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Research Progress on the Treatment of Ischemic Stroke by Regulating the Sonic Hedgehog Signaling Pathway with Traditional Chinese Medicine

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Abstract: ***Ischemic stroke (IS) is a series of pathological damages caused by the interruption of local cerebral blood flow. Its pathogenesis is extremely complex, involving multiple signaling pathways. Among them, the Sonic Hedgehog (Shh) signaling pathway has become a research hotspot in recent years. IS falls into the category of "apoplexy". Apoplexy is also known as stroke. Traditional Chinese medicine (TCM) has a long history in treating apoplexy. The comprehensive treatment methods of TCM mainly focus on syndrome differentiation and treatment. According to the changes of syndromes in different periods of apoplexy, treatment is carried out according to the syndrome. Chinese herbal medicine is inexpensive and has multiple targets of action. Based on the above background, this study investigates how Chinese herbal medicine alleviates the damage caused by IS by regulating the Shh signaling pathway, and points out its shortcomings, providing favorable conditions for subsequent research.***

Keywords: Chinese herbal medicine, Ischemic stroke, Shh signaling pathway, Review**.**

1. Introduction

Stroke is one of the most common diseases in neurology and has become one of the leading causes of premature death in our country [1]. Clinically, it is divided into ischemic stroke and hemorrhagic stroke. When the blood flow in local cerebral vessels is interrupted, the brain tissue becomes ischemic and hypoxic, and a series of reactions such as edema, necrosis, oxidative stress, and apoptosis occur locally. Ischemic stroke (IS) is characterized by high incidence, high disability rate, high mortality, high recurrence rate, and high economic pressure [2]. Once it occurs, not only does the patient suffer irreversible damage from the disease, but the patient's family also has to bear a double blow of economy and psychology. At present, the fundamental treatment for ischemic stroke lies in timely salvage of the ischemic penumbra and minimizing the damage to brain tissue. The treatments include: (1) Thrombolytic therapy. The most common thrombolytic drugs in our country are recombinant tissue-type plasminogen activator and urokinase, but they have strict time windows and contraindications. (2) Thrombectomy treatment: including endovascular mechanical thrombectomy, intra-arterial thrombolysis, and angioplasty. However, these treatments are only targeted at larger vessels and have certain limitations. (3) Antiplatelet, anticoagulant therapy, brain protection therapy, and volume expansion therapy are routine treatments. (4) Other drug treatments: fibrinolytic therapy, the efficacy of which is still not clear. The above treatment methods have many shortcomings in the treatment of ischemic stroke. Traditional Chinese medicine has obvious advantages in the treatment of ischemic stroke. Due to the complex components, multiple targets of action, and few side effects of traditional Chinese medicine, it has certain clinical significance in the prevention and treatment of apoplexy.

2. Introduction to the Shh Signaling Pathway

The Shh protein is a component of the Hh protein family. The Shh signaling pathway is very important for the development of the nervous system and the formation of organs [3]. The mechanism of the Shh signaling pathway has not yet been fully elucidated. The existing theory suggests that it is divided into the canonical pathway and the non-canonical pathway. The canonical pathway is mainly composed of Shh, Patched1 (Ptch1), Smoothened (Smo), and the downstream zinc-finger transcription factor Glioblastoma (Gli), as well as some effector target genes. The non-canonical pathway is a general term for the signal responses of one or more components of the Shh signaling pathway, and it is mainly divided into three types: Type I refers to the signal transduction mediated by Ptch, Type II is the signal transduction mediated by Smo, and Type III is the non-Smo-dependent activation of Gli-mediated signal transduction [4]. The canonical pathway is considered to be the main part that explains the Shh signaling pathway [5]. After cerebral ischemia and hypoxia, neurons in the brain secrete Shh protein, which can bind to Ptch protein, thereby releasing SMO molecules and triggering the expression of Gli1. After cerebral ischemia and hypoxia, the overexpression of Gli1 protein indicates the activation of the Shh signaling pathway [6]. After the Shh signaling pathway is activated, the activated Shh signaling pathway has multiple protective effects in the occurrence of ischemic stroke, such as protecting the blood-brain barrier, resisting oxidative stress, reducing apoptosis, and combating excitotoxicity [7].

