Animal Health Prod and Hyg (2022) 11 (2) : 50 - 55

Animal Health, Production and Hygiene

www.dergipark.or.tr/tr/pub/aduveterinary

Review

Intestinal Aquaporins

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ABSTRACT

Aquaporins (AQPs) are integral, hydrophobic, and transmembrane proteins that facilitate passive transport of water depending on the osmotic pressure on both sides of the cell membrane. Of these channel proteins, those that are permeable only to water are called “classical aquaporins”, those that allow the passage of small molecules such as glycerol in addition to water are called “aquaglyceroporins”, and those with different structures and cellular distributions are called “super aquaporins”. Aquaporins have a great role in the gastrointestinal tract as well as in the whole organism. Transepithelial transport of fluid in the intestine occurs spontaneously, either by paracellular or cellular routes, or both. The paracellular pathway is mediated by tight junctions in the intestinal epithelium and their passage is regulated based on the size and load of substances, while the cellular pathway is passive diffusion mediated by aquaporins and co-transporters. Among them, aquaporins are the major cellular pathway for bidirectional fluid transport in the gut. Aquaporins have important roles in the gut. Based on these roles, information, and research on whether aquaporins can be regulated by drugs and dietary supplements to increase intestinal health and improve their functions is increasing day by day. In this review, the functions of aquaporins in the intestinal tract, their situations in intestinal diseases, and the drugs and dietary supplements used for the treatment of these diseases are discussed together with current studies.

***Keywords**: Aquaporin, gut health, intestinal system*

ÖZET

Akuaporin (AQP)’ler hücre membranının her iki tarafındaki ozmotik basınca bağlı olarak suyun pasif transportunu kolaylaştıran integral, hidrofobik ve transmembran proteinlerdir. Bu kanal proteinlerinden sadece suya geçirgen olanlara “klasik akuaporin”, suya ek olarak gliserol gibi küçük moleküllerin geçişine izin verenlere “akuagliseroporin” ve yapıları ile hücresel dağılımları diğerlerinden farklı olanlara ise “süper akuaporin” denilmektedir. Akuaporinler tüm organizmada olduğu gibi gastrointestinal kanalda da büyük role sahiptir. Bağırsakta sıvının transepitel taşınması ya paraselüler veya selüler yollarla ya da her ikisi ile spontane olarak gerçekleşmektedir. Paraselüler yola intestinal epiteldeki sıkı bağlantılar aracılık eder ve maddelerin boyutları ile yükleri temel alınarak geçişleri düzenlenirken, selüler yol ise akuaporinler ve ko-transporterlerin aracılık ettiği pasif difüzyon şeklinde olmaktadır. Bunların arasında akuaporinler, bağırsakta iki yönlü sıvı taşınması için majör selüler yoldur. Akuaporinlerin bağırsakta önemli rolleri bulunmaktadır. Bu rollerine dayanarak akuaporinlerin, bağırsak sağlığını artırmak ve fonksiyonlarını geliştirmek için ilaçlar ve diyet takviyeleri tarafından düzenlenip düzenlenmeyeceklerine ilişkin bilgi ve araştırmalar her geçen gün daha fazla oranda artmaktadır. Bu derlemede akuaporinlerin intestinal kanaldaki fonksiyonları, disregülasyonları ile bu disregülasyonların sağaltımı amacıyla kullanılan ilaçlar ve diyet takviyeleri, güncel çalışmalar ile ele alınmıştır.

***Anahtar kelimeler**: Akuaporin, bağırsak sağlığı, intestinal sistem*

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Received Date: 05.09.2022 – Accepted Date: 20.10.2022

DOI: 10.53913/aduveterinary.1171043

Introduction

Aquaporins (AQPs) are integral, hydrophobic, and transmembrane proteins responsible for the passive transport of water in the direction of the osmotic pressure on both sides of the cell. The aquaporins responsible only for water transport are called "classical aquaporins". Studies have shown that aquaporins are also involved in the transport of small and uncharged molecules such as glycerol, urea and ammonia, in addition to water, in the direction of the concentration gradient. And they were called "aquaglyceroporins". There are also "super aquaporins", which are considered as a separate family due to their structural and permeability differences and very low homology with other aquaporins. Classical aquaporins include AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, and AQP8; aquaglyceroporins include AQP3, AQP7, AQP9 and AQP10, and super aquaporins include AQP11 and AQP12 (Li and Wang, 2017). Why are aquaporins essential in organisms? Because about 70% of the living organism is water. Therefore, to provide homeostasis, transport of water, solutes, ions, electrolytes, proteins, and nucleic acids between intracellular and extracellular fluids is crucial. Aquaporins play a major role in this regard (Brown, 2017). The essential function of aquaporins is to intercede the transmembrane transport of small solutes, glycerol, and water, to regulate the absorption and secretion of water in the intestine, and to maintain the balance and homeostasis of intestinal fluid movement (Fischbarg, 2010). In addition to these functions, aquaporins are also required for the proliferation and migration of immune cells. Thus, they mediate the intestinal immune response and participate in the regulation of natural host defense at the cell membrane level (Lv et al., 2022). Aquaporins have a primary role in water transport in the intestinal tract since the cell-cell connections in the intestinal mucosa are shaped by tight junctions (Laforenza, 2012). Nearly all discovered aquaporins are commonly found in the large and small intestines of mammals. Besides their normal physiological functions, aquaporins are closely related to intestinal diseases such as constipation, diarrhea, colitis, and colorectal cancer. There have been many studies targeting aquaporins for the development of drugs used in the treatment of intestinal diseases. The results show that drugs in which regulates the expression of aquaporins can improve the intestinal health of mammals (Lv et al., 2022).

