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Role of Vascular Endothelial Growth Factor in Adult Hippocampal Neurogenesis: Implications for the Pathophysiology and Treatment of Depression

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Abstract

It is now well established that the adult brain has the capacity to generate new neurons throughout life. Although the functional significance of adult neurogenesis still remains to be established, increasing evidence has implicated compromised hippocampal neurogenesis as a possible contributor in the development of major depressive disorder. Antidepressants increase hippocampal neurogenesis and there is evidence in rodent models that the therapeutic efficacy of these agents is attributable, in part, to this neurogenic effect. As such, considerable interest has been directed at identifying molecular signals, including neurotrophic factors and related signaling pathways that are associated with antidepressant action and could operate as key modulators in the regulation of neurogenesis in the adult hippocampus. One interesting candidate is vascular endothelial growth factor (VEGF), which is known to possess strong neurogenic effects. In this review, we will discuss the involvement of VEGF signaling in the etiology and treatment of depression.

Keywords

depression; neurogenesis; vascular endothelial growth factor; antidepressants; neurotrophic factors; stress

1. Introduction

Major depressive disorder (MDD) is a highly debilitating and pervasive illness affecting as many as one in five Americans [1]. Given that MDD is a leading cause of disability worldwide [2], a high priority of current research is to understand the cellular and molecular mechanisms underlying depression, including both its pathogenesis and recovery. Despite the difficulty in elucidating the neural substrates of MDD [3], a growing body of evidence has suggested that dysfunction of the hippocampus may underlie, at least in part, the etiology and treatment of this disorder [4, 5]. Recent neuroimaging and histopathological studies of postmortem tissue have confirmed this view and provide some interesting clues

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about the nature of the cellular changes in the hippocampus of depressed patients [6]. Along these lines, one of the most consistent findings reported in the literature is decreased hippocampal volume and altered cell morphology in patients with MDD, especially those with a long history of pharmacoresistant depression [7–11]. In addition, preclinical studies have also demonstrated that exposure to high levels of glucocorticoids or chronic stress can result in neuronal atrophy and cell loss in this region [12, 13]. Although several different mechanisms could contribute to the structural alterations and neuronal loss in the hippocampus, one of the most intriguing findings to emerge from this research is the possible involvement of neurogenesis in the etiology and treatment of stress-related illnesses, notably MDD.

It was believed that neurogenesis was restricted mainly to prenatal or early postnatal periods. However, over the last two decades, it has been shown that new neurons are continuously generated in discrete regions of the brain throughout life leading to wide acceptance that neurogenesis occurs in the adult brain. The two major germinal sites, the anterior portion of the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus, serve as the main regions of neurogenesis in the mature brain. Adult hippocampal neurogenesis in particular has received extensive study mainly due to its phylogenetic conservation across multiple species, including non-human primates and humans [14–16], and its possible relevance in various neuropsychiatric and neurological conditions, as well as playing a role in cognitive processes such as learning and memory. In the context of MDD, preclinical studies have found that stress and chronic antidepressant treatment exert opposing effects on hippocampal neurogenesis. That is, stress generally results in a reduction in hippocampal neurogenesis and chronic antidepressant treatments increase neurogenesis [17, 18] suggesting that adult hippocampal neurogenesis may be an important component in the therapeutic action of antidepressants.

Significant progress has been made at uncovering the molecular signals that regulate the division of neuronal progenitors in the adult hippocampus and could serve as potential candidates in the treatment of MDD. In this review, we will discuss one such target, vascular endothelial growth factor (VEGF), and the role of this multifunctional growth factor in both the pathophysiology and treatment of depression. We will first provide an overview of the neurogenic/neurotrophic hypothesis of depression and the role of VEGF signaling in adult neurogenesis. Finally, we will present the current state of knowledge of VEGF in animal models of stress and in the behavioral action of antidepressants.

2. The Neurogenic/Neurotrophic Hypothesis of Depression

The birth of new cells in the adult hippocampus of rodents can be detected by the presence of cells labeled by an injection with the DNA synthesis marker bromodeoxyuridine (BrdU) or by examining the expression of endogenous cell cycle marker proteins (e.g., PCNA, Ki67, phosphohistone H3). In the adult rat hippocampus, it has been estimated that over 9000 new cells are born each day [19]. Of the dividing cells that survive (~50%) [20], the vast majority express markers of neuronal lineage (e.g., doublecortin, NeuN) confirming that these newborn cells differentiate into neurons. These newly generated neurons migrate into the adjacent granule cell layer where they mature into functional neurons that participate in a variety of important functions, such as certain types of hippocampal-dependent learning and memory [21]. Although the number of new neurons produced in humans and nonhuman primates is thought to be much lower than in rodents [14, 15, 22], the presence of adult neurogenesis in a wide range of species suggests an important role for new neurons in shaping the form and function of the adult brain [23].

