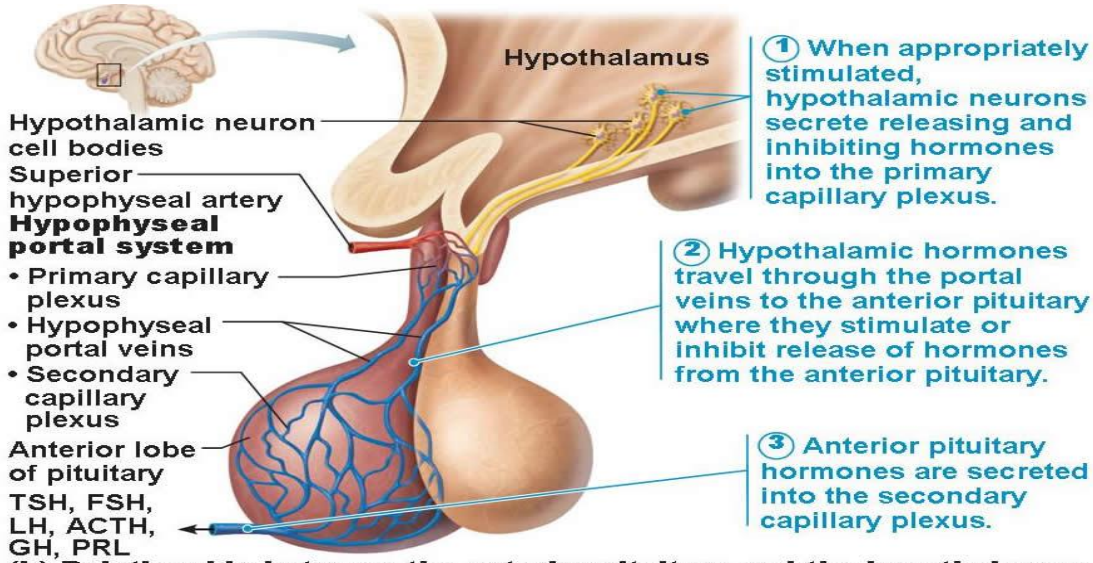
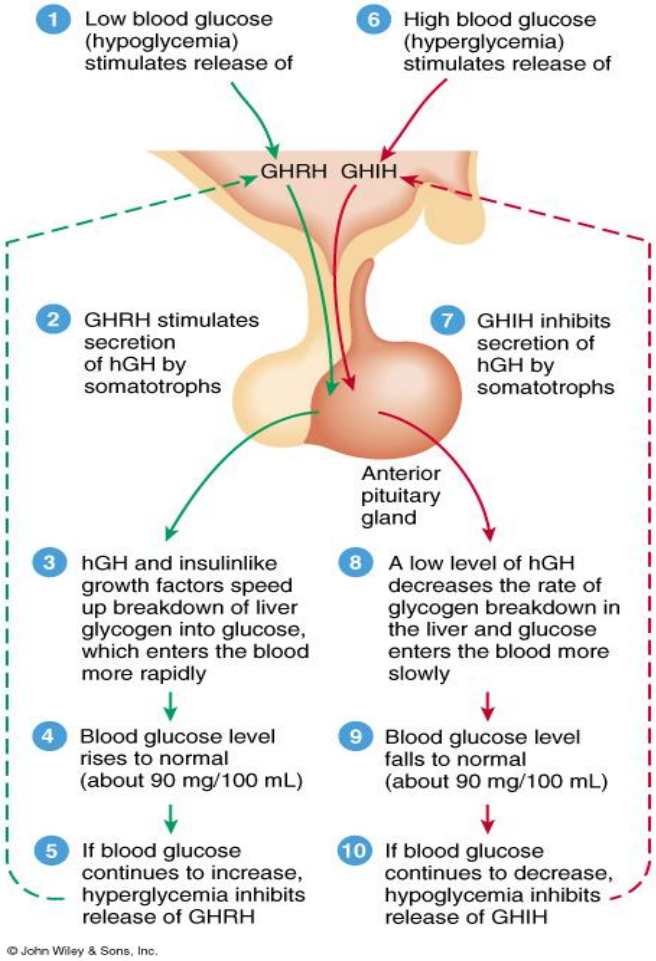
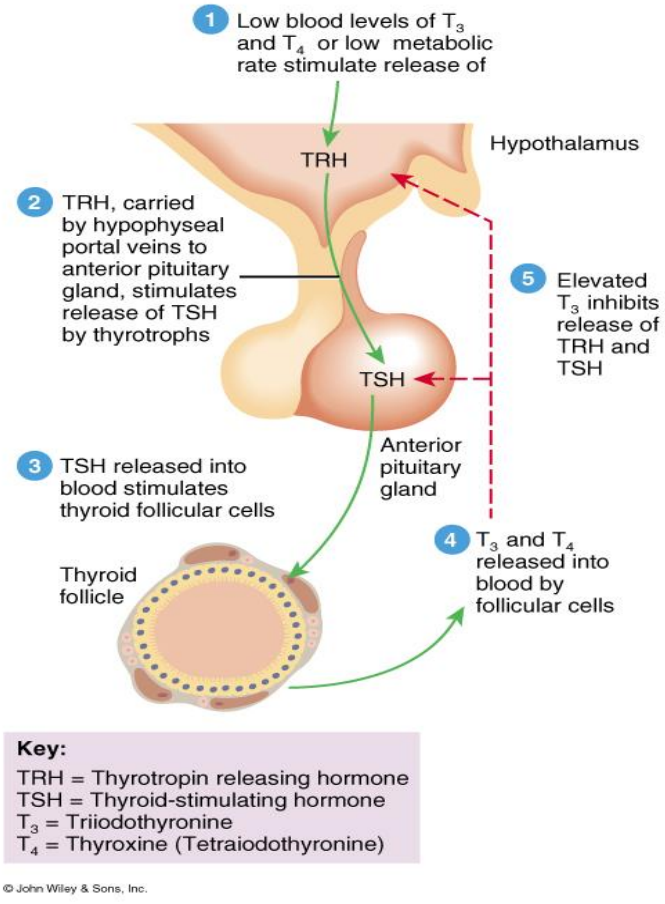
- Endocrine glands: Pituitary ,Thyroid ,Parathyroid ,Adrenal ,Pancreas ,Ovaries & Testes
- Hormone is a chemical substance released by group of cells to control the function of other type of cells.
- Target cells refer to cells that contain specific receptors (binding sites) for a particular hormone.
- **Three general classes of hormones:**
  - Proteins and polypeptides -: water soluble – RCs on the cell membrane
    (anterior and posterior pituitary, pancreas and parathyroid hormones) stored in vesicles until needed
  - Steroids-: lipid soluble- Derived from cholesterol – RCs in the cytoplasm
    (adrenal cortex, ovarian and testicular hormones) diffuse across the cell membrane
  - Derivatives of amino acid tyrosine -: Derived from tyrosine or tryptophan
    (thyroid hormones lipid soluble + RCs in the nucleus)&
    (catecholamines water soluble+ RCs on the cell membrane)
- Downregulation of hormonal receptors
  - Increase hormone concentration leads to decrease in the number of active receptors
  - Most **peptide** hormones have pulsatile secretion which prevents downregulation
- Upregulation of hormonal receptors
  - The hormone induces greater than normal formation of a receptor or intracellular signaling proteins
- Synergism : Combined action of hormones is more than just additive!
  Example: Blood glucose levels & synergistic effects of glucagon, cortisol and epinephrine
- Permissiveness :One hormone allows another hormone to have its full effect Especially during growth
  Example : Thyroid hormone have permissive effect on growth hormone action**.**
- Antagonism :Antagonistic hormones have opposing physiological actions –
  Example : Glucagon antagonizes the action of insulin
- **Control of anterior pituitary by hypothalamus**

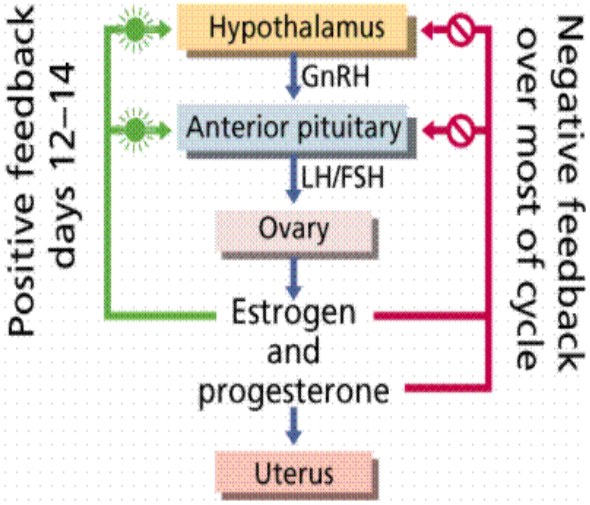


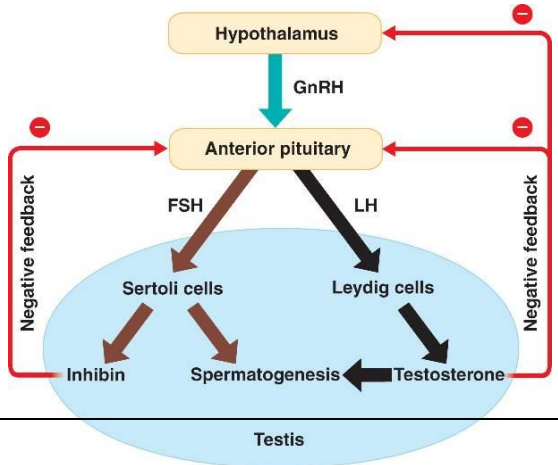
(b) Relationship between the anterior pituitary and the hypothalamus

