Deoxycorticosterone Upregulates PDS (Slc26a4) in Mouse Kidney
Role of Pendrin in Mineralocorticoid-Induced Hypertension


Abstract—Pendrin is an anion exchanger expressed along the apical plasma membrane and apical cytoplasmic vesicles of type B and of non-A, non-B intercalated cells of the distal convoluted tubule, connecting tubule, and cortical collecting duct. Thus, Pds (Slc26a4) is a candidate gene for the putative apical anion-exchange process of the type B intercalated cell. Because apical anion exchange–mediated transport is upregulated with deoxycorticosterone pivalate (DOCP), we tested whether Pds mRNA and protein expression in mouse kidney were upregulated after administration of this aldosterone analogue by using quantitative real-time polymerase chain reaction as well as light and electron microscopic immunolocalization. In kidneys from DOCP-treated mice, Pds mRNA increased 60%, whereas pendrin protein expression in the apical plasma membrane increased 2-fold in non-A, non-B intercalated cells and increased 6-fold in type B cells. Because pendrin transports HCO3− and Cl−, we tested whether DOCP treatment unmasks abnormalities in acid-base or NaCl balance in Pds (-/-) mice. In the absence of DOCP, arterial pH, systolic blood pressure, and body weight were similar in Pds (+/+) and Pds (-/-) mice. After DOCP treatment, weight gain and hypertension were observed in Pds (+/+) but not in Pds (-/-) mice. Moreover, after DOCP administration, metabolic alkalosis was more severe in Pds (-/-) than Pds (+/+) mice. We conclude that pendrin is upregulated with aldosterone analogues and is critical in the pathogenesis of mineralocorticoid-induced hypertension and metabolic alkalosis. (Hypertension. 2003;42: 356-362.)

Key Words: acid-base equilibrium • hypertension, mineralocorticoid • anions • mice • ion transport

Along the renal collecting duct, secretion of acid or base occurs through intercalated cells. Whether an intercalated cell secretes or absorbs net H+ equivalents depends at least in part on whether the H+-ATPase localizes to the apical or the basolateral plasma membrane. Therefore, intercalated cells are also subclassified on the basis of the presence or absence of the anion exchanger, AE1, and the distribution of the H+-ATPase within the cell. Each of these intercalated cell subtypes can be identified on the basis of ultrastructural characteristics. Type A intercalated cells are believed to secrete H+ equivalents. However, the physiologic role of non-A, non-B intercalated cells in acid-base homeostasis is unknown.

Rodents can ingest a substantial base load and yet develop only a mild elevation in serum HCO3−. The cortical collecting duct (CCD) is a critical component of the kidney’s robust ability to excrete OH- equivalents during metabolic alkalosis. However, the physiologic role of non-A, non-B intercalated cells in acid-base homeostasis is unknown.

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unmasked in *Pds* (-/-) mice under conditions that upregulate *Pds* in normal animals.

Whether *Pds* expression changes in tandem with activity of the putative apical anion exchanger is now a subject of intense interest. Both apical anion-exchange activity and pendrin protein expression are upregulated after NaHCO$_3$ ingestion. Aldosterone administration represents another model of metabolic alkalosis in which apical anion exchange is upregulated. However, the effect of aldosterone on *Pds* expression is unknown.

We therefore asked 3 questions: first, are *Pds* mRNA and protein upregulated in another model of metabolic alkalosis, ie, administration of an aldosterone analogue (deoxycorticosterone pivalate [DOCP])? Second, is the subcellular distribution of pendrin altered with DOCP administration? and finally, is a renal phenotype, such as an acid-base abnormality or dysregulation of fluid and/or electrolyte balance, unmasked with DOCP administration in *Pds* (-/-) mice?

