The secret life of parathyroid-hormone

by Alex Goodell | View online

Parathyroid glands

The parathyroids! We have four of them, in the back of he thyroid, normally embedded within the capsule of the thyroid. They are tiny — about 3x6mm each — and weigh a total of 400mg! Around each of the parathyroids is a capsule. Within the capsule are fibrous septa which separate many small glands made of secretory cells. There are two types of cells contained within these lobes:

- The **chief cells** (also called **principal cells**) are pale-staining small cells which secrete parathyroid hormone. On electron microscopy, you can see little secretory granules floating in the cytoplasm (not shown here). These cells release PTH directly into the blood.
- *Oxyphil* cells are found to a much lesser extent, and secrete a lower level of PTH. They have odd-shaped nuclei, stain pink, and are found more often in older individuals.

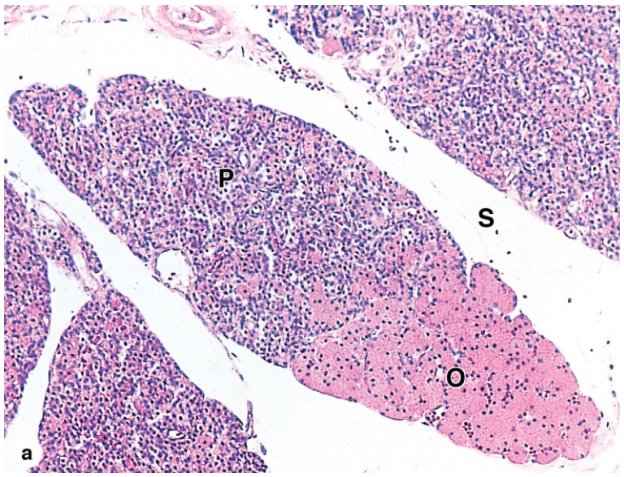

Figure 1. Histological image of the parathyroids

We are done! That was fast. Now on to PTH.

Release of parathyroid hormone (PTH)

PTH is a 84-amino-acid-long polypeptide that is mostly involved in calcium and potassium homeostasis. PTH is released when free, unbound **calcium** levels are **low**. Approximately 40% of serum calcium is ionized (free), while the other 60% is complexed, primarily to albumin. Changes in albumin concentration (from, e.g. liver disease) will affect the amount of total calcium, but will not affect the free calcium. Like all feedback mechanisms, PTH is responsive only to free, unbound calcium. Therefore, changes in albumin levels will not affect PTH!

Changes in free calcium levels are sensed by a Gq-linked extracellular Ca2+ receptor on the chief cells, and PTH is released from its secretory granules.

In addition, PTH is released in the setting of **high phosphate** or **low magnesium**.

Actions of PTH

Once the 84-amino-acid-long peptide is released into the blood stream, it has a very short half life of four minutes. It is quickly broken into two products: a N-terminal 34-amino acid segment called (1-34)-PTH, and a largely inactive C-terminal segment. This 1-34 PTH acts primarily on the **bone, kidney, and intestine** to increase calcium concentration and decrease phosphate concentration.

PTH IN THE BONE

PTH receptors are found primarily on **osteoblasts**, a bit on osteocytes, and not at all on osteoclasts. The actions of PTH on the bone come in two stages:

1. In the beginning, PTH paradoxically **promotes bone growth**, by acting on osteocytes. This only occurs during the beginning of having an elevated PTH. 1-34 PTH can thus be used intermittently for osteoperosis.

2. With continued use, PTH **promotes bone resorption**. Remember: it doesn't act directly on osteoclasts. Instead, it binds to osteoblasts and induces them to:

    - Secrete macrophage **colony stimulating factor** (M-CSF). Since osteoclasts are in the macrophage/monocyte lineage, M-CSF can exert local (paracrine) effects and trigger local proliferation of osteoclasts. This increase in osteoclasts will promote bone resorption (breaking down of bone and release of its minerals). This will increase calcium levels.

    - Secrete **RANK ligand** (aka RANKL), a cytokine. This will bind to the RANK receptor on local osteoclasts and their precursors, and stimulate them mature and to resorb bone. This will increase calcium levels. Note: **denosumab** is a monoclonal antibody that targets RANK ligand, and is used for the treatment of osteoporosis.

