Cortical distal nephron Cl⁻ transport in volume homeostasis and blood pressure regulation

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¹Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; ²Department of Physiology, Emory University School of Medicine, Atlanta, Georgia; ³Department of Physiology, Weill Medical College of Cornell, New York, New York; and ⁴Department of Physiology and Biophysics, Weill Medical College of Cornell, New York, New York

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Wall SM, Weinstein AM. Cortical distal nephron Cl⁻ transport in volume homeostasis and blood pressure regulation. Am J Physiol Renal Physiol 305: F427–F438, 2013. First published May 1, 2013; doi:10.1152/ajprenal.00022.2013.—Renal intercalated cells mediate the secretion or absorption of Cl⁻ and OH⁻/H⁺ equivalents in the connecting segment (CNT) and cortical collecting duct (CCD). In so doing, they regulate acid-base balance, vascular volume, and blood pressure. Cl⁻ absorption is either electrogenic and amiloride-sensitive or electroneutral and thiazide-sensitive. However, which Cl⁻ transporter(s) are targeted by these diuretics is debated. While epithelial Na⁺ channel (ENaC) does not transport Cl⁻, it modulates Cl⁻ transport probably by generating a lumen-negative voltage, which drives Cl⁻ flux across tight junctions. In addition, recent evidence indicates that ENaC inhibition increases electrogenic Cl⁻ secretion via a type A intercalated cells. During ENaC blockade, Cl⁻ is taken up across the basolateral membrane through the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC1) and then secreted across the apical membrane through a conductive pathway (a Cl⁻ channel or an electrogenic exchanger). The mechanism of this apical Cl⁻ secretion is unresolved. In contrast, thiazide diuretics inhibit electroneutral Cl⁻/HCO₃⁻ exchange mediated by a Na⁺-dependent Cl⁻/HCO₃⁻ exchange. The relative contribution of the thiazide and the amiloride-sensitive components of Cl⁻ absorption varies between studies and probably depends on the treatment model employed. Cl⁻ absorption increases markedly with angiotensin and aldosterone administration, largely by upregulating the Na⁺-dependent Cl⁻/HCO₃⁻ exchanger pendrin. In the absence of pendrin [Slc26a4⁻/⁻ or pendrin null mice], aldosterone-stimulated Cl⁻ absorption is significantly reduced, which attenuates the pressor response to this steroid hormone. Pendrin also modulates aldosterone-induced changes in ENaC abundance and function through a kidney-specific mechanism that does not involve changes in the concentration of a circulating hormone. Instead, pendrin changes ENaC abundance and function, at least in part, by altering luminal HCO₃⁻. This review summarizes mechanisms of Cl⁻ transport in CNT and CCD and how these transporters contribute to the regulation of extracellular volume and blood pressure.

Slc26a4; Pds; Cl⁻/HCO₃⁻ exchange; ENaC; pendrin; intercalated cells; blood pressure

DISTAL NEPHRON NaCl TRANSPORT is crucial to the renal regulation of extracellular volume. During volume contraction, distal nephron NaCl absorption increases, which restores extracellular volume to basal levels. Conversely, during volume overload, distal nephron NaCl absorption appropriately falls. Genetically defined models of hypertension are often associated with expanded extracellular volume due to derangements in distal NaCl transporters, which inappropriately increases distal NaCl absorption. Therefore, “essential” hypertension may result from occur as-of-yet-unrecognized, inherited transport defects in this region of the nephron.

The bulk of distal NaCl transport occurs in the cortex, within the distal convoluted tubule (DCT), connecting segment (CNT), and cortical collecting duct (CCD). However, the medullary collecting duct performs the final regulation of NaCl balance. The structure of the rat distal nephron is shown in Fig. 1. In this region, 36,000 DCTs transition to CNT and then merge in arcades to form ~7,200 CCDs (41). The “distal tubule” employed in micropuncture studies localizes to the superficial cortex and is made up of CNTs, which are branched, and DCTs, which are unbranched. Solute transport within these segments has been quantified using a variety of techniques, including micropuncture and electrophysiology of rat DCT and CNT as well in rat and rabbit CCDs perfused in vitro. More recently, these techniques have been extended to the study of genetically modified mice. In so doing, changes in solute transport can be quantified following the ablation of individual

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transporters or ablation of various components of a signaling pathway, thereby establishing the physiological significance of these transporters and/or signaling pathways.

Na\(^+\) absorption by the CCD and CNT is critical not only for NaCl balance but also for the regulation of K\(^+\) and H\(^+\) secretion. To facilitate the bookkeeping for all aspects of NaCl absorption, mathematical models of the distal nephron segments were developed. By collating data generated by a number of laboratories, these models stitched together an integrated picture of NaCl transport by the cortical distal nephron (109). While comprehensive reviews have focused on NaCl transport within the CNT and CCD, this review focuses instead on the loci and regulation of Cl\(^-\) transport within the CNT and CCD.

**NaCl Transport in the Micropuncture-Defined Distal Tubule**

“Distal delivery” refers to flow at the most proximal portion of the DCT that is accessible to micropuncture. Distal Na\(^+\) delivery should be just below 10% of the filtered load, assuming that early distal volume flow rate is ~20% of the glomerular filtration rate and that luminal Na\(^+\) concentration is just slightly less than half that of plasma (11, 14, 22, 35, 52, 86). Of the 10% of the filtered load that reaches the most proximal portion of the DCT, ~75% is absorbed before reaching the collecting duct. Therefore, ~6–8% (or three-fourths of 10%) of the filtered load is absorbed along the DCT and CNT. This component of the filtered load of Na\(^+\) is absorbed more or less equally along the early and late portions of the accessible distal tubule (10). Therefore, 3–4% of filtered Na\(^+\) load is absorbed along the 1-mm length of the DCT and another 3–4% of the filtered Na\(^+\) load is absorbed along the 1-mm length CNT. This implies a Na\(^+\) transport rate of 170 pmol·min\(^{-1}\)·mm\(^{-1}\) along the CNT and DCT, which is about half the transport rate observed in rat proximal tubule (Table 1). The rates of Na\(^+\) absorption, however, are dependent on filtered load and can vary severalfold. Na\(^+\) absorption depends on luminal NaCl concentration in both early and late segments, although Cl\(^-\) absorption is sensitive to luminal NaCl only in the early segment (16). K\(^+\) secretion occurs primarily in late segments (96) and can be a substantial fraction of Na\(^+\) flux. K\(^+\) secretion is also dependent on the anion composition of the luminal fluid. For example, K\(^+\) secretion doubles when gluconate is substituted for Cl\(^-\) in the luminal solution (96).

