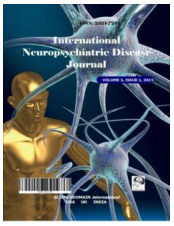

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The Aquaporins: Regulator for Brain Pathophysiology

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Authors' contributions

Author NK, designed the study, managed the literature search and wrote the first draft of the manuscript with assistance from author NK. Author DP edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Water transport is a fundamental process contributing to human physiology and pathophysiology. Water is primarily needed for all cell types but the water does not sit in the cells it moves through in very organized way. This process of movement is occurring through aquaporins. Aquaporins (AQPs) are expressed in tissues in which edema and fluid imbalances are of major concern. Three major water-channel proteins (AQP1, AQP4, AQP9) are expressed in brain. Potential roles of AQPs in brain are water homeostasis, edema, angiogenesis, cell migration and development. Beside their physiological expression patterns in the brain, AQPs are abnormally expressed in some pathological conditions e.g. cancer, neuroinflammatory diseases and neurodegenerative diseases, in which preservation of brain homeostasis is at risk. In mammalian brain, AQP4 water channels are localised in astroglial cells at the blood-brain-barrier interface; AQP1 channels are expressed in choroid plexus and serve in cerebral spinal fluid secretion. Some of glial cells and neurons also show the expression of AQPs though the function is still not known. These aquaporins being integral membrane proteins have an important role in various neurodegenerative diseases, thereby signifying their therapeutic importance. Furthermore the enhanced expression of AQP4 increases the water permeability of blood vessels which could be an important aspect for understanding the ill effects of hypoxia. Research in this field has significantly in last few years, and the review focuses on functional roles of AQPs in brain related to physiology and pathophysiology.

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1. INTRODUCTION

Water is the most essential molecule for life. Because of its distinct physical properties, living organisms depend upon it to survive. The neutral pH and nature make it a universal solvent for many of the solutes that life depends upon, such as essential ions and sugars that supply energy. Although living organisms are largely dependent on water to survive, water is not readily accessible to all parts of organisms. Fortunately, cell membranes are having the proteins called aquaporins (AQPs) that help water pass through cell membranes and help organisms carry out life's processes. AQPs are integral membrane proteins that enable the movement of water and other small solutes across biological membranes [1]. The aquaporin channel family was initially considered as a family of water channels; however it is now clear that some of these channels are also permeable to small solutes such as glycerol, urea and monocarboxylates.

Water is quantitatively the major component of all the organisms that maintain high water flux through plasma membranes [2]. Water crosses cell membranes mainly by two routes either by diffusion through the lipid bilayer or through water channels, aquaporins [3].

1.1 Aquaporins Family

Aquaporin-1 from human red blood cells was the first to be discovered and is probably the best studied [4]. There are, at present, thirteen (AQP 0-12) known members [5] of the mammalian aquaporin gene family. These genes encode for proteins which function as membrane channels, for water alone (AQP0, 1, 2, 4, 5, 6, 8, 10), or for water plus small molecules, mostly glycerol and urea (AQP 3, 7, 9) [6-10]. Not much information is available about the function of the two latest members discovered, AQP-11 and AQP-12 (Table 1). With continuing research on aquaporins, the repertoire now includes permeabilities in some subtypes of aquaporins to a variety of substrates including gasses [11-13] and ions [14,15]. AQP11 and AQP12 are the most distantly related paralogs [16]. They share only 20% homology with AQP family members, belong to an AQP subfamily with divergent Asparagine-Proline-Alanine (NPA) boxes [17], and may constitute a third functionally distinct evolutionary branch of this channel protein superfamily [18,16,19]. These proteins exhibit their ubiquitous nature thus demonstrating their central role in maintaining normal physiology of all organisms. Aquaporins are distributed widely throughout the body but notably in the kidney, brain astrocytes, red blood cells, lung and secretary epithelia such as the salivary glands [16,20].

