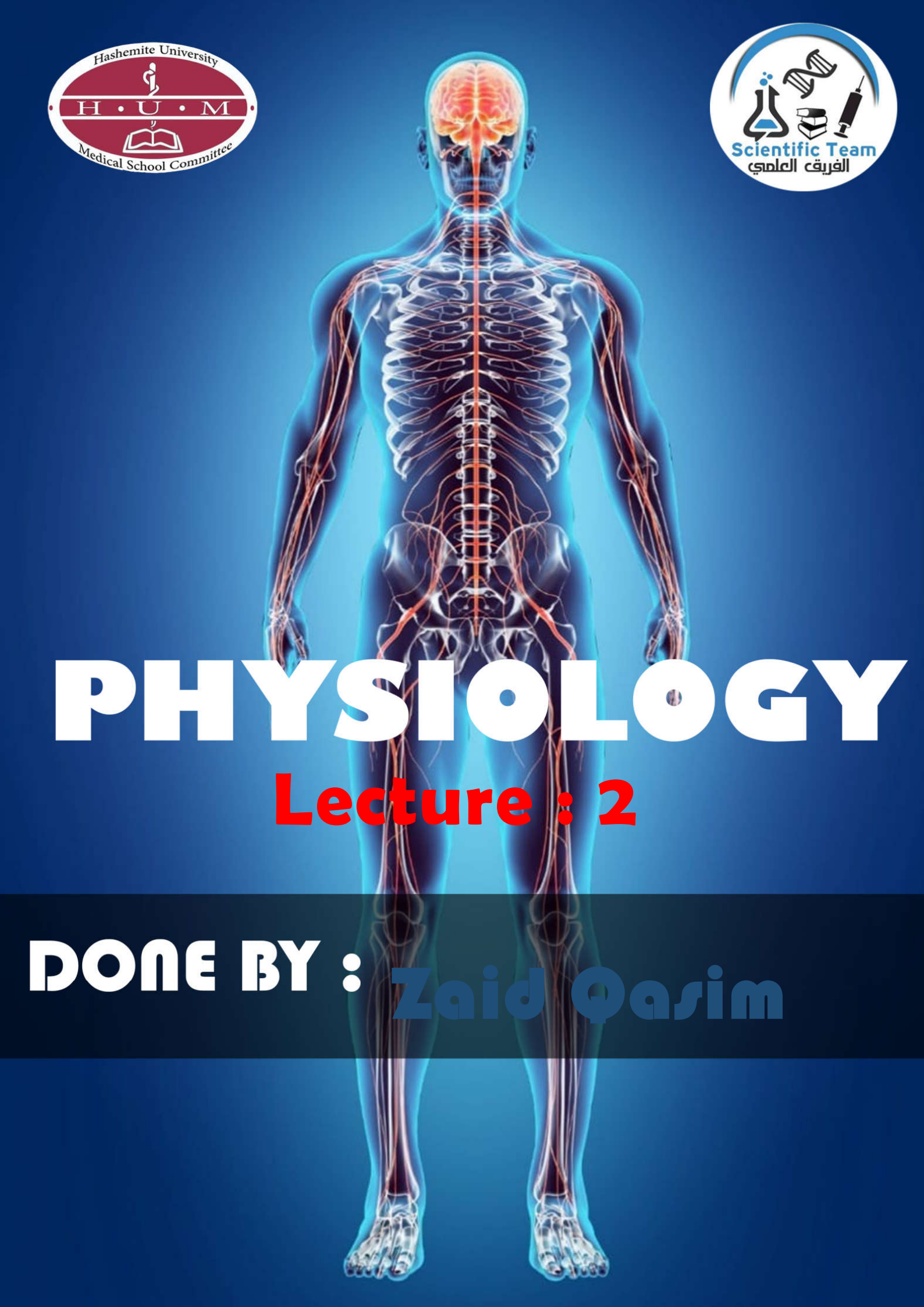


PHYSIOLOGY

Lecture : 2

DONE BY : Zaid Qasim

بسم الله الرحمن الرحيم

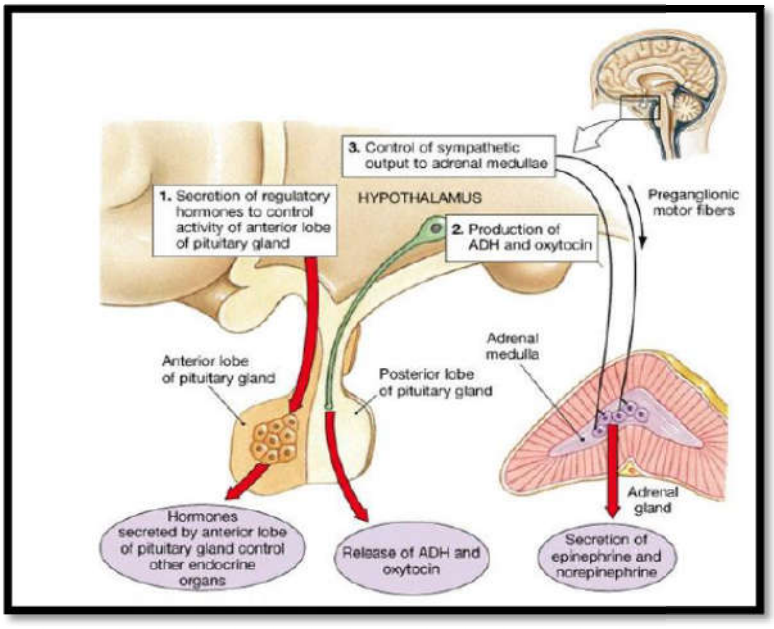
LECTURE 2 : Pituitary Hormones and Their Control by the Hypothalamus

- The Nervous system and the Endocrine system work in a coordinated manner.
- First of all, there are many ways through which the Hypothalamus (CNS) can control the Endocrine system throughout the body. These ways can be divided into three types:

1- Secretion of **regulatory** neuropetides /neurohormones by the hypothalamus and through the portal system they will be carried into the Anterior Lobe of the Pituitary gland. Different hormones will be secreted by the latter and transported by the blood circulation into their target organs.

