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REVIEW ARTICLE

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Oxidative stress in psychiatric disorders: evidence base and therapeutic implications

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Abstract

Oxidative stress has been implicated in the pathogenesis of diverse disease states, and may be a common pathogenic mechanism underlying many major psychiatric disorders, as the brain has comparatively greater vulnerability to oxidative damage. This review aims to examine the current evidence for the role of oxidative stress in psychiatric disorders, and its academic and clinical implications. A literature search was conducted using the Medline, Pubmed, PsycINFO, CINAHL PLUS, BIOSIS Previews, and Cochrane databases, with a time-frame extending to September 2007. The broadest data for oxidative stress mechanisms have been derived from studies conducted in schizophrenia, where evidence is available from different areas of oxidative research, including oxidative marker assays, psychopharmacology studies, and clinical trials of antioxidants. For bipolar disorder and depression, a solid foundation for oxidative stress hypotheses has been provided by biochemical, genetic, pharmacological, preclinical therapeutic studies and one clinical trial. Oxidative pathophysiology in anxiety disorders is strongly supported by animal models, and also by human biochemical data. Pilot studies have suggested efficacy of *N*-acetylcysteine in cocaine dependence, while early evidence is accumulating for oxidative mechanisms in autism and attention deficit hyperactivity disorder. In conclusion, multi-dimensional data support the role of oxidative stress in diverse psychiatric disorders. These data not only suggest that oxidative mechanisms may form unifying common pathogenic pathways in psychiatric disorders, but also introduce new targets for the development of therapeutic interventions.

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Key words: Antioxidant, mechanisms, oxidative stress, pathophysiology, psychiatric disorders.

Introduction

The aetiopathogenesis of psychiatric disorders is incompletely understood, which may partly account for the persisting dominance of the syndromic nosology in psychiatry, despite its widely recognized inadequacies. An obstacle to the furthering of aetiological understanding is the complex interplay of multitudinous variables, such that the precise delineation of aetiology may be an unattainable goal. In this context, a better understanding of fundamental pathophysiological pathways and their interactions may provide a broadly applicable conceptual framework and subsequent means of therapeutic intervention. Biomedical fields such as neurochemistry, psychoneuroendocrinology and psychoneuroimmunology are major contributors in this respect, and neurochemistry, in particular, informs most of the current biological treatments. In a similar vein, oxidation biology is emerging as a promising avenue of investigation, and has been actively pursued in other areas of medicine (Barnham et al., 2004; Mehta et al., 2006; Tsukahara, 2007).

The theory of oxidative stress as a pathophysiological mechanism, at its most basic, can be explained by the concept, sometimes referred to as the 'oxygen paradox', that while oxygen is essential for aerobic life, excessive amounts of its free radical metabolic by-products are toxic (Davies, 1995). In brief, these free radicals play integral roles in cellular signalling, physiological immunological responses and mitosis. However, being highly unstable molecules with unpaired electrons, they have differential oxidative strengths and hence potential to damage cellular proteins, lipids, carbohydrates and nucleic acids (Filomeni

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and Ciriolo, 2006). Under physiological conditions, multiple tiers of defence exist to protect against these free radicals, including the restriction of their production through the maintenance of a high oxygen gradient between the ambient and cellular environments, their removal by non-enzymatic and enzymatic antioxidants, and the reparation of oxidative damages by structural repair and replacement mechanisms (Davies, 2000; Sies, 1997). Despite the efficiency of this multi-faceted defence network, a degree of oxidative damage is inherent in aerobic life and is believed to underlie the ageing process and influence organismic lifespan (Finkel and Holbrook, 2000). Oxidative stress occurs when redox homeostasis is tipped towards an overbalance of free radicals, due to either their overproduction or deficiencies in antioxidant defence (Sies, 1997). The resultant cellular damage may range from cellular structural damage and mitotic arrest, to apoptosis and cell necrosis, depending on the level of oxidative stress severity (Davies, 2000; Finkel and Holbrook, 2000). The major classes of free radicals in living organisms are the reactive oxygen species (ROS) and the reactive nitrogen species (RNS), which are respective collective terms for oxygen- and nitrogen-derived radicals, as well as some non-radicals that readily convert into radicals (Halliwell, 2006; Pacher et al., 2007).

Oxidative stress mechanisms have been implicated in the pathogenesis of psychiatric disorders. This hypothesis has theoretical appeal, as the brain is considered particularly vulnerable to oxidative damage for several reasons. These include its comparatively high oxygen utilization and hence generation of free radical by-products, its modest antioxidant defences, its lipid-rich constitution that provides ready substrates for oxidation, the reducing potential of certain neurotransmitters, and the presence of redox-catalytic metals such as iron and copper (Halliwell, 2006; Valko et al., 2007). Additionally, the brain is also susceptible to secondary and self-perpetuating damage from oxidative cellular injury or necrosis, via the neurotoxic effects of released excitatory amines (mainly glutamate) and iron, and the activated inflammatory response (Halliwell, 2006). This intrinsic oxidative vulnerability of the brain, together with the growing evidence for neurodegenerative changes associated with many psychiatric syndromes, suggest that oxidative damage may be a plausible pathogenic candidate.

The focus of this review is on examining the evidence for oxidative stress involvement in psychiatric pathophysiology, and to comment on the therapeutic and research implications of this knowledge.

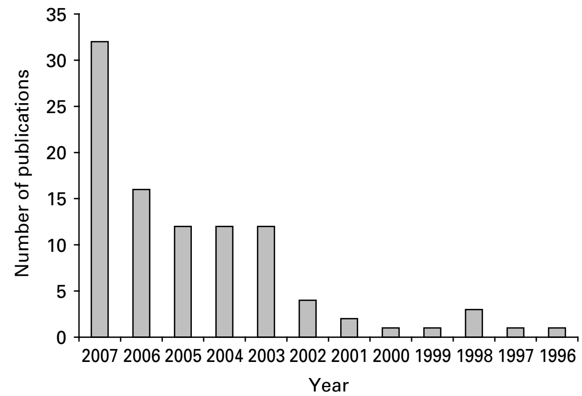

Figure 1. Estimated number of original research publications on oxidation biology in core psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders) by year, as gauged by Medline database search.

Methods

A literature search was conducted using the Medline, Pubmed, PsycINFO, CINAHL PLUS, BIOSIS Previews, and Cochrane databases, up until September 2007. Search terms entered included: 'oxidative, oxidative stress, reactive species, reactive oxygen species, reactive nitrogen species, antioxidants, lipid peroxidation, thiobarbituric acid reactive substances, DNA damage, psychiatry, pathogenesis, mental disorder, schizophrenia, bipolar disorder, depression, anxiety disorder, personality disorder, autism, attention deficit hyperactivity disorder, glutathione, *N*-acetylcysteine, and treatment', grouped in various combinations. This was supplemented by a hand search of references in selected articles, as well as references obtained from researchers of oxidative mechanisms in the field of psychiatry. Some references from this latter source have been published after the initial search date of September 2007.

Results

Over the last decade, there has been a proliferation of information on oxidative stress mechanisms in the psychiatric literature (Figure 1). The largest and most multi-faceted body of research exists for schizophrenia, followed by bipolar disorder and depression. A smaller collection of data has been published for anxiety disorders, substance abuse, autism and attention deficit hyperactivity disorder (ADHD). No studies were found for personality disorder, and the search did not yield oxidative stress literature pertaining to other psychiatric conditions.

Schizophrenia

The evidence behind oxidative stress mechanisms in schizophrenia can be grouped into three categories: first, those studies that illustrate disturbed oxidative homeostasis through oxidative enzyme genetic polymorphism and quantification of antioxidants, free radicals and markers of oxidative damage; second, those demonstrating antioxidant mechanisms of established antipsychotic drugs; third, those showing benefits from antioxidant therapies. These findings are summarized in Table 1.

Markers of oxidative disturbances

Assays of oxidants and antioxidants

Most data demonstrating oxidative disturbances have examined indirect measures of oxidative status, such as peripheral and brain levels of antioxidants, oxidative enzymes and products. The direct measurement of free radicals is hindered by their short half-lives and low titres. Some studies have examined peripheral concentrations of the free radical nitric oxide (NO) in patients with schizophrenia by measuring its metabolites, nitrites and nitrates, but have yielded inconsistent results. Whilst some have found elevated plasma NO (Akyol et al., 2002; Li et al., 2006; Taneli et al., 2004; Yanik et al., 2003; Zoroglu et al., 2002) and reduced polymorphonucleocyte NO (Srivastava et al., 2001) in those with schizophrenia compared with controls, no significant changes were found in plasma and platelet NO (Srivastava et al., 2001). Comparatively lower concentrations of the NO metabolites were found in the cerebrospinal fluid (CSF) of schizophrenia patients (Ramirez et al., 2004) compared with control patients who presented with non-inflammatory and non-degenerative neurological conditions, but these metabolites were significantly increased in a sample of post-mortem caudate specimens (Yao et al., 2004). The disparate sample sizes, patient characteristics, tissue specimen types and substances measured in these studies, and the many inherent metabolic variables in any given individual, make direct comparison of these results difficult, although they support the presence of abnormal NO metabolism in schizophrenia.

