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Regular Article

Oxidative mechanisms in schizophrenia and their relationship with illness subtype and symptom profile

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Aim: The aim of the present study was to investigate the differences in the antioxidant–oxidant balance (AO-OB) between schizophrenic patients and healthy individuals and to explore the relationship of AO-OB with illness subtypes and symptom profiles.

Methods: After a 15-day drug-free period, schizophrenia patients ($n = 50$) in a clinical sample, and age- and sex-matched healthy subjects ($n = 49$) were enrolled. Total antioxidant potentials (TAOP) and total peroxide levels (TPEROX) of all participants were measured and the oxidative stress index (OSI) was calculated. The assessment included structured measurements, including the Positive and Negative Syndrome Scale (PANSS), and the Brief Psychiatric Rating Scale (BPRS).

Results: TAOP had a significant positive correlation with age at onset of schizophrenia ($P = 0.013$), a negative correlation with the PANSS negative subscale scores ($P = 0.008$), a negative correlation with the PANSS total scores ($P < 0.001$), and a significant negative correlation with BPRS scores ($P = 0.001$). OSI had a significant negative correlation with age at onset ($P = 0.046$) and a significant positive correlation with PANSS negative subscale ($P = 0.015$). A multiple regression model indicated a significant linear combination of age, gender, duration of illness, subtype of schizophrenia, and PANSS scores, in which only the subtype of schizophrenia made a statistically significant contribution to predicting mean OSI ($F[5,35] = 2.44$, $P = 0.04$).

Conclusion: Several parameters in the pathogenesis of schizophrenia, such as age of onset, level of negative symptoms, and subtype of illness, but not the presence of the illness itself, are associated with the level of oxidative stress.

Key words: oxidative stress, PANSS, schizophrenia, total antioxidant potential, subtype.

THERE IS GROWING evidence that an excessive free radical production or oxidative stress may be implied in the pathogenesis of schizophrenia.[1–9] It was previously reported that oxidative stress, along with direct tissue damage, augments glutamate excitotoxicity and stimulates apoptosis by mitochondrial damage.[9,10] These processes are not independent and proceed concurrently.

Studies investigating the effect of free radicals in schizophrenia patients have primarily focused on superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) enzyme systems. The levels of SOD have consistently been found to be high in chronic schizophrenia patients[11–14] and to be low in neuroleptic-naive, first-episode schizophrenia patients.[15] The use of antioxidants, such as vitamins,[9,16] extract of Ginkgo biloba,[17,18] and essential polyunsaturated fatty acids[19,20] have been found to

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improve some of the psychopathological symptoms of schizophrenia. These findings provide further evidence that free radicals may be involved in the psychopathology of schizophrenia.

Excessive free radical production or oxidative stress may not be directly associated with the presence of the schizophrenia, but with the severity and/or subtypes of the disorder. In accordance with this hypothesis, a significant association between antioxidant enzyme levels and clinical features of schizophrenia has also been previously reported in several studies.[13,14,16,20–26] For instance, such abnormalities in antioxidant system lipid peroxidation have been associated with negative symptoms,[21] positive symptoms,[25] and tardive dyskinesia.[13,22] Several other studies, in which authors examined antioxidant status and lipid peroxidation in schizophrenia patients, found significant differences in SOD, CAT, and/or GSH-Px activities between different subtypes of schizophrenia patients.[27–29]

Although several studies explored specific antioxidant levels in schizophrenia patients, only a few assessed the total plasma antioxidant levels (TPAL).[8,23,30,31] Even though most of them suggested that TPAL are significantly lower in schizophrenia patients, the results differed with regard to TPAL compared to healthy control subjects. In addition, these differences may be associated with the severity and/or subtypes of the disorder.

The aims of the present study were therefore to (i) investigate differences in antioxidant–oxidant balance between schizophrenia patients and healthy control subjects; and (ii) determine the possible relationships between the antioxidant–oxidant balance and illness subtype and symptom profile.

METHODS

Participants

In Ankara Numune Training and Research Hospital psychiatry outpatient clinic, during 1 year, patients who were diagnosed as having schizophrenia by two psychiatry specialists according to DSM-IV criteria[32] using the Structured Clinical Interview Document (SCID) were assigned.

