Reduced antioxidant defense systems in schizophrenia and bipolar I disorder

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ABSTRACT

Numerous evidence and proofs suggest that the oxidative stress contributes to the pathogenesis of schizophrenia (SZ) and bipolar disorder (BD). The aim of this study is to determine the glutathione levels and the antioxidant enzyme activities in blood samples of patients suffering from SZ and patients with bipolar disorder in comparison with the healthy controlled subjects. It was a case-controlled study carried on upon three groups: forty-six SZ patients (41 men and 5 women, mean age = 33.2 ± 7 years), thirty BD patients (25 men and 5 women, mean age = 31.3 ± 8 years) and forty healthy controls (33 men and 7 women, mean age = 32.3 ± 7 years).

The glutathione levels are the total glutathione (GSHt), the reduced glutathione (GSHr), and the oxidized glutathione (GSSG) and the antioxidant enzyme activities that are the superoxide dismutase (SOD), the glutathione peroxidase (GPx), and the catalase (CAT) are determined by the spectrophotometer.

We noticed that the GSHt and the GSHr levels significantly decreased in both SZ and BD patients in comparison with the healthy control subjects. As for SOD and CAT activities they remained lower for the patients with SZ when compared both with the controls or the BD patients. We noticed as well that the CAT activity was significantly lower in the BD group than that in the control group, whereas, GPx activity showed no significant change in each group. Hence, this report of the decreased plasma levels of GSHt and GSHr, and the impaired antioxidant enzyme activities in SZ and BD patients aims at highlighting the GSH deficit that seems to be contributing to these disorders, and showing that it may be an important indirect biomarker of the oxidative stress for the SZ and BD.

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1. Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are both highly common and serious mental illnesses. They affect approximately 4% of the world's population. Both SZ and BD are illnesses that share many epidemiologic and clinical features as illustrated by the work of (Berrettini, 2000). Despite the fact that the pathophysiological mechanisms underlying these disorders remain unclear, many studies point toward the involvement of the oxidative stress in both SZ (Akyol et al., 2002; Gama et al., 2006; Grignon and Chianetta, 2007; Lohr and Browning, 1995; Mahadik and Mukherjee, 1996; Ng et al., 2008; Yao et al., 1998) and BD (Andreazza et al., 2007a; Kuloglu et al., 2002; Ranjekar et al., 2003; Steckert et al., 2010).

Oxidative stress is defined as a disturbance in the prooxidant which means the antioxidant balance in favor of the former, leading to a potential damage. Thus, the diminishing antioxidants or the increasing production of prooxidant will result in an oxidative damage not only of cell lipids, proteins, and enzymes but also of carbohydrates and even the DNA itself (Halliwell and Gutteridge, 2007).

The antioxidant pathways that form the major line of defense against the oxidative stress can be categorically divided into enzymatic and non-enzymatic systems. The major cellular antioxidant and redox-regulator is glutathione (GSH) that is the brain's dominant antioxidant (Wood et al., 2009). The enzymatic antioxidants include the following components: superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). These enzymes are constitutively expressed in all tissues.

For SZ and BD, the decrease of GSH, the brain's primary free radical scavenger, has been reported in the cerebrospinal fluid, in the prefrontal cortex using magnetic resonance spectroscopy, and in the post-mortem studies of the prefrontal cortex and the caudate nucleus (Selek et al., 2008; Yao et al., 2006).

Genetic polymorphisms of the GSH pathway, including the glutamate-cysteine ligase gene, have been linked to SZ (Gergerlioglu et al., 2007) and BD (Do et al., 2000).

Table 1
Demographic and clinical characteristics of study groups.

Demographic characteristics	SZ patients (n = 46)	BD patients (n = 30)	Healthy controls (n = 40)
Age (mean ± SD) (years)	33.2 ± 7	31.3 ± 8	32.3 ± 7
Min–Max	22–47	21–48	22–47
Gender (men/women)	41/5	25/5	33/7
Cigarette smoking n (%)			
Yes	26 (56.5%)	17 (56.6%)	18 (45%)
No	20 (43.3%)	13 (43.3%)	22 (55%)
Educational level n (%)			
Primary school	27 (58.7%)[*]	5 (12.5%)[**]	7 (23.3%)
Secondary school	17 (37%)	15 (37.5%)	22 (73.3%)
University	2 (4.34%)	10 (22.5%)	11 (36.6%)
Age of onset (mean ± SD) (years)	21.3 ± 4.4	22.9 ± 5.5	–
Min–Max	12–30	15–33	
Duration of illness (years)	12.2 ± 8.7	8.7 ± 6.03[***]	–
Min–Max	1–30	1–23	
Illness episode n (%)			
Depressive	–	5 (16.6%)	–
Euthymic	–	17 (56.6%)	–
Manic	–	8 (26.6%)	–
Subtypes n (%)			
Disorganized type	17 (37%)	–	–
Paranoid type	9 (19.6%)	–	–
Undifferentiated type	20 (43.5%)	–	–
Daily dosage of neuroleptics (mg) (mean ± SD)	510 ± 237	480 ± 291	

[*] SZ vs. controls: $\chi^2 = 18.3$; $p < 0.001$.
[**] SZ vs. BD: $\chi^2 = 18.14$; $p < 0.001$.
[***] SZ vs. BD: $p = 0.01$.

