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NOVEL MECHANISMS IN THE REGULATION OF PHOSPHORUS HOMEOSTASIS

Theresa Berndt and **Rajiv Kumar**
Nephrology Research, Departments of Medicine, Biochemistry and Molecular Biology, Mayo Clinic and Foundation, 200 First Street Southwest, Rochester, MN 55905

Abstract

Phosphorus plays a critical role in diverse biological processes, and therefore, the regulation of phosphorus balance and homeostasis are critical to the well-being of the organism. Changes in environmental, dietary and serum concentrations of inorganic phosphorus are detected by sensors that elicit changes in cellular function and alter the efficiency by which phosphorus is conserved. Short-term, post-cibal responses which occur independently of hormones previously thought to be important in phosphorus homeostasis may play a larger role than previously appreciated in the regulation of phosphorus homeostasis. Several hormones and regulatory factors such as the vitamin D endocrine system, parathyroid hormone, and the phosphatonins (FGF-23, sFRP-4, MEPE) among others, may play a role only in the long-term regulation of phosphorus homeostasis. In this review we will discuss how organisms sense changes in phosphate concentrations and how changes in hormonal factors result in the conservation or excretion of phosphorus.

Phosphorus is required for diverse biological processes

Phosphorus plays a critical role in cellular biology (5). Many cellular processes require phosphorus in one form or another, and include nucleic acid synthesis and metabolism (37), energy metabolism (42, 46), cellular signaling (38), membrane integrity (53, 58), muscle function (10, 33), enzyme activity (74), lipid metabolism (25) and bone mineralization (30). Phosphorus is present in virtually every bodily fluid. In human plasma or serum, phosphorus exists in the form of inorganic phosphorus or phosphate (P_i), lipid phosphorus and phosphoric ester phosphorus. Total serum phosphorus concentrations range between 89–149 mg/L (2.87–4.81 mmol/L), inorganic phosphorus (phosphate, P_i) concentrations between 25.6–41.6 mg/L (0.83–1.34 mmol/L) (these change with age) (5), phosphoric ester phosphorus concentrations between 25–45 mg/dL (0.81–1.45 mmol/L) and lipid phosphorus concentration between 69–97 mg/L (2.23–3.13 mmol/L) (22). In mammals, bone a contains substantial amount of phosphorus (approximately 10 g per 100-g dry fat-free tissue); in comparison, muscle contains a the 0.2 g per 100-g fat free tissue, and brain 0.33-g per 100-g fresh tissue (22).

Given its widespread distribution and critical role in vital cellular processes it is not surprising that a deficiency of phosphorus results in clinical disease including muscle weakness, rhabdomyolysis, impaired leukocyte function, and abnormal bone mineralization resulting in rickets or osteomalacia (34, 35, 64).

Progress Inquiries to: Dr. Rajiv Kumar, rkumar@mayo.edu; Telephone 507-284-0020; Facsimile 507-538-3954

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Organs involved in phosphorus homeostasis

The intestine and kidney play important roles in the absorption of phosphorus (in the form of P_i) from the diet and in the excretion of phosphorus (in the form of P_i) in the urine, respectively (4, 5). The quantitative aspects of phosphorus homeostasis in humans are shown in Figure 1 (5). In states of neutral phosphorus balance, the amount of phosphorus absorbed in the intestine (about 1–1.5 g/24 hours) is equivalent to the amount excreted in the urine. Various hormones and factors involved in the regulation of phosphorus homeostasis alter the efficiency of P_i absorption in the intestine or the reabsorption of Pi in the proximal tubule of the kidney. P_i absorption in the intestine is increased by $1\alpha,25(OH)_2D_3$, although there is evidence for a $1\alpha,25(OH)_2D_3$-independent increase in P_i transport during P_i deprivation that occurs in the absence of the $1\alpha,25(OH)_2D_3$ receptor (17, 20, 21, 63, 72, 78, 81). In the kidney, P_i is reabsorbed along the proximal convoluted and proximal straight tubule and P_i reabsorption is influenced by numerous factors, most importantly PTH (see Table 1) (4). In addition, the movement of P_i from the extracellular fluid into soft tissue and bone is controlled by numerous factors as well. Serum P_i concentrations can be altered significantly without changes in the absorption of P_i in the intestine or changes in excretion in the kidney.

The regulation of phosphorus homeostasis

In the regulation of a metabolic process, it is important to consider: 1) how environmental signals to which the metabolic process responds are sensed; 2) the nature of the responses that follow both with respect to changes in mediators, and the effects of mediators in different organs; 3) temporal differences between the responses. As we will demonstrate, in the case of P_i, short-term responses that occur shortly (minutes to hours) after the feeding of a high P_i meal may play a larger role than previously appreciated. Furthermore, changes in the concentrations of hormones previously thought to be important in this regard the regulation of P_i homeostasis may only be of relevance during long-term changes (over a period of days) in dietary P_i intake.

