The role of vascular endothelial growth factor in angiogenesis and brain circulation after stroke

The process of angiogenesis is paramount in blood vessel recovery and regeneration after a cerebrovascular accident. The reparative role of angiogenesis in the maintenance of brain circulation after an acute ischemic stroke (AIS) episode is mediated by cellular signaling cascades orchestrated through many molecules including an essential protein regulator of angiogenesis known as vascular endothelial growth factor (VEGF). The use of VEGF as a molecular target for therapeutic treatment of AIS events is complex, and its application involves an intricate timeline to minimize nervous system tissue damage and maximize blood vessel restoration. There are numerous ongoing investigations aimed at better understanding the cellular and molecular mechanisms of VEGF in the setting of AIS. These clinical and scientific studies have similar long-term goals, such as the development of rational drug therapies, including monoclonal antibodies and stem cells, and the improvement of patients’ functional outcomes and rehabilitative times.

In mammals, the VEGF family consists of five members, including Placental Growth Factor and VEGF-A/B/C/D. The outstanding molecule in this family is certainly VEGF-A due to its ability to promote angiogenesis and neurogenesis along with neuroprotection. After AIS, VEGF induces astrocyte transdifferentiation into new neurons, thus promoting neurogenesis. In theory, the supportive role of VEGF-A in both angiogenesis and neurogenesis makes it an attractive molecular target for rational drug therapy in the setting of AIS. Contrariwise, under these circumstances, the increase in endogenous VEGF levels and the use of exogenous VEGF in ischemic cerebral tissue is actually injurious in the early recovery phase after AIS. Perhaps, these inconsistencies are best reconciled through realizing the dual role of VEGF-A in AIS; it establishes the endothelial network through enhancing endothelial cell migration and proliferation, but also induces vascular leakiness and permeability.

The phosphorylation of tyrosine residues within VEGF-A activates its receptor tyrosine kinase activity and causes activation of its downstream target proteins in three important signal transduction pathways: (1) the Akt and phosphatidylinositol-3-kinase (PI3K) pathway, (2) the mitogen-activated protein kinase (MAPK) pathway, and (3) matrix metalloproteinases (MMPs). The VEGF-A molecule supports neuron survival in cell culture models of AIS, including the excitotoxicity model and the oxygen-and-glucose deprivation model. In the AIS setting, the upregulation of the first and second signaling pathways are beneficial for neuron proliferation and survival while increased MMP levels lead to VEGF-A-mediated cerebrovascular edema and inflammatory damage. A recent research study in a rodent middle cerebral artery occlusion (MCAO) model of AIS made four key conclusions: (1) the early secretion of VEGF contributes to endothelial leakiness after AIS, (2) the early inhibition of VEGF may reduce neurovascular permeability along with (3) decreasing infarct volume and increasing neurological functioning, and (4) these neuroprotective effects may decrease MMP 2 and 9 levels and simultaneously increase tight junction proteins such as occludin.

When implementing these treatments, there are important temporal constraints for physicians and scientists to consider. For example, the application of intravenous VEGF-A is contraindicated at both the 1–3 h up to 24 h time intervals after an episode of AIS. Instead the use of VEGF-A 1 day after AIS appears to confer neuroprotection through decreasing infarct volume and increasing vascular volume. In humans, the efficacy and timing of VEGF-A administration still need to be fully resolved to ensure its safe use in the recovery phase of AIS.

