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Aquaporins in the female reproductive system of mammals

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1. ABSTRACT

Water and ion accumulation is the driving force for rapid expansion of the amnion and allantois of mammalian placentae during early gestation, and, therefore, essential for embryonic/fetal growth and survival. Aquaporins (AQP) are a family of small integral plasma membrane proteins that primarily transport water across the plasma membrane. To date, thirteen AQP isoforms (AQP 0-12) have been identified in mammals. AQP 1, 2, 3, 4, 5, 6, 7, 8, 9, and 11 are expressed in the female reproductive tract. Based on their structural and functional properties, AQPs are divided into three subgroups: classical aquaporins (AQP 0, 1, 2, 4, 5, 6, and 8), aquaglyceroporins (AQP 3, 7, 9, and 10), and superaquaporins (AQP 11 and 12). Expression of AQPs in the uterus and placenta is regulated by hormones and nutrients to maintain fluid homeostasis in the conceptus. The underlying mechanisms may involve signal transduction pathways mediated by cAMP, MAPK, PKC, and PI3K/Akt/mTOR. Such new knowledge will advance basic understanding of mammalian reproductive biology to enhance embryonic/fetal survival, growth and development in women and livestock.

2. INTRODUCTION

Water is the major component of cells and tissues. Thus, water transport is essential for many metabolic processes in living organisms. It was assumed for years that water passes through biological membranes only by simple diffusion through lipid bilayers until the discovery of water channel proteins known as aquaporins (AQP) (1). Because water passes through cell membranes relatively slowly by simple diffusion, the rapid and specific water flow across biological membranes is primarily mediated by AQP (2). Aquaporins are a family of small (28-30 kD) integral membrane proteins that primarily transport water, and some APQ also transport glycerol, urea and other solutes across the plasma membrane of cells (3). The movement of water through the aquaporin channel is driven by osmotic gradients (3). To date, thirteen isoforms of AQP (AQP 0-12) have been discovered in mammals. AQP 1, 2, 3, 4, 5, 6, 7, 8, 9, 11 and 12 have been detected in the female reproductive system. The wide range of AQP isoforms in different cells and tissues indicates that water transporters may be involved in regulating many physiological processes and diseases. Transport and homeostasis of water in the female reproductive system, especially in endometrium, placenta and fetal membranes, is crucial for maintaining normal reproductive performance, as well as fetal growth and development. Previous studies have shown that the molecular mechanisms responsible for the regulation of AQP expression may involve various signal transduction pathways mediated by cAMP, mitogen-activated protein kinases (MAPK), protein kinase C (PKC), and phosphatidylinositide 3-kinases (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR). Therefore, this review is focused on recent developments concerning mammalian AQP in the female reproductive system to stimulate future research on their roles under both physiological and pathological conditions.

3. THE AQUAPORIN FAMILY

The discovery of a membrane protein involved in water transport was first reported over 25 years ago (4). This ground-breaking research led to the identification of the glycosylated component of 35-60 kD protein on the electrophoretogram of human erythrocytes (4). Several years later, a novel integral membrane protein in human erythrocytes having a non-glycosylated component of 28 kD and a glycosylated component of 35-60 kD was identified as a functional unit of membrane water transporter called CHIP28 (channel forming integral protein) (5). In 1993, CHIP28 was renamed AQP1 by Agre *et al.* (6), who won the 2003 Nobel Prize in chemistry for the discovery of water channels. AQP 0-12 have different patterns of tissue distribution and membrane localization (7). Based on their structural and functional properties, AQP are classified into three subgroups: (a) classical aquaporins (AQP 0, 1, 2, 4, 5, 6 and 8), which are highly selective to passage of water; (b) aquaglyceroporins (AQP 3, 7, 9 and 10), which can transport water, urea, glycerol and other small solutes; and (c) recently identified superaquaporins (AQP 11 and 12) (8, 9). The classification and permeability of AQP in mammals are summarized in Table 1. Notably, in addition to water, AQP6 is permeable to chloride, urea, and glycerol (10), AQP8 to urea and

Table 1. Classification and characteristics of aquaporins (AQP)

Classification	Isoform	Permeability
Aquaporin	AQP0	Water
	AQP1	Water, CO_2, NO, and NH_3
	AQP2	Water
	AQP4	Water, CO_2, O_2, and NO
	AQP5	Water and CO_2
	AQP6	Water, anions, urea, and glycerol
	AQP8	Water, urea, and NH_3
Aquaglyceroporin	AQP3	Water, urea, glycerol, and NH_3
	AQP7	Water, urea, glycerol, and NH_3
	AQP9	Water, urea, glycerol, other solutes, and NH_3
	AQP10	Water, urea, and glycerol
Superaquaporin	AQP11	Uncertain
	AQP12	Uncertain

ammonia (9), and AQP9 to neutral solutes, such as monocarboxylates (e.g., lactate), purines and pyrimidines (11). Furthermore, some isoforms of AQP transport certain gases (e.g., CO_2, O_2, NO, and NH_3) (12). For example, AQP1 facilitates the transport of CO_2, NO, and NH_3 across the plasma membrane (12), whereas AQP4 serves as a gas channel for NO and O_2 (13). Additionally, AQP5 transports CO_2 (14), and AQP8 can function as an NH_3 channel (15). Most AQP (AQP 0, 1, 3, 4, 7, 8, 9, and 10) are localized constitutively in the plasma membrane. However, some (AQP 6, 11, and 12) reside in intracellular membranes, while others (AQP 2 and 5) translocate from an intracellular membrane to the plasma membrane in response to stimuli (16). Aquaporins are widely distributed and it is not uncommon that more than one type of AQP can be present in the same cell or tissue to ensure provision of water to cells. AQP have a conserved structure of six transmembrane domains and two asparagine-proline-alanine (NPA) motifs with NH_2- and COOH- termini in the cytoplasm, forming a distinct hourglass-shaped water pore. Their diverse functions include not only water transport in fluid secretion, fluid absorption, and cell volume regulation, but also in other physiological processes not directly related to water transport, such as cell adhesion, cell migration, cell proliferation, and cell differentiation (17).

4. AQUAPORIN EXPRESSION IN MAMMALIAN FEMALE REPRODUCTIVE SYSTEMS

As noted previously, at least 11 isoforms of AQP (AQP 1, 2, 3, 4, 5, 6, 7, 8, 9, 11 and 12) have been identified in the female and male reproductive system of mammals, including human, rodents, sheep, and pigs (Tables 2-4). For comparison, the distribution of AQP in non-reproductive systems of mammals is summarized in Tables 5 and 6.

4.1. Humans

4.1.1. Vagina

There is compelling evidence for the presence of AQP 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, and 12 in the human female reproductive system (7, 18, 19). A recent study with premenopausal women demonstrated the presence of AQP 1, 2, 3, 5, and 6 in the vagina, even though AQP 4, 7, 8, and 9 were not detected in this tissue (18). Specifically, AQP1 was found to be mainly expressed in the capillaries and venules of the vagina, and AQP2 in the cytoplasm of the vaginal epithelium. Additionally, AQP3 was detected primarily in the plasma membrane of the vaginal epithelium, whereas AQP5 and AQP6 in the cytoplasm throughout the vaginal epithelium (18).

4.1.2. Ovary

In the ovary, AQP1 is localized mainly in ovarian microvascular and small vessel epithelial cells, but seldom in ovarian tumor cells (20, 21). Another study revealed the presence of mRNAs for AQP 1, 2, 3, and 4 in both the theca and granulosa cells of human follicles, with differential expression patterns during different stages of ovulation (22). Specifically, compared with the pre-ovulatory phase, mRNA levels for AQP1 increase in the late ovulatory and postovulatory phases, whereas mRNA levels for AQP 2 and 3 increase in the early ovulatory phase. In contrast, mRNA levels for AQP4 decrease during transition from the preovulatory to the early ovulatory phase (22). Thus, AQP expression in the human ovary is likely controlled by locally produced hormones.

