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Review

Aquaporins in salivary glands and pancreas ☆

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ABSTRACT

Background: Salivary glands and pancreas are involved in saliva secretion, pancreatic fluid secretion and insulin secretion. These functions are essential for proper oral, pancreatic and glucose homeostasis. Aquaporins are water-permeable transmembrane protein involved in the physiology of these secretory gland functions.
Scope of review: This review gives an overview of the morphology of salivary glands and pancreas, the expression and localization of aquaporins, the secretion roles and mechanisms, the physiological roles of aquaporins, and the role of aquaporins in pathophysiological conditions.
Major conclusions: Several aquaporins are expressed in salivary glands and pancreas, and some play important physiological roles. Modulation of aquaporin expression and/or trafficking may contribute to the pathogenesis of diseases affecting salivary glands and pancreas glands such as xerostomic conditions, pancreatic insufficiencies and diabetes.
General significance: Aquaporins are involved in physiological and pathophysiological processes in salivary glands and pancreas. They could represent therapeutic targets for the treatment of diseases affecting the salivary glands and pancreas. This article is part of a Special Issue entitled Aquaporins.

1. Introduction

Aquaporins (AQPs), a family of transmembrane channel proteins, account for water transcellular permeability in most living organisms [1,2]. AQPs are permeable to water, but also to small solutes as cations and glycerol [1,2]. According to their permeability and structure, AQPs can be subdivided into classical AQPs, primarily permeable to water but also to gasses and ions (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8) [1,3,4]; aquaglyceroporins also permeable to glycerol and other small solutes (AQP3, AQP7, AQP9, AQP10) [1,5,6]; and non classical AQPs with permeability specificity that has not been clearly established [7]. The expression and roles of AQPs have been studied in secretory glands where their main function is in fluid secretion. This review will give an overview of the expression and roles of AQPs in two types of secretory glands: the salivary glands (SG) and the pancreas.

2. Salivary glands

2.1. Morphology

The morphology of SG consists of acinar, ductal and myoepithelial cells [8]. Acinar cells synthesize, store and secrete proteins, and are either serous, mucous or seromucous [8]. The acinar cell secretions drain into intercalated ducts. Intercalated ducts converge into large intralobular ducts draining into extralobular ducts and finally into excretory ducts [9]. The ductal cells modify the primary fluid secretion secreted by the acinar cells. Both acinar and ductal cells are polarized epithelial cells characterized by the presence of an apical site and a basolateral site. The myoepithelial cell processes surrounding the basal area of acinar and ductal cells could contract and force fluid out of the ducts [10].

In mammals, SMG are comprised of three major pairs: parotid (PG), submandibular (SMG) and sublingual glands (SLG), as well as labial SG (LSG) scattered throughout the oral cavity [8]. Rodent and human PG are exclusively composed of serous acinar cells, whereas SMG and LSG contain both serous and mucous acinar cells. Human SMG contain more serous acinar cells than mucous acinar cells, while it is the opposite in LSG. Still both human SMG and LSG contain some seromucous acinar cells [9].

2.2. Aquaporin expression and localization

Prenatal development of SG consists of an initial epithelial bud which undergoes branching morphogenesis through processes involving repeated terminal bud branching, lumen formation, and cellular differentiation [8,11]. After birth SG continue to mature to reach the young adult stage. Several AQPs are expressed during morphogenesis of salivary glands. They could be involved in cell migration occurring during this

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process, as AQP involvement in cell migration has been described [12–14]. Table 1 summarizes AQP expression in salivary glands.

2.2.1. Rat

AQP1, AQP3, AQP4 and AQP5 expression has been documented during pre- and post-natal development in rat SMG [15]. Contradictory data exist concerning the absence [16,17] or presence [18] of AQP4 expression in adult rat SMG. While most studies have shown the lack of AQP5 expression in ductal cells from adult rat SMG [19–21], a few studies have detected apical AQP5 labelling [17,22]. AQP1 is expressed in blood vessels during pre- and post-natal development [15,19,23–25].

In adult rat PG both mRNA and protein of AQP1 [23] and AQP5 [26,27] are expressed. In rat PG acinar cells, AQP6 is expressed in the plasma membrane near tight junctions and the secretory granule membranes [28]. AQP8 is located in myoepithelial cells from rat SG acinar cells [29–31].

