Sodium Pump Distribution Is Not Reversed in the DBA/2FG-pcy, Polycystic Kidney Disease Model Mouse

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ABSTRACT
Recently, it has been reported that Na,K-ATPase in the renal epithelia of human autosomal dominant polycystic kidney disease and cpk mouse, a murine model of autosomal recessive polycystic kidney disease, mislocates to apical plasma membrane and that misplaced Na,K-ATPase causes the cyst formation. Whether the DBA/2FG-pcy mouse, which are presumably a suitable model for autosomal dominant polycystic kidney disease, also exhibit the reversal polarity of Na,K-ATPase localization was examined. Kidneys of newborn DBA/2FG-pcy mice, and those at early and late stages of cyst development were examined by immunohistochemical techniques. At any stage, abnormal distribution of Na,K-ATPase on the apical membranes of tubular epithelial cells could not be detected. It is suggested that cysts can be formed without reversed polarity of Na,K-ATPase distribution in pcy mice.

Key Words: Na,K-ATPase, immunohistochemistry, cell polarity, mislocation, cyst formation

Human hereditary polycystic kidney disease is commonly represented by autosomal dominant polycystic kidney disease (ADPKD) and by autosomal recessive polycystic kidney disease (ARPKD). In both cases, renal cysts are formed by the progressive accumulation of fluid in dilated tubules. The mechanism of the cyst formation and development, however, has not yet been elucidated.

In order to study the pathogenesis of human hereditary polycystic kidney disease, several mutant mouse models have been developed, such as C57BL/6J-cpk mice (cpk mice), which resemble ARPKD in genetic and clinical patterns (1,2). Recently, it has been reported that Balb/c-bpk mice (bpk mice), a new model of ARPKD, demonstrate both renal and biliary abnormalities (3).

DBA/2FG-pcy mice (pcy mice) are established by Takahashi et al. This disease is transmitted as an autosomal recessive trait. Cysts of pcy mice develop very slowly compared with those of cpk or bpk mice. The pcy mice can live for about 30 wk and sometimes develop intracranial aneurysms (4). Thus, the pcy mouse system appears to be a suitable model for ADPKD.

Recent studies have shown that Na,K-ATPase in the epithelial cells of cysts of human ADPKD is mislocated to the apical plasma membrane (5,6). Furthermore, some collecting tubule cells demonstrated the apical or apical-lateral localization of Na,K-ATPase at the early developmental stages of both normal and cpk mouse kidneys, and this apical Na,K-ATPase persists in cpk mice (7,8). Those reports suggested that misplaced Na,K-ATPase transports sodium ions and accompanying water from the basolateral surface to the renal tubular lumens; thus, fluid-filled cysts are consequently formed.

In this study, we have examined by immunohistochemical techniques whether Na,K-ATPase is mislocated to the apical membrane of renal epithelial cells during cyst development in pcy mice and have found that Na,K-ATPase is not detected on the apical membrane of the renal epithelial cells at any stage of cyst formation. This result suggests that cyst formation does not always necessitate the reversed apical distribution of Na,K-ATPase.

MATERIALS AND METHODS
Animals
We examined three stages of cyst development in DBA/2FG-pcy mice, which were classified into newborn (N = 5), early (3 wk old; N = 2), and late (19 to
Antibodies

The preparation and characterization of rabbit affinity-purified antibody against the α subunit of Na,K-ATPase from rat kidney were reported previously (9). Antisera against the α1, α2, α3, β1, and β2 subunits of rat Na,K-ATPase, which contain polyclonal antibodies against fusion protein corresponding to each subunit of rat Na,K-ATPase (10), were purchased from Upstate Biotechnical (Lake Placid, NY).

Immunoblot Analysis

Western blot analysis (11) was performed to examine whether the anti-rat Na,K-ATPase antibodies recognize the mouse enzyme. Kidneys of Sprague-Dawley rats and DBA/2N and DBA/2FG-pcy mice were removed, and the microsomes prepared from them were solubilized in 2.5% sodium dodecyl sulfate (SDS) and separated by SDS-polyacrylamide gel electrophoresis (12) in SDS-PAG Plate 4/20 (Daiichii Pure Chemicals Co., Tokyo, Japan). The electrophoresed proteins transferred to a nitrocellulose sheet were incubated overnight at 4°C with 5% skim milk in Tris-HCl-buffered saline (pH 7.6), then overnight with primary antibody (immunoglobulin G [IgG] against Na,K-ATPase α subunit, 0.5 μg/mL, or non-immunized rabbit serum, diluted 1:250). The sheet was incubated with goat IgG against rabbit IgG conjugated with horseradish peroxidase and was visualized with 3,3′-diamino-benzidine tetrahydrochloride color reagent and H2O2.

