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Oxidative stress and schizophrenia: recent breakthroughs from an old story

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Abstract

Purpose of review—Oxidative stress has become an exciting area of schizophrenia research, and provides ample opportunities and hope for a better understanding of its pathophysiology, which may lead to novel treatment strategies. This review describes how recent methodological advances have allowed the study of oxidative stress to tackle fundamental questions and have provided several conceptual breakthroughs to the field.

Recent findings—Recent human studies support the notion that intrinsic susceptibility to oxidative stress may underlie the pathophysiology of schizophrenia. More than one animal model that may be relevant to study biology of schizophrenia also shows sign of oxidative stress in the brain.

Summary—These advances have made this topic of paramount importance to the understanding of schizophrenia, and will play a role in advancing treatment options. This review covers topics from classic biochemical studies of human biospecimens to the use of magnetic resonance spectroscopy and novel mouse models, and focuses on highlighting promising areas of research.

Keywords

oxidative stress; magnetic resonance spectroscopy; olfactory cell; glutathione; superoxide dismutase

Introduction

Recent studies, in particular studies in human genetics, have indicated that multiple combinations of genetic and environmental factors underlie the etiology of schizophrenia (SZ) [1**, 2]. Although it is very important to explore the comprehensive landscape of genetic architecture of the disease, investigators and clinicians have also acknowledged the importance of understanding pathophysiological pathways that occur more commonly under the diagnostic label. Due to current diagnostic criteria, such as the Diagnostic and Statistical

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Manual of Mental Disorders (DSM), stemming more from reliability of clinical phenotypes rather than etiological validity, these pathways may not be purely disease or label specific (that is, they may underlie both SZ and bipolar disorder). Nonetheless, understanding of common pathophysiological pathways will prove to be very important in identifying biomarkers and drug discovery efforts.

Oxidative stress: timely and important topic in schizophrenia research as of 2014

Although first postulated in the 1930s by Roy Hoskins [3], the significance of oxidative stress in the pathophysiology of SZ has been underestimated. Oxidative stress is biologically important, but the involvement of this cascade occurs in multiple pathological conditions, including cancer, cardiovascular disease, and neurodegenerative disorders [4-6]. This non-specific nature of oxidative stress played a role in deterring psychiatric researchers from the field. Additionally, shortage of techniques for monitoring oxidative stress inside the brain was also a concern. However, at least four conceptual and technical advances in the past decade have changed the situation:

First, important studies that reported “specific” involvement of oxidative stress on key biological mechanisms that may underlie the endophenotypes relevant to SZ, such as role for nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in interneuron deficits, have generated new opportunities for research (described below in detail) [7].

Second, recent progress in cell biology has allowed us to access patient-derived cells with the potential to reproduce traits of brain cells, such as neurons, *in vitro*. The generation of induced pluripotent stem cells (iPS cells) is a hot topic given their potential to differentiate into neurons and glia [8**]. Furthermore, the use of cells from olfactory epithelium is also considered as an alternative approach [9, 10]. Olfactory cells are advantageous to iPS cells in that they possess neural traits, but require no reprogramming and are higher throughput [11*].

Third, an advance in brain imaging technique, in particular the capacity to measure the levels of glutathione (GSH), a major component of antioxidant defenses, by magnetic resonance imaging (MRS) has provided us with tools for *in vivo* studies [12].

Finally, although many studies of SZ patients have been challenged with regards to the effect of long-term medication and other confounding factors, recent reports have provided us with evidence of oxidative stress in recent-onset cases with minimal or no medication confounding [13**]. If oxidative stress is prominent in early stage of the disease, it is very reasonable that people expect such biological change to be a target of early detection and early intervention, which always confirm better treatment outcome in any disease in medicine [14]. Taken together, oxidative stress has become an exciting area of research in SZ.

What is oxidative stress?

Oxidative stress results from an imbalance between an overproduction of reactive oxygen species (ROS), and a deficiency of enzymatic or non-enzymatic antioxidants (Fig. 1). When this homeostasis is lost, oxidative stress damages cell structures. Major targets of oxidative stress are proteins, lipids, and DNA [15].

Physiological sources of ROS include oxidative phosphorylation, crucial for cellular energy generation is the predominant source, as well as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH-oxidase oxidizes NADPH, donating the electrons to an oxygen molecule (O_2) to produce superoxide (O_2^-).

Cellular antioxidant defenses include enzymatic components, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), as well as non-enzymatic components (GSH, uric acid, vitamin C, and albumin). SOD is responsible for converting the radical form of oxygen (O_2^-) into hydrogen peroxide (H_2O_2), which can be converted to oxygen and water by CAT or GSH-Px before it converts to harmful radicals. GSH is a tripeptide that is reduced to glutathione disulfide (GSSG) by GSH-Px to convert H_2O_2 to water.

Biochemical evidence in human biospecimens

The goal of this short review is to provide current opinions on exciting frontline research. Therefore, we acknowledge that our coverage of the past literatures is not exhaustive and only representative articles required for the present discussion are included.

