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Review article

Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism

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ABSTRACT

The pathophysiology of psychiatric diseases, including depression, anxiety, schizophrenia and autism, is far from being fully elucidated. In recent years, a potential role of the oxidative stress has been highlighted in the pathogenesis of neuropsychiatric disorders. A body of clinical and preclinical evidence indicates that psychiatric diseases are characterized by higher levels of oxidative biomarkers and with lower levels of antioxidant defense biomarkers in the brain and peripheral tissues. In this article, we review current knowledge on the role of the oxidative stress in psychiatric diseases, based on clinical trials and animal studies, in addition, we analyze the effects of drug-induced modulation of oxidative balance and explore pharmacotherapeutic strategies for oxidative stress reduction.

Contents

Abbreviations: CAT, catalase; GABA, γ-aminobutyric acid; GSH, glutathione; GSH-Px, glutathione peroxidase; GSH-R, glutathione reductase; MDA, malondialdehyde; NO, nitrite oxide; OSI, oxidative stress index; ROS, reactive oxygen species; SOD, superoxide dismutase; SSRI, selective serotonin reuptake inhibitors; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TOS, total oxidant status; XO, xanthine oxidase.

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Introduction

Oxidative stress occurs when reactive oxygen species (ROS) generation exceeds the antioxidant capacity of cells (see Part 1). This state provokes different kinds of oxidative damage of cellular components and leads to several disorders, including psychiatric diseases. A body of clinical and preclinical evidence indicates that in psychiatric diseases production of ROS prevails over the brain defense systems. Oxidative damage may play a crucial role in the pathophysiology of certain neuropsychiatric diseases, including depression, anxiety, schizophrenia and autism.

The present review summarizes the current knowledge on the role of oxidative stress in psychiatric diseases, based on clinical trials and animal studies, in addition, we analyze the effects of drug-induced modulation of oxidative balance and explore novel therapeutic strategies for oxidative stress reduction.

Psychiatric disorders

Depression

Depression, as one of the major lifestyle diseases of the twenty-first century, is a serious therapeutic problem in modern pharmacotherapy. According to DSM-V, depressive disorders are characterized by "the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function" [1]. Despite many preclinical and clinical studies on this brain disorder, the pathophysiology of depression is far from being fully elucidated. One of the newest attempts to explain the etiology of the disease is the hypothesis of oxidative stress [2].

Clinical studies

Oxidative biomarkers. A body of clinical evidence indicates that depression is characterized by a higher oxidant status. In fact, total oxidant status (TOS) and oxidative stress index (OSI) were increased in depressed patients as compared to normal controls in plasma [3,4] and serum [5,6]. Some studies demonstrated higher levels of plasma peroxides [7] and serum nitric oxide (NO) [5,6,8–10] in depressed patients, while Ozcan and co-workers reported lowered levels of NO in depressed patients in the pre-treatment period [11]. Plasma NO levels were also higher in suicidal depressed patients compared to non-suicidal depressed patients or control subjects [12]. In depression, xanthine oxidase (XO) levels were higher in clinical studies [10] as well as in *postmortem* studies which showed XO level increase in the thalamus and putamen [13].

In depressed patients, markers of lipid peroxidation were increased [5,6,11,14–18], especially during depressive episodes [3], while elevated levels of isoprostanes were present in urine [19,20], serum [21] and plasma [17]. Oxidative DNA damage was detected in serum [5,6,16,22], leukocytes [23] and urine [24], while higher protein peroxidation was seen in plasma [25] of depressed patients.

In *postmortem* analyses, the levels of lipid peroxidation was increased in the anterior cingulate cortex [26], while protein oxidation was higher in the prefrontal cortex of patients diagnosed with bipolar disorder [27]. Oxidative damage of RNA (rather than to DNA) was elevated in several regions (CA1, CA3 and dentate gyrus regions) of the hippocampus among patients with either bipolar disorder or major depressive disorder [28].

Antioxidant defense biomarkers. There are several lines of evidence indicating that antioxidant mechanisms are disturbed during depression, namely total antioxidant capacity (TAC) [3,4,6,29], non-enzymatic antioxidant molecules [glutathione (GSH) [30], coenzyme Q10 [31], alpha-tocopherol [32] and ascorbic acid [14]] fall, while enzymatic antioxidants, like glutathione peroxidase (GSH-Px) [11,30], catalase (CAT) [5,11], and superoxide dismutase (SOD) [5,6,8,10] show a trend to fall in depressed patients. This conclusion appears to be questioned by some reports, which indicated a rise of activities of glutathione reductase (GSH-R) [25,30] and GSH-S-transferase [25] in the late stage of the illness, without alteration in GSH-Px activity [3,25]. Similarly, higher levels of SOD activities were also found in serum and erythrocytes of depressed patients [14–16,18,30].

In *postmortem* studies of depressed patients, the concentration of SOD was found to be increased in the prefrontal cortex, but not in the hippocampus [2]. An increase in antioxidant defense biomarkers can be considered as a compensatory response to oxidative stress.

Modulation of oxidative balance by antidepressant drugs. As mentioned above, oxidative stress is enhanced during depression, while antidepressant treatments are connected with manipulation of biomarkers of oxidative damage. In fact, several studies revealed the normalization of GSH-Px activity after sub-chronic treatment with antidepressants [11], while 3-month antidepressant treatment let to reduction in TOS and OSI, and increases in TAC [29]. NO levels significantly decreased and normalized whereas SOD activity significantly increased but did not reach the control levels on the 30th day of antidepressants treatment [8]. After 8 weeks of antidepressants treatment, decreased SOD activities and increased NO and XO levels were normalized [10]. However, Sarandol and co-workers [15] indicated that oxidant-antioxidant system did not seem to be affected by 6 weeks of antidepressant treatment. After a 3-month treatment with selective serotonin reuptake inhibitors (SSRI), antioxidant enzyme activities and lipid peroxidation level in blood were decreased to normal levels [18]. Treatment with milnacipran, but not with paroxetine, increased the plasma NO levels by 4th and 8th week [9]. After 3 months of fluoxetine treatment, the examined parameters did not change significantly [3], but in the combined therapy with acetylsalicylic acid a decrease in the activity of SOD, CAT, GSH-Px, and malondialdehyde (MDA) concentration was reported [33]. An increase of the serum SOD activity and MDA levels was reversed after treatment with fluoxetine and citalopram [14].

Pharmacotherapeutic strategy to reduce oxidative stress. Human studies provide evidence that some antioxidants show antidepressant effect and potentiate the antidepressant therapy. Several clinical trials supported the usefulness of omega-3 acids (polyunsaturated fatty acids) [34] or N-acetylcysteine (a mucolytic drug) [35–39] in depressed patients.

Conclusions. Oxidative stress seems to be an important factor contributing to the pathogenesis of depression. However, based on the literature data it is still difficult to unequivocally