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PSYCHOSIS (AO AHMED, SECTION EDITOR)

Vascular Endothelial Growth Factor (VEGF) in Neurodevelopmental Disorders

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Abstract
Purpose of the Review Neurovascular dysfunction and the role of vascular endothelial growth factor (VEGF) have been explored in neurodevelopmental disorders including schizophrenia, bipolar disorder, major depressive and mood disorders, and autism. These disorders are correlated with hypoxia-ischemia insults during early life and are strongly associated with cognitive dysfunction. This review focuses on the hypoxia-regulated protein, VEGF, to discuss its crucial roles in brain development and function. These data implicate that alterations to VEGF signaling during early life can impair neural development, underlying the severe cognitive deficits observed in neurodevelopmental disorders.
Recent Findings VEGF has been linked to neurological processes that influence learning and memory. VEGF is advancing towards being a novel biomarker and possible therapeutic for neurological disorders. Prenatal environmental enrichment positively impacted neurotrophic factors, brain structure, and memory in rodent models.
Summary Understanding the molecular mechanisms of VEGF in neurodevelopment will create intervention strategies for at-risk children born to adverse early-life events. By proactively working with those in a pliable neurodevelopmental state, we hope to ameliorate cognitive deficits to increase their chance to develop into high-functioning adults with disabilities.

Keywords VEGF · Hypoxia-ischemia · Neurodevelopment · Cognition · Gene-environment interaction · Flk1

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Introduction

Vascular endothelial growth factor (VEGF) has been extensively studied in the fields of oncology and vascular disease given its crucial role in angiogenesis through endothelial cell proliferation to increase vascularization for nutrients and blood supply. It is also well-established that the regulation of VEGF is crucial for vasculogenesis and angiogenesis for proper placental development during gestation. In fact, alterations to VEGF signaling are biomarkers used in pregnancies complicated by placental insufficiency and subsequent hypoxic conditions, such as preeclampsia [1–3].

The VEGF family has numerous subtypes, including VEGF-A through VEGF-E and the placental growth factor (PlGF) [4]. VEGF-A ($VEGF_{165}$, VEGF in this review) is the founding member of the VEGF family and the most common isoform. VEGF has three cell surface tyrosine kinase receptors, fms-like tyrosine kinase-1 (VEGF receptor 1/Flt1), kinase insert domain-containing receptor (VEGF receptor 2/KDR/Flk1), and fms-like tyrosine kinase-4 (VEGF receptor 3/Flt4) (for a comprehensive review on VEGF signaling, see Simons et al. [5]).

VEGF has recently been recognized as an indispensable gene for neurodevelopment. In the brain, VEGF is crucial for neurological processes that include neurogenesis, plasticity, neuronal migration, neuronal survival, and axon guidance [6••, 7]. VEGF not only controls angiogenesis and regulates cerebral blood flow, but is also responsible for delivering

oxygen, glucose, lactate, and glycogen derived from the astroglia to the neurons to maintain the demands required for neural activity [7, 8].

Neurovascular dysfunction and the role of VEGF have been explored in neurodevelopmental disorders including schizophrenia, bipolar disorder, major depressive and mood disorders, and autism [9–14]. Although it is not well-understood how this neurovascular dysfunction occurs, individuals with neurodevelopmental disorders often experience long-term neurological consequences that are associated with early-life events that could impair VEGF signaling. For example, studies have shown that the pathophysiology of schizophrenia is strongly linked to microvascular anomalies and impaired angiogenesis [15], leading to blood brain barrier (BBB) hyperpermeability [9], decreased brain volumes [16] and cerebral blood flow [10, 15].

