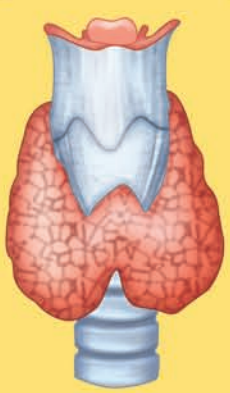
Section 6

Endocrinology



Introduction to Endocrinology

Chapter 64

INTRODUCTION

All the physiological activities of the body are regulated by two major systems:

1. Nervous system
2. Endocrine system.

These two systems interact with one another and regulate the body functions. This section deals with endocrine system and Section 10 deals with nervous system. Endocrine system functions by secreting some chemical substances called hormones.

CELL-TO-CELL SIGNALING

Cell-to-cell signaling refers to the transfer of information from one cell to another. It is also called **cell signaling** or intercellular communication. The cells of the body communicate with each other through some chemical substances called chemical messengers.

CHEMICAL MESSENGERS

Chemical messengers are the substances involved in cell signaling. These messengers are mainly secreted from endocrine glands. Some chemical messengers are secreted by nerve endings and the cells of several other tissues also.

All these chemical messengers carry the message (signal) from the **signaling cells (controlling cells)** to the **target cells.** The messenger substances may be the hormones or hormone-like substances.

Classification of Chemical Messengers

Generally the chemical messengers are classified into two types:

1. Classical hormones secreted by endocrine glands
2. Local hormones secreted from other tissues.

However, recently chemical messengers are classified into four types:

1. Endocrine messengers
2. Paracrine messengers
3. Autocrine messengers
4. Neurocrine messengers.

1. *Endocrine Messengers*

Endocrine messengers are the classical hormones. A hormone is defined as a chemical messenger, synthesized by endocrine glands and transported by blood to the target organs or tissues (site of action).

Examples are growth hormone and insulin.

2. *Paracrine Messengers*

Paracrine messengers are the chemical messengers, which diffuse from the control cells to the target cells through the interstitial fluid. Some of these substances directly enter the neighboring target cells through gap junctions. Such substances are also called **juxtacrine messengers** or **local hormones.**

Examples are prostaglandins and histamine.

3. *Autocrine Messengers*

Autocrine messengers are the chemical messengers that control the source cells which secrete them. So, these messengers are also called **intracellular chemical mediators.**

Examples are leukotrienes.

4. *Neurocrine or Neural Messengers*

Neurocrine or neural messengers are neurotransmitters and neurohormones (Fig. 64.1).

Neurotransmitter

Neurotransmitter is an endogenous signaling molecule that carries information form one nerve cell to another nerve cell or muscle or another tissue.

Examples are acetylcholine and dopamine.

Neurohormone

Neurohormone is a chemical substance that is released by the nerve cell directly into the blood and transported to the distant target cells.

Examples are oxytocin, antidiuretic hormone and hypothalamic releasing hormones.

Some of the chemical mediators act as more than one type of chemical messengers. For example, noradrenaline and dopamine function as classical hormones as well as neurotransmitters. Similarly, histamine acts as neurotransmitter and paracrine messenger.

■ ENDOCRINE GLANDS

Endocrine glands are the glands which synthesize and release the classical hormones into the blood. Endocrine glands are also called **ductless glands** because the

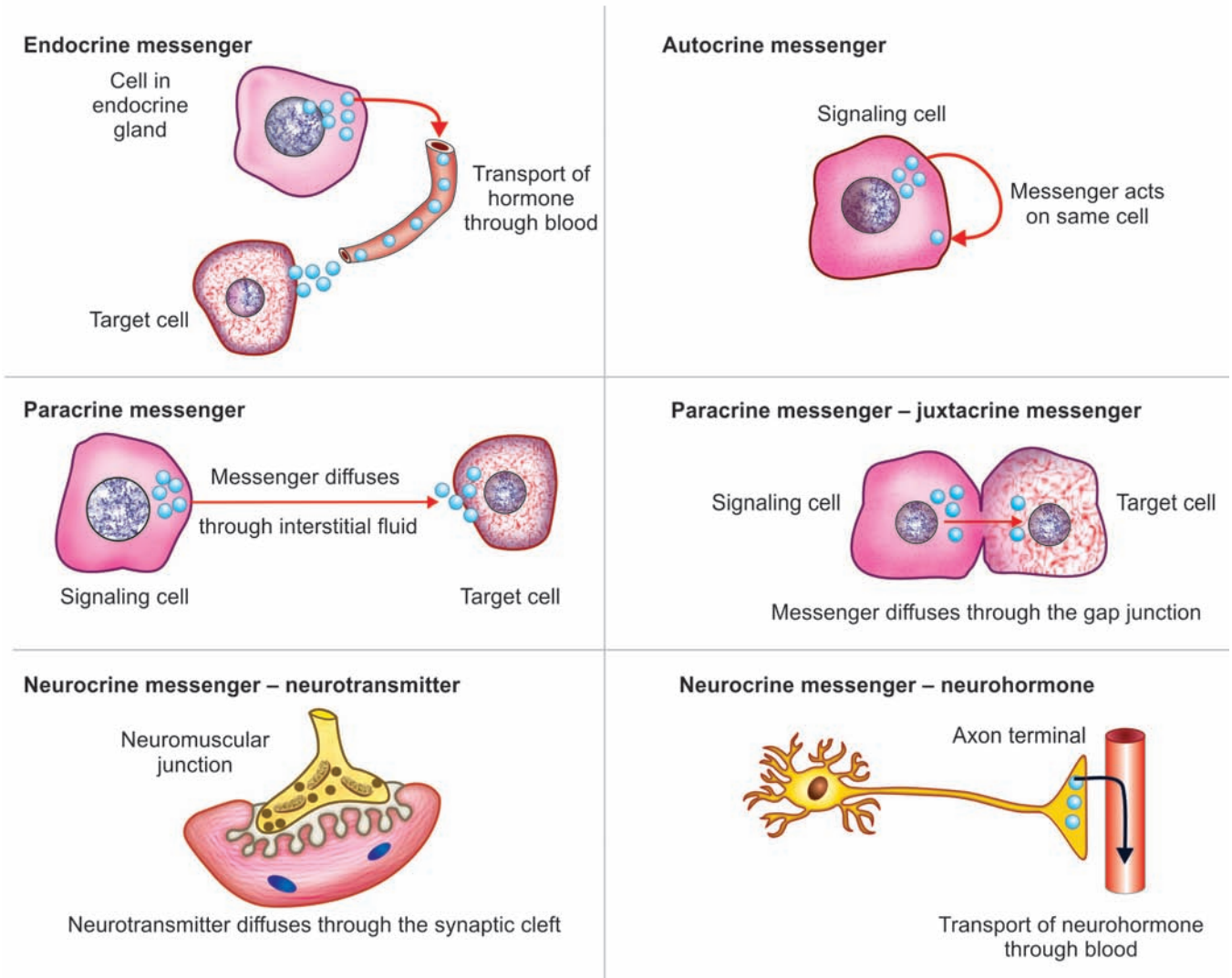


FIGURE 64.1: Chemical messengers

hormones secreted by them are released directly into blood without any duct. Endocrine glands are distinct from exocrine glands which release their secretions through ducts.

Endocrine glands play an important role in homeostasis and control of various other activities in the body through their hormones. Hormones are transported by blood to target organs or tissues in different parts of the body, where the actions are executed.

Major endocrine glands: Fig. 64.2.

Hormones secreted by endocrine glands: Table 64.1.

Hormones secreted by gonads: Table 64.2.

Hormones secreted by other organs: Table 64.3.

Local hormones: Table 64.4.

METHODS OF STUDY

STUDY OF ENDOCRINE GLANDS

Methods followed to study an endocrine gland:

1. *Functional Anatomy*

i. Situation
ii. Divisions or parts
iii. Histology
iv. Blood supply
v. Nerve supply.

2. *Functions*

i. Hormones secreted by the gland
ii. Actions of each hormone.

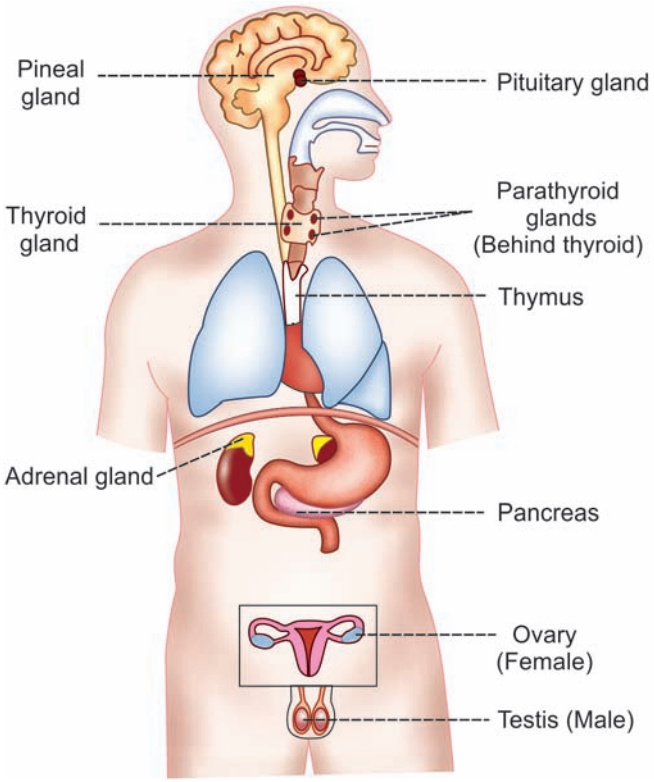


FIGURE 64.2: Diagram showing major endocrine glands

3. *Evidences to Support the Functions of the Gland*

i. Effects of **extirpation** (removal) of the gland
ii. Effects of administration of extract or the hormone of the gland
iii. Clinical observation.

TABLE 64.1: Hormones secreted by major endocrine glands

Anterior pituitary	1. Growth hormone (GH) 2. Thyroid-stimulating hormone (TSH) 3. Adrenocorticotropic hormone (ACTH) 4. Follicle stimulating hormone (FSH) 5. Luteinizing hormone (LH) 6. Prolactin	Adrenal cortex	*Mineralocorticoids* 1. Aldosterone 2. 11-deoxycorticosterone
			Glucocorticoids 1. Cortisol 2. Corticosterone
			Sex hormones 1. Androgens 2. Estrogen 3. Progesterone
Posterior pituitary	1. Antidiuretic hormone (ADH) 2. Oxytocin		
Thyroid gland	1. Thyroxine (T_4) 2. Triiodothyronine (T_3) 3. Calcitonin		
Parathyroid gland	Parathormone	Adrenal medulla	1. Catecholamines 2. Adrenaline (Epinephrine) 3. Noradrenaline (Norepinephrine) 4. Dopamine
Pancreas – Islets of Langerhans	1. Insulin 2. Glucagon 3. Somatostatin 4. Pancreatic polypeptide		

TABLE 64.2: Hormones secreted by gonads

Testis	1. Testosterone 2. Dihydrotestosterone 3. Androstenedion
Ovary	1. Estrogen 2. Progesterone

TABLE 64.3: Hormones secreted by other organs

Pineal gland	Melatonin
Thymus	1. Thymosin 2. Thymin
Kidney	1. Erythropoietin 2. Thrombopoietin 3. Renin 4. 1,25-dihydroxycholecalcifero (calcitriol) 5. Prostaglandins
Heart	1. Atrial natriuretic peptide 2. Brain natriuretic peptide 3. C-type natriuretic peptide
Placenta	1. Human chorionic gonadotropin (HCG) 2. Human chorionic somatomammotropin 3. Estrogen 4. Progesterone

TABLE 64.4: Local hormones

1. Prostaglandins	7. Serotonin
2. Thromboxanes	8. Histamine
3. Prostacyclin	9. Substance P
4. Leukotrienes	10. Heparin
5. Lipoxins	11. Bradykinin
6. Acetylcholine	12. Gastrointestinal hormones

4. *Regulation of Activity of the Gland*

i. By other endocrine glands
ii. By other factors
iii. By feedback mechanism.

5. *Applied Physiology*

i. Disorders due to hyperactivity of the gland
ii. Disorders due to hypoactivity of the gland.

■ STUDY OF HORMONES

A hormone is usually studied as follows:

1. Source of secretion (gland as well as the cell that secretes the hormone)
2. Chemistry
3. Half-life
4. Synthesis and metabolism
5. Actions
6. Mode of action
7. Regulation of secretion
8. Applied physiology
   i. Disorders due to hypersecretion of the hormone
   ii. Disorders due to hyposecretion of the hormone.

Half-life of the Hormones

Half-life is defined as the time during which half the quantity of a hormone, drug or any substance is metabolized or eliminated from circulation by biological process. It is also defined as the time during which the activity or potency of a substance is decreased to half of its initial value.

Half-life is also called biological half-life. Half-life of a hormone denotes the elimination of that hormone from circulation.

■ STUDY OF ENDOCRINE DISORDERS

An endocrine disorder is studied by analyzing:

1. Causes
2. Signs and symptoms
3. Syndrome.

1. *Causes*

Endocrine disorder may be due to the hyperactivity or hypoactivity of the concerned gland. Secretion of hormones increases during hyperactivity and decreases during hypoactivity.

2. *Signs and Symptoms*

A sign is the feature of a disease as detected by the doctor during the physical examination. So, it is the **objective physical evidence** of disease found by the examiner.

Examples of signs are yellow coloration of skin and mucous membrane in jaundice, paleness in anemia, enlargement of liver, etc.

A symptom is the feature of a disease felt by the patient. So, it is the **subjective evidence** perceived by the patient. In simple words, it is a noticeable change in the body, experienced by the patient.

Examples of symptoms are fever, itching, swelling, tremor, etc.

3. *Syndrome*

Syndrome is the combination of signs and symptoms (associated with a disease), which occur together and suggest the presence of a certain disease or the possibility of developing the disease.

Examples are **Stoke-Adams syndrome** and syndrome of inappropriate antidiuretic hormone hyper-secretion **(SIADH).**

Hormones

Chapter 65

CHEMISTRY OF HORMONES

Hormones are **chemical messengers,** synthesized by endocrine glands. Based on chemical nature, hormones are classified into three types (Table 65.1):

1. Steroid hormones
2. Protein hormones
3. Derivatives of the amino acid called tyrosine.

STEROID HORMONES

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

TABLE 65.1: Classification of hormones depending upon chemical nature

Steroids	Proteins	Derivatives of tyrosine
Aldosterone	Growth hormone (GH)	Thyroxine (T_4)
11-deoxycorticosterone	Thyroid-stimulating hormone (TSH)	Triiodothyronine (T_3)
Cortisol	Adrenocorticotropic hormone (ACTH)	Adrenaline (Epinephrine)
Corticosterone	Follicle-stimulating hormone (FSH)	Noradrenaline (Norepinephrine)
Testosterone	Luteinizing hormone (LH)	Dopamine.
Dihydrotestosterone	Prolactin	
Dehydroepiandrosterone	Antidiuretic hormone (ADH)	
Androstenedione	Oxytocin	
Estrogen	Parathormone	
Progesterone	Calcitonin	
	Insulin	
	Glucagon	
	Somatostatin	
	Pancreatic polypeptide	
	Human chorionic gonadotropin (HCG)	
	Human chorionic somatomammotropin.	

■ PROTEIN HORMONES

Protein hormones are large or small peptides. Protein hormones are secreted by pituitary gland, parathyroid glands, pancreas and placenta ('P's).

■ TYROSINE DERIVATIVES

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

■ HORMONAL ACTION

■ INTRODUCTION

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.

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 (Fig. 65.1)
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.**

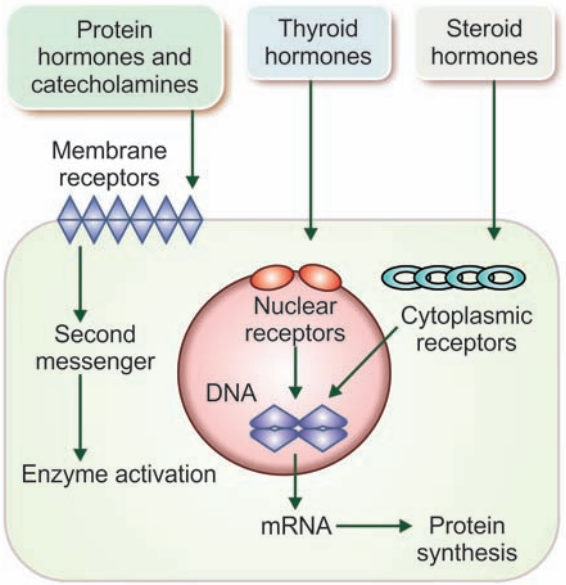


FIGURE 65.1: Situation of hormonal receptors

Hormone in the form of hormone-receptor complex enters the target cell by means of endocytosis and executes the actions. The whole process is called **internalization.**

After internalization, some receptors are recycled, whereas many of them are degraded and new receptors are formed. Formation of new receptors takes a long time. So, the number of receptors decreases when hormone level increases.

■ MECHANISM OF HORMONAL ACTION

Hormone does not act on the target cell directly. It combines with receptor to form hormone-receptor complex. This complex executes the hormonal action by any one of the following mechanisms:

1. By altering permeability of cell membrane
2. By activating intracellular enzyme
3. By acting on genes.

■ BY ALTERING PERMEABILITY OF CELL MEMBRANE

Neurotransmitters in 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 the permeability of the postsynaptic membrane for sodium, by opening the

ligand-gated sodium channels. So, sodium ions enter the neuromuscular junction from ECF through the channels and cause the development of endplate potential. Refer Chapter 32 for details.

■ BY ACTIVATING INTRACELLULAR ENZYME

Protein hormones and the catecholamines act by activating the intracellular enzymes.

First Messenger

The hormone which acts on a target cell, is called first messenger or **chemical mediator.** It combines with the receptor and forms hormone-receptor complex.

Second Messenger

Hormone-receptor complex activates the enzymes of the cell and causes the formation of another substance called the second messenger or **intracellular hormonal mediator.**

Second messenger produces the effects of the hormone inside the cells. Protein hormones and the catecholamines act through second messenger. Most common second messenger is cyclic AMP.

Cyclic AMP

Cyclic AMP, cAMP or cyclic adenosine 3'5'-monophosphate acts as a second messenger for protein hormones and catecholamines.

Formation of cAMP – Role of G proteins

G proteins or **guanosine nucleotide-binding proteins** are the membrane proteins situated on the inner surface of cell membrane. These proteins play an important role in the formation of cAMP

Each G protein molecule is made up of trimeric (three) subunits called α, β and γ subunits. The α-subunit is responsible for most of the biological actions. It is bound with **guanosine diphosphate** (GDP) and forms α-GDP unit. The α-subunit is also having the intrinsic enzyme activity called **GTPase** activity. The β and γ subunits always bind together to form the β-γ dimmer. It can also bring about some actions. In the inactivated G protein, both α-GDP unit and β-γ dimmer are united (Fig. 65.2: Stage 1).

Sequence of events in the formation of cAMP

i. Hormone binds with the receptor in the cell membrane and forms the hormone-receptor complex
ii. It activates the G protein
iii. G protein releases GDP from α-GDP unit

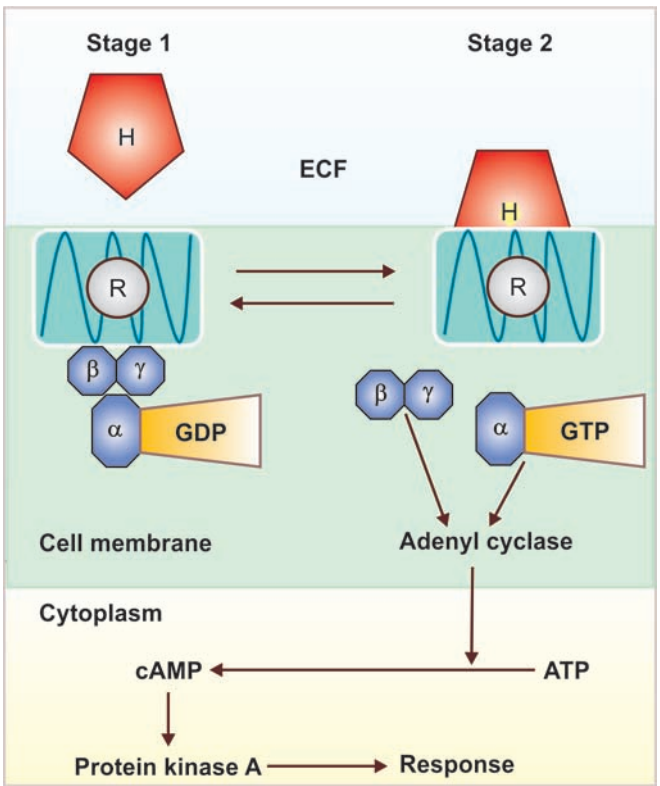


FIGURE 65.2: Mode of action of protein hormones and catecholamines. H = Hormone. R = Receptor, α, β, γ = G protein, GDP = Guanosine diphosphate, GTP = Guanosine triphosphate, ECF = Extracellular fluid, cAMP = Cyclic adenosine 3'5'-monophosphate, ATP = Adenosine triphosphate.

iv. The α-subunit now binds with a new molecule of GTP, i.e. the GDP is exchanged for GTP
v. This exchange triggers the dissociation of α-GTP unit and β-γ dimmer from the receptor
vi. Both α-GTP unit and β-γ dimmer now activate the second messenger pathways (Fig. 65.2: Stage 2)
vii. The α-GTP unit activates the enzyme adenyl cyclase, which is also present in the cell membrane. Most of the adenyl cyclase protrudes into the cytoplasm of the cell from inner surface of the cell membrane
viii. Activated adenyl cyclase converts the adenosine triphosphate of the cytoplasm into cyclic adenosine monophosphate (cAMP)

When the action is over, α-subunit hydrolyzes the attached GTP to GDP by its GTPase activity. This allows the reunion of α-subunit with β-γ dimmer and commencing a new cycle (Fig. 65.2: Stage 1).

Actions of cAMP

Cyclic AMP executes the actions of hormone inside the cell by stimulating the enzymes like protein kinase A.

Cyclic AMP produces the response, depending upon the function of the target cells through these enzymes.

Response produced by cAMP

Cyclic AMP produces one or more of the following responses:

i. Contraction and relaxation of muscle fibers
ii. Alteration in the permeability of cell membrane
iii. Synthesis of substances inside the cell
iv. Secretion or release of substances by target cell
v. Other physiological activities of the target cell.

Other Second Messengers

In addition to cAMP, some other substances also act like second messengers for some of the hormones in target cells.

i. *Calcium ions and calmodulin*

Many hormones act by increasing the calcium ion, which fucntions as second messenger along with another protein called calmodulin or troponin C. Calmodulin is present in smooth muscles and troponin C is present in skeletal muscles. Calcium-calmodulin complex activates various enzymes in the cell, which cause the physiological responses. Common enzyme activated by calcium-calmodulin complex is the **myosin kinase** in smooth muscle. Myosin kinase catalyses the reactions, resulting in muscular contraction (Chapter 33).

In the skeletal muscle, calcium ions bind with troponin C, which is similar to calmodulin (Chapter 31).

ii. *Inositol triphosphate*

Inositol triphosphate (IP_3) is formed from phosphatidylinositol biphosphate (PIP_2).

Hormone-receptor complex activates the enzyme phospholipase, which converts PIP_2 into IP_3. IP_3 acts on protein kinase C and causes the physiological response by the release of calcium ions into the cytoplasm of target cell.

iii. *Diacylglycerol*

Diacylglycerol (DAG) is also produced from PIP_2. It acts via protein kinase C.

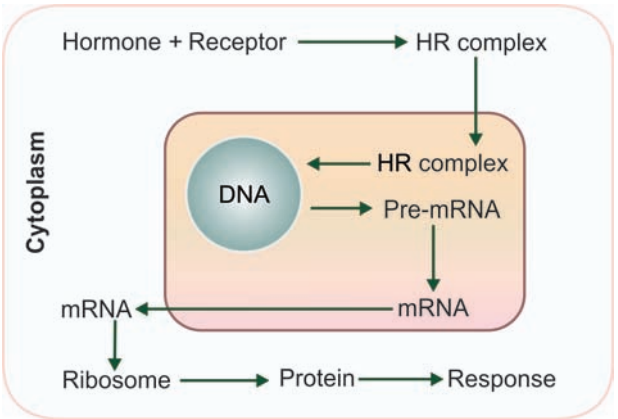


FIGURE 65.3: Mode of action of steroid hormones. Thyroid hormones also act in the similar way but their receptors are in the nucleus. HR = Hormone-receptor complex

iv. *Cyclic guanosine monophosphate*

Cyclic guanosine monophosphate (cGMP) functions like cAM P by acting on protein kinase A.

■ BY ACTING ON GENES

Thyroid and steroid hormones execute their function by acting on genes in the target cells (Fig. 65.3).

Sequence of Events during Activation of Genes

i. Hormone enters the interior of cell and binds with receptor in cytoplasm (steroid hormone) or in nucleus (thyroid hormone) and forms hormone-receptor complex
ii. Hormone-receptor complex moves towards the DNA and binds with DNA
iii. This increases transcription of mRNA
iv. The mRNA moves out of nucleus and reaches ribosomes and activates them
v. Activated ribosomes produce large quantities of proteins
vi. These proteins produce physiological responses in the target cells.

Pituitary Gland

Chapter 66

INTRODUCTION

Pituitary gland or **hypophysis** is a small endocrine gland with a diameter of 1 cm and weight of 0.5 to 1 g. It is situated in a depression called '**sella turcica',** present in the sphenoid bone at the base of skull. It is connected with the hypothalamus by the **pituitary stalk** or **hypophyseal stalk.**

DIVISIONS OF PITUITARY GLAND

Pituitary gland is divided into two divisions:

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

Both the divisions are situated close to each other. Still both are entirely different in their development, structure and function.

Between the two divisions, there is a small and relatively avascular structure called **pars intermedia.** Actually, it forms a part of anterior pituitary.

DEVELOPMENT OF PITUITARY GLAND

Both the divisions of pituitary glands develop from different sources.

Anterior pituitary is **ectodermal** in origin and arises from the **pharyngeal epithelium** as an upward growth known as **Rathke pouch.**

Posterior pituitary is **neuroectodermal** in origin and arises from hypothalamus as a downward **diverticulum.** Rathke pouch and the downward diverticulum from hypothalamus grow towards each other and meet in the midway between the roof of the buccal cavity and base of brain. There, the two structures lie close together.

■ REGULATION OF SECRETION

Hypothalamo-hypophyseal Relationship

The relationship between hypothalamus and pituitary gland is called hypothalamo-hypophyseal relationship. Hormones secreted by hypothalamus are transported to anterior pituitary and posterior pituitary. But the mode of transport of these hormones is different.

Hormones from hypothalamus are transported to anterior pituitary through hypothalamo-hypophysial portal blood vessels. But, the hormones from hypothalamus to posterior pituitary are transported by nerve fibers of hypothalamo-hypophyseal tract (see below for details).

■ ANTERIOR PITUITARY OR ADENOHYPOPHYSIS

Anterior pituitary is also known as the **master gland** because it regulates many other endocrine glands through its hormones.

■ PARTS

Anterior pituitary consists of three parts (Fig. 66.1):

1. Pars distalis
2. Pars tuberalis
3. Pars intermedia.

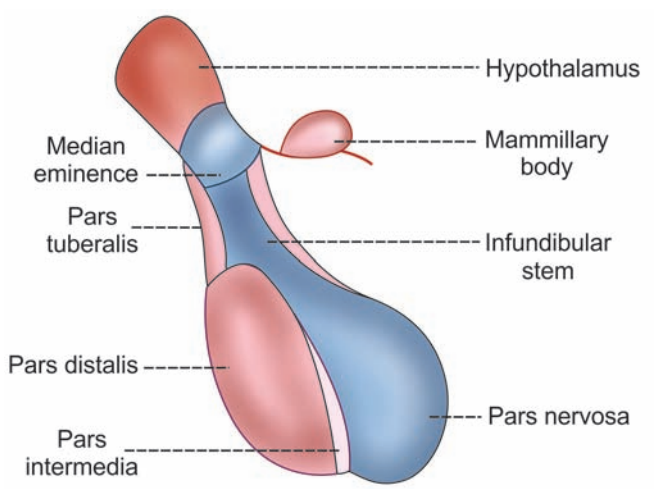


FIGURE 66.1: Parts of pituitary gland
Adenohypophysis Neurohypophysis

■ HISTOLOGY

Anterior pituitary has two types of cells, which have different staining properties:

1. Chromophobe cells
2. Chromophil cells.

Chromophobe Cells

Chromophobe cells do not possess granules and stain poorly. These cells form 50% of total cells in anterior pituitary. Chromophobe cells are not secretory in nature, but are the precursors of chromophil cells.

Chromophil Cells

Chromophil cells contain large number of granules and are darkly stained.

Types of chromophil cells

Chromophil cells are classified by two methods.

1. Classification on the basis of staining property: Chromophil cells are divided into two types:
   i. **Acidophilic cells** or **alpha cells,** which form 35%
   ii. **Basophilic cells** or **beta cells,** which form 15%.
2. Classification on the basis of secretory nature: Chromophil cells are classified into five types:
   i. **Somatotropes,** which secrete growth hormone
   ii. **Corticotropes,** which secrete adrenocorticotropic hormone
   iii. **Thyrotropes,** which secrete thyroid-stimulating hormone (TSH)
   iv. **Gonadotropes,** which secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
   v. **Lactotropes,** which secrete prolactin.

Somatotropes and lactotropes are acidophilic cells, whereas others are basophilic cells. Somatotropes form about 30% to 40% of the chromophil cells. So, pituitary tumors that secrete large quantities of human growth hormone are called acidophilic tumors.

■ REGULATION OF ANTERIOR PITUITARY SECRETION

Hypothalamus controls anterior pituitary by secreting the releasing and inhibitory hormones (factors), which are called **neurohormones.** These hormones from hypothalamus are transported anterior pituitary through hypothalamo-hypophyseal **portal vessels.**

Some special nerve cells present in various parts hypothalamus send their nerve fibers (axons) to median eminence and tuber cinereum. These nerve cells synthesize the hormones and release them into median

eminence and tuber cinereum. From here, the hormones are transported by blood via hypothalamo-hypophyseal portal vessels to anterior pituitary (Fig. 66.2).

Releasing and Inhibitory Hormones Secreted by Hypothalamus

1. Growth hormone-releasing hormone (GHRH): Stimulates the release of growth hormone
2. Growth hormone-releasing polypeptide (GHRP): Stimulates the release of GHRH and growth hormone
3. Growth hormone-inhibitory hormone (GHIH) or somatostatin: Inhibits the growth hormone release
4. Thyrotropic-releasing hormone (TRH): Stimulates the release of thyroid stimulating hormone
5. Corticotropin-releasing hormone (CRH): Stimulates the release of adrenocorticotropin
6. Gonadotropin-releasing hormone (GnRH): Stimulates the release of gonadotropins, FSH and LH
7. Prolactin-inhibitory hormone (PIH): Inhibits prolactin secretion. It is believed that PIH is dopamine.

■ HORMONES SECRETED BY ANTERIOR PITUITARY

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.

Recently, the hormone β-lipotropin is found to be secreted by anterior pituitary.

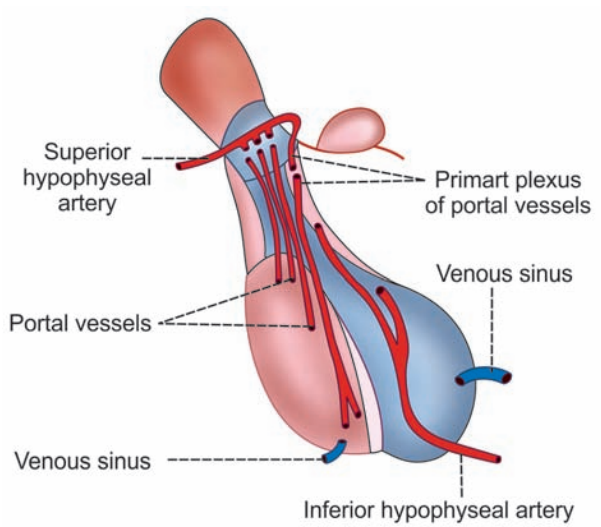


FIGURE 66.2: Blood supply to pituitary gland

Tropic Hormones

First five hormones of anterior pituitary stimulate the other endocrine glands. Growth hormone also stimulates the secretory activity of liver and other tissues. Therefore, these five hormones are called **tropic hormones.** Prolactin is concerned with milk secretion.

Gonadotropic Hormones

Follicle-stimulating hormone and the luteinizing hormone are together called **gonadotropic hormones** or **gonadotropins** because of their action on gonads.

■ GROWTH HORMONE

Source of Secretion

Growth hormone is secreted by somatotropes which are the acidophilic cells of anterior pituitary.

Chemistry, Blood Level and Daily Output

GH is protein in nature, having a single-chain polypeptide with 191 amino acids. Its molecular weight is 21,500.