Exclusion criteria included presence of any comorbid psychiatric disorder, severe systemic and neurologic illness, pregnancy, substance abuse or addiction, any medication history in the last 15 days or depot antipsychotics in the last month. Individuals having high levels of white blood cells, high sedimentation rate, abnormal platelet counts, or abnormal liver or renal function tests were also excluded. The patients ($n = 50$, 20 female, 30 male; mean age, 31.69 ± 7.34 years), who gave written informed consent to participate in the study and who did not meet the exclusion criteria were included. The control group (mean age, 28.28 ± 7.84 years) consisted of 22 women and 27 men, yielding a total of 49 age- and sex matched healthy subjects with no family history of schizophrenia in their first-degree relatives.

Procedure

Psychiatric diagnoses were assessed via SCID, a clinical interview form based on DSM-IV criteria.[32] Following 12 h of fasting, blood samples were drawn from the cubital vein into a heparinized tube between 07.00 hours and 09.00 hours, before the use of any medications or smoking. Blood samples were immediately placed on ice packs at +4 °C and centrifuged for 10 min at $1006 \times g$ to separate the plasma from the cells. Plasma samples were placed into cryo-Eppendorf tubes and stored at −40 °C until analysis.

The Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS) were completed concurrently. In addition, semi-structured forms were completed for each participant including records of personal history, family history and sociodemographic characteristics. These forms also included age, marital status, level of education, occupation, family history of psychiatric disorders, medication and smoking history, bodyweight, and height.

The Ethics Committee of the Ankara Numune Training and Research Hospital approved this study, and each participant provided written informed consent.

Biochemistry

Measurement of plasma total antioxidant potential

The total antioxidant potential (TAOP) of serum was determined using a novel automated measurement method, developed by Erel.[33] In this method, the hydroxyl radical, which is the most potent biological radical, is produced. In the assay, ferrous ion solution, which is present in reagent 1, is mixed with hydrogen peroxide, which is present in reagent 2. The

resulting products of this reaction, such as brown dianisidinyl radical cation, produced by the hydroxyl radical, are also potent radicals. Using this method, antioxidative effect of the sample against the potent free radical reactions is measured. The assay has been found to have excellent precision: <3%. The results are expressed as mmol Trolox Equiv./L.

Total plasma peroxide levels

Similarly, total peroxide levels (TPEROX) of serum was determined using a novel automated measurement method, developed by Erel.[34] Oxidants present in the sample oxidize the ferrous ion–o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H2O2 Equiv./L).

Oxidative stress index

The ratio of TPEROX to TAOP is referred as oxidative stress index (OSI). The OSI is calculated according to the following formula[35]:

$$\text{OSI (arbitrary unit)} = \text{TPEROX } (\mu\text{mol}H_2O_2 \text{ Equiv./L})/\text{TAOP (mmol Trolox Equiv./L)}.$$

Instruments

Brief Psychiatric Rating Scale

The BPRS is a widely used scale to evaluate the depressive and psychotic symptom severity and change in time.[36] It is completed by the clinician. It has 18 items that are rated on a 7-point scale ranging from 1 ('not at all a problem') to 7 ('the problem is severe in degree').

Positive and Negative Syndrome Scale

Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology.[37] It has 30 items (seven for negative symptoms, seven for positive symptoms, and 16 for general psychopathology) that are rated on a 7-point scale ranging from 1 ('not at all a problem') to 7 ('the problem is severe in degree'). Turkish translation and validation study was conducted by Kostakoglu and Tiryaki.[38]

Data analysis

For the evaluation of data, descriptive statistical methods, χ^2 test, and parametric tests (t-tests) and non-parametric tests (Mann–Whitney *U*-test and Kruskal–Wallis test) were used where appropriate. Spearman's rho correlation test was used to evaluate the correlation between the variables. Differences between subtypes were tested using Kruskal–Wallis test. The Mann–Whitney *U*-test was used for post-hoc analyses and Bonferroni correction was applied. To minimize Type I error, due to six comparisons we set alpha at $P < 0.01$ (i.e. 0.05 divided by 6). In addition, because multiple individual and environmental factors could be involved in maintaining antioxidant balance, predictors of OSI were assessed on multiple regression models, and predictors included age, gender, duration of illness, age of onset, subtype of schizophrenia, PANSS and BPRS scores, body mass index, and smoking status. All data were numerically entered into SPSS 11.0 (SPSS, Chicago, IL, USA). The level of significance was set to 0.05 and *P* was calculated using SPSS.