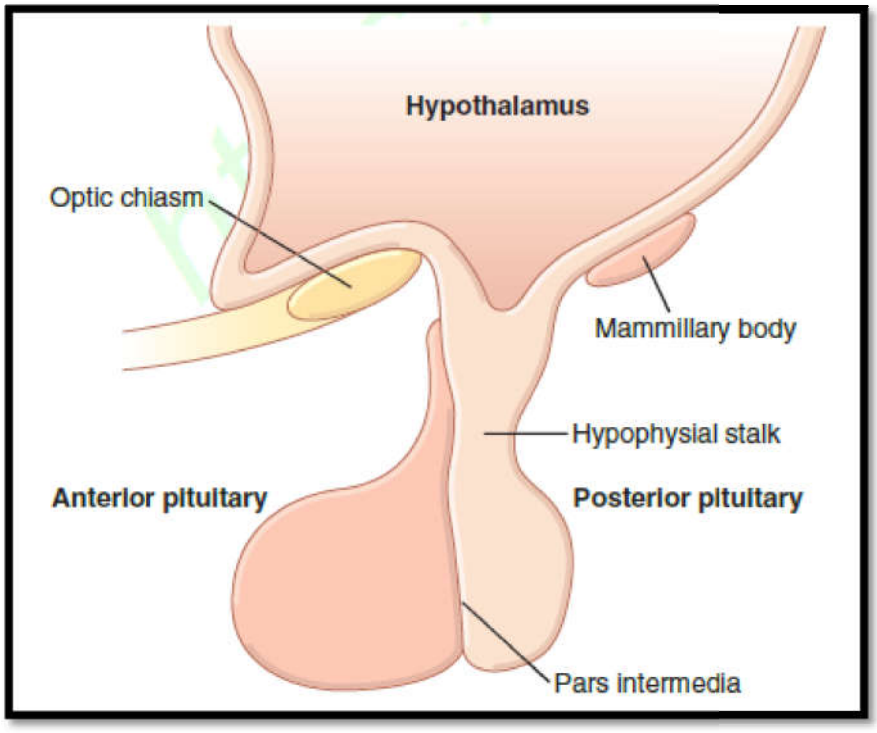
2- Neurosecretory neurons in the hypothalamus will produce certain hormones (the Antidiuretic Hormone (ADH) or Vasopressin and Oxytocin) and they will be secreted through the axon terminals in the Posterior Lobe of the Pituitary gland. The latter will act as a storage (the posterior lobe doesn't synthesize them) for these two hypothalamic hormones and it will release them into the bloodstream when they receive nerve signals that originate in the hypothalamus.

3- The hypothalamus also control the sympathetic output to the medulla of the adrenal gland (working mainly when someone is under stress). The adrenal medulla in turn will secrete its two main hormones: epinephrine and norepinephrine ,which have similar functions.



- The Anatomy of the Anterior and Posterior Lobes Of The Pituitary Gland :

- "The *pituitary gland,* also called the *hypophysis,* is a small gland—about 1 centimeter in diameter and 0.5 to 1 gram in weight—that lies in the *sella turcica,* a bony cavity at the base of the brain, and is connected to the hypothalamus by the *pituitary* (or *hypophysial*) stalk. Physiologically, the pituitary gland is divisible into two distinct portions: the *anterior pituitary,* also known as the *adenohypophysis,* and the *posterior pituitary,* also known as the *neurohypophysis.* Between these portions is a small, relatively avascular zone called the *pars intermedia,* which is much less developed in the human being but is larger and much more functional in some animals. Embryologically, the two portions of the pituitary originate from different sources—the anterior pituitary from *Rathke's pouch,* which is an embryonic invagination of the pharyngeal epithelium, and the posterior pituitary from a neural tissue outgrowth from the hypothalamus. The origin of the anterior pituitary from the pharyngeal epithelium explains the epithelioid nature of its cells, and the origin of the posterior pituitary from neural tissue explains the presence of large numbers of glial-type cells in this gland".

