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Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression

Tom K. Birkenhäger*, Sarah Geldermans, Walter W. Van den Broek, Nico van Beveren, Durk Fekkes

Department of Psychiatry, Erasmus Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

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ABSTRACT

Background: Since there are few data on the possible association between BDNF levels and characteristics of major depression, the present study assesses brain-derived neurotrophic factor (BDNF) levels in three drug-free patient samples, and explores whether episode duration, and severity correlate with serum BDNF levels.

Method: Serum BDNF levels were measured in 42 drug-free patients with major depression. The duration of the index episode and the presence of psychotic features were assessed with the Schedule for Affective Disorders and Schizophrenia, and the severity of depression was measured with the 17-item Hamilton Rating Scale for Depression. The sample was divided into three groups: severely depressed inpatients without psychotic features, severely depressed inpatients with psychotic features, and moderately depressed outpatients.

Results: Mean serum BDNF level in the total sample was 18.0 ± 2.8 ng/ml, with no significant difference between the three patient samples ($F = 1.80$, df = 2, $p = 0.18$). Mean serum BDNF level was significantly lower in patients with an index episode over one year, compared with patients who had a shorter index episode ($F = 4.90$, df = 1, $p = 0.033$).

Conclusion: These data show that patients with a long index episode have significantly lower serum BDNF levels. We found no influence of the presence of psychotic features and severity of depression on serum BDNF levels.

1. Introduction

There is evidence that brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of mood disorders (Post, 2007). BDNF is a neurotrophin which mediates synaptic efficacy, neuronal connectivity and neuroplasticity. It is the best studied member of the nerve growth factor family, which also includes nerve growth factor, neurotrophin 3, and neurotrophin 4. BDNF is found throughout the brain, with particularly large quantities in the hippocampus and the cerebral cortex (Altar, 1999). It regulates neuronal development/survival, and controls several neurotransmitter systems (Lewin and Barde, 1996). BDNF is produced both by central nervous system cells and by epithelial cells and circulating BDNF is stored by peripheral platelets, those serve as a 'buffer system' for BDNF. BDNF crosses the blood–brain barrier two-directionally, and there is controversial evidence concerning the correlation between central levels and blood levels of BDNF (Karege et al., 2002). Serum levels of BDNF have been found to be 200-fold higher than plasma levels (Rosenfeld et al., 1995); this difference between serum and plasma BDNF may be caused by the amount of BDNF contained by platelets (Fujimura et al., 2002).

Studies have shown lower plasma and serum BDNF levels in patients with major depression compared with healthy control subjects (Dell'Osso et al., 2010; Karege et al., 2002; Lee et al., 2007; Shimizu et al., 2003). Decreased BDNF levels are not limited to major depression, but have been described in other psychiatric disorders (Dell'Osso et al., 2009), notably schizophrenia (van Beveren et al., 2006) and bipolar disorder (Machado-Vieira et al., 2007). Studies attempting to find an association between the decrement in BDNF level and clinical characteristics of major depression, i.e. episode duration (Aydemir et al., 2007), severity of depression (Shimizu et al., 2003) and the presence of psychotic features (Lee et al., 2007), have shown variable results. These inconsistent results are probably due to heterogeneous patient samples, e.g. including both drug-free patients and patients on antidepressants. Furthermore, BDNF was determined in serum in some studies, whereas others investigated plasma BDNF.

* Corresponding author. Tel.: +31 10 4635871; fax: +31 10 4633217.
E-mail address: t.birkenhager@erasmusmc.nl (T.K. Birkenhäger).

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Since there are few data on the possible association between BDNF levels and characteristics of major depression, this study assesses BDNF levels in three drug-free patient samples, i.e. patients with psychotic depression, patients with severe non-psychotic depression and patients with moderate depression, and explores whether clinical characteristics are correlated with serum BDNF levels. The specific questions are: 1) do serum BDNF levels vary between these three groups?; and 2) does the duration of depression episode influence serum BDNF levels?

2. Subjects and methods

2.1. Subjects

The study was performed at both the inpatient depression unit and the outpatient department of the Dept. of Psychiatry of the Erasmus Medical Center. The inpatient depression unit has a supraregional function for the treatment of treatment-resistant depressed patients. The study protocol was approved by the local Medical Ethical committee and the study was conducted in accordance with the Declaration of Helsinki. Prior to inclusion, eligible patients, or their legal relatives in case of incapacity, provided written informed consent after study procedures were fully explained.