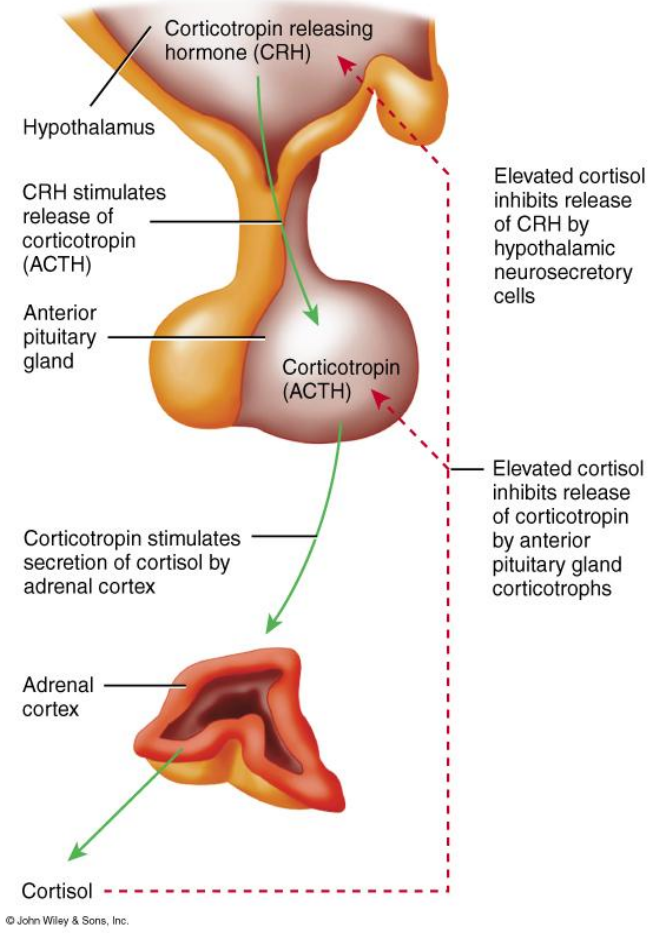
- Anterior pituitary contains 5 cell types:
  - Somatotrops: GH 40%
  - Corticotrops: ACTH 20%
  - Thyrotropes: TSH
  - Gonadotropes: LH & FSH
  - Lactotrops: PRL
- Anterior pituitary gland is connected to hypothalamus by portal system: **"hypothalamic-hypophysial portal vessels".**
- Growth hormone inhibiting hormone (GHIH) also called Somatostatin
- Prolactin inhibitory hormone (PIH) also known as Dopamine
- **Hypothalamic releasing and inhibiting gh hormones**


1 Low blood glucose (hypoglycemia) stimulates release of
6 High blood glucose (hyperglycemia) stimulates release of
GHRH GHIH
2 GHRH stimulates secretion of hGH by somatotrophs
7 GHIH inhibits secretion of hGH by somatotrophs
Anterior pituitary gland
3 hGH and insulinlike growth factors speed up breakdown of liver glycogen into glucose, which enters the blood more rapidly
8 A low level of hGH decreases the rate of glycogen breakdown in the liver and glucose enters the blood more slowly
4 Blood glucose level rises to normal (about 90 mg/100 mL)
9 Blood glucose level falls to normal (about 90 mg/100 mL)
5 If blood glucose continues to increase, hyperglycemia inhibits release of GHRH
10 If blood glucose continues to decrease, hypoglycemia inhibits release of GHIH
© John Wiley & Sons, Inc.


1 Low blood levels of T_3 and T_4 or low metabolic rate stimulate release of
Hypothalamus
TRH
2 TRH, carried by hypophyseal portal veins to anterior pituitary gland, stimulates release of TSH by thyrotrophs
5 Elevated T_3 inhibits release of TRH and TSH
TSH
Anterior pituitary gland
3 TSH released into blood stimulates thyroid follicular cells
4 T_3 and T_4 released into blood by follicular cells
Thyroid follicle
Key:
TRH = Thyrotropin releasing hormone
TSH = Thyroid-stimulating hormone
T_3 = Triiodothyronine
T_4 = Thyroxine (Tetraiodothyronine)
© John Wiley & Sons, Inc.


Positive feedback days 12–14
Hypothalamus
GnRH
Anterior pituitary
LH/FSH
Ovary
Estrogen and progesterone
Uterus
Negative feedback over most of cycle


Hypothalamus
GnRH
Anterior pituitary
FSH
LH
Sertoli cells
Leydig cells
Inhibin
Spermatogenesis
Testosterone
Negative feedback
Negative feedback
Testis


Corticotropin releasing hormone (CRH)
Hypothalamus
CRH stimulates release of corticotropin (ACTH)
Anterior pituitary gland
Corticotropin (ACTH)
Elevated cortisol inhibits release of CRH by hypothalamic neurosecretory cells
Elevated cortisol inhibits release of corticotropin by anterior pituitary gland corticotrophs
Corticotropin stimulates secretion of cortisol by adrenal cortex
Adrenal cortex
Cortisol
© John Wiley & Sons, Inc.

- Hormones synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and released in posterior pituitary
- Magnocellular neurons in paraventricular and supraoptic nuclei secrete **oxytocin** and **vasopressin** (ADH) directly into capillaries in the posterior lobe.
- Hypothalamo-hypophyseal tract connect between hypotlalamus & posterior pituitary gland .
- Anterior pituitary gland (adenohypophysis) is connected to hypothalamus by portal system: "hypothalamic-hypophysial portal vessels".
- **Indirect effect of GH** > Depends on **somatomedin C** (insulin– like growth factor 1) which is secreted by the liver, which is responsible for effect of GH on **bone** & cartilage growth and increase the synthesis of protein in skeletal muscles.
- **Metabolic effects of GH :**
  - **Protein metabolism** : Anabolic
  - **Fat metabolism:** Catabolic
  - **CHO metabolism:** Hyperglycemic
  - Stimulates the growth of all internal organs **excluding** the brain
  - Retention of Na^+ and K^+
  - Stimulates the immune system
- **Muscular exercise** → ↑ GH secretion.

- **Hypoglycemia** (fasting)→ ↑ GH secretion.
- **Intake of protein or amino acids** → ↑ GH secretion (after meals).
- **During sleep** → ↑ more in children.
- **Stress conditions**→ ↑ GH secretion
- ↑**FFAs** → ↓ GH secretion
- **Grelin (stomach)**→ ↑ GH secretion.

- ↑ **GH secretion:** Gigantism in childhood , acromegally in adults
- ↓**GH secretion** : pituitary dwarfism
- The major function of **p**rolactin is milk **p**roduction
- Release is inhibited by PIH (dopamine)
- Suckling response inhibits PIH release

- **Effect on the breast**
  - Increases mRNA
  - Increases production of casein and lactalbumin
  - **Inhibits the effects of gonadotropins**

- Prolctin level rises during **sleep**
- Prolctin level rises during **pregnancy**
- TRH increases PRL secretion

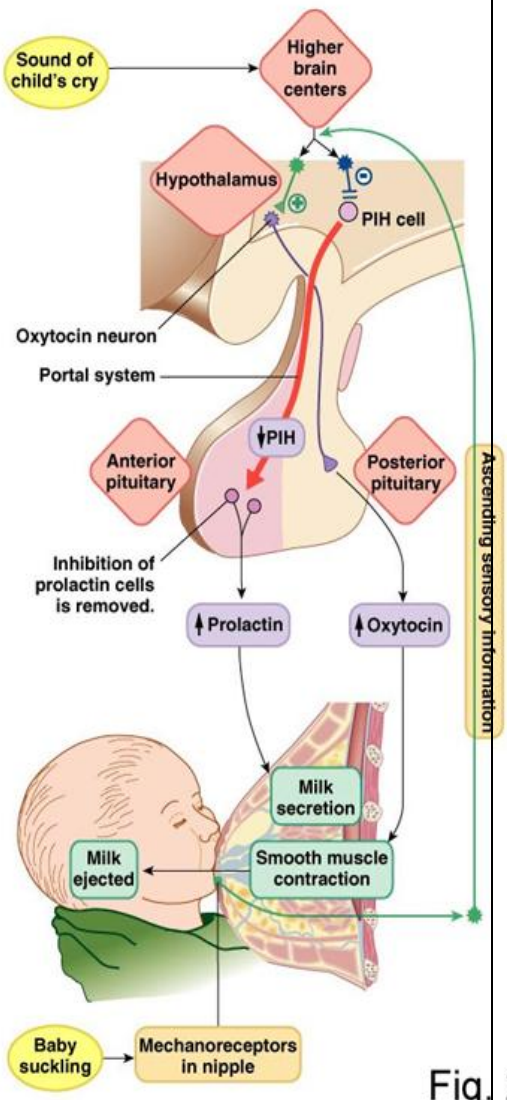
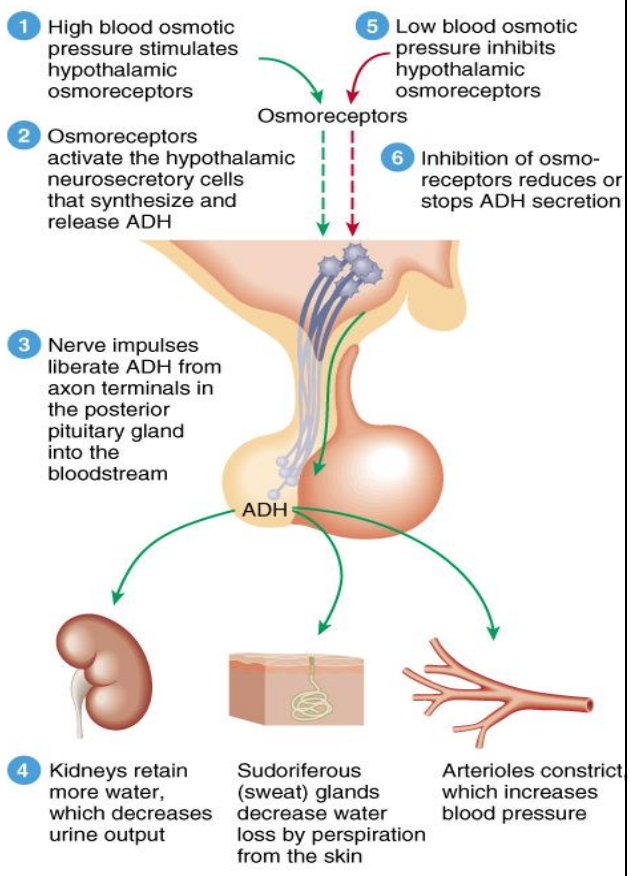


