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Reduced status of plasma total antioxidant capacity in schizophrenia

Jeffrey K. Yao [a,b,*], Ravinder Reddy [b], Luke G. McElhinny [a], Daniel P. van Kammen [a,b]

[a] *VA Pittsburgh Healthcare System, 7180 Highland Drive, Pittsburgh, PA 15206, USA*

[b] *Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 3811 O'Hara St., Pittsburgh, PA 15213, USA*

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Abstract

To examine whether antioxidant capacity is reduced in patients with schizophrenia, we determined plasma total antioxidant status (TAS) by quenching the absorbance of the radical cation formed by the reaction of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) with a metmyoglobin and hydrogen peroxide. TAS serves as an index of net antioxidant activity derived from various antioxidants in plasma. Male schizophrenic patients were compared with age- and sex-matched healthy control subjects, using a within-subject, repeated measures, on–off–on haloperidol treatment design. Drug-free patients were free of all psychotropic medications for an average of 32 days. Plasma TAS was significantly lower in patients with schizophrenia than in normal controls. Plasma TAS in patients was significantly and inversely correlated with symptom severity during the drug-free condition. There were no significant differences between on and off haloperidol-treatment conditions. When patients returned to haloperidol treatment after relapse, the plasma TAS remained fairly constant and was not significantly different from the same individuals during haloperidol-stabilization or drug-free periods. These findings are indicative of an impaired antioxidant defense system, not attributable to neuroleptic treatment, and lend further support to the notion that oxidative stress may have a pathophysiological role in schizophrenia.

Keywords: Antioxidant defense system; Total antioxidant status; Haloperidol

1. Introduction

Under normal physiological conditions, free-radical-induced oxidative stress is combated by a complex antioxidant defense system. A major contribution to the total antioxidant capacity comes from antioxidant molecules in plasma. Plasma, however, is not a simple chemical system for combating oxidative stress. In addition to the preventive antioxidants of the iron-scavenging proteins, e.g., transferrin and ceruloplasmin, plasma also contains 'chain-breaking' antioxidants that trap free radicals directly. The relative contribution of each antioxidant in vivo depends not only on the efficacy but also its concentration in biological fluids. Albumin, uric acid and ascorbic acid

* Corresponding author. Present address: VA Pittsburgh Healthcare System, 7180 Highland Drive, Pittsburgh, PA 15206, USA. Tel: (412) 365-4465; Fax: (412) 365-5917.

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account for >85% of the total antioxidant capacity in human plasma (Miller et al., 1993). This predominance is due largely to their high concentrations relative to those of other antioxidants in blood, e.g., bilirubin, α-tocopherol and β-carotene. Although individual antioxidants play a specific role in the antioxidant defense system, the above antioxidant molecules may act cooperatively in vivo to provide synergistic protection against oxidative damage (Winkler, 1992; Miller et al., 1993). Measuring levels of specific antioxidant molecules can yield valuable information, and low levels of such antioxidants provide suggestive, but not definitive, evidence of oxidative stress. However, determination of total antioxidant capacity provides an index of the *sum* of activities of all antioxidants.

There is mounting evidence that free radicals play a role in schizophrenia, probably via membrane pathology (Reddy and Yao, 1996; Mahadik and Mukherjee, 1996). Free radicals are reactive chemical species generated during normal metabolic processes and, in excess, can damage lipids, proteins and DNA. Regions, such as the brain, which have high oxygen consumption, lipid content and transition metals are at particular risk of oxidative damage. Elaborate antioxidant defense systems exist to protect against oxidative stress. In schizophrenia there is evidence for dysregulation of free radical metabolism, as detected by abnormal activities of critical antioxidant enzymes (Abdalla et al., 1986; Reddy et al., 1991; Wang, 1992; Vaiva et al., 1994) and other indices of lipid peroxidation (Kovaleva et al., 1989; Prilipko, 1992; Phillips et al., 1993; Mahadik et al., 1995) in plasma, red blood cells and cerebrospinal fluid. 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 purpose of the present study was to assess whether plasma total antioxidant status is altered in schizophrenic patients, using a within-subject, repeated measures, on–off–on haloperidol treatment design. Furthermore, we have also assessed the effects of smoking, known to alter some indices of antioxidant status, by measuring cotinine levels.