The distribution of aquaporins in the gastrointestinal tract is determined by their functions. For example, AQP3 and AQP4 are basolateral water channels more expressed in secretory epithelium (e.g., stomach), while apical water channels are more expressed in absorbent epithelium (e.g., small intestine). Apical and basolateral aquaporins, which are involved in both reabsorption and secretion of water, are expressed in the colon (Laforenza, 2012). Almost all discovered aquaporins are abundant in the small and large intestinal tissues of mammals and contribute to many physiological functions depending on their localization (Lv et al., 2022).

Functions of intestinal aquaporins

The main function of aquaporins is to mediate the transmembrane transport of glycerol, water, and small solutes, and to maintain the balance of intestinal fluid movement and intestinal homeostasis (Fischbarg, 2010). In addition to these functions, aquaporins are also required for the migration and proliferation of immune cells (Lv et al., 2022).

AQP1: It has been reported to be expressed in the mucosa of the ileum and endothelial cells of submucosal capillaries (Mobasheri and Marples, 2004) and endothelial cells of porcine small intestinal villi (Jin et al., 2006). In addition, it is thought that AQP1 may also be required in the digestion process of fats due to its location in the endothelial cells of the central lymphatic channels of the small intestinal villi, where chylomicrons are produced (Zhu et al., 2017).

AQP2: It is believed to be expressed in the rat colon (Chen et al., 2016; Guttman et al., 2007).

AQP3: According to a study, the most important and common aquaporin in the rat colon is aquaporin 3 (Ikarashi et al., 2011). Various studies have shown that AQP3 is found in the colonic mucosa (Cao et al., 2014; Thiagarajah et al., 2007) and jejunal villus epithelial cells (Zhang et al., 2017). It was observed that exposure to AQP3 inhibitor ($HgCl_2$ and $CuSO_4$) for more than one hour increased the water content in the faeces up to 4 times compared to the controls and a fulminant diarrhea was formed (Zhu et al., 2017).

In the trinitrobenzene sulfonic acid (TNBS)-induced colitis model, AQP3 expression was found to be down-regulated together with AQP8, and intestinal inflammation and damage were also shaped. In rats with inflammatory bowel disease, AQP3 expression increased in the adaptation process after small bowel resection and development of intestinal functions. This finding indicates that AQP3 may have a function in the pathogenesis of inflammatory bowel disease (Zhao et al., 2014; 2016).

In a sepsis-induced mucosal injury model, AQP3 expression was downregulated as result of sepsis-induced intestinal damage and inflammation (Zhu et al., 2019). In addition, trefoil factor peptides that stimulate epithelial cell migration to limit luminal damage in acute gastrointestinal mucosal damage and inflammation and prevent further damage and inflammation in chronic conditions (Aihara et al., 2017), increase the level of AQP3 expression to achieve epithelial cell migration. It gives the cell the ability to deform, and thus, epithelial cell migration towards the damaged area is ensured (Marchbank and Playford, 2018).

Cell damage model shows that AQP3 affects the H_2O_2 permeability of the membrane, inducing the production of actin-derived lamellipodia, thus contributing to endothelial cell migration and damaged epithelium repair (Thiagarajah et al., 2017).

AQP4: It has been reported to be expressed in the mouse colon and ileum (Jiang et al., 2014; Wang et al., 2000), as well as in the basolateral membrane of ileal epithelial cells (Zhu et al., 2017). In prairie rabbit intestine, AQP3 is found in colon epithelium, small intestinal villus epithelium, gastric fundus; AQP4 is found in colonic epithelium, small intestine glandular epithelium, gastric fundus (Zhang et al., 2019; Zhuang et al., 2019).

