Aquaporin-2 (AQP-2) is a water channel in the kidney collecting duct. AQP-2 is selectively permeable to water molecule and is translocated between the apical membrane and subapical endosomes in response to vasopressin. To investigate the localization and structure of the aqueous pathway of the AQP-2 water channel, a series of site-directed mutants was constructed and functionally analyzed. Insertion of N-glycosylation reporter sequence into each hydrophilic loop (HL) indicated that AQP-2 has a six-membrane spanning topology and that insertional mutations in HL-2 or HL-5 do not alter water channel function.

Mercury-sensitive site of AQP-2 is located near the second asparagine-proline-alanine (NPA) domain at cysteine 181, but not near the first NPA domain. Replacement of HL-3 or HL-4 with the corresponding part of Escherichia coli glycerol facilitator abolished water channel function without changing plasma membrane expression of the channel protein. Introduction of cysteine residues in His-122, Asn-123, Gly-154, Asp-155, or Asn-156 induced partial mercury sensitivity, and point mutations in asparagine 123 significantly altered water permeability. Our results implicate that the structure of AQP-2 is different from models previously proposed for AQP-1 and that HL-3 and HL-4 are closely located to the aqueous pathway.

Aquaporin-2 (AQP-2), previously reported as WCH-CD or AQP-CD), is a water channel in the apical membrane of the kidney collecting duct (1). Water permeability of this nephron segment is regulated by vasopressin through the membrane shuttle mechanism (2–4), in a mechanism by which AQP-2 is translocated between the apical membrane and endosomes under vasopressin regulation (5–7). Complementary DNAs for rat and human AQP-2 have been isolated (8, 9), and the primary structure of AQP-2 has been identified. AQP-2 is a very hydrophobic membrane-integral protein of a molecular mass of 29 kDa. It is a member of the MIP protein family (10) and is homologous to aquaporin-1 (AQP-1, previously reported as CHIP28) (11–13). Functional expression of AQP-2 showed that it is highly permeable to water molecule but not to urea, glyceral, and ions and that its water permeability is mercury-sensitive and temperature-insensitive (8). Furthermore, it has been shown that mutations in AQP-2 gene are responsible for deficient vasopressin antidiuresis in some patients with nephrogenic diabetes insipidus (14, 15). Despite accumulated knowledge of AQP-2 physiology implicating functional importance of AQP-2 in urine concentration and homeostasis of body fluid, the molecular structural basis of AQP-2 is not well known. The localization and higher order structure of the aqueous pathway of AQP-2 have to be elucidated to account for its selective permeability to water molecule and explain the mutation-related channel malfunction. The molecular structure of AQP-1, the first identified water channel, has been studied and partially resolved. It was shown that AQP-1 exists in plasma membrane with tetramer formation (16, 17) but that each monomer is functionally independent, thus leading to the assumption that single aqueous pore spans each monomer (18, 19). Regarding the structure of the aqueous pore in functionally active AQP-1 monomer, three structural models have been proposed (20): the hourglass model (21), the α-helical model (22), and the β-barrel model (23). According to the hourglass model, the aqueous pathway is located between transmembrane segments with α-helical conformation. In the β-barrel model, the aqueous pore is formed with 16 antiparallel β-sheets analogous to a porin channel of bacteria species (24). The validity of these models has not been sufficiently examined. Moreover, there have been no investigations regarding the molecular structure of aquaporins other than AQP-1. In addition to being significant for understanding the general structure of channels, elucidation of the structure of aquaporins will provide insights for the development of an AQP-2 inhibitor, which is potentially of remarkable use as a water diuretic.

This study examined membrane topology, mercury-sensitive sites, and functional roles of the two of the NPA-containing domains and other hydrophilic loops of AQP-2. We found significant participation of hydrophilic loops other than NPA-containing domains in the formation of the aqueous pathway of AQP-2. Based on our observations, a new structural model for AQP-2 is proposed.

