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ORIGINAL PAPER

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Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients

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Abstract Researchers have reported that serum brain-derived neurotrophic factor (sBDNF) of drug-free depressed patients are lower than those of healthy controls and proposed that low sBDNF levels might reflect failure of neuronal plasticity in depression. In this study, we compared sBDNF levels of depressed patients (n = 28) before and after 8 weeks of antidepressant treatment, with those of healthy controls (n = 18) to test the hypothesis that initially low sBDNF levels of drug-free depressed patients will increase parallel with their clinical response to antidepressant treatment. The severity of depression and response to treatment were assessed with Hamilton Rating Scale for Depression (HAM-D). sBDNF was assayed with the sandwich ELISA method. Baseline sBDNF levels of patients (mean, 20.8 ng/ml; [S. D., 6.7]) were significantly lower than those of controls (mean, 26.8 ng/ml; [S. D., 9.3]; p = 0.015), and were negatively correlated with HAM-D scores (r = –0.49, p = 0.007). After 8 weeks of treatment, sBDNF levels of patients had increased significantly (mean, 33.3 ng/ml; [S. D., 9.9]; p < 0.001) and no longer differed from those of controls. These results support the hypothesis that BDNF might play a critical role in the pathophysiology of major depressive disorder and successful antidepressant treatment increases the attenuated BDNF levels in depressed patients.

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Introduction

The word neuroplasticity denotes the capacity of the brain to adapt continually to the demands placed on it by experience. Neuroplastic changes are not restricted to a certain stage of development but occur throughout life (Spitzer 1999). One major neurotrophic factor, brain-derived neurotrophic factor (BDNF), has been found to play a critical role in long-term potentiation, a cellular mechanism of learning and memory, suggesting that this neurotrophic factor can influence plasticity (Figurov et al. 1996; Korte et al. 1995). BDNF is also needed for the survival and guidance of neurons during development and for the survival and function of neurons during adulthood (Duman et al. 2000; McAllister et al. 1999; Thoenen 1995).

Duman and colleagues (2000) propose a hypothesis that stress-related mood illness may be associated with failure of neuronal plasticity. Support for this hypothesis is provided by many studies demonstrating that structural alterations also occur in response to stress and in patients with mood disorder (Bremner et al. 1995; Sheline et al. 1999). The structural alterations might result from atrophy and death of vulnerable neurons and glia in areas such as the hippocampus and subgenual prefrontal cortex (Frodl et al. 2002; Ongur et al. 1998; Rajkowska 2000). The atrophy and loss of hippocampal or cerebral cortical neurons or glia could result from a stress-induced loss of neurotrophic factors or from other processes that compromise neuronal function and activity (e. g., hyperactivation of hypothalamic-pituitary-adrenal [HPA] axis, glutamatergic excitotoxicity, hypoglycemia, hypoxia-ischemia) or other insults, as a result of the patient's genetic background (Sapolsky 2000; Shelton 2000).

It has been shown that stress not only induces atro-

phy of apical dendrites of CA3 neurons but also decreases the neurogenesis of dentate granule neurons and synthesis of hippocampal BDNF in adult animals (Gould et al. 1997, 1998; Magarinos and McEwen 1995). Preclinical studies demonstrate that antidepressant treatments, including selective norepinephrine and serotonin reuptake inhibitors and electroconvulsive seizures, increase BDNF expression although each treatment modality has a different effect on four promoter regions of BDNF gene (Nibuya et al. 1995, 1996; Tapia-Arancibia et al. 2004; Vaidya et al. 1999). Administration of BDNF to stressed animals produces the antidepressant-like effect of antagonizing learned helplessness (Siuciak et al. 1997). Chen et al. (2001) found increased BDNF expression in hippocampal regions of patients treated with antidepressants at the time of death, compared to untreated patients.

Recently, Karege et al. (2002a) showed that sBDNF levels of drug-free depressed patients were lower than those of controls, and Shimizu et al. (2003) found that sBDNF levels of treated depressed patients were not different from control levels. Although these studies support the idea that sBDNF might play a role in pathophysiology of depression as a neurotrophic factor, there are no data showing directly that low sBDNF levels in depressed patients increase following successful treatment. Based on the failure of the neuroplasticity theory in major depression, in this study, we tested the hypothesis that sBDNF levels of drug-free depressed patients are lower than those of healthy controls but will increase to the levels of healthy controls after antidepressant treatment in patients who respond clinically.

