Review Article

Neurobiology of Schizophrenia Spectrum Disorders: The Role of Oxidative Stress

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Abstract

Mitochondrial dysfunction and oxidative stress are increasingly implicated in the pathophysiology of schizophrenia. The brain is the body's highest energy consumer, and the glutathione system is the brain's dominant free radical scavenger. In the current paper, we review the evidence of central and peripheral nervous system anomalies in the oxidative defences of individuals with schizophrenia, principally involving the glutathione system. This is reflected by evidence of the manifold consequences of oxidative stress that include lipid peroxidation, protein carboxylation, DNA damage and apoptosis – all potentially part of the process of neuroprogression in the disorder. Importantly, oxidative stress is amenable to intervention. We consider the clinical potential of some possible interventions that help reduce oxidative stress, via augmentation of the glutathione system, particularly *N*-acetyl cysteine. We argue that a better understanding of the mechanisms and pathways underlying oxidative stress will assist in developing the therapeutic potential of this area.

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The brain is, weight for weight, the most metabolically active tissue in the body and generates a high load of reactive oxygen moieties. This burden is increased by a number of factors, including the oxidative potential of monoamines such as dopamine and excitatory neurotransmitters such as glutamate, as well as the vulnerability of the brain's lipid components to oxidation.[1] Although free radicals are important for a number of physiological functions, such as mitosis and cellular signalling,[2] if their metabolism is dysregulated, they have the potential to damage most of the contents of the cell, including lipids via peroxidation, protein via carboxylation and nucleic acids via oxidative damage.[3]

What is Oxidative Stress?

Oxidative status is homeostatically regulated, and oxidative stress can occur due to either increased production of reactive nitrogen species (such as nitric oxide) or reactive oxygen species (including hydrogen peroxide or superoxide), or a reduction of oxidative defences. Many components of the oxidative stress pathway also act as signalling elements. The sources of oxidative stress, the key oxidative defence pathways and the consequences of oxidative stress are reviewed in Berk et al[4] and summarised in Figure 1. Briefly, the production of reactive species is a core part of mitochondrial energy generation, and these species are dealt with by the body in multiple ways. These include superoxide dismutase, which converts the superoxide radicals to hydrogen peroxide, which is then converted into water and oxygen by catalase and water by glutathione peroxidase (GSH-px). Glutathione is the brain's dominant cellular free radical scavenger,[2,5] and is a tripeptide composed of glutamate, cysteine and glycine. It shuttles between reduced monomeric (GSH) and oxidised dimeric forms (GSSG) in the scavenging process.

The Evidence for Oxidative Stress in Schizophrenia

The concept of oxidative stress is intimately linked with the notion that, in many psychiatric disorders, there is an abnormality in mitochondrial energy generation.[6] For example, molecular and genetic studies indicate that disturbances in redox reactions are part of the pathophysiology of schizophrenia, including evidence of changes in elements of the genetic transcript, protein and metabolite levels that are involved in mitochondrial function, energy metabolism and oxidative stress responses.[7]

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(i) NO: nitric oxide
(ii) $O_2^{\cdot-}$: hydroxyl
(iii) H_2O_2: superoxide
(iv) Cys: cysteine
(v) Gly: glycine
(vi) γ-GluCys: gamma glutamylcysteine
(vii) GSH: glutathione
(viii) GSSG: glutathione disulphide
(ix) GSHr: glutathione reductase
(x) GPx: glutathione peroxidase
(xi) NAC: N-Acetyl cysteine
(xii) ROS: reactive oxygen species
(xiii) SOD: superoxide dismutase.

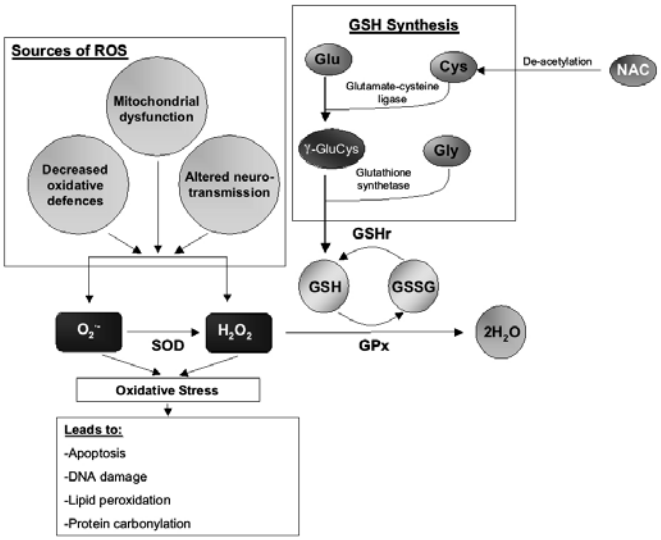

Fig. 1. Oxidative stress – sources and consequences.

