REVIEW

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The role of vascular endothelial growth factor in ischemic stroke

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Received January 8, 2021, accepted January 29, 2021

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Pharmazie 76: 127-131 (2021) *doi: 10.1691/ph.2021.1315*

Ischemic stroke is an injury caused by temporary or permanent cerebral vascular occlusion. It has a high incidence, mortality, and disability rate in clinical practice, and thus poses a considerable threat to public health as one of the top three major conditions endangering human health. Vascular endothelial growth factor is a specific mitogen of endothelial cells and a protein factor that is closely related to ischemic stroke. Vascular endothelial growth factor plays an important role in a multitude of physiological and pathological conditions. As a potential angiogenic protein for the treatment of ischemic stroke, vascular endothelial growth factor plays a role in promoting angiogenesis and neuroprotection and regeneration. At the same time, it plays a role in brain edema, collateral artery formation, and atherosclerosis. An increase in vascular endothelial growth factor levels contributes to the early pathological changes in patients with stroke and is closely related to the formation of cerebral edema in ischemic stroke complications. In theory, the neuroprotective and angiogenic effects of vascular endothelial growth factor make it an ideal candidate for the treatment of stroke. Here, we review the mechanism by which vascular endothelial growth factor participates in various stages of ischemic stroke and its prospects for use in the treatment of ischemic stroke.

1. Introduction

Stroke is one of the top three major diseases endangering human health and is characterized by acute cerebral blood circulation disorder, which leads to long-term disability and death (Naghavi et al. 2017). Because of its high incidence, disability, and mortality rate, stroke is severely affecting the quality of life of survivors and can place a considerable burden on the society and families of survivors (Benjamin et al. 2018). Stroke can be caused by cerebral vascular occlusion or rupture bleeding, which leads to local cerebral ischemia and hypoxia, resulting in corresponding neurological dysfunction (Yu and Zhou 2019). Stroke refers to both ischemic and hemorrhagic types, with the former being the most common form, accounting for approximately 87% of all strokes (Benjamin et al. 2018). Vascular endothelial growth factor (VEGF) is a research hotspot and potential target of ischemic stroke. Hypoxia is an important stimulator of VEGF expression. The increase in VEGF protein levels under hypoxia is due to the control of transcription and translation. Hypoxia-inducible transcription factor (HIF) binds to the hypoxia response element in the VEGF promoter, thereby upregulating VEGF transcription during hypoxia (Liu et al. 1995). VEGF is highly specific and participates in various stages of angiogenesis, including neurogenesis, angiogenesis, and regeneration. The high expression of VEGF promotes blood perfusion to nerves and the migration of neural stem cells, resulting in nerve protection and nerve cell growth promotion. This is the most important pivot in the connection between angiogenesis and nerve regeneration (He and Lin 2012). VEGF levels are closely related to the severity of a stroke; however, this association is currently controversial. One previous study (Matsuo 2013) found that in all stroke subtypes, plasma VEGF levels increased immediately after stroke, whereas another study (Lee 2010) found that an increase in VEGF levels may be associated with improved stroke recovery. In addition, VEGF has dual effects on cerebral ischemia injury; in contrast, VEGF significantly enhances angiogenesis in the ischemic brain and reduces neurological deficit during stroke recovery. It is also inhibited in the acute stage of stroke, reducing the risk of blood-brain barrier (BBB) permeability and bleeding transformation after focal cerebral ischemia. Therefore, it is becoming increasingly important to improve cerebral ischemia as an important therapeutic target of injury (Zhang et al. 2000). In contrast, VEGF is closely related to the increase in vascular permeability (VP), BBB disruption, and brain edema induction (Zhang et al. 2015).

2. VEGF family and its receptors

VEGF, also known as VP factor, is a key factor in tissue vascularization and an important target for controlling angiogenesis (Loureiro and D'Amore 2005). In humans, the VEGF family is mainly composed of VEGF-A (with different subtypes), VEGF-B, VEGF-C, VEGF-D, VEGF-E (viral VEGF), VEGF-F (snake venom VEGF), and placental growth factor (PlGF). Recently, endocrine gland-derived VEGF has been assigned to this family (Carmen et al. 2018). VEGF, with mitotic and anti-apoptotic effects on endothelial cells, promotes VP, migration, proliferation, and extracellular matrix degeneration of vascular endothelial cells and plays a key role in common eye aging-related diseases, age-related macular degeneration, and diabetic retinopathy (Marneros 2016; Papadopoulos 2020; Lu et al. 2020). In addition, as one of the important factors of angiogenesis, VEGF family members (mainly VEGF-A) are widely considered as tumor markers. Tumor growth can be inhibited by blocking or interfering with the VEGF/VEGF receptor (VEGFR) signal transduction pathway (Zhang et al. 2019; Wang et al. 2020). Biological anti-tumor drugs targeting VEGF, such as bevacizumab, have been successfully used in clinical settings (Potente et al. 2011). VEGF inhibition inhibits pathological angiogenesis in various tumor models, which has led to the clinical development of several VEGF inhibitors (Ferrara et al. 2003).

