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Antioxidants as potential therapeutics for neuropsychiatric disorders

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ABSTRACT

Oxidative stress has been implicated in the pathophysiology of many neuropsychiatric disorders such as schizophrenia, bipolar disorder, major depression etc. Both genetic and non-genetic factors have been found to cause increased cellular levels of reactive oxygen species beyond the capacity of antioxidant defense mechanism in patients of psychiatric disorders. These factors trigger oxidative cellular damage to lipids, proteins and DNA, leading to abnormal neural growth and differentiation. Therefore, novel therapeutic strategies such as supplementation with antioxidants can be effective for long-term treatment management of neuropsychiatric disorders. The use of antioxidants and PUFAs as supplements in the treatment of neuropsychiatric disorders has provided some promising results. At the same time, one should be cautious with the use of antioxidants since excessive antioxidants could dangerously interfere with some of the protective functions of reactive oxygen species. The present article will give an overview of the potential strategies and outcomes of using antioxidants as therapeutics in psychiatric disorders.

Contents

Abbreviations: PUFAs, Polyunsaturated fatty acids; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; NO, Nitrous oxide; NO+, Nitrosonium cation (NO+); NO−, Nitroxyl anion; ONOO−, Peroxynitrite; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; GR, Glutathione reductase; GST, Glutathione S transferase; GSH, Reduced glutathione; TAS, Total antioxidant status; TBARS, thiobarbituric acid reactive substances; NAC, N-acetyl- cysteine; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; EEG, Electroencephalography; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic; BDNF, Brain-derived neurotrophic factor.

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1. Introduction

Oxidative stress and constitutively produced reactive oxygen and nitrogen species (ROS and RNS) are known to affect cellular processes in a deleterious manner. Moreover, accumulating evidence indicate that oxidative free radicals play important roles in the pathophysiology of various neuropsychiatric disorders including schizophrenia, bipolar disorder and major depression. Such studies have also opened the possible avenues of new treatment strategies using antioxidants as adjunctive therapy in the above disorders. In this review, we present an overview of recent findings on the role of oxidative stress in the pathophysiology of neuropsychiatric disorders. We also discuss on the use of antioxidants as adjunctive therapy in the above psychiatric conditions.

This review has been prepared based on a literature search using the Medline, Pubmed, Google Scholar, BIOSIS Previews, and NIH Reporter databases, up until July 2012. Search terms included the following: oxidative stress, reactive oxygen species, reactive nitrogen species, antioxidants, antioxidant defense, lipid peroxidation, DNA damage, neuropsychiatric disorder, psychiatry, mental disorder, schizophrenia, bipolar disorder, depression, anxiety disorder, glutathione, N-acetylcysteine, alternative treatment, antipsychotic, antidepressant, and treatment, grouped in various combinations.

2. Free radicals

The main free radicals formed in the body are ROS and RNS. At least 5% of the inhaled oxygen is converted to reactive oxygen species (Harman, 1993). These radicals in excess result in oxidative stress, which has been implicated in the pathogenesis of several diseases including neuropsychiatric disorders. Most of the molecular oxygen consumed by aerobic cells during metabolism is reduced to water by using cytochrome oxidase in mitochondria. However, when the oxygen is partially reduced it becomes 'activated' and reacts readily with a variety of biomolecules such as proteins, carbohydrates, lipids and DNA. In the sequential univalent process by which oxygen undergoes reduction, several reactive intermediates such as superoxide, hydrogen peroxide, and extremely reactive hydroxyl radical are formed. The nitric oxide radical is produced in higher organisms by the oxidation of one of the terminal guanidonitrogen atoms of L-arginine (Ferret et al., 2000). This process is catalyzed by the enzyme nitric oxide synthase. Depending on the microenvironment, NO can be converted to various other reactive nitrogen species such as nitrosonium cation (NO^+), nitroxyl anion (NO^-) or peroxynitrite ($ONOO^-$) (Hughes, 1999). Some of the physiological effects may be mediated through the intermediate formation of S-nitroso-cysteine or S-nitroso-glutathione (Hogg et al., 1997).

