The Role of Pendrin in Renal Physiology

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Slc26a4, *Pds*, Cl^-/HCO_3^- exchange, ENaC, pendrin, intercalated cells, blood pressure

Abstract

Pendrin is a Na^+-independent Cl^-/HCO_3^- exchanger that localizes to type B and non-A, non-B intercalated cells, which are expressed within the aldosterone-sensitive region of the nephron, i.e., the distal convoluted tubule, the connecting tubule, and the cortical collecting duct. Type B cells mediate Cl^- absorption and HCO_3^- secretion primarily through pendrin-mediated Cl^-/HCO_3^- exchange. At least in some treatment models, pendrin acts in tandem with the Na^+-dependent Cl^-/HCO_3^- exchanger (NDCBE) encoded by *Slc4a8* to mediate NaCl absorption. The pendrin-mediated Cl^-/HCO_3^- exchange process is greatly upregulated in models of metabolic alkalosis, such as following aldosterone administration or dietary $NaHCO_3$ loading. It is also upregulated by angiotensin II. In the absence of pendrin [*Slc26a4* (−/−) or pendrin null mice], aldosterone-stimulated NaCl absorption is reduced, which lowers the blood pressure response to aldosterone and enhances the alkalosis that follows the administration of this steroid hormone. Pendrin modulates aldosterone-induced Na^+ absorption by changing 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 HCO_3^- and ATP concentrations. Thus, aldosterone and angiotensin II also stimulate pendrin expression and function, which likely contributes to the pressor response of these hormones. This review summarizes the contribution of the Cl^-/HCO_3^- exchanger pendrin in distal nephron function.

INTRODUCTION

NaCl transport in the distal nephron 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 falls. Genetic ablation of distal nephron NaCl transporters, such as pendrin, often results in contracted extracellular volume due to an inappropriate decrease in distal NaCl absorption.

Most distal NaCl transport occurs in the cortex, within the distal convoluted tubule (DCT), connecting tubule (CNT), and cortical collecting duct (CCD), although the medullary collecting duct performs the final regulation of NaCl balance (1). Distal delivery of a solute, such as Na^+, refers to flow at the most proximal portion of the DCT that is accessible to micropuncture and is just below 10% of the filtered Na^+ load (1–7). Of the 10% of the filtered load that reaches the most proximal portion of the DCT, ~75% is absorbed before reaching the CCD (1). Therefore, ~6–8% (or three-fourths of 10%) of the filtered load is absorbed along the DCT and CNT (1). The magnitude of Na^+ absorption is similar in the early and late portions of the distal tubule, or the early DCT and the initial collecting duct, which are segments accessible to measurements by micropuncture (1, 8). Therefore, 3–4% of filtered Na^+ load is absorbed along the DCT, and another 3–4% is absorbed along the CNT (1). Of the 2.5% of the filtered load that reaches the CCD, the degree to which it is absorbed depends largely on the treatment model employed.

The mechanism of ion transport in the CCD and CNT has been examined in studies that employed CCDs and CNTs perfused in vitro, although many more studies have been done in the former than in the latter due to the greater difficulty of perfusing CNTs in vitro. The initial studies that explored ion transport in CCDs perfused in vitro were performed in rats and rabbits (1). However, the introduction of genetically modified mice has provided a powerful tool by which to examine the physiological role of individual transporters. Therefore, more recent work has involved study of the mouse CCD. Collectively, these perfused tubule studies have shown that Na^+ and probably Cl^- absorption in the CCD is only approximately half of that found in the CNT, even when stimulated (9). Moreover, because CNTs merge to become the CCD, the total tubule length in vivo is sixfold greater in the CNT than in the CCD (1). These data strongly suggest that NaCl absorption in vivo is at least an order of magnitude greater in the CNT than in the CCD. Pendrin is expressed in both the CNT and the CCD within the minority cell type (intercalated cells) found in both segments (10–12). Because pendrin is more highly expressed in cells within the CNT than in cells within the CCD under both basal and stimulated conditions (10, 13) and because the CNT is longer than the CCD, pendrin probably modulates ion transport more along the CNT than along the CCD.

Principal cells and intercalated cells are the two cell types found within the CCD and CNT. Intercalated cells are divided into three subtypes: type A; type B; and non-A, non-B cells. This subclassification is based on the expression of the Cl^-/HCO_3^- exchanger AE1 (anion exchanger 1) and on the subcellular distribution of the H^+-ATPase within the cell (14–17) (**Figure 1**). This transporter distribution is important in that it predicts whether an intercalated cell secretes H^+ or OH^- equivalents (18, 19). Type A intercalated cells secrete H^+ equivalents through the apical plasma membrane H^+-ATPase (17), which is upregulated in models of metabolic acidosis. In contrast, type B intercalated cells secrete OH^- equivalents through electroneutral Cl^-/HCO_3^- exchangers on the apical plasma membrane (11, 20, 21), which act in series with the H^+-ATPase on the basolateral plasma membrane (15–17, 19, 21). Na^+-independent Cl^-/HCO_3^- exchangers expressed on the apical plasma membranes of type B cells, such as pendrin, increase in models of metabolic alkalosis, which attenuates the alkalosis by augmenting HCO_3^- secretion (11, 18). Although non-A, non-B intercalated cells also express apical Na^+-independent Cl^-/HCO_3^-