Methods

Subjects

Thirty-three patients (8 male and 25 female) diagnosed as having major depressive disorder according to DSM-IV (American Psychiatric Association 1994) were included in the study. Exclusion criteria were organic brain disorder, substance abuse, pregnancy or any physical illness as assessed by personal history, or abnormal signs in clinical examination or laboratory data (including complete blood count, serum electrolyte assay, liver function tests, thyroidal function tests, urine analysis, urine drug screen, hepatitis and HIV serology and electrocardiography). None of the patients had a history of a manic or hypomanic episode, or had a first-degree relative with bipolar disorder. The diagnosis was reached independently by at least two psychiatrists. Response to the treatment was defined as at least a 50 % decline in Hamilton Depression Rating Scale (HAM-D) scores. Patients (1 male and 4 female) who did not respond to the antidepressant treatment at the end of week 8 were excluded from the study because the primary objective was to compare baseline values with the values during response to treatment.

The mean age ± SD of patients included in the study (7 male and 21 female) was 35.5 ± 8.1 (range:19–45) years and the duration of the current depressive episode was 13.1 ± 9.7 weeks (Table 1). Thirteen of the patients were undergoing their first depressive episode and were drug-naïve. Another ten had been free from any psychotropic drug for more than one year. The remaining five patients had not taken any psychotropic drugs (including benzodiazepines) for at least 3 weeks (mean: 28 days). All patients gave written informed consent. The control group consisted of 18 physically and mentally healthy volunteers (6 male, 12 female). The control group was matched with the group of depressive patients in age, education and social status (Table 1).

Assessment of depression and treatment

After an initial assessment of depression, which was measured with the interviewer-rated 17-item HAM-D, antidepressant treatment was started. Antidepressants were chosen according to patients' tolerance and response in previous episodes. Ten of the patients received venlafaxine extended release (mean: 180 mg/day) while others received SSRI antidepressants (8 of the patients received sertraline at a mean dose of 100 mg/day, 5 received fluoxetine at a mean dose of 32 mg/day, 3 paroxetine at a mean dose of 30 mg/day and 2 of the patients 40 mg/day citalopram). Assessments were repeated at weeks 2, 4 and 8. For patients, the values obtained from the serum samples collected on the day before antidepressant initiation and at the end of week 8 were accepted as baseline and follow-up values. Serum samples from controls were collected once.

Laboratory assay

Serum samples (5 ml) from the patients and normal controls were collected in anticoagulant-free tubes between 11:00–12:00 AM after a

Table 1 Clinical variables and BDNF values of patients and controls

	Patients (N = 28)	Controls (N = 18)	Comparison
Gender (M/F)	7/21	6/12	$\chi^2 = 0.375$ df = 1 p = 0.73
Age (years)	35.5 ± 8.1	35.7 ± 5.8	t = 0.59 df = 44 p = 0.583
Age of onset (years)	30.6 ± 9.1	–	
Number of previous episodes	0.96 ± 1.3	–	
Duration of the last episode (weeks)	13.1 ± 9.7	–	
HAM-D scores			
Baseline	27.28 ± 3.53	–	
Follow-up	8.85 ± 3.15[a]	–	
BDNF			
Baseline	20.8 ± 6.7[b]	26.8 ± 9.3	
Follow-up	33.3 ± 9.89[c]	–	

[a] Significantly different from baseline values (t = 20.9 df = 27 p < 0.001)
[b] Significantly different from those of controls (t = 2.47 df = 44 p = 0.015)
[c] Significantly different from baseline values (t = 7.81 df = 27 p < 0.001)

rest of 45 minutes. They were kept at room temperature for 1 hour followed by 1 hour at 4 °C before serum was isolated. They were stored at –70 °C until the assay. sBDNF levels were measured using the BDNF Emax Immunoassay System kit (Promega; Madison, WI, USA) according to the manufacturer's instructions. For patients, values obtained before the day of antidepressant initiation and at the end of the 8th week were accepted as baseline and follow-up values.

Statistical analysis

The chi-squared test was used for the categorical variables, and Student's t-test was employed for the continuous variables. During the comparison of sBDNF levels of the groups, a was adjusted to 0.016 via a Bonferroni correction for preventing type I errors. The Mann-Whitney U test was used to assess any BDNF sex difference. Relationships between pairs of variables were examined using Pearson's correlation coefficient.

