Urolithiasis (2019) 47:35–42
https://doi.org/10.1007/s00240-018-01103-z

INVITED REVIEW

Inherited proximal tubular disorders and nephrolithiasis

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Received: 17 September 2018 / Accepted: 8 December 2018 / Published online: 23 January 2019

Abstract
The proximal tubule is responsible for reclaiming water, phosphates and amino acids from the tubular filtrate. There are genetic defects in both phosphate and amino acid transporters leading to nephrolithiasis. This review also explores genetic defects in regulators of phosphate and calcium transport in this nephron segment that lead to stone formation.

Keywords Nephrolithiasis · Physiology · Tubular

Introduction

Classically, the distal tubule is often linked to nephrolithiasis; however, several inherited proximal tubular disorders have also been associated with renal stone disease. While these conditions might be rare, they provide clues as to how the proximal tubule handles solutes involved in stone formation, and can also provide insights into the pathogenesis of more common forms of stone disease.

Overall functions of the proximal tubule

The proximal tubule is the workhorse of the human nephron responsible for claiming back the majority of the 160–170 L of glomerular filtrate produced every day. Specifically 60–70% of filtered NaCl and water, and all of the $NaHCO_3$ is reabsorbed in this nephron segment [1]. It is also the site of reabsorption for glucose, amino acids and several important anions (including phosphate and citrate). The proximal tubule also has a metabolic function. It is responsible for both the 1-alpha hydroxylation of vitamin D to its active form and the inactivation of this hormone via the 24-hydroxylase reaction [2]. Of the solutes reclaimed in the proximal tubule, phosphate is the one of the most important in relation to risk of nephrolithiasis.

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Phosphate and calcium homeostasis in the proximal tubule

The proximal tubule is responsible for reclaiming about 80% of the filtered phosphate under normal physiological conditions. Two sodium-dependent phosphate cotransporters of the *SCL34* solute carrier gene family carry out most of this [3]. The bulk (85%) is carried out by *SLC34A1* (NaPi-IIa). *SLC34A3* (NaPi-IIc) reabsorbs the remaining 15% [3]. *SCL34A2*, another member of this gene family, is mainly expressed in the small intestine.

Another family of sodium-dependent phosphate transporters, designated *SLC20*, is also expressed in the proximal tubule; however, the overall contribution of these transporters to phosphate reclamation is likely to be small [4]. The entry of phosphate through these cotransporters is driven by the cotransport of sodium, the electrochemical gradient of which is established by the sodium/potassium ATPase located on the basolateral cell membrane [5].

Expression of NaPi-IIa is at least partly regulated by parathyroid hormone (PTH). PTH binding to G-protein-coupled type 1 PTH receptors (PTH1R) activates protein kinase A (PKA) via cAMP, and protein kinase C (PKC) [6, 7]. Once activated, these kinases phosphorylate the PDZ domain of NHERF1 [8]. NHERF1 anchors NaPi-IIa to the cytoskeleton, but releases it when phosphorylated, leaving NaPi-IIa free to be endocytosed; see Fig. 1 [9]. The action of PTH, therefore, is to internalise NaPi-IIa, leading to phosphate wasting [10, 11]. The other action of PTH in this segment is inhibition of the sodium proton exchanger isoform 3 (NHE3) [12]. This exchanger extrudes protons into the tubular lumen in exchange for the reabsorption of sodium. The combination