4.1.3. Uterus and cervix

The vasculature and epithelium of the uterus has high levels of AQP expression. AQP1 was found in the endothelium of small blood vessels (23) and at a greater abundance in capillaries and arteries than in veins of human endometrial vessels (24). In contrast, AQP2 was prominent in luminal

Table 2. Tissue distribution of aquaporins (AQP) in female reproductive systems of mammals

AQP	Female reproductive system									
	Vagina[a]	Cervix[b]	Uterus[c]	Ovary[d]	Oviduct[e]	Oocytes[f]	Placenta[g]	Amnion[h]	Chorion[i]	Embryos[j]
AQP0	–	–	–	–	–	–	–	–	–	–
AQP1	++	+	++	++	++	–	++	++	++	++
AQP2	++	–	+	+	+	–	–	–	–	+
AQP3	++	++	+	+	–	+	++	++	++	++
AQP4	+	+	+	+	–	–	+	–	+	+
AQP5	+	+	++	+	++	–	–	–	–	++
AQP6	+	–	–	–	–	–	–	–	–	+
AQP7	–	–	+	+	–	+	–	–	–	++
AQP8	–	++	+	+	+	–	++	++	++	++
AQP9	–	–	+	++	++	+	++	++	++	++
AQP10	–	–	–	–	–	–	–	–	–	–
AQP11	–	–	–	+	–	–	–	–	+	++
AQP12	–	–	–	+	–	–	–	–	–	+
Ref.	(18, 42-44, 46)	(28, 47, 48)	(23-27, 50, 51, 72)	(20-22, 54-56, 67-70)	(19, 27, 45, 57, 67, 69)	(53, 60)	(30-39, 66)			(41, 60, 62, 63)
Major Functions	Vaginal lubrication	Cervical ripening; Cervix carcinogenesis	Implantation; Uterine imbibition; Blastocyst formation	Ovum transport and oviductal fluid balance; Follicle maturation; Oocyte cryopreservation			Placental and amniotic fluid homeostasis			Early embryo development and implantation

+ Reported in one species; ++ reported in more than two species; − not reported in any species. [a] reported for humans, rodents and guinea pigs; [b] reported for humans and rodents; [c] reported for humans, rodents, pigs, and dogs; [d]Humans, rodents, and pigs; [e] reported for humans, rats and pigs; [f] reported for rodents; [g-i] reported for humans, rodents and pigs; [j] reported for humans, rodents and horses; [k] reported for rodents, humans, and dogs; [l] reported for humans, rodents, cats and dogs; [m] reported for rodents; [n] reported for rodents and dogs; [o] reported for rodents and dogs

and glandular epithelial cells of the endometrium of healthy women with regular menstrual cycles and proven fertility (25, 26), as well as in premenopausal women (23). AQP3 was moderately expressed in basolateral membranes of human uterine endometrium and choroid plexus, and was also detected in human amniotic membranes, placenta and ovary (27). Furthermore, AQP 1, 3, and 8 were detected in cervical carcinoma tissues of Chinese Uygur women (28). In those subjects, AQP1 was predominantly present in the microvascular endothelial cells in the uterine stroma of women with mild cervicitis, cervical intraepithelial neoplasia and cervical carcinoma (28), whereas AQP3 and AQP8 were identified in the membranes of normal squamous epithelium and carcinoma cells (28). AQP3 was also highly expressed in human cervical cancer cell lines (29). Results of a study indicated that AQP9 protein was localized to the cytoplasm of epithelial cells of the human oviduct, and its expression was significantly reduced during tubal pregnancy as compared with normal pregnancy (19).

4.1.4. Placenta and fetal membranes

The placenta and its associated extraembryonic membranes express AQP in a spatial and temporal manner. For example, high mRNA levels for AQP1, 3, 9, and 11, but low mRNA levels for AQP 4, 5, and 8, are present in chorionic villi in the early stages of human pregnancy (between 10th and 14th weeks of gestation) (30).

Table 3. Tissue distribution of aquaporins (AQP) in male reproductive systems of mammals

AQP	Male reproductive system				
	Testis[k]	Epididymis[l]	Sperm[m]	ED[n]	VD[o]
AQP0	+	−	−	−	−
AQP1	++	++	+	++	+
AQP2	+	++	−	+	+
AQP3	+	+	+	−	−
AQP4	−	+	−	−	−
AQP5	+	++	−	−	−
AQP6	−	−	−	−	−
AQP7	+	++	+	−	+
AQP8	++	+	+	−	−
AQP9	++	++	+	+	+
AQP10	−	+	−	+	−
AQP11	+	+	−	−	−
AQP12	−	−	−	−	−
Ref.	(142-150)	(143, 145, 148, 151-157)	(158-161)	(99, 143, 145, 159)	(153, 162)
Major Functions	Spermatogenesis; seminiferous tubule fluid and spermatids	Spermatogenesis; Sperm maturation	Sperm maturation and storage	Fluid reabsorption	Transport of fluid and solute molecules

+ Reported in one species; ++ reported in more than two species; − not reported in any species; ED: efferent ducts; VD: vas deferens.
[a] reported for humans, rodents and guinea pigs; [b] reported for humans and rodents; [c] reported for humans, rodents, pigs, and dogs;
[d] Humans, rodents, and pigs; [e] reported for humans, rats and pigs; [f] reported for rodents; [g-i] reported for humans, rodents and pigs;
[j] reported for humans, rodents and horses; [k] reported for rodents, humans, and dogs; [l] reported for humans, rodents, cats and dogs;
[m] reported for rodents; [n] reported for rodents and dogs; [o] reported for rodents and dogs

Additionally, results of PCR, western blotting, and immunohistochemical analyses indicated that both mRNA and proteins for AQP 1, 3, 8, 9, and 11 are localized in amnion and chorion of the human placenta throughout gestation (31, 32). In the placenta, the AQP1 mRNA is detected in placental blood vessels and in the syncytiotrophoblast (33), and AQP3 in trophectoderm (32). In humans, both AQP1 and AQP3 proteins have been identified in amnionic epithelium and chorionic cytotrophoblast cells (32). Wang *et al.* further demonstrated the presence of AQP3 protein in human placental syncytiotrophoblast and cytotrophoblast cells of the chorionic and amnionic epithelium (34). Interestingly, AQP4 expression decreased in the syncytiotiophoblast, but increased in endothelial cells and stroma of placental villi between the first and the third trimesters of gestation (35). These results suggest a distinct expression profile of AQP at different stages of gestation in women.

Several studies have identified the presence of the AQP8 protein in human placental amniotic epithelium, and chorion cytotrophoblast and syncytiotrophoblast cells (36-38). In addition, AQP9 is localized to human amnionic epithelium, chorionic trophoblast cells, as well as chorionic cytotrophoblast and syncytiotrophoblast cells (39, 40). Similarly, AQP8 and AQP9 are expressed in chorionic cytotrophoblast and placental trophoblast cells (40). Available evidence also shows the presence of mRNAs for AQP 1, 2, 3, 4, 5, 7, 9, 11 and 12, but not for AQP 0, 6, 8, and 10, in human embryos at the 2~8 cell stage (41). Of note, AQP expression in the placental membranes is altered in some diseases. For example, compared with normal pregnancies, AQP8 and AQP9 are more abundant in the amnion, but less abundant in the chorion from gestating women with idiopathic polyhydramnios (40).

Table 4. Expression of aquaporins (AQP) at mRNA and/or protein levels in the female reproductive tract of mammals

AQP	Humans	Rodents	Sheep	Pig	Dog
AQP1	Vagina (18); Uterine endometrium (23); Ovary (20-22); Oviduct (19); Cervical carcinoma (28); Amnion and chorion (30-33); Embryo (41)	Vagina (42, 46); Oviduct (45); Uterine myometrium (50); Amnion and chorion (58); Embryo (62)	Placenta (64)	Ovarian; oviduct; Uterus (67-70)	Uterus (72)
AQP2	Vagina (18); Ovarian follicles (22); Oviduct (27); Uterine endometrium (23, 25, 26); Embryo (41)	Vagina (42)			Uterus (72)
AQP3	Vagina (18); Ovarian follicles (22); Uterine endometrium (27); Cervical carcinoma (28); Trophoblast, amnion and chorion (30-32, 34); Embryo (41)	Vagina (42-44); Cervix (47, 48); Oocyte (60); Trophectoderm (59); Morulae (52); Amnion and chorion (58) Embryo (62, 63)	Placenta (64)		
AQP4	Ovarian follicles (22); Placenta, trophoblast and chorion (30, 35); Embryo (41)	Vagina (44); Cervix (47); Uterus (50)			
AQP5	Vagina (18); Chorion (30); Embryo (41)	Cervix (47, 48); Ovary (55); Uterus (50, 51); Oviduct (57); Embryo (62)		Ovary, oviduct, and uterus (67-70)	Uterus (72)
AQP6	Vagina (18)	Embryo (62)			
AQP7	Embryo (41)	Uterus (51); Ovarian granulosa cells (54-56); Oocyte (60); Embryo (62, 63)			
AQP8	Cervical carcinoma (28); Placenta, trophoblast, amnion and chorion (30, 31, 36-38)	Cervix (47); Uterus (50, 51); Ovarian granulosa cells (54-56); Oviduct (57); Trophectoderm (59); Amnio and chorion (58); Embryo (60, 62)	Placenta (64)		
AQP9	Oviduct (19); placenta, trophoblast, amnion, and chorion (30, 31, 39, 40); Embryo (41)	Uterus (50, 51), Ovarian grannulosa cells (54); Oocyte (53); Oviduct (57); Trophectoderm (59); Amnion and chorion (58); Embryo (60, 62)	Amnion; Allantois (66)	Ovary, oviduct, and uterus (67-70)	
AQP11	Chorionic Villi (30); Embryo (41)	Ovary (55); Embryo (63)			
AQP12	Embryo (41)	Ovary (55)			
Values in parentheses are the numbers of cited references					

