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INVITED REVIEW

The importance of kidney calcium handling in the homeostasis of extracellular fluid calcium

Caroline Prot-Bertoye[1,2,3,4,5] · **Loïc Lievre**[1,2] · **Pascal Houillier**[1,2,3,4,5]

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Abstract

Extracellular fluid calcium concentration must be maintained within a narrow range in order to sustain many biological functions, encompassing muscle contraction, blood coagulation, and bone and tooth mineralization. Blood calcium value is critically dependent on the ability of the renal tubule to reabsorb the adequate amount of filtered calcium. Tubular calcium reabsorption is carried out by various and complex mechanisms in 3 distinct segments: the proximal tubule, the cortical thick ascending limb of the loop of Henle, and the late distal convoluted/connecting tubule. In addition, calcium reabsorption is tightly controlled by many endocrine, paracrine, and autocrine factors, as well as by non-hormonal factors, in order to adapt the tubular handling of calcium to the metabolic requirements. The present review summarizes the current knowledge of the mechanisms and factors involved in calcium handling by the kidney and, ultimately, in extracellular calcium homeostasis. The review also highlights some of our gaps in understanding that need to be addressed in the future.

Keywords Paracellular ion transport · Transcellular ion transport · Tight junction · Claudin · TRPV5 · Parathyroid hormone · Calcium-sensing receptor

The body of a healthy adult contains ~25 000 mmol (~1 kg) of calcium; the vast majority (> 99%) is part of the mineral component of bone and less than 1% (~20 mmol) is in the extracellular fluid (ECF). The calcium homeostatic system targets not so much the total body calcium content but rather the concentration of ECF calcium. In a given healthy individual, this value is remarkably stable over time, never deviating by more than 2% from its equilibrium value [101]. Under normal conditions, both ECF calcium concentration and body calcium content are maintained at fixed values; however, under pathological conditions, the maintenance of ECF calcium concentration may require an alteration in calcium balance and body calcium content.

Calcium fluxes in healthy adults

Three organs can create substantial calcium movement into or out of the ECF: the intestine, the bone, and the kidney. Net intestinal calcium absorption that follows a meal does not contribute to maintaining ECF calcium at its reference value; rather, it causes a transient increase in serum calcium value. Nevertheless, sufficient dietary calcium intake and normal intestinal calcium absorption are essential to maintain normal calcium balance and normal bone stores. On Western diets, fecal loss due to non-(re)absorbed intestinal fluid calcium never falls below ~3.75 mmol (150 mg) daily [101] and urinary loss rarely falls below ~2.5 mmol (100 mg) daily. Because of such significant obligatory losses, the minimal dietary calcium requirement, based on

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✉ Pascal Houillier
pascal.houillier@inserm.fr

1 Centre de Recherche Des Cordeliers, INSERM, Sorbonne Université, Université Paris Cité, 75006 Paris, France

2 CNRS ERL 8228 - Laboratoire de Physiologie Rénale Et Tubulopathies, 75006 Paris, France

3 Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Physiologie, 20 rue Leblanc, 75015 Paris, France

4 Centre de Référence Des Maladies Rénales Héréditaires de L'Enfant Et de L'Adulte (MARHEA), 75015 Paris, France

5 Centre de Référence Des Maladies Rares du Calcium Et du Phosphate, 75015 Paris, France

balance studies in normal subjects, is ~15 mmol (600 mg) per day [89].

In the fasting state, the ECF calcium concentration can be sustained only if the amount of calcium released from bone matches the obligatory loss of calcium in urine. When dietary calcium intake is inadequate (< 600 mg/day in young adults) and/or intestinal calcium absorption abnormal, the serum calcium level can be kept stable only at the expense of a progressive decrease in bone calcium stores. For instance, a daily calcium intake of ≤ 10 mmol (400 mg) results in a loss of 1–4 mmol (40–160 mg) of calcium from the body every day [101]. Thus, although intestinal calcium absorption does not participate, stricto sensu, in the control of serum calcium level, it provides enough calcium to maintain bone calcium stores within the normal range: the calcium lost in the fasting state is replaced by absorption of an identical amount of calcium from the gut lumen. Consequently, in healthy individuals who have completed their growth, and with the exception of pregnant or breastfeeding women, when dietary calcium intake and intestinal calcium absorption are normal, the amount of calcium excreted in urine is equal to the net amount being absorbed by the intestine.

Maintaining serum calcium at its equilibrium value

The regulation of serum calcium involves mechanisms that keep the calcium level at its reference value and mechanisms that correct variations from the reference value [102].

The bone and the kidney are the two organs that determine the serum calcium level in the fasting state. The calcium equilibrium value (reference value) is the value for which the net calcium inflow, from the bone pool to the ECF, matches the net outflow, from the ECF to the urine. This match is primarily achieved by an adequate release of parathyroid hormone (PTH) that increases the release of calcium from bone tissue and limits the renal loss of calcium by increasing tubular reabsorption of filtered calcium in the thick ascending limb (TAL) of the loop of Henle and in the distal tubule [73].

Importantly, this system also provides an efficient means to correct deviations from the calcium reference value. In the fasting state, serum calcium tends to decrease below its reference value because calcium is lost in the urine (Fig. 1). The parathyroid glands respond immediately by releasing larger amounts of PTH, which, in turn, stimulates calcium release from bone tissue and calcium reabsorption from the renal tubule, allowing serum calcium to return to the reference value. Bone calcium release is rapid, of marked amplitude, but of limited capacity: only superficial bone layers are supposed to be involved. These characteristics are well suited to the rapid correction of serum calcium levels [102].

