Pathophysiology of Acute Cerebral Hemorrhage Injury

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Abstract: The purpose of this paper is to explore the pathophysiological theory of acute cerebral hemorrhage. First of all, the early pathophysiological changes of hemorrhage, the further study of primary injury and secondary injury in the acute stage of cerebral hemorrhage were analyzed. The adult male SD rats were divided into four groups to establish cerebral hemorrhage model. The experimental results showed that the level of LC3 and Beclin. 1 protein in the right basal ganglia was not affected by hyperglycemia without ICH. Compared with the control group, the ratio of LC3-II / lc3-i and the level of Beclin. 1 protein in the brain tissue around hematoma increased 24 hours after ICH (20.13 ± 2.44% vs.0.56 ± 0.48%, $P < 0.01$; 107.69 ± 12.80% vs.65.42 ± 21.84%, $P < 0.01$). Compared with the group with normal blood glucose, acute hyperglycemia could reduce the LC3-II / lc3-i ratio and Beclin. 1 protein level (0.57 ± 0.48% vs.20.13 ± 2.44%, $P < 0.01$; 43.49 ± 13.88% vs.107.69 ± 12.80%, $P < 0.05$). After intracerebral hemorrhage, there were obvious neurological deficit symptoms and brain edema, and the autophagy level of the tissue around the hematoma increased.

1. Introduction

The pathophysiological mechanism of intracerebral hemorrhage has been a common concern. New progress in hematoma formation, ischemic penumbra, brain edema and secondary hyperfibrinolysis provide new clues for future research. The intervention treatment can be carried out according to the above links to improve the prognosis and quality of life of patients with cerebral hemorrhage. Cerebral hemorrhage accounts for 12-15% of all kinds of stroke, but its mortality is the highest. Different from ischemic cerebrovascular disease, there is no breakthrough in the treatment of cerebral hemorrhage, which may be related to the lack of understanding of its pathophysiological mechanism. At present, the mechanism of the occurrence and development of acute cerebral hemorrhage has not been fully elucidated, but a series of pathophysiological changes after cerebral hemorrhage can lead to the rise of intracranial pressure, which is life-threatening. At the same time, because neurons are compressed by hematoma, hematoma and its metabolites and other neurotoxic effects lead to brain tissue damage, a series of nerve function loss, so in the shortest time to reduce, the key to the treatment of acute cerebral hemorrhage is to prevent the occurrence. Brain hernia can increase perfusion pressure, reduce toxicity and brain edema, and reduce secondary brain injury to the lowest level. To study the pathological mechanism of acute cerebral hemorrhage, especially the mechanism of hematoma expansion in the early stage, can provide scientific guidance for the treatment plan of patients with acute cerebral hemorrhage, and provide scientific guidance for the treatment plan of patients with acute cerebral hemorrhage, and make a certain contribution to reduce the mortality and disability rate of patients with acute cerebral hemorrhage.

To explore the protective mechanism of lingxie Capsule on secondary nerve injury in rats with cerebral hemorrhage. The content of SOD and MDA in brain tissue was determined by fluorescence method, and the content of EAA in hippocampus was determined by HPLC. Results: lingxie capsule can reduce the concentration of injured nerve cells (Ca2 +, increase the activity of SOD and decrease the production of MDA in brain tissue. Conclusion: lingxie capsule has a certain therapeutic effect on cerebral hemorrhage in rats. Conclusion: lingxie capsule has a certain

therapeutic effect on cerebral hemorrhage in rats [11]. Prakash J demonstrated that free radical scavenger can inhibit heparin induced cerebral hemorrhage, and the combination of heparin and free radical scavenger can reduce infarct area and improve neurological symptoms. Our observation indicates that the combination of thrombolytic or antithrombotic drugs and free radical scavengers is significant for the treatment of human acute stroke [12].

The pathological mechanism of brain injury in the acute stage of cerebral hemorrhage is complex. There are many factors and links involved in it. The animal model of cerebral hemorrhage was established by injecting femoral artery blood into the right caudate nucleus. 30 minutes before the injection, 50% glucose solution (6ml / kg) was injected intraperitoneally to establish the model of acute cerebral hemorrhage in rats. To study the pathophysiological theory of acute cerebral hemorrhage. The levels of LC3 and beclin-1 in the cells around the hematoma were measured to explore the changes of autophagy after cerebral hemorrhage and the effect of acute hyperglycemia on autophagy after cerebral hemorrhage.

