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Antioxidant enzyme and malondialdehyde levels in patients with social phobia

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Abstract

A growing body of reports have indicated that free radicals are involved in the etiopathogenesis of some neuropsychiatric disorders. In the present study, we aimed to evaluate whether antioxidant enzymes (superoxide dismutase; SOD, glutathione peroxidase; GSH-Px, and catalase; CAT) activity levels and malondialdehyde (MDA), a product of lipid peroxidation, were associated with social phobia (SP). Eighteen patients diagnosed with SP and 18 healthy controls were enrolled. A clinical evaluation and measurements of MDA, SOD, GSH-Px and CAT were performed. Additionally, all patients were assessed with the Liebowitz Social Anxiety Scale (LSAC). The mean MDA, SOD, GSH-Px and CAT levels in the patient group were significantly higher than those in the control group. There was a positive correlation between LSAC scores and MDA, SOD, GSH-Px and LSAC levels, and between the duration of illness, and MDA, SOD and CAT levels in the patient group. In conclusion, our results suggest that there may be a relationship between increased antioxidant enzyme levels and MDA, and SP.

Keywords: Social phobia; Antioxidant enzyme; MDA

1. Introduction

Free radicals, with an unpaired electron in one of their orbits, are chemical species produced in many different ways, such as activation of phagocytes and the general immune system, lipid peroxidation, electron transport system in mitochondria, ischemia and trauma (Gutteridge, 1995). Free radicals have relatively short half-lives, and thus the determination of their levels is difficult. Therefore, they can be evaluated indirectly by measurement of some antioxidant enzyme levels such as superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GSH-Px), by products of lipid peroxidation such as malondialdehyde (MDA) or by some transition metal levels such as copper, zinc and iron (Leff, 1994). Predominantly superoxide, hydroxyl ion and nitric oxide are generated under physiological conditions during aerobic metabolism (Mahadik and Mukherjee, 1996). A small portion of the free radicals are involved in physiological processes, but the remainder are inactivated by antioxidant enzyme systems (Burton and Ingold, 1989). When free radicals are generated in excessive

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amounts or the enzymatic and nonenzymatic antioxidant defense systems are inefficient, some chain reactions causing cellular injury or even death of cells are activated (Stadtman, 1992).

Free radical damage has been investigated in the pathophysiology of neuropsychiatric disorders. There are numerous studies indicating that free radical-mediated neuronal dysfunction may be implicated in the pathophysiology of schizophrenia (Mahadik and Mukherjee, 1996). Buckman et al. (1987) reported that patients with chronic schizophrenia had levels of GSH-Px activity similar to those in healthy controls. Increased SOD activity levels in schizophrenia have been reported (Lohr, 1991). In addition, it has been suggested that patients with major depression, especially melancholia, show elevated antioxidant enzyme levels and lipid peroxidation (Bilici et al., 2001).

Another neuropsychiatric disorder in which free radicals might play a role is social phobia (SP). To the best of our knowledge, there has not yet been a study evaluating the association between free radicals and SP. Therefore, in the present study, we hypothesized that oxidative damage and antioxidant enzyme activity levels could be implicated in SP.

2. Methods

2.1. Subjects and clinical evaluation

The sample comprised 18 patients (aged 18–49 years) who had presented at the Department of Psychiatry of Firat University School of Medicine. The patients had been diagnosed with SP according to DSM-III-R criteria and met the admission criteria for the study. Written consent to participate in the study was obtained from the subjects after they were thoroughly informed about the research details. The research protocol was approved by the Firat University School of Medicine Ethics Committee.