**Methods**

**Animals**

**Series 1**

Male, non-Swiss albino mice (Harlan, Ardmore, Tex) weighing 20 to 30 g were fed a balanced 0.07% Na$^+$, 0.8% K$^+$ diet (53881300 Zeigler Brothers) prepared as a gel. Control and treated mice, chosen at random, were given 18 g of a gelled, 0.6% agar diet for 6 days before sacrifice. Mice received 13.5 mL water and 4.5 g mouse chow supplemented with 0.7 mM NaCl per day added to the gel. Treated mice received 1.7 mg DOCP (Ciba-Geigy Animal Health) by intramuscular injection 7 days before sacrifice.

**Series 2**

*Pds* (-/-) mice developed by Everett et al were bred in parallel with co-isogenic wild-type mice (129S6/SvEv Tac, Taconic Farms, Germantown, NY). For 6 days before sacrifice, age- and sex-matched *Pds* (+/+) and (-/-) mice were pair-fed 14 g of the gel diet supplemented with 0.8 mM NaCl daily.

**Series 3**

*Pds* (-/-) and *Pds* (+/+) mice, fed as in series 2, received 1.7 mg DOCP IM 7 days before sacrifice. Mice were placed in metabolic cages, and urine was collected on ice under oil for 24 hours before sacrifice. All mice were anesthetized with 4% isoflurane in 100% O$_2$ at 1 L/min before sacrifice. The Institutional Animal Care and Use Committee at Emory and the University of Texas Health Science Center (UTHSC) approved all animal treatment protocols.

**Measurement of Blood Pressure, Serum and Urine Chemistries, and Arterial Blood Gases**

Systolic blood pressure in conscious mice was measured by the tail-cuff method with use of a MOD 59 pulse amplifier (Innovators in Instrumentation) or BP-2000 (Visitech Systems). Blood was collected for serum chemistry analyses by cardiac puncture under isoflurane anesthesia. Unless noted, urine and serum chemistry values were measured with commercially available instruments (Hitachi 717 and 747 analyzers) at IDEXX Laboratories (West Sacramento, Calif). For arterial blood gases and serum K$^+$, mice were anesthetized with isoflurane for 15 minutes before sample collection. An abdominal incision was made, and 0.15 mL blood was drawn into a heparinized syringe through the abdominal aorta. The sample was placed on ice, and arterial blood gases and K$^+$ were measured immediately at the Hermann Hospital Clinical Laboratory on a commercially available instrument (IL 1620, Instrumentation Laboratories, or an AVL OPTI 1 Blood Gas Analyzer, AVL Medical Instruments). Urinary pH was measured immediately after collection of urine into a gas-tight syringe by bladder puncture of anesthetized mice. Urine osmolality was measured with a vapor pressure osmometer (Wescor). Urinary total ammonia concentration was measured on a continuous-flow fluorimeter and a kit (171-A, Sigma Chemical). Net acid excretion was taken as the sum of the 24-hour urinary excretion of total ammonia concentration plus titratable acid. Urinary HCO$_3^-$ concentration was assumed to be zero. Titratable acid was calculated by using the measured urinary pH and phosphorous concentration and a pK for phosphate of 6.8.

**Preparation of Total RNA and Quantitative Real-Time RT-PCR**

Total RNA was isolated from mouse kidney by using a mini-kit (Qiagen Rneasy, Qiagen). Quantitative real-time polymerase chain reaction (PCR) was performed in the Quantitative Genomics Core Laboratory in the Department of Integrative Biology and Pharmacology, UTHSC, with use of a sequence detector (7700 sequence detector, Applied Biosystems). Specific quantitative assays for mouse *Pds* and β-actin were used. β-Actin and *Pds* mRNAs were measured in the same samples and expressed per left kidney.

**Antibody**

The primary rabbit anti-pendrin antibody recognizes amino acids 766 to 780 of the human pendrin protein sequence. Polyclonal antibodies that target this amino acid sequence have been characterized previously in studies of mouse kidney.

**Pendrin Immunolocalization**

Kidneys were preserved and processed for light and electron microscopy as described previously. For light microscopy, pendrin immunoreactivity was localized by routine immunoperoxidase techniques. For electron microscopy, pendrin immunoreactivity was localized in ultrathin sections by immunogold cytochemistry. The CDDs, connecting segments (CNT), and initial collecting tubules (iCT) were identified as described previously. Type A, type B, and non-A, non-B intercalated cell subtypes were identified by morphological characteristics established in studies of rats and mice under basal conditions.