4.2. Rodents

4.2.1. Vagina

AQP 1, 2, 3, 4, 5, 7, 8, 9, 11, and 12 have been detected in the vagina of rodents, including mice and rats. Generally, patterns of expression and localization of AQP 1, 2, and 3 in the vagina are similar among healthy female Sprague-Dawley rats (42), diabetic rats (43) and premenopausal women (18). For example, in rats, AQP1 is localized mainly to the capillaries and venules, AQP2 to the cytoplasm of the vaginal epithelium, and AQP3 to the plasma membrane of the vaginal epithelium (42, 43). There are reports that AQP3 is also expressed in the plasma membrane of intermediate layer cells of the mouse vagina epithelium and that AQP4 is expressed in the basolateral membrane of its superficial layer cells (44). In addition, AQP1 is localized to visceral smooth muscle cells in the oviducts and vagina of rats (45), and to the capillaries and venules of the lamina propria of the vagina (46).

4.2.2. Uterus and cervix

Expression of AQP 3, 4, 5, and 8 in the cervix and uterus of pregnant mice is cell-specific (47, 48). AQP3 is localized primarily to the basal cell

Table 5. Tissue distribution of aquaporins (AQP) in respiratory, digestive and excretory systems of mammals

AQP	Respiratory system						Digestive system						Excretory system		
	TR[a]	BR[b]	PH[c]	LA[d]	Nose[e]	Lung[f]	SG[g]	TO[h]	ES[i]	LI[j]	PA[k]	GI[l]	KI[m]	BL[n]	UU[o]
AQP0	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–
AQP1	+	+	–	+	+	++	++	+	+	++	++	+	++	+	+
AQP2	+	+	+	+	+	–	–	+	+	–	–	–	++	++	+
AQP3	+	++	–	++	+	++	++	+	+	++	+	++	++	+	+
AQP4	+	++	–	+	+	++	++	–	–	+	+	++	++	–	–
AQP5	+	++	+	+	+	++	++	++	–	–	++	++	–	–	–
AQP6	–	–	–	+	–	–	+	–	–	–	–	–	+	–	–
AQP7	–	–	–	+	–	–	+	–	–	–	–	+	++	–	–
AQP8	+	–	–	+	–	+	–	–	+	++	++	++	+	–	–
AQP9	–	–	–	–	–	–	–	–	–	++	–	++	–	–	–
AQP10	–	–	–	–	–	–	–	–	–	–	–	++	–	–	–
AQP11	–	–	–	–	–	–	–	–	–	+	–	+	+	–	–
AQP12	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–
Ref.	(27, 150, 163)	(27, 164-166)	(27, 167)	(168-170)	(27, 171, 172)	(166, 173-178)	(157, 179)	(180, 181)	(27, 177, 182)	(178, 183-189)	(149, 178, 190-192)	(178, 182, 193-199)	(200-204)	(27, 205-207)	(207)

Abbreviations: TR: trachea; BR: bronchus; PH: pharynx; LA: Larynx; SG: salivary glands; TO: tongue; PA: pancreas; ES: esophagus; LI: liver; GI: gastrointestinal tract; KI: kidney; BL: bladder; UU: ureter/urethra; HE: heart; BV: blood vessels; SM: skeletal muscle; AD: adipocytes; SP: spleen; [a] reported for rats and humans; [b] reported for rats, mice and humans; [c] reported for mice and humans; [d] reported for rats, mice, and humans; [e] reported for rats and humans; [f] reported for rats, mice, humans, and pigs; [g] reported for rats, mice, and humans; [h] reported for rats and humans; [i] reported for rats and humans; [j] reported for rats, mice, humans, and pigs; [k] reported for rats and humans; [l] reported for rats, mice, humans, and pigs; [m] reported for rats, mice, humans, and pigs; [n] reported for rats and humans; [o] reported for rats

layers of the cervical epithelium, and AQP 4, 5, and 8 to the apical cell layers of the cervical epithelium (47). There is also evidence that AQP 1, 3, and 8 are constitutively expressed in uteri of ovariectomized mice, with AQP1 in the myometrium, AQP3 in luminal epithelial cells, and AQP8 in both the stromal cells and the myometrium (49). Additionally, Richard *et al.* (50) studied the expression of AQP 0 to 9 in uteri of mice on Days 1 to 8 of pregnancy (50). According to their results, AQP1 is localized mainly to the inner circular myometrium, AQP4 to the uterine luminal epithelium on Day 1 of pregnancy, and AQP5 to the basolateral region of the uterine glands. Furthermore, AQP8 is present in the inner cell mass and AQP9 in the mural trophectoderm of the implanting blastocyst of mice (50). Of note, compared with Day 0 of pregnancy, expression of AQP 5 and 9 increases in the glandular epithelium of the mouse uterus at the time of implantation when there is a reduction in the amount of fluid in the uterine lumen (51).

4.2.3. Oocytes, oviduct, and ovaries

AQPs exhibit temporal and spatial expression in oocytes, oviduct, and ovaries (52-57). For example, AQP3, a water channel permeable to both water and glycerol, has been detected in morulae, but not oocytes, from mice (52). In addition, AQP9 mRNA is present in oocytes recovered during proestrus, but estrus (53). Furthermore, McConnell *et al.* (54) reported that AQP 7, 8, and 9 are expressed in the granulosa cells of ovarian follicles of rats to mediate transcellular movement of water into the antral follicles during their maturation (54). Other studies confirmed the presence of AQP 5, 7, 8, 11 and 12 mRNA in ovaries of neonatal mice and in granulosa cells of ovarian follicles of 4-week-old mice (55). Finally, mRNA and proteins for AQP 5, 8, and 9 are localized to the oviductal epithelium in rats, with AQP 5 and 8 distributed in the cytoplasm and AQP9 in the apical plasma membrane (57).

Table 6. Tissue distribution of aquaporins (AQP) in circulatory, muscular, and other systems of mammals

AQP	Circulatory, muscular, and other systems								
	HE[p]	BV[q]	Skin[r]	SM[s]	AD[t]	Brain[u]	Eye[v]	Ear[w]	SP[x]
AQP0	–	–	–	–	–	–	+	–	–
AQP1	+	++	++	+	+	++	+	++	+
AQP2	–	–	+	++	–	+	–	+	–
AQP3	+	+	++	++	–	+	+	+	++
AQP4	++	–	–	++	–	++	+	++	+
AQP5	–	–	++	–	–	+	+	++	–
AQP6	–	–	–	–	–	–	–	++	–
AQP7	+	–	+	+	++	+	+	+	–
AQP8	+	–	–	–	–	+	+	–	+
AQP9	–	–	+	+		++	+	–	++
AQP10	–	–	+	–	+	–	–	–	–
AQP11	+	–	–	+		+	+	–	+
AQP12	–	–	–	–	–	–	–	–	–
Ref.	(177, 208, 209)	(27, 210)	(201-218)	(157, 219-224)	(183, 225-227)	(228-223) (233, 234)	(177, 193, 235)	(236-240)	(150, 177, 178, 241-243)

Abbreviations: HE: heart; BV: blood vessels; SM: skeletal muscle; AD: adipocytes; SP: spleen; [p]reported for rats, goats, and humans; [q] reported for rats and humans; [r] reported for rats, mice, and humans; [s] reported for rats, mice, and humans; [t] reported for rats, mice, humans, and pigs; [u] reported for rats, mice, and humans; [v] reported for rats, mice, and humans; [w] reported for rats, mice, and humans; [x] reported for rats, human, and pigs

4.2.4. Placenta and fetal membranes

Several lines of evidence support the notion that AQP 1, 3, 8, and 9 are expressed in the mouse placenta (58). First, results of immunohistochemical analysis indicated that AQP1 is localized to the placental vascular endothelium and AQP3 to the trophoblast (58). Second, AQP 3 and 8 are present in the basolateral membrane domains of the trophectoderm, AQP9 in the apical membrane domains of the trophectoderm, and AQP3 in the margins of all inner cell mass (ICM) cells (59). Third, AQP 3, 7 and 9 have been detected in mouse embryos at all stages of development (41, 60, 61). Fourth, AQP 1, 3, 5, 6, 7, and 9 are expressed in murine embryos from the one-cell stage to the blastocyst stage (62, 63).

