AQP4 CHANNELS AS THERAPEUTIC TARGET IN CNS DISORDERS

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ABSTRACT

Among the most prevalent molecules in the brain is aquaporin-4 (AQP4), which is especially abundant in the astrocyte membranes that line the blood-brain junctions. Despite being linked to several pathological processes, AQP4's function in brain physiology is still unclear. Extracellular volume regulation, potassium buffering, waste clearance, interstitial fluid resorption, cerebrospinal fluid circulation, neuroinflammation, osmosensation, cell migration, and Ca2+ signaling are among the processes in which it is engaged. Throughout the central nervous system (CNS), astrocyte plasma membranes express the water-transporting protein AQP4. An outline of AQP4's physiological functions in the brain, meta-analysis, structure and functions are provided here. This study also covers role of AQP4 in different CNS disorders like cerebral edema, ischemic stroke, spinal cord injury, migraine, meningitis, neuromyelitis optica, epilepsy, dementia caused by Parkinson's disease, Alzheimer's disease, vascular dementia, and Lewy body dementia. Previous years secondary data was collected from different sources like pubmed, google scholar, research gate etc.

Keywords: AQP4; CNS disorders; vascular dementia; Neuromyelitis optica; epilepsy; Alzheimer’s disease

1. INTRODUCTION

Water is bidirectionally transported into and out of the brain and circulation via the water channel protein AQP4, which is typically found at the terminals of astrocytes. Significant modulation affects the expression levels and localization of AQP4 in astrocytes. For instance, cytokines like IL-1 elevate AQP4 in inflammatory situations. [1]. Brain edema may result from dysregulation of AQP4 expression or function. [2, 3]. A study conducted on mice demonstrates that the presence of AQP4 leads to an increase in brain edema, which is in line with a decrease in cerebral ischemia-induced swelling or acute water intoxication. This effect is specifically observed in the astrocyte end feet [4]. AQP4 expression is enhanced in animal models. Hydrocephalus, an effect that appears to be productive revealed that both edema clearance and survival are lower in mice lacking AQP4[5]. Because arginine-vasopressin, one of the several known regulators of AQP4, can trigger AQP4-mediated radial water transport across the astrocyte syncytium [6, 7], AQP4 is a developing family of highly permeable molecular water channels identified in numerous bodily tissues; it will be crucial to continue investigating the control of this channel and evaluate whether manipulation of this channel is effective in the treatment of various diseases connected with brain edema.[8]. AQP4 channels have been identified as membrane water channel that plays a role in red blood cells swelling due to hydraulic action. Furthermore, some AQP4 subtypes have potential uses in cellular metabolism as they are also implicated in the transport of glycerol [9]. Moreover, it has been discovered

that AQPs are engaged in a number of biological processes, including tumour angiogenesis.[10], glial scar formation [11], pain [12], and neuroexcitation [13, 14]. It is also required for the olfactory system, inner ear, and retina of the eye to work normally. The AQP channel consists of six transmembrane helix proteins arranged so that there is a pore in the center that allows the transport of water through it [15, 16].

Various variants of AQP4 proteins have the ability to allow the passage of water, glycerol, urea, pyrimidine, and monocarboxylates. Mammalian AQPs are categorized based on their permeability. There are water-permeable AQPs (AQP0, AQP1, AQP2, AQP4, AQP5, and AQP6), aquaglyceroporins (AQP7, AQP3, and AQP8), urea channels, and neutral solute channels (AQP9) [17]. Aquaporin-4 (AQP4) proteins consist of two consecutive repetitions of three alpha helices embedded in the cell membrane, with the amino and carboxyl terminals positioned within the cytoplasm [18]. AQP1 is a homotetramer, which also shows the movement of water ions through them (Figure 1) [19].

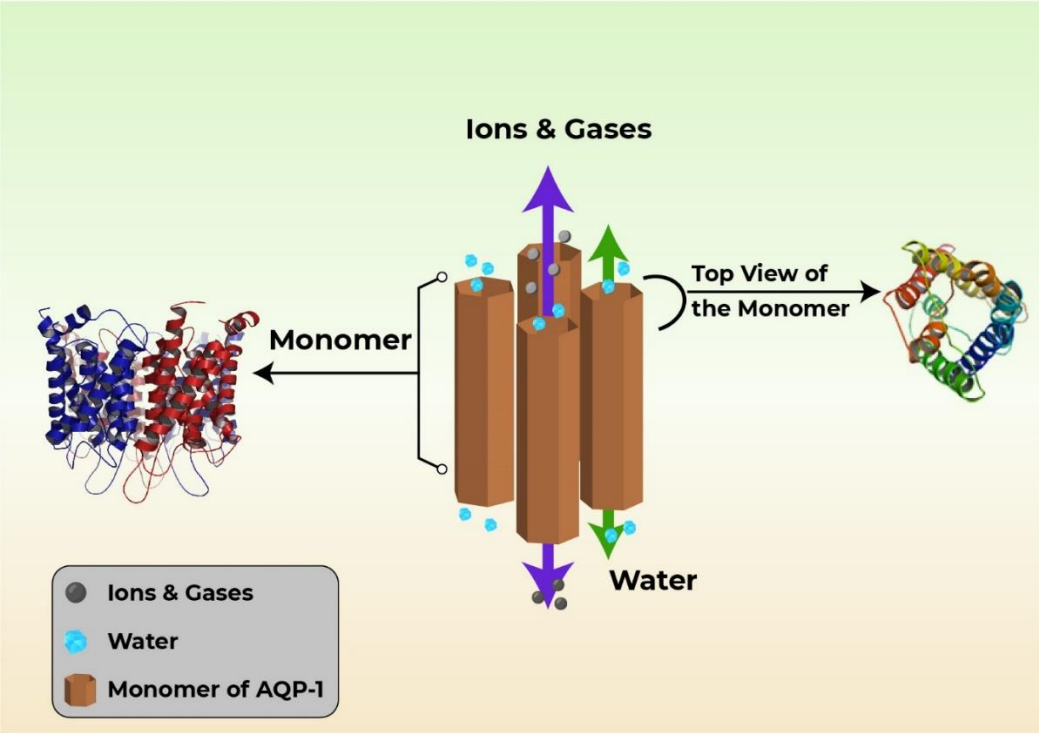


Fig. 1 3D Image of Aquaporin-1 channel.

2. STRUCTURE AND FUNCTIONS OF AQP4 CHANNELS

AQP4 is a water-specific membrane transport protein. It belongs to the aquaporin family. It has a crucial function in regulating the water balance in the blood-brain barrier (BBB). Its presence as a significant water transporter in the human brain has improved our knowledge of its function in human physiology and pathology. [20-23]

2.1 Structure of AQP4 Channel

AQP4 monomers assemble as a stable tetramer within membranes, with each monomer possessing an individual pore that selectively allows the passage of water. The AQP4 monomer has a molecular weight of around 30 kDa and consists of six transmembrane helix segments along with two shorter helical segments. AQP4 tetramers further form an orthogonal array of particles.[24]. The composition and distribution of AQP4 are shown in Figure 2, which shows how aquaporin 4 is arranged in a helical structure and how they are located in brain cells. The two-pore helices' highly conserved Asn–Pro–Ala motifs determine water selectivity.[25].

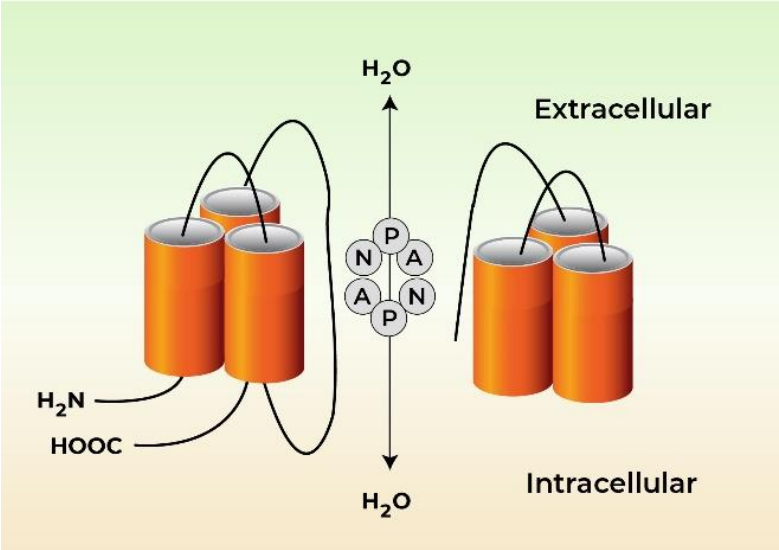


Fig. 2 Aquaporin-4's location and structure. Six membrane-spanning α-helices, with both termini situated intracellularly, make up each AQP4 monomer.

2.2 AQP4 Distribution in the brain

The primary functions of aquaporins-1 and 4 are to carry water between the brain's major compartments and to keep the body's water balance stable. [26] AQP4 channels are mostly expressed in astrocytes. [27] On the cell surfaces of the CSF-brain barrier and BBB, AQP4 is highly concentrated. which works together with the Kir4.1 potassium channel and acts as an H_2O-K transport complex. [28 & 29] While AQP1 is involved in the formation of cerebrospinal fluid and is mostly expressed in the apical membrane of the choroid plexus epithelium. 20-30% of the volume of CSF is the transcellular water flow of AQP1. [30] In the exocrine glandular epithelium, Aquaporin 4 was found in the dentate gyrus of the hippocampus, the cerebellum, the ependymal lining system, the supraoptic and paraventricular nuclei of the

hypothalamus, and the limiting glia. Additionally, the cerebral cortex, the medial habenular nucleus, and hippocampus areas including the nuclei of the stria terminalis all showed low but substantial levels of AQP4 mRNA. In addition to the central nervous system, AQP4 is expressed in the stomach, kidney, and skeletal muscle. [31–34] Fig: 3 depicts the expression of AQP4 in the brain and the pathways associated with water flow in vasogenic edema.[35]

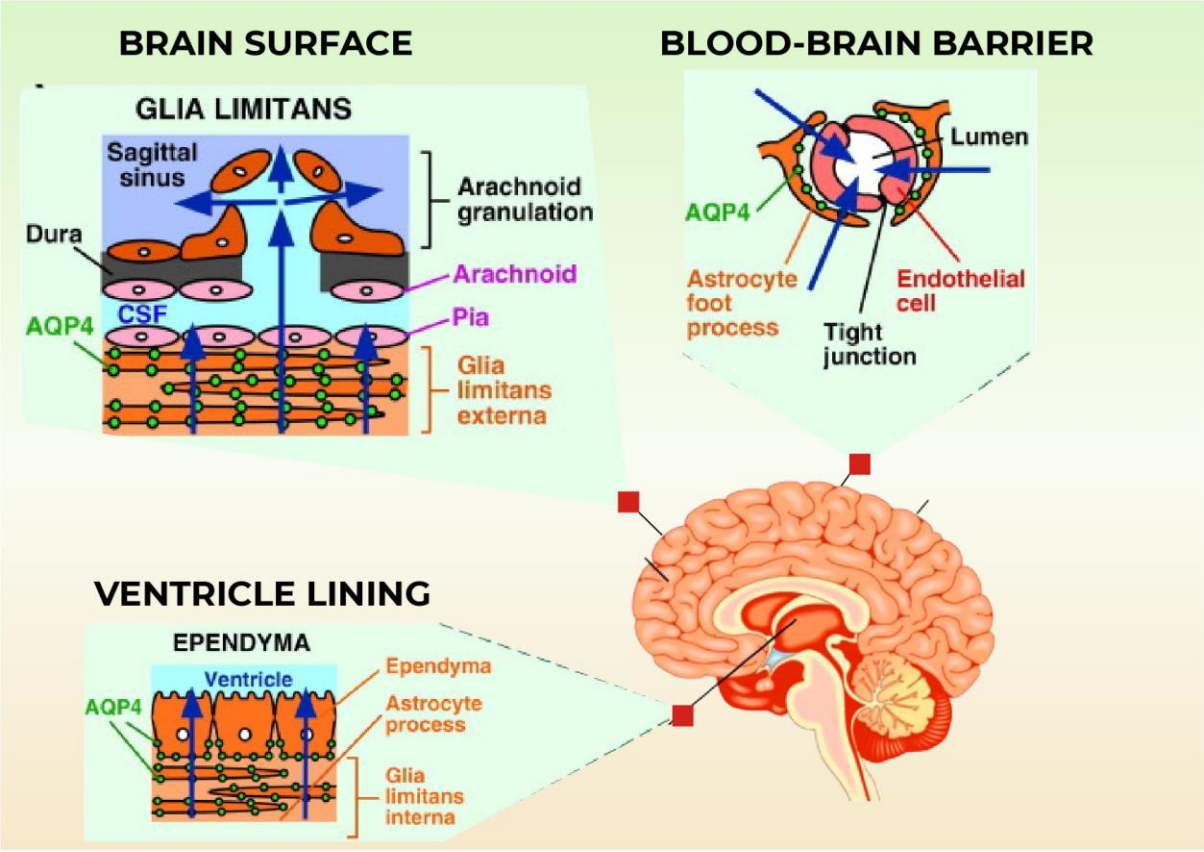


Fig. 3: The expression of AQP4 in the brain and the three routes for water efflux from the brain in vasogenic edema.