Fig. 2

- **Posterior Pituitary Gland**
  - Does not synthesize hormones
  - Consists of axon terminals of hypothalamic neurons
  - Secretions of the posterior pituitary are controlled by Nervous signals from hypothalamus
  - Relase (vasopressin"ADH" & oxytocin)
- **ADH**
  - ADH synthesized in the cell bodies of hypothalamic neurons(**supraoptic nucleus)**
  - ADH is stored in the neurohypophysis (posterior pituitary)—forms the most readily released ADH pool
- There are 3 types of receptors for ADH:
- **V1A** receptors mediate **vasoconstriction** , also found in the **liver** glycogenolysis
- **V1B** receptors are unique to **anterior pituitary** and mediate increased ACTH secretion
- **V2** receptors are located in the principle cells in distal convoluted tubule and collecting ducts in the kidneys
- MOA:
  - ADH binds to V2 receptors
  - Via adenylate cyclase/cAMP induces production and insertion of **aquaporin2** into the luminal membrane and enhances permeability of cell to water.
  - Increased membrane permeability to water permits back diffusion of solute-free water, resulting in **increased urine osmolality** (concentrates urine).
- The single most important function of ADH is to conserve body water by reducing urine output
- ADH secretion is very sensitive to changes in osmolality,Changes of 1-2% result in increased ADH secretion.
- **Regulation of ADH**
  - Dehydration > ADH released , Overhydration > ADH inhibited
  - **Osmotic pressure**:
    - Osmoreceptor mediated
    - ↑osmolality → ↑ADH secretion
    - ↓osmolality → ↓ ADH secretion
  - **Volume effects**
    - Baroreceptor mediated (vagus nerve)
    - ↑blood pressure → ↓ ADH secretion
    - ↓blood pressure → ↑ ADH secretion
  - **Stimuli that increase ADH secretion:**
    Pain ,Nausea ,Surgical stress & Emotional stress
  - **Stimuli that decrease ADH secretion:**
    Alcohol intake



- **Function of oxytocin**
  - Breast-feeding
    contracts the myoepithelial cells of the alveoli (classic neuroendocrine reflex)
  - Childbirth (parturition)
- in late pregnancy, uterine smooth muscle (myometrium) becomes sensitive to oxytocin (positive feedback)
- **Other stimuli that control release of oxytocin**
  - In humans, oxytocin is thought to be released during hugging, touching, and orgasm in both sexes.
  - Release increased during stress
  - Release inhibited by alcohol
  - In males secretion increases at time of ejaculation (contraction of smooth muscle of vas deferens)
- Autistic group (المصابين بالتوحد) had significantly **lower** plasma oxytocin levels than in the non-autism group

Diabetes insipidus

DI is a disorder resulting from deficiency of anti-diuretic hormone (ADH) or its action and is characterized by the passage of copious amounts of dilute urine.

Types of DI

- **Central DI** is due to failure of the pituitary gland to secrete adequate ADH
  - Defect in hypothalamus
  - Defect in pituitary stalk
  - Defect in posterior pituitary

CAUSES OF CENTRAL DI

- Idiopathic – 30-50% : Pituitary atrophy, possible autoimmune
- Brain tumors primary or secondary
  - Secondary (Lung cancer, leukemia, lymphoma most common)
- Head trauma
- Post-neurosurgery
- Congenital : Mutations of ADH gene, usually autosomal dominant
- Infiltrative diseases, such as Histiocytosis X or sarcoidosis
- Infection (meningitis).

Nephrogenic DI results when the renal tubules of the kidneys fail to respond to circulating ADH.

CAUSES OF NEPHROGENIC DI

- Acquired

- Drugs: lithium, amphotericin, gentamicin, loop diuretics
- Electrolyte disorders: hypercalcemia, hypokalemia
- Renal dz: obstructive uropathy, chronic renal failer , polysystic kidney, post-transplant, pyelonephritis
- Systemic processes: sarcoid, amyloid, multiple myeloma, sickle cell disease
- **Gestational diabetes insipidus** occurs only during pregnancy when an enzyme (*vasopressinase*) made by the placenta destroys ADH in the mother.
  - Congenital – rare
- Present in 1st week of life
- V2 ADH receptor defect – X-linked recessive
- AQP2 water channel defect –

Psychogenic (primary) polydipsia : physiological ADH inhibition

Symptoms and signs of DI

- Polyuria > 3 liters in 24 hrs
  - Sudden onset more typical of central DI
- Nocturia ,Polydipsia , Anorexia, constipation
- Dilute urine, urine osm < 200
- Serum Na>150 rare with free access to H2o
- Dehydration >> Dry mouth ,Muscle weakness ,Hypotension & Sunken appearance of the eyes
- Hyperthermia & lack of sweating
- Rapid heart rate
- Weight loss
- electrolyte imbalance : Hypernatremia & Hyperchloremia
- Seizure secondary to Hypernatremia can happen

Electrolyte imbalance can caus :
Headache ,Fatigu
Irritability and muscle pains

Treatment : **Desmopressin**

1. Desamino-desarginino-vasopressin(DDAVP)
2. V2-selective analogue
3. Little V1 (vasoconstrictor) activity
4. Drug of choice in Diabetes insipidus

❖ **Hormones of thyroid gland**

- T4 (tetraiodothyronine) (thyroxine) **90**%.
- T3 (Triiodothyronine)10%.
- Reverse T3
- Calcitonin.

Biosynthesis: *by the follicular cells*

1- Iodide pump. (Active transport)
2- Thyroglobulin synthesis.
3- Oxidation of iodide to iodine by Thyroid peroxidase
4- Iodination of **tyrosine . Binding of iodine with thyroglobulin then Catalyzed by thyroid peroxidase** to form mono-iodotyrosine (MIT) & di-iodotyrosine (DIT).

5- Coupling; MIT + DIT = Tri-iodothyronine, (**T3**).
DIT + DIT = Tetra-iodothyronine, (**T4**)/ Thyroxine.
6- Release.

❖ Wolff-chaikoff effect

(A reduction in thyroid hormone levels caused by administration of a large amount of iodine)

❖ **Thyroid hormones in the circulation**

1- Bound: 70- 80% bound to **thyroxine-binding globulin** (TBG) synthesized in the liver.
The reminder is bound to albumin.
2- Unbound (Free)

❖ **In hepatic failure:**
↓ TBG → ↑ free T3/T4 → *inhibition* of thyroid secretion.
❖ **In pregnancy:**
↑ estrogen → ↑ TBG → ↓freeT3/T4 → *stimulation* of thyroid secretion.
❖ Most of T4 is deionized to T3 by iodinase enzyme.
❖ **In the nucleus**, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes.
❖ ½ of T4 in the blood is released every 6 days.
❖ ½ of T3 in the blood is released every one day.
❖ **ACTION OF THYROID HORMONES**

1- Basal Metabolic Rate (BMR)
2- Metabolism
A) Effect on carbohydrate metabolism: increase glycogenolysis & increase gluconeogenesis
B) Effects on fat metabolism:
1- increase lipolysis.
2- decrease plasma cholesterol by increase loss in feces.
3- increase oxidation of free fatty acids.
C) Effect on protein metabolism : overall effect is **catabolic** leading to decrease in muscle mass.
3- Effects on the Cardiovascular system:

- increase heart rate & stroke volume >↑Cardiac output up to 60%
- decrease peripheral resistance.
- Thyroid hormones potentiate the effect of catecholamine in the circulation>activation of β-adrenergic receptors

6- Effects on the CNS:
A) Peri-natal period: decrease of hormones secretion → **irreversible mental retardation**
B) In adult:

- Increase in thyroid hormone secretion: hyperexcitability & irritability.
- Decrease in thyroid hormones secretion: slow movement + impaired memory & mental capacity.

