Hormonal control of calcium metabolism Part II

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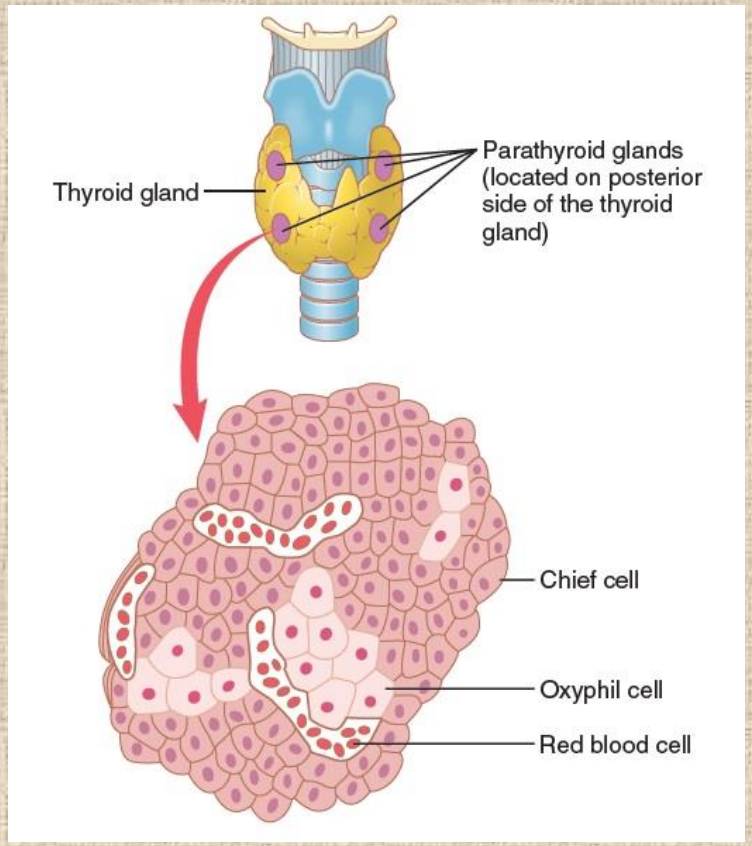
Lecture objectives:

- List the major physiological effects of PTH
- Explain the regulation of PTH secretion
- List the major physiological actions of calcitonin
- Illustrate the regulation of calcitonin secretion
- Compare between PTH and calcitonin as regulators of calcium levels

