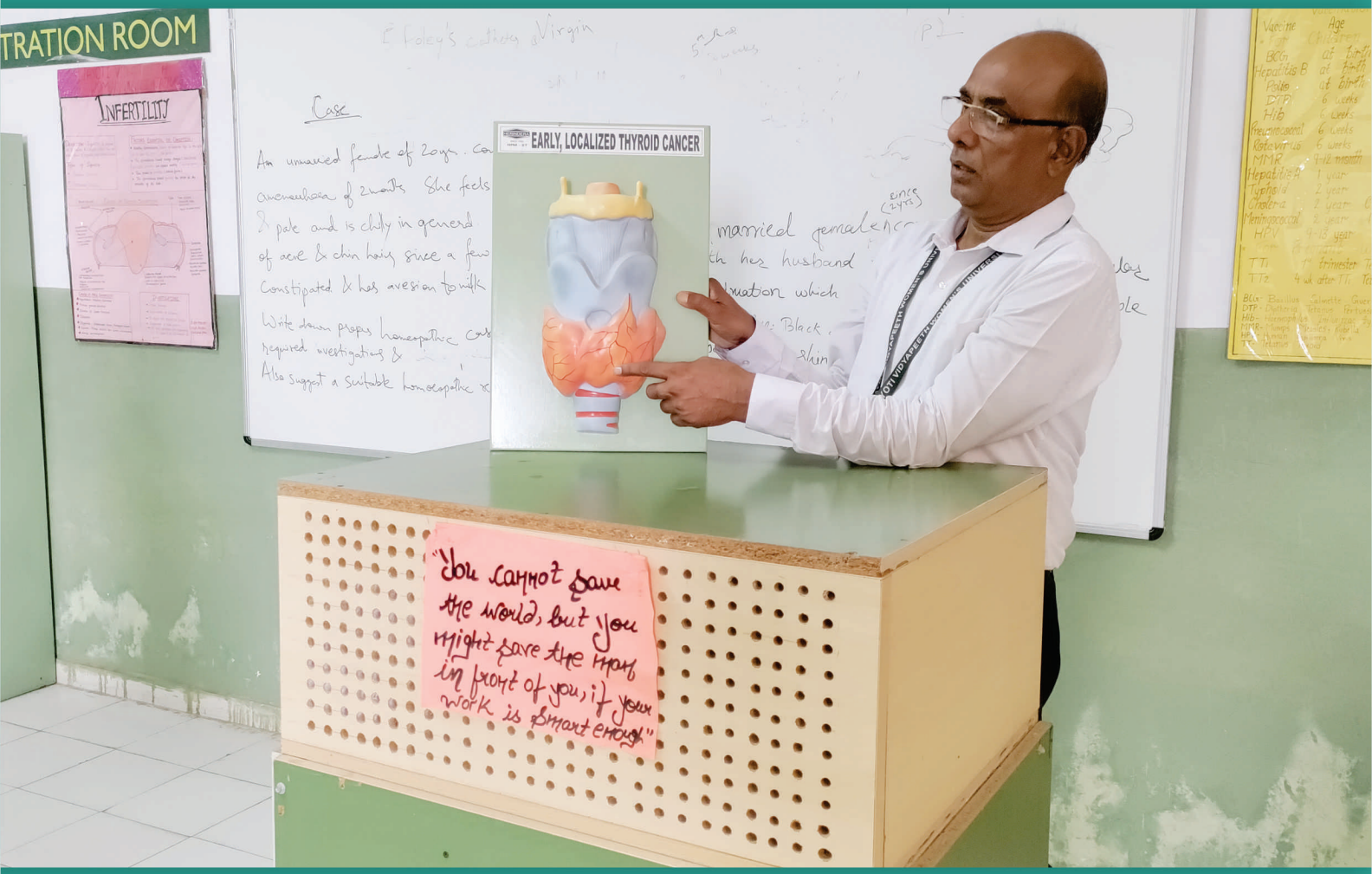
Women University Press
Jayoti Publication Desk
ISBN No. : 978-93-94024-37-3

