Antioxidant Interventions in Neuropsychiatric Disorders

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Abbreviations

$^1O_2$	Singlet oxygen
AA	Arachidonic acid
BDNF	Brain-derived neurotrophic factor
BPRS	Brief psychiatric rating scale
CAD	Coronary artery disease
CAT	Catalase
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
ethyl-EPA	Ethyl-eicosapentaenoic acid
GPx	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
IL-1	Interleukin-1
IL-6	Interleukin-6

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LTB_4	Leukotriene B_4
MADRS	Montgomery–Asberg Depression Rating Scale
MDD	Major depressive disorder
NAC	N-Acetylcysteine
NGF	Nerve growth factor
NO^-	Nitric oxide
NO^-_2	Nitrate
NO^-_3	Nitrite
NO•	Nitric oxide
O_2^-	Superoxide anion
OH•	Hydroxyl
PANSS	Positive and Negative Syndrome Scale
PGE_2	Prostaglandin E_2
PUFAs	Polyunsaturated fatty acids
RBC	Red blood cell
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TAS	Total antioxidant status
TD	Tardive dyskinesia
TNF-α	Tumor necrosis factor-α

1 Introduction

Oxidative stress is defined as higher cellular levels of reactive oxygen species (ROS) than the cellular antioxidant defense. Brain consumes approximately 20 % of the total amount of oxygen in the body. But the enhanced metabolic rate in the brain leads to the generation of excessive levels of ROS. Mostly, oxidative stress-mediated damage of the brain occurs due to higher lipid peroxidation in the cerebrospinal fluid and plasma along with reduced membrane polyunsaturated fatty acids (PUFAs) in the brain and red blood cell (RBC) membranes (Mahadik et al. 2001). Free radicals are produced through a variety of physiological and pathological processes (Fig. 1). The radicals generated from molecular oxygen are generally known as ROS, which include superoxide anion (O_2^-), hydroxyl (OH•), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and nitric oxide (NO•).

Oxidative stress occurs when the production of ROS exceeds the natural antioxidant defense mechanisms, causing damage to macromolecules such as DNA, proteins, and lipids. Cells are protected by antioxidant defense mechanisms that remove these free radicals to prevent oxidative damage. The antioxidant system comprises of different types of functional components such as enzymatic and nonenzymatic antioxidants (Fig. 1). The enzymatic antioxidants comprise of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase, and glutathione S transferase. The nonenzymatic antioxidants include reduced glutathione, vitamin C, vitamin E (α-tocopherol), uric acid, carotenoids, flavonoids, ubiquinol, etc.

