Review

Cellular Physiology and Biochemistry

Cell Physiol Biochem 2011;28:497-504

Accepted: August 22, 2011

The Anion Exchanger Pendrin (SLC26A4) and Renal Acid-base Homeostasis

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Key Words

Kidney • Collecting duct • Intercalated cells • Bicarbonate secretion • Alkalosis • Acidosis

Abstract

The anion exchanger pendrin (Pds, SLC26A4) transports various anions including bicarbonate, chloride and iodide. In the kidney, pendrin is exclusively expressed on the luminal pole of bicarbonate-secretory type B intercalated cells. Genetic ablation of pendrin in mice abolishes luminal chloride-bicarbonate exchanger activity from type B intercalated cells suggesting that pendrin is the apical bicarbonate extruding pathway. The renal expression of pendrin is developmentally adapted and pendrin positive cells originate from both the uretric bud and mesenchyme. In adult kidney, pendrin expression and activity is regulated by systemic acid-base status, dietary electrolyte intake (mostly chloride), and hormones such as angiotensin II and aldosterone which can affect subcellular localization, the relative number of pendrin expressing cells, and the overall abundance consistent with a role of pendrin in maintaining normal acid-base homeostasis. This review summarizes recent findings on the role and regulation of pendrin in the context of the kidneys role in acid-base homeostasis in health and disease.

Introduction

The kidneys control systemic acid-base homeostasis in concert with other organs including the lung, liver, bone, skeletal muscle or intestine. The kidneys continually sense, and control levels of protons and bicarbonate, in part by adapting the synthesis of bicarbonate from glutamine (by the proximal tubule) or CO_2 (by the collecting duct). Furthermore they regulate the reabsorption or excretion of bicarbonate, respectively, along the nephron to maintain acid base homeostasis. Several nephron segments participate in the reabsorption of filtered bicarbonate which takes places along the proximal tubule, the thick ascending limb of the loop of Henle, and is normally completed in the distal convoluted tubule. The late distal convoluted tubule (DCT2), the connecting tubule, and cortical collecting duct, however, are the only segments that can also actively secrete bicarbonate into urine, a process activated and important during metabolic or respiratory alkalosis. The cells responsible for bicarbonate secretion are type B intercalated cells [1].

At least two subtypes of intercalated cells can be distinguished based on morphological criteria and functional activities (Fig. 1) [1]. Type A intercalated cells secrete protons into urine and release bicarbonate across the basolateral membrane into blood. These cells are characterized by the luminal expression of V-type H^+-

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ATPases and the presence of the basolateral anion exchanger AE1 (anion exchanger1 (SLC4A1), also named Band 3) [1-3]. In contrast, type B intercalated cells secrete bicarbonate into urine and express basolateral V-type H^+-ATPases. On the luminal pole of type B intercalated cells, pendrin (SLC26A4) is present [1-2, 4-6]. Some authors propose a third type of intercalated cells, non-A, non-B intercalated cells that are characterized by the apical expression of pendrin and the apical localization of H^+-ATPases. In some of these cells, H^+-ATPases may be present on both poles [7-8]. It has remained controversial if the latter cell type is a distinct cell type or only one activity state of type B intercalated cells. Importantly, the different subcellular localizations of H^+-ATPases in type B intercalated cells may have an impact on the overall function of these cells (Fig. 1). Expression of pendrin and H^+-ATPases on opposing cell poles generate cells that are adding bicarbonate into urine and secreting protons into the blood thereby neutralizing and removing bicarbonate from the body and absorbing chloride. In contrast, concomitant expression of H^+-ATPases and pendrin on the luminal pole will cause the parallel secretion of protons and bicarbonate in exchange for chloride resulting in the net movement of chloride without affecting acid-base homeostasis. This would be consistent with the function of an elusive chloride-pumping ATPase described earlier in kidney preparations [9]. Whether the two states of type B intercalated cells are regulated during conditions that affect primarily either chloride homeostasis or acid-base status has not been investigated to date but would provide valuable insights into the role and regulation of these substates of type B intercalated cells.