2.2.2. Mouse

AQP1, AQP3, AQP4 and AQP5 mRNA is detected during pre- and post-natal development [32]. The subcellular localization of AQP5 and AQP11 varies during pre- and post-natal development [33–35]. AQP8 expression increases around birth [32]. Mouse PG express AQP5 at the apical membrane (APM) and basolateral membrane (BLM) of acinar cells [36].

2.2.3. Human

All SG express AQP1 [37–39] localized to capillaries and myoepithelial cells [40]. AQP3 is expressed in all human SG [38,39] and localized to BLM of both serous and mucous acinar cells, and not to ductal cells [38,41]. Even though AQP4 mRNA has been detected in all SG, AQP4 protein expression has not been confirmed [38,39]. In all SG, AQP5 is expressed and localized to the APM of acinar cells, but not to the ductal cells [38,39,42]. AQP5 expression is confined to the serous acinar cells and absent from the mucous acinar cells of both SMG and LSG [43]. AQP6 and AQP7 mRNAs are detected in SMG [39].

2.3. Secretion roles and mechanisms

In humans, 750 to 1000 ml of saliva is secreted daily. At rest, saliva is mainly secreted by the SMG and LSG, while under stimulation saliva is mainly secreted by PG. Saliva contributes to the protection and hydratation of mucosal structures, initiation of digestion and antimicrobial defences. Saliva secretion dysfunction therefore leads to multiple clinical manifestations [44].

Fluid secretion by SG involves two steps (Fig. 1A). During the first step, the acinar cells secrete an isotonic-like fluid rich in NaCl involving several ionic transporters [45,46]. Luminal ion accumulation generates a transepithelial osmotic gradient driving large water efflux through the apical AQP5 channels and possible paracellular pathways. The resulting primary fluid secretion then reaches the ductal lumen. During the second step, the ductal cells, relatively impermeable to water [47], modify the composition of the fluid by reabsorbing most of the Na^+ and Cl^-, and secreting HCO_3^- and K^+. The final saliva is hypotonic (Fig. 1B) [45,46].

Fluid and bicarbonate secretion are under the control of endocrine, paracrine and neuronal inputs [45,46,48,49]. The main neuronal regulation of salivation is achieved by parasympathetic and sympathetic nerve endings. Acetylcholine activates M3 and M1 (to a less extent) receptors in both acinar and ductal cells, leading to intracellular calcium release and mainly to fluid secretion [48,50]. Noradrenalin activates ß-adrenergic receptors, leading to intracellular cAMP increase and mainly to enzyme secretion from acinar cells, and fluid and electrolyte transport in ductal cells [51,52]. Purinergic receptors, such as P2X7, also play an important role in salivation [53,54].

Table 1
AQPs expression in salivary glands, exocrine and endocrine pancreas.

QP	Salivary gland			Exocrine pancreas			Endocrine pancreas		
	R	M	H	R	M	H	R	M	H
AQP1	Endoth	Endoth	Endoth Myo	Acinar Ductal Endoth	Ductal	Acinar Ductal Endoth			
AQP3	Acinar*	ND	Acinar						
AQP4	Ductal*	ND							
AQP5	Acinar Ductal*	Acinar	Acinar	Acinar Ductal	Ductal	Ductal		ß-cells	
AQP6	Acinar			ND					
AQP7				ND			ß-cells	ß-cells	
AQP8	Myo			Acinar		Acinar		ß-cells	
AQP11		Ductal Myo							
AQP12					Acinar	ND			

Acinar: acinar cells; Ductal: ductal cells; Endoth: Endothelial cells; Myo: myoepithelial cells; *: controversy; ND: cell type not determined (see text for details and references).

2.4. Physiological roles of aquaporins

AQP5 knockout mice revealed that AQP5 plays a major role in saliva secretion [55,56]. Indeed, AQP5 knockout mice displayed a 60% decrease in pilocarpine-stimulated saliva production and a more viscous and hypertonic saliva [55,56]. Furthermore, compared to wild type mice, water permeability decreased by 65% in parotid and 77% in sublingal acinar cells from AQP5 knockout mice submitted to osmotic challenges [56]. AQP1, AQP4 and AQP8 knockout mice revealed that these AQPs are unlikely involved in salivation [55,57,58]. Indeed, AQP1, AQP4 and AQP8 knockout mice displayed pilocarpine-induced saliva productions comparable to that of wild type mice [55,57,58]. The implication of other AQPs in salivation has not been demonstrated. Further studies will be required to precise the functional role and regulation of AQP5 in ductal cells.

