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Oxidative imbalance in bipolar disorder subtypes: A comparative study

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ABSTRACT

Objective: The oxidants are related with the membrane-associated pathologies in the central nervous system and may have an important role in neuropsychiatric disorders. Several studies were performed on the effects of free radicals in bipolar disorder. However, there are no studies investigating the effects of free radicals both in the subtypes of BD (Bipolar disorders I and II) and in antidepressant induced mania (AIM). In this study, we aimed to investigate the status of oxidative metabolism in BD and its subtypes.
Methods: 94 bipolar patients (BD I–II and AIM) diagnosed according to DSM IV and as control group 41 healthy subjects were included to the study. The total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) were examined in the properly obtained plasma samples of subjects and healthy controls included in the study.
Results: The patients' TAS, TOS and OSI were significantly higher than the controls. TAS is negatively correlated with the number of previous total episodes in BD I. The BD I group appeared to have higher TOS compared to BD II group.
Conclusions: Oxidative balance is impaired in bipolar disorder. Antioxidant levels may be increased compensatorily in response to increased oxidant levels. Another important result of our study was that in the comparison of the three disease subtypes BD I group was found to have higher TOS compared to the BD II group. This finding is compatible with the literature on BD I and may be associated with the more severe course of BD I.

1. Introduction

Oxidative stress is an excessive exposure to oxidants and/or reduction in antioxidant capacity. In biological systems atoms or molecules that contain one or more unshared electrons are called “oxidants” or “free radicals”. The oxidants impair the cell structure, extracellular matrix, cilia functions and the genetic structure by causing DNA damage (Guemouri et al., 1991). The body has developed several defense mechanisms to prevent the formation of free radicals and the damage they cause. Free radicals have a role in the pathogenesis of several diseases including atherosclerosis, neurodegenerative diseases, cancer, allergy, diabetes and cataract and therefore are one of the most studied topics (Guemouri et al., 1991).

Our studies on the role of oxidative stress in the course and treatment of psychiatric disorders demonstrated that oxidative balance is impaired in schizophrenia, autistic disorder, bipolar disorder, depression, panic disorder and adult attention deficit-hyperactivity disorder; in certain diseases this imbalance persisted even during remission. This imbalance is associated with some specific signs and in certain diseases it improves with treatment (Gergerlioglu et al., 2007; Herken et al., 2006; Kuloglu et al., 2002a; Savas et al., 2006; Selek et al., 2008a; Sogut et al., 2003; Yanik et al., 2003).

There are various assumptions as to how this impairment emerges. For instance, the oxidants may react with the membrane-associated proteins and impair enzymes or uptake of neurotransmitters involved in the normal process leading to a tendency to develop the disease. The oxidants are related with the membrane-associated pathologies in the central nervous system and may have an important role in neuropsychiatric disorders (Berk et al., 2008a; Kuloglu et al., 2002a; Ng et al., 2008). Some of the specific oxidants may lead to “adverse” increases in other components of the metabolism which may lead to specific symptoms of psychiatric disorders. For instance, the increased nitric oxide levels may lead to such an effect via the glutamate pathway in manic patients presenting with the psychotic symptom as delusion (Gergerlioglu et al., 2007). Also, *N*-acetyl cysteine (orally bioavailable precursor of glutathione) was found to be an effective augmentation strategy for depressive symptoms in bipolar disorder (Berk et al., 2008b).

According to the results of these studies, there exists an impaired oxidative balance in psychiatric disorders. In certain diseases, this impairment may improve even with clinical response to treatment, whereas the oxidative imbalance persists in moderate or severe

Abbreviation: BD, Bipolar Disorder; AIM, Antidepressant induced mania; TOS, Total oxidant status; TAS, Total antioxidant status; OSI, Oxidative stress index; CGI, Clinical global impression; NO, Nitric oxide, SOD, Superoxide dismutase.

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psychiatric disorders. The information regarding oxidative imbalance still does not explain the entire psychiatric pictures; however, they do enlighten some certain topics including the presence of alternative treatment, more specific monitorisation of treatment response with biological markers and screening of specific markers in plasma samples.

Several studies were performed on the effects of free radicals in bipolar disorder (BD) (Gergerlioglu et al., 2007; Hoekstra et al., 2006; Sadeghipour et al., 2007; Savas et al., 2006; Selek et al., 2008a). Recently published meta analysis has shown oxidative stress markers may play a role in the pathophysiology of bipolar disorder (Andreazza et al., 2008). However, there are no studies investigating the effects of free radicals both in the subtypes of BD (Bipolar disorders I and II) and in antidepressant induced mania (AIM).

AIM is classified as "BD III" by some authors (Akiskal and Pinto, 1999). Comparison of oxidative metabolism in the subtypes of BD, may prove its result in the clinical appearance between subtypes showing the biological sign of differentiation. In this study, we aimed to investigate the status of oxidative metabolism in BD and its subtypes.