AQP5: It is localized in the duodenum, on the apical membrane of secretory cells (Parvin et al., 2005). It has been indicated that AQP5 supports the development and invasion of some types of cancer (Huang et al., 2013). It has been suggested to be upregulated in several types of cancer, such as colon cancer or bile duct carcinoma (Zhu et al., 2017).

AQP6: It is expressed in the isthmus of the small and large intestine, and in the entire crypt villus axis (Laforenza et al., 2009).

AQP7: It has been detected in the gastrointestinal tract of humans, in superficial epithelial cells throughout the small intestine and colon (Zhu et al., 2017). In rats, it is thought to be necessary for rapid fluid movement in the villi epithelium, since it is found in the epithelial cells of the colon and caecum and in the apical regions of enterocytes in the villi (Lv et al., 2022).

AQP8: It is found in the colon, ileum, and jejunum, as well as in human colon villi and crypt epithelial cells (Ricanek et al., 2015; Laforenza et al., 2005).

AQP9: It has been required in goblet cell mucin synthesis and secretion, which is important in preventing intestinal infections (Okada et al., 2003). Therefore, the decreased expression of AQP9 in the ileal mucosa suggests that it may be associated with ileal mucosal damage (Xiang et al., 2018).

AQP10: It is detected in porcine jejunum, epithelial cells on the luminal villus side as well as in human ileum (Krone et al., 2019; Ansar et al., 2013).

In general, AQP1, AQP3, AQP7 and AQP11 are mostly found in the small intestine; AQP1, AQP3, AQP7 and AQP8 are plentifully expressed in the colon. Moreover, aquaporins are mostly located in intestinal villus and crypt epithelial cells. In terms of cell localization level, AQP7 and AQP10 are mostly located in the apical membrane of the cell, while AQP3 and AQP4 are in the basolateral membrane. Thus, the localization of aquaporins in the gut is compatible with their function in mediating intestinal water transport (Lv et al., 2022).

Aquaporins in intestinal diseases

Diarrhea is shaped because of disruption of water and electrolyte transport, thereby altering intestinal epithelial permeability and loss of fluid, solute, and lipid from the intestinal mucosa (Dong et al., 2020). It has been found that abnormal AQP expression, which causes diseases in the absorption and secretion of water by the gut, thus affecting intestinal membrane permeability and fluid transport also accompanies diarrhea (Engevik et al., 2018). For example, intestinal cell permeability and AQP1 expression can be inhibited by *Clostridium difficile*, leading to the occurrence and development of diarrhea (Hui et al., 2018). AQP3, AQP7 and AQP8 levels in rat colonic epithelial cells were considerably altered in the bile acid diarrhea model (Yde et al., 2016). The immunolocalization of AQP10 in the human ileum with tuberculosis disease suggests that it may cause secretory diarrhea in intestinal tuberculosis (Ansar et al., 2013). Furthermore, the abnormal decreased of aquaporin expression was showed in the antibiotic-associated rat diarrhea model (Zhang et al., 2018). Additionally, another study suggested that in the diarrhea model created by ETEC (Enterotoxigenic *Escherichia coli*), misplacement of AQP2 and AQP3 from the basolateral membrane to the infection site in the plasma membrane also occurs (Kassa et al., 2019). These data suggest that changes in the localization as well as their expression of aquaporins can alter water homeostasis in intestinal cells, thereby causing diarrhea (Lv et al., 2022).

AQP3, AQP7 and AQP8 expressions are decreased in the colon and ileum during inflammatory bowel disease (Zahn et al., 2007). In addition, downregulation of AQP1, AQP3 and AQP8 in the colon has been detected in rats with irritable bowel syndrome (IBS) (Chao and Zhang, 2018).

Constipation is a complex and common symptom of gastrointestinal diseases, and the main symptoms are dry faeces, forced defecation, and decreased defecation frequency. Normally faeces are gradually formed as a result of water absorption in colon. During this process, if the expression levels of aquaporins are high, excess water is carried from the lumen to the side of the vessel, causing hard faeces and constipation (Ikarashi et al., 2016). In various mouse constipation models, AQP2 and AQP4 expression was significantly increased in the colon (Gan et al., 2019).

Aquaporins may affect cell proliferation, migration and invasion and angiogenesis-related cell functions (Willaert et al., 2014). Therefore, there is a close relationship between cancer cell metabolism and aquaporins. Recently, aquaporins have been suggested as potential diagnostic and therapeutic targets for colorectal cancer (Kourghi et al., 2018). Various aquaporin expressions have been found to be closely associated with metastasis to lymph nodes in colon cancer in studies (Moon et al., 2003). Furthermore, prolonged downregulation of AQP8 in tumorigenesis plays an important role in terms of both potential biomarker and formation of colorectal cancer (Hong et al., 2018). In colon cancer, AQP3 has high expression levels and induce cell migration (Magouliotis et al., 2020; Moosavi and Elham, 2020). In colorectal cancer, increasing AQP5 expression is associated with late stage of lymphatic metastasis and poor prognosis (Shan et al., 2014). Aquaporins are a potential diagnostic and prognostic marker of colorectal cancer, as well as a curative target to predict treatment course (Lv et al., 2022).

