Endocrinology

Endocrine glands are the glands which synthesize and release the classical hormones into the blood. The endocrine glands are also called ductless glands because the hormones secreted by them are released directly into blood without any duct.

HORMONES

Hormones are **chemical messengers**, synthesized by endocrine glands. Based on chemical nature, hormones are classified into three types:

1-STEROID HORMONES

Steroid hormones are the hormones synthesized from cholesterol or its derivatives. Steroid hormones are secreted by adrenal cortex, gonads and placenta

2- PROTEIN HORMONES

Protein hormones are large or small peptides. Protein hormones are secreted by pituitary gland, parathyroid glands, pancreas and placenta

3- TYROSINE DERIVATIVES

Two types of hormones, namely thyroid hormones and adrenal medullary hormones are derived from the amino acid tyrosine.

HORMONAL ACTION

"

Hormone does not act directly on target cells. First it combines with receptor present on the target cells and forms a **hormone-receptor complex.** This hormone receptor complex induces various changes or reactions in the target cells.

HORMONE RECEPTORS

Hormone receptors are the large proteins present in the target cells. Each cell has thousands of receptors. Important characteristic feature of the receptors is that, each receptor is specific for one single hormone, i.e. each receptor can combine with only one hormone. Thus, a hormone can act on a target cell, only if the target cell has the receptor for that particular hormone.

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Situation of the Hormone Receptors

Hormone receptors are situated either in cell membrane or cytoplasm or nucleus of the target cells as follows:

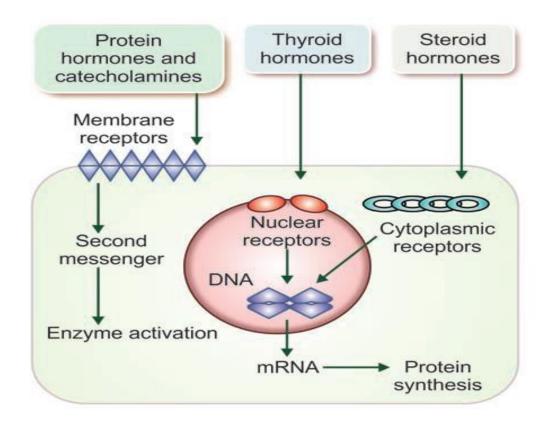
1. *Cell membrane:* Receptors of protein hormones and adrenal medullary hormones (catecholamines) are situated in the cell membrane .

2.*Cytoplasm:* Receptors of steroid hormones are situated in the cytoplasm of target cells.

3. Nucleus: Receptors of thyroid hormones are in the nucleus of the cell.

Regulation of Hormone Receptors

Receptor proteins are not static components of the cell. Their number increases or decreases in various conditions. Generally, when a hormone is secreted in excess, the number of receptors of that hormone decreases due to binding of hormone with receptors. This process is called **down regulation.** During the deficiency of the hormone, the number of receptor increases, which is called **upregulation**.



Situation of hormonal receptors

MECHANISM OF HORMONAL ACTION

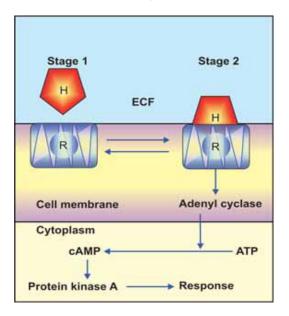
On the target cell, the hormone–receptor complex acts by any one of the following mechanisms:

1. By Altering the Permeability of Cell Membrane

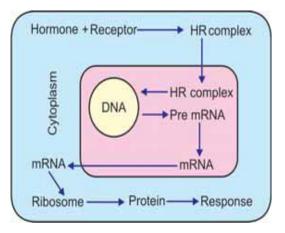
The neurotransmitter substances in a synapse or neuromuscular junction act by changing the permeability of postsynaptic membrane. For example, in a neuromuscular junction, when an impulse (action potential) reaches the axon terminal of the motor nerve, acetylcholine is released from the vesicles. Acetylcholine increases permeability of postsynaptic membrane by opening the ligand gated sodium channels. So, sodium ions enter the neuromuscular junction from ECF through the channels. Sodium ions alter the resting membrane potential so that, endplate potential is developed.

2. By Activating the Intracellular Enzyme

The protein hormones and the catecholamines act by activating the intracellular enzymes. The hormone, which acts on a target cell, is called first messenger or chemical mediator. This hormone, in combination with the receptor forms hormone-receptor complex. This in turn activates the enzymes of the cell and causes the formation of another substance called the second messenger.



Mode of action of protein hormones and catecholamines. H = Hormone, R = Receptor



Mode of action of steroid hormones. Thyroid hormones also act in the similar way. But their receptors are in the nucleus.HR=Hormone-receptor complex The second messenger produces the effects of the hormone inside the cells. The most common second messenger is adenosine monophosphate (cyclic AMP or cAMP).

Sequence of events in the activation of second messenger:

i. The hormone binds with the receptor in the cell membrane and forms the hormone-receptor complex which activates the enzyme adenyl cyclase

ii. Adenyl cyclase converts the ATP of the cytoplasm into cAMP. Cyclic AMP executes the actions of hormone inside the cell, by stimulating the enzymes like protein kinase A

3. By Acting on Genes

Thyroid and steroid hormones act by activating the genes of the target cells.

Sequence of events during activation of genes:

i. The hormone enters the interior of the cell and binds with receptor in cytoplasm (steroid hormone) or in nucleus (thyroid hormone) and forms hormone-receptor.

ii. This complex binds to DNA and increases transcription of mRNA

iii. The mRNA moves out of nucleus and reaches ribosomes and activates them.

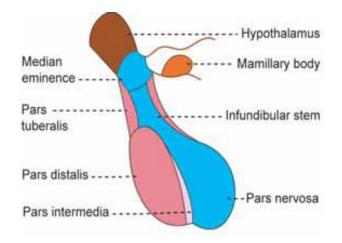
iv. The activated ribosomes produce large quantities of proteins which produce the physiological responses in the target cells.

The pituitary gland

The pituitary gland is also known as hypophysis. It is a small gland that lies at the base of the brain. It is connected with the hypothalamus by the pituitary stalk or hypophyseal stalk.

Pituitary gland is divided into two portions:

- 1. Anterior pituitary or adenohypophysis
- 2. Posterior pituitary or neurohypophysis.



Parts of pituitary gland

HORMONES SECRETED BY ANTERIOR PITUITARY

Anterior pituitary is also known as the master gland because it regulates many other endocrine glands. Six hormones are secreted by the anterior pituitary:

1. Growth hormone (GH) or somatotropic hormone (STH)

- 2. Thyroid stimulating hormone (TSH) or thyrotropic hormone
- 3. Adrenocorticotropic hormone (ACTH)
- 4. Follicle stimulating hormone (FSH)

5. Luteinizing hormone (LH in females) or interstitial cell stimulating hormone (ICSH in males)

6. Prolactin.

FSH and LH are together called gonadotropic hormones or gonadotropins because of their action on the gonads. Recently, the hormone β -lipotropin is found to be secreted by anterior pituitary.

REGULATION OF SECRETION OF ANTERIOR PITUITARY HORMONES

Secretion of anterior pituitary hormones is regulated by hypothalamus. Hypothalamus secretes some releasing and inhibitory hormones (factors) which are transported from hypothalamus to anterior pituitary through hypothalamo-hypophyseal portal vessels.

Releasing and Inhibitory Hormones Secreted by Hypothalamus

1. Growth hormone releasing hormone (GHRH)— stimulates the release of GH.

2.Growth hormone releasing polypeptide (GHRP) — stimulates the release of GHRH and GH.

3.Growth hormone inhibitory hormone (GHIH) or somatostatin — inhibits GH release.

4.Thyrotropic releasing hormone (TRH) —stimulates the release of TSH 5.Corticotropin releasing hormone (CRH) —stimulates the release of ACTH.

6.Gonadotropin releasing hormone (GnRH) —the release of the gonadotropins — FSH and LH.

7. Prolactin inhibitory hormone (PIH) — inhibits prolactin secretion.

GROTH HORMONE

GH is responsible for the growth of almost all tissues of the body, which are capable of growing. It actually increases the size and number of cells by increasing the mitotic division. GH also causes specific differentiation of certain types of cells like bone cells and muscle cells. GH also acts on the metabolism of all the three major types of foodstuffs in the body, viz. proteins, lipids and carbohydrates.

Regulation of GH Secretion

Secretion of GH is regulated by hypothalamus and feedback control. Role of hypothalamus in the secretion of GH Hypothalamus regulates GH secretion by releasing three hormones:

1.GHRH that increases the secretion of GH by stimulating the somatotropes of anterior pituitary.

2. GHRP that promotes the release of GHRH from hypothalamus and GH from pituitary

3. GHIH or somatostatin which inhibits the secretion of GH.

These three hormones are transported from hypothalamus to anterior

pituitary by hypothalamo-hypophyseal portal blood vessels.

Hypothalamus is in turn influenced by many factors which cause increase or decrease in GH secretion.

Factors which increase the GH secretion:

1. Hypoglycemia

- 2. Fasting
- 3. Starvation
- 4. Exercise
- 5. Stress and trauma
- 6. Initial stages of sleep.

Factors which decrease the GH secretion:

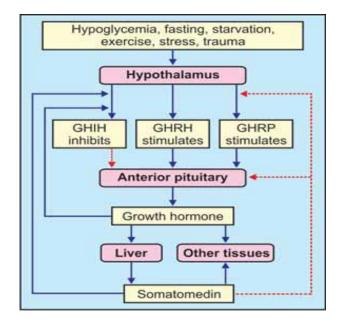
- 1. Hyperglycemia
- 2. Increase in free fatty acids in blood

3. Later stages of sleep.

Feedback control

GH secretion is under negative feedback control Hypothalamus releases GHRH and GHRP, which in turn promote the release of GH from anterior pituitary. GH acts on various tissues. It also activates the liver cells to secrete somatomedin-C (IGF-I).

