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BDNF plasma levels and genotype in depression and the response to electroconvulsive therapy

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ABSTRACT

Background: Brain derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of depression and the antidepressant response. Electroconvulsive therapy (ECT) is reported to increase BDNF levels in blood, though only a small number of studies have been conducted to date.
Objective: Our objectives were to: 1) compare plasma BDNF levels in medicated patients with depression and controls; 2) assess the effect of ECT on plasma BDNF levels in medicated patients with depression; 3) explore the relationship between plasma BDNF levels and the Val66Met (rs6265) *BDNF* polymorphism; and 4) examine the relationship between plasma BDNF levels and clinical symptoms and outcomes with ECT.
Methods: Plasma BDNF levels were analyzed in samples from 61 medicated patients with a major depressive episode and 50 healthy controls, and in patient samples following a course of ECT. Fifty-two samples from the depressed patient group were genotyped for the Val66Met *BDNF* polymorphism.
Results: There was no difference in plasma BDNF levels between the control and depressed groups, and there was no difference in plasma BDNF levels in patients following treatment with ECT. In line with previous reports, we show that, in medicated patients with depression, Met-carriers had higher plasma BDNF levels than Val-carriers, though genotype was not related to clinical response. We found no association between plasma BDNF levels and depression severity or the clinical response to ECT.
Conclusions: Our results suggest that plasma BDNF does not represent a suitable candidate biomarker for determining the therapeutic response to ECT.

1. Introduction

Depression is the leading cause of disability worldwide [1], with about 4.4% of the global population living with the disorder [2]. The neurotrophin hypothesis of depression postulates that depression results from stress-induced decreases in the neurotrophin brain derived neurotrophic factor (BDNF) in limbic structures involved in mood regulation [3]. BDNF is present in nearly all brain regions, in neurons, glia, and vascular compartments, and is involved in many central activities, including development, neurogenesis, gliogenesis, synaptogenesis, neuroprotection, and memory and cognition [4].

In support of the neurotrophin hypothesis, it has been shown that stress decreases hippocampal levels of BDNF in rodents [5], and chronic, though not acute, antidepressant administration increases brain BDNF levels [6] and can reverse or block the effects of stress on BDNF [3]. In humans, BDNF levels are reportedly decreased in platelets [7], plasma [8], serum [9,10], cerebrospinal fluid [11], and the brain [12,13] in patients with depression, and antidepressants are known to increase brain and blood BDNF levels in patients [14–19]. Notably, a functional variant of *BDNF* at codon 66 (Val66Met (rs6265) polymorphism) results in abnormal intracellular packaging and secretion of BDNF [20]. Met allele carriers are reported to have poor episodic memory and reduced hippocampal N-acetyl aspartate [20]. This polymorphism, i.e., a valine to methionine substitution at position 66 in the BDNF protein, has been shown to moderate the relationship between stress and depression, with a stronger interaction found for stressful life events than childhood adversity [21]. Interestingly, this

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polymorphism appears to be associated with response to antidepressant treatment, in particular in Asian subjects [22].

While many treatments exist for depression, electroconvulsive therapy (ECT) remains the most acutely effective treatment available for severe, often resistant and sometimes life-threatening, depression [23,24]. Despite its high clinical response and remission rates [24], its mechanism of action remains unclear. Electroconvulsive stimulation (ECS), the animal model equivalent of ECT, has provided some insight into the molecular mechanism of action of ECT [25–27]. In this regard, we and others have shown that brain BDNF levels increase in rats and primates following ECS [16,28–31].

To date, three meta-analyses have examined peripheral blood levels of BDNF in patients with major depressive episodes following ECT [16,32,33]. The meta-analysis by Rocha et al. (2016), including nine studies (n = 207 patients), indicated that BDNF levels in plasma or serum increase in patients with depression following a course of ECT [32]. Studies including patients with bipolar disorder were excluded from this meta-analysis. Another meta-analysis by Brunoni et al. (2014), including 11 studies (n = 221 patients), also indicated that, when serum and plasma data are combined, BDNF levels significantly increase following ECT [33]. Half of the studies included in this meta-analysis comprised patients with depression with psychotic features, though the presence of psychotic features or bipolar disorder had no impact on the results. Interestingly, the meta-analysis by Polyakova et al. (2015) indicated that plasma but not serum levels of BDNF are altered following ECT [16], which is in contrast to the effects of antidepressant medications on BDNF [34]. Four plasma studies met inclusion criteria (n = 108 patients) in this meta-analysis, and BDNF levels were found to increase following ECT [16]. The increase in plasma BDNF positively correlated with the number of ECT treatments. However, reported changes in BDNF have shown no relationship with clinical outcome in any of the above meta-analyses.