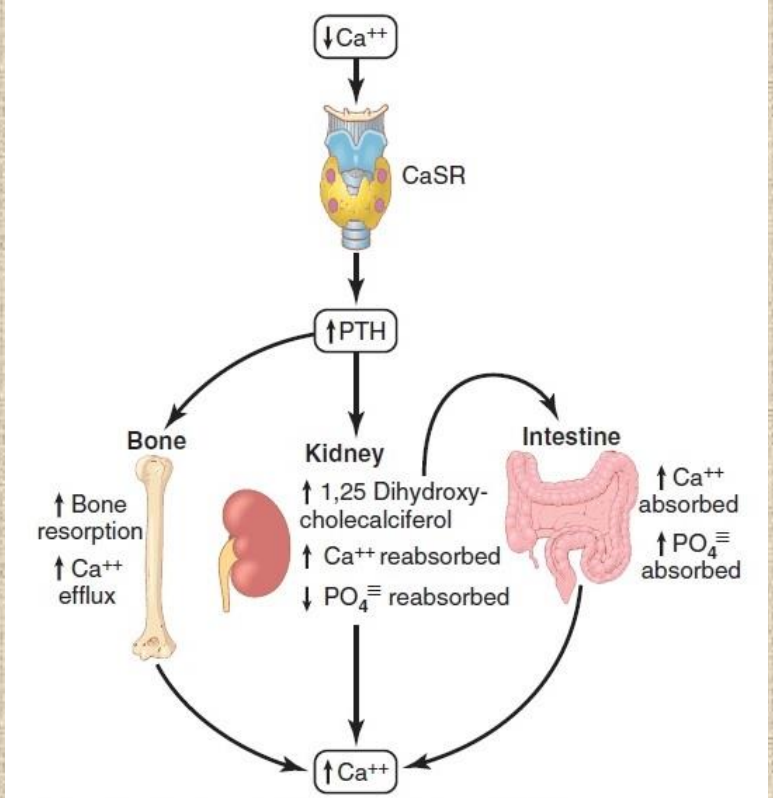
Parathyroid Hormone (PTH) Physiology

- Humans have **four** parathyroid glands, which are located immediately behind the thyroid gland - one behind each of the upper and each of the lower poles of the thyroid gland.
- Unlike the thyroid gland, the parathyroid glands are not under the control of the pituitary gland.
- Removal of half the parathyroid glands usually causes no major physiological abnormalities. Removal of three of the four normal glands causes transient hypoparathyroidism, but even a small quantity of remaining parathyroid tissue is usually capable of hypertrophying to satisfactorily perform the function of all the glands.
- The chief cells of the parathyroid glands are believed to secrete most, if not all, of the PTH.
- Mature and intact PTH is a polypeptide consists of 84 amino acids. PTH synthesis and release is continuous, with about 6–7 superimposed pulses each hour. PTH is degraded by the kidney and the liver to amino-terminal (10%) and carboxy-terminal fragments (80%). The amino-terminal fragments are the **biologically active form** of the PTH but have a short half-life (4–20 minutes). **Note:** intact plasma PTH levels is 10-65 pg/ml.



Parathyroid Hormone (PTH) Physiology (cont.)

- PTH has 3 major actions; on the bones, on the kidneys, and on the gut.
- PTH causes immediate rapid absorption of Ca and phosphate salts from bones (**osteolysis**) and induces **hypercalcemia**, whereas, it causes reduction in phosphate concentration (**hypophosphatemia**). This effect is because PTH decreases the excretion of Ca by the kidneys.
- The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.
- PTH has two effects to mobilize calcium and phosphate from bone. One is a rapid phase (begins in minutes). The second phase is a much slower one that requiring several days or even weeks to become fully developed.

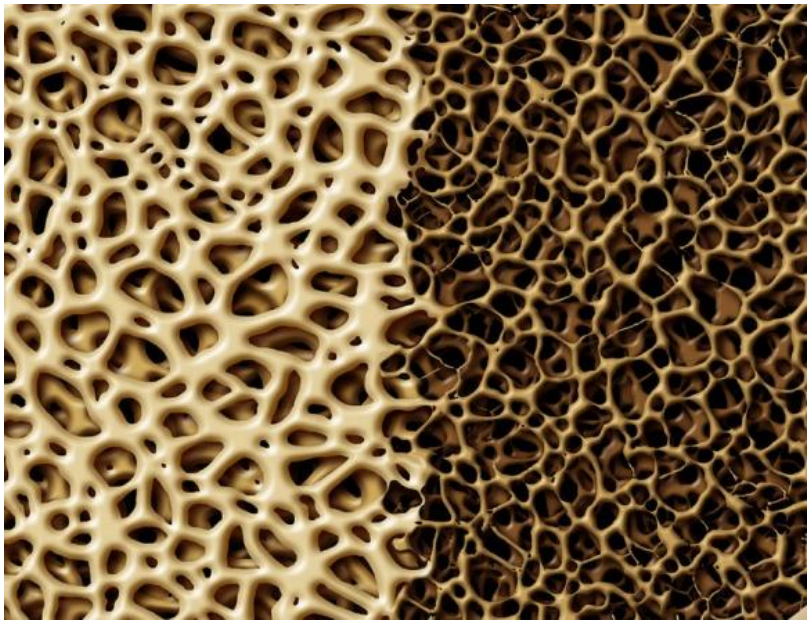


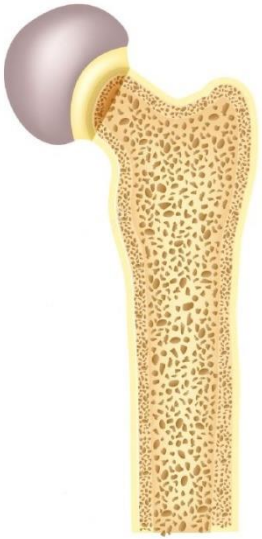
Summary of effects of parathyroid hormone *(PTH)* on bone, the kidneys, and the intestine in response to decreased extracellular fluid calcium ion concentration. CaSR, calcium-sensing receptor.

