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Regulation of Extracellular Fluid Volume and Blood Pressure by Pendrin

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Key Words

Intercalated cells • NDCBE • AQP5 • Distal nephron • Cell volume • ATP

Abstract

Na^+ is commonly designed as the culprit of salt-sensitive hypertension but several studies suggest that abnormal Cl^- transport is in fact the triggering mechanism. This review focuses on the regulation of blood pressure (BP) by pendrin, an apical Cl^-/HCO_3^- exchanger which mediates HCO_3^- secretion and transcellular Cl^- transport in type B intercalated cells (B-ICs) of the distal nephron. Studies in mice showed that it is required not only for acid-base regulation but also for BP regulation as pendrin knock-out mice develop hypotension when submitted to NaCl restriction and are resistant to aldosterone-induced hypertension. Pendrin contributes to these processes by two mechanisms. First, pendrin-mediated Cl^- transport is coupled with Na^+ reabsorption by the Na^+-dependent Cl^-/HCO_3^- exchanger NDCBE to mediate NaCl reabsorption in B-ICs. Second, pendrin activity regulates Na^+ reabsorption by the adjacent principal cells, possibly by interaction with the ATP-mediated paracrine signalling recently identified between ICs and principal cells. Interestingly, the water channel AQP5 was recently found to be expressed at the apical side of B-ICs, in the absence of a basolateral water channel, and pendrin and AQP5 membrane expressions are both inhibited by K^+ depletion, suggesting that pendrin and AQP5 could cooperate to regulate cell volume, a potent stimulus of ATP release.

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Introduction

Arterial hypertension is one of the most common diseases affecting the human population. Hypertension is a complex trait influenced by many environmental and genetic factors acting both alone and in concert. Several organs (*e.g.* the kidney, heart, vasculature and central nervous system) are involved in the maintenance of blood pressure. Transient disruption of any of these systems can lead to an acute variation in blood pressure.

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However, A. Guyton proposed almost 40 years ago, using a complex and sophisticated mathematical and computational analysis, that abnormal ion transport by the kidney and subsequent disruption of body fluid volumes are responsible for the development of hypertension [1]. The central role of the kidney in this pathology has since been confirmed by human genetic studies, which have shown that most of the genes mutated in monogenic forms of hypertension encode either ion transporters/channels of the distal nephron or their regulators [2].

Na^+ is commonly designated as the culprit in salt-sensitive hypertension. Several lines of evidence however suggest that it is in fact an increase in Cl^- transport that leads to an increase in extracellular volume and hypertension. In 1929, Berghoff et al. reported that blood pressure increased in seven hypertensive individuals on a high NaCl intake, but not on a high sodium bicarbonate intake [3]. This observation was subsequently confirmed [4]. In humans and animals with salt-sensitive hypertension, selective dietary loading of Na^+ without Cl^- has repeatedly failed to induce a pressor effect [5-9], leading to the proposal that Cl^- restriction might be more appropriate than Na^+ restriction in the treatment of essential hypertension [10]. Furthermore, in hypertensive and normotensive individuals, substitution of dietary NaCl with equimolar sodium bicarbonate leads to a blood pressure reduction [11, 12]. Finally, it has been proposed that primary alteration in distal Cl^- transport *per se* may have consequences on blood pressure [13, 14]. In this context, recent studies have highlighted the role of the Cl^-/HCO_3^- exchanger pendrin in the regulation of blood pressure.

Chloride transport in the distal nephon

As mentioned above, numerous studies have established that excessive ion transport in the distal nephron leads to the development of hypertension. This part of the nephron comprises the Distal Convoluted Tubule (DCT), the Connecting Tubule (CNT) and the Collecting Duct (CD). Each segment expresses a specific subset of ion transporters and channels, reflecting a high degree of functional specification [15].

DCT cells express the Na^+-Cl^- cotransporter NCC and are thus responsible for electroneutral Na^+ and Cl^- reabsorption. NCC activity is blocked by one of the most widely used class of anti-hypertensive agents, the thiazide diuretics [16]. Inactivating mutations of NCC in humans [17] and mice [18] cause Gitelman syndrome, an inherited recessive disease characterised by salt wasting and low blood pressure. Conversely, increased activity of this cotransporter triggers the development of Familial Hyperkalemic Hypertension [19, 20], a rare Mendelian form of human arterial hypertension, also known as Gordon's syndrome or Pseudohypoaldosteronism type II [21]. These studies thus demonstrated that NCC plays an important role in the regulation of blood pressure. However, given that it reabsorbs Na^+ and Cl^- concomitantly, the impact of Cl^- on blood pressure is not dissociable from that of Na^+ in DCT cells.

