Aquaporins in Glandular Secretion

16

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Abstract

Exocrine and endocrine glands deliver their secretory product, respectively, at the surface of the target organs or within the bloodstream. The release of their products has been shown to rely on secretory mechanisms often involving aquaporins (AQPs). This chapter will provide insight into the role of AQPs in secretory glands located within the gastrointestinal tract, including salivary glands, gastric glands, duodenal Brunner's glands, liver, gallbladder, intestinal goblets cells, and pancreas, as well and in other parts of the body, including airway submucosal glands, lacrimal glands, mammary glands, and eccrine sweat glands. The involvement of AQPs in both physiological and pathophysiological conditions will also be highlighted.

Keywords

Aquaporins · Exocrine glands · Endocrine glands · Secretion · Function · Expression

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16.1 Role of AQPs in Secretory Glands Located within the Gastrointestinal Tract

Aquaporins (AQPs) are expressed to several secretory glands located within the entire length of the gastrointestinal tract including salivary glands, gastric glands, duodenal Brunner's glands, liver, gallbladder, intestinal goblets cells, and pancreas. Figure 16.1 summarizes the involvement of AQPs in the secretory gland functions that is detailed in the following sections.

16.1.1 Salivary Glands

Major salivary glands, namely parotid, submandibular, and sublingual glands, and minor salivary glands contribute to whole saliva secretion [1, 2]. The secretory structure of the glands consists into several lobes subdivided into lobules. Lobules are made of secretory units namely acini (consisting into the association of multiple acinar cells) connected through a network of ducts formed of ductal cells. Myoepithelial cells surround the secretory epithelia [3]. The acinar cells are either serous, mucous or seromucous, based on their secretory products and characteristics [3]. The ductal system can be subdivided into intralobular (intercalated and striated), interlobular, interlobar (excretory) ducts. Saliva secretion relies on a two

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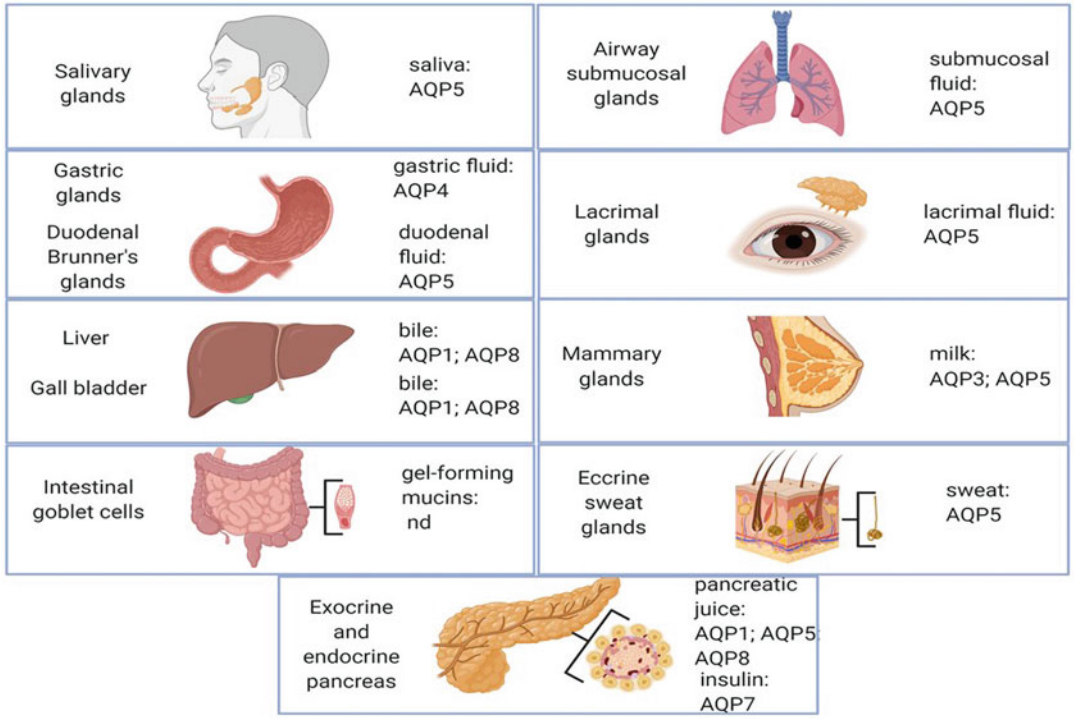

Fig. 16.1 Involvement of AQPs in secretory gland functions

steps mechanism in which acinar cells secrete an isotonic-like fluid rich in NaCl and water and ductal cells reabsorb some NaCl and secrete bicarbonate [4, 5]. These two steps mechanism results into the secretion of a final hypotonic saliva into the oral cavity.

In the first step, water flows to the lumen of the acini through the apically-located AQP5 thereof playing a major role in saliva secretion (Fig. 16.2) [6, 7]. Indeed, a 60% decrease in pilocarpine-stimulated saliva secretion, and a more viscous and hypertonic saliva have been observed in AQP5 knockout mice [6, 7]. Furthermore, substantial decrease in water permeability of parotid (65%) and sublingual (77%) acinar cells has been shown in AQP5 knockout mice [7]. Therefore, studies infer that AQP5 is responsible for acinar water movement [4, 5, 8, 9]. However, it has been suggested that AQP5 could act as an osmosensor controlling the tonicity of the transported fluid by mixing transcellular and paracellular water flows [10]. In response to muscarinic stimulation inducing intracellular calcium increase, AQP5 traffics from intracellular vesicles to plasma membrane [11–13]. Concomitantly to its physiological role, AQP5 expression is mostly confined to the apical membrane of serous acinar cells from all human salivary glands [14, 15] and from submandibular and parotid glands in rats [15–18] and mice [11, 19, 20]. The AQP5 expression reported in rat and mouse ductal cells [11, 18, 21, 22] is difficult to explain on a physiological point of view considering ductal cells are water impermeable [23]. Noteworthy, a naturally occurring point mutation of AQP5 has been identified in rats and associated with decreased AQP5 expression and saliva secretion [24]. Until now to our knowledge, no AQP5 mutation has been associated with saliva flow dysfunction in humans.

