Oxidative Stress in Psychiatric Disorders

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4.1 Introduction

Oxidative stress has been postulated as one of the pathophysiologic mechanisms implicated in various medical conditions, including neurologic and psychiatric disorders. In this chapter, we will start with the definition of oxidative stress, sources of cellular oxidative stress, and key components of the anti-oxidation system in the body. Then, we will summarize the evidence supporting the role of oxidative stress in various psychiatric disorders. We will also describe the molecular pharmacology of N-Acetylcysteine (NAC), a medication that has been shown to reduce oxidative stress. Finally, we will conclude by explaining the role of NAC in decreasing oxidative stress in psychiatric disorders.

4.2 Oxidative Stress and the Anti-oxidation System

4.2.1 Oxidative Stress

Oxidative stress is defined as an imbalance between the levels of prooxidants and antioxidants. This phenomenon is known to result in damage to macromolecules (i.e., proteins and DNA) and activation of redox-sensitive signals. The reactions to macromolecules are generally caused by prooxidant reactive chemicals containing oxygen or nitrogen and are called reactive oxygen species (ROS) and reactive nitrogen species (RNS), respectively.

One main source of ROS is the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) complexes in cell membranes and other cell organelles including mitochondria, peroxisomes, and endoplasmic reticulum. Mitochondria

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convert energy for the cell into a usable form, adenosine triphosphate (ATP), by oxidative phosphorylation. This process involves reduction of oxygen to water. However, this process does not occur perfectly all the time. A small percentage of oxidative phosphorylation will reduce the oxygen prematurely and form superoxide radical ($O_2^{-\bullet}$). The superoxide radical can then initiate lipid peroxidation. The lipid hydroperoxide will then be transformed to lipid radicals, which can further cause damage in cell membranes and even trigger a cascade of events leading to apoptosis. Other examples of ROS include singlet oxygen ($^1O_2$), hydroperoxyl radical ($HO_2^{\bullet}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\bullet}$), hydroxyl anion (OH^-), peroxyl radical ($ROO^{\bullet}$), lipid peroxyl radical ($LOO^{\bullet}$), hypochlorous acid (HOCl), hypobromous acid (HOBr), and hypothiocyanous acid (HOSCN) (Moniczewski et al. 2015). In regard to RNS, the key source is nitric oxide ($NO^{\bullet}$). Other examples of RNS include nitrogen dioxide ($NO_2^{\bullet}$), peroxynitrite ($ONOO^-$), nitrite (NO_2^-), nitrate (NO_3^-), and nitronium ion (NO_2^+). Nitrite is often used as a marker of NO activity. In addition to endogenous sources, ROS and RNS can also come from exogenous sources such as medications and environmental toxicants.

4.2.2 Antioxidant Systems in the Body

Under normal physiologic conditions, the body can neutralize ROS and RNS by anti-oxidation systems before significant cellular damage occurs. These systems can reverse oxidative damage by supplying electrons to ROS, RNS, proteins, and electrophilic xenobiotics, thereby maintaining redox balance. Superoxide radicals are typically transformed to hydrogen peroxide by superoxide dismutase (SOD). The resulting hydrogen peroxide is then converted to water by either catalase (CAT) or glutathione peroxidase (GPX). The glutathione system is the predominant antioxidant system in our body. Glutathione exists in two forms: reduced glutathione (GSH) and oxidized glutathione (GSSG) (see Fig. 4.1). The biotransformation between the two forms is central to the regulation of redox balance in the brain. The oxidation of GSH to GSSG is catalyzed by GPX, the same enzyme that converts hydrogen peroxide to water. This GSH→GSSG reaction is key in protecting proteins by coupling with the reduction of thiol groups in proteins via glutaredoxins (GRXs). The reduction of GSSG back to GSH is catalyzed by glutathione reductase (GR), which uses NADPH as a cofactor. In addition to the above biochemical functions, GSH plays a key role in neutralizing electrophilic xenobiotic compounds by conjugating to them via glutathione-*S*-transferases (GSTs). Other endogenous antioxidants include vitamin E and vitamin C, which convert lipid peroxyl radicals to stable vitamin radicals. Collectively, the anti-oxidation system plays a key role in cellular redox homeostasis and has special relevance to pathophysiology of several psychiatric disorders (e.g., schizophrenia and autism) and neurologic diseases (e.g., Alzheimer's disease and Parkinson's disease).