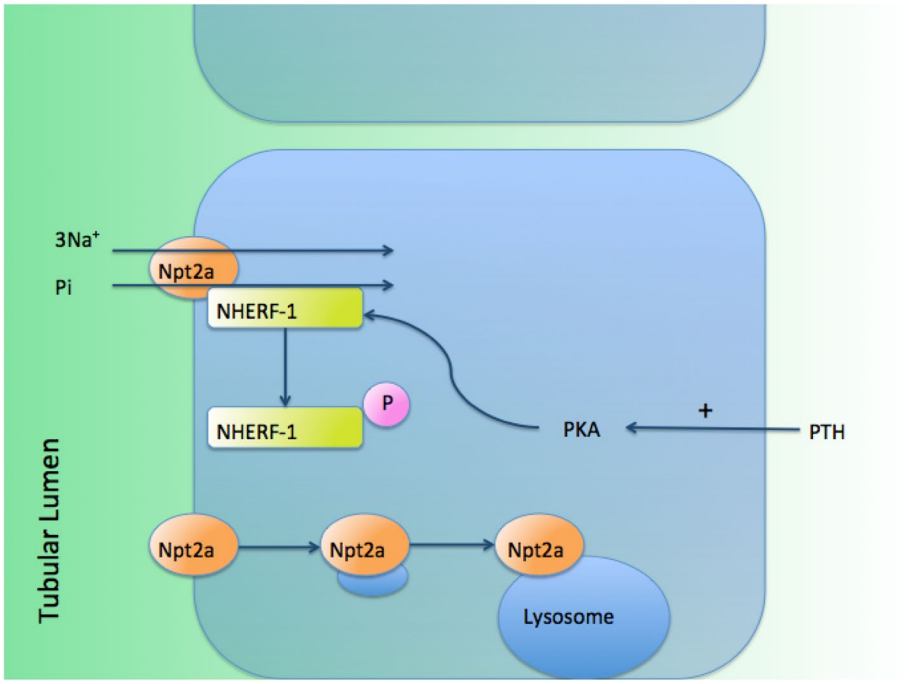

Fig. 1 Proximal tubular cell showing the sodium/phosphate cotransporter NaPi-IIa. The scaffolding protein NHERF-1 holds NaPi-IIa to the apical membrane facilitating sodium and phosphate reabsorption. The action of PTH activates protein kinase A (PKA), which in turn phosphorylates NHERF-1. Phosphorylated NHERF-1 no longer anchors NaPi-IIa, leaving it free to be endocytosed in lysosomes preventing phosphate and sodium reabsorption

of hydrogen ions with filtered bicarbonate allows for the effective reclamation of bicarbonate through passive diffusion of carbon dioxide across the tubular membrane. This exchanger also sets up a concentration gradient for the reabsorption of water molecules [13]. So, inhibition of NHE3 will lead to deceased sodium and water reabsorption and alkalisation of the tubular fluid. A result of this is to decrease calcium reabsorption. There are two mechanisms for this: first, paracellular calcium uptake in the proximal tubule appears to be coupled to sodium reabsorption; indeed, mice lacking NHE3 have an increased fractional excretion of calcium, despite elevated levels of activated vitamin D [14–16]. Second, the actions of NHE3 are to acidify the urine, this not only creates more ionised calcium for absorption in more distal segments, but also potentially increases the activity of the calcium transporter TRPV5. So, the PTH-mediated inhibition of NHE3 acts to decrease calcium reabsorption in the proximal tubule, the opposite of its overall effect on calcium excretion in vivo. Stimulation of the calcium-sensing receptor (CaSR) in this nephron segment opposes the actions of PTH; it abolishes PTH-mediated internalisation of NaPi-IIa and stimulates NHE3 [17, 18]. Stimulation of CaSR, therefore, leads to increased phosphate, sodium and water reabsorption, and acidification of tubular fluid. The net result of this is an increase in proximal tubular calcium reabsorption. It should be noted that the presence of CaSR in the proximal nephron is controversial. While mRNA and immunolocalization studies had demonstrated CaSR expression throughout the nephron [19, 20], Loupy and coworkers reported an expression confined to the thick ascending limb (TAL) [21]. More recently, a comprehensive study has shown that although expression of the CaSR is highest in the TAL, there is expression elsewhere including the proximal tubule [22]. Interestingly, CaSR expression in the proximal tubule and collecting duct is on the apical membrane while in the TAL it is basolateral [20]. It has been proposed that proximal tubular CaSR serves to mitigate overall calcium excretion and reduce the risk of calcium salt precipitation. The CaSR in the proximal nephron may, therefore, serve a role in protecting the kidney against stone formation.

Another important regulator of proximal tubular phosphate reabsorption is fibroblast growth factor-23 (FGF-23). FGF-23 binding to the FGF1c receptors leads to down-regulation of both NaPi-IIa and IIc [23]. FGF-23 also leads to decreased levels of $1,25(OH)_2D_3$ due to inhibition of one alpha hydroxylase activity [24].

