can react with 4-HNE via the action of GST to form GSH-HNE conjugates (Xie et al. 1998) which are then exported from the cells via transport-mediated efflux (Berhane et al. 1994). This process plays an important role in cellular detoxification. Furthermore, in the brain, GST detoxifies quinones that are formed during the oxidation of dopamine and other catecholamines (Baez et al. 1997; Dagnino-Subiabre et al. 2000). The latter reactions irreversibly consumes intracellular GSH, and without supplementation of GSH stores, the formation of glutathione S-conjugates can rapidly compromise cellular antioxidant capacity, finally leading to the enhanced production of ROS and disruption of the cellular redox balance.

2.4 Specific Function of Extracellular Glutathione in the Brain

The presence of GSH in the extracellular space has been confirmed using microdialysis method (Yang et al. 1994; Lada and Kennedy 1997). Experiments performed on brain slices demonstrated that GSH was released by depolarization induced by high K^+ concentration in a Ca^{2+} dependent manner, which indicates its origin from a neuronal compartment (Zängerle et al. 1992). The mechanism of this release is unknown; however, the fact that it is Ca^{2+} dependent suggests that GSH is released by a vesicular mechanism similar to that of classical neurotransmitters or its efflux is under the control of a released neurotransmitter. In the rat brain slices, the most prominent release of GSH was observed in the mesodiencephalon, cortex, hippocampus, and striatum and lowest in the pons-medulla and cerebellum (Zängerle et al. 1992). On the other hand, studies performed in cell culture have shown that astrocytes are mainly involved in GSH release and together with γ-GT affect its extracellular level (Sagara et al. 1996; Dringen et al. 1997). Consistently, it has been calculated that cultured astrocytes release about 10 % of the intracellular pool of GSH within one hour (Dringen et al. 1997). So, the astrocyte-mediated release of GSH is the process consuming the largest amount of this peptide.

Although GSH plays a crucial role in many cellular processes, its extracellular functions are less known. However, in the nervous system, besides these generally known functions, GSH may serve additionally as a modulator of ionotropic glutamate receptors or as a new neurotransmitter (Jánaky et al. 1998, 1999, 2000; Ogita et al. 1998; Pasqualotto et al. 1998). So, it has been demonstrated that GSH binds via γ-glutamyl moiety to ionotropic glutamate receptors, preferentially AMPA

and NMDA (Janáky et al. 1999). At micromolar concentrations, GSH displaces excitatory agonists from their binding sites, acting to halt their physiological actions on target neurons (Janáky et al. 1999; Oja et al. 2000). Since AMPA and NMDA receptors are colocalized and cooperate at postsynaptic membranes, the co-release of glutamate and GSH from nerve endings (Hjelle et al. 1998) may have profound consequences in synaptic transmission. According to the model of GSH synaptic actions proposed by Janáky et al. (1999), this peptide may inhibit the fast depolarization evoked by glutamate via AMPA receptors and thus inhibit the voltage-dependent opening of NMDA receptor ionophores. Hence, the co-release of glutamate and GSH would lead to a cascade of events enabling the receptors to be reactivated within the short time (Janáky et al. 1999; Oja et al. 2000). Moreover, GSH (at millimolar concentrations) acting via its cysteinyl thiol group can modulate the redox site of NMDA receptors (Janáky et al. 1999; Oja et al. 2000). As such modulation has been shown to increase NMDA receptor ion channel currents, this action may play a significant role in normal and abnormal synaptic activity. Finally, it has been demonstrated that GSH at nanomolar to micromolar range binds to at least two populations of binding sites that are distinct from any known glutamate receptor subtypes. It is believed that these binding sites represent a unique population of GSH receptors. GSH binds to these receptors via cysteinyl moiety and is not displaceable by glutamatergic agonists or antagonists (Shaw et al. 1996; Janáky et al. 1999, 2000). The application of GSH to cortical slices elicits a fast depolarizing potential that is markedly larger than that produced by NMDA and AMPA (Shaw et al. 1996). The GSH current appears to be linked to sodium ionophores as it was blocked by the absence of sodium ions but not by lowering of calcium or NMDA or AMPA antagonists (Shaw et al. 1996; Janáky et al. 1999, 2000). These reports suggest that GSH receptors may be a key component of cortical excitatory neurotransmission (Shaw et al. 1996).

3 Synthesis of GSH

3.1 Biosynthesis of GSH in the Brain

GSH is synthesized from its constituent amino acids, i.e., glutamate, cysteine, and glycine, in the cytosol of all mammalian cells by the consecutive action of two enzymes requiring adenosine triphosphate (ATP) as a co-substrate (Dringen 2000; Lu 2009):

$$\text{L-glutamate} + \text{L-cysteine} + \text{ATP} \rightarrow \gamma\text{-glutamyl-L-cysteine} + \text{ADP} + \text{Pi} \quad (1)$$

$$\gamma\text{-glutamyl} + \text{L-cysteine} + \text{L-glycine} + \text{ATP} \rightarrow \text{GSH} + \text{ADP} + \text{Pi} \quad (2)$$

In the first step of GSH biosynthesis, glutamate cysteine ligase (GCL, EC 6.3.2.2; formerly γ-glutamylcysteine synthetase) catalyzes the formation of the dipeptide γ-glutamyl-L-cysteine (γ-GluCys) from glutamate and cysteine (Reaction 1).

This reaction exhibits absolute requirement not only for ATP but also for Mg^{2+} or Mn^{2+} (Franklin et al. 2009). The second step of GSH biosynthesis is catalyzed by GSH synthase (GS, EC 6.3.2.3; formerly known as GSH synthetase) which ligates glycine to γ-GluCys, thus forming GSH (Reaction 2).

Cysteine is the rate-limiting substrate for GSH synthesis (Dringen et al. 1999). In the brain, mature neurons use exclusively cysteine for GSH synthesis, while astrocytes utilize both cystine and cysteine (Dringen et al. 1999; Dringen 2000). Cystine is taken up by astrocytes and microglial cells via cystine/glutamate exchanger also known as system xc^- (Shih et al. 2006). Only immature neurons express the xc(−) transport system (Murphy et al. 1990), while mature ones do not possess this transporter and therefore are unable to take up cystine for GSH synthesis. In the mature brain, neurons rely mainly on cysteine derived from GSH released by astrocytes into the extracellular space, where GSH is cleaved by sequentially acting the membrane-bound enzymes γ-GT and dipeptidase to constituent amino acids (Dringen et al. 1999; Dringen 2000). In addition to cysteine, neurons can utilize the cysteine-containing dipeptides γ-GluCys or cysteinylglycine (CysGly) for GSH synthesis (Dringen et al. 1999), although it is unclear how these dipeptides are taken up into neurons. Neural uptake of cysteine is mediated primarily by sodium-dependent excitatory amino acid transporter (EAAT) systems, known as excitatory amino acid carrier 1 (EAAC1 also termed EAAT3) (Shanker et al. 2001; Chen and Swanson 2003; Himi et al. 2003). EAAC1-deficient mice showed 30–40 % decreases in brain GSH levels, increased vulnerability to oxidative stress, as well as developed brain atrophy and behavioral abnormalities (Aoyama et al. 2006). The abovementioned data clearly indicate that transport of cysteine by EAAC1 system is also a rate-limiting factor for GSH synthesis in neurons.

3.2 Regulation of GSH Synthesis

Under physiological conditions, the rate of GSH synthesis depends on the expression and catalytic activity of GCL (Dalton et al. 2004; Dickinson et al. 2004). GCL is a heterodimeric protein composed of a heavy or catalytic (GCLC, Mr ~ 73,000) and a light or modifier (GCLM, Mr ~ 30,000) subunit, which are encoded in humans and rodents by different genes (Gipp et al. 1992; Dalton et al. 2004; Franklin et al. 2009). Only GCLC possesses all the enzymatic activity and is a subject of feedback inhibition by the end product GSH (Richman and Meister 1975; Seelig et al. 1984). GCLM is enzymatically inactive but plays an important regulatory function by increasing the V(max) and K(cat) of GCLC, by lowering the K(m) of GCL for glutamate and ATP, and by raising the K(i) for GSH-mediated feedback inhibition of GCL (Chen et al. 2005; Lu 2009; Yang et al. 2007). Thus, the holoenzyme is catalytically more efficient and less susceptible to inhibition by GSH than GCLC alone. GCLC-knockout mice showed embryonic lethality, demonstrating that the gene encoding this subunit was critical for development (Dalton et al. 2000, 2004). In turn, GCLM-knockout ($Gclm^{-/-}$) mice are viable, but in the absence of this subunit,

GCLC activity is insufficient, leading to a decrease of GSH level (Yang et al. 2002; Dalton et al. 2004). Alterations in GCL activity can result from regulation at multiple levels affecting only catalytic (GCLC) or both catalytic and modifier (GCLM) subunits of this enzyme. Many studies have focused on transcriptional regulation of GCL at the promoter level (Lu 2009).

GSH synthase (GS), the second enzyme participating in GSH biosynthesis, is composed of two identical subunits and has a Mr of approximately 118,000 Da. Mapping studies of the GS substrate binding sites indicate that the regions of the active site that bind glycine and the cysteinyl moiety of γ-GluCys are highly specific, while the γ-glutamyl moiety can be replaced by a variety of analogs. However, in contrast to GCL, GS is not subject to feedback inhibition by GSH. Moreover, GS overexpression had no effect on GSH level, whereas GCL overexpression markedly increased GSH level (Grant et al. 1997). Hence GCL, but not GS, is considered to be the rate-limiting enzyme in the GSH synthesis.

