The emerging role of pendrin in renal chloride reabsorption

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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-CI 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 channel proteins. Recent work by Palmer and Frindt (3) even analyzed these anion channels electrophysiological, suggesting that these channels may belong to the superfamily of CIC channels, namely, the CIC-Kb/Barttin heterodimer.

Indeed, expression of the CIC-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⁻/HCO₃⁻ 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 chloride absorption. In experimental studies, pendrin expression was upregulated when the lumen-negative Vₗ and net chloride absorption was generated and chloride flux was further enhanced by angiotensin II. Indeed, 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 Vₗ of ~0, net chloride absorption fell only partially. The availability of HCO₃⁻ as an intracellular substrate for pendrin depends on the hydration of carbon dioxide and the formation of HCO₃⁻ 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 HCO₃⁻ 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?

REFERENCES