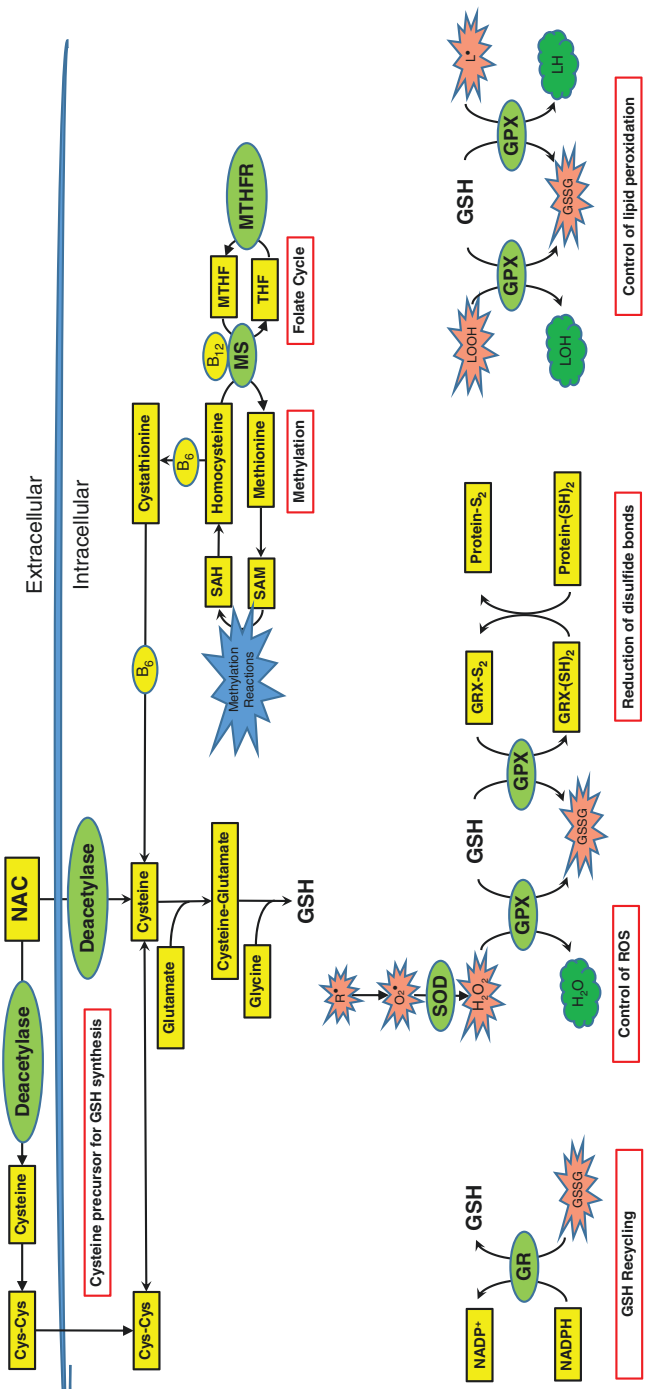

Fig. 4.1 Anti-oxidation systems of the body involving glutathione and the role of N-Acetylcysteine (NAC) in restoring glutathione

4.2.3 Biomarkers of Oxidative Stress

The level of oxidative stress can be assessed peripherally by measuring the concentrations of GSH and GSSG using high-performance liquid chromatography (HPLC) and fluorimetric assays and in the central nervous system using proton magnetic resonance spectroscopy (^{1}H MRS). Other common biomarkers of oxidative stress include the enzyme activities of CAT, GPX, and SOD. In addition to oxidative stress, downstream processes such as lipid peroxidation, oxidative protein damage, and oxidative DNA damage can also be monitored. Aconitase activity has been employed as a biomarker of mitochondrial superoxide production. Thiobarbituric acid reactive substances (TBARS) are common biomarkers for lipid peroxidation. 3-nitrotyrosine (3-NT) has been used to assess oxidative protein damage. 8-oxo-deoxyguanosine (8-oxo-dG) is a biomarker of oxidative DNA damage. 3-chlorotyrosine (3-CT) is an established biomarker of a chronic inflammatory response.

4.2.4 Oxidative Stress in the Developing Brain

Neurons are highly susceptible to oxidative damage due to high levels of ROS and RNS production, relatively low amounts of antioxidant enzymes, the high brain's lipid content and metabolic rate, and the non-regenerative nature of neurons. Of particular interest is the developing brain that has a high metabolic rate. When low levels of antioxidants and high levels of heavy metal ions are present, ROS levels will become elevated. The developing brain at an early age is sensitive to even small changes to redox balance, which can affect the signaling pathways and processes involved in neurogenesis, neuronal differentiation, and myelination. Therefore, oxidative stress is associated with neuronal injury in the developing brain when subjected to hypoxia, ischemia, and traumatic brain injury. Consequently, these insults may derail brain development and result in neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia.

4.3 Oxidative Stress and Psychiatric Disorders

Oxidative stress has been implicated in various psychiatric disorders including ASD, schizophrenia, bipolar disorder, and major depressive disorder (MDD). Here we will summarize the evidence of oxidative stress in these disorders (Table 4.1).

4.3.1 Oxidative Stress and Autism Spectrum Disorder

4.3.1.1 Peripheral Biomarkers of Redox Balance in ASD

ASD is characterized by deficits in socio-communicative abilities, stereotypic behaviors, restricted interests, cognitive inflexibility, and sensory aberrations. Like schizophrenia, many investigators in the field of autism have studied oxidative

Table 4.1 Summary of oxidation status assessed in the systemic circulation and brain for representative psychiatric disorders