**Morphometric Analysis**

Apical plasma membrane boundary length, cytoplasmic area, and gold label along the apical plasma membrane and over the cytoplasm, including cytoplasmic vesicles, were quantified in type B intercalated cells and non-A, non-B intercalated cells in 4 to 6 individual mice from each group. A least 5 of each intercalated cell type were selected randomly in each animal and photographed at a primary magnification of 5000× and examined at a final magnification of 18 200×. The exact magnification was calculated by using a calibration grid with 1134 lines/mm. Apical plasma membrane boundary length and cytoplasmic area were determined by using point and intersection counting, the Merz curvilinear test grid, and standard stereologic formulas.

**Statistical Analysis**

For morphometric data without normal distribution or equal variance, a Mann-Whitney rank-sum test was used. In all other studies, comparisons were made between 2 groups with an unpaired Student *t* test. A *P*<0.05 indicates statistical significance. Data are displayed as mean±SEM.

**Results**

**DOCP Upregulates Pendrin mRNA in Mouse Kidney**

Treatment of normal, non-Swiss albino mice with DOCP for 7 days in vivo caused systolic blood pressure to increase from 111±1 (n=7) to 132±3 mm Hg (n=10, *P*<0.05). Urinary pH was 6.87±0.22 (n=6) in controls versus 6.34±0.21 (n=6, *P*=NS) in DOCP-treated mice. Twenty-four-hour
urinary ammonium excretion was 0.165±0.021 mEq (n=6) in controls versus 0.268±0.074 mEq (n=9, P=NS) in DOCP-treated mice. Whereas differences between these groups did not all reach statistical significance, the means reported are consistent with previous reports that DOCP increases blood pressure while reducing urinary pH and increasing urinary ammonium excretion.

The effect of DOCP expression on Pds mRNA was examined. Pds mRNA/kidney was 4.37±0.38×10^3 template molecules (n=10) in controls but increased to 7.12±0.87×10^3 in DOCP-treated mice (n=10, P<0.05). In contrast, no difference in β-actin mRNA/kidney was observed between controls and DOCP-treated mice (1.53±0.13×10^1 template molecules in controls, n=10, versus 1.65±0.25×10^1 in DOCP-treated mice, n=10). We conclude that DOCP upregulates Pds message expression in kidney.

Effect of DOCP on the Expression and Subcellular Distribution of Pendrin

We tested the effect of DOCP on pendrin protein expression and the subcellular distribution of pendrin. By immunohistochemistry and light microscopy, pendrin labeling was similar in kidneys from control and DOCP-treated mice. In kidneys from both groups, pendrin labeling was observed over the apical region of a subset of cells within the iCT and the CNT (Figures 2a and 1b), as described previously.10,11 Within the CCD, pendrin immunoreactivity was present over apical cytoplasmic vesicles, a subapical band free of vesicles, and abundant mitochondria (Figure 3a).10 In control animals, the ultrastructural features and distribution of pendrin immunolabel were similar to our previous observations.10 Pendrin immunoreactivity was prevalent over apical cytoplasmic vesicles, but little immunolabel was present along the apical plasma membrane (Figure 3b). However, in DOCP-treated mice, type B intercalated cells typically exhibited a marked increase in apical plasma membrane microprojections and intense pendrin immunolabel along the apical plasma membrane (Figure 4). Morphometric analysis (Table 1) demonstrated more than a 2-fold increase in apical plasma membrane boundary length in type B cells from DOCP-treated mice relative to controls, and a 2-fold increase in pendrin label density along the apical plasma membrane. Thus, a 6-fold increase in pendrin immunolabel along the apical plasma membrane of the type B cell was measured. Moreover, the ratio of immunolabel in the apical plasma membrane to label in the cytoplasm and cytoplasmic vesicles increased 8-fold. However, no significant change in total pendrin labeling in type B intercalated cells was noted in mice treated with DOCP. We conclude that DOCP treatment induces a marked shift in the subcellular distribution of pendrin in the type B intercalated cell of the CCD, resulting in increased expression of pendrin in the apical plasma membrane with little change in total pendrin protein expression per cell.