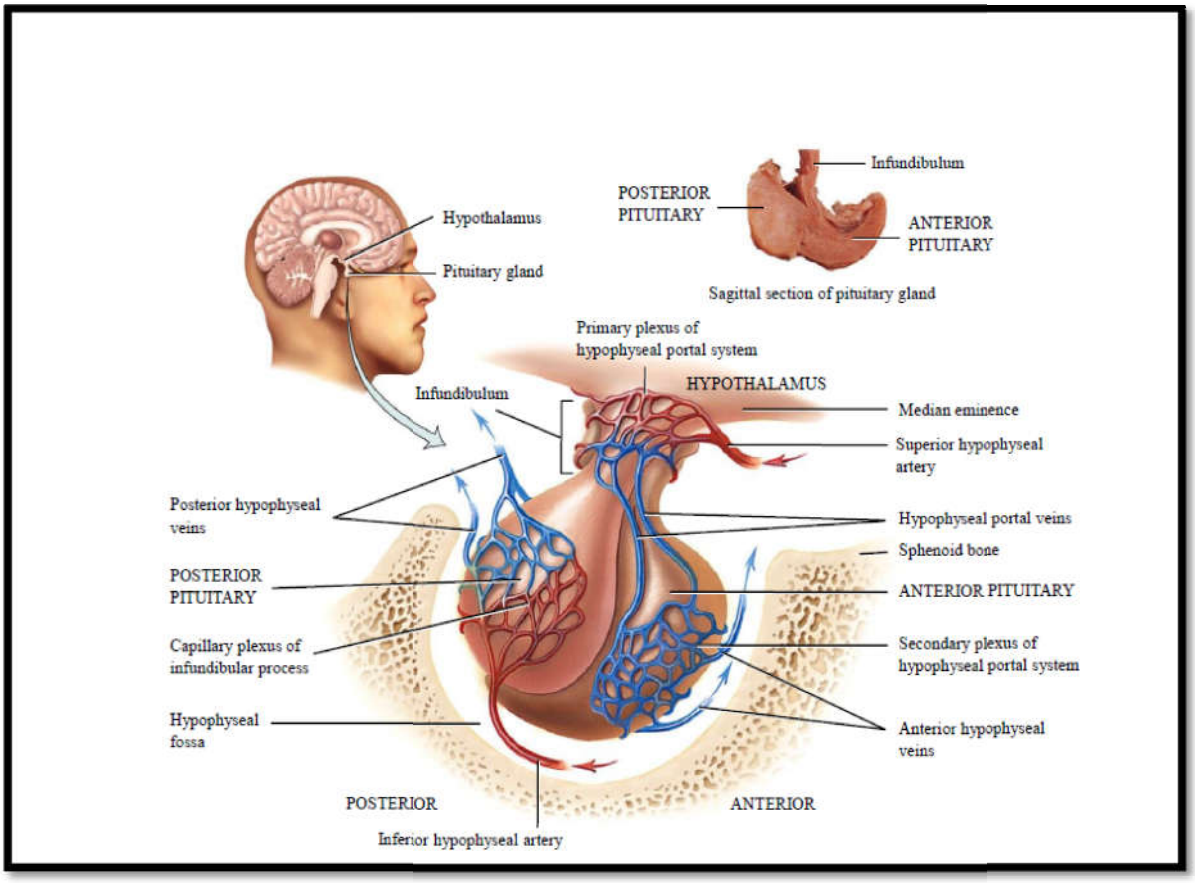


*** The connection between the hypothalamus and the pituitary is divided into two major types:**

(1) Neuronal connection with the posterior pituitary lobe termed the *Hypthalamo-hypophyseal tract.*

(2) Vascular connection with the anterior pituitary lobe termed the *Hypthalamo-hypophyseal portal circulation*.

- The blood supply to the posterior pituitary gland differ from that to the anterior pitituary gland in that, the *Inferior hypophyseal artery* supplies the posterior lobe of the gland and forms the capillary plexus upon the posterior lobe itself , then the venous blood will be drained by *Posterior hypophyseal veins*. However, the anterior lobe is supplied by the *Superior hypophyseal artery*. This artery will form the primary plexus of hypophyseal portal system (outside the anterior lobe) in the lowermost portion of the hypothalamus the so-called the *median eminence*. Small arteries penetrate into the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal blood vessels. These vessels pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses. The blood will eventually drain through the *Anterior hypophyseal veins.*