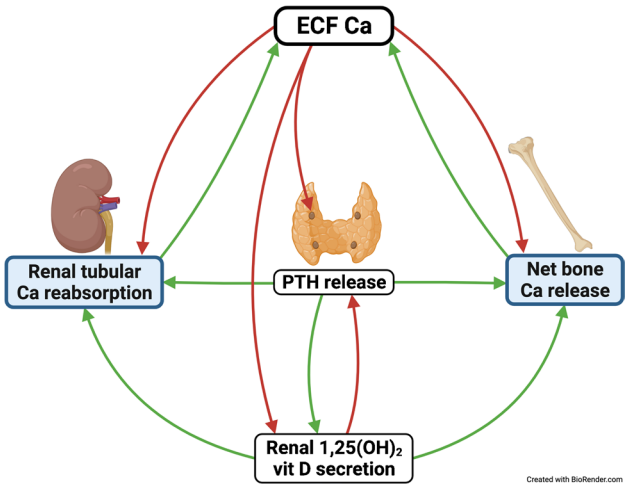

Fig. 1 Schematic representation of the main mechanisms ensuring the stability of extracellular fluid calcium under normal conditions. The regulation of calcium concentration involves parathyroid hormone (PTH), 1,25dihydroxyvitamin D and extracellular fluid calcium itself via the calcium-sensing receptor (CaSR) in the kidneys and the parathyroid glands. A decrease in serum calcium concentration stimulates PTH secretion by parathyroid glands, which increases calcium release from bone tissue and calcium reabsorption by the kidney both in the TAL and the DCT/CNT (see the "Parathyroid hormone" section for further details). Moreover, PTH and a decrease in serum calcium concentration stimulate $1,25(OH)_2$vitamin D secretion by the kidney, which increases calcium release from bone tissue and calcium reabsorption by the kidney in the DCT (see the "Vitamin D metabolites" section). In return, $1,25(OH)_2$vitamin D inhibits PTH secretion. Finally, a decrease in ECF calcium itself inactivates CaSR in the TAL and enhances calcium reabsorption by the kidney, by increasing paracellular permeability to calcium in the TAL. Thus, a decrease in serum calcium concentration stimulates calcium reabsorption by the kidney and net bone calcium release, allowing serum calcium to increase back to its reference value. Green arrow: increase; red arrow: decrease

Conversely, a rise in serum calcium (actually in the ionized fraction of serum calcium) decreases the secretion of PTH by activating the calcium-sensing receptor CaSR: this leads to a reduction in the amounts of calcium released from bone and reabsorbed in the kidney and, finally, to the normalization of serum calcium level.

Based on the above considerations, the renal handling of calcium (particularly, the reabsorption of calcium along the renal tubule) is a major determinant of the ability to maintain serum calcium values stable within the normal range.

Transepithelial transport pathways along the renal tubule

Calcium can cross the epithelium of the renal tubule only in its free form (Ca^{2+}) and either actively or passively, depending on the tubular segment. Active calcium transport can occur transcellularly only, at the expense of energy release,

for example from hydrolysis of ATP. Passive calcium diffusion between the apical and the basolateral compartment may be defined as the flow of calcium that occurs in response to the difference in electrochemical potentials of calcium between both compartments. Diffusion can occur across plasma membranes or along the paracellular pathway. Because of the existing transmembrane electrochemical potential differences, calcium cannot cross passively both apical and basolateral membranes: therefore, at some step, transcellular transport of Ca^{2+} requires energy expenditure. By contrast, passive paracellular diffusion of Ca^{2+} allows both transepithelial transport and energy saving [104]. The present review is a summary of our current knowledge of normal and abnormal Ca^{2+} ion transport along the mammalian renal tubule.

Segmental transport

Ca^{2+} enters into the nephron by ultrafiltration across the glomerular capillary wall, the glomerular basement membrane and the podocytes. Only calcium unbound to proteins (ultrafilterable calcium) can undergo ultrafiltration: calcium concentration has been measured in glomerular ultrafiltrate of normal rats [45, 51, 75] and equals approximately 60% of serum calcium concentration. Therefore, in an individual whose GFR is 100 $ml.min^{-1}$, the daily filtered load of calcium is 205 mmol (8200 mg) on average. Only a tiny fraction (~4–5 mmol) is excreted in urine, because most of the filtered calcium is reabsorbed along the renal tubule. Serum calcium concentration shows little variation across a wide range of GFR values [36]; therefore glomerular ultrafiltration rate is not an important determinant of serum calcium concentration.

Proximal tubule (Fig. 2)

Early micropuncture experiments demonstrated that calcium is reabsorbed in the rat and dog proximal tubule (PT) [3, 32, 44, 75] and found that the ratio of calcium concentration between tubular fluid and plasma is between 1.0 and 1.2 [3, 32, 44, 75], indicating that calcium reabsorption roughly parallels that of sodium and fluid along the proximal convolution.

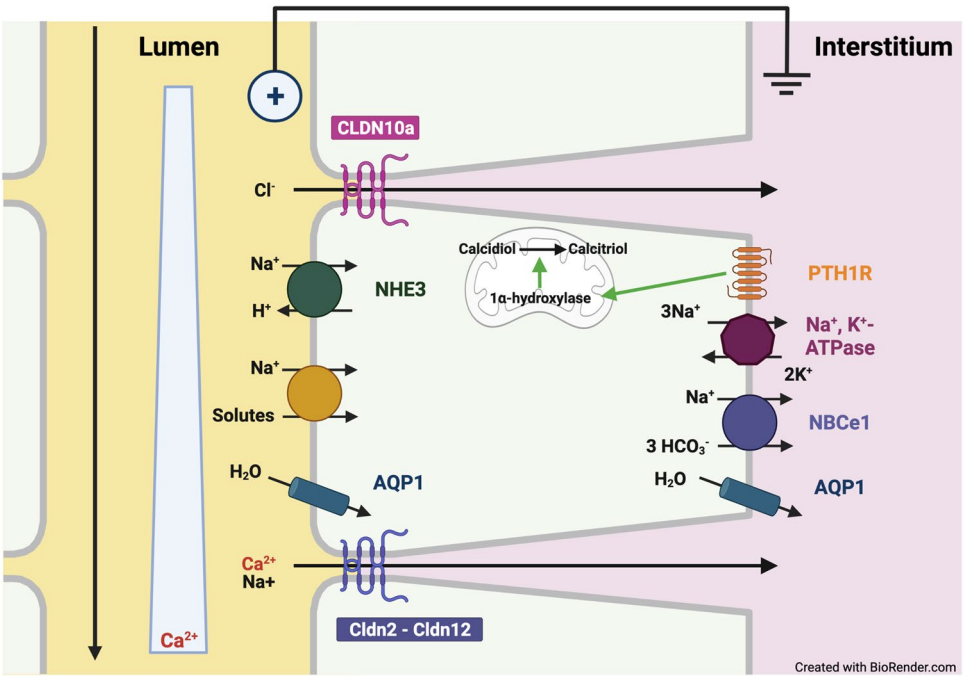

Fig. 2 Model of calcium reabsorption in the proximal tubule (PT). In the PT, calcium reabsorption takes place mainly along the paracellular pathway, and depends on (1) a paracellular permeability to cations owing to the expression of claudin (CLDN)-2 and CLDN-12 at the tight junction, (2) a transepithelial chemical gradient generated by water reabsorption, itself linked to a transepithelial reabsorption of Na^+ and anions, and (3) a small lumen-positive transepithelial potential difference in mid and late PT. Water reabsorption occurs either transcellularly via aquaporin 1 (AQP1) expressed at both apical and basolateral membrane or paracellularly. Na^+ is reabsorbed actively, largely via the apical Na^+/H^+ exchanger 3 (NHE3) and to a lesser extent by various apical Na^+ cotransporters (with glucose, phosphate, amino acids…). HCO_3^- ions are produced by dissociation of H_2CO_3 in the cell mediated by the carbonic anhydrase and exit the cell via the Na^+/HCO_3^- cotransporter (NBCe1). The expression of CLDN10a at the tight junction increases the paracellular permeability to anions ($Cl.^-$). The proximal tubule is also a main site of 1,25$(OH)_2$vitamin D synthesis, where it is activated by parathyroid hormone acting on the mitochondrial 1alpha hydroxylase (CYP27B2)

