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Glutathione: a novel treatment target in psychiatry

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There is accumulating evidence for oxidative stress mechanisms as common pathophysiological pathways in diverse psychiatric disorders, which offers novel treatment targets in oxidation biology systems. Of these the glutathione system has the most favourable theoretical foundation, given its dominance as the most generic of cellular antioxidants. Clinically, this hypothesis has been supported by several recently published studies that have reported on the efficacy of N-acetylcysteine, a glutathione precursor, in the treatment of various psychiatric disorders. This article outlines the multidimensional evidence that currently exists for oxidative stress mechanisms in psychiatric disorders and specifically discusses glutathione as a promising novel therapeutic target.

Introduction

Having lain fallow for almost three quarters of a century since its first reported findings in psychiatry [1], the field of oxidation biology is attracting renewed interest. This has emerged in the context of oxidation biology developments in other areas of medicine, recognition of the brain's particular susceptibility to oxidative damage (see Box 1) and encouraging findings relating to the role of oxidative stress in psychiatric disorders. As much remains unclear in our understanding and treatment of psychiatric disorders, oxidation biology offers a new perspective for investigation.

The concept of oxidative stress is centred on the imbalance of oxidants against antioxidants beyond physiological limits, and the significance of oxidative stress states lies in the resultant oxidative cellular damage and related sequelae that range from cellular dysfunction to cell death. There is accumulating evidence for the presence of oxidative stress states in different psychiatric disorders that, in view of their aetiological diversity, would suggest that oxidative stress mechanisms are active in the pathophysiology of the major psychiatric disorders. These pathways present potential treatment targets that might be applicable to multiple disorders. In particular the ubiquitous and dominant cellular antioxidant glutathione (GSH) stands out as a promising candidate. This article will outline the key evidence that implicates oxidative stress mechanisms in psychiatric disorders and argue for GSH to be a novel treatment target.

Oxidative stress can result from either increased production of reactive species from nitrogen (RNS, such as nitric oxide) or oxygen (ROS, including hydrogen peroxide H_2O_2) or diminution of oxidative defences, occurring in the context of mitochondrial energy generation. The antioxidant system has interacting components, including superoxide dismutase, whose role is to convert the superoxide radical to H_2O_2, which is converted into water and oxygen by catalase and water by glutathione peroxidase (GPx). Glutathione is a tripeptide composed of glutamate, cysteine and glycine and exists in reduced monomeric (GSH) and oxidised dimeric forms (GSSG). It is synthesized by using two enzymes, glutamate cysteine ligase (GCL or gamma-glutamylcysteine synthetase) and glutathione synthetase. GCL catalyses the ATP-dependent condensation of cysteine and glutamate to form the dipeptide gamma-glutamylcysteine. GCL is a heterodimeric enzyme composed of two proteins: GCL catalytic subunit (GCLC) possesses all of the catalytic properties, whereas GCL modifier subunit (GCLM) increases the catalytic efficiency of GCLC. GSH neutralises oxidative free radicals in nonenzymatic reactions and reactions with H_2O_2 catalysed by isoforms of glutathione peroxidase (GPx) and with nucleophile acceptors catalysed by isoforms of glutathione S transferase (GST) [2,3]. The GSH pathways are shown in Figure 1.

Alterations in brain energy generation in mood disorders are an established neuroimaging finding [4] and are supported by data showing that polymorphisms of genes, mRNA and mitochondrial complex proteins involved in the electron transport chain are altered in both schizophrenia and bipolar disorder [5]. Mitochondrial energy generation is the principal source of superoxide, which can further increase oxidative stress through damage to mitochondrial DNA. In psychiatric disorders altered mitochondrial ultrastructure, metabolic activity and gene expression are found [5]. Dopamine is implicated in the pathophysiology of schizophrenia, mania and depression [6,7], and the oxidative metabolism of dopamine is a further potential source of oxidative stress [8] (Figure 2). Oxidative stress also is a signalling mechanism and induces changes in multiple components of the antioxidant pathways as well as in receptors including

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Box 1. Factors that enhance the brain's susceptibility to oxidative damage

- High oxygen utilisation (thus generating higher amounts of free radical by-products) [62].
- Biochemical environment conducive to oxidation [62]:
  - high lipid content;
  - reducing potential of some neurotransmitters;
  - presence of redox-catalytic metals, for example iron and copper.
- Relatively limited antioxidant defences [62].
- Generation of secondary oxidative cellular insults through the neurotoxic effects of released excitatory amines (particularly dopamine and glutamate) and secondary inflammatory responses [8].

dopamine [9]. In this manner the oxidation of dopamine can induce glutathione [10].