2. Method

2.1. Subjects

The study population consisted of 94 patients who referred to the Mood Disorders Unit of Gaziantep University Department of Psychiatry between the dates of 15.11.2006–15.05.2007 and met the inclusion and exclusion criteria of the study. The control group is formed of 41 healthy subjects who were chosen among the doctors and hospital staff.

The inclusion criteria of the study included euthymic patients diagnosed with bipolar disease according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (DSM IV) (American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 2004) and a control group without any present or previous psychiatric disorder. BD I was accepted with at least one or more manic/mixed episodes. Major depressive episodes with spontaneous hypomania were assigned to BD II. AIMs were accepted when all the following criteria were met: 1. Antidepressant use for at least 3 days in the last 2 weeks, 2. Onset of symptoms within 16 weeks after beginning antidepressants (Tamada et al., 2004).

The exclusion criteria were: Patients having concomitant psychiatric or other medical diseases in the non-euthymic episode of the bipolar disease, hypertension, diabetes or other serious medical conditions including endocrinopathies, patients with or have history of alcohol and/or substance abuse, and patients that receive any antioxidant agents (e.g. vitamin E and C). Seventeen patients were excluded for not conforming to the exclusion criteria.

Among the 314 patients registered to the Mood Disorders Unit, 94 euthymic patients who had received a diagnosis of bipolar disease and attended a visit at the clinic between the above stated dates were included. Patients were evaluated by a psychiatrist (MY) according to the DSM IV criteria. All patient records in the Mood Disorders observation form were examined; sociodemographic parameters including age and sex and concomitant diseases and present medications as well as smoking status were noted. Clinical global impression (CGI) Scale (Guy, 1976), Young mania rating scale (YMRS) (Young et al., 1978) and Hamilton depression rating scale (Ham-D) (Hamilton, 1960) were applied to patients to determine disease severity. All of the patients were euthymic for at least 2 months, as confirmed by a HAM-D <8, YMRS <6 and CGI equal or less than 2.

The control group included healthy and volunteer 41 persons from hospital staff. The sociodemographic parameters including age and sex as well as smoking status of them were also noted. The control group consisted of individuals who had no history of medication or non-medication drug use in the last 6 weeks and no history or family history of psychiatric disorders.

Ethics committee approval was obtained for the study. Written informed consent was obtained from all participants.

2.2. Instrument

2.2.1. Gaziantep mood disorders observation form

Mood Disorders Unit of the Gaziantep University Department of Psychiatry is a clinic that follows up and treats patients with mood disorders on one day of the week since 2000. Each patient receives routine follow-up at this unit and side effect scales as well as Gaziantep Mood Disorders Observation Form are used to record the height, weight and laboratory results. Data regarding the patients were obtained via this form.

2.3. Biochemical analysis

Blood samples of the patient and control groups were drawn from the antecubital vein following a 12-h period of fasting. The blood samples were transferred to tubes and in the presence of ice their plasma were separated by centrifuging at 3000 rpm for 5 min to be in process within 6 h. The plasma were stored at −80 °C for determination of the total antioxidants status (TAS) and total oxidants status (TOS). TAS and TOS were measured and oxidative stress index (OSI) was calculated in the Biochemistry Laboratory of Harran University.

2.3.1. Measurement of total antioxidant status (TAS)

This is a full-automatic method designed by Erel et al. (2004a) and measures the total antioxidant capacity of the body against powerful free radicals.

Fe^{2+}-o-dianisidine complex gives a Fenton type reaction with the hydrogen peroxide to form the OH radical. This powerful reactive oxygen species reacts with the colorless o-dianisidine molecule at the reducting low pH and leads to the formation of yellow–brown dianisidyl radicals. Dianisidyl radicals participate in further oxidation reactions resulting in more color formation. However, antioxidants in the samples suppress these oxidation reactions and inhibit color formation. This reaction is measured spectrophotometrically in automatic analysers (Erel, 2004b).

2.3.2. Measurement of total oxidant status (TOS)

This is a full-automatic colorimetric method developed by Erel et al. (2005). The oxidants in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The glycerol in the media accelerates this reaction about three fold. Ferric ions form a colored compound with xylenol orange in the acidic media. This color is associated with the amount of oxidant in the sample and is measured spectrophotometrically (Erel, 2005).

2.3.3. Calculation of the oxidative stress index (OSI)

Oxidative stress index (OSI) was calculated by dividing the total oxidants status (TOS) with the total antioxidants status (TAS) (Kosecik et al., 2005).

2.4. Apparatus

A Cecil 3000 spectrophotometer with a temperature controlled cuvette holder (Cecil) and an Aeroset automated analyzer (Abbott) were used (Erel, 2004a).

2.5. Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 13.0 was used to perform the statistical analysis and $p<0.05$ was considered statistically significant. The Chi-Square test was used for the comparison of parameters with two variables such as sex and in ratios. The