Clinical Consequences of Mutations in Sodium Phosphate Cotransporters

Eleanor Lederer* and Ken-ichi Miyamoto†

Summary

Three families of sodium phosphate cotransporters have been described. Their specific roles in human health and disease have not been defined. Review of the literature reveals that the type II sodium phosphate cotransporters play a significant role in transepithelial transport in a number of tissues including kidney, intestine, salivary gland, mammary gland, and lung. The type I transporters seem to play a major role in renal urate handling and mutations in these proteins have been implicated in susceptibility to gout. The ubiquitously expressed type III transporters play a lesser role in phosphate homeostasis but contribute to cellular phosphate uptake, mineralization, and inflammation. The recognition of species differences in the expression, regulation, and function of these transport proteins suggests an urgent need to find ways to study them in humans.


Introduction

The roles of sodium phosphate cotransporter functions in human clinical physiology and disease processes have not been defined. In addition to maintaining phosphate homeostasis through facilitation of transepithelial transport and ensuring adequacy of intracellular phosphate stores, sodium-dependent phosphate transporters play a role in the transport of a number of other substances and have functions ostensibly unrelated to phosphate transport. Three families of sodium phosphate cotransporters have been identified, each with multiple members (1) (Table 1). They are all intrinsic membrane proteins exhibiting multiple membrane-spanning domains.

The aims of this review are to provide the audience with an updated inventory of identified sodium phosphate cotransporters (Table 2), to compare the human and animal syndromes associated with mutation or loss of each transporter, and to highlight the gaps in our understanding of the roles that these transporters play in human phosphate physiology and pathophysiology (figure 1 and Table 3).

Type I Sodium Phosphate Cotransporters

Npt1

Npt1 (NaPi-1, SLC17A1) was the first sodium phosphate cotransporter isolated in the early 1990s from a rabbit renal cortex library (2), followed shortly afterward by the human and mouse homologs (3–5). Immunohistochemical studies confirmed Npt1 localization to the renal proximal tubule, the site of regulated phosphate transport; however, the relatively low affinity of the transporter for phosphate and the lack of regulation by parathyroid hormone or ambient Pi suggested that phosphate was not the major transport substrate for this protein (6). Subsequent studies confirmed that Npt1 transported a variety of organic and inorganic anions more readily than phosphate (7–9).

Npt2a

Npt2a (NaPi-IIa, SLC34A1 [Napi-2, 3, 4, 5, 6, 7]) (23–27), the first identified member of the family of type II sodium phosphate cotransporters, is expressed predominantly on proximal renal tubule apical membrane and on osteoclast basolateral membrane (23–30). A substantial body of work suggests that it is the major regulated sodium phosphate cotransporter responsible

Npt2c

Npt2c (NaPi-IIc, SLC34A2 [Napi-2, 3, 4, 5, 6, 7]) (23–27), the second identified member of the family of type II sodium phosphate cotransporters, is expressed predominantly on proximal renal tubule apical membrane and on osteoclast basolateral membrane (23–30). A substantial body of work suggests that it is the major regulated sodium phosphate cotransporter responsible

Npt4

Npt4 (SLC17A3), an anion transporter with significant homology to Npt1, also seems to play a role in urate transport in the kidney. Several studies have demonstrated an association between Npt4 single nucleotide polymorphisms and uric acid concentration in the serum and gout (17–20). Npt4 interacts with diuretics such as furosemide and bumetanide, suggesting that it may be responsible for the renal proximal tubule secretion of diuretics (21). Although Npt4 has also been identified in liver cells as a microsomal phosphate transporter (22), Npt4 is not felt to play a significant role in phosphate homeostasis.

Type II Sodium Phosphate Cotransporters

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for proximal tubule phosphate reabsorption (31–36). In rodents, Npt2a is estimated to be responsible for >70% of proximal tubule phosphate reabsorption. Npt2a mRNA is at relatively low abundance at birth in mice but is markedly upregulated to adult levels during the first 2 weeks of life (37). Protein expression follows the mRNA expression peaking at 21 days of life and is dependent on expression of the vitamin D receptor (VDR) (38). Regulation of 1α hydroxylase by phosphate is not dependent on Npt2a expression (39). Provision of a high-phosphate diet to the VDR-null mice restores renal Npt2a expression to wild-type levels, suggesting the presence of a gut–kidney interaction in the neonatal period required for normal Npt2a expression, mediated by phosphate but likely facilitated by the VDR through its ability to enhance intestinal phosphate absorption (38). Studies of Npt2a expression in human tissue mirror the findings in mice, Npt2a expression occurring relatively late in development, peaking in the postnatal period, and then progressively falling with age (40).

