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Aquaporins in the Regulation of Intestinal Health: Postprint

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Abstract

Aquaporins are a class of cell membrane channel proteins that efficiently and selectively transport water molecules, widely distributed in the gastrointestinal tissues of humans and mammals, where they play important roles in bodily fluid transport and digestive physiology. This review summarizes the structure and classification of aquaporins, their expression and distribution in the gastrointestinal systems of humans, rodents, and piglets, and discusses the relationship and roles of aquaporins in processes such as diarrhea, intestinal epithelial cell migration and repair, intestinal barrier function, and intestinal inflammatory diseases.

Full Text

The Role of Aquaporins in Regulating Intestinal Health

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Abstract

Aquaporins (AQPs) are a class of plasma membrane channel proteins that efficiently and selectively transport water molecules. They are widely distributed in the gastrointestinal tissues of humans and mammals, playing important roles in fluid transport and digestive physiology. This review summarizes the structure and classification of aquaporins, their expression and distribution in the gastrointestinal systems of humans, rodents, and piglets, and elaborates on the

relationships and roles of aquaporins in processes such as diarrhea, intestinal epithelial cell migration and repair, intestinal barrier function, and intestinal inflammation-related diseases.

Keywords: aquaporins; intestinal health; diarrhea; barrier function; piglets

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Aquaporins (AQPs) are plasma membrane channel proteins that efficiently and selectively transport water molecules, widely present in many tissues and cells of animals, plants, and microorganisms. Research has confirmed the existence of at least 11 AQP subtypes in gastrointestinal tissues. These AQPs not only play crucial roles in water transport, secretion and absorption of digestive fluids, and cell volume regulation, but also influence important processes such as cell migration, proliferation, and differentiation [1]. This review will examine the relationship between AQPs and intestinal health, focusing on the expression and distribution of AQPs in gastrointestinal tissues and their roles in diarrhea, intestinal epithelial cell migration and repair, intestinal barrier function, and intestinal inflammation.

1.1 Structure of Aquaporins

Since American scientist Agre et al. [2] discovered and identified AQP1, a specific water-transporting channel protein, on the cell membrane of red blood cells, 13 AQP subtypes (AQP0–12) have been found in humans and mammals to date. Each AQP consists of a polypeptide chain of approximately 270 amino acids encoded by a distinct gene. Its primary structure contains six transmembrane domains, three extracellular loops, and two intracellular loops, forming a unique "hourglass" water channel with a mirror-symmetric structure. The asparagine-proline-alanine (Asn-Pro-Ala, NPA) motif is a characteristic structure shared by all AQP family members, highly conserved and located at the narrow central portion of the channel, directly participating in water molecule binding and selective passage [3]. Studies have found that a cysteine residue (Cys-189) preceding the NPA sequence is a specific mercury-sensitive binding site; when bound to mercuric chloride ($HgCl_2$), the channel can be inhibited. Except for AQP4 and AQP7, which are insensitive to $HgCl_2$, most AQP functions can be inhibited by $HgCl_2$ [3]. The secondary structure of AQPs comprises 40% α-helices and 42%–43% β-sheets and turns, while their tertiary structure exists as tetramers.

1.2 Classification of Aquaporins

Based on their structural and functional characteristics, AQPs can be divided into three classes. Class 1 is typically permeable only to water, including AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, and AQP8. Class 2 is permeable to other small solutes (such as glycerol and urea) in addition to water, including AQP3, AQP7, AQP9, and AQP10. Class 3 comprises the recently discovered aquaglyceroporin superfamily members (AQP11 and AQP12), whose specific functions

remain unclear [4]. Additionally, AQP6 can transport chloride ions, urea and glycerol [5], AQP8 can also transport urea and ammonia [6], and AQP9 is permeable to other small molecules such as purines and pyrimidines [7]. Studies have shown that certain AQP subtypes also function as gas channels (CO_2, O_2, NO, and NH_3) [8]. Most AQP subtypes (AQP0, AQP1, AQP3, AQP4, AQP7, AQP8, AQP9, and AQP10) are distributed on the cell membrane, while some subtypes (AQP6, AQP11, and AQP12) are primarily located on intracellular membranes; AQP2 and AQP5 translocate between the cell membrane and intracellular membranes in response to stimuli [9].

2 Expression and Distribution of AQPs in the Gastrointestinal Tract

To date, researchers have investigated the expression and distribution of AQPs in the gastrointestinal tissues of humans and mammals using techniques including reverse transcription PCR (RT-PCR), quantitative real-time PCR, Western blotting, in situ hybridization, immunohistochemistry, and immunofluorescence. At least 11 AQP subtypes have been reported to be expressed in the gastrointestinal tissues of humans [10–16], mice and rats [17–26], and pigs [27–30] (Table 1). These AQPs are widely distributed in various cells of the gastrointestinal tract (including intestinal epithelial cells, goblet cells, endothelial cells, and gastrointestinal endocrine cells) and localize to different regions of the cell membrane (apical and basolateral membranes) [31].

