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Review Article

Based on Microglial Polarization and Autophagy Activity after Intracerebral Hemorrhage Exploring the Anti-Injury-Promoting Repair Effect of Traditional Chinese Medicine Intervention Research Progress of Dual Action Mechanism

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Abstract:

Intracerebral hemorrhage is a common emergency in neurology. After the onset, primary and secondary injuries are formed, resulting in severe neurological deficits and brain damage. In response to this injury, the brain activates self-repair mechanisms such as microglia polarization and autophagy activity, aiming to maintain the homeostasis of the central nervous system by inhibiting injury and promoting repair. However, this endogenous repair has certain limitations. Therefore, exogenous intervention to promote the body to inhibit damage and promote repair is particularly important. In recent years, the treatment of cerebral hemorrhage with traditional Chinese medicine has received extensive attention due to its multi-target, multi-path, and multi-link action characteristics. To explore the dual mechanism of TCM intervention in promoting the body to inhibit damage and promote repair after cerebral hemorrhage will help to further clarify and improve the clinical efficacy of TCM in the treatment of cerebral hemorrhage.

Key words: chinese medicine intracerebral hemorrhage microglia cell autophagy injury

Intracerebral hemorrhage is a common emergency in neurology, and it is also the most deadly of cerebrovascular accidents; its incidence accounts for approximately 10% of all stroke types 10- 15%,1/3of patients after the onset of1Died within months, survivors are left with varying degrees of disability and a high risk of recurrent cerebral hemorrhage modern medicine past30The mortality rate after cerebral hemorrhage has been reduced to a certain extent over the years, but the early mortality rate is as high as 50% In addition, surgery did not improve the progression and outcome of cerebral hemorrhage, so it is particularly urgent to study the repair mechanism of cerebral hemorrhage. Primary injury and secondary injury can be formed after the onset of cerebral hemorrhage. Because the primary injury is caused by the hematoma mass and compression effect in the brain parenchyma, it is often irreversible, and the secondary injury becomes the key point of intervention after intracerebral hemorrhage. However, the pathological mechanism of secondary injury is complex. Thrombin, blood components, inflammatory mediators, etc. can stimulate cytotoxicity, excitotoxicity, oxidative stress and inflammatory responses, resulting in blood-brain barrier damage, brain edema, neuronal Apoptosis and other serious pathological damage. After intracerebral hemorrhage, the body immediately initiates the endogenous and extrinsic coagulation cascades to release coagulation due to self-protection mechanisms. blood enzymes to stop bleeding; when released in large quantities, activates the complement pathway and Gprotein-coupled receptors (Protease activated receptors, PARs) signaling pathway, where, PAR-1, PAR-3, PAR-4It has been reported to be a target receptor for thrombin, and its activation can be regulated by thrombin. activated complement pathway and PARs The pathway further activates microglia, induces inflammatory response, cytotoxicity, and induces apoptosis of neurons, vascular endothelial cells and astrocytes [4-6]. In addition to thrombin, after the blood components spilled into the brain parenchyma are degraded into hemoglobin, iron, free

radicals, etc., various inflammatory cells will be recruited and activated; among them, microglia and astrocytes in the brain are the earliest inflammatory cells; after activation of microglia, peripheral leukocytes, macrophages, The cells are also activated; the activated inflammatory cells further secrete inflammatory mediators, cytotoxic substances, etc.

control-induced inflammatory cascade [7]. ultimately cause the structure and function of the blood-brain barrier Energy destruction, resulting in vasogenic edema; the latter causes intracranial pressure to increase and normal brain tissue to be compressed, causing severe neurological deficits [8]. Of course, However, the brain also initiates self-healing mechanisms while experiencing damage, aiming to inhibit damage and promote repair to maintain the homeostasis of the central nervous system. The brain releasesIL-10,TGF-betaand other protective cytokines to regulate target cells to promote h ematoma absorption and remove cellular waste garbage, on the other hand it releases nerve growth factor (nerve growth factor, NGF), brain-derived neurotrophic factor (brain derived neurotrophic factor, BDNF) and other neurotrophic substances to protect damaged neurons and promote neuron regeneration; also release vascular endothelial growth factor (vascular endothelial cell growth factor, VEGF) to promote the proliferation of vascular endothelial cells and form new blood vessels and further release matrix [9]. metalloproteinases after the formation of new blood vessels (Matrix metalloproteinases, MMPs)2and9etc., to promote the migration, homing and differentiation of neuroblasts [10-11]. Because the endogenous repair of the brain has certain limitations, it is particularly important to deeply understand the mechanism of brain self-repair after intracerebral hemorrhage and the role of exogenous drug intervention in inhibiting injury and promoting repair. In recent years, microglia polarization and autophagy activities have attracted much attention because of their dual roles of damage and repair in the pathological progression of cerebral hemorrhage. Traditional Chinese medicine has also played a multi-targeted role in the treatment of cerebral hemorrhage. The role of point, multi-channel and multi-link has been paid much attention. In this paper, we mainly discuss traditional Chinese medicine based on the polarization and autophagy activity of microglia after intracerebral hemorrhage. The dual role of anti-injury-promoting repair played by drug intervention aims to provide certain ideas for the clinical treatment of cerebral hemorrhage with traditional Chinese medicine.

