Teaching Ca\(^{2+}\) and phosphate homeostasis in a physiology survey course for medical or graduate students is done very effectively with an integrated approach. The material can be taught in the endocrine section of the course, where the renal and gastrointestinal (GI) handling of Ca\(^{2+}\) and phosphate and bone remodeling can be linked under the umbrella of teaching parathyroid hormone (PTH), vitamin D, and calcitonin. This allows one teacher to pull the whole story together (and it really does hang together!).

Ca\(^{2+}\) and phosphate homeostasis can be taught in two lectures or in one lecture plus a pathophysiology problem solving session that illustrates and reteaches the physiology. (Ideally, the pathophysiology is covered in small groups but, if that is not possible, it can be taught interactively in a second lecture.)

Organizationally, there is a three-by-three matrix: three organ systems (GI, kidney, and bone) and three hormones (PTH, vitamin D, and calcitonin). Each of the three hormones has actions on each of the three organ systems, although the nine actions will receive different emphasis depending on their relevance. A decision to be made is whether the material should be organized by organ system (e.g., GI, renal, bone) or by hormone (e.g., PTH, vitamin D, calcitonin). The latter makes a more cohesive presentation that emphasizes the overall function of each hormone (e.g., PTH is for regulating serum Ca\(^{2+}\) concentration).

OVERVIEW OF CALCIUM ION HOMEOSTASIS

Forms of Ca\(^{2+}\) in Blood

The total blood Ca\(^{2+}\) includes a fraction that is bound to plasma proteins (mainly albumin) and a fraction that is unbound, or ultrafilterable (Fig. 1). The ultrafilterable component is further divided among a fraction that is bound to anions, such as phosphate and sulfate, and the remainder, which is free ionized Ca\(^{2+}\). Normally, the total blood Ca\(^{2+}\) concentration is 10 mg/dl, with 40% bound to plasma proteins, 60% ultrafilterable, and 50% in the ionized form.

Hypercalcemia, or an increase in the blood Ca\(^{2+}\) concentration, is characterized by neurological symptoms of lethargy, hyporeflexia, and even coma and death; constipation; and polydipsia and polyuria (due to the antidiuretic hormone (ADH) resistance that occurs when Ca\(^{2+}\) is deposited in the inner medulla of the kidney).

Hypocalcemia, or a decrease in the blood Ca\(^{2+}\) concentration, is characterized by twitching and spontaneous muscle cramps (even tetany), tingling of the fingers and toes, and numbness around the mouth. Hypocalcemia is dramatically illustrated by the Trousseau sign (carpopedal spasm invoked by inflation of a blood pressure cuff around the upper arm) or by the Chvostek sign (twitching of the upper lip when the supramandibular portion of the parotid gland is tapped). Initially, students may be confused by the fact that hypocalcemia increases contraction of skeletal muscle. They are confused because they recall that increases in intracellular ionized Ca\(^{2+}\) of muscle cells leads to increased tension. It is wise to anticipate this confusion and explain that hypocalcemia refers to decreased extracellular Ca\(^{2+}\), which increases excitability of the motoneurons innervating skeletal muscle; this increased excitability leads to increased frequency of action potentials in the nerves and the muscles, and thus increased frequency of contractions.
We must emphasize that only the free ionized Ca\(^{2+}\) is biologically active; stated another way, any Ca\(^{2+}\) bound to proteins or complexed to anions is inactive. We can then demonstrate several conditions in which the free ionized Ca\(^{2+}\) changes as follows.

Changes in total protein concentration are associated with changes in total Ca\(^{2+}\) concentration. However, it is difficult to predict, without other knowledge, whether the ionized Ca\(^{2+}\) will change in the expected direction. We are probably wise to leave these subtleties for inclusion in subsequent pathophysiology courses rather than entering these muddy waters in an introductory physiology course.

It is quite simple to explain what happens to ionized Ca\(^{2+}\) when there is an increase or decrease in the plasma concentration of a complexing anion such as phosphate, citrate, or sulfate. As the concentration of the anion increases, a greater fraction of the Ca\(^{2+}\) is complexed and the ionized Ca\(^{2+}\) concentration decreases.

