[Frontiers in Bioscience 17, 2371-2382, June 1, 2012]

# The expression and regulation of aquaporins in placenta and fetal membranes

**Yiwen Zhang[1], Shengdi Ding[1], Qi Shen[1], Jun Wu[1], Xueqiong Zhu[1]**

*[1]Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Wenzhou Medical College, Wenzhou 325027, China*

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## 1. ABSTRACT

Previous studies by our group as well as other researchers have found expression of Aquaporins (AQPs) 1, 3, 8, and 9 in human chorioamniotic membranes and placenta. Our previous study found that the alteration of the expression of AQPs 1, 3, 8, and 9 in placenta and fetal membranes was an adaptive response to maintain amniotic fluid homeostasis in case of abnormal amniotic fluid volume, which is likely to affect the intramembranous absorption and transport of water and solute from mother to fetus. However, the actual regulation mechanisms of intramembranous absorption and placental water flow are not yet clear, making it difficult to treat abnormal amniotic fluid volume effectively. Several studies found that many factors, including hormone levels, osmotic pressure, temperature, and oxygen concentration, regulate expression of AQPs in placenta, fetal membranes, and other mammalian organs through several signal transduction pathways, such as the cAMP, the MAPK, the PI3K/AKT, and the PKC pathways. These factors could provide potential therapeutic targets for the treatment of abnormal amniotic fluid volume.

## 2. INTRODUCTION

Abnormal amniotic fluid volume is associated with increased perinatal morbidity and mortality. Both placental water flow and the intramembranous pathway, as critical regulatory pathways for amniotic fluid volume homeostasis, play vital roles in amniotic fluid absorption via AQPs. Our previous study found that the alteration of the expression of AQPs 1, 3, 8, and 9 in placenta and fetal membranes was an adaptive response to maintain amniotic fluid homeostasis in case of abnormal amniotic fluid volume, which is likely to affect the intramembranous absorption and transport of water and solute from mother to fetus. However, the actual regulation mechanisms of intramembranous absorption and placental water flow are not yet clear, making it difficult to treat abnormal amniotic fluid volume effectively. Several studies found that many factors regulate expression of AQPs in placenta, fetal membranes, and other mammalian organs through several signal transduction pathways. These factors could provide potential therapeutic targets for the treatment of abnormal amniotic fluid volume.

## 3. EXPRESSION OF AQPS IN THE PLACENTA AND FETAL MEMBRANES

Aquaporins (AQPs) are trans-membrane proteins that organize in membrane as homotetramers with approximately 28 kD in size for monomers, They are channels facilitating the water and small neutral solutes across a variety of biological membranes (1-3).

To date, thirteen aquaporins (AQP0–AQP12) have been found in a variety of mammalian tissues (4-5). Expression of AQPs 1, 3, 8, and 9 has been detected in the human amnion, chorion, and placenta (2, 6-9). Unlike the exclusively water-permeable AQP1 and AQP8, AQP3 and AQP9 are highly permeable to glycerol and urea in addition to water.

Human AQP1, the first identified AQP, is widely expressed in many tissues and organs including erythrocytes, kidney, brain, heart and lung (10). AQP1 mRNA has been found in murine and ovine placentas, and AQP1 protein has been detacted in the fetal membranes throughout human pregnancy (1, 11-12). However, Johnston *et al* (11). observed AQP1 expression in endothelial cells of fetal and maternal blood vessels but not in epithelial cells of the ovine placenta or fetal membranes. Mann *et al* (7). went on to suggest that AQP1 play a critical role in the movement of water from the amniotic cavity across the amnion and chorion overlying the placenta directly into the fetal blood vessels beneath it. Our previous studies as well as those from other investigators revealed the expression of AQP1 in the endothelium of placental blood vessels but not in placental trophoblast cells (5). In contrast, AQP1 was detected in the syncytiotrophoblast in the human placenta (13-14). The AQP1 expression in the placental vasculature suggests a role in angiogenesis. It is noted that in certain species, such as sheep, a large amount of AQP1 protein may be found in the hemophagous zone, and this AQP1 is not from placental cells but from digested maternal red blood cells (15). It is reasonable to speculate that the AQP1 protein found in syncytiotrophoblast cells may originate exogenously from digested maternal red blood cells, not endogenous for placental cells.