The use of knockout mice models has not been able to show the involvement of other AQPs, i.e. AQP1, AQP4, and AQP8, in saliva secretion [6, 25, 26]. Therefore, AQP1 expressed in mouse salivary gland endothelial and myoepithelial cells [27] is not involved in saliva secretion. AQP1 is also expressed in human myoepithelial [28] and

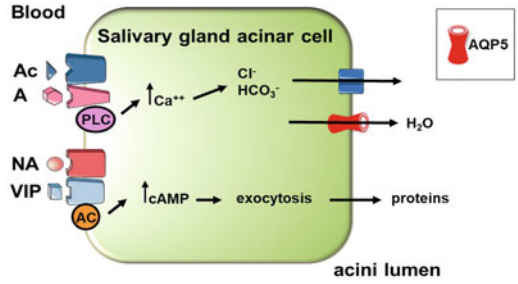

Fig. 16.2 Proposed mechanism of AQP-mediated water transport in saliva formation in salivary gland acinar cells. Upon nerve stimulation, acetylcholine and adrenalin bind to muscarinic receptors M1 and M3 and α1-adrenergic receptors leading to phospholipase C activation and subsequent intracellular calcium increase, while noradrenalin and vasoactive intestinal peptide bind to β1-adrenergic and VIP receptors leading to adenylyl cyclase activation and subsequent intracellular cyclic adenosine monophosphate (cAMP) increase. cAMP leads to protein kinase C activation and exocytosis of proteins, while intracellular calcium increase leads to Cl^- and HCO_3^- secretion driving water transport though AQP5 into the acini lumen. *AC* acetylcholine, *A* adrenalin, *PLC* phospholipase C, *NA* noradrenalin, *VIP* vasoactive intestinal peptide, *AC* adenylyl cyclase, *cAMP* cyclic adenosine monophosphate, *PKC* protein kinase C

endothelial [14, 15, 29, 30] cells, as well as in rat endothelial cells [22, 31–34].

Other AQPs have been detected in salivary glands. In human, AQP3 is located at the basolateral membrane of serous and mucous acini, but not the ducts [14, 29, 30] while only AQP4, AQP6, and AQP7 mRNAs have been detected [14, 30]. In rat, some controversy still exists concerning the expression of both AQP3 and AQP4 [21, 22, 35, 36]. In rat parotid glands, AQP6 is located to secretory granule membrane [37], while AQP8 is present in myoepithelial cells [38–40]. In mice, AQP3, AQP4, and AQP8 are expressed at the basolateral membrane of acinar and ductal cells [27]; AQP7 is located in endothelial cells; [20] AQP9 distribution remains to be determined [19, 20, 41]; AQP11 is found in ductal cells [19, 20]. Distinct patterns of AQPs expression have been found during the development of salivary glands in mouse, rat, and human [22, 42–45].

In some patients suffering from Sjögren's syndrome, an autoimmune disease characterized by lymphocytic infiltration of exocrine glands and particularly salivary and lacrimal glands, altered AQP5 localization is hypothesized to play a role in the disease pathogenesis and saliva flow reduction. However, altered AQP5 localization has not been detected in all patients suffering from Sjögren's syndrome [46–48]. These data could arise from the use of distinct patient subsets and/or antibodies. In mouse model of Sjögren's syndrome, altered AQP5 localization has indisputably been reported in several studies [49–54]. The presence of inflammatory infiltrates within salivary glands [51], cytokines [55–58], autoantibodies against muscarinic M3 receptors [59, 60] have been suggested to play a role in the modified AQP5 distribution. Even though altered expression and/or localization of AQP5 could not totally account for saliva impairment observed in Sjögren's syndrome patients, it could still play a role in the pathogenesis of the disease. Very recently, in salivary glands from patients suffering from Sjögren's syndrome, it has been shown that altered distribution of prolactin-inducible protein and ezrin, identified as new proteins partners of AQP5 in salivary glands under physiological conditions, may also account for abnormal AQP5 localization [61–63]. Anti-AQP5 antibodies have been detected in blood samples from patients suffering from Sjögren's syndrome and have been incriminated in disease manifestations. Indeed, anti-AQP5 antibodies may be directly linked to salivary gland dysfunction [64] and may represent additional useful biomarker for Sjögren's syndrome diagnosis. However, this remains to be confirmed as anti-AQP5 antibodies have not been detected in all patients with Sjögren's syndrome [65], possibly due to distinct patient subsets and methods of determination. Concerning AQP1, studies using knockout mice showed that this AQP is not involved in saliva secretion [6, 25]. However, decreased AQP1 expression in salivary gland myoepithelial cells from Sjögren's syndrome patients and reduced saliva flow [29] can be counteracted using Rituximab depleting B-cells [66]. Autoantibodies have been detected in patients with Sjögren's syndrome patients [65, 67] but were not associated with decreased saliva flow rate [67]. Therefore, further

investigation is required to better understand the role of AQP1 in salivary gland function. Abnormal distribution of AQP4 has also been described in salivary glands from patients suffering from Sjögren's syndrome [68], but its physiological significance remains to be further studied considering this AQP does not appear to be involved in saliva secretion using knockout mice [6, 25].

In patients with head and neck cancer treated with ionizing radiation therapy, decrease or loss of AQP5 expression [69, 70] and/or impaired AQP5 trafficking [71] could account for xerostomia. In mice and rats, ionizing radiation also induced decrease in AQP5 expression [72–76]. Pilocarpine, a muscarinic receptor agonist restored AQP5 expression and saliva flow in irradiated rats [77].

In diabetes, it is presently unclear whether high glucose induces [78] or not [79] an altered distribution of AQP5 and decreased AQP5 expression [80]. Distinct mouse species, experimental conditions, and analytical methods could account for these distinct results.

In salivary glands, AQPs represent new therapeutic targets or can be used as therapeutic agents to treat xerostomia. Cevimeline restored proper AQP5 trafficking [81–83]. DNA demethylation agents increased AQP5 expression [57, 84]. Treatment with cystic fibrosis transmembrane regulator (CFTR) corrector and potentiator allowing the correction of CFTR activity restored AQP5 expression and saliva secretion in mouse model of Sjögren's syndrome [85]. Furthermore, the delivery of a recombinant adenovirus vector coding for AQP1 (AdhAQP1) to irradiated glands of animals and human led to saliva flow restoration [86–90], as well as resolution of inflammation [91]. New viral vectors allowing more efficient and persistent expression of a transgene, such as, for instance, hAQP1, in salivary glands, would be useful to further study the usefulness of gene therapy to treat xerostomia. The use of CRISPR-CAS9 gene editing allowing the replacement of endogenous AQP1 gene promotor with the cytomegalovirus (CMV) promoter led to increased AQP1 expression and could open avenues to new gene therapy [92]. The gene therapy approaches described hereabove represent promising therapies for patients suffering from xerostomia consequent to head and neck irradiation therapy or Sjögren's syndrome, but the presence of autoantibodies against AQP1 may represent an obstacle to such therapeutic approach.

16.1.2 Gastric Glands

Mammalian gastric glands found in gastric pits within the gastric mucosa are composed of fundic glands (in the cardia), cardiac glands (in the fundus and body of the stomach), and pyloric glands (in the antrum of the pylorus). Gastric glands are made of distinct cell types with specific function. Indeed, foveolar cells produce mucous, parietal cells secrete gastric acid and bicarbonate ions, chief cells secrete pepsinogen, G cells secrete gastrin, and enterochromaffin-like cells release histamine [93].