The mechanism of ion transport in the distal nephron and collecting duct was examined in greater detail in studies that employed CCDs perfused in vitro. While most initial work was done in rabbit tubules, several studies were done in rat CCD. With the explosion in genetically modified mice, this technique has been applied much more in recent years to the study of mice. Data from these studies are summarized in Table 2. The salient observation is that Na\(^+\) transport in the CCD is variable and greatly depends on hormonal stimulation of the tubule. Moreover, Na\(^+\) absorption in the CCD is only about half of that found in the CNT, even when stimulated. K\(^+\) secretion is also variable and highly regulated by aldosterone. K\(^+\) secretion may be much smaller than Na\(^+\) flux, making NaCl absorption dominant. Conversely, K\(^+\) and Na\(^+\) flux may be similar in magnitude, such that Na\(^+\)/K\(^+\) countertransport is dominant. Because CNTs merge to become the CCD, total tubule length in vivo is sixfold greater in the CNT than in the CCD. Collectively, these data strongly suggest that NaCl absorption and K\(^+\) secretion in vivo are at least an order of magnitude greater in the CNT than that in CCD.

Each of the distal nephron segments from rat kidney have been simulated in mathematical models, which represent the fluxes and permeabilities of Na\(^+\), K\(^+\), Cl\(^-\), and H\(^+\)/OH\(^-\).
equivalents (110–114). These segmental models were subsequently integrated into a model of the full distal nephron. Luminal solute concentrations and flows predicted by the model are displayed in Fig. 2 (109). The model predicts that the bulk of the cortical NaCl absorption occurs in the DCT and CNT and that virtually all distal K⁺ secretion occurs in the CNT. Much lower rates of Na⁺ absorption are expected within the CCD relative to the CNT, since the CCD has a low luminal Na⁺ concentration and a high lumen-negative transepithelial voltage, which should reduce Na⁺ absorption. Moreover, the high luminal K⁺ concentration expected in the CCD should greatly attenuate K⁺ secretion in this segment. Net Cl⁻ transport in the CNT is also predicted to be much lower in the CCD than in the CNT. However, the CCD likely has an important role in fine-tuning distal NaCl absorption and K⁺ secretion and is an important experimental model for examining distal nephron transport.

**Paracellular Cl⁻ Absorption in the CCD and CNT**

While principal cells mediate electrogenic Na⁺ absorption through the epithelial Na⁺ channel (ENaC; Ref. 25), transepithelial Cl⁻ absorption is thought to be both paracellular (via tight junctions) and transcellular (across intercalated cells; Ref. 62). Paracellular Cl⁻ flux is electrically and driven by transepithelial electrical potential. However, the quantitative importance of paracellular Cl⁻ transport in CNT and CCD is uncertain, in part due to the changing ion concentrations along the tubule and due to the difficulty of dissecting CNTs and making these measurements. ENaC mediates Na⁺ absorption across the apical membrane of principal cells, which provides the driving force for K⁺ secretion through luminal K⁺ channels (25). The lumen-negative potential generated by ENaC also provides a driving force for Cl⁻ absorption across tight junctions and lateral intercellular spaces (106). ENaC inhibitors, such as amiloride or benzamil, eliminate the lumen-negative transepithelial voltage, which is thought to reduce Cl⁻ absorption by eliminating the driving force for paracellular Cl⁻ absorption (74, 106).

By freeze-fracture or transmission electron microscopy, tight junctions appear as fusions of opposing plasma membrane (40). Tight junctions are made up of transmembrane proteins that include occludins, claudins, and junctional adhesion molecules (31). Claudins interact with the cell membrane and between adjacent cells to form strands within tight junctions (30). Within the mouse and human kidney, claudins 3, 4, 7, 8, and 18 are found in the connecting tubule and in the collecting duct (30, 40). Claudins from both a paracellular barrier and a paracellular pore (30, 34). Claudin 4 is thought to be a pore

### Table 1. Solute flux rates obtained from early and late distal microperfusion of rat kidney

<table>
<thead>
<tr>
<th>Perfusion, nL/min</th>
<th>Perfusate Concentrations, mM</th>
<th>Early Reabsorption, pmol·min⁻¹·mm⁻¹</th>
<th>Late Reabsorption, pmol·min⁻¹·mm⁻¹</th>
<th>Condition</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET LT Na K Cl</td>
<td>Na K Cl</td>
<td>Na K Cl</td>
<td>Na K Cl</td>
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<tr>
<td>5.9 6.4</td>
<td>80 2</td>
<td>87 0</td>
<td>123</td>
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<tr>
<td>12.8 13.3</td>
<td>75 2</td>
<td>68 0</td>
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<td>115</td>
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</tr>
<tr>
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<td>4.5</td>
<td>110 25</td>
<td></td>
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<td>105</td>
</tr>
<tr>
<td>10.2 150</td>
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<td>0 25</td>
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<tr>
<td>12.8 13.3</td>
<td>75 2</td>
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<tr>
<td>13.2 14.5</td>
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<td>–110</td>
</tr>
<tr>
<td>10.1 9.8</td>
<td>150 4.5</td>
<td>110 25</td>
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<tr>
<td>12.3 12.3</td>
<td>75 2</td>
<td>2 15</td>
<td>29.2</td>
<td>29.2</td>
<td>28.6</td>
</tr>
<tr>
<td>12.4 12.2</td>
<td>70 2</td>
<td>59 15</td>
<td>32.9</td>
<td>32.9</td>
<td>10.7</td>
</tr>
<tr>
<td>12.1 12.1</td>
<td>70 2</td>
<td>59 15</td>
<td>150 –54.1</td>
<td>106 –88.3</td>
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<tr>
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<td>59 15</td>
<td>264 –59.3</td>
<td>208 –40.7</td>
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<tr>
<td>12.3 12.3</td>
<td>70 2</td>
<td>59 15</td>
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</tr>
<tr>
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<td>26 28</td>
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<td>–14 18</td>
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<tr>
<td>8.1 56 2</td>
<td>26 28</td>
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<td></td>
<td>–18 45</td>
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<tr>
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<td>26.0</td>
<td>26.0</td>
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<tr>
<td>Stationary 125 5</td>
<td>107 25</td>
<td>74.0</td>
<td>74.0</td>
<td>73.0</td>
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</tr>
</tbody>
</table>

ET and LT, early and late segments, respectively.

