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Physiology of the Aquaporins

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Abstract

Aquaporins (AQPs) form pores in the membranes of cells and selectively conduct water molecules through the membrane, while preventing the passage of ions such as sodium and potassium and other small molecules. The water movement through AQPs is considered to be facilitated simply dependent on the osmotic gradient. There are subtypes of AQPs; classical aquaporins or orthodox AQPs (AQP0, AQP1, AQP2, AQP4, AQP5) permeable only to water molecules ; aquaglyceroporins (AQP3, 7, 9 and 10) permeable to uncharged solutes, such as glycerol, CO2, ammonia and urea in addition to water and unorthodox AQPs, (AQP6, AQP8, AQP11 and AQP12) with unknown functions. The specific distribution of AQP in certain cell types of an organ often reflects a precise function. AQP0 is present in the eye lens for maintaining its transparency. AQP1 is widely distributed water channel in the body. It is mostly expressed in kidneys, lungs, red blood cells, liver, skin, intervertebral disc peripheral and central nervous system. It is involved in angiogenesis, cell migration, cell growth and countercurrent concentration. Its defect shows a protective action against edema in the lungs. AQP2 is expressed in kidney collecting duct and inner ear for water transport in presence of vasopressin; its mutations in kidney can cause nephrogenic diabetes insipidus and its mutation in inner ear provokes Menieres disease. AQP3 is the most abundant skin aquaglyceroporin, where AQP3 facilitated water and glycerol transport plays an important role in hydration of mammalian skin epidermis and proliferation and differentiation of keratinocytes. It is also found in kidney collecting duct, conjunctiva of the eye, oesophagus, colon, spleen, stomach, small intestine, intervertebral disc and respiratory tract airway epithelium. AQP4 is found in astroglial cells at blood – brain barrier and spinal cord, kidney collecting duct, glandular epithelia, airways, skeletal muscle, stomach and retina. AQP4 null mice showed altered cerebral water balance with protection from brain edema. AQP5 helps glandular water secretion so, it expressed in glandular epithelia, corneal epithelium, alveolar epithelium and gastrointestinal tract. AQP6 is expressed in kidney collecting duct intercalated cells, retina, parotid gland acinar cells, inner ear, and brain synaptic vesicles. It is involved in chloride, urea and nitrate permeability. AQP6 may functionally interact with H+-ATPase in the vesicles to regulate intra - vesicle pH and acid - base balance.

AQP7 is found mainly in fat tissue, and in testis, heart, skeletal muscle and kidney proximal tubule. In adipocytes, AQP7 is known to facilitate the secretion of glycerol. AQP8 is expressed in liver, pancreas intestine, salivary gland, testis, ovary and heart. In the kidney AQP8 was demonstrated to play an important role in the adaptive response of proximal tubule to acidosis. It may also facilitate the diffusion of hydrogen peroxide across membranes of mitochondrial in situations when reactive oxygen species are generated. AQP9 is found in liver, white blood cells, testis and brain, and is involved in water and small solutes permeability. AQP9 is supposed to be a glycerol channel in liver cells. The presence of AQP9 in the brain may play a role in energy metabolism. AQP10 is expressed in skin and small intestine for transport of water and glycerol. AQP11 is expressed in kidney, testis, liver, brain, intestine, heart, and adipose tissue, but its function is still unknown. AQP12 seems to be expressed specifically in pancreatic acinar cells but its function is still unknown and may be implicated in exocrine water execration.

Keywords: Aquaporins, Water channels, Water reabsorption and secretion, Glycerol transport, Cell migration

1. Introduction

Water is the major component of all human cells, and its movement into and out of the living cell is fundamental to life. The water permeability of biological membranes has been a longstanding problem in physiology, but the proteins responsible for this remained unknown until discovery of the aquaporins (AQPs) water channel proteins. The permeability of water across the cell membrane lipid layer is increased up to 50 times when AQPs are present relative to membranes lacking AQPs [1].

2. Classification of aqps

The AQP family is still growing with 13 members unequally distributed in human tissues. These members are designated AQP0 to AQP12. AQPs are integral, hydrophobic, transmembrane proteins that primarily facilitate the passive transport of water depending on the osmotic pressure on both sides of membrane. They have been divided into subgroups based on their structural and functional characteristics:

(1) Classical aquaporins or orthodox (water selective) AQPs (AQP0, AQP1, AQP2, AQP4 and AQP5) permeable only to water molecules and are involved in the migration of water in various cells. The selectivity of aquaporin water channels is so high that even protons (H3O+) are repelled. AQP1, AQP4 and AQP5 are permeable to water and CO2.

(2) Aquaglyceroporins (or glycerol channels) (AQP3, AQP7, AQP9 and AQP10) permeable to glycerol (AQP3, AQP7, AQP9 and AQP10) and urea (AQP7, AQP9 and AQP10) in addition to water. This type is associated with lipid metabolism by regulating glycerol levels [2].They also facilitate the diffusion of arsenite and antimonite and play a crucial role in metalloid homeostasis [3].

