Review Article

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Cerebral circulation improves with indirect bypass surgery combined with gene therapy

Alex Shear, Shingo Nishihiro[1], Tomohito Hishikawa[1], Masafumi Hiramatsu[1], Kenji Sugiu[1], Takao Yasuhara[1], Isao Date[1]

Abstract:

Angiogenesis involves new blood vessels sprouting from preexisting blood vessels. This process may serve to improve brain circulation. Moyamoya disease (MMD) is a cerebrovascular disorder causing intracranial stenosis which significantly reduces the blood supply to the brain. Mainly stroke is the first symptom of the disorder, so treatments that reduce the risk of stroke are used for patients with MMD. To prevent stroke for those with chronic cerebral hypoperfusion, more blood needs to flow to the brain, which was thought to be achieved by enhancing angiogenesis. Indirect bypass surgery, such as encephalo-myo-synangiosis (EMS), is used for revascularization. However, EMS alone sometimes cannot provide enough circulation to avoid ischemic strokes. The current study examined if EMS combined with high-mobility group box-1 (HMGB1) and vascular endothelial growth factor (VEGF) enhanced angiogenesis and increased cerebral circulation. The results indicated that HMGB1 administered with EMS increased angiogenesis through a VEGF-dependent mechanism. In addition, exercising and stem cell transplantation possess possible means to increase angiogenesis. Overall, EMS with gene therapy, maintaining fitness, and stem cell utilization may prevent or help one recover from stroke by enhancing brain angiogenesis. Thus, these treatments may be applicable for patients with MMD. This paper is a review article. Referred literature in this paper has been listed in the references section. The datasets supporting the conclusions of this article are available online by searching various databases, including PubMed.

Keywords:

Angiogenesis, cerebral hypoperfusion, encephalo-myo-synangiosis, endothelial progenitor cells, high-mobility group box-1, revascularization, vascular endothelial growth factor

Department of Neurosurgery and Brain Repair, College of Medicine, University of South Florida Morsani, Tampa, FL, USA, [1]Department of Neurological Surgery, Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Address for correspondence:
Dr. Takao Yasuhara, Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan.
E-mail: tyasu37@cc.okayama-u.ac.jp

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Treatment for Chronic Cerebral Hypoperfusion

Moyamoya disease (MMD) is a chronic cerebral hypoperfusion state with increased narrowing of the intracranial internal carotid artery.[1] Treatments such as direct and indirect revascularization surgery are used for patients with MMD.[2-5] Encephalo-myo-synangiosis (EMS) is a simple, indirect revascularization surgery for younger patients with MMD, yet EMS can provide inadequate collateral flow with a possible case of an ischemic stroke.[1,6,7] To enhance angiogenesis in the brain cortex, EMS should be combined with gene therapy. A previous study analyzed the results from an indirect revascularization surgery combined with vascular endothelial growth factor (VEGF) gene in the temporal muscle of a rat with chronic cerebral hypoperfusion.[8,9] In addition, the current study examined the effect of combined gene therapy with VEGF plus apelin during indirect revascularization surgery.[10] EMS showed indirect bypass surgery for the hypoperfusion state after bilateral common carotid artery ligation. Thus, angiogenesis in the brain cortex

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progressed when EMS worked with gene therapy. Other treatments for chronic hypoperfusion involve the use of limb remote ischemic conditioning (LRIC). This method is neuroprotective for white matter lesions after ischemia, but the means it protects after chronic cerebral hypoperfusion is unknown. A recent study did find that PTEN/Akt/mTOR signaling pathways were activated after LRIC.[11]

Most eukaryotic cells have a DNA binding protein in their nucleus called high-mobility group box-1 (HMGB1). HMGB1, which is also present in neural cells, supports nucleosome assembly and is involved in gene replication, transcription, and DNA repair.[12-14] In the acute phase after a stroke, HMGB1 promotes inflammation and death of cells. In the delayed phase after a stroke, HMGB1 enhances neurogenesis and angiogenesis.[13,15] This concept that HMGB1 promotes angiogenesis has been supported by experimental models of hindlimb ischemia,[16] intracerebral hemorrhage,[17] and cardiac ischemia.[18]

Encephalo-Myo-Synangiosis with Gene Therapy Enhances Angiogenesis for Moyamoya Disease Patients

Pediatric patients use indirect bypass surgery, such as EMS, rather than direct bypass surgery, such as STA-MCA bypass used for adults with MMD, as direct bypass surgery is more challenging to conduct on pediatric patients.[3,6] Although simpler, indirect bypass surgery sometimes provides inadequate collateral flow which leads to a weak clinical outcome.[7,13,19] Brain angiogenesis determines postsurgical results because of the transmuscular anastomosis from the hidden temporal muscle and enhanced cerebral blood flow (CBF).[20,21] CBF improves with enhanced collateral circulation, which results from exogenous angiogenic factors provided during indirect bypass surgery. Earlier research explained how the combination of the plasmid human VEGF with EMS augmented the number of vessels versus without VEGF administration. When EMS was administered with VEGF plus apelin, there was a major increase in the number of blood vessels versus EMS alone. In addition, the mature blood vessels were greatly developed compared with EMS without any gene therapy or compared with EMS with VEGF.[5,9] Therefore, EMS with the addition of other angiogenic factors may also strengthen angiogenesis, making cerebral circulation more efficient.