**Experimental Procedures**

Site-directed Mutagenesis and in Vitro RNA Synthesis—AQP-2 mutants were constructed using polymerase chain reaction-based site-directed mutagenesis. A fragment between SphI site at nucleotide 219 and StuI site at nucleotide 809 in pAQP-2/ev1 (8) was replaced by a polymerase chain reaction fragment coding for mutants. Potential glycosylation sites were produced by inserting an N-glycosylation reporter sequence (asparagine-threonine-serine, NTS) (25) into one of four hydrophilic loops of non-glycosylated mutant of AQP-2, N124D (Fig. 1). For hydrophilic loops (HL) 1, 2, 4, and 5, an NTS motif was inserted after serine 36 (producing 36NTS), alanine 65 (65NTS), glycine 154 (154NTS), and valine 194 (194NTS) of N124D, respectively. To directly compare the structure of AQP-2 and AQP-1, the insertion positions were chosen corresponding to the BamHI sequence insertion positions in the previous study (26). For determination of mercury sensitivity, some residues of mercury-resistant mutant of AQP-2, C181A, were substituted with cysteine. For recombination of HL-3 or HL-4, a cluster...
molecular biological procedures were used (27). RNApolymeraseand
*invitro* cRNA was synthesized using T3

\[ P_i = \frac{V_o \times d(V_o/dt)}{S \times V_o \times (osm_{in} - osm_{out})} \]  

E. coli
glycerol facilitator (GlpF), and ERRNDLGVSP in HL-4 of AQP-2 was replaced with DGNGVPRGP of GlpF, with RRRRDLGGSA of AQP-1, or with ERRGDNLGSP in HL-4 of AQP-2 was replaced with

\[ N_{\text{glycoside}}F \text{ digestion (Fig. 2).} \]

\[ N_{\text{glycosylation}} \text{ is not required for water channel function of AQP-2 (Fig. 3).} \]  

**RESULTS**

**AQP-2 Membrane Topology Determined from N-Glycosylation Site**—Immunoblot analysis of rat kidney membrane and oocyte expressing AQP-2 showed that AQP-2 consists of 49 kD and higher molecular mass components, which were removed by N-glycosidase F digestion (Fig. 2). N-Glycosylation was not observed when asparagine 124 (Asn-124) was replaced with aspartic acid, showing that AQP-2 is not glycosylated at Asn-124. Injection with N124D induced high osmotic water permeability that was comparable to that of wild type, suggesting that N-glycosylation is not required for water channel function of AQP-2 (Fig. 3). The sidedness of each hydrophilic loop was determined by the insertion of asparagine-threonine-serine (NTS) consensus motif and assessing the accessibility of N-glycosyltransferase. As shown in Fig. 2, AQP-2 mutants were glycosylated only when the NTS signal was inserted into the first or the fifth loop and not when NTS was inserted into the second or the fourth loop (Fig. 2, lanes 3–6). Molecular sizes of glycosylation in these mutants were the same as those in wild type of AQP-2. In both of these N-glycosylated mutants, the glycosylated 49 kDa protein was removed by digestion of N-glycosidase F (Fig. 2, lanes 7 and 8). These results indicated that the first, third, and fifth hydrophilic loops are localized extracellularly.

**Role of Hydrophilic Loops 2 and 5 in the Formation of AQP-2 Aqueous Pathway**—The effects of three amino acid insertions on the channel function were examined by looking at osmotic water permeability of oocytes expressing NTS-inserted mutants (Fig. 3). Insertions of a few amino acid residues into HL-2 and HL-5 had little effect on the function of AQP-2, in contrast to the fact that amino acid insertion into the corresponding position of AQP-1 completely abolished water channel function (26). Osmotic water permeability induced by NTS-inserted mutants was slightly lower than that induced by non-glycosylated mutant of AQP-2, N124D. Relative plasma membrane expressions assessed by radioimmunossay were 91 ± 3% (36NTS),