(3) Aqua-ammoniaporin (AQP8) is high permeable to ammonia and hydrogen peroxide in addition to water. It may facilitate the diffusion of hydrogen peroxide across membranes of mitochondrial in situations when reactive oxygen species is generated [4].

(4) Unorthodox AQPs, superaquaporins or subcellular aquaporins (AQP6, AQP11 and AQP12), were only recently identified, and their structures and functions remain uncertain [2]. AQP6 is poorly permeable to water while shows conductance to glycerol, nitrate and urea in response to acidic pH or Hg2+. But the physiological significance of these aquaporins (AQP6, AQP7, AQP9 and AQP10) in urea transport is not fully revealed [5].

3. Role of aquaporins in renal physiology

In the glomerulus, water and ions are freely filtered. As the filtrate moves along the tubules, ions are reabsorbed and water follows by osmosis [1]. Normally about 180 L of H2O are filtered through the glomeruli per day while at least 99% of filtered water is reabsorbed. The average urine volume is about 1 L per day. There are two types of water reabsorption; Obligatory not under control of antidiuretic hormone (ADH) at proximal tubule

(65%), loop of Henle (15 %), distal tubule (5 %) and collecting ducts (2 %) and facultative under control of ADH at late distal tubule and cortical (8 %) and medullary collecting ducts (4 %). The final stages of urinary concentration occur in the late distal tubules and collected ducts under the effect of ADH [6].

AQP2 is the most abundant one and also called the vasopressin-regulated water channel. AQP2, AQP3 and AQP4 are expressed in the membrane of principal cells of the kidney collecting duct where they are involved in regulation of urinary concentration [7]. AQP2 is located at collecting duct luminal membrane while AQP3 and AQP4 are located at collecting duct basolateral membrane. The vasopressin dependent flow of water into the collecting duct cells is through the AQP2 and outflow to the interstitium is via AQP3 and or AQP4. AQP3 transports glycerol as well as water; but the functional significance of this observation is unknown but may play a role in the regulation of the glycerol metabolism [1]. In the kidney, ADH binds to the basolateral G-protein coupled type II vasopressin receptor (V2), resulting in increased intracellular cAMP levels and altered intracellular signaling and causes urine concentration [8]. Individuals with mutations in the gene encoding AQP2 suffer from a severe form of nephrogenic diabetes insipidus (NDI) [9]. Mice lacking AQP3 have low basolateral membrane water permeability in cortical collecting duct and excrete large quantities of dilute urine. Mice lacking AQP4 have low water permeability in inner medullary collecting duct, but manifest only a mild defect in maximum urinary concentrating ability [10].

The mechanisms by which kidneys control urine acidification are less well defined but are likely to involve AQP6. It is expressed in vesicles in epithelial cells of the proximal tubule and in intercalated cells of the collecting duct. It may be involved in regulation of acid – base balance [5].AQP6 behaves as a pH-regulated anion channel with greatest selectivity for nitrate [11].The AQP6 may serve as a negative regulator for intracellular populations of H⁺ -ATPase, an enzyme known to be inhibited by nitric oxide [12].

AQP1 is localized at both apical and basolateral membranes of the proximal tubule [13], and plays role in water reabsorption in these segments. Also AQP1 has been present in both descending loop of Henel and the vasa recta. It has been proposed to contribute to the counter-current mechanisms - multiplication and exchanger - for maintain the corticomediary osmotic gradient. Deletion of AQP1 in mice causes severe polyuria [10]. But the role of AQP1 in human kidney epithelial cells appears to be relatively minor [8].

Other AQPs expressed in kidney, AQP7, AQP8 and AQP11 do not appear to be directly involved in water reabsorption. AQP7 is localized at the apical membrane of the proximal tubules and probably plays a role in glycerol absorption from luminal fluid. AQP8 is present in intracellular domains of the proximal and collecting duct cells. AQP11 is localized intracellularly in the proximal tubules. AQP11 null mice have been found to develop polycystic kidneys [5] control.

4. Role of aquaporins in nervous system physiology

Water homeostasis in the central nervous system (CNS) has physiological and clinical importance, since about 80% weight of brain is water. Normally, water transport is tightly regulated to maintain a strict homeostatic balance between the cerebral vascular, brain tissue, and cerebrospinal fluid (CSF) compartments. A disruption in this equilibrium causes an increase in brain water content that significantly contributes to the pathophysiology of traumatic brain injury, hydrocephalus, and a variety of neurological disorders [14].The rigid nature of the skull provides little capacity to buffer intracranial volume changes, and beyond a limited threshold the intracranial pressure (ICP) rises rapidly. The increased ICP can ultimately lead to the impairment of cerebral blood flow resulting in further brain injury and death [15].

At least nine AQPs have been identified in the CNS which includes AQP1, AQP3, AQP4, AQP5, AQP6, AQP7, AQP8, AQP9 and AQP11. In addition AQP1, AQP2 and AQP4 are also expressed in the peripheral nervous system (PNS). Little is known about the function and regulation of AQP3, AQP5, AQP6, AQP7, AQP8 and AQP11 in the CNS [16].

