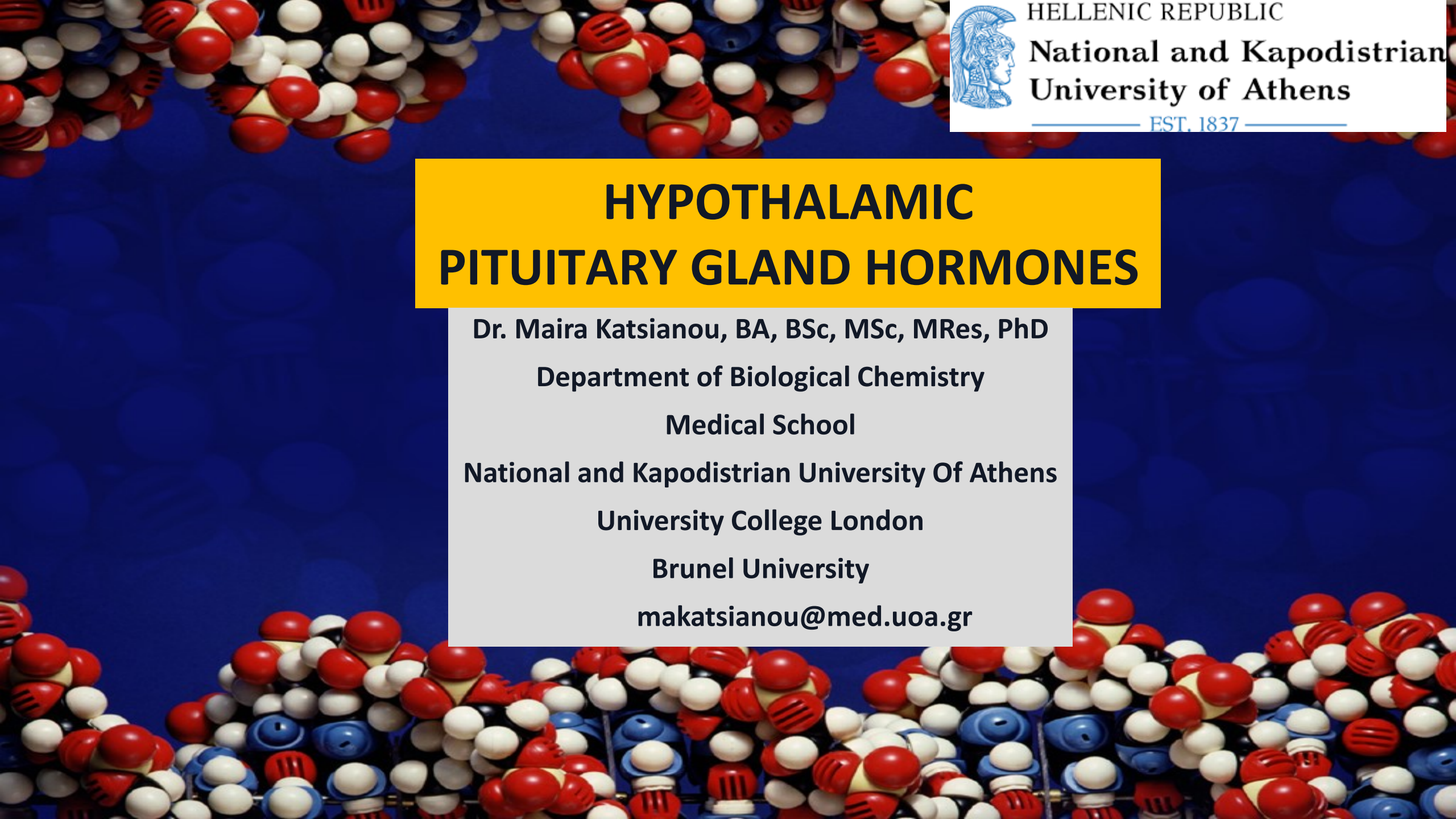

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# HYPOTHALAMIC PITUITARY GLAND HORMONES


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# EDUCATIONAL AIMS

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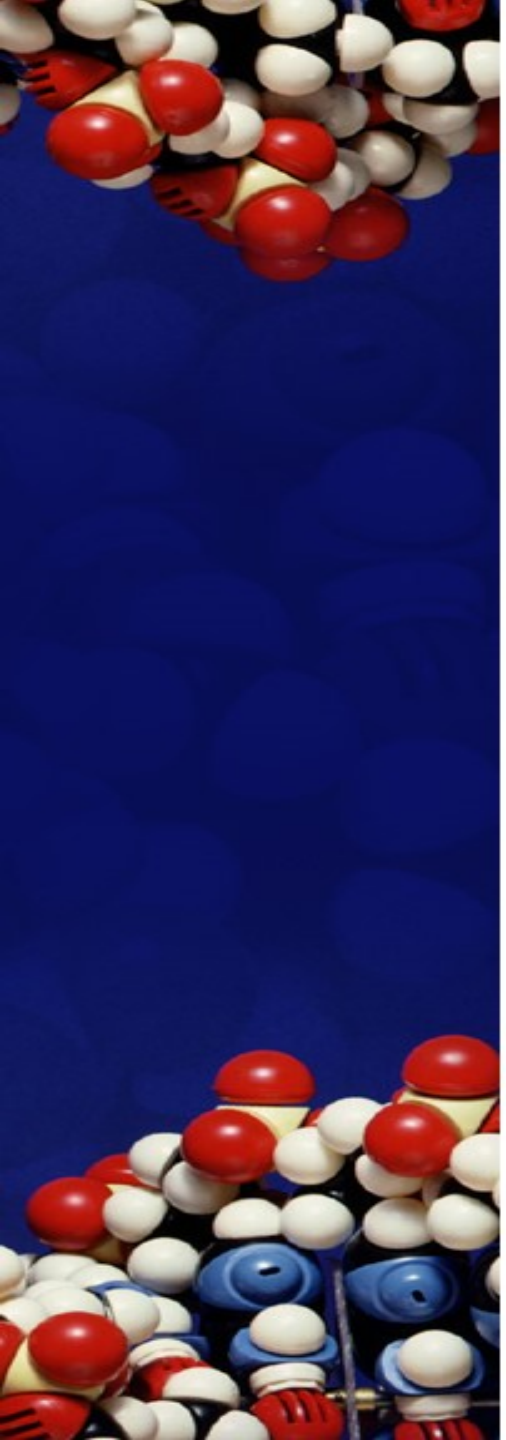
**Students should be able to:**

- **Understand** the **structure of hypothalamic, pituitary and pineal hormones**.
- **Understand their biosynthesis and metabolism**.
- **Understand** the **mechanism of action and regulation of the hormones' secretion.**
- **Understand** their **function in tissues and organs**.
- **Understand clinical correlations**.



# Hormones: Remember

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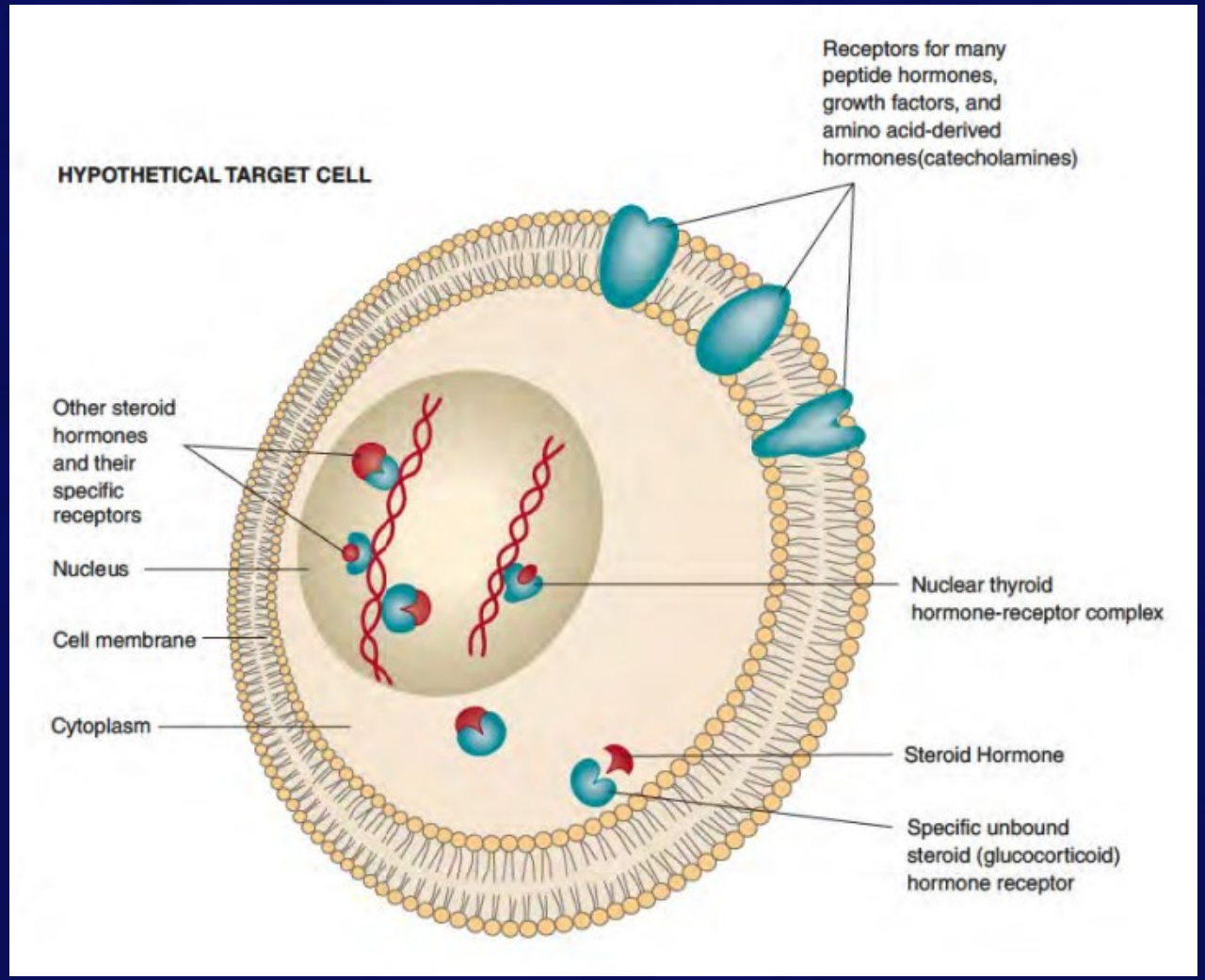
- Carry a “signal” to generate some alteration at the cellular level.
- **Endocrine hormones** are synthesized in one tissue or gland and travel through the general circulation to reach distant target cells that express cognate receptors.
- **Paracrine hormones** are secreted by a cell and travel a relatively short distance to interact with cognate receptors on a neighboring cell.
- **Autocrine hormones** are produced by a cell that is also the target for that hormone (neighboring cells may also be targets).
- **Endocrine hormones are frequently more stable than autocrine hormones that exert their effects over very short distances.**

# Hormones: three major categories

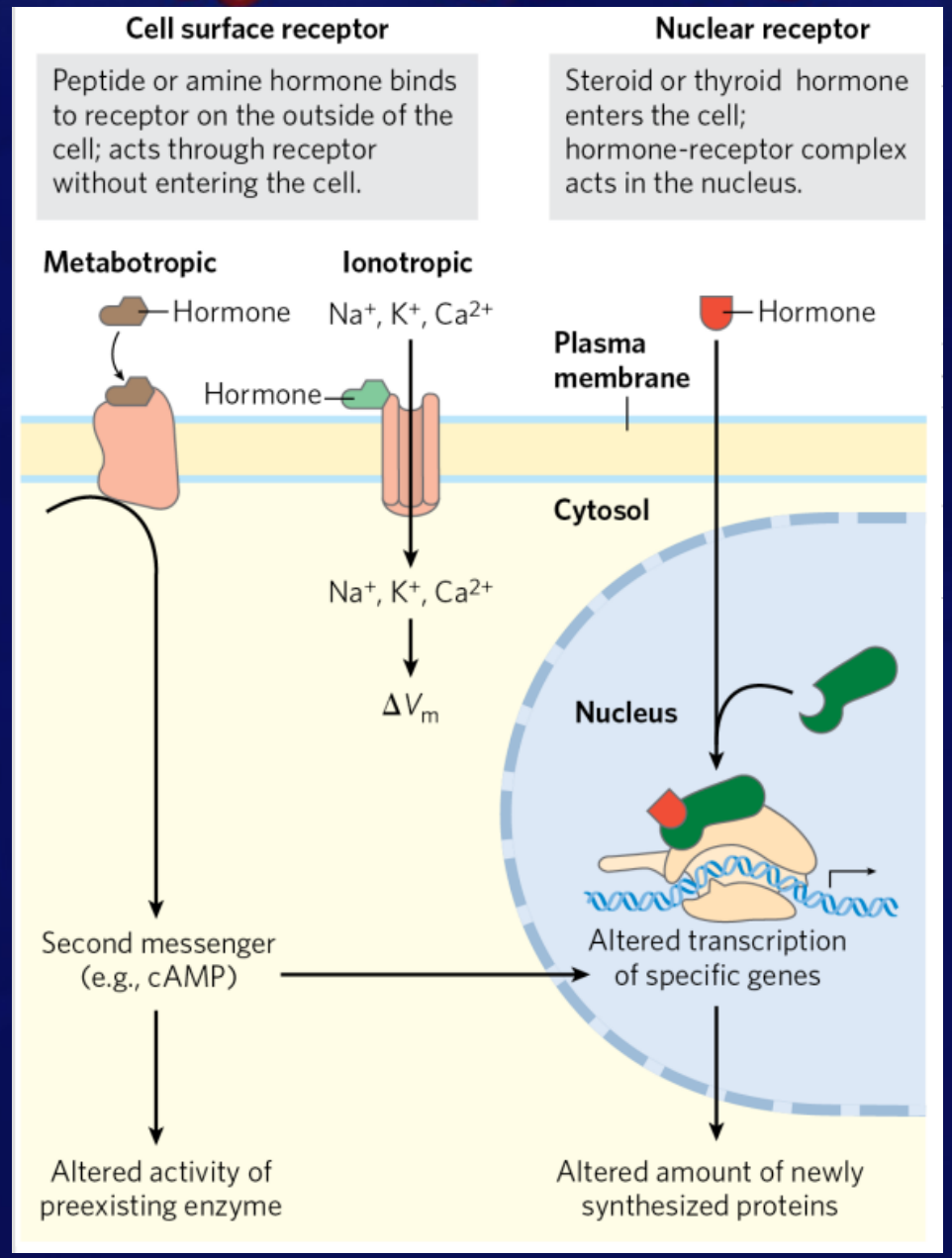



- peptide and protein hormones
- hormones derived from the amino acid tyrosine (thyroid hormones and the catecholamine hormones)
- steroid hormones