The formation of new neurons and their survival in the adult hippocampus is regulated by a diverse number of environmental and physiological stimuli. For example, hippocampal-dependent learning tasks [24, 25], wheel running [26], exposure to an enriched environment [26, 27], and increased levels of estrogen [28] have each been shown to increase the birth of new neurons or influence their survival. Conversely, neurogenesis is decreased with ageing [29], glucocorticoids [30], drugs of abuse [31], and stress [32]. These findings underscore that neurogenesis is not simply a passive process involving the simple replacement of lost neurons due to, for example ageing, but instead reflects an adaptive response to challenges imposed by an animal's environment or its internal state [33].

2.1 Opposing Actions of Stress and Antidepressants on Neurogenesis

Chronic stress is thought to play an important role in the etiology of MDD [34, 35], and is commonly used to elicit depressive-like behaviour in laboratory animals [36]. To date, several studies have found that stress has profound effects on neurogenesis, causing a rapid and robust reduction in the birth of new neurons in the hippocampus. Decreased neurogenesis has been reported following chronic exposure to most types of stressors, such as restraint [37, 38], isolation [39], social defeat [40], prolonged sleep deprivation [41], corticosterone [42], and mild intermittent stress [43, 44], and after acute exposure to predator odor [45] or inescapable footshock stress [46]. The effects of stress on neurogenesis can also be extremely long-lasting. For example, prenatal stress can result in a life-long reduction in neurogenesis of the dentate gyrus with concomitant impairment in hippocampal-dependent spatial learning in rodents [47] and heightened emotional reactivity in rhesus monkeys [48].

Although a sustained increase in circulating stress hormones could account for the decrease in hippocampal neurogenesis seen in these stress experiments [49], previous work has found that animals exposed to inescapable footshock, which results in a state of behavioural despair, also display a reduction in hippocampal cell proliferation and neurogenesis for at least 9 days after exposure to this stressor [46]. Importantly, no significant differences in circulating levels of glucocorticoids could be found between stressed and non-stressed animals at this time point strongly arguing that the persistent reduction in neurogenesis seen with inescapable shock is not simply due to the effects of acute stress but instead reflects the behavioral state of the animal at that time.

These findings have led to a proposal that deficiencies in neurogenesis, as well as the neurotrophic/growth factors that regulate this process, might be important in the development of MDD. This neurogenic/neurotrophic hypothesis states that prolonged exposure to stress and/or stress hormones leads to a decrease in the production of newborn dentate granule cells contributing to an overall impairment in corticolimbic function and in the eventual emergence of depressive-like symptoms [50]. Conversely, the hypothesis also proposes that enhanced neurogenesis is beneficial and viewed necessary for the treatment of MDD. Support for this aspect of the hypothesis has come from several lines of evidence. First, all major classes of antidepressants, including serotonin and noradrenalin reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants increase hippocampal neurogenesis in rodents and nonhuman primates [18, 51–54]. Interestingly, non-pharmacological interventions known to possess antidepressant-like properties, such as exercise and acute sleep deprivation, also promote neurogenesis [26, 55]. Second, chronic but not acute antidepressant administration is necessary to trigger hippocampal cell proliferation and neurogenesis, which parallels the therapeutic time-course of these drugs. Interestingly, a rapid and robust induction of neurogenesis has been found with electroconvulsive seizures (ECS) [56, 57]—a treatment with more rapid onset of antidepressant effects [58] and with superior efficacy in treating patients with pharmacoresistant depression [59]. Third, the neurogenic action of antidepressants appears

to be highly specific; these compounds influence proliferation, survival, and maturation of new neurons, but do not alter the fate-choice of undifferentiated precursor cells into neurons or glia [18, 51, 60]. Moreover, the lack of neurogenic effects when typical antipsychotics (e.g., haloperidol) [18] or drugs of abuse (e.g., opiates) [61] are given chronically further underscores the specificity of neurogenic effects with antidepressant treatment. However, treatment with atypical antipsychotic drugs, which are sometimes used as an adjunct therapy for some depressed patients [62], have been shown to increase neurogenesis [63]. And lastly, the most compelling evidence in support of the neurogenic hypothesis comes from studies showing that blockade of hippocampal neurogenesis blocks some of the behavioral effects of drugs. In one study, Santarelli and colleagues [53] demonstrated that targeted irradiation in mice, which kills dividing cells and blocks antidepressant-induction of neurogenesis in the hippocampus, also blocks the ability of antidepressants to produce a behavioral response in the novelty suppressed feeding (NSF) test, a paradigm sensitive to chronic antidepressant treatment. Similar findings have been confirmed in the rat. For example, Jiang and colleagues [64] reported that focal irradiation also blocks the neurogenic and behavioral effects of chronic treatment with the synthetic cannabinoid HU210 in rats.

