Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat

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Renal enlargement in polycystic kidney disease (PKD) is caused by the proliferation of mural epithelial cells and transepithelial fluid secretion into the cavities of innumerable cysts. Arginine vasopressin (AVP) stimulates the proliferation of human PKD cells in vitro via cAMP-dependent activation of the B-Raf/MEK (MAPK/ERK kinase/extracellular signal-regulated kinase (ERK) pathway. ERK activity is elevated in cells that line the cysts in animals with PKD, and AVP receptor antagonists reduce ERK activity and halt disease progression. For suppression of the effect of AVP physiologically, water intake was increased in PCK rats, a model of PKD, and the effect on renal morphology, cellular mechanism, and function was determined. The addition of 5% glucose in the drinking water increased fluid intake approximately 3.5-fold compared with rats that received tap water. In PCK rats, increased water intake for 10 wk reduced urinary AVP excretion (68.3%), and urine osmolality fell below 290 mOsmol/kg. High water intake was associated with reduced renal expression of AVP V2 receptors (41.0%), B-Raf (15.4%), phosphorylated ERK (38.1%), and proliferating cell nuclear antigen–positive renal cells (61.7%). High water intake reduced the kidney/body weight ratio 28.0% and improved renal function. Taken together, these data demonstrate that water intake that is sufficient to cause persistent water diuresis suppresses B-Raf/MEK/ERK activity and decreases cyst and renal volumes in PCK rats. It is suggested that limiting serum AVP levels by increased water intake may be beneficial to some patients with PKD.

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that was sufficient to suppress the renal effects of AVP decreased MEK/ERK activity in the kidneys and slowed the progression of cystic disease in PCK rats.

Materials and Methods

PKC Rat Model

PKC rats that originally were derived from a strain of the Sprague-Dawley rats are maintained at the Education and Research Center of Animal Models for Human Diseases of Fujita Health University. These animals have been characterized previously (15). PKC rats and normal Sprague-Dawley (+/+; Charles River Japan Inc., Kanagawa, Japan) rats were allowed free access to water and food throughout the study. PKC and +/+ rats were randomly assigned to either the control group (normal tap water) or high water intake (HWI) group (water that contained 5% glucose) and treated as such from 4 to 14 wk of age. Twenty-four-hour samples were collected in metabolic cages after 13.5 wk to determine urine volume, water intake volume, and food consumption. At 14 wk of age, rats were anesthetized with pentobarbital sodium (Schering-Plough Corp., Kenilworth, NJ), and both kidneys were removed rapidly, causing exsanguination. Total kidney weight was measured, and then the left kidney was homogenized in lysis buffer to determine protein content and the right kidney was sectioned and immersed in 4% paraformaldehyde.

Western Blot Analysis

Kidney lysate samples were prepared for immunoblot analysis (16,17). Contents of lysis buffer (TLB buffer) were 20 mmol/L Tris (pH 7.4), 137 mmol/L NaCl, 25 mmol/L β-glycerophosphate, 2 mmol/L EDTA, 1 mmol/L sodium orthovanadate, 2 mmol/L dithiothreitol, 1 mmol/L PMSF, 5 μg/ml aprotinin, and 5 μg/ml leupeptin with 1% Triton X-100. Membrane-blotted lysates (20 μg protein/lane) were separated by 10% SDS-PAGE and transferred to nitrocellulose membrane. Membranes were blocked with 5% milk in TBS-T (20 mmol/L Tris-HCl, 137 mmol/L NaCl, and 0.05% Tween 20) for 1 h at room temperature and then incubated overnight at 4°C in primary antibody diluted 1:2000 to 1:5000 in 5% milk in TBS-T. The membranes were washed three times with TBS-T and incubated with secondary antibody conjugated to horseradish peroxidase diluted 1:2000 to 1:5000 in 5% milk in TBS-T for 1 h at room temperature. The membranes were washed three times with TBS-T, and specific antibody signals were detected using an enhanced chemiluminescence system (ECL or ECL Advance Western Blotting Detection System; Amersham Life Sciences, Arlington Heights, IL). Images of the blots were captured, and the intensity of the protein bands was quantified using a CS Analyzer 2.0 with a CCD camera (ATTO Corp., Tokyo, Japan). Relative band intensity was compared with gender-matched +/+ kidneys from rats that received tap water (set to 1.0).

