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Blood levels of brain derived neurotrophic factor in women with bipolar disorder and healthy control women

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Abstract

Background—Brain-derived neurotrophic factor (BDNF) protein has been implicated in the pathophysiology of mood disorders, with early data suggesting that blood levels may vary by severity of mood symptoms. BDNF polymorphism, val66met, has also been implicated in mood disorders.

Methods—Euthymic women with bipolar disorder (BD) ($n=47$) and healthy control women ($n=26$), ages 18–45, were clinically rated using the Montgomery-Asberg Depression Rating Scale (MADRS) and sampled for plasma BDNF concentration, with a subset undergoing genetic analysis for the val66met.

Results—BD and control groups did not differ on any demographic variables, nor in plasma BDNF levels or val66met polymorphism. Plasma BDNF concentration did not differ by val66met or BD subtype, nor was it correlated with age or illness duration. Within women with BD, lower plasma BDNF concentrations were significantly associated with higher MADRS scores, even after controlling for psychotropic medication use and illness duration.

Limitations—The sample was relatively small and exclusive to women, with further research needed to investigate the links between BDNF markers and mood symptom severity in both men and women.

Conclusions—The study provides a gender-specific investigation of plasma BDNF levels and mood, and the results add further evidence of a significant interplay between BDNF markers and psychiatric symptomatology. Further, this association did not appear to be confounded by use of psychotropic medication. Studies with larger samples of both genders are needed to further delineate this relationship.

Keywords

Bipolar disorder; Brain-derived neurotrophic factor; Val66met; Women; Depressive symptomatology

1. Introduction

Mood disorders are widespread illnesses, with major depression and bipolar disorder (BD) affecting approximately 16% and 1.3% of the population, respectively (Angst et al., 2002;

Kessler et al., 2005). The underlying neuropathology of mood disorders remains a target of much scientific scrutiny and several prominent theories have been investigated. One such theory is the neurotrophic hypothesis of depression, supported in both animal and human research (Duman and Li, 2012), which states that depression may be due to decreased neurotrophin levels, leading to decreased hippocampal volume and neuronal atrophy (Duman and Monteggia, 2006).

Brain-derived neurotrophic factor (BDNF) is one of the most widely studied neurotrophic factors and has been shown to regulate neuronal structure and plasticity and be connected with long-term memory and learning (Huang and Reichardt, 2001; Maisonpierre et al., 1990; Schuman, 1999). BDNF protein crosses the blood–brain barrier and plasma BDNF concentrations have a high positive correlation with cortical BDNF protein levels (Karege et al., 2002). Early studies suggested a role of BDNF in the pathophysiology of various psychiatric disorders, with low BDNF protein levels being implicated in clinical mood disorders (Duman and Monteggia, 2006) and in animal models of mood disorders (Post, 2007). Several studies in patients with mood disorders have indicated the importance of polymorphism in the BDNF gene, val66met, (Neves-Pereira et al., 2002; Okada et al., 2006; Sklar et al., 2002; Vincze et al., 2008), including, along with early life stress, an additive adverse impact upon illness course (Miller et al., 2013). However, not all studies have confirmed such associations (Green et al., 2006; Zhang et al., 2006).

There is also a growing literature that suggests a correlation between BDNF protein concentrations in blood and symptom severity in patients with mood disorders, with more limited data on matched controls and corresponding BDNF genotype (val66met). Multiple studies have found an association between low plasma BDNF and higher levels of depression, with BDNF levels increasing upon recovery of depression (Aydemir et al., 2006; Chen et al., 2001; Gonul et al., 2005; Karege et al., 2002; Shimizu et al., 2003). Few previous studies have considered concurrent val66met polymorphism, psychiatric medication, age, and gender in investigations of the association of plasma BDNF protein levels and mood symptom severity. The current study sought to explore BDNF-mood relationships within a sample of reproductive-aged women with BD and matched healthy control women.

2. Methods

2.1. Participants

Euthymic women with BD between the ages of 18 and 45 were recruited from the Center for Neuroscience in Women's Health and the Bipolar Disorders Clinic in the Department of Psychiatry and Behavioral Sciences at Stanford University Medical Center, as well as from the surrounding community, using flyers, advertisements in local newspapers, and the registry of federally supported clinical trials (<http://clinicaltrials.gov>). Control subjects were recruited from the community using flyers and advertisements in local newspapers, and those with any history of psychiatric illness or history of ever having received psychotropic medication were excluded from the study. Exclusion criteria for all participants included illicit drug use in the past 6 months, uncontrolled medical conditions, peri- or post-menopause (as indicated by follicle stimulating hormone ≥ 40 mIU/mL), hormonal contraceptive use within the past 3 months, current pregnancy or breast-feeding, endocrine disease (i.e. diabetes and hypothyroidism), or any mood disorder secondary to a general medical condition. The diagnosis of BD was confirmed via administration of the Structured Clinical Interview for DSM-IV Diagnoses (SCID) (First et al., 1997), and screening criteria required rule out of an active mood episode within the past 4 weeks. Thirty percent of women with BD had not taken psychotropic medication for at least 3 months prior to the baseline study evaluation, while the other 70% of women with BD who were taking

psychotropic medication were required to have stable medications (e.g., no medication change) for at least 3 months prior to the evaluation.

