Serum BDNF levels before treatment predict SSRI response in depression☆

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ABSTRACT

Objectives: The “neurotrophin hypothesis” of depression posits a role of brain-derived neurotrophic factor (BDNF) in depression, although it is unknown whether BDNF is more involved in the etiology of depression or in the mechanism of action of antidepressants. It is also unknown whether pre-treatment serum BDNF levels predict antidepressant response.

Methods: Thirty un-medicated depressed subjects were treated with escitalopram (N=16) or sertraline (N=14) for 8 weeks. Twenty-five of the depressed subjects completed 8 weeks of antidepressant treatment and had analyzable data. Twenty-eight healthy controls were also studied. Serum for BDNF assay was obtained at baseline in all subjects and after 8 weeks of treatment in the depressed subjects. Depression ratings were obtained at baseline and after 8 weeks of treatment in the depressed subjects.

Results: Pre-treatment BDNF levels were lower in the depressed subjects than the controls (p=0.001) but were not significantly correlated with pre-treatment depression severity. Depression ratings improved with SSRI treatment (p=0.001), and BDNF levels increased with treatment (p=0.005). Changes in BDNF levels were not significantly correlated with changes in depression ratings. However, pre-treatment BDNF levels were directly correlated with antidepressant responses (p<0.01), and “Responders” to treatment (≥50% improvement in depression ratings) had higher pre-treatment BDNF levels than did “Non-responders” (p<0.05).

Conclusions: These results confirm low serum BDNF levels in un-medicated depressed subjects and confirm antidepressant-induced increases in BDNF levels, but they suggest that antidepressants do not work simply by correcting BDNF insufficiency. Rather, these findings are consistent with a permissive or facilitatory role of BDNF in the mechanism of action of antidepressants.

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1. Introduction

Brain-derived neurotrophic factor (BDNF) is an important regulatory protein in neurodevelopment, in synaptogenesis and neurogenesis and in protecting the viability of newly differentiated neurons (Duman and Monteggia, 2006); it also has multiple non-CNS effects (Wolkowitz et al., 2011). The “neurotrophin hypothesis of depression” posits that certain central BDNF deficiencies underlie depression, and that antidepressants work via restoration of central BDNF activity (Duman and Monteggia, 2006). Several studies have found that hippocampal and serum BDNF levels are low in un-medicated depressed patients, and that these levels increase with antidepressant treatment (Bocchio-Chiavetto et al.; Brunoni et al., 2008; Duman and Monteggia, 2006; Gass and Hellweg, 2010; Hashimoto, 2010; Sen et al., 2008). The neurotrophin hypothesis is further supported by findings that intra-crebroventricular and intra-hippocampal injections of BDNF produce antidepressant-like effects in animal models of depression (Hoshaw et al., 2005; Shirayama et al., 2002). Conversely, experimentally lowering brain BDNF (or lowering expression of its high affinity receptor, tyrosine kinase TrkB, in neural progenitor cells in the hippocampus) or inhibiting neurogenesis diminishes antidepressant efficacy in animal models (Adachi et al., 2008; Li et al., 2008; Santarelli et al., 2003). Still other studies suggest that region-specific expression of BDNF results in different behavioral consequences, as expression of BDNF in the meso-acumbens dopamine system is pro-depressive (Govindarajan et al., 2006; Krishnan and Nestler, 2008) and local knockdown of BDNF in the ventral tegmental area ameliorates the adverse effects of social defeat (Berton et al., 2006; Krishnan et al., 2007). This raises the possibility that brain region-specific BDNF deficiency (especially in areas of the brain such as the subgranular zone of the dentate gyrus of the hippocampus) may underlie the development of depression in humans,
and/or that treatment-associated increases in BDNF are important in the mechanism of action of antidepressants. While intriguing, not all data are consistent with the neurotrophin hypothesis (Castren et al., 2007; Castren and Rantamaki, 2008; Groves, 2007). BDNF’s role in the etiology of depression may be separate from its role in the mechanism of action of antidepressants (Groves, 2007; Martinowich et al., 2007), and evidence is more consistent with BDNF involvement in certain antidepressant actions than in causing depression (Groves, 2007; Henn and Vollmayr, 2004a; Henn and Vollmayr, 2004b; Larsen et al., 2010; Li et al., 2008; Sahay and Hen, 2007). For example, elimination of hippocampal neurogenesis has no effect on mouse sensitivity to unpredictable chronic mild stress, suggesting that reduced neurogenesis is not a cause of stress-related behavioral deficits (Surget et al., 2008). However, elimination of hippocampal neurogenesis does diminish the antidepressant-like effects of imipramine and fluoxetine, suggesting involvement of BDNF in antidepressant actions (Surget et al., 2008). In another study, heterozygous BDNF knockout mice (+/−), compared to wild-type (+/+) mice, failed to show increased vulnerability to chronic unpredictable mild stress exposure but did show dampened antidepressant effects in several behaviors (Ibarguen-Vargas et al., 2009). In contrast, however, heterozygous BDNF knockout rats did show increased sensitivity to social isolation stress compared to wild-type rats (Duman et al., 2007), and BDNF knockdown in the dentate gyrus induced depression-like behaviors in rats (Taliaz et al., 2010). These observations highlight the complexity of BDNF’s role in affective regulation, and may suggest that region-specific regulation of BDNF also underlies its behavioral effects. As further evidence of BDNF’s role in certain antidepressant actions, BDNF potentiates the effect of paroxetine on hippocampal extracellular serotonin levels in mice, and this effect is blocked by antagonism of BDNF’s high affinity TrkB receptor (Deltchev et al., 2008).