A Book on Endocrinology



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UGC Approved Under 2(f) & 12(b) | NAAC Accredited | Recognized by Statutory Councils

Printed by :
JAYOTI PUBLICATION DESK

Published by :
Women University Press
Jayoti Vidyapeeth Women's University, Jaipur

Faculty of Homoepoathic Science

Title: A Book on Endocrinology

Author Name: Dr M P Sharma

Published By: Women University Press

Publisher's Address: Jayoti Vidyapeeth Women's University, Jaipur
Vedant Gyan Valley,
Village-Jharna, Mahala Jobner Link Road, NH-8
Jaipur Ajmer Express Way,
Jaipur-303122, Rajasthan (India)

Printer's Detail: Jayoti Publication Desk

Edition Detail:

ISBN: 978-93-94024-37-3

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ENDOCRINOLOGY

INTRODUCTION

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

1. Nervous system
2. Endocrine system.

Nervous and endocrine systems interact with one another and regulate the body functions. Endocrine system functions by secreting some chemical substances called hormones.

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 known as neurotransmitter.

"

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

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.

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.

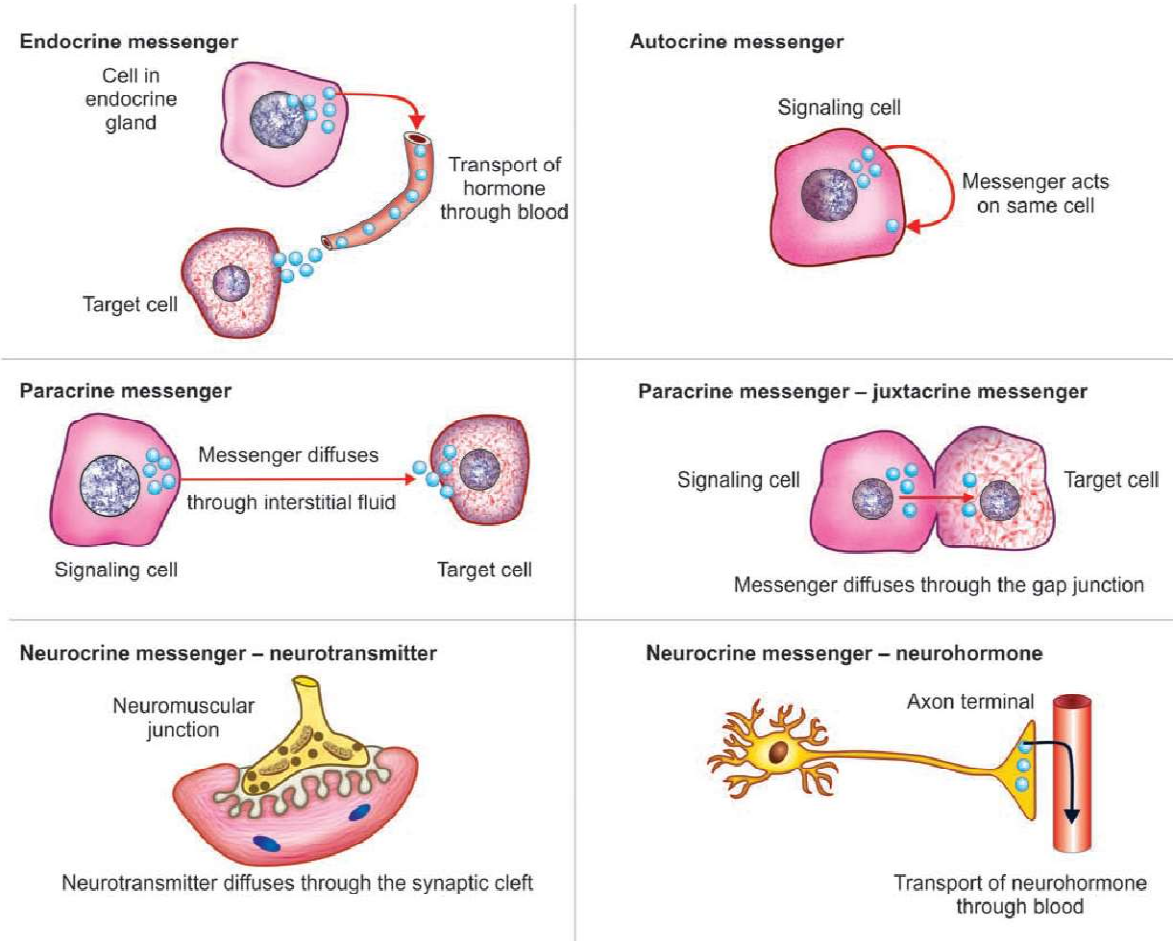
Paracrine messengers are the chemical messengers, which diffuse from the control cells to the target cells through the interstitial fluid. Some of these substances directly enter the neighboring target cells through gap junctions. Such substances are also called **juxtacrine messengers** or **local hormones.**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