2.2 Is Neurogenesis Crucial For The Emergence of Depressive or Anxiety Behavior?

At first glance, the ability of antidepressants to increase neurogenesis and block the effects of stress provides compelling evidence that neurogenesis might be a key contributor in the etiology and treatment of MDD and related anxiety disorders. There is, however, some conflicting data. For example, inescapable footshock stress produces helpless behavior in only a subset of animals, yet both helpless and non-helpless animals ostensibly show a similar reduction in hippocampal cell proliferation [65]. Moreover, exposing animals to escapable footshock stress does not induce helplessness, but still results in a decrease in cell proliferation [46]. It has also been shown that acute immobilization stress decreases the rate of cell proliferation, but does not lead to helpless behavior during escape/avoidance training nor does it increase vulnerability to acquire learned helplessness during training [65]. These findings suggest that while different forms of stress can lead to similar changes in proliferation rate, a reduction in cell proliferation alone does not necessarily contribute to the emergence of behavioral despair—at least not in the inescapable footshock paradigm. However, it should be pointed out that these studies only focus on acute changes in cell proliferation at one time-point and how this change in proliferation affects behavioral despair. It remains possible that alterations in cell survival or the proportion of new cells adopting glial or neuronal phenotypes may play a critical role in maintaining the helpless behavioral state once it has emerged. In other words, inescapable footshock may similarly reduce proliferation in both helpless and non-helpless animals, yet the successful induction of a “helpless” state may preferentially affect the differentiation and/or survival of new neurons in helpless versus non-helpless animals. This is an important factor to consider since there is evidence that chronic stress can decrease neurogenesis while preserving rates of cell proliferation [44]. Although the findings presented here argue that impaired neurogenesis does not appear to underlie behavioral despair in the learned helplessness model, it is important to consider that this could reflect limitations of this model in adequately reproducing the time course and features of depression. Clearly, additional research is necessary on this subject.

Attempts have been made to establish a more direct relationship between impaired neurogenesis and depressive or anxiety-related behavior. It was found that experimentally reducing levels of neurogenesis in wild-type animals does not affect anxiety behavior in the open-field, light-dark choice, NST, and elevated plus maze [66, 67], nor does it alter depressive behavior in the forced swim or sucrose consumption tests [53, 68]. One limitation of these earlier studies was that the methods used to block neurogenesis, e.g.,

methylazoxymethanol acetate or irradiation, also produce a myriad of side-effects that can confound the interpretation of the behavioral results. However, genetic approaches have been recently applied to selectively knockdown hippocampal neurogenesis and these studies have largely confirmed many of the earlier studies [66].

Although these findings suggest a non-casual role of impaired neurogenesis in the development of depressive behavior, more recent studies have found that experimentally manipulating levels of neurogenesis may be more important for inducing some behavioral features related to anxiety disorders [69–72]. For example, deletion of TrkB in adult progenitors [69] or forebrain-specific overexpression of follastin (an activin-inhibitory protein) [70] decreased neurogenesis and increased anxiety-like behavior. While these genetic manipulations (e.g., TrkB receptor, Activin) were found to affect neurogenesis, they are also likely to exert changes on additional biological functions that could contribute to the development of anxiety-related behavior. Therefore, direct evidence linking neurogenesis in the development of anxiety has been lacking. However, recent work by Revest and colleagues [72] shows that inducible overexpression of the pro-apoptotic protein Bax in Nestin-rtTA/Tet-Bax bigenic mice selectively kills neural precursors and produces a striking increase in anxiety-related behavior, such as increased avoidance of novel and potentially threatening environments. These authors also show that acute treatment with chlordiazepoxide reverses the enhanced anxiety behavior of these bigenic animals suggesting that hippocampal neurogenesis does not mediate the anxiolytic effect of benzodiazepines—a finding consistent with past work demonstrating that anxiolytic drugs do not impact neurogenesis. Taken together, the findings indicate that neurogenesis may play a more important role in the regulation of anxiety states, rather than depression, and could represent a novel target in the treatment of anxiety disorders.

2.3. Is Neurogenesis Crucial For Antidepressant Action?

Although impaired neurogenesis is neither necessary nor sufficient to generate depression in rodents, it may still be an important target in the treatment of depression and in the action of antidepressants. Indeed some of the strongest findings in support of this hypothesis have come from studies showing that induction of neurogenesis is necessary for the behavioral changes associated with chronic antidepressant treatment [53, 64, 73]. However, chronic fluoxetine treatment in BALB/c mice, a strain that exhibits high anxiety on several different behavioral measures, reduces anxiety- and depressive-like behavior in the NSF and forced swim test, but does not cause an increase in hippocampal cell proliferation [74]. In addition, SNAP9487, an antagonist of the melanin-concentrating hormone receptor, has antidepressant actions even after irradiation [75]. These findings suggest that neurogenesis is not the only process through which antidepressants exert their behavioral effects. Recent evidence has found that some behaviors might be more critically dependent on neurogenesis than others. For example, hippocampal irradiation in mice subjected to the chronic unpredictable mild stress paradigm blocks the antidepressant effect of a CRF₁ antagonist in the NSF test but not on two different tests of depressive behavior [73]. Furthermore, work by David et al. [76] shows that targeted hippocampal irradiation prevents the behavioral effects of the classic antidepressant fluoxetine on the NSF test, but not on the forced swim test or open field. In support of these observations, the finding that neurogenesis is involved in anxiety-related behavior (*see above*) is consistent with the evidence that blocking the neurogenic effects of antidepressants appears to more directly affect behavioral measures related to anxiety than depression, and further highlights the neurogenesis-dependent and -independent pathways underlying the behavioral effects of antidepressant drugs.