7- Effects on bone: promote bone formation

8- Effects on Respiration:

- increase ventilation rate.
- increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG

9- Effects on the GIT

1- increase *appetite* and food intake.
2- increase of digestive juices *secretion*.
3- increase of G.I tract *motility*.

10- Effects on Autonomic nervous system:

Produced the same action as *catecholamines* via β-adrenergic receptors including increase BMR & increase heart rate

- **Regulation of hormones secretion :** It is regulated by the hypothalamic-pituitary axis.
- **Investigations of hyperthyroidism**

1- Serum T3, T4 measurement.

- In primary hyperthyroidism : high T3, T4 and low TSH .
- In secondary hyperthyroidism: high T3, T4 and high TSH.

- **Indication for surgery in hyperthyroidism :**
  - a)- Relapse after medical treatment.
  - b)- Drug intolerance.
  - c)- Cosmetic.
  - d)- Suspected malignancy.

- **Investigations of hypothyroidism**

1- Serum T3,T4 are low.

- TSH is elevated in primary.
- TSH is low in secondary hypothyroidism.

- **CRETINISM :** Extreme hypothyroidism during infancy and child hood (failure of growth)
- **SYMPTOMS**
  - Infant is normal at birth but abnormality appears within weeks.
  - Protruding tongue.
  - Dwarf with short limbs.
  - Mental retardation.
  - Often umbilical hernia.
  - teeth.

*Changes are irreversible unless treatment is given early.

Table 9-9 Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves' disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T_3 or T_4 (factitious)	Thyroiditis (autoimmune or Hashimoto's thyroiditis) Surgery for hyperthyroidism I^- deficiency Congenital (cretinism) Decreased TRH or TSH
TSH Levels	Decreased (feedback inhibition of T_3 on the anterior lobe) Increased (if defect is in anterior pituitary)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy $^{131}I^-$ (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

- **Distribution of Ca++in Body**
  - Skeleton & Teeth = 99%
  - ICF (Endoplasmic Reticulum) = 1%
  - ECF = 0.1%
- Total body content of ca = 1300g
- Total plasma ca(in ECF) = 9 - 10.5 mg/dl
  - Calcium complexed to anions = 9% "diffusible"
  - Ionized calcium = 50% " diffusible"
  - Protein bound calcium = 41% "non-fiffusible "
- **Protein bound calcium**
  - Most of this calcium is bound to albumin & much smaller fraction is bound to globulin
    - Binding of calcium to albumin is pH-dependent
    - Acute respiraqory alkalosis increases calcium

- **Physiological importance of Calcium**
  - Calcium salts in bone provide structural integrity of the skeleton
  - Calcium ions in extracellular and cellular fluids is essentialto normal function for the biochemical processes
    - Neuoromuscular excitability
    - Hormonal secretion
    - Enzymatic regulation
    - Blood coagulation
    - Second messenger.
- Phosphate
  - Phosphorous is an essential mineral necessary for ATP, cAMP second messenger systems, and other roles
  - PO4 **plasma concentration** is around **4 mg/dL.**
  - Most of it is ionized (diffusible) around 50% of total
  - The remainder (50%) and much less of it is un-ionized (non-diffusible) and protein-bound
  - Calcium is tightly regulated with Phosphorous in the body
  - Total body content = 600 g
- **Daily requirements of calcium**
  - **Infants & adults > 12.5 – 25 mmol/day**
  - **Pregnancy, lactation & after menopause > 25 - 35 mmol/day**

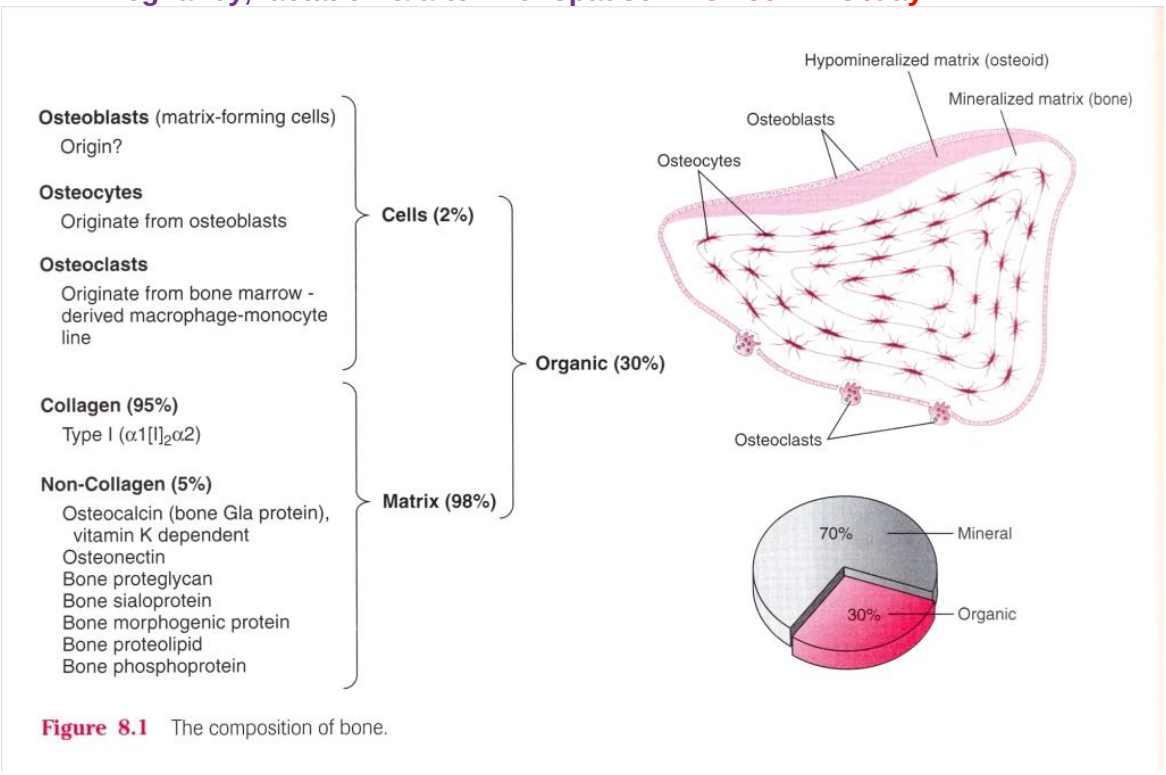


Figure 8.1 The composition of bone.

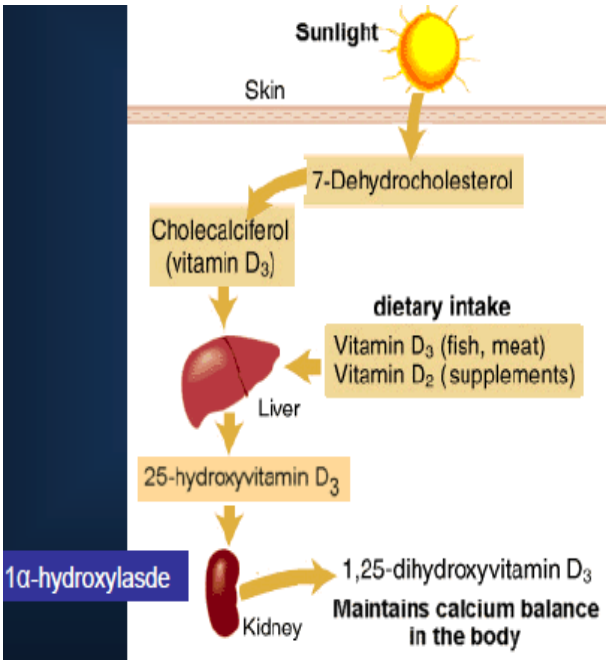
❖ Regulation on ca++ level by :
Calcitonin, Vit D ,parathyroid hormone

❖ Vitamin D = 1,25 Dihydroxycholecalciferol

❖ **Control of Vit D3:**

1- low Ca++ions
2- prolactin
3- PTH

All stimulate renal **1,alpha hydroxylase**.



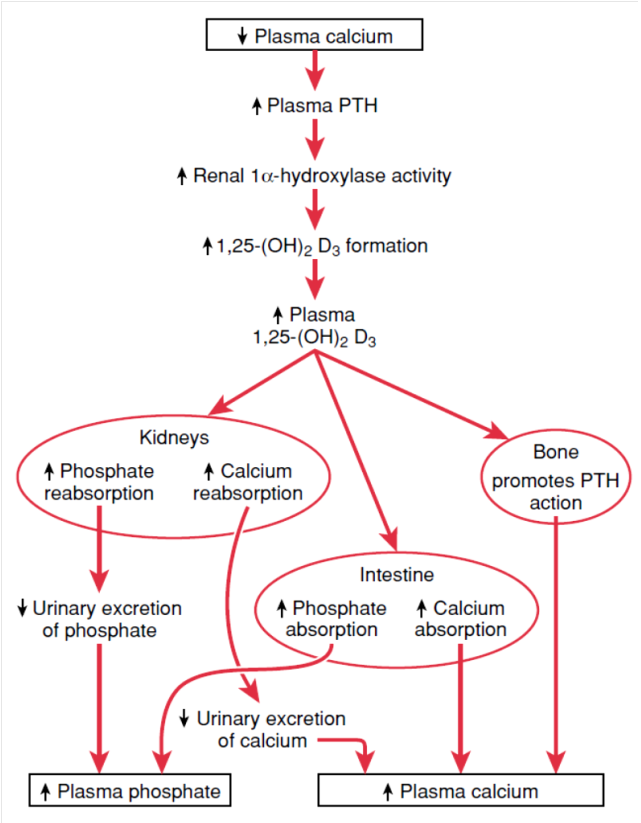
○ On the bone :by stimulate the formation of new osteoclasts & suppression of osteoblasts activity

○ Effects on Kidneys

1. ↓phosphate reabsorption from the proximal convoluted tubules (phosphaturic action).
   - ↑Phosphate excretion in the urineplasma
   - ↓phosphate concentration
2. ↑ Ca++& Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle.
3. ↑Formation of 1,25 vit D3 in the kidney.

