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Effects of antidepressant treatment on total antioxidant capacity and free radical levels in patients with major depressive disorder

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ABSTRACT

In this prospective study, we investigated the effects of antidepressant therapy on total antioxidant capacity and free radical levels in patients with major depressive disorder (MDD). We recruited thirty-five first-episode patients who met the criteria of the Fourth Edition of Diagnostic and Statistical Manual of Mental Disorders of MDD and 35 age- and sex-matched healthy controls. Superoxide and hydroxyl radicals were measured to investigate oxidative status and the total radical-trapping antioxidant parameter (TRAP) assay was performed to evaluate antioxidant capacity in healthy controls and in patients before and after receiving a 12-week regimen of sertraline. The severity of depression was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS). Before treatment, the mean HDRS score in patients with MDD was 26.11 $\pm$ 4.93. Of the 35 patients with MDD, 19 (54.29%) completed the 12-week treatment regimen and all achieved remission. Patients with MDD had significantly lower TRAP baseline values than healthy controls. After adjusting for age, sex, occupation, education and marital status, we found that HDRS score was negatively correlated with TRAP value and level of superoxide radicals. After treatment, the MDD group demonstrated significantly higher TRAP values and significantly lower levels of superoxide and hydroxyl radicals. In conclusion, MDD patients are accompanied by lowered antioxidant capacity than healthy individuals. Antidepressant treatment for 12 weeks results in increased antioxidant capacity and a decrease in circulating free radicals. Key words: major depressive disorder; antidepressant; antioxidant capacity; free radical, total radical-trapping antioxidant parameter (TRAP)

1. Introduction

Oxidative stress can result from increased production of reactive oxygen species (ROS) or decreased antioxidant defense system to repair oxidative damage. Oxidative stress has been shown to play an important role in the pathophysiology of several psychiatric illnesses, such as major depressive disorder (MDD), schizophrenia and bipolar disorder (Maes et al., 2000; Sarandol et al., 2007; Pandya et al., 2013). ROS such as hydroxyl radical and superoxide radical are generated during normal metabolism but can damage cell membranes and lipoproteins via peroxidation when present in excess amounts. In brain, overproduction of ROS has been shown to induce alterations in structural components of the cell membrane resulting in reduced membrane microviscosity as well as neurotransmitter dysfunction (Gutteridge, 1993).

Although there is a general consensus that MDD is associated with oxidative stress, not all studies support the association. Several studies have reported that patients with major depression have increased levels of lipid peroxidation products, such as malondialdehyde (Bilici et al., 2001; Sarandol et al., 2007) and 4-hydroxy-2-nonenal (Selley, 2004) and increased total antioxidant capacity (Bilici et al., 2001). Cumurcu et al. (2009) however, reported decreased total antioxidant capacity in patients with MDD (Cumurcu et al., 2009) and other researchers have reported no significant differences in antioxidant capacity between patients and controls (Sofic et al., 2002; Galecki et al., 2009). Results from a

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postmortem study revealed that oxidative stress plays an important role in the pathophysiology of MDD (Michel et al., 2007). In another post-mortem study, Gawryluk et al. (2011) found that the levels of glutathione, the main antioxidant in brain, were significantly lower than normal in the prefrontal cortex from patients with MDD, bipolar disorder, and schizophrenia, indicating that patients with psychiatric disorders are more susceptible to oxidative stress. Results from two meta-analyses pooling data from studies with different oxidative stress markers suggest that oxidative stress is increased (Palta et al., 2014; Black et al., 2015) and antioxidant defenses are decreased in patients with depression (Palta et al., 2014).

Although a number of studies have investigated the association between MDD and oxidative stress/antioxidants, few studies have focused on the effects of antidepressant drugs on antioxidant capacity and free radical levels in patients with MDD. Antidepressant drugs have been shown to reduce oxidative stress and improve antioxidant status (Bilici et al., 2001; Khanzode et al., 2003; Cumurcu et al., 2009). Their effects are partly related to the inflammation (Rawdin et al., 2013) or immune systems (Ravindran et al., 1995). However, other studies have reported that antidepressant medications do not result in lower levels of oxidative stress (Sarandol et al., 2007; Galecki et al., 2009; Chung et al., 2013).