Several human disease processes involving abnormal regulation of renal phosphate homeostasis have been described. X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, and oncogenic osteomalacia are characterized by low serum phosphate accompanied by inappropriate phosphaturia and osteomalacia (41). Studies in humans and animal models of these disorders have identified the presence of circulating substances, such as fibroblast growth factor 23 (FGF23), that decrease proximal tubule phosphate reabsorption producing phosphaturia (42–46). Although human renal Npt2a expression has not been examined directly, serum from patients affected with these disorders decreases phosphate transport and Npt2a expression in cultured proximal tubule cell lines, suggesting a similar in vivo phenomenon. Conversely, decreased FGF23/Klotho activity as seen with loss-of-function mutations in FGF23 or GALNT3, the enzyme responsible for O-glycosylation of FGF23, results in hyperphosphatemic tumoral calcinosis, characterized by hyperphosphatemia, decreased renal phosphate excretion, and extraskeletal calcifications (47–49). As for the phosphaturic syndromes, no studies have actually examined the renal expression of Npt2a in human participants with tumoral calcinosis.

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<thead>
<tr>
<th>Table 1. Distribution of sodium phosphate cotransporters</th>
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<td>Type I</td>
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<td>Type III</td>
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<td>PiT1</td>
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<th>Table 2. Functions of sodium phosphate cotransporters</th>
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A potential role for abnormal bone Npt2a expression or function in the clinical manifestations of these human diseases has been suggested but has not been directly tested. Npt2a and Npt2b are co-expressed in mineralization and upregulated before matrix mineralization and in the presence of high phosphate (50). Npt2a null adult mice do not exhibit bone findings consistent with human rickets (32,51,52), and adequate dietary phosphate ameliorates the bone mineralization defect in human hereditary rickets and the Npt2a null mouse. These findings suggest that the bone features of X-linked and autosomal dominant hypophosphatemic rickets result predominantly from defective renal Npt2a function. Mutations in Npt2a itself leading to human disease have rarely been described. Prié et al. (53) identified sequence variants in the Npt2a gene in 2 of 20 patients with hypophosphatemia, nephrolithiasis, and/or osteoporosis. Phosphate uptake in *Xenopus* oocytes expressing the genes of these two patients was decreased, suggesting a role for abnormal Npt2a function in nephrolithiasis and osteoporosis. Comparison of renal phosphate handling in >200 calcium stone formers compared with normal controls showed that the mean tubular maximum for phosphate (TmPi) in the stone formers was significantly less than in those who did not form stones. In contrast, Lapointe et al. (54) were unable to show similar changes in Npt2a-mediated phosphate transport even in cases in which significant sequence variants in the coding region of Npt2a were identified.

Mice deficient in Npt2a exhibit hypercalciuria, nephrocalcinosis, and kidney stone formation (32). The presumed pathogenesis for nephrocalcinosis and nephrolithiasis in the Npt2a null mouse is stimulation of 1,25 vitamin D production by hypophosphatemia, resulting in enhanced intestinal calcium absorption and subsequent hypercalciuria. Mice lacking Npt2a function show a high incidence of intratubular calcium phosphate crystals within the first month of life that diminish with age and interstitial calcium phosphate deposits that do not disappear with aging (55–59). The calcium deposits in the Npt2a-deficient mice are predominantly in the cortex and outer medulla, in contrast to human nephrocalcinosis associated with stone formation that generally occurs in the medulla and papilla.

In 2010, Magen et al. (60,61) described a homozygous Npt2a mutation with loss of function in two offspring of a consanguineous union who exhibited autosomal recessive Fanconi syndrome and hypophosphatemic rickets. *Xenopus* oocytes and opossum kidney cells expressing the mutated Npt2a showed decreased phosphate transport due to faulty trafficking of the transporter to the apical membrane. The affected individuals showed elevated 1,25 vitamin D levels and hypercalciuria during childhood.

