Psychiatry Research 225 (2015) 305–308

Contents lists available at ScienceDirect

Psychiatry Research

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

Bcl-2 associated with severity of manic symptoms in bipolar patients in a manic phase

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ARTICLE INFO

Article history:
Received 7 July 2014
Received in revised form
18 November 2014
Accepted 14 December 2014
Available online 20 December 2014

Keywords:
Bcl-2
Bipolar
Mania
YMRS

ABSTRACT

B cell lymphoma protein-2 (Bcl-2) may contribute to the pathophysiology of bipolar disorder, and may be involved in the therapeutic action of anti-manic drugs. The aim of this study was to investigate serum levels of Bcl-2 in bipolar patients in a manic phase, and evaluate the Bcl-2 changes after treatment. We consecutively enrolled 23 bipolar inpatients in a manic phase and 40 healthy subjects; 20 bipolar patients were followed up with treatment. Serum Bcl-2 levels were measured with assay kits. All 20 patients were evaluated by examining the correlation between Bcl-2 levels and Young Mania Rating Scale (YMRS) scores, using Spearman's correlation coefficients. The serum Bcl-2 levels in bipolar patients in a manic phase were higher than in healthy subjects, but without a significant difference. The YMRS scores were significantly negatively associated with serum Bcl-2 levels ($p=0.042$). Bcl-2 levels of the 20 bipolar patients were measured at the end of treatment. Using the Wilcoxon Signed Rank test, we found no significant difference in the Bcl-2 levels of bipolar patients after treatment. Our results suggest that Bcl-2 levels might be an indicator of severity of manic symptoms in bipolar patients in a manic phase.
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1. Introduction

The etiology of bipolar disorder remains unclear, but there is increasing evidence suggesting that it is associated with dysregulation of neurotrophic signaling cascades and apoptosis (Friedrich, 2005; Shaltiel et al., 2007; Uribe and Wix, 2012; Fries et al., 2014; Moutsatsou et al., 2014). The dysregulation of neurotrophic signaling cascades may be related to apoptosis and contribute to brain atrophy in bipolar disorder patients (Lyoo et al., 2004; Kim et al., 2010). B cell lymphoma protein-2 (Bcl-2) has been reported to be related to the pathology of bipolar disorder (Shaltiel et al., 2007; Machado-Vieira et al., 2011; Uemura et al., 2011; Soeiro-de-Souza et al., 2013). In addition, mood stabilizers have neuroprotective effects and can influence bcl-2 protein (Chuang, 2005; Wada et al., 2005; Hammonds and Shim, 2009; Soeiro-de-Souza et al., 2012; Leng et al., 2013).

Apoptosis is triggered through extrinsic and intrinsic (mitochondrial) pathways (Schulze-Osthoff et al., 1992; Wang et al., 2006; Uribe and Wix, 2012). Apoptosis pathways are related to many molecules such as Bcl-2, Bcl-2-associated death promoter (BAD), Bcl-2-associated X protein (BAX) caspase-3, caspase-9 and cytochrome c (Le Bras et al., 2006; Belizario et al., 2007; Guo et al., 2010; Grimm, 2012). The anti-apoptotic protein Bcl-2 prevents mitochondrial release of cytochrome c, which leads to apoptosis (Scorrano and Korsmeyer, 2003; Ohkubo et al., 2007). In addition, Bcl-2 may inhibit neuronal apoptosis and has a neuroprotective effect (Chen et al., 1997; Manji et al., 2000; Lei et al., 2012; Wei et al., 2013). Anti-apoptotic protein Bcl-2 may play a role in the pathophysiology of bipolar disorder (Benes et al., 2006; Kim et al., 2010).

Bcl-2 levels are significantly decreased in the prefrontal cortex of bipolar patients compared to healthy controls (Kim et al., 2010). Moutsatsou et al. (2014) reported increased BAX/Bcl-2 ratios in manic and depressed patients with bipolar disorder comparedto healthy controls. In addition, the Bcl-2 gene single nucleotide polymorphism (SNP) rs956572 was reported to be related to abnormal Bcl-2 gene expression in bipolar patients (Machado-Vieira et al., 2011). Our previous data revealed that there were no significant changes in Bcl-2 levels in schizophrenia patients who were in an acute phase and with 4-week treatment (Tsai et al., 2013). However, there is little data on the association between Bcl-2 level changes and manic episodes in bipolar patients.