2.2. Methods

The study was approved by the Stanford University Administrative Panel on Human Subjects. All subjects provided written and verbal informed consent prior to participation, i.e. prior to a SCID interview by a trained rater to verify the psychiatric diagnosis of BD and current remission from the most recent mood episode, and to rule out history of mood episodes or other psychopathology in control subjects. Assessment of eligibility included screening to assess general medical stability, a urine toxicology screening to rule out illicit drug use, a urine pregnancy test, and the collection of a medical history to rule out uncontrolled medical conditions. Detailed information was collected from all women with BD regarding current and previous psychotropic treatment, with confirmation by the patient's treating physician. After confirmation of eligibility per the screening protocol, a trained clinical interviewer rated each subject on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) to assess the severity of current depressive symptoms.

Procedures for collection of blood samples for plasma BDNF were conducted as part of a pilot investigation, with a resulting sample of 47 women with BD and 26 control women sampled during the early follicular phase of the menstrual cycle. Of these subjects, 41 women with BD and 16 healthy controls consented to donation of a genetic sample, which was analyzed for BDNF polymorphism. Subjects who were sampled for plasma BDNF did not differ with respect to demographic or illness characteristics compared to those subjects not sampled.

BDNF plasma and genetic samples were analyzed in duplicate by investigators blind to the subject group. Plasma BDNF concentrations were determined by the enzyme-linked immunosorbent assay (ELISA, BDNF Emax Immunoassay System, Promega, USA), according to manufacturer's instructions, with an assay sensitivity of 4 pg/mL. Genotyping was conducted per standardized protocol utilizing the following primers for G196A (rs6265) in the BDNF gene: forward 5'-ATC CGA GGA CAA GGT GGC-3' and reverse 5'-CCT CAT GGA CAT GTT TGC AG-3'. This generated polymerized chain reaction (PCR) products of 300 bp, subsequently digested by Pml I (New England Biolabs, Ipswich, MA) to yield either allele A (met; undigested, 300 bp) or allele G (val; digested to 180 bp & 120 bp bands), which were visualized on 7% polyacrylamide gel using a 50 bp marker.

2.3. Statistical analysis

Statistical analyses were performed using SPSS software version 19.0 (SPSS, Inc., Chicago, IL, USA). All statistical tests were two-tailed and conducted at the 0.05 significance level. *T*-tests and chi-square analyses were used to compare continuous and categorical demographic and clinical data, respectively, between women with BD and control women. Within-group Pearson correlations were conducted to examine the relationship between BDNF levels and MADRS scores, following analysis of BDNF blood levels with one-sample Kolmogorov-Smirnov tests within each group to test for assumptions of normal distribution (women with BD, $Z=1.280$, $p=0.075$; healthy control women, $Z=1.157$, $p=0.138$). Further analyses using analysis of covariance (ANCOVA) within women with BD considered the potential influence of psychotropic medication use.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics for women with BD versus healthy controls did not differ significantly, with the exception of MADRS score, which as expected had a higher mean among women with BD ($t(71)=4.573$, $p<0.001$; Table 1). BD Type I, Type II, and NOS were present in 27.7% ($n=13$), 42.6% ($n=20$), and 29.8% ($n=14$) of the sample, respectively. Plasma BDNF concentrations did not differ significantly between women with BD and control women, with mean concentrations of 54.4 ± 52.2 ng/mL (5.3–252.9 ng/mL) in women with BD and 43.5 ± 40.76 ng/mL (range 7.9–190.4 ng/mL) in controls ($t(72)=0.924$, $p=0.359$). No significant differences were observed with respect to MADRS scores or plasma BDNF levels between women with BD Type I, II, and NOS; furthermore, BDNF levels among women with BD did not appear to differ based on current use of psychotropic medication (treated vs. untreated mean (SD)=57.1 (61.3) vs. 53.3 (50.0); $t(46)=0.221$, $p=NS$, Table 1). Also, MADRS scores did not differ between women receiving psycho-tropic medication compared to those who were medication-free (11.7 ± 12.8 vs. 10.65 ± 8.2 ; $t(45)=0.136$, $p=NS$). Within the subsample of subjects with genetic data, val66met distribution was similar between women with BD and healthy controls, and between subtypes of BD (Table 1). The met allele was present in 43.5% of patients (met allele frequency 0.218) and 37.5% (met allele frequency 0.219) of controls ($X^2=0.075$, $p=NS$). MADRS scores did not differ by Val66Met genotype among women with BD (Val/Val= 12.3 ± 11.1 ; Val/Met= 7.8 ± 8.0 ; $F(1,39)=1.944$, $p=NS$).