In response to acetylcholine, AQP5 traffics *in vitro* from intracellular vesicles to the acinar plasma membrane [22,59]. However, *in vivo* trafficking of AQP5 could not be detected [60]. In rat PG, AQP5 is involved in the osmoregulation of acinar secretory granules [61]. Several experiments using submandibular glands submitted to hypertonic challenges provided evidences for the existence of paracellular flow, *via* tight junctions, during the process of saliva secretion [62,63]. An osmosensor feedback model was proposed in which osmosensor, likely AQP5 in salivary glands, controls the tonicity of the transported fluid by mixing transcellular and paracellular flows [64–66]. However, another model consisting of a simple transcellular-only osmotic mechanism sufficiently predicts the results of AQP knockout studies, even though AQP knockout studies do not give sufficient information to definitively rule out an additional paracellular pathway [67,68]. Therefore, the involvement of a paracellular *versus* transcellular pathway in saliva secretion still remains an ongoing debate.

2.5. Aquaporins and pathophysiological conditions

2.5.1. Senescence

In human and mice, declined salivation occurs gradually as age increases [69,70]. In senescent rats, decreased parotid NOS synthase accounts for decreased AQP5 translocation [71,72], while civimeline increased AQP5 expression at the APM and could therefore be used as a therapeutic agent for the treatment of age-related xerostomia [73]. DNA demethylation restores salivation in a murine aging model [70]. Analogs of acetylcholine, activators of NOS and DNA demethylation agents could represent useful drugs for xerostomia treatment in elderly individuals.

2.5.2. Radiation therapy

Ionizing radiation therapy represents a key component of therapy for most patients diagnosed with head and neck cancer (±500,000