4 Oxidative Stress and GSH Synthesis in Schizophrenia and Bipolar Disorder

4.1 Glutathione Deficiency as a Marker of Oxidative Stress in Schizophrenia

Several studies have shown that the level of GSH, the major antioxidant and redox regulator, is decreased in a cerebrospinal fluid and medial frontal cortex (by 27 % and 52 % of control level, respectively) of drug-naïve schizophrenic patients (Do et al. 2000) as well as in the postmortem striatum (by 40 % of control) (Yao et al. 2006) and prefrontal cortex of those treated earlier with antipsychotic drugs (Gawryluk et al. 2011a). Moreover, there was a significant negative correlation between GSH levels and the severity of negative symptoms in schizophrenic patients (Matsuzawa et al 2008). In periphery, significantly lower levels of GSH were found in erythrocytes (Altuntas et al. 2000; Raffa et al. 2009, 2011; Micó et al. 2011) and plasma (Zhang et al. 2007; Dietrich-Muszalska et al. 2009; Raffa et al. 2009) of antipsychotic-free and chronically medicated schizophrenic patients in comparison to healthy control. As indicated by some genetic studies, the GSH deficit in schizophrenia seems to be linked to polymorphisms of genes encoding both catalytic (GCLC) and modifier (GCLM) subunits of glutamate cysteine ligase (GCL), an enzyme responsible for the biosynthesis of this tripeptide (Tosic et al. 2006; Gysin et al. 2007, 2009, 2011).

In addition, the activity of glutathione peroxidase (GPx), a key antioxidant enzyme involved in the elimination of hydrogen peroxide and lipid peroxides, was found to be unchanged (Mukerjee et al. 1996; Yao et al. 1998; Evans et al. 2003; Raffa et al. 2009), increased (Kuloglu et al. 2002; Raffa et al. 2011; Micó et al. 2011), or decreased (Abdalla et al. 1986; Altuntas et al. 2000) in erythrocytes of drug-naïve and antipsychotic-free schizophrenic patients when compared to

controls. In a majority of chronically medicated schizophrenic patients treated with typical or atypical antipsychotic drugs, GPx activity in erythrocytes was found to be decreased (Altuntas et al. 2000; Ranjekar et al. 2003; Zhang et al. 2006; Ben Othmen et al. 2008; Raffa et al. 2009), while only in a few studies it was unchanged (Reddy et al. 1991; Evans et al. 2003) or increased (Herken et al. 2001; Akyol et al. 2002). Apart from the cytosolic form of GPx, there exists a related enzyme, called human plasma glutathione peroxidase (hpGPx), that is localized exclusively extracellularly. The level of this enzyme was significantly and positively correlated with the psychosis rating scores in schizophrenic patients both on and off haloperidol treatment (Yao et al. 1999). Decreased levels of GPx and glutathione reductase (GR), suggesting attenuated antioxidant functions of these two enzymes, were also found in the caudate region of brains from schizophrenic patients (Yao et al. 2006). Furthermore, a significantly lower level of Mu class of GST isoenzyme in the prefrontal cortex of schizophrenic patients than in nonpsychiatric controls has also been reported (Gawryluk et al. 2011b). The decreased level of GST Mu indicates that these patients had lesser ability to remove xenobiotics and also to detoxify endogenous substances such as quinines and lipid peroxidation products.

All the above-described results clearly indicate that due to a deficit of GSH and the decreased scavenging ability of GSH-related antioxidant enzymes, the redox balance of GSH/GSSG couple in peripheral tissues and in the brain cells of schizophrenic patients has to be shifted in favor of oxidative processes.

4.2 Changes in GSH Redox Status in Bipolar Disorder

Although the exact mechanisms underlying bipolar disorder (BD) are not completely understood, some studies suggest an involvement of oxidative stress and alterations in GSH redox status in the pathophysiology of the disease (Andreazza et al. 2007; Kuloglu et al 2002; Ranjekar et al. 2003; Machado-Vieira et al. 2007). In patients with BD, like in schizophrenic patients, oxidative stress was assessed indirectly by measuring the activities of antioxidant enzymes (glutathione peroxidase, GPx; superoxide dismutase, SOD; and catalase, CAT) in erythrocytes and serum as well as by determination of the content of thiobarbituric acid reactive substances (TBARS) as an index of lipid peroxidation. These studies, although less numerous than in schizophrenia, demonstrated that enzymatic activities of GPx, SOD, and CAT were impaired in BD (Kuloglu et al. 2002; Ranjekar et al. 2003; Ozcan et al. 2004; Andreazza et al. 2007; Kunz et al. 2008; Machado-Vieira et al. 2007) and lipid peroxidation was significantly enhanced when compared to nonpsychiatric control subjects (Kuloglu et al. 2002; Ranjekar et al. 2003; Ozcan et al. 2004; Machado-Vieira et al. 2007; Andreazza et al. 2007, 2008; Kunz et al. 2008). In line with studies on antioxidant enzymes in blood, a postmortem study of the hippocampus from BD patients demonstrated a lowered gene expression for several antioxidant enzymes in that structure, including GPx, CAT, SOD, and glutathione S-transferase (GST) (Benes et al. 2006). Moreover, recently diminished level of

both reduced (GSH) and oxidized (GSSG) forms of glutathione in the prefrontal cortex (Gawryluk et al. 2011a) as well as oxidative damage to mitochondrial proteins (Andreazza et al. 2010) in that structure, increased lipid peroxidation in the cingulate cortex, and RNA oxidation in the hippocampus (Wang et al. 2009; Che et al. 2010) have been reported in postmortem brain from BD patients.

In addition, in patients not medicated with mood stabilizers, the level of class Mu of GST was decreased, while in BD patients treated with these drugs, the level of this isoenzyme was not different from that observed in controls (Gawryluk et al. 2011b). The latter effect is consistent with previous studies which demonstrated that mood stabilizers such as lithium, lamotrigine, and olanzapine increased GST expression and activity in primary cultured rat cerebral cortical cells (Shao et al. 2008; Bakare et al. 2009). Furthermore, chronic treatment with lithium and valproate increased the glutamate cysteine ligase (GCL) expression and GSH levels in these cultures (Cui et al. 2007). Since GST conjugates GSH with a variety of oxidized compounds to form nontoxic products, it has been suggested that lithium and valproate selectively target GST isoenzymes in order to produce neuroprotective effects against oxidative stress (Cui et al. 2007; Shao et al. 2008).

Summing up, all these studies suggest that oxidative stress and disturbances in GSH homeostasis play a significant role in the etiology of other psychiatric illnesses besides schizophrenia, e.g., BD, and the drugs increasing GSH content exert beneficial therapeutic effects in the treatment of this disease.

5 GSH-Deficient Animal Models of Schizophrenia

In general, the lowering of GSH level may result either from genetically determined alterations in the activities of GSH synthesizing enzymes (Tosic et al. 2006; Gysin et al. 2007, 2009) or from the limited availability of cysteine, a substrate for GSH synthesis (Dringen 2000). In experimental animals, the tissue GSH content can be decreased by inhibition of GCL enzymatic activity using specific compounds (Broquist 1992), by modulation of genes encoding catalytic or modifier subunits of this enzyme (Yang et al. 2002; Dalton et al. 2000, 2004), or by GSH depletion evoked by different endogenous or exogenous compounds that oxidize or conjugate the thiol group of this tripeptide (Masukawa et al. 1989). All these models have been used to check whether GSH deficit can lead to behavioral, morphological, and biochemical anomalies similar to those observed in schizophrenic patients.

5.1 Behavioral Effects of Glutathione Deficiency in Animals

The consequences of brain GSH deficit on cognitive functions were examined in the abovementioned animal models. It has been demonstrated that the GSH deficit induced in adult rats by intracerebra, chronic administration of L-buthionine-(S,R)-sulfoximine (BSO) combined with intracerebral injection of dopamine (DA),

induced psychomotor (Shukitt-Hale et al. 1997) and spatial memory deficits in the water maze test (Shukitt-Hale et al. 1998).

According to the neurodevelopmental theory of schizophrenia, unknown gestational or perinatal events can impair brain development, leading to the establishment of an abnormal cerebral connectivity and detrimental effects of which may appear in adolescence, hence the consequences of GSH deficit during development were also studied in animal models (Rougemont et al. 2002; Castagné et al. 2004a, b; Cabungcal et al. 2007). It was found that rats treated with BSO between postnatal days 5 and 16 developed a strong ~50 % GSH deficit in various brain structures including the cortex (Rougemont et al. 2002). It is worth to mention that in the rat, the peak GSH concentration on postnatal day 7 is critical for brain development, as it occurs during a period of intensive synaptogenesis and may play the neuroprotective role during that time (Nanda et al. 1996). Rodents may compensate for GSH deficit by increasing ascorbic acid synthesis, as demonstrated in some studies on the Osteogenic Disorder Shionogi (ODS) mutant rats, which, like humans, cannot synthesize ascorbic acid (Castagné et al. 2004a, b; Cabungcal et al. 2007). Moreover, as the dysfunction of dopaminergic system is associated with schizophrenia, ODS rats were treated in the early postnatal period (between days 5 and 16) with BSO or the dopamine uptake inhibitor GBR 12909, alone and in combination, and later on in juvenile and adult rats, the object recognition test was performed (Castagné et al. 2004b). The object recognition test is based on the spontaneous tendency of rats to investigate objects and to favor novel objects versus familiar ones. In the latter study, it has been demonstrated that ODS rats receiving BSO and GBR 12909 failed to discriminate between familiar and novel objects, while ODS rats treated with either BSO or GBR 12909 alone had normal behavior in this test (Castagné et al. 2004b). Since after the combined treatment these rats preserved basic motor and sensory skills, the alterations observed in the test of object recognition can be attributed to cognitive impairment. The fact that ODS rats treated with BSO and GBR 12909 did not investigate more intensively the novel object than the familiar one suggests that increased dopaminergic tone coinciding with GSH deficiency during development can result in the long-term cognitive deficit observed in adult rats (Castagné et al. 2004b). Hence, the observed disturbances in the object recognition test in ODS rats treated with BSO and GBR 12909 are in line with the decreased object recognition capacity of schizophrenic patients as compared to healthy control subjects (Danion et al. 1999; Doniger et al. 2001; Heckers et al. 2000).