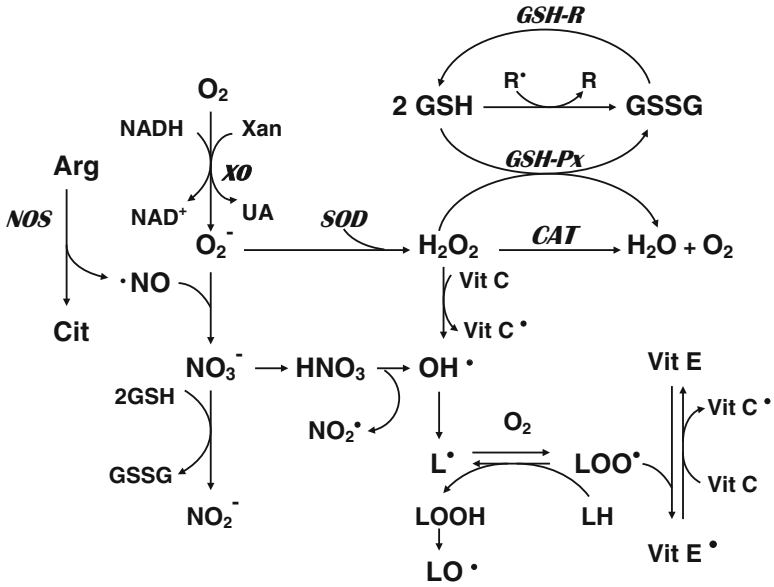

Fig. 1 Possible mechanisms involving production and removal of oxygen and nitrogen free radicals in mammalian cells (reprinted with permission from Yao and Keshavan 2011). Molecular oxygen can be converted to superoxide radicals (O_2^-•) in the presence of xanthine oxidase (XO). Subsequently, superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals to hydrogen peroxide (H_2O_2). Catalase (CAT) and glutathione peroxidase (GSH-Px) convert hydrogen peroxide to water. Glutathione (GSH) is utilized by GSH-Px to yield the oxidized form of glutathione (GSSG), which is converted back to GSH by glutathione reductase (GR). Hydrogen peroxide is susceptible to autoxidation to form hydroxyl radicals (OH•), particularly in the presence of metal catalysts such as iron. In addition, nitric oxide (NO), which is the product of a five-electron oxidation of the amino acid L-arginine, can also produce hydroxyl radicals as well as nitrogen dioxide radical. On the other hand, **α**-tocopherol (vitamin E) has the ability to inhibit lipid peroxidation as a chain-breaking antioxidant. Vitamin E radicals can be recycled back to their native form by ascorbic acid (vitamin C)

2 Oxidative Stress in Schizophrenia

Studies suggest that genetic factors, neuronal maldevelopment, impaired neurotransmission, viral infections, environmental factors, and stressors are the main triggers of schizophrenia (Kendler 2003; Jakob and Beckmann 1986; Thome et al. 1998; Carlsson et al. 1999; Kornhuber and Weller 1994; Pearce 2001). Evidence also indicates that mitochondrial pathology and oxidative stress may be the most critical components in the pathophysiology of schizophrenia (Goff et al. 1995; Whatley et al. 1998; Ben-Shachar and Laifenfeld 2004; Bubber et al. 2004; Yao and Keshavan 2011). Lipid peroxidation products, a marker for oxidative stress-mediated damage, were found to be increased in the cerebrospinal fluid and plasma (Mahadik et al. 2001). It has been also observed that oxidative damage leads to

reduced membrane PUFAs in the brain and RBC membranes (Mahadik et al. 2001). Moreover, levels of nitric oxide and superoxides (NO^- and O_2^-) as determined indirectly as nitrate (NO^-_2) and nitrite (NO^-_3) were higher in serum (Taneli et al. 2004), RBC (Herken et al. 2001), and postmortem brain (Yao et al. 2004) samples from schizophrenia subjects.

A significant reduction in plasma total antioxidant status (TAS) has been found in patients with chronic schizophrenia (Yao et al. 1998a) as well as first-episode drug-naive patients with schizophrenia (Li et al. 2011). Individual plasma antioxidants, albumin, bilirubin (Yao et al. 2000), and uric acid (Yao et al. 1998c) were also found lower in schizophrenia subjects. Moreover, decreases in plasma levels of total and reduced GSH, along with altered antioxidant enzyme activities, have been reported in drug-naive first-episode patients with schizophrenia when compared with healthy control subjects (Raffa et al. 2011). Suboticanec et al. (1990) have demonstrated that both plasma and urinary vitamin C levels were lower in chronic schizophrenia subjects, relative to normal controls, even after controlling for diet. McCreadie et al. (1995) found lower ratios of vitamin E to cholesterol in schizophrenic patients compared with normal control subjects. Later, Brown et al. (1998) also reported decreased lipid-corrected vitamin E levels in schizophrenic patients with tardive dyskinesia, relative to healthy controls, but not in patients without dyskinesia. Decreased levels of GSH, ascorbic acid, and plasma vitamin E levels were also found in erythrocytes from schizophrenic patients compared with healthy subjects (Surapaneni 2007).

Increased SOD activities have been reported in RBC of schizophrenic patients (Abdalla et al. 1986; Reddy et al. 1991; Yao et al. 1998b). A recent study did not find any change in plasma SOD activity in drug-naive first-episode schizophrenic patients compared to control subjects (Raffa et al. 2011). However, a meta-analysis showed that SOD activity was significantly decreased in the disorganized type of schizophrenia patients versus healthy controls (Zhang et al. 2010). A significant increase in GPx activity but decrease in CAT activity was found in plasma samples from drug-naive first-episode schizophrenic patients compared to control subjects (Raffa et al. 2011). Moreover, GPx activity was found to be lower in neuroleptic-treated chronic schizophrenia patients (Stoklasova et al. 1986), in drug-free female schizophrenia patients (Abdalla et al. 1986), and in neuroleptic-naive psychotic children (Golse et al. 1977). Schizophrenia patients had significantly lower RBC GPx activity than controls (Othmen et al. 2008). Zhang et al. (1998) have reported higher plasma GPx activities in long-term neuroleptic-free as well as neuroleptic-naïve schizophrenic patients, while Yao et al. (1999) did not find any significant difference between chronic schizophrenic patients and normal subjects. Decrease in CAT activity was also observed in clinically stable patients with schizophrenia and their unaffected siblings (Othmen et al. 2008). However, CAT activity was found unchanged in erythrocytes and plasma of drug-free schizophrenic patients (Yao et al. 1998b; Yao et al. 1999). A recent meta-analysis reported no significant difference in CAT activity between schizophrenia and control subjects (Zhang et al. 2010).