AQP4 is the most abundant water channel in the CNS [17]. Water transport between different

compartments of the CNS is assisted by AQP4. It is a bidirectional water channel that facilitates water transport into and out of the brain to maintain water balance within the CNS. AQP4 may facilitate water efflux from the brain parenchyma into the brain vessels, ventricles and subarachnoid space. It is also responsible for rapid water movement into the brain [17]. The AQP4 channels are highly concentrated in the blood-brain barrier (BBB), as well as in other cerebrospinal fluid barriers [18].It is expressed in astrocytes and ependymal cells throughout the brain and spinal cord, with a highly polarized distribution in glial membranes in direct contact with capillaries and astrocyte end-feet forming the glial limitans [19].This location suggests a role of AQP4 in water transport between different compartments of the CNS. AQP4 channels respond passively to osmotic gradients. Brains from AQP4 null mice show reduced osmotic water permeability [20].

AQP4 is also abundant in osmosensory regions of brain, including supraoptic nucleus where it is present in glial lamellae surrounding vasopressin-secretory neurons suggesting a role also in osmosensory mechanisms. From there, ADH is then transported along axons to the posterior pituitary, where it can subsequently be released [1].

Astrocytes mediated potassium (K+) homeostasis is of critical importance for the regulation of neuronal excitability. AQP4 is implicated in clearance of K+ released during neuronal activity. It is hypothesized that potassium released into the extracellular space during neuronal activity is taken up by astroglial inward rectifier potassium channels (Kir4.1) followed by influx of water through AQP4 in the perisynaptic space. This results in shrinkage of the extracellular space. Water is the next ruded into the perivascular space by AQP4 located at the end-feet and extracellular space volume returns to its initial state [21].

AQP4 has also a role in regulation of neurotransmission. Glutamate uptake is accompanied by water transport, which causes astrocyte processes to swell around the synapses, subsequently reducing the extracellular synaptic space during synaptic transmission and processing [22]. Previous studies also suggest that AQP4 is involved in the metabolism of dopamine, serotonin, and other neurotransmitters [23].

AQP4 also appears to be required for basic mechanisms of long term synaptic plasticity. Absence of AQP4 may impair long-term potentiation (LTP) by NMDA receptor (NMDAR) dysregulation. NMDAR is activated by increases in extracellular pH [24]. Bicarbonate acts as a pH buffering system and is regulated by $Na+/HCO3^-$ cotransporter which drives water into astrocytes through AQP4 [25].Thus, AQP4 deficiency may cause NMDAR dysregulation from extracellular pH imbalance but how this is achieved remains to be resolved. AQP4 deficiency also may impair LTP by modulation the neurotrophin brain-derived neurotrophic factor (BDNF) release that a central player in regulating synaptic plasticity. BDNF release leads to LTP and inhibits long term depression [26].

CSF is secreted by the choroid plexus and is absorbed primarily through arachnoid granulations into the venous sinuses and by other routes such as transependymal flow into the brain. CSF secretion involves the active transport of Na+ from the blood into the ventricles, which generates an osmotic gradient that drives the flow of water [1].

AQP1 is primarily distributed at the apical membrane in epithelial cells of the choroid plexus where the transcellular water movement via AQP1 contributes 25% of CSF production as shown by study on AQP1 null mice [27]. AQP1 has also been found in neurons of superficial layers of dorsal horn in spinal cord, which contains C-fibres involved in pain sensation. It is also expressed in neurons of the trigeminal ganglion that mediate nociception from the head. Osmotically induced spinal cord swelling was reduced in AQP1 null mice in dorsal horn [28], and markedly impaired pain sensation was demonstrated in response to thermal (tail flick test) and chemical (capsaicin injection) stimuli [29].

AQP9 is found in three cell types: (i) in glial cells, in particular tanycytes in the mediobasal hypothalamus and astrocytes. AQP9 in this site is implicated in the water movement between the cerebrospinal fluid and the brain parenchyma in these hypothalamic structures [30]. (ii) In endothelial cells of the pial vessels. AQP9 in this site may facilitate the water flow through the BBB. It should be noted, however that the BBB is also permeable to monocarboxylate and glycerol, and AQP9 could also participate in solute flux through the BBB [31].

(iii) In catecholaminergic neurons [30]. This AQP9 a glycerol – lactate-channel in this site could be implicated in brain energy metabolism as demonstrated by its presence in mitochondrial inner membranes and possibly in neuroendocrine effects of diabetes. Indeed, these channels can facilitate the diffusion of glycerol and lactate, which can consider as energetic substrates for nervous tissue [32].

5. Role of aquaporins in special senses physiology

The eye is a unique sensory organ consisting of multiple tissue types. The main optical elements, the cornea and lens, are avascular tissues where continuous movement of water and ions between ocular compartments and to the systemic circulation is required for maintaining transparency [33].