On the other hand, in the genetic model of GSH deficit, that is, in GCLM-knockout ($Gclm^{-/-}$) mice, some subtle alterations in behavior of animals were observed (Steullet et al. 2010). In particular, $Gclm^{-/-}$ mice (4–6 months old) displayed an increased novelty-induced exploration, altered behavior during the object recognition task, altered emotion and stress-related behaviors, and lower response to delayed fear conditioning but had intact spatial learning and spatial memory (Steullet et al. 2010). The authors of the latter study revealed that genetically compromised GSH synthesis in $Gclm^{-/-}$ mice affected the morphological and functional integrity of hippocampal parvalbumin-immunoreactive (PV-ir) fast-spiking interneurons (FSIs), which are known to be altered in schizophrenia. In that study, it was demonstrated that the decreased GSH level in $Gclm^{-/-}$ mice caused a selective reduction of PV-ir

interneurons in CA3 and dentate gyrus of the ventral hippocampus (VH) but not the dorsal hippocampus (DH) and a concomitant reduction of β/γ oscillations (Steullet et al. 2010). According to those authors, the altered behavior of Gclm$^{-/-}$ mice was associated with the functional disruption of the VH. Therefore, the hippocampus-dependent behaviors, known to implicate differentially the VH and DH, observed in Gclm$^{-/-}$ mice were discussed on the background of other literature data, in comparative manner. Mice with functional disruption of PV-ir FSI in the whole hippocampus had deficit in recognition of novel spatial arrangement of familiar objects and in novel object recognition (Fuchs et al. 2007). Gclm$^{-/-}$ mice that had dysfunctional only the VH recognized changes in spatial arrangement of objects, a task that requires functional DH (Gaskin et al. 2009), but explored novel and familiar objects with the same intensity. Thus, Gclm$^{-/-}$ mice recognized spatially displaced objects but showed altered behavior during an object recognition task. Moreover, mice with functional disruption of PV-ir FSI in the whole hippocampus had also impaired spatial working memory (Fuchs et al. 2007), while Gclm$^{-/-}$ mice that had normally functioning DH did not show such deficit. Consequently, mice with functional disruption of PV-ir FSI in the whole hippocampus were hypoactive, while Gclm$^{-/-}$ mice showed potent novelty-induced exploration. Steullet et al. (2010) suggest that hyperactivity in Gclm$^{-/-}$ mice could be induced by a decreased GABA inhibition in the VH. Finally, altered emotion and stress-related behaviors in Gclm$^{-/-}$ mice were in line with specific disruption of the VH but not the DH. It should be mentioned here that there is a growing evidence of structural and functional anomalies of the anterior hippocampus, a region of human brain that corresponds to the VH in rodents, in schizophrenic patients (Goldman and Mitchell 2004).

Moreover, in the most recent study, Kulak et al. (2012) using a different package of behavioral tests demonstrated that Gclm$^{-/-}$ mice displayed hyperlocomotion in the open field and forced swimming test but normal activity in home cage, suggesting that hyperlocomotion was selective to environmental novelty and mildly stressful situations. In the study by Kulak et al. (2012), similarly as in that performed by Steullet et al. (2010), spatial working memory in Gclm$^{-/-}$ mice remained unaffected. Gclm$^{-/-}$ mice showed a potentiated hyperlocomotor response to an acute amphetamine injection, impaired sensorimotor gating (prepulse inhibition), and altered social behavior when compared to wild-type mice (Kulak et al. 2012).

Altogether, the experimental data from different animal models of GSH deficiency reported above show that low level of this antioxidant and redox regulator can induce behavioral alterations that are relevant to those observed in schizophrenia.

5.2 Biochemical Consequences of Glutathione Deficiency in In Vitro and In Vivo Models

Glutathione deficiency seems to be related to the dysfunction of central dopaminergic, glutamatergic, and GABAergic neurotransmissions that are known to be implicated in the pathogenesis of schizophrenia (Laruelle et al. 2003; Moghaddam 2003; Cabungcal et al. 2006).

5.2.1 The Effect of Glutathione Deficit on Dopaminergic System Function

According to the dopaminergic hypothesis of the disease, a decrease in dopamine (DA) release in the prefrontal cortex (PFC) has been associated with negative symptoms, particularly cognitive deficits, while disinhibition of DA release in the dorsal striatum (nucleus accumbens) with the manifestation of positive symptoms, such as delusions and hallucinations. Evidence for dopaminergic dysfunction in schizophrenia is in majority indirect and is mainly based on the fact that most antipsychotic drugs being antagonists of DA D_2 receptors alleviate some symptoms of this disease (Seeman et al. 1975; Kane and Marder 1993), while DA-releasing stimulants, such as amphetamine, induce psychosis (Janowsky and Risch 1979). Although the mechanisms underlying dopaminergic dysfunction in schizophrenia have not been elucidated yet, the hypothesis of GSH deficiency creates possibility to explain, at least, some of its aspects.

The Potential Role of Glutathione Deficiency in the Loss of Dendritic Spines

Metabolism of DA is closely linked with both intracellular and extracellular levels of GSH. DA is a major source of ROS in the mammalian brain, as an excess of this neurotransmitter can easily auto-oxidize to produce DA quinones that have potent oxidizing properties (Baez et al. 1997; Dagnino-Subiabre et al. 2000). Moreover, DA, via monoamine oxidase activity or DA quinones, through redox cycling, can induce the formation of H_2O_2 and $O_2^{\bullet -}$, which are known to cause lipid peroxidation, DNA modification, and protein oxidation (Baez et al. 1997; Bains and Shaw 1997; Rabinovic and Hastings 1998). Under physiological conditions, GSH detoxified DA quinones and H_2O_2 via reactions catalyzed by GST and GPx, respectively (see Sects. 2.2 and 2.3). However, under conditions of GSH deficiency, an excess of reactive intermediates of DA can disrupt cellular functions (Grima et al. 2003; Hastings et al 1996; Hirrlinger et al. 2002a), and this could contribute to the pathogenesis of schizophrenia. Although schizophrenia is not considered to be a neurodegenerative disease (Harrison 1997; Stevens and Casanova 1988; Garey 2010), low level of GSH in the PFC (Do et al. 2000; Gawryluk et al. 2011a) can sensitize neurons to DA-mediated dendritic degeneration (Hastings et al. 1996; Rabinovic and Hastings 1998; Grima et al. 2003). Hence, peroxidation reactions can lead locally to microlesions, affecting the synaptic contacts on dendritic spines of cortical pyramidal neurons, where excitatory glutamatergic terminals converge with dopaminergic ones (Goldman-Rakic et al. 1989). This may lead to the reduction of neuropil, mainly dendritic spines density, reported in postmortem histological studies of the PFC of schizophrenic patients (Selemon and Goldman-Rakic 1999; Glanz and Lewis 2000; Garey 2010; Glausier and Lewis 2012). As a degeneration of spines with their synaptic contacts may lead to abnormal cortico-cortical connectivity, these postmortem findings imply that neuronal integrity is compromised in schizophrenia. Thus, abnormal connectivity in the PFC may be responsible for part of symptoms, particularly those involving cognitive and perceptive functions (Garey 2010).

In line with the "reduced neuropil hypothesis" by Selemon and Goldman-Rakic (1999), it has been demonstrated that the application of DA under conditions of GSH deficiency into cultures of primary mouse cortical neurons induced a significant decrease in the number of neuronal processes which are considered to be spines analogous (Grima et al. 2003). Also, a deficit in brain GSH combined with a DA uptake inhibition during rat postnatal development caused a decrease in the number of dendritic spines of pyramidal neurons in the PFC (Do et al. 2004). So, morphological changes found in in vitro and in vivo studies could be related to morphological alteration reported earlier in the PFC of schizophrenic patients. Moreover, abnormal connectivity in the PFC was suggested by in vivo nuclear magnetic resonance imaging (NMR) studies in which it was found that N-acetyl aspartate (NAA), a marker of neuronal integrity, was decreased in schizophrenic patients (Callicott et al. 2000; Deicken et al. 2000; Yamasue et al. 2002). Interestingly, GSH deficiency decreases NAA level in the rat brain (Heales et al. 1995; Jain et al. 1991). Thus, it is likely that GSH deficiency and neuronal impairment are functionally linked in schizophrenia.

The Potential Role of Glutathione Deficiency in the Amphetamine-Induced DA Release in Subcortical Regions of the Brain

Besides the possible role of GSH deficiency in the loss of dendritic spines in the PFC (Grima et al. 2003; Do et al. 2004), it is believed that pathological low level of this antioxidant could cause disturbances in the dopaminergic neurotransmission (Jacobsen et al. 2005). The effect of a short-lasting GSH deficiency induced by the GSH synthesis blocker, BSO, on extracellular DA level in the nucleus accumbens of mice receiving amphetamine was investigated using a microdialysis method (Jacobsen et al. 2005). The latter study revealed that extracellular DA release after amphetamine (5 mg/kg) was increased twofold in the nucleus accumbens of GSH-deficient mice as compared to control mice with normal GSH level (Jacobsen et al. 2005). GSH deficiency per se did not change basal extracellular level of DA in the examined brain structure. These results indicate that GSH-deficient mice may experience accumbal hyperdopaminergia when DA transmission is considerably enhanced. The exacerbated amphetamine-induced DA release in the mouse model of GSH deficiency is consistent with the elevated amphetamine-induced DA release in the striatum of schizophrenic patients demonstrated by means of a single photon emission computed tomography (SPECT) and positron-emission tomography (PET) methods (Laruelle et al. 1996; Breier et al. 1997). Moreover, Laruelle et al. (1996) have shown that the elevated amphetamine effect in schizophrenic patients was associated with emergence or worsening of positive psychotic symptoms. These results suggest that psychotic symptoms in schizophrenia are related with exaggerated stimulation of dopaminergic transmission.

The mechanism underlying the interplay between GSH and DA after amphetamine administration in conditions of GSH deficiency is difficult to explain. However, based on previous reports on the general properties of GSH and DA, plausible explanations for these findings can be suggested. It is well known that GSH

directly conjugates DA in vitro (Baez et al. 1997; Dagnino-Subiabre et al. 2000) and in vivo (Rabinovic and Hastings 1998). Since extracellular concentration of GSH is relatively high (1–2 μM; Lada and Kennedy 1997) and astrocytes permanently release this antioxidant into extracellular space (Dringen et al. 1997; Hirrlinger et al. 2002b), it is likely that GSH could scavenge the released DA. The amount of GSH released by astrocytes is correlated with the intracellular GSH content (Sagara et al. 1996). Therefore, deficit in intracellular GSH may lead to a concomitant decrease in extracellular pool of this antioxidant. Since GSH directly affects DA transmission by extracellular conjugation, deficit in its extracellular level could impair this mechanism that keeps the released DA under control. However, whether DA-GSH conjugation has functional significance remains to be established.