Neurodevelopmental disorders are thought to stem from gene-environment interactions that disrupt normal brain development during early life, leading to long-term consequences such as altered signaling and cognitive dysfunction. Meta-analyses of case-control studies have demonstrated that numerous psychiatric and neurocognitive disorders are of developmental origin and highly associated with hypoxic events during early life [17–22]. These neurodevelopmental disorders include, but are not limited to, schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD), autism, and developmental delay. Neonates born with birth complications such as severe perinatal hypoxic insults, preterm birth, or hypoxia-ischemia encephalopathy have also shown corresponding neurological outcomes similar to those born with intrauterine complications. Therefore, while we understand that hypoxia is the common factor, the elucidation of the impacts of in utero vs. postnatal regulation of VEGF is ongoing.

Numerous target genes, including VEGF, are regulated by the hypoxia-inducible factor (HIF) to mediate protein synthesis through HIF binding to the hypoxia response element region of target genes [23]. The extent of impact by alterations to VEGF created by hypoxic events to both the placenta and the fetus during early developmental periods has been difficult to elucidate, as transient gestational environmental insults observed in humans are challenging to replicate. Nonetheless, the field has been able to illustrate that VEGF is a crucial mediator of neural development and function given its role in angiogenesis, neurogenesis, and memory with rodent models. The long-term cognitive deficits observed in humans with neurodevelopmental disorders are not effectively treated with currently available medications. However, VEGF is advancing in the psychiatry field towards being a novel biomarker and possible therapeutic for neurodevelopmental disorders [11, 12, 14, 24–27].

Here, we will discuss how VEGF may be a possible mediator of the cognitive deficits observed in neurodevelopmental disorders, as extensive research indicates that hypoxia-related insults in utero and during early life impair brain development and function. Discerning the role of VEGF during this early developmental period is critically important for understanding the environmental impacts on fetal development and long-term outcomes. Understanding the mechanisms that influence aberrant brain development during vulnerable periods, when physiological control cannot be regulated, brings to light phases later in life where environmental and behavioral techniques may be key to intervention to mitigate cognitive deficits observed in individuals with neurodevelopmental disorders.

Hypoxia, VEGF, and Intrauterine Complications: Consequences of Early Developmental Insults

HIF1-α is controlled by proteosomal degradation, a process regulated by the presence of prolyl hydroxylases (PHDs), which are only active in the presence of oxygen [28]. When PHDs are deactivated during hypoxic conditions, circulating HIF1-α binds to the ever-present HIF1-β. This creates the stable HIF1 transcription factor, which binds to the hypoxia response element of the VEGF gene where transcriptional and post-transcriptional processes under hypoxic conditions control VEGF expression to increase oxygen availability [28]. The intricately designed HIF1 regulation mechanism allows normal homeostasis and neuroprotection by VEGF, roles that are rapidly gaining strength in the psychiatry field.

Studies have demonstrated the importance of HIF1 during embryonic development, determining that without one of the subunits (HIF1-α or HIF1-β), detrimental effects to the cardiovascular system occur and are embryonically lethal [29–31]. Semenza et al. [31] discovered that the lack of HIF1-α resulted in developmental defects involving the mouse heart and blood vessels, concluding that HIF1 regulates both acute and chronic responses to hypoxia. Although hypoxia induces the production of VEGF, it is uncertain how prolonged hypoxia impacts VEGF signaling and regulation. Moreover, while early-life hypoxic events are the most common complication corresponding with the later development of neurodevelopmental disorders [16, 17, 22, 32], the role of early-life insults on fetal programming and mechanistic development is still unclear [19, 21].

Pregnancy conditions that induce placental hypoxia include gestational hypertension, preeclampsia, placental insufficiency, and intrauterine growth restriction. The pathophysiology of these pregnancy complications is thought to be related to early vascular development and dysfunctional remodeling in the placenta. Preeclampsia is a hypertensive condition during pregnancy that manifests increased levels of soluble Flt1 (sFlt1), which is indicative of endothelial dysfunction and impaired angiogenesis [1, 2]. Patients with severe

hypertensive disorders have higher rates of preterm births and neonates that are small for gestational age, with increased adverse maternal outcomes [33]. Long-term studies indicate intrauterine imprinting of neurodevelopmental consequences that exhibit behavioral and functional sequelae observed in multiple disorders are strongly associated with hypoxia related to preeclampsia, intrauterine growth restriction, and placental insufficiency [16, 18, 20, 32, 34–37, 38•].