Similarly, studies involving blood assays of intrinsic antioxidants have collectively demonstrated significantly altered antioxidant activities. Deficiency of glutathione, the major intracellular antioxidant, in its reduced form (GSH), has been observed and suggested to be of pathophysiological significance in schizophrenia as early as 1934 (Looney and Childs, 1934), although differences did not reach statistical significance in that study. Significant GSH deficiency has subsequently been reported (Altuntas et al., 2000). Reduced levels of the major antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), have also been found in patients with schizophrenia compared with controls (Ben Othmen et al., 2007; Li et al., 2006; Ranjekar et al., 2003). Others have reported unchanged levels for these three enzymes (Srivastava et al., 2001), or altered concentrations of individual enzymes (Abdalla et al., 1986; Akyol et al., 2002; Altuntas et al., 2000; Dietrich-Muszalska et al., 2005; Herken et al., 2001; Kuloglu et al., 2002c; Zhang et al., 2006a). A strong negative correlation between blood GSH-Px and structural measures of brain atrophy was also reported by an early study (Buckman et al., 1987). Furthermore, some studies have differentiated enzymatic changes among the schizophrenia subtypes (Herken et al., 2001; Zhang et al., 2006a), and one study showed a linear correlation between antioxidant enzyme levels and positive symptom severity (Li et al., 2006). The antioxidants uric acid (Yao et al., 1998b), albumin and bilirubin (Yao et al., 2000), and the plasma total antioxidant status (TAS) (Yao et al., 1998a) have also been reported to be lower in patients with schizophrenia than in controls. Albumin, bilirubin and uric acid were shown to be significantly lower in neuroleptic-naive patients with first-episode schizophrenia, results that were independent of smoking status (Reddy et al., 2003), thus strengthening the evidence for defective antioxidant defence as an early pathophysiological change associated with the disease, rather than a sequela of drug effects, chronic disease and smoking. Interestingly, the same study found no impairment of antioxidative defence as determined using the same indices, in those with first-episode affective psychosis (Reddy et al., 2003), suggesting that oxidative stress may be involved at different stages in the two groups of disorders.

In tandem with the peripheral antioxidant abnormalities found in patients with schizophrenia, post-mortem brain tissue studies have reported significantly lower levels of glutathione in both its reduced (GSH) and oxidized forms (GSSG), and the two enzymes responsible for conversions between these two forms (GSH-Px, and glutathione reductase or GR), in the caudate region from donors with schizophrenia compared with those with other psychiatric conditions and without psychiatric conditions. A concomitant reduction in GSH:GSSG ratio, inverse correlations between age and GSSG and between age and GR, as well as the loss of normal correlations that exist in

Table 1. Data relating to oxidative stress disturbances in schizophrenia

			Compared with controls	Sample size (n) of patients
Markers of oxidative disturbances				
Assays of oxidants and antioxidants				
NO metabolites	Plasma		Increased	100 (Akyol et al., 2002); 82 (Zoroglu et al., 2002); 46 (Yanik et al., 2003); 20 (Taneli et al., 2004); 46 (Li et al., 2006)
			Unchanged	62 (Srivastava et al., 2001)
	PMN		Decreased	62 (Srivastava et al., 2001)
	Platelet		Unchanged	62 (Srivastava et al., 2001)
	CSF		Decreased	10 (Ramirez et al., 2004)
	PM brain		Increased	18 (Yao et al., 2004)
Glutathione	Erythrocyte		Decreased	48 (Altuntas et al., 2000)
	CSF		Decreased	26 (Do et al., 2000)
	MRS		Decreased	14 (Do et al., 2000)
	PM brain		Decreased	12 (Yao et al., 2006a)
Antioxidative enzymes	SOD	Plasma	Decreased	100 (Akyol et al., 2002); 92 (Zhang et al., 2006a)
		Erythrocyte	Increased	50 (Abdalla et al., 1986); 48 (Altuntas et al., 2000); 25 (Kuloglu et al., 2002c)
			Unchanged	65 (Herken et al., 2001)
			Decreased	31 (Ranjekar et al., 2003); 46 (Li et al., 2006); 60 (Ben Othmen et al., 2007)
		PMN	Unchanged	62 (Srivastava et al., 2001)
		Platelet	Decreased	36 (Dietrich-Muszalska et al., 2005)
		PM brain	Increased	13 (Michel et al., 2004)
	CAT	Erythrocyte	Increased	65 (Herken et al., 2001)
			Decreased	31 (Ranjekar et al., 2003); 46 (Li et al., 2006); 60 (Ben Othmen et al., 2007)
		PMN	Unchanged	62 (Srivastava et al., 2001)
	GSH-Px	Erythrocyte	Increased	39 (Herken et al., 2001); 25 (Kuloglu et al., 2002c)
			Unchanged	50 (Abdalla et al., 1986)
			Decreased	48 (Altuntas et al., 2000); 31 (Ranjekar et al., 2003); 46 (Li et al., 2006); 60 (Ben Othmen et al., 2007)
		PMN	Unchanged	62 (Srivastava et al., 2001)
		Plasma	Unchanged	100 (Akyol et al., 2002)
			Decreased	92 (Zhang et al., 2006a)
		PM brain	Decreased	12 (Yao et al., 2006a)
Uric acid	Plasma		Decreased	82 (Yao et al., 1998b)
Albumin, bilirubin	Plasma		Decreased	81 (Yao et al., 2000)
Total antioxidant status	Plasma		Decreased	45 (Yao et al., 1998a)
Assays of oxidative products				
TBARS/MDA	Plasma		Increased	26 (Mahadik et al., 1998); 100 (Akyol et al., 2002); 25 (Kuloglu et al., 2002c); 92 (Zhang et al., 2006a); 47 (Dietrich-Muszalska and Olas, 2007); 60 (Ben Othmen et al., 2007)
			Unchanged	31 (Ranjekar et al., 2003)
	Erythrocyte		Increased	48 (Altuntas et al., 2000); 65 (Herken et al., 2001)
	PMN		Unchanged	62 (Srivastava et al., 2001)
	Platelet		Increased	36 (Dietrich-Muszalska et al., 2005)
	CSF		Decreased	10 (Skinner et al., 2005)

Isoprostanes	Urine	Increased	47 (Dietrich-Muszalska and Olas, 2007)
DNA damage	PM brain	Increased	10 (Nishioka and Arnold, 2004)
	Lymphocyte	Unchanged	20 (Psimadas et al., 2004); 16 (Young et al., 2007)
Molecular and genetic studies			
Molecular studies	Altered proteins, RNA and metabolites relating to mitochondrial function and oxidative stress pathways		10, 54 (Prabakaran et al., 2004)
Susceptibility genes	Glutamate cysteine ligase modifier (GCLM) subunit		Multiple studies (Tosic et al., 2006)
	Glutamate cysteine ligase catalytic (GCLC) subunit		388 (Gysin et al., 2007)
	Manganese-SOD (-9Ala allele)		153 (Akyol et al., 2005)
	Glutathione S-transferase T1 (GSTT1)		292 (Saadat et al., 2007)
	ND4 subunit of NADH-ubiquinone reductase		181 (Marchbanks et al., 2003)
Antioxidant properties of antipsychotics			
Clinical studies	Improvement of antioxidants ± MDA disturbances with treatment		41 (Zhang et al., 2003); 16 (Evans et al., 2003); 48 (Dakhale et al., 2004)
	No reversal of oxidants, antioxidants ± MDA with treatment		20 (Taneli et al., 2004); 40 (Sarandol et al., 2007a)
Preclinical studies	Rats	Reversal of haloperidol-induced oxidative stress	Clozapine, olanzapine, risperidone (Pillai et al., 2007)
	In-vitro cell studies	Reversal of induced oxidative stress	Olanzapine (Wei et al., 2003); clozapine, olanzapine, quetiapine, risperidone (Wang et al., 2005)

Antioxidant therapies

	Trial design	Treatment outcomes	Sample size (n)
Vitamins C & E	RCT; 8 wk; vitamin C vs. placebo adjunctive to antipsychotic treatment	Reversal of MDA and ascorbic acid levels; superior BPRS outcomes	40 (Dakhale et al., 2005)
	Open-labelled; 4 months; adjunctive omega-3-fatty acids and vitamins C/E supplements	Symptomatic improvement; no significant change in TBARS	33 (Arvindakshan et al., 2003a)
		Improved positive and negative symptoms, extrapyramidal side-effects, SOD levels compared with baseline	17 (Sivrioglu et al., 2007)
	Open-labelled; 2 wk; ascorbic acid adjunctive to haloperidol	No symptomatic improvement	8 (Straw et al., 1989)
Ginkgo biloba extract	RCT; 12 wk; EGb vs. placebo adjunctive to haloperidol	Higher response rate; lower SAPS and SANS scores; reversal of SOD levels	109 (Zhang et al., 2001a,b)
	Single-blinded randomized trial; 8 wk; EGb plus olanzapine vs. olanzapine alone	Lower SAPS scores; reversal of SOD and CAT levels	29 (Atmaca et al., 2005)
NAC	RCT; 6 months; NAC vs. placebo adjunctive to antipsychotic treatment	Superior outcomes on CGI, PANSS, BAS	140 (Berk et al., unpublished observations)

BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; CAT, catalase; CGI, Clinical Global Impressions; CSF, cerebrospinal fluid; EGb, *Ginkgo biloba* extract; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; MRS, magnetic resonance spectroscopy; NAC, *N*-acetylcysteine; NO, nitric oxide; PANSS, Positive and Negative Symptoms Scale; PM, post-mortem; PMN, polymorphonucleocyte; RCT, randomized controlled trial; RNA, ribonucleic acid; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

dynamic equilibrium, were also identified in the schizophrenia group (Yao et al., 2006a). Together, these findings indicate the presence of disturbed redox coupling mechanisms in schizophrenia, which may be related to GSH deficiency and/or time-related reductions in GSSG and GR activities (Yao et al., 2006a). Another post-mortem study examined a number of cortical and subcortical areas from donors with schizophrenia and controls, and found elevated levels of two SOD isoenzymes in the frontal cortex and substantia innominata of those with schizophrenia, thereby suggesting neuroanatomical specificity of redox disturbances in schizophrenia (Michel et al., 2004). Further supportive evidence is provided by a study reporting a 27% reduction in the CSF glutathione level in neuroleptic-naive patients with schizophrenia compared with controls, which coexisted with a 52% glutathione reduction in the medial prefrontal cortex, as measured by magnetic resonance spectroscopy (Do et al., 2000). The low CSF glutathione appears to be consistent with previous findings of decreased levels of its metabolite, γ-glutamylglutamine, in the CSF of schizophrenia patients (Do et al., 1995).

Assays of oxidative products

Estimating levels of oxidative reactive products provide another useful strategy to determine the impact of oxidative stress. Published studies have predominantly examined products of lipid peroxidation and DNA oxidation as markers of oxidative damage. A widely used method of measuring lipid peroxidation is the performance of thiobarbituric acid reactive substances (TBARS) assays. TBARS are low-molecular-weight substances, consisting largely of malondialdehyde (MDA), which are formed from the decomposition of unstable lipid peroxidation products and react with thiobarbituric acid to form fluorescent adducts (Fukunaga et al., 1998). TBARS have been reported to be elevated in the plasma (Akyol et al., 2002; Dietrich-Muszalska and Olas, 2007; Kuloglu et al., 2002c; Mahadik et al., 1998; Ranjekar et al., 2003; Zhang et al., 2006a), erythrocytes (Altuntas et al., 2000; Herken et al., 2001), leucocytes (Srivastava et al., 2001) and platelets (Dietrich-Muszalska et al., 2005) of schizophrenia patients, in conjunction with abnormalities in antioxidant levels, and depleted essential polyunsaturated fatty acids, which are especially prone to lipid peroxidation (Arvindakshan et al., 2003b; Khan et al., 2002). Data on CSF levels of TBARS in schizophrenia are limited, but one small study has been published, reporting reduced levels in a group of actively psychotic patients compared with controls (Skinner et al., 2005). This unexpected finding raises questions about the origins of the elevated blood TBARS that has been broadly reported in the literature, although the CSF results may have been confounded by diminished neuronal membrane substrates in the patient cohort (Skinner et al., 2005) and replication of the study is required. The F_2 isoprostanes, products of the free radical-induced oxidation of arachidonic acid, have been suggested to be superior to TBARS as markers of lipid peroxidation, and a marked increase of urinary 8-isoprostaglandin $F_{2\alpha}$ has recently been reported in a sample of schizophrenia patients compared with healthy controls (Dietrich-Muszalska and Olas, 2007).

A smaller collection of studies has been published in relation to markers of DNA damage in schizophrenia. A post-mortem study examining the hippocampi of patients with 'poor outcome' schizophrenia and non-psychiatric controls, found a ten-fold higher presence of neuronal 8-hydroxy-2'-deoxyguanosine (8-OhdG) among the patients compared with controls, which correlated with elevated quantities of a cell-cycle activation marker (Ki-67) (Nishioka and Arnold, 2004). One study reported a trend increase in lymphocyte DNA damage in schizophrenia patients compared with control subjects (Young et al., 2007), but another found no difference, although those with schizophrenia showed a non-significant increase in sensitivity to externally induced DNA damage and decrease in DNA repair efficiency (Psimadas et al., 2004).

Molecular and genetic studies

Evidence from molecular and genetic studies support fundamental redox disturbances in the aetiopathogenesis of schizophrenia. In an integrative study of post-mortem prefrontal cortex, using a parallel transcriptomics, proteomics and metabolomics approach, a large proportion of alterations on the transcript, protein and metabolite levels were demonstrated to be associated with mitochondrial function, energy metabolism and oxidative stress responses. Furthermore, almost 90% of schizophrenia patients could be differentiated from controls in this study, including neuroleptic-naive patients and those with <1 yr of overt illness, based on a set of genes that encode for mitochondrial complexes and redox-sensing proteins (Prabakaran et al., 2004). This provides persuasive evidence that mitochondrial function and oxidative stress pathways are intrinsically involved in the pathogenesis of the disorder, although the exact nature of their roles, in particular whether they are primary or secondary changes, are yet to be clarified.

Other studies have identified links between schizophrenia and specific genes, such as those for the key glutathione-synthesizing enzyme, glutamate cysteine ligase modifier (GCLM) subunit (Tosic et al., 2006), and for the antioxidant enzymes manganese superoxide dismutase (Mn-SOD) (Akyol et al., 2005) and glutathione S-transferase T1 (GSTT1) (Saadat et al., 2007). The glutamate cysteine ligase (GCL) connection seems particularly promising, in view of recent data indicating reduced GCL activity, decreased expression of its catalytic subunit (GCLC), and GCLC polymorphism in those with schizophrenia (Gysin et al., 2007). A mitochondrial DNA sequence variation affecting a subunit of NADH-ubiquinone reductase (Complex I), a component of the electron transport chain responsible for generating superoxide, has also been associated with schizophrenia patients and with increased superoxide levels in post-mortem brain samples (Marchbanks et al., 2003). On a related subject, polymorphism of the glutathione S-transferase pi gene (GSTP1) has been reported to be associated with vulnerability to develop psychosis in the setting of methamphetamine abuse (Hashimoto et al., 2005), which may have some bearing on schizophrenia.

Antioxidant properties of antipsychotics

Clinical studies

Antioxidant effects of established antipsychotic agents provide indirect evidence for oxidative pathophysiological mechanisms in schizophrenia. Abnormalities in levels of antioxidants and oxidative products have been reported to reverse over the course of treatment with atypical antipsychotics, coinciding with symptomatic improvement (Dakhale et al., 2004; Zhang et al., 2003). In two published studies, baseline serum SOD (Dakhale et al., 2004; Zhang et al., 2003), MDA and ascorbic acid (Dakhale et al., 2004) levels in patients with schizophrenia significantly differed from those in age- and sex-matched controls, taking smoking status into consideration. Within the patient groups, their baseline levels significantly shifted towards normality after treatment with atypical antipsychotics over the study durations of 8 wk (Dakhale et al., 2004) and 12 wk (Zhang et al., 2003), respectively. Another study with a smaller sample size conducted over 6 months likewise showed normalization of the antioxidative enzymes SOD, CAT and GSH-Px with treatment (Evans et al., 2003). These oxidative marker changes correlated with symptomatic improvements as measured by validated scales, further substantiating an intrinsic link between oxidative stress status and psychotic symptomatology. In contrast, others did not find significant changes in a number of oxidative-antioxidative parameters (Sarandol et al., 2007a) or in serum NO metabolites (Taneli et al., 2004). Membrane essential polyunsaturated fatty acids (EPUFAs) depletion has been reported in schizophrenia, with one proposed mechanism being oxidative peroxidation (Evans et al., 2003; Khan et al., 2002; Ranjekar et al., 2003). Data showing repletion of EPUFAs with treatment (Evans et al., 2003) and higher levels of EPUFAs in medicated patients with chronic schizophrenia compared with never-medicated first-episode patients (Khan et al., 2002), although inconclusive, suggest an ameliorating effect of antipsychotics on disease-related oxidative stress status.

A differential impact on oxidative stress status may exist between typical and atypical antipsychotic medications. Higher levels of lipid peroxidation products have been reported in patients treated with typical than atypical drugs (Kropp et al., 2005), but contradictory results were reported by others (Gama et al., 2006; Zhang et al., 2006a). The differing pro-oxidant potentials of the antipsychotics have been postulated as a mediating factor in the more common development of tardive dyskinesia with typical agents (Andreassen and Jorgensen, 2000).

