Related Progress and Research of Brain Water Metabolism

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Abstract

Water accounts for about 80% of the brain, and water molecules flow between the cells in the brain, producing important physiological functions. At the same time, disorders of water metabolism in the brain can lead to the production and deterioration of the disease. With the continuous metabolism and circulation of water, various harmful substances produced by brain tissue will be taken away to maintain the internal environment of the brain. Studies have found that brain water metabolism is related to many types of diseases in clinical work, such as the occurrence of hydrocephalus caused by the direct increase of Cerebrospinal Fluid (CSF), as well as the early cell edema and late vasogenic edema caused by cerebral hemorrhage, cerebral infarction and other diseases. Changes in water metabolism caused by various causes will lead to an increase in intracranial pressure, resulting in compression and perfusion changes in brain tissue, and eventually lead to the deterioration of the disease. Cell edema in the brain, choroid plexus secretion and even the now popular spontaneous purification system of the brain has an important relationship with water metabolism. However, because we are not clear about the mechanism of controlling brain water transport, there is no effective targeted drug treatment for these conditions. This paper will discuss the various mechanisms of brain water metabolism.

Keywords: Brain water metabolism • Cerebrospinal fluid • Hydrocephalus • Cell edema • Blood-brain barrier

Introduction

Because of the lack of porous capillaries in the brain and a variety of tightly connected barriers limiting the free entry and exit of water, the production and transportation of water in different parts are not used. It is now found that the transmembrane transport of the water is mainly composed of passive and active transport in the brain. Passive transport is the control of the direction and speed of water transport through changing osmolality. The main representative proteins are Aquaporins (AQPs), which can increase the permeability of the plasma membrane. The expression in the brain mainly includes AQP 1 and AQP 4 [1,2]. Within the brain parenchyma, AQP 1 expression abundance is extremely low, with its expression mainly being [3] on the luminal membrane of choroid plexus epithelial cells. However, AQP 4 is mainly expressed in brain parenchymal cells, most of which gather around the end feet of astrocytes surrounding the cerebral vessels. This polarized expression of AQP 4 has a crucial role in ensuring the stability of the blood and brain barrier, and plays an important role in the purification of the brain [4]. This loss of polarized expression of AQP 4 has been shown to exist in normal aging processes and in many neurological diseases, accompanied by a decrease in fluid transport capacity within the brain parenchyma, resulting in impaired brain clearance [5,6]. The active mode of water transport is also a hot trend right now, and cotransporters on the cell membrane can couple the movement of water molecules to the transport of solute, through which water molecules can move [4,7] along the direction of the electrochemical gradient of transporting ions and solute. This review focuses on the multiple mechanisms of fluid production, transport, and outflow in the CNS.

