ENDOCRINOLLOGY

Learning Objectives

In this chapter, you'll learn:

1-The functions of endocrine glands
2-Hormone release and transportation in the endocrine system
3-The role of receptors in the influence of hormones on cells

Introduction

The **endocrine system** is a chemical messenger system comprising feedback loops of the hormones released by internal glands of an organism directly into the circulatory system, regulating distant target organs. In humans, the major endocrine glands are the thyroid gland and the adrenal glands.

In vertebrates, the hypothalamus is the neural control center for all endocrine systems. The study of the endocrine system and its disorders is known as endocrinology.

The three major components of the endocrine system are:

- Glands—specialized cell clusters or organs
- Hormones—chemical substances secreted by glands in response to stimulation
- Receptors—protein molecules that bind specifically with

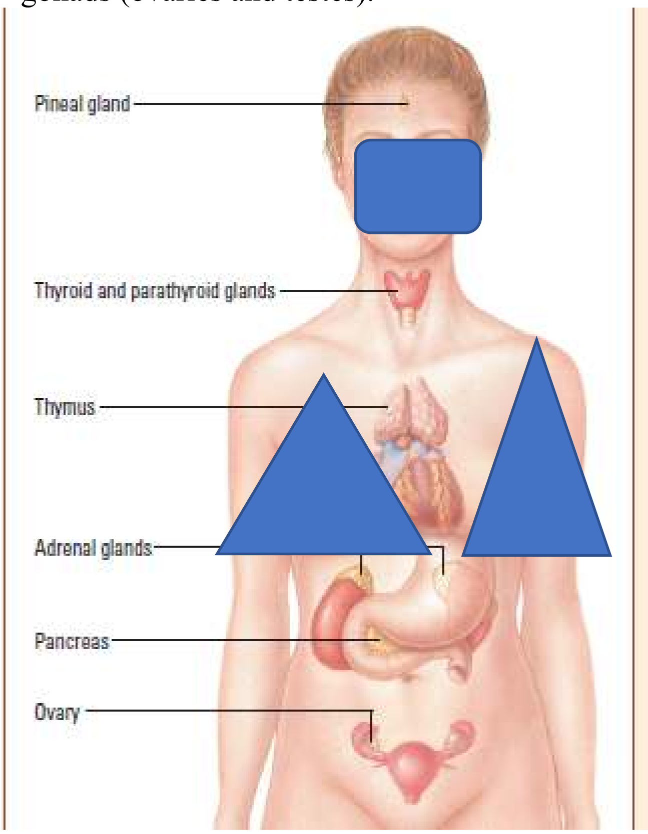
other molecules, such as hormones, to trigger specific physiologic changes in a target cell.

Glands

The major glands of the endocrine system are:

- pituitary gland
- thyroid gland
- parathyroid glands
- adrenal glands

• pancreas
• thymus
• pineal gland
• gonads (ovaries and testes).



Glands can be classified according to their function.

Harmones

A hormone is any of a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behaviour. Are substances released by glands in response to stimulation. They trigger or regulate the activity of an organ or a group of cells.

Hormones are:
Protein
Glycoproteins
Steroids
Catecholamine

Hormones have diverse chemical structures, mainly of 3 classes:

1-eicosanoids

2-steroids

3-amino acid/protein derivatives (amines, peptides, and proteins).

The glands that secrete hormones comprise the endocrine system.

Hormones are used to communicate between organs and tissues for physiological regulation and behavioral activities, such as digestion, metabolism, respiration, tissue function, sensory perception, sleep, excretion, lactation, stress, growth and development, movement, reproduction, and mood.

Hormones affect distant cells by binding to specific receptor proteins in the target cell resulting in a change in cell function. This may lead to cell type-specific responses that include rapid changes to the activity of existing proteins, or slower changes in the expression of target genes. Amino acid–based hormones (amines and peptide or protein hormones) are water-soluble and act on the surface of target cells via signal transduction pathways.

Steroid hormones, being lipid-soluble, move through the plasma membranes of target cells to act within their nuclei.

Cell signalling

The typical mode of cell signalling in the endocrine system is endocrine signaling, that is, using the circulatory system to reach distant target organs.

However, there are also other modes, i.e., paracrine, autocrine, and neuroendocrine signaling. Purely neurocrine signaling between neurons, on the other hand, belongs completely to the nervous system.

Autocrine

Autocrine signaling is a form of signaling in which a cell secretes a hormone or chemical messenger (called the autocrine agent) that binds to autocrine receptors on the same cell, leading to changes in the cells.

