Comprehensive Psychiatry 91 (2019) 29–33

Contents lists available at ScienceDirect

Comprehensive Psychiatry

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

Sex-based dimorphisms in expression of BDNF and BACE1 in bipolar patients

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ARTICLE INFO

Keywords:
Bipolar disorder
BDNF
BDNF-AS
BACE1
BACE1-AS

ABSTRACT

Bipolar disorder (BD) is a chronic, serious mental disorder distinguished by repeated episodes of mania and depression. Previous studies have demonstrated dysregulation of a number of transcripts in brain tissue or peripheral blood of BD patients. In the present study, we compared expression of two protein coding genes (*brain-derived neurotrophic factor* (*BDNF*) and *beta-secretase 1* (*BACE1*)) and their natural occurring anti-sense (AS) RNAs (*BDNF-AS* and *BACE1-AS*) in peripheral blood of 50 BD patients (mean age ± standard deviation (SD) = 36.5 ± 9.32) and 50 healthy subjects (mean age ± SD = 33.62 ± 8.59). *BDNF* and *BACE1* were significantly up-regulated in peripheral blood of total BD patients compared with total healthy subjects (Expression ratio = 2.2, *P* value = 0.003; Expression ratio = 2.2, *P* value = 0.002 respectively). However, comparison of their levels in sex-based subgroups showed their up-regulations only in male patients compared with male health subjects (Expression ratio = 2.48, *P* value = 0.006; Expression ratio = 2.1, *P* value = 0.01). No significant differences were found in expressions of *BDNF-AS* and *BACE1-AS* between BD and health subjects. We detected a significant correlation between *BDNF* expression and age at disease onset in BD group after adjustment of the effects of sex ($R = 0.26$, *P* value = 0.03). Moreover, there were trends toward correlations between *BDNF* expression and disease duration in BD group and between *BDNF* expression and age in health subjects (*P* values = 0.05). Combination of *BDNF*, *BDNF-AS* and *BACE1* expression levels could differentiate BD patients from healthy subjects with 68% sensitivity and 82% specificity (area under curve = 0.72, *P* value = 0.0001). The current study suggests a sex-based dimorphic pattern in expression of *BDNF* and *BACE1*. Moreover, our results imply that expression pattern of these genes could be diagnostic markers in BD. Future studies are needed to assess this speculation in larger patient samples.

1. Introduction

Bipolar disorder (BD) is a chronic, serious mental disorder distinguished by repeated episodes of mania and depression. This psychiatric disorder is associated with destructive social, personal, health, or professional issues [1]. Although BD has a robust genetic basis, no distinct gene has been unequivocally associated with it [2]. Gene expression analysis in postmortem tissues has shown dysregulation of several genes and pathways including those associated with ubiquitin pathway, synaptic function [2], intracellular protein trafficking and protein metabolic processes [1] in BD patients. A number of researches have also examined expression of candidate genes in peripheral blood of BD patients compared with healthy subjects and proposed putative markers for detection of this psychiatric disorder [3]. Moreover, a multi-source analysis of genome wide association studies (GWAS), anatomical magnetic resonance imaging (MRI) reports, and a whole genome/whole brain gene signature has suggested a role for expression pattern of BD-associated genes in recognition of novel candidate genes [4]. Assessment of expression patterns of candidate genes in the peripheral blood of BD patients not only would facilitate recognition of underlying mechanisms of BD, but also paves the way for identification of disease biomarkers. Among the proteins with putative roles in the pathogenesis of BD are the brain-derived neurotrophic factor (BDNF) and beta-secretase 1 (BACE1). BDNF has an essential function in diverse neural processes such as neurogenesis, neuronal persistence, normal development of neural pathways and synaptic plasticity [5]. BACE1 participates in the breakage of the amyloid precursor protein and production of amyloid β (Aβ), so it has a functional role in the pathogenesis of Alzheimer's disease [6]. Both genes have natural antisense (AS) transcripts. *BDNF-AS* and *BACE1-AS* are transcribed from the opposite

