Ontogeny of the mammalian kidney: expression of aquaporins 1, 2, 3, and 4

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Review article

Background: **Determining the expression and functions of aquaporins (AQPs) in the adult kidney has generated important information about the roles of this protein family in the renal regulation of water homeostasis. However, limited information describes the expression of AQPs in fetal kidneys, and most reports on fetal renal AQPs originate from animal studies. Although there are the maturation and regulation of the renal-concentrating mechanism, the ways in which changes in the expression of AQPs contribute to the formation of urine during the perinatal period remain unclear.**

Data sources: **This review summarizes current knowledge about the spatial and temporal expression patterns of AQP1, AQP2, AQP3, and AQP4 in the fetal and postnatal kidneys in different animal species and in human beings.**

Results: **AQP1 and AQP2 expression can be detected earlier in gestation in human beings and sheep compared with mice and rats. AQP1 expression is detected earlier in the proximal tubules than the expression of AQP2, AQP3, and AQP4 in the collecting ducts.**

Conclusion: **Further studies investigating the regulation of AQPs during kidney development may provide insights into normal water-handling mechanisms and the pathophysiology of fetal kidneys, which may determine new directions for the clinical treatment of kidney diseases.**

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Introduction

Aquaporins (AQPs) are a family of integral plasma membrane proteins called major intrinsic proteins that facilitate water transport across biological membranes. Indeed, the discovery of AQP1 by Agre et al[1,2] opened up a new avenue of study into water transport across cell membranes. So far, 13 mammalian isoforms of AQPs have been identified, and they are divided into 3 groups: water-selective AQPs (AQP0, 1, 2, 4, 5, 8, and 10), (AQP8 has additional functionaly in ammonia and hydrogen peroxide transport);[3,4] aquaglyceroporins (AQP3, 6, 7, and 9) that transport water as well as small molecules like glycerol, urea, or nitrate; and superaquaporins (AQP11 and 12) that are newly identified members of the AQP subfamily.[5-7]

AQPs are small membrane proteins with molecular masses of 28-30 KDa, and they have homologous amino acid sequences comprising 2 highly conserved asparagine-proline-alanine (NPA) motifs, which play vital roles in selective water conduction.[8,9] However, the first NPA motif of AQP11 and AQP12 is incompletely conserved.[8,9] AQPs can be detected in non-glycosylated forms, with molecular masses of 29-30 KDa, and in glycosylated forms, with molecular masses of 40-45 KDa.[10] Glycosylation is a posttranslational modification that can alter the properties of the target protein,[11] and it is an important feature underlying cell surface expression.[12]

Eight AQP isoforms (AQP1, 2, 3, 4, 6, 7, 8, and 11) are expressed in the kidney.[13-15] In the adult mammalian kidney, AQP1, AQP2, AQP3, and AQP4 play dominant roles in water reabsorption, and these isoforms are the main focus of this article. Water reabsorption mainly occurs in 3 different parts of the nephron, namely, the proximal tubule, the descending limb of the loop of Henle, the connecting tubule and the collecting duct (Fig.). Under normal circumstances, approximately 180 L of plasma fluid are filtered by the adult human kidney, but only 0.5-2 L of urine are produced every day. In most mammals, arginine vasopressin (AVP) is critical for the retention of water by increasing water absorption in the principal cells of the collecting ducts