The findings demonstrate exceptions regarding the role of neurogenesis in depression and in the behavioral action of antidepressants. However, it is possible that the current behavioral assays may not be sensitive enough to detect a subtle pro-depressive phenotype in animals

with reduced neurogenesis. Additionally, a reduction in neurogenesis may be insufficient to generate a depressive-like phenotype by itself, but may enhance the susceptibility to acquire MDD in the presence of other genetic or environmental risk factors. Indeed recent work has shown that suppression of neurogenesis increases HPA axis response to an acute stressor highlighting the importance of new neurons in regulating aspects of HPA axis and stress response reactivity to environmental stressors [71]. These results are in accordance with clinical observations that repeated episodes of stress combined with specific genetic anomalies can increase the likelihood of developing MDD later in life [77]. For example, genomic variants that alter 5-HT function during early development act on the neural circuitry underlying the expression of anxiety and fear [78]. Since genomic variations in neurotransmitters or neurotrophic factors would be potentially operative at any time over the lifespan of the organism, it is interesting to consider that these variations may have a more profound effect on the maturation and circuit integration of new neurons during key periods of development (e.g., early adolescence) or after periods of adverse environmental experiences. It is clear that further study will be necessary to determine if neurogenic anomalies arising from aberrant gene-environmental interactions contribute to the pathology and behavioral changes associated with MDD.

2.4 Is Impaired Neurogenesis Linked To Depression in Humans?

Another challenge to the neurogenic hypothesis of depression comes from the limited evidence of reduced hippocampal neurogenesis in patients with MDD relative to non-depressed patients [79, 80]. However, there is evidence that antidepressants can enhance hippocampal cell proliferation in both human [80] and non-human primates [54]. Thus it is plausible that a reduction in neurogenesis in patients with MDD could be masked by an antidepressant-mediated increase in cell proliferation and neurogenesis. Nonetheless these findings suggest that a level of caution must be taken when attempting to make a causal link between deficiencies in neurogenesis and the development of MDD.

3. Neurotrophic Factors Regulating Neurogenesis

The mechanism(s) through which antidepressants increase hippocampal neurogenesis has been the subject of intense experimental investigation. Although early theories of antidepressant action focused mainly on the ability of these compounds to reverse imbalances in monoamine neurotransmitters, such as dopamine, noradrenalin, and serotonin, it has become increasingly clear that elevations in intrasynaptic levels of biogenic amines alone cannot account for the therapeutic efficacy of antidepressants. For instance, acute treatment with antidepressants alter synaptic levels of monoamines within hours after administration, yet the onset of therapeutic and behavioral effects is slow and takes several weeks or even months of chronic administration to occur in humans [81] as well as in animals [82]. The necessity of chronic treatment has led to the widely accepted view that adaptations involving the regulation of neurotransmitter receptors, signal transduction events, and gene transcription are likely contributors in antidepressant action.

Among the many downstream changes associated with chronic antidepressant treatment, increasing evidence has implemented a role for neurotrophic factors in both the cellular and behavioral action of these drugs. Neurotrophic factors are instrumental in the regulation of neuronal growth and differentiation during development, but also play an important role in cell survival and plasticity in the adult brain [83–87]. There are several neurotrophic factors expressed in the central nervous system, such as brain-derived growth factor (BDNF), fibroblast growth factor-2 (FGF-2), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth (VEGF), and each are known to enhance specific aspects of adult neurogenesis and have been implicated as possible targets of antidepressant action (Table 1). One interesting candidate is vascular endothelial growth factor (VEGF). For excellent

summaries describing the role of other neurotrophins in depression and neurogenesis, please *see* [88–93].

3.1 Vascular Endothelial Growth Factor and Neurogenesis

Although most work has focused on the role of VEGF signaling in the context of angiogenesis, it has become increasingly clear that VEGF is a multifunctional growth factor that can influence neurons in a number of ways [94]. For example, VEGF acts as a neurotrophic factor that regulates neurite outgrowth and maturation during development [95–97], and can influence a variety of complex processes, such as learning and memory, in the adult brain [85]. Moreover, insights into the role of VEGF in stroke, motor neuron degeneration, and tumorigenesis, have suggested that VEGF or its downstream effectors might be promising therapeutic targets for the treatment of various neurological disorders [98].