Therapeutic Effects of High-Mobility Group Box-1 Administration

HMGB1 is a nuclear DNA-binding protein found in most eukaryotic cells and neural cells. HMGB1 functions in gene expression such as gene transcription, replication, and DNA repair.[12-14] In the early phase post brain injury or stroke, damaged cells passively release HMGB1, and immune cells actively secrete HMGB1, which promotes inflammation and necrosis.[13] However, in the late phase after neural ischemia, HMGB1 may strengthen angiogenesis which modifies tissues by endothelial activation and sprouting.[15] In addition, the enhancement of angiogenesis may activate endothelial progenitor cells (EPCs) after cerebral ischemia which induces neurovascular repair.[22] HMGB1 was injected into the ischemic hindlimb of diabetic mice which promoted angiogenesis and perfusion recovery through a VEGF-dependent apparatus.[16] A left anterior descending coronary artery ligation mouse model displayed enhanced angiogenesis and improved cardiac function after the use on HMGB1 transgenic mice.[18] In the current chronic cerebral hypoperfusion models in rats, there was a higher abundance of vessels in the operated side of the cortex on the HMGB1-treated group compared to the same side in the control group and significantly higher compared to the nonoperated side in the same group 14 days after EMS. Furthermore, the current study revealed that the VEGF expression level in the muscle on the operated side in the HMGB1-treated group was higher compared with the nonoperated side in the same group 4 days after EMS along with the VEGF expression level in the cortex did not change for both sides between the two groups. The promotion of endothelial cell proliferation and migration by HMGB1 directly increased vessel formation and the promotion of angiogenic factors such as VEGF by HMGB1 indirectly increased vessel formation.[22] Therefore, HMGB1 may enhance the production of angiogenic cytokines such as VEGF from endothelial cells and activated macrophages which has been analyzed in diabetic mice. In these diabetic mice, the administration of HMGB1 promotes ischemia-induced angiogenesis in a VEGF-dependent mechanism (0–800 ng).[16] The current study by Nishihiro *et al.*, preliminarily found that 1 μg of HMGB1 had stronger angiogenic potentials compared to the angiogenic potentials with less amount of HMGB1. This finding helped the study determine the dosage of HMGB1 to use. In addition, the present study determined that VEGF protein significantly amplified in the muscle on the operated side, and VEGF protein significantly induced angiogenesis in the cortex of the operated side in the HMGB1-treated group.[18] Thus, the VEGF-dependent mechanism enhanced angiogenesis, and the development of transmuscular anastomosis into the brain cortex below EMS.[8]

Shortly, after HMGB1 administration into the ischemic hindlimb of diabetic mice, the VEGF level and postischemic angiogenesis both increased when the tissue recovery and inflammatory response were

comparable.[16] Enhanced angiogenesis and then transmuscular anastomosis development below EMS resulted in decreased VEGF expression in the muscle on the operated side. This could improve the ischemic condition in the brain cortex. Previous reports explain that angiogenesis is enhanced by the direct injection of VEGF protein to the lateral ventricle,[23] or the direct injection of gene therapy using a virus or plasmid.[8,23] However, VEGF alone may produce newly formed immature vessels with side effects such as edema[23,24] or angioma formation.[25] For those with MMD, using a virus or plasmid for gene therapy may pose a risk for direct administration. DNA mutations can emerge in gene therapy, if the targeted genes are placed into the wrong location in the host DNA. After misplacement, the cells proliferate abnormally and form a tumor. Moreover, HMGB1 administration into the temporal muscle is the best treatment compared with gene therapy regarding safety as it reduces the amount of DNA mutations. This treatment is also simple and effective because the use of HMGB1 may induce angiogenesis by promoting the production of angiogenic factors such as VEGF. HMGB1 also directly enhances angiogenesis by promoting endothelial cell proliferation and migration.[15] HMGB1 also is important for nervous system regeneration [Figure 1].[26,27]

Postoperation Cerebral Blood Flow

Clinically, CBF improvement after direct or indirect bypass surgery can prevent ischemic stroke for patients with MMD[1] which proposes that hemodynamic improvement of cerebral circulation after revascularization is imperative for the postoperative outcome.[28,29] The ratio of cerebral perfusion for the operated side versus the nonoperated side in the HMGB1-treated group showed more elevation compared to the control.