Finally, we discuss the effects of acid-base changes on ionized Ca\(^{2+}\), which are easily explainable with a simple diagram of a plasma albumin molecule (Fig. 2). Plasma proteins have negatively charged sites that can bind either H\(^{+}\) or Ca\(^{2+}\). In acidemia, for example, when there is excess H\(^{+}\) in blood, more H\(^{+}\) is bound to plasma proteins and less Ca\(^{2+}\) is bound; thus the free ionized Ca\(^{2+}\) increases. On the other hand, in alkalemia, when there is a deficit of H\(^{+}\) in blood, less H\(^{+}\) is bound and more Ca\(^{2+}\) is bound; thus the ionized Ca\(^{2+}\) decreases. Symptomatic hypocalcemia is commonly seen in acute respiratory alkalosis, and students may already know about the tingling and numbness that accompanies psychogenic hyperventilation.

Overall Ca\(^{2+}\) Homeostasis
Ca\(^{2+}\) balance is maintained by the interplay of three organ systems: GI tract, bone, and kidney (Fig. 3). This type of diagram allows the student to appreciate the "big picture" of Ca\(^{2+}\) homeostasis and superimpose the important hormonal actions. Once the material is learned in more detail, the student can return to this diagram for summary and review. An adult ingesting 1,000 mg of elemental Ca\(^{2+}\) daily maintains Ca\(^{2+}\) balance as follows. Approximately 35%, or 350 mg, of the ingested Ca\(^{2+}\) is absorbed in the small intestine by a mechanism that is stimulated by vitamin D (more correctly, its active form, 1,25-dihydroxycholecalciferol). However, net absorption of Ca\(^{2+}\) is only 200 mg per day, because pancreatic and other GI secretions contain Ca\(^{2+}\). Bone turnover, or bone remodeling, is a continuous process involving both resorption of old bone and deposition of new bone; the bone resorptive processes are stimulated by the synergistic actions of 1,25-dihydroxycholecalciferol and PTH and are inhibited by calcitonin. Logically, to maintain perfect Ca\(^{2+}\) balance, the kidneys must excrete the same amount of Ca\(^{2+}\) that the GI tract absorbs, or 200 mg per day; this

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**FIG. 1.**
Forms of Ca\(^{2+}\) in blood [adapted with permission from L. S. Costanzo. *Physiology.* Philadelphia, PA: Saunders, 1998]. Percentages are percentage of total Ca\(^{2+}\) concentration in each form.

**FIG. 2.**

is accomplished by a combination of filtration of Ca²⁺ across the glomerular capillaries and subsequent reabsorption of most of the filtered Ca²⁺.

Whereas Fig. 3 demonstrates the situation of perfect Ca²⁺ balance (in which there is no net gain or loss of Ca²⁺ from the body), one can easily visualize other conditions of positive or negative Ca²⁺ balance. For example, in positive Ca²⁺ balance (e.g., the growing child), net Ca²⁺ absorption from the GI tract exceeds urinary excretion and the difference is deposited in the growing bones. In negative Ca²⁺ balance (e.g., pregnancy, lactation), net Ca²⁺ absorption from the GI tract is less than excretion and the difference comes from the maternal bone. (In the case of lactation, there is a second “excretory” route via the breast milk.)

At this point in the lecture, a large table can be constructed on the board with the following headings: hormone, stimulus for secretion or production, actions (on bone, kidney, and intestine), and overall effect on serum Ca²⁺ concentration and serum phosphate concentration (Table 1). The students will see how the lecture will be organized and where it is headed. We will teach the material by filling in the table and elaborating on points as we proceed. Such a table gives the students all of the salient points about Ca²⁺ and phosphate homeostasis and is a lasting way to review. (I have never been in favor of including such summary tables in the lecture syllabus—the students will be more actively involved in the lecture if they construct their own table with us!)

**PARATHYROID HORMONE**

The overall role of PTH is regulation of the serum ionized Ca²⁺ concentration. This regulation employs a simple negative feedback system. When the serum
ionized Ca\textsuperscript{2+} concentration decreases below normal, PTH secretion is stimulated. The hormone then has coordinated actions on bone, kidney, and intestine that raise the serum Ca\textsuperscript{2+} concentration and, simultaneously, decrease the serum phosphate concentration.