All subjects had been free of all medications for at least the previous 2 weeks. Each patient underwent diagnostic evaluation by one trained psychiatrist using the Structured Interview for DSM-III-R Outpatient Form (SCID-OP) (Spitzer et al., 1987). Patients with Axis I comorbidity were excluded, but patients with comorbid Axis II disorders were accepted for study. In the patient population, there were six patients with personality disorder (avoidant personality disorder in three patients, obsessive-compulsive personality disorder in two patients and dependent personality disorder in one patient) and no mental retardation as an axis II disorder. All subjects were evaluated by a semistructured form that summarized information about, for example, gender, age, marital status, education, socioeconomic status, and duration of illness. Liebowitz's 24-item Social Anxiety Scale (LSAC) (Liebowitz, 1987) was used to assess the patients' level of social fear and avoidance.

Eighteen healthy control subjects were chosen among the hospital staff. Controls were interviewed with the nonpatient version of the SCID (SCID-NP) to exclude any Axis I disorder (Spitzer et al., 1990).

All subjects underwent physical and neurological examinations, as well as liver and kidney function tests. Subjects with normal results and without exclusionary criteria were admitted to the study. Exclusionary criteria were as follows: alcohol and substance abuse or dependence; presence of a severe organic condition such as Wilson's disease, Down's syndrome, malnutrition, pregnancy, diabetes mellitus, chronic renal failure, cancer, liver cirrhosis, and thyroid disease, treatment with glucocorticoids, anticonvulsants, oral contraceptives, psychotropic drugs and any antioxidant agents such as vitamins (i.e. vitamins E and C), xantine oxidase inhibitors (allopurinol, folic acid), and non-steroidal anti-inflammatory drugs; presence of epilepsy and severe neurologic disorder such as Parkinson, Huntington, and Alzheimer diseases; presence of infectious disease and excessive obesity.

2.2. Blood sampling

Venous blood samples from a left forearm vein were collected into 5-ml vacutainer tubes containing potassium EDTA between 7 and 8 a.m. after overnight fasting. Some hematological parameters were measured with an auto-analyzer (Coulter Max M, Coulter Electronics Ltd, Luton, UK). The data on smoking were obtained from each patient using a questionnaire administered 1 day before blood drawing. Eleven of the patients and nine of the controls were smokers. Nine of eleven smoker patients had >20 cigarettes per day except for two patients who had between 10 to 20 cigarettes per day. On the other hand, eight of nine smoker controls had >20 cigarettes per day while one had 10 to 20 cigarettes per day. The mean durations for smoking in smoker patients and controls were 7.47±4.62 and 6.91±4.23 years, respectively. Smoking was not permitted after 23.00 h, one day before blood drawing. The prohibition against smoking on the day before the blood drawing had been specified in the consent process.

The blood samples were centrifuged at 4000 rpm for 10 min at 4 °C to remove plasma. The buffy coat on the erythrocytes sediment was separated carefully after

plasma was removed and was used in the assay of malondialdehyde levels. The erythrocyte sediment was washed three times with 10-fold isotonic NaCl solution to remove plasma remnant. After each procedure, the erythrocyte-saline mixture was centrifuged at 4000 rpm for 10 min at 4 °C. Aliquots of the samples were transferred into polyethylene tubes. Erythrocyte sediments were treated with ice-cold de-ionized water to obtain hemolysates.

2.3. Enzymes, chemicals and instruments

Xanthine oxidase, xanthine, nitroblue tetrazolium (NBT), thiobarbituric acid, and 1,1,3,3 tetramethoxypropane were purchased from Sigma Chemical Co. (St Louis, MO, USA). A Schimadzu UV-1201 spectrophotometer (Schimadzu Corp., Japan) was used to measure GSH-Px, SOD, catalase activity and malondialdehyde levels.

2.4. The determination of SOD, GSH-Px and CAT activities and MDA levels

Hemolysates of erythrocytes were used for measurement of total (Cu–Zn and Mn) SOD (EC 1.15.1.1) activity levels by the method of Sun et al. (1988). This method is based on reduction of superoxide, which is produced by the xanthine oxidase enzyme system, by nitroblue tetrazolium. A unit of SOD was determined as the amount that decreases nitroblue tetrazolium reduction by 50%. Results were expressed as U g^{-1} Hb.

