Endocrine System Part (I)

TABLE OF CONTENTS:

IMPORTANT NOTICE:

THESE NOTES ARE ONLY A **HELP** FOR STUDYING THE PHYSIOLOGY OF THE ENDOCRINE SYSTEM AND IT **SHOULD BE REFERED TO OTHER RESOURCES FOR THE EXAM PUPROSE.**

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.... WITH REGARDS

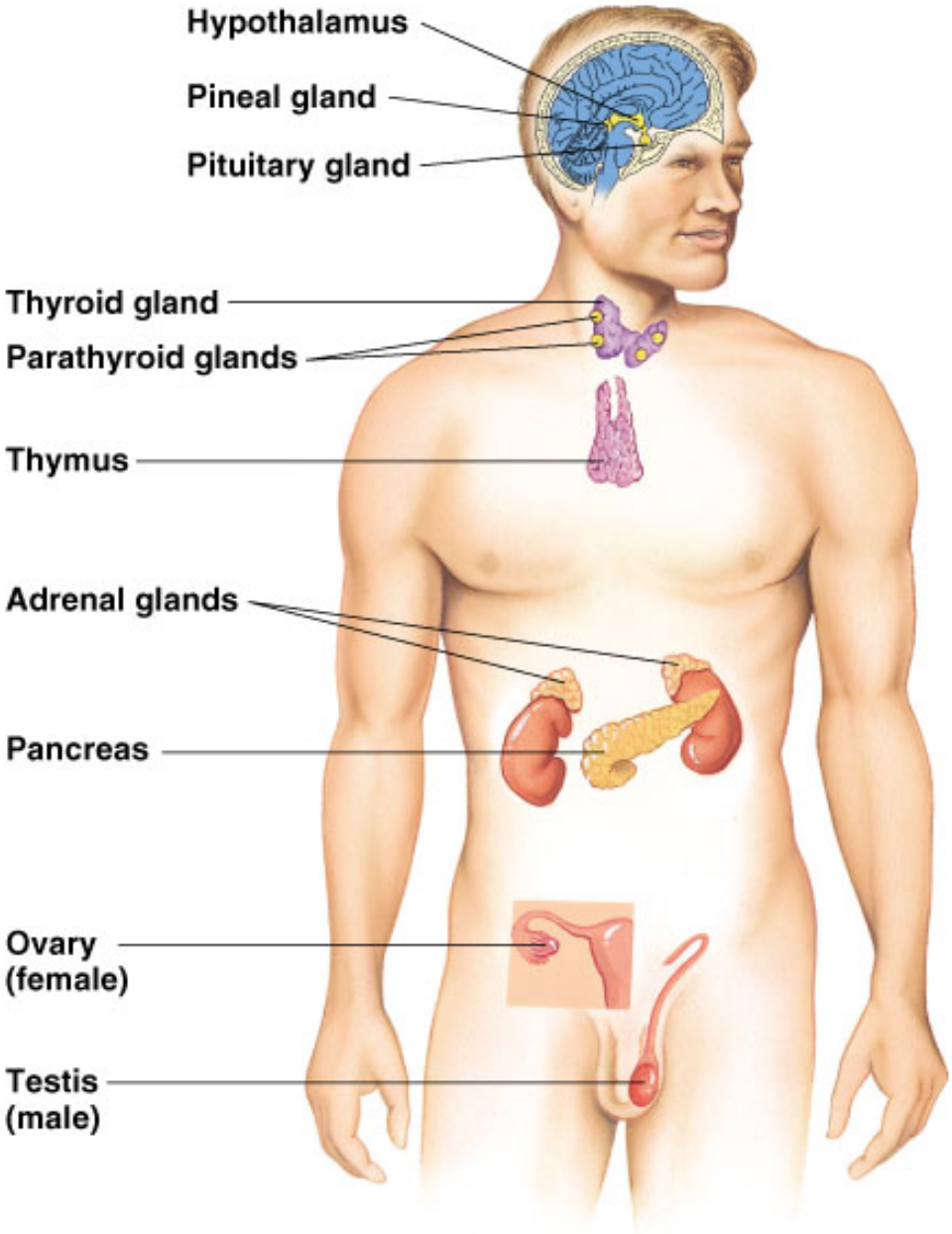
PSL TEAM (A) 427

I. INTRODUCTION TO ENDOCRINOLOGY

Components:

1. Endocrine Glands
2. Hormones
3. Target Cell

- These are many endocrine gland e.g. pituitary, hypothalamus, thyroid, parathyroid.



- **Endocrine** system & **nervous** system work with each other to **regulate** body metabolism.

Function (main function):

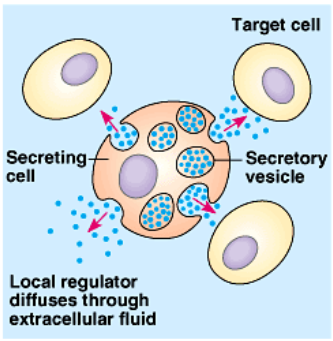
1. Maintain internal environment (**homeostasis**)
2. **Energy** production, utilization , and storage
3. **Growth** & development
4. **Reproduction**

Endocrine Glands Secret hormones:

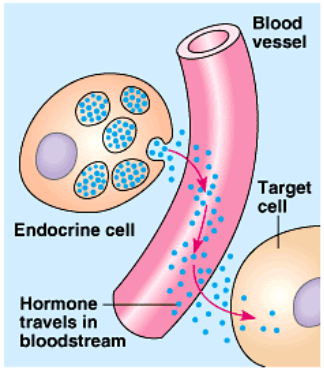
Hormone: Chemical messenger secreted by an endocrine gland

Ways of signal transportation:

- Transported by **blood** (hormonal transport)
- **paracrine** mechanism: Transport from the cell that produces it to **the near cell** by diffusion e.g. histamine – prostaglandin.



Paracrine signaling



(b) Long distance (hormonal) signaling

- **Autocrine**: affect the same cell that produces it. E.g. Prostaglandins

*Hormone are classified into **4 groups** according to their **chemical structure**:*

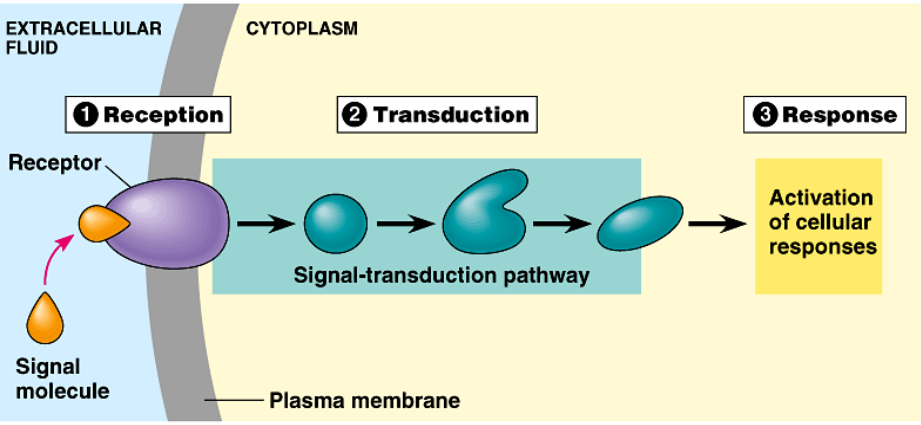
1. **Amino acid derivatives** (derived from tyrosine & tryptophan mainly):
   - **Adrenal medullary** hormones
   - **thyroid** hormone
2. **Polypeptide** (e.g. ADH) & **proteins** (eg. Growth hormone)
3. **Glycoprotein**. e.g. FSH & LH
4. **Cholesterol** (desired from lipids) (steroid hormones) e.g. testosterone , estrogen, progesterone adrenal cortical hormone (Vit. D can act as vit & hormone)

- All hormones are found in very **low concentration in blood** & certain sites of cells called receptor have high affinity to the hormone.

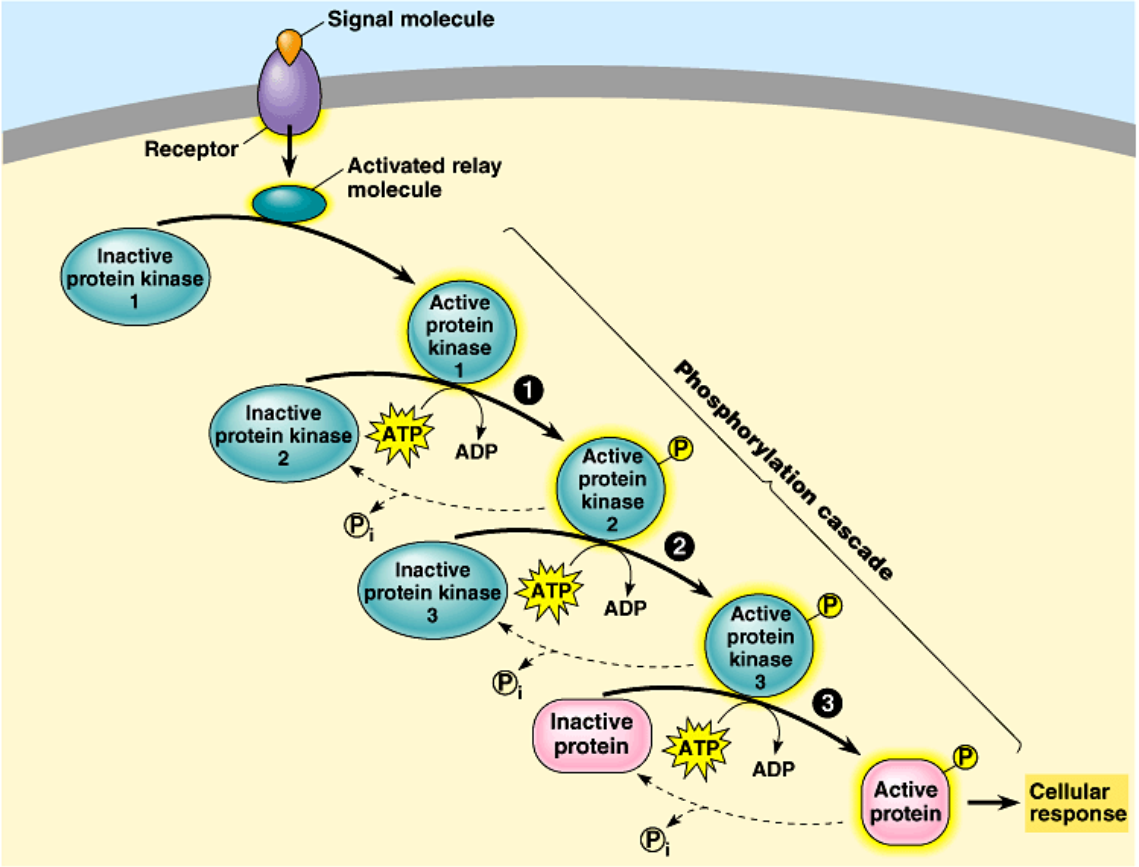
Receptors (properties):

1. Mainly **protein** in nature & can be **glycoprotein**.
2. **Most** of the receptors are **bound to the cell membrane** but it **can be intracellular receptor.** E. g. of intracellular receptor hormone:- Steroid hormone , Thyroid hormone , Vit. D
3. Combine with **high affinity with the hormone** ➔ concentrate the hormone in the cell (This is one of the ways to detect hormones even if the hormone concentration is ↓).
4. **Dynamic** in number: don't have constant number it can (↑ hormone) or (↓ Receptor).
   - If there is ↑ in hormone cone, down - regulation of the receptor occur.
   - If there is ↓ in hormone cone, up – regulation of the receptor occur.
5. **Switch** on the hormone action ➔ The **combination** of receptor & hormone **initiates sequence** of reactions.
6. Receptor **varies in distribution** according to different hormone. E.g. Insulin receptors are joined almost in all cells.

