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## Translational Nephrology



# What goes in must come out—the small intestine modulates renal phosphate excretion\*

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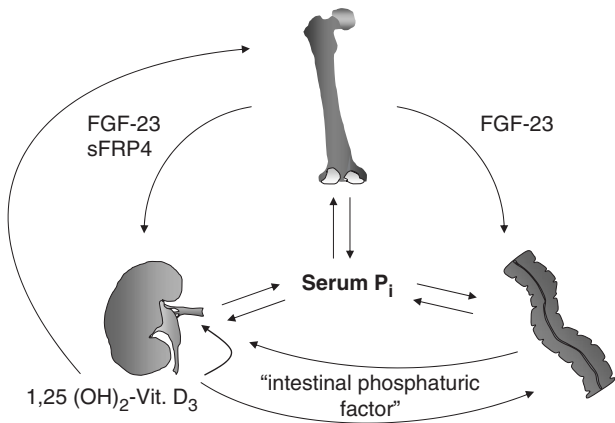
In a recent article in *PNAS*, Berndt *et al.* describe a novel and rapid regulation of renal phosphate excretion by phosphate instilled into the small intestine [1]. In a series of elegant experiments, renal phosphate clearance was measured before and during the infusion of a small amount of phosphate into the distal duodenum of rats. Twenty minutes after the infusion, massive phosphaturia was observed. This effect was specific for phosphate and was not seen when phosphate was instilled into the stomach or when NaCl was applied. Phosphaturia occurred without a measurable increase in serum phosphate and was independent of parathyroid hormone as it could also be observed in parathyroidectomized rats. Furthermore, other phosphaturic hormones, such as FGF23 and sFRP4, appear not to be involved. Alternatively, phosphaturia was preserved after denervation of the kidneys. Interestingly, infusion of a protein extract prepared from duodenum mucosa also induced phosphaturia similar to the intestinal phosphate infusion. Taken together, Berndt *et al.* suggest that upon phosphate ingestion, a phosphate-sensing mechanism in the duodenum releases a humoral signal which rapidly reduces renal phosphate reabsorption and thereby prevents an increase in the phosphate  $\times$  calcium product, which otherwise would trigger precipitations, calcifications and secondary hyperparathyroidism.

Systemic phosphate homeostasis is the product of regulated intestinal phosphate absorption from diet, deposition in skeleton, release from bone and soft tissue and tightly controlled renal reabsorption.

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Transport of phosphate in intestine, bone and kidney is mediated by several members of the type II sodium-dependent phosphate transporter family, SLC34, including the two renal isoforms NaPi-IIa and NaPi-IIc, and the intestinal NaPi-IIb transporter [2,3]. The importance of these transporters in phosphate balance has been highlighted by genetic knock-out of NaPi-IIa in a mouse model [4] and more importantly, in patients with hereditary hypophosphataemic rickets with hypercalciuria caused by mutations in the NaPi-IIc (SLC34A3) transporter [5,6]. Serum phosphate concentration has to be maintained in a narrow range. Hypophosphataemia can cause skeletal deformities or osteomalacia, muscle weakness or glucose intolerance [7], whereas when phosphate rises, it will exceed the solubility limit of the calcium  $\times$  phosphate product and precipitate. Consequences are tissue calcifications, arteriosclerosis or secondary hyperparathyroidism, as often seen in the setting of ESRD [8]. Under physiological conditions, phosphate balance is therefore tightly regulated by a number of hormones such as parathyroid hormone, 1,25 (OH)<sub>2</sub> vitamin D<sub>3</sub>, or the growing number of so-called phosphatonins (including FGF-23, sFRP4 or FGF-7) [3,9,10]. These factors have in common that they regulate expression of renal and intestinal phosphate transporters and thereby determine absorption and excretion [3,9]. Additionally, it has long been known that dietary phosphate intake influences intestinal absorption and renal excretion through only poorly understood mechanisms. Chronic changes in dietary phosphate intake may involve at least in part 1,25(OH)<sub>2</sub>-dependent changes in transporter expression [11]. Acute adaptation of renal reabsorption within hours leads to down-regulation of the renal NaPi-IIa transporter [12], an effect that can be mimicked in the renal OK cell line *in vitro* by adding phosphate to the medium [13]. These data strongly suggest the existence of a phosphate-sensing mechanism. The data by Berndt *et al.* point to an intestinal mechanism that would sense at the forefront of phosphate ingestion a potential phosphate load and acutely adapt renal excretion. This seems to make sense



**Fig. 1.** Serum phosphate levels are determined by the rate of intestinal phosphate absorption, renal reabsorption and its deposition in bone or storage in soft tissue, respectively. Extensive cross-talk exists between bone and kidney via phosphaturic factors, such as FGF-23 or FRP4, and influences renal and intestinal expression of phosphate transporters. In addition, 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub> modulates renal and intestinal phosphate transport and provides a feed-back loop to bone release of FGF-23. Parathyroid hormone directly inhibits renal phosphate reabsorption and stimulates renal synthesis of 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub>. The novel intestinal-renal axis may provide a means of balancing intestinal phosphate intake and renal excretion.

on the background that expression and activity of intestinal phosphate uptake transporters is only adapted slowly, reflecting long-term changes in dietary intake or hormonal status [14]. In contrast, the kidney can adapt rapidly to metabolic or hormonal alterations leading to acute internalization and degradation of NaPi-IIa cotransporters within 10–15 min [3,15]. Thus the body has two complementary mechanisms that adapt to acute or chronic changes in dietary phosphate intake and thereby maintains phosphate perfectly within a safe range required by metabolism.

Deranged phosphate handling is a severe problem in patients with ESRD requiring dialysis. Reduced renal phosphate clearance causes phosphate retention with the precipitation of calcium-phosphate deposits in tissue and arteries, a major life-limiting complication in these patients. Moreover, intestinal phosphate absorption is inadequately high in these patients, and a rat model of chronic renal failure showed recently that expression of intestinal NaPi-IIb transporters is inappropriately normal [16]. Our understanding of how systemic phosphate homeostasis is regulated is at the very early stages. The recent discoveries of phosphaturic hormones and co-factors, such as FGF-23 and klotho, have added new complexity to the system [9,10,17]. However, if we aim to understand mechanisms that regulate systemic phosphate balance, we may ultimately also be able to devise strategies for the treatment of hyperphosphataemia in ESRD patients. The discovery of an intestinal phosphate-sensing mechanism and the cross-talk with renal phosphate handling led to a number of interesting questions as to

the nature of this putative ‘phosphate-sensor’ and its signal transduction to the kidney, the mechanism of inducing phosphaturia, and its potential role as a therapeutic target.

*Conflict of interest statement.* None declared.

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