2.2 The roles and purposes of AQP4 channels

AQP4 serves a vital role in enabling the transfer of water from the blood arteries to the brain tissue across the blood-brain barrier. Additionally, it contributes to the removal of harmful protein clumps from the brain through a mechanism known as "glymphatic". [36, 37] It also led to the clearance of solute from the brain parenchyma into the Para venous spaces through the extracellular space of the brain parenchyma, astrocyte migration, nerve signal transmission. [38-40] It also led to the removal of the solution from the brain tissue into the Para venous spaces through neuroinflammation. It activates astrocyte calcium signaling through TRPV4 in response to osmotic stimulation. [41] The movement of water molecules, mainly using AQP4, is well understood and illustrated in Fig: 4.

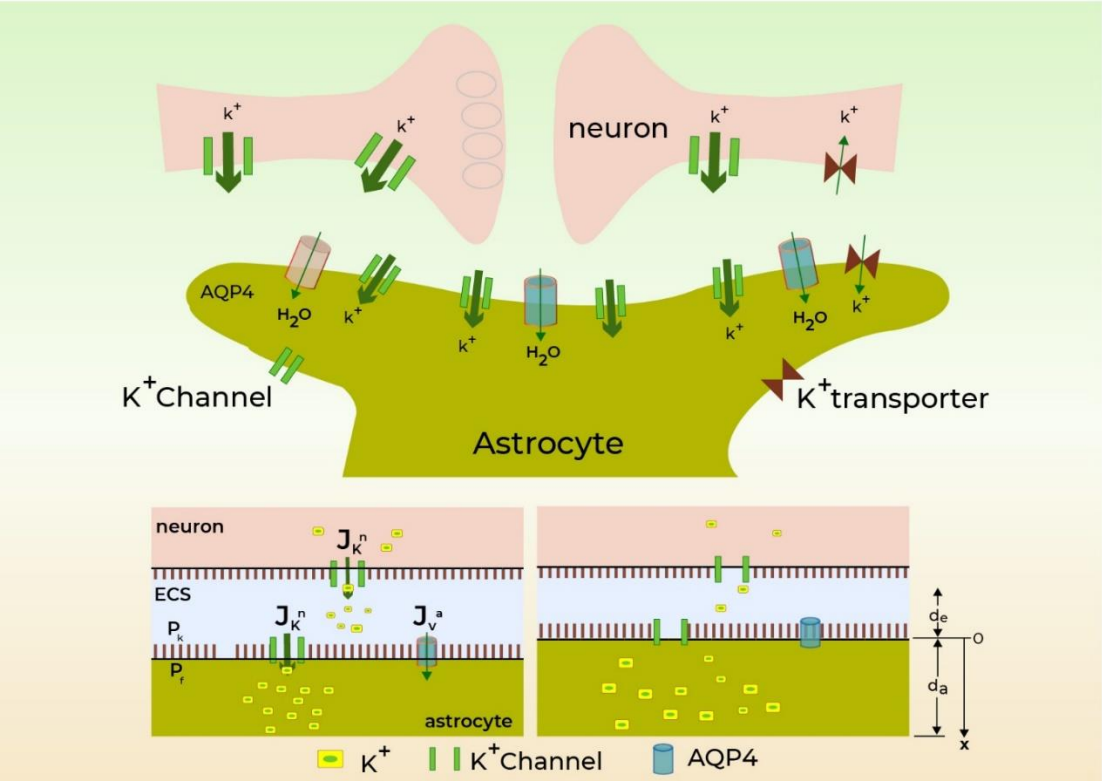


Fig. 4 Movement of K^+ ions and water molecule between astrocyte and neurons using AQP4 channels.

Additionally, it resulted in the removal of the solution from the brain tissue and its transfer into the para venous spaces due to neuroinflammation. It triggers the activation of astrocyte calcium signaling via TRPV4 in response to osmotic stimulation. [18] Moreover, result was corroborated by in vivo tests, and astrocytes from wild-type mice moved quicker than those from AQP4 knockout animals. [42–45] It was demonstrated that AQP4 facilitates the movement of astrocytes, which in turn contributes to the creation of glial scars. Furthermore, AQP4 also regulates brain excitability in epilepsy. [46-48] Binder et al. showed that the time delay of generalized seizures was considerably shorter in normal mice compared to animals with AQP4 deletion. [49] Subsequently, this research team investigated the mechanism and found that in mice lacking AQP4, the duration of seizures was prolonged due to a deceleration in potassium kinetics. [50] Mice that did not have α-syntrophin had comparable effects in terms of extending the clearance of potassium ions. [28] Nevertheless, the involvement of AQP4 in potassium ion regulation is a subject of debate, since Haj-Yasein et al. found no impact on potassium ion restoration following synaptic stimulation when AQP4 was deleted. [48] In addition to potassium ions, AQP4 null mice have also been reported to have reduced calcium

ion bursts in astrocytes initiated by hypo-osmotic stress, suggesting that AQP4 is involved in calcium signaling [8]. Furthermore, AQP4 has the ability to impact synaptic plasticity. [51] Skukas and colleagues have shown that the lack of AQP4 specifically hinders neurotrophin-dependent synaptic plasticity. [9] Consistently, research conducted by other organizations also demonstrates that AQP4 plays a crucial role in preserving the proper consolidation of long-term memories that rely on the hippocampus. It achieves this by facilitating the integration of new neurons into spatial memory networks. [51] Furthermore, it is hypothesized that AQP4 facilitates the process of neurogenesis. Hui's team demonstrated that the removal of AQP4 hinders the growth, viability, movement, and development of neural stem cells originating from the subventricular zone by disturbing the internal dynamics of calcium ions. [45] Their following experiment, utilizing a depression model, demonstrates that AQP4 is essential for the antidepressant properties of fluoxetine via regulating the generation of new neurons in the adult hippocampus. [11]

AQP4 TRANSLATIONAL CONTROL

Gene expression regulation is the first step in controlling AQP4 protein function. Application of microRNAs that target AQP4 is a growing area in AQP4 regulation. [52] Messenger RNAs (mRNAs) are selectively subjected to RNA sequences formed from majority introns that originate from within the organism itself known as microRNAs (miRNAs) for degradation or translation suppression. [53–55] Several recent studies have shown a connection between different miRNAs and AQP4, which might have important consequences for therapy. This information is summarized in Table 1. A notable rise in miR-224 levels was observed when the expression of the rat AQP4 (rAQP4) gene was reduced in living organisms and the expression of the mouse AQP4 (mAQP4) gene was reduced in a controlled environment. The expression of both miR-19a and miR-224, which target the same proteins, showed a substantial increase in response to the reduction of Cx43. [56] Indicating that these two miRNAs likely have important functions in regulating both astrocyte connectivity and water permeability. It has been determined that MiR-29b, previously identified as being downregulated in ischemic stroke, directly affects the expression of mAQP4. [57] In mice with ischemia, the increased expression of miR-29b was linked to a decrease in mAQP4 expression, as well as reductions in infarct volume, edema, and disruption of the blood-brain barrier (BBB). An excessive expression of miR-29b can lead to the development of cerebral edema in typical conditions. [58] The exposure to 1,2-Dichloroethane (1,2-DCE) resulted in abnormal overexpression of miR-29b, which subsequently led to a decrease in the levels of rAQP4 and mAQP4. This

exposure also promoted the development of cerebral edema in Sprague-Dawley rats and CD-1 mice. [58] Further evidence is presented to support the notion that miR-29b acts by selectively regulating the expression of AQP4. Using an in vitro model of ischemia called oxygen-glucose deprivation, we studied the effects on primary cultured rat astrocytes, miR-145, another miRNA linked to both AQP4 and ischemia, was discovered to lessen rAQP4-induced astrocyte injury. [59] MiR-320a is a miRNA of particular significance that has attracted attention in cerebral edema and glioblastoma. [60, 61] In vivo, miR-320a-targeted antibodies increased rAQP4 and rAQP1 expression while decreasing infarct volume; however, in the presence of cerebral edema, miR-320a expression was shown to downregulate rAQP4 and rAQP1 expression. [60] Although it appears to be advantageous to downregulate miR-320a expression in cerebral edema patients, Research has demonstrated that miR-320a can inhibit the invasion and migration of glioma cells by specifically targeting human AQP4 (hAQP4). [61] Blocking the function of hAQP4 with miR-320a reduces the invasion and migration of glioma cells in laboratory settings, which has implications for cell movement in living organisms. [61] Astrocytes depend on cell volume alterations as a crucial mechanism to adjust the size of the cell and facilitate its movement within the intracellular space.

Table 1- list of identified microRNAs (miRNAs) that affect the regulation of aquaporin-4, together with information about the species of AQP4 that each miRNA is associated with, the proteins that each miRNA targets, and its function in endogenous settings.

AQP4 Species	MicroRNA	Role	Effect	Reference
Mouse, Rat	miR-224/miR-19a	Astrocyte connectivity and water permeability	Downregulates AQP4 and Cx43	64
Rat	miRNA-145	The response to reduced blood flow, mitigates damage to astrocytes caused by AQP4.	Downregulates AQP4	59
Human, Rat	miRNA-130a	The reaction to decreased blood flow helps to alleviate the harm to astrocytes induced by AQP4.	Downregulates AQP4 M1	62
Rat	miRNA-130b	Ischemia-induced reaction that reduces the damage caused by AQP4-induced insult to astrocytes.	Downregulates AQP4	55

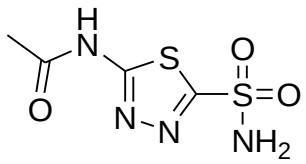
Mouse, Human, Rat	miRNA-320a	Enhances the size of the damaged area in cerebral edema caused by reduced blood flow, hinders the invasion and movement of glioma cells	Downregulates AQP4 and AQP1	60, 61
Mouse	miR-29b	The response to ischemia results in a decrease in the size of the infarct, as well as a reduction in edema and disruption of the blood-brain barrier.	Downregulates AQP4	57, 58

Similar to miR-320a, it has been demonstrated that targeting the use of miR-130a in conjunction with anti-miR-130a antibodies reduces the size of the edema in rats following cerebral ischemia. [54] While miR-320a controls both isoforms of AQP4, it is interesting to note that miR-130a has been shown to specifically regulate the M1 isoform of both rAQP4 and hAQP4 by targeting their promoter regions, enabling specialized control of AQP4 M1. [62] Upregulation of miR-130b was found to protect against cerebral ischemia damage (CII), demonstrating that miR -130b has a protective effect in ischemic situations. [63] Despite the fact that many of these studies indicate that miRNAs have the capacity to control the regulation of AQP4 in the future, more research is necessary to learn what problems artificially upregulating or downregulating miRNAs can bring about.

