Renal phosphate excretion and serum level are critically determined by several sodium-dependent phosphate transporters expressed in the proximal tubule, among them NaPi-IIa and NaPi-IIc.1,2 In humans, mutations in NaPi-IIc (SLC34A3) cause hereditary hypophosphatemic rickets with hypercalciuria. In contrast, the role of NaPi-IIa (SLC34A1) in renal syndromes of hyperphosphaturia and nephrolithiasis has been controversial. In rodents, NaPi-IIa is the major renal isoform responsible for the reabsorption of approximately 70% of the filtered phosphate load. Iwaki et al.3 demonstrate now that a single missense mutation in mouse NaPi-IIa transporter causes an autosomal recessive form of hyperphosphaturia, hypophosphatemia, and hypercalciuria with early development of renal calcifications and cystic kidney degeneration. This mutation abolishes membrane expression of NaPi-IIa both in a cell culture model and in vivo, suggesting that protein misfolding may occur. Although this study confirms the importance of NaPi-IIa in renal phosphate handling in mouse kidney, it remains unresolved how much this transporter contributes to phosphate handling in human kidney.

Studies of mice lacking NaPi-IIa demonstrate that NaPi-IIa (Slc34a1) is responsible for approximately 60 to 70% of total phosphate transport in the luminal membrane, the remaining 30 to 40% being reabsorbed by NaPi-IIc (Slc34a3) and by at least one more unidentified transporter.1,2,4 The absence of NaPi-IIa induces massive renal losses of phosphate, leading to hypophosphatemia, rickets, and hypercalciuria. Hypercalciuria is the consequence of elevated vitamin D3 levels stimulating intestinal calcium hyperabsorption and subsequent renal excretion. NaPi-IIa abundance and function is regulated by a variety of factors known to affect renal phosphate excretion, including parathyroid hormone, vitamin D3, fibroblast growth factor-23, dopamine, dietary phosphate intake, and acid-base status.1,5,6 The level of expression of the NaPi-IIc co-transporter is much lower than NaPi-IIa, is resistant to parathyroid hormone, but regulated by dietary phosphate intake and possibly during growth.7 Deletion of NaPi-IIc (Slc34a3) in mice is fully compensated because no hyperphosphaturia or hypophosphatemia occurs.4

The role of these transporters in human kidney is much less clear. Missense mutations and large deletions in the NaPi-IIc (SLC34A3) gene in patients with hereditary hypophosphatemic rickets with hypercalciuria indicate that NaPi-IIc is critical for determining serum phosphate levels and urinary phosphate excretion.8,9 For some of these missense mutations, reduced transport activity and/or decreased surface expression in the OK cell system support the role of NaPi-IIc in the pathogenesis of renal phosphate wasting and its sequelae.10

The role of NaPi-IIa in heritable forms of hyperphosphaturia is controversial. In 2002, Prie et al.11 reported two patients with hyperphosphaturia and found two sequence changes in the human NaPi-IIa (SLC34A1) gene; however, these sequence differences were found only on one allele, postulating an autosomal dominant pattern of inheritance. Unfortunately, no data were presented as to the genetic status of parents or siblings. Expression of these two transporter variants in Xenopus oocytes results in lower electrogenic transport activities and even suppresses coexpressed wild-type transporters. In contrast, a more detailed analysis of the reported NaPi-IIa variants in Xenopus oocytes and OK cells yielded no functional differences or impaired expression of the affected transporters. Also, the dominant negative effect of the transporter variants was not found.12 Thus, the biologic significance of these two NaPi-IIa variants remains to be determined. Alternatively, Lapointe et al.13 demonstrated convincingly that NaPi-IIa mutations may not be the major cause of hyperphosphatemia in humans. They reported a cohort of 98 pedigrees with hypercalciuria and elevated urinary phosphate excretion. In that cohort, several NaPi-IIa variants, including small deletions, were detected where all carriers were heterozygous. Kinetic analysis indicated reduced expression levels of some mutants in Xenopus oocytes; however, these variants were also identified in a general population and no significant differences in renal phosphate excretion were observed between carriers and noncarriers of NaPi-IIa variants. Whether these mutants cause hyperphosphatemia when present on two alleles has not been determined and is unknown presently.

The mouse model presented by Iwaki et al.3 in this issue demonstrates now that single point mutations in the murine NaPi-IIa co-transporter can indeed severely affect the renal handling of phosphate. They identified a mouse model carrying two missense mutations in NaPi-IIa and went on to demonstrate one of the mutations abrogated expression of the co-transporter in the OK cell system as well as in vivo. Thus, this mouse model is very reminiscent of a previously published mouse lacking NaPi-IIa completely as a result of
genetic deletion of the corresponding gene. From the mouse model carrying NaPi-IIa mutations, several points can be made: The mutations impair renal phosphate handling only in the homozygous state and abolish completely NaPi-IIa expression in vivo, and this type of mutation apparently interferes with protein stability, possibly leading to early and rapid degradation of the mutant protein. Thus, Iwaki et al. provide proof-of-principle that single mutations in NaPi-IIa possibly cause a syndrome of renal phosphate wasting but only if both alleles are affected.

At this point, the intriguing question that emerges is whether men and mice (or rodents in general) do differ with respect to the relative contribution of NaPi-IIa and NaPi-IIc to renal phosphate reabsorption and systemic phosphate homeostasis. We may face the inconvenient truth that mice and men are different, because genetic studies of patients with NaPi-IIc mutations show a major phenotype comparable to the phenotype observed in mice lacking NaPi-IIa as reported previously by Beck et al. and now by Iwaki et al.; however, all genetic evidence available at this point suggests that NaPi-IIa mutations or variants may exist but bear only minor relevance for the control of renal phosphate excretion and systemic phosphate balance. In syndromes in which regulators of renal phosphate reabsorption are mutated, such as fibroblast growth factor-23, PHEX, or Klotho, it seems these regulators may control both NaPi-IIa and NaPi-IIc expression in kidney.

Thus, final proof for the role of NaPi-IIa in human kidney must come from genetic studies identifying patients with hyperphosphaturia and functionally relevant mutations in NaPi-IIa. Although previous reports suggested gene variants in NaPi-IIa seem to be relatively common, they may represent not more than functionally irrelevant polymorphisms. Conversely, NaPi-IIa may play only a minor role in human kidney, and its defects could be fully compensated by the putative major human isoform NaPi-IIc.

DISCLOSURES

None.

REFERENCES


See related article, “A Missense Mutation in the Sodium Phosphate Co-transporter Slc34a1 Impairs Phosphate Homeostasis,” on pages 1753–1762.