Many AQPs have been localized to various areas of the stomach. The fundus express AQP1, AQP3, AQP4, AQP5, AQP7, AQP8, AQP10, and AQP11 mRNA and the antrum of the pylorus express AQP1, AQP2, AQP3, AQP5, AQP7, and AQP11 mRNAs [94–96]. Both parietal and chief cells express AQP4 protein at their basolateral membrane [36, 97–100]. AQP4 internalizes in a vesicle-recycling compartment and undergo phosphorylation upon histamine stimulation in gastric cells [101]. AQP4 is unlikely involved in acid and fluid secretion as shown using AQP4 knockdown mice [102], even though other AQPs could compensate for the lack of AQP4. However, it remains to be determined if AQP4 could still be involved in gastric cell volume maintenance. AQP5 is strictly localized to the apical and lateral membranes of pyloric glands [103].

Several AQPs promote or are involved in chronic gastritis and gastric cancer [96, 104–111]. Particularly AQP3 and AQP5 play significant roles in gastric cancer [112] and promote gastric cancer cell epithelial-mesenchymal transition [106, 113]. Lower levels of miR-877 and miR874, shown to regulate AQP3 and AQP5 expression, respectively, may account for the

increased AQP3 and AQP5 expression and epithelial mesenchymal transition [114, 115]. AQP3 and AQP5 expression has been shown to be positively correlated with gastric mucosal disease progression in gastric carcinoma and other stages of gastric diseases as well as with *Helicobacter pylori* infection [116, 117]. *Helicobacter pylori* promote AQP3 and AQP5 expression (through the activation of downstream HIF-1α or ERK1/2, MEK, respectively) that could be used as novel molecular targets for therapeutic interventions [116, 117]. Furthermore, as the expression of certain AQPs is associated with better or poor overall survival of patients with gastric cancer, it can be used as predictive prognostic gastric cancer biomarker [110, 118].

In light of the involvement of AQPs in gastric cancers, they have been considered as additional molecular targets for therapeutic intervention [119].

16.1.3 Duodenal Brunner's Gland

The role of AQPs in duodenal Brunner's gland function remains poorly understood due to the limited number of studies performed so far. Brunner's gland cells express AQP5 at their apical, lateral, and secretory granule membranes [103] and AQP1 at their apical and lateral membranes [120]. The secretion of bicarbonate and protein as well as the overall flow rate of rat Brunner's gland are increased by the vasoactive intestinal peptide (VIP) acting though a cAMP-dependent signaling pathway [121]. In addition, VIP induces the trafficking of AQP5, but not of AQP1, from secretory granules to apical plasma membrane [120, 122]. The resulting presence of AQP5 at the apical plasma membrane could account for increased water flow and fluid secretion. This hypothesis is further supported by the co-localization and co-trafficking of cystic fibrosis transmembrane conductance regulator (CFTR) and AQP5 providing a parallel pathway for electrolyte secretion and osmotic water movement [122]. The expression of AQP5 in Brunner's gland was decreased in celiac disease and cystic fibrosis and may consequently be involved in the pathogenesis of these diseases characterized by altered duodenal secretion [122].

16.1.4 Liver, Bile Ducts, and Gallbladder

Bile is a complex fluid composed of an aqueous solution (95% of water) of organic and inorganic compounds [123]. The major organic compounds are represented by three lipids, bile acids, cholesterol, and phospholipids, and the bile pigments. Proteins and metabolites deriving from various endogenous substances (i.e., hormones) are present at low concentrations [123]. Ions Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, and HCO_3^- are the major inorganic electrolytes whose concentrations in the common duct bile are very close to those found in plasma.

Bile is the main route for the excretion of body cholesterol in the form of unesterified cholesterol or as bile acids. In turn, biliary bile acids assist the emulsification and absorption of lipids at intestinal level. Also, bile mediates the elimination of drugs and toxins from the body. In health, humans secrete about 0.8–1.0 L of hepatic bile daily at a rate of 30–40 mL per hour. Bile production is about six times higher in rats [124], a species lacking gallbladder. Human canalicular bile is remodeled into the lumen of the bile ductules and duct through secretory and absorptive processes operated by the ductal epithelial cells. Bile is stored and concentrated in the gallbladder, and released into the duodenum [125, 126]. Bile water is mostly reabsorbed in the proximal segment of the small intestine [127] while bile salts are recovered in distal ileum to be carried back to the liver by the enterohepatic circulation [128, 129]. Bile formation starts at the bile canaliculus triggered by an osmotic process that involves solutes and water and where the driving force needed to bile formation is represented by the active concentration of bile acids and other biliary constituents in the bile canaliculi [124]. Canalicular bile flow can also be found in the absence of bile acids or at low bile acid outputs, indicating the existence of two components for canalicular bile formation, the

bile acid-dependent bile flow (i.e., bile flow related to bile acid secretion) and the bile acid-independent bile flow (i.e., bile flow attributed to active secretion of osmotically active inorganic electrolytes and organic anions). Lastly, total bile flow consists of constant ductal/ductural secretion and total canalicular bile flow with a linear relation in both total bile flow and total canalicular bile flow.

The epithelial cells of the mammalian hepatobiliary tract express several AQPs variously localized among the different system sections (Table 16.1). Endothelial cells express AQP1 [34] and AQP7 [130]. AQPs are also present in Kupffer cells [130, 131] and hepatic stellate cells [132–136].

16.1.4.1 Liver

Rodent hepatocytes express AQP8, AQP9, and AQP11 [130, 137–142]. Two more homologues, AQP3 and AQP7, have been reported in human hepatocytes. The distinctive subcellular localization and transport selectivity featured by these AQP channels may explain their redundancy in hepatocytes [143]. Important roles have been ascribed to AQP8, AQP9, and AQP11 in hepatocytes whereas the function (if any) of hepatic AQP3 and AQP7 is unclear.