Phosphate and calcium transport, and nephrolithiasis

SLC34A1/NaPi-IIa

SLC34A1 lies on chromosome 5q35 and consists of 13 exons and 12 introns. SLC34A1 transports three sodium ions together with one divalent phosphate ion [25, 26]. Bi-allelic mutations in this gene have been reported in a Palestinian family with hypophosphataemic rickets [27]. More recently, homozygous mutations have been found in a family with idiopathic infantile hypercalciuria (IIH) that did not have a mutation in *CYP24A1* [28]. Secondary increases in vitamin D and hypercalciuria were also seen, as well as renal tract calcification. Neither of the

two Palestinian cases had nephrolithiasis; the authors speculated that this was probably due nutritional vitamin D deficiency. In the absence of a nutritional defect, phosphate wasting should lead to increased activation of vitamin D, leading to increased intestinal calcium absorption and hypercalciuria. The patients also had a generalised renal Fanconi-type defect, leading to citrate wasting; this may also have protected them against stone formation. The mutation in this family was an in-frame-inserted duplication in *SLC34A1* (p.I154 V160dup-NaPiIIa). The mutation leads to a trafficking defect and retention of the protein in the endoplasmic reticulum (ER). The same authors later speculated that disruption of the ER by the mutant protein could affect other proteins in the cell, explaining the generalised proximal tubulopathy [27, 29].

A candidate gene approach in individuals with hypophosphataemic nephrolithiasis with osteoporosis revealed heterozygous mutations of *SLC34A1* [30]. The pathogenic significance of this finding is not clear; the mutation has not been found in other kindred with the same phenotype, and the expression of mutant *SLC34A1* did not affect phosphate transport in cell models [31].

Mutations in sodium–hydrogen exchanger regulator factor 1 (NHERF1) have also been found in individuals with hypophosphataemic nephrolithiasis with osteoporosis. NHERF1 binds to NaPi-IIa and PTH. PTH regulates phosphate by reducing NaPi-IIa expression at the apical membrane of proximal tubule cells. Members of NHERF family of proteins are proposed to scaffold various transporters at the apical membrane, preventing their internalisation into endosomes. The PDZ1 domain of NHERF1 is crucial for its interaction with NaPi-IIa and phosphorylation of this domain decreases its affinity for NaPi-IIa, leaving it free to be internalised into endosomes. Activation of PTHR1 by PTH causes increased cAMP production, activating the protein kinase A (PKA) pathway that ultimately leads to phosphorylation of the PDZ1 domain of NHERF1. NHERF1 is crucial for producing the phosphaturic effects of PTH. Indeed, the coupling of apical PTHR1 stimulation to downregulation of NaPi-IIa expression is completely abolished in NHERF1$^{-/-}$ mice [32]. NHERF1 also modulates the amount of cAMP produced by the PTHR1 receptor in response to PTH stimulation. This interaction occurs via the PDZ2 domain of NHERF1. Mutations of the PDZ2 domain abolish the interaction between NHERF1 and PTHR1, leading to unabated cAMP production in response to PTH and, therefore, an increased phosphaturic effect. Such mutations have been shown to produce phosphaturia and nephrolithiasis in humans [33]. Subsequently, a mutation has been described in the PDZ1 domain, leading to phosphaturia and nephrolithiasis [34]. As PDZ1 does not interact with PTHR1, this mutation limits NaPi-IIa expression in a PTH-independent fashion.

Variants in *SLC34A1* have also been implicated in stone formers who do not have Mendelian disease. A Japanese genome-wide association study (GWAS) of 5892 patients with calcium-containing stones found three loci associated with stone formation, one of which occurred in intron 4 of *SLC34A1* [35]. Although the authors found an association of this variant with reduced renal function, there was no significant association with serum phosphate. However, a previous GWAS did find an association of serum phosphate and variants at *SLC34A1* [36]. Furthermore, knockout mice for NaPi-IIa develop phosphate wasting with secondary hypervitamin D production and hypercalciuria [37].

SLC34A3/NaPi-IIc

SLC34A3 gene spans 5 kb, contains 13 exons and is located on chromosome 9. It transports two sodium ions for every divalent phosphate ion and is, therefore, electro-neutral [38, 39]. Hereditary hypophosphataemic rickets with hypercalciuria (HHRH) is an autosomal recessive condition presenting with bone disease, hypercalcaemia and nephrolithiasis [40]. Compound heterozygous mutations have been reported to cause the condition [38]. Individuals with just one mutated allele do not have the HHRH phenotype, but varying degrees of hyperphosphaturia and hypercalciuria have been reported in the literature [41].

A linkage study performed in a Spanish kindred identified a locus spanning *SLC34A3* on the long arm of chromosome nine associated with autosomal dominant inherited nephrolithiasis [42]. Another group has shown that in family members of HHRH sufferers, heterozygotes of *SLC34A3* mutations were more susceptible to kidney stones with a threefold increase in risk compared with the general population [43].

