Aquaporins in Secretory Glands and their Role in Sjögren's Syndrome

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Abstract Salivary, lacrimal and pancreatic secretions are known to account for multiple physiological functions. These exocrine secretions are watery fluids containing electrolytes, and a mixture of proteins, and can be stimulated by a number of agonists. Since water movement is involved in exocrine secretion, aquaporins (AQPs) have been hypothesised to contribute to fluid production in exocrine glands. This chapter will focus on the expression, localisation and function of AQPs in salivary and lacrimal glands and pancreas. The role of multiple water and ion transporters and channels in exocrine fluid secretion will also be reviewed. Finally, this chapter will address the potential role of AQPs in Sjögren's syndrome.

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E. Beitz (ed.), *Aquaporins,* Handbook of Experimental Pharmacology 190,

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1 Introduction

Aquaporins (AQPs), a family of water-permeable channel proteins, have been shown to account for transcellular permeability in many organisms (Agre 2004; Verkman 2005). As the main function of secretory glands is fluid secretion, hypothesis was made that such glands could express AQPs. Numerous studies evaluated the expression of AQPs in secretory glands, such as salivary and lacrimal glands, and pancreas. Functional roles of AQPs in secretory glands have been investigated using physiological and biochemical approaches, and analyzing the phenotype of transgenic mice lacking an AQP.

In this chapter, an overview of the expression and role of aquaporins in secretory tissues (salivary and lacrimal glands, and pancreas) and the role of AQPs in Sjögren's syndrome will be discussed.

2 Aquaporins

Based on membrane permeability measurements performed in epithelia and various cell types, the existence of a protein channel allowing passage of water was hypothesised for many years. The first water-specific channel, named CHIP28 (channel-forming integral protein of 28 kDa) and renamed aquaporin-1 (AQP1), was isolated from red blood cells as a 28-kDa protein, prior to it being cloned and biophysically characterised (Smith and Agre 1991; Preston and Agre 1991; Preston et al. 1992). AQP1 presents high amino acid homology with major intrinsic protein (MIP) of the lens, indicating AQP1 is a member of the MIP family of membrane proteins (Preston and Agre 1991). Since the discovery of AQP1, several other aquaporins have been cloned from a wide range of organisms including mammals (Agre 2004; Verkman 2005), anurans (Suzuki et al. 2007), yeast (Pettersson et al. 2005), bacteria (Tanghe et al. 2006), parasites (Beitz 2006) and plants (Maurel 2007). In mammals, aquaporin family has 13 members: AQP0 to AQP12.

AQPs are small hydrophobic integral membrane proteins of approximately 270 amino acids. They exist as monomers of 28–30-kDa that can associate in tetramers (Verbavatz et al. 1993). AQPs present six transmembrane domains in each monomer, as well as three extracellular and two intracellular loops (Preston and Agre 2001). Two repeating Asn-Pro-Ala (NPA) sequences, present in the first intracellular and third extracellular loop, represent the amino acid signature sequence motifs of the AQPs (Agre 2004). On the basis of their permeability characteristics and their amino acid sequences, members of the AQPs family can be divided in three groups: aquaporins, aquaglyceroporins, and aquaporins containing unusual NPA motifs. Aquaporins (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8) are primarily permeable to water, whereas aquaglyceroporins (AQP3, AQP7, AQP9, AQP10) also transport glycerol and small solutes (Agre 2004; King et al. 2004; Takata et al. 2004; Krane and Goldstein 2007). Aquaporins containing unusual NPA motifs appear to be more distantly related to other mammalian aquaporins and aquaglyceroporins (Agre 2004; Ishibashi 2006).

3 Morphology of Salivary and Lacrimal Glands, and Pancreas

Typical exocrine secretory glands include salivary glands, lacrimal glands and pancreas. Exocrine secretory glands are multilobular tissues mainly composed of acinar, ductal and myoepithelial cells. Acinar cells are the sites of synthesis, storage and secretion of proteins. Acinar cells are either serous, mucous, or seromucous. The terms serous and mucous derive from classical histological terminology defining the physical consistency of secretions of acinar cells as being either viscous or watery, respectively (Denny et al. 1997). Mucous acinar cells secrete mucins-large glycoproteins negatively charged, contributing to the viscosity of mucous secretions. Serous acinar cells secrete a variety of proteins and lack mucins. Seromucous acinar cells are more closely related to mucous than serous cells due to their functional and biochemical properties, and their substantial secretion of mucins. Acinar cells drain into the intercalated ducts, and groups of intercalated ducts converge into larger intralobular ducts. These in turn drain into extralobular ducts and finally to the main collecting duct (pancreas) or excretory ducts (salivary and lacrimal glands). The primary function of ductal cells is to modify the primary fluid secreted by acinar cells. The multiple processes of myoepithelial cells surround the basal area of acinar and ductal cells. Myoepithelial cells, containing α-smooth muscle actin, are thought to contract and force fluid out of the ducts.

