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Imbalanced free radicals and antioxidant defense systems in schizophrenia: A comparative study*

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Abstract: Objective: To examine changes of blood oxidative-antiovidative level in schizophrenic patients and its relationship with clinical symptoms. Methods: Forty-six Chinese patients met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria for schizophrenia and fifty age- and sex-matched healthy controls were enrolled in the present study. Baseline psychiatric symptom severity was assessed with brief psychiatric rating scale, positive and negative syndrome scale on the blood draw day. Fresh blood samples were collected to measure levels of nitric oxide and lipid peroxide in plasma as well as activities of superoxide dismutase, catalase and glutathione peroxidase in red blood cells by spectrophotometric assays simultaneously. Results: Comparison of the biochemical parameters indicated that the level of nitric oxide and lipid peroxide increased in patient group, which represented a positive correlation with positive scale scores; while the activities of three critical enzymes decreased and showed a negative linear correlation. Conclusion: This study showed that there are dysregulation of free radical metabolism and poor activities of the antioxidant defense systems in schizophrenic patients. Excess free radicals formation may play a critical role in the etiology of schizophrenia. Using antioxidants might be an effective therapeutic approach to partially alleviate or prevent the symptoms of schizophrenia.

Key words: Schizophrenia, Nitric oxide (NO), Lipid peroxide (LPO), Glutathione peroxidase (GSH-Px), Catalase (CAT), Superoxide dismutase (SOD), Symptom

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder; its etiology still remains elusive. In the last few decades, dopamine hyperactivity hypothesis predominates in the research field all the time. Recently more and more converging evidence indicates that oxidative mechanisms may play a role in schizophrenia (Akyol *et al*., 2004; Lohr and Browning, 1995; Yao *et al*., 2001). Free radicals, primarily plasma nitric oxide (NO) was found to be higher (Taneli *et al*., 2004; Zoroğlu *et al*., 2002) or unchanged (Suzuki *et al*., 2003) in whole chronic patients but lower in deficit patients (Suzuki *et al*., 2003). And it was also reported less in the cerebrospinal fluid (Ramirez *et al*., 2004) and more in the caudate region of postmortem brain (Yao *et al*., 2004) from patients with schizophrenia. Animal researches showed that nitric oxide synthase inhibitor can resist this reaction (Bujas-Bobanovic *et al*., 2000; Wiley, 1998). Excess NO production further leads to changes of neuron structure and function involving neuronal membrane damage (Yao *et al*., 2000a) and increased indices of lipid peroxidation (Herken *et al*., 2001a). Antioxidant defense status changes accordingly (Herken *et al*., 2001a; Yao *et al*., 1998a). Superoxide dismutase (SOD), a key enzyme involved in the detoxification of superoxide radicals, has been consistently found increased (Vaiva *et al*., 1994; Yao *et al*., 1998b; Zhang *et al*., 2003a) in drug-free patients or those with TD (tardive dyskinesia) (Yao *et al*., 1998b; Zhang *et al*., 2003a), unchanged (Herken *et al*., 2001a) or decreased (Zhang *et al*., 2006) in chronic schizophrenic patients. Another enzyme named glutathione peroxidase (GSH-Px) activity was reported increased in drug-free patients