**Structure, Synthesis, and Secretion of PTH**

In humans, there are four parathyroid glands, which are located in the neck under the thyroid gland. The chief cells of the parathyroid glands synthesize and secrete PTH, which is an 84-amino acid single-chain polypeptide. The biologic activity of PTH resides entirely in the 34 NH\textsubscript{2}-terminal amino acids. Thus it is important that radioimmunoassays for PTH be directed to the NH\textsubscript{2} terminus rather than the COOH terminus, particularly for use in parathyroid disorders in which hormone fragments may be circulating.

PTH is synthesized on the ribosomes as preproPTH, which has 115 amino acids. A 25-amino acid signal peptide is cleaved as synthesis is being completed on the ribosomes, forming a 90-amino acid proPTH, which is transported to the Golgi apparatus. There, 6 more amino acids are cleaved, yielding the 84-amino acid peptide, which is stored in secretory vesicles for subsequent secretion.

PTH secretion is regulated by the plasma Ca\textsuperscript{2+} concentration (Fig. 4). When the total Ca\textsuperscript{2+} concentration is in the normal range (10 mg/dl) or higher, PTH is secreted at a low, basal rate. However, when the plasma Ca\textsuperscript{2+} concentration decreases to <10 mg/dl, PTH secretion is strongly stimulated, reaching maximal rates when the Ca\textsuperscript{2+} concentration falls to 7.5 mg/dl. The students should note that although PTH secretion is plotted on the graph as a function of total Ca\textsuperscript{2+} concentration, actually it is the ionized Ca\textsuperscript{2+} that regulates secretion by the chief cells. The response of the chief cells to a decrease in ionized Ca\textsuperscript{2+} is remarkably prompt, within seconds, and the faster the ionized Ca\textsuperscript{2+} falls, the greater the PTH secretory response.

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because they may recall that many endocrine cells (e.g., β-cells of the pancreas) secrete their hormones in response to an increase in intracellular Ca\(^{2+}\). Actually, there is no paradox, because the chief cells sense a decrease in extracellular Ca\(^{2+}\), not intracellular Ca\(^{2+}\).

The mechanism of PTH secretion is explained as follows. The chief cell membrane contains a Ca\(^{2+}\) sensor, which detects a decrease in extracellular ionized Ca\(^{2+}\) concentration. This Ca\(^{2+}\) sensor is coupled, via a G\(_s\) protein, to adenylyl cyclase. Thus, when extracellular Ca\(^{2+}\) concentration decreases, adenyl cyclase is activated and catalyzes the conversion of ATP to cAMP. After a series of phosphorylation steps, there is exocytosis of PTH from secretory vesicles into the bloodstream.

These events describe the response of the chief cells to an acute decrease in Ca\(^{2+}\) concentration. However, there are additional effects of chronic hypocalcemia (e.g., due to chronic renal failure or vitamin D deficiency). Chronic hypocalcemia causes secondary hyperparathyroidism, which is characterized by increased transcription of the gene for preproPTH, increased synthesis and storage of PTH, and hyperplasia of the parathyroid glands. Conversely, chronic hypercalcemia causes decreased synthesis and storage of PTH and increased breakdown of stored PTH.

Mg\(^{2+}\) has effects parallel to those of Ca\(^{2+}\) on the chief cells. Hypomagnesemia stimulates PTH secretion, and hypermagnesemia inhibits PTH secretion. An exception is the case of severe hypomagnesemia associated with chronic Mg\(^{2+}\) depletion (e.g., alcoholism), in which PTH synthesis and secretion are inhibited, leading to hypoparathyroidism and hypocalcemia.

**Actions of PTH**

To introduce the actions of PTH, it is helpful to reemphasize that the actions of PTH on bone, kidney, and intestine are coordinated to produce an increase in plasma ionized Ca\(^{2+}\) concentration.

At this point in the lecture it is tempting to discuss the cellular mechanisms of action of PTH on bone and kidney, which occur via a G\(_s\) protein and activation of adenyl cyclase. However, in the interest of efficiency, this is best briefly noted and deferred to the discussion of the phosphaturic action of PTH in the renal proximal tubule (where it naturally fits).