The function of the AQP4 channel in cerebral edema

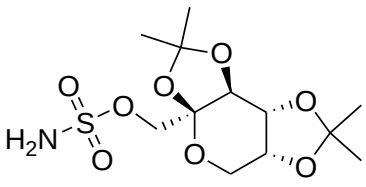
Cerebral edema is a medical condition characterized by the enlargement of brain tissue due to an elevation in the amount of water in the brain. This can occur as a result of trauma, tumor, ischemia, or inflammation. Cerebral edema occurs as a result of elevated intracranial pressure and impaired cerebral blood flow. Cerebral edema is categorized into two types: cytotoxic edema and vasogenic edema. Cytotoxic edema occurs when the sodium and potassium pump in the cell membrane malfunctions, causing water to move from the space between cells to the inside of the cells. Osmotic shifts cause cells to take in more water, which leads to swelling. [65] Conversely, vasogenic edema arises from the disturbance of the integrity of the blood-brain barrier (BBB), resulting in the breakdown of the tight junctions between vascular endothelial cells. This resulted in the infiltration of fluid and protein from blood vessels into the gaps between cells, leading to an increase in the size of the brain's extracellular compartment. [66]

The findings from many animal models investigating the role of AQP4 in brain edema etiology indicate that AQP4 aids in the removal of vasogenic brain edema in situations where fluid buildup occurs in the space outside of cells. The study of AQP4-knockout mice yielded valuable information on the systems involved in water transportation during the formation of cerebral edema. [67] Studies have demonstrated that removing AQP4 hampers the absorption of water by cells and decreases the amount of water in the brain. This, in turn, leads to a reduction in the magnitude of brain damage caused by lack of blood flow, the volume of lesions, and the values of intracranial pressure in cases of sudden restriction of blood supply to the brain. [16] hydro intoxication [17] and traumatic brain harm or injury. On the other hand, in central nervous system (CNS) disorders such brain tumors, cold brain damage, and prolonged ischemia, edema occurs due to the escape of isosmolar fluid across a faulty blood-brain barrier (BBB) into the extracellular space of the brain. This results in vasogenic edema. Deleting AQP4 in these mice led to a deterioration of cerebral edema and increased intracranial pressure. [18] A research demonstrated the involvement of an AQP4-dependent mechanism in the removal of excessive water in the brain during vasogenic edema. [19] Vincent j. Huber and colleagues identified aryl sulfonamides as an AQP4 inhibitor, and among them, acetazolamide was found to be the most effective drug. [68]

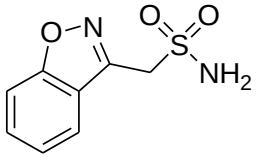


acetazolamide

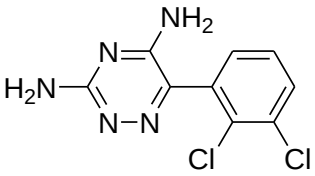
In addition, some antiepileptic drugs such as topiramate, zonisamide and lamotrigine are also effective in inhibiting aquaporin-4. [65]



Topiramate



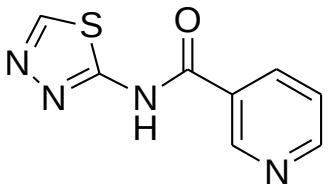
Zonisamide



Lamotrigine

TGN-020 is a new inhibitor of AQP4, namely 2-Nicotinamide-1, 3, 4-Thiadiazole., that significantly reduces the size of cerebral edema linked to ischemic injury. Since inflammation

is a major inducer of AQP4, therefore any drug that can suppress the inflammatory response can be used as an AQP4 inhibitor. AMD3100 (plerixafor), a CXCR4 antagonist medication, effectively inhibits the inflammatory response and mitigates blood-brain barrier (BBB) disruption in cases of stroke. [69]



2-Nicotinamide 1,3,4-Thiadiazole

Goreisan, a Japanese herbal medicine that inhibits the upregulation of aquaporin The mixture comprises Alisma rhizome, Atractylodes rhizome, Cinnamon rhizome, and Cinnamon bark. Hayashi described the impact of Goreisan on cerebral edema exacerbated by the central nervous system. [70] Goreisan therapy appears to lower brain water content and AQP4 expression following cerebral ischemia and appears to alleviate motor dysfunction after cerebral ischemia. [71] It also appears that goreisan may be used as a new adjunctive therapy to improve brain function after the ischemic stroke. [70]

ROLE OF AQP4 CHANNEL FOR SCHEMIC STROKE

Ischemic stroke, a complicated and severe neurological condition, is a major contributor to global mortality. [72] All this leads to swelling of the brain and the subsequent rise in intracranial pressure, which can result in further deterioration of the patient's condition. Mortality and severe disability are greater in patients with stroke-induced brain edema. [73] To reduce all these disabilities and serious complications, the main focus of research has been shifted towards modulating the manifestation of AQP4. PKC Pathway has been observed to downregulate AQP4 by thrombin. Activation of PKC has been demonstrated to enhance phosphorylation of AQP4, resulting in a reduction in water permeability. [32] Earlier, hydrogen sulfide (H_2S) has been known as a neural regulatory factor and gaseous mediator [33] and is considered as a neuroprotective agent using various methods in vivo and in vitro in an animal model [34, 35]. The main mechanism involves exogenous hydrogen sulfide inhibiting swelling around pyramidal neurons, as well as inhibiting ischemia-induced nuclear shrinkage. [36] 5-*p*-hydroxyphenyl-1, 2-dithiol-3-thione and NaHS reduce stroke-induced vasogenic edema, and they maintain BBB integrity. [74]

ROLE OF AQP4 CHANNEL FOR SPINAL CORD INJURY

Spinal cord edema leads to the advancement of spinal cord damage. Administration of AQP4 inhibitors, such as TGN-020, and the NKCC1 antagonist, bumetanide, effectively decreased swelling and damage to the spinal cord. Spinal cord injury refers to the harm inflicted on any segment of the spinal cord, resulting in alterations in bodily functions located below the site of injury. [40] Acute spinal cord injury (SCI) often involves a sequential sequence of events, where the initial mechanical damage is followed by a number of secondary injuries. These secondary injuries encompass ischemia (reduced blood flow), electrolyte imbalance, edema (swelling), vascular abnormalities, and impaired energy metabolism. Progressive neuronal death is caused by ischemia arising from thrombosis and vasospasm, which also worsens various secondary damage. [75] It was observed that in the first phase of spinal cord injury there was an accumulation of water and the formation of spinal edema was associated with this. [42] Spinal cord AQP4 levels were increased after following chronic SCI, and its levels relates with spinal cord water levels and were also associated with spinal cord edema. [44] AQP4 has been discovered to have a crucial function in the pathogenic mechanisms that occur after a spinal cord injury. Treatment with TGN-020, an inhibitor of AQP4, effectively decreased focal cerebral ischemia caused by cerebral edema. [76] Bumetanide has also been reported to decrease cerebral edema following traumatic brain injury. [46] Therefore, co-administration of AQP4 and NKCC1 inhibitor would be beneficial in spinal cord injury. Blockade of AQP4 and NKCC1 by co-administration of bumetanide and TGN-020 provides protection against cerebral edema and loss of spinal cord tissue caused by spinal cord injury (SCI). [77, 78]

ROLE OF AQP4 CHANNEL IN MIGRAINE

Migraine is a chronic neurovascular disorder manifesting as a headache lasting between 4 and 72 hours, followed by symptoms of nausea and vomiting, and accompanied by sensitivity to light. [79] Approximately 25% of those who get migraines describe a temporary episode of neurological symptoms, referred to as an aura, that occurs with the headache. Migraine is a debilitating health condition that has significant impacts on both the individual suffering from it and society as a whole. Migraines predominantly impact around 15-25% of females and 6-8% of males. Manifesting as a headache lasting from 4 to 72 hours, followed by symptoms of nausea and vomiting, and accompanied by sensitivity to light. [80-81] Migraine is widely recognized as one of the most incapacitating long-term illnesses, and the financial impact of

migraine is significant. [82] Migraine is highly influenced by genetics and is likely inherited through several factors. [83] Patients with familial hemiplegic migraine (FHM), a rare autosomal dominant type of migraine with aura, have been shown to have mutations in three genes that encode nerve ion channels. [84] Nevertheless, FHM has not been successful in uncovering genetic abnormalities linked to common kinds of migraine, and the specific genes responsible for the condition have not yet been found. [85] The pathophysiological processes responsible for migraine are now not well comprehended. [86] A potential alteration in the blood-brain barrier during migraine episodes has recently been proposed. [87] Magnetic resonance imaging (MRI) revealed a notable disruption of the blood-brain barrier (BBB) limited to the cortex, along with preceding swelling of the cortical region, in a patient diagnosed with familial hemiplegic migraine (FHM). [88] Furthermore, the level of matrix metalloproteinase 9, an enzyme that relies on zinc and breaks down the blood-brain barrier, is notably elevated in individuals with migraines, both during the actual attacks and in the periods between them. [89] AQP4 gene polymorphisms have been hypothesized to Alter the frequency and symptomatic characteristics of migraine.

Various AQP4 inhibitors, such as acetazolamide and AEDs, have been found to be somewhat effective in preventing and treating migraines. [90] Topiramate, sodium valproate, and other antiepileptic drugs (AEDs) that have been shown to block AQP4 in laboratory tests have been licensed for clinical use in preventing migraines. However, these drugs do not seem to have any general pain-relieving characteristics. [91] Propranolol, a beta-receptor antagonist, has been found to be useful in preventing migraines. [92] Recent research has indicated that the process of triggering migraines involves not only the widening of blood vessels (vasodilation) but also a neurological aspect.

ROLE OF AQP4 CHANNEL IN MENINGITIS

Streptococcus pneumoniae is the predominant and very virulent causative agent of meningitis. The prevalence of pneumococcal meningitis is increasing, [93] and the presence of penicillin-resistant S. pneumoniae complicates therapy. [94] The significance of the upregulation of AQP4 expression in meningitis-induced brain edema remains uncertain, as studies using AQP4 inhibitors have demonstrated that AQP4 is the primary factor influencing water permeability across the blood-brain barrier (BBB). Despite receiving good therapy, the death rate for

pneumococcal meningitis is from 10% to 30%. Additionally, 30% to 50% of patients experience chronic neurological impairments. [95]

Brain edema is a significant consequence of bacterial meningitis that can result in increased pressure inside the skull, leading to brain ischemia, herniation, and death. [96] The molecular mechanism behind the process of excess fluid production and absorption in brain edema associated with meningitis is currently not well comprehended. There are two primary forms of cerebral edema, namely cytotoxic and vasogenic edema. [97] Cytotoxic edema, which is observed in ischemic stroke, is characterized by the swelling of astroglia cells. Vasogenic edema, which is observed in brain tumors, is characterized by the buildup of excessive fluid in the extracellular spaces of brain tissue due to a compromised blood-brain barrier. Both kinds of cerebral edema are believed to coexist in meningitis. [66] Different types of decreased pressure within the skull and increased storage of fluid in the brain, leading to improved neurological condition and increased chances of life. The presence of a pneumococcal infection resulted in a significant rise, specifically 7 times higher, in the expression of AQP4 protein in the brain. This increase in protein expression further enhanced the permeability of the blood-brain barrier, leading to the accumulation of excessive amounts of water in the brain. Studying experimentally whether the increase in AQP4 expression is crucial to meningitis-induced brain edema is feasible, as inhibitors of AQP4 data have demonstrated that AQP4 is the primary factor determining BBB water permeability. Approximately 80% of the surplus water in meningitis resulted in a much-improved outcome compared to mice with the normal genetic makeup. Additionally, there was a notable increase in activity in the brain of a human patient with brain swelling caused by acute bacterial meningitis, indicating that a similar process may take place in humans. Multiple data sources indicate that in cases of meningitis, there is an accumulation of extra brain water largely in the intracellular compartment. The presence of extensive astroglia foot process swelling and the decrease in macromolecular transport in brain extracellular spaces provide morphological and biophysical evidence, respectively, supporting this claim. [98] During meningitis, the astroglia loses its ability to control the balance of ions across the plasma membrane. This leads to the buildup of sodium, chloride, and water inside the cells, causing them to swell. Several factors found in the cerebrospinal fluid (CSF) of animals with acute bacterial meningitis have been suggested to hinder the cells' ability to regulate their ion balance. These factors include cytokines, free radicals, excitatory amino acids, interleukin-1beta, tumor necrosis factor-alpha, and hydrogen peroxide. [62]