# Hormones-signaling

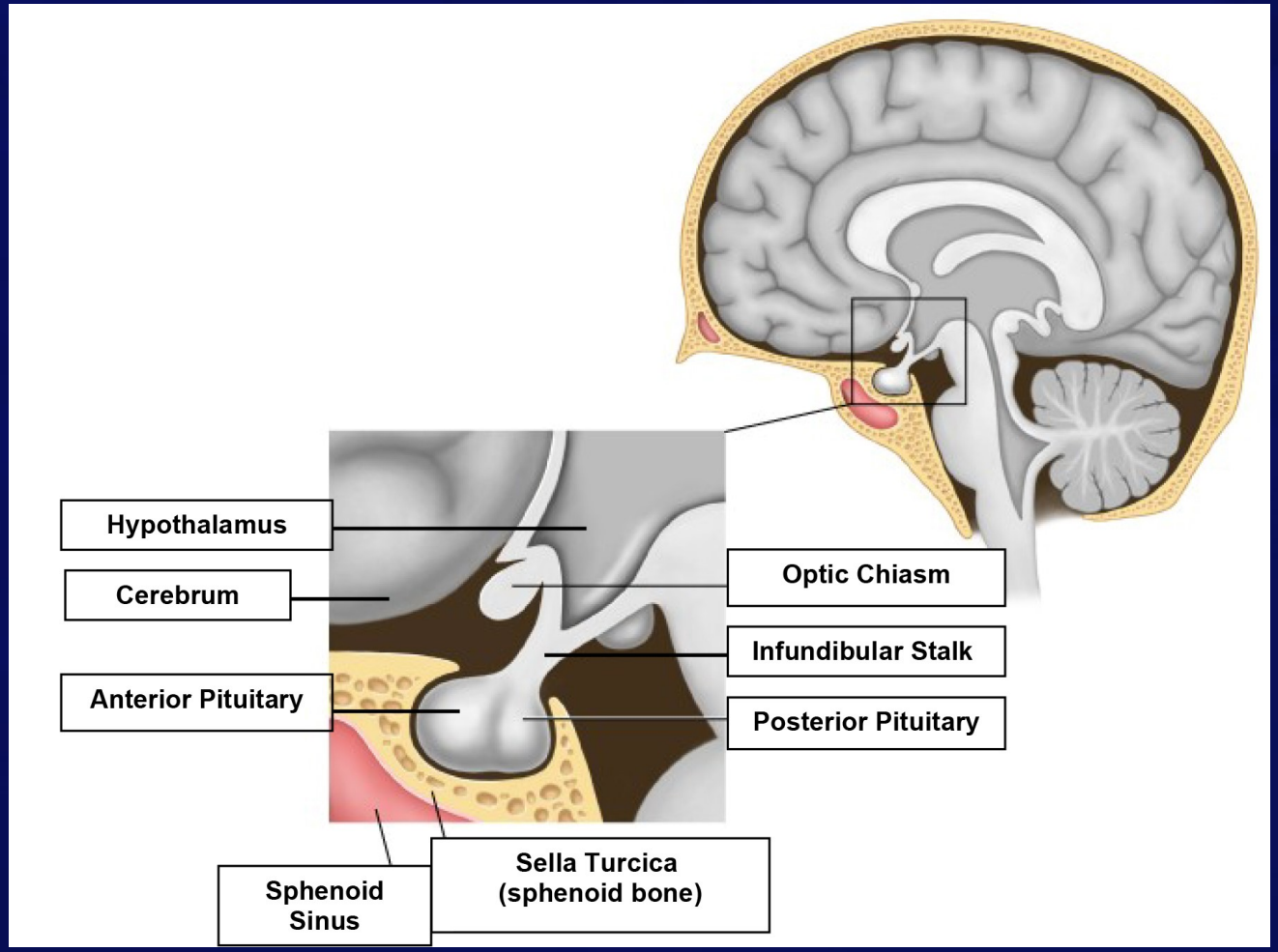
- **The peptide hormones and the catecholamine hormones interact with cell surface receptors and transmit their signals through second messengers that are generated intracellularly.** The binding of insulin to its cell surface receptor activates an intrinsic tyrosine kinase activity.

- Steroid hormones are derived from cholesterol and include glucocorticoid hormones, mineralocorticoid hormones, and the sex hormones. **Steroid hormones diffuse freely across the plasma membrane and bind to intracellular receptors that function as ligand-activated transcription factors .**



# The endocrine system

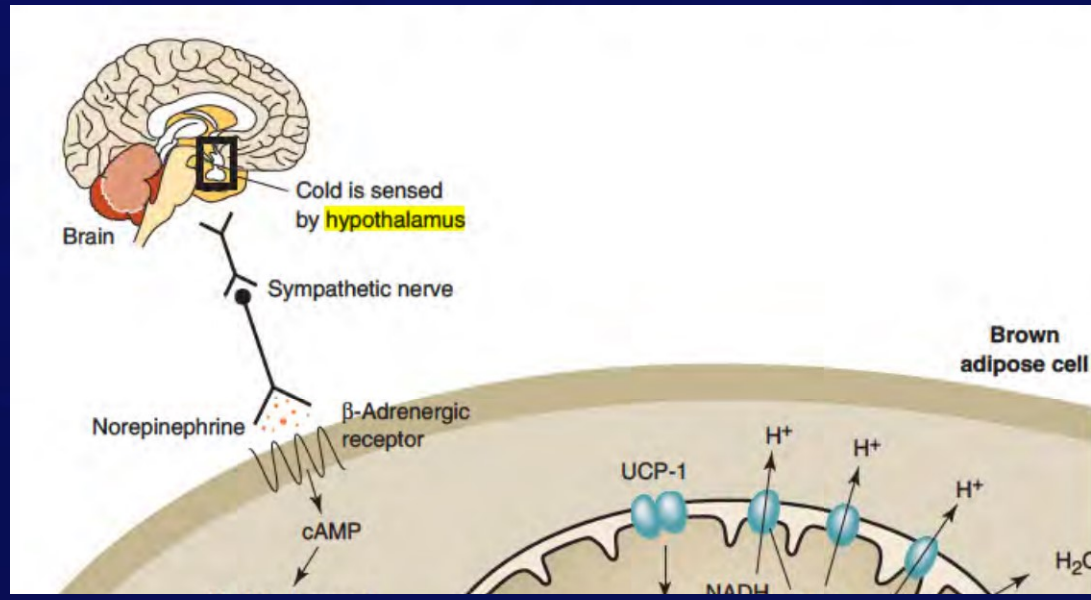
- At least three brain sections are part of the endocrine system: **the hypothalamus—the pituitary or hypophysis, and the pineal gland.**
- The hypothalamus and posterior pituitary are **composed of neurons and neurosecretory cells**
- **The anterior pituitary and the pineal gland are bona fide glands.**



# Hypothalamus I

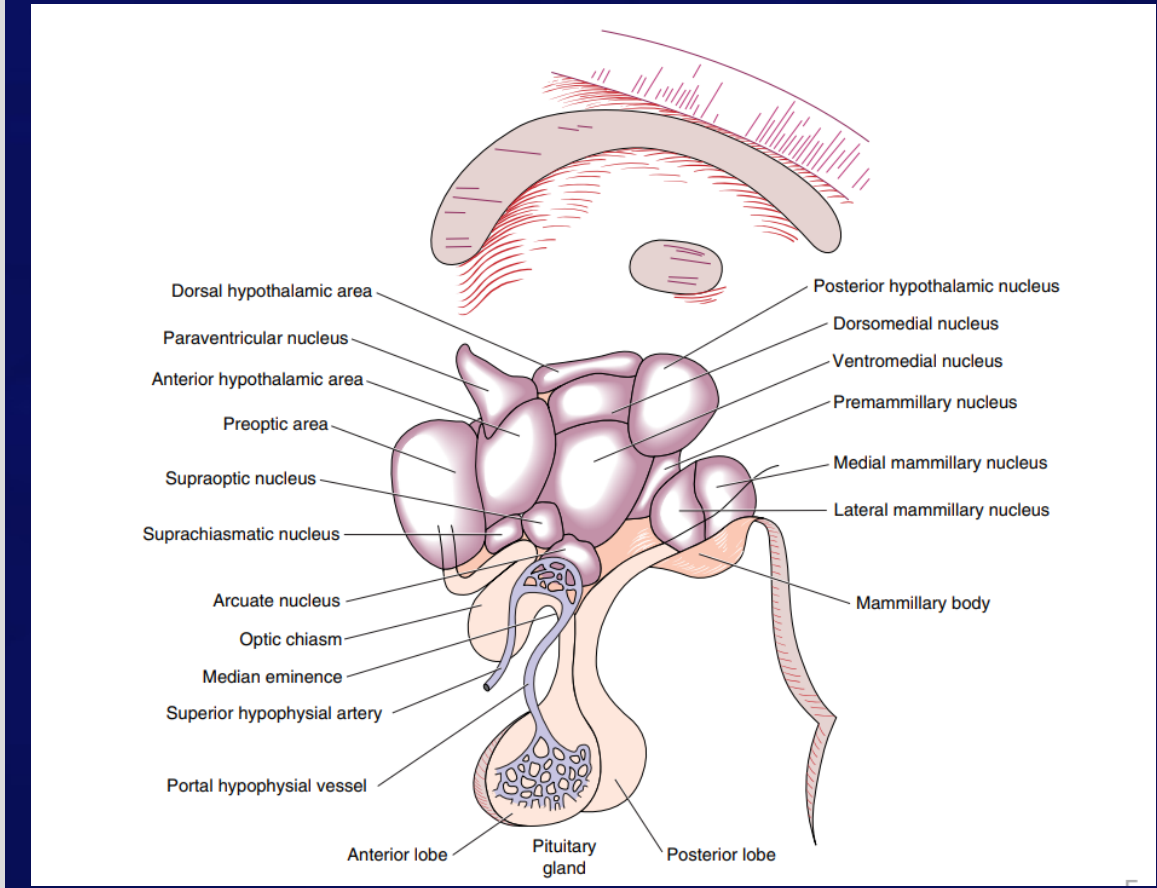
- The hypothalamus forms **during the first trimester**
- **It is composed of different nuclei with distinct functions that synthesize different hormones in response to physiological changes**
- **Impairment or damage to any of the hypothalamic nuclei causes a deficit in its function**. **Abnormalities such as Poor heat dissipation/ Excessive heat dissipation/ Increase in appetite/ Decrease in appetite/ Circadian rhythm dysfunction**
- These impairments can be caused by intracranial masses, vascular abnormalities, ischemia, and also by certain medications such as antipsychotics

**Neurosecretory cells of the hypothalamus** differ from other nerve cells in that they do not control other cells via synapses; rather, they **release their hormones into the circulation.**



# Hypothalamus II

- **Receives many signals from various regions of the brain and in return, releases both releasing and inhibiting hormones, which then act on the pituitary gland to direct the functions of the thyroid gland, adrenal glands, and reproductive organs**
- Influences **growth, fluid balance, and milk production**
- **It is also involved in the non-endocrine functions of temperature regulation, regulation of the autonomic nervous system, and the control of appetite.**



# Hypothalamus III

- The hypothalamus functions in conjunction with the **pituitary gland through the hypothalamic-pituitary axis.**
- **The hypothalamus itself contains several types of neurons that release different hormones.**

thyrotropin-releasing hormone (TRH)

gonadotropin-releasing hormone (GnRH)

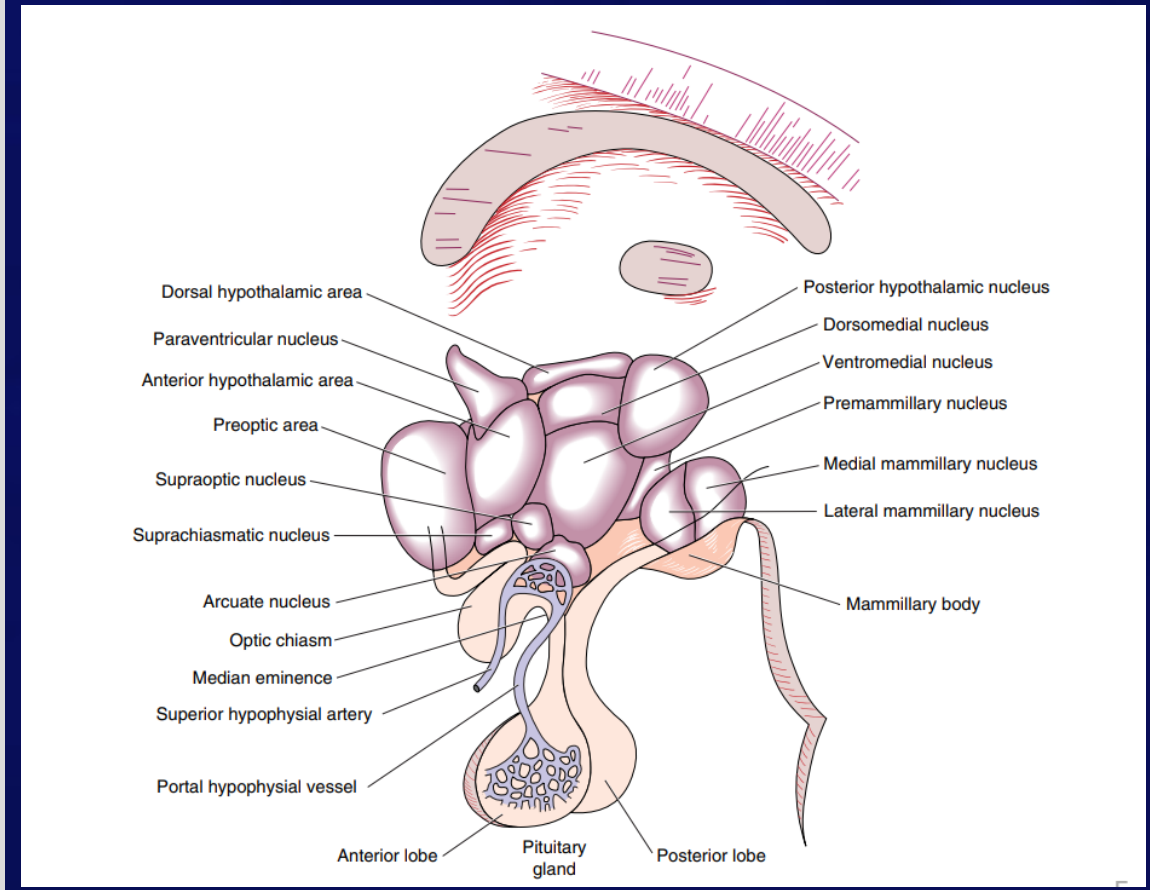
growth hormone-releasing hormone (GHRH)

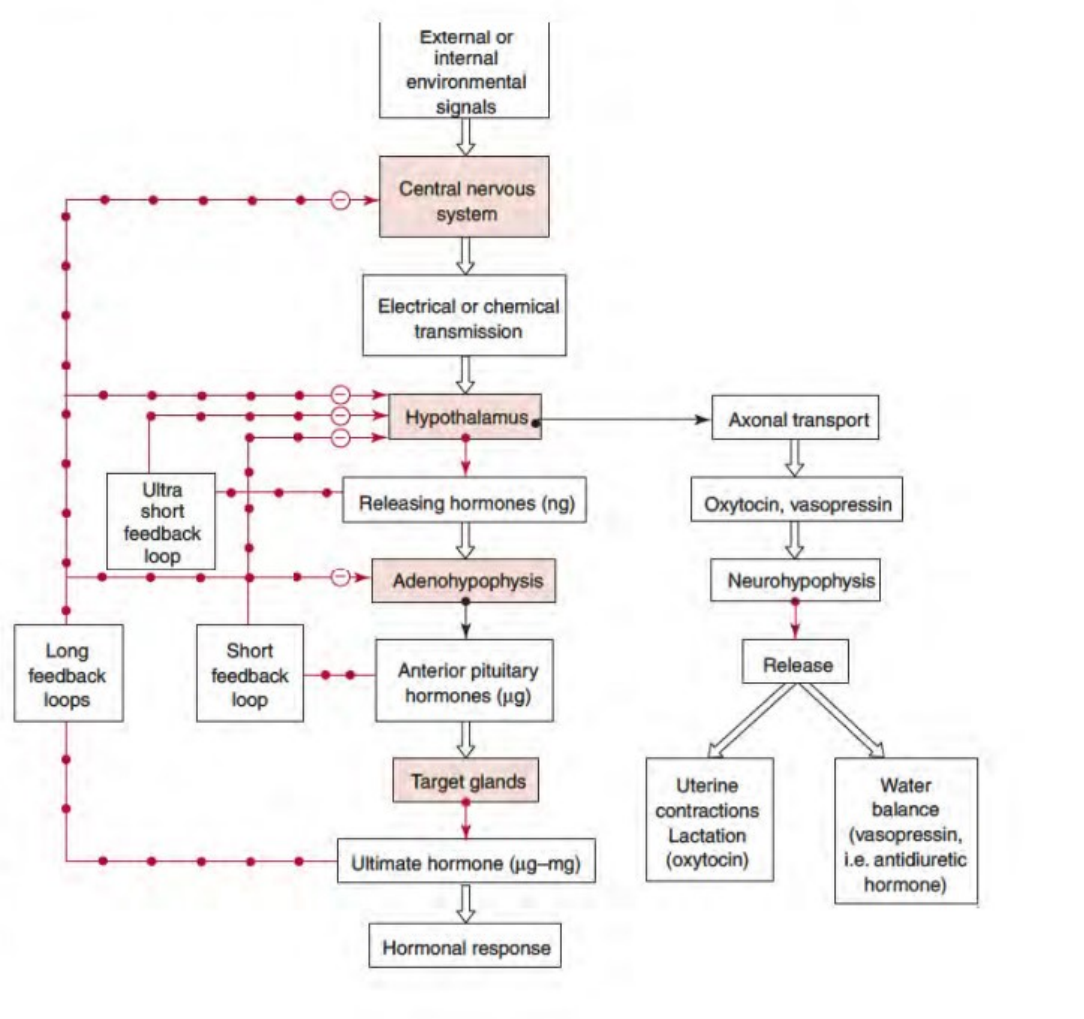
corticotropin-releasing hormone (CRH)

somatostatin

dopamine

**are released from the hypothalamus into the blood and travel to the anterior pituitary**






- **Aminergic neurons respond to various types of internal or external signals.**

Their activities account for:

❖ **the pulsatile release of hormones such as gonadotropin-releasing hormone (GnRH)**

❖ **the rhythmic cyclic release of hormones like cortisol.**

# Hypothalamic hormones



**secreted into hypophysial portal blood vessels**

**secreted by the anterior pituitary gland directly into the general circulation**

The **hypophysiotropic hormones that regulate the secretion of anterior pituitary hormones** include growth hormone–releasing hormone (GHRH), somatostatin (growth hormone–inhibiting hormone [GHIH]), dopamine, thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and gonadotropin-releasing hormone (GnRH).