The Potential Role of Glutathione Deficiency in the DA-Mediated Modulation of Glutamatergic Transmission in the Prefrontal Cortex

GSH plays an important role in the redox control of various signal transduction pathways and gene expression (Sen 2000; Esposito et al. 2004). Thus, GSH deficit can alter the function of redox-sensitive proteins implicated in neurotransmission and synaptic plasticity such as NMDA receptors (Köhr et al. 1994; Choi et al. 2001), $GABA_A$ receptors (Amato et al. 1999), and ryanodine receptors (Bull et al. 2003) as well as calcium-activated K^+ channels (DiChiara and Reinhart 1997) and L-type calcium channels (Campbell et al. 1996). These redox-sensitive proteins could affect neurotransmitter systems, i.e., dopaminergic, glutamatergic, and GABAergic, that are known to be dysfunctional in schizophrenia. In this section, a potential role of GSH deficiency in the DA-mediated modulation of glutamatergic transmission in the prefrontal cortex (PFC) will be discussed.

In the PFC, DA plays an important role in cognitive functions including working memory, reword, and attention. DA-containing neurons are localized in the ventral tegmental area and project to the PFC. A critical function of DA in this brain region is a modulation of glutamatergic transmission. NMDA responses are known to be modulated by DA via the activation of D_1 and D_2 receptors through multiple pathways acting on different targets, including NMDA receptors and voltage-gated calcium channels (Tseng and O'Donnell 2004). In brain slices obtained from developmentally matured rats, it was demonstrated that the application of NMDA and D_1 agonist SKF38393 induced concentration-dependent excitability increases measured by whole-cell patch clamp technique, whereas the application of the D_2 receptor agonist quinpirole induced concentration-dependent excitability decrease. The NMDA-mediated responses were potentiated by a D_1 agonist while they were attenuated by a D_2 agonist (Tseng and O'Donnell 2004).

The hypofunction of NMDA receptors reported in schizophrenia (Laruelle et al. 2003; Moghaddam 2003; Labrie and Roder 2010) could be evoked by pathologically low level of GSH in the brain. Therefore, it was interesting to check whether GSH deficiency could change DA receptor-mediated signaling in the PFC. Consistently, Steullet et al. (2008) examined, in cultures of embryonic cortical

mouse neurons treated with BSO, how GSH deficiency influenced intracellular pathways implicated in DA signaling, namely, DA modulation of calcium responses to NMDA. In this study, it was shown that in the absence of DA, calcium responses evoked by NMDA were significantly larger in GSH-deficient neurons than in control ones (Steullet et al. 2008). In further experiments, it was established that the increased calcium responses to NMDA were due to the increased function of both L-type calcium channels and ryanodine receptors (RyRs), but not NMDA receptors. So, caffeine, an agonist of RyRs, induced significantly larger calcium release from internal stores in BSO-treated neurons than in control ones, confirming in this way the enhanced function of RyRs in the GSH-deficient neurons (Steullet et al. 2008). Moreover, the increase in the function of RyRs in neurons with low GSH content was in line with the finding that RyRs were redox sensitive, with oxidative conditions enhancing their function (Bull et al. 2003).

DA administration decreased calcium responses evoked by NMDA in GSH-deficient neurons but enhanced them in control ones. To exclude unspecific effects of BSO, it was evidenced that replenishing GSH levels by administration a membrane-permeable GSH analog abolished DA-mediated decrease in calcium responses to NMDA in the cultured GSH-deficient neurons. Since the blockade of DA D_2 receptor by sulpiride caused a significant increase in calcium responses in GSH-deficient neurons but not in control ones, it was concluded that DA acting via DA D_2 receptors decreased calcium responses evoked by NMDA under conditions of GSH deficiency (Steullet et al. 2008). In contrast, the blockade of DA D_1 receptors with SCH23290 did not have any significant effect on DA-mediated modulation of calcium responses in GSH-deficient neurons while tending to decrease them in control neurons. The latter effect suggested that the activation of DA D_1 receptors was involved in DA-induced increase of calcium responses evoked by NMDA only in control neurons.

So, the above-described results showed that a GSH deficit changed DA modulation of calcium responses evoked by NMDA. In cultured cortical neurons, NMDA-evoked calcium responses resulted from an initial calcium influx via the activation of NMDA receptors followed by secondary calcium influxes, through voltage-gated calcium channels (L-type channels) and calcium release from intracellular stores via the activation of RyRs (Hayashi et al. 1997). Steullet et al. (2008) examined which of these calcium sources contributing to the total response evoked by NMDA were altered by DA modulation under conditions of GSH deficiency. Consequently, it was demonstrated that DA decreased the calcium influx through L-type channels in GSH-deficient neurons but enhanced it in control ones. Such an effect of a GSH deficit on L-type channels was also observed when these channels were activated by either KCl or by specific agonist, BAY-K8644. DA is known to either increase the function of L-type channels via the activation of DA D_1 receptors or decrease it via the activation of DA D_2 receptors (Tseng and O'Donnell 2004). Hence, the results presented by Steullet et al. (2008) suggested that a GSH deficit strengthened DA D_2 receptor-mediated decrease in the function of L-type calcium channels, occluding DA D_1 receptor-mediated increase in the function of these channels.

Regarding internal source of calcium, Steullet et al. (2008) have found that the alteration of DA signaling in GSH-deficient neurons required the redox-sensitive RyRs. Because of the enhanced function of RyRs under condition of oxidative stress, DA evoked a larger release of calcium from intracellular stores in neurons containing a low level of GSH than in normal control. This, in turn, promoted in GSH-deficient neurons a decrease in the function of L-type channels via DA D_2 receptor-mediated calcium-dependent pathway, whereas in control neurons, the function of these channels was enhanced. So, the deficit of GSH affected DA modulation of L-type channels but not the other calcium sources implicated in the responses to NMDA. As a consequence of the specific alteration of DA modulation of L-type channels, DA decreased NMDA responses in GSH-deficient neurons but increased them in normal neurons. So, GSH deficit, as that observed in some groups of schizophrenic patients (Do et al 2000; Yao et al. 2006; Gawryluk et al. 2011a), could play a significant role in the pathophysiology of this disease via dysregulation of dopaminergic and glutamatergic transmissions.

5.2.2 The Effect of Glutathione Deficiency on Glutamatergic System Function

In addition to dopaminergic abnormalities, also glutamatergic dysfunction has been associated with the pathogenesis of schizophrenia (Laruelle et al. 2003; Moghaddam 2003; Labrie and Roder 2010). Consistent with this view, reduced NMDA receptor function has been proposed as a cause of schizophrenia, because noncompetitive NMDA receptor antagonists like phencyclidine and ketamine induce psychotic and cognitive symptoms in healthy humans (Moghaddam 2003; Kantrowitz and Javitt 2010) and exacerbate symptoms in schizophrenic patients (Javitt and Zukin 1991; Krystal et al. 1994, 2005). Moreover, a loss of dendritic spines from cortical and hippocampal pyramidal neurons may be combined with the glutamatergic hypothesis of schizophrenia as NMDA receptors are present on their dendrites and probably dendritic spines. It is well documented that the vast majority of excitatory synapses (80–95 %) in the central nervous system are formed onto dendritic spines (Wilson 2007) and, as such, the spines perform a significant role in regulating neuronal excitability. In mature neuronal systems, pharmacological blockade of AMPA receptors or surgical deafferentation of glutamatergic inputs resulted in decreased spine density (Smart and Halpain 2000; Jacobs et al. 2003). Additionally, two recent studies showed that a constitutive reduction in NMDA receptor activity results in decreased spine density and cortical volume in the PFC and sensory cortex (Balu et al. 2012; DeVito et al. 2011). Although the loss of dendritic spines in schizophrenia was reported earlier (Glausier and Lewis 2012), the cause of NMDA receptor hypofunction in this disease has not been established as yet. However, an increasing number of experimental data suggest that GSH deficit may be an important factor contributing to this phenomenon (Steullet et al. 2006, 2010; Do et al. 2009). The potential role of DA in the loss of dendritic spines in condition of GSH deficiency

has been presented in section "The Potential Role of Glutathione Deficiency in the Amphetamine-Induced DA Release in Subcortical Regions of the Brain", whereas the role of this antioxidant in the regulation of NMDA and AMPA receptor functions is presented in Sect. 2.4.

GSH can affect NMDA receptor function via binding to its regulatory, redox-sensitive site and to glutamate recognition site. Redox sites of NMDA receptor are unusually sensitive to the oxidizing potential of the extracellular environment (Aizenman et al. 1989). Hence, oxidizing agents diminish NMDA receptor function, while reducing compounds, including GSH, enhance it (Köhr et al. 1994; Choi et al. 2001). Since GSH is the main regulator of the brain redox systems, it was assumed that GSH deficiency of the same magnitude as in schizophrenic patients (about 50 % of the control level) could lead to the dysfunction of NMDA receptors. A low GSH level could also alter NMDA receptor function via non-redox mechanisms because GSH can bind via its γ-glutamyl moiety to the glutamate recognition sites of NMDA and AMPA receptors and in this way modulate their function (Varga et al. 1997; see Sect. 2.4). To check experimentally whether GSH deficit could be a causal factor for NMDA hypofunction reported in schizophrenia, Steullet et al. (2006) examined in the CA1 region of the rat hippocampus how GSH deficit, induced by BSO administration, altered basal neurotransmission, cell excitability, and short-term and long-term plasticity. Using electrophysiological techniques, it was demonstrated that in hippocampal slices with low GSH level, the basal excitatory synaptic transmission that mostly depends on the AMPA receptor activation was not changed but NMDA receptor function was markedly depressed (Steullet et al. 2006). An extracellular level of GSH depends on its intracellular content and on the rate of GSH release from the glial compartment (Sagara et al. 1996; Hirrlinger et al. 2002b). Therefore, a deficit in intracellular GSH may result in a concomitant decrease in the extracellular content of this antioxidant. Consequently, the GSH deficit could lead to an excessive oxidation of the extracellular redox-sensitive site of NMDA receptors and to subsequent attenuation of their function. Results by Steullet et al. (2006) partially confirmed this view, as DTNB (5,5'-dithiobis(2-nitrobensoic acid)), a membrane-impermeable thiol-oxidizing compound, diminished pharmacologically isolated NMDA receptor-mediated field excitatory postsynaptic potentials (fEPSPs) in control, but not in BSO-treated slices. In turn, TCEP (tris(carboxyethyl)phosphine hydrochloride), a membrane-impermeable disulfide-reducing agent, increased NMDA responses more distinctly in BSO-treated slices than in control. These data indicate that under experimental conditions, the extracellular redox sites of NMDA receptors were fully oxidized in BSO-treated slices but were partially reduced in the control ones. Hence, the hypofunction of NMDA receptors under conditions of GSH deficit can be explained at least in part by an excessive oxidation of the extracellular redox-sensitive sites of NMDA receptors. In the above-reported study, it was also found that NMDA receptor-dependent long-term potentiation induced by high-frequency stimulation was impaired in GSH-depleted slices. The impairment of such synaptic plasticity could have adverse effects on normal brain functioning, including cognitive processing.