GSH-Px (EC 1.6.4.2) activity levels in hemolysates of erythrocytes were measured using the method of Paglia and Valentine (1967) in which GSH-Px activity was coupled to the oxidation of NADPH by glutathione reductase. The oxidation of NADPH was followed spectrophotometrically at 340 nm at 37 °C. The reaction mixture consisted of 50 mM potassium phosphate buffer (pH: 7), 1 mM EDTA, 1 mM NaN_3, 0.2 mM NADPH, 1 mM glutathione, and 1 U/ml of glutathione reductase. The absorbance at 340 nm was recorded for 5 min. The activity was the slope of the lines as μmol of NADPH oxidized per min. Results were expressed as U g^{-1} Hb.

CAT (EC 1.11.1.6) activity was determined by the method of Aebi (1974). The principle of the assay is based on the determination of the rate constant k (dimension: s^{-1}) of the hydrogen peroxide decomposition. By measuring the absorbance changes per minute, the rate constant of the enzyme was determined. Activities were expressed as k g^{-1} Hb.

Levels of plasma MDA were measured by the thiobarbituric acid (TBA) method, which was modified from methods of Satoh (1978) and Yagi (1984). Peroxidation was measured as the production of MDA, which in combination with TBA forms a pink chromogen compound whose absorbance at 532 nm was measured. MDA results were expressed as $nmol^{-1}$ ml.

2.5. Statistical analysis

The data were evaluated by SPSS Windows program 9.05 (SPSS, 1998). Student's t test, chi-square tests, and Pearson correlations were used. The level of significance was set at $P<0.05$.

3. Results

A total of 18 patients (8 females and 10 males) were enrolled in this study. The control group ($n=18$) contained nine (50%) females and nine (50%) males. There were no significant differences in age, female/male ratio, and smoking status (rate and duration) between the patients and controls ($P>0.05$). The mean

Table 1
Antioxidant enzyme and malondialdehyde (MDA) levels in social phobia (SP) and control groups*

Groups	SOD (U g^{-1} Hb)	GSH-Px (U g^{-1} Hb)	CAT (k g^{-1} Hb)	MDA ($nmol^{-1}$ ml)
SP group ($n=18$)	1218.64±213.23	31.23±3.87	281.34±54.27	4.63±0.49
I. Smokers ($n=11$)	1223.42±229.12	30.88±3.67	286.66±58.13	4.70±0.55
II. Non-smokers ($n=7$)	1211.13±208.77	31.78±3.93	272.98±47.46	4.52±0.42
Statistical values**	$t=0.12$, $P>0.05$	$t=0.21$, $P>0.05$	$t=5.1$, $P>0.05$	$t=1.1$, $P>0.05$
Control group ($n=18$)	998.45±101.24	24.87±3.09	238.28±41.56	2.39±0.43
I. Smokers ($n=9$)	987.76±99.31	25.85±3.77	243.11±43.23	2.46±0.52
II. Non-smokers ($n=9$)	1009.48±111.33	23.89±3.13	233.45±37.34	2.32±0.38
Statistical values**	$t=0.76$, $P>0.05$	$t=0.87$, $P>0.05$	$t=1.1$, $P>0.05$	$t=1.4$, $P>0.05$
Statistical values***	$t=9.81$, $P<0.01$	$t=12.45$, $P<0.001$	$t=8.16$, $P<0.01$	$t=11.05$, $P<0.001$

* Student's t test.
**, between I and II within group.
***, between the patients and controls.

duration of illness for the patient group was 6.36± 3.56 years.