Basal level of GH concentration in blood of normal adult is up to 300 g/dL and in children, it is up to 500 ng/dL. Its daily output in adults is 0.5 to1.0 mg.

Transport

Growth hormone is transported in blood by GH-binding proteins (GHBPs).

Half-life and Metabolism

Half-life of circulating growth hormone is about 20 minutes. It is degraded in liver and kidney.

Actions of Growth Hormone

GH is responsible for the general growth of the body. Hypersecretion of GH causes enormous growth of the body, leading to **gigantism.** Deficiency of GH in children causes stunted growth, leading to **dwarfism.**

GH is responsible for the growth of almost all tissues of the body, which are capable of growing. It increases the size and number of cells by 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.

1. *On metabolism*

GH increases the synthesis of proteins, mobilization of lipids and conservation of carbohydrates.

a. On protein metabolism

GH accelerates the synthesis of proteins by:

i. *Increasing amino acid transport through cell membrane:* The concentration of amino acids in the cells increases and thus, the synthesis of proteins is accelerated.

ii. *Increasing ribonucleic acid (RNA) translation:* GH increases the translation of RNA in the cells (Refer Chapter 1 for details of translation). Because of this, ribosomes are activated and more proteins are synthesized.

GH can increase the RNA translation even without increasing the amino acid transport into the cells.

iii. *Increasing transcription of DNA to RNA:* It also stimulates the transcription of DNA to RNA. RNA, in turn accelerates the synthesis of proteins in the cells (Refer Chapter 1 for details of transcription).

iv. *Decreasing catabolism of protein:* GH inhibits the breakdown of cellular protein. It helps in the building up of tissues.

v. *Promoting anabolism of proteins indirectly:* GH increases the release of insulin (from β-cells of islets in pancreas), which has anabolic effect on proteins.

b. *On fat metabolism*

GH mobilizes fats from adipose tissue. So, the concentration of fatty acids increases in the body fluids. These fatty acids are used for the production of energy by the cells. Thus, the proteins are spared.

During the utilization of fatty acids for energy production, lot of acetoacetic acid is produced by liver and is released into the body fluids, leading to ketosis. Sometimes, excess mobilization of fat from the adipose tissue causes accumulation of fat in liver, resulting in **fatty liver.**

c. *On carbohydrate metabolism*

Major action of GH on carbohydrates is the conservation of glucose.

Effects of GH on carbohydrate metabolism:

i. Decrease in the **peripheral utilization** of glucose for the production of energy: GH reduces the peripheral utilization of glucose for energy production. It is because of the formation of acetyl-CoA during the metabolism of fat, influenced by GH. The acetyl-CoA inhibits the glycolytic pathway. Moreover, since the GH increases the mobilization of fat, more fatty acid is available for the production of energy. By this way, GH reduces the peripheral utilization of glucose for energy production.

ii. Increase in the deposition of glycogen in the cells: Since glucose is not utilized for energy production by the cells, it is converted into glycogen and deposited in the cells.

iii. Decrease in the uptake of glucose by the cells: As glycogen deposition increases, the cells become saturated with glycogen. Because of this, no more glucose can enter the cells from blood. So, the blood glucose level increases.

iv. Diabetogenic effect of GH: Hypersecretion of GH increases blood glucose level enormously. It causes continuous stimulation of the β-cells in the islets of Langerhans in pancreas and increase in secretion of insulin. In addition to this, the GH also stimulates β-cells directly and causes secretion of insulin. Because of the excess stimulation, β-cells are burnt out at one stage. This causes deficiency of insulin, leading to **true diabetes mellitus** or **full-blown diabetes mellitus.** This effect of GH is called the **diabetogenic effect.**

2. *On bones*

In embryonic stage, GH is responsible for the differentiation and development of bone cells. In later stages, GH increases the growth of the skeleton. It increases both the length as well as the thickness of the bones.

In bones, GH increases:

i. Synthesis and deposition of proteins by chondrocytes and osteogenic cells

ii. Multiplication of **chondrocytes** and **osteogenic cells** by enhancing the intestinal calcium absorption

iii. Formation of new bones by converting chondrocytes into osteogenic cells

iv. Availability of calcium for mineralization of bone matrix.

GH increases the length of the bones, until epiphysis fuses with shaft, which occurs at the time of puberty. After the **epiphyseal fusion,** length of the bones cannot be increased. However, it stimulates the **osteoblasts** strongly. So, the bone continues to grow in thickness throughout the life. Particularly, the membranous bones

such as the jaw bone and the skull bones become thicker under the influence of GH.

Hypersecretion of GH before the fusion of epiphysis with the shaft of the bones causes enormous growth of the skeleton, leading to a condition called **gigantism.** Hypersecretion of GH after the fusion of epiphysis with the shaft of the bones leads to a condition called **acromegaly.**

Mode of Action of GH – Somatomedin

GH acts on bones, growth and protein metabolism through somatomedin secreted by liver. GH stimulates the liver to secrete somatomedin. Sometimes, in spite of normal secretion of GH, growth is arrested (dwarfism) due to the absence or deficiency of somatomedin.

Somatomedin

Somatomedin is defined as a substance through which growth hormone acts. It is a polypeptide with the molecular weight of about 7,500.

Types of somatomedin

Somatomedins are of two types:

i. Insulin-like growth factor-I (IGF-I), which is also called somatomedin C
ii. Insulin-like growth factor-II.

Somatomedin C (IGF-I) acts on the bones and protein metabolism. Insulin-like growth factor-II plays an important role in the growth of fetus.

Duration of action of GH and somatomedin C

GH is transported in blood by loose binding with plasma protein. So, at the site of action, it is released from plasma protein rapidly. Its action also lasts only for a short duration of 20 minutes. But, the somatomedin C binds with plasma proteins very strongly. Because of this, the molecules of somatomedin C are released slowly from the plasma proteins. Thus, it can act continuously for a longer duration. The action of somatomedin C lasts for about 20 hours.

Mode of action of somatomedin C

Somatomedin C acts through the second messenger called cyclic AMP (refer previous Chapter).

Growth hormone receptor

GH receptor is called **growth hormone secretagogue** (GHS) receptor. It is a transmembrane receptor, belonging to cytokine receptor family. GH binds with the receptor situated mainly in liver cells and forms the hormone-receptor complex. Hormone-receptor complex induces various intracellular enzyme pathways, resulting in somatomedin secretion. Somatomedin in turn, executes the actions of growth hormone.

Regulation of GH Secretion

Growth hormone secretion is altered by various factors. However, hypothalamus and feedback mechanism play an important role in the regulation of GH secretion

GH secretion is stimulated by:

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

GH secretion is inhibited by:

1. Hyperglycemia
2. Increase in free fatty acids in blood
3. Later stages of sleep.

Role of hypothalamus in the secretion of GH

Hypothalamus regulates GH secretion via three hormones:

1. Growth hormone-releasing hormone (GHRH): It increases the GH secretion by stimulating the somatotropes of anterior pituitary
2. Growth hormone-releasing polypeptide (GHRP): It increases the release of GHRH from hypothalamus and GH from pituitary
3. Growth hormone-inhibitory hormone (GHIH) or somatostatin: It decreases the GH secretion. Somatostatin is also secreted by delta cells of islets of Langerhans in pancreas.

These three hormones are transported from hypothalamus to anterior pituitary by hypothalamo-hypophyseal portal blood vessels.

Feedback control

GH secretion is under **negative feedback** control (Chapter 4). 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 the release of GH from pituitary. Somatomedin also inhibits release of GHRP from hypothalamus. It acts on pituitary directly and inhibits the secretion of GH (Fig. 66.3).

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.

Role of ghrelin in the secretion of GH

Ghrelin is a peptide hormone synthesized by epithelial cells in the fundus of stomach. It is also produced in smaller amount in hypothalamus, pituitary, kidney and placenta (Chapter 44). Ghrelin promotes secretion of GH by stimulating somatotropes directly.

■ OTHER HORMONES OF ANTERIOR PITUITARY

Thyroid-stimulating Hormone (TSH)

TSH is necessary for the growth and secretory activity of the thyroid gland. It has many actions on the thyroid gland. Refer Chapter 67 for details of TSH.

Adrenocorticotropic Hormone (ACTH)

ACTH is necessary for the structural integrity and the secretory activity of adrenal cortex. It has other functions also. Refer Chapter 70 for details of ACTH.

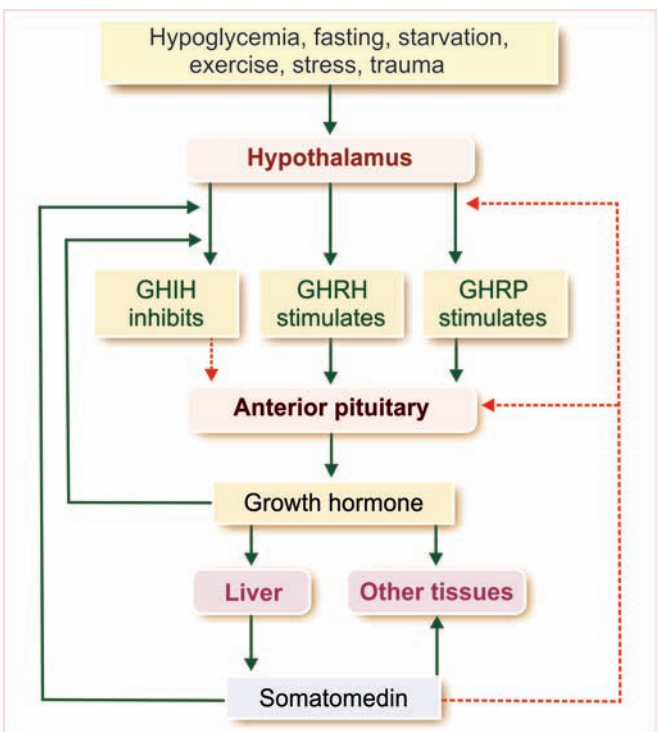


FIGURE 66.3: Regulation of GH secretion. GHIH = Growth hormone-inhibiting hormone, GHRH = Growth hormone-releasing hormone, GHRP = Growth hormone-releasing polypeptide. Growth hormone and somatomedin stimulate hypothalamus to release GHIH . Somatomedin inhibits anterior pituitary directly. Solid green line = Stimulation/secretion, Dashed red line = Inhibition.

Follicle-stimulating Hormone (FSH)

Follicle-stimulating hormone is a glycoprotein made up of one α-subunit and a β-subunit. The α-subunit has 92 amino acids and β-subunit has 118 amino acids. The half-life of FSH is about 3 to 4 hours.

Actions of FSH

In males, FSH acts along with testosterone and accelerates the process of **spermeogenesis** (refer Chapter 74 for details).

In females FSH:

1. Causes the development of **graafian follicle** from primordial follicle
2. Stimulates the theca cells of graafian follicle and causes secretion of estrogen (refer Chapter 79 for details)
3. Promotes the **aromatase activity** in granulosa cells, resulting in conversion of androgens into estrogen (Chapter 80).

Luteinizing Hormone (LH)

LH is a glycoprotein made up of one α-subunit and one β-subunit. The α-subunit has 92 amino acids and β-subunit has 141 amino acids. The half-life of LH is about 60 minutes.

Actions of LH

In males, LH is known as **interstitial cell-stimulating hormone** (ICSH) because it stimulates the interstitial cells of Leydig in testes. This hormone is essential for the secretion of testosterone from Leydig cells (Chapter 74).

In females, LH:

1. Causes maturation of vesicular follicle into graafian follicle along with follicle-stimulating hormone
2. Induces synthesis of androgens from theca cells of growing follicle
3. Is responsible for **ovulation**
4. Is necessary for the formation of corpus luteum
5. Activates the secretory functions of corpus luteum.

Prolactin

Prolactin is a single chain polypeptide with 199 amino acids. Its half-life is about 20 minutes. Prolactin is necessary for the final preparation of mammary glands for the production and secretion of milk.

Prolactin acts directly on the epithelial cells of mammary glands and causes localized **alveolar hyperplasia.** Refer Chapter 87 for details.

β-lipotropin

β-lipotropin is a polypeptide hormone with 31 amino acids. It mobilizes fat from adipose tissue and promotes lipolysis. It also forms the precursor of endorphins. This hormone acts through the adenyl cyclase.

■ POSTERIOR PITUITARY OR NEUROHYPOPHYSIS

■ PARTS

Posterior pituitary consists of three parts:

1. Pars nervosa or infundibular process
2. Neural stalk or infundibular stem
3. Median eminence.

Pars tuberalis of anterior pituitary and the neural stalk of posterior pituitary together form the **hypophyseal stalk.**

■ HISTOLOGY

Posterior pituitary is made up of neural type of cells called pituicytes and unmyelinated nerve fibers.

Pituicytes

Pituicytes are the fusiform cells derived from glial cells. These cells have several processes and brown pigment granules. Pituicytes act as supporting cells and do not secrete any hormone.

Unmyelinated Nerve Fibers

Unmyelinated nerve fibers come from supraoptic and paraventricular nuclei of the hypothalamus through the pituitary stalk.

Other Structures

Posterior pituitary also has numerous blood vessels, hyaline bodies, neuroglial cells and mast cells.

■ HORMONES OF POSTERIOR PITUITARY

Posterior pituitary hormones are:

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

Source of Secretion of Posterior Pituitary Hormones

Actually, the posterior pituitary does not secrete any hormone. ADH and oxytocin are synthesized in the hypothalamus. From hypothalamus, these two hormones are transported to the posterior pituitary through the nerve fibers of **hypothalamo-hypophyseal tract** (Fig. 66.4), by means of axonic flow. Proteins involved in transport of these hormones are called neurophysins (see below).

In the posterior pituitary, these hormones are stored at the nerve endings. Whenever, the impulses from hypothalamus reach the posterior pituitary, these hormones are released from the nerve endings into the circulation. Hence, these two hormones are called **neurohormones.**

Experimental Evidence

Secretion of posterior pituitary hormones in hypothalamus and their transport to posterior pituitary are proved by experimental evidences. When the pituitary stalk is cut above the pituitary gland, by leaving the entire hypothalamus intact, the hormones drip through the cut end of the nerves in the pituitary stalk. This proves the fact that the hormones are secreted by hypothalamus.

Neurophysins

Neurophysins are the binding proteins which transport ADH and oxytocin from hypothalamus to posterior pituitary via hypothalamo-hypophyseal tract and storage of these hormones in posterior pituitary. Neurophysin I or oxytocin-neurophysin is the binding protein for oxytocin and neurophysin II or ADH-neurophysin is the binding protein for ADH.

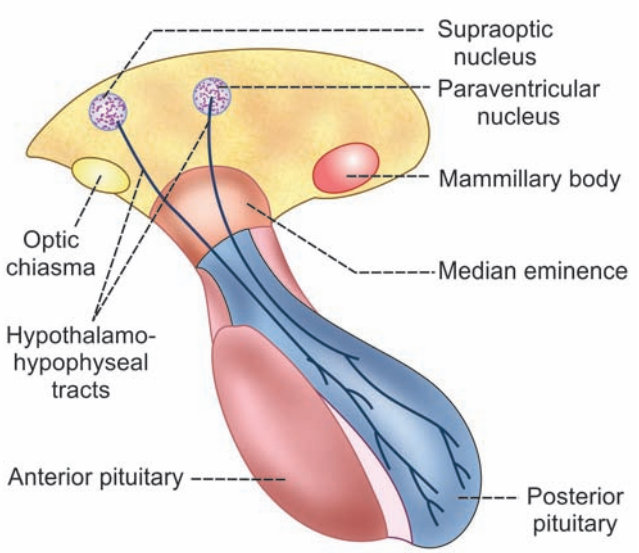


FIGURE 66.4: Hypothalamo-hypophyseal tracts

■ ANTIDIURETIC HORMONE

Source of Secretion

Antidiuretic hormone (ADH) is secreted mainly by **supraoptic nucleus** of hypothalamus. It is also secreted by **paraventricular nucleus** in small quantity. From here, this hormone is transported to posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract, by means of axonic flow.

Chemistry and Half-life

Antidiuretic hormone is a polypeptide containing 9 amino acids. Its half-life is 18 to 20 minutes.

Actions

Antidiuretic hormone has two actions:
1.Retention of water
2.Vasopressor action.

1. *Retention of water*

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 (Chapter 52).

In the absence of ADH, the distal convoluted tubule and collecting duct are totally impermeable to water. So, reabsorption of water does not occur in the renal tubules and dilute urine is excreted. This leads to loss of large amount of water through urine. This condition is called **diabetes insipidus** and the excretion of large amount of water is called diuresis.

Mode of action on renal tubules

ADH increases water reabsorption in tubular epithelial membrane by regulating the **water channel proteins** called **aquaporins** through **V2 receptors** (Chapter 52).

2. *Vasopressor action*

In large amount, ADH shows vasoconstrictor action. Particularly, causes constriction of the arteries in all parts of the body. Due to vasoconstriction, the blood pressure increases. ADH acts on blood vessels through V_{1A} receptors.

However, the amount of ADH required to cause the vasopressor effect is greater than the amount required to cause the **antidiuretic effect.**

Regulation of Secretion

ADH secretion depends upon the volume of body fluid and the osmolarity of the body fluids.

Potent stimulants for ADH secretion are:
1. Decrease in the extracellular fluid (ECF) volume
2. Increase in osmolar concentration in the ECF.

Role of osmoreceptors

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 ECF volume and restores the normal osmolarity.

■ OXYTOCIN

Source of Secretion

Oxytocin is secreted mainly by **paraventricular nucleus** of hypothalamus. It is also secreted by **supraoptic nucleus** in small quantity 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 hypothalamo-hypophyseal tract. When suitable stimuli reach the posterior pituitary from hypothalamus, oxytocin is released into the blood. Oxytocin is secreted in both males and females.

Chemistry and Half-life

Oxytocin is a polypeptide having 9 amino acids. It has a half-life of about 6 minutes.

Actions in Females

In females, oxytocin acts on mammary glands and uterus.

Action of oxytocin on mammary glands

Oxytocin causes ejection of milk from the mammary glands. Ducts of the mammary glands are lined by myo-epithelial cells. Oxytocin causes contraction of the myo-epithelial cells and flow of milk from alveoli of mammary glands to the exterior through duct system and nipple. The process by which the milk is ejected from alveoli of mammary glands is called 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 nipple, the touch receptors are stimulated. The impulses discharged from touch receptors are carried by the somatic afferent nerve fibers to paraventricular and supraoptic nuclei of hypothalamus.

Now hypothalamus, in turn sends impulses to the posterior pituitary through hypothalamo-hypophyseal tract. Afferent impulses 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 (Fig. 66.5).

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.**

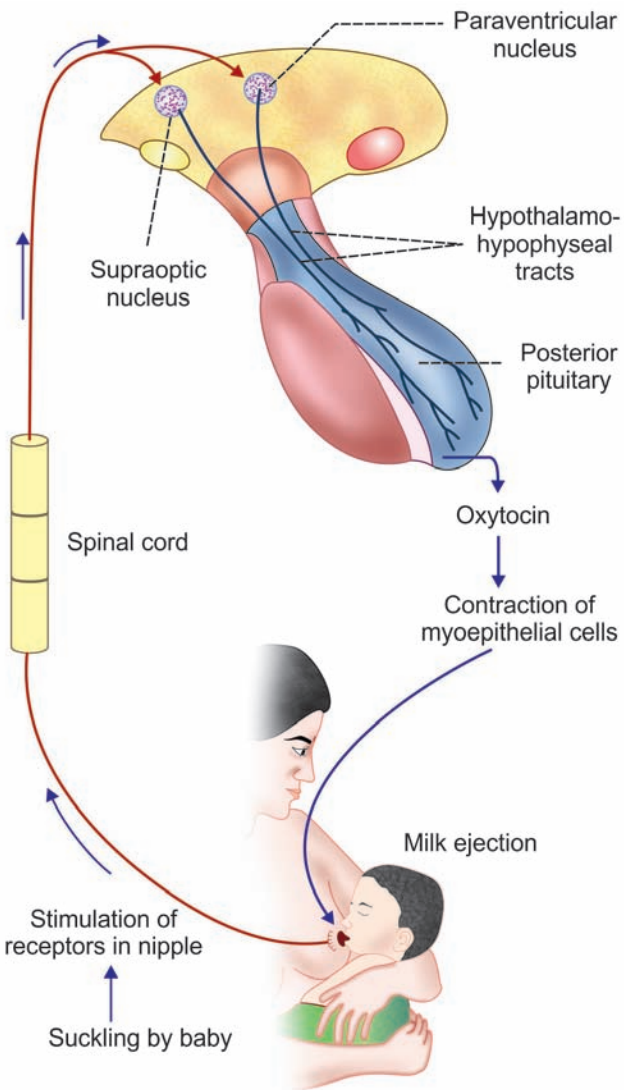


FIGURE 66.5: Milk ejection reflex

Action on uterus

Oxytocin acts on pregnant uterus and also non-pregnant uterus.

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 the later stages of pregnancy, the number of receptors for oxytocin increases in the wall of the uterus. Because of this, the uterus becomes more sensitive to oxytocin.

Oxytocin secretion increases during **labor.** At the onset of labor, the cervix dilates and the fetus descends through the birth canal. During the movement of fetus through cervix, the receptors on the cervix are stimulated and start discharging large number of impulses. These impulses are carried to the paraventricular and supraoptic nuclei of hypothalamus by the somatic afferent nerve fibers. Now, these two hypothalamic nuclei secrete large quantity of oxytocin, which enhances labor by causing contraction of uterus (Chapter 84).

Throughout 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 (Fig. 4.5).

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

On non-pregnant uterus

The action of oxytocin on non-pregnant uterus is to facilitate the transport of sperms through female genital tract up to the fallopian tube, by producing the uterine contraction during sexual intercourse.

During the sexual intercourse, the receptors in the vagina are stimulated. Vaginal receptors generate the impulses, which are transmitted by somatic afferent nerves to the paraventricular and supraoptic nuclei of hypothalamus. When, these two nuclei are stimulated, oxytocin is released and transported by blood. While reaching the female genital tract, the hormone causes antiperistaltic contractions of uterus towards the fallopian tube. It is also a **neuroendocrine reflex.**

Sensitivity of uterus to oxytocin is accelerated by estrogen and decreased by progesterone.

Action in Males

In males, the release of oxytocin increases during ejaculation. It facilitates release of sperm into urethra by causing contraction of smooth muscle fibers in reproductive tract, particularly vas deferens.

Mode of Action of Oxytocin

Oxytocin acts on mammary glands and uterus by activating **G-protein coupled oxytocin receptor.**

■ APPLIED PHYSIOLOGY – DISORDERS OF PITUITARY GLAND

Disorders of pituitary gland are given in Table 66.1.

■ 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 to 8 feet.

Causes

Gigantism is due to hypersecretion of GH in childhood or in pre-adult life before the **fusion of epiphysis** of bone with shaft. Hypersecretion of GH is because of tumor of acidophil cells in the anterior pituitary.

Signs and symptoms

i. General overgrowth of the person leads to the development of a huge stature, with a height of more than 7 or 8 feet. The limbs are disproportionately long
ii. Giants are hyperglycemic and they develop glycosuria and pituitary diabetes. Hyperglycemia causes constant stimulation of β-cells of islets of Langerhans in the pancreas and release of insulin. However, the overactivity of β-cells of Langerhans in pancreas leads to degeneration of these cells and deficiency of insulin and ultimately, diabetes mellitus is developed
iii. Tumor of the pituitary gland itself causes constant headache
iv. Pituitary tumor also causes **visual disturbances.** It compresses the lateral fibers of optic chiasma, leading to **bitemporal hemianopia** (Chapter 168)

2. *Acromegaly*

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

Causes

Acromegaly is due to hypersecretion of GH in adults after the fusion of epiphysis with shaft of the bone. Hypersecretion of GH is because of tumor of acidophil cells in the anterior pituitary.

Signs and symptoms

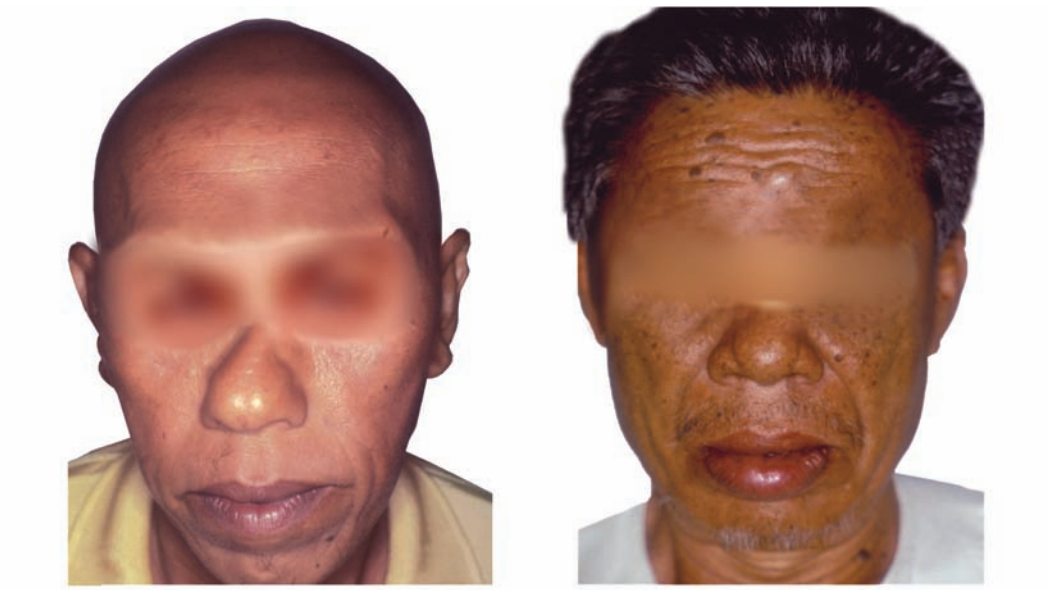
i. Acromegalic or **gorilla face:** Face with rough features such as protrusion of supraorbital ridges, broadening of nose, thickening of lips, thickening and wrinkles formation on forehead and **prognathism** (protrusion of lower jaw) (Fig. 66.6)
ii. Enlargement of hands and feet (Fig. 66.7)
iii. Kyphosis (extreme curvature of upper back – thoracic spine)
iv. Thickening of scalp. Scalp is also thrown into folds or wrinkles like **bulldog scalp**
v. Overgrowth of body hair
vi. Enlargement of visceral organs such as lungs, thymus, heart, liver and spleen
vii. Hyperactivity of thyroid, parathyroid and adrenal glands
viii. Hyperglycemia and glucosuria, resulting in diabetes mellitus
ix. Hypertension
x. Headache
xi. Visual disturbance **(bitemporal hemianopia).**

3. *Acromegalic Gigantism*

Acromegalic gigantism is a rare disorder with symptoms of both gigantism and acromegaly. Hypersecretion of GH

TABLE 66.1: Disorders of pituitary gland

Parts involved	Hyperactivity	Hypoactivity
Anterior pituitary	Gigantism Acromegaly Acromegalic gigantism Cushing disease	Dwarfism Acromicria Simmond disease
Posterior pituitary	Syndrome of inappropriate hypersecretion of ADH (SIADH)	Diabetes insipidus
Anterior and posterior pituitary	–	Dystrophia adiposogenitalis



Gorilla face: Protrution of supraorbital ridges, broad nose, thickened lips and protrution of lower jaw.

Wrinkled forehead, with other features of acromegalic face.

FIGURE 66.6: Acromegaly (*Courtesy:* Prof Mafauzy Mohamad)

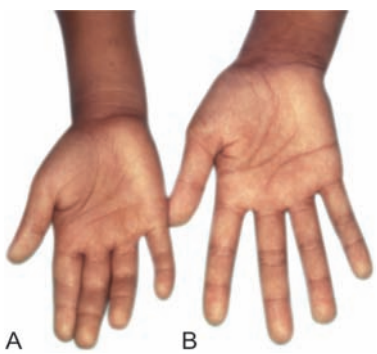


FIGURE 66.7: A. Normal hand; B. Acromegalic hand (*Courtesy:* Prof Mafauzy Mohamad)

in children, before the fusion of epiphysis with shaft of the bones causes gigantism and if hypersecretion of GH is continued even after the fusion of epiphysis, the symptoms of acromegaly also appear.

4. *Cushing Disease*

It is also a rare disease characterized by obesity.

Causes

Cushing disease develops by basophilic adenoma of adenohypophysis. It increases the secretion of adreno-corticotropic hormone, which in turn stimulates the adrenal cortex to release cortisol. Cushing disease also develops by hyperplasia or tumor of adrenal cortex.

Usually, the disorder due to the pituitary cause is called **Cushing disease** and when it is due to the adrenal cause, it is called **Cushing syndrome.**

Details of this condition are given in Chapter 70.

■ HYPOACTIVITY OF ANTERIOR PITUITARY

1. *Dwarfism*

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

Causes

Reduction in GH secretion in infancy or early childhood causes dwarfism. It occurs because of the following reasons:

i. Tumor of chromophobes: It is a non-functioning tumor, which compresses and destroys the normal cells secreting GH. It is the most common cause for hyposecretion of GH, leading to dwarfism
ii. Deficiency of GH-releasing hormone secreted by hypothalamus
iii. Deficiency of somatomedin C
iv. Atrophy or degeneration of acidophilic cells in the anterior pituitary
iv. **Panhypopituitarism:** In this condition, there is reduction in the secretion of all the hormones of anterior pituitary gland. This type of dwarfism is associated with other symptoms due to the deficiency of other anterior pituitary hormones.

Signs and symptoms

i. Primary symptom of hypopituitarism in children is the stunted skeletal growth. The maximum height of anterior pituitary dwarf at the adult age is only about 3 feet
ii. But the proportions of different parts of the body are almost normal. Only the head becomes slightly larger in relation to the body
iii. Pituitary dwarfs do not show any deformity and their mental activity is normal with no mental retardation
iv. Reproductive function is not affected, if there is only GH deficiency. However, during panhypopituitarism, the dwarfs do not obtain puberty due to the deficiency of gonadotropic hormones.

Laron dwarfism

Laron dwarfism is a genetic disorder. It is also called **GH insensitivity.** It occurs due to the presence of abnormal growth hormone **secretagogue** (GHS) receptors in liver. GHS receptors become abnormal because of the mutation of genes for the receptors.

GH secretion is normal or high. But the hormone cannot stimulate growth because of the abnormal GHS receptors. So, dwarfism occurs.

Psychogenic dwarfism

Dwarfism occurs if the child is exposed to extreme emotional deprivation or stress. The short stature is because of deficiency of GH. This type of dwarfism is called psychogenic dwarfism, **psychosocial dwarfism** or **stress dwarfism.**

Dwarfism in dystrophia adiposogenitalis

Dystrophia adiposogenitalis or **Fröhlich syndrome** is a pituitary disorder (see below). Dwarfism occurs if it develops in children.

Dwarfism in panhypopituitarism

Panhypopituitarism is the pituitary disorder due to reduction in secretion of all anterior pituitary hormones. These dwarfs do not attain puberty.

2. *Acromicria*

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

Causes

Deficiency of GH in adults causes acromicria. The secretion of GH decreases in the following conditions:

i. Deficiency of GH-releasing hormone from hypothalamus
ii. Atrophy or degeneration of acidophilic cells in the anterior pituitary
iii. Tumor of chromophobes: It is a non-functioning tumor, which compresses and destroys the normal cells secreting the GH. This is the most common cause for hyposecretion of GH leading to acromicria
iv. Panhypopituitarism: In this condition, there is a reduction in secretion of all the hormones of anterior pituitary gland. Acromicria is associated with other symptoms due to the deficiency of other anterior pituitary hormones.

Signs and symptoms

i. Atrophy and thinning of extremities of the body, (hands and feet) are the major symptoms in acromicria
ii. Acromicria is mostly associated with hypothyroidism
iii. Hyposecretion of adrenocortical hormones also is common in acromicria
iv. The person becomes lethargic and obese
v. There is loss of sexual functions.

3. *Simmond Disease*

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

Causes

It occurs mostly in panhypopituitarism, i.e. hyposecretion of all the anterior pituitary hormones due to the atrophy or degeneration of anterior pituitary.

Symptoms

i. A major feature of Simmond disease is the rapidly developing **senile decay.** Thus, a 30-years-old person looks like a 60-years-old person. The senile decay is mainly due to deficiency of hormones from target glands of anterior pituitary, i.e. the thyroid gland, adrenal cortex and the gonads
ii. There is loss of hair over the body and loss of teeth
iii. Skin on face becomes dry and wrinkled. So, there is a shrunken appearance of facial features. It is the most common feature of this disease.

■ 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.

Causes

SIADH occurs due to cerebral tumors, lung tumors and lung cancers because the **tumor cells** and **cancer cells** secrete ADH.

In normal conditions, ADH decreases the urine output by facultative reabsorption of water in distal convoluted tubule and the collecting duct. Urine that is formed is concentrated with sodium and other ions. Loss of sodium decreases the osmalarity of plasma, making it hypotonic. Hypotonic plasma inhibits ADH secretion resulting in restoration of plasma osmolarity.

