Role and mode of action of parathyroid hormone (PTH)

Parathyroid hormone (PTH) is a hormone synthesized by four tiny *parathyroid* glands in the neck region. The parathyroid glands are located on the posterior, medial aspect of each lobe of the thyroid gland.

Primary action of PTH is to maintain the blood calcium level within the critical range of 9 to 11 mg/dL.

Parathyroid Gland Histology

There are two types of cells within the parathyroid gland, the **chief cells** and the **oxyphil cells**.

- **Chief cells**– The role of this cell type is to secrete parathyroid hormone. They contain prominent Golgi apparatus and endoplasmic reticulum to allow for the synthesis and secretion of parathyroid hormone. The chief cells are the smaller of the two cell types, however they are more abundant.
- **Oxyphil cells**– These cells are much larger but less abundant than chief cells. Their purpose is unknown. It is interesting to note however that the number of oxyphil cells increases with age and few are seen before puberty.

Parathyroid hormone Receptors

Parathyroid hormone receptors (PTH receptors) are of three types.

PTHR1, PTHR2 and PTHR3,

These receptors are which are G protein coupled receptors.

PTHR1 is physiologically more important than the other two types. PTHR1 mediates the actions of PTH and PTH-related protein.

Role of PTHR2 and PTHR3 is not known clearly.

On the target cells, PTH binds with PTHR1 which is coupled to G protein and forms hormone-receptor complex.

Hormone-receptor complex causes formation of cAMP, which acts as a second messenger for the hormone. It is the effect of PTH by which phosphate is excreted through urine.

PTH increases phosphate excretion by inhibiting reabsorption of phosphate from renal tubules. It acts mainly on proximal convoluted tubule.

Actions of parathyroid hormone on blood calcium level

Primary action of PTH is to maintain the blood calcium level within the critical range of 9 to 11 mg/dL. The blood calcium level has to be maintained critically because, it is very important for many of the activities in the body.

PTH maintains blood calcium level by acting on;

a) Bones
b) Kidneys
c) Gastrointestinal tract
a) Bone

Parathyroid hormone enhances the resorption of calcium from the bones (osteoclastic activity) by acting on osteoblasts and osteoclasts of the bone.

i) Rapid phase

When large quantities of PTH are injected, the calcium ion concentration in the blood begins to rise within minutes, long before any new bone cells can be developed.

PTH causes removal of bone salts from two areas in the bone:

(1) from the bone matrix in the vicinity of the osteocytes lying within the bone and

(2) in the vicinity of the osteoblasts along the bone surface.

ii) Slow phase

PTH stimulates osteoclast activity and bone resorption, but this process occurs through an indirect mechanism.

The bone-resorbing osteoclast cells do not have PTH receptors. Instead, the osteoblasts signal osteoclast precursors to form mature osteoblasts.

Two osteoblast proteins responsible for this signaling are receptor activator for nuclear factor ?-B ligand (RANKL) and macrophage colonystimulating factor, which both appear to be necessary for formation of mature osteoclasts.

PTH binds to receptors on the adjacent osteoblasts, stimulating synthesis of RANKL, which is also called osteoprotegerin ligand (OPGL).

RANKL binds to its receptors (RANK) on preosteoclast cells, causing them to differentiate into mature multinucleated osteoclasts.

The mature osteoclasts then develop a ruffled border and release enzymes and acids that promote bone resorption gobbling up the bone over weeks and months.

b) Kidney

PTH increases the reabsorption of calcium from the renal tubules along with magnesium ions and hydrogen ions. It increases calcium reabsorption mainly from distal convoluted tubule and proximal part of collecting duct.

PTH also increases the formation of 1,25 dihydroxycholecalciferol (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys.

c) Gastrointestinal Tract

PTH increases the absorption of calcium ions from the GI tract indirectly. It increases the formation of 1,25- dihydroxycholecalciferol in the kidneys.

This vitamin, in turn increases the absorption of calcium from GI tract. Thus, the activated vitamin D is very essential for the absorption of calcium from the GI tract.

And PTH is essential for the formation of activated vitamin D.

Actions of parathyroid hormone on blood phosphate level

PTH decreases blood level of phosphate by increasing its urinary excretion. It also acts on bone and GI tract.

a) On the Bone
Along with calcium resorption, PTH also increases phosphate absorption from the bones.
b) On the Kidney
PTH decreases phosphate reabsorption at the proximal convoluted tubule.
c) On Gastrointestinal Tract
Parathyroid hormone increases the absorption of phosphate from GI tract through Calcitriol.

Sequence of events

i. PTH converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (Calcitriol active form of vitamin D in the kidney).

ii. Calcitriol increases the synthesis of calcium induced ATPase in the intestinal epithelium

iii. ATPase increases the synthesis of alkaline phosphatase

iv. Alkaline phosphatase increases the absorption of phosphate from intestine along with calcium.

Metabolism and degradation

60 – 70% of PTH is degraded by Kupffer cells of liver, by means of proteolysis.

Degradation of about 20% to 30% PTH occurs in kidneys and to a lesser extent in other organs.

About 5mmol/dl is eliminated in urine as the rest is reabsorbed.

Parathyroid Hormone Regulation

The secretion of PTH is regulated by a **classical negative feedback loop**, with serum **ionized calcium ($Ca^{2?}$)** serving as the primary regulator:

- When **serum calcium levels are high**, calcium binds to the **CaSR** on chief cells.
- Activation of CaSR leads to **inhibition of adenylate cyclase** and a **reduction in intracellular cAMP**, which suppresses **PTH gene transcription** and **PTH release**.
- Conversely, when **serum calcium levels drop**, less calcium binds to the CaSR, leading to **disinhibition of PTH secretion** [Lecturio, UpToDate].

This feedback loop ensures tight control of blood calcium concentration, typically maintaining it within a narrow physiological range (about 8.5 to 10.5 mg/dL or 2.1 to 2.6 mmol/L).

Additional Modulators of PTH Secretion

Although **calcium** is the principal regulator, other factors modulate PTH secretion:

1. **Phosphate**: Elevated serum phosphate stimulates PTH secretion indirectly by reducing free calcium through precipitation and promoting vitamin D degradation [Osmosis].
2. **Vitamin D (Calcitriol)**: The active form of vitamin D, **1,25-dihydroxyvitamin D?**, provides **negative feedback** to parathyroid cells, inhibiting **PTH synthesis** and possibly **proliferation of parathyroid tissue** [NCBI, AMBOSS].
3. **Magnesium**:

- Mild to moderate hypomagnesemia stimulates PTH release.
- Severe hypomagnesemia paradoxically **inhibits** PTH release and causes **resistance to PTH action**, contributing to **hypocalcemia**.