Oxidative stress in psychiatric disorders

The greatest volume of oxidation biology data are present in schizophrenia, bipolar and major depressive disorders, and they will accordingly be the focus of this paper. Anxiety disorders, substance abuse and autism also are accumulating a literature base. Sources of data include measures of oxidative status, functional neuroimaging and genetic and molecular studies. Demonstration of the antioxidative effects of established therapeutic agents and clinical trials of antioxidant therapies complete the evidence base. Such manifold evidence in providing various perspectives helps to strengthen the hypothesis that oxidative stress is a common pathophysiological process in several major psychiatric disorders.

Quantifying levels of oxidative stress

As the direct measurement of free radical concentrations is not feasible because of their short half-lives and low concentrations, oxidative status has been gauged by assays of reactive species metabolites (e.g. nitric oxide metabolites), antioxidative enzymes (e.g. superoxide dismutase, catalase and glutathione peroxidase), antioxidants (e.g. GSH, vitamins C and E, albumin, bilirubin) and oxidation products (e.g. lipid peroxidation products). Although all components in the complex and dynamic oxidation biological system cannot be simultaneously captured, the partial snapshots that these studies provide collectively indicate oxidative disturbances in disease states. In essence these studies have demonstrated reduced concentrations of antioxidants such as albumin and bilirubin in schizophrenia and major depressive disorder, GSH dysregulation and increased lipid peroxidation in schizophrenia, bipolar and major depressive disorders [11–15]. Oxidative stress might induce telomere shortening [16] as well as DNA damage [17]. Levels of nitric oxide metabolites and antioxidative enzymes have been reported to be altered in