**Actions of PTH on bone.** PTH has actions on all three cell types in bone: osteocytes, osteoblasts (responsible for bone formation), and osteoclasts (responsible for bone resorption). Initially, PTH stimulates osteolysis in osteocytes, which results in dissolution of surface bone. As a result of this action, Ca\(^{2+}\) moves from bone canalicular fluid into the osteocytes and then into the extracellular fluid. In a second, slower action, PTH stimulates osteoclasts to increase resorption of previously mineralized bone, releasing both Ca\(^{2+}\) and phosphate into extracellular fluid. The organic portion of bone matrix, primarily type I collagen, also is resorbed, and a major component of collagen, hydroxyproline, is released and then excreted in urine. (Thus urinary hydroxyproline excretion is an indicator of bone resorption.) In a still later phase, PTH inhibits osteoblasts and bone formation. Interestingly, receptors for PTH are found on osteocytes and osteoblasts, but not on osteoclasts. An interpretation of this observation is that the hormonal effects on osteoclasts are mediated by paracrine signals from osteocytes and osteoblasts.

The overall effect of PTH on bone, therefore, is to promote bone resorption, delivering both Ca\(^{2+}\) and phosphate to extracellular fluid. However, it is very important to emphasize that these effects on bone alone cannot account for the ultimate action of the hormone to increase the plasma ionized Ca\(^{2+}\) concentration. The reason is that both Ca\(^{2+}\) and phosphate are released from bone—the phosphate will complex with the Ca\(^{2+}\) and limit the increase in ionized Ca\(^{2+}\) concentration. Therefore, an additional mechanism must coordinate with the action on bone to eliminate the phosphate from the body. That takes us to the kidney and the all-important phosphaturic action of PTH.

**Actions of PTH on kidney.** PTH has two major actions on the kidney: inhibition of phosphate reabsorption and stimulation of Ca\(^{2+}\) reabsorption. To introduce these topics, it is first necessary to teach the students about the renal handling of phosphate and Ca\(^{2+}\) more generally.
Phosphate handling in the nephron

70% PTH

15%


Ca²⁺ handling in the nephron

67% Thiazide diuretics

8%

25%

Furosemide


The renal handling of phosphate is shown in Fig. 5. Phosphate is mainly unbound in the plasma and therefore is almost freely filtered. Subsequent to filtration, ~70% of the filtered phosphate is reabsorbed in the proximal convoluted tubule and ~15% is reabsorbed in the proximal straight tubule. The remainder of the nephron reabsorbs little, if any, phosphate (a debatable issue that need not concern our students). Thus 15% of the filtered phosphate is normally excreted, and it is surely worth mentioning that this excreted phosphate serves as a major urinary buffer for excretion of H⁺ (called titratable acid). PTH inhibits the phosphate reabsorption process and increases the fraction of phosphate excreted (see below for a detailed description).

The renal handling of Ca²⁺ is shown in Fig. 6. Ca²⁺ filtration deserves special comment because such a large percentage of Ca²⁺ in plasma is bound to proteins (40%) and, therefore, is not filterable across glomerular capillaries. Sixty percent of the plasma Ca²⁺ is ultrafilterable. Ca²⁺ differs from phosphate in that several segments of the nephron participate in its reabsorption. In the proximal tubule, Ca²⁺ reabsorption follows Na⁺ and water reabsorption, primarily via a paracellular pathway; water reabsorption initially causes a small increase in luminal Ca²⁺ concentration, which then drives Ca²⁺ reabsorption between the...
cells. As evidence of this linkage, the percentage of Ca\(^{2+}\) reabsorbed in the proximal tubule is exactly the same as for Na\(^{+}\)(67%). Any maneuver that alters Na\(^{+}\) reabsorption in the proximal tubule (e.g., volume expansion or volume contraction) alters Ca\(^{2+}\) reabsorption in the same direction and to the same extent. In the thick ascending limb, Ca\(^{2+}\) reabsorption also follows Na\(^{+}\) reabsorption (again, Ca\(^{2+}\) is moving by a paracellular path). In this case, Ca\(^{2+}\) reabsorption is driven by the normal lumen-positive potential difference that is generated by the Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) cotransporter; lumen positivity drives the passive reabsorption of Ca\(^{2+}\), a divalent cation. Loop diuretics such as furosemide inhibit the Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) cotransporter, eliminate the lumen-positive potential, and, as a consequence, inhibit Ca\(^{2+}\) reabsorption, an effect that can be exploited in the treatment of hypercalcemia. In the distal tubule, Ca\(^{2+}\) is reabsorbed independent of Na\(^{+}\)(in contrast to the other nephron segments in which these two ions are linked). In fact, because of the presence of a Na\(^{+}\)/Ca\(^{2+}\) exchanger in the basolateral membrane of distal tubule cells, the reabsorption of these ions is inversely related. As an aside, this inverse relationship is nicely demonstrated by the effect of thiazide diuretics in the distal tubule: Na\(^{+}\) reabsorption is inhibited, whereas Ca\(^{2+}\) reabsorption is augmented. Because thiazide diuretics increase Ca\(^{2+}\) reabsorption and decrease Ca\(^{2+}\) excretion, they are used to treat idiopathic hypercalciuria with the intention of preventing urinary stone formation.

