

## ORIGINAL PAPER

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# Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment

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**Abstract** A growing body of evidence indicates that oxidative stress is involved in the etiopathogenesis of some psychiatric disorders. In our previous study, we have found that social phobia (SP) seems to be associated with elevated antioxidant enzymes and malondialdehyde (MDA) levels, a lipid peroxidation product. In the present investigation, we sought to determine whether the increased radical burden observed in patients with SP would be attenuated with alleviation of symptoms. Thirty-nine patients diagnosed with generalized SP and 39 healthy controls participated in this study. The measurements of MDA, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) were performed before and after a period of 8 weeks of citalopram treatment. In this period, the patients received citalopram but controls did not. The initial dose of citalopram was 20 mg, with 20 mg increments occurring every 2 weeks, to a maximum dose of 60 mg, with the mean daily dose of  $38.9 \pm 13.3$  mg/day. All patients were evaluated by using Liebowitz Social Anxiety Scale (LSAS). The mean MDA, SOD, GSH-Px and CAT levels of the patient group at baseline were significantly higher than those of controls. Antioxidant enzymes and MDA levels decreased significantly through citalopram treatment. Significant and positive correlation was observed between decrease in the total LSAS scores, and SOD or CAT levels. In conclusion, our results

suggest that, in patients with SP, subchronic treatment with citalopram may decrease antioxidant enzymes and MDA values and that they are state markers of SP because they return to normal values with treatment.

**Key words** Antioxidant enzyme · citalopram · malondialdehyde · social phobia

## Introduction

Free radicals (FRs), predominantly oxyradicals, e.g. superoxide ( $O_2^-$ ), hydroxyl ion (OH), and nitric oxide (NO), are oxygen containing chemical substances which are generated under physiological conditions during aerobic metabolism (Mahadik and Mukherjee 1996). The main sources of FRs are as follows: the activation of immune cells, oxidative process, lipid peroxidation and oxidative stress (Lohr et al. 1991). When oxidative stress is generated in excess or the enzymatic and nonenzymatic antioxidant defense systems are inefficient, they can stimulate some chain reactions causing cellular injury or even death of cells (Stadtman 1992). There are numerous studies indicating that free radical-induced neuronal damage has an important role in the pathophysiology of schizophrenia and depression, probably via membrane pathology (Mahadik and Mukherjee 1996; Bilici et al. 2001). The brain, which consumes a large amount of oxygen, and has high lipid content and transition metals, is at risk for oxidative damage. Yao et al. (1998) found a significant decrease of uric acid, a selective antioxidant, concluded that this might be due to a defect in the antioxidant defense system. Depression is associated with significantly lower  $\omega 3$  polyunsaturated fatty acid fractions and oxidative potential index of serum phospholipids (Maes et al. 1999), demonstrating oxidative damage. However, limited studies have been carried out in anxiety disorders, e.g. obsessive-compulsive disorder (OCD) (Kuloglu et al. 2002a), social phobia (SP) (Atmaca et al. 2002, in press). In our previous study (Atmaca et al. in press), we found that SP was

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associated with the elevated antioxidant enzymes and malondialdehyde (MDA) levels. Whether the alterations in antioxidant enzymes and MDA are modified by antidepressant drugs or they constitute state or trait markers of SP is currently unknown. It has been reported that selective serotonin reuptake inhibitors (SSRIs) inhibit cytochrome enzymes (Glue and Banfield 1996) and suppress the number of leukocytes and neutrophils that cause increased radical burden (Maes et al. 1997). In the present investigation, we sought to determine whether the increased radical burden observed in patients with SP is attenuated with alleviation of symptoms by citalopram treatment.

## Methods

In this study, a total of 78 subjects were recruited, comprising 39 patients who had applied to Firat University School of Medicine Department of Psychiatry and diagnosed with generalized SP on the basis of Structured Interview for DSM-III-R Outpatient Form (SCID-OP) (Spitzer et al. 1987), and 39 healthy controls. Written consent to participate in the study was obtained from the subjects after they were thoroughly informed about the research details. The study protocol was approved by the Local Ethics Committee of the Firat University School of Medicine.