The sample numbers in the studies included in the meta-analyses discussed above are small overall. Thus, our aim was to extend knowledge about changes in BDNF levels following ECT in a real-world clinical setting by carrying out exploratory analyses in a relatively larger sample pre- and post-ECT, and also in comparison to healthy controls. We also took the opportunity to carry out exploratory analyses to examine the effect of the *BDNF* Val66Met polymorphism on BDNF levels and treatment response.

2. Material and methods

2.1. Participants

This study was carried out in accordance with the Declaration of Helsinki [35] and was approved by the St Patrick's University Hospital Research Ethics Committee. All participants provided written informed consent. As previously described [36,37], all patients with depression were recruited between 2008 and 2012 in St Patrick's Mental Health Services as part of the EFFECT-Dep Trial (Enhancing the Effectiveness of ECT in Severe Depression; ISRCTN23577151), a pragmatic, patient- and rater-blinded, non-inferiority trial comparing the effects of twice-weekly moderate-dose bitemporal (1.5 × seizure threshold) and high-dose unilateral (6 × seizure threshold) ECT in real-world practice. ECT was administered twice-weekly with hand-held electrodes. Inclusion criteria were age >18 years, referral for ECT for treatment of a major depressive episode diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders [38], and a pre-treatment Hamilton Depression Rating Scale, 24-item version (HAM-D-24) [39] score ≥21. Exclusion criteria were substance misuse in the previous 6 months, being medically unfit for general anesthesia, ECT in the previous 6 months, dementia, or other axis I diagnosis.

Fasting blood samples were taken 07:30–09:30 before the first ECT treatment and 1–3 days after the end of treatment. Ten mL of peripheral blood were collected into K_2EDTA tubes (BD, UK). For plasma analyses, tubes were centrifuged at 2000 × rpm for 10 min at room temperature within 30 min of collection following standard guidelines for plasma collection. Plasma aliquots were collected at 4 °C and then stored at −20 °C for 24 h prior to long-term storage at −80 °C until analysis. For DNA analyses, tubes were stored at −80 °C within 1 h of collection.

Healthy controls were recruited through advertisements in local newspapers and social media. Fasting control blood samples were taken between 07:30–09:30 on assessment days.

Participants with an acute or chronic infectious disease or immune disorder, type I or type II diabetes, or major neurological illness (Parkinson's disease, stroke) were excluded from molecular analyses.

2.2. Clinical assessments

Demographic data, medical and treatment history, and medication changes were documented. Depression severity and response to ECT were assessed using the HAM-D-24. Response was defined as ≥60% reduction in HAM-D-24 score and a score ≤16 at end of treatment. Remission was defined as ≥60% reduction in HAM-D-24 score and a score ≤10 for two weeks.

2.3. BDNF ELISA

BDNF concentrations were determined using a DuoSet® ELISA kit (human BDNF DY248, R&D Systems, UK) as per manufacturer's instructions. Samples were diluted 1:20 in assay diluent prior to addition to the immuno plates (Thermo Scientific, Denmark). The concentration of BDNF in each sample was determined by comparison against a standard curve. Results are expressed as $\log_{10}$ ng/ml. The intra-assay % coefficient of variation (CV) was <3% and the inter-assay % CV was <17%.

2.4. Genotyping

Genomic DNA was extracted using the Autopure LS© (Qiagen, Germany) system by Trinity College Dublin's Biobank Facility (https://www.tcd.ie/ttmi/facilities/trinity-biobank/). Purified DNA had an A260/A280 ratio of 1.7–1.9. Extracted DNA samples were stored at −20 °C until analysis.

The rs6265 single nucleotide polymorphism (SNP) was analyzed using a TaqMan® SNP genotyping assay on a 7900HT sequence detection system (Applied Biosystems, UK). The TaqMan® genotyping call rate was >95% and the samples were in Hardy-Weinberg equilibrium ($p > 0.05$). A small number of HapMap CEU DNA samples (http://www.hapmap.org) were also genotyped for quality-control purposes and were concordant with available HapMap data for this SNP.

2.5. Statistical analyses

Statistical analyses were performed using SPSS, version 21 (IBM Corporation, NY, USA). All data were tested for normality using Q-Q plots and a Shapiro-Wilk test, and log-transformed where necessary. Baseline clinical and demographic characteristics are presented as means with standard deviations (SD) or number (%) per group where appropriate, unless otherwise stated. We adjusted for potential variance owing to body mass index (BMI) and smoking, as these have previously been associated with BDNF levels and mood [40–43]. Smoking status was dichotomized into current versus non-smoker. We also adjusted for age, sex, and educational level.

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