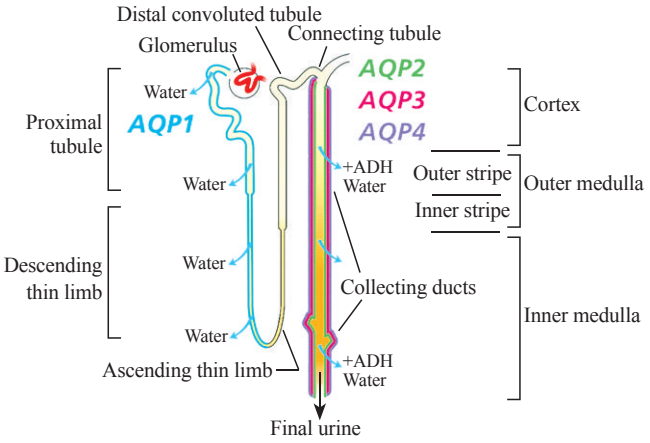

Fig. The location of the different aquaporins in the nephron and the collecting duct system in the adult mammalian kidney. Aquaporin (AQP)1 (blue) is present in the proximal tubule and the descending thin limb. AQP2 (green) is abundant in the apical and subapical regions of collecting duct principal cells, whereas AQP3 (red) and AQP4 (purple) are both present in the basolateral plasma membrane of the collecting duct principal cells. ADH: antidiuretic hormone. (This figure was reproduced from Nielsen S, et al[15] with permission.)

in the distal part of the nephron.

AQP1 is predominantly located in the apical and basolateral plasma membranes of the proximal tubule and the descending thin limb of the loop of Henle, where most of the water in the glomerular filtrate is reabsorbed.[16-19] Mice that have had the *AQP1* gene deleted have reduced abilities to concentrate urine to the maximum.[20] AQP2 is present in the apical plasma membranes and in intracellular storage vesicles in the connecting tubules, and in the principal cells of the collecting ducts. *AQP2*-total-knockout mice fail to thrive and die postnatally, because they lose excessive amounts of extracellular fluid, indicating that the concentration of urine depends chiefly on the presence of AQP2.[21] AVP regulates the activity of AQP2 via two independent mechanisms: (1) short-term regulation of AQP2 trafficking to and from the apical plasma membrane, and (2) long-term regulation of the total abundance of the AQP2 protein in the collecting duct principal cells.[22-24] Driven by an osmotic gradient, water traverses the cell membrane through AQP2 and leaves the cell on the basolateral side via AQP3 and AQP4 water channels.[25,26] AQP3 is regulated by long-term AVP stimulation,[25,27,28] and it is very sensitive to the extracellular pH.[29,30] In addition to transporting water, AQP3 also transports glycerol and urea.[25,31] AQP4 is characterized by its high water permeability and its mercurial insensitivity.[26] While AQP3 null mice have polyuria accompanied by severe defects in their urinary concentrating ability,[32] a milder form of the urinary concentrating defect is seen in transgenic mice that are deficient in AQP4.[33] Furthermore, *AQP3*/*AQP4* double-knockout mice have marked polyuria and lower urine osmolality values than *AQP3* single-knockout mice, indicating that AQP3 and AQP4 might play important roles in the ability of the kidney to concentrate urine.[32]

The identification of AQPs and their distributions within the tissues of the adult kidney suggest the involvement of renal AQPs in the urinary concentration mechanism. Although some understanding of the roles of AQPs in human development might be obtained from studies of mice with deletions of different *AQP* genes, extrapolating this information from mice to humans is complicated by the fact that much of the normal organ development occurs postnatally in rodents, while it occurs prenatally in humans.[34] The literature describing patterns of AQP expression in developing kidneys is limited and most of it describes studies of sheep, rats, and mice.[13,35,36] Indeed, the information in this review that depicts AQP expression in the mouse kidney comes from a single article only.[13] The expression of AQPs and their relationships with renal development, particularly during the early stages of life in animals and human beings, is important for understanding the mechanisms underlying urine formation and the ability of the developing kidney to concentrate urine. This review describes studies that have explored the spatial and temporal expressions of AQP1, AQP2, AQP3, and AQP4 in both fetal and postnatal kidneys in rodents, sheep, and humans.