Various findings suggests that AQP4 water permeability inhibitors are expected to decrease brain swelling in conditions such as meningitis, early stroke, hyponatremia, and other diseases characterized by cytotoxic edema. Due to the fact that the bulk of the excessive brain water in meningitis is caused by increased AQP4 expression, medications that prevent the up-regulation of AQP4 may be more effective than AQP4 channel blockers. Efficiently reducing cerebral edema in meningitis can be achieved by using inhibitors that up-regulate AQP4, without the possible negative effects associated with inhibiting AQP4 water permeability. [99]

ROLE OF AQP4 CHANNEL IN NEURO MYELITIS OPTICA (NMO)

Neuromyelitis Optica is a central nervous system (CNS) disease that result in the inflammation of the optical nerve and spinal cord. This disease is defined by detection of the auto antibody AQP4-IgG, which is an inflammatory marker that acts on AQP4 water channels present in the brain. This antibody is used to differentiate between multiple sclerosis and NMO. [100]

ROLE OF AQP4 CHANNEL IN EPILEPSY

Compelling evidence suggests that the glial water channel AQP-4 is crucial for the transportation of water in the brain. Aquaporin-4 (AQP4) is present in astrocytes and, in conjunction with the inward potassium (K+) channel Kir4.1, plays a crucial role in maintaining the balance of water and potassium ions (K+) during brain activity. Given the significant impact of osmolarity and K+ on the likelihood of experiencing seizures, AQP4 and its molecular counterparts might serve as promising targets for the treatment of seizures. Seizure length is much longer in transgenic mice that do not have AQP4. This is linked to alterations in the removal of extracellular K+ and the communication across gap junctions. Human epileptic tissue exhibits dysfunctional control and altered subcellular localization of AQP4, as well as disrupted K+ homeostasis. Further investigation is needed to determine the implications of these results on the development of epilepsy in the hippocampus and its relevance to human epilepsy.[101]

The restoration of water and potassium (K+) balance in epileptic tissue is a novel therapeutic notion. AQP4 likely participates in the exchange of water and ions between glial cells and neurons, as well as in the communication between glial cells and blood vessels across the blood-brain barrier. Consequently, AQP4 plays a vital role in both normal tissue metabolism and abnormal physiological states. Recent findings indicate that AQP4 may play a role in

osmo-sensing by working along with the vanilloid channel TRPV4 and Ca2+ signaling in astrocytes. [102] The significance of these discoveries in relation to epilepsy is presently being examined. Aquaporin-4 (AQP4) is present in astrocytes and, in conjunction with the inward potassium (K+) channel Kir4.1, plays a crucial role in maintaining the balance of water and potassium (K+) during brain activity. Given the significant impact of osmolarity and K+ levels on the likelihood of experiencing seizures, it is possible that AQP4 and its molecular counterparts might serve as innovative targets for the treatment of seizures. Seizure length is notably prolonged in transgenic mice that do not have AQP4. This is linked to alterations in the removal of extracellular K+ and the communication across gap junctions. Abnormal control of potassium (K+) levels and disrupted balance, together with changes in the distribution of AQP4 within cells, have been noted in epileptic tissue from humans. Further investigation is necessary to determine the implications of these results on the development of epilepsy in the hippocampus and its relevance to human epilepsy. The restoration of water and potassium (K+) balance in epileptic tissue is a novel therapeutic notion. AQP4 has a significant function: it is found in both astrocytes and astroglial processes that surround synapses. AQP4 is likely involved in the exchange of water and ions between glial cells and neurons, as well as in the interaction between glial cells and blood vessels through the blood-brain barrier. As a result, AQP4 plays a critical role in both normal tissue metabolism and in abnormal physiological conditions. Recent findings indicate that AQP4 may have a role in osmosensing by working along with the vanilloid channel TRPV4, as well as in Ca2+ signaling in astrocytes. The significance of these discoveries in relation to epilepsy is presently being examined. [103]

ROLE OF AQP4 CHANNEL IN ALZHEIMER DISEASE

Among the many forms of degenerative cognitive loss seen in the elderly, Alzheimer's disease (AD) stands out. Extensive research on the lymphatic system and AQP4 has shown a robust association between AQP4 and the main pathological features of Alzheimer's disease, including the abnormal accumulation of extracellular Aβ, the development of neurofibrillary tangles caused by tau protein buildup, and the impairment of synaptic function. All signs point to AQP4 dysfunction or abnormal distribution playing a role in AD development and progression. Throughout the process of examining the bodies of the deceased, Researchers found that AQP4 expression was higher in the brains of people with Alzheimer's disease and cerebral amyloid angiopathy (CAA) than in the brains of healthy persons. This indicates that AQP4 may be involved in the impairment of water transportation in AD and CAA [104]. Latest

multi-cohort profiling data demonstrate significantly higher AQP4 expression in CSF from AD patients compared to healthy controls. This indicates that AQP4 has the potential to be used as a biomarker to indicate the development of AD. [105]

The disparity between the clearance and synthesis of Aβ is widely acknowledged as one of the primary factors impacting synaptic function in individuals with AD. [106] Soluble amyloid-beta (Aβ) undergoes a transformation into insoluble Aβ plaques, resulting in the buildup of Aβ. [107] Amyloid-beta (Aβ) plaques impair synaptic function, which is considered a crucial link and initiating component in the progression of Alzheimer's disease (AD). [77-78] Previously, it was believed that the elimination of Aβ mostly depended on active transport across the blood-brain barrier (BBB) due to the absence of a conventional lymphatic system in the brain. [108] The glymphatic system is an alternative pathway by which the brain tissue eliminates Aβ without relying on blood vessels. [109] Animal studies have demonstrated that the lack of AQP4 in APP/PS1 mice, which are used as a model for Alzheimer's disease, leads to an increase in the accumulation of Aβ and a decrease in synaptic proteins. As a result, this worsens cognitive impairment. Furthermore, mice missing AQP4 exhibited a 55% decrease in the rate at which Aβ is removed. This reduction can be primarily attributed to a significant 70% decline in the clearance of Aβ through the glymphatic system inside the interstitial space. [110] During a postmortem study of the human brain, it was shown that the distribution of AQP4 immunoreactivity closely matched that of neuroinflammatory Aβ plaques. There is a significant link between AQP4 and the accumulation of Aβ. [111] Multiple studies have indicated that the disturbance of AQP4 localization is a critical factor in the buildup of Aβ in Alzheimer's disease (AD). According to Zeppenfeld's study, [82] the presence and spread of AQP4 are connected to the extent of brain aging. An elevated level of AQP4 expression may be considered an indication of brain aging. This rise in expression may be a response to the rise in Aβ metabolism, serving as a compensatory mechanism. The abnormal localization of AQP4 in Alzheimer's dementia (AD) may have a significant impact on the incorrect accumulation of Aβ. However, it is also believed that the depolarization of AQP4 is caused by the aggregation of insoluble Aβ. [112] Therefore, the precise characteristics of the interaction between AQP4 and Aβ are still a topic of discussion. [113] In addition, the absence of AQP4 reduces the production of low-density lipoprotein receptor-related protein-1 (LRP1), which is responsible for facilitating the removal of Aβ. [85-88] A recent study utilized two-photon in vivo imaging to examine vasculature by employing sulforhodamine 101 (SR101). The study found that mice treated with the AQP4 inhibitor TGN-020 had a considerably higher amount of perivascular

Aβ deposition compared to the control group. This provides conclusive proof that suppressing the activity of AQP4 can decrease the outflow of Aβ through blood vessels. [114]

Vascular dementia

Cerebrovascular disorders are a significant contributor to cognitive impairment. Statistics indicate that vascular cognitive impairment (VCI) is the second leading cause of dementia cases, after only Alzheimer's disease (AD). There is empirical data indicating a link between Alzheimer's disease (AD) and vascular cognitive impairment (VCI). [115] VCI is a prevalent disorder among individuals with sporadic AD. Research has indicated that individuals with Vascular Cognitive Impairment (VCI) should be specifically focused on for the purpose of preventing dementia, hospitalization, and mortality, since the occurrence of these events is notably higher in patients with VCI. VCI encompasses a broad spectrum of cognitive impairment, ranging from moderate vascular cognitive impairment to the more severe condition known as vascular dementia (VaD). [116] All types of cognitive impairment linked to cerebrovascular illness should be encompassed. Stroke, which includes both ischemic stroke and hemorrhagic stroke, is well recognized as a significant contributor to Vascular Cognitive Impairment (VCI). Numerous comprehensive research has extensively examined the involvement of AQP4 in stroke. [117] The expression of AQP4 is upregulated during cerebral ischemia. Several studies have demonstrated that the absence of AQP4 can enhance prognosis and neurological function, decrease the volume of tissue damage caused by reduced blood flow, increase the pace at which neurons survive, and prevent programmed cell death and inflammation following a lack of blood supply to the brain. Aquaporin-4 (AQP4) plays a role in safeguarding the blood-brain barrier (BBB) in cases of intracerebral hemorrhage, employing many methods. A recent study shown that mice lacking the AQP4 gene exhibit increased hematoma areas and more severe blood-brain barrier (BBB) damage in a newly developed model of hematoma growth. [118]

The investigation of the molecular mechanism of VCI has been limited for a significant period due to the challenge of developing a single animal model. Recent research on VCI have emphasized the presence of both moderate and severe vascular injury, which leads to a decrease in blood flow to the brain. [119] Prolonged inadequate blood flow results in alterations in the configuration and connectivity of brain tissue, ultimately causing the deterioration of secondary areas, mostly affecting the integrity of white matter. The multiple micro infarct (MMI) model

is now an extensively utilized model for vascular cognitive impairment (VCI). The MMI model is capable of more accurately replicating the pathogenic features of human VCI, leading to notable cognitive decline. Venkat [96] observed evident axonal and white matter injury, reduced AQP4 expression around blood vessels, and impaired glymphatic function in the MMI model. The researchers treated mice with MMI using human umbilical cord blood cells (HUCBCs) and showed that HUCBCs may enhance the production of serum microRNA-126 (miR-126) and perivascular AQP4. This treatment also reversed the delayed clearing of the glymphatic system. [120] Peng Yu [98] demonstrated that MMI has the ability to decrease cerebral blood flow and suppress the production of miR-126 in mice. MiR-126 is a microRNA involved in angiogenesis, which is the formation of new blood vessels. It plays a role in regulating vascular function and indirectly influences the activity of AQP4, a protein involved in water transport in the brain. miR-126 knockout mice exhibited more damage to AQP4 and the glymphatic system compared to control mice, leading to more pronounced white matter injury and neuroinflammation.