Tissue Preparation for Immunohistochemistry

For localization of Na,K-ATPase in the DBA/2FG-pcy mice kidney, we used the avidin-biotinylated peroxidase complex (ABC) method on paraffin sections, the IgG-gold silver enhancement method on LR-White sections for light microscopy, or the protein A gold method on LR-White sections for electron microscopy (9). DBA/2FG-pcy mice and DBA/2N mice at the early and late stages of cyst development were anesthetized with ether, perfused from the left ventricle with Hanks' solutions for 1 min, fixed by perfusion with 4% paraformaldehyde containing 1% glutaraldehyde in Hanks’ solution (pH 7.4) for 10 min, and then washed for 3 min with phosphate-buffered saline (pH 7.4) (PBS) containing 50 mM ammonium chloride. The kidneys were removed and cut into small pieces. The kidneys of newborn DBA/2N and 2FG-pcy mice were fixed by immersion with 4% paraformaldehyde in sodium phosphate buffer (pH 7.4) when the kidneys were to be embedded in paraffin. When these kidneys were to be embedded in LR-White, 0.1% glutaraldehyde was added to the above fixative. The pieces of kidneys were dehydrated in graded ethanol and then embedded in paraffin by conventional methods or in LR-White resin (Bio Rad Microscience Division, Watford, United Kingdom) containing 0.5% benzoin methyl ether at −20°C with an ultraviolet-ray polymerizer TUV-200 (Dosaka EM Co., Kyoto, Japan).

Avidin-Biotinylated Peroxidase Complex Method

Serial paraffin sections cut vertical to the long axis of the kidney were incubated with 20% goat serum in PBS containing 0.5% BSA and 0.3% Triton X-100 and then with the antibody (IgG against Na,K-ATPase α subunit; 2 μg/mL) or with antiserum against the Na,K-ATPase α1 subunit (diluted 1:200) for 1 h at room temperature. The sections were then washed three times with PBS containing 0.3% Triton X-100 and reacted with biotinylated goat anti-rabbit IgG (5 μg/mL) for 30 min. Subsequently, they were washed with PBS containing 0.3% Triton X-100 and then treated with avidin-biotinylated peroxidase complex (Vecta stain ABC kit; Vector Laboratories, Inc. Burlingame, CA). After dianimobenzidine-H2O2 reaction and counterstaining with hematoxylin, they were observed under a light microscope. To identify collecting ducts, one of the serial sections was stained with biotinylated peanut lectin agglutinin (PNA) by the ABC method as described above. PNA especially binds to the luminal surface of collecting ducts (13,14).

IgG-Gold Silver Enhancement Procedure

The IgG-gold silver enhancement procedure was carried out by the method of Taatjes et al. (15). Large LR-White semithin sections containing all renal epithelial cells from cortex to inner medulla were cut with a diamond knife (Diatome, Bienne, Switzerland) and were mounted on a glass coverslip. They were incubated with 0.5% BSA in PBS for 10 min and then for 60 min with the antibody (IgG against Na,K-ATPase α subunit; 5 μg/mL) or with antiserum against the Na,K-ATPase α1 subunit (diluted 1:100). Subsequently, they were washed six times with 0.5% BSA in PBS, incubated for 30 min with goat anti-rabbit IgG-gold complex (1 nm in diameter; Bio Cell, Cardiff, United Kingdom), washed six times with 0.1 M sodium cacodylate buffer (pH 7.4), and then post-
fixed with 2% glutaraldehyde in the cacodylate buffer. After being washed with distilled water, they were stained by an intenSEM silver enhancement kit (Amersham International, Buckinghamshire, United Kingdom) under light microscopic observation and were counterstained with toluidine blue. As a control, the same concentration of IgG or diluted serum from nonimmunized rabbits was used.