The intraocular pressure (IOP) is maintained by the aqueous humour. The ciliary epithelium consists of two epithelial layers: the pigmented epithelium and the non-pigmented epithelium that cover the ciliary body. The non-pigmented epithelium is responsible for aqueous humor production while aqueous humor drainage (outflow) occurs through the trabecular meshwork into the canal of Schlemm. The balance between aqueous humor secretion and outflow is critically important in maintaining IOP [34].The retinal pigment epithelium lines the outer blood-retinal barrier, preventing fluid leak between the neural retina and choroidal capillaries [35].

At least five AQPs (AQP0, AQP1, AQP3, AQP4 and AQP5) are known to be expressed in the special sense organs. AQP0 expression was observed in lens fiber cells and ciliary epithelium and retina [36]. AQP1 was localized to the corneal epithelium and endothelium, apical and basolateral plasma membranes of iris epithelium and ciliary non-pigmented epithelial cells, lens anterior epithelium, retinal pigment epithelial, photoreceptor, glycernic amacrine, and Müller cells [37]. AQP3 was localized to conjunctiva [35]. AQP4 expression was observed in in the basolateral plasma membrane of non-pigmented epithelial cells in ciliary epithelium, retina [38] supporting cells within the cochlea (Hensen's cells, Claudius cells, inner sulcus cells), the vestibular end organs and the olfactory epithelium [39]. AQP5 was located in corneal and lacrimal gland epithelia [40].

Water movement across membrane barriers in the eye follows osmotic gradients generated by active and secondary active solute transport. One exception is aqueous fluid drainage, in which hydrostatic pressure drives bulk fluid flow. AQPs are expressed in eye where their primary function is to facilitate transmembrane flow of water in response to osmotic gradients [35].

The corneal endothelium expresses AQP1 and is responsible for transport of the major part of water out of the corneal stroma [41]. The outer stratified epithelium of the anterior corneal epithelium expresses AQP3 and AQP5, and facilitates water transport away from the cornea. Deletion of AQP5 in mice increases the corneal thickness and the osmotic water permeability across the corneal epithelium is reduced [42]. The stratified corneal epithelium expresses the water- and glycerol transporting AQP3. AQP3-facilitated cell migration has also been demonstrated in wound healing in skin [43].

The transport of water into the lens is mediated by AQP1 in the epithelial cells and AQP0 expressed by the lens fibers [44]. Also in lens, AQP0 forms tight junctions and assists in maintaining minimal space between the fibers. Thus, AQP0 facilitates microcirculation and also interfiber adhesion within the lens and consequently contributes to maintaining transparency of the lens. Mutations in AQP0 produce congenital cataracts in humans. Possible mechanisms include loss of AQP0-facilitated fiber-fiber adherence [45], and impaired fiber cell dehydration [46].

A significant decrease in IOP was observed in AQP1 and AQP4 null mice and this was attributed to decreased aqueous humor production rather than alternations in outflow facility [47]. AQP5 in lacrimal glands might be an osmoregulator to maintain an isotonic tear solution rather than function in tear secretion [40].

AQP9 is expressed by the retinal ganglion cells. It may facilitate the uptake of lactate or glycerol into the retinal ganglion cells and photoreceptors [48].

AQP4 involvement in cell volume regulation may be an important mechanistic component of acoustic signal transduction [49]. The hearing impairment in the knockout mice was attributed to absence or dysfunction of AQP4 in the supporting cells surrounding the sensory hair cells and not due

to an adverse biological effect upon propagation of the neural signal in the auditory nerve [50].

The presence of several AQPs (AQP1, AQP3, AQP4 and AQP5) in middle ear Eustachian tube capillaries suggesting that may regulate water transport between blood and cells of these tissues and may play various roles in the pathophysiology of otitis media [51]. Furthermore, the involvement of AQPs in neuronal signal transduction as well as regulating cell movement and lipid metabolism suggests that these findings may be used to develop new treatments for otitis media [52].

Five water channels (AQP1, AQP2, AQP3, AQP4 and AQP5) have been identified in the inner ear. AQP1, AQP2, AQP3, AQP4 and AQP5 are present in the endolymphatic sac. AQP2 expression is regulated by ADH which is thought to regulate the endolymphatic volume by re-absorption [51]. AQP4 is to provide osmotic balance in supporting epithelium cells within the organ of Corti by recycling K+. AQP5 appears in the organ of Corti and Reissner`s membrane [53].

6. Role of aquaporins in digestive physiology

Secretion and absorption, two of the main functions of the digestive system, both require the transfer of fluid across cellular membranes. The water entering the digestive system derives in part from the diet (about 2 L/day) and in part by secretion of digestive juices (about 7 L/day). In healthy humans, 65% – 80% of this water (9 L) is absorbed in association with nutrient and electrolyte absorption in the small intestine and so the colon receives only 1500 – 2000 mL. The colon absorbs most of this remaining fluid with high efficiency so that normally only about 100 mL is excreted in the stool [54].

Gut epithelia have two pathways for water transport: (1) the paracellular route, through the spaces between cell junctions, (2) the transcellular route, through apical and the basolateral cell membranes [55].The transcellular route may happen using three different mechanisms: (a) passive diffusion through the phospholipid bilayer, (b) cotransport with ions and nutrients (c) diffusion through water channels called aquaporins (AQPs) [56].

