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# Aquaporins in the Kidney

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## INCREASING NUMBER OF AQUAPORINS

The discovery of AQP1 in 1992 by Agre and co-workers(Preston et al, 1991, 1992) and subsequent designation of "aquaporin" have opened a new field in membrane transport physiology (Agre P et al, 1993). The original definition of aquaporin was "the MIP26 homologue proteins which rapidly and selectively permeate water". MIP26 is the major intrinsic protein of mammalian lens cloned in 1984 (Gorin et al, 1984), and many homologous proteins since discovered make a large and growing family of membrane integral proteins, the MIP family (Park et al, 1996). Thus, a more simple definition of aquaporin is "MIP family members whose water channel function is confirmed". The basic structure of MIP proteins is summarized in Fig. 1. Each molecule consists of 6 transmembrane domains, with the amino- and carboxy-terminal ends located in the cell interior. The first half and the last half of the sequences are homologous (tandem repeats), indicating the occurrence of gene duplication during the evolution. Each half has the conserved motif of asparagine-proline- alanine (NPA box). Most MIP proteins are small proteins which consist of 260~300 amino acids. As MIP family members can be easily cloned by PCR- based cloning strategy using the conserved NPA motif, their numbers have drastically increased. Most cloned MIP proteins have not been examined for their water channel function, and thus they remain categorized as MIP proteins. Some of them which have been proven to be water channel, thereby have acquired a new name, "aquaporin". Some of MIP proteins have been shown not to be permeable to water, but instead permeable to small nonionic solutes such as glycerol and urea. These proteins are not called aquaporin. Accordingly, there are fewer aquaporins than MIP proteins. Nonetheless, most MIP proteins may still be proven to be aquaporins if they are adequately examined for their water channel function. For example, MIP26 was originally thought to be a non-selective ion channel, but recent careful expression study in Xenopus oocytes has shown its small water channel function. Thus MIP26 is now called AQP0. Many research in this field and genome projects in many organisms have identified plenty of MIP proteins (Park et al, 1996). *E. coli* has two MIP proteins with a distinct functional difference; one is an aquaporin (AqpZ) (Calamita et al, 1995) and the other is a glycerol facilitator (GlpF). Like bacteria, other organisms have many MIP proteins. For example, *C. elegans* has 8 and yeast has at least 4 members (Park et al, 1996, Ishibashi et al, in press). There are many MIP proteins in the plant kingdom (for example, Arabidopsis has more than 23 members). So far 10 aquaporins have been reported for mammals (Fig. 2). Thus, the number of identified MIP members has increased drastically, and the prevalence of MIP/AQP proteins in almost all organisms clearly indicates their indispensable roles in the body, possibly as water and small neutral solute transporters. The phylogenetic analysis of mammalian aquaporins (Fig. 2)

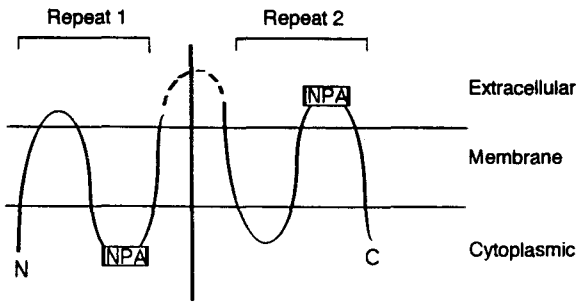


**Fig. 1.** Proposed membrane topology of the MIP/AQP proteins and their basic characteristics.

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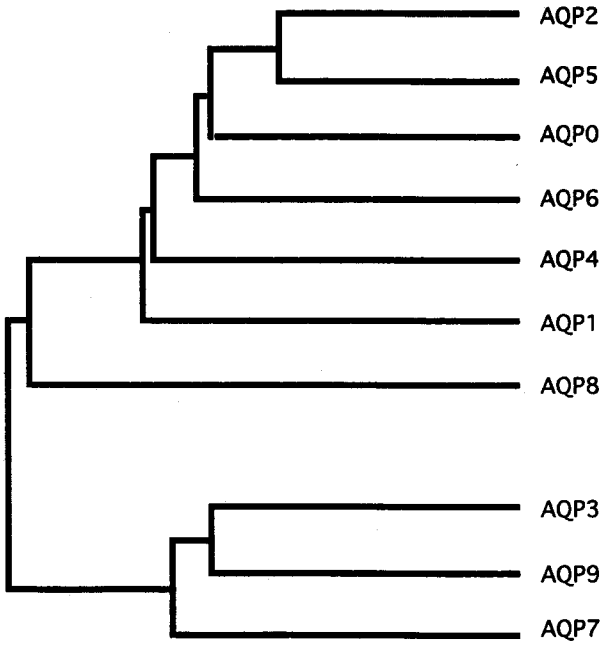