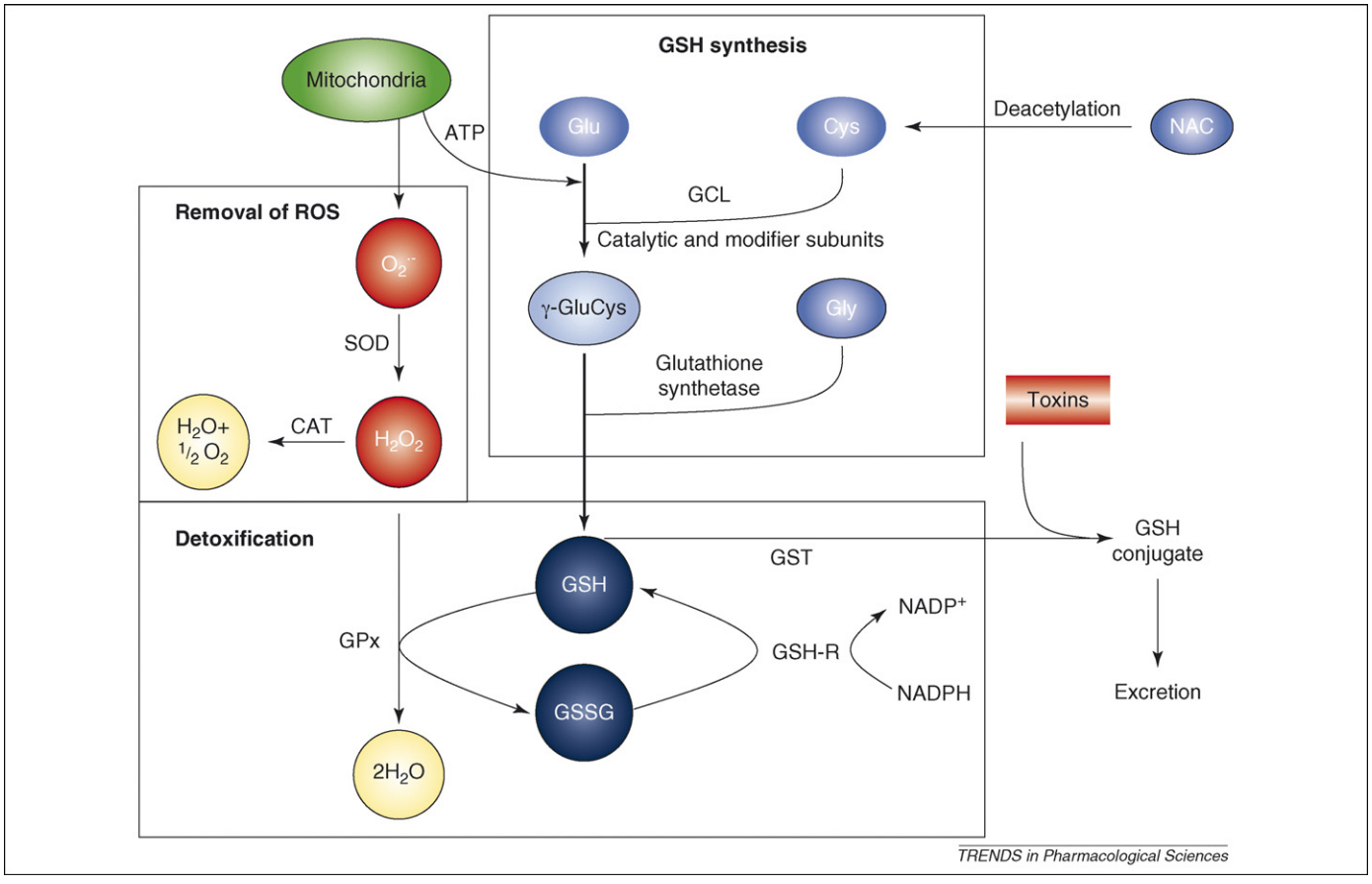

Figure 1. Oxidative defence pathway. Mitochondrial respiration (green) leads to the production of ROS (red) including superoxide O_2^- and H_2O_2. Removal of these ROSs might be via superoxide dismutase (SOD) and subsequently by catalase (CAT) or through the glutathione pathway (dark blue). GSH reduces H_2O_2 to water catalysed by glutathione peroxidase (GPx). GSSG is then reduced by glutathione reductase (GSH-R). Production of GSH also is depicted here (precursors appear in light blue circles). Glutatmate (Glu) and cysteine (Cys) form a dipetide catalysed by GCL and subsequently the gamma-glutamylcysteine (γ-GluCys) dipetide forms GSH through the addition of glycine (Gly) by glutathione synthetase. NAC can increase GSH production because Cys is the rate-limiting factor.