**Immunoelectron Microscopy**

Ultrathin LR-White sections of the kidney were picked up on collodion-coated nickel grids, floated on a drop of 0.5% BSA in PBS for 10 min, and then incubated for 60 min with anti-Na,K-ATPase \( \alpha \)-subunit antibody (5 \( \mu \)g/mL; 20 \( \mu \)L). After being washed with 0.5% BSA in PBS, the grids were incubated for 10 min with protein A-gold conjugates (8 nm in diameter; optical density at 525 nm = 0.08), washed with 0.1 M cacodylate buffer (pH 7.4), and then post-fixed in 5% glutaraldehyde in the cacodylate buffer (pH 7.4). After being washed with distilled water, the grids were stained for 10 min with uranyl acetate, subsequently for 20 s with lead citrate, and then observed under a Hitachi H-7000 electron microscope.

**RESULTS**

**Immunoblot Analysis of Mouse Kidney Microsomes**

We examined by immunoblot analysis whether the affinity-purified antibody against the Na,K-ATPase \( \alpha \)-subunit of rat kidney can recognize the Na,K-ATPase \( \alpha \)-subunit of pcy mice kidney. In all of the microsome fractions prepared from kidneys of normal rats, pcy mice, and normal mice, a single band appeared at around the 100-kd position corresponding to the \( \alpha \)-subunit of Na,K-ATPase (Figure 1). We obtained the same result with the antisera against the rat Na,K-ATPase \( \alpha 1 \)-subunit. No specific bands were detected when incubated with nonimmunized rabbit serum.

**Light Microscopic Localization of Na,K-ATPase in Normal Mouse Kidney**

Figure 2A shows a vertical section of DBA/2N normal adult mouse (34-wk-old) kidney that was stained by the ABC technique with the antibody against the \( \alpha \)-subunit of Na,K-ATPase. The distal straight and convoluted tubules were heavily stained. In contrast, the thin limbs of Henle’s loop and the collecting ducts were only slightly stained.

When the section was stained by the IgG-gold silver enhancement procedure with the same antibody and observed at a higher magnification, the distal straight and convoluted tubule cells, which are characterized by very well-developed basal infoldings, were heavily stained with silver grains (Figure 2B). In all of these cells, the apical surface was not stained. When the corresponding sections were incubated with nonimmunized rabbit IgG as a control experiment, staining was not observed.

**Light Microscopic Localization of Na,K-ATPase in Newborn pcy and Normal Mouse Kidney**

The kidney of the newborn pcy mouse demonstrates some dilated tubules among immature tubules and glomeruli (Figure 3A). However, it was difficult to follow whether these dilated tubules develop to cysts, or whether they are in the middle of normal tubular development.

Avner et al. reported that some collecting tubules of normal and cpk mouse kidney demonstrate an apical distribution of Na,K-ATPase (7). We used biotinylated PNA to identify the collecting duct (13,14). When the sections of newborn pcy mice were incubated with PNA, the apical surface of some tubules was heavily stained (Figure 3B). These tubules may develop to collecting ducts. The corresponding serial sections were incubated with anti-Na,K-ATPase \( \alpha \)-subunit antibody, and it revealed that, in the epithelial cells of both the dilated tubules and the immature tubules, including the collecting ducts of cortex and medulla, only the basolateral surfaces were stained; the apical surfaces were not stained in any of the pcy mice (N = 5) (Figure 3C and D). Some tubules that are likely to develop into a distal tubule were heavily stained. Also, in normal mice (N = 4), Na,K-ATPase localized only on the basolateral surface of the tubules (photographs not shown).
Figure 2. Light microscopic demonstration of Na,K-ATPase in the normal adult mouse kidney (34 wk old). (A) Immunostaining by the ABC method. Distal tubules are heavily stained. Hematoxylin counterstain. Scale bar, 100 μm. (B) Immunostaining by the IgG-gold silver enhancement procedure. Basolateral surfaces of the distal straight tubule cells are heavily stained with silver grains deposited along the basal infoldings. The apical surface shown by a dotted line is not stained at all. Toluidine blue counterstain. Scale bar, 5 μm.