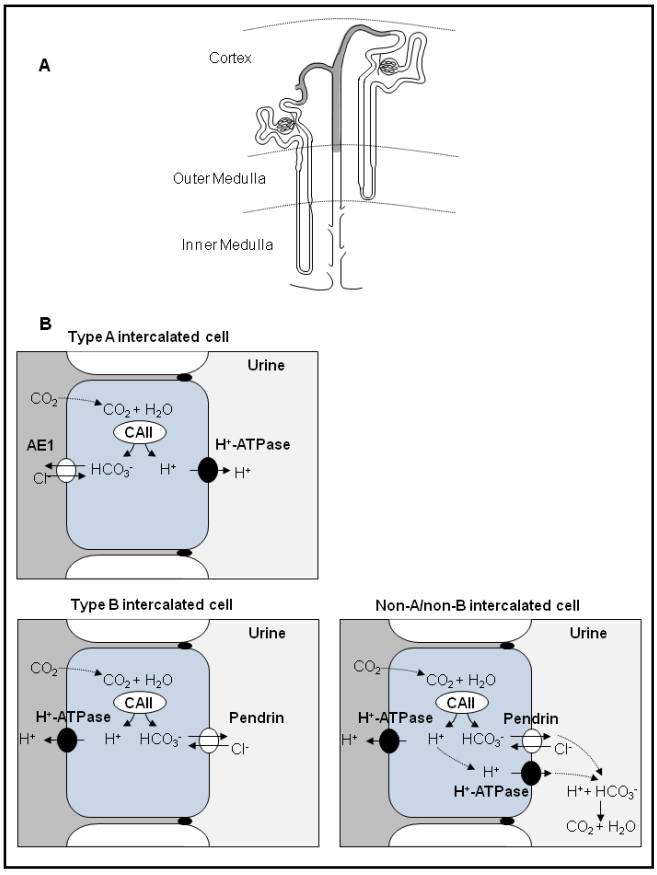

Fig. 1. Localization of pendrin in kidney and transport mode of various intercalated cells. (A) Scheme of mammalian nephron indicating the segments expressing pendrin (grey shaded) starting from the late distal convoluted tubule (DCT2) and extending to the initial part of the outer medullary collecting duct including also the connecting tubule and cortical collecting duct. (B) Schematic models of different subtypes of intercalated cells. Type A intercalated cells (upper panel) express basolaterally AE1 and apically H^+-ATPases resulting in urinary acidification and release of newly formed bicarbonate into blood. Two different types of non-type A intercalated cells can be found (lower panel), type B intercalated cells and non-A/non-B intercalated cells. Type B intercalated cells express pendrin and H^+-ATPases on opposite membranes resulting in the net excretion of bicarbonate and the generation of a proton released into blood (lower left panel). In contrast, non-A/non-B intercalated cells coexpress pendrin and H^+-ATPases together on the luminal membrane with variable presence of basolateral H^+-ATPases. This type of intercalated cells absorbs chloride but does not cause the net movement of acid-base equivalents (lower right panel).

Pendrin functions as an anion exchanger

Pendrin (SLC26A4) was identified as the gene mutated in patients with Pendred syndrome (OMIM #274600) [10]. Pendred syndrome is inherited in an autosomal recessive manner and clinically characterized by hypothyroidism and goiter as well as sensorineural deafness due to inner ear malformations including the enlarged vestibular aqueduct syndrome [11-12]. Subsequent studies demonstrated first the ability of pendrin to transport iodide [13], later to function as an obligatory exchanger for various anions including chloride, bicarbonate, nitrate, and formate when expressed in a heterologous expression system like *Xenopus* oocytes [14]. *In ex vivo* preparations of isolated cortical collecting ducts, pendrin dependent transport of chloride and bicarbonate has been documented [4, 15-17]. Whether formate or nitrate are *in vivo* substrates remains an open question. Mice lacking pendrin have lower serum iodide levels and a higher urinary iodide excretion suggesting a role of pendrin in iodide absorption, possibly in exchange

for intracellular bicarbonate [18]. Unfortunately, no specific blocker of pendrin transport function is available to date.