5.2.3 The Effect of Glutathione Deficiency on GABAergic System Function

An alteration of the GABAergic system in the prefrontal cortex (Lewis et al. 2005) and hippocampus (Zhang and Reynolds 2002) is a characteristic feature of the pathology of schizophrenia. Postmortem studies of these brain tissues have provided strong evidence that the GABAergic system is impaired in schizophrenia. These studies showed decreases in the concentration of cortical GABA (Perry et al 1979); in the activity of glutamic acid decarboxylase 67 (GAD-67), the GABA-synthesizing enzyme (Akbarian et al 1995; Hashimoto et al. 2003); and in the content of the calcium-binding protein parvalbumin (PV) in the fast-spiking interneurons (FSIs) of the prefrontal cortex and hippocampus (Hashimoto et al. 2003; Reynolds et al. 2004; Torrey et al. 2005). The existence of GABAergic deficit in schizophrenia was supported by in vivo studies using noninvasive methods. GABA measured in the human brain by magnetic resonance spectroscopy was shown to be decreased in schizophrenic patients (Rosso et al. 2006). Moreover, GABAergic inhibitory activity, as measured by transcranial magnetic stimulation (Daskalakis et al. 2002), was reduced.

NMDA receptor hypofunction could contribute to these abnormalities in the GABAergic system because the administration of NMDA receptor antagonists can cause the loss of parvalbumin and GAD-67 (Keilhoff et al. 2004; Kinney et al. 2006), alter GABA-mediated inhibitory control of cortical neurons (Homayoun and Moghaddam 2007), and disrupt the development of GABAergic neurons (Abekawa et al. 2007). Hence, the hypofunction of NMDA receptors induced by GSH deficiency (Sect. 5.2.2) could also affect the functioning of the GABAergic system in an indirect way. In line with this assumption, in the pharmacological (ODS rats treated with BSO + GBR during early postnatal development; see Sect. 5.1) and genetic ($Gclm^{-/-}$ mice) models of GSH deficiency, it was demonstrated that low level of this antioxidant caused a selective decrease of PV-ir interneurons in the rat prefrontal cortex (Cabungcal et al. 2006) and in the mouse dorsal hippocampus (Steullet et al. 2010). In the latter structure, a concomitant reduction of γ oscillations was also documented. Interestingly, γ oscillations were reduced in schizophrenic patients during impaired performance in cognitive tasks (Cho et al. 2006; Uhlhaas et al. 2008).

The decline of PV-ir FSIs has functional consequences because the activity of cortical pyramidal neurons is regulated by FSIs. These interneurons are necessary for the generation of γ neuronal synchrony that facilitates information processing and transfer within and between brain regions during cognitive tasks (Bartos et al. 2007; Sohal et al. 2009). Chronic GSH deficit in $Gclm^{-/-}$ mice affected the structural and functional integrity of PV-ir FSIs (Steullet et al. 2010), impairing information processing in the VH and leading to specific behavioral alterations, such as enhanced novelty-induced exploration and inadequate responses to stress described in more detail in Sect. 5.1. In conclusion, the alterations observed in the GABAergic system in animal models of GSH deficiency are consistent with that found in schizophrenic patients. Therefore, the participation of GSH deficiency in the pathogenesis of schizophrenia seems to be more and more convincing.

6 N-Acetylcysteine in the Treatment of Psychiatric Disorders

Considering GSH deficiency in the context of characteristic symptoms of schizophrenia, Matsuzawa et al. (2008) described the existence of a negative correlation between the brain GSH levels and the severity of negative symptoms of this disease. This observation suggested that agents increasing GSH levels could be potential therapeutic drugs for the treatment of negative symptoms of schizophrenia (Matsuzawa et al. 2008). The best thiol compound that fulfills such criterion seems to be N-acetylcysteine (NAC), as it acts as a precursor for GSH synthesis by supplying cysteine. NAC has been shown to penetrate successfully the blood-brain barrier and raise brain GSH levels in animal models (Farr et al. 2003). It enters the cell readily (Mazor et al 1996) and is then deacetylated to form L-cysteine. In addition to providing cysteine for GSH production, NAC acts as a direct antioxidant, although with less potency than that of GSH (Aruoma et al. 1989; Hussain et al. 1996).

For more than 30 years, NAC has been used for the treatment of paracetamol overdose, but now it is widely used as a mucolytic agent and in the treatment of HIV infection. As more information comes to light about NAC mode of action, its clinical applications are extending. Currently, potential application of NAC in the treatment of psychiatric disorders particularly in schizophrenia and bipolar disorder is being considered. Recently, in the double-blind, placebo-controlled study, it has been demonstrated that NAC addition (1 g twice daily over 24-week period) to antipsychotic therapy alleviated the negative symptoms, measured on the Positive and Negative Syndrom Scale. Furthermore, improvements in global functioning and reduction of abnormal movements, particularly akathisia, were also found in patients with chronic schizophrenia (Berk et al. 2008a). In addition, NAC relieved the depressive symptoms of bipolar disorder (BD) patients (Berk et al. 2008b). In another clinical study, Lavoie et al. (2008) reported that NAC application (1 g two times daily for 60 days) in schizophrenic patients mitigated an impaired mismatch negativity, which is an auditory evoked potential component related to NMDA receptor function. The abovementioned studies suggest that NAC has the potential to become a therapeutic drug for negative symptoms in schizophrenia and depressive symptoms in BD. These findings are particularly interesting because currently used antipsychotic drugs are rather ineffective against negative symptoms of schizophrenia.

References

Abdalla DS, Monteiro HP, Oliveira JA, Bechara EJ (1986) Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. Clin Chem 32: 805–807

Abekawa T, Ito K, Nakagawa S, Koyama T (2007) Prenatal exposure to an NMDA receptor antagonist, MK-801 reduces density of parvalbumin-immunoreactive GABAergic neurons in the medial prefrontal cortex and enhances phencyclidine-induced hyperlocomotion but not behavioral sensitization to methamphetamine in postpubertal rats. Psychopharmacology (Berl) 192:303–316

Aizenman E, Lipton SA, Loring RH (1989) Selective modulation of NMDA responses by reduction and oxidation. Neuron 2:1257–1263

Akbarian 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 schizophrenics. Arch Gen Psychiatry 52:258–266

Akyol O, Herken H, Uz E, Fadillioğlu E, Unal S, Söğüt S, Ozyurt H, Savaş HA (2002) The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients. The possible role of oxidant/antioxidant imbalance. Prog Neuropsychopharmacol Biol Psychiatry 26:995–1005

Altuntas I, Aksoy H, Coskun I, Cayköylü A, Akçay F (2000) Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. Clin Chem Lab Med 38:1277–1281

Amato A, Connolly CN, Moss SJ, Smart TG (1999) Modulation of neuronal and recombinant GABAA receptors by redox reagents. J Physiol 517:35–50

Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Ceresér KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Gonçalves CA (2007) Serum S100B and antioxidant enzymes in bipolar patient. J Psychiatr Res 41:523–529

Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN (2008) Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord 111:135–144

Andreazza AC, Shao L, Wang JF, Young LT (2010) Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry 67:360–368

Aoyama K, Suh SW, Hamby AM, Liu J, Chan WY, Chen Y, Swanson RA (2006) Neuronal glutathione deficiency and age-dependent neurodegeneration in the EAAC1 deficient mouse. Nat Neurosci 9:119–126

Aruoma OI, Halliwell B, Hoey BM, Butler J (1989) The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. Free Radic Biol Med 6:593–597

Baez S, Segura-Aguilar J, Widersten M, Johansson AS, Mannervik B (1997) Glutathione transferases catalyse the detoxication of oxidized metabolites (o-quinones) of catecholamines and may serve as an antioxidant system preventing degenerative cellular processes. Biochem J 324:25–28

Bains JS, Shaw CA (1997) Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. Brain Res Brain Res Rev 25:335–358

Bakare A, Shao L, Cui J, Young LT, Wang JF (2009) Mood stabilizing drugs lamotrigine and olanzapine increase expression and activity of glutathione S-transferase in primary cultured rat cerebral cortical cells. Neurosci Lett 455:70–73

Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL (2009) Glutathione dysregulation and the etiology and progression of human diseases. Biol Chem 390:191–214

Balu DT, Basu AC, Corradi JP, Cacace AM, Coyle JT (2012) The NMDA receptor co-agonists, D-serine and glycine, regulate neuronal dendritic architecture in the somatosensory cortex. Neurobiol Dis 45:671–682

Bartos M, Vida I, Jonas P (2007) Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 8:45–56

Ben Othmen L, Mechri A, Fendri C, Bost M, Chazot G, Gaha L, Kerkeni A (2008) Altered antioxidant defense system in clinically stable patients with schizophrenia and their unaffected siblings. Prog Neuropsychopharmacol Biol Psychiatry 32:155–159

