Research Progress on the Injury Mechanism and the Protective Effect of Blood-Brain Barrier

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Abstract: The Blood-Brain Barrier (BBB) is important structure to maintaining the stabilization of central nervous system. It is composed of endothelial cell and tight junction, the basal lamina, astrocytic endfeet. BBB's injuries is a important symbol when central nervous system generate lesion in cerebral ischemical reperfusion injury (CIRI), its' the injury mechanism including that matrix metalloproteinases' activity raise induce that basal lamina and extracellular matrix degradation, the augmentation of Aquaporin-4's expression cause vasogenic edema, destruction of tight junction and decrease of related protein expression lead to raise of BBB permeability, the adhesion molecules and cytokines stimulate the inflammatory reaction, a lot of free radicals production and nitric oxide toxicity can pose the damage of endothelial cells and basal lamina. BBB's protection mainly by reducing the change of BBB's morphological structure; decreasing BBB's permeability; reducing the harmful substances go into BBB; maintaining stabilize of central nervous system's internal environment. Now the mechanism was constantly expounded that BBB's injury, adjustment and repair, more and more medicines will be applied to the prevention and treatment of the BBB. In this paper, we will review about research progress on the injury mechanism of BBB and the protective effect of it.

Keywords: Matrix metalloproteinases, Aquaporin, Tight junction, Adhesion molecules, Cytokines.

1. INTRODUCTION

The Blood-Brain Barrier (BBB) was first discovered by German bacteriologist Paul Ehrlich. Its structure mainly including [1-5]: (1) no fenestrated endothelial cell and tight junction within its; (2) The basal lamina that connected to endothelial cell and enzymatic barrier that make up with nucleotidase and non-specific choline esterase; (3) The gelatinous membrane that structure by astrocytic endfeet to surrounding blood vessels under basal lamina. BBB has strict screening effect in the aspect of material exchange between blood and brain tissue fluid. On the one hand, the nutrients in blood can through BBB; on the other hand, BBB can also selectively that harmful matter would be pump out of the brain [6]. So that BBB can play the important role of maintaining the stabilization of central nervous system.

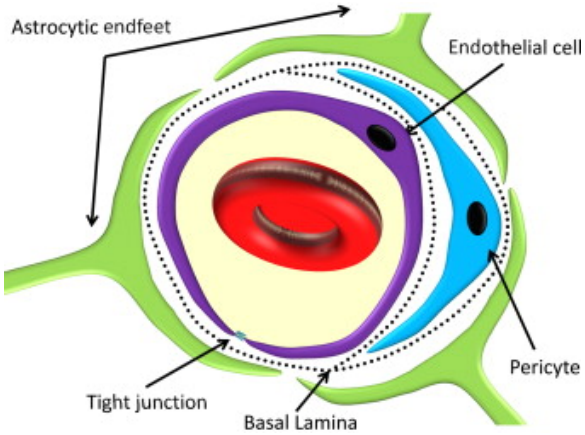

Figure 1: The structure of blood-brain barrier.

BBB's injuries is a important symbol when central nervous system generate lesion in cerebral ischemical reperfusion injury (CIRI). Its result is that endothelial cell and basal lamina were damaged. BBB's permeability is incremental. Barrier function was destruction. Various medias are take participate in the damage of BBB structure and function such as matrix metalloproteinases, Aquaporin, inflammatory factor et. In the structure, these medias have an impact on endothelial cell, astrocytic end feet and basal lamina [7,8]. In the function, these medias raise BBB's

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permeability [9]. So it is important significance for the treatment and prognosis of ischemic cerebrovascular disease that we can effectively control the damage of BBB pathophysiological process by that reduce the damage of BBB during the process of CIRI.

