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Phosphate Sensing

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Abstract

Purpose of review—To discuss findings suggesting the presence of a phosphate sensing mechanism in the various organs and the presence of a novel intestinal effector that alters renal phosphate excretion after the ingestion of a phosphate-containing meal.

Recent findings—Although phosphate homeostasis is controlled by a variety of hormones (such as parathyroid hormone and 1, 25 dihydroxyvitamin D), peptides (the phosphatonins -- FGF-23, sFRP-4, MEPE) and small molecules (dopamine) which regulate the efficiency of phosphate absorption in the intestine and phosphate excretion in the renal tubule, recent data suggest that post-cibal changes in renal phosphate excretion following a meal containing phosphate, are mediated by signals generated within the intestine that alter the efficiency of phosphate excretion in the kidney. The intestine detects luminal phosphate and signal to the kidney via the release of the mediator that increases renal phosphate excretion.

Summary—Such information would imply the existence of a phosphate sensing mechanism within the intestine and the presence of intestinal factors that influence renal phosphate handling.

Keywords

Vitamin D; PTH; phosphatonins; phosphate sensors

Introduction

Phosphate is important in several biological processes ranging from energy homeostasis, cell signaling, membrane integrity to bone mineralization [1]. A variety of mechanisms have evolved to increase the efficiency of phosphate retention in states of phosphate deficiency, and conversely, to decrease retention in states of phosphate excess. Clearly, a necessary first step in the regulation of phosphate homeostasis is the ability of a cell or organism to sense changes in phosphate concentrations in its environment. This would imply the existence of a sensor within or on the surface of cells that is able to detect changes in the concentration of phosphate. In this review I will present information that is consistent with evidence for such a phosphate sensing mechanism in mammals and humans. I will also review information about mechanisms by which prokaryotic and eukaryotic unicellular organisms respond to phosphate.

Rapid and long-term adaptations to changes in dietary phosphate; factors/ hormones that regulate phosphate homeostasis in mammals

The intestine and kidney are important in the absorption, reabsorption and excretion of phosphate [1]. The vitamin D endocrine system, particularly 1α, 25-dihydroxyvitamin D, increases the efficiency of phosphate absorption in the intestine [2–4]. Parathyroid hormone

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(PTH), and the phosphatonins (fibroblast growth factor 23 (FGF-23), secreted frizzled related protein-4 (sFRP-4), matrix extracellular phosphoglycoprotein (MEPE), FGF-7), as well as a variety of other factors such as dopamine, renal nerve activity, and acid base status, influence the excretion of phosphate in the renal tubule [1]. The reviewer is referred to recent publications by our laboratory concerning the interactions amongst these various factors and their role in controlling intestinal phosphate absorption or renal phosphate excretion [1,5–7].

It is important to conceptualize the regulation of phosphate transport in terms of rapid, short-term changes that occur within a short period after the ingestion of a phosphate-containing meal and those that occur over the long-term in association with chronic changes in the dietary intake of phosphate. It is very likely that the short-term changes are mediated by processes that are distinct from those required for more long-term adaptations to changes in dietary phosphate. Immediately following a meal containing phosphate, rapid alterations in the renal excretion of phosphate occur that are not associated with substantial changes in the vitamin D endocrine system, parathyroid hormone, or the phosphatonins [8]. Also, the feeding of humans and experimental animals diets containing large amounts of phosphate over a period of weeks is associated with modest changes in the vitamin D endocrine system, parathyroid hormone and the phosphatonins [7,9]. Adaptations to a low phosphate diet can occur in the absence of the vitamin D receptor. Segawa and colleagues have demonstrated that increases in the expression of the sodium-phosphate cotransporter IIB, which plays a role in the intestinal phosphate transport, occur when vitamin D receptor knockout mice are fed a low phosphate diet [10]. This would imply that the intestine is capable of responding to low dietary phosphate levels by up-regulating phosphate transport independent of 1, 25 dihydroxyvitamin D. The intestine has been recently shown to contain a factor or factors that alter the renal excretion of phosphate [11]. Such information suggests the presence of an enteric-renal signaling axis for phosphate, and also implies the existence of a mechanism by which the intestine detects changes in luminal phosphate.