Now, back to the specific actions of PTH on the kidney. The first action of PTH on the kidney is to inhibit the Na\(^{+}\)-phosphate cotransporter in the proximal convoluted tubule, which results in inhibition of phosphate reabsorption and phosphaturia (see Fig. 5). The mechanism of this action of PTH is shown in Fig. 7. PTH binds to its receptors on the basolateral membrane. These receptors are coupled, via a G\(_{s}\) protein, to adenylyl cyclase. When activated, adenylyl cyclase catalyzes the conversion of ATP to cAMP, which activates a series of protein kinases and ultimately phosphorylates intracellular proteins, leading to inhibition of the Na\(^{+}\)-phosphate cotransporter in the luminal membrane. As a result of this inhibition, a greater fraction of the filtered phosphate is excreted, i.e., phosphaturia. In addition to increased phosphate excretion, the cAMP produced in proximal tubule cells diffuses into the urine; increased urinary cAMP is a hallmark of PTH action and was the basis for bioassay until these were replaced by radioimmunoassays. The phosphaturic action of PTH is critically important for the overall “mission” of the hormone (to raise ionized Ca\(^{2+}\) concentration), because phosph...

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**FIG. 7.**

The second action of PTH is to increase Ca\(^{2+}\) reabsorption in the distal tubule, also via an adenylyl cyclase mechanism (see Fig. 6). This hypocalciuric action complements the action of PTH on bone and assists in increasing the plasma Ca\(^{2+}\) concentration.

**Action of PTH on intestine.** The action of PTH on intestinal Ca\(^{2+}\) absorption is indirect. PTH stimulates the 1\(\alpha\)-hydroxylase enzyme in the kidney that is responsible for production of the active form of vitamin D, 1,25-dihydroxycholecalciferol. In turn, 1,25-dihydroxycholecalciferol stimulates intestinal Ca\(^{2+}\) absorption.

**Pathophysiology of PTH**

Disorders of the parathyroid gland beautifully demonstrate the physiology of PTH, its feedback regulation by Ca\(^{2+}\), and its actions on target tissues. The pathophysiology falls in three categories: hormone excess, or hyperparathyroidism; hormone deficiency, or hypoparathyroidism; and hormone resistance, or pseudohypoparathyroidism. Before embarking on this portion of the teaching, we emphasize once again that, by knowing the physiology well, one can perfectly predict the characteristics of each disorder.