Preclinical studies

Animal data have demonstrated elevated oxidative stress markers with 45-d and 90-d administration of haloperidol, but not atypicals (Parikh et al., 2003). In extending this study in rats to 180 d, haloperidol was again associated with the greatest level of oxidative stress, but oxidative stress as gauged by significant reductions in enzymatic activities were also seen with chlorpromazine and the atypical agents ziprasidone, risperidone and olanzapine. Both typical and atypical agents were associated with increased lipid peroxidation after 180 d, except for olanzapine. In addition, clozapine, olanzapine, and to a lesser extent risperidone, were able to reverse the changes induced by haloperidol (Pillai et al., 2007). Haloperidol-induced oxidative stress parameters in rats have also been shown to be ameliorated by the antioxidant drug, *N*-acetylcysteine (NAC) (Harvey et al., 2007). In-vitro cell studies have demonstrated a protective effect of atypicals, such as olanzapine and quetiapine, on PC12 cells exposed to oxidative stress (Wang et al., 2005; Wei et al., 2003).

Antioxidant therapies

Clinical trials investigating adjunctive antioxidants in the treatment of schizophrenia have utilized vitamins C and E, *Ginkgo biloba* extract (EGb), and NAC.

Vitamins C and E

The vast majority of vitamin E studies in schizophrenia has focused on its preventive and therapeutic roles in tardive dyskinesia. Conflicting results have been found for dyskinetic symptoms (Adler et al., 1998, 1999), but some have reported efficacy in psychopathology (Lohr and Caligiuri, 1996). A small ($n=40$) randomized, controlled trial comparing vitamin C and atypical antipsychotics with atypical antipsychotics alone (placebo) found that at the end of 8 wk, the baseline plasma ascorbic acid and MDA abnormalities had been significantly reversed in the vitamin C group compared with the placebo group. Symptomatic outcome, as measured with the Brief Psychiatric Rating Scale (BPRS), was also significantly better for the vitamin C group (Dakhale et al., 2005). Other studies reported positive treatment outcomes, in terms of symptoms, functioning and extrapyramidal side-effects, with the supplementation of a combination of omega-3-fatty acids and vitamins C and E (Arvindakshan et al., 2003a; Sivrioglu et al., 2007). However, these findings are difficult to interpret in view of the small sample sizes ($n=17$ and $n=33$), the studies' open-label and non-randomized designs, and concomitant use of antioxidants and polyunsaturated fatty acids. Lack of efficacy was reported by a small ($n=8$), 2-wk open-label trial of vitamin C (Straw et al., 1989).

Ginkgo biloba *extract*

A small body of literature has suggested efficacy of supplementary EGb in schizophrenia. In a 12-wk, double-blind, randomized trial comparing EGb and placebo adjunctive to haloperidol in treatment-resistant patients with schizophrenia ($n=109$), those treated with EGb showed superior outcomes as measured by a higher response rate (57.1% vs. 37.7%) and significant score reductions on the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS). Scores on these scales did not significantly vary in the placebo group, although both groups improved on BPRS scores. Furthermore, treatment-emergent behavioural and neurological side-effects were significantly lower in the EGb group (Zhang et al., 2001b). This group also showed superior improvements in peripheral T cell subsets (CD3+, CD4+, CD8+ and IL-2-secreting cells), which were diminished at baseline (Zhang et al., 2006b). These authors additionally reported elevated pre-treatment SOD levels among patients with treatment-resistant schizophrenia, correlating with positive symptomatic severity, which was selectively reduced in patients receiving EGb but not placebo (Zhang et al., 2001a, 2006b; Zhou et al., 1999), thereby suggesting that antioxidant activity, schizophrenia symptoms and peripheral immune functions may be interrelated. A confounder in this group of studies is the use of haloperidol as treatment base, which through its potential in inducing oxidative stress and cognitive blunting, may have added iatrogenic complexities to the disease and treatment process, such that it is difficult to determine whether the superior outcomes were due to lessened adverse effects, underlying psychopathology, or both. This concern was minimized in a subsequent placebo-controlled trial of EGb adjunctive to olanzapine, which also found significantly lower SAPS scores, SOD and CAT levels among the EGb group, although this study had other limitations, such as its single-blinded design and underpowered sample size ($n=29$) (Atmaca et al., 2005).

N-acetylcysteine

NAC is a cysteine prodrug with high bioavailability, which is thought to exert antioxidative effects primarily through enhancing stores of the major intracellular antioxidant, glutathione, by stimulating its formation from cysteine (Atkuri et al., 2007). A series of experiments using an animal model has demonstrated that the pharmacodynamic actions of NAC involve the cystine-glutamate antiporter and extrasynaptic group II metabotropic glutamate receptors (mGluR) (Baker et al., 2007). This may have particular relevance in schizophrenia, as glutamatergic dysfunction has been implicated as a pathophysiological pathway (Goff and Coyle, 2001).

NAC has been studied as an adjunctive treatment in schizophrenia in a recently completed 6-month, double-blind, randomized, placebo-controlled trial ($n=140$), which found significant advantages of NAC over placebo on several scales that include the Clinical Global Impressions (CGI) (effect size of 0.43), the Positive and Negative Symptoms Scale (PANSS) (effect size of 0.57) and the Barnes Akathisia Scale (BAS) (effect size of 0.44) (Berk et al., unpublished observations). In a subset of patients enrolled in this study ($n=11$), NAC was also associated with an increase in plasma glutathione and the amelioration of mismatch negativity, an auditory evoked potential component characteristically impaired in schizophrenia, which may indicate the ability of NAC to correct more fundamental neurophysiological dysfunction (Lavoie et al., 2007).

Bipolar disorder

Similar types of studies, albeit more limited in scope, have provided evidence for oxidative dysfunction in bipolar disorder (Table 2). The majority is derived from biochemical and pharmacological data.

Markers of oxidative disturbances

Oxidative disturbances have been demonstrated in both animal models and human studies.

Animal studies

In animal models of mania, where amphetamine was administered to rats, raised levels of protein oxidation markers were detected in brain tissues following both single and repeated dosing, with the additional induction of lipid peroxidation markers on repeated exposure (Frey et al., 2006a). Exposure to amphetamine has also been linked to SOD and CAT alterations (Frey et al., 2006c), as well as to increased superoxide production in submitochondrial particles in the rat brain (Frey et al., 2006b). In these studies, the striatum, hippocampus and prefrontal cortex have shown differential vulnerability and adaptivity (Frey et al., 2006a, c).

Human assays of oxidants, antioxidants and oxidative products

Human data of oxidative markers in bipolar disorder are often derived from studies with patient samples that include other psychiatric disorders. In two such studies, increased SOD activities as compared with healthy controls were associated with both bipolar disorder and schizophrenia (Abdalla et al., 1986; Kuloglu et al., 2002c), whereas another study found a trend for reduced SOD in bipolar disorder and significantly reduced CAT levels for both groups (Ranjekar et al., 2003). However, GSH-Px changes were reported for schizophrenia only (Kuloglu et al., 2002c; Ranjekar et al., 2003). An increase in the lipid peroxidation product, TBARS, was also reported for both bipolar disorder and schizophrenia (Kuloglu et al., 2002c), as was a decrease in EPUFAs (Ranjekar et al., 2003). In a study involving patients with bipolar disorder, major depressive disorder and schizoaffective disorder, the pooled data showed reduced NO, CAT and GSH-Px levels, unchanged SOD and elevated MDA levels compared with controls, but the results were not analysed according to diagnosis (Ozcan et al., 2004).

A comparatively large study was conducted solely on bipolar disorder patients, who were at various phases of the illness, thus allowing the exploration of phase-specific changes in oxidative stress status. Interestingly, raised TBARS levels were observed regardless of illness phase, whereas GSH-Px activity was only elevated in euthymia but not in depressed or manic phases. Increased SOD activity was associated with manic and depressive episodes but not euthymia, and CAT reduction with mania and euthymia but not depression (Andreazza et al., 2007). An oxidative profile consistent with these findings were reported in a twin case report of mania (Frey et al., 2007). However, another study reported lowered SOD levels in bipolar depression, in conjunction with elevated NO levels (Selek et al., 2007). In a study comparing both unmedicated and lithium-treated patients in manic episodes with healthy controls, TBARS, SOD and CAT levels were significantly higher in manic patients compared with controls, with the lithium-treated group showing lower levels of TBARS and SOD than unmedicated patients, suggesting possible corrective effects of lithium on oxidative parameters (Machado-Vieira et al., 2007). Elevated NO and nitrite levels have been reported in bipolar disorder patients (Gergerlioglu et al., 2007; Savas et al., 2006; Yanik et al., 2004b), and have been correlated with the number of manic episodes (Gergerlioglu et al., 2007; Savas et al., 2006).