Salivary glands in mammals are composed of three major pairs of parotid, submandibular and sublingual glands, as well as numerous minor salivary glands scattered throughout the oral cavity. Parotid glands of most species, including rodents and human, are entirely composed of serous acinar cells, whereas submandibular and sublingual glands contain both serous and mucous acinar cells. In human submandibular glands, serous acinar cells outnumber mucous acinar cells, whereas the opposite is true for the human sublingual glands. Seromucous cells, featuring secretory granules rich in sialomucin, are present in both submandibular and sublingual glands. Lacrimal glands possess an acinous structure similar to salivary glands and are made of serous acinar cells; the exocrine pancreas is also composed of serous acinar cells. Contrary to salivary and lacrimal glands, the terminal portion of the pancreatic duct system extends into the acini, so that flattened duct cells (known as centroacinar cells) are interposed between some of the acinar cells and the lumen. Salivary and lacrimal glands, and pancreas, possess intercalated ducts.

4 AQP Expression and Localisation in Salivary and Lacrimal Glands and Pancreas

4.1 Salivary Glands

Parotid glands, both AQP1 mRNA and protein were detected in rats (Li et al. 1994) (Table 1). Immunolocalisation studies revealed the presence of AQP1 on both apical and basolateral membranes from non-fenestrated endothelial cells of capillaries and

Table 1 AQPs expressed in salivary and lacrimal glands, and pancreas

Secretory gland	AQP	Cell type	Subcellular localization		Remarks
			Rat	Human	
Salivary gland	AQP1	Endothelial myoepithelial	A + B	A + B	
	AQP3	Acinar		B	Controversy
	AQP4	Ductal	B		Controversy
	AQP5	Acinar	A + B SG	A + B	B: controversy Not confirmed
		Ductal	A		Controversy
	AQP8	Myoepithelial			
Lacrimal gland	AQP5	Acinar	A		
	AQP4	Acinar	B		
Pancreas	AQP1	Acinar	SG		Not confirmed
		Endothelial	A + B	A + B	
		Ductal	A + B	A + B	
	AQP5	Ductal	A	A	
	AQP8	Acinar	A	A	

A apical; *B* basolateral; *SG* secretory granules (see text for detail and references)

venules, while no labelling of the glandular tissue was detected (Li et al. 1994; Nielsen et al. 1993; He et al. 1997; Delporte et al. 1997). In rat submandibular glands, AQP1 is constitutively expressed in the microvasculature (King et al. 1997; Akamatsu et al. 2003). In human parotid, submandibular and labial glands, AQP1 mRNA was seen (Gresz et al. 1999; Gresz et al. 2001; Wang et al. 2003) and AQP1 protein was located in myoepithelial and endothelial cells, rather than in glandular tissues (Gresz et al. 1999; Gresz et al. 2001; Mobasheri and Marples 2004).

AQP5 was detected in rat and mouse parotid, submandibular and sublingal glands (King et al. 1997; Raina et al. 1995; Krane et al. 1999). In rat submandibular glands, AQP5 expression was noted in the apical membrane of serous acinar cells (He et al. 1997; Nielsen et al. 1997; Funaki et al. 1998). It was shown from Sprague–Dawley rats that AQP5 expression level could be high or low in rat submandibular glands (Murdiastuti et al. 2002). In animals expressing high levels of AQP5, the AQP5 protein was identified at the apical, basal and lateral membranes of acinar cells, while in animals expressing low levels of AQP5, the AQP5 protein was located at the apical and/or lateral membranes of acinar cells (Murdiastuti et al. 2002). AQP5 was also detected in rat parotid acinar secretory granules, with amino and carboxyl domain of the protein being localized at the luminal side (Matsuki et al. 2005). While most studies could not detect AQP5 labelling in rat submandibular ductal cells (He et al. 1997; Funaki et al. 1998; Murdiastuti et al. 2002), few studies reported AQP5 expression at the apical membranes of intercalated ducts in submandibular glands (Nielsen et al. 1997; Matsuzaki et al. 1999) and intracellular in interlobular ducts in parotid glands (Ishikawa et al. 2005). In rat minor salivary glands of the tongue, AQP5 was mainly located at the apical membranes of the acinar cells (Matsuzaki et al. 2003). In human parotid, submandibular and labial glands, AQP5 labelling was

