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Research Progress Regarding the Mechanism of Acupuncture in the Treatment of Stroke on the Nervous System

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Abstract. Stroke is one of the leading causes of disability and death worldwide. Acupuncture, as a traditional Chinese medicine, has received considerable attention recently for its use in stroke-related nervous system treatments. Acupuncture exerts therapeutic effects through multiple mechanisms, including stimulating and regulating related factors and signaling pathways to play anti-inflammatory, neuronal repair and protective effects; controlling glial cell polarization to promote self-repair after brain injury, etc. Acupuncture has been shown to markedly decrease the inflammatory response following a stroke, facilitate nerve regeneration and cell proliferation within the central nervous system, enhance cerebral blood flow in ischemic regions, diminish neuron apoptosis, and ultimately lead to improvements in neurological function and quality of life for stroke patients. Nevertheless, the precise neural mechanisms underlying acupuncture's effects on stroke remain incompletely elucidated, warranting further comprehensive investigation. This article reviews the research progress on the neural mechanisms of acupuncture in the treatment of stroke in recent years, with a view to providing scientific basis and reference for its clinical application.

Keywords: Acupuncture, Stroke, Nervous system, Neural mechanisms.

1. Introduction

Stroke, also referred to as a cerebral vascular accident (CVA), ranks among the top causes of mortality and long-term disability globally. The World Health Organization reports approximately 15 million new stroke cases annually, of which about two-thirds can lead to death and disability. Therefore, stroke not only has a huge impact on personal health and family, but also brings a heavy burden to society and the economy [1].

The pathogenesis of stroke is complex, mainly including ischemic stroke (IS) and hemorrhagic stroke (HS). Modern medicine plays a pivotal role in the treatment of stroke. In the acute treatment, mechanical thrombolysis has significant efficacy in the treatment of IS, and its combination with intravenous thrombolysis can prolong the treatment time window in the acute phase of stroke and improve the prognosis of patients with acute IS. Tenecteplase IV is gradually replacing the traditional oral thrombolytic drugs due to its higher fibrin specificity and longer half-life. However, Western medicine is lacking in the sequelae of stroke as well as in the later stages of rehabilitation, and many patients still face long-term dysfunction and decreased quality of life [2]. Acupuncture, as a traditional Chinese medicine treatment method, effectively improves patients' neurological function through specific

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acupoint stimulation. Acupuncture plays a significant role in the treatment of neurological mechanisms in stroke due to its advantages of inexpensive, convenient and safe operation [3].Recent research indicates that acupuncture can activate specific signaling pathways to facilitate nerve regeneration and cell proliferation, while also reducing inflammatory responses and apoptosis, with pronounced effects observed in the regions surrounding cerebral infarctions. Additionally, acupuncture modulates levels of various neurotransmitters and nerve growth factor (NGF), which are crucial for nerve repair and neuroplasticity. By enhancing synaptic connections, neuronal communication, and enhancing long-term potentiation as well as memory functions that are impaired by stroke, acupuncture supports brain function recovery. These findings establish a scientific basis for utilizing acupuncture in stroke management.

2. Neuropathic mechanisms of stroke

2.1. IS

IS (also known as CVA) is the most common type of stroke. Its main causes include atherosclerosis, cardiogenic factors, abnormal blood components and vascular lesions, which lead to blockage or severe narrowing of cerebral blood vessels [4], which in turn triggers cerebral tissue ischemia and hypoxia, resulting in death of brain tissues in areas supplied by cerebral blood vessels. IS has a high recurrence rate, disability rate and death rate, with clinical manifestations such as impaired consciousness, numbness of limbs and hemiparesis of the body.

2.2. HS

HS, representing approximately 15% of all stroke cases, occurs due to the rupture of a cerebral blood vessel, resulting in bleeding into the brain tissue or submeningeal space. This hemorrhage results in compression and subsequent damage to the brain tissue. Its main causes are hypertension, aneurysms, cerebrovascular malformations and trauma.

3. Mechanisms of nerve damage after stroke

3.1. Neuronal death

Neuronal death is one of the main mechanisms of brain injury after stroke and is associated with cell necrosis, pyroptosis, and apoptosis. Studies have shown that after stroke [5], necrosis occurs first in the ischemic core area, resulting in acute death of a large number of neurons and glial cells within a few hours, seriously impairing brain function. Entering the ischemia-reperfusion phase [6], intraneuronal reactive oxygen species(ROS)and calcium overload trigger the activation of the NOD-like receptor family pyrin domain-containing 3 inflammasome, resulting in caspase-1-mediated pyroptosis, resulting in neuronal death and brain injury. Doyle et al [7]. found that damage-associated molecular patterns (DAMPs) and inflammatory mediators released by necrotic cells not only induced pyroptosis, but also induced apoptosis by activating the death receptor pathway, further amplifying cell damage.

