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Regular Article

Total antioxidant response in patients with schizophrenia

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Abstract There is a large amount of convincing data demonstrating that reactive oxygen species (ROS) are involved in initiation and development of many different forms of neuropsychiatric disorders. The levels of oxidants and antioxidants in schizophrenia have been evaluated. However, measurements of total antioxidant response (TAR) were not evaluated up to now. Therefore, the objectives of this study are to investigate plasma TAR levels in schizophrenia subtypes. A total of 76 patients with schizophrenia and 25 healthy volunteers were included in the study. Positive and Negative Syndrome Scale (SANS and SAPS, respectively) were applied to patients. TAR values were determined in the plasma of normal healthy controls and patients with schizophrenia. Plasma TAR levels of each schizophrenia subtype were significantly lower than healthy controls ($P < 0.01$ for disorganized, residual and undifferentiated subtypes and $P < 0.01$ for paranoid subtype). When intragroup comparisons were performed, paranoid subtype had higher plasma TAR levels compared to other subtypes ($P < 0.01$). Accordingly, as a whole group, patients with schizophrenia had lower plasma TAR levels compared to controls. Plasma TAR levels were significantly and negatively correlated with SANS scores, and duration of illness was evaluated but not related to other parameters. Consequently, the present study further emphasizes the growing consideration that free radical damage may have an important etiopathogenetic role on the development of schizophrenia and suggests that decreased plasma total antioxidant levels may be related to the progression of illness.

Key words paranoid, residual, schizophrenia, total antioxidant response.

INTRODUCTION

Reactive oxygen species (ROS) are continuously produced by the body's metabolism and exert a physiological and pathologic process by many different ways, such as activation of phagocytes and the general immune system, lipid peroxidation, the electron transport system in mitochondria, ischemia and trauma.[1,2] Consequently, excess ROS can cause oxidative damage in vulnerable targets such as unsaturated fatty acids in membranes, thiol groups in proteins, and nucleic acid bases in deoxyribonucleic acid.[3,4] However, when oxidative stress occurs, all organisms enzymatic and non-enzymatic antioxidant systems serve to protect them against the harmful oxidative reactions due to endogenous ROS production.[5] Recently, there is growing evidence demonstrating that the free radical damage has an important role in the etiopathogenesis of various neuropsychiatric disorders.[6,7] There are some recent studies focused on role(s) of free radicals in the pathogenesis of neuropsychiatric disorders and numerous studies indicating that free radical-mediated neuronal dysfunction have roles in the pathophysiology of schizophrenia.[8,9] Many studies reported great evidences that ROS may play an important role in the pathogenesis of schizophrenia.[10–14] Yao *et al*. have previously demonstrated that individual antioxidants, albumin, bilirubin and uric acid, were significantly reduced in plasma of patients with chronic schizophrenia, during on and off haloperidol treatment conditions.[15] Yao *et al*. showed that superoxide dismutase (SOD) activity but not Glutathione peroxidase (GSH-Px) and catalase activities in schizophrenia during the

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drug-free period became significantly higher compared to normal controls. Another study reported increased plasma nitric oxide (NO) levels, decreased SOD activity and unchanged GSH-Px activity compared to the control group in schizophrenia.[16]

NO is known to be both a ROS and a neurotransmitter in the central nervous system (CNS) and peripheral nervous systems. Although NO is described as an atypical neurotransmitter in the nervous system, it seems more appropriate to place it in the second messenger.[17] NO is produced by the family of nitric oxide synthase (NOS) and is known to affect the neurodevelopmental process in the CNS.[18] Therefore, it should be very valuable to determine the interference of NO generation in schizophrenia. In recent years, there has been great interest in the role of NO in neuropsychiatric disorders including schizophrenia.[16,19–21] Consequently, under certain conditions, increases in oxidants, malondialdehyde, lipide peroxide and NO and decreases in antioxidants cannot be prevented and occurs with oxidative stress.

The levels of oxidants and some antioxidants in schizophrenia were evaluated. However, measurements of plasma total antioxidant response (TAR) were not evaluated up to now. Therefore, the objectives of this study were to investigate plasma TAR levels, which may include the effects of all enzymatic and nonenzymatic antioxidants, albumin, haptoglobin, uric acid, and vitamin E, together with others, in schizophrenia and subytypes.

