



5. HORMONAL CONTROL OF CALCIUM METABOLISM.

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Calcium Regulation

- Calcium is distributed all over the body and is important for most bodily functions:

- 1- responsible for normal permeability of cell membranes .

- 2- responsible for messenger activity in muscle cells , gland secretion , and transmitter release etc..

- 3- blood coagulation .

- 4- bone and teeth formation .

- The plasma calcium level is normally kept constant within a range of $\pm 3\%$ of its normal value of 10 mg/100 ml, half of this value exists as free calcium, The Plasma calcium level is regulated by three hormones:

1. 1,25-Dihydroxycholecalciferol (1,25-DHCC):

It is the active metabolite of vitamin D3. It is formed in the body by the kidney (it could be regarded as a hormone) . The release of this active form from the kidney is increased by low plasma calcium concentration. Together with parathyroid hormone 1,25-DHCC increases intestinal absorption . So , it acts to increase the plasma Ca^{++} concentration .

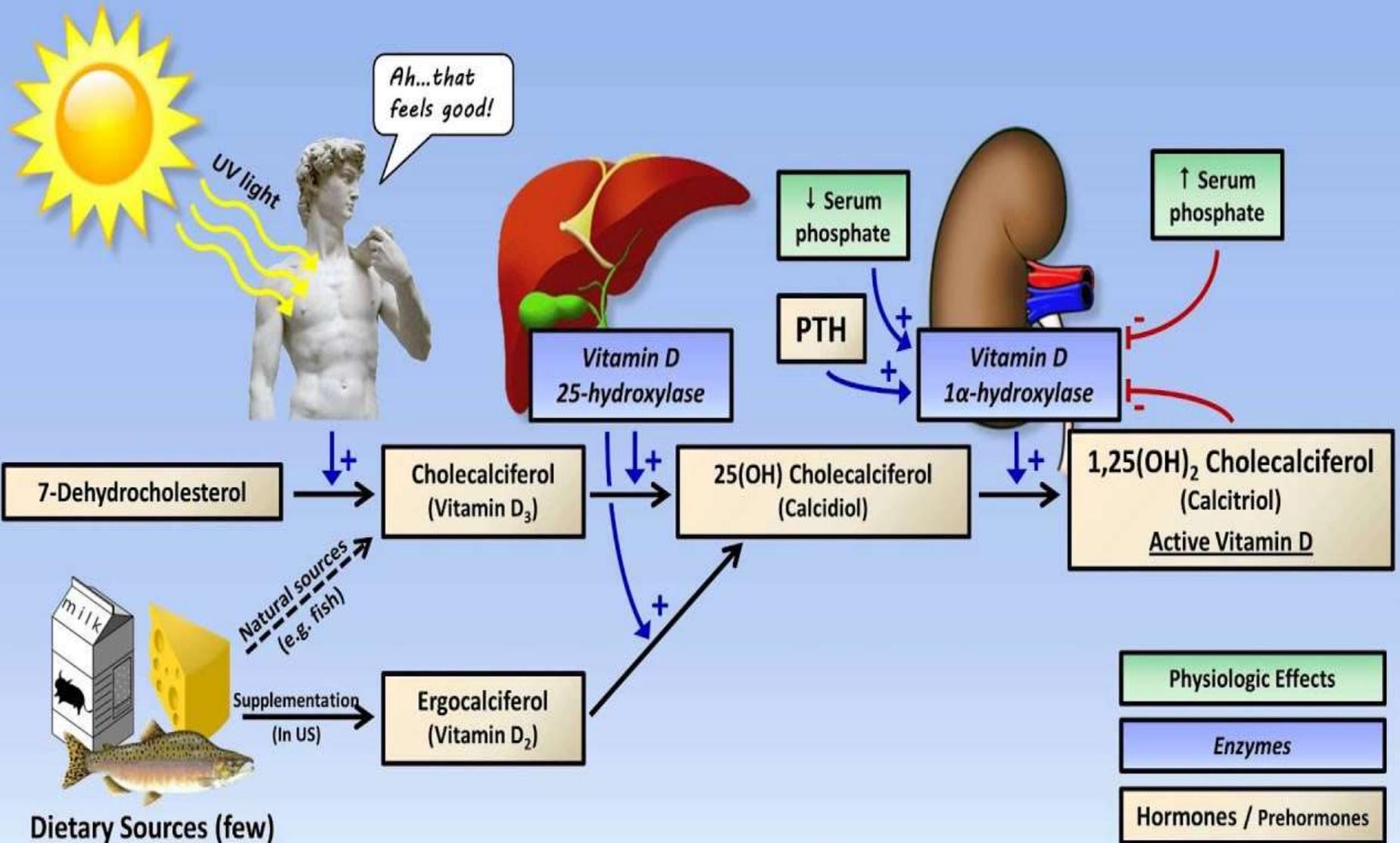
2. Parathyroid Hormone (PTH):