VEGF is a 45 kDa basic heparin binding homodimeric glycoprotein that belongs to a family of highly conserved vasoactive growth factors. VEGF was first characterized for its role in vascular permeability [99], and was later described as a potent stimulator of endothelial cell proliferation and blood vessel formation. There are five main members of the VEGF family: VEGF A, VEGF B, VEGF C, VEGF D, and placental derived growth factor. VEGF A is the most abundantly expressed growth factor of this family in the nervous system. It is a key molecular regulator of angiogenesis and neurogenesis, and is integral to the events discussed in this review. Other growth factors in this family, VEGF B, C, and D show limited expression in the nervous system (e.g., VEGF B) or are involved mainly in lymphatic development (VEGF C and D). Alternate exon splicing of a single VEGF gene results in the generation of four different molecular species of VEGF mRNA: VEGF₁₂₁, VEGF₁₆₅, VEGF₁₈₉, and VEGF₂₀₆. The predominate isoform in most vertebrate tissue, including adult brain, is VEGF₁₆₅. VEGF binding to its receptors fetal liver kinase (Flk-1 or VEGFR2) and fms-like tyrosine kinase (Flt-1) results in activation of the intracellular tyrosine kinase domains of these receptors that in turn influence the activity of several downstream signaling pathways, many of which are important in neurogenesis [100–102].

In the adult hippocampus, neurogenesis is closely linked with ongoing angiogenesis. For example, seminal studies by Palmer and colleagues [103] showed that mitotically active neuronal precursors proliferate in dense clusters around dividing vascular endothelial cells. These endothelial cells in turn release soluble factors that induce the differentiation of neural precursors, thus defining an angiogenic or neurovascular niche that is permissive for neuronal growth and development to occur [103]. This close association between neurogenesis and angiogenesis suggests a mechanism by which neurogenesis can respond and adapt to a variety of factors either derived from or carried by the vasculature [104]. Emerging evidence indicates that VEGF participates in this cross-talk between endothelial cells and neuronal precursors in the adult SGZ. VEGF can promote neurogenic effects indirectly by stimulating endothelial cell production and the release of key neurotrophic factors (e.g., BDNF) which in turn supports the survival and integration of newborn neurons [105]. However, VEGF can also exert direct mitogenic effects on neuronal precursors in vitro and in vivo through an Flk-1-dependent mechanism [106–109]. In vitro studies using neurospheres from mice lacking the Flk-1 receptor demonstrate the importance of VEGF signaling through this receptor system in the survival of cultured neural stem cells [110]. Finally, intracerebroventricular administration of VEGF stimulates adult neurogenesis in the SVZ and SGZ [107, 109].

4. VEGF and Depression: Blood, Sweat, and Tears

Recently, there has been intense effort made to examine the role of vascular dysfunction in the development of MDD. It has been known that cerebrovascular diseases, including stroke, are associated with a high incidence of MDD [111]. Decreased cerebral blood flow and metabolism in the hippocampus and prefrontal cortices are frequently found in patients with treatment resistant depression [112, 113]. In this context, it is worth mentioning that endothelial cell dysfunction, decreased endothelial progenitor proliferation, and decreased capacity for neovascularization also occurs with ageing [114], a finding that may explain the frequent association of depression in the elderly population [115]. Because dysfunction in angiogenesis and neurogenesis are common features of depression, VEGF may serve as a common thread that connects angiogenesis and neurogenesis related changes with the pathophysiology and treatment of MDD.

One of the first studies to provide a link between VEGF and the treatment of MDD came from an extensive microarray analysis conducted by our laboratory to examine neurotrophic factor changes after ECS [116]. We found that ECS treatment results in a robust up-regulation of VEGF gene expression. Although little is known about the underlying molecular action of ECS, several studies have implicated synaptic remodeling and neurogenesis in the hippocampus [56, 117]. These findings were recently extended by our laboratory. In one study, we showed [118] that a single ECS treatment was sufficient to induce cell proliferation in the hippocampus 48 hrs later. This neurogenic effect of ECS treatment could be effectively blocked by pretreatment with SU5416, a small molecule inhibitor of the VEGF-Flk-1 receptor. Surprisingly, we also found that ECS and VEGF infusion both stimulated the proliferation of certain populations of neuronal precursor/progenitor cell cohorts. For example, acute ECS or VEGF treatments preferentially stimulated the early division of Type 1 quiescent stem cell-like precursors (QNP; BrdU+/GFAP+/Sox2+) followed by division of Type 2 transiently amplifying progenitor cells (ANP; BrdU+/GFAP-/Sox2+) at later time points. Interestingly, recent studies of chemical antidepressants demonstrate a mechanism different from ECS. In these studies, nestin-reporter mice show a preferential increase in ANP but not QNP proliferation after chronic fluoxetine treatment [119]. Taken together, the ability of different classes of antidepressants to modulate distinct stages of neurogenesis suggests that the superior efficacy of ECS over chemical antidepressants to treat refractory MDD might be related to its ability to stimulate both QNP and ANP proliferation through an up-regulation in VEGF-dependent signaling (Figure 1).