Within women with BD, higher MADRS scores were significantly correlated with lower BDNF levels ($r(47)=-0.321$, $p=0.028$), while no significant association was observed within healthy control women ($r(26)=0-0.188$, $p=NS$) (see Fig. 1). The relationship between BDNF and MADRS scores remained significant with ANCOVA ($F(1,44)=5.103$, $p=0.029$) after controlling for current use of any psychotropic medication ($F(1,44)=0.046$, $p=NS$). Further ANCOVA models also showed that controlling for current use of mood stabilizing medication ($F(1,44)=1.014$, $p=NS$) or antipsychotic medication ($F(1,44)=0.476$, $p=NS$) did not alter the significant association between MADRS scores and BDNF levels ($F(1,44)=6.000$, $p=0.018$, and $F(1,44)=4.563$, $p=0.038$, respectively). MADRS scores and BDNF levels also appeared to be significantly associated when controlling for both subtype of BD illness and BD illness duration ($F(1,43)=5.223$, $p=0.028$), neither of which were significant predictors of MADRS scores ($F(1,43)=0.113$, $p=NS$, and $F(1,43)=0.051$, $p=NS$).

4. Limitations

Limitations of the study include the small sample size, including a cross-sectional design that did not allow for longitudinal evaluation of BDNF over disease course or through multiple mood states in the same subject, limiting our capacity to explore potential causal relationships. The sample was also exclusive to women, with further research needed to investigate the links between BDNF markers and mood symptom severity in both men and women. As measurement of cognitive function was not conducted as part of this study, it was not possible to assess whether BDNF played a role in cognitive decline in BD, and this requires specific study.

5. Conclusions

The current results confirm previous reports of a significant association between depressive symptom severity and serum BDNF levels in patients with mood disorders. The relationship appeared independent of psychotropic medication use, subtype of BD illness, or duration of

BD illness. Results from the subsample of subjects with available val66met polymorphism data did not suggest differential distribution between women with BD and healthy controls, nor differential depressive symptomatology among polymorphisms. The present sample is noteworthy for its homogeneity in terms of gender, reproductive age range, and exclusion of hormonal contraceptives that might otherwise affect BDNF levels or mood.

To our knowledge, this is the first study to examine both plasma BDNF concentrations and val66met genotype specifically in women with BD and matched control women. While previous studies of plasma BDNF concentrations in BD populations reported that typically between 50–70% of study participants enrolled were women, very few, if any, studies reported analysis by gender. In healthy populations, findings are variable. While at least one study did not report differences in plasma BDNF concentration by gender (Choi et al., 2011), at least two studies found higher mean plasma BDNF concentrations in healthy women compared to men, including a methodological study published of 200 healthy control subjects in 2007 (Lommatzsch et al., 2006; Trajkovska et al., 2007). Mean plasma BDNF concentrations in the current study were within the range previously reported in both healthy and psychiatric populations (Choi et al., 2011; Cunha et al., 2006; Komulainen et al., 2008; Lommatzsch et al., 2006; Machado-Vieira et al., 2007; Palomino et al., 2006; Trajkovska et al., 2007; Yoshimura et al., 2010).

Results from previous studies investigating the val66met polymorphism in mood disorders have been variable. Several studies have shown genotype associations in patients with mood disorders (Neves-Pereira et al., 2002; Okada et al., 2006; Sklar et al., 2002; Vincze et al., 2008). However, like some other studies (Green et al., 2006; Zhang et al., 2006), our results did not find differential distribution of the val66met polymorphism in subjects with and without BD. Indeed, women with BD and controls in the current sample had polymorphism distribution similar to the U.S. population (Val/Met or Met/Met genotype, U.S. population combined prevalence approximately 27.1% and Val/Val genotype, U.S. population prevalence approximately 68.4%) (Shimizu et al., 2004), and did not deviate from the expected Hardy–Weinberg equilibrium rates.