The patients with any kind of axis I comorbidity were excluded. Additionally, all subjects were evaluated by a semi-structured questionnaire form which was arranged in accordance with clinical experience and available information sources and included gender, age, marital status, educational condition, socioeconomic status, duration of illness. To determine the level of social anxiety and avoidance, the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz 1987) was used. As SP is frequently comorbid with the depressive disorders, in patients 7 points for Hamilton Depression Rating Scale (HAM-D) was accepted as the cut-off score.

A total of 39 healthy control subjects according to exclusion criteria were chosen among the hospital staff. Controls were interviewed with the non-patient version of the SCID (SCID-NP) to exclude any axis I disorder (Spitzer et al. 1990).

All subjects underwent a full physical examination, and routine blood tests, e.g. serum electrolytes, alanine and aspartate transaminase, urea, creatinine, glucose, and lactate dehydrogenase. All participants were carefully assessed to exclude autoimmune, pulmonary, infectious diseases and neoplasms. Exclusion criteria included alcohol and substance abuse or dependence, presence of severe organic condition and antioxidant agent use (i.e. E and C vitamins), presence of epilepsy, severe neurologic and infectious disease, excessive obesity (having BMI over 30), and treatment with any psychotropic drug within the last two weeks.

All subjects were free of all medications at least two weeks prior to baseline blood sampling. The patients received citalopram for 8 weeks of the treatment period but controls did not. The initial dose of citalopram was 20 mg, with 20 mg increments occurring every 2 weeks, to a maximum dose of 60 mg, as determined by treatment response and side effects (range, 20–60 mg), with the mean daily dose of  $38.9 \pm 13.3$  mg/day. The medications were received each morning after breakfast. The only concurrent medication permitted was alprazolam. Blood sampling from patients as well as from healthy controls was carried out on the initial test day and after 8 weeks of treatment. Venous blood samples from 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 by using an autoanalyzer (Coulter Max M, Coulter Electronics Ltd, Luton, UK). The data on smoking were obtained from each patient by using a questionnaire one day before blood drawing. Smoking was not permitted after 23.00 h, one day before blood drawing. 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.

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. GSH-Px (EC 1.6.4.2) activity levels in hemolysates of erythrocytes were measured by using the method of Paglia and Valentine (1967) in which GSH-Px activity was coupled to the oxidation of NADPH by glutathione reductase. 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  $k$  (units:  $s^{-1}$ ) of the hydrogen peroxide decomposition. 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 determined as the production of MDA which in combination with TBA forms a pink chromogen compound whose absorbance at 532 nm was measured.

Data obtained were evaluated by SPSS Windows program 9.05 (SPSS, 1998). Group mean differences were examined by means of unpaired (for groups comparisons) or paired (for within group comparisons before and after treatment) t-test. Chi-square test was used to compare categorical variables. Correlation analysis was performed by Pearson correlations and Spearman Rank correlations test, whenever appropriate. The significance level was  $P < 0.05$ .

## Results

The mean age, female/male ratio, and the proportion of smokers to non-smokers in the patient group did not significantly differ from controls. The mean duration of illness for the patient group was  $5.6 \pm 3.1$  years. The mean total LSAS score significantly changed during the study (from 121.9 to 65.6) ( $P < 0.001$ ).

SOD activity levels were significantly higher in the SP group compared to the control group ( $1198.23 \pm 188.45$  U  $g^{-1}$  Hb and  $997.11 \pm 112.09$  U  $g^{-1}$  Hb, respectively;  $P < 0.05$ ). The mean GSH-Px activity levels were higher in SP as compared to controls ( $29.78 \pm 4.03$  U  $g^{-1}$  Hb and  $24.23 \pm 2.89$  U  $g^{-1}$  Hb, respectively,  $P < 0.01$ ). The mean CAT activity levels were also higher in SP than in controls ( $293.67 \pm 41.56$  kg $^{-1}$  Hb and  $241.62 \pm 35.13$  kg $^{-1}$  Hb,  $P < 0.01$ ). The mean MDA levels in SP group and controls were  $4.68 \pm 1.02$  nmol  $ml^{-1}$  and  $2.96 \pm 0.65$  nmol  $ml^{-1}$ , respectively ( $P < 0.01$ ) (Table 1). The only parameter exhibiting the gender difference was SOD, being higher in females than males ( $P < 0.05$ ).

