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RENAL REABSORPTION OF SODIUM and chloride is tightly linked in most segments, often occurring even through the same transport proteins such as the Na-K-2Cl$^-$ cotransporter NKCC2 or the Na-Cl cotransporter NCC in the thick ascending limb or the distal tubule, respectively (1, 6). In the proximal tubule and in parts of the collecting system, the transport of chloride and sodium is mediated by separate mechanisms and chloride fluxes occur through both paracellular and transcellular routes (8). Claudins have been implicated in regulating paracellular chloride fluxes, and a role for claudins 1–4 in the collecting duct has been proposed (13). However, the nature of the transcellular chloride transport pathway(s) in the collecting duct, particularly in the connecting tubule (CNT) and cortical collecting duct (CCD), has not been fully resolved. In these segments, sodium is reabsorbed via the luminal epithelial Na channel ENaC and the basolateral Na-K-ATPase in principal cells. However, these cells appear to have almost no chloride conductance on both membranes, excluding them as the route for transcellular chloride transport. In contrast, neighboring intercalated cells express a number of anion transport and anion channel proteins. Recent work by Palmer and Frindt (3) even analyzed these anion channels electrophysiologically, suggesting that these channels may belong to the superfamily of ClC channels, namely, the ClC-Kb/Barttin heterodimer.

Indeed, expression of the ClC-Kb/Barttin heterodimeric Cl$^-$ channel has been described by immunohistochemistry in all types of intercalated cells localized to the basolateral membrane (2). In acid-secretory type A intercalated cells, these Cl$^-$ channels have been suggested to participate together with the KCC4 K$^+$-Cl$^-$ cotransporter in the recycling of chloride across the basolateral membrane, which may be important for optimal function of the AE1 Cl$^-$/HCO_3^- exchanger. In contrast, in type B intercalated cells these channels may contribute to transepithelial chloride absorption (7, 8). The clinical picture of patients with mutations in both subunits as in Bartter syndrome type III and IV, however, has not helped to elucidate their role in type B intercalated cells, and experimental proof is still required. However, it should be noted that these patients suffer from a salt-losing tubulopathy and part of the defect may lie in the loss of transcellular chloride absorption via type B intercalated cells. The recent work of Eladari and colleagues (5, 9) and Wall and co-workers (10, 12) has shed new light on the apical chloride transport pathway in type B intercalated cells. Eladari et al. (5, 9) noted that pendrin expression strongly correlated with urinary chloride excretion, being low when large amounts of chloride are delivered to the connecting tubule and cortical collecting duct and being upregulated during chloride depletion. Similarly, Wall and colleagues (10, 12) described pendrin upregulation during NaCl restriction. In a contribution to this issue, Pech and co-workers (4) went one step further and directly analyzed chloride fluxes in isolated perfused mouse CCDs. They show that in CCDs from mice on a NaCl-replete diet, pendrin is downregulated and transepithelial voltage, V_T, and net chloride flux are close to zero. Application of angiotensin II has no effect on V_T and chloride flux. During treatment with furosemide, pendrin expression was upregulated, while a lumen-negative V_T with net chloride absorption was generated and chloride flux was further enhanced by angiotensin II. In contrast, in CCDs from pendrin-deficient mice (*Slc26a4−/−*) treated identically, they observed a V_T close to zero and net chloride secretion in both the absence and presence of angiotensin II. What is the driving force for chloride absorption via pendrin? Since pendrin, like apical anion exchange, is likely electroneutral, it may not be directly affected by the V_T. Pech et al. measured chloride absorption when the driving force for paracellular chloride absorption was eliminated by inhibiting the epithelial Na channel ENaC with benzamil. At a V_T of ~0, net chloride absorption fell only partially. The availability of HCO_3^- as a intracellular substrate for pendrin depends on the hydration of carbon dioxide and the formation of HCO_3^- and H^+ catalyzed by carbonic anhydrase II. Protons are removed through the action of vacuolar H^+-ATPases, thereby leaving the bicarbonate as a driving force for pendrin-mediated chloride absorption (11). When the vacuolar H^+-ATPases were inhibited, benzamil-insensitive chloride absorption was completely abolished, demonstrating the tight coupling of H^+-ATPases and pendrin function and the requirement for HCO_3^- to drive chloride absorption.