Phosphate sensing and cellular responses to changes in phosphate concentrations in the environment

An important question regarding the regulation of phosphorus homeostasis is how the organism or individual senses changes in P_i concentrations in the environment and adjusts metabolic processes to accommodate such changes. Thus, in states of phosphorus deficiency, following a change in the concentrations of P_i, the acquisition and retention of P_i by the organism should be accelerated, whereas, in states of phosphorus excess, P_i acquisition and retention should be reduced. Individual cells or uni-cellular organisms sense changes in extracellular (or in some cases intracellular) P_i concentrations (ΔC) via specific “phosphate sensors” (41, 51, 76). The sensors, in turn, alter intracellular protein metabolism, generally by altering the phosphorylation state of intracellular proteins, and subsequent nuclear transcription events (Figure 2). Proteins synthesized in response to changes in gene transcription increase the efficiency with which phosphorus is retained by the cell, and may be components of the cellular P_i sensor.

a. Phosphate-sensing in cells—Responses to changes in extra cellular phosphate in *Escherichia coli* and *Saccharomyces cerevisiae* are illustrative. For details the reader is referred to two recent reviews, (41, 51). Briefly, in *E. coli* a set of proteins in the peri-plasmic membrane (PstS, PstC, PstA and PstB in association with a protein PhoU) sense low concentrations of P_i in the external environment and enhance the uptake of P_i into the cell (41). Phosphorylation of histidine residues on a protein, PhoR occurs; phosphorylated PhoR, in turn, phosphorylates PhoB on aspartase residues. Phosphorylated PhoB acts as a

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transcription factor by binding to DNA sequences known as “PHO boxes” to increase the transcription of genes in the *Pho* regulon. When P_i concentrations on no longer limiting, PhoR his de-phosphorylated and no longer phosphorylates PhoB; PhoB in its on-phosphorylated state is incapable of binding PHO boxes and activating transcription. Many of the genes in the *Pho* regulon help the organism adapt to changes in phosphorus concentrations. In *Saccharomyces cerevisiae*, when P_i in the environment is limited, the cyclin-dependent kinase (CDK) inhibitor Pho81 inactivates the Pho80-Pho85 complex (51). As a result the transcription factor, Pho4 is un-phosphorylated and active, leading to the induction of *PHO* genes, one of which encodes a protein, Pho84, that functions has a high affinity P_i transporter and scavenges phosphate from the medium. When P_i is no longer limiting, Pho84 is degraded and the transcription factor Pho4 is phosphorylated and exported from the nucleus to the cytoplasm, thereby turning off the expression of the *PHO* genes.

In multicellular organisms, the same sorts of processes that occur in unicellular organisms are likely to occur in cells that are present in the intestine and kidney, although the specific sensors and effector proteins are likely to be different. However, in multi-cellular organisms it is likely that various signaling molecules are also elaborated by the sensing cell that subsequently alter of the efficiency of P_i absorption in other organs in a hormonal or autocrine/paracrine fashion. Markowitz *et al* have shown that renal epithelial cells maintained in culture are capable of responding directly to changes in environmental P_i concentrations by altering the efficiency of P_i uptake (48). The authors grew opossum kidney cells in high or low P_i media and were able to show changes in the efficiency of sodium-dependent P_i absorption within one hour of changing medium P_i concentrations. Given the manner in which the cells were grown, it is unlikely that changes in a hormonal factor were involved in changing the efficiency of sodium-dependent P_i uptake. Several investigators have suggested that intestinal cells may also respond directly to changes in P_i concentrations by altering the efficiency of P_i transport (45, 57, 63). Others have demonstrated that non-epithelial cells such as osteoblasts and marrow stromal cells are capable of responding to changes in medium P_i concentrations by altering BMP-4 expression, Runx2/Cbfa1 localization and alkaline phosphatase secretion (26–28). These results would suggest the presence of a phosphate sensor in mammalian cells. However, the exact biochemical nature of this sensor is not known.

b. Phosphate sensing in animals—Martin and colleagues demonstrated the presence of phosphate signaling in the gastrointestinal tract and the parathyroid gland in rodents (50). Uremic animals were fed a high phosphate diet for 4 weeks, and were then administered a low phosphate diet on the day of the experiment. There was a rapid reduction in serum concentrations of parathyroid hormone within 2 hours without changes in serum calcium. Serum phosphate concentrations decreased. When uremic rats fed a high phosphate diet were gavaged with a high phosphate diet on the day of the experiment, PTH levels increased with only modest changes in serum phosphate during the first 30 minutes of the experiment. Phosphonoformic acid, a phosphorus uptake inhibitor, also rapidly increased PTH concentrations with no significant changes in serum phosphorus. The administration of intravenous phosphate was associated with a rapid increase in PTH with no changes in serum calcium and modest increases in serum phosphorus. These data would suggest the presence of a phosphate sensor in the intestine and in the parathyroid gland as well. The nature of the sensor is not known. Sensors involved in calcium and PTH homeostasis such as the calcium sensing receptor (12) are present in the intestine where they may play a role in sensing concentration of luminal amino acids (16). Whether the Ca sensing receptor or a similar g-protein coupled receptor is involved in sensing phosphate remains unknown. Our laboratory performed experiments in which phosphate was administered into the duodenum of intact or parathyroidectomized rats (6). Changes in the fractional excretion of phosphate were examined 5, 10, 20 and 30 minutes after the infusion of phosphate into the duodenum.

