Psychoneuroendocrinology (2009) **34**, 353—357

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journal homepage: www.elsevier.com/locate/psyneuen

Angiogenic factors in patients with current major depressive disorder comorbid with borderline personality disorder

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Received 3 October 2007; received in revised form 23 September 2008; accepted 24 September 2008

KEYWORDS
Major depressive disorder;
Borderline personality disorder;
VEGF;
FGF-2;
Angiogenesis;
Comorbidity

Summary
Background: Major depression has been associated with endocrine and immune alterations, in particular a dysregulation of the hypothalamus—pituitary—adrenal system with subsequent hypercortisolism and an imbalance of pro- and anti-inflammatory cytokines. Recent studies suggest that vascular endothelial growth factor (VEGF), a cytokine involved in angiogenesis and neurogenesis, may also be dysregulated during stress and depression. These observations prompted us to examine VEGF and other angiogenic factors in patients with major depressive disorder.
Methods: Twelve medication-free female patients with a major depressive episode in the context of borderline personality disorder (MDD/BPD) and twelve healthy women were included. Concentrations of VEGF, VEGF receptors 1 and 2, basic fibroblast growth factor-2 (FGF-2), hepatocyte growth factor (HGF), angiopoetin-2, interleukin-8 (IL-8) and transforming growth factor-β1 (TGF-β1) were determined from serum profiles.
Results: Increased concentrations of VEGF and FGF-2 were found in MDD/BPD patients compared to the healthy comparator group. No group differences were found concerning the other angiogenic factors examined.
Conclusion: Depressive episodes in the context of borderline personality disorder may be accompanied by increased serum concentrations of VEGF and FGF-2. Similar findings have been observed in patients with major depression without a borderline personality disorder. A dysregulation of angiogenic factors may be another facet of the endocrine and immunologic disturbances frequently seen in patients with depressive episodes.

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0306-4530/$ — see front matter
doi:10.1016/j.psyneuen.2008.09.016

1. Introduction

A dysregulation of the hypothalamic–pituitary–adrenal system (HPAS) and increased concentrations of pro-inflammatory cytokines (such as interleukin-6 and tumor-necrosis factor-α) have often been described in major depressive disorder (MDD) (reviews in Heuser, 1998; Schiepers et al., 2005; Dantzer and Kelley, 2007). Similar findings have been observed in patients suffering from major depression comorbid with borderline personality disorder (Kahl et al., 2006). The above-mentioned alterations have been implicated in the development of type 2 diabetes mellitus (T2DM) and cardiovascular disorders, which are more prevalent in depressed patients when compared to non-depressed healthy subjects (Katon, 2003; Musselman et al., 2003).

Recent reports suggest that vascular endothelial growth factor (VEGF) may also be dysregulated during states of stress and depression. VEGF is an angiogenic cytokine able to induce vascular endothelial cell proliferation, migration and vasopermeability in different cell types (Ferrara et al., 2003). VEGF has also been demonstrated to increase the proliferation of neurons in the adult hippocampus, and has been shown to be upregulated after electroconvulsive seizures in rat brains (Newton et al., 2003). The neurogenic/neurotrophic hypothesis of depression states that depression results at least in part from the decreased neurogenesis and/or depletion of neurotrophic factor support, and that this loss may eventually lead to structural abnormalities and compromised neuronal function (Duman et al., 1997). Taken together, this neurotrophic hypothesis of depression led to the assumption that low concentrations of VEGF and other trophic factors, in particular brain derived neurotrophic factor, may be involved in depression.