New Moyamoya Disease Findings

Brain circulation describes the movement of blood toward the brain. Diseases such as MMD have blocked cerebral arteries, preventing oxygenated blood to flow to the brain. The mechanism causing these narrowed or blocked arteries is still unknown. Recently, a study identified mutations in the RING finger protein 213 (RNF213) in 95% of East Asian familial MMD cases. Previously, environmental factors such as inflammation, angiogenic factors, and EPCs have been the focus of research. Currently, most research regarding MMD focuses on the biological effect of mutant RNF213.[30]

Furthermore, revascularization surgery has shown to be successful for MMD patients; however, the associated risks are important to consider. The purpose of revascularization surgery is to increase intracranial blood flow using branches of the external carotid system to prevent ischemic stroke. During the surgery, an approximate 39% chance exists for a younger patient with MMD to have a preoperative stroke at a median of 3 months. After the operation, 21.5%–50% suffer hyperperfusion syndrome, and the excess increase in brain blood flow causes neurological changes.[11] Another means to prevent ischemia is through dietary restrictions involving calories as these restrictions provide a preconditioning state that can aid in protecting the brain.[31] For patients in a chronic hypoperfusion state, a significant increase in brain blood flow is necessary, and this can be done through angiogenesis. This process repairs the brain circulation system after an acute ischemic stroke episode and is regulated by cell signal cascades such as VEGF which regulates angiogenic proteins. The role of VEGF is critical in maximizing blood vessel restoration but minimizing the damage to nervous system tissues. Many studies continue to examine the complexity of VEGF's functions, involving the balance between blood vessel repairment and nervous tissue damage.[32]

Exercise Reveals Protective Benefits for Stroke

Exercise may enhance angiogenesis and thus prevent or decrease the neurological damage after a stroke. A current study demonstrated that exercised rats prior to stroke induction displayed increased levels of endothelial/angiogenesis markers, VEGF, VEGF receptor-2, and angiopoietin-2 after stroke compared with nonexercised rats. Therefore, exercising may provide neuroprotection by strengthening cerebrovascular potency.[33] Gradually with exercise, the human body upregulates hypoxic-induced factor 1α and consumes more ATP which results in a hypoxic condition. This condition induces angiogenesis and neurogenesis in which a neurovascular unit consisting of microvascular endothelium, astroglia, neurons, and the extracellular matrix is enhanced.[34] With hypoxic preconditioning in the brain, cellular mechanisms cause reduced energy demand, protection against cell death, and responses that reduce the severity of hypoxia.[35]

Regarding fitness, exercise can improve the integrity of the blood–brain barrier (BBB) which is critical in that disruption of the BBB can negatively affect the brain's microenvironment. For example, a study revealed that exercising 30 min a day for 3 weeks displayed improved basal lamina due to strengthened collagen IV.[36] EPCs contribute to angiogenesis and vasculogenesis, allowing EPCs to reconstruct the BBB following stroke. EPC therapy remains a field warranting further research to help the brain recover after a stroke.[37]

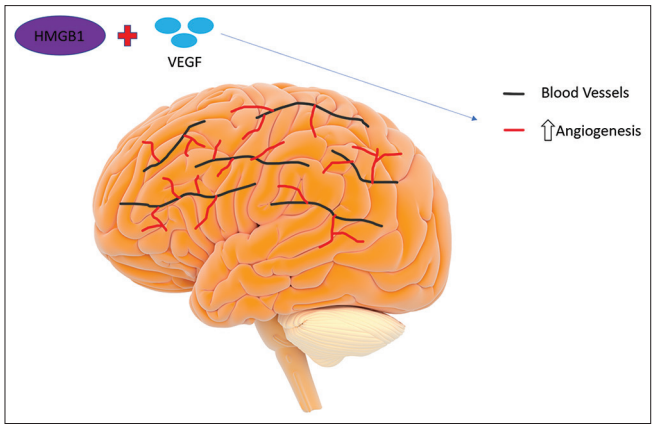

Figure 1: High-mobility group box-1, vascular endothelial growth factor, and stroke. The treatment of high-mobility group box-1 and vascular endothelial growth factor may confer neuroprotection against stroke by targeting the blood vessels to enhance angiogenesis

Stem Cells and Endothelial Progenitor Cells are Important for Future Research

Furthermore, stem cell transplantation currently represents a promising treatment for stroke. Stem cells can differentiate and regenerate lost tissues, induce endogenous regenerations, and stimulate future neuroprotection. Stem cell regeneration is two-fold with cell replacement and trophic factor release. Trophic factors naturally secreted by stem cells can maximize endogenous repair, neuroprotection, and the decrease of inflammation.[38] A healthy brain has its endothelium providing growth and trophic factors for neuroprotection, while a pathogenic brain's endothelium advances the disease progression by downregulating vasculogenic factors. The cerebral endothelium can also secrete molecules that control disease processes after ischemic stroke, known as stroke vasculome. Therefore, the endothelium in the brain plays a crucial role, so angiogenesis enhancement which stimulates EPCs is critical for one to recover after a stroke.[39]

Conclusion

For patients with chronic hypoperfusion such as those with MMD, HMGB1 administration with EMS surgery stimulates angiogenesis through a VEGF-dependent mechanism which likely promotes more efficient cerebral circulation. This treatment may become an effective therapy by avoiding strokes for those with MMD. In general, future research focusing on stem cells, EPCs, and exercising may advance knowledge for stroke as these factors may enhance angiogenesis which might cause improved neurological changes.

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Conflicts of interest

There are no conflicts of interest.

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