Control of Renal Solute Excretion by Enteric Signals and Mediators

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ABSTRACT
Renal solute excretion is important for the homeostasis of various ions. It is widely believed that hormones such as aldosterone, parathyroid hormone, the vitamin D endocrine system, and growth factors are responsible for alterations in renal ion transport in response to increased absorption of enteric solutes. In the cases of sodium, potassium, and phosphorus, moieties produced in the gastrointestinal tract alter renal ion transport when foods that have high concentrations of cognate ions are ingested. The gastrointestinal tract senses the presence of increased luminal concentrations of these ions, presumably via specific “sensors,” and responds by releasing effector substances into the intestinal wall and portal circulation. These substances rapidly increase renal excretion or reduce renal tubular reabsorption and thus blunt large increases in the serum concentrations of these ions. The characterization of enteric solute sensors and mediators will greatly advance our understanding of physiologic mechanisms that control solute homeostasis and will allow the development of specific drugs that stimulate or inhibit these pathways.

ENTERIC MODULATION OF RENAL SODIUM AND POTASSIUM

Dietary sodium induces a more marked natriuresis than intravenous sodium. The regulation of renal excretory or reabsorptive processes exclusively depends on the activity of various hormones or local renal factors, the synthesis or release of which depends on alterations in the serum or extracellular fluid concentrations of the various ions. Decreases in renal sodium excretion in response to a low-salt diet depend on changes in aldosterone synthesis. Indeed, a lack of aldosterone synthesis is responsible for many of the manifestations of Addison’s disease. The role of aldosterone (and inhibition of its synthesis) in increasing salt excretion is less clearly defined when a high-sodium diet is ingested. Data suggest that other factors play a role in this process and that the role of aldosterone is minimal in the adaptation to high-sodium meals. Carey and others have demonstrated that salt-depleted individuals who were given oral sodium chloride excreted much more sodium in their urine than did individuals who were given the same amount of sodium chloride intravenously. Plasma aldosterone...
concentrations were the same whether the sodium load was given orally or intravenously. In addition, patients with documented hypoaldosteronism also excreted more sodium in the urine when a sodium chloride load was given orally than when sodium was given intravenously. This conclusively demonstrates that the exaggerated response to oral sodium chloride loading is independent of aldosterone. Carey suggested the data also indicate “the presence of a splanchnic input monitor for sodium which partially regulates renal sodium excretion and is not dependent upon a turn-off mechanism for sodium excretion.” By implication, an effector substance or mechanism to signal the kidney to increase its capacity to increase sodium excretion must exist. Previous work demonstrated that the liver may contain substances that induce a natriuresis when administered intravenously. Guanylin and uroguanylin may fulfill the role of just such effector substances. These small peptides increase sodium excretion in the intestine and diminish sodium reabsorption in the proximal tubule by increasing guanylate cyclase activity in these cells.

There also are gut factors that induce kaliuresis. Similar to enteric factors that influence renal sodium handling, evidence suggests the presence of gut factors that act independent of aldosterone to regulate renal potassium excretion. Elevated serum potassium directly alters potassium excretion by collecting duct cells and thereby promotes kaliuresis, An elevation in serum potassium concentration also increases aldosterone synthesis, which, in turn, increases kaliuresis. Rabinowitz argued that the increase in serum potassium after a high-potassium meal is too small (0.5 mEq/L) to initiate either of these adaptive responses and that an intestinal signal is responsible for the increase in renal potassium excretion after a high potassium meal. Recent, interesting work from Lee et al. further strengthened this observation. Lee et al. showed that the administration of potassium by intravenous, intraportal, or intragastric method has a similar effect on plasma potassium and renal potassium excretion profiles in the fasting state but that the administration of a low-potassium meal along with intragastric potassium infusion substantially reduces the increase in plasma potassium and greatly enhances renal potassium excretion. These findings suggest the presence of a gut factor that mediates increased renal potassium excretion. Lee et al. suggested that this unique enteric factor might be released from the intestine. The factor does not seem to be insulin, and the chemical identity of such a factor has not been determined. Their experiments, however, make a persuasive case for the existence of such a factor.

