The Endocrine Physiology

Calcium Homeostasis

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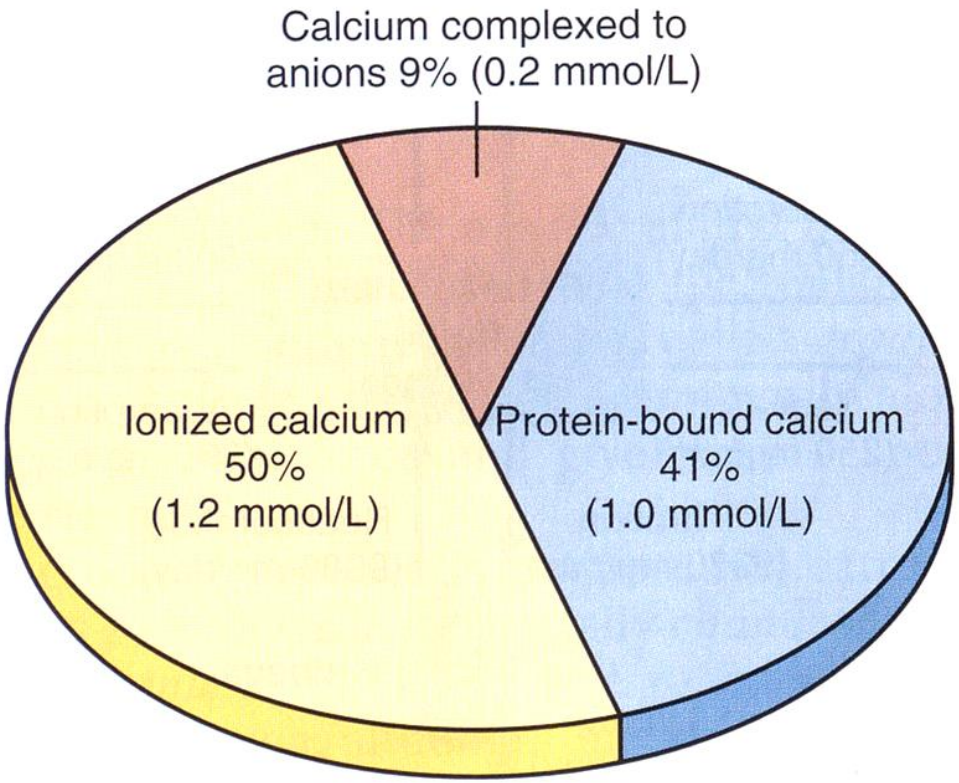
1. Identify the normal range of dietary calcium intake, calcium distribution in the body, and routes of calcium excretion.
2. Identify the normal range of dietary phosphate intake, phosphate distribution in the body, and routes of phosphate excretion.
3. Know the cells of origin for parathyroid hormone,
4. List the target organs and cell types for parathyroid hormone and describe its effects on each.
5. Describe the functions of the osteoblasts and the osteoclasts in bone remodeling.
6. Describe the regulation of parathyroid hormone secretion and the role of the calcium-sensing receptor.

1. Understand the causes and consequences of a) over-secretion, and b) under-secretion of parathyroid hormone, as well as its therapeutic use.
2. Describe the normal function of parathyroid hormone related protein (PTHrP) and its role as a marker for some cancers.
3. Identify the sources of vitamin D and diagram the biosynthetic pathway and the organs involved in modifying it to the biologically active 1,25(OH2)D3 (1-25 dihydroxycholecalciferol).
4. Identify the target organs and cellular mechanisms of action for vitamin D.
5. Describe the negative feedback relationship between parathyroid hormone and the biologically active form of vitamin D [1,25(OH2)D3].
6. Describe the consequences of vitamin D deficiency and vitamin D excess.
7. Name the stimuli that can promote secretion of calcitonin, its actions, and identify which (if any) are physiologically important.

Plasma Calcium

- Plasma calcium totals 2.4 mM (9.4 mg/dl)
  - Ionized calcium is 1.2 mM (50% of total calcium), it is the physiologically active form.
  - 41% protein-bound, 9% complexed to anions



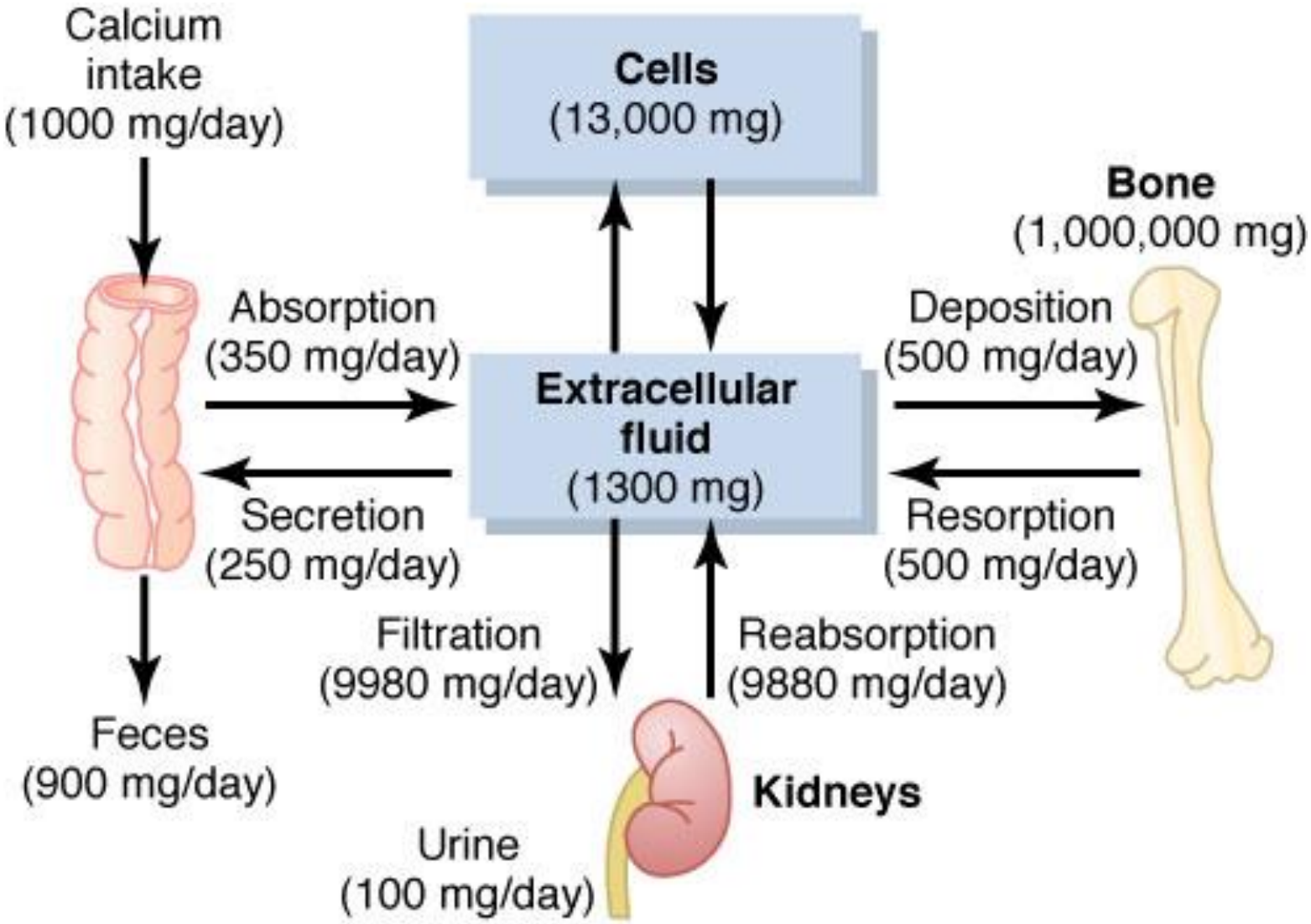
Phosphate

- Approximately 85 % of the body's phosphate is stored in bones,
- 14-15 % is in the cells,
- Less than 1% is in the extracellular fluid.
- Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.

