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Exploring the Pathway of Neuronal Apoptosis after Cerebral Ischemia and Intervention of Traditional Chinese Medicine

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Abstract: Due to the acceleration of the aging process of our country's population, and with the development of the economy, people have formed many bad eating and living habits, and the cerebrovascular disease has a younger trend, and the morbidity and mortality are increasing year by year. Therefore, further research on cerebrovascular diseases is one of the most important topics in medicine. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is produced by Escherichia coli implanted with human granulocyte-colony-stimulating factor (G-CSF) gene through recombinant DNA technology and has the same biological activity as natural G-CSF and amino acid sequence, is a protein consisting of 175 amino acids. After cerebral ischemia, neuron apoptosis is caused by a series of biochemical cascade reactions, resulting in dysfunction of corresponding areas of the brain and a series of ischemic symptoms. Therefore, it is particularly important to find effective drugs to inhibit the apoptosis of neurons after cerebral ischemia to improve the prognosis of ischemic stroke.

Keywords: Neuronal Apoptosis; Cerebral Ischemia; Traditional Chinese Medicine

1. INTRODUCTION

The death receptors on the cell surface are members of the tumor necrosis factor receptor (TNFR) superfamily. Mainly include Fas (CD95), TNFR-1, DR3 (death receptor 3), DR4(death receptor 4), DR5(death receptor 5). The most clearly studied is the Fas-Fas-L signaling pathway. Fas-L exists as a homotrimeric complex. Each Fas-L trimer can bind three Fas molecules, resulting in the DD (Death domain) in the cell of the three Fas molecules connected in series. The DD of tandem Fas can be combined with the DD of FADD (Fas-associated death domain).

And this combination leads to the combination of DED (Death effect domain) of FADD and DED similar region of Caspase-8 zymogen, which is a kind of CARD (Caspase recruitment domain), thereby activating Caspase-8, and Caspase-8 further activates the downstream Caspase eventually leads to cell apoptosis. my country's population aging process is accelerating. By 2030, the population over 60 years old in my country will exceed 300 million, and about 2/3 of the first onset of cerebrovascular diseases are elderly people over 60 years old.

Therefore, the incidence of cerebrovascular disease in my country will continue to rise, and the harm caused will become increasingly serious. With the development of my country's economy, in recent years, due to diet and living habits, the incidence of cerebrovascular diseases has become younger. Bad eating habits such as excessive salt, too much fat, and too little fiber in the diet, as well as bad living habits, such as driving a car, working at a desk for a long time, and lack of physical exercise, can easily lead to obesity and coronary atherosclerosis. Islam et al "Just in the model of incomplete ischemia caused by permanent ligation of one side of the carotid artery and transient ligation of the other side。 In the model of transient forebrain ischemia in gerbils, selection apoptosis occurs in delayed neuron death, and recent research reports further suggest that the mechanism of delayed neuron death is apoptosis. Therefore, apoptosis is also one of the important ways of cell death in cerebral ischemia, especially the mechanism of delayed neuron damage in vulnerable areas is likely to be apoptosis. The release of pro-apoptotic factors from mitochondria can be regulated by B-cell lymphoma-2 (Bcl-2) protein, Bcl-2 family proteins can be divided into two categories, one is the inhibitory cell the apoptotic ones mainly include Bcl-2, Bcl-xL, Bcl-w, and Mcl-1, etc. The other kind is the ones that promote apoptosis, mainly including Bax, Bak, Bcl-xs, Bad, Bik, Bid and so on. Bcl-2 protein can directly combine with the voltage-dependent ion channel (VDAC) to close; while Bax, etc. can accelerate the opening of VDAC and make CytC leak from VDAC. The protein expression of Bcl-2 is regulated by the P53 gene. It was found that there is a P53 negative response element at the 5′ end of bcl-2, and the combination of P53 can inhibit the transcription of the bcl-2 gene. Hematopoietic stem cells (HSCs) can self-renew and differentiate. In a specific microenvironment, HSCs can differentiate into neurons and glial cells.