Immunohistochemistry

Sections that were obtained from paraffin blocks were heated to 100°C for 15 min in 10 mM sodium citrate buffer (pH 6.0) to unmask antigens. Endogenous peroxidase activity was destroyed by incubating sections in 0.3% H2O2/methanol for 30 min, and then the sections were incubated with primary antibody (1:3000) for phosphorylated ERK (P-ERK) or proliferating cell nuclear antigen (PCNA) overnight at 4°C. Sections were rinsed with PBS, incubated with biotinylated anti-mouse secondary antibody, and then incubated with streptavidin conjugated to peroxidase (Histofine; Nichirei Biosciences, Tokyo, Japan). Immunoreaction products were developed using 3,3′-diaminobenzidine. Cystic surface area was measured from 10 random fields (× 100 magnification) of hematoxylin-eosin–stained sections of renal cortex (n = 3 PCK rats).

Table 1. Effect of HWI on urine volume and osmolality and urinary AVP

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>n</th>
<th>Water Intake (mL)</th>
<th>Urine Volume (mL)</th>
<th>Urine Osmolality (mOsmol/kg H2O)</th>
<th>Urinary AVP (pg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKC</td>
<td>CONT</td>
<td>8</td>
<td>18 ± 1</td>
<td>18 ± 2</td>
<td>1088 ± 96</td>
<td>257 ± 22</td>
</tr>
<tr>
<td>PKC</td>
<td>HWI</td>
<td>10</td>
<td>68 ± 5b</td>
<td>58 ± 5b</td>
<td>232 ± 47b</td>
<td>114 ± 46b</td>
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<tr>
<td>+/+</td>
<td>CONT</td>
<td>8</td>
<td>10 ± 5</td>
<td>9 ± 1</td>
<td>1498 ± 130</td>
<td>160 ± 19</td>
</tr>
<tr>
<td>+/+</td>
<td>HWI</td>
<td>8</td>
<td>94 ± 26c</td>
<td>91 ± 10b</td>
<td>197 ± 73b</td>
<td>88 ± 38</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKC</td>
<td>CONT</td>
<td>10</td>
<td>18 ± 3</td>
<td>16 ± 2</td>
<td>982 ± 74</td>
<td>435 ± 83</td>
</tr>
<tr>
<td>PKC</td>
<td>HWI</td>
<td>8</td>
<td>63 ± 9b</td>
<td>49 ± 8b</td>
<td>284 ± 52b</td>
<td>111 ± 59b</td>
</tr>
<tr>
<td>+/+</td>
<td>CONT</td>
<td>7</td>
<td>13 ± 5</td>
<td>12 ± 1</td>
<td>1559 ± 211</td>
<td>335 ± 49</td>
</tr>
<tr>
<td>+/+</td>
<td>HWI</td>
<td>10</td>
<td>107 ± 10b</td>
<td>80 ± 11b</td>
<td>131 ± 25b</td>
<td>31 ± 4b</td>
</tr>
</tbody>
</table>

aAddition of 5% glucose to drinking water increased water intake 3.5-fold in PCK rats and 8.2-fold in normal Sprague-Dawley (+/+ rats (composites of male and female rats). Rats drink more water that contained glucose because they have a preference for sweet fluid (33). Urine volume increased accordingly. High water intake (HWI) decreased urine osmolalities below 290 mOsmol/kg H2O. Urinary arginine vasopressin (AVP), an indicator of plasma AVP levels, decreased significantly in both PCK and +/+ rats with HWI. Statistical differences between HWI and control (CONT) rats (either +/+ or PCK) were determined by one-way ANOVA.