Hyperparathyroidism can be primary (originating in the parathyroid gland) or secondary (secondary to hypocalcemia). Primary hyperparathyroidism is most commonly caused by a parathyroid adenoma that secretes excessive amounts of PTH. The consequences of primary hyperparathyroidism are predictable from the known physiological actions of PTH: increased bone resorption, increased Ca\(^{2+}\) reabsorption from kidney and absorption from intestine, and decreased phosphate reabsorption (phosphaturia). As a result of these actions, there will be hypercalcemia and hypophosphatemia. Persons with primary hyperparathyroidism excrete excessive amounts of phosphate and cAMP in their urine and, perhaps unexpectedly, also excrete large amounts of Ca\(^{2+}\). Does increased Ca\(^{2+}\) excretion make sense, in light of the hypocalciuric action of PTH that we just taught? Yes, it does, but we must explain that, whereas the direct action of PTH is to increase Ca\(^{2+}\) reabsorption, once the blood Ca\(^{2+}\) concentration increases, the filtered load of Ca\(^{2+}\) also increases and overwhelms the reabsorptive capacity of the nephron; the Ca\(^{2+}\) that is not reabsorbed is spilled in the urine. Persons with primary hyperparathyroidism are said to have “stones,” “bones,” and “groans”—stones from hypercalciuria, bones from increased bone resorption, and groans from constipation. Treatment of primary hyperparathyroidism is parathyroidectomy. In secondary hyperparathyroidism, the parathyroid glands secrete excessive PTH secondary to hypocalcemia (e.g., from chronic renal failure or vitamin D deficiency). In secondary hyperparathyroidism, circulating levels of PTH are elevated and plasma Ca\(^{2+}\) levels are either low (hypocalcemia) or normal, but never high. Thus secondary hyperparathyroidism is distinguished from primary hyperparathyroidism by the absence of hypercalcemia.

Hypoparathyroidism is a relatively common inadvertent or unavoidable consequence of thyroid or parathyroid surgery. Autoimmune and congenital hypoparathyroidism are rare. The characteristics of hypoparathyroidism are, once again, predictable on the basis of the physiology: low circulating levels of PTH, decreased bone resorption, decreased renal reabsorption and intestinal absorption of Ca\(^{2+}\), and increased phosphate reabsorption. As a consequence of these actions, there is hypocalcemia and hyperphosphatemia.

Pseudohypoparathyroidism was first described by the endocrinologist Fuller Albright as follows. A subset of patients with hypocalcemia and hyperphosphatemia had a characteristic phenotype consisting of short stature, short neck, obesity, subcutaneous calcification, and shortened fourth metatarsals and metacarpals. This phenotype is referred to as Albright’s hereditary osteodystrophy. Pictures of patients with this disorder are available in textbooks and can provide a high-impact and memorable association for the students. While patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia, just as in hyperparathyroidism, circulating levels of PTH are increased, not decreased. The inevitable conclusion is that the defect lies in the end organs (bone and kidney). In fact, pseudohypoparathyroidism type Ia is caused by a defect in the G\(_s\) protein in...
bone and kidney; PTH cannot have its physiological actions on these tissues because the second messenger, cAMP, is not generated. In addition to type 1a, other variants of the disorder are types 1b, 1c, and II, which involve defects at other steps in the second messenger pathway including the PTH receptor, the adenylyl cyclase, and the protein kinases. Given the rarity of these disorders, I cannot imagine any value (other than because “it’s very interesting”) in having students learn which variant has which defect.

**VITAMIN D**

A slide showing a child with vitamin D-deficient rickets makes a nice transition from PTH to vitamin D. We then want to emphatically state the overall role of vitamin D and compare it to that of PTH. PTH is for regulating the ionized Ca\(^{2+}\) concentration in plasma. Vitamin D is for mineralization of bone, and its actions, therefore, are coordinated to increase both Ca\(^{2+}\) and phosphate concentrations in blood so that these elements can be deposited in new bone mineral. Recall that we have a table growing on the board and have now moved to our second hormone, vitamin D. First, we will make a digression to its metabolism (Fig. 8).

**Vitamin D Metabolism**

There are two sources of cholecalciferol, or vitamin D\(_3\), in the body. It is either ingested in the diet, or it is synthesized in the skin from 7-dehydrocholesterol in the presence of ultraviolet light. Cholecalciferol itself is physiologically inactive. It is hydroxylated in the liver to form 25-hydroxycholecalciferol, which also is inactive; this hydroxylolation step occurs in the endoplasmic reticulum and requires NADPH, O\(_2\), and Mg\(^{2+}\), but not cytochrome P-450. 25-Hydroxycholecalciferol is bound to an \(\alpha\)-globulin in plasma and is the principal circulating form of vitamin D.