AQP3, originally isolated from rat kidneys, has also been found in numerous tissues including ear, eye, skin, gut, and muscle (16). Whether it is expressed during pregnancy is still under debate. In a study by Mann *et al.* (7) neither AQP3 mRNA nor protein was detected in the human amnion. Likewise, Johnston *et al* (11). reported that AQP3 expression was not detectable in ovine amnion epithelial cells. In contrast, Wang *et al.* (6) found both AQP3 mRNA and protein in the human amnion and placenta, which is consistent with our findings (5). Damiano *et al.* (9) also found AQP3 expression in the apical membranes of the human term placental syncytiotrophoblast. This discrepancy remains unresolved and more experiments are needed before drawing any conclusion.

AQP9 mRNA is detected in the epithelia of the ovine amnion (16-17). Our previous study, as well as others', has shown AQP8 and AQP9 expression in human fetal membranes and placenta during pregnancy (8-9, 17-18). Wang *et al.* (8) reported the evidence of AQP8 expression in the human placenta and chorioamniotic membranes using reverse transcription PCR and *in situ* hybridization. However, AQP8 expression at protein level has not been studied in great depth. In another study by Wang *et al.* (17), AQP9 mRNA and protein expression in the human placenta and chorioamniotic membranes were shown by Northern blot and *in situ* hybridization and further by immunohistochemistry. Damiano *et al.* (9) also showed the presence of AQP9 mRNA and protein in the apical membranes of the syncytiotrophoblasts of human term placentas.

## 4. THE RELATIONSHIP BETWEEN EXPRESSION OF AQPS 1, 3, 8, AND 9 AND ABNORMAL AMNIOTIC fluID VOLUME

Recently, several studies have investigated the relationship between the expression of AQPs in fetal membranes and abnormal amniotic fluid volume (19-21). Transgenic AQP1 knockout mice have a greater volume of amniotic fluid and lower amniotic fluid osmolality (19). The authors hypothesized that the disruption of AQP1 probably cause idiopathic polyhydramnios. Mann *et al.* (20), however, found in their following study that, relative to pregnancies with normal amniotic fluid volume, AQP1 expression in the human amnion was higher in patients with idiopathic polyhydramnios, suggesting that increase of AQP1 expression is a compensatory response to and not a cause of idiopathic polyhydramnios. Our previous study showed that compared to pregnancies with normal amniotic fluid volume, there was a significant increase in AQP8 expression in the amnion and AQP9 expression in both the amnion and chorion during pregnancies with idiopathic polyhydramnios (18). Expression levels of AQP8 and AQP9 in the placentas of patients with idiopathic polyhydramnios decreased significantly compared to those in normal amniotic fluid volume pregnancies. However, this alteration of AQP8 expression in the amnion and placenta in case of polyhydramnios was not totally consistent with the findings from Huang *et al.* (22). They showed that AQP8 mRNA and protein levels in the placenta of patients with idiopathic polyhydramnios increased compared to those of the control group. The discrepancy may be due to the different medical conditions of the patients with idiopathic polyhydramnios. That report did not mention the diagnostic criteria for the different stages of individual patients, nor did it mention the overall medical conditions.

Shioji *et al.* (21) established an oligohydramnios model using prostaglandin-F2a receptor-deficient mice and showed that AQP8 expression in the fetal membrane decreased in case of oligohydramnios. Beall *et al.* (1) found that amniotic fluid volume was negatively correlated with AQP1 expression in fetal membranes and AQP1 and AQP9 expression in placenta; it also positively correlated with placental AQP3 expression level. In light of these findings, AQP1 appears to regulate fetal membrane water flow, and AQP3 is likely a candidate for the regulation of placental

water flow. Additionally, we were the first to show a significant decrease of AQP1 expression in the amnion and AQP3 expression in both the amnion and chorion in patients with isolated oligohydramnios. In contrast, there was a significant increase of AQP3 expression in the placenta compared to pregnancies with normal amniotic fluid volume. There were no significant differences of AQP1 expression in the chorion or placenta between the normal and patients (5).

The alteration of expression levels of AQPs 1, 3, 8, and 9 in the placenta and fetal membranes may be an adaptive response to abnormal amniotic fluid volume. By mediating the movement of water and solutes from the amniotic cavity directly into the fetal blood vessels beneath the placental surface across the amnion and chorion overlying the placenta AQPs contribute to the maintenance of amniotic fluid homeostasis (19).

To date, there have been few reports on factors regulating AQPs 1, 3, 8, and 9 expression in the placenta and fetal membranes, but some groups have explored these in other organs.