Figure 3. (A) Newborn pcy mouse kidney. Some dilated tubules are observed (arrows). Hematoxylin and eosin staining.
Light Microscopic Localization of Na,K-ATPase in the Early-Stage pcy Mouse Kidney

In the kidney of the early-stage pcy mouse, a number of dilated tubules were observed in the cortex and the medulla (Figure 4A). These dilated tubules, lined with slightly flattened cells, and rounded cysts, lined with fully flattened cells, occasionally developed among the kidney parenchyma. However, typical enlarged cysts protruding to the renal capsule were not yet observed, and many normal tubules and glomeruli remained.

When the Na,K-ATPase α subunit in the kidney section of these mice was stained by the ABC technique, the normal distal tubule cells were heavily stained, as in the normal mouse kidney (Figure 4A). In slightly dilated tubules, a level of immunostaining was not changed to nondilated tubules on the same nephron segments (Figure 4B). However, all of the cyst-lining cells that were flattened fully were slightly stained (Figure 4C). In any case, the reactions were exclusively localized on the basolateral surfaces of the distal and proximal tubule cells and of the dilated tubule cells; no apical staining was observed.

Light Microscopic Localization of Na,K-ATPase in the Late-Stage pcy Mouse Kidney

In the late-stage pcy mice, which is the end stage of cyst development, there were many dilated tubules and cysts of various forms and sizes in the kidney parenchyma, although a small number of tubules had a normal appearance. Figure 5A shows a 19-wk-old pcy mouse kidney section incubated with anti-Na,K-ATPase α subunit antibody. In the epithelial cells of the cysts and of the normal tubules, only the basolateral surfaces were stained; the apical surfaces were not stained. In addition, these fully flattened epithelial cells of the cysts usually showed only a weak staining, as indicated in Figure 5B. The cyst-lining cells indicated in Figure 5C were exceptionally heavily stained with silver grains, suggesting that this cyst may originate from the distal tubule. We obtained the same results when the kidneys were fixed with 3% paraformaldehyde.

We also examined the localization of Na,K-ATPase using anti-α1, α2, α3, β1, and β2 subunit antibodies in the pcy mice kidneys at the early and the late stages. When the sections were incubated with anti-α1 and β1 subunit antibodies, we obtained the same results as those with the affinity-purified anti-α subunit antibody. No silver grains were observed when incubated with anti-α2, α3, and β2 subunit antibodies.

Electron Microscopic Localization of Na,K-ATPase in pcy Mouse Kidney

We examined the electron microscopic localization of Na,K-ATPase using the protein A-gold technique in the early-stage (3-wk-old) pcy mouse kidney, which had some cystic tubules as well as normal tubules. In all of the tubular cells that appeared to be normal in morphology, Na,K-ATPase was exclusively localized on the basolateral plasma membranes. Figure 6A shows a normal distal straight tubule cell studded with numerous gold particles showing the presence of Na,K-ATPase along the basal infoldings of plasma membranes, which are sandwiching elongated mitochondria. It is noted that gold particles barely bound to the basal membranes, which were in direct contact with the basal lamina. Gold particles were barely observed on the apical plasma membranes, whereas several gold particles were localized on the lateral plasma membranes (Figure 6B).

Figure 7A shows a fully flattened epithelial cell of cystic tubule in the outer medulla of this mouse kidney. Intracellular organelles such as mitochondria were barely observed, and basal infoldings were poorly developed in these flattened epithelial cells. Gold particles were not detected on the apical plasma membranes, whereas on the lateral plasma membranes, which were separated from the apical membranes by tight junctions, a few gold particles could be observed (Figure 7B). In addition, gold particles were barely observed on the basal membranes, which were in tight contact with the basal lamina.

DISCUSSION

The pathobiology of cyst formation in ADPKD has been studied extensively, and abnormalities in the extracellular matrix or cellular proliferation or in the secretion of cyst epithelial cells have been pointed out (16). Recently, it has been suggested that an abnormal distribution and an increase in the activity of Na,K-ATPase play an important role in the cyst formation.
Figure 4. Na,K-ATPase localization in the early-stage (3-wk-old) pcy mouse kidney. (A) Some dilated tubules are seen, and distal tubules are heavily stained. Scale bar, 100 μm. ABC method; hematoxylin counterstain. (B) Slightly dilated proximal tubule. The basolateral surfaces are stained with silver grains deposited along the basal infoldings (arrowheads). (C) Fully flattened cyst-lining cells. Basolateral, especially lateral surfaces, are stained with silver grains (arrows). Apical surfaces are not stained. The distal tubules (D) are markedly stained. CL, cystic lumen. (B and C) IgG-gold silver enhancement procedure; toluidine blue counterstain. Scale bar, 5 μm.