Abnormalities in mitochondrial DNA are also documented, such as an increased rate of deletions.[6]

While there are strong links between oxidative stress anomalies and the pathophysiology of schizophrenia, in vivo measurement of free radical concentrations is impractical because their reactive nature results in short half-lives and low levels. Oxidative status in clinical populations are typically assessed in other ways, such as the measurement of oxidative defences, particularly key enzymes such as catalase, peroxidase and glutamate cysteine ligase, parallelled by assessment of the consequences of oxidative stress such as plasma lipid peroxides.[8]

Assays of endogenous antioxidant enzymes have, on the whole, shown evidence of dysregulation. Reduced levels of the antioxidant enzymes, superoxide dismutase, catalase and GSH-px are reported in patients with schizophrenia compared with controls,[9,10] although there are both negative studies and studies that have only partially replicated the positive findings.[11-17] An inverse relationship between blood GSH-px and structural measures of brain atrophy has been documented, suggesting a link between oxidative dysregulation and progressive structural changes.[18] Other antioxidant systems, including the antioxidant proteins albumin and bilirubin, uric acid, and the plasma total antioxidant status, are lower in schizophrenia than controls,[19,20] and also in neuroleptic-naïve patients with first-episode schizophrenia.[21] Interestingly, this latter study also found no impairment of antioxidant defences, providing a clue that there may be a disease stage related progression with regard to oxidative stress, with additional dysregulation being associated with neuroprogression.[21]

There is also evidence of the sequelae of oxidative stress, providing further support that the system is disrupted. Estimating levels of reactive oxidative products provides another useful strategy to determine the impact of oxidative stress. Lipid peroxidation is often assayed by measuring thiobarbituric acid reactive substances (TBARS), elevated levels of which have been shown in plasma, erythrocytes, leucocytes and platelets of schizophrenia patients.[10-13,15-17] CSF levels of TBARS have, however, been reported as lower in patients compared with controls.[22] The extent of lipid peroxidation has been found to correlate positively with the severity of symptoms in never-medicated patients,[23] and inversely with the levels of membrane-essential polyunsaturated fatty acids such as arachidonic acid.[24]

Other studies have examined peripheral concentration of the free radical nitric oxide (NO) by measuring its metabolites. While there are some reports of higher NO plasma levels in schizophrenia,[25] others have not found this.[13] Similarly conflicting findings have been reported for central nervous system measures; lower NO metabolite concentrations in the cerebrospinal fluid of patients with schizophrenia,[26] but elevated concentrations in post-mortem tissue.[27]

Increased protein carboxylation (suggestive of protein oxidation), increased levels of 8-OH deoxyguanosine (a product of DNA damage) as well as more direct measures of DNA damage such as telomere shortening have been reported. Furthermore, these changes seem to be more prevalent in those with a poor clinical outcome – for example, 8-OH deoxyguanosine levels are increased 10-fold in the hippocampi of poor outcome patients,[28] and treatment refractory patients show telomere shortening.[29] Greater oxidative stress has also been shown in individuals with schizophrenia complicated by tardive dyskinesia than in either controls or people with schizophrenia who do not have tardive dyskinesia.[30]

In vivo Measurement of Glutathione in Schizophrenia

The role of glutathione (GSH) in schizophrenia was initially examined as early as 1934,[31] where decreased circulating glutathione and increased lactate were reported. These findings have been neglected for almost three quarters of a century, but have recently attracted renewed attention.[2,5,32] Reduced levels of GSH have been associated with a number of neurological diseases, presumably as a result of increased oxidative stress.[33]

There are a number of lines of evidence specifically implicating disturbance of central GSH in the pathophysiology of schizophrenia. There is a 27% reduction in the cerebrospinal fluid levels of GSH in untreated patients with schizophrenia,[32] and a reduction of comparable magnitude (41%) has been reported in post-mortem assays of the caudate.[34] Further, an increased risk of schizophrenia is associated with polymorphisms of the genes for a number of key enzymes in the GSH synthetic pathway,[35,36] and decreased expression of GSH itself has been shown in cultured fibroblasts from individuals with schizophrenia.[37]