Inflammatory responses induced by proinflammatory T cells provide a source of free radicals that leads to damage of proteins, lipids, and nucleic acids in neuronal cells. Increased cytokine (IL-1β, IL-6, TNF-α) levels are known to generate ROS in

the cells. A microarray gene analysis of T cells from schizophrenia patients showed prominent transcript alterations in cell cycle machinery, intracellular signaling, metabolism, and oxidative stress, suggesting that altered T cell response might induce oxidative stress in schizophrenia (Craddock et al. 2007).

3 Oxidative Stress in Bipolar Disorder

Bipolar disorder is a major mood disorder affecting an estimated 1–3 % of the population (Belmaker 2004; Kupfer 2005; Merikangas et al. 2007). Oxidative stress has also been implicated in the pathophysiology of bipolar disorder. Several studies have reported that bipolar disorder patients have significant alterations in antioxidant enzymes, lipid peroxidation, and nitric oxide levels; however, the results are conflicting. A meta-analysis by Andreazza et al. (2008) found that bipolar disorder patients have increased lipid peroxidation and increased NO levels but failed to find significant changes in GPx activity in bipolar disorder (Andreazza et al. 2009). An earlier study has found lower levels of SOD and catalase in bipolar disorder patients (Ranjekar et al. 2003). However, the above data was not in agreement with the findings by Kuloglu et al. (2002), where an increase in SOD levels with no changes in GPx was found in bipolar patients. Serum levels of NO and SOD were found significantly higher in bipolar disorder patients, with a correlation between the number of the manic episodes and NO levels (Savas et al. 2006). A recent review by Marazziti et al. (2012) indicated that mitochondrial dysfunction could contribute to cell metabolism errors and apoptosis in disorders such as schizophrenia and bipolar disorder.

4 Oxidative Stress in Major Depression

Major depression is characterized by significantly lower plasma levels of a number of key antioxidants, such as vitamin E, zinc, and coenzyme Q10, as well as lower glutathione peroxidase activity (Maes et al. 2011). A significant association has been found between depression and polymorphisms in genes involved in oxidative pathways such as manganese superoxide dismutase and catalase (Maes et al. 2011). Galecki et al. (2009) showed increases in CAT activity levels during acute episodes of depression, whereas Kodydkova et al. (2009) demonstrated decreases in GPx activity from female patients with depression. Such reduced levels of GPx were further shown in postmortem prefrontal cortex samples from patients with major depression and schizophrenia (Gawryluk et al. 2011).

In addition, accumulating evidence exists that demonstrates the presence of membrane fatty acid defects in patients with major depression (Hibbeln and Salem 1995; Peet et al. 1998; Edwards et al. 1998). Specifically, an increased ratio of 5,8,11,14-eicosatetraenoic acid (arachidonic acid, AA) to 5,8,11,14,17-eicosapentaenoic acid (EPA) and decreased levels of ω-3 fatty acids have been observed in the serum and RBC lipids of depressive patients. Furthermore, the AA/EPA ratio in serum and RBC

membrane phospholipids was correlated positively with the severity of illness (Maes et al. 1996; Seko et al. 1997). The above findings are consistent with the epidemiological studies demonstrating an association between decreased ω-3 fatty acid consumption and increased rates of depression (Hibbeln and Salem 1995). Patients with major depression may have an abnormal intake of ω-3 fatty acids (Edwards et al. 1998; Hibbeln 1998).