4.3. Sheep

There is limited information on AQP expression in the ovine female reproductive tract. Nonetheless, Liu *et al*. (64) reported the presence of AQP 1, 3, and 8 mRNA in ovine placentae on Days 27, 45, 66, 100 and 140 days of gestation. Those authors found that AQP3 was quantitatively the most highly expressed AQP isoform in the placenta at 66, 100, and 140 days of gestation and that only AQP1 was localized to the vasculature of the placenta at 27 days of gestation before significant development of the chorioallantois (64). In contrast, Butkus *et al.* (65) could not detect AQP1 in the mesonephros of developing ovine fetuses at either Day 27 or Day 41 of gestation, although a small amount of the glycosylated form of AQP1 was found in the fetal kidney at Day 94 of gestation (65). Moreover, AQP9 was detected in ovine amnionic and allantoic epithelia, but not in the chorion or umbilical cord (66).

4.4. Pigs

Like other livestock species, research on AQP expression in the reproductive tract of female swine is limited. Three isoforms of water channel

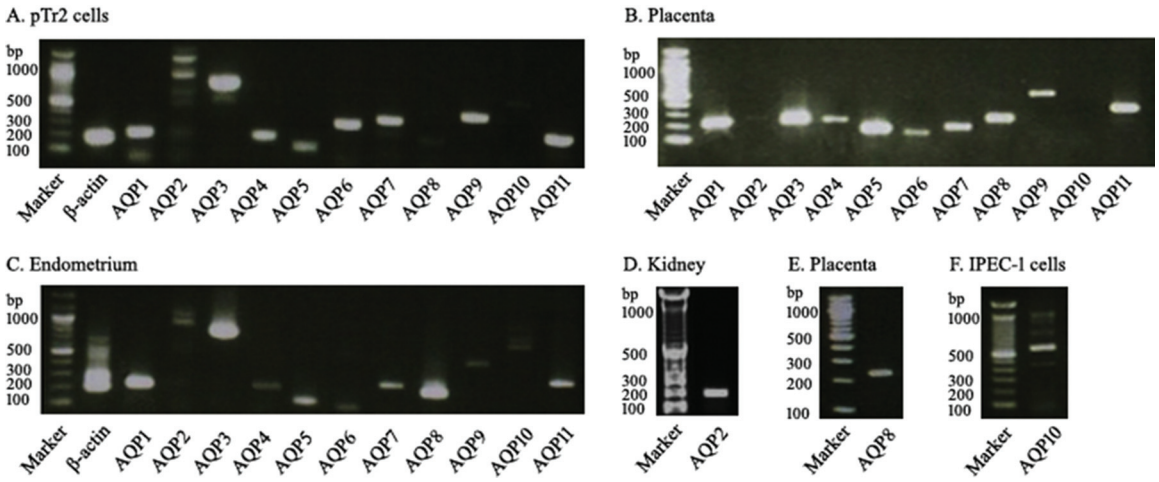

Figure 1. Auaporin (AQP) mRNAs in cells and tissues from pigs. Total RNA was isolated from pig placentae, endometrium, kidneys, conceptus trophectoderm cells, or intestinal epithelial cells, using Trizol (Invitrogen) according to the manufacturer's instructions, and then used for quantification of AQP mRNAs using specific primers (Table 7), as described previously (119). Briefly, cDNA samples were synthesized and used to amplify the target AQP genes. Semi-quantitative PCR (35 cycles) was performed with 20 ng/μl cDNA using the following amplification conditions: preheating at 95 for 15 min, denaturation at 95oC for 30s, annealing at 54°C to 61°C (depending on specific primers) for 30s, and elongation at 72°C for 1 min. PCR products were separated on 1.5.% agarose gels and stained with ethidium bromide. (A) Porcine conceptus trophectoderm cells (pTr2); (B) The pig placenta at Day 25 of gestation; (C) The pig endometrium at Day 25 of gestation; (D) The pig kidney was used as a positive control for AQP2; (E) The pig placenta at Day 25 of gestation; (F) IPEC-1 cells (intestinal porcine epithelial cells from newborn pigs) were used as a positive control for AQP10.

proteins (AQP 1, 5, and 9) have been detected in the porcine ovary, oviduct, and uterus (67-70). On Days 17-19 of the estrous cycle (follicular phase), AQP1 was identified in the capillary endothelium of the ovary, and AQP5 was detected in the flattened follicle cells of primordial follicles, granulosa cells of developing follicles, and epithelial cells of the oviduct and uterus (67). AQP9 was detected in granulosa cells of developing ovarian follicles, as well as the luminal epithelial cells of the oviduct and uterus (67). There are reports of expression of AQP 1, 5, and 9 in the uterus (68) and oviduct (69) of gilts at the early (Days 2-4), middle (Days 10-12), and late (Days 14-16) stages of the estrous cycle. AQP 1, 5, and 9 have also been detected in porcine uteri (68) and oviducts (69) in the late (Days 18-20) stages of the follicular phase of the estrous cycle, as well as during the onset (Days 14-16) and at the end (Days 30-32) of implantation and the beginning of placentation. AQP 1, 5, and 9 are expressed in the reproductive tract at all stages of the estrous cycle and pregnancy (68, 69).

There is evidence that, in pigs, AQP1 is localized within blood vessels of the uterus and oviduct, AQP5 in both smooth muscle cells and epithelial cells of the uterus and oviduct, and AQP9 in epithelial cells of the uterus and oviduct (68, 69). However, AQP 1, 5, and 9 exhibit distinct patterns of expression during different phases of the estrous cycle and early pregnancy (68, 69), suggesting possible cell-specific regulation of their gene expression by reproductive hormones (70). For example, in cyclic gilts, the abundance of AQP 1, 5, and 9 proteins in the uterus do not appear to differ between Days 10-12 and Days 14-16 of the estrous cycle, but may increase on Days 2-4 and 18-20 of the estrous cycle (68). During the estrous cycle and early pregnancy, AQP1 is expressed in endothelial cells of the pig peri-ovarian vascular complex (70). Additionally, our results indicate that at least 9 AQP (AQP 1, 3, 4, 5, 6, 7, 8, 9, and 11) are expressed in the placentae of gilts on Day 25 of gestation (Figure 1A). We could not detect mRNAs for AQP 2 or AQP 10 in the porcine placenta, although those primers (Table 7) worked well for detecting AQP2 and 10 in porcine kidney and enterocytes as positive controls (Figures 1B and 1C). To date, we have identified proteins for AQP 1, 3, 5 and 9 in the porcine placenta and uterine endometrium, as well as in a porcine trophectoderm cell line (pTr2 cells) (Figure 2).