Localization and expression of pendrin in the kidney

In the kidney, pendrin is exclusively expressed by non-type A intercalated cells and only at the apical pole of these cells [4-6, 19-20]. Localization of pendrin has been reported in much detail from mouse and rat kidney, and also been described to be present in human kidney. However, the exact distribution in human kidney has been examined with much less detail to date. In adult rodent kidney, pendrin positive cells are detected in the late distal convoluted tubule (DCT2), along the connecting tubule (CNT), and cortical collecting duct (CCD) [4-6, 19-20]. Some pendrin positive cells extend to the initial part of the outer medullary collecting duct (OMCD). This distribution perfectly matches the localization of type B intercalated cells as described previously by electron microscopy, functional experiments, and binding of specific lectins [7-8, 21].

During rat kidney development, pendrin positive cells are detected first around embryonic day E14 in the cortex and E18 in the medulla consistent with the start of differentiation of the collecting duct and its cells in rodent kidney [20]. In contrast to adult kidney, pendrin positive cells are found also in the inner medulla and inner part of the outer medulla [20]. The existence of type B intercalated cells in these regions in rodent embryonic kidney had been reported earlier based on the typical appearance of these cells by electron microscopy. Pendrin positive cells persist for several days after birth in mouse and rat kidney and disappear as the postnatal maturation of the kidney is completed [20, 22]. Removal of pendrin positive type B intercalated cells involves most likely apoptosis of these cells [20, 23]. In human kidney, pendrin positive cells are first observed around gestation week 26 but restricted to the cortex. During further development, pendrin positive cells were only detected in the cortex but not in the inner or outer medulla [24]. Moreover, the relative percentage of pendrin positive intercalated cells was lower in human kidney (approx. 30 %)[24] than in rodent kidney where a majority of intercalated cells in the CNT and CCD are pendrin positive [5-6, 25-26].

The factors that regulate pendrin expression and the differentiation of type B intercalated cells are not well understood. Several factors that affect intercalated cell differentiation in mouse kidney have been described including Foxi1, CP2L1, the bradykinin receptor 2, and putatively Klf4 [27-30].

Lack of pendrin abolishes bicarbonate secretion by type B intercalated cells

Important insights into the function of pendrin in mammalian kidney have been gained from mice lacking pendrin (*Pds* KO mice). Royaux and colleagues reported a *Pds* KO mouse and used *in vitro* microperfusion experiments of isolated cortical collecting ducts from mice made alkalotic by a combination of sodium bicarbonate and the aldosterone analogue DOCP [4]. In cortical collecting ducts from wild type mice this treatment induced a bicarbonate secretory response as expected. In contrast, in cortical collecting ducts from *Pds* KO mice no bicarbonate secretion could be detected demonstrating that pendrin is required for bicarbonate secretion by type B intercalated cells [4]. The laboratory of Susan Wall demonstrated that luminal chloride/bicarbonate exchanger activity is absent from type B intercalated cells in cortical collecting ducts isolated from *Pds* KO mice. Taken together, these data provide strong evidence that pendrin represents the apical chloride/bicarbonate exchanger of type B intercalated cells and that no other pathway can substitute for the loss of pendrin activity. These results were later confirmed in a second independent *Pds* KO mouse model [17].

Whether pendrin has a similar function in human kidney has not been reported to date. Two case reports from patients with Pendred syndrome describe the occurrence of massive metabolic alkalosis in the setting of extracellular volume contraction consistent with a possible role of pendrin in renal bicarbonate secretion and the defense against metabolic alkalosis [31-32]. However, the degree of metabolic alkalosis might be only the result of severe volume depletion. Since urine data were not reported in sufficient detail, and no clinical test for the bicarbonate-secretory function of type B intercalated cells has been designed to date, it is impossible to distinguish these two possibilities from the studies conducted.

Regulation of Pendrin by acid-base status

In vitro regulation of pendrin expression and activity

The regulation of pendrin by various factors has been studied *in vitro* in several renal and non-renal cell lines

expressing a series of promoter constructs of the human pendrin gene [33]. These studies measuring luciferase activity demonstrated that acidification of the cell culture medium reduced luciferase activity in HEK293 cells transfected with the human pendrin promoter construct. In contrast, alkalinization of the medium increased luciferase activity suggesting that the promoter may have a pH responsive element. However, this pH-sensitive response may also depend on the cellular context since it was not observed in all cell lines used in this study. The same study also explored the interaction of aldosterone with the human pendrin promoter and observed a 40 % reduction in luciferase activity when cells were exposed to 10 nM aldosterone [33].