## 5. THE REGULATION OF AQPS 1, 3, 8, AND 9 EXPRESSION

### 5.1. Hormones

#### 5.1.1. Aldosterone

Aldosterone, a hormone from adrenal cortex zona glomorulosa, may regulate, at least in part, AQP3 expression as well as Na+ and K+ transport in the collecting ducts and thus regulates renal water reabsorption. Aldosterone deficiency was found to be associated with dramatic downregulation of AQP3 abundance in rat kidney. Consistently, an increase of endogenous aldosterone level or an exogenous aldosterone infusion in either normal rats or vasopressin-deficient Brattleboro rats was found to cause a significant increase in AQP3 level (23). However, the regulation mechanism is yet unclear.

#### 5.1.2. Glucocorticoid

Glucocorticoid, a hormone from the adrenal cortex zona fasciculata, regulates the expression of AQPs 1, 3, 8, and 9. Stocnoiu et al. (24) showed that glucocorticoid up-regulate AQP1 expression in the endothelium of the blood vessels of the peritoneal membrane and thus improve water permeability, while the glucocorticoid receptor antagonist RU-486 was found to completely abolish the effect of dexamethasone (a type of glucocorticoid) in rats. These data have shown that the regulation of AQPs play important roles in body water homeostasis. The induction of AQP1 by glucocorticoids in peritoneal capillaries has been found at the transcription level; as glucocorticoid response elements have been identified in the promoter region of the mouse AQP1 gene (25).

Dexamethasone has been found to up- regulate AQP1 expression in renal brush border membrane vesicles in neonatal rabbits, rat brain microvascular endothelial cells, mouse lungs, and cultured 9L gliosarcoma cells (26-29).

Treatment of pregnant ewes (and their fetuses) at 64 and 74 days of gestation with dexamethasone resulted in a small but statistically significant increase in AQP1 mRNA in the fetuses (30). In addition, compared to controls, dexamethasone-treated rats showed a higher level of AQP1 in the inner medulla, outer medulla and cortex; AQP3 expression is also increased in the outer medulla and cortex (31). Both Tanaka *et al.* (32) and Ben *et al.* (33) found that dexamethasone can up-regulate AQP3 expression in the epithelial cells lining human airways. However, King *et al.* (34) found that glucocorticoid did not induce AQP3 expression, but did induce AQP1 expression in the lungs.

#### 5.1.3. Glucagon and insulin

Insulin suppressed expressions of AQPs in adipocytes (35). Higuchi *et al.* (36) found that the expression of AQP3 was repressed by insulin. Badaut *et al.* (37,38) found the expression of AQP9 is negatively regulated by high concentrations of insulin in the brain, suggesting that AQP9 could be involved in brain energy metabolism, but the function of brain AQP9 are still speculative. Kuriyama *et al.* (39) found insulin down-regulated the levels of both AQP9 mRNA and protein in mouse cultured hepatocytes, possibly due to the promoter region of AQP9 contained the negative insulin response element. Castro-Parodi *et al.* (40) observed that in normal placental explants insulin treatment downregulated AQP9 expression but not AQP3.

The treatment of isolated hepatocytes with glucagon induced the trafficking of AQP8 from the intracellular vesicles to the hepatocyte plasma membrane, thus improved membrane water permeability (41,42). AQP9 expression was found to be sensitive to glucagon. In primary cultures of porcine hepatocytes, glucagon was found to enhance AQP9 expression (43).

#### 5.1.4. Sex hormones

There is some evidence that the expression of various AQPs can be regulated by steroid sex hormones (44-48). Feng *et al.* (44) showed the cyclic expression of endometrial AQP1, correlated with steroid hormone levels, to be essential for normal endometrial function. To a lesser extent, AQP1 is partially regulated by estrogen in the myometrium and in the myometrial smooth muscle and estrogen levels in these tissues may be associated with uterine edema (45). Diethylstilbestrol caused the downregulation of AQP9 in the hepatic periportal zone (46). AQP1 and AQP9 expression was significantly reduced in the efferent ductules of mice deficient with estrogen receptors (47). Moreover, androgens were found to modulate AQP9 in the efferent ducts of rats (48).

#### 5.1.5. Oxytocin

The administration of oxytocin significantly increased the protein level of AQP3 in the inner medulla, outer medulla, and cortex (49). This oxytocin-induced effect was blocked by treatment with the vasopressin V2 receptor antagonist SR121463B but not by treatment with the oxytocin receptor antagonist GW796679X. Therefore, it can be concluded that vasopressin V2 receptors specifically mediate the antidiuretic effects of oxytocin.