Parathyroid Hormone (PTH) Physiology (cont.)

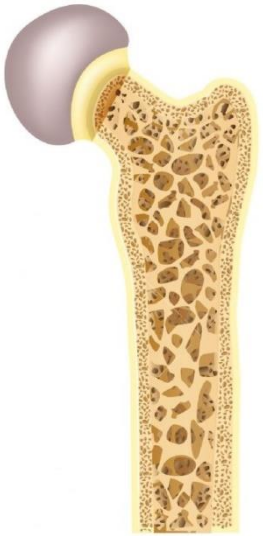
- In the rapid phase PTH causes removal of bone salts from two areas in the bone from the bone matrix in the vicinity of the osteocytes lying within the bone and in the vicinity of the osteoblasts along the bone surface → early ***osteolysis***.
- In the slow phase the prolonged effect of PTH is mediated through its (indirect) activation and proliferation of **osteoclasts**. Mature osteoclasts have no receptors for PTH; activation and proliferation appear to be stimulated by cytokines released by activated **osteoblasts** and **osteocytes** or by differentiation of immature osteoclast precursors that possess PTH and vitamin D receptors → advanced osteolysis with active resorption of bone's fibrous and gel matrix.
- Prolonged secretion of PTH (months) → weak bones → spontaneous fracture.
- Other hormones that affect bones and their Ca content are:
  - Estrogens: promote bone growth. When estrogens are reduced at menopause, ***osteoporosis*** is accelerated (loss of bone mass caused by a deficiency in calcium, vitamin D, magnesium and other vitamins and minerals)
  - Testosterone: stimulates bone and cartilage growth
  - Growth hormone: promotes bone and cartilage growth and increases intestinal absorption of Ca

OSTEOPOROSIS





Normal Bone



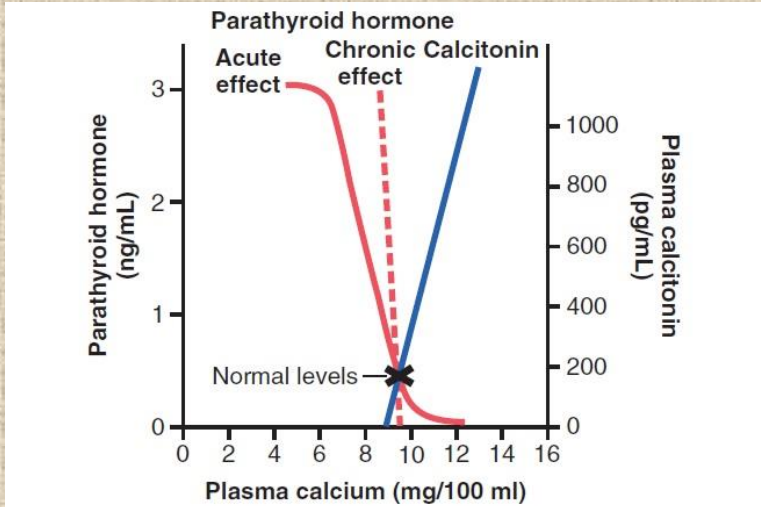
Bone with Osteoporosis

Parathyroid Hormone (PTH) Physiology (cont.)

- On the kidneys, PTH diminishes proximal tubular reabsorption of phosphate ions (i.e. increases phosphate excretion) by decreasing the expression of the type II Na^{+}/PO_4^{2-} cotransporter.
- It also increases reabsorption of Ca mainly in the late distal tubule, collecting tubules, early collecting ducts, and possibly the ascending loop of Henle to a lesser extent. However, the net result is an increase in Ca loss by the kidneys (renal calcium resorption) that would eventually deplete both the extracellular fluid and the bones of Ca.
- PTH enhances Ca and phosphate absorption from the intestine by increasing the formation of 1,25-dihydroxycholecalciferol from vitamin D by activation of the enzyme 1-hydroxylase in the proximal tubules of the kidneys.