Calcium permeability of the PT is relatively high, in the same order of magnitude as that of sodium, supporting passive calcium reabsorption; accordingly, most of calcium reabsorption in the proximal convolution is passive, driven by sodium and water reabsorption [135]. Potential difference is typically low across the PT epithelium, slightly negative in the early part and slightly positive in the remainder of the segment [116]. Although transepithelial potential is low it may contribute to calcium reabsorption as the paracellular permeability is high and calcium has two positive charges. In addition, water reabsorption concentrates calcium ion in the tubular fluid and increases the transepithelial chemical gradient, which drives calcium reabsorption across the PT epithelium. The permeability to calcium depends on the properties of the tight junction and more specifically on that of specialized tight junction proteins, named claudins [111]. Several recent studies have examined the role of claudins in passive calcium reabsorption in the PT. Three claudins, at the minimum, are expressed at the tight junction of proximal tubular cells: claudin-2, claudin-10a, and claudin-12. Heterologous expression studies in cell lines have shown that claudin-10a increases the permeability to chloride [68] and is probably not determining permeability to calcium [49]. A recent study conducted in the mouse confirms that claudin-10a is the major paracellular anion permeability in the proximal tubule [17]. Conversely, male mice with deletion of claudin-2 (*Cldn2* gene is located on the X chromosome in the mouse) exhibit a ~ threefold increase in urinary fractional excretion of calcium [28] and nephrocalcinosis. Accordingly, a rare missense variant of the *CLDN2* gene in humans is associated with hypercalciuria in one family of Iranian origin. However a direct effect of CLDN2 on the proximal paracellular permeability to calcium (P_{Ca}) has not been determined, so far. Mice with biallelic deletion of claudin-12 do not show hypercalciuria [8]; however, mice with deletion of both claudin-2 and claudin-12 display a higher fractional urinary excretion of calcium than mice with deletion of claudin-2 only, suggesting that both claudin-2 and claudin-12 participate in the proximal P_{Ca}. Plain et al. isolated proximal straight tubules (PST) and measured ion permeability ratio: both sodium to chloride and calcium to sodium permeability ratios were lower in *claudin-12* knock-out (KO) than in wild-type mice [108].

Several studies provided evidence of a small but finite active calcium reabsorption along the PT [11, 135]. The molecular mechanisms of such an active transport remain elusive, however.

In summary, most of calcium reabsorbed along the PT is transported along the paracellular pathway that is made permeable enough to calcium by the co expression of claudin-2 and claudin-12 at the tight junction.

Thick ascending limb of the loop of Henle (Fig. 3)

The thin descending and ascending limbs of the loop of Henle display very low permeability to calcium and are not a site of significant transepithelial calcium transport, at least in the rabbit [120]. Because an estimate of ~ 20–25% of the filtered load of calcium is reabsorbed in the loop of Henle [75], the thick ascending limb has to be a major place of transepithelial calcium transport. The TAL actively absorbs NaCl. The initial step is the entry of 1 Na^+, 1 K^+, and 2 Cl^- into the cell via the apical, electroneutral cotransporter NKCC2. Then, most of the potassium that enters the cell is secreted back into the lumen via the apical, electrogenic K^+ channel ROMK, thereby hyperpolarizing the apical membrane. Most of the chloride absorbed from the lumen exits the cell through the basolateral chloride channel ClCkb; this electrogenic diffusion of chloride depolarizes the basolateral membrane. From an electrophysiological standpoint, the overall consequence of NaCl reabsorption in the TAL is a lumen-positive transepithelial potential difference (PD_{te}) that exists in both the medullary and cortical TAL. Nevertheless, quantitative differences exist between the medullary (M-TAL) and cortical subsegments of the TAL (C-TAL). Under baseline conditions, the absorption of calcium by the M-TAL of the rodent is very low [7, 88, 128, 129, 146]. Only one study reported a significant absorption of calcium by the mouse M-TAL, to our knowledge [35] and, in the rabbit, Suki et al. reported a quantitatively similar net calcium absorption by the M-TAL and the C-TAL [131].

In both subsegments, most investigators found that calcium transport was inhibited by luminal furosemide and was passive, driven by the lumen-positive PD_{te} [14, 15, 66, 124, 130]. Bourdeau and Burg provided definitive evidence that calcium reabsorption is passive in the C-TAL, driven by the lumen-positive PD_{te}. Calcium reabsorption increased almost linearly with increasing PD_{te} and was not significantly different from null in the absence of PD_{te} [14]. Similar data were obtained by independent investigators [35, 88]. The observation that calcium secretion occurred at lumen-negative PD_{te} (under in vitro conditions) was consistent with passive diffusion of calcium, presumably along the paracellular pathway.

As other tubular segments, the C-TAL of human and rodent kidney expresses a specific association of claudins, likely accounting for the specific properties of the paracellular pathway of that segment: the C-TAL specifically expresses high levels of claudin-10b, claudin-16, and claudin-19 [110]. TAL tight junctions show a mosaic pattern of expression of either CLDN10b or CLDN16/CLDN19 [94]. Loss-of-function variants of claudin-16 and claudin-19 cause familial hypomagnesemia with hypercalciuria and nephrolithiasis (FHHNC), an autosomal recessive disease, characterized by an excessive urinary loss of Ca^{2+} and Mg^{2+}, resulting in hypomagnesemia and hypercalciuria. Patients