In this study, we sought to determine whether serum BDNF levels are low in un-medicated depressed subjects compared to matched healthy controls, whether serum BDNF levels increase in response to antidepressant treatment, and whether baseline serum BDNF levels and treatment-associated changes in serum BDNF levels are related to concurrent depression ratings. These findings would add to an already large body of evidence regarding serum BDNF levels in depression, and our major goal was not to replicate prior findings of diminished BDNF levels in depression and of BDNF increases with treatment, but to determine whether pre-treatment serum levels of BDNF predict antidepressant response. Finding that higher pre-treatment BDNF levels predict better antidepressant response would argue against a BDNF “deficiency-correcting” effect of antidepressants, and would support a permissive or facilitatory role of BDNF in the mechanism of action of antidepressants.

2. Methods and materials

2.1. Subjects

Thirty subjects with unipolar Major Depressive Disorder (MDD) (DSM-IV) (American Psychiatric Association, 2000), with a minimum score of 17 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1967), who were medication-free for at least 6 weeks before entry into the study, were enrolled. Depressed subjects were recruited from outpatient psychiatric clinics, physician referral, posted fliers and newspaper and internet advertisements (e.g., craigslist.com). The average baseline HDRS-17 rating was 26.1 ± 8.3. Individuals with co-morbid panic disorder were excluded, since they may poorly tolerate typical starting doses of antidepressants (Louie et al., 1993), and individuals with co-morbid post-traumatic stress disorder were excluded, since they may have neuroendocrine regulatory responses different from those of depressed subjects without PTSD (Yehuda, 2006). Other comorbid anxiety diagnoses were allowed if the MDD diagnosis was considered primary. Twenty-eight matched healthy controls with no history of psychiatric illness were also enrolled. Controls were recruited by posted fliers and newspaper and internet advertisements (e.g., craigslist.com). Demographics, including age, BMI, gender distribution and menopausal status, are presented in Table 1. Exclusion criteria for both groups included recent (within 6 months) alcohol or drug abuse as defined by DSM-IV criteria, concurrent psychotherapeutic interventions, poor medical health or abnormal clinical labs, active suicidality, and use of medications that could interfere with the study. All subjects were screened for medical illness by complete medical review of systems, cardiopulmonary and physical examinations by a Board-certified physician and laboratory testing (combined blood count [CBC], electrolytes, renal function, hepatic enzymes, thyroid stimulating hormone). At the time of testing, subjects were also required to pass urine toxicology screens (assessing the presence of drugs of abuse), and women of child-bearing capacity were required to test negative for pregnancy.