1. TCM understanding of cerebral hemorrhage

Intracerebral hemorrhage is classified as "stroke" in traditional Chinese medicine. Earliest recorded in The Yellow Emperor's Internal Classic, "For those with yang qi, the anger will destroy the form and qi, and the blood will be poured on it, causing people are thin", "Blood and Qi, and walking on top, is a great Jue". "Medicine Chinese Refugees and Western Records [12] There are also records of two types of "stroke", cerebral congestion and cerebral anemia. Among them, "Western people call it cerebral hemorrhage" is cerebral congestion, and the etiology believes that "the liver and wood are out of harmony, the wind arises from the liver, and the lung qi declines, the kidney qi is not satisfied, and the stomach qi goes up again, so the qi of the viscera is If the chemical rises too much, and the blood is poured into the brain, it also causes the blood vessels to be congested and the nerves are involved." The understanding of stroke in modern Chinese medicine is based on "wind", "fire", "phlegm", "stasis", "poison", "Virtual" six ends are the main pathogenic factors. "Intracerebral hemorrhage TCM diagnosis and treatment guideline" South"[13] It is pointed out that the pathogenesis of stroke is the dysfunction of the viscera; the imbalance of yin and yang causes the qi and blood to be chaotic, and the brain is attacked. "fire certificate", "phlegm syndrome", "Yin deficiency syndrome", in which "wind "Certificate" is the triggering factor, "Blood stasis syndrome" runs through the beginning and "Fire end of evidence" the disease, in acute period is the most prominent. Treatment can start from opening the orifices to refresh the mind, clearing phlegm and eliminating wind, promoting blood circulation and removing blood stasis. Nie Yuting, etc [14]. From phlegm, blood stasis and toxin, the treatment principle of "common cause" in the treatment of cerebral hemorrhage is discussed, and it is believed that phlegm turbidity, blood stasis and poisonous evil are important pathogenic factors affecting the occurrence and development of cerebral hemorrhage. Obstruction of the collaterals and damage to the brain and marrow are important reasons for the aggravation of the disease. Dangtongyin can be used to remove phlegm, disperse blood stasis and detoxify.

2. Brain damage after intracerebral hemorrhage-Repair dual action mechanism

With the in-depth study of the pathological process of cerebral hemorrhage, its endogenous repair the recovery mechanism has gradually attracted attention. After intracerebral hemorrhage, on the one hand, the brain is affected by various pathological reactions produced by the blood spilled into the brain parenchyma; microglia polarized Activation and autophagy are the key mechanisms for the dual role of damage and repair in the brain after ICH.

2.1 The role of microglia in injury-repair mechanism after cerebral hemorrhage

As macrophages of the central nervous system, microglia are responsible for Homeostatic monitoring of the brain homeostasis. can differentiate into M1type, M2 two types of microglia.M1Microglia release pro-inflammatory factors or communicate with other cells, inducing an inflammatory cascade and causing brain damage. After intracerebral hemorrhage, microglia respond rapidly and persist for weeks. Detection of tissue around hematoma in rats with cerebral hemorrhageIL-1beta, IL-6, TNF wait for inflammatory factors after hemorrhage3The expression rises in hours and3Tianda peak [15]; CD16, CD32 and iNOS Wait M1Type markers were also found after intracerebral hemorrhage1,3day height expression [16]. M2Microglia mainly remove tissue debris through phagocytosis and release anti-inflammatory and neurotrophic factors to create a favorable environment for brain tissue repair. According to its detail Cell surface markers can be divided into three subtypesM2a, M2bandM2c, in M2 amainly involved in cell regeneration, M2bandM2cis involved in phagocytosis and removal of tissue debris [17]. after cerebral hemorrhage1day or so, microgliaM2type markerArg1, Ym1andCD206wait, the expression rises, but in3began to increase significantly after days [18], which is also consistent with the repair time after intracerebral hemorrhage. M2In addition to secreting anti-inflammatory factors, microglia IL-4, IL-10, TGF-beta Involved in suppressing inflammation [19], also induced by different mechanisms CD36 [20], CD47[twenty-one], CD163[twenty-two] Molecular activation involved in hematoma Clearing and phagocytosing tissue debris; not only relieved the inflammatory response in the acute phase to a certain extent, but also jointly created a favorable environment for the repair of damaged tissue after cerebral hemorrhage. aM1type, M2Different roles of type polarization at different stages after intracerebral hemorrhage enable targeted microglia inhibitionM1type, promote M2type or promoteM1patternM2type conversion has a certain potential significance. Transcription factor NF-κB, signaling and activating transcription proteins (Signal transducer and activator of transcription proteins, STAT), nuclear factor erythroid2Correlation factor (Nuclear factor erythroid 2-related factor 2, Nrf2) plays an important role in regulating microglial polarization. After cerebral hemorrhage, NF-κB secreted by microgliaTLR2andTLR4activation, and then further regulation M1typerelated inflammatory factor expression [twenty-three]. STAT The family is closely related to cell proliferation, immunity, apoptosis and inflammation, and each member plays a different role in microglial polarization. inSTAT1, STAT3in promoting microgliaM1play an important role in type polarization STAT6in promoting

