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Reduced plasma total antioxidant status in first-episode drug-naive patients with schizophrenia

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ABSTRACT

Excessive free radical production leading to oxidative stress may be involved in the pathophysiology of schizophrenia. Determination of total antioxidant status (TAS) provides an index of the sum of activities of all antioxidants. However, there have been few systematic studies to examine the relationship between TAS levels and psychopathology in first-episode and drug-naive patients with schizophrenia.

TAS levels were determined in the plasma of 60 never-medicated first-episode patients with schizophrenia and 68 healthy control subjects. The schizophrenia symptomatology and the depressive symptoms were assessed by the positive and negative syndrome scale (PANSS) and the Hamilton rating scale for depression (HAMD). The results showed that TAS levels were significantly lower in first-episode patients with schizophrenia than in healthy control subjects (159.8 ± 45.8 U/ml *vs* 211.4 ± 46.8 U/ml, $F = 39.5$, $df = 1, 126$, $p < 0.001$). A trend toward significant inverse correlation between TAS levels and PANSS negative subscore was observed ($r = 0.25$, $df = 60$, $p = 0.06$). Our results suggest that oxidative stress occurs in an early course of schizophrenia and may have an important role in pathogenesis and perhaps, negative symptomatology of schizophrenia.

1. Introduction

Under normal physiological conditions, free-radical-induced oxidative stress is combated by a complex antioxidant defense system (Lohr, 1991; Lohr and Browning, 1995; Bitanihirwe and Woo, 2011; Yao and Reddy, 2011). A major contribution to the total antioxidant capacity comes from antioxidant molecules in plasma. There are several antioxidant molecules in plasma, such as albumin, uric acid and ascorbic acid which account for >85% of the total antioxidant capacity in human plasma (Yao et al., 1998a), as well as other antioxidants in blood, e.g., bilirubin, a-tocopherol and b-carotene (Yao et al., 2000; Reddy et al., 2003). Although measuring levels of specific antioxidant molecules can yield valuable information, determination of total antioxidant status (TAS) provides an index of the sum of activities of all antioxidants (Yao et al., 1998a).

Excessive free radical production leading to increased oxidative stress may be involved in the pathophysiology of patients with schizophrenia (Lohr and Browning, 1995; Ng et al., 2008; Bitanihirwe and Woo, 2011; Yao and Reddy, 2011). For example, abnormal activities of critical anti-oxidant enzymes (Yao et al., 1998b; Zhang et al., 2003a, b), reduced levels of anti-oxidants (Yao et al., 1998a; Reddy et al., 2003; Gama et al., 2006; Ustundag et al., 2006; Pazvantoglu et al., 2009; Raffa et al., 2009; Virit et al., 2009; Chittiprol et al., 2010), and increased levels of lipid peroxidation in plasma, red blood cells, and cerebrospinal fluid (McCreadie et al., 1995; Mahadik et al., 1998; Herken et al., 2001; Akyol et al., 2002; Khan et al., 2002; Dietrich-Muszalska and Kontek, 2010; Padurariu et al., 2010) were observed in patients with schizophrenia. Yet, there is a discrepancy in the study results regarding antioxidant enzymes and lipid peroxidation products in schizophrenia.

However, studies to date have generally been exploratory. Further elucidation of the role of free radicals and antioxidants in schizophrenia and its treatment will require systematic investigation. The study of first-episode psychosis is particularly advantageous in understanding the neurobiology of schizophrenia in part because of the opportunity to minimize the potential impact of confounds, such as illness duration, medication effects, and the psychiatric and medical comorbidities that are associated with chronicity of illness (Buckley

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CNS, central nervous system; CSF, central spinal fluid; FEP, first-episode psychosis; FRAP, ferric reducing antioxidant potential; HAMD, Hamilton rating scale for depression; LSD, least significant difference; PANSS, positive and negative syndrome scale; SOD, superoxide dismutase; SCID, Structured Clinical Interview for DSM-IV; TAS, total antioxidant status.

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and Evans, 2006). Only a few studies have reported the oxidative stress in first-episode patients with schizophrenia (Reddy et al., 2003; Chittiprol et al., 2010). However, these studies featured small sample sizes. The purposes of the study therefore were to investigate: (1) whether plasma TAS was altered in first-episode and drug naive schizophrenic patients (FEDNS); (2) whether there was a correlation between the altered TAS and psychopathological parameters of patients.

2. Methods

2.1. Subjects

Study participants were recruited in to Beijing Huilongguan hospital, a Beijing-city owned psychiatric hospital, which provides all psychiatric inpatient care for a catchment area with approximately 20 million inhabitants. The study included 60 subsequently hospitalized patients (male, 34 and female, 26) who met the following criteria: (1) a DSM-IV diagnosis of first episode schizophrenia by two independent experienced psychiatrists on the basis of the Structured Clinical Interview for DSM-IV (SCID); and (2) drug-naive status in terms of using medications. Each subject filled out a detailed questionnaire that recorded general information, sociodemographic characteristics, and medical and psychological conditions. Additional information was collected from available medical records and collateral data (from family and/or treating clinician). Medical records potentially relevant for diagnostic purposes or to identify possible earlier administration of psychotropic medication were reviewed. Patients who previously had taken any antipsychotic, antidepressant or mood stabilizing drug were excluded from participation in the study. The identified patients were assessed and followed-up for 3 months as inpatients, and diagnosed with first-episode patients with schizophrenia only if both evaluations showed the same. The same raters rated individual patients on second occasions. Their clinical subtypes were: paranoid, 31 (51.7%), undifferentiated, 22 (36.7%); disorganized 6 (10.0%); others 1 (1.7%). The patients had a mean age of 24.5 ± 5.5 years (range: 16–45 year), a mean duration of illness of 22.1 ± 18.2 months and a mean education of 11.9 ± 2.9 years.