There are a close relationship between AQPs location and function. a) Basolateral water channels (AQP3 and AQP4) appear more abundant in secretive epithelia. AQP3 protein in humans has been observed only in selected cells of antral and oxyntic gastric mucosa [57] and is thought to provide a supply of water from the sub-epithelial side of these cells which face harsh conditions, such as the low pH of the stomach, to prevent them from dehydration [58]. AQP4 is expressed in the basolateral membrane of the crypt cells located at the bottom of the crypt in small intestine, and the basolateral membrane of surface epithelial cells in the colon. It is suggested that AQP4 is involved in colonic fluid transport [54]. It is also expressed in the basolateral membrane of gastric parietal and chief cells, and may be involved in gastric juice secretion. AQP3 expression in the small intestine was subsequently localized to basolateral membranes of enterocytes, goblet cells and Paneth cells of ileal crypts. It is localized on the basolateral membrane of the epithelial cells lining the distal colon and rectum lumen [58]. Inhibition of AQP3 in rats induced severe diarrhoea, suggesting a role for AQP3 in regulating faecal water content [59]. AQP3 may mediate the reabsorption of water from faeces by transporting it from the lumen, across the endothelial layer into the blood vessels via AQP1 [60].

Whereas b) apical water channels (AQP7, 10 and possibly 11) are more highly expressed in absorbing epithelia (e.g., small intestine). AQP7 was shown in upper villi cells while it was faint or absent in the crypts; expression was particularly intense at the apical domain of enterocytes and at intracellular sites, but not at enterocyte basolateral membranes nor in goblet cells. In human proximal small intestine, AQP10 was located in the brush-border membrane of absorptive enterocytes of the upper villus [61]. And c) In the colon, that can both absorb and secrete water, both apical and basolateral AQPs are expressed. In the gastrointestinal tract, aquaglyceroporins AQP 3, 7 and 10 are mainly expressed in absorptive epithelia suggesting an importance of these channels in small solute absorption as well [62].

The salivary gland expresses multiple aquaporins including AQP1 in the myoepithelial and endothelial cells, AQP3 in the basolateral

membrane of serous and mucous acini, AQP5 in the apical membrane of the secretory acinar and ductal cells, and AQP8 transcript in acinar cells. AQP5 plays a major role in saliva secretion. AQP5 knockout mice displayed a 60% decrease in pilocarpine-stimulated saliva secretion, as well as a more viscous and hypertonic saliva [63]. Salivary AQPs can increase fluid movement across epithelial cells in process of primary saliva secretion. Saliva secretion involves active salt transport into the acinar lumen across epithelial cells, which drives osmotic water transport across AQPs [60].

Pancreatic juice secretion involves a first step during which acinar cells secrete a small volume of isotonic fluid. The primary isotonic fluid then reaches the ductal lumen. During the second step, ductal cells secrete Na+, Cl− and HCO3 − as well as most of the water [64]. The presence of AQP8 at the apical membrane of acinar cells allows water to move to the acinar lumen [65]. The presence of AQP1, at both the apical and basolateral plasma membrane of ductal cells, and of AQP5, at the apical plasma membrane of ductal cells, allows water to move from ductal cells to the pancreatic ductal lumen [66].

AQP8 is the most abundant AQP in hepatocytes. It may has a role in bile secretion in hepatocytes, which is responsible for the formation of bile before it is secreted into the bile duct and modified by cholangiocytes [67].

AQP9 is located at the hepatocyte basolateral plasma membrane [68]. It is likely involved in glycerol metabolism and energy balance. Glycerol, as a product from adipose triglycerides during lipolysis, flows into the liver through the portal vein. And it takes part in gluconeogenesis later. AQP9 is localizes at the sinusoidal plasma membrane facing the portal vein [69]. AQP9 may be also important for the rapid shifts of water across, into, or out of the hepatocyte underlying the hepatocellular hydration state, an efficient mechanism of short-term control of canalicular secretion and hepatocyte volume [70]. A role for AQP9 as exit channel for urea produced within the hepatocyte or solutes, such as purines and pyrimidines derived from nucleotide synthesis de novo, lactate and ketone bodies has been also hypothesized [71]. Based on its proven capacity to transport certain heavy metals, AQP9 is speculated to represent the entry route of arsenic in hepatocyte whose consequent poisoning is known to lead to hepatocellular damage and hepatocellular carcinoma [72]. AQP11 knockout mice display hepatocyte vacuolization, suggesting that AQP11 is involved in rough endoplasmic reticulum homeostasis and liver regeneration [4].

AQP1 is expressed at sites in the proximal gastrointestinal tract that play a role in dietary fat processing including cholangiocytes in liver (bile production), pancreatic microvascular endothelium (pancreatic fluid production), gall bladder microvascular endothelium (bile storage) and intestinal lacteal endothelium (chylomicron absorption). The AQP1 null mice on a high fat diet developed steatorrhea and had reduced serum triglyceride concentration. The null mice had elevated concentrations of pancreatic enzymes in their small intestine and stool, normal pH in duodenalm fluid, and normal bile/pancreatic fluid production, suggesting a defect in absorption rather than digestion [60]. AQP1 also was expressed in capillary endothelium of the mucosa and submucosa throughout the human ileum [73]. This confirms results previously obtained in rodents [54] and may suggest a main role of AQP1 in the passage of water between the gastrointestinal mucosa and blood stream.