2.2. Procedure

The study was approved by the UCSF Committee on Human Research, and all participants gave written informed consent.

### Table 1

<table>
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<th>Demographics, Depression Ratings and Serum BDNF Levels</th>
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<td>Serum BDNF (ng/ml)</td>
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* “MDD- Baseline” excludes the one early placebo responder who was excluded from analysis.

† “MDD-Treated” comparisons between baseline and Week 8 include data only from those subjects who completed 8 weeks of treatment and had all data available.

‡ Twenty-five of the 27 combined subjects had Week 8 BDNF data available.

† Ten of the 12 MDD subjects treated with sertraline had Week 8 BDNF data available.

Based on sertraline group data only.

Based on escitalopram group data only. BMI data not available for the escitalopram group.

*** Different from “MDD- Baseline”: p < 0.001.

** Different from “MDD-Baseline”: p < 0.01.

* Different from “MDD-Baseline”: p < 0.05.
Depressed subjects were studied in two separate studies, one involving the serotonin selective reuptake inhibitor (SSRI), escitalopram, and the other, the SSRI, sertraline. Because the study methodologies were similar, (although see below for differences in study designs) data were pooled to increase statistical power. Secondary analyses examining the results of each group separately are also presented here. In the escitalopram group, 16 depressed subjects (all male) began treatment with placebo for 1 week, followed by escitalopram for 8 weeks (10 mg per day × 4 weeks, followed by 20 mg per day × 4 weeks, as tolerated) in a single-blind, fixed-order, within-subject cross-over manner. Only two subjects did not tolerate the increase to 20 mg per day and were kept on lower doses. The depressed subjects and the psychiatric rater were unaware of the study design and the sequence and duration of treatments. Subjects and the rater were informed only that the subjects would be receiving escitalopram and placebo at various times during the study. Subjects received a fixed number (two) of identically-appearing medication capsules each day of the study, so they would not know when medication changes or adjustments were being made. A study physician who had no role in the psychiatric ratings was responsible for adjusting escitalopram doses based on study protocol, clinical tolerability and response. Depressed subjects showing a greater than 20% improvement in depression ratings during the placebo week were discontinued from the study. One subject met this criterion, leaving 15 escitalopram-treated depressed subjects for analysis. Each of these completed all 8 weeks of active escitalopram treatment. In the sertraline group, 14 depressed subjects (nine female, five male) were treated with sertraline, prescribed in an open-label manner (beginning with 50 mg per day, and the dose was increased to a maximum of 200 mg per day, as tolerated and as warranted by clinical response). In two cases, the beginning dose was initially lowered to 25 mg per day due to transient side effects. Two depressed subjects dropped out of the study before completion for non-study-related reasons (one for school/work commitments and one due to geographical relocation). Twelve depressed subjects completed all 8 weeks of treatment. Serum samples for Week 8 BDNF assays were unavailable for two of these subjects, leaving 10 sertraline-treated depressed subjects with complete sets of data. In all, 27 depressed subjects completed 8 weeks of SSRI treatment and 25 had all blood data available (Table 1). Medication compliance was monitored by pill counts and by plasma antidepressant levels (described below) at Week 8 of treatment for both drugs.

At baseline (pre-treatment for the depressed subjects), all subjects underwent venipuncture to obtain blood for BDNF assays. The controls underwent venipuncture once, and the depressed subjects underwent venipuncture just prior to beginning active antidepressant treatment and again after 8 weeks of antidepressant treatment. In the escitalopram group, the baseline sample for BDNF was drawn after the placebo week but just before the beginning of active drug treatment. Depressed subjects had blood drawn at the same time of day on both occasions (Baseline and Week 8) to facilitate interpretation of within-subject BDNF changes with treatment. In the escitalopram cohort, blood was drawn in the morning (1000 h) or afternoon (1400 h), and in the sertraline cohort, blood was always drawn at 1000 h. The matched control for each depressed subject had blood drawn at the same time of day as the depressed subject to facilitate between-group comparisons.