Additionally, it is important to understand that there is a counterpart to RANK ligand, called **osteoprotegerin** (OPG), which is also released by the osteoblasts and acts on osteoclasts, but it inhibits bone resorption. Glucocorticoids act to increase the level of RANK ligand and decrease the level of osteoprotegerin secreted by osteoblasts.

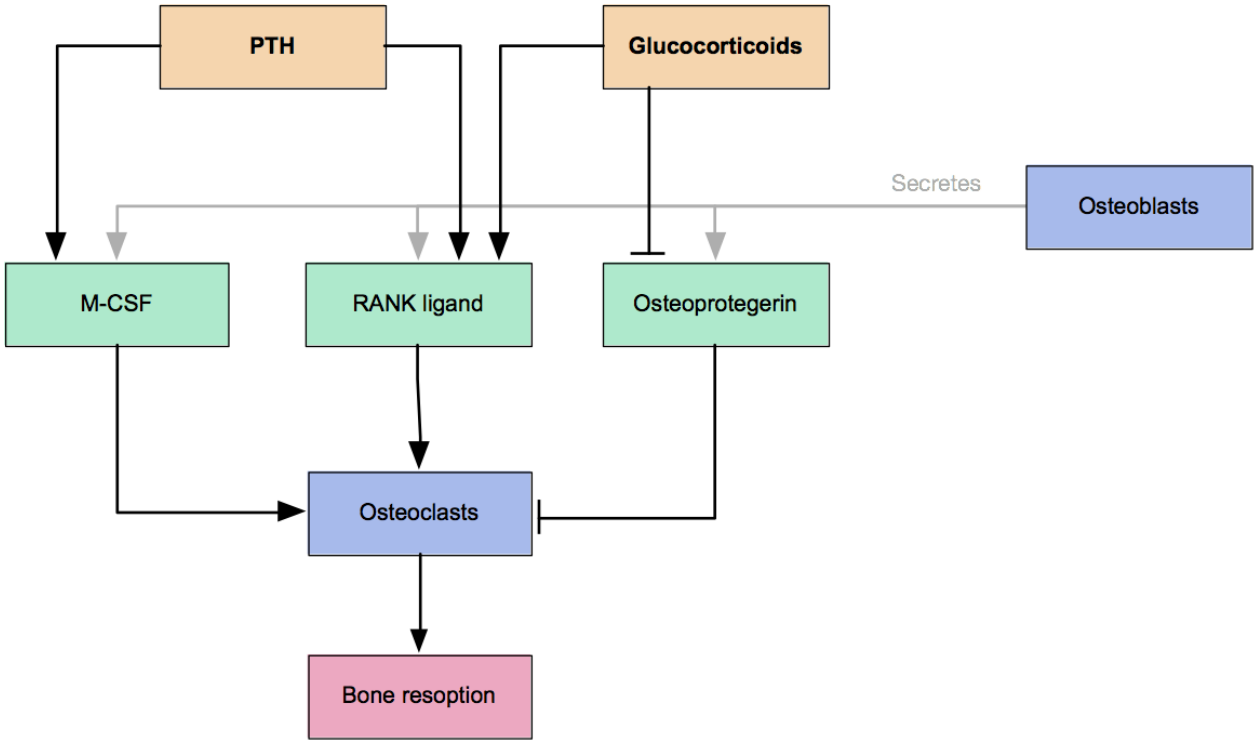

Figure 2. Flowchart showing the actions of PTH on bone

Ok, now we've run into a problem. PTH resorbed a bunch of bone, putting lots of Ca2+ and phosphate into the serum. These two minerals are what make up bone, and if we keep both of these in the blood at high levels, they will precipitate and start making little bony deposits all around our body (aka **pathologic calcification**). For this reason, when PTH resorbs bone, it must also quickly increase the phosphate excretion from the kidneys. Let's take a look.