Human biospecimens that have been used for the study of oxidative stress include postmortem tissues as well as biopsied samples, such as bloods (e.g., red blood cells, plasma, serum, lymphocytes, and lymphoblasts), fibroblasts, and cerebrospinal fluid (CSF). In addition, recent reports have utilized cutting-edge resources, such as iPS cells and olfactory cells [16**, 17]. In summary, evidence from biochemical studies of protein contents and activity in human biospecimens has suggested that oxidative stress may exist in the pathophysiology of SZ. However, as discussed below, there exist substantial discrepancies amongst results.

Postmortem brain analysis has suggestively shown the trace of excess oxidative stress [18, 19]. Though the study of postmortem brain is important, this has faced difficulty due to the employment of indirect measurements of oxidative stress. Furthermore, confounding factors, such as variability in the postmortem interval are inevitable.

SZ is a condition with onset in young adulthood. Many investigators have questioned whether autopsied brain from aged patients may truly reflect the active pathophysiology. Therefore, there is great potential in the study of biopsied cells/tissues from living patients. The levels of SOD were reduced in red blood cells from subjects with first-episode psychosis as well as those from stably medicated outpatient subjects [13**, 20]. Consistent observation was also reported in CSF from recent onset SZ patients [21]. However, studies have shown an increase in the levels of SOD in plasma from SZ patients [22]. The levels of

GSH-Px were decreased in red blood cells from SZ patients in acute relapse phases and chronic inpatient subjects [23]. Discrepancies in this result, though present, were found to be insignificant [13**]. Likewise, some, but not all studies have reported a reduction of CAT in red blood cells [13**, 24].

As described above, researchers have recently welcomed technical advances that enable us to study cells with neural traits obtained from living patients [10, 17, 25]. For example, the importance of stress-associated pathways has been underscored in a study with olfactory cells: of special interest were antioxidant enzyme pathways, which include proteins, such as microsomal glutathione-S-transferase 1 (MGST1) [17]. As far as we are aware, only a few studies utilized iPS cells in schizophrenia research. Nonetheless, two exploratory studies have already suggested involvement of oxidative stress: one case report indicated an increase in reactive oxygen species in SZ [26]. Another group showed that SZ-derived iPS cells had difficulty of differentiating to neurons and exhibited substantial mitochondrial deficits [16**].

Provided that these results are supportive to the notion that oxidative stress may underlie the pathophysiology of SZ, it is important to account for contradictory results in these studies. We regard that there are at least three possible reasons: first, SZ is highly heterogeneous under the same clinical diagnosis. Second, redox dysfunction may be, at least in part, state dependent. Third, tissue-specific change may underlie the pathophysiology. Meta-analyses that consider these points will be useful to the field.

Magnetic resonance spectroscopy (MRS)

As described above, most current biochemical studies utilize peripheral tissues, such as blood materials. A major breakthrough in the past decade is the use of MRS in measuring brain levels of GSH in living subjects directly [27, 28]. A pioneering study in schizophrenia research was made with ^1H -MRS at 1.5-Tesla and reported a 52% reduction of GSH in medial prefrontal cortex of drug free patients with SZ [29]. Subsequent studies, however, found difficulties in replication. The second report on brain GSH in medicated patients with SZ at 4-Tesla did not report a difference in the level of GSH in the anterior cingulate [30]. The third study also failed to observe the change in prefrontal cortex using a 3-Tesla machine, but noted a negative correlation of GSH with negative symptoms [31]. The fourth group studying subjects with first episode psychosis reported an increase in GSH in the medial temporal lobe also at 3-Tesla [32].

Although the direct measurement of GSH in the brain of living subjects is tempting, the results are thus far inconsistent in studies of SZ. This discrepancy might be explained in part because different sequences are used for measurement and analyses in each study. The first study had been reported even before the introduction of the editing sequence [33]. In addition, although acceptable as brain imaging study each study had rather small sample size, and observed slightly different brain regions. More fundamentally, MRS cannot distinguish intracellular from extracellular GSH: this distinction is biologically crucial given the large difference in GSH concentrations. Thus, careful discussion on how to analyze the

data of brain GSH measured by MRS is required for valid interpretation. A meta-analysis will be valuable once more studies with MRS are published.

What does oxidative stress elicit in the context of SZ pathophysiology?

Multiple groups have identified neuropathological defects associated with interneurons, in particular parvalbumin (PV)-positive interneurons, in the brains of SZ patients [34*-36]. Proper function of interneurons is required for the maintenance of gamma oscillations, which are responsible for cognition and are altered in SZ patients [37, 38]. Recent studies in preclinical models have shown that oxidative stress preferentially affects interneurons [7, 39*-41**]. The effectiveness of antioxidants in rescuing parvalbumin interneurons, give credence to antioxidant therapies [41**].