Plasma Calcium Regulation

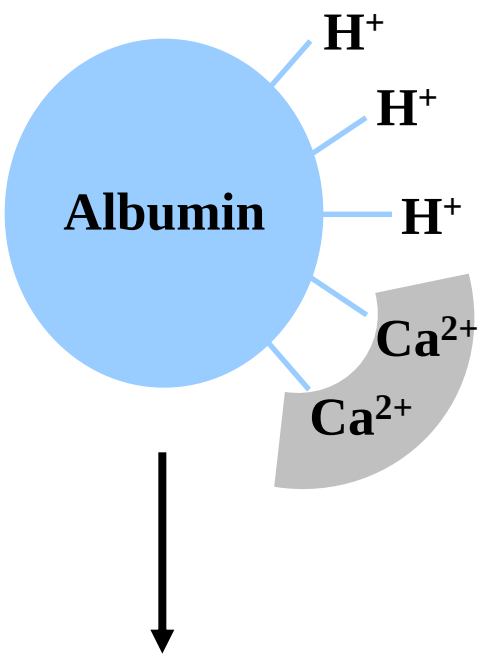
- Free calcium is tightly regulated (±5%)
  - Too low = neuronal hyper-excitability
  - Too high = neuronal depression
- Control points for calcium
  - Absorption – Via intestines
  - Excretion – Via urine
  - Temporary storage – Via bones

Calcium Metabolism



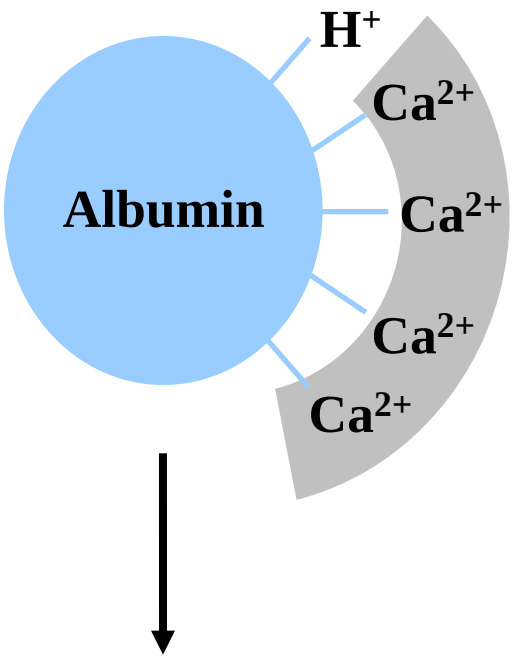
Effects of Acid-Base Disturbances on Ionized Calcium

Acidemia



↑ Ionized [Ca^{2+}]

Alkalemia



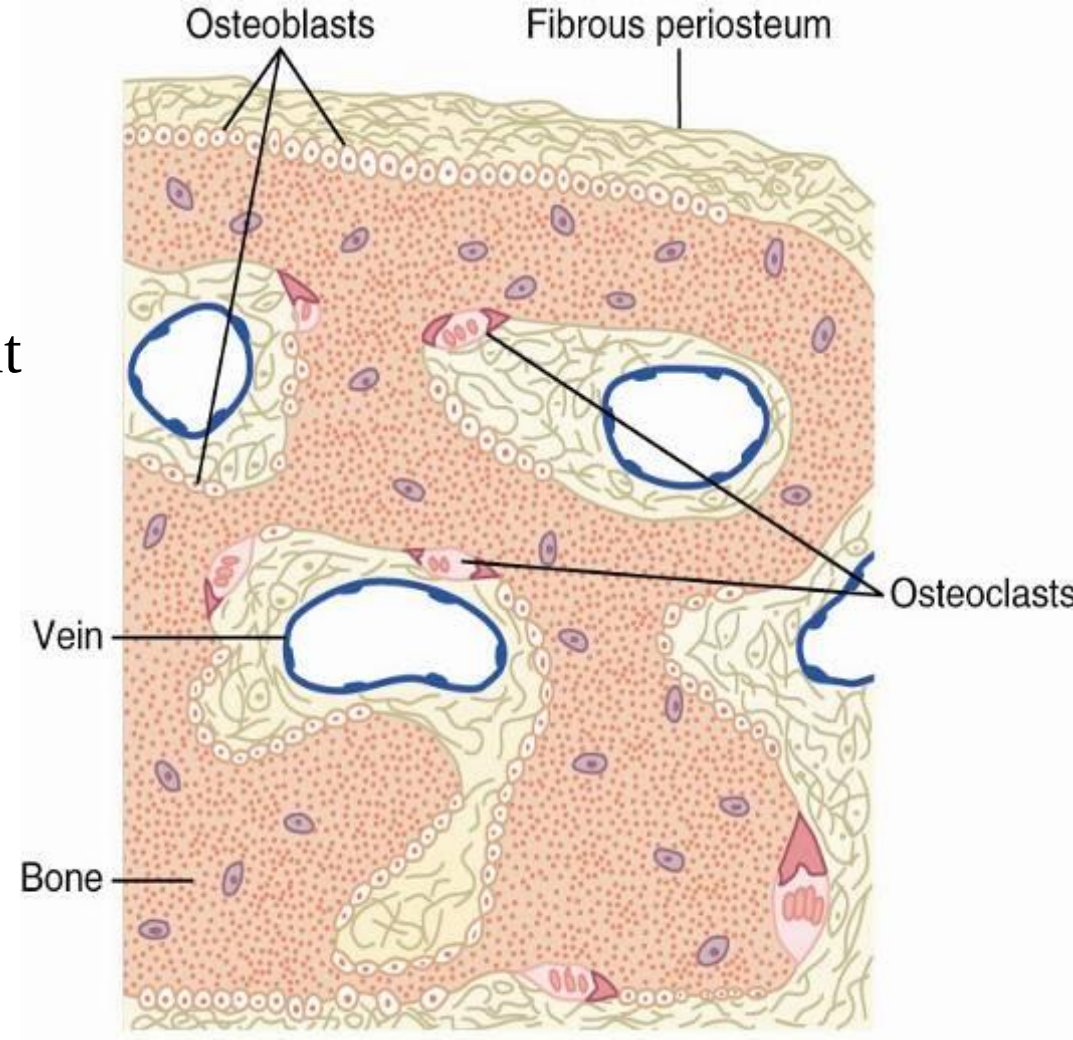
↓ Ionized [Ca^{2+}]

Hormonal Control of Calcium

- Vitamin D3
  - Diet and sun
- Parathyroid hormone
  - Parathyroid gland
- Calcitonin
  - Thyroid gland

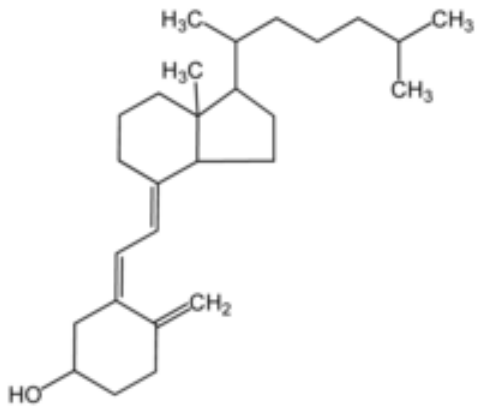
Remodeling of Bone

Bone is continually being deposited by *osteoblasts*, and it is continually being resorbed where *osteoclasts* are active