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https://doi.org/10.1016/j.comppsych.2019.02.008

strands of *BDNF* and *BACE1* respectively; and are possibly involved in the regulation of their expressions [7,8]. In the present study, we compared expression of *BDNF*, *BACE1* and their AS transcripts in the peripheral blood of BD patients and healthy subjects. Based on the significant roles of long non-coding RNAs in diverse cell functions [9], we hypothesized that these AS transcripts might have altered expressions in BD patients compared with healthy subjects. We also expected altered pattern of expression of *BDNF* and *BACE1* in different stages of BD course in a sex-based manner. However, due to availability of participants, we limited this study to euthymic participants. In addition, we assessed correlations between expression levels of each gene and its AS to evaluate the roles of AS transcripts in regulation of sense transcripts in the context of BD. As we hypothesized that transcript levels of these genes can be used for differentiation of BD patients from healthy subjects, we finally assessed the diagnostic power of all mentioned transcripts using receiver operating characteristic (ROC) curves.

2. Material and methods

2.1. Study participants

In the current study, we enrolled 50 bipolar patients and 50 healthy subjects. All patients were in euthymia phase. The exclusion criteria for BD were diagnosis of schizophrenia or schizoaffective disorder in any time, diagnosis of primary anxiety disorder at the time of recruitment in the study, substance dependence, pregnancy or breast-feeding. No individual left the study after primary recruitment. The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences. Written consent forms were obtained from all study participants. Patients were diagnosed by a psychiatrics based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) Diagnostic Criteria [10]. Health subjects had no history of psychiatric diseases, neurodegenerative diseases, mental retardation, malignancy or infection. They were non-smokers and were not on any drug. Absence of psychiatric disorders in healthy subjects was verified by the Mini International Neuropsychiatric Interview [11].

2.2. Expression analysis

Expression analyses were performed on peripheral blood samples of all study participants. Total RNA was extracted from blood samples using Hybrid-R Blood RNA (GeneAll Biotech, Korea). Then, cDNA was produced from RNA samples using PrimeScript 1st strand cDNA Synthesis Kit (Clontech, Japan). Expression study was executed in Rotor Gene 6000 real-time PCR system using the primer and probes recorded in Table 1 and the RealQ Plus Master Mix (Ampliqon, Denmark). The *HPRT1* gene was used as normalizer.

Table 1
The nucleotide sequences of primers and probes used for expression assay.

Gene name	Primer and probe sequence	Product length
HPRT1	F: AGCCTAAGATGAGAGTTC R: CACAGAACTAGAACATTGATA FAM -CATCTGGAGTCCTATTGACATCGC- TAMRA	88
BACE1	F: CCAAGACGACTGTTACAA R: GAAGCCCTCCATGATAAC FAM-TTGCCATCTCACAGTCATCCAC-TAMRA	79
BACE1-AS	F: GACACTGTACCATCTCTTTTACCC R: CACCACCAACCTTCGTTTGC FAM - AGTCCACTCACGGAGGAGGTCGCC -TAMRA	113
BDNF	F: GATGCTGCAAACATGTCCATGAG R: TTTTGTCTGCCGCCGTTACC FAM-CCACTCTGACCCTGCCCGCCGA-TAMRA	109
BDNF-AS	GTGGGTCCATTCCGTGTGTG AGCTGGTGCAGGTATCAGATTAG FAM-TCCAGTGGAAACGCTGCCTCACCA-TAMRA	97

Table 2
Demographic and clinical data of study participants.

Study groups	Parameters		Values
BD	Sex	Male (Number (%))	35 (70%)
		Female (Number (%))	15 (30%)
	Age (mean ± SD (range))		36.5 ± 9.32 (17–56)
	Age at onset (mean ± SD (range))		32.64 ± 8.04 (15–48)
	Disease duration (mean ± SD (range))		3.86 ± 2.66 (1–14)
Health subjects	Sex	Male (Number (%))	35 (70%)
		Female (Number (%))	15 (30%)
	Age (mean ± SD (range))		33.62 ± 8.59 (14–52)

2.3. Statistical analysis

The SPSS 22.0 software (IBM, Chicago, IL, USA) was used for data analysis. The significance of difference in genes expressions between BD patients and health subjects was judged using independent *t*-test. The correlation between gene expression and clinicopathologic data of patients including age, age at disease onset, disease duration were assessed using regression model. $P < 0.05$ was regarded as significant.