confined to the apical membrane of acinar cells, but absent in ductal cells (Wang et al. 2003; Steinfeld et al. 2001).

Though originally AQP8 was reported as being expressed in rat salivary gland acinar cells (Koyama et al. 1997; Wellner et al. 2000), it is now believed to be located in myoepithelial cells (Elkjaer et al. 2001; Wellner et al. 2006). The expression of AQP3 and AQP4 in salivary gland remains controversial. In rat submandibular glands, AQP3 mRNA was noted (Akamatsu et al. 2003), but the expression of the AQP3 protein was not observed (Nielsen et al. 1993; King et al. 1997). Although not confirmed by others, AQP3 mRNA was detected in human parotid, submandibular, sublingual and labial glands, (Gresz et al. 2001; Wang et al. 2003) and AQP3 protein was localized at basal and lateral membranes of both serous and mucous acinar cells (Gresz et al. 2001; Beroukas et al. 2002). In rat and human salivary glands, AQP4 mRNA (Gresz et al. 2001; Wang et al. 2003; Akamatsu et al. 2003; Hasegawa et al. 1994; Delporte and Steinfeld 2006), as well as AQP4 protein detection (Gresz et al. 2001; King et al. 1997; Frigeri et al. 1995; Nielsen et al. 1997) was not consistent. The detection of AQP6 and AQP7 mRNA in human parotid glands (Wang et al. 2003) has not been confirmed by other studies.

4.2 Lacrimal Glands

In mouse extraorbital and intraorbital lacrimal glands, AQP4 labelling was located at the basolateral membrane of acinar cells, while AQP5 was situated at the apical membrane of acinar and ductal cells (Ishida et al. 1997; Hamann et al. 1998). In response to pilocarpine-induced lacrimal secretion, the AQP5 protein expression was increased at the apical membrane of acinar cells (Ishida et al. 1997). In rat extraorbital and intraorbital lacrimal glands, AQP5 mRNA was by Northern blot analysis (Raina et al. 1995) and AQP5 protein was exclusively located at the apical membrane of acinar cells (Matsuzaki et al. 1999; Hamann et al. 1998; Funaki et al. 1998) (Table 1).

4.3 Pancreas

In rat exocrine pancreas, while AQP1, AQP4, AQP5 and AQP8 mRNA was detected, only the expression of the AQP1, AQP5 and AQP8 proteins was observed (Hurley et al. 2001; Burghardt et al. 2003) (Table 1). AQP1 expression was seen in rat intralobular and interlobular ducts (Furuya et al. 2002) and microvasculature (Hurley et al. 2001), but not in acinar cells, centroacinar cells, and intercalated ducts (Furuya et al. 2002; Ko et al. 2002). In intralobular and interlobular ductal cells, AQP1 was located at the apical and basolateral membranes, as well as in caveolae and vesicle-like structures (Furuya et al. 2002; Ko et al. 2002). AQP1 was also found in pancreatic acinar zymogen granules (Cho et al. 2002). AQP5

was located at the apical membrane of centroacinar and intercalated ductal cells (Burghardt et al. 2006). AQP8 expression was confined to the apical membrane of acinar cells (Hurley et al. 2001).

In human pancreas, while AQP1, AQP3, AQP4, AQP5 and AQP8 mRNA are noted, only the expression of AQP1, AQP5 and AQP8 protein was observed (Burghardt et al. 2003). AQP1 was located in capillaries, centroacinar cells, and in both apical and basolateral membranes of intercalated ductal cells (Burghardt et al. 2003). AQP5 was observed at the apical membrane of intercalated ductal cells, while AQP8 was confined to the apical membrane of acinar cells (Burghardt et al. 2003).