Regulation of PTH secretion

- PTH secretion by parathyroid glands is regulated by the free level of Ca ions in the blood. Decreased Ca concentration in extracellular fluid → ↑ PTH secretion and vice versa. Although not well elucidated, 1,25-dihydroxycholecalciferol appears to exert a mild inhibitory effect on the parathyroid gland as well. Chronic depression of plasma Ca levels → parathyroid glands hypertrophy such as in **Rickets**, pregnancy, and lactation.
- Changes in extracellular fluid Ca ion concentration are detected by a ***calcium-sensing receptor (G protein–coupled receptor)*** on parathyroid chief cell membranes; it is also found in kidney tubule cells and thyroid C cells. Stimulation of these receptors →↑ intracellular inositol 1,4,5-triphosphate and diacylglycerol formation →↓ PTH secretion.
- Vitamin D [1,25$(OH)_2$D] inhibits PTH release by decreasing PTH gene expression.

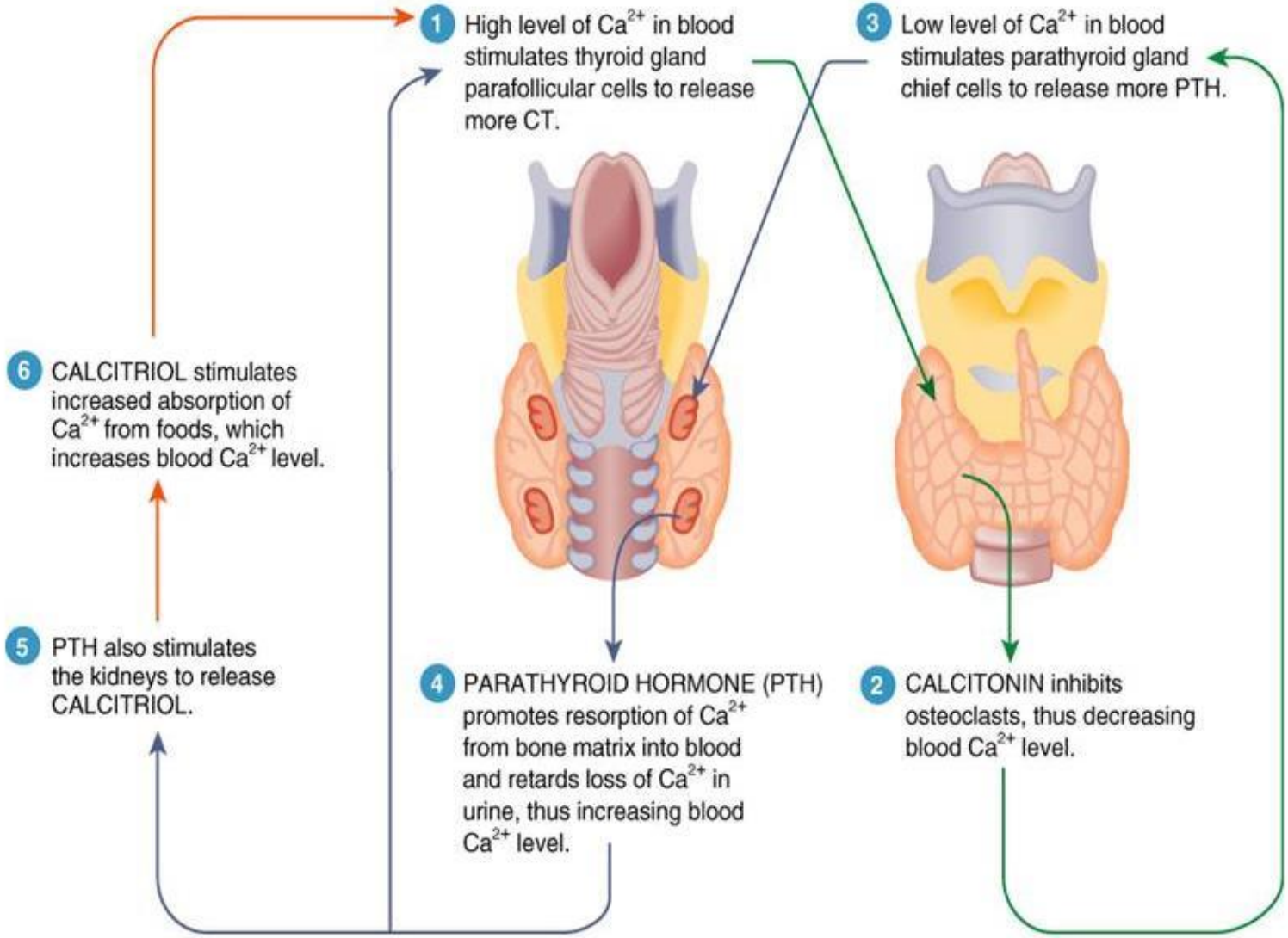


The approximate effect of plasma calcium concentration on the plasma concentrations of parathyroid hormone and calcitonin. Note especially that long-term changes in calcium concentration of only a few percentage points can cause as much as 100 percent change in parathyroid hormone concentration.

Vitamin D deficiency rickets

Calcitonin

- Calcitonin is the third hormone involved in calcium homeostasis, although to a lesser extent than PTH and vitamin D.
- It is a 32 amino acid peptide hormone secreted by the thyroid gland from C cells or parafollicular cells. These cells constitute only about 0.1% of the human thyroid gland.
- The main physiologic function of calcitonin is to **decrease plasma Ca^{2+}** and phosphate concentrations, mainly by decreasing bone resorption. This effect is opposite to that of PTH (Stimulates osteoblasts, inhibits osteoclasts). However, in the adult human PTH effect overrides that of calcitonin.
- The release of calcitonin is regulated by plasma calcium levels through a Ca^{2+} receptor on the parafollicular cells. Elevations in plasma Ca^{2+} **higher than 9 mg/dl** stimulate the release of calcitonin. In contrast, PTH secretion is stimulated by decreased calcium concentration.
- The role of calcitonin is to cause removal of Ca from serum to calcify new bone. This role is greater in children because of the rapid bone remodeling.