The effect of DOCP on the distribution of pendrin in non-A, non-B intercalated cells differed from its effect in type B intercalated cells (Table 1). In non-A, non-B intercalated cells from mice treated with DOCP, boundary length did not change; however, pendrin label in the apical plasma membrane increased 2-fold owing to increased density of pendrin labeling. Moreover, total pendrin label per cell was increased 2-fold in this cell type.

In mouse CCDs, we had observed previously that the majority of non-A intercalated cells are type B intercalated cells.5 Thus, pendrin protein expression in the apical plasma membrane and apical cytoplasmic vesicles was quantified in type B intercalated cells from both untreated and DOCP-treated mice by immunogold cytochemistry, transmission electron microscopy, and morphometric analysis. Type B cells typically exhibit a smooth apical plasma membrane surface, numerous cytoplasmic vesicles, a subapical band free of vesicles, and abundant mitochondria (Figure 3a).10 In control animals, the ultrastructural features and distribution of pendrin immunolabel were similar to our previous observations.10 Pendrin immunoreactivity was prevalent over apical cytoplasmic vesicles, but little immunolabel was present along the apical plasma membrane (Figure 3b). However, in DOCP-treated mice, type B intercalated cells typically exhibited a marked increase in apical plasma membrane microprojections and intense pendrin immunolabel along the apical plasma membrane (Figure 4). Morphometric analysis (Table 1) demonstrated more than a 2-fold increase in apical plasma membrane boundary length in type B cells from DOCP-treated mice relative to controls, and a 2-fold increase in pendrin label density along the apical plasma membrane. Thus, a 6-fold increase in pendrin immunolabel along the apical plasma membrane of the type B cell was measured. Moreover, the ratio of immunolabel in the apical plasma membrane to label in the cytoplasm and cytoplasmic vesicles increased 8-fold. However, no significant change in total pendrin labeling in type B intercalated cells was noted in mice treated with DOCP. We conclude that DOCP treatment induces a marked shift in the subcellular distribution of pendrin in the type B intercalated cell of the CCD, resulting in increased expression of pendrin in the apical plasma membrane with little change in total pendrin protein expression per cell.

Figure 1. Effect of DOCP on pendrin expression in the cortical labyrinth. a, Pendrin labeling in the cortical labyrinth from an untreated mouse (Series 1). Distribution of pendrin immunolabel is similar to that reported previously.10 A subpopulation of cells in the iCT and CNT (arrows) exhibits intense apical immunoreactivity for pendrin even under basal conditions. b, Pendrin immunolabeling in a subpopulation of cells (arrows) in the iCT and CNT from a mouse treated with DOCP. By light microscopy, pendrin labeling was similar in the cortical labyrinth of control and DOCP-treated mice.

Figure 2. Effect of DOCP on pendrin expression in medullary rays. a, Pendrin immunolabeling in the CCD from an untreated mouse (Series 1). Pendrin labeling was observed in a subset of cells within the CCD, as observed previously. b, Pendrin labeling in the cortical labyrinth from a mouse treated with DOCP. Pendrin immunolabel was present in a subpopulation of cells in the CCD (arrows), as in control animals, but the apical label appeared to be more intense and more discrete in mice treated with DOCP.
We conclude that pendrin apical plasma membrane label density is increased by DOCP treatment to a similar extent in type B intercalated cells and in non-A, non-B intercalated cells. However, pendrin expression in the apical plasma membrane is increased to a greater extent in type B intercalated cells than in non-A, non-B cells because of the marked increase in apical plasma membrane boundary length that occurs in the type B cell after administration of this aldosterone analogue.