In contrast, Na^+ and Cl^- transport are not molecularly linked in the CNT and CD. These segments are composed of two cell types: the Principal Cells (PCs) and Intercalated Cells (ICs). While Na^+ is reabsorbed in PCs by the Epithelial Na^+ Channel ENaC, Cl^- transport occurs in ICs and, at least in theory, through a paracellular pathway [22]. At least two subtypes of ICs coexist in the CNT and CD [23, 24]. The A-type (A-ICs) secrete H^+ through an apical vacuolar H^+-ATPase and reabsorb HCO_3^- via a basolateral Cl^-/HCO_3^- exchanger while the B-type secretes HCO_3^-. *In vitro* microperfusion and patch-clamp experiments on isolated CDs show that Cl^- can only be actively reabsorbed by the B-type, via an apical electroneutral Cl^-/HCO_3^- exchanger. Cl^- then exits this cell via a basolateral Cl^- channel. This anion exchange process, which can also operate in a Cl^- self-exchange mode and is regulated chronically by *in vivo* acid-base status [22], is mediated by pendrin [25].

Pendrin localisation and regulation in the distal nephron

Pendrin, encoded by the *Slc26a4* gene, was originally identified by the genetic analysis of the Pendred syndrome, a syndromic deafness with progressive sensorineural hearing loss associated with goiter [26]. It can operate as a Cl^-/iodine, Cl^-/formate or Cl^-/HCO_3^- exchanger [27-29]. In addition to being expressed in the inner ear and the thyrocytes, pendrin is localised at the apical membrane of the B-ICs [25, 30, 31] and microperfusion studies in CD isolated from *Scl26a4*$^{-/-}$ knock-out mice clearly showed that pendrin is responsible for the Cl^-/HCO_3^- exchange in these cells [25]. Importantly, the same study also demonstrated that pendrin-mediated Cl^- transport is the most important, if not the only, pathway for Cl^- absorption in the CNT and CD.

The role of pendrin in kidney homeostasis has first been assessed by describing its regulation in response to several challenges *in vivo*. As pendrin was identified as

the apical mechanism of bicarbonate secretion by B-IC, the first studies were initially designed to test the effects of metabolic alkalosis and acidosis and logically observed that pendrin expression is decreased by metabolic acidosis and increased by metabolic alkalosis as reviewed extensively elsewhere in this issue (reviewed by C.Wagner in this issue of the journal). However, we also reported that pendrin expression in rat is increased when Cl^- excretion decreases and vice-versa, independently of the administered cation or acid-base status [32, 33].

Vascular volume depletion and aldosterone administration are known for triggering metabolic alkalosis and aldosterone increases apical anion exchange in B-ICs [34, 35]. Accordingly, aldosterone was shown not only to increase pendrin transcription level but to also induce a shift of pendrin subcellular distribution towards the apical membrane of B-ICs [31]. Angiotensin II also stimulates pendrin expression in the kidney [36].

Taken together, the aforementioned studies supported the critical role of pendrin in acid-base regulation. However, the observation that Cl^- might be an even stronger regulator than acid-base status and that pendrin is stimulated by component of the renin-angiotensin-aldosterone axis raised the possibility that pendrin might also be involved in the control of extracellular fluid volume.

Regulation of extracellular fluid volume by pendrin

Genetic inactivation of pendrin in humans (Pendred patients) and mice (*Slc26a4*$^{-/-}$ model) does not apparently impair acid-base and electrolyte balance [25]. Verlander et al. tested the hypothesis that a renal phenotype could be unmasked by "stressing the phenotype" of *Scl26a4*$^{-/-}$ mice [31]. The authors therefore submitted *Slc26a4*$^{+/+}$ and *Slc26a4*$^{-/-}$ mice to a chronic administration of DOCP (deoxycorticosterone pivalate), an aldosterone analogue. They observed that, following this treatment, mice devoid of pendrin develop metabolic alkalosis and that CCDs isolated from these mice are not able to secrete HCO_3^-. However, the authors also observed that, while *Slc26a4*$^{+/+}$ mice receiving DOCP chronically gain weight and become hypertensive, the body weight and blood pressure of the mutant mice remain stable. This study thus demonstrated that, in the absence of pendrin, aldosterone is not able to provoke renal NaCl retention and extracellular fluid expansion. The same group then studied the effect of dietary NaCl restriction on acid-base and electrolyte balance as well as blood pressure in *Slc26a4*$^{-/-}$ mice [37]. Under a moderate NaCl restriction, *Slc26a4*$^{-/-}$ mice have increased urinary volume and Cl^- excretion. Under these conditions, blood pressure level is not modified, even though the mice show signs of hypovolemia, whereas they develop hypotension under complete NaCl restriction. Taken together, these studies demonstrate that a perturbation of pendrin function could lead to variation of the blood pressure level in mice.