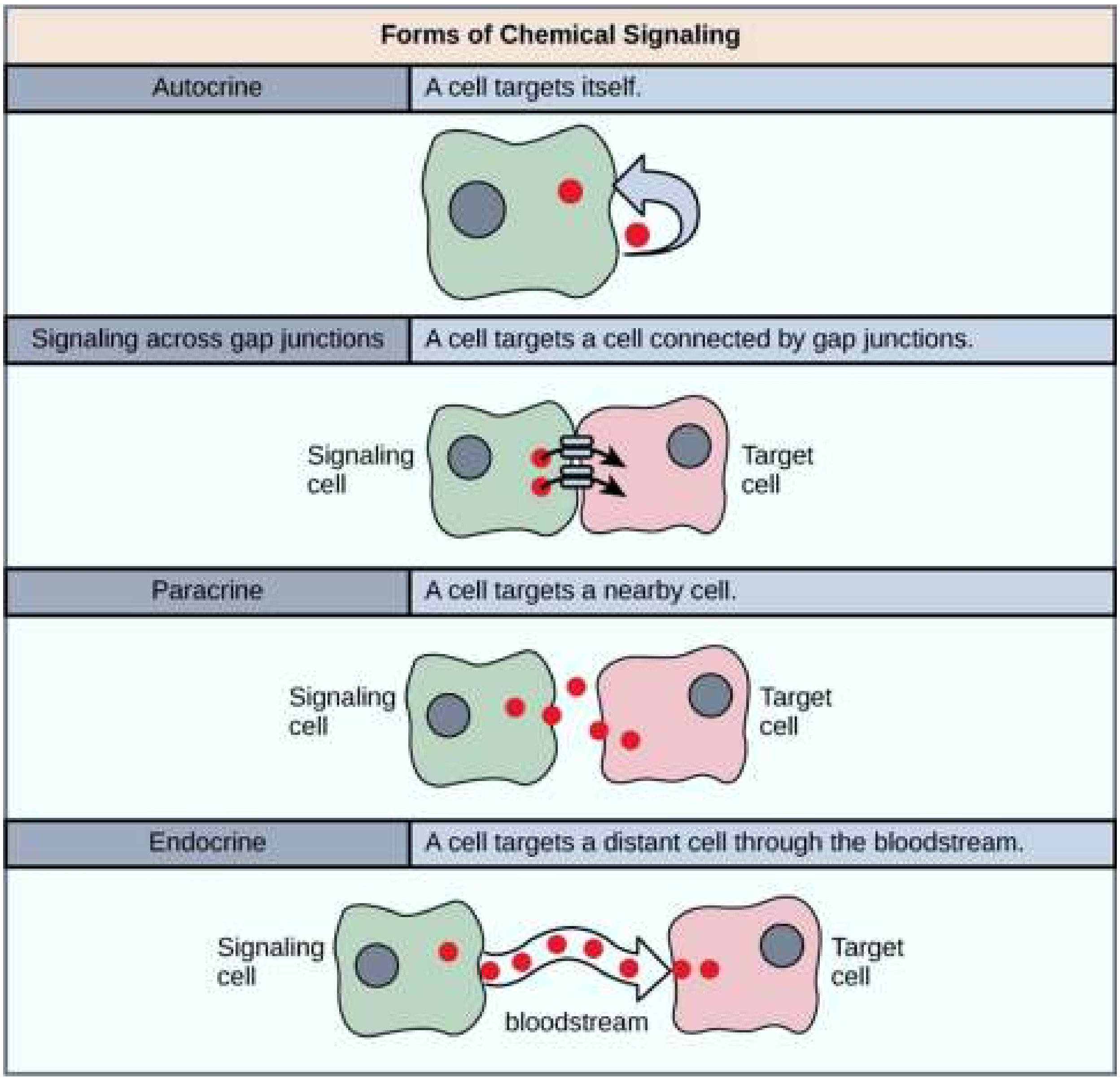
Paracrine

Some endocrinologists and clinicians include the paracrine system as part of the endocrine system, but there is not consensus. Paracrines are slower acting, targeting cells in the same tissue or organ. An example of this is somatostatin which is released by some pancreatic cells and targets other pancreatic cells.

Juxtacrine

Juxtacrine signaling is a type of intercellular communication that is transmitted via oligosaccharide, lipid, or protein components of a cell membrane, and may affect either the emitting cell or the immediately adjacent cells.

It occurs between adjacent cells that possess broad patches of closely opposed plasma membrane linked by transmembrane channels known as connexons. The gap between the cells can usually be between only 2 and 4 nm



Pre-Pro-Hormone - Pro-Harmones converted into Hormone.
There is **carrier pro**tein required for:

Steroids

Thyroxin

Insuline related growth factor.

If Carrier Protein increases it lowers free harmone (Active) - It
Increases trophicH - increasing Total H

Oral E2 increase level of binding proteins and total harmone but free harmone level is fixed.

Classification of harmones.

Molecular structure	Gland	Harmone
Polypeptides **Made of many amino acids connected by peptide bonds**	**Anterior pituitary** **Posterior pituitary** **Parathyroid** **Pancrease**	**GH,LH,FSH,TSH** **ADH-Oxytocin** **Parathormone** **Insuline -Glucagon**
Glycopeptides are :		TSH LH F S H HCG MIF Alfa feto protein Renin (Enzyme) Erythropoietin

Steroids **Derived from cholesterol**	**Adrenal gland** **Ovary** **Testis**	**Aldosterone-Cortisol** **Estrogen-Progesterone** **Testosterone**
Amines Derived from tyrosine	**Thyroid** **Adrenal medulla**	**T4 &T3** **Epinephrine,Norepinephrine and Dopamine**

TSH,GH (191 aa) and prolactin(199) are glycolproteins.

Transport of harmones

When a harmone reaches its target cells /site it binds to specific receptors and produces physiologic changes,depending on its target site and its specific action at that site.

A particular harmone may have different effects at different target sites.

Harmones produced by placenta

Placenta can not produce steroids independently like the ovary. It depends upon the precursors derived from the foetal and partly from the maternal sources. Precursors from foetal origin are required for synthesis oestrogen.

LDL cholesterol, derived from the mother, is used for progesterone synthesis.

Prostaglandins and leukotrienes

These hormones are collectively known as the eicosanoids and are derived from arachidonic acid. Synthesis usually occurs in the cell wall.