Benes FM, Matzilevich D, Burke RE, Walsh J (2006) The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry 11:241–251

Ben-Yoseph O, Boxer PA, Ross BD (1996) Assessment of the role of the glutathione and pentose phosphate pathways in the protection of primary cerebrocortical cultures from oxidative stress. J Neurochem 66:2329–2337

Berhane K, Widersten M, Engström A, Kozarich JW, Mannervik B (1994) Detoxication of base propenals and other alpha, beta-unsaturated aldehyde products of radical reactions and lipid peroxidation by human glutathione transferases. Proc Natl Acad Sci U S A 91:1480–1484

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Judd F, Katz F, Katz P, Ording-Jespersen S, Little J, Conus P, Cuenod M, Do KQ, Bush AI (2008a) N-acetyl cysteine as a glutathione precursor for schizophrenia–a double-blind, randomized, placebo-controlled trial. Biol Psychiatry 64:361–368

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008b) N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468–475

Bitanihirwe BK, Woo TU (2011) Oxidative stress in schizophrenia: an integrated approach. Neurosci Biobehav Rev 35:878–893

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A 94:2569–2574

Broquist HP (1992) Buthionine sulfoximine, an experimental tool to induce glutathione deficiency: elucidation of glutathione and ascorbate in their role as antioxidants. Nutr Rev 50:110–111

Bull R, Marengo JJ, Finkelstein JP, Behrens MI, Alvarez O (2003) SH oxidation coordinates subunits of rat brain ryanodine receptor channels activated by calcium and ATP. Am J Physiol Cell Physiol 285:C119–C128

Cabungcal JH, Nicolas D, Kraftsik R, Cuénod M, Do KQ, Hornung J-P (2006) Glutathione deficit during development induces anomalies in the rat anterior cingulate GABAergic neurons: relevance to schizophrenia. Neurobiol Dis 22:624–637

Cabungcal JH, Preissmann D, Delseth C, Cuénod M, Do KQ, Schenk F (2007) Transitory glutathione deficit during brain development induces cognitive impairment in juvenile and adult rats: relevance to schizophrenia. Neurobiol Dis 26:634–645

Callicott JH, Bertolino A, Egan MF, Mattay VS, Langheim FJ, Weinberger DR (2000) Selective relationship between prefrontal N-acetylaspartate measures and negative symptoms in schizophrenia. Am J Psychiatry 157:1646–1651

Campbell DL, Stamler JS, Strauss HC (1996) Redox modulation of L-type calcium channels in ferret ventricular myocytes. Dual mechanism regulation by nitric oxide and S-nitrosothiols. J Gen Physiol 108:277–293

Castagné V, Cuenod M, Do KQ (2004a) An animal model with relevance to schizophrenia: sex-dependent cognitive deficits in osteogenic disorder-Shionogi rats induced by glutathione synthesis and dopamine uptake inhibition during development. Neuroscience 123:821–834

Castagné V, Rougemont M, Cuenod M, Do KQ (2004b) Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia. Neurobiol Dis 15:93–105

Che Y, Wang JF, Shao L, Young T (2010) Oxidative damage to RNA but not DNA in the hippocampus of patients with major mental illness. J Psychiatry Neurosci 35:296–302

Chen Y, Swanson RA (2003) The glutamate transporters EAAT2 and EAAT3 mediate cysteine uptake in cortical neuron cultures. J Neurochem 84:1332–1339

Chen Y, Shertzer HG, Schneider SN, Nebert DW, Dalton TP (2005) Glutamate cysteine ligase catalysis: dependence on ATP and modifier subunit for regulation of tissue glutathione levels. J Biol Chem 280:33766–33774

Cho RY, Konecky RO, Carter CS (2006) Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci U S A 103:19878–19883

Choi Y, Chen HV, Lipton SA (2001) Three pairs of cysteine residues mediate both redox and Zn2+ modulation of the NMDA receptor. J Neurosci 21:392–400

Commandeur JN, Stijntjes GJ, Vermeulen NP (1995) Enzymes and transport systems involved in the formation and disposition of glutathione S-conjugates. Role in bioactivation and detoxication mechanisms of xenobiotics. Pharmacol Rev 47:271–330

Cui J, Shao L, Young LT, Wang JF (2007) Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. Neuroscience 2007(144):1447–1453

Dagnino-Subiabre A, Cassels BK, Baez S, Johansson AS, Mannervik B, Segura-Aguilar J (2000) Glutathione transferase M2-2 catalyzes conjugation of dopamine and dopa o-quinones. Biochem Biophys Res Commun 274:32–36

Dalle-Donne I, Rossi R, Giustarini D, Colombo R, Milzani A (2007) S-glutathionylation in protein redox regulation. Free Radic Biol Med 43:883–898

Dalton TP, Dieter MZ, Yang Y, Shertzer HG, Nebert DW (2000) Knockout of the mouse glutamate cysteine ligase catalytic subunit (Gclc) gene: embryonic lethal when homozygous, and proposed model for moderate glutathione deficiency when heterozygous. Biochem Biophys Res Commun 279:324–329

Dalton TP, Chen Y, Schneider SN, Nebert DW, Shertzer HG (2004) Genetically altered mice to evaluate glutathione homeostasis in health and disease. Free Radic Biol Med 37:1511–1526

Danion JM, Rizzo L, Bruant A (1999) Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. Arch Gen Psychiatry 56:639–644

Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S (2002) Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. Arch Gen Psychiatry 59:347–354

Deicken RF, Johnson C, Eliaz Y, Schuff N (2000) Reduced concentrations of thalamic N-acetylaspartate in male patients with schizophrenia. Am J Psychiatry 157:644–647

DeVito LM, Balu DT, Kanter BR, Lykken C, Basu AC, Coyle JT, Eichenbaum H (2011) Serine racemase deletion disrupts memory for order and alters cortical dendritic morphology. Genes Brain Behav 10:210–222

DiChiara TJ, Reinhart PH (1997) Redox modulation of hslo Ca2+–activated K+ channels. J Neurosci 17:4942–4955

Dickinson DA, Levonen AL, Moellering DR, Arnold EK, Zhang H, Darley-Usmar VM, Forman HJ (2004) Human glutamate cysteine ligase gene regulation through the electrophile response element. Free Radic Biol Med 37:1152–1159

Dietrich-Muszalska A, Olas B, Głowacki R, Bald E (2009) Oxidative/nitrative modifications of plasma proteins and thiols from patients with schizophrenia. Neuropsychobiology 59:1–7

Do KQ, Trabesinger AH, Kirsten-Krüger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P, Cuénod M (2000) Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur J Neurosci 12:3721–3728

Do KQ, Bovet P, Cuenod M (2004) Schizophrenia: glutathione deficit as a new vulnerability factor of for the disconnectivity syndrome. Swiss Arch Neurol Psychiatry 155:375–385

Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M (2009) Redox dysregulation, neurodevelopment, and schizophrenia. Curr Opin Neurobiol 19:220–230

Doniger GM, Silipo G, Rabinowicz EF, Snotgrass JG, Javitt DC (2001) Impaired sensory processing as a basis for object-recognition deficits in schizophrenia. Am J Psychiatry 158:1818–1826

Dringen R (2000) Metabolism and functions of glutathione in brain. Prog Neurobiol 62:649–671

Dringen R, Hamprecht B (1997) Involvement of glutathione peroxidase and catalase in the disposal of exogenous hydrogen peroxide by cultured astroglial cells. Brain Res 759:67–75

Dringen R, Kranich O, Hamprecht B (1997) The gamma-glutamyl transpeptidase inhibitor acivicin preserves glutathione released by astroglial cells in culture. Neurochem Res 22:727–733

Dringen R, Kussmaul L, Hamprecht B (1998) Rapid clearance of tertiary butyl hydroperoxide by cultured astroglial cells via oxidation of glutathione. Glia 23:139–145

Dringen R, Pfeiffer B, Hamprecht B (1999) Synthesis of the antioxidant glutathione in neurons: supply by astrocytes of CysGly as precursor for neuronal glutathione. J Neurosci 19:562–569

Esposito F, Ammendola R, Faraonio R, Russo T, Cimino F (2004) Redox control of signal transduction, gene expression and cellular senescence. Neurochem Res 29:617–628

Esterbauer H, Schaur RJ, Zollner H (1991) Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med 11:81–128

Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP (2003) Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. Prostaglandins Leukot Essent Fatty Acids 69:393–399

Farr SA, Poon HF, Dogrukol-Ak D, Drake J, Banks WA, Eyerman E, Butterfield DA, Morley JE (2003) The antioxidants alpha-lipoic acid and N-acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice. J Neurochem 84:1173–1183

Franklin CC, Backos DS, Mohar I, White CC, Forman HJ, Kavanagh TJ (2009) Structure, function, and post-translational regulation of the catalytic and modifier subunits of glutamate cysteine ligase. Mol Aspects Med 30:86–98

Fuchs EC, Zivkovic AR, Cunningham MO, Middleton S, Lebeau FE, Bannerman DM, Rozov A, Whittington MA, Traub RD, Rawlins JN, Monyer H (2007) Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. Neuron 53:591–604

Garey L (2010) When cortical development goes wrong: schizophrenia as a neurodevelopmental disease of microcircuits. J Anat 217:324–333

Gaskin S, Gamliel A, Tardif M, Cole E, Mumby DG (2009) Incidental (unreinforced) and reinforced spatial learning in rats with ventral and dorsal lesions of the hippocampus. Behav Brain Res 202:64–70

Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT (2011a) Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int J Neuropsychopharmacol 14:123–130

Gawryluk JW, Wang JF, Andreazza AC, Shao L, Yatham LN, Young LT (2011b) Prefrontal cortex glutathione S-transferase levels in patients with bipolar disorder, major depression and schizophrenia. Int J Neuropsychopharmacol 14:1069–1074

Gipp JJ, Chang C, Mulcahy RT (1992) Cloning and nucleotide sequence of a full-length cDNA for human liver gamma-glutamylcysteine synthetase. Biochem Biophys Res Commun 185:29–35

Glanz LA, Lewis DA (2000) Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 57:65–73