In order to better understand how pendrin can regulate extracellular volume and blood pressure, the expression of the Na^+ channels and transporters along the nephron was quantified in *Slc26a4*$^{-/-}$ mice, compared to *Slc26a4*$^{+/+}$, at baseline or under conditions of increased circulating aldosterone level [36]. Immunoblotting experiments showed that the expression of the α- and γ-subunits of ENaC is lower in the mutant than in the control mice when aldosterone is increased. The decreased expression of the two subunits is associated with a decrease in activity of the channel, as evidenced by decreased amiloride-sensitive Na^+ transport in microperfused CD isolated from *Slc26a4*$^{-/-}$ mice compared to that of control mice. This difference could be due to a lower level of aldosterone-induced ENaC stimulation in *Slc26a4*$^{-/-}$ mice. Another potential mechanism is the inhibition of ENaC activity by a decreased distal luminal HCO_3^- concentration, as ENaC activity is pH-dependent and metabolic alkalosis decreases the expression of ENaC subunits. An increase in luminal HCO_3^-, following inhibition of HCO_3^- reabsorption in the proximal tubule by acetazolamide, indeed restores ENaC expression and function in aldosterone-treated pendrin-null mice [38].

Taken together, these studies clearly demonstrate that an alteration of Cl^- transport in B-ICs influences Na^+ reabsorption by the neighbouring PCs. Interestingly, an ATP-dependent paracrine regulation of ion transport in the distal nephron and blood pressure has very recently been identified. Several sets of data showed that ATP binds the P2Y purinoceptor 2 (P2Y2) present at the apical side of CNT and CD cells and reduces ENaC activity and that inhibition of this system leads to the development of salt-sensitive hypertension in mice (for review, see [39]). Elegant studies involving the use of a fluorescent biosensor to measure ATP release by the different cell types showed that the main ATP-releasing cell type is the IC [40]. The role of pendrin in this paracrine signaling remains to be established. However, as detailed in the following paragraph, one possibility is that pendrin can provoke cell swelling and thereby might trigger the release of ATP by intercalated cells.