CYP24A1

IIH type 1 is caused by inactivating mutations in the *CYP24A1* gene that encodes 25-OH-D_1-24-hydroxylase, the enzyme responsible for inactivating vitamin D [44]. This was first recognised in the 1950s with children presenting with symptomatic hypercalciuria when given milk fortified with vitamin D. However, the same defect is also found in those presenting for the first time as adults with nephrocalcinosis and calcium phosphate nephrolithiasis [45]. Without *CYP24A1*, vitamin D continues to exert its effects, including increased calcium reabsorption, leading to hypercalcaemia and the development of nephrolithiasis.

Hypophosphataemic rickets

It is worth touching on this condition associated with phosphate wasting, but not with nephrolithiasis. The phosphate wasting is due to increased activity of FGF-23 that decreases

the activity of both NaPi-IIa and NaPiIIc. However, FGF-23 also leads to less active vitamin D and so hypercalciuria does not ensue. This highlights that hypophosphaturia alone is probably not enough to cause nephrolithiasis, which may be because it requires calcium to crystalize.

CaSR

The CaSR has a key role in regulating both calcium and phosphate excretion in the kidney. Variants in *CASR* are associated with nephrolithiasis [46]. Work by an Italian group has shown that the *CASR* polymorphism Arg990Gly was more common in hypercalciuric stone formers than controls. In vitro work revealed that this was a gain-of-function mutation [47]. However, other investigators failed to show any interaction with the SNP and calcium homeostasis [48]. The SNP rs6776158 located in the first promoter of *CASR* has also been associated with calcium nephrolithiasis. Further work revealed that the minor G allele of this SNP caused decreased transcription in renal cell lines. Soldati's group suggested that the combination of rs6776158 and Arg990Gly polymorphisms potentiates the risk of nephrolithiasis [49]. This seems strange, given that these two SNPs appear to have opposite effects on CaSR expression. However, given the complex role that CaSR has in regulating calcium homeostasis in the kidney, it may well be that disrupting this regulation (either positive or negative) is enough to tip the balance in favour of calcium salt precipitation. Gain-of-function mutations can easily be imagined to cause nephrolithiasis, given that the actions of CaSR are to promote calcium wasting in the urine. Decreased expression of the receptor in certain areas of the nephron could also have detrimental consequences. For example, decreased expression in the proximal tubule would abolish the protective affects (i.e. calcium reabsorption) at this site, leading to more calcium delivery to the distal nephron. This speculative mechanism needs further work to clarify the exact effects these variants have on renal calcium handling.

Renal Fanconi syndrome and other transporters

The renal Fanconi syndrome describes a generalised loss of proximal tubular function including wasting of bicarbonate, phosphate, glucose and amino acids. Children with Fanconi syndrome present with failure to thrive and rickets. A number of inherited disorders have been described that cause Fanconi syndrome. Despite phosphate wasting being a feature of many of these conditions, nephrolithiasis is really only a feature of Dent disease and Lowe syndrome.

Dent disease

Dent and Friedman first described the condition in 1964 in two children with rickets, aminoaciduria, phosphaturia and hypercalciuria [50]. Further characterisation of the condition by Wrong [51] identified both nephrocalcinosis and nephrolithiasis as features of this condition. Several linkage studies in the 1990s mapped the causative gene to Xp11.22, confirming it as an X-linked condition [52]. Shortly afterwards, *CLCN5* (encoding the chloride channel; CLC-5) was suggested as the candidate gene [53]. CIC-5 is found in lysosomes involved in endocytosis of proximal tubule proteins. Defects in the channel impair trafficking of the lysosomes to the apical membrane, leading to failure of the normal function of endocytosis and leading to the generalised failure in the re-absorptive function of the proximal tubule. The cause of the hypercalciuria seen in the condition has not been clearly delineated. It has been postulated that excess loss of phosphate and vitamin D-binding protein in the urine leads to secondary increased vitamin D3 synthesis [54]. Another proposed mechanism is that decreased chloride reabsorption in the proximal tubule leads to reduced calcium absorption in downstream nephron segments (presumably by reducing the trans-tubular electrochemical gradient necessary for cation transport [55]). Nephrocalcinosis may occur in Dent patients without hypercalciuria [56] and there is some evidence that defective ClC-5 in collecting duct cells may cause decreased clearing of calcium crystals from the apical cell surface [57]. Also, decreased proximal tubular endocytosis of parathyroid hormone (PTH) results in an increased luminal concentration of PTH, which stimulates increased 1-alfa hydroxylation and causes a decreased expression of NaPi2 at the apical membrane and phosphaturia, favouring calcification [58]. About a third of patients do not have a defect in *CLCN5*, but have a mutation in the gene *OCRL* [59]. This is also on the X-chromosome and encodes phosphatidylinositol 4,5-bisphosphate 5-phosphate, a protein that sits on the Golgi apparatus and directs proteins to the appropriate membrane. Again, it is thought that mutations in this gene lead to impaired trafficking of endosomes to the apical membrane. Dent patients with this mutation are sometimes referred to as Dent disease type 2. A related condition, Lowe syndrome is also caused by *OCRL* mutations; these patients have ocular defects and learning difficulties, along with renal Fanconi syndrome [59]. Patients with type 2 Dent disease and those with Lowe syndrome may actually form a spectrum of disease, rather than being phenotypically distinct cohorts. End-stage renal disease is a variable feature of Dent's disease, with an estimated 30–80% of affected males developing this complication [51].

