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REVIEW ARTICLE

Factors affecting aquaporin-4 and its regulatory mechanisms in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a common neurodegenerative disorder, with its core pathological features being the excessive deposition of amyloid-beta (Aβ) protein and the abnormal phosphorylation of tau protein. This review introduces the crucial role of aquaporin-4 (AQP4) in AD, particularly in the glymphatic system, where it facilitates the clearance of Aβ and other metabolic waste. It describes the structure and function of AQP4, its involvement in AD, and the factors affecting it, including Aβ, tau protein, glutamate transporters, adenosine, exercise, sleep, and diet. The article reviews the relationship between the loss of AQP4 polarity and the reduced efficiency of Aβ clearance and summarizes potential therapeutic strategies to restore AQP4 polarity to enhance waste clearance. The authors point out that AQP4 holds great potential as a therapeutic target for AD, propose the possibility of restoring AQP4 function through drug interventions and lifestyle adjustments, and suggest that further research into AQP4 regulatory mechanisms will provide new directions and insights for the prevention and treatment of AD.

Keywords: Alzheimer's disease, aquaporin-4, regulatory mechanisms

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disorder, accounting for approximately 60%-70% of patients with cognitive impairment. The excessive production, impaired clearance, and subsequent deposition of Aβ in the brain are central mechanisms in the development of AD. Beyond active transport and passive diffusion across the blood-brain barrier, the glymphatic system also plays a crucial role in Aβ clearance. The glymphatic system operates by facilitating cerebrospinal fluid (CSF) flow along perivascular spaces surrounding arteries, where it exchanges with interstitial fluid within brain tissues, before draining along perivenous spaces and eventually into the internal jugular vein via lymphatic vessels. Factors influencing glymphatic flow include pressure gradients induced by arterial pulsations and synchronized action potentials within the neural network.[1] During inhalation, thoracic pressure is transmitted through the interconnected venous plexuses within the spinal canal, facilitating the flow of CSF and influencing the dynamics of intracranial and spinal venous circulation.[2] Aquaporin-4 (AQP4) plays a central role in the glymphatic system, regulating the flow of CSF and interstitial fluid to clear metabolic waste from the brain. The density of AQP4 is highest in the vascular endfeet of astrocytes, a phenomenon referred to as the polarized expression of AQP4. Loss of AQP4 polarity occurs when AQP4 expression is mislocalized within astrocytes, becoming broadly distributed rather than concentrated at the perivascular endfeet, impairing its efficiency in fluid transport and waste clearance.[3] In AD, the function and polarization of AQP4 are influenced by various factors, leading to a decline in the glymphatic system's clearance capacity. This impairment exacerbates the accumulation of Aβ, contributing to the progression of AD pathology.[4] Studies have shown that various factors, such as APOE4 and Aβ, influence the structure and function of AQP4, thereby regulating glymphatic system flow and affecting cognitive function. This article reviews the factors influencing AQP4 in AD and its regulatory mechanisms, aiming to provide new insights for therapeutic strategies targeting AQP4 as a potential approach to treat AD.

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STRUCTURE AND FUNCTION OF AQP4

AQP4 is a member of the aquaporin family, widely present in various tissues and organs but most abundantly expressed in the central nervous system. It has a tetrameric structure, with each tetramer composed of four identical monomers. Each monomer contains six transmembrane helices that surround and form a water channel. Its selective filtration function is determined by arginine and histidine residues, ensuring the passage of water molecules.[5,6] In the cell membrane, AQP4 often exists in the form of orthogonal arrays of particles (OAPs), particularly in the astrocytic endfeet near blood vessels, where it plays a role in regulating water and ion balance.[7,8]