bP < 0.01.
cP < 0.05.
Secondary antibodies conjugated to horseradish peroxidase were goat anti-rabbit IgG (SC-2054) and rabbit anti-mouse IgG (SC-2055) from Santa Cruz Biotechnology. Primary antibodies to AVPV2R (AB1797P; Chemicon International), PCNA (P8825; Sigma Chemical, St. Louis, MO) and P-ERK (M5670; Sigma) were used for immunohistochemistry. Secondary antibody, conjugated to biotin, for immunohistochemistry studies was rabbit anti-mouse IgG/H11001 IgA/H11001 IgM (HISTOFINE 426032) obtained from Nichirei (Tokyo, Japan).

Measurement of Urine AVP, Creatinine and Osmolality, and Serum Urea Nitrogen

Urine AVP levels were measured with a Correlate-EIA™ arg8–Vasopressin Enzyme Immunoassay Kit (cat. no. 900-017; Assay Designs, Inc., Ann Arbor, MI). Urine creatinine measurements were determined by a colorimetric microplate assay kit (Kit CR01; Oxford Biomedical Research, Inc., Oxford, MI). For an AVP concentration below the level of detection (<3.39 pg/ml), a value of 3.38 pg/ml was used for the calculation of AVP per creatinine concentration (pg ml⁻¹).

![Figure 1](image1.png)

**Figure 1.** Effect of high water intake (HWI) on kidney weight of PCK and normal rats. (A) The addition of 5% glucose to the drinking water did not affect body weight of either the PCK or normal Sprague-Dawley (+/+ rats). (B) HWI caused a significant decrease in total kidney weight, represented as percentage of body weight in both male and female PCK rats. By contrast, HWI had no effect on total kidney weight of +/+ rats. Statistical differences between HWI and control (CONT) rats (either +/+ or PCK) were determined by one-way ANOVA; **P < 0.01.

![Figure 2](image2.png)

**Figure 2.** Effect of HWI on serum urea nitrogen (SUN) in PCK and normal rats. Male PCK rats at 14 wk of age had an elevated SUN compared with age-matched +/+ rats. HWI decreased SUN to control levels in PCK rats. The small but significant decrease in SUN in +/+ rats with HWI is consistent with increased urea excretion as a result of elevated fluid flow in the distal nephron. Statistical differences between HWI and control (CONT) rats (either +/+ or PCK) were determined by one-way ANOVA; *P < 0.05, **P < 0.01.

![Figure 3](image3.png)

**Figure 3.** Effect of HWI on renal cyst development in male and female PCK rats. Micrographs of representative kidney sections, stained with hematoxylin-eosin, were taken at the same magnification from a PCK male rat with normal water intake (A), a PCK male rat with HWI (B), a PCK female rat with normal water intake (C), and a PCK female rat with HWI (D). (E) Surface area of cysts (mean ± SE) from representative sections of male and female PCK kidneys was measured by morphometric analysis. Increased water intake decreased cyst area 60 and 50% in male and female PCK kidneys, respectively. Comparison between HWI and CONT rats (male or female), **P < 0.01.
Table 2. Effect of HWI on male Han SPRD (Cy/+).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>n</th>
<th>Body Weight (g)</th>
<th>Total Kidney Weight (g)</th>
<th>Kidney Weight/Body Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy/+</td>
<td>CONT</td>
<td>10</td>
<td>337 ± 17</td>
<td>7.15 ± 0.27^b</td>
<td>2.17 ± 0.16^b</td>
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<tr>
<td>Cy/+</td>
<td>HWI</td>
<td>11</td>
<td>327 ± 7</td>
<td>7.53 ± 0.40</td>
<td>2.31 ± 0.13^b</td>
</tr>
<tr>
<td>+/+</td>
<td>CONT</td>
<td>5</td>
<td>370 ± 11</td>
<td>2.88 ± 0.05</td>
<td>0.78 ± 0.03</td>
</tr>
<tr>
<td>+/+</td>
<td>HWI</td>
<td>4</td>
<td>339 ± 26</td>
<td>2.44 ± 0.20</td>
<td>0.72 ± 0.03</td>
</tr>
</tbody>
</table>

^aComparison between Cy/+ and control (+/+), P < 0.001, determined by unpaired t test. The lack of an effect of HWI on kidney weight in Cy/+ rats suggests that vasopressin may not contribute significantly to the progression of the proximal tubule cysts in kidneys of Cy/+ rats.