Multiple median regression model was used to examine the association between relative expression of genes and BD with adjusting the effects of age and sex. In regression model, the Bonferroni procedure was used for approximate joint confidence intervals as well as pairwise comparison within sex. These analyses were performed in R 3.5.1 environment using qreg, and ddCt packages. The statistical significance assessed by 95% Confidence Interval (95% CI).

The suitability of mentioned genes as diagnostic biomarkers was evaluated by ROC curve analysis by plotting the true positive rate against the false positive rate at various threshold levels. The diagnostic power of transcript levels of each gene was assessed through calculation of the area under curve (AUC) in the ROC curves. AUC values as effective and joined measure of sensitivity and specificity show the essential capability of the transcript levels of genes in distinguishing between the diseased and healthy study groups. Sensitivity and specificity values were presented through prediction performance with AUC.

3. Results

3.1. General information of study participants

General data of study participants are summarized in Table 2.

3.2. Expression assays

BDNF and *BACE1* were significantly up-regulated in peripheral blood of total BD patients compared with total healthy subjects (Expression

Table 3
Relative expression of genes in patients compared with health subjects.

		Total patients vs. health subjects (50 vs. 50)	Male patients vs. male health subjects (35 vs. 35)	Female patients vs. female health subjects (15 vs. 15)
BDNF	Expression ratio	2.2	2.48	1.68
	P-value	0.003	0.006	0.29
BDNF –AS	Expression ratio	1.65	1.86	1.3
	P-value	0.06	0.07	0.5
BACE1	Expression ratio	2.2	2.21	2.1
	P-value	0.002	0.01	0.08
BACE1-AS	Expression ratio	1.24	1.71	0.6
	P-value	0.42	0.1	0.22

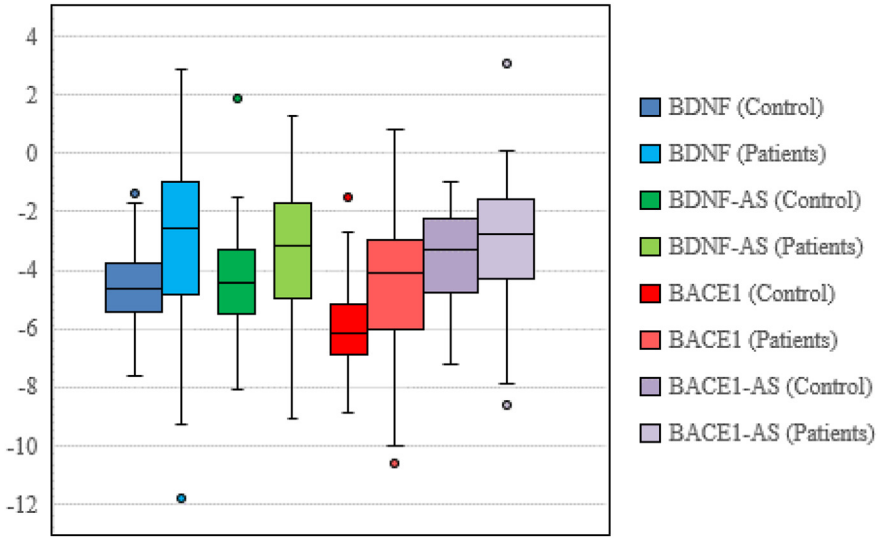

Fig. 1. Relative expression of genes in BD patients and healthy subjects. The differences between Ct (Cycle threshold) values of each gene and normalizer gene have been measured in each study group.

ratio = 2.2, *P* value = 0.003; Expression ratio = 2.2, *P* value = 0.002 respectively). However, comparison of their levels in sex-based subgroups showed their up-regulations only in male patients compared with male health subjects (Expression ratio = 2.48, *P* value = 0.006; Expression ratio = 2.1, *P* value = 0.01). No significant differences were found in expressions of *BDNF-AS* and *BACE1-AS* between BD and health subjects (Table 3 and Fig. 1).

