Oxidative/Nitrosative Stress in Psychiatric Disorders: Are We There Yet?

Patricio O’Donnell*,1, Kim Q. Do2, and Celso Arango3

1Neuroscience Research Unit, Pfizer Inc, Cambridge, MA; 2Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, CHUV, Lausanne-Prilly, Switzerland; 3Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, IISGM, CIBERSAM, Madrid, Spain

While oxidative stress has a clear role in neurodegenerative diseases, its involvement in psychiatric disorders is only beginning to be understood. Evidence for oxidative stress and redox dysregulation in psychiatric disorders is rapidly mounting, and preclinical data are increasingly suggesting oxidative stress can affect brain circuits involved in schizophrenia, yielding altered behaviors. This issue of Schizophrenia Bulletin covers some recent developments in human and animal studies highlighting the possibility of oxidative and nitrosative stress contributing to abnormal behaviors. Hayes et al.1 present data of inflammation-related measures in patients, at-risk subjects, and healthy controls revealing altered cytokines in the cerebrospinal fluid (CSF) of patients and at-risk mental state subjects. Fournier et al.2 provide an interesting metabolomics approach in cells derived from patients and controls that highlight the possibility of using metabolic signatures of oxidative stress reactivity as biomarkers for prodrome or early psychosis. Overall, the articles point to the use of oxidative/nitrosative stress and inflammation measures as biomarkers for early psychosis and may pave the way to novel therapeutic approaches.

A possible role of oxidative stress in psychiatric disorders has been suspected for some time.3 Besides heterogeneous reports of oxidative stress in peripheral tissues,4,5 increasing evidence also point to oxidative and nitrosative stress contributing to abnormal behaviors. Hayes et al.1 present data of inflammation-related measures in patients, at-risk subjects, and healthy controls revealing altered cytokines in the cerebrospinal fluid (CSF) of patients and at-risk mental state subjects. Fournier et al.2 provide an interesting metabolomics approach in cells derived from patients and controls that highlight the possibility of using metabolic signatures of oxidative stress reactivity as biomarkers for prodrome or early psychosis. Overall, the articles point to the use of oxidative/nitrosative stress and inflammation measures as biomarkers for early psychosis and may pave the way to novel therapeutic approaches.

DISC1 is of particular interest because a transgenic mouse expressing a dominant-negative mutant displays morphological and behavioral deficits typical of schizophrenia6 and shows an augmentation of the nuclear glyceraldehydes-3-phosphate-dehydrogenase cascade elicited by oxidative stress.17

GSH is the most abundant endogenous antioxidant and redox regulator and is responsible for maintaining cellular oxidative balance.18 Decreased GSH levels have been observed in peripheral tissues, CSF, and postmortem brains of schizophrenia patients,4,8 and the GSH precursor N-acetyl cysteine (NAC) increases peripheral GSH levels and improves neurophysiological deficits in patients.19,20 Two recent studies also demonstrate that chronic patients improve with add-on NAC, particularly in their negative symptoms.21,22 Furthermore, brain GSH levels assessed with magnetic resonance spectroscopy (MRS) are decreased in the prefrontal cortex (PFC) of patients with schizophrenia.18 Rodent models with GSH deficit or mitochondrial dysfunction show electrophysiological, morphological, and schizophrenia-related behavioral anomalies23 that are reversed with NAC,13,24 indicating that GSH is critical for proper postnatal brain maturation. More recently, Cabungcal et al.25 reported that the perineuronal nets that surround parvalbumin interneurons are protective against oxidative stress. As loss of parvalbumin is a highly replicated observation in postmortem studies26 and a highly convergent finding in diverse animal models that yield adult-onset abnormal PFC-dependent behaviors.27 It is possible that the final common mechanism affecting interneurons by several different etiological or risk factors entails oxidative stress in this cell population.28

Animal studies are increasingly revealing oxidative stress as a consequence of diverse genetic or environmental insults. Manipulations such as neonatal...
N-methyl-d-aspartate (NMDA) antagonists or social isolation produce oxidative stress in cortical interneurons. Mice with NMDA receptor hypofunction also show oxidative stress in parvalbumin interneurons when social isolation is added, reinforcing the notion that the 2-hit model could be applied to mechanisms driving inflammation and oxidative stress. The role of parvalbumin interneurons as a susceptible population to oxidative stress is highlighted in GSH-deficient mice that reveal deficits in interneuron function and NMDA receptor function and in adult rats with a neonatal ventral hippocampal lesion, which show oxidative stress in the majority of parvalbumin interneurons in the anterior cingulate cortex. 

An emerging notion in animal studies is that inflammatory processes during development can result in altered adult function by altering postnatal developmental trajectories. Thus, preclinical data support the idea that developmental alterations can impact cortical function via oxidative stress.

The role of oxidative stress in schizophrenia has important implications for understanding its pathophysiology and identifying biomarkers. First, it will be important to further research into the mechanisms that promote oxidative stress as well as protective mechanisms; the field needs to explore molecular links between genetic and environmental risk factors with inflammatory responses and oxidative stress. This is an avenue of exploration that can take advantage of the several different animal models that produce oxidative stress. Second, it will be critical to identify biomarkers that can reveal redox state in the human brain. MRS can be used to identify GSH levels, and peripheral blood samples can be used as well. It remains to be determined how well peripheral GSH correlates with brain GSH.

Of particular interest as possible biomarkers for oxidative stress are some neurophysiological alterations observed in schizophrenia patients. A reduction in mismatch negativity (MMN) is consistently observed in schizophrenia patients, and this deficit can be reversed with antioxidant treatment. Peripheral GSH has a striking correlation with MMN in normal volunteers. Much more needs to be done to determine the impact of oxidative stress on symptoms and how to identify patient subpopulations in which this may be the primary pathophysiological mechanism.

Patient stratification may be critical for the development of novel therapeutics that target oxidative stress or inflammatory mechanisms. There have been several trials with the GSH precursor, NAC, as well as with other antioxidant and anti-inflammatory toks, including omega-3 fatty acids, aspirin, minocycline, among others. Overall, the results have been mixed. It is critical to elucidate whether early stages of the disorder are more amenable to this type of intervention. It is also necessary to determine whether certain clinical manifestations and not others are the result of oxidative stress. Lastly, it will be critical to refine the pharmacological tools to target redox mechanisms and inflammation selectively in the brain regions and cell populations affected.

Several open questions remain for the role of oxidative stress in schizophrenia. What are the symptom domains associated with oxidative stress? If cortical regions are primarily affected, one would expect that cognitive deficits are the main outcome and that by addressing oxidative stress, this poorly treated disease manifestation could be more properly addressed. Is oxidative stress a trait of early or chronic stages of the disease? Are there different oxidative stress mechanisms playing a role in the disease? These questions are important to determine when and whom to treat. What is the role of current medications on oxidative stress? Antipsychotic drugs have been suspected to generate increased oxidative stress. If oxidative stress is present in early stages, is it safe to treat prodromal patients with antioxidants? What would the consequences be of antioxidant treatment on people who would otherwise not develop the disease? Can we identify a specific subset of subjects that will benefit from these approaches? Is it important to stratify patients in order to select a specific type of antioxidant or anti-inflammatory approach? Although the possible role of oxidative stress in schizophrenia has been raised some time ago, the idea needs further validation. It is critical to continue exploring this issue to advance the field. The articles in this special issue bring us up to speed with the current state of this field and highlight what is needed.

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