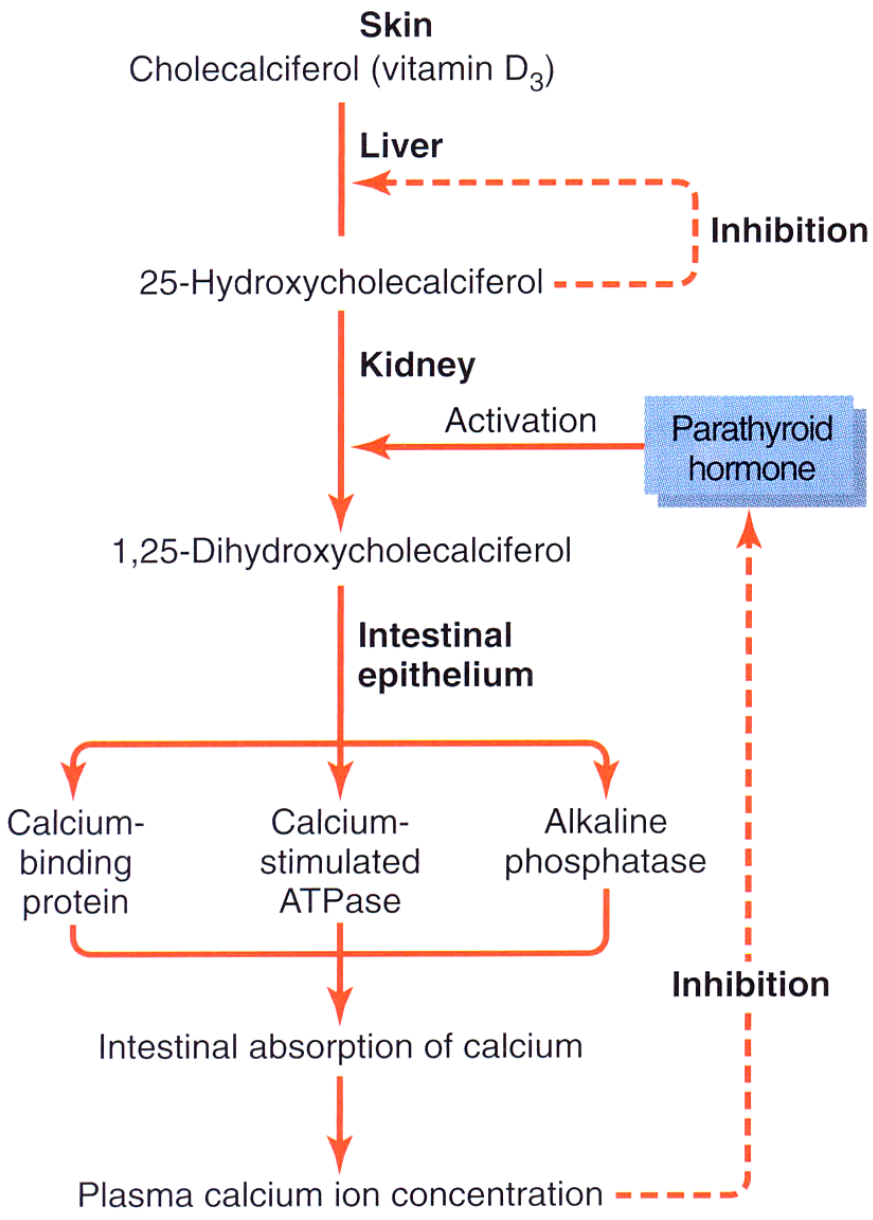


Vitamin D3 and Calcium Control

- Vitamin D3 (Cholecalciferol) is formed in the skin from (7-dehydrocholesterol)
  - Stored in the liver
  - Converted to in the liver to 25-Hydroxycholecalciferol
  - Feedback control limits concentration
- Converted to active form in kidney
  - 1,25-Dihydroxycholecalciferol (calcitriol)
  - Under the feedback control of parathyroid hormone (PTH)



Activation of Vitamin D3



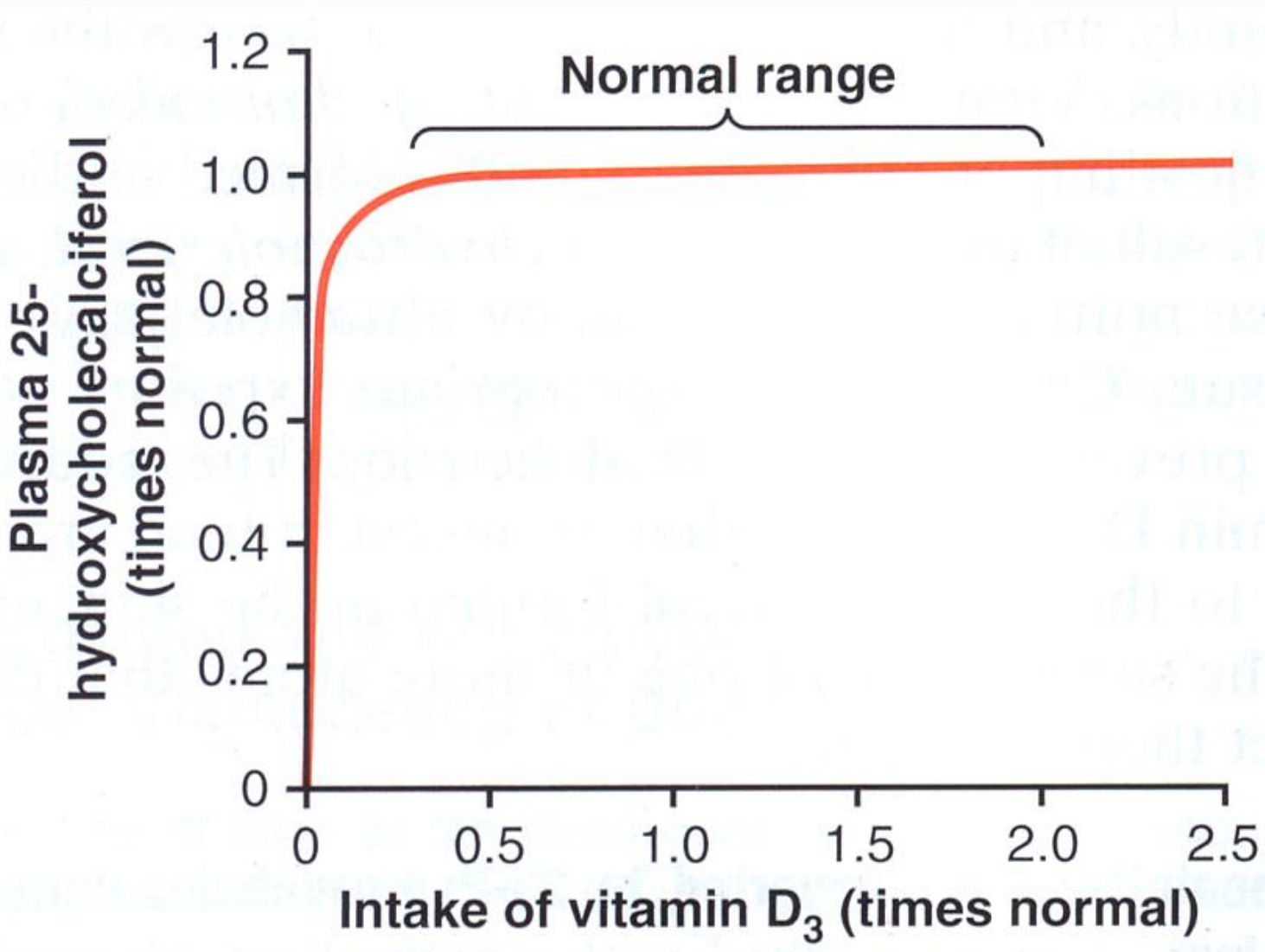
Effects of Active Form of Vit D3

- Promotes intestinal absorption of calcium and phosphates
- Causes synthesis of calcium-binding protein and related facilitated transport
- Takes a couple of days to fully develop response
- Has slight effect to increase calcium re-absorption in kidneys
- Works with PTH to cause calcium absorption from bone