The potential role of VEGF in the actions of chemical antidepressants has also been examined. Multiple classes of antidepressants, including selective serotonin and noradrenalin reuptake inhibitors, increase the expression of VEGF mRNA and protein in the hippocampus [107, 120]. However, induction of VEGF requires chronic administration (i.e., 2 weeks) of these chemical antidepressants, a much slower onset of action compared to ECS. Pharmacological inhibitors of the VEGF-Flk-1 receptor block the neurogenic response of these treatments [107, 116]. Given these findings, it is surprising that chemical antidepressants differ from ECS in stimulation of ANP and QNP progenitor cells, respectively. One possibility is that this slower onset of VEGF induction by chemical antidepressants is sufficient to only promote ANP but not QNP proliferation, which in turn leads to an overall lower neurogenic effect and slower time course relative to ECS (Figure 1).

Importantly, VEGF signaling is also critical in mediating the behavioral effects of antidepressants. A summary of the behavioural responses associated with VEGF treatment is provided in Table 2. Briefly, we found that intracerebroventricular infusion of VEGF

mimics the action of antidepressants on several behavioral paradigms that are responsive to subchronic or chronic administration of chemical antidepressants (e.g., learned helplessness, forced swim test, and NSF task) [107]. Importantly, infusion of SU5416 blocked the behavioral effects of desipramine (a selective noradrenalin reuptake inhibitor) and fluoxetine (a selective serotonin reuptake inhibitor) on the learned helplessness and forced swim test (Table 2). Many of these findings have been independently confirmed using a transgenic animal model in which VEGF gene expression is controlled by the cyclic AMP cascade [121].

Although these findings provide compelling evidence that VEGF-Flk-1 dependent signaling is important in mediating antidepressant-like effects [107, 120], they do not address whether a decrease in VEGF signaling occurs with depression. There is, however, some evidence that stress can affect VEGF signaling. For example, Bergstrom and colleagues [122] showed that exposing animals to chronic stress decreases VEGF expression in the hippocampus. In addition, one study found that chronic stress results in a decrease in both VEGF expression and the number of proliferating cells in proximity to capillaries in the SGZ [123]. Moreover, following a 3 week recovery, proliferating cells near vascular zones were still reduced in number compared to proliferating cells in less vascular covered regions of the SGZ [123]. Interestingly, there is clinical evidence that polymorphic variations in the VEGF gene might contribute to the susceptibility in developing treatment resistant depression in some human patients [124]. In accordance with these findings, we have also shown that blockade of VEGF expression blocks the beneficial effects of antidepressants, either fluoxetine or desipramine, in animals subjected to a chronic unpredictable stress paradigm providing strong evidence that VEGF signaling is important in mitigating the deleterious effects of chronic stress in the brain [96] [120].

In addition to modulation by antidepressants, VEGF can also be regulated by other stimuli that impact neurogenesis. Studies have shown that the neurogenic effects of exercise in mice requires peripheral VEGF [125], which can be actively transported into the brain and thereby directly influence neurogenesis in the adult hippocampus. Importantly, exercise possesses antidepressant-like effects [126]. However, it is not presently known if blockade of peripheral VEGF contributes to the behavioral or neurogenic effects of antidepressant drugs. Finally, although the exact contribution of VEGF-induced adult neurogenesis remains unclear, VEGF has been found to be effective in a number of tasks previously shown to be associated with neurogenesis. For instance, rats housed in an enriched environment or trained in the Morris water maze (a hippocampal-dependent learning task) show an elevation in hippocampal mRNA and protein expression of VEGF [85]. Moreover, bilateral infusion of an adeno-associated viral vector encoding VEGF into the hippocampus increased neurogenesis and improved learning, while silencing hippocampal VEGF expression had negative effects on neurogenesis and learning [85]. Finally, irradiation-induced deficits in hippocampal neurogenesis and context-dependent fear conditioning can also be rescued by ECS, through a mechanism involving VEGF signaling [127].

Together, these findings suggest that VEGF signaling may be important in mediating not only cell proliferative effects but also functional neurogenesis in the adult hippocampus. However, it should be acknowledged that many of these behaviors (e.g., environmental enrichment) also produce effects that are mediated by neurogenesis-independent pathways [128] but see [129]. Interestingly, a study by Licht and colleagues [130] recently demonstrated that VEGF can modulate the plasticity of mature neurons and improve memory through a process not mediated by changes in vascular perfusion or neurogenesis. These findings reveal a surprising role for VEGF in modulating key aspects of plasticity and highlight the diverse pleiotropic functions that VEGF can have in the central nervous system.