The total radical-trapping antioxidant parameter (TRAP) assay, developed by Wayner et al. (1985), is the most widely used method for evaluating plasma antioxidant capacity and may represent a more reliable estimation of serum antioxidant capacity than the measurement of each antioxidant (Ghiselli et al., 1995; Ceriello et al., 1997). Plasma antioxidant capacity is the result of the interaction of many different compounds and systemic metabolic interactions which may include antioxidants not yet recognized or not easily measured. Therefore TRAP measurement can provide information on an individual's overall antioxidant status (Ghiselli et al., 1995; Tsai et al., 2000; Erel, 2004). TRAP levels have been shown to be decreased in patients with diabetes, chronic hepatitis C, and systemic inflammation (Ceriello et al., 1997; Tsai et al., 2000; Venturini et al., 2010). Whether TRAP levels are lower in patients with MDD has yet to be investigated.

The purpose of our study was to evaluate TRAP, superoxide, and hydroxyl radical levels in patients with first-episode MDD and to investigate their changes after treatment with sertraline.

2. Materials and methods

2.1. Study subjects

Participants ($n=35$) who met the DSM-IV diagnostic criteria for first-episode MDD were recruited from the psychiatric outpatient clinic at the Chung Shan Medical University Hospital from January 2009 to December 2009. Diagnosis was reviewed by the chart record and the patient was interviewed by a board certified psychiatrist using Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Patients ranged in age from 20 to 55 years (mean, 39.14 ± 10.23 years) and comprised 13 men and 22 women. The mean age of onset was 38.1 ± 10.1 years. All participants were required to receive sertraline for 12 weeks.

Thirty-five age- and sex- matched control subjects (11 men, 24 women, mean age, 39.37 ± 8.5 years) were recruited from the health screening clinic at the same hospital. All subjects had no history of chronic medical illness, no indication of acute infection and none of them were pregnant. Rates of employment ($\chi^2=8.1$, df$=1$, $p=0.004$) and education levels (14.94 years, $p=0.001$) were significantly higher among controls than among patients with MDD. Control subjects were interviewed using MINI and none had a history of major psychiatric disorders. In addition, all patients and controls were non-smokers and none of them were taking psychotropic agents. This study was approved by the Institutional Review Board of the Chung Shan Medical University Hospital and was conducted in accordance with the Declaration of Helsinki.

Severity of depression was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Patients with new-onset MDD were required to have an HDRS score of at least 18 at baseline and to be antidepressant-free for at least 4 weeks prior to the study. Patients with an Axis I disorder other than MDD or with an Axis II disorder were excluded. Patients with a history of major health problems (cardiovascular disease, endocrine disorders, metabolic illnesses or stroke) were also excluded. After explaining the purpose of this study and obtaining written informed consent, the following data were collected: age, gender, employment status, level of education, marital status, and onset age.

2.2. Procedures

Blood (10 mL) was withdrawn from a vein in the antecubital fossa in a fasting state to measure free radicals and TRAP. For MDD patients, HDRS, free radicals and TRAP were measured at baseline and after 12 weeks of treatment with sertraline. The initial treatment dose of sertraline was 25 mg/day, but could be increased to 100 mg/day depending on the clinical condition of the patient. The severity of depression at baseline in patients with MDD was classified as mild (HDRS: 15–18, $n=2$), moderate (HDRS: 19–22, $n=11$), or severe (HDRS: ≥ 23, $n=22$). Response to sertraline was defined as a $\geqq$50% decrease in HDRS score compared to the baseline level, and remission was defined as an HDRS score $\leqq$7 after treatment.

2.3. Laboratory assessments

Unlike ordinary molecules, free radicals are highly reactive and cannot be easily isolated or purified, making them difficult to analyze. The method of ultraweak chemiluminescence offers such an advantage that it is very sensitive in detecting the presence of highly reactive radicals (Vladimirov and Proskurnina, 2009).

Superoxide generation was carried out in a reaction mixture (2.1 mL) comprising 1.0 mL of phosphate-buffered saline (pH 7.4), 0.05 mL of 1.0 M arginine, 0.05 mL of 1.4 *i*M methylglyoxal, and 1.0 mL of 2.0 mM lucigenin. After gently mixing the reagents, the quartz round-bottomed cuvette containing the reaction mixture was put into the black-box unit of the ultraweak chemiluminescence analyzer. The ultraweak photon was measured using a BJL-ultraweak chemiluminescence analyzer with a high-sensitivity detector (3.3×10^{-15} W/cm^2.count) (Jye Horn Co.,Taipei, Taiwan) as reported previously (Park et al., 2003).