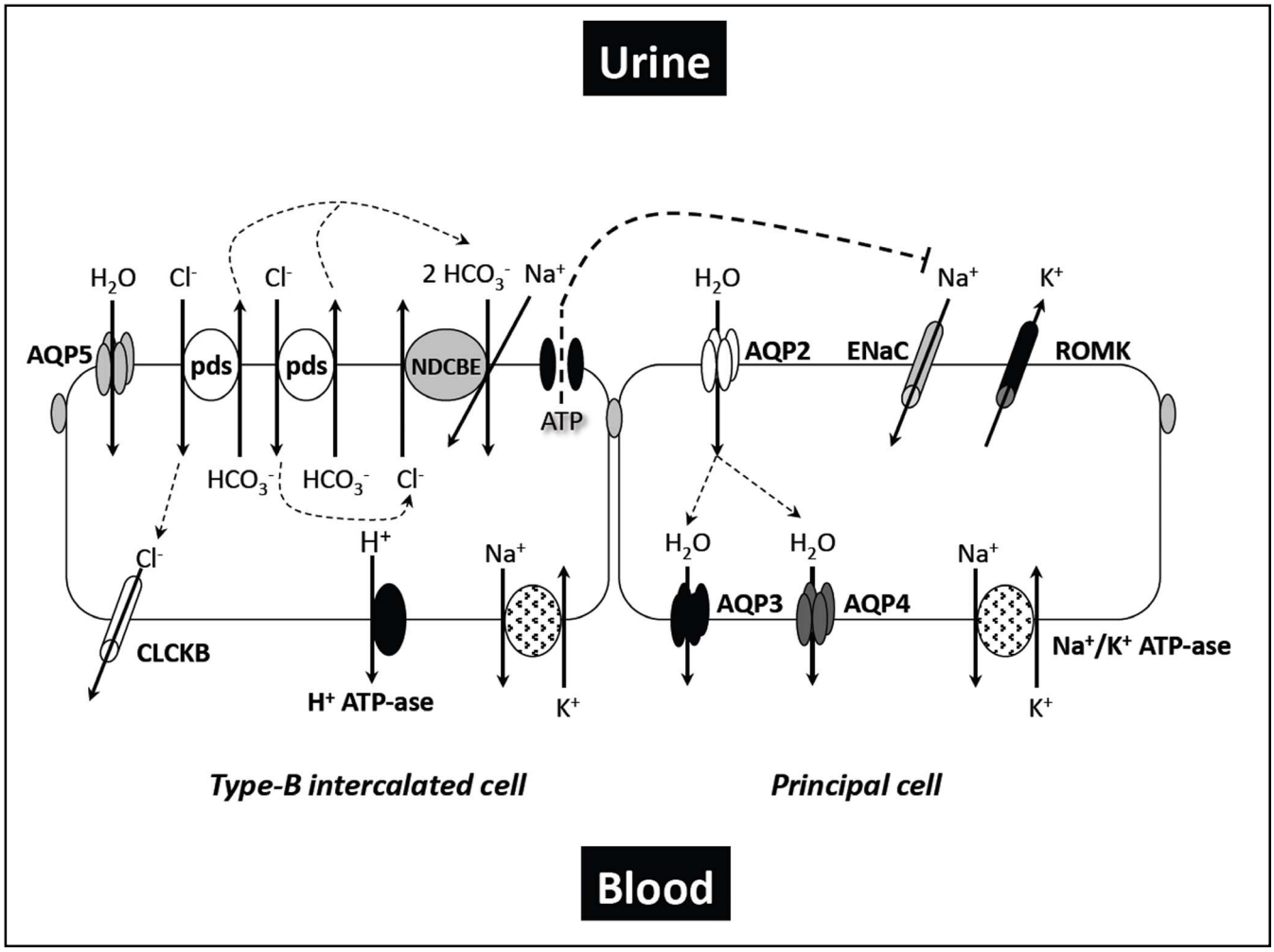

Fig. 1. Proposed model for Na^+, Cl^- and water transport by the CNT and CD. In principal cells, Na^+ is reabsorbed by ENaC, whose membrane expression is regulated by pendrin by yet unknown mechanism. One potential candidate is ATP, released by B-ICs in response to change in cell volume, which could be modulated by water entry through AQP5. In addition, Na^+ reabsorption in the distal nephron could directly involved pendrin, as two cycles of pendrin and one of NDCBE would result in net NaCl reabsorption with the recycling of one Cl^- and two HCO_3^- ions.

Pendrin, Aquaporin 5 and paracrine signalling in the distal nephron

ATP release at the cell membrane is strongly stimulated by an increase in cell volume [41, 42]. The recent discovery of the expression of the water channel AQP5 at the apical membrane of B-ICs [43] raises the possibility that modification of B-ICs cell volume could be involved in ATP release by these cells and activation of the purinergic signaling described above.

The aquaporins are a family of membrane channel proteins that serve as selective pores through which water crosses the plasma membranes of many human tissues and cell types [44, 45]. Of the known 13 aquaporin isoforms expressed in mammals (AQP0-12), at least 8 have been found in the kidney at distinct sites along the nephron: AQP1-4, AQP6-8 and AQP11 [46-49]. Interestingly, we recently reported for the first time that AQP5, a water channel never identified in the kidney, co-localizes with pendrin at the apical membrane of type-B intercalated cells (B-ICs) in the kidney cortex [43] (Fig. 1).

The *AQP5* gene was first cloned from salivary gland cDNA and then evidenced in eye, salivary and lachrymal glands, lung, trachea and cochlea, displaying an apical localization in each case [26, 50-52]. Of note,

the co-expression of AQP5 and pendrin in the same cell type is a common feature of several epithelia, such as the cochlea [52, 53] and bronchial epithelial cells [54]. The strict association of pendrin and AQP5 in the same membrane domain may reflect a functional interaction between the two proteins.

