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Increased activities of both superoxide dismutase and catalase were indicators of acute depressive episodes in patients with major depressive disorder

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ABSTRACT

Oxidative stress may play an important role in the pathophysiology of major depressive disorder (MDD). The aim of this study was to investigate the serum levels of oxidative stress biomarkers and S100B in patients with MDD in an acute phase, and evaluate the changes in superoxide dismutase (SOD), protein carbonyl content (PCC), glutathione peroxidase (GPX), 8-hydroxy 2'-deoxyguanosine after treatment (8-OHdG), catalase (CAT), thiobarbituric acid reactive substances (TBARS) and S100B. We consecutively enrolled 21 MDD inpatients in an acute phase and 40 healthy subjects. Serum oxidative stress markers were measured with assay kits. Serum SOD and CAT activities in MDD patients in an acute phase were significantly higher than those of healthy subjects, and serum PCC levels were significantly lower. The HAM-D scores had a significantly positive association with S100B levels. Eighteen depressed patients were followed up, and there was no significant difference among all of the markers after treatment. In conclusion, our results suggest that increased activities of both SOD and CAT might be indicators of acute depressive episodes in MDD patients.

1. Introduction

The pathophysiology of major depressive disorder (MDD) is complex and in need of clarification. There is a growing evidence suggesting that the imbalance between the antioxidant system and oxidative stress might be associated with MDD (Maes et al., 2011; Chung et al., 2013; Kokacya et al., 2014; Xu et al., 2014; Black et al., 2015). Increased oxidative stress might play an important role in the pathogenesis of MDD (Szuster-Ciesielska et al., 2008; Chung et al., 2013; Moylan et al., 2014; Ormonde do Carmo et al., 2015). Reactive oxygen species (ROS) are produced both during the mitochondrial electron transport of aerobic respiration, and through normal physiologic processes. Excessive ROS may lead to cellular injuries, lipid peroxidation, harmful autoimmune responses, DNA damage, apoptosis and protein carbonylation (Berg et al., 2004; Filomeni and Ciriolo, 2006; Maes et al., 2013). Several antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione reductase (GSR), can remove free radicals and prevent oxidative damage to brain cells (Chelikani et al., 2004; Dringen et al., 2005; Lushchak, 2014). In addition, lower gene expressions of SOD1, SOD2, CAT and GPX1 were noted in patients with MDD (Szebeni et al., 2014).

The data on oxidative stress markers, including CAT, SOD, and GPX, in patients with MDD are controversial (Sarandol et al., 2007; Szuster-Ciesielska et al., 2008; Maes et al., 2011; Stefanescu and Ciobica, 2012). SOD, GPX and CAT are important antioxidant enzymes that metabolize ROS into less toxic molecules and counter oxidative stress to prevent oxidative damage (Winterbourn, 1993; Halliwell, 2007; Sabens Liedhegner et al., 2012). SOD catalyzes the conversion of superoxide anions (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen (O_2). Previous studies reported SOD activities were decreased or increased in depressed patients (Sarandol et al., 2007; Szuster-Ciesielska et al., 2008; Stefanescu and Ciobica, 2012). Furthermore, GPX can reduce free hydrogen peroxide to water (Bhabak and Mugesh, 2010). GPX activities were decreased in patients with MDD in some reports (Kodydkova et al., 2009; Maes et al., 2011; Stefanescu and Ciobica, 2012; Rybka et al., 2013), and revealed no significant changes compared to healthy controls in other reports (Bilici et al., 2001; Kotan et al., 2011; Lukic et al., 2014). In addition, CAT catalyzes H_2O_2 into water and oxygen, which has been reported to be increased in depressed patients (Szuster-Ciesielska et al., 2008; Galecki et al., 2009; Xu et al., 2014).

It is well known that oxidative stress is associated with DNA damage and lipid peroxidation, and these were also found in

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patients with MDD (Moylan et al., 2014; Black et al., 2015). Lipid peroxidation produces malondialdehyde (MDA). The thiobarbituric acid reactive substances (TBARS) assay was used to measure MDA. In addition, F2-isoprostanes were used to reflect lipid peroxidation (Niki, 2014). Biomarkers of lipid peroxidation (MDA, TBARS or F2-isoprostanes) were increased in depressed patients (Bilici et al., 2001; Galecki et al., 2007; Yager et al., 2010; Chung et al., 2013; Rybka et al., 2013), but TBARS levels showed a difference from those in control subjects (Magalhaes et al., 2012). In addition, 8-hydroxy-2-deoxyguanosine (8-OHdG), an oxidized guanosine of DNA, is the most frequently measured type of DNA damage. Levels of 8-OHdG were increased in patients with MDD compared to healthy groups (Forlenza and Miller, 2006; Maes et al., 2009). Free radicals also react with protein and cause protein damage, which is measured by protein carbonyl content (PCC). But levels of PCC in patients with MDD showed no difference compared to healthy controls (Magalhaes et al., 2012).

S100B is a protein biomarker of brain injury and reflects severity of central nervous system injury (Bloomfield et al., 2007). S100B protein was associated with depressive symptoms in patients with hemodialysis (Kim et al., 2012). In addition, S100B levels were increased in patients with MDD compared to healthy controls (Grabe et al., 2001). However, one study reported that S100B levels did not differ between patients with MDD and normal controls (Jang et al., 2008).