However, in SIADH, secretion of ADH from tumor or cancer cells is not inhibited by hypotonic plasma. So there is continuous loss of sodium, resulting in persistent plasma hypotonicity.

Signs and symptoms

1. Loss of appetite
2. Weight loss
3. Nausea and vomiting
4. Headache
5. Muscle weakness, spasm and cramps
6. Fatigue
7. Restlessness and irritability.

In severe conditions, the patients die because of convulsions and coma.

■ HYPOACTIVITY OF POSTERIOR PITUITARY

Diabetes Insipidus

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

Causes

This disorder develops due to the deficiency of ADH, which occurs in the following conditions:

i. Lesion (injury) or degeneration of supraoptic and paraventricular nuclei of hypothalamus
ii. Lesion in hypothalamo-hypophyseal tract
iii. Atrophy of posterior pituitary
iv. Inability of renal tubules to give response to ADH hormone. Such condition is called nephrogenic diabetes insipidus (see below).

Signs and symptoms

i. *Polyuria:* Excretion of large quantity of dilute urine, with increased frequency of voiding is called polyuria. Daily output of urine varies between 4 to 12 liter. In the absence of ADH, the epithelial cells of distal convoluted tubule in the nephron and the collecting duct of the kidney become impermeable to water. So, water is not reabsorbed from the renal tubule and collecting duct, leading to loss of water through urine.
ii. *Polydipsia:* Intake of excess water is called polydipsia. Because of polyuria, lot of water is lost from the body. It stimulates the thirst center in hypothalamus, resulting in intake of large quantity of water.
iii. *Dehydration:* In some cases, the thirst center in the hypothalamus is also affected by the lesion. Water intake decreases in these patients and loss of water through urine is not compensated. So, dehydration develops which may lead to death.

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus is a genetic disorder due to inability of renal tubules to give response to ADH. It is caused by mutations of genes of V_2 receptors or aquaporin 2.

■ 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 syndrome** or **hypothalamic eunuchism.**

Causes

Dystrophia adiposogenitalis is due to hypoactivity of both anterior pituitary and posterior pituitary. Common cause of this disease is the tumor in pituitary gland and hypothalamic regions, concerned with food intake and gonadal development. Other causes are injury or atrophy of pituitary gland and genetic inability of hypothalamus to secrete luteinizing hormone-releasing hormone.

Symptoms

Obesity is the common feature of this disorder. Due to the abnormal stimulation of feeding center, the person overeats and consequently becomes obese. Obesity is accompanied by **sexual infantilism** (failure to develop secondary sexual characters) or eunuchism. **Dwarfism** occurs if the disease starts in growing age. In children, it is called infantile or prepubertal type of Fröhlich syndrome.

This disease develops in adults also. When it occurs in adults, it is called adult type of Fröhlich syndrome. In adults, the major symptoms are obesity and atrophy of sex organs.

Other features of this disorder are behavioral changes and loss of vision. Some patients develop diabetes insipidus.

Thyroid Gland

Chapter 67

- INTRODUCTION
- HISTOLOGY OF THYROID GLAND
- HORMONES OF THYROID GLAND
- SYNTHESIS OF THYROID HORMONES
- STORAGE OF THYROID HORMONES
- RELEASE OF THYROID HORMONES
- TRANSPORT OF THYROID HORMONES IN THE BLOOD
- FUNCTIONS OF THYROID HORMONES
- MODE OF ACTION OF THYROID HORMONES
- APPLIED PHYSIOLOGY – DISORDERS OF THYROID GLAND
- TREATMENT FOR THYROID DISORDERS
- THYROID FUNCTION TESTS

INTRODUCTION

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** (Fig. 67.1). It weighs about 20 to 40 g in adults. Thyroid is larger in females than in males. The structure and the function of the thyroid gland change in different stages of the sexual cycle in females. Its function increases slightly during pregnancy and lactation and decreases during menopause.

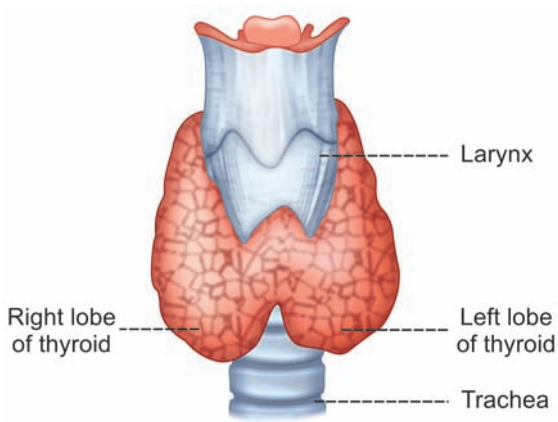


FIGURE 67.1: Thyroid gland

HISTOLOGY OF THYROID GLAND

Thyroid gland is composed of large number of closed **follicles.** These follicles are lined with cuboidal epithelial cells, which are called the **follicular cells.** Follicular cavity is filled with a colloidal substance known as **thyroglobulin,** which is secreted by the follicular cells. Follicular cells also secrete tetraiodothyronine (T_4 or thyroxine) and tri-iodothyronine (T_3). In between the follicles, the **parafollicular cells** are present (Fig. 67.2). These cells secrete calcitonin.

HORMONES OF THYROID GLAND

Thyroid gland secretes three hormones:

1. Tetraiodothyronine or T_4 (thyroxine)
2. Tri-iodothyronine or T_3
3. Calcitonin.

T_4 is otherwise known as **thyroxine** and it forms about 90% of the total secretion, whereas T_3 is only 9% to 10%. Details of calcitonin are given in next chapter.

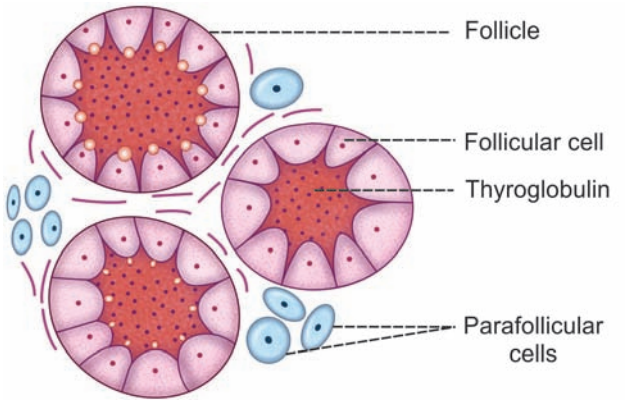


FIGURE 67.2: Histology of thyroid gland

Chemistry

Both T_4 and T_3 are iodine-containing derivatives of amino acid **tyrosine.**

Potency and Duration of Action

The potency of T_3 is four times more than that of T_4. T_4 acts for longer period than T_3. Duration of T_4 action is four times more than T_3 action. This is because of the difference in the affinity of these hormones to plasma proteins. T_3 has less affinity for plasma proteins and combines loosely with them, so that it is released quickly. T_4 has more affinity and strongly binds with plasma proteins, so that it is released slowly. Therefore, T_3 acts on the target cells immediately and T_4 acts slowly.

Half-life

Thyroid hormones have long half-life. T_4 has a long half-life of 7 days. Half-life of T_3 is varying between 10 and 24 hours.

Rate of Secretion

Thyroxine	=	80	to	90	µg/day
Tri-iodothyronine	=	4	to	5	µg/day
Reverse T_3	=	1	to	2	µg/day.

Plasma Level

Total T_3	=	0.12 µg/dL
Total T_4	=	8 µg/dL.

Metabolism of Thyroid Hormones

Degradation of thyroid hormones occurs in muscles, liver and kidney.

■ 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 tract.

For the synthesis of normal quantities of thyroid hormones, approximately 1 mg of iodine is required per week or about 50 mg per year. To prevent iodine deficiency, common table salt is iodized with one part of sodium iodide to every 100,000 parts of sodium chloride.

■ STAGES OF SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones occurs in five stages:

1. Thyroglobulin synthesis
2. Iodide trapping
3. Oxidation of iodide
4. Transport of iodine into follicular cavity
5. Iodination of tyrosine
6. Coupling reactions.

1. *Thyroglobulin Synthesis*

Endoplasmic reticulum and Golgi apparatus in the follicular cells of thyroid gland synthesize and secrete thyroglobulin continuously. Thyroglobulin molecule is a large glycoprotein containing 140 molecules of amino acid tyrosine. After synthesis, thyroglobulin is stored in the follicle.

2. *Iodide Trapping*

Iodide is actively transported from blood into follicular cell, against electrochemical gradient. This process is called iodide trapping.

Iodide is transported into the follicular cell along with sodium by sodium-iodide symport pump, which is also called iodide pump. Normally, iodide is 30 times more concentrated in the thyroid gland than in the blood. However, during hyperactivity of the thyroid gland, the concentration of iodide increases 200 times more.

3. *Oxidation of 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. Absence or inactivity of this enzyme stops the synthesis of thyroid hormones.

4. *Transport of Iodine into Follicular Cavity*

From the follicular cells, iodine is transported into the follicular cavity by an **iodide-chloride pump** called **pendrin.**

5. *Iodination of Tyrosine*

Combination of iodine with tyrosine is known as iodination. It takes place in thyroglobulin. First, iodine is transported from follicular cells into the follicular cavity, where it binds with thyroglobulin. This process is called **organification** of thyroglobulin. Then, iodine (I) combines with tyrosine, which is already present in thyroglobulin (Fig. 67.3). Iodination process is accelerated by the enzyme iodinase, which is secreted by 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.

6. *Coupling Reactions*

Iodotyrosine residues get coupled with one another. The coupling occurs in different configurations, to give rise to different thyroid hormones.

Coupling reactions are:

i. One molecule of DIT and one molecule of MIT combine to form tri-iodothyronine (T_3)

ii. Sometimes one molecule of MIT and one molecule of DIT combine to produce another form of T_3 called reverse T_3 or rT_3. Reverse T_3 is only 1% of thyroid output

iii. Two molecules of DIT combine to form tetraiodothyronine (T_4), which is thyroxine.

Tyrosine + I = Monoiodotyrosine (MIT)
MIT + I = Di-iodotyrosine (DIT)
DIT + MIT = Tri-iodothyronine (T_3)
MIT + DIT = Reverse T_3
DIT + DIT = Tetraiodothyronine or Thyroxine (T_4)

■ STORAGE OF THYROID HORMONES

After synthesis, the thyroid hormones remain in the form of vesicles within thyroglobulin and are stored for long period. Each thyroglobulin molecule contains 5 or 6 molecules of thyroxine. There is also an average of 1 tri-iodothyronine molecule for every 10 molecules of thyroxine.

In combination with thyroglobulin, the thyroid hormones can be stored for **several months.** 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.

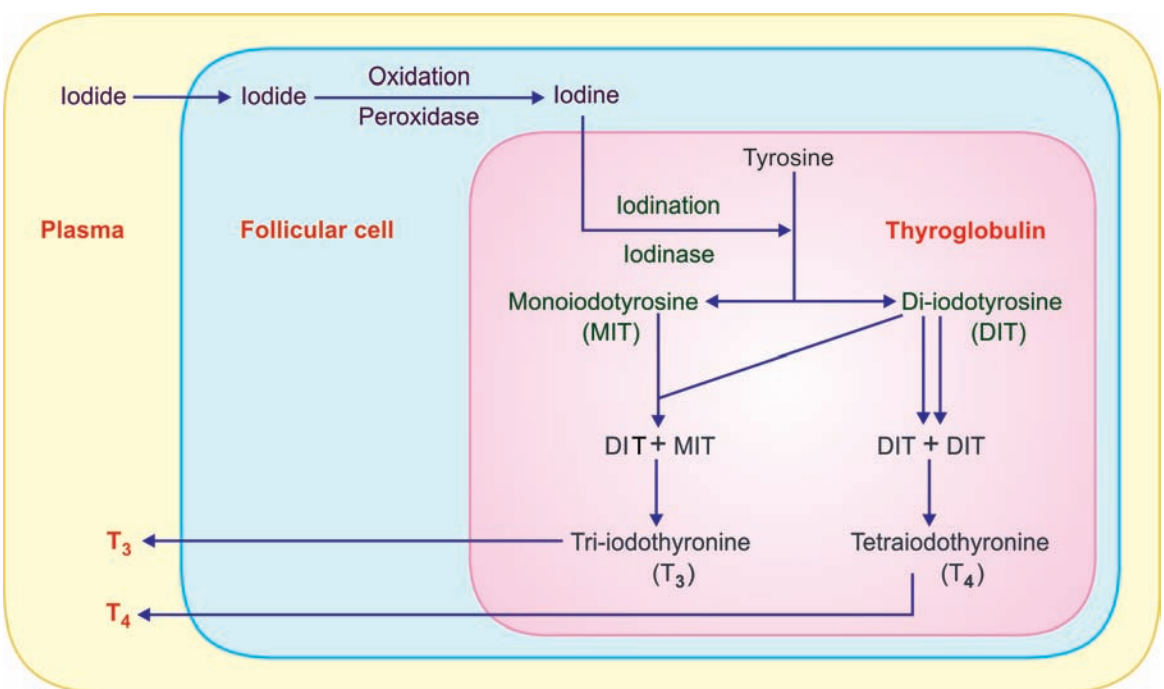


FIGURE 67.3: Synthesis of thyroid hormones

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 thyroglobulin and released into the blood.

Sequence of Events

1. Follicular cell sends foot-like extensions called **pseudopods,** which close around the thyroglobulin-hormone complex. This process is mediated by a receptor-like substance called **megalin,** which is present in the membrane of follicular cell
2. Pseudopods convert thyroglobulin-hormone complex into small **pinocytic vesicles**
3. Then, lysosomes of the cell fuse with these vesicles
4. Digestive enzymes such as proteinases present in lysosomes digest (proteolysis) the thyroglobulin and release the hormones
5. Now, the hormones diffuse through base of the follicular cell and enter the capillaries.

Only T_3 and T_4 are released into the blood. In the peripheral tissues, T_4 is converted into T_3. A small amount of inactive reverse T_3 is also formed. It is the biologically inactive form of T_3 and it is produced when T_4 is converted into T_3.

MIT and DIT are not released into blood. These iodotyrosine residues are deiodinated by an enzyme called iodotyrosine deiodinase, resulting in the release of iodine. The iodine is reutilized by the follicular cells for further synthesis of thyroid hormones. During congenital absence of iodotyrosine deiodinase, MIT and DIT are excreted in urine and the symptoms of iodine deficiency develop.

TRANSPORT OF THYROID HORMONES IN THE BLOOD

Thyroid hormones are transported in the blood by three types of proteins:

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

1. *Thyroxine-binding Globulin (TBG)*

Thyroxine-binding globulin is a glycoprotein and its concentration in the blood is 1 to 1.5 mg/dL. It has a great affinity for thyroxine and about one third of the hormone combines strongly with this protein.

2. *Thyroxine-binding Prealbumin (TBPA)*

TBPA transports one fourth of the thyroid hormones. It is also called transthyretin (TTR).

3. *Albumin*

Albumin transports about one tenth of the thyroid hormones.

FUNCTIONS OF THYROID HORMONES

Thyroid hormones have two major effects on the body:

I. To increase basal metabolic rate
II. To stimulate growth in children.

The actions of thyroid hormones are:

1. ACTION ON BASAL METABOLIC RATE (BMR)

Thyroxine increases the metabolic activities in most of the body tissues, except brain, retina, spleen, testes and lungs. It increases BMR by increasing the oxygen consumption of the tissues. The action that increases the BMR is called calorigenic action.

In hyperthyroidism, BMR increases by about 60% to 100% above the normal level and in hypothyroidism it falls by 20% to 40% below the normal level.

2. ACTION ON PROTEIN METABOLISM

Thyroid hormone increases the synthesis of proteins in the cells. The protein synthesis is accelerated by the following ways:

i. *By Increasing the Translation of RNA*

Thyroid hormone increases the translation of RNA in the cells. Because of this, the ribosomes are activated and more proteins are synthesized.

ii. *By Increasing the Transcription of DNA to RNA*

Thyroid hormone also stimulates the transcription of DNA to RNA. This in turn accelerates the synthesis of proteins in the cells (see above).

iii. *By Increasing the Activity of Mitochondria*

In addition to acting at nucleus, thyroid hormone acts at mitochondrial level also. It increases the number and the activity of mitochondria in most of the cells of the body. Thyroid hormone accelerates the synthesis of RNA and other substances from mitochondria, by activating series of enzymes. In turn, the mitochondria increase the production of ATP, which is utilized for the energy required for cellular activities.

iv. *By Increasing the Activity of Cellular Enzymes*

Thyroid hormones also increase the activity of at least 100 or more intracellular enzymes such as alpha-glycerophosphate dehydrogenase and oxidative enzymes. These enzymes accelerate the metabolism of proteins and the carbohydrates.

Though thyroxine increases synthesis of protein, it also causes catabolism of proteins.

■ 3. ACTION ON CARBOHYDRATE METABOLISM

Thyroxine stimulates almost all processes involved in the metabolism of carbohydrate.

Thyroxine:

i. Increases the absorption of glucose from GI tract
ii. Enhances the glucose uptake by the cells, by accelerating the transport of glucose through the cell membrane
iii. Increases the breakdown of glycogen into glucose
iv. Accelerates gluconeogenesis.

■ 4. ACTION ON FAT METABOLISM

Thyroxine decreases the fat storage by mobilizing it from adipose tissues and fat depots. The mobilized fat is converted into free fatty acid and transported by blood. Thus, thyroxine increases the free fatty acid level in blood.

■ 5. ACTION ON PLASMA AND LIVER FATS

Even though there is an increase in the blood level of free fatty acids, thyroxine specifically decreases the cholesterol, phospholipids and triglyceride levels in plasma. So, in hyposecretion of thyroxine, the cholesterol level in plasma increases, resulting in **atherosclerosis.**

Thyroxine also increases deposition of fats in the liver, leading to **fatty liver.** Thyroxine decreases plasma cholesterol level by increasing its excretion from liver cells into bile. Cholesterol enters the intestine through bile and then it is excreted through the feces.

■ 6. ACTION ON VITAMIN METABOLISM

Thyroxine increases the formation of many enzymes. Since vitamins form essential parts of the enzymes, it is believed that the vitamins may be utilized during the formation of the enzymes. Hence, **vitamin deficiency** is possible during hypersecretion of thyroxine.

■ 7. ACTION ON BODY TEMPERATURE

Thyroid hormone increases the heat production in the body, by accelerating various cellular metabolic processes and increasing BMR. It is called **thyroid hormone-induced thermogenesis.** During hypersecretion of thyroxine, the body temperature increases greatly, resulting in excess sweating.

■ 8. ACTION ON GROWTH

Thyroid hormones have general and specific effects on growth. Increase in thyroxine secretion accelerates the growth of the body, especially in growing children. Lack of thyroxine arrests the growth. At the same time, thyroxine causes early closure of epiphysis. So, the height of the individual may be slightly less in hypothyroidism.

Thyroxine is more important to promote growth and development of brain during fetal life and first few years of postnatal life. Deficiency of thyroid hormones during this period leads to **mental retardation.**

■ 9. ACTION ON BODY WEIGHT

Thyroxine is essential for maintaining the body weight. Increase in thyroxine secretion decreases the body weight and fat storage. Decrease in thyroxine secretion increases the body weight because of fat deposition.

■ 10. ACTION ON BLOOD

Thyroxine accelerates erythropoietic activity and increases blood volume. It is one of the important general factors necessary for erythropoiesis. Polycythemia is common in hyperthyroidism.

■ 11. ACTION ON CARDIOVASCULAR SYSTEM

Thyroxine increases the overall activity of cardiovascular system.

i. *On Heart Rate*

Thyroxine acts directly on heart and increases the heart rate. It is an important **clinical investigation** for diagnosis of hypothyroidism and hyperthyroidism.

ii. *On the Force of Contraction of the Heart*

Due to its effect on enzymatic activity, thyroxine generally increases the force of contraction of the heart. But in hyperthyroidism or in thyrotoxicosis, the heart may become weak due to excess activity and protein catabolism. So, the patient may die of **cardiac decompensation.**

Cardiac decompensation refers to failure of the heart to maintain adequate circulation associated with **dyspnea, venous engorgement** (veins overfilled with blood) and edema.

iii. *On Blood Vessels*

Thyroxine causes vasodilatation by increasing the metabolic activities. During increased metabolic activities, a large quantity of metabolites is produced. These metabolites cause vasodilatation.

iv. *On Arterial Blood Pressure*

Because of increase in rate and force of contraction of the heart, increase in blood volume and blood flow by the influence of thyroxine, cardiac output increases. This in turn, increases the blood pressure. But, generally, the mean pressure is not altered. Systolic pressure increases and the diastolic pressure decreases. So, only the pulse pressure increases (Chapter 103).

■ 12. ACTION ON RESPIRATION

Thyroxine increases the rate and force of respiration indirectly. The increased metabolic rate (caused by thyroxine) increases the demand for oxygen and formation of excess carbon dioxide. These two factors stimulate the respiratory centers to increase the rate and force of respiration (Chapter 126).

■ 13. ACTION ON GASTROINTESTINAL TRACT

Generally, thyroxine increases the appetite and food intake. It also increases the secretions and movements of GI tract. So, hypersecretion of thyroxine causes diarrhea and the lack of thyroxine causes constipation.

■ 14. ACTION ON CENTRAL NERVOUS SYSTEM

Thyroxine is very essential for the development and maintenance of normal functioning of central nervous system (CNS).

i. *On Development of Central Nervous System*

Thyroxine is very important to promote growth and development of the brain during fetal life and during the first few years of postnatal life. Thyroid deficiency in infants results in abnormal development of synapses, defective myelination and **mental retardation.**

ii. *On the Normal Function of Central Nervous System*

Thyroxine is a stimulating factor for the central nervous system, particularly the brain. So, the normal functioning of the brain needs the presence of thyroxine. Thyroxine also increases the blood flow to brain.

Thus, during the hypersecretion of thyroxine, there is excess stimulation of the CNS. So, the person is likely to have extreme nervousness and may develop psychoneurotic problems such as **anxiety complexes, excess worries** or **paranoid thoughts** (the persons think without justification that other people are plotting or conspiring against them or harassing them).

Hyposecretion of thyroxine leads to **lethargy** and **somnolence** (excess sleep).

■ 15. ACTION ON SKELETAL MUSCLE

Thyroxine is essential for the normal activity of skeletal muscles. Slight increase in thyroxine level makes the muscles to work with more vigor. But, hypersecretion of thyroxine causes weakness of the muscles due to catabolism of proteins. This condition is called **thyrotoxic myopathy.** The muscles relax very slowly after the contraction. Hyperthyroidism also causes fine muscular **tremor.** Tremor occurs at the frequency of 10 to 15 times per second. It is due to the thyroxine-induced excess neuronal activity, which controls the muscle. The lack of thyroxine makes the muscles more sluggish.

■ 16. ACTION ON SLEEP

Normal thyroxine level is necessary to maintain normal sleep pattern. Hypersecretion of thyroxine causes excessive stimulation of the muscles and central nervous system. So, the person feels tired, exhausted and feels like sleeping. But, the person cannot sleep because of the stimulatory effect of thyroxine on neurons. On the other hand, hyposecretion of thyroxine causes **somnolence.**

■ 17. ACTION ON SEXUAL FUNCTION

Normal thyroxine level is essential for normal sexual function. In men, hypothyroidism leads to complete loss of libido (sexual drive) and hyperthyroidism leads to **impotence.**

In women, hypothyroidism causes menorrhagia and **polymenorrhea** (Chapter 80). In some women, it causes irregular menstruation and occasionally **amenorrhea.** Hyperthyroidism in women leads to **oligomenorrhea** and sometimes **amenorrhea** (Chapter 80).

■ 18. ACTION ON OTHER ENDOCRINE GLANDS

Because of its metabolic effects, thyroxine increases the demand for secretion by other endocrine glands.

■ MODE OF ACTION OF THYROID HORMONES

In the target cells (particularly cells of liver, muscle and kidney), most of the T_4 is deiodinated to form T_3. So, the true intracellular hormone is T_3, rather than T_4. Moreover, T_3 is found freely in the plasma and T_4 is usually bound

with plasma proteins. So, at the site of action, T_3 acts more quickly than T_4. T_3 also has got high binding affinity for thyroid hormone receptor.

Thyroid hormones act by activating the genes and increasing the **genetic transcription** (Chapter 65). In addition, the thyroid hormone also acts at mitochondrial level by stimulating the synthesis of proteins and RNA.

Sequence of Events

1. Thyroid hormones enter the nucleus of cell and bind with thyroid hormone receptors (TR), which are either attached to DNA genetic strands or in close proximity to them.
2. TR is always bound to another receptor called **retinoid X receptor** (RXR). Exact role of RXR is not clear. Thyroid hormones bind with receptors and form the hormone-receptor complex
3. This complex initiates the transcription process by activating the enzymes such as RNA polymerase and phosphoprotein kinases
4. It also stimulates the synthesis of nuclear proteins. Thus, a large number of mRNA is formed, which activate the ribosomes to synthesize the new proteins
5. New proteins are involved in many activities including the enzymatic actions.

■ REGULATION OF SECRETION OF THYROID HORMONES

Secretion of thyroid hormones is controlled by anterior pituitary and hypothalamus through feedback mechanism. Many factors are involved in the regulation of thyroid secretion.

■ 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. It is also necessary for the growth and the secretory activity of the thyroid gland. Thus, TSH influences every stage of formation and release of thyroid hormones.

Chemistry

Thyroid-stimulating hormone is a peptide hormone with one α-chain and one β-chain.

Half-life and Plasma Level

Half-life of TSH is about 60 minutes. The normal plasma level of TSH is approximately 2 U/mL.

Actions of Thyroid-stimulating Hormone

Thyroid-stimulating hormone increases:

1. The number of follicular cells of thyroid
2. The conversion of cuboidal cells in thyroid gland into columnar cells and thereby it causes the development of thyroid follicles
3. Size and secretory activity of follicular cells
4. Iodide pump and iodide trapping in follicular cells
5. Thyroglobulin secretion into follicles
6. Iodination of tyrosine and coupling to form the hormones
7. Proteolysis of the thyroglobulin, by which release of hormone is enhanced and colloidal substance is decreased.

Immediate effect of TSH is proteolysis of the thyroglobulin, by which thyroxine is released within 30 minutes. Effect of TSH on other stages in thyroxine synthesis takes place after some hours, days or weeks.

Mode of Action of TSH

TSH acts through cyclic AMP mechanism.

■ ROLE OF HYPOTHALAMUS

Hypothalamus regulates thyroid secretion by controlling TSH secretion through thyrotropic-releasing hormone (TRH). 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 (Fig. 67.4).

■ 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. This effect of iodide is called **Wolff-Chaikoff effect.**

■ ROLE OF OTHER FACTORS

Many other factors are involved in the regulation of thyroid secretion in accordance to the needs of the body.

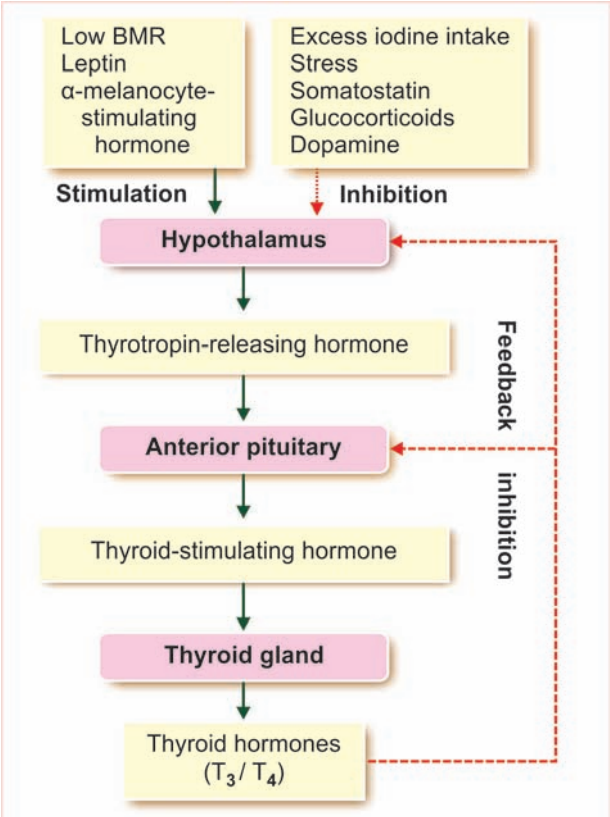


FIGURE 67.4: Regulation of secretion of thyroid hormones

Factors increasing the secretion of thyroid hormones:

1. Low basal metabolic rate
2. Leptin
3. α-melanocyte-stimulating hormone

Leptin (from adipose tissue) and **α-melanocyte-stimulating hormone** (from pituitary) increase the release of TRH and synthesis of T_4. The low body temperature also stimulates the synthesis of thyroid hormones. However, this occurs only in infants.

Factors decreasing the secretion of thyroid hormones:

1. Excess iodide intake
2. Stress
3. Somatostatin
4. Glucocorticoids
5. Dopamine.

These factors decrease the secretion of thyroid hormones, by inhibiting the release of TRH.

■ APPLIED PHYSIOLOGY – DISORDERS OF THYROID GLAND

■ HYPERTHYROIDISM

Increased secretion of thyroid hormones is called hyperthyroidism.

Causes of Hyperthyroidism

Hyperthyroidism is caused by:

1. Graves' disease
2. Thyroid adenoma.

1. *Graves' disease*

Graves' disease is an autoimmune disease and it is the most common cause of hyperthyroidism. Normally, TSH combines with surface receptors of thyroid cells and causes the synthesis and secretion of thyroid hormones. In Graves' disease, the B lymphocytes (plasma cells) produce autoimmune antibodies called **thyroid-stimulating autoantibodies** (TSAbs). 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.

Antibodies act for a long time even up to 12 hours in contrast to that of TSH, which lasts only for an hour or so. The high concentration of thyroid hormones caused by the antibodies suppresses the TSH production also. So, the concentration of TSH is low or almost zero in plasma of most of the hyperthyroid patients.

2. *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. It is not associated with autoimmunity. As far as this adenoma remains active, the other parts of thyroid gland cannot secrete the hormone. This is because, the hormone secreted from adenoma depresses the production of TSH.

Signs and Symptoms of Hyperthyroidism

1. Intolerance to heat as the body produces lot of heat due to increased basal metabolic rate caused by excess of thyroxine
2. Increased sweating due to vasodilatation
3. Decreased body weight due to fat mobilization
4. Diarrhea due to increased motility of GI tract
5. Muscular weakness because of excess protein catabolism
6. Nervousness, extreme fatigue, inability to sleep, mild tremor in the hands and psychoneurotic symptoms such as hyperexcitability, extreme anxiety or worry. All these symptoms are due to the excess stimulation of neurons in the central nervous system
7. Toxic goiter (see below)
8. Oligomenorrhea or amenorrhea (Chapter 80)
9. Exophthalmos (see below)
10. Polycythemia
11. Tachycardia and atrial fibrillation

12. Systolic hypertension
13. Cardiac failure.

Exophthalmos

Protrusion of eye balls is called exophthalmos. Most, but not all hyperthyroid patients develop some degree of protrusion of eyeballs.

Causes for exophthalmos

Exophthalmos in hyperthyroidism is due to the edematous swelling of retro-orbital tissues and degenerative changes in the extraocular muscles.

Effect of exophthalmos on vision

Severe exophthalmic condition leads to blindness because of two reasons:

1. Protrusion of the eyeball, which stretches and damages the optic nerve, resulting in **blindness** or
2. Due to the protrusion of eyeballs, the eyelids cannot be closed completely while blinking or during sleep. So, the constant exposure of eyeball to atmosphere causes dryness of the cornea, leading to irritation and infection. It finally results in ulceration of the cornea leading to blindness.

■ HYPOTHYROIDISM

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

Myxedema

Myxedema 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 thyrotropin-releasing hormone.

Common cause of myxedema is the autoimmune disease called **Hashimoto's thyroiditis,** which is common in late middle-aged women (Chapter 17). In most of the patients, it starts with glandular inflammation called **thyroiditis** caused by autoimmune antibodies. Later it leads to destruction of the glands.

Signs and symptoms of myxedema

Typical feature of this disorder is an edematous appearance throughout the body. It is associated with the following symptoms:

1. Swelling of the face
2. Bagginess under the eyes
3. Non-pitting type of edema, i.e. when pressed, it does not make pits and the edema is hard. It is because of accumulation of proteins with **hyaluronic acid** and **chondroitin sulfate,** which form a hard tissue with increased accumulation of fluid
4. Atherosclerosis: It is the hardening of the walls of arteries because of accumulation of fat deposits and other substances. In myxedema, it occurs because of increased plasma level of cholesterol which leads to deposition of cholesterol on the walls of the arteries.

Atherosclerosis produces **arteriosclerosis,** which refers to thickening and stiffening of arterial wall. Arteriosclerosis causes hypertension.