SOD activity levels in SP group and controls were 1218.64±213.23 U g^{-1} Hb and 998.45±101.24 U g^{-1} Hb, respectively. SOD activity levels were significantly higher in the SP group than in the control group ($P<0.01$). In the SP group, the mean GSH-Px activity levels were 31.23±3.87 U g^{-1} Hb and 24.87±3.09 U g^{-1} Hb for the SP and control groups, respectively. There was a statistically significant difference with respect to GSH-Px activity levels between groups ($P<0.001$). The mean CAT activity levels in the SP group and the control group were 281.34±54.27 kg^{-1} Hb and 238.28±41.56 kg^{-1} Hb, respectively. There were statistically significant differences between groups ($P<0.01$). To evaluate levels of lipid peroxidation, MDA levels were determined in controls and patients. The mean MDA levels in the SP group and the control group were 4.63±0.49 $nmol^{-1}$ ml and 2.39±0.43 $nmol^{-1}$ ml, respectively ($P<0.001$) (Table 1).

To examine if antioxidant enzymes and MDA levels were affected by cigarette smoking, these levels were compared between smokers versus non-smokers in both the patients and controls. No significant differences were found between smokers and non-smokers for SOD, GSH-Px and MDA in both groups and for CAT in controls ($P>0.05$). However, in patients, there was only a trend toward statistical significance for CAT levels ($P=0.03$). There were no statistically significant between-group differences for hematological parameters ($P>0.05$).

LSAC scores in the patient group were positively correlated with MDA, SOD, CAT and GSH-Px levels ($r=0.68$, $P<0.01$; $r=0.56$, $P<0.05$; $r=0.58$ $P<0.05$; $r=0.54$, $P<0.05$, respectively). There were also significant relationships between the duration of illness and MDA ($r=0.56$, $P<0.05$), SOD ($r=0.70$, $P<0.01$) and CAT ($r=0.57$, $P<0.05$) levels for the patient group. (See Table 2 for details).

4. Discussion

To the best of our knowledge, this is the first study regarding antioxidant enzyme activity and malondialdehyde levels in patients with SP. The major findings of our study are as follows: (1) Patients with SP have significantly higher antioxidant enzyme (SOD, CAT and GSH-Px) activity and malondialdehyde levels compared with those in controls. (2) There were positive correlations between each of these levels and severity of SP, as determined by the LSAC, and between the duration of illness, and MDA, SOD, or CAT.

The brain is especially vulnerable to free radical damage because it is a highly oxygenated organ that accounts for one-fifth of the oxygen use by the body. In addition, the brain contains large amounts of iron and polyunsaturated fatty acids and relatively low levels of antioxidants such as catalase (Halliwell and Gutteridge, 1986; Halliwell, 1989). In previous studies, inconsistent results were found in patients with psychiatric disorder. Abdalla and co-workers reported that schizophrenic patients had higher erythrocyte SOD activity levels than healthy controls (Abdalla et al., 1986). Cohen et al. (1986, 1987) compared schizophrenic patients with healthy controls in respect to SOD activity and toxic oxygen metabolites and did not find any significant difference. Herken et al. (2001), who investigated the importance of free radicals in schizophrenia subtypes, reported that oxidative stress might have a pathophysiological role in all the subtypes of schizophrenia. In an earlier study by our group (Kuloglu et al., 2002), significant differences between lipid peroxidation product (MDA) and antioxidant enzymes (SOD and GSH-Px) activity levels were found in patients with schizophrenia and bipolar disorder compared with controls. In another study (Bilici et al., 2001), it was suggested that patients with major depression, especially melancholia, had elevated antioxidant enzyme levels and lipid peroxidation. Controlled studies demonstrate high levels of monoamine oxidase

Table 2
Correlation analyses between parameters studied in the patients and controls