3. The Role of Shh Signaling Pathway in IS

3.1 Inhibition of Oxidative Stress Response

After cerebral ischemia, an excessive amount of reactive oxygen species (ROS) can be produced, leading to oxidative stress, aggravating neuronal damage, and causing severe functional defects [8]. ROS play an important role in the pathogenesis of neuronal cell death in acute central nervous system injury [9]. ROS can cause cell necrosis and organism damage by destroying the structure of the cytoskeleton, DNA, proteins, and other processes. The antioxidant capacity of

body tissues is the main endogenous defense mechanism against ROS damage. Antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPH-PX), together with glutathione (GSH), prevent the production of ROS and lipid peroxidation in tissues [10]. It has been reported in studies [11] that in rats with middle cerebral artery occlusion (MCAO), the levels of ROS and malondialdehyde (MDA) increase, and the antioxidant activity is significantly reduced. The ROS products formed in tissues are effectively detoxified by the antioxidant defense system such as SOD and GSH-PX. Specifically, SOD can react with O2 to generate H2O2, which is then decomposed into H2O and O2 by catalase, thereby preventing the production of hydroxyl radicals. GSH-PX can also oxidize GSH into glutathione disulfide, thereby reducing H2O2 to H2O [12]. Unsaturated fatty acids in the cell membrane can interact with reactive free radicals and undergo lipid peroxidation, which can be decomposed and produce several secondary products, among which MDA is relatively important [13]. The more MDA accumulates, the more severe the lipid peroxidation of cerebral ischemia is, and the greater the damage to the body [14].

After the activation of the Shh signaling pathway, the expression of MDA can be reduced, while the expression of SOD and GSH-PX can be increased, reducing the damage of oxygen free radicals to brain tissue and increasing cell viability, thereby reducing the oxidative stress damage after cerebral ischemia and hypoxia [15]. Experiments [16] have confirmed that the Shh/Gli1 signaling pathway is activated in patients with cerebral ischemia, and at the same time, oxidative markers are reduced, and the activity of antioxidant enzymes (including SOD and GSH-PX) in neurons is increased. Studies have shown [15] that after cerebral ischemia and hypoxia, the Shh signaling pathway is activated, reducing the damage of oxidative stress to the brain.

3.2 Anti-apoptosis

Apoptosis is a gene-regulated active death process aimed at maintaining homeostasis and is one of the main mechanisms of cerebral ischemia-reperfusion injury. The B lymphocyte tumor 2 (Bcl-2) family, as a key factor affecting cell apoptosis, can be divided into pro-apoptotic proteins (Bax, BaR) and anti-apoptotic proteins (Bcl-2, Bcl-xl) according to their functions. The cysteine protease (Caspase) family belongs to cysteine proteases and plays an important role in cell apoptosis. The activation of cysteine protease-3 (Caspase-3) is a key step in initiating apoptosis, which can activate downstream apoptotic genes and induce cell apoptosis [17].

The Shh signaling pathway, as an indispensable signaling pathway in the development process, can inhibit cell apoptosis when activated [18]. For example, both Gli1 and Gli3 can down-regulate the pro-apoptotic protein caspase3 and up-regulate the anti-apoptotic Bcl2 gene [19, 20]; Ptch regulates cell apoptosis through the activation of caspase in the neural tube [21]. In existing studies, after the activation of the Shh signaling pathway, it can affect downstream signaling pathways such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling, p53 pathway, inflammatory factor pathway (NLRP3 inflammatory signaling pathway, etc.), non-receptor protein tyrosine kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway, P-AKT/mammalian target of rapamycin (mTOR) signaling pathway, etc. [22], thereby exerting anti-apoptotic effects.