The hydroxyl radical generating system used in this study was based on the Fenton reaction ($Fe^{2+} + H_2O_2$). The reaction mixture (2.75 mL) comprised the following sequentially added reagents: 0.05 mL of 10 mM EDTA, 1.0 mL of 3 μM IBG [dissolved in phosphate-buffered saline (PBS), pH 7.4], 1.6 mL of 3% H_2O_2, and 0.1 mL of 1.0 mM $FeSO_4$. After gently mixing the reagents, the quartz round-bottomed cuvette containing the reaction mixture was put into the black-box unit of the ultraweak chemiluminescence analyzer (Tsai et al., 2000). Measurement of the ultraweak chemiluminescence photon was analogus to that of the superoxide-generating system.

TRAP was measured by chemiluminescence as described by Tsai et al. with slight modification (Tsai et al., 2000). Briefly, hydrosoluble and/or liposoluble plasma antioxidants were detected by measuring the chemiluminescence inhibition time induced by 2,2-azobis (2-amidinopropane) hypochloride (ABAP). ABAP rapidly

generates peroxyl radicals via interaction with carbon-centered radicals and molecular oxygen. These free radicals then react with luminol (which act as an amplifier), producing chemiluminescence. The addition of plasma reduces the chemiluminescence at baseline levels for a period (induction time) proportional to the concentration of plasma antioxidants (TRAP) until free radicals are regenerated, returning to initial levels of chemiluminescence (Ghiselli et al., 1995). The system was calibrated with the vitamin E analog Trolox, and the values of TRAP were expressed in mM of Trolox.

2.4. Statistical analysis

The Shapiro-Wilk test was used to test for the normality of the data. Continuous variables in the two groups were compared using student's *t*-test. Because of skewness in distribution of variance, superoxide and hydroxyl radicals were corrected by natural logarithmic transformation. Categorical variables were analyzed using the chi-square test or Fisher's exact test. The paired *t*-test was used to compare pre- and post-treatment values in the MDD group. We also used G*Power 3.1 to calculate the effect size of treatment. A generalized linear model was applied to test the relation between HDRS score and free radicals or TRAP level after adjusting for age, sex, marital status, employment status and education level. All statistical tests performed were two-tailed. The significance level was set at 0.05. All statistical analyses were performed with the statistical package SPSS (Version 17, SPSS Inc., Chicago, IL, USA).

3. Results

Demographic characteristics, baseline clinical findings and oxidative–antioxidative parameters in both groups are shown in Table 1. There were no significant differences in age, gender or marital status between patients and controls. Mean HDRS score at baseline in patients with MDD ($n=35$) was 26.11 ± 4.93. During the 12-week treatment period, 5 patients discontinued treatment because of side effects and 11 patients refused post-treatment blood draw. Data from these patients were excluded from the final analysis. Therefore, of the 35 patients enrolled, 19 (54.29%) completed the 12-week treatment regimen and all achieved complete remission. Patients with MDD had significantly lower TRAP values at baseline than healthy controls ($p=0.011$). There were no significant differences in baseline levels of superoxide and hydroxyl radicals between patients with MDD and control subjects (Table 1). After adjusting for age, sex, education, employment and marital status, female gender was independently associated with higher HDRS score ($p=0.005$). We also found that HDRS score was inversely correlated with TRAP as well as with level of superoxide radical ($p=0.033$ and $p=0.01$, respectively) (Table 2).

At the end of the 12-week treatment regimen, TRAP values were significantly higher ($p<0.001$, effect size 1.58) and the levels of superoxide radical and hydroxyl radical were significantly lower than baseline values ($p<0.001$, effect size 1.22; $p<0.001$, effect size 1.46, respectively) (Table 3, Figs. 1 and 2). In addition, HDRS subscores (depressive mood and anhedonia) and total HDRS scores were significantly lower than baseline values ($p<0.001$) (Table 3). Because of the high dropout rate (45.71%) and in order to reduce type I error, we included all patients regardless of subsequent withdrawal from treatment or deviation from the protocol in an intention-to-treat analysis. Baseline observational data from patients who withdrew from the study were carried forward. Results of the analysis showed that differences in pre- and post-treatment HDRS scores, TRAP values, levels of superoxide and hydroxyl radicals remained significant (effect sizes: 0.98, 0.75, 0.66, 0.65).

Table 1
Demographic characteristics and oxidative–antioxidative parameters in patients with major depressive disorder (MDD) and in healthy controls.