Development and function of fetal kidneys in different animal species

Urine production rates are much higher in human and ovine fetuses (240 mL/kg per day) than in adult human beings and sheep (30 mL/kg per day), and the urine is very hypotonic. The relatively large volume of dilute urine is essential for the maintenance of amniotic fluids in primates and for the maintenance of amniotic and allantoic fluids in many species.[37]

Kidneys in mammalian fetuses develop in three stages: pronephros, mesonephros, and metanephros. Compared with mice and rats, the mesonephros appears much earlier and for a longer period during gestation in sheep and human beings. Nephrogenesis is completed before birth in human beings and sheep, but not in mice and rats, through the process of metanephros, which is the permanent kidney in mammals.[34] Indeed, kidney development is at an antenatal stage when mice and rats are born, which have gestational periods of 20 days and 21 days, respectively,[34] whereas kidney development is completed during the third trimester of gestation in human beings and sheep, which have gestational periods of 40 weeks[6] and 145-150 days,[38] respectively.

Expression of aquaporins in the fetal mouse kidney

Aquaporin 1 expression in the fetal mouse kidney

Parreira et al[13] investigated the expression of AQPs during tubular maturation in the kidneys of inbred (C57BL/6J) and outbred (CD-1) mice. The effect of genetic variability on the resultant phenotype could be minimized in the inbred mouse strain, whereas the outbred mouse strain maintained a high degree of genetic variability in relation to the expression of AQPs, which reflects the genetic variations seen in wild mouse populations. Parreira et al[13] found that *AQP1* mRNA was detectable on embryonic day (E) 13.5 in the CD-1 mouse kidney, and that it increased continuously until it reached the levels that are expressed in adult mice. They also found that *AQP1* mRNA expression was earlier in the CD-1 mouse kidney than in the C57BL/6J mouse kidney, in which it was detected on E14.5. The expression and maturation of AQP1 protein levels during kidney development were similar in both strains.[13] Immunoblotting showed that the non-glycosylated 28-kDa AQP1 protein, which is the core isoform, was detected on E16.5, and that it gradually increased during nephrogenesis.[13] Furthermore, the glycosylated 35-50-kDa isoform was not detected within the fetal mouse kidney, but it was detected after birth.[13] During nephrogenesis, AQP1 was located in the apical membranes of the developing proximal tubules and in some descending thin limbs of the loops of Henle during the embryonic stage, and a substantial increase in the numbers of AQP1-positive tubules occurred in the cortex from the embryonic to the postnatal periods.[13]

Aquaporin 2 expression in the fetal mouse kidney

A study of mouse kidneys demonstrated that *AQP2* mRNA was weakly expressed on E15.5 during the early embryonic stage, then it increased sharply to levels expressed on E17.5 in adult mice, with overexpression occurring during postnatal development, from postnatal day (P)1 to P28; and this was followed by a decline to the levels expressed in adult mice.[13] Unlike AQP1 protein, AQP2 protein exhibited both the glycosylated and non-glycosylated bands at the same developmental stages in fetal mouse kidneys.[13]

The distribution of AQP2 was restricted to the apical membrane region of the collecting duct principal cells in developing and mature C57BL/6J mouse kidneys. AQP2 expression increased markedly in the region from the sinus to the outer strip of the medulla from the embryonic to postnatal stages, but it was downregulated in the outer medulla of adult kidneys.[13]

Aquaporin 3 and 4 in the fetal mouse kidney

A study of fetal kidneys from mice showed that the expression of *AQP3* and *AQP4* mRNA was similar to that of *AQP2* at the different stages of kidney development, which has been described previously in this paper.[13] AQP3 and AQP4 were expressed earlier and reached adult levels more rapidly in outbred (CD-1) kidneys compared with inbred (C57BL/6J) kidneys, which concurred with the differences observed in the temporal expression of AQP1 between the 2 strains.[13] Like AQP2, AQP3 exhibited both glycosylated and non-glycosylated bands at the same stages of development, with the increased expression of glycosylated isoform after birth, which was earlier and more abundant than AQP1 expression.[13]

Aquaporin 1 expression in the mouse renal vasculature

In a study of the segmental distribution of AQP1 during CD-1 mouse nephrogenesis, AQP1 was strongly expressed at the luminal surfaces of the medullary blood vessels during the early embryonic stage.[13] There are no reports on the expression patterns of AQP2, AQP3, and AQP4 in animal fetal renal vasculature.