microgliaM2important in type polarization [25]. Nrf 2It is a protective transcription factor, which helps to clear the hematoma after cerebral hemorrhage and plays a role in brain protection. The study found that this is related to its downstream molecules. HO-1closely related; the latter can also induce macrophage differentiation into M2 type [26]. Identifying the regulatory targets of microglia polarization provides a feasible way for exogenous intervention to change the direction of microglia polarization, and mediating the polarization phenotype of microglia is also the promotion of the body's self-esteem after intracerebral hemorrhage.

The important mechanism of repair lies.

Chang Wait [27] Study on microglia polarization after cerebral hemorrhage on the clearance of hematoma after cerebral hemorrhage1-1.5h, microglia responded rapidly to hemorrhagic injury with a "protective" activation phenotype; but over time, a large number of activated microglia and newly recruited monocytes showing early alternation Activates the phenotype and induces an inflammatory cascade. Further studies found hematoma clearance, improvement in neurological deficits, and microglia surface markers CD206up-regulation of expression is closely related, and the latter depends onIL-10regulation of intraventricular injection of activated cytokinesIL-10can accelerate the regression of the hematoma, andIL-10Receptor neutralization disrupts the phagocytic capacity of microglia. Zhao Wait [28]Study finds transcription factorNrf2Plays a major role in hematoma clearance, discovered using cultured microgliaNrf2 Activator induces antioxidant defense components, reduces superoxide formation, and upregulates phagocytosis-mediated scavenger receptors CD36and enhance erythrocyte phagocytosis; animal experiments also found thatNrf2The activator sulforaphane induces cerebral hemorrhage in miceCD36expresses and accelerates hematoma clearance,Nrf2Hematoma clearance was significantly impaired in knockout mice.

2.2 The role of autophagy in injury-repair mechanism after intracerebral hemorrhage

Autophagy is a way of reducing the homeostasis of eukaryotes Dissolution/recycling catabolic mechanisms, mediated by lysosomes, break down digested or dysfunctional organelles and cytoplasm to remove harmful proteins and recycle Ring reuse material. At present, autophagy is mainly divided into four types: micro autophagy, molecular chaperone-mediated autophagy, selective autophagy and macro autophagy. most researched It is macro autophagy, and its specific biological processes include: initiation, formation of autophagy precursors, formation of autophagosomes, fusion of autophagosomes with lysosomes/vacuoles, acid hydrolase degradation of autophagosome-encapsulated substances and degradation product release. just Under normal physiological conditions, cells mainly maintain metabolism and regulate internal environment homeostasis through autophagy, and the level is extremely low. When stimulated by stress, autophagy is further activated and plays a protective role by removing abnormal organelles or substances such as the cytoplasm. When autophagy is overactivated, it causes autophagic death [29-30].