Results

Baseline comparison

Table 1 shows the clinical variables and sBDNF values of patients and controls. The baseline sBDNF levels of patients were lower than those of controls (Fig. 1) and there was a significant negative correlation between BDNF levels and HAM-D scores ($r = 0.49$; $p = 0.007$). sBDNF levels of depressed female patients (19.5 ± 5.8 ng/ml) were lower than those of male patients (24.6 ± 7.6 ng/ml); however this difference did not reach statistical significance ($U = 40.0$ $p = 0.08$). The severity of depression assessed by HAM-D was not different between the male and female patients ($U = 62.0$; $p > 0.05$). Nevertheless, analysis of covariance indicated that both the severity of depression and the gender of the patient accounted for the negative correlation between sBDNF and depression ($F = 12.24$ and 6.83, $P = 0.002$ and 0.015, for severity and gender, respectively). Family history and duration of the previous depressive episode were unrelated to sBDNF levels of patients (data not shown).

Follow-up comparison

After 8 weeks of antidepressant treatment, HAM-D scores had decreased significantly ($t = 20.9$; d. f. = 27; $p < 0.001$). Correspondingly, patient sBDNF levels had increased significantly ($t = 7.81$; d. f. = 27; $p < 0.001$; Fig. 1) to the point where they no longer differed from normal control levels ($t = 2.45$; d. f. = 44; $p = 0.03$). After treatment sBDNF levels and HAM-D scores continued to show no significant difference between female and male patients. No significant correlation remained between HAM-D scores and sBDNF levels after treatment ($r = 0.15$; $p = 0.44$).

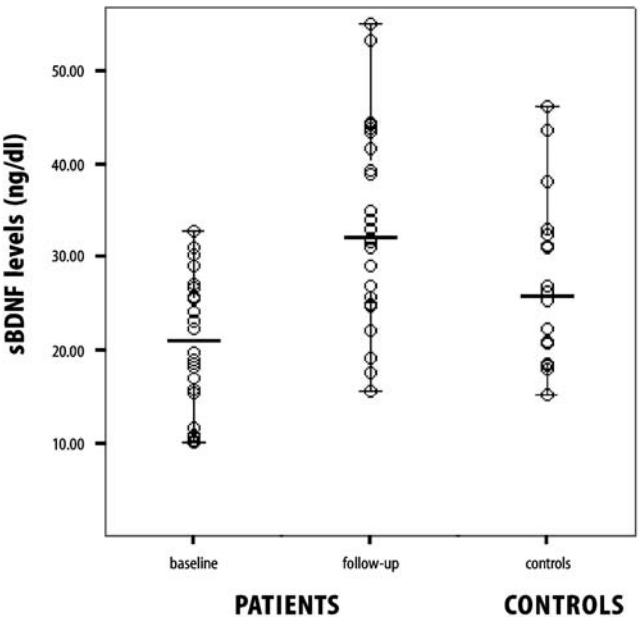

Fig. 1 The sBDNF levels of patients during baseline and follow-up, and the control group. The baseline sBDNF of depressed patients (mean ± SD: 20.8 ± 6.7) increased significantly after treatment (mean ± SD: 33.3 ± 9.89) during the follow-up period ($t = 7.81$; d. f. = 27; $p < 0.001$). Follow-up sBDNF values of patients were higher than those of controls (mean ± SD: 26.8 ± 9.3); however, this difference did not reach statistical significance after α was adjusted to 0.016 with Bonferroni correction ($t = 2.45$; d. f. = 44; $p = 0.03$)

Discussion

The main findings of this study were that prior to treatment the sBDNF levels of depressed patients were significantly lower than those of healthy controls, with the magnitude of the difference corresponding to the magnitude of the depression. After treatment the BDNF increased to normal control levels among patients who responded clinically.

In this study, we used platelets for assessing the BDNF levels of patients and controls. Human platelets which are developed from neural crest, the embryonic precursor of neurons, have long been used to study monoaminergic systems especially in mood disorders (Pearse 1980). It is thought that changes in the components of these systems reflect the changes within the brain (Sofuoglu et al. 1995; Bianchi et al. 2002). A similar model can be proposed for BDNF. Platelets bind, store and release BDNF upon activation in a manner similar to that of serotonin (Radka et al. 1996; Fujimura et al. 2002). It also has been reported that BDNF can cross the barrier from the brain to blood via a high-capacity saturable transport system (Pan et al. 1998). Brain and blood BDNF levels undergo similar changes during maturation and aging in rats (Karege et al. 2002b) and there is a positive correlation between serum and cortical BDNF levels.