AQP4 has two main isoforms, M1 and M23, which are generated through alternative splicing. These isoforms can assemble in different ways to form heterotetramers, providing flexible functional regulation under various physiological conditions.[7-9] M23 tends to form larger aggregates in the cell membrane, promoting more efficient water channel formation. The functional efficiency of AQP4 depends on its polarized distribution in astrocytes and the expression ratio of its two main isoforms, AQP4-M1 and AQP4-M23. Enhanced polarization of AQP4 indicates a more localized concentration on the vascular side of astrocytic endfeet, forming part of the blood-brain barrier. This distribution is beneficial for controlling edema after neural injury, maintaining potassium ion concentration, and facilitating neural signal transmission. Moreover, AQP4 is closely associated with various central nervous system diseases, such as cerebral edema, brain injury, and epilepsy.[6,9,10]

THE ROLE OF AQP4 IN ALZHEIMER'S DISEASE

AQP4 is a critical component of the brain's glymphatic system. By regulating water flow, it facilitates the entry of CSF into the brain interstitial space and promotes the removal of metabolic waste, such as Aβ and tau proteins. This clearance mechanism is essential for maintaining brain health. Dysfunction of AQP4 leads to the accumulation of metabolic waste like Aβ and tau proteins in the brain, exacerbating the pathological progression of AD.[11]

Compared with mild cognitive impairment, the expression level of AQP4 in AD patients shows a declining trend, particularly in more advanced stages of pathological damage, where its dysfunction becomes more pronounced. This indicates a correlation between AQP4 and the severity of AD.[12] In AD model mice, AQP4 redistributes from the polarized location in astrocytic endfeet to the cell body and processes. This redistribution reduces the clearance efficiency of Aβ, thereby exacerbating the neuropathological progression associated with AD.[13,14] The loss or functional decline of AQP4 reduces Aβ clearance in the mouse brain by 55%.[15] Studies have shown that 5xFAD mice with AQP4 gene knockout exhibit significantly increased Aβ deposition in the cerebral cortex, accompanied by reduced densities of astrocytes and microglia around plaques. Additionally, the loss of AQP4 is associated with the severity of neural damage. This suggests that AQP4 plays a protective role in AD by supporting the structural plasticity of astrocytes and facilitating the formation of a reactive glial network around plaques, thereby helping to shield neurons from the harmful effects of Aβ.[13] Furthermore, inhibiting AQP4 activity significantly enhances the aggregation and lateral propagation of tau protein in the brains of AD mouse models, particularly in the hippocampal region.[16] Recent studies have found that AQP4 expression in the perivascular regions of AD patients is significantly reduced and is closely associated with NFT Braak staging, Aβ load, and age. The reduction in AQP4 may also impair the support that astrocytes provide to the blood-brain barrier (BBB), leading to BBB dysfunction and exacerbating brain inflammation. This suggests that the downregulation of AQP4 expression is an important driver of the pathological progression of AD and is closely linked to factors such as APOE4 and age.[17] However, overexpression of AQP4 can also have adverse effects on the brain. For instance, in reperfusion injury mouse models, AQP4 overexpression is closely associated with the formation of brain edema, increased permeability of astrocytic endfeet, exacerbated neuroinflammatory responses, and heightened neural damage.[18]

FACTORS INFLUENCING AND REGULATORY MECHANISM OF AQP4

Aβ

Under normal conditions, AQP4 regulates the homeostasis of the blood-brain barrier and brain water balance through its polarization in astrocytic endfeet. It also facilitates effective exchange between CSF and interstitial fluid

(ISF) and clears excessive Aβ from the brain via the glymphatic system. However, Aβ can, in turn, regulate the polarization and function of AQP4.[19] On one hand, abnormal accumulation of Aβ causes AQP4 depolarization, reducing the exchange efficiency between CSF and ISF, which in turn decreases the clearance of Aβ.[20] On the other hand, Aβ accumulation can trigger astrocyte activation and inflammatory responses, leading to increased production of inflammatory factors. These inflammatory factors can regulate AQP4 expression and its localization within astrocytes through various cellular signaling pathways, such as activation of the PI3K/Akt pathway. This further disrupts AQP4's function and normal distribution.[21] Given AQP4's role in maintaining the integrity of the blood-brain barrier (BBB) and regulating the brain's adaptability to external pressure changes, Aβ-induced AQP4 dysfunction may compromise BBB stability, increase CNS inflammation, and accelerate the progression of neurodegenerative disorders.[22] The overexpression of AD risk factors APP/PS1 not only leads to excessive production and deposition of Aβ but also affects the localization and function of AQP4 in astrocytes. Thus, AQP4 is both a key factor in Aβ clearance and a target regulated by Aβ. Once Aβ accumulates in the brain, it induces AQP4 dysfunction, further promoting Aβ deposition. Conversely, enhanced Aβ clearance supports the recovery of AQP4 function, which in turn accelerates Aβ clearance.[23,24]

