ANTIOXIDANTS & REDOX SIGNALING
Volume 15, Number 7, 2011

DOI: 10.1089/ars.2010.3646

Oxidative Stress in Schizophrenia: Pathogenetic and Therapeutic Implications

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Abstract

Over a century, a wide-ranging variety of pathophysiological models and causal hypotheses have been conceptualized for schizophrenia. One among these is the role for free radical-mediated pathology in schizophrenia, indicating impaired antioxidant defense system (AODS) and presence of oxidative stress in patients with schizophrenia. For the past two decades, the whole investigative domain of AODS and oxidative stress has broadened to include the wider AODS components, direct central nervous system assays of AODS, chemical imaging studies, proteomics, genetics of AODS, and, of importance to sufferers of schizophrenia, antioxidant therapeutics. These are some of the perspectives that are reviewed by several articles in this Forum. Overall, there has been growing recognition of the importance of oxidative stress in the pathophysiology of schizophrenia and in treatment-related side effects. The totality of the evidence from biochemistry, metabolomics, proteomics, genetics, and *in vivo* brain imaging points to the presence of multifarious abnormalities in the AODS and redox signaling in schizophrenia. *Antioxid. Redox Signal.* 15, 1999–2002.

"SCHIZOPHRENIA IS STILL one of the most mysterious and costliest mental disorders in terms of human suffering and societal expenditure" (28). Since over a century that schizophrenia has been conceptualized there have been wide-ranging variety of pathophysiological models and causal hypotheses of schizophrenia (14). One among these is the role for free radical-mediated pathology in schizophrenia that was proposed more than half century ago (12). In the intervening decades there has been a steady stream of evidence demonstrating impaired antioxidant defense system (AODS) and the presence of oxidative stress in patients with schizophrenia (33). The earliest studies focused on the enzymatic components of the AODS, primarily superoxide dismutase (SOD) which has been discovered by McCord and Fridovich in 1968, and revolutionized the study of oxygen free radicals in biochemistry (1). Subsequent studies reported a variety of alterations in glutathione peroxidase (GSHPx) and catalase (CAT) levels (33). Prilipko and Lideman (21) were the first to report excess lipid peroxidation in patients with schizophrenia, proving that altered enzymatic AODS was indeed resulting in oxidative stress. The first, and critical, connection between peripheral indices of impaired AODS and central pathology in schizophrenia was the finding of inverse relations between peripheral GSHPx activity and cortical sulcal prominence on CT scan (5). As our understanding of the interrelations of the components of the AODS enlarged, it was clear that examining one AODS enzyme in isolation may have limited value for elucidating the role of impaired AODS in neuropsychiatric disease processes, suggesting that the dynamic aspects of the AODS likely have more salience to understanding the pathophysiology of schizophrenia (23). In the following two decades the whole investigative domain of AODS and oxidative stress has broadened to include the wider AODS components, direct central nervous system assays of AODS, chemical imaging studies, proteomics, genetics of AODS and, of importance to sufferers of schizophrenia, antioxidant therapeutics. These are some of the perspectives that will be reviewed by several articles in this Forum.

This Forum includes a comprehensive review of the reactive oxygen species (ROS) and the AODS, including the perturbations of these systems in schizophrenia (31). Yao and Keshavan review systematically the evidence of alterations within the multiple domains of AODS and redox signaling, and relations of these systems to altered phospholipid/polyunsaturated fatty acids and immune dysfunction also seen in schizophrenia. The body of evidence yields a complex picture that shows pathological alterations in multiple pathways involved in balancing ROS and the AODS in patients with schizophrenia, both prior to treatment initiation and after long-term treatment. Indices of oxidative stress and AODS

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have been examined in peripheral samples (whole blood, plasma, serum, red blood cell membranes, platelets, and urine) and the central nervous system (postmortem brain and cerebrospinal fluid). These findings in patients with schizophrenia include decreased nonenzymatic antioxidants in plasma (albumin, uric acid, and ascorbic acid and vitamin E), and GSH deficits in prefrontal cortex *in vivo*, caudate region of postmortem brains, and in cerebrospinal fluid. Altered levels of scavenging antioxidant enzymes (SOD, GSHPx peroxidase, and catalase) have been reported for the past three decades. Most of these changes are in the direction that favors oxidative stress. More recently, there has been increasing interest in nitric oxide (NO) signaling. Yao *et al.* (32) provided the first evidence of an increased NO production in postmortem caudate nucleus from patients with schizophrenia. A variety of findings of plasma nitrite, serum NO, red blood cell NO, and platelets NO synthase activity, however, have been inconsistent. Further, alterations in the metabolism of several neurotransmitter systems can both contribute to, and be modified by oxidative stress (or membrane dysfunction).