- Calcitonin has minor effects on calcium handling in the kidney tubules and the intestines.
- Calcitonin has been used therapeutically for the prevention of bone loss and for the short-term treatment of hypercalcemia of malignancy.
- The ability of calcitonin to inhibit osteoclast-mediated bone resorption has made it a useful agent for the treatment of osteoporosis; it also relieves pain in osteoporotic patients with vertebral crush fractures.


1 High level of Ca^{2+} in blood stimulates thyroid gland parafollicular cells to release more CT.
3 Low level of Ca^{2+} in blood stimulates parathyroid gland chief cells to release more PTH.
6 CALCITRIOL stimulates increased absorption of Ca^{2+} from foods, which increases blood Ca^{2+} level.
5 PTH also stimulates the kidneys to release CALCITRIOL.
4 PARATHYROID HORMONE (PTH) promotes resorption of Ca^{2+} from bone matrix into blood and retards loss of Ca^{2+} in urine, thus increasing blood Ca^{2+} level.
2 CALCITONIN inhibits osteoclasts, thus decreasing blood Ca^{2+} level.

Major Ca regulatory hormones

	Production	**Function**
Parathyroid hormone	Made by parathyroid glands (4 bodies imbedded in the thyroid gland). A peptide with 84 amino acids. Approximate half life is 10 minutes	Raises blood Ca. Reduces kidney excretion, raises intestinal absorption and releases bone Ca into blood
Vitamin D (Cholecalciferol, Calcitriol)	Made in steps by 3 different organs: skin, liver, kidney	Raises blood Ca. Promotes intestinal absorption of Ca
Calcitonin	Made by C cells of thyroid gland. A 32 amino acid peptide. Half life is approximately 5 minutes	Reduces blood Ca. Inhibits bone resorption by reducing osteoclasts

Test Question

After prolonged exercise on a hot summer day, a 43-year-old male is admitted to the emergency room for severe pain in his left flank, radiating to the groin. Urine examination reveals blood in the urine. He is hydrated, and additional diagnostic procedures are done. Laboratory values show serum Ca^{2+} of 12 mg/dl, and PTH values of 130 pg/ml. the mechanism underlying the abnormalities observed is:

A. Increased calcitonin release
B. Decreased 25-hydroxylase activity
C. Increased osteoclast apoptosis
D. Loss of negative feedback regulation of PTH release
E. Decreased urinary Ca excretion