**EVIDENCE FOR AN ENTERIC–RENAL PHOSPHATE–TRANSPORT REGULATING AXIS**

The key physiologic roles of the intestine and kidney in phosphate ho-

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**Table 1. Serum calcium, phosphorus, PTH, and 1,25-dihydroxyvitamin D concentrations in men and women fed a high-phosphorus and low-calcium diet**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>High-Pi, Low-Ca Diet</td>
</tr>
<tr>
<td><strong>Serum measurement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized Ca (mg/dl)</td>
<td>5.05 ± 0.03</td>
<td>4.96 ± 0.03</td>
</tr>
<tr>
<td>Total Ca (mg/dl)</td>
<td>9.48 ± 0.10</td>
<td>9.30 ± 0.08</td>
</tr>
<tr>
<td>Pi (mg/dl)</td>
<td>4.40 ± 0.20</td>
<td>4.70 ± 0.10ª</td>
</tr>
<tr>
<td>Mean daytime Pi (mg/dl)</td>
<td>4.30 ± 0.10</td>
<td>4.70 ± 0.10ª</td>
</tr>
<tr>
<td>iPTH (pmol/L)</td>
<td>12.60 ± 0.80</td>
<td>15.40 ± 1.00ª</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/ml)</td>
<td>32.40 ± 2.80</td>
<td>36.20 ± 3.10ª</td>
</tr>
<tr>
<td><strong>Urine measurement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cAMP (nmol/100 ml GFR)</td>
<td>4.07 ± 0.20</td>
<td>4.65 ± 0.35ª</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>86.60 ± 6.00</td>
<td>79.60 ± 6.00</td>
</tr>
<tr>
<td>FE Pi % 0800 to 1600 h</td>
<td>11.6 ± 1.10</td>
<td>23.60 ± 2.20ª</td>
</tr>
<tr>
<td>FE Pi % 1600 to 2400 h</td>
<td>12.10 ± 1.70</td>
<td>18.00 ± 1.30ª</td>
</tr>
<tr>
<td>FE Pi % 2400 to 0800 h</td>
<td>10.20 ± 0.60</td>
<td>14.30 ± 0.90ª</td>
</tr>
</tbody>
</table>

ªUrinary variables on the same subjects include nephrogenous cAMP, GFR, and FE Pi. Adapted from Calvo et al., with permission.

ªªP < 0.05.

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**Figure 1. Phosphorus homeostasis in humans.** Adapted from Berndt and Kumar, with permission.
meostasis are appreciated by all nephrologists (Figure 1). The regulation of renal phosphate transport by widely known hormones such as parathyroid hormone (PTH), the vitamin D–endocrine system, the phosphatonin (fibroblast growth factor-23 [FGF-23] and secreted frizzled-related protein-4 [sFRP-4]), and the role of renal phosphate transporters in the kidney and intestine have been the subjects of recent reviews, and the reader is referred to them for further information.

The prevailing concepts regarding the regulation of phosphate homeostasis, largely based on changes in concentrations of PTH and the vitamin D–endocrine system, are detailed in Figure 2. The roles of PTH and the vitamin D–endocrine system in the scheme shown are clear. The phosphatoins, to the extent that they may be physiologic regulators of phosphate homeostasis, are shown to function as regulators of 25-hydroxyvitamin D 1α-hydroxylase activity.

Several lines of evidence suggest that changes in PTH cannot fully account for the enhancement of renal phosphate excretion that has been observed after administration of increasing amounts of dietary phosphate. First, feeding normal humans a high-phosphate diet is associated with large changes in the fractional excretion of phosphate (FE Pi) but with only modest increases in the concentration of circulating PTH (measured every hour throughout a 24-h period) and urinary nephrogenous cAMP and with no decrease in 1α,25-dihydroxyvitamin D (Table 1). This suggests that increases in PTH and changes in 1α,25-dihydroxyvitamin D cannot fully account for the increase in urinary phosphate excretion. That PTH is not the sole regulator of renal phosphate transport is also supported by earlier data from Steele et al., who showed that chronically parathyroidectomized rats were able to respond to changes in dietary phosphate intake with an appropriate increase in urinary phosphate excretion.