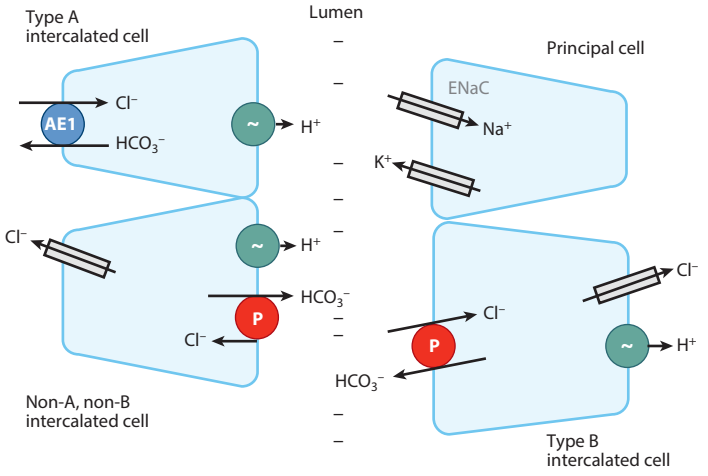

Figure 1

Cell types and transporters in the cortical collecting duct (CCD). The distribution of ion transporters within intercalated and principal cells in the CCD is shown. Intercalated cell subtypes are identified on the basis of the expression of AE1 (anion exchanger 1) and the subcellular distribution of the H^+-ATPase. In type A intercalated cells, the H^+-ATPase is expressed on the apical plasma membrane, whereas the Cl^-/HCO_3^- exchanger AE1 localizes to the basolateral plasma membrane. Type B and non-A, non-B intercalated cells express pendrin in the region of the apical plasma membrane. Type B intercalated cells, however, express the H^+-ATPase on the basolateral plasma membrane, whereas non-A, non-B intercalated cells express this H^+-pump on the apical plasma membrane. Principal cells express the epithelial Na^+ channel (ENaC) in the region of the apical plasma membrane, which generates a lumen-negative transepithelial voltage that provides the driving force for K^+ secretion.

exchange, because this cell type is found primarily within the CNT rather than within the CCD (10), its transport properties are poorly understood due to the technical difficulty of perfusing CNTs in vitro. Nevertheless, because non-A, non-B intercalated cells express both the H^+-ATPase and pendrin on the apical plasma membrane, it is intriguing to speculate that HCO_3^- (or H^+) is recycled across the apical plasma membrane in this cell type, thereby providing net NaCl absorption with little change in net H^+ secretion. This review therefore discusses the contribution of pendrin to the apical Cl^-/HCO_3^- exchange observed in the type B intercalated cell.

Principal cells mediate the absorption of Na^+, primarily through the epithelial Na^+ transporter ENaC, but mediate little net Cl^- absorption (22). Instead, most Cl^- absorption within the CCD occurs through transcellular transport across intercalated cells (22), such as through the electroneutral exchanger pendrin (23), which localizes to the apical regions of type B and non-A, non-B intercalated cells of the CCD and CNT (10–12). ENaC and pendrin therefore act in tandem to mediate net absorption of NaCl. This review discusses the regulation of pendrin-mediated ion transport and the contribution of pendrin to renal acid-base and fluid and electrolyte balance.

THE ROLE OF PENDRIN IN RENAL PHYSIOLOGY

Cloning of the Gene Responsible for Pendred Syndrome

In 1896 Dr. Vaughan Pendred observed a family in which 2 of the 10 children suffered from deafness and goiter (Pendred syndrome) (24). Pendred syndrome is inherited in an autosomal

recessive fashion and is seen in 7.5 per 100,000 persons, making it one of the leading causes of congenital deafness (25). In 1997 Everett and colleagues cloned the gene responsible for Pendred syndrome by positional cloning (26). This gene was subsequently named *Slc26a4*, and the protein encoded by *Slc26a4* is referred to as pendrin. Determining the structure of *Slc26a4* enabled pendrin-mediated transport to be better characterized and enabled better study of pendrin's distribution and regulation. Initial studies of pendrin when expressed in heterologous expression systems showed that it is an electroneutral, Na^+-independent Cl^-/HCO_3^-, Cl^-/Cl^-, and Cl^-/I^- exchanger (27–30). Localization studies showed high levels of pendrin expression in the thyroid and inner ear (31, 32), as expected given the ear and thyroid phenotype observed in Pendred syndrome. Surprisingly, high levels of pendrin expression were also observed in the kidney (11). In particular, pendrin was found to be expressed in intercalated cells, which are a minority cell type found within the aldosterone-sensitive region of the nephron, i.e., the distal portion of the DCT, the CNT, and the CCD (10–12).

Pendrin Localizes to Type B and to Non-A, Non-B Intercalated Cells in the Cortical Collecting Duct, Where It Mediates Cl^-/HCO_3^- Exchange

Pendrin localizes to the apical regions of type B and non-A, non-B intercalated cells (10–12). Because pendrin is a Na^+-independent Cl^-/HCO_3^- exchanger that is expressed in the apical regions of cells that secrete HCO_3^- and absorb Cl^-, we hypothesized that pendrin-mediated transport is responsible for the Cl^- absorption and HCO_3^- secretion observed within the rodent CCD. To test this hypothesis, we examined the effect of pendrin gene ablation on Cl^- and total CO_2 (HCO_3^-) transport in the CCD (11, 23). Mice were treated with an aldosterone analog and were given $NaHCO_3$ in their drinking water to upregulate apical Cl^-/HCO_3^- exchange in the type B cell (21, 33). In CCDs from wild-type mice that were perfused in vitro, we observed HCO_3^- secretion and Cl^- absorption. In contrast, Cl^- absorption and HCO_3^- secretion were not observed in CCDs from the pendrin null mice (11, 23). Therefore, apical Cl^-/HCO_3^- exchange in the type B intercalated cell depends largely upon pendrin expression.

