CHEMISTRY,BIOSYNTHESIS AND MECHANISM OF ACTION OF PARATHYROID HARMONE 1

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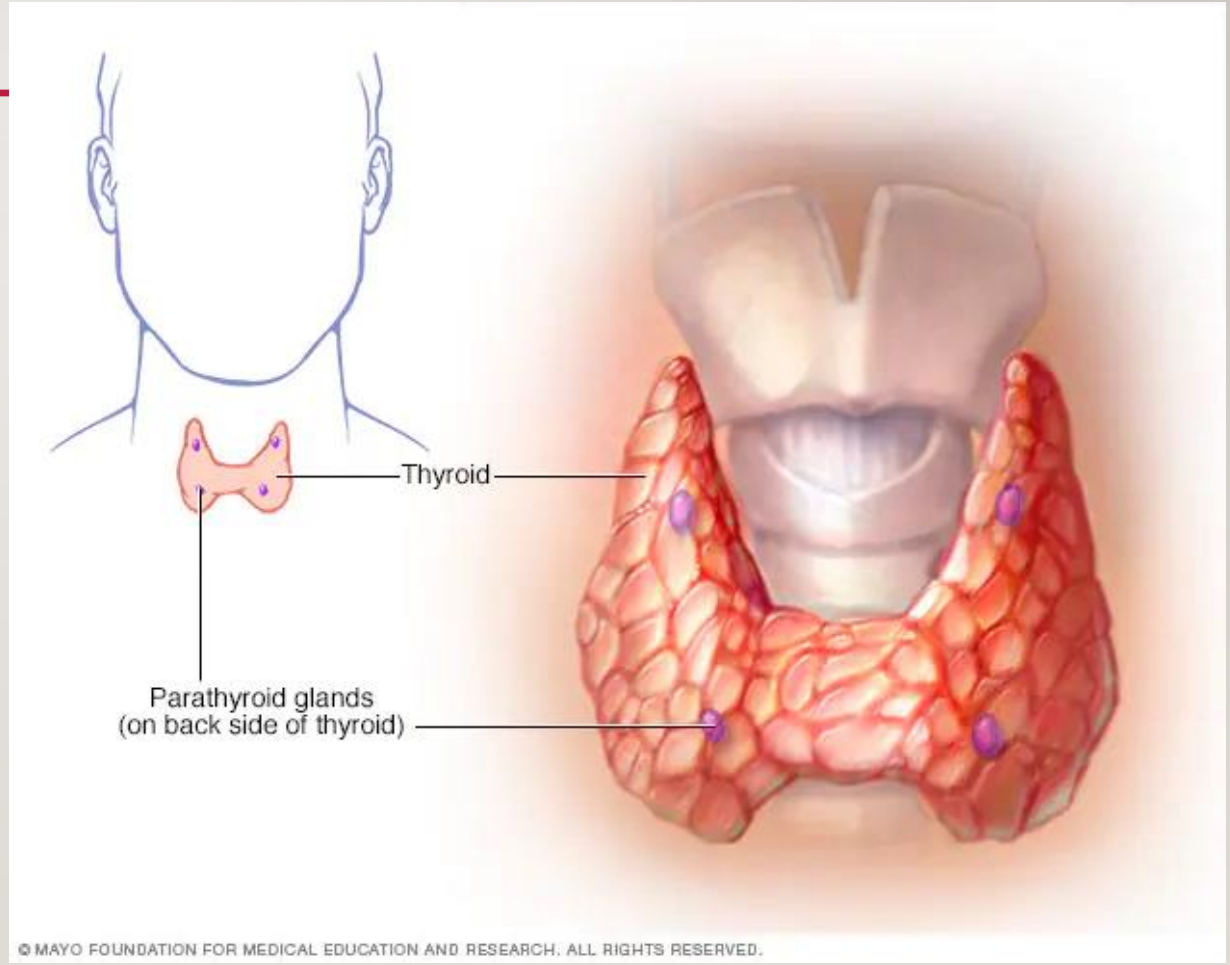
LEARNING OBJECTIVES