2.3. Behavioral ratings

Depression severity was assessed in all depressed subjects at Baseline and at the end of Week 8 of antidepressant treatment with the HDRS-17, which was our principal dependent variable. In the escitalopram group only, general clinical improvement was also assessed with the Clinical Global Impression-Severity (CGI-S) scale (Guy, 1976), which was a secondary dependent variable in that group. This latter is a 7-point scale that assesses global severity of illness ranging from “1” = “normal, not at all ill” to “4” = “moderately ill” to “7” = “among the most extremely ill patients.”

2.4. Blood processing and assay methods

Blood for BDNF was collected into serum separator tubes (Vacutainer; BD, Franklin Lakes, NJ). After sitting at room temperature for 1 h to allow clotting, followed by 1 h at 4 °C for platelet activation (Karege et al., 2002), blood was centrifuged at 2000 × g for 20 min, and serum was separated and stored at −80 °C until assay. Serum was assayed for BDNF in duplicate, using a commercial BDNF ELISA assay kit (R&D Systems, Minneapolis, MN, USA). sera were diluted 1:60 with diluent supplied by the kit manufacturer, to obtain BDNF concentrations within the linear range of the standard curve. To evaluate inter-assay variability, an internal control consisting of serum obtained from a single individual, frozen in multiple aliquots, was run on each plate processed. BDNF concentrations of this control sample were measured on several different days and multiple 96-well plates. The R&D Systems Human BDNF Quantikine ELISA Kit was found to have an acceptable 8–14% inter-assay variability of this control sample, when measured on each plate run with human MDD and control subject samples. Intra-assay CV was <10%, or samples were re-assayed. Depressed subjects’ baseline and Week 8 samples, and samples from their matched controls, were run in the same assay batch. Blood for assay of antidepressant and metabolite levels was collected into EDTA (powder) coated tubes. Plasma citalopram and two metabolites, desmethyl- and didesmethyl-citalopram, were measured using a published liquid chromatographic method (Oye-haug et al., 1982). Plasma sertraline and its metabolite, N-desmethyldesmethyl-sertraline, were measured using high-performance liquid chromatography with fluorescence detection, as previously described (Serebruany et al., 2005). Assays were performed by Thomas B. Cooper (Analytical Psychopharmacology Laboratory, Nathan Kline Institute, Orangeburg, NY 10962).

2.5. Statistics

Differences in serum BDNF levels between groups, and changes within subjects, were assessed with independent sample and paired t-tests (or by Mann–Whitney U tests for non-normal distributions), respectively, and correlations between BDNF levels and clinical ratings were assessed with Spearman correlation coefficients. As described above, four subjects had baseline serum BDNF levels but did not have Week 8 levels. This was handled as follows, and depended upon the statistical question being asked in each analysis. To compare baseline serum BDNF levels between depressed individuals and healthy controls, all subjects with baseline data were included (29 depressed and 28 controls). For all analyses that depended upon treatment condition or upon Week 8 biochemical data, only depressed subjects with Week 8 BDNF data were included (25 depressed individuals). Accordingly all within-subject data analyses only included the 25 depressed individuals with both baseline and Week 8 BDNF data. As neither age nor sex was significantly correlated with serum BDNF levels or with HDRS ratings (at baseline or during treatment), analyses were not co-varied for age or sex, although co-varying for these variables did not substantially alter the results. Alpha was set at 0.05 for two-tailed tests.