Table 16.1 Reported localization and suggested physiological relevance of hepatobiliary aquaporins expressed at significant levels

Hepatobiliary section	Aquaporin	Cellular location and species	Subcellular location	Suggested functional involvement
Liver parenchyma	AQP3	Hepatocytes (h)	Undefined	Unclear
	AQP7	Hepatocytes (h)	Undefined	Unclear
	AQP8	Hepatocytes (r, m, h)	APM, SAV, IMM, SER	Canalicular bile secretion; cytoplasmic osmotic homeostasis; mitochondrial ammonia detoxification and ureagenesis; mitochondrial H_2O_2 release hepatocyte cholesterol biosynthesis; regulation of metabolic signaling
	AQP9	Hepatocytes (r, m, h)	BLM	Uptake of glycerol during starvation; lipid homeostasis; import of water from sinusoidal blood; catabolic urea extrusion
	AQP11	Hepatocytes (m)	RER	RER homeostasis; liver regeneration
Intrahepatic bile ducts	AQP1	Cholangiocytes (m, r, h)	APM, SAV, BLM	Secretion and absorption of ductal bile water
	AQP4	Cholangiocytes (m, r)	BLM	Secretion and absorption of ductal bile water
Gallbladder	AQP1	Epithelial cells (m, h)	APM, BLM, SAV	Cystic bile absorption/secretion
	AQP8	Epithelial cells (m, h)	APM, SAV	Cystic bile absorption (?)
Portal sinusoids; PVP; BV	AQP1	Endothelial cells (h)	APM, BLM	Bile formation and flow
Other hepatic cell types	AQP3	Kupffer cells (h)	PM	Cell migration and proinflammatory cytokines secretion (?)
	AQP8	Kupffer cells (r)	PM	Repopulation of Kupffer cells during liver regeneration (?)
	AQP3	Stellate cells (h)	PM	Adiponectin-mediated inhibition of hepatic stellate cells activation
	AQP11	Stellate cells (r)	Undefined	Control of activated hepatic stellate cells proliferation

APM apical plasma membrane, *BLM* basolateral plasma membrane, *BV* blood vessels, *IMM* inner mitochondrial membrane, *PM* plasma membrane, *PVP* peribiliary vascular plexus, *RER* rough endoplasmic reticulum, *SAV* subapical membrane vesicles, *SER* smooth endoplasmic reticulum

Likely due to its multiple subcellular localizations [138, 139] and ability to allow transport of ammonia and hydrogen peroxide in addition to water, several functions have been suggested for AQP8 in hepatocytes such as those of facilitating the secretion of canalicular bile water [144], preserving the cytoplasm osmolarity during the synthesis and degradation of glycogen, [139] transporting ammonia in mitochondrial ammonium detoxification and ureagenesis [145–147], and mediating the release of hydrogen peroxide from mitochondria [148, 149]. Peroxiporin mitochondrial AQP8 has been suggested to intervene in the hepatocyte cholesterol biosynthesis controlled by the sterol regulatory element-binding protein (SREBP) [150–152]. The AQP8-facilitated diffusion of H_2O_2 across the hepatocyte plasma membrane has been recently reported to be involved in the differential regulation of metabolic signaling by α1- and β-adrenoceptors (ARs) and to induce Ca^{2+} mobilization. Since H_2O_2 inhibits the β-AR-mediated activation of the glycogenolytic, gluconeogenic, and ureagenic responses induced by α_1-AR this observation was suggested to be a novel NOX2-H_2O_2-AQP8-Ca^{2+} signaling cascade acting downstream of α_1-AR in hepatocytes. The inhibitory effect exerted by H_2O_2 on β-AR signaling leads to negative crosstalk between the two pathways [153]. Intense is the investigation addressed to the role exerted by AQP8 in the secretion of canalicular bile. After stimulation by choleretic agonists, such as dibutyryl cyclic adenosine monophosphate or glucagon, subapical AQP8 was suggested to translocate to the apical plasma membrane via phosphatidylinositol-3-kinase-dependent microtubule-associated trafficking [154]. This redistribution raises the hydric permeability of the canalicular plasma membrane facilitating the osmotically driven transport of water into the bile canaliculus (Fig. 16.3) [144, 155, 156]. A similar cAMP-induced redistribution to the canalicular membrane also occurs for carriers implicated in canalicular bile secretion such as the isoform 2 of the Cl^-/HCO_3^- exchanger (AE2) and the multidrug resistance-associated protein 2 (MRP2). This mechanism is in line with a work with rat primary hepatocytes where glucagon increased the expression AQP8 reducing its degradation through a process involving cAMP-PKA and PI3K signal pathways [157]. However, in another study, hepatocytes isolated from AQP8 knockout mice showed water permeability comparable to that of hepatocytes from wild type mice [26]. This apparent discrepancy may be explained by the redundancy of AQPs in hepatocytes and/or to the functional modification to which other genes may undergo in response to the disruption of the *Aqp8* gene. On the other hand, in rat hepatocytes it has been observed that a 60% decrease in AQP8 level in the apical membrane leads to a 15% decrease in the overall osmotic permeability of the canalicular membrane [158].

AQP9 is an aquaglyceroporin of broad selectivity allowing transport of a wide variety of non-charged solutes including glycerol and other polyols, hydrogen peroxide, urea, carbamides, nucleosides, monocarboxylates, purines, pyrimidines, and metalloid arsenic besides to water. It is mainly expressed in liver parenchyma, at the sinusoidal plasma membrane of hepatocytes [137]. In rodents, AQP9 is the main pathway through which glycerol is taken up from portal blood to hepatocytes during short-term fasting [159–161]. Once transported into the cells, by means of the glycerol kinase glycerol is promptly converted into glycerol-3-phosphate (G3P) to be used as substrate for gluconeogenesis. Hepatocyte AQP9 is also involved in lipid homeostasis as G3P is required for the synthesis of triacylglycerols (TAGs) [162]. AQP9 has also been suggested to contribute to rodent bile formation [163] and to the extrusion of catabolic urea [164]. In rodents, the transcriptional expression of hepatocyte AQP9 is negatively regulated by insulin [165], an observation that may explain why liver AQP9 is increased in conditions of insulin resistance [166, 167]. Functional significance for AQP9 in glucose and lipid homeostasis and energy balance is also indicated by *Aqp9* knockout mice where the ablation of AQP9 is associated to reduced liver glycerol permeability and increased levels of plasma glycerol and TAGs [164, 168]. Mouse models of obesity and obese patients with type 2 diabetes show reduced