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In the intact rats, we observed a rapid increase in the fractional excretion of phosphate in the kidney without changes in serum phosphate concentrations. Rats infused sodium chloride into the duodenum showed no changes in the fractional excretion of phosphate. In thyro-parathyroidectomized rats, there was a similar increase in the fractional excretion of phosphate following the administration of intra-duodenal phosphate. The latter experiments clearly show that increases in the renal fractional excretion of phosphate following intra-duodenal phosphate infusion are independent of PTH. We also measured serum concentrations of the phosphaturic peptides, PTH, FGF-23, and sFRP-4 in both intact and parathyroidectomized rats following the infusion of intra-duodenal phosphate or intra-duodenal sodium chloride. There were no significant differences between the serum concentrations of these three phosphaturic peptides throughout the experiment. Our data show that there is a sensor for phosphate in the intestine that causes an increase in the fractional excretion of phosphate in the kidney within a short period of time following the exposure of the intestinal mucosa to increased phosphate concentrations. Furthermore, the response that occurs in the kidney is not mediated by any of the known phosphaturic factors that regulate the excretion of phosphorus in the kidney. An important caveat is that concentrations of MEPE and FGF-7 were not measured and it is not known whether concentrations of these phosphaturic substances increased following the instillation of Pi into the intestine. It should also be kept in mind that the amount of Pi instilled in to the intestine was large compared to normal dietary P_i intake. What then is the signal emanating in the intestine that tells the kidney to increase the fractional excretion of phosphate? Renal nerves are not involved in this process since we demonstrated that renal denervation did not alter the phosphaturic response following the intra-duodenal infusion of phosphate. We next prepared homogenates of the duodenum and infused filtered proteins derived from the intestine into rats. We demonstrated the presence of a factor in the duodenal mucosa that was capable of inducing phosphaturia in the intact rats. Taken together the data shows that the intestine senses an increase in luminal phosphate concentrations and releases a substance into the circulation that inhibits renal phosphate reabsorption.

Experiments performed by Segawa and colleagues have shown that the intestine is capable of responding to changes in dietary phosphate independent of vitamin D (63). In vitamin D receptor knockout mice these investigators were able to demonstrate the up-regulation of the sodium-phosphate cotransporter IIB by the low dietary phosphate. This would suggest that intestinal cells have the ability to detect changes in luminal phosphate concentrations and increase the uptake of phosphate via up regulation of the synthesis of the sodium-phosphate cotransporter.

Thus, information reviewed so far would support: 1) the capacity of unicellular organisms to respond to changes in environmental phosphate; 2) the capacity of intestinal cells and renal cells to respond directly to changes in phosphate concentrations in the medium and the capacity of the intestinal cells to respond to changes in dietary phosphate content; 3) the capacity of the intestine and kidney to alter phosphate handling independent of 1, 25-dihydroxyvitamin D, PTH and the phosphatonins.

c. PTH, the vitamin D endocrine system, and the phosphatonins in the regulation of phosphate homeostasis—What is the role of the vitamin D endocrine system, PTH, and the phosphatonins in the regulation of phosphate transport? The role of these factors in regulating phosphate concentrations is shown in Figure 4. The phosphatonins, FGF-23 and sFRP-4 (3, 7, 43, 56, 62, 65–68), decrease, and IGF-1 increases (18) the activity of the 25-hydroxyvitamin D 1α-hydroxylase (“growth factors” in Figure 4). They may, if one accepts the debatable proposition that their levels are modulated by serum phosphate concentrations (see discussion below), also directly modulate renal phosphate reabsorption (13, 44, 52, 54, 71).

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Animals fed a low phosphate diet have decreased serum phosphate concentrations that are associated with a reciprocal increase in circulating plasma calcium concentrations. The increase in plasma calcium concentrations inhibits PTH release, which in turn, reduces the renal excretion of phosphate. Inorganic phosphate may also directly influence PTH release (50). Additionally, a low phosphate diet and reductions in serum P_i are associated with increased $1\alpha,25(OH)_2D_3$ synthesis as a result of stimulation of 25-hydroxyvitamin D 1α-hydroxylase activity (72, 77, 78). It is important to note that the increases in 25-hydroxyvitamin D 1α-hydroxylase activity that occur in animals fed a low phosphate diet, are independent of PTH, as they occur in parathyroidectomized animals. Conversely, when animals are fed a high phosphate diet, serum calcium concentrations decrease and PTH release is increased. Given the importance of phosphate ions in cellular function, a variety of other mechanisms must exist in order to maintain phosphate balance. For example, dietary phosphate deprivation markedly decreases Pi excretion yet this adaptation to decreases in Pi intake is similar in the presence and absence of PTH (73).

The "phosphatonins" induce renal phosphate wasting in patients with tumor-induced osteomalacia (TIO) (14, 23). Such patients typically exhibit low serum phosphate concentrations, normal or slightly low serum calcium concentrations, normal PTH concentrations, low or inappropriately normal serum $1\alpha,25(OH)_2D$ concentrations, renal phosphate wasting and a defect in bone mineralization. Conditioned media from tumors associated with this syndrome produce substances that inhibit sodium-dependent Pi transport in cultured opossum kidney cells. Of note, this phenotype is also observed in patients with autosomal dominant hypophosphatemic rickets (ADHR), X-linked hypophosphatemic rickets (XLH), and autosomal recessive hypophosphatemic rickets (ARHR) and the serum of such patients also contains phosphatonin-like activity (9, 39, 62, 64). Subsequent work by several laboratories has shown that factors such as fibroblast growth factor (FGF-23), secreted frizzled related protein (sFRP-4), fibroblast growth factor (FGF-7) and MEPE are present in these tumors and may contribute to the phosphaturia associated with this syndrome (3, 5, 9, 11, 19, 59, 60, 67). Identification of these phosphatonin molecules has led to the recognition that these proteins are also involved in numerous pathophysiological conditions associated with phosphate wasting and may be important regulators of phosphate homeostasis (Table 2) (64). While there is no question as to the importance of these factors in the pathophysiology of phosphate in the various disorders described, it remains somewhat uncertain as to whether the phosphatonins play a role in normal phosphate homeostasis.