The review also sheds light on homeostatic imbalance of AODS which has been examined for GSH redox coupling and purine catabolism. Both systems show alterations that would favor oxidative stress. The most direct evidence for oxidative injury in schizophrenia, however, comes from the findings of increased lipid peroxidation and protein modifications. Thus, the unchecked effects of free radicals can lead to structural and functional defects of cellular membranes. Such an imbalanced AODS may provide the basis for an increased release of specific cytokines as well as membrane abnormalities that have been reported in schizophrenia. There is ample evidence for the existence of membrane phospholipid and fatty acid defects in early course and chronic schizophrenia.

The incidence of schizophrenia is approximately 0.53 per 1000 population. Several environmental risk factors such as perinatal viral infections, obstetric trauma, and maternal malnutrition have been identified, as well as familial clustering (13, 24). The heritability for schizophrenia has been estimated at 60–80%, and complex segregation analyses have consistently rejected monogenic models in favor of polygenic inheritance (18). Hence, the gene mapping effort attempts to find genetic variants that explain all or a portion of the variance in a trait in a population. This can typically be attained in a family study setting ("linkage"), or through unrelated individuals ("association"). Like other genetically complex disorders, linkage studies in schizophrenia have been relatively unsuccessful. Later studies investigated "positional candidates," that is, genes localized to linked regions that are expressed in the brain and plausibly have a role in pathogenesis of schizophrenia, reviewed in this Forum by Chowdari *et al.* (8), yielding several positional candidates: Dysbindin (*DTNBP1*), Neuregulin 1 (*NRG1*), D-amino-acid oxidase (*DAO*), and *G72* (also named D-amino acid oxidase activator [*DAOA*]) (26).

One of the more exciting developments has been the introduction of gene mapping of the numerous genes that encode antioxidant factors (9). Genetic association studies have been conducted with polymorphisms in some of these genes, reviewed by Chowdari *et al.* (8). They review GSH synthesis genes, GSH-related genes (*GSTM1*, *GSTP1*, *GSTO1*, *GSTT1*, and *GSTT2*), manganese SOD (*MnSOD*), and peptide methionine sulfoxide reductase (*MSRA*). Given the central role mitochondria have in redox signaling, there is a great deal of interest in mitochondrial genes. For example, using parallel transcriptomics, proteomics, metabolomics approach, and hierarchical clustering, Prabakaran *et al.* (19) identified 59 genes related mainly to mitochondria and energy metabolism. The review by Chowdari *et al.* (8) suggests several promising candidate genes and suggestive genetic associations. For example, the associations with *NOS1*, *MnSOD*, and *MSRA*, in conjunction with the reported cellular studies and the published clinical studies of schizophrenia suggest a pathogenic role for the related protein products.

The term "proteome" was defined originally as "the study of the total set of expressed proteins by a cell, tissue or organism at a given time under a determined condition" (29). The most traditional proteomic method is a combination of two-dimensional gel electrophoresis (2DE) for protein separation and mass spectrometry (MS) for identification. This combination of technologies allows the simultaneous separation of many hundreds of proteins in a single experiment. Direct MS-based approaches have also been employed, known as shotgun proteomics or liquid chromatography–tandem MS (LC–MS/MS) which utilize distinct chromatographic separation prior to the MS stage (15). While 2DE-MS and LC–MS/MS approaches have been used to reveal the global protein expression of a given tissue, other methods such as Western blot, immunoadsorbent assay, multiple reaction monitoring MS, and multiplex immunoassay are employed commonly for validation of differentially expressed proteins. However, this method has only been implemented recently in studies of brain disorders (7). Since all of these methods have their merits and weaknesses, the combination approach is best to maximize coverage of the relevant molecular pathways.

Mitochondria produce around 95% of the energy requirements in eukaryotic cells. These organelles are highly concentrated in the brain due to the high energy demands of this tissue. As reviewed by Martins-de-Souza *et al.* (16), abnormally high mitochondrial concentrations can lead to mitochondrial disorder (4). Glucose is the key molecule for generation of cellular energy in mitochondria. Alterations in glucose homeostasis in the schizophrenia brain have been shown (10, 27). These effects also appear to be reflected in peripheral tissues such as red and white blood cells and tissues such as liver (20, 25). Thus, it has been hypothesized that the broad mitochondrial processes are affected in schizophrenia such as calcium homeostasis, neurotransmitter transport, synaptic plasticity, and exacerbate ROS production (2). Most probably, higher ROS concentrations are not properly processed in early schizophrenia patients because key processes of stress response such as the purine catabolism are disturbed (30), leading to DNA damage, impaired energy production, altered gene and protein expression and, finally, in apoptosis and cell death, together leading to faulty neuronal plasticity, and perturbed neurotransmission. Such processes may start during neurodevelopment in schizophrenia and coincide with manifestation of symptoms during early adulthood (3, 33).