Within the CCD, Cl^- absorption occurs through two mechanisms, each of which is sensitive to different diuretics. The first is sensitive to the ENaC inhibitor amiloride, whereas the second is sensitive to thiazides (34). The relative contributions of the thiazide-sensitive and the amiloride-sensitive components of NaCl absorption to total NaCl absorption have varied between studies and probably depend on the treatment model employed (34, 35).

Thiazides inhibit the NaCl cotransporter (NCC), encoded by *Slc12a3*. However, this transporter localizes to the DCT and is not expressed within the CCD (35). Therefore, the gene that encodes the thiazide-sensitive component of Cl^- absorption in the CCD has required further characterization (35). Leviel and collaborators (35) demonstrated that the thiazide-sensitive component of Cl^- absorption within the CCD occurs through a Na^+-dependent Cl^-/HCO_3^- exchanger (NDCBE) encoded by *Slc4a8*. During dietary NaCl restriction, pendrin-mediated Cl^-/HCO_3^- exchange, together with this Na^+-dependent Cl^-/HCO_3^- exchange, mediates electroneutral NaCl absorption in the CCD while conserving K^+ (35) (**Figure 2**). Functional data have shown that NDCBE localizes to intercalated cells (35), but the renal localization of the protein encoded by *Slc4a8* has not been determined.

Inhibiting ENaC with amiloride reduces not only Na^+ absorption but also Cl^- absorption. Because ENaC does not transport Cl^-, amiloride does not directly inhibit Cl^- transport. Instead, this diuretic must alter Cl^- movement by changing the activity of an exchanger or another channel that mediates Cl^- transport either by altering the release of a signaling molecule or by changing the driving force for Cl^- movement. Although the Cl^- transport mechanism targeted by

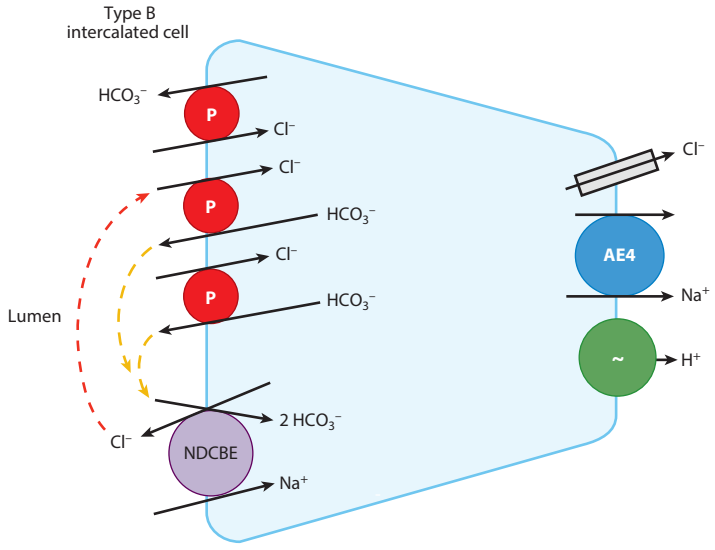

Figure 2

Transporters within type B intercalated cells. Type B intercalated cells mediate Cl^- absorption and HCO_3^- secretion through the apical plasma membrane Cl^-/HCO_3^- exchanger pendrin. At least in some treatment models, HCO_3^- secreted by pendrin is recycled across the apical plasma membrane and absorbed through the Na^+-dependent Cl^-/HCO_3^- exchanger (NDCBE) encoded by *Slc4a8*. The result is net NaCl absorption with less net HCO_3^- secretion. Cl^- exits the basolateral plasma membrane through Cl^- channels or possibly through an unidentified exchange process. The Na^+/HCO_3^- cotransporter AE4 (encoded by *Slc4a9*) mediates Na^+ exit across the basolateral plasma membrane. From Reference 36.

ENaC inhibition is unknown, it does not appear to be mediated by pendrin or the cystic fibrosis transmembrane regulator (37, 38).

Aldosterone Upregulates Pendrin

Aldosterone administration increases NaCl absorption and HCO_3^- secretion in the CCD (21). This steroid hormone increases renal NaCl absorption and hence blood pressure, in part by increasing the abundance and function of NaCl transporters such as ENaC (39) and pendrin (13). Whereas apical plasma membrane pendrin immunoreactivity in type B intercalated cells is low under basal conditions (10, 13), it increases sixfold in response to aldosterone, primarily through subcellular redistribution (13). The increase in Cl^- absorption and HCO_3^- secretion observed in the CCD of aldosterone-treated mice occurs through stimulation of pendrin-mediated transport (21, 33, 40, 41) because HCO_3^- secretion and Cl^- absorption are greatly reduced in aldosterone-treated pendrin null mice relative to wild-type mice (11, 23).