5. Future Directions and Conclusions

The prevalence of MDD is on the rise, resulting in an enormous health care burden that not only affects the individual but permeates throughout all avenues of social, work, and family life. Progress has been made in revealing candidate molecular pathways and neural substrates that could serve as important targets for pharmacological intervention. Strategies targeting adult hippocampal neurogenesis have received considerable attention in the possible treatment of MDD. However, several key questions still remain. First, it is unclear why neurogenesis is important in mediating some of the behavioural actions of antidepressants, yet a decline in neurogenesis itself does not produce a pro-depressive phenotype. Second, it is also not known if directly increasing neurogenesis is sufficient to confer antidepressant-like effects on its own. It is important to emphasize that the neurogenic action of antidepressants is only one aspect of a myriad of cellular and molecular effects that accompany their use. Along these lines, both neurogenesis-dependent and -independent effects have been described for the different behavioral effects of certain antidepressant treatments. One strategy to help unravel the specific role of neurogenesis in the development of MDD and the therapeutic action of antidepressants is to use transgenic mice that allow for conditional, stage-specific loss of adult hippocampal progenitor cells. These genetic tools will ultimately permit researchers to directly examine which specific stages of hippocampal neurogenesis (e.g., proliferation, survival, and functional integration) are critical in mediating the cognitive and emotional changes associated with MDD [131].

The emphasis of current research has been on cell proliferative effects of antidepressant action. This has left us with limited knowledge of the possible role of immature neurons in the behavioral and cognitive changes associated with MDD. Because new neurons require approximately 1 to 1.5 months to fully mature, this may contribute to the delayed onset of therapeutic efficacy with antidepressant treatment. However, as new neurons mature and integrate into the dentate gyrus circuitry, they also transiently exhibit unique functional properties (e.g., heightened excitability, lower threshold for LTP induction) that allow them to make key contributions to synaptic plasticity and network function [132]. It has been found that the speed of maturation and integration can be modulated by a variety of factors, such as experience [133] and seizures [134]. Along these lines, Wang and colleagues [60] recently showed that chronic fluoxetine treatment accelerates the structural and functional maturation of immature neurons, which coincides with enhanced LTP induction in the dentate gyrus. Thus, it is possible that the accelerated maturation of new neurons with antidepressant treatment can reestablish deficient network function and help amplify information processing in the hippocampus of chronically depressed patients. Indeed, patients with major depression often report difficulties in various areas related to learning and memory function [135–139].

Finally, the discovery that VEGF is important in the neurogenic and behavioral action of several different classes of antidepressants provides further support that neurotrophic factors are important in the treatment of MDD. Indeed recent work has implemented the importance of other neurotrophic signaling factors, such as BDNF and its receptor tyrosine kinase B, in regulating hippocampal neurogenesis and behavioral sensitivity to antidepressant treatment [140, 141]. While several studies point to an involvement of VEGF and its downstream signaling targets in the consequences of stress, several issues still remain. First, the signaling pathways involved in the neurogenic and behavioral effects of VEGF in the adult brain are poorly understood, although an involvement of Erk and Akt signaling pathways has been implemented (Fournier, Lee, & Duman unpublished observations). Second, it is not known if a decrease in VEGF signaling itself actually increases the vulnerability for developing depressive-like behavior. However, there is evidence that polymorphic variations in the VEGF gene contributes to treatment resistant

depression in some patients suggesting that alterations in VEGF may influence susceptibility to MDD [124]. Lastly, there is considerable cross-talk in the molecular signaling pathways shared by VEGF and other neurotrophic factors, raising the question of whether VEGF can act synergistically with other neurotrophic factors (e.g., BDNF) to enhance the neurogenic and behavioral effects of antidepressants.

It is interesting to note that decreased BDNF or TrkB signaling impairs the therapeutic action of various chemical antidepressants [92] in manner similar to what has been observed earlier with VEGF loss (see above). These findings suggest the presence of a mutual interaction between VEGF and BDNF at the intracellular level. Consistent with this view, it is well known that VEGF can stimulate the production of angiogenic growth factors (such as VEGF) as well as neurogenic growth factors (such as BDNF, BMP-2, and FGF-2) from endothelial cells, astrocytes, and neurons [142–145]. Co-immunolabeling studies with proliferation markers have also confirmed that neuronal precursors and progenitor cells possess TrkB [69] and Flk-1 [109, 118] receptors indicating that both neuronal and non-neuronal (vascular) sources of VEGF (and possibly BDNF) could mediate some of the neurogenic actions of antidepressant drugs. In this regard, the localization of receptors for BDNF and VEGF on neuroblasts raises the possibility that these neurotrophic factors could work both independently and/or cooperatively to influence specific stages of neurogenesis. For instance, BDNF is well known to enhance the survival of new neurons [90, 146, 147], whereas VEGF appears to play a more important role in initiating cell cycle entrance, division, and survival [98, 148]. Future studies will be necessary to further clarify the interaction between VEGF and other growth factors in neurogenesis as well as in action of antidepressants.