Despite the redundancy of AQP isoforms in the kidney, a clear physiological role in the process of urine concentration occurring along the kidney tubule has been attributed only to AQP1-4 by studying knock-out animal models and naturally occurring mutations in humans [46]. The role of the other renal AQPs, including AQP5, is still unknown and under investigation. The absence of a basolateral aquaporin in B-IC cells suggests that AQP5 does not mediate a net transepithelial water reabsorption and supports the hypothesis that B-ICs can be subjected to important changes in cell volume. A role for AQP5 as an osmosensor in this tract of the nephron might be an intriguing possibility. It has been previously reported that association between transient receptor potential vanilloid 4 (TRPV4) and AQP5 controls the Regulatory Volume Decrease (RVD) in salivary gland cells exposed to hypotonicity [55]. One could therefore speculate that AQP5 and pendrin control the cell volume of CNT/CCD intercalated cells, constantly bathed by the hypotonic luminal solution produced by the thick ascending limb and DCT. Indeed, a rapid increase in pendrin activity is expected to transiently increase intracellular osmoles that might drive water influx through AQP5, thereby leading to cell swelling.

Preliminary results obtained in our lab would support this hypothesis (Procino et al., 2011, unpublished results). Dietary K^+ depletion, a treatment that elicits metabolic alkalosis [56], results in redistribution of pendrin from the apical membrane to the cytosol with concomitant reduction of pendrin-positive cells as previously described [56]. Strikingly, immunofluorescence analysis of AQP5 in the kidney indicated that, in K^+-restricted animals, AQP5 also shifted from the apical membrane to the cell cytosol. These preliminary results suggest that pendrin and AQP5 might be subjected to a common regulatory pathway and that AQP5-dependent water flux is coupled to pendrin-mediated Cl^- influx. The co-regulation of pendrin and AQP5 membrane expression by changes in luminal ion concentration suggests that these two molecules could cooperate to sense an alteration of luminal ion fluxes and participate to adapt the distal nephron response accordingly. This aspect is worth further investigation *in vitro* and *in vivo*.

Pendrin and thiazide-sensitive NaCl transport in the distal nephron

In addition to modulating Na^+ transport in adjacent PCs, pendrin also participates directly in Na^+ reabsorption by B-ICs (Figure 1). This new concept emerged from our study of the thiazide-sensitive Na^+ transport in the CNT and CD [38]. As described above, the classical view of PCs and ICs is that the latter contribute to the regulation of acid-base status while the former are the only site of Na^+ reabsorption via ENaC. However, the presence of an electroneutral Na^+ transport in the CD was first evidenced by the group of M. Knepper in 1986 [57] and was subsequently found to be thiazide-sensitive in 1990 [58]. Using genetically engineered mouse models with specific deletion of Na^+ transporters and channels, we re-examined the existence of this transport and identified the molecules involved [38]. The measure of transepithelial Na^+, K^+ and Cl^- fluxes in isolated microperfused CCDs first allowed us to detect two components of Na^+ reabsorption in this segment: the first is electrogenic, is inhibited by amiloride and therefore depends upon ENaC. The second is electroneutral (simultaneous reabsorption of Na^+ and Cl^-) and thiazide-sensitive. This last component is still present in *NCC*$^{-/-}$ knock-out mice and therefore does not rely on this transporter. Since (i) Na^+-dependent Cl^- transport occurs through the functional coupling of a Cl^-/HCO_3^- exchanger and a Na^+/H^+ exchanger in many epithelia, and (ii) since Cl^- transport is completely abolished in pendrin-null mice, we hypothesized that the electroneutral NaCl transport could result from the coupling of pendrin-mediated Cl^-/HCO_3^- exchange reabsorption with a H^+/HCO_3^--dependent Na^+ transporter. Accordingly, we detected the presence of a thiazide-sensitive Cl^- and Na^+-dependent bicarbonate transporter in the apical membrane of intercalated cells [38]. Among the many HCO_3^- transporters identified, only one, NDCBE (encoded by *Slc4a8*) mediates Na^+ and Cl^--dependent HCO_3^- transport in mammals and is expressed in the mouse CD [38]. Abolition of the amiloride-resistant component of Na^+ transport in the CD of *Slc4a8*$^{-/-}$ confirmed that NDCBE is required for Na^+ absorption via intercalated cells. Moreover, thiazide compounds still retain some natriuretic effects in the absence of their canonical target NCC (i.e., in *NCC*$^{-/-}$ mice), demonstrating further that pendrin and NDCBE mediate a significant amount of NaCl absorption *in vivo* [38].