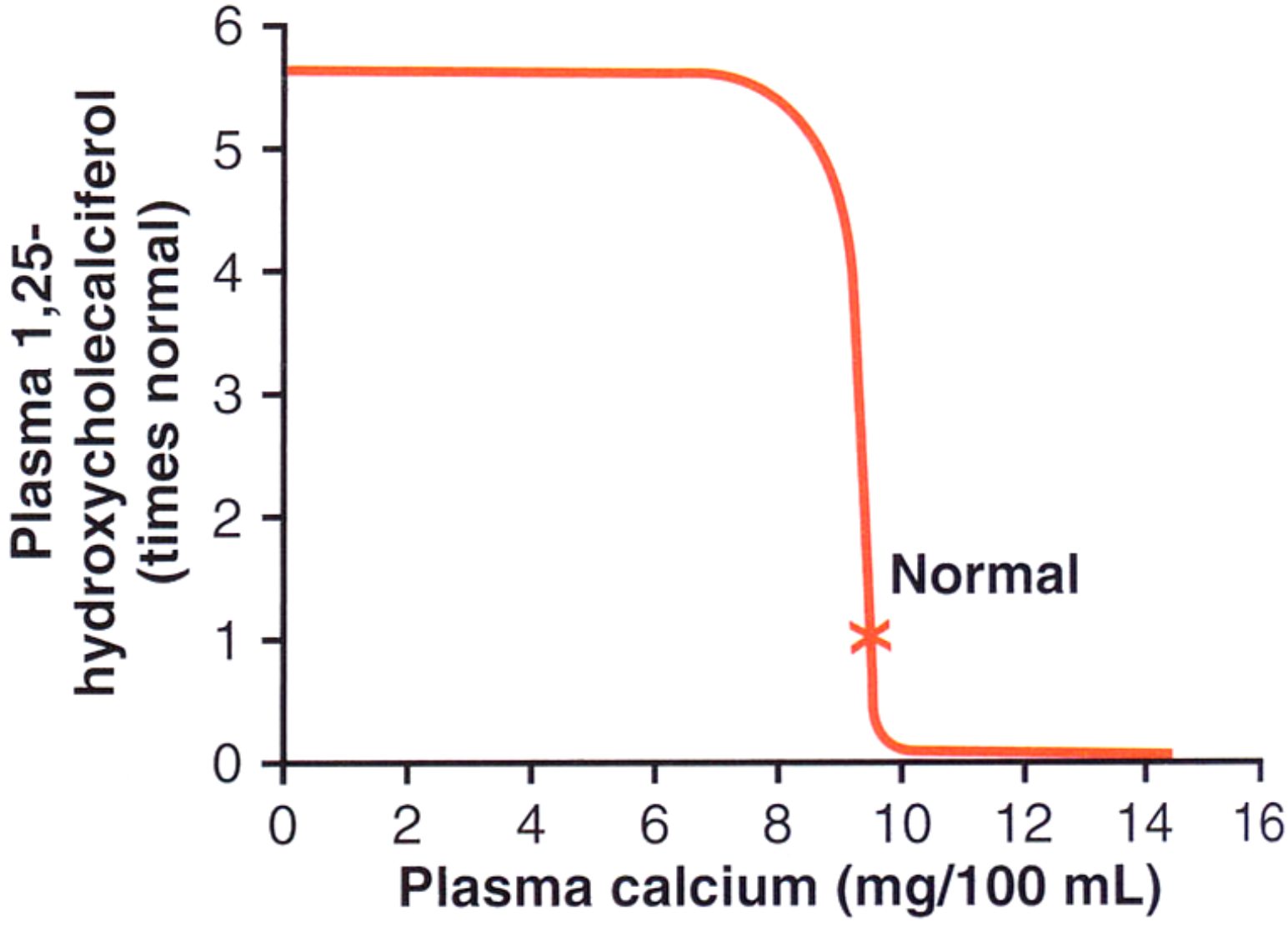
Vitamin D Actions

- **Intestine**
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption
- **Bone**
  - ↑ mineralization
  - ↑ bone resorption
- **Kidney**
  - ↑ Ca^{2+} reabsorption (weak effect)
  - ↑ phosphate reabsorption (weak effect)

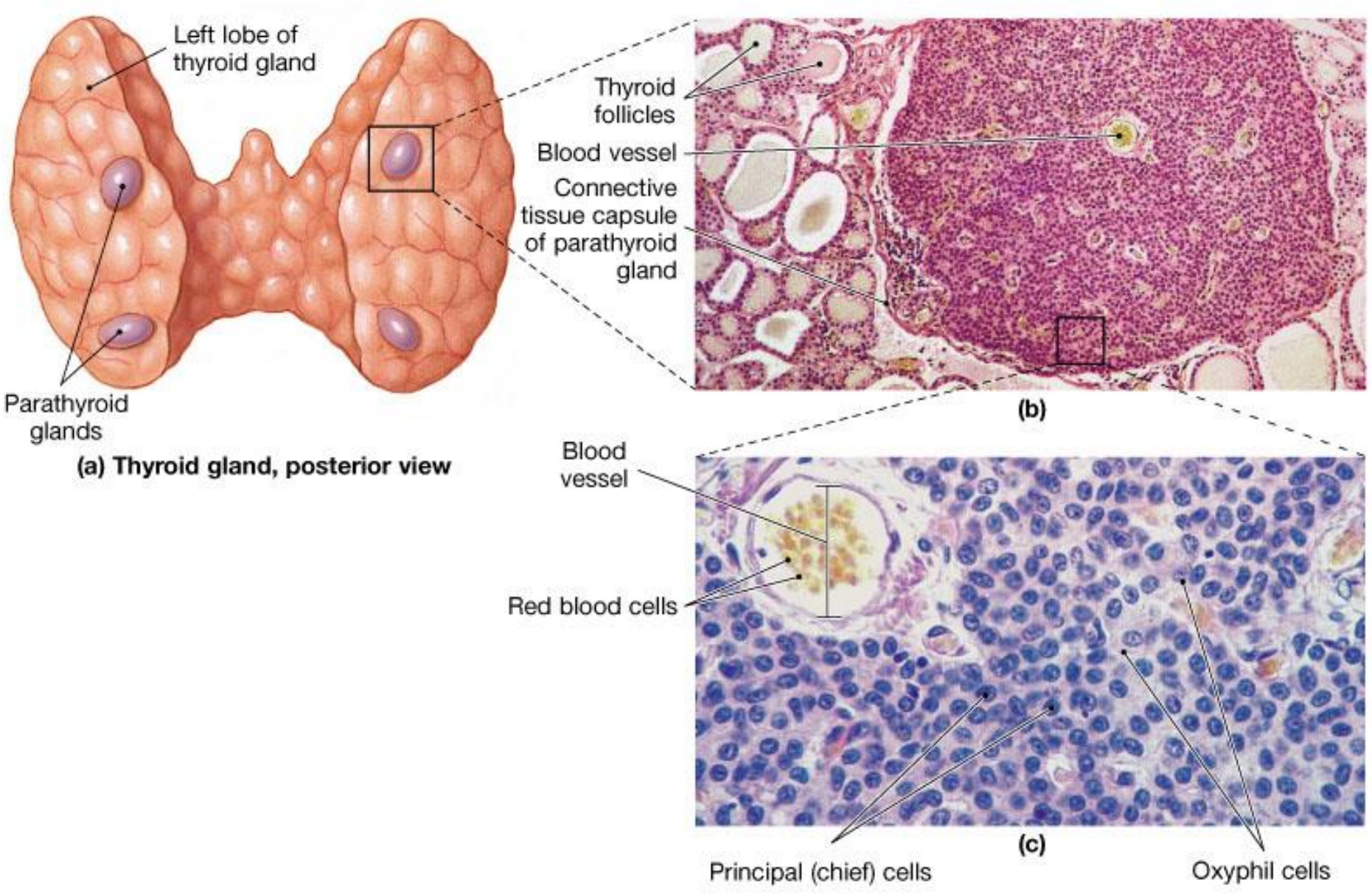
feedback inhibitory effect of 25-hydroxy vit D3



Calcium Ion Concentration Controls the Formation of 1,25-Dihydroxycholecalciferol