○ Effects on the intestine

↑absorption of calcium and phosphate indirectly through stimulating formation of 1,25 –(OH)2-D3in kidney



❖ **Regulation of PTH secretion**

•Secretion of PTH is inversely related to plasma [Ca2+] because
•Plasma Ca2+ level is the dominant regulator of PTH secretion :

•Plasma Ca2+level **< 3.5** mg/dL → stimulates PTH secretion
•PlasmnaCa2+level **> 5.5** mg/dL → inhibits PTH secretion

❖ **Function of Calcitonin**

- Decrease blood Ca++level very rapidly within minutes.
- Opposite effect to PTH

❖ **Actions of calcitonin :**

○ On bone

- [1] ↑ Cadeposition of bone
- [2] Inhibit Bone resorption:
  - inhibition of osteoclasts
  - ↓ formation of osteoclasts

○ On kidney

- ↓ ↓ Ca++ reabsorption
- ↑ ↑ Ca++ excretion (in addition to phosphate)

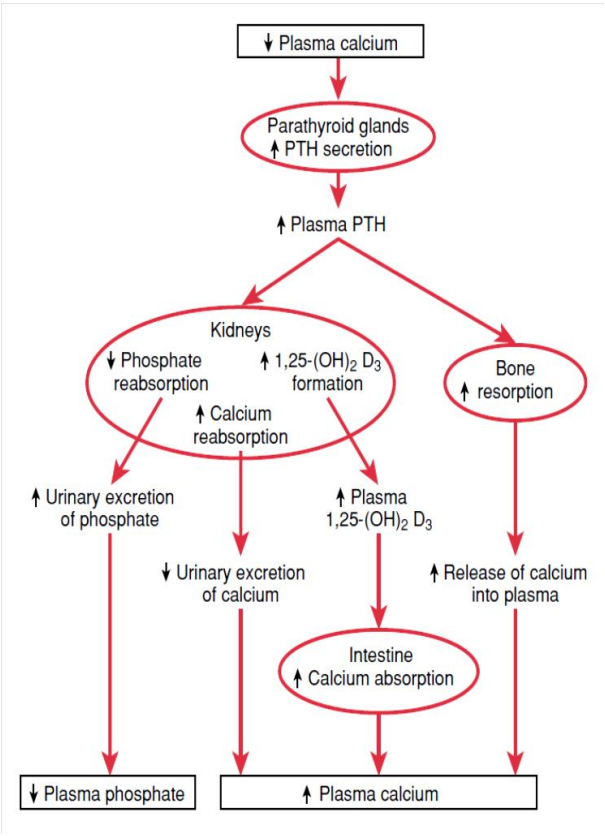
❖ **abnormalities**

- **Rickets (In children)**

• **Cause**: lack of vitamin D leading to calcium/phosphate deficiency in ECF

• **Features**:
  - Low plasma calcium and phosphate
  - Weak bones
  - Tetany > blood level of calcium falls below 7 mg/dl → signs of tetany
  - positive Chvostek'ssign is facial nerve irritability/spasms elicited by tapping the nerve
  - Death: tetanic respiratory spasm**Tetany**

- **Treatment of Rickets:**
  supplying adequate calciumand phosphatein the diet and, administering large amounts of vitamin D.

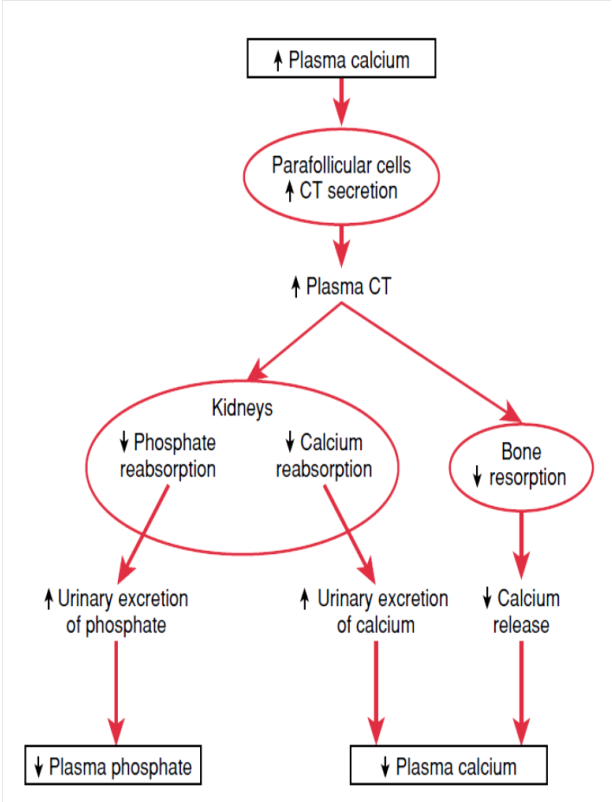


❖ **Osteomalacia-"AdultRickets".**(rare).
- Serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat).
- Almost never proceed to the stage of tetany but often is a cause of severe bone disability.

❖ **Osteoporosis—Decreased Bone Matrix**

•Osteoporosis is the most common of all bone diseases in adults,especially in oldage.
•results from loss of organic bone matrix and minerals resulting in loss of bone mass and strength

•The osteoblastic activity in the bone usually is less than normal,and consequently the rate of bone osteoid deposition is depressed.
(But occasionally,as in hyperparathyroidism,the cause of the diminished bone is excess osteoclastica)



- **causes of osteoporosis:**

•(1) lack of physical stress
•(2) malnutrition
•(3) lack of vitamin C
•(4) postmenopausal lack of estrogen
•(5) old age
•(6) Cushing's syndrome

❖ **Hypoparathyroidism(rare)**

- **Causes**
  - Injury to the parathyroid glands (surgery).
  - Autoimmune

- **Signs & symptoms**
  (due to hypocalcaemia)Tingling in the lips, fingers, and toes Dry hair, brittle nails, and dry, coarse skinMuscle cramps and pain in the face, hands, legs, and feetCataracts on the eyes Malformations of the teeth, including weakened tooth enamel.Loss of memory Headaches

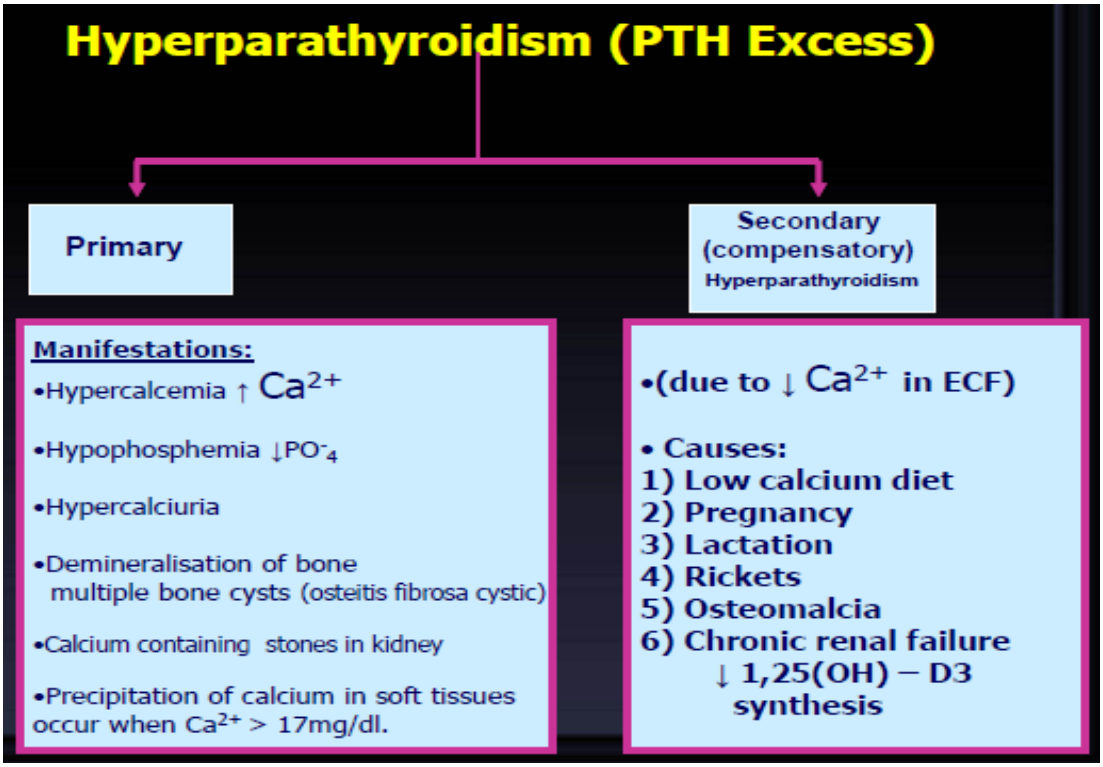
- **Signs of Hypoparathyroidism**

  - Positive Chvostek's(facial muscle twitch) sign
  - Positive Trousseau's (carpal spasm) sign
  - Delayed cardiac repolarizationwith prolongation of the QT interval
  - Paresthesia
  - Tetany

- **Treatment**: Calcium carbonate and vitamin D supplements

- Tetanycan be overt or latent
- **Chorostek'ssign:** Tapping the facial nerve as it emerge from the parotid gland in front of the ear → causes contraction of facial muscles.
- **Trousseau's sign :**
  Arresting (stopping) blood flow to the forearm for few minutes (e.g., by sphygmomanometer) → causes flexion at the wrist, thumb and metacarpophalangealjoints.