VEGF and VEGFR family members play a role through downstream signaling pathways, including the mek-mapk (proliferation and migration), PI3K-Akt (survival), and Src-eNOS (permeability)

pathways. There are two main types of VEGFRs: tyrosine kinase and non-tyrosine kinase receptors. Members of the VEGF family, namely, VEGF-A, - B, and - C, bind to their receptors, with differing affinities to tyrosine kinases and non-tyrosine kinases receptors (shown in Fig.). The former contains three types of structure-related receptors: VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3. Non-tyrosine kinase receptors include neuropeptide-1 (NPR-1) and NPR-2. VEGFR-1 not only binds to VEGF-A but also to VEGF-B and PIGF, and its primarily acts as a "bait receptor," which negatively regulates angiogenesis by blocking the binding of VEGF and VEGFR-2 (Ma et al. 2012). Under hypoxia, HIF-1 upregulates the expression of VEGFR-1. VEGFR-2 functions with VEGF-A, VEGF-C, and VEGF-D and is the primary factor for VEGF to promote mitosis, improve neovascularization, and enhance VP (Chen et al. 2004). Therefore, angiogenesis requires the balance of VEGFR-1 and VEGFR-2. Notably, VEGFR-2 has a stronger affinity for VEGF-A and VEGF-E but has lower affinity for VEGF-C and VEGF-D. In pathological processes, VEGFR-2 often participates in tumor angiogenesis (Dong and Zhai 2014; Hoeben et al. 2004). The blockade of VEGFR-2 by its inhibitors is a promising method for inhibiting anti-tumor angiogenesis and effective for inhibiting tumor growth (Liu et al. 2017, Xu and Yao 2018, Zhang 2017). VEGFR-3 combined with VEGF-C and VEGF-D promotes the growth of corresponding cell subsets and inhibits apoptosis induced by chemotherapy drugs, which may mediate the occurrence of neural cell maturation after cerebral ischemia (Shin et al. 2010). NPR-1 functions with VEGF-A165, VEGF-B, and PIGF and NPR-2 functions with VEGF-A165, VEGF-C, and PIGF, which then promote the development of embryonic capillaries and play an important role in tumor enlargement and angiogenesis (Shen 2014).

3. The role of VEGF in ischemic stroke

3.1. Pathophysiological role of VEGF in ischemic stroke

3.1.1. Collateral circulation formation

In ischemic stroke, collateral vessels provide an alternative pathway for arterial blood flow and constitute the first line of defense after tissue ischemia. The collateral blood sources of cerebral circulation include extracranial and intracranial vessels, and the adequacy of collateral circulation is helpful in determining stroke severity and treatment response (Zhang 2019). Protection of collateral circulation can reduce ischemic brain injury and has significant value in the treatment of ischemic stroke (Wufuer et al. 2019, Bang et al. 2011). Blood flow shear stress, inflammation, and growth factors are the primary factors that mediate collateral vessel growth. The signal pathway, mediated by VEGF, promotes the formation of coronary collateral vessels and promotes angiogenesis (Wang et al. 2016; Lucitti et al. 2012).

Eiji Toyota and others have found that endogenous VEGF is necessary for coronary artery collateral growth, that blocking endogenous factors will disrupt collateral growth, and that anti-VEGF completely blocks collateral growth. Clayton et al. (2008) have found that VEGF plays a vital role in the formation of collateral vessels. The expression of VEGF-A affects the density of primary collaterals vessels in healthy tissues and mainly mobilizes leukocytes through VEGFR-1 and promotes the collection of leukocytes into the peripheral space, which mediates the collateral growth of ischemic diseases.

