Increased Plasma Concentration of Brain-Derived Neurotrophic Factor With Electroconvulsive Therapy: A Pilot Study in Patients With Major Depression

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Objective: The therapeutic mechanism of electroconvulsive therapy (ECT) is unknown. Animal research supports a neurotrophic effect of ECT. To investigate a neurotrophic effect in humans, we examined whether plasma concentration of brain-derived neurotrophic factor (BDNF) increases in patients receiving ECT for major depression.

Method: We conducted a prospective, self-controlled study of 15 patients with a DSM-IV diagnosis of major depressive episode who were referred for ECT at the University of Maryland Medical Center (Baltimore, Md.) between January 2004 and September 2005. Plasma BDNF concentration was measured by enzyme-linked immunosorbent assay before and during an acute course of ECT. Depression severity was measured using the 21-item Hamilton Rating Scale for Depression (HAM-D).

Results: ECT resulted in a significant increase in plasma BDNF ($Z = 2.897$, $p = .004$) from a pre-ECT median of 84.9 pg/mL to a post-ECT median of 141.2 pg/mL. This change was accompanied by a significant decrease in HAM-D score ($Z = 3.411$, $p = .001$) from a pre-ECT median of 30.0 to a post-ECT median of 9.0. BDNF increased in 13 (86.7%) of 15 subjects.

Conclusion: This is the first report of an increase in plasma BDNF concentration in patients receiving ECT. These preliminary results encourage further investigation of a neurotrophic mechanism for the antidepressant effect of ECT.

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In use since 1938, electroconvulsive therapy (ECT) is a highly effective treatment for major depression and mania. ECT affects multiple central nervous system (CNS) variables, including neurotrophic factors, hormones, neuropeptides, and neurotransmitters.[1] Possibly because of the broad-ranging CNS effects of ECT, the therapeutic mechanism of ECT remains elusive. Knowledge of the therapeutic mechanism of ECT would be of significant clinical benefit, as it could reduce stigma associated with the treatment, contribute to novel treatments, and lead to a biomarker of therapeutic response.

Investigators have long sought a quantifiable biomarker of ECT treatment response that could allow psychiatrists to more accurately and reliably determine how many ECT treatments are indicated by following the biomarker. Current methods for determining when to stop a course of ECT are limited to clinical impression of mood change as well as changes in scores on symptom rating scales. Data obtained through these methods can be confounded by ECT-induced cognitive impairment and may lag behind the biological effect of the treatment, resulting in additional, unnecessary ECT treatments. Unnecessary treatments put the patient, particularly the older patient, at increased risk for complications without therapeutic benefit. Alternatively, some patients may receive too few treatments, resulting in residual symptoms and greater vulnerability to relapse.

Given the broad-ranging effects of ECT, potential biomarkers that have been studied include cortisol, adrenocorticotropic hormone, corticotrophin-releasing factor, thyroid-releasing hormone, thyroid-stimulating hormone, prolactin, oxytocin, vasopressin, dehydroepiandrosterone sulfate, and, most recently, tumor necrosis factor α.[1,2] One of the most extensively studied biomarkers is response to the dexamethasone suppression test.[3] However, results with the dexamethasone suppression test, as with other biomarkers studied, have been generally inconsistent and not compelling.[4,5] Therefore, no biomarker of ECT is routinely used in clinical practice.

Accumulating evidence from animal studies supports a neurotrophic effect of ECT. Serial electroconvulsive seizures (ECS) in rodents increase brain-derived neurotrophic factor (BDNF) gene expression, BDNF protein levels, and neuronal sprouting in brain.[6,7] BDNF is a member of the neurotrophin family of peptides and is essential to neuron plasticity, regrowth, and maintenance in the adult brain.[8] BDNF has been hypothesized to play a role in a number of psychiatric disorders, including depression. Although the precise mechanism by which increased BDNF expression could be therapeutic in depression is not known, Duman and colleagues[9,10] have hypothesized that BDNF-induced neuronal sprouting in brain regions, including hippocampus and cerebral cortex, could improve synaptic connectivity and function of neural circuits involved in mood regulation.