Table 7. Sequences, product lengths, and annealing temperatures of aquaporin (AQP) genes

Gene	Primer sequence (5'-3')	Product length (base pairs)	Tm (°C)	Data bank accession number or Ref.
AQP1	F: TTGGGCTGAGCATTGCCACGC R: CAGCGAGTTCAGGCCAAGGGAGTT	221	61	(68)
AQP2	F: TCAACCCTGCCGTGACTGTAG R: GTTGTTGCTGAGGGCATTGAC	173	58	EU636238.1
AQP3	F: ACCCTTATCCTCGTGATGTTT R: CATTCGCATCTACTCCTTGTG	789	58	HQ888860.1
	F: TGACCTTCGCTATGTGCTTCC R: GTCCAAGTGTCCAGAGGGGTAG	212	58	
AQP4	F: TCTGGCTATGCTTATCTTTGTCC R: CGATGCTAATCTTCCTGGTGC	212	59	NM_001110423.1
AQP5	F: TGAGTCCGAGGAGGATTGGG R: GAGGCTTCGCTGTCATCTGTTT	147	58	NM_001110424.1
AQP6	F: TCTGGATGACTGTCAGCAAAGC R: TCTCTCGGATGTCCTCAGGTATG	330	58	NM_001128467.1
	F: GCTGTCCTGGCTTCGCTGAT R: GGCTCCTCCCCTTCCACTTT	119	60	
AQP7	F: ATAAGGCACTTCAGCAGACATC R: AAACTTCTTCCAGGACATTCG	388	54	NM_001113438.1
AQP8	F: GGTGCCATCAACAAGAAGACG R: CCGATAAAGAACCTGATGAGCC	227	60	EU220426.1
AQP9	F: TTTGCTGATGGAAAACTGCTC R: CTCTGGTTTGTCCTCCGATTGT	471	55	NM_001112684.1
AQP10	F: TGGGCGTTATACTAGCCATCTAC R: GGTTGGGCACAGTTTACTTCCT	658	57	EU582021
AQP11	F: CGTCTTGGAGTTTCTGGCTACC R: CCTGTCCCTGACGTGATACTTG	229	57	EU220425
	F: TGTCCGCTGAGATAGGTGGA R: CTCCTGTTAGACTTCCTCCTGC	303	59	
β-actin	F: TCCCTGGAGAAGAGCTACGA R: TGTTGGCGTAGAGGTCCTTC	182	58	Ref. 247

F, forward; R, reverse; TM, temperature

4.5. Other mammalian species

In horses, a microarray analysis revealed that AQP5 mRNA levels in conceptuses increased on Days 10, 12, and 14 of pregnancy by 4.6.-, 9.5.-, and 10.7.-fold, respectively, compared with those at Day 8 of gestation (71). In dogs, AQP 1, 2, and 5 are expressed in the uterine wall of the bitch during different phases of the reproductive cycle (72). Specifically, AQP1 was localized within uterine mesometrial, myometrial, and endometrial blood vessels, as well as in the circular and longitudinal layers of myometrium (72). Moreover, AQP2 was expressed in the glandular and luminal epithelia of endometrium (72), whereas AQP5 was localized to the apical plasma membrane of uterine epithelial cells (72).

5. PHYSIOLOGICAL AND NUTRITIONAL SIGNIFICANCE OF WATER TRANSPORT IN FEMALE REPRODUCTION

5.1. Vaginal lubrication

The rapid movement of water and the increase in blood flow into vaginal tissues is very

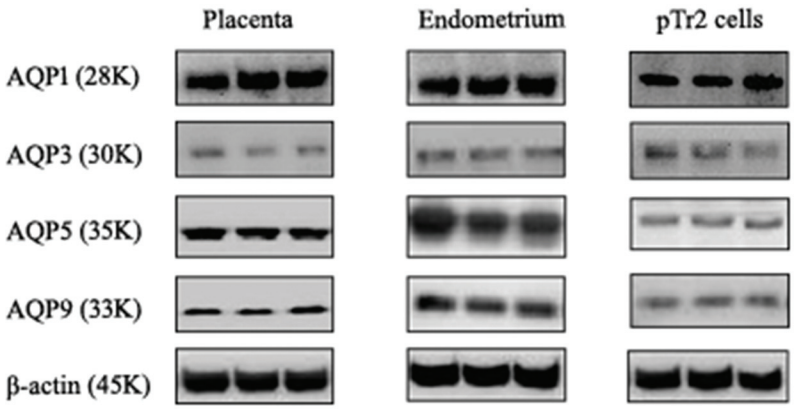

Figure 2. Auaporin (AQP) proteins in cells and tissues from pigs. Western blot analysis of AQP proteins was performed as previously described (120, 121). Briefly, cells ($10x10^6$) were lysed for 30 min at 4°C in 0.5. ml of a buffer consisting of 1% Triton X-100, 0.5.% Nonidet P-40, 150 mM NaCl, 10 mM Tris-HCl (pH 8.0.), 1 mM EDTA, 1 mM EGTA, 0.2. mM Na_3VO_4, 0.2. mM phenylmethylsulfonylfluoride, 50 mM NaF, 30 mM $Na_4P_2O_7$, and 1% protease inhibitor cocktail. Tissues (~50 mg) were homogenized at 4°C in 0.5. ml of the same buffer for 2 min. The cell lysates or tissue homogenates were centrifuged (16,000 g for 15 min at 4°C). Protein concentration in the supernatant fluid was determined using the bicinchoninic acid assay (Pierce, Rockford, IL) with bovine serum albumin as the standard. All samples were adjusted to an equal protein concentration and then diluted with 2 x loading buffer (0.6.3 ml of 0.5. M Tris-HCl (pH 6.8.), 0.4.2 ml 75% glycerol, 0.1.25 g sodium dodecyl sulfate (SDS), 0.2.5 ml β-mercaptoethanol, 0.2. ml 0.0.5% solution of bromphenol blue, and 1 ml water) to a final volume of 2.5. ml and heated in boiling water for 5 min. After cooling on ice to room temperature (25°C), the solution was used for western blot analysis of soluble denatured proteins. (A) The pig placenta at Day 25 of gestation; (B) The pig endometrium at Day 25 of gestation; and (C) Porcine conceptus trophectoderm cells (pTr2).

important for female mammals during sexual arousal characterized as genital swelling and increased vaginal lubrication (73). Although the mechanisms responsible for vaginal lubrication are not fully understood, few studies in rats and women have indicated potential roles for AQP 1, 2, 3, 5, and 6 in vaginal lubrication (18, 42). Expression of AQP2, but not AQP1, was less in the vagina of diabetic rats (74). Moreover, AQP1 in smooth muscle cells of the rat vagina appears to play an important role in rapid movement of water across the vaginal smooth muscle cells, which can occur during sexual stimulation and intercourse (45). These results indicate that AQP participate in the regulation of secretion of vaginal fluids and, therefore, vaginal lubrication.

5.2. Ovum transport and follicle maturation

In mammals, the oviduct serves as the passageway for ovum transport towards the uterus, and as the site of fertilization and early embryonic development. AQP in the oviduct may influence oviductal fluid production, which provides a physiological medium for the survival, growth, and development of oocytes (75). Moreover, large amounts of fluid pass into the antral cavity of developing ovarian follicles, which facilitates the development of a fluid-filled antrum and maturation of the follicles (75). Expansion of the antrum in response to gonadotropin stimulation requires rapid and massive transport of water. Accordingly, expression of AQP 7, 8 and 9 in the granulosa cells of the rat ovary mediates the passage of water across granulosa cells of antral follicles predominantly through transcellular mechanisms (54). Moreover, overexpression of AQP3 improved water and glycerol permeability, as well as the survival of oocytes after cryopreservation (76).

5.3. Uterine luminal fluid balance and implantation of of blastocyst

The uterus is a major female reproductive organ responsive to steroid hormones in mammals. Previous results suggested that several members of AQP are involved in peri-implantation fluid homeostasis (77). Some of them (AQP 1, 4, 5, 8 and 9) are expressed in mouse blastocysts and cells of the ovary, thereby contributing to blastocyst and uterine fluid homeostasis during implantation of the blastocyst (78). There is a dramatic reduction in uterine luminal fluid at the time of implantation for close apposition between the trophectoderm of the blastocyst and uterine luminal epithelial cells for successful implantation (79). Thus, the reabsorption of glandular fluid via AQP 5 and 9, and of luminal fluid via AQP 1 and 5 in uterine luminal epithelial

cells, is likely crucial for the regulation of luminal fluid volume, leading to a reduction in luminal fluid at the time of implantation and to positioning of the blastocyst for implantation in rats (51, 80, 81). Likewise, AQP1 plays an important role in water transport in the human uterus (82). Additionally, in the rat myometrium, AQP1 may be involved in stromal edema, uterine closure, and formation and orientation of the blastocyst during implantation (81). Consistent with these observations, high levels of expression of AQP2 by human endometrial cells occurs at the time of implantation (mid-secretory phase) of the blastocyst, which suggests that AQP2 modulates uterine receptivity to implantation (26). Also, AQP 3, 4, 5, and 8 help to maintain cervical water balance during pregnancy and parturition (47). Furthermore, the abundance of basolateral AQP3 in epithelial tissues and many non-epithelial cells suggests that this aquaglyceroporin is a major participant in barrier hydration, as well as water and osmolyte homeostasis in the body (27). Collectively, these results implicate significant roles for members of the AQP family in blastocyst and uterine fluid homeostasis during implantation (78).