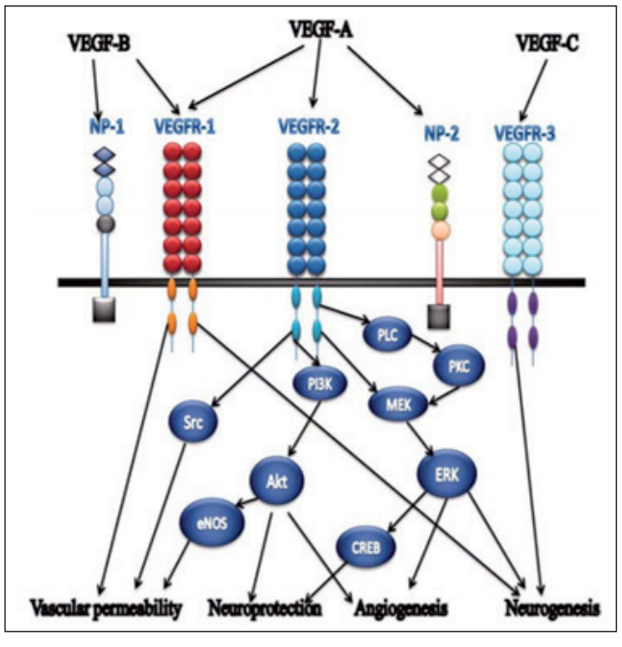

Fig: Illustration of the three main VEGF family members in humans as well as tyrosine kinase and non-tyrosine kinase receptors and downstream signals activated by these tyrosine kinase receptors (Cited from Yihui Ma et al. 2012).

3.1.2. Neuroprotection

VEGF is not only the mitogen of endothelial cells of arteries, veins, and lymphatic vessels but also acts on other cells, including neurons (Mackenzie and Ruhrberg 2012). Moreover, it has a mitotic effect on astrocytes. The direct effect on neurons and Schwann cells is mainly mediated by VEGFR-2, whereas the effect on astrocytes and microglia is mediated by VEGFR-1 (Schratzberger et al. 2000; Forstreuter et al. 2002). VEGF is considered a type of hypoxia-induced neurotrophic factor, which has neurotrophic and neuroprotective effects in both the peripheral and central nervous systems. It can induce VEGF in central nervous system disorders and helps with direct in vitro management of several nerve cells (including autonomic nerves, sensory nerves, and dopaminergic, hippocampus, cerebellum, and cortical neurons). VEGFR-2 is mainly involved in the nutrient effect (Storkebaum et al. 2004). After stroke, endogenous neuro VEGF increases in the ischemic brain and plays a neuroprotective role in the pathophysiological process. Exogenous VEGF, through gene transfer into the rat brain directly or through overexpression, reduces ischemic cerebral infarction and hypoxic neuronal death (Sun and Guo 2005). The neuroprotective mechanisms of VEGF include (1) regulating the phosphatidylinositol 3'-kinase (PI3K)/Akt/NF-KB signaling pathway, inhibiting caspase-3 activity, and reducing neuronal apoptosis; (2) inhibiting the outward delayed rectifier potassium channel current and increasing the ischemia-induced protein tyrosine phosphorylation of the Kv1.2 potassium channel by activating the PI3K pathway; and (3) increase neural precursor cells in the subventricular area after stroke. The improvements in proliferation, migration, striatal neurogenesis, and maturation of new neurons can help with the repair of brain injury (Sun and Guo 2005).

Neuroprotection and functional recovery after cerebral ischemia induced by CIMT may be mediated by the increased expression of endogenous HIF-1 α and VEGF, and subsequent neurogenesis and angiogenesis (Li et al. 2017). Sun and Guo (2005) observed, for the first time, that VEGF plasmid injection significantly promotes neurogenesis and the maturation of new striatal neurons, which transfers the VEGF plasmid to the lateral ventricle, resulting in the overexpression of VEGF, thus, enhancing the neuroprotection of neonatal neurons in adult rats with ischemic injury. In a model of middle cerebral artery occlusion, the neuroprotective effect of VEGF has been confirmed, and an increase in VEGF levels is closely related to the improvement of cerebral infarction and the promotion of peripheral neurogenesis (Zheng et al. 2019; Wang et al. 2019). Injection of VEGF into the lateral ventricle one day after perfusion reduces the infarct area, improves the neurological function, increases the survival rate of new neurons in the dentate gyrus and subventricular area, and stimulates angiogenesis, which highlights the therapeutic potential of VEGF in the treatment of stroke (Sun et al. 2003). In addition, the neuroprotective effect of VEGF was demonstrated in an oxygen glucose deprivation (OGD) model. The expression of PlGF in the VEGF family was significantly increased after cerebral ischemia. The addition of 0.01 ng/

ml PlGF to primary cultured cortical neurons could increase the mitochondrial activity after OGD, thus, exerting a neuroprotective effect on cerebral ischemia injury. This suggests that PlGF may be a regulator of angiogenesis and a potential regulator of angiogenesis after ischemic injury (Du et al. 2010).