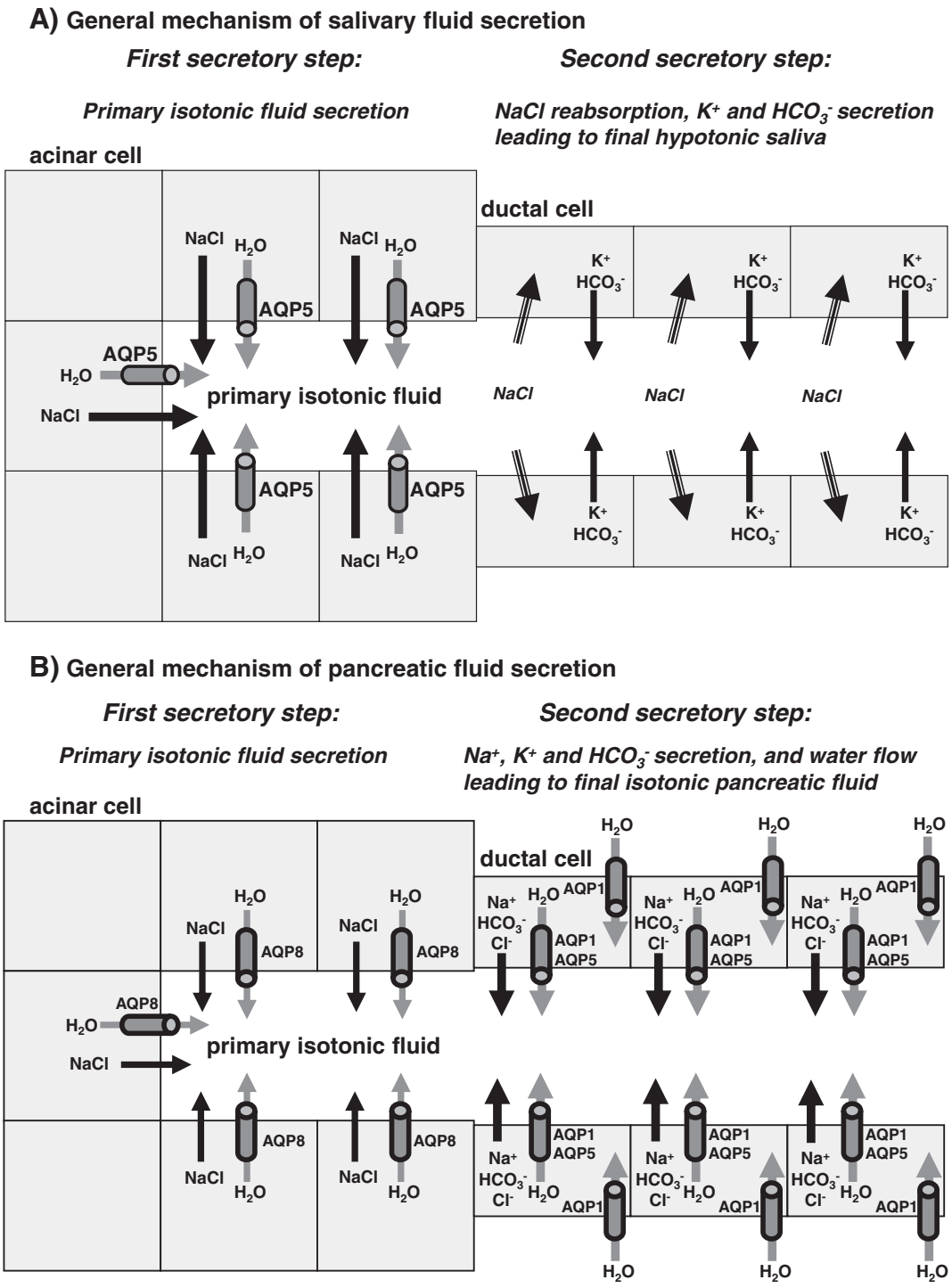

Fig. 1. General mechanisms of salivary and pancreatic fluid secretions. (A) General mechanism of salivary fluid secretion. Acinar cells secrete a large volume of isotonic-like fluid rich in NaCl. The generation of a transepithelial osmotic gradient drives water flow through apical AQP5 and paracellular pathways. Ductal cells, relatively impermeable to water, reabsorb most NaCl and secrete K^+ and HCO_3^-. (B) General mechanism of pancreatic fluid secretion. Acinar cells secrete a small volume of isotonic-like fluid rich in NaCl. Water flows though acinar AQP8. Ductal cells secrete Na^+, HCO_3^-, Cl^- as well as most of the water *via* AQP1 and AQP5.

new cases per year worldwide). However, an adverse effect of this therapy is damage to the SG acinar cells lying in the radiation field [73]. Loss of AQP5 expression may account for the loss of salivation observed in irradiated rat SG [25,74,75]. Rat irradiated SG present decreased AQP5 labelling intensity, reduced number of AQP5-lallebed intercalated ducts [76], and loss of AQP5 labelling in acinar cells (Delporte, Redman and Baum, unpublished data; [77]). Irradiated PG present reduced salivation due to a perturbation in AQP5 translocation, rather than in intracellular calcium mobilization [75].

Based on the understanding of the normal physiology of SG ductal cells, it was hypothesized that following irradiation therapy, ductal cells could generate an osmotic gradient (extracellular lumen > intracellular) allowing fluid secretion if a facilitated water pathway was introduced [25,78]. Gene transfer of AQP1 was achieved using a recombinant adenoviral vector coding for human AQP1 (AdhAQP1) driving both AQP1 expression and osmotically-driven fluid secretion in epithelial cells [25,79,80]. AdhAQP1 delivery restored saliva secretion in irradiated SMG from rats [25], non-

human primates [81] and miniature pigs [82]. In a clinical trial using subjects with prior irradiated PG, AdhAQP1 vector delivery was safe, induced increased parotid flow rate and relieved symptoms in a subset of subjects [83]. This clinical trial is unique by conducting gene therapy in the oral cavity for a non malignant condition, and in using AQP as a therapeutic agent.

2.5.3. Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocyte infiltrates of the exocrine glands, mainly salivary and lachrymal, and the production of autoantibodies [84]. Patients may present primary or secondary SS [85,86]. Worldwide prevalence of primary SS is estimated to 0.5% with a 9:1 female:male ratio. Pathogenesis of SS appears to be multifactorial [87–90]. The degree of glandular destruction is not necessarily correlated to the level of secretory dysfunction [91]. Autoantibodies against pancreatic ductal cells (cross-reacting with SG) [92] and against CA19-9 (a marker of pancreatic tumour) have been detected in SS patients [93]. Several animal models for SS allow studying its progression and the multiple aspects of its pathogenesis [94–96]. The role of new players, such as AQPs, possibly intervening in the pathogenesis of SS has been studied.