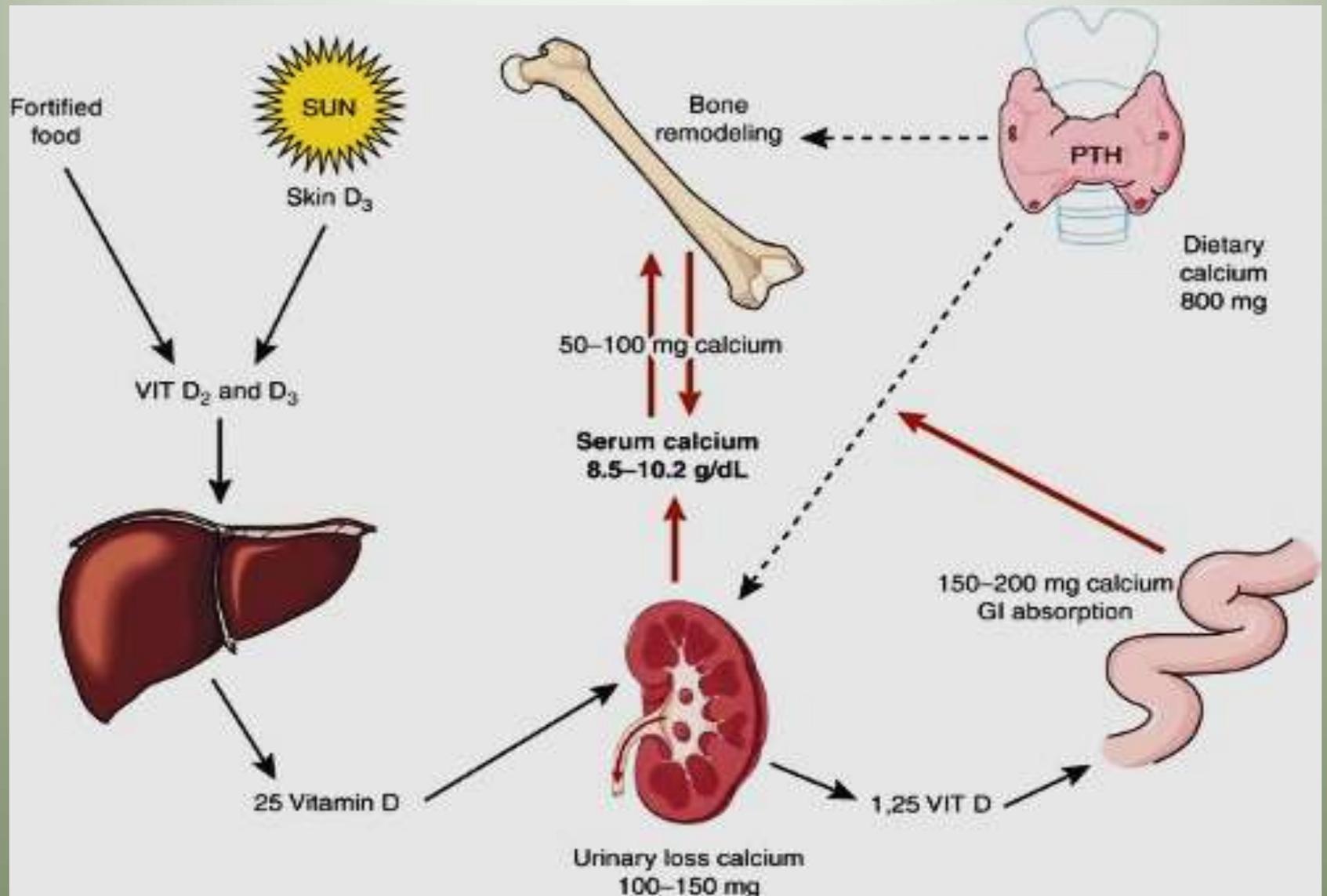
The hormone acts on the surface of the target cell producing the intracellular messenger cAMP . In addition to its action on calcium movements in bone, gut and kidney, it also increases renal loss of phosphate . This action means that the product of Ca phosphate in the blood is not increased by its action and so precipitation does not occur.