Expression of aquaporins in the fetal rat kidney

Aquaporin 1 expression in the fetal rat kidney

In 1993, Smith et al[39] reported the immunohistochemical detection of AQP1 in the proximal tubules and in the descending thin limbs of gestational day 18 rat kidneys. They reported that while AQP1 expression was intense at the same sites 2 days after birth, *AQP1* mRNA expression was not detected during the embryonic period.[40] Subsequently, Yamamoto et al[35] reported that *AQP1* mRNA was weakly detected in gestational day 18 rat kidneys using the ribonuclease protection assay. They also reported that *AQP1* mRNA was significantly expressed in the kidney 1 week after birth, that it had reached to levels expressed in the adult rat.[35]

Aquaporin 2 expression in the fetal rat kidney

Both *AQP2* mRNA and its protein are expressed in the epithelial cells of the ureteric buds and collecting ducts of fetal and postnatal rats, and a possible age-dependent basolateral localization of AQP2 has been proposed.[35,41] Immunohistochemistry was used to detect AQP2 in the apical membranes of the large ureteric buds of fetal rat kidneys on E20 and E21. However, only scant and moderate apical membrane staining for AQP2 was observed in the ureteric buds of the kidneys taken from E18 and E19 rats, respectively. AQP2 was not expressed in the branching ureteric buds of E15 rat kidneys.[41] However, the expression of *AQP2* mRNA was detectable as early as E16 in fetal rat kidneys. It was apparent on E18 or on approximately

E17 of rat metanephric kidney development, and increased gradually to reach a plateau 4 weeks after birth.[35,41,42]

Aquaporin 3 and 4 in the fetal rat kidney

AQP3 protein was detected on E18 of fetal development in the ureteric buds of the rat kidney.[41] Another study[35] found that *AQP3* mRNA and *AQP4* mRNA were almost undetectable in the fetal rat kidney, but they were present after birth and maintained a stable level throughout life.

Aquaporin 1 expression in the rat renal vasculature

The expression of AQP1 in the rat renal vasculature during kidney development was first reported by Kim et al[43] in 1999. They demonstrated that on E16 and E17, AQP1 was located in the endothelium of a few scattered capillary plexuses at the border between the nephrogenic zone and the renal medulla; and that AQP1 was expressed in the endothelium of the small blood vessels extending from the arcuate arteries into the renal cortex and medulla. Many of the AQP1-positive vessels descended directly from the arcuate arteries into the deep part of the medulla and formed capillary plexuses surrounding the medullary collecting ducts. However, there was no AQP1 immunoreactivity in the venous system, including the arcuate veins.[43] On E18 and E20, AQP1 immunoreactivity was observed in the endothelium of the arcuate arteries, interlobular arteries, and the afferent arterioles in the renal cortex. AQP1 expression in the blood vessels reduced in intensity on E18 and E20 compared with that observed on E16 and E17. AQP1 immunoreactivity was not observed in the efferent arterioles of the cortical glomeruli.[43] While the expression of AQP1 in the arcuate arteries, interlobular arteries, and afferent arterioles gradually declined after birth and disappeared at two weeks of age, the expression of AQP1 in the descending vasa recta, which appeared on E18, persisted and increased after birth.[43]

Expression of aquaporins in the fetal sheep kidney

Aquaporin 1 expression in the fetal sheep kidney

In fetal sheep, Butkus et al[38] found that *AQP1* mRNA was expressed at 40 days of gestation in the proximal tubules of the metanephros using *in situ* hybridization, but there was no *AQP1* mRNA expression at any stage of mesonephros development. They also analyzed AQP1 protein levels using immunoblotting techniques and found both the non-glycosylated and glycosylated forms present in fetal sheep kidneys at 94 days of gestation. Wintour et al[36] found *AQP1* mRNA expression in fetal sheep kidneys at 60 days of gestation using northern blotting techniques, and that the abundance of *AQP1* mRNA increased approximately 7-fold between 100 days and 140 days of gestation. The expression of *AQP1* mRNA at 140 days of gestation was two-thirds of that in the adult and it reached adult levels 6 weeks after birth. Using immunohistochemical staining techniques, Wintour et al[36] found weak AQP1 staining in some proximal tubules and more intense staining in some proximal straight tubules at 74 days of gestation, which suggests that *AQP1* mRNA has been translated into protein at this stage of sheep fetal development.