The role that the phosphatoins FGF-23 and sFRP-4 might play in renal adaptation to changes in dietary phosphate has also been explored. Whereas FGF-23 and sFRP-4 change in rodent models in a manner that would be predicted (high-phosphate diet increases circulating FGF-23 and renal sFRP-4), the changes in humans are quite variable and modest when measured after high- or low-phosphate diets of long duration (days). Such changes may not fully account for changes in renal phosphate excretion that occur after meals. Humans consuming diets containing increasing amounts of phosphate have decreases in FGF-23 concentration despite large increases in the FE Pi; therefore, changes in FGF-23 cannot entirely account for changes in the FE Pi seen after phosphate feeding.

The intestine may be a phosphate sensor and regulator of renal phosphate transport. To describe better the adaptations to changes in dietary phosphate, we hypothesized that the intestine might

![Figure 2](image-url) The PTH–vitamin D endocrine system in hypo- and hyperphosphatemic states. Adapted from Berndt and Kumar, with permission.

![Figure 3](image-url) Evidence for an intestinal mediator of renal phosphate excretion. Mean FE Pi in intact or thyro-parathyroidectomized (TPTX) rats after the intestinal administration of sodium phosphate or sodium chloride. Groups of rats were administered either sodium phosphate or sodium chloride, and FE Pi was measured at 0, 5, 10, 20, and 30 min after commencement of the infusion. Intact rats given intestinal sodium phosphate; TPTX rats given intestinal sodium phosphate; Intact + intestinal NaP, TPTX + intestinal NaP; Intact + intestinal NaCl, TPTX + intestinal NaCl. Adapted from Berndt et al., with permission.
“sense” changes in dietary phosphate and elaborate substances that influence the renal excretion of phosphate. To investigate this possibility, we infused phosphate into different segments of the bowel to determine whether the infusion elicited changes in renal phosphate excretion.31

When sodium phosphate is infused into the duodenum of fasted rats, there is a rapid increase in the FE Pi (Figure 3). This phenomenon is observed within 10 min of the infusion of phosphate into the duodenum. Serum phosphate concentrations and the GFR do not change during the experiments, thereby demonstrating that a change in the filtered load cannot account for the change in FE Pi. The fractional excretion of sodium and calcium is also not altered appreciably. Peptides that induce phosphaturia, such as PTH, FGF-23, and sFRP-4, are unchanged. Furthermore, the increase in FE Pi after the intestinal infusion of phosphate occurs in parathyroidectomized rats in an equally efficient and rapid manner, showing that PTH is not the mediator of this response. Earlier, Martin et al.32 showed the intestinal administration of phosphate to rats is associated with a rapid increase in PTH concentrations that would likely induce a phosphaturic response. The amount of phosphate administered was greater than in our experiments. A PTH-independent mechanism was not investigated by these investigators.

There is no change in FE Pi when an equivalent amount of sodium chloride was infused in to the duodenum, thereby showing that the process is specific for the phosphate ion. It is interesting that when sodium phosphate is infused into the stomach of rats in which the gastric outlet had been ligated, no increase in FE Pi is observed, suggesting that luminal phosphate concentrations are not sensed in the stomach.