PTH IN THE KIDNEY

The role of PTH in the kidney is to (1) decrease phosphate reabsorption, (2) increase calcium reabsorption, and (3) stimulate activation of vitamin D:

1. PTH **inhibits phosphate reabsorption** by binding to Gs-linked receptor on the epithelial cells of the proximal convoluted tubule. The PCT is the primary place where phosphate reabsorption occurs, this has a major effect. One bound to the receptor PTH (like all Gs systems) increases the level of cAMP, which activates a series of protein kinases, results in the **inactivation of a sodium-phosphate co-transporter**. Interesting aside - I didn't know this, but the proximal tubule has a transporter for cAMP on it's lumen. During periods of increased PTH, you will actually see an elevated level of **urinary cAMP**.

2. PTH also **increases calcium reabsorption** in the distal tubule. Most of our ~250 mmol of calcium filtered each day is reabsorbed in the proximal tubule (~65%) and thick ascending limb (~25%). The distal tubules are absorb an additional **5% to 10%**, with ~0.5% remaining in the urine. Since PTH acts at the distal tubule, it has a much more *gradual* effect on calcium reabsorption. Similarly to phosphate, it works through a Gs-linked system, but acts on a sodium-calcium co-transporter. Another interesting

aside: throughout the nephron, calcium is reabsorbed with sodium, especially in the loop of Henle. The distal tubules are the exception; here, calcium reabsorption is unlinked to sodium reabsorption. The take away from this: loop diuretics can cause hypocalcemia, while thiazides lead to *hypercalcemia*.

3. Lastly, PTH works in the kidney **activate vitamin D**. In particular, it activates 1a-hydroxylase to convert 25-hydroxycholecalciferol to the active form, 1,25-dihydroxycholecalciferol.