3.3 Alleviation of Brain Edema

After local ischemia, the interruption of ATP synthesis in brain tissue, energy deficiency, and ion homeostasis damage lead to the destruction of the structure of the blood-brain barrier (BBB) and increased permeability, resulting in brain edema [23]. The BBB is composed of tightly arranged vascular endothelial cells, astrocytes, pericytes and other cells, which can control the physical and biochemical barriers of the brain's internal environment homeostasis. Tight junction (Tjs) proteins connect endothelial cells, ensuring the physiological integrity of the BBB, and one of the main proteins of Tjs is Cldn5. When the structure of the BBB is destroyed, the paracellular permeability of vascular endothelial cells increases, leading to brain tissue edema; at the same time, it allows inflammatory factors, plasma and serum proteins to enter the central nervous system, causing neuroinflammation, further aggravating the destruction of the BBB and forming a vicious cycle. Aquaporin 4 (AQP4) is the main water channel protein in the brain, functioning as an extracellular osmoreceptor and water balance regulator, playing a dominant role in the transport of water molecules in brain tissue, and is of great importance in maintaining the stability of the brain tissue's internal environment [24]. After cerebral ischemia, the electrolyte balance inside and outside astrocytes is disturbed, the osmotic pressure gradient changes, the expression of AQP4 is up-regulated, the cell membrane structure is changed, leading to astrocyte edema [25], increasing the permeability of the BBB and cell water permeability, and accelerating the flow of intravascular fluid and surrounding cerebrospinal fluid into the brain parenchyma. The Shh signaling pathway can repair Tjs proteins in MCAO animal models, significantly reduce brain edema and maintain the permeability of the BBB, while the Shh signal transduction inhibitor cyclopamine can reverse this effect [26].

3.4 Anti-neuroinflammation

Inflammatory response is one of the main pathological reactions after IS. Microglia are the resident immune cells in the central nervous system, playing a role in local immune surveillance and participating in the regulation of brain inflammatory responses [27]. After ischemic stroke, activated microglia are a double-edged sword in ischemic stroke. In the acute phase of cerebral ischemic injury, over-activated microglia accelerate inflammatory responses and neurological dysfunction by releasing pro-inflammatory factors such as tumor necrosis factor-α, interleukin-1β, interleukin-6 and interferon-γ. In the subacute and chronic phases of stroke, activated microglia promote tissue and vascular remodeling by secreting anti-inflammatory factors such as interleukin-10, as well as vascular endothelial growth factor, transforming growth factor-β and brain-derived neurotrophic factor. Therefore, inhibiting the over-activation of microglia is crucial for reducing ischemic brain damage. Exploring drugs or methods that can inhibit the abnormal activation of microglia in the acute phase of stroke and improve

neurological function after stroke has great clinical transformation potential. Neuroinflammation has both destructive and protective effects in brain injury and is a trigger for Shh signaling. Neuroinflammation may be an early neuroprotective mechanism in stroke, during which cell proliferation is induced to repair the damaged BBB. Activating Shh can reduce the mRNA levels of microglia/macrophage markers and pro-inflammatory cytokines IL-6, TNF-α and IL-1β in the ischemic cortex of rats after middle cerebral artery occlusion.