**5.1.6. Human chorionic gonadotropin (HCG)**

In normal placental explants treated with different concentrations of recombinant human chorionic gonadotropin, Marino *et al.* (50) found that AQP9 protein expression increased significantly compared to the non-treated explants. This effect on AQP9 expression was dependent on human chorionic gonadotropin concentrations. In addition, increase of AQP9 protein expression was related to an increase of 1.6-fold in transcellular water flux.

**5.1.7. Vasopressin**

Data from a *Xenopus* oocyte assay suggest that AQP1 may be regulated by arginine vasopressin (51). Additionally, the vasopressin-sensitive AQP3 is the target for long-term regulation by vasopressin (52,53), but Dibas *et al.* (54) found that while AQP3 contributes to water reabsorption in the kidney collecting ducts, it is unresponsive to vasopressin.

In contrast to previous findings in cultured mouse medullary cells by Jenq *et al.* (55), vasopressin did not affect AQP1 expression in primary cells of human renal proximal tubule epithelium under hyper-osmotic conditions (56). Kwon *et al.* (57) demonstrated that there was a significant vasopressin-resistant down-regulation of AQP1 and AQP3 associated with the polyuria in rat chronic renal failures. Li *et al.* (58) found that reduced level of AQP1 in unobstructed kidneys contribute to the compensatory increase in urine production and down-regulation of AQP1 and AQP3 in vasopressin-deficient Brattleboro rats. This supports the hypothesis that vasopressin-independent pathways may be involved in AQP3 regulation in obstructed kidneys.

Several reports showed that renal AQP3 expression increases together with increased arginine vasopressin response in diabetic rats, which suggests a vasopressin-mediated compensatory increase in response to the severe polyuria (59-60). Both 48-hour water restriction in Sprague-Dawley rats and 5-day arginine vasopressin infusion in Brattleboro rats caused a significant increase in AQP3 expression in the inner medulla, outer medulla, and cortex, while the level of AQP1 remained unchanged (61). Additionally, Chen *et al.* (62) found that plasma vasopressin concentration was elevated, which was probably associated with increased expression of AQP1 in the renal cortex and AQP3 in the inner medulla of hypothyroid rats. Activation of vasopressin receptor by 1-deamino-8-d-arginine vasopressin also increased AQP3 abundance in the cortical collecting ducts of AQP1 null mice (63).

**5.1.8. Angiotensin**

Angiotensin-(1-7) causes antidiuresis associated with up-regulation of AQP1 and diuresis in late gestation with down-regulation of AQP1 in virgin rats (64).

AQP1 expression increases in fetuses infused with angiotensin I for three days in the last third of the gestation period (30). Additionally, AQP1 expression *in vitro* and *in vivo* is up-regulated through the angiotensin II pathway, providing an important regulatory mechanism to link proximal tubular water reabsorption to body fluid homeostasis via the renin-angiotensin system (65). However, Jenq *et al.* (66) showed that angiotensin II, vasopressin, and/or atrial natriuretic peptide did not affect AQP1 expression. Therefore, the effect of the angiotensin II on AQP1 is still under debate.

**5.1.9. Thyroxine**

Both hypothyroidism and hyperthyroidism may change urinary production through regulating AQP1 and AQP3 expression in renal cells. Hypothyroidism has been associated with decreases in the rate of glomerular filtration and renal plasma flow (67-68). Additionally, Yeum *et al.* (69) found that expression levels of AQP1 and AQP3 increased in renal cortex of individuals with hypothyroidism, suggesting that these water channels in part account for the water retention observed in hypothyroidism.

Hyperthyroidism causes polyuria associated with an osmotic diuresis. The downregulation of AQP1 expression in thyroxin-treated animals mimicked that observed in patients with hyperthyroidism. The decreased expression of AQP1 results in the increase in distal delivery to the macula densa, which may alter the sensitivity of the tubular glomerular feedback mechanism (70).

AQP8 expression increased in the livers of rats with hypothyroidism and decreased by triiodothyronine treatment, probably through a negative thyroid hormone response element (71). The modulation of hepatic AQP8 expression may be related to the regulation of the mitochondrial metabolism by thyroid hormones. However, the negative modulation exerted by T3 on AQP8 seems not to be the case for AQP9 in rats whose hepatic mRNA level was unchanged in thyroid cells (72). Caperna *et al.* (43), however, found that the absence of T3 regulation in rat liver did not result in any increase in AQP9 expression. Indeed, the T3-induced enhancement of AQP9 transcription was not accompanied by an increase in AQP9 protein level.

