ASSOCIATION OF OXIDATIVE STRESS WITH THE PATHOPHYSIOLOGY OF DEPRESSION AND BIPOLAR DISORDER

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Abstract - The production of free radicals in an organism is under the control of various antioxidant mechanisms. If their production overcomes the capacity of antioxidant protection, oxidative stress occurs which is capable of damaging different cellular structures and biomolecules, leading to various diseases. The importance of oxidative stress was proven in many psychiatric diseases among which are depression and bipolar disorder. Different studies show the significant improvement of clinical presentation when antioxidant substances are administered, suggesting that redox imbalance can influence their symptoms appearance and severity. In addition, oxidative stress is intercrossed with the different comorbidities that appear among depressive and bipolar patients. Beside the clinical presentation, oxidative stress influences the chronicity of depression, which was demonstrated in patients with recurrent depressive disorder. Better understanding of oxidant/antioxidant imbalance and its role in the pathophysiology of depression and bipolar disorder could be useful for the development of a novel therapeutic approach to the management of these diseases.

Key words: Oxidative stress, depression, bipolar disorder

REDOX BIOLOGY AND OXIDATIVE STRESS

During various physiological processes in the organism, molecules are exposed to numerous chemical alterations that include oxidation and reduction. Oxidation is a process in which an atom or molecule loses an electron, while reduction occurs when an atom or molecule gains an electron. These two processes can create highly reactive free radicals capable of damaging cellular and subcellular structures such as membranes, proteins, lipids and nucleic acids (Jones, 2008).

The most important free radicals include reactive oxygen species (ROS), among which there are superoxide radical (O₂⁻), peroxide radical (H₂O₂), hydroxyl radical (OH⁻) and singlet oxygen (O₂) (Taniyama and Griendling, 2003). ROS play an important role in different physiological processes that include cellular signalization, inflammation and immune defense. Normally, ROS concentrations are relatively small due to the activity of antioxidant protection mechanisms that can be enzymatic and nonenzymatic (Kohen and Nyska, 2002). Superoxide dismutase (SOD) represents the first line of defense against ROS by catalyzing the dismutation of superoxide into peroxide radical. It appears in three different isoforms, mitochondrial Mn²⁺-SOD, cytosolic Cu²⁺/Zn²⁺-SOD and extracellular Cu²⁺/Zn²⁺-SOD (Borković-Mitić et al., 2011). Peroxide which is formed as a result of peroxide radical (O₂⁻), peroxide radical (H₂O₂), hydroxyl radical (OH⁻) and singlet oxygen (O₂) (Taniyama and Griendling, 2003). 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SOD activity is reduced to water by selenium-dependent glutathione peroxidase (GPx) and catalase (CAT). The glutathione redox cycle is a main defensive mechanism against low and moderate free radical production, while CAT becomes significant during the presence of very high ROS levels (Ghosh et al., 2011).

Beside the mentioned enzymes, the nonenzymatic components of the antioxidant defense mechanism include vitamins C and E, carotenoids, bilirubin, uric acid, several serum proteins, etc. If the free radical production overcomes the capacity of antioxidant protection, oxidative stress occurs (Djurašević et al., 2010). Oxidative stress induces different types of structural damages to the cell, metabolic deregulation and disintegration of signaling pathways. These changes have great influence on the development and progression of many different diseases (Choi, 2012).

ROLE OF OXIDATIVE STRESS IN MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) is a chronic, highly disabling condition and both short- and longer-term treatment outcomes are not optimal (Schmidt et al., 2011). Various researches linked the pathophysiology of MDD with different biomarkers, demonstrating the complexity of this disorder and its appearance in different pathological states such as genetic diseases of small and medium blood vessels (Sternic et al., 2009).

Oxidative stress has been implicated in the pathophysiology of several neuropsychiatric diseases, including MDD (Herken et al., 2007, Sarandol et al., 2007). Both total antioxidant capacity (TAC) and total oxidant status (TOS) are altered in depressive patients, and they can be used as a means for the estimation of the redox status. The study of Cumurcu et al. showed the direct relationship between TAC and TOS in MDD. Serum TOS was significantly higher and TAC was significantly lower among patients with MDD compared to the control group. In this study, the authors also investigated the relationship between antidepressive medications and redox status, and it was found that TOS was higher and TAC was lower in the pre-treatment stage than in the post-treatment stage of MDD patients (Cumurcu et al., 2009).