Other general features of hypothyroidism in adults are:

1. Anemia
2. Fatigue and muscular sluggishness
3. Extreme somnolence with sleeping up to 14 to 16 hours per day
4. Menorrhagia and polymenorrhea
5. Decreased cardiovascular functions such as reduction in rate and force of contraction of the heart, cardiac output and blood volume
6. Increase in body weight
7. Constipation
8. Mental sluggishness
9. Depressed hair growth
10. Scaliness of the skin
11. Frog-like husky voice
12. Cold intolerance.

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.

Features of cretinism

1. A newborn baby with thyroid deficiency may appear normal at the time of birth because thyroxine might have been supplied from mother. But a few weeks after birth, the baby starts developing the signs like sluggish movements and **croaking sound** while crying. Unless treated immediately, the baby will be mentally retarded permanently.
2. Skeletal growth is more affected than the soft tissues. So, there is stunted growth with bloated

body. The tongue becomes so big that it hangs down with dripping of saliva. The big tongue obstructs swallowing and breathing. The tongue produces characteristic guttural breathing that may sometimes **choke** the baby.

Cretin Vs dwarf

A cretin is different from pituitary dwarf. In cretinism, there is mental retardation and the different parts of the body are disproportionate. Whereas, in dwarfism, the development of nervous system is normal and the parts of the body are proportionate (Fig. 67.5). The reproductive function is affected in cretinism but it may be normal in dwarfism.

■ 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 – Non-toxic Goiter

Non-toxic goiter is the enlargement of thyroid gland without increase in hormone secretion. It is also called **hypothyroid goiter** (Fig. 67.6).

Based on the cause, the non-toxic hypothyroid goiter is classified into two types.

1. Endemic colloid goiter
2. Idiopathic non-toxic goiter.

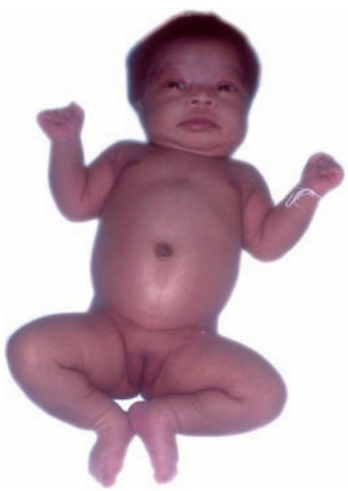


FIGURE 67.5: Cretinism (3-month-old baby)
(*Courtesy:* Prof Mafauzy Mohamad)

1. *Endemic colloid goiter*

Endemic colloid goiter is the non-toxic goiter caused by iodine deficiency. It is also called **iodine deficiency goiter.** Iodine deficiency occurs when intake is less than 50 µg/day. Because of lack of iodine, there is no formation of hormones. By feedback mechanism, hypothalamus and anterior pituitary are stimulated. It increases the secretion of TRH and TSH. The TSH then causes the thyroid cells to secrete tremendous amounts of thyroglobulin into the follicle. As there are no hormones to be cleaved, the thyroglobulin remains as it is and gets accumulated in the follicles of the gland. This increases the size of gland.

In certain areas of the world, especially in the Swiss Alps, Andes, Great Lakes region of United States and in India, particularly in Kashmir Valley, the soil does not contain enough iodine. Therefore, the foodstuffs also do not contain iodine. The endemic colloid goiter was very common in these parts of the world before the introduction of iodized salts.

2. *Idiopathic non-toxic goiter*

Idiopathic non-toxic goiter is the goiter due to unknown cause. Enlargement of thyroid gland occurs even without iodine deficiency. The exact cause is not known. It is suggested that it may be due to thyroiditis and deficiency of enzymes such as **peroxidase, iodinase** and **deiodinase,** which are required for thyroid hormone synthesis.

Some foodstuffs contain **goiterogenic substances** (goitrogens) such as **goitrin.** These substances contain antithyroid substances like propylthiouracil. **Goitrogens** suppress the synthesis of thyroid hormones. Therefore, TSH secretion increases, resulting in enlargement of the gland. Such goitrogens are found in vegetables like turnips and cabbages. Soybean also contains some amount of goitrogens.

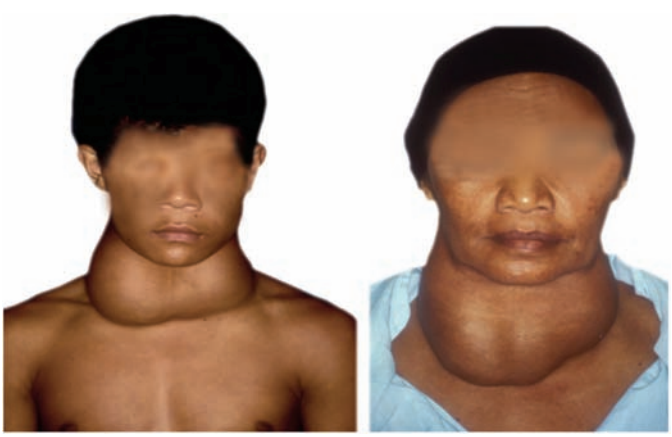


FIGURE 67.6: Non-toxic goiter
(*Courtesy:* Prof Mafauzy Mohamad)

The goitrogens become active only during low iodine intake.

TREATMENT FOR THYROID DISORDERS

TREATMENT FOR HYPERTHYROIDISM

1. *By using Antithyroid Substances*

Antithyroid substances are the drugs which suppress the secretion of thyroid hormones. Hyperthyroidism in early stage can be treated by antithyroid substances.

Three well-known antithyroid substances are:

i. Thiocyanate
ii. Thiourylenes
iii. High concentration of inorganic iodides.

i. *Thiocyanate*

Thiocyanate prevents synthesis of thyroxine by inhibiting iodide trapping. The active pump which transports iodide into the thyroid cells, can transport thiocyanate ions also. So, administration of thiocyanate in high concentrations causes competitive inhibition of iodide transport into the cell. So, iodide trapping is inhibited, leading to the inhibition of synthesis of thyroxine.

ii. *Thiourylenes*

Thiourylenes are the thiourea-related substances such as propylthiouracil and methimazole, which prevent the formation of thyroid hormone from iodides and tyrosine. It is achieved partly by blocking peroxidase enzyme activity and partly by blocking coupling of iodinated tyrosine to form either T_3 or T_4.

During the use of these two antithyroid substances, even though the synthesis of thyroid hormone is inhibited, the formation of thyroglobulin is not stopped. The deficiency of the hormone increases the TSH secretion, which increases the size of thyroid gland with more secretion of thyroglobulin. Thyroglobulin accumulates in the gland and causes enlargement of the gland, resulting in non-toxic goiter.

iii. *High concentration of inorganic iodides*

Iodides in high concentration decrease all phases of thyroid activity, including the release of hormones. So, the size of the gland is also reduced with decreased blood supply. Because of this, iodides are frequently administered to hyperthyroid patients for 2 or 3 weeks, prior to surgical removal of the thyroid gland.

2. *By Surgical Removal*

In advanced cases of hyperthyroidism, treatment by using antithyroid substances is not possible. So, thyroid gland of these patients must be removed. Surgical removal of thyroid gland is called **thyroidectomy.** Before surgery, the patient is prepared by reducing the basal metabolic rate. It is done by injecting propylthiouracil for several weeks, until basal metabolic rate reaches almost the basal level. The high concentration of iodides is administered for 2 weeks. It decreases the size of the gland and blood supply to a very great extent. Because of these precautions, the mortality after the operation decreases very much.

TREATMENT FOR HYPOTHYROIDISM

The only treatment for hypothyroidism is the administration of thyroid extract or ingestion of pure thyroxine in the form of tablets, orally.

THYROID FUNCTION TESTS

Functional status of thyroid gland is assessed by the following tests:

1. Measurement of plasma level of T_3 and T_4: For hyperthyroidism or hypothyroidism, the most accurate diagnostic test is the direct measurement of concentration of "free" thyroid hormones in the plasma, i.e. T_3 and T_4.
2. Measurement of TRH and TSH: There is almost total absence of these two hormones in hyperthyroidism. It is because of negative feedback mechanism, by the increased level of thyroid hormones.
3. Measurement of basal metabolic rate: In hyperthyroidism, basal metabolic rate is increased by about 30% to 60%. Basal metabolic rate is decreased in hypothyroidism by 20% to 40%.

Parathyroid Glands and Physiology of Bone

Chapter 68

■ INTRODUCTION

Human beings have four parathyroid glands, which are situated on the posterior surface of upper and lower poles of thyroid gland (Fig. 68.1). Parathyroid glands are very small in size, measuring about 6 mm long, 3 mm wide and 2 mm thick, with dark brown color.

Histology

Each parathyroid gland is made up of **chief cells** and **oxyphil cells.** Chief cells secrete parathormone. Oxyphil cells are the degenerated chief cells and their function is known. However, these cells may secrete parathormone during pathological condition called **parathyroid adenoma.** The number of oxyphil cells increases after puberty.

■ PARATHORMONE

Parathormone secreted by parathyroid gland is essential for the maintenance of blood calcium level within a very narrow critical level. Maintenance of blood calcium level is necessary because calcium is an important inorganic ion for many physiological functions (see below).

Source of Secretion

Parathormone (PTH) is secreted by the chief cells of the parathyroid glands.

Chemistry

Parathormone is protein in nature, having 84 amino acids. Its molecular weight is 9,500.

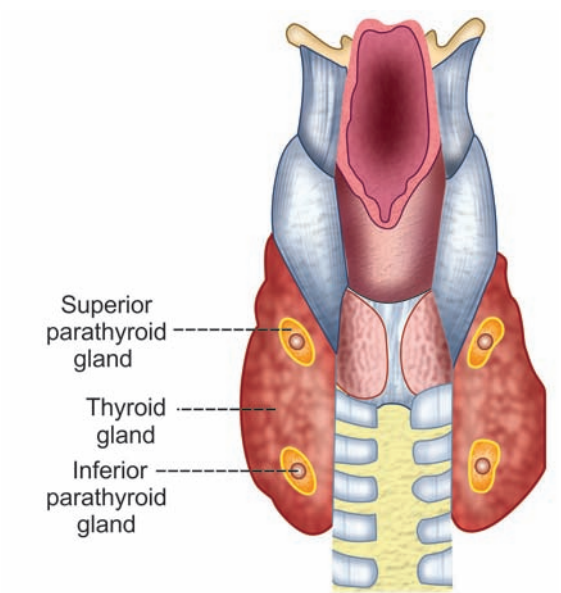


FIGURE 68.1: Parathyroid glands on the posterior surface of thyroid gland

Half-life and Plasma Level

Parathormone has a half-life of 10 minutes. Normal plasma level of PTH is about 1.5 to 5.5 ng/dL.

Synthesis

Parathormone is synthesized from the precursor called **prepro-PTH** containing 115 amino acids. First, the prepro-PTH enters the endoplasmic reticulum of chief cells of parathyroid glands. There it is converted into a prohormone called **pro-PTH,** which contains 96 amino acids. Pro-PTH enters the Golgi apparatus, where it is converted into PTH.

Metabolism

Sixty to seventy percent of PTH is degraded by **Kupffer cells** of liver, by means of proteolysis. Degradation of about 20% to 30% PTH occurs in kidneys and to a lesser extent in other organs.

■ ACTIONS OF PARATHORMONE

PTH plays an important role in maintaining blood calcium level. It also controls blood phosphate level.

■ ACTIONS OF PARATHORMONE ON BLOOD CALCIUM LEVEL

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 blood calcium level by acting on:

1. Bones
2. Kidney
3. Gastrointestinal tract.

1. On Bone

Parathormone enhances the resorption of calcium from the bones **(osteoclastic activity)** by acting on **osteoblasts** and **osteoclasts** of the bone.

Resorption of calcium from bones occurs in two phases:

i. Rapid phase
ii. Slow phase.

Rapid phase

Rapid phase occurs within minutes after the release of PTH from parathyroid glands. Immediately after reaching the bone, PTH gets attached with the receptors on the cell membrane of osteoblasts and osteocytes. The hormone-receptor complex increases the permeability of membranes of these cells for calcium ions. It accelerates

the calcium pump mechanism, so that calcium ions move out of these bone cells and enter the blood at a faster rate.

Slow phase

Slow phase of calcium resorption from bone is due to the activation of osteoclasts by PTH. When osteoclasts are activated, some substances such as proteolytic enzymes, citric acid and lactic acid are released from lysosomes of these cells. All these substances digest or dissolve the organic matrix of the bone, releasing the calcium ions. The calcium ions slowly enter the blood.

PTH increases calcium resorption from bone by stimulating the proliferation of osteoclasts also.

2. *On Kidney*

PTH increases the reabsorption of calcium from the renal tubules along with magnesium ions and hydrogen ions. It increases calcium reabsorption mainly from distal convoluted tubule and proximal part of collecting duct.

PTH also increases the formation of **1,25-dihydroxycholecalciferol** (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys (see below).

3. *On Gastrointestinal Tract*

PTH increases the absorption of calcium ions from the GI tract indirectly. It increases the formation of 1,25-dihydroxycholecalciferol in the kidneys. This vitamin, in turn increases the absorption of calcium from GI tract.

Thus, the activated vitamin D is very essential for the absorption of calcium from the GI tract. And PTH is essential for the formation of activated vitamin D.

Role of PTH in the activation of vitamin D

Vitamin D is very essential for calcium absorption from the GI tract. But vitamin D itself is not an active substance. Instead, vitamin D has to be converted into 1, 25-dihydroxycholecalciferol in the liver and kidney in the presence of PTH. The 1,25-dihydroxycholecalciferol is the active product.

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 (Fig. 68.2).

First step

Cholecalciferol (vitamin D3) is converted into 25-hydroxycholecalciferol in the liver. This process is limited and is inhibited by 25-hydroxycholecalciferol itself by feedback mechanism. This inhibition is essential for two reasons:

i. Regulation of the amount of active vitamin D
ii. Storage of vitamin D for months together.

If vitamin D3 is converted into 25-hydroxycholecalciferol, it remains in the body only for 2 to 5 days. But vitamin D3 is stored in liver for several months.

Second step

25-hydroxycholecalciferol is converted into 1,25-dihydroxycholecalciferol **(calcitriol)** in kidney. It is the active form of vitamin D3. This step needs the presence of PTH.

Role of Calcium Ion in Regulating 1, 25-Dihydroxycholecalciferol

When blood calcium level increases, it inhibits the formation of 1,25-dihydroxycholecalciferol. The mechanism involved in the inhibition of the formation of 1,25-dihydroxycholecalciferol is as follows:

i. Increase in calcium ion concentration directly suppresses the conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol. This effect is very mild

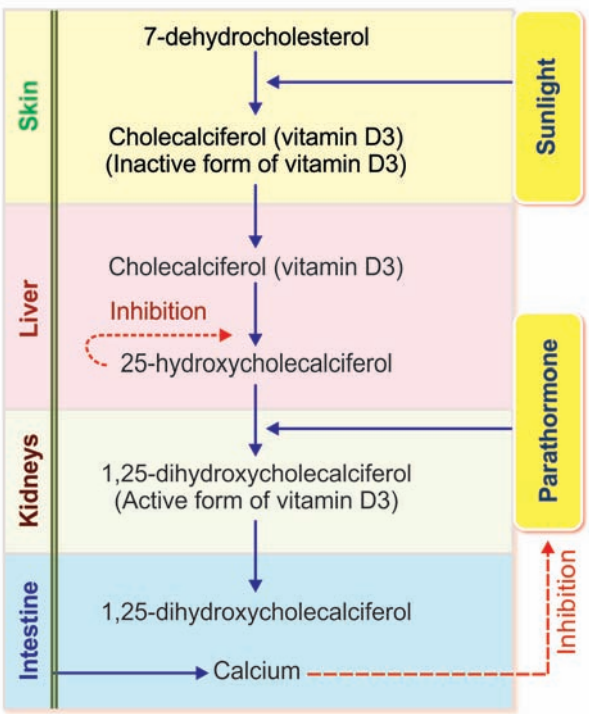


FIGURE 68.2: Schematic diagram showing activation of vitamin D

ii. Increase in calcium ion concentration decreases the PTH secretion, which in turn suppresses the conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol.

This regulates the calcium ion concentration of plasma itself indirectly, i.e. when the PTH synthesis is inhibited, the conversion of 25-hydroxycholecalciferol into 1,25-hydroxycholecalciferol is also inhibited. Lack of 1,25-dihydroxycholecalciferol, decreases the absorption of calcium ions from the intestine, from the bones and from the renal tubules as well. This makes the calcium level in the plasma to fall back to normal.

Actions of 1, 25-Dihydroxycholecalciferol

1. It increases the absorption of calcium from the intestine, by increasing the formation of calcium-binding proteins in the intestinal epithelial cells. These proteins act as carrier proteins for facilitated diffusion, by which the calcium ions are transported. The proteins remain in the cells for several weeks after 1,25-dihydroxycholecalciferol has been removed from the body, thus causing a prolonged effect on calcium absorption
2. It increases the synthesis of calcium-induced ATPase in the intestinal epithelium
3. It increases the synthesis of alkaline phophatase in the intestinal epithelium
4. It increases the absorption of phosphate from intestine along with calcium.

■ ACTIONS OF PARATHORMONE ON BLOOD PHOSPHATE LEVEL

PTH decreases blood level of phosphate by increasing its urinary excretion. It also acts on bone and GI tract.

1. *On Bone*

Along with calcium resorption, PTH also increases phosphate absorption from the bones.

2. *On Kidney*

Phosphaturic action

It is the effect of PTH by which phosphate is excreted through urine. PTH increases phosphate excretion by inhibiting reabsorption of phosphate from renal tubules. It acts mainly on proximal convoluted tubule.

3. *On Gastrointestinal Tract*

Parathormone increases the absorption of phosphate from GI tract through calcitriol.

Sequence of events

i. PTH converts 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol (calcitriol: active form of vitamin D3) in kidney
ii. Calcitriol increases the synthesis of calcium induced ATPase in the intestinal epithelium
iii. ATPase increases the synthesis of alkaline phophatase
iv. Alkaline phosphatase increases the absorption of phosphate from intestine along with calcium.

■ MODE OF ACTION OF PARATHORMONE

Parathormone Receptors

Parathormone receptors (PTH receptors) are of three types, PTHR1, PTHR2 and PTHR3, which are G protein-coupled receptors. PTHR1 is physiologically more important than the other two types. PTHR1 mediates the actions of PTH and **PTH-related protein** (see below). Role of PTHR2 and PTHR3 is not known clearly.

On the target cells, PTH binds with PTHR1 which is coupled to G protein and forms hormone-receptor complex. Hormone-receptor complex causes formation of cAMP, which acts as a second messenger for the hormone.

■ REGULATION OF PARATHORMONE SECRETION

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

Blood Level of Calcium

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

Conditions when PTH secretion decreases are:

1. Excess quantities of calcium in the diet
2. Increased vitamin D in the diet
3. Increased resorption of calcium from the bones, caused by some other factors such as bone diseases.

On the other hand, decrease in calcium ion concentration of blood increases PTH secretion, as in the case of rickets, pregnancy and in lactation.

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.

■ APPLIED PHYSIOLOGY – DISORDERS OF PARATHYROID GLANDS

Disorders of parathyroid glands are of two types:

I. Hypoparathyroidism
II. Hyperparathyroidism.

■ HYPOPARATHYROIDISM – HYPOCALCEMIA

Hyposecretion of PTH is called hypoparathyroidism. It leads to hypocalcemia (decrease in blood calcium level).

Causes for Hypoparathyroidism

1. Surgical removal of parathyroid glands **(parathyroidectomy)**
2. Removal of parathyroid glands during surgical removal of thyroid gland **(thyroidectomy)**
3. Autoimmune disease
4. Deficiency of receptors for PTH in the target cells. In this, the PTH secretion is normal or increased but the hormone cannot act on the target cells. This condition is called **pseudohypoparathyroidism.**

Hypocalcemia and Tetany

Hypoparathyroidism leads to hypocalcemia, by decreasing the resorption of calcium from bones. Hypocalcemia causes neuromuscular hyperexcitability, resulting in hypocalcemic tetany. Normally, tetany occurs when plasma calcium level falls below 6 mg/dL from its normal value of 9.4 mg/dL.

Hypocalcemic Tetany

Tetany is an abnormal condition characterized by violent and painful **muscular spasm** (spasm = involuntary muscular contraction), particularly in feet and hand. It is because of hyperexcitability of nerves and skeletal muscles due to calcium deficiency.

Signs and symptoms of hypocalcemic tetany:

1. *Hyper-reflexia and convulsions*

Increase in neural excitability results in hyper-reflexia (overactive reflex actions) and convulsive muscular contractions.

2. *Carpopedal spasm*

Carpopedal spasm is the spasm in hand and feet that occurs in hypocalcemic tetany. During spasm, the hand shows a peculiar attitude (Fig. 68.3).

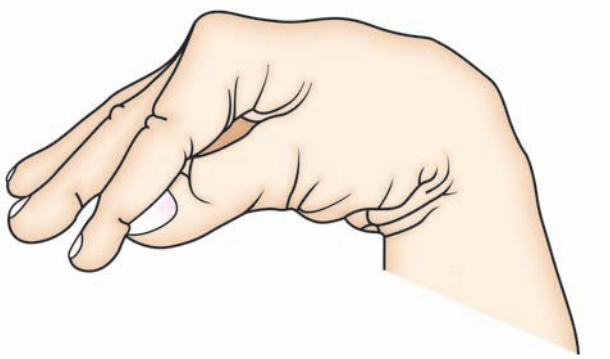


FIGURE 68.3: Carpopedal spasm

Attitude of hand in carpopedal spasm includes:

i. Flexion at wrist joint
ii. Flexion at metacarpophalangeal joints
iii. Extension at interphalangeal joints
iv. Adduction of thumb.

3. *Laryngeal stridor*

Stridor means noisy breathing. Laryngeal stridor means a loud crowing sound during inspiration, which occurs mainly due to **laryngospasm** (involuntary contraction of laryngeal muscles). Laryngeal stridor is a common dangerous feature of hypocalcemic tetany.

4. *Cardiovascular changes*

i. Dilatation of the heart
ii. Prolonged duration of ST segment and QT interval in ECG
iii. Arrhythmias (irregular heartbeat)
iv. Hypotension
v. Heart failure.

5. *Other features*

i. Decreased permeability of the cell membrane
ii. Dry skin with brittle nails
iii. Hair loss
iv. Grand mal, petit mal or other seizures (Chapter 161)
v. Signs of mental retardation in children or dementia in adults (Chapter 162).

When the calcium level falls below 4 mg/dL, it becomes fatal. During such severe hypocalcemic conditions, tetany occurs so quickly that a person develops spasm of different groups of muscles in the body. Worst affected are the laryngeal and bronchial muscles which develop respiratory arrest, resulting in death.

Latent Tetany

Latent tetany, also known as **subclinical tetany** is the **neuromuscular hyperexcitability** due to hypocalcemia

that develops before the onset of tetany. It is characterized by general weakness and cramps in feet and hand. Hyperexcitability in these patients is detected by some signs, which do not appear in normal persons.

1. *Trousseau sign*

Trousseau sign is the spasm of the hand that is developed after 3 minutes of arresting the blood flow to lower arm and hand. The blood flow to lower arm and hand is arrested by inflating the blood pressure cuff 20 mm Hg above the patient's systolic pressure.

2. *Chvostek sign*

Chvostek sign is the twitch of the facial muscles, caused by a gentle tap over the facial nerve in front of the ear. It is due to the hyperirritability of facial nerve.

3. *Erb sign*

Hyperexcitability of the skeletal muscles even to a mild electrical stimulus is called Erb sign. It is also called **Erb-Westphal sign.**

■ HYPERPARATHYROIDISM – HYPERCALCEMIA

Hypersecretion of PTH is called hyperparathyroidism. It results in hypercalcemia. Hyperparathyroidism is of three types:

1. Primary hyperparathyroidism

Primary hyperparathyroidism is due to the development of tumor in one or more parathyroid glands. Sometimes, tumor may develop in all the four glands.

2. *Secondary hyperparathyroidism*

Secondary hyperparathyroidism is due to the physiological compensatory hypertrophy of parathyroid glands, in response to hypocalcemia which occurs due to other pathological conditions such as:

i. Chronic renal failure
ii. Vitamin D deficiency
iii. Rickets.

3. *Tertiary hyperparathyroidism*

Tertiary hyperparathyroidism is due to **hyperplasia** (abnormal increase in the number of cells) of all the parathyroid glands that develops due to chronic secondary hyperparathyroidism.

Hypercalcemia

Hypercalcemia is the increase in plasma calcium level. It occurs in hyperparathyroidism because of increased resorption of calcium from bones.

Signs and symptoms of hypercalcemia

i. Depression of the nervous system
ii. Sluggishness of reflex activities
iii. Reduced ST segment and QT interval in ECG
iv. Lack of appetite
v. Constipation.

Depressive effects of hypercalcemia are noticed when the blood calcium level increases to 12 mg/dL. The condition becomes severe with 15 mg/dL and it becomes lethal when blood calcium level reaches 17 mg/dL.

Other effects of hypercalcemia:

i. Development of bone diseases such as osteitis fibrosa cystica
ii. Development of parathyroid poisoning. It is the condition characterized by severe manifestations that occur when blood calcium level rises above 15 mg/dL. In hyperparathyroidism, the concentration of both calcium and phosphate increases leading to formation of calcium-phosphate crystals. Concentration of phosphate also increases because, kidney cannot excrete the excess amount of phosphate resorbed from the bone
iii. Deposition of **calcium-phosphate crystals** in renal tubules, thyroid gland, alveoli of lungs, gastric mucosa and in the wall of the arteries, resulting in dysfunction of these organs. **Renal stones** are formed when it is deposited in kidney.

■ PARATHYROID FUNCTION TESTS

1. Measurement of blood calcium level
2. Chvostek sign and Trousseau sign for hypoparathyroidism.

■ CALCITONIN

Source of Secretion

Calcitonin is secreted by the **parafollicular cells** or **clear cells (C cells),** situated amongst the follicles in thyroid gland. In lower animals, the parafollicular cells are derived from ultimobranchial glands, which develop from fifth pharyngeal pouches. In human being, the ultimobranchial glands and fifth pharyngeal pouches are rudimentary and their cells are incorporated with fourth pharyngeal pouches and distributed amongst the follicles of thyroid gland.

Recently, calcitonin is found in brain, prostate and bronchial cells of lungs. However, the physiological role of calcitonin from non-thyroid tissues is not known.

Chemistry and Synthesis

Calcitonin is a polypeptide chain with 32 amino acids. Its molecular weight is about 3,400. It is synthesized from procalcitonin.

Plasma Level and Half-life

Plasma level of calcitonin is 1 to 2 ng/dL. It has a half-life of 5 to 10 minutes.

Metabolism

Calcitonin is degraded and excreted by liver and kidney.

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

iii. *On intestine*

Calcitonin 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 the deposition of phosphate on bones.

ii. *On kidney*

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

■ REGULATION OF CALCITONIN SECRETION

High calcium content in plasma stimulates the calcitonin secretion through a calcium receptor in parafollicular cells. Gastrin also is known to stimulate the release of calcitonin.

■ CALCIUM METABOLISM

■ IMPORTANCE OF CALCIUM

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

1. Bone and teeth 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.

■ NORMAL VALUE

In a normal young healthy adult, there is about 1,100 g of calcium in the body. It forms about 1.5% of total body weight. 99% of calcium is present in the bones and teeth and the rest is present in the plasma. Normal blood calcium level ranges between 9 and 11 mg/dL.

■ TYPES OF CALCIUM

Calcium in Plasma

Calcium is present in three forms in plasma:

i. Ionized or diffusible calcium: Found freely in plasma and forms about 50% of plasma calcium. It is essential for vital functions such as neuronal activity, muscle contraction, cardiac activity, secretions in the glands, blood coagulation, etc.

ii. Non-ionized or non-diffusible calcium: Present in non-ionic form such as calcium bicarbonate. It is about 8% to 10% of plasma calcium

iii. Calcium bound to albumin: Forms about 40% to 42% of plasma calcium.

Calcium in Bones

Calcium is constantly removed from bone and deposited in bone. Bone calcium is present in two forms:

i. Rapidly exchangeable calcium or exchangeable calcium: Available in small quantity in bone and helps to maintain the plasma calcium level

ii. Slowly exchangeable calcium or stable calcium: Available in large quantity in bones and helps in bone remodeling.

Process of calcium metabolism is explained schematically in Fig. 68.4.

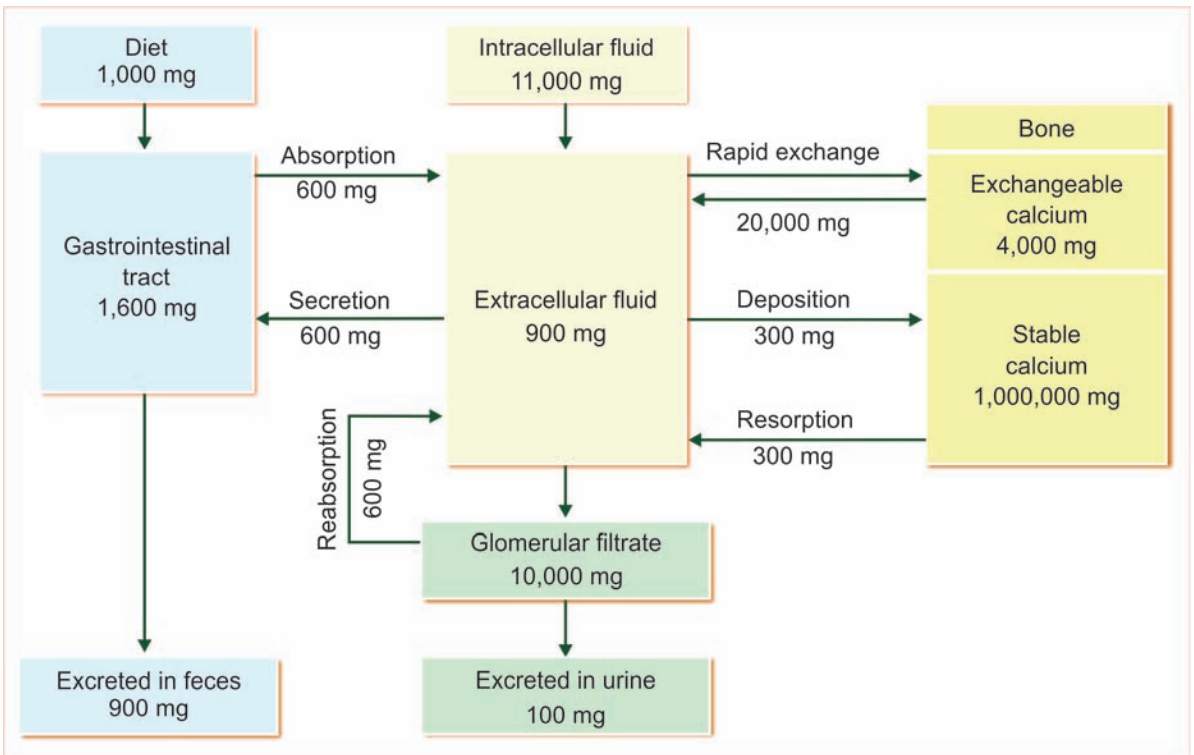


FIGURE 68.4: Schematic diagram showing calcium metabolism. Values belong to adults

■ SOURCE OF CALCIUM

1. *Dietary Source*

Calcium is available in several foodstuffs. Percentage of calcium in different food substance is:

Whole milk	= 10%
Low fat milk	= 18%
Cheese	= 27%
Other dairy products	= 17%
Vegetables	= 7%
Other substances such as meat, egg, grains, sugar, coffee, tea, chocolate, etc.	= 21%

2. *From Bones*

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

■ DAILY REQUIREMENTS OF CALCIUM

1 to 3 years	= 500 mg
4 to 8 years	= 800 mg
9 to 18 years	= 1,300 mg
19 to 50 years	= 1,000 mg
51 years and above	= 1,200 mg
Pregnant ladies and lactating mothers	= 1,300 mg

■ ABSORPTION AND EXCRETION OF CALCIUM

Calcium taken through dietary sources is absorbed from 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.

Absorption from Gastrointestinal Tract

Calcium is absorbed from duodenum by carrier-mediated active transport and from the rest of the small intestine, by facilitated diffusion. Vitamin D is essential for the absorption of calcium from GI tract.

Excretion

While passing through the kidney, large quantity of calcium is filtered in the glomerulus. From the filtrate, 98% to 99% of calcium is reabsorbed from renal tubules into the blood. Only a small quantity is excreted through urine.

Most of the filtered calcium is reabsorbed in the distal convoluted tubules and proximal part of collecting duct. In distal convoluted tubule, parathormone increases the reabsorption. In collecting duct, vitamin D increases the reabsorption and calcitonin decreases reabsorption.