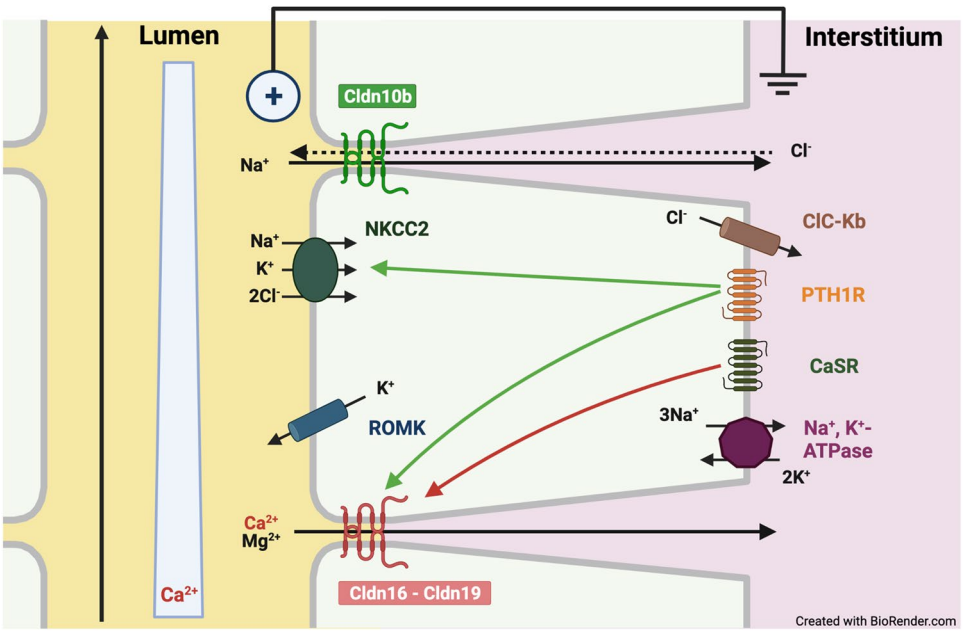

Fig. 3 Model of calcium reabsorption in the C-TAL of Henle's loop. In the C-TAL of Henle's loop, calcium reabsorption occurs paracellularly and depends on (1) a selective paracellular permeability to divalent cations (Ca^{2+} and Mg^{2+}) owing to the expression of the claudin (CLDN)-16 and CLDN-19 heterodimeric complex at the tight junction and (2) the lumen positive transepithelial voltage generated by the active transcellular transport of NaCl via the apical Na^+-K^+-$2Cl^-$ cotransporter (NKCC2). A large amount of K^+ that enters the cell recycles back to the lumen via the apical potassium channel (ROMK), thereby hyperpolarizing the apical membrane. Most of the chloride leaves the cell via the basolateral chloride channel (ClC-Kb), resulting in membrane depolarization. Calcium reabsorption is controlled by the activation of calcium-sensing receptor (CaSR) and parathyroid hormone receptor type 1 (PTH1R) both expressed at the basolateral membrane. CaSR activation decreases the paracellular permeability to $Ca.^{2+}$ while PTH1R activation increases it. PTH1R activation also increases the lumen positive transepithelial voltage by increasing NaCl reabsorption via NKCC2

have nephrocalcinosis (a parenchymal deposition of calcium–based crystal in the renal parenchyma) and renal failure that may progress toward end-stage renal disease early in life [24, 38, 71, 126, 141].

CLDN16 and CLDN19 can interact with each other [60], forming a cis heterodimer at the cell membrane in vitro [41]. Their co-expression increases cation selectivity of the tight junction [60].

The exact function of CLDN16 regarding paracellular permeability remains controversial. Depending on the experimental model, CLDN16 expressed in cell lines increases Ca^{2+} and/or Mg^{2+} and/or Na^+ permeability [48, 59, 60, 64, 65, 70, 91]. *Cldn16* KO mice have hypomagnesemia and hypercalciuria [142]. C-TAL isolated from *Cldn16* KO mice show decreased ion paracellular permeability ratio P_{Ca}/P_{Na} and P_{Mg}/P_{Na} but unaltered P_{Na}/P_{Cl} and PD_{te} [16]. Renal abnormalities and electrolyte imbalances have not been investigated in *Cldn19* KO mice [95].

Experiments conducted on isolated, perfused TAL from *Cldn16* KD mice show decreased P_{Na}/P_{Cl} but unaffected P_{Na}/P_{Mg} [61]. The total transepithelial resistance and NKCC2-dependent transepithelial voltage were not different. The investigators concluded that CLDN16 is a non-specific cation channel [61]: a low CLDN16 protein expression would decrease P_{Na}/P_{Cl} and thereby the diffusion potential generated at a dilute luminal fluid at the end of the C-TAL and decrease the driving force for Mg^{2+} reabsorption [52, 61]. In contrast, the total transepithelial resistance was higher in *Cldn10b* KO mice, which also have a lower P_{Na}/P_{Cl}. The higher NKCC2-dependent PD_{te}, due to higher paracellular electrical resistance and/or higher NKCC2 activity, resulted in a higher Mg^{2+} reabsorption in the TAL [18]. In this model, the high PD_{te} may elevate passive paracellular Mg^{2+} and Ca^{2+} reabsorption at the entry to the C-TAL. The different observations with respect to divalent cation permeabilities between *claudin-16* RNAi KD versus *claudin-16* KO remain obscure.

In summary, an increase in P_{Ca} and P_{Mg} caused by CLDN16 expression at the tight junction of the TAL better accounts for the bulk of observations made in both humans and mice.

Distal convoluted tubule (DCT) and connecting tubule (CNT) (Fig. 4)

Early micropuncture studies showed that the distal tubule reabsorbs calcium despite a low epithelial permeability [125], consistent with an active reabsorption. In addition,