After the hormone activity is switched on the combination of receptor & hormone ➔ sequence of reaction



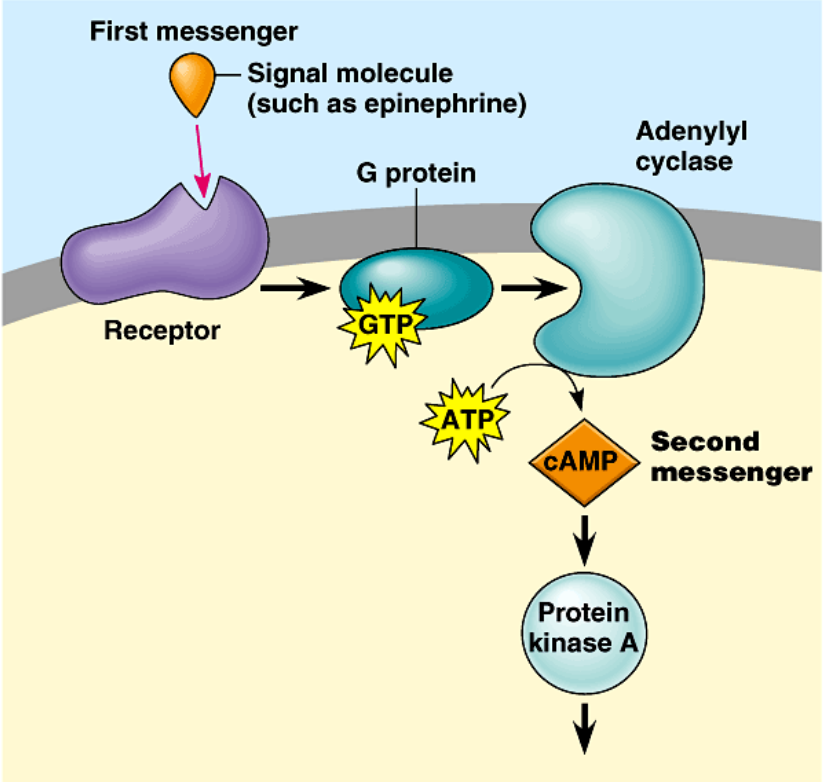
Second messenger: molecular action ➔ relay the hormone, amplify the reaction.



Types of 2nd Messenger:

1. **Cyclic Nucleotides** e.g.**:**

    - cAMP .It is very common. e.g. of hormone that uses cyclic AMP as a second messenger: - Glucagon, L.H. , Epinephrine.

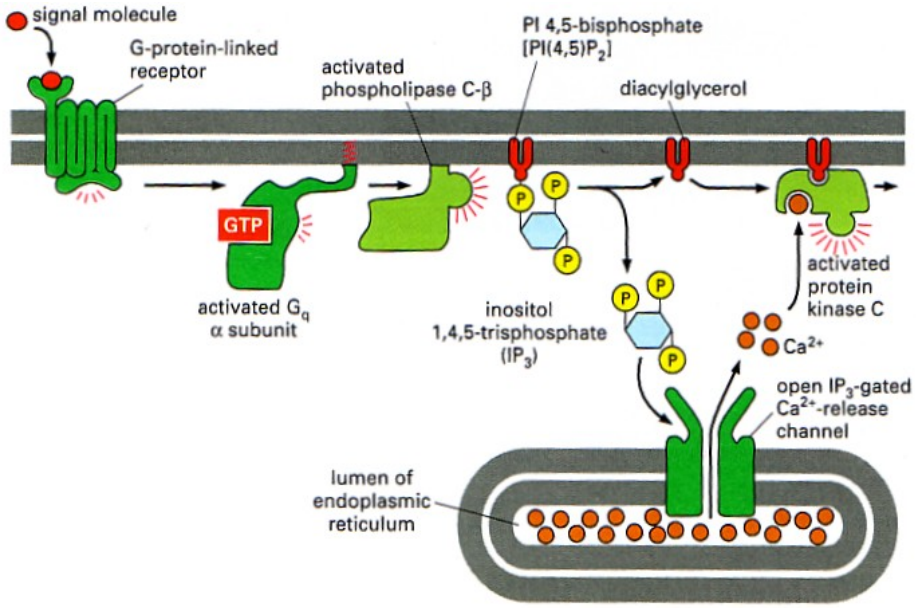


- cGMP (cyclic Guanosine monophosphate). It is limited & uncommon, and the receptor is intracellular. E.g. of hormone the uses cGMP as a second messenger: ANP, Nitric Oxide.

2. **Inositol Triphosphate (IP3) Diacyl glycerol (DAG)**. When the hormone binds to the receptor it stuimulates Gq protein which binds GTP instead of GDP ➔ phosphliapace C cleaves certain phospholipids in cell membrane ➔ releasing IP3 & DAG.

   - IP3 stimulates Ca++ relaease from ER. & binding of calmoduling
   - DAG activates protein kinase C

   E.g. of hormones: vasopressin, TSH



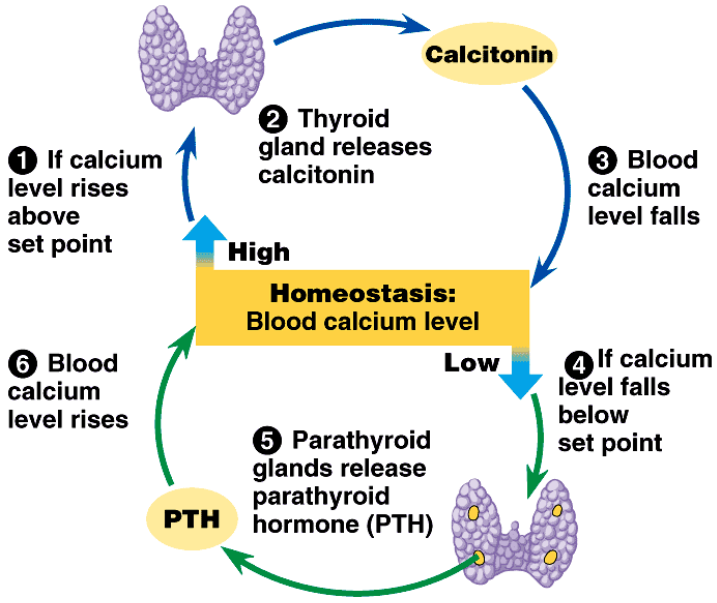
3. **Calcium (calmodulin):** act as a 2nd or 3rd messenger**.**

Control of hormone actions is by feed-back mechanism…1

- **Negative feed back mechanism**. It is the most common control. It can either increase or decrease hormone secretion depending on hormone concentration:
    - ↑ hormone reception ➔ negative feedback after the action of the hormone ➔ ↓ hormone action & secretion.
    - ↓ hormone reception ➔ negative feed back after the action of the hormone ➔ ↑ hormone action & secretion.

[1] For more information regarding feedback mechanism see Guyton Physiology 11th ed. p.7-9

An example of negative feedback is Ca++ control as seen below



- **Positive feed back mechanism** in which↑ hormone reception ➔ ↑ hormone action & secretion. (e.g. oxytocin)

Solubility Properties of Hormones (generally)… Hormones can be

1. **hydrophilic** (water soluble) e.g. peptide & proteins or
2. **hydrophobic** (water insoluble) e.g. steroid & thyroid and **need carrier protein for:**
    - Making the hormone more **soluble**
    - ↑ hormone **half life**

Stimuli for hormone secretion:

1. **Chemical stimuli** (e.g. glucose ➔ insulin secretion)
2. **Neural stimuli** (e.g. acetyl choline (ACh) which is secreted by sympathetic neurons to adrenal medulla ➔ ↑ epinephrine & norepinephrine secretion)
3. **Hormonal Stimuli** (↑ ACTH ➔ ↑ adrenal cortex secretion)

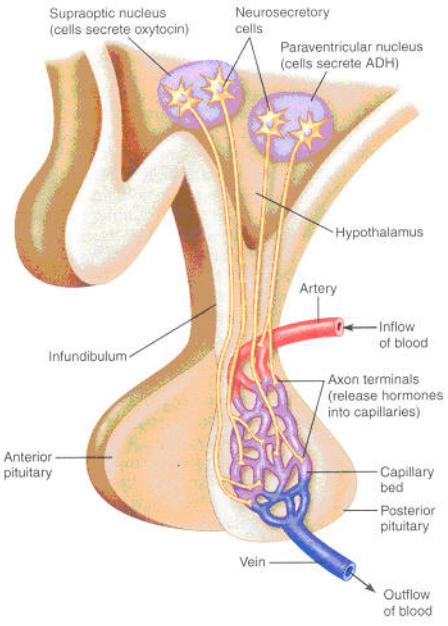
Endocrinopathies (Diseases related to the endocrine system):

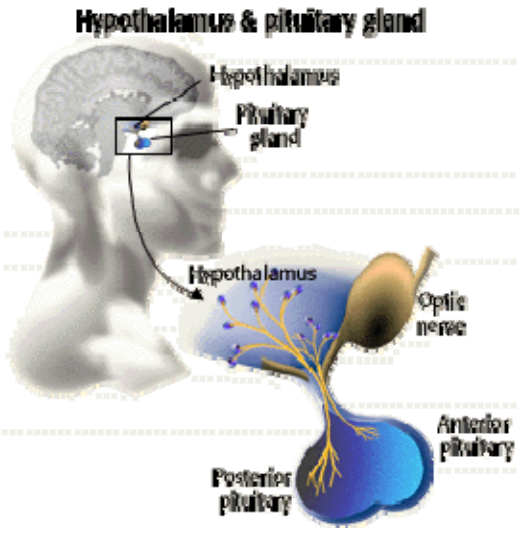
1. Too little hormone secretion
2. Too much hormone secretion
3. End organ insensitivity or resistance e.g. no receptors.