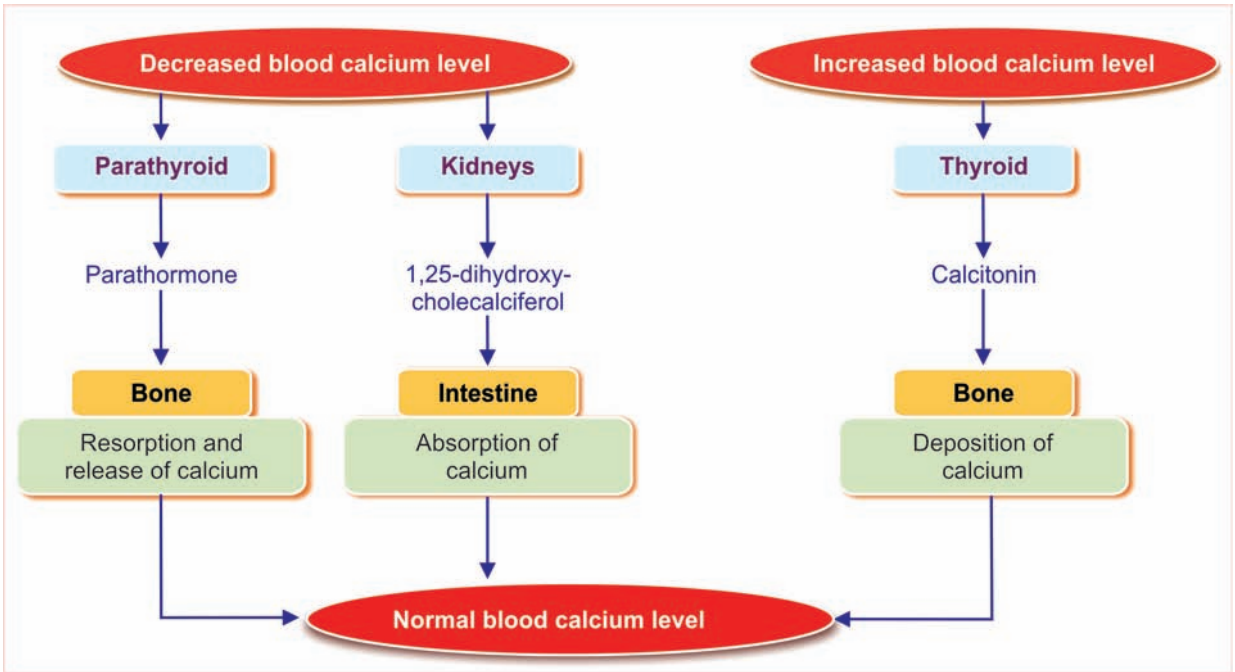


FIGURE 68.5: Schematic diagram showing regulation of blood calcium level

About 1,000 mg of calcium is excreted daily. Out of this, 900 mg is excreted through feces and 100 mg through urine.

■ REGULATION OF BLOOD CALCIUM LEVEL

Blood calcium level is regulated mainly by three hormones (Figs 68.5 and 68.6):

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

1. *Parathormone*

Parathormone is a protein hormone secreted by parathyroid gland and its main function is to increase the blood calcium level by mobilizing calcium from bone (resorption) (See above for details).

2. *1,25-dihydroxycholecalciferol – Calcitriol*

Calcitriol is a steroid hormone synthesized in kidney. It is the activated form of vitamin D. Its main action is to increase the blood calcium level by increasing the calcium absorption from the small intestine (see above for details).

3. *Calcitonin*

Calcitonin secreted by parafollicular cells of thyroid gland. Thyroid gland is a calcium-lowering hormone. It reduces the blood calcium level mainly by decreasing bone resorption (see above for details).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also influence the calcium level.

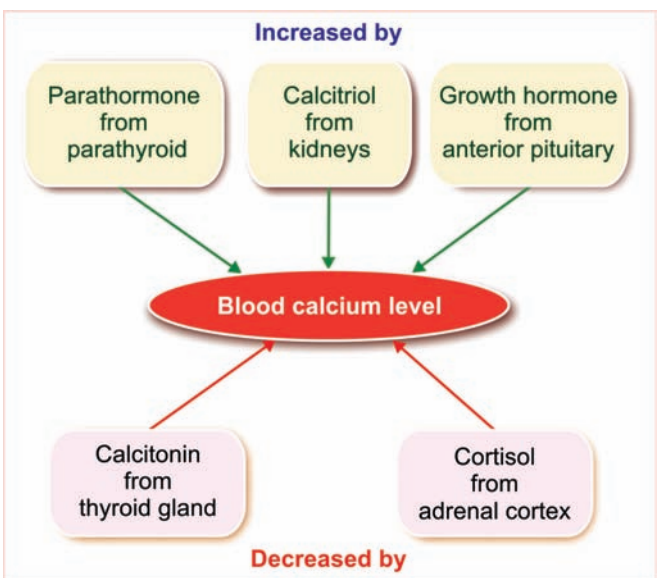


FIGURE 68.6: Effect of hormones on blood calcium level

1. *Growth hormone*

Growth hormone increases the blood calcium level by increasing the intestinal calcium absorption. It is also suggested that it increases the urinary excretion of calcium. However, this action is only transient.

2. *Glucocorticoids*

Glucocorticoids (cortisol) decrease blood calcium by inhibiting intestinal absorption and increasing the renal excretion of calcium.

■ PHOSPHATE METABOLISM

Phosphorus (P) is an essential mineral that is required by every cell in the body for normal function. Phosphorus is present in many food substances, such as peas, dried beans, nuts, milk, cheese and butter. Inorganic phosphorus (Pi) is in the form of the **phosphate** (PO_4). The majority of the phosphorus in the body is found as phosphate. Phosphorus is also the body's source of phosphate. In body, phosphate is the most abundant intracellular anion.

■ IMPORTANCE OF PHOSPHATE

1. Phosphate is an important component of many organic substances such as, ATP, DNA, RNA and many intermediates of metabolic pathways
2. Along with calcium, it forms an important constituent of bone and teeth
3. It forms a buffer in the maintenance of acid-base balance.

■ NORMAL VALUE

Total amount of phosphate in the body is 500 to 800 g. Though it is present in every cell of the body, 85% to 90% of body's phosphate is found in the bones and teeth. Normal plasma level of phosphate is 4 mg/dL.

■ REGULATION OF PHOSPHATE LEVEL

Phosphorus is taken through dietary sources. It is absorbed from GI tract into blood. It is also resorbed from bone. From blood it is distributed to various parts of the body. While passing through the kidney, large quantity of phosphate is excreted through urine.

Blood phosphate level is regulated mainly by three hormones:

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

1. *Parathormone*

Parathormone stimulates resorption of phosphate from bone and increases its urinary excretion. It also increases the absorption of phosphate from gastrointestinal tract through calcitriol. The overall action of parathormone decreases the plasma level of phosphate.

2. *Calcitonin*

Calcitonin also decreases the plasma level of phosphate by inhibiting bone resorption and stimulating the urinary excretion.

3. *1,25-Dihydroxycholecalciferol – Calcitriol*

Calcitriol hormone increases absorption of phosphate from small intestine (Fig. 68.7).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also influence the phosphate level.

1. *Growth hormone*

Growth hormone increases the blood phosphate level by increasing the intestinal phosphate absorption.

2. *Glucocorticoids*

Glucocorticoids (cortisol) decreases blood phosphate by inhibiting intestinal absorption and increasing the renal excretion of phosphate.

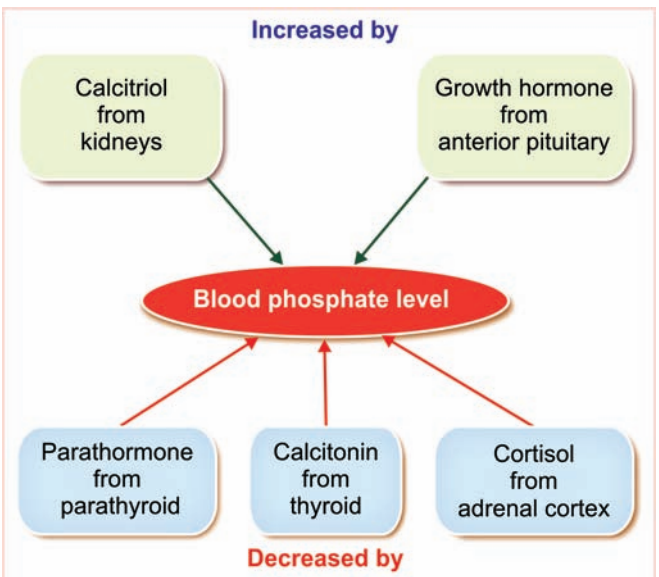


FIGURE 68.7: Effect of hormones on blood phosphate level

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 the life, bone is renewed by the process of bone formation and bone resorption.

FUNCTIONS OF BONE

1. *Protective function:* Protects soft tissues and vital organs of the body
2. *Mechanical function:* Supports the body and brings out various movements of the body by their attachment to the muscles and tendons
3. *Metabolic function:* Plays an important role in the metabolism 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.

CLASSIFICATION OF BONE

Depending upon the size and shape, the bones are classified into five types:

1. Long bones: Bones of the limbs
2. Short bones: Bones in the wrist and ankle
3. Flat bones: Skull bones, mandible, scapula, etc.
4. Irregular bones: Vertebra
5. Sesamoid bones: Patella.

PARTS OF BONE

Long bones are formed by a cylindrical tube of bone tissue, which has three portions:

1. Diaphysis: Midportion or midshaft
2. Epiphysis: Wider extremity or the head on either end
3. Metaphysis: Portion between the diaphysis and the epiphysis (Fig. 68.8).

In growing age, a layer of cartilage called **epiphyseal cartilage** or **epiphyseal plate** or **growth plate** is present in between epiphysis and metaphysis. Epiphyseal plate is responsible for the longitudinal growth of the bones.

COMPOSITION OF BONE

Bone consists of the tough organic matrix to which the bone salts are deposited.

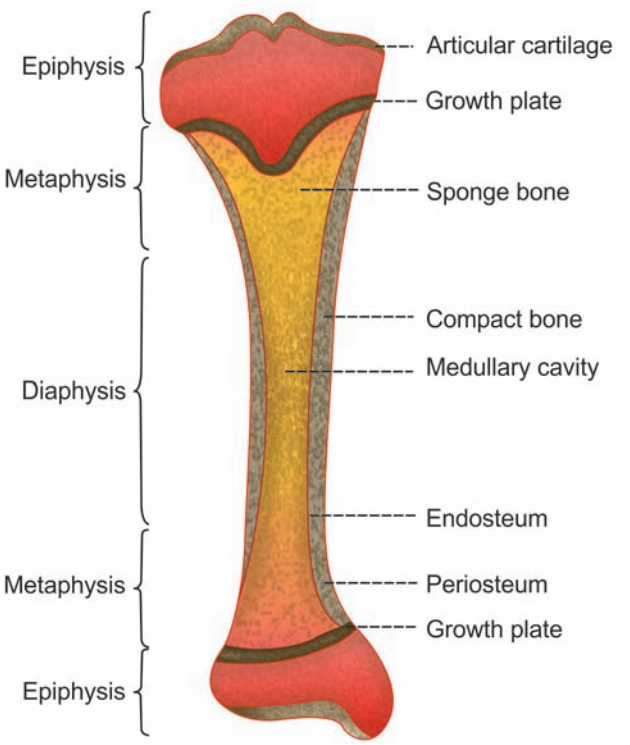


FIGURE 68.8: Parts of long bone

Matrix

Bone matrix is composed of protein fibers called **collagen fibers,** which are embedded in the gelatinous ground substance. These collagen fibers form about 90% of the bone. The ground substance is formed by ECF and **proteoglycans.** Proteoglycans are **chondroitin sulfate** and **hyaluronic acid,** which are concerned with the regulation and deposition of bone salts.

Bone Salts

The crystalline salts present in bones are called **hydroxyapatites,** which contain calcium and phosphate. Apart from these substances, some other salts like sodium, potassium, magnesium and carbonate are also present in the bone. The salts of the bone strengthen the bone matrix.

STRUCTURE OF BONE

Bone is covered by an outer white fibrous connective layer called **periosteum** and an inner dense fibrous membrane called endosteum. The tendons from the muscles are attached to periosteum. The heads (epiphysis) of bone are covered by a **hyaline cartilage.** It forms the synovial joint with adjoining bones.

Bones have two layers of structures:

1. Outer compact bone
2. Inner spongy bone.

In most of the bones, both compact and spongy forms are present. However, the thickness of each type varies in different regions. The epiphysis contains large amount of spongy bone and outer thin compact bone. In diaphysis, the amount of compact bone is more and the spongy bone is very thin.

Compact Bone

Compact or cortical bone is the hard and dense material forming about 80% of bone in the body. Its main functions are mechanical function and the protection of bone marrow.

Compact bone consists of minute cylindrical structures called **osteones** or **Haversian systems** (Fig. 68.9), which are formed by concentric layers of collagen. Collagen lamellae are called **Haversian lamellae.** In the center of each osteon, there is a canal called **Haversian canal** that contains the blood vessels, lymph vessels and nerve fibers. The Haversian systems communicate with each other by transverse canals called **Volkmann canal.**

Within the Haversian systems, there are small cavities called **lacunae,** inside which the **osteocytes** are trapped. Osteocytes send long processes called **canaliculi.** The canaliculi from neighboring osteocytes unite to form tight junctions.

Marrow cavity

Compact bone has a large narrow cavity called **marrow cavity** or medullary cavity, which contains yellow bone marrow.

Spongy Bone

Spongy or **trabecular** or **cancellous bone** forms 20% of bone in the body and it contains red bone marrow. It is made of **bone spicules,** which are separated by spaces.

■ TYPES OF CELLS IN BONE

Bone has three major types of cells:

1. Osteoblasts
2. Osteocytes
3. Osteoclasts.

1. *Osteoblasts*

Osteoblasts are the bone cells concerned with bone formation **(osteoblastic activity).** These cells are situated in the outer surface of bone, the marrow cavity and

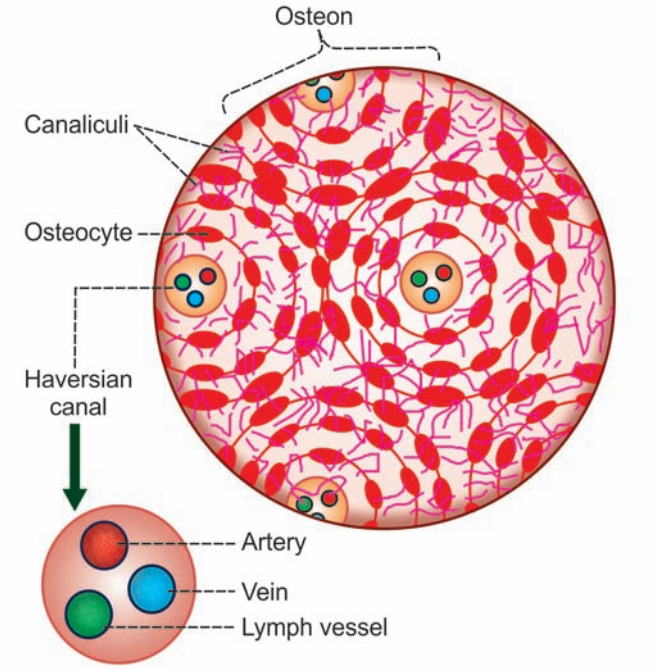


FIGURE 68.9: Structure of compact bone

epiphyseal plate. The osteoblasts arise from the giant multinucleated primitive cells called the **osteoprogenitor** cells. Differentiation of osteoprogenitor cells into osteoblasts (Table 68.1) is accelerated by some hormones and some bone proteins called **skeletal growth factors.** These growth factors stimulate the growth of osteoblasts also.

Functions of osteoblasts

i. *Role in the formation of bone matrix*

Osteoblasts are responsible for the synthesis of bone matrix by secreting type I collagen and a protein called **matrix gla protein** (MGP) or **osteocalcin.** Other proteins involved in the matrix synthesis are also produced by the osteoblasts. Such proteins are transforming growth factor (TGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF).

ii. *Role in calcification*

Osteoblasts are rich in enzyme alkaline phosphatase, which is necessary for deposition of calcium in the bone matrix **(calcification).**

iii. *Synthesis of proteins*

Osteoblasts synthesize the proteins called matrix gla protein and osteopontin, which are involved in the calcification.

Fate of osteoblasts

After taking part in bone formation, the osteoblasts differentiate into osteocytes, which are trapped inside the lacunae of calcified bone.

2. Osteocytes

Osteocytes are the bone cells concerned with maintenance of bone. Osteocytes are small flattened and rounded cells, embedded in the bone lacunae. These cells are the major cells in developed bone and are derived from the matured osteoblasts. The cytoplasmic processes from osteocytes run into canaliculi and ramify throughout the bone matrix. The processes from neighboring osteocytes have contact with each other forming tight junctions.

Functions of osteocytes

i. Help to maintain the bone as living tissue because of their metabolic activity
ii. Maintain the exchange of calcium between the bone and ECF.

3. Osteoclasts

Osteoclasts are the bone cells that are concerned with bone resorption **(osteoclastic activity).** Osteoclasts are the **giant phagocytic multinucleated cells** found in the lacunae of bone matrix. These bone cells are derived from hemopoietic stem cells via monocytes colony forming units-M (CFU-M).

Functions of osteoclasts

i. Responsible for bone resorption during bone remodeling
ii. Synthesis and release of lysosomal enzymes necessary for bone resorption into the bone resorbing compartment.

■ BONE GROWTH

Embryo has a cartilaginous skeleton. The **cartilage** is composed of large amount of solid but flexible matrix. The matrix is derived from a protein called **chondrin,** that is secreted by the **cartilage cells** or **chondriocytes.** Some of the cartilage is converted into bones.

Ossification and Calcification

Ossification is the conversion of cartilage into bone. At the time of birth, the skeleton consists of 50% cartilage and 50% bone. At the age of 2 years and thereafter, the skeleton consists 35% cartilage and 65% bone.

Ossification is carried out by the osteoblasts, which enter the cartilage and lay down the matrix around them. Osteoblasts synthesize collagen fibers, which produce the matrix called osteoid. Then, calcium is deposited on the matrix. The deposition of calcium is called calcification.

Growth in Length

During growth, the epiphysis at the end of each long bone is separated from diaphysis by a plate of proliferative cartilage termed as **epiphyseal plate.**

Increase in the length of the bone occurs due to the formation of new bone from epiphyseal plate. The thickness of the epiphyseal plate reduces as the length of bone increases. Increase in length of the bone occurs as long as the epiphyseal plates remain separated from diaphysis (shaft). The growth of the bone stops when the epiphysis fuses with the shaft. The process by which epiphysis fuses with shaft is called the **epiphyseal fusion** or closure. It occurs usually at the time of puberty. Width of the bone increases due to increase in thickness of periosteum or the outer layers of compact bone.

■ BONE REMODELING

Bone remodeling is a dynamic lifelong process in which old bone is resorbed and new bone is formed. Usually, it takes place in groups of bone cells called the **basic multicellular units** (BMU). The entire process of remodeling extends for about 100 days in compact bone and about 200 days in spongy bone.

Processes of bone remodeling

1. Bone resorption: Destruction of bone matrix and removal of calcium (osteoclastic activity).
2. Bone formation: Development and mineralization of new matrix (osteoblastic activity).

Bone Resorption – Osteoclastic Activity

Osteoclastic activity is the process that involves destruction of bone matrix, followed by removal of calcium. Osteoclasts are responsible for bone resorption by their osteoclastic activity.

Part of the bone to be resorbed is known as bone resorbing compartment. The osteoclast present in this compartment attaches itself to the periosteal or endosteal surface of bone through villi-like membranous extensions. This process is mediated by the surface receptors called **integrins.** At the point of attachment, a ruffled border is formed by folding of the cell membrane.

Resorption of that particular compartment occurs by some substances released from membranous extensions of osteoclasts such as:

1. Collagenase
2. Phosphatase

3. Lysosomal enzymes
4. Acids like citric acid and lactic acid.

Sequence of events during bone resorption

1. Citric acid and lactic acid cause acidification of the area and decrease pH to 4
2. Lysosomal enzymes are activated at this pH
3. Activated enzymes digest or dissolve the collagen
4. Enzymes also dissolve the hydroxyapatite and form solution of bone salts
5. All the dissolved materials are now released into ECF
6. Some elements enter the blood
7. Remaining elements are cleaned up by the macrophages
8. A shallow cavity is formed in the bone resorbing compartment.

Bone Formation – Osteoblastic Activity

Osteoblastic activity is the process which involves the synthesis of collagen and formation of bone matrix that is mineralized. Osteoblasts are concerned with bone formation. Osteoblasts synthesize and release collagen into the shallow cavity formed after resorption in the bone resorbing compartment. The collagen fibers arrange themselves in regular units and form the organic matrix called osteoid.

Mineralization

Mineralization is the process by which the minerals are deposited on bone matrix. Mineralization starts about 10 to 12 days after the formation of osteoid. First, a large quantity of calcium phosphate is deposited. Afterwards, the hydroxide and bicarbonate ions are gradually added causing the formation of **hydroxyapatite crystals.** The process of mineralization is accelerated by the enzyme alkaline phosphatase, secreted by osteoblast. The process also requires the availability of adequate amount of calcium and phosphate in the ECF.

The completely mineralized bone surrounds the osteoblast. Now, the synthetic activity of osteoblast is reduced slowly and the cell is converted into osteocytes. Later, the bone is arranged in concentric lamellae on the inner surface of the cavity. At the end of the formation of new bone, the cavity is reduced to form Haversian canal.

Significance of Bone Remodeling

In children

1. Thickness of bone increases
2. Bone obtains strength in proportion to the growth
3. Shape of the bone is realtered in relation to growth of the body.

In adults

1. Toughness of bone is maintained
2. Mechanical integrity of skeleton is ensured throughout life
3. Blood calcium level is maintained.

Regulation of Bone Remodeling

Bone remodeling occurs continuously throughout the life. So a balance is maintained always between the bone resorption and bone formation.

However, in persons like athletes, soldiers and others, in whom the bone stress is more, the bone becomes heavy and strong. It is because of the stimulation of osteoblastic activity and mineralization of bone by repeated physical stress.

Apart from the physical stress, a variety of hormonal substances and growth factors are involved in regulation of bone resorption and bone formation (Table 68.1).

■ REPAIR OF BONE AFTER FRACTURE

The process of healing after bone fracture involves joining of broken ends by the deposition of new bone.

Stages of Bone Repair after Fracture

1. Formation of **hematoma** between the broken ends of bone and surrounding soft tissues. Hematoma means swelling or mass of blood clot confined to a tissue or space due to rupture of blood vessel
2. Development of acute inflammation
3. Phagocytosis of hematoma, debris and fragments of bone by macrophages
4. Formation of granular tissue and development of new blood vessels
5. Development of new osteoblasts and formation of new bone called callus
6. Spreading of new bone to fill the gap between the broken ends of bones
7. Reshaping of new bone by osteoclasts, which remove excess callus and formation of canal in the new bone.

■ APPLIED PHYSIOLOGY – DISEASES OF BONE

1. *Osteoporosis*

Osteoporosis is the bone disease characterized by the loss of bone matrix and minerals. Osteoporosis means **'porous bones'.**

TABLE 68.1: Factors regulating bone remodeling

Event	Stimulating factors	Inhibiting Factors
Bone formation	1. Growth hormone 2. Calcitonin 3. Insulin 4. Testosterone 5. Estrogen 6. Insulin-like growth factor 7. Transforming growth factor-β 8. Skeletal growth factor 9. Bone-derived growth factor 10. Platelet-derived growth factor	Cortisol
Mineralization	1. Calcitonin 2. Insulin 3. Vitamin D	Cortisol
Bone resorption	1. Parathormone 2. Thyroxine 3. Cortisol 4. Prostaglandins 5. Interleukin-1 6. Estrogen 7. Calcitonin	Testosterone

Causes of osteoporosis

Osteoporosis occurs due to excessive bone resorption and decreased bone formation. Osteoporosis is common in women after 60 years. The various risk factors are given in Box 68.1.

Manifestations of osteoporosis

Loss of bone matrix and minerals leads to loss of bone strength, associated with architectural deterioration of bone tissue. Ultimately, the bones become fragile with high risk of fracture. Commonly affected bones are vertebrae and hip.

2. *Rickets*

Rickets is the bone disease in children, characterized by inadequate mineralization of bone matrix. It occurs due to vitamin D deficiency. Vitamin D deficiency develops due to insufficiency in diet or due to inadequate exposure to sunlight.

BOX 68.1: Risk factors for osteoporosis

1. Sedentary life
2. Genetic factor
3. Early menopause or ovariectomy
4. Excessive smoking
5. Excessive alcohol or caffeine intake
6. Prolonged high intake of protein
7. Prolonged medication with drugs like corticosteroids and cyclosporin
8. Endocrine disorders like hypothyroidism, Cushing syndrome, acromegaly and hypogonadism.

Deficiency of vitamin D affects the reabsorption of calcium and phosphorus from renal tubules, resulting in **calcium deficiency.** It causes inadequate mineralization of epiphyseal growth plate in growing bones. This defect produces various manifestations.

Causes of rickets

Causes of rickets are given in Table 68.2.

Features of rickets

i. Collapse of chest wall: Due to the flattening of sides of thorax with prominent sternum. This deformity of the chest with projecting sternum is called **pigeon chest** or **chicken chest** or **pectus carinatum.**
ii. Rachitic rosary: A visible swelling where the ribs join their cartilages. It is because of the development of nodules at sternal end of ribs, which forms the rachitic rosary
iii. Kyphosis: Extreme forward curvature of the upper back bone (thoracic spine) with convexity backward (forward bending). Severe kyphosis

TABLE 68.2: Common causes of rickets and osteomalacia

Deficiency of vitamin D	Low dietary intake Inadequate synthesis in skin Reduced absorption from intestine
Renal diseases	Chronic renal failure Dialysis-induced bone disease Renal tubular acidosis.

causes formation of a hump (protuberance) which is called **humpback, hunchback** or **Pott curvature**

iv. Lordosis: Extreme forward curvature of back bone in lumbar region: also called **hollow back** or **saddle back**
v. Scoliosis: Lateral curvature of spine
vi. Harrison sulcus: A groove in rib cage due to pulling of diaphragm inwards
vii. Bowing of hands and legs
viii. Enlargement of liver and spleen
ix. Tetany: In advanced stages, the patient may die because of tetany, involving the respiratory muscles.

3. *Osteomalacia*

Rickets in adults is called **osteomalacia** or **adult rickets.**

Causes of osteomalacia

Osteomalacia occurs because of deficiency of vitamin D. It also occurs due to prolonged damage of kidney (renal rickets).

Features of osteomalacia

i. Vague pain
ii. Tenderness in bones and muscles
iii. **Myopathy** leading to **waddling gait** (gait means the manner of walking). In waddling gait, the feet are wide apart and walk resembles that of a duck
iv. Occasional hypoglycemic tetany.

Endocrine Functions of Pancreas

Chapter 69

- ISLETS OF LANGERHANS
- INSULIN
- GLUCAGON
- SOMATOSTATIN
- PANCREATIC POLYPEPTIDE
- REGULATION OF BLOOD GLUCOSE LEVEL
- APPLIED PHYSIOLOGY

ISLETS OF LANGERHANS

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

SOURCE OF SECRETION

Insulin is secreted by B cells or the β-cells in the islets of Langerhans of pancreas.

CHEMISTRY AND HALF-LIFE

Insulin is a polypeptide with 51 amino acids and a molecular weight of 5,808. It has two amino acid chains called α and β chains, which are linked by disulfide bridges. The α-chain of insulin contains 21 amino acids and β-chain contains 30 amino acids. The biological half-life of insulin is 5 minutes.

PLASMA LEVEL

Basal level of insulin in plasma is 10 μU/mL.

SYNTHESIS

Synthesis of insulin occurs in the rough endoplasmic reticulum of β-cells in islets of Langerhans. It is synthesized as **preproinsulin,** that gives rise to **proinsulin.** Proinsulin is converted into insulin and C peptide through a series of peptic cleavages. C peptide is a connecting peptide that connects α and β chains. At the time of secretion, C peptide is detached.

Preproinsulin → Proinsulin
Peptic cleavage ↓
Insulin

METABOLISM

Binding of insulin to insulin receptor is essential for its removal from circulation and degradation. Insulin is degraded in liver and kidney by a cellular enzyme called **insulin protease** or **insulin-degrading enzyme.**

ACTIONS OF INSULIN

Insulin is the important hormone that is concerned with the regulation of carbohydrate metabolism and blood glucose level. It is also concerned with the 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 glucose level. Insulin reduces the blood glucose level by its following actions on carbohydrate metabolism:

i. *Increases transport and uptake of glucose by the cells*

Insulin facilitates the transport of glucose from 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. But, it is not required for glucose uptake in some tissues such as brain (except hypothalamus), renal tubules, mucous membrane of intestine and RBCs. Insulin also increases the number of glucose transporters, especially GLUT 4 in the cell membrane.

Glucose transporters: Usually, glucose is transported into the cells by **sodium-glucose symport pump.** In addition to symport pump, most of the cells have another type of transport proteins called **glucose transporters (GLUT).** So far, seven types of GLUT are identified (GLUT 1–7). Among these, **GLUT4** is insulin sensitive and it is located in cytoplasmic vesicles. It is present in large numbers in muscle fibers and adipose cells.

When insulin-receptor complex is formed in the membrane of such cells, the vesicles containing GLUT4 are attracted towards the membrane and GLUT4 is released into the membrane. Now, GLUT4 starts transporting the glucose molecules from extracellular fluid (ECF) into the cell. The advantage of GLUT4 is that it transports glucose at a faster rate.

ii. *Promotes peripheral utilization of glucose*

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

iii. *Promotes storage of glucose – glycogenesis*

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

v. *Inhibits gluconeogenesis*

Insulin prevents gluconeogenesis, i.e. the formation of glucose from proteins by inhibiting the release of amino acids from muscle and by inhibiting the activities of enzymes involved in gluconeogenesis.

Thus, insulin decreases the blood glucose level by:

i. Facilitating transport and uptake of glucose by the cells
ii. Increasing the 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 by the following actions:

i. Facilitating the transport of amino acids into the cell from blood, by increasing the permeability of cell membrane for amino acids
ii. Accelerating protein synthesis by influencing the transcription of DNA and by increasing the translation of mRNA
iii. Preventing protein catabolism by decreasing the activity of cellular enzymes which act on proteins
iv. Preventing conversion of proteins into glucose.

Thus, insulin is responsible for the conservation and storage of proteins in the body.

3. On Fat Metabolism

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

Actions of insulin on fat metabolism are:

i. *Synthesis of fatty acids and triglycerides*

Insulin promotes the transport of excess glucose into cells, particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:

a. Glucose into fatty acids
b. Fatty acids into triglycerides.

ii. *Transport of fatty acids into adipose tissue*

Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. *Storage of fat*

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes which degrade the triglycerides.

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 cell and synthesis of proteins in the cells. It also has the **protein-sparing effect,** i.e. it causes conservation of proteins by increasing the glucose utilization by the tissues.

Houssay Animal

The importance of insulin and growth hormone in the growth of the body is demonstrated by Houssay animal. Houssay animal is one in which both anterior pituitary and pancreas are removed. Administration of either insulin or growth hormone alone does not induce growth in this animal. However, the administration of both the hormones stimulates the growth. This proves the synergistic actions of these two hormones on growth.

■ MODE OF ACTION OF INSULIN

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

Insulin Receptor

Insulin receptor is a glycoprotein with a molecular weight of 340,000. It is present in almost all the cells of the body.

Subunits of insulin receptor

Insulin receptor is a **tetramer,** formed by four glycoprotein subunits (two α-subunits and two β-subunits). The α-subunits protrude out of the cell and the β-subunits protrude inside the cell (Fig. 69.1). The α and β subunits are linked to each other by disulfide bonds. Intracellular surfaces of α-subunits have the enzyme activity – **protein kinase (tyrosine kinase)** activity.

When insulin binds with α-subunits of the receptor protein, the tyrosine kinase at the β-subunit (that protrudes into the cell) is activated by means of autophosphorylation.

Activated tyrosine kinase acts on many intracellular enzymes by phosphorylating or dephosphorylating them so that some of the enzymes are activated while others are inactivated.

Thus, insulin action is exerted on the target cells by the activation of some intracellular enzymes and by the inactivation of other enzymes.

■ REGULATION OF INSULIN SECRETION

Insulin secretion is mainly regulated by blood glucose level.