Intrauterine hypoperfusion is often observed in preterm births, where adverse neurological development results in long-term cognitive consequences [34]. Preterm neonates show decreased cerebral and cerebellar volumes, believed to be associated with perinatal hypoxia-induced damage to the interneurons, oligodendrocytes, and astroglia [18, 34]. In rodents, prenatal ischemia-induced white matter damage underlay the manifestation of behavioral and cognitive abnormalities [39]. Mild intrauterine hypoperfusion in rodents reflects neurological clinical symptoms observed in children born preterm or with intrauterine growth restriction who later developed neurodevelopmental disorders [34]. VEGF plays a role in learning and memory, specifically acting through Flk1, while increases in PlGF, which binds to Flt1, inhibited neurogenesis and learning [40]. These data correlate to the cognitive dysfunction observed in children born to mothers with preeclampsia [35, 37, 38•, 41], where VEGF signaling is known to be switched towards anti-angiogenesis through PlGF/sFlt1 alterations. Recent studies have shown promise for using VEGF as a cognitive therapeutic [6••, 26]. In rodent models, the enhancement of VEGF showed increased long-term potentiation, improved plasticity, and improved cognition [6••, 40] mediated by its receptor, Flk1 [42].

Suboptimal intrauterine environments, growth restriction, and adverse early-life events (i.e., preterm birth and hypoxia-ischemia encephalopathy) have been associated with disorders including autism, ADHD, psychiatric disorders, and intellectual disability [19, 20, 41, 43–46]. These data suggest that improper placental development and function are strongly associated to the later manifestation of neurodevelopmental disorders [19, 34, 38•]. Recent studies have found that children born to mothers who experience obstetric complications that induce placental hypoxic conditions display significant deficits in cognitive function and developmental delay [32, 36–38•, 41], although the mechanisms behind this altered developmental trajectory are not well-understood. While the common pathway in both vasculature and neuronal plasticities is VEGF, we appreciate that VEGF is only one of many neurotrophic factors that are implicated in the neurodevelopmental hypothesis of gene-environment interaction-induced disorders.

The heterogeneity of diseases among mothers, along with the compensatory physiological mechanisms that are provided by the mother during gestation to protect the fetus, makes rodent models of clinical disorders difficult to validate. For example, although chemical injection of sFlt1 can create hypertensive phenotypes, reliable rodent models for spontaneous, gestation-induced hypertensive disorders observed in humans are unavailable. Moreover, although there is strong evidence that vascular dysfunction underlies gestation hypertensive complications which impair placental function and fetal growth, the molecular mechanisms are far from understood [33].

Although the field is garnering information that the placenta plays a critical role on environmental neural programming, targeting VEGF signaling pharmacologically during gestation may be unsafe for both the mother and the child. It may be beneficial for clinicians to incorporate techniques that induce neurotrophic factors in mothers who are experiencing obstetric complications to increase bioavailability to the unborn child. However, we must also recognize that the increase in VEGF would need to physiologically act on Flk1 and not be sequestered peripherally by sFlt1 in those who are experiencing gestational hypertensive disorders to be effective on vascularization and neurodevelopment—physiological parameters that are beyond control. Evidences that VEGF induces neural development, plasticity, and cognition are positive outcomes that are worth pursuing given the great complexity of neurodevelopment. Therefore, the field must work to understand the outcomes related to altered VEGF signaling at both the molecular and functional levels. This will require long-term follow-up at various time points of children born with adverse early-life events, whether intrauterine or perinatal.