Sex Hormone Binding globulin

In circulation, some of the hormones are bound to the carrier proteins.

The free hormone or unbound is active and is available to bind to the specific receptors.

All steroid hormones are bound to some extent to albumin. The majority of the principal sex steroids are bound to sex hormone binding globulin (SHBG).

SHBG is a -globulin that transports androgens [e.g. testosterone, dihydrotestosterone (DHT), androstenedione , dehydroepiandrosterone] and oestradiol in plasma. It is produced in the liver.

SHBG binds testosterone with an affinity 50,000 times greater than that of albumin. However, none of steroids are metabolically active in the bound form. Serum levels of SHBG are increased by Estradiol and decreased by testosterone.

Reduced levels	Increased levels
Hypothyroidism Obesity Cushing's syndrome Nephrotic syndrome Acromegaly Elevated levels of GH Testodterone,corticosteroids,androgens,progestins,insuline,insuline like growth factor-IGF-1	Cirrhosis of liver Hyperthyroidism Pregnancy Estrogen use Advancing age

Harmones can be bound to albumen,sex harmone binding globulin or free/unbound.

Sex harmone	Free fraction	Albumin bound	Sex harmone bound
Estrogen	2	58	40
Progesterone	1	54	Transcortin bound 48
DHEAS	4	88	8
Testosterone	1	30	69
Di-hydro testosterone	1	71	28
Androstendione	7	85	8

Molecular weights of different harmones:

< 10 000	3500	Calcitonin
	3500	Glucagon
	4500	Insulin / ACTH / (IGF1 = 7000)
	9500	Parathormone
> 20 000	21 500	GH / HPL (GH = 22,000 Daltons
	23 000	Erythropoietin
	24 000	Prolactin
30 000	30 000	FSH / LH
	32 000	Inhibin
	38 000	HCG
Above	65 000	Rennin / HG
	660 000	TG

Receptors

Receptors are proteins classified into :
Upregulation - An increase in the number of receptors on the surface of target cells, making the cells more sensitive to a hormone -it is Downregulation.

1-Intracellular (Nuclear) receptors:

Steroid Harmones I **T3**/ **Vit. D** /**Retinoic**

Hormones must enter intracellular space.

Biologically active as long the H attached to **receptor** only.

Structurally related to some Oncogenes.

Long ½ **Life :** so need **low concentration** to work e.g.**ER**

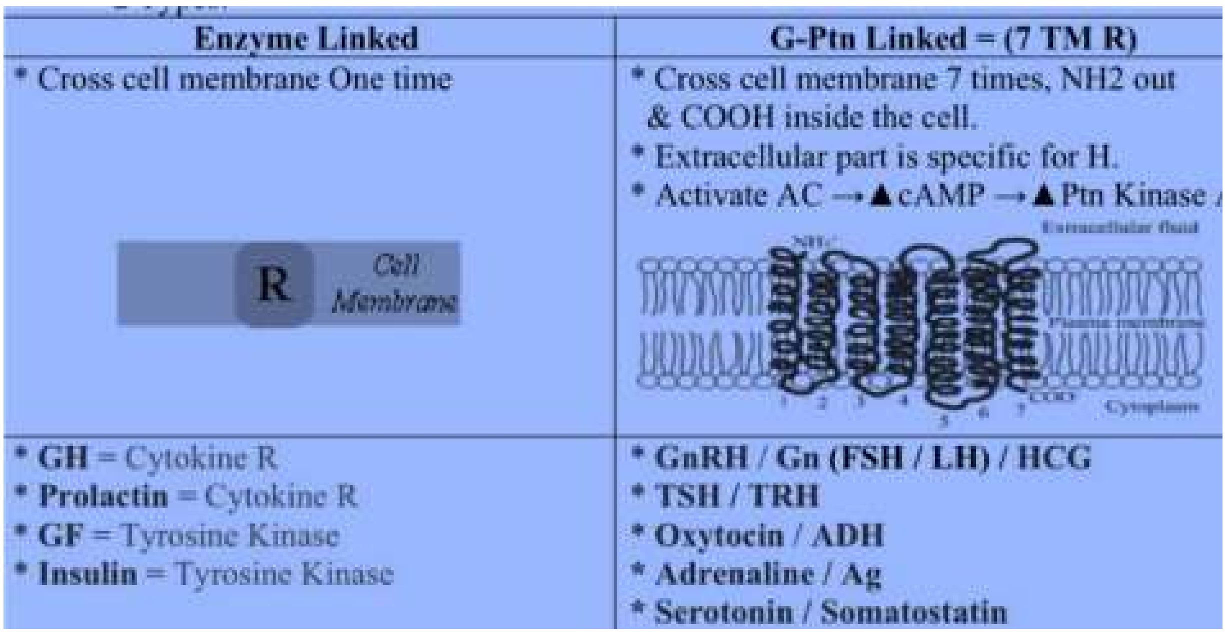
Short ½ **Life:** so need-high concentration to work e.g. **Prolactin /Corticotropin Releasing harmone.**

Receptors consists of 2 **Non-Binding subunits + 1 DNA binding unit.**

Hormones attach to **DNA binding units-** Conformational change---+ Displace **HSP 90** (Inhibitory Protein) &Expose DNA binding units- Gene activation & xpression -Products.

2-Membranous receptors-

Protein harmones ; they just bind to surface receptors;they don't enter the cells.