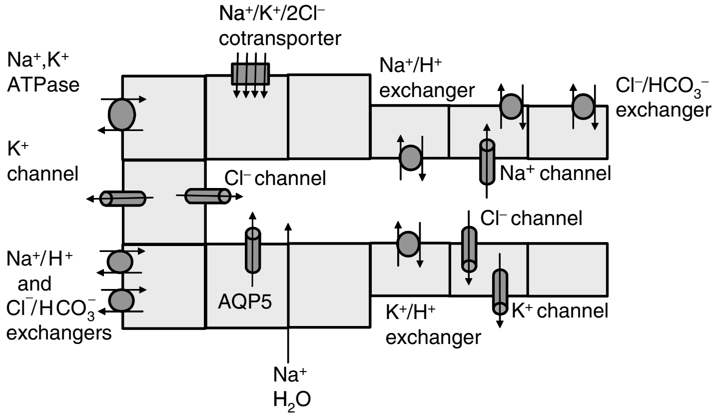
AQP12 protein was noticed intracellularly in mouse pancreatic acinar cells (Itoh et al. 2005).

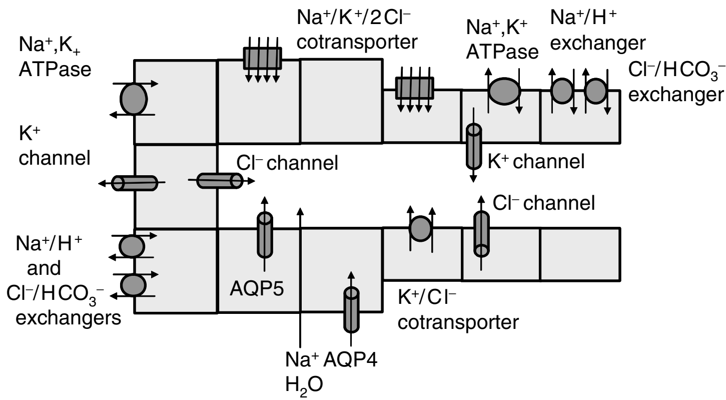
5 Secretion and Fluid Transport Mechanisms in Salivary Glands, Lacrimal Glands and Pancreas

5.1 Salivary Glands

The average daily output of saliva in man is about 750–1,000 ml. The functions of saliva include protection and hydratation of mucosal structures within the oral cavity, oropharynx and oesophagus. Saliva also contributes to initiation of digestion, and contains many antimicrobial agents. Salivary dysfunction clinically manifests as dysphagia, oral pain, dental caries, and infections from opportunistic microorganisms (Ship et al. 2002).

Secretion of primary isotonic fluid by acinar cells into the lumen of the acini requires coordinated regulation of many water and ion transporters and channels (Fig. 1a) (Melvin et al. 2005; Turner and Sugiya 2002; McManaman et al. 2006). The Na^+/K^+ ATPase, located at the basolateral membrane of acinar cells, leads to an inwardly-directed Na^+ chemical gradient. The intracellular Cl^- concentration is increased beyond its electrochemical gradient by the $Na^+/K^+/2Cl^-$ co-transporter using the Na^+ gradient, located at the basolateral membrane, as well as by the paired basolateral Cl^-/HCO_3^- and Na^+/H^+ exchangers. The opening of K^+ and Cl^- channels, located respectively at both the basolateral and apical membranes, is triggered by agonist-stimulation and subsequent intracellular Ca^+ mobilization, leading to negative electrical potential difference allowing passive movements of cations across acinar cell tight junctions. HCO_3^- is secreted across the apical membrane via an ion channel, possibly through the same Cl^- channel involved in Cl^- secretion. Accumulation of ions into the lumen generates a transepithelial osmotic gradient driving water movement through the apical AQP5 channels and paracellular pathways. While the primary isotonic fluid secretion passes through ducts, NaCl is reabsorbed through Na^+ channels, Cl^- channels and Na^+/H^+ exchangers, while K^+ and HCO_3^- are secreted via Cl^-/HCO_3^- and K^+/H^+ exchangers. The final hypotonic secreted saliva results from relative water impermeability of the ducts