Now, the somatomedin-C increases the release of GHIH from hypothalamus. GHIH in turn inhibits release of GH from pituitary. Somatomedin also inhibits the release of GHRP from hypothalamus. It acts on pituitary directly and inhibits the secretion of GH.



Regulation of GH secretion

GH inhibits its own secretion by stimulating the release of GHIH from hypothalamus. This type of feedback is called short-loop feedback control. Similarly, GHRH inhibits its own release by short-loop feedback control. Whenever, the blood level of GH decreases, the GHRH is secreted from the hypothalamus. It in turn causes secretion of GH from pituitary.

OTHER HORMONES OF ANTERIOR PITUITARY

Thyroid Stimulating Hormone (TSH)

TSH is necessary for the growth and the secretory activity of the thyroid gland.

Adrenocorticotropic Hormone (ACTH)

ACTH is necessary for the structural integrity and the secretory activity of adrenal cortex.

Follicle Stimulating Hormone (FSH)

Stimulates development of ovarian follicles; regulates spermatogenesis in the testis.

Luteinizing hormone (LH)

Causes ovulation and formation of the and corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis.

Prolactin

Prolactin is necessary for the final preparation of mammary glands for production and secretion of milk.

Lipotropin

It mobilizes fat from adipose tissue and promotes lipolysis.

HORMONES OF POSTERIOR PITUITARY

Posterior pituitary hormones are:

- 1. Antidiuretic hormone (ADH) or vasopressin
- 2. Oxytocin.

Actually, the posterior pituitary does not secrete any hormone. ADH and oxytocin are synthesized in the hypothalamus. Hence, these two hormones are called neurohormones.

1-ANTIDIURETIC HORMONE

ADH is secreted mainly by supraoptic nucleus of hypothalamus and in small quantity by paraventricular nucleus. From here, this hormone is transported to the posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract by means of axonic flow Antidiuretic hormone is a polypeptide, containing 9 amino acids.

The major function of ADH is retention of water by acting on kidneys. It increases the facultative reabsorption of water from distal convoluted tubule and collecting duct in the kidneys ADH increases water

reabsorption in the tubular epithelial membrane by regulating the water channel proteins called aquaporins through V2 receptors.

In large amount, the ADH shows vasoconstrictor action in all parts of the body. Due to the vasoconstriction, the blood pressure increases. ADH acts on blood vessels through V1A receptors.

Regulation of Secretion

The secretion of ADH depends upon the volume of body fluid and the osmolarity of the body

fluids.

The potent stimulants for ADH secretion are:

1. Decrease in the ECF volume

2. Increase in osmolar concentration in the ECF.

Role of osmoreceptors

The osmoreceptors are the receptors, which give response to change in the osmolar concentration of the blood. These receptors are situated in the hypothalamus near supraoptic and paraventricular nuclei. When osmolar concentration of blood increases, the osmoreceptors are activated. In turn, the osmoreceptors stimulate the supraoptic and paraventricular nuclei which send motor impulses to posterior pituitary through the nerve fibers and cause release of ADH.

ADH causes reabsorption of water from the renal tubules. This increases the volume of the ECF and restores the normal osmolarity.

Oxytocin

Oxytocin is secreted mainly by the paraventricular nucleus and a small quantity is secreted by the supraoptic nucleus in the hypothalamus. And it is transported from hypothalamus to posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract.

In the posterior pituitary, the oxytocin is stored in the nerve endings of hypothalamohypo-physeal tract. When suitable stimuli reach the posterior pituitary from hypothalamus, oxytocin is released into the blood. Oxytocin is secreted in both males and females. Oxytocin is a polypeptide, having 9 amino acids.

oxytocin acts on mammary glands and uterus.

Action of oxytocin on mammary glands

It causes ejection of milk from the mammary glands. The ducts of the mammary glands are lined by myoepithelial cells. Oxytocin causes contraction of the myoepithelial cells and squeezes the milk from alveoli of the mammary glands to the exterior through the duct system and nipple. The process by which the milk is ejected from the alveoli of mammary glands is called the milk ejection reflex or milk let down reflex. It is one of the neuroendocrine reflexes.

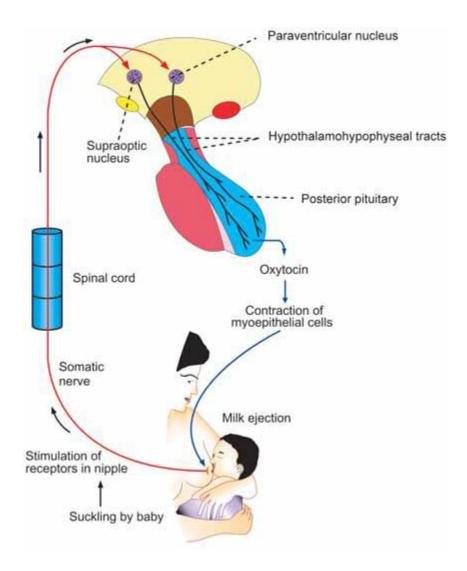
Milk ejection reflex Plenty of touch receptors are present on the mammary glands, particularly around the nipple. When the infant suckles mother's nipple, the touch receptors are stimulated and impulses are discharged. Impulses from here are carried by the somatic afferent nerve fibers and reach the paraventricular and supraoptic nuclei of hypothalamus.

Now, hypothalamus in turn, sends impulses to the posterior pituitary through hypothalamohypophyseal tract and cause release of oxytocin into the blood. When the hormone reaches the mammary gland, it causes contraction of myoepithelial cells resulting in ejection of milk from mammary glands. As this reflex is initiated by the nervous factors and completed by the hormonal action, it is called a neuroendocrine reflex. During this reflex, large amount of oxytocin is released by positive feedback mechanism.

Action oxytocin On pregnant uterus

Throughout the period of pregnancy, oxytocin secretion is inhibited by estrogen and progesterone. At the end of pregnancy, the secretion of these two hormones decreases suddenly and the secretion of oxytocin increases. Oxytocin causes contraction of uterus and helps in the expulsion of fetus. During labor, large quantity of oxytocin is released by means of positive feedback mechanism, i.e. oxytocin induces contraction of uterus, which

in turn causes release of more amount of oxytocin. The contraction of uterus during labor is also a neuroendocrine reflex. Oxytocin also stimulates the release of prostaglandins in the placenta. The prostaglandins intensify the uterine contraction induced by oxytocin.



APPLIED PHYSIOLOGY—DISORDERS OF PITUITARY GLAND

HYPERACTIVITY OF ANTERIOR PITUITARY

1. Gigantism

Gigantism is the pituitary disorder characterized by excess growth of the body. The subjects look like the giants with average height of about 7-8 feet.

2. Acromegaly

It is the disorder characterized by the enlargement, thickening and broadening of bones, particularly in the extremities of the body.

3. Acromegalic Gigantism

It is a rare disorder with symptoms of both gigantism and acromegaly. Hypersecretion of GH in children, before the fusion of epiphysis with shaft of the bones causes gigantism. And, if hypersecretion of the GH is continued even after the fusion of epiphysis, the symptoms of acromegaly also appear.

4. Cushing's Disease

It is also a rare disease characterized by obesity.

HYPOACTIVITY OF ANTERIOR PITUITARY

1. Dwarfism

It is a pituitary disorder in children characterized by the stunted growth.

2. Acromicria

It is a rare disease in adults characterized by the atrophy of the extremities of the body.

3. Simmond's Disease

It is a rare pituitary disease. It is also called pituitary cachexia.

HYPERACTIVITY OF POSTERIOR PITUITARY Syndrome of Inappropriate Hypersecretion of Antidiuretic Hormone

(SIADH)

SIADH is the disease characterized by loss of sodium through urine due to hypersecretion of ADH.

HYPOACTIVITY OF POSTERIOR PITUITARY Diabetes Insipidus

Diabetes insipidus is a posterior pituitary disorder characterized by excess excretion of water through urine.

HYPOACTIVITY OF ANTERIOR AND POSTERIOR PITUITARY

Dystrophia Adiposogenitalis

Dystrophia adiposogenitalis is a disease characterized by obesity and hypogonadism affecting mainly the adolescent boys. It is also called Fröhlich's syndrome or hypothalamic eunuchism.

Thyroid Gland

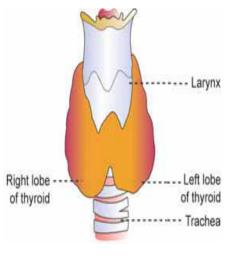
Thyroid is an endocrine gland situated at the root of the neck on either side of the trachea. It has two lobes, which are connected in the middle by an isthmus. It weighs about 20 to 40 gm in adults.

Thyroid gland is composed of large number of closed follicles. The follicles are lined with cuboidal epithelial cells, which are cafollicular cells. The follicular cavity is filled with a colloidal substance known as thyroglobulin which is secreted by the follicular cells. Follicular cells secrete tetraiodothyronine (T4 or thyroxine) and tri-iodothyronine (T3). In between the follicles, the parafollicular cells are present. These cells secrete calcitonin.

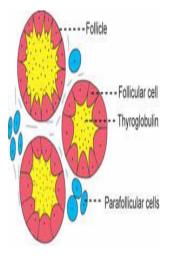
Thyroid gland secretes three hormones:

- 1. Tetraiodothyronine T4 (thyroxine)
- 2. Tri-iodothyronine T3
- 3. Calcitonin.

T4 is otherwise known as thyroxine and it forms about 90% of the total secretion, whereas, T3 is only 9 to 10%. But the potency of T3 is four times more than that of T4.



Thyroid gland



Histology of thyroid

SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones takes place in thyroglobulin present in follicular cavity. Iodine and tyrosine are essential for the formation of thyroid hormones. Iodine is consumed through diet. It is converted into iodide and absorbed from GI tract. Tyrosine is also consumed through diet and is absorbed from the GI. For the synthesis of normal quantities of thyroid hormones, approximately 1 mg of iodine is required per week or about 50 mg per year.