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(Yao *et al*., 1998b) while unchanged (Yao *et al*., 1999) or decreased (Zhang *et al*., 2006) in chronic patients. Other antioxidant enzyme activity such as catalase (CAT) increased (Herken *et al*., 2001a) in different form of schizophrenia. And plasma proteins including albumin, uric acid and bilirubin in blood are reported lower in haloperidol-managed (Yao *et al*., 2000b) and first episode schizophrenic patients (Reddy *et al*., 2003). Furthermore, some indices are related to severity of psychosis (Vaiva *et al*., 1994; Yao *et al*., 1999; Zhang *et al*., 2003a) or age (Yao *et al*., 2000b). Some studies (Taneli *et al*., 2004; Yao *et al*., 1998a; 1998b; 1999; 2000b; Zhang *et al*., 2006) indicated that antipsychotic drugs have no significant regulatory action on the antioxidative defense system. However, more studies revealed that antioxidant enzyme activities are associated with the treatment of schizophrenic patients with different neuroleptics (Parikh *et al*., 2003; Pillai *et al*., 2006; Reddy *et al*., 2003; Vaiva *et al*., 1994; Yao *et al*., 1998b; Zhang *et al*., 2001a; 2001b; 2003b). While these researches mainly focused on a few critical antioxidant enzymes and chronic, drug-medicated schizophrenia, the evidence is not consistent and sufficient. To further make up for previous limitations and explore whether there is an imbalance in oxidant and antioxidant status in schizophrenia, we systematically tested more blood indices in Chinese schizophrenic patients and analyzed the relationship between clinical symptoms and the above values in the patients by linear regression. Proceeding on existing knowledge and former evidences, we hypothesized that the level of NO and lipid peroxide (LPO) in patients are higher than that in controls, inversely the antioxidant level such as activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) will show lower. The total antioxidant capacity decreased in patients. These findings may lead to attempt new therapeutic approaches using appropriate antioxidants, which might partially alleviate or prevent the symptoms of schizophrenia.

MATERIALS AND METHODS

Subjects

Forty-six Chinese schizophrenic patients were consecutively recruited from the outpatients or inpatients of the Department of Psychiatry, the Second Affiliated Hospital, School of Medicine, Zhejiang University, China. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 1994) for schizophrenia. It includes 22 males and 24 females, the average age was (29.7±12.0) years (range, 15~56 years) and duration of illness was range from 1 month to 2.5 years. None of the patients had significant other psychiatric or somatic comorbidity. Other clinical characteristics of the patients are shown in Table 1. At the start of this study, all patients had to be medication-free for at least 2 weeks and not must have received any other kind of therapy. Fifty Chinese normal control subjects with no individual and familial history of mental illness were recruited to participate in this study. They included 25 males and 25 females. Their ages ranged from 15 to 60 years with mean age (30.2±12.8) years. Both patients and controls were of Chinese Han ethnic origin and recruited during the same period from Zhejiang Province. Matching between the patients and controls was done according to sex and age (χ^2=0.045, t=0.197, P>0.05). Study subjects were currently within normal ranges in their routine blood, urine and feces tests, electrocardiograph and radiographs; disorders associated with heart, brain, lung, liver, kidney and other pivotal organs were excluded.

Table 1 Clinical demographic features of schizophrenic patients enrolled (n=46)

Schizophrenic patients	Mean±*SD*
Age of onset of psychosis (years)	27.1±11.1
Age (years)	29.7±12.0
Gender (M/F)	22/24
Duration of illness (months)	8.0±6.5
Family history (positive/negative)	9/37
Positive and negative syndrome scale score	79.5±14.1

All subjects did not take any antioxidant supplements such as vitamin C, vitamin E, β-carotene, gingko biloba or other similar substances within one month prior to blood draw. Taking of smoke, caffeine and alcohol was also restricted. A standard diet was given to all inpatients. The project was carried out with the approval of the local ethical committee and was in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants prior to examination.

Procedure

Five milliliters of fasting venous blood was drawn from each subject at approximately 6:30 a.m. Samples were heparinized and centrifuged at 1500×g at 4 °C for 5 min, and the separate plasma and erythrocytes were then kept at 4 °C in a thermostat immediately. On the same day, baseline psychiatric symptom severity was assessed with brief psychiatric rating scale (BPRS) (Overal and Gorhan, 1962), positive and negative syndrome scale (PANSS) and sub-scales (Kay *et al*., 1987) by researcher who was specially trained and blind to the laboratory assays.