RESULTS

Fifty patients diagnosed with schizophrenia according to DSM-IV criteria and who were free of treatment for at least 2 weeks, and 49 healthy controls with no family history of schizophrenia in their first-degree relatives were included in the study. Among the patients with schizophrenia, 10 patients were in their first episode and had never used antipsychotic medication. Sixteen patients (32%) had paranoid schizophrenia, another 16 (32%) had undifferentiated subtypes. Nine (18%) had disorganized, and the remaining nine patients had residual subtypes of schizophrenia. Sociodemographic and clinical characteristics of the groups are listed in Table 1.

There were no gender or smoking status differences between antioxidant and oxidant parameters among

Table 1. Subject characteristics

	Control ($n = 49$)	Patient ($n = 50$)	P
Gender (M/F)	27/22	30/20	0.653†
Age (years)	31.69 ± 7.34	28.28 ± 7.84	0.550‡
Age at onset disease (years)	–	22.12 ± 6.32 (14–47)	
Disease duration (years)	–	6.14 ± 5.68 (1–30)	
PANSS (+) subscale	–	25.06 ± 5.35	
PANSS (−) subscale	–	29.08 ± 6.51	
PANSS total	–	110.60 ± 14.37	
BPRS	–	63.50 ± 8.05	
Smoker/Non-smoker	23/26	23/27	0.980†

†χ^2 test; ‡Student's *t*-test.
BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.

the patients. In the healthy control group, the TPEROX of smokers were found to be higher compared to non-smokers ($P = 0.035$), and antioxidant levels were higher among the men compared to the women ($P = 0.022$). Mean TAOP, TPEROX and OSI of the patient and control groups are given in Table 2. All mean levels were found to be higher among patients compared to the control subjects, but this was not statistically significant.

Correlations between TAOP, TPEROX, OSI and clinical parameters of the patients are shown in Table 3.

Total antioxidant potential had a significant positive correlation with age at onset of schizophrenia ($P = 0.013$), a negative correlation with the PANSS negative subscale scores ($P = 0.008$), a negative correlation with the PANSS total score ($P < 0.001$), and a significant negative correlation with BPRS scores ($P = 0.001$). TPEROX was significantly positively correlated with PANSS positive subscale total scores ($P = 0.013$), PANSS total score ($P = 0.020$), and BPRS scores ($P = 0.008$). OSI had a significant negative correlation with age at onset ($P = 0.046$) and a significant positive correlation with PANSS negative subscale ($P = 0.015$; Table 3). In addition, mean TAOP, TPEROX and OSI in different schizophrenia subtypes are given in Table 4.

Only mean OSI was statistically significantly different between schizophrenia subtypes. Post-hoc analysis showed that patients with residual subtype had higher OSI compared to patients with the paranoid subtype of schizophrenia.

A simultaneous regression model, in which multicollinearity was corrected, indicated a significant linear combination of age, gender, duration of

Table 2. Mean TAOP (mmol Trolox Equiv./L), TPEROX (μmol H_2O_2 Equiv./L) and OSI [arbitrary unit: (TPEROX μmol H_2O_2 Equiv./L)/(TAOP mmol Trolox Equiv./L)]

		n	Mean	SD	P
TAOP	Patient	50	1.7606	0.133	0.583
	Control	49	1.7438	0.157	
TPEROX	Patient	50	18.9655	1.318	0.471
	Control	49	18.7683	1.236	
OSI	Patient	50	10.7909	0.971	0.832
	Control	49	10.8396	1.086	

Calculated with the student *t*-tests.
OSI, oxidative stress index; TAOP, total antioxidant potentials; TPEROX, total peroxide levels.

Table 3. Correlations (Spearman's rho) for oxidative mechanisms and clinical parameters

	TAOP	TPEROX	OSI
Disease duration	−0.088	−0.038	0.114
Age at onset	0.367*	0.075	−0.326*
Positive subscale	−0.210	0.382*	−0.180
Negative subscale	−0.392**	0.014	0.391*
PANSS total	−0.591**	0.358*	0.229
BPRS total	−0.475**	0.403**	0.079

*$P < 0.05$; **$P < 0.01$; rho values without an asterisk are not significant.
BPRS, Brief Psychiatric Rating Scale; OSI, oxidative stress index; PANSS, Positive and Negative Syndrome Scale; TAOP, total antioxidant potentials; TPEROX, total peroxide levels.

