

Study on the Effects of HIF-1 α on Ischemic Stroke

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Abstract: Stroke is one of the diseases with high incidence of cardiovascular and cerebrovascular diseases in the world. Its disability rate ranks first in cardiovascular and cerebrovascular diseases. The pathophysiology of this disease is that cerebral blood circulation leads to cerebral ischemia and hypoxia, which leads to softening and necrosis of brain tissue. Hif-1 α is a nuclear transcription factor produced by the body under hypoxia, which activates a series of target genes to produce hypoxia tolerance response and maintain environmental balance in the body. Hif-1 α is a nuclear protein produced under hypoxia. By regulating downstream cells, it can promote the formation of new blood vessels, resist neuronal apoptosis, and alleviate ischemia and hypoxia injury. Hif-1 α is a key hypoxia receptor, which can be expressed rapidly in brain hypoxia, and its level is closely related to hypoxia. The role of hypoxia-inducible factor-1 α (HIF-1 α) in ischemic stroke has become a research hotspot in recent years.

Keywords: Stroke, HIF-1 α , Hypoxia

1. Introduction

Stroke is one of the diseases with high incidence of cardiovascular and cerebrovascular diseases in the world. Its disability rate ranks first among cardiovascular and cerebrovascular diseases^[1]. Stroke, commonly known as stroke, includes ischemic stroke (cerebral infarction) and hemorrhagic stroke. It is a disease in which brain cells and tissues die. Stroke is the leading cause of death and disability among adults in China. The burden of stroke in China is exploding as society ages and urbanization speeds up, unhealthy lifestyles are prevalent among residents and cardiovascular risk factors are widely exposed. The prevention and treatment of stroke in China still faces great challenges, and the prevention and treatment system needs to be further strengthened^[2]. Ischemic strokes account for 75 to 90 percent of all strokes, while hemorrhagic strokes account for only 10 to 25 percent. The most common type of ischemic stroke in Chinese medicine is qi deficiency and blood stasis. The pathophysiology of this disease is that cerebral ischemia and hypoxia are caused by blood circulation of cerebrovascular, resulting in softening and necrosis of brain tissues^[3].

Hif-1 α is a nuclear transcription factor produced by the body under hypoxia, which activates a series of target genes to produce hypoxia tolerance response and maintain environmental balance in the body^[4]. Hif-1 α is a nuclear protein produced under hypoxia. Regulating downstream cells can promote the generation of new blood vessels, resist neuronal apoptosis, and alleviate ischemia and hypoxia injury^[5]. Hif-1 α is a key hypoxia receptor, which can be expressed rapidly under brain hypoxia, and its level is closely related to hypoxia^[6]. How hypoxia-inducible factor-1 α (HIF-1 α) plays a role in ischemic stroke has become a research hotspot in recent years^[7]. In 1992, Semenza identified a protein named hypoxia-inducible factor-1 (HIF-1) in the nuclear extract of human HEP3B cell line, which specifically binds the oligonucleotide sequence of the enhancer of the erythropoietin (EPO) gene. With the further research, it has been found that it is closely related to various reaction mechanisms of ischemia/hypoxia^[8].

2. HIF-1 α is associated with hypoxia adaptation and inflammatory response

Hif-1 alpha HIF-1 response to hypoxia and inflammation alpha It is a nuclear protein located on human chromosome 14. It has transcriptional regulation and activation functions. It is associated with hypoxic adaptation and inflammatory response. Sun et al.^[9] found that the upregulation of HIF-1 expression in vascular endothelial cells of patients with acute sepsis injury is related to the occurrence of lung inflammatory injury. Decreased hippocampal HIF-1 expression level in rats with early brain injury after treatment indicates that the impairment of BBB function is alleviated^[10]. Hajime et al.^[11] showed that the expression of HIF-1 α and pro-inflammatory factors can promote the progression of atherosclerosis under hypoxia. Jeong et al.^[12] confirmed that EGF can induce hif-1 α protein expression

and promote ectodermal cell proliferation under hypoxia.