	Control group ($n=35$) Mean ± SD or *n* (%)	MDD group ($n=35$) Mean ± SD or *n* (%)	*p* value
Age (year)	39.37 ± 8.50	39.14 ± 10.23	0.92
Sex			
Male	11 (31.43%)	13 (37.14%)	0.62
Female	24 (68.57%)	22 (62.86%)	
Education (year)	14.94 ± 3.39	12.06 ± 3.83	0.001*
Employment status			
Unemployed	3 (8.57%)	13 (37.14%)	0.004*
Employed	32 (91.43%)	22 (62.86%)	
Marriage			
Single	11 (31.43%)	14 (40.00%)	0.58
Married	23 (65.71%)	19 (54.29%)	
Widowed	1 (2.86%)	2 (5.71%)	
Age of onset (year)	–	38.1 ± 10.1	
HDRS score	–	26.11 ± 4.93	
TRAP (μM Trolox)	569 ± 114	500 ± 109	0.011*
Superoxide radicals [a]	10.91 ± 1.17	11.15 ± 1.11	0.38
Hydroxyl radicals [a]	11.37 ± 1.55	11.80 ± 1.61	0.26

HDRS: Hamilton depression rating scale.
TRAP: Total radical-trapping antioxidant parameter.
[a] Natural log-transformation.
* $p<0.05$.

Table 2
Generalized linear model to identify independent clinical variables associated with major depression.

	HDRS score at baseline		
	B	95% Wald CI	*p* value
Age	−0.092	−0.302 ~ 0.117	0.387
Female/male	4.032	1.191 ~ 6.873	0.005*
Education	−0.277	−0.699 ~ 0.145	0.199
Employment status (unemployed/employed)	1.109	−1.947 ~ 4.166	0.477
Marital status (unmarried/married)	3.061	−0.878 ~ 1.340	0.753
TRAP	−0.02	−0.038 ~ −0.002	0.033*
Superoxide radicals [a]	−2.047	−3.615 ~ −0.48	0.01*
Hydroxyl radicals [a]	0.136	−0.821 ~ 1.093	0.781

HDRS: Hamilton depression rating scale.
TRAP: Total radical-trapping antioxidant parameter.
[a] Natural log-transformation.
* $p<0.05$.

4. Discussion

To the best of our knowledge, this is the first study in Taiwan to investigate the effect antidepressant agents have on TRAP and free radical levels in patients with major depressive disorder. We found

Table 3
Depressive scores and oxidative–antioxidative parameters in patients with MDD before and after 12 weeks of antidepressant treatment.

	Before treatment ($n=19$) Mean ± SD or n (%)	After treatment ($n=19$) Mean ± SD or n (%)	*Effect size*	p value
HDRS score	25.21 ± 4.85	4.11 ± 2.31	4.5	< 0.001
Depressive score in HDRS	3.16 ± 0.60	0.79 ± 1.08	2.23	< 0.001
Anhedonia score in HDRS	2.42 ± 0.69	0.58 ± 0.69	1.82	< 0.001
Suicide score in MINI	4.79 ± 7.19	0.37 ± 0.96	0.65	0.011
Sertraline dose(mg/day)	–	66.07 ± 23.22		
TRAP (μM Trolox)	473 ± 110	635 ± 88	1.58	< 0.001
Superoxide radicals[a]	11.33 ± 1.17	9.84 ± 1.16	1.22	< 0.001
Hydroxyl radicals[a]	11.93 ± 1.71	10.26 ± 1.67	1.46	< 0.001

HDRS: Hamilton depression rating scale.
MINI: Mini-international neuropsychiatric interview.
TRAP: Total radical-trapping antioxidant parameter.
[a] Natural log-transformation.

that baseline plasma TRAP values were significantly lower in patients with MDD than in healthy controls and that baseline HDRS depression scores were inversely correlated with baseline TRAP values and levels of superoxide radical. After taking sertraline for 12 weeks, patients showed a significant increase in plasma TRAP and a significant decrease in superoxide and hydroxyl radical levels.