Another important aspect of pendrin function is the regulation by acid-base status and local pH (see also below for *in vivo* studies). The anion exchanger activity of heterologous expressed pendrin is sensitive to changes of intra- and extracellular pH where low intra- or extracellular pH stimulate pendrin activity [34]. Removal of two different N-glycosylation sites abolished the sensitivity to extracellular pH revealing a novel function of glycosylations in membrane transport proteins [34].

In vivo regulation by acid-base status

Expression of pendrin in rodent kidney is regulated by systemic acid-base status. Down-regulation of pendrin protein abundance was shown in mice and rats given NH_4Cl in food or drinking water to induce metabolic acidosis [19, 35-36]. In rat kidney, downregulation of pendrin occurs on mRNA and protein levels [19, 35] and is associated with reduced luminal chloride/bicarbonate exchanger activity in type B intercalated cells as determined in isolated and microperfused cortical collecting ducts from NH_4Cl-loaded rats [35]. Conversely, induction of metabolic alkalosis with sodium bicarbonate added to drinking water or food increased pendrin protein expression in mouse [36] and rat kidney [19].These experiments were collectively interpreted as regulation of pendrin protein abundance by acid-base status where acidosis would decrease and alkalosis increase pendrin expression and possibly function.

However, subsequent work by the groups of Susan Wall and Dominique Eladari uncovered a potent regulation of pendrin expression and function by dietary chloride intake, systemic chloride status and urinary chloride excretion [37-40]. Acid-base status and chloride homeostasis are intricately linked, and most types of acidosis are associated with hyperchloremia and hyperchloruria. However, alkalosis is often linked to hypochloremia and low urinary chloride excretion. Thus, the interpretation of the effects of NH_4Cl, and $NaHCO_3$ containing diets on renal pendrin expression is much less straight forward as previously thought. We approached the question whether pendrin expression in mouse kidney was regulated by chloride alone, or systemic acid-base status as well by feeding mice different diets where different cations and anions were systematically replaced. These studies demonstrated that chloride is a major determinant of renal pendrin expression but that systemic acidosis is another independent factor down regulating pendrin expression even if chloride depletion is present (which would otherwise stimulate pendrin expression) [41]. Additional support for this concept comes from experiments where rats were treated with the carbonic anhydrase inhibitor acetazolamide and a decrease in pendrin protein abundance was found [42].

Regulation by angiotensin II and aldosterone

Angiotensin II and aldosterone are major hormones involved in maintaining extracellular NaCl and fluid balance thereby determining circulating blood volume and blood pressure. Another important function of these hormones is to regulate the renal adaptation to acid-loading or acidosis [1]. Angiotensin II stimulates pendrin-dependent chloride absorption in microperfused mouse cortical collecting ducts. Unfortunately, the effects on net bicarbonate secretion were not measured under the same conditions. However, Weiner at al. reported that peritubular angiotensin II stimulates luminal alkalinization, hence bicarbonate secretion, in rabbit early cortical collecting duct [43]. Moreover, the stimulatory effect of angiotensin II on chloride absorption was completely blocked by an inhibitor of the V-type H^+-ATPase demonstrating that this pump provides the driving force for pendrin mediated anion exchange (see also below). In line with these observations, we found that angiotensin II directly stimulates V-type H^+-ATPase activity in mouse cortical collecting duct intercalated cells and enhances membrane H^+-ATPase staining [44].

Verlander et al. reported that treatment of mice with the aldosterone analogue deoxycorticosterone pivalate (DOCP) stimulated pendrin mRNA and protein expression and enhanced pendrin localization at the luminal membrane [16]. More recently, we compared the treatment of mice with deoxycorticosterone actetate (DOCA), $NaHCO_3$ or with combination of both. In mice receiving DOCA or $NaHCO_3$ alone we did not observe a change in pendrin mRNA or protein expression after 7 days of treatment, whereas mice receiving the

combination had elevated pendrin mRNA and protein abundance (Mohebbi et al. unpublished data). *In vitro* data had suggested that alkaline pH would increase pendrin transcription whereas aldosterone would decrease it [33]. The *in vivo* data from Verlander and our observations are not consistent with these *in vitro* data and it remains open if these discrepancies are species-specific (human vs mouse) or represent an experimental difference (*in vitro* vs. *in vivo*).