Enzyme Linked	G-Ptn Linked = (7 TM R)
* Cross cell membrane One time R Cell Membrane	* Cross cell membrane 7 times, NH2 out & COOH inside the cell. * Extracellular part is specific for H. * Activate AC → ▲cAMP → ▲Ptn Kinase
* **GH** = Cytokine R * **Prolactin** = Cytokine R * **GF** = Tyrosine Kinase * **Insulin** = Tyrosine Kinase	* **GnRH / Gn (FSH / LH) / HCG** * **TSH / TRH** * **Oxytocin / ADH** * **Adrenaline / Ag** * **Serotonin / Somatostatin**

Hormone release and transport

Although all hormone release results from endocrine gland stimulation, release patterns of hormones vary greatly. For example:

• Corticotropin (secreted by the anterior pituitary) and cortisol (secreted by the adrenal cortex) are released in spurts in response to body rhythm cycles. Levels of these hormones peak in the morning.

• Secretion of PTH (by the parathyroid gland) and prolactin (by the anterior pituitary) occurs fairly evenly throughout the day.

• Secretion of insulin by the pancreas can occur at a steady rate or sporadically, depending on blood glucose levels.

Diurnal variation is characteristic of hormones such as cortisol, testosterone and melatonin and to a lesser extent growth hormone (GH) (pulses).

During sleep there is a fall in the circulating level of cortisol, insulin and adrenaline, whereas that of antidiuretic hormone (ADH) and GH increases. During sleep, ADH levels increase. This rises as plasma osmolality rises; water is lost but not replaced during sleep. GH levels increase, allowing growth and anabolic repair of tissue wear and tear.

Adrenaline is releasd in response stress, which is again reduced during sleeping.

Secretion of inusline and parathyroid harmone even throughout the day.

Insuline secretion occurs at a steady rate or sporadically in response to blood sugar level.

Hormonal action

When a hormone reaches its target site, it binds to a specific receptor on the cell membrane or within the cell. Polypeptides and some amines bind to membrane receptor sites. The smaller, more lipid-soluble steroids and thyroid hormones diffuse through the cell membrane and bind to intracellular receptors.

Effect on target sites

After binding occurs, each hormone produces unique physiologic changes, depending on its target site and its specific action at that site. A particular hormone may have different effects at different target sites.

Hormonal regulation

To maintain the body's delicate equilibrium, a feedback mechanism regulates hormone production and secretion. The mechanism involves hormones, blood chemicals and metabolites, and the nervous system. This system may be simple or complex.

The feedback loop.

Negative feedback mechanism helps regulate the endocrine system.

Simple feedback occurs when the level of one substance regulates the secretion of hormones (simple loop).

For example, a low serum calcium level stimulates the parathyroid gland to release parathyroid hormone (PTH).

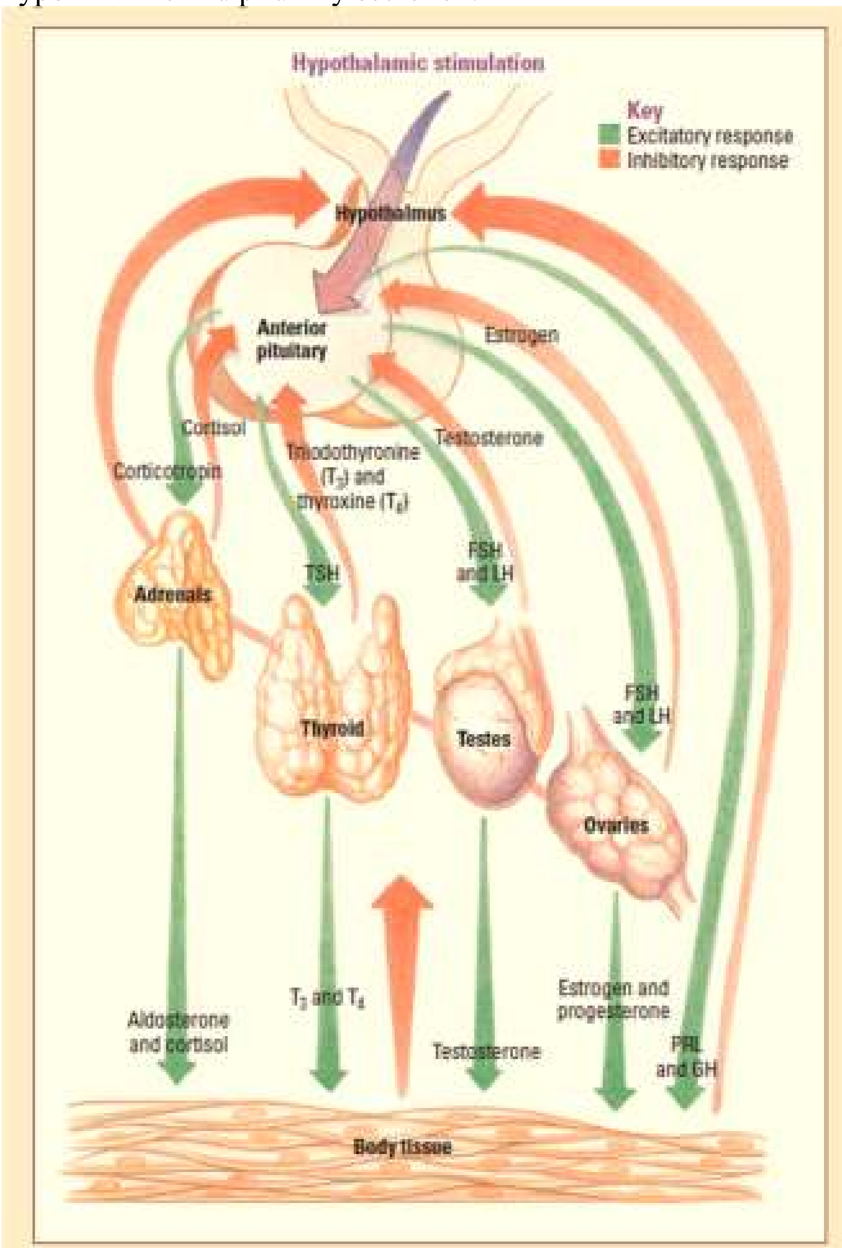
PTH, in turn, promotes resorption of calcium from the GI tract, kidneys, and bones. A high serum calcium level inhibits PTH secretion.