	SP group				Control group			
	MDA	SOD	CAT	GSH-Px	MDA	SOD	CAT	GSH-Px
SOD	n.c.	–	0.61*	n.c.	0.60*	–	0.58*	n.c.
CAT	n.c.	0.61*	–	n.c.	n.c.	0.58*	–	n.c.
GSH-Px	n.c.	n.c.	n.c.	–	n.c.	n.c.	n.c.	–
Age	n.c.	n.c.	0.50	n.c.	n.c.	0.52*	n.c.	n.c.
LSAC	0.68**	0.56*	0.58*	0.54*	–	–	–	–
Duration of illness	0.56*	0.70**	0.57*	n.c.	–	–	–	–

**$P<0.01$, *$P<0.05$.
n.c., No correlation.

(MAO) activity in major depression (Pandey et al., 1992). The fact that major depression responds to MAO inhibitors may reflect this relationship. It has been suggested that there may be a relationship between excessive production of free radicals and increased monoamine oxidation (Gutteridge, 1995). Both irreversible MAO inhibitors such as phenelzine (Gelertner et al., 1991; Liebowitz et al., 1992) and reversible MAO inhibitors such as moclobemide and brofaromine (Versiani et al., 1992; Fahlen et al., 1995) MAO inhibitors have been shown to be efficacious in the patients with SP. On the other hand, it was reported that increased free radical production might cause the destruction of phospholipids and altered viscosity of neuron membranes; change in membrane viscosity may affect serotonergic and catecholaminergic receptor functions (Van der Vliet and Bast, 1992). Moreover, MDA has an inhibitory effect on serotonin binding sites on the receptor (Britt et al., 1992). As a result, the relationships mentioned above may be considered to reflect a possible etiopathogenetic association between free radicals and SP.

Catecholamines, including dopamine and norepinephrine, are probably associated with the production of free radicals, and conditions causing increased catecholamine metabolism may increase the radical burden (Graham, 1978, 1979). Pharmacologic studies suggest that the metabolism of serotonin, noradrenaline and dopamine might be affected in patients with SP (Tancer and Uhde, 1989; Tancer, 1993). In neuroimaging studies, possible metabolic and structural differences (in basal ganglia) have been shown in patients with SP compared with healthy controls (Davidson et al., 1993). This is in accordance with dopaminergic and serotonergic abnormalities. Moreover, it has been reported that the most important source of free radicals is glial cells, and free radicals produced by these cells have been associated with neuropsychiatric disorders such as Sydenham's chorea and Parkinson's disease etc. (Lohr, 1991). Both diseases have been associated with the basal ganglia, as is also the case for SP. Thus, it is possible that free radicals may have an important role in the pathogenesis of SP. Meanwhile other features of SP beyond a direct neurochemical relationship with free radicals should be taken into consideration since these factors may contribute to the changes in antioxidant enzymes and MDA levels. Because of its nature, SP itself can impact the patients' behaviors, i.e. eating and diet habits, smoking, and sun exposure, all of which can relate to oxidative mechanisms. For example, sun exposure in these patients may affect levels of melatonin, a strong non-enzymatic antioxidant, and consequently oxidative metabolism. Smoking rate in the patients was not different from the healthy controls in the present study beyond the fact that there were no significant differences between smokers and non-smokers in regard to antioxidant enzymes and MDA levels in both groups. It seems worthwhile to systematically investigate in larger patient populations the issue of whether or not the conditions mentioned above affect the antioxidant enzymes and MDA levels.

Several limitations should be taken into consideration when interpreting our results. First, the relatively small sample size might not be completely representative of patients with SP. Apart from this, we could not control some confounding factors related to outpatient habits, i.e. exercise, life style and so on, which might be related to antioxidant enzymes and MDA values. In addition, as mentioned above, dietary changes may affect the production of free radicals, although the patients and controls came from similar socioeconomic backgrounds and had similar characteristics regarding age, female/male ratio, and smoking status (rate and duration). In conclusion, our results suggest that SP may be associated with free radicals, but our sample is too small to allow us to conclude that this alteration is an important biological indicator for the disorder. Our results need to be confirmed by more comprehensive and detailed studies to decipher the exact roles of free radicals in SP.

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