UNIT 1

INTRODUCTION TO ENDOCRINOLOGY

Structure

1.1 INTRODUCTION

Endocrinology is a scientific discipline in which we study about cell-to-cell signaling with a focus on specific chemicals called hormones that travel through the bloodstream to influence remote targets. Further, endocrinology requires a multidisciplinary approach to understand hormones and their role in the body physiology. Our body's endocrine system is composed of hypothalamus, pituitary, pineal, thyroid, parathyroid, adrenal, pancreas, gastro-intestinal tract and gonad (testis and ovary). Additionally, it also encompasses many other organs that respond to, modify or metabolize hormones. The dynamic concert of feedback regulation and cellular actions of the hormones of the endocrine system underwrites the internal homeostasis of the human body.

In this unit you will study about endocrine glands, different classes of hormones secreted by them and the underlying mechanism of hormone signaling. You will also learn about the functions and regulation of various hormones and how they are circulated, metabolized and excreted.

Expected Learning Outcomes

After studying this unit, you should be able to:

- define and classify hormones;
- explain various types of hormonal signaling;
- explain the transport of hormones in the circulation and their half-lives, metabolism and excretion; and
- explain the versatile functions of hormones and their regulation.

1.2 ENDOCRINE GLANDS

The endocrine system comprises of a set of glands and organs that regulate and control various functions of the body by producing and secreting hormones into the extracellular fluid. The endocrine system establishes the homeostasis in various physiological activities of the organism, regulates its development throughout life, and helps to respond to nutritional and other external environmental changes.

Hormones are chemical substances that gain access to the bloodstream, often via fenestrated capillaries and act in concert as messengers and thus, regulate and coordinate target organs throughout the body.

Endocrine gland: The hormones are secreted by the group of specific cells, in the **endocrine glands**, and are carried by the circulation to exert their actions on tissues distant from the site of their secretion. Each endocrine gland entails an assembly of specialized cells that have a common origin in the developing embryo.

The endocrine gland releases hormones into the bloodstream, whereas exocrine gland secretes their contents through a duct opening onto an external or internal surface of the body. Salivary and sweat glands are examples of exocrine glands.

The major glands of the endocrine system produce one or more specific hormones, are as follows:

Endocrine Glands	Hormones	Molecular Characteristics	Target Organs	Functions
Hypothalamus	Hypothalamic releasing and inhibiting hormones	Peptide	Anterior pituitary	Regulate anterior pituitary hormone
Anterior Pituitary	Thyroid stimulating (TSH)	Glycoprotein	Thyroid	Stimulates thyroid
	Adrenocorticotropic	Peptide	Adrenal cortex	Stimulates adrenal cortex
	Gonadotropic (FSH, LH)	Glycoprotein	Gonads	Sex hormone production, egg and sperm production
	Prolactin (PRL)	Protein	Mammary glands	Milk Production

	Growth Hormone (GH)	Protein	Soft Tissue, bones	Cell division, protein synthesis and bone growth
Posterior Pituitary	Oxytocin	Peptide	Uterus, mammary glands	Stimulates uterine contraction, breast contraction for milk release
	Anti-diuretic Hormone (Vasopressin)	Peptide	Kidneys	Stimulates reabsorption of water from kidney tubules
Pineal gland	Melatonin	Serotonin derived	Various tissues	Circadian rhythm, Reproduction
Thyroid Gland	Thyroxine (T4) Triiodothyronine (T3)	Iodinated amino acid	All tissues	Increase metabolic rate, regulates growth and development
	Calcitonin	Peptide	Bones, kidneys and intestine	Lowers blood calcium level
Parathyroids	Parathyroid hormone (PTH)	Peptide	Bones, kidneys and intestine	Raises blood calcium level
Adrenal Cortex	Glucocorticoids (Cortisol)	Steroid	All tissues	Raise blood glucose level, stimulates breakdown of protein
	Mineralocorticoids (Aldosterone, Cortisol)	Steroid	Kidneys	Reabsorb sodium and secrete potassium
Adrenal Medulla	Epinephrine and Norepinephrine	Catecholamines	Cardiac and other muscles	Released in emergency situations, raises blood glucose level, 'fight or flight' response
Stomach	Gastrin	Peptide	Enterochromaffin-like (ECL) cells	Stimulates secretion of gastric acid
Pancreas	Insulin	Protein	Liver, muscles, adipose tissue	Lowers blood glucose levels, promotes formation of glycogen
	Glucagon	Protein	Liver, muscles, adipose tissue	Raise blood glucose levels
	Somatostatin (Growth Hormone-inhibiting hormone)	Protein	All tissues	Exerts an inhibitory action on numerous physiological functions – production of hormones; unnatural rapid reproduction of cells (in tumors)
Duodenum and Jejunum	Secretin	Protein	Pancreas and Stomach	Regulates water homeostasis throughout the body

	Cholecystokinin	Protein	Gallbladder	Causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively; acts as a hunger suppressant
Ovary	Estrogen, androgen, Progesterone	Steroid	Gonads, skin, muscles and bone	Stimulates female sex characteristics
Testis	Androgens (Testosterone)	Steroid	Gonads, skin, muscles and bone	Stimulates male sex characteristics

SAQ 1

a) Tick [√] mark the correct statement:

i) Oxytocin and vasopressin are peptides and secreted by posterior pituitary.

ii) Insulin increases blood glucose levels and promotes formation of glycogen.

iii) Gastrin stimulates secretion of gastric acid.

b) Fill in the blanks with appropriate words:

i) Salivary and sweat glands are examples of ……...

ii) Vasopressin is also known as ……..

1.3 CHEMICAL SIGNALING

Chemical signals are molecules secreted by cells into the extracellular fluid. The cells that respond to chemical signals are called target cells. Chemical signals are accountable for utmost communication within the body. Chemical signals act as *ligands* that bind to receptor ptoteins to initiate a response.

In order to rapidly respond to changes in their environment, cells undergo fundamental cellular process of cell-cell signaling. Cell signaling, which is also known as signal transduction or transmembrane signaling, is the vital process for communicating specific information from the cell surface to cytoplasm leading to changes in gene expression in the nucleus. As a process, cell signaling denotes to a vast network of communication between and/or within the cells or with their external environment. All cells have the capacity to accomplish this to some degree, although with an extensive variation in purpose, mechanism, and response.

Cells stereotypically communicate using chemical signals, which can be proteins, short peptides, amines, nucleotides, steroids, even gases or other molecules produced by the **signaling cell**, released into the **extracellular fluid** around cells which are recognized and bound by a specific receptor protein in the **target cell**. The signal molecule binding to the receptor sets off a cascade of events in the target cell. The receptors are broadly of two types – cell surface and intracellular (Fig. 1.1).

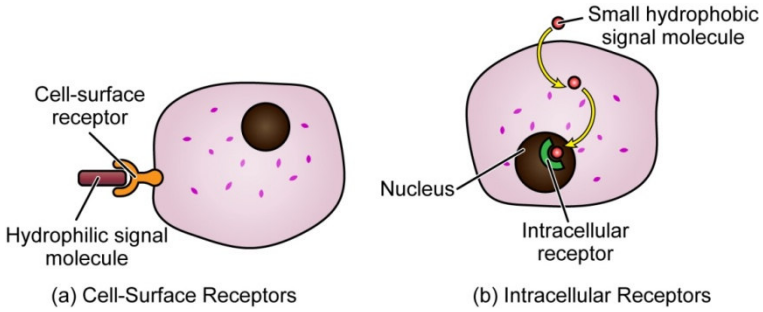

Fig. 1.1: Types of Receptors. (a) Cell-surface receptors, also known as membrane or transmembrane receptors are embedded in the plasma membrane of cells and act in cell signaling by binding to extracellular molecules; (b) Intracellular Receptors reside in the cytoplasm or in the nucleus. Their actions involve membrane permeable ligands.

The cascade of signaling events can be divided into three steps:

1. ***Reception:*** Cell perceives a signaling molecule from the exterior of the cell.

2. ***Transduction:*** Binding of signaling molecule to the receptor changes the three dimensional configuration of receptor protein. This change initiates the process of transduction.

3. ***Response:*** Finally, the signal triggers a specific cellular response.

In a multicellular organism, the average cell is exposed to numerous signals of varying kinds but the cell responds to specific signals primarily depending upon the receptors that the cell possesses. If a cell is deficit of a receptor for a signal, it cannot respond to it. Different cells have a specific set of receptors, so accordingly, they respond to only some signals and not others. However, regardless of a limited set of receptors, cells respond to a stunning array of signals with an inordinate diversity of responses because:

i. A single ***signal*** can generate a variety of responses in a target cell.

ii. Each relayed signal depends on the cell type and different cells may respond to the same signal in a different way (Fig. 1.2).

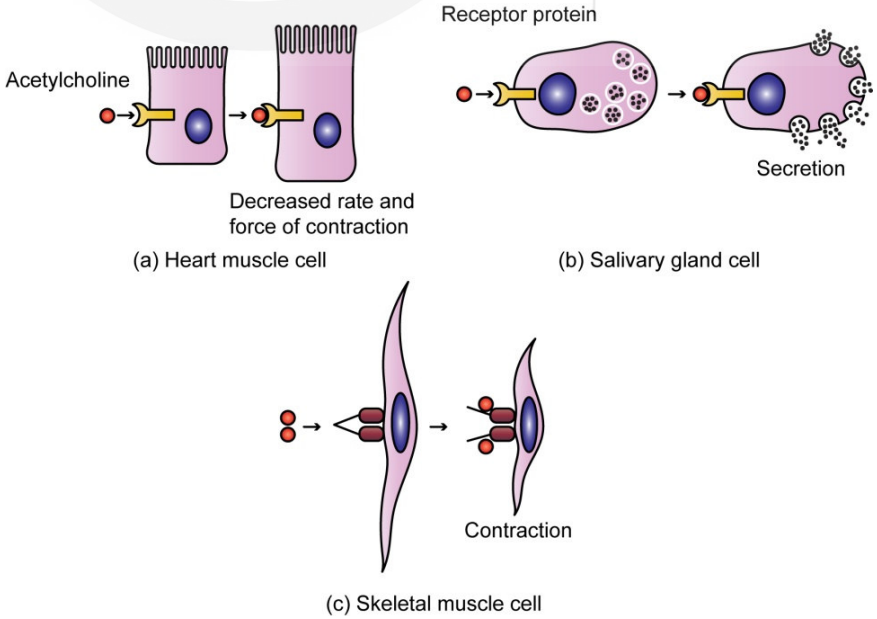

Fig. 1.2: Cell Signaling involves a receptor, a cellular protein that recognizes the signaling molecule and transmitted signal depends on the cell type. Different cells respond in a diverse way to the same signal.

iii. Since the cell has several receptors, a given cell can receive dozens of signals at the same time. The occurrence of one signal can affect the response to another signal, which means the cell can have diverse responses depending on the blends of signals received (Fig 1.3).

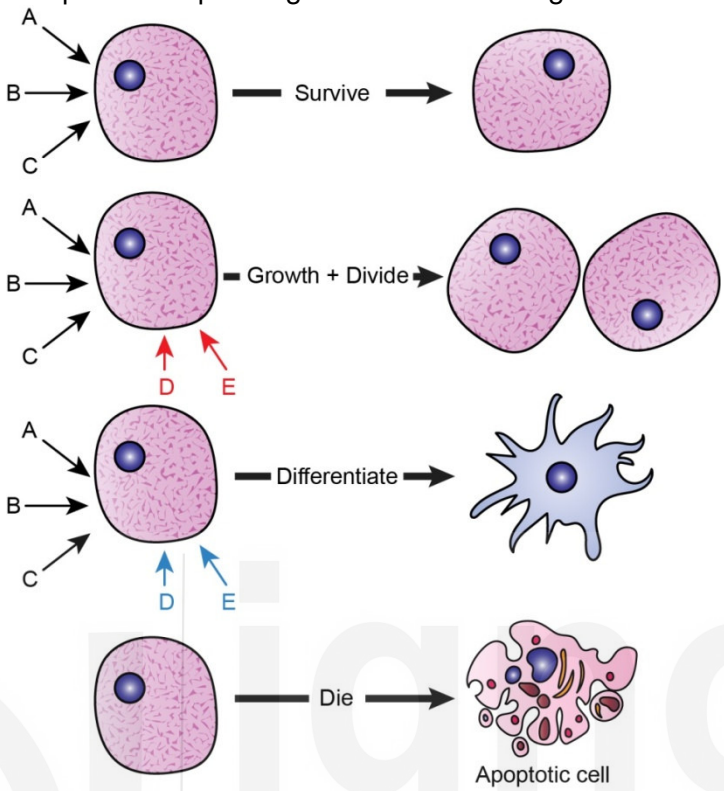

Fig. 1.3: Cell Signaling: Each cell type shows a set of receptors which allows it to respond to a conforming set of signal molecules formed by other cells. These signal molecules regulate the behavior of cells by working in combinations. As shown here, a specific cell involves numerous signals (blue arrows) to persist and added signals (red arrow) to divide or differentiate (green arrows). If appropriate survival signals are not present, a cell will undergo apoptosis.

Modes of cell-cell signaling: Cell signaling can take place in different ways:

Cryptocrine system- exudation of a hormone into a closed milieu and entails intimacy between cells, for instance connotation between Sertoli's cells and spermatids.

a) Local Signaling

i) *Cell-cell* contact dependent signals require interaction between membrane molecules on two cells (Fig. 1. 4A).

ii) *Gap Junctions* form direct cytoplasmic connections between adjacent cells (Fig. 1.4A).

iii) *Autocrine signaling* - a cell signals itself through a signaling molecule that it synthesizes and to which it also responds by a secreted chemical interacting with receptors on the surface of the same cell (Fig. 1.4B).

iv) *Paracrine signaling* - a molecule released from one cell and diffuses locally to interact with the receptors on the nearby target cells (Fig. 1.4C). Examples:

- Release of cytokines leading to an inflammatory response in the area.
- Release of neurotransmitters at synapses.

b) Long Distance Signaling

i) *Endocrine signaling* - hormones (chemicals secreted into the blood) are carried through the circulatory system to act on distant target cells (Fig. 1.4D).

ii) *Neural Signaling* - signaling molecules (neurotransmitters) are released by the axon terminal of a presynaptic neuron and bind to and react with the receptors on the dendrites of a postsynaptic neuron (Fig. 1.4E).