Various stages involved in the synthesis of thyroid hormones are:

1. Thyroglobulin Synthesis

The endoplasmic reticulum and Golgi apparatus in the follicular cells of the thyroid gland synthesize and secrete a thyroglobulin continuously. Each thyroglobulin molecule contains 140 tyrosine molecules. After synthesis, the thyroglobulin is stored in the follicle.

2. Iodide Trapping or Iodide Pump

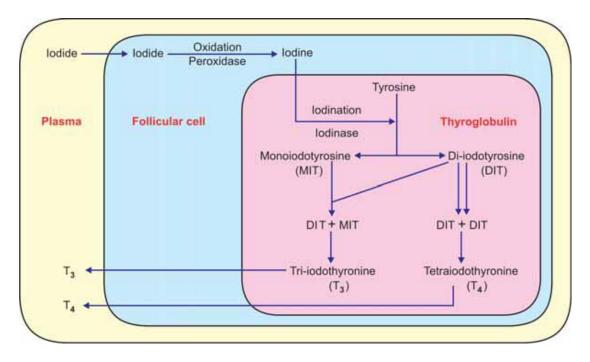
Iodide is transported actively from the blood into the follicular cell against the electrochemical gradient by a process called iodide trapping. Iodide is pumped with sodium into the follicular cell by sodium-iodide symport pump. From here, iodide is transported into the follicular cavity by an iodide-chloride pump.

3. Oxidation of the Iodide

Iodide must be oxidized to elementary iodine because only iodine is capable of combining with tyrosine to form thyroid hormones. The oxidation of iodide into iodine occurs inside the follicular cells in the presence of thyroid peroxidase.

4. Iodination of Tyrosine

The combination of iodine with tyrosine is known as iodination. It takes place in the follicle within thyroglobulin. First, iodine is released from follicular cells into the follicular cavity where it binds with thyroglobulin. This process is called organification of thyroglobulin. In the thyroglobulin, iodine combines with tyrosine which is already present there. Binding of iodine (I) with tyrosine is accelerated by the enzyme iodinase which is secreted by the follicular cells. Iodination of tyrosine occurs in several stages. Tyrosine is iodized first into monoiodotyrosine (MIT) and later into di-iodotyrosine (DIT). MIT and DIT are called the iodotyrosine residues.



Synthesis of thyroid hormones

5. Coupling Reactions

The iodotyrosine residues get coupled with one another through coupling reactions. The coupling occurs in different configurations to give rise to different thyroid hormones.

STORAGE OF THYROID HORMONES

After synthesis, the thyroid hormones remain in the form of vesicles within thyroglobulin. Incombination with thyroglobulin, the thyroid hormones can be stored for several months.

And, thyroid gland is unique in this, as it is the only endocrine gland that can store its hormones for a long period of about 4 months. So, when the synthesis of thyroid hormone stops, the signs and symptoms of deficiency do not appear for about 4 months.

RELEASE OF THYROID HORMONES FROM THE THYROID GLAND.

Thyroglobulin itself is not released into the bloodstream. On the other hand, the hormones are first cleaved from the thyroglobulin. Only T3 and T4 are released into the blood. In the peripheral tissues T4 is converted into T3.

TRANSPORT OF THYROID HORMONES IN THE BLOOD

The normal plasma level of total T3 is 0.12 mg/dL and that of total T4 is 8 mg/dL. The thyroid hormones are transported in the blood in combination with three types of plasma proteins.

- 1. Thyroxine binding globulin (TBG)
- 2. Thyroxine binding prealbumin (TBPA)
- 3. Albumin.

FUNCTIONS OF THYROID HORMONES

Thyroid hormones have two major effects on the body:

- I. To increase the overall metabolic rate in the body
- II. To stimulate growth in children.

REGULATION OF SECRETION OF THYROID HORMONES

The secretion of thyroid hormones is controlled by anterior pituitary and hypothalamus through feedback mechanism.

ROLE OF PITUITARY GLAND

Thyroid Stimulating Hormone

Thyroid stimulating hormone (TSH) secreted by anterior pituitary is the major factor regulating the synthesis and release of thyroid hormones.

ROLE OF HYPOTHALAMUS

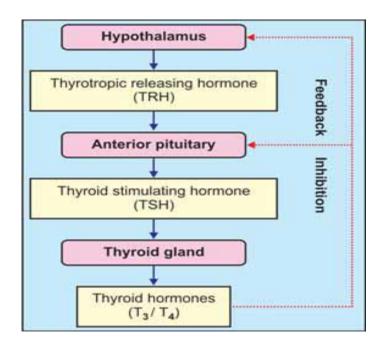
Hypothalamus regulates thyroid secretion by controlling TSH secretion through thyrotropic releasing hormone (TRH) from hypothalamus. From hypothalamus, TRH is transported through the hypothalamo-hypophyseal portal vessels to the anterior pituitary. After reaching the pituitary gland, the TRH causes the release of TSH.

FEEDBACK CONTROL

Thyroid hormones regulate their own secretion through negative feedback control by inhibiting the release of TRH from hypothalamus and TSH from anterior pituitary.

ROLE OF IODIDE

Iodide is an important factor regulating the synthesis of thyroid hormones. When the dietary level of iodine is moderate, the blood level of thyroid hormones is normal. However, when iodine intake is high, the enzymes necessary for synthesis of thyroid hormones are inhibited by iodide itself resulting in suppression of hormone synthesis.



Regulation of secretion of thyroid hormones

APPLIED PHYSIOLOGY—DISORDERS OF THYROID GLAND

1. HYPERTHYROIDISM Causes for Hyperthyroidism

i. Graves' disease

Graves' disease is an autoimmune disease. Normally, thyroid stimulating hormone (TSH) combines with surface receptors of thyroid cells and causes the synthesis of thyroid hormones. In Graves' disease the B lymphocytes (plasma cells) produce autoimmune antibodies called thyroid stimulating autoantibodies. These antibodies act like TSH by binding with membrane receptors of TSH and activating cAMP system of the thyroid follicular cells. This results in hypersecretion of thyroid hormones.

ii. Thyroid adenoma

Sometimes, a localized tumor develops in the thyroid tissue. It is known as thyroid adenoma and it secretes large quantities of thyroid hormones.

2. HYPOTHYROIDISM

Decreased secretion of thyroid hormones is called hypothyroidism. Hypothyroidism leads to myxedema in adults and cretinism in children.

Myxedema

It is the hypothyroidism in adults characterized by generalized edematous appearance.

Causes for myxedema

Myxedema occurs due to diseases of thyroid gland, genetic disorder or iodine deficiency. In addition, it is also caused by deficiency of thyroid stimulating hormone or thyrotropic releasing hormone.

Cretinism

Cretinism is the hypothyroidism in children characterized by stunted growth.

Causes for cretinism

Cretinism occurs due to congenital absence of thyroid gland, genetic disorder or lack of iodine in the diet.

3. GOITER

Goiter means enlargement of the thyroid gland. It occurs both in hypothyroidism and hyperthyroidism.

Goiter in Hyperthyroidism — Toxic Goiter

Toxic goiter is the enlargement of thyroid gland with increased secretion of thyroid hormones caused by thyroid tumor.

Goiter in Hypothyroidism — Nontoxic Goiter

Nontoxic goiter is the enlargement of thyroid gland without increase in hormone secretion. It is also called hypothyroid goiter.

Based on the cause, the nontoxic hypothyroid goiter is classified into two types:

i. Endemic colloid goiter

It is the nontoxic goiter caused by iodine deficiency. It is also called iodine deficiency goiter.

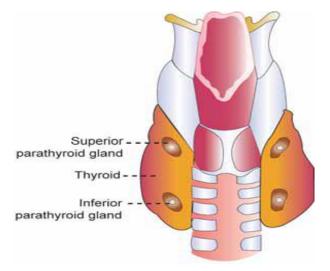
ii. Idiopathic nontoxic goiter

It is the goiter due to unknown cause. Enlargement of thyroid gland occurs even without iodine deficiency. The exact cause is not known.

Parathyroid Glands and Physiology of Bone

There are four parathyroid glands located immediately behind thyroid gland at the upper and lower poles. The parathyroid glands are very small in size measuring about 6 mm long, 3 mm wide and 2 mm thick with dark brown color.

Each parathyroid gland is made up of chief cells and oxyphil cells. The chief cells secrete parathormone. Parathormone is essential for the maintenance of blood calcium level within a very narrow critical level.



Parathyroid glands on the posterior surface of thyroid gland

ACTIONS OF PARATHORMONE

PTH maintains the blood calcium level and blood phosphate level.

On Blood Calcium Level

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

- 1. Bones.
- 2. Kidneys.
- 3. GI tract.

1. On bone

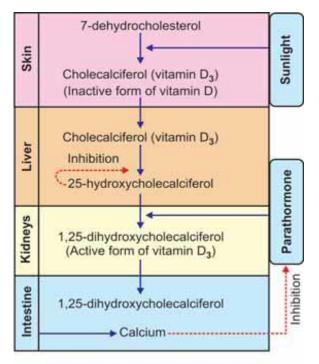
PTH increases resorption of calcium from the bones by acting on osteoblasts, osteocytes and osteoclasts of the bone.

2. On kidneys

PTH increases the reabsorption of calcium from distal convoluted tubule and proximal part of collecting duct into the plasma. It also increases the formation of 1,25-dihydroxycholecalciferol (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys which is necessary for absorption of calcium form GI tract.

3. On gastrointestinal tract

PTH increases the absorption of calcium from GI tract by increasing the formation of 1,25-dihydroxycholecalciferol in the kidneys.



Schematic diagram showing activation of vitamin D

Activation of vitamin D: There are various forms of vitamin D but, the most important one is vitamin D3. It is also known as cholecalciferol. Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol by the action of ultraviolet rays from the sunlight. It is also obtained from dietary sources. The activation of vitamin D3 occurs in two steps.

In the first step, cholecalciferol (vitamin D3) is converted into 25hydroxycholecalciferol in the liver. This process is limited and is inhibited by 25-hydroxycholecalciferol itself by feedback mechanism. In the second step, 25-hydroxycholecalciferol is converted into 1,25dihydroxycholecalciferol (calcitriol) in kidney. And, it is the active form of vitamin D3. This step needs the presence of PTH. The 1,25dihydroxycholecalciferol increases the absorption of calcium and phosphate from intestine.