AVP/mg creatinine. Osmolality was determined with a freezing-point osmometer (Osmostat OM-6040; Kyoto Diichi Kagaku, Kyoto, Japan). Serum urea nitrogen (SUN) determinations were performed using a colorimetric assay kit using a Urease-Indophenol method (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Statistical Analyses

Data represent mean and SE. Statistical significance was determined by one-way ANOVA and Student-Newman-Keuls post test for multiple comparisons or unpaired t test for comparison between control and treated animals.

Results

In PCK rats and normal Sprague-Dawley (+/+) rats that were offered water that contained 5% sucrose increased fluid intake from 64 ± 5 ml (n = 6) to 155 ± 8 ml (n = 15). There was no effect of HWI on body weight, total kidney weight, or kidney weight/body weight.

Increased Water Intake Slows PKD Progression


[Image: Figure 4. Effects of HWI on the expression of the vasopressin V2 receptor (AVP2V) and renal activity of the B-Raf/MEK (MAPK/ERK kinase)/extracellular signal-regulated kinase (ERK) pathway in PCK and +/+ rats. Immunoblot analysis was used to compare expression levels of AVP2V, B-Raf, phosphorylated ERK (P-ERK), and total ERK in kidneys of PCK and +/+ rats that drank normal water (CONT) and 5% glucose (HWI). AVP2V, B-Raf, and P-ERK were elevated in the PCK kidneys compared with control kidneys. HWI decreased levels of AVP2V, B-Raf, and P-ERK in PCK kidneys. Total ERK levels were similar between +/+ and PCK kidneys and were unaffected by HWI. A summary of the effects of HWI on the relative expression of AVP2V, B-Raf, P-ERK, and ERK is presented in Table 3.]
Discussion

We determined whether reduction of plasma AVP levels by increased water intake slows the progression of renal cystic disease in PCK rats. The central observations are that increased water intake (1) decreased urine osmolality; (2) reduced renal expression of AVPV2 receptors, B-Raf, P-ERK, and PCNA-positive renal cells; (3) decreased the size of renal cysts and total kidneys; and (4) improved renal function. Therefore, physiologic inhibition of AVP by simply increasing fluid intake was sufficient to suppress cAMP-dependent B-Raf/MEK/ERK activity and proliferation of the cyst-lining cells to slow renal enlargement in the PCK rat.

ARPKD is characterized as a disease that affects predominantly the collecting ducts. In ADPKD, cysts can arise from glomeruli and most segments of the nephron; however, several studies have demonstrated that the majority of ADPKD cysts are derived from collecting ducts and distal tubules. Verani and Silva (23) found that 69% of human ADPKD cysts (ranging in size from 0.1 to 6 cm in diameter) stained Arachis hypogaea, a lectin that is specific for collecting ducts. By contrast, cysts of proximal tubule origin could not be identified using the lectin Lotus tetragonolobus. Previously, we found that the majority of cells that were cultured from a mixed population of surface cysts from an ADPKD kidney stained Arachis hypogaea and Dolichos biflorus (another marker for collecting duct and distal nephron) (9). Relatively few cells stained Lotus tetragonolobus. Immunocytochemical studies for the localization of aquaporin-1 and gp330, a proximal tubule marker, in human ADPKD kidneys suggest that only 30 to 44% of >1000 cysts examined were derived from proximal tubules (24,25). More recently, 70 to 80% of the cysts in the renal cortex of PKD2<sup>WS25/WS25</sup> mice, a disease homologous to human ADPKD, were identified as being of either distal tubule or collecting duct origin (26). The morphology of these cysts was indistinguishable from that of human ADPKD cysts. Therefore, both ADPKD and ARPKD cysts seem to be derived largely from collecting ducts and distal tubules.

