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Research report

Neurotrophic factors in depression in response to treatment

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor A (VEGF) have been suggested to play a role in the pathophysiology of depression. The neurotrophic model of depression hypothesises that the serum level of e.g. BDNF is decreased during depression and increased in response to treatment. The aim of the present study was to investigate BDNF and VEGF as potential predictors of response to antidepressant treatment.
Methods: We investigated the longitudinal associations between depression scores and serum levels of these neurotrophic factors during antidepressant treatment in 90 individuals with depression of at least moderate severity. Serum levels were measured at baseline and after 8 and 12 weeks of treatment with nortriptyline or escitalopram.
Results: No baseline or longitudinal correlations between depression scores and serum levels of BDNF and VEGF were found, and the baseline serum levels did not predict the MADRS depression score after 12 weeks of treatment or the improvement in depression scores. Interestingly, we observed a significant baseline and longitudinal correlation between serum levels of BDNF and VEGF. The two classes of antidepressant treatment did not affect the results differently.
Limitations: Information on potential factors influencing the serum levels is missing.
Conclusion: Our results do not support the neurotrophic model of depression, since a significant decrease in serum BDNF and VEGF levels after 12 weeks of antidepressant treatment was observed. Our study encourages future studies with large sample sizes, more observations and a longer follow-up period.

1. Introduction

Depression may involve neurodegeneration and aberrant neuronal network function (Duman, 2002; Kubera et al., 2011). As neurotrophic factors are critical regulators of the formation and plasticity of neuronal networks, these factors are recognised as important for a deeper understanding of depression. The neurotrophic hypothesis suggests that mood disorders are associated with a dysfunction of neuronal networks under the influence of neurotrophic factors. A neurotrophic model of depression implicates a stress-induced decline in neurotrophins and in the atrophy in limbic structures which ultimately results in mood disorders that may be reversed or blocked by antidepressants (Duman and Monteggia, 2006).

One of the most extensively investigated targets with respect to neuroplasticity is brain-derived neurotrophic factor (BDNF). BDNF is an important member of the neurotrophin family, abundant in the brain and the periphery and has been suggested to play a pathophysiological role in depression. The first paper to report differences in serum BDNF levels between depressed individuals and healthy controls was published more than 12 years ago (Karege et al., 2002). Since then, a large number of papers have been published as reviewed in a recent meta-analysis (Molendijk et al., 2014). Most papers have shown decreased serum levels in un-medicated depressed individuals compared to healthy controls (Molendijk et al., 2014). Serum BDNF levels of un-medicated depressed patients have been reported to increase to the levels of healthy controls after antidepressant treatment (Shimizu et al., 2003; Aydemir et al., 2005). No significant differences in BDNF

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concentrations among antidepressant treated depressed individuals and healthy controls were observed in the above-mentioned meta-analysis (Molendijk et al., 2014). A functional single nucleotide polymorphism (SNP) within BDNF (rs6265/Val66Met) has been investigated in numerous genetic studies of depression. Some studies have likewise investigated the association between rs6265 and serum BDNF levels in addition to the association between rs6265 and depression scores (Duncan et al., 2009; Lang et al., 2009; Verhagen et al., 2010; Yoshimura et al., 2011; Elfving et al., 2012). In general, the findings from these studies are varied and await further research.

Vascular endothelial growth factor A (VEGF) was originally described as an angiogenic mitogen in 1989 (Leung et al., 1989). More recently, pleiotrophic effects of VEGF in the central nervous system (CNS) have been shown as reviewed by Nowacka and Obuchowicz (2012). VEGF exhibits neurotrophic and neuroprotective effects in the CNS and in the peripheral nervous system, and has also been shown to stimulate neurogenesis (Jin et al., 2002). The relationship between VEGF and depression is therefore of interest.

The first clinical study of VEGF in depressed individuals was published in 2007 and showed a significant increase of mRNA VEGF levels in depressed individuals compared to control individuals (Iga et al., 2007). Since then, more than 12 studies have been published, most of which are included in a recent review by Clark-Raymond and Halaris (2013). The studies have been conflicting as some found a higher VEGF level in depressed subjects versus controls (Kahl et al., 2009; Lee and Kim, 2012; Elfving et al., 2014) and some found no significant differences (Dome et al., 2009; Ventriglia et al., 2009; Kotan et al., 2012). Clinical evidence on the effect of antidepressants on VEGF levels is insufficient and inconclusive. However, most published studies found no significant differences in VEGF mRNA, plasma or serum levels in response to treatment (Iga et al., 2007; Ventriglia et al., 2009; Halmai et al., 2013; Fornaro et al., 2013).