❖ Hyperparathyroidism



الى هنا جزئيه المد ،،

- **Cortisol**
  - It is a steroid hormone (lipid soluble) , 90-95% bound to plasma protein (cortisol binding **globulin**) .
  - Only unbound ~2% steroid hormones are biologically active , metabolized in liver & excreted by kidney in urine .
  - Under control primary by ACTH, cortisol will be evident 15 to 30 min after ACTH has been produced.
  - There are 7 -15 episodes per day.
  - **Stimulated by:**

1. Coffee consumption
2. Exercise
3. ↓Testosterone
4. Physical trauma
5. Infections
6. Extreme cold & hot
7. Extreme mental anxiety

Physiological effects of cortisol :

1) On carbohydrate metabolism

- Increase blood glucose level by ↑ glucogenesis & ↓ utilization of glucose by cells

2) Protein metabolism

- Increase amino acid blood level & Reduce protein formation

3) Fat metabolism

- Lipolytic ,↑ fatty acid & glycerol blood level ,

4) Anti inflammatory effects

- ↓ vasodilatation, ↓ permeability of capillaries ,↓ migration of WBC , ↓immune system .

5) Effects on blood cells & immunity

- Decrease production of eoisinophils , lymphocytes , cells & antibodies > ↓ immunity .
- Decrease immunity is useful during transplant operation.

6) Effect on the circulation

- maintain body fluid volumes & vascular integrity
- BP regulation
- Maintins normal renal function

7) CNS responses:

- Negative feedback control on release of ACTH
- Modulates perception & emotion

8) Mineral metabolism:

- Anti-vitamin D effect

9) GIT:

- Increases HCl secretion

10) Developmental functions:

- Permissive regulation of fetal organ maturation
- Surfactant synthesis (phospholipid that maintains alveolar surface tension).
- Inhibition of linear growth in children due to direct effects on bone & connective tissue

Disorders of Cortisol Secretion (**Cushing syndrome**)

❖ Causes

Exogenous

- Most cortisol excess is induced by steroid therapy (prednisone) to manage disease
  1. asthma
  2. rheumatoid arthritis
  3. lupus
  4. other inflammatory diseases
  5. immunosuppression after transplantation

Endogenous

- Due to excessive production of cortisol:

- ACTH- independent:
  Primary adrenal defect (adenoma)
- ACTH-dependent:
  Overproduction of ACTH by pituitary or Overproduction of ACTH by ectopic ACTH-producing tumor

Carbohydrate metabolism

↑ blood glucose levels
↓ sensitivity to insulin, “Adrenal diabetes”

Protein metabolism

- ↑ protein loss
- muscle atrophy
- thin skin
- (-) collagen deposition in the skin (striea)
- bone matrix & mass losses; bone formation ↓lessCa2+ absorbed & more excreted in urine
- osteoporosis

Fat metabolism

redistribution of body fat:↑trunk & face fat deposition & ↓ extremities fat deposition.

Buffalo torso

- Redistribution of fat from lower parts of the body to the thoracic and upper abdominal areas

Moon Face

- Edematous appearance of face
- Acne & hirsutism(excess growth of facial hair)

circulation

- Hypertension due to Na retention & K excretion.
- Hypervolemia
- Hypernatremia due to increased Na absorption.
- Hypokalemia due to increased K excretion.

inflammation & immunity

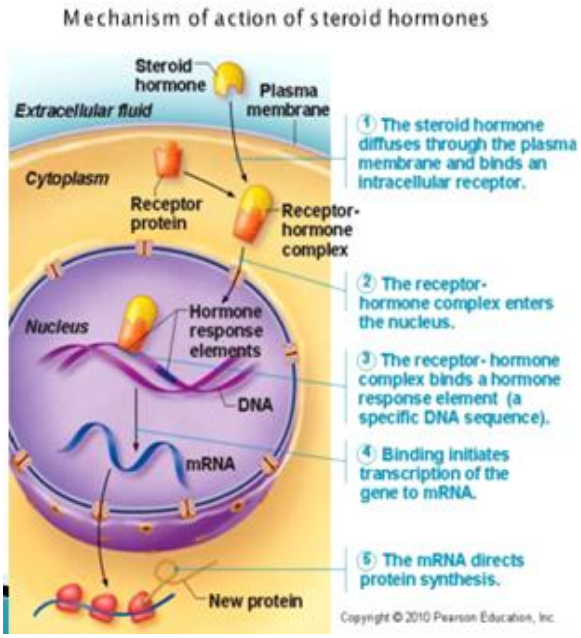
- Decreases inflammatory response
- Increased infection susceptibility
- Ab synthesis suppressed & normal immune responses to infecting pathogens suppressed
- Decrease in fibrous tissue formation & impaired wound healing.

Treatment

- Removal of adrenal tumor if this is the cause
- Microsurgical removal of hypertrophied pituitary elements to reduce ACTH secretion

Hormones of Adrenal gland

- **Cortex: (Secretes steroid hormones)**
  - Glucocorticoids.
  - Mineralocorticoids.
  - Androgens.
- **Medulla (Amino acid secretions)**
  - Catecholamines



❖ Aldosterone

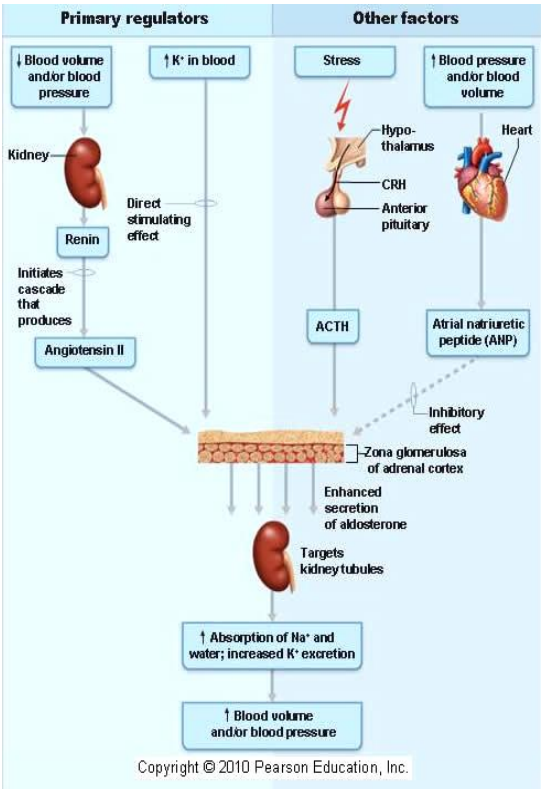
- A steroid hormone, secreted by Zona glomerulosa
- Responsible for regulating Na^+ reabsorption in the distal tubule and the cortical collecting duct.
- Target cells are called “principal (P) cell”.
- Metabolized in the liver to tetrahydroglucuroind derivative.

Aldosterone action

- Maintains extracellular fluid volume by conserving body sodium
- Stimulates the active secretion of potassium from the tubular cell into the urine.
- Stimulates secretion of H+ by the kidney

Role of ACTH in Aldosterone synthesis/release

- ACTH also stimulates aldosterone synthesis.
- Aldosterone levels fluctuate diurnally—highest concentration being at 8 AM, lowest at 11 PM, in parallel to cortisol rhythms.



juxtaglomerular apparatus (JGA)

A specialized collection of two cell types located at the juncture of the afferent and efferent arterioles with a portion of the distal convoluted tubule of the nephron of the kidney

- **Macula densa cells**
  - Specialized **chemoreceptor** cells in the wall of the distal convoluted tubule
  - respond to changes in solute concentration (especially sodium levels) in the urine
  - sensory information is conveyed to the juxtaglomerular cells
- **Juxtaglomerular cells**
  - Specialized smooth muscle cells which act as mechanoreceptors which stretch in response to increases in the blood pressure of the afferent arteriole
  - synthesize and secrete the enzyme renin

Role of <u>AngII</u> in Aldosterone synthesis

- acts on the zona glomerulosa to stimulate aldosterone synthesis.
- acts via increased intracellular cAMP to stimulate aldosterone synthesis

❖ Hypoadrenalism – **Addison's Disease**

Causes:

autoimmunity against cortices 80% ,tuberculosis, drugs, cancer/ irradiation

- **Lack of aldosterone:**
  - Increased sodium, chloride, water loss
  - Decrease ECF volume
  - Hyperkalemia
  - Mild acidosis
  - Increase RBC concentration
  - Plasma sodium decreases and may lead to circulatory collapse. Decrease cardiac output – shock - death within 4 days to a 2 weeks if not treated.