BNDF can be measured in the CNS as well as the periphery. Investigators have reported that serum and plasma BDNF concentrations are reduced in individuals with major depression and that, in some patients, serum levels increase with chronic antidepressant treatment.[11–16] BDNF concentrations in serum are approximately 100 to 250 times greater than in platelet-poor plasma.[17,18] Platelets are the major source of serum BDNF, as they sequester (but do not produce) large quantities of BDNF, which are released during clotting.[17] Sources of circulating plasma BDNF include vascular endothelial cells as well as brain. Using radiolabeling techniques, 2 animal studies demonstrate that BDNF crosses the blood-brain barrier from brain to blood.[19,20] Furthermore, Karege and colleagues[21] report a high positive correlation ($r = 0.81$) between serum and cortical BDNF concentrations for developing rats, suggesting that central and peripheral BDNF changes occur in parallel.

In the present study, we measured BDNF in platelet-poor plasma because we intended to measure recent ECT-induced changes in BDNF. Plasma BDNF turns over completely about every 6 minutes,[19] while platelets have a life span of approximately 10 days.[22] Therefore, because it is minimally affected by the amount stored in platelets, platelet-poor plasma BDNF is likely to be a more recent index of brain BDNF levels. Based on the above-mentioned animal and human studies, the clinical aim of this pilot study was to determine whether plasma BDNF concentration has the potential to be used as a biological marker of treatment response. We hypothesized that ECT would increase plasma levels of BDNF in individuals with major depression.

METHOD

Subjects

The study was conducted at the University of Maryland Medical Center (Baltimore, Md.) between January 2004 and September 2005. The 15 subjects studied were individuals who had enrolled in a study of metabolic and neurotrophic markers of mood disorders with the following eligibility criteria: age 18 years or older and DSM-IV diagnosis of either major depressive disorder or bipolar disorder with current major depressive episode with or without psychotic features. After study procedures and possible side effects were fully explained, subjects provided written informed consent to participate in our Institutional Review Board–approved protocol. Upon enrollment, structured clinical interview by a board-certified psychiatrist (W.T.R.) confirmed psychiatric diagnosis.[23] Study personnel also administered the 21-item Hamilton Rating Scale for Depression (HAM-D) to evaluate the presence and severity of the current major depressive episode.[24]

ECT Protocol

The research protocol procedures were limited to venipuncture, structured interview, and administration of rating scales and did not constrain the method of ECT or any other aspect of clinical care. All subjects underwent our standard pre-ECT clinical evaluation including full physical and neurologic exam, magnetic resonance imaging or computed tomography of the brain, complete blood count, and comprehensive metabolic panel as well as blood thyroid stimulating hormone level, rapid plasma reagin test, and vitamin B_{12} and folate levels. According to our ECT protocol, anesthesia was induced by methohexital or propofol, both at doses of 0.5 to 1.0 mg/kg. Neuromuscular blockade was induced with succinylcholine at doses of 0.5 to 1.0 mg/kg. ECT was administered 3 times per week (Monday, Wednesday, and Friday) using a brief-pulse, constant-current Thymatron DGX machine (Somatics Incorporated, Lake Bluff, Ill.). Stimulus electrode placement was either bitemporal or bifrontal. For initial stimulus intensity, we used the percent of maximum energy that most closely approximated a stimulus dose (in millicoulombs) of 2.5 × patient age in years.[25] We increased the percent of maximum energy as needed throughout ECT course to achieve a seizure duration of 25 seconds or greater.

As concomitant antidepressant pharmacotherapy is increasingly the norm for patients receiving ECT[26] and because study protocol did not constrain ECT methods, all patients except 1 in our study received antidepressant medications during ECT. Ten subjects were on stable antidepressant doses during their ECT course, and 4 subjects underwent dose increases during their course. Antidepressants (and number of subjects on treatment with each medication) were bupropion (N = 3), citalopram (N = 1), escitalopram (N = 2), imipramine (N = 1), mirtazapine (N = 3), nortriptyline (N = 4), paroxetine (N = 1), and sertraline (N = 2).