The most extensively studied phosphatonin is FGF-23, a 251 amino acid secreted protein (1, 5, 8, 9). Recombinant FGF-23 administered intraperitoneally to mice or rats, induces phosphaturia and inhibits 25-hydroxyvitamin D 1α-hydroxylase activity (1, 5, 8, 9). The minimal sequence needed for phosphaturic activity resides between amino acids 176 and 210 (8). Transgenic animals over expressing FGF-23 are hypophosphatemic, phosphaturic and show the presence of rickets and reduced serum $1\alpha,25(OH)_2D$ concentrations or 25-hydroxyvitamin D 1α-hydroxylase activity (2, 43, 68). Conversely, mice in which the FGF-23 gene has been ablated demonstrate hyperphosphatemia, reduced phosphate excretion, markedly elevated serum $1\alpha,25(OH)_2D$ concentrations and renal 25-hydroxyvitamin D 1α-hydroxylase mRNA expression, vascular calcification and early mortality (65, 69). The ablation of the vitamin D receptor in FGF-23 null mice has been reported to rescue this phenotype supporting an important role for vitamin D in the pathogenesis of the abnormal phenotype seen in FGF-23 null mice (70). Feeding FGF-23 null mice a low phosphate diet results in decreased serum Pi and a reversal of vascular calcification. When the FGF-23 null mice were fed a vitamin D deficient diet, serum Pi and vascular calcification were improved minimally (75). FGF-23 binds and signals through FGF receptors 1c, 3c, and FGFR4 (40) although this is not been established in mice *in vivo* (47). A co-receptor, klotho, is necessary for FGF-23 to exhibit bioactivity (40, 80). The role

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of klotho in FGF-23 signaling is supported by the observation that klotho knock out mice have a phenotype identical to that of FGF-23 knock out mice (79).

From a physiological perspective, it would be appropriate for FGF-23 concentrations to be regulated by the intake of dietary phosphorus and by serum phosphate concentrations. In humans, in the short-term (over a period of hours) the feeding of meals containing increasing amounts of phosphate does not increase serum FGF-23 concentrations even though the previously administered meal induces a robust and dose-dependent phosphaturia (52). Nishida *et al* have shown that the administration of high phosphate diets to humans increases the fractional excretion of phosphate within an hour of the ingestion of a high phosphate meal (52). In this study, there were modest increases in PTH and no biologically relevant changes in FGF-23 after administration of a high phosphate diet (52). Ito *et al* have also failed to demonstrate an effect of infused P_i on FGF-23 concentrations (31). Likewise, in a study by Larsson *et al* human subjects fed normal, high or low phosphate diets for a period of 72 hours showed no differences in serum FGF-23 concentrations (44). Other studies conducted over a period of days, however, have shown changes in serum FGF-23 concentrations following alterations in the content of phosphate in the diet. For example, Ferrari et al administered a high or a low phosphate diet to humans over several days. Concomitant changes in dietary calcium designed to minimize changes in PTH were also made. Modest decreases or increases of serum FGF-23 within normal range were observed following the intake of a low or high phosphate diet, respectively (24). Others have shown similar changes when dietary phosphate is altered over a period of several weeks (13). In mice, Perwad *et al* have shown that a high phosphate diet increased and a low phosphate diet decreased, serum FGF-23 levels in these animals within 5 days of a changing dietary phosphate intake (55). The changes in serum FGF-23 correlated with changes in serum phosphate concentrations. Studies from our laboratory performed in rats fed a low, normal or high phosphate diet demonstrate that serum FGF-23 levels significantly decrease in animals fed a low phosphate diet, and increase in animals fed a high phosphate diet within 24 hours of altering dietary phosphate intake but do not correlate with serum phosphate in the animals fed a high phosphate diet (71). These data suggest that early and rapid changes in renal phosphate excretion occur following ingestion of a high of phosphate meal and are independent of FGF-23.

FGF-23 synthesis is regulated by $1\alpha,25(OH)_2D$. Increasing doses of $1\alpha,25(OH)_2D$ increase FGF-23 concentrations in the serum within 24 hours but statistically significant changes are observed 4 hours after $1\alpha,25(OH)_2D$ treatment (36, 61). In the physiologic sense, it is possible that FGF-23 is a negative feedback regulator of the 25-hydroxyvitamin D 1α-hydroxylase enzyme.