Disorder	Systemic circulation		Brain
	Individual studies	Meta-analysis	
Autism spectrum disorder	Decreased GSH (Han et al. 2015; Geier et al. 2009; James et al. 2006) Decreased GSH/GSSG (Han et al. 2015) Increased GSSG (Geier et al. 2009; James et al. 2006) Increased homocysteine (Han et al. 2015) Increased SOD (Al-Gadani et al. 2009; Zoroglu et al. 2004), decreased SOD (Meguid et al. 2011; Yorbik et al. 2002), no difference in SOD (Ghezzo et al. 2013) Decreased CAT (Zoroglu et al. 2004), no difference in CAT (Al-Gadani et al. 2009; Ghezzo et al. 2013) Decreased GPX (Meguid et al. 2011; El-Ansary and Al-Ayadhi 2012; Laszlo et al. 2013), increased GPX (Al-Gadani et al. 2009)	Decreased GSH (Frustaci et al. 2012) Increased GSSG (Frustaci et al. 2012) No difference in homocysteine (Frustaci et al. 2012) No difference in SOD (Frustaci et al. 2012) Decreased GPX (Frustaci et al. 2012)	*MRS* No difference in GSH in basal ganglia and dorsomedial PFC in adults (Durieux et al. 2016) *Postmortem* Decreased GSH in cerebellum and temporal cortex (Rose et al. 2012) Increased 3-NT and 3-CT in cerebellum and temporal cortex (Rose et al. 2012) Decreased aconitase in cerebellum and temporal cortex (Rose et al. 2012)
Schizophrenia	Decreased GSH (Altuntas et al. 2000; Mico et al. 2011; Raffa et al. 2009; Raffa et al. 2011) Increased GSSG (Raffa et al. 2009; Raffa et al. 2011)	Decreased TAS in FEP but increased in chronic patients (Flatow et al. 2013) Decreased CAT in FEP but increased in chronic patients (Flatow et al. 2013) Increased nitrite in FEP but decreased in chronic patients (Flatow et al. 2013)	*MRS* Decreased GSH in PFC (Do et al. 2000; Matsuzawa and Hashimoto 2011) No difference in GSH in ACC (Terpstra et al. 2005) No difference in GSH in posterior medial frontal cortex (Matsuzawa et al. 2008) Increased GSH in medial temporal lobe (Wood et al. 2009) Positive correlation between GSH in medial PFC and FA in patients with schizophrenia (Monin et al. 2015) No correlation between GSH in medial PFC and rsFC in patients with schizophrenia (Monin et al. 2015) *Postmortem* Decreased GSH in PFC (Gawryluk et al. 2011) and striatum (Yao et al. 2006)

(continued)

Table 4.1 (continued)

Disorder	Systemic circulation		Brain
	Individual studies	Meta-analysis	
Bipolar disorder	Decreased GSH (Rosa et al. 2014), no difference in GSH (Tuncel et al. 2015) Increased GSSG (Rosa et al. 2014), no difference in GSSG (Tuncel et al. 2015) No difference in SOD (Tuncel et al. 2015; Tsai and Huang 2015) Decreased GPX (Tsai and Huang 2015) No difference in CAT (Tsai and Huang 2015) Increased TBARS only in manic patients after treatment (Tsai and Huang 2015) No difference in 3-NT in older bipolar patients	No difference in SOD (Brown et al. 2014) No difference in GPX (Brown et al. 2014) No difference in CAT (Brown et al. 2014)	*MRS* No difference in GSH in PFC (Godlewska et al. 2014), ACC (Soeiro-de-Souza et al. 2016; Lagopoulos et al. 2013), and occipital cortex (Godlewska et al. 2014) Increased lactate in dorsal ACC (Soeiro-de-Souza et al. 2016) Correlation between GSH and lactate in dorsal ACC (Soeiro-de-Souza et al. 2016) *Postmortem* Increased 3-NT in PFC (Andreazza et al. 2013)
Major depressive disorder	Decreased SOD (Wei et al. 2009; Selek et al. 2008), increased SOD (Kodydkova et al. 2009; Khanzode et al. 2003; Sarandol et al. 2007; Bilici et al. 2001) Decreased GPX (Ozcan et al. 2004; Kodydkova et al. 2009), no difference in GPX (Andreazza et al. 2009) Decreased CAT (Ozcan et al. 2004; Wei et al. 2009) Increased GR (Kodydkova et al. 2009; Andreazza et al. 2009) Increased GST (Andreazza et al. 2009; Galecki et al. 2009)		*MRS* Decreased GSH in occipital cortex (Godlewska et al. 2015) Negative correlation between GSH and anhedonia in patients with MDD (Lapidus et al. 2014) Escitalopram did not change brain GSH levels (Godlewska et al. 2015) Increased GSH in ACC of elderly at risk for MDD (Godlewska et al. 2015) In elderly at risk for MDD, GSH correlates positively with depression and negatively with cognitive function (Godlewska et al. 2015) *Postmortem* Increased SOD in PFC (Michel et al. 2007) No difference in SOD in the hippocampus (Michel et al. 2007)