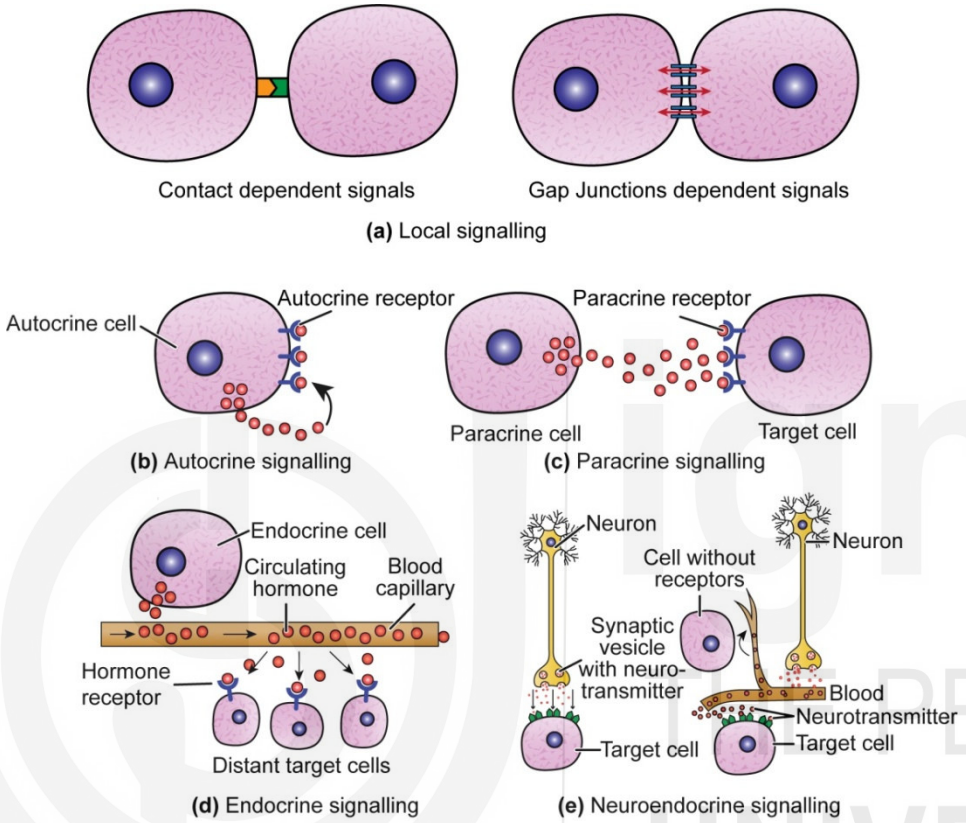

Fig. 1.4: Different modes of Cell Signaling. (a) Local signaling Involves either contact dependent signals which require interaction between membrane molecules on two cells or via gap junctions that form direct cytoplasmic connections between adjacent cells, (b) Autocrine signaling: the signaling molecules act on the same cell that secreted them, (c) Paracrine signaling: the signaling molecules released by a cell affect target cells only in close proximity, (d) Endocrine signaling: hormones secreted by the endocrine glands or cells into the blood and only target cells with receptors for the hormones respond to the signals, (e) Neuroendocrine signaling involves neurotransmitters secreted by neurons into the blood for action on distant target cells.

SAQ 2

Fill in the blanks with appropriate words:

i) Cell-surface receptors, also known as……. are recruited in the plasma membrane of cells.

ii) Neuroendocrine signaling involves ……secreted by neurons into the blood for action on distant target cells.

iii) Release of cytokines leading to an inflammatory response in the area is an example of ……..

1.4 CHEMICAL CLASSIFICATION OF HORMONES

Hormones can be allocated into two groups based on where they function in a target cell:

- ***Hormones that do not enter cells*** and signal through interactions with receptors at the cell surface. All polypeptide hormone (e.g., growth hormone), monoamines (e.g., serotonin), and prostaglandins (e.g., prostaglandin E2), use cell surface receptors.
- ***Hormones that can enter cells*** and signal by binding to intracellular receptors that function in the nucleus of the target cell to regulate gene expression. Classic hormones that use intracellular receptors include thyroid and steroid hormones.

Chemical Classes of Hormones: Based on chemical nature, hormones can be classified into two major groups- those that are soluble in lipids, and those that are soluble in water.

- ***Lipid-soluble Hormones:*** The lipid-soluble hormones comprise of steroid hormones (eg, cortisol), and lipids (eg, prostaglandins).
- ***Water-soluble Hormones:*** The water-soluble hormones include protein /peptide/ catecholamine / amino acid derived hormones.

A ***prohormone*** is a precursor of a hormone, such as a polypeptide that requires further cleavage before the mature hormone is produced.

The chemical nature of a hormone determines:

- How it is synthesized, stored, released and carried in the blood
- Its biologic half-life ($t_{½}$), mode of clearance and its cellular mechanism of action

Protein/Peptide Hormones: Based on the differences with their chain length protein hormones can be further classified as:

- Proteins hormones that contains 50 or more amino acids (eg, adrenocorticotropin)
- Peptides - consist of two or more amino acids (eg, vasopressin)
- Monoamines - synthesized from the amino acid tyrosine (eg, norepinephrine)
- amino acid derivatives (eg, triiodothyronine)

The characteristic features of the protein hormones are as follows:

- Synthesized as prehormones or preprohormones
- Hydrophilic and signal through transmembrane receptors
- Stored in membrane-bound secretory vesicles (sometimes called *secretory granules*) stored in the cells of gland.

- Protein hormones are not secreted incessantly but are released by *exocytosis* through the regulated secretory pathway (secreted in response to a stimulus).
- Tend to circulate in blood predominantly in unbound form but may circulate in bound form too.

***Receptors for Protein Hormones*:**

Protein and peptide hormones, such as follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), prolactin (PRL) and luteinizing hormone (LH), bind to receptors entrenched in the cell membrane of receptive cells. These receptors are large protein molecules that stereotypically have three key domains (Fig. 1.5):

- *Extracellular domain*- a portion of the receptor with ligand binding site that protrude outside the cell.
- *Transmembrane domain*- anchors the receptor within the plasma membrane.
- *Intracellular domain*- a part of the receptor protein that resides within the cell cytoplasm.

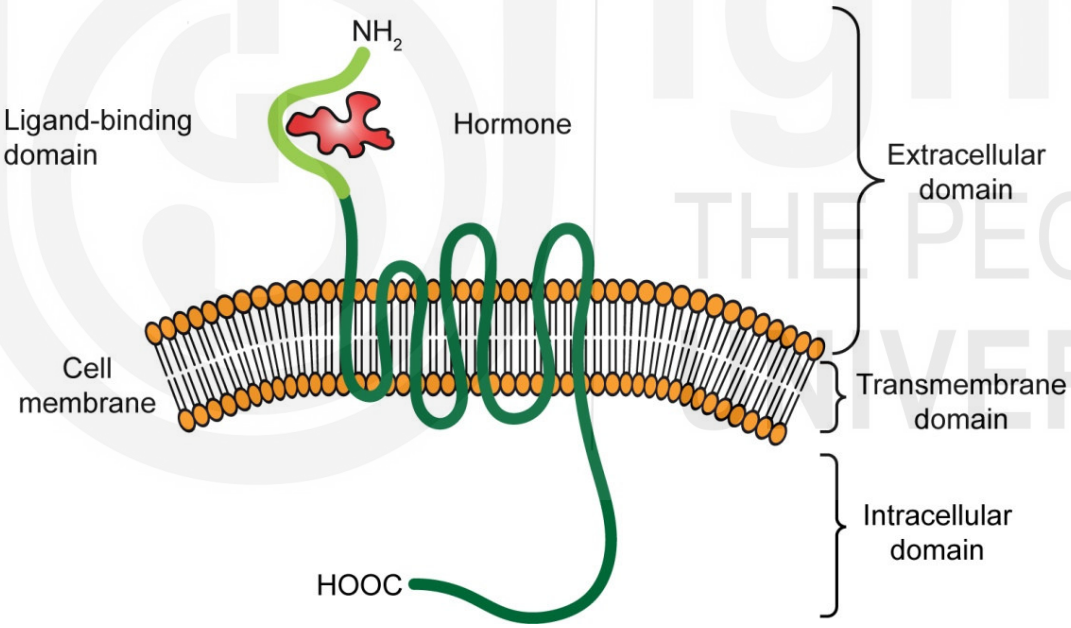

Fig. 1.5: Illustration of a cell surface receptor molecule displaying the ligand-binding domain (dark purple) as a portion of the extracellular domain. The transmembrane domain spans the plasma membrane of the cell, and the intracellular domain outspreads into the cytoplasm.

Binding of the ligand to its receptor leads to a conformational (shape) change in the receptor, which triggers a specific interaction amongst the cytoplasmic proteins in the cell, triggering the release of a second messenger e.g., cAMP and Ca^{2+} (the first messenger being the hormone itself) (Fig. 1.6). This "paraphrase" of the hormonal communication to the cell's interior is called signal transduction. A very small quantity of hormone can be augmented to amend thousands of molecules in the cell. Response to a protein/peptide hormone can occur in seconds or minutes after receptor binding.

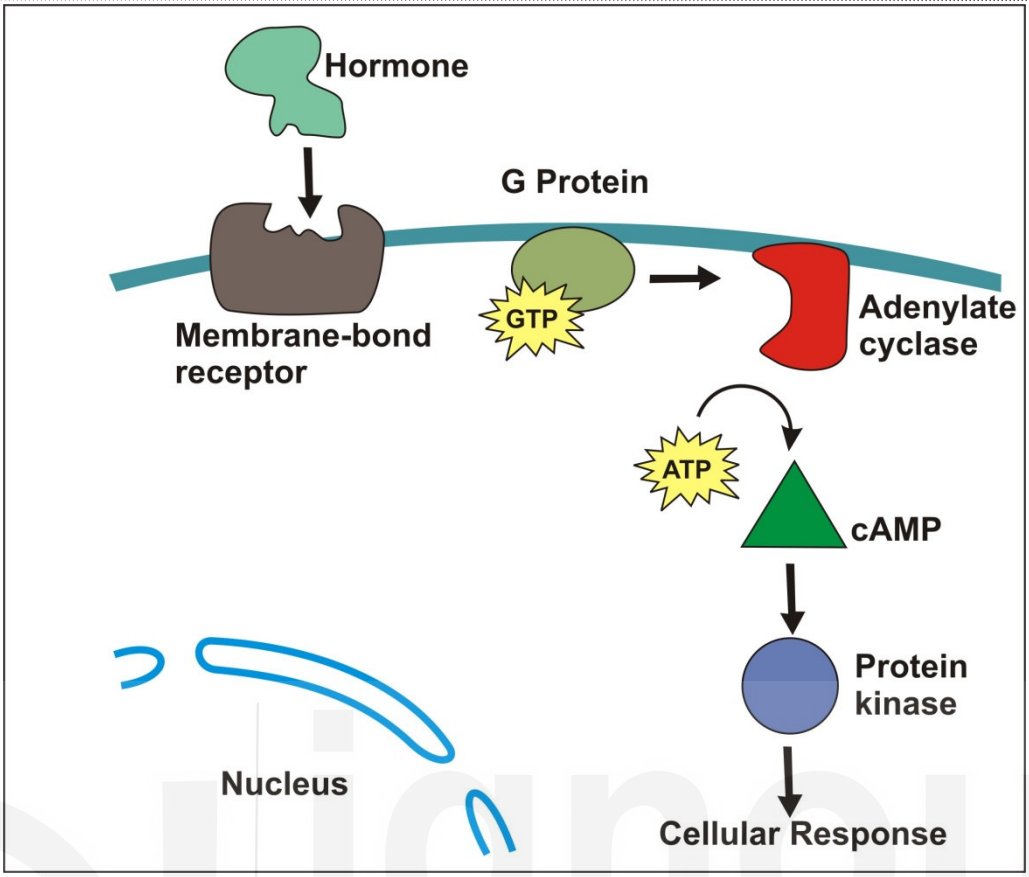

Fig. 1.6: Mechanism of action of a peptide hormone. Binding of a ligand to a cell surface receptor, generally activates a G protein, triggering the release of a second messenger (here, cAMP) that alters the activity of cytoplasmic enzymes in a consequential manner.

Steroid hormones are a set of hormones derived from a common precursor, cholesterol, which being fat-soluble organic molecules can effortlessly pass through cell membranes. Steroid hormones, in general, are made by the adrenal cortex, ovaries, testes, and placenta. The pattern of chemical bonds and modifications on the side chain make steroid hormones structurally diverse and thus categorized as follows:

- Progestins: 21-carbon steroids;
- Corticoids: 21-carbon steroids
- Androgens (male sex steroids): 19- carbon steroids
- Estrogens (female sex steroids): 18-carbon steroids

The characteristic features of the steroid hormones are as follows:

- Being lipophilic, these are carried in the blood in protein-bound form, by transport/carrier proteins which make them plasma-soluble.
- They cannot be stored in secretory vesicles due to their lipophilic nature.
- All steroid hormones are the derivative of **cholesterol**, which is either taken up from the extracellular fluid by the cells or produced by intracellular enzymes.

Receptors for Steroid Hormones

Steroid hormones being lipid soluble can effortlessly pass through the phospholipid bilayer of the plasma membrane.

The receptors for the steroid hormones are present within cytoplasm or nucleus of the target cells (Fig. 1.7). The binding of the steroid to its receptor causes a conformational change in its receptor thereby exposing its DNA-binding domain. The DNA-binding domain, in turn binds to a regulatory region of a steroid-responsive gene and thus turning on or off gene transcription. Steroid-receptor complex interacts with cofactors (nuclear proteins), which trigger or prevent transcription. The presence of different cofactors in different cells helps explain why the same hormone can have different effects on various cell types. Steroid hormones, in general, take some time (at least 30 minutes) to exert their action, as they modify gene expression, and transcription and translation of a protein and have long lasting effects.

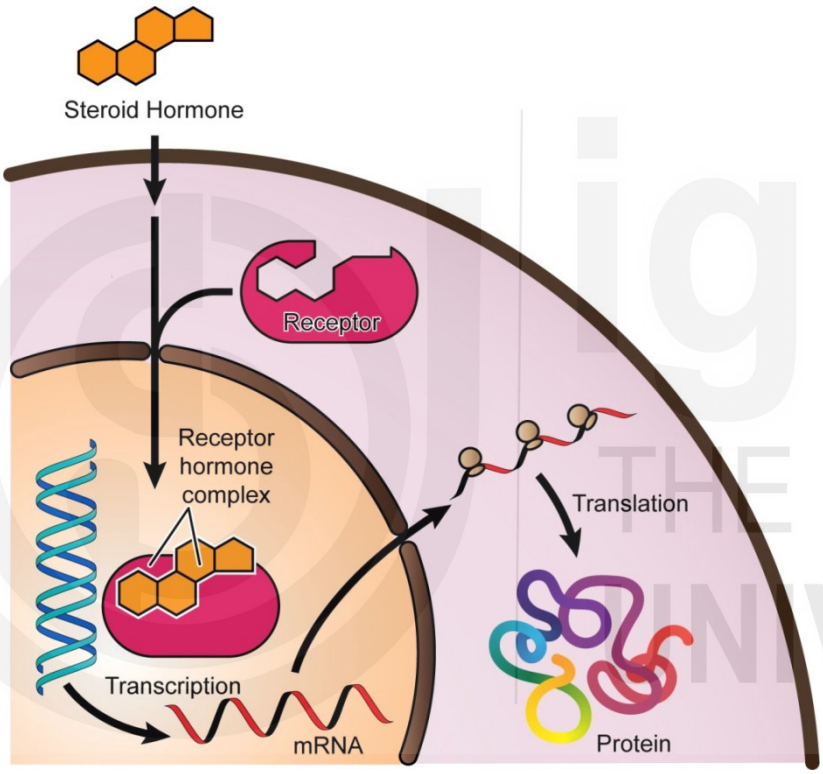

Fig. 1.7: Mechanism of action of a steroid hormone. Lipid soluble steroid hormone molecules pass through the plasma membrane via diffusion and bind to receptors present in the cytoplasm or nucleus. Thereafter, the steroid/receptor complex binds to regulatory regions of DNA, affecting the expression of specific steroid-responsive genes.