Table 4. Mean TAOP (mmol Trolox Equiv./L), TPEROX (μmol H_2O_2 Equiv./L) and OSI [arbitrary unit: (TPEROX μmol H_2O_2 Equiv./L)/(TAOP mmol Trolox Equiv./L)] levels in schizophrenia subtypes

	TAOP (Mean ± SD)	TPEROX (Mean ± SD)	OSI (Mean ± SD)
1-Paranoid ($n = 16$)	1.07 ± 0.11	18.67 ± 1.11	17.37 ± 1.67
2-Indifferentiated ($n = 16$)	1.07 ± 0.13	19.08 ± 1.49	18.24 ± 2.64
3-Dysorganized ($n = 9$)	0.97 ± 0.09	18.65 ± 0.94	19.15 ± 2.04
4-Residual ($n = 9$)	1.00 ± 0.08	19.63 ± 1.64	20.11 ± 1.84
P	0.089 (n.s.)	0.587 (n.s.)	0.027*
1–2	n.s.	n.s.	n.s.
1–3	n.s.	n.s.	n.s.
1–4	n.s.	n.s.	0.009**
2–3	n.s.	n.s.	n.s.
2–4	n.s.	n.s.	n.s.
3–4	n.s.	n.s.	n.s.

*$P < 0.05$ (Kruskal–Wallis test); **$P < 0.01$ (post-hoc test; i.e. 0.05 divided by 6).
OSI, oxidative stress index; TAOP, total antioxidant potentials; TPEROX, total peroxide levels.

illness, subtype of schizophrenia, and PANSS scores as predictors of mean OSI. The beta weights, presented in Table 5, suggest that only the subtype of schizophrenia makes a statistically significant contribution to predicting mean OSI. This combination of variables significantly predicted mean OSI ($F(5,35) = 2.44$, $P = 0.04$). The adjusted R^2 was 0.15. This indicates that 15% of the variance in mean OSI was explained by the model.

DISCUSSION

The role of the antioxidant system in schizophrenia has attracted considerable attention in recent years. It is not clear, however, whether the disturbances in the antioxidant system are the results or causes of pathologic process in schizophrenia. Studies performed in schizophrenia patients have generally suggested the presence of a compromised antioxidant system, but this is not consistent with specific observed parameters. In the present study we evaluated plasma TAOP, plasma TPEROX, and additionally the OSI, which is calculated as a ratio of the former two parameters. We did not find any significant differences in these three parameters between schizophrenia patients and healthy controls.

It is a commonly held idea in the literature that the severity of symptoms exerts some effects on the antioxidant system.[24,39–42] Total bilirubin levels in one study, and plasma uric acid levels in another have been found to be significantly correlated with BPRS scores.[23,43] Each antioxidant has a critical role within the system, but all of them act together in a synergistic interaction. In this respect, some studies reported a significant inverse correlation between plasma TAOP and both BPRS and PANSS.[8,43] A decrease was observed in total antioxidant levels with increasing symptom severity. This suggests that decreased plasma TAOP could be implicated in the pathologic process in schizophrenia. In the present study, in which we used BPRS and PANSS to evaluate the severity of the symptoms, TAOP was found to be significantly negatively correlated, while TPEROX was significantly positively correlated with the scores of these symptom scales. That is, the severity of symptoms was associated with decreased antioxidant levels and increased peroxide (oxidant) levels. Decreased levels of antioxidants and/or increased

Table 5. Simultaneous multiple regression

Variable	B	SEB	β
Age	−0.08	0.06	−0.30
Gender	−1.02	0.72	−0.22
Duration of illness	0.07	0.076	0.18
Subtype of schizophrenia	0.60	0.254	0.36*
PANSS scores	−0.019	0.025	−0.11
Constant	22.69	3.62	

$R^2 = 0.15$, $F(5,35) = 2.44$, $P = 0.04$. *$P < 0.05$.
PANSS, Positive and Negative Syndrome Scale; SEB, Standard Error of B value.

levels of oxidants could be effective in worsening symptoms. In accordance with the present results, in previous studies, various antioxidant levels have been found to be related to negative symptoms, neurological findings, poor premorbid functions and computed tomography (CT) abnormalities.[44] In this respect, negative symptoms have attracted particular attention. In a recent study, bilirubin levels were found to be decreased among a patient subgroup with prominent negative symptoms.[40] Decreased peripheral glutathione peroxidase activity has been found to be associated with negative symptoms as well as marked cortical sulcus observed on cranial CT.[41] Decreased levels of essential polyunsaturated fatty acids, normally known to decrease in schizophrenia patients (particularly in patients with prominent negative symptoms), represent a striking finding.[24,39,42] In the present study TAOP was negatively correlated with negative subscales of PANSS, but there was no correlation with positive symptoms. Similarly, OSI was positively correlated with negative subscales. The results of this as well as previous studies suggest that alterations in antioxidant capacity might play a role (particularly in patients with prominent negative symptoms) in the severity and characteristics of schizophrenia symptoms.