Moreover, multiple median regression model was used to examine the association between relative expression of gene sand BD with adjusting the effects of age and sex (Table 4). After adjustment of the effects of age and sex, expressions of *BDNF* and *BACE1* were different between male patients and male health subjects. (See Table 4.)

We detected a significant correlation between *BDNF* expression and age at disease onset in BD group after adjustment of the effects of sex (R = 0.26, *P* value = 0.03). Moreover, there were trends toward correlations between *BDNF* expression and disease duration in BD group and between *BDNF* expression and age in health subjects (*P* values = 0.05). No other significant correlations were detected between expressions of genes and demographic data (Table 4).

Significant pairwise correlations were found between expression levels of all genes in both study groups except for *BACE1*/ *BACE1-AS* and *BACE1*/ *BDNF* in health subjects (Table 5).

3.3. ROC curve analysis

While *BDNF*, *BDNF-AS* and *BACE1* were all specific markers of BD, none of them had an acceptable sensitivity value. However, combination of *BDNF*, *BDNF-AS* and *BACE1* expression levels improved the diagnostic power (AUC = 0.72, *P* value = 0.0001) (Table 6 and Fig. 2).

4. Discussion

Previous studies have shown a multifaceted neuroanatomical basis including defects in brain connectivity in BD [4]. Such defects have been associated with dysregulation of several genes and pathways both in peripheral and central tissues of BD patients [1,3]. In the current study, we selected two genes with known functions in some neuropsychiatric disorders to assess their expression in BD patients compared with healthy subjects. We also evaluated expression of their natural occurring antisense genes in both groups. We did not find any significant difference in the expression of *BDNF-AS* and *BACE1-AS* between BD and health subjects. Although expression levels of both *BDNF* and *BACE1* were significantly higher in male BD patients compared with male health subjects, such differences were not detected in female subjects. BDNF has a key participation in the preservation, differentiation, and proliferation of a number of peripheral and central neurons both in childhood and in later life [12,13]. This neurotropic factor also contributes in use-dependent plasticity processes including continuing

Table 4
The results of multiple nonparametric regression model for assessment of association between relative expression of genes and BD with adjusting the effects of age and sex (*P* values are estimated based on Bonferroni procedure).

Gene	Beta	SE	t	*P*-value	95% CI	
BDNF	2.51	0.70	3.57	0.001	[1.11, 3.9]	
BDNF-AS	1.42	0.74	1.91	0.059	[−0.05, 2.89]	
BACE1	1.79	0.58	3.10	0.003	[0.64, 2.94]	
BACE1-AS	1.23	0.55	2.23	0.028	[0.13, 2.33]	
BDNF	Male	2.51	0.68	3.70	<0.0001	[1, 4.04]
	Female	0.72	1.02	0.71	0.97	[−1.57, 3.01]
BDNF-AS	Male	1.42	0.72	1.96	0.108	[−0.2, 3.04]
	Female	1.21	0.88	1.39	0.354	[−0.75, 3.18]
BACE1	Male	1.78	0.61	2.90	0.01	[0.41, 3.16]
	Female	2.20	1.24	1.78	0.174	[−0.58, 4.98]
BACE-AS	Male	1.23	0.56	2.22	0.06	[−0.02, 2.48]
	Female	−0.55	0.86	−0.64	>0.999	[−2.49, 1.38]

Table 4
Partial correlation between expression of genes and patients data (controlled for sex).

	BDNF		BDNF-AS		BACE1		BACE1-AS		
	R		*P* value	R	*P* value	R	*P* value	R	*P* value	
BD	Age	- 0.06		0.33	0.05	0.35	0.09	0.24	0.04	0.38
	Age at onset	0.26		0.03	0.14	0.15	0.09	0.26	−0.05	0.34
	Disease duration	0.22		0.05	0.12	0.2	0.1	0.23	−0.03	0.4
Health subjects	Age	0.22		0.05	0.15	0.15	0.003	0.49	−0.09	0.26

Table 5
Pairwise correlations between expression levels of genes (R^2 values are demonstrated).