SAQ 3

Fill in the blanks with appropriate words.

i) The …… nature of the steroids permits them to freely diffuse across lipid bilayers.

ii) …….. is an extension of the receptor protein within the cell cytoplasm.

iii) All steroid hormones are derived from……..

1.5 TRANSPORT AND METABOLISM OF HORMONES

Once a hormone molecule is produced within an endocrine cell, it must be secreted from the producing cell before yielding a physiological effect.

Because of hydrophobic nature, steroid and thyroid hormones cannot circulate in the blood in their free-original forms contrary to the protein/peptide hormones which are hydrophilic and water soluble, in general. But, some protein /peptide hormones also remain bound with the carrier protein in blood. The examples of steroid/thyroid -binding proteins *are* corticosteroid-binding globulin, retinol-binding protein, sex hormone–binding globulin (SHBG), thyroxine-binding globulin, and vitamin D– binding protein. These serum binding proteins specially bind an exclusive class of steroid hormones.

However, protein/peptide hormones are stored inside the membrane-bound secretory vesicles in the cells which produce them and are secreted when required. For example, insulin is synthesized and densely packed in pancreatic β-cells and secreted in response to stimuli such as high blood glucose levels. Being insoluble in lipids, protein/peptide hormones do not readily cross hydrophobic cell membranes and thus exert their actions by binding to the receptors existing on the surface of the target cells.

Generally, once secreted, peptide hormones are not bound to carrier proteins in the bloodstream because these hormones are soluble in aqueous solvents. Consequently, they are rapidly degraded by serum proteases, resulting in shorter half-life. By contrast, the nonpeptide steroid and thyroid hormones have comparatively longer plasma half-lives as they circulate in association with specific binding proteins. However, there are some protein/peptide hormones like growth hormone (GH) and insulin-like growth factors (IGF-1 and IGF-2) which do circulate in association with binding proteins.

The hormone concentration in plasma depends not only upon its synthesis and secretion rate by the endocrine gland/cell but also upon its rate of removal from the blood, either by excretion or by its metabolism. The excretion or removal of hormone is required to prevent excessive, probably detrimental effects from the continued exposure of target cells to hormones. The liver and the kidneys are the key organs that excrete or metabolize hormones. However, occasionally a hormone is also metabolized by the cells upon which it acts whereby endocytosis of hormone–receptor complexes on plasma membrane empowers the cell to remove the hormone quickly from its surface and catabolize it intracellularly. Further, the receptors are recycled to the plasma membrane. Additionally, specific enzymes in the blood also breakdown some hormones, which tend to remain in the bloodstream. In contrast, removal of the circulating steroid and thyroid hormones usually takes relatively longer time, often several hours to days because these are protected from excretion or metabolism by enzymes as long as they remain bound with binding proteins. Fig. 1.8 depicts fate of a hormone.

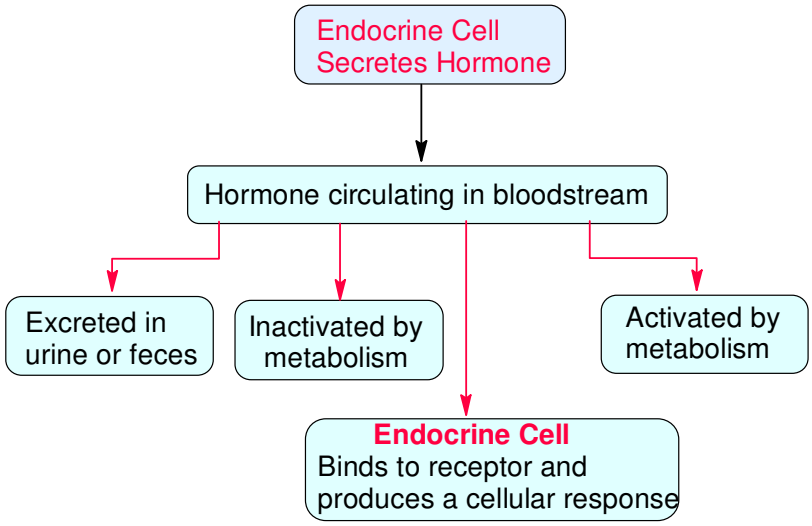

Fig. 1.8: Probable fates and actions of a hormone following its secretion by an endocrine cell. Not all paths apply to all hormones. Many hormones are activated by metabolism inside target cells.

1.6 FUNCTIONS OF HORMONES AND THEIR REGULATION

Hormones coordinate almost all biological activities, primarily metabolism, growth, development and reproduction, within an organism. Functions of some important hormones have already been tabulated in the Table 1.1.

By altering receptors, the hormones can alter the response of target cells either by upregulating or downregulating the number of hormones receptors. In certain cases, hormones can down-regulate or up-regulate not only their specific receptors but the receptors of other hormones as well. The effectiveness of a hormone will be dropped if it is down regulated by the receptor of another hormone. Alternatively, a hormone may induce a surge in the number of receptors for a second hormone and consequently, effectiveness of the second hormone is amplified.

Up-regulation is an upsurge in the number of a hormone's receptors in a cell, often due to extended exposure to a low concentration of the hormone.

This phenomenon in which one hormone is vital for another hormone to exert its full effect on the target cell is called permissiveness. For example, in presence of permissive amounts of thyroid hormone, epinephrine stimulates the release of fatty acids into the blood from adipocytes (Fig. 1.9).

Down-regulation is a decline in number of receptors often due to exposure to a high concentration of the hormone. This momentarily declines target-cell sensitivity to the hormone, thus avoiding overstimulation.

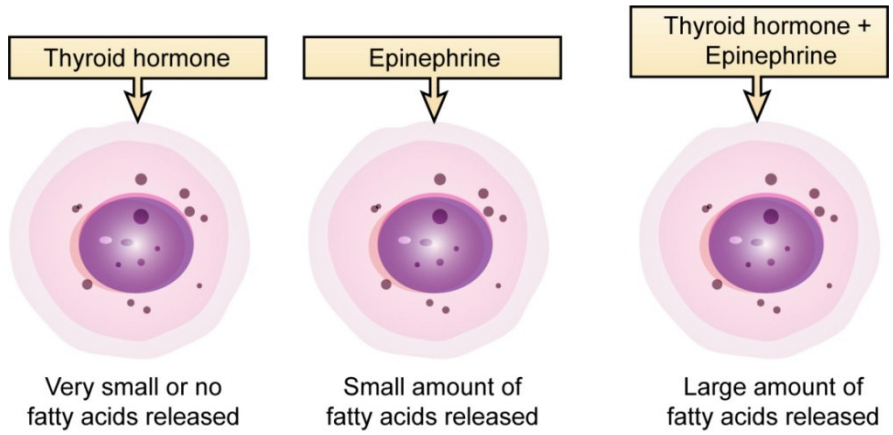

Fig. 1.9: Permissiveness: The capability of thyroid hormone to "permit" epinephrine-induced release of fatty acids from adipose tissue cells. Thyroid hormone exerts this effect by causing an increased number of beta-adrenergic receptors on the cell. Thyroid hormone by itself stimulates only a small amount of fatty acid release.

1.7 SUMMARY

Let us summarize what we have learnt so far:

- The endocrine system comprises of all the glands and organs that secrete hormones - the chemical messengers carried by the blood to target cells somewhere else in the body.
- Based on chemical nature, hormones can be classified into two major groups- those that are soluble in lipids, and those that are soluble in water.
- The lipid-soluble hormones comprise of steroid hormones (eg, cortisol), and lipids (eg, prostaglandins). The water-soluble hormones include protein-based hormones.
- Most hormones are peptides, many of which are synthesized as larger inactive molecules, which are then cleaved into active fragments, whereas the steroid hormones are principally produced from cholesterol by the adrenal cortex and the gonads.
- In general, protein/peptide hormones circulate dissolved in the bloodstream, but steroid hormones circulate mainly bound to serum-binding proteins.
- The liver and kidneys are the key organs involved in removal of the hormone from the circulation by metabolizing or excreting them. The protein/peptide hormones are rapidly removed from the blood, whereas the steroid hormones are removed gradually, mainly because they are bound to plasma proteins.
- After their secretion, some hormones are metabolized to more active molecules in their target cells or other organs.
- Most receptors for steroid hormones are inside the target cells whereas those for the peptide hormones are present on the surface of the plasma membrane.
- Hormones can up-regulate and down-regulate their own receptors and those of other hormones to exert increase in the effectiveness of the hormone.
- Hormones coordinate almost all biological activities, primarily metabolism, growth, development and reproduction of animals.

1.8 TERMINAL QUESTIONS

1. Why do only target cells respond to hormones?
2. What is the advantage of packaging peptide hormones in secretory vesicles?
3. Why are steroid hormones not packaged into secretory vesicles?

1.9 ANSWERS

Self-Assessment Questions

1. a) i) True

   ii) False

   iii) True

   b) i) Exocrine glands

   ii) Antidiuretic hormone (ADH)

2. i) Membrane or transmembrane receptors

   ii) Neurotransmitters

   iii) Paracrine signaling

3. i) Lipophilic

   ii) Intracellular domain

   iii) Cholesterol

Terminal Questions

1. A given hormone generally affects only a restricted number of cells called target cells. A target cell responds to a specific hormone because it bears receptors for the hormone.

2. By storing large quantities of hormone in an endocrine cell, the plasma concentration of the hormone can be increased within seconds when the cell is stimulated. Such rapid responses may be critical for an appropriate response to a challenge to homeostasis. Packaging peptides in vesicles also prevents intracellular degradation.

3. Because steroid hormones are derived from cholesterol, they are lipophilic. Consequently, they can freely diffuse through lipid bilayers, including those that constitute secretory vesicles. Therefore, once a steroid hormone is synthesized, it diffuses out of the cell.

UNIT 2

HYPOTHALAMIC HORMONES

Structure

2.1 INTRODUCTION

In Unit 1, you learnt about the hormones, their chemical nature and role in cell signaling. You also understood how these are transported to their specific targets through blood and metabolized. Functions performed by various hormones were briefed. In order to understand the mechanism and regulation of functions performed by hormones, we shall take up detailed discussion of the hormones secreted by different organs.

We shall begin with hypothalamus in this unit. This organ has two major roles: homeostasis and hormones. We shall focus on hormonal aspect of the organ. In the present unit, you will learn about various hypothalamic nuclei in mammals along with the various connections it has with different parts of the brain. You will also be made aware of the different hormones secreted by these hypothalamic nuclei into the circulation system along with their structure and function.

Expected Learning Outcomes

After studying this unit, you should be able to:

- explain location of hypothalamus;
- describe the structure and different pathways associated with the hypothalamus;
- define hypothalamo-hypophyseal portal system;
- explain the structure and function of different hypothalamic hormones; and
- explain some of the important diseases associated with the malfunctioning of hypothalamus.

2.2 STRUCTURE OF THE HYPOTHALAMUS

The hypothalamus, a relatively small-sized area in the diencephalon is located below thalamus. According to the anatomy of the hypothalamus, it extends from the level of the optic chiasm and the attached lamina terminalis to coronal plane just posterior to the mammillary bodies. Hypothalamus is connected at the middle region to the pituitary gland (also known as hypophysis) by the infundibular stalk, through median eminence. The median eminence, along with the pituitary stalk contains the portal vessels that carry releasing and inhibiting hormones from the hypothalamus to the anterior lobe of the hypophysis. These substances influence the secretion of the hypophyseal tropic hormones.

The word Hypothalamus is derived from two Greek words: hypo- means "under"; and thalamos which literally means "bridal couch", "nuptial chamber" or "innermost room".

2.2.1 Hypothalamic Nuclei

Hypothalamus in a broad aspect may be divided, based on antero-posterior plane in to three regions namely, **anterior or rostral hypothalamus**; **middle or tuberal hypothalamus** and **posterior or caudal hypothalamus**. Each of these regions contains many nuclei (Fig. 2.1).

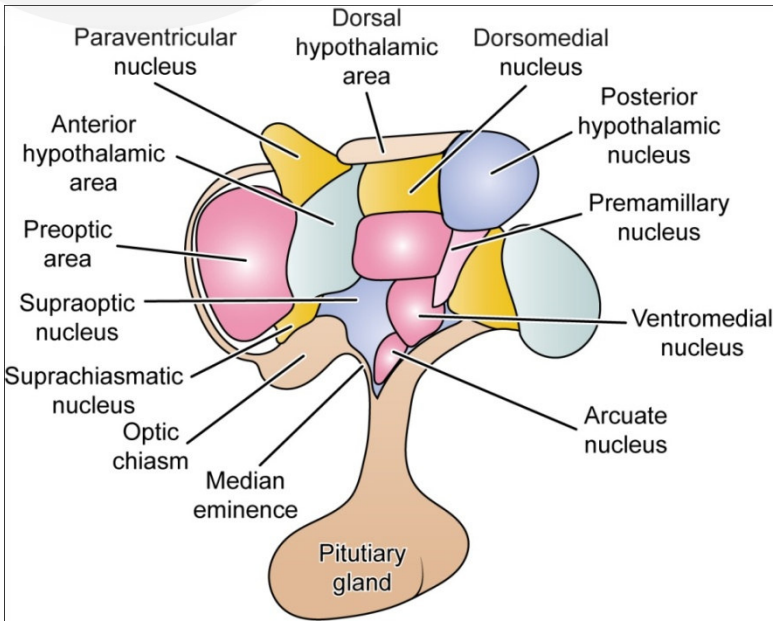

Fig 2.1: Various Hypothalamic Nuclei in Mammals.

These different hypothalamic nuclei are an aggregation of different size of neurons with varied function as elaborated in Table 2.1.

Table 2.1: Generalized classification of Hypothalamic Nuclei in mammals based on its location in the hypothalamus in to three parts namely anterior (rostral), middle (tuberal) and posterior (caudal) hypothalamus.

