Blood Levels of Brain-Derived Neurotrophic Factor Correlate with Several Psychopathological Symptoms in Anorexia Nervosa Patients

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Abstract

Background: Evidence of a role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of eating disorders (ED) has been provided by association studies and by murine models. BDNF plasma levels have been found altered in ED and in psychiatric disorders that show comorbidity with ED. Aims: Since the role of BDNF levels in ED-related psychopathological symptoms has not been tested, we investigated the correlation of BDNF plasma levels with the Symptom Checklist 90 Revised (SCL-90R) questionnaire in a total of 78 ED patients. Methods: BDNF levels, measured by the enzyme-linked immunoassay system, and SCL-90R questionnaire, were assessed in a total of 78 ED patients. The relationship between BDNF levels and SCL-90R scales was calculated using a general linear model. Results: BDNF plasma levels correlated with the Global Severity Index and the Positive Symptom Distress Index global scales and five of the nine subscales in the anorexia nervosa patients. BDNF plasma levels were able to explain, in the case of the Psychoticism subscale, up to 17% of the variability (p = 0.006). Conclusion: Our data suggest that BDNF levels could be involved in the severity of the disease through the modulation of psychopathological traits that are associated with the ED phenotype.
Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are complex psychiatric conditions in which genetic and environmental factors are involved [1]. Among those genes with a role in satiety, appetite and weight regulation, brain-derived neurotrophic factor (BDNF) is widely accepted to participate in the pathophysiology of eating disorders (ED) [2–11]. BDNF protein levels have been studied for ED and other comorbid psychiatric disorders, such as schizophrenia, panic disorder and depression [12–17]. Results have revealed decreased BDNF blood levels in most disorders [18–20]. In the case of ED, however, contradictory results regarding BDNF levels have been reported [4, 10, 11, 21].

High levels of psychopathology traits in ED, such as depression, anxiety, impulsiveness and obsessionality, have been reported in the literature [22–24] and are linked to ED severity [25] and poorer prognosis [26].

To test if BDNF blood levels contribute to the phenotypic variability and severity of ED, possibly through the modulation of related psychopathological traits, we assessed the correlation between BDNF plasma levels and the Symptom Checklist 90 Revised (SCL-90R) psychometric parameters in a group of ED patients.

Material and Methods

Subjects

The clinical sample consisted of 78 Spanish Caucasian patients with ED consecutively admitted to the Psychiatric Unit of the Hospital de Bellvitge between 1999 and 2002. All patients were female, fulfilled DSM-IV criteria for ED and were diagnosed using
the Structured Clinical Interview for Mental Disorders, research version 2.0 [27]. The study consisted of 44 AN (25 binge-eating purging AN and 19 restricting AN) and 33 purging BN patients. The lifetime minimum body mass index (BMI) was 15.3 kg/m² (SD = 1.37) for AN patients and 19.2 kg/m² (SD = 2.8) for BN patients. The average age at assessment was 24.5 years (SD = 6.0) for AN patients and 25.8 years (SD = 5.0) for BN patients. The average age at onset of weight loss was 18.4 years (SD = 4.3) for AN patients, and 18.5 years (SD = 4.6) for BN patients.

Demographic-clinical information including age, weight, height and clinical-psychopathological variables were also obtained. Additional demographic information on education, occupation and living arrangements was obtained via semistructured interview. Patients completed the SCL-90R interview, which is a widely used 90-item scale for assessing self-reported psychological distress and psychopathology [28, 29].

*SCL-90R Inventory*

The SCL-90R inventory measures a broad range of psychological problems and symptoms of psychopathology through three global indexes (Global Severity Index, Positive Symptom Distress Index and Positive Symptom Total) and nine primary symptom dimensions comprising a total of 83 items (Somatization, Obsessive-Compulsiveness, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism). The Global Severity Index, which is the participant’s mean score (using all 90 items), is a widely used global index of distress. This scale has been validated in a Spanish population, obtaining a mean internal consistency of 0.75 [30].

*Assessment of BDNF Blood Levels*
Plasma was obtained by centrifugation from fresh peripheral blood samples and stored at –20 °C until used for the assay. BDNF levels were measured by the enzyme-linked immunoassay system (BDNF Emax Immunoassay System kit; Promega, Madison, Wisc., USA). Patients were split into AN and BN as they might present different associated psychopathology [31]. A general linear model was used to test the link between BDNF blood levels and SCL-90R psychopathological traits, using R statistical package (http://www.r-project.org/).