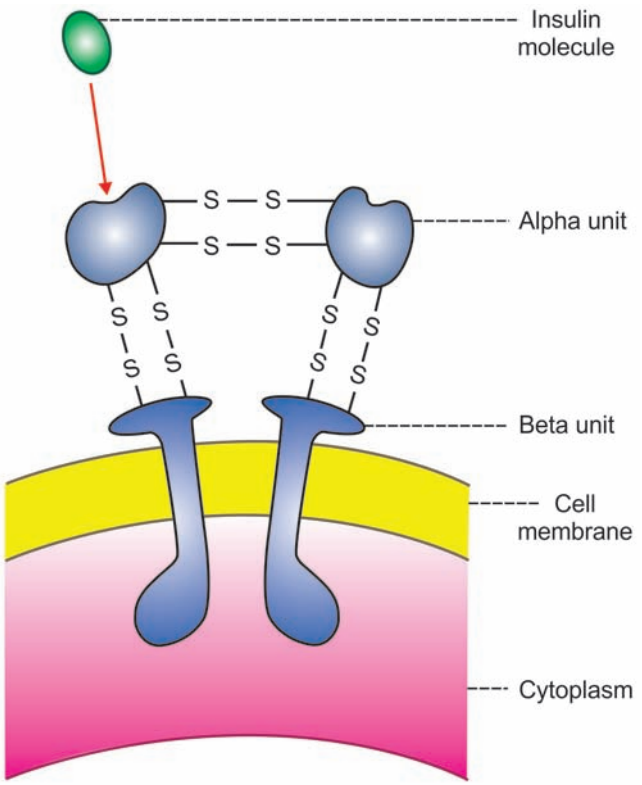


FIGURE 69.1: Diagram showing the structure of insulin receptor. S–S = Disulfide bond.

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

Biphasic effect of glucose

Action of blood glucose on insulin secretion is biphasic.

i. Initially, when blood glucose level increases after a meal, the release of insulin into blood increases rapidly. Within few minutes, concentration of insulin in plasma increases up to 100 μU/mL from the basal level of 10 μU/mL. It is because of release of insulin that is stored in pancreas. Later, within 10 to 15 minutes, the insulin concentration in the blood reduces to half the value, i.e. up to 40 to 50 μU/mL of plasma.

ii. After 15 to 20 minutes, the insulin secretion rises once again. This time it rises slowly but steadily. It reaches the maximum between 2 and 2½ hours. The prolonged increase in insulin release is due to the formation of new insulin molecules continuously from pancreas (Fig. 69.2).

2. *Role of Proteins*

Excess amino acids in blood also stimulate insulin secretion. Potent amino acids are **arginine** and **lysin.** Without any increase in blood glucose level, the amino acids alone can cause a slight increase in insulin secretion. However, amino acids potentiate the action of glucose on insulin secretion so that, in the presence of amino acids, elevated blood glucose level increases insulin secretion to a great extent.

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 such as gastrin, secretin, CCK and GIP.

5. *Role of Endocrine Hormones*

Diabetogenic hormones like glucagon, growth hormone and cortisol also stimulate insulin secretion, indirectly.

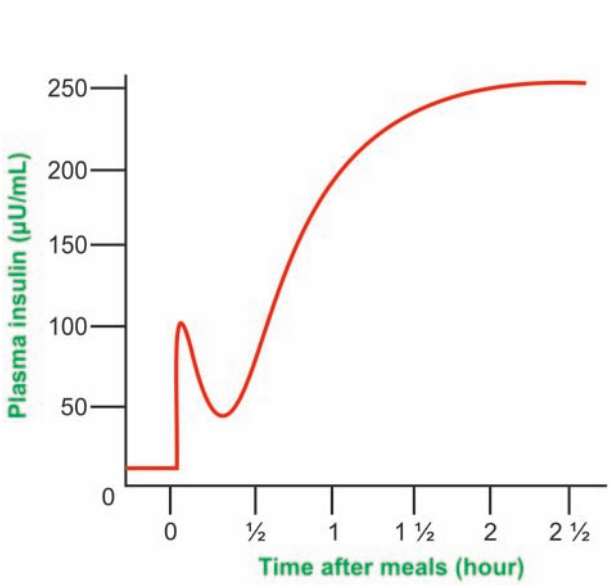


FIGURE 69.2: Changes in plasma level of insulin after meals. Increase in blood glucose level after meals produces biphasic effect on plasma level of insulin.

All these diabetogenic hormones increase the blood glucose level, which stimulates β-cells of islets of Langerhans. So insulin secretion is increased.

Prolonged hypersecretion of these hormones causes exhaustion of β-cells, resulting in diabetes mellitus.

6. *Role of Autonomic Nerves*

Stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion. Chemical neurotransmitter involved is acetylcholine. Stimulation of sympathetic nerves inhibits the secretion of insulin and the neurotransmitter is noradrenaline.

However, the role of these nerves on the regulation of insulin secretion under physiological conditions is not clear.

■ GLUCAGON

■ SOURCE OF SECRETION

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.

■ CHEMISTRY AND HALF-LIFE

Glucagon is a polypeptide with a molecular weight of 3,485. It contains 29 amino acids. Half-life of glucagon is 3 to 6 minutes.

■ SYNTHESIS

Glucagon is synthesized from the preprohormone precursor called **preproglucagon** in the α-cells of islets. Preproglucagon is converted into **proglucagon,** which gives rise to glucagon.

■ METABOLISM

About 30% of glucagon is degraded in liver and 20% in kidney. The cleaved glucagon fragments are excreted through urine. 50% of the circulating glucagon is degraded in blood itself by enzymes such as **serine** and **cysteine proteases.**

■ ACTIONS OF GLUCAGON

Actions of glucagon are antagonistic to those of insulin (Table 69.1). It increases the blood glucose level, peripheral utilization of lipids and the conversion of proteins into glucose.

1. *On Carbohydrate Metabolism*

Glucagon increases the blood glucose level by:

i. Increasing glycogenolysis in liver and releasing glucose from the liver cells into the blood.

TABLE 69.1: Differences between insulin and glucagon

Features	Insulin	Glucagon
Source of secretion	β-cells of islets of langerhans	α-cells of islets of langerhans
Action on carbohydrate metabolism	*Decreases blood glucose level by:* 1. Facilitating transport and uptake of glucose by all cells except liver cells 2. Increasing peripheral utilization of glucose 3. Increasing glycogenesis in liver and muscle 4. Preventing glycogenolysis 5. Preventing gluconeogenesis	*Increases blood glucose level by:* 1. Facilitating glucose transport into liver cells 2. Increasing glycogenolysis 3. Increasing gluconeogenesis
Action on protein metabolism	1. Facilitates amino acid transport 2. Accelerates protein synthesis 3. Prevents protein catabolism 4. Prevents conversion of proteins into glucose	1. Increases transport of amino acids into liver cells 2. Increases utilization of amino acids for gluconeogenesis
Action on fat metabolism	1. Increases synthesis and storage of fat 2. No ketogenic effect	1. Increases lipolysis 2. Promotes ketogenesis
Blood fatty acids	Decreases	Increases
Hypersecretion leads to	Hypoglycemia	Hyperglycemia
Hyposecretion leads to	Diabetes mellitus	Hypoglycemia

Glucagon does not induce glycogenolysis in muscle

ii. Increasing gluconeogenesis in liver by:
   a. Activating the enzymes, which convert pyruvate into phosphoenol pyruvate
   b. Increasing the transport of amino acids into the liver cells. The amino acids are utilized for glucose formation.

2. *On Protein Metabolism*

Glucagon increases the 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.

4. *Other Actions*

Glucagon:

i. Inhibits the secretion of gastric juice
ii. Increases the secretion of bile from liver.

■ MODE OF ACTION OF GLUCAGON

On the target cells (mostly liver cells), glucagon combines with receptor and activates adenyl cyclase via G protein. Adenyl cyclase causes the formation of cyclic adenosine monophosphate (AMP) which brings out the actions of glucagon. Glucagon receptor is a peptide with a molecular weight of 62,000.

■ REGULATION OF GLUCAGON SECRETION

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

1. *Role of Blood Glucose Level*

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 and more glucagon is released. Glucagon, in turn increases the blood glucose level. On the other hand, when blood glucose 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.

3. *Role of Other Factors*

Factors which increase glucagon secretion:

i. Exercise
ii. Stress
iii. Gastrin

iv. Cholecystokinin (CCK)
v. Cortisol.

Factors which inhibit glucagon secretion:

i. Somatostatin
ii. Insulin
iii. Free fatty acids
iv. Ketones.

SOMATOSTATIN

SOURCE OF SECRETION

Somatostatin is secreted from:

1. Hypothalamus
2. D cells (δ-cells) in islets of Langerhans of pancreas
3. D cells in stomach and upper part of small intestine.

CHEMISTRY AND HALF-LIFE

Somatostatin is a polypeptide. It is synthesized in two forms, namely somatostatin-14 (with 14 amino acids) and somatostatin-28 (with 28 amino acids). Both the forms have similar actions. Half-life of somatostatin is 2 to 4 minutes.

SYNTHESIS

Somatostatin is synthesized from the precursor prosomatostatin. Prosomatostatin is converted mostly into somatostatin-14 in the D cells of islets in pancreas. However, in the intestine, large amount of somatostatin-28 is produced from prosomatostatin.

METABOLISM

Somatostatin is degraded in liver and kidney.

ACTIONS OF SOMATOSTATIN

1. Somatostatin acts within islets of Langerhans and, inhibits β and α 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 gastrin, CCK, GIP and VIP
4. Hypothalamic somatostatin inhibits the secretion of GH and TSH from anterior pituitary. That is why, it is also called **growth hormone-inhibitory hormone** (GHIH).

MODE OF ACTION OF SOMATOSTATIN

Somatostatin brings out its actions through cAMP.

REGULATION OF SECRETION OF SOMATOSTATIN

Pancreatic Somatostatin

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

Gastrointestinal Tract Somatostatin

Secretion of somatostatin in GI tract is increased by the presence of chyme-containing glucose and proteins in stomach and small intestine.

PANCREATIC POLYPEPTIDE

SOURCE OF SECRETION

Pancreatic polypeptide is secreted by F cells or PP cells in the islets of Langerhans of pancreas. It is also found in small intestine.

CHEMISTRY AND HALF-LIFE

Pancreatic polypeptide is a polypeptide with 36 amino acids. Its half-life is 5 minutes.

SYNTHESIS

Pancreatic polypeptide is synthesized from pre-prohormone precursor called **prepropancreatic** polypeptide in the PP cells of islets.

METABOLISM

Pancreatic polypeptide is degraded and removed from circulation mainly in kidney.

ACTIONS OF PANCREATIC POLYPEPTIDE

Exact physiological action of pancreatic polypeptide is not known. It is believed to increase the secretion of glucagon from α-cells in islets of Langerhans.

MODE OF ACTION OF PANCREATIC POLYPEPTIDE

Pancreatic polypeptide brings out its actions through cAMP.

REGULATION OF SECRETION

Secretion of pancreatic polypeptide is stimulated by the presence of chyme containing more proteins in the small intestine.

REGULATION OF BLOOD GLUCOSE LEVEL (BLOOD GLUCOSE LEVEL)

NORMAL BLOOD GLUCOSE LEVEL

In normal persons, blood glucose level is controlled within a narrow range. In the early morning after overnight **fasting,** the blood glucose level is low ranging between 70 and 110 mg/dL of blood. Between first and second hour after meals **(postprandial),** the blood glucose level rises to 100 to 140 mg/dL. Glucose level in blood is brought back to normal at the end of second hour after the meals.

Blood glucose 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 glucose level. Among all the hormones, insulin is the only hormone that reduces the blood glucose level and it is called the **antidiabetogenic hormone.** The hormones which increase blood glucose level are called **diabetogenic hormones** or **anti-insulin hormones.**

Necessity of Regulation of Blood Glucose Level

Regulation of blood glucose (sugar) 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 GLUCOSE LEVEL

Liver serves as an important **glucose buffer system.** When blood glucose level increases after a meal, the excess glucose is converted into glycogen and stored in liver. Afterwards, when blood glucose 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.

ROLE OF INSULIN IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Insulin decreases the blood glucose level and it is the only antidiabetic hormone available in the body (Refer the actions of insulin on carbohydrate metabolism in this Chapter).

ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Glucagon increases the blood glucose level (Refer actions of glucagon on carbohydrate metabolism in this Chapter).

ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Other hormones which increase the blood glucose level are:

1. Growth hormone (Chapter 66)
2. Thyroxine (Chapter 67)
3. Cortisol (Chapter 70)
4. Adrenaline (Chapter 71).

Thus, liver helps to maintain the blood glucose level by storing glycogen when blood glucose level is high after meals; and by releasing glucose, when blood glucose level is low after 2 to 3 hours of food intake. Insulin helps to control the blood glucose level, especially after meals, when it increases. Glucagon and other hormones help to maintain the blood glucose level by raising it in between the meals.

APPLIED PHYSIOLOGY

HYPOACTIVITY – DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by high blood glucose level, associated with other manifestations. **'Diabetes'** means **'polyuria'** and **'mellitus'** means **'honey'.** The name 'diabetes mellitus' was coined by Thomas Willis, who discovered sweetness of urine from diabetics in 1675.

In most of the cases, diabetes mellitus develops due to deficiency of insulin.

Classification of Diabetes Mellitus

There are several forms of diabetes mellitus, which occur due to different causes. Diabetes may be primary or secondary. Primary diabetes is unrelated to another disease. Secondary diabetes occurs due to damage or disease of pancreas by another disease or factor.

Recent classification divides primary diabetes mellitus into two types, Type I and Type II. Differences between the two types are given in Table 69.2.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to deficiency of insulin because of destruction of β-cells in islets of Langerhans. This type of diabetes mellitus may occur at any age of life. But, it usually occurs before 40 years of age and the persons affected by this require insulin injection. So it is also called **insulin-dependent diabetes mellitus (IDDM).** When it develops at infancy or childhood, it is called juvenile diabetes.

Type I diabetes mellitus develops rapidly and progresses at a rapid phase. It is not associated with **obesity,** but may be associated with **acidosis** or ketosis.

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. It is due to the development of antibodies against β-cells (Refer Chapter 17 for details).

Other forms of type 1 diabetes mellitus

1. **Latent autoimmune diabetes in adults (LADA):** LADA or slow onset diabetes has slow onset and slow progress than IDDM and it occurs in later life after 35 years. It may be difficult to distinguish LADA from type II diabetes mellitus, since pancreas takes longer period to stop secreting insulin.
2. **Maturity onset diabetes** in young individuals **(MODY):** It is a rare inherited form of diabetes mellitus that occurs before 25 years. It is due to hereditary defects in insulin secretion.

Type II Diabetes Mellitus

Type II diabetes mellitus is due to insulin resistance (failure of insulin receptors to give response to insulin). So, the body is unable to use insulin. About 90% of diabetic patients have type II diabetes mellitus. It usually occurs after 40 years. Only some forms of Type II diabetes require insulin. In most cases, it can be controlled by oral hypoglycemic drugs. So it is also called **noninsulin-dependent diabetes mellitus (NIDDM).**

Type II diabetes mellitus may or may not be associated with ketosis, but often it is associated with obesity.

Causes for type II diabetes mellitus

In this type of diabetes, the structure and function of β-cells and blood level of insulin are normal. But insulin receptors may be less, absent or abnormal, resulting in insulin resistance.

Common causes of insulin resistance are:

1. Genetic disorders (significant factors causing type II diabetes mellitus)
2. Lifestyle changes such as bad eating habits and physical inactivity, leading to obesity
3. Stress.

Other forms of type II diabetes mellitus

1. Gestational diabetes: It occurs during pregnancy. It is due to many factors such as hormones secreted during pregnancy, obesity and lifestyle before and during pregnancy. Usually, diabetes disappears after delivery of the child. However, the woman has high risk of development of type II diabetes later.
2. **Pre-diabetes:** It is also called **chemical, subclinical, latent** or **borderline diabetes.** It is the stage between normal condition and diabetes. The person does not show overt (observable) symptoms of diabetes but there is an increase in blood glucose level. Though pre-diabetes is reversible, the affected persons are at a high risk of developing type II diabetes mellitus.

TABLE 69.2: Differences between type I and type II diabetes mellitus

Features	Type I (IDDM)	Type II (NIDDM)
Age of onset	Usually before 40 year	Usually after 40 year
Major cause	Lack of insulin	Lack of insulin receptor
Insulin deficiency	Yes	Partial deficiency
Immune destruction of β-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

Secondary Diabetes Mellitus

Secondary diabetes mellitus is rare and only about 2% of diabetic patients have secondary diabetes. It may be temporary or may become permanent due to the underlying cause.

Causes of secondary diabetes mellitus

1. Endocrine disorders such as gigantism, acromegaly and Cushing's syndrome.
   Hyperglycemia in these conditions causes excess stimulation of β-cells. Constant and excess stimulation, in turn causes burning out and degeneration of β-cells. The β-cell exhaustion leads to permanent diabetes mellitus.
2. Damage of pancreas due to disorders such as chronic pancreatitis, cystic fibrosis and hemochromatosis (high iron content in body causing damage of organs)
3. Pancreatectomy (surgical removal)
4. Liver diseases such as hepatitis C and fatty liver
5. Autoimmune diseases such as celiac disease
6. Excessive use of drugs like antihypertensive drugs (beta blockers and diuretics), steroids, oral contraceptives, chemotherapy drugs, etc.
7. Excessive intake of alcohol and opiates.

Signs and Symptoms of Diabetes Mellitus

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

1. Increased blood glucose 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*

Glucosuria is the loss of glucose in urine. 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*

Osmotic diuresis is the diuresis caused by osmotic effects. Excess glucose in the renal tubules develops osmotic effect. 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 the frequency of voiding urine is called polyuria. It is due to the osmotic diuresis caused by increase in blood glucose level.

4. *Polydipsia*

Increase in water intake is called polydipsia. Excess loss of water decreases the water content and increases the 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*

Loss of strength is called asthenia. Body becomes very weak because of this. Asthenia occurs due to protein depletion, which is caused by lack of insulin. Lack of insulin causes decrease in protein synthesis and increase in protein breakdown, resulting in protein depletion. Protein depletion also occurs due to the utilization of proteins for energy in the absence of glucose utilization.

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.

One more reason for acidosis is that the ketoacids are excreted in combination with sodium ions through urine **(ketonuria).** Sodium is exchanged for hydrogen ions, which diffuse from the renal tubules into ECF adding 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 **life-threatening** 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*

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

11. *Coma*

Due to Kussmaul breathing, 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 the blood glucose 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. Development of these complications is directly proportional to the degree and duration of hyperglycemia. However, the patients with well-controlled diabetes can postpone the onset or reduce the rate of progression of these complications.

Initially, the untreated chronic hyperglycemia affects the blood vessels, resulting in vascular complications like atherosclerosis. Vascular complications are responsible for the development of most of the complications of diabetes such as:

1. Cardiovascular complications like:
   i. Hypertension
   ii. 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 glucose
2. Postprandial blood glucose
3. Glucose tolerance test (GTT)
4. Glycosylated (glycated) hemoglobin.

Determination of glycosylated hemoglobin is commonly done to monitor the glycemic control of the persons already diagnosed with diabetes mellitus.

Abnormal response in diagnostic tests

Abnormal response in diagnostic tests occurs in conditions like **pre-diabetes** (see above). There is an increased fasting blood glucose level or impaired (decreased) glucose tolerance.

Treatment for Diabetes Mellitus

Type I diabetes mellitus

Type I diabetes mellitus is treated by exogenous insulin. Since insulin is a polypeptide, it is degraded in GI tract if taken orally. So, it is generally administered by subcutaneous injection.

Type II diabetes mellitus

Type II diabetes mellitus is treated by oral hypoglycemic drugs. Patients with longstanding severe diabetes mellitus may require a combination of oral hypoglycemic drugs with insulin to control the hyperglycemia.

Oral hypoglycemic drugs are classified into three types.

1. *Insulin secretagogues:* These drugs decrease the blood glucose level by stimulating insulin secretion from β-cells. Sulfonylureas (tolbutamide, gluburide, glipizide, etc.) are the commonly available insulin secretagogues
2. *Insulin sensitizers:* These drugs decrease the blood glucose level by facilitating the insulin action in the target tissues. Examples are biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone)
3. *Alpha glucosidase inhibitors:* These drugs control blood glucose level by inhibiting α-glucosidase. This intestinal enzyme is responsible for the conversion of dietary and other complex carbohydrates into glucose and other monosaccharides, which can be absorbed from intestine. Examples of α-glucosidase inhibitors are acarbose and meglitol.

■ 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*

Blood glucose level falls below 50 mg/dL.

2. *Manifestations of central nervous system*

Manifestations of central nervous system occur when the blood glucose 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 the damage of neurons.

Chapter 70

Adrenal Cortex

- IMPORTANCE OF ADRENAL GLANDS
- FUNCTIONAL ANATOMY
- HISTOLOGY OF ADRENAL CORTEX
- HORMONES
- SYNTHESIS, TRANSPORT AND FATE OF ADRENOCORTICAL HORMONES
- MINERALOCORTICOIDS
- GLUCOCORTICOIDS
- ADRENAL SEX HORMONES
- EXOGENOUS STEROIDS
- APPLIED PHYSIOLOGY

IMPORTANCE OF ADRENAL GLANDS

Adrenal glands are called the **'life-saving glands'** or **'essential endocrine glands'.** It is because the absence of adrenocortical hormones causes death within 3 to 15 days and absence of adrenomedullary hormones, drastically decreases the resistance to mental and physical stress.

FUNCTIONAL ANATOMY OF ADRENAL GLANDS

There are two adrenal glands. Each gland is situated on the upper pole of each kidney. Because of the situation, adrenal glands are otherwise called **suprarenal glands.** Each gland weighs about 4 g.

PARTS OF ADRENAL GLAND

Adrenal gland (Fig. 70.1) is made of two distinct parts:

1. **Adrenal cortex:** Outer portion, constituting 80% of the gland
2. **Adrenal medulla:** Central portion, constituting 20% of the gland.

These two parts are different from each other in development, structure and functions. Adrenal medulla develops from the neural crest, which gives origin to sympathetic nervous system. So, its secretions and functions resemble that of sympathetic nervous system. Adrenal cortex develops from the **mesonephros,** which give rise to the renal tissues. It secretes entirely a different group of hormones known as **corticosteroids.**

HISTOLOGY OF ADRENAL CORTEX

Adrenal cortex is formed by three layers of structure. Each layer is distinct from one another.

1. Outer zona glomerulosa
2. Middle zona fasciculata
3. Inner zona reticularis.

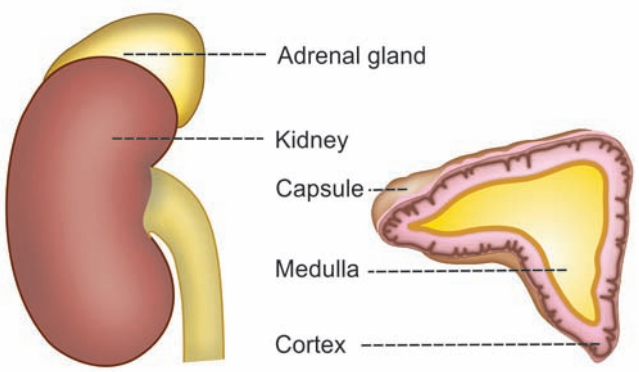


FIGURE 70.1: Adrenal gland

HORMONES OF ADRENAL CORTEX

Adrenocortical hormones are steroids in nature, hence the name **'corticosteroids'.** Based on their functions, corticosteroids are classified into three groups:

1. Mineralocorticoids
2. Glucocorticoids
3. Sex hormones.

SYNTHESIS, TRANSPORT AND FATE OF ADRENOCORTICAL HORMONES

SYNTHESIS

All adrenocortical hormones are steroid in nature and are synthesized mainly from cholesterol that is absorbed directly from the circulating blood. Small quantity of cholesterol is also synthesized within the cortical cells from acetylcoenzyme A (acetyl-CoA). Synthesis of aldosterone is given in Fig. 70.2.

TRANSPORT

Mineralocorticoids

Mineralocorticoids are transported in blood by binding with plasma proteins, especially globulins. The binding is loose and 50% of these hormones are present in free form.

Glucocorticoids

Glucocorticoids are transported by a special plasma protein known as **glucocorticoids-binding globulin** or **transcortin.** Ninety four percent of glucocorticoids are transported by this protein, whereas about 6% of them are found free in plasma. Albumin plays a very little role in glucocorticoid transport.

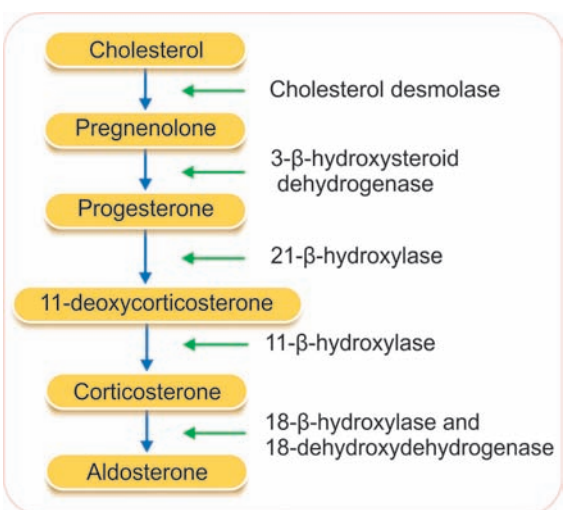


FIGURE 70.2: Synthesis of aldosterone

Sex Hormones

Adrenal sex hormones are transported by another special plasma protein known as **sex hormone-binding globulin.**

FATE OF CORTICOSTEROIDS

Corticosteroids are degraded mainly in the liver and conjugated to form glucuronides and to a lesser extent, form sulfates. About 25% of corticosteroids are excreted in bile and feces and remaining 75%, in the urine.

MINERALOCORTICOIDS

Mineralocorticoids are the corticosteroids that act on the minerals (electrolytes), particularly sodium and potassium.

Mineralocorticoids are:

1. Aldosterone
2. 11-deoxycorticosterone.

SOURCE OF SECRETION

Mineralocorticoids are secreted by zona glomerulosa of adrenal cortex.

CHEMISTRY AND HALF-LIFE

Mineralocorticoids are C_{21} steroids having 21 carbon atoms. Half-life of mineralocorticoids is 20 minutes.

DAILY OUTPUT AND PLASMA LEVEL

Daily output and plasma level of mineralocorticoids are given in Table 70.1.

FUNCTIONS OF MINERALOCORTICOIDS

Ninety percent of mineralocorticoid activity is provided by aldosterone.

Life-saving Hormone

Aldosterone is very essential for life and it maintains the osmolarity and volume of ECF. It is usually called

TABLE 70.1: Daily output and plasma level of mineralocorticoids

Hormone	Daily output (µg)	Plasma level (µg/dL)
Aldosterone	0.15	0.006
11-Deoxycorticosterone	0.2	0.006

life-saving hormone because, its absence causes death within 3 days to 2 weeks. Aldosterone has three important functions.

It increases:

1. Reabsorption of sodium from renal tubules
2. Excretion of potassium through renal tubules
3. Secretion of hydrogen into renal tubules.

Actions of aldosterone are:

1. *On Sodium Ions*

Aldosterone acts on the distal convoluted tubule and the collecting duct and increases the reabsorption of sodium. During hypersecretion of aldosterone, the loss of sodium through urine is only few milligram per day. But during hyposecretion of aldosterone, the loss of sodium through urine increases **(hypernatriuria)** up to about 20 g/day. It proves the importance of aldosterone in regulation of sodium ion concentration and osmolality in the body.

2. *On Extracellular Fluid Volume*

When sodium ions are reabsorbed from the renal tubules, simultaneously water is also reabsorbed. Water reabsorption is almost equal to sodium reabsorption; so the net result is the increase in ECF volume.

Even though aldosterone increases the sodium reabsorption from renal tubules, the concentration of sodium in the body does not increase very much because water is also reabsorbed simultaneously.

But still, there is a possibility for mild increase in concentration of sodium in blood (mild hypernatremia). It induces thirst, leading to intake of water which again increases the ECF volume and blood 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 administration or 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 volume of ECF 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 (Fig. 70.3).

Besides ANP, two more natriuretic peptides called **brain natriuretic peptide** (BNP) and **C-type natriuretic peptide** (CNP) are also secreted by cardiac muscle (Chapter 72). BNP and CNP also have similar actions of ANP on sodium excretion.

Significance of aldosterone escape

Because of aldosterone escape, edema does not occur.

4. *On Potassium Ions*

Aldosterone increases the potassium excretion through the renal tubules. When aldosterone is deficient, the potassium ion concentration in ECF increases leading to hyperkalemia. Hyperkalemia results in serious cardiac toxicity, with weak contractions of heart and development of arrhythmia. In very severe conditions, it may cause cardiac death. When aldosterone secretion increases, it leads to **hypokalemia** and **muscular weakness.**

5. *On Hydrogen Ion Concentration*

While increasing the sodium reabsorption from renal tubules, aldosterone causes tubular secretion of hydro-

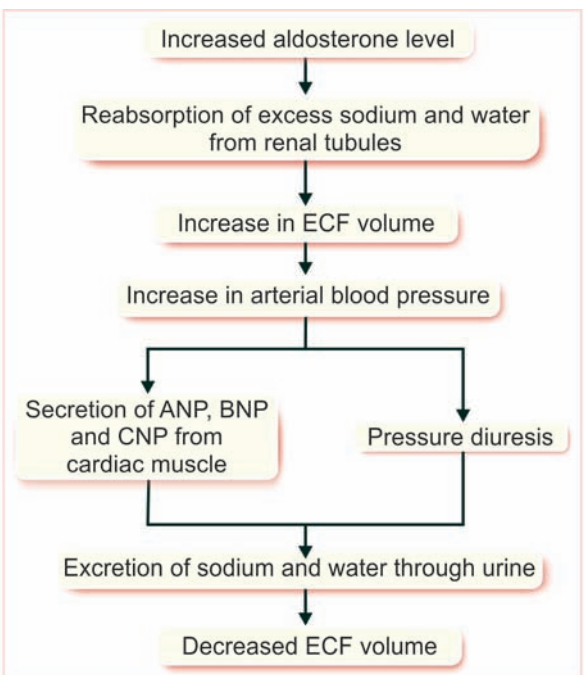


FIGURE 70.3: Aldosterone escape

gen ions. To some extent, secretion of hydrogen ions is in exchange for sodium ions. It obviously reduces the hydrogen ion concentration in the ECF. In normal conditions, aldosterone is essential to maintain acid-base balance in the body. In hypersecretion, it causes **alkalosis** and in hyposecretion, it causes **acidosis.**

6. *On Sweat Glands and Salivary Glands*

Aldosterone has almost the similar effect on sweat glands and salivary glands as it shows on renal tubules. Sodium is reabsorbed from sweat glands under the influence of aldosterone, thus the loss of sodium from the body is prevented. Same effect is shown on saliva also. Thus, aldosterone helps in the conservation of sodium in the body.

7. *On Intestine*

Aldosterone increases sodium absorption from the intestine, especially from colon and prevents loss of sodium through feces. Aldosterone deficiency leads to **diarrhea,** with loss of sodium and water.

■ MODE OF ACTION

Aldosterone acts through the messenger RNA (mRNA) mechanism.

Sequence of Events

1. Since aldosterone is lipid soluble, it diffuses readily into the cytoplasm of the tubular epithelial cells through the lipid layer of the cell membrane
2. In the cytoplasm, aldosterone binds with the specific receptor protein
3. Aldosterone-receptor complex diffuses into the nucleus where it binds to deoxyribonucleic acid (DNA) and causes formation of mRNA
4. The mRNA diffuses back into the cytoplasm and causes protein synthesis along with ribosomes. Most of the synthesized proteins are in the form of enzymes. One of such enzymes is sodium-potassium ATPase, which helps in the transport of sodium and potassium.

■ REGULATION OF SECRETION

Aldosterone secretion is regulated by four important factors (Fig. 70.4) which are given below in the order of their potency:

1. Increase in potassium ion (K^+) concentration in ECF
2. Decrease in sodium ion (Na^+) concentration in ECF
3. Decrease in ECF volume
4. Adrenocorticotropic hormone (ACTH).

Increase in the concentration of potassium ions is the most effective stimulant for aldosterone secretion.