Hypothalamic Nuclei	Classification of Hypothalamic Nuclei	Hormones Produced by The Nuclei	Functional Roles	Sexually Dimorphic Nucleus
Pre-Optic Area (POA)	**Anterior Hypothalamus**, also known as Rostral Hypothalamus	Gonadotropin releasing hormone (GnRH), Thyroid releasing hormone (TRH), Estrogen receptor alpha (ERα), Estrogen receptor beta (ERβ), Progesterone receptor (PR), Androgen receptor (AR)	Neurosecretory regulation of Hypothalamo-hypophyseal gonadal axis, hypothalamo-pituitary thyroid axis, male sexual behaviour	Males>Females
Anterior Hypothalamic area (AHA)			Parasympathetic control, thermoregulation (control of body temperature)	
Periventricular Nuclei		Somatostatin, Kisspeptin, ERα, ERβ	Inhibition of Growth hormone secretion, control of ovulatory cycle	
Suprachiasmatic Nuclei (SCN)		Vasopressin, Vasoactive intestinal peptide (VIP)	Biological rhythms	Females>males
Paraventricular Nuclei (PVN), Supra-optic Nuclei (SON) – Magnocellular Neurons		Oxytocin, Vasopressin	Electrolyte and water balance, blood pressure (Vasopressin), milk ejection, uterine contractility (Oxytocin)	
Paraventricular Nuclei (PVN) – Parvicellular Neuron		Corticotropin releasing hormone (CRH), Thyroid releasing hormone (TRH), Glucocorticoid receptors GR	Stress responses, Neurosecretory control of Hypothalamo-pituitary adrenal (HPA) and Hypothalamo-pituitary thyroid (HPT) axis	
Arcuate Nucleus	**Middle Hypothalamus,** also known as tuberal	Pro-opiomelanocortin (POMC), Neuropeptide Y	Food Intake, energy expenditure, neurosecretory	

	Hypothalamus	(NPY), Agouti related peptide (AgRP), Growth Hormone releasing hormone (GHRH), Dopamine (DA), Kisspeptin, Estrogen receptor alpha (ERα), Progesterone receptor (PR), Glucocorticoid receptors (GR), Leptin receptors	control of prolactin (PRL) and Growth Hormone (GH)	
Ventromedial Nucleus (VMN)		GHRH, ERα, PR	Satiety, female sexual behaviour	
Dorsomedial Nucleus (DMN)		Neuropeptide Y (NPY), Glucocorticoid receptors (GR)	Behavioural rhythms, blood pressure, heart rate	
Lateral Hypothalamic Area (LHA)			Appetite and body weight control	
Posterior hypothalamic nucleus (PHN)	**Posterior Hypothalamus**, also known as caudal Hypothalamus		Sympathetic control, thermoregulation	
Pre-mammillary Nucleus (PMN)			Emotion and short-term meory	

Two of the hypothalamic nuclei POA and SCN show sexual dimorphism, while volume of the POA nuclei is more in males than in females and neurons with suprachiasmatic nucleus in the females tend to be more elongated than in males.

2.2.2 Hypothalamic Pathways

The hypothalamus is connected to the different regions of the brain by different tract and pathways (Fig. 2.2), the notable being the retino-hypothalamic tract (a connection between the eye and the hypothalamus); the hypothalamo-hypophyseal tract (a connection between the middle region of the hypothalamus to the pituitary); the fornix (the afferent hypothalamic pathway connecting the hypothalamus with the hippocampus); the medial forebrain bundle (extremely ill defined, but has connections to different parts of the brain such as cortex etc.); stria medullaris (assemble posterior to the anterior commissure connecting primarily the lateral preoptic area to the habenular nuclei along the dorsomedial surface of the thalamus); stria terminalis (innervating the bed nucleus of stria terminalis- BnST); spino-hypothalamic tract (a connection between the spinal cord and the hypothalamus); mammillothalamic tract (originates from the mammillary body and splits in to mammillothalamic and mammillotegmental tracts and projects into the anterior thalamic nuclei).

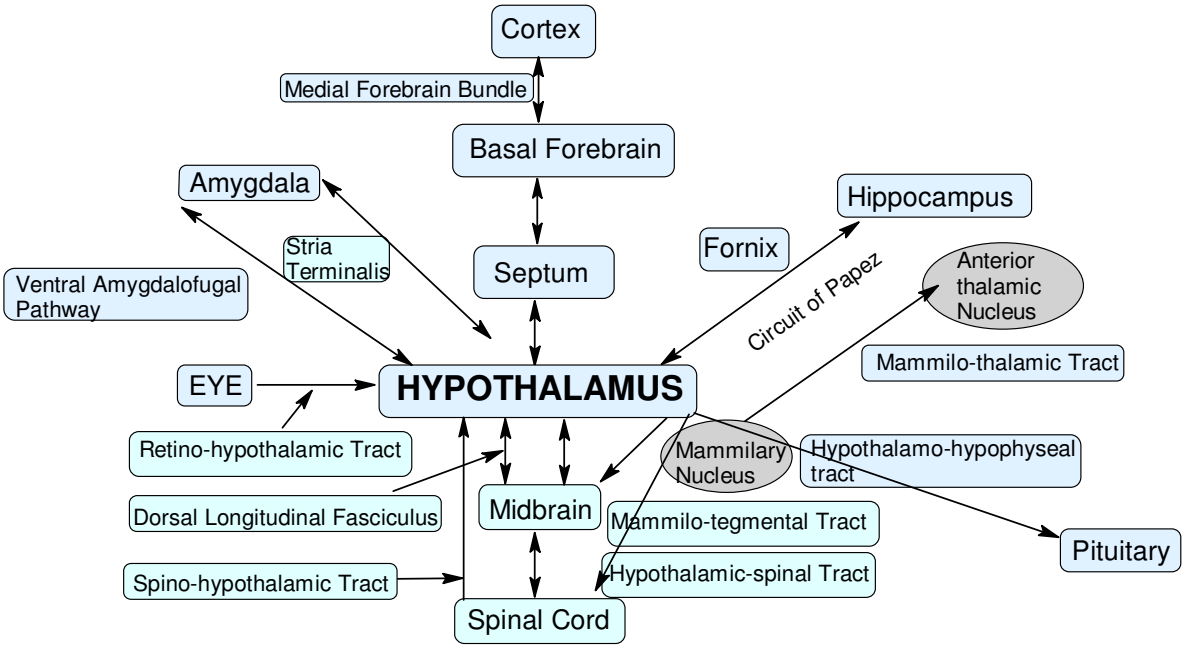

Fig. 2.2: Diverse hypothalamic Pathways showing connections of the hypothalamus with different parts of the brain.

SAQ 1

a) Tick [√] mark the correct statement:

i) Eye sends input to hypothalamus through retino-hypothalamic tract. [True/False]

ii) Pre-optic area is involved in female sexual behavior.[True/False]

iii) Supra-chiasmatic nucleus regulates daily body rhythm. [True/False]

iv) Hypothalamus is connected to the hippocampus by the pathway known as Circuit of Papez. [True/False]

b) Fill in the blanks with appropriate words:

i) Hypothalamus is divided into three parts namely ……, …… and ……..

ii) Paraventricular and supra-optic nuclei innervate the posterior gland and synthesize two hormones ……

iii) Based on the structure of the hypothalamic nucleus, pre-optic area in males show …… volume than the female and thus exhibit ……

iv) The hormone Kisspeptin is produced by …….. of the hypothalamus.

2.3 HYPOTHALAMIC-PITUITARY AXIS

The hypothalamus, as we have seen is connected to the pituitary gland by the infundibulum or the pituitary stalk. Though, once pituitary was considered the master endocrine gland, regulating widespread physiological effects throughout the body, it itself is under the control of the hypothalamus and hence, is no more considered as the master endocrine gland. Thus, hypothalamic hormones regulate the secretion of the pituitary hormones via negative feedback loops and secretions.

The pituitary gland, or **hypophysis** is located at the base of the brain, in a depression of the sphenoid bone and is divided into three divisions or lobes (Fig. 2.3).

(i) **Adenohypophysis or anterior pituitary or pars distalis**, contains cords of closely compacted epithelial cells, which secrete many hormones such as Growth hormone, Follicle Stimulating Hormone, Leutinizing Hormone etc.;

(ii) **Intermediate lobe or pars intermedia**, sandwiched between the anterior pituitary and the **posterior pituitary** and

(iii) **Neurohypophysis or the posterior pituitary or** pars nervosa. The posterior pituitary receive neurosecretory cell nerve endings from the hypothalamus and its hormones are synthesized by cell bodies of the hypothalamus but released from the neural cells that populate the posterior pituitary.

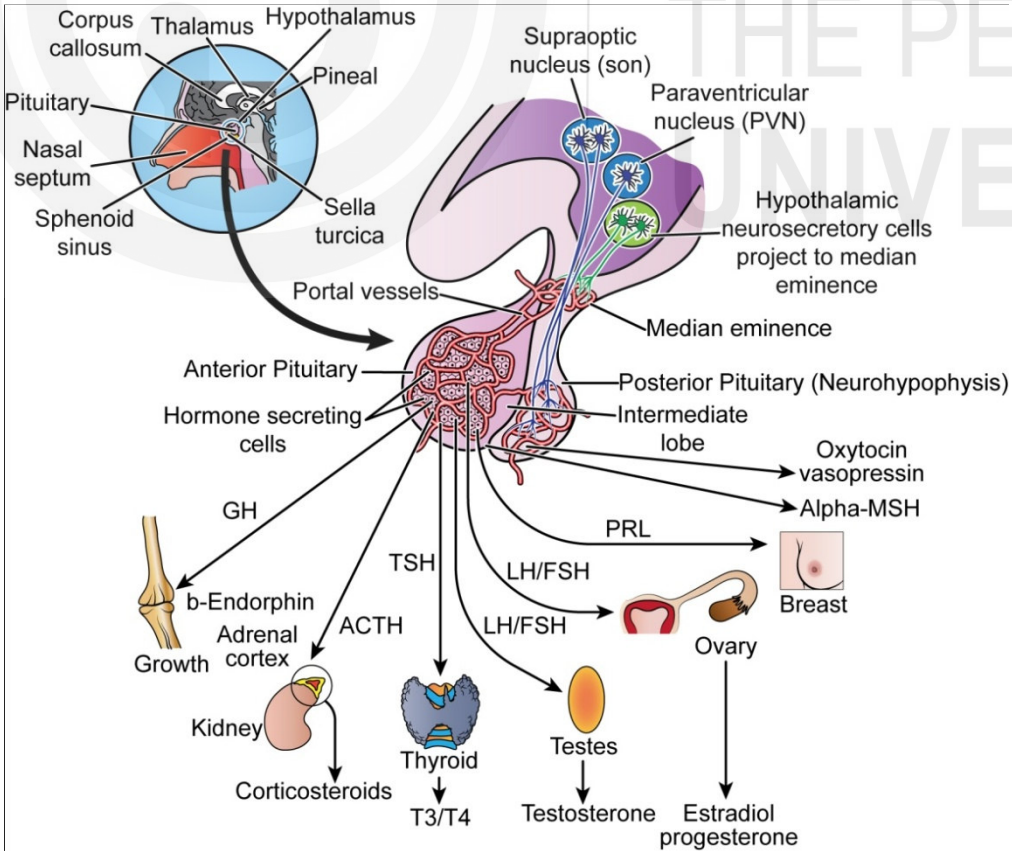

Fig. 2.3: Neuroanatomy of the Hypothalamo-Hypophyseal Axis along with the Hypothalamo-Hypophyseal portal blood system.

The secretion of the anterior pituitary hormones is under the control of the cells in the hypothalamus producing the hormones, known as releasing hormones or in some cases releasing-inhibiting hormone. These hormones are produced in a very small amount and impact the activity of the pars distalis cells by special arrangement of blood vessels between hypothalamus and the anterior pituitary, known as the **hypothalamic-hypophyseal portal blood system.**

Hypothalamo-Hypophyseal Portal Blood System: In simple words, hypothalamo- hypophyseal portal blood system is the venous blood that drains from the hypothalamus, mixes with arterial blood and passes to anterior pituitary before it goes into the general venous circulation. Thus, the superior hypophysial artery provides blood supply to the median eminence and pituitary stalk, from where blood passes via capillary loops through the long portal vessels to the sinusoids of the pars details. The importance of this system was confirmed by experiments showing that placing a foil barrier between the hypothalamus and pituitary markedly inhibited the secretion of all the anterior pituitary hormones except prolactin. The pituitary gland also receives oxygenated arterial blood from the arterial branches of the circle of Willis.

SAQ 2

Fill in the blanks with appropriate words:

i) The pituitary gland receives oxygenated arterial blood from the arterial branches of the ……..

ii) Dorsomedial nuclei secretes hormones …….

iii) Posterior hypothalamus comprises of hypothalamic nuclei known as ……

iv) Suprachiasmatic artery provides blood supply to the basal part of the …….. just above the optic chiasm

2.4 HYPOTHALAMIC HORMONES

Hypothalamus produces various hormones known as releasing hormones (see the Table 2.1). These are synthesized as part of larger precursor proteins, known as pre-pro hormones encoded by mRNA transcribed from the gene for the releasing hormone. These pre-pro hormones are proteolytically processed within the same neuron in which they are synthesized to yield the mature peptide. This processing takes place as the secretory vesicles containing the maturing peptide travel from the cell body down the axon to its terminus where the peptide will be released. Let us discuss the structure, chemical nature and function of these hormones one by one.

2.4.1 Gonadotropin-Releasing Hormone (GnRH)

The gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide hormone (Fig. 2.4) and its primary structure appears to be identical across all mammals except in guinea pig, with a high degree of GnRH sequence conservation across the vertebrates. GnRH is synthesized from precursor protein consisting of (from the amino to the carboxyl terminus) a 23-amino acid

signal peptide, GnRH, a proteolytic cleavage site (GKR), and the 56-amino acid GnRH associated peptide (GAP). This precursor protein is also highly conserved across species. GAP is co-secreted with GnRH following processing of the precursor into the mature peptides in the secretory granules of the GnRH neurons.

Isoforms of GnRH have also been identified with amino acid variation in position number 5, 7, and/or 8 which differ in species and tissue distribution. The number of GnRH neurons is relatively few in number (approximately 600-800) per brain.

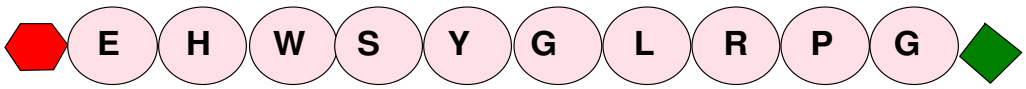

Fig 2.4: Structure of the decapeptide, Gonadotropin Releasing Hormone (GnRH). Left (Red colour) denotes amino terminal while right (Green colour) denotes carboxyl terminal.

The receptor for the GnRH, the G-Protein coupled receptor (GPCR) has a seven trans-membrane domain structure in which the cytoplasmic tail is absent from the GnRH receptor. GnRH acts through second messenger system by activating phospholipase C, release of IP3 and DAG (diacylglycerol), and activation of protein kinase C. These signals are transmitted to the nucleus through the JNK (c-jun N-terminal kinase) pathway to activate transcription of the gene for the β-subunit of either LH or FSH. In addition, elevated cyclic AMP and intracellular Ca^{2+} from activation of voltage-sensitive calcium channels both contribute to stimulus of secretion of stored GnRH.

GnRH is secreted in a pulsatile manner and is essential for the maintenance of reproductive function. Absence of GnRH secretion leads to partial or complete diminution of the two gonadotrophic hormones; the luteinizing hormone (LH) and follicle stimulating hormone (FSH). The pulsitility of the GnRH neurons are now thought to lie in the combination of the neuropeptides kisspeptin, neurokinin B and dynorphin, referred to as KNDy neurons and have been proposed to be located in the pre-optic area of the hypothalamus. These KNDy neurons project in to the GnRH neurons of the hypothalamus and thus help in regulating reproductive function. In recent years, it has been shown that mutations in the kisspeptin gene lead to hypogonadism and infertility in animals.