3. Results

Pre-treatment serum BDNF levels were significantly lower in the 29 depressed subjects who had baseline BDNF values than in the healthy controls (mean ± S.D. = 14.88 ± 5.41 ng/ml vs. 20.91 ± 7.07 ng/ml, respectively) (t = 3.58, p = 0.001; Fig. 1). This difference remained statistically significant when only the 25 depressed subjects who had
both baseline and Week 8 BDNF data were included (t = 3.09, p = 0.003). Baseline BDNF levels were not significantly different in men vs. women (t = -0.28, ns). The difference between depressed and control individuals was statistically significant in both females (t = 2.65, p < 0.02) and in males (t = 2.42, p = 0.02). Mean pre-treatment serum BDNF levels did not differ between the escitalopram- and the sertraline-treated subjects (t = 0.06, ns). Also, the mean serum BDNF levels did not differ in morning blood samples vs. afternoon blood samples in the escitalopram cohort (t = 0.00, ns). Further, baseline serum BDNF levels (across groups) were not significantly correlated with age (r = -0.05, ns) or body-mass index (r = -0.32, ns). Baseline serum BDNF levels were not significantly correlated with platelet counts within the depressed sample (r = -0.09, ns) or within the entire group of subjects (r = 0.27, ns) but tended to be positively correlated within the control group (r = 0.53, p < 0.10). Pre-treatment serum BDNF levels were not significantly correlated with pre-treatment HDRS-17 depression severity ratings (r = 0.21, ns) or with pre-treatment CGI-S ratings (r = 0.04, ns) in the depressed sample.

As expected, HDRS-17 depression ratings significantly improved with antidepressant treatment (Baseline = 26.1 ± 8.3, Week 8 = 13.2 ± 8.9) (t = 6.35, p < 0.001). The escitalopram- and the sertraline-treated subjects had significantly different pre-treatment HDRS-17 ratings (Table 1; t = 5.76, p < 0.001), but treatment-related improvement in depression ratings was statistically significant within each drug treatment group (escitalopram: t = 6.08, p < 0.001; sertraline: t = 4.25, p < 0.02). CGI-S global ratings also significantly improved (Baseline = 3.80 ± 0.68, Week 8 = 2.00 ± 1.07) (t = 5.78, p < 0.001). The mean plasma (escitalopram + citalopram) level at Week 8 was 47.5 ± 26.4 ng/ml; range: 4–94 ng/ml, and the mean plasma (sertraline + N-desmethylsertraline) level at Week 8 was 66.8 ± 36.5 ng/ml; range: 10–146 ng/ml. All individuals had plasma concentrations within the range of published steady state concentrations for these drugs at therapeutic doses (Mauri et al., 2002; Rao, 2007), indicating good compliance with medication treatment.

Serum BDNF levels significantly increased with treatment (from 15.07 ± 5.41 ng/ml at the pre-treatment point to 18.75 ± 6.97 ng/ml at Week 8; t = 3.12, p = 0.005; Fig. 1). (Note that these baseline BDNF values are slightly different than those used to compare MDD subjects with controls at baseline [a between-groups comparison], since the present within-subject analyses only include MDD subjects with BDNF values both at baseline and at Week 8.) This increase was statistically significant within each individual drug treatment group (escitalopram: t = 2.17, p < 0.05; sertraline: t = 2.60, p < 0.05). Escitalopram and sertraline-associated increases in serum BDNF levels did not significantly differ (t = 1.57, ns). By Week 8 of treatment, serum BDNF levels in the depressed subjects were statistically indistinguishable from those in the controls (18.75 ± 6.97 ng/ml, vs. 20.91 ± 7.07 ng/ml) (t = 1.13, p = 0.26). Changes in serum BDNF levels from pre-treatment to Week 8 were not significantly correlated with concurrent changes in HDRS-17 depression ratings (rs = 0.36, ns) or in CGI-S ratings (r = 0.30, ns). BDNF values with the two different SSRI's are presented in Table 1.