Our finding of decreased sBDNF levels corresponding to the severity of clinical depression supports the findings of the previous studies (Karege et al. 2002a;

Shimizu et al. 2003). We found further that sBDNF levels of depressed patients increased significantly with the response to the antidepressant treatment. This result, in accordance with previous preclinical studies, suggests that antidepressant treatment may up-regulate the cAMP-CREB cascade and expression of BDNF (Dowlatshahi et al. 1998; Duman et al. 2000). Nibuya et al. (1995) showed that long-term antidepressant pretreatment blocks the stress-induced down-regulation of BDNF in the hippocampus. It is thought that antidepressants activate the cAMP-CREB cascade via stimulating serotonin and norepinephrine receptors (Duman et al. 2000; Markstein et al. 1999; Roseboom and Klein 1995). This idea was supported by the finding that antidepressant treatment increases CREB phosphorylation and CRE-mediated gene expression in limbic brain regions (Thome et al. 2000). The promotor of the BDNF gene contains CRE and can be induced by CREB (Shieh et al. 1998; Tao et al. 1998).

When BDNF is directly infused into the midbrain, it behaves like an antidepressant in the forced swim and learned helplessness models (Siuciak et al. 1997; Shirayama et al. 2002). However, our knowledge about how BDNF shows its antidepressant effect is very restricted. It was suggested that upregulation of CREB and BDNF in response of antidepressant treatment could regulate neuronal apoptosis and trigger survival signals to counteract cellular death cascades (D'sa and Duman 2002). Malberg et al. (2000) reported that chronic antidepressant treatment increased not only BDNF expression, but also neurogenesis in the adult rat hippocampus. Beside its role in survival, BDNF is necessary for synaptic activity and acts both pre-and post-synaptically in an activity dependent manner (D'sa and Duman 2002).

It is unclear whether low BDNF levels in depressed patients are primary or secondary. Single or repeated immobilization stress application or exogenously applied corticosterone markedly reduces BDNF mRNA and protein levels in the rat hippocampus (Schaaf et al. 1999; Ueyama et al. 1997). Inversely, adrenalectomy or pre-treatment with antidepressants increases BDNF mRNA levels in this structure (Chao et al. 1998). Thus, one might suggest that reduced BDNF due to stress might increase vulnerability to neuronal damage that is also associated with stress leads to clinical depression. The results of this study support the idea that restoring BDNF levels by antidepressant treatment may reverse the pathophysiological process under major depression.

The BDNF gene has a complex structure with short 5' non-coding exons containing separate promotors and one 3' exon encoding the mature BDNF protein (Timmusk et al. 1994). Alternative usage of these promoters and differential splicing generates a total of 8 different transcripts. The biological significance of the eight distinct BDNF mRNAs is unknown and intriguing since each BDNF mRNA encodes an identical BDNF protein. Recent studies suggest that antidepressants (and also electroconvulsive therapy and exercise) have a very different manner on encoding these promoter regions (Dias et al. 2003; Russo-Neustadt et al. 2004). Thus, based on these findings, we tested the idea that antidepressants from different classes (SSRIs versus serotonin-norepinephrine reuptake inhibitors, like venlafaxine) might cause a significant difference in sBDNF levels during treatment. However, we could not detect any difference between the sBDNF levels of patients who received SSRI or venlafaxine (repeated measures of ANOVA, drug X treatment interaction, $F = 0.2$ $df = 1.26$ $p = 0.88$). Thus, generation of different transcripts might not have an effect on sBDNF levels in patients who clinically responded.

Karege et al. (2002a) found that female patients were more depressed and had lower sBDNF levels. Shimizu et al. (2003) found no sex differences in the groups they studied, nor did we. In principle, a number of factors like estrogen may affect the levels of BDNF in female patients (Berchtold et al. 2001), but Karege et al.'s finding should be clarified before using it as evidence for vulnerability of women to depression.

Like other neurotrophic factors, BDNF regulates the survival and differentiation of neurons not only during development but also in adulthood. As expected, there is a growing evidence of an alteration in BDNF expression that contributes to other pathologies such as epilepsy, eating disorders, schizophrenia, addiction disorders, Alzheimer's and Parkinson's diseases (reviewed by Tapia-Aranciba et al. 2004). This situation prevents altered sBDNF levels that can be accepted as a marker for major depression. In spite of this, our findings are a clear support of the hypothesis that low BDNF might contribute to the pathophysiology of major depressive disorder and, furthermore, show that successful antidepressant treatment increases the attenuated BDNF levels to the normal range.

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