2.4.2 Thyrotropin-Releasing Hormone (TRH)

TRH is a tripeptide hormone Fig. 2.5 and like the GnRH, is synthesized from the pre-pro TRH molecule. The mature thyroid releasing hormone is formed by the process of amidation of glycine at the carboxy terminus and the modification of the N-terminal by glutaminyl cyclase. Human preproTRH is 242 amino acids and contains six copies of the tripeptide releasing hormone within its sequence. These progenitor TRH sequences are flanked by pairs of basic amino acids (Lys-Arg or Arg-Arg), the signals for the prohormone convertases (PC) 1 and 2, the proteolytic enzymes responsible for the processing of preproTRH and proTRH.

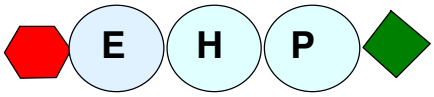

Fig 2.5: Structure of the tripeptide, Thyroid Releasing Hormone (TRH). Left (Red colour) denotes amino terminal while right (Green colour) denotes carboxyl terminal.

The receptor for TRH, located in the target cells of the anterior pituitary as well as elsewhere in the body, is a typical GPCR of the rhodopsin family with an extracellular amino terminus, three extracellular loops, seven transmembrane regions, three intracellular loops, and an intracellular carboxyl terminus. Two forms of TRH receptor, encoded by separate genes exist namely TRH-R1 and TRH-R2. In the pituitary, TRH-R1 mediates the TRH signal through binding to Gq/11 and induction of protein kinase C (PKC)-, phosphophatidyl-inositol- and $Ca2^{+}$-mediated signaling pathways.

Synthesis of pre-proTRH is stimulated by norepinephrine, enabling the hypothalamic- pituitary-thyroid axis to respond to cold and stress by increasing the rate of metabolism, a hallmark of thyroid hormone activity. The TRH neuron is also activated by appetite-stimulating hormones such as α-MSH and inhibited by anorexic or appetite-suppressing peptides such as AgRP (which binds to the α-MSH receptor and antagonizes its actions) and neuropeptide Y. To increase food intake, the adipose hormone leptin stimulates the TRH neuron either directly (through its receptor OB-Rb) or indirectly through the stimulation of α-MSH. Thus, the TRH neuron integrates important information about the environment relating to its effects on temperature, food intake, and stress and responds by activating the hypothalamic- pituitary-thyroid axis.

Negative feedback control of TSH secretion by the peripheral hormone T3 is thought to occur primarily at the thyrotrophs in the pituitary rather than the hypothalamus, but thyroid hormones also play a role in the hypothalamic neurons. T3, bound to its nuclear receptor TRβ2, inhibits the synthesis of mRNAs encoding both prepro-TRH and the enzymes that process it into mature releasing hormone.

TRH neurons have projections to areas of the central nervous system other than the anterior pituitary. Some axon terminals in the spinal cord have quite high TRH levels and contribute to the regulation of cardiovascular function. TRH from the dorsal motor nucleus of the vagus nerve affects gastrointestinal motility and gastric acid secretion. TRH has been identified in many peripheral tissues such as the retina, the adrenal medulla, and the pancreas, where it plays a role in the specialized functions of these cells.

2.4.3 Corticotropin-Releasing Hormone (CRH)

The 41 amino acid long primary structure of CRH (Fig. 2.6) is located in the carboxyl terminus of the 196-amino acid pre-prohormone. Pre-proCRH is encoded by the second of the two exons in its gene. Processing involves the prohormone convertase catalyzed cleavage of CRH from the prohormone precursor and the amidation of the carboxy terminal; this amide group is required for biological activity.

CRH stimulates the secretion of adrenocorticotropic hormone (ACTH), β-endorphin and proopiomelanocortin (POMC) derived peptides from the corticotroph cells of the anterior pituitary gland. CRH is also an important mediator to stress response in other areas of the brain and acts as a placental hormone during parturition. CRH is found in other areas of the central nervous system including the cerebral cortex, limbic system, cerebellum, brain stem, and spinal cord.

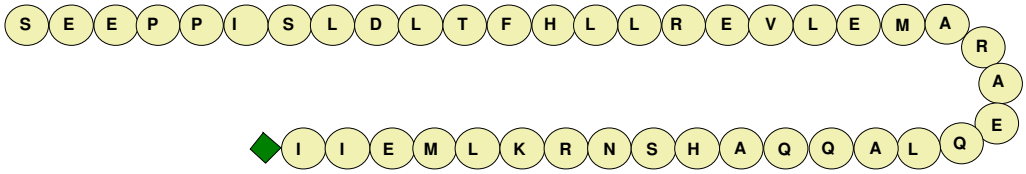

Fig 2.6: Structure of the Corticotropin Releasing Hormone (CRH). Green colour denotes carboxyl terminal.

Gamma aminobutyric acid (**GABA**) and β-endorphin are naturally occurring neuropeptides which have opposite roles. While **GABA** is considered an inhibitory neurotransmitter because it blocks, or inhibits certain brain signals and decreases activity of the nervous system; β- endorphin are involved in relieving of pain and stress.

The cell bodies of the neurons that synthesize and secrete CRH into the hypothalamic-pituitary portal system are located in the paraventricular nucleus of the hypothalamus. Neuronal input to these CRH secreting neurons comes from the limbic system (amygdala and hippocampus) and brain stem regions governing autonomic functions. CRH secretion from nerve terminals is regulated by the negative feedback of glucocorticoids as well as a number of neurotransmitters and neuropeptides. β- endorphin stimulates CRH release, whereas GABA is inhibitory.

CRH secretion also shows a circadian rhythm, and in humans there is an increase in CRH/ACTH/ cortisol release in the morning hours. The CRH peptide is also synthesized and released elsewhere in the brain, where it acts as a neuromodulator in addition to its role in the regulation of ACTH secretion. Thus, CRH gene expression is detectable in a wide variety of brain sites, including the cerebral cortex, amygdala and lateral hypothalamus, in addition to PVN.

Moreover, stress-related noradrenergic and glutamatergic excitatory signals can activate the gene, in part via activation of the transcription factor CREB (cyclic AMP response element binding protein). A second protein, TORC (transducer of regulated CREB activity), plays a vital role in cyclic AMP mediated regulation of CRH expression in these neurons. The regulation of CRH gene expression is localization-specific; for example, in other areas of the brain and in the placenta, glucocorticoids stimulate, rather than inhibit, CRH gene transcription.

2.4.4 Growth Hormone-Releasing Hormone (GHRH)

GHRH is secreted by the arcuate nucleus of the hypothalamus and is derived from a 108 amino-acid pre-prohormone yielding either GHRH (1-44) or GHRH (1-40), shortened at the carboxyl terminal Fig. 2.7). Both forms of GHRH are found in the human hypothalamus and since the full biological activity of GHRH lies in amino acid residues 1–29, the physiological differences between the two GHRH forms are likely minimal.

Growth hormone-releasing hormone (GHRH) was originally isolated from ectopic tumors producing it (and thereby causing observable derangements in growth), rather than from the hypothalamus. Its structure was determined in 1982.

Structurally, GHRH belongs to a family of proteins that includes secretin, glucagon, glucagon-like peptides (GLP-1 and GLP-2), and vasoactive intestinal peptide (VIP). Following secretion from its neurons into the portal circulation, GHRH binds to its receptor, GHRH-R, a G-protein coupled receptor on the somatrophs of the anterior pituitary. Increased cyclic AMP production leads to the increased synthesis of GH. Cyclic AMP also stimulates the opening of Ca^{2+} and K^{+} ion channels, which play roles in the secretion of existing GH from the cell, in its characteristic pulsatile fashion. Phospholipid signaling may also be involved in the exocytosis associated with the release of GH by the somatotroph when stimulated by GHRH. In addition to its effect on GH secretion and synthesis by somatotrophs, GHRH stimulates proliferation of these cells through the activation of the MAP kinase pathway.

GHRH and/or its receptor also occur outside the central nervous system in tissues such as the pancreas where it stimulates insulin, glucagon and somatostatin release; in the gastrointestinal tract where it stimulates gastrin release and epithelial cell division; and in tumors of many types.

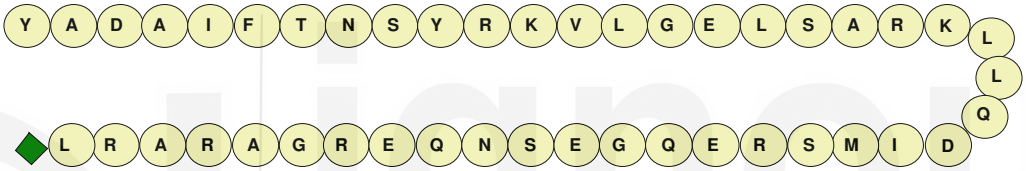

Fig 2.7: Structure of the Growth Hormone Releasing Hormone (GHRH). Green colour denotes carboxyl terminal.

2.4.5 Somatostatin

Somatotrophs are the cells on anterior lobe of the pituitary gland that produce the hormone somatotropin.

The stimulatory effect of GHRH on GH release from the anterior pituitary somatotroph is countered by the GH release-inhibiting hormone, somatostatin (SST), also known as somatotropin release inhibiting hormone (SRIH). Somatostatin 28 and somatostatin 14 (Fig. 2.8), names based on the length of the amino acid sequence of the two forms, play the major role in the regulation of pituitary function in humans.

The periventricular nucleus (located rostral to the paraventricular nucleus) is the major site of somatostatin producing neurons in the hypothalamus. In addition to its inhibitory effect on GH secretion by somatotrophs, for which it was named; somatostatin also modulates a much broader range of peptides from the pituitary (e.g., TSH), as well as from the stomach, brain, intestine, and pancreas. For example, one of the somatostatin receptors (SSTR4) acts in the brain to decrease the levels of Alzheimer's related amyloid β peptide by increasing their rate of degradation.

There are five somatostatin receptors, designated SSTR1–SSTR5. These are encoded by separate genes on separate chromosomes. They differ in their tissue expression patterns, their affinities for various somatostatin agonists, and the G-proteins, and therefore the cell signaling pathways, to which they are coupled. Clearly, this degree of variation allows somatostatin to have diverse effects in many different target tissues. Somatostatin14 has greatest affinity for SSTR2, which is responsible for the inhibition of the secretion of pituitary hormones, including GH. SSTR2 activation also initiates opening of K^{+} channels and closure of Ca^{2+}channels. Both mechanisms contribute to the suppression of pituitary growth hormone secretion.

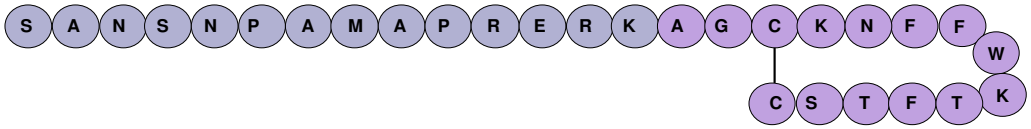

Fig 2.8: Structure of somatostatin hormone.

2.4.6 Hypothalamic Control of Prolactin Secretion

In mammals, the primary hypothalamic control of prolactin secretion is predominantly through the inhibitory action of dopamine, secreted by neurons in the dorsomedial area of the arcuate nucleus and the inferior ventromedial nucleus of the hypothalamus. Prolactin is the only pituitary hormone regulated in this fashion— that is, showing unrestrained secretion in the absence of hypothalamic input.

The most immediate (within seconds) response to dopamine is increased potassium conductance and inactivation of voltage sensitive Ca^{2+} channels. The resulting diminished intracellular Ca^{2+} leads to reduced exocytosis of secretory vesicles containing prolactin. Within a few minutes, inhibition of adenyl cyclase reduces intracellular Ca^{2+} leading to decreased prolactin gene expression. Sustained exposure to dopamine input leads to decreased lactotroph proliferation.

TRH and vasoactive intestinal peptide (VIP) have also been shown to be capable of stimulating prolactin secretion. These effects are exerted through the signaling pathways and result in increased expression of the prolactin gene. The physiological role of these stimulatory peptides in humans remains somewhat unclear, however, and by far the most powerful positive influence on prolactin secretion is neuronal one exerted by the suckling.

2.5 HYPOTHALAMIC DISEASE

Damage to the hypothalamus or to the fragile structures connecting the hypothalamus to the anterior pituitary, the stalk and the connecting blood portal system, can have serious and far-reaching consequences. This kind of damage can happen through trauma to the head or through tumor invasion of the area. These conditions can be collectively listed under panhypopituitarism or hypothalamic hypofunction.

Many of the releasing hormones will fail to arrive at their receptors on the plasma membranes of the specific anterior pituitary cell, and the hypothalamic–pituitary– end organ axis will be broken. There is usually an order to the loss of hormonal secretions in hypopituitarism. GH deficiency occurs early followed by LH, FSH, and TSH, and ACTH deficiencies. One rarely sees PRL deficiency. Since prolactin is under predominantly negative control of dopamine from the hypothalamus, hyperprolactinemia is the result of damage to the connection between the hypothalamus and the pituitary.

Diagnosis of disruption of hypothalamic– pituitary communication is now possible through the availability of the releasing hormone assays. Often patients with these syndromes are treated with the hormone of the terminal gland in the pathway, such as the adrenal hormones, gonadal steroid hormones, or thyroid hormones.

The isolated deficiency of GnRH leads to Kallman's syndrome, which refers to anosmic (lacking a sense of smell) patients with hypogonadotropic hypogonadism. There is a cluster of genetic variations that lead to one or more features of this syndrome, with some variants lacking some of the clinical manifestations present in the overt syndrome. The syndrome may originate from an arrest of the migration of the GnRH neurons from the medial part of the nasal epithelium to the hypothalamus/ preoptic area at the appropriate time in development. Treatment of individuals with this syndrome usually involves pulsatile administration of GnRH.

Hypopituitarism

The hypothalamus and pituitary gland are tightly integrated. Damage to the hypothalamus impacts the responsiveness and normal functioning of the pituitary. Hypothalamic disease may cause insufficient or inhibited signalling to the pituitary leading to deficiencies of one or more of the following hormones: thyroid-stimulating hormone, adrenocorticotropic hormone, beta-endorphin, luteinizing hormone, follicle-stimulating hormone, and melanocyte–stimulating hormones. Treatment for hypopituitarism involves hormone replacement therapy.

Neurogenic diabetes insipidus

Neurogenic diabetes insipidus may occur due to low levels of ADH production from the hypothalamus. Insufficient levels of ADH result in increased thirst and urine output, and prolonged excessive urine excretion increases the risk of dehydration.