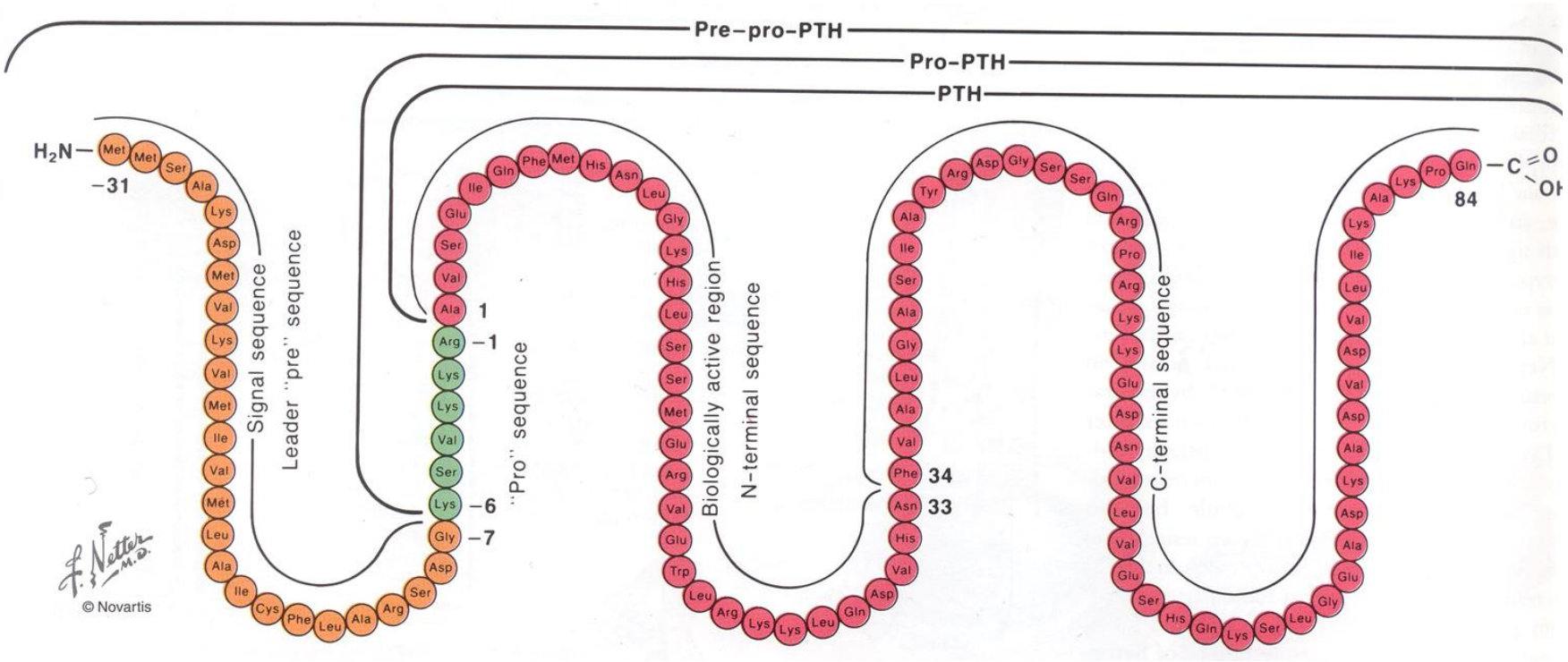
Parathyroid Gland

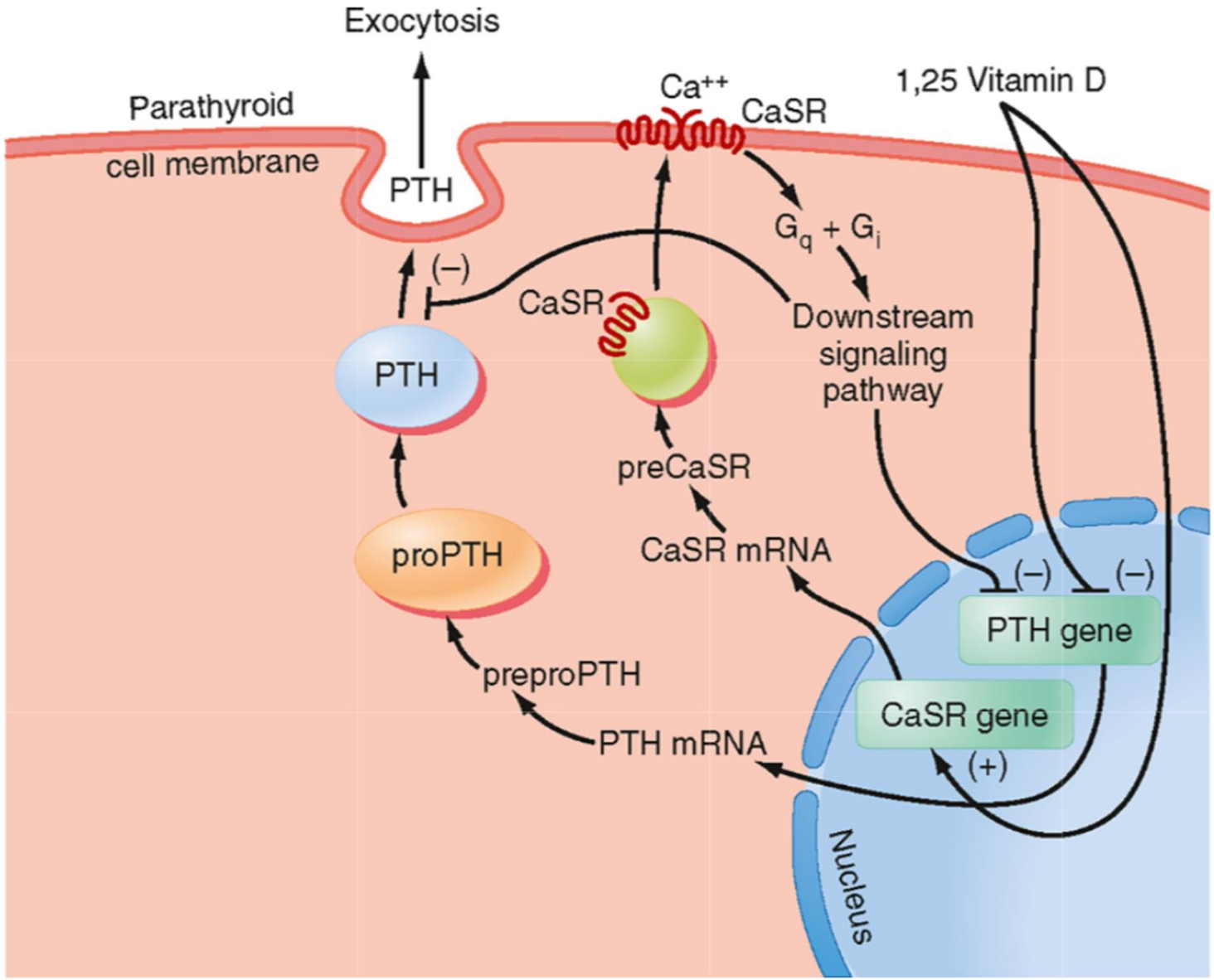


Parathyroid Hormone

- Secreted by Chief (principal) cells of the parathyroid glands
  - Rapid response to reduced calcium (minutes)
- Polypeptide
  - 84 amino acid residues
  - 9,500 daltons M.W.
- Operates in tissues via GPCRs, cAMP second messenger