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. Neurocrine or neural messengers are neurotransmitters and neurohormones .

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 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, ant diuretic hormone and
Hypothalamic releasing hormones.

Some of the chemical mediators act as more than one type of chemical messengers. For example, nor adrenaline and dopamine function as classical hormones as well as neurotransmitters. Similarly, histamine acts as neurotransmitter and paracrine messenger.



Chemical messengers

Endocrine glands are the glands which synthesize and release the classical hormones into the blood. Endocrine glands are also called **ductless glands** because the 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: .Hormones secreted by endocrine glands:. Hormones secreted by gonads: Hormones secreted by other organs .

STUDY OF ENDOCRINE GLANDS

Methods followed to study an endocrine gland:

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.

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

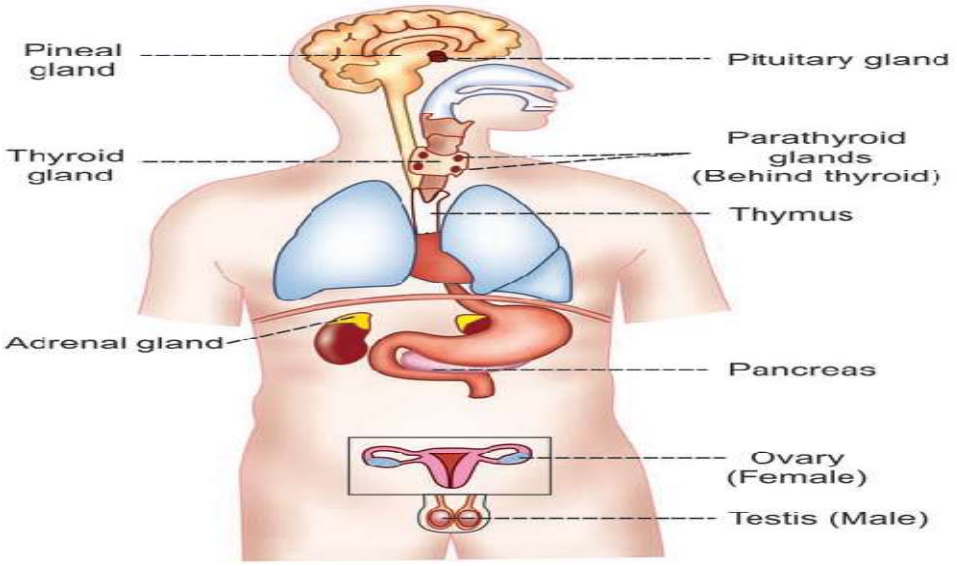


Diagram showing major endocrine glands

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.

A hormone is usually studied as follows:

1. Source of secretion (gland as well as the cell that secretes the hormone)
2. Chemistry
3. Halflife
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

Halflife 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. Halflife is also called biological halflife. Halflife 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 hypersecretion

(SIADH).