Aquaporin 2 expression in the fetal sheep kidney

Using polymerase chain reaction techniques, Butkus et al[44] demonstrated renal *AQP2* mRNA expression at 40 days of gestation in fetal sheep. However, northern blot analysis showed that *AQP2* mRNA was detectable at 75 days of gestation, and that the *AQP2* mRNA level increased by about 2.4-fold between 100 and 140 days of gestation.[44] At 140 days of gestation, the expression of *AQP2* mRNA was 41% of the adult level and it remained at that level until 1-2 weeks after birth; the level of *AQP2* mRNA expression subsequently increased by another 2.5-fold until the adult stage. Immunohistochemical analysis at 64 days of gestation showed that AQP2 was detectable at the apical membrane of the collecting duct in the fetal sheep kidney.[44]

Expression of aquaporins in the fetal human kidney

Aquaporin 1 in the human fetal and infant kidneys

Studies investigating the expression of AQPs in human fetal kidneys are very limited. In 1996, Devuyst et al[45] studied AQP1 and AQP2 expression in human fetal kidneys during the second trimester, in newborn babies, and in infants. They reported that the non-glycosylated isoform of AQP1 protein can be detected as early as 12 weeks of gestation, and at this stage AQP1 was located in the newly forming proximal tubule structures in the inner cortex. In the period between 15 and 20 weeks of gestation, AQP1 expression was predominantly located in the apical membrane region of the epithelial cells of the more differentiated proximal tubule structures in the cortex, and this extended towards the medulla as well as being apparent in the newly forming descending limbs of the loops of Henle.[45] By 24 weeks of gestation, AQP1 protein expression was clearly restricted to the apical membranes of the proximal tubules in the cortex and the apical membranes of the descending thin limbs of the loops of Henle in the medulla. The glycosylated

isoform of AQP1 protein was only detectable after birth.[45]

Agre et al[46] published a description of the temporal and spatial distribution of *AQP1* mRNA in fetal human kidneys in 1994. Using immunohistochemistry, AQP1 was detected in the newly developing proximal tubules of the fetal kidney at 14 weeks of gestation. At 17 weeks of gestation, AQP1 was detected in the apical membranes of the newly formed proximal tubules and in the descending thin limbs of the loops of Henle in the outer cortex. By 24 weeks of gestation, AQP1 was also detected in the thin limbs of the loops of Henle in the medulla, which resembled the distribution of the protein in postnatal and adult kidneys.[46]

Aquaporin 2 in the fetal human kidneys

The human fetal kidney contains a low level of AQP2 during the second half of gestation,[45] and both full-term and premature neonates with normal urinary tracts produce hypoosmotic urine during the first month after birth.[47] The urine excreted by both full-term and premature infants contains low levels of AQP2 protein, and the level of AQP2 excretion correlates with urine osmolality in premature infants, but not full-term infants.[47] *AQP2* mRNA expression was detected exclusively in the ureteric bud-derived structures in fetal human kidneys at 12 weeks of gestation,[45] and AQP2 was located in the apical membrane region of these epithelial cells throughout gestation. During the early stages of gestation, AQP2 was observed in the branching ureteric buds, extending from the medulla to the cortex;[45] then by 18 weeks of gestation, AQP2 was restricted to the developing medullary collecting ducts. A major band at 29 kDa, which represented the non-glycosylated form of AQP2 protein, was observed in the fetal human kidney in addition to more diffuse bands at 35-50 kDa, which represented the glycosylated form of AQP2 protein. The 29 kDa protein reached 34% of the adult level in the fetal kidney at a gestational age of 20 weeks.[45]

The expression of AQPs in the developing kidneys of different mammalian species is summarized in Table.