1.2 Structure and Functions of Aquaporins

The aquaporins are small (≈30kDa), hydrophobic, intrinsic membrane proteins that exhibit a common structure of six membrane spanning alpha helical domains with intracellular carboxyl (C) and amino (N) termini, three extracellular loops A, C and E and intracellular loops B and D of variable length (Fig. 1). Monomer sizes of the mammalian aquaporins range from 26 to 34 kDa. They contain a consensus motif Asn-Pro-Ala (NPA), implied in pore formation1. All AQPs form tetramers with each monomer functioning as an independent pore [21].

The primary amino acid sequence analysis shows a strong similarity between the two halves of the molecule, indicating a probable evolutionary intergenic duplication that gave rise to the current gene structure. A highly conserved three amino acid motif, Aspargine-Proline-Alanine (NPA) is present in the B and E loops of nearly all AQPs. Three-dimensional structural analyses have deduced that the NPA motifs, although located in the non-membrane spanning helices are inserted into the membrane. The intracellular loop B and extracellular loop E fold into the membrane and interact with one another, forming what has come to be known as the “hour-glass model”, characterized by wide external openings to the channel with a narrow central constriction where the NPA motifs interact, forming the functional water pore. Mercurial sensitivity is conferred by a cysteine residue in the extracellular loop E (residue 189), which is situated close to the pore. Although each individual AQP is a functional water pore, they assemble in groups of four identical protein channels (tetramers) in the membranes. Movement of water through each pore can be bidirectional, though the actual direction of water flow in a physiological system is determined by the osmotic gradient or bulk absorption of solutes [22].

Although most of the aquaporins discovered in humans were found in the kidneys, the expressions of these proteins in other organs are expected to equally important. Aquaporins can be used to treat some human medical disorders, such as brain edema after stroke and dry eye syndrome. One of the causes of brain edema is by the swelling of damage tissue in the brain after a stroke. The swelling can be a result of an excess accumulation of water in the intracellular or extracellular spaces of the brain. Dry eye syndrome can be caused by the inability of the lacrimal gland to produce the tears needed to aid in eye lubrication. Further study of aquaporins may help scientists discover ways to increase or decrease the flow of water through the protein and help treat these disorders [23-27].

2. Role of Aquaporins in Brain Physiology and Pathophysiology in Rodents

Recent studies have demonstrated the presence of different types of AQPs especially in rodent brain. Currently, seven AQP subtypes (AQP1, AQP3, AQP4, AQP5, AQP8, AQP9 and AQP12) have been described in brain cells of the rodents [28]. However, only three aquaporins have been clearly identified in brain cells in vivo: AQP1, AQP4 and AQP9 [1]. The AQP4, the most studied of these brain water channels, was first discovered in brain astrocytes [29]. Other AQPs have also been well described in vivo (AQP1 and AQP9). The aquaporins expression and their respective contributions in brain physiology and pathophysiology are summarized below.

2.1 Aquaporins and Brain Physiology

2.1.1 Aquaporin-1

AQP1 is expressed in the apical membrane of the choroid plexus, and plays a role in forming Cerebrospinal fluid (CSF) [30]. AQP1 is unregulated in choroid plexus tumours [29], which are associated with increased CSF production, again supporting a role for AQP1 in CSF secretion.

2.1.2 Aquaporin-4

AQP4, the principal AQP in mammalian brain, was first cloned from rat lung [31] and was found in electrically excitable tissues including brain, spinal cord, retina, inner ear and skeletal muscle [29,32-35]. Brain AQP4 is strongly expressed at the borders between brain parenchyma and major fluid compartments including astrocyte foot processes (brain–blood), glia limitans (brain–subarachnoid cerebrospinal fluid (CSF)), as well as ependymal cells and subependymal astrocytes (brain–ventricular CSF) [29,33]. This pattern of distribution suggests that AQP4 controls water flow into and out of the brain. AQP4 is known to be involved in water movement in vitro and in vivo in normal brain tissue [36], which underscores its importance in edema formation.