The Wnt antagonist, secreted frizzled related protein-4 (sFRP-4) is highly expressed in tumors associated with renal phosphate wasting and osteomalacia (19). Recombinant sFRP-4 is phosphaturic in rats and prevents the up-regulation of the 25-hydroxyvitamin D 1α-hydroxylase enzyme seen in the presence of hypophosphatemia (3). sFRP-4 decreases Na^+-P_i co-transporter abundance in the brush border membrane of the proximal tubule, and reduces the surface expression of the Na^+-P_i IIa co-transporter in proximal tubules of the kidney, as well as, on the surface opossum kidney cells (7). sFRP-4 expression is increased in bone samples and serum from X-linked hypophosphatemic mice, in mice with a global knockout of the *phex* gene but not in mice in which the *phex* gene has been knocked out in bone alone (82). sFRP-4 protein concentrations are increased in the kidneys of rats fed a high phosphate diet for two weeks but not in animals fed a low phosphate diet suggesting a possible role for sFRP-4 during increases in phosphate intake (71). This suggests that sFRP-4 concentrations are altered in the kidney of animals fed high phosphate diet and could play a role in the long-term adaptations to high phosphate intake.

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Matrix extracellular phosphoglycoprotein (MEPE) is abundantly over-expressed found in tumors associated with renal phosphate wasting and osteomalacia (59). Recombinant MEPE is phosphaturic and reduces serum phosphate concentrations when administered to mice *in vivo* (60). The protein inhibits sodium-dependent phosphate uptake in opossum kidney cells. The protein has also been demonstrated to reduce intestinal Pi absorption directly (49). MEPE also inhibits bone mineralization in vitro, and MEPE null mice have increased bone mineralization (29). Thus, it is possible that MEPE is important in the pathogenesis of hypophosphatemia in renal phosphate wasting observed in patients with TIO. However, MEPE infusion does not recapitulate the defect in vitamin D metabolism seen in patients with TIO (60). Infusion of MEPE reduces serum phosphate concentrations, and serum 1α, $25(OH)_2D$ concentrations increase following MEPE as would be expected in the face of hypophosphatemia. Thus, in patients with TIO, it is likely that MEPE contributes to the hypophosphatemia, but other products such as FGF-23 and sFRP-4 inhibit $1\alpha,25(OH)_2D$ concentrations by inhibiting the activity of the 25-hydroxyvitamin D 1α-hydroxylase. MEPE may play a role in the pathogenesis of X-linked hypophosphatemic rickets, in which there is phosphate wasting, and evidence for a mineralization defect that is independent of low phosphate concentrations in the extracellular fluid (82). MEPE expression is increased in mice with the Hyp mutation, and mice with a global knockout of the *phex* gene but not in mice with a bone specific knockout of the *phex* gene. It is not known whether MEPE is regulated by phosphate concentrations although Jain *et al* have demonstrated that it is correlated with serum Pi concentration in normal humans (32).

Another growth factor, FGF-7, also known as keratinocyte growth factor, is overexpressed in tumors associated with phosphate wasting and osteomalacia (15). FGF-7 inhibits sodium-dependent phosphate transport in OK cells, and we have demonstrated that FGF-7 inhibits renal phosphate reabsorption in vivo. FGF-7 is present in normal plasma and is significantly increased in patients with renal failure (personal observations). Whether or not FGF-7 is regulated by phosphate concentrations is unknown.

Conclusions

The regulation of phosphate transport in vivo should be thought of in terms of rapid, short-term adaptive processes that occur within a timeframe of a few hours after the administration of a meal containing large amounts of phosphate. These processes involve phosphate sensing in the intestine and the elaboration of novel factors that alter the efficiency of phosphate transport in the kidney and possibly directly in the intestine itself. The more long-term adaptations to changes in phosphate transport are likely to be mediated by the vitamin D endocrine system and PTH. The role of the phosphatonins in normal human physiology remains to be established, although there is no question as to their importance in the pathophysiology of diseases associated with alterations in serum phosphate homeostasis.