Molecular and genetic studies

Genetic studies have identified certain polymorphisms in bipolar disorder patients that play a role in oxidative homeostasis. A single-nucleotide polymorphism of the TRPM2 gene, which encodes for a calcium channel receptor, has been strongly associated with bipolar disorder and is understood to cause cellular calcium dysregulation in response to oxidative stress (McQuillin et al., 2006). Dysregulation of second-messenger calcium has been described in bipolar disorder, and the modulation of this is thought to be a therapeutic mediating mechanism of lithium (Berk et al., 1995, 1996). Innate dysregulation of the apoptosis and oxidative processes has been suggested by a recent study, in which the hippocampal expression of genes encoding DNA repair and antioxidant enzymes were found to be down-regulated in bipolar disorder, while many apoptosis genes were up-regulated (Benes et al., 2006).

A related theoretical framework for the pathophysiology of bipolar disorder has centred on impaired mitochondrial metabolism as the primary defect in

Table 2. Data relating to oxidative stress disturbances in bipolar disorder

			Compared with controls	Sample size (*n*) of patients
Markers of oxidative disturbances				
Assays of oxidants and antioxidants				
NO metabolites	Serum		Increased	43 (Yanik et al., 2004b); 27 (euthymia) (Savas et al., 2006); 30 (depressed phase) (Selek et al., 2007); 29 (manic phase) (Gergerlioglu et al., 2007)
	Erythrocyte		Decreased	30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
Antioxidative enzymes	SOD	Plasma or serum	Increased	27 (euthymia) (Savas et al., 2006); 84 (manic and depressed phases only) (Andreazza et al., 2007); 45 (manic phase) (Machado-Vieira et al., 2007)
			Decreased	30 (depressed phase) (Selek et al., 2007); 29 (manic phase) (Gergerlioglu et al., 2007)
		Erythrocyte	Increased	20 (Abdalla et al., 1986); 23 (Kuloglu et al., 2002c)
			Unchanged	10 (Ranjekar et al., 2003); 30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
	CAT	Plasma or serum	Increased	45 (manic phase) (Machado-Vieira et al., 2007)
			Decreased	84 (manic phase and euthymia only) (Andreazza et al., 2007)
		Erythrocyte	Decreased	10 (Ranjekar et al., 2003); 30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
	GSH-Px	Serum	Increased	84 (euthymia only) (Andreazza et al., 2007)
		Erythrocyte	Unchanged	20 (Abdalla et al., 1986); 23 (Kuloglu et al., 2002c); 10 (Ranjekar et al., 2003)
			Decreased	30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
Assays of oxidative products				
TBARS/MDA		Plasma or serum	Increased	23 (Kuloglu et al., 2002c); 84 (Andreazza et al., 2007); 45 (manic phase) (Machado-Vieira et al., 2007)
			Unchanged	10 (Ranjekar et al., 2003)
		Erythrocyte	Increased	30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
Molecular and genetic studies				
Susceptibility genes		TRPM2		600 (McQuillin et al., 2006)
	Increased expression of neuronal NOS1, altered expression of GSH-Px 4, glyoxylase, esterase D-formylglutathione hydrolase, glutathione synthetase, glutathione S-transferase A2, M5 and omega, CAT, SOD			9 (Benes et al., 2006)
Antioxidant properties of established therapeutic agents				
Clinical studies	Improvement of lowered SOD but no significant change in NO elevation with treatment in manic patients			29 (Gergerlioglu et al., 2007)
	Improvement of reduced GSH-Px with treatment			30 (18 bipolar disorder; 12 other affective disorders) (Ozcan et al., 2004)
	Improvement of elevated SOD and TBARS in the twin treated for mania compared with the other twin who refused anti-manic treatment			Monozygotic twin case study (Frey et al., 2007)
	Rise in blood GSH 2–4 h after ECT			20 (mixed diagnoses) (Henneman and Altschule, 1951)

Table 2 (*cont.*)

			Agent studied
Preclinical studies	Rats	Prevention/reversal of lipid peroxidation in rat model of mania	Lithium, valproate (Frey et al., 2006d)
		Lithium increased total antioxidant reactivity, increased SOD, and reduced ROS formation; unable to prevent stress-induced disturbances in oxidative parameters	Lithium (de Vasconcellos et al., 2006)
	In-vitro cell studies	Inhibited ferric chloride-induced lipid peroxidation and protein oxidation	Valproate (Wang et al., 2003)
		Inhibited glutamate-induced MDA, protein carbonyls, DNA fragmentation and cell death	Lithium, valproate (Shao et al., 2005)
		Inhibited hydrogen peroxide-induced cell death; increased GSH and GCL expression	Lithium, valproate, carbamazepine, lamotrigine (Cui et al., 2007)
		Cytoprotective effects against hydrogen peroxide-induced neural cell death	Lithium, valproate (Lai et al., 2006)

Antioxidant therapies

	Trial design	Treatment outcomes	Sample size (*n*)
NAC	RCT; 6 months; NAC vs. placebo adjunctive to treatment-as-usual	Superior outcomes on BDRS, MADRS and functional measures	75 (Berk, 2007)

BDRS, Bipolar Depression Rating Scale; CAT, catalase; ECT, electroconvulsive therapy; GCL, glutamate cysteine ligase; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; MADRS, Montgomery–Åsberg Depression Rating Scale; MDA, malondialdehyde; NAC, *N*-acetylcysteine; NOS1, nitric oxide synthase; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

bipolar disorder (Kato, 2006; Young, 2007). This concept is supported by data from a number of sources, including magnetic resonance spectroscopy evidence of decreased brain energy metabolism, maternal hereditary patterns, comorbid mitochondrial diseases, mitochondrial mechanisms of mood stabilisers, and mitochondrial DNA deletions, mutations and polymorphisms (Kato, 2007).

Antioxidant properties of established therapeutic agents

Clinical studies

Indirect support for the pathophysiological role of oxidative stress in bipolar disorder comes from clinical studies that demonstrate normalisation of oxidative parameters over the course of treatment (Frey et al., 2007; Gergerlioglu et al., 2007; Henneman and Altschule, 1951; Ozcan et al., 2004). This has been elegantly illustrated by a case report of twins presenting with mania, where increased TBARS, SOD and DNA damage, and decreased CAT were observed in both patients prior to treatment. Whilst the twin who was successfully treated showed normalization of TBARS and SOD, the oxidative parameters remained unchanged for the other twin who refused treatment and continued to be manic (Frey et al., 2007). In addition, the evidence behind the antioxidant properties of antipsychotics is also relevant for bipolar disorder, considering their efficacy in its treatment, particularly of mania. An early study of psychiatric patients, including those with bipolar disorder, also bears some relevance to the current discussion through demonstrating a rise in blood glutathione 2–4 h following electroconvulsive therapy (Henneman and Altschule, 1951).

Preclinical studies

The antioxidant properties of mood stabilisers have been further strengthened by findings from animal and cell studies. In a rat model of mania using amphetamine, both lithium and valproate were able to prevent and reverse amphetamine-induced hyperactivity, prevent lipid peroxidation in the hippocampus and reverse lipid peroxidation in the prefrontal cortex. No alterations were seen for protein carbonyl formation in this model, and changes in antioxidant enzymes were variable (Frey et al., 2006d). Others have supported the antioxidant effects of lithium, but have not found it able to prevent stress-induced oxidative damage in rats (de Vasconcellos et al., 2006). Treatment with valproate has been shown to inhibit lipid peroxidation and protein oxidation in primary cultured rat cerebrocortical cells exposed to an oxidant (Wang et al., 2003). Using similar cell cultures, treatment with lithium or valproate was also shown to inhibit the glutamate-induced intracellular calcium release, lipid peroxidation, protein oxidation, DNA fragmentation and cell death (Shao et al., 2005). Other cell culture studies have associated lithium and valproate with increased expression of the endoplasmic reticulum stress proteins GRP78, GRP94 and calreticulin (Chen et al., 2000; Shao et al., 2006), increased levels of the anti-apoptotic factor bcl-2 (Chen et al., 1999), glutathione and glutamate-cysteine ligase (Cui et al., 2007), and reduced cytochrome *c* release and caspase-2 activation (Lai et al., 2006), thereby implying that multiple pharmacodynamic actions may underlie the neuroprotective effects of these agents against oxidative stress. However, increased glutathione levels and glutamate-cysteine ligase gene expression found with other mood stabilizers such as carbamazepine and lamotrigine suggest that glutathione may be a common neuroprotective target among mood stabilizers (Cui et al., 2007). Furthermore, evidence from human cell studies have found neuroprotective effects from lithium and valproate in neural but not glial cells (Lai et al., 2006), suggesting a specificity to their therapeutic effects.

Antioxidant therapies

Clinical studies

A recent randomized, placebo-controlled trial of adjunctive NAC in the treatment of bipolar disorder ($n=75$) has shown favourable outcomes, as assessed by a number of symptomatic, global and functional scales. The primary findings were improvement in depressive symptomatology, on both the Bipolar Depression Rating Scale (BDRS) and the Montgomery–Åsberg Depression Rating Scale (MADRS), with significant benefits on functioning and quality of life also documented (Berk, 2007).

Preclinical studies

In the rat model of mania, pre-treatment with NAC significantly attenuated the methamphetamine-induced hyperlocomotion, behavioural sensitization, and striatal dopamine depletion in a dose-dependent fashion (Fukami et al., 2004).