2. Methods

2.1. Clinical design

The schizophrenic subjects ($n=45$) were recruited from the predominantly male veteran outpatient population of the Highland Drive VA Pittsburgh Healthcare System. Clinically stable patients who met both DSM-III-R criteria and Research Diagnostic Criteria (RDC) for schizophrenia were hospitalized after they had signed informed consent forms. Table 1 presents means, standard deviations and ranges of demographic variables in the schizophrenic patients. The diagnosis of schizophrenia was made using the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1989) and a DSM-III-R checklist. All patients adhered to a low-monoamine, alcohol-free and caffeine-restricted diet. All meals were given as a standard diet consisting of 100 g protein, 295 g carbohydrates and 95 g fat (unsaturated fatty acids to saturated fatty acids = 2/1), providing daily energy of 2400 kcal. Current smoking status was ascertained by interview.

Each patient was treated with antipsychotic drugs for ≥3 months before the blood draw. If patients were not already on haloperidol, their medication was converted to an equipotent dose (5–20 mg/day) of haloperidol for at least 3 months before the first blood drawing. To assure medication compliance, plasma haloperidol (HD) levels were measured by high performance liquid chromatography. No other medications were used during the last 2 weeks of haloperidol treatment.

After patients were stabilized on oral haloperidol, it was then replaced overnight by a placebo

Table 1
Demographic variables

Schizophrenic patients	Mean	SD	Range
Age (years)	39	7	25–49
Age of onset (years)	24	5	16–33
Illness duration (years)	16	7	3–27
Height (cm)	175	8	158–196
Weight (kg)	86	16	64–134
Haloperidol dose (mg/day)	10	4	4–20
Days drug-free	32	10	17–56

in identical looking capsules for a period of up to 3 months. The second and third blood samples were collected from patients who had been free of all psychotropic medications for a period ranging from 3 to 8 weeks. Patients meeting relapse criteria were restarted on haloperidol treatment. A final blood sample was collected from those patients who had returned to haloperidol treatment for 1 month. Of these 45 patients, 36 patients had completed both HD treatment and drug-free phases. All blood samples were taken in the morning after overnight fasting. In addition, smoking was prohibited after 11 p.m. before the next day blood draw.

Relapse criteria consisted of a mean increase of at least 3 points on the Bunney–Hamburg (BH) psychosis score (Bunney and Hamburg, 1963) for 3 days compared with the mean of the daily psychosis ratings of the last week on haloperidol treatment (van Kammen et al., 1989).

2.1.1. Behavioral ratings

Clinical staff, blind to the treatment condition, clinically rated patients weekly with the BH psychosis ratings of depression, mania and anxiety, the Brief Psychiatric Rating Scale (BPRS), and the Scale for the Assessment of Negative Symptoms (SANS). The rating-scale data and weight measurements were taken from the week of the blood draw.

2.1.2. Normal controls

Age-matched healthy males (35 ± 10 years, $n = 34$) were recruited as normal control subjects to participate in the study. They were screened for DSM-III-R Axis I and II diagnoses using the SADS-L and the Minnesota Multiphasic Personality Inventory. Pre-study evaluations included a complete medical history, physical examination and a urine and blood drug-screen for alcohol and drug use. All control subjects were on a low-monoamine, alcohol-free and caffeine-restricted diet for 2 weeks preceding the blood draw.

2.2. Biochemical assays

2.2.1. Total antioxidant status

A kit manufactured by Randox Laboratories (Cat. No. NX 2332) enables the total antioxidant status to be measured in human plasma or serum. The Randox kit utilizes ABTS® (2,2′-azino-di-[3-ethyl-benzthiazoline sulphonate]) which is converted to its cation form when incubated in the presence of a peroxidase (metamyoglobin) and H_2O_2. This cation has a fairly stable blue–green color which can be measured at 600 nm. Antioxidants present in the sample suppress this color formation in the proportion of their concentration. A Cobas Fara centrifugal analyzer (Roche Diagnostics Systems, Branchburg, NJ) is used for the assay. Exactly 4 μl of platelet-poor-plasma (PPP) or a standard of known concentration is incubated with 200 μl of a reagent containing metamyoglobin and ABTS® at 37°C for 15 s, during which two measurements are taken. Next, 40 μl of H_2O_2 is added and thoroughly mixed, starting the reaction. The reaction is followed for exactly 3 min. The reaction rate of the sample is compared to that of the standard and a blank to determine the concentration of total antioxidants present in the sample and is expressed as μmol/l or mmol/l of PPP.