3. Calcitonin:

The main action is to decrease the calcium coming out of the bone .

Synthesis and Regulation of Calcitriol (Vit. D3)





The Parathyroid gland

- There are 4 parathyroid glands embedded in the thyroid gland tissue , each is oval in shape and about 5 mm long.
- The parathyroid glands are essential for life .It secretes a Parathormone hormone (PTH), a protein having a molecular weight of 9500 .That contains 84 amino acids.

• Parathormone receptors:

Parathormone hormone binds to two types of membrane receptors:

1. Parathormone type 1 receptors (PAT1R):

They are found in bone and kidney. They mediate mineral ions(Ca^{++} , phosphate) homeostasis. They act via increasing intracellular Ca^{++} in a cAMP dependent way.

2. Parathormone type 2 receptors (PAT2R):

They are recently identified. They are found in the brain, pancreas, testis and placenta. They are also detected in arterial and cardiac endothelium and vascular smooth muscles and within the lungs. They are responsible for the cardiovascular actions of parathormone.

Function of Parathormone :

A. Role of PTH in calcium homeostasis:

- The parathormone plays an important part in the main-tenance of the plasma calcium level at 10 mg % , and also the phosphate level in order to maintain the solubility product = $[\text{Ca}^{++}] \times [\text{PO}_4\text{-3}]$ constant.

- The actions of Parathormone may be summarized as follows:

1-On bone :

-It stimulates bone resorption by increased activity of the osteoclasts (bone eating cells) → demineralization of bone → increases the blood Ca^{++} level .

-It also stimulates destruction of bone matrix and inhibits collagen synthesis by activation of collagenase and acid phosphatase and hyaluronidase enzymes (this effect is blocked by calcitonin hormone), vitamin D is necessary for this action.

2-On kidney :

- It increases the excretion of phosphate in urine by inhibiting reabsorption in the proximal tubules and stimulates phosphate secretion in the distal tubules → decreases plasma phosphate level.

- It decreases calcium excretion → rises Ca^{++} plasma level (+ action on bone) more than the filtered load of Ca^{++} → increases Ca^{++} excretion.

3-On intestine :

- It increases absorption of Ca^{++} in the presence of vitamin D.

B-Cardiovascular Functions of PTH:

1-Cardiac hypertrophic effect: PTH was found to increase protein synthesis and protein mass in isolated cardiocytes indicating direct hypertrophic effect on the heart. This action is mediated via **protein C activation** and increase in Ca^{++} influx.

2-Chronotropic effect: PTH was found to increase markedly the heart rate (+ve chronotropic effect).However, it has no direct effect on contractility. The chronotropic effect of PTH is mediated also via protein C activation.

3-Effect on vascular smooth muscles (vasodilator Action):

PTH causes vasodilatation and decreases the mean arterial blood pressure. PTH is also a potent coronary vasodilator and increases renal blood flow. This action is mediated by a cAMP dependent inhibition of L- Ca^{++} channels i.e. decreases Ca^{++} influx in the smooth muscle cells.

•Control of Secretion:

-The parathyroid is not under the control of CNS or anterior pituitary. It is controlled by the level of **calcium ions** in plasma by a **simple negative feedback mechanism** i.e. increase in Ca^{++} ions → inhibits parathormone secretion , while the decrease in calcium ions concentration stimulates parathormone production.

-Moreover, it was found that adrenaline increases PTH secretion via β -receptor stimulation, an effect which can be abolished by β -blockers such as propranolol

• Disorders of Parathyroid function:

1-Hypoparathyroidism:

-Causes:

- Parathyroid deficiency may occur as a primary disorder in which the glands do not secrete sufficient Parathormone as an immune disorder .
- The commonest cause however is **accidental removal of the parathyroids surgically** with the thyroid in cases of total thyroidectomy for thyroid carcinoma .

-Clinical Picture :

1-Increase in phosphates in blood.

2- Calcium level in blood falls from the normal 10 mg to 7 mg% → Tetany due to : - decrease in calcium absorption from the GIT

-Inactivity of the osteoclasts of bone and depressed bone resorption . The bones are usually normal, though new growth of bone may be suppressed . In growing child the growth of new teeth is inhibited (due to decrease total body calcium)

3-Hypocalcaemia → neuromuscular hyperexcitability → Tetany .