METHODS AND MATERIALS

The sample consisted of 76 patients (36 females and 40 males) who applied to the Department of Pyschiatry, School of Medicine at Firat University, Elazig, Turkey, and were diagnosed with schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). A DSM-IV diagnosis of schizophrenia was established on the basis of independent clinical interviews by one senior psychiatrist. Patients with any kind of axis I psychiatric disorder were excluded. After the complete description of the study to the subjects, all subjects gave informed written consent which was in accordance with the Declaration of Helsinki and was approved by the local ethic committee. Control group consisted of 25 healthy subjects matched for age and gender (mean age, 34.12 ± 4.25 years; range, 20–42 years) according to exclusion criteria among the hospital staff who had no history of a psychiatric disorder. The severity of negative and positive symptoms of schizophrenia was evaluated by Positive and Negative Syndrome Scale (Positive Syndrome Scale; SANS).[22,23]

Physical and neurological examinations were performed for each of the patients and controls. Liver and kidney function tests were evaluated. Subjects who had normal results and without any exclusion criteria were admitted to the study. Exclusion criteria were as follows: alcohol and substance abuse or dependence; presence of severe organic condition such as Wilson's disease, Down syndrome, malnutrition, pregnancy, diabetes mellitus, chronic renal failure, cancers, liver cirrhosis and thyroid diseases, treatment with glucocorticoids, anticonvulsants, oral contraceptives, psychotropic drugs and any antioxidant agents such as vitamins (i.e. E and C vitamins), xantin oxidase inhibitors (allopurinol, folic acid), and non-steroidal anti-inflamatory drugs; presence of epilepsy and severe neurologic disorder such as Parkinson, Huntington, and Alzheimer diseases; presence of infectious disease; and excessive obesity. All patients and controls were free of all medications at least in the previous 2 weeks apart from those taking depot antipsychotics in whom the duration was 2 months. But no patient had already taken depot antipsychotic medication.

Blood samples

Venos blood samples from the left forearm vein were collected into heparinized tubes between 07.00 and 08.00 hours after overnight fasting. The blood samples were centrifuged at 3000 r.p.m. for 10 min at 4°C to remove plasma. The bufy coat on the eryhtrocyte sediment was separated carefully. Plasma samples were stored –80°C until analysis.

Measurement of total antioxidant status of plasma

The total antioxidant status of the plasma was measured using a novel automated colorimetric measurement method for the plasma TAR developed by Erel.[24] In this method, the hydroxyl radical, the most potent biological radical, is produced by the Fenton reaction, and reacts with the colorless substrate O-dianisidine to produce the dianisyl radical, which is bright yellowish-brown in color. Upon the addition of a plasma sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the plasma preventing color change and thereby providing an effective measure of the total antioxidant capacity of the plasma. The assay results are expressed as mmoL Trolox ed./L and the precision of this assay is excellent being lower than 3%.[24]

The obtained data were evaluated by SPSS 11.0 program (SPSS Inc., Chicago, IL, USA). The comparisons

between all groups were performed by one-way ANOVA and were performed post ANOVA test Tukey-B comparison for two groups. For correlation evaluations, Pearson's correlation (two-tailed) was used. The comparison of sociodemographic characteristics was performed by Student's *t*-test and χ^2 test (Fischer's exact test). The statistical significance was accepted as $P < 0.05$.

RESULTS

There were no significant differences in age and female/male ratio between the patients and controls, with a ratio of 36/40 versus 11/14 and with a mean age of 35.76 ± 8.34 years (range, 19–48) versus 34.12 ± 4.25 years (range, 20–42) in patient and control groups, respectively ($P > 0.05$). The sociodemographic characteristics of the patients and controls were not statistically different (Table 1; $P > 0.05$).

Plasma TAR levels of each schizophrenia subtype were significantly lower than healthy controls ($P < 0.01$ for disorganized, residual and undifferentiated subtypes and $P < 0.01$ for paranoid subtype). When intragroup comparisons were performed, paranoid subtype had higher plasma TAR level compared to other subtypes. Accordingly, as a whole group, patients with schizophrenia had lower plasma TAR levels compared to control group ($P < 0.001$). Plasma TAR levels of the groups are shown in Table 2 and Fig. 1.