Shibata et al. (42) made the novel observation that angiotensin II dephosphorylates S843 of the mineralocorticoid receptor (MR) ligand-binding domain uniquely within intercalated cells. This dephosphorylation enhances the ability of aldosterone to activate the MR, thereby upregulating the abundance of intercalated cell transporters, such as pendrin and the H^+-ATPase. However, because aldosterone regulates apical plasma membrane pendrin abundance primarily through subcellular redistribution, rather than through changes in total protein abundance (13), it remains to be determined whether this angiotensin II–dependent MR dephosphorylation event significantly changes the effect of aldosterone on pendrin-mediated transport. Moreover, the kinase that phosphorylates the MR within intercalated cells remains to be identified.

Pendrin Regulates Acid-Base Balance

Because pendrin mediates Cl^-/HCO_3^- exchange, there has been great interest in the effect of pendrin gene ablation on acid-base and fluid and electrolyte balance in people and in mice. Although *Slc26a4*/*SLC26A4* expression is high in both the rodent and human kidney, in both human and mouse models of Pendred syndrome, no acid-base or fluid and electrolyte abnormalities are seen under basal conditions, i.e., following a balanced, NaCl-replete diet (11, 13, 23, 43). The lack of an observed renal phenotype in pendrin null mice under basal conditions is likely due to compensatory changes in the expression of other renal Cl^- and/or H^+/OH^- transporters. For example, thiazide-sensitive NCC may be upregulated with pendrin gene ablation (44). Conversely, thiazide-sensitive NCC (*Slc12a3*) gene ablation greatly upregulates renal pendrin protein abundance (45). This increase in pendrin abundance may compensate for the loss of the NCC-mediated NaCl absorption that follows NCC gene ablation and may explain the absence of changes in blood pressure and NaCl balance in NCC null mice given a NaCl-replete diet (basal conditions) (46). Therefore, although acid-base abnormalities are not observed under basal conditions with pendrin gene ablation alone (13), with ablation of both the pendrin (*Slc26a4*) and NCC (*Slc12a3*) genes, profound metabolic alkalosis and vascular volume contraction are observed (47). Moreover, in people with Pendred syndrome, inhibiting NCC with thiazide administration can lead to profound metabolic alkalosis and volume contraction (43). How NCC and pendrin interact to maintain acid-base and fluid and electrolyte balance is, however, unknown.

Although pendrin null mice have a very mild renal phenotype under basal conditions, changes in acid-base and fluid and electrolyte balance are observed in these mutant mice under conditions that stimulate pendrin expression. For example, a renal phenotype is observed in mice with pendrin gene ablation alone in models of metabolic alkalosis, such as that following the administration of aldosterone or $NaHCO_3$ (13, 48). In these treatment models, pendrin null mice have enhanced metabolic alkalosis and apparent vascular volume contraction relative to wild-type mice, presumably due to a reduced capacity of the mutant mice to secrete HCO_3^- and absorb Cl^- (13, 23, 48).

Pendrin Regulates Fluid and Electrolyte Balance and Blood Pressure

Because pendrin is a Cl^- transporter, our laboratory explored its role in fluid balance (23). Following a NaCl-replete diet, a treatment model in which renin and aldosterone are suppressed, apparent vascular volume is similar in wild-type mice and in pendrin null mice (23, 48). However, following NaCl restriction, which results in the appropriate stimulation of renin and aldosterone, pendrin null mice have enhanced excretion of Na^+ and Cl^- relative to wild-type mice (44, 48). Moreover, NaCl-restricted pendrin null mice lose more body weight and have a greater increment in their blood urea nitrogen concentration relative to wild-type mice, consistent with greater apparent vascular volume contraction in the former relative to the latter. Therefore, the lower blood pressure observed in the mutant relative to the wild-type mice is at least partly due to the impaired ability of the pendrin null mice to fully conserve urinary Na^+ and Cl^- (23, 44, 48).

Blood pressure is lower in pendrin null relative to wild-type mice, particularly when measured by telemetry (13, 49). The difference in blood pressure observed between pendrin null and wild-type mice is greater in treatment models that upregulate pendrin, such as with aldosterone administration (13, 49). Moreover, pendrin null mice have a blunted pressor response to this steroid hormone (13).

Whereas pendrin null mice are hypotensive, mice that overexpress pendrin have salt-sensitive hypertension (50). In particular, in mice that overexpress pendrin, blood pressure is very sensitive to Cl^- intake (50). Because mice that overexpress pendrin develop NaCl-sensitive hypertension,

there is great interest in whether pendrin contributes to the pathogenesis of human hypertension. Although the physiological role of pendrin in the pathogenesis of hypertension has not been explored fully, people with Pendred syndrome may be protected from the development of hypertension (51). In a retrospective chart review, the incidence of hypertension in persons with Pendred syndrome was compared with the incidence of hypertension in their unaffected family members (51). Although the study was inadequately powered, it raised the possibility that pendrin gene ablation is protective against the development of hypertension.

