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Oxidative–antioxidative systems and their relation with serum S100 B levels in patients with schizophrenia: Effects of short term antipsychotic treatment

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Abstract

Oxidative stress may be a contributing factor in the etiopathophysiology of schizophrenia, which may be exacerbated by the treatment with antipsychotics with pro-oxidant properties. Increased levels of S100 B are associated with neurodegenerative disorders, including schizophrenia. The aim of the present study was to investigate the role of oxidative cell damage in the pathogenesis of schizophrenia. Forty patients who fully met the fourth Diagnostic and Statistical Manual of Mental Disorders criteria for schizophrenia and 35 healthy control subjects were included in the study. Serum S100 B level was determined to investigate brain damage. Plasma malondialdehyde (MDA) levels and susceptibility of red blood cell (RBC) to oxidation were determined to investigate the oxidative status and plasma vitamin E, vitamin C, serum total carotenoid levels and total antioxidant capacity and RBC superoxide dismutase (SOD) and whole blood glutathione peroxidase activities were measured to investigate the antioxidative defence before and after 6 weeks of antipsychotic treatment. Plasma MDA and serum S100 B levels and RBC–SOD activity were significantly higher in the schizophrenia group than those of the control group. Treatment did not modify any of the oxidative–antioxidative system parameters or serum S100 B levels. S100 B level was significantly higher in patients with negative symptoms than the patients with positive symptoms and the control subjects. S100 B levels were significantly reduced after 6 weeks of treatment in patients with negative symptoms. The results of the present study might support the oxidative cell injury hypothesis of the schizophrenia. Furthermore, the underlying mechanisms of the subgroups of schizophrenia might be different as suggested by the increased S100 B levels and its decrement after treatment in patients with negative symptoms.

Keywords: Antipsychotic; Oxidative stress; S100 B; Schizophrernia; Zalondialdehyde

1. Introduction

Oxidative stress is the imbalance between the oxidative and antioxidative systems in favor of the former and there is growing evidence that oxidative stress is implicated in the pathophysiology of schizophrenia (Yao et al., 2001). Oxidative stress might lead to oxidative cell damage and contribute at varying degrees to the observed neuropathology of schizophrenia (Mahadik et al., 2006). It has also been suggested that some antipsychotics, primarily typical antipsychotics may have pro-oxidant effects and increase the oxidative stress and oxidative cell injury (Cadet and Lohr, 1989; Cadet and Perumal, 1990; Jeding et al., 1995). So it was hypothesized that oxidative cell injury may be a contributing factor in the etiopathophysiology of schizophrenia, which may be exacerbated by the treatment with antipsychotics with pro-oxidant properties (Mahadik et al., 2006).

In patients with schizophrenia, the indices of oxidative stress and oxidative cell injury are generally studied in blood, and very rarely in cerebrospinal fluid. Since oxidative stress is systematic and some of the oxidative products of the brain tissue do end up in the blood, peripheral indices have been accepted to reflect the brain oxidative injury (Mahadik et al.,

Abbreviations: BPRS, Brief Psychiatric Rating Scale; GPx, Glutathione peroxidase; MDA, Malondialdehyde; PANSS, Positive and the negative syndrome scale; RBC, Red blood cells; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; SOD, Superoxide dismutase; TAOC, Total antioxidant capacity.

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2006). One of the most used indices of oxidative stress and oxidative cell injury is the increased levels of malondialdehyde (MDA), which is an end product of lipid peroxidation. Several (Arvindakshan et al., 2003; Khan et al., 2002; Mahadik et al., 1998), but not all (Ranjekar et al., 2003; Skinner et al., 2005), investigators, reported increased plasma/serum MDA levels in schizophrenia. On the other hand, the results of the studies that investigated the antioxidant system also yielded conflicting results which might be related to the heterogeneity of the characteristics of the study groups; duration of the illness, treated or untreated subjects, symptoms, etc. (Evans et al., 2003; Mukerjee et al., 1996; Yao et al., 2000, 1998a,b; Zhang et al., 2003).