Functional interaction with H^+-ATPases and carbonic anhydrases

Pendrin functions most likely as electroneutral chloride/bicarbonate exchanger in the collecting duct system [15]. Thus, the main driving force for transport must come from substrate gradients for chloride, bicarbonate or both. The gradient for chloride may not be sufficient and elegant microperfusion experiments suggested that bicarbonate gradients provide the main driving force for chloride absorption [15]. Bicarbonate is generated by intercalated cells from the intracellular hydration of CO_2 and the conversion of H_2CO_3 to H^+ and HCO_3^- catalyzed by carbonic anhydrase II (CAII). Ultimately, the efficacy of this reaction will depend on the removal of protons or bicarbonate from the intracellular compartment. Thereby the activity of V-type H^+-ATPases becomes critical for driving bicarbonate secretion through pendrin as secretion of protons will increase the availability of intracellular bicarbonate for pendrin dependent chloride absorption and bicarbonate secretion. Indeed, pharmacological blockade of H^+-ATPases abolishes pendrin mediated chloride absorption in microperfused cortical collecting ducts [15].

Similarly, genetic ablation of the B1 subunit of H^+-ATPases affects pendrin function. The B1 subunit (ATP6V1B1) is highly expressed in all types of intercalated cells and forms part of both apical and basolateral H^+-ATPases. Humans with ATP6V1B1 mutations develop distal renal tubular acidosis and this phenotype is mimicked in mice lacking *Atp6v1b1* when challenged with an acid-load [45, 46]. Interestingly, B1 deficient mice appear to be also more prone to develop metabolic alkalosis when treated with $NaHCO_3$ and DOCA (Kovacikova et al. unpublished data). In wild type animals, this treatment increases pendrin expression and is associated with the presence of H^+-ATPases containing the B1 subunit as well as other H^+-ATPase subunits (A, a4) at the basolateral pole of type B intercalated cells. In B1 KO mice, being more alkalotic under this treatment, pendrin expression is reduced despite an increase in the relative number of pendrin expressing cells and H^+-ATPase complexes are not found at the basolateral side along with a reduced H^+-ATPase activity in cortical collecting duct intercalated cells. Apical H^+-ATPases maintain localization and residual activity as the B2 isoform can partly compensate for the absence of B1 [45, 47, 48]. Thus, pharmacological and genetic evidence suggests that H^+-ATPase function is of critical importance for pendrin function and possibly expression.

Along the same line, generation of intracellular bicarbonate depends on carbonic anhydrase activity catalyzing the reaction of CO_2 and water. In intercalated cells the predominant isoform is carbonic anhydrase II (CA II). Mutations in the gene encoding carbonic anhydrase II in humans (OMIM #259730) lead to a mixed type of renal tubular acidosis with proximal tubular defects in bicarbonate reabsorption and distal impairment of type A, type B, and non-A/non-B intercalated cells with diminished urinary acidification and net acid excretion [49]. In mice lacking carbonic anhydrase II a major reduction in the number of all types of intercalated cells has been detected [50] and a consistent decrease in pendrin mRNA and protein excretion [51]. Whether the decrease of pendrin expression is only the result of a reduced number of intercalated cells or also affected by the metabolic acidosis caused by the loss of carbonic anhydrase has not been tested [52].

Regulation of pendrin in disease models

Aberrant pendrin expression has been reported in a number of disease models where pendrin may be involved either directly contributing to the patho-mechanism or being regulated as a consequence of pathologic processes.

The direct involvement of pendrin in the pathogenesis of aldosterone and chloride dependent hypertension has been deduced from a series of experiments demonstrating the regulation of pendrin expression by dietary salt and particularly chloride intake, its regulation by aldosterone analogues, and the fact that pendrin deficient mice are resistant to aldosterone and salt induced hypertension [15-16, 37-40]. There are several excellent reviews covering this aspect of pendrin function and regulation [53-55].