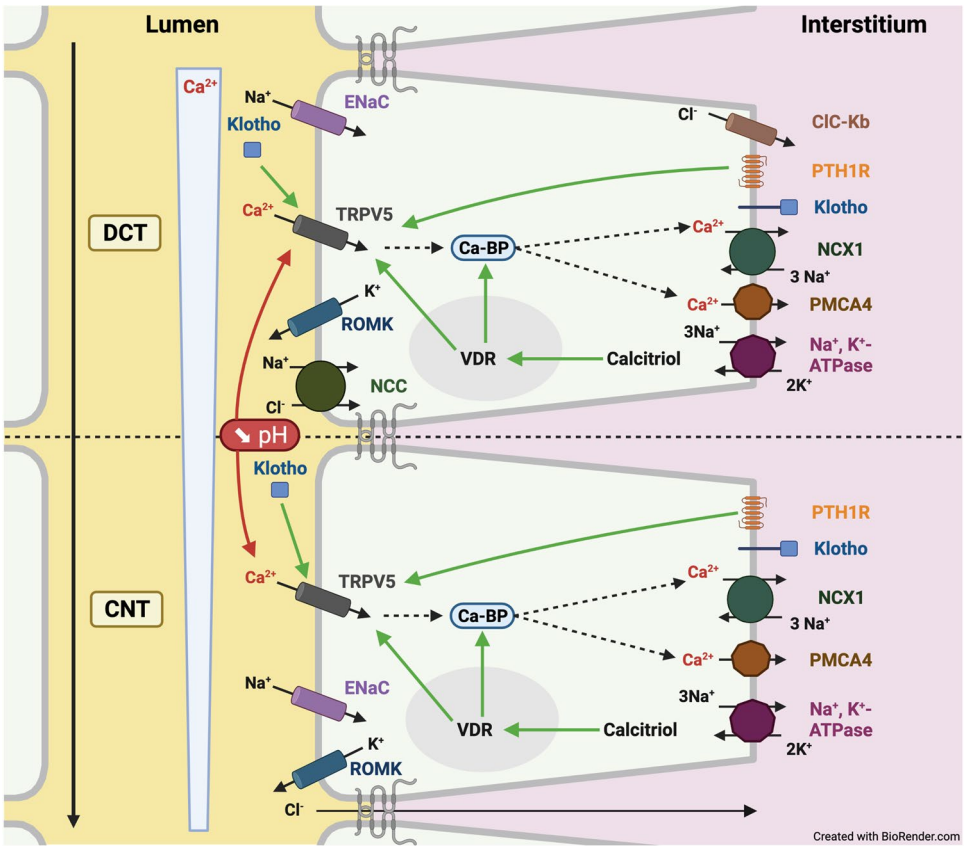

Fig. 4 Calcium reabsorption in the distal tubule (DT). In the DT, calcium reabsorption occurs transcellularly both in the distal convoluted tubule (DCT) and the connecting tubule (CNT). Ca^{2+} enters the cell thanks to (1) the expression of the apical transient receptor potential vanilloid 5 (TRPV5) and (2) an electrochemical free calcium gradient between the lumen and the cytosol, due to Ca^{2+} binding to calbindin-D28K and D9K (calcium-binding protein Ca-BP). Then, Ca^{2+} is ferried to the basolateral membrane and exits the cell via two transporters: the Na^+/Ca^{2+} exchanger (NCX1) and the plasma membrane Ca^{2+}-ATPase (PMCA4). Na^+ enters the cell via the apical Na^+-Cl^- cotransporter (NCC) in the DCT and the epithelial Na^+ channel (ENaC) in the CNT. In the DCT, Cl^- leaves the cell via the basolateral chloride channel (ClC-Kb) while in the CNT, Cl^- is reabsorbed along the paracellular pathway. In both DCT and CNT, PTH1R activation and Klotho increase calcium reabsorption by enhancing TRPV5 activity; 1,25 $(OH)_2$ vitamin D increases TRPV5 and Ca-BP expression. A drop in urine pH decreases calcium reabsorption in the DT by decreasing TRPV5 activity

because calcium but not water is reabsorbed in the TAL, calcium concentration in the luminal fluid is lower than that in plasma at the beginning of DCT accessible to micropuncture and decreases further along the distal tubule (~0.3 mmol/L at the junction with another tubule) [26]. Together with the lumen-negative PD_{te}, it results that passive reabsorption of calcium is not possible in this tubular segment [147]. Transepithelial calcium reabsorption is a 3-step process: calcium entry into the cell across the apical membrane, intracellular buffering and shuttling of calcium, and calcium exit across the basolateral membrane. The pathway for calcium entry in the distal tubule cell has been identified about 20 years ago, and initially named epithelial calcium channel-1 (ECaC-1) in the rabbit and calcium transporter-2 (CaT-2) in the rat [55, 105]: it is now known as transient receptor potential cation channel subfamily V member 5/and 6 (TRPV5/6). TRPV5 is strongly expressed at the apical membrane of DCT and CNT cells [54] and is activated by membrane hyperpolarization [56]. The critical role of TRPV5 was established in mice with bi allelic disruption of the *Trpv5* gene. The *Trpv5*KO mice are hypercalciuric because of a defect in distal reabsorption of calcium and show adaptive increase in intestinal calcium absorption [57].

Two calcium-buffering proteins, calcium-binding protein (Ca-BP), Ca-BP-D28K, and Ca-BP-D9K, are expressed in the DCT/CNT [34, 50, 127]. However, although intracellular ferry of calcium is critical for transcellular calcium absorption, Ca-BP-D28K KO mice are only mildly hypercalciuric [78, 79]. Parvalbumin is another intracellular calcium-binding protein expressed in the distal tubule together with the Na-Cl cotransporter NCC; however, no phenotype affecting calcium transport has been seen in mice not expressing parvalbumin [9].

Exit of calcium across the basolateral membrane occurs via the $3Na^+/1Ca^{++}$ exchanger NCX1 and/or the plasma membrane calcium ATPase isoform 4 (PMCA4) [4]. PMCA4 can be detected at the basolateral membrane of DCT/CNT and cortical TAL, macula densa, and early distal tubules. The relative contributions of NCX1 and PMCA4 for basolateral calcium export are debated, but a mathematical model of calcium reabsorption in the DCT/CNT proposed that NCX1 is the main regulated basolateral exit pathway, while PMCA4 has housekeeping functions [12].

Determinants of calcium reabsorption along the renal tubule

Extracellular calcium concentration and calcium-sensing receptor (CaSR)

Changes in ECF calcium concentration can affect the renal handling of various ions and water, independently of changes in PTH level. For example, hypercalcemia decreases tubular reabsorption of calcium, sodium, and magnesium in the loop of Henle [106, 114]. These and other effects of hypercalcemia on the renal tubule have been previously reviewed [117].