Conclusion

The crucial role of Cl^- in triggering hypertension has been described a long time ago. However, this role is usually underestimated and the mechanisms by which Cl^- transport influences blood pressure have, until recently, not been studied. The Cl^-/HCO_3^- exchanger pendrin, expressed in type B intercalated cells, is a strong candidate for mediating the hypertensive effect of Cl^- transport in the distal nephron. A stimulation of pendrin could indeed result in increased NaCl reabsorption either directly via its coupling to NDCBE or by activating ENaC membrane expression. However, some data suggest that pendrin could also have an anti-hypertensive effect, through the stimulation of ATP release by B-ICs upon changes in cellular volume, thereby inhibiting ENaC activity in PCs. A potential explanation is that pendrin-AQP5 induced ATP-release serves as a negative feedback loop with protective effect in case of excessive pendrin stimulation.

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References

1 Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr: Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 1972;52:584-594.

2 Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA: Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 2005;85:679-715.

3 Berghoff RS, Geraci AS: The influence of sodium chloride on blood pressure. Br Med J 1929;56:395-397.

4 Morgan TO: The effect of potassium and bicarbonate ions on the rise in blood pressure caused by sodium chloride. Clin Sci 1982;63:407-409.

5 Kurtz TW, Al-Bander HA, Morris RC Jr: "Salt-sensitive" essential hypertension in men. Is the sodium ion alone important? N Engl J Med 1987;317:1043-1048.

6 Kurtz TW, Morris RC Jr: Dietary chloride as a determinant of "sodium-dependent" hypertension. Science 1983;222:1139-1141.

7 Schmidlin O, Tanaka M, Bollen AW, Yi SL, Morris RC Jr: Chloride-dominant salt sensitivity in the stroke-prone spontaneously hypertensive rat. Hypertension 2005;45:867-873.

8 Tanaka M, Schmidlin O, Yi SL, Bollen AW, Morris RC Jr: Genetically determined chloride-sensitive hypertension and stroke. Proc Natl Acad Sci USA 1997;94:14748-14752.

9 Whitescarver SA, Ott CE, Jackson BA, Guthrie GP Jr, Kotchen TA: Salt-sensitive hypertension: contribution of chloride. Science 1984;223:1430-1432.

10 McCarty MF: Should we restrict chloride rather than sodium? Med Hypotheses 2004;63:138-148.

11 Luft FC, Zemel MB, Sowers JA, Fineberg NS, Weinberger MH: Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. J Hypertens 1990;8:663-670.

12 Schorr U, Distler A, Sharma AM: Effect of sodium chloride- and sodium bicarbonate-rich mineral water on blood pressure and metabolic parameters in elderly normotensive individuals: a randomized double-blind crossover trial. J Hypertens 1996;14:131-135.

13 Schambelan M, Sebastian A, Rector FC Jr: Mineralocorticoid-resistant renal hyperkalemia without salt wasting (type II pseudohypoaldosteronism): role of increased renal chloride reabsorption. Kidney Int 1981;19:716-727.

14 Take C, Ikeda K, Kurasawa T, Kurokawa K: Increased chloride reabsorption as an inherited renal tubular defect in familial type II pseudohypoaldosteronism. N Engl J Med 1991;324:472-476.

15 Loffing J, Kaissling B: Sodium and calcium transport pathways along the mammalian distal nephron: from rabbit to human. Am J Physiol Renal Physiol 2003;284:F628-643.

16 Ellison DH, Loffing J: Thiazide effects and adverse effects: insights from molecular genetics. Hypertension 2009;54:196-202.

17 Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, Vaara I, Iwata F, Cushner HM, Koolen M, Gainza FJ, Gitleman HJ, Lifton RP: Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet 1996;12:24-30.

18 Schultheis PJ, Lorenz JN, Meneton P, Nieman ML, Riddle TM, Flagella M, Duffy JJ, Doetschman T, Miller ML, Shull GE: Phenotype resembling Gitelman's syndrome in mice lacking the apical Na^+-Cl^- cotransporter of the distal convoluted tubule. J Biol Chem 1998;273:29150-29155.

19 Lalioti MD, Zhang J, Volkman HM, Kahle KT, Hoffmann KE, Toka HR, Nelson-Williams C, Ellison DH, Flavell R, Booth CJ, Lu Y, Geller DS, Lifton RP: Wnk4 controls blood pressure and potassium homeostasis via regulation of mass and activity of the distal convoluted tubule. Nat Genet 2006;38:1124-1132.