Complex feedback

Hypothalamic stimulation can also trigger a complex feedback mechanism. First, the hypothalamus sends releasing and inhibiting factors or hormones to the anterior pituitary.

In response, the anterior pituitary secretes tropic hormones, such as growth hormone (GH), prolactin (PRL), corticotropin,

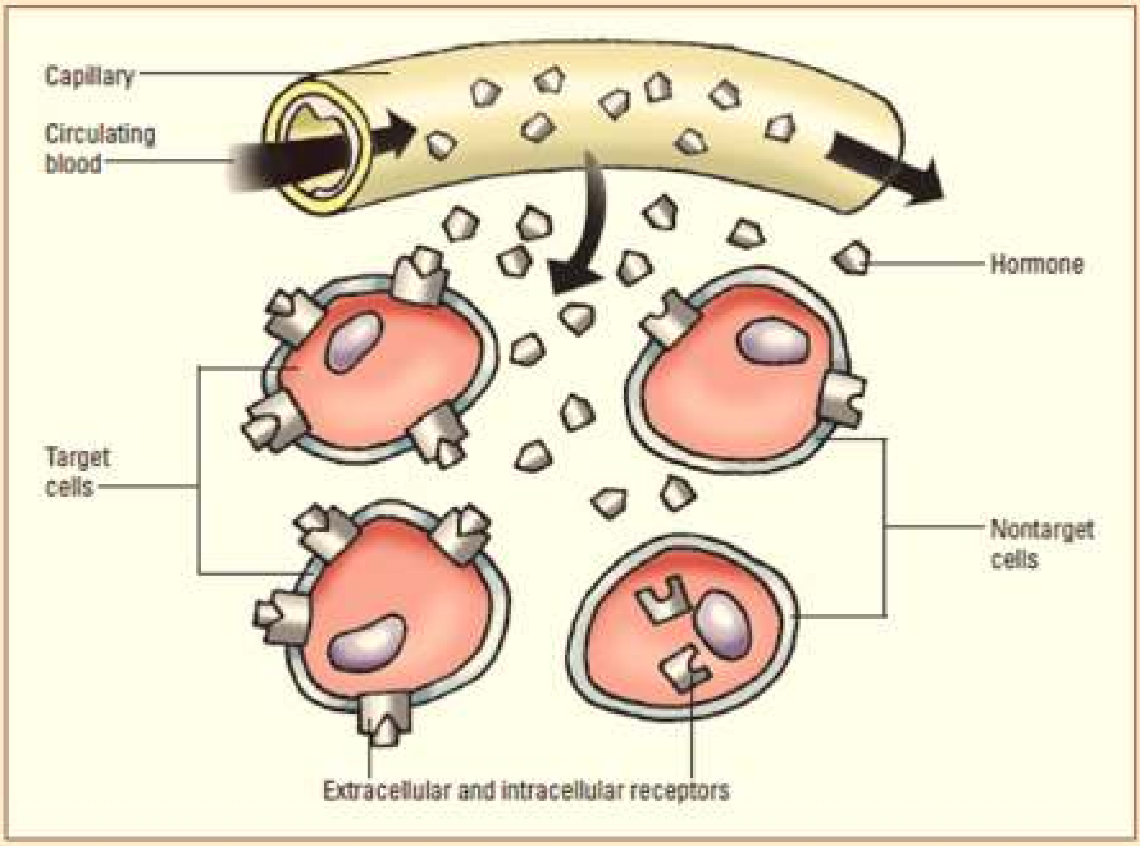
thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). At the appropriate
target gland, these hormones stimulate the target organ to release other hormones that regulate various body functions.
When these hormones reach normal levels in body tissue, a feedback mechanism inhibits further hypothalamic and pituitary secretion.



Signaling secretory cells
For normal function, each gland must contain enough appropriately programmed secretory cells to release active hormones on demand. Secretory cells need supervision. A secretory cell can’t sense on its own when to release the hormone or how much to release.

It gets this information from sensing and signaling systems that integrate many messages. Together, stimulatory and inhibitory signals actively control the rate and duration of hormone release.
When released, the hormone travels to *target cells,* where a receptor molecule recognizes it and binds to it.

A hormone acts only on cells that have receptors specific to that hormone. The sensitivity of a target cell depends on how many receptors it has for a particular hormone. The more receptor sites, the more sensitive the target cell.



Mechanisms that control hormone release
Four basic mechanisms control hormone release:

1-the pituitary-target gland axis
2-the hypothalamic-pituitary-target gland axis
3-chemical regulation
4-nervous system regulation.

Pituitary-target gland axis
The pituitary gland regulates other endocrine glands—and their hormones—through secretion of *trophic hormones* (releasing and inhibiting hormones). These hormones include:

• corticotropin, which regulates adrenocortical hormones

• TSH, which regulates T4 and T3
• LH, which regulates gonadal hormones.