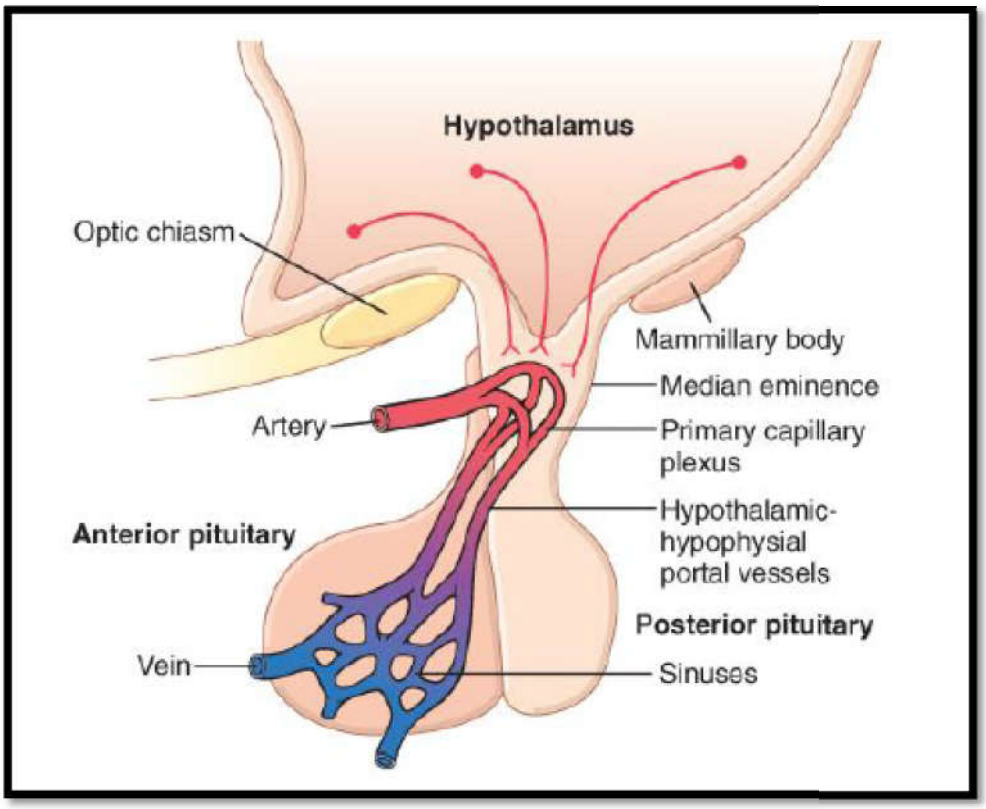


- Note that the nervous control between the hypothalamus and the posterior pituitary gland compromises of neuronal cell bodies or what is called nuclei and axons terminating in the posterior pituitary gland itself. There are two nuclei, the Supraoptic nucleus which secretes ADH and the Paraventicular nucleus which secretes Oxytocin.

  Q: By which mechanism of transport the hypothalamus secrete ADH and Oxytocin into the posterior pituitary gland?

  The answer is Axonal transport or Axoplasmic transport.
- The hormones that are secreted by the anterior pituitary gland are called Trophic Hormones.

- Certain Neurosecretory neurons will secrete their hormones into the primary plexus of the hypophyseal portal system, then those hormones will be carried by *Hypthalamo-hypophyseal portal vessels* that terminate within the anterior pituitary gland in the secondary plexus of hypophyseal portal system or the Sinuses affecting the anterior pituitary gland functions to secrete its own hormones into the circulation by the hypophyseal veins.
- Both Hypthalamo-hypophyseal portal circulation and Hypthalamo-hypophyseal tract pass on the infundibular stalk of the pituitary gland.



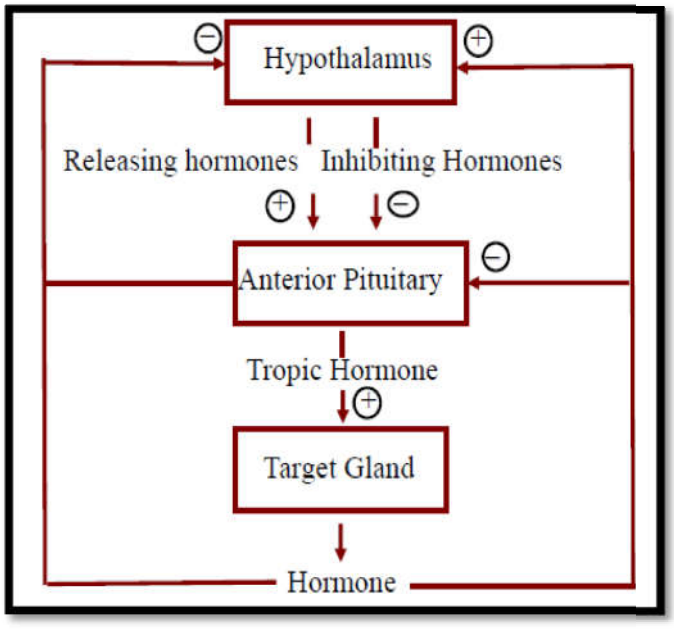
- **Hypothalamic Releasing and Inhibitory Hormones Are Secreted into the Median Eminence and Control Anterior Pituitary Secretion**

  " Special neurons in the hypothalamus synthesize and secrete the *hypothalamic releasing* and *inhibitory hormones* that control secretion of the anterior pituitary hormones. The function of the releasing and inhibitory hormones is to control secretion of the anterior pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control". The major 6 hypothalamic releasing and inhibitory hormones, which are summarized in the following table . . .

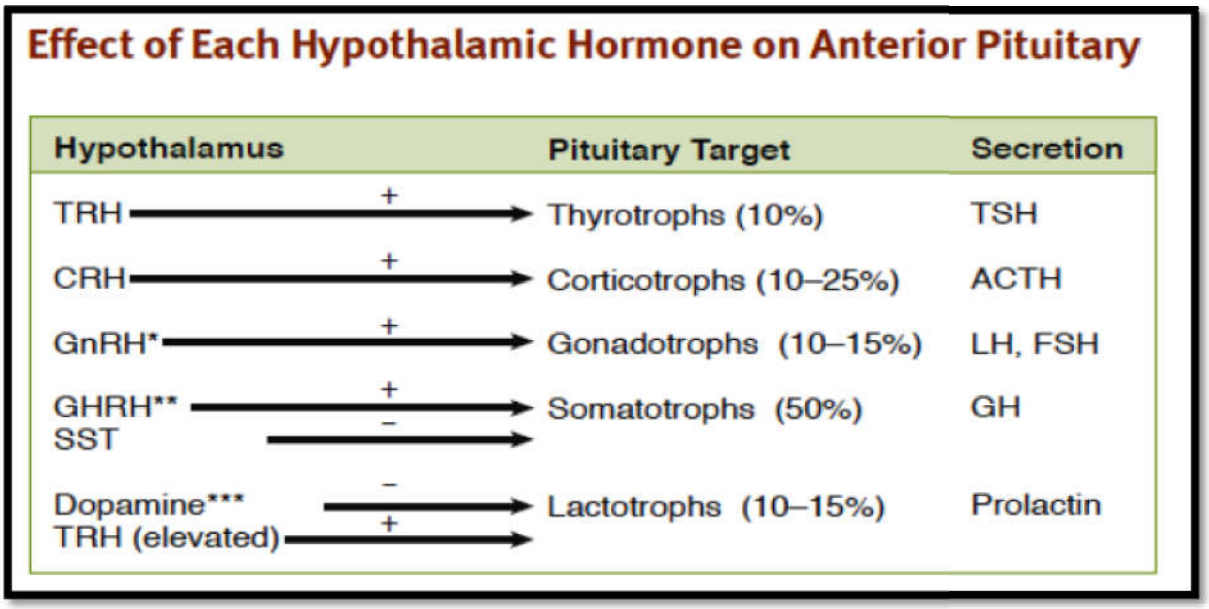
Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone–releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits synthesis and secretion of prolactin by lactotropes