3.1.3. Angiogenesis

An increase in new capillary density in the injured area is closely related to the prognosis and mortality of patients with ischemic stroke, suggesting that positive angiogenesis may be a promising method for stroke recovery (Manoonkitiwongsa et al. 2001). Angiogenesis, whether in the early stage (angiogenesis) or starting from the existing vessels (neovascularization), occurs under the synergistic effect of growth factors (Ucuzian et al. 2010). VEGF plays a very significant role as it is the most important mitogen in the process of angiogenesis (Beck and Plate 2009; Greenberg and Jin 2005). VEGF to VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1) on the endothelial cell surface activates intracellular tyrosine kinase, triggers a variety of downstream signals, and promotes angiogenesis. VEGF participates in angiogenesis through the following mechanisms (Shen 2014): (1) promoting the proliferation and migration of vascular endothelial cells, inducing the expression of corresponding ligands and receptors on endothelial cells; (2) increasing the expression of intercellular adhesion molecules and vascular cell adhesion molecules; (3) increasing the expression of integrin receptors on endothelial cells, inducing them to bind to bone bridge adhesion protein; and (4) upregulation of serine protein expression. The activity of white enzymes can degrade the extracellular matrix.

In the ischemic brain, VEGF has an acute neuroprotective effect and affects new neuron survival and angiogenesis. This mechanism is the primary pathway for angiogenesis after ischemia. Reportedly, VEGF treatment following ischemia resulted in increased VEGF/VEGFR expression in the penumbra, which was consistent with the time and distribution of neovascularization in the ischemic brain. This indicated that VEGF is related to angiogenesis in time and space (Zhang et al. 2002). Sun et al. (2003) found that after VEGF treatment for ischemia, vWF staining intensity increased in the penumbra of the ischemic striatum, indicating improved angiogenesis; however, no effects were observed in the dentate gyrus. Huang et al. (2004) studied a model of hypoxic-ischemic encephalopathy in neonatal rats. The density of capillaries in the hypoxic-ischemic brain tissue of the model group was significantly higher than that of the sham operation group, and the expression of VEGF mRNA in the brain tissue was upregulated after hypoxia-ischemia. Evidently, VEGF likely plays an important role in this process. In the middle cerebral artery occlusion model, delayed VEGF treatment after transient middle cerebral artery occlusion in rats reduced neonatal cerebral ischemia injury, partly owing to the induction of angiogenesis by reducing neuronal death and supporting the vascular system (Dzietko et al. 2013). In the ischemic rat brain, intravenous injection of VEGF triggered angiogenesis, indicating that the number and volume of cerebral cortex microvessels increased after seven days of FITC-glucan perfusion (Zhang et al. 2000). Intranasal administration of VEGF after cerebral ischemia in rats also induces angiogenesis at the ischemic border and improves behavioral recovery. Compared with that in the sham operation group and the normal saline group, the number of cerebral vessels in the ischemic border area of rats increased. This finding may provide a powerful strategy for the treatment of stroke (Yang et al. 2010).

3.2. Related factors and complications of ischemic stroke

3.2.1. Atherosclerosis

Atherosclerosis is a complex inflammatory and degenerative disease that mainly affects large- and medium-sized arteries. It is caused by multiple factors, with the primary risk factors being hypertension, hyperlipidemia, smoking, and genetic factors. Atherosclerosis is the main cause of coronary heart disease, ischemic stroke, and peripheral vascular disease. There is a close correlation between ischemic stroke and intracranial atherosclerotic stenosis, and the recurrence rate of atherosclerosis is also affected by the degree of vascular stenosis (Wang and Li 2020). However, whether VEGF is a pro- or anti-atherosclerotic factor remains controversial.

Some publications (Zhang and Hui 2005) have stated that VEGF plays a critical regulatory role in vascular development, remodeling, and maturation and can promote atherosclerotic injury through inflammatory infiltration and neovascularization. Some animal studies (Celletti et al. 2001; Ohtani et al. 2004) have shown that VEGF promotes the formation of atherosclerosis. Zhao and Zhang (2018) believe that VEGF-A signaling promotes endothelial cell proliferation, macrophage infiltration, and foam cell formation as well as plays a key role in the pathogenesis of atherosclerosis. VEGF-A and alternative splicing of VEGF165 before angiogenesis may promote atherosclerosis by increasing aortic endothelial cell proliferation and macrophage apoptosis. Kimura et al. (2007) considered that serum VEGF concentration may be closely related to atherosclerosis accelerating factors, especially in men. However, Howell et al. (2005) confirmed that VEGF polymorphism is related to the occurrence of atherosclerosis. This may support the protective role of VEGF in atherosclerosis mediated by the regulation of this factor.