HYPOTHALAMUS & PITUITARY GLAND

General Introduction

- **Hypothalamus** is found in a **small depression** at the base of the **skull** and acts as a part of endocrine or neuronal system.
- **Hypothalamus** is in **direct relation** to the **pituitary gland**.
- The pituitary is 1 cm in diameter & 1 gm in weight & found at he base of the skull.
- Pituitary gland: 2/3 is the anterior portion (adenohypophysis) & 1/3 is the posterior portion (neurohypophysis).





- **Posterior gland** is considered as a **part of the hypothalamus** and **stores hormones secreted by hypothalamus.**
- The **hypothalamus** is connected to **posterior pituitary** gland by **nerves** originated from the hypothalamus.
- The **hypothalamus** is connected to the **anterior pituitary gland** by **portal blood vessels**.
- The **control** of the secretion of the hormones from the **hypothalamus** to the **anterior pituitary gland** is through **releasing hormones** secreted through the **blood** vessels **NOT by nervous system.**

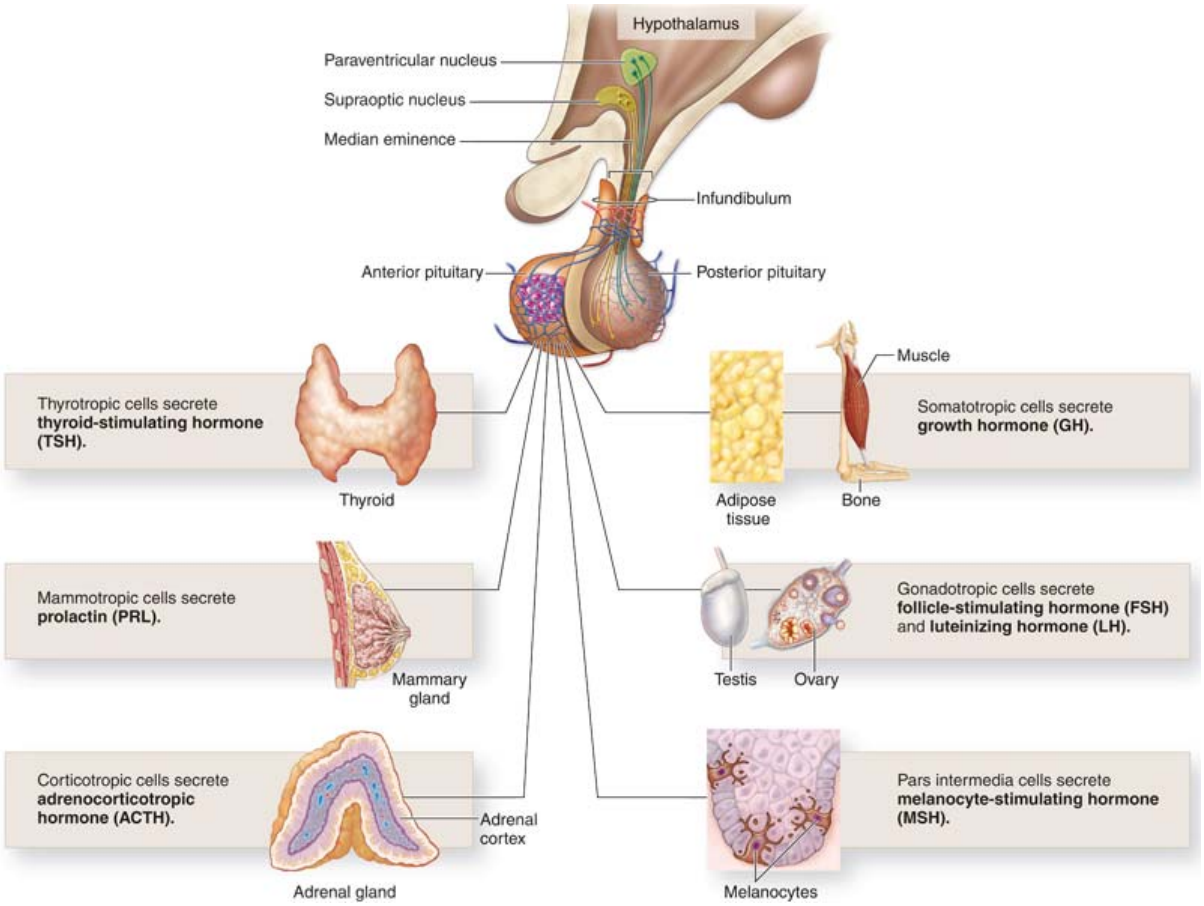
Hypothalamic Releasing Hormones:

1. **Corticotropin Releasing Hormone** ➔ ↑ ant gland AdrenoCorticoTrophic Hormone (**ACTH**) secretion ➔ ↑ **adrenal cortex** hormone secretion (e.g. glucocorticoids, androgens).

2. **Thryrotropin Releasing Hormones** ➔ ↑ ant. gland Thyroid Stimulating Hormone (**TSH**) secretion ➔ ↑ **Thryoid gland hormones** (e.g. T_3, T_4).
3. **Gonadotropin Releasing Hormones** ➔ ↑ ant. Gland **L.H & FSH** ➔ ↑ **gonads sex hormones** & ovulation.
4. **Growth Hormone Releasing Hormone** ➔ ↑ ant. Gland **Growth hormone secretion**
5. **Somatostatin**: **inhibit TSH & Growth hormone**. Can be secreted from hypothalamus and from D cell in pancreas. It is usually inhibitory.
6. **Dopamine: inhibit prolactin**. (It is a catecholamine such as epinephrine).

Anterior Pituitary Hormones:

1. AdrenoCorticoTrophic Hormone (**ACTH**) ➔ ↑ adrenal cortex hormone secretion (e.g. glucocorticoids, androgens).
2. Thyroid Stimulating Hormone (**TSH**) ➔ ↑ **Thryoid gland hormones** (e.g. thryotropin, T_3, T_4).
3. Luteinizing Hormone (**LH**) & 4. Follicle Stimulating Hormone (**FSH**) ➔ ↑ **gonads sex hormones** & ovulation
5. Growth Hormone ➔ **directly** to target organs stimulating growth (discussed in this section)
6. Prolactin ➔ **directly** to target tissue(discussed in this section)



Intermediae lobe…

- Only in fetal life & disappears in adults
- It releases the polypeptide pro opio melano cortin. This is the precursor of:
    - **ACTH**: secreted also from ant. Pituitary.
    - **MSH** (Melanocyte stimulating hormone: Disappears in adult life
    - **β-endorphin**: also secreted from brain. It has morphine like action (pain killer) It is inactivated in rest condition, and it only becomes activated in stress conditions.
- The relation between ACTH & MSH can be shown if there is excess secretion of ACTH (i.e. Addison's disease), the patient will have skin pigmentation because ACTH & MSH have similar amino acid sequence.

Growth Hormone (a hormone for growth & metabolism..)

- Secreted throughout life, and its effects are:
    - In children: Growth & developmental effects

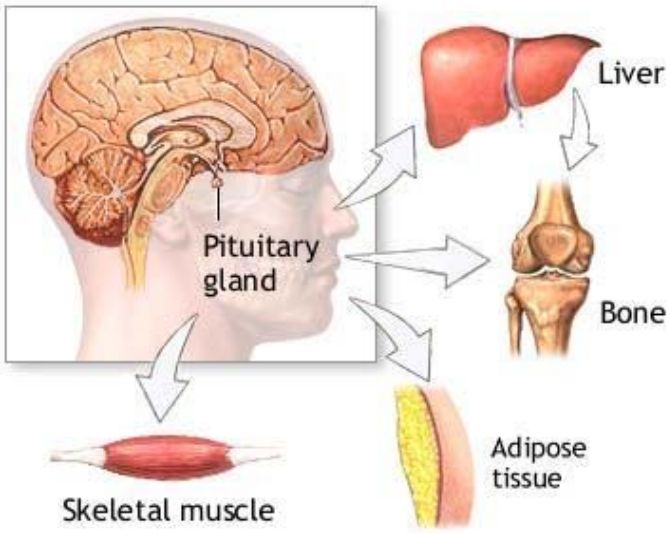
- In adults: mostly metabolic effects (except in some pathologies discussed later)

Metabolic effects:

- **Proteins: anabolic**
  - Enhancement of amino acid transport through cell membrane
  - RNA translations & synthesis by ribosomes
  - DNA ➔ RNA
- **Carbohydrates: hyperglycemic**
  - ↓ **entry of glucose** in skeletal muscles & adipose tissue
  - **Inhibiting insulin action** ➔ ↑ blood glucose level
  - Receptors in pancreas detect hyperglycemia and stimulate **insulin** secretion as a **compensation.**
  - Chronic (مزمن) excess hormone secretion can lead to **diabetes mellitus**.
- **Fats: catabolic**
  - Enhancement of **cleavage** of triacylglycerol ➔ ↑ fatty acid in blood
  - Chronic (مزمن) excess hormone secretion can lead to **ketoacidosis** (↑ fatty acid degradation ➔ ↑ production of ketone bodies ➔ ketoacidosis.