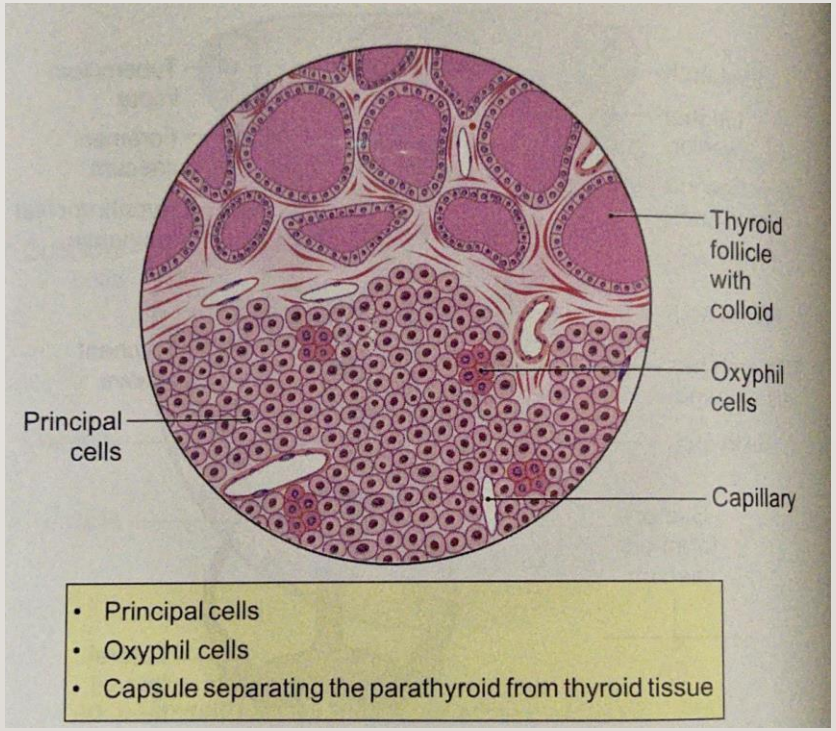
- Brief anatomy of Parathyroid gland
- Chemistry of Parathyroid harmone
- Biosynthesis of Parathyroid harmone
- Mechanism of action of Parathyroid harmone

PARATHYROID GLAND ANATOMY

- Located behind the thyroid at the bottom of our neck.
  - 4 glands- one behind each pole of thyroid gland
  - Size = 6x3x2 mm
  - Gland consists of
    - Chief cells - hormonal production
    - Oxyphil cells – parathyroid-relevant genes found in the chief cells,produce additional factor like PTHrP



HISTOLOGY


Thyroid follicle with colloid
Oxyphil cells
Principal cells
Capillary
• Principal cells
• Oxyphil cells
• Capsule separating the parathyroid from thyroid tissue

INTRODUCTION:

- The parathyroid glands are intimately concerned with regulation of the concentration of Ca and PO4 ions in the blood plasma.
- This is accomplished by secretion of a hormone PARATHORMONE by the chief cells ,the net effect of which is

A. To increase the concentration of Ca in blood plasma

B. Decrease the PO4 in blood plasma

PARATHORMONE (PTH)

CHEMISTRY:

Parathormone is a

- linear polypeptide consisting of 84 amino acids.
- Has molecular weight of 9500
- N-terminal amino acid is ALANINE
- C-terminal amino acid is GLUTAMINE

CORE OF ACTIVITY

- Physiological action --- N-terminal
- Calcium mobilizing effect --- Methionine

PARATHYROID HORMONE BIOSYNTHESIS:

- PTH is initially synthesized in chief cells as a pro-hormone
- PRE-PRO-PTH:

Consisting of 115 amino acids is first formed in polysomes, adhering on the rough ER membrane.

PARATHORMONE BIOSYNTHESIS CONTINUED:

- PRO-PTH:

Before the formation of Pre-pro-PTH is completed, its N-terminal end protrudes into the lumen of rough ER and a signal peptidase of rough ER membrane hydrolyses the molecule to split off 25 amino acid and thus pre-pro-PTH is changed to PRO-PTH having 90 aminoacids.