		BACE1-AS	BACE1	BDNF-AS
BDNF	Health subjects	0.23**	0.03	0.26**
	BD	0.32**	0. 62**	0.63**
BDNF-AS	Health subjects	0.44**	0.19*	
	BD	0.49**	0.62**	
BACE1	Health subjects	0.07		
	BD	0.42**		

Table 6
The results of ROC curve analysis (a: Youden index, b Significance level P (Area = 0.5), Estimate criterion: optimal cut-off point for gene expression).

	Estimate criterion	AUC	J[a]	Sensitivity	Specificity	*P*-value[b]
BDNF	≤2.6	0.68	0.4	52	88	0.0009
BDNF-AS	≤1.9	0.63	0.28	34	94	0.02
BACE1	≤4.8	0.69	0.42	62	80	0.0008
Combination of BDNF, BDNF-AS and BACE1	>0.51	0.72	0.5	68	82	0.0001

potentiation, learning, and memory [14]. Previous studies have reported a crucial role for BDNF in the pathogenesis of BD. BDNF participates in the neuroplasticity alteration in BD patients. Although its serum concentrations are reduced in depressive and manic phases, they go back to normal quantities in euthymia [5]. We hypothesize that the observed higher levels of *BDNF* in male patients compared with male health subjects in our study might reflect a compensatory mechanism which is switched on in euthymia phase. Previous studies have reported similar compensatory processes after major depression or BD episodes. For instance, functional MRI studies have shown higher rate of normalization in prefrontal and limbic cortices and continuous systematic modifications in neuronal networks after an episode of major depression [15]. Moreover, the observed elevated concentrations of lactate in euthymic BD patients which was correlated with glutathione levels might represent a compensatory mechanism [16]. However, the difference in males and females regarding this compensatory mechanism needs to be explored further.

We also detected a significant correlation between *BDNF* expression and age at disease onset and a trend toward correlation between its expression and disease duration in BD group. A previous study in healthy subjects has demonstrated an inverse correlation between plasma BDNF levels and age, while platelet levels were not correlated with age [17]. Others have reported a significant decrease in serum BDNF in the later stage of BD compared to the early stage [18]. As expression level of BDNF follow distinct patterns in certain elements of blood and in certain stages of BD, our results cannot be compared with the mentioned studies unless we conduct a longitudinal study and assess expression of *BDNF* in each blood compartment. Although previous studies detected sexual dimorphisms in BDNF expression, the results are contradictory in some cases. A previous study has reported lower platelet BDNF levels in female subjects compared with males [17]. However, BDNF expression in some brain regions and the propensity of emerging BDNF-deficient-associated diseases such as depression is greater in female rats [19]. Contrary to rats, BDNF expression in the hippocampus, cortex and brain stem of male mice is higher than in female mice [20]. In humans, BDNF levels were reduced within the frontopolar prefrontal cortex of females with depression who died by suicide but not in males. However, depressed male but not female suicides demonstrated substantial decreases in BDNF protein levels within their hippocampus [21]. Taken together, BDNF might affect neuronal functions in a sex-based manner. However, the underlying mechanism of such effect needs to be elaborated in future studies.

