Colon water transport in transgenic mice lacking aquaporin-4 water channels

KASPER S. WANG,1 TONGHUI MA,2 FERDA FILIZ,1 A. S. VERKMAN,2 AND J. AUGUSTO BASTIDAS1

1Department of Surgery, Stanford University School of Medicine, Stanford 94305-5408; and 2Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, California 94143-0521

Received 13 December 1999; accepted in final form 9 May 2000

Wang, Kasper S., Tonghui Ma, Ferda Filiz, A. S. Verkman, and J. Augusto Bastidas. Colon water transport in transgenic mice lacking aquaporin-4 water channels. Am J Physiol Gastrointest Liver Physiol 279: G463–G470, 2000.—Transgenic null mice were used to test the hypothesis that water channel aquaporin-4 (AQP4) is involved in colon water transport and fecal dehydration. AQP4 was immunolocalized to the basolateral membrane of colonic surface epithelium of wild-type (+/+) mice and was absent in AQP4 null (−/−) mice. The transepithelial osmotic water permeability coefficient (Pf) of in vivo perfused colon of +/- mice, measured using the marker 14C-labeled polyethylene glycol, was 0.016 ± 0.002 cm/s. Pf of proximal colon was greater than that of distal colon (0.020 ± 0.004 vs. 0.009 ± 0.003 cm/s, P < 0.01). Pf was significantly lower in −/− mice when measured in full-length colon (0.009 ± 0.002 cm/s, P < 0.05) and proximal colon (0.013 ± 0.002 cm/s, P < 0.05) but not in distal colon. There was no difference in water content of cecal stool from +/- vs. −/− mice (0.80 ± 0.01 vs. 0.81 ± 0.01), but there was a slightly higher water content in defecated stool from −/− mice (0.68 ± 0.01 vs. 0.65 ± 0.01, P < 0.05). Despite the differences in water permeability with AQP4 deletion, theophylline-induced secretion was not impaired (50 ± 9 vs. 51 ± 8 µl·min⁻¹·g⁻¹). These results provide evidence that transepithelial water transport through AQP4 channels in colonic epithelium facilitates transepithelial osmotic water permeability but has little or no effect on colonic fluid secretion or fecal dehydration.

AN IMPORTANT ROLE OF THE COLONIC epithelium is the desiccation of stool. Although the small intestine absorbs most of the 10 liters of fluid entering the gastrointestinal tract daily by a near-isosmolar transport mechanism, the colon absorbs an additional ~2 l of fluid against considerable osmotic gradients to produce a compact, hard stool (20). Because of differences in length and luminal surface area, it is estimated that the colon absorbs more water per unit of luminal surface area than the small intestine (7).

It has been thought that a significant portion of transepithelial water absorption in the small intestine occurs via the lateral intercellular space (24). The small intestine contains a leaky epithelium with low electrical resistance and low reflection coefficients for small solutes (25). Recently, the possibility of tranacellular water movement across enterocytes in small intestine has been considered. It has been proposed that sodium-glucose and other sodium-coupled cotransporters might serve as active water transporters by which water moves together with sodium and solutes (12). There is also evidence that aquaporin-type water channels are present on enterocyte plasma membranes (reviewed in Ref. 15). Aquaporin-4 (AQP4) has been immunolocalized to the basolateral membrane of deep glands of the small intestine and aquaporin-8 (AQP8) mRNA to villous epithelium (9).

In contrast, the colon is a tight epithelium with a high electrical resistance (36). There is considerable interest in the mechanisms by which the colon is able to extract water from feces yet, under some conditions, secrete large quantities of fluid. It was initially postulated that the secretory and absorptive functions in the colonic epithelium are compartmentalized, with fluid secretion occurring in the crypt and fluid absorption in the surface epithelium (34). More recently, Naftalin and colleagues (21, 22, 37) proposed a role for the colonic crypt epithelium in water absorption. They...
G464

AQP4 AND COLON WATER TRANSPORT

postulated that the generation of a hypertonic absorbate across the crypt epithelium creates a hydraulic vacuum, which extracts water from the luminal fecal matter. Furthermore, the crypts in the distal colon are more capable of generating a hypertonic absorbate than the proximal colon (22). Singh et al. (27) showed that the unstimulated isolated perfused colonic crypt absorbs water, whereas the crypt epithelium can secrete fluid strongly in response to cAMP agonists including theophylline and cholera toxin (1, 4, 23). Thus, although fluid secretion in colon probably occurs by mechanisms similar to those in other secretory epithelia, the mechanisms of colonic fluid absorption are less clear.