There have been recent therapeutic efforts to molecularly target VEGF-A through using stem cells, chemical agents, and alternative medicines to improve neurological outcomes in the recovery phase of AIS. Foremost, the injection of stem cells overexpressing VEGF-A has been demonstrated to induce angiogenesis in nervous system tissue. Similarly, transplantation of human neural stem cells into rat cerebral cortex 1-week post-MCAO decreased behavioral deficits and infarct volume and these positive effects were diminished through administration of bevacizumab, a human monoclonal antibody against VEGF-A. Next, the application of the chemical agent dl-3-n-butylphthalide in eighty human patients after AIS was recently shown to be salubrious because it decreased neurological deficits and increased serum VEGF levels. Furthermore, the application of a traditional Chinese medicinal herb, xueshuantong (Panax notoginseng), is reputed to be beneficial in the treatment of AIS in humans.
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Conflicts of interest
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References
1. Beck H, Plate KH. Angiogenesis after cerebral ischemia. Acta Neuropathol 2009;117:481-96.
2. Namiecińska M, Marciniak K, Nowak JZ. VEGF as an angiogenic, neurotrophic, and neuroprotective factor. Postepy Hig Med Dosw (Online) 2005;59:573-83.
3. Góra-Kupilas J, Jośko J. The neuroprotective function of vascular endothelial growth factor (VEGF). Folia Neuropathol 2005;43:31-9.
4. Cao L, Jiao X, Zazza DS, Liu Y, Fong DM, Young D, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. Nat Genet 2004;36:827-35.
5. Dzietko M, Derugin N, Wendland MF, Vedder ZS, Ferriero DM. Delayed VEGF treatment enhances angiogenesis and recovery after neonatal focal rodent stroke. Transl Stroke Res 2013;4:189-200.
6. Nishijima K, Ng YS, Zhong L, Bradley J, Schubert W, Jo N, et al. Vascular endothelial growth factor – A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. Am J Pathol 2007;171:33-67.
7. Ma Y, Zechariah A, Qu Y, Herrmann DM. Effects of vascular endothelial growth factor in ischemic stroke. J Neurolsci Res 2012;90:1873-82.
8. Shen SW, Duan CL, Chen XH, Wang YQ, Sun X, Zhang QW, et al. Neurogenic effect of VEGF is related to increase of astrocytes transdifferentiation into new mature neurons in rat brains after stroke. Neuropsychopharmacology 2016;108:451-61.
9. Marti HJ, Bernaudin M, Bellail A, Schoch H, Euler M, Petit E, et al. Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. Am J Pathol 2000;156:965-76.
10. Kanazawa M, Igarashi H, Kawamura K, Takahashi T, Takahashi H, et al. Inhibition of VEGF signaling pathway attenuates hemorrhage after tPA treatment. J Cereb Blood Flow Metab 2011;31:1461-74.
11. Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, et al. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. J Clin Invest 2000;106:829-38.
12. Weis SM, Chernes DA. Pathophysiological consequences of VEGF-induced vascular permeability. Nature 2005;437:497-504.
13. Matsuzaki H, Tamatani M, Yamaguchi A, Namikawa K, Kiyama H, Vitek MP, et al. Vascular endothelial growth factor rescues hippocampal neurons from glutamate-induced toxicity: Signal transduction cascades. FASEB J 2001;15:1218-20.
14. Svensson B, Peters M, König HG, Poppe M, Levkau B,
Rothermundt M, et al. Vascular endothelial growth factor protects cultured rat hippocampal neurons against hypoxic injury via an antiexcitotoxic, caspase-independent mechanism. J Cereb Blood Flow Metab 2002;22:1170-5.

15. Jin KL, Mao XO, Greenberg DA. Vascular endothelial growth factor: Direct neuroprotective effect in in vitro ischemia. Proc Natl Acad Sci U S A 2000;97:10242-7.

16. Zhang HT, Zhang P, Gao Y, Li CL, Wang HJ, Chen LC, et al. Early VEGF inhibition attenuates blood-brain barrier disruption in ischemic rat brains by regulating the expression of MMPs. Mol Med Rep 2017;15:57-64.

17. Kaya D, Gürsoy-Ozdemir Y, Yemisci M, Tuncer N, Aktan S, Dalkara T, et al. VEGF protects brain against focal ischemia without increasing blood–brain permeability when administered intracerebroventricularly. J Cereb Blood Flow Metab 2005;25:1111-8.

18. Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, et al. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. J Clin Invest 2003;111:1843-51.

19. Yang JP, Liu HJ, Liu XF. VEGF promotes angiogenesis and functional recovery in stroke rats. J Invest Surg 2010;23:149-55.

20. Lee HJ, Kim KS, Park IH, Kim SU. Human neural stem cells over-expressing VEGF provide neuroprotection, angiogenesis and functional recovery in mouse stroke model. PLoS One 2007;2:e156.

21. Horie N, Pereira MP, Niizuma K, Sun G, Keren-Gill H, Encarnacion A, et al. Transplanted stem cell-secreted vascular endothelial growth factor effects poststroke recovery, inflammation, and vascular repair. Stem Cells 2011;29:274-85.

22. Tang SC, Luo CJ, Zhang KH, Li K, Fan XH, Ning LP, et al. Effects of dl-3-n-butyolphthalide on serum VEGF and bFGF levels in acute cerebral infarction. Eur Rev Med Pharmacol Sci 2017;21:4431-6.

23. Gao L, Zhao H, Liu Q, Song J, Xu C, Liu P, et al. Improvement of hematoma absorption and neurological function in patients with acute intracerebral hemorrhage treated with xueshuantong. J Neurol Sci 2012;323:236-40.

24. Guo H, Adah D, James PB, Liu Q, Li G, Ahmadu P, et al. Xueshuantong injection (Lyophilized) attenuates cerebral ischemia/Reperfusion injury by the activation of Nrf2-VEGF pathway. Neurochem Res 2018;43:1096-103.

25. Yang J, Yang B, Xiu B, Qi J, Liu H. Effect of combination therapy with neuroprotective and vasoprotective agents on cerebral ischemia. Can J Neurol Sci 2018;45:325-31.

26. Slevin M, Krupinski J, Slowik A, Kumar P, Szczudlik A, Gaffney J, et al. Serial measurement of vascular endothelial growth factor and transforming growth factor-beta1 in serum of patients with acute ischemic stroke. Stroke 2000;31:1863-70.

27. Matsuo R, Ago T, Kamouchi M, Kuroda J, Kuwashiro T, Hata J, et al. Clinical significance of plasma VEGF value in ischemic stroke – Research for biomarkers in ischemic stroke (REBIOS) study. BMC Neurol 2013;13:32.

28. Lee SC, Lee KY, Kim YJ, Kim SH, Koh SH, Lee YJ, et al. Serum VEGF levels in acute ischaemic strokes are correlated with long-term prognosis. Eur J Neurol 2010;17:45-51.