Tertiary hypothyroidism

The thyroid gland is an auxiliary organ to the hypothalamus-pituitary system. Thyrotropin-releasing hormone (TRH) produced by the hypothalamus signals to the pituitary to release thyroid-stimulating hormone (TSH), which then stimulates the thyroid to secrete T_4 and T_3 thyroid hormones. Secondary hypothyroidism occurs when TSH secretion from the pituitary is impaired, whereas tertiary hypothyroidism is the deficiency or inhibition of TRH.

Thyroid hormones are responsible for metabolic activity. Insufficient production of the thyroid hormones results in suppressed metabolic activity and weight gain. Hypothalamic disease may therefore have implications for obesity.

Developmental disorders

Growth hormone-releasing hormone (GHRH) is another releasing factor secreted by the hypothalamus. GHRH stimulates the pituitary gland to secrete growth hormone (GH), which has various effects on body growth and sexual

development. Insufficient GH production may cause poor somatic growth, precocious puberty or gonadotropin deficiency, failure to initiate or complete puberty, and is often associated with rapid weight gain, low T_4, and low levels of sex hormones.

Diagnosis and treatment of diseases with neuroendocrine components must always consider the multidimensional nature of the controlled neuroendocrine system. Diseases that cause dysregulation in the neuroendocrine homeostatic axes are considered primary, if they involve the major end organ of the axis, or secondary, if defects occur at antecedent levels (pituitary or hypothalamus). Neuroendocrine diseases are usually diagnosed with the aid of X-rays, MRIs and other imaging diagnostic procedures, along with measurements of pituitary and endorgan hormones in serum. In some cases, provocative tests of a target- organ function are conducted with stimulatory hormone preparations.

2.6 SUMMARY

Let us summarize what we have learnt so far:

- Hypothalamus regulates various physiological functions of the body, thus helping in maintenance of body homeostasis.
- Based on the cytoarchitecture of the hypothalamus, it is divided into three parts namely anterior, middle and posterior hypothalamus containing almost 11 hypothalamic nuclei.
- Some of the hypothalamic nuclei such as pre-optic area and supra-chiasmatic nuclei exhibit sexual dimorphism.
- The hypothalamus is connected to different parts of the brain known as hypothalamic pathways.
- In addition to the connections with different parts of the brain, the hypothalamus is also connected to the pituitary by the infundibulum or the pituitary stalk, forming the hypothalamo-pituitary axis.
- Venous blood drains from the hypothalamus, mixes with the arterial blood and passes to the anterior pituitary in to the general venous circulation through a system known as hypothalamo-hypophyseal portal system.
- Hypothalamus secretes various releasing and inhibiting -hormones such as GnRH, TRH, CRH, PRL, GHIH etc. helping to maintain the various physiological functions of the body.
- Damage to the hypothalamus or to the fragile structures connecting the hypothalamus to the anterior pituitary, the stalk and the connecting blood portal system may lead to disruption of many hormonal activities. These conditions are collectively known as panhypopituitarism or hypothalamic hypofunction.

2.7 TERMINAL QUESTIONS

1. What is hypothalamus? Explain about its parts.
2. Name the hormones produced by Pre-optic area, paraventricular nuclei and supra-optic nuclei? What are their functions?
3. Explain the structure of thyroid releasing hormone.
4. Explain symptoms of Kallman's syndrome.
5. Define hypothalamo-hypophyseal portal system?

2.8 ANSWERS

Self-Assessment Questions

1. a) i) True
   ii) False
   iii) True
   iv) False
   b) i) Anterior or Rostral, Middle or Tuberal and Posterior or Caudal hypothalamus
   ii) Oxytocin and Vasopressin
   iii) Greater, sexual dimorphism
   iv) Periventricular and Arcuate nucleus
2. a) i) Circle of Willis
   ii) Neuropeptide Y (NPY), glucocorticoid receptors (GR)
   iii) Posterior hypothalamic nuclei and pre-mammillary nucleus
   iv) Pre-optic area

Terminal Questions

1. The hypothalamus, a relatively small-sized area in the diencephalon is located inferior to the thalamus. According to the anatomy of the hypothalamus, it extends from the level of the optic chiasm and the attached lamina terminalis to coronal plane just posterior to the mammillary bodies. Hypothalamus is connected at the middle region to the pituitary gland (also known as hypophysis) by the infundibular stalk, through median eminence. Refer to the section 2.2 for more details.
2. The hormones produced by pre-optic area are gonadotropin releasing hormone (GnRH), thyroid releasing hormone (TRH), estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), progesterone receptor (PR), androgen receptor (AR). Major function of this nucleus is neurosecretory regulation of hypothalamo-hypophyseal gonadal axis, hypothalamo-pituitary thyroid axis and male sexual behavior. The hormones produced

by paraventricular and supra-optic nuclei, also referred to as magnocellular neurons are oxytocin and vasopressin. Their major functions are electrolyte and water balance, blood pressure (vasopressin), milk ejection and uterine contractility (oxytocin).

3. TRH is a tripeptide hormone and, is synthesized from the pre-pro TRH molecule. The mature thyroid releasing hormone is formed by the process of amidation of glycine at the carboxy terminus and the modification of the N-terminus by glutaminyl cyclase. Human preproTRH has 242 amino acids and contains six copies of the tripeptide releasing hormone within its sequence. These progenitor TRH sequences are flanked by pairs of basic amino acids (Lys-Arg or Arg-Arg), the signals for the prohormone convertases (PC) 1 and 2, the proteolytic enzymes responsible for the processing of preproTRH and proTRH.

4. The isolated deficiency of GnRH leads to Kallman's syndrome, which refers to anosmic (lacking a sense of smell) patients with hypogonadotropic hypogonadism. There is a cluster of genetic variations that lead to one or more features of this syndrome, with some variants lacking some of the clinical manifestations present in the overt syndrome. The syndrome may originate from an arrest of the migration of the GnRH neurons from the medial part of the nasal epithelium to the hypothalamus/ preoptic area at the appropriate time in development. Treatment of individuals with this syndrome usually involves pulsatile administration of GnRH.

5. Hypothalamo- hypophyseal portal blood system is the venous blood that drains from the hypothalamus, mixes with arterial blood and passes to anterior pituitary before it goes into the general venous circulation. Thus, the superior hypophysial artery provides blood supply to the median eminence and pituitary stalk, from where blood passes via capillary loops through the long portal vessels to the sinusoids of the pars distalis. The importance of this system was confirmed by experiments showing that placing a foil barrier between the hypothalamus and pituitary markedly inhibited the secretion of all the anterior pituitary hormones except prolactin.

UNIT 3

PITUITARY HORMONES

Structure

3.1 INTRODUCTION

You learnt about the hypothalamus and how it controls the activities of various other organs by secreting the releasing hormones in Unit 2. In this unit we shall discuss about the pituitary gland also known as hypophysis. Earlier, it was considered as the master endocrine gland, however, as you have seen in the previous unit, this gland is under the control of hypothalamus, hence it is no more referred to as the Master Gland. In this unit, we shall elaborate its anatomical division into the posterior and anterior pituitary.

Both, anterior and posterior pituitary, secrete distinct set of hormones. Structure and physiological roles of these hormones will be explained. You will also learn about the physiological conditions that follow due to abnormal secretion of growth hormones. How a feedback mechanism at the level of hypothalamus and pituitary affect the target cells in a specific manner through their hormones will also be described. In the last section, we shall discuss about diabetes inspidus, a disorder associated with hypothalamus- pituitary axis, its causes, symptoms and management.

Expected Learning Outcomes

After studying this unit, you should be able to:

- describe the embryonic origin of the pituitary gland;
- explain why pituitary is more considered as the master endocrine gland;
- describe the structure of the different parts of the pituitary gland;
- categorize the different pituitary hormones and explain their functions;
- explain some of the important diseases associated with the malfunctioning of pituitary gland and its secretion.

3.2 ANATOMY OF THE PITUITARY GLAND

The embryonic development of the lobes of the pituitary gland is completely distinct. The anterior lobe is derived from an inward invagination of the primitive mouth cavity (oral ectoderm) known as Rathke's pouch while the neural lobe arises from the neural ectoderm of the floor of the developing forebrain, the infundibulum of diencephalon. Cells of the anterior wall of Rathke's pouch develop into the pars distalis, containing most of the hormone-producing cells of the adenohypophysis (Fig. 3.1).

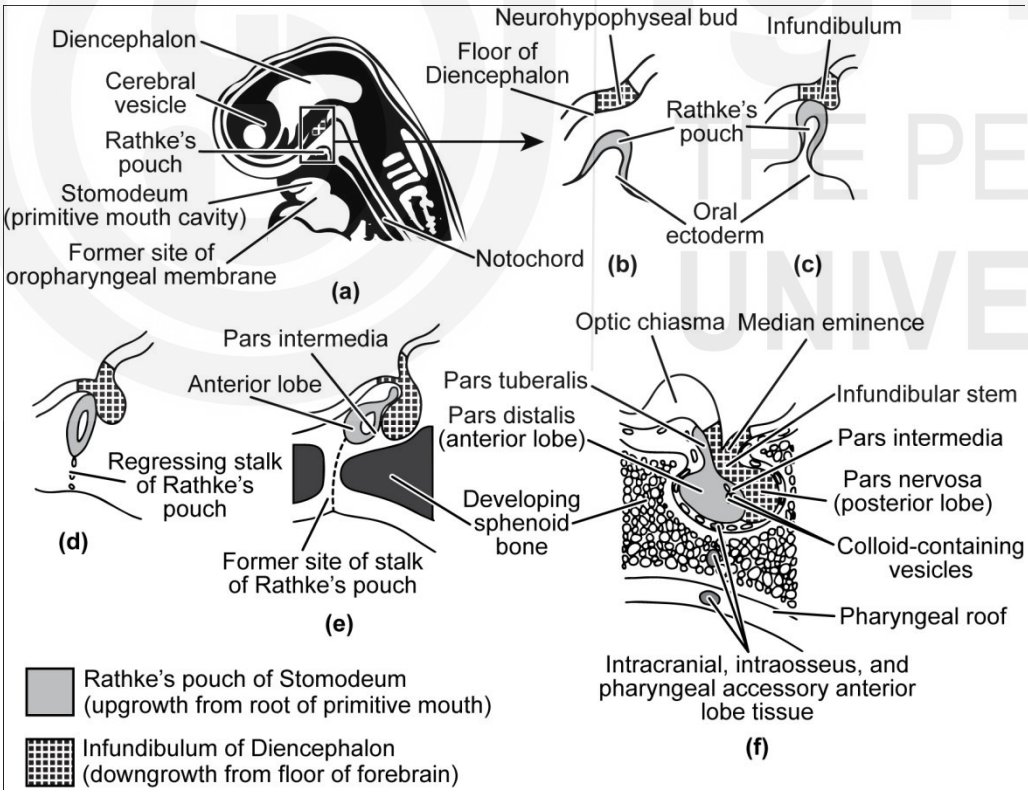

Fig. 3.1: Embryonic development of different lobes of pituitary gland.

The pituitary gland comprises of three parts, the adenohypophysis (alternatively referred to as the anterior lobe or the Pars Distalis), the intermediate lobe (or Pars Intermedia) and the neurohypophysis (also called the posterior lobe or Pars Nervosa). The adenohypophysis is primarily

PVN: Paraventricular Nuclei, SON: Supra-optic Nuclei are the hypothalamic nuclei mentioned in Unit 2.

glandular tissue and receives hormones through the hypothalamo-hypophyseal portal system, while the neurohypophysis consists of nerve inputs that originate from the soma of neurosecretory neurons in the PVN and SON of hypothalamus. These nerve endings travel through the median eminence that is continuous with the infundibulum, or pituitary stalk, and ultimately release the hormones in the posterior lobe. Before we discuss about the details of various hormones, let us learn about the anatomy of pituitary gland.

Anatomy of the Anterior Pituitary Gland

The cell types of the pituitary gland are categorized based on the type of hormones secreted.

The anterior pituitary gland is composed of various cell types secreting several hormones: **corticotropes** (adrenocorticotropic hormone; ACTH), **somatotropes** (growth hormone; GH), **lactotropes** (prolactin; PRL), **gonadotropes** (luteinizing hormone; LH, and follicle-stimulating hormone; FSH) and **thyrotropes** (thyroid-stimulating hormone; TSH).

The anterior lobe of the pituitary extends dorsally to form a non-secretory tissue that wraps around the infundibular stalk known as Pars Tuberalis (Fig. 3.2). An intermediate lobe develops between the two lobes that can vary greatly in size among different species; in humans, this regress and disappears in adults. In many vertebrates the intermediate lobe produces hormones that include melanotropins, such as melanocyte-stimulating hormone (MSH) (Please refer to the Table 3.1 for details).

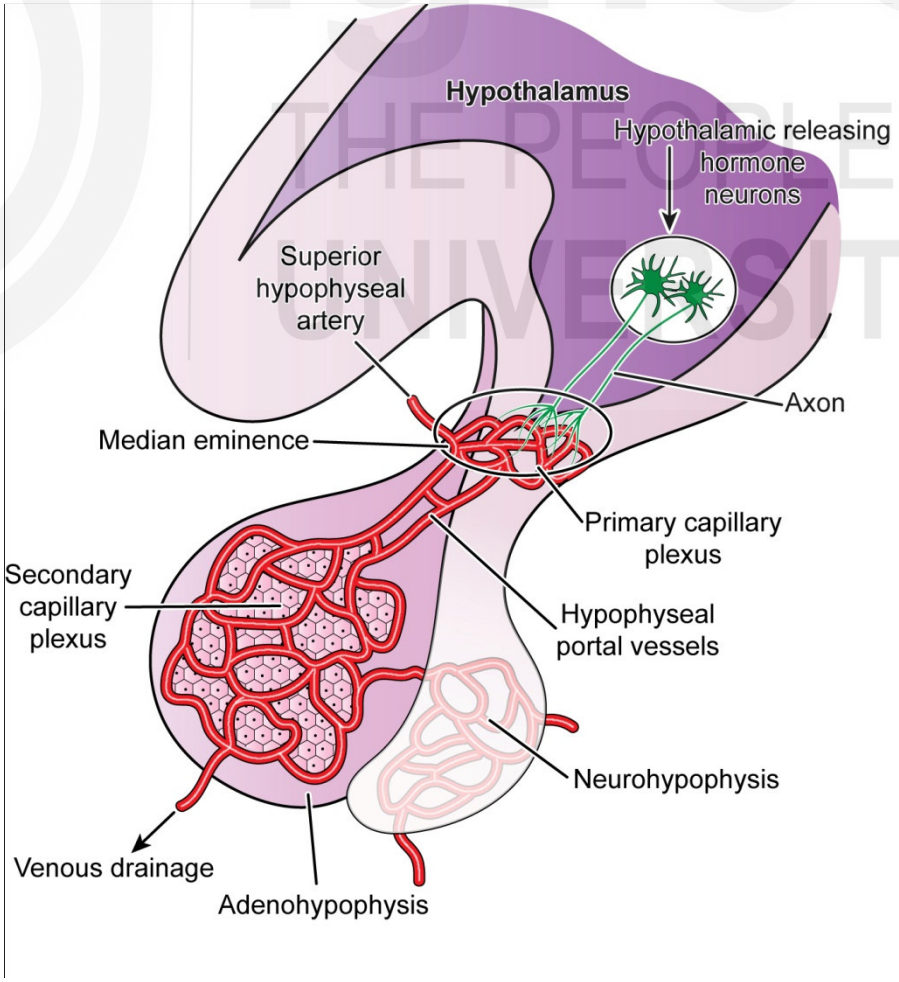

Fig. 3.2: Neuroanatomy of the Pars Distalis – the Anterior Pituitary Gland.