❖ **Hyper**aldosteronism

can be caused by:

- Primary overproduction of aldosterone in conditions such as Conn's syndrome.
- Conditions of low cardiac output are also known to stimulate synthesis of aldosterone.
- Both conditions result in sustained hypertension.

- **Clinical Features of Primary Aldosteronism**
  - Hypertension.
  - Hypokalemia
  - Nocturnal polyuria & polydipsia
  - Increased tubular (intercalated cells) hydrogen ion secretion, with resultant mild alkalosis.
  - Neuromuscular manifestation : weakness, paresthesia & intermittent paralysis

❖ Adrenal Androgens

- Androgens are the hormones that exert masculinizing effects.
- They promote anabolism and growth.
- Testosterone from the testis is the major active ,androgen
- Zona reticularis : Produces small amounts of androgens, mostly dehydroepiandosterone (DHEA), DHEA may be converted into estrogens
- Hormone Control: Believed to be ACTH
- Target tissue: General body cell
- The adrenal cortex produces both androgens i.e."male sex hormones" and estrogens or "female sex hormones.
- The adrenal cortex in both sexes produces small amounts of sex hormone of the opposite sex.
- Additional small amounts of sex hormones come from nonadrenal sources. Some testosterone in males is converted into **estrogen** by the enzyme **aromatase** found in adipose tissues.
- In females, ovaries produce androgen as an intermediate step in estrogen production. Little of this androgen is released in the blood instead of being converted into estrogen.

❖ **Adrenal androgens**, includes :

1) dehydroepiandrosterone (DHEA),
2) androstenedione

Dehydroepiandrosterone (DHEA):

- A steroid hormone produced in the adrenal cortex from cholesterol. It is the primary precursor of natural estrogens.
- It is the most abundant adrenal androgen

Androstenedione:

- An androgenic steroid produced by the **testes**, **adrenal cortex**, and **ovaries**.
- Androstenediones are converted metabolically to testosterone and to estrogens in the fat and other peripheral tissues. It is an **important source of estrogen in men** and **postmenopausal women**.
- Androstenedione were used as an athletic or body building supplement.

Effects of adrenal androgens:
- Control androgen-dependent processes in the female as:

- growth of pubic and axillary hair,
- pubertal growth spurt,
- development and maintenance of female sex drive

Congenital adrenal hyperplasia (Adrenogenital Syndrome)

Causes: Inherited as autosomal recessive diseases and can affect both boys and girls.
The defect is **lack of an enzyme (21-hydroxylase)** needed by the adrenal gland to make the major steroid hormones of the adrenal cortex: cortisol and aldosterone. Due to the block in synthesis of these hormones, there is abnormal 'feedback' and steroids are 'diverted' to becoming androgens, a form of male sex hormones.

- In pre-pubertal males it causes the rapid develop of secondary sexual characters
- in females causes beard growth, deeper voice, masculine distribution of body hair, and growth of the clitoris to resemble a penis.

*Picture:
Virilizing adrenal hyperplasia in a newborn female baby, DHEA was converted to testosterone

❖ **Adrenal Insufficiency**

Causes:
Primary: due to failure of adrenal glands (Addison's Dis)
Secondary :failure of HPA axis ,due to chronic exogenous glucocorticoid administration pituitary failure .
Tertiary :Hypothalamic dysfunction

- Primary Adrenal Insufficiency
  - Loss of all three types of adrenal steroids
  - 90% of glands must be destroyed to manifest clinically

- **Addison disease** (Primary Adrenal Insufficiency)

Causes

- autoimmune
- Thrombosis/hemorrhage
- Sepsis, DIC, antiphospholipid syndrome
- Infiltrative diseases
- Bilateral cancer metastasis

Clinical presentation:

- Are due to deficiency of glucocorticoids and aldosterone
- Fatigue, anorexia, weight loss, loss of libido
- Headaches, visual changes, diabetes insipidus
- Pain in GI , nausea, vomiting, diarrhea
- Skin pigmentaions
- Muscle & joint pain
-

Chronic Insufficiency

Clinical presentation

- Hypotension/Orthostasis
- Cachexia
- Thin axillary and pubic hair in women
- Hypoglycemia
- Normocytic anemia
- Hyponatremia
- Hyperkalemia
- mild acidosis

Adrenal Crisis (Addisonian Crisis)

Clinical presentation

- Life-threatening emergency
- HYPOTENSION
- Typically resistant to catecholamine and IVF resuscitation

Cause: Abrupt adrenal failure usually from gland hemorrhage or infection or thrombosis

Clinical manifestations of Addisonian Crisis:

- Sudden penetrating pain in the legs, lower back or abdomen Severe vomiting and diarrhea, resulting in dehydration.
- Low BP
- Loss of consciousness
- Hypoglycemia
- Severe lethargy
- Hyponatremia
- Hyperkalemia
- Convulsions
- **Fever**

Treatment

- **Use glucocorticoids only** (no mineralcorticoids)
- Correct volume and sugar deficits

❖ Hormones of the **Adrenal Medulla**

- Adrenaline (epinephrine) 80 %
- Noradrenaline (norepinephrine) 20%

*Hormones are secreted and stored in the adrenal medulla and released in response to appropriate stimuli

Mechanism of Action

- Receptor mediated – adrenergic receptors
- Peripheral effects are dependent upon the type and ratio of receptors in target tissues

- **Epinephrine** > norepinephrine : in terms of cardiac stimulation leading to greater cardiac output (β stimulation).
- Epinephrine < **norepinephrine** : in terms of constriction of blood vessels – leading to increased peripheral resistance – increased arterial pressure.
- **Epinephrine** > norepinephrine : in terms of increasing metabolism Epi = 5-10 x Norepi. = 100% normal

Effects of Epinephrine

Metabolism

- ↑ Glycogenolysis in liver and skeletal muscle >> can lead to hyperglycemia
- Mobilization of free fatty acids
- Increase metabolic rate >> O_2 consumption increases

Cardiovascular

- ↑ Heart rate & cardiac contractility
- ↑ BP

Respiration

- ↑ Oxygen consumption & respiratory rate

Pheochromocytoma

- A catecholamine-secreting **tumour** of chromaffin cells of the adrenal medulla

Signs and Symptoms of Pheochromocytoma

- resistant hypertension (95%)
- headache
- sweating
- palpitations
- chest pain
- anxiety
- glucose intolerance
- increased metabolic rate

Diagnosis and Treatment

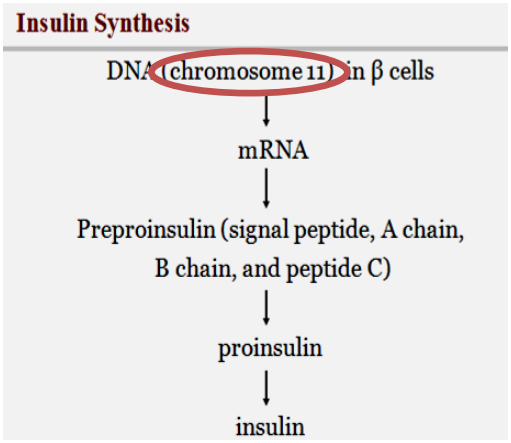
- Diagnosed by high plasma catecholamines and increased metabolites [**VMA**] in urine
- Treatment is surgical resection

❖ Pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (**islets of Langerhans**) produce hormones involved in regulating fuel storage and use.

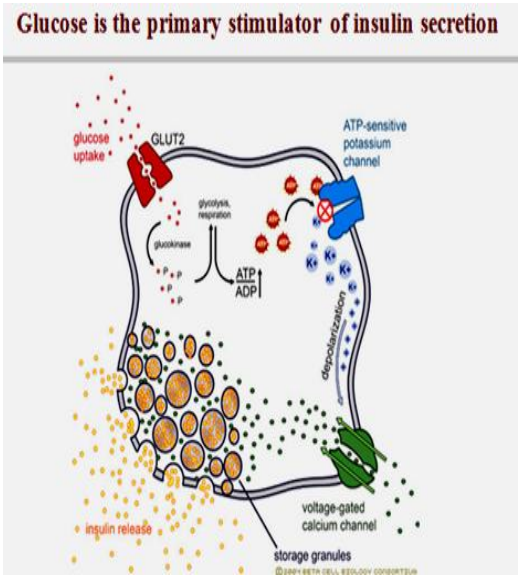
❖ Islets of Langerhans : 1-2 million islets

- Beta (β) cells produce insulin (70%)
- Alpha (α) cells produce glucagon (20%)
- Delta (δ) cells produce somatostatin (5%)
- F cells produce pancreatic polypeptide (5%)



❖ Insulin

- Hormone of nutrient abundance
- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.