All findings are relative to controls

3-CT 3-chlorotyrosine, *3-NT* 3-nitrotyrosine, *ACC* anterior cingulate cortex, *CAT* catalase, *MDD* major depressive disorder, *FA* fractional anisotropy, *FEP* first-episode psychosis, *GSH* reduced glutathione, *GPX* glutathione peroxidase, *GR* glutathione reductase, *GSSG* oxidized glutathione, *GST* glutathione-S-transferase, *PFC* prefrontal cortex, *rsFC* resting-state functional connectivity, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TBARS* thiobarbituric acid reactive substances

stress. Han et al. reported that GSH levels as well as the GSH/GSSG ratio showed significantly lower values in children with ASD compared to control subjects (Han et al. 2015). Other investigators showed that children with ASD had lower levels of plasma GSH but higher levels of GSSG than typically developing children (Geier et al. 2009; James et al. 2006). Furthermore, homocysteine and GSSG levels were significantly higher in children with ASD (Han et al. 2015). Finally, homocysteine levels were found to correlate positively with Childhood Autism Rating Scale (CARS) scores in children with ASD. The associations between other oxidative stress parameters and ASD have not been consistent. The SOD activity was either increased in erythrocytes (Al-Gadani et al. 2009; Zoroglu et al. 2004) or decreased in plasma and erythrocytes (Meguid et al. 2011; Yorbik et al. 2002). The CAT activity was reduced in erythrocytes (Zoroglu et al. 2004) but unchanged in plasma (Al-Gadani et al. 2009). The GPX activity was reduced in plasma (El-Ansary and Al-Ayadhi 2012; Laszlo et al. 2013) and erythrocytes (Meguid et al. 2011) but increased in plasma (Al-Gadani et al. 2009).

Ghezzo et al. evaluated oxidative stress parameters in children with ASD and neurotypical controls. While some oxidative stress biomarkers including TBARS, urinary isoprostane, and hexanoyl-lysine adduct levels in RBC were found to be elevated in ASD, many others (RBC SOD and CAT activities, urinary 8-oxo-dG, plasma radical absorbance capacity, and carbonyl groups) were not different between the two groups (Ghezzo et al. 2013). Interestingly, Na^+/K^+-ATPase activity and RBC membrane fluidity were found to be reduced in ASD compared to TD (Ghezzo et al. 2013). Furthermore, fatty acid membrane profile was altered in ASD; children with ASD demonstrated an increase in monounsaturated fatty acids, decrease in eicosapentaenoic acid (EPA), decrease in docosahexaenoic acid (DHA)-ω3, and increase in the ω6/ω3 ratio as compared to controls (Ghezzo et al. 2013).

Existing evidence is not consistent and small sample sizes and effects limit many studies. Frustaci and his colleagues, who completed a recent systematic review and meta-analyses of oxidative stress-related biomarkers in autism, recognized this problem. This meta-analysis showed the children with autism consistently demonstrated decreased blood levels of reduced GSH, GPX, methionine, and cysteine and increased concentrations of GSSG relative to controls across multiple studies, whereas SOD, homocysteine, and cystathionine were not consistently different between ASD and controls across published studies (Frustaci et al. 2012).

Building on the above findings, Frye and his colleagues studied the connection between oxidative stress and mitochondrial dysfunction in children with ASD. Compared to typically developing controls, children with ASD [with or without comorbid mitochondrial disease (MD)] showed lower GSH and GSH/GSSG. Compared to children with ASD only, children with ASD + MD were found to have significantly higher GSH/GSSG and lower levels of GSSG. Furthermore, the authors demonstrated that signs of chronic inflammation were present in both groups of children with ASD, as evidenced by higher levels of 3-chlorotyrosine (3-CT). Finally, children with ASD + MD were found to have lower scores on the daily living skill and communication subscales of the Vineland Adaptive Behavior Scale (VABS) despite having similar language and ASD symptoms. This study

suggested that different subgroups of children with ASD have different abnormalities in their redox balance, which may arise from different etiologies.

4.3.1.2 Evaluation of Brain GSH Levels in Individuals with ASD by ^{1}H MRS

Using ^{1}H MRS, no difference in brain GSH was found in either basal ganglia or dorsomedial prefrontal cortex in adults with ASD (Durieux et al. 2016).

4.3.1.3 Assessing Redox Balance from Postmortem Brain Samples of Individuals with ASD

Using postmortem brain samples of individuals with ASD, central nervous system levels of oxidative stress biomarkers were measured (Rose et al. 2012). Consistent with previous studies on plasma and immune cells, the oxidative stress biomarkers GSH and GSH/GSSG, as measured by HPLC, were significantly decreased in both ASD cerebellum and temporal cortex as compared to controls.

A significant increase in 3-NT, a biomarker of oxidative protein damage, in the cerebellum and temporal cortex was found in ASD (Rose et al. 2012). Similarly, 8-oxo-dG, a biomarker of oxidative DNA damage, was elevated in cerebellar and temporal cortices in individuals with ASD in comparison to controls and was inversely correlated with GSH/GSSG in the cerebellum (Rose et al. 2012). An increase in levels of 3-CT, a biomarker of chronic inflammatory response, in both brain regions was also observed. Finally, the activity of aconitase, a biomarker of mitochondrial superoxide production, was significantly decreased in cerebellar tissue of individuals with ASD cerebellum and was negatively correlated with GSH/GSSG (Rose et al. 2012). Together, these results indicate that decreased GSH/GSSG redox/antioxidant capacity and increased oxidative stress in the brain tissue from individuals with ASD may have functional consequence in terms of a chronic inflammatory response, increased mitochondrial superoxide production, and oxidative protein and DNA damage. Finally, in a similar study, cerebellar tissues from individuals with ASD were examined, and the activities of GSH-related enzymes GPX, GST, GR, and glutamate-cysteine ligase (GCL) were measured (Gu et al. 2013). Compared to that of the control group, the activities of GPX, GST, and GCL were significantly decreased in ASD.