3.2. Neuroinflammation

Neuroinflammation due to stroke is complex and varied, involving ischemia-reperfusion injury, immune cell activation, release of inflammatory mediators, activation of cell signaling pathways, disruption of the blood-brain barrier (BBB), and neuronal damage. Ischemia-reperfusion injury triggers intracellular energy depletion, oxidative stress, and cell membrane damage, leading to the release of large amounts of DAMPs [8]. Activation of immune cells also triggers an inflammatory response, and studies have shown that the high mobility group protein B1 is an important proinflammatory mediator that promotes M1 polarization in microglia [9]. This process can exacerbate the inflammatory response through the release of several inflammatory mediators, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-c1 beta (IL-1β), and IL-6. Inflammatory mediators further exacerbate the inflammatory response through the activation of signaling pathways, including Nuclear Factor kappa B (NF-κB) and Mitogen-

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Activated Protein Kinase (MAPK), and increasing inflammatory gene expression. In addition, the action of inflammatory mediators and immune cells disrupts the BBB and increases vascular permeability, allowing leukocytes and inflammatory mediators to infiltrate into the brain tissue, further exacerbating inflammation and neuronal damage. A deeper understanding of these mechanisms could help develop more effective therapeutic strategies to reduce neuroinflammation and neurological damage after stroke.

3.3. BBB disruption

In IS, brain tissue is damaged due to ischemia, resulting in increased intracellular calcium, oxidative stress, and an inflammatory response. These reactions increase the permeability of the BBB, allowing cytokines, inflammatory mediators, and plasma components in the blood to penetrate into brain tissue, exacerbating brain damage. In hemorrhagic stroke, the rupture of blood vessels directly destroys the BBB, allowing red blood cells and plasma proteins to penetrate into brain tissue, triggering local inflammation and neuronal damage.

4. Acupuncture acts on the neural mechanisms of stroke

4.1. Basic principles of acupuncture

According to traditional Chinese medicine theory, the human body has a meridian system responsible for the circulation of Qi and blood, connecting the internal organs, and integrating the interior and exterior of the body. Acupuncture stimulates specific meridians and acupoints, such as Baihui (GV20), Qubin (GB7), Sishencong (EX-HN1), and Shuigou (GV26), to regulate Qi and blood, and balance Yin and Yang, thereby achieving therapeutic effects. The locations and functions of these acupoints within the meridian system help regulate the central nervous system and promote the recovery of neural function.

4.2. Effects of acupuncture on the nervous system

4.2.1. Neuronal protection

Following cerebral hemorrhage, blood components infiltrate adjacent brain tissues, inducing neurotoxicity and rapidly leading to neuronal damage [10]. Post-stroke [11], the expression of NADPH oxidase 1 and Acyl-CoA Synthetase Long Chain Family Member 4 in neurons increases, promoting the production of large amounts of lipid peroxides and ROS through the Fenton reaction, ultimately leading to ferroptosis. NGFs and neurotransmitters play key roles in the stroke process. Research has indicated that acupuncture can elevate the expression of superoxide dismutase, reduce the production of ROS, thereby mitigating oxidative stress-induced damage to the BBB. Additionally, acupuncture promotes neuronal repair, improving neurological function and daily living abilities.

4.2.2. Anti-inflammatory effect and blood-brain barrier protection

Acupuncture can inhibit the activation of microglial cells following hypoxia and ischemia, reduce levels of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α in brain tissues, and promote the release of anti-inflammatory cytokines like IL-10, thereby alleviating neuroinflammatory responses. Moreover, acupuncture can decrease the expression of pro-inflammatory factors in the peri-infarct cortex, inhibit inflammatory responses, and mitigate ischemia-reperfusion injury [12].

5. Cellular and molecular mechanisms

5.1. The impact of acupuncture on neurons and glial cells

Acupuncture, particularly electroacupuncture (EA), stimulates the proliferation and differentiation of neural stem cells (NSCs) in the Subventricular Zone and Subgranular Zone by upregulating neurogenesis-related factors and activating cellular signaling pathways. Studies have shown that EA can induce NSCs to differentiate into astrocytes and mature neurons, supporting moderate proliferation of

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astrocytes and secreting brain-derived neurotrophic factor (BDNF), thereby safeguarding the brain from ischemic injury and promoting neurological recovery. Additionally, acupuncture can restrain theexcessive proliferation and differentiation of astrocytes in the later stages of stroke, thus reducing the overproduction of harmful substances that impede axonal regeneration and fostering self-repair following brain injury [13].

Upon ischemic activation, microglia rapidly shift from a resting state to an active state, a process known as microglial polarization. Activated microglia can differentiate into M1 and M2 types. M1 microglia exacerbate inflammation by releasing pro-inflammatory mediators, whereas M2 microglia facilitate tissue repair through the release of anti-inflammatory mediators and neurotrophic factors. Acupuncture has been shown to lower the proportion of M1 microglia, reduce their production of pro-inflammatory factors, and increase the proportion of M2 microglia, thereby enhancing the release of anti-inflammatory mediators and neurotrophic factors, thereby aiding in neural repair and functional recovery while reducing post-stroke inflammation [14].