There were no statistically significant differences between hematological parameters of groups. There was significant positive correlation between each of MDA, SOD, and GSH-Px levels and total LSAS scores for the patient group at baseline ( $r = 0.62$ ,  $P < 0.05$ ;  $r = 0.54$ ,  $P < 0.05$ ; and  $r = 0.59$ ,  $P < 0.05$ , respectively). In addition, the duration of illness was correlated with MDA ( $r = 0.53$ ,  $P < 0.05$ ), SOD ( $r = 0.74$ ,  $P < 0.01$ ) and CAT ( $r = 0.55$ ,  $P < 0.05$ ) levels for the patient group. There was no correlation between all the parameters studied and age or weight.

Table 2 demonstrates the results of MDA, SOD, GSH-Px levels, and CAT levels in patients before and after treatment with citalopram. Antioxidant enzymes and

**Table 1** Antioxidant enzyme and MDA levels in the groups at baseline

	SOD (U g <sup>-1</sup> Hb)	GSH-Px (U g <sup>-1</sup> Hb)	CAT (kg <sup>-1</sup> Hb)	MDA (nmol ml <sup>-1</sup> )
SP group (n = 39)	1198.23 ± 188.45	29.78 ± 4.03	293.67 ± 41.56	4.68 ± 1.02
Control group (n = 39)	997.11 ± 112.09	24.23 ± 2.89	241.62 ± 35.13	2.96 ± 0.65
Statistic values	t = 3.24, P < 0.05	t = 8.64, P < 0.01	t = 9.18, P < 0.01	t = 8.08, P < 0.01

**Table 2** Antioxidant enzyme and MDA levels in the patient group before and after treatment

Groups	SOD (U g <sup>-1</sup> Hb)	GSH-Px (U g <sup>-1</sup> Hb)	CAT (kg <sup>-1</sup> Hb)	MDA (nmol ml <sup>-1</sup> )
Pretreatment (n = 39)	1198.23 ± 188.45	29.78 ± 4.03	293.67 ± 41.56	4.68 ± 1.02
Posttreatment (n = 36)	1083.21 ± 92.14	25.93 ± 3.45	246.13 ± 38.41	3.16 ± 0.78
Statistic values	t = 3.34, P < 0.05	t = 4.27, P < 0.05	t = 9.46 P < 0.01	t = 3.68, P < 0.05

MDA levels significantly lowered throughout the treatment. Significant and positive correlations were observed between decrease in the total LSAS scores, and SOD or CAT levels ( $r = 0.55, P < 0.05$ ;  $r = 0.61, P < 0.05$ , respectively). Citalopram dosing was correlated with the reductions in SOD ( $r = 0.59, P < 0.05$ ) and CAT ( $r = 0.60, P < 0.05$ ) levels.

All but three patients completed the study. One patient withdrew from the study because of a medical condition and prematurely discontinued the treatment. The remaining two were discontinued between weeks 2 and 3 owing to symptom deterioration.

## Discussion

The present study confirmed that citalopram could effectively reduce the symptoms of SP (Van der Linden et al. 2000; Bouwer and Stein 1998), and that SP might be associated with oxidative stress (Atmaca et al. 2002, in press). Our results revealed that patients with SP had significantly higher antioxidant enzymes and MDA levels compared to those of controls. Moreover, citalopram was well tolerated and limited drop-outs because of adverse events were observed. There is no placebo-controlled study evaluating the efficacy of citalopram in SP in contrast to other SSRIs. Fluvoxamine was the first SSRI shown to be superior to placebo in the treatment of SP, in a parallel, double-blind, 12-week study involving 30 patients (Van Vliet et al. 1994).

The brain is prone to free radical damage due to its oxygen expenditure totalling nearly 20% of the body's use. Furthermore, the brain consists of oxyradical sensitive polyunsaturated fatty acids and is relatively poor in terms of antioxidants (Mahadik and Mukherjee 1996). Thus, neurons and glial cells seem to be more vulnerable to oxidative stress than their actions on other cell types and cellular structures (Mahadik and Mukherjee 1996). The hypothesis that oxidative stress plays an important role in schizophrenia as well as neurodegenerative disorders remains speculative, and there have been no detailed studies to test this hypothesis. It is suggested that increased production of FRs and/or decreased

