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VEGF as a Potential Target for Therapeutic Intervention in Depression

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Summary

Antidepressants are among the most widely prescribed drugs, however the mechanism underlying their therapeutic efficacy is not known. Neurotrophic factors represent a promising class of targets for antidepressant treatments. We recently characterized a role for vascular endothelial growth factor (VEGF) in cellular and behavioral antidepressant responses. VEGF is a potent mitogen and survival factor for endothelial cells and neurons, and modulator of synaptic transmission. Because VEGF has been implicated in a variety of diseases, understanding the molecular and cellular specificity of antidepressant-induced VEGF will be critical to determine its potential as a therapeutic target in depression.

Introduction

One in 10 women and 4 in 100 men are currently taking antidepressant medications (<http://www.cdc.gov/nchs/pressroom/04news/hus04.htm>). Although antidepressants are widely prescribed, their mechanism of action is not yet understood. Therapeutic responses are delayed for weeks and accompanied by numerous unpleasant side-effects, posing a significant clinical problem for the millions who suffer with Major Depression. Although synaptic levels of neuromodulators like serotonin and norepinephrine are increased immediately by antidepressant treatments, there is typically a 6-8 week delay before therapeutic efficacy is reported, suggesting that a cascade of events including neural adaptations to these treatments is responsible for the relief of depressive symptoms. Over the past decade, a neurotrophic and neurogenic hypothesis of antidepressant action has described an essential role for neurotrophic factors in mediating the therapeutic response to antidepressants.

Clinical and preclinical studies of depression find alterations in neuronal morphology, glial number, and the volume of limbic and cortical brain regions, which can also be altered by antidepressant treatments (for review, see [1]). Neurotrophins, such as brain derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) mediate cell survival and plasticity, making them attractive candidates for the cellular mechanisms underlying both depression-induced changes and antidepressant responses. BDNF, for example, is differentially regulated by stress and antidepressants, and is induced by antidepressants at time points that are consistent with therapeutic and behavioral responses. While there are some challenges associated with directly administering these factors to patients, the potential for neurotrophins as antidepressant targets is a promising area of research [1]

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There are a number of limbic brain structures that have been implicated in the pathophysiology of depression. However, our laboratory and others have focused on the hippocampus for a variety of reasons (for review, see [2,3]) and have accumulated a strong body of evidence in support of a neurotrophic hypothesis. These data include reports that (1) antidepressants promote hippocampal neurogenesis and neuronal survival [4-6]; (2) antidepressants increase hippocampal expression of trophic factors, including vascular endothelial growth factor (VEGF) as well as BDNF [7-10]; (3) central infusions of these trophic factors exert an antidepressant-like effect in rodent behavioral models of depression [11-14] and (4) ablation of hippocampal neurogenesis by irradiation exposure blocks the behavioral effects of antidepressant treatment [15]. Taken together, these studies strongly suggest that trophic factors play a critical role in the actions of antidepressants. In the current review, we focus on VEGF for its involvement in the cellular and behavioral actions of antidepressants and for its potential as a therapeutic target.

VEGF in the Central Nervous System: Beyond Angiogenesis

VEGF was first characterized (and named) for its role in vascular permeability [16] and was later described as a potent endothelial cell mitogen and survival factor. Most well-studied for its role in tumor angiogenesis [17,18], recent work has identified roles for VEGF that extend beyond the vasculature.

There are six members of the VEGF family: VEGF-A, -B, -C, -D, -E, and placental-derived growth factor (PlGF). VEGF-A is the prototypical member of the family and four splice variants of VEGF-A have been identified: VEGF₁₈₈, VEGF₁₆₄, VEGF₁₂₀, and VEGF₁₁₅. VEGF₁₂₀ and VEGF₁₆₄ are the predominant brain isoforms. VEGF₁₂₀ is more highly expressed early in development whereas VEGF₁₆₄ is up-regulated in adulthood.

VEGF binds to two high affinity receptor tyrosine kinases: fetal liver kinase (Flk-1 or VEGFR2) and fms-like tyrosine kinase (Flt-1) and to a family of putative co-receptors called Neuropilins (NRP). VEGF receptor expression varies across cell types, brain regions, and developmental stages. In adults, Flt-1 is expressed by endothelial cells and astrocytes [19,20], whereas Flk-1 is most highly expressed in the rodent hippocampus, by mature neurons, neuronal progenitors and endothelial cells [21-25]. VEGF signaling through its receptors is best characterized in endothelial cells in which Flk-1 activates ERK and PI3K signaling pathways, stimulating cell proliferation and survival [26]. Beyond endothelial cells, research from ischemia/hypoxia models have demonstrated that the neuroprotective actions of VEGF in the brain are mediated by modulation of PI3K pathways, inhibition of ischemia-induced neuronal apoptosis via caspase-3 inhibition, and by enhancing proliferation and migration of neural progenitors (for review, see [27]). In addition to its regulation of endothelial cells and blood vessel formation/permeability, it is clear VEGF has taken a new role in the brain, as a true neurotrophic factor.

