Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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

Cheng-Chen Chang [a,b,1], Chun-Te Lee [c,d,1], Tsuo-Hung Lan [e,f], Po-Chung Ju [c,d], Yi-Hsien Hsieh [g], Te-Jen Lai [a,c,*]

[a] Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[b] Department of Psychiatry, Changhua Christian Hospital, Changhua, Taiwan
[c] Department of Psychiatry, Chung Shan Medical University Hospital, Taichung, Taiwan
[d] School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[e] School of Medicine, National Yang-Ming University, Taipei, Taiwan
[f] Department of Psychiatry, Taichung Veterans General Hospital, Taichung, Taiwan
[g] Department of Biochemistry, School of Medicine, Chung Shan Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form
15 September 2015
Accepted 3 October 2015

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

* Correspondence to: Department of Psychiatry, Institute of Medicine, Chung Shan Medical University Hospital, No.110, Section 1, Jianguo N. Road, Taichung 402, Taiwan
E-mail addresses: tejenlai@hotmail.com, ltj3123@csmu.edu.tw (T.-J. Lai).
[1] These authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.psychres.2015.10.006
0165-1781/

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

Please cite this article as: Chang, C.-C., et al., Effects of antidepressant treatment on total antioxidant capacity and free radical levels in patients with major depressive disorder. Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.10.006