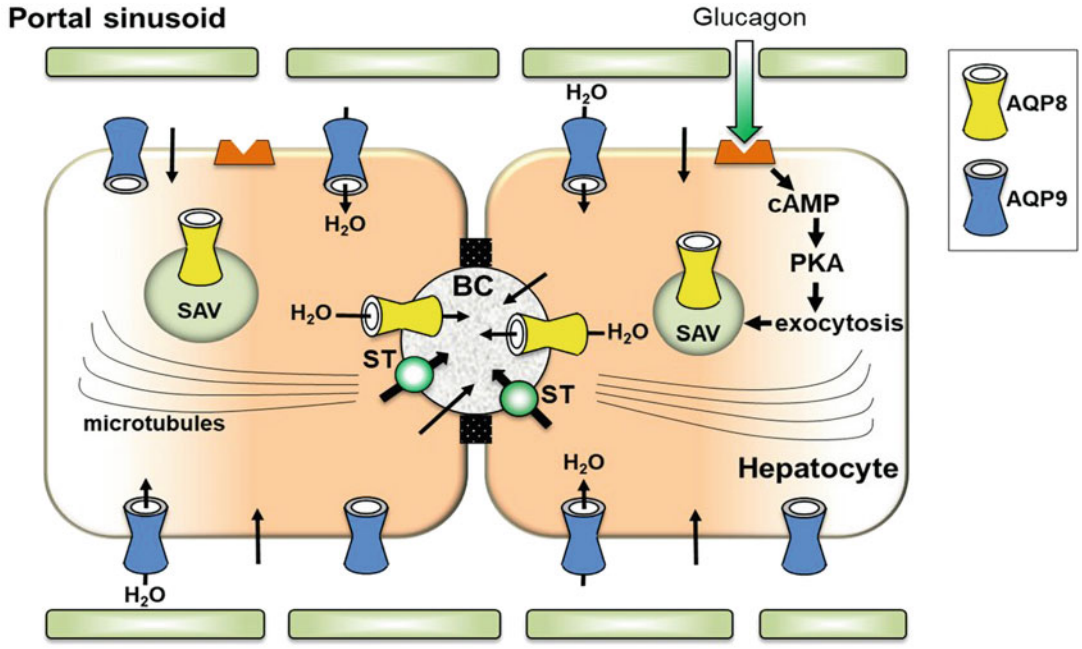

Fig. 16.3 Proposed mechanism of AQP-mediated water transport in canalicular bile formation and secretion in hepatocytes. AQP8 facilitates the osmotic secretion of water into the bile canaliculus, whereas AQP9 contributes to the diffusion of water from the sinusoidal blood into the cell. Choleretic hormones, such as glucagon, can stimulate the microtubule-dependent canalicular targeting of AQP8-containing subapical vesicles. AQP8 is also found in mitochondria and smooth endoplasmic reticulum where it is suggested to play other roles other than facilitating the canalicular secretion of bile water. AQP9 is also the main pathway through which glycerol is imported by hepatocytes (see Table 16.1). *BC* bile canaliculus, *PKA* protein kinase A, *SAV* subapical vesicles, *ST* salt transporters

levels of hepatocyte AQP9 with a significant decrease of the liver glycerol permeability [169, 170]. Liver AQP9 is also regulated by leptin [162, 171]. However, the regulation played by both insulin and leptin on the gene transcription of AQP9 seems to differ between rodents and humans [167]. Sex-specific dimorphism of hepatic AQP9 expression is found both in rodents and humans consistent with the differences with which the two genders handle glycerol [171–174].

Sex-dependent differences were also seen regarding two other aquaglyceroporins of metabolic relevance, AQP3 and AQP7, in fat tissue [171]. Hepatocyte AQP9 has been recently found to be involved in the lipid-lowering activity of the nutraceutical phytocompound silybin through modulation of autophagy and lipid droplets composition [175]. A role of liver AQP9 in the early acute phase of the inflammatory reactions triggered by TLR4 ligands has been suggested where AQP9-facilitated uptake of hydrogen peroxide would be implicated in the production of inflammatory NO and O_2^- through the involvement of the NF-kB pathway [176]. AQP11 has been found in mouse and human hepatocytes where roles are suggested in rough endoplasmic reticulum homeostasis and liver regeneration [130, 141]. The recent functional identification of AQP11 as a peroxiporin opens new horizons about the potential function of this homologue to the regulation of intracellular H_2O_2 homeostasis to prevent ER stress [177]. Further studies are expected to assess the role of AQP11 in liver.

16.1.4.2 Bile Ducts

Cholangiocytes, the epithelial cells lining the biliary tree, account for secretin-induced ductal bile secretion through a cAMP-dependent pathway [124] and activation of Cl^- efflux via cystic fibrosis transmembrane conductance regulator (CFTR) that drive the extrusion of HCO_3^- into the lumen via apical AE2 (i.e., the chloride/bicarbonate exchanger). Both HCO_3^- and Cl^- provide the main driving force for the osmotic movement of water by means of apical AQP1 into the biliary lumen [124]. AQP1 is expressed in human and rodent cholangiocytes [34, 178] where it plays a key role in the apical water secretion during both basal- and hormone-regulated ductal bile formation [179]. AQP1 is also located in subapical membrane vesicles [180] where co-expression with AE2 and CFTR was observed [181]. Secretin regulates the exocytic insertion of these vesicles into the cholangiocyte apical membrane leading to the novel concept of functional bile secretory unit [180, 181]. At their basolateral plasma membrane cholangiocytes express AQP4 and AQP1 [180, 182]. AQP-facilitated water movement would allow the relative isosmolar status of the cell to be maintained during ductal bile formation. This is consistent with the physical association between the basolateral membrane of cholangiocytes and the peribiliary vascular plexus that surrounds bile ducts and from which bile water originates explaining the relative isosmolar status seen during ductal bile formation (Fig. 16.4) [143, 183]. Surprisingly, cholangiocytes from *Aqp1*$^{-/-}$ knockout mice did not show impairment in water movement [184]. Lack of AQP1 could lead to compensatory upregulation of other AQPs expressed in mouse cholangiocytes [185, 186] such as AQP8. Intrahepatic bile ducts not only secrete but also absorb water. Osmotically induced net water absorption has been demonstrated in isolated rodent intrahepatic bile duct units [187]. Water would be absorbed osmotically following the active absorption of sodium-coupled glucose and bile salt by means of the SGLT1 and ASBT cotransporters, respectively [124]. Hormones decreasing the intracellular levels of cholangiocytes cAMP such as somatostatin, gastrin, and insulin could act by inhibiting the secretin-induced vesicular transport of AQP1, CFTR, and AE2 to the cholangiocytes apical membrane with a decrease of the ductal bile secretion. This mechanism could explain why somatostatin can cause inhibition of ductal secretion and stimulation of net ductal water absorption.

16.1.4.3 Gallbladder

The mammalian gallbladder acts as a storage compartment for bile fluid produced by hepatobiliary secretion with important roles in maintaining digestive and metabolic homeostasis. Water movement across gallbladder epithelium is driven by osmotic gradients created from active salt absorption and secretion. Human and mouse gallbladder epithelial cells express AQP1 and AQP8. Both in human and mouse AQP1 is localized at the apical and basolateral domains of the plasma membrane of the epithelial cells that line the neck of the organ [188, 189]. In mouse gallbladder, additional immunoreactivity was seen at the corpus portion with staining at level of subapical vesicles and over the plasma membrane [190]. Leptin was found to slightly upregulate AQP1 in mouse gallbladder [191]. AQP8 has been found at the plasma membrane and, at lesser extent, at intracellular level of the gallbladder epithelium of different species [34, 138]. Recently, liver X receptor β (LXRβ), an oxysterol-activated transcription factor strongly expressed in the gallbladder epithelium, was seen to regulate the expression of AQP1 and AQP8 and the cystic fibrosis transmembrane conductance regulator (CFTR) [192]. Constitutively high water permeability in mouse gallbladder epithelium involving transcellular water transport through AQP1 was found in a study using AQP1 knockout mice [193]. Subapical AQP1 was hypothesized to translocate to the apical membrane to secrete water as in the bile duct epithelium, a functional homologue of the gallbladder epithelium. Based on its pattern of