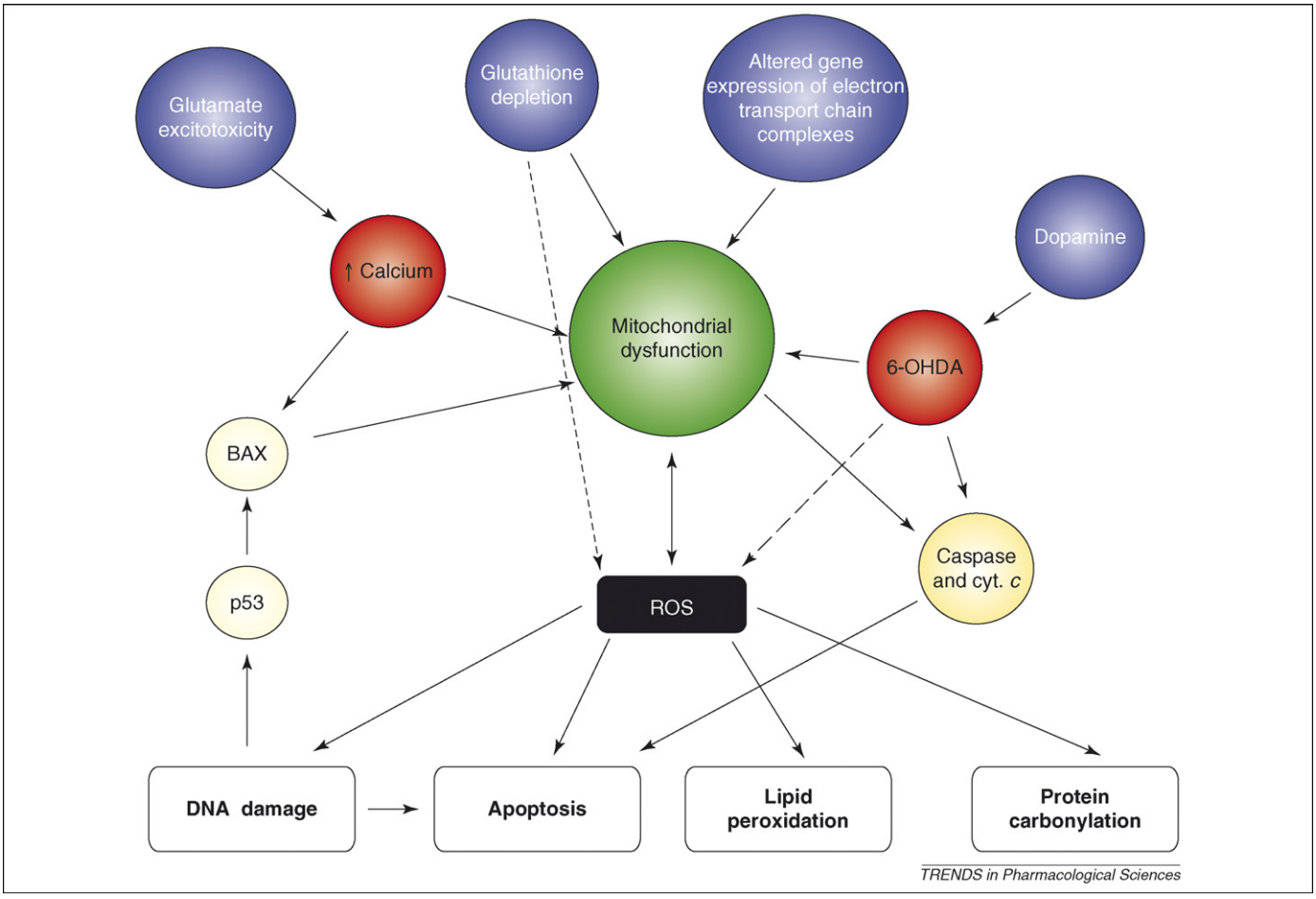

Figure 2. Several factors (blue circles) might contribute to mitochondrial dysfunction (green) and the production of ROS (black), ultimately leading to cellular dysfunction (white boxes), including the production of 6-hydroxydopamine (6-OHDA; red), glutathione depletion, glutamate excitotoxicity and altered mitochondrial gene expression. The cascade of events (yellow circles), promoted by translocation of BCL2-associated X protein (BAX) mediated by protein 53 (p53) and further activating cytochrome *c* (cyt. *c*) and caspase, leads to greater mitochondrial dysfunction. Further consequences (white boxes) include lipid peroxidation, protein carbonylation, DNA damage and apoptosis.

these disorders [11,15,18–22], but the results have been less consistent, perhaps reflecting differences in tissue specimen, diagnosis and illness phase. Notably, disturbances in oxidative stress indices have been correlated with symptomatic severity [13] and bipolar illness phase [15], and symptomatic resolution has been associated with a reversal of these disturbances [13,18,23,24], therefore suggesting that oxidative mechanisms might be intrinsic to active disease pathophysiology and might play a role in allostatic load [25]. Oxidative stress is impacted by factors including increased homocysteine and one-carbon metabolism, which affect the expression of antioxidant enzymes, GSH and neurotrophins [26,27], and is further influenced by nutrient status including vitamin D, folate and B12 [28–30].