3. Antioxidants

The antioxidant defense mechanisms protect the cells by removing the free radicals. The antioxidant system comprises of different types of functional components such as enzymatic and nonenzymatic antioxidants. The enzymatic antioxidants comprise of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione S transferase (GST). The non-enzymatic antioxidants include reduced glutathione (GSH), vitamin C (ascorbic acid), vitamin E (α tocopherol), N-acetyl-cysteine (NAC), uric acid, carotenoids, flavanoids ubiquinol etc. Oxidative stress occurs when the production of ROS exceeds the natural antioxidant defense mechanisms, causing damage to macromolecules such as DNA, proteins and lipids. The oxidation of lipids by ROS, notably lipid peroxidation of polyunsaturated fatty acids (PUFA), results in reactive products such as croton aldehyde, malondialdehyde and 4-hydroxyalkenals. These intermediates can react with DNA bases in vitro and in vivo to form exocyclic DNA adducts characterized as propano and etheno DNA-base adducts.

Although ROS are generally known for their destructive effects in the cells a number of biological reactions require ROS for their protective functions. It is known that phagocytes as well as neutrophils protect cells from intruding bacteria via NADPH dependent ROS mechanism (Babior, 1978; Rossi and Zatti, 1980). ROS play an important role in cytochorme P450-dependent detoxification reactions (Ghosh et al., 1997). It has been shown that ROS are essential mediators of apoptosis (Slater et al., 1995; Johnson et al., 1996). Therefore, one should be cautious with the use of antioxidants since excessive antioxidants could dangerously interfere with some of the protective functions of reactive oxygen species.

4. Oxidative stress in psychiatric disorders

The brain is considered particularly vulnerable to oxidative injury due to high oxygen utilization and hence generation of free radicals, insufficient antioxidant defense mechanisms, high lipid content and excitotoxicity. Increasing evidence indicates that disturbances of antioxidant defense mechanisms can play a part in a wide range of neuropsychiatric disorders (Table 1). Below, we discuss the role of free radicals and antioxidants in the pathophysiology of schizophrenia, bipolar disorder and major depression.

4.1. Schizophrenia

A number of factors including neuronal maldevelopment, impaired neurotransmission, viral infections, environmental and genetic factors have been found to be associated with the pathophysiology of schizophrenia (Carlsson et al., 1999; Jakob and Beckmann, 1986; Kendler, 2003; Kornhuber and Weller, 1994; Pearce, 2001; Thome et al., 1998). Evidence also indicate that mitochondrial pathology and oxidative stress may be the most critical components in the pathophysiology of schizophrenia (Ben-Shachar and Laifenfeld, 2004; Bubber et al., 2004; Goff et al., 1995; Whatley et al., 1998). Mitochondrial electron transfer chain is considered as a major source of ROS. Many studies have indicated increases in free radicals, alterations in antioxidant defense mechanism, increases in lipid peroxides and higher levels of pro-apoptotic markers in subjects with neuropsychiatric disorders (Ben Othmen et al., 2008; Boskovic et al., 2011; Casademont et al., 2007; Rezin et al., 2009).

4.1.1. Non-enzymatic antioxidants in the pathophysiology of schizophrenia

The total antioxidant status (TAS) represents the sum of activities of all the antioxidants. Yao et al. (1998a, 1998b) reported a significant and inverse correlation of plasma TAS levels with symptom severity during the drug-free condition. They did not find any significant differences in plasma TAS levels between on and off haloperidol-treatment conditions, indicating a possible role of TAS in the pathophysiology of schizophrenia. A decrease in plasma TAS has also been reported in chronic schizophrenia subjects and the TAS levels showed a weak to moderately significant negative correlation with total, positive and general psychopathology PANSS scores (Virit et al., 2009). Recently, reduced levels of plasma TAS have been shown in first-episode drug-naive patients with schizophrenia (Li et al., 2011). Moreover, TAS levels were also found lower in erythrocytes in children and adolescents with a first psychotic episode as compared to healthy controls (Mico et al., 2011).

Individual plasma antioxidants, albumin, bilirubin and uric acid were also found lower in schizophrenia subjects (Yao et al., 1998a, 2000). Moreover, decreases in plasma levels of total and reduced glutathione (GSH), along with altered antioxidant enzyme activities have been reported in drug-naive first-episode patients (Raffa et al., 2011). Significant decreases in the levels of reduced, oxidized, and total GSH were found in postmortem prefrontal cortex samples

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