Cells respond to changes in phosphate concentrations in their environment independent of known phosphate regulatory hormones

Bacterial cells and the unicellular yeast, *Saccharomyces cerevisiae* are able to detect changes in phosphate concentrations in the environment and appropriately increase the retention or rejection of phosphate [12–16]. In *E. coli*, periplasmic proteins (PstS, PstC, Pst and, and PstB in association with PhoU) detect low concentrations of inorganic phosphate in the environment and increase the efficiency of phosphate retention by the bacterial cells [13]. When phosphate concentrations are limiting, phosphorylation of histidine residues on the protein, PhoR, is increased. Phospho-PhoR, in turn, phosphorylates the protein PhoB on aspartate residues. Phospho-PhoB is a transcription factor that binds specific DNA sequences (so-called PHO boxes) to increase the transcription of genes in the Pho regulon. Proteins encoded by DNA sequences within the PHO regulon allow the organism to adapt to reduced phosphate concentrations. When phosphate concentrations are adequate, PhoR is de-phosphorylated and no longer phosphorylates PhoB, which in its un-phosphorylated state is incapable of binding to PHO boxes in the PHO regulon.

In *Saccharomyces cerevisiae,* reduced phosphate concentrations in the environment results in the in-activation of the Pho80-Pho85 by the cyclin--dependent kinase inhibitor, Pho81 [16]. As a consequence, 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 as a high-affinity phosphate transporter. When phosphate 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 PHO genes.

In unicellular organisms, the responses to altered phosphate in the environment have been well characterized. It is unclear as to whether a single molecule acts as the sensor for phosphate on the surface of the cell or whether many of the observed changes in gene expression occur as a result of altered intracellular phosphate concentrations.

Cultured mammalian cells and parathyroid hormone organ cultures respond to extracellular phosphate concentrations

There is evidence that renal and intestinal cells are capable of responding to changes in phosphate concentrations in their environment. For example, incubating cultured renal epithelia in the presence of either a high or low phosphate concentration rapidly changed the efficiency of phosphate uptake by cells [17]. A low phosphate medium increased phosphate uptake, whereas a high phosphate medium decreased phosphate uptake. There is also evidence that intestinal cells respond to changes in medium phosphate concentrations by increasing phosphate transport [10,18,19]. Non-epithelial cells such as osteoblasts and marrow stromal cells also respond to changes in phosphate concentrations in the medium by altering the expression of growth factors, the localization of transcription factors and the secretion of various enzymes [10,18–22]. This would suggest the presence of phosphate sensors within mammalian cells.

Freshly excised parathyroid glands respond to high phosphate concentrations in the surrounding medium. Almaden and colleagues incubated freshly isolated rat parathyroid glands in a media with varying phosphorus concentrations [23–25]. In the presence of 1.25 mM calcium, parathyroid hormone secretion rates were 3- and 4-fold higher in the presence of 3 and 4 mM phosphate in comparison to 1 or 2 mM phosphate. In the presence of 4 mM phosphate, calcium had a less inhibitory effect on parathyroid hormone secretion than in the presence of 1 or 2 mM phosphate. These data are consistent with the ability of parathyroid glands to respond to phosphate concentrations independent of calcium. Parathyroid cell growth and arachadonic acid metabolism were also affected by phosphate.