Previous studies have failed to demonstrate such an association between disease duration and antioxidant levels.[8,10,23,30,39] Similarly, we did not find a significant relationship between TAOP, TPEROX, OSI and disease duration. In one study, however, age at disease onset was reported to be positively correlated with plasma uric acid levels.[43] In the present study age at onset was positively correlated with TAOP and negatively correlated with OSI. These findings may be interpreted as onset at earlier age increases the risk of decreasing antioxidant and/or increasing peroxide levels. The prodromal signs before the onset of positive psychotic symptoms as well as premorbid conditions such as introversion, social isolation, a decline in school success and failure in inter-individual relations can be associated with disturbances in the antioxidant system.[10,24,40,42]

In contrast, SOD and GSH-Px activities were found to be lower and the activities of antioxidant enzymes were found to be different between subtypes of schizophrenia.[10,27,28] Similarly, we found that OSI is significantly different between schizophrenia subtypes, particularly between paranoid and residual subtypes. In a previous study there was a significant increase in SOD activity in the residual group compared to the paranoid group, and CAT activity was found to be increased in disorganized (148%), paranoid (147%), and residual (165%) groups compared to the control group.[27] Similarly in a more recent study, SOD and GSH-Px activities were found to be significantly lower in paranoid and residual subtypes compared to both disorganized subtype and the control groups.[28] Brain glutathione levels are decreased in schizophrenia. *N*-acetyl cysteine (NAC) increases brain glutathione in rodents.[45] A recent study was conducted to evaluate the effectiveness of oral NAC as an add-on to maintenance medication for the treatment of chronic schizophrenia over a 24-week period. There were significantly greater improvements observed in the NAC treatment group compared with the placebo group for PANSS negative scores at week 24 when compared with baseline.[45] Because NAC treatment were efficacious for negative symptoms but not for the positive symptoms, this result is in accordance with the present results. In another recent study, authors investigated whether GSH levels are altered in the posterior medial frontal cortex of schizophrenia patients, and they examined correlations between GSH levels and clinical variables in patients.[46] Similarly, in accordance with the present results, there was a significant negative correlation between GSH and negative symptom scores, and there were no significant correlations between GSH level and positive symptom scores in schizophrenia patients.[46]

It should be kept in mind that multiple individual and environmental factors are involved in maintaining antioxidant balance, and none have been found to be superior to another. In the present study there were no gender differences between antioxidant and oxidant parameters among patients, but antioxidant levels were higher among the men in the control group, as has been reported in previous studies.[7,10,40] In agreement with the literature, in the healthy control group the TPEROX of smokers in the present study was found to be higher compared to non-smokers.[10–24] In conclusion, the effects of smoking on the antioxidant system are more evident in healthy subjects than in schizophrenia patients and their role in schizophrenia patients may be overlooked due to the presence of multiple factors influencing this system. In the present study a multiple regression model indicated a significant linear combination of age, gender, duration of illness, subtype of schizophrenia, and PANSS scores as predictors of mean

OSI. The beta weights suggest that only the subtype of schizophrenia makes a statistically significant contribution to predicting mean OSI. Only 15% of the variance in mean OSI, however, was explained by the model.

Limitations

Some of the previous studies examining the effects of neuroleptic medications on antioxidant enzymes in schizophrenia reported significant differences in the levels of SOD, CAT and GSH-Px.[11,30,47] In the present study we did not explore the effect of medication on antioxidant levels, but all participants were drug free at least for 15 days. A prospective design and a longer study period are required to assess the effects of drug use on the outcomes. In addition, as another limitation, because antioxidants in the diet have an important effect on tested antioxidant potential, the diet of patients and the control group should have been taken into account.

CONCLUSIONS

The present results indicated that several parameters in the pathogenesis of schizophrenia, such as age of onset, level of negative symptoms, and subtype of the illness but not the presence of the illness itself are associated with the level of oxidative stress. Future studies that clearly introduce the etiologic relation between disturbances in the antioxidant system and schizophrenia (particularly in certain subtypes) through measurements of pre- and post-therapy antioxidant and oxidant levels may provide prophylactic treatments as well as new treatment algorithms in addition to available antipsychotic regimens.

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