### Table 2. Solute flux rates measure in isolated perfused cortical collecting ducts of rat kidney

<table>
<thead>
<tr>
<th>Perfusion, nL/min</th>
<th>Perfusate Concentrations, mM</th>
<th>Condition</th>
<th>Absorption, pmol·min⁻¹·mm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na K Cl</td>
<td>Na K Cl</td>
<td>AVP Aldo</td>
<td>Na K Cl</td>
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<td>--------------------------</td>
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<tr>
<td>1.7 1.7</td>
<td>144 4.0</td>
<td>118 25</td>
<td>+</td>
</tr>
<tr>
<td>1.7 1.7</td>
<td>146 4.0</td>
<td>118 25</td>
<td>+</td>
</tr>
<tr>
<td>6–12</td>
<td>136.3 5.0</td>
<td>139 3.5</td>
<td>+</td>
</tr>
<tr>
<td>10–20</td>
<td>90.8 5.0</td>
<td>97 3.6</td>
<td>+</td>
</tr>
<tr>
<td>1.9</td>
<td>148 5</td>
<td>105 25</td>
<td>+</td>
</tr>
<tr>
<td>10–20</td>
<td>94 6</td>
<td>118 25</td>
<td>+</td>
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<tr>
<td>6–12</td>
<td>146 4.0</td>
<td>118 25</td>
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<tr>
<td>1.9</td>
<td>148 5</td>
<td>105 25</td>
<td>+</td>
</tr>
</tbody>
</table>
claudin since knockdown of this protein reduces paracellular permeability and increases transepithelial resistance in heterologous expression systems (30). In contrast, claudin 7 is considered to be a barrier claudin since knockdown of this protein reduces transepithelial resistance in heterologous expression systems (30, 34). Moreover, mice with genetic ablation of claudin 7 have severe renal salt wasting, which may be due to compromised barrier function of renal tight junctions (90). However, since most of these studies were done in cell culture and since the effect of claudin expression on transepithelial resistance and paracellular permeability depends on the cell line used to overexpress these claudins (30), additional studies in native tissue are needed.

Certain mutations in the serine theonine kinases with no lysines WNK1 and WNK4 produce pseudohypoaldosteronism (PHAII), a condition associated with hypertension and hyperkalemia. WNK4 modulates blood pressure and K⁺ (PHAII), a condition associated with hypertension and hyperkalemia. WNK4 modulates blood pressure and K⁺ (PHAII), a condition associated with hypertension and hyperkalemia. WNK4 also regulates paracellular permeability and increases K⁺ secretion, despite the increase in total Cl⁻ absorption that follows the administration of aldosterone in vivo (62).

The quantitative importance of tight junctional Cl⁻ flux depends on the permeability of this pathway. In turn, permeability depends on the relationship of ion flux to its electrochemical driving force. In renal epithelial models, paracellular ion flux, J (mmol/s·cm²) is calculated from the Goldman relation:

\[ J = h \cdot \zeta \cdot \left( \frac{C_a - C_e e^{-\zeta}}{1 - e^{-\zeta}} \right) \]

where \( C_a \) and \( C_e \) are luminal and peritubular ion concentrations (mM), \( h \) (cm/s) is the tight junctional ion permeability, and \( (\Psi_a - \Psi_b) \) is the transepithelial electrical potential difference (mV). In this formulation, \( \zeta \) is a normalized electrical potential, obtained by application of the ion valence, \( z = -1 \), the Faraday, \( F = 96.5 \text{ C/mmol} \), and the product of the gas constant and absolute temperature, \( RT = 2.57 \text{ J/mmol} \). With this notation, the ionic current, \( I = zFJ \), and the ionic conductance, \( G \) (mS/cm²) is

\[ G = \frac{\partial I}{\partial \psi} = \frac{z^2F^2}{RT} \frac{\partial J}{\partial \zeta} \]

Therefore, while permeability is a basic attribute of the permeation pathway, conductance depends on the ambient solute concentrations and the electrical potential itself. This formula allows translation between electrophysiologic conductance measurements and solute permeability determinations.

Mathematical models of rabbit (88) and rat CCD (110) predict that the low luminal Na⁺ concentration observed experimentally is critically dependent on a very low tight junctional Na⁺ permeability. However, tight junctional permeability is difficult to quantify, particularly under physiological conditions. Junctional conductance was measured in the rabbit, and rat CCD has been used to predict paracellular NaCl transport. CCD tight junctions are slightly more selective for Cl⁻ than Na⁺, since the Cl⁻-/Na⁺ conductance ratio is about 1.2–1.3 (74, 106), and total junctional conductance is higher in rat than in rabbit CCD (i.e., 11–13 vs. 1.2–1.3 mS/cm²; Refs. 45, 55, 57, 74, 106). Permeability is also greater for Cl⁻ than Na⁺ in both rat and rabbit CCD (75, 77). The model of rat CCD (110) employed a tight junctional Cl⁻ permeability of 6 × 10⁻⁶ cm/s, which yields a Cl⁻ conductance of 2.5 mS/cm². Junctional permeabilities of rat CNT were taken to be twice those measured in the CCD (112). With the use of these values, Cl⁻ absorption in the rat CNT was predicted to be 1.5 μmol/min for the ensemble of coalescing tubules, which is ~35 pmol·min⁻¹·mm⁻¹ per tubule. If one assumes that luminal Cl⁻ concentration is about half that of plasma and that transepithelial voltage is approximately ~32 mV, the model predicts that ~50% of CNT Cl⁻ absorption is
paracellular, while the other 50% is transcellular. However, because junctional permeability can only be estimated and because luminal Cl⁻ concentration along the CNT is variable, the magnitude of the paracellular and transcellular components of Cl⁻ absorption in the CNT is not precisely known. For rat CCD, the model predicts that as luminal Cl⁻ increases from 36 to 80 mM along the length of the tubule, tight junctional Cl⁻ flux will increase from 2.9 to 19.2 pmol·min⁻¹·mm⁻¹ while transepithelial flux of Cl⁻ across the type B cell will remain relatively constant at 5.4 pmol·min⁻¹·mm⁻¹ (110). Thus the model predicts that transepithelial transport of Cl⁻ across type B cells is similar in magnitude to that of tight junctional Cl⁻ flux in rat CCD.