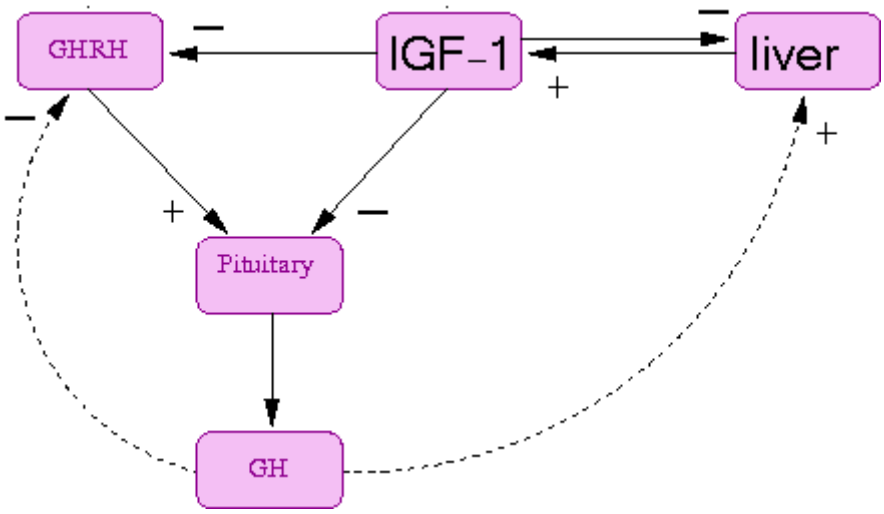
Growth Effects (it is the most important factor on postnatal growth):

- **Bone:** ↑ proliferation of epiphyseal cartilage plates ➔ ↑ linear growth (height)
- **Connective tissue:** ↑ proliferation (skin), thickening of skin
- **Soft tissues:** ↑ growth ➔ hypertrophy & hyperplasia (↑ in # & size of cells).



Somatomedins (IGF)

- Growth hormone ➔ liver which produces somatomedin C [Insulin Like Growth Facto I (IGF-1)] ➔ act mainly on cartilage ➔ ↑ proliferation of ephphseal cartilage ➔ ↑ linear growth.
- One of the reasons of having somatomedins is to have a **longer effect** of the hormone (half life of growth hormone = 20 minutes, half life of IGF = 20 hours!!!).



Factors controlling Growth Hormone:

1. **Hypothalamus:**
    - **Growth Hormone Releasing Hormone** ➔ ↑ ant. Gland **Growth hormone secretion**
    - **Somatostatin** ➔ ↓ growth hormone
2. **↑ Protein & amino acids ➔ ↑ GH**

3. **Hypoglycemia ➔ ↑ GH,,,, Hyperglycemia ➔ ↓ GH**
4. **Exercise ➔ ↑ GH**
5. **Stress condition** (e.g. trauma & emotion) **➔ ↑ GH**
6. **Sleep ➔** ↑ **GH** especially in children
7. **Aging ➔** ↓ **GH**
8. **Cortisol, glucose ➔ ↓ G.H.** (Children getting glucocorticoids drugs ➔ ↓ growth)

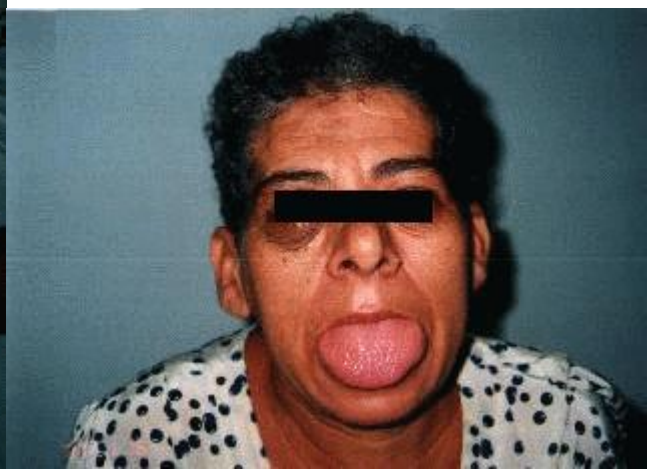
Other hormones that are necessary for growth & act together with growth hormone:

1. **Insulin ➔**
    - **anabolic** (especially **proteins**),
    - enhance protein synthesis & storage)
    - Interacts with IGF-1
2. **Thyroid** Hormone ➔
    - skeletal growth,
    - CNS Growth (especially brain growth).
    - Stimulates growth hormone secretion.
3. **Androgens**: anabolic hormones for nutrient especially protein ➔ ↑ G.H. secretion & ncr epiphyseal closure (terminate the linear growth)
4. **Estrogen ➔** ↑ closure of the epiphysis
5. **Cortisol ➔** inhibit growth

Abnormalities

1. **Excess GH secretion in:**
    - A **child ➔ Gigantism**
    - **Adults ➔ Acromegaly**:
        - characterized by **growth** & proliferation in **soft bone** especially the hands & in **soft tissue ➔** ↑ in size of tongue, gut, ↑ thickness of skin.
        - occurs usually at the **age 40-50**.
        - Affects **females more** than males.

- can lead to **diabetes mellitus** because of **hyperglycemia**.



2. **Deficiency of GH:**
    - **Children ➔ dwarfism** (don't affect the brain, no mental retardation)
    - **Adults ➔ no effect** (because its actions could be compensated by other hormones)

Prolactin Hormone

- Secreted from **anterior pituitary gland**
- Acts **directly** on the target tissue.

Actions:

- ↑ **milk production** by the lactating breast
- ↑ **development** of the **breast**

Control

- **Suckling ➔** ↑ prolactin
- **Visual & Auditory** stimuli (secondary stimuli) **➔** ↑ prolactin
- From the **hypothalamus**: Thyrotropin Releasing Hormone (**TRH**) (also called Prolacine Releasing Hormone) **➔** stimulates the **ant. Pituitary.**releasing of TSH & **Prolactine**
- From the **hypothalamus ➔ Dopamine** (prolactin inhibiting hormone) inhibit prolactin secretion

HyperProlactenemia (Due to adenoma (benign tumor) of the ant. Pituitary gland)

Excessive prolactin secetion **➔** ↓ gonadotropin (negative feedback mechanism)

- **In females: hyperprolacenima ➔**
    - **Amenorrhea** (no menstrual cycle)**, infertility**
    - **Galactorrhea ➔** ↑ milk secretion
- **In males: HyperProlactenemia ➔**
    - **Infertility**
    - **Gynecomastia** (increased breast tissue in male)

Treatment: removing the tumor

Posterior Pituitary Gland (general)….

- It does **not synthesize hormones** but **stores** hormones synthesized by the **hypothalamus** especially by para-ventricular nucleus & supra-optic nucleus.
- Hormone will flow from hypothalamus by **Axoplasmic** flow to post. Gland.

1. Antidiuretic hormone (ADH) (also called vasopressin)

Synthesized in supra-optic nucleus. It transports in axons by axoplasmic flow to post. Pituitary.

Actions

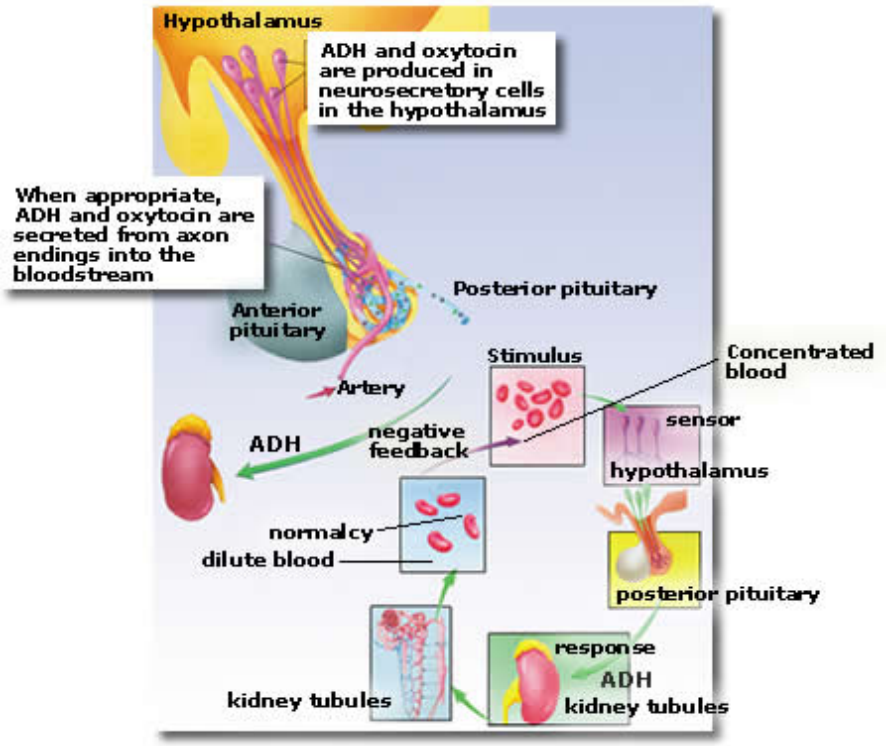
1. **(Main function): Water reabsorption** by the distal tubules through **V_2** Receptor. The hormone will bind with the V_2 receptor & **activate adenyl cyclase** that converts ATP ➔ cAMP ➔:
    - Formation of **water channel proteins** called aquaporions**. It is synthesized in plasma &** then it is **inserted** to cell membrane ➔
        - ↑ H_2O reabsorption
        - ADH also ↑ urea reabsorption that will be accompanied by H_2O reabsorption.
2. ↑ **Smooth muscle contraction** of the blood vessels (vasoconstriction) through **V_1** Receptor. The hormone will bind to V_1 receptor on the blood vessel ➔ **release of Ca^{++}** as a second messenger ➔ vasoconstriction.

Control

1. ↑ plasma **osmotic pressure** (**highly sensitivite** at 1% change in osmolarity) ➔ ↑ ADH. It happens in case of vomiting, diarrhea, etc (loss of hypotonic fluid) ➔ Osmoreceptors ➔ ↑ ADH.
2. ↓ **blood volume** (less sensitive at 10% change in volume) ➔ ↑ ADH. Receptors found in right atrium & in great veins.

Note: ↓ in **blood volume** have **stronger effect** in ↑ ADH secretion than ↑ in osmotic pressure.

3. **↓ in B.P. ➔ ↑ ADH**
4. **Stress** condition, **trauma**, **anxiety** ➔ ↑ ADH
5. **Drugs** like barbiturate, **Morphine**, nicotine ➔ ↑ ADH
6. **Surgery** ➔ ↑ ADH ➔ ↑ water reabsorption ➔ hyponatremia.
7. **Age** ➔ ↑ ADH
8. **Alcohol** ➔↓ ADH
9. **caffeine** ➔ ↓ ADH



Deficiency of ADH

➔ Diabetes Insipidus [the patient will have polyuria (above normal urination), polydepsia (above normal thirst)].
➔ ↑ plasma osmolarity, ↓ urine osmolarity, ↓ specific gravity of urine.