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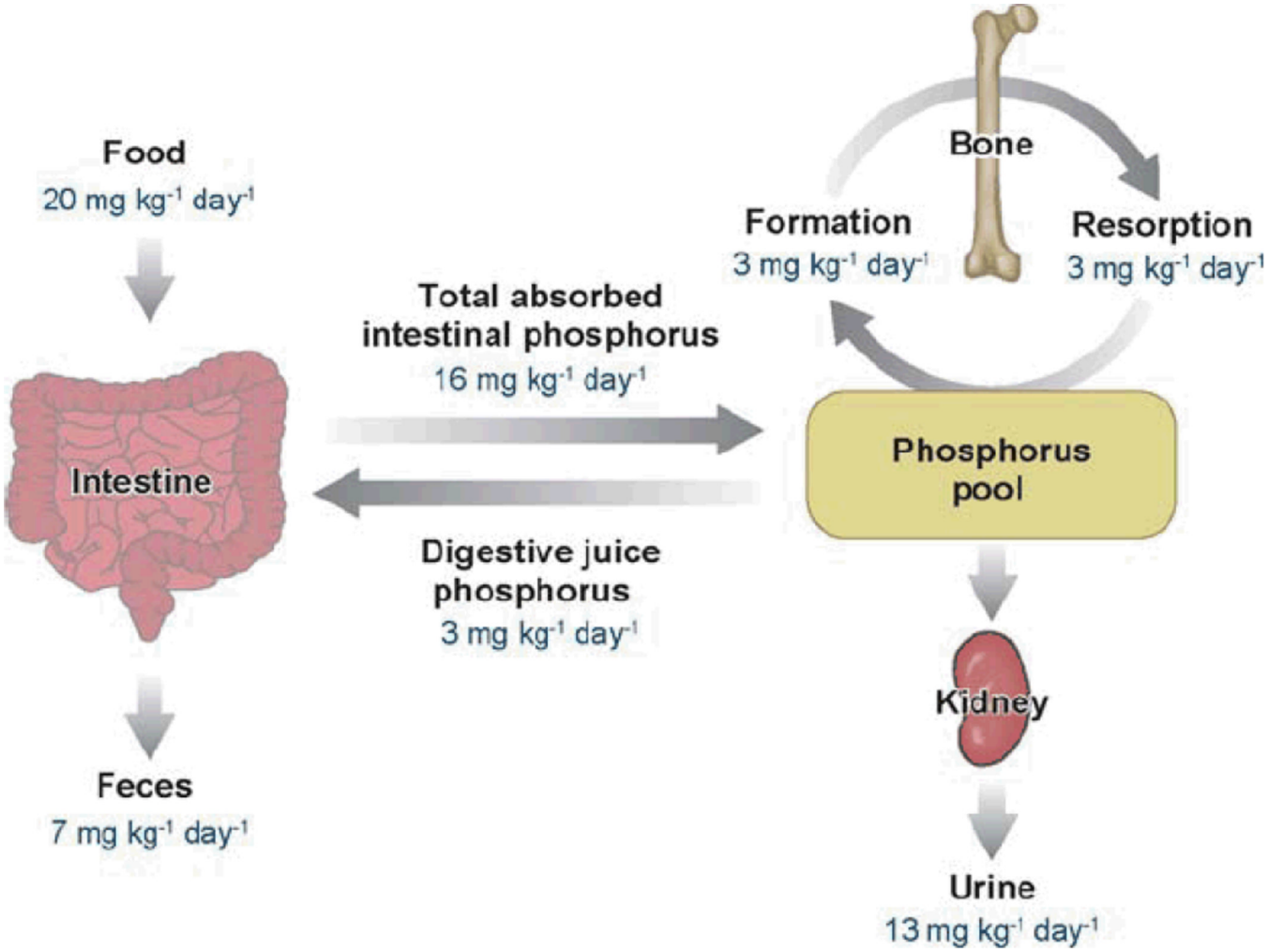

Figure 1.
Phosphorus homeostasis in normal humans (5).

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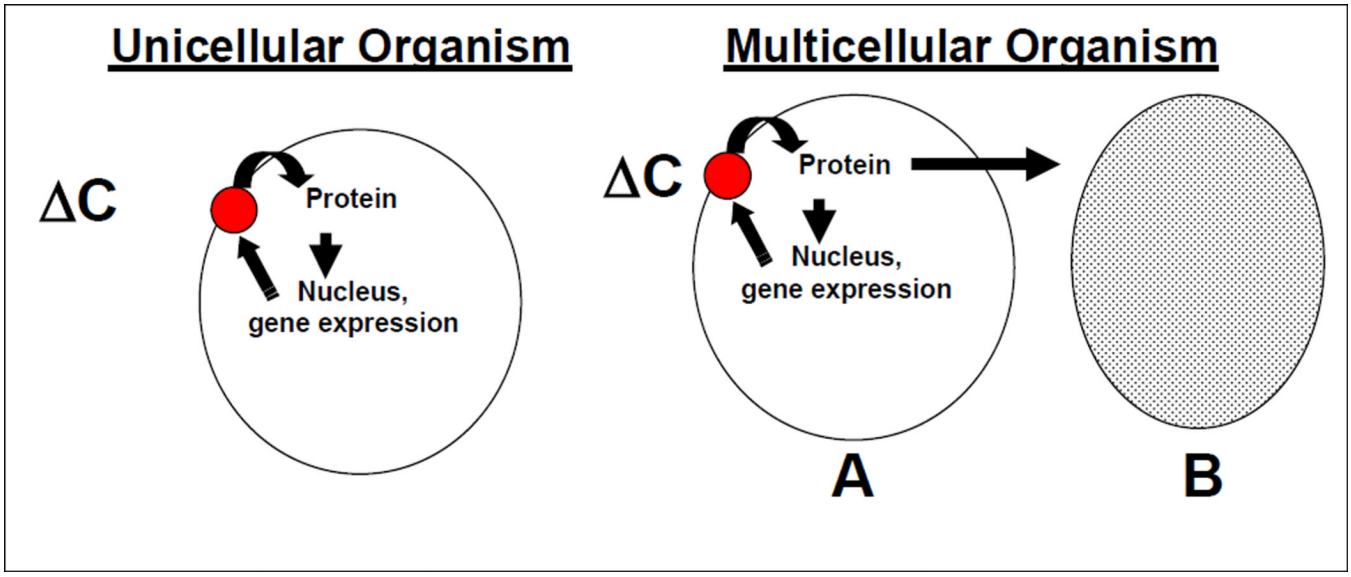

Figure 2.
Mechanisms by which cells and organisms respond to alterations in the extracellular phosphorus concentrations. See text for details.