**Fig. 2.** Phylogenetic tree of mammalian aquaporins cloned to date. The Clustal method by a computer was used.

shows that they can be separated into two subgroups. This sequence homology-based separation can be applicable to the entire MIP/AQP family and detailed discussion for this is available in elsewhere (Ishibash et al, in press, Sasaki et al, 1998). The upper group consists of 7 aquaporins; AQP0, 1, 2, 4, 5, 6, 8. and the lower group consists of 3; AQP3, 7, 9. Functional studies have indicated that the upper members permeate water selectively, while the lower members permeate small solutes such as glycerol and urea. This functional difference may come from their prototypes in *E. coli.* One MIP protein in *E. coli.* is AqpZ and function as an aquaporin with no permeability to other solutes (Calamita et al, 1995). The other is a glycerol facilitator (GlpF) which permeates glycerol and excludes water. Our recent study comparing functional characteristics of AQP2 and AQP3 has indicated that pore structure of the two groups is the same and water and small solutes pass through the same pore (Kuwahara et al, 1997). Identification of the mechanism of selectivity of the pore of MIP/AQP proteins would be a big challenge in this field of research. Comparison of these two subgroups may provide some important insights. Recent advance in an electron crystallography will be of great help for this purpose (Walz et al, 1997).

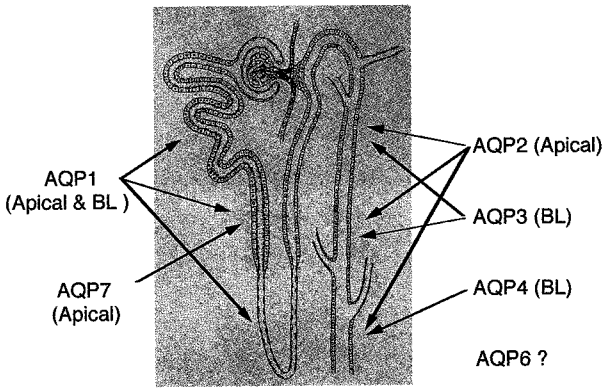


**Fig. 3.** Localization of mammalian aquaporins in the kidney. Apical and basolateral localization are indicated.

## LOCALIZATION AND PHYSIOLOGICAL ROLES OF MAMMALIAN AQUAPORINS IN THE KIDNEY AND BODY

By 1995, mammalian aquaporins, AQP0-AQP6, had been successively identified and reported. Very recently, three new aquaporins (AQP7, AQP8, and AQP9) have been cloned (Ishibash et al, 1997 (1, 2), 1998, Koyama et al, 1997). The presence of at least 10 aquaporins in the body suggests that aquaporins play essential roles in mammals as well. In the kidney, the presence of 6 members; AQP1, 2, 3, 4, 6, and 7, have been reported (Fig. 3). With increases in aquaporin members, it has been apparent that some cells may have several different AQP proteins, for example, kidney collecting duct principal cells express AQP2, AQP3, and AQP4. Moreover, the expression of several aquaporins in a single organ is a more common feature, as shown in the eye where AQP0, 1, 3, 4, 5, and possibly 7 and 9 are expressed. This redundancy may help to facilitate compensation among aquaporins when one aquaporin is lost or non-functioning for some reason.

### *AQP0*

Major intrinsic protein of lens of 26-kDa (MIP or MIP26) was isolated as a protein which constitutes more than 60% of the total membrane protein of lens fiber cells. Recent studies have disclosed that MIP functions as a water channel when expressed in *Xenopus* oocytes, although the increase in water permeability is less than those of other aquaporins (Mulders et al, 1995). No ionic permeability was observed in the oocytes system, which was different from previous studies in planar lipid

bilayers. Localization of MIP is limited to the eye and does not exists in the kidney. As the lens is avascular, lens cells need to gain nutrients from the interstitial fluids. These findings suggest that MIP may be crucial for water transport and maintenance of transparency of the lens. Furthermore, MIP may be related not only to increased water retention in the lens, but also to the development of cataract. It has been reported that mutations in the MIP gene cause a hereditary cataract in mice (Shiels et al, 1996).