2.2.2. Plasma cotinine level

Cotinine is the major metabolite of nicotine. The half-life of cotinine in blood is far longer than that of nicotine (Langone et al., 1973, 1975). Moreover, cotinine levels remain fairly constant in individuals with regular tobacco consumption. Thus, plasma cotinine levels provide us with a better marker than nicotine for smoking status (Langone et al., 1973; Hall et al., 1984; Jarvis et al., 1987). The DRI (Diagnostic Reagents, Inc., Sunnyvale, CA) enzyme immunoassay kit is applied to measure plasma cotinine level. The DRI immunoassay is based on the competition between a cotinine-labeled enzyme glucose-6-phosphate dehydrogenase (G-6-PDH) and the free cotinine in the sample for a fixed number of cotinine-specific antibody binding sites. In the absence of cotinine, the cotinine-labeled G-6-PDH is bound to the antibody and the enzyme activity is inhibited. The G-6-PDH activity is measured spectrophotometrically at 340 nm by converting NAD to NADH. The plasma sample is first centrifuged to remove any interfering debris. In a typical assay, 20 μl of sample is used. The

standard curve is obtained from the cotinine calibrators provided by the DRI kit. A normal plasma sample spiked with a known amount of cotinine standard is used as a control for each assay. A Cobas Fara centrifugal analyzer (Roche Diagnostics Systems, Branchburg, NJ) is used to measure the enzymatic reaction rate at 37°C.

2.3. Statistical analyses

Group means (±SD) were compared by one-way analysis of variance (ANOVA). Antipsychotic drug withdrawal, length of drug-free period, as well as neuroleptic treatment were evaluated in the same individuals by two-tailed paired *t*-tests. Pearson correlations and Spearman Rank correlations were used, whenever appropriate, to determine whether plasma total antioxidant status was correlated with clinical ratings or plasma cotinine levels.

3. Results

Schizophrenic patients, relative to healthy volunteers, had significantly lower plasma TAS ($p<0.02$, ANOVA) during both haloperidol-treated and drug-free treatment conditions (Table 2).

To test whether plasma TAS is affected by antipsychotic drug withdrawal, the length of the drug-free period, as well as haloperidol treatment, we first compared schizophrenic patients stabilized with haloperidol to the same individuals after haloperidol withdrawal. We also compared patients who were drug-free for less than 5 weeks to the same individuals after they had been drug-free for longer than 5 weeks. Finally, we compared drug-free patients to the same individuals following re-introduction to haloperidol treatment for 1 month. No significant differences were found among patients who had undergone the above different clinical phases (Table 3).

When drug-free patients were divided into relapsed and clinically stable groups, plasma TAS was not significantly different between these two subgroups of patients (Table 4).

To test whether plasma TAS is related to the severity of psychopathology, we compared plasma total antioxidant status of drug-free patients with the 3-day mean Bunney–Hamburg Psychosis Ratings (BHPR), Brief Psychiatric Rating Scales (BPRS), or the Scale for the Assessment of Negative Symptoms (SANS). Plasma total antioxidant status was inversely and significantly correlated with the BHPR ($r=-0.4146$, $p=0.0148$, $n=34$), total BPRS ($r=-0.4295$, $p=0.0112$, $n=34$), or the 5-item SANS ($r=-0.3887$, $p=0.0231$, $n=34$) scores (Fig. 1).

In the present study, all the subjects were between 25 and 49 years old. The mean age and SD of the schizophrenic patient group (39 ± 7 years) was not significantly different from that of healthy volunteers (35 ± 10 years). Moreover, there are no significant correlations between age and plasma TAS in either healthy volunteers or schizophrenic patients (Fig. 2).