When the patients and control group were divided into smokers and non-smokers, all schizophrenia subtypes exhibited statistically significant differences except the disorganized subtype, while the controls did not show any difference (Table 3). In addition, as a whole group, smokers with schizophrenia had significantly lower plasma TAR levels compared to non-smokers with schizophrenia ($P < 0.01$). In smoker patients with schizophrenia, there were no differences between those having 0–10 years of duration of illness compared to those having 10 years or more of duration of illness ($P > 0.05$; Table 4). Plasma TAR levels were significantly and negatively correlated with SANS scores ($r = -0.581$, $P < 0.05$), and duration of illness ($r = -0.643$; $P < 0.05$) but not related to other evaluated parameters.

Table 2. The level of plasma total antioxidant response of patients with schizophrenia and the control groups

	Total antioxidant response (mmoL/Trolox/L)
Control ($n = 25$)	1.91 ± 0.26[a,b,c]
Schizophrenia (TS; $n = 76$)	1.18 ± 0.37
DS ($n = 20$)	1.05 ± 0.24[d,e]
RS ($n = 16$)	0.81 ± 0.24[f,g]
PS ($n = 21$)	1.67 ± 0.00.13[h]
US ($n = 19$)	1.08 ± 0.25

[a] $P < 0.001$ C-TS, [b] $P < 0.001$ C-DS, C-RS, C-US; [c] $P < 0.01$ C-PS; [d] $P < 0.05$ DS-RS; [e] $P < 0.001$ DS-PS; [f] $P < 0.001$ RS-PS; [g] $P < 0.05$ RS-US; [h] $P < 0.001$ PS-US.

C, control; DS, disorganized schizophrenia; PS, paranoid schizophrenia; RS, residual schizophrenia; TS, total schizophrenia; US, undifferentiated schizophrenia.

Table 1. Sociodemographics of patients with schizophrenia and the control groups

		Schizophrenia (TS; $n = 76$)			
	Control ($n = 25$)	DS ($n = 20$)	RS ($n = 16$)	PS ($n = 21$)	US ($n = 19$)
Age (year)	34.12 ± 4.25	37.46 ± 8.19	34.57 ± 8.52	37.21 ± 7.16	34.87 ± 9.18
Gender (Female/Male)	11/14	6/14	11/5	14/7	5/14
Duration of illness (year)					
0–5 years		1	10	7	10
5–10 years		12	4	9	4
10–20 years		6	1	3	2
20 years and more		1	1	2	1
Attack number					
0–1		6	8	6	10
2 and above		14	8	15	9
Smoke use					
Smoker	13	15	9	9	9
Non-smoker	12	5	7	12	10

DS, disorganized schizophrenia; PS, paranoid schizophrenia; RS, residual schizophrenia; US, undifferentiated schizophrenia.

Table 3. The level of plasma total antioxidant response of smoker and non-smoker patients with schizophrenia and the control group

	Total antioxidant response (mmoL Trolox/L)		
	Smoker	Non-smoker	*P*
Control ($n = 25$)	1.91 ± 0.29 ($n = 13$)	1.92 ± 0.21 ($n = 12$)	>0.05
Schizophrenia (TS; $n = 76$)	1.06 ± 0.35 ($n = 42$)	1.34 ± 0.32 ($n = 34$)	<0.01
DS ($n = 20$)	1.05 ± 0.18 ($n = 15$)	1.06 ± 0.15 ($n = 5$)	>0.05
RS ($n = 16$)	0.62 ± 0.13 ($n = 9$)	1.04 ± 0.11 ($n = 7$)	<0.001
PS ($n = 21$)	1.61 ± 0.11 ($n = 9$)	1.72 ± 0.12 ($n = 12$)	<0.05
US ($n = 19$)	0.95 ± 0.15 ($n = 9$)	1.25 ± 0.19 ($n = 10$)	<0.01

DS, disorganized schizophrenia; PS, paranoid schizophrenia; RS, residual schizophrenia; TS, total schizophrenia; US, undifferentiated schizophrenia.