Although pre-treatment serum BDNF levels were not significantly correlated with pre-treatment HDRS-17 depression ratings or with pre-treatment CGI-S ratings, pre-treatment serum BDNF levels were significantly correlated with improvements in HDRS-17 depression ratings (r = -0.53, p < 0.01; Fig. 2) and CGI-S ratings (r = -0.60, df = 12, p = 0.03). Specifically, depressed subjects with relatively higher pre-treatment serum BDNF levels showed larger antidepressant response (decreases in HDRS ratings) and overall clinical improvement with antidepressant treatment. Further, pre-treatment serum BDNF levels were significantly higher in the “Responders” (improvement in depression ratings of ≥50%) than in the “Non-Responders” (16.88 ± 5.81 ng/ml vs. 12.70 ± 4.50 ng/ml, respectively) (t = 2.11, p < 0.05) (Fig. 3). The pre-treatment serum BDNF level in the “Responders” tended to be lower than that in the controls, but this was not statistically significant (“Responders”: 16.88 ± 1.50 vs. Controls: 20.91 ± 1.34; t = 1.89, p = 0.07). The relationship between pre-treatment serum BDNF levels and change in depression ratings remained significant after controlling for time of blood draw (morning vs. afternoon) (r = -0.68, df = 12, p = 0.007). Considering the two treatment groups separately, baseline serum BDNF levels significantly predicted antidepressant response (change in HDRS-17 ratings) in the escitalopram group (r = -0.67, p < 0.01) and tended to predict it in the sertraline group (r = -0.60, p = 0.07) (Fig. 2).

4. Discussion

Many studies have already examined serum BDNF levels in unmedicated depressed subjects, and nearly all have found decreased BDNF levels in un-medicated depressed subjects compared to controls (Bocchio-Chiavetto et al.; Brunoni et al., 2008; Groves, 2007; Sen et al.,...
pre-clinical animal studies suggest that BDNF knockout in the hippocampus facilitates depression (Taliaz et al., 2010; Ikeda et al., 2008; Joe et al., 2007; Mitoma et al., 2008). Our current findings are in accord with these prior reports in showing low serum BDNF levels in un-medicated MDD subjects. We also found that serum BDNF levels increased over the course of antidepressant treatment, again in accord with most prior studies (Brunoni et al., 2008; Groves, 2007; Sen et al., 2008). We did not, however, find that baseline serum BDNF levels were significantly correlated with baseline depression ratings, nor did we find that the change in serum BDNF levels with antidepressant treatment was significantly correlated with the change in depression ratings. These findings are consistent with some studies (Hellweg et al., 2008; Lang et al., 2006; Lee et al., 2007; Molendijk et al., 2010; Monteleone et al., 2008; Piccinni et al., 2009) but not with others (Gervasoni et al., 2005; Gonul et al., 2005; Huang et al., 2008; Karege et al., 2002; Lee and Kim, 2008; Lee and Kim, 2008; Mattrisciano et al., 2009; Shimizu et al., 2003; Yoshimura et al., 2007).

Increases in hippocampal and serum BDNF levels with antidepressant treatment have been reported in multiple human and preclinical studies (Bocchio-Chiavetto et al.; Brunoni et al., 2008; Duman and Monteggia, 2006; Groves, 2007; Hashimoto et al., 2004; Sen et al., 2008), yet the mechanistic and therapeutic significance of this is uncertain. Our data, which showed significant increases in serum BDNF levels with antidepressant treatment, but no significant relationship between the changes in serum BDNF levels and changes in depression ratings, suggest that serum BDNF increases per se are not necessarily involved in the therapeutic action of these drugs. Our findings do suggest that BDNF activity (as reflected in serum BDNF levels) is involved in major depression, but not in a simple linear manner regarding the severity of depression across patients. Despite considerable evidence supporting the neurotrophic hypothesis of depression, questions remain as to the extent to which BDNF activity is relevant to the pathogenesis of depression, to the mechanism of action of antidepressants, or to both. For example, there is little convincing evidence that inhibition of BDNF signaling leads to depression (Martinowich et al., 2007) (although see Taliaz et al., 2010)). In contrast, considerable preclinical evidence suggests that BDNF signaling, as well as neurogenesis capacity, is necessary for antidepressant-like effects to occur (Li et al., 2008; Martinowich et al., 2007; Saarelainen et al., 2003; Santarelli et al., 2003). However, this effect may be region-specific (hippocampal), since other pre-clinical animal studies suggest that BDNF knockout in the accumbens is anti-depressive (Berton et al., 2006; Govindarajan et al., 2006; Krishnan et al., 2007; Krishnan and Nestler, 2008). Thus, BDNF's role in depression and its role in antidepressant activity may be separable (Martinowich et al., 2007) and region-specific, with greater evidence of a role in antidepressant actions in the hippocampus. Specifically, BDNF may be a target of antidepressant action or it may facilitate antidepressant action, but it may not be integrally involved in the development or maintenance of depression itself (Martinowich et al., 2007).