In recent years, people have made great progress in identifying, isolating, and purifying HSCs and confirming their characteristics. It is generally believed that HSCs mainly exist in CD34+ cell populations, and both clinical and laboratory sorting of HSCs are based on CD34+ cells. The transformation of HSC often occurs in pathological conditions, migrating to the pathological site, becoming the precursor cells of pathologically damaged tissues, and can differentiate into terminal mature cells. Ginseng: the active ingredient ginsenoside №1 extracted from ginseng can improve learning and memory and treat senile diseases.

2. THE PROPOSED METHODOLOGY

2.1 Cerebral Ischemia and Apoptosis

Li Junking et al. 21 using Ho. echst33342 and PI double staining and agarose gel electrophoresis techniques, observed the effects of different concentrations of ginsenoside №l (0.1, 1, 10mnol/1) on the apoptosis of primary cultured rat cerebral

cortex neurons, found that the cells When cultured for 14 days, changing to serum-free medium (serum-free, n=6) could lead to apoptosis of neurons, and the number of apoptotic cells (%) on day 16 was 94.9±3.6, which was comparable to that cultured with serum Compared with the control group (2.2 4-0.9, n=6), there was a very significant difference (P<0.01), while the number of apoptotic cells in the experimental group containing Rgl (n=6) decreased. The concentration increased, and the number of apoptotic cells in the three groups were: 90.6±3.2, 56.7±2.1, 20.4±0.7, of which the lumol/ and 10umol/1 groups were the same as the serum-free group The difference was significant (P<0.05, P<0.01). The concentration of 10umolfl had the best effect, which could minimize the number of apoptotic cells.

It is suggested that ginsenoside Rgl can inhibit the apoptosis of rat cerebral cortex neurons caused by deserum removal, and the inhibitory effect is dose dependent.]Using the focal cerebral ischemia model in rats to observe the effect of Angelica sinensis on cerebral ischemic injury and the expression of Bcl-2 and box proteins. The results found that Angelica can inhibit the expression of Bax protein, but has no effect on Bcl-2 protein, suggesting that Angelica may reduce the occurrence of apoptosis in cerebral ischemic area by reducing the expression of Bax protein. At present, some scholars inject stem cells induced in vitro into the body to treat cerebral ischemia, but whether these cells can adapt to the microenvironment of the body after returning to the body, how safe is this method, and whether the culture failure and pollution will cause harm to the patient. The risks, as well as whether the cells stimulated by cytokines in vitro have the possibility of mutation, etc., have not been fully elucidated. Therefore, it has seriously affected the clinical application of this method.

It has been reported that subcutaneous injection of rhG-CSF mobilizes HSC self-transplantation, HSC differentiates in the microenvironment of cerebral ischemia, and is more likely to survive. The method is simple, safe, and non-invasive. There are also many problems such as the difficulty of HSC source, immune rejection and medical ethics faced by allogeneic HSC transplantation, and it is expected to become a new technology. The author used the method of middle cerebral artery occlusion (MCAO) to make a model of cerebral ischemia-reperfusion in rats. 30 minutes before ischemia and 30 minutes after reperfusion, 1.5ml of breviscapine injection was injected intraperitoneally (according to the active ingredient flavonoid glycosides 27mg/kg). TUNEL staining method was used to detect the number of apoptosis cells, and the effect of the drug on different phases of ischemia-reperfusion (before ischemia, 30rain, 6h, 24h, 4d after ischemia-reperfusion), each group (n: 6) The results showed that the number of TUNEL-positive cells in the ischemic center area was significantly reduced in the treatment group compared with the model group 30 minutes to 24 hours after ischemia-reperfusion.

2.2 Effects of Traditional Chinese Medicine on Neuronal Apoptosis after Cerebral Ischemia

The mouse neuroblastoma cell line N2a cultured in vitro was used to establish the ischemia-reperfusion model, and the effect of puerarin, the active ingredient of Pueraria lobata root, on the apoptosis of neurons after ischemia and the activity of Caspase-3 enzyme was studied. The results showed that, Puerarin can inhibit the apoptosis of nerve cells after ischemia and can inhibit the activity of Caspase-3 enzyme. Cao et al. used the acute global cerebral ischemia-reperfusion model in rats to explore the effect of puerarin on the apoptosis of nerve cells and the expression of Bcl-2 and Bax proteins. The results showed that puerarin may up-regulate Bcl-2 and down-regulate Bax Protein expression to inhibit apoptosis of neuronal cells after ischemia.

