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Rapid Antidepressant Changes with Sleep Deprivation in Major Depressive Disorder are Associated with Changes in Vascular Endothelial Growth Factor (VEGF): a Pilot Study

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Abstract

While conventional antidepressants benefit many patients with major depressive disorder (MDD), as much as eight to 12 weeks can elapse before significant improvements in depressive symptoms are seen. Treatments that act more rapidly in MDD are urgently needed. Sleep deprivation (SD) has been shown to produce a rapid antidepressant response within one day in 50–60% of patients with MDD; thus, identifying its antidepressant mechanism may contribute to the development of antidepressants that act more rapidly. The present study evaluated the effects of 39 hours of SD on mood, as well as on plasma levels of brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) in patients with MDD. After a drug-free period of at least two weeks, 11 patients (6 males, 5 females; ages 25–62) who met DSM-IV criteria for MDD underwent total SD. Plasma samples for BDNF and VEGF assays were collected on Days 1 (baseline) and 2. The six-item Hamilton Rating Scale for Depression (HAM-D-6) was the primary outcome measure. HAM-D-6 scores decreased significantly after SD (Day 2). SD was negatively correlated with change in HAM-D-6 score and change in VEGF levels, indicating that as depression scores decreased following SD, VEGF plasma levels increased. In contrast, SD did not alter plasma BDNF concentrations, nor was an association found between BDNF levels and clinical improvement on the HAM-D-6. These results suggest that SD is associated with mood-related changes in plasma VEGF levels, but not plasma BDNF levels. Further studies using larger sample sizes are needed to confirm these preliminary findings.

Keywords

antidepressant; depression; neurotrophic factors; sleep deprivation

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1. INTRODUCTION

A major impediment to the successful treatment of patients with major depressive disorder (MDD) is that weeks or months can elapse before the therapeutic effects of traditional antidepressants emerge (Rush, et al., 2006). This lag in onset of therapeutic effects exerts a major toll on individuals' well-being and ability to function (Birnbaum, et al., 2010), and places them at increased risk for suicidal behaviors (Claassen, et al., 2007). More uniformly effective and rapidly acting treatments for MDD are urgently needed, as is the identification of biomarkers of early and effective improvement associated with such novel treatments.

The rapid antidepressant effects of a single night of total sleep deprivation (SD) have been well documented; however, the biological mechanism underlying these effects is complex and, as yet, unidentified (Wu and Bunney, 1990). Furthermore, while SD has been shown to improve mood—sometimes within hours—this rapid improvement is typically transient, with mood returning to baseline often within 24 hours (Wu and Bunney, 1990). Understanding the physiological changes that occur during acute SD may therefore provide clues to the molecular and/or cellular mechanisms associated with its rapid antidepressant effect as well as subsequent relapse. Insight gleaned from SD studies could then be used to develop better treatments.

One promising line of investigation has linked brain derived neurotrophic factor (BDNF) with antidepressant treatment response as well as sleep-wake physiology (Cirelli and Tononi, 2000; Wirz-Justice, et al., 1981). BDNF mediates cell survival and plasticity and is extensively expressed in the central nervous system (CNS) (Karege, et al., 2002). A large number of clinical trials have demonstrated lower serum and plasma BDNF levels in antidepressant-naïve patients with MDD compared to patients receiving antidepressants or normal controls (Sen, et al., 2008), and other studies have noted that most antidepressant treatments are associated with increased BDNF levels (Lee and Kim, 2010). Furthermore, these antidepressant-induced BDNF elevations are associated with improvement in depression scores (Shimizu, et al., 2003), which has led some investigators to pursue BDNF agonists as mediators of rapid antidepressant response (Hoshaw, et al., 2005). In addition, decreased hippocampal volume is a well-known finding in MDD, typically ascribed to neuronal atrophy and cell loss (Duman and Monteggia, 2006; Monteggia, et al., 2004); interestingly, increased hippocampal BDNF levels reverse this cell loss and mimic the behavioral effects of antidepressants (Duman and Monteggia, 2006).

To our knowledge, only one human study examined the relationship between SD, MDD, and BDNF levels. In that study, a single night of SD decreased scores on the Hamilton Depression Rating Scale (HAM-D) and increased serum BDNF levels in patients with MDD; HAM-D scores were correlated with BDNF levels (Gorgulu and Caliyurt, 2009). At least one preclinical investigation also observed that total SD had antidepressant-like effects in the learned helplessness rodent model of depression; these behavioral effects were associated with increased BDNF levels and hippocampal neurogenesis (Zucconi, et al., 2006).