Effects of pharmacotherapeutics on oxidative status

Besides clinical data that demonstrate that the oxidative disturbances reported in schizophrenia, bipolar and major depressive disorders shift towards control values after treatment [13,18,23,24], preclinical studies have illustrated more directly the antioxidative effects of established antipsychotics [31,32], mood stabilizers [33] and antidepressants [34,35]. These studies also have reported on the cytoprotective effects of mood stabilizers such as lithium and valproate [33] as well as antidepressants [34] against oxidative stress, indicating a potential neuroprotective role of these agents.

Genetics and molecular biology

Genetic and molecular studies have supplied evidence for a more fundamental involvement of oxidative stress in psychiatric aetiopathogenesis, with emerging data for schizophrenia and bipolar disorder. GSH pathways feature prominently in the schizophrenia data and have associated susceptibility to the illness with GSTT1 [36] polymorphisms as well as polymorphisms of genes for the GCLC and the GCLM that lead to reduced GSH synthesis [37,38]. Interestingly, polymorphism of the *GSTP1* gene encoding GST Pi has been implicated in the propensity to develop methamphetamine-related psychosis [39]. Genetic variations of mitochondrial manganese superoxide dismutase [40] and the mitochondrial enzyme NADH-ubiquinone reductase [41] as well as molecular changes pertaining to energy metabolism and redox pathways [42] also have been associated with schizophrenia. Polymorphism and altered expression of genes involved in the oxidative stress response similarly have been reported for bipolar disorder [43,44].

Targeting oxidative stress in the clinical setting

There are few published clinical trials of antioxidants in primary psychiatric disorders and fewer with a randomized, placebo-controlled design. Trials of conventional antioxidants such as vitamins E and C and of gingko biloba have reported benefits [45–47], but a shift in the focus of research from supplementation with radical scavengers to the reinforcement of endogenous antioxidant pathways has led to the study of N-acetylcysteine (NAC), a GSH-precursor drug. Omega-3 fatty acids, which are of value in mood disorders and possibly schizophrenia, increase brain GSH [48].

Several recent studies have found encouraging results for NAC in the psychiatric setting. Of these the adjunctive value of NAC in the treatment of schizophrenia and bipolar disorder has been supported by one randomized, placebo-controlled trial for each condition. In the schizophrenia trial ($n = 140$) [49] patients treated with NAC showed superior outcomes compared with those on placebo over the 6-month study period, in terms of the Positive and Negative Symptoms Scale (PANSS) Negative, General and Total scales, the Clinical Global Impression (CGI) Improvement and Severity scales and the Barnes Akathisia Scale (BAS). The bipolar trial ($n = 75$) [50], likewise, had significant efficacy results, showing moderate to high effect sizes on measures of depression [Montgomery-Åsberg Depression Rating Scale (MADRS) and Bipolar Depression Rating Scale (BDRS)], quality of life and functionality. In both trials the clinical effects of treatment were lost 1 month after treatment discontinuation. Aside from these larger studies, a double-blind crossover trial ($n = 15$) of NAC in cocaine dependence has reported reduced desire for use and reactivity to cocaine cues during treatment [51], and another study with both open-labelled and double-blind randomisation phases ($n = 27$) indicated benefits of NAC in pathological gambling [52]. NAC also has been reported to treat refractory obsessive compulsive disorder (OCD) [53] and OCD spectrum disorders [54].

Implications of oxidative stress research

The current broad array of data demonstrates the presence of oxidative stress in several psychiatric disorders. The precise mechanisms responsible for generating the oxidative stress states are not yet clear but are likely to be diverse, in view of the heterogeneity of psychiatric syndromes and the fundamentality of the oxidative biochemical pathways. Any process associated with excessive oxygen metabolism, defective antioxidative defences or redox imbalance might generate oxidative stress, which might become self-perpetuating or amplifying. Data are available that indicate the presence of impaired mitochondrial energy generation in bipolar disorder, including hallmarks of decreased energy metabolism on functional MRI scans and decreased expression of genes involved in the mitochondrial electron transport chain [55]. These findings support a primary dysfunction in oxidative energy generation that might be an alternative mechanism for oxidative stress states in psychiatric disoders.