The demonstration of CaSR expression in the kidney has been helpful to understand how extracellular calcium affects the functions of the renal tubule [19]. Soon after CaSR was identified in the parathyroid gland, its expression in the mammalian kidney was studied in great detail [119], providing a potential molecular explanation for the direct effects of extracellular calcium on the kidney. The initial studies, performed by Riccardi and colleagues, were mRNA expression experiments on dissected glomeruli and tubular segments from rat kidney. High expression of *CaSR* transcripts was reported in the M-TAL and C-TAL [119]. These findings were confirmed by Yang et al. in the rat kidney [150], by Loupy et al. in rat and mouse kidneys [84] and by Graca et al. in rodent and human kidneys [43]. Using various antibodies, all investigators concluded that the CaSR protein is highly expressed at the basolateral membrane of the TAL in the mature rodent kidney [84, 118, 133] and in the mature human kidney [43, 84], as well as the developing human kidney [27]. However, significant expression of CaSR in other parts of the kidney, either as mRNA or as protein, remains debated. In addition to TAL expression, Riccardi et al. and Graca et al. reported that *CaSR* mRNA is present in glomeruli and in almost all tubular and collecting duct (CD) segments, including the proximal convoluted tubule (PCT), the proximal straight tubule (PST), the DCT, the cortical CD (CCD), and the inner medullary CD (IMCD) [43, 119]. *CaSR* expression in the thin limbs and the CNT was not examined. CaSR protein expression was reported for the PCT, PST, MTAL, CTAL, DCT and CCD in the rat kidney [43, 118], localized to the apical brush-border membrane in the PT [118] and in the IMCD [121], whereas basolateral membrane expression was described for the DCT [118]. Studies performed by other groups showed significant differences. Yang et al. demonstrated *CaSR* mRNA expression in DCT and CCD cells of the rat kidney, but did not detect any expression in glomeruli or in other tubular segments [150]. Loupy et al. performed quantitative PCR experiments from mRNA in microdissected tubular segments from rat and mouse kidneys [84]. Only weak expression of *CaSR* was found in the CCD, whereas no expression could be detected in other nephron segments (DCT, IMCD and thin limbs were not studied). Immunohistochemistry and/or immunofluorescence experiments utilizing various anti-CaSR antibodies have also yielded conflicting results. Loupy et al. found no expression of CaSR in the PCT, PST, DCT, CNT or CD [84]. Predominant expression of *CaSR* in the TAL of the mouse kidney was subsequently confirmed by Toka et al. [133]. Crisi et al. reported CaSR expression in the TAL and the distal tubule of the developing human kidney [27].

In summary, CaSR is highly expressed in the M- and C-TAL in rodent and human kidneys. The expression of CaSR at lower level in other tubular segments remains debated.

Various genetic models and pharmacological intervention studies showed that disruption/inactivation of the renal CaSR elicits an increase in renal tubular calcium reabsorption [72, 84, 133, 134]. Conversely, activating variants of CaSR are associated with lower tubular calcium reabsorption, in Humans with autosomal dominant hypocalcemia (ADH) type 1 (OMIM #601298) as in mice [62, 103, 148]. In general, none of the available animal models of disrupted or mutated *CaSR* display any significant changes in NaCl, water, or magnesium homeostasis [53, 62, 72, 133, 134]. Approximately 100 pathogenic monoallelic variants have been described in patients with ADH. Out of those, only 6 variants (p.Lys29Glu, p.Leu125Pro, p.Cys131Trp, p.Tyr829Cys, p.Ala843Glu, and p.Ile857Ser) have been reported to cause ADH with a Bartter-like syndrome phenotype [23, 42]. This indicates that some few and specific variations of the CaSR protein may affect NaCl transport across the TAL cells, whereas most of the variants may not. Possibly, the ability of those specific variants to interact with NaCl reabsorption may stem from conformational changes in the protein or signaling bias, independent of the effect of CaSR on calcium and magnesium transport.

An increase in either peritubular calcium or magnesium concentrations decreases calcium and magnesium absorptions in the TAL in dogs, rats, and mice [29, 114, 115]. Patch clamp studies showed that calcium and neomycin, two non-specific CaSR agonists, reduce the activity of the apical K^+ channel through generation of arachidonic acid metabolites via the cytochrome P-450 pathway [138, 139]. However, it is unknown whether inhibition of this K^+ channel is able

to decrease PD_{te} in the TAL, the driving force for the reabsorption of divalent cations. NPS R-467, an allosteric CaSR activator, decreases PTH-stimulated calcium absorption without altering the PD_{te} in microperfused mouse C-TAL; this suggests that CaSR may directly control P_{Ca} [97]. Similarly, NPS 2143, an allosteric inhibitor of CaSR, increases basal as well as PTH-stimulated calcium absorption and P_{Ca}, but alters neither the PD_{te} nor the transport of Na^+ or Cl^- in in vitro microperfused rat C-TAL [84].

Of note, some investigators reported that the non-specific agonists of CaSR, calcium and neomycin, decrease both the PD_{te} and chloride transport in the microperfused rat C-TAL [69]. Such effects cannot be reproduced by more specific activators of CaSR [97], suggesting that more than one single "calcium-sensing" mechanism might exist in the TAL. These differences could also be accounted for by the ligand-biased properties of CaSR.

CLDN14 can directly interact with CLDN16 and decrease the CLDN16/CLDN19 heterodimer-dependent paracellular permeability to cations [40]. Hypercalcemia increases the expression of CLDN14, which potentially explains the long-term inhibitory effects of hypercalcemia on calcium absorption in the TAL [40]. Using pharmacological tools, Gong et al. further demonstrated that CaSR controls CLDN14 via the calcineurin-NFATc1-microRNA pathway [39]. In vivo, the disruption of CaSR in the TAL decreases the abundance of the *Cldn14* mRNA and increases that of the *Cldn16* mRNA [133]. Treatment by the calcimimetic (CaSR agonist) cinacalcet increases the abundance of *Cldn14* mRNA [30]. Recent findings show that CaSR can also induce CLDN14 via a PLC-stimulated p38 pathway [76]. The mechanisms described above may play an important role in mediating the effects of chronic hyper- or hypocalcemia on calcium transport in the TAL. However, it remains unclear how CaSR alters the paracellular pathway permeability within minutes and which mediators are involved in this process [84].

Besides its direct effect on calcium reabsorption, CaSR may also indirectly affect calcium homeostasis. Activation of renal CaSR may promote Klotho shedding in the distal nephron (see below the effects of Klotho) [152]. In addition, extracellular calcium can affect transepithelial transport by altering transporter expression and/or activity. For example, ECF calcium inhibits Na^+,K^+-ATPase activity in the PT, which may participate in the natriuretic effect of hypercalcemia [82]. Both extracellular calcium and gadolinium are able to increase the expression of the vitamin D receptor (VDR) in a proximal tubule-derived cell line, an effect mediated by the p38alpha MAP kinase pathway [86, 87].

Parathyroid hormone

Parathyroid hormone (PTH) increases renal tubular calcium reabsorption [149]. PTH-sensitive adenylate cyclase activity has been detected in PCT, PST, M-TAL, C-TAL, and DCT but not in CCD in human nephron [20]; similar results were obtained in rabbit, rat, and mouse nephron, with the difference that M-TAL was not responsive to PTH but CNT (not assessed in humans) was (reviewed in [96]). In human kidney, PTH receptor type 1 is mainly expressed at the basolateral membrane of PT, TAL and DCT/CNT cells [85].

Early micropuncture studies showed that PTH acutely decreases sodium and calcium reabsorption in the dog PT ([3, 132]; however, whether proximal calcium reabsorption remains diminished during long term exposure to PTH is unknown.