20 Yang SS, Morimoto T, Rai T, Chiga M, Sohara E, Ohno M, Uchida K, Lin SH, Moriguchi T, Shibuya H, Kondo Y, Sasaki S, Uchida S: Molecular pathogenesis of pseudohypoaldosteronism type II: generation and analysis of a Wnk4(D561A/+) knockin mouse model. Cell Metab 2007;5:331-344.

21 Gordon RD, Klemm SA, Tunny TJ, Stowasser M: Gordon's syndrome: a sodium-volume-dependent form of hypertension with a genetic basis; in Laragh JH (ed): Hypertension: Patholgy, Diagnosis and Management. Christchurch, Raven Press Ltd, 1995, pp 2111-2113.

22 Schuster VL, Stokes JB: Chloride transport by the cortical and outer medullary collecting duct. Am J Physiol 1987;253:F203-212.

23 Alper SL, Natale J, Gluck S, Lodish HF, Brown D: Subtypes of intercalated cells in rat kidney collecting duct defined by antibodies against erythroid band 3 and renal vacuolar H^+-ATPase. Proc Natl Acad Sci U S A 1989;86:5429-5433.

24 Teng-umnuay P, Verlander JW, Yuan W, Tisher CC, Madsen KM: Identification of distinct subpopulations of intercalated cells in the mouse collecting duct. J Am Soc Nephrol 1996;7:260-274.

25 Royaux IE, Wall SM, Karniski LP, Everett LA, Suzuki K, Knepper MA, Green ED: Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc Natl Acad Sci USA 2001;98:4221-4226.

26 Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED: Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997;17:411-422.

27 Kraiem Z, Heinrich R, Sadeh O, Shiloni E, Nassir E, Hazani E, Glaser B: Sulfate transport is not impaired in pendred syndrome thyrocytes. J Clin Endocrinol Metab 1999;84:2574-2576.

28 Scott DA, Karniski LP: Human pendrin expressed in Xenopus laevis oocytes mediates chloride/formate exchange. Am J Physiol Cell Physiol 2000;278:C207-211.

29 Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP: The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet 1999;21:440-443.

30 Kim YH, Kwon TH, Frische S, Kim J, Tisher CC, Madsen KM, Nielsen S: Immunocytochemical localization of pendrin in intercalated cell subtypes in rat and mouse kidney. Am J Physiol Renal Physiol 2002;283:F744-754.

31 Verlander JW, Hassell KA, Royaux IE, Glapion DM, Wang ME, Everett LA, Green ED, Wall SM: Deoxycorticosterone upregulates PDS (Slc26a4) in mouse kidney: role of pendrin in mineralocorticoid-induced hypertension. Hypertension 2003;42:356-362.

32 Quentin F, Chambrey R, Trinh-Trang-Tan MM, Fysekidis M, Cambillau M, Paillard M, Aronson PS, Eladari D: The Cl-/HCO3- exchanger pendrin in the rat kidney is regulated in response to chronic alterations in chloride balance. Am J Physiol Renal Physiol 2004;287:F1179-1188.

33 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. JASN 2006;17:2153-2163.

34 Garcia-Austt J, Good DW, Burg MB, Knepper MA: Deoxycorticosterone-stimulated bicarbonate secretion in rabbit cortical collecting ducts: effects of luminal chloride removal and in vivo acid loading. Am J Physiol 1985;249:F205-212.

35 Knepper MA, Good DW, Burg MB: Mechanism of ammonia secretion by cortical collecting ducts of rabbits. Am J Physiol 1984;247:F729-738.

36 Kim YH, Pech V, Spencer KB, Beierwaltes WH, Everett LA, Green ED, Shin W, Verlander JW, Sutliff RL, Wall SM: Reduced ENaC protein abundance contributes to the lower blood pressure observed in pendrin-null mice. Am J Physiol Renal Physiol 2007;293:F1314-1324.

37 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 2004;44:982-987.

38 Leviel F, Hubner CA, Houillier P, Morla L, El Moghrabi S, Brideau G, Hassan H, Parker MD, Kurth I, Kougioumtzes A, Sinning A, Pech V, Riemondy KA, Miller RL, Hummler E, Shull GE, Aronson PS, Doucet A, Wall SM, Chambrey R, Eladari D: The Na^+-dependent chloride-bicarbonate exchanger SLC4A8 mediates an electroneutral Na+ reabsorption process in the renal cortical collecting ducts of mice. J Clin Invest 2010;120:1627-1635.