Furthermore, the lipid-rich white matter is sensitive to oxidative stress [42]. Thus, oxidative stress may underlie myelin-associated deficits in SZ [43, 44]. Oxidative stress can affect cellular signaling cascades, which may underlie the disease pathophysiology [45, 46].

Insight from animal models

In the present chapter, we have introduced a brief summary of human studies on SZ and oxidative stress. When attempting to elucidate the pathophysiology of a human disease or condition, study of human subjects is essential. Nonetheless, animal models are useful in linking the pathophysiology to the pathological trajectory during neurodevelopment, and in clarifying the molecular changes in the context of neural circuitry disturbance and behavioral changes.

In a strict sense, there is no animal model for SZ. However, for the present discussion we will consider animals that show behavioral changes relevant to some endophenotypes of SZ with some level of genetic evidence. Under this less stringent criterion, there exist at least three animal models that show signs of excess oxidative stress.

The first model focuses on Glutamate-cysteine ligase (GCL): this is the rate-limiting enzyme in GSH production, which is composed of modifier (GCLM) and catalytic (GCLC) subunits. A trinucleotide-repeat polymorphism in the *GCLC* gene is reportedly associated with SZ [47]. *Gclm* knockout mice showed a robust reduction in the level of GSH [48]. Of interest, this mouse model displayed reduced PV immunoreactivity in the CA3 and dentate gyrus, as well as predicted deficits in gamma oscillations [49]. The animals also showed deficits in prepulse inhibition and hyperlocomotion selective to environmental novelty and stress, and in response to acute amphetamine injection [50, 51]. Oxidative stress is prominent in adolescence, but the behavioral phenotypes relevant to SZ become more prominent after puberty, suggesting an idea that oxidative stress may be involved in early stage of the pathological trajectory [49, 52]. Finally some of these abnormalities were normalized by administration of the GSH precursor *N*-acetylcysteine (NAC) [52].

DISC1 is a representative gene in which a rare variant provides strong biological influence on mental disease, such as depression and schizophrenia [53]. Transgenic mice expressing a putative dominant-negative mutant displayed a reduction in the levels of parvalbumin

immunoreactivity, indicating interneuron deficits [54]. Consequently, several behavioral deficits have also reported [39*, 54]. Given that interneuron deficits occur as downstream of oxidative stress, our group studied whether excess of oxidative stress may exist, and observed the sign in the frontal cortex, in particular orbitofrontal cortex [39*]. Of special interest, these mice showed an augmentation of the nuclear glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) cascade, which is reportedly elicited by oxidative stress [39*, 55]. The nuclear GAPDH pathway is important in gene transcriptional and epigenetic controls upon stressors [56], thus the augmentation of this cascade triggered by oxidative stress may underlie stress-mediated epigenetic contribution to the disease pathophysiology.

The third model mice are deficient in excitatory amino acid transporter 3 (EAAT3/EAAC1) encoded by the gene *Eaac1/Slc1a1*, which reduces GSH production by limiting neuronal glutamate uptake [57]. Recent genetic studies have provided some evidence of *Eaac1* association with SZ [58, 59].

Treatment perspectives

In an animal model (*Gclm* knockout mice) that is relevant to study biology of SZ, oxidative stress occurs in early phase of the pathological trajectory and administration of NAC ameliorated the abnormal behaviors [41**]. Although NAC is not a compound purely specific to oxidative stress, the preclinical study provided us with a hope to use NAC and related compounds in the treatment of SZ, in particular earlier phase of SZ [49]. In another model (*Disc1* dominant-negative model), the nuclear GAPDH stress cascade was augmented [39*]. Because a set of selective compounds that block this cascade is available in humans [60], they may be tried for possible treatment of SZ.

Conclusion

In this short review, we have described how the story of oxidative stress in SZ has been rediscovered in the past decade, according to recent methodological advances in science. This biological process can be intervened in many ways, providing us with hope of developing novel treatment strategies to this devastating mental condition.

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Key points

Recent meta-analyses and replication studies with human biospecimens have further suggested the presence and role of oxidative stress in schizophrenia.

New techniques, such as magnetic resonance spectroscopy and stem cells obtained from living patients, have allowed more thorough studies.

Genetic mouse models relevant to schizophrenia show the signs of excess oxidative stress

We may develop novel strategies for treatment of schizophrenia by targeting oxidative stress in its pathophysiology.

Key mediators of oxidative stress. Oxidative stress results from an imbalance between overproduction of reactive oxygen species (ROS) and a deficiency of enzymatic or non-enzymatic antioxidants. Representative molecules of ROS include $\text{O}_2^{\bullet-}$ (superoxide) and H_2O_2 (hydrogen peroxide). Key sources of ROS are the mitochondria, as a by-product of oxidative phosphorylation, and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Superoxide dismutase (SOD) is responsible for the conversion of superoxide to hydrogen peroxide, which is further converted to non-radicals by catalase (CAT) or the glutathione (GSH) pathway that includes enzymes like glutathione peroxidase.