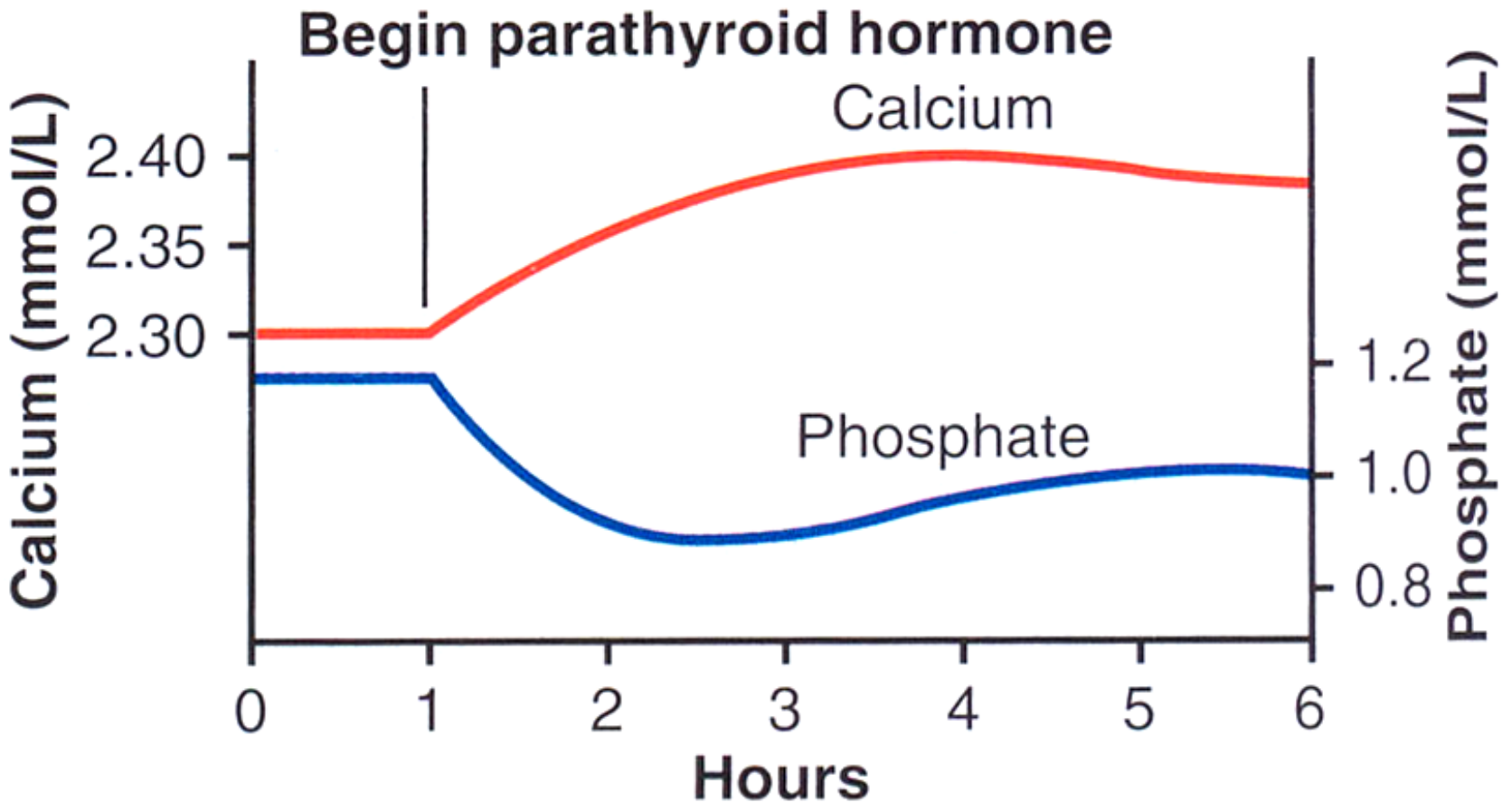
Parathyroid Hormone




Exocytosis
Parathyroid
cell membrane
PTH
Ca++
CaSR
1,25 Vitamin D
Gq + Gi
(–)
CaSR
Downstream
signaling
pathway
PTH
preCaSR
proPTH
CaSR mRNA
(–)
(–)
PTH gene
preproPTH
CaSR gene
PTH mRNA
(+)
Nucleus

Effects of PTH

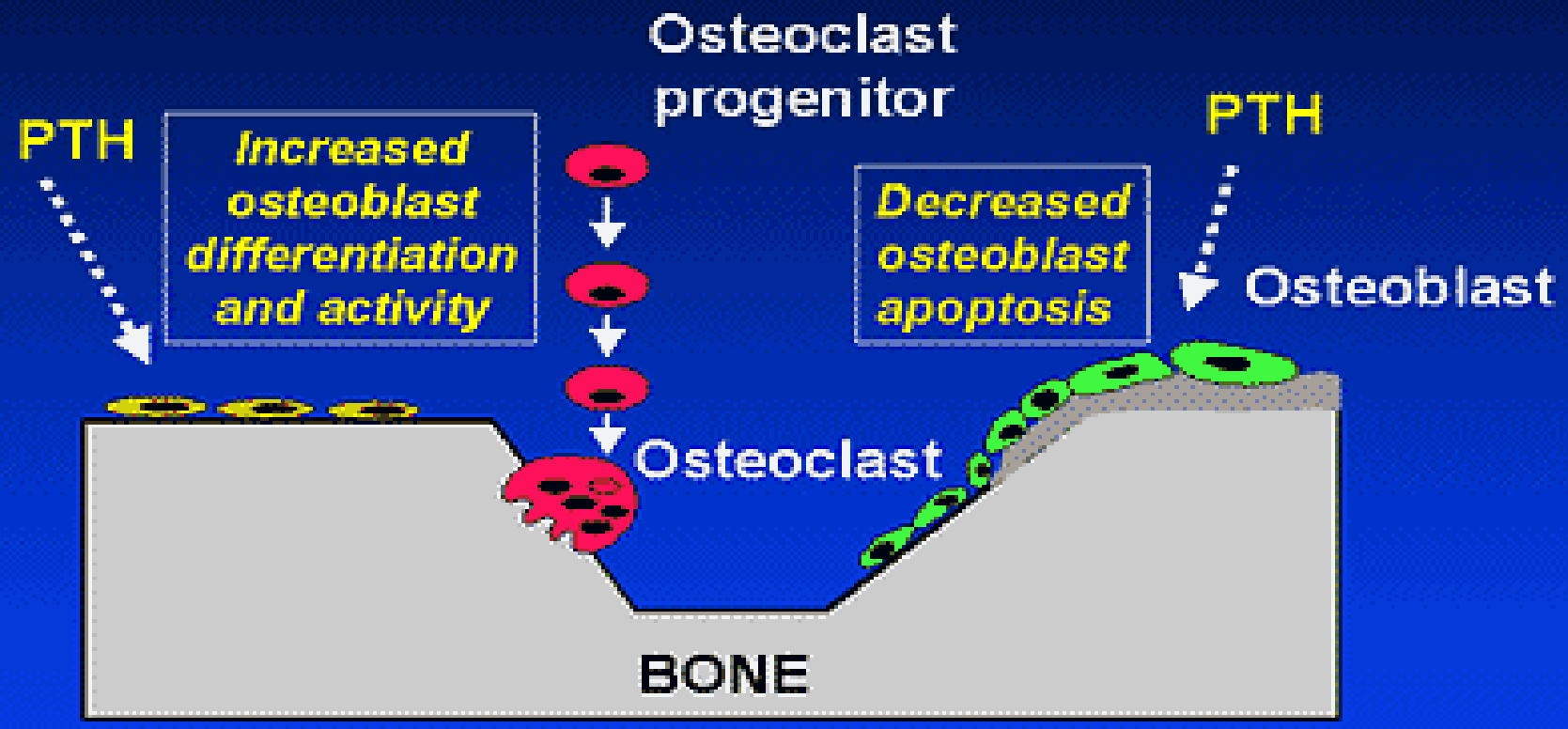
- Increases Calcium and Phosphate Absorption from the Bone
  - Existing osteocytes stimulated (minutes to hours) to transport calcium – calcium pumps
  - Existing osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium and phosphate.
    - Stimulated indirectly by osteoblasts


Begin parathyroid hormone
Calcium
Phosphate
Calcium (mmol/L)
2.40
2.35
2.30
1.2
1.0
0.8
Phosphate (mmol/L)
0
1
2
3
4
5
6
Hours