Feedback
The pituitary gland gets feedback about target glands by continuously monitoring levels of hormones produced by these glands. If a change occurs, the pituitary gland corrects it in one of two ways:

• By increasing the trophic hormones, which stimulate the target gland to increase production of target gland hormones
• By decreasing the trophic hormones, thereby decreasing target gland stimulation and target gland hormone levels.

Hypothalamic-pituitary-target gland axis
The hypothalamus also produces trophic hormones that regulate anterior pituitary hormones. By controlling anterior pituitary hormones, which regulate the target gland hormones, the hypothalamus affects target glands as well.

Chemical regulation
Endocrine glands not controlled by the pituitary gland may be controlled by specific substances that trigger gland secretions.
For example, blood glucose level is a major regulator of glucagon and insulin release.
When blood glucose level rises, the pancreas is stimulated to increase insulin secretion and suppress glucagon secretion.
A depressed level of blood glucose, on the other hand, triggers increased glucagon secretion and suppresses insulin secretion.

Nervous system regulation
The central nervous system (CNS) helps to regulate hormone secretion in several ways.

Hypothalamus
The hypothalamus controls pituitary hormones. Because hypothalamic nerve cells stimulate the posterior pituitary to secrete
ADH and oxytocin, these hormones are controlled directly by the CNS.

Stimuli
Nervous system stimuli—such as hypoxia (oxygen deficiency), nausea, pain, stress, and certain drugs—also affect
ADH levels.

Autonomic Nervous System
The ANS controls catecholamine secretion by the adrenal medulla.

Stress
The nervous system also affects other endocrine hormones. For

example, stress, which leads to sympathetic stimulation, causes
the pituitary to release corticotropin

Endocrine diseases

Common, including conditions such as diabetes mellitus, thyroid disease, and obesity.

Endocrine disease is characterized by misregulated hormone release (a productive pituitary adenoma)

Inappropriate response to signaling (hypothyroidism)

Lack of a gland (diabetes mellitus type 1, diminished erythropoiesis in chronic kidney failure)
Structural enlargement in a critical site such as the thyroid (toxic multinodular goitre).

Hypofunction of endocrine glands can occur as a result of loss of reserve, hyposecretion, agenesis, atrophy, or active destruction. Hyperfunction can occur as a result of hypersecretion, loss of suppression, hyperplastic or neoplastic change, or hyperstimulation.

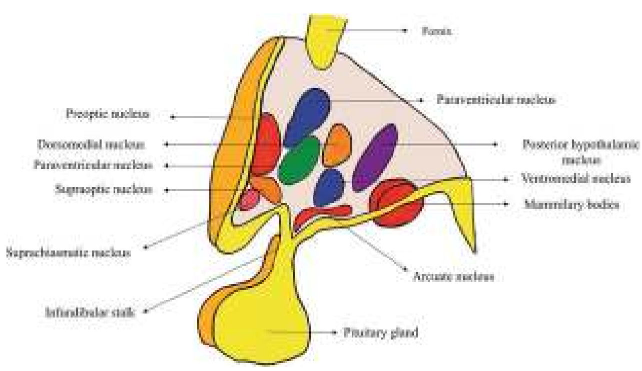
Endocrinopathies are classified as primary, secondary, or tertiary.

Primary endocrine disease inhibits the action of downstream glands.

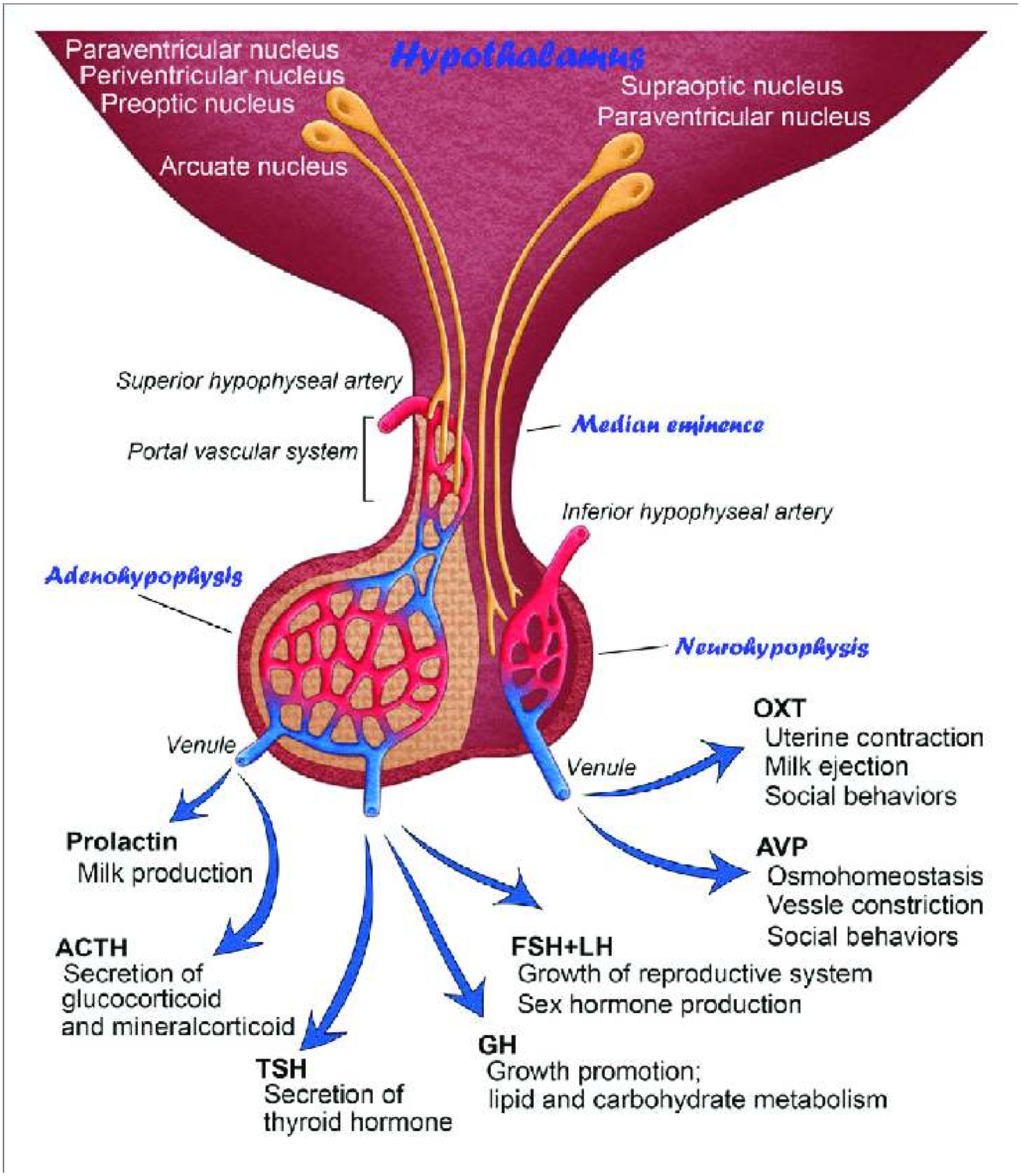
Secondary endocrine disease is indicative of a problem with the pituitary gland.