In our study, total antioxidant capacity at baseline was significantly lower in patients with MDD than in healthy controls. This finding is consistent with a growing body of evidence that oxidative stress plays a role in the pathophysiology of major depressive disorder (Michel et al., 2007). Oxidative stress is caused by the imbalance between generation of reactive oxygen species and an organism's antioxidant defenses. Hydroxyl radical, superoxide radical, and other reactive oxygen species can destroy the polyunsaturated fatty acids, then causes lipid peroxidation of cell membrane. The integrity and fluidity of the cell membrane are compromised and eventually leads to destruction of the cell itself. However it is still not clear whether oxidative stress is primarily or secondarily involved in the pathophysiology of major depressive disorder. Previous findings of altered antioxidant enzyme levels in the blood of patients with MDD are conflicting, with some studies showing evidence of increased levels of superoxide dismutase (SOD) (Selley, 2004; Sarandol et al., 2007), glutathione peroxidase and gluthatione reductase (Bilici et al., 2001), and others showing decreased SOD levels (Herken et al., 2007). Malondialdehyde (MDA), an end-product of lipid peroxidation, is a widely used indicator of oxidative stress. Galecki et al. (2009) found that the concentration of MDA in erythrocytes was significantly higher in patients with depression than in healthy controls. Bilici et al. and Khanzode et al. also found that MDA levels were significantly higher in patients with MDD (Bilici et al., 2001; Khanzode et al., 2003). In contrast, Sofic et al. reported no significant difference in serum antioxidant capacity between patients who had yet to receive antidepressant treatment and healthy controls (Sofic et al., 2002).

After adjusting for other covariates, we found that female gender was independently associated with greater severity of depression. This finding is consistent with findings reported in previous studies (Kornstein et al., 1995; Kornstein et al., 2000). We also found that HDRS score was inversely correlated with TRAP and superoxide radical level, indicating that total antioxidant capacity and superoxide radical level are lower in patients with severe depression than in those with milder degrees of depression. This result might be attributed to the fact that 22 of the 35 patients (62.9%) in our study were severely depressed (HDRS≧23). TRAP may provide more biologically relevant information than that obtained from measuring concentrations of a single antioxidant (Tsai et al., 2000; Erel, 2004). TRAP can be regarded as a type of acute phase response, characterized by a change in plasma level during acute inflammation. Maes et al. proposed that activation of inflammatory, oxidative and nitrosative stress pathways is a key pathophysiological factor in major depression (Maes et al., 2011). These responses may either participate in initiating or sustaining the inflammatory process, or may only have adaptive roles. This implies that MDD patients tend to have increased levels of oxidative stress and inflammation, which can be improved after antidepressant treatment. However, the contrary could also be true. Rawdin et al. found that F2- isoprostane (F2-IsoP, a marker of oxidative stress) concentrations were positively correlated with Interleukin-6 (IL-6, a marker of inflammation) concentrations and negatively correlated with IL-10 concentrations in unmedicated MDD patients. After 8 weeks of treatment with sertraline, F2-IsoP was no longer significantly correlated with IL-6 or IL-10 (Rawdin et al., 2013).

In our study, all of the patients who completed the 12-week regimen of sertraline achieved complete remission. In addition, free radical levels were significantly lower and total antioxidant capacity was significantly higher in patients after treatment (Figs. 1–3). These findings are consistent with previous studies, which found that antidepressant agents resulted in reduced oxidative stress and improved antioxidant status (Bilici et al., 2001; Khanzode et al., 2003; Cumurcu et al., 2009). Herken et al. reported that SOD activity increased markedly in patients with MDD after 8 weeks of antidepressant treatment (Herken et al., 2007). Michalakeas et al. found that sertraline treatment for 3 months resulted in a reduction in depressive symptoms and a reduction in

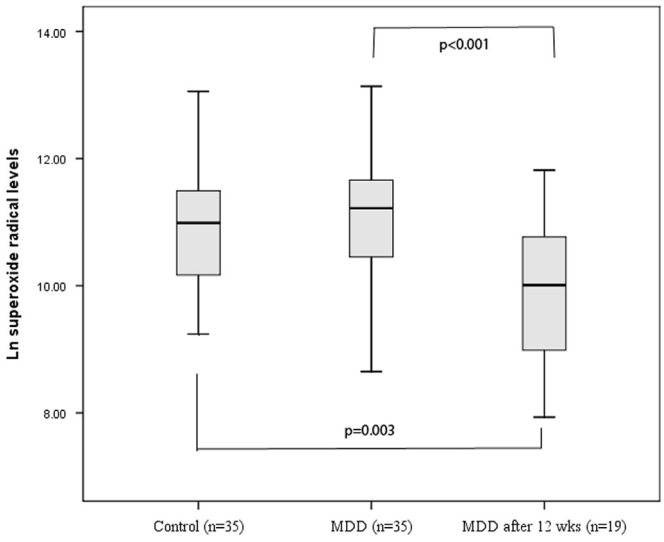

Fig. 1. Superoxide radical levels in the controls and MDD patients.