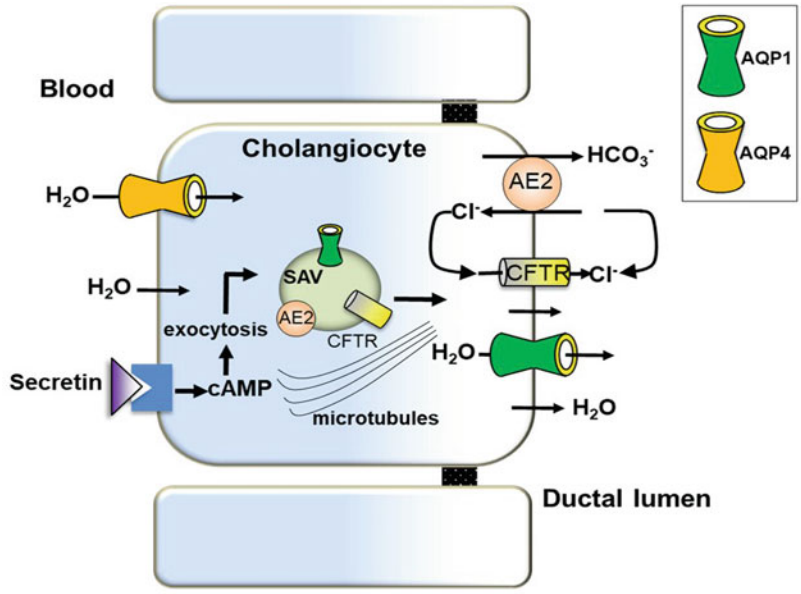

Fig. 16.4 Proposed mechanism of AQP-mediated water movement in ductal bile secretion. Intrahepatic bile ducts cholangiocytes. Secretin hormone, via cAMP, induces the microtubule-dependent apical targeting and exocytic insertion of subapical vesicles containing AQP1 and CFTR Cl^- channels, and the Cl^-/HCO_3^- exchanger AE2 into the apical membrane. The efflux of Cl^- via CFTR provides the luminal substrate to drive the extrusion of HCO_3^- into the lumen by means of AE2. HCO_3^- and Cl^- ions provide the osmotic driving force for the movement of water from blood plasma (mostly through basolateral AQP4) to biliary lumen (through apical AQP1). *AE2* anion exchanges isoform 2, *CFTR* cystic fibrosis transmembrane conductance regulator, *SAV* subapical vesicles

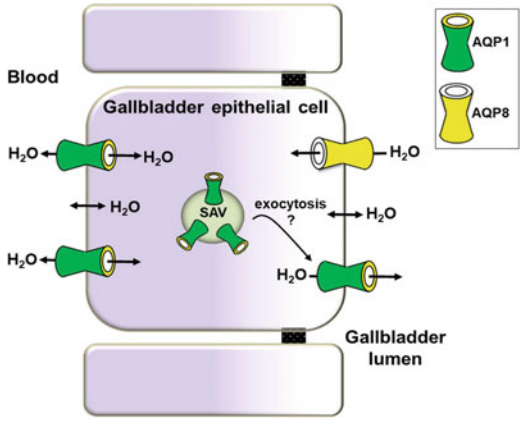

Fig. 16.5 Proposed mechanism of AQP-mediated water in cystic bile absorption/secretion. Gallbladder epithelial cells. AQP8 and AQP1 facilitate the osmotic absorption and secretion of water into and from the gallbladder lumen, respectively. Basolateral AQP1 mediates the entry/extrusion of water into/out of the epithelial cells. *SAV* subapical vesicle

subcellular localization gallbladder AQP8 was suggested to contribute to the secretion of water and to facilitate the absorption of water (Fig. 16.5) [138]. However, the physiological importance of AQP1 and AQP8 roles in gallbladder function remain debated matter due to the discrepant results reported in literature. Bile salt concentration was of similar extent in gallbladders from wild type and *Aqp1* knockout mice with AQP8 that was not appearing to functionally substitute for AQP1 [193]. This observation was not consistent with previous studies showing temporal association between decreased gallbladder concentrating function and reduced AQP1 or AQP8 expression [190], and leptin-deficient mice submitted to leptin replacement where leptin was altering the gallbladder volume likely by influencing the AQP-mediated absorption/secretion of water [194]. Additional work is needed to clarify the question.

16.1.5 Intestinal Goblet Cells

Current knowledge concerning the role of AQPs in intestinal goblets cells is very limited. So far, only AQP9 mRNA has been detected in a subset of mucus-secreting intestinal goblet cells [195]. Therefore, additional studies would be valuable to further study the expression and function of AQPs in these cells.

16.1.6 Exocrine Pancreas

The exocrine pancreas accounts for about 90% of the total pancreas and morphologically resembles salivary glands despite few differences. Indeed, it contains serous acinar cells only and centroacinar cells (extension of intercalated ducts into each acinus). In addition, the exocrine pancreatic fluid secretion drains into a main collecting duct. The major role of pancreatic fluid is to neutralize the stomach acid and the food digestion. Pancreatic fluid secretion is regulated by several neurotransmitters (i.e., acetylcholine, cholecystokinin, and secretin) that stimulate both pancreatic enzyme and fluid secretion or mainly fluid secretion, and that exert potentiated effects [196].

AQP1, AQP3, AQP4, AQP8, and AQP12 mRNAs are expressed in human exocrine pancreas. However, only few AQPs proteins have been detected, i.e., AQP1, AQP5, and AQP8 [197, 198]. Endothelial cells, centroacinar cells (apical membrane), intercalated ductal cells [197], and pancreatic zymogen granules express AQP1 [199, 200]. Intercalated ductal cells (apical membrane) express AQP5 [197]. AQP12 expression localization remains to be determined [198].

AQP1, AQP4, AQP5, AQP8, but not AQP12, mRNAs are expressed in rat exocrine pancreas [197, 198, 201]. AQP1 is localized to the apical and basolateral membranes as well as caveolae and vesicle-like structures of intralobular and intralobular ductal cells [202, 203], in acinar zymogen granules [199] and in endothelial cells [201]. AQP5 is expressed at the apical membrane of centroacinar and intercalated ductal cells [204]. AQP8 is located at the apical acinar cell membrane [198].

AQP1, AQP5, and AQP12 are expressed in mouse exocrine pancreas. Indeed, AQP1 and AQP5 are located at the apical membrane of interlobular ductal cells, and AQP5 is also expressed at the apical membrane of intercalated and intralobular ductal cells [204]. AQP12 is expressed intracellularly in acinar cells [205].