Perinatal Brain Injury: Hypoxic-Ischemic Encephalopathy

It is usually straightforward to identify when a child has motor sequela (“cerebral palsy”) from hypoxic perinatal brain injury (i.e., periventricular white matter injury of prematurity, hypoxic-ischemic encephalopathy, or stroke). Infants with mild brain injury are of particular risk for neurodevelopmental issues. These children have increased risk for learning disabilities, behavioral issues such as ADHD, or even delayed memory impairments that manifest in adulthood [46]. Moreover, cognitive and behavioral concerns may be more subtle and are oftentimes under-recognized [46]. The delay in diagnosis thus prevents this population of at-risk children from receiving early intervention therapies that may mitigate developmental delays and behavioral manifestations that could positively shape their development.

The fetal brain is particularly susceptible to hypoxic injury due to an insufficient antioxidant system combined with the selective vulnerability of the oligodendrocytes [47]. Studies have shown that inflammation can either downregulate or enhance VEGF [48], providing VEGF with neuroprotective and neurotoxic regulatory functions. VEGF can be involved in

neurogenesis as well as neurorepair both de novo and in response to injury [49–51].

During normal embryonic development, VEGF stimulates cerebral angiogenesis [52, 53] and regulates neuronal migration [54]. Alternatively, VEGF downregulation during hypoxic events may impede angiogenesis and therefore heighten ischemic injury [53]. Neonatal stroke models demonstrate VEGF increases in response to hypoxic stress [52, 53]. When pathologically upregulated, VEGF can increase BBB permeability [47, 53]. Breakdown of the BBB increases oxidative stress by direct introduction of inflammatory products, while downstream signaling changes affect the sensitive redox system [47] to impair perfusion and oxygenation [55, 56].

Preterm babies or those born with low birth weight are of particular risk for brain injury and adverse neurodevelopmental outcomes. In fact, it is estimated that approximately one in five infants with very low birth weight (< 1500 g) and up to half of infants with extremely low birth weight (< 1000 g) go on to exhibit adverse neurodevelopmental outcomes including ADHD [57]. In the ongoing ELGAN study of extremely low-birth-weight preterm babies, VEGF levels obtained from reconstituted newborn blood spots were associated with increased risk of ADHD at 10 years old [58]. One explanation posited by the authors is that neurotrophic proteins, including VEGF, modulate the increased risk of ADHD in conjunction with systemic inflammation, an endophenotype observed in neurodevelopmental disorders [59, 60].

In terms of newborns, hypoxic-ischemic encephalopathy (HIE) is the most common cause of brain injury, with an incidence of approximately 1.5 per 1000 live births. Although therapeutic hypothermia has been shown to improve outcomes, adverse neurodevelopmental outcomes are still seen in up to 40% of these patients [61]. Studies of VEGF and HIE are limited and mixed and may reflect the heterogeneous nature of this clinical syndrome.

Serum VEGF has been shown to be upregulated in newborns with mild HIE compared to moderate or severe HIE [62], which may allude to the protective effect of VEGF in that subset of mildly asphyxiated infants. In another study, cord blood VEGF levels were elevated in newborns with birth asphyxia and moderate HIE [63]. It is important to note that both studies are limited due to small sample sizes and lack of long-term follow-up for neurodevelopmental outcomes. In a recent association study, Chalak et al. [64] demonstrated that VEGF, along with multiple inflammatory biomarkers, was increased in neonates born experiencing HIE. These data also correlated with adverse neurologic outcomes in toddlerhood [64]. In a larger prospective study of newborns with HIE, increasing levels of VEGF in the cerebrospinal fluid (CSF) correlated with worsening severity of HIE, with preterm newborns at particularly high risk [65]. Although cerebral VEGF concentrations are most accurately measured in newborn CSF, CSF VEGF is not practical (or in some instances, ethical) to measure in neonates. Thus, given that serum samples do not accurately reflect the fetal environment, we draw attention for increased importance of animal models for HIE and its influence on neurodevelopmental disorder-related research.