On Blood Phosphate Level

PTH decreases blood level of phosphate by acting on:

- 1. Bones
- 2. Kidneys
- 3. GI tract.
- 1. On bone

PTH increases the phosphate absorption from bones.

2. On kidneys

Phosphaturic action: Phosphaturic action is the effect of PTH by which phosphate is excreted in urine. PTH inhibits reabsorption of phosphate from renal tubules so that excretion of phosphate through urine increases.

3. On gastrointestinal tract

PTH increases the formation of 1,25-dihydroxycholecalciferol in the kidneys. This vitamin in turn increases the absorption of phosphate along with calcium.

Mode of Action of PTH

On the target cells, PTH executes its action through cAMP.

REGULATION OF PARATHORMONE SECRETION

Blood level of calcium is the main factor that regulates the secretion of PTH. Blood phosphate level also influences PTH secretion.

Blood Level of Calcium

PTH secretion is inversely proportional to blood calcium level. Increase in blood calcium level decreases PTH secretion.

Blood Level of Phosphate

PTH secretion is directly proportional to blood phosphate level. Whenever the blood level of phosphate increases, it combines with ionized calcium to form calcium hydrogen phosphate.

This decreases ionized calcium level in blood which stimulates PTH secretion.

CALCITONIN

Source of Secretion

Calcitonin is secreted by the parafollicular cells or clear cells (C cells) situated amongst the follicles in thyroid gland.

ACTIONS OF CALCITONIN

1. On Blood Calcium Level

Calcitonin plays an important role in controlling the blood calcium level. It decreases the blood calcium level and thereby counteracts parathormone. Calcitonin reduces the blood calcium level by acting on bones, kidneys and intestine.

i. On bones

Calcitonin stimulates osteoblastic activity and facilitates the deposition of calcium on bones. At the same time, it suppresses the activity of osteoclasts and inhibits the resorption of calcium from bones. It inhibits even the development of new osteoclasts in bones.

ii. On kidney

Calcitonin increases the excretion of calcium through urine, by inhibiting the reabsorption of calcium from the renal tubules.

iii. On intestine

It prevents the absorption of calcium from intestine into the blood.

2. On Blood Phosphate Level

With respect to calcium, calcitonin is an antagonist to PTH. But it has similar actions of PTH with respect to phosphate. It decreases the blood level of phosphate by acting on bones and kidneys.

i. On bones

Calcitonin inhibits the resorption of phosphate from bone and stimulates deposition of phosphate on bones.

ii. On kidney

Calcitonin increases the excretion of phosphate through urine, by inhibiting phosphate reabsorption from renal tubules.

REGULATION OF CALCITONIN SECRETION

High calcium content in plasma stimulates the calcitonin secretion through a calcium receptor in parafollicular cells.

CALCIUM METABOLISM IMPORTANCE OF CALCIUM

Calcium is very essential for many activities in the body such as:

- 1. Teeth and bone formation
- 2. Neuronal activity
- 3. Skeletal muscle activity
- 4. Cardiac activity
- 5. Smooth muscle activity
- 6. Secretory activity of the glands
- 7. Cell division and growth
- 8. Coagulation of blood.

The values belong to adults of total body weight. Ninety nine percent of calcium is present in the bones and teeth and the rest is present in the plasma. The normal blood calcium level ranges between 9 and 11 mg/dL.

SOURCE OF CALCIUM

1. Dietary Source

Calcium is available in several foodstuffs such as milk, cheese, vegetables, meat, egg, grains, sugar, coffee, tea, chocolate, etc.

2. From Bones

Besides dietary calcium, blood also gets calcium from bones by resorption.

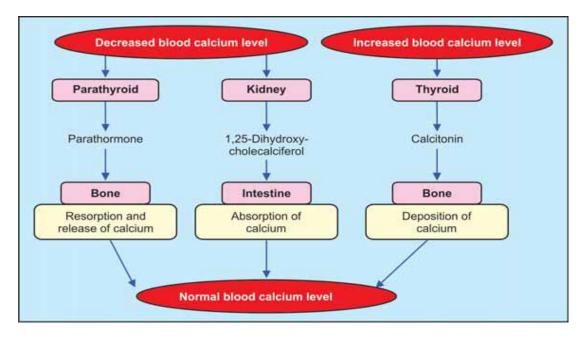
ABSORPTION AND EXCRETION OF CALCIUM

Calcium taken through dietary sources is absorbed from the GI tract into blood and distributed to various parts of the body. Depending upon the blood level, the calcium is either deposited in the bone or removed from the bone (resorption). Calcium is excreted from the body through urine and feces.

REGULATION OF BLOOD CALCIUM LEVEL

Blood calcium level is regulated mainly by three hormones

- 1. Parathormone
- 2. 1,25-dihydroxycholecalciferol (calcitriol).
- 3. Calcitonin.



Schematic diagram showing regulation of blood calcium level

PHYSIOLOGY OF BONE

Bone or osseous tissue is a specialized rigid connective tissue that forms the skeleton. It consists of special type of cells and tough intercellular matrix of ground substance. The matrix is formed by organic substances like collagen and it is strengthened by the deposition of mineral salts like calcium phosphate and calcium carbonate. Throughout life, the bone is renewed by the process of bone formation and bone resorption.

FUNCTIONS OF BONE

1. Protective function – protects the soft tissues and vital organs of the body.

2. Mechanical function – supports the body and brings out various movements of the body.

3. Metabolic function – metabolism and homeostasis of calcium and phosphate in the body

4. Hemopoietic function – red bone marrow in the bones is the site of production of blood cells.

CELL TYPES OF BONE

Bone has three major types of cells:

- 1. Osteoblasts
- 2. Osteocytes
- 3. Osteoclasts.

Endocrine Functions of Pancreas

ISLETS OF LANGERHANS

The endocrine function of pancreas is performed by the islets of Langerhans. Human pancreas contains about 1 to 2 million islets. Islets of Langerhans consist of four types of

Cells:

- 1. A cells or α cells which secrete glucagon
- 2. B cells or β cells which secrete insulin
- 3. D cells or δ cells which secrete somatostatin
- 4. F cells or PP cells which secrete pancreatic polypeptide.

INSULIN

Insulin is secreted by B cells or the β cells in the islets of Langerhans of pancreas. Insulin is a polypeptide with 51 amino acids. It has two amino acid chains called α and β chains which are linked by disulfide bridges.

ACTIONS

Insulin is the important hormone that is concerned with regulation of carbohydrate metabolism and blood sugar level. It is also concerned with metabolism of proteins and fats.

1. On Carbohydrate Metabolism

Insulin is the only antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that reduces blood sugar level. Insulin reduces the blood sugar level by its following actions on carbohydrate metabolism are:

i. Increases transport and uptake of glucose by the cells Insulin facilitates the transport of glucose from the blood into the cells by increasing the permeability of cell membrane to glucose. Insulin stimulates the rapid uptake of glucose by all the tissues particularly liver, muscle and adipose tissues.

ii. Promotes peripheral utilization of glucose Insulin promotes the peripheral utilization of glucose. In the presence of insulin, the glucose which enters the cell is oxidized immediately. The rate of utilization depends upon intake of glucose.

iii. Promotes storage of glucose — glycogenesis

Insulin promotes the rapid conversion of glucose into glycogen (glycogenesis), which is stored in muscle and liver. Thus, glucose is

stored in these two organs in the form of glycogen. Insulin activates the enzymes, which are necessary for glycogenesis. In liver, when glycogen content increases beyond its storing capacity, insulin causes conversion of glucose into fatty acids.

iv. Inhibits glycogenolysis

Insulin prevents the breakdown of glycogen into glucose in muscle and liver.

v. Inhibits gluconeogenesis

Insulin prevents gluconeogenesis, i.e. the formation of glucose from proteins. Thus, insulin decreases the blood sugar level by:

i. Facilitating transport and uptake of glucose by the cells

ii. Increasing peripheral utilization of glucose

iii. Increasing the storage of glucose by converting it into glycogen in liver and muscle

iv. Inhibiting glycogenolysis

v. Inhibiting gluconeogenesis

2. On Protein Metabolism

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins .

3. On Fat Metabolism

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue.

4. On Growth

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins. It enhances the transport of amino acids into the cells and synthesis of proteins in the cells.

MODE OF ACTION

On the target cells, insulin binds with the receptor protein and forms the insulin-receptor complex. This executes the action by activating the intracellular enzyme system.

REGULATION OF SECRETION

Insulin secretion is mainly regulated by blood glucose level. In addition, other factors like amino acids, lipid derivatives, gastrointestinal and endocrine hormones and autonomic nerve fibers also stimulate insulin secretion.

1. Role of Blood Glucose Level

When the blood glucose level is normal (80 to 100 mg/dL), the rate of insulin secretion is low (up to 10 μ U/minute). When the blood glucose level increases between 100 to 120 mg/dL, the rate of insulin secretion rises rapidly to 100 μ U /minute. When the blood glucose level rises above 200 mg/dL, the rate of insulin secretion also rises very rapidly up to 400 μ U /minute.

2. Role of Proteins

The excess amino acids in blood also stimulate insulin secretion.

3. Role of Lipid Derivatives

The β ketoacids such as acetoacetate also increase insulin secretion.

4. Role of Gastrointestinal Hormones

Insulin secretion is increased by some of the gastrointestinal hormones.

5. Role of Endocrine Hormones

The diabetogenic hormones like glucagon, growth hormone, and cortisol increase the blood sugar level which, in turn, stimulate insulin secretion indirectly. The prolonged hypersecretion of these hormones causes exhaustion of β cells resulting in diabetes mellitus.

6. Role of Autonomic Nerves

The stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion.

GLUCAGON

Glucagon is secreted from A cells or α cells in the islets of Langerhans of pancreas. It is also secreted from A cells of stomach and L cells of intestine. Glucagon is a polypeptide with 29 amino acids.