*AQP1*

AQP1 was discovered from red blood cells as a discrete integral membrane protein of 28-kDa. The cDNA cloning (Preston et al, 1991) and the deduced amino acid sequence suggested its homology with MIP (AQP0). Expression of AQP1 cRNA in Xenopus oocytes demonstrated a mercury-sensitive water channel function (Preston et al, 1992). AQP1 mRNA expression has been found in the kidney, eye, salivary gland, and heart by Northern blot analysis (Moon et al, 1993). In the eye, AQP1 has been localized in corneal endothelial cells, lining the internal surface of the cornea. AQP1 has also been found in nonfenestrated capillary endothelium of systemic organs such as the salivary glands, lacrimal glands, pancreas, and heart. The vascular endothelial AQP1 may contribute to transition of vascular fluid to interstitium and glandular epithelium. AQP1 has been shown to be abundant in the kidney at both the mRNA and protein levels (Zhang et al, 1993). Immunohistochemistry demonstrated its selective localization in proximal convoluted and straight tubules and descending thin limbs of Henle's loop in rat kidney (Nielsen et al, 1993). The presence of AQP1 in the kidney could be important as AQP1 is localized in highly water-permeable nephron segments (Fig. 3). In the proximal tubular epithelia, immunolabeling of AQP1 was shown to be intense in the microvilli of the apical brush border and less intense in the basolateral membrane (Nielsen et al, 1993). AQP1 was also localized to both the apical and basolateral membranes of descending thin limbs with nearly equal abundance. Negligible immunostaining of AQP1 has been observed in the cytoplasmic area of these AQP1-expressing cells. AQP1 was also observed in the endothelia of the vasa recta. AQP1 may work as a constitutive water channel in the kidney, because no induction of mRNA or change in intracellular localization have been observed.

*AQP2*

AQP2 cDNA was isolated as the second mammalian aquaporin from rat kidney by us and was found to be exclusively expressed in the kidney (Fushimi et al, 1993). Immunohistochemistry has localized AQP2 only in collecting duct principal cells and medullary collecting duct cells, where vasopressin-regulated water reabsorption takes place. Intense immunolabeling was observed in the subapical region, while the staining was minimal in the basolateral region. By immunoelectron microscopy, most AQP2 molecules were demonstrated

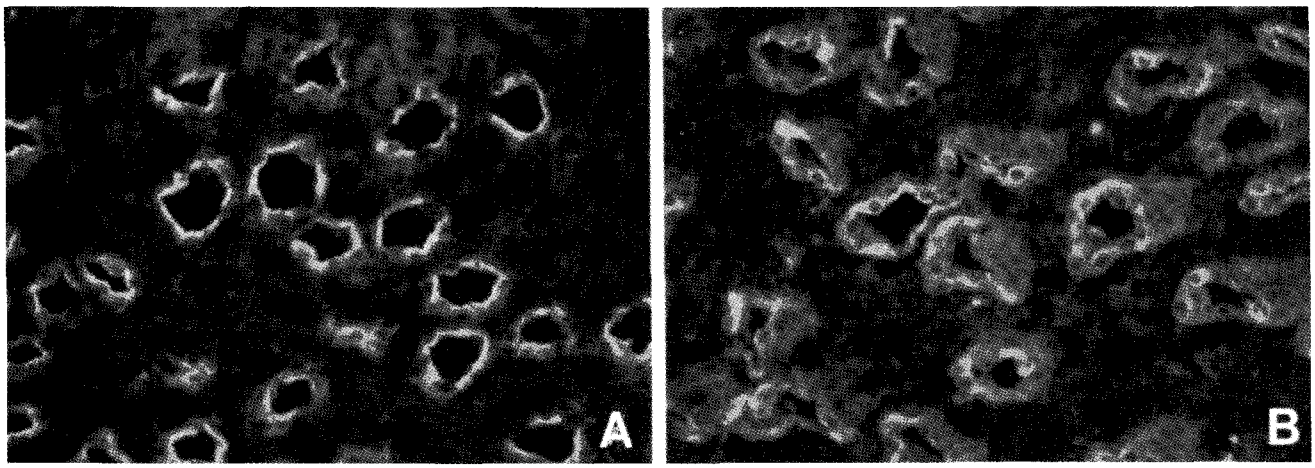


**Fig. 4.** Redistribution of apical AQP2 to intracellular region. Innermedullary collecting ducts from 2-days dehydrated rats showed a predominant staining of AQP2 at the apical membrane (A). After 30 min of forced water drinking (B), AQP2 distributed diffusely into the cytoplasm.