In animal models of various types of metabolic or respiratory acidosis, downregulation of pendrin is observed [19, 35-36, 41, 56, 57]. Inappropriately high expression of pendrin was observed in rats treated with the calcineurin

inhibitor FK506 (tacrolimus) and loaded with NH_4Cl [26]. In contrast, the susceptibility to develop a more pronounced metabolic acidosis in hypothyroid rats is not associated with dysregulated pendrin expression [25]. The interpretation of these results is complicated by the fact that most conditions are associated with hyperchloremia and increased urinary chloride excretion causing downregulation of pendrin expression per se.

Chronic hypokalemia increases renal acid excretion and thereby can cause metabolic alkalosis. In mouse kidney, chronic hypokalemia downregulates pendrin expression [36]. This down regulation would impair the renal response to metabolic alkalosis and contribute to the maintenance of metabolic alkalosis. However, hypokalemia causes also a fall in intracellular pH due to the shift of intracellular potassium into the extracellular space in exchange for protons. As discussed above, intracellular low pH stimulates the anion exchanger activity of pendrin [34] which may counteract the metabolic alkalosis despite lower pendrin protein expression levels.

Administration of loop diuretics such as furosemide can be associated with the development of hypokalemia and metabolic alkalosis. In rats treated for 7 days with furosemide and substitution of salt and potassium with drinking water, no obvious hypokalemia or metabolic alkalosis developed but pendrin subcellular localization was shifted from a more cytosolic pool to the luminal membrane together with increased expression of H^+-ATPases [58]. A third model of metabolic alkalosis was reported by Wang et al, inducing hypercalcemic metabolic alkalosis in rats with PTH infusions. In this model, various acid-base transporters were regulated, however, no change in pendrin protein abundance or subcellular localization was reported [59].

Lithium therapy can be associated with the development of nephrogenic diabetes insipidus and also distal renal tubular acidosis [60, 61]. In rats treated with lithium, diabetes insipidus was induced and the recovery from an NH_4Cl load delayed consistent with an incomplete distal renal tubular acidosis [62]. Renal expression of pendrin was not altered despite changes in several other renal acid-base transport proteins [62].

Unilateral ureter obstruction (UUO) and other forms of obstructive renal disease lead to tubular remodeling and may be associated in some forms with transient or persistent forms of renal tubular acidosis, mostly distal renal tubular acidosis [63, 64]. In a rat model of adult bilateral ureter obstruction (for 24 hrs), a strong decrease in the expression of some acid-base transporting protein such as NHE3 or NBCn1 was documented. Pendrin, however, was only modestly downregulated [65]. In rats with unilateral ureter obstruction performed 48 hrs after birth, pendrin was initially upregulated and after 14 weeks of obstruction slightly down regulated together with a reduced ability of the rats to clear an NH_4Cl acid-load [66]. A detailed study in human kidneys from patients with inborn ureter obstructions demonstrated that pendrin positive cells appeared earlier during gestation and were more abundant at different prenatal stages. After birth, the number of pendrin positive cells declined sharply and was lower than in age-matched control kidneys. Whether these changes in pendrin protein abundance in rat experimental models and pendrin positive cells in human kidney are the result of collecting duct remodeling in response to altered urinary flow and pressure or caused by the ensuing metabolic acidosis has not been elucidated to date. Remodeling of the collecting duct may involve also the extracellular matrix protein hensin that has been shown in a mouse model to be required for the presence of type A intercalated cells that might originate from cells expressing pendrin [67].

Summary and outlook

The function and regulation of pendrin in the kidney has received much attention since the identification of this important anion exchanger. However, important questions have remained open. The role of pendrin and type B intercalated cells in the defense against alkalosis is not settled. Mouse data demonstrate impressively that pendrin is required for bicarbonate secretion during alkalosis, is regulated during alkalosis, and that lack of pendrin impairs the renal response to alkalosis. However, no information on renal function and the response to alkalosis is available from patients with Pendred syndrome. Few case reports suggest a possible link but this will require more systematic and detailed analysis. Moreover, the regulation of pendrin by hormones, second messengers, and transcription factors is not fully elucidated.

Acknowledgements

Work in the authors laboratory was supported by grants from the Swiss National Science Foundation and the 7th EU Frame work project EUNEFRON.

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