There are also conflicting data concerning the activities of the antioxidant enzymes in SZ and BD (Mico et al., 2011). For schizophrenic patients SOD, GPx and CAT antioxidant activities have been reported to be increasing (Dakhale et al., 2004; Kuloglu et al., 2002; Rukmini et al., 2004; Surapaneni, 2007; Zhang et al., 2006), decreasing (Carmeli et al., 2008; Ranjekar et al., 2003; Zhang et al., 2007) or unchangeable (Akyol et al., 2002; Herken et al., 2001).

For patients with BD, decreased activities of SOD and CAT have been shown (Kuloglu et al., 2002; Steckert et al., 2010). Kunz et al. (2008) reported an increased SOD activity in SZ, as well as in depressed and manic bipolar patients.

Thus, the purpose of the present study is to assess whether the total plasmatic glutathione GSHt, the reduced glutathione GSHr and the oxidized glutathione GSSG levels, in addition to the red blood cell (RBC) SOD, GPx, and the CAT activities were altered for SZ and BD patients as compared to the healthy control subjects.

2. Methods

2.1. Subjects

This study was approved by the Local Ethical Committee of the University Hospital of Monastir, and all subjects were of Tunisian origin.

Three groups studied were: forty-six schizophrenia (GI) and thirty BD (GII) inpatients, followed in the Psychiatric Department of the University Hospital of Monastir and thirty healthy control subjects (GIII) recruited from blood donors in the blood center of the University Hospital of Monastir. The three groups were age-matched. All BD patients of the current study belong to the bipolar I type. The BD has generally been subdivided into bipolar type I, bipolar type II and cyclothymia. In addition to depression, which is seen in all three types, bipolar type I is characterized by the presence of mania. The diagnosis was confirmed according to the DSM-IV-TR criteria (American Psychiatric Association, 2000) for SZ and BD. The healthy control subjects were evaluated by trained psychiatrists and were recorded to have no evidence of psychiatric illnesses.

When the blood samples were collected at the admission, 26 schizophrenic patients and 22 BD patients had been receiving treatment with antipsychotic medication (mood stabilizers: valproic acid, lithium or carbamazepine, and classical (haloperidol, fluphenazine, or chlorpromazine) or atypical antipsychotics (risperidone or olanzapine) for at least two weeks. The other patients had stopped taking antipsychotic treatment voluntarily due to their intolerance to it and to their low compliance and had been admitted to the psychiatric department for the exacerbation of the SZ or BD symptoms. The exclusion criteria considered for the two groups were the same and included the following parameters: seizure disorders, head injury with loss of consciousness, dependence on alcohol and other substances (except dependence on tobacco), vitamin supplementation followed for 6 months prior to inclusion in the study, and the denial to take part in the present study. Additional exclusion criteria for the control subjects included personal or family history of psychosis. All signed subjects gave their consent after a full explanation of the study. The demographic and clinical characteristics of the SZ, BD and the healthy control subjects are summarized in Table 1.

2.2. Biochemical procedures

Five milliliters of blood was drawn from control subjects and patients by simple venipuncture between 7.00 and 9.00 a.m., after overnight fasting and tobacco abstinence for more than 12 h. The samples were centrifuged for 10 min at 3500 rpm. Plasma red blood cells (RBC) were then separated, aliquoted and stored at −80 °C until analysis. Each evaluated parameter was assayed in duplicate for all samples. Throughout the investigations, the biochemical assays were conducted ignoring the available clinical information. The GSH levels were measured spectrophotometrically in deproteinized blood samples by the method of Akerboom and Sies (1981), using 5,5 dithiobis (2-nitrobenzoic acid). Absorbance values were compared with standard curves generated from known amounts of GSH standards. The total SOD activity was determined using pyrogallol as a substrate by applying the Marklund and Marklund (1974) method. This method is based on pyrogallol oxidation by the superoxide anion (O_2) and its dismutation by SOD. One unit (U) of total SOD is defined as the amount of enzyme required to inhibit the rate of pyrogallol autoxidation by 50%. GPx activity was assayed by the subsequent oxidation of NADPH at 240 nm with t-buthyl-hydroperoxide as substrate (Gunzler et al., 1974). CAT activity was determined using