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Review article

Role of trophic factors GDNF, IGF-1 and VEGF in major depressive disorder: A comprehensive review of human studies

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ABSTRACT

Rationale: The neurotrophin hypothesis of major depressive disorder (MDD) postulates that this illness results from aberrant neurogenesis in brain regions that regulates emotion and memory. Notwithstanding this theory has primarily implicated BDNF in the neurobiology of MDD. Recent evidence suggests that other trophic factors namely GDNF, VEGF and IGF-1 may also be involved.
Purpose: The present review aimed to critically summarize evidence regarding changes in GDNF, IGF-1 and VEGF in individuals with MDD compared to healthy controls. In addition, we also evaluated the role of these mediators as potential treatment response biomarkers for MDD.
Methods: A comprehensive review of original studies studies measuring peripheral, central or mRNA levels of GDNF, IGF-1 or VEGF in patients with MDD was conducted. The PubMed/MEDLINE database was searched for peer-reviewed studies published in English through June 2nd, 2015.
Results: Most studies reported a reduction in peripheral GDNF and its mRNA levels in MDD patients versus controls. In contrast, IGF-1 levels in MDD patients compared to controls were discrepant across studies. Finally, most studies reported high peripheral VEGF levels and mRNA expression in MDD patients compared to healthy controls.
Conclusions: GDNF, IGF-1 and VEGF levels and their mRNA expression appear to be differentially altered in MDD patients compared to healthy individuals, indicating that these molecules might play an important role in the pathophysiology of depression and antidepressant action of therapeutic interventions.
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Abbreviations: MDD, major depressive disorder; YLD, years lost due to disability; BDNF, brain derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; BD, bipolar disorder; TGF-β, transforming growth factor-β; GFR α1, GDNF-family receptors A1; IGF-IR, tyrosine kinase receptor; ECS, electroconvulsive therapy; CSF, cerebrospinal fluid; DSM, diagnostic and statistical manual; ICD, international classification of diseases; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors; HDRS, hamilton depression rating scale; USA, United States of America; GDS, geriatric depression scale; GH, growth hormone

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1. Introduction

The neurotrophin hypothesis of depression was initially formulated by Duman, Heninger, and Nestler (Duman et al., 1997). It postulated that MDD is secondary to aberrant neurogenesis in discrete brain regions subserving emotion and memory regulation[1]. According to this theoretical framework, stress-related alterations in BDNF signaling mediate aberrant neurogenesis in MDD. In addition, this theory indicates that antidepressants are efficacious because they increase BDNF expression, and thus resolve aberrant neuronal plasticity. Preclinical evidence allowing for mechanistic insights seems to fit well with these predictions. For example, Taliaz et al. demonstrated that in rats a reduction in BDNF in the dentate gyrus impairs neurogenesis and induces depressive-like behaviors (Taliaz et al., 2010).

The neurotrophin theory is supported by studies demonstrating a decrease in BDNF in the postmortem brain of patients with MDD compared to non-depressed controls. Analyses of such postmortem brains, that were harvested from depressed patients, found significant reduction in BDNF mRNA and protein levels in critical regions such as hippocampus, prefrontal cortex and amygdala (Dwivedi et al., 2003; Guilloux et al., 2012; Karege et al., 2005). Interestingly, treatment with antidepressant medications was found to increase BDNF levels in the hippocampus, which further substantiated important role of this neurotrophin in MDD (Chen et al., 2001). Blood levels of BDNF in MDD patients were also reported to be significantly low (Karege et al., 2002), which gets restored to normal after antidepressant treatment (Lee and Kim, 2008). Recently, a large meta-analysis study indicated that peripheral BDNF levels are significantly lower in MDD patients compared to controls. In addition, antidepressant treatment increases peripheral BDNF levels in patients with MDD. Electroconvulsive therapy (ECT) also increases peripheral BDNF levels in MDD although the evidence is less compelling.

Thus, the biomedical literature is inundated with myriad of reports highlighting importance of BDNF in the MDD pathophysiology and treatment. In addition to BDNF's role in the pathophysiology of MDD, other trophic factors may also contribute to neuroplasticity abnormalities in this disorder. For instance, glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) were shown to contribute to maturation and maintenance of developing neurons, and modulate adult neurogenesis (Hoshaw et al., 2005; Naumenko et al., 2013). The major objective of the present review is to compile and discuss comprehensively the role of these 3 trophic factors (i.e. GDNF, VEGF, and IGF-1) in MDD.

1.1. Glial cell line-derived neurotrophic factor (GDNF)

GDNF is member of the transforming growth factor-β (TGF-β) superfamily, and is broadly expressed in the mammalian brain. GDNF exerts its effects primarily through binding to GDNF-family receptors α1 (GFR α1) and activation of tyrosine kinase signaling[4]. GDNF is envisaged as a crucial factor for survival and maintenance of both dopaminergic and serotonergic neurons (Lin and Tseng, 2015; Naumenko et al., 2013) due to its neuroprotective properties, particularly against oxidative and neuro-inflammatory damage. Additionally, the interplay between GDNF and dopaminergic pathways seems to be involved in memory and learning (Naumenko et al., 2013).

Preclinical evidence indicates that animals exposed to chronic unpredictable stress (CUS)-a model for depression, exhibit depression-like behavior, and decrease in GDNF expression in their hippocampus (Liu et al., 2012). Interestingly, chronic tricyclic antidepressant treatment helps to reverse depression-like behavior and restores hippocampal GDNF expression to normal (Liu et al., 2012).The role of GDNF in the pathophysiology of MDD has also been investigated in human studies. For example, studies that examined the serum, plasma and mRNA GDNF levels in MDD patients reported a significant reduction compared to healthy controls (Lin and Tseng, 2015). A recent meta-analysis that evaluated GDNF changes in patients with depression strengthened this hypothesis (Lin and Tseng, 2015). Thus, there seems to be a general trend for reduction in GDNF levels in MDD patients. However, there are few studies that reported increase in GDNF levels in the specific brain regions of MDD patients (Michel et al., 2008). For example, one post-mortem study reported an increase in GDNF levels in the parietal cortex of the MDD patients (Michel et al., 2008). Such discrepancy may be attributed to relatively smalls groups of MDD patients (n=7) and healthy controls (n=14) selected for this study.

1.2. Insulin-like growth factor-1 (IGF-1)

Insulin-like growth factor-1 (IGF-1) is an endogenous peptide mainly produced in the liver, but also expressed in the brain. A pioneer study by Bach et al. (1991) examined IGF-1 mRNA expression in the rat brain starting from embryonic day 16 to postnatal day 82. It suggested that IGF-1 mRNA expression is regulated by the pre- and post-natal developmental time, especially in brain regions such as olfactory bulb, cerebral cortex, and hypothalamus (Bach et al., 1991). In contrast, IGF-1 mRNA expression in the brainstem and cerebellum remained constant throughout the