Sudduth's team created a new version of VCI that incorporates neuroinflammation, cognitive impairment, and BBB degradation. [121] An apparent reduction in DP71 protein expression was noted in mice with diet-induced hyperhomocysteinemia (HHcy). DP71 protein is responsible for anchoring two important potassium channels, Kir4.1 and MaxiK, as well as AQP4, in the footpad membrane. This anchoring function helps maintain the balance of ions and osmotic pressure. In addition, they also showed AQP4 displacement and fragmentation of astrocyte end-feet in mice with high homocysteine levels (HHcy). The cognitive function further deteriorated in conjunction with the previously reported astrocytic alterations. Based on the provided facts, it is probable that astrocyte end feet play a crucial role in the process of VCI. [122]

In other cognitive disorders

Parkinson's disease dementia (PDD) and Lewy body dementia (LBD) are two types of neurodegenerative illnesses that have different clinical symptoms and pathological changes. These individuals exhibit a high presence of α-synuclein Lewy bodies in both the cortex and subcortex, as well as β-amyloid plaques and tau lesions similar to those found in Alzheimer's disease. A growing number of specialists maintain the idea that these two disorders are separate stages of the same clinical process. [100-102] Currently, the precise method by which the pathogen causes disease has not yet been fully understood. A function for AQP4 has been found

in PD, involving heightened activation of microglia, which generates cytotoxic substances such nitric oxide (NO), tumor necrosis factor-α, and interleukin-1, resulting in neuronal demise. The results showed that in a PD model, the inflammatory response of microglia in the AQP4 knockout group was much higher than that in the AQP4 wild-type control group, leading to more severe neuronal damage. [123] The absence of AQP4 may also trigger the release of inflammatory cytokines, leading to further damage to neurons. The presence and arrangement of AQP4 and AQP1 may influence the accumulation of α-synuclein in the cerebral cortex of individuals with cerebral palsy (CP). Additional investigation is necessary to understand the functioning of AQP4 in LBD. [104]

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder characterized by rapid cognitive deterioration and other abnormalities in the central nervous system (CNS). Pathological changes include elevated neuronal hydration, enlarged neurons, and the development of vacuoles in nerve fibers. Studies have shown that both human and animal prion diseases have elevated levels of AQP4 and AQP1. This finding helps to explain why neurons have an abnormality in maintaining water balance. [105,106] An elevation in AQP4 levels can be seen as a mechanism by which neurons safeguard themselves during a situation of water-ion imbalance. [124]

Frontotemporal dementia (FTD) is the term used to describe dementia that occurs as a result of deterioration in the frontotemporal lobe. FTLD-tau is distinguished by the atypical accumulation of tau protein, resulting in the formation of inclusion bodies. [108] The buildup of tau protein causes a disruption in the balance of neuronal excitability. [109] As previously stated, AQP4 has a distinct function in removing tau protein. Nevertheless, the specific role of AQP4 in the pathogenic mechanism of FTD or FTLD remains uncertain. [125]

Patients with hyperthyroidism have also been shown to experience dementia, however the specific mechanism behind this has not yet been determined. [126] Thyroid hormones are widely recognized for their role in controlling the expression of aquaporins. The expression of AQP4 is controlled by triiodothyronine (T3) during the process of growth. [127] Research has demonstrated that T3 has the ability to suppress the production of AQP4 in a model of brain infarction, leading to a decrease in cerebral edema. [128, 129] The study of hyperthyroidism-induced dementia is still in its early stages, and thyroid hormones might be a promising initial approach to controlling the expression of aquaporin in the central nervous system. [130]

The effects of AQP4 on neuropathologies

Since multiple studies have linked AQP4 with various disorders, particularly those affecting the neurological system, interest in AQP4 has grown. [131-134] The majority of these investigations used in vitro experiments, post-mortem brain tissue measurements, or AQP4 defective mice. According to previous descriptions, normal AQP4 is typically polarised; however, under neuropathological circumstances, AQP4 expression and localization are changed. [135] In order to cope with the excess fluid, AQP4 is upregulated in cases of hydrocephalus and reabsorbs some of it. [136] However, it is yet unknown whether AQP4 hastens or slows down this disease. [131] Studies using mutant mice revealed that this pathology progressed more quickly, [132] whereas the overexpression of AQP4 has been suggested to be involved in the initial development of hydrocephalus. [131] Potential treatment methods for AQP4 regulation include increasing CSF clearance in advanced stages or lowering water transport in the locations where CSF is produced at the onset of the disease. Clinical trials for drugs that modulate AQP4 function are still being conducted for the treatment of hydrocephalus. [132] Additionally, AQP4 has been linked to neuromyelitis optica, an autoimmune condition in which it functions as the target antigen. Preclinical research on AQP4-blocking antibodies is ongoing, and eculizumab, a complement inhibitor, is under clinical testing. A new treatment approach to address this problem may involve blocking AQP4, which is highly expressed at the location of tissue damage in ischemic stroke. None of the known therapies for this condition address the acute oedema consequence. The effects of the AQP4 inhibitor TGN020 have been investigated in an ischemic rat stroke model. [137] In conclusion, AQP4 is a water channel that is an intriguing prospective pharmaceutical target because changes in its expression are connected to a number of diseases. The complex has significant limitations as a therapeutic target because of its poor druggability, despite the description of certain promising AQP modulators. [138]

Table 2- AQP4's expression, consequences and processes in different cognitive diseases.

Cognitive disorders	Expression of AQP4	Effects and mechanisms of AQP4
AD	Depolarization/increased expression [139-141]	1. Decreased Aβ excretion and Aβ plaque deposition [142] 2. Decreased tau excretion

		and deposition [143] 3. Protection of reactive glial net construction to prevent damage caused by unaggregated Aβ [144, 145] 4. Increased glutamate transporter-1 expression to clear glutamate [146] 5. Regulation of sleep quality [147, 148]
iNPH	Depolarization/decreased expression [149, 149]	1. Decreased Aβ excretion and plaque deposition [150] 2. Association with inflammation and intracranial compliance [151, 152] 3. Restoration of glymphatic system dysfunction [153]
VCI	Depolarization/decreased expression [154]	1. Reduced axonal and white matter damage and neuroinflammation [155, 156] 2. Prevention of glymphatic system damage[157] 3.Possibly decreased deposition of Aβ and tau[158]
PDD	Decreased expression [159]	1. Inhibition of inflammatory cytokine release 2. Effect on α-synuclein deposition [160]
CJD	Increased expression	Regulation of water and ion imbalance [161]
Hyperthyroidism	Decreased expression [162]	Downstream pathway of T3 [163]

AQP4: aquaporin-4; AD: Alzheimer's disease; VCI: vascular cognitive impairment; iNPH: idiopathic normal-pressure hydrocephalus; PDD: Parkinson's disease dementia; FTD:

frontotemporal dementia; CJD: Creutzfeldt-Jakob disease; T3: L-triiodothyronine; Aβ: amyloid-β.

CONCLUSION

The cerebral vasculature and the blood-brain barrier (BBB) play crucial roles in allowing significant amounts of water to enter when the BBB is compromised. The neurovascular compartment, which includes blood arteries, neurons, and astrocytes, plays a crucial role in regulating the movement of water. AQP4, found in astrocytes, plays a crucial role in maintaining the balance of water in the brain. The review has highlighted the significance of AQPs in astrocytes and their potential involvement in the development of edema. The development of novel, targeted pharmaceuticals to inhibit water channels is of great therapeutic significance and is necessary to enhance our comprehension of the mechanisms behind the regulatory functions of AQPs. This will benefit individuals suffering from chronic illnesses. Aquaporin4 is essential for the production of edema in many pathological conditions. Interfering with Aquaporin4 might potentially lead to the creation of effective pharmacological therapies for edema formation following brain damage, as well as aid in the recovery during the acute phase of cerebral edema. The data collected over the past decade provide evidence for the involvement of aquaporins in the central nervous system (CNS), both in normal physiological settings and in abnormal ones such as brain edema. Therefore, it can be inferred that inhibiting AQP4 is a new and promising method for lowering cerebral edema. This strategy shows potential for creating a distinct group of drugs that may effectively treat brain ischemia in a clinical setting. The efficacy of AQP4 inhibitors has been investigated in several brain illnesses including migraine, cerebral edema, meningitis, ischemia, stroke, and spinal cord injury. Several pharmacological families, including as antiepileptics, some herbal medicines, amides, and valproates, were discovered to serve as inhibitors of AQP4. These medications target the same location on AQP4 but employ distinct mechanisms. Despite several completed tests and ongoing research, further studies are required to fully investigate this specific spot. It would be advantageous and aid in the treatment of several central nervous system illnesses. An extensive examination of AQP4 is expected to yield novel perspectives on therapeutic approaches for cognitive disorders.

REFERENCES

1. Laird MD, Sukumari-Ramesh S, Swift AEB, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? J Neurochem 2010; 113:637– 648.
2. Lin MS, Lee YH, Chiu WT, Hung KS. Curcumin provides neuroprotection after spinal cord injury. J Surg Res 2010 Aug 5 [Epub ahead of print].
3. Zador Z, Bloch O, Yao X, Manley GT. Aquaporins: role in cerebral edema and brain water balance. Prog Brain Res 2007; 161:185–194.
4. Kim JH, Lee YW, Park KA, Lee WT, Lee JE. Agmatine attenuates brain edema through reducing the expression of aquaporin-1 after cerebral ischemia. J Cereb Blood Flow Metab 2010; 30:943–949.
5. Filippidis AS, Kalani MY, Rekate HL. Hydrocephalus and aquaporins: lessons learned from the bench. Childs Nerv Syst 2010 Jul 13 [Epub ahead of print].
6. Benarroch EE. Neuron-astrocyte interactions: partnership for normal function and disease in the central nervous system. Mayo Clinic Proceedings 2005; 80:1326 –1338.
7. Nag S, Manias J, Stewart D. Pathology and new players in the pathogenesis of brain edema. Acta Neuropathological 2009;118: 197–217
8. Seifert G, Schilling K, Steinhäuser C. Astrocyte dysfunction in neurological disorders: a molecular perspective. Nat Rev Neurosci 2006; 7:194 –206.
9. Verkman AS. More than just water channels: unexpected cellular roles of aquaporins. J Cell Sci. 2005; 118:3225–3232. [PubMed: 16079275].
10. Hara-Chikuma M, Verkman AS. Physiological roles of glycerol-transporting aquaporins: the aquaglyceroporins. Cell Mol Life Sci. 2006; 63:1386–1392. [PubMed: 16715408]
11. Saadoun S, Papadopoulos MC, Hara-Chikuma M, Verkman AS. Impairment of angiogenesis and cell migration by targeted aquaporin-1 gene disruption. Nature. 2005a; 434:786–792. [PubMed: 15815633]
12. Saadoun S, Papadopoulos MC, Watanabe H, Yan D, Manley GT, Verkman AS. Involvement of aquaporin-4 in astroglial cell migration and glial scar formation. J Cell Sci. 2005b; 118:591–598.
13. Oshio K, Watanabe H, Yan D, Verkman AS, Manley GT. Impaired pain sensation in mice lacking aquaporin-1 water channels. Biochem Biophys Res Commun. 2006; 341:1022–1028. [PubMed: 16476579]

14. Binder DK, Yao X, Zador Z, Sick TJ, Verkman AS, Manley GT. Increased seizure duration and slowed potassium kinetics in mice lacking aquaporin-4 water channels. Glia. 2006; 53:631–636. [PubMed: 16470808]
15. Padmawar P, Yao X, Bloch O, Manley GT, Verkman AS. K+ waves in brain cortex visualized using a long-wavelength K+-sensing fluorescent indicator. Nat Methods. 2005; 2:825–827. [PubMed: 16278651]
16. Rash JE, Yasumura T, Hudson CS, Agre P, Nielsen S. Direct immunogold labeling of aquaporin-4 in square arrays of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. Proc Natl Acad Sci U S A. 1998; 95:11981–11986. [PubMed: 9751776]
17. Badaut J, Lasbennes F, Magistretti J. Pierre, Regli L. Aquaporin in brain: Distribution, physiology, and pathophysiology. Journal of cerebral Blood flow and metabolism.2002;22(4):168
18. Wolburg H, Wolburg-Buchholz k, Fallier-Becker P. structure and function of aquaporin-4-based orthogonal arrays of particles. Int rev Cell Mol Biol.2011;287(1):1-41
19. Nakhjavani, Maryam & Hardingham, Jennifer &Palethorpe, Helen & Tomita, Yoko & Smith, Eric & Price, Timothy & Townsend, Amanda. (2019). Ginsenoside Rg3: Potential Molecular Targets and Therapeutic Indication in Metastatic Breast Cancer. Medicines. 6. 17. 10.3390/medicines601001
20. Agre P.Molecular physiology of water transport, aquaporin nomenclature workshop. Biol cells.1997;89:255-257.
21. Jung J.S., Bhat R.V., Preston G.M., Guggino W.B., Baraban J.M., Agre P. Proc Natl acad sci.1994;(91):255-257
22. Agre P, King S.S, Yasui M, Guggino W.B., Otterson O.P., Fujiyoshi Y, Engel A, Nielson S.J, Frigeri A, Gropper M.A, Umenishi F. Localisation of MIWC and GLIP water channel homologs in neuromuscular, epithelial and glandular tissues. J cells sci.1995; 108:2993-002
23. Sulyok E, Vajda Z, Doczi T, Nielsen S. Acta neurochir.2004;146:955-960
24. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP. Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci. 1997; 17:171–180. [PubMed: 8987746]