7. Role of aquaporins in respiratory physiology

Handling of water in the vascular, interstitial and airspace compartments of the lung is essential for normal gas exchange and lung defense [60]. Four water channels (AQP1, AQP3, AQP4 and AQP5) have been identified in the respiratory system. AQP1 is expressed in the endothelium of pulmonary capillaries, veins and arteries [74]. It is also expressed at apical membrane of visceral and parietal pleura, and apical membrane of endothelial cell within visceral membrane. AQP1 could facilitate the osmotic fluid transport within pleural space, and deletion of AQP1 could significantly reduce osmotic fluid transport [75].

AQP3 is expressed in the basolateral membrane of basal epithelial cells in nasopharynx and trachea and in apical membrane of alveolar type II cells. AQP4 is expressed at the basolateral membrane of surface ciliated epithelial cells in bronchi and trachea. AQP3 and AQP4 are also

expressed in the basolateral membrane of the secretory glands of the nasopharyngeal epithelium. AQP5 is present in the apical membrane of alveolar type I cells and nasopharyngeal secretory glands [60].

Deletion of AQP1 or AQP5 separately produced a remarkable decrease in water permeability. Also presence of water channel in the epithelium, subepithelial vasculature and subepithelial glands of the airways and nasopharynx predicts participation in fluid transport in alveolar space (AQP1, AQP3, AQP4 and AQP5) [76], airway humidification (AQP5) [77] and glandular secretion [1].

8. Role of aquaporins in reproductive physiology

The flow of water across cell membranes is important in many of the processes underlying both the male and female reproductive systems, it is essential for spermatogenesis, sperm osmoadaptation and folliculogenesis [78].

8.1 Male reproduction

Water and solute movement across the epithelium of the male reproductive tract is responsible for balancing the luminal environment for spermatogenesis; for the maturation, storage, transport and liberation of sperm; and for increasing sperm concentration [79].

Multiple AQPs have been recognized in the testis (AQP0, AQP1, AQP7, AQP8 and AQP9), efferent ducts (AQP1, AQP9 and AQP10), epididymis (AQP1, AQP3, AQP9 and AQP10), vas deferens (AQP1, AQP2 and AQP9) and accessory glands (AQP1 and AQP9) of adult mammals. AQP0 and AQP9 are expressed in Leydig cells and may be involved in endocrine functions of testis [80]. AQP0 and AQP8 are localized to Sertoli cells. Sertoli cells in spermatogenic epithelium are known to secrete fluid to form a fluid-filled tubular lumen, serving as the vehicle for transporting sperm from the testis to the epididymis [81].

Spermatogenesis and sperm concentration are associated with considerable fluid secretion and/or absorption in the testis. AQP0, AQP1, AQP7, AQP8 and AQP9 could be involved in the early stages of spermatogenesis and in the secretion of tubule liquid. During spermatogenesis, and especially in the metamorphosis of round spermatids into elongated spermatids, one of the most distinct morphological changes is a striking reduction of germ cell volume, largely because of the osmotically driven fluid efflux [79].

AQP3 and AQP9 are localized to the epithelial layer of epididymis and are thought to play an important role in transepithelial water transport and sperm concentration [78]. AQP9 also allows transepithelial flow of solutes such as glycerol, urea, mannitol and sorbitol and is modulated by androgens in male adult rats. AQP3 is also localized exclusively to the basal cell membranes of the epididymis and it is expressed within the smooth muscle and endothelium of the vascular channels throughout the epididymis [82], together with AQP10 [80].

Several AQPs are localized to the plasma membranes of epithelial cells of prostate (AQP1), seminal vesicle (AQP1) and coagulating gland (AQP9), all of which show both secretory and reabsorptive functions [83].

On ejaculation, sperm are confronted with a drop in extracellular osmolality. This necessitates the process of regulatory volume decrease in spermatozoa to counteract the tendency of cell swelling [84].

AQP3 and AQP7 play an important role in sperm osmoadaptation, motility and morphology. They play an important role in sperm cell volume regulation. Inhibition of volume regulation in human ejaculated spermatozoa leads to failure in the penetration of and migration through surrogate cervical mucus, because of reduced swimming velocity of the swollen cells [85]. AQP3 mutant cells show decreased motility, increased swelling and tail bending after entering the hypotonic environment of the uterus therefore hindering the sperm's chances of reaching the oviduct and mediating a fertilization event [85].There is a specific correlation between normal sperm AQP7 and sperm motility and morphology [86].

8.2 Female reproduction

Metabolic actions during female reproduction depend on fluid secretion and reabsorption. The AQP1, AQP2, AQP3, AQP4, AQP5 AQP7, AQP8 and AQP9 have been shown to be expressed in the female reproductive tract. Their specific expression pattern suggests that they play a role in water

movement between the intraluminal, interstitial, and capillary compartments [79].