Anatomy of the Posterior Pituitary

The posterior pituitary primarily consists of neural tissue and it receives input from the supraoptic and paraventricular neurons of the hypothalamus. The axons of the neurons traverse the supraoptico-hypophyseal tract and terminate on capillaries, where hormones are released into the circulation. These neurons produce either vasopressin (VP) or oxytocin. The paraventricular nucleus also contains smaller parvicellular neurons which project through the median eminence to the primary plexus of the anterior pituitary and co-secrete vasopressin and corticotrophin releasing hormone (CRH). The sites of VP synthesis in the hypothalamus appear to be close to the osmoreceptor sites, which sense changes in electrolyte (solute) concentrations in circulation and signal release of the hormone from neuronal terminals in the posterior pituitary (Fig. 3.3). The osmoreceptor is close to the thirst center in the hypothalamus and interacts with the renin-angiotensin system. Collectively, these systems appear to be the primary elements for regulation of water balance (Please refer to the Table 3.1 for details).

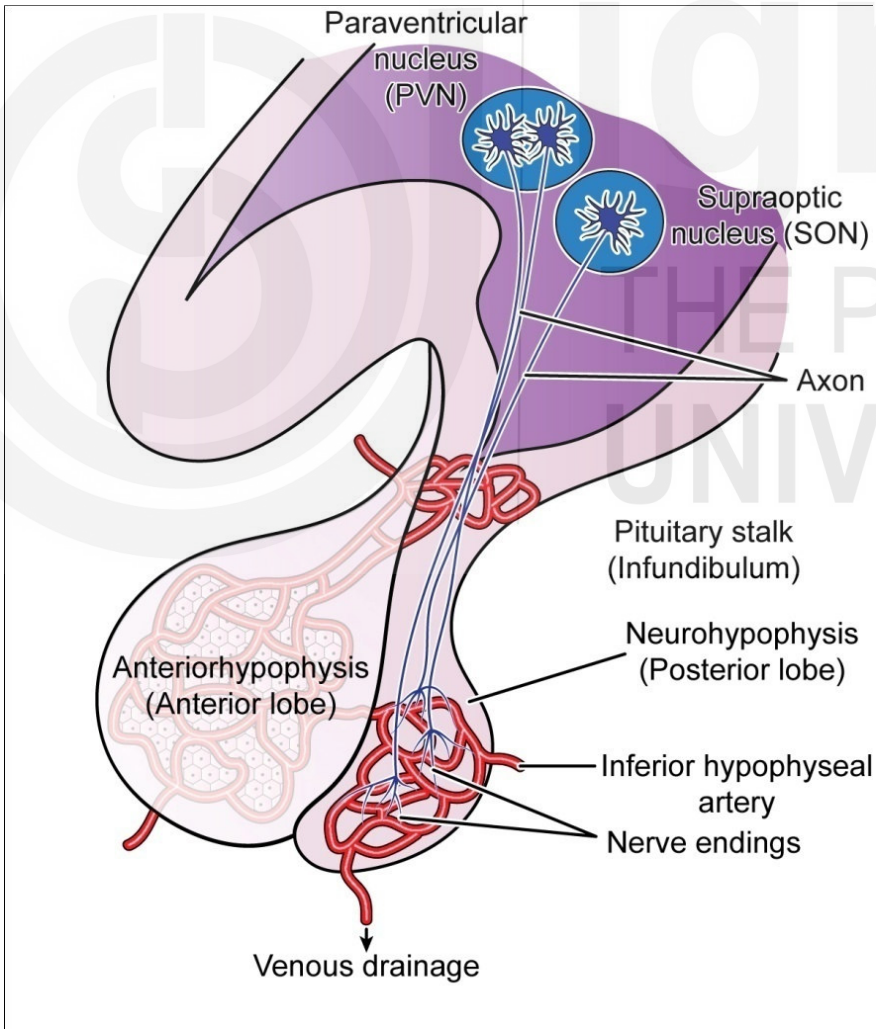

Fig 3.3: Neuroanatomy of the Pars Nervosa – the Posterior Pituitary Gland.

Table 3.1: Hormones of the Anterior and Posterior Pituitary, their targets, functions and hypothalamic regulators

Hormones of the Pituitary Gland	Cell Type and Location	Structure	Target	Functions	Hypothalamic Regulators
Gonadotropic Hormones	Anterior Pituitary (adenohypophysis or Pars Distalis)	**Glycoprotein Hormones**			
Follicle Stimulating Hormone (FSH)	Gonadotrophs - Anterior Pituitary (adenohypophysis or Pars Distalis)		Gonads (Ovary, testes)	stimulates growth of the primary follicle and estradiol secretion from the ovary in females; sperm production and inhibin secretion in the testis of males. FSH secretion is also regulated locally by two factors produced in folliculostellate cells (i.e. follistatin and activin).	GnRH
Luteinizing Hormone	Gonadotrophs - Anterior Pituitary (adenohypophysis or Pars Distalis)		Gonads (Ovary, testes)	stimulates ovulation, formation of the corpus luteum and progesterone secretion in females; stimulates Leydig (interstitial) cells to secrete androgens (testosterone) in males	GnRH (LHRH)
Thyroid-Stimulating Hormone (TSH)	Thyrotrophs - Anterior Pituitary (adenohypophysis or Pars Distalis)		Thyroid Gland	Stimulates thyroxine (T4) and triiodothyronine (T3) secretion from the thyroid gland	TRH, STT, DA
Growth Hormone (GH)	Somatotrophs -Anterior Pituitary (adenohypophysis or Pars Distalis)	**Somatomammotrophic Family**	Muscle, bone, liver, all tissues	Promotes protein synthesis, reduction of fat mass, and carbohydrate	GHRH, STT

				metabolism; direct stimulatory effect on muscle mass; increases bone growth by first stimulating somatomedin (IGF-1) release from the liver	
Prolactin	Lactotrophs - Anterior Pituitary (adenohypophysis or Pars Distalis)		Breast, gonads, brain, immune cells	Initiates milk production in the mammary gland; stimulation of gonads	
Adrenocorticotropic Hormone (ACTH)	Corticotrophs - Anterior Pituitary (adenohypophysis or Pars Distalis)	**Proopiomelanocortin Family**	Adrenal cortex	Stimulates glucocorticoid secretion from the adrenal cortex	CRH, AVP
α-Melanocyte-stimulating Hormone(α-MSH)	Melanotrophs - Intermediate Pituitary (Pars Intermedia)		Melanocytes	stimulates melanophores to darken skin color in amphibia. Some evidence for a similar effect in human, e.g. in Addison's disease	DA
β-Endorphin	Melanotrophs - Intermediate Pituitary (Pars Intermedia)		Brain, immune cells	acts as a neuromodulator in the brain to regulate neurotransmitter release, and possibly as a circulating analgesic. Also secreted from anterior pituitary.	DA
Oxytocin	Oxytocin Neurons - Posterior Pituitary (Neurohypophysis or Pars Nervosa)	**Nonapeptide Hormones**	Smooth muscle of mammary ducts, uterus	stimulates uterine muscle contractions and milk ejection from the mammary glands via contraction of myoepithelial cells	
Vasopressin	Vasopressin Neurons - Posterior Pituitary (Neurohypophysis or Pars Nervosa)		Renal tubules, vascular smooth muscle cell	elevates blood pressure and promotes reabsorption of water by the kidneys	

3.3 HORMONES OF THE ANTERIOR PITUITARY

As discussed earlier, the anterior pituitary gland secretes various hormones which may be categorized into three main types.

1. Glycoprotein Hormones (LH, FSH and TSH)

2. Somatomammotrophic Hormones (GH and PRL)

3. Pro-Opiomelanocrotin Hormones (ACTH, MSH and β-Lipotropin)

3.3.1 Glycoprotein Hormones

The glycoprotein hormones of the anterior pituitary gland are heterodimeric and share a common α-subunit and have distinct β- subunits. The α- and β-subunits are each stabilized by disulfide bonds, and disruption of these bonds by reducing agents alters the internal configuration of the peptide chains, causing dissociation of the heterodimer. It is the β-subunit that confers the specificity on the structure of the hormone so that each of the four heterodimers interacts only with its specific receptor.

Thyroid Stimulating Hormone (TSH): TSH, also known as thyrotropin or thyrotropic hormone, is produced in thyrotroph cells of the anterior pituitary. TSH stimulates the synthesis and release of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland.

The gonadotropic hormones

The gonad-stimulating or gonadotropic hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are produced in the gonadotroph cells of the anterior pituitary.

Follicle-stimulating hormone (FSH)

Follicle-stimulating hormone has a similar function in both sexes: it promotes the development of the gametes and the secretion of gonadal hormones. In the female, FSH stimulates the growth of the primary follicle in the ovary, promoting development of the ovum, and the secretion of the female sex hormone estradiol. In the male, FSH stimulates sperm production (spermatogenesis) and the secretion of the hormone inhibin by acting on the Sertoli cells of the testis.

Luteinizing hormone (LH)

In the female, luteinizing hormone stimulates ovulation by rupturing the follicle and releasing the ovum. The residual cells of the follicle then form the progesterone-secreting luteal cells (corpora lutea) in the ovary. In the male, luteinizing hormone stimulates the Leydig cells (also called interstitial cells) to secrete androgens such as testosterone.

3.3.2 Somatomammotrophic Hormones

Growth hormone (GH): Growth hormone is also known as somatotropin or somatotropic hormone. The suffix –tropin – refers to a substance that has a stimulating effect on its target organ; thus, somatotropin is a body- (soma-) stimulating hormone. Growth hormone is the most abundant hormone of the

anterior pituitary and is produced in somatotroph cells. GH has effects in almost all body cells: bone, muscle, brain, heart, fat, etc. Growth hormone has direct effects on some cells, such as muscle, and therefore it increases muscle mass. However, its effect on bone growth, and therefore height, occurs indirectly by stimulating the release of somatomedin, a peptide growth factor (also known as insulin-like growth factor; IGF-1) from the liver. GH also stimulates the liver to increase glucose output.

Prolactin: Prolactin is produced in lactotroph (or mammotroph) cells in the anterior pituitary. Prolactin is essential for initiating milk production in the mammary glands and has many functions related to growth, osmoregulation, fat and carbohydrate metabolism, reproduction, and parental behavior. In many of these actions, prolactin interacts with other hormones, including estradiol, progesterone and oxytocin.

3.3.3 Pro-Opiomelanocortin Family Hormones

Adrenocorticotropic hormone (ACTH): ACTH is produced in the corticotroph cells of the anterior pituitary and acts to stimulate the synthesis and release of glucocorticoid hormones (cortisol, corticosterone, etc.) in the adrenal cortex. It does this with a distinct rhythm so that levels of ACTH, and cortisol, are high in the early morning. ACTH is also involved in regulating the immune system.

Melanocyte Stimulating Hormone (MSH) and β-Lipotropin: The POMC molecule contains the sequences for many pituitary peptides, including ACTH, α-MSH, β-lipotropin (LPH), and β-endorphin. First, ACTH and β-LPH are cleaved off from the propeptide and this occurs in both the anterior and intermediate pituitary. ACTH and β-LPH are both secreted by the anterior pituitary, but all the ACTH in the intermediate lobe is converted to α-MSH. In the anterior pituitary, all the β-LPH is converted to β-endorphin and γ-lipotropin. Thus, the anterior pituitary co-releases ACTH, β-endorphin, and β-LPH from the same corticotroph cells. In terms of hormone-like effects, β-endorphin and γ-LPH have no known function when released into the bloodstream, but β-endorphin has a wide range of neuropeptide functions in analgesia, learning and memory, psychiatric diseases, feeding, thermoregulation, blood pressure regulation, and reproductive behavior.

In amphibians, α-MSH acts on the melanophores to darken their skin to match background color. α-MSH can also affect pigmentation in mammals, including humans. The secretion of α-MSH from the intermediate lobe of the pituitary may occur in the human fetus, although it has not been detected in normal healthy adults. In patients with Addison's disease, however, where cortisol levels are low and ACTH secretion high, there is a pronounced darkening of the skin that might be caused by α-MSH secreted along with ACTH. An important non-pituitary source of α-MSH is the hypothalamus, where α-MSH plays a critical role in influencing feeding behavior. α-MSH may also act to modulate the immune system.

3.4 PATHOPHYSIOLOGY

Gigantism (Excessive GH in Childhood)

There are four types of growth patterns that can result in heights more than 2 standard deviations from the normal mean. These are: intrinsic tallness, the expression of the genetic potential of the individual; advanced growth, where growth occurs earlier and stops earlier at normal adult height; prolonged growth, i.e., beyond the normal time at the end of puberty, often from a deficiency of sex steroid hormones; and accelerated growth, due to excessive GH levels. This last type is the one we will focus on here. Hyperproduction of growth hormone can result from a tumor of the somatotroph (pituitary adenoma) during growth. The resulting accelerated growth results in gigantism, which is characterized by a height age that is greater than either bone age or chronological age and a supranormal growth rate. This form of GH overproduction is relatively rare. If left untreated, the tumor destroys the functional gland, impairing the other pituitary hormones and resulting in death. This disease often involves enlargement of the *sella* but is principally manifested by unusually high circulating levels of GH. Therapy involves removal of the tumor, radiation of the tumor, and/or a GH receptor antagonist.

Dwarfism (Growth Hormone Deficiency in Childhood)

In childhood, there are many possible causes, both genetic and environmental, of short stature and a slow growth rate. Careful laboratory and clinical evaluations, including measurements of IGF-1 levels, are required to determine whether the cause is a deficiency of growth hormone. If present, GH deficiency may be either congenital (e.g., defective GH or GHRH synthesis or secretion) or acquired (through a tumor or injury to the head). The GH deficiency may be isolated, i.e., GH is the only hormone involved, or there may be disruptions in other pituitary hormones as well. GH deficiency untreated in childhood leads to adults with proportionate extreme short stature. The true incidence of GH deficiency, most of which is idiopathic (cause unknown) is estimated to be around 1 in 3500 children. The child usually has a normal birth weight but exhibits growth failure and abnormal facial development during the first two years of life. The objective of treatment with replacement recombinant human GH is to normalize height during childhood. Growth rate is most accelerated during the first year of treatment (the “catch-up” phase) with average rates of 8–10 cm/year. If, thereafter, the growth rate slows too much, then other factors such as hypothyroidism or nutritional factors should be considered.