The expression patterns of AQPs vary across different species in the same tissue region. A single AQP subtype may be distributed in different gastrointestinal tissues, and multiple AQP subtypes may be co-expressed in the same tissue region (Table 1). Currently, more reports are available on AQP expression in human and rodent gastrointestinal systems, with fewer studies in pigs. Research has identified six AQP subtypes expressed in the porcine gastrointestinal system: AQP1, AQP3, AQP7, AQP8, AQP10, and AQP11 [28,29]. Specifically, Tai [29] detected mRNA expression of at least six AQP subtypes—AQP1, AQP3, AQP7, AQP8, AQP10, and AQP11—in the gastrointestinal system (stomach, duodenum, jejunum, ileum, colon, and cecum) of piglets before and after weaning using quantitative real-time PCR. Jin et al. [27] first cloned porcine AQP1 cDNA and examined its expression in the porcine digestive system, finding AQP1 expression in epithelial and endothelial cells of many digestive organs (stomach, jejunum, ileum, and colon). Li et al. [30] further prepared a polyclonal antibody against porcine AQP1 and used it to detect AQP1 expression in endothelial cells of small intestinal central lacteals, small bile duct epithelial cells, renal proximal tubular epithelial cells, and choroid plexus epithelial cells in the brain.

Table 1 Expression and distribution of AQPs in the gastrointestinal tracts of humans and mammals

Subtype	Human [10–16]	Rodents [17–26]	Pigs [27–30]
	Stomach	Small intestine	Large intestine

Subtype	Human [10–16]	Rodents [17–26]	Pigs [27–30]
AQP1			
AQP3			
AQP4			
AQP5			
AQP6			
AQP7			
AQP8			
AQP9			
AQP10			
AQP11			

Note: + indicates positive expression; -indicates not yet reported or not detected.

3 Roles of AQPs in Regulating Intestinal Health

Water transport across intestinal epithelial cells occurs primarily through two pathways: the paracellular route and the transcellular route (Figure 1 [Figure 1: see original paper]) [31]. The paracellular pathway is mainly mediated by tight junction proteins between intestinal epithelial cells, whereas the transcellular route is mediated by simple diffusion, cotransporters (such as sodium-glucose transporters, sodium-hydrogen exchangers, and potassium-chloride cotransporters), and specific AQPs expressed on the apical and basolateral membranes of intestinal epithelial cells [31–34]. While the paracellular pathway was once considered the primary route for water transport in the small intestine, subsequent research revealed that water permeability across small intestinal brush-border membranes is likely accomplished mainly through specific AQPs and simple diffusion mechanisms [35].

The gastrointestinal tract is the largest organ for absorption and secretion after the kidneys, with approximately 10 liters of fluid being rapidly transported and utilized daily, and AQPs play important roles in this process. Their expression sites, levels, and activity changes correlate with gastrointestinal physiological functions and pathological states.

3.1 AQPs and Diarrhea The essence of diarrhea is the dysfunction of water and electrolyte absorption and secretion in the gastrointestinal tract, leading to abnormal water-salt metabolism, often associated with disturbances in water transport and ion balance [36,37]. Current studies in humans and rodents suggest that changes in AQP expression and distribution may correlate with the development of diarrhea induced by bacteria, cholera, rotavirus, or allergies.

When mice are infected with *Citrobacter rodentium*, the expression of AQP4 and AQP8 in the intestine is significantly upregulated, causing abnormal water and electrolyte transport, fluid loss or dehydration, and resulting in intestinal

inflammation and diarrhea [38]. In humans, AQP10 expression in duodenal mucosa is significantly downregulated during the acute peak phase of cholera-induced diarrhea [39]. Similarly, in celiac disease patients, mRNA expression and immunohistochemical staining of AQP3, AQP7, AQP10, and AQP11 in the duodenum are significantly reduced [16]. Additionally, allergic diarrhea significantly decreases AQP4 and AQP8 expression at both mRNA and protein levels in the anterior colon of mice, suggesting that allergic diarrhea is associated with downregulation of AQP4 and AQP8 expression [36]. These results indicate that dysregulation of certain AQP subtypes may be one of the molecular mechanisms underlying diarrhea.