- **Causes of Diabetes Insipidus (DI):**
    - Central (**Neurogenic**) **damage** to **supra-optic nucleus** (the **producer**)➔ no ADH secretion. This is managed by administration of synthetic ADH.
- **Nephrogenic:** ADH secretion is normal, but there is **no reception in kidney** due to **cancer** or any damage to kidneys or hormone sensitivity.

Excess ADH Secretion

- **Causes:**
    - Ectopic **tumor** secreting ADH
    - **Nausea**, **Vomiting**, Trauma, Anxiety ➔ ↑ ADH
    - **Lung** disease
    - After **surgery**
    - **Drugs** like barbiturate, norepinephrine, nicotine.

Oxytocin

- Synthesized in **hypothalamus** (in para-ventricular nucleus) & released by post. Pituitary.

Actions:

1. ↑ Myoepithelial cell contraction of the lactating **mammary duct ➔ milk ejection** (let down reflex)
2. ↑ **uterine contraction during labour** (last period of pregnancy)… if there is no contraction, the mother will be given synthetic oxytocin (cyntocinon).
    - ↑ Estrogen (more sensitive to oxytocin).
    - ↑ Progestrone: (less sensitive to oxytocin, so its level will drop sharply ➔ delivery.
3. Studies in animal show that oxytocin have effect on **social behaviour** (e.g. trust).

Control

- **Visual & Auditory** stimuli (secondary stimuli) ➔ ↑ oxytocin
- **Distension of uterus & stretching of the cervix during labour ➔ ↑ oxytocin (positive feedback)**
- **Coitus (sexual intercourse) ➔ ↑ oxytocin**
- **Psychological factors:**
    - **Fear ➔ ↓ oxytocin**
    - **Anxiety, pain ➔ ↑ xytocin**
- **Alcohol ➔ ↓ oxytocin**

Problems that occur to pituitary gland…

1. Sheehan's Syndrome (discovered in 1961):

Excessive **bleeding** ➔ vasopressin & generalized **vasoconstriction** ➔ infarction or **death** of the **pituitary** gland. If the **entire gland** is affected ➔ **Pan hypo pituiterism**. If part of it the condition is called hypopituiterism. If Pan hypo pituiterism occurs ➔:

- ↓ ACTH ➔ ↓ cortisol ➔ death!!
- ↓ TSH ➔ hypothyroidism
- ↓ Growth Hormone ➔ dwarfism
- ↓ FSH & LH ➔ infertility, absence of seconday sexual characteristics
- ↓ prolactin ➔ failure of lactation. This is the first sign of Sheehan's syndrome.

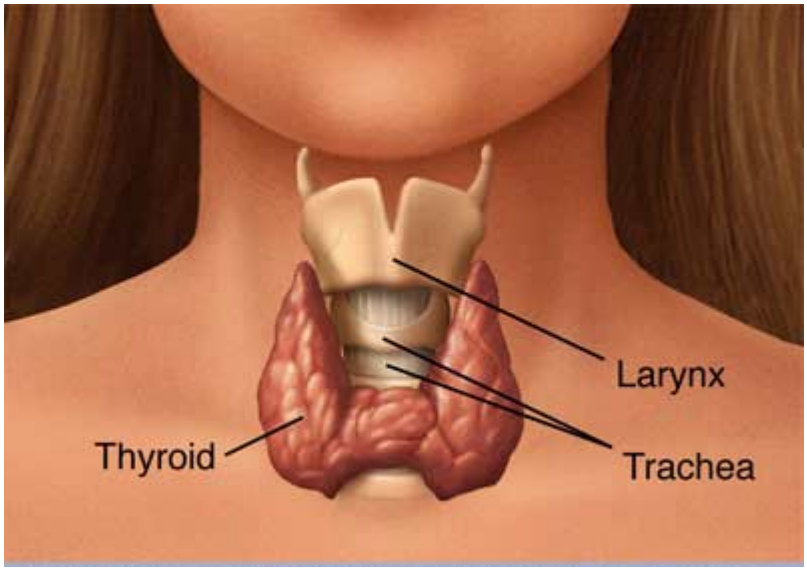
The treatment for pituitary insufficiency is lifelong hormone substitute medication, including estrogen and progesterone hormone replacement. Thyroid and adrenal hormones also must be taken.

2. Adenoma of the pituitary gland: (slowly growing benign tumor), and has two effects:
    a. **Neurological:** The tumor will press the optic chiasm that are located near pituitary gland & that will lead to ↓ vision.
    b. **Secretory effect:**
        i. ↓ if cells are **sensitive to pressure** e.g. growth hormone, FSH & LH
        ii. ↑ other hormones secretion:
            1. ↑ **ACTH** ➔ ↑ cortisol ➔ **Cushing's** Syndrome
            2. ↑ TSH ➔ hyperthyroidism
            3. ↑ prolactin ➔ hyperprolactenemia
            4. ↑ ADH ➔ ↑ H_2O retension ➔ ↑ Blood volume & pressure ➔ edema
            5. ↑ oxytocin (no specific disease)

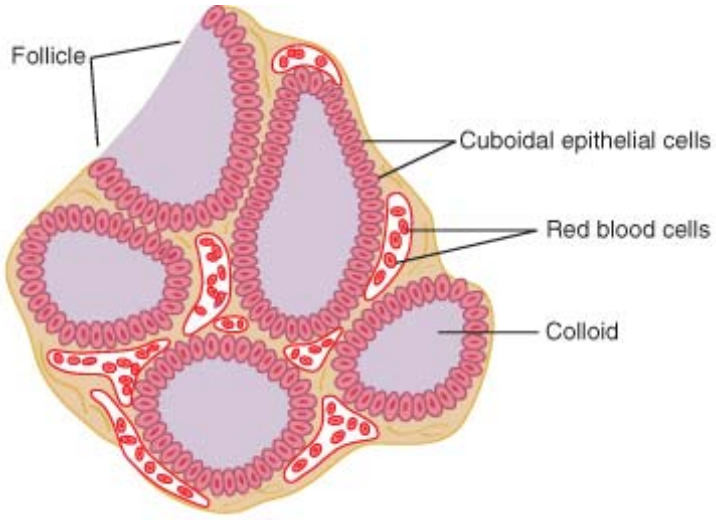
    The treatment is the **surgical removal** of the tumor.

THYROID HORMONE

- Thyroid gland lies **below the larynx** & consist of **2 lobes** on each side of the trachea.



- It **differs in the size** by age, sex, pregnancy, lactation.
- Thyroid gland secretes:
    - **From follicular cells:** Thyroxine (T_4, half life = 1 week), Tri-iodo-thyronine (T_3 Half life = 1,3 days).
    - **Parafollicular cells (c cells):** calcitonine.



- T_3 and T_4 **regulate metabolic function** (Basal Metabolic Rate BMR: the minimum amount of energy required per day OR the minimum amount of energy required at complete physical & mental rest after fasting for 12 hours)
- They are very **important for growth & brain development** of neonates.
- They are usually **stored for 3 months** (if any deficiency occurs it doesn't show immediately).

- **Deficiency ➔ cretinism** (dwarfism & mental retardation) ←➔ (unlike growth hormone deficiency leading to dwarfism but NO mental retardation).

Properties

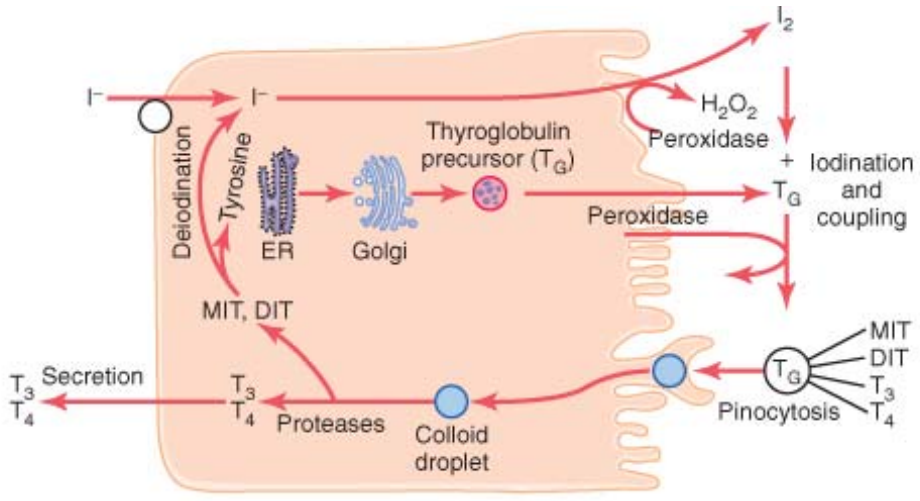
- Thyroid hormones are **hydrophobic** so they are insoluble in water & need a carrier which is globulin that ↑ the solubility of these hormones, prolonged half life.
- They have **nuclear receptors** found in the DNA.
- They have **sluggish** (slow reacting) **action** because:
    - Long **storage** duration in the thyroid gland
    - **Slow degradation** rate
    - **Long half life** in the blood (compared with other hormones)
    - **Long term effects** in the target organs.
- **Iodide** is needed for **synthesis** of thyroid hormone:
    - Sources: in **food** (mainly seafood, iodized salts).
    - It is found in the form of NaI or KI
    - We need **1 gm/week** (50 gm/year).
    - The daily intake of Iodide by food = **100-150** µg/day.
    - **30-50 %** of the daily intake is **absorbed**, the remnant is excreted.
    - **95%** of iodide in circulation is **taken by the thyroid gland**
    - **5%** is taken by **breast & salivary gland**.
    - The **follicular cells** of the thyroid gland **have iodide pump** (iodide trapping) which is **active transport** that lead to **concentrate** the iodide inside the cell on the basal surface.
    - The iodide is **30 times more** in the **thyroid gland** than in blood (it can be 250 times more in case of hyperthyroidism).

Hormone Synthesis

Follicular cells have:

- Apical Surface facing the colloid (have pseudopodia which take part in endocytosis of colloid)
- Basal Surface facing the circulation.