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**Figure 1.** Distribution of phosphate transporters and diseases associated with dysregulation/dysfunction. This figure depicts the locations for sodium phosphate cotransporters identified in human organs (transporter underlined). Diseases associated with dysregulation or dysfunction of the transporter are listed under the transporter. Proposed but not identified disease associations are indicated by a question mark (†).
that resolved by adulthood, attributed to the development of nutritional vitamin D deficiency. The authors suggested that accumulation of protein within the cell exerted toxic effects leading to Fanconi syndrome. An alternative explanation is that Npt2a-mediated phosphate transport is critical for maintenance of normal proximal tubule function through provision of adequate intracellular phosphate. The global loss of transport function in these individuals is reminiscent of the demonstration by Brazy et al. (62) of the marked decrease in fluid transport seen in proximal tubules perfused with phosphate-free medium.

Notable differences between human and murine loss of Npt2a function stand out. Nephrocalcinosis and stone formation are seen in Npt2a knockout mice but not the human participants lacking Npt2a function. Fanconi syndrome is seen in the human participants but not the Npt2a null mouse. Skeletal abnormalities are transient in the Npt2a null mouse but severe and persistent in patients with phosphaturic syndromes such as X-linked hypophosphatemic rickets and oncogenic osteomalacia. The reasons for these contrasting phenotypic features are unknown and emphasize the need for direct studies of Npt2a in human participants. It may be that in humans, Npt2a plays a lesser role in renal phosphate transport than in mice. Alternatively, the role of Npt2a in maintenance of bone homeostasis may differ between the two species.

Of perhaps greater interest are newer genome-wide association studies showing an association between Npt2a variants, serum phosphate level, and the development of CKD (63,64). These studies not only reaffirm the importance of Npt2a in human phosphate homeostasis but suggest a more central role for phosphate homeostasis in cardiovascular health because several studies have now correlated serum phosphate level with cardiovascular morbidity and mortality, as reviewed by Kendrick et al. (65). The link between serum phosphate and cardiovascular disease has not been defined but could involve a number of mechanisms including regulation of FGF23, Klotho, or vascular calcification and/or remodeling.

**Npt2b**

Compared with Npt2a, Npt2b (NaPi-IIb, SLC34A2) has a much broader range of organ expression. Initially described by Hilfiker et al. in the mouse small intestine, the protein shows substantial homology (57%–70%) but significant divergence from Npt2a (66). Immunohistochemical studies in mice have identified Npt2b protein in small intestine, lung in type II alveolar cells, salivary duct cells, mammary duct cells, epididymis, and liver cells (67–70). The Npt2b knockout is lethal, with embryonic death at midgestation (71). Conditional and tissue-specific knockouts have confirmed a significant role for Npt2b in intestinal phosphate transport (72). Absence of the protein results in a 50% reduction in intestinal phosphate absorption and a compensatory reduction in renal phosphate excretion accompanied by an increase in renal proximal tubule Npt2a expression. Animal studies have also suggested roles for regulated Npt2b expression in surfactant production, male fertility, biliary phosphate concentration, and odontogenesis.

The mRNA for Npt2b has been identified in small intestine, kidney, lymphoid tissue, lung, placenta, uterus, prostate, testis, liver, pancreas, thyroid, salivary gland, and multiple fetal tissues (73–75). Individuals with homozygous Npt2b loss-of-function mutations develop pulmonary alveolar microlithiasis (76,77), an unusual disorder characterized by the development of respiratory failure accompanied by alveolar calcifications in middle age. Some patients exhibit calcifications in a number of other organs in which Npt2b mRNA has been identified, including kidneys, pleura, seminal vesicles, urethra, and gall bladder. Whether these individuals exhibit diminished intestinal phosphate absorption has not been explicitly studied. Corut et al. (76) stated that investigation of one of their affected individuals showed 92% maximal renal tubular reabsorption but did not define the conditions of this study. All patients had normal serum phosphate. The human manifestation of loss of Npt2b function contrasts sharply with the embryonic lethality of the Npt2b null mouse and suggests divergent embryonic functions for Npt2b in mice and humans.