Figure 5. Na,K-ATPase localization in the late-stage (19-wk-old) pcy mouse kidney. (A) Markedly dilated tubules occupy a renal parenchyma. Scale bar, 100 μm. (B) Cyst-lining epithelia. A basal surface is weakly stained with silver grains.
Figure 6. Electron microscopic localization of Na,K-ATPase in a nonaffected distal straight tubule cell (3-wk-old pcy mouse). (A) Numerous gold particles revealing antigenic sites bind to the basal infoldings (arrowheads), which are sandwiching elongated mitochondria (M). The basal membranes directly in contact with the basal lamina (BL) are barely labeled (arrows). Scale bar, 0.5 μm. (B) The apical and the lateral membranes of the same cell. Gold particles are not observed on the apical membranes, whereas some gold particles are seen on the lateral membranes (arrowheads). The two domains are divided by a tight junction (arrow). Scale bar, 0.5 μm.

(arrowheads). In marked contrast, a normal distal tubule (D) is heavily stained. Scale bar, 2 μm. (C) The basal plasma membrane of this dilated tubule are comparatively heavily stained (arrowheads). Scale bar, 5 μm. CL, cystic lumen. P, proximal tubule. D, distal tubule. (A) ABC method. Hematoxylin counterstain. (B and C) IgG-gold silver enhancement procedure. Toluidine blue counterstain.

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Figure 7. Electron microscopic localization of Na,K-ATPase in a fully flattened epithelial cell (3-wk-old pcy mouse). (A) Fully flattened cyst-lining epithelial cell in the outer medulla. CL, cystic lumen. Scale bar, 2 μm. (B) A high-magnification view of the region of the epithelial cell shown by a bracket in Panel A. Gold particles are not observed on the apical membranes, whereas a few gold particles are localized on the lateral membranes (arrowheads). The two domains are divided by a tight junction (arrow). The basal membranes in this region are in direct contact with the basal lamina (BL). Scale bar, 0.1 μm.

formation in ADPKD or in the cpk mouse, a murine model of ARPKD. Wilson et al. (5,6) showed that Na,K-ATPase, ankyrin, and fodrin, which usually locate on basolateral membranes (17–19), mislocate to the apical membrane of cyst-lining epithelial cells in human ADPKD and that the specific activity of Na,K-ATPase is increased in the early stage of cyst development. Avner et al. also showed an abnormal distribution of Na,K-ATPase on the apical or apicallateral membranes of collecting duct cells of the cpk mouse (7,8). They hypothesized that mislocated Na,K-ATPase may lead to abnormal sodium and fluid transport into tubular lumens in the polycystic kidneys, leading to the cyst formation.

In this study, we examined whether Na,K-ATPase is also distributed abnormally in the pcy mouse kidney. We derived and developed the DBA/2FG-pcy mouse strain from the spontaneous mutant mouse of the KK strain, a model of diabetes mellitus, which had a cystic gene originally (20). Polycystic kidney disease of the pcy mouse is inherited as an autosomal recessive gene that locates on chromosome 9 (4) and
that is distinct from the cpk mouse mutation locating on chromosome 12 (21). Polycystic kidney disease of the pcy mouse appears to be more similar to human ADPKD than that of the cpk mouse, because the cystic enlargement and renal insufficiency proceed slowly. An intracranial aneurysm, which sometimes occurs in the pcy mouse, is a common complication in human ADPKD patients (4). Consequently, we suggest that the pcy mouse is a more suitable animal model for ADPKD than the cpk mouse.

We expected that the DBA/2FG-pcy mouse may also show an abnormal distribution of Na,K-ATPase in cyst-lining epithelial cells of the kidney, as in human ADPKD. However, we could not detect apical localization of Na,K-ATPase in pcy mice kidney epithelium at any stage of cyst development, and the immunoreactivity of Na,K-ATPase in most of the cyst-lining epithelial cells was much weaker than that in normal epithelial cells. These results are consistent with the report that the Na,K-ATPase of cysts derived from both proximal and collecting tubules in human ARPKD was localized on the basolateral membranes (22).