5.4. Placental and fetal fluid homeostasis

Pregnancy demands greater amounts of food, water, and electrolytes for conceptus growth (83). The placenta is a key organ for supporting fetal growth by acting as an interface between mother and fetus to regulate exchanges of nutrients, gases, water, ions, and waste products. Among all these substances, significant volumes of water are required to support normal fetal movement, growth and development (84). Dynamic changes in fetal fluid accumulation and fetal weight, as well as placental weight, take place during gestation (Figure 3) (85, 86). Typically, water is transported to the fetus from the maternal circulation across the placenta and amnion. Thus, placental water transport is essential for fetal water acquisition.

Amniotic fluid is derived from both the fetus (kidneys, lungs, epidermis, and fetal blood vessels in the placenta and umbilical cord) and the mother (blood vessels via amniotic membranes) (87). This fluid is removed by both the fetus and the mother through absorption and blood circulation, along with the participation of the fetal intestine after swallowing. Water constitutes greater than 95% of amniotic fluid (87). Rates of placental water flow, as well as the balance between amniotic fluid production and reabsorption, affect amniotic fluid volume (84), which reflects both the amount of water transferred across the placental membrane and the flux of water across the amnion. Available evidence shows that rates of embryonic survival and growth are positively correlated with allantoic and amniotic fluids in mammals (88-92). Conversely, abnormal dynamics in amniotic fluid volume, either excessive (polyhydramnios) or insufficient (oligohydramnios), are associated with significant fetal morbidity and mortality (84). However, despite the long-standing, intriguing biological phenomenon of the marked changes in the volume and composition of allantoic and amniotic fluids during gestation, little is known about the regulation of water and ion transport into conceptuses of any mammalian species, including swine.

Accumulating results indicate that: (a) AQPs are associated with the regulation of maternal-fetal fluid exchanges and the maintenance of amniotic fluid homeostasis and (b) abnormal changes in AQP expression may contribute to the pathogenesis of diseases that are characterized by alterations in fluid transport, such as polyhydramnios and oligohydramnios (32, 40, 93-95). Aberrant changes of AQP1 and AQP3 expression in the human amnion, chorion and placenta may also play a role in the pathophysiology of oligohydramnios (32). Interestingly, AQP1 mRNA levels in fetal membranes increase steadily in gestating women with idiopathic polyhydramnios probably due to a compensatory mechanism affecting water transport (95). These clinical observations are supported by results from studies of AQP1 gene knockout mice (96). Specifically, these AQP1-null mice had a greater amount of amniotic fluid, compared to their wild-type counterparts (96). Similarly, another study found that AQP1 in placental vessels negatively regulated water flow across the fetal membrane, while AQP3 in trophectoderm cells positively regulated placental water flow (58). Thus, AQP1 and 3 likely facilitate maternal to fetal water flow and intramembranous water flow, respectively (58).

Besides AQP 1 and 3, other AQP may be crucial for water transport in the conceptus. The up-regulated expression of AQP4 in human placentae throughout pregnancy may help control ion homeostasis and water balance during maternal-fetal fluid exchanges (97). AQP8 may be another water channel that mediates amniotic fluid resorption by the intramembranous pathway (38). Pregnant mice with AQP8 knockout have a significantly greater amount of amniotic fluid and greater placental weights, resulting in a greater litter size

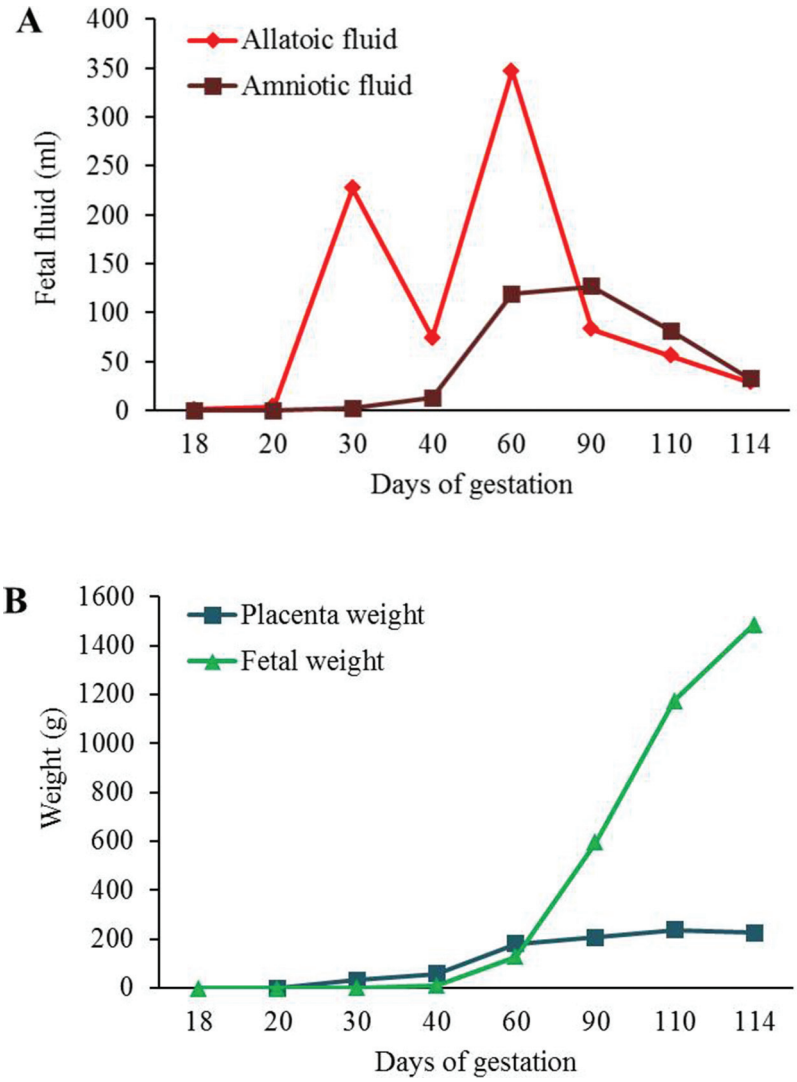

Figure 3. Dynamic changes of fetal fluid volumes as well as placental and fetal weights during gestation in pigs. Values are means for six gilts on each day of gestation. Data were adapted from Bazer (86) and Wu *et al*. (85).

and greater fetal and neonatal weights, compared to wild-type mice, although no evidence of placental pathology was found in either group (66). Moreover, AQP9 may be the most important water channel mediating intramembranous water and solute resorption of amniotic fluid due to its permeability to water and other neutral solutes (39). These findings from animal studies help explain the salient clinical observation that expression of AQP 8 and 9 in the amnion is decreased, but their expression in the chorion increases in gestating women with oligohydramnios, leading to a deficiency of amniotic fluid (94).

In livestock (e.g., pigs, cattle, and sheep), the allantoic sac is a functional component of the conceptus (85). Allantoic fluid is derived from maternal and fetal secretions, and is absorbed by the allantoic epithelium into the fetal-placental circulation. The volume of allantoic fluid increases rapidly during early gestation (e.g., from 1 ml on Day 18 to 200-250 ml on Day 30 of gestation in swine), which helps expand the placental membranes and forces the chorioallantois into apposition with the uterine endometrium (85). We are not aware of any published data in the English literature regarding AQP expression in the allantoic membranes of livestock species.

5.5. Cervical ripening

The cervix, which is composed mainly of smooth muscle and collagen fibers, undergoes significant biochemical changes during gestation and parturition (such as cervical ripening) (93). Basically, cervical ripening refers to the softening of the cervix, which results from the progressive decrease in cross-linking of fibers in the collagen network and an increase of water content, contributing to successful cervical dilation and the passage of the offspring through the birth canal (47, 93). Thus, by facilitating water transport, AQP regulates cervical fluid balance during these physiological processes in the cervix. This was demonstrated in mouse models of preterm and delayed cervical ripening, as AQP 3, 4, 5, and 8 modulate distinct aspects of cervical water balance during pregnancy and parturition (47).