PARATHORMONE BIOSYNTHESIS:

- PTH:

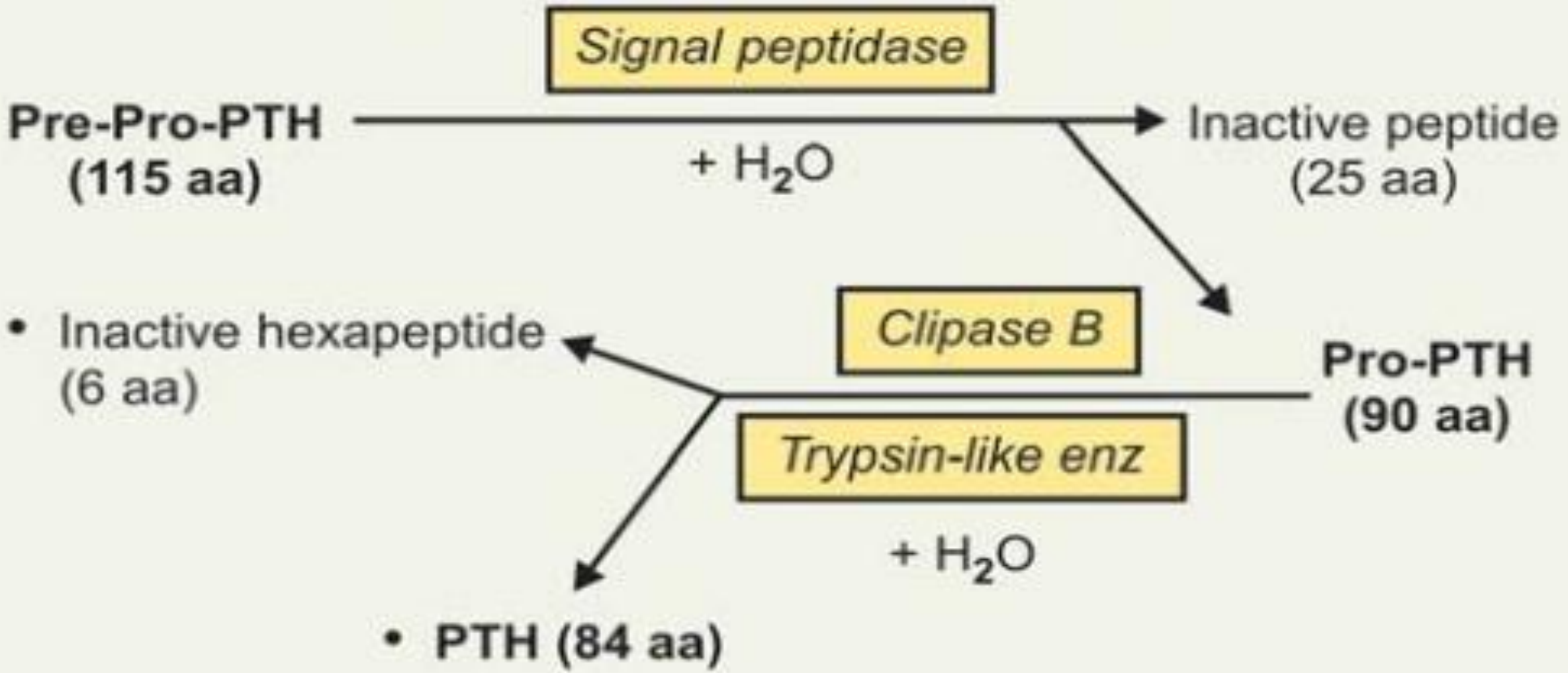
Pro-PTH is transferred to rough ER lumen and moves to Golgi apparatus.

A trypsin-like enzyme, called CLIPASE B hydrolyses its N-terminal end amino acid and removes 6 amino acids , thus converting the Pro-PTH to PTH.

PARATHORMONE BIOSYNTHESIS:

- PTH thus formed is packaged and stored in secretory vesicles.
- Increased c-AMP concentration and a low Ca level stimulates its release from secretory vesicles.
- On the other hand, a high concentration of Ca stimulates the degradation of the stored PTH in secretory vesicles instead if its release.

Biosynthesis of Parathormone



MECHANISM OF ACTION :

- Increasing c-AMP levels
- Role of Ca
- pH change in tissues

A) INCREASING C-AMP LEVELS:

- PTH binds to specific receptors on the plasma membrane of bone cells , renal tubule cells , it activates the adenyl cyclase to form c- AMP in the cells .
- C-AMP acts as a second messenger which activates specific c-AMP dependent protein kinases, which phosphorylates and thereby modulates the activities of specific proteins in the bone cells and kidney cells.

cAMP causes

Secretion of enzymes and acids by osteoclasts

- Proliferation of osteoclasts
- ↑activity of osteocytic pump
- ↑formation of enzymes to form 1,25,DHCC in kidneys

B) ROLE OF CALCIUM:

c-AMP also increases the calcium concentration in these cells , which inturn may act as a messenger to modulate the activities of some intracellular proteins.