Glausier JR, Lewis DA (2012) Dendritic spine pathology in schizophrenia. Neuroscience 251: 90–107. http://dx.doi.org/10.1016/j..neuroscience.2012.04.044

Goldman MB, Mitchell CP (2004) What is the functional significance of hippocampal pathology in schizophrenia? Schizophr Bull 30:367–392

Goldman-Rakic PS, Leranth C, Williams SM, Mons N, Geffard M (1989) Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. Proc Natl Acad Sci U S A 86:9015–9019

Grant CM, MacIver FH, Dawes IW (1997) Glutathione synthetase is dispensable for growth under both normal and oxidative stress conditions in the yeast Saccharomyces cerevisiae due to an accumulation of the dipeptide gamma-glutamylcysteine. Mol Biol Cell 8:1699–1707

Grima G, Benz B, Parpura V, Cuenod M, Do KQ (2003) Dopamine-induced oxidative stress in neurons with glutathione deficit: implication for schizophrenia. Schizophr Res 62:213–224

Gysin R, Kraftsik R, Sandell J, Bovet P, Chappuis C, Conus P, Deppen P, Preisig M, Ruiz V, Steullet P, Tosic M, Werge T, Cuénod M, Do KQ (2007) Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. Proc Natl Acad Sci U S A 104:16621–16626

Gysin R, Riederer IM, Cuénod M, Do KQ, Riederer BM (2009) Skin fibroblast model to study an impaired glutathione synthesis: consequences of a genetic polymorphism on the proteome. Brain Res Bull 79:46–52

Gysin R, Kraftsik R, Boulat O, Bovet P, Conus P, Comte-Krieger E, Polari A, Steullet P, Preisig M, Teichmann T, Cuénod M, Do KQ (2011) Genetic dysregulation of glutathione synthesis predicts alteration of plasma thiol redox status in schizophrenia. Antioxid Redox Signal 15:2003–2010

Harrison PJ (1997) Schizophrenia: a disorder of neurodevelopment? Curr Opin Neurobiol 7:285–289

Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, Sampson AR, Lewis DA (2003) Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J Neurosci 23:6315–6326

Hastings TG, Lewis DA, Zigmond MJ (1996) Role of oxidation in the neurotoxic effects of intrastriatal dopamine injections. Proc Natl Acad Sci U S A 93:1956–1961

Hayashi T, Kagaya A, Takebayashi M, Oyamada T, Inagaki M, Tawara Y, Yokota N, Horiguchi J, Su TP, Yamawaki S (1997) Effect of dantrolene on KCl- or NMDA-induced intracellular Ca2+ changes and spontaneous Ca2+ oscillation in cultured rat frontal cortical neurons. J Neural Transm 104:811–824

Heales SJ, Davies SE, Bates TE, Clark JB (1995) Depletion of brain glutathione is accompanied by impaired mitochondrial function and decreased N-acetyl aspartate concentration. Neurochem Res 20:31–38

Heckers S, Curran T, Goff D, Rauch SL, Fischman AJ, Alpert NM, Schacter DL (2000) Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. Biol Psychiatry 48:651–657

Herken H, Uz E, Ozyurt H, Söğüt S, Virit O, Akyol O (2001) Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia. Mol Psychiatry 6:66–73

Himi T, Ikeda M, Yasuhara T, Nishida M, Morita I (2003) Role of neuronal glutamate transporter in the cysteine uptake and intracellular glutathione levels in cultured cortical neurons. J Neural Transm 110:1337–1348

Hirrlinger J, Schulz JB, Dringen R (2002a) Effects of dopamine on the glutathione metabolism of cultured astroglial cells: implications for Parkinson's disease. J Neurochem 82:458–467

Hirrlinger J, Schulz JB, Dringen R (2002b) Glutathione release from cultured brain cells: multidrug resistance protein 1 mediates the release of GSH from rat astroglial cells. J Neurosci Res 69:318–326

Hjelle OP, Rinvik E, Huster D, Reichelt W, Ottersen OP (1998) Antibodies to glutathione: production, characterization, and immunocytochemical application to the central nervous system. In: Shaw CA (ed) Glutathione in the nervous system. Taylor & Francis, Washington, DC, pp 63–88

Hogg N (2002) The biochemistry and physiology of S-nitrosothiols. Annu Rev Pharmacol Toxicol 42:585–600

Homayoun H, Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 27:11496–11500

Hussain S, Slikker W Jr, Ali SF (1996) Role of metallothionein and other antioxidants in scavenging superoxide radicals and their possible role in neuroprotection. Neurochem Int 29:145–152

Jacobs B, Creswell J, Britt JP, Ford KL, Bogen JE, Zaidel E (2003) Quantitative analysis of cortical pyramidal neurons after corpus callosotomy. Ann Neurol 54:126–130

Jacobsen JP, Rodriguiz RM, Mørk A, Wetsel WC (2005) Monoaminergic dysregulation in glutathione-deficient mice: possible relevance to schizophrenia? Neuroscience 132:1055–1072

Jain A, Mårtensson J, Stole E, Auld PA, Meister A (1991) Glutathione deficiency leads to mitochondrial damage in brain. Proc Natl Acad Sci U S A 88:1913–1917

Jánaky R, Varga V, Jenei Z, Saransaari P, Oja SS (1998) Glutathione and glutathione derivatives: possible modulators of ionotropic glutamate receptors. In: Shaw CA (ed) Glutathione in the nervous system. Taylor & Francis, Washington, DC, pp 163–196

Janáky R, Ogita K, Pasqualotto BA, Bains JS, Oja SS, Yoneda Y, Shaw CA (1999) Glutathione and signal transduction in the mammalian CNS. J Neurochem 73:889–902

Janáky R, Shaw CA, Varga V, Hermann A, Dohovics R, Saransaari P, Oja SS (2000) Specific glutathione binding sites in pig cerebral cortical synaptic membranes. Neuroscience 95:617–624

Janowsky DS, Risch C (1979) Amphetamine psychosis and psychotic symptoms. Psychopharmacology (Berl) 65:73–77

Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308

Jones DP (2006) Redefining oxidative stress. Antioxid Redox Signal 8:1865–1879

Jones DP (2008) Radical-free biology of oxidative stress. Am J Physiol Cell Physiol 295:C849–C868

Kane JM, Marder SR (1993) Psychopharmacologic treatment of schizophrenia. Schizophr Bull 19:287–302

Kantrowitz JT, Javitt DC (2010) N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? Brain Res Bull 83:108–121

Keilhoff G, Becker A, Grecksch G, Wolf G, Bernstein HG (2004) Repeated application of ketamine to rats induces changes in the hippocampal expression of parvalbumin, neuronal nitric oxide synthase and cFOS similar to those found in human schizophrenia. Neuroscience 126:591–598

Kemp M, Go YM, Jones DP (2008) Nonequilibrium thermodynamics of thiol/disulfide redox systems: a perspective on redox systems biology. Free Radic Biol Med 44:921–937

Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM (2006) A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. J Neurosci 26:1604–1615

Köhr G, Eckardt S, Lüddens H, Monyer H, Seeburg PH (1994) NMDA receptor channels: subunit-specific potentiation by reducing agents. Neuron 12:1031–1040

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Krystal JH, Perry EB Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985–994

Kulak A, Cuenod M, Do KQ (2012) Behavioral phenotyping of glutathione-deficient mice: relevance to schizophrenia and bipolar disorder. Behav Brain Res 226:563–570

Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N (2002) Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct 20:171–175

Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, Belmonte-de-Abreu PS, Berk M, Kapczinski F (2008) Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32:1677–1681

Labrie V, Roder JC (2010) The involvement of the NMDA receptor D-serine/glycine site in the pathophysiology and treatment of schizophrenia. Neurosci Biobehav Rev 34:351–372

Lada MW, Kennedy RT (1997) In vivo monitoring of glutathione and cysteine in rat caudate nucleus using microdialysis on-line with capillary zone electrophoresis-laser induced fluorescence detection. J Neurosci Methods 72:153–159

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93:9235–9240

Laruelle M, Kegeles LS, Abi-Dargham A (2003) Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. Ann N Y Acad Sci 1003:138–158

Lavoie S, Murray MM, Deppen P, Knyazeva MG, Berk M, Boulat O, Bovet P, Bush AI, Conus P, Copolov D, Fornari E, Meuli R, Solida A, Vianin P, Cuénod M, Buclin T, Do KQ (2008) Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33:2187–2199

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

Lu SC (2009) Regulation of glutathione synthesis. Mol Aspects Med 30:42–59

Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr, da Silva VR, Kapczinski F, Portela LV, Souza DO, Salvador M, Gentil V (2007) Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett 421:33–36

Masukawa T, Sai M, Tochino Y (1989) Methods for depleting brain glutathione. Life Sci 44:417–424

Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H, Iyo M, Hashimoto K (2008) Negative correlation between brain glutathione level and negative symptoms in schizophrenia: a 3 T 1H-MRS study. PLoS One 3:e1944