**5.2. Ionic compounds**

The activities of most mammalian AQPs have been shown to be inhibited by heavy metal ions (73-76). Hirano *et al.* (73) found that mercury disrupts the water pore of AQP1 through local conformational changes. $HgCl_2$, an AQP1 inhibitor by blocking the pore region of the AQP channel, alters the water permeability of the parietal peritoneal membrane (74). Gold and silver also inhibit AQP1, however, the molecular mechanism for inhibition has not been revealed (75).

$Hg^{2+}$ irreversibly inhibited the water flux in AQP3-expressing cells, while $Ni^{2+}$ reversibly blocked the AQP3 channels (76). The function of human AQP3 was inhibited by metal ions such as copper and nickel, and at least three amino acid residues---- Trp128, Ser152, and His241, are involved in the inhibition (77).

**5.3. pH**

pH directly regulates the expression and activities

of mammalian AQPs.

Studies on human AQP3 have revealed that the amnio acid residues His53, Tyr124, Ser152, and His154, are involved in the regulation of its activity by extracellular pH (77). The water permeability of AQP3 is inhibited at low pH, whereas that of other AQPs is not. The reduced transepithelial osmotic water permeability under low pH condition in the basal (but not apical) membrane provides indirect evidence for the function of AQP3--the only pH-regulated AQP in airway in human bronchial epithelial basolateral membranes (78). pH regulation on AQP expression in the lung may be physiologically important considering the fact that $CO_2$ diffuses through airway epithelial cells, which can affect the local pH.

**5.4. Oxygen concentration**

Low oxygen concentration has different influences on the expression of different AQPs, suggesting that some AQPs may be associated with oxygen transport.

Compared to normal brain, AQP1 expression increased in glioblastoma cells, which was induced by hypoxia (79). Echevarria *et al.* (80) showed that knocking down of AQP1 resulted in activation of hypoxia-inducible genes in normoxic endothelial cells. Moreover, AQP1 expression in the lung was markedly up-regulated in animals exposed to hypoxia, suggesting that AQP1 works as an O2 channel and thus facilitates O2 movement across the cell membranes.

Ding *et al.* (81) demonstrated a significant increase in expression of manganese superoxide dismutase (MnSOD), hypoxia inducible factor-1 (HIF-1α), and AQP9 after injury. Pharmacological inhibition of HIF-1α by 2-methoxyestradiol reduced the up-regulation of AQP9 after traumatic brain injury. Recently, several studies have suggested that hypoxic conditions indicated by MnSOD expression after closed head injury contribute to HIF-1α expression. HIF-1α, in turn, up-regulates the expression of AQP9. In addition, Yamamoto *et al.* (82) found that AQP9 expression in cultured astrocytes was dramatically decreased during hypoxia, suggesting a role of oxygen in AQP regulation but the biological reason for the alternation remained to be resolved. It may regulate the rates of water transport to maintain the proper osmomolality for normal neuronal functions of the brain.

**5.5. Temperature**

The marked increase in nucleation temperature coincides with the appearance of AQP3 in mouse early morulae (the compacted eight-cell stage) (83). Additionally, a marked decrease in the expression of AQP9 mRNA in rat astrocytes was observed at 37, which confirmed by Western blot analysis. However, under 32 (mild hypothermia) AQP9 expression was not further decreased compared to 37 (84).

**5.6. Osmotic pressure**

**5.6.1. Hypertonicity**

AQP1 is upregulated by hypertonicity caused by either NaCl or mannitol (65,85).

A significant increase in AQP1 expression was induced by hypertonic treatment in cultured mouse medullary cells and in the primary cells of human renal proximal tubule epithelium (56, 86). Jenq *et al.* (66) suggested that AQP1 was translocated from the cytosol to the membrane of human renal proximal tubule epithelium cells and hyperosmolarity enhanced this translocation. In addition, Kuboshima *et al.* (87) found that hyperosmotic stimuli could elevate AQP1 level in the plasma membrane by translocation of AQP1 protein from recycling or early-stage endosomes to the plasma membrane, rather than by protein synthesis via newly transcribed mRNA.