The initiation of renal cyst formation is caused by mutations in PKD genes (PKD1, PKD2, and PKDH1), whereas AVP mediated by intracellular cAMP seems to be central for cyst progression in both ADPKD and ARPKD (20,27,28). The underlying

<table>
<thead>
<tr>
<th>Table 3. Effects of HWI on AVPV2 expression and B-Raf/MEK/ERK activity in PCK and +/+ kidneys&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Male</td>
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<td></td>
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<sup>a</sup>Summary of the fold changes in renal expression of AVPV2R, 95-kd isoform of B-Raf, P-ERK, and total ERK in PCK and +/+ rats (male and female) treated with normal water intake (CONT) or HWI. These data were obtained from animals listed in Table 1. MEK, MAPK/ERK kinase; AVPV2R, vasopressin V2 receptor; P-ERK, phosphorylated extracellular signal-regulated kinase.

Comparisons between PCK and +/+ rats, <sup>b</sup><em>P</em> < 0.05, <sup>c</sup><em>P</em> < 0.01; comparison between HWI and control (CONT) rats (either +/+ or PCK), <sup>d</sup><em>P</em> < 0.01, <sup>e</sup><em>P</em> < 0.05.
basis for the cAMP-mitogenic phenotype in PKD seems to be due to dysregulation of intracellular $Ca^{2+}$ secondary to mutations in the PKD genes (5,6). ARPKD and ADPKD cyst-derived cells have $[Ca^{2+}]_i$, that is lower than tubule cells derived from noncystic regions of ADPKD kidneys or normal human kidneys. Therefore, cyst-lining cells are associated with lower basal $[Ca^{2+}]_i$, and cAMP-dependent activation of B-Raf/MEK/ERK and cell proliferation. The cellular pathway for $Ca^{2+}$ regulation of the cAMP-mitogenic phenotype remains to be established, but the phosphatidylinositol 3-kinase/Akt pathway seems to be involved (5,6). Basal Akt activity was found to be reduced in ADPKD cells compared with normal human kidney cells, and agents that increased $[Ca^{2+}]_i$ also stimulated Akt and blocked cAMP-dependent B-Raf activation of the MEK/ERK pathway. Recently, Boca et al. (29) showed that the expression of full-length polycystin-1 in renal cells increased the activity of phosphatidylinositol 3-kinase/Akt signaling pathway, supporting a role for this pathway in cystogenesis.

Normal plasma AVP levels which respond to fluctuations in extracellular fluid osmolality are likely to maintain renal intracellular cAMP at levels that activate the MEK/ERK pathway and proliferation of PKD cystic epithelial cells, promoting cyst

Figure 5. Effect of HWI on cell proliferation in PCK and +/+ kidneys. Representative kidney sections from PCK and +/+ rats (male and female) that were treated with normal water intake (CONT) or HWI. Sections were stained with an antibody to proliferating cell nuclear antigen (PCNA), a proliferation marker. Micrographs show PCNA-positive nuclei in cells of kidney sections from PCK-CONT (A), PCK-HWI (B), +/+ CONT (C), and +/+ -HWI rats (D). (E) Number of cells (percentage of total) that were positive for PCNA. Kidney sections of +/+ rats had very few PCNA-positive cells. By contrast, approximately 40% of the cells in the PCK kidney stained positive for PCNA. Increased water intake decreased the percentage of proliferating cells in the kidneys of PCK rats. Comparison between HWI- and CONT-treated PCK rats (male or female), *P < 0.05, **P < 0.01.