In the uterus, steroid hormones induce water imbibition in uterine endometrium. This water then crosses the epithelial cells into the lumen, leading to a decrease in viscosity of uterine luminal fluid. Several AQPs are localized to the stroma (AQP8), myometrium (AQP1, AQP2 and AQP8), endometrium (AQP1 and AQP2) and in glandular (AQP 5 and AQP 9) and luminal epithelial cells (AQP2, AQP3 and AQP5) of the uterus [87].AQP2 is menstrual cycle dependent and reaches a high level at the midsecretory phase the time of embryo implantation [88].AQP1, AQP2, AQP3 and AQP8, might participate in water movement during uterine imbibition. AQP2 may contribute to the fluid volume at the time of blastocyst implantation [89].In addition, AQP3, AQP4, AQP5 and AQP8 are also present in cervix and may contribute to the changes in the organization of the collagen network and water content in cervical connective tissue that occur during gestation, which allows cervical dilatation during labor. Also AQP5, AQP8 and AQP9 are localized in epithelial cells of oviduct [90]. AQPs in the oviduct could influence the production of oviductal fluid, which provides the physiological medium for fertilization and early embryonic development [79]. It was proven that AQP1, 3, 8, 9, and 11 play crucial roles in the transfer of water across the placenta [91].

The role of AQP7, AQP8 and AQP9 in the ovary, specifically the ovarian follicle, have been well studied. During folliculogenesis, the antrum is expanded by a large, rapid influx of water through the granulosa cell (GC) lining; it is mediated by transcellular flow through AQP channels [78]. The permeability of immature oocytes is mediated by AQP9, whereas that of mature oocytes may be mediated by AQP3 [79].

9. Role of aquaporins in cardiovascular physiology

In the heart, water moves from the interstitial space, across endothelia and into blood vessels. This process is typically attributed to paracellular water transport through the endothelium of the heart since it is considered to be ‘leaky' compared to the endothelium of other organs [92]. AQP1, AQP4, AQP7 and AQP9 have been found in cardiovascular system. They distribute to the heart, endothelial cells and vascular smooth muscle, participate in water transportation, glycerol and lactic acid which play an important role in vascular physiology [78].

The major AQP of the cardiovascular system is AQP1, which is expressed in microvascular (capillaries and small veins) endothelial cells and vascular smooth muscle cells. AQP1 regulates water permeability of the heart's capillary networks by mediating the flow of water through the endothelial layer into the blood. AQP1 in endothelial cells may aid the entering of nitric oxide to regulate vascular tone and blood pressure [93].

AQP4 has only been detected at the protein level within human cardiomyocytes [94]. AQP4 and AQP9 have the common functions in extracellular water homostasis and edema formation [95]. They were implicated in absorption of excess water from interstitial space into to capillaries. Cardiac oedema arises when tissue with a reduced blood supply (ischemic) becomes hypertonic, causing water to flow from the capillaries (possibly via AQP1) into cardiomyocytes; this causes cell swelling and reduced cardiac output [78].

AQP7 is expressed in cardiac tissues and capillary endothelial cells. It is inhibited by insulin. AQP7 knockout mice have lower cardiac glycerol and ATP content. In healthy cardiomyocytes, ATP is the source of chemical energy for all energy-consuming reactions [96].

10. Role of aquaporins in musculoskeletal system

AQP1 and AQP4 are expressed in skeletal muscle. AQP1 was found in the endothelial cells of capillaries within the muscle tissue and AQP4 on the plasma membrane of muscle fibre cells. The localization of AQP1 and AQP4 within the muscle tissue suggests that AQPs may function together as transporters for water between the blood and myofibrils during muscular contraction (contraction induced muscle swelling) [97].

Articular cartilage and intervertebral disc tissue are specialized biomechanical structures that are under constant compressive loads. The cells within these avascular tissues are exposed to constantly harsh conditions as the intervertebral disc is ~80% water and articular cartilage tissue is

around ~70% water [98]. The intervertebral disc is composed of three distinct regions: the gelatinous nucleus pulposus, which is encapsulated by the annulus fibrosus and the cartilaginous end plates. The native cells of the nucleus pulposus and cartilage tissue both secrete proteoglycans and type II collagen; the collagen meshwork traps negatively-charged proteoglycans (such as aggrecan) which attract cations (mainly K+, Na+ and Ca2+) resulting in the influx of water; this process is responsible for the high osmotic potential of these tissues enabling them to resist static and dynamic biomechanical loads [73]. AQP1 and AQP3 have also been identified within the nucleus pulposus cells of the human intervertebral disc. AQPs are involved in cell swelling during mechanistic load [99].

AQP9 was found in osteoclast cells, but it is not essential for osteoclast function or differentiation under normal physiological conditions [100].