25. Connors NC, Kofuji P. Dystrophin Dp71 is critical for the clustered localization of potassium channels in retinal glial cells. J Neurosci. 2002; 22:4321–4327. [PubMed: 12040037]
26. Nagelhus EA, Mathiisen TM, Ottersen OP. Aquaporin-4 in the central nervous system: cellular and subcellular distribution and coexpression with KIR4.1. Neuroscience. 2004; 129:905–913. [PubMed: 15561407]
27. Bloch O, Auguste KI, Manley GT, Verkman AS. Accelerated progression of kaolin-induced hydrocephalus in aquaporin-4-deficient mice. J Cereb Blood Flow Metab. 2006; 26:1527–1537. [PubMed: 16552421]
28. Manley G.T., Binder D.K., Papadopoulos M.C., Verkman. A.S. Neurosciences.2004;146:955-960
29. Jung J.S., Bhat R.V., Preston G.M., Guggino W.B., Barban J, M., Agre P. Molecular characterization of an aquaporin cDNA from brain, candidate osmoregulatory and regulator of water balance. Proc Natl Acad sci.1994; 91:13052-13056
30. Venero J.L., Vizzutti M.L., Ilunan A.A., Machado A, Echevarria M, Canoj Detailed localization of aquaporin 4 messenger RNA in the CNS, Preferential expression in periventricular organs. Neuroscience.1999;94:239-250
31. Bonomini Francesca and Rita Rezzani, Aquaporin and Blood Brain Barrier, Curr. Neuropharmacol. 2010 Jun; 8(2): 92–96.
32. Papadopoulos MC, Manley GT, Krishna S, Verkman AS. Aquaporin-4 facilitates reabsorption of excess fluid in vasogenic brain edema. FASEB J. 2004; 18:1291–1293. [PubMed: 15208268]
33. Huber V.J., Tsujita M., Kwee I.L., Nakada T. Inhibition of aquaporin 4 by antiepileptics drugs. Bioorg. Med. Chem.2009; 17:418-424
34. Gunnarson E, Song y, Kowalewski J.M. Brismar H, Brines m, Cerami A, Andersson U, Zelenina M, Aperia A. Erythropoietin modulation of astrocyte water permeability as a component of neuroprotection. Proc Natl Acad sci. 2009; 106:1602-1607
35. Igarashi H, Huber V.J., Tsujita M, Nakada T. Pretreatment with novel aquaporin 4 inhibitor, TGN-020 significantly reduces ischemia cerebral edema. Neuroli.2011;32:113-116
36. Huang J, Li Y, Tang Y, Tang G, Yang G.Y., Wang Y. CXCR4 antagonist AMD3100 protects blood brain barrier integrity and reduces infactory response after focal ischemia in mice. Stroke.2013;44:190-197

37. Hayashi A. Effectiveness of goreisan for eliminating brain edema due to intracranial malignant brain tumors. KAIM.2010;5:10-16
38. Isohama Y. Risuizai Goreisan no sayo mekanizum. Kampo Igaku.2005;29:213-215
39. Mitsuhashi T, Nagase M, Arai H. Efficacy of goreisan for asymptomatic bilateral and unilateral cheonic subdural hematoma. Tradit Kampo Med.2016; 3:28-32
40. Isohama Y. Aquaporin modification, a new molecular mechanism to concern. J pharm soc.2006; 126:70-73
41. Verkman A.S., Papadopoulos C. Marios. Potential utility of aquaporin modulator for therapy of brain disorder.PMC.2013;2019
42. Papadopoulos M.C., Verkman A.S. Aquaporin 4 and neuromyletis optica. Lancet Neurol.2012; 1:535-544
43. Thrane, A.S.; Rappold, P.M.; Fujita, T.; Torres, A.; Bekar, L.K.; Takano, T.; Peng, W.; Wang, F.; Rangroo Thrane, V.; Enger, R.; et al. Critical role of aquaporin-4 (AQP4) in astrocyte Ca^{2+} signaling events elicited by cerebral edema. *Proc. Natl. Acad. Sci. USA* 2011, *108*, 846–851. [Google Scholar] [CrossRef] [PubMed]
44. Skucas, V.A.; Mathews, I.B.; Yang, J.; Cheng, Q.; Treister, A.; Duffy, A.M.; Verkman, A.S.; Hempstead, B.L.; Wood, M.A.; Binder, D.K.; et al. Impairment of select forms of spatial memory and neurotrophin-dependent synaptic plasticity by deletion of glial aquaporin-4. *J. Neurosci.* 2011, *31*, 6392–6397. [Google Scholar] [CrossRef] [PubMed]
45. Kong, H.; Sha, L.L.; Fan, Y.; Xiao, M.; Ding, J.H.; Wu, J.; Hu, G. Requirement of AQP4 for antidepressive efficiency of fluoxetine: Implication in adult hippocampal neurogenesis. *Neuropsychopharmacology* 2009, *34*, 1263–1276. [Google Scholar] [CrossRef] [PubMed]
46. Binder, D.K.; Nagelhus, E.A.; Ottersen, O.P. Aquaporin-4 and epilepsy. *Glia* 2012, *60*, 1203–1214. [Google Scholar] [CrossRef] [PubMed]
47. Binder, D.K.; Oshio, K.; Ma, T.; Verkman, A.S.; Manley, G.T. Increased seizure threshold in mice lacking aquaporin-4 water channels. *Neuroreport* 2004, *15*, 259–262. [Google Scholar] [CrossRef] [PubMed]
48. Haj-Yasein, N.N.; Bugge, C.E.; Jensen, V.; Østby, I.; Ottersen, O.P.; Hvalby, Ø.; Nagelhus, E.A. Deletion of aquaporin-4 increases extracellular K (+) concentration during synaptic stimulation in mouse hippocampus. *Brain Struct. Funct.* 2015, *220*, 2469–2474. [Google Scholar] [CrossRef] [PubMed]

49. Scharfman, H.E.; Binder, D.K. Aquaporin-4 water channels and synaptic plasticity in the hippocampus. *Neurochem. Int.* 2013, *63*, 702–711. [Google Scholar] [CrossRef] [PubMed]
50. Fan, Y.; Liu, M.; Wu, X.; Wang, F.; Ding, J.; Chen, J.; Hu, G. Aquaporin-4 promotes memory consolidation in Morris's water maze. *Brain Struct. Funct.* 2013, *218*, 39–50. [Google Scholar] [CrossRef] [PubMed]
51. Kong, H.; Fan, Y.; Xie, J.; Ding, J.; Sha, L.; Shi, X.; Sun, X.; Hu, G. AQP4 knockout impairs proliferation, migration and neuronal differentiation of adult neural stem cells. *J. Cell Sci.* 2008, *121*, 4029–4036. [Google Scholar] [CrossRef] [PubMed]
52. Zador Z, Stiver S, Wang V, Manley GT. Role of aquaporin-4 in cerebral edema and stroke. Aquaporins. 2009:159-70.
53. Tang G, Yang GY. Aquaporin-4: A potential therapeutic target for cerebral edema. International journal of molecular sciences. 2016 Sep 29;17(10):1413.
54. Sorby-Adams AJ, Marcoionni AM, Dempsey ER, Woenig JA, Turner RJ. The role of neurogenic inflammation in blood-brain barrier disruption and development of cerebral oedema following acute central nervous system (CNS) injury. International journal of molecular sciences. 2017 Aug 17;18(8):1788.
55. Huber VJ, Tsujita M, Yamazaki M, Sakimura K, Nakada T. Identification of arylsulfonamides as Aquaporin 4 inhibitors. Bioorg Med Chem Lett. 2007 Mar 1;17(5):1270-3
56. Chu H, Ding H, Tang Y, Dong Q. Erythropoietin protects against hemorrhagic blood–brain barrier disruption through the effects of aquaporin-4. Laboratory investigation. 2014 Sep;94(9):1042-53.
57. Nakamura Y, Suzuki Y, Tsujita M, Huber VJ, Yamada K, Nakada T. Development of a novel ligand,[11C] TGN-020, for aquaporin 4 positron emission tomography imaging. ACS chemical neuroscience. 2011 Oct 19;2(10):568-71.
58. Das S, Mishra KP, Chanda S, Ganju L, Singh SB. CXCR7: A key neuroprotective molecule against alarmin HMGB1 mediated CNS pathophysiology and subsequent memory impairment. Brain, Behavior, and Immunity. 2019 Nov 1; 82:319-37.
59. Yano Y, Yano H, Takahashi H, Yoshimoto K, Tsuda S, Fujiyama K, Izumo-Shimizu Y, Motoie R, Ito M, Tanaka J, Ishii E, Fukuda M. Goreisan Inhibits Upregulation of Aquaporin 4 and Formation of Cerebral Edema in the Rat Model of Juvenile Hypoxic-Ischemic Encephalopathy. Evid Based Complement Alternat Med. 2017; 2017:3209219. Doi: 10.1155/2017/3209219.

60. Goto S, Kato K, Yamamoto T, Shimato S, Ohshima T, Nishizawa T. Effectiveness of Goreisan in Preventing Recurrence of Chronic Subdural Hematoma. Asian J Neurosurg. 2018 Apr-Jun;13(2):370-374.
61. Li Y, Zhong W, Jiang Z, Tang X. New progress in the approaches for blood–brain barrier protection in acute ischemic stroke. Brain research bulletin. 2019 Jan 1; 144:46-57.
62. Papadopoulos MC, Verkman AS. Potential utility of aquaporin modulators for therapy of brain disorders. Prog Brain Res. 2008; 170:589-601. Doi: 10.1016/S0079-6123(08)00446-9.
63. Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. Nat Rev Neurol. 2010 Jul;6(7):383-92.
64. Duan T, Tradtrantip L, Phuan PW, Bennett JL, Verkman AS. Affinity-matured 'aquaporumab' anti-aquaporin-4 antibody for therapy of seropositive neuromyelitis optica spectrum disorders. Neuropharmacology. 2020 Jan 1; 162:107827.
65. Zhang S, He WB, Chen NH. Causes of death among persons who survive an acute ischemic stroke. Curr Neurol Neurosci Rep. 2014 Aug;14(8):467.
66. Dietrich W, Erbguth F. Hirndruck und Hirnödem [Increased intracranial pressure and brain edema]. Med Klin Intensivmed Notfmed. 2013 Mar;108(2):157-69; quiz 170-1. German. doi: 10.1007/s00063-013-0232-4. Epub 2013 Mar 17.
67. Hubbard JA, Hsu MS, Seldin MM, Binder DK. Expression of the Astrocyte Water Channel Aquaporin-4 in the Mouse Brain. ASN Neuro. 2015 Oct 21;7(5):1759091415605486.
68. Asgari N, Owens T, Frøkiaer J, Stenager E, Lillevang ST, Kyvik KO. Neuromyelitis optica (NMO)–an autoimmune disease of the central nervous system (CNS). Acta Neurologica Scandinavica. 2011 Jun;123(6):369-84.
69. Huberfeld G, Blauwblomme T, Miles R. Hippocampus and epilepsy: Findings from human tissues. Revue neurologique. 2015 Mar 1;171(3):236-51.
70. Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP, Amiry-Moghaddam M. 2011. **An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes**. *Proc Natl Acad Sci U S A* 108: **2563**– 2568.
71. Selkoe DJ, Lansbury PJ. Alzheimer's disease is the most common neurodegenerative disorder. Basic Neurochemistry: molecular, cellular and medical aspects. 1999; 6:101-2.