In in vitro experiments, in contrast to the above mentioned hypothesis, an increase in VEGF mRNA expression and higher VEGF protein concentrations were found after stimulation with cortisol or norepinephrine in two ovarian cancer cell lines and in brown adipocytes (Fredriksson et al., 2000; Lutgendorf et al., 2003). In women suffering form ovarian carcinoma an association between increased VEGF concentrations, feelings of helplessness, and low social well-being was observed. Women who reported higher levels of social well-being had lower VEGF concentrations (Lutgendorf et al., 2002). Depression and cancer related concerns have also been associated with high pre- and postoperative VEGF concentrations in patients suffering from colorectal carcinoma (Sharma et al., 2008). Very recently, Iga and colleagues reported higher VEGF mRNA expression in peripheral leucocytes from drug-naive depressed patients compared to healthy subjects (Iga et al., 2007).

The allocation system comprises all neuroendocrine and vegetative functions that control the distribution of metabolic energy between the brain and the periphery (Peters et al., 2004). Increased VEGF is part of the defensive response of the allocation system to hypoglycaemia (Dantz et al., 2002). This activation of the allocation system is similar to the endocrine alterations seen in depression. Taken together, the published data point towards a dysregulation of VEGF secretion in depression. However, there is uncertainty about the direction of this alteration.

Other angiogenic factors have not yet been studied systematically in depressed patients. As such, we tested our hypothesis of altered concentrations of angiogenic factors by determining the concentrations of VEGF, VEGF receptors 1 and 2, FGF-2, HGF, angiopoetin-2, IL-8 and TGF-β1 in serum profiles of physically healthy, young depressed women.

Earlier studies revealed that ''pure depression'' can be found only in about 20% of the affected population (Melartin et al., 2002). Up to 70% of major depressive episodes in young women occur in the context of personality disorders, and about 30% of depressed patients may suffer from borderline personality disorder (BPD; Corruble et al., 1996; Rossi et al., 2001). Patients with both BPD and Major Depression are characterised by high disease severity and chronicity and report high levels of exposure to childhood and life adversities (Bellino et al., 2005). For this reason we chose to examine young depressed women with BPD in order to study a group with high disease severity and homogeneity regarding the comorbid axis-II diagnosis.

2. Methods

The study was approved by the local ethics committee, and all women in the patient and the comparator group gave their written informed consent prior to the beginning of the study. Twelve unmedicated female patients consecutively admitted to our hospital who met DSM-IV diagnostic criteria for current major depressive episode (MDD) and borderline personality disorder (BPD) were included. All patients were drug-free at the time of testing, and had not received antidepressant, neuroleptic or other medication during the previous 8 weeks. Exclusion criteria were anorexia nervosa, substance-related disorders, schizophrenia, mental retardation, pregnancy, amenorrhea, medical illness (including (auto-) inflammatory disease and cancer), and an age of 17 years or younger. Diagnosis was made using the German version of the Structured Clinical Interview for DSM-IV (SCID I and II). The comparator group consisted of twelve healthy women who also underwent diagnosis by SCID I and II. Subjects with a personal or family history (first degree relatives) of psychiatric illness, personal history of substance abuse or personality disorder according to SCID II were excluded. None of the subjects in the comparator group had a history of single or repeated trauma.

Further psychological examinations for the whole study group included the German version of the Symptom Checklist (SCL-90-R), and the German version of the Beck Depression Inventory (BDI). For data on the psychometric properties of the German version of these scales see Hautzinger et al. (1995) and Schmitz et al. (2000). Physical activity was determined using a 6-point Likert scale (Cuppett and Latin, 2002). Smoking habits were expressed as packyears (cigarettes per day $\times$ years of smoking/20). In all study subjects, menstruation was reported to be regular with intervals ranging from 24 to 35 days during the previous year. None of the study subjects received oral contraception.

The serum of each participant was collected during the early menstrual phase (between day 3 and day 5 after the onset of menstruation) between 15:00 h and 19:00 h at 10 min intervals through an intravenous catheter. Patients were sitting in a quiet room in a semireclined position during the procedure and abstained from eating, drinking, smoking, watching TV or hearing music (Kahl et al., 2006). The serum samples obtained from each participant were then stored at -40° until analysis. Vascular endothelial growth factor (VEGF), VEGF receptors 1