The aims of this study were to investigate the serum levels of Bcl-2 in bipolar patients in a manic phase, and to determine the relationship between Bcl-2 levels and Young Mania Rating Scale (YMRS) scores in bipolar patients in a manic phase. In addition, we investigated the changes in Bcl-2 levels in patients after treatment. This was the first study to evaluate Bcl-2 serum levels in bipolar disorder patients.

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http://dx.doi.org/10.1016/j.psychres.2014.12.020
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2. Methods

2.1. Patients and study design

All patients with bipolar I disorder in a manic phase were enrolled from the inpatient ward of Kaohsiung Chang Gung Memorial Hospital, and all of them were diagnosed by the same psychiatrist using the Structured Clinical Interview (SCID) and DSM-IV criteria. The YMRS was administered by two board-certified psychiatrists at baseline and at the endpoint of the study to evaluate severity of disease. Data including age, sex, body mass index (BMI: kg/m^2), and serum Bcl-2 levels was collected. All participants were above age 18 and below age 65. They had no history of substance dependence, and underwent chest X-ray, blood pressure, and electrocardiogram (EKG) examinations and routine blood tests. None of them were heavy smokers. If patients with significant physical illnesses or systemic diseases were found, they were excluded.

The control group included 40 healthy subjects who were recruited at Kaohsiung Chang Gung Memorial Hospital. They had no mental disorders and were excluded if they had any severe medical disease. These healthy participants were also free of medication.

The study was performed at Kaohsiung Chang Gung Memorial Hospital from November 2012 to October 2013 and was approved by the Institutional Review Board of the hospital, and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants signed informed consent forms after receiving a full explanation of this study.

2.2. Laboratory data

We collected venous blood samples before breakfast after overnight fasting (fasting for at least 8 h). We immediately separated the serum samples by centrifugation at 3000 *g* for 10 min, and then stored the serum samples at −80 °C for analysis. We used commercially available assay kits to assay serum Bcl-2 protein (Merck KGaA, Darmstadt, Germany). A standard curve must be determined each time the assay was performed. Standards should be assayed in duplicate. We did not dilute serum sample. We added serum samples and each of the bcl-2 standards (in duplicate) by pipetting 50 μl into appropriate wells. The bcl-2 ELISA can distinguish < 1 ng/ml of bcl-2 from zero. The bcl-2 ELISA assay protocol website is http://www.emdmillipore.com/TW/en/product/Bcl-2-ELISA-Kit,EMD_BIO-QIA23?CategoryName=00000012000291170006002 3&CategoryDomainName=Merck-MerckMillipore#anchor_USP.

2.3. Statistical analysis

Our data are expressed as mean ± standard deviation (S.D.). Data were examined for normality using the Kolmogorov–Smirnov test. The changes in serum Bcl-2 levels in bipolar patients after treatment were analyzed with the Wilcoxon Signed Rank test for data that were not normally distributed. Spearman's correlation coefficients were used to evaluate the relationship between YMRS scores and Bcl-2 levels for data that were not normally distributed; a *p* value lower than 0.05 was considered to indicate statistical significance. Statistical analyses were performed with SPSS for Windows, version 18.

3. Results

We consecutively enrolled 23 bipolar inpatients in a manic phase and 40 healthy subjects (20 men and 20 women). Three bipolar patients dropped out of the study, leaving 20 patients (12 men and 8 women) who were followed up. The 20 patients had mean hospitalization durations of 25.8 ± 5.0 days. In addition, all the patients had at least YMRS = 20 at baseline (Table 3). The serum Bcl-2 levels in the bipolar patients (0.65 ± 0.48 ng/ml) in a manic phase were higher than those in the healthy subjects (0.46 ± 0.45 ng/ml), but without a significant difference ($p = 0.471$) (Table 1). The medications the bipolar patients received are shown in Table 2. The YMRS scores were significantly negatively associated with serum Bcl-2 levels ($p = 0.042$, Spearman correlation coefficient = −0.458).