The placental-fetal relationship is important in the interplay between hypoxia, neurotrophic proteins, inflammation, and neurodevelopmental outcomes. The complex association between hypoxia, physiological responses, and the later onset of neurodevelopmental disabilities has not been adequately studied. More evidence is being garnered from animal models implicating the link between placental and fetal VEGFs. For example, rodent studies have shown that the placenta and the brain have common hypoxia-responsive genes (i.e., VEGF) when exposed to acute hypoxia [66]. Importantly, it has also been demonstrated that placental-induced VEGF expression was associated with HIE [67]. Preeclampsia is the prototypical model of the hypoxic placenta, with pathological VEGF angiogenesis implicated as an important player in placental dysfunction [68–70]. Although preeclampsia is associated with adverse neurodevelopmental outcomes [36, 37, 41], it is unclear if those outcomes are strictly from gestational age effects or direct effects of the placental injury of hypoxic insults on the fetal brain.

A major limitation to animal studies is that the hypoxic exposure is post-natal rather than in utero or is applied systemically to the pregnant female for a determined amount of time. Neither method accurately reflects the human hypoxic placenta and intrauterine environment. A fairly new, interesting concept is mild intrauterine hypoperfusion (MIUH). MIUH may more precisely reflect the human intrauterine hypoxic environment rather than traditional ex utero animal models. In a rat model of MIUH, behavioral testing showed significantly increased pivoting time in the rats exposed to MIUH compared to controls [34]. Furthermore, female rats exposed to MIUH exhibited hyperactivity behavior. Placental analysis showed that VEGF levels were significantly increased in the MIUH group, suggesting MIUH induces VEGF upregulation. The authors further reported that the morphologic analysis of the MIUH brains was consistent with brain morphology found in human preterm newborns and children with ADHD [34].

VEGF alone cannot be implicated in the pathogenesis—as well as in the treatment target—of these fetal hypoxic brain injuries and outcomes. The processes are complex and multifactorial, making the quest for the definitive biomarker panel for diagnosis and prevention unobtainable at this juncture. Additionally, targeting VEGF alone may be dangerous given the delicate interplay of its neuroprotective and neurotoxic effects. Therefore, strategies for rehabilitation and global neurorecovery may currently be the most practical goal.

Environment enrichment (EE) is an animal model concept of rehabilitation which combines physical activity, novel exposures, social interaction, and sensory and cognitive

stimulations [71]. EE has been shown to improve neurodevelopmental outcomes in asphyxiated neonatal rats [72–74] through increased expression of VEGF and other neurotrophic factors [73]. Furthermore, EE can mitigate the effects of pathologically increased VEGF on BBB dysfunction after neonatal hypoxic injury [75].

In an intriguing new study, the effect of prenatal (i.e., maternal) EE on neurodevelopmental outcomes for neonates exposed to postnatal hypoxia ischemia was examined [76••]. When pregnant dams were exposed to EE, the offspring had improved spatial memory in adulthood. Histological brain analysis showed that although VEGF was overall decreased in the parietal cortex of HIE offspring compared to sham, levels of VEGF were higher in the maternal EE-HIE group compared to standard care HIE rats. These findings suggest long-lasting effects of prenatal EE on neurotrophic factors and brain structure. Thus, these data may be translatable to human obstetrical care and inpatient activities in high-risk hospitalized pregnant women beyond standard bed rest, including social support groups, changes in routine, mild exercise (when safe), and cognitive tasks such as puzzles or games.

The Link Between VEGF, Cognition, and Neurodevelopmental Disorders

Decreased VEGF, Flk1, Reelin, and NR2B activations have been associated with disorders including schizophrenia, bipolar disorder, autism, and Alzheimer's [14, 77–84]. Recently, VEGF has become a novel target for neurological diseases such as Parkinson's and Alzheimers' [85, 86] while showing promise as a plausible biomarker for schizophrenia, depression, and autism [13, 24, 25, 87•, 88•]. Hypoxia-ischemia insults during early life result in severe behavioral and functional abnormalities, and hypoxia-regulated VEGF signaling anomalies are often associated with psychiatric disease [10, 14, 15, 27].