AQP1 expression decreases by 38% in LSG biopsies from SS patients, while no changes were detected in endothelial cells [97]. SS patient treated with rituximab (an anti-CD20 monoclonal antibody) markedly increased AQP1 expression in myoepithelial cells, as well as saliva flow [98]. As M3 receptor activation induces the contraction of myoepithelial cells [97] and AQP1 traffics in response to acetylcholine, AQP1 might participate to saliva secretion [99]. However, this hypothesis is not supported by studies performed with AQP1 knockout mice [55,56].

Release of AQP5 into resting and stimulated human saliva is proportional to saliva flow [69]. Therefore, salivary AQP5 levels could be of diagnostic value in xerostomic conditions, such as SS.

Abnormal AQP5 localization (mostly basolateral instead of being apical) has been detected in SG [42] from SS patients, and from animal models for SS including non-obese diabetic (NOD) mice [100–102], IQI/JIC mice [102], specific T-cell class IA phosphoinositide 3-kinase (r1ΔT/r2n) knockout mice [102], mice immunized with SMG autoantigen [103] and NOD/SCID.E2f1$^{-/-}$ mice [104]. Altered AQP5 distribution in SG from IQI/JIC, NOD and r1ΔT/r2n mice appears to be concomitant to the presence of inflammatory infiltrates and acinar destruction [102]. Cytokines modulate AQP5 expression; as toll-like receptor activation and TNF-α decrease AQP5 expression in SG [105,106], while IFN-α (shown to improve xerostomia in SS patients [107,108]) increase AQP5 expression [109]. Antoantibodies against M3 receptors, present in SS patients, inhibit AQP5 trafficking in SG cells [110,111]. These data suggest that altered AQP5 localization could participate to the pathogenesis of SS, even though it could not directly account for saliva impairment [101].

Rituximab appears to be a promising therapy for the treatment of SS as it improves xerostomia and glandular manifestations of the disease, induces complete remission of lymphoma in some cases [112,113], and increases AQP5 expression at the APM of SG acinar cells [114]. DNA demethylation agents, reported to increase AQP5 expression [70,115] and restore saliva function in an aging murine model, as well as adenoviral vectors (see above) or other safe viral vectors, could also represent a promising therapy for the treatment of SS.

2.5.4. Diabetes

The worldwide prevalence of diabetes is estimated to be 4.4% in 2030 (366 million) [116]. Type-1 diabetes results from a loss of ß-cell function to secrete insulin, while type-2 diabetes results from impaired insulin-receptor signalling in muscle and adipose tissue. In both cases, diabetes leads to inappropriate glycaemia regulation and complications. Diabetes also represents a common cause of xerostomia [117,118]. In mice, streptozotocin-induced type-1 diabetes resulted in reduced saliva flow without altered AQP5 localization and inflammatory infiltrates in SG [119]. Streptozotocin-treated rats present increased AQP5 mRNA level, decreased AQP5 protein level, and normal AQP5 localization in unstimulated SG [120]. However, in cevimeline-stimulated SG, AQP5 trafficking was decreased but could be restored by the injection of insulin [120]. Further studies would be required to fully appreciate the role of AQP5 in diabetic xerostomia.

3. Exocrine pancreas

3.1. Morphology

In mature pancreas, exocrine pancreatic cells accounts for 90% of total pancreatic cells. Exocrine pancreas morphology resembles greatly SG, albeit the presence of few differences. Only serous acinar cells are present and the exocrine secretion finally drains into a main collecting duct. The terminal portion of the ductal system extends into acini, so that centroacinar cells are interposed between the acinar cells and the lumen. Table 1 summarizes AQP expression in exocrine pancreas.

3.2. Aquaporin expression and localization

3.2.1. Rat

The presence of AQP1, AQP4, AQP5 and AQP8 mRNAs has been detected in rat pancreas [121,122]. AQP1 protein is located in the APM and BLM, caveolae and vesicle-like structures of intralobular and interlobular ductal cells [123,124], in acinar zymogen granules [125], and in endothelial cells [121]. AQP5 expression is located at the APM of centroacinar and intercalated ductal cells [126]. AQP8 protein is present at the APM of acinar cells [121]. Rat pancreas is devoid of AQP12 expression [127].