C) pH CHANGE IN TISSUES:

The hormone increases the amounts of both LACTIC ACID and CITRIC ACID in the tissues and both of these acids may act to aid bone resorption.

SOURCES;

- MN Chatterjea – Textbook of medical Biochemistry
- Google images


Thank you!

METABOLIC ROLE OF PARATHYOID HARMONE II

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LEARNING OBJECTIVES

- Action of PTH on kidneys
- Action of PTH on bones
- Action of PTH on alkaline phosphate
- Action of PTH on intestine
- Regulation of PTH secretion
- Summary of metabolic role of PTH
- PTHRP

THE ACTIONS OF PTH ARE REFLECTED IN THE CONSEQUENCES OF:

- Its administration and
- Removal of the parathyroid glands

ACTIONS ON DIFFERENT ORGANS:

(A) ACTION ON KIDNEYS:

- PTH acts by increasing c-AMP. It binds to specific ‘receptors’ on plasma membrane of renal cortical cells of both proximal and distal tubules and stimulates adenyl cyclase to produce c-AMP ↑. c-AMP then is transported to apical/luminal part of the cell where it activates c-AMP dependent protein kinase, which phosphorylates specific proteins of the apical membrane to affect the several mineral transport, across the membrane.

- PTH decreases the transmembrane transport and reabsorption of filtered Pi in both proximal and distal tubular cells and increases the urinary excretion of inorganic phosphate ↑ (phosphaturic effect).
- Fall in serum inorganic PO4 level leads to mobilisation of PO4 from bones which also mobilises Ca++ along with, resulting to hypercalcaemia.

- PTH stimulates α-1-hydroxylase enzyme located in mitochondria of proximal convoluted tubule cells, which converts 25-OHcholecalciferol, to 1-25, di-OH-cholecalciferol which in turn increases the intestinal and renal absorption of Ca++ resulting to hypercalcaemia.
- PTH inhibits the transmembrane transport of K+ and HCO3– to decrease their reabsorption by renal tubules.

- PTH increases the transmembrane transport and reabsorption of filtered Ca++ in the distal tubules resulting initially to decrease urinary excretion of Ca++. But later on, PTH-induced hypercalcemia enhances the amount of filtered Ca++ which increases the renal excretion

(B) ACTION ON BONES

Following actions are seen:

1)Osteoclastic activity: It stimulates the differentiation and maturation of precursors cells of osteoclasts to mature osteoclasts.

2)Osteoclastic osteolysis: PTH stimulates the osteoclasts through “second messenger” c-AMP to increase the resorption of bones which enhances mobilisation of Ca and P from bones.

3)Osteocytic osteolysis: PTH also stimulates osteocytes which increases bone resorption thus mobilising Ca++ and Pi. There occurs enlargement of bone lacunae.

ACTION ON ALKALINE PHOSPHATASE

- Alkaline phosphatase activity varies as per PTH concentration. At low concentrations, PTH stimulates the sulfation of cartilages and increases the number of osteoblasts and alkaline phosphatase activity of bone osteoblasts.
- At higher levels of physiological concentrations, PTH inhibits alkaline phosphatase activity and collagen synthesis in osteoblasts and decreases the Ca++ retaining capacity of bones.

- PTH induced rise in intracellular c-AMP in osteoclasts/and osteocytes leads to secretion of lysosomal hydrolases/and collagenases which increase breakdown of collagen and MPS in bones matrices.

(D) ACTION ON INTESTINAL MUCOSA

- PTH does not act directly on intestinal mucosal cells as the cells do not possess the specific ‘receptors’ for PTH. But it increases the absorption of Ca++ and PO4 through production, 1-25, di-OH-cholecalciferol (calcitriol).

REGULATION OF SECRETION OF PTH

- Hypocalcemia is the most important stimulus for PTH production & secretion
- Hypocalcemia→ hypertrophy of parathyroid gland e.g.
  - In pregnancy
  - During lactation
  - In rickets
- Hypercalcemia →↓activity and size of parathyroid gland

SUMMARY

- Increase in serum Ca++ concentration ↑ .
- Decrease in serum inorganic PO4 ↓ concentration.
- Increased urinary Ca++ ↑ following an initial decrease.
- Increased urinary PO4 ↑ .