Both ω-6 and ω-3 PUFAs are involved the regulation of inflammatory response system. The ω-6 PUFAs, particularly AA, have the proinflammatory features, since AA is the precursor of proinflammatory eicosanoids, prostaglandin E_2 (PGE_2), and leukotriene B_4 (LTB_4) and the increase production of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and IL-6 (Soyland et al. 1994; Tashiro et al. 1998). On the other hand, the ω-3 PUFAs, EPA, and docosahexaenoic acid (DHA) suppress the production of AA-derived eicosanoids, thus having anti-inflammatory and immunosuppressive effects (Calder 1998). Several groups have reported that ω-3 PUFA-enriched diets (e.g., fish oil) can lead to partial replacement of AA by EPA in inflammatory cell membranes and significantly reduce the ex vivo production of proinflammatory cytokines (Soyland et al. 1994; Calder 1998; James et al. 2000). Therefore, an imbalance of ω-6/ω-3 PUFAs may result in an increased production of proinflammatory cytokines. Smith (1991) proposed that abnormal fatty acid composition might be related to the inflammatory response system underlying pathophysiology of major depression. Further, Maes et al. (2000) have substantiated the role of ω-3 PUFAs in predicting the response of proinflammatory cytokines to psychological stress.

5 Antioxidant Supplementation as Adjunctive Therapy

In the above sections, we have discussed the role of free radicals and antioxidant enzymes in the pathophysiology of schizophrenia, bipolar disorder, and major depression. Accumulating evidence from clinical, preclinical, and epidemiological studies suggests that many of the antioxidant compounds possess neuroprotective and anti-inflammatory properties and could be considered as important adjunctive therapy for schizophrenia (Pillai 2008). We discuss below a few important antioxidants for their therapeutic potential in the above neuropsychiatric disorders.

5.1 Antioxidant Interventions in Schizophrenia

The section below will discuss the recent findings in studies using antioxidants as adjunctive therapeutics in schizophrenia. The major compounds explored in the treatment of schizophrenia for their antioxidant potential are vitamins, N-acetylcysteine (NAC), and ω-3 fatty acids.

5.1.1 Vitamins

Vitamin C and vitamin E are the well-studied essential nutrients that function as the major chain-breaking antioxidants. They are the first line of defense against lipid peroxidation and protecting cell membranes from free radical damage in the human body. It has been shown that the oral supplementation of vitamin C with atypical antipsychotic reverses ascorbic acid levels, reduces oxidative stress, and improves BPRS score in schizophrenic patients (Dakhale et al. 2005). Arvindakshan et al. (2003) also reported reduction in BPRS and PANSS and increase in Henrich's quality of life score after supplementation with ω-3 fatty acids, vitamin E, and vitamin C. It has been suggested that a combination of a hydrophobic agent such as vitamin E, to protect membranes, and a hydrophilic agent such as vitamin C in intracellular protection provides complete antioxidant defense (Mahadik et al. 2001). A number of studies have used vitamin E as a supplement in chronic schizophrenic patients with TD (reviewed by Yao and Keshavan 2011). Supranormal doses of vitamin E have been safely and effectively used to reduce the severity of TD. Several studies, albeit with relatively small sample sizes, have reported decreases in the severity of dyskinesia by vitamin E treatment (Peet et al. 1993; Elkashef and Wyatt 1999; Adler et al. 1993) though there are some contradictory findings (Corrigan et al. 1993; Shriqui et al. 1992).

5.2 N-Acetylcysteine (NAC)

NAC is the precursor of glutathione, which is known to restore the primary endogenous antioxidant GSH and maintain the oxidative balance in the cell. In addition, NAC has been also shown to scavenge oxidants directly, particularly the reduction of the hydroxyl radical and hypochlorous acid (Aruoma et al. 1989). A number of studies have tested the efficacy of NAC as an adjunctive therapy in schizophrenia (Berk et al. 2008a; Bulut et al. 2009; Dodd et al. 2008; Dean et al. 2011). The above studies have suggested that NAC seems to be a safe, effective, tolerable, and affordable adjunctive antioxidant molecule for the treatment of schizophrenia.

5.2.1 Omega-3 Fatty Acid

Membrane deficits have been well documented in subjects with schizophrenia (Mahadik and Yao 2006; Yao and Keshavan 2011). Therefore, boosting the lower levels of membrane phospholipid EPUFAs, predominantly AA (20:4n-6, ω6-EPUFA) and DHA (22:6n-3, ω3-EPUFA), by dietary supplementation is an attractive approach to protect the membrane from cellular damage in schizophrenia. A recent study has shown that high intake of fish, ω-3 or ω-6 PUFA has a lower rate of schizophrenic symptoms in women (Hedelin et al. 2010).

Long-chain ω-3 fatty acids have been shown to reduce the risk of progression to psychotic disorder, particularly in the early stages of illness, and may propose a safe and efficacious adjunctive strategy to prevent from psychiatric condition (Amminger et al. 2010). Thus, ω-3 fatty acids provide numerous health benefits to a variety of psychiatric symptoms (Perica and Delas 2011). Taken together, the above findings suggest the therapeutic potential of ω-3 fatty acid in the treatment of schizophrenia.