2. THE MECHAMISM OF THAT CIRI CAUSE BBB DAMAGE AND THE RESEARCH OF BBB'S PROTECTION IN THE PRESENT

BBB's protection mainly by reducing the change of BBB's morphological structure; decreasing BBB's permeability; reducing the harmful substances go into BBB; maintaining stabilize of central nervous system's internal environment. At present, a large number of participants can improve BBB's permeability; reduce cerebral edema,and increase local volume of blood flow to the brain in the cell and animal models. But all the BBB'protectants was not used for clinic only at the experimental stage. So as mechanisms were constantly expounded that BBB's injury, adjustment, repair. The research of BBB's protectant proceed mainly from the following several aspects.

2.1 Matrix Metallopreteinases' Activity Raise Induce that Basal Lamina and Extracellular Matrix Degradation

Matrix metalloproteinases (MMPs) is a set of proteolytic enzyme of depending zinc. It can almost degrade all Extracellular Matrix (ECM). It also is the most important of the ECM degradation enzymes *in vivo*. CIRI can strengthen the expression of MMPs.The MMPs antibodies or MMPs inhibitor can improve CIRI injury, reduce vasogenic edema, and protect nerve cells from damage [10]. So reasonable regulate MMPs is expected to become an effective method for the prevention and treatment of BBB injury and the formation of vasogenic edema. Looking for MMPs inhibitor is becoming a hot spot of current research.

Plasminogen activator (tPA) combine broad spectrum MMPs inhibitor application.

tPA is the only thrombolytic drugs by the FDA approved. Dut tPA suitable for a small number of patients because of its clinical treatment time window is too short. And after thrombolysis, there will be CIRI injury. So if it is great significance for CIRI's treatment and prognosis that drugs cure CIRI injury when tPA proceed the treatment of thrombolysis in acute cerebral stroke[11].

Mishiroconducted research on cerebral ischemia mice model by combining use of tPA and GM6001 (a kind of new broad spectrum MMPs inhibitor). The result showed that combination therapy may reduce the mortality rate of mice after application tPA7dthrough protecting tight junction (TJ) protein [12]. And research of the tPA and BB-94 (broad spectrum gelatin inhibitor) combination therapy find that BB-94 can protect BBB by inhibiting MMP-2,3,9 [13].

Lischperand his group [14] proof that SB-3CT of selective MMP-2\3's inhibitors can retard cerebral ischemia injury through adjust the degradation and redistribution of closed protein in the early. Chlorogenic acid [15] can inhibit the expression and activity of MMP-2 and MMP-9 after CIRI; Astragalus glycosides 4 [16] and lipoxinA4 [17] can inhibit the expression of MMP-9 after CIRI, relieve cerebral edema degree; Monosialotetrahexosyl Ganglioside can decrease the serum level of MMP-2 and MMP-9, and inhibit the degradation of extracellular matrix degradation [18]. Epigallocatechin 3 gallate (EGCG) [19], Butylphthalide [20], Progesterone [21] and Melatonin [22] can protect the integrity of the BBB through adjusting TIMP-1 (MMPs inhibitor) to inhibit the expression of MMP-9.

2.2. The Augmentation of AQP4's Expression Cause Vasogenic Edema

Aquaporin (AQP) is a set of membrane channel proteins found in nearly 10 years. It is a kind of membrane that control water's bilateral transmembrane transport *in vivo*. It can mediate hydrone transmembrane transport, adjust the permeability of BBB to hydrone, kalium ion and the size of nerve cells' diastema. AQP4 is the most widely aquaporin in the central nervous system. It take part in the opening of BBB and the formation of brain edema [23]. It also is an important molecular basis of brain edema occurred.

During the CIRI, AQP4 expression level increased, and its level of expression is closely related to the BBB integrity. AQP4 expression raised for seven days, its express peak appears in the third day after CIRI 48h. The expression quantity in around ischemia area is higher than the central area. The progress is almost same in time with the occurrence and fade of cerebral edema [24]. AQP4 gene intervention can affect the morphology and function of the BBB in the CIRI model rats [25]. The high expression of AQP4 in around ischemia area plays an important role in the process of the development of brain edema.