3.2.2. Cerebral edema

Cerebral edema, a pathological phenomenon of increased brain water and brain volume, is a common and fatal complication of stroke. Cerebral edema is mainly classified as vascular and cytotoxic edema. After ischemic stroke, cytotoxic edema is reportedly observed within hours and then decreases within 1 day. On the contrary, angiogenic edema occurs within 2-3 days and lasts for several days. VEGF participates in cerebral edema, which not only reduces cerebral edema but also aggravates it. The use of a VEGF antagonist can reduce cerebral edema to a certain extent to achieve a protective effect (Shotaro and Yutaka 2015). The increase in VEGF expression induced by hypoxic-ischemic injury may play a role in altering BBB permeability and inducing cerebral edema. VEGF downregulates the expression of the ORM1 gene and protein by inhibiting the NF-kB pathway, which may be the mechanism of VEGF-induced cerebral edema (Chen et al. 2020).

VEGF can greatly promote the formation and growth of blood vessels and nerve cells. Simultaneously, it can significantly increase the permeability of blood vessels and promote cerebral edema, thus aggravating brain injury (Wu et al. 2017). A high dose of VEGF-inducing angiogenesis can aggravate brain edema and worsen the results of ischemia (Manoonkitiwongsa et al. 2004). Shin et al. (2013) found that estrogen receptor B reduces vascular edema caused by BBB rupture after ischemic stroke by inhibiting the expression of HIF-1a and VEGF. Kimura et al. (2005) first confirmed that the inhibitory effect of VEGF reduces VP and cerebral venous infarction in the acute phase, suggesting that the inhibition of VEGF may be a novel alternative for the treatment of brain edema. Early treatment with VEGF may lead to brain edema, whereas late treatment seems to have an ideal protective effect on the brain.

4. Conclusion

At present, the role of anti-VEGF therapy in various diseases, such as cancer, ischemia, inflammation (such as rheumatoid arthritis), and degenerative diseases, has been elucidated. VEGF is widely involved in ischemic stroke and plays an indispensable role. Alternative methods to promote VEGF signal transduction are regarded as new research directions for stroke treatment. Many traditional Chinese medicine compounds (Beck and Plate 2005; Zheng et al. 2018) can improve stroke by regulating VEGF, promoting angiogenesis, and playing a neuroprotective role. Meanwhile, VEGF intervention in cerebral ischemia appears to be closely related to the dosage, time, and route of administration. However, studies (Manoonkitiwongsa et al. 2004) have shown that high-dose VEGF

may induce brain edema and further worsen ischemia. Early VEGF treatment may lead to brain edema, but late treatment has a protective effect on the brain (Zhang et al. 2000). Late administration of VEGF, that is, on the first to third days of reperfusion, improves neurological function results (Sun et al. 2003). At present, the main administration routes of animal experimental models include direct intracerebral injection or local infiltration, intravenous injection, and gene therapy. A large number of animal experiments have shown that intravenous injection of VEGF or intravenous injection of VEGF plus transplantation of neural stem cells have therapeutic effects on stroke models. Additionally, nasal feeding of VEGF may also promote angiogenesis and functional recovery to alleviate ischemic stroke (Yang et al. 2010). Although VEGF has two sides in the treatment of ischemic stroke, it is still a potential treatment method based on its angiogenesis, neovascularization, and neuroprotection.

VEGF is widely involved in the treatment of ischemic stroke; however, there are pros and cons to its use. Understanding the neuroprotective effect of VEGF on cerebral ischemic tissue to prevent and reduce brain tissue damage, such as brain edema, simultaneously, is of great significance in the future application of VEGF treatment.

Funding sources: This work was jointly supported by grants from the National Natural Science Foundation of China (No.81774230, 81473587), Zhejiang Provincial Natural Science Foundation of China (No.LY21H270012), and Zhejiang Science and Technology Plan of Traditional Chinese Medicine (No.2020ZB159).

Funding sources: This work was jointly supported by grants from the Zhejiang Provincial Natural Science Foundation of China (No. LY21H270012), National Natural Science Foundation of China (No. 81774230, 81473587), Zhejiang Science and Technology Plan of Traditional Chinese Medicine (No. 2020ZB159).

Author contributions: Bing Chen and Yishu Zhang both searched literatures. Bing Chen wrote the paper. All authors discussed the content and contributed to the final paper.

Conflicts of interest: The authors have no conflicts of interest to declare.

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