Tertiary endocrine disease is associated with dysfunction of the hypothalamus and its releasing hormones

Hypothalamus



A part of forebrain.



Connected to Ant. Pituitary by Portal Hypophyseal vessels (PortalC)

Connected to Post. Pituitary by Hypothalamo-Hypophyseal tract.

Neuroendocrine transducer = Hypothala1nus + Adrenal Medulla + Pineal Body.

Anatomy :

Above: Thalamus separated from it by hypothalamic sulcus.

Medially & Above: 3rd ventricle i.e. forms the floor of 3rd V.

Below: connected to pituitary by stalk.

In front: Optic chias1n a / Behind: Mammillary body

Bloodsupply:

Independent artery
Circle of Willis, Supraoptic Nucleus has the richest supply.There are capillaries draining it to median eminence.
Hypothalamic-pituitary hormones:

Releasing harmones-TRH,CRH.GnRH,GHIH.
Inhibitory harmones-Dopamine ,somatostatin.

TRH
Has 3 amino acids.
Produced in Supra optic nucleus.
Increases TSH,Prolactin(exogenous TRH) and ACTH in pregnancy.
Increases TSH, prolactin increased TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion causing galactorrhea.

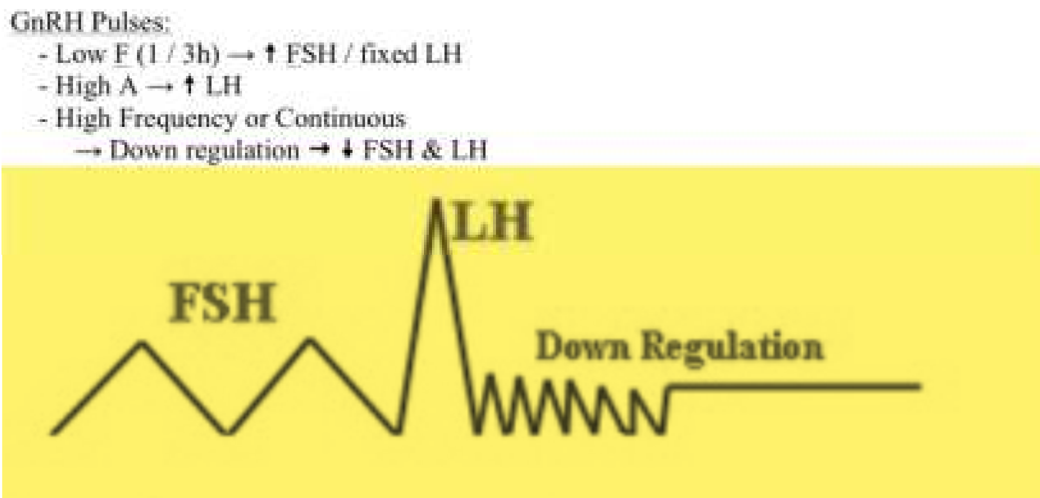
CRH -corticotrophin releasing harmone
Has 41 amino acids.Produced by Paraventricular nucleus of hypothalamus.
Increases ACTH, MSH, β-endorphin .It will be low in chronic exogenous steroid use.

GHRH
Hass 44 amino acids.
Produced in Arcuate nucleus.Increases GH.

Raises GH Analogue (tesamorelin) used to treat HIV-associated lipodystrophy.

GnRH
A deca -peptide .10 aminoacids.
Half life is 2-4 minutes.
Has autocrine and paracrine effects.