Figure 6. Effect of HWI on P-ERK–positive cells in PCK and +/+ kidneys. Number of cells (percentage of total) positive for P-ERK was measured from micrographs of kidney sections of PCK and +/+ rats (male and female) that were treated with CONT or HWI. Male and female PCK rats on HWI had a significant reduction in the number of cells that stained positive for P-ERK, indicating that the renal MEK/ERK activity was reduced by increased water intake. Comparison between HWI- and CONT-treated PCK rats (male or female), *P < 0.05.

Figure 7. Effect of HWI on cellular apoptosis in PCK and +/+ kidneys. The number of apoptotic cells (percentage of total) in kidney sections of CONT- and HWI-treated PCK and +/+ rats was determined using a terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling method. There was a striking elevation in the percentage of apoptotic cells in the PCK kidneys compared with +/+ kidneys. Increased water intake (HWI) decreased the percentage of apoptotic cells 52 and 65% in the male and female PCK rats, respectively. Comparison between HWI- and CONT-treated PCK rats (male or female), **P < 0.01.
and kidney enlargement. Several rodent models of PKD, including the PCK rat, have been reported to have elevated renal cAMP levels (12,21). Gattone and Torres (reviewed by Torres [13]) found that novel AVPV2R antagonists OPC-31261 and OPC-41061 (Tolvaptan; Otsuka Pharmaceutical, Tokyo, Japan) reduced renal cAMP levels and halted PKD progression in four different animal models, including PKD2^{NWS27/−} mice, as well as PCK rats (13,20,28). Treatment with OPC-41061 caused a concomitant reduction in renal levels of B-Raf and P-ERK (22). On the basis of these studies, the capacity for OPC-41061 to reduce PKD progression is being examined in clinical trials (30).

As with other models of PKD, PCK rats are characterized by tubular epithelial cell hyperplasia and increased rates of apoptosis, hallmarks of human PKD (31). We used immunohistochemistry to evaluate the effect of HWI on the proliferation and apoptosis of cyst-lining cells in PCK rat kidneys. The number of cells that stained positive for PCNA, a mitotic indicator, was measured in thin kidney sections from PCK rats. Consistent with a reduction in cyst area and kidney weight, HWI decreased cell proliferation of cyst epithelial cells (PCNA-positive cells decreased approximately 60%; Figure 5E). Inhibition of cell proliferation was associated with decreased levels of B-Raf and P-ERK, suggesting that increased water intake diminished the renal activity of the MEK/ERK pathway. Moreover, the number of apoptotic cells in the cyst epithelium of water-loaded PCK rats was significantly reduced compared with control-treated PCK rats (Figure 7). Male PCK rats at 14 wk of age were found to have increased SUN. Elevated SUN was corrected by increased water intake, demonstrating that suppression of plasma AVP decreased renal cyst formation and improved renal function.

In a retrospective analysis of patients with chronic renal insufficiency, Hebert et al. (32) found that high urine volume was associated with a faster decline of GFR. The authors suggested that high urine volume and low urine osmolality may be risk factors for the progression of renal disease, including PKD. Conversely, an inability to concentrate urine as kidney function declines could account for the high urine volume in their study. Therefore, it is impossible to establish a cause–effect relationship between water intake and the decline in GFR on the basis of their results. In this study, we found that high fluid intake slowed the progression of PKD and significantly improved renal function in the PCK rats. On the basis of these results, we suggest that increased water intake may be beneficial to patients with PKD.

Conclusion

This study provides evidence for a central role of AVP in cAMP-dependent activation of the B-Raf/MEK/ERK pathway in cyst-lining cells and renal cyst enlargement. Increased water intake that was sufficient to cause a sustained reduction in plasma AVP levels decreased AVPV2R expression, reduced ERK activity and renal cell proliferation, and slowed PKD progression in PCK rats. We propose that sustained hydration by increased water intake may be beneficial to some patients with PKD by limiting the detrimental effects of AVP on renal cyst growth.

Acknowledgments

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