2. Proposed Method

2.1 Early Pathophysiological Changes of Cerebral Hemorrhage

(1) Amyloid deposits may block ruptured blood vessels

About 10% of patients with lobar hemorrhage have amyloidosis. For a long time, cerebral amyloidosis has been considered as one of the important causes of lobar hemorrhage in the elderly. It is generally believed that the deposition of amyloid in cerebral vessels can lead to vascular smooth muscle cell defect and vascular wall damage.

(2) Change of swelling volume

In recent years, the focus of research has shifted to hematoma enlargement, which is considered to be one of the important reasons for the early deterioration of neurological function. In the past, intracerebral hemorrhage was considered to be a monophasic event. Within a few minutes after the start of hemorrhage, the bleeding could be stopped due to coagulation and the filling of surrounding brain tissue. Thus, the cause of nerve injury was attributed to brain edema. In recent years, CT observation has found that the hematoma continues to expand after intracerebral hemorrhage.

(3) Ischemic penumbra

Because there is no effective treatment, neurologists are still in an awkward position when dealing with cerebral hemorrhage. The decrease of blood flow perfusion should be the result of the decrease of metabolism and the lower demand of metabolism in brain tissue around hematoma, not the cause of nerve injury.

2.2 Pathophysiological Changes in Middle and Late Stage after Hemorrhage

(1) Brain edema

The formation of brain edema after cerebral hemorrhage involves a series of mechanisms. Over time, the formation of edema has experienced at least three stages (7I): the formation of super early stage (within hours after the onset) is due to hydrostatic pressure and the contraction of blood clots; the second stage (within 2D) involves the coagulation cascade reaction and the role of thrombin; the third stage (3D) is due to the dissolution of red blood cells and the release of hemoglobin.

(2) Thrombin and brain edema

Thrombin not only plays an important role in coagulation, but also aggravates edema and nerve cell damage. Thrombin is one of the main substances causing brain edema. However, low dose thrombin has neuroprotective effect.

(3) Fibrinolysis system

Compared with thrombin, the study of signal transduction and related factors is still in its infancy. The process of fibrinolysis is helpful to remove clots, but it also has many toxic effects on normal brain tissue, including edema. The process of fibrinolysis includes the transformation from plasminogen to plasmin, and the involvement of tissue plasminogen activator (TPA). After the formation of plasmin, fibrin can be further hydrolyzed, at this time, fibrin degradation products and

D. dimer are produced. Plasmin can be neutralized with an anti plasmin and lose its potency. TPA is regulated by its inhibitor P Yue.

2.3 Primary and Secondary Injury in Acute Stage of Cerebral Hemorrhage

(1) Calcium influx

Calcium is an important second messenger substance in cells, which plays a certain role in maintaining the balance of water and electrolyte. The "last channel" of degeneration and necrosis of nerve cells is abnormal calcium signal transduction. After cerebral hemorrhage, the cells are squeezed and deformed.

(2) Thrombin production

It can induce the increase of vascular endothelial growth factor, destroy the blood-brain barrier and lead to brain edema. Thrombin can induce inflammatory cell infiltration, mesenchymal cell proliferation, angiogenesis, reactive astrocytosis, up regulate and activate protease activated receptor 1. In addition, thrombin is also a "double-edged sword", which has protective effect on hemorrhagic stroke at low concentration and is harmful at high concentration.

3. Experiments

3.1 Materials and Methods

(1) Laboratory animal

Adult male SD rats weighing 275-3259 (provided by the experimental animal center of the Academy of Medical Sciences, grade II cleaning, Certificate No. scxk). 0001 is selected. Free food and water, 12 hours of light, alternating light and dark.

(2) Main instruments

Body locator: World precision instruments

Micropump: World precision instruments

Skull drill: strone-90

PH meter: Beckman company

(3) Main experimental reagents and materials

Chloral hydrate powder, POM powder, anti desquamation slide

3.2 Animal Grouping and Cerebral Hemorrhage Model

(1) Grouping of experimental animals

The rats were divided into the following four groups: normal control group (Group C), hyperglycemia group (group G), cerebral hemorrhage group (group I), cerebral hemorrhage group with acute hyperglycemia (Ig group).

Group I: the model of cerebral hemorrhage in rats.

IG group: rats were injected with 50% glucose (6ml / kg) intraperitoneally 30 minutes before the injection of $100\mu1$ into the right basal ganglia of the brain. The other steps were the same as group I.