Venipuncture and Rating Scales

We performed venipuncture prior to beginning ECT (median days from blood draw to first ECT treatment = 1,

Table 1. Characteristics and Response of 15 Subjects Receiving Electroconvulsive Therapy (ECT) for a Major Depressive Episode

Variable	Value
Age, median (range), y	50 (27–84)
Sex, N (%)	
Male	11 (73.3)
Female	4 (26.7)
Diagnosis, N (%)	
Unipolar depression	10 (66.7)
Bipolar depression	5 (33.3)
Psychosis present, N (%)	6 (40.0)
Lead placement, N (%)	
Bitemporal	9 (60.0)
Bifrontal	6 (40.0)
No. of ECT treatments in acute course, median (range)	7 (4–10)
Plasma BDNF level, pg/mL	
Pre-ECT, median (IQR)	84.9 (78.4)
Post-ECT, median (IQR)	141.2 (295.6)*
Percent change, median (IQR)	153.4 (150.4)
HAM-D score	
Pre-ECT, median (IQR)	30.0 (9.0)
Post-ECT, median (IQR)	9.0 (6.0)**
Percent change, median (IQR)	70.9 (20.6)

*Differs significantly from pre-ECT value at p = .004.
**Differs significantly from pre-ECT value at p = .001.
Abbreviations: BDNF = brain-derived neurotrophic factor, HAM-D = 21-item Hamilton Rating Scale for Depression, IQR = interquartile range.

interquartile range = 4) and again no earlier than after the fourth ECT treatment. We measured plasma BDNF in blood drawn after the fourth ECT because animal studies have shown that brain BDNF concentrations increase significantly over baseline after 4 electroconvulsive seizures administered once daily.[7] Blood was drawn into BD Vacutainer whole blood/plasma tubes containing sodium citrate (BD, Franklin Lakes, N.J.). Tubes were placed on ice immediately, centrifuged at 3000 g at 4°C for 15 minutes to obtain platelet-poor plasma, and then stored at –80°C until assay. We also administered the HAM-D weekly throughout the ECT course and at the time of the blood draws to monitor change in depressive symptoms. Response to ECT was defined as a 50% decrease in HAM-D score at the end of the acute ECT course.

BDNF Assay

We measured BDNF using the ChemiKine BDNF sandwich ELISA kit (Chemicon International, Temecula, Calif.) according to manufacturer's instructions. Briefly, BDNF protein standard solution was diluted to concentrations from 500 pg/mL to 7.82 pg/mL to create a standard curve plotting BDNF concentration against optical density measured at 450 nm with a microplate reader (Molecular Devices, Sunnyvale, Calif.). Plasma was diluted 1:2 with sample buffer similar to the method of Lommatzsch et al.[18] and assayed blind to clinical information in duplicate. Plasma BDNF concentrations were obtained from optical density values using a standard curve with a 4 parameter linear fit model ($y = a + bx$) and curve fitting software (CurveExpert 1.37; Daniel G. Hyams, Hixson, Tenn.). Assay sensitivity is 7.8 pg/mL per the manufacturer. In our lab, intra-assay and inter-assay coefficients of variation were 6.4% and 9.6%, respectively.

Statistical Methods

As data distributions were not Gaussian, pretreatment and posttreatment BDNF levels and HAM-D scores were compared using the nonparametric, paired Wilcoxon signed rank test. To assess the relationship of dichotomous variables to percent change in BDNF, we used the Mann-Whitney U test. To assess relationships to continuous variables, we used the Spearman rho (ρ). All tests were 2-tailed, with α set at $p \leq .05$, and performed using SPSS 12.0 for Windows (SPSS, Inc., Chicago, Ill.).

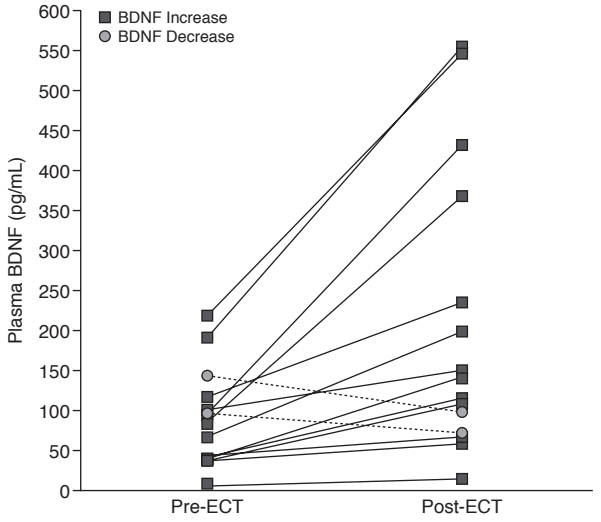
RESULTS

Table 1 shows patient characteristics and results for the 15 subjects receiving ECT for a major depressive episode. We found a statistically significant increase in plasma BDNF following ECT ($Z = 2.897$, $p = .004$). This change in plasma BDNF was accompanied by a significant decrease in HAM-D score ($Z = 3.411$, $p = .001$) from a pre-ECT median of 30.0 to a post-ECT median of 9.0. Figure 1 shows pre-ECT and post-ECT BDNF values for all subjects. Thirteen (86.7%) of 15 subjects responded to ECT. Of ECT responders, 12 (92.3%) of 13 subjects had an increase in BDNF. Of the 2 ECT nonresponders, 1 subject had increased BDNF and 1 subject had decreased BDNF.