Avner et al. reported that, in newborn cpk mice, apical distribution of Na,K-ATPase was observed in 63% of cystic medullary collecting tubules (7). However, in cystic proximal tubules of the cpk mouse, an abnormal distribution of Na,K-ATPase was not demonstrated. Nidess et al. reported that the proximal tubular degeneration appeared initially in the developing tubules of the embryonic cpk mouse kidney (23). It is suggested that a transient apical distribution of Na,K-ATPase in the cystic proximal tubules occurs at a fetal stage in the cpk mouse kidney. In pcy mice, the apical distribution of Na,K-ATPase was not detected in any tubule cell at any postnatal stage of cyst development. It is not probable that Na,K-ATPase in the proximal and collecting tubules is transiently localized in the apical plasma membrane in a fetal stage of pcy mice, because the cyst of the pcy mouse develops more slowly in the life of the pcy mouse than in that of the cpk mouse.

It has been reported that Na,K-ATPase expression of the apical membrane was demonstrated in the cortical portion of the fetal collecting duct of cultured rabbit kidney epithelia (24). A transient apical distribution of Na,K-ATPase in some tubules of newborn normal mice kidney was also demonstrated (7). However, we could not detect the apical distribution of Na,K-ATPase in kidneys of newborn DBA/2N mice used as an experimental control. These inconsistent results may be because of differences in the animal (rabbit versus mouse) or in the mouse (C57BL versus DBA mouse) strains.

Previous studies suggested that the increased Na,K-ATPase activity plays an important role in cyst formation and fluid accumulation. Avner et al. demonstrated that increased Na,K-ATPase activity may lead to cyst formation in proximal tubules in the cpk mouse kidney (25). Similarly, Wilson et al. indicated that, in early-stage ADPKD kidneys, Na,K-ATPase activity was increased by 300% compared with that in age-matched controls (5). In this study, however, an immunoreactivity against Na,K-ATPase in cyst-lining epithelial cells of the pcy mouse decreased with the cyst dilatation. In the enlarged cysts, which are lined with fully flattened epithelial cells, Na,K-ATPase immunoreactivity was as weak as in the normal thin limbs of Henle’s loop. A similar result has been reported with regard to the Han:SPRD/cy rat (26), a model of ADPKD (27). These observations are consistent with the electron microscopic observation that these flattened cells contain few mitochondria and poorly developed basal infoldings.

Na,K-ATPase actively drives sodium and potassium ion transport by hydrolyzing ATP, which is supplied from the mitochondria. The distal tubule cells are characterized by very well-developed basal infoldings, usually sandwiching elongated mitochondria, and these infoldings are heayly loaded with a large amount of Na,K-ATPase (9). In marked contrast, the epithelial cells of thin limb of Henle’s loop, containing few mitochondria, demonstrate very low Na,K-ATPase activity (9,28,29). In addition, the basal plasma membranes of the thin limb of Henle’s loop, which are generally in tight contact with the basal lamina, are loaded with less Na,K-ATPase than the lateral membranes (9). Similarly, the basal plasma membranes of fully flattened cyst-lining cells, which are in tight contact with the basal lamina, demonstrate a low immunoreactivity of Na,K-ATPase.

It is to be pointed out that Na,K-ATPase is usually located on the basolateral surface of the transporting epithelial cells, in both the isotonic and hypertonic absorbers and isotonic and hypertonic secretors (30). According to a recent fluid and electrolyte secretion model, Na,K-ATPase localized on the basolateral membranes of exocrine acini can drive NaCl and fluid secretion into the glandular lumen (31). This means that the mislocation of Na,K-ATPase is not always necessary for cyst formation in polycystic kidney disease epithelia.

In conclusion, we suggest that in the pcy mouse, cysts can be formed without a reversed polarity and an increase in the activity of Na,K-ATPase in cyst-lining epithelial cells. The mechanism for cyst formation in the pcy mouse may be different from that in human ADPKD or in the cpk mouse.

REFERENCES