In addition to the above compounds, a number of other antioxidants such as glutathione (Berk et al. 2008b), rutin (Bishnoi et al. 2007), Ginkgo biloba (Singh et al. 2010), melatonin (Ortiz et al. 2008; Maldonado et al. 2009), hydroxytyrosol (Young et al. 2007), caffeic acid phenethyl ester (Ozyurt et al. 2007), resveratrol and quercetin (Dietrich-Muszalska and Olas 2009), and lycopene (Rao and Rao 2004) have also been suggested as alternative treatments in schizophrenia (reviewed by Bošković et al. 2011).

5.3 Antioxidant Interventions in Bipolar Disorder

As discussed above, alterations in lipid peroxidation and antioxidant enzymes have been found in subjects with bipolar disorder. In an effort to find the therapeutic potential of antioxidants in bipolar disorder, NAC has been extensively used as adjunctive therapy in bipolar disorder. A recent systematic review of clinical trials showed that adjunct treatment of NAC with standard pharmacotherapies for bipolar disorder shows positive evidence with large effect sizes (Sarris et al. 2011). NAC as an add-on treatment was found to be beneficial in few individuals in relationship to mood and functional outcomes (Magalhães et al. 2011). It has been suggested that long-chain ω-3 fatty acid supplementation has therapeutic potential to improve the disease condition of both major depression and bipolar disorder (McNamara 2013). Increase in brain-derived neurotrophic factor (BDNF) expression following ω-3 fatty acids has been suggested as a possible mechanism that may mediate at least in part the enhancing effects of ω-3 fatty acids in bipolar disorder (Balanzá-Martínez et al. 2011). Frangou et al. (2006) reported a significant improvement in depressive symptoms with ethyl-EPA (ethyl-eicosapentaenoic acid) treatment compared with placebo in subjects with bipolar disorder. In addition, an open-label study with supplementation of 1.5–2 g/day of the ω-3 fatty acids for up to 6 months showed significant improvement in depressive symptoms in bipolar disorder subjects (Osher et al. 2005). Significant changes in mania and depression were reported in an open-label study supplemented with 360 mg of EPA per day and 1,560 mg of DHA (docosahexaenoic acid) per day for 6 weeks in juvenile bipolar disorder subjects (Clayton et al. 2009). Thus, ω-3 fatty acids' intervention represents a promising therapeutic strategy for bipolar disorder.

5.4 Antioxidant Interventions in Major Depression

5.4.1 Omega-3 Fatty Acids

Increased ratio of ω-6/ω-3 PUFAs may contribute to an increased incidence of coronary artery disease (CAD) (Smith 1991; Linscheer and Vergroesen 1988). Moreover, it is now recognized that MDD is robustly associated with an increased risk of CAD. Thus, the increased ratio of ω-6/ω-3 PUFAs may be responsible for the association between MDD and CAD (Maes et al. 1996; Linscheer and Vergroesen 1988). The administration of ω-3 PUFAs has a demonstrated efficacy in reducing cardiac events and triglycerides with minimal side effects (O'Keefe and Harris 2000). The beneficial effect of dietary and supplemental ω-3 fatty acids on CAD was further supported by a recent meta-analysis of 11 randomized controlled trials of both EPA + DHA and alpha-linolenic acid (Bucher et al. 2002). Several potential mechanisms including hypotriglyceridemic, antithrombogenic, antiarrhythmic, and antiatherogenic properties might be responsible for the protective effect of ω-3 fatty acids on CAD (Connor 2000).

In addition, there have been promising results for the use of low-dose ethyl-EPA in treatment-resistant unipolar depression (Peet and Horrobin 2002; Emsley et al. 2003). The effect appears to be specific to EPA, and not DHA (Marangell et al. 2003; Ross et al. 2007; Martins 2009). There also appear to be dose-specific effects; high-dose EPA may not be effective (EPA 6 g/day) (Post et al. 2003). Of particular note is the onset of response with EPA. Peet and Horrobin (2002) found significant reduction in severity of depressed mood as early as 2 weeks and maximally at 4 weeks. Emsley et al. (2003) found significant treatment response at 4 weeks. Thus, response to EPA occurs relatively rapidly. This may be important in managing patients who are not responding to conventional treatments and remain at risk for complications of depression, such as suicide. In the above placebo-controlled trials, there were no dropouts due to EPA-related side effects. An additional advantage is that EPA is not known to alter levels of psychotropic drugs used in treatment of depression. Epidemiological data suggests that there is an inverse relation between risk of depression and postpartum depression and fish consumption (Hibbeln and Salem 1995).