Pancreatic juice is produced by acinar cells secreting a small volume of isotonic fluid and ductal cells secreting ions and ensuring most of the water movement [4, 206]. The presence of AQP8 located at the apical acinar cell membrane, AQP1 located at both apical and basolateral ductal cell membranes, and AQP5 located at the apical ductal cell membrane ensure water movement to the acinar or ductal lumen [204]. AQP8 accounts for most water permeability (90%) in rat pancreatic acinar cells [201]. However, exocrine pancreatic function is unmodified in AQP8 knockout mice, possibly due to the fact the much contribution of acinar cells than ductal cells to the overall water movement [26]. In rat pancreatic acinar zymogen granules, AQP1 contributes to basal and GTP-mediated vesicle water movement and swelling [199, 200]. In rat interlobular ductal cells, AQP1 account for most of secretin-stimulated pancreatic juice secretion [203]. However, AQP1 knockout mice display normal exocrine pancreatic function, like the AQP5 knockout mice [197]. These data may be due to weak level of AQP1 and AQP5 expression or functional redundancy. In this context, double AQP1 and AQP5 knockout mice might be useful to assess the specific contribution of each of these AQP to the exocrine pancreatic function. In addition, further studies are necessary to shed light on the possible role of AQP12 in pancreatic juice secretion.

16.1.7 Endocrine Pancreas

Endocrine pancreatic cells account for a minor fraction of total pancreatic cells (about 10). They form the islets of Langerhans composed of insulin-producing β-cells surrounded by glucagon-producing α-cells, somatostatin-producing δ-cells, and pancreatic polypeptide-

producing PP cells [207]. The major function of human endocrine pancreas, and in particular of the β-cells, is to secrete insulin [208, 209]. Insulin secretion by β-cells relies on the following subsequent steps: glucose entry via the glucose transporter type 2 (GLUT2), glucose metabolization, intracellular ATP concentration increase, ATP-sensitive K^+ channels inhibition, membrane depolarization, voltage-dependent Ca^{2+} channels opening, intracellular calcium elevation, and finally insulin-containing granules exocytosis [208]. Moreover, glucose induces β-cell swelling [210] that triggers subsequent volume-regulated anion channel (VRAC) activation, cell membrane depolarization, voltage-dependent Ca^{2+} channels activation, calcium entry and insulin secretion [211, 212].

Although to our knowledge the expression of AQPs in human endocrine pancreas remains to be assessed, it has been shown that rat β-cells express AQP7 [213–215] and mouse β-cells express AQP5, AQP7, and AQP8 [214]. Nevertheless, the expression of AQPs remains to be determined in the other cell types composing the rat and mouse islets of Langerhans.

Functional studies have shown the involvement AQP7 in the regulation of intracellular glycerol content, insulin production, and secretion in β-cells. Indeed, AQP7 knockout mice displayed a reduction in β-cell size and mass, insulin content and cAMP-driven glycerol release [215, 216] and an increase in basal and glucose-stimulated insulin secretion rates, glycerol and triglyceride contents and glycerol kinase activity [215]. However, genetic background influences the AQP7 knockout mouse phenotype. Indeed, according to their genetic background, AQP7 knockout mice had hyperinsulinemia [215, 216] with [216] or without [215] hyperglycemia, or had normal glycaemia with undetermined insulin levels [217]. In both β-cells and rat pancreatic β-cell line BRIN-BD, the addition of extracellular isosmotic glycerol induces sequential cell swelling, VRAC activation, membrane depolarization, electrical activity, and insulin secretion (Fig. 16.6) [213, 218, 219]. The entry of glycerol

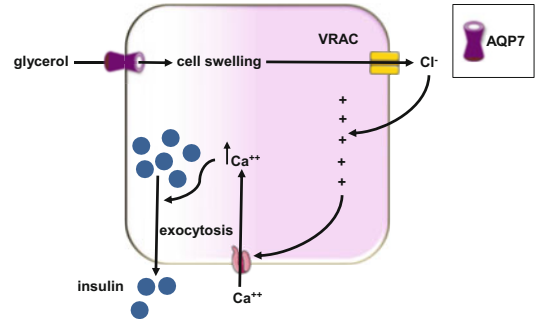

Fig. 16.6 Proposed mechanism of AQP7-mediated insulin secretion in pancreatic β-cells. Glycerol entry via AQP7 induces sequential cell swelling, VRAC activation, membrane depolarization, electrical activity, and insulin secretion. VRAC Volume-regulated anion channel

and its subsequent metabolization are likely contributing to the activation of β-cells [213]. Compared to AQP7 wildtype mice, AQP7 knockout mice had reduced insulin release in response to increased D-glucose concentration, extracellular hypotonicity or extracellular isosmotic addition of glycerol [214]. AQP7 regulates insulin release by allowing both glycerol entry and exit, and by acting directly or indirectly at a distal downstream site in the insulin exocytosis pathway [214]. So far, no clear conclusion has been drawn regarding the association between mutations or single-nucleotide polymorphisms of AQP7 and diabetes and/or obesity [220–224]. In rat pancreatic β-cell line RIN-m5F, tumor necrosis factor α decreased AQP7 expression and insulin expression but increased AQP12 expression, while lipopolysaccharides increased AQP7 and AQP12 expression but decreased insulin secretion. In addition, in cells treated by tumor necrosis factor α or lipopolysaccharides, overexpression and silencing of AQPs revealed the involvement of AQP7 in insulin secretion and of AQP12 in inflammation [225]. In rat RIN-m5F β-cells, AQP8, located in the mitochondrial and plasma membranes, has been shown to play a role in attenuating cytokine-mediated cell toxicity [226]. Further studies are required to pursue deciphering the physiological and pathophysiological role of AQPs within β-cells.

16.2 Airway Submucosal Glands

Airways submucosal gland are present in the human trachea and bronchial airways or in rat and mouse trachea. They are made of serous and mucous acinar cells forming secretory tubules, and ductal cells forming lateral and collecting ducts [227]. The airway submucosal glands secrete a fluid rich in water, ions, and mucins to ensure proper hydration of the airway surfaces, mucociliary transport, and reception of secreted molecules such as mucins [227]. Acetylcholine and VIP stimulate submucosal gland secretion [227]. The secretion of Cl^- and HCO_3^- creates an electrical gradient allowing paracellular movement of cations such as Na^+. This leads to the formation of an osmotic gradient driving the transcellular movement of water to the glandular lumen [227]. AQP5, located at the apical membrane of submucosal serous epithelial cells, plays a role in the transcellular water movement [228, 229] as shown in AQP5 knockout mice displaying a 50% reduction in submucosal secretion as compared to wild type mice [230]. Interestingly, in patients suffering from chronic obstructive pulmonary disease, AQP5 expression is decreased in submucosal glands and correlated to the disease's severity [231]. Submucosal glands from asthmatic patients displayed increased AQP5 expression [232]. In an animal model of asthma, AQP5 deletion decreased both mucin secretion and inflammatory cytokines levels [232]. Therefore, it is hypothesized that AQP5 is involved in the development of mucous hyperproduction and inflammation during chronic asthma [232, 233]. Further studies will contribute to a better understanding of the regulation and role of AQP5 in submucosal glands in relation to pulmonary diseases.