The aims of this study were to investigate the serum levels/activities of oxidative stress biomarkers, including SOD, GPX, CAT, TBARS, PCC and 8-OHdG, in MDD patients in an acute phase compared to healthy subjects. In addition, we assessed the relationship between these markers and the 17-item Hamilton Depression Rating Scale (HAM-D) (Akdemir et al., 2001) in MDD patients in an acute phase. We also investigated the changes in these markers in depressed patients after treatment. Furthermore, oxidative stress might lead to brain damage. Therefore, we assessed S100B as a way of knowing the relationship between oxidative stress and brain damage in MDD patients in an acute phase.

2. Methods

2.1. Patients and study design

All MDD patients in an acute depressive episode were consecutively recruited from the psychiatry inpatient ward of Kaohsiung Chang Gung Memorial Hospital. Diagnoses of MDD were assessed by psychiatrists using Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria. All patients were hospitalized. The 17-item Hamilton Depression Rating Scale (HAM-D) (Akdemir et al., 2001) was used to assess the severity of depressive symptoms, which were evaluated at baseline and at the endpoint after treatment. The HAM-D was used by two board-certified psychiatrists. Data including sex, age, body mass index (BMI: kg/m^2), serum SOD, GPX, CAT, 8-OHdG, TBARS, PCC and S100B levels or activities were collected. The MDD patients were above age 18 and below age 65. They were not heavy smokers and had no substance dependence. MDD patients with a history of liver disease, renal disease, and unstable physical problems were excluded.

The healthy controls included 40 individuals who were recruited at Kaohsiung Chang Gung Memorial Hospital. Those with a history of mental disorders and medical disease were excluded. They were not regular drinkers and did not take psychotropic drugs. They were free of medication.

This study was performed at Kaohsiung Chang Gung Memorial Hospital from November 2013 to October 2014. It was approved by the Institutional Review Board of the hospital. All participants gave written consent after a full explanation of the study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Laboratory data

Venous blood samples were collected by venipuncture after 8-h fasting. The serum samples were immediately separated by centrifugation at 3000*g* for 10 min and were stored at −80 °C for further analysis. Commercially available ELISA (enzyme-linked immunosorbent assay) test kits were used to measure SOD, CAT, GPX, 8-OHdG, TBARS, and PCC (Cayman Chemical Company, Ann Arbor, USA). S100B was also measured using an ELISA kit (Merck Millipore, Darmstadt, Germany). All analyses were performed at the same laboratory and according to the manufacturer's protocol.

2.3. Statistical analysis

SPSS version 18.0 for Windows software was used for the statistical analysis of the data. All results were expressed as the means ± standard deviation (SD). Data were examined for normality using the Kolmogorov–Smirnov test. Only TBARS data achieved normality. The SOD, GPX, CAT, 8-OHdG, PCC and S100B data did not follow a normal distribution. Changes in the TBARS levels of the MDD patients after treatment were analyzed by paired *t*-test. Correlations between TBARS levels and HAM-D scores were performed using Pearson's correlation coefficient. The non-parametric tests used for analysis were the Mann-Whitney *U* test, Wilcoxon Rank Signed test and Spearman correlation. A *p* value of less than 0.05 was used to indicate statistical significance.

3. Results

We consecutively enrolled 21 MDD inpatients (17 women and 4 men) in an acute phase and 40 healthy subjects (30 women and 10 men). The serum SOD and CAT activities ($p=0.021$, $p=0.008$, respectively) of the MDD patients in an acute phase were significantly higher than those of the healthy subjects, and serum PCC levels were significantly lower than those of the healthy subjects ($p<0.001$). Serum levels/activities of GPX, TBARS, 8-OHdG and S100B did not differ significantly between the 2 groups ($p>0.05$) (Table 1). The HAM-D scores of the MDD patients were positively correlated with serum levels of S100B ($r=0.569$, $p=0.007$, Table 2.1), but the serum SOD, GPX, CAT, TBARS, PCC and 8-OHdG levels or activities showed no significant association with HAM-D scores ($p>0.05$) (Table 2.1). In addition, serum CAT activities had a

Table 1
Demographic characteristics and oxidative-stress markers of depressed patients in an acute phase and healthy controls.

Variable	Patients ($n=21$)	Controls ($n=40$)	Total ($n=61$)
Age, years	49.6 ± 7.0*	33.0 ± 5.7	38.7 ± 10.0
BMI, kg/m^2	24.3 ± 6.2	22.2 ± 2.8	22.9 ± 4.4
SOD, U/ml	2.2 ± 0.6	1.9 ± 0.6*	2.0 ± 0.6
CAT, nmol/min/ml	108.2 ± 91.7	44.3 ± 31.9*	66.3 ± 66.4
GPX, nmol/min/ml	319.0 ± 41.3	309.3 ± 31.5	312.6 ± 35.1
TBARS, umole/L	10.9 ± 2.2	9.5 ± 3.2	10.0 ± 2.9
PCC, nmol/mg	0.7 ± 0.6	1.4 ± 1.0*	1.1 ± 0.9
8-OHdG, pg/ml	9097.9 ± 5811.5	8069.7 ± 4242.1	8423.7 ± 4816.4
S100B, pg/ml	16.6 ± 12.6	15.6 ± 15.1	15.9 ± 14.2

± Values are given as mean ± standard deviation.
Abbreviation: BMI=body mass index; SOD=superoxide dismutase; CAT=catalase; GPX=glutathione peroxidase; TBARS=thiobarbituric acid reactive substances; PCC=protein carbonyl content; 8-OHdG=8-hydroxy 2'-deoxyguanosine
* $p<0.05$.