A recent meta-analysis of 13 studies examining various mood states in BD compared to controls noted that in all studies except one, BD patients with active mania, hypomania, or depression uniformly showed lower mean plasma BDNF concentrations compared to controls (Fernandes et al., 2011). Furthermore, the results of the meta-analysis showed that plasma BDNF concentrations in manic and depressed BD patients were significantly lower than controls with large effect sizes (-0.81 , CI -1.11 to -0.52 and -0.97 , CI -1.79 to -0.51 , respectively). However, in euthymic BD patients, the results were more variable and the meta-analysis did not find an overall association (Fernandes et al., 2011).

Multiple studies have found an association between low serum BDNF and severity of depression, with BDNF levels increasing upon recovery of depression (Aydemir et al., 2006; Chen et al., 2001; Gonul et al., 2005; Karege et al., 2002; Shimizu et al., 2003). Similarly, serum BDNF and post-mortem brain tissue levels have been found to be low in both depressive and manic episodes of bipolar disorder (BD), although meta-analyses do not suggest this to be the case in euthymic patients (Cunha et al., 2006; Lin, 2009). BDNF levels have also been observed to be lower in mood-disordered patients who are untreated or who are pharmacotherapy non-responders (Cunha et al., 2006; Machado-Vieira et al., 2007; Suwalska and Sobieska, 2010). However, not all studies have reported differences in plasma BDNF levels between individuals with BD and controls (Dias et al., 2009; Neves et al., 2011). It may be the case that relationships between BDNF and BD are more complex, such as involving gene $\times$ environment interactions (Miller et al., 2013) or BD illness duration or stage. Indeed, a few studies have shown an association between plasma BDNF levels and

illness duration, with patients in later stages of BD showing lower levels of BDNF (Berk et al., 2011; Dias et al., 2009; Kapczinski et al., 2008; Kauer-Sant'Anna et al., 2009). However, data in our study did not suggest an association between plasma BDNF levels and duration of BD illness.

In summary, the current findings support previous reports of the association between greater depressive symptom severity and increasing plasma BDNF levels in patients with BD, and this relationship appears independent of psychotropic medication use, subtype of BD illness, or duration of BD illness. The results did not suggest differential val66met polymorphism across women with BD and healthy controls, nor differential plasma BDNF levels or mood state according to val66met polymorphism.

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Fig. 1.
Plasma BDNF levels in relation to MADRS scores among women with BD Type 1, Type II, and NOS.

Table 1

Demographic and clinical descriptors, plasma BDNF protein levels, and val66met genotype among women with BD ($N = 47$ ^{*}) and health control women ($n = 16$ ^{*}).

	BD Type 1 ($n = 13$)	BD Type 2 ($n = 20$)	BD NOS ($n = 14$)	Healthy Controls ($n = 26$)
	Mean (SD)			
Age	32.9 (6.4)	32.1 (6.3)	34.3 (6.9)	31.8 (6.4)
Duration of BD Illness (months)	60.5 (68.1)	51.5 (54.0)	41.7 (39.4)	N/A
Age at bipolar disorder diagnosis	24.23 (4.44)	27.45 (8.30)	29.14 (6.93)	N/A
Age of first manic/hypomanic episode	21.08 (5.24)	18.35 (6.86)	22.62 (7.85)	N/A
Age of first depressive episode	19.46 (5.83)	15.18 (6.06)	19.08 (6.61)	N/A
Age at first mood episode (any)	18.31 (5.04)	14.25 (5.48)	18.14 (6.86)	N/A
MADRS score	8.5 (6.42)	9.75 (8.08)	13.5 (13.27)	1.85 (2.12)
BMI (kg/m ²)	25.97 (7.65)	27.12 (7.56)	26.51 (6.71)	24.55 (4.65)
Years of Education	16.62 (1.45)	15.90 (1.49)	15.93 (1.94)	16.31 (1.52)
Plasma BDNF protein level (ng/mL)	59.9 (65.3)	51.5 (53.9)	51.6 (39.4)	43.5 (40.8)
Marital Status	<i>n</i> per subgroup			
Single/divorced/widowed	6	9	7	20
Married/partnered	7	11	7	6
Ethnicity				
Caucasian	10	15	12	17
Hispanic	1	4	0	5
Black	0	0	0	1
Asian	2	1	2	3
* Within partial sample with val66met polymorphism ($N = 55$), <i>n</i> per subgroup				
	BD Type 1 ($n = 12$)	BD Type 2 ($n = 14$)	BD NOS ($n = 13$)	Healthy Controls ($n = 16$)
Val/Val (<i>n</i>)	9	7	6	10
Val/Met (<i>n</i>)	3	7	7	5
Met/Met (<i>n</i>)	0	0	0	1

* Genetic data were available for 39 (of 47) women with BD and 16 (of 27) healthy control women.