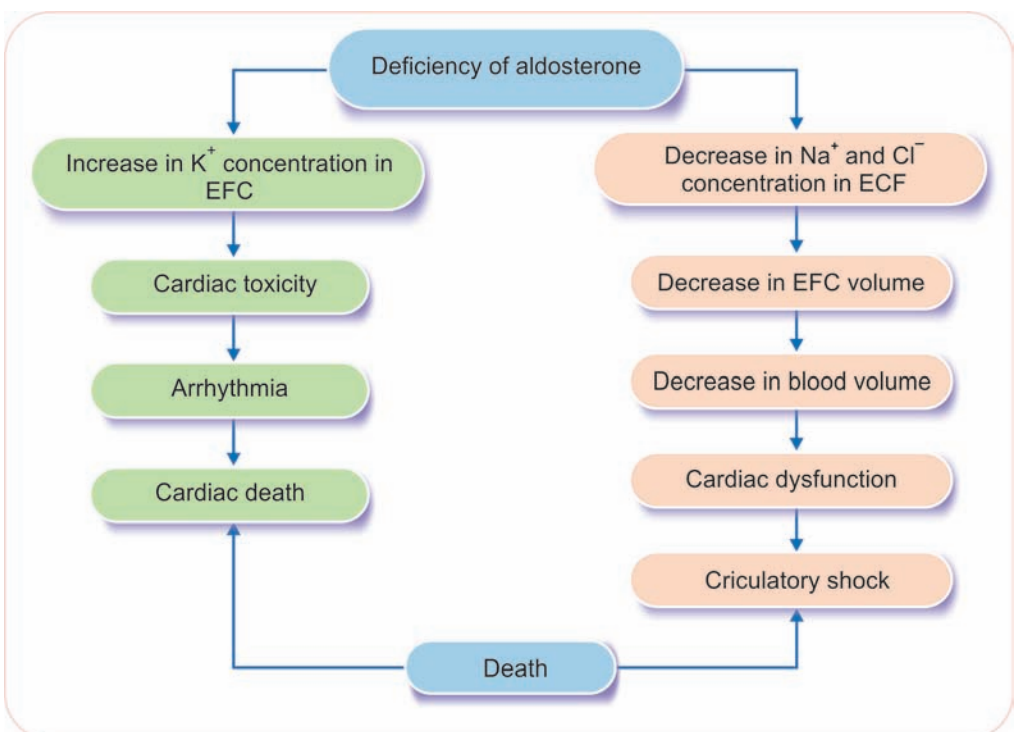


FIGURE 70.4: Importance of aldosterone. ECF = Extracellular fluid.

It acts directly on the 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. This leads 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 (Fig. 70.5).

Adrenocorticotropic hormone mainly stimulates the secretion of glucocorticoids. It has only a mild stimulating effect on aldosterone secretion.

GLUCOCORTICOIDS

Glucocorticoids act mainly on glucose metabolism.

Glucocorticoids are:

1. Cortisol
2. Corticosterone
3. Cortisone.

SOURCE OF SECRETION

Glucocorticoids are secreted mainly by zona fasciculata of adrenal cortex. A small quantity of glucocorticoids is also secreted by zona reticularis. Synthesis of cortisol is given in Fig. 70.6.

CHEMISTRY AND HALF-LIFE

Glucocorticoids are C_{21} steroids having 21 carbon atoms. Half-life of cortisol is 70 to 90 minutes and that of corticosterone is 50 minutes. Half-life of cortisone is not known.

DAILY OUTPUT AND PLASMA LEVEL

Daily output and plasma level of glucocorticoids are given in Table 70.2.

FUNCTIONS OF GLUCOCORTICOIDS

Cortisol or hydrocortisone is more potent and it has 95% of glucocorticoid activity. Corticosterone is less potent,

TABLE 70.2: Daily output and plasma level of glucocorticoids

Hormone	Daily output (µg)	Plasma level (µg/dL)
Cortisol	10.0	13.9
Corticosterone	3.0	0.4

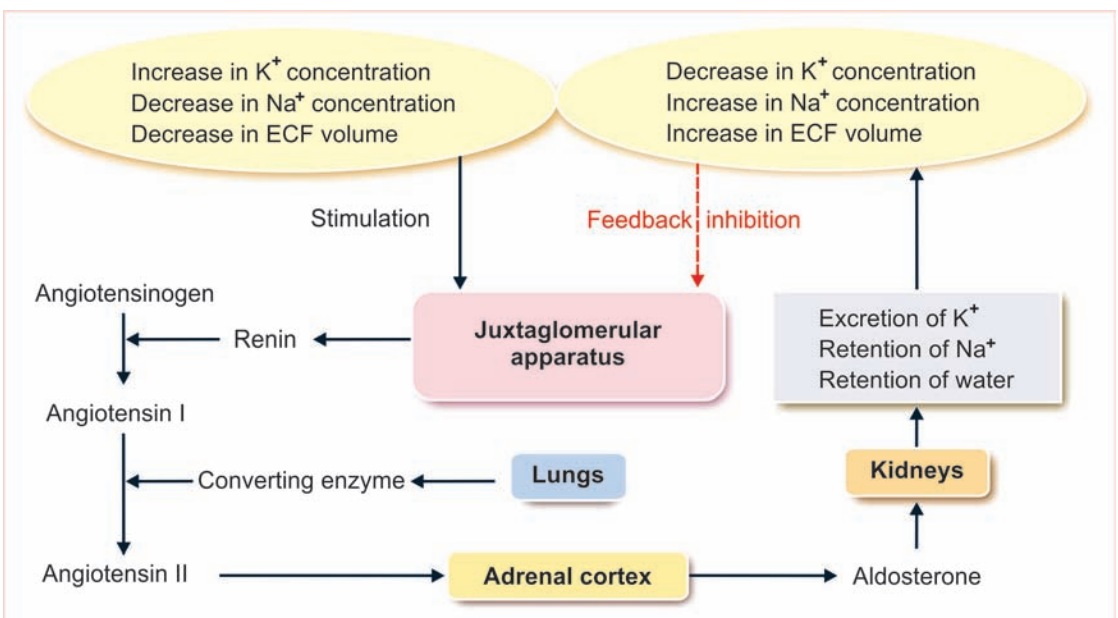


FIGURE 70.5: Regulation of aldosterone secretion

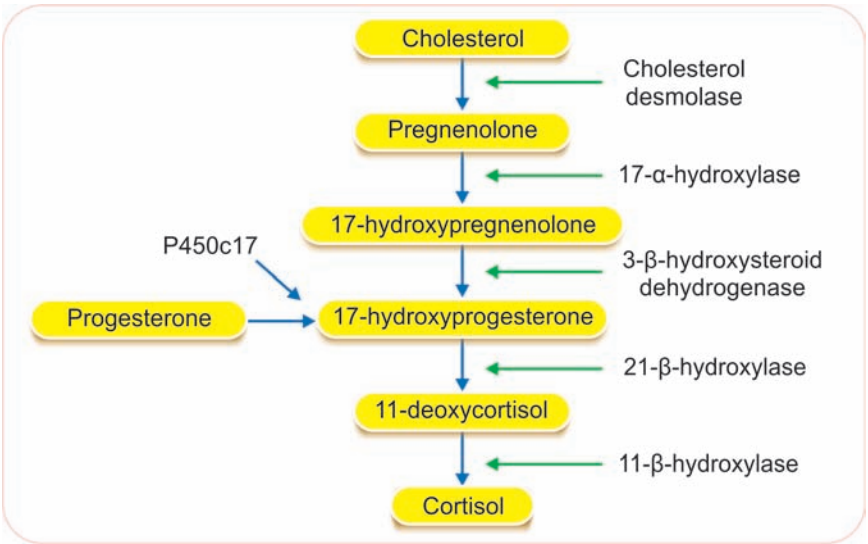


FIGURE 70.6: Synthesis of cortisol

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. Removal of adrenal glands in human beings and animals causes disturbances of metabolism. Exposure to even mild harmful stress after **adrenalectomy,** leads to **collapse** and **death.**

1. *On Carbohydrate Metabolism*

Glucocorticoids increase the blood glucose level by two ways:

i. By promoting gluconeogenesis in liver from amino acids: Glucocorticoids enhance the breakdown of proteins in extrahepatic cells, particularly the muscle. It is followed by release of amino acids into circulation. From blood, amino acids enter the liver and get converted into glucose (gluconeogenesis)
ii. By inhibiting the uptake and utilization of glucose by peripheral cells: This action is called **anti-insulin action** of glucocorticoids.

Hypersecretion of glucocorticoids increases the blood glucose level, resulting in hyperglycemia, glucosuria and adrenal diabetes. Hyposecretion of these hormones causes hypoglycemia and fasting during adrenal insufficiency will be fatal. It decreases blood glucose level to a great extent, resulting in death.

2. *On Protein Metabolism*

Glucocorticoids promote the catabolism of proteins, leading to:

i. Decrease in cellular proteins
ii. Increase in plasma level of amino acids
iii. Increase in protein content in liver.

Glucocorticoids cause catabolism of proteins by the following methods:

i. By releasing amino acids from body cells (except liver cells), into the blood
ii. By increasing the uptake of amino acids by hepatic cells from blood. In hepatic cells, the amino acids are used for the synthesis of proteins and carbohydrates (gluconeogenesis).

Thus, glucocorticoids cause mobilization of proteins from tissues other than liver. In hypersecretion of glucocorticoids, there is excess catabolism of proteins, resulting in muscular wasting and **negative nitrogen balance.**

3. *On Fat Metabolism*

Glucocorticoids cause mobilization and redistribution of fats. Actions on fats are:

i. Mobilization of fatty acids from adipose tissue
ii. Increasing the concentration of fatty acids in blood
iii. Increasing the utilization of fat for energy.

Glucocorticoids decrease the utilization of glucose. At the same time, these hormones mobilize fats and make the fatty acids available for utilization, by which energy is liberated. It leads to the formation of a large amount of ketone bodies. It is called **ketogenic effect** of glucocorticoids.

Hypersecretion of glucocorticoids causes an abnormal type of **obesity** by increasing the deposition of fat in certain areas such as abdomen, chest, face and buttocks.

4. *On Water Metabolism*

Glucocorticoids play an important role in the maintenance of water balance, by accelerating excretion of water. The adrenal insufficiency causes water retention and **water intoxication** after intake of large quantity of water.

5. *On Mineral Metabolism*

Glucocorticoids enhance the retention of sodium and to lesser extent, increase the excretion of potassium. Thus, hypersecretion of glucocorticoids causes edema, hypertension, hypokalemia and muscular weakness. Glucocorticoids decrease the blood calcium by inhibiting its absorption from intestine and increasing the excretion through urine.

6. *On Bone*

Glucocorticoids stimulate the bone resorption **(osteoclastic activity)** and inhibit bone formation and mineralization **(osteoblastic activity).** So, in hypersecretion of glucocorticoids, **osteoporosis** occurs.

7. *On Muscles*

Glucocorticoids increase the catabolism of proteins in muscle. So, hypersecretion causes muscular weakness due to loss of protein.

8. *On Blood Cells*

Glucocorticoids decrease the number of circulating eosinophils by increasing the destruction of eosinophils in reticuloendothelial cells. These hormones also decrease the number of basophils and lymphocytes and increase the number of circulating neutrophils, RBCs and platelets.

9. *On Vascular Response*

Presence of glucocorticoids is essential for the constrictor action of adrenaline and noradrenaline. In adrenal insufficiency, the blood vessels fail to respond to adrenaline and noradrenaline, leading to vascular collapse.

10. *On Central Nervous System*

Glucocorticoids are essential for normal functioning of nervous system. Insufficiency of these hormones causes personality changes like irritability and lack of concentration. Sensitivity to olfactory and taste stimuli increases in adrenal insufficiency.

11. *Permissive Action of Glucocorticoids*

Permissive action of glucocorticoids refers to execution of actions of some hormones only in the presence of glucocorticoids.

Examples:

i. Calorigenic effect of glucagon
ii. Lipolytic effect of catecholamines
iii. Vascular effects of catecholamines
iv. Bronchodilator effect of catecholamines.

12. *On Resistance to Stress*

Exposure to any type of stress, either physical or mental, increases the secretion of adrenocorticotropic hormone (ACTH), which in turn increases glucocorticoid secretion. The increase in glucocorticoid level is very essential for survival during stress conditions, as it offers high resistance to the body against stress.

Glucocorticoids enhance the resistance by the following ways:

i. Immediate release and transport of amino acids from tissues to liver cells for the synthesis of new proteins and other substances, which are essential to withstand the stress
ii. Release of fatty acids from cells for the production of more energy during stress
iii. Enhancement of vascular response to catecholamines and fatty **acid-mobilizing action** of catecholamines, which are necessary to withstand the stress
iv. Prevention of severity of other changes in the body caused by stress.

13. *Anti-inflammatory Effects*

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. These substances produce series of reactions in the affected area:

i. Chemical substances such as histamine, serotonin, leukotrienes, prostaglandins and bradykinin, which are released from damaged tissue cause vasodilatation and **erythema** (rushing of blood) in the affected area
ii. From blood, many leukocytes, particularly neutrophils and monocytes infiltrate the affected area. Leukocytes play an important role in the **defensive mechanism** (Chapter 16)
iii. Vasodilator substances released in the affected area increase the permeability of capillary membrane, resulting in oozing out of fluid from blood into interstitial space
iv. Coagulation occurs in the interstitial fluid because of fibrinogen and other proteins, which are leaked out from blood
v. Finally, **edema** occurs in that area which may be non-pitting type because of hard clot formation.

Glucocorticoids prevent the inflammatory reactions. Even if inflammation has already started, the glucocorticoids cause an early resolution of inflammation and rapid healing.

Glucocorticoids prevent the inflammatory changes by:

i. Inhibiting the release of chemical substances from damaged tissues and thereby preventing vasodilatation and erythema in the affected area
ii. Causing vasoconstriction through the permissive action on catecholamines. This also prevents rushing of blood to the injured area
iii. Decreasing the permeability of capillaries and preventing loss of fluid from plasma into the affected tissue
iv. Inhibiting the migration of leukocytes into the affected area
v. Suppressing T cells and other leukocytes, so that there is reduction in the reactions of tissues which enhance the inflammatory process.

14. *Anti-allergic Actions*

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

15. *Immunosuppressive Effects*

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

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 bind with receptors to form hormone-receptor complex, which activates DNA to form mRNA. mRNA causes synthesis of enzymes, which alter the cell function.

■ REGULATION OF SECRETION

Anterior pituitary regulates glucocorticoid secretion by secreting adrenocorticotropic hormone (ACTH). ACTH secretion is regulated by hypothalamus through corticotropin-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 and it plays only a minor role in the regulation of mineralocorticoid secretion.

Source of secretion

ACTH is secreted by the basophilic chromophilic cells of anterior pituitary.

Chemistry, plasma level and half-life

ACTH is a single chained polypeptide with 39 amino acids. The daily output of this hormone is 10 ng and the concentration in plasma is 3 ng/dL. Half-life of ACTH is 10 minutes.

Synthesis

ACTH is synthesized from a protein called prepro-opiomelanocortin (POMC). Along with ACTH, the POMC gives rise to some more byproducts called β-lipotropin, γ-lipotropin and β-endorphin. Two more byproducts, namely **α-melanocyte-stimulating hormone** (α-MSH) and **β-melanocyte-stimulating hormone** (β-MSH) are also secreted in animals. However, MSH activity is shown by ACTH and other byproducts from POMC in human beings.

Actions

ACTH is necessary for the structural integrity and secretory activity of adrenal cortex. It has other functions also.

Actions of ACTH on adrenal cortex (Adrenal actions)

1. Maintenance of structural integrity and vascularization of zona fasciculata and zona reticularis of adrenal cortex. In hypophysectomy, these two layers in the adrenal cortex are atrophied
2. Conversion of cholesterol into pregnenolone, which is the precursor of glucocorticoids. Thus, adrenocorticotropic hormone is responsible for the synthesis of glucocorticoids
3. Release of glucocorticoids
4. Prolongation of glucocorticoid action on various cells.

Other (Nonadrenal) actions of ACTH

1. Mobilization of fats from tissues
2. Melanocyte-stimulating effect. Because of structural similarity with melanocyte-stimulating hormone (MSH), ACTH shows melanocyte-stimulating effect. It causes darkening of skin by acting on melanophores, which are the cutaneous pigment cells containing melanin.

Mode of action of ACTH

ACTH acts by the formation of cyclic AMP.

Role of Hypothalamus

Hypothalamus also plays an important role in the regulation of cortisol secretion by controlling the ACTH secretion through **corticotropin-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 the 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 (Fig. 70.7).

Circadian rhythm of ACTH

ACTH secretion follows circadian rhythm (Chapter 149), i.e. it varies in different periods of the day. The rate of secretion of both ACTH and CRF is high in the morning and low in the evening. Hypothalamus plays an important role in the **circadian fluctuations of ACTH** secretion.

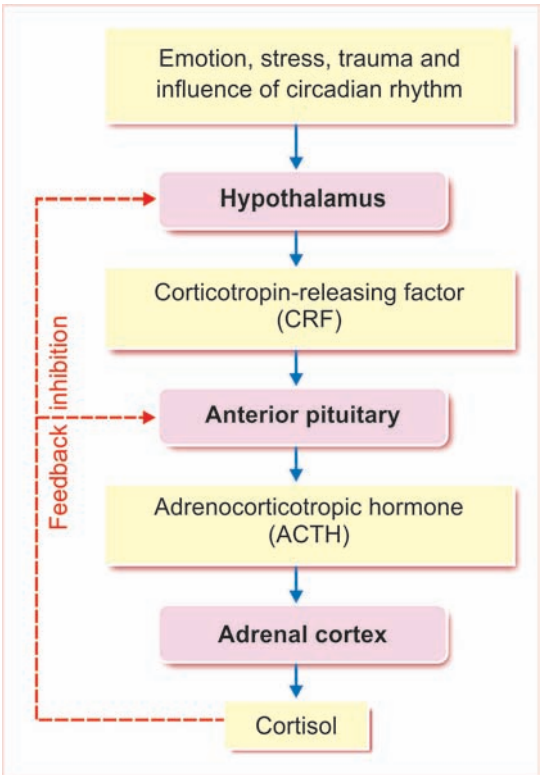


FIGURE 70.7: Regulation of cortisol secretion

■ ADRENAL SEX HORMONES

Adrenal sex hormones are secreted mainly by zona reticularis. Zona fasciculata secretes small quantities of sex hormones. Adrenal cortex secretes mainly the male sex hormones, which are called **androgens.** But small quantity of **estrogen** and **progesterone** are also secreted by adrenal cortex. Synthesis of sex hormones is given in Fig. 70.8.

Androgens secreted by adrenal cortex:

1. Dehydroepiandrosterone
2. Androstenedione
3. Testosterone.

Dehydroepiandrosterone is the most active adrenal androgen. Androgens, in general, are responsible for masculine features of the body (Chapter 74). But in normal conditions, the adrenal androgens have insignificant physiological effects, because of the low amount of secretion both in males and females.

In **congenital hyperplasia** of adrenal cortex or tumor of zona reticularis, an excess quantity of androgens is secreted. In males, it does not produce any special effect because, large quantity of androgens are produced by testes also. But in females, the androgens produce **masculine features.** Some of the androgens are converted into testosterone. Testosterone is responsible

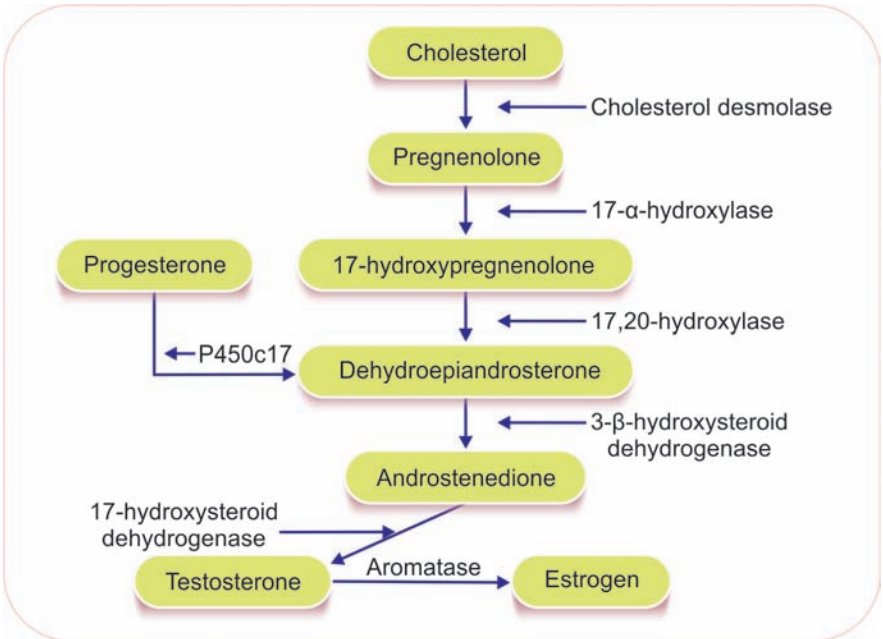


FIGURE 70.8: Synthesis of adrenal sex hormones

for the androgenic activity in adrenogenital syndrome or congenital adrenal hyperplasia.

■ EXOGENOUS STEROIDS

Corticosteroids are used as drugs since long. Exogenous steroids are extracted from adrenal cortex of animals or prepared artificially.

Commercially available synthetic drugs with corticosteroid effects are widely used. These drugs are either used as replacement of natural hormones (replacement therapy) in patients with deficiency disorders such as Addison disease or to treat a variety of other conditions such as arthritis, allergic conditions, asthma, skin disorders, etc.

■ SYNTHETIC STEROIDS

Synthetic steroids that are commonly used are:

1. **Cortisone** and **hydrocortisone,** which are used for replacement therapy have both glucocorticoid and mineralocorticoid effects
2. **Prednisolone** has more glucocorticoid activity than mineralocorticoid activity
3. **Fludrocortisone** (9-fluorocortisol) has more mineralocorticoid activity than glucocorticoid activity. It has most potent mineralocorticoid effect.
4. **Dexamethasone** has only glucocorticoid effect.

■ APPLIED PHYSIOLOGY

■ HYPERACTIVITY OF ADRENAL CORTEX

Hypersecretion of adrenocortical hormones leads to the following conditions:

1. Cushing syndrome
2. Hyperaldosteronism
3. Adrenogenital syndrome.

■ CUSHING SYNDROME

Cushing syndrome is a disorder characterized by obesity.

Causes

Cushing syndrome is due to the hypersecretion of glucocorticoids, particularly cortisol. It may be either due to pituitary origin or adrenal origin.

If it is due to pituitary origin, it is known as **Cushing disease.** If it is due to adrenal origin it is called **Cushing syndrome.** Generally, these two terms are used interchangeably.

Pituitary Origin

Increased secretion of ACTH causes hyperplasia of adrenal cortex, leading to hypersecretion of glucocorticoid. ACTH secretion is increased by:

i. Tumor in pituitary cells, particularly in basophilic cells which secrete ACTH

ii. Malignant tumor of non-endocrine origin like cancer of lungs or abdominal viscera
iii. Hypothalamic disorder causing hypersecretion of corticotropin-releasing hormone.

Adrenal Origin

Cortisol secretion is increased by:

i. Tumor in zona fasciculata of adrenal cortex
ii. Carcinoma of adrenal cortex
iii. Prolonged treatment of chronic inflammatory diseases like rheumatoid arthritis, with high dose of exogenous glucocorticoids
iv. Prolonged treatment with high dose of ACTH, which stimulates adrenal cortex to secrete excess glucocorticoids.

Recently, Cushing syndrome is classified into two types:

i. **ACTH-dependent Cushing syndrome** which is due to hypersecretion of ACTH
ii. **ACTH-independent Cushing syndrome** in which the secretion of ACTH is normal. The syndrome develops due to abnormal membrane receptors for some peptides like interleukin-1, gonadotropin-releasing hormone and gastric inhibitory polypeptide in the cells of zona fasciculata. The binding of these peptides to the abnormal receptors increases secretion of glucocorticoids, resulting in Cushing syndrome. Cushing syndrome that is developed by treatment with exogenous glucocorticoids also belongs to this type.

Signs and Symptoms

i. Characteristic feature of this disease is the disproportionate distribution of body fat, resulting in some abnormal features:
   a. *Moon face:* The edematous facial appearance due to fat accumulation and retention of water and salt
   b. *Torso:* Fat accumulation in the chest and abdomen. Arms and legs are very slim in proportion to **torso** (torso means trunk of the body)
   c. *Buffalo hump:* Due to fat deposit on the back of neck and shoulder
   d. *Pot belly:* Due to fat accumulation in upper abdomen (Fig. 70.9).
ii. *Purple striae:* Reddish purple stripes on abdomen due to three reasons:
   a. Stretching of abdominal wall by excess subcutaneous fat

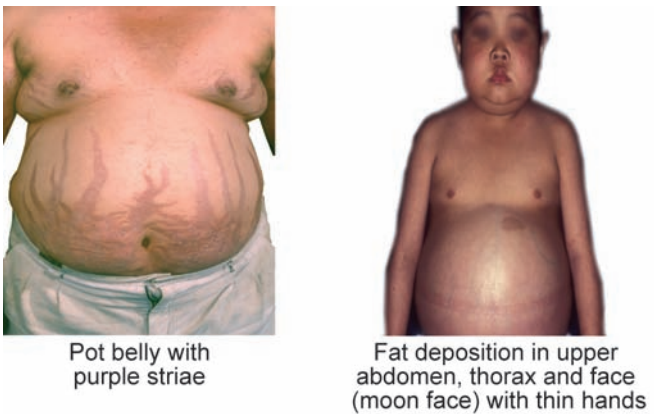


FIGURE 70.9: Cushing syndrome (*Courtesy:* Prof Mafauzy Mohamad)

   b. Rupture of subdermal tissues due to stretching
   c. Deficiency of collagen fibers due to protein depletion.
iii. Thinning of extremities
iv. Thinning of skin and subcutaneous tissues due to protein depletion caused by increased catabolism of proteins
v. Aconthosis: Skin disease characterized by darkened skin patches in certain areas such as axilla, neck and groin
vi. Pigmentation of skin, especially in ACTH-dependent type due to hypersecretion of ACTH which has got melanocyte-stimulating effect
vii. Facial plethora: Facial redness
viii. Hirsutism: Heavy growth of body and facial hair
ix. Weakening of muscles because of protein depletion
x. Bone resorption and osteoporosis due to protein depletion. Bone becomes susceptible to easy fracture
xi. Hyperglycemia due to gluconeogenesis (from proteins) and inhibition of peripheral utilization of glucose. Hyperglycemia leads to glucosuria and adrenal diabetes
xii. Hypertension by the mineralocorticoid effects of glucocorticoids – retention of sodium and water results in increase in ECF volume and blood volume, leading to hypertension
xiii. Immunosuppression resulting in susceptibility for infection
xiv. Poor wound healing.

Tests for Cushing Syndrome

i. Observation of external features
ii. Determination of blood sugar and cortisol levels
iii. Analysis of urine for 17-hydroxysteroids.

Treatment for Cushing Syndrome

Treatment depends upon the cause of the disease. Treatment may include cortisol-inhibiting drugs, surgical removal of pituitary or adrenal tumor, radiation or chemotherapy.

Nelson syndrome

Nelson syndrome is a disorder that develops after surgical removal of both adrenal glands. It is because of the growth of pituitary tumor that secretes excess ACTH. The features include headache and visual problems. Nelson syndrome can be treated with radiation or surgical removal of the pituitary gland.

■ HYPERALDOSTERONISM

Increased secretion of aldosterone is called hyperaldosteronism.

Causes and Types

Depending upon the causes, hyperaldosteronism is classified into two types:

i. Primary hyperaldosteronism
ii. Secondary hyperaldosteronism.

Primary Hyperaldosteronism

Primary hyperaldosteronism is otherwise known as **Conn syndrome.** It develops due to tumor in zona glomerulosa of adrenal cortex. In primary hyperaldosteronism, edema does not occur because of escape phenomenon.

Secondary Hyperaldosteronism

Secondary hyperaldosteronism occurs due to extra adrenal causes such as:

i. Congestive cardiac failure
ii. Nephrosis
iii. Toxemia of pregnancy
iv. Cirrhosis of liver.

Signs and Symptoms

i. Increase in ECF volume and blood volume
ii. Hypertension due to increase in ECF volume and blood volume
iii. Severe depletion of potassium, which causes renal damage. The kidneys fail to produce concentrated urine. It leads to polyuria and polydipsia
iv. Muscular weakness due to potassium depletion
v. Metabolic alkalosis due to secretion of large amount of hydrogen ions into the renal tubules. Metabolic alkalosis reduces blood calcium level causing tetany.

■ 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. Testosterone is responsible for the **androgenic activity** in adrenogenital syndrome.

Causes

Adrenogenital syndrome is due to the tumor of zona reticularis in adrenal cortex.

Symptoms

Adrenogenital syndrome is characterized by the tendency for the development of secondary sexual character of opposite sex.

Symptoms in females

Increased secretion of androgens causes development of male secondary sexual characters. The condition is called **adrenal virilism.** Symptoms are:

i. Masculinization due to increased muscular growth
ii. Deepening of voice
iii. Amenorrhea
iv. Enlargement of clitoris
v. Male type of hair growth.

Symptoms in males

Sometimes, the tumor of estrogen secreting cells produces more than normal quantity of estrogens in males. It produces some symptoms such as:

i. Feminization
ii. Gynecomastia (enlargement of breast)
iii. Atrophy of testis
iv. Loss of interest in women.

■ HYPOACTIVITY OF ADRENAL CORTEX

Hyposecretion of adrenocortical hormones leads to the following conditions:

1. Addison disease or chronic adrenal insufficiency
2. Congenital adrenal hyperplasia.

■ ADDISON DISEASE OR CHRONIC ADRENAL INSUFFICIENCY

Addison disease is the failure of adrenal cortex to secrete corticosteroids.

Types of Addison Disease

i. Primary Addison disease due to adrenal cause
ii. Secondary Addison disease due to failure of anterior pituitary to secrete ACTH
iii. Tertiary Addison disease due failure of hypothalamus to secrete corticotropin-releasing factor (CRF).

Causes for Primary Addison Disease

i. Atrophy of adrenal cortex due to autoimmune diseases
ii. Destruction of the gland because of tuberculosis
iii. Destruction of hormone-secreting cells in adrenal cortex by malignant tissues
iv. Congenital failure to secrete cortisol
v. Adrenalectomy and failure to take hormone therapy.

Signs and Symptoms

Signs and symptoms develop in Addison disease because of deficiency of both cortisol and aldosterone. Common signs and symptom are:

i. Pigmentation of skin and mucous membrane due to excess ACTH secretion, induced by cortisol deficiency. ACTH causes pigmentation by its melanocyte-stimulating action
ii. Muscular weakness
iii. Dehydration with loss of sodium
iv. Hypotension
v. Decreased cardiac output and decreased workload of the heart, leading to decrease in size of the heart
vi. Hypoglycemia
vii. Nausea, vomiting and diarrhea. Prolonged vomiting and diarrhea cause dehydration and loss of body weight
viii. Susceptibility to any type of infection
ix. Inability to withstand any stress, resulting in Addisonian crisis (see below).

Tests for Addison Disease

i. Measurement of blood level of cortisol and aldosterone
ii. Measurement of amount of steroids excreted in urine.

Addisonian Crisis or Adrenal Crisis or Acute Adrenal Insufficiency

Adrenal crisis is a common symptom of Addison disease, characterized by sudden collapse associated with an increase in need for large quantities of glucocorticoids. The condition becomes fatal if not treated in time.

Causes

i. Exposure to even mild stress
ii. Hypoglycemia due to fasting
iii. Trauma
iv. Surgical operation
v. Sudden withdrawal of glucocorticoid treatment.

■ CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia 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.

Causes

Even though the size of the gland increases, cortisol secretion decreases. It is because of the congenital deficiency of the enzymes necessary for the synthesis of cortisol, particularly, 21-hydroxylase.

Lack of this enzyme reduces the synthesis of cortisol, resulting in ACTH secretion from pituitary by feedback mechanism. ACTH stimulates the adrenal cortex causing hyperplasia, with accumulation of lipid droplets. Hence, it is also called **congenital lipid adrenal**

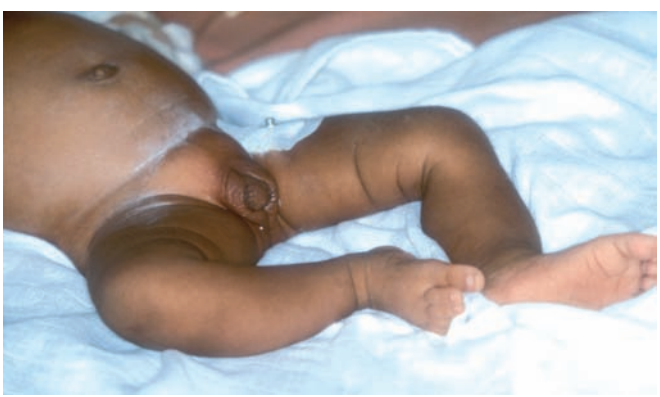


FIGURE 70.10: Congenital adrenal hyperplasia (Macrogenitosomia praecox) (*Courtesy:* Prof Mafauzy Mohamad)

hyperplasia. Cortisol cannot be synthesized because of lack of 21-hydroxylase. Therefore, due to the constant simulation of adrenal cortex by ACTH, the secretion of androgens increases. It results in sexual abnormalities such as virilism.

Symptoms

In boys

Adrenal hyperplasia produces a condition known as **macrogenitosomia praecox** (Fig. 70.10).

Features of macrogenitosomia praecox:

i. Precocious body growth, causing stocky appearance called **infant Hercules**
ii. Precocious sexual development with enlarged penis even at the age of 4 years.

In girls

In girls, adrenal hyperplasia produces masculinization. It is otherwise called **virilism.** In some cases of genetic disorders, the female child is born with external genitalia of male type. This condition is called **pseudohermaphroditism.**

Adrenal Medulla

Chapter 71

INTRODUCTION

Medulla is the inner part of adrenal gland and it forms 20% of the mass of adrenal gland. It is made up of interlacing cords of cells known as **chromaffin cells.** Chromaffin cells are also called **pheochrome cells** or **chromophil cells.** These cells contain fine granules which are stained brown by potassium dichromate.