While these studies have used direct measures in fluid or post-mortem tissue, an alternative approach to the study of GSH is the use of proton magnetic resonance spectroscopy (^{1}H-MRS) a technique that allows the *in vivo* measurement of important brain metabolites such as neurotransmitters or bioenergetic molecules. This provides a non-invasive means to measure brain GSH in a larger and more representative population of patients across illness stages. To our knowledge, there are only 4 reports using MRS to measure the *in vivo* concentration of glutathione in schizophrenia. In the first,[32] 14 male patients (5 schizophreniform, 9 schizophrenia) were compared to 10 age-, but not gender-, matched subjects. Spectra were obtained from a 17.4 mL voxel placed mid-sagittally in the prefrontal cortex, and a roughly 50% reduction in glutathione levels was found in the patient group. In the second,[38] 13 patients (8 male, 11 schizophrenia and 2 schizoaffective) were compared to 9 controls (4 male). Again, spectra were obtained from a 17 mL mid-sagittal voxel in the prefrontal cortex, but no significant differences were found (there was roughly a 6% reduction in the patient group). Similar findings were reported by the third study,[39] which compared 20 patients (12 male, all schizophrenia) to 16 controls (12 male). GSH concentration in an 18.6 mL mid-sagittal prefrontal voxel was 13% lower in the patient group, but this was again not a significant reduction. While there are power issues for all 3 studies that may have resulted in type 2 errors, another plausible reason for the difference between these studies was medication – all patients were medicated in the latter 2 studies, but only 5 of the 14 in the first cited study. While there is evidence that haloperidol can provoke a significant increase in oxidative stress,[40] atypical antipsychotics such as olanzapine seem to have little or no effect on this system.[41] The variation in gender ratio between the 3 studies could also explain the differences, although the evidence for gender differences in oxidative stress is equivocal.[42]

It should additionally be noted that all but one of the patient groups reported in these previous MRS studies had established illness, and all had onset of symptoms at least 8 months before scanning. It is by no means certain that first-episode patients with shorter illness duration would show similar reductions in GSH concentration. There is some evidence that first-episode patients tend to show less consistent neurobiological abnormalities compared to established schizophrenia cases,[43,44] as predicted by the concept of clinical staging.[45]

We have recently investigated the brain glutathione concentration of 30 first-episode psychosis patients to try to address some of these questions, using MRS.[46] Somewhat surprisingly, we found that instead of a reduction, the glutathione levels of the first-episode group were 22% *higher* than controls. This increase did not seem to be related to treatment status (13 of the patients were scanned neuroleptic-naïve), psychotic diagnosis (7 of the patients had a non-schizophrenia spectrum diagnosis) or smoking status. However, the increase was greatest in those patients who failed to show the normal skin-flush response to topical niacin.

Applying niacin (a B vitamin) to the skin results in an increase of intracellular cyclic adenosine monophosphate production, which causes vasodilation of superficial skin microvessels.[47] This phenomenon is mediated by prostaglandins, the precursors of which are membrane bound long-chain fatty acids such as arachidonic acid that are known to be affected by oxidative stress.[24] Since there is a direct relationship between a failure to respond to niacin and low arachidonic acid levels,[48] non-sensitivity to niacin is likely to be associated with oxidative stress.

As a result, we interpreted our findings as evidence that a subgroup of patients with first-episode psychosis are experiencing oxidative stress, and mounting a compensatory response to a pathological mechanism present in only a proportion of patients with early psychosis. A similar compensatory response to oxidative stress is seen following exercise.[49] Potentially this mechanism could be part of the explanation of psychotic symptoms, since oxidative stress is a potent intracellular signalling mechanism that induces changes in the dopamine D2 receptor.[50] Dopamine and its metabolites are equally oxidative stressors. Presumably, though, this compensatory response is overwhelmed with continued illness (perhaps through apoptosis of astrocytes important for the glutathione cycle[51]), leading to the lower levels reported in chronic patients (see above). Such a

failure of compensatory mechanisms as part of disease progression has been hypothesised as a key mechanism in affective disorders.[52] There is preliminary evidence for differential activity of enzymes in the GSH pathway between early and late stages of schizophrenia (Andreazza – personal communication), which provides some additional support for a stage-dependant change in the GSH defence system. A strikingly similar pattern of data pertaining to oxidative biology exists in bipolar disorder – increased levels of glutathione-*S*-transferase and glutathione reductase have been shown specifically in late-stage disorder,[53] possibly reflecting a failure of compensatory signalling mechanisms as part of the process of neuroprogression.[54]