The molecular mechanisms regulating autophagy are complex [31-33], mainly through autophagy-related genes (autophagy-related genes, Atg) mediate. The autophagy core machinery includesAtg1-Atg13-Atg17Complex, Vps34 Complex, Atg5-Atg12andAtg8-PE Two ubiquitin-like linkage systems, Atg2-Atg18andAtg9-Atg23-Atg27.Atg1-Atg13-Atg17 The complex mainly initiates the occurrence of autophagy, in whichAtg1is the core gene of the complex. Homologues of the latter in mammalian cells areULK1/ 2, under physiological conditions its activity is mTOR inhibit, and cannot be combined with AMPK combine. after stress TOR decreased activity, AMPK combine ULK1, activationULK1The complex initiates autophagy. on the other hand,ULK1/ 2activatableBeclin1to adjustPI3K Activity initiates autophagy.Vps34 complex including complex I and II two types, complex I Primarily initiates autophagy, complex II responsible for vesicular transport, and both can be AMPK Phosphorylation producesPI3Pactive.Atg5-Atg12andAtg8-PETwo ubiquitin-like junction systems are closely involved in the formation of phagocytic membranes, in mammalsAtg8The homologue of isLC3.Atg2-Atg18It further regulates the extension of the autophagic separation membrane.Atg9-Atg23-Atg27Plays a localization role in providing membrane components to autophagosomes. inLC3, Beclin-1is a commonly used indicator for the detection of autophagy.LC3is a marker of autophagosome membranes, LC3- I combinePEpost-formationLC3-IIIt promotes the formation of phagosome membranes and is expressed on mature autophagosomes, but is released after fusion with lysosomes and becomes a marker of autophagosomes. Beclin-1YesAtg6Homologues in mammals not only participate in the formation of autophagosome membranes, but also play an important role in regulating autophagic death.

After intracerebral hemorrhage, the surrounding tissue of the hematoma can be observed within the nerve cells Ultrastructure of autophagic vesicles formed [34], the detection also found autophagy-related genes Beclin1, LC3The expression level was significantly up-regulated [35], lysosomal markers cathepsin D obviously increase [36]; suggesting that the occurrence of cerebral hemorrhage induces the activation of autophagy. Further research found that thrombin after cerebral hemorrhage [37], iron overload[38]Can significantly up-regulate the excessive activation of autophagy, aggravate cell death and brain damage; inhibit thrombin or iron overload can reduce autophagy, which can significantly reduce cell death and brain damage;3-Methyladenine and rapamycin achieve the same effect directly on heme-treated neurons [39];surface The injury effect of autophagy after cerebral hemorrhage is closely related to autophagic death related. A recent study found that after cerebral hemorrhage6Autophagy is excessive in hours and participates in the formation of brain damage;7Autophagy levels are restored after days and may play a cerebral protective role by clearing the cellular garbage overproduced by early autophagy use [40]. It is suggested that autophagy plays a dual role in different stages after intracerebral hemorrhage. On the one hand, autophagy can clear cell debris and reduce hematoma, and on the other hand, excessive autophagy can lead to autophagic death of cells. How to be in moderation Decrease autophagy levels in acute phase and prolong autophagy time in recovery phase to reduce autophagic cell death and provide a favorable environment for tissue repair, the mechanism still needs further study.

3. The anti-injury effect of traditional Chinese medicine intervention-Repair-promoting dual action

3.1 Anti-injury-promoting effects of traditional Chinese medicine on microglia after cerebral hemorrhage

CaiWait [41]Using Shengdi Dahuang Decoction to interfere with collagenase induced cerebral hemorrhage in a rat model, it was found that Shengdi Dahuang Decoction could reduce the expression of microglia around the cerebral hemorrhage, thereby reducing inflammatory factors.NF-κB,TNF-alphaand IL-1betarelease and improve the inflammatory response.QiaoWait[42]The study found that Artemisia annua extract iszelanflavin can inhibit the migration of microglia and reduce the lysis-induced red blood cell lysis.BV2inflammatory cytokines in cells NF-κB production and intracellular reactive oxygen species levels. Lan Wait [16] Fibrocystin was found to reduce classically activated M1number of microglia, but did not affect theM2the number of microglia; M1relatedTNF-alpha, IL-1beta, IL-6, iNOSdown-regulation of inflammatory substances, andTLR4pathway inhibition. Shiet al studied the effect of sinomenine on cerebral hemorrhage model mice and found that sinomenine can promoteM2increased and decreased expression in

microgliaM1At the same time, it can protect hippocampal neurons from microglia-mediated toxic effects after intracerebral hemorrhage, reduce brain water content, improve neurological deficits, and protect brain function. Yang Shusheng et al [44] To study the therapeutic effects of Dachengqi decoction and emodin on cerebral hemorrhage in ratsNrf2/Src/MAPKs Pathway effects found after intracerebral hemorrhage3d, activated microglia around the hemorrhagic center regionM1typebased, and in7dlater M2predominant microglia. The treatment of Dachengqi decoction and emodin passedNrf2/Src Activation of the signaling pathway significantly changes the morphology and function of microglia:M1reduced microglia, MAPKs Inhibited, proinflammatory factorIL-1betaDown-regulation, reduced inflammatory response and brain damage; at the same timeM2increased microglia, anti-inflammatory factors Arg1, IL-10Up-regulated, microglia migration and phagocytosis are enhanced, hematoma expansion is restricted, and brain tissue is protected.