The predictive utility of pre-treatment (baseline) serum BDNF levels for subsequent response to antidepressants has rarely been examined. One study found a non-significant trend (p = 0.10) toward lower pre-treatment serum BDNF levels predicting better response to sertraline (Umene-Nakano et al., 2009). In another study, baseline plasma BDNF levels did not significantly differentiate responders vs. non-responders to SSRIs or SNRIs (Yoshimura et al., 2009). Reasons for the apparent discrepancies with our findings are not immediately clear. However, other studies, utilizing non-pharmacologic treatments, did find that higher baseline BDNF levels were associated with larger antidepressant responses in panic disorder patients receiving 10 weeks of Cognitive-Behavioral Therapy (CBT), higher pre-treatment serum levels of BDNF predicted better responses to CBT (Kobayashi et al., 2005). Further, depressed patients (who were non-remitters to antidepressants alone) who had relatively higher baseline serum or plasma BDNF levels responded significantly better to ECT (Piccinni et al., 2009) and to exercise (Toups MS et al., in press) augmentation of antidepressants. The latter investigators hypothesized that baseline BDNF may function as an “augmentation moderator,” and that treatments that raise baseline BDNF levels may improve the efficacy of augmentation strategies.

Our finding that subjects with initially higher serum BDNF levels showed larger antidepressant responses to sertraline or escitalopram after 8 weeks of treatment is interesting in light of findings that depression is characterized by low serum BDNF levels. It is possible that subjects with relatively higher pre-treatment serum BDNF levels may be less depressed or may already be nearing an incipient remission, e.g., their BDNF expression is already nearing that of the healthy controls, and this presages earlier clinical improvement. This explanation is not supported by our data, however, since we found no significant relationship between pre-treatment serum BDNF levels and pre-treatment depressive severity. Alternatively, higher pre-treatment serum BDNF levels may indicate more intrinsic “restorative” capacity and a greater ability of ambient BDNF to synergize with the actions of antidepressants to alleviate depression (Mattson et al., 2004a; Mattson et al., 2004b). It has been suggested, for example, that adequate BDNF concentrations during antidepressant treatment are essential in mediating the therapeutic effects of antidepressants by augmenting activity-dependent neuronal plasticity, restoring mood-related network functioning, facilitating neural adaptations to the environment (Castren and Rantamaki, 2010; Kozisek et al., 2008) and increasing antidepressant effects on hippocampal serotonin levels (Dellthell et al., 2008). Also, relatively higher brain BDNF activity may provide greater neurotrophic support for those neurons being acted upon by antidepressants (D’Sa and Duman, 2002; Groves, 2007; Hashimoto et al., 2004; Mattson et al., 2004b), especially serotonin neurons (Mamounas et al., 1995; Mamounas et al., 2000; Mattson et al., 2004b; Sicilia et al., 1996). Lastly, BDNF exerts other effects in an animal model of spinal cord injury (Joosten and Houweling, 2004). It is possible that such effects of BDNF could synergize with certain antidepressants (Wolkowitz et al., 2011). Regardless of the explanation, our finding that relatively higher pre-treatment serum BDNF levels predict enhanced response to SSRIs suggests that these antidepressants do not work simply by correcting baseline states of BDNF insufficiency.

