Psychiatry Research 261 (2018) 237–242

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Thiol/disulphide homeostasis in bipolar disorder

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ARTICLE INFO

Keywords:
Oxidative stress
Mania
Remission
Mood disorder
Oxidative markers

ABSTRACT

Bipolar disorder (BD) patients have increased oxidative stress, which can disturb thiol/disulphide homeostasis, causing disulphide formation. The aim of the study is to investigate dynamic thiol/disulphide (SH/SS) homeostasis in BD patients, which is a novel evaluation method of oxidative status. Ninety-four BD patients (50 in the manic episode and 44 in remission) and 44 healthy controls were included in the study. Blood serum native thiol (SH) and total thiol (ToSH) concentrations were measured in a paired test. The half value of the difference between native thiol and total thiol concentrations was calculated as the disulphide (SS) bond amount. Serum native thiol levels of the mania group were found to be lower than the remission and the control groups. There was a significant difference between the remission group and the control group in terms of native thiol. Serum total thiol level was lower in mania group than the control group. Detection of oxidative molecules for BD could be helpful, especially in treatment, follow-up periods and reducing morbidity. The results of our study besides the data available in the literature support that thiol and disulphide levels are useful markers for BD and promising therapeutic targets in terms of future pharmacological modulation.

1. Introduction

Bipolar disorder (BD) is associated with increased mortality (Laursen et al., 2007) and one of the most debilitating psychiatric disorders characterized by disruptive episodes of mania/hypomania and depression (Anderson et al., 2012). Understanding the etiology of BD has always been an important research topic. The roles of inflammatory processes and oxidative stress are being investigated with possible etiologic factors due to BD's indeterminate pathophysiology (Bauer et al., 2014; Gubert et al., 2013).

Oxidative stress, which means the excess of reactive oxygen species (ROS), could have a role in the etiology of BD (Raffa et al., 2012). Excessive ROS may cause cellular injuries, lipid peroxidation, damage, apoptosis and protein carbonylation (Berg et al., 2004; Filomeni and Ciriolo, 2006; Maes et al., 2013). As the brain tissue is more susceptible to oxidative damage, the body also has an antioxidative mechanism against this oxidative damage (Ciobica et al., 2011). The antioxidant mechanism of the body includes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-px) (Pavlović et al., 2002).

Studies investigating the oxidative stress in patients with BD are conducted in the literature. Thiobarbituric acid reactive substances (TBARS) as lipid peroxidation marker, have been also investigated in these studies. TBARS have been by far the most widely used markers of oxidative stress in clinical studies (Grignon and Chianetta, 2007; Andreazza et al., 2008). Related to that point, Machado-Vieira et al. (2007) reported higher levels of TBARS and antioxidant enzyme activities (SOD and CAT) in unmedicated patients with BD in manic episode. According to results of this study, initial manic episodes are considered to be associated with both increased oxidative stress parameters and activated antioxidant defenses, which could be related to dysfunctions on energy metabolism and neuroplasticity pathways. Kunz et al. (2008) also found that serum SOD activity was significantly increased in patients with BD who are either in mania or in depression but not euthymic. TBARS levels were also found to be significantly higher

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https://doi.org/10.1016/j.psychres.2017.12.062
Received 12 April 2017; Received in revised form 31 October 2017; Accepted 30 December 2017
Available online 02 January 2018
0165-1781/

in patients with schizophrenia, bipolar euthymic group, bipolar manic group and bipolar depressed group compared to controls (Kunz et al., 2008).

Thiols also have a significant role in antioxidant defence (Sen and Packer, 2000). Thiols can experience oxidation reaction through oxidants and form disulphide bonds (Cremers and Jakob, 2013). Oxidation of cysteine residues can prompt to reversible development of mixed disulfides between low-molecular mass thiols and protein thiol groups when oxidative stress enhances. Thiol disulphide homeostasis is maintained by reducement of formed disulphide bonds to thiol groups (Jones and Liang, 2009; Biswas et al., 2006). Thiol/disulphide ratio (TDR) has critical roles in detoxification, antioxidant protection, signal transduction, regulation of enzymatic activity, apoptosis, and cellular signaling mechanisms (Biswas et al., 2006; Circu and Aw, 2010).

Determination of dynamic thiol disulphide homeostasis can provide significant information on different normal or abnormal biochemical processes, because the abnormal thiol disulphide homeostasis state is involved in the pathogenesis of a variety of diseases, including schizophrenia and neurodegenerative disorders (Smeyne and Smeyne, 2013; Steele et al., 2013; Topcuoglu et al., 2017). Methods that measure only thiol values can only provide information about the status of the antioxidant buffer system. However, thiol disulphide homeostasis, which is the dynamic redox system of the organism, can be evaluated objectively with the method of Erel et al. (Erel and Neselioglu, 2014). To evaluate the thiol/disulphide balance globally, both thiol and disulphide need to be measured by this method (Vural et al., 2017).