5.2. Regulation of neurotransmitters and receptors by acupuncture

Studies have demonstrated that acupuncture can effectively enhance neurological function and behavioral performance in stroke patients by modulating neurotransmitter and receptor levels and activity [15]. Acupuncture at Zusanli (ST36) and Taichong (LR3) points can increase dopamine release in the striatum of stroke rats, improving motor function and emotional state. Additionally, acupuncture can upregulate the expression of dopamine D2 receptors, enhancing dopamine signaling and promoting neural function recovery. In the serotonin system, acupuncture at Baihui (GV20) and Neiguan (PC6) points can significantly increase brain 5-Hydroxytryptamine(5-HT)levels in stroke rats, alleviating depression and anxiety symptoms. Acupuncture can also regulate the expression of 5-HT1A and 5-HT2A receptors, enhancing 5-HT signaling, thereby improving post-stroke emotional disorders. Studies have shown that glutamate serves as the primary excitatory neurotransmitter in the central nervous system, and its excessive release leads to excitotoxicity, exacerbating brain damage. Acupuncture at Shuigou (GV26) and Hegu (LI4) points can regulate glutamate release in the brains of stroke rats, reducing excitotoxic neuronal damage. Moreover, acupuncture can modulate NMDA and AMPA receptor activity, protecting neurons from glutamate-induced damage, thereby promoting neural function recovery. BDNF has become a key regulatory factor in neuroplasticity during post-stroke motor learning and rehabilitation. Acupuncture and EA stimulate nerve trunks and terminals, triggering action potentials and inducing the autocrine or paracrine signaling of neurotrophic factors such as BDNF, increasing their expression and release, and promoting neuronal repair. Acupuncture can also regulate neurotransmitters like gamma-aminobutyric acid and norepinephrine(NE)and their receptors, reducing neuronal excitability to exert anticonvulsant and sedative effects, and improving attention and cognitive function by increasing NE levels.

5.3. Regulation of signaling pathways by acupuncture

Studies have shown that acupuncture regulates BDNF levels, affecting the BDNF/TrkB signaling pathway, which activates downstream PI3K/Akt and MEK/ERK pathways to facilitate neural repair. The MAPK/ERK signaling pathway is crucial for regulating cell proliferation, differentiation, and survival, and acupuncture regulates this pathway through specific acupoint stimulation. Research has found that acupuncture at Zusanli (ST36) can downregulate ERK1/2 phosphorylation levels, reducing inflammation and exerting anti-inflammatory effects [16]. Within the central nervous system, the MAPK/ERK signaling pathway plays a role in the survival and regeneration of neural cells. Acupuncture at Baihui (GV20) and Dazhui (GV14) points can reduce ischemia-reperfusion injury [17], thereby improving functional recovery after neural damage. Additionally, acupuncture at Zusanli (ST36) can upregulate the PI3K/Akt pathway, promoting neural cell survival and reducing apoptosis [18]. Acupuncture can also regulate the expression of antioxidant enzymes through this pathway, reducing oxidative stress-induced neural damage [19]. Meanwhile, the NF-κB signaling pathway is essential in regulating the immune response, inflammation, and cell survival. Studies have found that acupuncture

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at Neiguan (PC6) and Quchi (LI11) points can inhibit NF-κB activation, downregulate NF-κB p65 nuclear translocation, thereby reducing the release of inflammatory factors and alleviating inflammatory responses.

6. Conclusion

Acupuncture exerts its effects in stroke treatment through various cellular and molecular mechanisms, improving neurological function and overall rehabilitation. Its primary mechanisms involve glial cells, such as astrocytes and microglia, and their secretion of neurotrophic factors like BDNF and NGF, supporting and promoting neuronal reconstruction post-stroke. Early acupuncture treatment in stroke not only inhibits pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α, but also promotes the release of anti-inflammatory cytokines. Additionally, it upregulates antioxidant enzyme activity, reduces ROS production, alleviates neuroinflammation and oxidative stress-induced BBB damage, promotes neural repair, and improves neurological function.

The advantages of acupuncture in treating stroke are becoming increasingly prominent, but in actual application, there are still irregularities in acupoint selection, acupuncture methods, treatment frequency, and treatment duration. Different acupoint combinations and acupuncture methods also have different effects on brain tissue activity and brain function. Additionally, current studies have discovered that acupuncture affects the polarization state of microglia at different stages of stroke are not in-depth enough, and are limited to observations and measurements at specific time points after stroke. There is a lack of dynamic observation of the stroke recovery process, and it is impossible to reflect the effects and mechanisms of acupuncture at different time points. In particular, the bidirectional regulatory effect of acupuncture at the cellular and molecular levels deserves further exploration.

In summary, this article explains the research on the neural mechanism of acupuncture treatment from the aspects of pathophysiological mechanism, clinical efficacy, and neural mechanism, which will offer novel insights for the future clinical prevention and management of stroke.

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