Cell Types and Transporters Present in the CCD

The rodent CCD is made up of two cell types: principal and intercalated cells. Intercalated cells are classified as type A, type B, or non-A, non-B cells based on the expression of the Cl⁻/HCO₃⁻ exchanger, AE1, and the subcellular distribution of the H⁺-ATPase within the cell (1, 7, 37, 91) (Fig. 3). The distribution of these transporters predicts whether an intercalated cell secretes H⁺ or OH⁻ equivalents (18, 79). Type A intercalated cells secrete H⁺ equivalents through the apical plasma membrane H⁺-ATPase (1, 91), which acts in series with a kidney-specific splice variant of the red cell anion exchanger (AE1) expressed on the basolateral plasma membrane (1). These transporters are upregulated during metabolic acidosis (4, 21), which increases secretion of H⁺ equivalents, thereby attenuating the acidosis.

Type B intercalated cells express Na⁺-independent, electroneutral, Cl⁻/HCO₃⁻ exchange on the apical plasma membrane, which is mediated primarily by pendrin (2, 70). Within the aldosterone-sensitive distal nephron, i.e., DCT, CNT, and CCD, pendrin is found in the apical regions of type B and non-A, non-B intercalated cells (Fig. 3) (38, 70, 102). Pendrin gene ablation markedly reduces but does not eliminate apical Cl⁻/HCO₃⁻ exchange in mouse CCD (2). Since pendrin-positive intercalated cells do not express AE1 and do not express the H⁺-ATPase in the apical regions, pendrin has been used as a marker of type B and non-A, non-B intercalated cells (38, 70, 102). In type B cells, apical Cl⁻/HCO₃⁻ exchange acts in series with the H⁺-ATPase on the basolateral plasma membrane (1, 18, 37, 84, 91) to mediate secretion of OH⁻ equivalents into the luminal fluid. When these B-cell transporters are upregulated, HCO₃⁻ secretion increases (70, 79), which helps correct a metabolic alkalis

The functional distinction of intercalated cell subtypes is not predicted fully by H⁺-ATPase subcellular distribution, however. Type A cells are identified by H⁺-ATPase labeling on the apical plasma membrane and in subapical vesicles and AE1 labeling on the basolateral membrane. Cells with these properties account for 50–64% of intercalated cells in the mouse CCD (37, 91). Type B cells of mouse CCD are identified by with basolateral or diffuse H⁺-ATPase labeling and apical pendrin labeling and account for the other 46–50% of intercalated cells (37, 38, 91, 102). Functional data taken from mouse and rabbit CCDs perfused in vitro have shown that apical Na⁺-independent Cl⁻/HCO₃⁻ exchange is observed in 90% of intercalated cells, while only 4–14% of intercalated cells lack Na⁺-independent apical anion exchange (type A) (17, 19). Since the abundance of intercalated cells with apical Na⁺-independent Cl⁻/HCO₃⁻ exchange activity greatly exceeds the abundance of intercalated cells that express pendrin and since pendrin gene ablation reduces but does not eliminate apical Cl⁻/HCO₃⁻ exchange in intercalated cells, Na⁺-independent apical Cl⁻/HCO₃⁻ exchange occurs through pendrin-independent pathways. One such candidate is Slc4a11, which
is expressed in the apical regions of type A cells and acts as an electronegic $\text{Cl}^-/\text{HCO}_3^-$ exchanger or a $\text{Cl}^-$ channel (Fig. 3) (117).

**Transepithelial Transport of $\text{Cl}^-$ Through Electrogenic and Electroneutral Pathways**

In the CCD, transepithelial transport of $\text{Cl}^-$ occurs primarily across intercalated cells rather than across principal cells (76). However, intercalated cells, unlike principal cells, do not have a significant transcellular conductance (106). Instead, Stoner et al. (87) noted 4 decades ago that most $\text{Cl}^-$ flux in the CCD is electrically silent. Further work by Schuster and Stokes (80) demonstrated that $\text{Cl}^-$ absorption occurs through $\text{Cl}^-/\text{Cl}^-$ or $\text{Cl}^-/\text{HCO}_3^-$ exchange. Weiner and Hamm (107), Emmons and Kürz (19), and Star et al. (84) demonstrated electroneutral, $\text{Na}^+$-independent $\text{Cl}^-/\text{HCO}_3^-$ exchange across the apical plasma membrane of intercalated cells. Thus under most experimental conditions, most $\text{Cl}^-$ absorption in the CCD occurs through electroneutral anion exchange, rather than through a conductive pathway (87). Electroneutral $\text{Cl}^-/\text{HCO}_3^-$ exchange is a tightly controlled process that is upregulated by cAMP (78), aldosterone (24), angiotensin II (108), carbonic anhydrase (54), and CO$_2$ (54).