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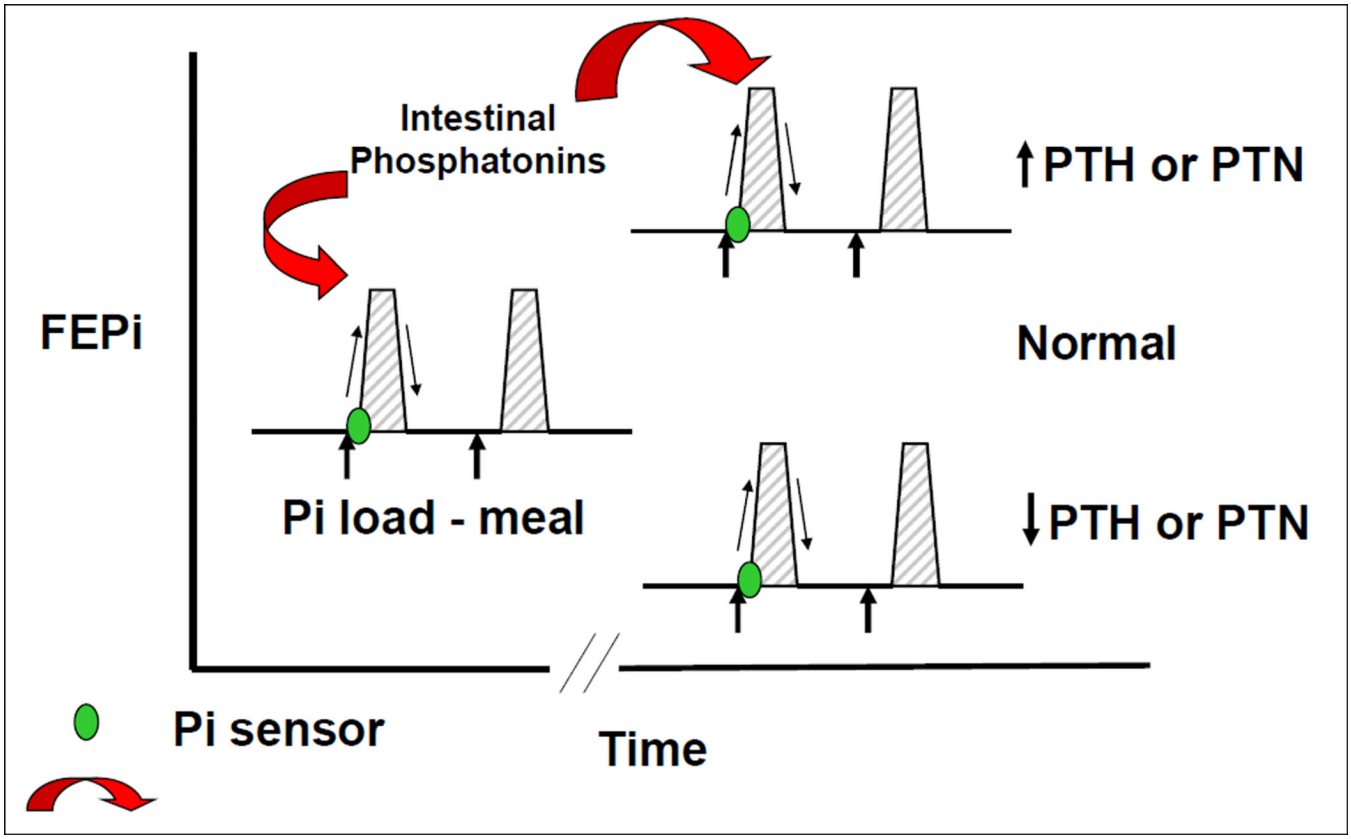

Figure 3.
Intestinal phosphate sensing increases the fractional excretion of phosphorus in the kidney following increases in intestinal luminal phosphate concentrations by the release of an intestinal mediator ("intestinal phosphatonin").