Depression

There is evidence for oxidative disturbances in major depression, as demonstrated by oxidative marker studies and those examining the antioxidant effects of antidepressants (Table 3). There is no data of antioxidants as therapeutic agents for this condition.

Markers of oxidative disturbances

Animal studies

Data from animal models have demonstrated the depletion of glutathione (Pal and Dandiya, 1994), reduction of GSH-Px and vitamin C, and rise in lipid peroxidation and NO (Eren et al., 2007b) in association with stress-induced behavioural depression.

Human assays of oxidants, antioxidants and oxidative products

Human studies have reported a number of oxidative disturbances in patients with major depression, including oxidative damage in erythrocytic membranes as suggested by the depletion of omega-3 fatty acids (Peet et al., 1998); elevated lipid peroxidation products (Bilici et al., 2001; Khanzode et al., 2003; Sarandol et al., 2007b; Selley, 2004); oxidative DNA damage (Forlenza and Miller, 2006); reduced serum vitamins C (Khanzode et al., 2003) and E (Maes et al., 2000; Owen et al., 2005), the latter of which was not accounted for by dietary insufficiency (Owen et al., 2005); increased concentrations of the endogenous inhibitor of endothelial NO synthase asymmetric dimethylarginine (ADMA) (Selley, 2004) and decreased NO (Selley, 2004; Srivastava et al., 2002). Albumin, which has antioxidant activity, has also been reported to be compromised in major depression (Van Hunsel et al., 1996). Findings of altered antioxidant enzyme levels have been mixed, with reports of elevated SOD (Bilici et al., 2001; Khanzode et al., 2003; Sarandol et al., 2007b), GSH-Px and GR (Bilici et al., 2001), diminished SOD (Herken et al., 2007), and no change (Srivastava et al., 2002). In one study of major depressive disorder patients who had been medication-free for at least 2 months, the plasma total antioxidant potential and

Table 3. Data relating to oxidative stress disturbances in major depressive disorder

			Compared with controls	Sample size (*n*) of patients
Markers of oxidative disturbances				
Assays of oxidants and antioxidants				
NO metabolites	Plasma		Decreased	25 (Selley, 2004)
	Serum		Unchanged	36 (Herken et al., 2007)
	PMN		Decreased	30 (Srivastava et al., 2001)
Peroxide	Plasma		Increased	21 (Yanik et al., 2004a)
Antioxidative enzymes	SOD	Serum	Increased	62 (Khanzode et al., 2003)
			Decreased	36 (Herken et al., 2007)
		Erythrocyte	Increased	12, 18 (Bilici et al., 2001); 96 (Sarandol et al., 2007b)
		PMN	Unchanged	15 (Srivastava et al., 2001)
	CAT	Erythrocyte	Unchanged	12, 18 (Bilici et al., 2001)
		PMN	Unchanged	26 (Srivastava et al., 2001)
	GSH-Px	Plasma	Unchanged	12, 18 (Bilici et al., 2001)
		Erythrocyte	Increased	12 (Bilici et al., 2001)
			Unchanged	18 (Bilici et al., 2001)
		PMN	Unchanged	12 (Srivastava et al., 2001)
Vitamin C	Plasma		Decreased	62 (Khanzode et al., 2003)
Vitamin E	Plasma or serum		Decreased	42 (Maes et al., 2000); 49 (Owen et al., 2005)
Albumin, total serum protein	Plasma or serum		Decreased	37 (Van Hunsel et al., 1996)
Uric acid	Plasma		Decreased	21 (Yanik et al., 2004a)
Total antioxidant potential	Plasma		Decreased	21 (Yanik et al., 2004a)
Assays of oxidative products				
TBARS/MDA	Plasma or serum		Increased	12, 18 (Bilici et al., 2001); 62 (Khanzode et al., 2003); 96 (Sarandol et al., 2007b)
	Erythrocyte		Increased	12, 18 (Bilici et al., 2001); 96 (Sarandol et al., 2007b)
HNE	Plasma		Increased	25 (Selley, 2004)
8-OHdG	Serum		Increased	84 (Forlenza and Miller, 2006)
Antioxidant properties of antidepressants				
Clinical studies	Improved lipid peroxidation and antioxidative enzyme levels after treatment with SSRIs for 3 months			30 (Bilici et al., 2001)
	Improved MDA, SOD and vitamin C levels with SSRIs for 3 months			62 (Khanzode et al., 2003)
	Improved SOD and NO levels after antidepressant treatment for 8 wk			36 (Herken et al., 2007)
	No significant changes in oxidative markers with 6 wk of antidepressant treatment			96 (Sarandol et al., 2007b)
Preclinical studies	Mice	Replenish glutathione depletion; prevent and/or reverse shock-induced behavioural depression		Imipramine, maprotiline, fluvoxamine, trazodone (Pal and Dandiya, 1994)
	Rats	Correction of GSH-Px, glutathione, vitamin C, and lipid peroxidation levels in the stress-induced depression model		Venlafaxine (Eren et al., 2007b)
		Modulation of antioxidant proteins		Venlafaxine, fluoxetine (Khawaja et al., 2004)
		Improvement of depression-related lipid peroxidation, and GSH-Px, glutathione and vitamin C depletion		Lamotrigine, aripiprazole, escitalopram (Eren et al., 2007a)
	In-vitro cell studies	Attenuate anoxia- and glutamate-induced cell death		Moclobemide (Verleye et al., 2007)
		Attenuate cell loss from chemical oxidative stress; antioxidant effects		Phenelzine (Lee et al., 2003)

8-OhdG, 8-hydroxy-2′-deoxyguanosine; CAT, catalase; GR, glutathione reductase; GSH-Px, glutathione peroxidase; HNE, (*E*)-4-Hydroxy-2-nonenal; MDA, malondialdehyde; NO, nitric oxide; PMN, polymorphonucleocyte; SOD, superoxide dismutase; SSRI, selective serotonin reuptake inhibitor; TBARS, thiobarbituric acid reactive substances.

uric acid were reduced in patients compared with controls, whereas their total plasma peroxide levels and oxidative stress index were both higher (Yanik et al., 2004a). Moreover, a significant positive correlation was found between oxidative stress index and the Hamilton Depression Rating Scale (HAMD) (Yanik et al., 2004a). Similarly, other studies have also reported correlations between depressive severity and the magnitude of disturbances in their respective oxidative indices (Bilici et al., 2001; Forlenza and Miller, 2006; Owen et al., 2005; Sarandol et al., 2007b), although one study found no such relationship (Herken et al., 2007).

The enhanced oxidation of apolipoprotein B-containing lipoproteins, correlating with the severity of major depression, along with significant reductions in serum paraoxonase/arylesterase activities following antidepressant treatment, have been demonstrated (Sarandol et al., 2006). As oxidation of lipoproteins and low paraoxonase activity have been implicated in atherogenesis and coronary artery disease, these results may be relevant in understanding the link between major depression and cardiovascular disease (Sarandol et al., 2006). Others have also suggested oxidative changes, such as cumulative oxidative DNA damage, to be a common pathophysiological mechanism underlying major depression and medical comorbidities (Forlenza and Miller, 2006).

Antioxidant properties of antidepressants

Clinical studies

A small group of studies, by demonstrating reversals of antioxidant and oxidative disturbances after antidepressant treatments, has provided evidence for the antioxidant effects of these drugs (Bilici et al., 2001; Herken et al., 2007; Khanzode et al., 2003). Relating to this observation, oxidative parameters have been nominated by some authors to be candidate markers of antidepressant efficacy (Bilici et al., 2001; Herken et al., 2007). However, studies have not been unanimous in associating normalization of oxidative parameters with antidepressant treatment. One comparatively larger study found that 6 wk of antidepressant treatment did not affect oxidative-antioxidative systems, regardless of the response or remission status of the patients (Sarandol et al., 2007b).

For drugs other than antidepressants, the antioxidant effects of lithium may also lend support for oxidative stress mechanisms behind major depression, as it has an established role as adjunctive treatment.

Preclinical studies

In animal studies, antidepressants of different classes have been shown to replenish, to varying degrees, the glutathione depletion seen in the inescapable shock behavioural paradigm of depression (Pal and Dandiya, 1994). Venlafaxine was associated with the correction of several depression-specific oxidative markers in the rat cortex (Eren et al., 2007b). A proteomic study using rats has found multiple protein modulations in the hippocampus after venlafaxine or fluoxetine administration. Antioxidant and anti-apoptotic proteins were among those identified (Khawaja et al., 2004). In another animal study, lamotrigine, aripiprazole and escitalopram were all shown to improve depression-related GSH-Px, glutathione and Vitamin C depletion, and lipid peroxidation increase. Of the three drugs, lamotrigine was associated with the greatest anti-oxidative protective effects (Eren et al., 2007a). An in-vitro study of rat cerebrocortex neuronal and astroglial cultures showed that moclobemide could attenuate cell death induced by anoxia and glutamate, a process involving oxidative stress pathways (Verleye et al., 2007). The monoamine oxidase inhibitor phenelzine was able to attenuate the loss of differentiated rat PC12 cells exposed to chemical oxidative stress, and demonstrated antioxidant effects including the reduction of ROS formation and the scavenging of the pro-oxidant hydrogen peroxide (Lee et al., 2003).