Group C: except for the right basal ganglia of rats injected with normal saline $100\mu1$ to replace the autogenous blood, the other steps were compared with group I.

Group G: except for the right basal ganglia of rats injected with normal saline $100\mu1$ instead of auto blood, the other steps were compared with group IG.

(2) Cerebral hemorrhage model

The rat model of cerebral hemorrhage was established by slow injection of non heparinized arterial blood into the right basal ganglia. After weighing, rats were anesthetized intraperitoneally with 10% chloral hydrate at 400mg / kg to separate the right femoral artery and intubate: rats were fixed on the operating table on their back, the right groin area was exposed to the femoral artery and separated, the anterior fontanelle was fully exposed and positioned, 0.2mm in front of the anterior fontanelle, and 3.5mm in the right side was opened to drill through the skull with a micro cranial drill (the tip diameter of the drill bit is LMM). After 300 μ l blood was collected through femoral

artery catheterization, $10\mu1$ was injected into the right caudate nucleus of rats with a micro pump at the rate of $100\mu1$ / min, and needles were kept for 10 minutes to prevent blood backflow. The head skin of rats was sutured after needle withdrawal. The temperature of the constant temperature pad was maintained at 37 ℃, rats were fasted overnight before operation, and blood glucose was monitored before, during and after operation.

4. Discussion

4.1 Symptom Score of Neurological Deficit after Cerebral Hemorrhage

In this experiment, rats were fasted overnight before operation. After fasting blood glucose was measured, blood glucose continued to be monitored during operation and after operation. It was found that the blood glucose of rats with intracerebral hemorrhage had little fluctuation during operation and 24 hours after operation, and it was always within the normal range. The acute hyperglycemia model induced by single intraperitoneal injection of hyperglycemic solution had no theory of ICH, and the blood glucose fluctuation was similar. It can be seen that the blood glucose increased significantly after 0.5 hours, even if no hypoglycemic treatment was carried out, the blood glucose after 24 hours All returned to normal. This also shows that a single intraperitoneal injection of high glucose solution only causes transient high glucose similar to acute stress response, so the cerebral hemorrhage model with acute hyperglycemia established in this experiment can observe the effect of acute stress high glucose on ICH.

Before operation, there was no significant difference in neurological deficit symptom score. After 24 hours of cerebral hemorrhage, there were obvious neurological deficit symptoms. The scores of rotation angle test and forelimb movement asymmetry test were all increased (92 ± 11.35% vs. 51 ± 7.38%, $P < 0.01$; 33.54 - 7.84% vs. - 0.5 ± 7.98%, $P < 0.01$). After 24 hours of cerebral hemorrhage with or without acute hyperglycemia, the angle test scores were all close to 100% (92 ± 11.35 vs. 96 ± 9.66, $P > 0.05$). Compared with the cerebral hemorrhage group with normal blood glucose, acute hyperglycemia significantly increased the score of forelimb movement asymmetry test (33.5 ± 7.84 vs. 53.5 ± 11.07, P < O.05) 24 hours after cerebral hemorrhage, as shown in Figure 1.