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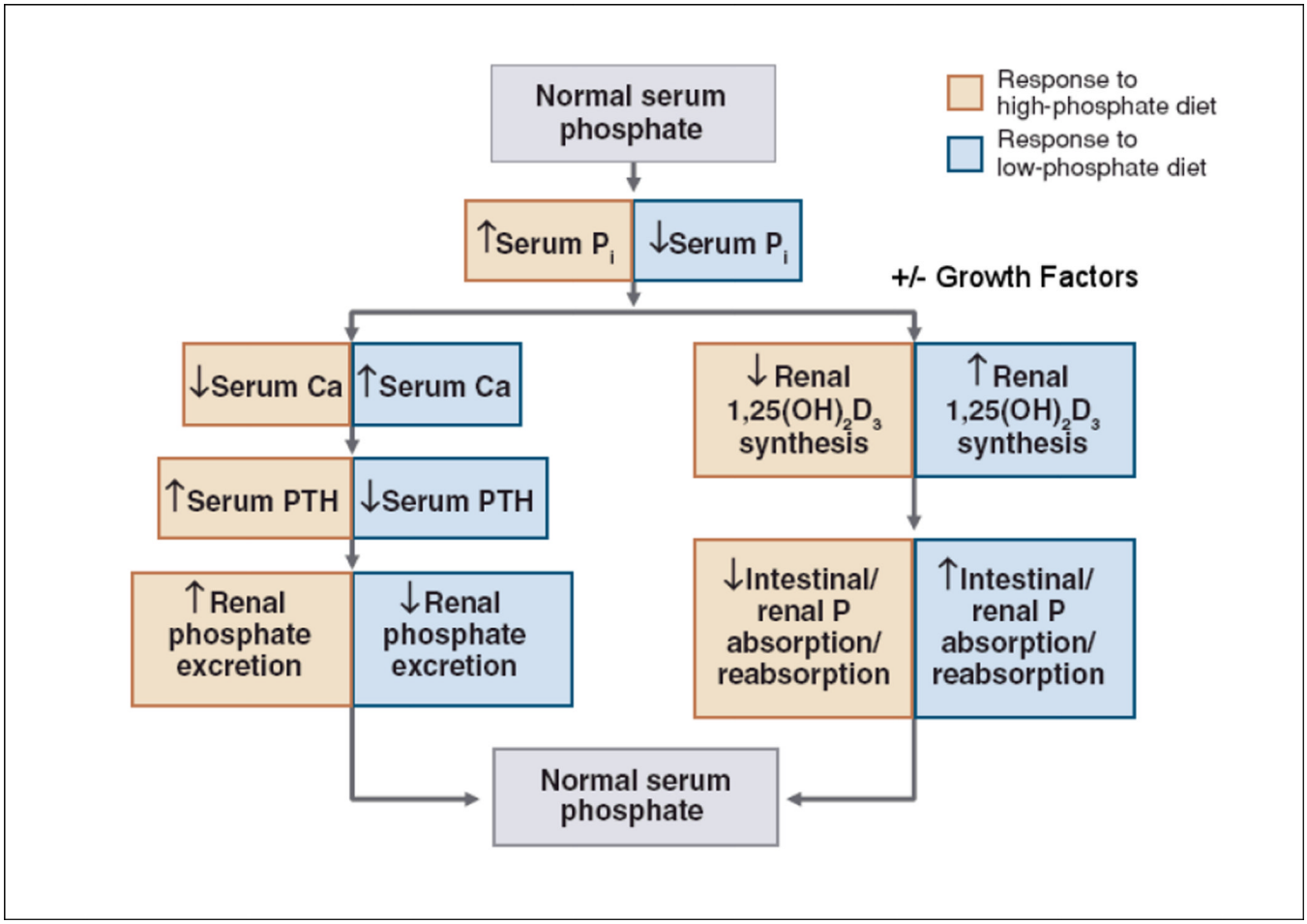

Figure 4.
Adaptations to changes in dietary phosphate (5).

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TABLE I

Factors Influencing Phosphate Absorption or Reabsorption in The Intestine And Kidney

Intestine	
Factors that increase Pi absorption	
•**1**	Reduced dietary intake of phosphate
•**2**	Elevated serum 1α,25-dihydroxyvitamin D
Factors that reduce Pi absorption	
•**3**	Reduced serum 1α,25-dihydroxyvitamin D
•**4**	Elevated concentrations of calcium salts in intestinal lumen
•**5**	MEPE

Kidney			
Factors that increase Pi reabsorption			
•**1**	Phosphate depletion	•**4**	Volume contraction
•**2**	Parathyroidectomy	•**5**	Hypocalcemia
•**3**	$1\alpha,25(OH)_2D$	•**6**	Hypocapnia
Factors that decrease Pi reabsorption			
•**1**	Phosphate Loading	•**7**	Glucose and alanine
•**1**	Parathyroid hormone and cyclic AMP	•**8**	Acid-base disturbances
•**3**	Volume expansion		Increased bicarbonate
•**4**	Hypercalcemia		Hypercapnia
•**5**	Carbonic anhydrase inhibitors	•**1**	Metabolic inhibitors
•**6**	Dopamine		Arsenate
		•**2**	FGF-23
		•**3**	sFRP-4
		•**4**	MEPE
		•**5**	FGF7

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TABLE 2

The pathophysiology of disorders of phosphate homeostasis associated with altered phosphatonin production/ circulating concentrations (64).

Clinical Disorder	Clinical phenotype	Pathophysiology
Hypophosphatemic Disorders		
Tumor-induced osteomalacia (TIO)	Hypophosphatemia, hyperphosphaturia, reduced 1α, $25(OH)_2D$ concentrations or inappropriately normal 1α, $25(OH)_2D$ concentrations for the level of serum phosphate, osteomalacia or mineralization defect	Excess of production of phosphatonins -- FGF-23, sFRP- 4, MEPE, FGF-7.
X-linked hypophosphatemic rickets (XLH)	As in TIO	Mutations in the endopeptidase PHEX that result in increased concentrations of FGF-23, sFRP-4 and MEPE.
Autosomal dominant hypophosphatemic rickets (ADHR)	As in TIO	Mutations in the FGF-23 gene that results in the formation of a mutant form of FGF-23 that is resistant to proteolysis.
Autosomal recessive hypophosphatemia (AR HP)	As in TIO	Mutations in the gene for DMP-1; associated with elevated concentrations of FGF-23.
Hyperphosphatemic Disorders		
Tumoral calcinosis	Hyperphosphatemia, hypophosphaturia, elevated or normal 1α, $25(OH)_2D$ concentrations, ectopic calcification	Mutations in the genes for GALNT3, FGF-23, and Klotho. Some patients with GALNT3 and FGF-23 mutations have diminished concentrations of intact FGF-23. The one patient with a Klotho mutation had very high FGF-23 concentrations.
Renal failure	Hyperphosphatemia, hypophosphaturia, reduced 1α, $25(OH)_2D$ concentrations.	Elevated FGF-23 and FGF-7 concentrations