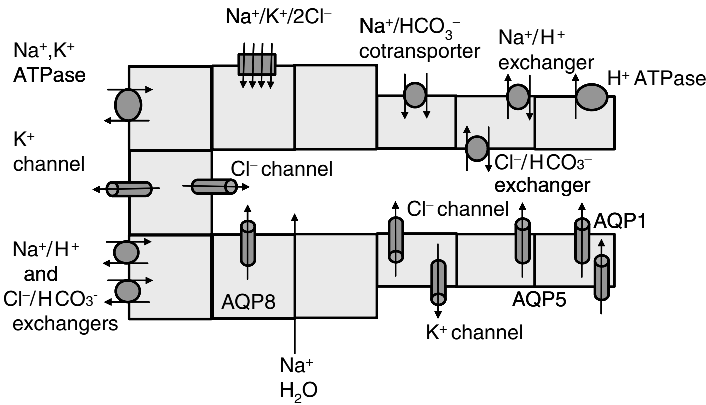


Fig. 1 Salivary, lacrimal and pancreatic secretions. Acinar cells (*grey squares*) secrete a primary fluid which is modified by ductal cells (*grey rectangles*). Water and ion transporters and channels expressed in acinar and ductal cells are indicated in figure (see text for details)

(Mangos and McSherry 1970; Mangos et al. 1973; Baum 1993; Cook et al. 1994; Turner and Sugiya 2002). The composition of saliva depends on both the origin of the stimulation (sympathic or parasympathic) and the type of salivary gland stimulated (Proctor and Carpenter 2007).

In rat parotid acinar secretory granules, inhibition of AQP5 induces secretory granules swelling and lysis (Matsuki et al. 2005). Due to the involvement of AQP5 in the osmoregulation of rat parotid secretory granules and the hypothesis that AQPs can function as osmosensors, rather that water channels (Shachar-Hill and Hill 2002; Hill et al. 2004), AQP5 is suggested to act as an osmosensor in these secretory granules (Sugiya and Matsuki 2006). AQP5 is also suggested to play the role of an osmosensor controlling the paracellular flow in rat salivary glands (Murakami et al. 2006; Hill and Shachar-Hill 2006).

Intracellular AQP5 labelling has been found in rat parotid acinar cells (Matsuzaki et al. 1999) and AQP5 is reported to translocate from intracellular vesicles to plasma membrane in vitro in response to stimulation of muscarinic receptors (Ishikawa et al. 1998), although such translocation has not been detected in vivo (Gresz et al. 2004).

Transgenic mice lacking AQP are helpful in understanding the role of AQP in saliva secretion. Transgenic mice lacking AQP1 (Ma et al. 1999; Verkman et al. 2000) or AQP8 (Yang et al. 2005) revealed no defect in pilocarpine-induced saliva secretion (not in volume or in composition), suggesting that neitherAQP1, nor AQP8 plays a major role in the salivation process. However, transgenic mice lacking AQP5 displayed reduced pilocarpine-stimulated saliva secretion ($\pm 60\%$), hypertonic (420 mosm) and more viscous saliva, while amylase and protein secretion were not modified (Ma et al. 1999). Other studies showed that hyposalivation was due to a dramatic reduction in water membrane permeability of acinar cells, rather than changes in whole body fluid homeostasis (Krane et al. 2001). Latter data suggests that AQP5 plays a key role in saliva secretion. No data is currently available to assess a possible role of other AQPs in the salivary secretion process. While contradictory data exists concerning localisation of AQP5 in ductal cells (see above), further studies will be needed to investigate the functional role of AQP5 in the absorption and/or secretion of small solutes in ductal cells.

5.2 Lacrimal Glands

The average daily output of lacrimal secretion in man is about 5 ml. Lacrimal secretion contributes to the aqueous layer of the precorneal tear film. The rate of lacrimal secretion is controlled by parasympathetic and sympathetic innervations. Since the acinar cells secrete an isotonic fluid, and the final lacrimal secretion is hypertonic, it is suggested that ductal cells secreted additional K^+ and Cl^- (Mircheff 1989; Matsuzaki et al. 1999; Hamann et al. 1998; Funaki et al. 1998; Mircheff et al. 1994).