Aquaporins in treatment of intestinal diseases

Today, aquaporins are frequently used as targets in the treatment of the above-mentioned diseases. There are plant extracts, drugs, probiotics, and diets used in this regard (Lv et al., 2022).

For example, it has been suggested that AQP4 expression in intestinal cells is downregulated due to the *Rotavirus* infection (Lundgren et al., 2000). Genistein, an isoflavone, can hinder *Rotavirus* replication and increase intestinal AQP4 expression. Thus, fluid absorption through intestinal cells is rearranged to manage diarrhea (Huang et al., 2015). As another example, one of the quaternary ammonium alkaloid, berberine is used as an antibiotic due to the its antidiarrheal effect by increasing water absorption due to the possible regulator effects on the expression of AQP4 in human intestinal epithelial cells (Zhang et al., 2012; Gu et al., 2011).

Several laxatives exert laxative effects by causing upregulation of AQP3 expression. Magnesium sulphate, one of the osmotic laxatives may has functions in case of osmotic pressure increase in the intestinal tract and upregulation of AQP3 expression (Zhu et al., 2017; Ikarashi et al., 2012). Bisacodyl, on the other hand, is a stimulant laxative and does not form an osmotic pressure difference, it has a laxative effect by increasing intestinal motility. It has inhibitory activity on AQP3. Because both motility is accelerated and AQP3 expression is decreased, water cannot be fully absorbed from the colon, resulting in diarrhoea (Ikarashi et al., 2011, 2012).

In a diphenoxylate-induced constipation model, therapeutic rhein decreased AQP3 expression and reduced constipation symptoms (Sun et al., 2018). However, in a loperamide-induced constipation model, the mechanism of action of loperamide was to cause inhibition of AQP3, as well as reducing intestinal motility. Naringenin, used for treatment in this model, increased the expression of AQP3 in both the basolateral and apical membranes, increased transport of water from the blood to the lumen in the direction of the osmotic gradient, and cured constipation (Yin et al., 2018).

As with osmotic and stimulant laxatives, in the case of naringenin and rhein both increase and decrease in AQP3 expression cause laxative effect. There may seem to be a contradiction here, but the reasons for these contradictions are the mechanisms that cause the disease, the mechanisms of action of the drugs used in the treatment, the positions of aquaporins in the cell membrane and the state of other aquaporins at that time.

Besides the drugs mentioned above, probiotic products and some diets may also enhance intestinal water transport function by regulating aquaporins. Non-enterotoxigenic *Bacteroides fragilis* (NTBF) is considered a gut-protecting probiotic and has been used to treat diarrhoea by increasing the expression of AQP3 and AQP8 (Zhang et al., 2018). In another study, a probiotic mixture (consisting of *Lactobacillus acidophilus* DM8302, *Bifidobacterium breve* DM8310 and *Lactobacillus casei* DM8121, mixed in a 1:1:1 ratio and grown as a bacterial mass) can regulate AQP3 expression to augment the water content of the faeces and ultimately enhance constipation (Deng et al., 2018).

As well as probiotics, diets containing trihexanoin (Wu et al., 2018), alpha ketoglutaric acid (He et al., 2017), functional complex amino acids (Yi et al., 2018), low protein, and high carbohydrate (Fan et al., 2017) are also used in the treatment of diarrhoea by increasing the expression of various aquaporins.

Conclusion

The widespread expression of aquaporins in the intestinal tract of mammals suggests that these channels are closely related to the normal physiological function and health of the intestines. When the pathophysiology of intestinal diseases is examined, it is seen that abnormal expression and localization of aquaporins in intestinal epithelial cells may play a role in the pathogenesis of diseases. Therefore, regulation of aquaporins by drugs and/or dietary supplements to improve intestinal physiological state is of great importance in preventing or treating intestinal diseases. However, the way to regulate aquaporin gene expression is still controversial. Therefore, further studies are needed to develop more specific drugs and/or dietary supplements for aquaporins and their regulation, as well as to elucidate the role of aquaporins as a marker of intestinal health status and a target of intestinal health-regulating agents.

Acknowledgements

This review article was prepared from the first doctoral seminar of Miray AYKOÇ.

Conflict of Interest

No conflict of interest was declared by the authors.

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