on the membranes of small cytoplasmic vesicles which distributed in the subapical region, and a small number were present in the apical membrane in a normally hydrated condition (Yamamoto et al, 1995). Translocation of AQP2 from the cytoplasmic vesicles to the apical membrane in response to vasopressin was observed (Yamamoto et al, 1995). Furthermore, retrieval of apical AQP2 into the cytoplasm was observed after termination of vasopressin stimulation by forced water drinking (Fig. 4) (Saito et al, 1997). These observation verified AQP2 as a vasopressin- regulated water channel, and also confirmed the "shuttle hypothesis" for water channel trafficking by vasopressin. Recent study showed that this trafficking is triggered by its own phosphorylation at serine 256 by protein kinase A (PKA) (Fushimi et al, 1997). Besides the translocation of AQP2 in response to vasopressin, increases in the expression of AQP2 mRNA and protein in the kidney have been shown by 48-hr water restriction, and this effect was mediated by vasopressin V2R receptor (Hayashi M et al, 1994; Yamamoto et al, 1995). These results suggest that these animals also respond to vasopressin by increasing the total amount of AQP2 protein, resulting in an enhancement of the water permeability in the reabsorption of collecting duct. This mechanism underlies the long-term adaptation of urinary concentrating ability observed in water- deprived animals and humans. A part of this vasopressin-stimulated AQP2 mRNA expression and AQP2 protein synthesis is mediated by stimulated transcription of the AQP2 gene. The presence of cAMP-responsive element has been shown in the 5' flanking region of the gene (Uchida et al, 1994) and cAMP-stimulated transcription has been demonstrated in a promoter assay (Matsumura et al, 1997). Phosphorylation of AQP2 by PKA increased its water permeability by 50% in the oocytes expression system. This effect was specific as mutations introduced to the phosphorylation site (serine 256) abolished the PKA effect (Kuwahara et al, 1995). This indicates that water permeating pathway (pore) of AQP2 is directly regulated by phosphorylation. Similar phenomenon are observed in plant aquaporins.

*AQP3*

AQP3 was isolated from rat kidney and shown to be a unique water channel which permeates nonionic small solutes such as urea and glycerol (Ishibashi et al, 1994). The expression of AQP3 mRNA was also demonstrated in gastrointestinal tracts (stomach, small and large intestines). Immunohistochemistry identified AQP3 localization in the basolateral membranes of the tracheal epithelia, the meningial cells of the brain, and the conjunctival epithelia of the eyes. In the kidney, AQP3 has been exclusively shown in the collecting ducts. Immunostaining was predominant in the segments in the cortex and outer medulla, but it was weak in the inner medulla. AQP3 would serve as a water exit route across the basolateral membrane. Immunoelectron microscopy demonstrated a predominant labeling of AQP3 on the basolateral membranes and a scarce labeling in cytoplasm, suggesting that this water channel was not regulated through trafficking between the intracellular vesicles and basolateral membranes (Yamamoto et al, 1995). Expression of AQP3 mRNA and the amount of protein were slightly upregulated by long-term water deprivation (Ishibashi et al, 1997), although the degree of upregulation was much less than that of AQP2.

*AQP4*

AQP4 was cloned from rat lung and brain cDNA libraries as a mercury-insensitive water channel (MIWC), a type distinct from other aquaporins. Predominant expression of AQP4 was found in the brain at both the mRNA and protein levels. Intense immunolabeling was demonstrated in meningial cells of pia mater, ependymal cells of the central ventricles, and glial cells. In the lung, AQP4 was localized in the basolateral membrane of tracheal and bronchial epithelia, but not in that of alveolar epithelium (Frigeri et al, 1995). In the trachea, AQP4 colocalized with AQP3, indicating a shared function in hydration of the airway to maintain mucociliary clearance in the postnatal period and in water transport in the prenatal period. The prominent localization of AQP4 on the basolateral membrane of the airway epithelia also predicts the existence of other water channels in the apical membrane. In the eye, AQP4 was immunostained on the basolateral membranes of the nonpigmented epithelial cells of the ciliary body and in the contiguous pigmented cells of the iris (Frigeri et al, 1995). AQP4 was localized in the basolateral membrane of collecting duct principal cells in the kidney, and is regarded as a constitutively expressed water channel, the same type as AQP3. Intense labeling of AQP4 was predominant in the most distal part of the inner medullary collecting ducts. No apparent change in AQP4 expression was observed in kidneys from water-restricted rats. Recently, gener-

ation of AQP4-knockout mice has been reported. Interestingly, a small decrease in maximally urine concentrating ability was observed when water deprivation was forced, indicating the contribution of AQP4 in this process (Ma et al, 1997).