In this study, we aimed to evaluate BD patients who were on manic episode and in remission in terms of thiol disulphide balance, and to compare them with healthy controls.

2. Methods

Before recruiting the participants, an experienced clinician interviewed patients according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fifth version (DSM–5), to confirm manic episode diagnosis of manic episode group members, to acknowledge that patients in the remission group did not meet DSM-5 criteria for any BD episode (i.e., depressive, mixed, manic, or hypomanic) in last 6 months, and that healthy control group members showed no evidence of any present or previous psychiatric disease. The Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) were also used to support the diagnoses of remission (i.e., HAM-D score < 7 or YMRS score < 4) and mania (i.e., YMRS score > 20). Our study was approved by the ethics committee of the Ankara Numune Training and Research Hospital. Written consents were obtained from each patient and one of their first-degree relatives and also from controls. Clinician filled out a socio-demographic data form. A 5 cc of venous blood was collected from each subject. Blood cells were separated from serum and serum samples were stored at − 80 °C. Biochemical analyses were performed on these samples. All patients underwent laboratory tests, including complete blood count, blood lipids, fasting blood glucose, C-Reactive Protein (CRP) and insulin measurements. Height, weight, waist and hip circumferences of the subjects were measured. Gender and age of each subject were recorded. When collecting data in our study, the amount of cigarette consumption was obtained for each patient and patients with obesity were excluded from the study. Mental retardation, pregnancy, previous electroconvulsive therapy (ECT) history and having any systemic or metabolic disease were also included in the exclusion criteria.

2.1. Hamilton Depression Rating Scale (HAM-D)

Designed by Hamilton (1960), the original version of the HAM-D contains 17 items, each scored from 0 to 4 for a maximum total score of 53. Decades later, Williams (1988) developed the Structured Interview for HAM-D-21 as another version of the HAM-D that improved its interrater reliability. The Turkish version of the scale was found to be valid and reliable (Akdemir et al., 2001). In our study, patients were evaluated with the 17-item version.

2.2. Young Mania Rating Scale (YMRS)

YMRS is an 11-item diagnostic questionnaire used to measure the severity of ME. Each item measures five degrees of severity; seven items are answered by using a five-point Likert-type scale, while four items are answered by using a 9-point Likert-type scale. The Turkish version of the scale was found to be both valid and reliable (Karadağ et al., 2002).

2.3. Biochemical tests

Fasting blood samples were obtained from the patients and the controls in plain tubes. Serum samples were separated after centrifugation at 1300*g* for 10 min and stored at − 80 °C until the analysis was conducted. Thiol disulphide homeostasis tests were performed. Reducible disulphide bonds were first reduced to form free functional thiol groups. Unused reductant sodium borohydride was consumed and removed with formaldehyde, and all thiol groups including reduced and native thiol groups were determined after the reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid (DTNB). Half of the difference between the total thiols and the native thiols gave the dynamic disulphide amount. After the native and total thiols were determined, disulphide amounts, disulphide/total thiol percent ratios (SS/SH + SS), native thiol/total thiol percent ratios (SH/SH + SS), and disulphide/native thiol percent ratios (SS/SH) were calculated (Erel and Neselioglu, 2014).

2.4. Statistical analysis

The data was examined by the Shapiro Wilk test whether or not it presents normal distribution. One-way ANOVA was applied for comparison of 3 groups. For pairwise comparison, Tukey test was used. Mann-Whitney *U* test was used for the comparison of 2 groups and Kruskal Wallis test was used to compare more than two groups were used when the data was not normally distributed. Categorical variables were compared using Pearson's chi-squared test and Fisher-Freeman-Halton test. Correlations between variables were tested using Pearson and Spearman correlation coefficients. $p < 0.05$ was considered as significance levels. Statistical analysis was performed using IBM Statistics SPSS 23.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3. Results

Mania and remission groups were presented similar results when data concerning gender (df = 2, $\chi^2 = 0.535$, $p = .765$), age (df = 2, F = 0.033, $p = .968$), marital status (Fisher-Freeman-Halton = 2.320 $p = .696$), BMI (Body Mass Index) (df = 2, F = 1.598, $p = .206$) and smoking (df = 2, F = 1.805, $p = .171$) were compared (Table 1). When the demographic and clinical characteristics of mania and remission groups were examined; a statistically significant difference between the groups was found in terms of monthly income, which was lower in mania group (Fisher-Freeman-Halton = 2.870 $p = .378$). The number of antipsychotic users was found to be higher in mania group (Fisher-Freeman-Halton = 10.399, $p = .004$). There was no statistically significant difference obtained between mania and remission groups in terms of blood count, lipids, insulin, CRP, fasting glucose ($p > .05$). While 96% of mania group had antipsychotic medication, this ratio was found to be 73% in the remission group.

Of the mania group, 64% were using valproic acid/sodium valproate, 12% were using lithium, 8% were using carbamazepine, 2% were using lithium and valproic acid/sodium valproate, and 14% were