VEGF and Neurogenesis

Although it was previously thought that new neurons were not added to the adult brain, it is now clear that neuronal cell birth or neurogenesis occurs in the adult brains of most animals, including humans. Moreover, neurogenesis in the adult brain is a dynamic process that is regulated by a variety of stimuli. Hippocampal neurogenesis is stimulated by environmental enrichment and exercise and is inhibited by stress. Although the function of these newborn neurons remains to be determined, a number of recent papers have begun to shed light on its impact in psychiatric disease. For example, ablation of neurogenesis by irradiation exposure significantly impacts fear and depression-related behaviors [15,28] and neurogenesis is one of the most reproducible and consistent actions of antidepressants and has been targeted for antidepressant drug development [29].

VEGF is a critical player in the neurovascular stem cell niche of the hippocampus. Palmer and colleagues [24] first described the association between the vasculature and proliferating cells in the neurogenic subgranular zone in the hippocampus. Neural progenitors are found proliferating in dense clusters associated with the vasculature. They also demonstrate that as many as one third of proliferating cells in the SGZ are immunopositive for markers of endothelial cells and describe a vascular niche for hippocampal neurogenesis. It is possible that factors such as VEGF promote neuronal cell proliferation indirectly, by stimulating endothelial cell proliferation which in turn induces neural progenitor cell division. Soluble factors released from endothelial cells promote embryonic and adult neural stem cell self-renewal [30]. However, it is also likely that VEGF exerts a direct mitogenic effect on neural progenitors to stimulate their proliferation. VEGF is expressed and released by endothelial cells [31,32] and its receptor Flk-1 is expressed by adult neural progenitors [22]. Recent studies demonstrate that VEGF signaling through Flk-1 increases proliferation of neuronal progenitors [33], stimulates adult neurogenesis *in vitro* and *in vivo* [34], and promotes neurite outgrowth [35,36]. The relationship between endothelial cells and neuronal precursors is dynamic and reciprocal, and *in vitro* models suggest a critical role for VEGF in the cross-talk between neuronal progenitors and endothelial cells [37].

Microarray studies first identified VEGF as a factor robustly regulated in the hippocampus by electroconvulsive seizures (ECS), the most effective treatment for depression [7,8]. These findings were extended in a recent study from our laboratory demonstrating that multiple classes of chemical antidepressants, including serotonin selective reuptake inhibitors (SSRI) (e.g., Prozac) or norepinephrine selective reuptake inhibitors increase VEGF expression in the hippocampus [9] (Figure 1). Moreover, we found that signaling through Flk-1 receptors is required for the induction of neurogenesis by antidepressant treatments [10]. Antidepressants increase VEGF mRNA in the granule cell neurons of the hippocampus [10], and in endothelial cells in the GCL (unpublished data). Among antidepressants, ECS is also the most robust stimulator of hippocampal neurogenesis in rodents [4,5]. A single ECS is sufficient to increase cell proliferation, but this effect is not observed until 72 hours after treatment [4,10]. Interestingly, the induction of VEGF in GCL neurons is observed 24 hours after ECS, returning to baseline by 72h. However, the induction of VEGF in GCL endothelial cells is maintained at the 72h time point (unpublished data). We speculate that endothelial cell-derived VEGF induces neuronal progenitor proliferation, however, we cannot exclude the possibility that mature GCL neurons also contribute to the pool of VEGF that mediates antidepressant-induced progenitor cell proliferation.

In addition to regulation by antidepressants, VEGF can be regulated by other stimuli that impact neurogenesis and depression. Exercise is a potent stimulator of neurogenesis [38,39] and also alleviates the symptoms of depression [40]. Exercise-induced neurogenesis requires peripheral VEGF signaling, suggesting that VEGF is a member of both central and somatic signaling networks that regulate neurogenesis [21]. In contrast to the actions of exercise and antidepressants, stress, which can precipitate or worsen depression, reduces VEGF expression in the hippocampus [41]. This decrease in VEGF expression in the hippocampus could contribute to the inhibitory effect of stress on neurogenesis.

Behavioral consequences of increased VEGF

In addition to its critical role in the cellular actions of antidepressants, VEGF also mediates the behavioral responses to antidepressants. Although it is difficult to model depression in rodents and results of these tests must be interpreted with caution, the currently available models have some validity and are predictive of antidepressant responses [2]. One of the best approaches is to use multiple behavioral models that together provide different types of information regarding the actions of a particular agent. For our recent study, we utilized two classic

behavioral models that predict antidepressant activity (the Forced Swim and Learned Helplessness paradigms) and two tests that are sensitive to chronic antidepressant treatment (Sucrose Preference and Novelty Suppressed Feeding). We found that central infusions of VEGF mimic the action of antidepressants in these models and that blockade of Flk-1 signalling blocks the action of desipramine, a noradrenergic antidepressant [10] (Figure 1). Follow-up studies have demonstrated that VEGF also mediates the behavioral response to the selective serotonin reuptake inhibitor fluoxetine [42].