Table 4. The relation between duration of illness and plasma total antioxidant response level in patients with schizophrenia and the control group

	Total antioxidant response (mmoL Trolox/L)		
	Duration of illness (0–10 years)	Duration of illness (10 years and more)	*P*
Control ($n = 25$)	–	–	
Schizophrenia (TS; $n = 76$)	1.21 ± 0.27 ($n = 50$)	1.25 ± 0.33 ($n = 26$)	>0.05
DS ($n = 20$)	1.06 ± 0.15 ($n = 12$)	1.05 ± 0.18 ($n = 8$)	>0.05
RS ($n = 16$)	0.81 ± 0.21 ($n = 12$)	0.76 ± 0.22 ($n = 4$)	>0.05
PS ($n = 21$)	1.65 ± 0.11 ($n = 12$)	1.69 ± 0.14 ($n = 9$)	>0.05
US (n = 19)	1.11 ± 0.0.24 ($n = 14$)	1.12 ± 0.17 ($n = 5$)	>0.05

DS, disorganized schizophrenia; PS, paranoid schizophrenia; RS, residual schizophrenia; TS, total schizophrenia; US, undifferentiated schizophrenia.

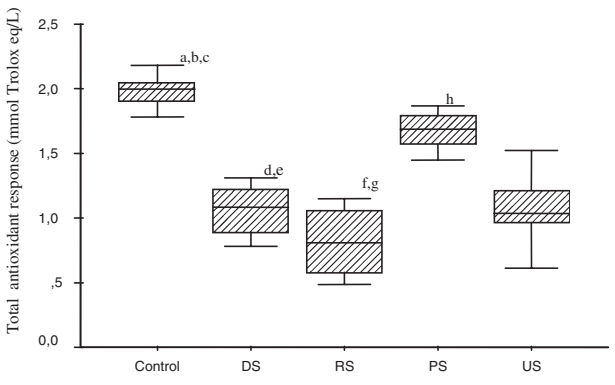

Figure 1. The level of plasma total antioxidant response in patients with schizophrenia and the control group. C, control; DS, disorganized schizophrenia; PS, paranoid schizophrenia; RS, residual schizophrenia; TS, total schizophrenia; US, undifferentiated schizophrenia. C, control; [a] $P < 0.001$ C-TS; [b] $P < 0.001$ C-DS, C-RS C-US; [c] $P < 0.01$ C-PS; [d] $P < 0.05$ DS-RS; [e] $P < 0.001$ DS-PS; [f] $P < 0.001$ RS-PS; [g] $P < 0.05$ RS-US; [h] $P < 0.001$ PS-US.

DISCUSSION

The present study demonstrates for the first time a significant decrease of plasma TAR in patients with schizophrenia in comparison to healthy controls. Therefore, first, the authors want to emphasize the important findings of this study: (i) Plasma TAR levels of each schizophrenia subtype were significantly lower than healthy controls ($P < 001$ for disorganized, residual and undifferentiated subtypes and $P < 0.01$ for paranoid subtype). When intragroup comparisons were performed, paranoid subtype had higher plasma TAR levels compared to other subtypes. Accordingly, as a whole group, patients with schizophrenia had lower plasma TAR levels compared to the control group; (ii) When the patients and controls were divided into smokers and non-smokers, all schizophrenia subtypes exhibited statistically significant differences except the disorganized subtype, while controls did not show any difference. In addition, as a whole group,

smokers with schizophrenia had significantly lower plasma TAR levels compared to non-smokers with schizophrenia; and (iii) Plasma TAR levels were significantly and negatively correlated with SANS scores and duration of illness.