Cystinuria

Cystinuria is characterised by the failure to reabsorb the amino acids such as cysteine, lysine, ornithine and arginine. The resulting concentration of cysteine in the urine is high enough to result in cystine (the oxidised dimer of cysteine) formation, which is highly insoluble, and its precipitation causing cystine nephrolithiasis. Both decreased GFR and elevated blood pressure are increasingly recognised complications of the condition [60]. Cystinuria type A is due to mutations in *SCL3A1*, while cystinuria type B is due to mutations in *SCL7A9*, which encode the heavy t (rBAT) and light x ($b^{0,+}$AT) subunits, respectively, of the renal amino acid transporter $b^{0+,}$ [61, 62]. The heavy subunit facilitates the localisation of the channel to the apical membrane in proximal tubule epithelial cells. The light subunit carries out the catalytic functions of the transporter. b^{0+} transports cysteine and dibasic amino acids in exchange for neutral amino acids [63]. Not surprisingly, *SCL3A1* mutations lead to trafficking defects, while *SCL7A9* mutations lead to loss of function of the exchanger. Although this condition leads to failure to reabsorb cysteine, lysine, ornithine and arginine, it is cysteine to cystine that causes the clinical problem due to the very low solubility of cystine in urine at neutral and acidic pH [64].

URAT1 renal hypouricaemia

The final transporter to be considered in this review is the proximal tubular uric acid exchanger URAT1. The protein is encoded by *SLC22A12* and is responsible for reclaiming uric acid in exchange for anions. Several Japanese patients have been reported with either homozygous or compound heterozygous loss of function mutations of URAT1 [65]. These patients are characterised by low serum uric acid levels, and high fractional excretion of uric acid. These patients have a propensity to develop uric acid nephrolithiasis and exercise-induced acute kidney injury (EIAKI) [66]. Those developing EIAKI had a lower estimated glomerular filtration rate than their counterparts without this complication, suggesting they are at risk of developing chronic kidney disease in the future [66]. The observation that loss of function mutations in URAT1 lead to hypouricaemia make it a potential drug target for the treatment of gout. Indeed, recent studies combining an oral URAT1 inhibitor with a xanthine oxidase inhibitor, to reduce the risk of urate stone formation, have shown an enhanced efficacy in reducing serum urate levels in the treatment of hyperuricaemia with gout [67].

Conclusions

The proximal tubule has an important role to play in maintaining many normal physiological processes in the body. While the distal nephron segments can fine-tune the final composition of urine, the heavy work, at least in relation to solute reclamation, has already occurred in the proximal tubule. Of all the processes occurring in the immediate postglomerular nephron, it is abnormalities of phosphate reabsorption that are more commonly implicated in nephrolithiasis. The first transporter in this segment to be associated with nephrolithiasis was NaPi-IIc, despite it only transporting a fraction of the phosphate transported by NaPi-IIa. For a long time, no convincing evidence could be found linking NaPi-IIa to human disease. However, in the last 10 years has seen a number of mutations linked to dysfunctional NaPi-IIa and nephrolithiasis. However, there is marked phenotypic heterogeneity seen with mutations in these transporters, from an isolated phosphate leak to a more generalised proximal tubulopathy, and even a full-blown Fanconi syndrome. Uncovering what lies behind these differences will lead to a better understanding of the factors governing stone risk attributable to altered proximal tubule function.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare.

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