72. Bergström S, Remnestål J, Yousef J, Olofsson J, Markaki I, Carvalho S, Corvol JC, Kultima K, Kilander L, Löwenmark M, Ingelsson M. Multi-cohort profiling reveals elevated CSF levels of brain-enriched proteins in Alzheimer's disease. Annals of clinical and translational neurology. 2021 Jul;8(7):1456-70.
73. Li Y, Zhang J, Wan J, Liu A, Sun J. Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: A potential therapeutic molecule for Alzheimer's disease. Biomedicine & Pharmacotherapy. 2020 Dec 1; 132:110887.
74. Attems J, Jellinger KA (2014). The overlap between vascular disease and Alzheimer's disease--lessons from pathology. *BMC Med*, 12:206. [PMC free article] [PubMed] [Google Scholar]
75. Moftakhar P, Lynch MD, Pomakian JL, Vinters HV (2010). Aquaporin expression in the brains of patients with or without cerebral amyloid angiopathy. *J Neuropathol Exp Neurol*, 69:1201-1209. [PMC free article] [PubMed] [Google Scholar]
76. Bergstrom S, Remnestal J, Yousef J, Olofsson J, Markaki I, Carvalho S, et al. (2021). Multi-cohort profiling reveals elevated CSF levels of brain-enriched proteins in Alzheimer's disease. *Ann Clin Transl Neurol*, 8:1456-1470. [PMC free article] [PubMed] [Google Scholar]
77. Ferreira ST, Klein WL (2011). The Abeta oligomer hypothesis for synapse failure and memory loss in Alzheimer's disease. *Neurobiol Learn Mem*, 96:529-543. [PMC free article] [PubMed] [Google Scholar]
78. Gallina P, Scollato A, Conti R, Di Lorenzo N, Porfirio B (2015). Abeta Clearance, "hub" of Multiple Deficiencies Leading to Alzheimer Disease. *Front Aging Neurosci*, 7:200. [PMC free article] [PubMed] [Google Scholar]
79. Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Frangione B, et al. (2000). Clearance of Alzheimer's amyloid-ss (1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. *J Clin Invest*, 106:1489-1499. [PMC free article] [PubMed] [Google Scholar]
80. Silva I, Silva J, Ferreira R, Trigo D (2021). Glymphatic system, AQP4, and their implications in Alzheimer's disease. *Neurol Res Pract*, 3:5. [PMC free article] [PubMed] [Google Scholar]
81. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. (2012). A Para vascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med*, 4:147ra111. [PMC free article] [PubMed] [Google Scholar]

82. Zeppenfeld DM, Simon M, Haswell JD, D'Abreo D, Murchison C, Quinn JF, et al. (2017). Association of Perivascular Localization of Aquaporin-4 With Cognition and Alzheimer Disease in Aging Brains. *JAMA Neurol*, 74:91-99. [PubMed] [Google Scholar]
83. Smith AJ, Duan T, Verkman AS (2019). Aquaporin-4 reduces neuropathology in a mouse model of Alzheimer's disease by remodeling peri-plaque astrocyte structure. *Acta Neuropathol Commun*, 7:74. [PMC free article] [PubMed] [Google Scholar]
84. Hoshi A, Yamamoto T, Shimizu K, Ugawa Y, Nishizawa M, Takahashi H, et al. (2012). Characteristics of aquaporin expression surrounding senile plaques and cerebral amyloid angiopathy in Alzheimer disease. *J Neuropathol Exp Neurol*, 71:750-759. [PubMed] [Google Scholar]
85. Querfurth HW, LaFerla FM (2010). Alzheimer's disease. *N Engl J Med*, 362:329-344. [PubMed] [Google Scholar]
86. Guenette SY (2003). Astrocytes: a cellular player in Abeta clearance and degradation. *Trends Mol Med*, 9:279-280. [PubMed] [Google Scholar]
87. Xu Z, Xiao N, Chen Y, Huang H, Marshall C, Gao J, et al. (2015). Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Abeta accumulation and memory deficits. *Mol Neurodegener*, 10:58. [PMC free article] [PubMed] [Google Scholar]
88. Yang W, Wu Q, Yuan C, Gao J, Xiao M, Gu M, et al. (2012). Aquaporin-4 mediates astrocyte response to beta-amyloid. *Mol Cell Neurosci*, 49:406-414. [PubMed] [Google Scholar]
89. Rosu GC, Catalin B, Balseanu TA, Laurentiu M, Claudiu M, Kumar-Singh S, et al. (2020). Inhibition of Aquaporin 4 Decreases Amyloid Abeta40 Drainage Around Cerebral Vessels. *Mol Neurobiol*, 57:4720-4734.
90. O'Brien JT, Thomas A (2015). Vascular dementia. *Lancet*, 386:1698-1706. [PubMed] [Google Scholar]
91. Dichgans M, Leys D (2017). Vascular Cognitive Impairment. *Circ Res*, 120:573-591. [PubMed] [Google Scholar]
92. Chu H, Ding H, Tang Y, Dong Q (2014). Erythropoietin protects against hemorrhagic blood-brain barrier disruption through the effects of aquaporin-4. *Lab Invest*, 94:1042-1053. [PubMed] [Google Scholar]

93. Chu H, Xiang J, Wu P, Su J, Ding H, Tang Y, et al. (2014). The role of aquaporin 4 in apoptosis after intracerebral hemorrhage. *J Neuroinflammation*, 11:184. [PMC free article] [PubMed] [Google Scholar]
94. Chu H, Yang X, Huang C, Gao Z, Tang Y, Dong Q (2017). Apelin-13 Protects against Ischemic Blood-Brain Barrier Damage through the Effects of Aquaporin-4. *Cerebrovasc Dis*, 44:10-25. [PubMed] [Google Scholar]
95. Chu H, Gao Z, Huang C, Dong J, Tang Y, Dong Q (2020). Relationship Between Hematoma Expansion Induced by Hypertension and Hyperglycemia and Blood-brain Barrier Disruption in Mice and Its Possible Mechanism: Role of Aquaporin-4 and Connexin43. *Neurosci Bull*, 36:1369-1380. [PMC free article] [PubMed] [Google Scholar]
96. Venkat P, Chopp M, Zacharek A, Cui C, Zhang L, Li Q, et al. (2017). White matter damage and glymphatic dysfunction in a model of vascular dementia in rats with no prior vascular pathologies. *Neurobiol Aging*, 50:96-106. [PMC free article] [PubMed] [Google Scholar]
97. Venkat P, Culmone L, Chopp M, Landschoot-Ward J, Wang F, Zacharek A, et al. (2020). HUCBC Treatment Improves Cognitive Outcome in Rats With Vascular Dementia. *Front Aging Neurosci*, 12:258. [PMC free article] [PubMed] [Google Scholar]
98. Yu P, Venkat P, Chopp M, Zacharek A, Shen Y, Ning R, et al. (2019). Role of microRNA-126 in vascular cognitive impairment in mice. *J Cereb Blood Flow Metab*, 39:2497-2511. [PMC free article] [PubMed] [Google Scholar]
99. Sudduth TL, Weekman EM, Price BR, Gooch JL, Woolums A, Norris CM, et al. (2017). Time-course of glial changes in the hyperhomocysteinemia model of vascular cognitive impairment and dementia (VCID). *Neuroscience*, 341:42-51. [PMC free article] [PubMed] [Google Scholar]
100. Jellinger KA (2018). Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)*, 125:615-650. [PubMed] [Google Scholar]
101. Jellinger KA, Korczyn AD (2018). Is dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Med*, 16:34. [PMC free article] [PubMed] [Google Scholar]
102. Sezgin M, Bilgic B, Tinaz S, Emre M (2019). Parkinson's Disease Dementia and Lewy Body Disease. *Semin Neurol*, 39:274-282. [PubMed] [Google Scholar]

103. Tamtaji OR, Behnam M, Pourattar MA, Jafarpour H, Asemi Z (2019). Aquaporin 4: A key player in Parkinson's disease. *J Cell Physiol*, 234:21471-21478. [PubMed] [Google Scholar]

104. Xue X, Zhang W, Zhu J, Chen X, Zhou S, Xu Z, et al. (2019). Aquaporin-4 deficiency reduces TGF-beta1 in mouse midbrains and exacerbates pathology in experimental Parkinson's disease. *J Cell Mol Med*, 23:2568-2582. [PMC free article] [PubMed] [Google Scholar]

105. Rodriguez A, Perez-Gracia E, Espinosa JC, Pumarola M, Torres JM, Ferrer I (2006). Increased expression of water channel aquaporin 1 and aquaporin 4 in Creutzfeldt-Jakob disease and in bovine spongiform encephalopathy-infected bovine-PrP transgenic mice. *Acta Neuropathol*, 112:573-585. [PubMed] [Google Scholar]

106. Sadashima S, Honda H, Suzuki SO, Shijo M, Aishima S, Kai K, et al. (2020). Accumulation of Astrocytic Aquaporin 4 and Aquaporin 1 in Prion Protein Plaques. *J Neuropathol Exp Neurol*, 79:419-429. [PubMed] [Google Scholar]

107. Assentoft M, Larsen BR, MacAulay N (2015). Regulation and Function of AQP4 in the Central Nervous System. *Neurochem Res*, 40:2615-2627. [PubMed] [Google Scholar]

108. Lin LC, Nana AL, Hepker M, Hwang JL, Gaus SE, Spina S, et al. (2019). Preferential tau aggregation in von Economo neurons and fork cells in frontotemporal lobar degeneration with specific MAPT variants. *Acta Neuropathol Commun*, 7:159. [PMC free article] [PubMed] [Google Scholar]

109. Sohn PD, Huang CT, Yan R, Fan L, Tracy TE, Camargo CM, et al. (2019). Pathogenic Tau Impairs Axon Initial Segment Plasticity and Excitability Homeostasis. *Neuron*, 104:458-470 e455. [PMC free article] [PubMed] [Google Scholar]

110. Cooper DS, Samuels MH (2020). Hyperthyroidism and Dementia. *Thyroid*, 30:648-650. [PubMed] [Google Scholar]

111. Costa LES, Clementino-Neto J, Mendes CB, Franzon NH, Costa EO, Moura-Neto V, et al. (2019). Evidence of Aquaporin 4 Regulation by Thyroid Hormone During Mouse Brain Development and in Cultured Human Glioblastoma Multiforme Cells. *Front Neurosci*, 13:317. [PMC free article] [PubMed] [Google Scholar]

112. Sadana P, Coughlin L, Burke J, Woods R, Mdzinarishvili A (2015). Anti-edema action of thyroid hormone in MCAO model of ischemic brain stroke: Possible

association with AQP4 modulation. *J Neurol Sci*, 354:37-45. [PubMed] [Google Scholar]

113. Gomes, A.; da Silva, I.V.; Rodrigues, C.M.P.; Castro, R.E.; Soveral, G. The Emerging Role of microRNAs in Aquaporin Regulation. Front. Chem. 2018, 6, 238.

114. Bushati, N.; Cohen, S.M. microRNA Functions. Annu. Rev. Cell Dev. Biol. 2007, 23, 175–205.

115. Cai, X.; Hagedorn, C.H.; Cullen, B.R. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. RNA 2004, 10, 1957–1966.

116. Kim, Y.-K.; Kim, V.N. Processing of intronic microRNAs. EMBO J. 2007, 26, 775–783. 48. Jullienne, A.; Fukuda, A.M.; Ichkova, A.; Nishiyama, N.; Aussudre, J.; Obenaus, A.; Badaut, J. Modulating the water channel AQP4 alters miRNA expression, astrocyte connectivity and water diffusion in the rodent brain. Sci. Rep. 2018, 8, 4186.

117. Wang, Y.; Huang, J.; Ma, Y.; Tang, G.; Liu, Y.; Chen, X.; Zhang, Z.; Zeng, L.; Wang, Y.; Ouyang, Y.-B.; et al. MicroRNA-29b is a therapeutic target in cerebral ischemia associated with aquaporin 4. J. Cereb. Blood Flow Metab. 2015, 35, 1977–1984.

118. Zhong, Y.; Liang, B.; Hu, M.; Liu, J.; Lin, L.; Jiang, J.; Lin, X.; Huang, Y.; Lu, L.; Jiang, L.; et al. MicroRNA-29b-3p aggravates 1,2-dichloroethane-induced brain edema by targeting aquaporin 4 in Sprague-Dawley rats and CD-1 mice. Toxicol. Lett. 2020, 319, 160–167.