Strengths of the present study include a minimum 6-week medication-free period before baseline, an 8-week period of antidepressant treatment verified by plasma antidepressant assays, the use
of matched healthy control subjects and the use of an in-house verified BDNF assay kit. Limitations include the use of a relatively small sample, the use of only two single time-point blood samples to characterize BDNF levels and the assessment of antidepressant response only at Week 8. It is possible that earlier or later assessments of antidepressant response could show different relationships with serum BDNF levels. Also, we studied only two SSRI antidepressant drugs, and some studies have noted different BDNF responses to different classes of antidepressants and even to different antidepressants within the same class (Hellweg et al., 2008; Larsen et al., 2008; Matrisiciano et al., 2009; Molendijk et al., 2010) as well as differences in brain regions acted upon (Balu et al., 2008). The present study was not powered to detect differences between escitalopram and sertraline, although our findings with the two drugs were generally similar. Another limitation is the lack of a double-blind design. It is unlikely, but possible, that non-specific “placebo effects” yielded the observed BDNF-clinical outcome correlations. For example, it is conceivable that individuals with higher pre-treatment serum BDNF levels are more likely to be “placebo responders.” Also, there are several non-specific confounds that may affect serum BDNF levels, such as non-fasting status, later measurement, longer sample storage, binge drinking, smoking, exercise, urbanicity and menstrual phase (The latter has been found to affect plasma BDNF levels but has not yet [to our knowledge] been studied in serum) (Bus et al., 2011; Lommatzsch et al., 2005; Seifert et al., 2010; Zoładz et al., 2008). In our study, females were studied in follicular as well as luteal menstrual phases, and the sample sizes were too small to evaluate the effect of menstrual phase on our findings. In our study, non-fasting status, time of blood draw and smoking history did not affect BDNF levels. Binge drinking was associated with higher BDNF levels in our sample (in contrast to Bus et al., who found binge drinking to be associated with lower BDNF levels (Bus et al., 2011)), but the rate of binge drinking in our study was nearly identical in the depressed and control groups (p=0.80), and individuals with recent diagnoses of alcohol abuse were excluded from participation. Although some studies have noted increased BDNF levels following chronic exercise training in humans (Seifert et al., 2010; Zoładz et al., 2008), we noted no significant relationship between self-reported exercise levels and serum BDNF levels in our sample. We also observed no significant relationship between current tobacco consumption and serum BDNF levels. Finally, the relationship between serum BDNF levels and BDNF levels in the brain is unknown, and nothing in our data directly provides no funding and which had no role in study design, implementation, analysis or reporting) and Pfizer Pharmaceuticals (which provided sertraline tablets, but which had no role in study design, laboratory collections and assays, Thomas B. Cooper of the Analytical Psychopharmacology Laboratory at the Nathan Kline Institute (Orangeburg, NY) for assaying plasma antidepressant concentrations, and the nursing and other staff of the UCSF CTsi’s Clinical Research Center. This study was funded by a grant from NIMH (1 R01 MH083784), the O’Shaughnessy Foundation and grants from the UCSF Academic Senate and the UCSF Research Evaluation and Allocation Committee (REAC). This project was also supported by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. This study was also partially supported by Forest Labs (which provided partial funding and escitalopram and matching placebo capsules, but which had no role in study design, implementation, analysis or reporting) and Pfizer Pharmaceuticals (which provided sertraline tablets, but which provided no funding and which had no role in study design, implementation, analysis or reporting).

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Statement of interest

Drs. Mellon and Wolkowitz received an investigator-initiated grant award from Forest Labs, which markets escitalopram. No other authors have financial ties to these or any other pharmaceutical companies. None of the granting agencies had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Ethics statement

This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the Uniform Requirements for manuscripts submitted to Biomedical Journals.

5. Conclusion

The present findings, especially the novel finding that pre-treatment serum BDNF levels predict antidepressant response, require replication. If confirmed, these findings raise the possibility that serum BDNF is a peripheral marker for antidepressant mechanisms of action. In turn, these findings may lead to better predictive tests and a better understanding of both the biology of depression and the factors conducive to better antidepressant response.


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