Individuals with neurodevelopmental disorders present severe cognitive dysfunction. VEGF has been linked to neurogenesis, plasticity and overall neurodevelopment through neuronal migrations, oligodendrocyte precursor cell migration, and axon growth and guidance to influence learning and memory [6••, 26, 40, 54, 89]. Thus, understanding altered VEGF signaling caused by hypoxia-ischemia during neurodevelopment is important to create novel treatments to improve cognition. The NR2B subunit of *N*-methyl-D-aspartate receptors (NMDAR) has been implicated in neurodevelopmental and psychiatric disorders via dysregulated NMDAR-Wnt-Catenin signaling and cognitive deficits in working memory [84, 90]. NR2B subunits are the predominant receptor in embryonic neurons [91] and can inhibit hypoxia-ischemia damage [92], further drawing attention to their importance during early neurodevelopment.

VEGF modulates NMDA receptor activity and granule cell migration through activation of the Src kinases via Flk1 [91]. Moreover, recent pharmacological studies of VEGF found that off-label drugs that act as antidepressants in bipolar disorder patients act through Flk1 signaling [93]. As NMDAR are known to be involved in synaptogenesis and synaptic plasticity, this data identifies a link between the importance of VEGF, NMDA activity, and synaptic plasticity which is implicated in numerous psychiatric disorders.

Reelin is secreted by the Cajal-Retzius cells, crucial for neuron migration and synaptic plasticity, and is a candidate gene for several neurodevelopmental disorders including schizophrenia, bipolar disorder, and autism [80]. Animal studies using hypoxia-ischemia models have demonstrated that hypoxia causes a downregulation in NR2B [90] and is critical in mitigating hypoxia-ischemia insults [92]. Recent data showed that VEGF activates the Reelin pathway through the adaptor protein Disabled 1 (Dab1) to create crosstalk between the two pathways [94], highlighting the intricacies of neuroprotection via multiple mechanisms.

Reelin has been a candidate gene in multiple neurodevelopmental disorders [79, 95], and the interplay between the Reelin and VEGF pathways may play a key role in both neurological disease and cognitive deficits. For example, VEGF activation of the Reelin pathway for motor coordination is indicated by use of VEGF as a neurological treatment in Parkinson's patients [85]. Furthermore, the VEGF-induced activation of Dab1 and NR2B phosphorylation depends on the VEGF receptor, Flk1 [94], whose expression is regulated by stress [78]. Importantly, data indicates that the postmortem prefrontal cortex from individuals with schizophrenia has decreased Flk1 expression levels compared to controls [78], while preliminary data from high-risk, living individuals indicates angiogenesis and immunological dysfunction early in psychosis with increased levels of sFlt1, an anti-angiogenic factor that binds VEGF to prevent signaling and activation [88•]. These data correspond to a previous cohort that displayed significantly increased VEGF and IL-6 levels whose patients had inversely correlated decreased frontal cortex volumes compared to healthy controls [24].

Recent studies indicate that VEGF may be an important protein to study in the pathophysiology of disorders including schizophrenia as well as major depressive disorder, where patients showed differential expression of HIF1 and VEGF [12, 27, 87•]. While studies are limited on VEGF and Flk1 expressions for disorders like schizophrenia, it is plausible that the alterations in the VEGF pathway may be due to multiple factors. First, it cannot be ruled out that the upregulation of VEGF in patients may be a compensatory response to the systemic inflammation observed in psychiatric disorders [24, 27, 59, 88•, 96]. This inflammation subsequently disrupts the BBB and could be associated with cardiovascular disease interrelated with schizophrenia and bipolar disorder [9, 60, 96].