In acinar cells, the underlying mechanisms responsible for lacrimal secretion are quite similar to those occurring during salivary and pancreatic secretion (Fig. 1b). The presence of AQP4 and AQP5, at the basolateral and the apical membrane of

acinar cells respectively, suggested the involvement of those AQPs in the lacrimal secretory process (Ishida et al. 1997; Hamann et al. 1998). However, knockout mice lacking AQP1, AQP3, AQP4 or AQP5 displayed no modification in basal and pilocarpine-stimulated lacrimal secretion (not in volume or in composition). This strongly suggests that these AQPs do not play a major role in tear formation. The role of ductal cells in the K^+ and Cl^- secretion has recently been elucidated (Toth-Molnar et al. 2007). Following parasympathetic stimulation, Na^+ and Cl^- enter ductal cells in response to the activation of Na^+/H^+ and Cl^-/HCO_3^- exchangers at the basolateral membrane (Fig. 1b). Additionally, Na^+ was also shown to enter the cells via the $Na^+/K^+/2Cl^-$ cotransporters (Walcott et al. 2005). Intracellular available H^+ and HCO_3^-, necessary for Na^+ and Cl^- influx, are generated by the dehydration of carbonic acid by carbonic anhydrase. The elevated intracellular Na^+ can be exchanged for K^+ through the basolateral Na^+/K^+ ATPase and consequently induces an intracellular increase in the K^+ concentration. Both intracellular Cl^- and K^- are finally secreted into the ductal lumen through Cl^- (CFTR) and K^- channels, and/or K^+/Cl^- cotransporters (Toth-Molnar et al. 2007).

5.3 Pancreas

In humans, approximately 1,500 ml of pancreatic fluid is secreted per day. The functions of the pancreatic fluid include neutralization of fluid arriving from the stomach, hydrolysis of starch, proteins, lipids and nucleic acids. Contrary to salivary and lacrimal glands, most fluid secretion generated by the pancreas derives from ductal rather than acinar cells.

The ionic mechanisms responsible for pancreatic secretion by acinar cells are quite similar to those described for salivary glands (McManaman et al. 2006) and lead to production of a NaCl-rich isotonic fluid (Fig. 1c). Water moves to the acinar lumen through tight junctions and possibly via AQP8 located at the apical membrane (Hurley et al. 2001; Burghardt et al. 2003). The contribution of AQP8 to the water membrane permeability of rat pancreatic acinar cells, evaluated using video microscopy to measure the cell swelling in response to hypotonic stress following or not the exposure to $HgCl_2$ (an AQP blocker), was estimated at 90% (Hurley et al. 2001). However, probably due to small amount of fluid generated by acinar cells, knockout mice lacking AQP8 seemed to display normal pancreatic function since there was no obvious defect in the processing of dietary fat (Yang et al. 2005). On the other hand, in rat pancreatic acinar zymogen granules, AQP1 was shown to participate in basal as well as GTP-mediated vesicle water entry and swelling (Cho et al. 2002; Abu-Hamdah et al. 2004). Pancreatic ductal cells secrete most of the fluid rich in HCO_3^- to alkalinize and hydrate the primary fluid secreted by the acinar cells (Fig. 1c).

At the basolateral membrane of ductal cells, HCO_3^- uptake is achieved by Na^+-HCO_3^- cotranporters and also by H^+ ATPase and Na^+/H^+ exchangers acting together with carbonic anhydrase. At the apical membrane, HCO_3^- secretion is

explained by the combined activity of Cl^-/HCO_3^- exchangers and Cl^- conductance; also either the CFTR or a Ca^{2+}-activated Cl^- channel (Steward et al. 2005; McManaman et al. 2006). In rat interlobular ducts, shown to express AQP1, fluid secretion evoked by secretin was almost completely abolished by $HgCl_2$ (80–90% decrease), suggesting that AQP1 represented the main water pathway (Ko et al. 2002). In rodents, knockout mice lacking either AQP1 or AQP5 have not yet shown any abnormality in pancreatic secretion. Several explanations might account for this data: the weak expression of AQP1 and AQP5 or the redundancy of having them expressed in the intercalated ducts thought to be the main site of fluid secretion (Burghardt et al. 2003), or the possible existence of a slow secretory rate. Analysis of double AQP1 and AQP5 knockout mice would be valuable in determining the joint contribution of these AQPs to pancreatic fluid secretion.