AQP4 is important molecular basis of brain edema's generation because increase of AQP4 is involved in the

opening of BBB and the formation of brain edema. Brain edema is a common and significant squeal of ischemic cerebrovascular disease and it can increase nerve dysfunction. Because AQP4 has play a vital part in the formation and development of brain edema, so looking for drugs that regulation of AQP4 expression will likely become the new way for treatment of ischemic cerebrovascular disease [26].

Calcitonin gene-related Peptide (CGRP) is by far the strangest encephalic micrangium expander. Studies have shown that it can protect CIRI injury through promoting the expression of inhibits AQP4. Picroside II [27], Physcion [28], Curcumin [29], Bilobalide B [30], etc can decrease the degree of brain edema through different ways to regulate the expression of AQP4 and improve the permeability of BBB.

2.3. Destruction of Tight Junction and Decrease of Related Protein Expression Lead to Raise of BBB Permeability

BBB is endothelial cell membrane what coverd in the surface of 99% encephalic capillary lumen. Tight junction (TJ) is central part of adjusting BBB permeability and important factor of maintaining BBB interity between the brain microvascular endothelial cells [31,32]. TJ is a complexes form by a variety of transmembrane protein (including double strands proteins: claudin, occludin) associated with the membrane protein (ZO-1, ZO-2, and JAM). A variety of endogenous and exogenous signaling pathways adjust BBB permeabiity by these protein [33]. TJ protein expression quantity change, the change of location distribution and structural function abnormalities may destroy the integrity of TJ, cause the opening of connection between cells, lead to change in BBB permeability. And now studies have been confirmed [34], BBB permeability increase mechanism is that largely due to the synthetic and expressed diminution of TJ's related protein example ZO-1, occludin, claudin-5 and destroyed the TJ structure, which result in the increase of BBB permeability. CIRI decrease TJ protein expression and redistribution, thus destroying the BBB. BBB's function changes associated with TJ's opening or closing, and TJ's opening or closing associated with related protein expression. It will cause BBB's functional change that the transcription or expression of TJ's protein change and structural rearrangement. The studies of TJ's related protein expression changes after CIRI will provide new ideas for clinical prevention and treatment of brain injury. The relationship between BBB and TJ's protein also prompt that treatment resulted from abnormal BBB disease can influence from the corresponding protein.

Dexamethasone [35] belongs to glucocorticoid hormones, can protect basal lamina integrity, and maintain the expression of TJ proteins, which play an important role in vessel wall integrity. Hydroxysafflor yellow A can improve the claudin-5 expression and reduce BBB's permeability [36]. Pinocembrin [37] what is one of the most abundant flavonoids in the propolis can improve model rats' neurological scoring induced by GCI/R, reduce brain edema, reduce the content of Evans blue and NAF in the brain tissue. Thereby it can reduce BBB damage. CG is a compound that clinically used for ischemic stroke. Studies have found [38] that after CIRI its can reduce TJ related protein (claudin-5, JAM-1, occludin) degradation. Thus it can reduce BBB permeability and brain edema.

2.4. The Adhesion Molecules and Cytokines Stimulate the Inflammatory Reaction

Inflammatory cascade reaction throughout the whole process of cerebral ischemia injury. In the process of CIRI, the inflammatory mechanisms of BBB's damage is complex involved in the interaction of a lot of factors and links. Cytokines' increase and adhesion molecule's expression can lead to leucocyte by the migration of endothelial cells and BBB. So leucocyte recruitment can trigger signal transduction cascade, leading to TJ division and BBB damage [39,40].

Adhesion molecules (AMs) is a kind of glycoprotein in sueface of the membrane mediated between cells and cells, cells and extracellular matrix adhesion. Intercellular adhesion molecule (ICAM) of BBB endothelial cell expression plays an important role in the process of CIRI [39]. Such as cell adhesion molecule (ICAM-1, L-selectin, P-selectin) can cause cytoskeleton rearranged and intercellular space increases by mediating the adhesion of leukocytes and generating signals inside the cell. So as AMs is participate in the process of BBB damage.