3. The role of HIF-1 α in acute ischemic stroke

Hypoxia-inducible factor-1 (HIF-1) is a nuclear transcription factor that maintains oxygen homeostasis and tolerates hypoxia in tissue cells under hypoxia. Studies have shown that HIF-1 α can regulate the expression of a series of genes (mainly related to hypoxia) to repair nerve cell damage [13]. Some studies have also shown that hiF-1 overexpression in brain tissue α induced by severe sustained hypoxia and ischemia can activate notch-1, p53 and other genes, activate inflammatory cells and inflammatory mediators, and promote the recovery of neural function [14].

4. HIF-1 α regulates a series of gene expression to repair nerve cell damage

Under normal conditions, plasma hiF-1 levels in HIF-1 α are very low. However, during cerebral ischemia and hypoxia, hiF-1 transcription and expression in nerve cells are increased and hiF-1 degradation occurs, while α prolyl hydroxylase and ubiquitin proteasome systems are inhibited [15]. In addition, ischemic hypoxia injury leads to impaired nerve cell integrity. The BBB permeability increases and hiF-1 α leakage increases its plasma content. Cerebral thrombosis leads to ischemia and hypoxia in brain tissue, and increases hiF-1 α expression in nerve cells. In recent years, studies [16,17] have found that hiF-1 α can regulate many hypoxia-related genes, such as vascular endothelial growth factor, glucose transporter, erythropoietin, inducible nitric oxide synthase, b-cell lymphoma gene 2, caspase, adenovirus interfering protein 3, Ngb, heat shock protein 70, etc. These genes increase ATP release by promoting anaerobic metabolism, promote microcirculation reconstruction and vascular dilation, promote erythropoiesis, increase oxygen load, reduce neuronal apoptosis, and reduce brain tissue damage after ischemic stroke.

5. HiF-1 α overexpression activates inflammatory cells and inflammatory mediators

Overexpression of HIF-1 α in brain tissue induced by severe sustained hypoxia and ischemia can activate p53, Notch 1 and other genes, promote apoptosis, activate a large number of inflammatory cells (neutrophils and macrophages) and inflammatory mediators (NF - XB and COX-2), and increase brain edema and blood-brain barrier permeability. However, knockout of hiF-1 α gene or inhibition of HIF-1 α expression can alleviate brain tissue damage after ischemic stroke and promote the recovery of neurological function [18]. The level of hiF-1 in α plasma was significantly increased in patients with stroke. The larger the infarct size was, the higher the level of HIF-1 was in patients with ischemic stroke. Stroke can lead to elevated levels of hiF-1 in serum α . The more severe the stroke, the more elevated hiF-1 levels were. The possible mechanism is that when cerebral infarction occurs, there is repeated hypoxic-reoxygenation process, which leads to the hypoxia environment of tissues or organs, thus initiating oxidative stress response and inducing hiF-1 α expression, and inhibiting hiF-1 α degradation and increasing its level [19].

6. Conclusion and outlook

Therefore, in view of the different effects of HIF-1 α in different periods, we must strictly control the treatment time window and drug dose when applying HIF-1 α in the treatment of ischemic stroke, so as to let the neuroprotective effect of HIF-1 α play a leading role and reduce its neurological injury function as much as possible, so as to better treat ischemic stroke. As a nuclear transcription factor, HIF-1 α plays an important role in the physiological and pathological processes of mammalian growth and development. Regulation of HIF-1 α activity is the entry point for treatment of many diseases. Although the study of HIF-1 α in the nervous system is just beginning, further study of hiF-1 α will provide a deeper understanding of the pathological mechanism of stroke, and also provide a new treatment for cerebral hypoxia disease.