Literature Review

Production of the liquid

Choroid plexus: The choroid plexus is highly vascularized connective tissue, as a single layer of epithelial tissue. Several classical experiments have proved that the vast majority of the (80% -90%) of CSF produces [8,9] by the choroid plexus. Numerous experiments have demonstrated the existence of multiple transport mechanisms for CSF secretion, and the extent to which each mechanism contributes to the production of CSF is still inconclusive. A high density of AQP 1 expression exists in the apical membrane of the choroid, and it was once thought that the penetration model mediated by AQP 1 was the main mode of CSF secretion [10]. One experiment found that if the penetration pathway produced CSF at a rate equal to the actual CSF production rate observed in different mammals, the osmotic pressure of the cerebrospinal fluid must be 250 mOsm higher than the plasma penetration pressure (and analysis of samples from mammals found that the two were almost the same) [11-14]. Furthermore, Oshio et al. [3] found that CSF secretion in mice was only about 25%. Thus conventional aquaporin-mediated penetration pathways are not sufficient to maintain the rate of CSF production observed in mammals. Now the choroid collaborative transport protein expression gradually attention, through the solute transport and water molecule transport direct coupling, the coupling transport occurs inside the protein, this way allows water independent of the osmotic gradient, and even against the osmotic gradient, that is, this kind of collaborative transport protein can water active transport [2,7,15,16]. A large number of cotransporters have been found to perform water cotransport, such as Na + / K + / 2 Cl-Cotransporter 1 (NKCC 1), K + / Cl-cotransporter (KCC), Sodium / Glucose Cotransporter 1 (SGLT 1), γ -aminobutyric acid transporter subtype 1 (GAT 1), and Excitatory Amino Acid Transporter 1 (EAAT 1) [15,17-19]. There are several transporters selectively distributed in the apical membrane and basement membrane of choroid plexus epithelial cells. Na + / K + -ATP + (NKA) and Na + / K + / 2 Cl-Cotransporter 1 (NKCC 1) are present in the apical membrane of the choroid plexus, while K + / Cl-Cotransporter 1 (KCC 1) is localized in the basement membrane [10,20,21]. In the experiment, direct intraventricular administration of bumetanide (NKCC inhibitor) or furosemide (KCC, NKCC inhibitor) reduced the production of CSF by about 50%, indicating that this coupling water transport has an important role in the production of CSF [18,20,22]. We still need to further prove and explore the extent that other transporters contribute to CSF production and how to use this class of proteins as the target for disease treatment. In a recent experiment, Deffner et al. [23] observed the expression of AQP 4 in choroid epithelial cells from eight elderly subjects and found an inverse correlation between the expression of AQP 4 and Na + / K + -ATP enzyme (NKA). For this phenomenon, we can speculate that the choroid plexus can increase water influx through AQP 4 expression to compensate for the normal fluid production pathway impaired by aging, or that AQP 4 in CP is simply misexpressed and slows down CSF production. Further studies are needed to prove the exact mechanism of this phenomenon.

Blood-brain barrier: The Blood-Brain Barrier (BBB) is composed of the endothelial cells of the cerebral blood vessels, the foot end of the astrocytes surrounding the endothelium, and the pericytes forming the basement membrane between the blood vessels and glial cells. It was once believed that CSF was all secreted by the choroid plexus, but the experiment found that surgical removal of the choroid plexus could not completely eliminate the generation of CSF. At the same time, according to the MRI measurement of cerebrospinal fluid flow, the fluid flow of the bone in the foramen magnum was several times larger than that in the midbrain aqueduct. These experiments all proved that the choroid plexus was not the only source of

cerebrospinal fluid [24-26]. Numerous experiments have demonstrated that fluid can enter the brain through the endothelial cell layer of the blood-brain barrier and can enter the ventricular [9,27] through the ependymal cell layer. However, the contribution score of BBB in different experiments is not unique, and it is generally believed that 20% of CSF produces [4] through the endothelial cell layer of BBB. The tight connection between endothelial cells, and the high resistance it has, suggests that the endothelial cell layer is one of the lowest water-permeable [28]. While the brain is highly vascularized tissue containing 100 cm 2 of endothelial membrane, this rich capillary area can allow large amounts of water to pass through the BBB into the circulating [4,29]. Beyond the endothelial cell layer, surrounding about 85% of the surface of brain capillaries [30]. Under pathological conditions such as ischemia and hypoxia, it can cause energy-dependent loss of solute homeostasis, which leads to the swelling of perivascular astrocytes, causing the damage of the blood-brain barrier that may have been damaged, and eventually resulting in the accumulation of fluid in the extracellular space and cerebral edema. The swelling of glial cells is mainly mediated by AQP 4. A series of experiments found that Protein Kinase A (PKA), PKC or PKG can phosphorylate Ser111 and Ser180 of AQP 4, opening a door within the protein to pass through the water, and ultimately improving the water permeability [4,31] of the cell membrane. In a group of animal experiments, it was found that the remembrane of AQP 4 could be seen in pathological conditions, and it was important for the occurrence and progression of edema through early interference of AQP 4 intracellular translocation [32]. The study concluded that under ischemia and hypoxia, the transient receptor potential vanilloid receptor type 4 channel protein (transient receptor potential vanilloid 4, TRPV 4) opens Ca 2 + and ions flow into the astrocytes, thus activating CaM. CaM interacts with adenylylate cyclase to activate cAMP-dependent PKA, which phosphorylates AQP 4 at Ser276 to relocalize it to the plasma membrane. Second, CaM can directly bind to AQP 4, and this regulatory interaction drives the subcellular relocalization of AQP 4. In this experiment, triflurazine (CaM antagonist) squeezed the T8 segment, while treated rats showed significant recovery within 2 weeks, while untreated rats still had functional defects after 6 weeks. This may be mainly due to ischemic hypoxia leading to changes in solute homeostasis of astrocytes, while triggered early cytotoxic edema, resulting in disruption of the blood-brain barrier, and induced late vasogenic edema. This fully demonstrates the complexity of the mechanism of brain water metabolism, and its significance for the development of the disease.