- **Iodide** is **pumped** inside the cell. The process is r**equires TSH**.
- Iodide is **oxidized** to iodine by **perioxidase** enzyme. (deficiency of the enzyme will lead to deficiency of the hormone).
- Follicular cells will **synthesize** glycoprotein called **thyroglobulin** which is found in the colloid of follicular cell. Thyroglobulin contains about **70 tyrosine** amino acids.
- **One iodine** will bind to **tyrosine** to form Mono-Iodo-Tyrosin (**MIT**). **Iodinaze** enzyme (I-Enzyme) will facilitate the binding of tyrosine with iodine. This enzyme is found in the thyroglobulin molecule.
- **2 iodine** will bind to **tyrosine** to form Di-Iodo-Tyrosine (DIT).
- Both of them are formed in thyroglobuin
- DIT + MIT ➔ T_3
- DIT + DIT ➔ T_4
- Only 1/6 of tyrosine in thyroglobuin will form MIT & DIT
- 25% of MIT & DIT will form T_3 & T_4
- Proportion: 93% T_4, 7% T_3.
- Lysosome will **degrade** the **colloid droplet to T_3 and T_4** which enter the circulation & to **DIT and MIT that undergo deiodonation** to form iodide by enzyme **deiodinase**. Iodide is reused in the thyroid hormone synthesis.



blood colloid

- In the **tissues** most of **T_4** is **converted** to **T_3 by deioidantion** because **T_3 is more potent than T_4** & nuclear **receptor has got more affinity** to T_3 compared to T_4 by 4-5 times.

➔ 90% of T_3 binding to receptor, 10% of T_4

- **T_4 can be converted to Reverse T_3 (rT_3) which is inactive**. It is formed only in the target organ. In **stress** condition when there is ↑ **cortisol** that will lead to ↑ formation of rT_3 & that will lead to conditions called hypothyroidism.
    - rT_3 sill **compete T_3 for the same receptor**.
    - rT_3 is formed in case of stress condition e.g. starvation.

Metabolic effects of thyroid hormone

- *Anabolic (Mostly active in normal thyroid hormone concentration):*
    - ↑ **synthesis of proteins.**
    - ↑ **synthesis of fats.**
    - ↑ **synthesis of glycogen.**
    - ↑ **gluconogenesis.**
- *Catabolic (Active during hyperthyroidism):*
    - ↑ **degradation** of **proteins**
    - ↑ **degradation** of **fats**.
    - ↑ **degradation** of **glycogenolysis**.
- *Enhancement of:*
    - **Insulin** secretion
    - **Growth Hormone** Action
    - ↑ **sympathetic** effects.
- *Physiologic effects:*
    - Proteins:- ↑ mRNA ➔ formation of **many intracellular new proteins**. These proteins can be:
        - **Enzymes.**
        - **Transport proteins**
        - **Structural proteins.**

        Synthesis of proteins ➔ overall activation of the body.
    - ↑ Number & activity of **mitochondria** ➔ ↑ ATP ➔ hydrolysis of ATP ➔ heat.

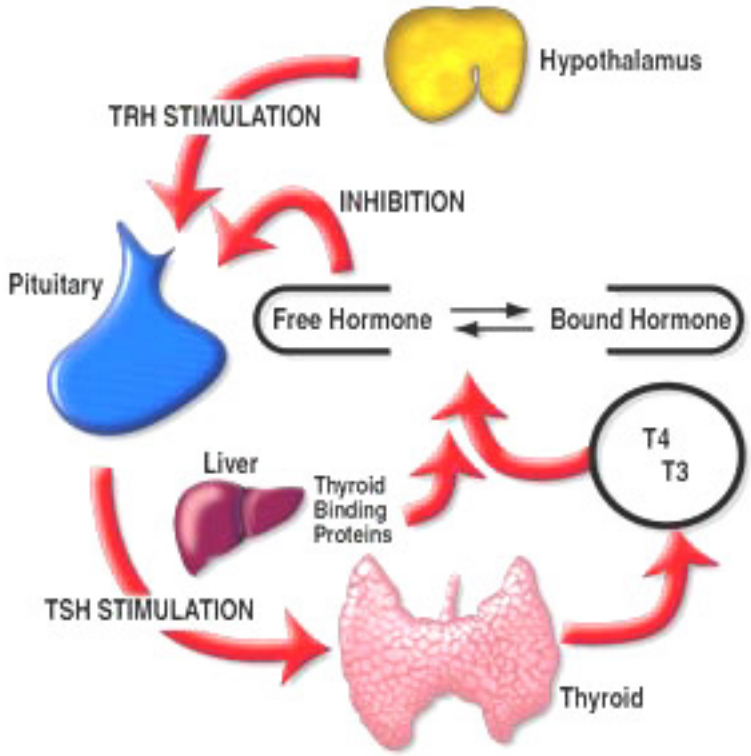
- ↑ **BMR**[2]
- **Growth** (especially children): body growth & **brain** development. It is very **crucial for brain growth** in:
  - Fetal life: 2nd and 3rd trimester.
  - Neonatal life: 0-6 months.

  After the 6 months it is also needed for brain growth but it is not crucial. Deficeincy in that period will affect the brain but to a less extent than the crucial period.
- **Carbohydrates**: (**normoglycemic** both ↑ degradation & synthesis of glucose).
  - ↑ glucose **absorption**
  - ↑ **gluconeogenesis**
  - ↑ **glycolysis**
  - ↑ **insulin** secretion.
- **GIT: ↑ motility & ↑ secretion.**
- **Muscles**:
  - **Hyperthyroidism ➔ muscle weakness** (due to protein catabolism) & muscle tremors (fine tremor of the finger when the hand is streched)
  - **Hypothyroidism ➔ slow** muscle **relaxation** after contraction.
- **Brain**:
  - **Hyperthyroidism ➔ anxiety**, restlessness & insomnia (low sleeping).
  - **Hypothyroidism ➔** the patient will sleep too much (**prolonged sleep**)
  - If there is **↑ sleeping pulse** (85-90) ➔ hyperthyroidism… (measurement of sleeping pulse is important to test the thyroid gland function).
- **CVS: ↑ Heart Rate, ↑ Cardiac Output**.
- **↑ Respiration** (↑ metabolism)➔ ↑ CO_2 ➔ stimulation of respiration center ➔ ↑ Respiratory Rate & depth).

[2] To know more about BMR see the beginning of this chapter THYROID HORMONE

Control

- **Thryrotropin Releasing Hormones** (from hypothalamus) ➔ ↑ ant. gland Thyroid Stimulating Hormone (**TSH**) secretion ➔ ↑ **Thryoid gland hormones** T_3, T_4.
- **Cold** temperature ➔ ↑ both TSH & Thyrotropin Releasing Hormone.
- **Hot** temperature ➔ ↓ both TSH & Thyrotropin Releasing Hormone.
- **Stress** condtiton ➔ ↑ cortisol ➔ ↓ both TSH & Thyrotropin Releasing Hormone.
- **Sleep** ➔↓ both TSH & Thyrotropin Releasing Hormone.
- **Starvation** will inhibit the conversion of T_4 tp T_3 & stimulates the conversion of T_4 to rT_3.



Pathophysiology of T_3/T_4:

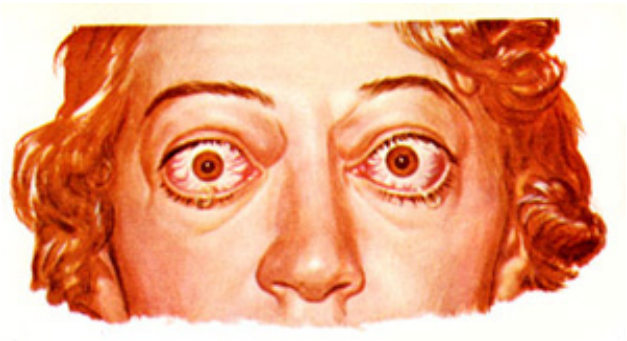
Hypothyroidism ➔ ↓ BMR:

- **Intolerance to cold**
- **Cold & dry skin**
- **Constipation**
- **↓ appetite**

- **↑ body weight (because of prolonged sleeping)**
- **edema (general edema) due to edema in the larynx.**
- **Hoarse (rough) voice & weak voice**
- **Coarse (rough) hair**
- **Mental Weakness**
- **Impaired memory**

Hyperthyroidism ➔ ↑ BMR:

- **Intolerance to heat**
- **Warm & wet skin** (due to sympathetic stimulation).
- **↑ Appetite, ↓ body weight** (due to excessive activity)
- **Diarrhea**
- **Insomnia**
- **Restless, Anxiety (due to stimulation of CNS).**
- **Muscle weakness, tremors (due to ↑ metabolism)**
- **Exophthalmos** (protrusion of the eyes) due to retro-orobital edema with upper lid retraction. (we can see the whit sclera above the cornea). If not treated it will cause damage to optic nerve ➔ blindness. **Eye symptom:** Grave's disease



- **↑ respiration (due to ↑ CO_2).**

Goitre ➔ enlarged thyroid

Causes of Goitre:

- **Grave's disease** (the **most common** cause of hyperthyroidism). it's **primary** (due to a condition related to the thyroid gland itself). It is an **autoimmune** disease caused by **TSI** (Thyroid Stimulating

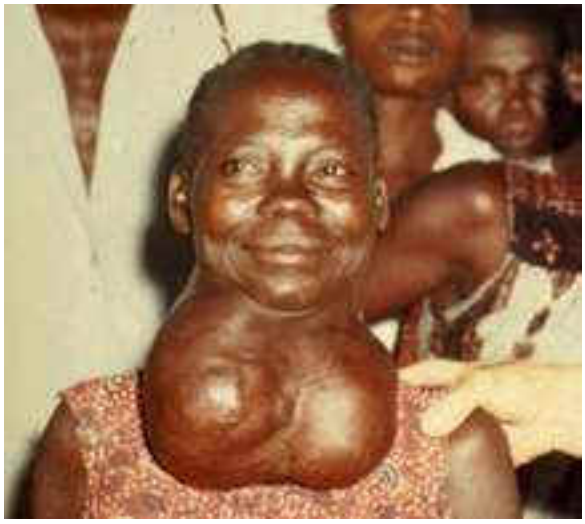
Immunoglobulin) which is an antibody of **IgG** class. It is also called **LATS** (Long Acting Thyroid Stimulator). TSI will:

- **Bind TSH Receptor**
- **↑ iodide uptake**
- **↑ T_3/T_4.**
- **↓ TSH** (due to negative feedback mechanism).

