

Editorial

The Redox Brain and Nitric Oxide: Implications for Psychiatric Illness

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Psychiatric disorders, such as major psychosis and mood disorders, are among the world's ten most disabling illnesses and taken together, mood disorders (major depression and bipolar depression [BPD]) and schizophrenia (SCZ) affects about 10.6% of the adult U.S. population yearly [1,2]. As such, these brain illnesses cause substantial individual suffering and societal financial burden; indeed the costs for mental health services of United States of America in 2006 totaled \$57.5 billion (Agency for Healthcare Research and Quality's and Medical Expenditure Panel Survey). BPD and SCZ are complex and severe brain diseases affecting approximately 1% of the population respectively [1]. While there are clear differences in clinical symptomatology and manifestation between these disorders, they share several endophenotypes, signified by psychosis, relapse and progression into chronic brain illness. Current diagnostic criteria for psychiatric illness are based on self-reports and behavioral observation, which lack reliable biological validation. Consequently, it is imperative to identify novel biomarkers reflecting underlying pathophysiological mechanisms for brain diseases such as BPD and SCZ.

One potential target mechanism for BPD and SCZ is oxidative stress. Enhanced markers of oxidative stress have been found both peripherally (in blood) and centrally (post mortem brain) in patients with BPD and SCZ [3,4]. For example, increased lipid peroxidation (oxidative damage to lipids) constitute the most consistent pathophysiological finding associated with BPD [5] and we recently illustrated that serum lipid peroxidation levels correlated with prefrontal white matter abnormalities, indicating that serum lipid peroxidation may be used as a biomarker associated with brain damage in patients with BPD [6]. Increased lipid peroxidation also occurs in patients with SCZ [7], however the association seems less well established. On the other hand, accumulating research suggests that oxidative damage through nitric oxide (NO) may be involved in the pathophysiology of SCZ [8-10] as recent clinical studies indicate that decreasing NO-signaling may be effective for improving SCZ symptomatology [11,12]. There is also evidence for NO-imbalance in BPD, for example high levels of 3-nitrotyrosine in post mortem

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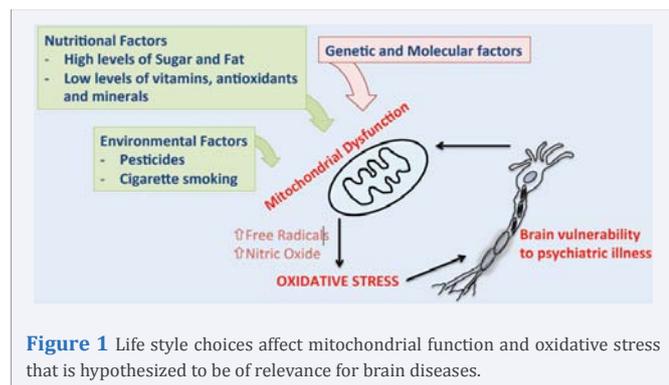
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prefrontal cortex from patients with BPD [13]. The involvement of oxidative stress in BPD and SCZ is also supported by findings of decreased expression of mitochondrial electron transport chain subunits [14] which lead to increase the production of reactive oxygen species and therefore, increasing the susceptibility to oxidative stress damage.

The exact causes of mitochondrial dysfunction in these patients remain unknown. However, high levels of dopamine (as indicated in BPD and SCZ) and glutamate (as indicated in SCZ) have been shown to induce oxidative stress in the brain. Moreover, several genetic studies have associated mutations in the calcium channel, voltage-dependent, L type, alpha 1C (CACNA1C) as one of the risk factors in BPD and SCZ [14]. The regulation of levels of calcium inside the cells is essential to maintain the mitochondrial function and for regulating NO production; thus patients with calcium-channel mutations may have higher levels of oxidative stress. NO is also involved in various physiological functions including inflammation. Interestingly, a recent, large population-based study (N=3.56 million) demonstrated that infections and autoimmune diseases poses risk factors for development of mood disorders [15].

In addition, it is of note that the mitochondria are particularly vulnerable to alterations in nutrients as well as to environmental toxins, e.g. pesticides. Today, a major dietary issue is imbalance in blood sugar levels, high levels of fat consumption and decrease in nutrients, such as vitamins, which are powerful antioxidants. For example, large blood sugar increases induce formation of advanced glycolytic enzymes, which lead to induction of free radicals. Several pesticides, including rotenone, directly inhibit the mitochondrial oxidative phosphorylation. Consequently, life style choices are likely to influence mitochondrial function and brain cells.

While a healthy life style is often associated with prevention of cardiovascular diseases, moderate consumption of sugar and fat, higher intake of vitamins, minerals and antioxidants and regular exercise, the same remedy would likely improve brain health. In particular, patients with brain diseases are likely to benefit



from healthy lifestyle changes by creating homeostasis in the protective, antioxidant brain system (Figure 1). As an example, the essential amino acid L-lysine, found in high-protein foods, may be used to decrease NO-levels. As such, our research group found that an add-on of 6 gram/day L- lysine treatment to patients with SCZ, was safe, trended to improve positive symptoms, however needs further investigation [11]. Because oxidative stress damage is involved in neuronal damage, regulating nutrient levels and decreased the exposure to toxins, lifestyle changes could aid in slowing down the illness progression and severity, ultimately promoting a healthier brain and higher quality of life.

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