While $\text{Cl}^-$ absorbed by electroneutral, $\text{Na}^+$-independent $\text{Cl}^-/\text{HCO}_3^-$ exchange occurs independent of electrical potential, there is an electrical impact of coordinated intercalated cell transport. In non-A, non-B cells, the apical membrane expresses both the $\text{H}^+$/ATPase and pendrin-mediated $\text{Na}^+$-independent $\text{Cl}^-/\text{HCO}_3^-$ exchange, which leads to the secretion of $\text{H}^+$ and $\text{HCO}_3^-$ in tandem by this cell type. $\text{H}^+$ and $\text{HCO}_3^-$ are also secreted in tandem vis-à-vis the apical $\text{H}^+$/ATPase in type A cells and through apical $\text{Cl}^-$/HCO$_3^-$ exchange in type B intercalated cells, acting in parallel. In both of these models, neutral CO$_2$ is generated, which is absorbed with $\text{Cl}^-$. Thus intercalated and principal cells act together to mediate the absorption of NaCl with little change in net secretion of $\text{H}^+$ or $\text{OH}^-$ equivalents. This scheme predicts that during volume depletion, transporters within type A and type B cells or within non-A, non-B cells are upregulated, which greatly increases NaCl absorption without significantly changing net $\text{H}^+$ flux. This is illustrated quantitatively in Fig. 4, which displays calculations using the CCD model of Weinstein (110). In Fig. 4, CCD transport rates for Na$^+$, K$^+$, Cl$^-$, and HCO$_3^-$ are displayed for a 2-mm tubule segment in which a late distal fluid enters at 3 nl/min. When only principal cell transport is scaled up, Na$^+$ transport increases and K$^+$ flux changes from net absorption to net secretion. $\text{Cl}^-$ absorption also increased due to increased paracellular flux, driven by the lumen-negative transepithelial voltage. As type B-cell function increases further, $\text{Cl}^-$ absorption continues to rise but with the appearance of net HCO$_3^-$ secretion. With increased type A-cell function, $\text{H}^+$ secretion increases, which limits the rise in luminal HCO$_3^-$ concentration that follows $\text{Cl}^-$/HCO$_3^-$ exchange-mediated HCO$_3^-$ secretion. Moreover, $\text{H}^+$ secretion should shunt the current generated by ENaC-mediated Na$^+$ absorption, thereby augmenting Na$^+$ absorption. Finally, K$^+$ absorption by the luminal H-K-ATPase should attenuate the net K$^+$ secretion generated by the lumen-negative voltage (81, 82).

There is functional evidence that apical $\text{Cl}^-$/HCO$_3^-$ exchange in B cells functions in parallel with the “gastric” H-K-ATPase, HKα1, encoded by ATP4α, which localizes to intercalated cells within the rat and rabbit CCD (46, 116). In this model, apical $\text{Cl}^-$/HCO$_3^-$ exchange-mediated $\text{Cl}^-$ absorption and HCO$_3^-$ secretion functions in tandem with H-K-ATPase-mediated K$^+$ absorption and $\text{H}^+$ secretion (50, 118). When these two transport processes act together, net absorption of KCl is expected without a significant change in the secretion of $\text{H}^+$ equivalents (53, 83, 118). However, since no change in renal K$^+$ handling or acid-base balance has been observed following genetic ablation of either the α5 (gastric)- or the α2 (colon)-isoforms of the H-K-ATPase (50), the significance of the H-K-ATPase isoforms in the renal excretion of K$^+$ and net acid remains to be determined (50).

$\text{Cl}^-$ absorption is mediated, in part, through an electronegative, thiazide-sensitive mechanism that is distinct from the thiazide-sensitive NaCl cotransporter expressed in the DCT (48). In mouse and rat CCD, application of thiazides to the perfusate reduces the absorption of Na$^+$, $\text{Cl}^-$, and HCO$_3^-$, without changing transepithelial voltage or K$^+$ flux (48, 92). Therefore, thiazide-sensitive $\text{Cl}^-$ absorption occurs through electroneutral, $\text{Na}^+$-dependent $\text{Cl}^-$/HCO$_3^-$ exchange (48, 92). While the gene(s) that encode this exchange process are not fully defined, Na$^+$-dependent Cl$^-$/HCO$_3^-$ exchange encoded by Scl4a8 participates in this transport pathway (48, 92) and may operate in parallel with other electroneutral Na$^+$-independent Cl$^-$/HCO$_3^-$ exchangers, such as pendin, to mediate this thiazide-sensitive electroneutral NaCl absorption (48). Whether Scl4a8 localizes to principal and/or intercalated cells is unresolved, although functional data suggest that this exchanger localizes to type B intercalated cells (48). How Scl4a8 and
pendrin might function in tandem is shown in Fig. 3 (13). In this model (13), Slc4a8 mediates NaHCO₃ absorption and Cl⁻ secretion across the apical membrane of type B intercalated cells. The secreted Cl⁻ is absorbed by pendrin-mediated apical Cl⁻/HCO₃⁻ exchange and therefore recycled. In turn, pendrin-mediated HCO₃⁻ secretion is absorbed by Slc4a8. When two pendrin (Slc26a4) molecules and one Slc4a8 molecule act in tandem, NaCl is absorbed without an appreciable change in Cl⁻ flux. However, this stoichiometry has not yet been proven experimentally.

The relative contribution of the thiazide-sensitive component of Cl⁻ absorption to total transepithelial Cl⁻ absorption varies widely depending on the treatment model employed (48, 62, 92). For example, in the CCD of salt-deprived mice, Cl⁻ absorption is thiazide-sensitive but amiloride-insensitive (48). However, following the administration of aldosterone and a NaCl-rich diet, Cl⁻ absorption is sensitive to amiloride analogs (benzamil), while a thiazide-sensitive component of Cl⁻ absorption is undetectable (62). Inhibiting the epithelial sodium channel with drugs such as amiloride or benzamil reduces Cl⁻ absorption through a mechanism separate from that of thiazide-sensitive Cl⁻ absorption that involves stimulating conductive Cl⁻ secretion, rather than directly inhibiting Cl⁻ absorption (62). This Cl⁻ secretory pathway likely localizes to type A intercalated cells, since this cell type mediates Cl⁻ secretion in the outer medullary collecting duct (OMCD) and since conductive Cl⁻ secretion is dependent on NKCC1, which localizes to type A intercalated cells in mouse CCD and OMCD (27, 62, 101). In this model, during ENaC blockade Cl⁻ is taken up across the basolateral membrane of type A intercalated cells in the CCD through the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC1) and is then secreted into the luminal fluid through a conductive pathway (Fig. 3) (62). Whether this conductive Cl⁻ secretion occurs through a channel or an electronegic transporter remains unresolved.