119. Zheng, L.; Cheng, W.; Wang, X.; Yang, Z.; Zhou, X.; Pan, C. Overexpression of MicroRNA-145 Ameliorates Astrocyte Injury by Targeting Aquaporin 4 in Cerebral Ischemic Stroke. Biomed. Res. Int. 2017, 2017, doi:10.1155/2017/9530951.

120. Sepramaniam, S.; Armugam, A.; Lim, K.Y.; Karolina, D.S.; Swaminathan, P.; Tan, J.R.; Jeyaseelan, K. MicroRNA 320a Functions as a Novel Endogenous Modulator of Aquaporins 1 and 4 as Well as a Potential Therapeutic Target in Cerebral Ischemia. J. Biol. Chem. 2010, 285, 29223–29230.

121. Xiong, W.; Ran, J.; Jiang, R.; Guo, P.; Shi, X.; Li, H.; Lv, X.; Li, J.; Chen, D. miRNA-320a inhibits glioma cell invasion and migration by directly targeting aquaporin 4. Oncol. Rep. 2018, 39, 1939–1947.

122. Sepramaniam, S.; Ying, L.K.; Armugam, A.; Wintour, E.M.; Jeyaseelan, K. MicroRNA-130a Represses Transcriptional Activity of Aquaporin 4 M1 Promoter. J. Biol. Chem. 2012, 287, 12006–12015.

123. Jullienne, A.; Fukuda, A.M.; Ichkova, A.; Nishiyama, N.; Aussudre, J.; Obenaus, A.; Badaut, J. Modulating the water channel AQP4 alters miRNA expression, astrocyte connectivity and water diffusion in the rodent brain. Sci. Rep. 2018, 8, 4186.

124. Wang, Y.; Huang, J.; Ma, Y.; Tang, G.; Liu, Y.; Chen, X.; Zhang, Z.; Zeng, L.; Wang, Y.; Ouyang, Y.-B.; et al. MicroRNA-29b is a therapeutic target in cerebral ischemia associated with aquaporin 4. J. Cereb. Blood Flow Metab. 2015, 35, 1977–1984.

125. Zhong, Y.; Liang, B.; Hu, M.; Liu, J.; Lin, L.; Jiang, J.; Lin, X.; Huang, Y.; Lu, L.; Jiang, L.; et al. MicroRNA-29b-3p aggravates 1,2-dichloroethane-induced brain edema by targeting aquaporin 4 in Sprague-Dawley rats and CD-1 mice. Toxicol. Lett. 2020, 319, 160–167.

126. Zheng, L.; Cheng, W.; Wang, X.; Yang, Z.; Zhou, X.; Pan, C. Overexpression of MicroRNA-145 Ameliorates Astrocyte Injury by Targeting Aquaporin 4 in Cerebral Ischemic Stroke. Biomed. Res. Int. 2017, 2017, doi:10.1155/2017/9530951.

127. Sepramaniam, S.; Armugam, A.; Lim, K.Y.; Karolina, D.S.; Swaminathan, P.; Tan, J.R.; Jeyaseelan, K. MicroRNA 320a Functions as a Novel Endogenous Modulator of Aquaporins 1 and 4 as Well as a Potential Therapeutic Target in Cerebral Ischemia. J. Biol. Chem. 2010, 285, 29223–29230.

128. Xiong, W.; Ran, J.; Jiang, R.; Guo, P.; Shi, X.; Li, H.; Lv, X.; Li, J.; Chen, D. miRNA-320a inhibits glioma cell invasion and migration by directly targeting aquaporin 4. Oncol. Rep. 2018, 39, 1939–1947.

129. Sepramaniam, S.; Ying, L.K.; Armugam, A.; Wintour, E.M.; Jeyaseelan, K. MicroRNA-130a Represses Transcriptional Activity of Aquaporin 4 M1 Promoter. J. Biol. Chem. 2012, 287, 12006–12015.

130. Zheng, Y.; Wang, L.; Chen, M.; Pei, A.; Xie, L.; Zhu, S. Upregulation of miR-130b protects against cerebral ischemic injury by targeting water channel protein aquaporin 4 (AQP4). Am. J. Transl. Res. 2017, 9, 3452– 3461

131. Mader, S., & Brimberg, L. (2019). Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. Cells, 8(2), 90 Available at: https:// doi.org/10.3390%2Fcells8020090.

132. Desai B, Hsu Y, Schneller B, Hobbs JG, Mehta AI, Linninger A. Hydrocephalus: the role of cerebral aquaporin-4 channels and computational modeling considerations of cerebrospinal fluid. Neurosurgical Focus. September 2016; 41(3): E8. Available at: https://doi. org/10.3171%2F2016.7. focus16191

133. Zhao, Z. A., Li, P., Ye, S. Y., Ning, Y. L., Wang, H., Peng, Y., et al. (2017). Perivascular AQP4 dysregulation in the hippocampal CA1 area after traumatic brain injury is alleviated by adenosine A2A receptor inactivation. Science Reports, 7, 2254 Available at: https://doi.org/10.1038/s41598-017- 02505-6.

134. Aoki, K., Uchihara, T., Tsuchiya, K., Nakamura, A., Ikeda, K., & Wakayama, Y. (2003). Enhanced expression of aquaporin 4 in human brain with infarction. Acta Neuropathologica, 106, 121–124 Available at: https://doi.org/10.1007/ s00401-005-1052-2.

135. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid b [Internet]. 2012. Available at: https://doi.org/10.1126/scitranslmed.3003748.

136. Skjolding, A. D., Rowland, I. J., Søgaard, L. V., Praetorius, J., Penkowa, M., & Juhler, M. (2010). Hydrocephalus induces dynamic spatiotemporal regulation of aquaporin-4 expression in the rat brain. Cerebrospinal Fluid Research, 7, 20 Available at: https://doi.org/10.1186/1743-8454-7-20.

137. Pirici I, Balsanu T, Bogdan C, Margaritescu C, Divan T, Vitalie V, et al. Inhibition of Aquaporin-4 Improves the Outcome of Ischaemic Stroke and Modulates Brain Paravascular Drainage Pathways. International Journal of Molecular Sciences. December 2017; 19(1):46. Available at: https://doi.org/1 0.3390%2Fijms19010046

138. Verkman, A. S., Anderson, M. O., & Papadopoulos, M. C. (2014). Aquaporins: Important but elusive drug targets. Nature Reviews Drug Discovery [Internet]., 13(4), 259–277 Available at: https://doi.org/10.1038%2Fnrd4226.

139. Moftakhar P, Lynch MD, Pomakian JL, Vinters HV (2010). Aquaporin expression in the brains of patients with or without cerebral amyloid angiopathy. *J Neuropathol Exp Neurol*, 69:1201-1209.

140. Zeppenfeld DM, Simon M, Haswell JD, D'Abreo D, Murchison C, Quinn JF, et al. (2017). Association of Perivascular Localization of Aquaporin-4 With Cognition and Alzheimer Disease in Aging Brains. *JAMA Neurol*, 74:91-99.

141. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, et al. (2014). Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci*, 34:16180-16193.

142. Mader S, Brimberg L (2019). Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. *Cells*, 8.

143. Harrison IF, Ismail O, Machhada A, Colgan N, Ohene Y, Nahavandi P, et al. (2020). Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain*, 143:2576-2593.

144. Smith AJ, Duan T, Verkman AS (2019). Aquaporin-4 reduces neuropathology in a mouse model of Alzheimer's disease by remodeling peri-plaque astrocyte structure. *Acta Neuropathol Commun*, 7:74.

145. Huang Y, Happonen KE, Burrola PG, O'Connor C, Hah N, Huang L, et al. (2021). Microglia use TAM receptors to detect and engulf amyloid beta plaques. *Nat Immunol*, 22:586-594.

146. Soni N, Reddy BV, Kumar P (2014). GLT-1 transporter: an effective pharmacological target for various neurological disorders. *Pharmacol Biochem Behav*, 127:70-81.

147. Ulv Larsen SM, Landolt HP, Berger W, Nedergaard M, Knudsen GM, Holst SC (2020). Haplotype of the astrocytic water channel AQP4 is associated with slow wave energy regulation in human NREM sleep. *PLoS Biol*, 18: e3000623.

148. Rainey-Smith SR, Mazzucchelli GN, Villemagne VL, Brown BM, Porter T, Weinborn M, et al. (2018). Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Abeta-amyloid burden. *Transl Psychiatry*, 8:47.

149. Gavrilov GV, Stanishevskiy AV, Gaydar BV, Paramonova NM, Gaykova ON, Svistov DV (2019). Pathological changes in human brain biopsies from patients with idiopathic normal pressure hydrocephalus. *Zh Nevrol Psikhiatr Im S S Korsakova*, 119:50-54.

150. Hasan-Olive MM, Enger R, Hansson HA, Nagelhus EA, Eide PK (2019). Pathological mitochondria in neurons and perivascular astrocytic endfeet of idiopathic normal pressure hydrocephalus patients. *Fluids Barriers CNS*, 16:39.

151. Reeves BC, Karimy JK, Kundishora AJ, Mestre H, Cerci HM, Matouk C, et al. (2020). Glymphatic System Impairment in Alzheimer's Disease and Idiopathic Normal Pressure Hydrocephalus. *Trends Mol Med*, 26:285-295.

152. Plog BA, Lou N, Pierre CA, Cove A, Kenney HM, Hitomi E, et al. (2019). When the air hits your brain: decreased arterial pulsatility after craniectomy leading to impaired glymphatic flow. *J Neurosurg*: 1-14.

153. Eide PK, Hansson HA (2018). Astrogliosis and impaired aquaporin-4 and dystrophin systems in idiopathic normal pressure hydrocephalus. *Neuropathol Appl Neurobiol*, 44:474-490.

154. Yokota H, Vijayasarathi A, Cekic M, Hirata Y, Linetsky M, Ho M, et al. (2019). Diagnostic Performance of Glymphatic System Evaluation Using Diffusion Tensor Imaging in Idiopathic Normal Pressure Hydrocephalus and Mimickers. *Curr Gerontol Geriatr Res*, 2019:5675014.

155. Chu H, Huang C, Ding H, Dong J, Gao Z, Yang X, et al. (2016). Aquaporin-4 and Cerebrovascular Diseases. *Int J Mol Sci*, 17.

156. Ouyang F, Jiang Z, Chen X, Chen Y, Wei J, Xing S, et al. (2021). Is Cerebral Amyloid-beta Deposition Related to Post-stroke Cognitive Impairment? *Transl Stroke Res*.

157. Tamtaji OR, Behnam M, Pourattar MA, Jafarpour H, Asemi Z (2019). Aquaporin 4: A key player in Parkinson's disease. *J Cell Physiol*, 234:21471-21478.

158. Xue X, Zhang W, Zhu J, Chen X, Zhou S, Xu Z, et al. (2019). Aquaporin-4 deficiency reduces TGF-beta1 in mouse midbrains and exacerbates pathology in experimental Parkinson's disease. *J Cell Mol Med*, 23:2568-2582.

159. Sadana P, Coughlin L, Burke J, Woods R, Mdzinarishvili A (2015). Anti-edema action of thyroid hormone in MCAO model of ischemic brain stroke: Possible association with AQP4 modulation. *J Neurol Sci*, 354:37-45.

160. Nagelhus EA, Ottersen OP (2013). Physiological roles of aquaporin-4 in brain. *Physiol Rev*, 93:1543-1562.

161. Assentoft M, Larsen BR, MacAulay N (2015). Regulation and Function of AQP4 in the Central Nervous System. *Neurochem Res*, 40:2615-2627.

162. Sadashima S, Honda H, Suzuki SO, Shijo M, Aishima S, Kai K, et al. (2020). Accumulation of Astrocytic Aquaporin 4 and Aquaporin 1 in Prion Protein Plaques. *J Neuropathol Exp Neurol*, 79:419-429.

163. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. (2009). Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*, 326:1005-1007.