**Results**

As it has been proposed that ED subtypes differ in physiological and psychological traits [32, 33], we decided to assess the correlation between BDNF plasma levels and the different ED-related phenotypes by splitting the patients into the two main clinical subtypes, AN and BN. A general linear model was used to assess all the correlations and R² as a measure of the variance that is explained by the model. BDNF plasma levels did not correlate with BMI, minimum BMI or maximum BMI in any of the clinical subgroups, which rules out the possibility that BDNF is involved in the regulation of these physiological traits (data not shown). No differences were observed between the two subgroups of AN, binge-eating purging AN or restricting AN (t test, p value = 0.7). Nutritional state was also established by measuring the prealbumin concentration. No correlation was found between BDNF levels and prealbumin levels (data not shown). Neither actual BMI nor prealbumin levels were found to correlate with any of the SCL-90R items (data not shown).

We found that BDNF levels were negatively correlated with the Global Severity Index \( (R^2 = 0.12; p = 0.023) \) and the Positive Symptom Distress Index \( (R^2 = 0.14; p = 0.013) \)
in the subgroup of AN patients. Once we considered the different SCL-90R subscales, we found negative correlations between BDNF plasma levels and Obsessive-Compulsiveness ($R^2 = 0.13; p = 0.015$), Interpersonal Sensitiviy ($R^2 = 0.12; p = 0.022$), Depression ($R^2 = 0.12; p = 0.021$), Anxiety ($R^2 = 0.15; p = 0.009$), and Psychoticism ($R^2 = 0.17; p = 0.006$) (fig. 1).

**Discussion**

Some psychopathological traits and comorbid disorders, which persist after normalization of body weight and have strong heritability, could influence the susceptibility to both AN and BN. In agreement with our results, it has been described that serum BDNF levels are decreased in untreated major depression patients and the severity of the depression negatively correlates with BDNF levels, which in turn increases with medication response [34, 35]. A significant negative correlation between BDNF levels and the Hamilton Depression Rating Scale has also been reported [36]. BDNF serum concentration has been found to negatively correlate with the depression-related factor neuroticism [37]. We have recently reported increased BDNF levels for ED [11]. Moreover, high comorbidity between ED and Axis I or Axis II disorders, such as affective disorders, personality disorders, anxiety disorders, obsessive compulsive disorders, impulse control disorders and substance abuse, has been described [13–17, 22–24]. Accordingly, the degree of comorbidity could be modulated by BDNF expression levels. As some authors have suggested, a link between internalizing syndromes (e.g. social anxiety, obsessionality) and AN is more prevalent [31, 38], whereas externalizing symptoms (e.g. self-harm and self-injurious behaviors, drug and alcohol abuse) and higher psychopathological traits, namely depression, general anxiety and impulsivity are more frequent among BN patients [23, 24]. It might
be suggested that levels of BDNF may function as a mediator of these psychopathological traits, influencing the outcome and the prognosis of the patient.

This study has some limitations that have to be considered. First, we measured plasma concentrations, which have low correlation with serum BDNF levels [39]. While potential sources of plasma BDNF include endothelial and smooth muscle cells [40–42], activated macrophages or lymphocytes [41, 43, 44], and neurons and glia cells from the central nervous system [45–47], most BDNF in serum likely reflects the amount of BDNF accumulated in platelets, which is released during the clotting process [48]. Thus, the interpretation of changes in BDNF plasma levels should be taken with caution when comparing with results of other groups that studied serum BDNF in different pathologies. Second, the lack of significant results in the BN group could be due to the limited sample size and hence the reduced statistical power. Third, we did not consider ED clinical categories to correct for multiple testing, as it might be too stringent to detect a moderate correlation with different endophenotypes, taking into account that the different ED subtypes and SCL-90R are not independent factors, a requirement for the application of Bonferroni correction.

Even though BDNF plasma levels have been previously reported to be decreased in healthy sisters of 50 of the ED patients included in the present study [11], we have not been able to test BDNF correlation with SCL-90R scales, as this questionnaire was not evaluated in healthy sisters. The correlation of BDNF plasma levels and SCL90 symptoms in controls or in patients recovered from the disease should be evaluated in order to assess if it follows the same trend observed in our patients and therefore disclose whether the correlation is diagnosis-specific or not. Lastly, the possibility that
other influencing factors related to weight reduction are correlated with BDNF cannot
be ruled out, although the lack of correlation between BMI and SCL-90R or BDNF
makes it quite unlikely.

To our knowledge, this is the first study that assesses the relationship between ED-
related psychopathological traits and BDNF blood levels in ED patients, although the
results should be taken with caution until replicated in a larger sample. We also confirm
the correlation of depressive symptoms in our sample, and give some insights into
other psychopathological traits that might be modulated by BDNF. In summary, we
propose that BDNF levels could act as modulators of ED psychopathological traits,
although these results should be replicated in a larger sample, before considering BDNF
plasma levels as a possible marker of the severity of the disease.

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References


Fig. 1. Dot plot representing the correlation between blood levels and several SCL-90R symptom scales. $R^2$ was calculated using a general linear model (GLM).