Through special displaying, NO and LPO in plasma as well as activities of SOD, CAT and GSH-Px in red blood cells were detected by spectrophotometric assays. Since NO is a very labile molecule, its direct measurement in the biological samples is very difficult. In solution, NO reacts with molecular oxygen and accumulates in the plasma as nitrite and nitrate ions. Therefore, plasma nitrite concentration was accepted as an indicator of NO. The major chemical reagents including SOD, CAT, α-naphthylamide, 1,2,3-trihydroxybenzene, 1,1,3,3-tetraethoxypropane and 2-thiobarbituric acid were all purchased from Sigma Chemical Company (USA), and the other analytical-grade reagents were produced in China. UV-754 spectrophotometer and 721 spectrophotometer were used to examine each parameter under their excited wavelengths respectively. A detailed description of the assays is available elsewhere (Herken *et al*., 2001b; Zhou *et al*., 2000). All the operations accord with the guidelines of the apparatus; and samples were measured by a technician who was unaware of the diagnostic status of the subjects.

Statistical analysis

The above mentioned data were statistically analyzed by means of SPSS 11.0 Windows Statistical software on a Dell Personal Computer. Test for normality was accomplished by the normality plots and Kolmogorov-Smirnov test. All data showed normal distributions. Student's *t*-test was used for group comparison. And Pearson's correlation coefficients were used to determine whether the level of biochemical parameters relates to PANSS and sub-scales of the patients. All analyses were two-tailed and used a P of 0.05 or less to determine significance. Data were expressed as means±*SD*.

RESULTS

Table 2 summarizes all analyzed biochemical parameters. Among them the average levels of NO and LPO in patient group were higher than that of control group. Incontrast, the mean levels of erythrocyte activities of SOD, CAT and GSH-Px were lower in patient group. These differences between the two groups reached statistically significance (P<0.001). No effects of age and gender were noted either for the total group or for the patient and control subgroups examined separately.

Pearson's correlations analyses between the parameters and clinical symptoms indicated that NO and LPO had positive correlation with positive scale score (PSS) significantly, SOD, CAT and GSH-Px were inversely correlated with PSS (Table 3). In this study, no correlations were observed between the level of all the tested biochemical parameters and

Table 2 Comparison of various determinations between patients and controls

Group	NO (nmol/L)	LPO (μmol/L)	SOD (U/g Hb)	CAT (k/g Hb)	GSH-Px (U/g Hb)
Patients (n=46)	467.6±8.8*	12.3±1.9*	20.9±4.0*	245.2±8.6*	24.8±3.0*
Controls (n=50)	327.7±86.4	10.1±1.6	26.0±7.6	321.2±37.7	31.8±3.8

*P<0.001, compared with controls; Hb: Hemoglobin

Table 3 Pearson's correlation between positive psychiatric symptoms and the values determined in the patients (n=46)

	NO	LPO	SOD	CAT	GSH-Px
r	0.460	0.458	–0.304	–0.411	–0.442
P	0.002	0.002	0.043	0.005	0.002

PANSS total score, negative scale score or BPRS. No significant relationships were found between onset age of psychosis or duration of illness and these indices.