ACTIONS

Actions of glucagon are antagonistic to those of insulin. It increases the blood sugar level and peripheral utilization of lipids and facilitates the conversion of proteins into glucose.

1. On Carbohydrate Metabolism

Glucagon increases the blood glucose level by increasing glycogenolysis and gluconeogenesis in liver and releasing glucose into the blood.

2. On Protein Metabolism

Glucagon increases transport of amino acids into liver cells. The amino acids are utilized for gluconeogenesis.

3. On Fat Metabolism

Glucagon shows lipolytic and ketogenic actions. It increases lipolysis by increasing the release of free fatty acids from adipose tissue and making them available for peripheral utilization. The lipolytic activity of glucagon, in turn, promotes ketogenesis (formation of ketone bodies) in liver.

MODE OF ACTION

On the target cells (mostly liver cells) glucagon causes formation of cyclic AMP which brings out the actions of glucagon.

REGULATION OF SECRETION

The secretion of glucagon is controlled mainly by blood glucose and amino acid levels in the blood.

1. Role of Blood Glucose Level

The important factor that regulates the secretion of glucagon is the decrease in blood glucose level. When blood glucose level decreases below 80 mg/dL of blood, α cells of islets of Langerhans are stimulated The glucagon in turn increases the blood glucose level. On the other hand, when the blood sugar level increases, α cells are inhibited and the secretion of glucagon decreases.

2. Role of Amino Acid Level in Blood

Increase in amino acid level in blood stimulates the secretion of glucagon. Glucagon, in turn, converts the amino acids into glucose.

SOMATOSTATIN

Somatostatin is secreted from hypothalamus, D cells (δ cells) in islets of Langerhans of pancreas and D cells in stomach and upper part of small intestine. Somatostatin is a polypeptide.

ACTIONS

1. Somatostatin acts within islets of Langerhans and, inhibits α and β cells, i.e. it inhibits the secretion of both glucagon and insulin

- 2. It decreases the motility of stomach, duodenum and gallbladder.
- 3. It reduces the secretion of gastrointestinal hormones.

4. Hypothalamic somatostatin inhibits secretion of GH and TSH from anterior pituitary. That is why, it is also called growth hormone inhibitory hormone (GHIH).

MODE OF ACTION

Somatostatin brings out its actions through cAMP.

REGULATION OF SECRETION

The secretion of pancreatic somatostatin is stimulated by glucose, amino acids and cholecystokinin. The tumor of D cells of islets of Langerhans causes hypersecretion of somatostatin. It leads to hyperglycemia and other symptoms of diabetes mellitus.

REGULATION OF BLOOD SUGAR LEVEL (BLOOD GLUCOSE LEVEL)

NORMAL BLOOD SUGAR LEVEL

In normal persons, blood sugar level is controlled within a narrow range. In the early morning after overnight fasting, the blood sugar level is low ranging between 70 and 110 mg/dL of blood. Between first and second hour after meals (postprandial), the blood sugar level risesto 100 to 140 mg/dL. The sugar level in the blood is brought back to normal at the end of second hour after the meals. The blood sugar regulating mechanism is operated through liver and muscle by the influence of the pancreatic hormones insulin and glucagon. Many other hormones are also involved in the regulation of blood sugar level. Among all the hormones, insulin is the only hormone that reduces the blood sugar level and it is called the antidiabetogenic hormone.

The hormones, which increase blood sugar level, are called diabetogenic hormones or antiinsulin hormones.

Necessity of Regulation of Blood Glucose Level

Regulation of blood sugar (glucose) level is very essential because, glucose is the only nutrient that is utilized for energy by many tissues such as brain tissues, retina and germinal epithelium of the gonads.

ROLE OF LIVER IN THE MAINTENANCE OF BLOOD SUGAR LEVEL

Liver serves as an important glucose buffer system. When blood sugar level increases after a meal, the excess glucose is converted into glycogen and stored in liver. Afterwards, when blood sugar level falls, the glycogen in liver is converted into glucose and released into the blood. The storage of glycogen and release of glucose from liver are mainly regulated by insulin and glucagon

APPLIED PHYSIOLOGY

HYPOACTIVITY — DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by high blood sugar (glucose) level associated with other manifestations. In most of the cases, the diabetes mellitus develops due to the deficiency of insulin.

Types of Diabetes Mellitus

Diabetes mellitus is of two types, Type I and Type II.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to the deficiency of insulin. So it is also called insulin dependent diabetes mellitus (IDDM). Type I diabetes mellitus may occur at any age of life but, it usually occurs before 40 years of age. When it occurs at infancy (due to congenital disorder) or in childhood, it is called juvenile diabetes.

Causes of type I diabetes mellitus

- 1. Degeneration of β cells in the islets of
- Langerhans of pancreas
- 2. Destruction of β cells by viral infection
- 3. Congenital disorder of β cells
- 4. Destruction of β cells during autoimmune diseases.

Type II Diabetes Mellitus

It is due to the absence or deficiency of insulin receptors. It usually occurs after 40 years hence, it is called maturity onset diabetes mellitus. This type of diabetes mellitus is also called noninsulin dependent diabetes mellitus (NIDDM).

Causes for type II diabetes mellitus

In this type of diabetes the structure and function of β cells and the blood level of insulin are normal. But the insulin receptors are reduced in number or absent in the body. The major causes for type II diabetes are:

- 1. Hereditary disorders
- 2. Other endocrine disorders.

Features	Type I (IDD M)	Type II (NIDDM)
Age of onset	Usually before 40 years	Usually after 40 years
Major cause	Lack of insulin	Lack of insulin receptor
Insulin deficiency	Yes	Partial deficiency
Immune destruction of ß cells	Yes	No
Involvement of other endocrine disorders	No	Yes
Hereditary cause	Yes	May or may not be
Need for insulin	Always	Not in initial stage May require in later stage
Insulin resistance	No	Yes
Control by oral hypoglycemic agents	No	Yes
Symptoms appear	Rapidly	Slowly
Body weight	Usually thin	Usually overweight
Stress induced obesity	No	Yes
Ketosis	Yes	May or may not be

Signs and Symptoms of Diabetes Mellitus

Various manifestations of diabetes mellitus develop because of three major setbacks of insulin deficiency:

1. Increased blood sugar level (300 to 400 mg/dL) due to reduced utilization by tissue

2. Mobilization of fats from adipose tissue for energy purpose, leading to elevated fatty acid content in blood. This causes deposition of fat on the wall of arteries and development of atherosclerosis

3. Depletion of proteins from the tissues.

Following are the signs and symptoms of diabetes mellitus:

1. Glucosuria

Loss of glucose in urine is known as glucosuria. Normally, glucose does not appear in urine. When glucose level rises above 180 mg/dL in blood, glucose appears in urine. It is the renal threshold level for glucose.

2. Osmotic diuresis

Diuresis due to osmotic effects is called osmotic diuresis. The excess glucose in the renal tubules develops osmotic effect. The osmotic effect decreases the reabsorption of water from renal tubules resulting in diuresis. It leads to polyuria and polydipsia.

3. Polyuria

Excess urine formation with increase in frequency of voiding urine is called polyuria. It is due to the osmotic diuresis caused by increase in blood sugar level.

4. Polydipsia

The increase in water intake is called polydipsia.

The excess loss of water decreases water content and increases salt content in the body. This stimulates the thirst center in hypothalamus. Thirst center in turn increases the intake of water.

5. Polyphagia

Polyphagia means the intake of excess food. It is very common in diabetes mellitus.

6. Asthenia

The loss of strength is called asthenia. The body becomes very weak. There is loss of energy.

Asthenia is because of protein depletion which is caused by lack of insulin.

7. Acidosis

During insulin deficiency glucose cannot be utilized by the peripheral tissues for energy. So, a large amount of fat is broken down to release energy. It causes the formation of excess ketoacids leading to acidosis.

8. Acetone breathing

In cases of severe ketoacidosis, acetone is expired in the expiratory air, giving the characteristic acetone or fruity breath odor. It is a lifethreatening condition of severe diabetes.

9. Kussmaul breathing

Kussmaul breathing is the increase in rate and depth of respiration caused by severe acidosis.

10. Circulatory shock

The osmotic diuresis leads to dehydration, which causes circulatory shock. It occurs only in severe diabetes.

11. Coma

Due to Kussmaul breathing, a large amount of carbon dioxide is lost during expiration. It leads to drastic reduction in the concentration of bicarbonate ions causing severe acidosis and coma. It occurs in severe cases of diabetes mellitus.

Increase in blood sugar level develops hyperosmolarity of plasma which also leads to coma.

It is called hyperosmolar coma.

Complications of Diabetes Mellitus

Prolonged hyperglycemia in diabetes mellitus causes dysfunction and injury of many tissues resulting in some complications such as:

1. Cardiovascular complications like hypertension and myocardial infarction

2. Degenerative changes in retina called diabetic retinopathy

3. Degenerative changes in kidney known as diabetic nephropathy

4. Degeneration of autonomic and peripheral nerves called diabetic neuropathy.

Diagnostic Tests for Diabetes Mellitus

Diagnosis of diabetes mellitus includes the determination of:

- 1. Fasting blood sugar
- 2. Postprandial blood sugar
- 3. Glucose tolerance test (GTT)
- 4. Glycosylated (glycated) Hb.

HYPERACTIVITY — HYPERINSULINISM

Hyperinsulinism is the hypersecretion of insulin.

Cause of Hyperinsulinism

Hyperinsulinism occurs due to the tumor of β cells in the islets of Langerhans.

Signs and Symptoms of Hyperinsulinism

1. Hypoglycemia

The blood sugar level falls below 50 mg/dL.

2. Manifestations of central nervous system

Manifestations of central nervous system occur when the blood sugar level decreases. All the manifestations are together called neuroglycopenic symptoms.

Initially, the activity of neurons increases resulting in nervousness, tremor all over the body and sweating. If not treated immediately, it leads to clonic convulsions and unconsciousness. Slowly, the convulsions cease and coma occurs due to damage of neurons.