Next, decreased mRNA levels in the prefrontal cortex [77] may be a compensatory downregulation of protein synthesis in response to increased levels of peripheral VEGF in patients [24]; this could stem from a decreased availability of Flk1 receptors in schizophrenia patients [78] or from an imbalance in angiogenic signaling [88•]. Although the association between hypoxia-ischemia and the gene-environment interaction paradigm is highly correlated with early-life programming and genetic susceptibility, the neurodevelopmental disorder field is far from understanding the complex nature of these disorders. The recent association between increased VEGF levels in patients with schizophrenia, bipolar disorder, depression, and autism and the promise of mitigating cognitive impairments demonstrates that VEGF is a major player worthy of further attention.

In summary, if a genetically predisposed individual has reduced proteins important for neural programming (i.e., Reelin and Flk1), their NR2B expression in the embryonic neurons are more susceptible to hypoxic insults during early life than normal individuals. Moreover, these babies will not respond fully to the upregulation of VEGF signaling to benefit from its neuroprotective properties, thus inducing abnormalities that may underlie the strong association with hypoxic insults during early development that manifest behavioral and neurocognitive dysfunctions later in life. This further demonstrates how numerous candidate genes in neurodevelopmental disorders play key roles in neuroplasticity and impact cognition and memory, which are highly affected by stress during early development. However, recent studies have indicated that inducing the neuroprotective properties of VEGF may not be out of reach, but may involve a broader signaling cascade and activation than currently known.

Environmental enrichment reversed neurodevelopment and memory impairments from hypoxia-ischemia encephalopathy [76••], while the use of VEGF as a therapeutic for enhanced neuronal plasticity in mature neurons showed promise with improved memory in adult mice [6••]. Early intervention strategies to activate the VEGF pathway in high-risk or at-risk individuals may be the key to curtailing severe cognitive deficits in neurodevelopmental disorders associated with hypoxia-ischemia insults during early life. Understanding the array of molecular mechanisms of VEGF involved in neurodevelopment will allow us to develop targeted therapeutic strategies that may alleviate cognitive deficits, one of the most detrimental, yet non-treatable, phenotypes associated with developmental disorders.

Conclusion

VEGF plays a significant role in angiogenesis and neurodevelopment, and the balance of VEGF during vulnerable time frames is critical for normal brain development. Multiple neurodevelopmental disorders are associated with hypoxia-ischemia insults during early life, both intrauterine and perinatal, and are strongly associated with cognitive dysfunction. Here, we reviewed the roles of VEGF in neurodevelopment and cognition as the field begins to recognize the importance of the neurotrophic factor and its plausible role in neurodevelopmental disorders.

Moreover, clinicians who use cognitive behavioral and psychosocial therapies for patients with these disorders may consider examining VEGF levels to determine if peripheral VEGF is increased by environmental enrichment. Some groups have started prospective studies for this important work with at-risk neonates to examine VEGF as a biomarker [64, 97]. This knowledge will allow the development of early-life intervention strategies for at-risk children born to adverse early-life events that are susceptible to neurodevelopmental disorders with cognitive deficiencies.

The hope is that the induction of neurotrophins including VEGF through behavioral and environmental enrichments would rescue abnormal neural development while brain development is immature and plastic. The goal is to proactively work with at-risk individuals in a pliable neurodevelopmental state (i.e., early childhood) using cognitively stimulating and environmentally rich therapies. With these interventions, increased VEGF may lead to enhanced neurogenesis and plasticity, NR2B activation, and long-term potentiation, allowing those individuals to benefit from VEGF as a neuroprotective molecule. Therefore, the cognitive delay strongly associated with neurodevelopmental disorders may be ameliorated such that these at-risk children may have an increased quality of life with an improved chance to develop into high-functioning adults with disabilities.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they do not have conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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