S100 B is a calcium-binding protein, produced and secreted by astrocytes and it modulates the proliferation and differentiation of neurons and glia (Donato, 2001). Increased levels of this protein are associated with brain damage and its persistent elevation appears to be involved in neurodegenerative disorders (Rothermundt et al., 2003), including schizophrenia (Lara et al., 2001; Rothermundt et al., 2004a,b; Schroeter et al., 2003; Wiesmann et al., 1999). Data about the interaction between oxidative stress and protein S100 B yielded conflicting results. It was reported that high doses of S100 B might be involved in neuronal death by apoptosis, as a result of increased production of reactive oxygen species (Huttunen et al., 2000). It was also suggested that increased S100 B levels might reflect the oxidative cell injury in the brain tissue of the schizophrenic patients (Gama et al., 2006). However, evidence has been shown in vitro that S100 B plays a role in the induction of oxidative stress (Esposito et al., 2006; Huttunen et al., 2000).

The role of oxidative stress in the pathophysiology of schizophrenia needs still further investigation (Young et al., 2007). Data about serum S100 B in schizophrenia is limited and conflicting and to the best of our knowledge there is not any previous study investigating the association of S100 B with oxidative–antioxidative system parameters in schizophrenia. In the present study, our aim was to investigate the role of oxidative–antioxidative systems, serum S100 B levels and their association in unmedicated schizophrenic patients before and after treatment. For this purpose we evaluated the oxidative–antioxidative systems and their relation with serum S100 B levels. We also aimed to investigate the effects of short term treatment on the oxidative–antioxidative systems in patients with schizophrenia. In order to evaluate the oxidative status, we measured plasma MDA levels and determined susceptibility of red blood cells (RBC) to in vitro oxidation. We analyzed RBC superoxide dismutase (SOD) activity, whole blood glutathione peroxidase (GPx) activity and serum total antioxidant capacity (TAOC) and other serum antioxidant parameters (vitamin E and C, total carotenoids, total bilirubin, albumin and uric acid) in order to evaluate the antioxidative status of the patients with schizophrenia. All of the psychiatric and laboratory examinations were performed before and after 6 weeks of antipsychotic treatment in drug-naive or drug-free schizophrenic patients.

2. Methods

2.1. Subjects

Forty patients, 22 women and 18 men (mean age ±S.D.: 34.9±9.9 years, range: 19–54), diagnosed as having schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994) were included in the study. There were 9 patients who had never taken antipsychotics (drug-naive) and 31 patients who had not taken antipsychotics for at least 3 weeks prior to the study (drug-free). Five of the patients were outpatients and the remaining 35 were inpatients. The patients were examined by 2 independent specialists in psychiatry using the Scale for Assessment of Positive Symptoms (SAPS) (Erkoc et al., 1991a), the Scale for Assessment of Negative Symptoms (SANS) (Erkoc et al., 1991b) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Depressive symptoms had been assessed using the Calgary Depression Scale for schizophrenia (Aydemir et al., 2000). All subjects were screened for any major health problems. None of the subjects was a regular drinker, or had been taking any psychotropic, medical, herbal or illicit drugs that will affect the parameters of the study. Exclusion criteria were medical illnesses including endocrine, metabolic or autoimmune disorders and history of injection of depot antipsychotics in the previous 6 months. Laboratory examinations, including complete blood count, serum electrolyte assays, liver function tests, thyroid function tests and urine analyses were performed to all subjects.

In order to provide a convenient sample, 35 control subjects who were matched according to age, gender and smoking status were recruited among the hospital–university staff. The control group consisted of 18 women and 17 men (mean age±S.D.: 33.5±9.2 years, range: 19–54). They were assessed by a semi-structured psychiatric interview and the same laboratory test protocol was applied to the control subjects as it was applied to the patient group. The control subjects were free of any medication for at least 3 weeks prior to blood sampling. Exclusion criteria for the control group were: having a physical or psychiatric disorder as judged from their clinical and laboratory examinations. None of the control subjects were drinkers, had ever taken psychotropic drugs. They had no family history of psychiatric disorder.

The patients were treated with various antipsychotic drugs; 22 with second generation antipsychotics (7 with risperidone [mean chlorpromazine equivalents (CPE): 486±107 mg/day], 5 with olanzapine [CPE: 640±219 mg/day], 5 with clozapine [CPE: 460±134 mg/day], 3 with quetiapine [800±173 mg/day] and 2 with amisulpride [350±70 mg/day]) 11 with classic antipsychotics (haloperidol, CPE: 167±0 mg/day) and 7 with long-acting antipsychotics (long-acting risperidone, CPE: 414±107 mg/day) in standard doses. After 6 weeks of treatment, blood samples from the 36 of the patients, could be obtained.

In the present study, the patients were categorized according to i) the presence of negative symptoms or positive