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

- As we discussed before, the releasing & inhibitory hormones go through the portal system into the anterior pituitary gland increasing & decreasing the secretory activity of the gland *respectively*. The anterior pituitary gland will then release its own tropic hormone to stimulate the last target gland of the endocrine system to secrete different hormones as shown in the table above.
  - When the hormone level gets elevated in the circulation, it will reach the hypothalamus SUPPRESSING the hypothalamus secretion of the releasing hormones and STIMULATING it to secrete the inhibitory hormones.
    Also, when hormone's level gets elevated it will go to and inhibit the secretion of the anterior pituitary gland. Example: When the Growth Hormone (GH) increases in the circulation (such as in hypoglycemia) it will inhibit the hypothalamus from secretion of Growth Hormone-Releasing Hormone (GHRH) and it will also inhibit the pituitary gland from releasing the (GH). On the other hand, (GH) will stimulate the hypothalamus to release the Inhibitory hormone, that is, the Somatostatin which in turn further suppresses the release of (GH) from the anterior pituitary gland. This is called the "feedback mechanism" as shown in this figure . . .



- This table summarizes the hypothalamic releasing and inhibitory hormones and the Anterior pituitary tropic hormones and the percentages of the different anterior pituitary hormone-releasing cells . . .



Note that :

(1) When the hypothalamus release Corticotrophin-Releasing Hormone(**CRH**) it will stimulate the anterior pituitary gland to release Adrenocorticotropic hormone (**ACTH**) into the circulation which in turn stimulates adrenal cortex cells to release glucocorticoids such as cortisol and androgens. This is known as ***hypothalamic-pituitary-adrenal axis***. The increase in cortisol provides a negative feedback system to then decrease the amount of CRH released from the hypothalamus. The same principle is applied to other hormones and target organs.

(2) Somatotrophs constitute the majority of the cells within the anterior pituitary gland (50%).

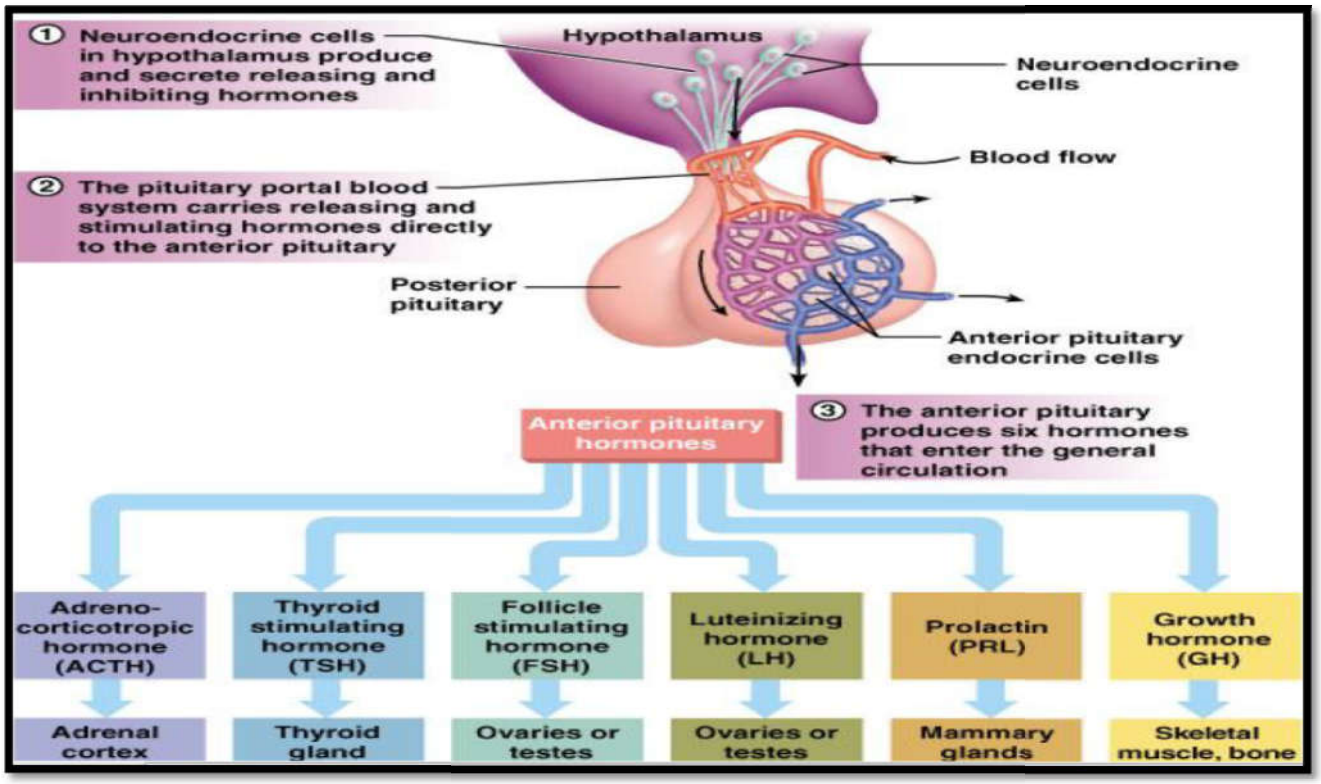
(3) There are two inhibitory hypothalamic hormones: Somatostatin (**SS)** that inhibits Growth hormone (**GH)** release from anterior pituitary gland & Dopamine which inhibits Prolactin release from the gland. The other four are stimulatory (or releasing) hormones.