- **Most of the anterior pituitary hormones are controlled by stimulatory hormones, but GH and especially PRL are also regulated by inhibitory hormones.**
- Some hypophysiotropic hormones are multifunctional.
- **The hormones of the hypothalamus are secreted episodically and not continuously, and in some cases there is an underlying circadian rhythm.**

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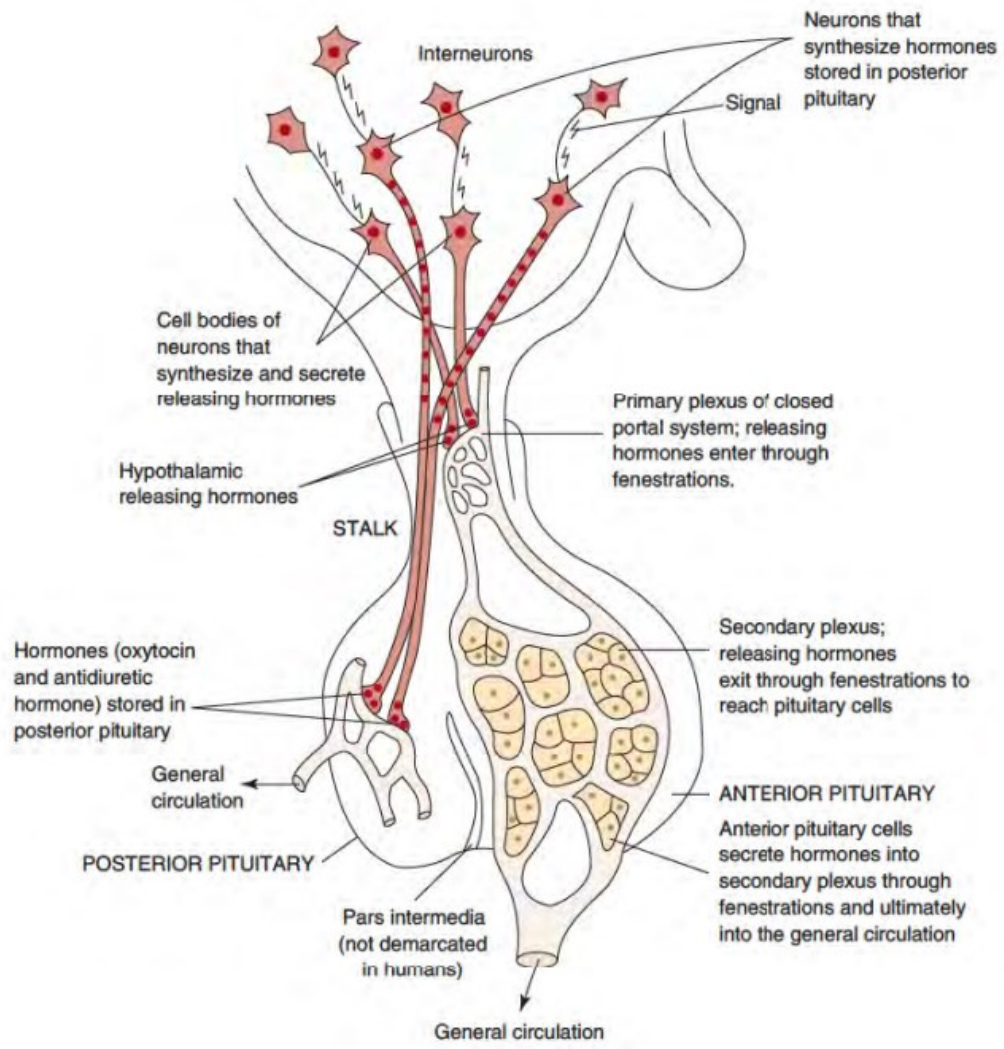
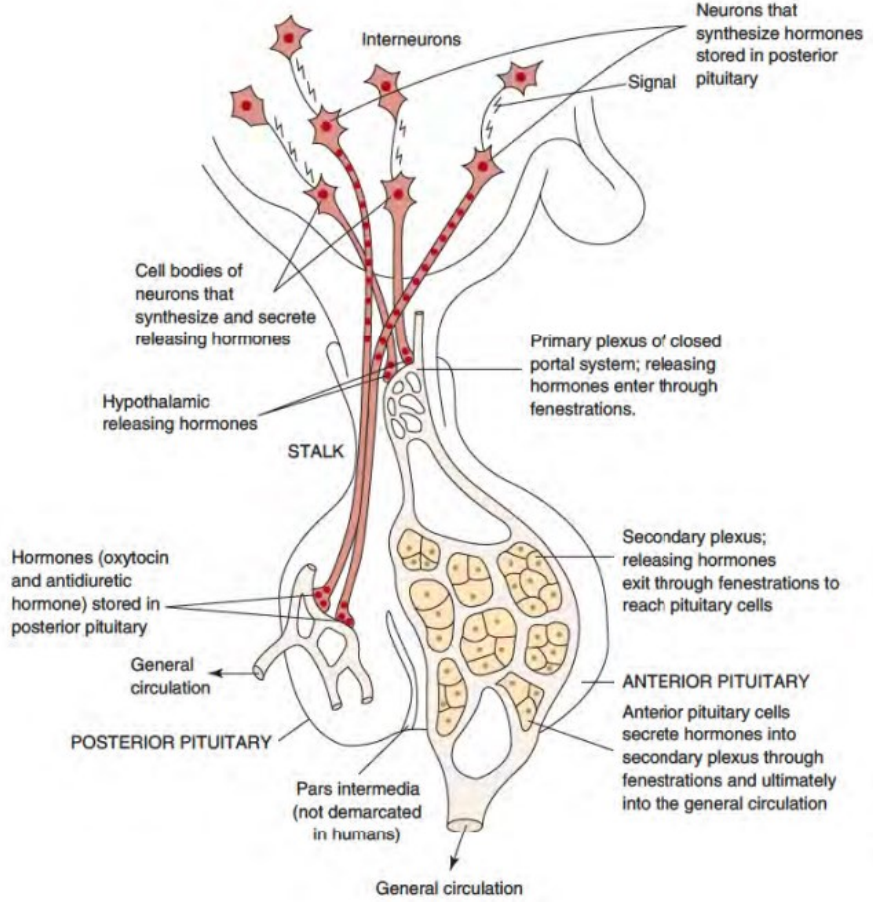
# Pituitary Gland I




- **The pituitary gland lies at the base of the skull in a portion of the sphenoid bone called the sella turcica (Turkish saddle)-** it is behind the nose and immediately beneath the hypothalamus.
- The pituitary gland is attached to the hypothalamus by **a stalk composed of neuronal axons and the so-called hypophyseal-portal veins.**
- **The human pituitary is composed of the anterior pituitary and the posterior pituitary**
- **Its weight in normal adult humans ranges from about 500 to 900 mg**

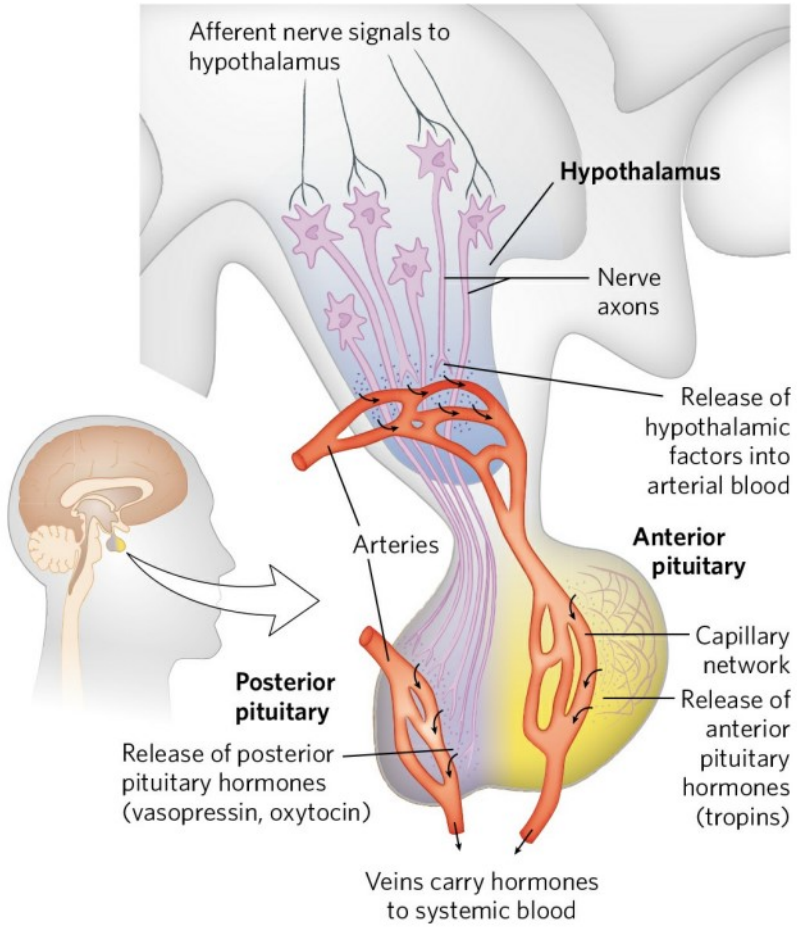
# Pituitary Gland II




- **The pituitary gland plays a central role in regulating the endocrine status of mammals by secreting a variety of hormones that regulate the function of other organs including the liver, thyroid, adrenal, and reproductive glands.**
- Release of these hormones is **regulated by neurotransmitters, neuropeptides, and other hormones released by the hypothalamic region of the brain**.

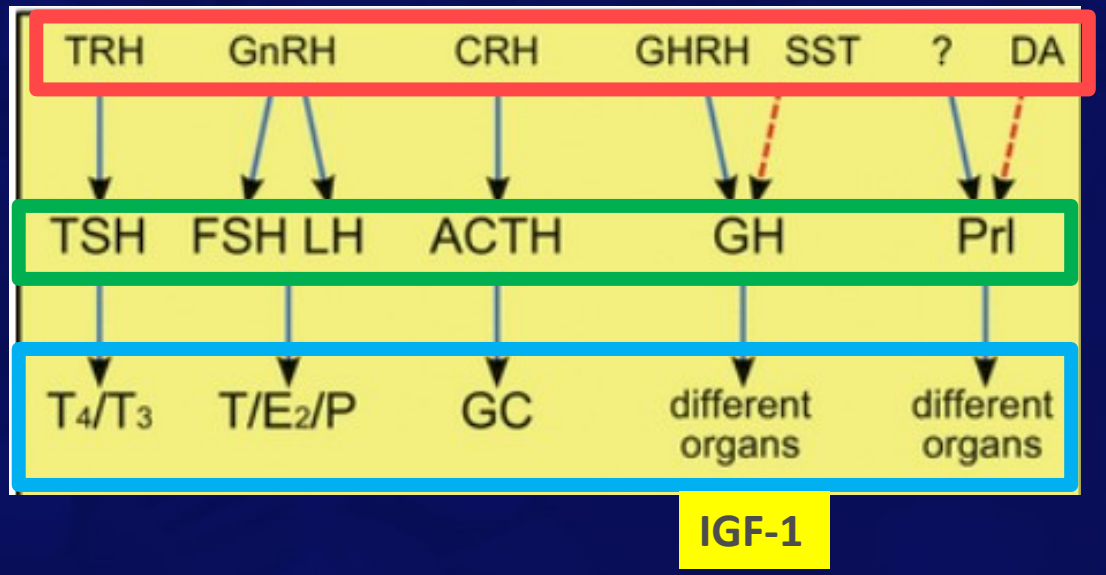
The six major anterior pituitary hormones—**ACTH, GH, PRL, TSH, LH, and FSH—may be classified into three groups:** ACTH-related peptides (ACTH itself, β-lipotropin [β-LPH], melanocyte-stimulating hormone [MSH], and endorphins); the somatomammotropin proteins (GH and PRL); and the glycoproteins (LH, FSH, and TSH).

# Hypothalamic-Pituitary Axis I



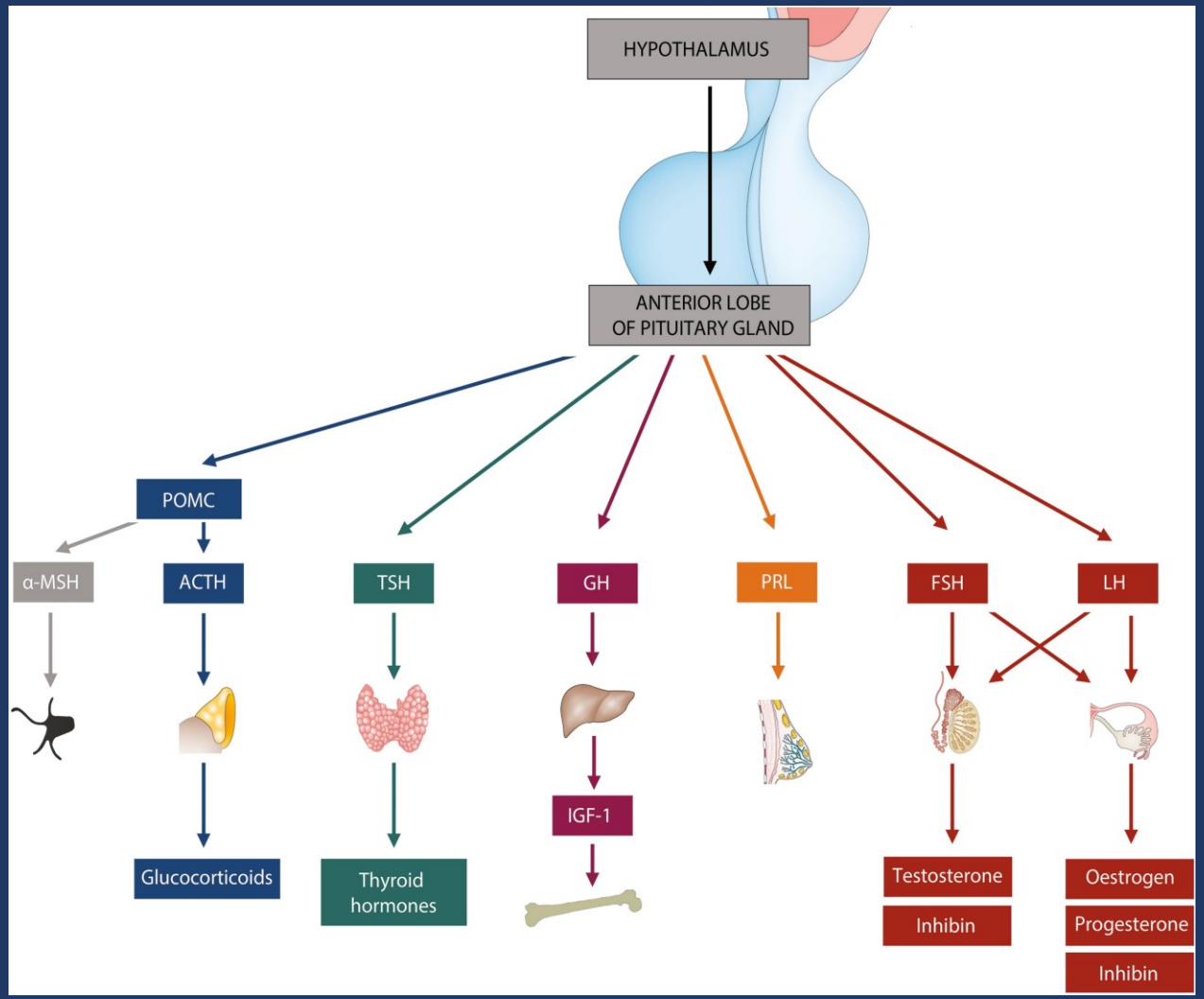

1. Signals from connecting neurons stimulate the hypothalamus to secrete releasing factors into a blood vessel that carries the hormones directly to a capillary network in the anterior pituitary.
2. In response to each releasing factor, the anterior pituitary releases the appropriate hormone into the general circulation.
3. Posterior pituitary hormones are synthesized in neurons arising in the hypothalamus
4. The hormones are transported along axons to nerve endings in the posterior pituitary and stored there until released into the blood in response to a neuronal signal

# Hypothalamic-Pituitary Axis II




Endocrine regulation via hypothalamic–pituitary axes. The upper row shows the hypothalamic releasing hormones which induce or inhibit tropic hormone release in the pituitary—thyrotropin, gonadotropins, adrenocorticotropic hormone (ACTH), somatotropin (SST), and prolactin (Prl). These in turn regulate the release of thyroid hormones, steroids, glucocorticoids (GC), insulin-like growth factor, and other factors.