In the kidney, 25-hydroxycholecalciferol undergoes one of two routes of hydroxylation. It can be hydroxylated at C-1 to produce 1,25-dihydroxycholecalciferol, which is the physiologically active form, or it can be hydroxylated at C-24 to produce 24,25-dihydroxycholecalciferol, which is inactive. C-1 hydroxylation is catalyzed by the enzyme 1\(\alpha\)-hydroxylase in the renal mitochondria and requires NADPH, O\(_2\), Mg\(^{2+}\), and cytochrome P-450.

Whether the renal cells produce 1,25-dihydroxycholecalciferol (the active metabolite) or 24,25-dihydroxycholecalciferol (the inactive metabolite) depends on the Ca\(^{2+}\) status of the body. When Ca\(^{2+}\) is sufficient, with adequate dietary intake of Ca\(^{2+}\) and normal or increased plasma Ca\(^{2+}\) concentration, the inactive metabolite is preferentially produced because there is no need for more Ca\(^{2+}\). When Ca\(^{2+}\) is insufficient, with a low dietary intake of Ca\(^{2+}\) and decreased plasma Ca\(^{2+}\) concentration, the active metabolite is preferen-
tially synthesized to ensure that additional Ca\(^{2+}\) will be absorbed from the GI tract.

Production of the active metabolite 1,25-dihydroxycholecalciferol is regulated by changing the activity of the 1\(\alpha\)-hydroxylase. 1\(\alpha\)-Hydroxylase activity is increased by each of the following (which should be listed on the board in the column of factors that increase secretion or production): decreased plasma Ca\(^{2+}\) concentration, increased circulating PTH, and decreased plasma phosphate concentration. (We can recommend that students learn the factors in this order because it is easiest to remember that decreased plasma Ca\(^{2+}\) leads to increased PTH, which leads to decreased plasma phosphate.)

**Actions of Vitamin D**

To reemphasize, the overall action of vitamin D (or more correctly, 1,25-dihydroxycholecalciferol) is to increase the plasma concentrations of both Ca\(^{2+}\) and phosphate to promote bone mineralization. In this effort, vitamin D has the following actions on intestine, kidney, and bone.

**Actions of vitamin D on intestine.** The major actions of 1,25-dihydroxycholecalciferol are in the small intestine, where it increases both Ca\(^{2+}\) and phosphate absorption. Far more is known about its effect on Ca\(^{2+}\) absorption, which involves induction of the synthesis of a vitamin D-dependent Ca\(^{2+}\)-binding protein called calbindin D-28K (a cytosolic protein with four binding sites for Ca\(^{2+}\)). The mechanism of intestinal Ca\(^{2+}\) absorption and a proposed role of calbindin D-28K is shown in Fig. 9. Ca\(^{2+}\) diffuses from the lumen into the cell down its electrochemical gradient. In the cell, it is bound to or chelated by calbindin D-28K. Subsequently, it is pumped across the basolateral membrane by a Ca\(^{2+}\) ATPase. The exact role of calbindin D-28K is uncertain. It may act as an intracellular shuttle, moving Ca\(^{2+}\) from the luminal to the basolateral side of the cell, or it may act as a Ca\(^{2+}\) buffer to keep intracellular Ca\(^{2+}\) low, thus maintaining the concentration gradient for Ca\(^{2+}\) diffusion across the luminal membrane.

**Actions of vitamin D in the kidney.** The actions of 1,25-dihydroxycholecalciferol on the kidney are parallel to its actions in the intestine—it stimulates both Ca\(^{2+}\) and phosphate reabsorption. These renal actions are clearly distinguishable from those of PTH. (Recall that PTH increases Ca\(^{2+}\) reabsorption but inhibits phosphate reabsorption.)

**Actions of vitamin D on bone.** In bone, 1,25-dihydroxycholecalciferol and PTH act synergistically to stimulate osteoclast activity and bone resorption. This synergistic action of 1,25-dihydroxycholecalciferol may at first seem paradoxical, because the overall role of this hormone is to promote bone mineralization. However, we can explain that, yes, 1,25-dihydroxycholecalciferol promotes the resorption of “old” bone, bringing more Ca\(^{2+}\) and phosphate in to the extracellular fluid, to facilitate the formation of “new” bone (or bone remodeling).