PTH has no effect on the M-TAL of rodents [144]. In contrast, in the C-TAL, PTH stimulates NaCl, as well as magnesium and calcium reabsorption [128, 129, 145, 146]. However, the effect on calcium absorption is proportionally greater than that on Na and Cl transport, suggesting that PTH is able to increase the paracellular pathway permeability to divalent cations. In the rabbit C-TAL, PTH stimulates the divalent cation transport but not that of NaCl [130]. Indirect evidence that CLDN14 could be involved in the effect of PTH on calcium reabsorption in the mouse TAL has been reported [122]; however, it would not explain how PTH is effective under regular conditions when CLDN14 is barely detectable.

In the DCT/CNT, parathyroid hormone enhances TRPV5 activity, via a cyclic AMP-mediated, PKA-dependent phosphorylation [47]. Phosphorylation of residue T709 diminishes calmodulin binding to TRPV5 and thereby enhances channel open probability [46]. On the long term, PTH increases TRPV5 protein expression in the DCT/CNT [1].

Vitamin D metabolites

Vitamin D receptor (VDR) transcript is expressed in all cortical segments of rat and mouse kidney, the highest expression being found in DCT and CNT [22, 77]. A significant expression of the VDR protein is restricted to the C-TAL, DCT, and CNT [83]. Early studies showed that vitamin D metabolites increase renal tubular calcium reabsorption in thyroparathyroidectomized dogs and rats [25, 112, 113, 149], and one micropuncture study showed that the effect was taking place beyond the PT [143]. Deficit in 1,25dihydroxyvitamin D, the most biologically powerful metabolite of vitamin D, causes a decrease in TRPV5 expression at the apical membrane of DCT/CNT cells and in Ca-BP-D28K [58], disorders that are corrected by treatment by 1,25dihydroxyvitamin D. Accordingly, the promoter of the *TRPV5* gene contains a vitamin D response element [58]. Conditions of excessive 1,25dihydroxyvitamin D concentration, such as idiopathic infantile hypercalcemia type 1 due to loss-of function of the *CYP24A1* gene encoding 24-hydroxylase, are commonly associated with hypercalcemia [123]; whether

hypercalcemia is, in part, caused by increased calcium reabsorption in the DCT/CNT is likely, albeit not directly demonstrated.

The effect of vitamin D metabolites on calcium transport in other tubular segments has not been described, to our knowledge.

Extracellular fluid volume

Changes in ECF volume have major effects on urinary calcium excretion [2, 137]. Calcium excretion increases with sodium excretion [92]. Early micropuncture studies showed that saline loading increases proportionally the fractional delivery of calcium and sodium out of the proximal tubule [2, 109], indicating that saline loading decreases both sodium and calcium reabsorption in the PT. Accordingly, Nijenhuis et al. showed that thiazide-induced decrease in ECF volume increases calcium reabsorption in the PT [100]. A study conducted in 4 people with idiopathic hypercalciuria also concluded that thiazide diuretics increase calcium and sodium reabsorption in the PT [10]. However, the molecular mechanisms linking sodium chloride balance and tubular calcium handling remain poorly understood [151] and whether NaCl balance can affect calcium reabsorption beyond the PT is unknown.

The renal effects of thiazide diuretics on renal tubular calcium reabsorption cannot explain the sustained decrease in urinary calcium excretion under long-term treatment. In fact, a chronically low urinary calcium excretion implies that net entry of calcium in the ECF volume is low: this can be obtained only by a sustained decrease in net intestinal calcium absorption and/or in net bone calcium release; however, the mechanisms involved in lower intestinal calcium absorption or bone release remain to be identified.

Acid–base status

Metabolic acid load causes an increase in urinary calcium excretion [80, 81]. Older studies showed that both acute and chronic metabolic acidosis decrease renal tubular calcium reabsorption, independent of PTH [63, 80, 81]. The molecular mechanisms involved in the effect of metabolic acidosis on calcium handling in the kidney are likely multiple: TRPV5 expression in mouse kidney is lower under metabolic acidosis [99] and calcium uptake by TRPV5 decreases at low urine pH [13]. This can account for the acidosis-induced defect in the calcium reabsorption in DCT/CNT. Earlier studies have also shown that acute acidosis elicits a decrease in calcium reabsorption in the TAL [63], the mechanism of which remains unsettled. The sensing of change in extracellular pH may involve the G protein-coupled receptor OGR1, a proton-activated receptor. OGR1 is present in several tubular segments and renal interstitial cells. Metabolic acidosis does not induce hypercalciuria and does not decrease TRPV5 and Ca-BP-D28K expression in *Ogr1*$^{-/-}$ mice [67]. Metabolic acidosis also decreases Klotho concentration [152] (see the "Fibroblast growth factor (FGF23), Klotho and tissue kallikrein" section).

Fibroblast growth factor (FGF23), Klotho, and tissue kallikrein

Klotho is a ß-glucuronidase that is abundantly expressed in the distal nephron. Klotho-deficient mice are hypercalcemic [74]. Membrane-bound Klotho also functions as the co-receptor for the bone-derived hormone fibroblast growth factor-23 (FGF23). Various studies have suggested that Klotho, either directly via its enzymatic activity or indirectly by promoting the action of FGF23, increase the apical membrane abundance and/or activity of TRPV5 [6, 21]. However, whether klotho-deficient mice have a defect in distal reabsorption of calcium has not been established, even though Klotho-deficient mice are hypercalciuric [5, 6].

Tissue kallikrein is another enzyme expressed in the DCT and CNT; tissue kallikrein expression increases on a low calcium diet and loss of kallikrein in the mouse results in hypercalciuria [107]. Tissue kallikrein stabilizes TRPV5 expression at the apical membrane, which involves a PKC-mediated phosphorylation [37].

Renal mechanisms underlying abnormalities in serum calcium

As indicated above, the equilibrium value of ECF calcium depends on the balance between the amount of calcium entering the ECF (mainly from bone) and that leaving the ECF (in urine). Consequently, an increase in the ECF calcium value may result from (i) a decrease in the ability of the kidney to excrete calcium entering the ECF, the amount of calcium entering the ECF being normal or slightly increased, and (ii) an increase in the inflow of calcium into ECF of sufficient magnitude to overwhelm the ability of the kidney to excrete the required amount of calcium in the urine.

Schematically, the first condition is typical of calcium homeostasis disorders related to a primary alteration in PTH secretion (either primary hyperparathyroidism caused by parathyroid tumor or familial hypocalciuric hypercalcemia (FHH) caused by defective CaSR signaling). Under this condition, the main determinant of the change in ECF calcium concentration is the increase in renal tubular calcium reabsorption [90, 140]. However, because CaSR expressed by renal tubular cells is activated by hypercalcemia in patients with primary hyperparathyroidism whereas it is, by definition, inactivated in patients with FHH, it is expected that the renal reabsorption of calcium is not

stimulated to the same extend in patients with primary hyperparathyroidism and those with FHH. This assumption is partially correct because the average urinary calcium excretion is lower in patients with FHH than in those with primary hyperparathyroidism [136]. Nevertheless, the huge overlap between urinary calcium excretion values in patients with FHH or primary hyperparathyroidism suggests that, besides PTH value and the state of CaSR activation, several distinct factors are important to modulate the handling of calcium.