Conclusions

The discovery of AQPs by Agre et al[1,2] represented a milestone in the study of water transport across cell membranes. Most of our knowledge about AQPs is derived from animal studies, because studies on the distribution of AQPs in human fetuses are very limited.

AQP1 and AQP2 can be detected at earlier stages of gestation in human beings and sheep compared with mice and rats, because of the earlier onset of metanephros development in these animals compared with rodents. Studies on *AQP1*-, *AQP2*-, *AQP3*-, and *AQP4*-knockout mice showed that these AQPs, and particularly AQP2, play important roles in the ability of the kidney to concentrate urine. AQP1 expression is detected earlier in the proximal tubules than the expression of AQP2, AQP3, and AQP4 in the collecting ducts, because the glomeruli and the proximal and distal tubules form earlier than the collecting ducts

Table. Summary of the expression patterns of AQP1-4 in the fetal kidneys of human beings, sheep, rat, and mice and other renal AQPs function in adult mammalian

AQPs	Location	Function	Human beings	Sheep	Rats	Mice
AQP1	PT and DTL, both APM and BLM	Water transport	AQP1 protein was detectable at 12 weeks and located in the PT in the inner cortex.[45,46]	*AQP1* mRNA was detected in the PT of the metanephros on E40;[38] AQP1 protein was present in the PT on E74.[36]	*AQP1* mRNA and protein were detectable on E18;[35] AQP1 was located in the PT and DTL.[39]	*AQP1* mRNA was detectable on E13.5; AQP1 protein was detectable on E16.5, and located in the APM of the PT and DTL in the cortex on E17.5.[13]
AQP2	CD-APM	Water transport, long- and short term AVP-sensitivity	AQP2 protein was detectable at 12 weeks of gestation and located in the APM of the branching ureteric buds from the cortex to the medulla. By 18 weeks of GA, AQP2 was present in the CD in the medulla.[45]	*AQP2* mRNA was detectable on E40 and the AQP2 protein was detectable in the APM of the CD on E64.[44]	*AQP2* mRNA was detectable on E16 and the protein was detectable on E18; AQP2 was located in the large ureteric buds and CD.[35,41]	*AQP2* mRNA was detectable on E15.5. AQP2 protein was detectable and located in the APM of the CD in the medulla on E17.5.[13]
AQP3	CD-BLM	Water transport, glycerol and urea transport, long-term AVP-sensitivity			*AQP3* mRNA was detectable on E18.[41]	*AQP3* mRNA was present on E13.5.[13]
AQP4	CD-BLM	Water transport, mercury insensitive			*AQP4* mRNA was undetectable in the fetal rat kidney.[35]	*AQP4* mRNA was present on E13.5.[13]

AQP: aquaporins; PT: proximal tubule; DTL: descending thin limb; CD: collecting duct; APM: apical membrane; BLM: basolateral membrane; E: embryonic day; AVP: arginine vasopressin, number in brackets means reference; GA: gestational age.

and papillae during kidney development.[37] Studies on the expression patterns of AQPs in both animal and human fetal kidneys may help us to understand the pathophysiology of urine formation in developing kidneys and the mechanisms underlying the formation of hypotonic urine, the increased urinary flow rate, and the high glomerular filtration rates in fetuses, which are important for maintaining the volume of amniotic fluid. Further studies of AQPs, particularly during human kidney development, might provide insights into the ways in which water is handled by fetal kidneys and they may enable us to understand the mechanisms underlying congenital hydronephrosis and other abnormalities that occur in the human fetal kidney. This might, in turn, help us to understand the pathophysiology of the kidney and determine new directions for the clinical treatment of kidney diseases.

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