Another report showed that osmotic changes induced phosphorylation-dependent AQP1 trafficking, which results in the increase of AQP1 on the plasma membrane and enhanced water transport (88).

Hypertonic media increased AQP3 expression in human peritoneal mesothelial cells and in cultured human keratinocytes, while AQP1 and AQP9 expression remained unchanged under hypertonic conditions (89-90). However, hyperosmotic stress increased AQP9 expression in cultured rat astrocytes and in the rat brain cortex (91).

**5.6.2. Hypotonic**

Suh *et al.* (92) showed the lack of osmotic effects on AQP8 expression. High glucose induced the translocation of AQP8 from the intracellular membrane to the plasma membrane, while mannitol has no effect on such translocation. Therefore, it seems the translocation is not just due to osmotic pressure itself, and it is dependent on certain specific osmolyte. However, Qi *et al.* (93) found that hypotonic media significantly enhanced AQP8 expression on intracellular membrane of amnion epithelial cells compared to isotonic media, while hypertonic media significantly decreased its expression. More thorough investigation is needed to reconcile the discrepancies.

**6. SIGNAL TRANSDUCTION PATHWAYS**

Several studies have suggested that various signal transduction pathways may be responsible for the regulation of expression of AQPs 1, 3, 8, and 9. Although there are few papers focused on AQP expression in the placenta and fetal membranes, results from other organs suggest that various signal transduction pathways may be involved in the regulation of AQP expression.

**6.1.Cyclic-adenosine-monophosphate-protein-kinase-A-dependent (cAMP- PKA- dependent) pathway**

The cAMP-PKA-dependent pathway is associated with expression of AQPs 1, 3, 8, and 9 in the placenta and fetal membranes. Wang *et al.* (6) found AQP3 expression was significantly increased following the introduction of forskolin or SP-cAMP into the primary amnion epithelial cell culture. In a later study, Wang *et al.* (94) showed the expression of AQPs 1, 8, and 9 in the epithelial cells of the human amnion was up-regulated by cAMP. The expression levels were simulated by forskolin, an adenylate cyclase stimulator that causes cellular production of cAMP (Figure 1). In contrast, the lack of any

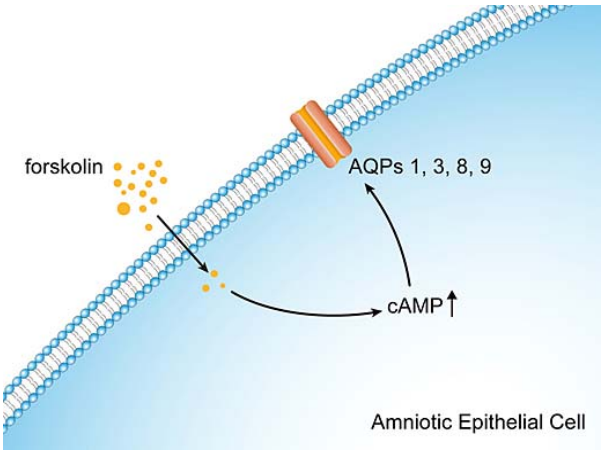


**Figure 1.** AQPs 1, 3, 8, and 9 expression regulated by cAMP-PKA-dependent pathway. The expression of AQPs 1, 8, and 9 in the epithelial cells of the human amnion was up-regulated by cAMP. And the expression levels were simulated by forskolin, an adenylate cyclase stimulator that causes cellular production of cAMP.

effect of SP-cAMP, the PKA activator, on the expression of AQPs 1, 8, or 9 suggests that cAMP up-regulates the expression of AQPs 1, 8, and 9 in the epithelial cells of the human amnion via a PKA-independent pathway.

In a study of trophoblast cells, Belkacemi *et al.* (13) found that both forskolin and SP-AMP up-regulated AQP1 expression in first- trimester-derived extravillous cytotrophoblasts (HTR8-/SVneo cells) and two highly proliferative carcinoma trophoblast-like cell lines. This took place via a number of functional features of the syncytiotrophoblast, namely JAR and JEG-3 cells.

By the above means, the expression of human AQPs 1, 3, 8, and 9 in the placental trophoblast and the epithelial cells of amnion were found up-regulated by the second-messenger cAMP.