Pendrin Modulates ENaC Abundance and Function in High-Aldosterone States

The absence of pendrin-mediated Cl^- absorption contributes to the chloriuresis observed in NaCl-restricted pendrin null mice. However, pendrin modulates blood pressure not only by mediating renal Cl^- absorption, but also by changing renal Na^+ absorption (44). Because pendrin gene ablation produces a natriuresis without directly mediating Na^+ transport, we asked whether pendrin modulates the expression of a major renal Na^+ transporter. Therefore, renal Na^+ transporter abundance was quantified in kidneys from wild-type and pendrin null mice following treatment models in which circulating aldosterone concentration was either low or high (44). When mice consumed a NaCl-replete diet, which suppresses circulating plasma renin and aldosterone concentration, pendrin gene ablation did not significantly alter renal Na^+ transporter abundance. In particular, abundances of the proximal tubule Na^+/H^+ exchanger NHE3, the α1 subunit of the Na^+,K^+-ATPase, the thick-ascending-limb Na^+-K^+-$2Cl^-$ cotransporter (NKCC2), ENaC in the collecting duct, and NCC in the distal convoluted tubule were similar in lysates from wild-type and *Slc26a4* null mice following a balanced, NaCl-replete diet (44). However, with increased circulating aldosterone, which follows dietary NaCl restriction or an aldosterone infusion, pendrin gene ablation reduces β and γ ENaC subunit abundance in the kidney (44, 49). In particular, the aldosterone-induced increment in the abundance of the mature, 70-kDa fragment of γ ENaC is blunted in pendrin null mice. Therefore, pendrin gene ablation blunts the increment in ENaC subunit abundance observed with aldosterone administration.

Because pendrin gene ablation reduces ENaC subunit abundance, we explored ENaC function in wild-type and pendrin null mice. Mice were treated with furosemide to stimulate pendrin and ENaC abundance and function (52–55). Transepithelial voltage (V_T) was measured in CCDs perfused in vitro before and after the application of the ENaC inhibitor benzamil to the luminal fluid (44). The change in voltage observed with benzamil application was taken as an index of ENaC-mediated Na^+ absorption. We observed a lumen-negative V_T in CCDs from wild-type mice, which was obliterated with benzamil application to the luminal fluid, consistent with robust, ENaC-mediated Na^+ absorption. However, in CCDs from pendrin null mice, V_T was very low in either the presence or the absence of benzamil (44), indicating lower ENaC-mediated Na^+ absorption in CCDs from pendrin null relative to wild-type 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.

Pendrin Modulates ENaC Abundance in the Kidney by Changing Downstream Luminal Fluid Composition

In human and rodent kidneys, both pendrin and ENaC localize to the aldosterone-sensitive region of the nephron, i.e., the terminal portion of the DCT (DCT2), the CNT, the initial collecting tubule (iCT), and the CCD (10–12). However, these transporters localize to different cell types in these segments. Whereas pendrin localizes to the apical regions of intercalated cells, ENaC is expressed in the apical regions of principal cells (10–12, 56) (**Figure 1**), where it mediates Na^+

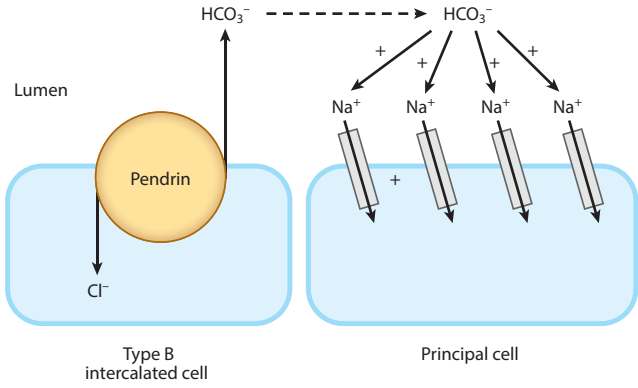

Figure 3

Pendrin mediates HCO_3^- secretion, which stimulates ENaC subunit abundance and ENaC function. Pendrin mediates the secretion of HCO_3^- into the luminal fluid, which increases ENaC subunit abundance and function.

absorption, which depolarizes the apical plasma membrane, thereby providing the driving force for K^+ secretion.

Further studies explored the mechanism whereby pendrin changes ENaC abundance and function (49). ENaC and pendrin cannot communicate through a direct protein-protein interaction, because they localize to different cell types. Moreover, the reduced ENaC abundance observed in pendrin null mice also cannot be explained by changes in circulating levels of hormones that regulate ENaC, such as vasopressin, aldosterone, angiotensin II, corticosterone, and thyroid hormone (44). Finally, the effect of pendrin gene ablation on ENaC function appears limited to the kidney because pendrin gene ablation does not change ENaC abundance in the thyroid or in the colon (44). Moreover, pendrin gene ablation paradoxically increases ENaC expression and function in the inner ear (57).

Because ENaC may be pH sensitive (49), we hypothesized that pendrin stimulates ENaC by raising luminal HCO_3^- concentration (**Figure 3**). To test this hypothesis, we gave pendrin null and wild-type mice $NaHCO_3$ and aldosterone to stimulate pendrin-mediated HCO_3^- secretion (33). In other experiments, we increased luminal HCO_3^- concentration through a pendrin-independent mechanism. Here mice received aldosterone and $NaHCO_3$ plus a carbonic anhydrase inhibitor (acetazolamide). The addition of this carbonic anhydrase inhibitor increased distal HCO_3^- delivery from upstream segments while greatly downregulating pendrin expression and pendrin-mediated apical Cl^-/HCO_3^- exchange (49, 58). In this second model, luminal HCO_3^- concentration was therefore increased through a pendrin-independent mechanism. We observed that with aldosterone and $NaHCO_3$ treatment alone, pendrin null mice developed more severe metabolic alkalosis and had lower renal ENaC subunit abundance and function relative to the wild type (49). However, when mice received this treatment plus acetazolamide, acid-base balance and ENaC subunit abundance and function were similar in kidneys from wild-type and pendrin null mice (49). Thus, stimulating distal HCO_3^- delivery from upstream segments rescues pendrin null mice from the expected fall in ENaC abundance and function.