**Pathophysiology of Vitamin D**

In children, vitamin D deficiency causes rickets, a condition in which there is insufficient Ca\(^{2+}\) and phosphate to mineralize growing bones. Rickets is characterized by growth failure and skeletal deformities. (This condition is rare in parts of the world where vitamin D is supplemented in the diet or where there is adequate exposure to sunlight.) In adults, vitamin D deficiency causes osteomalacia, in which the failure to
mineralize new bone results in bending and softening of the weight-bearing bones.

Vitamin D resistance occurs if the kidney is unable to produce the active metabolite 1,25-dihydroxycholecalciferol. These conditions are called “resistant” because, no matter how much vitamin D is supplied in the diet, it will be inactive because the C-1 hydroxylation step in the kidney is impaired or is missing. Vitamin D resistance can be caused by congenital absence of 1α-hydroxylase or, more commonly, by chronic renal failure. Chronic renal failure is associated with a constellation of bone abnormalities (called renal osteodystrophy) including osteomalacia (due to the lack of 1,25-dihydroxycholecalciferol).

**CALCITONIN**

The details of calcitonin physiology usually are deemphasized because it is unclear what physiological role this hormone plays in Ca²⁺ homeostasis. In contrast to PTH, calcitonin does not participate in the minute-to-minute regulation of the plasma Ca²⁺ concentration. In fact, neither thyroidectomy (with decreased calcitonin levels) nor thyroid tumors (with increased calcitonin levels) causes a derangement of Ca²⁺ metabolism, as would be expected if this hormone had a key regulatory role.

**Synthesis, Secretion, and Actions of Calcitonin**

Calcitonin is a straight-chain peptide with 32 amino acids. It is synthesized and secreted by the parafollicular or C cells (“C” for calcitonin) of the thyroid gland. The calcitonin gene directs the synthesis of preprocalcitonin, a signal peptide is cleaved to yield procalcitonin, other peptide sequences are cleaved, and the final hormone, calcitonin, is stored in secretory granules for subsequent release.

Conceptually, calcitonin is the “mirror image” of PTH. The major stimulus for calcitonin secretion is an increased plasma Ca²⁺ concentration. The major action of calcitonin is to inhibit bone osteoclasts and to inhibit bone resorption. As a consequence, calcitonin decreases the plasma Ca²⁺ concentration acutely and, in theory, can be used to treat hypercalcemia.

**CASE STUDY OF RENAL OSTEODYSTROPHY**

If time permits, a case study of renal osteodystrophy (the bone disease that accompanies chronic renal failure) illustrates a significant amount of the physiology of Ca²⁺ and phosphate homeostasis.

For example, a 30-year-old female with advanced renal failure is receiving peritoneal dialysis while awaiting transplantation. She is admitted to the hospital for evaluation because, in the preceding month, she experienced severe bone pain and pruritus (itching). Upon admission, she had increased blood phosphate (hyperphosphatemia), decreased blood Ca²⁺ (hypocalcemia), increased circulating PTH, and decreased circulating 1,25-dihydroxycholecalciferol. Radiological examination revealed increased bone resorption, osteomalacia, and soft-tissue calcification.

The key points that illustrate the physiology in this case are as follows. Her chronic renal disease, with decreased renal mass and decreased GFR, led to decreased filtration of phosphate and phosphate retention. The increased blood phosphate then complexed Ca²⁺ and caused a decrease in ionized Ca²⁺ concentration. The decreased renal mass also led to decreased production of 1,25-dihydroxycholecalciferol and, as a consequence, decreased intestinal Ca²⁺ absorption and a further decrease in plasma Ca²⁺ concentration.

The decrease in plasma Ca²⁺ caused increased secretion of PTH and hyperplasia of the parathyroid glands (i.e., secondary hyperparathyroidism). The increased circulating levels of PTH caused increased bone resorption, and this, coupled with osteomalacia caused by the decreased 1,25-dihydroxycholecalciferol, is “renal osteodystrophy.” Calcification and pruritus resulted from deposition of Ca²⁺-phosphate salts in soft tissues and skin (i.e., the complexation of Ca²⁺ and phosphate already mentioned). Treatment includes attempting to limit the increase in blood phosphate by dietary phosphate restriction or phosphate-binding in the intestine, administration of synthetic 1,25-dihydroxycholecalciferol to replace what the kidneys fail to produce, and, if necessary, a parathyroidectomy.

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