The ductal cells demonstrate apical Npt2b expression in human salivary glands, whereas the acinar cells exhibit predominantly basolateral expression, suggesting phosphate secretion by the acini and phosphate reabsorption by the ducts (77). These findings have formed the basis for the development of a phosphate binder in chewing gum form. Npt2b is highly expressed in lactating breast tissue and may contribute

Table 3. Comparison of human and murine phenotypes for sodium phosphate cotransporter deficiency

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Knockout Mouse Phenotype</th>
<th>Human Deficiency Phenotype</th>
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<tbody>
<tr>
<td>Type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Npt1</td>
<td>Mild decrease phosphate excretion</td>
<td>Gout</td>
</tr>
<tr>
<td>Npt4</td>
<td>None</td>
<td>Gout</td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Npt2a</td>
<td>Hypophosphatemia, phosphaturia, hypercalciuria, nephrocalcinosis, transient osteomalacia</td>
<td>Osteoporosis, nephrolithiasis, Fanconi syndrome</td>
</tr>
<tr>
<td>Npt2b</td>
<td>Lethal</td>
<td>Pulmonary microlithiasis</td>
</tr>
<tr>
<td>Npt2c</td>
<td>Hypercalciuria</td>
<td>Hereditary hypophosphatemia with hypercalciuria</td>
</tr>
<tr>
<td>Type III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiT1</td>
<td>Lethal</td>
<td>Unknown</td>
</tr>
<tr>
<td>PiT2</td>
<td>Unknown</td>
<td>Familial idiopathic basal ganglia calcification</td>
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</table>

The table lists the knockout mouse phenotypes and human deficiency phenotypes associated with different sodium phosphate cotransporters. The table highlights the importance of these transporters in various organ systems and their roles in disease processes such as osteopetrosis, nephrolithiasis, Fanconi syndrome, and Fanconi syndrome.
to the relatively low phosphate content of human milk compared with cow milk (78). Npt2b is expressed on the surface of several cancers including breast, ovarian, renal, and lung and is being investigated as a potential therapeutic target for ovarian and breast cancer (79,80).

**Npt2c**

Npt2c (NaPi-IIc, SLC34A3) is the most recently described member of the type II sodium phosphate cotransporters, with expression limited exclusively to the apical membrane of the proximal renal tubule (81). Early studies demonstrated age dependent expression in rodents with the highest expression in weanling animals and regulation by dietary phosphate and parathyroid hormone. Mice homozygous for the disrupted Npt2c gene (Npt2c<sup>−/−</sup>) exhibit hypercalcemia, hypercalciuria, and increased plasma 1,25-dihydroxyvitamin D3 levels, but not hypophosphatemia, hyperphosphaturia, renal calcification, rickets, or osteomalacia (82). Sodium phosphate cotransport in renal brush border membrane vesicles is not decreased in Npt2c KO mice. Npt2c seems to have only a minor role in renal Pi reabsorption in rodents. Although Npt2c KO mice do not exhibit hypophosphatemia, plasma levels of FGF23 and FGF25 immunoactivity in the osteocytes of Npt2c KO mice are decreased compared with wild-type mice, suggesting that Npt2c is necessary for regulation of the vitamin D/FGF23 axis.

In contrast to the relatively benign effects of loss of function of Npt2c in mice, recent studies identified a mutation of the Npt2c (NaPi-IIc, SLC34A3) transporter gene as the cause of the human disease, hereditary hypophosphatemic rickets (HHRH). This autosomal recessive disorder is characterized by hypophosphatemia, renal Pi wasting, increased serum 1,25 dihydroxyvitamin D3 concentrations, hypercalciuria, rickets, and osteomalacia (83–88). A genome-wide scan combined with homozygosity mapping using DNA from 10 patients with HHRH (83) identified a single nucleotide deletion (c.228delC) in all individuals in the initial cohort affected with HHRH. A variety of mutations including compound heterozygous deletion and missense mutations in Npt2c have been identified in other families with HHRH. Pi transport studies in a Xenopus oocyte system revealed that NPT2c gene mutations significantly decreased Na<sup>+</sup>-dependent Pi transport activity (88). These observations suggest that NPT2c has an important role in renal Pi reabsorption and bone mineralization, and that it may be a key determinant of plasma Pi concentration in humans. Segawa et al. compared biochemical findings in Npt2a null, Npt2c null, and double null animals to assess the relative importance of Npt2a and Npt2c (89). The animals lacking both transporters exhibited severe hypophosphatemia, hypercalciuria, and rickets, similar to that seen in HHRH. A high Pi diet reversed the bone abnormalities in the double null animals, as in HHRH. This study showed that in mice Npt2a and Npt2c have independent roles in the regulation of plasma Pi and bone mineralization.

As noted for the Npt2a and Npt2b knockout mice, absence of Npt2c produces a different phenotype in mice compared with humans. Whereas Npt2a and Npt2c have clearly non-redundant roles in mouse phosphate homeostasis, the similarity of the double knockout to the clinical presentation of HHRRH suggests that the function of Npt2a and Npt2c may be interdependent in humans. This provocative suggestion has yet to be investigated in human participants.