Testis

1. Testosterone
2. Dihydrotestosterone
3. Androstenedion

Ovary 1. Estrogen

2. Progesterone

Hormones secreted by other organs

Pineal gland Melatonin

Thymus 1. Thymosin

2. Thymin

Kidney

1. Erythropoietin

2. Thrombopoietin

3. Renin

4. 1,25dihydroxycholecalcifero

(calcitriol)

5. Prostaglandins

Heart

1. Atrial natriuretic peptide

2. Brain natriuretic peptide

3. Ctype

natriuretic peptide

Placenta

1. Human chorionic gonadotropin (HCG)

2. Human chorionic somatomammotropin

3. Estrogen

4. Progesterone

Local hormones

1. Prostaglandins

2. Thromboxanes

3. Prostacyclin

4. Leukotrienes

5. Lipoxins

6. Acetylcholine

7. Serotonin

8. Histamine

9. Substance P

10. Heparin

11. Bradykinin

12. Gastrointestinal hormones

CHEMISTRY OF HORMONES

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

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.

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

Hormone does not act directly on target cells. First itcombines with receptor present on the target cells and forms a **hormone-receptor complex.** This hormonereceptor 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.** 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.

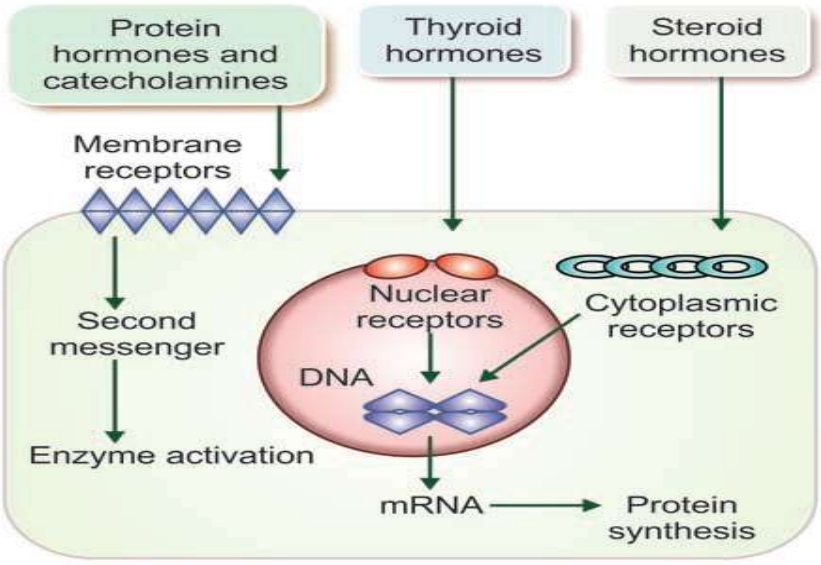
MECHANISM OF HORMONAL ACTION

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 Situation of hormonal receptore.



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Pituitary Gland-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.

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.