Adrenal gland

FUNCTIONAL ANATOMY OF ADRENAL GLANDS

There are two adrenal glands. Each gland is situated on the upper pole of each kidney. Each gland is made of two parts, the adrenal cortex and adrenal medulla. Adrenal cortex is the outer portion constituting 80% of the gland. Adrenal medulla is the central portion of gland constituting 20%.

Adrenal cortex is formed by three distinct layers of structures

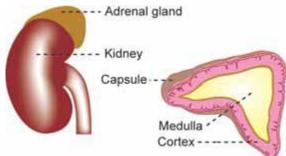
- 1. Zona glomerulosa outer layer
- 2. Zona fasciculata middle layer
- 3. Zona reticularis inner layer

HORMONES OF ADRENAL CORTEX

The hormones secreted by adrenal cortex are collectively known as adrenocortical hormones

or corticosteroids. Based on their functions the corticosteroids are classified into three groups:

- 1. Mineralocorticoids
- 2. Glucocorticoids
- 3. Sex hormones



Adrenal gland

MINERALOCORTICOIDS

Mineralocorticoids are the corticosteroids that act on the minerals (electrolytes) particularly sodium and potassium. The mineralocorticoids are secreted by zona glomerulosa of adrenal cortex.

Mineralocorticoids are:

- 1. Aldosterone
- 2. 11-Deoxycorticosterone.

FUNCTIONS OF MINERALOCORTICOIDS

Ninety percent of mineralocorticoid activity is provided by aldosterone.

Life Saving Hormone

Aldosterone is very essential for life and it is usually called life saving hormone because, the total loss of this hormone causes death within 3 days to 2 weeks. It is mainly because of loss of mineralocorticoids which are essential to maintain the osmolarity and volume of ECF.

Actions of aldosterone are:

1. On Sodium Ions

Aldosterone increases reabsorption of sodium from distal convoluted tubule and the collecting duct in kidney.

2. On Extracellular Fluid Volume

When sodium ions are reabsorbed from the renal tubules, almost an equal amount of water is also reabsorbed. So the net result is the increase in ECF volume.

3. On Blood Pressure

Increase in ECF volume and the blood volume finally leads to increase in blood pressure.

Aldosterone escape or escape phenomenon

Aldosterone escape refers to escape of the kidney from salt-retaining effects of excess secretion of aldosterone as in the case of primary hyperaldosteronism.

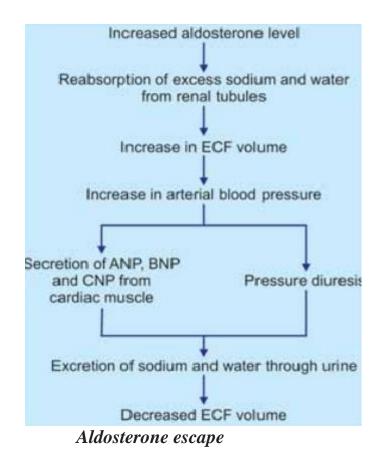
Mechanism of aldosterone escape

When aldosterone level increases, there is excess retention of sodium and water. This increases the ECF volume and blood pressure.

Aldosterone induced high blood pressure decreases the ECF volume through two types of reactions:

i. It stimulates secretion of atrial natriuretic peptide (ANP) from atrial muscles of the heart: ANP causes excretion of sodium in spite of increase in aldosterone secretion ii. It causes pressure diuresis (excretion of excess salt and water by high blood pressure) through urine. This decreases the salt and water content in ECF in spite of hypersecretion of aldosterone.

Because of aldosterone escape, edema does not occur in primary hyperaldosteronism.



MODE OF ACTION

Mineralocorticoids act through the messenger RNA mechanism.

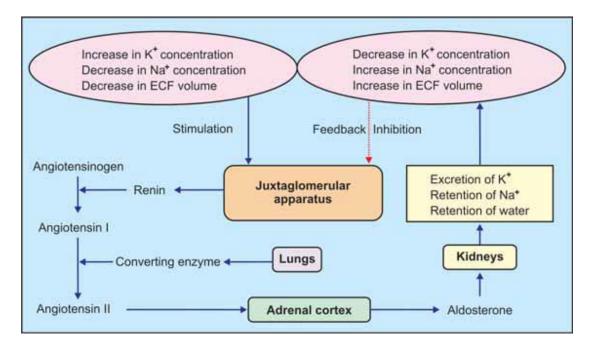
REGULATION OF SECRETION

Aldosterone secretion is regulated by four important factors.

- 1. Increase in potassium ion concentration in ECF
- 2. Decrease in sodium ion concentration in ECF
- 3. Decrease in ECF volume
- 4. Adrenocorticotropic hormone.

Increase in the concentration of potassium ions is the most effective stimulant for aldosterone secretion. It acts directly on zona glomerulosa and increases the secretion of aldosterone. Decrease in sodium ion concentration and ECF volume stimulates aldosterone secretion through renin-angiotensin mechanism.

Renin secreted from juxtaglomerular apparatus of kidney acts on angiotensinogen in the plasma and converts it into angiotensin I, which is converted into angiotensin II by converting enzyme (ACE) secreted by lungs. Angiotensin II acts on the zona glomerulosa to secrete more aldosterone. Aldosterone, in turn, increases the retention of sodium and water and excretion of potassium leading to increase in the sodium ion concentration and ECF volume. Now, the increased sodium ion concentration and the ECF volume inhibit the juxtaglomerular apparatus and stop the release of renin. So, angiotensin II is not formed and release of aldosterone from adrenal cortex is stopped. Adrenocorticotropic hormone mainly stimulates the secretion of glucocorticoids. It has only a mild stimulating effect on aldosterone secretion.



Regulation of aldosterone secretion

GLUCOCORTICOIDS

Glucocorticoids are the corticosteroids which act mainly on glucose metabolism. Glucocorticoids are secreted mainly by zona fasciculata of adrenal cortex. A small quantity of glucocorticoids is also secreted by zona reticularis.

Glucocorticoids are:

- 1. Cortisol
- 2. Corticosterone
- 3. Cortisone.

FUNCTIONS OF GLUCOCORTICOIDS

Cortisol or hydrocortisone is more potent and it has 95% of glucocorticoid activity. Corticosterone is less potent showing only 4% of glucocorticoid activity. Cortisone with 1% activity is secreted in minute quantity.

Life Protecting Hormone

Like aldosterone, cortisol is also essential for life but in a different way. Aldosterone is a life saving hormone, whereas cortisol is a life protecting hormone because, it helps to withstand the stress and trauma in life. Glucocorticoids have metabolic effects on carbohydrates, proteins, fats and water. These hormones also show mild mineralocorticoid effect.

Anti-inflammatory Effects Glucocorticoids

Inflammation is defined as a localized protective response induced by injury or destruction of tissues. When the tissue is injured by mechanical or chemical factors, some substances are released from the affected area, which produce series of changes in the affected area.

Glucocorticoids prevent the inflammatory changes in the injured or infected tissues by:

i. Inhibiting the release of proteolytic enzymes responsible for inflammation

ii. Preventing rush of blood to the injured area by enhancing vasoconstrictor action of catecholamines

iii. Inhibiting migration of leukocytes into the affected area

iv. Preventing loss of fluid from plasma into the affected tissue by decreasing the permeability of capillaries

v. Reducing the reactions of tissues by suppressing T cells and other leukocytes.

In addition to preventing inflammatory reactions, if inflammation has already started, the glucocorticoids cause an early resolution of inflammation and rapid healing.

Anti-allergic Actions of Glucocorticoids

Corticosteroids prevent the various reactions in allergic conditions as in the case of inflammation.

Immunosuppressive Effects of Glucocorticoids

Glucocorticoids suppress the immune system of the body by decreasing the number of circulating T lymphocytes. It is done by suppressing lymphoid tissues (lymph nodes and thymus) and proliferation of T cells. Glucocorticoids also prevent release of interleukin-2 by T cells.

Thus, hypersecretion or excess use of glucocorticoids decreases the immune reactions against all foreign bodies entering the body. It leads to severe infection causing death. The immunological reactions, which are

Common during organ transplantation, may cause rejection of the transplanted tissues.

Glucocorticoids are used to suppress the immunological reactions, because of their immunosuppressive action.

MODE OF ACTION

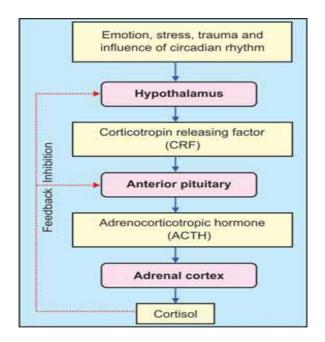
Glucocorticoids act through the messenger RNA mechanism.

REGULATION OF SECRETION

Anterior pituitary regulates glucocorticoid secretion by secreting ACTH. ACTH secretion is regulated by hypothalamus through corticotrophin releasing factor (CRF).

Role of Anterior Pituitary — ACTH

Anterior pituitary controls the activities of adrenal cortex by secreting ACTH. ACTH is mainly concerned with the regulation of cortisol secretion. It plays only a minor role in the regulation of mineralocorticoid secretion.



Regulation of cortisol secretion

Role of Hypothalamus

Hypothalamus also plays an important role in the regulation of cortisol secretion by controlling the ACTH secretion through corticotrophin releasing factor (CRF). It is also called corticotropin releasing hormone. CRF reaches the anterior pituitary through the hypothalamo-hypophyseal portal vessels.

CRF stimulates the corticotropes of anterior pituitary and causes synthesis and release of ACTH.

CRF secretion is induced by several factors such as emotion, stress, trauma and circadian rhythm. CRF in turn, causes release of ACTH, which induces glucocorticoid secretion.

Feedback Control

Cortisol regulates its own secretion through negative feedback control by inhibiting the release of CRF from hypothalamus and ACTH from anterior pituitary.

ADRENAL SEX HORMONES

Adrenal sex hormones are secreted mainly by zona reticularis. Zona fasciculata secretes small quantities of sex hormones. Most of the hormones are male sex hormones (androgens). But small quantities of estrogen and progesterone are also secreted by adrenal cortex.