Following Cl⁻ absorption, Cl⁻ may exit across the basolateral membrane of type A or B cells through an exchanger or a Cl⁻ channel, such as CIC-K2. CIC-K2 is found in the basolateral regions of the thick ascending limb, the DCT, principal, and intercalated cells of the CNT and in type A and B intercalated cells of the collecting duct (Fig. 3) (33, 43, 44). Since Cl⁻ channel activity is higher in intercalated cells than in principal cells of the CCD (58) and since the biophysical properties of this intercalated cell Cl⁻ channel are more consistent with CIC-K2 than other classes of Cl⁻ channels (58), CIC-K2 is a candidate for the Cl⁻ channel activity observed on the basolateral plasma membrane of intercalated cells. Because activation mutations of CIC-K2 lead to hypertension (32), this transporter likely fosters Cl⁻ absorption. While this Cl⁻ channel may participate in the process of Cl⁻ absorption within the CCD, it may instead participate in Cl⁻ recycling across the basolateral membrane, which promotes the flux of another ion (33).

Electroneutral, Na⁺-independent Cl⁻/HCO₃⁻ exchange is observed across the basolateral membrane in the majority of intercalated cells and probably mediates Cl⁻ uptake. Of these, the best characterized is AE1, which localizes to the basolateral membrane of type A intercalated cells (Fig. 3) (1). In type A cells, the apical H⁺-ATPase appears to function in series with AE1 to mediate the secretion of net H⁺ equivalents. The source of H⁺ for apical H⁺ secretion by type A intercalated cells is CO₂ (100). Within type A intercalated cells, carbon dioxide combines with H₂O to generate H⁺ and HCO₃⁻. H⁺ is secreted across the apical membrane, which acidifies the luminal fluid, whereas HCO₃⁻ exits the cell across the basolateral membrane through Cl⁻/HCO₃⁻ exchangers, such as AE1. With elimination of AE1, an impaired ability of type A cells to secrete H⁺ equivalents is predicted. While the effect of AE1 gene ablation on total CO₂ flux has not been tested directly in mouse CCD, it is well established that AE1 gene ablation in mice and in people results in a severe metabolic acidosis (85).

**Implication of Intercalated Cell Cl⁻ Transport in the Maintenance of Extracellular Fluid Volume**

In humans, the clinical consequences of pendrin gene disruption were first described in 1896. In this landmark paper, Dr. Vaughn Pendrin described a family in which 2 of the 10 children suffered from deafness and goiter (Pendred Syndrome) (65). The gene responsible for Pendred Syndrome was reported by Everett et al. 101 yr later (20). Pendred Syndrome is now known to be an autosomal recessive disorder associated with more than 47 disease-producing allele variants of Slc26a4 (8). While pendrin has long been known to be critical in hearing and thyroid function, more recent evidence points to an important role of this transporter in the renal regulation of NaCl balance. Moreover, patients with Pendred Syndrome may be protected from the development of hypertension (51).

While Na⁺ intake is important in the pathogenesis of hypertension, in human and in rodent models of hypertension, blood pressure is also modulated by Cl⁻ intake (47). Extracellular volume expansion likely occurs in part from increased intake of Cl⁻ coupled with upregulation of renal transporters that mediate Cl⁻ absorption. Studies of transgenic mice have shown that electroneutral, Na⁺-independent Cl⁻/HCO₃⁻ exchangers, such as pendrin modulate blood pressure. Following NaCl restriction, where renin and aldosterone release are appropriately stimulated, pendrin null mice have enhanced excretion of Na⁺ and Cl⁻ and lower blood pressure relative to wild-type mice (39, 99, 103). Blood pressure is lower in pendrin null relative to wild-type mice following other treatment models, such as during selective dietary Cl⁻ restriction (99). Therefore, the lower blood pressure observed with pendrin gene ablation (39, 99, 103) occurs, at least in part, from the impaired ability of the pendrin null mice to fully conserve urinary Na⁺ and Cl⁻.

Aldosterone increases blood pressure, in part, by increasing the abundance and function of NaCl transporters such as ENaC (12) and pendrin (97) in tandem. In rats and rabbits, Cl⁻ absorption and HCO₃⁻ secretion increase markedly in CCDs following aldosterone treatment in vivo (24, 29, 42, 84). This aldosterone-induced increase in Cl⁻/HCO₃⁻ exchange occurs by upregulating apical, electroneutral, Na⁺-independent Cl⁻/HCO₃⁻ exchangers, such as pendrin (97). While B-cell apical plasma membrane pendrin immunoreactivity is low under basal conditions (97, 102), aldosterone increases apical membrane pendrin abundance sixfold, primarily through subcellular redistribution (97), which markedly increases pendrin-mediated transport (62). The Cl⁻ absorption and HCO₃⁻ secretion observed in the CCD of aldosterone-treated mice is completely dependent on pendrin, since HCO₃⁻ secretion and Cl⁻ absorption are not observed in aldosterone-treated pendrin null mice (70, 103). In the absence of pendrin (pendrin null mice), a
blunted hypertensive response to aldosterone is observed (97). Thus pendrin participates in the pressor response to aldosterone, likely by enhancing renal Cl⁻ absorption.

**Interaction Between Intercalated Cells and Principal Cells Following Aldosterone Administration**

The chloriuresis observed in pendrin null mice occurs, at least in part, from the absence of pendrin-mediated Cl⁻ absorption (99, 103). However, since pendrin does not transport Na⁺, the mechanism of the natriuresis observed in pendrin null mice was not obvious (39). We asked if the pendrin null mice have a reduced ability to conserve urinary Na⁺, due to reduced renal Na⁺ transporter expression. Thus renal Na⁺ transporter abundance was quantified in kidneys from wild-type and pendrin null mice following treatment models in which circulating aldosterone concentration is either low or high (39). The abundance of NHE3, α₁-Na-K-ATPase, NKCC2, ENaC, and NCC is similar in kidneys from wild-type and Slec26a4 null mice when consuming a balanced NaCl-replete diet (39). However, under conditions that increase serum aldosterone concentration, such as with NaCl restriction or an aldosterone infusion, β- and γENaC subunit abundance is reduced in kidneys from Slec26a4⁻/⁻ mice (39, 60). In particular, we observed a blunted increment in the abundance of the mature, 70-kDa fragment of γENaC in kidneys from Slec26a4 null mice following aldosterone administration (39). Changes in ENaC abundance observed in pendrin null mice appear limited to the kidney and cannot be explained by altered endocrine function (39).