❖ Insulin Synthesis

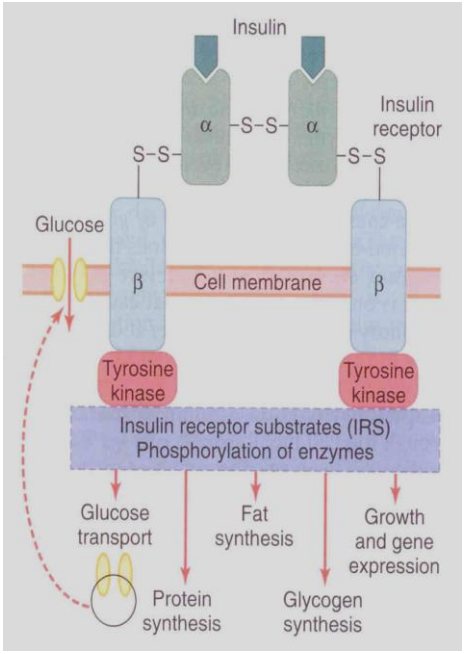
- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
- Threshold of glucose-stimulated insulin secretion is **100 mg/dl.**
- Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene

❖ Insulin Receptor

- the insulin receptor is a transmembrane receptor
- belongs to the large class of **tyrosine kinase receptors**
- Made of two alpha subunits and two beta subunits

❖ Actions of insulin

- Raapid (seconds)
  - (+) transport of glucose, amino acids, K+ into insulin-sensitive cells
- Intermediate (minutes)
  - (+) protein synthesis
  - (-) protein degradation
  - (+) of glycolytic enzymes and glycogen synthase
  - (-) phosphorylase and gluconeogenic enzymes
- Delayed (hours)
  - (+) mRNAs for lipogenic and other enzymes



❖ Action of insulin on Adipose tissue

- (+) glucose entry
- (+) fatty acid synthesis
- (+) glycerol phosohate synthesis
- (+) triglyceride dep0sition
- (+)lipoprotein lipase
- (-) of hormone-sensitive lipase
- (+) K uptake

❖ **Action of insulin on Muscle:**

- (+) glucose entry
- (+) glycogen synthesis
- (+) amino acid uptake
- (+) protein synthesis in ribosomes
- (-) protein catabolism
- (-) release of gluconeogenic aminco acids
- (+) ketone uptake
- (+) K uptake

❖ **Action of insulin on Liver:**

- (-) ketogenesis
- (+) protein synthesis
- (+) lipid synthesis
- (-)gluconogenesis, (+) glycogen synthesis, (+) glycolysis.

❖ **Glucose Transport**

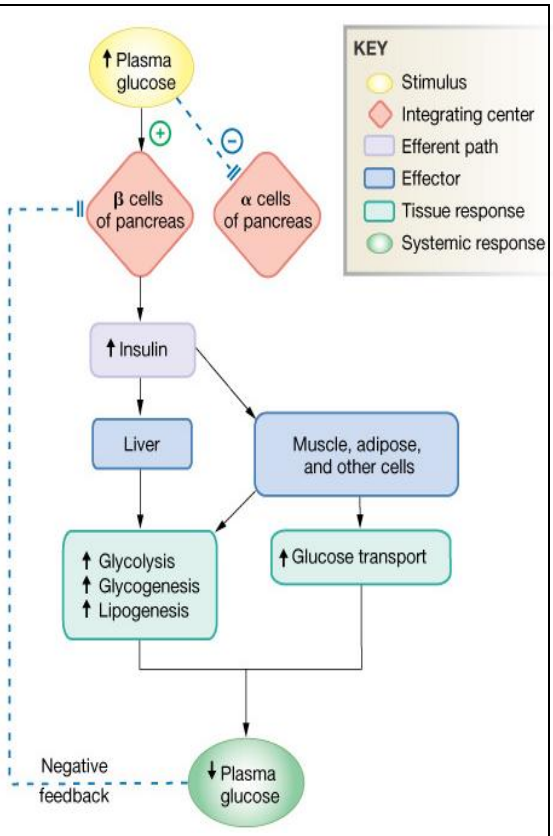
- GLUT1 (erythrocytes, brain)
- GLUT2 (liver, pancreas, small intestines)
- GLUT3 (brain)
- **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)

❖ **Glucagon**

- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Produced by α cells in the pancreas

❖ **Glucagon Actions**

- Its major target is liver:
  - Glycogenolysis
  - Gluconeogenesis
  - Lipid oxidation (fully to CO2 or partially to produce keto acids "**ketone bodies**").
  - Release of glucose to the blood from liver cells



SYNTHESIS

DNA in α cells (chromosome 2)

↓

mRNA

↓

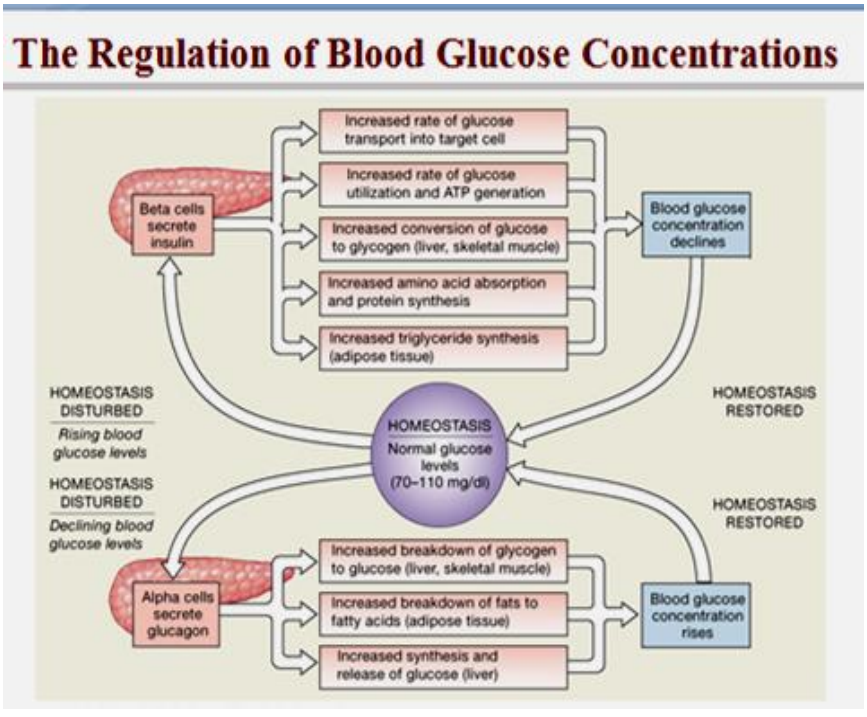
Preproglucagon

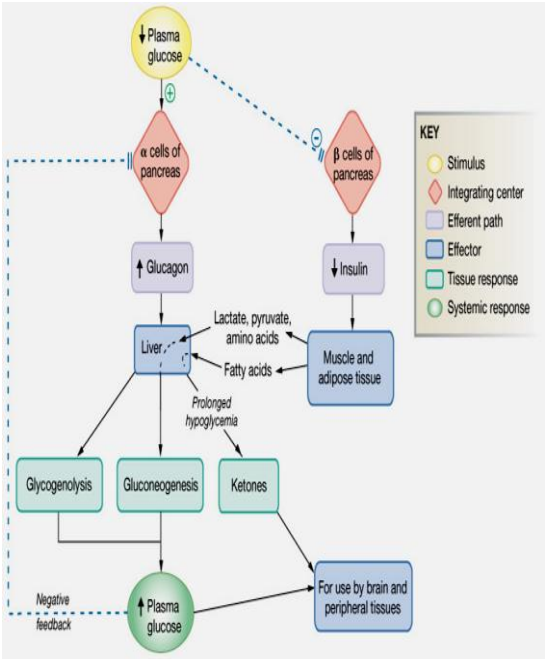
↓

proglucagon

↓

glucagon





Diabetes

- Diabetes is probably the most important metabolic disease.
- It affects every cell in the body and affects carbohydrate, lipid, and protein metabolism.
- characterized by the polytriad:

  - **Polyuria** (excessive urination)
  - **Polydypsia** (excessive thirst)
  - **Polyphagia** (excessive hunger).

❖ Diabetes Mellitus Type I

- Caused by an immune-mediated selective destruction of β cells
- β cells are destroyed while α cells are preserved:

  No insulin→ high glucagon → high production of glucose and ketones by liver
  ↑ glucose & ketones → osmotic diuresis
  ↑ keto acids → diabetic ketoacidosis

❖ Diabetes Mellitus: Type II

- More common in some ethnic groups
- Insulin resistance keeps blood glucose too high
- Chronic complications: atherosclerosis, renal failure & blindness

❖ *Glucose Tolerance Test*

- Both the FPG and OGTT tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.
- The oral glucose tolerance test (OGTT):
  - FPG test
  - Blood is then taken 2 hours after drinking a special glucose solution
  - Following the oral administration of a standard dose of glucose, the plasma glucose concentration normally rises but returns to the fasting level within 2 hours.
  - If insulin activity is reduced, the plasma glucose concentration takes longer than 2 hours to return to normal and often rises above 200 mg/dl.
  - Measurement of urine glucose allows determination of the renal threshold for glucose.

❖ <u>The following results suggest different conditions:</u>

- **Normal values:**
- FPG <100 mg/dl
- 2hr PPG < 140 mg/dL
- **Impaired glucose tolerance**
- 2hr PPG = 140 - 199 mg/dL
- **Diabetes**
- **FPG ≥ 126 mg/dl**
- **2hr PPG levels ≥ 200 mg/dL**

إن اصبت فمن الله و إن اخطئت فمن نفسي والشيطان

وصلى الله و سلم على نبينا محمد وعلى آله وصحبه اجمعين

دعواتي للجميع بالتوفيق و لا تنسوني من صالح دعائكم

أختكم : سديم الدواس