While a strong association has been reported between peripheral and central BDNF levels (Karege, et al., 2002), a relevant issue is whether circulating levels of BDNF correlate with CNS concentrations. A bi-directional transport mechanism allows BDNF to cross the blood-brain barrier, allowing passage from blood to brain and reabsorption from the cerebral spinal fluid (CSF) to blood (Pan, et al., 1998). Antidepressant treatment increases central BDNF expression and, as noted above, this is correlated with a decrease in depressive symptoms (Malberg, et al., 2000). BDNF also has acute effects on synaptic plasticity and neurotransmitter release, including glutamate, dopamine, and serotonin (Manji and Zarate,

2002). Indeed, rapid changes in peripheral BDNF have been suggested as a surrogate marker of antidepressant efficacy in humans (Gorgulu and Caliyurt, 2009; Tadic, et al., 2010).

Because of its involvement in the cellular and behavioral actions of antidepressants and its potential as a therapeutic target, vascular endothelial growth factor (VEGF) has also been the focus of recent investigations. However, the relationship between VEGF and MDD is less consistent than between BDNF and MDD. Recently, a VEGF polymorphism was reported to be associated with MDD (Viikki, et al., 2010). Preclinical models of depression have noted that VEGF mediates antidepressant response in rats, and that its major receptor—FLK-1—is expressed in the hippocampus by electroconvulsive therapy (ECT) (Greene, et al., 2009). VEGF was also found to be induced by other antidepressants such as fluoxetine and desipramine at time points that coincided with their therapeutic action (Warner-Schmidt and Duman, 2007). Nevertheless, clinical studies of chronic antidepressant treatment (eight to 12 weeks) obtained conflicting results; some studies found increased VEGF levels while others observed no change in VEGF levels (Iga, et al., 2007; Ventriglia, et al., 2009).

To date, no studies have examined the relationship between the antidepressant effects of SD in individuals with MDD and the neurotrophic factor VEGF, nor have studies examined the concomitant effects of SD on BDNF and VEGF. This study sought to assess the changes associated with acute SD on BDNF and VEGF plasma levels in patients with MDD.

2. MATERIAL AND METHODS

2.1 Subjects

Eleven subjects participated in the study. Patients were 18 to 65 years old with a diagnosis of MDD single episode or recurrent, without psychotic features, as diagnosed by means of the Structured Clinical Interview for Axis I DSM-IV Disorders—Patient Version (First, et al., 2002). Subjects were required to have a score of ≥ 18 on the HAM-D (Hamilton, 1960) at screening and at the start of SD, with no greater than a 25% decrease in total HAM-D scores between these time points. Patients also had to be experiencing a current major depressive episode lasting at least four weeks. Specific exclusion criteria in the study population included history of antidepressant- or substance-induced hypomania or mania, generalized anxiety disorder, panic disorder, posttraumatic stress disorder, schizophrenia, any other psychotic disorder, primary sleep disorder, drug or alcohol dependency or abuse within the preceding three months, current serious risk of suicide or homicide, or history of more than six DSM-IV mood episodes in the past 12 months. Individuals who had previously not responded to total SD treatment were also excluded, as were those with a clinically significant medical illness, or any clinically significant deviation from the reference range in clinical laboratory test results.

Patients could not have received antipsychotic, mood stabilizer, anticonvulsant, anxiolytic, hypnotic, or antidepressant medications within two weeks of total SD intervention, monoamine oxidase inhibitors (MAOIs) within four weeks of SD, fluoxetine within five weeks of SD, or clozapine or ECT within three months of SD. Thus, all patients were unmedicated for at least two weeks before total SD and in good physical health as determined by medical history, physical examination, routine blood labs, electrocardiogram (EKG), urinalysis, and urine toxicology.

The study was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health (NIH). All subjects received a complete description of the study and written informed consent was obtained before entry into the study. Each patient was assigned a clinical research advocate from the NIH Subject's Protection Unit to monitor the consent process as well as research participation throughout the study.

2.2 Study Design

On Day 1, which followed a drug-free period of at least two weeks, blood samples and clinical ratings were obtained. At 07:00 on Day 1, patients began SD and remained awake until 22:00 the next day (Day 2) when recovery sleep was allowed. The total waking interval was about 39 hours. SD took place on the psychiatry inpatient research unit at the NIH, and patients remained under constant observation by the research staff. Usual daytime lighting patterns were maintained; subjects were not permitted naps, snacks, caffeinated beverages, or cigarettes during SD.