HYPERACTIVITY OF ADRENAL CORTEX

- 1. Cushing's syndrome
- 2. Hyperaldosteronism
- 3. Adrenogenital syndrome.
- 1. Cushing's Syndrome

Cushing's syndrome is a disorder characterized by obesity. Cushing's syndrome is due to the hypersecretion of glucocorticoids, particularly cortisol. It may be due to either pituitary origin or adrenal origin.

2. Hyperaldosteronism

Increased secretion of aldosterone is called hyperaldosteronism

3. Adrenogenital Syndrome

Under normal conditions, adrenal cortex secretes small quantities of androgens which do not have any significant effect on sex organs or sexual function. However, secretion of abnormal quantities of adrenal androgens develops adrenogenital syndrome.

HYPOACTIVITY OF ADRENAL CORTEX

1. Addison's disease or chronic adrenal insufficiency: It is the failure of adrenal cortex to secrete corticosteroids.

2. Congenital Adrenal Hyperplasia: It is a congenital disorder characterized by increase in size of adrenal cortex. Size increases due to abnormal increase in the number of steroid secreting cortical cells

Adrenal Medulla

Medulla is the inner part of the adrenal gland and it forms 20% of mass of adrenal gland.

HORMONES OF ADRENAL MEDULLA

Adrenal medullary hormones are the amines derived from catechol and so these hormones are called catecholamines. Three catecholamines are secreted by medulla:

- 1. Adrenaline or epinephrine
- 2. Noradrenaline or norepinephrine
- 3. Dopamine

ACTIONS OF ADRENALINE AND NORADRENALINE

Adrenaline and noradrenaline stimulate the nervous system. Adrenaline has significant effects on metabolic functions and both adrenaline and noradrenaline have significant effects on cardiovascular system.

MODE OF ACTION OF ADRENALINE AND NORADRENALINE -ADRENERGIC RECEPTORS

Adrenaline and noradrenaline execute their actions by binding with receptors called adrenergic receptors which are present in the target organs.

Adrenergic receptors are of two types:

1. Alpha adrenergic receptors

2. Beta adrenergic receptors.

Alpha receptors and, beta receptors are divided into beta1 and beta2 receptors.

ACTIONS

The effects of adrenaline and noradrenaline on various target organs depend upon the type of receptors present in the cells of the organs.

Adrenaline acts through both alpha and beta receptors equally. Noradrenaline acts mainly through alpha receptors and occasionally through beta receptors.

REGULATION OF SECRETION OF ADRENALINE AND NORADRENALINE

Adrenaline and noradrenaline are secreted from adrenal medulla in small quantities even during rest. During stress conditions, due to sympathoadrenal discharge, a large quantity of catecholamines is secreted. These hormones prepare the body for fight or flight reactions.

Catecholamine secretion increases in exposure to cold and hypoglycemia also.

DOPAMINE

Dopamine is secreted by adrenal medulla. The type of cells secreting this hormone is not known.

Dopamine is also secreted by dopaminergic neurons in some areas of brain particularly, basal ganglia. In brain, this hormone acts as a neurotransmitter.

Endocrine Functions of Other Organs

PINEAL GLAND

SITUATION AND STRUCTURE

Pineal gland is otherwise called epiphysis. It is a small cone shaped structure. In human, it is about 10 mm long. Pineal gland is located in diencephalic area of brain above the hypothalamus.

In human, pineal gland has two types of cells:

- 1. Parenchymal cells, which are large epithelial cells
- 2. Neuroglial cells.

In adults, the pineal gland is calcified. But, the epithelial cells exist and secrete the hormonal substance.

FUNCTIONS

Pineal gland has two functions:

1. It controls the sexual activities in animals by regulating the seasonal fertility. However, the pineal gland plays little role in regulating the sexual functions in human being.

2. The parenchymal cells of pineal gland secrete a hormonal substance called melatonin.

Melatonin

Melatonin is secreted by the parenchymal cells of pineal gland.

Actions

Melatonin acts mainly on gonads. Its action differs from species to species. In some animals, it stimulates the gonads while in other animals it inhibits the gonads.

THYMUS SITUATION

It is situated in front of trachea below the thyroid gland. Thymus is small in newborn infants and gradually enlarges till puberty, and then decreases in size.

FUNCTIONS

Thymus has lymphoid function and endocrine function. It plays an important role in development of immunity in the body. It has two functions:

- 1. Processing the T lymphocytes
- 2. Endocrine function.

1. *Processing the T Lymphocytes*

Thymus plays an essential role in the development of immunity by processing the T lymphocytes. The lymphocytes, which are produced in bone marrow, are processed in thymus into T lymphocytes.

2. Endocrine Function of Thymus

Thymus secretes two hormones:

i. Thymosin

ii. Thymin.

Thymosin

Thymosin is a peptide. It accelerates lymphopoiesis and proliferation of T lymphocytes.

Thymin

It is also called thymopoietin. It suppresses the neuromuscular activity by inhibiting acetylcholine release. Hyperactivity of thymus causes myasthenia gravis.

KIDNEYS

Kidneys secrete five hormonal substances:

- 1. Erythropoietin
- 2. Thrombopoietin
- 3. Renin
- 4. 1,25-Dihydroxycholecalciferol (calcitriol)
- 5. Prostaglandins.

Recently, it is discovered that kidney secretes small quantity of C-type natriuretic peptide.

HEART

Heart secretes the hormones atrial natriuretic peptide and brain natriuretic peptide.

ATRIAL NATRIURETIC PEPTIDE

ANP is secreted during overstretching of atrial muscles in conditions like increase in blood volume. ANP in turn increases excretion of sodium (followed by water excretion) through urine and helps in the maintenance of ECF volume and blood volume. It also lowers blood pressure.

Effect of ANP on Sodium Excretion

ANP increases excretion of sodium ions through urine by:

- 1. Increasing glomerular filtration rate
- 2. Inhibiting sodium reabsorption from distal convoluted tubules and collecting ducts.
- 3. Increasing the secretion of sodium into the renal tubules.

Escape phenomenon

Thus, ANP is responsible for escape phenomenon, and prevention of edema in primary hyperaldosteronism in spite of increased ECF volume

Effect of ANP on Blood Pressure

ANP decreases the blood pressure by:

- 1. Vasodilatation
- 2. Inhibiting renin secretion from juxtaglomerular apparatus
- 3. Inhibiting vasoconstrictor effect of angiotensin II
- 4. Inhibiting vasoconstrictor effects of catecholamines.

BRAIN NATRIURETIC PEPTIDE

Brain natriuretic peptide (BNP) is also called B-type natriuretic peptide. It is a polypeptide with 32 amino acids. It is secreted by the cardiac muscle. It is also secreted in some parts of brain. The stimulant for its secretion is not known.

On brain, its actions are not known.

LOCAL HORMONES SYNTHESIZED IN TISSUES

Local hormones are the substances which act on the same area of their secretion or in immediate neighborhood. The endocrine hormones are secreted in one place but execute their actions on some other remote place.

Local hormones are produced in tissues and blood. These hormones are usually released in an inactive form and are activated by some conditions or substances.

Local hormones are classified into two types:

- I. Hormones synthesized in tissues
- II. Hormones synthesized in blood.

LOCAL HORMONES SYNTHESIZED IN TISSUES

The local hormones synthesized in the tissues are:

- A. Prostaglandins and related substances
- B. Other local hormones synthesized in tissues.

PROSTAGLANDINS AND ITS RELATED HORMONES

Prostaglandins and other hormones which are derived from arachidonic acid are collectively called eicosanoids. The eicosanoids are:

- 1. Prostaglandins
- 2. Thromboxanes
- 3. Prostacyclin
- 4. Leukotrienes
- 5. Lipoxins.
- 1. Prostaglandins

Prostaglandins were first discovered and isolated from human semen. However, now it is believed that almost all the tissues of the body including renal tissues synthesize prostaglandins.

Pro-staglandins are unsaturated fatty acids with a cyclopentane ring and 20 carbon atoms.

Types

A variety of prostaglandins are identified. Active forms of prostaglandins are PGA2, PGD2, PGE2, and PGF2.

2. Thromboxanes

Thromboxanes are derived from arachidonic acid. Thromboxanes are of two types:

i. Thromboxane A2 which is secreted in platelets

ii. Thromboxane B2 the metabolite of thromboxane A2.

The thromboxane A2 causes vasoconstriction.

It plays an important role in hemostasis by accelerating aggregation of platelets. It also accelerates the clot formation.

3. Prostacyclin

Prostacyclin is also a derivative of arachidonic acid. It is produced in the endothelial cells and smooth muscle cells of blood vessels. It causes vasodilatation and inhibits platelet aggregation.

4. Leukotrienes

Leukotrienes are derived from arachidonic acid via 5-hydroperoxy eicosatetraeonic acid (5-HETE). Leukotrienes are the mediators of allergic responses. These hormones also promote inflammatory reactions. The release of leukotrienes increases when some allergic agents combine with antibodies like IgE.

The leukotrienes cause: i. Bronchiolar constriction ii. Arteriolar constriction iii. Vascular permeability iv. Attraction of neutrophils and eosinophils towards the site of inflammation.

5. Lipoxins

Lipoxins are of two types namely, Lipoxin A and Lipoxin B. Lipoxin A causes dilation of minute blood vessels. Both the types inhibit the cytotoxic effects of killer T cells.

OTHER LOCAL HORMONES SYNTHESIZED IN TISSUES

In addition to prostaglandins and related hormonal substances, tissues secrete some more hormones which are listed below.

- 1. Acetylcholine
- 2. Serotonin
- 3. Histamine
- 4. Substance P
- 5. Heparin
- 6. Leptin
- 7. GI hormones.

The reproductive system

The Male reproductive system

The testes are made up of loops of convoluted seminiferous tubules. In the walls of which the spermatozoa are formed from the primitive germ cells (spermatogenesis).. Between the tubules of testes there are cells containing lipid granules called **interstitial cells of Leydig** which secrete **testosterone**.

The Sertoli cells secrete:

I. Mullerian inhibiting substance (MIS)

2. Inhibin that inhibit FSH secretion.

3. Androgen binding protein

4. Estrogen is produced as Sertoli cells contain (aromatase) the enzyme responsible for conversion of androgen to estrogen.