Recently, a meta-analysis study has shown that supplements containing EPA ≥ 60 % of total EPA + DHA, in a dose range of 200–2,200 mg/d of EPA in excess of DHA, were effective against primary depression (Sublette et al. 2011), which is in accordance with an early meta-regression analysis from those double-blind placebo-controlled clinical trials by Ross et al. (2007). On the other hand, another recent systematic review and meta-analyses by Bloch and Hannestad (2011) indicated only a small, nonsignificant, benefit of ω-3 fatty acids treatment in major depression. However, Martins et al. (2012) questioned the validity of their conclusions on the basis of inclusion/exclusion criteria, study subgroup selection, strategy for selecting outcome measures, standard mean difference estimates, and choice of effect modifiers.

5.4.2 Zinc Supplement

Zinc is an essential metal, which plays an important role in improving depressive symptoms (Maes et al. 2011). Zinc has been found to have antidepressive effects by normalizing antioxidant concentrations (Maes et al. 2011). People with depression have significantly lower serum zinc levels than controls (Maes et al. 1994; McLoughlin and Hodge 1990. The transport of zinc to the brain occurs by crossing the blood–brain and blood–cerebrospinal fluid barriers, concentrating in areas such as the hippocampus, amygdala, and neocortex (Frederickson et al. 2000; Takeda and Tamano 2009). Zinc plays an essential role in adult hippocampal neurogenesis and synaptogenesis (Szewczyk et al. 2011). Chronic zinc treatment in high doses is required to increase BDNF mRNA and protein levels in the frontal cortex, while the hippocampus BDNF expression increased with lower, more acute doses of zinc (Cichy et al. 2009; Franco et al. 2008; Nowak et al. 2004; Sowa-Kucma et al. 2008). Earlier studies found that zinc can also regulate nerve growth factor (NGF) directly via the modulation of the zinc binding site (Szewczyk et al. 2011). The induction of NGF by zinc might serve to support neuron survival (Chen and Liao 2003; Mocchegiani et al. 2005).

5.4.3 N-Acetylcysteine (NAC)

In addition to schizophrenia and bipolar disorder, low levels of glutathione (GSH) were also found in postmortem prefrontal cortex from patients with depression (Gawryluk et al. 2011). As described above, the use of NAC in restoring GSH levels has been well established (Dodd et al. 2008). Previously, Berk et al. (2008a) have shown that NAC treatment caused a significant improvement on the Montgomery–Asberg Depression Rating Scale (MADRS) and most secondary scales at end point. A recent open-label study by this same research group also found a robust decrease in depression scores with NAC treatment in 149 individuals with moderate depression for 2 months (Berk et al. 2011).

6 Conclusion

Given the complex pathophysiology of the neuropsychiatric disorders, it is difficult to suggest that a single mechanism could explain the diversity of impairments found in these disorders. As discussed above, a large body of studies provides compelling evidence to show that oxidative stress plays an important role in the pathophysiology of schizophrenia, bipolar disorder, and major depression. However, the biochemical mechanisms underlying these psychiatric disorders remain unclear. A number of studies have suggested that important relationships exist between redox signaling molecules and neuroplasticity-related molecules. For example, neurotrophic factors such as BDNF are known to rescue cerebellar granule neurons

from oxidative stress-mediated cellular damage (Skaper et al. 1998). In addition, both peripheral and brain levels of neurotrophins are lower in subjects with schizophrenia or mood disorder (Pillai 2008). It would be important to determine whether increases in oxidative stress lead to reductions in neurotrophin levels in these psychiatric disorders. As oxidative stress is known to disturb the neuroplasticity, attempts to normalize such impairments are of great therapeutic value in psychiatry research. A few such studies using antioxidants as adjunctive therapy have shown promising leads in the treatment of schizophrenia and mood disorder. However, additional studies using large number of subjects are required to identify further viable therapeutic strategies to restore the oxidative stress-induced cellular, molecular, and behavioral deficits. Such studies will provide exciting opportunity for the treatment and long-term management of neuropsychiatric disorders.

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