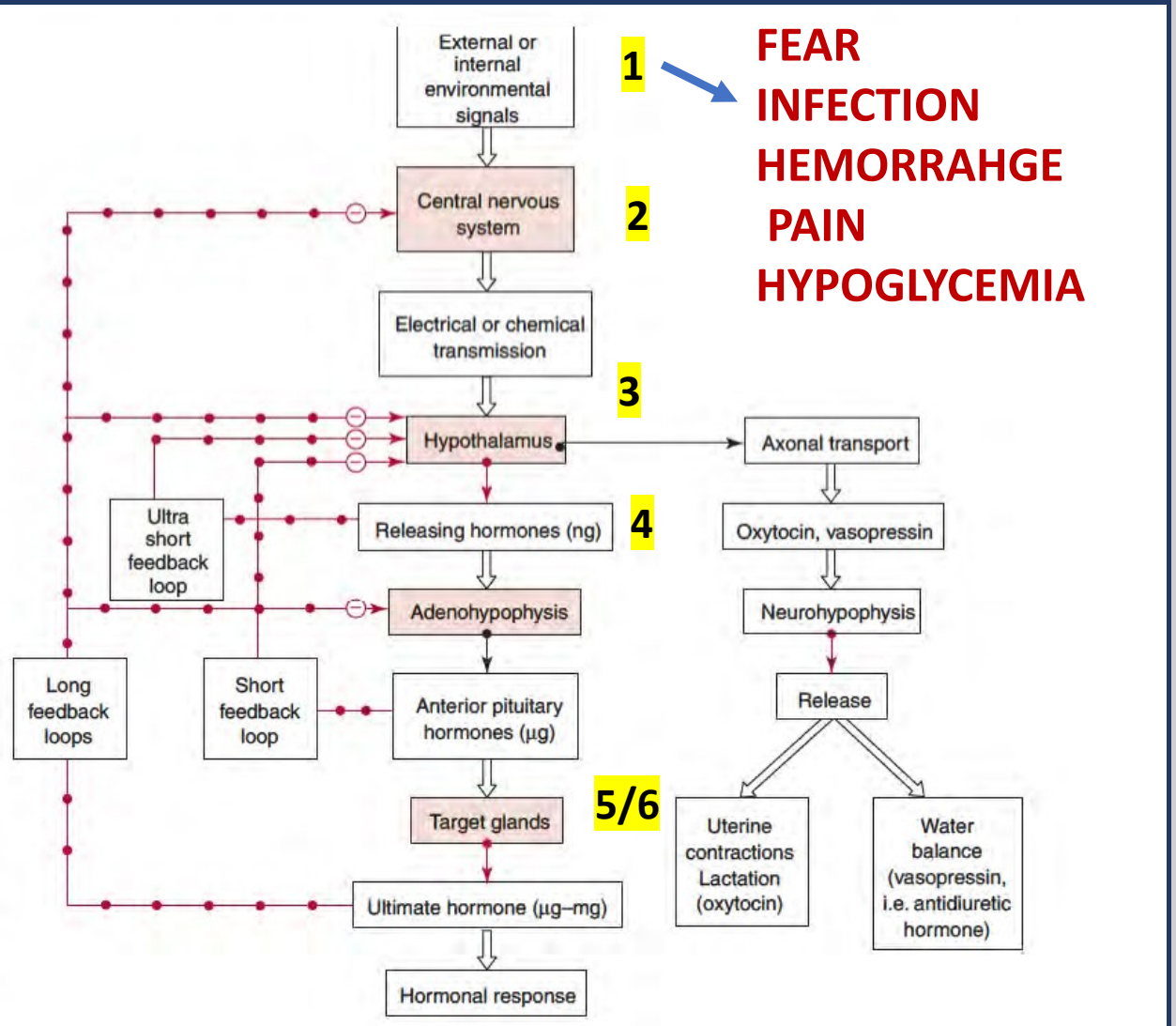
# Hormonal cascade of signals from CNS to ultimate hormone




Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Mol Cell Endocrinol. 2021 Apr 5;525:111173. doi: 10.1016/j.mce.2021.111173. Epub 2021 Feb 4. PMID: 33549603.

**Other systems** operate through similar cascades although through different specific releasing hormones, anterior pituitary tropic hormones, and ultimate hormones. Clearly, **the number of target cells affected depends on their expression of receptor for ultimate hormones.**

# Hormonal cascade of signals from CNS to ultimate hormone




1. external or internal signal
2. signal transmitted first to the CNS and may involve the limbic system, including the hippocampus and amygdala
3. Innervate the hypothalamus which responds by secreting (nanogram amounts) a specific releasing hormone.
4. Releasing hormones are transported down a closed portal system to the anterior pituitary, where they cause secretion of microgram amounts of specific anterior pituitary hormones.
5. These access the general circulation through fenestrated local capillaries and trigger release of an ultimate hormone in microgram to milligram daily amounts.
6. The ultimate hormone generates its response by binding to receptors in target tissues.

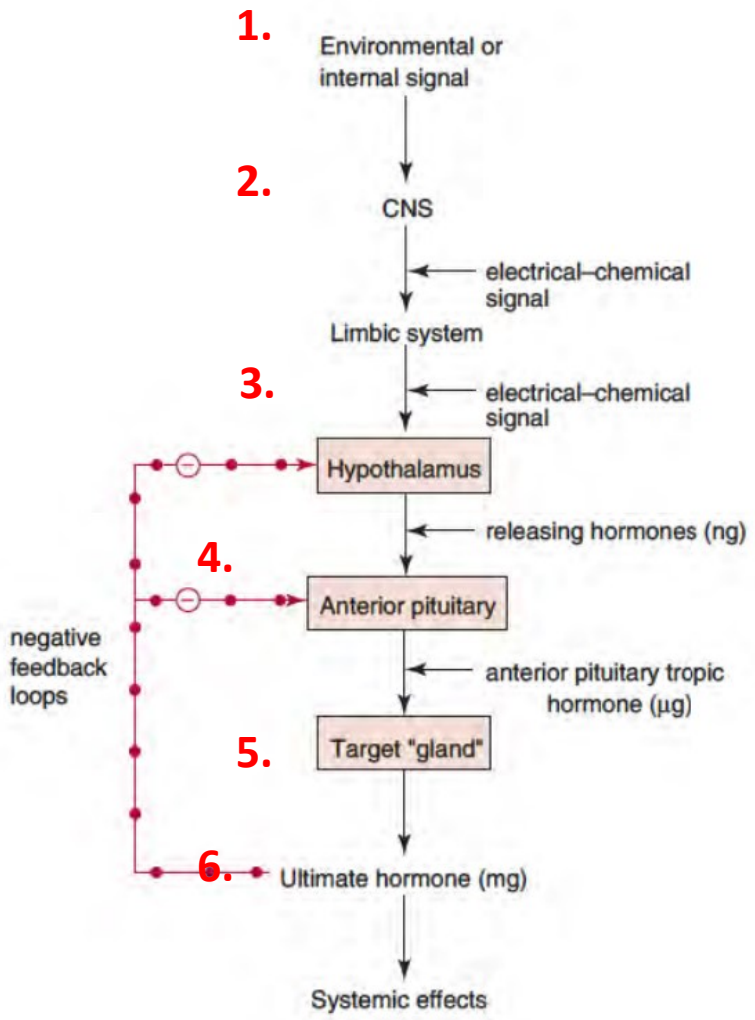
# Hormonal cascade of signals from CNS to ultimate hormone cortisol: CRH/ACTH: Example

**1. An environmental message such as change in temperature , noise, or traüma**: signal limbic system for release of a hypothalamic-releasing hormone, corticotropin-releasing hormone (CRH)

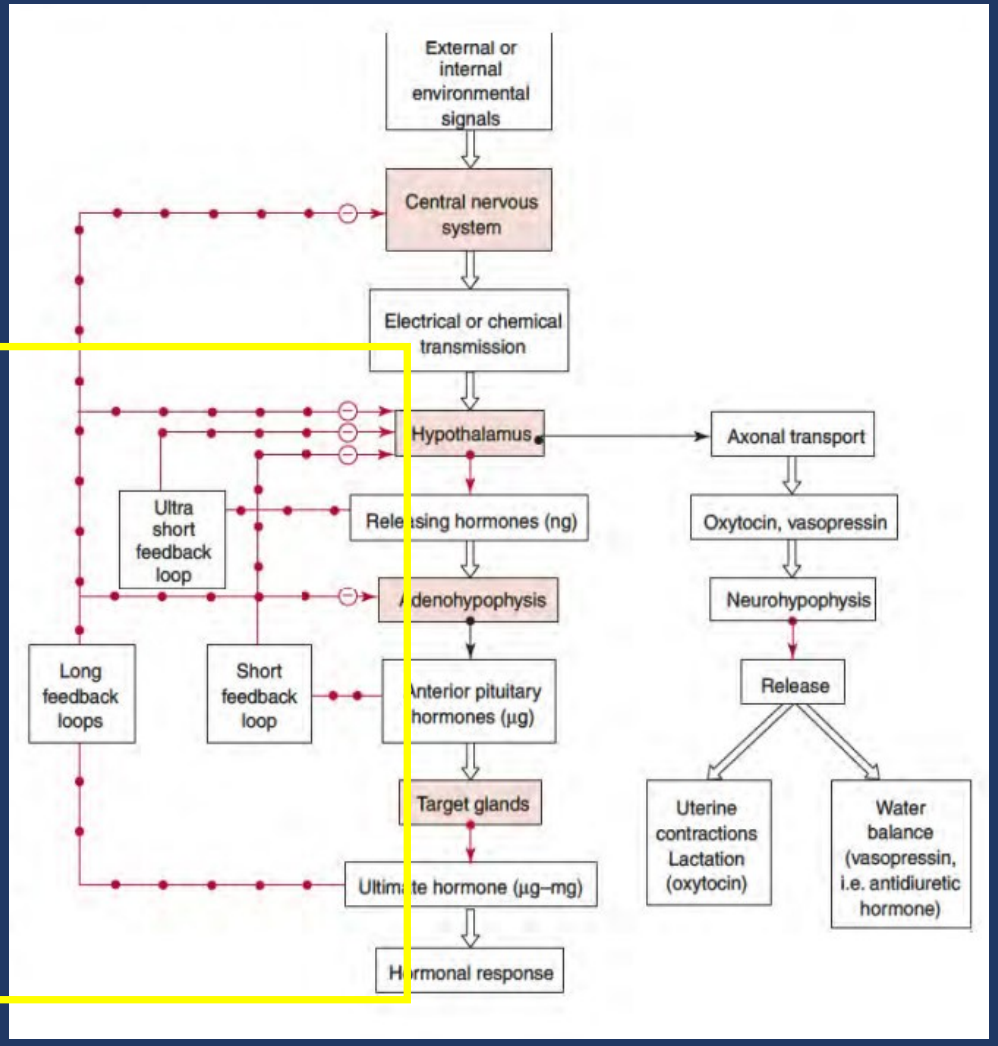
**2. CRH travels down a closed portal system to the anterior pituitary**, where it **binds its cognate receptor in the membrane of corticotropic cells** and **initiates intracellular events** :release of adrenocorticotropic hormone (ACTH) and β-lipotropin.

**3. ACTH circulates until it binds to its cognate receptors expressed on the membranes of cells in the target gland:** synthesis and **release of the steroid hormone cortisol (the ultimate hormone)**

**4. Cortisol then interacts with target cells throughout the body that express intracellular glucocorticoid receptors. The ultimate hormone, cortisol, feeds back negatively on cells of the anterior pituitary and hypothalamus and reduces its own rate of synthesis and secretion from the adrenal cortex.**



# The negative feedback




- Operates when sufficiently high levels of an **ultimate hormone have been secreted**.
- In long-loop feedback, **the final hormone binds a cognate receptor in/on cells of the anterior pituitary , hypothalamus, and CNS to prevent further synthesis/secretion of releasing hormones.**
- Short-loop feedback **is exemplified by the pituitary tropic hormone that feeds back negatively on the hypothalamus and operates through a cognate receptor.**
- In ultrashort feedback loops **the hypothalamic releasing factor feeds back on the hypothalamus to inhibit its own further secretion**

# Hypopituitarism-Causes



**Hypopituitarism is defined as the total or partial loss of anterior and posterior pituitary gland function that is caused by pituitary or hypothalamic disorders**

## Primary hypopituitarism

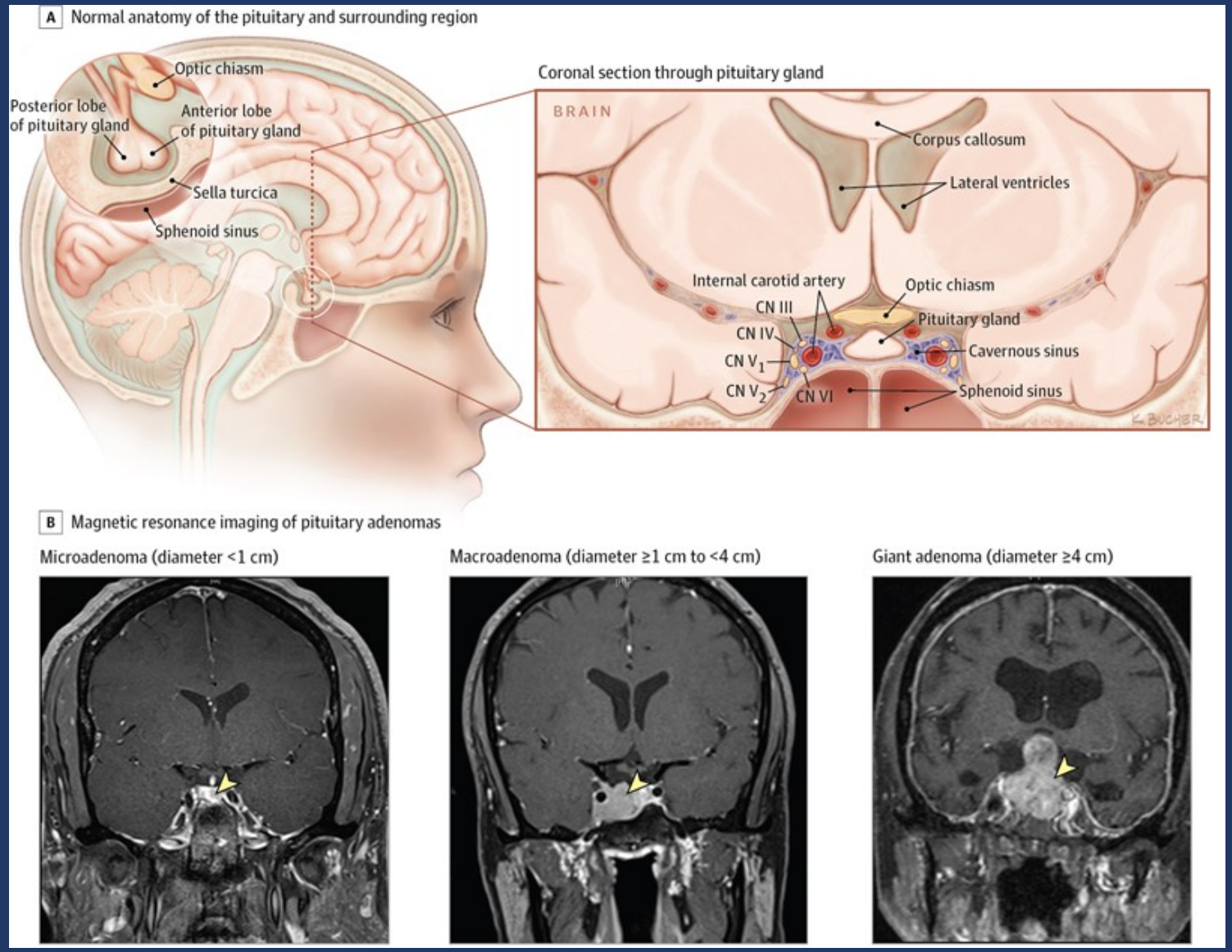
**Disorders of the pituitary gland:** loss, damage, or dysfunction of pituitary hormone secreting cells e.g **pituitary adenoma** and **complications from surgery or radiation therapy** for the treatment of pituitary adenoma

## Secondary hypopituitarism

The result of **diseases of the hypothalamus or pituitary stalk interrupting the nerve or vascular connections to the pituitary gland**, thereby reducing the secretion of the pituitary hormones e.g damage to the pituitary stalk: head and/or neck injury, stalk accidentally severed during surgery, central nervous system disorders involving the hypothalamus, such as **craniopharyngioma**

# Hypopituitarism






Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. *JAMA.* 2017;317(5):516–524. doi:10.1001/jama.2016.19699

# Hypopituitarism

**Panhypopituitarism:** the overall deficiency of anterior pituitary hormones.

**Tumors of the pituitary gland:** all of the anterior pituitary hormones may not be shut off to the same degree, or the secretion of some may disappear sooner than others.