3.2 Anti-injury-pro-repair effect of traditional Chinese medicine on autophagy after cerebral hemorrhage

Liao Yuan sheng et al [45]Study on the relationship between autophagy and perihematoma tissue after intracerebral hemorrhage The relationship between rheumatoid arthritis and syndrome deprivation found that autophagy caused secondary damage after cerebral hemorrhage, and the number of autophagic vesicles, the number of autophagic vesicles, the cathepsin Dexpression and bleeding volume, NIHS score is positively correlated with GCS The scores were negatively correlated; and autophagy was more serious in de-identified cells than in closed-in syndrome. Qiu Zhifu, etc [46]. Study on Buyang Huanwu Decoction's effect on brain tissue of cerebral hemorrhage model ratsCXCR4-PI3Kautophagy signaling pathway andBeclin-1It was found that Buyang Huanwu Decoction can regulate the autophagy of hemorrhagic tissue cells in rats with cerebral hemorrhage, reduce the rate of apoptosis, and improve neurological function. The mechanism may be related to activation. PI3K/AKT signaling pathway, reducedBeclin-1associated with up-regulation of autophagic capacity; on the other hand, chemokine receptorsCXCR4with activatedPI3Kcan be combined to form CXCR4-PI3KAutophagy axis, affects autophagy activity and promotes neural repair and brain protection. Chen Rongrong, etc [47]. After brain hemorrhage in rats, study finds6 hours,12 hours,24 hours,72 hours Autophagy activation can be seen around the hematoma at each time point, and the activation law is manifested after cerebral hemorrhage.6 hours autophagy occurs,12-24 hours reach the peak,72 hours decline. After Naoxuetong intervention treatment, the time of autophagy activation did not change, but the overall activation range was reduced compared with the control group, and the neurological deficit score was significantly improved, suggesting that Naoxuetong could improve neurological deficits in rats with cerebral hemorrhage by inhibiting autophagy. Wu Chenghan et al [48] Study on the effect of Angong Niuhuang Pill on autophagy protein in peripheral nerve cells of hematoma in rats with cerebral hemorrhageLC3The effect of expression showed that the autophagy activity in the nerve cells around the hematoma was activated after intracerebral hemorrhage,4dAfter testing, it was found that there was no difference in the level of autophagy between the control group and the model group. After Angong Niuhuang Pill was added, the level of autophagy was up-regulated.4dThe detection was still different from the autophagy level of the model group. It shows that Angong Niuhuang Pill can Properly prolong the autophagy time to protect nerve cells.

Conclusion and Outlook

Primary injury and subsequent brain injury caused by hematoma after intracerebral hemorrhage In the study of cytotoxicity, excitotoxicity, oxidative stress response and inflammatory response induced by thrombin, blood components, inflammatory mediators and other mechanisms that cause blood-brain barrier damage, brain edema, neuronal apoptosis and other pathological damages , it is not only necessary to clarify the target mechanism of the injury and explore new drugs to intervene and treat, but also need to achieve a macro understanding of the immune regulation function of the body itself after the occurrence of the disease. from the discovery of microglia Cells play an inflammatory role after intracerebral hemorrhage to define microglial polarization Different types have different effects after intracerebral hemorrhage, from the discovery that autophagy promotes autophagic death and aggravates brain injury after intracerebral hemorrhage, to the recognition that autophagy plays a role in promoting injury or injury at different stages after intracerebral hemorrhage.

It has a dual effect of promoting repair; it suggests that there is a certain self-repair function in the brain after cerebral hemorrhage. And there is still a lot of room for these repair mechanisms to study, for example, the time demarcation point of different effects, if the damage can be inhibited and repaired at the appropriate time point The exertion of the function can make the repair of cerebral hemorrhage move forward in time as a whole, and reduce the damage as much as possible, which should provide greater help for the overall treatment of cerebral hemorrhage. History of Traditional Chinese Medicine in Treating Cerebral Hemorrhage

It has a long history, emphasizes the overall concept, and acts on diseases with multiple targets, multiple pathways, and multiple links, which can not only play a role in inhibiting damage, but also promote the development of the body's own immune function; this may also be the advantage of traditional Chinese medicine in treating diseases. However, the anti-injury-promoting mechanism of TCM intervention in cerebral hemorrhage still needs to be further studied to clarify the real way of TCM's therapeutic effect and the clinical treatment of cerebral hemorrhage. Blood diseases provide some ideas.

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