Further studies used cultured mouse principal cells to determine whether HCO_3^- directly affects ENaC abundance and function (49). We observed that ENaC abundance and function rose when HCO_3^- concentration was increased on the apical side of the monolayer. Thus, pendrin modulates ENaC at least in part by raising luminal HCO_3^- concentration. Whether pendrin

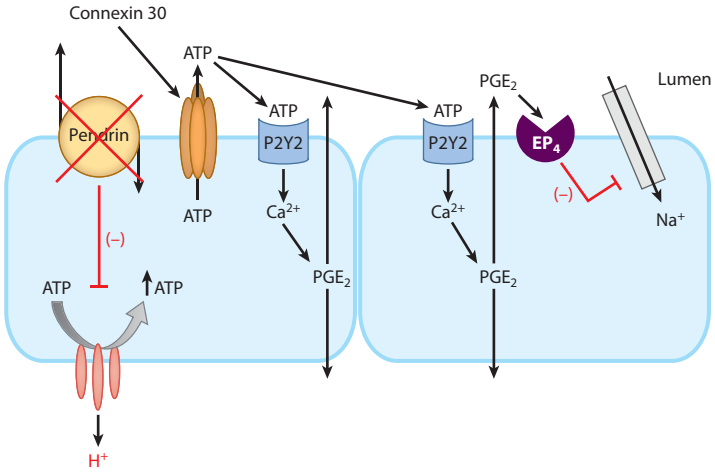

Figure 4

Pendrin changes ENaC abundance and function by modulating luminal ATP concentration. Pendrin gene ablation almost obliterates the expression of the H^+-ATPase in the type B intercalated cell. ATP rises in the type B intercalated cell, which stimulates ATP secretion into the luminal fluid through connexin 30. Luminal ATP acts through apical plasma membrane purinergic receptors to stimulate Ca^{2+} release, which augments the production of prostaglandin E_2 (PGE_2). PGE_2 acts through a receptor-mediated mechanism [prostaglandin E_4 receptor (EP_4)] to reduce ENaC abundance and function.

modulates ENaC by changing luminal pH or by changing luminal HCO_3^- concentration remains to be determined.

Other studies indicate that pendrin modulates ENaC abundance and function by changing luminal ATP concentration (**Figure 4**). Because pendrin gene ablation markedly downregulates the H^+-ATPase in type B intercalated cells (59), the fall in ENaC abundance and function observed in pendrin null mice may result from downregulation of the type B cell H^+-ATPase. Gueutin et al. (60) observed that with H^+-ATPase gene ablation, renal cortical ENaC abundance and function are markedly reduced. They also observed that when the B cell H^+-ATPase is blocked with chemical inhibitors, intracellular Ca^{2+} increases dramatically, which stimulates prostaglandin E_2 (PGE_2) release. This PGE_2 release is blocked with purinergic receptor blockers or ATP scavengers. Gueutin et al. (60) concluded that pendrin gene ablation downregulates the B cell H^+-ATPase, which increases ATP secretion, thereby raising luminal ATP concentration. Luminal ATP then acts through apical purinergic receptors to stimulate Ca^{2+} release within principal cells, which increases PGE_2 production, thereby attenuating ENaC abundance and function (60). In summary, recent data indicate that pendrin gene ablation reduces ENaC abundance and function by changing the downstream luminal concentrations of ATP and HCO_3^-.

Angiotensin II Upregulates Pendrin and ENaC

Angiotensin II increases renal NaCl absorption through short- and long-term effects that are mediated, at least in part, through pendrin- and ENaC-dependent mechanisms (54, 61–64). This angiotensin II–stimulated renal NaCl absorption contributes to the pressor response observed with administration of this peptide hormone. Angiotensin II increases ENaC-mediated Na^+ absorption in the CCD through a mechanism that is dose dependent and is mediated by the angiotensin type 1a receptor (AT_{1a} receptor) (61, 63, 64).

Our laboratory asked whether angiotensin II also increases Cl^- absorption in the CCD (54). We observed that CCDs from wild-type mice do not absorb Cl^- under basal conditions. However, upon administering furosemide, which upregulates pendrin abundance, we observed Cl^- absorption, which doubles with angiotensin II application to the bath (54). However, Cl^- absorption was not observed in either the presence or the absence of angiotensin II in CCDs from furosemide-treated pendrin null mice. Therefore, angiotensin II increases Cl^- uptake in CCDs from wild-type mice through a pendrin-dependent mechanism.

Angiotensin II may stimulate Cl^- absorption in the mouse CCD through a paracellular or a transcellular pathway. For example, angiotensin II may increase the lumen-negative V_T, which increases the driving force for paracellular Cl^- absorption. However, because angiotensin II application to the bath increased Cl^- absorption without changing V_T (54), this peptide hormone likely stimulates Cl^- absorption through a transcellular rather than a paracellular mechanism (54).