Piglets also frequently develop diarrhea during weaning, though it remains unclear whether this is related to changes in intestinal AQP expression and activity. However, Tai [29] used quantitative real-time PCR to detect changes in AQP mRNA expression in gastrointestinal tissues of piglets before and after weaning, finding that mRNA expression of AQP1, AQP3, AQP7, AQP10, and AQP11 generally increased in the intestine after weaning, while AQP3 and AQP8 mRNA expression significantly increased in gastric tissue. Furthermore, both enterotoxigenic *Escherichia coli* and lipopolysaccharide (LPS) can significantly downregulate AQP8 expression in the jejunum of weaned piglets [28,40]. These studies suggest that diarrhea in weaned piglets may be related to changes in AQP expression in gastrointestinal tissues, though the underlying mechanisms require further investigation.

3.2 AQPs and Intestinal Epithelial Cell Migration Cell migration plays a crucial role in intestinal injury repair and barrier function. The renewal cycle of intestinal epithelial cells is generally 2–4 days, and recent studies have found that AQP3, AQP4, and AQP9 can promote cell migration, thereby regulating intestinal epithelial cell renewal and injury repair [41,42]. Research has confirmed that intestinal epithelial cell migration is severely impaired in AQP3 knockout mice, inhibiting the self-renewal capacity of intestinal epithelial cells and making them more susceptible to enteritis [43]. Notably, recent studies have shown that AQPs also participate in the proliferation and migration of intestinal cancer cells; AQP4 promotes the migration of human colon adenocarcinoma cells and may be an important factor in colon cancer invasion and metastasis [44]. However, no studies have reported whether AQPs can regulate the proliferation and migration of porcine intestinal epithelial cells to control intestinal tissue repair in weaned piglets, which requires future investigation.

3.3 AQPs and Intestinal Barrier Function The intestinal epithelial layer, along with its tight junction proteins and mucus layer, constitutes an important component of the intestinal barrier. Recent studies have shown that AQPs may play important roles in intestinal barrier function. AQP3 in the digestive epithelium is important for maintaining intracellular osmotic pressure and cell volume [45]. Intestinal AQP3 expression is negatively regulated by miR-874, which subsequently reduces expression of tight junction proteins—occludin and

claudin-1—thereby increasing intestinal permeability [46]. Similarly, silencing the AQP3 gene in Caco-2 cells severely impairs barrier function, manifested by increased *E. coli* translocation, decreased transepithelial electrical resistance, and increased permeability [47]. Interestingly, AQP4 knockout mice show no significant differences in fecal water content or colonic secretory function, but exhibit increased colonic permeability [18]. Additionally, AQP8 is expressed in normally proliferating human colonic epithelial cells, participates in colonic water transport, and plays an important role in regulating mucus layer viscosity and modifying the mucosal barrier [48]. Although studies in mice suggest that AQPs may participate in regulating intestinal barrier function, research on their role in porcine intestinal barrier function remains very limited and requires further investigation.

3.4 AQPs and Intestinal Inflammatory Diseases Inflammatory bowel disease (IBD) is a common chronic intestinal inflammatory disorder comprising ulcerative colitis and Crohn' s disease, though its etiology and pathogenesis remain unclear. Studies have shown that both human IBD and dextran sulfate sodium-induced murine colitis models exhibit significantly decreased AQP4 and AQP8 expression at mRNA and protein levels in the colon, leading to altered colonic fluid secretion, suggesting that intestinal inflammatory injury in IBD correlates with downregulation of certain AQP subtypes [23]. Additionally, in mice with infectious enteritis, differentially expressed genes in the intestine are mainly related to protein metabolism, transport, and intracellular macromolecule metabolism, while expression and activity of water and ion transporters [AQP4, AQP8, the chloride channel cystic fibrosis transmembrane conductance regulator (CFTR), and the sodium-hydrogen exchanger (NHE)] are severely affected [38]. In a trinitrobenzene sulfonic acid-induced rat enteritis model, AQP3 and AQP8 expression in the colon is significantly reduced, exacerbating intestinal inflammation and injury [49]. Conversely, AQP8 mRNA and protein levels are significantly increased in the colon of ulcerative colitis patients [50], suggesting that the mechanisms by which AQP8 regulates different intestinal inflammatory diseases may differ.

In summary, AQPs are abundantly expressed in intestinal tissues and participate in the regulation of water secretion, absorption, and intracellular water balance during intestinal water metabolism and digestive physiology. In recent years, their roles in intestinal health have received increasing attention, and changes in AQP expression sites, levels, and activity have been found to correlate importantly with intestinal disorders and diseases, though their specific mechanisms require further investigation. As functional studies of AQPs continue to deepen, AQPs are expected to become regulatory targets for many intestinal disorders related to water metabolism and transport, attracting increasing attention and providing new insights for preventing and treating intestinal disorders and diarrheal diseases in humans and young animals.

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