We further analyzed our data to determine whether numerous variables had a relationship to the change in plasma BDNF. We found no significant relationship between the percent change in plasma BDNF and the following continuous variables: age, baseline plasma BDNF, ECT treatment number prior to second blood draw, stimulus energy of ECT treatment prior to second blood draw, seizure duration of ECT treatment prior to second blood draw, elapsed time from most recent ECT treatment to second blood draw, pre-ECT HAM-D score, post-ECT HAM-D score, percent change in HAM-D score, time from baseline blood draw to first ECT treatment, and total ECT treatments in the acute course ($p > .137$). We also found no significant relationship between the percent change in plasma BDNF and the following dichotomous variables: race, lead placement, diagnosis, response to ECT, increase in antidepressant medication during ECT, and type of anesthetic administered ($p > .312$).

We did find a significant relationship between percent change in plasma BDNF and the presence of psychosis, with greater percent increases in BDNF in subjects with psychosis ($Z = 2.771$, $p = .007$). For subjects without psychosis, median BDNF more than doubled during ECT,

Figure 1. Plasma Brain-Derived Neurotrophic Factor (BDNF) Concentration Values Before and After a Course of Electroconvulsive Therapy (ECT) in 15 Subjects With a Major Depressive Episode[a]



[a]Pre-ECT values are from single blood samples drawn prior to beginning a course of ECT. Post-ECT values are from single samples drawn no sooner than after the fourth ECT treatment. Post-ECT values differ significantly from pre-ECT values ($Z = 2.897$, $p = .004$). Thirteen subjects had a post-ECT increase in plasma BDNF, and 2 subjects had a post-ECT decrease in plasma BDNF.

with a median (interquartile range) change of 114.9% (147.7%). For subjects with psychosis, median BDNF more than tripled, with a median (interquartile range) change in BDNF of 254.7% (377.1%). We also found a trend between the percent change in plasma BDNF and sex, with men showing greater increases in BDNF ($Z = 1.697$, $p = .090$).

DISCUSSION

This pilot study aimed to determine whether plasma BDNF concentration changes with ECT treatment for a major depressive episode. Consistent with our hypothesis, we found that plasma levels of BDNF increased significantly in individuals receiving ECT for major depression. This increase occurred in 13 of the 15 subjects studied and was accompanied by a significant decrease in depressive symptoms in these patients. In the 13 patients who responded to ECT treatment, 12 had an increase in plasma BDNF. We will briefly discuss these findings as well as their implications for the therapeutic mechanism and clinical practice of ECT in light of study limitations.

With regard to ECT's therapeutic mechanism, our findings of a simultaneous increase in plasma BDNF and decrease in HAM-D score are consistent with a neurotrophic mechanism of ECT. However, they are certainly not conclusive. Without a central measure of BDNF or another brain neurotrophic marker for comparison, we cannot conclude that increased plasma BDNF reflects increased brain BDNF. Cerebrospinal fluid (CSF) BDNF, although less practical as a biomarker due to the invasiveness of lumbar punctures, would be a central measure. However, attempts to measure CSF BNDF in adults have often found BDNF levels below the limit of detection.[27,28] Another putative brain neurotrophic marker is N-acetylaspartate (NAA),[29] which Michael and colleagues[30] measured using magnetic resonance spectroscopy and found to increase in the left amygdala in depressed patients who responded to ECT. Though indirect and correlative, the simultaneous measurement of brain NAA and plasma BDNF may help to determine whether changes in plasma BDNF reflect neuronal changes in brain.