Acromegaly (Excessive GH in Adults)

Excessive GH secretion in adults leads to a constellation of symptoms known as acromegaly and most commonly results from one of several types of GH-secreting pituitary tumors. Hypothalamic tumors that oversecrete GHRH may also be responsible. Acromegaly is quite rare, and its incidence is not well established. It generally has a slow progression and can be present for a decade or more before being accurately diagnosed. Since the acromegaly is of adult onset and the epiphyseal growth plates of the long bones close at the

end of puberty, the hypersecretion of GH results in excessive growth of only those tissues still capable of responding to it. These include the mandible, bringing about changes of facial structure and the hands and feet, which become enlarged. These changes in appearance are often so gradual that they are not the patient's initial complaint upon presentation. Rather, the headache resulting from the growing tumor is the most common symptom that the Hypothalamus and Anterior Pituitary brings the patient to the clinic. Soft-tissue overgrowth causes several symptoms including neuropathy; cardiomyopathy and cardiovascular disease; debilitating arthritis; sleep apnea due to airway obstruction; respiratory disease and, because of the role of GH in carbohydrate metabolism, carbohydrate intolerance. Untreated acromegaly leads to a 2- to 4-fold increase in mortality compared to age-matched controls. The primary goal of treatment of acromegaly is to reduce excessive GH levels. Surgery is one method to achieve this but is accompanied by serious risks, one of which is the difficulty in removing all the tumor without damaging nearby structures. Radiation of the tumor has also been used, but the response in terms of lower GH levels is much slower than with surgery. Pharmaceutical therapies include GH receptor antagonists and somatostatin receptor ligands that block GH secretion by the tumor cells and reduce tumor size.

3.5 HORMONES OF POSTERIOR PITUITARY

Two important hormones are secreted from the posterior pituitary in both males and females. These are vasopressin (VP), the antidiuretic hormone, and oxytocin (OT), which in female mammals is important in parturition (birth) and lactation. The two hormones are structurally closely related nonapeptides that are derived from a common ancestral gene. Each is synthesized in a specific group of cells in the hypothalamus and is released from the axon termini of these neurons in the posterior pituitary. Here the hormones are stored until the appropriate signal brings about their release into the bloodstream.

Oxytocin

Oxytocin has two primary functions: it promotes uterine contractions during parturition (childbirth) and it stimulates milk ejection, or letdown, from the mammary glands during lactation. Oxytocin also has several neuropeptide functions in the brain.

Vasopressin

Vasopressin (antidiuretic hormone, ADH) acts to raise blood pressure and to promote water reabsorption in the kidneys – that is, it acts as an antidiuretic. As a neuropeptide, vasopressin may enhance memory. Besides these two hormones, the posterior pituitary releases two large proteins called neurophysins that function as carrier proteins for oxytocin and vasopressin.

3.6 FEEDBACK REGULATION CYCLE

As we have learned in the previous sections, the pituitary gland is under the control of the hypothalamus. The hypothalamus secretes various releasing and release-inhibiting hormone, which in turn influences the function of the pituitary gland. Thus, these hormones have specific effects on the target cells and via feedback mechanism at the level of pituitary or hypothalamus, regulate its actions. Fig. 3.4 a shows one long feedback loop; however short and ultrashort feedback may also influence the hypothalamic function (Fig. 3.4 b).

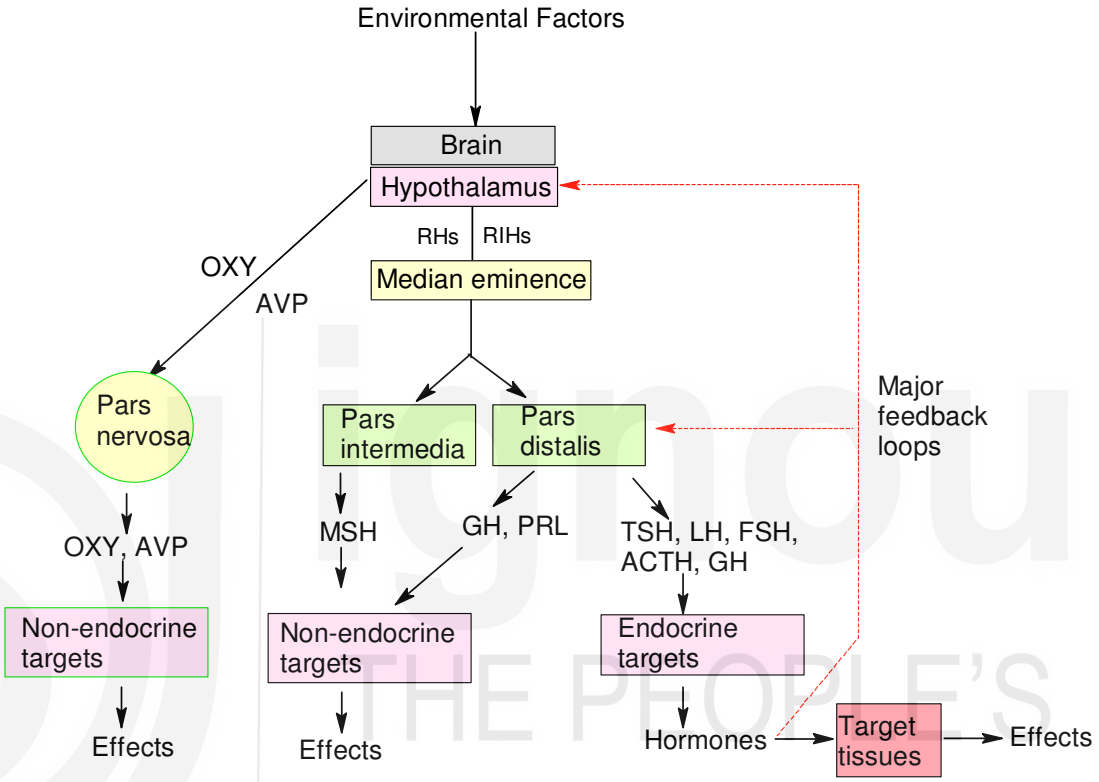

Fig. 3.4 a: The Vertebrate endocrine system showing one long feedback loop.

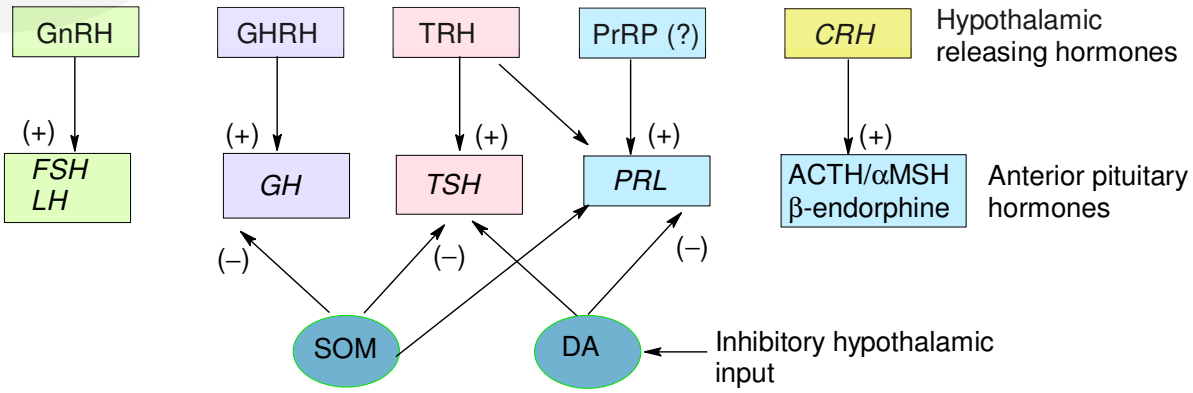

Fig. 3.4 b: Summary of the hypothalamic releasing and inhibiting hormones that modulate the secretion of anterior pituitary hormones.

3.7 DIABETES INSIPIDUS

Lack of vasopressin action, due to damage to the hypothalamus or pituitary or a gene mutation in either the gene for the hormone or for the receptor in the kidney, leads to the condition known as diabetes insipidus (literally urine that is

tasteless). This condition is to be distinguished from diabetes mellitus (urine that is sweet) which is due to lack of or resistance to insulin (Chapter 6). Diabetes insipidus (DI) is characterized by polyuria (excessive urine volume) and polydipsia (excessive thirst/water intake). The most common cause of hypothalamic DI in both children and adults is a primary brain tumor that impacts the hypothalamic magnocellular neurons that secrete vasopressin. Inherited forms of DI, resulting from defects in vasopressin gene expression, occur in both autosomal dominant and recessive forms; symptoms are generally recognized during the child's second year of life when parents become more aware of the child's need for water. In nephrogenic diabetes insipidus (NDI) the kidney is unresponsive to vasopressin, due to a defect in the receptor or the signaling pathway. In congenital NDI, polyuria and polydipsia must be recognized at birth and treated immediately to avoid life-threatening dehydration. NDI can also be acquired through chronic renal disease, the use of one of several drugs including lithium and alcohol, and other disease states such as multiple myeloma and sarcoidosis. Hypothalamic DI can be treated with replacement vasopressin or its therapeutic analog desmopressin, which has some beneficial pharmacokinetic properties. Dosages can be tailored to the individual by monitoring urine volume and osmolality. Treatment of nephrogenic DI is more complex since it is resistant to hormone replacement therapy. Most approaches involve treating the symptoms with low-sodium diet and drugs such as thiazide diuretics.

SAQ 1

a) Tick [√] mark the correct statement:

i) Anterior pituitary gland develops from the infundibulum. [True/False]

ii) Pituitary gland is the master endocrine gland. [True/False]

iii) Glycoprotein hormone are LH, FSH and TSH. [True/False]

iv) Corticotrophs produce the hormone ACTH. [True/False]

b) Fill in the blanks with appropriate words.

i) Pituitary gland is divided in to three parts as……

ii) Secondary capillary plexus innervates the …… pituitary gland.

iii) Nonapeptide hormones of the posterior pituitary gland are ……

iv) Pro-opiomelanocortin family hormones constitute the …… hormones.

c) Fill in the blanks with appropriate words:

i) Oxytocin stimulates …… from the mammary glands during ……..

ii) Vasopressin is also known as ……. hormone.

iii) Diabetes insipidus is characterized by polyuria and …….

iv) Excessive secretion of growth hormone in adults leads to a disease known as ……..

3.8 SUMMARY

Let us summarize what we have learnt so far:

- The embryonic origin of parts of pituitary gland is distinct. The anterior part develops from oral ectoderm known as Rathke's pouch while the posterior part develops from the neural ectoderm (infundibulum) of the diencephalon.
- Pituitary gland is divided in to three parts namely anterior pituitary (Pars Distalis); intermediate pituitary (Pars Intermedia) and Posterior posterior pituitary (Pars nervosa) based on its embryonic development.
- The anterior pituitary has goandotrophs, thyrotrophs, lactotrophs, somatotrophs, corticotrophs and melanotrphs cell types in its anatomical structure.
- The hormones of the anterior pituitary belong to three families of hormones as glycoprotein hormones, somatomammotrophic hormones and proopiomelanocortin family of hormones.
- Posterior pituitary receives innervation from the magnocellular part (PVN and SON) of the hypothalamus and secretes hormones oxytocin and vasopressin.
- Thus, the pituitary is itself under the control of hypothalamus for its various physiological functions, hence the Pituitary gland is no more referred to as the "Master Endocrine Organ".
- Major diseases associated with pituitary gland are dwarfism, gigantism, acromegaly and diabetes insipidus.

3.9 TERMINAL QUESTIONS

1. Describe the embryonic origin of the pituitary gland.
2. What are the cell types of the anterior pituitary gland and hormones secreted by them?
3. What is acromegaly? Explain.
4. Discuss the role of the two nonapeptides, oxytocin and vasopressin.

3.10 ANSWERS

Self-Assessment Questions

1. a) i) False
   ii) False
   iii) True
   iv) True

b) i) Pars Distalis, pars intermedia and pars nervosa

ii) Anterior

iii) Oxytocin and vasopressin

iv) ACTH, α-MSH and β-Lipotropin

c) i) Milk ejection, lactation

ii) Anti-diuretic hormone (ADH)

iii) Polydipsia

iv) Acromegaly

Terminal Questions

1. The embryonic development of the lobes of the pituitary gland is completely distinct. The anterior lobe is derived from an inward invagination of the primitive mouth cavity (oral ectoderm) known as Rathke's pouch while the neural lobe arises from the neural ectoderm of the floor of the developing forebrain, the infundibulum of diencephalon. Cells of the anterior wall of Rathke's pouch develop into the pars distalis, containing most of the hormone-producing cells of the adenohypophysis.

2. The anterior pituitary gland is composed of various cell types secreting several hormones such as corticotropes (adrenocorticotropic hormone; ACTH), somatotropes (growth hormone; GH), lactotropes (prolactin; PRL), gonadotropes (luteinizing hormone; LH, and follicle-stimulating hormone; FSH) and thyrotropes (thyroid-stimulating hormone; TSH). These cell types may be categorized in to three types as glycoprotein hormones (LH, FSH and TSH), proopiomelanocortin family hormones (ACTH, MSH and β-Lipotropin) and somatomammotrophic family hormones (GH and PRL) based on their structure.

3. Excessive GH secretion in adults leads to a constellation of symptoms known as acromegaly and most commonly results from one of several types of GH-secreting pituitary tumors. Hypothalamic tumors that oversecrete GHRH may also be responsible. Acromegaly is quite rare, and its incidence is not well established. It generally has a slow progression and can be present for a decade or more before being accurately diagnosed. Since the acromegaly is of adult onset and the epiphyseal growth plates of the long bones close at the end of puberty, the hypersecretion of GH results in excessive growth of only those tissues still capable of responding to it. These include the mandible, bringing about changes of facial structure and the hands and feet, which become enlarged. These changes in appearance are often so gradual that they are not the patient's initial complaint upon presentation. Rather, the headache resulting from the growing tumor is the most common symptom that the Hypothalamus and Anterior Pituitary brings the patient to the clinic. Soft-tissue overgrowth causes several symptoms including neuropathy; cardiomyopathy and cardiovascular disease; debilitating arthritis; sleep apnea due to airway obstruction; respiratory disease and,

because of the role of GH in carbohydrate metabolism, carbohydrate intolerance. Untreated acromegaly leads to a 2- to 4-fold increase in mortality compared to age-matched controls. The primary goal of treatment of acromegaly is to reduce excessive GH levels. Surgery is one method to achieve this but is accompanied by serious risks, one of which is the difficulty in removing all the tumor without damaging nearby structures. Radiation of the tumor has also been used, but the response in terms of lower GH levels is much slower than with surgery. Pharmaceutical therapies include GH receptor antagonists and somatostatin receptor ligands that block GH secretion by the tumor cells and reduce tumor size.

4. Oxytocin has two primary functions: it promotes uterine contractions during parturition (childbirth) and it stimulates milk ejection, or letdown, from the mammary glands during lactation. Oxytocin also has several neuropeptide functions in the brain. Vasopressin (antidiuretic hormone, ADH) acts to raise blood pressure and to promote water reabsorption in the kidneys – that is, it acts as an antidiuretic. As a neuropeptide, vasopressin may enhance memory. Besides these two hormones, the posterior pituitary releases two large proteins called neurophysins that function as carrier proteins for oxytocin and vasopressin.