Yang et al. used a similar method to observe that puerarin can inhibit the expression of P53 and Fas protein to play the role of anti-ischemic nerve cell apoptosis. When calcium ions in the cytoplasm increase, calpain is activated to play its role:

(1) Excessive degradation of cytoskeleton and structural proteins: it can participate in the degradation of many important cellular proteins such as proto-oncogenes, corticosteroid receptors, protein kinases, and microtubules Cytoskeletal proteins such as protein and microtubule-associated protein 2 (MAP2) and other cytoskeletal proteins.

(2) Lysosomal membrane disruption: after transient ischemia in primates, Calpain is activated in neurons in the CAI region of the hippocampus, resulting in lysosomal membrane disruption After ischemia-reperfusion, the activity of cathepsin, a lysosomal protease in neurons and nerve fiber reticulum in the hippocampal CAI area, increased.

(3) Mitochondrial damage: some studies have found that ischemic neurons damage can damage the mitochondrial membrane, causing the release of cytochrome C, the inhibition of mitochondrial oxidative phosphorylation, the disappearance of the coupling effect, and the obstacle of ATP production. At the same time, calpain causes the mitochondrial permeability transition pore to open, making the molecules and ions in the mitochondria released into the cytoplasm, resulting in increased permeability of L-type calcium channels and further damage to neurons. In vitro experiments showed that calpain inhibitor I can enhance neurons' resistance to cytotoxicity caused by sodium cyanide and increase protein content.

Cbz-Val-Phe-H is a kind of peptide Calpain inhibitor with better specificity, which can pass through the cell membrane and has the same effect when administered intravenously. In rats with focal cerebral ischemia, treatment with Calpain inhibitor (CGS 19755) resulted in a significantly smaller infarct area compared with the control group. To observe the therapeutic effect of Calpain inhibitors on cerebral ischemia more directly, the Calpain inhibitor AK275 was directly infused into the ischemic cortex of rats by cortical perfusion method. It was found that the administration began 3 hours after ischemia and continued for 21 hours. h, the infarct volume of the treatment group was reduced by 75% compared with the control group, and its curative effect increased with the increase of the dose. Using the middle cerebral artery ischemia-reperfusion model in rats, the effect of compound salvia militarize on the hippocampus and hippocampus after cerebral ischemia-reperfusion in rats was investigated. Apoptosis of dentate gyrus nerve cells and the effect of Bcl-2 mRNA expression. The results showed that the expression of Bcl-2 mRNA in nerve cells in the compound Danshen group was significantly stronger than that in the ischemia-reperfusion group, and the number of apoptotic nerve cells was significantly lower. It is suggested that compound Danshen can increase the expression of Bcl-2 mRNA in nerve cells, inhibit the apoptosis of nerve cells, and reduce the injury of hippocampus and dentate gyrus of rats after ischemia-reperfusion.

3. CONCLUSION

At present, research on traditional Chinese medicines that have the effect of inhibiting neuronal cell apoptosis after cerebral ischemia, whether single or compound, are mainly focused on promoting blood circulation and removing blood stasis, followed by tonic medicines. And the research still has the following problems. First, the level of research is not deep enough, and the quality needs to be improved. The main reason is that there are many observations of general drug effects, and relatively few in-depth discussions on the mechanism of action of traditional Chinese medicines. Second, the indicators for research and detection are single, and most of them focus on one point in the pathway, and there are few studies on the entire pathway. There have been studies on traditional Chinese medicine monomers and their active ingredients, but there is no research report on traditional Chinese medicine compound prescriptions formulated according to the theory of traditional Chinese medicine. It is of great significance to intensify the research on traditional Chinese medicine on nerve cell apoptosis caused by ischemic injury.

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