VEGF's remarkable versatility in affecting a number of cellular processes, such as neurogenesis, cell survival, and synaptic plasticity, presents us with a difficult task in narrowing down which specific aspects of VEGF signaling are critical in its antidepressant action. In a similar vein, how do we separate VEGF's effects on endothelial cells from its effect on glial or neuronal cells? Although pharmacological strategies have been important in elucidating the role of VEGF in neurogenesis, there are always issues concerning the specificity of these effects. An alternative approach is to use conditional gene knockouts, which represents an extremely powerful approach to study the function of single genes in the nervous system and offers a higher degree of molecular specificity over pharmacological blocking agents. We are presently utilizing a conditional gene knockout approach to study the role of VEGF and Flk-1 in the neurogenic and behavioral action of antidepressants. Together these current and future studies will provide a greater understanding of VEGF in the pathophysiology of depression and in neurogenesis and will thereby aid in the discovery of novel treatments for MDD and related disorders.

Research Highlights

Stress decreases and antidepressant treatment increases VEGF levels in limbic structures of the brain, most notably hippocampus.

VEGF is necessary and sufficient for the neurogenic and behavioral actions of antidepressant treatments.

Rapid and robust induction of VEGF expression can increase the proliferation of quiescent neural progenitor cells, and lead to a robust increase in neurogenesis.

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Abbreviations

ANP	transient amplifying neuronal progenitor cell
BDNF	brain derived neurotrophic factor
BrdU	bromodeoxyuridine
ECS	electroconvulsive seizure
FGF-2	fibroblast growth factor
IGF-1	insulin-like growth factor
MDD	major depressive disorder
NSF	novelty suppressed feeding
QNP	quiescent neuronal precursor cell
SGZ	subgranular zone
SVZ	subventricular zone
VEGF	vascular endothelial growth factor

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Figure 1.

A) Stages of adult neurogenesis in the dentate subgranular zone of the hippocampus. Quiescent stem cell-like precursors (QNPs, Type 1 cell) divide asymmetrically to give rise to transient amplifying neural progenitor cells (ANPs, Type 2 cell). In turn, ANPs divide under resting conditions and undergo rapid proliferation in response to various stimuli, including physical exercise and antidepressants. Complete exit from the cell cycle occurs at the Type 3 stage. These neuroblasts begin terminal differentiation into immature dentate granule cells and develop axons and dendrites, which facilitates their functional integration into the existing hippocampal network. B) Antidepressants and ECS treatment impact different stages of hippocampal neurogenesis. Acute and chronic ECS leads to a rapid elevation in VEGF-Flk1 signaling in the dentate gyrus and increased proliferative activity of QNP and ANP cells. In contrast, chronic treatment with antidepressants fluoxetine or desipramine result in a delayed induction of VEGF and proliferation of ANP but not QNP cells.

Table 1

Effect of various neurotrophic factors on key stages of adult hippocampal neurogenesis

Neurotrophic Factor	Species / Route of Administration	Proliferation	Differentiation	Survival	Reference
VEGF	Rat (ICV)	↑	-	-	[107]
	Rat (ICV, 8 days)	-	-	↑	[108]
BDNF	Rat (IH, 14 days)	-	-	↑	[149]
	Mice (BDNF+/-)	↓	-	↓	[150]
	Mice (BDNF +/-)	↑	-	↑	[151]
EGF	Rat (ICV)	-	-	-	[152]
FGF-2	Rat (ICV, 14 days)	-	-	↑	[153]
	Mouse (FGF-IR -/-)	↓	↓	↓	[154]
IGF-1	Rat (ICV, 42 days)	↑	-	↑	[155]
	Rat (peripheral, 20 days)	↑	↑	↑	[156]
NGF	Rat (ICV)	-	-	↑	[157]

Abbreviations: BDNF, brain derived growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; FGF-IR, fibroblast growth factor receptor 1; ICV, intracerebral ventricular; IH, intrahippocampal; IGF (insulin-like growth factor); NGF, nerve growth factor; VEGF, vascular endothelial growth factor

Table 2

VEGF Produces Antidepressant Effects in Cellular and Behavioral Models of Depression

Endpoint	VEGF	VEGF Inhibitor	References
<i>Neurogenesis</i>	Increase	Blocks SNRI, SSRI	[109, 118, 125, 158]
<i>Anhedonia</i>			
Sucrose Preference	Antidepressant	Blocks SNRI, SSRI	[120]
<i>Despair</i>			
Learned Helplessness	Antidepressant	Blocks SNRI, SSRI	[107]
Forced Swim Test	Antidepressant	Blocks SNRI, SSRI	[107, 120]
<i>Anxiety</i>			
NSF	Anxiolytic/Antidepressant	Blocks SNRI, SSRI	[107, 120]
<i>Locomotor Activity</i>	None	No Effect	[107]

Abbreviations: SNRI, selective noradrenalin reuptake-inhibitors; SSRI, selective serotonin reuptake inhibitor, NSF, novelty suppressed feeding test