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PITUITARY GLAND

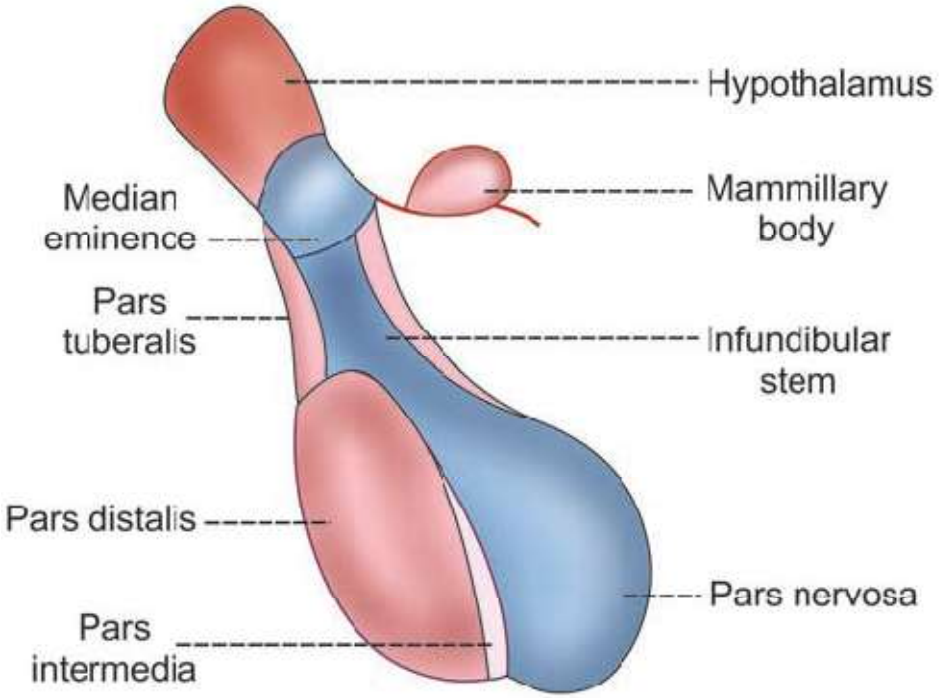
DEVELOPMENT OF PITUITARY GLAND

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. 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 trac 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 :

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



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 .

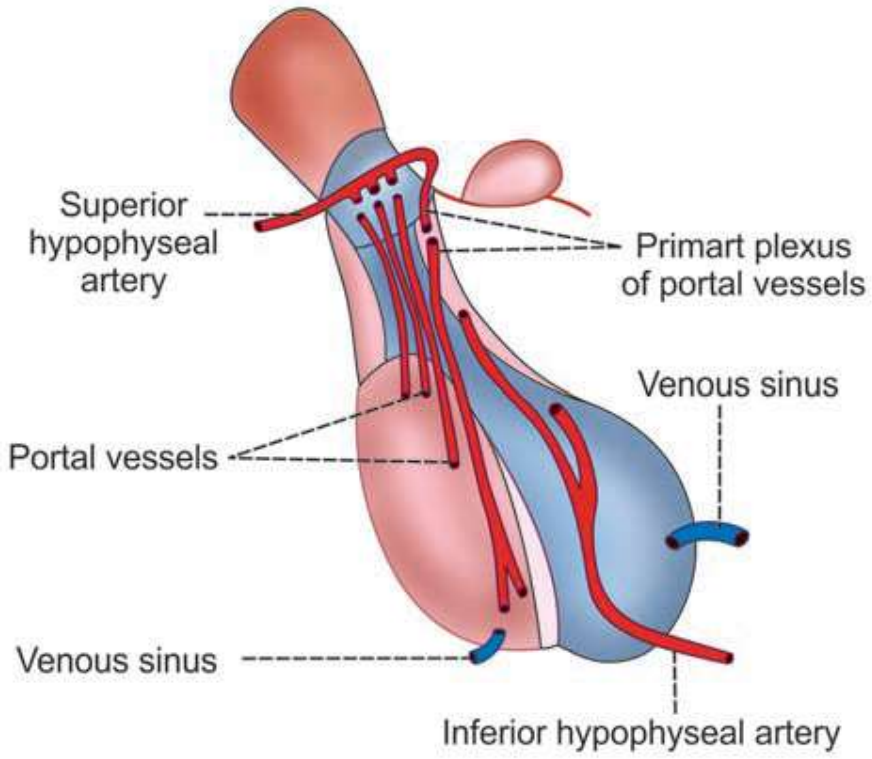
Releasing and Inhibitory Hormones Secreted by Hypothalamus

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)



Blood supply to pituitary gland

5. Luteinizing hormone (LH) in females or interstitialcell- stimulating hormone (ICSH) in males

6. Prolactin.

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

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

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 lGH 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 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 .

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 theike bone cells and muscle cells. 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 thicknes throughout the life. Particularly, the membranous bone

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 hypothalamohypophyseal portal blood vessels.

Feedback control

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

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(Only Speed Post is Received at University Campus Address, No. any Courier Facility is available at Campus Address)

Pages	: 23
Book Price	: ₹ 150/-

Women University Press

Jayoti Publication Desk

Year & Month of Publication- 9/1/2022