The phosphatoninins and the regulation of phosphate homeostasis

R. Kumar

Division of Nephrology and Hypertension, Departments of Medicine and Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN 559805, USA.

Reprint request: R. Kumar, address above.

THE BIOLOGICAL ROLE OF PHOSPHORUS AND THE CONSEQUENCES OF ALTERED PHOSPHATE HOMEOSTASIS

Understanding the regulation of Pi homeostasis is important because of the biological role of Pi in a variety of cellular processes including the formation of hydroxyapatite in bone, cellular signaling, growth and nucleic acid synthesis, as well as, membrane stability and function [1-5]. Hypophosphatemia is often associated with significant clinical defects including rhabdomyolysis, hemolysis, defective platelet and neutrophil function, and most importantly, impaired bone mineralization resulting in rickets and osteomalacia [6-10]. Conversely, hyperphosphatemia, as occurs in patients with chronic renal failure and end-stage renal disease, is often associated with secondary hyperparathyroidism and renal osteodystrophy [3, 11-14].

THE REGULATION OF PI HOMEOSTASIS

Much information is available concerning the regulation of Pi homeostasis. The major organs responsible for the regulation of Pi metabolism include the intestine, the kidney, and bone. Figure 1 summarizes the movement in Pi across these various organs in normal humans [5, 15]. Many factors control the absorption of phosphorus in the intestine and the excretion of Pi in the kidney [16]. The regulation of Pi absorption in the intestine is modulated by dietary phosphate intake acting mostly, although not entirely, through changes in 1,25(OH)2D. Figure 2 summarizes some of the factors that are important in the reabsorption of Pi in the kidney which occurs predominantly, if not exclusively, in the proximal tubule. Additionally, many of the same factors such as PTH and 1,25(OH)2D, regulate the movement of phosphorus in and out of bone. It is important to bear in mind that changes in the excretion of Pi by the kidney can occur very rapidly independent changes in hormones and sterols/steroids that are known to alter Pi reabsorp-

Figure 1: Phosphorus metabolism in Humans.

Figure 1 : Métabolisme du phosphore chez l'homme.

Figure 2: Factors affecting phosphate reabsorption in the proximal tubule.

Figure 2 : Facteurs ayant une influence sur la réabsorption au niveau du tubule proximal.
is increasing evidence that FGF 23 and sFRP-4 may play a role in this regard [5, 8, 10, 19]. Space does not permit an exhaustive review of mechanisms by which phosphate transport is regulated at the level of the intestine and the kidney. *Figures 3 and 4*, however, summarize some of the salient features of phosphate regulation by the vitamin D-endocrine system and PTH. Additionally, a wealth of evidence suggests that Na-Pi co-transporters are critical in the intestinal absorption and renal reabsorption of phosphate where they are regulated by vitamin D and PTH [20-29]. A recent review from our laboratory deals with phosphate regulation in greater detail [5].

**THE PHOSPHATONINS AND THE REGULATION OF PHOSPHATE TRANSPORT**

“Phosphatonin” was identified by our laboratory as a factor (or factors) responsible for renal phosphate wasting, hypophosphatemia and osteomalacia in a patient with a syndrome of tumor-induced osteomalacia (TIO) [30, 31]. Tumors associated with the syndrome elaborate circulating factors that induce phosphaturia by mechanisms that are independent of PTH and cyclic AMP. In addition, these factors prevent compensatory increases in 1, 25-dihydroxyvitamin D concentrations that normally occur in hypophosphatemic states. A number of factors appear to be responsible for, or at least associated with, the syndrome of TIO [32-37]. These include: FGF 23, sFRP-4, MEPE and most recently FGF 7. The administration of FGF 23 or sFRP-4 causes an inhibition of Na+-dependent Pi transport in models of proximal tubular cells (opossum kidney cells) and hypophosphatemia and hyperphosphaturia in rats and mice [15, 33, 36, 38-40]. In addition, compensatory changes in renal 25(OH)D1α(OH)ase activity, and resultant increases in serum 1,25(OH)2D concentrations, fail to occur following the administration of FGF 23 or sFRP-4 [36, 40]. Results from experiments performed in FGF 23 null mutant mice and FGF 23 transgenic mice have given results that are consistent with its role as a hypophosphatemic agent [38]. In addition, it is to be noted that both FGF 23 and sFRP-4 also are capable of inhibiting bone mineralization — a prominent feature in patients with TIO [5, 38]. In the case of MEPE, however, hypophosphatemia induced by the protein is associated with increases in serum 1,25(OH)2D concentrations [35]. MEPE null mutant mice, while not hypophosphatemic, do have increases in bone mineral content and trabecular thickness consistent with all role of MEPE in bone mineralization [41]. Much this information is available concerning the bioactivity of FGF 7 which has been shown to inhibit phosphate transport in cultured renal epithelia [37]. No information is available concerning the bioactivity of FGF 7 in vivo and its effects on 25(OH)D1α(OH)ase activity and 1, 25-dihydroxyvitamin D concentrations are unknown.