Serum Bcl-2 levels of the 20 bipolar patients were measured at the end of treatment. The levels were higher in patients after treatment than in patients with manic episodes. However, we found no significant difference in Bcl-2 levels in the bipolar patients after treatment, using the Wilcoxon Signed Rank test (baseline: 0.65 ± 0.48 ng/ml; endpoint: 0.84 ± 0.40 ng/ml; $p = 0.126$). In addition, the changes in YMRS scores were not significantly associated with the changes in Bcl-2 levels in bipolar patients who had received treatment ($p = 0.172$); the changes in YMRS scores are shown in Table 3.

Table 1
Demographic characteristics and Bcl-2 levels of patients in a manic phase and healthy controls.

Variable	Patients ($n = 20$)	Controls ($n = 40$)	*p*-Value
Length of illness, years	15.8 ± 11.7		
Age, years	40.8 ± 12.3	30.4 ± 5.0	0.002*
BMI, kg/m^2	22.6 ± 3.3	22.1 ± 3.3	0.556
Gender/female	8 (40%)	20 (50%)	0.468
Bcl-2, ng/ml	0.65 ± 0.48	0.46 ± 0.45	0.471

Plus-minus values are given as mean ± standard deviation. Abbreviation: BMI = body mass index; Bcl-2 = B cell lymphoma protein-2.

* $p < 0.05$.

4. Discussion

The most important finding in our study is that the serum Bcl-2 levels of bipolar patients in a manic phase were significantly negatively associated with YMRS scores.

Bcl-2 might have neuronal anti-apoptotic and neuroprotective effects (Manji et al., 2000; Lei et al., 2012; Wei et al., 2013). Oxidative stress causes brain damage in bipolar patients (Wang et al., 2009); therefore, Bcl-2 levels in bipolar patients in a manic phase might decrease. Our result suggested that Bcl-2 levels might be an indicator of severity of manic symptoms in bipolar patients in a manic phase.

Second, serum Bcl-2 levels were increased in bipolar manic patients who had received treatment. However, no significant difference was noted. There is little data on the association between Bcl-2 level changes and manic phases in bipolar patients after treatment. Previous studies reported that Bcl-2 could be related to apoptosis, which might contribute to the pathology of bipolar disorder (Soeiro-de-Souza et al., 2012, 2013; Moutsatsou et al., 2014). There might be several reasons for elevated Bcl-2 levels. First, Bcl-2 protein has both neuroprotective and anti-apoptotic effects (Adams and Cory, 1998; Sadoul, 1998; Chipuk et al., 2010). Second, there are accumulating reports of an association between mood stabilizers and Bcl-2 (Manji and Chen, 2002; Chuang, 2005; Wada et al., 2005; Keshavarz et al., 2013). Increased Bcl-2 levels were found in the frontal cortex, hippocampus, and striatum of rats with chronic lithium treatment (Manji et al., 1999). Another study reported bcl-2 levels were increased in rat primary astrocyte cells with chronic lithium treatment (Keshavarz et al., 2013). The anti-apoptotic effect of lithium and valproate might be related to Bcl-2 (Song et al., 2012). However, we lacked data in our study on bipolar manic patients treated with lithium or valproate only. In addition, a mice study found Bcl-2 might play a role in affective disorder (Lien et al., 2008). Taken together, evidence points to the important role Bcl-2 protein might play in bipolar disorder. Future studies should investigate the relationship between mood stabilizers and Bcl-2 levels in bipolar patients with a manic episode.

Serum Bcl-2 levels were higher in bipolar patients in a manic phase than in healthy subjects, but the result was without statistical significance. In the literature review, no reports were found that compared the differences in serum Bcl-2 levels in bipolar patients in a manic phase to those in healthy controls. Therefore, our result might be the first peripheral blood data of Bcl-2 levels in bipolar patients in a manic episode. However, Bcl-2 levels were reported to be significantly reduced in the prefrontal cortex of bipolar patients in a postmortem study, compared to

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