Of course, the focus of our study on the medial temporal lobes limits its comparability with the previous reports that assessed the medial prefrontal region. It would also be useful to have a direct measure of oxidative stress such as TBARS or 8-OH deoxyguanosine, rather than rely on the indirect topical niacin skin flush test. It is also entirely feasible that these discordant data reflect the methodological complexity inherent in the spectroscopic quantification of metabolites present at very low levels. Nonetheless, these findings do suggest that alterations to GSH levels are not a consistent feature of schizophrenia, and this may be related to stage of illness. This provides support for both the staging model of schizophrenia, and the notion of early intervention in the disorder, prior to both failure of compensatory mechanisms and secondary damage.[45]

Can Treatment Improve Oxidative Defences in Schizophrenia?

In addition to the potential impact of oxidative stress on the dopaminergic system, mentioned above, there may also be an effect on glutamatergic signalling via GSH. GSH can potentiate the activity of redox-sensitive proteins such as NMDA and dopamine receptors,[55] and during oxidative stress (when GSH is oxidised) this is lost. It has been suggested that impairments in NMDA receptor activity might contribute to the pathophysiology of schizophrenia,[56,57] and drugs such as ketamine, which are NMDA receptor antagonists, have been shown to be psychotomimetic.[58] Presumably, if lower GSH concentrations were associated with the symptoms of schizophrenia, increasing GSH levels would improve symptoms. Certainly glutathione depletion has been associated with both negative symptoms and cognitive dysfunction.[39,59]

Glutathione itself is not bioavailable, and therefore cannot be given directly to patients. It is, however, readily replenished via *N*-acetyl cysteine (NAC), which is a precursor of cystine, the rate limiting step in synthesis.[60] Provision of NAC to patients with chronic schizophrenia, at a dose of 2 g daily, has been shown to improve measures such as the Clinical Global Impression scale and negative symptoms, and akathisia, but interestingly positive psychotic symptoms were unchanged.[61] Effect sizes in the trial were in the moderate range, which is comparable to the therapeutic advantage conferred by clozapine.[62] This is supported by a trial of the essential fatty acid ethyl-eicosapentaenoic acid (EPA) in first-episode psychosis[63] – MRS data over the 12 weeks of the trial showed that adjunctive treatment with EPA produced a marked increase in GSH concentrations in the medial temporal lobes, and this increase was correlated with reductions in negative symptoms.[64]

Non-competitive NMDA receptor antagonists, such as the dissociative anaesthetics phencyclidine and ketamine, reproduce the cardinal symptomatic features of schizophrenia.[65] Alteration in peripheral glutamate receptor linkage to second messenger intracellular calcium is also reported in schizophrenia.[56,57] Another link between NMDA hypofunction and GSH comes from the study of mismatch negativity (MMN). MMN is an auditory evoked potential that is elicited by deviant stimuli in an otherwise unchanging set of events, and is known to be blocked by NMDA receptor antagonists.[66] Furthermore, MMN amplitude is attenuated in schizophrenia,[67] leading to the possibility that increasing brain levels of GSH in schizophrenia would improve MMN generation and other brain function.[68] One study has investigated this using augmentation with NAC in a double-blind, crossover design of 11 patients with chronic schizophrenia.[69] Although reaction time and response accuracy were not affected by NAC, there was a robust MMN following NAC but not placebo treatment, and source analysis suggested that this was due to stronger activity within the superior temporal cortex bilaterally.

Summary

In schizophrenia there is a growing evidence base supporting dysregulation of mitochondrial energy generation and a parallel increase in oxidative stress. Evidence derives from central and peripheral changes in oxidative defences, principally the glutathione system, mirrored by consequences of oxidative stress including lipid peroxidation, protein carboxylation, DNA damage and apoptosis, which is congruent with the process of neuroprogression leading to structural brain changes.[44] Such oxidative stress is amenable to intervention, firstly via the known effects particularly of atypical antipsychotics in reducing oxidative stress, and by promising therapeutic options that augment the glutathione system, particularly NAC. Further research is necessary to shed light on the mechanisms and pathways underlying oxidative stress, and to develop the therapeutic potential of this knowledge.

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