We also examined whether plasma TAS was affected by storage time. Samples from normal

Table 2
Comparison of plasma total antioxidant status between schizophrenic patients and healthy volunteer subjects[a]

Subjects	*n*	TAS (μmol/l)	*p* (unpaired *t*-test)	
			HV vs S-HD	HV vs S-DF
Healthy volunteers	34	1128±145		
Schizophrenics				
S-HD	45	1056±110	0.020	
S-DF	36	1058±101		0.024

[a]One-way analysis of variance (ANOVA): $F=4.232$; df = 2,112; $p=0.017$.
HV, healthy volunteers; S-HD, haloperidol-treated schizophrenics; S-DF, drug-free schizophrenic patients; TAS, total antioxidant status.

Table 3
Effect of antipsychotic drug withdrawal, drug-free period and antipsychotic drug treatment on plasma total antioxidant status

Schizophrenic patients	*n*	TAS (μmol/l)	*p* (paired *t*-test)
1. Antipsychotic drug withdrawal			
HD treatment	34	1069±118	0.576
After HD withdrawal	34	1059±104	
2. Drug-free period			
<5 weeks	12	1104±110	0.634
>5 weeks	12	1119±77	
3. Antipsychotic drug effect			
Drug-free	14	1059±89	0.810
Return to HD treatment	14	1054±127	

HD, haloperidol; TAS, total antioxidant status.

Table 4
Comparison of plasma total antioxidant status between relapsed and clinically stable schizophrenic patients during drug-free condition

Drug-free schizophrenic patients	*n*	TAS (μmol/l)	*p* (unpaired *t*-test)
Relapsed	14	1066±180	0.694
Non-relapsed	18	1088±94	

subjects that were stored at −70°C for various time periods up to 7 years, and had never been thawed previously, showed no significant trends in the levels of plasma TAS (Fig. 3).

To determine whether plasma TAS is affected by tobacco consumption, plasma cotinine levels were measured in both schizophrenic patients and healthy volunteers. Not surprisingly, the number of smokers in the patient group was much higher than that of healthy volunteers (Fig. 4). All, except one, healthy volunteers had plasma cotinine levels below 200 ng/ml. By contrast, more than 50% of the schizophrenic patients exhibited plasma cotinine levels greater than 200 ng/ml. However, the mean plasma TAS of patients with plasma cotinine levels >200 ng/ml is not significantly different from those with plasma cotinine levels <200 ng/ml. Moreover, there are no significant correlations between plasma TAS and cotinine levels in either HD-treated ($r=0.057$, $n=45$, $p=0.697$) or drug-free ($r=0.008$, $n=36$, $p=0.964$) schizophrenic patients.

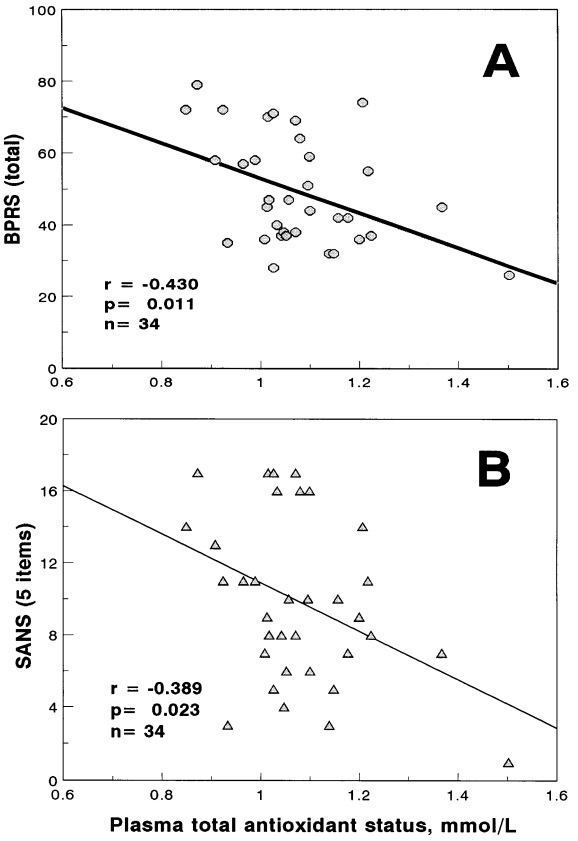

Fig. 1. Relationships of plasma total antioxidant status to Brief Psychiatric Rating Scales (A) and the Scales for the Assessment of Negative Symptoms (B) in drug-free schizophrenic patients. BPRS, Brief Psychiatric Rating Scales; SANS, Scales for the Assessment of Negative Symptoms.