Over the course of Days 1 and 2, trained clinicians rated patients' mood every three hours between 08:00 on Day 1 and 20:00 on Day 2 with the HAMD-6, a modified version of the 21-item HAM-D, as well as with the Young Mania Rating Scale (YMRS) (Young, et al., 1978). The HAMD-6, which was the primary outcome measure, comprises the following subscales of the HAM-D: depressed mood, feelings of guilt, work and activities, psychomotor retardation, psychological anxiety, and general somatic symptoms. Two self-administered rating scales—the Visual Analogue Scale (VAS) (Aitken, 1969), which measures mood, and the Stanford Sleepiness Scale (SSS), which measures how sleepy an individual feels in their current state (the scale is scored from 1–7, with higher scores representing greater sleepiness) (Hoddes, et al., 1973)—were administered hourly; another self-administered rating scale—the Profile of Mood State (POMS) (McNair, et al., 1971)—was administered every three hours. The POMS measures six dimensions of mood: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment, and yields a total mood disturbance score as well as subscales for each dimension.

2.3 BDNF and VEGF assays

Two plasma samples from each patient were collected for the BDNF assay between 10:30 and 11:00, one on Day 1 and the second on Day 2. Blood samples were centrifuged at 1,000 rpm at 4°C for five minutes and stored at –80°C until assay. BDNF was measured using an anti-BDNF sandwich ELISA kit (Chemicon International, Temecula, California) according to the manufacturer's instructions. Plasma was diluted 1:2 with sample buffer and the experiment was carried out in duplicate, blind to clinical information. BDNF standard solution was diluted to concentrations from 7.8 to 500 pg/ml of BDNF in a microplate reader in order to create the standard curve for BDNF levels. After the addition of streptavidin enzyme, substrate, and stop solution, BDNF levels were determined by absorbance in 450nm using optical density values based on standard curve values.

Plasma samples for the VEGF assay were similarly collected for each patient between 10:30 and 11:00 on Days 1 and 2. VEGF levels were measured using a Quantikine VEGF ELISA Kit (R&D Systems, Minneapolis, Minnesota, USA, Catalogue # DVE00) according to the manufacturer's instructions with some minor modifications. Briefly, standards and plasma samples (100 µl) were pipetted into an antibody-coated, 96-well plate containing 50 µl assay diluent and incubated for two hours at room temperature on a shaker. The wells were then washed, 200 µl of VEGF conjugate (enzyme-linked polyclonal antibody specific for VEGF) was added to each well, and then incubated for two hours at room temperature. Following more washes, 200 µl of substrate solution consisting of stabilized hydrogen peroxide mixed with chromogen (tetramethylbenzidine, both supplied by the manufacturer) was added to the wells and incubated for 30 minutes at room temperature. The reaction was stopped by adding 50 µl stop solution, and absorption was measured at 450 nm with a correction set at 570 nm using a Vector3 Spectrophotometer (PerkinElmer, Waltham, MA). All measurements were performed in duplicate. Standards included serial dilutions of VEGF from 7.8 to 500 pg/ml.

2.4 Statistics

The frequent HAMD-6 ratings were used to assess mood change in response to SD over the brief period of time under assessment. Clinical ratings and self-ratings from the various scales were pooled into AM (08:00, 11:00 on both days) and PM (14:00, 17:00 on both days) scores in order to examine diurnal mood variation and SD response.

ANOVAs were used to examine the course of change in clinical ratings over time. Within subjects' factors for TIME of day (AM vs. PM) and TREATMENT (Day 1 vs Day 2) were included along with their interaction. Spearman correlations were used to examine changes in VEGF and BDNF levels as well as changes in the HAMD-6 and SSS. Given the small size of the sample, partial correlations were performed using ranked data.

Patient ratings were performed by trained clinicians who trained together to establish reliability. High interrater reliability was obtained for the HAMD-6 (ICC=0.92) and the YMRS (ICC=0.92). Throughout the study, the same rater conducted most ratings for an individual patient.

3. RESULTS

Table 1 shows the demographic and clinical characteristics of the patients. Nine out of 11 subjects had been taking an antidepressant prior to enrollment and underwent medication taper for the study. One subject was treatment-naïve, and one subject was not taking an antidepressant for their current episode.

3.1 Ratings

Baseline HAMD-6 scores (combined AM and PM scores) for all subjects were 11.7 ± 0.7 (mean $\pm$ sem). Significant mood improvement was seen as a result of SD (TREATMENT: $p=.002$; Figure A). A significant main effect was seen for diurnal mood variation ($p=.04$), with lower values in PM ratings. The interaction between TREATMENT and TIME was not significant ($p=.32$). Using a similar ANOVA model with the YMRS, no main effect was noted for TIME ($p=.19$), nor was the interaction between TREATMENT and TIME significant ($p=.44$). YMRS scores decreased after TREATMENT (SD), but not significantly ($p=.08$).