**Effect of DOCP on Pds (+/+)** and **Pds (-/-)** Mice

Because pendrin is upregulated with DOCP, further studies investigated whether a renal phenotype is unmasked in *Pds (-/-)* mice treated with aldosterone analogues (Figures 5 and 6 and Table 2). In the absence of DOCP, after 7 days of paired intake of the gelled diet, systolic blood pressure was similar in *Pds (+/+)* and *Pds (-/-)* mice. Moreover, weight was unchanged in both groups over the treatment period (Figure 5). When mice were treated with DOCP and then ate the gelled diet for 6 days, wild-type mice gained weight and became hypertensive, whereas *Pds (-/-)* mice treated with DOCP had no change in blood pressure and did not gain weight, despite an identical intake of the diet during this period (79.2±2.9 g, *Pds (+/+)*; 78.8±2.3 g, *Pds (-/-)*; *P*=NS, Figure 5). Table 2 shows that serum electrolytes and 24-hour urinary NaCl excretion were the same in wild-type and *Pds (-/-)* mice 7 days after administration of DOCP. Thus, pendrin is critical in the process of DOCP-induced hypertension and weight gain.

Because pendrin transports HCO$_3$\textsuperscript{-}, arterial blood gases were measured in *Pds (+/+) and (+/-) mice. In the absence of DOCP, arterial pH and calculated HCO$_3$\textsuperscript{-} were similar in both groups. After DOCP treatment, both *Pds (+/+) and Pds (-/-) mice developed metabolic alkalosis. However, the metabolic alkalosis was more severe in DOCP-treated *Pds (-/-) mice. Seven days after DOCP treatment, *Pds (-/-) mice had a lower urinary pH than did wild-type mice, although net acid excreted over 24 hours was similar. We conclude that pendrin attenuates DOCP-induced metabolic alkalosis.

**Discussion**

Aldosterone is critical to the regulation of both net acid secretion and absorption of NaCl along the collecting duct. In the CCD, aldosterone administration in vivo leads to increased secretion of HCO$_3$\textsuperscript{-} and K$^+$. Aldosterone administration in vivo also increases absorption of NaCl through...
upregulation of the Na\(^+\) channel ENaC,\(^{23}\) the thiazide-sensitive NaCl cotransporter,\(^{24}\) and the Na,K-ATPase,\(^ {25}\) which causes Na\(^+\)/H\(^+\) retention and increased blood pressure. Which renal Cl\(^-\) transporters are regulated by aldosterone is poorly understood. Moreover, the extent to which aldosterone-induced hypertension occurs through changes in Cl\(^-\)-transporter expression in the kidney is unknown.\(^ {26}\) To our knowledge, this study is the first to show a role for a Cl\(^-\)-transporter in aldosterone-induced hypertension.

Administration of aldosterone in vivo induces a dramatic increase in both Cl\(^-\) absorption and HCO\(_3\)^- secretion in the CCD. After DOC administration in vivo, the Cl\(^-\) concentration in the collected luminal fluid of rabbit CCD drops to 89 mEq/L from

### Table 1. Subcellular Distribution of Pendrin Labeling in Type B and Non-A, Non-B Intercalated Cells

<table>
<thead>
<tr>
<th></th>
<th>Type B</th>
<th></th>
<th>Non-A, Non-B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=6)</td>
<td>DOCP (n=5)</td>
<td>Control (n=5)</td>
</tr>
<tr>
<td>Apical plasma membrane boundary length ×10(^{-2}) mm</td>
<td>1.018±0.117</td>
<td>2.640±0.459*</td>
<td>3.545±0.456</td>
</tr>
<tr>
<td>Apical plasma membrane label density, gold particles/mm Apical membrane</td>
<td>893±134</td>
<td>1900±340*</td>
<td>1198±58</td>
</tr>
<tr>
<td>Gold label along apical plasma membrane, gold particles/cell</td>
<td>9.3±2.0</td>
<td>55.7±16.2*</td>
<td>41.6±4.0</td>
</tr>
<tr>
<td>Gold label over cytoplasm and cytoplasmic vesicles, gold particles/cell</td>
<td>75.8±8.4</td>
<td>53.7±6.8</td>
<td>42.3±5.0</td>
</tr>
<tr>
<td>Cytoplasmic label density, gold particles ×10(^3)/mm(^2)</td>
<td>1870±216</td>
<td>1413±185</td>
<td>830±88</td>
</tr>
<tr>
<td>Subcellular label redistribution ratio, apical plasma membrane gold/cytoplasmic gold</td>
<td>0.130±0.028</td>
<td>1.211±0.426*</td>
<td>1.074±0.208</td>
</tr>
<tr>
<td>Total gold/cell</td>
<td>85.0±8.9</td>
<td>109.4±12.8</td>
<td>83.9±3.4</td>
</tr>
</tbody>
</table>