Spermatogenesis: Spermatogenesis follows the following steps: Spermatogonin (primitive germ cell at basal lamina) \rightarrow primary spermatocytes \rightarrow secondary spermatocytes \rightarrow spermatids \rightarrow spermatozoa (sperm). A Both testes forms 120 x 10⁶ sperms per day.

Several hormones play essential roles in spermatogenesis:

1. Testosterone: necessary for maturation of spermatids to spermatozoa.

2. **FSH:** [1] Acts on sertoli cell to facilitate last step of spermatid maturation. [2] Stimulates production of ABP.

3. LH: stimulates the production of androgen from interstitial cells of Leydig.

4. Estrogen.

5.Growth hormones: necessary for controlling background metabolic function of testes and promote early maturation of spermatogonla.

<u>Actions of Testosterone</u>: During development it is responsible for development of male internal and external sex organs and also help in testes descending.

1. Development of secondary sexual characters of males at puberty.

•Mental: More aggressive, active attitude, interest in opposite sex develops.

•External genitalia: Penis increase in size and width, scrotum becomes pigmented and rugges.

•Internal genitalia: Seminal vesicles enlarges and secretes and begins to form fructose.

• Prostate: With bulbourethral glands enlarge and secretes.

•Voice: Larynx enlarge, vocal cords increase in length and thickness, voice becomes deeper.

•Hair growth: Beard appears, male pattern hair of scalp and pubic and axilla, general body hair increase and may result in androgenic allopecia.

•Body conformation: Shoulder broaden, muscle enlargement.

Skin: Acne formation.

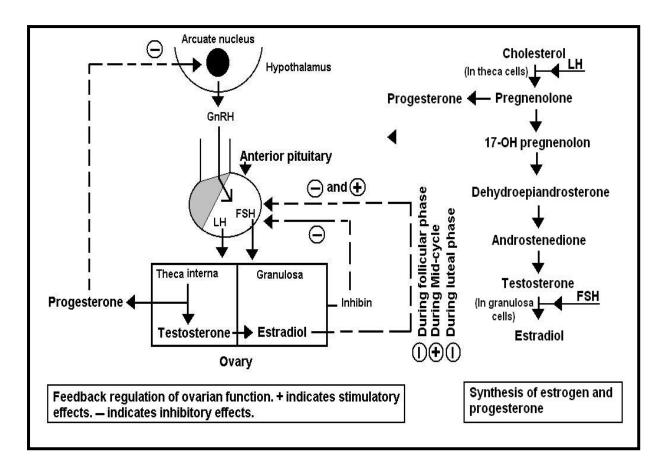
2. Anabolic Effects

Female reproductive system

The reproductive system of the female, unlike that of the male, shows regular (Cyclic) rhythmical changes in the rate of secretion of female hormones and corresponding changes in ovaries and sexual organs, which may be regarded as periodic preparation for fertilization and pregnancy.

Control of ovarian functions:

[1] Hypothalamus control: Hypothalamus secretes gonadotrophin-releasing hormone (GnRH) to the pituitary gland. GnRH stimulates FSH and LH



[2] Pituitary control: FSH from pituitary is responsible for maturation of ovarian follicles. The ovarian follicles, under the effect of FSH, secrete estrogen. Then at the end of follicular phase, a <u>burst of LH secretion occurs (LH surge)</u> which is responsible for ovulation and initial formation of corpus luteum. LH stimulates the secretion of estrogen and progesterone from the corpus luteum.

[3] Cyclic control: Small amounts of estrogen had – ve Feedback on FSH, LH and GnRH, while large amounts of estrogen had + ve Feedback on the FSH, LH and GnRH. Progesterone and inhibin had – ve feedback effect on FSH, LH, and GnRH.

Estrogen had two peaks during menstrual cycle; first one is two days before ovulation and the second peak during luteal phase while progesterone had only one peak in luteal phase. FSH and LH had one peak 36-48 hours before ovulation and this peak could be explained by feedback effects of:

Ovarian (menstrual) cycle

Ovarian cycle has 3 phases:

[A] The first phase: The Follicular phase: The first day of bleeding is regarded as first day of the cycle. The follicular phase extends from the 5th day of the

cycle to the 14th day during which FSH will induce maturation of the primordial follicles \rightarrow vesicular follicles \rightarrow mature follicles (called Graffian follicles). Many follicles start to mature but only one follicle reaches maturation per cycle. The Graffian follicle contains 3 layers, theca externa, theca interna and granulosa layer with the follicular fluid inside the antrum which contains the estrogen secreted by theca interna and granulosa under the influence of FSH. The main source of circulating estrogen is the theca interna while the granulosa cells mainly form the estrogen in the antral fluid.

[B] The second phase: Ovulation: Occurs 14 days before menses, regardless of the cycle length. Thus, in a 28-day cycle, ovulation occurs on day 15; In ovulation, rupture of Graafian follicle occurs, this process <u>consists of two events, occur under</u> <u>the effect of LH</u>.

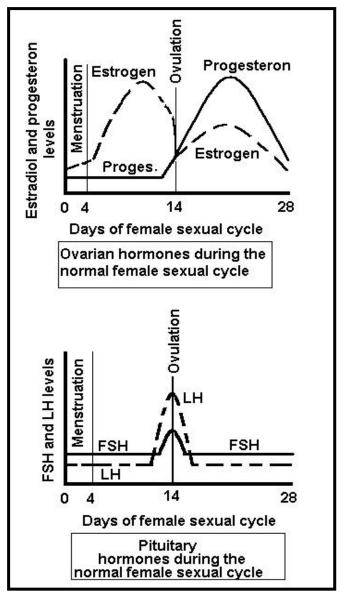
1- Theca externa release proteolytic enzymes leading to dissolution of the wall.

2- Rapid growth of new blood vessels into the follicle wall and at the same time prostaglandins are secreted (local hormones that cause vasodilatation) into the follicular fluid leading to plasma transudation into the follicle and follicular swelling, then rupture, and discharges the ovum to the abdominal cavity.

36 – 48 h. before ovulation, <u>the</u> estrogen feedback becomes positive leading to <u>burst in LH secretion (LH surge) that produce</u> <u>ovulation.</u> FSH also peaks despite little rise of inhibin level probably because of strong stimulation of FSH and LH by GnRH.

[C] The third phase: Luteal phase: Begins from the $14^{th} -28^{th}$ day of the cycle, <u>under the control of LH</u>. The high levels of estrogen, progesterone and inhibin lead to – ve feedback so result in low FSH and LH.

The ruptured follicle is filled with



blood forming corpus haemorrhagicum. Minor bleeding from the rupture follicle in to the abdominal cavity causes lower abdominal pain due to peritoneal irritation which may be severe and misdiagnosed as acute appendicitis. The theca cells and granulosa cells start to proliferate and blood inside the corpus haemorrhagicum is replaced by luteal cells forming <u>mature corpus luteum</u>. <u>Luteal cells secrete estrogen</u> <u>and progesterone</u>. If pregnancy occur, corpus luteum will persist and no menstruation occur till pregnancy is over. If pregnancy does not occur, corpus

luteum will degenerate in the 24th day of the cycle forming <u>regressed corpus luteum</u> and then replaced by scar forming <u>corpus albicans</u>

Indications of ovulation:

- 1- Endometrial biopsy:
- 2- Cervical mucus: Thick,
- **3- Basal body temp:** Since progesterone is thermogenic, therefore, at the time of ovulation, basal body temp is increased by 0.5°C.
- 4- **Progesterone level:** Is increased in blood and urine during ovulation because LH is increased.

Ovum can survive for 72 hours and sperm can survive 72 hours in the female genital tract so the fertile period is about 120 hours (taking in consideration 24 hours of overlapping time). Therefore, before the 9th days and after the 20th days of the cycle there is a little chance of conception.

Ovarian Hormones:

[1] Estrogens: Estradiol is the most potent. They are secreted by theca interna and granulosa cells of ovarian follicle, the corpus luteum and placenta. The secreted estrogen during menstrual cycle is of ovarian origin with two peaks of secretion: one just before ovulation and the other in the mid–luteal phase.

The effects of estrogens are:

[A] Effects on female genitilia:

- [a] Estrogens facilitate growth of ovarian follicle.
- [b] Increase motility of fallopian tubes
- [c] Cyclic changes of endometrium, cervix and vagina as mentioned previously.
- [d] Increases uterine blood flow.
- [e] Increases the amount of uterine muscle
- [f] Estrogen makes uterus more sensitive to oxytocin.
- [g] Vaginal epithelium is changed from cuboidal to startified columnar epith.

[B] Effect on development of secondary sexual characters:

[a] Female body configuration: Narrow shoulder, broad hip, converged thigh, diverged arm. Fat

distribution in buttocks and breast .

[b] Larynx: Voice becomes high pitched.

[c] Skin: Soft, smooth, but thicker than childhood, more vascular

[d] Sebaceous glands secretions become more fluid so reduced acne formation.

[e] Breasts Become enlarged due to growth of stromal tissue, ductal system deposition of fat, pigmentation of areola and apperance of mature female breast.

[C] Behavioral effects: Estrogens are responsible for a increase libido in human

[D] Effect on skeleton

[E] Matabolic effects: On proteins it causes protein anabolic effect

[2] **Progesterone:** It is <u>secreted mainly from corpus luteum</u>, placenta and less by the follicle.

The effects of progesterone are:

On uterus:

- [a] Cyclic changes on vagina and cervix.
- [b] Progestational changes on endometrium.
- [c] Antiestrogenic effect on

[3] Relaxin: Polypeptide hormone produced by corpus luteum, uterus, placenta and mammary glands in women and from prostate in man. During pregnancy it relaxes pubic symphysis and other pelvic joints and softens and dilates uterine cervix to facilitate delivery. It also inhibits uterine contractions and may play a role in the development of mammary glands. In non – pregnant woman it's function is unknown. In men relaxin is found in semen and it may help to maintain sperm motility and aid sperm penetration to the ovum.