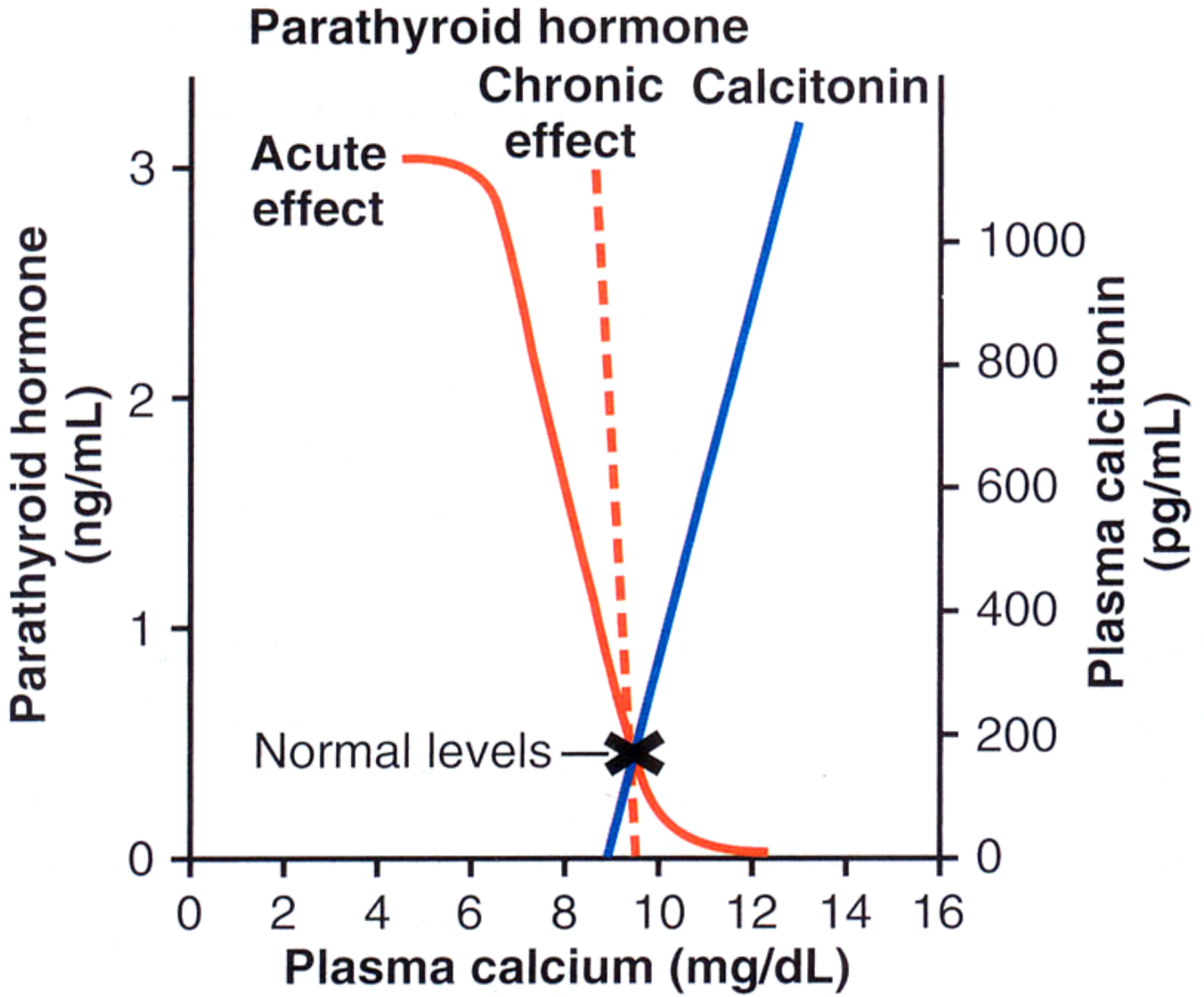
Other Effects of PTH

- Decreases excretion of calcium by kidneys
  - Important to prevent bone deterioration
- Increases phosphate excretion by the kidney
- Increases calcium absorption by the intestines
  - Effect manifested via Vitamin D3
    - Produces most active form of D3 in the kidney (1,25-dihydroxy-cholecalciferol)
- It also increases phosphate absorption

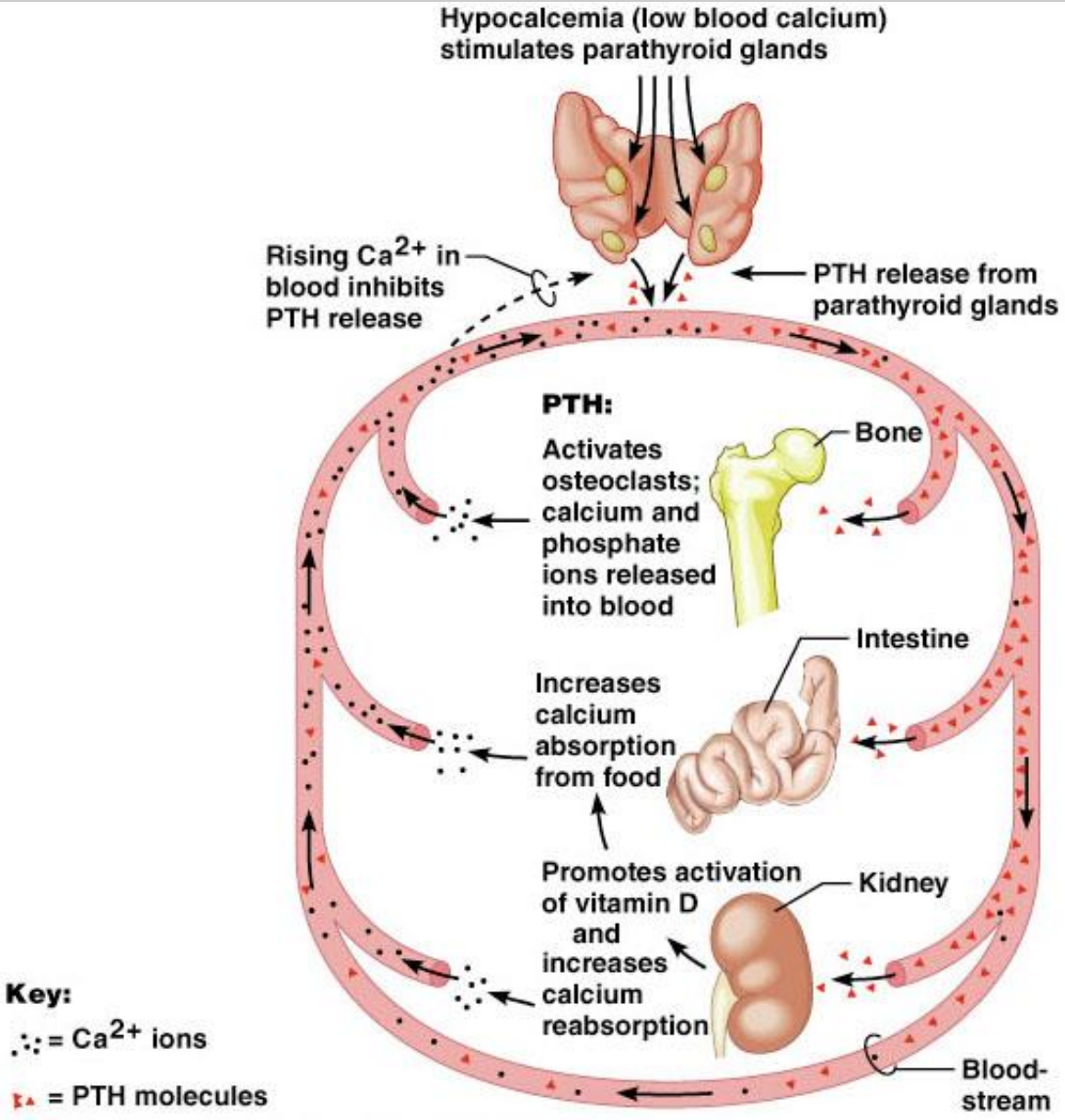
Intermittent Low-Dose PTH Increases Bone Formation



Effects of plasma calcium concentration on PTH & calcitonin

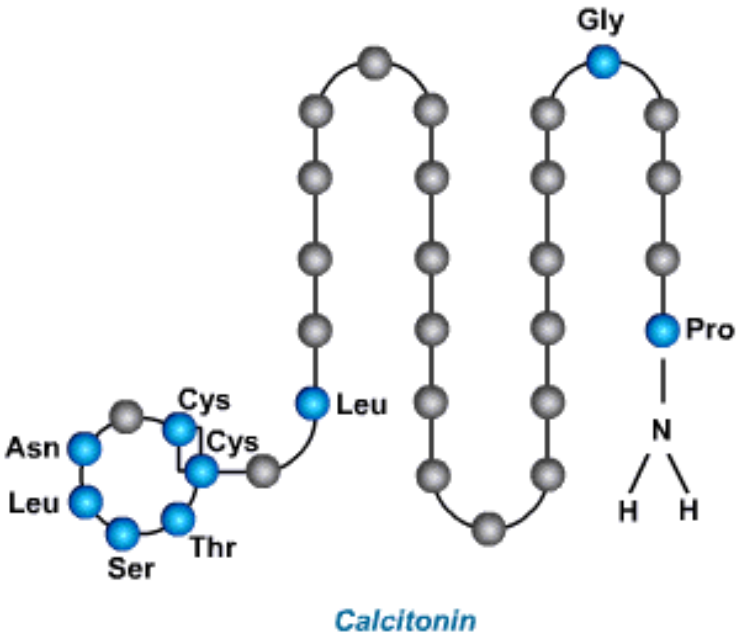


Effects of Parathyroid Hormone

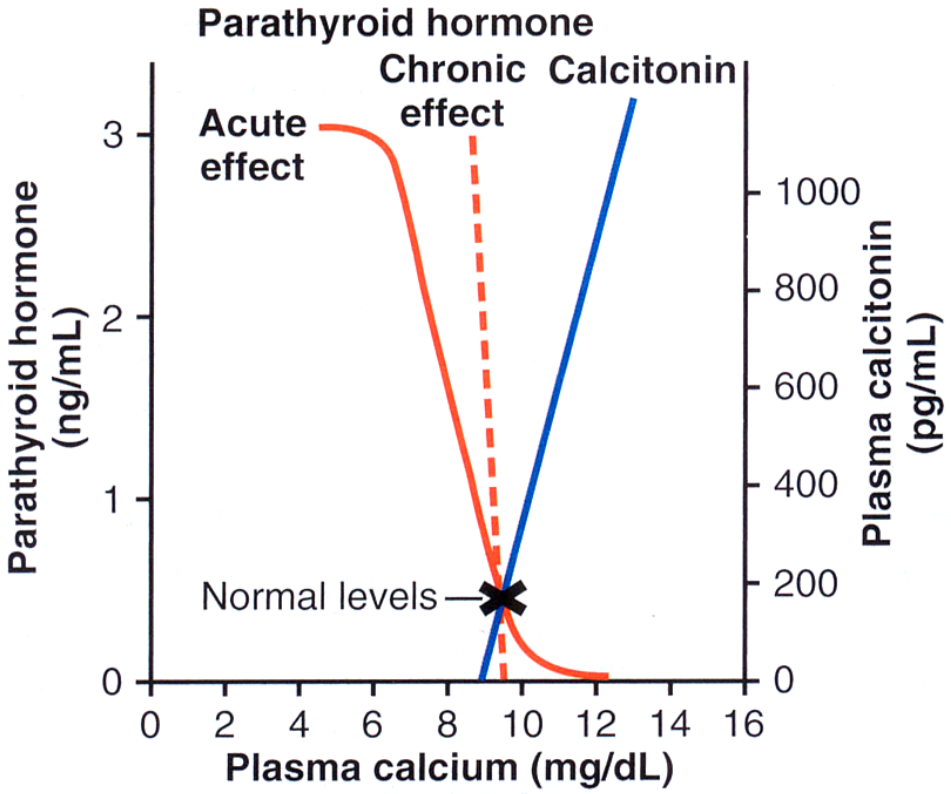


Calcitonin

- A peptide hormone , 32 amino acids
- produced by the parafollicular, or C cells of the thyroid gland