A similar statistical model was used with the self-rating scales. On the Depression subscale of the VAS, no significant effect was noted for TIME ($p=.67$), TREATMENT ($p=.15$), or the interaction between TIME and TREATMENT ($p=.85$). Similarly, on the POMS total score, no significant effect was noted for TIME ($p=.12$), TREATMENT ($p=.36$), or the interaction between TIME and TREATMENT ($p=.74$).

On the SSS, a main effect was noted for TIME ($p=.03$), so that PM ratings were lower. TREATMENT did not significantly alter SSS scores ($p=.13$), nor was there an interaction between TIME and TREATMENT ($p=.64$).

3.2 Neurotrophic factors and SD

SD was associated with no significant changes in BDNF ($p=.85$) or VEGF ($p=.73$) levels.

3.3 Relationship between change in mood and neurotrophic factors

3.3.1 BDNF—No correlations were found between change in BDNF levels and change in HAMD-6 AM or PM scores (AM: $r=.29$, $p=.41$; PM: $r=.49$, $p=.15$). Similarly, no significant correlations were noted between change in BDNF levels and change in any of the other rating scales (YMRS, VAS, SSS, POMS).

3.3.2 VEGF—A negative correlation was found between change in VEGF levels and change in AM HAMD-6 scores (AM: $r=-.64$, $p=.047$; PM: $r=-.07$, $p=.85$) (Figure B). In addition, a negative correlation was found between change in VEGF levels and change in AM SSS scores (AM: $r=-.78$, $p=.005$; PM: $r=-.38$, $p=.25$) (Figure C). No significant correlations were noted between change in VEGF levels and change in any of the other rating scales (YMRS, VAS, POMS).

Change in AM HAMD-6 did not significantly correlate with change in AM SSS ($r=.34$, $p=.34$). Correlations with change in AM VEGF levels were not substantially altered when AM SSS was removed from the correlation with AM HAMD-6 ($r=-.63$, $p=.069$), or when AM HAMD-6 was removed from the correlation with AM SSS ($r=-.82$, $p=.006$). Thus, changes in AM HAMD-6 and AM SSS appear to be independently related to change in AM VEGF levels.

4. DISCUSSION

This pilot study is the first to note a negative correlation between change in VEGF levels and change in HAMD-6 scores following SD. Notably, this indicates that as depression rating scale scores decreased, VEGF plasma levels increased. In contrast, SD did not alter BDNF levels, nor was an association found between BDNF levels and improvement on the HAMD-6 rating scale.

Previous reports found that a single treatment of ECT modulated brain VEGF expression within hours (Altar, et al., 2004; Newton, et al., 2003). Moreover, central infusion of VEGF has been found to produce an acute antidepressant response in animal models of depression (Warner-Schmidt and Duman, 2007). VEGF is also induced by other antidepressants such as fluoxetine and desipramine at time points that coincide with its antidepressant-like effects (Warner-Schmidt and Duman, 2007). However, clinical studies to date have been inconsistent, showing both a decrease and no change in mRNA and serum VEGF in conjunction with antidepressant treatment. One study of 25 patients with MDD found that eight to 12 weeks of escitalopram treatment did not modulate serum VEGF levels (Ventriglia, et al., 2009). Another study measuring VEGF mRNA levels in the peripheral leukocytes of drug-naïve MDD patients treated with eight weeks of paroxetine found that the magnitude of the decrease in VEGF mRNA levels was significantly correlated with clinical improvement (Iga, et al., 2007). Interestingly, in the present study we observed a significant negative correlation ($p<.005$) between SD-induced changes in AM sleepiness scores and changes in VEGF, such that five of the six subjects with increased sleepiness scores after SD had decreased VEGF levels, whereas five of five subjects who reported no change or decreased sleepiness scores had increased VEGF levels. Because AM HAMD-6 and AM SSS ratings appear to have an independent relationship with AM VEGF levels in the present study, future studies should examine the possibility that daytime sleepiness, or interventions that affect sleep homeostasis, could have contributed to the disparate study findings regarding VEGF and antidepressant effects.

While our patients were carefully monitored by research staff to ensure continued wakefulness, future large studies might also employ the use of ambulatory EEG monitoring to examine the relationship between daytime sleepiness and VEGF change and clinical response. No clinical studies have been conducted to date investigating the effects of rapid antidepressant interventions such as SD, ECT, or ketamine on VEGF levels. However, given that neither ECT nor ketamine affect BDNF (discussed below), but that SD does affect VEGF, it would be interesting to examine ketamine's effect on this neurotrophic factor.

