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Review

Peripheral vascular endothelial growth factor as a novel depression biomarker: A meta-analysis

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ABSTRACT

Background: The neurotrophic hypothesis of major depressive disorder (MDD) postulates that the pathology of this illness incorporates a down-regulation of neurotrophin signaling. Brain-derived neurotrophic factor (BDNF) is the most studied neurotrophic mediator regarding the neurobiology of MDD. Nevertheless, emerging evidence has implicated the multi-competent angiogenic and neurogenic molecule – vascular endothelial growth factor (VEGF) – in hippocampal neurogenesis and depression pathophysiology.
Objective: To compare peripheral levels of VEGF between individuals with MDD and healthy controls.
Methods: We performed a systematic review and meta-analysis of original studies measuring peripheral levels of VEGF in participants with MDD compared to healthy controls. We searched the Pubmed/MEDLINE, EMBASE and PsycInfo databases for studies published in any language through December 16th, 2014.
Results: Fourteen studies met eligibility criteria ($N = 1633$). VEGF levels were significantly elevated in individuals with MDD when compared to healthy controls (Hedges's $g = 0.343$; 95% CI: 0.146–0.540; $P < 0.01$). Funnel plot inspection and the Egger's test did not provide evidence of publication bias. A significant degree of heterogeneity was observed ($Q = 38.355$, df = 13, $P < 0.001$; $I^2 = 66.1\%$), which was explored through meta-regression and subgroup analyses. Overall methodological quality, sample for assay (plasma versus serum), as well as the matching of MDD and control samples for age and gender emerged as significant sources of heterogeneity.
Conclusions: Taken together, extant data indicate that VEGF shows promise as a biomarker for MDD, and supports that this mediator may be involved in neuroplasticity mechanisms underlying the pathophysiology of MDD.

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Contents

1. Introduction

The neurotrophic hypothesis, initially postulated by Duman et al. (1997), characterizes major depressive disorder (MDD) as related to aberrant neuroplastic pathways in brain areas subserving emotional and cognitive processing. According to this framework, exposure to chronic unremitting stress results in a down-regulation of brain-derived neurotrophic factor (BDNF) signaling mechanisms, which would impair neurogenesis and resilience (Taliaz et al., 2011). Furthermore, the neurotrophic hypothesis also predicts that the amelioration of depressive symptoms afforded by antidepressants is a result of a relative increase in hippocampal BDNF expression and activity (Duman and Monteggia, 2006). At least five previously published meta-analyses have shown that peripheral BDNF levels were consistently lower in MDD patients when compared to healthy controls, while antidepressant therapy and non-pharmacological treatments such as electroconvulsive therapy (ECT) increased low circulating BDNF levels (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2014, 2008; Sen et al., 2008). Conversely, peripheral BDNF levels did not appear to change following treatment with non-invasive brain stimulation interventions (Brunoni et al., 2015). Nevertheless, a recent extensive meta-analysis indicated that the difference in serum BDNF levels between individuals with MDD and healthy controls is slimmer than once thought (Molendijk et al., 2014).

The initial neurotrophic hypothesis has been updated with evidence pointing to the additional involvement of vascular endothelial growth factor (VEGF) in the neurobiology of MDD (Nowacka and Obuchowicz, 2012). VEGF is a well-known cellular mitogen widely expressed in neurons, which participates in pathophysiological processes related to angiogenesis, such as cancer (Smith et al., 2014) and cardiovascular diseases (De Winter and Klomp, 2010). Moreover, during the past decade, accumulating evidence has suggested a role for VEGF in the pathophysiology of MDD as well as in the mechanism of antidepressant drug action (Fournier and Duman, 2012). For instance, experiments using the chronic unpredictable stress (CUS) and the novelty suppressed feeding (NSF) models for depression have shown that diverse antidepressant drugs as well as electroshock increase the expression of VEGF in the hippocampus of rodents (Warner-Schmidt and Duman, 2007). In addition, antagonism to VEGF type 2 receptors – VEGFR2 – abolishes antidepressant-like behavioral effects in preclinical models for depression (Greene et al., 2009; Warner-Schmidt and Duman, 2007). In individuals with MDD, two studies found no increase in VEGF levels after treatment with antidepressants (Iga et al., 2007; Ventriglia et al., 2009), while a previous report evidenced increments in circulation VEGF after ECT treatment (Minelli et al., 2011). Thus, the effects of antidepressant drug treatment and non-pharmacological intervention on peripheral levels of VEGF remain inconclusive (Clark-Raymond and Halaris, 2013). Furthermore, in the hippocampus, neurogenesis is closely related to angiogenesis (Palmer et al., 2000), and VEGF stimulates adult neurogenesis in the subgranular and subventricular zones, with important implications for the pathophysiology and treatment of MDD (Jin et al., 2002).

Notwithstanding compelling preclinical evidences implicating VEGF as a key mediator involved in MDD pathophysiology, individual clinical studies have provided mixed results, with some studies reporting higher peripheral levels of VEGF in patients with MDD compared to healthy controls (Elfving et al., 2014 Takebayashi et al., 2010), whereas other investigations had found unaltered levels (Ventriglia et al., 2009). These divergent results are likely due to heterogeneous samples, assay techniques, and treatment regiments (Clark-Raymond and Halaris, 2013). For example, Elfving and colleagues (Elfving et al., 2014) investigated a large sample of individuals with MDD ($n = 155$) and healthy controls ($n = 280$), and found higher serum VEGF levels among individuals with depression. However, these authors have also shown that body mass index (BMI) predicted higher VEGF serum levels.

In the present study we aimed to perform a meta-analysis of studies comparing peripheral VEGF levels among persons with MDD versus healthy controls. Additional aims of this study were to determine the degree of heterogeneity and to investigate the potential influence of some moderators, such as BMI and smoking, might have on circulating VEGF levels. This will help to clarify the role of VEFG in MDD.

2. Methods

The protocol for this systematic review and meta-analysis followed recommended guidelines of the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) statement