6. EFFECTS OF HORMONES AND NUTRIENTS ON AQUAPORIN EXPRESSIONS IN MAMMALS

6.1. Steroid hormones

6.1.1. Estrous cycle and pregnancy state

Expression of endometrial AQP 1 and 2 correlates with steroid hormone levels to maintain normal endometrial function during the estrous cycle. Decreases in their expression in endometrial vessels or epithelium may be involved in the occurrence of anovulatory uterine bleeding (23). The abundance of AQP 1, 5, and 9 proteins is influenced by stage of the estrous cycle and pregnancy. Higher expression occurs in the oviduct on Days 2-4 and Days 18-20 than on Days 10-12 and Days 14-16 of the estrous cycle which implicates effects of estrogens (69). Hormonal regulation of water channels in the oviductal epithelium might control water transport to the oviductal lumen (98). Furthermore, steroid hormones upregulate expression of mRNA and protein of AQP9, whereas other ovarian signals control the expression of AQP 5 and 8 in the oviductal epithelium (98).

6.1.2. Estrogen

Estrogen is one of the steroid hormones that can regulate AQP expression in the female reproductive system (uterus, vagina, ovary, cervix, and placenta) (99, 100). Studies with mice have shown that estrogen induces a shift in AQP1 expression from the myometrium to the uterine stromal vasculature (78). Additionally, estrogen up-regulates expression of AQP2 and AQP3 in the epithelial cells and myometrium of the mouse uterus (49). Similarly, in women, there is a positive correlation between AQP2 expression levels in the endometrium and concentrations of 17β-estradiol in serum (26). Thus, physiological concentrations of estrogen stimulate water imbibition in the uterine endometrium and increase water permeability of luminal epithelial cells. This allows for an increased amount of water to cross the epithelial cells into the lumen, leading to a decrease in viscosity of uterine luminal fluid and uterine preparation for implantation of the blastocyst.

6.1.3. Progesterone

Progesterone, the required hormone for maintaining pregnancy (101), up-regulates the expression of AQP1 in both the placenta and the inner circular layer of the rat uterine myometrium (81). The abundance of the AQP5 protein in the apical plasma membrane of rat uterine epithelial cells is also enhanced by progesterone (81). AQP5 is exclusively localized to the uterine glandular epithelium after blastocyst attachment and an induction in its expression is dependent on estrogen stimulation of the progesterone-primed uterus (78). Like estrogen, there is a positive correlation between AQP2 expression levels in endometrium and concentrations of progesterone in serum (26). Thus, an increase in progesterone during pregnancy plays an important role in rapid water accumulation in the conceptus.

6.1.4. Other factors

A concentration-dependent effect of human chorionic gonadotrophin (hCG) is to increase the abundance of AQP9 protein in human placentae (104). In addition, high levels of hCG up-regulate AQP9 protein expression in explants from pre-eclamptic placenta (104). Similarly, relaxin increases AQP3 mRNA abundance in the cervix of late pregnant mice and changes glycosaminoglycan composition by increasing synthesis of hyaluronan in the cervix (48). There are reports that administration of dexamethasone to pregnant ewes on Days 64-74 of gestation augments AQP1 mRNA levels in the Day 74 fetuses (105).

6.2. Angiotensin and arginine vasopressin

Angiotensin is a peptide hormone that causes vasoconstriction and a subsequent increase in blood pressure. AQP1 mRNA levels in fetuses are up-regulated after a 3 day-infusion of angiotensin I during the last third of gestation in ewes (105). However, angiotensin-(1-7) produces antidiuresis in association with up-regulation of AQP1 in virgin rats, while causing diuresis with down-regulation of

AQP1 in pregnant rats during late gestation (106). A reduction in AQP2 expression in response to urinary tract obstruction in rats is mediated by angiotensin II (107). Arginine vasopressin is a peptide hormone that helps to retain water in the body and to constrict blood vessels. AQP1 expression in trophoblast-like cells is up-regulated by both arginine vasopressin and cAMP agonists, suggesting that modulation of AQP1 expression by maternal hormones may contribute to fetal-placental-amnion water homeostasis during gestation (108).

6.3. Insulin

Insulin is known to regulate carbohydrate, protein and fat metabolism in the body. Several studies demonstrated that insulin could affect AQP expression in reproductive systems of mammals (109-111). It appears that effects of insulin on AQP expression vary with tissues and AQP isoforms. For example, results of both immunohistochemical and western blot analyses indicate that hyperglycemia in streptozotocin-induced diabetic rats (an animal model of type I diabetes mellitus) decreased the expression of AQP 1, 2, and 3 in vaginal tissues through an estrogen-independent mechanism, leading to a reduction in the volume of vaginal fluid after pelvic nerve stimulation (110). Similarly, AQP2 expression in the rat vagina was reduced in streptozotocin-induced diabetic rats, which was prevented by insulin treatment (112). Likewise, expression of AQP 3, 7, and 9 in cultured adipocytes and hepatocytes was enhanced by insulin (111). In contrast, transcription of the AQP3 gene in cultured Caco-2 cells is repressed by insulin through induced expression of forkhead box a2 (109). Also, Castro-Parodi *et al.* observed that insulin reduced AQP9 expression in explants of normal human placentae in a dose-dependent manner (113). Likewise, in obese type 2 diabetes patients, expression of AQP 3, 7, and 9 in visceral adipose tissue is increased, but expression of AQP7 in subcutaneous adipose tissue and AQP9 in liver is decreased, as compared to normal subjects (111).

6.4. Nutrients

To our knowledge, little is known about effects of nutrients on AQP expression in female reproductive tissues of any animal species. It has been reported that maternal dietary fat could alter the composition of n-3 and n-6 polyunsaturated fatty acids in amniotic fluid and fetal intestinal-cell membranes (114) possibly affecting water transport by the fetal gut. Emerging evidence shows that amino acids not only serve as building blocks for tissue protein synthesis, but also regulate key metabolic and signaling pathways that support embryonic/fetal survival, growth, and development (115-121). However, little is known about effects of amino acids on AQP expression in the female reproductive tract, although we found that dietary supplementation with arginine to gilts markedly increased amniotic fluid volume at Day 25 of gestation (91). Thus, it is likely that arginine stimulates expression of AQP in the uterus, placenta, and fetal membranes to enhance water transport from mother to fetus. When the provision of amino acids from maternal diets is inadequate, the abundance of AQP in the conceptus may be substantially reduced to inhibit water transport. In support of this view, a substantial decrease in expression of renal vasopressin-related AQP2 was observed in female rats fed a low-protein diet during gestation (122).

7. SIGNALING PATHWAYS REGULATING AQP EXPRESSION IN MAMMALS

Various signal transduction pathways are known to regulate AQP expression in animals (123). These pathways involve cAMP, mitogen-activated protein kinase (MAPK), protein kinase C (PKC), and PI3K/Akt/mTOR pathways in a cell-specific manner. Most of the mechanistic studies have been conducted with cells and tissues that are not components of the reproductive tract.

7.1. cAMP

Cyclic adenosine monophosphate (cAMP) is a second messenger in cell signaling pathways. The cAMP-PKA-dependent pathway plays a role in regulating expression of AQP 1, 3, 8, and 9 in the placenta and fetal membranes (108, 123). For example, cAMP-dependent kinases mediate a stimulatory effect of arginine vasopressin on AQP1 gene expression in trophectoderm cells (108). Similar results were obtained with cAMP agonists. These findings suggest that modulation of AQP1 expression by maternal hormones contributes to fetal-placental-amnion water homeostasis during gestation. In addition, cAMP regulates AQP5 expression in a murine lung epithelial cell line (MLE-12) at both the transcriptional and post-transcriptional levels through a cAMP-dependent protein kinase A (PKA) pathway (124). It should be borne in mind that the response of mouse or human lung epithelial cells to acute and chronic cAMP exposures may be quite different, because short-term exposure to cAMP appears to induce increased internalization of AQP5 and a decrease in protein abundance on the plasma

membrane, while long-term exposure to cAMP can promote AQP5 localization in the plasma membrane and increase AQP5 abundance (125). Furthermore, cAMP up-regulates expression of AQP3 in primary human amnionic epithelial cells (34), AQP8 in cells derived from human amnionic epithelium (37), as well as AQP 1, 8, and 9 in epithelial cells of the human amnion (126).