3.5 Promotion of Angiogenesis

The specific mechanism of angiogenesis after ischemic stroke is relatively complex. Some scholars have reported that after ischemic stroke, growth factors related to angiogenesis, such as angiopoietin-1 (Ang-1) and vascular endothelial growth factor (VEGF), are activated and their receptors are activated and release enzymes related to downstream pathways, thereby producing a series of changes [29-31]. After ischemic stroke, VEGF plays an important role in the early process of promoting angiogenesis, and after VEGF binds to vascular endothelial growth factor receptor 2 (VEGFR2), it promotes angiogenesis [32]. At the same time, the Ang family and the VEGF family have complementary effects, and the Ang family and the VEGF family can regulate angiogenesis after ischemic stroke [33, 34]. Molecules of the Ang family can promote the process of angiogenesis after ischemic stroke together with the VEGF family, among which Ang-1 mainly promotes the closure and maturation of new blood vessels by improving the survival of endothelial cells [35-37]. Shh promotes angiogenesis and neuronal survival by increasing the expression of VEGF. Xu Junjie and other experiments showed that the Shh signaling pathway promotes angiogenesis and improves the neurological function of MCAO rats and reduces the inf.

4. Pharmacological Regulation of the Shh Signaling Pathway in the Intervention of IS

4.1 Tongqiao Huoxue Decoction (Decoction for Unblocking the Orifices and Activating Blood)

The principal drug of Tongqiao Huoxue Decoction is musk, whose main active ingredient is muscone [39]. It has various effects such as improving the permeability of the blood-brain barrier, alleviating brain edema, and reducing central nervous system damage [40]. The main active ingredients of Ligusticum chuanxiong are phthalide compounds [41, 42], which can reduce cell apoptosis and necrosis, decrease the volume of cerebral infarction, and improve the neurological function and blood-brain barrier damage in the rat model of middle cerebral artery occlusion [43]. The main components of ginger include ginger volatile oil and total ginger phenols, etc. Studies have found that ginger volatile oil can improve the symptoms of focal cerebral ischemia in rats, reduce neuronal apoptosis, and lower the water content of brain tissue [44, 45]. Bai Ma Ruixue et al. [46] found in experiments that Tongqiao Huoxue Decoction may protect the integrity of the blood-brain barrier by activating the Shh signaling pathway, increasing the expression of Cldn5 and reducing the expression of AQP4, thereby alleviating brain edema. Ye Yufeng [47] found in experiments that Tongqiao Huoxue Decoction can inhibit neuronal apoptosis by activating the Shh signaling pathway, thereby reducing the neurological damage in rats with cerebral ischemia. It can be seen that Tongqiao Huoxue Decoction can protect the blood-brain barrier, alleviate brain edema, and inhibit cell apoptosis by activating the Shh signaling pathway.

4.2 Naoluoxintong Formula (Brain Network Refreshing and Unblocking Formula)

The Xin'an Wang's Internal Medicine has inherited and developed the treatment concept of "tonifying qi, activating blood and dredging collaterals" for apoplexy in long-term theoretical research and clinical practice. The fifth-generation inheritor, Mr. Wang Letao, created the Naoluoxintong Formula, which consists of Astragalus, Ligusticum chuanxiong, Notoginseng, Gastrodia, Angelica sinensis, Carthamus, and Scolopendra. The method of tonifying qi, activating blood and dredging collaterals promotes the proliferation of neural stem cells and vascular regeneration after ischemia. After medication, the expression of proteins such as BDNF, VEGF, and Ang-2 is significantly increased, indicating that Naoluoxintong may promote the proliferation of neural stem cells, vascular regeneration, and synaptic reconstruction by regulating the SHH signaling pathway [48]

4.3 Atractylodes Macrocephala

Atractylodes macrocephala is the dried rhizome of the plant Atractylodes macrocephala Koidz. of the family Asteraceae. It has a fragrant aroma, warm nature, and sweet and bitter taste. It is known for its effects of tonifying qi, strengthening the spleen, and stopping perspiration. It is commonly used to treat symptoms such as poor appetite due to spleen deficiency, chronic diarrhea, edema, and spontaneous sweating. Pharmacological studies have shown that Atractylodes macrocephala also has antibacterial, anti-aging, and immune-regulating effects, and it also has a certain regulatory effect on the nervous system [49]. Its main component is Atractylodin III. Zhou Qian [50] and others have experimentally proven that ATIII can improve the neurological deficits in rats with ischemic stroke by activating the Shh signaling pathway.