A longstanding issue in the AODS research in schizophrenia has been the primacy of peripheral tissue investigation, and the relevance of peripheral findings to a brain disorder. Thus, the increasing access to the brain *in vivo* to investigate the AODS has begun to put these concerns to rest.

Matsuzawa and Hashimoto (17) review recent studies utilizing magnetic resonance spectroscopy (MRS) to investigate GSH in the intact human brain. Four different measurement sequences including double quantum coherence filtering, Mescher–Garwood-point resolved spectroscopy, stimulated echo acquisition mode, and point resolved spectroscopy have been used to evaluate the ^{1}H-MRS measurement of GSH in the brains of patients with schizophrenia. What is apparent is that this area of investigation is in its early stages, but the findings merit further investigation.

The discovery of impaired AODS, lipid peroxidation, and other indices of oxidative stress in schizophrenia (31) offers an obvious therapeutic approach to countering the potential oxidative damage, and its clinical sequela, in the form of antioxidants. However, investigation of the therapeutic potential of antioxidants for schizophrenia symptoms has lagged the evidence that oxidative damage is associated with poorer clinical outcome. By contrast, there has been a long-standing interest in utilizing antioxidants for treatment-emergent adverse effects such as tardive dyskinesia (6). Reddy and Reddy (22) review the therapeutic use of antioxidants in schizophrenia as adjuncts to antipsychotic agents. Some of these trials have utilized a controlled design but many others are open label. More evidence is available for the use of antioxidants for treatment-related side effects, including tardive dyskinesia and metabolic syndrome. The body of the evidence to date suggests that specific antioxidants, such as N-acetyl cysteine and vitamin E, may offer meaningful benefits for patients with schizophrenia.

The remaining article of the Forum presents original data by Gysin *et al.* (11), examining the functional implications of AODS genes. They follow up on studies that have shown an association between schizophrenia and a GAG trinucleotide repeat (TNR) polymorphism in the catalytic subunit (*GCLC*) of the glutamate cysteine ligase (GCL), the key enzyme for GSH synthesis. They examined the effect of *GCLC* GAG TNR genotypes on plasma thiols and fibroblast GSH levels in patients with schizophrenia with either a low-risk *GCLC* GAG TNR genotype or a high-risk genotype. They found high-risk schizophrenia genotypes were characterized by altered plasma thiols and free amino acid levels that reflect a dysregulation of redox control and an increased susceptibility to oxidative stress.

Overall, there has been growing recognition of the importance of oxidative stress in the pathophysiology of schizophrenia and in treatment-related side effects. The totality of the evidence from biochemistry, metabolomics, proteomics, genetics, and *in vivo* brain imaging points to the presence of multifarious abnormalities in the AODS and redox signaling in schizophrenia. A great deal more systematic research with appropriate methodology is required before the two primary goals of this area of research are fully realized: the elucidation of the pathophysiological role of AODS and redox signaling and the promise of antioxidant therapeutics is fulfilled.

Acknowledgments

This work was supported in part by the grants from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biomedical Laboratory R&D (Merit Reviews and Senior Research Career Scientist Award), VA Pittsburgh Healthcare System, and National Institute of Health (MH58141 [J.K.Y.]). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this article. The contents of this article do not represent the views of the Department of Veterans Affairs or the United States Government.

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Date of first submission to ARS Central, December 5, 2010; date of acceptance, January 1, 2011.

Abbreviations Used

2DE = two-dimensional gel electrophoresis
AODS = antioxidant defense system
GCLC = catalytic subunit of glutamate cysteine ligase
GSHPx = glutathione peroxidase
LC–MS/MS = liquid chromatography–tandem mass spectrometry
MnSOD = manganese superoxide dismutase
MRS = magnetic resonance spectroscopy
MS = mass spectrometry
MSRA = methionine sulfoxide reductase
NO = nitric oxide
ROS = reactive oxygen species
SOD = superoxide dismutase
TNR = trinucleotide repeat

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