Tau

Tau protein is a microtubule-associated protein, and its hyperphosphorylation leads to the formation of neurofibrillary tangles (NFTs), which are key pathological events in AD and other neurodegenerative disorders.[25] In the pathological progression of AD, abnormal tau aggregation not only directly damages the microtubule structure of neurons but may also influence the brain microenvironment by regulating surrounding glial cells. In the presence of tau aggregation, the expression of AQP4 in astrocytes changes, possibly due to alterations in the intracellular signaling environment induced by tau aggregation, particularly the activation of inflammatory signals. Inflammatory signals such as IL-1β and TNF-α can regulate the expression and distribution of AQP4.[26]

In the P301L mouse model, previous studies observed a significant increase in AQP4 expression around areas of tau deposition. This phenomenon is thought to result from tau aggregation enhancing the reactive state of astrocytes, which subsequently affects the distribution and function of AQP4. These changes influence brain hydrodynamics and the clearance mechanisms for metabolic waste. Additionally, increased expression of astrocytic markers GFAP and S100β, as well as microglial markers CD68 and Iba1, was observed in regions surrounding Tau deposition. This suggests that neuroinflammation and neuronal damage may further promote abnormal AQP4 expression.[27] The accumulation of tau protein may affect the expression and localization of AQP4 on astrocyte endfeet, indirectly interfering with the expression and activation of AQP4.[28,29]

Glutamate transporters

Glutamate is a major excitatory neurotransmitter in the brain, playing a critical role in cognitive functions such as learning and memory. However, an excessive accumulation of glutamate in the synaptic cleft can lead to excitotoxicity, known as glutamate toxicity. This toxicity can cause an excessive influx of calcium ions (Ca^{2+}) into neurons, triggering a cascade of internal events leading to neuronal damage and death. The Glutamate-Aspartate Transporter 1 (GLT-1) is the primary astrocytic glutamate transporter in the brain, playing a crucial role in regulating glutamate concentrations in the synaptic cleft and preventing excitotoxic damage.[30] Previous study indicates that there is functional coupling between GLT-1 and AQP4 on the membranes of astrocytes. AQP4 and GLT-1 may form large molecular complexes, jointly regulating the balance of water and glutamate in the brain. This interaction highlights a sophisticated mechanism by which astrocytes maintain homeostasis in the neural environment, influencing both neurotransmitter clearance and osmotic balance, critical for preventing excitotoxicity and ensuring proper neural function.[30,31] When GLT-1 activity is inhibited, not only is the ability to clear glutamate impaired, but the water channel function associated with AQP4 may also be affected. A decline in GLT-1 function or expression is relatively common in AD. This change not only increases the concentration of glutamate in the neuronal extracellular space, raising the risk of excitotoxicity, but may also indirectly affect AQP4 function by reducing the flow of water and waste.[20,32]

A2A receptor

The A2A receptor (A2AR) is a classical G protein-coupled receptor (GPCR). Upon activation by its

ligand, A2AR couples with Gs proteins, leading to a significant increase in intracellular cyclic adenosine monophosphate (cAMP) levels. cAMP is an important second messenger that activates protein kinase A (PKA), initiating a series of downstream phosphorylation events.[33,34] The activated PKA regulates various target proteins, including AQP4, through phosphorylation, thereby affecting the gene expression of AQP4 and its distribution on the cell membrane. In astrocytes, this regulatory pathway is crucial for the stability and function of aquaporins and plays a key role in pathological processes such as the regulation of neuroinflammation and brain edema.[33,35]