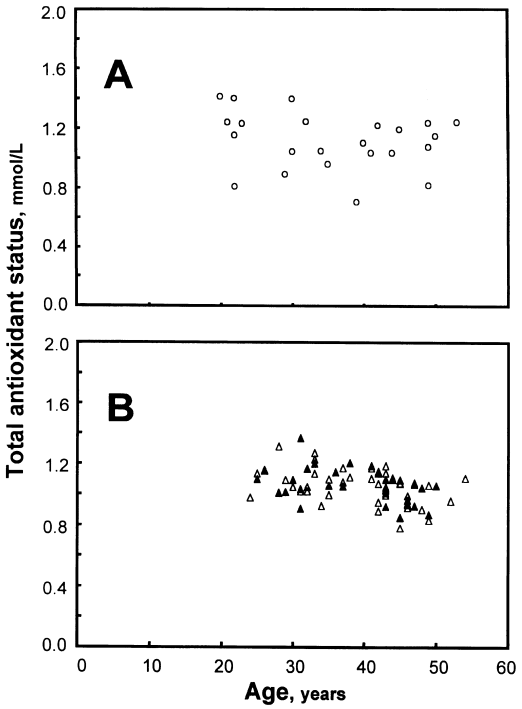

Fig. 2. Effect of age on plasma total antioxidant status from healthy volunteers (A) and schizophrenic patients (B). ○, healthy volunteers; △, haloperidol-treated patients; ▲, drug-free patients.

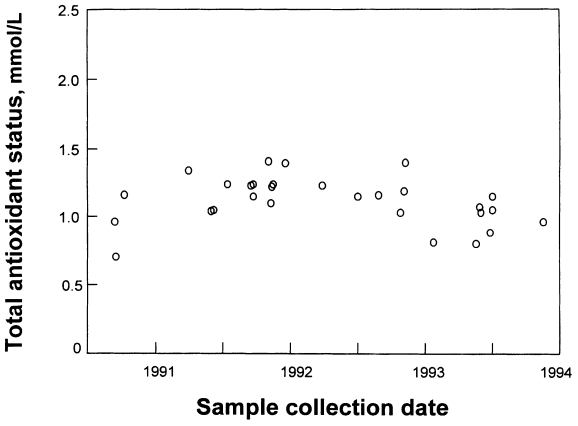

Fig. 3. Trending profile of plasma total antioxidant status in stored samples from healthy volunteers.

4. Discussion

The present data demonstrate that plasma total antioxidant capacity was found to be significantly lower in schizophrenic patients than in normal controls. Such a decrease was not related to age, antipsychotic drug treatment (e.g., haloperidol), length of drug-free period, or relapse status.

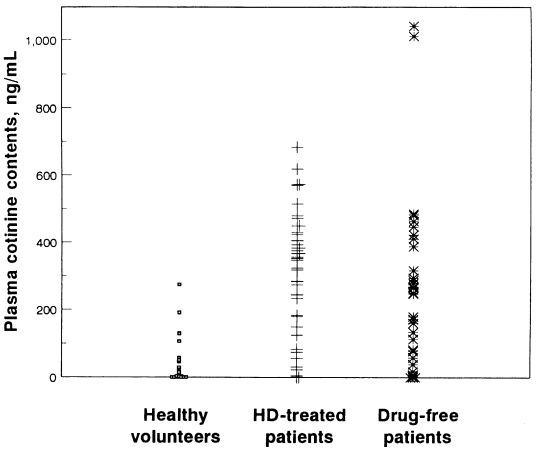

Fig. 4. Plasma cotinine levels from healthy volunteers, and schizophrenic patients before and after haloperidol (HD) withdrawal.