Transport of the liquids

The cerebrospinal fluid flows from the ventricle, through the median hole of the fourth ventricle to the subarachnoid space, wrap the entire central nervous system, buffer the brain and spinal cord pressure, and has protective and supporting effects on the brain and spinal cord. Part of the fluid in the subarachnoid space is absorbed by the arachnoid particles and enters the blood circulation, and the other part is transported from the brain surface to the brain parenchyma through the special structure of the arterial perivascular space, merging with the fluid produced by the endothelium to perform the clearance function similar to the lymphatic circulation [33,34].

Brain lymphoid system: In physiological states, the CNS requires rapid delivery of energy metabolites and removal of waste products to maintain its homeostasis. However, unlike peripheral tissues, the anatomical structure of the lymphatic system is not seen in the brain parenchyma, and the brain limits material transport across the membrane. Under these conditions, the "brain-like lymphatic system" of the perivascular space can act as a conduit for rapid and efficient delivery of nutrients and metabolites as a surrogate for the lymphatic vasculature not present in the CNS by delivering excess fluid, metabolites and waste proteins from the parenchyma to the peripheral circulation [34,35]. Through the heart cycle pressure through the arteriovenous pressure gradient, fresh CSF in the "pump" along the vascular-astrocytic foot formation into the unique perivascular space into the deep brain, CSF and ISF and metabolites in the brain, the flow of water drives the flow of solute, eventually astrocytes foot AQP 4 liquid absorption, the dissolved nerve activity during protein waste will be absorbed through the paracellular pathway, eventually transferred to the perivenous space will take it out [34,36]. Iliff et al and Thrane et al respectively used two-photon microscopy in mice that the CSF tracer enters along the arterial perivascular space of the cortex and rapidly appears in the venous perivascular space [34, 37]. And related experiments have shown that the perivascular space has little resistance to the arterial pulse-driven CSF inflow [38-40]. Grady uses horseradish peroxidase into the lateral ventricles or cisternae of cats and dogs, and after just ten minutes after infusion, the perivascular system is outlined by tracers around the arterial and venous areas, thus indicating that flow is much faster than might be obtained by simple diffusion [41]. Multiple sets of experiments demonstrated that the normal function of the brain lymphoid system is highly dependent on the polarized expression of [42-44] at the astrocytic end. Loss of AQP 4 polarization leads to reduced CSF influx and reduced solute clearance, causing the accumulation of neurodegenerative disease proteins such as amyloid- β, tau, and α -synuclein, and ultimately causing the development of diseases such as Alzheimer's and Parkinson's disease. We have found that the knockout of the gene encoding AQP 4 caused a 42.4% reduction in the brain lymphoid system in mice, and observed a 55% reduction in the clearance of exogenous β –amyloid [34]. Thus, it is now well recognized that the AQP 4-dependent paravascular lymphoid pathway is the primary clearance of the stromal fluid solute in the brain parenchyma.