16.3 Lacrimal Glands

Lacrimal glands are made of multi lobules. Each lobule is made of acinar cells secreting a fluid into a network of ducts made of intralobular, interlobular, intralobar, interlobar, and ducts. Acinar cells are surrounded by myoepithelial cells. Acetylcholine and adrenalin are the major neurotransmitter controlling lacrimal glands secretion. The main function of lacrimal glands is to secrete a fluid rich in water, lipids, mucins, and antimicrobial substances to protect cornea from exogenous and environmental insults, thus facilitating the maintenance of a refractive surface necessary for clear vision [234].

Rat lacrimal glands express several AQPs. Indeed, AQP1 and AQP5 are expressed in endothelial cells express. Acinar cells express AQP3 at their basolateral membrane, AQP4 at their lateral membrane, AQP5 at their apical membrane, and AQP11 intracellularly [235]. Mouse lacrimal acinar cells express AQP3 only in fetal tissue but not in adult tissue [236], AQP4 at their basolateral membranes, and AQP5 at their apical membranes [16, 236, 237]. Mouse lacrimal ductal cells express AQP5 at their apical membrane [236, 238]. Mouse lacrimal ductal and myoepithelial cells express both AQP8 and AQP9 [236].

Lacrimal fluid secretion results from the formation of a primary isotonic fluid by acinar cells and its subsequent modification by the ductal cells [239]. However, ductal cells have been considered to also play a role in electrolytes and water secretion [240, 241]. The final lacrimal fluid composition may vary according to the flow rate and species considered [239]. AQPs expressed in both acinar and ductal cells are likely contributing to tear secretion. However, the involvement of AQPs in lacrimal fluid secretion has not been confirmed using knockout mice for AQP1, AQP3, AQP4, or AQP5 [238, 242]. However, one study showed significant in situ tear film hypertonicity in AQP5 knockout mice [243]. Recently, it was shown that AQP5 knockout mice presented primary dye eye phenotype that may result from the differential expression of circular RNA [244]. Genetic background and/or ways to generate AQP5 knockout mice could account for these phenotypic differences in terms of lacrimal fluid secretion. Therefore, further studies are necessary to address the assumption that AQPs may not be required for low rates such as in lacrimal glands [245] and to further

study the role of AQPs in lacrimal glands, and particularly AQP8 that has recently been shown to be expressed in ductal cells.

Defective AQP5 trafficking has been shown in lacrimal acinar cells from patients suffering from Sjögren's syndrome, an autoimmune disease characterized by dry eyes and dry mouth [246]. In addition, animal model of Sjögren's syndrome displayed modified AQP5 mRNA and protein levels in ductal (increased) and acinar (decreased) cells, as well as AQP4 expression in ductal cells (decreased) [247]. Altered calcium signaling and volume regulation occurring in Sjögren's syndrome may account these modifications [248]. Further experimentation is necessary to decipher the role of AQPs pathologies affecting lacrimal glands.

16.4 Mammary Glands

Mammary glands are apocrine glands made of alveoli lined with milk-secreting cuboidal acinar cells surrounded by myoepithelial cells, and lactiferous ducts (intralobular and interlobular ducts) draining milk to the openings in the nipple [249]. Milk is composed of sugars, lipids, proteins, vitamins, minerals, and water [250]. According to species and physiological status considered, milk contains variable percentage of water [251].

Rat and mouse mammary glands express AQP3 at the basolateral membrane of acinar cells and in intralobular and interlobular ductal cells, and AQP5 at the apical membrane of acinar cells [252]. They also express AQP1 at the apical and basolateral membranes of endothelial cells [253]. Bovine mammary glands express AQP3 and AQP4 respectively at the basolateral membrane of acinar cells and at the apical membrane of some ductal cells [254]. In addition, AQP7 is present at the apical membrane of some acinar cells and AQP1 is expressed in endothelial and myoepithelial cells [254].

AQP3 may be involved in both water and glycerol transport that are essential for milk synthesis and secretion [253]. Glycerol uptake via AQP3 may participate to milk triglycerides synthesis [253]. Interestingly, the expression pattern of AQP3 and AQP5 is distinctly regulated by lactogenic hormones in acinar and ductal mammary cells before and after parturition [255]. Besides, AQP5 may regulate milk osmolarity [255]. In mammary glands with mastitis, proinflammatory cytokines reduce milk production possibly by inducing decreased AQP3 expression [256]. Higher AQP3 expression induced by polyherbal formula accounts for increased milk production in rats [257]. AQPs are likely to play a role in mammary tumors and breast cancer [107, 258, 259]. However, it is unclear whether altered AQP expression is the cause or the consequence of neoplasia [258]. The use of *Aqp* knockout mice models and further studies will be valuable for a better understanding of the role of AQPs in milk secretion under physiological and pathological conditions, and to determine if AQPs could be used as therapeutic targets, diagnostic or prognostic biomarkers.

16.5 Eccrine Sweat Glands

Eccrine sweat glands are made of single tubular structure containing acinar cells and ductal cells. Mouse, rat, and human eccrine sweat gland acinar cells express AQP5 at their apical membrane [260–262]. Upon stimulation, AQP5 traffics to that location [260]. Acinar cells secrete a primary fluid rich in ions and water that undergoes salt reabsorption when reaching the ductal cells [263].

Whether AQP5 plays a role in eccrine sweat glands remains an open debate due to variable data obtained using different *Aqp5* knockout mice strains and methods to assess the secretion [261, 264]. Therefore, further studies will help precising the role of AQP5, and possibly as well other AQPs, in sweat secretion.

Various skin pathologies are characterized by modified AQP5 expression within the eccrine sweat glands [265–267]. Activin a receptor type 1 and cholinergic receptor nicotinic alpha 1 subunit are involved in the AQP5 overexpression detected in hyperhidrosis [268, 269]. In addition,

mutations of AQP5 gene are responsible for palmoplantar keratoderma [270–273].

16.6 Conclusions

A variety of exocrine and endocrine gland express AQPs that play a role in exocrine or endocrine secretory processes. Furthermore, some AQPs are involved in some secretory gland dysfunction or diseases. Despite considerable efforts made to understand the role of AQPs in the physiology and pathophysiology of secretory glands, further studies are still necessary to further advance the current knowledge in the field.

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