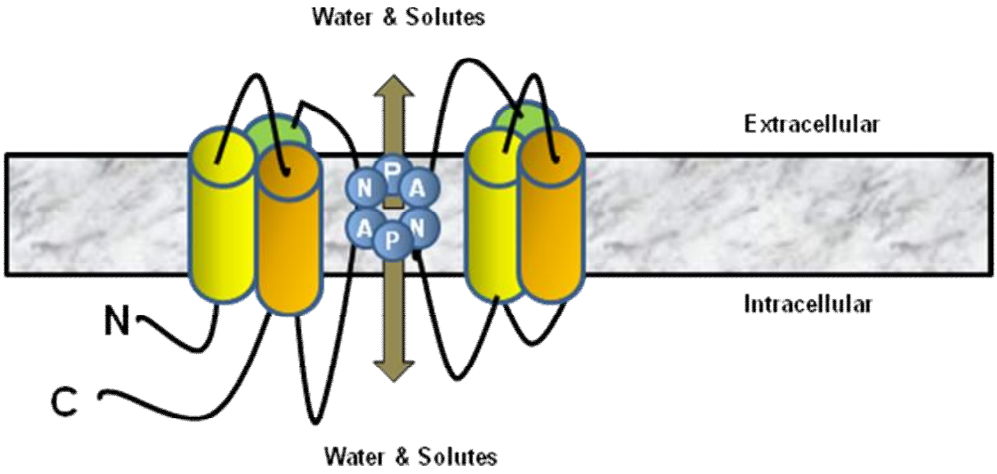

Fig. 1. Structural representation of aquaporins in plasma membrane

Table 1. Localization and role of aquaporins in different tissues

AQP isoform	Tissue/cellular localization	Role / function
Aquaporin-0	Eye: lens fiber cells	Fluid balance within the lens
	Red blood cells	Osmotic protection
Aquaporin-1	Kidney: proximal tubule	Concentration of urine
	Eye: ciliary epithelium	Production of aqueous humor
	Brain: choriod plexus	Production of cerebrospinal fluid
	Lung: alveolar epithelial cells	Alveolar hydration state
Aquaporin-2	Kidney: collecting ducts	Mediates antidiuretic hormone activity
Aquaporin-3	Kidney: collecting ducts Epidermal keratinocytes	Reabsorbtion of water into blood, Skin hydration and epidermal proliferation
	Trachea: epithelial cells	Secretion of water into trachea
Aquaporin-4	Kidney: collecting ducts	Reabsorbtion of water
	Brain: ependymal cells	CSF fluid balance
	Brain: hypothalamus	Osmosensing function
	Lung: bronchial epithelium	Bronchial fluid secretion
	Brain: astrocytes	Water permeability
Aquaporin-5	Salivary glands	Production of saliva
	Lacrimal glands	Production of tears
Aquaporin-6	Kidney	Very low water permeability
Aquaporin-7	Fat cells	Transports glycerol out of adipocytes
Aquaporin-8	Colon, pancreas, liver, others	Colonic water adsorption hepatocyte bile formation
Aquaporin-9	Brain, Leukocytes	Transports energy substrates
Aquaporin-10 (aquaglyceroporins)	epithelia of organs	Permeate neutral solutes such as glycerol and urea
Aquaporin-11	Brain, Kidney, heart, endoplasmic reticulum	Physiological role not clear
Aquaporin-12	Pancreatic acinar cells	Secretion of digestive enzymes and fluids

2.1.3 Aquaporin-9

AQP9 is an aquaglyceroporin that facilitates the diffusion of water and other solutes (e.g. glycerol, urea and monocarboxylate) and has been identified in rodent and primate brains [37]. AQP9 immunoreactivity in rat brain has been observed in some white-matter astrocytes, Bergmann glia and a subpopulation of glia called tanycytes [38]. Because AQP9 transports energy substrates (glycerol, lactate), AQP9 also play a role in controlling cerebral energy metabolism. In general, AQP9 protein expression becomes up regulated in several brain diseases [38].