4.3.1.4 Oxidative Stress and Mitochondrial Dysfunction in ASD

The relationship of oxidative stress and mitochondrial dysfunction was also demonstrated in a subset of individuals with ASD (Rose et al. 2014, 2015). Using lymphoblastoid cell lines (LCLs) derived from children with ASD, Rose et al. reported that this subset of ASD children had an abnormal mitochondrial reserve capacity before and after exposure to ROS. LCLs from a subset of children with ASD displayed high reserve capacity at baseline but a precipitous drop in reserve capacity when challenged with ROS. In a recent study, this group demonstrated that this metabolic phenotype was related to worse repetitive and stereotyped behaviors (Rose et al. 2017). Interestingly, in this ASD LCL subgroup, pretreatment with NAC prevented this sharp decline of anti-oxidation reserve capacity and improved GSH

metabolism, suggesting a role for altered GSH metabolism associated with this type of mitochondrial dysfunction (Rose et al. 2015). Collectively, these results suggested that a subgroup of children with ASD might have alterations in mitochondrial function, which could cause increased vulnerability to prooxidants.

4.3.2 Oxidative Stress and Schizophrenia

4.3.2.1 Peripheral Biomarkers of Redox Balance in Schizophrenia

Schizophrenia is a psychiatric disorder characterized by hallucinations, delusions, and cognitive dysfunction. This disorder has been viewed as a neurodevelopmental disorder due to the known risk factors of early life insult and genetic loading. Redox regulation has been hypothesized as one of the components of a "central hub" in the pathophysiology of schizophrenia (Steullet et al. 2010). Redox dysregulation, NMDA hypofunction, and neuroinflammation were hypothesized as the three components of this hub, which mediates the impairment of microcircuits and macrocircuits, thereby causing aberrations in circuit connectivity and psychopathologic findings in schizophrenia (Steullet et al. 2010). Peripheral (blood and plasma) GSH levels in patients with schizophrenia have been found to be lower than in healthy volunteers (Altuntas et al. 2000; Mico et al. 2011; Raffa et al. 2009, 2011). Further, blood GSSG concentrations were found to be higher in patients with schizophrenia (Raffa et al. 2009, 2011). GSH levels correlated positively with the Scale for the Assessment of Positive Symptoms (SAPS) (Raffa et al. 2011).

In addition to GSH and GSSG levels, the disorder was found to be associated with aberrations in other oxidative stress parameters based on a recent meta-analysis of oxidative stress of 44 studies involving individuals with schizophrenia (Flatow et al. 2013). Compared to control subjects, serum or plasma total antioxidant status (TAS) levels were significantly lower in patients who underwent first episodes of psychosis (FEP). However, TAS levels were found to be significantly higher in patients who have been treated with antipsychotic medications after acute exacerbations of psychosis. Similarly, cross-sectional studies revealed that red blood cell (RBC) CAT and plasma nitrite were significantly decreased in FEP and significantly increased in stable outpatients. Based on these results, the authors concluded that plasma or serum TAS, plasma nitrite, and RBC CAT were state-related biomarker of oxidative stress in individuals with schizophrenia. In contrast, compared to control subjects, RBC SOD was found to be lower in FEP, acutely relapsed inpatients, and stable outpatients, and therefore, SOD appeared to be a trait-related biomarker for schizophrenia. Collectively, these findings supported that abnormalities in oxidative stress in FEP might be independent of antipsychotic medications.

One genetic factor that has been reported to influence GSH concentrations in the systemic circulation is the GAG trinucleotide repeat (TNR) polymorphism in the gene coding for the catalytic subunit of glutamate-cysteine ligase (GCL), the rate-limiting enzyme for GSH synthesis. Importantly, polymorphism of this catalytic subunit of GCL (GCLC) was associated with schizophrenia in two case-control studies. As compared with GCLC low-risk genotypes, GCLC high-risk genotypes

were more frequent in patients with schizophrenia and were associated with lower GCLC protein expression, GCL activity, and GSH levels in fibroblasts when challenged with oxidative stress conditions. In their recent studies in patients with early psychosis, Xin et al. found that glutamate concentrations in the mPFC as measured by MRS were lower in patients with low-risk GCLC genotypes, but this was not the case for patients with high-risk genotypes (Xin et al. 2016). Furthermore, the authors revealed that the GSH levels in the mPFC, as measured by ^{1}H MRS, correlated negatively with GPX levels in RBC in patients with schizophrenia. In contrast to individuals with early psychosis, GSH levels in the mPFC of healthy volunteers correlated positively with GPX levels in RBC (Xin et al. 2016).

4.3.2.2 Evaluation of Brain GSH Levels in Individuals with Schizophrenia by ^{1}H MRS

Regarding GSH levels in the brain, Do and her colleagues found that the GSH concentrations in cerebrospinal fluid (CSF) of inpatients with schizophrenia or schizophreniform disorder were lower than those of age- and gender-matched healthy controls (Do et al. 2000). They examined the prefrontal cortex (PFC) of these participants by proton magnetic resonance spectroscopy (^{1}H MRS), which revealed the GSH levels in the PFC to be lower in patients with schizophrenia than healthy volunteers (Do et al. 2000). This finding was replicated by ^{1}H MRS of the frontal cortex in patients with schizophrenia (Matsuzawa and Hashimoto 2011).