*P<0.05.

![Figure 5](image1.png)

**Figure 5.** Effect of DOCP on body weight and systolic blood pressure in Pds (-/-) and Pds (+/+ ) mice. All mice were pair-fed a balanced, high-salt, gelled diet. Some mice were treated with DOCP. After 7 days of diet alone or diet plus DOCP, systolic blood pressure and weight change for the treatment period were measured.

![Figure 6](image2.png)

**Figure 6.** Effect of DOCP on arterial pH, Pco\(_2\), and HCO\(_3\)^- in Pds (-/-) and Pds (+/+ ) mice. Mice were treated as described in the legend to Figure 5. After 7 days of diet alone or diet plus DOCP, arterial blood gases were measured.
membrane of the type B intercalated cell and a 6-fold increase in pendrin immunoreactivity in the apical plasma membrane. After DOCP treatment, we observed a study is the first to demonstrate regulation of pendrin by an aldosterone analogue. Across intercalated cells, aldosterone-stimulated, active Cl⁻ absorption downregulated in models of metabolic acidosis, eg, with NH₄Cl and pendrin protein expression are both pendrin and the putative apical anion exchanger of the type B intercalated cell transport Cl⁻ and HCO₃⁻. Both apical anion-exchange activity and pendrin protein expression are downregulated in models of metabolic acidosis, eg, with NH₄Cl ingestion, and are upregulated in models of metabolic alkalosis, eg, with NaHCO₃ ingestion. Apical anion exchange in the CCD is also upregulated by DOCP. This study is the first to demonstrate regulation of pendrin by an aldosterone analogue. After DOCP treatment, we observed a 6-fold increase in pendrin immunoreactivity in the apical plasma membrane of the type B intercalated cell and a 2-fold increase in the apical plasma membrane of the non-A, non-B intercalated cell. This observation is consistent with previous reports that demonstrated greater change in pendrin expression in the type B intercalated cell than in the non-A, non-B cell with changes in acid-base balance.

Aldosterone administered in vivo is a well-established model of hypokalemic metabolic alkalosis. Thus, DOCP might upregulate pendrin indirectly through hypokalemia and/or metabolic alkalosis. However, in another model of hypokalemic metabolic alkalosis (dietary K⁺ restriction), pendrin expression is reduced in the apical plasma membrane. Thus, pendrin is not upregulated in all models of hypokalemic metabolic alkalosis. However, whether the effect of DOCP pendrin expression is a direct effect of the hormone or an indirect effect, such as through changes in vascular volume, will require examination of other treatment models.

Apical Na⁺-independent Cl⁻/HCO₃⁻ exchange of the type B cell and pendrin participate in secretion of OH⁻ equivalents during metabolic alkalosis. In mice treated with DOCP and ingesting NaHCO₃, secretion of HCO₃⁻ in the CCD is Pds dependent. During metabolic alkalosis, CCD from wild-type, Pds (+/+) mice secrete HCO₃⁻. However, CCDs from Pds (-/-) mice absorbed HCO₃⁻ when studied under the same treatment conditions. In the present study, we observed that after DOCP treatment, Pds (-/-) mice had a more severe metabolic alkalosis than did wild-type mice, consistent with the defect in secretion of OH equivalents demonstrated previously in the CCD of Pds (-/-) mice.