The influence of several antidepressive drugs on the melioration of the oxidant/antioxidant balance is substantial. Subchronic treatment with selective serotonin re-uptake inhibitors (SSRIs), such as fluoxetine, sertraline, fluvoxamine and citalopram for 3 months reduced the production of malondialdehyde (MDA) and TAC, pointing to their deleterious effect on free radical production (Bilici et al., 2001). In addition, administering fluoxetine as well as imipramine and venlafaxine to rats with depressed phenotypes was shown to significantly reverse the biochemical effect of oxidation, including protein carbonylation in brain tissue (Zafir et al., 2009). These pharmacodynamic properties of SSRIs are also accompanied by a lowering of oxidative stress during MDD, resulting in significant clinical improvement. Sarandol et al. (2007) reported a significant positive correlation between the severity of MDD and SOD activity, implying that an increased severity of depression increases the total antioxidant enzyme levels. Another important antioxidant mechanism that involves glutathione and glutathione reductase (GR) is depleted in the blood of depressive patients as well as in post mortem analyzed frontal cortices of MDD patients (Gawryluk et al., 2011). Oxidative modifications of proteins often manifest as protein carbonylation at specific amino acids proline, threonine, lysine and arginine, leading to significant alterations in or destruction of a protein's structure and function (Oliver, 1987). Increased protein carbonylation is confirmed in the pathophysiology of MDD, often affecting protein kinase A (PKA) and protein kinase C (PKC), which are important components of cellular redox signaling, leading to the deregulation of an internal cell's communication and the integration of numerous pathways (Giorgi et al., 2010, Humphries et al., 2007). Reactive oxygen species (ROS) produced in excess during oxidative stress can damage nucleic acids, beside lipids and proteins. Although many damaged DNA lesions have been identified, 8-hydroxy-2’-deoxyguanosine (8-OHdG) remains
the most frequently used biomarker of oxidative damage of nucleic acids, due to its stability in biological fluids and tissues (Cheng et al., 1992). Forlenza and Miller demonstrated in their study that depressive patients have higher levels of 8-OHdG than healthy controls. In addition, an important finding is that 8-OHdG levels directly correspond to the severity of depressive disorder, perceived workload, psychological distress and negative mood (Forlenza and Miller, 2006).

ROLE OF OXIDATIVE STRESS IN RECURRENT DEPRESSIVE DISORDER

Depression is a disorder in which both relapse and recurrence are common. It is reported that the majority (77.5%) of patients with depression will relapse or have a chronic course (Howell et al., 2008). In such patients, longer and more frequent depressive episodes appear to increase vulnerability for further episodes, precipitating an accelerating and progressive illness course leading to functional decline. Lately there is a growing amount of evidence that recurrent MDD is an inflammatory disorder, as shown by the increased levels of proinflammatory cytokines that, in turn, lead to increased oxidative stress (Maes et al., 2012). In this way, it is possible for the pathways of oxidative stress to underpin the pathophysiology of recurrent MDD and it seems that oxidative stress can affect the chronicity of this disease (Galecki et al., 2012). Stefanescu and Ciobica revealed increased oxidative stress among patients with recurrent depressive disorder, with increased levels of MDA and decreased glutathione peroxidase (GPx) activity.

However, it seems that the first line of defense against free radicals, reflected in SOD activity, is functional and upregulated. Increased SOD and decreased GPx activity leads to an accumulation of hydrogen peroxide, which stimulates the lipid peroxidation and protein oxidation process, resulting in cellular deficits and rapid consumption of antioxidants (Stefanescu and Ciocu, 2012). Augmented MDA levels and antioxidant enzyme activities are also associated with the severity of symptoms, cognitive decline and memory impairment among patients with recurrent depression (Talarowska et al., 2012).

ROLE OF OXIDATIVE STRESS IN BIPOLAR DISORDER

Bipolar disorder has been classically described as a cyclical illness, with full-blown manic or depressive episodes interspaced with normal euthymic periods. This traditional view needs to be changed, as evidence now suggests that patients experience a more subtle chronic course than initially thought, characterized by residual symptoms, emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, and increased risk for psychiatric and medical comorbidity in between mood episodes (Leboyer and Kupfer, 2010). There is a very limited number of studies that describe the role of oxidative stress in the pathogenesis of bipolar disorder. However, oxidative stress and inflammation may mediate part of the association between bipolar disorder and medical comorbidity, functional impairment and cognitive deficit (Berk et al., 2010, Grande et al., 2011). Magalhaes et al. (2012) showed that systemic administration of N-acetyl cysteine, a precursor of glutathione, improves the functioning of patients with bipolar disorder, suggesting that the use of antioxidant substances can be of great assistance in the treating of this disease. At present there is a great need for more extensive experimental and clinical studies on this topic, in order to clarify the role of oxidative stress in the pathogenesis of bipolar disorder.

CONCLUSION

Numerous experimental studies have revealed the significant role of oxidative stress in the development, progression and severity of psychiatric disorders, among which are depression and bipolar disorder. Some of them proved this link directly, by accessing the concentrations of biomarkers of redox imbalance, while others used an indirect approach by administering antioxidant substances and revealing the clinical improvement. However, there is still insufficient data about the exact role of oxidative stress in
the pathophysiology of affective disorders and their clinical presentation. It is still not immediately clear how depressed people might come to higher levels of oxidative stress. First, clinically depressed people may alter their behavior in such a way as to increase the oxidative stress, by increased smoking, alcohol consumption, diet and various comorbid diseases. Second, the depression contributes to oxidative damage with an activation of the innate immune response and promotion of inflammation, which is a significant source of ROS (Forlenza and Miller 2006). The incidence of depression has a rising trend in many countries and it is of great importance to clarify the exact mechanism that underlies this disease (Pavlović et al., 2009, Lačković 2010). Understanding the role of oxidative stress in the pathophysiology of depression and bipolar disorder could lead us to the formulation of novel therapeutic concepts and toward a reduction in symptom severity.

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