Despite the consistent findings of reduced GSH in the frontal cortex, decreased GSH levels were not found in other areas of the brain. For example, a ^{1}H MRS study detected no changes in GSH levels in the anterior cingulate (Terpstra et al. 2005) and posterior medial frontal cortex (Matsuzawa et al. 2008), whereas GSH concentrations in the medial temporal lobe were increased in patients with their first episode of schizophrenia (Wood et al. 2009). Collectively, these results suggested that perturbation in the GSH levels may be regionally specific in schizophrenia.

4.3.2.3 Assessing Redox Balance from Postmortem Brain Samples of Individuals with Schizophrenia

According to postmortem studies, the concentrations of GSH in the prefrontal cortex (Gawryluk et al. 2011) and striatum (Yao et al. 2006) of schizophrenic patients were lower than controls. Such decreases were linked with lowered activity of related enzymes, such as GPX, GSH-R, and GSH-S-transferase mu isoform (Gawryluk et al. 2011; Yao et al. 2006). Furthermore, increased oxidation and nitration was also found in the postmortem PFC samples of patients with schizophrenia (Kim et al. 2014).

Among brain cells, oligodendrocytes are known to be highly vulnerable to oxidative stress. Monin and his colleagues investigated the interplay between glutathione and myelin (Monin et al. 2015). In control subjects, a positive association was found between mPFC GSH levels as assessed by MRS and both fractional anisotropy (FA) and resting-state functional connectivity along the cingulum bundle. In contrast, in early psychosis patients, mPFC GSH levels were correlated only with FA measures.

Therefore, redox regulation has a critical role in myelination processes and white matter maturation in the mPFC of patients with schizophrenia.

4.3.2.4 Oxidative Stress and Other Pathophysiologic Mechanisms of Schizophrenia

On one hand, oxidative stress can cause damage in the cellular machinery for neurotransmission. On the other hand, abnormalities in the neurotransmission system can trigger changes in oxidative stress. For example, hypofunction of the NMDA receptor (NMDAR) can trigger the downregulation of antioxidant genes, leading to ROS generation through the activation of NADPH oxidase (NOX). NMDAR hypofunction can also result in circuit-level disinhibition of cortical networks. These events cause GSH depletion, which in turn can further repress NMDAR activity. Consequently, during brain development, oxidative stress and GSH deficits caused by NMDAR hypofunction can cause cellular impairment of specific neurons including parvalbumin-expressing interneurons (PVIs), leading to excitation-inhibition (E/I) imbalance (Do et al. 2015; Morishita et al. 2015). The E/I imbalance may lead to the alterations in sensory processing, cognition, and behavior in individuals with schizophrenia.

4.3.3 Oxidative Stress and Bipolar Disorder

4.3.3.1 Peripheral Biomarkers of Redox Balance in Bipolar Disorder

Bipolar disorder is a mood disorder characterized by discrete episodes of manic and depressive symptoms. The findings on redox status are mixed and are mostly from data obtained from studies of adult individuals with bipolar disorder. Rosa et al. found that bipolar patients had significantly lower plasma levels of GSH and higher levels of GSSG, compared to controls (Rosa et al. 2014). This investigation also revealed a correlation between total GSH levels and age of illness onset, so that lower plasma levels of GSH were associated with later onset of disease, not length of illness. Interestingly, Tuncel et al. however could not replicate the difference in plasma GSH levels between bipolar patients and control subjects (Tuncel et al. 2015). Additionally, the activity of SOD was found to be similar between bipolar patients and healthy volunteers (Tuncel et al. 2015; Tsai and Huang 2015). Serum GPX activity in bipolar patients was found to be significantly lower than that of control subjects and correlated negatively with severity of manic symptoms as measured by the Young Mania Rating Scale (YMRS) (Tsai and Huang 2015). No difference in CAT activity was found between bipolar patients and control subjects. However, serum CAT activity was associated positively with YMRS (Tsai and Huang 2015).

Tuncel et al. also examined other oxidation markers of lipid peroxidation, protein oxidation, and total oxidized guanine species, in adult bipolar patients during manic and euthymic episodes (Tuncel et al. 2015). Significant increase in the level of lipid peroxidation was found in the bipolar disorder manic episode group compared to the control group. Furthermore, the level of total oxidized guanine species was

statistically higher in bipolar groups compared to the control group. Tsai and colleagues replicated the increased lipid peroxidation (Tsai and Huang 2015). Serum levels of TBARS in bipolar patients in a manic phase were significantly higher than those of healthy volunteers. Furthermore, these authors found significantly decreased changes in TBARS levels only in bipolar manic patients after treatment, suggesting that TBARS levels might be a state biomarker of oxidative stress in bipolar patients (Tsai and Huang 2015).

Brown et al. conducted a meta-analysis of studies that examined markers of oxidative stress in bipolar patients compared to healthy volunteers (Brown et al. 2014). Bipolar disorder patients were found to have significantly higher markers of lipid peroxidation and DNA/RNA damage, as compared to healthy controls. While the effect size for lipid peroxidation was very high, GPX, SOD, and CAT in bipolar patients were not different from that of healthy volunteers.