These data suggest that duodenum or some part of the intestine distal to the duodenum is able to sense phosphate in the lumen of the bowel. The precise nature of this sensor is not known. Whether phosphate uptake into intestinal cells is a prerequisite for this sensing mechanism is uncertain. It is plausible that a cell-surface phosphate sensor is involved in sensing changes in luminal phosphate concentrations. Receptors on the surface of cells are involved in sensing small molecules on various parts of the tongue and within the gastrointestinal tract.33,34 G-protein–coupled taste receptors for sweet, bitter, and umami flavors are distributed on the surface of the tongue, and nutrient sensors resembling taste receptors are also found on the surface of enteroendocrine and other cells are present throughout the gastrointestinal tract.33,34 The calcium-sensing receptor, besides detecting calcium, functions as an amino acid sensor.35 The calcium-sensing receptor is present in gastric G cells and acid-secreting parietal cells of the stomach, where it could play a role in regulating acid secretion in that organ in response to meal-induced changes in luminal amino acid concentrations.35 The calcium-sensing receptor is also present in the intestine and colon, where it might influence the movement of ions such as sodium and chloride.36–38 Whether any G-protein–coupled receptors are involved in sensing alterations in phosphate in the intestine is unknown.

What triggers the phosphaturic response in the kidney? Neural circuits might potentially be involved. Activation of vagal, spinal, and myenteric nerves in the intestinal wall could relay a neural signal centrally, and subsequently modulate renal nerve activity to reduce phosphate reabsorption. To address this possibility, we instilled phosphate into the duodenum of rats that had undergone a unilateral renal denervation. Denervation did not alter the phosphaturic response to phosphate instillation into the duodenum, thereby demonstrating that renal nerves are not involved in this process.

The intestine might also elaborate substances that alter renal phosphate reabsorption. To test this possibility, we administered extracts of the duodenum to rats intravenously. These extracts induced phosphaturia in rats, showing that the intestine, itself, is the source of a phosphaturic substance that is released upon phosphate infusion into the intestine. The cell type elaborating such a substance is unknown. The intestine is rich in enteroendocrine cells that elaborate various hormones.33,34,39 Examples include the incretin peptides (glucose-dependent insulinotropic peptide, glucagon-like peptide-1), glucagon-like peptide-2, oxyntomodulin, cholecystokinin, gastrin, and other factors.33,34,39 In addition, intestinal absorptive cells produce factors such as apolipoprotein A IV that modulate satiety.33,34,39 The source of the phosphaturic substance may be any one of these cells or some other cell type found in the intestinal wall. Efforts
to identify the chemical identity of this factor are under way.

What is an integrated view of the regulation of phosphate homeostasis? Phosphate homeostasis can be thought of in terms of processes that regulate phosphate over the short and long term (Figure 4). Both of these processes play a role in phosphate homeostasis, but the short-term processes are probably more important in the postcibal regulation of concentrations of this ion. Short-term processes involve the rapid postcibal increase in renal phosphate excretion by the kidney and are likely to be mediated by novel intestinal factors—“intestinal phosphatonin”—the chemical nature of which remains to be determined. These factors, released soon after meals high in phosphorus, enter the intestine and reset (lower) the tubular maximum for phosphate such that increases in serum phosphate levels that occur after a meal are reduced rapidly and large excursions in serum phosphate after a meal are reduced rapidly and large excursions in serum phosphate after a meal do not occur. In the long term, hormones such as parathyroid hormone and 1α,25-dihydroxyvitamin D play a role in modulating phosphate homeostasis, although their role may be mainly to change the basal tubular maximum for phosphate in circumstances of high or low phosphate intakes. The postcibal changes in renal phosphate handling mediated by enteric factors still occur as noted previously.

What is the relevance of the enteric—renal solute–transport regulating axis? The physiologic relevance of this axis is clear not just because it better explains observations relevant to phosphate homeostasis but because relevant sensors and mediators also represent targets for drugs that can be used to treat hyperphosphatemia seen in renal failure. Thus, one might speculate that the FE Pi could be increased in early renal failure by “turning on” the sensor for phosphate with a nonabsorbed molecule. The net result would be a decrease in phosphate retention and concomitant hyperparathyroidism. Alternatively, if an intestinal effector molecule could be chemically characterized and synthesized, then administration in early renal failure could reduce hyperphosphatemia after ingestion of meals containing phosphate. Finally, it is conceivable that an intestinal mediator might reduce intestinal phosphate absorption by preventing postcibal hyperphosphatemia. These concepts could be extended to other ions such as sodium and potassium as well.

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DISCLOSURES

None.

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