3.2.2. Mouse

AQP1 expression is very low and confined to the APM of interlobular ducts [126]. AQP5 is detected at the APM of intercalated, intralobular and interlobular ducts [126]. AQP12 is expressed intracellularly within acinar cells [128].

3.2.3. Human

While AQP1, AQP3, AQP4 and AQP8 mRNAs are present, only AQP1, AQP5 and AQP8 proteins have been detected [122]. AQP1 expression is localized to the capillaries, centroacinar cells and intercalated ductal cells [122]. AQP1 is present in pancreatic zymogen granule membranes [125,129]. AQP5 is expressed at the APM of intercalated ductal cells, while AQP8 is located to the APM of acinar cells [122]. The site of AQP12 expression remains to be determined [127].

3.3. Secretion roles and mechanisms

In humans, the pancreas secretes 1 to 2 l of pancreatic juice daily. Pancreatic fluid juice contributes to neutralize the stomach acid and to the digestive process. Pancreatic fluid dysfunction, resulting from acute and chronic pancreatitis and cancer, leads to exocrine pancreatic insufficiency.

Pancreatic juice secretion involves a first step during which acinar cells secrete a small volume of isotonic fluid. The primary isotonic fluid then reaches the ductal lumen. During the second step, ductal cells secrete Na^+, Cl^- and HCO_3^- as well as most of the water (Fig. 1B) [46,130]. The presence of AQP8 at the APM of acinar cells allows water to move to the acinar lumen [46,121,122]. The presence of AQP1, at both the APM and BLM of ductal cells, and of AQP5, at the APM of ductal cells, allows water to move from ductal cells to the pancreatic ductal lumen (Fig. 1B). In rats, the lower AQP1 expression in ductal cells could account for the relatively low pancreatic fluid output compared with other species [126].

Acetylcholine acts on M1 and M3 receptors on both acinar and ductal cells [131]. Additional neurotransmitters also participate to pancreatic

fluid secretion [132,133] or its inhibition [134,135]. Cholecystokinin induces both pancreatic enzyme and fluid secretion, while secretin induces mainly fluid secretion [136], and they exert a potentiated effect [137]. Paracrine control of pancreatic fluid secretion is mainly ensured by ATP, secreted by acinar cells, and purinergic receptors, expressed on ductal cells [138]. Both AQP1 and AQP5 are expressed in the ductal tree regions involved in secretin-induced pancreatic fluid secretion: the intercalated ducts in humans, and the interlobular ducts in rodents [126].

3.4. Physiological roles of aquaporins

AQP8 accounts for 90% of the APM water permeability of rat pancreatic acinar cells [121]. However, AQP8 knockout mice display normal pancreatic function, likely because acinar cells generate small amount of fluid compared to ductal cells [58]. AQP1, present in rat pancreatic acinar zymogen granules, contributes to basal and GTP-mediated vesicle water entry and swelling [125,129].

In rat interlobular ducts, AQP1 accounts for 80 to 90% of secretin-stimulated pancreatic fluid secretion [139]. However, AQP1 and AQP5 knockout mice display normal pancreatic functions [122], probably due to the weak expression of AQP1 and AQP5, or their redundant functions. Double AQP1 and AQP5 knockout mice would be required to determine the possible combined contribution of these AQPs to fluid secretion.

The role of AQP12 in pancreatic function remains to be elucidated [128].

3.5. Aquaporins and pathophysiological conditions

3.5.1. Pancreatitis

Pancreatitis refers to inflammatory syndromes of the pancreas and can be either acute or chronic. Acute pancreatitis results from a sudden onset characterized clinically by typical abdominal pain, increased serum levels of digestive enzymes and typical abdominal imaging. Chronic pancreatitis results from irreversible damage to the pancreas and is usually characterized by chronic inflammation with variable pain, calcifications, necrosis, fibrosis and other complications.