detoxification ability of CNS cells might cause increased oxidative stress in neuronal and glial cells. Oxidative stress has been widely examined in a variety of neuropsychiatric disorders. It has been reported that the most important source of FRs is glial cells and FRs produced by these cells are associated with neuropsychiatric disorders such as Sydenham Chorea and Parkinson disease etc. (Lohr 1991). Herken et al. (2001) reported that oxidative stress might have a pathophysiological role in all subtypes of schizophrenia. We have previously shown significant differences between lipid peroxidation product (MDA) and antioxidant enzymes (SOD and GSH-Px) activity levels in patients with schizophrenia and bipolar disorder compared to controls (Kuloglu et al. 2002b). In another study, it was suggested that patients with major depression, especially melancholic, were associated with elevated antioxidant enzyme levels and lipid peroxidation (Bilici et al. 2001). Controlled studies reveal elevated MAO activity in patients with major depression (Pandey et al. 1992). Therefore, this relationship may account for the efficacy of MAO inhibitors in depressive disorders. Monoamine oxidation seems to be associated with production of FRs (Gutteridge 1995). Both irreversible (such as phenelzine; Gellertner et al. 1991; Liebowitz et al. 1992) and reversible (such as moclobemide and brofaromine; Versiani et al. 1992; Fahlen et al. 1995) MAO inhibitors have been shown to be efficacious in patients with SP. On the other hand, it has been reported that increased free radical production may cause the destruction of phospholipids and altered viscosity of neuron membranes, and consequently the changes in membrane viscosity may affect serotonergic and catecholaminergic receptor functions (Van der Vliet and Bast 1992). Moreover, MDA has an inhibitor effect on the receptor binding sites of serotonin (Britt et al. 1992). The catecholamines including dopamine and norepinephrine are associated with the oxidative stress, thus conditions causing the increased catecholamine metabolism may increase the radical burden, as observed in SP (Graham 1978). As a result, it is tempting to speculate that these relationships support a possible etiopathogenetic association between oxidative stress and SP.

Another main result of the present study is that citalopram treatment decreased the antioxidant enzymes and MDA levels. In addition, significant and positive correlations were observed between the decrease in total LSAS scores, and SOD or CAT levels. The question whether citalopram exerts a direct effect on oxidative stress and antioxidant enzymes, and MDA levels has arisen. However, the control group should have been treated for this to be determined exactly. Some speculations may be done regarding this issue. It has been reported that antidepressant treatment may suppress immune cells including natural killer cells (Ravindran et al. 1995). Suppression of immune cells by means of the treatment with a SSRI, citalopram, may cause decrease the oxidative stress. Similarly, Bilici et al. (2001) reported that in major depressed patients, subchronic SSRI treatment reduced the antioxidant enzyme and MDA levels. Furthermore, all SSRIs including citalopram inhibit P450 enzymes which contribute to oxidative stress. It may be concluded that citalopram may decrease antioxidant enzyme levels via reducing immune cells and inhibiting the P450 enzyme system. Citalopram is metabolized by CYP2C19 to N-desmethylcitalopram which further interacts with CYP2D6 (Sindrup et al. 1993). It has been reported that citalopram is a weaker inhibitor of CYP2D6 when compared with the other SSRIs (Baumann and Rochat 1995) and drug-drug interactions with citalopram may not be as much of a problem as with other SSRIs. However, it should be noted that N-desmethylcitalopram, a metabolite of citalopram, is 5–10 times stronger than the parent drug at inhibiting CYP2D6 in vitro in human liver microsomes and is almost as potent as fluoxetine at inhibiting 2-hydroxylation of imipramine in vitro in such a model (Crewe et al. 1992; Skjelbo and Broesen 1992). Today, there is a paucity of information available about the significance of inhibition of CYP2D6 in clinical applications. On the other hand, decreases in MDA values may be explained by means of SSRIs' inhibiting effects on iron-dependent lipid peroxidation. Consequently, it may be speculated that antioxidant enzymes and MDA are state markers of SP because values return to normal through treatment. However, this merits further investigations.

The findings of the present study should be considered as preliminary and subject to some limitations. First of all, the sample size was small. Furthermore, no placebo control group was used. Our results need to be confirmed by placebo-controlled studies with a larger number of samples. In conclusion, our results provide encouraging evidence for the role of oxidative stress in the pathogenesis of SP and suggest that subchronic treatment with citalopram may decrease antioxidant enzymes and MDA values, and that they seem to be state markers of SP owing to their return to normal by treatment.

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