To assess ENaC function, transepithelial voltage, V₁, was measured in CCDs perfused in vitro before and after the application of the ENaC inhibitor to the luminal fluid (39). Mice were given furosemide for 5 days to upregulate pendrin and ENaC (36, 56, 59, 67). In CCDs from furosemide-treated wild-type mice, a lumen-negative V₁ was observed, which was obliterated with the application of the ENaC inhibitor benzamil to the luminal fluid. However, in CCDs from furosemide-treated pendrin null mice, V₁ was very low and unchanged with benzamil (39). These data are consistent with robust ENaC-mediated Na⁺ absorption in CCDs from wild-type mice and low ENaC-mediated transport in CCDs from pendrin null mice. Thus both ENaC abundance and function are markedly reduced in kidneys from pendrin null mice. This reduction in ENaC function contributes to the lower blood pressure observed in these mutant mice.

In human and rodent kidney, pendrin and ENaC both localize to the aldosterone-sensitive region of the nephron, i.e., the terminal portion of the DCT (DCT2), CNT, the initial collecting tubule, and CCD (28, 38, 70, 102). However, these transporters localize to different cell types within these segments. Pendrin localizes to the apical regions of type B and non-A, non-B intercalated cells (38, 70, 102), whereas ENaC is expressed in the apical regions of principal cells (28) (Fig. 3). Since ENaC and pendrin localize to different cell types, this communication cannot occur through a direct protein-protein interaction.

Further studies explored how pendrin changes ENaC abundance and function (60). While Slec26a4/Slc26a4 expression is high in both rodent and human kidney, in both human and in mouse models of Pendred Syndrome, no acid-base or fluid and electrolyte abnormalities are seen under basal conditions (70, 97, 103). However, with aldosterone or NaHCO₃ administration, which upregulates pendrin abundance in wild-type mice, a more severe metabolic alkalosis is observed in pendrin null mice probably due to their reduced capacity to secrete HCO₃⁻ (97, 99, 103). While the renal phenotype has been well studied in mouse models of Pendred Syndrome, the effect of pendrin gene ablation on acid-base and fluid and electrolyte balance in people has had limited study. However, Pela et al. (64) observed a person with Pendred Syndrome who developed a severe metabolic alkalosis following treatment with thiazide diuretics. This case report is consistent with the alkalosis observed in rodent models of Pendred Syndrome.

Since pendrin mediates HCO₃⁻ secretion and since ENaC may be pH sensitive (60), we hypothesized that pendrin stimulates ENaC by raising luminal HCO₃⁻ concentration (60). To test this hypothesis, pendrin null and wild-type mice were given NaHCO₃ and aldosterone to stimulate pendrin-mediated HCO₃⁻ secretion (42). In other experiments, mice were given this treatment plus a carbonic anhydrase inhibitor (acetazolamide) to increase luminal HCO₃⁻ concentration by stimulating distal HCO₃⁻ delivery from upstream segments, while inhibiting pendrin-mediated apical Cl⁻/HCO₃⁻ exchange (54). Thus luminal HCO₃⁻ concentration in the CCD and CNT increased through a pendrin-independent mechanism. We observed a more severe metabolic alkalosis and lower renal ENaC subunit abundance and function in pendrin null relative to wild-type mice following treatment with aldosterone and NaHCO₃ (60). However, when acetazolamide was added to the protocol, acid-base balance as well as ENaC subunit abundance and function were similar in kidneys from wild-type and pendrin null mice (60). Thus stimulating distal HCO₃⁻ delivery from upstream segments rescues pendrin null mice from the expected fall in ENaC abundance and function. To determine if HCO₃⁻ has a direct effect on ENaC abundance and function, further experiments used cultured mouse principal cells (mpkCCD; Ref. 60). We observed that increasing HCO₃⁻ concentration on the apical side of the monolayer augmented ENaC abundance and function. Thus pendrin modulates ENaC, at least in part, by raising luminal HCO₃⁻ concentration. Whether this occurs from a direct effect of HCO₃⁻ or from the pH change that occurs when HCO₃⁻ concentration is varied remains to be determined. Moreover, there are likely additional mechanisms whereby pendrin modulates ENaC abundance and function. For example, ENaC may be regulated by ATP released by intercalated cells, which is somehow coupled to pendrin function (13).

**Regulation of Intercalated Cell Transporters by Angiotensin II**

Angiotensin II modulates blood pressure (98), in part, by increasing renal NaCl absorption in the collecting duct through short- and long-term effects (5, 6, 59, 66). Early studies employed micropuncture to examine the impact of luminal angiotensin II on distal transport. Angiotensin increases Na⁺ and Cl⁻ absorption in both early and late segments (i.e., the DCT and CNT; Ref. 104) and stimulates HCO₃⁻ absorption in the early, but not in the late segment (3, 49, 104). However, rather than stimulating K⁺ secretion, angiotensin actually reduces K⁺ transport in the late segment (104).

Subsequent studies examined the molecular pathway(s) by which angiotensin II increases distal NaCl absorption. Angio-
tensin II increases αENaC abundance in vivo through an AT₁α receptor-dependent process (5, 6). In the CCD, angiotensin II also stimulates ENaC-mediated Na⁺ absorption in vitro in a dose-dependent fashion (66). Since angiotensin II stimulates ENaC-mediated Na⁺ absorption, further experiments by our laboratory asked if angiotensin II also increases Cl⁻ absorption in the CCD (59). While CCDs from wild-type mice do not absorb Cl⁻ under basal conditions, when pendrin abundance is upregulated with furosemide administration, Cl⁻ absorption is observed (59), which doubles with angiotensin II application in vitro (59). However, in CCDs from furosemide-treated pendrin null mice, Cl⁻ absorption was not observed either in the presence or the absence of angiotensin II. Therefore, in CCDs perfused in vitro, angiotensin II increases Cl⁻ uptake in wild-type mice through a pendrin-dependent mechanism.