Cytokines that glial cells and vascular endothelial cells secrete tumor necrosis factor (TNF-α), interleukin (IL-α) etc after CIRI is an important mediator that triggering inflammation and immune response. It involved in BBB damage process.

In the process of CIRI, the expression of inflammatory and adhesion molecules cause the

change of BBB permeability by the ischemic damage to the inflammatory damage. Therefore, research about inflammatory factor of BBB damage mechanism will help to expound CIRI injury mechanism, and help to guide the clinical application of targeted treatment measures.

Sodium channel blockers and antioxidants (AM-36) [41] can reduce the damage of BBB and adjust the neutrophilic inflammation by lowering the proportion positive ED-1 macrophages and positive PMN neutrophils, as well as reducing the encephalic parenchymal neutrophils accumulate. Tetramethylpyrazine can intervene rats' ischemic stroke. It can reduce the number of immune cells to inhibit inflammation [42]. Celastrol can protect nerve cells by antiinflammatory action in the CIRI [43]. Angiopoietin-1 (Ang1) can reduce cerebral vascular inflammation [44]. Marijuana CB2 [45], Rolipram (phosphodiesterase-4 inhibitor) [46], Salidroside [47] can protect BBB by inhibit the expression of cytokines and adhesion molecules.

2.5. A lot of Free Radicals Production and NO Toxicity can Pose the Damage of Endothelial Cells and Basal Lamina

Free radical chain reaction is one of the important cause leading to the BBB permeability increase [48]. Cerebral ischemia will cause mitochondrial damage. Mitochondrion will create a large number of free radicals and free fatty acids what they can oxide membranes and basilar membrane because it cannot provide enough electrons to achieve reduction. Free radicals and free fatty acids can cause vascular endothelial cells and undermine the integrity of the BBB [49]. No is the important molecule of messenger and effector with functions of neurotransmitters and qualitative in organism.it can broadly participate in physiological and pathological actions. NO can possible educe the dual role of damage or protection according to the difference of ischemia and reperfusion period, NO cell types, NO process conditions in the process of CIRI. NOS is capital NO's synthetase. It can be classified as neurons (nNOS), induce (iNOS), endothelial (eNOS). NOS is mainly eNOS in endothelial cells, through it produces NO can expand cerebrovascular and increase cerebral blood flow to protect brain. NOS is mainly nNOS in nerve cells, through it produces NO can produce nerve poison. And NO can also be produced by iNOS aggravate ischemic brain damage [50].

With the deepening of scientific research, the role of resistance to oxidative stress (OS) in CIRI has wide attention by people. Now there are a lot of resistance to OS protectant exists, but the brain protective agent is still a lack of clinical curative effect and widely agreed. So it is necessary that looking for new resistance to OS protectant what the curative effect is distinct.

Mangiferin [51], olive extract [52], onion extract [53], Mimusopselengilin (The water and alcohol extract of flowers) [54] etc can prevent what cerebral edema, BBB permeability increases and the destruction of TJ proteins through these antioxodant effect (inhibiting excessive generation of free radicals and NO).

3. PERORATION

BBB is basal structure that engine block can maintain stabilize of central nervous system's internal environment. It occupies an important place in the CIRI. The mechanism that CIRI lead to change of BBB is a complex pathological process of multiple factors. These factor including MMPs, AQP4, TJ, cytokines, ICAM, free radicals, NO. The current we study on protective effect and mechanism of BBB from the morphological basis and physiological of BBB's opening to the approach of that a variety of media to participate in the comprehensive effect, from the whole macro research to the micro morphology; tissue structural and molecular level. The current research is limited to experimental research. A large number of drugs can improve the permeability of BBB, reduce brain edema, and increase local volume of blood flow to the brain. But there is no approved drugs used in clinical. It has a good application prospect that from the perspective of the protection of BBB's drug for treatment of ischemic cerebrovascular disease.

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