**Type III Sodium Phosphate Cotransporters**

Type III sodium phosphate cotransporters, PiT1 and PiT2, are highly conserved, high-affinity phosphate transporters with broad organ expression, which were initially described as viral receptors, Glvr-1 and Ram-1 (1,90). The major clue to their potential function as phosphate transporters derived from their similarity to the fungal transporter, Pho-4+. These proteins express little homology to either type I or type II sodium phosphate cotransporters. Despite the redundancy in their amino acid sequences, PiT1 and PiT2 possess non-redundant functions. Very little information on the roles of these proteins in human physiology is available.

**PiT1**

Rodent studies show the strongest PiT1 (Glvr-1, SLC20A1) mRNA expression in bone marrow and brain but wide distribution in multiple organs including kidney, thymus, lung, liver, and heart (91). Deletion of PiT1 expression in mouse results in fetal demise due to failure of liver development (92,93). Although adult liver expresses little PiT1, fetal liver expresses very high levels of PiT1. In adult animals, partial hepatectomy results in a marked increase in PiT1 expression during liver regeneration. Interestingly, PiT2 expression doubled in the PiT1-deficient animals but could not rescue them, emphasizing the nonredundant nature of their respective roles. Studies in mouse distal collecting tubule cells did suggest a role for both PiT1 and PiT2 in distal phosphate reabsorption (94). PiT1 and PiT2 have been identified in human salivary glands (75).

A number of studies demonstrate a role for PiT1 in osteoblast- and chondrocyte-mediated mineralisation (95–97). PiT1 expressed on matrix vesicles derived from the parent cell provides phosphate needed for mineralization. A potential role for PiT1 in the development of medial vascular calcification seen in CKD, diabetes, and aging has been suggested on the basis of multiple animal studies (98–100). Factors that enhance smooth muscle calcification such as prolonged exposure to high calcium, BMP2, and Pdgf increase PiT1 expression. Inhibition of PiT1 expression results in decreased smooth muscle calcification in response to these stimuli. A role for PiT1 in human vascular calcification is supported by the finding that patients with Werner syndrome show enhanced expression of PiT1 at sites of vascular calcification (101).

PiT1 may play a critical role in regulation of apoptosis and cell proliferation, independent of its transport function (102–104). In human cancer cell lines, inhibition of PiT1 expression decreased cell proliferation and tumor formation. Salaun et al. also demonstrated that PiT1 but not PiT2 deficiency sensitized HeLa cells to TNF-induced apoptosis. PiT1 deficient HeLa cell proliferation was rescued by transfection of a transport-deficient PiT1 construct (104).

**PiT2**

Expression of PiT2 (Ram-1, SLC20A2) mRNA in rodents is highest in liver, heart, and brain but is also seen in kidney, thymus, lung, bone, and muscle. A PiT2-deficient mouse has not been described. PiT2 is expressed on the
apical membrane of mouse proximal renal tubule cells and likely is responsible for at least a small percentage of phosphate reabsorption (105,106). Its expression increases in the Npt2a-deficient animal, although it is not able to rescue the phenotype entirely. As with PiT1, the transport and viral receptor functions of PiT2 can be dissociated (107). Interestingly, the oligomeric organization of PiT2 on the cell surface can respond to changes in ambient phosphate, suggesting that PiT2 oligomers may function as phosphate sensors. An association was recently described between PiT2 mutations and familial idiopathic basal ganglia calcification (107).

Summary

An emerging picture of the functions of the sodium phosphate cotransporters offers some opportunities for hypothesis generation with regard to the contributions of each of them to human physiology and pathophysiology. Type I transporters, although upregulated under pathophysiological conditions of severe phosphate deprivation, play a more important role in the metabolism of uric acid and organic ions. The type II transporters on transepithelial transporting tissue clearly are the major contributors to phosphate homeostasis. Type III transporters with their ubiquitous expression, like the type I transporters, may make some contribution to phosphate homeostasis under pathophysiological conditions but seem to play a more important role in non-epithelial cell phosphate transport, the mineralization process, and inflammation. Through intensive investigation in cell and animal models, paradigms of regulation of sodium phosphate cotransporter expression and function with respect to tissue, age, and sex are emerging. However, we are simultaneously discovering that significant species variability exists and application of knowledge from those models to human physiology and pathophysiology may be limited.

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Disclosures

None.

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