Several other diseases such as X-linked hypophosphatemic rickets (XLH) and autosomal dominant hypophosphatemic rickets (ADHR) have phenotypes that are identical to that seen in patients with TIO [42-45]. Several lines of evidence have shown that humans and animal models of X-linked hypophosphatemic rickets also express a phosphatonin-like factor [46, 47]. It came as a surprise, therefore, that the gene mutated in XLH encoded an endopeptidase known as PHEX [48]. It is currently believed that individuals and mice with XLH have increased circulating concentrations of FGF 23 that fails to get processed by PHEX. The ADHR Consortium has identified activating mutations of FGF 23 as the cause of the syndrome [49]. The mutant FGF-23 has a long half-life as a result of resistance to cleavage by the protease, furin. These concepts are summarized in *figure 5*. Other
diseases such as renal failure, and the post-transplant state, have circulating serum phosphatonin-like activity that is likely attributable to increases in FGF 23 [50].

**CLINICAL CONDITIONS ASSOCIATED HYPOPHOSPHATEMIA AND ALTERED PHOSPHATONIN CONCENTRATIONS**

Although a number of phosphatonins have been isolated from patients with tumor-induced osteomalacia, clinical assays are available, and have been widely applied, only in the case of FGF-23. A number of clinical conditions associated with hypophosphatemia have now been shown to be associated with elevated concentrations of FGF-23. Some, but not all patients, with tumor-induced osteomalacia have elevated FGF-23 serum concentrations [51-53]. Following removal of the tumor, FGF-23 concentrations generally return to normal. Some patients with X-linked hypophosphatemic rickets also have elevated concentrations of FGF-23 [54-56]. Elevated FGF-23 concentrations are seen in patients with humoral hypercalcemia of malignancy, in patients with chronic renal failure, and in patients with fibrous dysplasia [15, 57-60]. Patients with primary hyperparathyroidism have marginally elevated FGF-23 concentrations that are not substantially altered following parathyroidectomy [57, 61-63]. Interestingly, patients with stage III and IV ovarian cancer, and no alterations in serum phosphate concentrations, also have elevated FGF-23 concentrations [64]. Conditions associated with hyperphosphatemia are also associated with increases in FGF-23. These conditions include chronic renal failure, tumoral calcinosis, hypoparathyroidism and hyperthyroidism [65-69]. In these latter conditions, it is thought that FGF-23 concentrations are elevated in order to reduce the persistent hyperphosphatemia.

**REGULATION OF THE PHOSPHATONINS BY DIETARY PHOSPHATE AND VITAMIN D**

In humans, short-term alterations in dietary phosphate intake do not appear to influence concentrations of FGF-23. Larsson et al. fed human subjects normal, high or low phosphate diets for a period of 72 hours. FGF-23 concentrations did not change substantially in this study, suggesting that dietary phosphate did not regulate FGF-23 concentrations [70]. Others have shown that high or low phosphate diets given to humans with concomitant changes in dietary calcium designed to minimize changes in PTH are associated with modest increases or decreases in FGF-23 that are within the normal range [71]. In neither of these studies were short-term changes in urinary phosphate excretion studied to determine whether temporal changes in the renal excretion of phosphate directly correlated with temporal changes in FGF-23. Thus, in humans, it appears that dietary variation in phosphate intake has no effect, or at most an extremely modest effect, on phosphate excretion in the kidney. In neither of these studies was an effect of dietary phosphate on 1α,25(OH)2D3 studied, nor was the effect of 1α,25(OH)2D3 on FGF-23 examined. In rodents, however, high or low of dietary phosphate intake is associated with significant increments or decrements in FGF-23. With respect to the regulation of FGF-23 by 1α,25(OH)2D3, Saito et al. have shown that serum FGF-23 increases following the administration of 1α,25(OH)2D3 to intact rats in a dose-dependent manner [72]. In the short-term, the changes in FGF-23 following 1α,25(OH)2D3 administration are independent of changes in serum phosphorus, whereas, a modest increases in serum FGF-23 and serum phosphorus are seen following the longer-term administration of 1α,25(OH)2D3.

The identification of several phosphatonins has opened an exciting new area with respect to the regulation of phosphate transport and new information in the homeostatic control of this important ion should be forthcoming.

**REFERENCES**

The phosphatonin and the regulation of phosphate homeostasis


34. Rowe PS, de Zoya PA, Dong R et al. MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. Genomics 2000 ; 67 : 54-68.