**The symptoms of hypopituitarism sometimes develop slowly.**

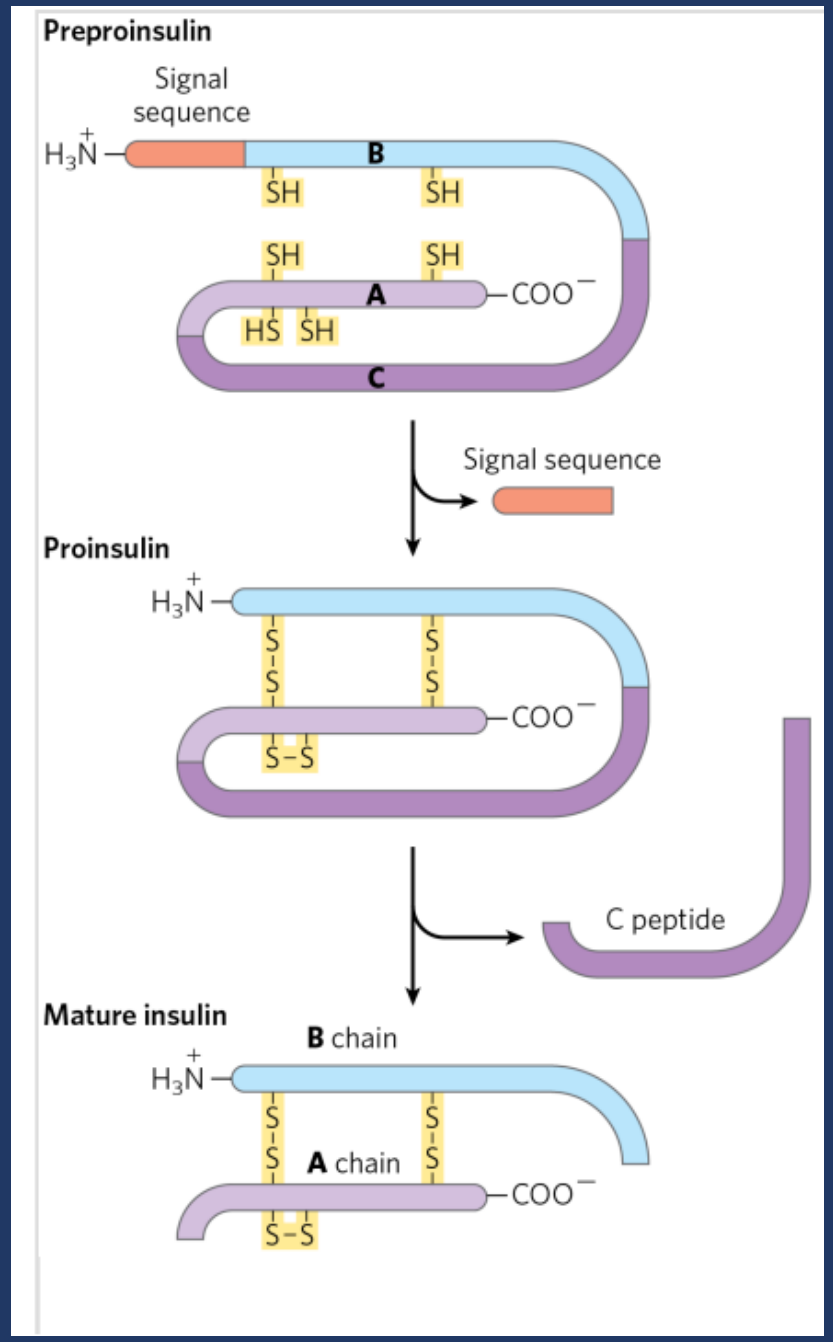
In any case, if hypopituitarism occurs, this condition may result in **a life-threatening situation** in which **the clinician must determine the extent of loss of each of the pituitary hormones,** especially ACTH

**Posterior pituitary hormones: oxytocin and vasopressin - may also be lost,** resulting in **excessive urination** (vasopressin deficiency)

Panhypopituitarism can also result in an **increased sensitivity to the actions of insulin because of the decreased secretion of the insulin antagonists, growth hormone and cortisol**, leading to **hypoglycemia**.

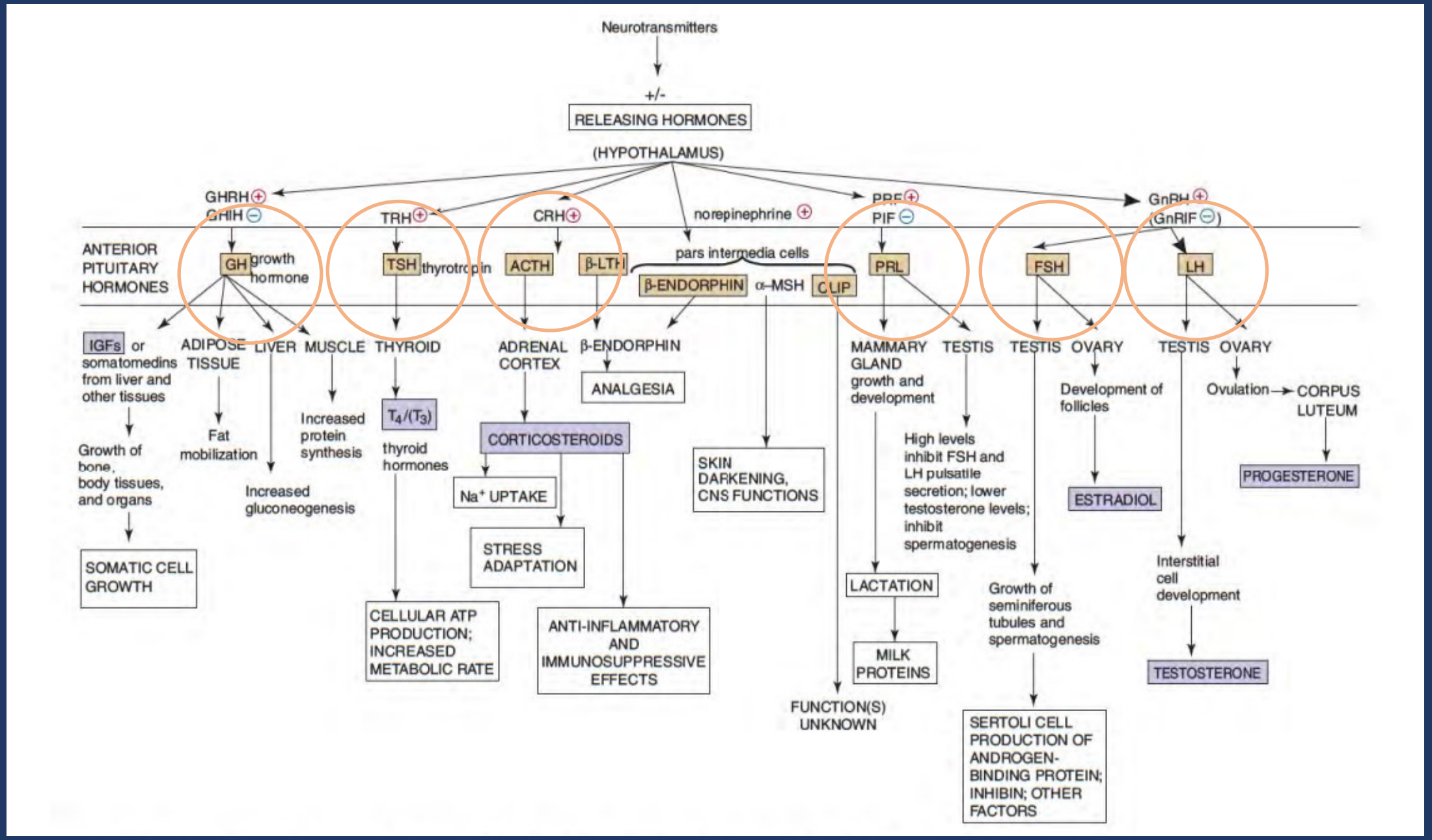
# Peptide Hormones I

- Vary in size, from 3 to more than 200 amino acid residues.
- **They include the pancreatic hormones insulin, glucagon, and somatostatin; the parathyroid hormone calcitonin; and all the hormones of the hypothalamus and the pituitary.**
- These hormones are synthesized on ribosomes in the form of longer, precursor proteins (prohormones), then packaged into secretory vesicles and proteolytically cleaved to form the active peptides.
- In many peptide hormones the terminal residues are modified



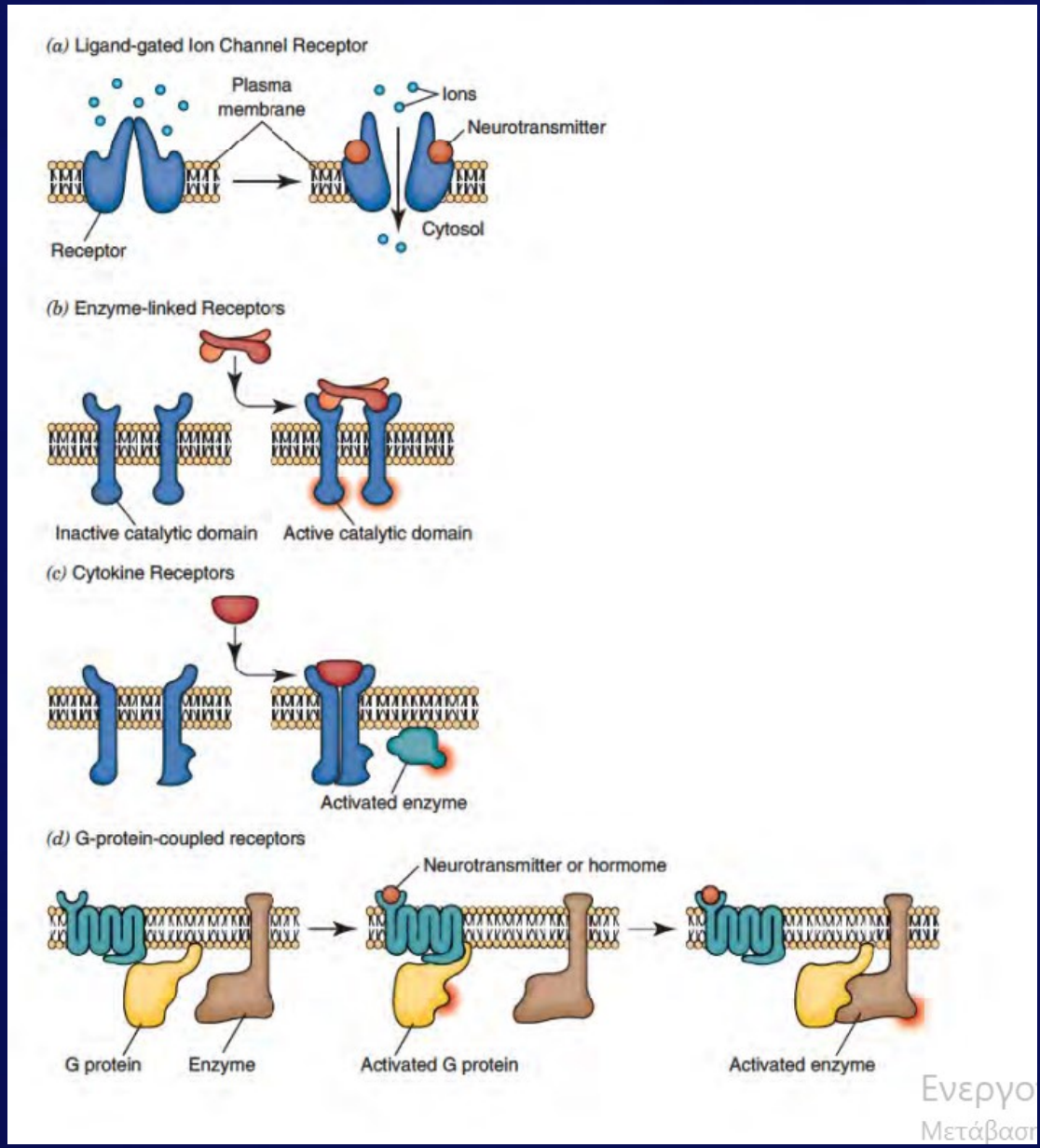
# PEPTIDE HORMONES II





# Peptide Hormones III

- Hormones: **source-cause hormonal release-cascade**
- Polypeptide hormones: **bind to membrane receptors expressed specifically on target cells.**
- The receptor recognizes structural features of the hormone with an affinity.
- This activates or inactivates an effector protein in or on the membrane.
- **Some receptors undergo internalization to the cell interior and others open a membrane ion channel**