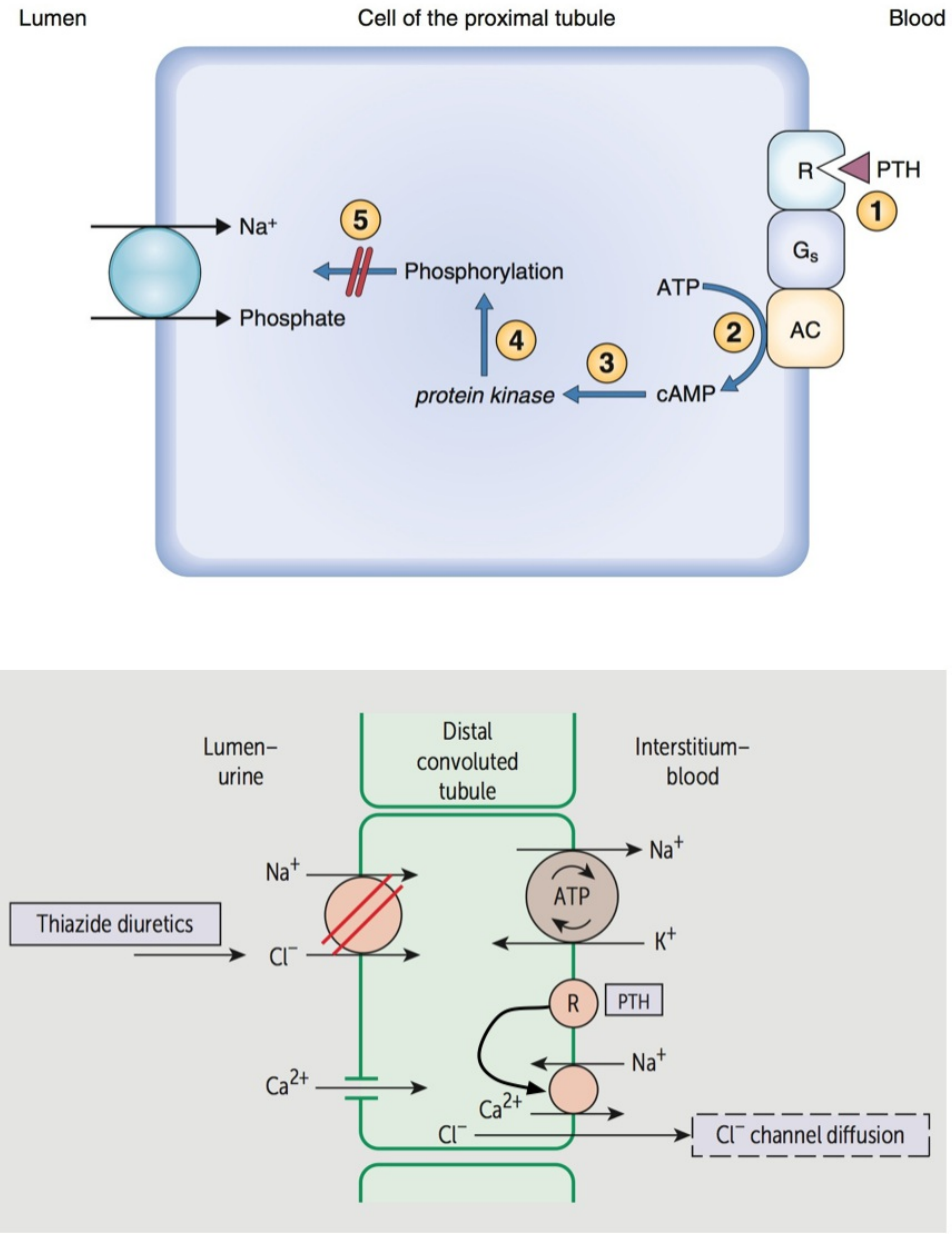

Figure 3. Diagram showing the inhibition of phospate absorbption and increase in calcium reabsorption

PTH IN THE INTESTINE

The actions of PTH in the intestine aren't very special: essentially, since it has activated vitamin D, vitamin D now works to increase absorption of calcium. It does this by inducing the synthesis of a vitamin D–

dependent Ca-binding protein called **calbindin D-28 K**. This protein can bind four calcium ions, and allows for more absorption of calcium. Entry into the cell is by simple gradient diffusion (1), where it binds to calbindin D-28 K (2). Then transport of Ca2+ into the lumen occurs with an ATPase (3).

To a less extent, vitamin D also increases absorption of phosphate, though an unclear mechanism.

Since we're here, I thought it would be useful to review the effects of vitamin D in the kidney and bone as well. The kidney: As opposed to PTH which increased absorption of calcium and decreases absorption of phosphate, vitamin D stimulates the reabsorption of both calcium and phosphate. In the bone, vitamin D stimulate both resorption and mineralization, but with a net effect of increasing mineralization. The idea is: you have to break down bone to build bone. Emma will likely touch on this more.

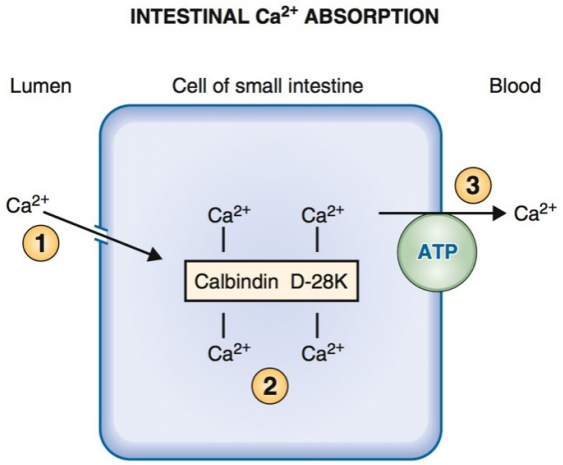

Figure 4. Calcium in the intestine

Now that we've looked at the anatomy and physiology of PTH, let's take a look at some pathology that might occur.

Hyperparathyroidism

There are three types of hyperparathyroidism: primary, secondary, and tertiary. Let's look at them each stepwise.

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is most communally caused by a adenoma in the parathyroid that secretes high amounts of PTH. Based on what we just learned, it is easy to predict the lab findings of this condition:

- **Hypercalciumia** (↑ bone resorption and renal reabsorption)
- **Hypophosphatemia** and **phosphaturia** (↓ renal reabsorption)
- **Hypercalciuria** (we overwhelmed the reabsorptive capacity of nephron)
- ↑ **Alkaline phosphatase** (AlkPhos is used in bone remodeling and is often elevated in a range of bone disorders; bone need an alkaline environment to remodel).