(4) Prolactin secretion is achieved mainly by the inhibition of dopamine release from the hypothalamus, although elevated level of Thyrotropin-Releasing Hormone (**TRH**) can increase prolactin secretion by the anterior pituitary gland.

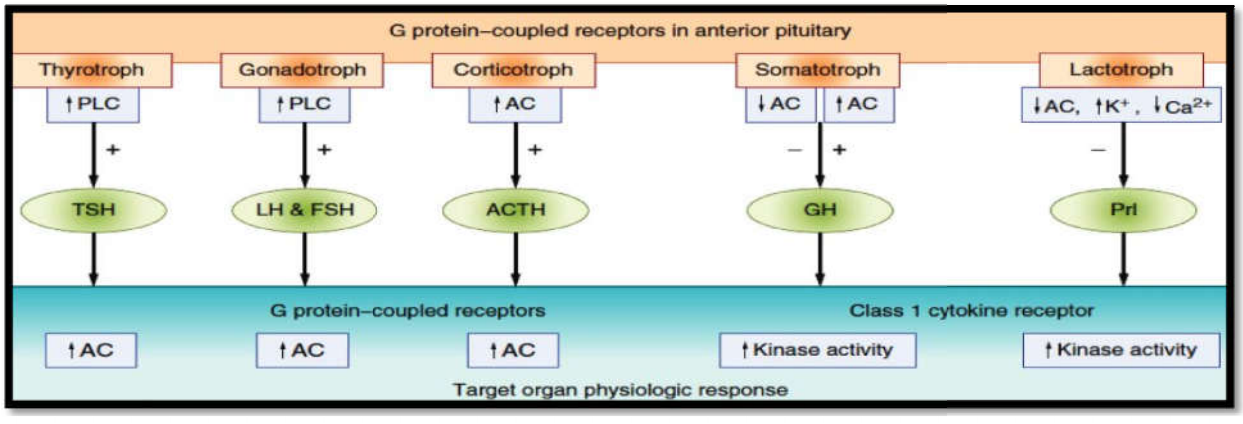
(5) Some hormones like (TRH) & (CRH) are released from the Paraventricular nucleus of the hypothalamus whereas (GnRH), (GHRH) & (PIH) are released from the arcuate nucleus. The growth hormone-inhibiting hormone(SS) is released by both nuclei.

(6) All of them with the exception of dopamine are peptide hormones (consisting of many amino acids). Dopamine is a tyrosine-derivative hormone

- The following figure is just summarizing all what we talked about . . . notice the target organs for the different trophic hormones :



- All of the hypothalamic hormones released into the median eminence are carried by the hypthalamo-hypophyseal portal circulation into the anterior pituitary gland affecting its different types of secretory cells. All of the hypothalamic hormones act on G-protein coupled surface receptors. Gs receptors are coupled with the enzyme adenyl cycles which forms (cAMP) whereas Gq receptors are coupled with the enzyme Phospholipase C (PLC) which forms inositol triphosphate (IP_3) and diacylglycerol (DAG).

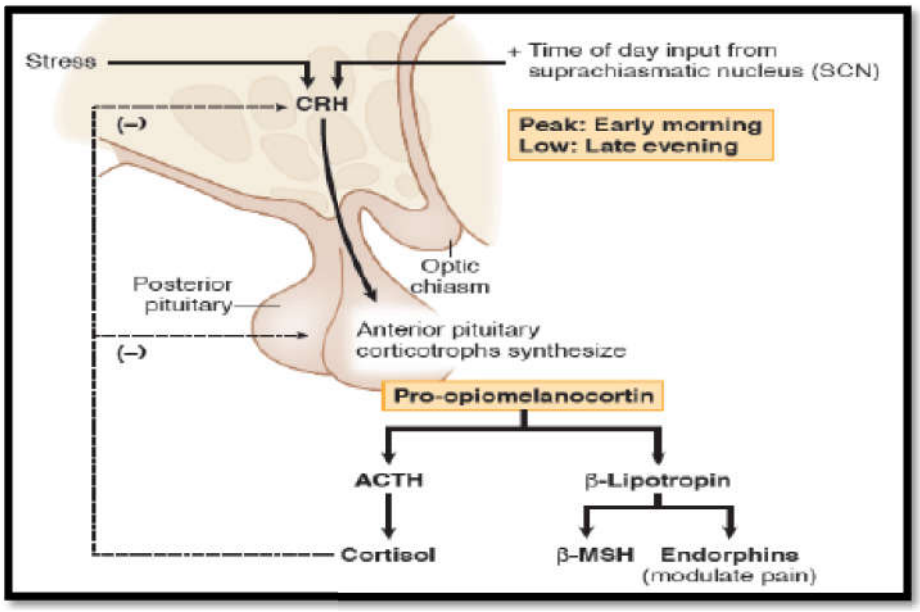


- The hormones of the anterior pituitary gland can affect the target organ physiologic responses via two different types of receptor :
  1- TSH, LH & FSH and ACTH stimulate their target organ via G protein-coupled receptor (increasing adenyl cyclase activity).
  2- GH &Prolactin work via class 1 cytokine receptor increasing kinase activity in their target organs.
- This table summarizes the six hormones of the anterior pituitary gland and their physiologic action on their target organs :