Table 1 shows a list of monogenic human diseases affecting the renal handling of calcium. With the notable exception of the diseases affecting CaSR, FHH and autosomal dominant hypocalcemia, the others are commonly not associated with abnormal serum calcium concentration. The likely explanation is that the excessive loss or retention of calcium by the kidney is compensated for by adaptive changes in bone calcium release or intestinal calcium absorption. For example, tubular calcium reabsorption is higher than normal and urinary calcium excretion is lower than normal in patients with Gitelman syndrome [98]; however, patients are not hypercalcemic, probably because low entry of calcium into the ECF, due to low bone turnover and bone calcium release, prevents it [98].

Open questions, challenges, and future directions

In spite of the considerable amount of knowledge accumulated for the last 60 years, several gaps persist and need to be addressed in the future. We shall consider a few of them.

Mechanisms of paracellular Ca permeability and plasticity

The molecular mechanisms sustaining paracellular Ca permeability in the proximal tubule and TAL have been identified. Nevertheless, the exact function of CLDN16 remains a matter of controversy, and the function of CLDN19 is even more elusive. Experimental evidence indicates that the permeability to calcium of the paracellular pathway is tightly controlled both acutely and chronically; however, with the exception of the role of CLDN14, we ignore almost everything regarding how the factors involved in the control of paracellular permeability can act at the molecular level. It is sound to believe that the function of claudins can be altered at the level of gene expression, intracellular trafficking and post translational alteration; very little is known regarding those processes and how important they are regarding the overall function. May be even more intriguing is the mosaic

Table 1 Inherited disorders affecting renal tubular calcium reabsorption

Syndrome	OMIM	Inheritance	Gene	Protein	Effect on calcium reabsorption
OAZON	301060	X-LR	*CLDN2*	Claudin-2	Decreased
Bartter syndrome, type 1	601678	AR	*SLC12A1*	NKCC2	Decreased
Bartter syndrome, type 2	241200	AR	*KCNJ1*	ROMK	Decreased
Bartter syndrome, type 3	607364	AR	*CLCNKB*	ClC-Kb	N or decreased
Bartter syndrome, type 4A	602522	AR	*BSND*	Barttin	Variable
Bartter syndrome, type 4B	613090	AR	*CLCNKA* + *CLCNKB*	ClC-Ka + ClC-Kb	Variable
Bartter syndrome, type 5	300971	X-LR	*MAGED2*	MAGE-D2	Decreased
Familial hypocalciuric hypercalcemia type 1	145980	AD	*CASR*	CaSR	Increased
Familial hypocalciuric hypercalcemia type 2	145981	AD	*GNA11*	Guanine nucleotide-binding protein subunit alpha-11	Increased
Familial hypocalciuric hypercalcemia type 2	600740	AD	*AP2S1*	AP-2 complex subunit sigma	Increased
Autosomal dominant hypocalcemia, type 1	601198	AD	*CASR*	CaSR	Decreased
Autosomal dominant hypocalcemia, type 2	615361	AD	*GNA11*	GNA11	Decreased
HELIX	617671	AR	*CLDN10B*	Claudin-10b	Increased
FHHNC	248250	AR	*CLDN16*	Claudin-16	Decreased
FHHNC with severe ocular involvement	248190	AR	*CLDN19*	Claudin-19	Decreased
Gitelman syndrome	263800	AR	*SLC12A3*	NCC	Increased

X-LR X-linked recessive, *AR* autosomal recessive, *AD* autosomal dominant, *OAZON* obstructive azoospermia with nephrolithiasis, *HELIX* hypohidrosis, electrolyte disturbances, lacrimal deficiency, ichthyosis, xerostomia, *FHHNC* familial hypomagnesemia with hypercalciuria and nephrocalcinosis

pattern of expression of CLDN-10/CLDN-16/CLDN-19 in the TAL: one given cell can share a CLDN10-expressing tight junction with one neighbor cell and one CLDN16-CLDN19-expressing tight junction with another one: how this is determined and how quickly it can change remains obscure, despite the fact that remodeling of tight junctions is likely an essential aspect of adaptive functional plasticity of the TAL.

Epigenetic control

The spectrum of kidney diseases associated with genetic alterations has been considerably expanding. More recently, it emerged that epigenetic control of renal functions may be equally important. Epigenetic alterations are heritable traits that impact the phenotype by interfering with gene expression independent of DNA sequence [33]. So far, the three basic epigenetic mechanisms (DNA methylation, histone modification, and microRNAs) have mostly been studied in acute kidney injury, chronic kidney disease, kidney fibrosis, and diabetic kidney disease [31]. Most likely, epigenetic mechanisms are at work in the control of ion transport and homeostasis, as well. One supporting evidence is provided by the variability of the phenotype of many monogenic kidney diseases: although the difference in phenotype between affected and non-affected subjects is often easily measurable and significant, the variability of the main phenotypic trait(s) between affected human subjects (or mice) cannot be explained by the genetic defect itself, in many cases. One possible explanation is that the variability is due, at least in part, to epigenetic mechanisms. The control of CLDN14 by microRNA is just one example and likely many more are to be discovered.

Therapeutic targeting

Epithelial cells forming the renal tubule and the collecting duct are highly specialized: regarding calcium reabsorption, it explains that many distinct mechanisms, and therefore, molecules are involved in renal tubular calcium reabsorption. When a defect in calcium reabsorption occurs, it usually affects one segment and, sometimes, one single molecule in one specific cell type. Then, even if a drug able to correct the defect is available, it has to be properly delivered to the target and not to cells or tissues not involved in the deficient process in order to avoid unwanted side effects. Nanoparticles can be used to deliver drugs to their target [93].

The importance of tightly controlled tubular reabsorption of calcium in the kidney in the overall calcium homeostasis is now well established. Our knowledge has continuously been expanding with more and more accurately defined mechanisms of transport and factors of control. Nevertheless, with more and more actors identified as participants in the renal handling of calcium, we lack an integrated view with a clear understanding of how every factor interacts with others and account for overall kidney calcium handling and systemic calcium homeostasis. This is one of the challenges we have to face.

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Declarations

Competing interests The authors declare no competing interests.

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