Clinically, these patients present with the H&P findings from hypercalcemia. Although some of these

symptoms are difficult to intuit, I will attempt to provide an explanation:

- **Weakness** and **constipation** ("groans") - as a general principle, high calcium raises the threshold potential of neurons/muscles, making them less excitable. This creates muscle weakness (including the smooth muscles of the gut, leading to constipation.)
- Pain in **bones** ("bones") - This makes sense since bones are being broken down!
- Flank pain from **kidney stones** ("stones") - 80% of kidney stones are calcium, so this makes sense as well.
- **Polyuria** (porcelain "thrones") - As calcium rises, kidney will locally * decrease action of NKCC pump to avoid absorbing more calcium… essentially, the body's own loop diuretic.
- **Depression** ("psychiatric overtones") - Fits with the general principle of raising threshold potential, decreasing excitability

SECONDARY HYPERPARATHYROIDISM AND RENAL OSTEODYSTROPHY

Secondary hyperparathyroidism is caused not by a primary tumor, but any condition that causes hyperparathyroidism secondary to **chronic hypocalcemia** or hyperphosphotemia, such as vitamin D deficiency. In this condition, we would expect to find a high circulating level of PTH, with a simultaneous low serum calcium. In addition, we would expect to find hypophosphotemia, due to the actions of PTH. Because of bone remodeling, you could also expect a ↑ AlkPhos.

One particularly potent example of secondary hyperparathyroidism is **renal osteodystrophy**. Renal osteodystrophy refers to the dysregulation of calcium and phosphate during kidney failure. It is also called *chronic kidney disease-mineral and bone disorder*. It is fairly complicated, and probably the most common and serious example of secondary hyperparathyroidism we will see in our careers, so lets take a closer look:

In end-stage renal disease, we have a low GFR and are having problems excreting most of our minerals. In particular, **phosphate** is one mineral which builds up. In addition, since vitamin D is activated in the kidneys and out kidneys are failing, we are unable to activate sufficient levels of vitamin D. This leads to a **low serum calcium**. The low calcium and high phosphate activate the secretion of PTH. PTH attempts to correct the low calcium and high phosphate, but is unable to compensate because two of its main forms of compensation are compromised due to kidney failure. Note that in kidney failure, there is an *elevated* phosphate, while in other forms of secondary hyperparathyoidism, such as simple vitamin D deficiency, we would expect a *depressed* phosphate.