Calcitonin



Effects of Calcitonin

- Attenuates absorptive ability of osteoclasts
- Inhibits formation of new osteoclasts
  - Osteoclast decrease causes osteoblast decrease
  - Effect to decrease calcium is transitory
  - Causes reduced bone turnover
- Has weak effect in kidney and intestines

Hypoparathyroidism

Causes Hypocalcemia ,hyperphosphatebia neuromuscular irritability, numbness, cramps, anxiety , Tetany, carpopedal spasms. Severe Hypocalcemia is followed by convulsions, strider, dystonia, and depression.

Two signs of Hypocalcemia are:

- Chvostek's sign
- Trousseau's sign

A prolonged QT interval on the ECG can also be seen.

Two signs of Hypocalcemia are

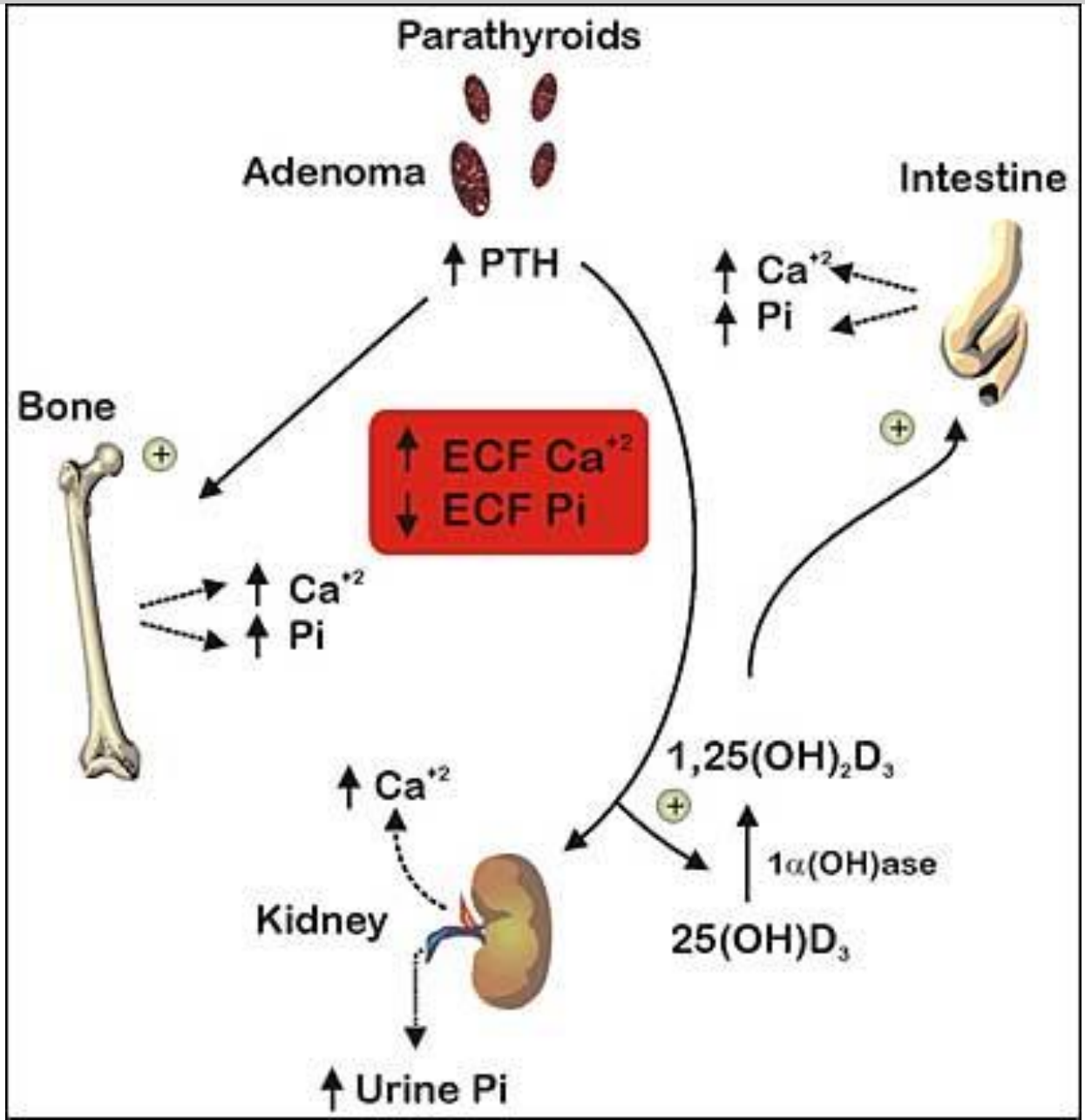
- **Chvostek's sign**. It refers to an abnormal reaction to the stimulation of the facial nerve. When the facial nerve is tapped at the angle of the jaw (i.e. masseter muscle), the facial muscles on the same side of the face will contract momentarily (typically a twitch of the nose or lips) because of hypocalcemia.

- **Trousseau's sign**. To elicit the sign, a blood pressure cuff is placed around the arm and inflated to a pressure greater than the systolic blood pressure and held in place for 3 minutes. This will occlude the brachial artery. In the absence of blood flow, the patient's hypocalcemia and subsequent neuromuscular irritability will induce spasm of the muscles of the hand and forearm. The wrist and metacarpophalangeal joints flex.

Common causes of hypercalcemica

- PTH mediated
  - Primary hyperparathyroidism
- Non-PTH mediated
  - PTHrp, vitamin D intoxication, granulomatous disorders, osteolytic bone metastases, malignancy
- Medications
  - Thiazide diuretics, lithium
- Misc
  - Hyperthyroid, immobilization, Milk-alkali, etc…

Hyperparathyroidism



Hyperparathyroidism

- Primary
  - Adenoma (90%)
  - Multiple gland enlargement (10%)
    - MEN 1
    - MEN 2A
    - Familial hyperparathyroidism
  - Carcinoma (<1%)
  - Familial benign hypercalcemia (FBH)
- Secondary (normo- or hypocalcemic)
  - Renal failure
  - Vitamin D deficiency

Primary hyperparathyroidism

- Affects approximately 100,000 patients a year (in the US).
- Prevalence: 0.1 to 0.3% of the general population.
- More common in women (1:500) than in men (1:2000).
- Patients with single adenoma (~90%): minimally invasive surgery
  - Sestamibi imaging ~90% sensitive, ~98% specific
  - Minimally invasive = incision length < 2.5 cm
  - Intraoperative PTH testing confirms biochemical cure

Hypercalcemia - Treatment

Severe hypercalcemia:

- Indications for therapy
  - Symptoms of hypercalcemia
  - Plasma [Ca] >14 mg/dl
- Principles of therapy
  - Expand ECF volume
  - Increase urinary calcium excretion
  - Decrease bone resorption

Hypercalcemia - Treatment

- NS bolus to restore volume; then 100 – 200 ml/hr
- Bisphosphonates (onset 24-48 hrs)
- Calcitonin 4 – 8 IU q6-8 hrs (onset immediate, resistance develops in 24-48 hrs)

Hypocalcemia: causes

- **Hypoparathyroidism**
  - **Surgical** (thyroid, parathyroid surgery)
  - Autoimmune
  - Magnesium deficiency
- PTH resistance (pseudohypoparathyroism)

- Vitamin D deficiency
- Vitamin D resistance

- Other: renal failure, pancreatitis, tumor lysis