We observed that Pds (+/+) mice treated with DOCP gained weight and developed hypertension. However, pair-fed, DOCP-treated Pds (-/-) mice did not become hypertensive and did not gain weight. This DOCP resistance likely occurred because of the inability of the DCT, CNT, and CCD of Pds (-/-) mice to absorb Cl⁻ fully. However, this hypothesis requires further study. Abnormalities in fluid absorption and secretion have been observed in other organ systems with disruption of the Pds gene. Patients with the Pendred syndrome and Pds-knockout mice have deafness and structural abnormalities of the inner ear, including endolympathic hydrops. In both the inner ear and kidney, pendrin might participate in the absorption of Cl⁻. The functional absence of pendrin might lead to loss of Cl⁻ in the

| TABLE 2. Serum and Urine Chemistries in Pds (-/-) and (+/+) Mice Taken 7 Days After DOCP Treatment |
|---------------------------------|---------------------------------|
|                                  | Pds (+/+) | Pds (-/-) |
| Serum                           |           |          |
| Na, mEq/L                       | 148±1 (n=5) | 149±1 (n=5) |
| K, mEq/L                        | 2.9±0.3 (n=5) | 2.8±0.2 (n=5) |
| Cl, mEq/L                       | 105±1 (n=5) | 104±1 (n=5) |
| Creatinine, mg/dL               | 0.4±0 (n=5) | 0.4±0 (n=5) |
| Blood urea nitrogen, mg/dL      | 19±2 (n=5) | 22±3 (n=5) |
| 24-Hour urine collection        |           |          |
| Urine volume, mL/24 h           | 7.7±0.5 (n=12) | 7.9±0.4 (n=9) |
| Na, mmol/24 h                   | 0.689±0.030 (n=12) | 0.757±0.031 (n=9) |
| K, mmol/24 h                    | 0.482±0.020 (n=12) | 0.487±0.021 (n=9) |
| Cl, mmol/24 h                   | 0.744±0.028 (n=12) | 0.785±0.031 (n=9) |
| Osmolality, mOsm/kg H₂O per 24 h| 4.606±0.187 (n=12) | 5.025±0.167 (n=9) |
| Urinary pH                       | 6.29±0.1 (n=12) | 5.88±0.36 (n=10) |
| P₀, mmol/24 h                   | 0.0356±0.0045 (n=9) | 0.0374±0.0053 (n=6) |
| ΔH₂PO₄ (at measured and neutral pH), mmol/24 h | 0.0184±0.0031 (n=9) | 0.0259±0.0038 (n=6) |
| NH₄⁺, mmol/24 h                 | 0.333±0.032 (n=9) | 0.320±0.03 (n=6) |
| Net acid excretion, mmol/24 h   | 0.3510±0.033 (n=9) | 0.346±0.029 (n=6) |

Data are displayed as mean±SE. *P<0.05.
urine and retention of Cl in the endolymphatic fluid of the ear. The endolymphatic sac of the ear contains mitochondria-rich, type A–like cells that express the H-ATPase on the apical plasma membrane and type B–like cells that express pendrin on the apical plasma membrane. Thus, cells of the endolymphatic sac resemble renal intercalated cells both ultrastructurally and functionally. It is likely that with 7 days of DOCP treatment, the cumulative excretion of NaCl and net acid differ in Pds (+/+), and (+/-) mice. However, because 24-hour urinary NaCl and net acid excretion did not differ between the 2 groups of mice after 7 days of DOCP treatment, differences in excretion most likely occurred within the first 6 days of DOCP administration. In conclusion, Pds protein and mRNA expression are upregulated in parallel in mouse kidney after DOCP administration. Moreover, DOCP treatment increases expression of pendrin in the apical plasma membrane in non-A, non-B and type B intercalated cells. Pendrin attenuates aldosterone-induced metabolic alkalosis by augmenting secretion of OH equivalents. Pendrin-dependent Cl uptake likely contributes to aldosterone-induced fluid retention and hypertension.

**Perspectives**

The present study is the first to demonstrate a role for pendrin in mineralocorticoid-induced hypertension. Moreover, this study raises the possibility that pendrin could be the target of future antihypertensive and/or diuretic drugs.

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