The role of AQP1 in pancreatitis remains poorly understood, as contradictory data exist concerning its expression according to the species [140–143]. During experimental acute necrotizing pancreatitis in rats, global AQP1 pancreas mRNA expression was decreased [142]. In liver X receptor ß (LXRß) knockout mice displaying pancreatic exocrine insufficiency, AQP1 expression was specifically reduced in ductal cells and not endothelial cells, suggesting that AQP1 expression is regulated by LXRß [143]. The possibility that AQP1 could be the target of LXRß was provided by increased AQP1 mRNA expression in response to LXR agonist treatment in wild type mice [143]. In contrast with animal models of pancreatic insufficiency, patients with autoimmune pancreatitis display increased AQP1 expression at both apical and lateral membranes from pancreatic ducts contrasting with severe impairment of the exocrine function [140]. This discrepancy could be explained by either the loss of AQP1 protein partners necessary for its functionality or the existence of a compensatory mechanism inducing increased AQP1 expression in response to reduced pancreatic fluid secretion.

While AQP12 knockout mice present normal pancreatic phenotype [144], they display increased susceptibility to caerulein-induced acute pancreatitis and larger acinar exocytotic vesicles [144]. Further studies will be necessary to assess the role of AQP12 in the exocrine pancreas function.

3.5.2. Cystic fibrosis

Cystic fibrosis results from mutations occurring in the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is a cyclic AMP regulated chloride channel mainly expressed in pancreatic ductal cells and playing an important role in pancreatic fluid secretion [141].

Knockdown of guinea-pig CFTR reduces both CFTR and AQP1 expression in pancreatic ductal cells, as well as fluid secretion [145]. However, the mechanisms responsible for the reduced AQP1 expression in CFTR knockdown model remain to be investigated. Further studies are required to determine if AQP1 could represent a therapeutic target in the treatment of cystic fibrosis.

4. Endocrine pancreas

4.1. Morphology of the pancreas

In mature pancreas, endocrine pancreatic cells account for 90% of total pancreatic cells. Endocrine cells are non polarized epithelial cells, in contrast with exocrine acinar and ductal epithelial cells. The endocrine pancreas is organized in islets of Langerhans made of insulin-producing ß-cells surrounded by glucagon-producing α-cells, somatostatin-producing δ-cells, and pancreatic polypeptide-producing PP cells [146].

4.2. Aquaporin expression and localization

Table 1 summarizes AQP expression in endocrine pancreas.

4.2.1. Rat

Rat endocrine pancreas expresses AQP7 mRNA and protein in ß-cells [147,148].

4.2.2. Mouse

Mouse endocrine ß-cells express AQP5 [148], AQP7 [148,149] and AQP8 [148], but not AQP3 and AQP9 [149].

4.3.3. Human

No data are currently available concerning the expression of AQPs in human endocrine pancreas.

4.3. Secretion roles and mechanisms

In human, endocrine pancreas secretes about 35 units of insulin per day in healthy individuals, while >100 units per day in obese insulin-resistant individuals. Insulin secretion is triggered by post-prandial elevated concentrations of plasma glucose, free fatty acids and amino acids [150,151]. Insulin maintains normal glycaemia by promoting glucose uptake by muscle and adipose tissue. In response to increased glucose levels, glucose is massively transported inside of ß-cells by the glucose transporter type 2 (GLUT2) as GLUT2 displays a high capacity but a low affinity for glucose. As the consequence of glucose entry and its subsequent metabolization, the intracellular ATP concentration increases. The latter induces the inhibition of ATP-sensitive K^+ channels, subsequent membrane depolarization, voltage-dependent Ca^{2+} channel opening, and increased intracellular Ca^{2+} concentration which finally triggers exocytosis of insulin-containing granules [152,153] (Fig. 2A). Moreover, glucose metabolism induces signals that amplify the Ca^{2+}-induced exocytosis of insulin-containing granules in response to non-metabolized secretagogues [152,154]. ß-cell volume increases in response to glucose [155] and may affect ß-cell activity as well. Indeed, ß-cells exposed to hypotonic stress encounter cell swelling which activates volume-regulated anion channel and cell depolarization, leading to activation of voltage-sensitive Ca^{2+} channels, calcium entry and thereby insulin secretion [156,157] (Fig. 2A).