39 Eladari D, Chambrey R, Peti-Peterdi J: A New Look at Electrolyte Transport in the Distal Tubule. Annu Rev Physiol 2011; in press.

40 Sipos A, Vargas SL, Toma I, Hanner F, Willecke K, Peti-Peterdi J: Connexin 30 deficiency impairs renal tubular ATP release and pressure natriuresis. J Am Soci Nephrol 2009;20:1724-1732.

41 Darby M, Kuzmiski JB, Panenka W, Feighan D, MacVicar BA: ATP released from astrocytes during swelling activates chloride channels. J Neurophysiol 2003;89:1870-1877.

42 Wang Y, Roman R, Lidofsky SD, Fitz JG: Autocrine signaling through ATP release represents a novel mechanism for cell volume regulation. Proceedings of the National Academy of Sciences of the United States of America 1996;93:12020-12025.

43 Procino G, Mastrofrancesco L, Sallustio F, Costantino V, Pisani F, Schena FP, Svelto M, Valenti Gi: AQP5 Is Expressed In Type-B Intercalated Cells In The Collecting Duct System of the Rat, Mouse And Human Kidney. Cell Physiol Biochem 2011;28:in press.

44 Preston GM, Agre P: Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: member of an ancient channel family. Proc Nat Acad Sci USA 1991;88:11110-11114.

45 Preston GM, Carroll TP, Guggino WB, Agre P: Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein. Science 1992;256:385-387.

46 Ishibashi K, Hara S, Kondo S: Aquaporin water channels in mammals. Clin Exp Nephrol 2009;13:107-117.

47 Nielsen S, Kwon TH, Frokiaer J, Agre P: Regulation and dysregulation of aquaporins in water balance disorders. J Inter Med 2007;261:53-64.

48 Noda Y, Sohara E, Ohta E, Sasaki S: Aquaporins in kidney pathophysiology. Nature reviews. Nephrology 2010;6:168-178.

49 Nejsum LN: The renal plumbing system: aquaporin water channels. Cell Mol Life Sci 2005;62:1692-1706.
50 Ishida N, Hirai SI, Mita S: Immunolocalization of aquaporin homologs in mouse lacrimal glands. Biochem Biophys Res Commun 1997;238:891-895.
51 Nielsen S, King LS, Christensen BM, Agre P: Aquaporins in complex tissues. II. Subcellular distribution in respiratory and glandular tissues of rat. Am J Physiol 1997;273:C1549-1561.
52 Mhatre AN, Steinbach S, Hribar K, Hoque AT, Lalwani AK: Identification of aquaporin 5 (AQP5) within the cochlea: cDNA cloning and in situ localization. Biochem Biophys Res Commun1999;264:157-162.
53 Royaux IE, Belyantseva IA, Wu T, Kachar B, Everett LA, Marcus DC, Green ED: Localization and functional studies of pendrin in the mouse inner ear provide insight about the etiology of deafness in pendred syndrome. J Assoc Res Otolaryngol 2003;4:394-404.
54 Krane CM, Fortner CN, Hand AR, McGraw DW, Lorenz JN, Wert SE, Towne JE, Paul RJ, Whitsett JA, Menon AG: Aquaporin 5-deficient mouse lungs are hyperresponsive to cholinergic stimulation. Proc Nat Acad Sci USA 2001;98:14114-14119.
55 Liu X, Bandyopadhyay BC, Nakamoto T, Singh B, Liedtke W, Melvin JE, Ambudkar I: A role for AQP5 in activation of TRPV4 by hypotonicity: concerted involvement of AQP5 and TRPV4 in regulation of cell volume recovery. J Biol Chem 2006;281:15485-15495.
56 Wagner CA, Finberg KE, Stehberger PA, Lifton RP, Giebisch GH, Aronson PS, Geibel JP: Regulation of the expression of the Cl^-/anion exchanger pendrin in mouse kidney by acid-base status. Kidney Int 2002;62:2109-2117.
57 Tomita K, Pisano JJ, Burg MB, Knepper MA: Effects of vasopressin and bradykinin on anion transport by the rat cortical collecting duct. Evidence for an electroneutral sodium chloride transport pathway. J Clin Invest 1986;77:136-141.
58 Terada Y, Knepper MA: Thiazide-sensitive NaCl absorption in rat cortical collecting duct. Am J Physiol 1990;259:F519-528.