The evidence of oxidative stress appears to persist into later life in individuals with bipolar disorder (Andreazza et al. 2015). Andreazza et al. compared the levels of oxidative damage to proteins and lipids in plasma from 110 euthymic older patients with bipolar disorder (mean age, 62 years) and found that these patients showed higher levels of lipid hydroperoxide (LPH) and 4-hydroxynonenal (4-HNE) than age-matched healthy volunteers. However, no significant differences for PC, 3-NT, and 4-HNE were found between the two groups. These results support the persistent effect of oxidative stress in patients with bipolar disorder into later life.

4.3.3.2 Brain GSH Levels in Individuals with Bipolar Disorder by ^{1}H MRS

GSH levels were assessed in prefrontal (Godlewska et al. 2014), anterior cingulate (Soeiro-de-Souza et al. 2016; Lagopoulos et al. 2013), and occipital (Godlewska et al. 2014) cortices of patients with euthymic bipolar disorder. No difference in GSH levels between bipolar participants and controls was found. Similarly, participants showed no difference from controls in other measured cortical metabolites including GABA, glutamate, and NAA. Although no difference in GSH levels was found in the brain regions studied, lactate levels in the dorsal anterior cingulate cortex were found to be higher in bipolar disorder patients, as compared to healthy controls. Interestingly, lactate and GSH levels in the dorsal anterior cingulate cortex correlated positively in euthymic bipolar patients only (Soeiro-de-Souza et al. 2016). While no alterations of markers of the oxidative system were observed in euthymic individuals with bipolar disorder, it remains to be determined whether abnormalities in this system might be observed during active clinical activities, either manic or depressive.

4.3.3.3 Assessing Redox Balance from Postmortem Brain Samples of Individuals with Bipolar Disorder

Pathologic studies have also examined the antioxidant system in individuals with bipolar disorder. Andreazza et al. examined the postmortem PFC samples from patients with bipolar disorder and isolated mitochondria, synaptosomes, and myelin

(Andreazza et al. 2013). They found decreased complex I subunit levels in bipolar subjects compared with healthy volunteers, but no difference in complex III subunits. Additionally, carbonylation was increased in synaptosomes from the bipolar group, while 3-NT was increased in mitochondria from the bipolar group. These results suggest that mitochondrial proteins in the PFC of bipolar patients are more susceptible to potentially reversible nitrosative damage, while more long-standing oxidative damage occurs to synaptic proteins.

Kim et al. found increased oxidation of dopamine transporter (DAT)-immunoreactive regions and decreased nitration of tyrosine hydroxylase (TH)-immunoreactive regions in the PFC of patients with bipolar disorder (Kim et al. 2014). On the other hand, these authors found increased global levels of oxidation in patients with bipolar disorder. (Kim et al. 2014) These findings suggest alterations in levels of protein oxidation and nitration in DA-rich regions of the prefrontal cortex in patients with bipolar disorder.

4.3.4 Oxidative Stress and Major Depressive Disorder

4.3.4.1 Peripheral Biomarkers of Redox Balance in Major Depressive Disorder (MDD)

Major depressive disorder is a psychiatric disorder characterized by discrete episodes of low mood, sadness, and hopelessness accompanied by vegetative symptoms of depression involving alterations of sleep and appetite. Several lines of evidence support that the redox balance in patients with MDD is perturbed. However, findings of oxidative stress parameters are mixed. While various studies revealed that systemic levels of GPX (Ozcan et al. 2004; Kodydkova et al. 2009), CAT (Ozcan et al. 2004; Wei et al. 2009), and SOD (Wei et al. 2009; Selek et al. 2008) were lower in MDD patients than healthy volunteers, opposite results were also published. Some reports indicated the rise of activities of GR (Kodydkova et al. 2009; Andreazza et al. 2009) and GST (Andreazza et al. 2009) in the late stage of MDD, without alteration in GPX activity (Andreazza et al. 2009; Galecki et al. 2009). Higher levels of SOD activities were also found in serum and erythrocytes of patients with MDD (Kodydkova et al. 2009; Khanzode et al. 2003; Sarandol et al. 2007; Bilici et al. 2001).

4.3.4.2 Evaluation of Brain GSH Levels in Individuals with Major Depressive Disorder by ^{1}H MRS

GSH concentration in the occipital cortex of patients with MDD was determined by ^{1}H MRS (Lapidus et al. 2014; Godlewska et al. 2015). Patients with MDD were found to have lower GSH levels in the occipital cortex than control participants; however, GABA and glutamate levels between MDD patients and controls were similar (Godlewska et al. 2015). Furthermore, the severity of anhedonia was found to correlate negatively with occipital GSH levels (Lapidus et al. 2014). Effects of the selective serotonin reuptake inhibitor, escitalopram, on GSH levels were also examined in one study. After a 6-week escitalopram treatment, brain

levels of GSH, GABA, and glutamate in the occipital cortex remained unchanged (Godlewska et al. 2015).

Oxidative stress and depressive symptoms were investigated in one study of older adults at risk for depression (Duffy et al. 2015). Compared to age-matched controls, the elderly "at-risk" individuals had increased GSH levels in the anterior cingulate cortex (ACC). Additionally, the increased GSH levels were associated with greater symptoms of depression and worse cognitive performance.

4.3.4.3 Assessing Redox Balance from Postmortem Brain Samples of Individuals with MDD

A limited number of studies examined the redox balance in postmortem brain tissue in individuals with MDD. In one study, the concentration of SOD was found to be increased in the prefrontal cortex, but not in the hippocampus in postmortem brain samples of individuals with depression in comparison to controls (Michel et al. 2007).