*AQP5*

AQP5 was cloned from a salivary gland cDNA library. Its expression is abundant in the salivary gland, eye, and lung, suggesting a role in water secretion in these organs. As AQP5 immunostaining was found in the apical membrane of mucus gland acinal cells of the salivary gland and corneal epithelium of the eye, it is likely to play a role in the secretion of saliva and maintenance of corneal transparency. AQP5 was present on alveolar type I epithelial cells in the lung. AQP5 is absent in the kidney at both the mRNA and protein levels.

*AQP6*

Rat and human AQP6 (initially designated WCH-3 or hKID) were isolated from rat and human kidney cDNA as a new aquaporin demonstrating highest homology to AQP2 and MIP. The reported water permeability of AQP6 was much smaller than that all of other aquaporins except MIP (AQP0). Among several organs examined, the kidney was the only organ in which AQP6 mRNA was intensely expressed, just as in the case of AQP2 mRNA. Surprisingly, cellular localization of AQP6 in the kidney has not been reported.

*AQP7*

AQP7 was recently isolated from rat testis. This new water channel is unique since it facilitates the transport of glycerol and urea just as AQP3 does. Northern blot analysis showed AQP7 mRNA expression intensely in the testis, kidney, and heart, and less intensely in skeletal muscle and brain (Ishibashi et al, 1997). In situ hybridization and Immunohistochemistry have localized AQP7 mRNA and protein in the cells of late-stage spermatogenesis and maturing spermatids in the testis. The presence of AQP7 at these sites may account for the unexpectedly high water permeability, which is mercury-resistant, of sperms (Ishibashi et al, 1997). The physiological role of AQP7 in sperms remains to be clarified. The presence of AQP7 in human adipose tissue has been reported, suggesting its role in glycerol/lipid metabolism in this tissue (Kuriyama et al, 1997). In the kidney, immunohistochemical study by us indicates its localization at brush border of the proximal straight tubules. Proximal convoluted tubules were negative for the staining.

*AQP8*

AQP8 was identified from rat testis (Ishibashi K et al, 1997(2)), and pancreas and liver (Koyama et al, 1997) as a mercury-sensitive water channel. The deduced amino acid sequence revealed the highest homology among the MIP family members to a plant water channel, gTIP, which localizes in the intracellular tonoplast membranes. Expression and localization of this water channel were confined in spermatids and sperms of the testis, hepatocytes, pancreatic acinal cells, and absorptive epithelia of colon, thus suggesting roles in reproduction, the excretion of bile and pancreatic fluids, and the absorption of water in the colon. No mRNA expression and immunostaining of AQP8 has been shown in the kidney. Although rat AQP8 permeates only water, unique channel selectivity of mouse AQP8; permeates water and urea, but excludes glycerol, has been suggested.

*AQP9*

AQP9 is the latest aquaporin to have been cloned (Ishibahi et al, 1998). It was cloned from liver cells and has highest homology with AQP3 (48% amino acid identity). AQP9 permeates water and urea, but surprisingly does not permeates glycerol. This channel property clearly indicates that the pore of MIP/AQP proteins can discriminates among small nonionic solutes, for example, glycerol vs. urea. Northern blot analysis of human AQP9 mRNA showed its predominant expression in peripheral leukocytes and less expression in liver, lung, and spleen. Because the liver is the main organ of urea production, some transport mechanism for urea exit from the hepatocytes is necessary. AQP9 may contribute to this process. Inspection of Fig. 3 clearly indicates that AQP1 works in water reabsorption in the proximal convoluted and straight tubules and descending loop of Henle. These segments are well known to have a constitutively high water permeability. AQP7 also contributes to water transport in only straight portion (S3 segment) of the proximal tubules. It is noteworthy that no aquaporins are present in the thin and thick ascending limb of Henle's loop where a very low water permeability was reported. In the

collecting ducts, AQP2 is present at the apical region throughout from the cortex to papilla. At the basolateral membrane, AQP3 and AQP4 colocalize in the same cells with some segmental preference; AQP3 is rich in cortical and outer medullary region and AQP4 is abundant in innermedullary region. These three aquaporins, collaborating each other, mediate water reabsorption in this final nephron segment, AQP2 works as a key player in the limiting step of this process, water entry across the apical membrane. Functional significance of these kidney aquaporins are now becoming clear from clinical observations (nephrogenic diabetes insipidus patients caused by AQP2 gene mutations) and mouse knockout models for AQP1 and AQP4 (Ma et al, 1997, 1998). This new development of this research area will be discussed elsewhere (Sasaki et al, 1998). Nevertheless, more studies are clearly needed to identify each aquaporin's role in the body.

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