Further, the findings of significant inverse correlation of TAS to various behavior rating scores (3-day mean BHPR, total BPRS and 5-item SANS) suggest that the alterations in antioxidant functions may be a consequence of changed symptom severity rather than direct effects of antipsychotic drug treatment. Thus, the reduced status of plasma total antioxidant capacity may have pathophysiological significance in schizophrenia. This is consistent with previous findings where alterations in various indices of the antioxidant defense system have been associated with tardive dyskinesia, negative symptoms, neurological signs, poor premorbid function and CT scan abnormalities (reviewed in Reddy and Yao, 1996).

Diet, food and alcohol are the major factors affecting both the antioxidant system and the production of free radicals and reactive oxygen-containing species (Papas, 1996). Plasma antioxidants of dietary origin (e.g., tocopherols, ascorbic acid, carotenoids, etc) are influenced directly by nutritional supplements as well as by food and alcohol consumption (Becker et al., 1994; Parfitt et al., 1994; Lecomte et al., 1994). In the present

study, all the patients were hospitalized and maintained on a control balanced diet without alcohol consumption. Therefore, it is unlikely that decreased total antioxidant status in plasma of schizophrenic patients resulted from a dietary deficiency or alcohol consumption as compared to their healthy volunteer counterparts.

In addition, lower levels of plasma antioxidants of dietary origin were also found in subjects who smoke cigarettes (Pryor and Stone, 1992; Chow, 1992; Stegmayr et al., 1993). One of the major compounds in the gas phase of tobacco smoke is nitric oxide. It has been suggested that nitric oxide reacts with smoke olefins to form carbon-centered radicals (Pryor and Stone, 1992). On the other hand, the tar phase consists of a semiquinone radical that promotes hydrogen peroxide formation. Furthermore, tobacco smoke may increase free-radical formation by activating neutrophils. In the present study, higher levels of plasma cotinine (major nicotine metabolite) did not account for the lower levels of plasma TAS seen in schizophrenic patients. It is not clear, however, whether plasma TAS is affected by chronic tobacco consumption. Future investigations will need to determine whether plasma TAS can be improved after cessation of smoking.

The principle used to measure plasma total antioxidant status in the present study (Randox kit) is essentially the same as that described by Miller et al. (1993). This procedure is based primarily on the inhibition by the antioxidants of the absorbance of the radical cation of $ABTS^{+}$, which has a relatively stable blue–green color at 600 nm. Recently, Schofield and Braganza (1996) have questioned the accuracy and suitability of the Randox kit for measuring total antioxidant capacity in plasma, since the kinetics of chromophore generation from three key plasma antioxidants (albumin, ascorbic acid and uric acid) vary markedly. They believe that all plasma antioxidants contributing to the total antioxidant capacity should act in an analogous manner. Therefore, the monitoring of individual antioxidants in physiological samples is more essential than determining plasma TAS. Lamont et al. (1997), however, argue that all antioxidants contribute to the total antioxidant capacity in an analogous manner is neither realistic nor necessary. These authors suggest that antioxidants do not have the same reaction kinetics in vivo and may interact with one another. It is thus more meaningful to measure the total antioxidant capacity since the antioxidant system consists of a number of elements that exert their actions in different ways (Halliwell and Gutteridge, 1990; Jacob, 1995). Nevertheless, we have also conducted studies to measure some key plasma antioxidants in the same patient groups. Preliminary findings also demonstrated that plasma levels of uric acid and albumin were significantly lower in schizophrenic patients than in normal controls (Yao et al., 1997, 1998).

If the findings reported here are replicated by other investigators, and the specific contributors (individual antioxidant) to decreased TAS are identified, then there exists the possibility of developing adjunctive treatment strategies that may attenuate illness severity. However, the pathophysiological implications of decreased TAS will ultimately require the demonstration that oxidative stress indeed occurs in the brain. Since TAS is a measure of capacity to scavenge free radicals, the consequences of decreased TAS in plasma may lead to an increased free radical-mediated cellular insult, such as lipid peroxidation, in the brain. Studies have been initiated in our laboratory to examine a variety of measures of oxidative stress in post-mortem brain tissue and cerebrospinal fluid.

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