2.2 Aquaporins and Brain Pathology

2.2.1 Brain edema

Brain edema is a severe clinical complication in a number of pathologies and is a major cause of increased morbidity and death. The swelling of astrocytes caused by a disruption of water and ion homeostasis is the primary event contributing to the cytotoxic form of brain edema [39]. Recent studies indicate a direct involvement of AQP4 in physiological processes such as water transport and cell plasticity, as well as in the pathogenesis of brain edema [36,39]. The AQPs in rodent brain as water-channels are likely to play an important role in extracellular homeostasis, and thus may sustain normal neuronal activity [1]. A profound perturbation of the brain environment usually induces a regional cerebral edema, as observed in ischemia. Brain edema which leads to an expansion of brain volume has a crucial impact on morbidity and mortality after stroke as it increases intracranial pressure, favours herniations, and contributes to additional ischemic injuries [40]. Despite its complexity, brain oedema has been defined as an increase in net brain water content which leads to an increase in tissue volume [41]. The two major types of brain edema, cytotoxic and vasogenic, both occur after brain ischemia. Cytotoxic edema is characterized by intracellular water accumulation involving both astrocytes and neurons and depending mainly on the

perturbation of ionic gradients [42]. Vasogenic edema is characterized by a protein rich exudates derived from plasma, as a result of an increased permeability of the capillary endothelial cells to albumin and other plasma proteins [43].

Although soma and processes of astrocytes have been noted to swell, the most prominent swelling was observed in perivascular end-feet. After ischemia, the astrocytic uptake of osmolytes such as Na^+, K^+, Cl^- and neurotransmitters from the extracellular space is followed by the concomitant passage of water into the intracellular space [44]. Therefore, water channels are likely to be involved in brain edema formation [1,45].

Currently, there are no specific inhibitors to block the AQP4 and such compounds are essential for evaluating the role and treatment of edema. Recent studies have proposed a range of compounds that may block AQP4, including bumetanide, which blocks the AQP4 channel and water permeability in oocytes [46].

2.3 Neurodegenerative Disorders

Millions of people world-wide are affected by neurodegenerative disease, a heterogeneous group of diseases affecting specific areas of Central Nervous System (CNS). Neuronal injury and oxidative stress (primary events in the development of these kinds of disorders) lead to increased production of pro-apoptotic and pro-inflammatory cytokines as well as altered homeostasis of water, extracellular ions and amino acid neurotransmitters resulting in disturbed brain homeostasis observed in many of these pathologies. Authors have hypothesized a possible role for aquaporin family members in their pathogenetic mechanisms [47]. AQP4 knockout strongly inhibited the formation of glial cell-derived neurotrophic factor in Parkinson's disease mice [48]. These findings indicate that AQP4 plays a vital role in modulating astrocytic functions. In addition to providing structural, metabolic, and tropic support for neurons, astrocytes have been also shown to play much more active roles in adult neurogenesis [49]. Studies have revealed that astrocytes fill a unique niche composed of different ions, neurotransmitters, hormones, neurotrophic factors, and extracellular substrates for adult neurogenesis *in vivo* [50-52]. In cultured cell model, the interaction between astrocytes and adult neural stem cells (ANSCs) promoted the generation of new neurons from ANSCs [53]. These studies suggest that astrocytes within the neurogenic niche are specialized and contribute to the properties of the niche to regulate ANSCs. Thus, AQP4 may participate in adult neurogenesis by regulating astrocytic function. More importantly, AQP4 is the main subtype of AQP in ANSCs [54]. However, it is unclear whether AQP4 involves adult hippocampal neurogenesis [55].