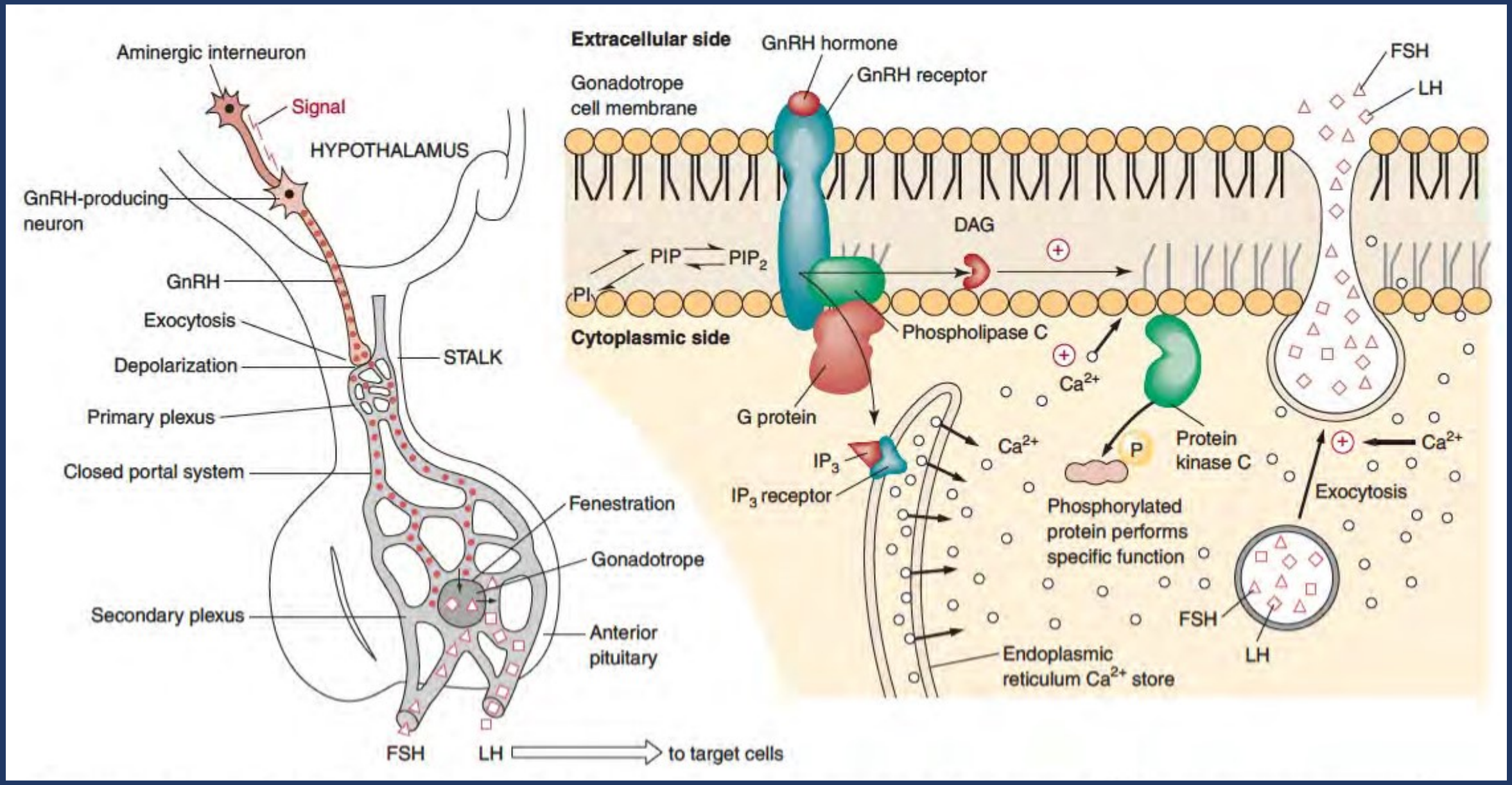


# Intracellular Signal Cascade: Second Messengers

- After binding to their **cognate membrane receptors, many peptide and protein hormones transmit their signal intracellularly via second messengers**, which transmit and amplify the hormonal signal
- Some hormones transmit their signal by increasing the **intracellular concentration of one second messenger, while others increase the concentration of several second messengers, either simultaneously or sequentially**

**Second messengers include cyclic AMP (cAMP), cyclic GMP (cGMP), inositol trisphosphate (IP3), diacylglycerol (DG), and phosphatidylinosito l 3,4,5-trisphosphate (PIP3).**

# SIGNAL TRANSDUCTION-PEPTIDE VS STEROID HORMONES

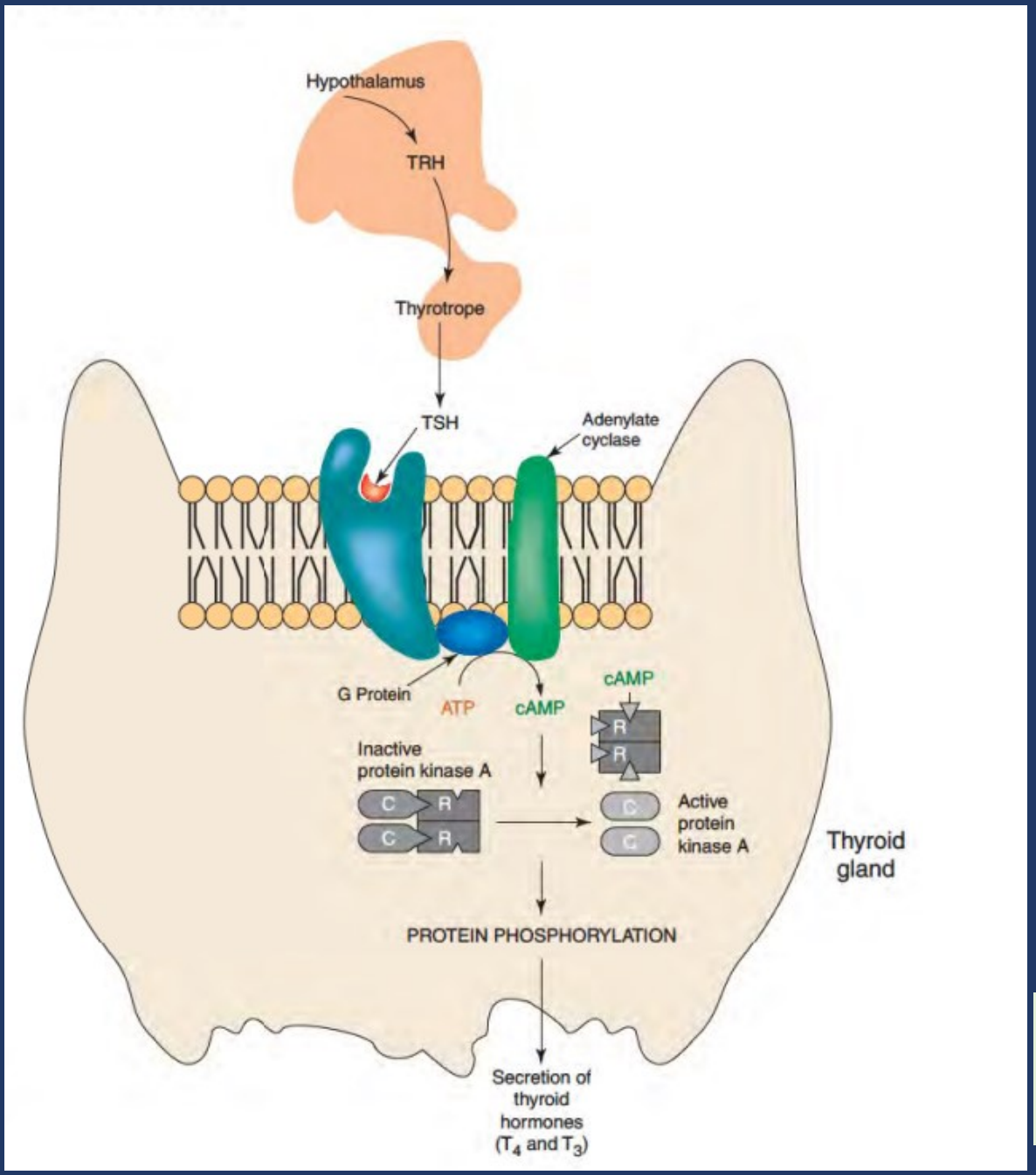


# SIGNAL TRANSDUCTION-PEPTIDE HORMONES



- Different hormones **bind to receptors that activate either a stimulatory or an inhibitory G protein subunit** (Gs or Gi, respectively)
- **Result in activation or inhibition of an effector enzyme**
- Thus, an **increase or decrease in the corresponding intracellular second messenger.**
- The **intracellular second messengers activate specific kinases that initiate a cascade of phosphorylation/ dephosphorylation reactions and result in activation of some, and inactivation of other, enzymes**
- **Stimulation of adenylate cyclase by G protein-coupled receptors generates cAMP, which activates protein kinase** A
- **Stimulation of guanylate cyclase by different G protein-coupled receptors generates cGMP, which activates protein kinase G.**

**The next slide is an example of a hormone that transduces a signal via the generation of a second messenger**




**1.** Thyrotropin-releasing hormone-TRH- synthesized by hypothalamic neurons reaches the thyrotropes in the anterior pituitary and stimulates them to synthesize and secrete thyroid-hormone- stimulating hormone (TSH) .

**2.** TSH binds to its G protein-coupled membrane receptors in the thyroid gland and activates adenylate cyclase with generation of cAMP.

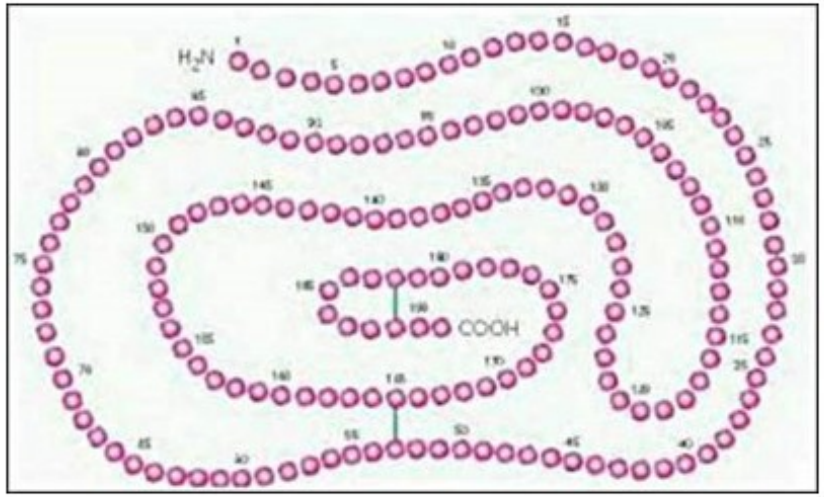
**3.** cAMP in turn binds to the regulatory subunits in the inactive form of protein kinase A leading to their dissociation from the catalytic subunits, which are fully active

**4.** Initiate a cascade of protein phosphorylations that results in secretion of thyroid hormone.

# Growth hormone-releasing hormone-GHRH

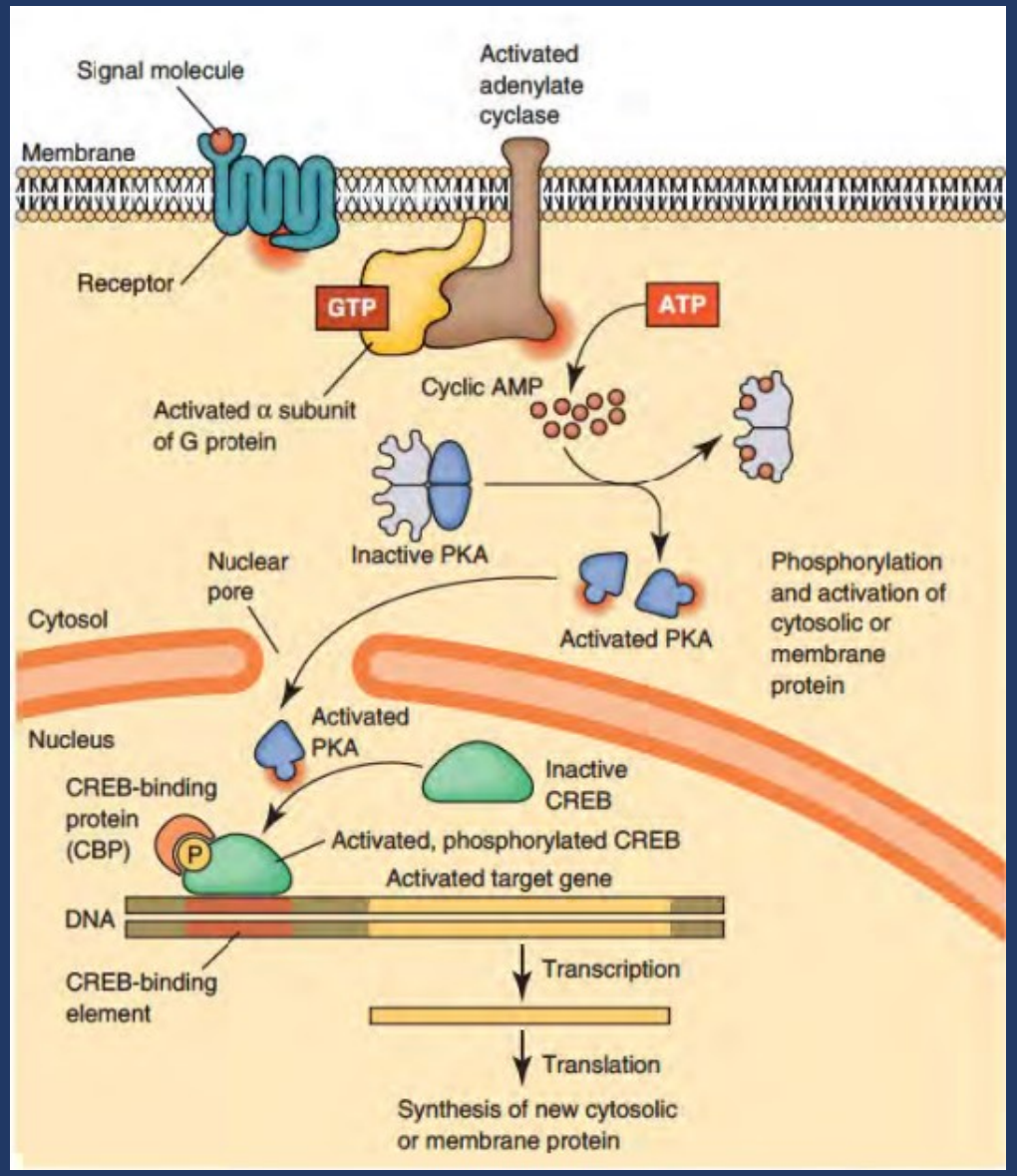


- **GHRH or somatotropin stimulates the secretion of growth hormone by the anterior pituitary.** An 191-amino-acid polypeptide hormone (MW 21,500) **synthesized and secreted by the somatotrophs of the anterior pituitary**
- First isolated from a pancreatic tumor in a patient with clinical manifestations of GH excess (acromegaly) associated with somatotroph hyperplasia.
- Human GHRH is a member of a homologous family of peptides that includes secretin, glucagon, vasoactive intestinal peptide (VIP), and others.
- **The half-life of GHRH is approximately 3 to 7 minutes.**