Eligible for inclusion were patients aged 18–65 years who fulfilled the DSM-IV criteria (American Psychiatric Association, 1994) for major depressive disorder that was diagnosed by the administration of the depression section of the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott, 1978). For depressed inpatients, a 17-item Hamilton Rating Scale for Depression (HAM-D) (Bech et al., 1986) score ≥ 18 was required. Subject exclusion criteria were: schizophrenia, paranoid psychosis, schizoaffective disorder, bipolar disorder, organic brain syndrome, chronic alcohol or drug abuse, and clinically relevant somatic illness. Psychotropic drugs were discontinued after admission and patients had to be drug-free for at least one week prior to baseline assessment. Duration of the index episode was assessed retrospectively during the diagnostic interview.

2.2. Serum BDNF determination

Blood samples were drawn between 8:00 and 9:00 a.m., blood was allowed to clot and, after centrifugation for 20 min at 2650 g, serum was stored at −80 °C until analysis. Serum BDNF was analyzed in duplicate with a commercial double antibody sandwich ELISA Kit (Promega, Madison, WI, USA) as described by the manufacturer. The absorbances were measured with an automated microplate reader at 450 nm.

2.3. Statistical analysis

SPSS software version 17.0 (SPSS Inc., Chicago, Ill) was used for the analyses. Differences with 2-sided $p < 0.05$ were considered statistically significant. We assessed whether BDNF levels and pretreatment HAM-D score were normally distributed using descriptive statistics for determining skewness, the Shapiro–Wilk test and visual inspection of the Q/Q plots. Since both BDNF and HAM-D scores showed a Gaussian distribution we applied parametric tests. Analysis of variance (ANOVA) was used to compare the mean serum BDNF concentrations between the three samples. Serum BDNF levels between patients with and long versus short index episode were compared with a *t*-test. The Pearson correlation test was performed to calculate the correlation between HAM-D score and age.

3. Results

Of the 42 patients participating in the study, 30 inpatients had severe major depression and 12 outpatients had moderate major depression. Table 1 shows the demographic and clinical characteristics, as well as the serum BDNF levels of all patients. All patients with melancholic features showed observable psychomotor retardation. All patients diagnosed with psychotic depression showed mood-congruent delusions, e.g. delusions of guilt, delusions of poverty and nihilistic delusions. None of the patients with psychotic depression suffered from hallucinations. None of the patients participating in the present study met criteria for atypical depression. BDNF showed a normal distribution, according to the Shapiro–Wilk test (statistic = 0.98, df = 41, $p = 0.47$). Mean serum BDNF level in the total sample was 18.0 ± 2.8 ng/ml, with no significant difference between the three patient samples ($F = 1.80$, df = 2, $p = 0.18$), as shown by Fig. 1. Mean serum BDNF level was significantly lower in patients with an index episode over one year, compared with patients who had a shorter index episode ($F = 4.90$, df = 1, $p = 0.033$) (see Fig. 2). Age and severity of depression are two possible confounding factors which may have influenced the relation between episode duration and BDNF. It was not possible to include severity of depression in the analysis, since severity appeared to be correlated with episode duration ($R = -0.25$, $p = 0.09$). A linear regression analysis adjusted for age as co-variable showed

Table 1
Demographic and clinical characteristics of the study sample ($n = 42$).

	Inpatients without psychotic features ($n = 19$)	Inpatients with psychotic features ($n = 11$)	Outpatients ($n = 12$)	*p*-value
Age in years (mean ± SD)	54.2 ± 8.6	53.0 ± 9.9	37.8 ± 10.6	0.001[a]
Sex (M/F)	13/6	6/5	5/7	0.14
HAM-D score (mean ± SD)	25.5 ± 5.6	31.6 ± 6.3	15.1 ± 4.3	0.001[b]
Melancholic features	18 (95%)	10 (91%)	6 (50%)	0.004[a]
Index episode > 1 year	8 (42%)	2 (18%)	9 (75%)	0.02[c]
No of previous episodes (mean ± SD)	1.4 ± 1.1	1.1 ± 1.0	1.6 ± 0.9	0.28
BDNF (ng/ml) (mean ± SD)	18.9 ± 4.7	18.5 ± 2.9	16.1 ± 4.2	0.18
BDNF (ng/ml) range	8.0–26.8	14.5–23.9	9.8–23.7	

SD: standard deviation.
HAM-D: 17-item Hamilton Rating Scale for Depression.
BDNF: brain-derived neurotrophic factor.
p-values are from Fisher's exact tests for categorical variables and from analysis of variance for continuous variables.
[a] Significant difference between both inpatient samples and the outpatient sample.
[b] Significant difference between all three samples.
[c] Significant difference between psychotic inpatients and the outpatient sample.