Although much is known about the role of ion channels and cotransporters in colonic fluid transport, little attention has been given to the pathways for water movement. Water channels AQP3 and AQP4 are expressed in the basolateral membrane of rat colonic surface epithelium (5). AQP8 is also expressed in colonic surface epithelium (14) but has not yet been immunolocalized. A substantial body of evidence indicates that aquaporin water channels have physiological importance in kidney, lung, and other tissues (reviewed in Refs. 29 and 32); however, their significance in gastrointestinal function has not been established. The recent generation of transgenic null mice lacking specific aquaporins permits elucidation of their role in organ physiology.

The purpose of this study was to characterize the water-transporting pathway in mouse colon and to establish the role of AQP4 in colonic absorptive and secretory function. By immunohistochemistry, AQP4 was localized to the colonic surface epithelium of wild-type but not AQP4 knockout mice. It was found that AQP4 deletion is associated with slightly greater stool water content, decreased transepithelial colonic water permeability, and decreased agonist-induced colonic fluid absorption, whereas agonist-induced colonic fluid secretion was not affected.

**METHODS**

**Transgenic mice.** Transgenic knockout mice deficient in AQP4 protein were generated by targeted gene disruption as described previously (13). Studies were performed in 30- to 40-g wild-type and AQP4 knockout mice in a CD1 background. Genotype analysis of tail DNA was done by PCR at age 5 days. As reported previously, the AQP4 knockout mice were normal in appearance compared with wild-type mice. The investigators were blinded to genotype information for colon water permeability measurements, absorption/secretion studies, and immunohistochemistry. All mouse protocols were approved by the Stanford University Administrative Panel on Laboratory Animal Care.

**In vivo colon water permeability measurements.** For colon perfusion studies, mice were anesthetized with pentobarbital sodium (5 mg/kg ip). Core body temperature was monitored by rectal probe and maintained at 37°C with an electrical heating pad and overhead lamp. The proximal colon beyond the cecum was cannulated with a 6-Fr inflow catheter (Portøgård), and the colon was flushed with saline to remove fecal contents. The distal colon was cannulated with PE-240 tubing (Becton Dickinson, Sparks, MD) for effluent collection. Colonic segments (4.5–5.5 cm) were repeatedly flushed with saline solution until clear. For independent perfusion of proximal and distal colons, a silk ligature was placed at the mid-transverse colon, dividing the colon into proximal and distal segments (each 2- to 3-cm length). PE-240 tubing was inserted into the distal end of each segment for effluent collection, and inflow catheters were inserted into the proximal ends of each segment. Catheters were secured in place with 4-0 silk ligatures. Colonic segments were flushed with luminal perfusate containing 140 mM Na⁺, 5.2 mM K⁺, 119.8 mM Cl⁻, 25 mM HCO₃⁻, 1.2 mM Ca²⁺, 1.2 mM Mg²⁺, 2.4 mM HPO₄²⁻, 0.4 mM H₂PO₄⁻, 5 g/l polyethylene glycol (PEG, mol wt 3,000; Sigma, St. Louis, MO) containing 5 μCi/ml ¹⁴C-labeled PEG (New England Nuclear, Boston, MA), 1.5 mM Cl⁻/H₂O (New England Nuclear) and 0, 100, 150, or 300 mM mannitol (mol wt 182). Perfusion osmolalities were determined at the Stanford University Hospital Clinical Chemistry Laboratory by standard freezing point osmometry. The inflow catheter was connected to a variable-flow peristaltic pump (VWR, San Francisco, CA) at a rate of 0.5 cm/h. After an initial 20-min stabilization, effluent was collected over two 20-min intervals. In some experiments, colons were perfused serially with up to four solutions of different osmolalities. In some experiments mannitol was replaced by equimolar raffinose (mol wt 595) or PEG (mol wt 1,000; Baker, Phillipsburg, NJ). Effluent samples were assayed for ¹⁴C and ³H radioactivity by liquid scintillation counting (LS 6000SC, Beckman Instruments, Brea, CA) and for Na⁺ concentration by flame photometry.