The regulation of AQP expression is also associated with the cAMP-PKA pathway in other organs. Han *et al.* (95) reported that the water channel activity of AQP1 was significantly increased by PKA activators such as cyclic-AMP (cAMP) and forskolin. Iton *et al.* (96) found both vasoactive intestinal polypeptide (VIP) and cAMP upregulated AQP3 expression via a PKA-independent pathway in human colonic epithelial cells.

Either incubation with or injection of 8-bromo-cAMP into Xenopous oocytes expressing AQP1 cRNA significantly increased membrane permeability to water, suggesting that stimulation of AQP1 activity is cAMP-dependent (51). Another study suggested that the catalytic subunit of PKA significantly increased the phosphorylated form and the plasma membrane fraction of AQP1, indicating that the redistribution of AQP1 from the intracellular vesicles to the plasma membrane may be regulated by cAMP-dependent phosphorylation (95).

The plasma level of arginine vasopressin and the expression of AQP1 and AQP3 in medullary regions were found to increase in the kidneys of male spontaneously hypertensive rats compared to the kidneys of age-matched Wistar-Kyoto rats. The adenylyl cyclase activity stimulated by arginine vasopressin was then augmented along with increased type VI adenylyl cyclase expression, which suggested that the increase in AQP1 and AQP3 expression is associated with activated arginine vasopressin/cAMP pathway (97). However, Preisser *et al.* (98) found the down-regulation of AQP3 expression to be independent of vasopressin-mediated cAMP accumulation in the medullary collecting ducts. Moreover, following the glycyrrhizic acid treatment, reduced expression of 11 beta-hydroxysteroid dehydrogenase type 2 was found to result in up-regulation of AQP3, in which arginine vasopressin/cAMP-dependent mechanisms are unlikely to be involved (99).

In primary culture of chicken hepatocytes, high glucose levels induced the movement of AQP8 from the intracellular membrane to the plasma membrane and also improved the level of intracellular cAMP, suggesting that high glucose levels stimulate AQP8 via the cAMP pathway (92).

Another study found that activation of PKA by dibutyryl cAMP induced an increase in AQP9 expression in cultured rat astrocytes mentioned above (100). In addition, potent activators of dibutyryl cAMP/PKA, such as oxidative mediators, cytokine productions, and other proinflammatory molecules, are likely to activate the pathways and may increase AQP9 expression (101). Therefore, the AQP9 over-expression observed in animals with lipopolysaccharides-induced brain edema may be resulted from the activation of the dibutyryl cAMP/PKA pathway by proinflammatory and oxidative mediators.

### 6.2. Mitogen- activated- protein- kinase- dependent (MAPK- dependent) pathway

MAPK is associated with the regulation of the expression of AQPs 1, 3, 8, and 9. There are five distinct groups of MAPK in mammals: extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun amino-terminal kinases/stress-activated protein kinases

(JNK/SAPK), P38, ERK3/4, and ERK5 (4, 20, 102). The most extensively studied groups of MAPK are the ERK1/2, JNK, and P38 kinases (103).

### 6.3. ERK1/2

Maruyama *et al.* (104) showed that transient activation of the ERK pathway was crucial for the induction of AQP1 expression in response to hyperosmotic stress. The down-regulation of AQP1 using siRNA following lipofectamine-mediated transfection in corneal endothelial and epithelial cells resulted in reduced cell proliferation and migration with a significant decrease in phosphorylated ERK, suggesting that AQP1 plays a role in human corneal endothelial cells proliferation and migration via the ERK signaling pathway (105). On the other hand, McCoy *et al.* (106) were able to mimic a cortical stab wound in astrocytic cultures and showed *in vitro* that AQP1 expression is induced following injury and blocked by U0126 (inhibitor of MEK1/2), which suggests that AQP1 is specifically induced via the mitogen-activated protein kinase signaling pathway.

Interestingly, ultraviolet radiation induced the down-regulation of AQP1 and AQP3 expression via the MEK/ERK pathway in human retinal pigment epithelial cells and in cultured keratinocytes (107-108). MEK/ERK inhibitors PD98059 and U0126 inhibited ultraviolet radiation-induced AQP3 loss (109). All-trans retinoic-acid up-regulated AQP3 expression was partly mediated by EGFR/ERK signaling in cultured human skin keratinocytes. Nicotinamide attenuated all-trans-retinoic-acid-induced up-regulation of AQP3 expression through inhibition of EGFR/ERK signal transduction and eventually decreases water permeability and water loss (110).