**Aqueous Pathway**—The effects of three amino acid insertions on the channel function were examined by looking at osmotic water permeability of oocytes expressing NTS-inserted mutants (Fig. 3). Insertions of a few amino acid residues into HL-2 and HL-5 had little effect on the function of AQP-2, in contrast to the fact that amino acid insertion into the corresponding position of AQP-1 completely abolished water channel function (26). Osmotic water permeability induced by NTS-inserted mutants was slightly lower than that induced by non-glycosylated mutant of AQP-2, N124D. Relative plasma membrane expressions assessed by radioimmunossay were 91 ± 3% (36NTS),
Roles of HL-3 and HL-4 in the Formation of AQP-2 Aqueous Pathway—Participation of HL-3 and HL-4 in the formation of the aqueous pathway was revealed by the replacement of these domains with the corresponding part of E. coli GlpF (Fig. 4). GlpF was chosen because its function has been examined in detail and because it is known to be permeable to glycerol but not to water (31). Recombinant HL-3 or HL-4 to GlpF did not induce osmotic water permeability (Fig. 4). In contrast, replacement of HL-4 with other water channels, AQP-1 and MIP, induced osmotic water permeability to a level comparable to that of the wild type. To exclude the possibility of the decrease in readily assembled protein and plasma membrane expression, localization of AQP-2 in total membrane fractions or in plasma membrane fractions was examined by immunoblots. Oocyte membrane was fractionated through a sucrose gradient by ultracentrifugation, and plasma membrane fraction was collected. Immunoblot of fractionated membranes from oocytes injected with GlpF recombinants cRNA indicated that the amounts of synthesized mutants and mutants expressed in plasma membrane were comparable to those of the wild type (Fig. 5). Independent analysis of the amount of the plasma membrane expression was performed by radiolmmunobassay. Binding of antibody against external domain of intact oocytes expressing mutants was assayed. Specificity and sensitivity of the antibody were confirmed by immunoblotting (data not shown). Relative expression to the wild type was 65 ± 10% for HL-3 mutant and 68 ± 12% for HL-4 mutants, indicating substantial expression of immunoreactive protein on oocyte plasma membrane. Intact glycosylation of recombinant HL-4 suggested natural maturation of the mutants. When HL-3 was replaced with GlpF, glycosylation was not observed because of removal of the natural glycosylation site of AQP-2.

A series of single-residue substitutions in HL-3 and HL-4 was performed to investigate the interaction of these loops with the aqueous pathway. Replacement of native residues to cysteine has successfully been used to determine the localization of the aqueous pathway of aquaporins (21). The rationale is that there is a high probability that cysteine residues near the aqueous pathway interact with imposed mercury agents and inhibit water channel function. When a cysteine residue was introduced into amino acid 122 or 123 of mercury-resistant mutant of AQP-2, C181A, up to 40% inhibition by low concen-

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Fig. 3. Osmotic water permeability of oocytes expressing N-glycosylation mutants of AQP-2. Summary of a series of osmotic water permeability (P_f) measurements (n = 20–30) are shown. Hatched bar, mean P_f of oocytes injected with wild-type and mutant cRNA; open bar, P_f of oocytes after incubation with Barth’s buffer containing 1 mM HgCl₂ for 10 min. Data are shown as means and S.E.
tration of HgCl₂ was observed, which was significantly higher than that for C181A (p < 0.001, n = 20). The mercury inhibition, although it is not complete, implicated that Asn-123 is likely located near the aqueous pathway. Subsequently, a residue Asn-123 was replaced with a series of amino acids to examine the interaction of the lateral moiety with the aqueous pathway. Osmotic water permeability was decreased roughly in accordance with the size of the lateral moiety (Fig. 4). This may be interpreted as the localization of the constriction of the aqueous pathway at Asn-123 and the occlusion by the larger lateral moiety. Plasma membrane expressions of the series of Asn-123 mutants were comparable to those of the wild type as assessed by immunoblot (Fig. 6) and radioimmuno assay (60 ± 10% for N123A, 65 ± 12% for N123Q, 65 ± 12% for N123D, 65 ± 12% for N123W, relative to the wild type, n = 3–5), showing substantial expression of N123 mutants in the plasma membrane. A similar analysis was done for HL-4. Cysteines in 154, 155, and 156 exhibited high mercury sensitivity, with the highest at Asp-155 (p < 0.001 versus C181A, n = 20), implicating close localization of Asp-155 to presumed aqueous pathway.

DISCUSSION

In this study, we have examined the structure of the aqueous pathway of rat AQP-2 and found that the contribution of HL-3 and HL-4 is significant in the formation of the aqueous pathway. It was suggested that the structure of the aqueous pore is somehow different from that of AQP-1 proposed previously (21–23). A six-transmembrane topology and mercury-sensitive positions in AQP-2 are identical to AQP-1 hourglass model (21). However, mutations near NPA boxes in HL-2 and HL-5 did not
significantly alter water channel function, and cysteine residues inserted near the first NPA box did not induce the alternative mercury-sensitive site. Alternatively, based on the findings that the replacement of HL-3 and HL-4 with hydrophobic residues decreased water permeability without affecting plasma membrane expression and that mercury sensitivity was found in these domains, it was suggested that HL-3 and HL-4 are located near the aqueous pore.