Angiotensin II may stimulate pendrin-dependent transepithelial transport through increased apical plasma membrane pendrin abundance, through covalent modification of pendrin, or through creation of a more favorable driving force for pendrin-mediated transport. To examine the effect of angiotensin II on pendrin subcellular distribution, we perfused CCDs in vitro in the presence or absence of angiotensin II in the bath. Tubules were then fixed, and pendrin subcellular distribution was quantified by immunogold cytochemistry with morphometric analysis. We observed that angiotensin II application in vitro did not change pendrin subcellular distribution and did not increase the abundance of pendrin on the apical plasma membrane (65). Therefore, angiotensin II does not increase pendrin-dependent Cl^- absorption in vitro by increasing apical plasma membrane pendrin expression.

We hypothesized that angiotensin II stimulates Cl^- uptake by changing the driving force for pendrin-mediated Cl^-/HCO_3^- exchange. In particular, angiotensin II may stimulate basolateral plasma membrane H^+-ATPase abundance in type B intercalated cells, which increases intracellular HCO_3^- concentration, thereby stimulating apical Cl^-/HCO_3^- exchange. In support of this hypothesis, we observed that angiotensin II application in vitro did not stimulate Cl^- uptake in CCDs perfused in vitro when the basolateral plasma membrane H^+-ATPase was inhibited with bafilomycin (54). Therefore, further studies explored whether angiotensin II increases type B cell basolateral plasma membrane or type A cell apical plasma membrane H^+-ATPase abundance (65). Thus, H^+-ATPase subcellular distribution was quantified by immunogold cytochemistry with morphometric analysis in CCDs perfused in vitro in the presence and in the absence of angiotensin II. Although we did not observe an effect of angiotensin II on basolateral plasma membrane H^+-ATPase abundance in type B cells, in type A intercalated cells angiotensin II application increased apical plasma membrane H^+-ATPase expression nearly threefold through subcellular redistribution. Moreover, in CCDs perfused in vitro, angiotensin II increased net absorption of HCO_3^-, consistent with stimulation of apical plasma membrane H^+-ATPase activity. Thus, angiotensin II applied in vitro upregulates type A cell apical plasma membrane H^+-ATPase expression in both the mouse CCD and outer medullary collecting duct (65, 66). Whether increased apical H^+ secretion augments the driving force for pendrin-mediated Cl^- absorption remains to be determined. Angiotensin II may increase Cl^- uptake by acting on another H^+, OH^-, or Cl^- transporter, thereby facilitating Cl^- exit or net H^+ exit across the basolateral plasma membrane. Such exit would reduce intracellular Cl^- or increase intracellular HCO_3^- concentration, thereby providing a more favorable driving force for apical Cl^-/HCO_3^- exchange.

Angiotensin II also regulates pendrin in vivo through long-term, chronic mechanisms. Angiotensin II administered in vivo acts through the AT_{1a} receptor to shift pendrin immunolabel from the subapical space to the apical plasma membrane, through a mechanism that is not mediated by aldosterone (62). However, angiotensin II application in vivo also activates the angiotensin

type 2 receptor (AT_2 receptor), which acts through nitric oxide to reduce pendrin protein abundance without changing the relative subcellular distribution of pendrin (62). Therefore, the AT_2 receptor provides a feedback loop to modulate the effect of angiotensin II–induced AT_{1a} receptor activation on apical plasma membrane pendrin abundance.

Shibata et al. (42) made the novel observation that aldosterone upregulates pendrin protein abundance through a mechanism that depends on angiotensin II. In this model, angiotensin II dephosphorylates the S843 residue of the mineralocorticoid receptor (MR) (MR^{S843-P}) of intercalated cells, which facilitates the stimulation of pendrin by aldosterone. When wild-type mice were switched from a high-salt to a low-salt diet, Shibata et al. observed dephosphorylation of MR^{S843-P} within intercalated cells, which correlated with increased pendrin total protein abundance. However, dietary salt restriction did not dephosphorylate MR^{S843-P} or stimulate pendrin abundance in mice lacking the AT_{1a} receptor (AT_{1a} null mice). Conversely, an angiotensin II infusion dephosphorylated MR^{S843-P} and stimulated pendrin protein abundance, both of which were inhibited by administration of AT_{1a} receptor blockers. These investigators concluded that angiotensin II dephosphorylates MR^{S843-P}, which enables aldosterone to bind to and activate the intercalated cell MR. The result is increased protein abundance of intercalated cell transporters such as pendrin. However, on the basis of the experimental data of other laboratories, further studies are needed. First, in normal mice, apical plasma membrane pendrin abundance is regulated primarily through changes in subcellular distribution (13), rather than through changes in total protein abundance (13), which was the focus of the Shibata et al. (42) study. Second, apical plasma membrane pendrin expression increases in treatment models associated with increased circulating aldosterone, whether circulating angiotensin II is high or low. For example, apical plasma membrane pendrin abundance and total pendrin protein abundance per cell increase with the administration of aldosterone (13), a treatment model in which circulating aldosterone concentration is high while angiotensin II production is low, as well as following dietary NaCl restriction, when both circulating aldosterone concentration and angiotensin II production are high (23). Therefore, aldosterone appears to alter pendrin subcellular distribution and total pendrin protein abundance largely independently of the expected changes in angiotensin II production.