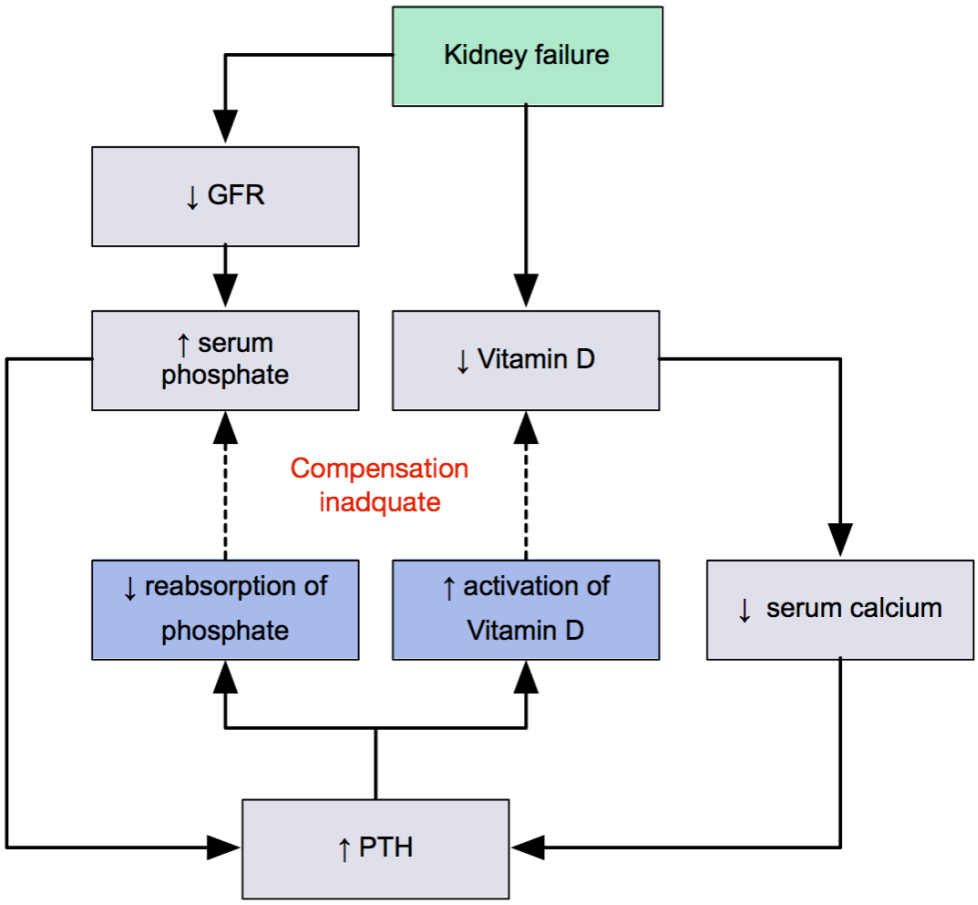

Figure 5. Flowchart showing the effects of renal osteodystrophy

TERTIARY HYPERPARATHYROIDISM

Tertiary hyperparathyroidism is an confusing term to me - but it refers to the idea that a hyperactive parathyroid sometimes won't turn off once the stimulus for secondary hyperparathyroidism is corrected. This may happen in the context of someone who had hyperparathyroidism secondary to renal failure and underwent a kidney transplant, and continued to secrete excess levels of PTH after the transplant. Parathyroidectomy may be necessary, according to Robbins.

One serious complication of any form of hyperarathyroidism is called osteitis fibrosa cystic. In this disease, there is significant damage to an area of the bone through osteoclastic activity that a cystic bone space forms. Hemorrhaging into this bone space eventually deposits iron in the form of hemosiderin, causing what are referred to as brown tumors. You can see two in the hand below.

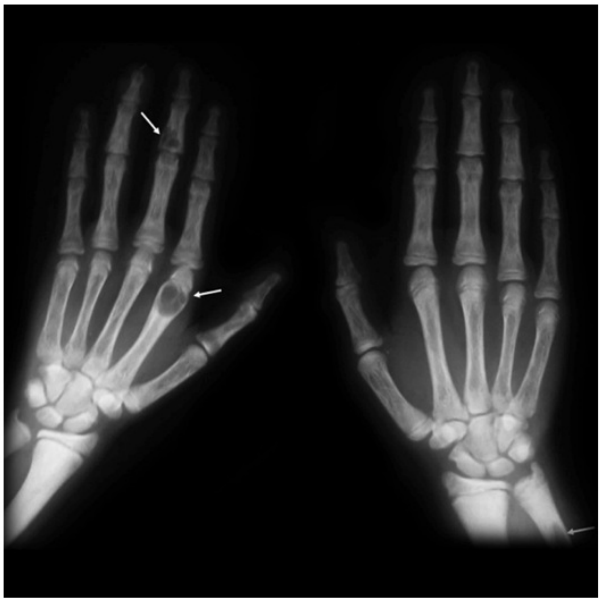

Figure 5. Radiograph of a brown tumor

OTHER DIFFERENTIALS FOR HYPERCALCEMIA

When you see hypercalcemia, think about a few things:

- Hyperparathyroidism—Understandable.
- Renal failure — I thought we had hypocalcemia is renal failure? Turns out we can have either. From StepUpToMedicine: "RF usually results in hypocalcemia, but sometimes secondary hyperparathyroidism elevates PTH levels high enough to cause hypercalcemia"
- Malignancy - there are two mechanisms by which cancers cause hypercalcemia:
    - The most common mechanism (80%) is the one neoplastic one discussed by Liz: secretion of PTH-related peptide (PTHrP). PTHrP is almost the same as PTHrP, and binds to all the same receptors; however, it does not activate the conversion of vitamin D in the kidney, so lacks the intestinal absorptive effects.
    - Cancers can also directly metastasize to the bone, and stimulate osteoblastic/osteoclastic activity there. Multiple myeloma is well known for its lysis of bone by tumor cells and activation of osteoclasts by myelmoa cells. These produce lytic bone lesions.
- Other diagnoses to consider: Paget's disease of the bone, acromegaly, Addison's disease, thiazides, Vitamin D intoxication, sarcoidosis