Recent studies have found that A2AR can form heteromeric complexes with A2B receptors (A2BR) under pathological conditions such as neuroinflammation. These complexes may exert feedback regulation on A2AR signaling in astrocytes. Previous study indicates that the formation of A2AR-A2BR heteroreceptor complexes reduces A2AR's efficiency in activating the cAMP-PKA pathway, thereby limiting excessive A2AR activity. This feedback mechanism effectively regulates the distribution and stability of AQP4 on the cell membrane, accommodating various physiological or pathological demands such as neuroinflammation and cellular edema.[34,36] The formation of this complex under specific pathological conditions may help better regulate water balance in the brain.[33] Additionally, the activation of A2AR has a significant impact on cellular water permeability, primarily achieved by regulating the activity of AQP4. AQP4 is the primary water channel protein in the brain and spinal cord, controlling water transport across the membranes of astrocytes. Under conditions such as increased extracellular osmotic pressure or localized injury, A2AR activation may induce the redistribution of AQP4, facilitating the rapid redistribution of water to maintain local tissue osmotic pressure and ion balance.[35,37] Particularly under conditions of nervous system edema or hyperosmotic stress, regulating the localization and function of AQP4 through A2AR helps reduce tissue damage and alleviate edema symptoms, providing an effective mechanism for maintaining water balance in neuropathological conditions.[33,34]

Exercise

Exercise can effectively enhance fluid flow in the brain and promote the clearance of metabolic waste such as Aβ. Studies have shown that regular aerobic exercise, particularly through running wheel activity in aged mice, increases the flow of the glymphatic system, facilitates the exchange of CSF and ISF, and protects the brain from damage.[20,38]

Studies have found that sustained training can gradually enhance the expression and polarized distribution of AQP4 in the hippocampal region. Exercise promotes the polarized expression of AQP4, thereby accelerating the clearance function of the glymphatic system in the brain to remove neurotoxic substances such as Aβ.[39] Additionally, studies have found that exercise can promote the polarized distribution of AQP4 by influencing the caveolin-1 signaling pathway, thereby reducing the occurrence of brain edema.[40] Furthermore, exercise improves the function of astrocytes by maintaining the expression of AQP4 in the astrocytic endfeet, thereby enhancing the exchange of CSF and ISF. Exercise also reduces neuroinflammation in the brain by lowering the activation levels of astrocytes and microglia, alleviating inflammatory states associated with AQP4 dysfunction. This further supports the normal function of AQP4 and the clearance of Aβ, contributing to the delay of Alzheimer's disease progression.[41]

Sleep

Sleep quality plays a critical role in the regulation of neurodegenerative diseases. Sleep deprivation can disrupt the expression and function of AQP4, thereby impairing the efficiency of the glymphatic system and leading to the accumulation of neurotoxic substances. Different sleep stages have varying effects on AQP4 expression. In the early stages of AD, sleep fragmentation leads to an upregulation of AQP4, whereas this change is not observed in the later stages of AD.[42] This suggests that changes in sleep quality during AD may play different roles in the regulation of AQP4 at various stages, thereby influencing the progression of AD. Sleep deprivation can disrupt the distribution of AQP4, reducing its polarization on the cell membrane. This impairs the waste clearance capacity of the glymphatic system and may result in the accumulation of metabolic waste in the brain.[43] Previous studies have observed through experiments that sustained sleep disturbances significantly affect the sleep patterns of mice and impair the polarization of AQP4. This disruption may lead to further reductions in CSF flow, thereby exacerbating the pathological features of AD.[44]