Both aldosterone and angiotensin II stimulate apical plasma membrane abundance in vivo, primarily through changes in subcellular distribution (13, 62). However, they probably change apical plasma membrane pendrin abundance through different mechanisms. Whereas aldosterone increases apical plasma membrane pendrin expression more in type B than in non-A, non-B intercalated cells (13), angiotensin II acting through the AT_{1a} receptor stimulates apical plasma membrane pendrin expression more in non-A, non-B than in type B intercalated cells (62). In contrast, aldosterone administration changes in total protein abundance per cell more in non-A, non-B intercalated cells than in type B intercalated cells (13), whereas angiotensin II, acting through the AT_{1a} receptor, changes pendrin total protein abundance more in type B intercalated cells than in non-A, non-B intercalated cells (62). Second, the effect of angiotensin II/AT_{1a} receptor on pendrin total protein abundance occurs largely through changes in AT_2 receptor–induced nitric oxide production (62). Therefore, further studies are needed not only to further explore the interaction of aldosterone and angiotensin II on the MR within specific intercalated cell subtypes, but also to examine the role of MR^{S843-P} dephosphorylation in pendrin-mediated transport.

PENDRIN IS REGULATED BY K^+ INTAKE

During vascular volume depletion, angiotensin II production rises, which stimulates the adrenal gland to produce more aldosterone (42). Increased serum K^+ also stimulates aldosterone release but does so instead by depolarizing glomerulosa cells within the adrenal cortex, independently

of angiotensin II (42). Although increased circulating aldosterone concentration is observed both during vascular volume contraction and during hyperkalemia, these treatment models affect pendrin total protein abundance in very different ways. Whereas pendrin total protein abundance is stimulated during vascular volume contraction, it falls during hyperkalemia (42). The fall in pendrin protein abundance observed with increased dietary KCl intake has been attributed to a relative increase in MR S843 phosphorylation (42). However, the accompanying anion may affect the experimental results. For example, with increased dietary intake of KCl, pendrin total protein abundance falls, whereas pendrin total protein abundance is either unchanged or increased if dietary K^+ is given as $KHCO_3$ (52). Therefore, future studies examining the possible interaction of K^+ with the MR need to exclude a possible effect of the accompanying anion.

Although models of vascular volume contraction, such as dietary NaCl restriction, increase apical plasma membrane pendrin expression, the effects of changes in K^+ homeostasis on apical plasma membrane pendrin abundance are less well understood. For example, with changes in K^+ intake, apical plasma membrane pendrin abundance and pendrin total protein abundance in kidney may not change in tandem (67).

Pendrin and ENaC Are Upregulated with Increased Water Intake

It is well established that ENaC-mediated Na^+ absorption increases with increased luminal flow (68). Thus, our laboratory examined the effect of increased water intake on pendrin abundance. Raising water intake from 4 to 9 mL/day increased the relative expression of pendrin on the apical plasma membrane relative to the cytoplasm by ~75%, although total pendrin protein abundance was unchanged. Because water intake modulated pendrin subcellular distribution even when circulating vasopressin levels were clamped (69), increased water intake more likely stimulates pendrin by raising luminal flow rather than through a vasopressin receptor–mediated mechanism. Moreover, water intake modulated pendrin subcellular distribution without changing the circulating concentrations of hormones such as renin and aldosterone or without changing serum osmolality or arterial pH (69).

Mechanism of Pendrin Regulation by NaCl Intake

Dietary NaCl intake appears to regulate pendrin expression at least in part through the action of uroguanylin (70). Uroguanylin is a low-molecular-weight peptide hormone that is produced primarily within the intestine in response to dietary NaCl intake. The result is enhanced urinary NaCl and water excretion (70). Uroguanylin increases renal NaCl excretion at least in part by downregulating pendrin by inhibiting transcription through its action on the heat shock element of the pendrin promoter (70). Whether uroguanylin reduces apical plasma membrane pendrin abundance and whether it changes pendrin-mediated transport remain to be determined.

CONCLUSIONS

Both ENaC and pendrin localize to the CNT and the CCD, although these transporters are found within different cell types in these nephron segments. ENaC and pendrin are upregulated by angiotensin II, aldosterone, and increased water intake. The result is increased renal absorption of NaCl, which leads to vascular volume expansion and hypertension. Pendrin modulates ENaC abundance and function in kidney at least in part by increasing luminal HCO_3^- concentration and by reducing luminal ATP.

SUMMARY POINTS

1. Aldosterone administration in vivo stimulates pendrin and ENaC in tandem to augment electrogenic NaCl absorption in the CCD.
2. During NaCl restriction, pendrin acts in tandem with the Na^+-dependent Cl^-/HCO_3^- exchanger encoded by *Slc4a8* to mediate electroneutral, thiazide-sensitive NaCl absorption in the CCD.
3. Pendrin is upregulated by the renin–angiotensin II–aldosterone system.
4. Pendrin modulates ENaC abundance and function by increasing the luminal concentration of HCO_3^- and by reducing luminal ATP concentration.

FUTURE ISSUES

1. The signaling cascade whereby aldosterone stimulates the insertion of pendrin into the apical plasma membrane needs to be elucidated.
2. The molecular mechanism of the amiloride-sensitive component of Cl^- absorption within the CCD should be determined.
3. The effect of MR^{S843-P} dephosphorylation on aldosterone-stimulated Cl^- uptake in the CCD remains to be determined.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. This manuscript is not under consideration by another journal.

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