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References

- [1] Tsujio S, Chono A, Kawahira K, et al. 605 Development of function recovery training assistant system on one cerebral apoplexy paralysis leg: 2nd report: A method for calculation and evaluation of inverse kinematic [J]. *Am J Prev Med*, 2015, 39 (6): 605-606.
- [2] Wang Longde, Liu Jianmin, Yang Yi, Peng Bin, Wang Yilong. Stroke prevention and treatment in China: An overview of the Chinese Stroke Prevention and Treatment Report 2018 [J]. *Chinese journal of circulation*, 2019, 34(02): 105-119.
- [3] Zhang Chengfa, Wang Fuxin. 315 cases of ischemic stroke risk factors Logistic Regression analysis [J]. *Heilongjiang medical science*, 2015, 38 (2): 153-155.
- [4] Wu Junli, Huang Wei. Enhancement of blood lipid on acute cerebral infarction and TOAST of all types Study on the influence of different types of patients [J]. *Heilongjiang med sci*, 2016,39 (4): 42-44.
- [5] Barteczek P, Li L, Ermst AS, et al. Neuronal HIF-1 and HIF-2a deficiency improves neuronal survival and sensorimotor function in the early acute phase after ischemic stroke [J]. *J Cereb Blood Flow Metab*, 2017, 37(1): 291 - 306.
- [6] Sun Ruixue, Jiang Hong, Zhang Ningmei, et al. Correlation analysis of serum Copeptin, HIF-1 α and CT-1 levels with neonatal sepsis myocardial injury [J]. *Journal of Central South Medical Science*, 2019, 47(5): 462-464.
- [7] Lu Linmin, Song Xuedong, Luo Ning. Diagnostic value of magnetic resonance imaging combined with serum hypoxia-induced factor-1 in neonates with hypoxic ischemic encephalopathy [J]. *Medical Journal of PLA*, 2018, 30(2):41-45.
- [8] SemenzaGL, WangGL. A nuclear factor induced by hypoxiaviade novoprote in synthesis birds to the humanery thopoitin gene enhancer at a site required for transcriptinalactivation [J]. *MDcellBio1*, 1992, 12 (12): 5447-5454.
- [9] Sun HD, Liu YJ, Chen J, et al. Research on the role of HIF-1 α in septic stroke induced by its subjunctive mesenteric lymph [J]. *Biomed Pharmacother*, 2017, 91 (1): 476-484.
- [10] Xu W, Xu R, Li X, et al. Downregulating hypoxia-induc-ible factor-1 α expression with perfluorooctyl-bromide nanopar ticles Early Clinical data analysis of clinical data in rats [J]. *Am J Transl Res*, 2016, 8 (5): 2114 -2126
- [11] Abe H, Semba H, Takeda N, et al. Role of hypoxia signaling in pathogenesis of cardiovascular diseases [J]. *J Atheroscler Thromb*, 2017, 24 (9): 884-894.
- [12] Jeong W, Bazer FW, Song G, et al. Expression of hypoxia - inducible factor -1 by trophectoderm cells in response to hy- poxia and epidermal growth [J]. *Biochem Biophys Res Commun*, 2016, 469 (2): 176-182.
- [13] Pan F, Barbi J, Pardoll DM. Hypoxia-inducible Factor 1: A link between differentiation and T cell differentiation and A potential therapeutic target [J]. *Oncoimmunology*, 2012, 1 (4): 510-515.
- [14] Wu Yudan, Ni Jiayan, Chen Yaoting, et al. Effects of hiF-1 α gene silencing on the proliferation of rat hepatocellular carcinoma cells [J]. *Chinese journal of pathophysiology*, 2013, 29 (7):1207-1212.
- [15] Semenza GL. Oxygen homeostasis [J]. *Wiley Interdiscip Rev Syst Biol Med*, 2010; 2 (3): 336-61.
- [16] Zhang ZY, Yan JQ, Taheri S, Et al. Hypoxia-inducible factor1 contributes n-acetylcysteine's protection against stroke [J]. *Free Radical Biol Med*, 2014; 68 (1): 8-21.
- [17] Ogle ME, Gu XH, Espinera AR, et al. Inhibition of prolyl hydroxylases by dimethylxaloylglycine after stroke reduces ischemic brain injury and Requires Hypoxia inducible factor-1 α [J]. *Neurobiol Dis*, 2012; 45 (2):733-42
- [18] Cheng YL, Park JS, Manzanero S, Et al. Evidence that collaboration between HIF-1 α and notch-1 promotes neuronal cell death in ischemic stroke [J]. *Neurobiol Dis*, 2014; 62 (1): 286-95.
- [19] Zhu Shaoliang, Tu Qiang, Huang Yi. Expression of HIF-1 α and Ng2 in patients with cerebral apoplexy [J]. *Journal of clinical laboratory science*, 2016, 34(07): 578-580.