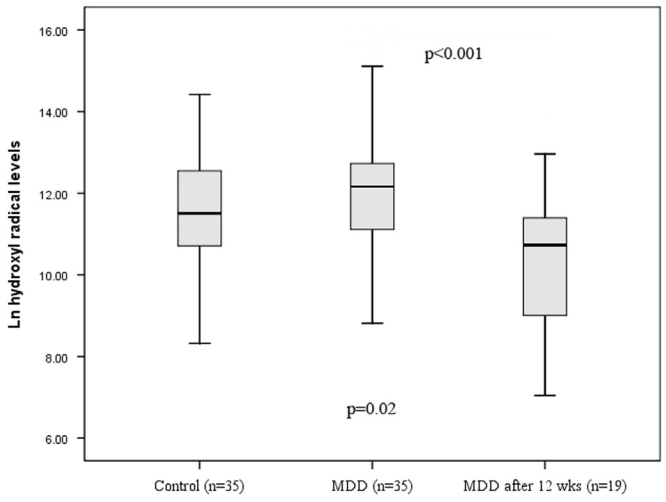

Fig. 2. Hydroxyl radical levels in the controls and MDD patients.

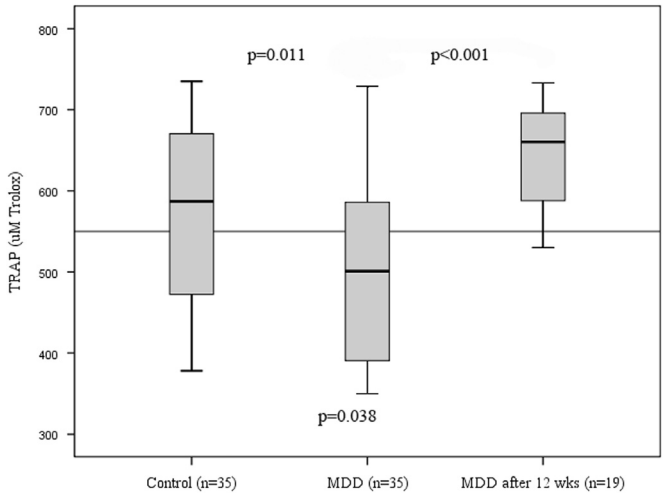

Fig. 3. TRAP levels in the controls and MDD patients.

MDA levels in depressed patients with congestive heart failure (Michalakeas et al., 2011). It is possible that recovery from a major depressive episode is associated with antidepressant drug-induced normalization of antioxidant potential. Several preclinical studies have shown that antidepressant agents have some antioxidant effects (Behr et al., 2012). Contrary to our findings, Sarandol et al. found that short-term (6 weeks) use of antidepressant agents did not seem to have an effect on the oxidative–antioxidative system (Sarandol et al., 2007). Aside from treatment duration, dosage may also influence the oxidative–antioxidative system. For example, Galecki et al. found no evidence of significant improvement in SOD or CAT activity after three months of fluoxetine therapy (20 mg/day), even in patients who achieved complete remission (Galecki et al., 2009). These results suggest that alternative mechanisms, beyond oxidative stress, may be involved in the development of depression and subsequent responses to treatment.

There are several limitations in this study. First, all of the patients who completed the 12-week sertraline treatment achieved remission. This might be because that our patients never had MDD before and 16 subjects (45.71%) discontinued treatment or refused blood draw. Those highly-motivated patients who continued on treatment often reported a better outcome. However, it is not clear whether sertraline itself results in increased antioxidant capacity or whether oxidative stress is one of many other parameters that are affected by sertraline. Second, the sample size was small. Nonetheless, we were still able to test the hypothesis that a selective serotonin re-uptake inhibitor can affect the oxidative–antioxidative system. Third, we only measured TRAP instead of individual antioxidant enzymes such as SOD or CAT. However, measurement of TRAP has been demonstrated to be a more reliable method of estimating antioxidant capacity than measuring antioxidant enzymes individually. Fourth, several factors that might affect oxidative stress and/or antioxidant status were not analyzed, such as body mass index, alcohol use, physical activity, diet, and vitamin supplement use. Nevertheless, after adjustment, HDRS score was still inversely correlated with levels of TRAP and superoxide radicals.

In summary, the results of our study support the hypothesis that MDD is associated with oxidative stress, which may occur early in the course of the illness. Antidepressant treatment may reduce oxidative stress and increase antioxidant capacity. Whether oxidative stress is primarily or secondarily involved in the pathophysiology of MDD needs further investigation.

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