### 6.4. JNK

Umenishi *et al.* (86) showed that hypertonicity-induced AQP1 expression in cultured mouse medullary cells involves the activation of the c-Jun NH2-terminal kinase (JNK) pathway. Inhibition of JNK prevented c-Jun phosphorylation and suppressed AQP1 expression in rats after subarachnoid hemorrhage (111).

The inhibition of AQP8 translocation from intracellular membrane to plasma membrane by SP 600125 (a JNK inhibitor) in primary culture chicken hepatocytes suggests that the translocation is via the MAPK pathway and may be activated by JNK phosphorylation induced by high glucose level (92).

### 6.5. P38

In that study of primary culture of chicken hepatocytes, authors also found SB 203580 (a p38 MAPK inhibitor) blocked high-glucose-induced AQP8 translocation, showing that high glucose levels stimulate AQP8 also via p38 kinase pathway (92).

Several sets of data showed that hypertonicity-induced AQP1 expression involves the activation of p38 kinase pathway in cultured mouse medullary cells (86). P38 was also implicated in an increase of AQP9 expression after osmotic stress. Hyperosmotic stress induced AQP9 expression in cultured rat astrocytes and a p38 MAPK inhibitor, suppressed AQP9 expression, suggesting that p38 MAPK is activated in this process **(**91). Additionally, Horie *et al.* (112) found that tumor necrosis factor-alpha not only decreased AQP3 protein expression and plasma membrane water permeability but also decreased AQP3 mRNA expression and promoter activity, which was abolished by inhibitors of p38. These data indicated that tumor necrosis factor-alpha decreased AQP3 gene expression through p38 activation.

### 6.6. Phosphatidylinositol 3-kinase( PI3K)/Akt

In primary culture of chicken hepatocytes, high-glucose induced Akt phosphorylation and induced AQP8 translocation from intracellular membrane to plasma membrane. LY 294002 (a PI3K inhibitor) inhibited this process suggesting that high-glucose levels stimulate AQP8 translocation related the PI3K/Akt pathway (92).

Researchers found that insulin treatment reinforced the expression of AQP9 in the plasma membrane of human adipocytes, and the effect was abrogated by the PI3K inhibitor, suggesting the involvement of the PI3K/Akt pathway (113).

### 6.7. Protein kinase C (PKC)

The observed increase in water permeability is associated with increased AQP3 in the plasma membrane of the epithelial cells of rat renal collecting ducts. It is very likely that isoforms of calcium-dependent PKC are involved in the vasopressin signaling pathway and contribute to the sensitivity to this hormone (114). In primary culture of chicken hepatocytes, staurosporine, a PKC inhibitor, blocked high-glucose-induced AQP8 translocation, suggesting that high glucose levels stimulate AQP8 related PKC pathways (92). Yamamotoa *et al.* (115) found that signal transduction via PKC play important roles in regulating the expression of AQP9 in cultured rat astrocytes.

## 7. CONCLUSIONS

Water-selective AQP1 and AQP8, and aquaglyceroporin AQP3 and AQP9 are expressed in the human amnion, chorion, and placenta. Under conditions of abnormal amniotic fluid volume, expression of these AQPs may be altered and used as adaptive response to maintain the amniotic fluid homeostasis from mother to fetus. Several factors such as hormone levels, osmotic pressure, temperature, oxygen concentration may regulate AQP expression in the placenta, fetal membranes, and other mammalian organs via various signal pathways. Studies on the regulation of AQP expression and function during pregnancy will pave the road for effective treatment of abnormal amniotic fluid volume.

## 8. ACKNOWLEDGMENTS

This work was supported by grants from Zhejiang Provincial Natural Science Foundation (No. Y2100933) and International cooperation project of Wenzhou city (No. H20100067).

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**Abbreviations:** AQPs: Aquaporins; MnSOD: manganese superoxide dismutase; HIF-1α: hypoxia inducible factor-1; cAMP: cyclic-AMP; VIP: vasoactive intestinal polypeptide; ERK1/2: extracellular signal-regulated kinases 1 and 2; JNK/SAPK: c-Jun amino-terminal kinases/stress-activated protein kinases

**Key Words:** Aquaporins, Placenta, Regulation, Abnormal amniotic fluid volume, Review

**Send correspondence to:** Xueqiong Zhu, Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Wenzhou Medical College, No. 109 Xueyuan Xi Road, Wenzhou, Zhejiang, 325027, China, Tel: 86-577-88816374, Fax: 86-577-88816191, E-mail: zjwzzxq@yeah.net