11. Role of aquaporins in integumentary system physiology

The skin is the largest organ in the human body; its main function is to serve as a barrier to the external world. The stratum corneum is the most superficial layer of skin, consisting of a lamellar lipid layer and terminally differentiated keratinocytes that originate from actively proliferating keratinocytes in lower epidermis. Stratum corneum hydration is an important determinant of skin appearance and physical properties, and depends on several factors including the external humidity, and stratum corneum structure, lipid/protein composition, barrier properties, and concentration of water retaining osmolytes [101].

Four water channels (AQP1 AQP3, AQP5 and AQP7) have been identified in the human skin. AQP1 is present in dermal fibroblasts, melanocytes and vascular endothelial cells. The main function of AQP1 occurs in the vascular endothelial cells, where it exchanges water between the blood and dermis to maintain hydration. AQP3 is most abundant skin AQP. It is expressed strongly in the basal layer of keratinocytes. Both water and glycerol transports by AQP3 appear to play an important role in hydration and elasticity of skin epidermis. AQP3- null mice, also shows decreased skin hydration and elasticity [102]. The reduced skin hydration and elasticity in AQP3 deficiency is caused by impaired epidermal-cell glycerol permeability, resulting in reduced glycerol content in the stratum corneum and epidermis [103]. Finally AQP3 is also believed to be important in wound healing as a water channel by facilitating cell migration, and as a glycerol transporter by enhancing energetics and signaling keratinocyte proliferation and differentiation [104].

AQP5 is present in the apical membranes of sweat glands and is involved in sweat secretion. AQP5 null mouse has markedly diminished sweat secretion [105].

AQP7 in skin plays a crucial role during the process of lipolysis by transporting glycerol out of the adipocytes to allow maintained triglyceride breakdown [106]. An absence of AQP7 has been shown to lead to obesity and insulin resistance due to glycerol accumulation and subsequent adipocyte hypertrophy. Adipocytes in mice lacking AQP7 exhibit increased intracellular glycerol, enhanced uptake of fatty acids, and accelerated triglyceride synthesis Due to these findings, modulation of AQP7 has been suggested as a possible therapy for obesity [107].

Finally, AQP7 may be involved in primary cutaneous immune responses. This idea is based on the fact that not only is AQP7 expressed in Langerhans cells (epidermal dendritic cells) and dermal dendritic cells of the skin, but also that AQP7 knockout mice show impairment of their contact hypersensitivity response and decreased sensitization [108].

12. Role of aquaporins in cell migration process

Migration is a fundamental property of cells that occurs during many physiological and pathological processes including organogenesis in the embryo, repair of damaged tissue after injury, the inflammatory response, formation of new blood vessels, and the spread of cancer [109]. Cell migration has been divided into four processes: polarization, protrusion, traction, and retraction. Initially, cells detect a chemotactic gradient and polarize into a predominantly front part and a retracting rear part, defined by distinct signaling events. Plasma

membrane protrusions form by actin reorganization, consisting of spike-like filopodia, which sense and explore the local environment, and broad lamellipodia, which provide a foundation for the cell to move forward. The newly extended protrusions adhere to the extracellular matrix through integrins, with traction forces being generated at these adhesion sites by myosin II interaction with actin [110]. To extend protrusions, adhesions transiently disassemble and, once the protrusion has extended, adhesions reassemble allowing traction for the cell to pull forward on the substratum. This tension opens stretch-activated Ca2+ channels, activating calpain, which contributes to adhesion disassembly at the cell rear by cleaving focal adhesion proteins [111].

The idea that AQPs facilitate formation of the lamellipodium is consistent with the polarization of AQPs to the leading end of migrating cells. It has been suggested that AQPs also facilitate the rapid changes in cell shape that take place as a migrating cell squeezes through the tortuous extracellular space [110]. Such changes in cell volume are likely to require rapid flow of water into and out of the cell. Some authors have recently suggested that cells may utilize directed water permeation mediated by AQPs to create a net inflow of water and ions at the cell leading edge and a net outflow of water and ions at the trailing edge leading to net cell displacement [112]. This mechanism, termed the osmotic engine model, may allow cell migration through confined micro-spaces without the need for actin depolymerization – polymerization or myosin II-mediated contractility. It is important to note migration towards a chemotactic stimulus less efficient. Thismay explain why AQP-nullmice develop normally in utero even though cell migration is an important component of embryogenesis. AQPs do not increase the speed of migrating cells, but by polarizing to the leading edge, AQPs ensure that the lamelli podium forms in the direction of the chemotactic gradient. This effect may enhance the directionality of migration i.e. cells expressing AQPs follow a less tortuous route towards their target compared with cells lacking AQPs. AQP1 is important for endothelial cell migration that takes place during angiogenesis, which is vital to permit solid tumors to grow rapidly. Melanoma tumors grow faster in wild type than AQP1 null mice [113].

The emerging roles of water movement in cell migration are not only important in our mechanistic understanding of the migration process, but may also have a wide range of therapeutic implications including augmentation of wound healing (AQP3 activator), reduction of glial scarring and glioma infiltration (AQP4 inhibitor), and reduction of tumor growth (AQP1 inhibitor). Currently, non-toxic AQP-modulating drugs are not available, but their search is the subject of considerable interest [17].

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