- Removes Ca from bones, particularly if dietary intake of Ca is inadequate.
- Increase in ‘citrate’ ↑ content of blood plasma, kidney and bones.
- Activates vit D in renal tissue by increasing the rate of conversion of 25-OH-cholecalciferol to 1,25-di-OH-cholecalciferol, by stimulating α-1-hydroxylase enzyme.

PTHRP (PARATHORMONE-RELATED PEPTIDE):

- Also called as Humoral hypercalcaemic factor of malignancy (HHFM)
- It is a peptide containing 141 amino acids.
- Produced by a number of tumours specially squamous cells carcinomas of lungs, oesophagus, cervix and head and neck.
- PTHrP can bind to parathormone receptor and can mimic the action of parathormone (PTH).

- Target tissues are bones and kidneys and produces hypercalcaemia, hypophosphataemia like PTH and also increases urinary cyclic AMP.
- PTHrP is produced by a gene on chromosome 12 which is distinct from PTH gene which is located on chromosome 11.

CLINICAL IMPORTANCE

- Serum level of PTHrP are low or absent in normal healthy persons and in patients with primary hyperparathyroidism
- High in majority of patients in malignancy and is responsible for HHM (humoral hypercalcaemia of malignancy).
- Determination of serum PTHrP - an important diagnostic tool in evaluation of hypercalcemia.

SOURCES;

- MN Chatterjea – Textbook of medical Biochemistry
- Google images


Thank you!

CALCITONIN

INTRODUCTION:

- Calcitonin is a calcium regulating hormone.
- Originates from special called C-cells , parafollicular cells.
- C-cells constitute an endocrine system which , are derived from neural crest and are found in thyroid , parathyroid and in thymus.

CALCITONIN

- Polypeptide of 32 amino acids
- MW = 3600
- Effects are opposite to parathyroid hormone
- Decreases the calcium level in the blood

MAINTENANCE OF BLOOD CALCIUM LEVEL

- Normal blood calcium level = 9-11 mg/dl
- PTH→ ↑blood calcium level
  - Resorption from the bones
  - Reabsorption from the renal tubules
  - Absorption from GIT

MECHANISM OF ACTION

1. Role of Cyclic AMP: Calcitonin binds to specific calcitonin receptors on the plasma membrane of bone osteoclasts and renal tubular epithelial cells, activates adenyl cyclase which increases c-AMP level ↑ which mediates the cellular effects of the hormone. This is the principal method by which calcitonin acts.

2. Cellular Shift: It has been suggested that calcitonin may directly affect the relative distribution of bone cells. The hormone both in vitro and in vivo produced a cellular shift, in which the number of osteoclasts decreased.

3. pH Change: Calcitonin may regulate pH at cellular level producing more alkaline medium which diminishes resorption.

METABOLIC ROLE

- Calcitonin acts both on

(a) bone

(b) kidneys.

- Indirectly, the effects of these two organ systems is:

• Hypocalcaemia and

• Hypophosphataemia.

A) ACTION ON BONES:

Calcitonin inhibits the resorption of bones by osteoclasts and thereby reduced mobilisation of Ca and inorganic PO4 from bones into the blood.

- It also stimulates influx of phosphates in bones.
- There is decrease in activities of lysosomal hydrolases, pyrophosphatase and alkaline phosphatase in bones.
- Decrease in collagen metabolism and decreased excretion of urinary OH-proline. Whether or not calcitonin promotes bone formation is uncertain and controversial. But it has been
- established that the hormone in addition to
- causing a decrease in number of osteoclasts, it
- increases osteoblasts cells, which are thought to
- be involved in bone laying.

EFFECTS ON BONES

- Immediate effects
- Calcitonin →
  - ↓ Osteoclastic activity
  - ↓ Activity of osteocytic calcium pump
  - ↓ Osteolysis
  - ↑ Osteoblastic activity
  - Remodeling process shifted towards more deposition than Resorption of bone

EFFECTS ON BONES

- Prolonged effects
- Calcitonin →
  - ↓ Formation of new osteoclasts
  - ↑activity of osteoblasts
  - ↓ Calcium level
  - ↓ Formation of new osteoblasts (because osteoblastic activity follows osteoclastic activity
  - Finally ↓activity of both osteoclasts and osteoblasts
  - Hypocalcemic effect is transient