The establishment of pendrin as a pathway for transcellular chloride absorption in the connecting tubule and cortical collecting segment certainly emphasizes the role of intercalated cells not only in acid-base transport but also in the control of electrolyte homeostasis and ultimately blood pressure.

Many questions remain open: what is the relative importance of pendrin as transcellular transport pathway in relation to paracellular pathways under various conditions; how are pendrin abundance and activity regulated and coordinated with ENaC activity; what is the chloride sensor that mediates pendrin upregulation during chloride depletion; and is pendrin involved in the development of hypertension?

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REFERENCES

1. **Biner HL, Arpin-Bott MP, Loffing J, Wang X, Knepper M, Hebert SC, Kaissling B.** Human cortical distal nephron: distribution of electrolyte and water transport pathways. *J Am Soc Nephrol* 13: 836–847, 2002.
2. **Estevez R, Boettger T, Stein V, Birkenhager R, Otto E, Hildebrandt F, Jentsch TJ.** Barttin is a Cl$^-$ channel beta-subunit crucial for renal Cl$^-$ reabsorption and inner ear K$^+$ secretion. *Nature* 414: 558–561, 2001.
3. **Palmer LG, Frindt G.** Cl$^-$ channels of the distal nephron. *Am J Physiol Renal Physiol* 291: F1157–F1168, 2006.
4. **Pech V, Kim YH, Weinstein AM, Everett LA, Pham TD, Wall SM.** Angiotensin II increases chloride absorption in the cortical collecting duct

in mice through a pendrin-dependent mechanism. *Am J Physiol Renal Physiol* 292: F914–F920, 2007.

5. **Quentin F, Chambrey R, Trinh-Trang-Tan MM, Fysekidis M, Cambillau M, Paillard M, Aronson PS, Eladari D.** The Cl^-/HCO_3^- exchanger pendrin in the rat kidney is regulated in response to chronic alterations in chloride balance. *Am J Physiol Renal Physiol* 287: F1179–F1188, 2004.
6. **Reilly RF, Ellison DH.** Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. *Physiol Rev* 80: 277–313, 2000.
7. **Schuster VL.** Cortical collecting duct bicarbonate secretion. *Kidney Int Suppl* 33: S47–S50, 1991.
8. **Schuster VL, Stokes JB.** Chloride transport by the cortical and outer medullary collecting duct. *Am J Physiol Renal Fluid Electrolyte Physiol* 253: F203–F212, 1987.
9. **Vallet M, Picard N, Loffing-Cueni D, Fysekidis M, Bloch-Faure M, Deschenes G, Breton S, Meneton P, Loffing J, Aronson PS, Chambrey R, Eladari D.** Pendrin regulation in mouse kidney primarily is chloride-dependent. *J Am Soc Nephrol* 17: 2153–2163, 2006.
10. **Verlander JW, Kim YH, Shin W, Pham TD, Hassell KA, Beierwaltes WH, Green ED, Everett L, Matthews SW, Wall SM.** Dietary Cl^- restriction upregulates pendrin expression within the apical plasma membrane of type B intercalated cells. *Am J Physiol Renal Physiol* 291: F833–F839, 2006.
11. **Wagner CA, Finberg KE, Breton S, Marshansky V, Brown D, Geibel JP.** Renal vacuolar-ATPase. *Physiol Rev* 84: 1263–1314, 2004.
12. **Wall SM, Kim YH, Stanley L, Glapion DM, Everett LA, Green ED, Verlander JW.** NaCl restriction upregulates renal Slc26a4 through subcellular redistribution: role in Cl^- conservation. *Hypertension* 44: 982–987, 2004.
13. **Yamauchi K, Rai T, Kobayashi K, Sohara E, Suzuki T, Itoh T, Suda S, Hayama A, Sasaki S, Uchida S.** Disease-causing mutant WNK4 increases paracellular chloride permeability and phosphorylates claudins. *Proc Natl Acad Sci USA* 101: 4690–4694, 2004.