4.4. Physiological roles of aquaporins

Pancreatic ß-cells from AQP7 knockout mice display reduced size, mass, insulin content, forskolin-induced glycerol release induced by cAMP stimulation, and increased rates of both basal and glucose-stimulated insulin secretion, glycerol and triglyceride contents and glycerol kinase activity [149]. Several AQP7 knockout mice phenotypes,

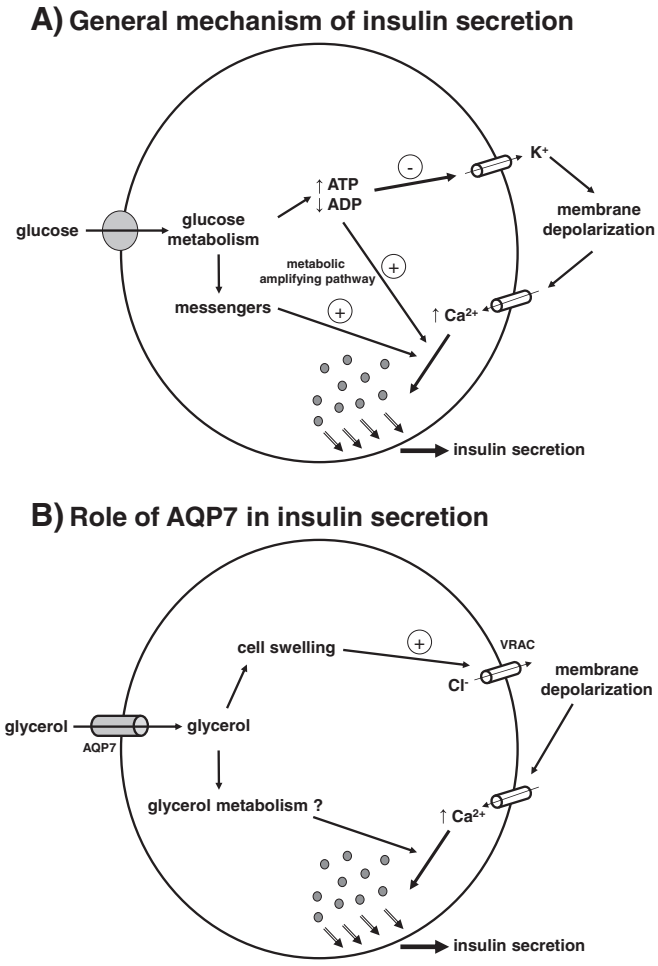

Fig. 2. Mechanism of insulin secretion. (A) General mechanism of insulin secretion. (B) Role of AQP7, by way of its glycerol transport, in insulin secretion (see text for details).

which could be ascribed to the different genetic backgrounds, have been identified. In some AQP7 knockout mice, hyperinsulinemia [149,158] was accompanied [159] or not [149] by hyperglycaemia. Other AQP7 knockout mice displayed normal glycaemia, while insulinemia has not been determined [159]. In the last AQP7 knockout mice model, no data concerning the insulin and glucose concentrations were available [160]. All together, AQP7 appears to play a key regulator role in intraislet glycerol content as well as insulin production and secretion. Under isoosmotic extracellular addition of glycerol, rat ß-cells undergo sequential cell swelling, VRAC activation, membrane depolarization, electrical activity and concomitant insulin release [147]. Furthermore, data suggest that ß-cell activation by glycerol results from its transport into the cells as well as additional actions resulting from glycerol metabolism [147]. A study using BRIN-BD cells confirmed those data [161]. AQP7 knockout mice showed lower insulin release in response to a rise in D-glucose concentration, extracellular hypotonicity, and isoosmotic addition of glycerol, as compared to wild type mice [148]. Together, the data suggest that AQP7 is likely to play a dual role in the regulation of insulin release, by allowing the entry or exit of glycerol, and by acting directly or indirectly at a distal downstream site in the insulin exocytosis pathway [148] (Fig. 2B).

4.5. Aquaporins and pathophysiological conditions

The association between mutations or single-nucleotide polymorphisms of AQP7 with diabetes and/or obesity has been investigated [162–166], but no clear conclusions have been made. Nevertheless, the regulation of AQP7 expression could become an additional drug-target for type-2 diabetes and obesity.

5. Summary and directions for further studies

Several AQPs have been shown to be expressed in SG and in both exocrine and endocrine pancreas. However, direct participation of AQPs in exocrine and endocrine pancreatic secretions remains to be clearly demonstrated. Additional studies are required to fully understand the involvement of AQPs in pathophysiological conditions of salivary glands exocrine and endocrine pancreas.

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