This problem is **more common in females**, and the treatment could be:

- Sulfonamides inhibiting thyroid gland.
- Irradiation
- Surgery

- **Hashinto's Thyroditis**
  - Lead to **hypothyroidism** (**primary** because thyroid itself is affected).
  - It is **autoimmune** disease
  - **Antibody ➔ inhibit perioxidase** enzyme ➔ ↓ T_3 & T_4 ➔ ↑ TSH.
- **Simple Goitre**: due to iodine difficiency in the diet.
  - **The patient will have ↓ T_4, T_4.**
  - **↑ TSH ➔ hypertrophy of the thyroid gland.**



Secondary Hyperthyroidism

Adenoma of pituitary ➔ ↑ TSH, T_3, T_4

Seconday hypothyroidism

Infarction of pituitary gland ➔ ↓ TSH, T_3, T_4

CALCIUM HOMEOSTASIS

Ca^{++} is important in:

- **Muscle contraction**
- **Structure of bone**
- **2nd & 3rd messenger**
- **Release of ACh**

↓ Plasma Ca++ (which is more dangerous than ↑)➔ ↑ membrane permeability to Na^+ ➔:

- **Spontaneous action potential**
- **Hyper reflexia** (low threshold)
- **Tetany** (continued contraction) can lead to death because it could lead to continued contraction of larynx & prevent the entry of the air. (**laryngeal** spam ➔ **death**).

↑ Plasma Ca++ ➔ ↓ Na^+ permeability ➔:

- **Hyporeflexia** (high threshold)
- **Stone** formation
- Peptic **ulcer**
- Cardiac **arrhythmias**.

Properties

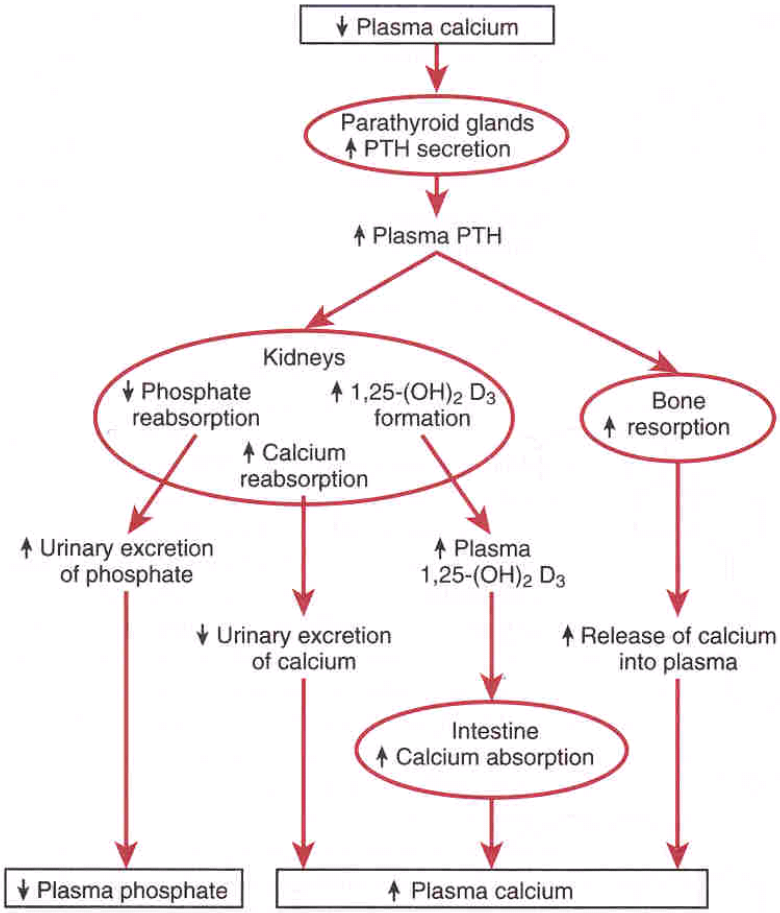
- **Normal** Ca++ concentration is **10 mg/dl** (2.5 mmol/L)
- **50% of calcium is free** (5mg/dl) & this is the only for of Ca++ which is biologically active.
- **Forms** of Ca++ in blood:
    - **Protein bound (40%)**
    - **Ultra filterable (60%):**

- **Complemented to anion 10% (phosphate, sulfate, citrate).**
- **Ionized Ca++ 50% (the free active Ca++)**

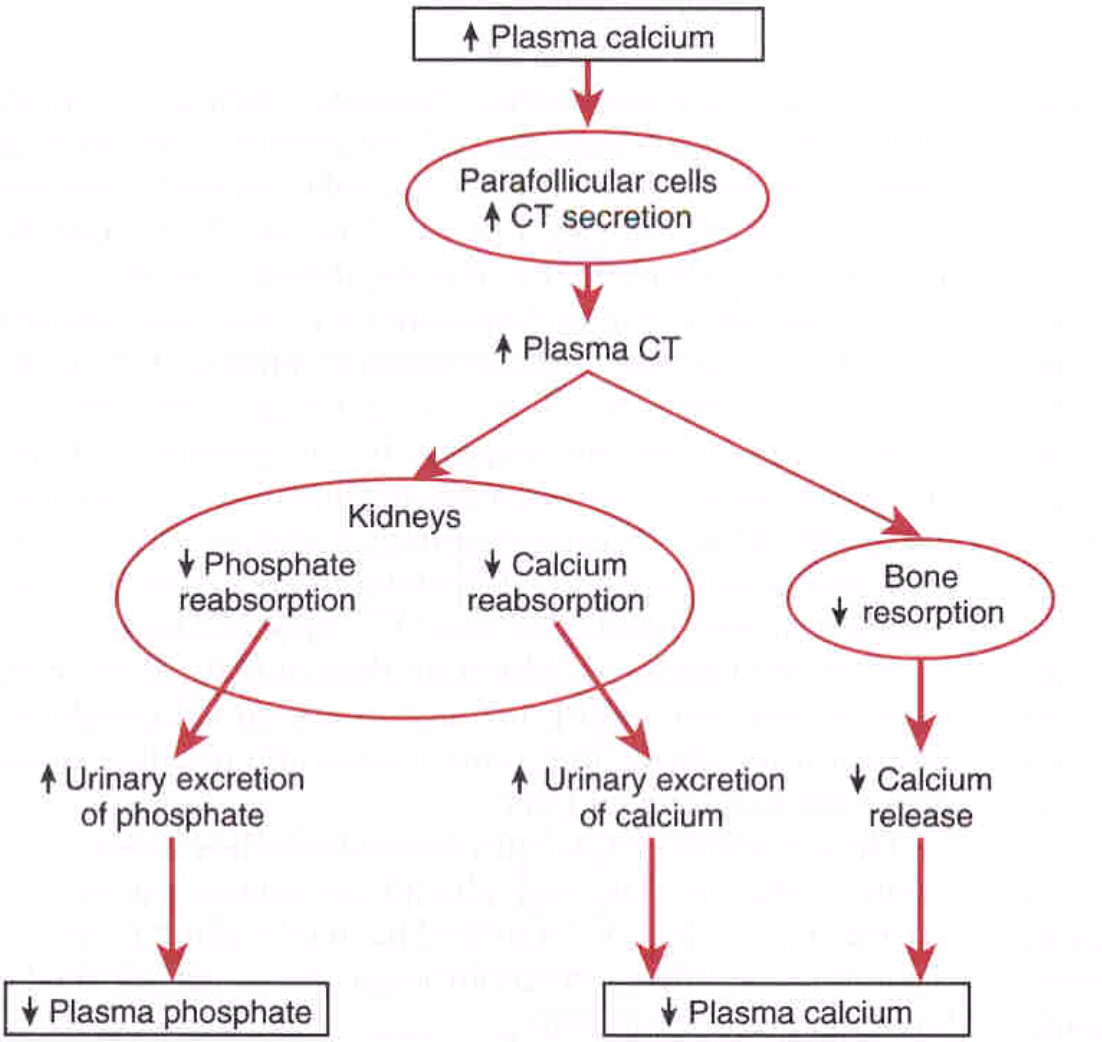
- **If there is ↑ or ↓ in plasma protein** there will be **↑ or ↓ in the total Ca++** but it has **no effect on the ionized calcium**.
- If there is ↑ in anions (**phosphate, sulfate or citrate) it will ↓ ionized Ca++**.
- **Acid-base abnormalities alter the ionized Ca++** concentration by changing the fraction of Ca++ bound to the plasma albumin:
  - Albumin has negatively charged sites which can bind to either H^+ or Ca++
  - In case of **acidosis** too much hydrogen will be bound to albumin releasing the Ca++ already in albumin ➔ **hypercalcemia**
  - In case of **alkalosis** too little hydrogen will be bound to the albumin getting the free active form of Ca++ from the plasma ➔ **hypecalcemia**.
  - **Hyperventilation** ➔ Respiratory alkalosis ➔ ↓ ionized Ca++ ➔ **tetany**.

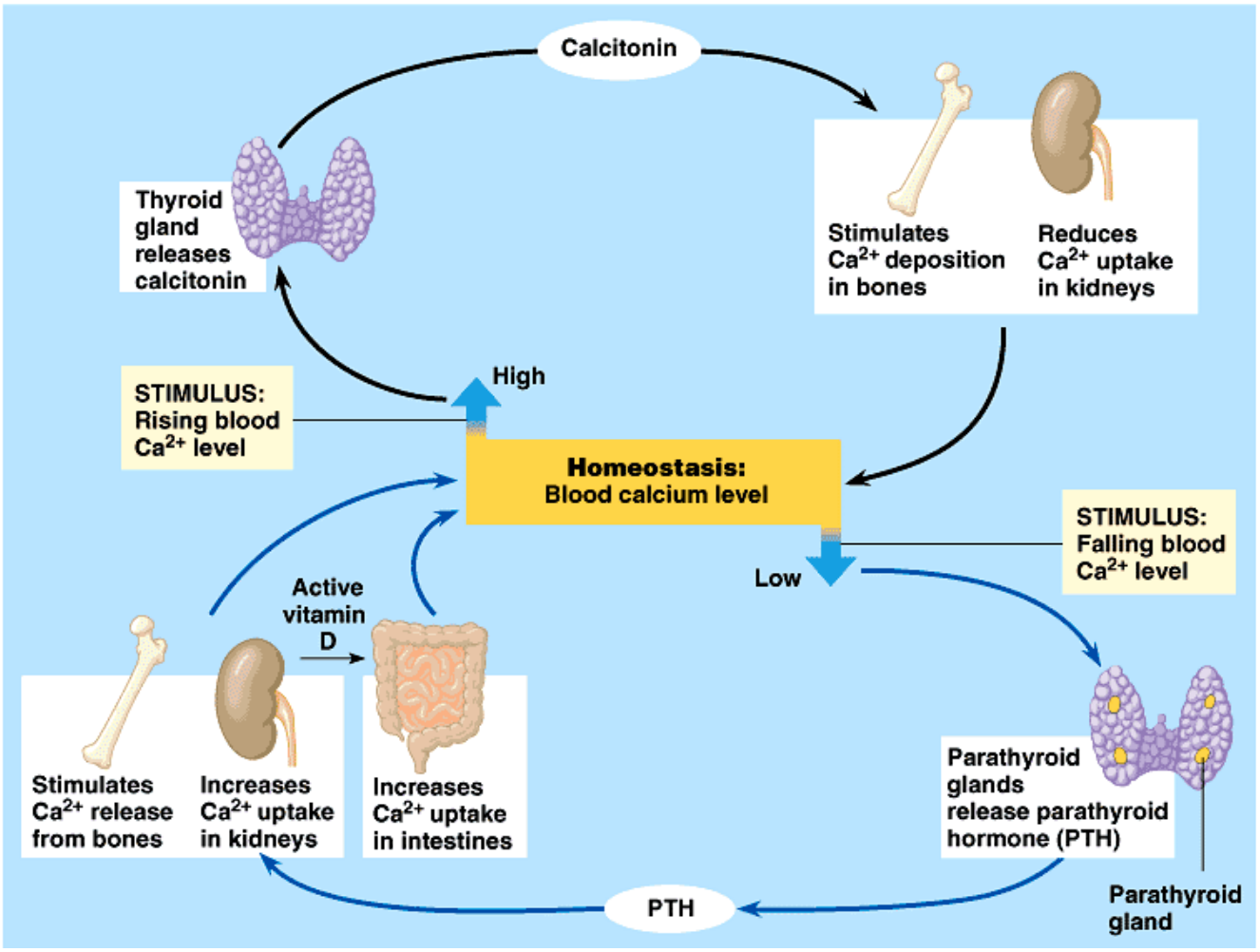
Hormones controlling plasma Ca^{++} level:-