The BDNF results obtained here are in accordance with a recent study investigating the link between ketamine's antidepressant effects and BDNF levels. While MDD patients who underwent a single ketamine infusion experienced significant improvement in Montgomery Asberg Depression Rating Scale (MADRS) scores after ketamine treatment, no changes in BDNF levels were observed compared with baseline, nor were BDNF levels associated with antidepressant response (Machado-Vieira, et al., 2009). Similarly, another study investigating the link between ECT and BDNF levels found that while MADRS scores were significantly improved in patients with MDD immediately after ECT, a time lag of one month after the last ECT session was needed to observe changes in serum BDNF levels (Bocchio-Chiavetto, et al., 2006). While results of that study suggest that a lengthier period of time might be needed to observe changes in BDNF levels associated with antidepressant response, it is worth noting that contrasting findings were observed by Fernandes and colleagues (2009). In that study, HAM-D scores were significantly improved in a group of depressed patients receiving ECT, but no changes in serum BDNF levels were found either before or after treatment (levels were assessed three times a week; the mean number of ECT treatments was 11) (Fernandes, et al., 2009).

To our knowledge, only one human study investigated the correlation between serum BDNF levels and the rapid antidepressant effects of a single night of SD. Gorgulu and colleagues found that a single night of SD therapy improved HAM-D scores and significantly increased serum BDNF levels in depressed patients; HAM-D scores were correlated with changes in BDNF levels ($r = -0.46$) (Gorgulu and Caliyurt, 2009). Several factors could account for the discrepancies between that study and the present one. First, we measured plasma BDNF levels while Gorgulu and colleagues measured serum BDNF levels. Because the major source of serum BDNF in blood is platelets, the lower serum levels seen in depressed patients might be related to lower platelet release. Correlations have been reported between platelet counts and serum BDNF (Teixeira, et al., 2010), suggesting that the reduced serum BDNF levels seen in the study by Gorgulu and colleagues could be due to decreased release of BDNF from platelets in patients with MDD. Second, the clinical characteristics and treatment history of the patient populations varied. The study by Gorgulu and colleagues excluded patients who were actively receiving antidepressant treatment for their current episode, whereas in our sample nine of eleven patients were taking antidepressant medication for the current episode, which were withdrawn two weeks before SD; given that antidepressant treatment affects BDNF levels, these differing treatment histories might have affected the BDNF response to SD.

5. CONCLUSIONS

This study is the first to provide evidence that in MDD, SD treatment is associated with mood-related changes in plasma VEGF levels; BDNF levels were not affected by SD. Further studies using larger samples are needed to confirm these preliminary findings, and to further clarify the unique role of VEGF in neurogenesis and synaptic plasticity, as well as to determine the utility of plasma BDNF and VEGF as biomarkers for the rapid treatment of depressive symptoms.

Highlight

Research Highlights for Ibrahim et al., "Rapid Antidepressant Changes with Sleep Deprivation in Major Depressive Disorder are Associated with Changes in Vascular Endothelial Growth Factor (VEGF): a Pilot Study"

- SD produces a rapid antidepressant response within one day in 50–60% of patients with MDD

- This study evaluated the effects of 39 hours of SD on mood and plasma levels of BDNF and VEGF in MDD.
- 11 patients with MDD underwent SD. HAMD-6 scores decreased significantly after SD.
- As HAM-D scores decreased, VEGF levels increased. SD did not alter BDNF concentrations.
- SD is associated with mood-related changes in plasma VEGF levels, but not plasma BDNF levels.

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Figure A.
Depression (HAMD-6) levels before and after SD in the AM and PM.

Figure B.
Relationship between AM changes in VEGF levels and changes in depressive symptoms (HAMD-6) associated with SD.

Figure C.
Relationship between SD-induced changes in AM VEGF levels and AM SSS ratings

Table 1

Patient demographics and illness characteristics.

	<u>N</u>	<u>%</u>
Gender (Female)	5	45
Ethnicity		
• Caucasian	9	82
• Hispanic	1	9
• African American	1	9
Married	4	36
Employed	5	45
Dysthymia	2	18
Social Phobia	4	36
College Educated	6	55
Depression Type		
• Atypical	2	18
• Melancholic	2	18
• Neither	4	36
	<u>Mean</u>	<u>SD</u>
Age	43.36	9.36
Age of Onset	25.00	13.03
Length of Illness (Years)	19.18	11.22
Current Episode (Months)	46.27	72.61
Number of Previous Episodes	3.36	3.59
Weight (Pounds)	188.37	53.93
BMI	29.41	9.43