4- Tachycardia → irregular rhythm .

5- Nausea and vomiting

-Treatment : 1-Parathormone : is not used (short duration and inactivated by antibodies) .

2- Vitamin D : Causes increase in calcium absorption from the GIT , also causes a weak effect in promoting calcium and phosphate absorption (mobilization) from bones , so it increases the blood calcium level.

3. A.T.10 (Di-hydroxycholesterol) : Has the same effect as parathormone but it does not develop anti-hormones on repeated injection.

Tetany

• Definition:

It is a state of increased neuromuscular excitability caused by a decrease in the serum calcium ions concentration.

• Causes :

1- Hypo-parathyroidism → hypocalcaemia.

2- Alkalemia → decrease solubility product → precipitation of calcium phosphate → decrease un-ionized serum calcium level. **Alkalemia** occurs in the following conditions :

- Hyperventilation .
- Vomiting (alkali reserve).
- Ingestion of large amounts of NaHCO_3 , as a treatment for hyperacidity .

3- Administration of citrates (as in blood transfusion) → precipitates calcium as unionized calcium citrate .

4- Decreased calcium ions absorption from the GIT due to:

- Steatorrhea (fatty diarrhoea) .
- Low calcium intake .
- Lack of vitamin D .
- Increased alkalinity of GIT content.

•Types of tetany:

1. Manifest tetany:

In which plasma Ca^{++} level is **below 7 mg%** and hypocalcaemia manifest itself by :

- Cramps of the limbs in the form of : **Carpal Spasm** (Accoucheur's hand = Obstetrician's hand) flexion at the elbow , wrist , metacarpophalangeal joints, extension at the interphalangeal joints and adduction of the thumb . **Pedal spasm** : Dorsiflexion of the foot and planter flexion of the toes. Asphyxia due to laryngeal spasm , it may be fatal

2. Latent tetany:

- In which plasma Ca^{++} level is **above 7 mg % and below 9 mg%** .

-No tetanic symptoms are present, only appear after exposure to stresses; during pregnancy, lactation, hyperventilation ... etc.

- **Diagnosis of Latent tetany:** 1- Determination of Ca^{++} ion level in blood

2- Erb's sign; Stimulation of the motor nerve by sub-minimal galvanic current → carpal spasm (increased neuro-muscular excitability)

3- Chvostek's sign : Sharp tap on the facial nerve at the angle of mandible produces a twitch of the facial muscles.

4- Trousseau's Sign : Is the induction of carpal spasm by reducing the blood flow in the arm with a sphygmomanometer cuff in less than three minutes (the pressure must be more than the systolic pressure)

-Treatment :

- During attack ; Calcium gluconate 10% 10 C.C.by slow intravenous injection

- For Latent tetany : - Vitamin D₂ . - AT 10 . - Oral calcium.

-Acidifying salts (NH_4Cl) increase the calcium ionization .

2-Hyperparathyroidism:

-Causes: The primary cause is mostly an adenoma (a tumor) of a **single parathyroid** gland in 80 % of cases. In 15 % of cases multiple adenomas or hyperplasia are responsible , while in less than 5 % of cases a carcinoma of the parathyroid is found.

-The clinical features :

1- Stimulation of osteoclast → mobilization of Ca^{++} and phosphate from bones to the blood → decalcification of bones causes : **Osteitis Fibrosa Cystica**.

Manifested by: bone pains , fragile easily broken bone responsible for pathological fractures , bone cysts in lone bones and the jaw.

2-Hypercalcaemia : depression of excitability → weakness of skeletal muscles as a result of :

- Depression of sensory and motor nerves activity . - Histologically verifiable myopathy .

3- Tiredness , lethargy and mental confusion leading if untreated to coma and even death.

4- Parathormone and hypercalcaemia together have a stimulating effect on gastric acid secretion → dyspepsia and duodenal ulceration.

5- Deposition of calcium in soft tissues :

- In the **heart** : bradycardia , arrhythmia in the form of heart block.

- In the **kidney** tissues : Nephro-calcinosis : deposition of multifocal calcium salts within the kidney parenchyma → decreases renal absorption → polyuria (Nephrogenic diabetes insipidus) ,impaired glomerular function → progressive renal glomerular failure.

6- Formation of **Stones** (Renal Calculi).

Thank You