Furthermore, we demonstrated higher *BACE1* expression in male patients compared with male healthy subjects. BACE1 has a role in enzymatic cleavage of Sez6L [22], a protein whose function has been associated with BD [23]. The sex-based difference in BACE1 expression has been noted previously where 50% BACE1 down-regulation decreased Aβ42, plaques, and BACE1-cleaved amyloid β protein precursor fragments in female, but not in male transgenic mice [24]. Notably, a recent study has shown the effects of a microdose lithium preparation in suppression of BACE1 expression. More importantly, this formulation could reverse memory deficiency and early phase of amyloid deposition in neurons [25]. Future studies are needed to elaborate the effects of

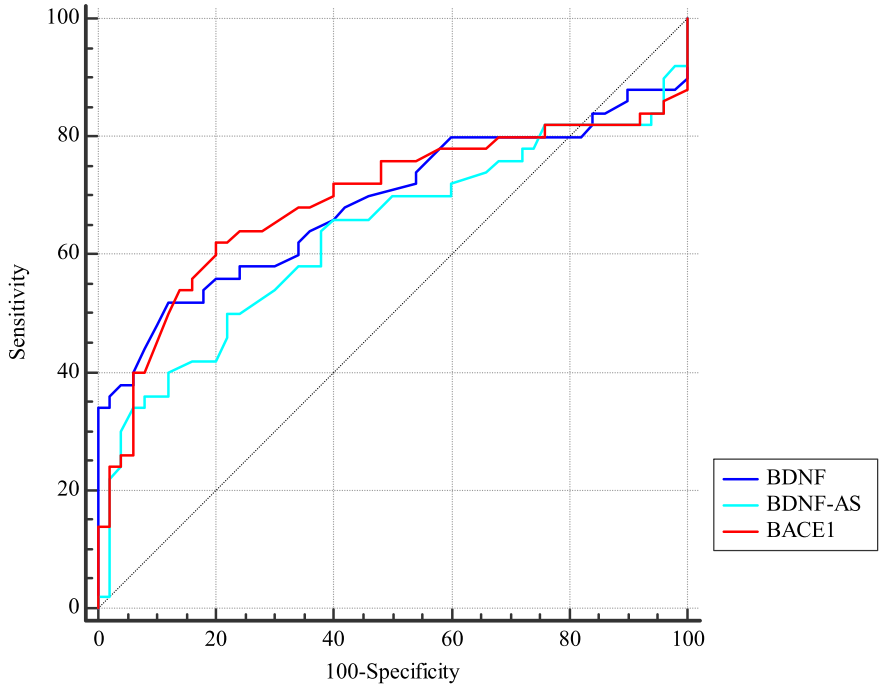

Fig. 2. ROC curve analysis for assessment of diagnostic power of *BDNF*, *BDNF-AS* and *BACE1* in BD.

BACE1 up-regulation in BD patients and whether such up-regulation affect cognitive functions of these patients.

We also detected significant pairwise correlations between expression levels of all genes in both study groups except for *BACE1*/ *BACE1-AS* and *BACE1*/ *BDNF* in health subjects. This data suggests the existence of a context-dependent regulatory mechanism for these genes. Notably, lack of correlation between *BACE1* and *BACE1-AS* in health subjects implies that the effects of natural occurring anti-senses on the expression of their sense transcripts do not always follow a direct and simple route.

Finally, we evaluated diagnostic power of mentioned genes both individually and in combination. As we expected combination of *BDNF*, *BDNF-AS* and *BACE1* expression levels increased the AUC value and enhanced the diagnostic power. So we suggest these genes as putative components of a putative panel of genes for discrimination of BD patients from healthy subjects even during euthymia. At present BD is diagnosed based on assessment of history, interview and behavioral survey, thus requiring an unbiased, biological authentication. Consequently, appropriate biomarkers can decrease diagnostic problems such as underdiagnosis or misdiagnosis [26].

Our research had some limitations. First, we just studied expression of genes in euthymia. Further assessment of expression of genes in depressive and manic patients would elaborate the role of these genes in the pathogenesis of BD. Moreover, we could not perform a longitudinal study to assess level of transcripts during disease course. So our study lacks the results of the results of expression pattern of these genes throughout the life of patients and during different phases of disease.

In brief, the current study suggests a sex-based dimorphic pattern in expression of *BDNF* and *BACE1* and proposes expression pattern of these genes as diagnostic markers in BD. Future studies are needed to assess this speculation in larger patient samples.

Acknowledgement

The current study was supported by a grant from Shahid Beheshti University of Medical Sciences.

Conflict of interest

The authors declare they have no conflict of interest.

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