Diet

A high-fat diet can trigger inflammatory responses in the brain, further affecting the expression and function of AQP4.[45] According to the study by Delle *et al*.[45], long-term high-fat diets can influence the expression and function of AQP4 through various mechanisms, including alterations in vascular hemodynamics and perivascular neural regulation. While a high-fat diet increases AQP4 expression in the hypothalamic region and enhances its polarized arrangement around blood vessels—improving the efficiency of CSF and ISF exchange as an adaptive response to sustained metabolic stress—these changes may also exacerbate neuroinflammatory responses in the brain. Researchers observed significant neuroinflammation and glial cell activation in this region, suggesting that such acute inflammatory responses may lay the groundwork for prolonged metabolic dysregulation.yhuj[46,47] Thus, the enhanced expression and polarization of AQP4 may facilitate the clearance of inflammatory mediators, but at the same time, it could disrupt brain water homeostasis and cellular environmental stability, contributing to the maintenance or exacerbation of chronic inflammation. This, in turn, may further compromise the health of neural functions and structures.[20,48]

Intermittent fasting may improve cognitive functions associated with AD by restoring AQP4 polarity. This is primarily achieved by enhancing the polarized distribution of AQP4 and regulating the ratio of its two major isoforms, AQP4-M1 and AQP4-M23. Such adjustments enhance AQP4 functionality and promote the clearance of Aβ.[22,49] During fasting, the levels of β-hydroxybutyrate rise in the body, and as an endogenous histone deacetylase inhibitor, it may enhance the expression of microRNAs, such as miR-130a, to further regulate AQP4 transcription activity and polarity. The combined effects of these mechanisms may not only directly improve AQP4 polarity and function but also indirectly provide protective effects by altering metabolic and signaling pathways in the brain. This could help slow down or prevent the progression of AD.[49]

Physical stimulation

Recent study has revealed how various non-invasive stimulation techniques can influence the pathological progression of AD by modulating the function of AQP4 in astrocytes. Both 40 Hz multisensory stimulation and light flashing can improve the function of the glymphatic system by enhancing the polarized distribution of AQP4 on astrocyte end-feet, promoting the exchange between cerebrospinal fluid (CSF) and interstitial fluid (ISF), accelerating the clearance of metabolic waste, particularly Aβ, and slowing down the progression of AD.[50,51] Very low intensity ultrasound (VLIUS) activates transient receptor potential vanilloid 4 (TRPV4), which induces calcium ion influx into astrocytes, thereby activating calmodulin (CaM). This promotes the transport of AQP4 to the cell surface, enhancing the exchange between cerebrospinal fluid and brain tissue, and improving the efficiency of waste clearance, including Aβ.[52] Under the influence of intermittent theta burst stimulation (iTBS), the function of AQP4 is also affected. iTBS, by inducing cortical plasticity changes, may alter the brain's waste clearance mechanisms, further impacting the progression of AD.[53] In addition, pulsed infrared light (PIR) regulates calcium signaling by activating TRPV4 and TRPA1 channels, thereby altering the polarized distribution of AQP4. This promotes the transport of AQP4 from the cell body to the perivascular end-feet, enhancing water flow and facilitating the clearance of Aβ and other waste products.[54] In summary, these stimuli regulate the function of AQP4 through different mechanisms, thereby improving the efficiency of the glymphatic system and promoting the clearance of AD-related metabolic waste. This provides potential non-invasive intervention strategies for the treatment of AD.

SUMMARY AND OUTLOOK

The central role of AQP4 in clearing metabolic waste during the complex pathophysiological progression of AD is gaining increasing attention. Dysfunction of AQP4, particularly the disrupted polarized distribution in astrocytic endfeet, is considered a key factor underlying impaired Aβ clearance by the glymphatic system. AQP4 holds great potential as a therapeutic target for AD. Drug development and lifestyle interventions, such as aerobic exercise and dietary regulation, are promising approaches to restore AQP4 polarity and enhance its metabolic waste clearance capacity, thereby slowing the pathological progression of AD. Personalized treatment strategies incorporating genetic factors may also become a new direction in AD therapy. Further exploration of AQP4 regulatory mechanisms will provide novel insights into the prevention and treatment of AD.

DISCLOSURE

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