2.3.1 Role of aquaporins in depression

It has been demonstrated that impairments of several glial functions (such as glutamate metabolism and deficiency in neurotrophic factors) are likely to contribute to the pathophysiology of depression [56]. Depression is one of the major causes of physical or mental condition worldwide. Astrocyte may participate in neuropathology of major depression. Aquaporin 4 is the most important leading form of aqauporins in the brain, and is essentially expressed in the astrocytes throughout the central nervous system. They modulate the activities of astrocyte and have role in adult neurogenesis. Therefore involves in the pathogenesis of depression, highlighting a novel profile of AQP4 as a possible target for the treatment for depression [57]. Various studies reported the role of Aquaporins 4 in pathophysiology of depression [58]. In addition, a decrease in the expression of mRNA for AQP4 was identified in locus coeruleus in MDD (major depressive disorders) [59].

Post mortem histological analysis of the frontal cortex [60,61] and hippocampus [62] demonstrated a decreased number of astrocyte in patients suffering from major depression. Moreover, long-term psychosocial stress-induced loss of hippocampal astrocytes was reversed by chronic treatment of antidepressants [56]. These findings suggest that astrocytes may contribute to the pathophysiology of depression as well as to the cellular actions of antidepressants.

2.3.2 Hypoxic Stress & AQP's

Cellular responses to hypoxia can be acute or chronic. Acute responses rely mainly on O_2-regulated ion channels, which mediate adaptive changes in cell excitability, contractility, and secretary activity. Chronic responses depend on the modulation of hypoxia-inducible transcription factors, which determine the expression of numerous genes encoding enzymes, transporters and growth factors. O_2-regulated ion

channels and transcription factors are part of a widely operating signalling system that helps provide sufficient O_2 to the tissues and protect the cells against damage due to O_2 deficiency.

During the last decade new functions, locations, and regulatory pathways have been described for AQP1. Its canonical function as a specific channel for water transport across cell membranes has become wider and it has been suggested that it contributes to transmembrane gas permeation (CO_2, NO, NH_3 and O_2) in several different cell types [13,63,12,64]. Chronic hypoxia induces the expression of several genes by activation of hypoxia-inducible transcription factors (HIF), mainly HIF-1α and HIF-2α [65-67]. These transcription factors, stabilized by hypoxia, play an essential role in numerous adaptive or pathophysiological processes, such as erythropoiesis, glycolysis, angiogenesis, inflammation and tumor progression, among others [68,69]. Participation of HIF-1α in the transcriptional regulation of some AQPs has recently been demonstrated [70-73]. For instance, in the cerebellum of rats subjected to hypoxia, increments in the mRNA and protein levels of vascular endothelial growth factor (VEGF) and AQP4 were found to be closely associated to an increase in HIF-1α expression. Increased expression of AQP4 enhances water permeability of blood vessels and contributes its role in edema formation [74]. Consistently with this, a direct correlation was observed between expression of AQP4 and of VEGF and HIF-1α in glioma cells and peritumoral edematous tissue [75]. Furthermore AQP1 is also involved in hypoxia-inducible angiogenesis in retinal vascular endothelial cells through a mechanism that is independent of the VEGF signalling pathway [68]. In an ischemic/hypoxic model, traumatic brain injury induces HIF-1α which, in turn, up-regulates expression of AQP4 and AQP9. Additionally, inhibition of HIF-1α by 2-methoxyestradiol reduced the up-regulated levels of both these AQPs [72]. Hypoxia is thought to be a common precursor to neovascularisation in many retinal diseases, including diabetic retinopathy. The levels of AQP1 mRNA and protein expression were found to be significantly increased under hypoxia.

3. CONCLUSION

Aquaporins play a critical role in various biological processes and several isoforms of AQPs (0-12), have diverse functions in the different tissues. Since AQPs are integral membrane proteins playing a role in various neurodegenerative diseases and in brain edema, they could be of high therapeutic relevance. Importantly, increased expression of AQP4 enhances water permeability of blood vessels and contributes to their role in edema formation, which is a crucial aspect for understanding the ill effects of hypoxia. We hope that in the next decade we will witness the discovery of AQP modulators to be used for treating several pathological conditions of the brain including edema, tumour, seizures, neurodegeneration as well as hypoxia induced perturbations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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