DISCUSSION

This study investigated both oxidant and antioxidant systems in the same blood samples from schizophrenic patients. From the results obtained, we can conclude that there was serious deregulation of oxidative and antioxidative metabolism system during schizophrenia and increased oxidative stress and decreased enzymatic antioxidants, both of which may be relevant to the pathophysiology of schizophrenia. Obviously, the level of NO increases in patients and alters with alleviating of psychiatric positive symptoms as proposed; which is quite consistent with the work of Herken *et al*.(2001b). It seemed that NO may play a critical role in schizophrenia. Previous studies (Das *et al*., 1995; Elkashef *et al*., 2002; Montague *et al*., 1994; Seol *et al*., 2004; Volterra *et al*., 1994) suggested that NO is functionally linked to both dopaminergic and glutamatergic systems. Glutamate-mediated N-methyl-D-aspartate (NMDA) receptor activation drives a calcium-induced L-arginine-nitric oxide pathway; NO produced in the following NMDA receptor further stimulates dopamine release. At the same time, excess NO generated by increased glutamate transmission can further inhibit the glutamate uptake, thereby contributing to further increase in glutamate activity and producing neurotoxic effects (Volterra *et al*., 1994). NO, as a neurotransmitter, diffuses intracellularly and combines with guanylate cyclase which precipitate during transferring GTP into cGMP. Prolonged duration of ion channel results in increased calcium mobilization, and neuron necrosis occurs due to calcium overload. Moreover, NO, as a free radical, also damages mitochondria, lipids, proteins and DNA. Dopamine antagonist haloperidol can markedly inhibit nitric oxide production from RAW 264.7 cells (Seol *et al*., 2004). Some nitric oxide synthase inhibitor studies on phencyclidine-induced effects support this explanation (Bujas-Bobanovic *et al*., 2000; Wiley, 1998). In addition, dopamine hyperactivity can also produce other free radicals through self-metabolism or monoamine oxidase (MAO) and catechol-O-methytransferase (COMT) metabolism.

Under physiological conditions, this free radical-mediated damage can be balanced by the antioxidant defense system, comprised of a series of enzymatic and non-enzymatic components i.e. SOD, CAT, GSH-Px as well as vitamin C, vitamin E, β-carotene. Produced free radicals induce metabolism enzymes activity to a certain degree, while excess free radicals such as superoxide ion and hydroxyl radicals will, in turn, injure enzymes and so that more free radicals are accumulated. High-density polyunsaturated fatty acid (PUFA) is quite sensitive to free radicals. Increased lipid peroxidation reaction occurs and produces more LPO that damages the neuron membranes (Herken *et al*., 2001a; Yao *et al*., 2000a); this may explain the increased LPO level in the patient group.

On the other hand, previous (Zhang *et al*., 2006) and present studies all revealed that the plasma total antioxidant status decreases in schizophrenia. Though the results are not completely identical, it mainly presents on three critical antioxidant enzymes SOD, CAT and GSH-Px; a possible explanation may be different subtype or drug effects. More important, this study revealed that the level change is negatively related to PSS. We can deduce that altered antioxidant participates in the pathogenesis basis of schizophrenia, especially positive psychiatric symptom. Generally, most antioxidative vitamins such as vitamin C, vitamin E, β-carotene, PUFA (polyunstarurated fatty acid) and Q-enzyme must be acquired from dietary sources because these substances cannot be self-synthesized in the human body. Based on these findings and theoretical grounds, new treatment strategies such as using antioxidants and nitric oxide synthase (NOS) inhibitors in treating schizophrenia may be an effective and safe additional approach. Nevertheless, high intake of sufficient vitamin E dietary supplementation is beneficial for scavenging free radicals, and can keep the dynamic balance between oxidation and antioxidation (Mahadik *et al*., 2001) and thus it may improve outcome and prognosis of schizophrenia. Studies developed by Zhang *et al*.(2001a; 2001b) indicated that ginkgo biloba adds haloperidol attribute to chronic or resistant schizophrenia. And supplementation of vitamin C with atypical antipsychotics can reduce oxidative stress and improve the outcome

of schizophrenia (Dakhale *et al*., 2005).

In conclusion, imbalanced oxidative and antioxidative systems may be involved in the pathogenesis basis of schizophrenia. The correlation between positive psychiatric symptom and the oxidative-antioxidative levels underline the clinical interest of our study. But these results need to be confirmed by further studies, which should also explore whether the response to antipsychotic treatment is associated with normalization of the oxidative and antioxidative levels in schizophrenic patients. If so, adequate supplements of antioxidants may be a preferable therapeutic approach to improve outcome and prognosis of schizophrenia. Of course, we got all the results only from peripheral blood in this study; further advanced technique should be adopted to make sure whether it mirrored the exact status in the brain. On the other hand, sub-group analysis according to age, symptom and duration of illness has not yet been applied; so evidence must be provided by larger cases study.

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