Phosphate sensing in vivo

Recently, several laboratories have published information suggesting the presence of phosphate sensors in experimental animals. Martin and colleagues have suggested the presence of a phosphate sensing mechanism in the parathyroid gland [26]. These investigators fed uremic animals a high phosphate diet for one month, and on the day of the experiment, administered the rats a low phosphate diet. A reduction in serum concentrations of parathyroid hormone was observed within two hours. In this experiment, serum phosphate concentrations decreased but serum calcium concentrations did not change. The administration of low phosphate or high phosphate diets by gavage allowed an analysis of changes in PTH over a shorter time frame. Administration of a low phosphate diet by gavage was associated with a decrease in PTH and serum phosphate within 15 minutes. Conversely, when uremic rats fed a high-phosphate diet were gavaged with a high-phosphate diet, PTH concentrations increased with modest changes in serum phosphate. The infusion of phosphate into the duodenum of normal rats was associated with a change in PTH concentrations along with changes in serum phosphate. Phosphonoformic acid, a phosphate uptake inhibitor, when infused into the duodenum also rapidly increased PTH concentrations with no significant changes in serum phosphorus. The intravenous infusion of phosphate to normal rats fed a low phosphate diet was associated with modest increases in serum phosphate and a rapid increase in PTH concentrations. No changes in serum calcium were observed. The infusion of sodium chloride to such rats was not associated with changes in parathyroid hormone. This data would suggest that the parathyroid gland is capable of sensing changes in phosphate concentrations in the absence of changes in

serum calcium and implies the existence of a phosphate sensing mechanism in the parathyroid gland.

We performed experiments in which intact or parathyroidectomized rats were administered phosphate into the duodenum [11]. In control experiments, an equivalent amount of sodium chloride was administered into the duodenum. We examined changes in the fractional excretion of phosphate in the kidney. We found that in intact rats, the administration of phosphate into the duodenum was associated with a very rapid change in the fraction excretion of phosphorus in the kidney. At the early time points, there were minimal changes in serum phosphorus concentrations. Rats administered sodium chloride did not show a change in the fraction excretion of phosphate. Concentrations of parathyroid hormone, FGF-23 and sFRP-4, factors that are known to increase phosphate excretion in the kidney, did not change despite changes in the fraction excretion of phosphate following the administration of intra-duodenal phosphate. These observations were confirmed by showing that parathyroidectomy did not alter the response to the administration of intra-duodenal phosphate. Thus, the intestine is able to detect an increase in luminal phosphate concentrations (phosphate sensing) and signal to the kidney to increase the excretion of phosphate. We demonstrated that the increase in the fraction excretion of phosphate in the kidney following the administration of intra-duodenal phosphate was not mediated by renal nerves. Homogenates of the intestine infused into rats increased the fraction excretion of phosphate in the kidney demonstrating the presence of a factor within the intestine capable of increasing renal phosphate excretion. The chemical nature of this factor is currently being investigated.

Rapid enteric-renal responses and solute sensing for other ions

There is evidence that a mechanism similar to that noted for phosphate exists in the case of other ions as well. For example, it is known that natriuretic responses following oral sodium chloride feeding are more marked than the responses seen following the intravenous infusion of sodium chloride, suggesting the presence of both sensing and effector mechanisms in the intestine for sodium [27–30]. Guanylin has been identified as a sodium-specific effector molecule made in the intestine that alters renal sodium transport [31–35]. Gastrointestinal sensing has also been identified in the case of potassium [36–39]. Finally, the calcium-sensing receptor is expressed in the gastrointestinal tract and responds to dietary amino acids [28]. It is possible that there exist enteric-renal signaling mechanisms for a number of solutes besides phosphate.

Concluding remarks and future directions

Bacteria, yeast, renal and intestinal epithelial cells, osteoblasts and marrow cells respond to alterations in phosphate concentrations in the medium. Parathyroid glands and intestine also appear to sense phosphate concentrations in vivo. It is unknown if the phosphate sensing mechanism in mammalian organisms is a cell surface receptor that binds to phosphate or is an intracellular protein which response to changes in intracellular phosphate concentrations that are produced as a result of changes in the extracellular phosphate. Changes in phosphate in the external medium trigger a series of transcriptional events in bacteria and yeast that enhance or diminish the efficiency of phosphate retention. Changes in the extracellular phosphate concentrations in the medium of epithelial cells enhances or diminishes the efficiency of phosphate uptake by these cells presumably by alterations in the level of expression of sodium-phosphate co-transporters. In the intestine, changes in the extracellular phosphate concentration result in the release of a factor that enters the circulation and alters renal phosphate transport.

Future experiments will need to be directed at understanding the nature of the phosphate sensing mechanism in mammalian cells and the characteristics of the factor released by the intestine that modulates renal phosphate reabsorption.

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