Antioxidant therapies

Preclinical studies

As no clinical trials of antioxidant therapies have been published for major depressive disorder, the primary evidence for antioxidant efficacy at present is derived from the previously cited animal study, which demonstrated the prevention and reversal of shock-induced behavioural depression with glutathione (Pal and Dandiya, 1994).

Indirect clinical studies

A small ($n = 16$), open-label study of adjunctive EGb in the treatment of patients with major depressive has been published, reporting positive outcomes in terms of improved sleep efficiency and awakenings, but depressive outcomes were not reported (Hemmeter et al., 2001). The beneficial effects of NAC on mood in a non-clinically depressed population have been reported from a double-blind, placebo-controlled study of NAC in patients with mild chronic bronchitis. NAC recipients showed significantly superior outcomes on the General Health Questionnaire (GHQ), which predominantly measures mood, compared with the placebo group (Hansen et al., 1994). The limitations to generalizing these indirect results to depression are apparent.

Anxiety disorders

The notion of oxidative stress mechanisms underlying anxiety disorder has been in existence for some years, with the earlier suggestion that NO and peroxynitrite might play a major role in setting up a vicious aetiological cycle involving free radicals and inflammatory cytokines in post-traumatic stress disorder (Miller, 1999; Pall and Satterlee, 2001). However, oxidation biology research in anxiety disorders is still at its infancy, and the bulk of the limited literature originates from animal studies, which have nevertheless generated intriguing findings.

Animal studies

An interesting set of animal experiments have linked glyoxalase 1 (Glo1) and glutathione reductase 1 (GR) genes, both of which protect against oxidative stress, with anxiety in mice (Hovatta et al., 2005). By using behavioural analysis of six inbred mouse strains to determine anxiety phenotypes and quantitative gene expression profiling of seven pertinent brain regions, 17 candidate genes were identified, of which both Glo1 and GR showed positive correlations between their expressed activity levels and phenotypic anxiety status. The causal role that these genes may play in anxiety were supported by a series of experiments, which confirmed a highly significant positive correlation between the expressed activities of these genes and anxiety in cross-bred mice, and demonstrated that over-expression of Glo1 and GR in the cingulate cortex increased anxiety behaviours, while inhibition of Glo1 gene expression reduced such behaviours (Hovatta et al., 2005). The over-expression of Glo1 in innately anxious mice has also been reported by others (Landgraf et al., 2007).

Further evidence for oxidative pathways being involved in mouse models of anxiety can be derived from the association of vitamin E depletion and increased oxidative stress markers and anxiety behaviours in phospholipid transfer protein (PLTP) knock-out mice (Desrumaux et al., 2005), and from a positive correlation between peripheral blood oxidative stress markers and anxiety behaviours (Bouayed et al., 2007b). The pro-oxidative vitamin A has been demonstrated to induce oxidative stress in the rat hippocampus, as measured by increased lipid peroxidation, protein carbonylation, protein thiol oxidation, and altered SOD and CAT levels, as well as causing anxiety behaviours in the animal model (de Oliveira et al., 2007). In addition, green tea polyphenol (–)-epigallocatechin gallate (EGCG), a potent antioxidant, showed anxiolytic effects on mice with a dose-dependent relationship (Vignes et al., 2006). Anxiolytic effects have also been reported in mice with chlorogenic acid, a dietary polyphenol and antioxidant (Bouayed et al., 2007a). Inconsistent results have been reported for whortleberry extracts in rats, and vitamin E was found to increase anxiety in the same study (Kolosova et al., 2006).

Human studies

In humans, only a handful of relevant studies have been published. These have reported elevated lipid peroxidation products and antioxidant changes in obsessive–compulsive disorder (Ersan et al., 2006; Kuloglu et al., 2002a), panic disorder (Kuloglu et al., 2002b) and social phobia (Atmaca et al., 2004), but not in post-traumatic stress disorder (Tezcan et al., 2003). The study on social phobia also found a reversal of these disturbances following 8 wk of citalopram treatment (Atmaca et al., 2004). A study of anxious women found reduced total antioxidant capacity among this group compared with non-anxious controls, in conjunction with several parameters of impaired immune functioning (Arranz et al., 2007). A case series has reported improvement in trichotillomania, pathological nail-biting and skin-picking, conditions that have similarities with obsessive–compulsive disorder, using NAC (Odlaug and Grant, 2007).

Substance abuse

Substance abuse and dependence are important to consider in psychiatric disorders, given the substantial overlap between the two in terms of syndromal manifestations and causality. A solid body of literature exists in support of the association between oxidative stress and common drugs of abuse, including nicotine (Petruzzelli et al., 2000), alcohol (Peng et al., 2005), cannabis (Sarafian et al., 1999), heroin (Pan et al., 2005), cocaine (Dietrich et al., 2005) and amphetamines (Frey et al., 2006c). Although their precise roles are yet to be fully understood, oxidative mechanisms have been proposed to mediate both the processes of drug addiction and toxicity (Kovacic, 2005; Kovacic and Cooksy, 2005), and antioxidants may thus have therapeutic potential in the management of these conditions. Preclinical evidence has indicated antioxidants to be promising in alcohol (Amanvermez and Agara, 2006), heroin (Zhou and Kalivas, 2007) and cocaine dependence (Baker et al., 2003). Pilot clinical trial data of NAC in cocaine dependence have been promising, suggesting that craving and withdrawal symptoms (LaRowe et al., 2006) as well as cue-evoked desire are reduced with the administration of NAC (LaRowe et al., 2007).

Other conditions

A growing literature has been published that cites evidence for oxidative disturbances in autism, including genetic polymorphisms affecting oxidative metabolic pathways (James et al., 2006), reduced antioxidant capacity (Chauhan et al., 2004; James et al., 2004, 2006), antioxidant enzyme changes (Sogut et al., 2003; Yorbik et al., 2002; Zoroglu et al., 2004) and enhanced oxidative stress biomarkers (Chauhan et al., 2004; James et al., 2004; Ming et al., 2005; Sogut et al., 2003; Yao et al., 2006b; Zoroglu et al., 2004). Impaired oxidative status has also been reported for ADHD, and a randomized, controlled trial of Pycnogenol, a pine bark extract with potent antioxidant properties, in children diagnosed with ADHD ($n=61$) has found symptomatic and biochemical improvements (Chovanova et al., 2006; Dvorakova et al., 2006; Trebaticka et al., 2006). On the other hand, a small ($n=24$) study comparing Pycnogenol and methylphenidate in adult ADHD has failed to show any advantage of either treatment over placebo (Tenenbaum et al., 2002).

Discussion

Currently, the most robust and multi-dimensional evidence for the pathophysiological involvement of oxidative stress is for schizophrenia, followed by bipolar disorder, with both having support from preclinical and clinical research. The data is less extensive for the other psychiatric disorders, but there is accumulating evidence indicating a role of oxidative stress in their aetiopathogenesis. In summary, there is evidence for glutathione depletion in schizophrenia; increased lipid peroxidation in schizophrenia, bipolar and major depressive disorders; and reduction in antioxidants such as albumin and bilirubin in schizophrenia and major depressive disorder. Findings in relation to NO and antioxidative enzymes in these disorders have been less consistent. Data from molecular and genetic studies have implicated oxidative metabolic pathways in the aetiopathogenesis of schizophrenia, bipolar disorder and possibly anxiety disorders. Antipsychotics, mood stabilizers and antidepressants have all been demonstrated to have antioxidative effects, and some antioxidants have been reported to be of therapeutic benefit, including vitamins C and E and EGb for schizophrenia, and NAC for schizophrenia and bipolar disorder.

In the interpretation of mass data, the context and limitations of each investigation must be borne in mind. In view of the complexities of psychiatric conditions and biological systems, and the diversity of research areas, the collective significance of study findings would be expected to have greater strength than individual results. For instance, a substantial portion of the existing evidence base is derived from the comparison of oxidative biochemical status of patients with controls, and such studies have yielded apparently inconsistent results, with varying presence, directions or combinations of disturbances in markers of oxidant and antioxidant activities. Such variations in cross-sectional profiles of selected oxidant/antioxidant markers may merely reflect their dynamic status in the wider oxidative biochemical system, which in turn exists in intricate balance with other biological pathways and systems. Moreover, psychiatric syndromes are aetiologically heterogeneous, commonly chronic and multiphasic, and often overlapping, thus further complicating the specificity of individual marker changes. Alternatively, it is possible that the mixed findings may signify an indirect pathophysiological role of the relevant oxidative markers in the disorders. However, on balance, the literature as a whole seems to provide sufficient consistent evidence that oxidative stress balance is significantly altered in patient groups. In particular, findings of elevated oxidative products across disorders supply fairly direct evidence of increased oxidative stress, while its aetiological significance is supported by genetic and molecular studies that link specific oxidative pathway polymorphisms or gene expression to specific disorders. Genetic manipulation experiments demonstrating positive correlations between the expression of specific oxidative genes and anxiety behaviours in animal models further validate this aetiopathogenic hypothesis. However, it is difficult to distinguish from current data whether oxidative stress results from primary excessive mitochondrial energy generation, primary dysfunction within oxidative homeostatic mechanisms, or both. Impaired mitochondrial energy metabolism has also been suggested to be a fundamental defect in bipolar disorder (Kato, 2007; Young, 2007), with hypometabolism, energy imbalance and oxidative stress assuming secondary roles, and may present an alternative hypothesis. In practical terms, pharmacological and clinical studies have established the antioxidant properties of efficacious pharmacotherapies, and antioxidant treatment data, although limited in quantity, have reported promising therapeutic potentials.