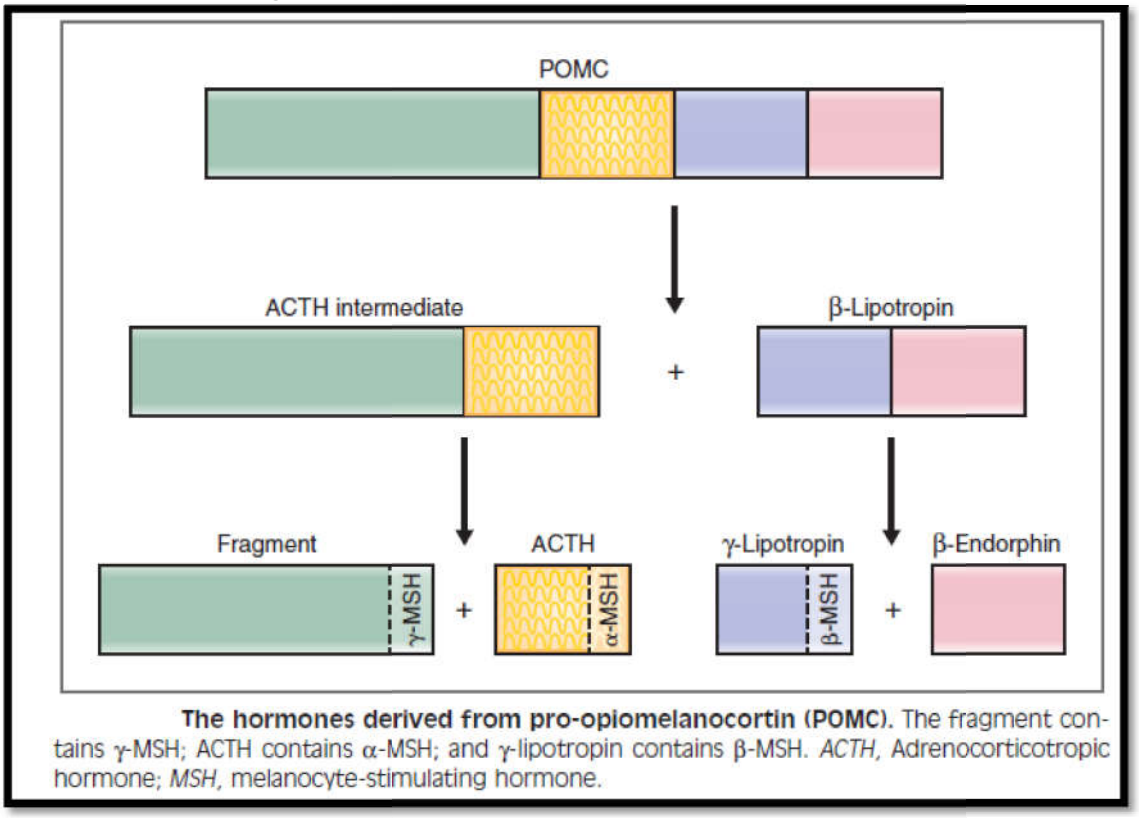
Cell	Hormone	Chemistry	Physiologic Actions
Corticotropes	Adrenocorticotropic hormone (corticotropin; ACTH)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (thyrotropin; TSH)	Glycoprotein having two subunits, α (89 amino acids) and ß (112 amino acids)	Stimulates production of thyroid hormones, T4 and T3, by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein having two subunits, α (89aa) and ß (115aa)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
Gonadotropes	Lutenizing hormone (LH)	Glycoprotein having two subunits, α (89aa) and ß (115aa)	Causes ovulation and formation of corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Mammotropes, Lactotropes	Prolactin (PRL)	Single chain of 198 amino acids	Essential for milk production by lactating mammary gland
Somatotropes	Growth hormone (somatotropin; GH)	Single chain of 191 amino acids	Stimulates postnatal body growth; stimulates secretion of IGF-1; stimulates triglyceride lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism

لازم نعرف شو وظيفة كل هرمون على العضو الهدف تبعه .. واعذروني على كثرة الصور والجداول، بس هيك هي السلايدات للأسف:(بس إن شاء الله انهم سهلات

- **Proopiomelanocortin hormones.**
- As we talk above, the (CRH) which is released by the hypothalamus stimulates the anterior pituitary gland to secret (ACTH). Actually, the (ACTH) is produced by the cleavage (hydrolysis) of a single large precursor protein called *Proopiomelanocortin***.**
- The pro-opiomelanocortin gives many other hormones rather than (ACTH) when it is cleaved including:
  - ACTH
  - γ- lipotropin,
  - β-lipotropin,
  - β-endorphin, and
  - Melanocyte-stimulating hormone (MSH).
- "ACTH is the only hormone in this family with well-established physiologic actions in humans. MSH is involved in pigmentation in lower vertebrates but has some activity in humans. β-Endorphin is an endogenous opiate".