Produced from Arcuate nucleus.
Increases FSH/LH,Prolactin by raising estrogen.
Released in pulses.High level in follicular phase of menstrual cycle.
Stimulates FSH, LH Suppressed by hyperprolactinemia. Tonic GnRH suppresses HPG axis.
Pulsatile GnRH leads to puberty, fertility.
Amplitude and frequency of GnRH pulses increases in late follicular phase.
Amplitude and frequency decrease in luteal phase of menstrual cycle.



Kallman Syndrome
is a condition characterized by delayed or absent puberty and an impaired sense of smell- anosmia;hearing can be affected .
More common in males.
Caused by failure of migration of GnRH secreting neurons from their site of origin in olfactory bulbs. This disorder is a form of hypogonadotropic hypogonadism, which is a condition resulting from a lack of production of certain hormones that direct sexual development.
Defect may be in placenta or in ovaries.Low production of E2 pulses leading to low response from pituitary gland(negative feedback).

MSH
Stimulates melanogenesis by melanocytes Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin.
Inhibitoy harmones from Hypothalamus

Dopamine
1 amino acid.Produced in Arcuate nucleus.
Decreases Prolactin and GH.
It inhibits prolactin, TSH Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia.

Somatostatin;GHIH
Has 14 amino acids.
Produced in periventricular nucleus.Inhibits GH and TSH.

<u>Paracrine effect of Somatostatin (Produced by many tissues):</u>

D-cells of pancreas produce it.which inhibit insulin & Glucagon.

In stomach it decreases HCl & Pepsin.

In intestine it decreases VIP ,Motilin ,CCK-PZ
If pituitary stalk is cut -hyperprolacinema occurs

Releasing Hormones:

Exogenous pulsatile RH increase trophic harmones to reach maximum level. After 20 min.

Their continuous administration will cause down regulation. E.g. GnRH Implants can be used for contraception.

Pulses & release depends on the mainly on Frequency (not amplitude).

Neurotransmitters in hypothalamus

Dopamine

Noradrenaline

Serotonin

Substance P

Calcitonin

Gamma amino-butyric acid.

E**ndorphins:** _. Increase Prolactin(decrease Dopamine) increase GH / **decrease** Frequency of GnRH.

Functions of hypothalamus:

Regulation of pituitary harmone release

Maintain body weight and calories

Thermoregulation

Satiety centre appetite and thirst center.

We should know all about 5 endocrine glands in the body:

Pituitary

Thyroid

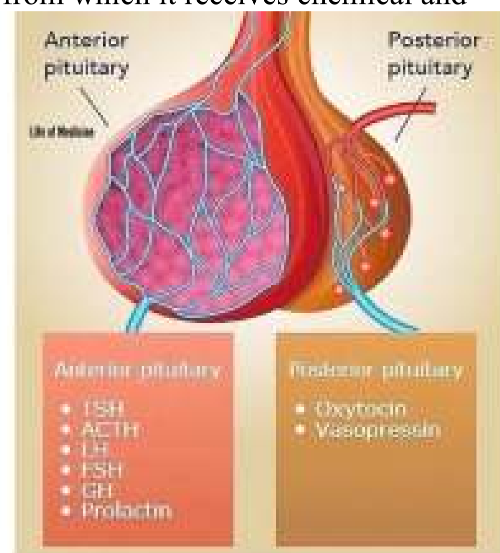
Pancrease

Adrenals

Gonades

The pituitary gland

The pituitary gland (also called the hypophysis or master gland) Lies in the sella turcica, a depression in the sphenoid bone at the base of the brain. This pea-sized gland connects with the hypothalamus via the infundibulum, from which it receives chemical and



nervous stimulation.

The pituitary gland is formed within the rostral neural plate.

The Rathke's pouch, a cavity of ectodermal cells of the oropharynx, forms between the fourth and fifth week of gestation and upon full development, it gives rise to the anterior pituitary gland. By seven weeks of gestation, the anterior pituitary vascular system begins to develop. During the first 12 weeks of gestation, the anterior pituitary undergoes cellular differentiation. At 20 weeks of gestation, the hypophyseal portal system has developed. The Rathke's pouch grows towards the third ventricle and fuses with the diverticulum. This eliminates the lumen and the structure becomes Rathke's cleft.

The posterior pituitary lobe is formed from the diverticulum.

The functional development of the anterior pituitary involves regulation of transcription factors expressed in pituitary stem cells and dynamic gradients of local soluble factors. The coordination of the dorsal gradient of pituitary morphogenesis is dependent on neuroectodermal signals from the infundibular bone morphogenetic protein 4 (BMP4). This protein is responsible for the development of the initial invagination of the Rathke's pouch. Other essential proteins necessary for pituitary cell proliferation are Fibroblast growth factor 8 (FGF8), Wnt4 and Wnt5.

Ventral developmental patterning and the expression of transcription factors is influenced by the gradients of BMP2 and sonic hedgehog protein (SHH). These factors are essential for coordinating early patterns of cell proliferation.

By seven weeks of gestation, the anterior pituitary is capable of secreting ACTH.

Within eight weeks of gestation, somatotroph cells begin to develop with cytoplasmic expression of human growth hormone. Once a fetus reaches 12 weeks of development, the thyrotrophs begin expression of Beta subunits for TSH, while gonadotrophs being to express beta-subunits for LH and FSH. Male fetuses predominately produced LH-expressing gonadotrophs, while female fetuses produce an equal expression of LH and FSH expressing gonadotrophs. At 24 weeks of gestation, prolactin-expressing lactotrophs begin to emerge.