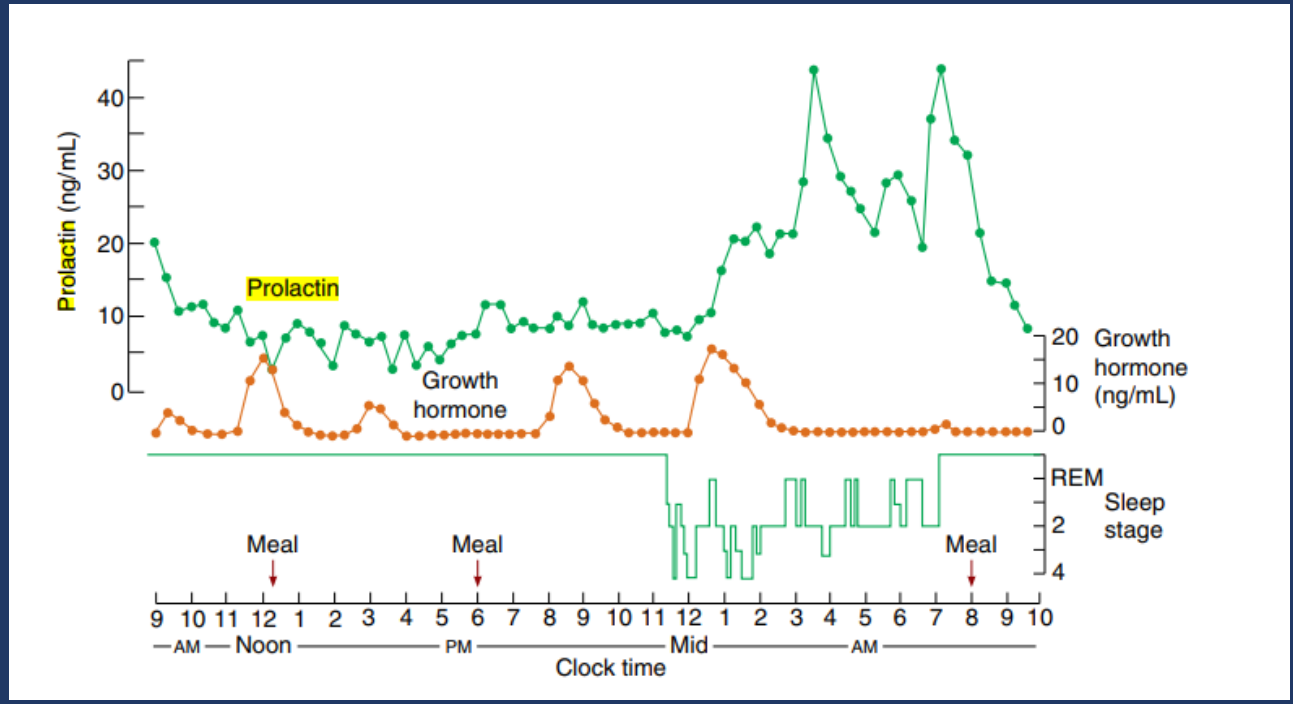

Pharaoh Akhenaton (Amenhotep IV): possibly the first known acromegaly patient

# Growth Hormone

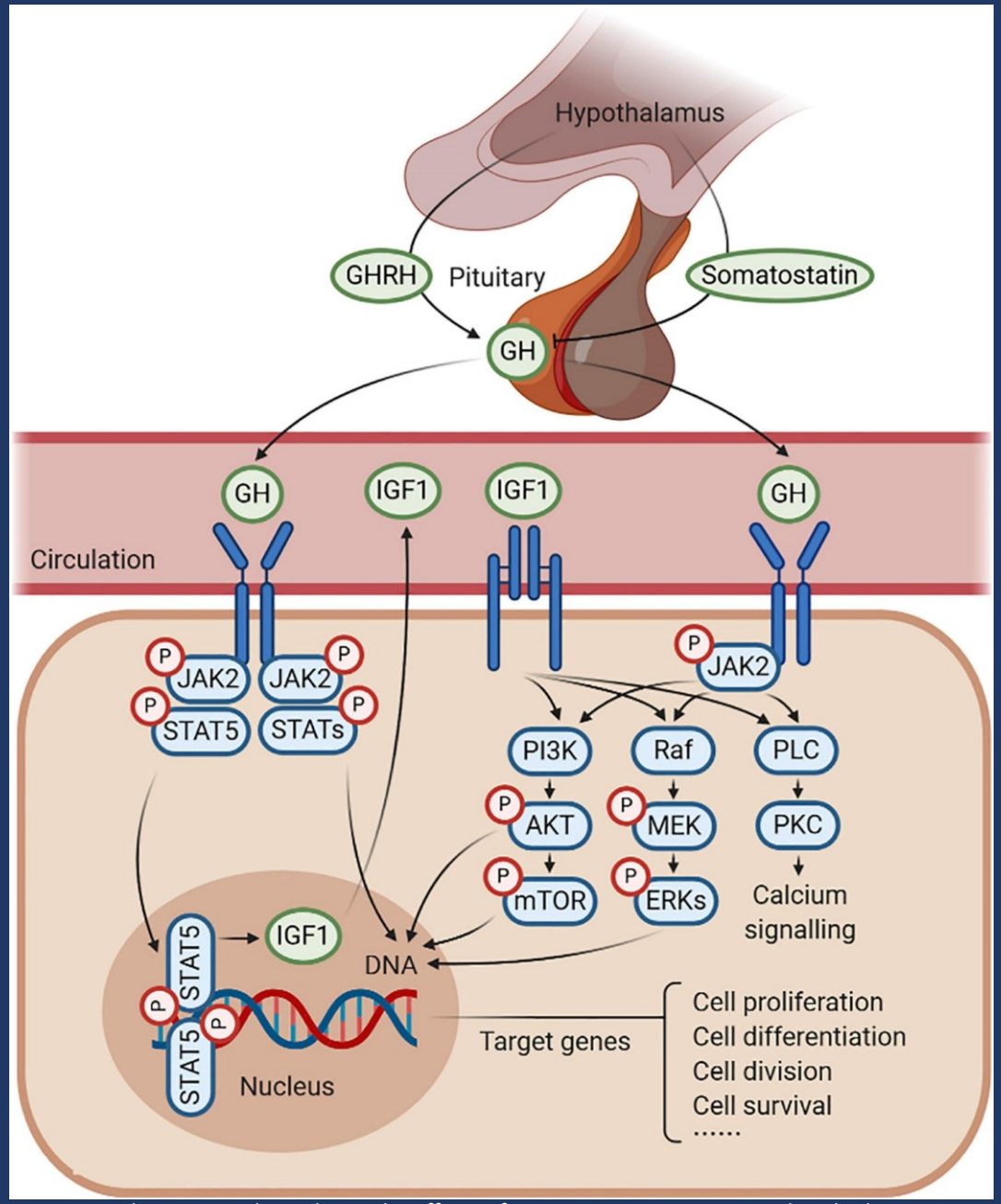



- **The hypothalamus and pituitary cells known as somatotrophs act in concert to control the release of Growth Hormone (GH)**
- The hypothalamus-derived Growth Hormone Releasing Hormone (GHRH) is an agonist for a $G_s$ protein coupled receptor which is expressed by pituitary somatotroph cells.
- **Increased cAMP triggered by this receptor activates CREB-dependent transcription of the GH gene and results in increased synthesis and release of GH.**

- The primary **function of GH is the promotion of linear growth.**
- **GH release is pulsatile and reaches (in children) maximal rates about 1 h after the onset of deep sleep.**
- **Adult men have six to eight pulses in 24 h whereas women have a less regular pulse rate.**
- **Women release, per pulse, higher GH rates** than men, most probably due to a **stronger estrogen influence.**



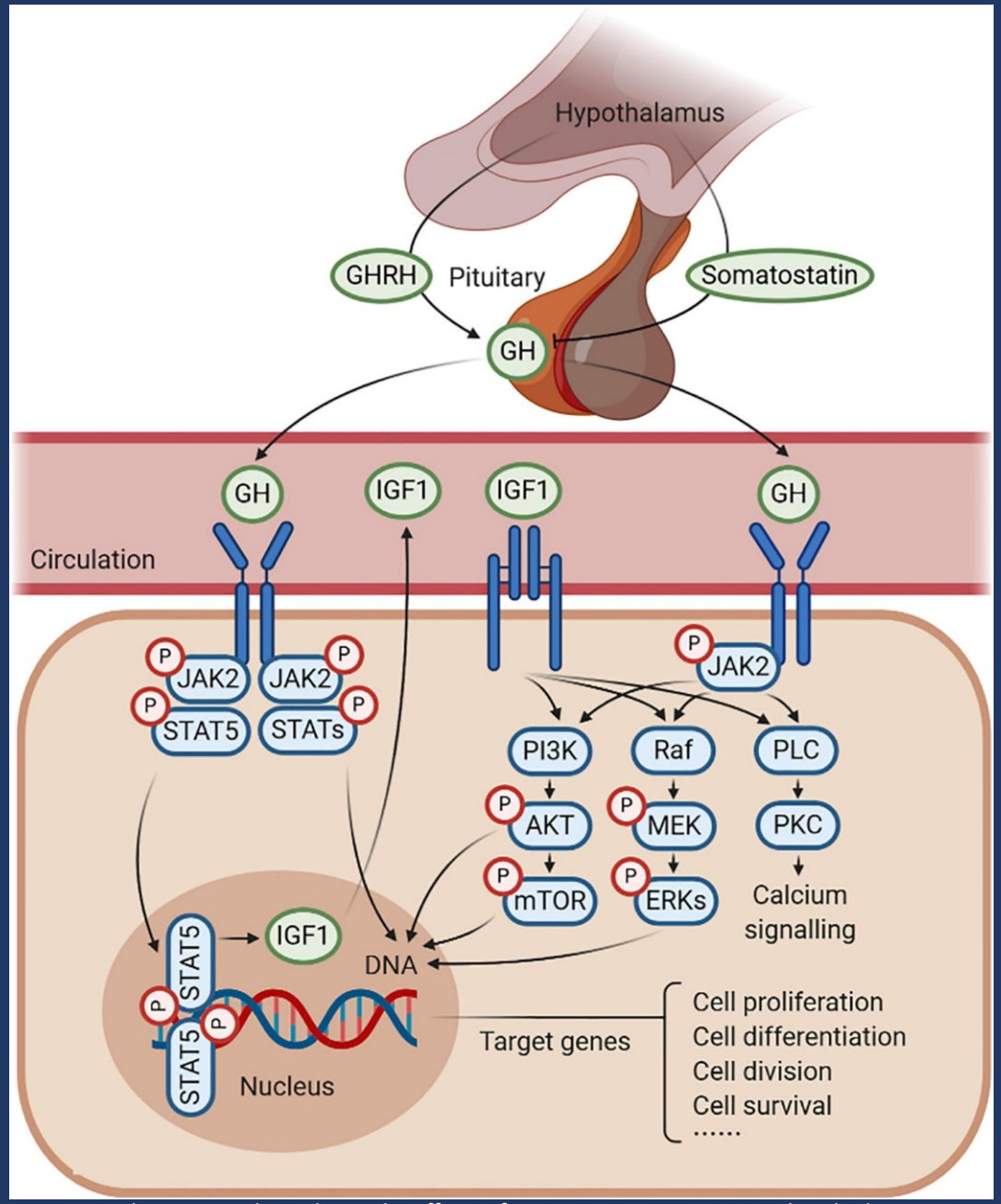
- GH is produced by the pituitary gland, which is under the positive control of the hypothalamic peptide GH-releasing hormone (GHRH) and the negative feedback of somatostatin or somatomedins (Insulin-like Growth Factors - IGFs): insulin-like growth factor 1 (IGF-1)
- GH mediates its functions directly through its receptor (GHR) or indirectly via insulin-like growth factor 1 (IGF1)
- IGF1 is formed in hepatocytes stimulated by GH.
- GH, via IGF-1, increases protein synthesis by enhancing amino acid uptake and directly accelerating the transcription and translation of mRNA.




Hu B, Li H, Zhang X. A Balanced Act: The Effects of GH-GHR-IGF1 Axis on Mitochondrial Function. Front Cell Dev Biol. 2021 Mar 18;9:630248. doi: 10.3389/fcell.2021.630248. PMID: 33816476; PMCID: PMC8012549.

- IGF-I is primarily produced in the liver but also in other tissues such as muscles and bones.
- It has a similar molecular structure as insulin and plays a significant role in childhood development.
- Its action occurs when IGF-1 binds to its receptor on cells.
- Very high levels of IGF-1 are associated with a greater risk of cardiovascular diseases, breast cancer, and prostate cancer.

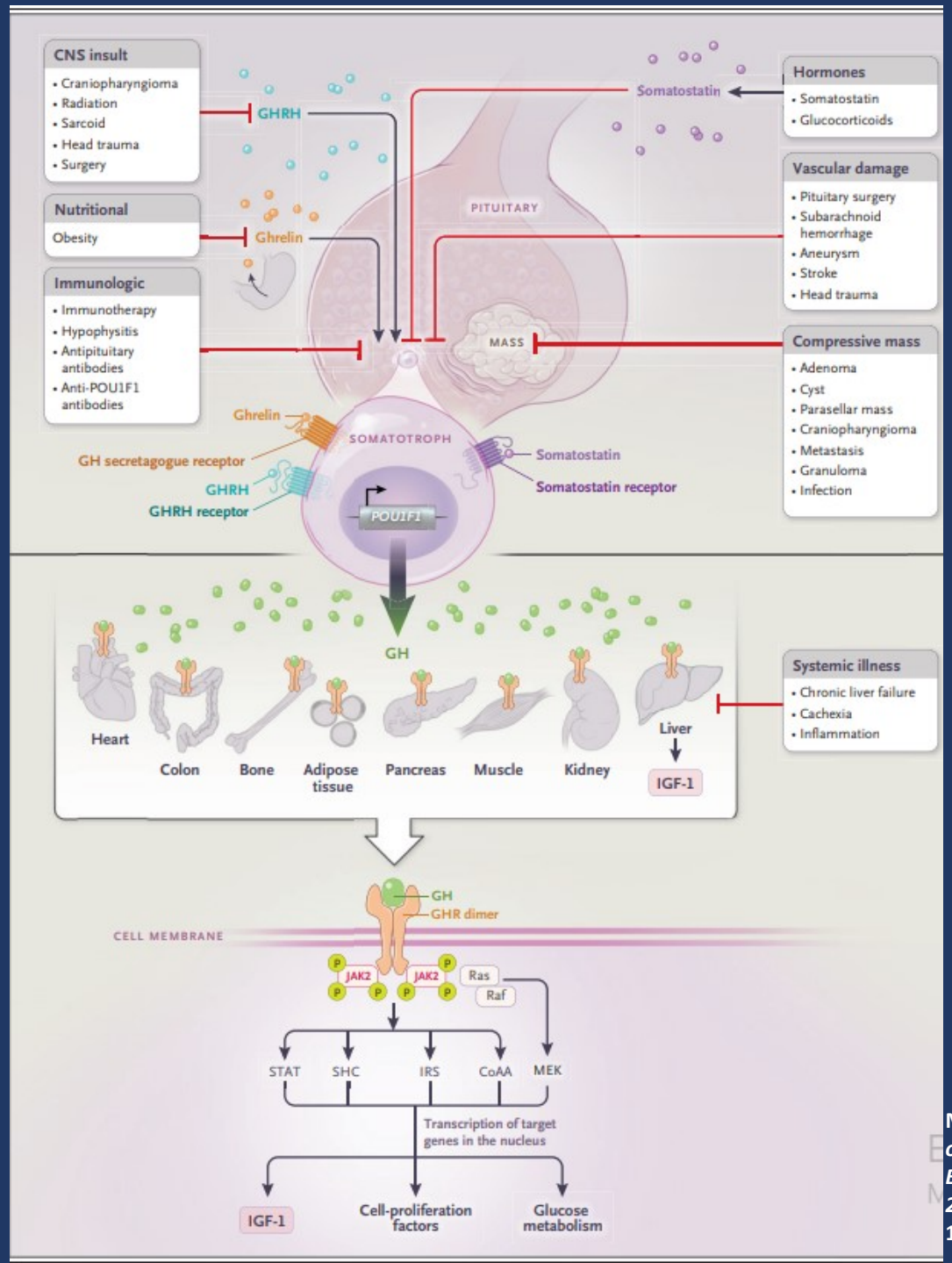
- The main role of IGF-II is as a growth hormone during pregnancy. It also plays a role in the menstrual cycle of women, acting as a supplementary hormone to FSH and LH.



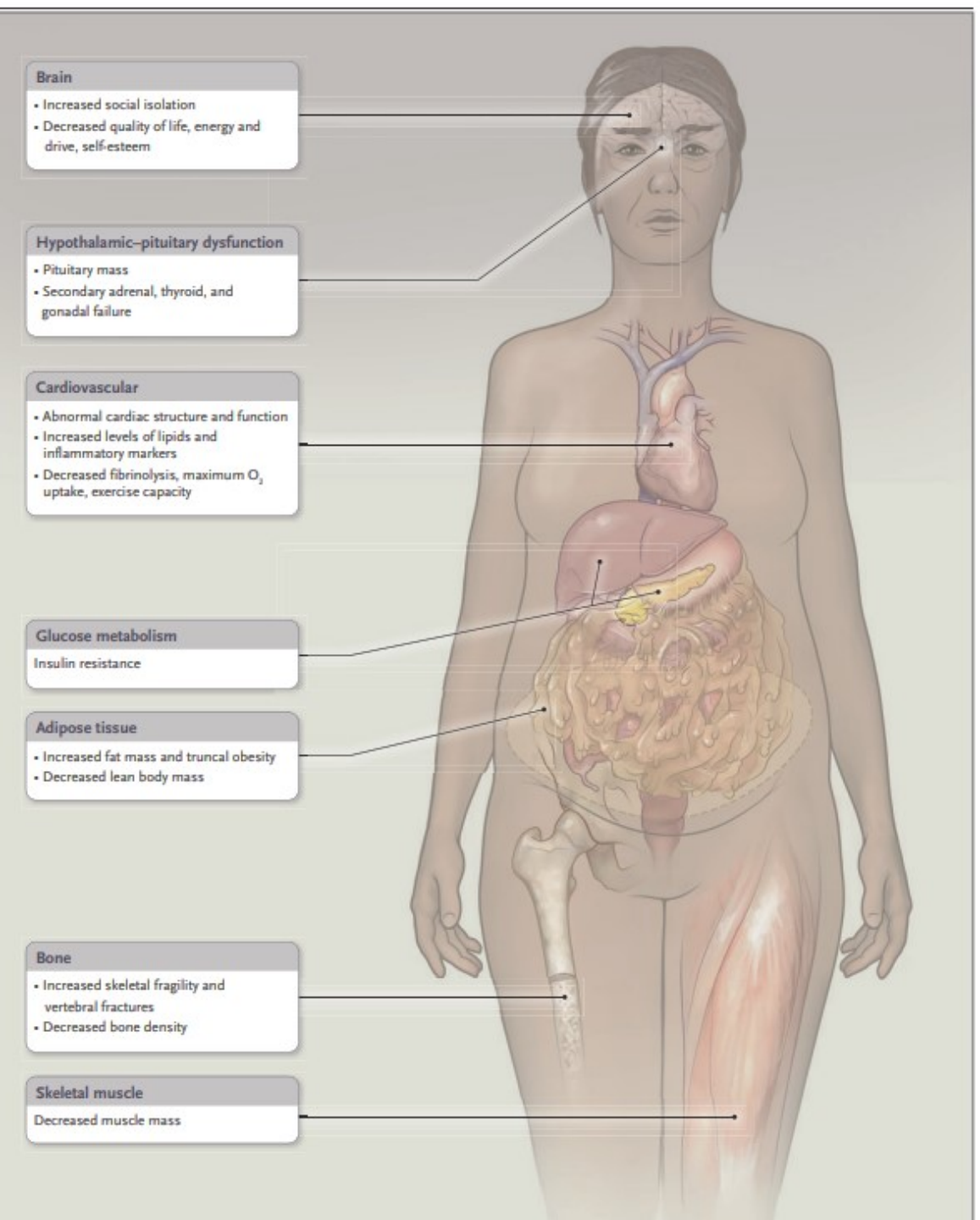

Hu B, Li H, Zhang X. A Balanced Act: The Effects of GH-GHR-IGF1 Axis on Mitochondrial Function. Front Cell Dev Biol. 2021 Mar 18;9:630248. doi: 10.3389/fcell.2021.630248. PMID: 33816476; PMCID: PMC8012549.