**In vivo colon water secretion.** For intravenous infusions, the right jugular vein was exposed through a right-sided longitudinal incision and catheterized with PE-10 tubing (Becton Dickinson). Saline was infused at a rate of 10 ml·kg⁻¹·h⁻¹ by a KDS100 infusion pump (KD Scientific, Beston, MA). The colon was then cannulated and perfused and as described in *In vivo colon water permeability measurements*. After the continuous collection of two 20-min samples from the colon, 1 mM theophylline (Sigma) was added to the isomolar luminal perfusate (325 mosM), and effluent was collected over 40 min.

**Calculation of osmotic and diffusional water permeability.** Apparent osmotic water permeability (Pₒ) and diffusional water permeability coefficients (P_d) were calculated assuming a smooth right cylinder for the surface area (A) of the colonic segment. Surface area was calculated from the perfused colon diameter (d) and length (L). Pₒ was calculated from the relation (11)

\[
Pₒ = -\frac{(V_c/C_o - V_a/C_l)}{A} \left(\frac{C_o - C_l}{C_o C_l - A}\right) - \frac{C_l^2}{C_o} \ln\left(\frac{C_o - C_l}{C_o - C_i}\right) \tag{1}
\]

where \(V_c\) is the perfusion rate (ml/min), \(V_a\) is the partial molar volume of water (18 ml/mol), \(C_o\) is the perfusate osmolality, \(C_l\) is serum osmolality, and \(C_i\) is calculated osmolality at the distal end of the colon. Because ¹⁴C radioactivity is linearly proportional to its concentration, \(C_l\) was calculated from the product of \(C_o\) and the ratio of ¹⁴C radioactivity in the presence and absence of a transepithelial osmotic gradient. P_d was calculated from the relation

\[
P_d = (V_a/A) \ln\left(\frac{C_i}{C_mC_out}\right) \tag{2}
\]

where \(C_m\) is the fraction of ³H₂O in the luminal perfusate (\(C_m = 1.0\)) and \(C_out\) is the fraction of ³H₂O at the measuring area at the distal end of the colonic segment. Net water flux \(J_w\) was calculated from the relation...
Immunohistochemistry. Colons from wild-type and AQP4 knockout mice were flushed with saline and then with 4% paraformaldehyde in PBS. Proximal and distal colons were removed, sliced, and postfixed in the same solution for 2–4 h at room temperature. Tissues were then processed and stained with an immunopurified polyclonal anti-AQP4 antibody as previously described (5). Fluorescence from a secondary FITC-conjugated goat anti-rabbit IgG (Life Technologies, Gaithersburg, MD) was visualized on an epifluorescence microscope with a charge-coupled device camera detector (Leica).

Reverse transcriptase-polymerase chain reaction. mRNA was isolated from mouse colon and kidney and reverse transcribed to yield cDNA. The cDNAs were used as the template for PCR amplification of fragments of aquaporin coding regions using specific primers designed to flank the coding sequences of mouse AQP3 (720 bp in length), AQP4 (370 bp), and AQP8 (350 bp). Primers were designed according to database sequences for AQP3 and AQP4 (Genbank accession numbers AF104416 and U88623, respectively) and the published AQP8 sequence (14).

Stool water content. Mice were given free access to water and standard mouse chow. Spontaneously defecated stool was immediately collected and weighed. Cecal contents were obtained in anesthetized (pentobarbital sodium 5 mg/kg ip) mice through a midline abdominal incision. Cecal contents and stool were dried at 120°C for >3 h and weighed to determine percent water content.

Statistical analyses. All data are expressed as means ± SE. All analyses comparing wild-type (+/+ ) to AQP4 null (−/−) mice were performed using unpaired t-test or ANOVA with post hoc Scheffé’s test.

RESULTS

AQP4 was immunolocalized in +/+ mice to the basolateral membrane of surface colonicocytes. The immunofluorescence signal appeared to be qualitatively more intense in the proximal colon compared with the distal colon (Fig. 1, A vs. C). No signal was detected in the colon of −/− mice (Fig. 1, B and D). These results are in agreement with AQP4 localization in rat colon (5).

To determine whether the absence of AQP4 gene expression resulted in upregulation of other aquaporins that might be expressed in colon, semiquantitative RT-PCR was performed. Figure 2 shows equivalent RT-PCR amplification of 400-bp β-actin PCR fragments in +/+ and −/− mouse colon and kidney. AQP4 PCR fragments (370 bp) were expressed in colon and kidney of +/+ mice but not in −/− mice. AQP3 transcript was not detected in mouse colon, as reported previously (23), but was present in kidney of +/+ and −/− mice (720 bp). AQP8 (350 bp) was present in comparable quantities in colons of +/+ and −/− mice.