- **Parathyroid** Hormone (PTH): ↓ Ca++ ➔ ↑ PTH, ↑ Ca++ ➔ ↓ PTH. Effects are:
  - ↑ **bone resorption** (breakdown releasing calcium).
  - **↑ reabsorption** of **Ca++** by the **kidneys.**
  - **↓ phosphate reabsorption** by the **kidneys.**
  - ↑ activation of vit.D in the kidneys. (vit. D) ➔ ↑ Ca++ absorption by the intestine.



- **Calcitonin**: ↑ Ca++ ➔ ↑ calctionin ↓ Ca++ ➔ ↓ calcitonin. Effects are:
  - ↓ **bone resorption**
  - ↓ **reabsorption** of **Ca++** from the **kidney**
  - ↓ **reabsorption of phosphate from the kidney.**
  - Net results:
    - ↓ **Ca++ plasma level**
    - ↓ **phosphate plasma level**


↑ Plasma calcium
Parafollicular cells
↑ CT secretion
↑ Plasma CT
Kidneys
↓ Phosphate reabsorption
↓ Calcium reabsorption
Bone
↓ resorption
↑ Urinary excretion of phosphate
↑ Urinary excretion of calcium
↓ Calcium release
↓ Plasma phosphate
↓ Plasma calcium

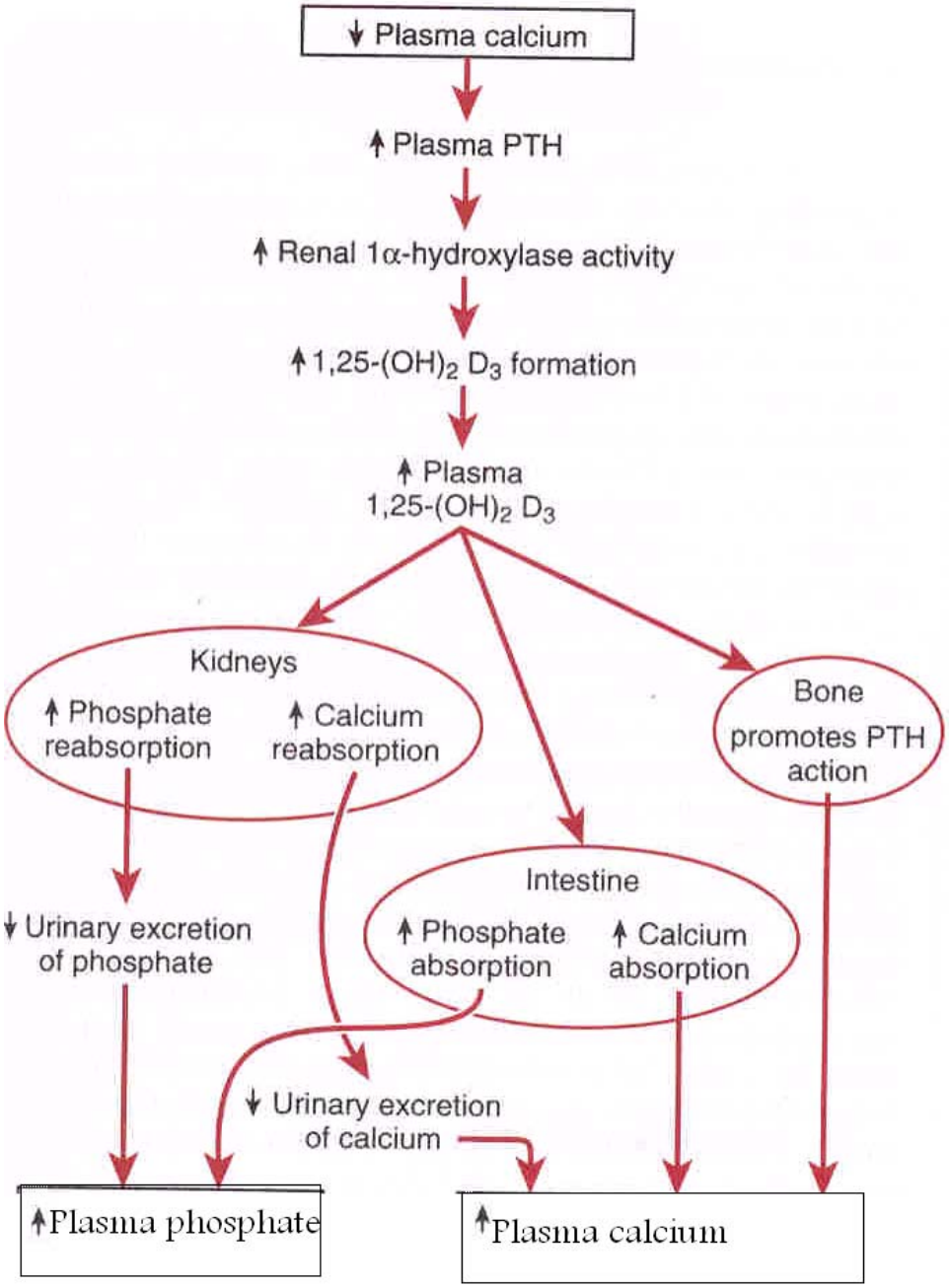


- Vitamin D_3:
  - Where to be gained from:
    - It can be **gained from the diet**
    - can be **synthesized by the body** (in the skin) through T-dehydrochloestrol + ultraviolet light.
  - Vit D_3 ➔ **hydroxylation** in the **liver** ➔ 25 – hydroxycholecalciferol (inactive form of vitamin D_3) ➔ **hydroxylation** by the **kidney** ➔ 1,25 dihydroxycholecalciferol (**active** form) (1,25 Vit D_3).
  - Active form will lead to:
    - ↑ **Ca++ absorption** by the **intestines**
    - ↑ **Ca++** reabsorption by the **kidneys**
    - ↑ **phosphate** reabsorption by the **kidney**.

(by the above actions It helps in bone building by ↑ mineral in bone)

- **Activate ParaThyroidHormone** action in bone not in kidney.

- Net result of Vit. D action:
  - ↑ **Ca++ plasma level**
  - **↑ phosphate plasma level**
- **Deficiency** of Vitamin D:
  - ↓ **mineralization** of bone ➔ soft & weak bone.
    - Children ➔ **rickets** ➔ bow (bent) leg
    - **Adults ➔ osteomalacia ➔ easy fracture** of bone & pain.
  - **Causes** of deficiency of vit. D
    - **Malnutrion**
    - **Liver** disease, **kidney** disease.



Clinical Problems…

osteoporosis: loss of bone mass

- Caused by:
    - ↓ **Ca++ level for a long time**

- Disease **atrophy** (not using the bone) e.g. in case of **paralysis**, plaster (جبس), weightlessness ➔ ↓ muscle size & bone size.
- **Age**: ↑ Age ➔ ↑ in loss of bone mass ➔ osteoporosis.
- **Females** have more problems in osteoporosis because of ↓ estrogen (so, they are given small doses of estrogen after menopause)

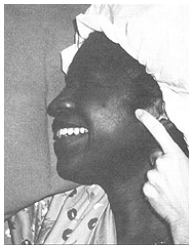
Paget's disease

- Paget's disease is known as a bone **remodeling** disorder. (Bone is constantly undergoing 'turnover' or replacement. New bone is formed, and old bone is absorbed. This process is known as bone remodeling (e.g. exchange of Ca++ from bone to ECF & from ECF to bone)
- This will lead to **easy bone fracture**.
- It is mostly a **congenital** disease (genetic).

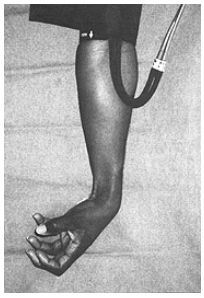
Hypoparathyroidism:

There is a defect in parathyroid gland ➔ ↓ PTH. It can be caused by:

- Accidental **removal of parathyroid gland** during thyroidectomy ➔ ↓ PTH. To test if the parathyroid gland has been removed or not the following tests could be done:
  - The **Chvostek sign** (also **Weiss sign**):- When the **facial nerve is tapped** in front of the **jaw**, the **facial muscles** on the same side of the face will **contract** momentarily[3] (typically a twitch of the nose or lips) because of **hypocalcaemia** with resultant **hyperexcitability** of nerves.



  - **Trousseau's** sign (test): we **inflate** (fill with air) the **cuff** ➔ ↑ **Blood Pressure** above systole for few minutes ➔ **spasm** (involuntary muscle contraction) in the **hand and wrist** (flexion of arm, wrist, metacarpals & extension of interpharyngeal joints).



[3] Within a short period of time