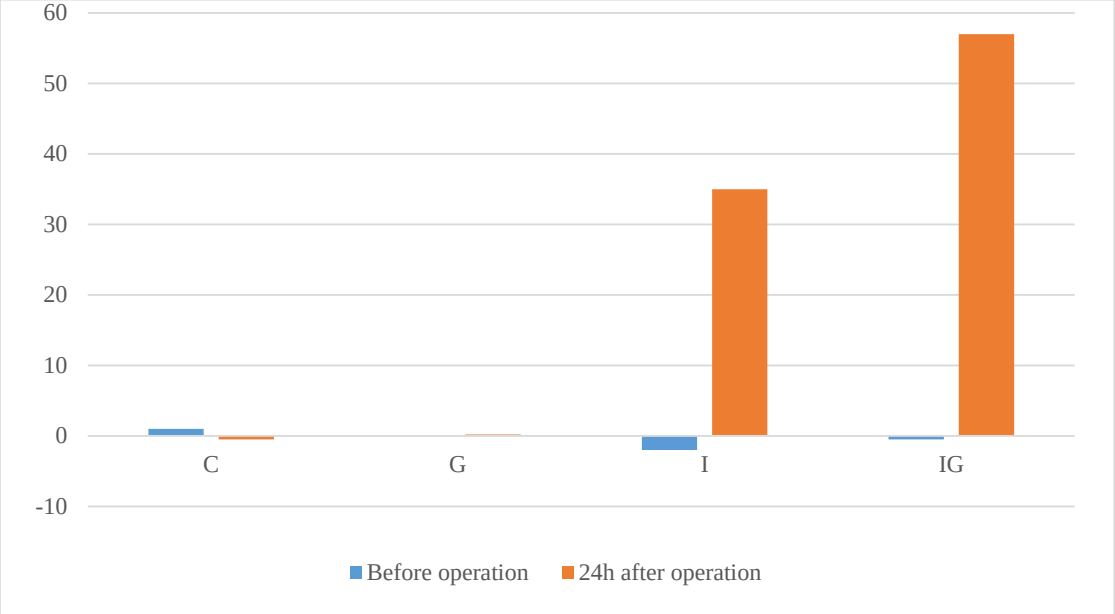

Figure 1. Test score

Without ICH, hyperglycemia alone did not affect the water content of the right basal ganglia (78.34 ± 0.51% vs.78.28 ± 0.49%, $P > 0.05$). There was obvious brain edema 24 hours after cerebral hemorrhage (79.66 ± 0.52% vs.78.34 ± 0.51%, $P < 0.05$). Compared with cerebral hemorrhage group with normal blood glucose, acute hyperglycemia aggravated cerebral edema after

cerebral hemorrhage (79.66 ± 0.52% vs.80.80 ± 0.97%, P < 0.01).

4.2 Brain Histopathology

Hyperglycemia without ICH did not cause the changes of LC3 and Beclin. 1 in the right basal ganglia of rats. After 24 hours of intracerebral hemorrhage, many positive cells of LC3 and Beclin. 1 with brown cytoplasm were found around the hematoma, and the staining was deeper than that of the normal control group; acute hyperglycemia made the staining of LC3 and Beclin. 1 positive cells around the hematoma shallower after intracerebral hemorrhage.

Without ICH, hyperglycemia alone did not affect the levels of LC3 and Beclin. 1 in the right basal ganglia. Compared with the control group, the ratio of LC3-II / lc3-i and the level of Beclin. 1 protein in the brain tissue around hematoma increased 24 hours after ICH (20.13 ± 2.44% vs.0.56 ± 0.48%, P < 0.01; 107.69 ± 12.80% vs.65.42 ± 21.84%, P < 0.01). Compared with the cerebral hemorrhage group with normal blood glucose, acute hyperglycemia can reduce the LC3-II / lc3-i ratio and Beclin. 1 protein level (0.57 ± 0.48% vs. 20.13 ± 2.44%, P < 0.01; 43.49 ± 13.88% vs. 107.69 ± 12.80%, P < 0.05) in the brain tissue around the hematoma as shown in Table 1.

Table 1. Acute hyperglycemia can reduce the LC3-II / lc3-i ratio and Beclin. 1 protein level in brain tissue around hematoma

	C	G	I	IG
Ratio	0.57±0.48%	20.13 ± 2.44%	43.49 ± 13.88%	107.69 ± 12.80%

The state of acute hyperglycemia before ischemia can aggravate the nerve injury after cerebral ischemia, and it is probably because acute hyperglycemia can aggravate the damage of blood-brain barrier after cerebral ischemia. Although there is no clear study on the effect and mechanism of acute hyperglycemia on BBB after ICH, the results of this experiment show that acute hyperglycemia can aggravate nerve injury after cerebral hemorrhage, indicating that hyperglycemia should be paid attention to in the process of diagnosis and treatment of cerebral hemorrhage, and hyperglycemia dehydration treatment of brain edema should also be cautious.

5. Conclusions

ICH is a kind of cerebrovascular disease with high morbidity and mortality. In recent years, it was found that some ICH patients had hyperglycemia when they were admitted to hospital, which indicated poor prognosis. Adult male SD rats were divided into four groups to establish cerebral hemorrhage model and study the pathophysiological theory of acute cerebral hemorrhage injury. The results showed that there were obvious neurological deficit symptoms and brain edema after cerebral hemorrhage, and the autophagy level of the tissue around the hematoma increased. Sexual hyperglycemia can reduce autophagy level of cells around hematoma by adding symptoms of neurological deficit and brain edema after major cerebral hemorrhage.

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