A bidirectional relationship might exist between neurotransmitter activity and oxidative stress status and places the relevance of oxidative stress mechanisms within the more familiar context of neurotransmitter pathogenic theories [6,7]. As an example, hyperdopaminergic states associated with psychosis and mania might increase oxidative stress, whereas oxidative stress might impinge on neurotransmitter metabolism, leading to dopamine auto-oxidation and impaired glutamatergic neurotransmission [56]. Illness acuity also has been associated with oxidative stress together with decreased levels of brain-derived neurotrophic factor, implicating oxidative stress in the pathways leading to neurostructural and neurofunctional changes [57].

On a practical level if oxidative stress is a common pathophysiological outcome across various psychiatric disorders, correction of the redox imbalance might have therapeutic and/or neuroprotective roles regardless of the underlying causative mechanisms. This pragmatic ramification of the oxidative stress hypothesis is one of its major attractions and offers alternative treatment pathways to the existing primarily neurotransmitter targets.

GSH as a novel treatment target

The wide variability in antioxidant properties needs to be appreciated in selecting a suitable treatment that targets oxidative stress. Antioxidants are often viewed as an undifferentiated class of agents, despite very different pharmacokinetic and pharmacodynamic profiles. For instance vitamin E buffers lipid radicals, vitamin C is a free radical scavenger in aqueous media and coenzyme Q10 minimizes mitochondrial ROS generation. Application of antioxidants to the treatment of psychiatric disorders without consideration of their bioavailability, dosage, affinity for lipid phase and mechanism of action might have contributed to the inefficacious and mixed results of clinical trials in disorders such as dementia and schizophrenia.

From a mechanistic perspective the most generic cellular antioxidant is GSH, which enhances its appeal as a treatment target in the absence of a precise understanding of more fundamental oxidative stress mechanisms. GSH is found abundantly in the cytosol, mitochondria and cell nucleus, and its synthesis is dependent on two rate-limiting steps, which are the supply of L-cysteine and the activity of GCLC. As the acetylated precursor of L-cysteine, NAC protects the amino acid from oxidation in the alimentary tract and deacetylates after absorption, making *l*-cysteine available for intracellular glutathione synthesis [58]. NAC, therefore, serves as an effective precursor to GSH, and although it has some intrinsic antioxidant properties, this is considered to be its major antioxidant action. Studies have demonstrated that neurones are capable of synthesizing GSH in a concentration-dependent fashion during culture with NAC [59], that NAC (or its metabolites) can cross the blood-brain barrier and that systemic delivery leads to neuroprotective effects in animals [60,61]. Together with the aforementioned clinical trials in schizophrenia and bipolar disorder, these preclinical studies support the therapeutic potential of NAC and treatments targeting the glutathione pathways.

Conclusions

The use of GSH precursors to treat major psychiatric disorders is a departure from conventional paradigms.

Conventional psychiatric pharmacotherapy is focussed on receptor activities, and there is little successful precedent for the use of metabolic precursors in psychiatry (e.g. L-tryptophan) in contrast to neurology in which L-DOPA is an enormously successful drug. The outlined trial data support the use of GSH precursors in an array of superficially distinct conditions, which in itself challenges conventional nosology and the canon of illness-specific therapeutic agents. The role of oxidation biology in these disorders might be operating at different and perhaps more distal levels, such that the primary pathologies of the individual disorders might converge onto a common potentially neurotoxic path that involves oxidative stress and secondary damage. Oxidative stress is capable of causing neuronal toxicity via DNA damage, lipid peroxidation and reduction in neurotrophins and is, thus, a plausible candidate mechanism for the neurostructural and cognitive changes that are widely reported in major psychiatric disorders [62,63]. Remediation of oxidative stress might, therefore, not only be of benefit in symptomatic treatment but also might be a promising pathway for neuroprotection.

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