Mazor D, Golan E, Philip V, Katz M, Jafe A, Ben-Zvi Z, Meyerstein N (1996) Red blood cell permeability to thiol compounds following oxidative stress. Eur J Haematol 57:241–246
Micó JA, Rojas-Corrales MO, Gibert-Rahola J, Parellada M, Moreno D, Fraguas D, Graell M, Gil J, Irazusta J, Castro-Fornieles J, Soutullo C, Arango C, Otero S, Navarro A, Baeza I, Martínez-Cengotitabengoa M, González-Pinto A (2011) Reduced antioxidant defense in early onset first-episode psychosis: a case–control study. BMC Psychiatry 11:26
Mieyal JJ, Gallogly MM, Qanungo S, Sabens EA, Shelton MD (2008) Molecular mechanisms and clinical implications of reversible protein S-glutathionylation. Antioxid Redox Signal 10:1941–1988
Moghaddam B (2003) Bringing order to the glutamate chaos in schizophrenia. Neuron 40:881–884
Mukerjee S, Mahadik SP, Scheffer R, Correnti EE, Kelkar H (1996) Impaired antioxidant defense at the onset of psychosis. Schizophr Res 19:19–26
Murphy TH, Schnaar RL, Coyle JT (1990) Immature cortical neurons are uniquely sensitive to glutamate toxicity by inhibition of cystine uptake. FASEB J 1990(4):1624–1633
Nanda D, Telputt J, Collard KJ (1996) Changes in brain glutathione levels during postnatal development in the rat. Dev Brain Res 94:238–241
Ng F, Berk M, Dean O, Bush AI (2008) Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol 11:851–876
Ogita K, Shuto M, Maeda H, Minami T, Yoneda Y (1998) Possible modulation by glutathione of glutamatergic neurotransmission. In: Shaw CA (ed) Glutathione in the nervous system. Taylor & Francis, Washington, DC, pp 137–161
Oja SS, Janáky R, Varga V, Saransaari P (2000) Modulation of glutamate receptor functions by glutathione. Neurochem Int 37:299–306
Ozcan ME, Gulec M, Ozerol E, Polat R, Akyol O (2004) Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clin Psychopharmacol 19:89–95
Pasqualotto BA, Curry K, Shaw CA (1998) Excitatory actions of GSH on neocortex. In: Shaw CA (ed) Glutathione in the nervous system. Taylor & Francis, Washington, DC, pp 197–227
Perry TL, Kish SJ, Buchanan J, Hansen S (1979) Gamma-aminobutyric-acid deficiency in brain of schizophrenic patients. Lancet 1:237–239
Rabinovic AD, Hastings TG (1998) Role of endogenous glutathione in the oxidation of dopamine. J Neurochem 71:2071–2078
Raffa M, Mechri A, Othman LB, Fendri C, Gaha L, Kerkeni A (2009) Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 33:1178–1183
Raffa M, Atig F, Mhalla A, Kerkeni A, Mechri A (2011) Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. BMC Psychiatry 11:124
Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP (2003) Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. Psychiatry Res 121:109–122
Rauhala P, Lin AM, Chiueh CC (1998) Neuroprotection by S-nitrosoglutathione of brain dopamine neurons from oxidative stress. FASEB J 12:165–173
Reddy R, Sahebarao MP, Mukherjee S, Murthy JN (1991) Enzymes of the antioxidant defense system in chronic schizophrenic patients. Biol Psychiatry 30:409–412
Reynolds GP, Abdul-Monim Z, Neill JC, Zhang ZJ (2004) Calcium binding protein markers of GABA deficits in schizophrenia–postmortem studies and animal models. Neurotox Res 6:57–61
Richman PG, Meister A (1975) Regulation of gamma-glutamyl-cysteine synthetase by nonallosteric feedback inhibition by glutathione. J Biol Chem 250:1422–1426
Rosso IM, Coyle JT, Ke J, Gruber SA, Olson DP, Renshaw PF, Yurgelun-Todd DA (2006) Cingulate cortex GABA concentration in schizophrenia: a two-dimensional proton magnetic resonance spectroscopy study. Biol Psychiatry 59(Suppl):1515
Rougemont M, Do KQ, Castagné V (2002) New model of glutathione deficit during development: effect on lipid peroxidation in the rat brain. J Neurosci Res 70:774–783

Sagara J, Makino N, Bannai S (1996) Glutathione efflux from cultured astrocytes. J Neurochem 66:1876–1881
Salinas AE, Wong MG (1999) Glutathione S-transferases–a review. Curr Med Chem 6:279–309
Seelig GF, Simondsen RP, Meister A (1984) Reversible dissociation of gamma-glutamylcysteine synthetase into two subunits. J Biol Chem 259:9345–9347
Seeman P, Chau-Wong M, Tedesco J, Wong K (1975) Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci U S A 72:4376–4380
Selemon LD, Goldman-Rakic PS (1999) The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry 45:17–25
Sen CK (2000) Cellular thiols and redox-regulated signal transduction. Curr Top Cell Regul 36:1–30
Shanker G, Allen JW, Mutkus LA, Aschner M (2001) The uptake of cysteine in cultured primary astrocytes and neurons. Brain Res 902:156–163
Shao L, Cui J, Young LT, Wang JF (2008) The effect of mood stabilizer lithium on expression and activity of glutathione s-transferase isoenzymes. Neuroscience 151:518–524
Shaw CA, Pasqualotto BA, Curry K (1996) Glutathione-induced sodium currents in neocortex. Neuroreport 7:1149–1152
Shih AY, Erb H, Sun X, Toda S, Kalivas PW, Murphy TH (2006) Cystine/glutamate exchange modulates glutathione supply for neuroprotection from oxidative stress and cell proliferation. J Neurosci 26:10514–10523
Shukitt-Hale B, Denisova NA, Strain JG, Joseph JA (1997) Psychomotor effects of dopamine infusion under decreased glutathione conditions. Free Radic Biol Med 23:412–418
Shukitt-Hale B, Erat SA, Joseph JA (1998) Spatial learning and memory deficits induced by dopamine administration with decreased glutathione. Free Radic Biol Med 24:1149–1158
Smart FM, Halpain S (2000) Regulation of dendritic spine stability. Hippocampus 10:542–554
Sohal VS, Zhang F, Yizhar O, Deisseroth K (2009) Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. Nature 459:698–702
Steckert AV, Valvassori SS, Moretti M, Dal-Pizzol F, Quevedo J (2010) Role of oxidative stress in the pathophysiology of bipolar disorder. Neurochem Res 35:1295–1301
Steullet P, Neijt HC, Cuenod M, Do KQ (2006) Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: relevance to schizophrenia. Neuroscience 137:807–819
Steullet P, Lavoie S, Kraftsik R, Guidi R, Gysin R, Cuénod M, Do KQ (2008) A glutathione deficit alters dopamine modulation of L-type calcium channels via D2 and ryanodine receptors in neurons. Free Radic Biol Med 44:1042–1054
Steullet P, Cabungcal JH, Kulak A, Kraftsik R, Chen Y, Dalton TP, Cuenod M, Do KQ (2010) Redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations, and related behaviors. J Neurosci 17:2547–2558
Stevens JR, Casanova MF (1988) Is there a neuropathology of schizophrenia? Biol Psychiatry 24:727–729
Thomas DD, Ridnour LA, Espey MG, Donzelli S, Ambs S, Hussain SP, Harris CC, DeGraff W, Roberts DD, Mitchell JB, Wink DA (2006) Superoxide fluxes limit nitric oxide-induced signaling. J Biol Chem 281:25984–25993
Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB (2005) Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. Biol Psychiatry 57:252–260
Tosic M, Ott J, Barral S, Bovet P, Deppen P, Gheorghita F, Matthey ML, Parnas J, Preisig M, Saraga M, Solida A, Timm S, Wang AG, Werge T, Cuénod M, Do KQ (2006) Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene. Am J Hum Genet 79:586–592
Tseng KY, O'Donnell P (2004) Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. J Neurosci 24:5131–5139
Uhlhaas PJ, Haenschel C, Nikolić D, Singer W (2008) The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. Schizophr Bull 34:927–943

Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39:44–84

Varga V, Jenei Z, Janáky R, Saransaari P, Oja SS (1997) Glutathione is an endogenous ligand of rat brain N-methyl-D-aspartate (NMDA) and 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors. Neurochem Res 22:1165–1171

Wang JF, Shao L, Sun X, Young LT (2009) Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. Bipolar Disord 11:523–529

Wilson CJ (2007) GABAergic inhibition in the neostriatum. Prog Brain Res 160:91–110

Winterbourn CC, Metodiewa D (1994) The reaction of superoxide with reduced glutathione. Arch Biochem Biophys 314:284–290

Xie C, Lovell MA, Markesbery WR (1998) Glutathione transferase protects neuronal cultures against four hydroxynonenal toxicity. Free Radic Biol Med 25:979–988

Yamasue H, Fukui T, Fukuda R, Yamada H, Yamasaki S, Kuroki N, Abe O, Kasai K, Tsujii K, Iwanami A, Aoki S, Ohtomo K, Kato N, Kato T (2002) 1H-MR spectroscopy and gray matter volume of the anterior cingulate cortex in schizophrenia. Neuroreport 13:2133–2137

Yang CS, Chou ST, Lin NN, Liu L, Tsai PJ, Kuo JS, Lai JS (1994) Determination of extracellular glutathione in rat brain by microdialysis and high-performance liquid chromatography with fluorescence detection. J Chromatogr B Biomed Appl 661:231–235

Yang Y, Dieter MZ, Chen Y, Shertzer HG, Nebert DW, Dalton TP (2002) Initial characterization of the glutamate-cysteine ligase modifier subunit Gclm(−/−) knockout mouse. Novel model system for a severely compromised oxidative stress response. J Biol Chem 277:49446–49452

Yang Y, Chen Y, Johansson E, Schneider SN, Shertzer HG, Nebert DW, Dalton TP (2007) Interaction between the catalytic and modifier subunits of glutamate-cysteine ligase. Biochem Pharmacol 74:372–381

Yao JK, Keshavan MS (2011) Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid Redox Signal 15:2011–2035

Yao JK, Reddy R, McElhinny LG, van Kammen DP (1998) Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. J Psychiatr Res 32:385–391

Yao JK, Reddy RD, van Kammen DP (1999) Human plasma glutathione peroxidase and symptom severity in schizophrenia. Biol Psychiatry 45:1512–1515

Yao JK, Leonard S, Reddy R (2006) Altered glutathione redox state in schizophrenia. Dis Markers 22:83–93

Zängerle L, Cuénod M, Winterhalter KH, Do KQ (1992) Screening of thiol compounds: depolarization-induced release of glutathione and cysteine from rat brain slices. J Neurochem 59:181–189

Zhang ZJ, Reynolds GP (2002) A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. Schizophr Res 55:1–10

Zhang XY, Tan YL, Cao LY, Wu GY, Xu Q, Shen Y, Zhou DF (2006) Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. Schizophr Res 81:291–300

Zhang XY, Tan YL, Zhou DF, Cao LY, Wu GY, Haile CN, Kosten TA, Kosten TR (2007) Disrupted antioxidant enzyme activity and elevated lipid peroxidation products in schizophrenic patients with tardive dyskinesia. J Clin Psychiatry 68(5):754–760