4.3.5 Summary

While several investigations have assessed the antioxidant defense system in neuropsychiatric disorders, findings have not been very consistent. Additional studies are warranted to examine large sample sizes in a developmental approach and longitudinally to determine the stability of some of the observations over time and the effect of age and treatment on the abnormalities observed. Using a multimodal approach is also needed where markers of oxidative system are examined peripherally and centrally by innovative imaging methodologies.

4.4 Pharmacology of N-Acetylcysteine

N-Acetylcysteine (NAC) is a well-known antidote against acetaminophen overdose, which works by increasing the concentrations of GSH through supplementation of cysteine. Cysteine can also be oxidized to cystine, which is a substrate for the glutamate-cystine antiporter. In exchange of the cystine taken by the glial cells, the antiporter transports glutamate into the extracellular space. The non-vesicular glutamate released into the extracellular space activates the type 2/3 metabotropic glutamate receptors, which inhibit the release of vesicular glutamate, thereby decreasing glutamatergic neurotransmission.

NAC has been shown to prevent oxidative damage in animal models, such as the *Gclm* knockout mice which have impaired synthesis of GSH (Cabungcal et al. 2013). Without supplementation of NAC, the redox dysregulation in the *Gclm* knockout mice was found to cause oxidative stress in the brain. In particular, parvalbumin (PV)-containing GABAergic interneurons, but not GABAergic interneurons containing calbindin or calretinin, were found to be especially vulnerable to oxidative damage. This effect was revealed to persist into adulthood of the *Gclm* knockout mice and could be prevented with NAC.

4.5 Role of NAC in Relieving Oxidative Stress in Patient Population

NAC has been tested as adjunctive treatments for patients with ASD (Hardan et al. 2012; Dean et al. 2016), schizophrenia (Berk et al. 2008a; Farokhnia et al. 2013; Lavoie et al. 2008), bipolar disorder (Berk et al. 2008b, 2012), depression (Berk et al. 2014), and other psychiatric disorders. While many of these studies found that NAC resulted in behavioral improvements, only one study had confirmed the mechanism of action of NAC in patient populations (Lavoie et al. 2008). Here we will summarize the evidence for the modulation of the redox system in the brain as demonstrated by clinical trials of NAC.

As discussed above, redox dysregulation and NMDA hypofunction have been demonstrated in patients with schizophrenia. Based on these pathophysiologic mechanisms of schizophrenia, several investigators had conducted randomized, double-blind trials of NAC. Lavoie et al. performed the only study to date that measured the GSH levels in the systemic circulation (Lavoie et al. 2008). After a 6-week treatment of NAC, the mean concentration of GSH in whole blood was 0.89 μmol/mL, which was significantly higher than the mean GSH concentration after placebo treatment (0.81 μmol/mL).

One study has also been completed to examine the effect of NAC on the antioxidant system in mood disorders. Das and her colleagues conducted a multicenter, randomized, double-blind, placebo-controlled study of MDD patients treated with NAC (Das et al. 2013). Participants ($n = 76$) from one site completed ^{1}H MRS of the ACC at the end of treatment (12 weeks). MR spectra from the ACC yielded absolute concentrations of glutamate (Glu), glutamate+glutamine (Glx), *N*-acetyl-aspartate (NAA), and myoinositol (mI), but not GSH. Binary logistic regression analysis was performed to determine whether metabolite profiles could predict NAC versus placebo group. While controlling for the severity of depression and gender, the regression model including concentrations of Glx, NAA, and mI resulted in 75% accuracy in predicting group outcome (NAC or placebo). The finding of higher Glx and NAA levels being predictive of the NAC group provides preliminary support for the putative anti-oxidative role of NAC in MDD. The authors stated that the links between Glx and GSH synthesis (Dodd et al. 2008) and between NAA and GSH levels (Heales et al. 1995) would support that GSH levels were likely elevated by NAC.

Despite the overwhelming evidence of GSH depletion in multiple psychiatric disorders, monitoring of brain levels of GSH before and after oral NAC treatment has not been conducted to date. The closest attempt to this strategy was performed by Holmay et al., who showed that a single-dose, intravenous administration of NAC resulted in an increase in GSH in the occipital cortices of patients with Gaucher and Parkinson diseases (Holmay et al. 2013). Clearly, the use of ^{1}H MRS is at its infancy.

4.6 Future Directions

The evidence supporting the role of the antioxidant system in the pathophysiology in neuropsychiatric disorders is mounting. Treatment studies examining the effect of NAC on behavioral improvement are of interest to many

investigators, and attempts are being made to replicate existing findings in larger trials. More importantly, there is a dire need to examine the direct effect of NAC on the antioxidant system either peripherally or centrally. Therefore, measuring GSH concentrations in the brain before and after NAC treatment is essential not only important to confirm the mechanism of action of NAC but also provide a potential avenue to develop biomarkers that can track disease progression and predict response to treatment. This strategy will be facilitated by the development of advanced MRS methodologies to allow the reliable measurement of GSH in the brain using acquisition sequences that are of short duration to facilitate the participation of individuals with severe neuropsychiatric disorders.

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