Membrane topology and mercury-sensitive cysteine residues have first been determined experimentally in this study, and it was shown that AQP-2 is similar to AQP-1 proposed as the hourglass model in its topological presentation. Membrane topology was partially determined from the presence of N-glycosylation, which indicates extracellular localization of the site. N-Glycosylation site insertion has been successfully used to map membrane topology of the cystic fibrosis transmembrane regulator (25) and the glutamate receptor (32). The N-glycosylation insertion was used in the present study because the glycosylation is natural and the consensus glycosylation sequence minimally perturbs the native sequence and structure (25). Immunoblot results indicated the extracellular localization of the site. N-Glycosylation site insertion has been successfully used to map membrane topology of the cystic fibrosis transmembrane regulator (25) and the glutamate receptor (32). 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including AQP-1, AQP-3, MIP, and γ-TIP showed that hydrophilicity of these domains is a common feature of water channels (33, 34). Thus, it is reasonable to speculate that HL-3 and HL-4 contribute to the structure of the aqueous pore and to selective permeability. Disappearance of water permeability by the replacement of HL-4 with GlpF but not with AQP-1 or MIP implicated that hydrophilicity of this domain may be critical for water permeability. Furthermore, the findings that mercury sensitivity was maximum at positions Asn-123 and Asp-155 and that substitutions of Asn-123 with larger residues decreased P₅ can be interpreted that Asn-123 and Asp-155 are the closest to the presumed constriction of the aqueous pore of an expected size of ∼2 Å (21–23). However, our observations may raise several questions, which must be resolved before any definitive conclusions can be made. First, although mercury inhibition found in HL-3 and HL-4 was significant compared to C181A, it was lower than that for wild type. The lower mercury sensitivity can be explained by the possibility that HL-3 and HL-4 are located further to the aqueous pathway than Cys-181. Second, insertion of NTS after the residue 154, which should be the critical site for water channel function according to our data, did not alter P₅. This may be because hydrophilicity of inserted residues minimally disturbed the pore structure. Further structural analyses will be required to interpret our current observations and those of the previous studies and to describe a more precise structure of the aqueous pore.

Care must be taken for the interpretation of mutational analysis of aquaporins because it has been well known that mutations in aquaporins sometimes disturb synthesis, assembly, and plasma membrane expression of mutant proteins in oocytes (19, 21, 35). Thus, functions of mutated channel have to be normalized with the amount of protein in the plasma membrane. Therefore, we undertook immunological analysis of synthesized mutants to ensure that mutants were readily synthesized and expressed in the plasma membrane. Plasma membrane expression of mutated channel was successfully resolved by two methods. For this purpose, we did not use immunohistochemical staining of oocyte membranes, which is less quantitative compared to the two methods we used. All mutations in HL-3 and HL-4 examined here did not significantly affect plasma membrane expression, confirming that the mutations only minimally perturb the channel structure.

On the basis of our results, we propose a structure model for AQP-2 water channel (Fig. 7). Between six transmembrane α-helices, a central channel may be formed, the diameter of which would be larger than the expected size for selective aqueous pore. Constrictions with a pore size of ∼2 Å that determine selective water permeability may be assembled in the association of HL-3 and HL-5 in the extracellular side and in the association of HL-2 and HL-4 in the cytoplasmic side. These hydrophilic loops may be partially folded into the large pore, forming constrictions and hydrophilic apparatus that exclude charged ions and large molecules. Since N-glycosylation of HL-3 or HL-5 did not influence pore structure, it is likely that these domains are not folded deep into lipid bilayer as described in the hourglass model. The roles of the NPA boxes, which are strictly conserved among the MIP family, are not clear from our study. It is speculated that the NPA boxes are critical to correctly assemble three-dimensional structures of aquaporins because AQP-2 proteins with mutations near NPA boxes were suggested to be folded improperly (35).

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Liqun Bai, Kiyohide Fushimi, Sei Sasaki and Fumiaki Marumo

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