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Brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) levels in post-mortem brain tissue from patients with depression compared to healthy individuals – a proof of concept study

A. Sheldrick^a, S. Camara^b, M. Ilieva^c, P. Riederer^{a,b,c,d,e}, T.M. Michel^{a,c,d,e,*}

^a Department Psychiatry Odense, Psychiatry in the Region of Southern Denmark, J.B. Winslowsvej 20, 5000 Odense C, Denmark

^b Clinical Neurochemistry, Department Psychiatry and Psychotherapy, University Hospital Würzburg, Fürchleinstr. 15, 97080 Würzburg, Germany

^c Department of Psychiatry, Institute for Clinical Research, University of Southern Denmark, J.B. Winslowsvej 19, 5000 Odense C, Denmark

^d Department Neurobiology, Institute for Molecular Medicine, 5000 Odense C, Denmark

^e Center for applied Neuroscience, BRIDGE, Odense University Hospital, Psychiatry in the Region of Southern Denmark, University of Southern Denmark, 5000 Odense C, Denmark

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ABSTRACT

The neurotrophic factors (NTF) hypothesis of depression was postulated nearly a decade ago and is widely acknowledged nowadays. Previous reports suggest that cerebral concentrations of NTF may be reduced in suicide victims who received minimal or no antidepressant pharmacotherapy. Recent evidence suggests that antidepressant treatment may improve or normalise cerebral concentrations of neurotrophic factors. Therefore, we examined the concentration of the brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) in different brain regions (cortex, cingulate gyrus, thalamus, hippocampus, putamen and nucleus caudatus) of 21 individuals – 7 patients of which: 4 patients with major depressive disorder (MDD) and overall age 86.8 ± 5 years who received antidepressant pharmacotherapy (selective serotonin re-uptake inhibitors [SSRI]; tricyclic antidepressants [TCA]), 3 patients with MDD without antidepressant treatment and overall age 84.3 ± 5 years versus 14 unaffected subjects at age 70.3 ± 13.8 . We detected significant elevation of BDNF (parietal cortex) and NT3 (parietal, temporal and occipital cortex, cingulate gyrus, thalamus, putamen and nucleus caudatus regions) between MDD patients receiving antidepressant medication compared to MDD untreated patients and controls. Moreover, we detected significant decreasing in NT3 levels in the parietal cortex of MDD non-treated patients comparing to healthy individuals. Although the limited statistical power due to the small sample size this proof of concept study corroborates data from previous studies, which show that treatment with antidepressants, mediates alterations in neuroplasticity via the action of NTF. However, more research using post-mortem brain tissue with larger samples needs to be carried out as well as longitudinal studies to further verify these results.

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1. Introduction

The neurotrophic factors (NTF) hypothesis of depression was established over a decade ago and is widely acknowledged nowadays [1–5]. NTF are thought to play an important role in the structural alterations seen in distinct brain regions of patients with major depressive disorder (MDD) [6–9]. The NTF hypothesis of depression is also supported by animal studies which showed that on the one hand, infusion of BDNF into the rodent

hippocampus induces antidepressant effects [10] and that on the other hand, antidepressant effects are inhibited in BDNF or tyrosine kinase receptor B (TrkB) mutant rats [11].

A decrease of serum levels of NTF has been reported during the course of MDD [9,12]. Serum levels of BDNF have been shown to be positively correlated with self-rated mood of patients and outcome of psychometric measures [13,14]. Reduced serum BDNF levels of untreated patients suffering from MDD have been shown to recover to baseline levels after successful pharmacological antidepressant treatment [15]. Therefore, NTF such as BDNF have been hypothesised to play an important role in the therapeutic effect of antidepressants [14,16]. BDNF immunoreactivity has been reported to be increased in the hippocampus of patients suffering from MDD who were treated with antidepressants [17]. In

* Corresponding author. Department Psychiatry, Odense universitetsfunktion, Institute for Clinical Research, University of Southern Denmark, J.B. Winslowsvej 20, 5000 Odense C, Denmark. Fax: +45 2 434 0111.

E-mail address: tmichel@sdu.health.dk (T.M. Michel).

contrast, a significant decrease in BDNF and NT3 levels has been reported in the hippocampus and prefrontal cortex (PFC) (only BDNF) of suicide victims who were drug-free compared with non-suicide controls. In antidepressant-treated suicide victims, NT3 levels were not significantly different from non-suicide controls [18]. In addition, animal models [19] and patients [20] suggest that non-pharmacological treatments known to improve depressive mood, particularly electroconvulsive therapy (ECT) seem to have a similar effect.

A hypermethylation of the BDNF gene promoter leading to downregulation of BDNF expression has been observed in MDD patients. A post-mortem analysis of DNA methylation in the Wernicke's area of individuals who committed suicide reveals lower BDNF expression associated with increased DNA methylation of BDNF promoter 4 [21]. Hypermethylation of the same loci has also been detected in the blood [22] and buccal epithelium [23] of MDD patients, suggesting that DNA methylation at BDNF promoters reflect the changes in the brain. In the same time, the global DNA methylation in Wernicke's area, as well as DNA methylation of *TrkB* gene remained similar to control subjects [21,24].