The implications of the expanding data on oxidative stress mechanisms in psychiatric disorders are twofold, having salience in both furthering their aetiopathogenic understanding and treatment options. In relation to the former, the aetiopathogenic mechanisms for psychiatric disorders remain largely elusive, despite the growth of hypotheses on multiple conceptual levels that include sociocultural systems, personality, cognitive schemata, behavioural learning, neuroanatomy, psychoneuroendoimmunology, biomolecules and genetics. Given the complexities of human psychobehavioural systems and the infinite deterministic variability behind their manifestations, basic biopathway pathologies may present tangible and widely applicable pathophysiological models, as all psychobehavioural manifestations must have fundamental biological underpinnings. There is gathering evidence for oxidative stress to be one such biopathway, as oxidative damage is believed to be a major mechanism underlying cell dysfunction and death in both ageing and disease processes, although its temporal role in and relative contribution to these processes is likely to vary. Theoretically, oxidative stress may result from the overproduction of free radicals, defective oxidative homeostasis, or a combination of both. Each of these situations, in turn, is likely to stem from different causes, which may include overactive oxidative metabolism driven by physiological stress, pathogens or the inflammatory response, genetic polymorphisms and physiological factors that undermine the oxidative defence capacity of the individual, and differential expression of mitochondrial and metabolic enzymes. Once established, secondary amplifications or self-perpetuating oxidative cascades may also play a role in the pathogenesis of illnesses, the continuation of symptoms and vulnerability to future illness relapses.

Evidence for the interdependent relationships between oxidative pathways and those involving neurotransmitters, hormones and inflammatory mediators further enhance the plausibility of the oxidative stress hypothesis, and provide a unifying framework for the various conceptual theories of causality. Dopaminergic, noradrenergic and glutamatergic overactivity have been demonstrated to induce cytotoxicity via oxidative stress among other mechanisms (Chan et al., 2007; Chen et al., 2003; Penugonda et al., 2005), and this cytotoxicity has been suggested to be specific for neurones (Chan et al., 2007). There is also evidence for a link between neuro-inflammatory processes and oxidative stress, which may be mediated by the overproduction of free radicals by activated glial cells during inflammatory states, and/or via the activation of the cyclooxygenase (COX) and lipoxygenase (LOX) pathways or pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 and interferon-γ (Hayley et al., 2005; Tansey et al., 2007). These connections provide a basis for explaining phenomena such as drug-induced and organic psychiatric syndromes, as well as comorbid somatic and psychiatric disorders. The association of particular neurochemical pathways with oxidative stress induction, combined with the differing vulnerabilities of neuronal and glial cells to oxidative damage according to their types and anatomical positions, may help to explain the involvement of specific neurological sites in psychiatric syndromes. This specificity of site can be observed in neuroimaging studies (Ettinger et al., 2007; Sheline et al., 2003; van Erp et al., 2004), and may be useful in attempting to understand both the acute and long-term syndromal manifestations of the various psychiatric conditions. The involvement of similar sites across conditions may also account for their symptomatic overlap and diagnostic mutability.

Apart from conceptual utility, a theory of value should also demonstrate practical applicability. An appealing aspect of the oxidative stress theory is that regardless of the precise defect(s), this state of disequilibrium can theoretically be corrected by bolstering the total antioxidant capacity, providing that the supplementary antioxidants are bioactive and able to access the brain. The practical utility of this theory has already garnered support from the existing literature, which has found benefits from the use of vitamins C and E, EGb, NAC and other antioxidants in psychiatric disorders. NAC, in particular, seems to hold the most promising evidence for efficacy across diagnoses, with benefits recently reported for schizophrenia, bipolar disorder, cocaine dependence, and impulsive control disorders. This may relate to its bioavailability and putative mechanisms of replenishing and enhancing glutathione stores (Dean et al., 2004), which possibly has a more weighted impact in the brain than other antioxidants. Further clinical evidence is required to consolidate the efficacies of antioxidants for the various conditions, but their potential in acute and maintenance treatment settings are clearly implied on theoretical grounds. Furthermore, these treatments may be useful in the prevention of long-term sequelae by minimizing cell damage and cell death, as well as primary prevention in vulnerable individuals.

These treatments are generally associated with low occurrence of side-effects, which is an attractive feature conducive to long-term treatment adherence.

The investigation of antioxidants in psychiatric disorders has perhaps been hampered by several unfavourable factors, the main ones probably relating to the conventional aetiopathophysiological understanding of psychiatric disorders and to misconceptions about antioxidants. Traditionally, psychiatric teachings and research have focused on neurotransmitter aetiological theories, such as the dopamine theory for schizophrenia and the monoamine hypothesis for depression, and these have provided a basis for therapeutic manipulations. Entwined with this situation is the fact that the majority of established biological treatments, where their mechanisms of action are clarified, have primary discernible effects on neurotransmitter receptors and/or their biodegradation. Antioxidants serve a buffering role in oxidative physiology, and are often regarded as 'natural' remedies rather than pharmacological therapies. However, the usefulness of precursor compounds to 'natural' endogenous substances is not unfamiliar in medicine, as exemplified by L-dopa in the treatment of Parkinson disease, a drug which can be analogously compared with the cysteine precursor, NAC. The unfamiliar mechanisms of action of antioxidants to clinical psychiatry may thus have contributed to their peripheral therapeutic status. Furthermore, the heterogeneity within antioxidants as a class is not widely appreciated. Differences exist among the antioxidants in their targets of action, as well as in their pharmacokinetic properties. Vitamin E, for example, has a principal antioxidant action of scavenging peroxyl radicals in biological lipid phases (Traber and Atkinson, 2007), in addition to multiple non-antioxidant properties that include modulation of signal transduction, transcriptional and translational processes (Zingg and Azzi, 2004), yet its antioxidant efficacy in pathological redox states has not been established (Azzi, 2007). Vitamin C, on the other hand, is a scavenger of free radicals in water phases (Rodrigo et al., 2007), while *Ginkgo biloba* has antioxidant properties that probably include the prevention of lipid peroxidation (Drieu et al., 2000). The specific antioxidant actions of these agents, when applied to neuropsychiatric conditions where the precise oxidative defects are not yet clear, may account for some inefficacious trial findings (Boothby and Doering, 2005). In this respect, glutathione may be the most generic of cellular antioxidants in terms of its molecular actions, which may explain the promising findings with NAC.

Besides pharmacological treatments, lifestyle and dietary manipulations are relevant in optimizing oxidative balance. A diet rich in natural antioxidants and the avoidance of oxidative stress-inducing habits such as cigarette smoking and substance abuse are prudent measures. Diets high in saturated fats may increase oxidative stress (Shih et al., 2007), and their intake are best minimized. Physical exercise, specifically endurance training, has also been suggested to have a beneficial impact on oxidative stress status, possibly mediated by increasing total antioxidant capacity and GSH-Px activity (Fatouros et al., 2004).

The other major practical implication ensuing from the oxidative stress theory of pathogenesis is the potential use of oxidative/antioxidant profiles and oxidative products as biomarkers of psychiatric disorders, their activity status and treatment response. Although the current state of evidence is not yet mature enough to adopt this in clinical practice, findings of syndrome- (Reddy et al., 2003) and phase-specific (Andreazza et al., 2007) profiles, and treatment-related normalization (Bilici et al., 2001; Dakhale et al., 2004; Frey et al., 2007; Gergerlioglu et al., 2007; Henneman and Altschule, 1951; Herken et al., 2007; Khanzode et al., 2003; Ozcan et al., 2004; Zhang et al., 2003) support this as a possible future application. Genetic polymorphisms of antioxidant enzymes, associated with psychiatric disorders (Akyol et al., 2005; Saadat et al., 2007; Tosic et al., 2006), may have potential in assisting the identification of at-risk individuals.

In research, broad areas remain to be explored on both preclinical and clinical levels, especially for mood and anxiety disorders which have an early evidence base. The use of antioxidants in their treatment is both substantiated and promising, in view of the internally consistent theoretical framework, convincing early evidence, wide-ranging potential therapeutic benefits, the high population prevalence and overall disease burden associated with these disorders, and the limited efficacies of existing pharmacotherapies.

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Statement of Interest

None.

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