The outflow of the fluid

The cerebrospinal fluid of the human brain is produced at a rate of approximately 600 ml per day. Because of the existence of the skull around the brain, there is no space for expansion in the brain space, which requires a balance between cerebrospinal fluid outflow from the central nervous system and the formation of new cerebrospinal fluid. Otherwise, excessive accumulation of CSF or any other fluid causes a significant increase in intracranial pressure. The outflow of the intracranial fluid and its constituent solutes from the central nervous system is a complex and multifaceted process. Blood flow to once arachnoid granules and the superior sagittal sinus has been considered the main outlet site of CSF, and the cervical lymphatic vessels are considered an auxiliary pathway [45]. However, quantitative data indicate that the proportion of CSF excreted through blood and neck lymphatic vessels is roughly the same [46]. Moreover, the structure of arachnoid particles is not observed in rodents and human children, and arachnoid villi are also sparse, it seems that arachnoid particles may have little role in CSF outflow [47, 48].

For the lymphatic drainage pathway, fluid can be drained through the dural lymphatic vessels and sagittal paradural space or through the perineuronal route, but that effect is more inconclusive [47,49-51]. The dural lymphatic vessels exist in the superior sagittal sinus of the brain and the dorsal side of the transverse sinus and the base of the phosphorus sinus, which can absorb the macromolecular material from the cerebrospinal fluid [49,52]. The morphological features of the basal dural lymphatic vessels suggest that these canals may be having a better lymphatic drainage effect than the dorsal dural lymphatics. Non-vessel-like structures designated as the parsagittal dural space were also found in the dura. These gaps can deliver CSF to lymphatic vessels in the dura or to arachnoid granules [53]. For perineuronal drainage, along olfactory outflow appears to be the volumetrically largest outflow pathway in humans and other species [47]. Through local injection of the fibrosis inducer kaolin, surgical removal of the olfactory nerve, or sealing of the cribriform plate with glue, some experiments could block the exit along the olfactory nerve pathway, and cause an 87% reduction in the total cerebrospinal fluid drainage of cervical lymphatic vessels [54]. In animal experiments, administration of contrast medium into the subarachnoid space of monkeys and sheep revealed that contrast material passes through the accrepina and accumulates in the submucosa, the nasal septum and turbinate tissue, suggesting an important contribution of the olfactory nerve pathway to CSF outflow [55,56]. Hyposmia or loss in the elderly was found as a significant risk factor for the development of Alzheimer's disease and other neurodegenerative diseases [57,58]. Rodent-related studies have found that olfactory nerve degeneration leads to a decrease in cerebrospinal fluid outflow. Thus supporting the hypothesis that diminished olfactory nerve pathway outflow can contribute to the development of Alzheimer's disease. Meanwhile, the outlet of the CSF along the other cranial nerves also facilitates the outflow of the [59,60] to the peripheral lymphatic vessels. However, the extent to which these neural outflow pathways contribute to CSF outflow, and the ultrastructure of them and the peripheral lymphatic vessels are currently unknown, and more experiments are needed to prove them.

Conclusions and Outlook

This paper mainly discusses the mechanism of action and its function of brain water metabolism. The main argument is that brain tissue, like peripheral tissue, has basic homeostatic requirements for fluid flow to take away metabolites and export waste. Because of the special properties of the

central nerve, such as the presence of a tight blood-brain barrier and the lack of a brain parenchymal lymphatic system, a more complex fluid transport network is needed to maintain this basic function. The network includes fluid production (choroid plexus epithelium and blood-brain barrier), fluid flow (perivascular space and polarized expression of AQP 4 water channels at the feet of astrocytes), and fluid outflow (venous sinuses, dural lymphatic vessels, and perineural pathways). Reduced function of the cerebral lymphoid system has been documented in experimental models of Alzheimer's disease, Parkinson's disease, traumatic brain injury, and subarachnoid hemorrhage. Cerebral water metabolism disorders may not be the direct cause of the disease, but it can cause disorders of solute homeostasis in the fluid, cause abnormal brain states, and eventually lead to the deterioration and progression of the disease. Brain water metabolism is involved in most physiological and pathological processes in the CNS, covering various fields of neurology, which provides us with new perspectives on the interpretation of certain phenomena. However, there is a lack of definite conclusion about the mechanism of brain water metabolism, which requires further study and discussion.

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