6 Sjögren's Syndrome

6.1 Pathogenesis of Sjögren's Syndrome

Sjögren's syndrome is an autoimmune lacrimal and salivary gland disease characterised by lymphocyte infiltrates of the exocrine glands and/or the production of auto-antibodies. Clinically, patients suffering from Sjögren's syndrome present keratoconjunctivitis sicca and xerostomia. A subset of patients may develop systemic nonglandular manifestations (Thanou-Stavraki and James 2007; Garcia-Carrasco et al. 2006). Patients may have either primary or secondary (including another autoimmune disease, e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylysis ...) Sjögren's syndrome (Fox 2005; Konttinen et al. 2006). Primary Sjögren's syndrome has a prevalence of 0.5% and a female predominance ratio of 9:1 compared with men. The American-European criteria for diagnosis of Sjögren's syndrome published in 2002 (Vitali et al. 2002) includes inflammatory infiltrates in lip biopsy, auto-antibodies and clinical features. Despite extensive molecular, histological and clinical studies, the underlying cause of Sjögren's syndrome remains unknown. Pathogenesis seems to be multifactorial, where several steps are necessary to establish the disease. The initial step in the establishment of the disease probably involves glandular epithelial cells, vascular endothelial cells, stromal and dendritic cells (Fox 2005). Further steps include environmental triggers (such as viral infection of the glands or intercurrent infection stimulating dendritic or glandular epithelial cells), participation of genetic factors, migration of lymphocytes to the gland in response to cytokines and chemokines, co-stimulation of innate and acquired immune systems, glandular destruction, apoptosis, activation of T- and B-lymphocytes within the glands, production of auto-antibodies (for example against the muscarinic M3 type receptor for acetylcholine, the nuclear proteins Ro/SSA and La/SSB, α-fodrin...), and development of eye and mouth dryness (Fox 2005; Ramos-Casals and Font 2005; Garcia-Carrasco et al. 2006).

Salivary and lacrimal glands of patients with Sjögren's syndrome display infiltrating lymphocytes and local glandular destruction (Fox 2005). The degree of glandular destruction does not necessarily correlate with secretory dysfunction (Humphreys-Beher et al. 1999). There is evidence that subclinical exocrine pancreatic disease may also be present in some patients with Sjögren's syndrome. Auto-antibodies against pancreatic duct cells (also cross-reacting with parotid, submandibular and lacrimal ductal cells (Ludwig et al. 1977)), and increased serum antibodies against CA 19–9, a marker of pancreatic tumour that can also be elevated with pancreatitis, have been reported in some patients suffering from Sjögren's syndrome (Safadi et al. 1998). Functional pancreatic impairment, such as elevated immunoreactive trypsin, amylase and pancreatic isoamylase, appear to be more severe in patients with longer disease duration, and related to the degree of alteration of salivary flow rather than the degree of histological salivary gland changes or the type of Sjögren's syndrome (primary or secondary) (Coll et al. 1989; Ostuni et al. 1996; Pal et al. 1987).

Ethical issues and delay in the appearance of symptoms, makes it difficult to study the wide array of factors intervening in the pathogenesis of Sjögren's syndrome in human patients. To circumvent this problem, several animal models have been developed for studying different aspects of the physiopathology of the disease. Most of the animal models for Sjögren's syndrome present a loss of secretory lacrimal and salivary functions (van Blokland and Versnel 2002; Soyfoo et al. 2007a).

6.2 AQPs and Sjögren' Syndrome

In labial salivary gland biopsies of Sjögren's syndrome patients, AQP1 distribution in myoepithelial cells decreased by 38%, while no changes were observed in endothelial cells of non-fenestrated capillaries (Beroukas et al. 2002). This decreased AQP1 expression in myoepithelial cells led to the hypothesis that myoepithelial cell dysfunction plays a role in its pathogenesis (Beroukas et al. 2002). The treatment of a patient suffering from Sjögren's syndrome with rituximab revealed great improvement of xerostomia, a marked increase in AQP1 expression in myoepithelial cells (Ring et al. 2006). Type 3 muscarinic receptor activation by acetylcholine induced the contraction of myoepithelial cells (Beroukas et al. 2002) and cell volume modification mediated by AQP1 could participate to vascular smooth muscle cell contraction (Shanahan et al. 1999). A hypothesis has been proposed that if AQP1 translocates, similar to AQP5 (Ishikawa et al. 1998), in response to acetylcholine stimulation, AQP1 might participate in rapid myoepithelial cell volume modifications and contraction (Shanahan et al. 1999). The contraction of myoepithelial cells, embracing the acini, will constrict the acini lumen and facilitate saliva flow. However, this hypothesis is not supported by data obtained with transgenic mice lacking AQP1 (Ma et al. 1999; Verkman et al. 2000).