Osmotically driven water transport between the colonic lumen and capillary compartments was measured in vivo in +/+ mice. Colons were perfused with solutions of different osmolalities containing [14C]PEG as a volume marker. Figure 3A shows that net water movement across the colonic epithelium is linear and nonrectifying. Computed 1/Pf (0.016 ± 0.002 cm/s, n = 20) was independent of the magnitude and direction of the osmotic gradient (Fig. 3B). To test for unstirred layers, 500 μg/ml of amphotericin B, which creates artificial transmembrane pores, was added to the perfusate. Pf was increased 2.5-fold in the presence of amphotericin B (Fig. 3C), suggesting that there was little or no unstirred layer effect. In addition, Pf was independent of perfusion flow rate over a sevenfold range (Fig. 3D), supporting the conclusion that unstirred layers were minimal or absent in the in vivo Pf measurements here. To evaluate the contribution of paracellular water movement to osmotically induced transepithelial water transport in the colon, Pf was measured using osmotic solutes of different sizes, including mannitol (mol wt 182), raffinose (595), and PEG (1,000). Pf would depend on solute size if significant paracellular water transport occurred, as is the case in small intestine (10, 24). There was no significant difference in colon Pf for the different osmolytes (Fig. 3E), suggesting mainly transcellular water movement.

To determine the contribution of AQP4 to transepithelial osmotic water permeability in colon, Pf was compared in full-length, proximal, and distal colons of +/+ and −/− mice. Pf was significantly higher in +/+ mice (0.017 ± 0.003 cm/s (n = 17) vs. 0.009 ± 0.002 cm/s (n = 11), P < 0.05, unpaired t-test; Fig. 4A). When proximal and distal halves (2- to 3-cm length each) of +/+ mouse colons were perfused independently, Pf of proximal colon was significantly higher than in distal colon (0.020 ± 0.004 vs. 0.009 ± 0.003 cm/s, n = 8; P < 0.05, paired t-test). Pf of proximal colon in −/− mice was significantly lower than that of the proximal colon in +/+ mice (0.013 ± 0.002 cm/s, n = 8; P < 0.05, unpaired t-test), but Pf of distal colon was not different.
To determine whether this difference was related to intrinsically different water permeabilities or to different effective surface areas for water transport, $P_d$ was measured. For a complex epithelium like colon, $P_d$ is unstirred layer limited by several orders of magnitude and thus provides a semiquantitative measure of effective surface area. $P_d$ values did not differ between proximal and distal colon and were unaffected by AQP4 deletion (Fig. 4B), so that the ratio $P_t/P_d$ (Fig. 4C), which normalizes water permeabilities for effec-

---

Fig. 2. Reverse transcriptase-polymerase chain reaction of 10 and 50 ng of β-actin, AQP4, AQP3, and AQP8 in +/+ and −/− mouse colon (C) and kidney (K) (right lanes, FX174 DNA/Hae III, GIBCO BRL) Molecular weight markers are indicated on left.

Fig. 3. Characterization of in vivo water permeability in +/+ mouse colon. A: transepithelial water flux ($J_w$) in colons as a function of osmotic gradient size (means ± SE). B: computed osmotic water permeability coefficient ($P_f$) values for the data in A. C: effect of luminal amphotericin B (500 μg/ml) on $P_f$. D: effect of luminal perfusion flow on $P_f$. E: effect of solute size on $P_f$; numbers in parentheses are molecular weights.
tive surface areas, was significantly higher in full-length colons of +/+ mice than in −/− mice (211 ± 35 vs. 110 ± 21, *P* < 0.05). Similarly, *P*/*P* of proximal colon of +/+ mice (263 ± 67) was higher than that of distal colon of +/+ mice (139 ± 48, *P* < 0.05) and of proximal colon of −/− mice (140 ± 17, *P* < 0.05).

To confirm that significant Na⁺ transport did not occur under the conditions of the osmotic water permeability measurements, Na⁺ concentrations were measured in the effluent by flame photometry. Osmotic water transport was driven by the addition of 100 mM mannitol to isotonic perfusate. In +/+ mice, the ratio of effluent to infusate Na⁺ concentrations was 0.87 ± 0.02 and the ratio of effluent to infusate [¹⁴C]PEG concentrations was 0.89 ± 0.01 (*n* = 7). The similar changes in Na⁺ and [¹⁴C]PEG concentrations indicate that little Na⁺ transport occurs during the osmosis measurements.