- "The preprohormone for this group, preproopiomelanocortin**,** is transcribed from a single gene. The signal peptide is cleaved in the endoplasmic reticulum, yielding POMC, the precursor to the ACTH family. Endopeptidases then hydrolyze peptide bonds in POMC and intermediates to produce the members of the ACTH family" as shown in the figure below.



The hormones derived from pro-opiomelanocortin (POMC). The fragment contains γ-MSH; ACTH contains α-MSH; and γ-lipotropin contains β-MSH. *ACTH,* Adrenocorticotropic hormone; *MSH,* melanocyte-stimulating hormone.

- "It is noteworthy that MSH activity is found in POMC and in several of its products: The "fragment," which is left over from hydrolysis of the ACTH intermediate, contains γ-MSH; ACTH contains α-MSH; and γ-lipotropin contains β-MSH. These MSH-containing fragments can cause skin pigmentation in humans if their blood levels are increased.

- For example, in ***Addison disease*** (primary adrenal insufficiency), POMC and ACTH levels are increased by negative feedback and because POMC and ACTH contain MSH activity, skin pigmentation is a symptom of this disorder".

-You can see the following video for more understanding: https://www.youtube.com/watch?v=73NfVUC51QM ☺

α-MSH بما انه الـ
ACTHبتطلع من ال
ACTH إذا تغير عندنا إفراز الـ
في الجسم، رح يتأثر برضو الـ
Pigmentation of skin and hair

- So, the α-MSH is produced by the proteolytic cleavage of POMC mainly in the pars-intermedia of the pituitary gland which is not well developed in man.
- Only small amounts of α-MSH are produced in human pituitary under normal conditions. Melanocortin peptides exert their effects through Melanocortin receptors (MCRs) found in melanocytes, which are key components of the skin's pigmentary system. So, pigmentary changes in some human endocrine diseases are due to changes in the circulating (ACTH).
  - Hypopituitarism (low ACTH) will be accompanied by abnormal pallor of the patient's skin
  - Patients with adrenal insufficiency, in which the low amount of cortisol fails to inhibit the release of (CRH) from the hypothalamus resulting in higher amounts of (ACTH) and α-MSH in the circulation. This will lead eventually to Hyperpigmentation.
- MCRs mediated the effects of POMC-derived peptides including the 1.skin, 2.adrenal steroid hormone production and 3.thermoregulation. Also, MCRs has been implicated in 4.feeding behavior and 5.appetite regulation.

- Another product is the β-endorphin which mainly mediates pain. It is actually one of the products formed by hydrolysis of POMC & one of the most abundant endogenous opioid peptide. The physiologic effects of this opioid peptide are mediated by binding to opiate receptors, multiple cell types in the brain as well as in peripheral tissues. Its main physiologic effects include analgesia (β-endorphin is one of important transmitters released by neurons and suppresses the brain signalling through brain analgesic system) , behavioural effects and neuromodulator functions.

- HOW TO EVALUATE THE ANTERIOR PITUITARY FUNCTION ?

- Measurements of anterior pituitary hormone concentrations and of the respective target gland hormone levels are used to assess the functional status of the system.

- For example, paired measures of TSH and thyroid hormone, FSH and estradiol, and ACTH and cortisol are used to evaluate the integrity of the respective systems.
- In addition, stimulation and inhibition tests can be used to assess the functional status of the pituitary gland.
- These tests are based on the normal physiologic feedback mechanisms that control tropic hormone release.
- For example, administration of the amino acid arginine can be used to elicit an increase in GH release in patients with suspected GH deficiency.
- In contrast, suppression tests can be used to diagnose Cushing syndrome, a clinical state resulting from prolonged inappropriate exposure to excessive endogenous secretion of cortisol (Low dose Dexamethasone test).

Pituitary Disorders :

(A) Hypersecretion:

- pituitary adenoma , usually benign neoplasm (Prolactinomas are the most common)
- GH-secreting adenomas can be associated with acromegaly or bone and soft tissue overgrowth in adults and gigantism in children.
- ACTH-releasing adenomas are associated with excess cortisol production or Cushing disease
- Clinical presentation Central obesity, proximal myopathy ,hypertension, and hyperglycemia and skin pigmentation… etc
- Gonadotroph pituitary adenomas are frequently inefficient in hormone production (not of clinical importance in affecting the reproductive functions).
- Thyrotropin-secreting tumors are rare and are frequently large when diagnosed (even with measurement of thyrotropin levels it is hard to diagnose such tumors).

(B) Hypopituitarism:

- Can be congenital or acquired. Acquired form can result from Head trauma, surgery, penetrating injury.
- *Craniopharyngloma* is a rare type of brain tumor derived from pituitary gland embryonic tissue that Occurs most commonly in children, but also affects adults.
- It may present at any age, even in the prenatal and neonatal periods, but peak incidence rates are childhood-onset al 5-14 years and adult-onset at 50-74 years.

- Severe blood loss and decreased blood flow (ischemia) of the pituitary. Such ischemic damage to the pituitary gland or hypothalamic-pituitary stalk during the peripartum period *Sheehan syndrome*.

- Pan hypopituitarism in adults leads to:
  - Hypothyroidism.
  - Adrenal insufficiency.
  - Hypogonadism (failure to resume normal menses in women).
  - Loss of lactation in lactating mothers.
  - GH deficiency which will cause growth retardation leading to dwarfism in children and sexual immaturity before puberty.

… and I'm sorry for any unintended mistake :))

THE END