Furthermore, in our study, subjects received concomitant antidepressant medication, which could have contributed to the post-ECT rise in BDNF. To our knowledge, no studies have examined changes in platelet-poor plasma BDNF concentrations with antidepressant pharmacotherapy. Reports of increased serum BDNF levels in patients on antidepressant medication treatment have found increases after at least 6 (and typically after 8 or more) weeks of treatment.[12–14,16] In the present study, however, post-ECT BDNF levels were obtained only 7 to 22 days after the first treatment. It is also important to note that we found no relationship between an increase in antidepressant medications during the ECT course and the percent change in plasma BDNF.

A further concern is that 1 subject had a clinically significant decrease in HAM-D score despite a decrease in BDNF, which may suggest that increased BDNF is not necessary for ECT response in some patients. Alternatively, we may have missed the increase in plasma BDNF in this ECT responder due to insufficient sampling. Another subject had an increase in BDNF but did not respond to ECT, which may suggest that BDNF increase may be necessary but not alone sufficient for a response to ECT. This possibility is consistent with animal work by Vaidya and colleagues.[6] Their study found that although ECS-induced neuronal sprouting is diminished in BDNF heterozygote knockout mice (indicating that BDNF contributes to sprouting), infusion of BDNF into the hippocampus without ECS does not induce sprouting. An animal study by Chen and colleagues[31] also suggests that BDNF may be necessary but not sufficient for a therapeutic response to ECT. They report that pretreatment with the *N*-methyl-D-aspartate (NMDA) antagonist ketamine attenuated ECS-induced mossy fiber sprouting, indicating that perhaps ECS induces sprouting through the combination of increased BDNF and NMDA receptor activation.

With regard to the clinical practice of ECT, this pilot study suggests both the possibilities and the limitations of using plasma BDNF as a biomarker of therapeutic re-

sponse to ECT. BDNF concentrations increased in most subjects; however, concentrations varied considerably among subjects from 5.7 (below the detection limit of the assay) to 553.6 pg/mL. This variation is consistent with other studies using platelet-poor plasma[17,18,32] and may reflect the influence of a number of factors including age and weight[18] or the presence of conditions such as asthma[32] or metabolic syndrome[33] that have been shown to affect plasma BDNF concentration in humans. To attempt to account for some of this variation, we analyzed the relationship between baseline BDNF and the following dichotomous variables using the Mann-Whitney U test: sex, diagnosis (unipolar or bipolar), presence of psychosis, and change in antidepressant medications during treatment. We found no significant relationship between these variables ($p \geq .194$) with the exception of sex. We found that men had a lower baseline BDNF compared to women ($Z = 2.221$, $p = .026$). However, this relationship must be viewed with caution given that our sample contains many more men ($N = 11$) than women ($N = 4$). We also analyzed the relationship of baseline BDNF to the following continuous variables using Spearman's rho: age, weight, BMI, and baseline HAM-D. We found no significant relationship with any of these variables ($p \geq .195$). Again, given our small sample size, these findings should be interpreted with caution.

Given this substantial inter-individual variation, absolute BDNF concentration may have little predictive value in determining ECT response. However, as suggested by our results, use of an individual patient's percent increase in plasma BDNF may hold promise as a biomarker of response. Toward this end, future studies should include drawing of blood after each ECT treatment at fixed intervals to better determine the time course of plasma BDNF changes during a course of ECT. To better understand if plasma BDNF values are abnormally low in depressed subjects and normalize with ECT, future studies should also compare BDNF levels in patients to a matched group of healthy controls.

Our finding that the presence of psychosis was associated with a greater percent increase in plasma BDNF is interesting in light of studies suggesting that patients with psychotic depression are particularly responsive to ECT.[34–36] Although strictly correlative, this finding also suggests that plasma BDNF concentration may be an indicator of treatment response. Furthermore, it may represent yet another biological difference between psychotic and nonpsychotic depression, lending support to the idea that psychotic major depression represents a distinct clinical syndrome.[37]

In spite of limitations, our results suggest that plasma BDNF holds promise as a biomarker of the neurotrophic and antidepressant effects of ECT and merits further study to assess its clinical utility in determining the number and frequency of treatments required for therapeutic response. An easily accessible and quantitative biomarker of treatment response could be useful in individualizing the course of ECT treatment and in preventing adverse effects due to unnecessary treatments.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), escitalopram (Lexapro and others), imipramine (Tofranil and others), ketamine (Ketalar and others), methohexital (Brevital), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), propofol (Diprivan and others), sertraline (Zoloft and others), succinylcholine (Quelicin, Anectine).

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