Recently the presence of a mutual interaction between VEGF and BDNF at an intracellular level has been suggested (Fournier and Duman, 2012). The localisation of receptors for BDNF and VEGF on neuroblasts has raised the possibility that these neurotrophic factors could work both independently and/or cooperatively to influence specific stages of neurogenesis (Fournier and Duman, 2012).

Most previous studies investigating the longitudinal changes in BDNF and VEGF levels have focused on response to treatment and included less than 40 individuals. We measured depression scores in addition to serum levels of BDNF and VEGF at baseline and after 8 and 12 weeks of antidepressant treatment in 90 depressive individuals from the Danish contribution to the Genome-Based Therapeutic Drugs for Depression (GENDEP) project.

2. Methods

2.1. Study sample

The GENDEP trial was a 12-week open label part-randomised study of depression with two active pharmacological treatment arms. The study was conducted in nine European academic psychiatry centres from July 2004 to June 2008. It was designed to establish clinical and genetic determinants of therapeutic response to two antidepressants. Subjects were allocated to either escitalopram, a selective inhibitor of the serotonin transporter, or nortriptyline, a tricyclic antidepressant inhibiting the noradrenaline transporter (Uher et al., 2009). The response to treatment was assessed by clinicians using three established measures of depression severity: the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). Measurements were performed at baseline and weekly for 12 weeks. A psychometric analysis found that MADRS was more internally consistent with higher information content than HRSD (Uher et al., 2008), and therefore MADRS was used as the primary depression outcome measure in the present baseline and longitudinal analyses. If relevant in comparison to other studies, the BDI or HRSD depression scores were used.

The present study included the Danish contribution to the GENDEP trial and comprised 92 adult subjects diagnosed with ICD-10/DSM-IV unipolar major depression of at least moderate severity established in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview. A detailed description of the combined GENDEP sample is available elsewhere (Uher et al., 2009).

We included depression scores obtained at baseline, week 8 (T1) and week 12 (T2); however, some depression scores were missing. Depression scores at all three sampling times were available for 57 individuals. Further details on the availability of depression scores are illustrated in Fig. 1.

Response to treatment was defined as a 50% reduction in MADRS score from baseline to T2 and remission was defined as a MADRS score of 10 or less at T2 (Uher et al., 2009). Improvements of MADRS depression scores were calculated as the depression score at baseline minus the depression score at T2.

The study was approved by the ethics boards.

2.2. Serum assessment

Blood for serum samples was collected in anticoagulant-free tubes between 9 am and 3 pm and centrifuged (1550 g, 10 min, 4 °C). Whenever possible, serum was collected at baseline, T1 and T2 (Fig. 1) and stored in aliquots at −80 °C. Serum at all three sampling times (baseline, T1 and T2) was available from 56 individuals. Serum samples from two individuals were not available, leaving 90 individuals for analyses.

Serum VEGF and BDNF levels were measured during summer 2013 using the Quantikine Human VEGF or BDNF Immunoassay (R&D Systems Inc., Minneapolis, MN, USA), respectively. The same batch number was used for the entire experiment. The determination was processed according to the manufacturer's specifications, and the absorbance was measured at 450 nm with wavelength correction set to 540 nm (EL 800 Universal Microplate Reader, Bio-Tek Instruments Inc., Winooski, VT, USA). The standard curves and the samples were run in duplicates.

Serum samples for VEGF measurements were analysed undiluted in order to be within the range of the standard curves. The standard curves ranged from 23 to 1000 pg/ml VEGF. Three internal VEGF controls (low: 114–186 pg/ml, medium: 345–541 pg/ml, high: 706–1094 pg/ml), commercially available (R&D Systems Inc., Minneapolis, MN, USA), were included on each plate.

In contrast, serum samples for BDNF were diluted 1:75 or 1:60 to be within the range of the standard curve. The standard curves ranged from 31 to 1000 pg/ml BDNF. Three internal controls (low: 259–447 pg/ml, medium: 809–1359 pg/ml, high: 1533–2794 pg/ml) commercially available from R&D Systems (USA), were included on each plate.

In general, duplicate determinations of absorbency with an intra-assay variance above 5% were determined again another day and the non-reliable measure discarded. The mean value of the duplicates was used in the statistical analyses.