A study uncovered higher post-mortem BDNF levels in the PFC of individuals with antidepressant treatment, associated with lower histone methylation at BDNF promoter 4, compared to healthy controls and depressed individuals without antidepressant treatment [25]. Such increase in BDNF levels associated with a reduction of the inhibitive methylation at BDNF promoter 4 is also observed in blood samples after antidepressant treatment [26], indicating that blood levels can reflect central neuroadaptations. Interestingly, methylation at BDNF promoter 4 is inversely correlated with serum BDNF levels and treatment efficacy [26,27].

To the best of our knowledge, there is only one study investigating BDNF concentrations in the hippocampus of patients with depression [17]. A further study was carried out investigating BDNF and NT3 levels in post-mortem brain tissue of suicide victims [18]. Another study examining BDNF levels in the amygdala of female patients with depression [28], one third of the patients had died of natural causes and the remaining two thirds had committed suicide. To our knowledge, there is no post-mortem data on BDNF and NT3 cerebral levels in geriatric patients with MDD who died of natural causes and had been chronically treated with antidepressant medication. Therefore, we focused on this patient population and we hypothesised that chronic antidepressant pharmacotherapy would change/tune BDNF and NT3 levels in key cortical and limbic regions implicated in the pathophysiology of MDD.

2. Materials and methods

2.1. Subjects

Human brain specimens were obtained from the brain bank held at the laboratory for neurochemistry at the University of Würzburg. Brain tissue from patients suffering from psychiatric illnesses was collected via autopsies performed at the Department of Psychiatry, General Hospital, Mauer, Austria and from controls at the Institute of Forensic Medicine, University of Würzburg, Germany following the standard procedure, including informed consent. The Ethics Committee of the University of Würzburg, Germany, approved of this study (study number 78/79 from 5/7/1999).

We selected specimens of all cortical regions as well as of limbic areas (hippocampus, regio entorhinalis), basal ganglia (putamen, caudate nucleus), thalamus and cingulate gyrus from 7 (2 males and 5 females) individuals with an ante-mortem diagnosis of MDD based on ICD 10 criteria (F33.0–F33.8). Four of them had received

no psychotropic medication (see Table 1) other than selective serotonin re-uptake inhibitors (SSRI) or tricyclic antidepressants (TCA) 6 months prior to death and three of them did not receive any antidepressant treatment (Table 1, ^a marked). The onset of major depressive disorder was before the age of 40 years. Further, we selected 14 control individuals who had no history of psychiatric disorders or treatment with psychotropic drugs (see Table 2). Additional selection criteria for both patient and control groups were:

- no lifetime history of alcohol and substance abuse or dependence;
- no evidence of degenerative disorders or brain injury on histological examination;
- no evidence that death resulted from suicide.

All individuals were German-speaking Caucasians who had died between the ages of 61 to 93 years (except one individual, who was 30 years old). The mean age of death was ($\pm$ SD) 84.3 ± 5 years for MDD group, 86.8 ± 5 years for MDD treated group, and 70.29 ± 13.83 years in the control group. Individuals in all groups had died of similar causes, such as cardiovascular disease, pneumonia, sepsis and hepatic failure. According to the clinical notes, all individuals had exhibited signs of vascular diseases, defined as the presence of one or more of the following conditions: history of myocardial infarction, coronary artery disease, and hypertension or hypertensive cardiomyopathy at the time of death.

2.2. Brain homogenates

The dissection was carried out according to standardized procedures [29]. The left hemisphere was freshly frozen at -80°C whilst the right hemisphere was kept in formalin for neuropathological examination. We selected specimens of all cortical regions as well as limbic areas (hippocampus, regio entorhinalis), basal ganglia (putamen, caudate nucleus), thalamus and cingulate gyrus. Brain extracts were prepared by homogenisation in 20 volumes (w/v) of cold 100 mM Tris–HCl buffer, pH 7.0, containing 400 mM NaCl, 0.05% sodium azide, 4 mM EDTA, 2% BSA, 2% gelatine, 1 mM phenylmethylsulfonyl fluoride (PMSF) and 500,000 KIE aprotinin (all chemicals from Sigma Aldrich), with a Polytron homogenizer (potter S.B. Brown) $12 \times g$ for 30 s, followed by sonification (Branson Sonifier 250, power 2, pulsation's, 20 s). Cellular debris was removed by centrifugation at room temperature at $18,000 \times g$ for 15 min and the supernatants were used for assessing BDNF and NT3 concentrations.

2.3. Protein concentration

The protein content of each sample was measured using the commercial total protein assay Kit (Sigma Diagnostics Inc. St Louis, USA) as described by Lowry et al. [30].

2.4. Neurotrophic factor concentrations

Total concentrations of BDNF and NT3 were measured in the total homogenate with the commercially available sandwich-type ELISA (enzyme linked immunosorbent assay), R&D-Systems: Development System human BDNF DY 248 (range of detection of protein 23.40–1500 pg/mL, specificity: no cross-reactivity at 50 ng/mL with β -NGF, GDNF, NT3, and NT4) and human NT3 DY 267 (range for detection of protein 31.20–2000 pg/mL, specificity: no cross-reactivity at 50 ng/mL with BDNF, CNTF, GDNF, NT4, and β -NGF) according to the instructions of the manufacturer. The measurements are made in double replications and the results are present in ng/mg protein.

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