Further experiments explored how angiotensin II stimulates pendrin-dependent Cl⁻ absorption in mouse CCD. We reasoned that if angiotensin II increases the lumen-negative transepithelial voltage (Vₜ) it should magnify the driving force for paracellular Cl⁻ absorption. However, while Cl⁻ absorption increased with angiotensin II application, transepithelial voltage, Vₜ, was unchanged (59). Therefore, it is unlikely that angiotensin II stimulates Cl⁻ absorption by increasing paracellular Cl⁻ absorption (59).

Angiotensin II might increase pendrin-dependent transepithelial transport through increased apical plasma membrane pendrin abundance through covalent modification of pendrin or by creating a more favorable driving force for pendrin-mediated transport. However, since angiotensin II did not increase the abundance of pendrin on the apical plasma membrane in B cells (63), it does not increase pendrin-dependent Cl⁻ absorption in vitro through changes in pendrin subcellular distribution. Since angiotensin II might stimulate Cl⁻ uptake by changing the driving force for pendrin-mediated HCO₃⁻/Cl⁻ exchange, further studies explored whether angiotensin II increases the activity and the abundance of the apical (A cell) or the basolateral (B cell) H⁺-ATPase (63). Because angiotensin did not change B-cell basolateral plasma membrane H⁺-ATPase abundance, this hormone does not stimulate Cl⁻ absorption by changing ion gradients through increased basolateral plasma membrane H⁺-ATPase abundance. However, angiotensin II might increase Cl⁻ absorption through covalent modification of the B-cell H⁺-ATPase.

Angiotensin II applied in vitro upregulates A-cell apical plasma membrane H⁺-ATPase expression in both mouse CCD and OMCD (63, 69). In type A cells, angiotensin II application in vitro increases apical plasma membrane H⁺-ATPase expression nearly threefold through subcellular redistribution and changed total CO₂ flux from net secretion to net absorption (63), consistent with increased H⁺ secretion. Since inhibiting the apical H⁺-ATPase does not change Cl⁻ flux in CCDs from aldosterone-treated mice (61), stimulating apical H⁺ secretion with angiotensin II application probably does not markedly change pendrin-mediated Cl⁻ absorption. Angiotensin II application may instead covalently modify pendrin, which stimulates anion exchange. Alternatively, this peptide hormone may instead facilitate Cl⁻ exit or net H⁺ exit across the basolateral plasma membrane through subcellular redistribution or through covalent modification of a basolateral membrane H⁺, OH⁻, or Cl⁻ transporter, which reduces intracellular Cl⁻ or increases intracellular HCO₃⁻ concentration, thereby providing a more favorable driving force for apical Cl⁻/HCO₃⁻ exchange.

**Interplay of Angiotensin and Aldosterone in the Cortical Distal Nephron**

As discussed above, angiotensin acts in the CNT and CCD to enhance transport in principal and in type A and B intercalated cells. These two intercalated cell subtypes act in tandem to generate net electrogenic Cl⁻ absorption. By promoting the absorption of an anion, the lumen negative electrical potential should fall, thereby decreasing K⁺ secretion. Increased ENaC activity augments the lumen-negative voltage, which blunts the fall in voltage expected with electrogenic anion absorption.

Application of either aldosterone or angiotensin II increases ENaC-mediated Na⁺ absorption, which increases the lumen-negative voltage, thereby stimulating K⁺ secretion. The relationship between K⁺ secretion and NaCl transport was recently addressed (115). In the DCT in vivo, NaCl restriction increases thiazide-sensitive NaCl absorption by upregulating angiotensin II, which stimulates the NaCl cotransporter (NCC) of the DCT (15). Angiotensin II increases apical plasma membrane NCC abundance in the DCT through subcellular redistribution (72), which activates NCC transport activity (71, 95), thereby increasing NaCl absorption in this segment (104). However, activating NaCl absorption in the DCT reduces Na⁺ delivery to the CNT, which reduces ENaC-mediated Na⁺ absorption. Therefore, K⁺ secretion declines due to the fall in ENaC-mediated Na⁺ absorption and the fall in CNT volume flow. However, the distal nephron model predicts that with increased DCT NaCl absorption, K⁺ secretion can be preserved by concomitant activation of principal cell transporters (115). Thus a picture emerges in which ENaC and pendrin are upregulated by angiotensin II and aldosterone in a coordinate manner, acting to restore extracellular volume while preserving K⁺ excretion. In this scheme, there may be communication from the type B intercalated cell to the principal cell through pendrin-mediated HCO₃⁻ secretion. Whether dysfunction of this transport configuration can also mediate the volume-dependent component of essential hypertension remains to be determined.

**Unanswered Questions and Future Directions**

As mentioned above, diuretics such as amiloride and thiazides reduce Cl⁻ absorption in the rodent CCD is not fully explained. While amiloride has been thought to reduce Cl⁻ absorption by eliminating the lumen-negative transepithelial voltage, which provides the driving force for paracellular Cl⁻ absorption, this has never been directly tested and other mechanisms are possible. For example, by eliminating the lumen-negative voltage, the driving force for Cl⁻ secretion mediated by an apical plasma membrane Cl⁻ channel is greatly increased. Therefore, amiloride analogs may reduce Cl⁻ absorption by stimulating Cl⁻ channel-mediated Cl⁻ secretion. Thiazide analogs also reduce Cl⁻ absorption, at least in part, by inhibiting the Na⁺-dependent Cl⁻/HCO₃⁻ exchanger Slc4a8. However, whether thiazides inhibit Slc4a8 alone or inhibits a transporter complex is unknown.

Pendrin-mediated apical Cl⁻/HCO₃⁻ exchange is the best understood mechanism of Cl⁻ absorption in the rodent CCD. Pendrin is highly regulated by aldosterone through changes in...
subcellular distribution. However, how aldosterone modulates the subcellular distribution of pendrin is unknown. Potential interaction with ubiquitin ligases may regulate this exchanger’s distribution and function.

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DISCLOSURES

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Author contributions: S.M.W. and A.M.W. prepared figures; S.M.W. and A.M.W. drafted manuscript; S.M.W. and A.M.W. edited and revised manuscript; S.M.W. and A.M.W. approved final version of manuscript.

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