7.2. Mitogen-activated protein kinase (MAPK)

MAPK plays a role in regulating the expression of AQP 1, 3, 8, and 9 in animal cells (7, 16, 123). The activation of ERK, p38, and JNK pathways and the hypertonicity response element in the AQP1 promoter are involved in hypertonicity-induced AQP1 expression in mouse medullary cells (127). An injury-induced increase in AQP1 protein abundance in astrocytes is blocked by a MEK1/2 inhibitor (128). Results of other studies also indicate that the MEK/ERK pathway mediates the ultraviolet-radiation-induced decrease in AQP1 expression and water permeability impairment in human retinal pigment epithelial cells (129). AQP1 plays a role in the proliferation of human corneal endothelial and epithelial cells via the ERK signaling pathway (130). Moreover, AQP1 expression in human pleural mesothelial cell lines (MeT-5A) is down-regulated by peptidoglycan via the p38 MAPK pathway and by LPS via the p38/JNK/ERK pathways (131). MAPK14/11 mediates embryonic responses to changes in culture medium osmolarity by regulating the abundance of AQP 3 and 9 in mouse embryos (61). The p38 MAPK may regulate AQP4 expression in cortical astrocytes after ischemic injury (132). An LPS-induced reduction in AQP5 mRNA in the parotid gland is mediated via the NF-κB and p-c-Jun/c-Fos pathway (133). Another study also showed that LPS decreased both mRNA and protein levels for AQP5 in a human airway submucosal gland cell line (SPC-A1) via the p38/JNK signaling pathway (134). Furthermore, an ERK inhibitor attenuates increases in mRNA and protein levels for AQP 3, 5, and 8 in rat astrocytes in response to exposure to a hyperosmotic solution, while a p38 inhibitor reduces mRNA and protein levels for AQP 4 and 9 in the cells (135). Thus, expression of different AQP can be regulated by distinct MAPK signal transduction pathways even within the same cell.

7.3. Protein kinase C

Phosphorylation of AQP1 by PKC directly causes an increase in the water permeability of Xenopus oocytes independent of cyclic nucleotides (136). In HEK293 cells, hypotonic conditions induce PKC- and microtubule-dependent phosphorylation of AQP1, resulting in its trafficking to the plasma membrane (137). The regulation of AQP1 expression in human prostate cancer cells is also dependent on calcium and PKC (138). Similar results have been reported for AQP 4 and 9 (139).

7.4. PI3K/Akt/mTOR

Aquaglyceroporins (AQP 3, 7, and 9) regulate the entry of glycerol into cells beyond water transport in human adipocytes and hepatocytes (111). Insulin and leptin regulate expression of these AQP isoforms through the PI3K/Akt/mTOR pathway in these cells (111). Moreover, exposure to fibroblast growth factor-2 (FGF-2) increases the abundance of the AQP3 protein in cultured human breast cancer cells and facilitates their migration via PI3K-dependent and independent mechanisms (140). Thus, these effects of FGF-2 can be partially blocked by addition of a PI3K inhibitor LY294002 or MEK1/2 inhibitor PD98059 to cell cultures (140). In addition, hyperandrogenism in the follicular fluid of women with polycystic ovarian syndrome (PCOS) results in a reduced abundance of AQP9 in granulosa cells that involves the PI3K pathway (141).

8. CONCLUSION AND PERSPECTIVES

Aquaporin water channels (AQP 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, and 12) have been identified in female reproductive systems of mammals (e.g., human, rodents, sheep, pigs, and horse). Their patterns of expression are cell- and tissue-specific as they fulfill their important roles in facilitating water movement across the biological membranes of maternal and fetal-placental tissues and organs, as well as between mother and her fetus. Thus, AQP exert crucial influences on female reproductive physiology and embryonic/fetal survival, growth and development. Hormones (e.g., estrogen, progesterone, angiotensin, arginine vasopressin, and insulin) affect AQP expression in the reproductive systems of mammals through several signal transduction pathways involving cAMP, MAPK, PKC, and PI3K/Akt/mTOR. At present, little is known about effects of nutrients (e.g., amino acids, glucose, fatty acids, vitamins, and minerals) on mRNA or protein levels for AQP in animal cells. There are many unanswered questions about roles for AQP in water transport by placenta, endometrium, and fetal membranes

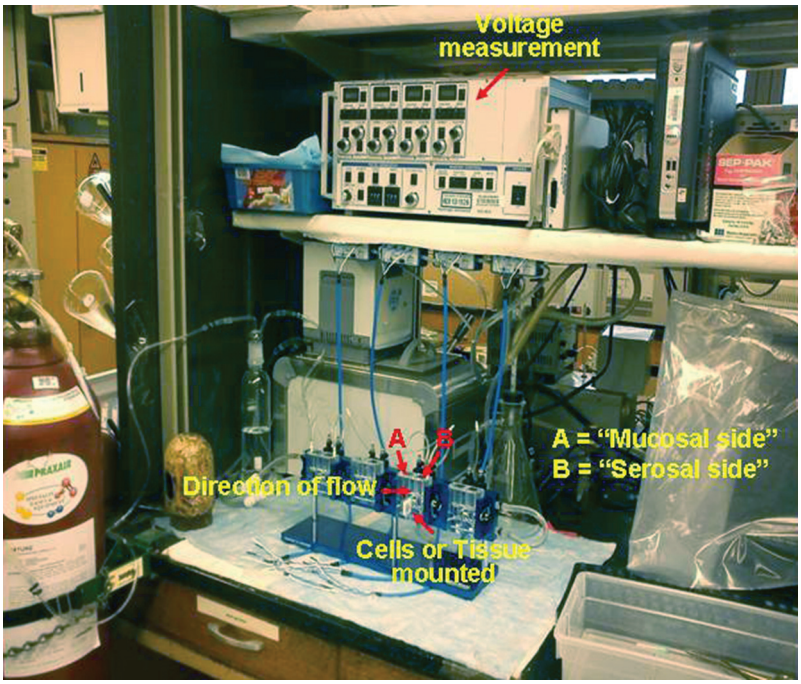

Figure 4. Ussing chambers for measuring water and ion transport by cells (e.g., porcine conceptus trophectoderm cells) and epithelial tissues (e.g., porcine placenta or small intestine). Four sets of Ussing chambers (Physiologic Instruments, CA, USA) are shown herein, as described by Wang *et al*. (245). Both chambers in each set contain the same volume of Krebs bicarbonate buffer (37°C, pH 7.4.) that is continuously gassed with 95% O_2/5% CO_2. Fresh tissue is mounted on a regular slider (Cat. # P2305, Physiologic Instruments), whereas a snap-well insert (Cat. #3801, Fisher Scientific) containing cultured cells is mounted to a special slider (Cat # P2302, Physiologic Instruments). A = addition of a tested substance to the "mucosal side" of the chamber (i.e., allantoic membrane side). B = sampling, from the "serosal side" of the chamber (i.e., chorion side) of a solution containing the tested substance transported by the mounted cells or tissue (e.g., placenta). Water transport is measured using ^3H_2O, whereas ion transport is measured simultaneously by an ohmmeter as transepithelial voltage changes.

during gestation or about the underlying regulatory molecular mechanisms. Studies on the regulation of AQP expression and function will offer potential therapies for pregnancy-associated diseases and disorders involving water imbalances. Powerful methodologies include measurements of mRNA and protein (total and phosphorylated) abundances in cells and tissues using quantitative real-time PCR and western blotting techniques. Additionally, as for other nutrients (244, 245), transport of ^3H_2O and ions by cells or tissues in the Ussing chamber system provides a functional indication of AQP abundance and/or activity (Figure 4). Future investigations of AQP in the mammalian female reproductive system require specific AQP blockers/inhibitors or animal models with defined phenotypes for AQP deficiencies. Knowledge of AQP biochemistry and physiology will not only advance basic understanding of mammalian reproductive biology, but will also accelerate the mechanism-based translation of fundamental research to improving reproduction (i.e., enhancing embryonic/fetal survival and growth (246) in women and livestock species.

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Abbreviations: Akt, protein kinase B; AQP, aquaporin; cAMP, cyclic adenosine monophosphate; CHIP, channel forming integral protein; ERK, extracellular signal-regulated kinases; FGF-2, fibroblast growth factor-2; hCG, human chorionic gonadotropin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NPA, asparagine-proline-alanine; NOS, nitric oxide synthase; PCOS, patients with polycystic ovary syndrome; PCR, polymerase chain reaction; PI3K, phosphatidylinositide 3-kinases; PKC, protein kinase C.

Key Words: Aquaporin, Female Reproductive System, Pregnancy, Water Channel Protein, Review

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