Dacryoadenitis mice models such as MRL/lpr (24-week-old), NOD/Shi Jci (10-week-old), NFS/s-TX (10-week-old), or lipopolysaccharide-injected mice (Hirai

et al. 2000) exhibited higher AQP5 protein concentration in tears, suggesting that AQP5 leaks into tears, when acinar cells of lacrimal glands are damaged by lymphocyte infiltration. Similar results were further obtained with patients suffering from Sjögren's syndrome and presenting a dry eye syndrome (Ohashi et al. 2003).

Immunohistochemical distribution of AQP5 in normal human labial salivary (Steinfeld et al. 2001; Beroukas et al. 2001) and lacrimal glands (Tsubota et al. 2001) revealed that AQP5 was expressed at the apical membrane of acinar cells, similar to its localisation in human parotid glands (Gresz et al. 2001). In contrast to its normal apical localization in acinar cells, AQP5 was abnormally contained at either the basal membrane or the cytoplasm of acinar cells from respective minor salivary (Steinfeld et al. 2001) or lacrimal glands (Tsubota et al. 2001) for patients suffering from Sjögren's syndrome. Contradictory data documenting normal AQP5 distribution in minor salivary gland biopsies from patients suffering from Sjögren's syndrome (Beroukas et al. 2001) could be explained by the use of distinct antibodies, or differences existing between the investigated populations. More recently, in non-obese diabetic (NOD) mice, generally considered to be a good animal model for Sjögren's syndrome (Humphreys-Beyer et al. 1994; Cha et al. 2002; Soyfoo et al. 2007a), abnormal AQP5 distribution was also observed in salivary glands (Konttinen et al. 2005; Soyfoo et al. 2007b). Indeed, in NOD mice, two independent studies reported that AQP5 distribution was not restricted to apical membrane of acinar cells as in control mice, but rather, present at both apical and basolateral membranes (Konttinen et al. 2005; Soyfoo et al. 2007b). This data further supports observations that implied a loss of ordered and polarised expression of AQP5 in human minor salivary and lacrimal glands of patients suffering from Sjögren's syndrome. Reduced AQP1 expression in myoepithelial cells of salivary glands (Beroukas et al. 2002) and abnormal AQP5 expression in acinar cells of both salivary and lacrimal glands (Steinfeld et al. 2001; Tsubota et al. 2001; Konttinen et al. 2005; Soyfoo et al. 2007b) suggested that both AQP1 and AQP5 could participate in the pathogenesis of Sjögren's syndrome, although they could not directly account for salivary and lacrimal secretory defects.

B-cell-depleting therapies, such as rituximab (anti-CD20), appear promising for the treatment of Sjögren's syndrome (Thanou-Stavraki and James 2007; Ramos-Casals and Brito-Zeron 2007). Several studies using rituximab have shown improvement of sicca features and glandular manifestations, as well as complete remission of lymphoma in some cases (Ramos-Casals and Brito-Zeron 2007). Interestingly, rituximab was reported to improve xerostomia and increase the AQP5 expression at the apical membrane of acinar cells in patients with Sjögren's syndrome (Ring et al. 2006). It has also been suggested that treatment of ductal cells (which preferentially survive in secretory glands of patients with Sjögren's syndrome) with 5-aza-2′-deoxycytidine (a DNA demethylation agent) could result in increased expression of AQP5 (Motegi et al. 2005).

Further studies in Sjögren's syndrome patients are required to elucidate if changes of AQP5 expression and/or localisation are directly linked to the inflammatory mechanisms or are secondary effects caused by prolonged hyposecretion.

7 Conclusion

Several AQPs have been shown to be expressed in salivary and lacrimal glands and pancreas.Though, water movement contributes to exocrine secretions, a direct participation of AQPs has not been demonstrated in all secretory glands. Indeed, while certain data supports the involvement of AQP5 in the salivary secretion, a major role of AQPs in lacrimal and pancreatic secretion has not yet been clearly demonstrated. In Sjögren's syndrome patients, modification of AQP1 and AQP5 expression and abnormal AQP5 distribution might be either linked to the inflammatory mechanisms or are secondary effects caused by prolonged hyposalivation; they are however unlikely to directly account for salivary and lacrimal secretory defects.

Acknowledgments We acknowledge the contributions of Dr Bruce Baum and Dr Martin Steward in helpful comments and discussion. This work was supported by grant 3.4604.05 from the Fund for Medical Scientific Research (FRSM, Belgium).

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