The colon progressively desiccates luminal contents as they move downstream. Figure 5 shows the percent water content of cecal matter and excreted feces from +/+ and −/− mice. There was no significant difference in cecal stool water content between +/+ mice and −/− mice (0.80 ± 0.01 vs. 0.81 ± 0.01, *n* = 10). However, the water content of stool collected immediately on defecation was significantly higher in AQP4 −/− mice (0.68 ± 0.01 vs. 0.65 ± 0.01, *n* = 114; *P* < 0.05).

To determine whether fluid secretory function is defective in AQP4 knockout mice, in vivo colon perfusions were performed in the absence and presence of luminal theophylline. Figure 6 shows that basal net

---

**Fig. 4.** Comparison of *P* (A), diffusional water permeability coefficient (*P*; B), and *P*/*P* (C) for full-length colon and proximal and distal colon of +/+ and −/− mice (means ± SE).

**Fig. 5.** Water content of cecal and defecated stool in +/+ and −/− mice. Cecal stool was collected via cecotomy (*n* = 10 mice), and spontaneously defecated stool was collected from a separate group of mice (*n* = 114). Data are expressed as means ± SE.
water movement with isosmolar perfusate was not significantly different in +/+ vs. −/− mice (−7 ± 12 vs. −6 ± 11 μL · min⁻¹ · g⁻¹, n = 21). Theophylline induced a substantial but similar net water secretion in both groups (50 ± 8 and 51 ± 9 μL · min⁻¹ · g⁻¹, respectively), indicating that agonist-stimulated water secretion is not altered in −/− mice.

**DISCUSSION**

The goal of this study was to test the hypothesis that water channel AQP4 plays a role in colonic fluid transport. AQP4 was immunolocalized to the basolateral membrane of surface colonocytes of +/+ mice and was absent in −/− mice. The transepithelial water permeability of the proximal colon was higher than that of the distal colon, and AQP4 deletion resulted in the reduction of water permeability in proximal but not distal colon. The water content in defecated stool was slightly higher in AQP4 knockout mice than in wild-type mice, whereas the water content of cecal stool did not differ. Theophylline-stimulated colonic water secretion was not impaired by AQP4 deletion. Together these data imply that AQP4 has a role in transepithelial water movement across surface colonocytes but that surface colonocytes play little or no role in fecal dehydration and colonic fluid secretion.

Welsh and colleagues (34) originally showed by micropuncture of rabbit surface and crypt colonocytes that the colonic surface epithelium is involved in fluid absorption and the crypt epithelium is involved in fluid secretion. Subsequent data suggested that compartmentalization of absorption and secretion in colon is not absolute. A series of elegant studies by Naftalin and colleagues (21, 22) demonstrated that the colonic crypts are critical to fecal dehydration. They showed that the decrease in stool water content from >80% to <65% requires a substantial suction pressure of 4–10 atm (21, 22) that appears to be produced by absorption of hypertonic fluid across the crypt epithelium. The cecum, which possesses a higher pericrypt permeability to NaCl, is incapable of absorbing fluid against significant hydraulic resistance (22). The mildly elevated defecated stool water content in −/− mice and the reduction in proximal but not distal $P_f$ is consistent with the majority of colonic water absorption required for fecal dehydration occurring in the distal colon.