4.4 Curcuma Zedoaria

Curcuma zedoaria contains curcumin, zedoary ketone, α-zedoarylen, bisdemethoxycurcumin, methoxycurcumin, etc., which have various pharmacological activities such as anti-inflammatory, antioxidant, anti-platelet aggregation, and regulation of cell apoptosis [51]. Curcumin can effectively reduce neuronal loss and apoptosis, and prevent neurological disorders caused by cerebral ischemia-reperfusion by promoting the activation of the Shh signaling pathway, thereby exerting a neuroprotective effect [52].

4.5 Other Ditional Chinese Medicines

The main components of dried tangerine peel (cheTranpi) and aurantium fruit (zhishi) are naringenin, which has strong anti-neuronal apoptosis and antioxidant capabilities [53]. Shan Ping [54] and others experimentally confirmed that naringenin can alleviate neuronal oxidative damage and

apoptosis by activating the Shh signaling pathway. Resveratrol is one of the main components of mulberries. Resveratrol can exert its effects in preventing and treating cerebral infarction through various pathways such as inhibiting inflammatory responses, antioxidant stress responses, enhancing cellular autophagy and energy metabolism, promoting synaptic growth, reducing neuronal apoptosis in the ischemic brain area, and protecting the function and structure of the blood-brain barrier. Yu et al. [55] used 10 mg/kg resveratrol to intervene in rats with cerebral ischemia and found that it could activate the Shh signaling pathway, thereby reducing mNSS, Bederson, Longa scores and neurological deficits, promoting the proliferation and migration of neural stem cells and precursor cells, promoting the differentiation and maturation of neurons, and promoting the remodeling and biogenesis of neuronal synapses.

5. Summary

In recent years, the incidence trend of IS has gradually become younger, which brings a heavy psychological burden to patients and their families. Currently, there are certain limitations in Western medicine treatment. In recent years, traditional Chinese medicine (TCM) has developed rapidly. Treatments such as acupuncture, moxibustion, and cupping are convenient, simple, and have few side effects, with a high acceptance rate among patients. The characteristics of traditional Chinese medicine, such as complex composition, multiple targets of action, and few adverse reactions, make it highly acceptable to patients. Compound Chinese medicine can be used flexibly according to syndrome differentiation for precise treatment of the lesion. The research on the treatment of IS with TCM has gradually become a hot topic. Activating the Shh signaling pathway can repair the blood-brain barrier, alleviate neuroinflammatory reactions, reduce oxidative stress, promote angiogenesis, and resist apoptosis, thereby improving various post-stroke sequelae of ischemic stroke. This article reviews the possible potential mechanisms of treating IS with traditional Chinese medicine by regulating the Shh signaling pathway, summarizes compound Chinese medicine and monomers, and finds that most of the current research is still in the experimental stage, lacking large-scale clinical trials for verification. Therefore, conducting clinical trials to evaluate the efficacy and safety of treating ischemic stroke with traditional Chinese medicine by regulating the Sonic Hedgehog signaling pathway is an important direction for future research, in order to promote its clinical application. More in-depth research is needed in the future to clarify the specific molecular mechanisms of treating ischemic stroke with traditional Chinese medicine by regulating the Sonic Hedgehog signaling pathway, including the interaction between the active ingredients of traditional Chinese medicine and the key molecules in the Sonic Hedgehog signaling pathway, as well as the specific functions of this pathway in different pathological stages. Interdisciplinary joint research in TCM, neurobiology, molecular biology, and other fields is encouraged. A variety of research methods and technical means should be comprehensively used to deeply explore the scientific connotation of treating ischemic stroke with traditional Chinese medicine by regulating the Sonic Hedgehog signaling pathway, providing a solid theoretical basis for the development of new TCM treatment strategies.

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