Types of chromaffin cells

Adrenal medulla is formed by two types of chromaffin cells:

1. Adrenaline-secreting cells (90%)
2. Noradrenaline-secreting cells (10%).

HORMONES OF ADRENAL MEDULLA

Adrenal medullary hormones are the amines derived from **catechol** and so these hormones are called **catecholamines.**

Catecholamines secreted by adrenal medulla

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

PLASMA LEVEL OF CATECHOLAMINES

1. Adrenaline : 3 µg/dL
2. Noradrenaline : 30 µg/dL
3. Dopamine : 3.5 µg/dL

HALF-LIFE OF CATECHOLAMINES

Half-life of catecholamines is about 2 minutes.

SYNTHESIS OF CATECHOLAMINES

Catecholamines are synthesized from the amino acid **tyrosine** in the chromaffin cells of adrenal medulla (Fig. 71.1). These hormones are formed from **phenylalanine** also. But phenylalanine has to be converted into tyrosine.

Stages of Synthesis of Catecholamines

1. Formation of tyrosine from phenylalanine in the presence of enzyme **phenylalanine hydroxylase**
2. Uptake of tyrosine from blood into the chromaffin cells of adrenal medulla by active transport
3. Conversion of tyrosine into dihydroxyphenylalanine **(DOPA)** by **hydroxylation** in the presence of **tyrosine** hydroxylase

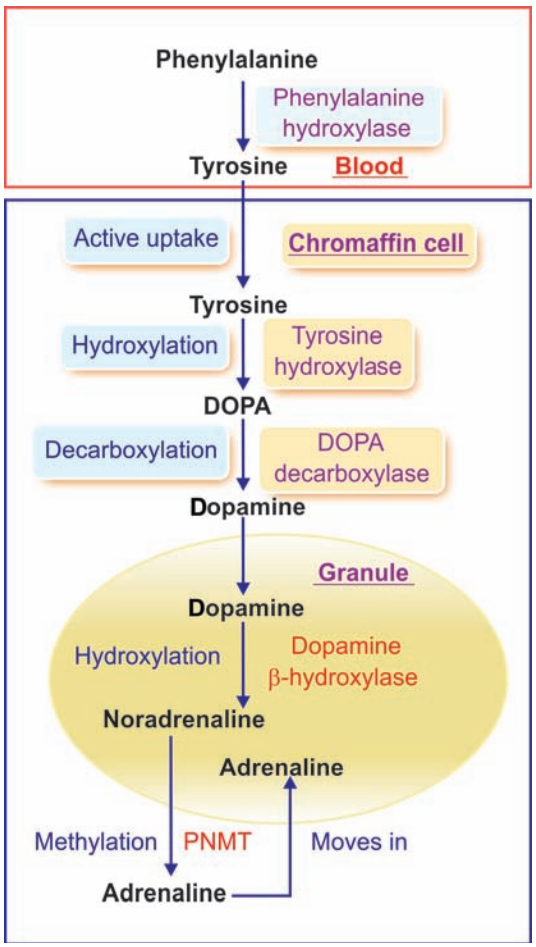


FIGURE 71.1: Synthesis of catecholamines. DOPA = Dihydroxyphenylalanine, PNMT = Phenylethanolamine-N-methyltransferase.

4. **Decarboxylation** of DOPA into dopamine by **DOPA decarboxylase**
5. Entry of dopamine into granules of chromaffin cells
6. **Hydroxylation** of dopamine into noradrenaline by the enzyme dopamine **beta-hydroxylase**
7. Release of noradrenaline from granules into the cytoplasm
8. **Methylation** of noradrenaline into adrenaline by the most important enzyme called **phenylethanolamine-N-methyltransferase (PNMT).** PNMT is present in chromaffin cells.

■ METABOLISM OF CATECHOLAMINES

Eighty five percent of noradrenaline is taken up by the sympathetic adrenergic neurons. Remaining 15% of noradrenaline and adrenaline are degraded (Fig. 71.2).

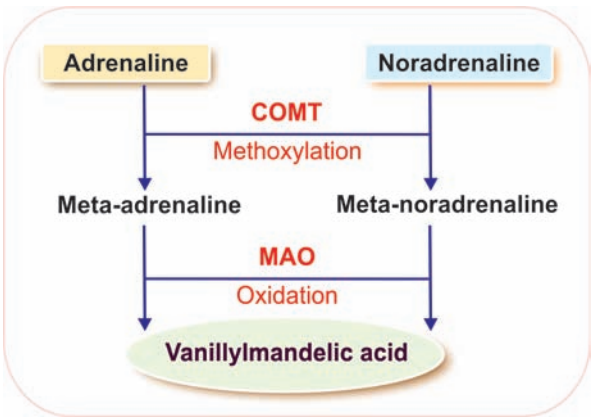


FIGURE 71.2: Metabolism of catecholamines. COMT = Catechol-O-methyltransferase, MAO = Monoamine oxidase.

Stages of Metabolism of Catecholamines

1. **Methoxylation** of adrenaline into **meta-adrenaline** and noradrenaline into **metanoradrenaline** in the presence of **'catechol-O-methyltransferase'** (COMT). **Meta-adrenaline** and meta-noradrenaline are together called metanephrines
2. **Oxidation** of metanephrines into **vanillylmandelic acid (VMA)** by **monoamine oxidase (MAO)**

Removal of Catecholamines

Catecholamines are removed from body through urine in three forms:

i. 15% as free adrenaline and free noradrenaline
ii. 50% as free or conjugated meta-adrenaline and meta-noradrenaline
iii. 35% as vanillylmandelic acid (VMA).

■ 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

Actions of adrenaline and noradrenaline are executed by binding with receptors called adrenergic receptors, which are present in the target organs.

Adrenergic receptors are of two types:

1. **Alpha-adrenergic receptors,** which are subdivided into alpha-1 and alpha-2 receptors
2. **Beta-adrenergic receptors,** which are subdivided into beta-1 and beta-2 receptors.

Refer Table 71.1 for the mode of action of these receptors.

■ ACTIONS

Circulating adrenaline and noradrenaline have similar effect of sympathetic stimulation. But, the effect of adrenal hormones is prolonged 10 times more than that of sympathetic stimulation. It is because of the slow inactivation, slow degradation and slow removal of these hormones.

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.

1. *On Metabolism (via Alpha and Beta Receptors)*

Adrenaline influences the metabolic functions more than noradrenaline.

i. General metabolism: Adrenaline increases oxygen consumption and carbon dioxide removal. It increases basal metabolic rate. So, it is said to be a calorigenic hormone
ii. Carbohydrate metabolism: Adrenaline increases the blood glucose level by increasing the glycogenolysis in liver and muscle. So, a large quantity of glucose enters the circulation
iii. Fat metabolism: Adrenaline causes mobilization of free fatty acids from adipose tissues. Catecholamines need the presence of glucocorticoids for this action.

2. *On Blood (via Beta Receptors)*

Adrenaline decreases blood coagulation time. It increases RBC count in blood by contracting smooth muscles of splenic capsule and releasing RBCs from spleen into circulation.

3. *On Heart (via Beta Receptors)*

Adrenaline has stronger effects on heart than noradrenaline. It increases overall activity of the heart, i.e.

i. Heart rate **(chronotropic effect)**
ii. Force of contraction **(inotropic effect)**
iii. Excitability of heart muscle **(bathmotropic effect)**
iv. Conductivity in heart muscle **(dromotropic effect).**

4. *On Blood Vessels (via Alpha and Beta-2 Receptors)*

Noradrenaline has strong effects on blood vessels. It causes constriction of blood vessels throughout the body via alpha receptors. So it is called **'general vasoconstrictor'.** Vasoconstrictor effect of noradrenaline increases total peripheral resistance.

Adrenaline also causes constriction of blood vessels. However, it causes dilatation of blood vessels in skeletal muscle, liver and heart through beta-2 receptors. So, the total peripheral resistance is decreased by adrenaline.

Catecholamines need the presence of glucocorticoids, for these vascular effects.

5. *On Blood Pressure (via Alpha and Beta Receptors)*

Adrenaline increases **systolic blood pressure** by increasing the force of contraction of the heart and cardiac output. But, it decreases **diastolic blood pressure** by reducing the total peripheral resistance. Noradrenaline increases **diastolic pressure** due to general vasoconstrictor effect by increasing the total peripheral resistance. It also increases the **systolic blood pressure** to a slight extent by its actions on heart. The action of catecholamines on blood pressure needs the presence of glucocorticoids.

TABLE 71.1: Adrenergic receptors

Receptor	Mode of action	Response
Alpha-1 receptor	Activates IP_3 through phospholipase C	Mediates more of noradrenaline actions than adrenaline actions
Alpha-2 receptor	Inhibits adenyl cyclase and cAMP	
Beta-1 receptor	Activates adenyl cyclase and cAMP	Mediates actions of adrenaline and noradrenaline equally
Beta-2 receptor	Activates adenyl cyclase and cAMP	Mediates more of adrenaline actions than noradrenaline actions

IP_3 = Inositol triphosphate

Thus, hypersecretion of catecholamines leads to hypertension.

6. *On Respiration (via Beta-2 Receptors)*

Adrenaline increases rate and force of respiration. Adrenaline injection produces apnea, which is known as **adrenaline apnea.** It also causes **bronchodilation.**

7. *On Skin (via Alpha and Beta-2 Receptors)*

Adrenaline causes contraction of **arrector pili.** It also increases the secretion of sweat.

8. *On Skeletal Muscle (via Alpha and Beta-2 Receptors)*

Adrenaline causes severe contraction and quick fatigue of skeletal muscle. It increases glycogenolysis and release of glucose from muscle into blood. It also causes **vasodilatation** in skeletal muscles.

9. *On Smooth Muscle (via Alpha and Beta Receptors)*

Catecholamines cause contraction of smooth muscles in the following organs:

i. Splenic capsule
ii. Sphincters of gastrointestinal (GI) tract
iii. Arrector pili of skin
iv. Gallbladder
v. Uterus
vi. Dilator pupillae of iris
vii. Nictitating membrane of cat.

Catecholamines cause relaxation of smooth muscles in the following organs:

i. Non-sphincteric part of GI tract (esophagus, stomach and intestine)
ii. Bronchioles
iii. Urinary bladder.

10. *On Central Nervous System (via Beta Receptors)*

Adrenaline increases the activity of brain. Adrenaline secretion increases during **'fight or flight reactions'** after exposure to stress. It enhances the cortical arousal and other facilitatory functions of central nervous system.

11. *Other Effects of Catecholamines*

i. On salivary glands (via alpha and beta-2 receptors): Cause vasoconstriction in salivary gland, leading to mild increase in salivary secretion
ii. On sweat glands (via beta-2 receptors): Increase the secretion of apocrine sweat glands
iii. On lacrimal glands (via alpha receptors): Increase the secretion of tears
iv. On ACTH secretion (via alpha receptors): Adrenaline increases ACTH secretion
v. On nerve fibers (via alpha receptors): Adrenaline decreases the latency of action potential in the nerve fibers, i.e. electrical activity is accelerated
vi. On renin secretion (via beta receptors): Increase the rennin secretion from juxtaglomerular apparatus of the kidney.

■ 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 during exposure to cold and hypoglycemia also.

■ DOPAMINE

Dopamine is secreted by adrenal medulla. 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.

Injected dopamine produces the following effects:

1. Vasoconstriction by releasing norepinephrine
2. Vasodilatation in mesentery
3. Increase in heart rate via beta receptors
4. Increase in systolic blood pressure. Dopamine does not affect diastolic blood pressure.

Deficiency of dopamine in basal ganglia produces nervous disorder called parkinsonism (Chapter 151).

■ APPLIED PHYSIOLOGY – PHEOCHROMOCYTOMA

Pheochromocytoma is a condition characterized by hypersecretion of catecholamines.

Cause

Pheochromocytoma is caused by tumor of chromophil cells in adrenal medulla. It is also caused rarely by tumor of sympathetic ganglia **(extra-adrenal pheochromocytoma).**

Signs and Symptoms

Characteristic feature of pheochromocytoma is hypertension. This type of hypertension is known as **endocrine** or **secondary hypertension.**

Other features:

1. Anxiety
2. Chest pain
3. Fever
4. Headache
5. Hyperglycemia
6. Metabolic disorders
7. Nausea and vomiting
8. Palpitation
9. Polyuria and glucosuria
10. Sweating and flushing
11. Tachycardia
12. Weight loss.

Tests for Pheochromocytoma

Pheochromocytoma is detected by measuring metanephrines and vanillylmandelic acid in urine and catecholamines in plasma.

Endocrine Functions of Other Organs

Chapter 72

PINEAL GLAND

SITUATION AND STRUCTURE

Pineal gland or **epiphysis** is located in the diencephalic area of brain above the hypothalamus. It is a small cone-shaped structure with a length of about 10 mm.

Pineal gland has two types of cells:

1. Large epithelial cells called parenchymal 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. It secretes the hormonal substance called melatonin.

Melatonin

Source of secretion

Melatonin is secreted by the parenchymal cells of pineal gland.

Chemistry

Melatonin is an **indole** (N-acetyl-5-methoxytryptamine).

Actions of melatonin

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.

In humans, it inhibits the onset of puberty by inhibiting the gonads.

Diurnal variation in melatonin secretion

Melatonin secretion is more in darkness than in daylight. In animals, the secretion of melatonin varies according to activities in different periods of the day, i.e. **circadian**

rhythm (Chapter 149). Hypothalamus is responsible for the circadian fluctuations of melatonin secretion.

THYMUS

SITUATION

Thymus 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.

Thymus 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 (Chapter 17). The lymphocytes which are produced in bone marrow are processed in thymus into T lymphocytes. It occurs during the period between 3 months before birth and 3 months after birth. So, the removal of thymus 3 months after birth, will not affect the cell-mediated immunity.

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

Thymin 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 (see below).

ERYTHROPOIETIN

Source of Secretion

Endothelial cells of peritubular capillaries in the kidney secrete erythropoietin. The stimulant for its secretion is hypoxia. Erythropoietin is a glycoprotein with 165 amino acids.

Action of Erythropoietin

Erythropoietin stimulates the bone marrow and causes erythropoiesis. More details are given in Chapter 10.

THROMBOPOIETIN

Source of Secretion

Thrombopoietin is a glycoprotein. It is secreted by kidneys and liver.

Action of Thrombopoietin

Thrombopoietin stimulates the production of platelets.

RENIN

Source of Secretion

The granular cells of juxtaglomerular apparatus of the kidney secrete renin.

Actions of Renin

When renin is released into the blood, it acts on a specific plasma protein called **alpha-2 globulin.** It is also called angiotensinogen or **renin substrate.**

Renin converts angiotensinogen into angiotensin I, which is converted into angiotensin II by a converting enzyme. The other details of renin and angiotensin II are given in Chapter 50.

1,25-DIHYDROXYCHOLECALCIFEROL – CALCITRIOL

Formation of 1,25-dihydroxycholecalciferol

1,25-dihydroxycholecalciferol is otherwise known as **calcitriol** or **activated vitamin D.** It is formed from cholecalciferol, which is present in skin and intestine. The cholecalciferol (vitamin D3) from skin or intestine is converted into 25-hydroxycholecalciferol in liver. This in turn, is activated into 1,25-dihydroxycholecalciferol by parathormone in kidney (refer Chapter 68).

Actions of 1,25-Dihydroxycholecalciferol

The activated vitamin D plays an important role in the maintenance of blood calcium level. It acts on the intestinal epithelium and enhances absorption of calcium from intestine into the blood. Details are given in Chapter 68.

■ PROSTAGLANDINS

Source of Secretion

Prostaglandins secreted from kidney are PGA_2 and PGE_2. These hormones are secreted by juxtaglomerular cells and type I interstitial cells present in medulla of kidney.

Action of Prostaglandins

Prostaglandins decrease the blood pressure by systemic vasodilatation, diuresis and natriuresis. Details of prostaglandins are given in Chapter 73.

■ HEART

Heart secretes the hormones atrial natriuretic peptide and brain natriuretic peptide. Recently, another peptide called C-type natriuretic peptide is found in heart.

■ ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is a polypeptide with 28 amino acids. It is secreted by **atrial musculature** of the heart. Recently, it is found in hypothalamus of brain also. However, its action in brain is not known.

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 extracellular fluid (ECF) volume and blood volume. It also lowers blood pressure.

Effect of ANP on Sodium Excretion

Atrial natriuretic peptide increases excretion of sodium ions through urine by:

1. Increasing glomerular filtration rate by relaxing **mesangeal cells** and dilating afferent arterioles
2. Inhibiting sodium reabsorption from distal convoluted tubules and collecting ducts in kidneys
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 (Refer Chapter 70 for details).

Effect of ANP on Blood Pressure

ANP decreases the blood pressure by:

1. Vasodilatation by relaxing the smooth muscle fibers, mainly in arterioles and venules
2. Inhibiting renin secretion from juxtaglomerular apparatus of kidney
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 the brain. The stimulant for its secretion is not known.

BNP has same actions of ANP (see above). On brain, its actions are not known.

Clinical Importance of BNP

Measurement of plasma level of BNP (BNP test) is becoming an important diagnostic tool for heart diseases. Normally, blood contains very small amount of BNP. However, in conditions like heart failure, BNP level is increased in blood.

■ C-TYPE NATRIURETIC PEPTIDE

C-type natriuretic peptide (CNP) is the newly discovered peptide hormone. It is a 22 amino acid peptide. Initially, it was identified in brain. Now, it is known to be secreted by several tissues which include myocardium, endothelium of blood vessels, gastrointestinal tract and kidneys. The functions of this hormone are not fully studied. It is believed that it has similar action of atrial natriuretic peptide.

Local Hormones

Chapter 73

INTRODUCTION

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 usually released in an inactive form and are activated by some conditions or substances.

Classification of Local Hormones

Local hormones are classified into two types:

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

LOCAL HORMONES SYNTHESIZED IN TISSUES

Local hormones synthesized in the tissues are:

1. Prostaglandins and related substances
2. 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

Synthesis of eicosanoids

Phospholipids of the cell membrane are released by the action of phospholipase A_2. Phospholipids are converted into arachidonic acid. Arachidonic acid is converted into an **endoperoxide** called **prostaglandin G_2** (PGG_2), which is converted into **prostaglandin H_2** (PGH_2). PGH_2 gives rise to **prostaglandins, prostacyclin** and **thromboxanes** (Fig. 73.1).

1. *Prostaglandins*

Prostaglandins were first discovered and isolated from human semen by Ulf von Euler of Sweden, in 1930. He thought that these hormones were secreted by prostate gland hence the name prostaglandins. However, now it is believed that almost all the tissues of the body including renal tissues (Chapter 72) synthesize prostaglandins.

Chemistry

Prostaglandins are unsaturated fatty acids with a cyclopentane ring and 20 carbon atoms.

Synthesis

Prostaglandins are synthesized from arachidonic acid.

Types

A variety of prostaglandins are identified. Active forms of prostaglandins are PGA_2, PGD_2, PGE_2 and PGF_2.

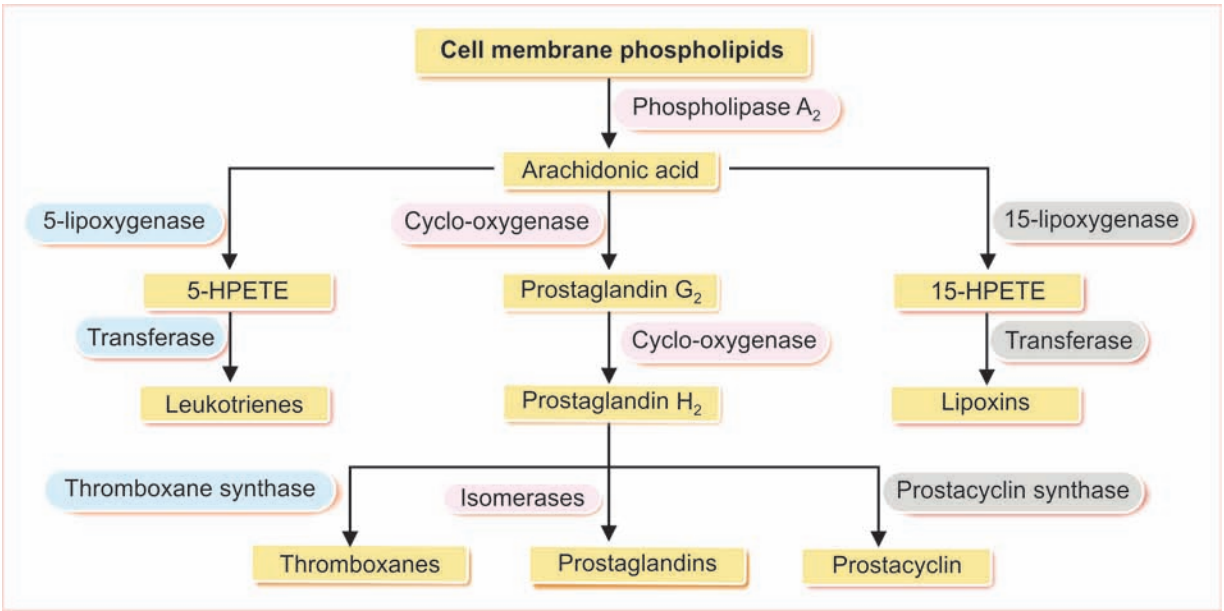


FIGURE 73.1: Synthesis of prostaglandins and related hormones.
HPETE = Hydroperoxyeicosatetraenoic acid

Actions

Prostaglandins show variety of physiological actions in the body. Various actions of prostaglandins are:

i. *On blood:* Prostaglandins accelerate the capacity of RBCs to pass through minute blood vessels.
ii. *On blood vessels:* PGE_2 causes vasodilatation.
iii. *On GI tract:* The prostaglandins reduce gastric secretion. In experimental animals, prostaglandins inhibit the formation of peptic ulcer.
iv. *On respiratory system:* PGE_2 causes bronchodilatation.
v. *On lipids:* Some of the prostaglandins are antilipolytic agents. These hormones inhibit the release of free fatty acids from adipose tissue.
vi. *On nervous system:* In brain, prostaglandins control or alter the actions of neurotransmitters.
vii. *On reproduction:* Prostaglandins play an important role in regulating the reproductive cycle. These hormones also cause degeneration of corpus luteum **(luteolysis).** Prostaglandins increase the receptive capacity of cervical mucosa for sperms and cause **reverse peristaltic movement** of uterus and fallopian tubes during coitus. This in turn, increases the velocity of sperm transport in female genital tract.

Prostaglandins (PGE_2) play an important role during parturition and facilitate labor by increasing the force of uterine contractions. Prostaglandins are secreted from uterine tissues, fetal membranes and placenta. Their concentration increases in maternal blood and amniotic fluid at the time of **labor.** Prostaglandins increase the force of uterine contractions by elevating the concentration of calcium ions in the smooth muscle fibers of uterus.

When injected **intra-amniotically** during pregnancy, prostaglandins induce **abortion.** When injected during last stages of pregnancy, prostaglandins induce labor.

viii. *On kidney:* The prostaglandins stimulate juxtaglomerular apparatus and enhance the secretion of renin, diuresis and natriuresis.

Mode of action of prostaglandins

Prostaglandins mainly act by the formation of second messenger cyclic AMP.

2. *Thromboxanes*

Thromboxanes are derived from arachidonic acid.

Thromboxanes are of two types:

i. Thromboxane A_2, which is secreted in platelets
ii. Thromboxane B_2, the metabolite of thromboxane A_2.

Actions

Thromboxane A_2:

i. Causes vasoconstriction
ii. Plays an important role in hemostasis by accelerating aggregation of platelets
iii. Accelerates 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.

Actions

It causes vasodilatation and inhibits platelet aggregation.

4. *Leukotrienes*

Leukotrienes are derived from arachidonic acid via 5-hydroperoxyeicosatetraeonic acid (5-HPETE). 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.

Actions

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 also derived from arachidonic acid via 15-hydroperoxyeicosatetraeonic acid (15-HPETE). Lipoxins are of two types namely, lipoxin A and lipoxin B.

Actions

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. Gastrointestinal hormones.

1. *Acetylcholine*

Acetylcholine is the cholinergic neurotransmitter (Chapter 164). It is the transmitter substance at neuromuscular junction. It is also secreted by other nerve endings and other cells.

Source of secretion

i. Presynaptic terminals
ii. Preganglionic parasympathetic nerve
iii. Postganglionic parasympathetic nerve
iv. Preganglionic sympathetic nerve
v. Postganglionic sympathetic cholinergic nerves such as:
   a. Nerves supplying eccrine sweat glands
   b. Sympathetic vasodilator nerves in skeletal muscle
vi. Nerves in amacrine cells of retina
vii. Mast cell
viii. Gastric mucosa
ix. Lungs
x. Many regions of brain.

Actions

Acetylcholine:

i. Produces excitatory function of synapse by opening the sodium channels
ii. Activates smooth muscles in GI tract, urinary tract and skeletal muscles
iii. Inhibits cardiac function
iv. Causes vasodilatation.

Destruction

Acetylcholine is very quick in action. Immediately after executing the action, it is destroyed by **acetylcholinesterase.** This enzyme is present in **basal lamina** of the **synaptic cleft.**

2. *Serotonin*

Serotonin is otherwise known as 5-hydroxytryptamine.

Source of secretion

Serotonin is secreted in the following structures:

i. Hypothalamus
ii. Limbic system
iii. Cerebellum
iv. Spinal cord

v. Retina
vi. Gastrointestinal tract
vii. Lungs
viii. Platelets.

Actions

Serotonin:

i. Is an inhibitory substance (Chapter 141)
ii. Inhibits impulses of pain sensation in posterior gray horn of spinal cord
iii. Causes mood depression and induces sleep (Chapter160)
iv. Causes vasoconstriction.

3. *Histamine*

Source of secretion

Histamine is secreted in nerve endings of hypothalamus, limbic cortex and other parts of cerebral cortex and spinal cord. Histamine is also released from tissues during allergic condition, inflammation or damage.

Actions

i. It is an excitatory neurotransmitter substance
ii. Histamine released from tissues causes vasodilatation and enhances the capillary permeability for fluid and plasma proteins from blood into the affected tissues. So, the accumulation of fluid with proteins develops local edema
iii. In GI tract, histamine increases the motility.

4. *Substance P*

Source of secretion

i. Nerve endings (first order neurons of pain pathway) in spinal cord and retina (Chapters 141 and 145)
ii. GI tract (by the presence of chyme).

Actions

i. Substance P is the neurotransmitter for pain
ii. It is also the neurotransmitter substance in GI tract. In GI tract, it increases the mixing and propulsive movements of small intestine.

5. *Heparin*

Source of secretion

i. Mast cells
ii. Basophils.

Actions

Heparin is a naturally produced anticoagulant (Refer Chapter 20 for other details).

6. *Leptin*

Leptin (in Greek, it means thin) is a protein hormone with 167 amino acids.

Source of secretion

Leptin is secreted by adipocytes in adipose tissues.

Actions

Leptin plays an important role in controlling the adipose tissue and food intake. Leptin acts on hypothalamus and inhibits the feeding center, resulting in stoppage of food intake (Chapter 149). At the same time, it also stimulates the metabolic reactions involved in utilization of fat stored in adipose tissue for energy. Thus, the circulating leptin level informs the brain about the energy storage and the necessity to regulate metabolic reactions, food intake and body weight.

Mode of action of leptin

Refer Chapter 149 for mode of leptin and leptin receptors.

7. *Gastrointestinal Hormones*

Gastrointestinal hormones are explained in Chapter 44.

■ LOCAL HORMONES PRODUCED IN BLOOD

Local hormones produced in the blood are:

1. Serotonin
2. Angiotensinogen
3. Kinins.

Serotonin is described above. Angiotensinogen is explained in Chapter 50.

■ KININS

Kinins are biologically active protein hormones which are circulating in blood. Kinins are of two types:

1. Bradykinin
2. Kallidin.

Along with other proteins of their family, kinins form the **kinin system** or **kinin-kallikrein system.**

Formation of Kinins

Kinins are cleaved from their precursors which are of two types:

1. **High-molecular-weight kinogen (HMW kinogen)** – precursor of bradykinin
2. **Low-molecular-weight kinogen (LMW kinogen)** – precursor of kallidin.

The cleavage of kinins from their precursors occurs by proteases called kallikreins, which are of two types, plasma kallikrein and tissue kallikrein.

Formation of bradykinin from HMW kinogen

HMW kinogen is α-2-globulin secreted in liver. It is hydrolyzed by plasma kallikrein to form bradykinin. Plasma kallikrein is circulating in blood in its inactive form called **prekallikrein.** Prekallikrein is converted into active **kallikrein** by activated factor XII, which initiates the intrinsic pathway of blood coagulation. Kallikrein also activates factor XII (see below).

Formation of kallidin LMW kinogen

LMW kinogen is secreted in many tissues. It is hydrolyzed by tissue kallikrein to form kallidin, which is also known as **lysylbradykinin.** Tissue kallikrein is present in many tissues like salivary glands, pancreas, intestine, sweat glands, kidneys and prostate.

Actions of Kinins

Bradykinin:

1. Dilates the blood vessels and decreases the blood pressure. It is considered as a potent vasodilator
2. Increases the blood flow throughout the body by its vasodilator action
3. Increases permeability of capillaries during inflammatory conditions, resulting in edema in the affected area
4. Stimulates pain receptors
5. Causes contraction of extravascular smooth muscles, especially smooth muscles of intestine.

Kallidin:

Kallidin is also a vasodilator hormone.

Actions of Kallikreins

1. Kallikreins hydrolyze the kinogens to form kinins (see above)
2. Along with HMW kinogen, the plasma kallikrein activates factor XII during blood coagulation (Chapter 20)
3. Kallikreins are potent **vasodilators.**

QUESTIONS IN ENDOCRINOLOGY

LONG QUESTIONS

1. Enumerate the hormones secreted by pituitary gland. Describe the actions and regulation of secretion of growth hormone. Write in brief about effects of hypersecretion of anterior pituitary gland.
2. Give an account of hypothalamo-hypophyseal relations.
3. Describe the synthesis, storage, release, transport, functions and regulation of secretion of thyroid hormones.
4. Explain the functions and regulation of secretion of parathormone. Add a note on the disorders of parathormone.
5. What is the importance of calcium in the body? Explain the regulation of blood calcium level. Add a note on tetany.
6. Enlist the hormones secreted by pancreas. Explain the functions and regulation of secretion of insulin.
7. Describe in detail the regulation of blood sugar level.
8. Classify the hormones secreted by adrenal cortex. Explain the actions and regulation of secretion of cortisol.
9. Enumerate the corticosteroids. Describe the actions and regulation of secretion of aldosterone.
10. What are catecholamines? Explain the synthesis, metabolism, actions and regulation of secretion of catecholamines.

SHORT QUESTIONS

1. Mechanism of hormonal action.
2. Mechanism of action of protein hormones.
3. Mechanism of action of steroid hormones.
4. Second messenger.
5. Growth hormone.
6. Thyroid-stimulating hormone.
7. Adrenocorticotropic hormone.
8. Gonadotropins.
9. Somatomedin.
10. Oxytocin.
11. Antidiuretic hormone.
12. Neuroendocrine reflex.
13. Milk ejection reflex.
14. Disorders of anterior pituitary gland.
15. Gigantism.
16. Acromegaly.
17. Dwarfism.
18. Acromicria.
19. Simmond disease.
20. Fröhlich syndrome.
21. Disorders of posterior pituitary gland.
22. Hypothalamo-hypophyseal relations.
23. Diabetes insipidus.
24. Synthesis of thyroid hormones.
25. Thyroglobulin.
26. Thyroxine.
27. Hyperthyroidism/thyrotoxicosis/Graves disease.
28. Hypothyroidism.
29. Goiter.
30. Cretinism.
31. Myxedema.
32. Antithyroid substances.
33. Parathormone.
34. Tetany.
35. Hypercalcemia/hypocalcemia.
36. Insulin.
37. Glucagon.
38. Somatostatin.
39. Diabetes mellitus.
40. Hyperinsulinism.
41. Cortisol.
42. Non-metabolic actions of cortisol.
43. Aldosterone.
44. Aldosterone escape.
45. Adrenal androgens.
46. Cushing syndrome or disease.
47. Hyperaldosteronism.
48. Atrial natriuretic peptide or endocrine function of heart.
49. Adrenogenital syndrome.
50. Virilism.
51. Addison disease.
52. Addisonian crisis.
53. Synthesis of catecholamines.
54. Actions of catecholamines.
55. Adrenergic receptors.
56. Dopamine.
57. Pheochromocytoma.
58. Functions of pineal gland.
59. Melatonin.
60. Functions of thymus.
61. Endocrine functions of kidney.
62. Local hormones.
63. Prostaglandins.
64. Acetylcholine.
65. Leptin.
66. Kinins.