Sixty-eight healthy volunteers (male, 46 and female, 22) were recruited by advertisements at the local community. The controls had mean age 24.6 ± 5.6 years and a mean education of 12.2 ± 3.6 years. They were matched for gender, age and education with the above first-episode schizophrenic patients (Tables 1). Current mental status and personal or family history of any mental disorder were assessed by unstructured interviews. None of them presented a personal or family history of psychiatric disorder.

All subjects were Han Chinese from the Beijing area. They were in good physical health, and any subjects with medical illnesses or drug and alcohol abuse/dependence were excluded. The Institutional Review Board for the Beijing Huilongguan hospital approved the research protocol, and all subjects provided written informed consent.

2.2. Psychopathological assessment in patients

The positive and negative syndrome scale (PANSS) and the Hamilton rating scale for depression (HAMD) were measured by two psychiatrists who had simultaneously attended a training session in the use of the PANSS and HAMD before the start of the study. After training, a correlation coefficient greater than 0.8 was maintained for both the PANSS and the HAMD total scores by repeated assessment. Mean scores on the PANSS were: positive subscore, 25.7 ± 6.4; negative subscale, 18.4 ± 7.4; general psychopathology subscale, 39.8 ± 11.8 and total PANSS score, 83.9 ± 19.2. The mean total score of the HAMD was 13.6 ± 9.2.

Table 1
Demographics of first-episode patients and normal control subjects.

	Schizophrenia (n = 60)	Control subjects (n = 68)
Sex (M/F)	34/26	46/22
Age (years)	24.5 ± 5.5	24.6 ± 5.6
Education	11.9 ± 2.9	12.2 ± 3.6
BMI (kg/m^2)	22.6 ± 3.9	23.0 ± 4.1
Smokers	20 (33.3%)	24 (35.2%)
Duration of illness (months)	22.1 ± 18.2	NA
Age of onset (years)	23.5 ± 6.6	NA

Note: BMI = body mass index; NA = not applicable.

2.3. Plasma TAS measurements

The TAS of fasting plasma was measured as ferric reducing antioxidant potential (FRAP) by using a commercially available kit in all subject samples. In this assay, antioxidants are evaluated as reductants of Fe^{3+} to Fe^{2+}, which is chelated by TPTZ to form a Fe^{2+}–TPTZ complex absorbing at 593 nm (Benzie and Strain, 1996). Briefly, 10 μl plasma samples diluted 1:4 in water were mixed in a 96-well plate with 300 μl of a reagent solution containing 1.7 mM $FeCl_3$ and 0.8 mM TPTZ in 300 mM sodium acetate, pH 3.6. The samples were incubated for 15 min at 37 °C, and the absorbance at 593 nm was recorded using the Multiskan microplate reader (FlowLabs, McLean, VA, USA). Activity was expressed as Units per milliliter plasma (U/ml).

2.4. Data analysis

Since the TAS variables were normally distributed in patients and normal controls (Kolmogorov–Smirnov one sample test; both $p > 0.05$), the principal outcome analysis consisted of one-way analysis of variance (ANOVA). Post hoc comparisons were made using the Fisher's least significant difference (LSD) procedure. Where there was a significance in ANOVA, the effect of sex, age, education, smoking, and body mass index (BMI) was tested by adding these variables to the analysis model as covariates (Table 2). Relationships between variables have been assessed with Pearson's product moment correlation coefficients. Bonferroni corrections were applied to each test to adjust for multiple testing.

3. Results

Patients and control groups were matched with respect to age, gender, education, smoking, and BMI. There were no significant relationships between TAS levels and sex ($r = -0.09$, $n = 60$, $p = 0.52$ for patients; $r = 0.03$, $n = 68$, $p = 0.82$ for controls), age ($r = -0.15$, $n = 60$, $p = 0.19$ for patients; $r = -0.11$, $n = 68$, $p = 0.22$ for controls), education ($r = 0.05$, $n = 60$, $p = 0.69$ for patients; $r = 0.03$, $n = 68$, $p = 0.90$ for controls), BMI ($r = 0.24$, $n = 60$, $p = 0.07$ for patients; $r = -0.09$, $n = 68$, $p = 0.56$ for controls), and smoking ($r = 0.13$, $n = 60$, $p = 0.25$ for patients; $r = 0.18$, $n = 68$, $p = 0.19$ for controls). Age of onset of psychosis ($r = 0.10$, $p = 0.38$), duration of illness ($r = -0.11$, $p = 0.36$), age of hospitalization ($r = 0.11$, $p = 0.38$), and family history of psychosis ($r = -0.11$, $p = 0.31$) did not significantly correlate with TAS levels in the patient group.

Table 2
The TAS levels (U/ml) in schizophrenia and normal controls categorized by gender, smoking and BMI.

Clinical parameter		Schizophrenia	Controls
Sex	Male	163.3 ± 48.7	210.7 ± 48.7
	Female	155.4 ± 42.1	213.8 ± 41.4
Smoking	Smokers	164.5 ± 49.9	213.1 ± 46.6
	Non-smoker	153.9 ± 43.7	210.9 ± 54.9
BMI	<24 kg/m^2	172.5 ± 51.7	212.3 ± 52.7
	24–28 kg/m^2	165.7 ± 53.2	206.3 ± 53.5
	>28 kg/m^2	144.7 ± 37.8	204.9 ± 49.7

Note: There was no any significant difference in TAS levels categorized by gender, smoking and BMI either for the whole group or when the normal controls and patients were examined separately (all $p > 0.1$), although a trend toward a significant difference was noted in the BMI subgroups in schizophrenia ($F = 3.22$, $df = 2, 58$, $p = 0.07$).