These findings provide important information regarding the role of VEGF in the behavioral actions of antidepressants that can be appreciated when these models are examined more closely. Two of these models, the forced swim and learned helplessness paradigms, have been used to screen for antidepressant agents and have relatively good validity for this purpose [2]. Moreover, the learned helplessness paradigm, in which exposure to uncontrollable stress leads to helpless behavior also produces other vegetative and endocrine symptoms observed in depressed patients. However, a limitation of these tests is that acute or short-term antidepressant administration produces a response, which is not consistent with the therapeutic time course for these agents or the time lag required for up-regulation of neurogenesis [2]. This implies that VEGF is acting on some other neural process (e.g., neural plasticity) that is independent of adult neurogenesis.

The other two models are used less often for drug screening because they are labor intensive and difficult to establish, but most importantly require chronic antidepressant treatment with a time course (2 to 3 weeks) similar to therapeutic actions of antidepressants [2]. The requirement for chronic treatment is also consistent with the time required for antidepressant induction of neurogenesis, including proliferation, maturation and differentiation of newborn neurons. In addition, the requirement for neurogenesis in these models has been functionally demonstrated [14]. Moreover, chronic unpredictable stress leads to anhedonia (measured by sucrose consumption) that is a core symptom of depression.

The effects of VEGF are not limited to depression-related behaviors. In an elegant study by Cao et al. [43], viral gene transfer experiments demonstrate that VEGF mediates the effects of environmental enrichment on neurogenesis and cognition. In addition, inhibition of neurogenesis by irradiation exposure impairs contextual fear conditioning [28], a behavioral paradigm that requires the hippocampus [44]. ECS partially restores neurogenesis and improves fear-learning in irradiated animals, and this effect requires VEGF signalling through Flk-1 receptors (Warner-Schmidt, et al. unpublished data). However, the direct effects of VEGF on fear conditioning have not yet been reported.

VEGF as a therapeutic target for antidepressants

Most well known for its role in tumor angiogenesis [17,18], a role for VEGF has been identified in a wide variety of conditions and diseases including stroke, Amyotrophic Lateral Sclerosis [45,46], Parkinson's Disease [47], and Alzheimer's Disease [48,49], making its potential as a therapeutic target complex. Blockade of VEGF signalling is also a key target for cancer medications, acting to inhibit the tumor vascularization. It has also not yet been determined which cells in the brain are most affected by antidepressant-induced VEGF and which mediate the behavioral effects of VEGF delivery. Based on our studies, cells in the hippocampus are involved, however, VEGF expression in other brain regions involved in depression-related behaviors, such as the frontal cortex or nucleus accumbens [50], has not yet been investigated. Further characterization of the signaling pathway that mediates the antidepressant effects of VEGF could identify upstream or downstream regulators that could be more specific targets.

There is a strong correlation between cardiovascular disease and depression in patients [51], suggesting a possible role for vascular abnormalities in depression. Since VEGF is such a

critical player in the vascular system, it could be a molecular link between these two diseases. It is also possible that VEGF could become a biomarker for a subtype of depression that is linked to cardiovascular dysfunction.

Conclusions

VEGF expression is induced by multiple classes of antidepressants and signaling through its receptor Flk-1 is required for cellular and behavioral responses to these treatments in rodent models [10]. The behavioral consequences of VEGF could be mediated by alterations in neurogenesis, neuronal cell survival, synaptic plasticity and/or antidepressant-induced increases of endothelial cell number and function. Neurogenesis is required for the behavioral actions of antidepressants in chronic paradigms such as novelty suppressed feeding [15], but it cannot explain the antidepressant-like responses to VEGF in paradigms such as the forced swim and learned helplessness tests. Therefore, it is both possible and likely that VEGF exerts its antidepressant-like effects via multiple cellular mechanisms, including but not limited to, its essential involvement in antidepressant-induced neurogenesis. Furthermore, since VEGF is implicated in a variety of diseases, it will be important to determine which brain regions and cell sub-types mediate the antidepressant actions of VEGF. In addition, characterization of the signaling pathway involved in the neurogenic and behavioral effects of VEGF will provide additional therapeutic targets. Finally, future studies in humans examining serum VEGF levels and genetic analyses will tell us whether VEGF can be used as a biomarker for depression. Taken together, these data support a neurotrophic hypothesis and provide a potential molecular link between depression and cardiovascular disease. Since VEGF influences vascular permeability, angiogenesis, and a variety of disease states, additional studies are required to determine its potential as a therapeutic target for depression.

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Figure 1. Antidepressants and stress differentially regulate VEGF expression, neurogenesis, and depression-related behaviors

In the dentate gyrus of the hippocampus, antidepressants increase VEGF mRNA and protein expression in granule cell layer (GCL) neurons (grey circles) and endothelial cells (EC) (white ovals), stimulating proliferation of EC and neuronal precursor cells (NPC) (black circles) in the subgranular zone (SGZ). Induction of VEGF expression is required for antidepressant behavioral responses in both neurogenesis dependent and neurogenesis independent paradigms, suggesting that VEGF also exerts its effects through additional cellular mechanisms, such as neural plasticity. NSF=novelty suppressed feeding; CUS=chronic unpredictable stress; FST=forced swim test; TST=tail suspension test; LH=Learned Helplessness.