An in vivo colon perfusion model was developed for the measurement of transepithelial water transport. Compared with in vitro perfusion models, the in vivo technique used here permits the measurement of osmotically driven and agonist-induced fluid transport measurements under physiological conditions and with excellent vascular perfusion. Vascular perfusion is very important in minimizing unstirred layer effects, which in the complex epithelium in colon are predicted to be rate limiting in (nonperfused) in vitro models (30). The increased $P_f$ after amphotericin B treatment, the high $P_f$ values, and the independence of $P_f$ from lumen flow suggest that unstirred layer effects are minimal or absent in the measurements here. Higher rates of perfusion, which theoretically would further reduce the unstirred layer, resulted in trauma to the colonic wall. The $P_f$ of proximal colon reported here, 0.023 cm/s, was computed for a hypothetically smooth colonic wall assumed to be a cylinder of constant diameter. Compared with other epithelia that express aquaporins, $P_f$ in the in vivo colon was lower than that of in vitro microperfused mouse kidney proximal tubule (0.15 cm/s) and collecting duct (0.056 cm/s) but higher than that of the in vitro guinea pig distal airway epithelium (0.005 cm/s) and type II pneumocytes (0.013 cm/s). However, because the luminal and basolateral membranes of the colon are convoluted, the apparent transepithelial $P_f$ computed for a smooth-walled cylinder represents an overestimate of the $P_f$ per unit surface area of colonic wall. Nevertheless, the $P_f$ values determined in this study do describe the actual in vivo colon water permeabilities and are useful for comparisons of relative water permeability. Because morphometric determination of effective surface areas in colon is not possible, we measured transepithelial $P_d$ as a semiquantitative index of the functionally effective surface area for water transport. $P_d$ values were not different in proximal and distal colon and with AQP4 deletion, providing evidence for different intrinsic water permeabilities of proximal vs. distal colon and of colon from wild-type vs. AQP4 knockout mice.

The characteristics of a pore-mediated water pathway include high $P_f$, a high $P_f/P_d$, and a weakly temperature-dependent $P_f$ and can include inhibition by mercurial compounds and low-reflection coefficients for small solutes (31). Analysis of the temperature dependence of $P_f$ was impractical in vivo because hypothermia-induced vasoconstriction impairs vascular perfusion. Mercurial inhibition could not be performed in the in vivo colon because the existing mercurial water...
channel inhibitors are highly toxic and AQP4-mediated water transport is not inhibited by mercurials (8).

Although there is evidence that fluid absorbed in the crypts of the descending colon is hypertonic, fluid absorption or secretion by various epithelia such as renal proximal tubule, salivary gland, choroid plexus, and gallbladder probably occurs by a near-isosmolar process (21, 22, 6, 35). As reviewed by Spring (28), a high tranacellular water permeability in epithelia is probably essential for isosmolar fluid transport. Schnermann et al. (26) demonstrated directly that decreased transepithelial water permeability of proximal tubule in AQP1 knockout mice resulted in impaired isosmolar fluid absorption. Ma et al. (16) found defective agonist-stimulated saliva secretion in mice lacking AQP5 water channels. Conversely, a low tranacellular water permeability is essential for the generation of hypertonic fluid absorption in the crypts of the colon (21, 22).

In the colon studies here, agonist-induced fluid secretion using intraluminal theophylline infusion did not differ significantly between wild-type and AQP4 knockout mice. The unimpaired fluid secretion in AQP4 null mice is consistent with an exclusively cryptal site for colonic fluid secretion. Active fluid absorption, as assessed by fecal water content, was affected little by AQP4 deletion. These results are consistent with the crypt being a major site for colonic fluid absorption and also with the relatively low rate of active fluid transport in colon compared with kidney or salivary gland (see Ref. 30 for further discussion). A similar situation was found recently in lung. Although deletion of AQP1 or AQP5 each caused a 10-fold reduction in airspace-capillary water permeability, alveolar fluid clearance by an active, isosmolar transport mechanism was unimpaired (2, 18, 33). It thus appears that the need for aquaporins in active fluid transport depends on the magnitude of fluid movement per unit surface of limiting membrane. For simple osmotic phenomena, such as water transport in thin descending limb of kidney (3) and hyponatremia-induced brain edema (19), aquaporins play an important physiological role.

In summary, we conclude that AQP4 expressed at the basolateral membrane of surface colonocytes contributes to the relatively high proximal colon water permeability. Further dehydration of feces in the distal colon may rely primarily on aquaporin-independent, hypertonic cryptal absorption mechanisms. The colon also expresses AQP8 and, possibly, as yet unidentified aquaporins that may contribute to transepithelial fluid transport and active absorptive/secretory processes. Analysis of colonic fluid transport in AQP8 null mice, when available, and mice containing multiple aquaporin deletions may be useful in assessing the role of each aquaporin in colon physiology.

We thank Dr. Gary M. Gray (Dept. of Medicine, Stanford Univ. School of Medicine) for advice on intestinal epithelial transport. We thank Irina Cross for technical support and Jian Yang for the breeding and genotyping of the mice.

This work was supported by National Institutes of Health Grants DK-09526, DK-35124, HL-59198, HL-60288, and DK-43840 and grants from the Society for Surgery of the Alimentary Tract Career Development and National Cystic Fibrosis Foundation.

REFERENCES