TRANSIENT HYPOCALCEMIA

- Effect of Calcitonin does not persist for longer duration
- Slight hypocalcemia→ PTH production
  - PTH opposes the effects of Calcitonin
- Daily turn over of calcium in adults is slow compared to children
- About 5 grams of calcium turnover in children
- Calcitonin has more marked effects on stimulation of osteoblastic activity in children

CONTROL OF CA^{++} CONCENTRATION

- Hypocalcemia or hypercalcemia has to be corrected quickly
- Two defense lines for calcium control
  1. Buffer function of exchangeable calcium
  2. Hormones PTH and Calcitonin

EXCHANGEABLE CALCIUM

- Amorphous calcium salts in bone
- $CaHPO_4$, $Ca(H_2PO_4)_2$, $Ca_3(PO_4)_2$
- Loosely bound
- Reversible equilibrium with ECF Ca & PO_4
- 0.5-1% of total bone calcium (5-10 gm)
- Total surface area > 1 acre
- Hypocalcemia→ quick removal of this Ca
- Hypercalcemia →quick deposition of Ca
- Mitochondria in all the cells of the body also contain exchangeable calcium about 10 grams

HORMONES – 2ND LINE OF DEFENSE

- Hypercalcemia→
  - ↑Calcitonin→
    - ↑osteoblastic activity→ more deposition
  - ↓PTH→
    - ↓osteoclastic activity
    - ↑ excretion in urine

↓ Calcium level

- Hypocalcemia →
  - ↓Calcitonin→
    - ↓ osteoblastic activity→ less deposition
  - ↑PTH→
    - ↑osteoclastic activity
    - ↓ excretion in urine

↑Calcium level

DISEASES

HYPOPARATHYROIDISM

- ↓Parathyroid hormone
- ↓osteocytic calcium pump
- ↓osteoclastic activity
- ↑excretion of calcium in urine
- Hypocalcemia & ↑↑ PO_4 in blood
- Tetany
- Laryngeal muscle spasm is cause of death
- Treatment
  - PTH
  - High doses of calcium and Vitamin D
  - 1,25,DHCC

HYPERPARATHYROIDISM

- Tumor in the parathyroid gland
- ↑↑ level PTH
- ↑osteoclastic activity
- ↑Calcium level
- ↓PO_4 level
- Bones weakened, decalcified, multiple fractures
- Giant cell in the cavities
- Osteitis fibrosa cystica
- Secondary ↑osteoblastic activity
- ↑alkaline phosphatase

HYPERCALCEMIA

- Calcium level 12-17 mg/dl
- CNS depressed
- Sluggish reflexes
- Muscle weakness
- Constipation
- Lack of appetite
- Abdominal pain
- Peptic ulcer
- ↓QT interval of the heart
- Parathyroid poisoning

PARATHYROID POISONING

- Hypercalcemia
- Supersaturated state of calcium and phosphate
- Precipitation of calcium in
  - Alveoli of the Lungs
  - Renal tubules
  - Stomach mucosa
  - Arterial walls
  - Kidney stones

RICKETS

- Vitamin D deficiency in children
- Usually due to inadequate exposure to sun
- ↓formation of Cholecaciferol
- Hypocalcemia
- ↑PTH secretion→ ↑osteoclastic activity of the bones
- Followed by ↑osteoblastic activity
- Osteoblasts can lay only matrix
- ↓calcification of bones
- Bones are elastic and can bend under pressure
- Tetany some times develops
- Treatment – vitamin D and calcium, exposure to sun

OSTEOMALACIA

- Adult Rickets
- Vitamin D deficiency
- Not dietary deficiency
- Steatorrhea is the usual cause
- Bones are weak
- Osteoblastic activity is not more as in children
- Easy pathological fracture
- Tetany usually does not develop
- Treatment – calcium and vitamin D

RENAL RICKETS AND OSTEOMALACIA

- Prolonged renal damage
- Removal of the kidneys
- Some kidney diseases
- ↓ formation of 1,25 DHCC
- Hypocalcemia
  - Rickets in children
  - Osteomalacia in adults
- Congenital hypophosphatemia
  - Excessive excretion of phosphate in the urine
  - Vitamin D resistant rickets
  - Treated with high doses of phosphates

OSTEOPOROSIS

- ↓ bone matrix
- ↓osteoblastic activity
- ↓Osteoid formation
- Usual causes
  - Lack of physical activity
  - Protein malnutrition
  - Lack of vitamin C
  - Postmenopausal age- lack of estrogens
  - ↓GH
  - Cushing’s disease


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