The brain is particularly more vulnerable to the damaging effects of free radicals (FR), when compared with other organs of the body, because they have a high rate of oxidative metabolic activity (e.g. catecholamine degradation etc.), a low level of protective antioxidant enzymes, a high ratio of membrane surface area to cytoplasmic volume, a neuronal anatomical network vulnerable to disruption, and high concentrations of readily oxidizable membrane polyunsature fatty acide.[25] Probably, catecholamines including dopamine and norepinephrine are related to FR production. Likewise, trauma and ischemia of brain may lead to FR burden. Recently, there is growing evidence demonstrating that the FR damage has an important role in the etiopathogenesis of various neuropsychiatric disorders. The hypothesis that ROS play an important role in schizophrenia as well as neurodegenerative disorders remained speculative and there have been no detailed studies to test this hypothesis. There have been a lot of evidences that ROS may play an important role in the pathogenesis of schizophrenia.[11–13,26,27] The controversial data reported in the literature show variation for the activities of antioxidant enzymes. Red blood cell SOD activity was found to be increased,[28] unchanged,[12] or decreased[8] and catalase and GSH-Px activities were found to be increased,[12] or unchanged[15] in patients with schizophrenia. In contrast, clinical studies have indicated that antioxidant enzyme activities are associated with the treatment of patients with schizophrenia with neuroleptics[15,29,30] and so, the changes in the activities of the enzymes may possibly be due to the neuroleptic treatment. Haloperidol induces a six-fold increase in levels of ROS, which are generated from mitochondria, but not from the metabolism of catecholamines by monoamine oxidases.[31] The changes of the generation of ROS may affect the antioxidant enzyme activities. In a study reported by Buckman *et al.*, low peripheral GSH-Px activity was found to be associated with both cortical sulcal prominence on computed tomography and prominent negative symptoms.[32]

The present study shows a relative deficiency in antioxidants and subsequent oxidative stress during the acute phase of neuroleptic syndrome, resulting in a relative defect in antioxidant/oxidant balance. Plasma TAR includes the antioxidant effects of all the antioxidants in the plasma including albumin, haptoglobin, uric acid, and vitamin E, together with other, undefined substances. The total antioxidant plasma capacity is not a simple sum of the various antioxidant substances, but includes a dynamic equilibrium that is influenced by the interactions between different serum antioxidant constituents. As mentioned above, to date, no investigation has evaluated plasma TAR levels in patients with schizophrenia. So, the authors can not compare their results with other study results. However, an important point that the authors' found in the present study is that when the intragroup comparisons were performed paranoid subtype had highest and residual type had lowest TAR levels compared to other subtypes. This finding suggests that plasma TAR levels may be associated with the chronical course of illness, since residual subtype has considerable chronic progress. Actually, it is established that paranoid subtype occurs in late life compared to other subtypes. In contrast, the authors' found that that plasma TAR levels were significantly and negatively correlated with SANS scores which supports the notion mentioned above because the residual type of schizophrenia is a subtype dominantly including negative symptoms. Furthermore, the authors also found a relationship between plasma TAR levels and duration of illness. This demonstrates that decreased plasma antioxidant levels appear to be associated with the progression of illness. Meanwhile, in the present study, in which the status of plasma antioxidant was completely demonstrated, the authors' found that as a whole group, smokers with schizophrenia had significantly lower plasma TAR levels compared to non-smokers with schizophrenia and that there were no differences between those having 0–10 years of duration of illness compared to those having 10 years or more of duration of illness in smoker patients with schizophrenia. Cigarette smoking is associated with lower plasma antioxidants of dietary origin.[33–35] One major compound in the gas phase of tobacco smoke is NO. It has been suggested that NO combines with smoke olefins to form carbon centered radicals.[34] In the various studies, in patients with schizophrenia, smoking was demonstrated to increase oxidative stress and to significantly decrease some antioxidant parameters.[34,36] Nevertheless, in some studies, smoking did not affect antioxidant parameters.[15,37] In fact, in the studies aforementioned, the antioxidants measured were alone and did not show the status of plasma antioxidant capacity. Also, the population of these studies was mainly first episodic patients, so there might have been a lot of factors affecting plasma antioxidant status.[15,37]

There are some methodological limitations of the present study that must be acknowledged. First, sample size is relatively small. Apart from this, it is worth mentioning that some confounding factors related to outpatient habits, that is, exercise, lifestyle, and dietary changes may affect the levels of plasma TAR.

Consequently, the present study further emphasizes the growing consideration that free radical damage may have an important etiopathogenetic role in the development of schizophrenia and suggests that decreased plasma antioxidant levels may be related to the progression of illness.

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