# Causes of Acquired Adult GH Deficiency

**Suppression of growth hormone production** in adults may be caused by **structural insults, such as an expanding intrasellar mass compressing somatotroph function**, **damaged hypothalamic–pituitary neuroendocrine pathways**, or **local vascular compromise resulting from surgery, radiation therapy, or head trauma**




Melmed, S. (2019). *Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. New England Journal of Medicine, 380(26), 2551–2562.* doi:10.1056/nejmra1817346
10.1056/nejmra1817346

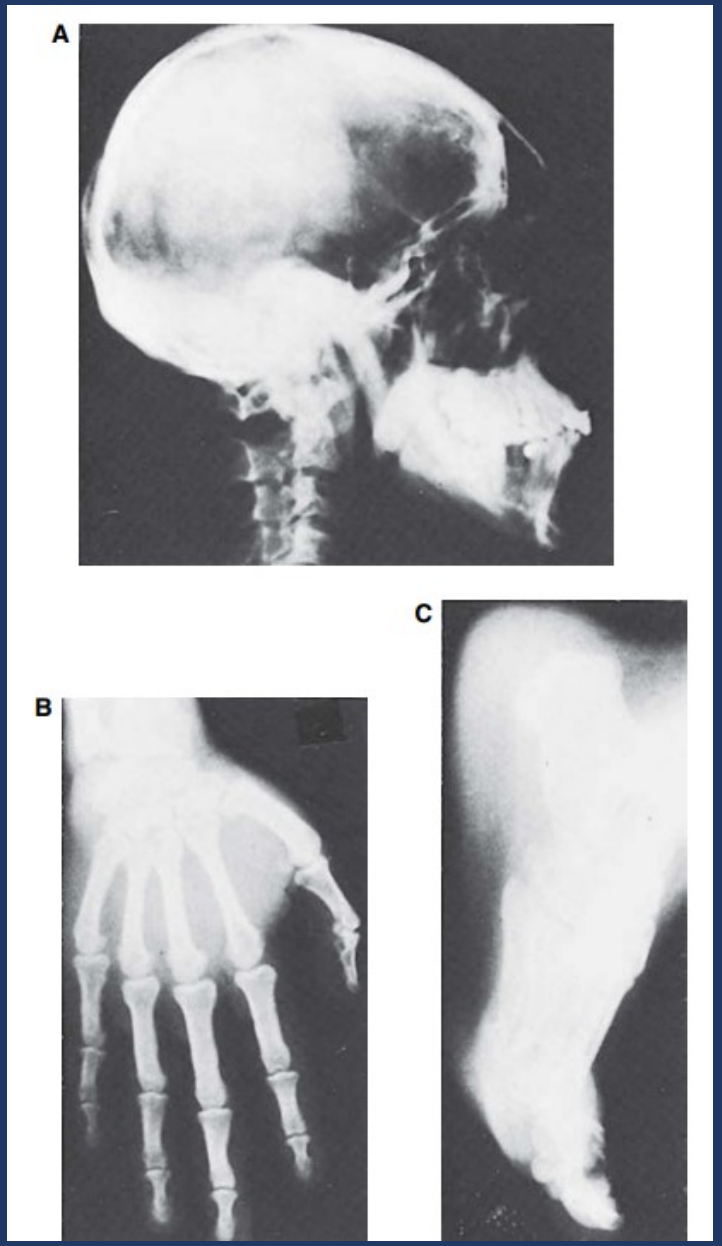



# Results of Acquired Adult GH Deficiency

Melmed, S. (2019). *Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. New England Journal of Medicine, 380(26), 2551–2562.* doi:10.1056/nejmra1817346
10.1056/nejmra1817346

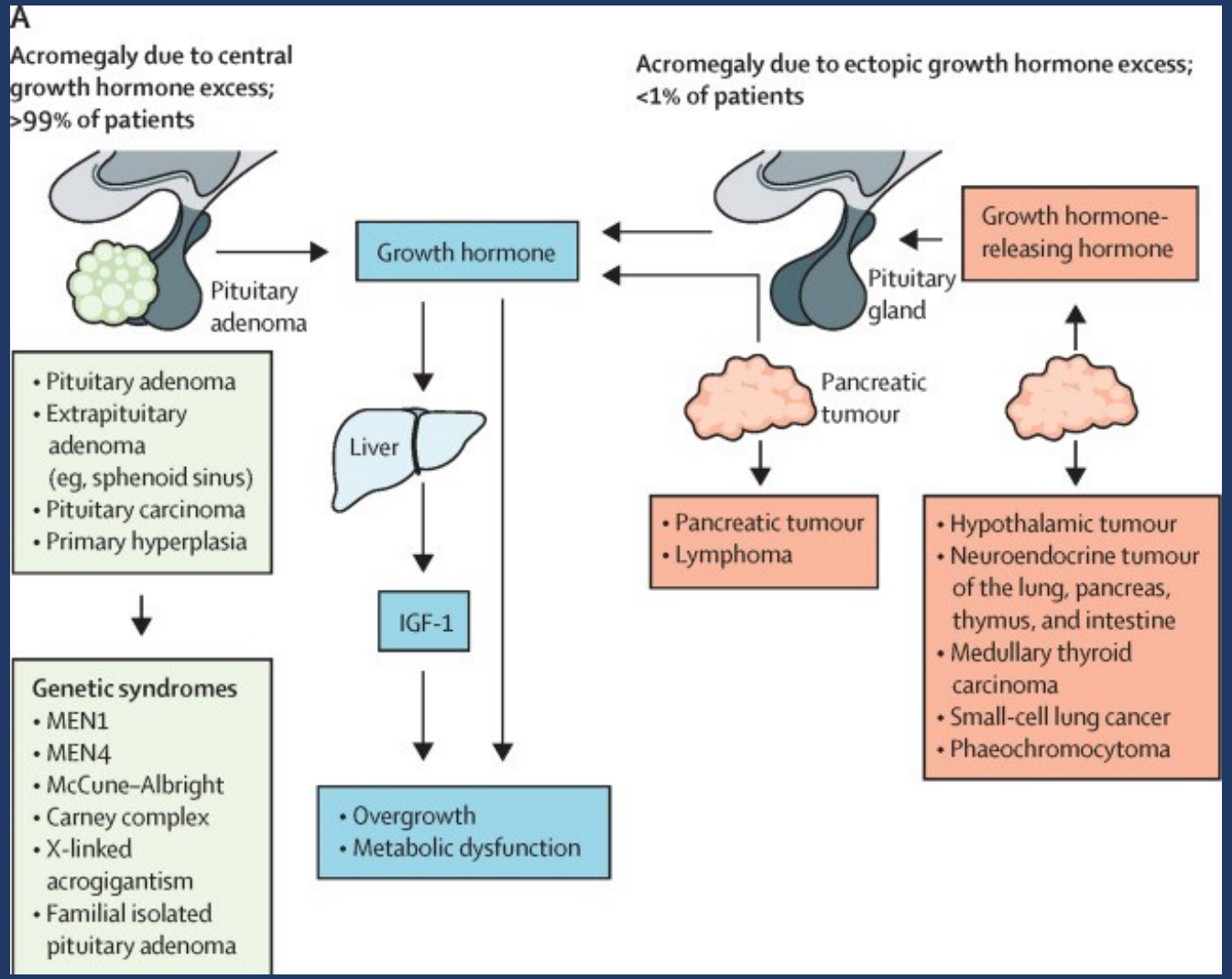
# Acromegaly

- **Certain pituitary tumors cause the hypersecretion of GH**, which in adults causes acromegaly, **a condition characterized by abnormal growth patterns in many tissues.**
- Such **tumors are generally non-metastatic** and believed to arise from the replication of single, transformed pituitary cells that have acquired a growth or survival advantage due to spontaneous mutations in key regulatory genes.
- **GH deficit or non-functional GH receptors can cause dwarfism. Individuals with Laron dwarfism, a form of GH insensitivity characterized by mutations in the GH receptor, usually have abnormally low levels of GHBP**.
- **Pertinently elevated GH concentrations e.g. due to pituitary tumors may lead to acromegaly.**



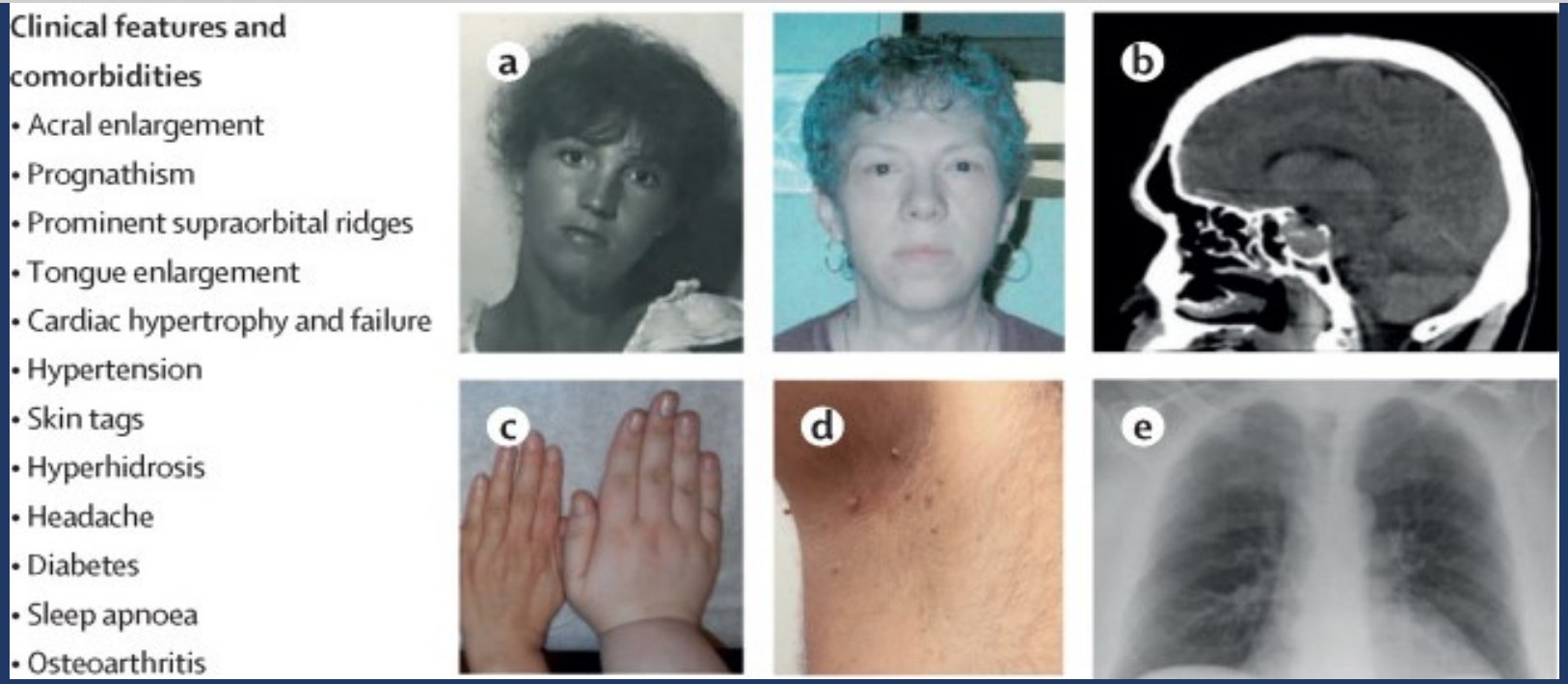
# Acromegaly

- **GH-secreting pituitary adenomas are second in frequency** to prolactinomas for functioning pituitary tumors and cause the classic clinical syndromes
- **Ectopic GHRH secretion has been identified as another cause of GH hypersecretion and acromegaly** in a few patients with carcinoid or islet cell tumor




Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol. 2022 Nov;10(11):804-826. doi: 10.1016/S2213-8587(22)00244-3. Epub 2022 Oct 6. PMID: 36209758.

- The syndrome is characterized by **local overgrowth of bone, skull and mandible.**
- **The sex incidence of acromegaly is approximately equal/ the mean age at diagnosis is approximately 40 years**; and the duration of **symptoms is usually 5 to 10 years before the diagnosis** is established.




Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol. 2022 Nov;10(11):804-826. doi: 10.1016/S2213-8587(22)00244-3. Epub 2022 Oct 6. PMID: 36209758.

# Prolactin- PRL I

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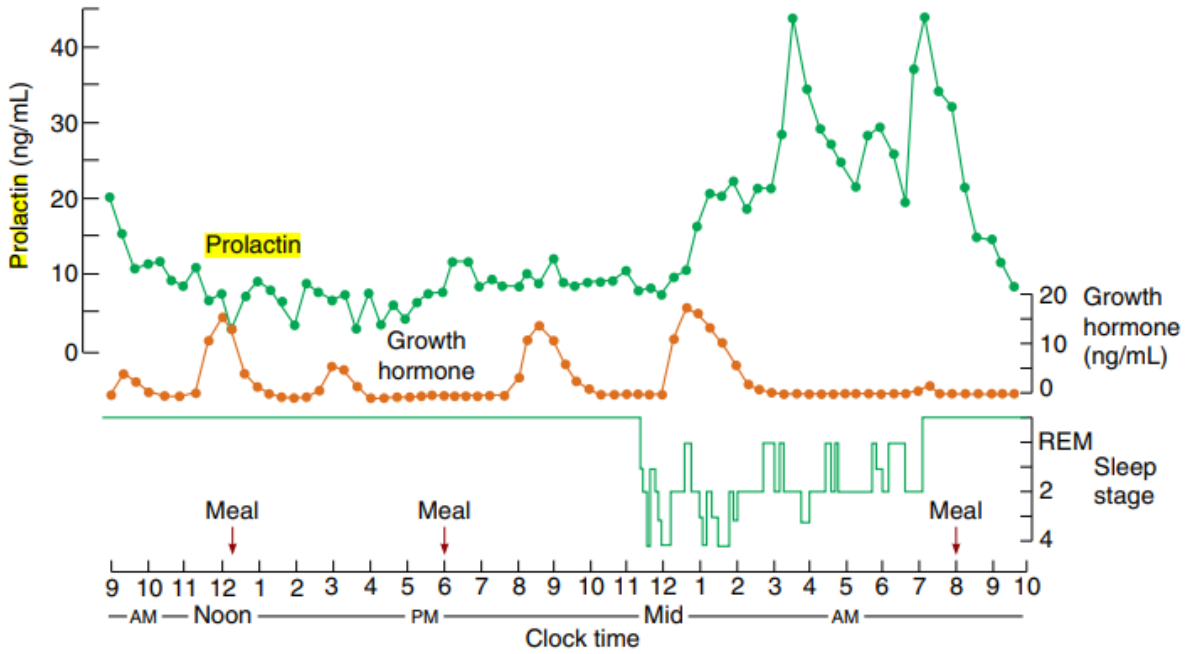
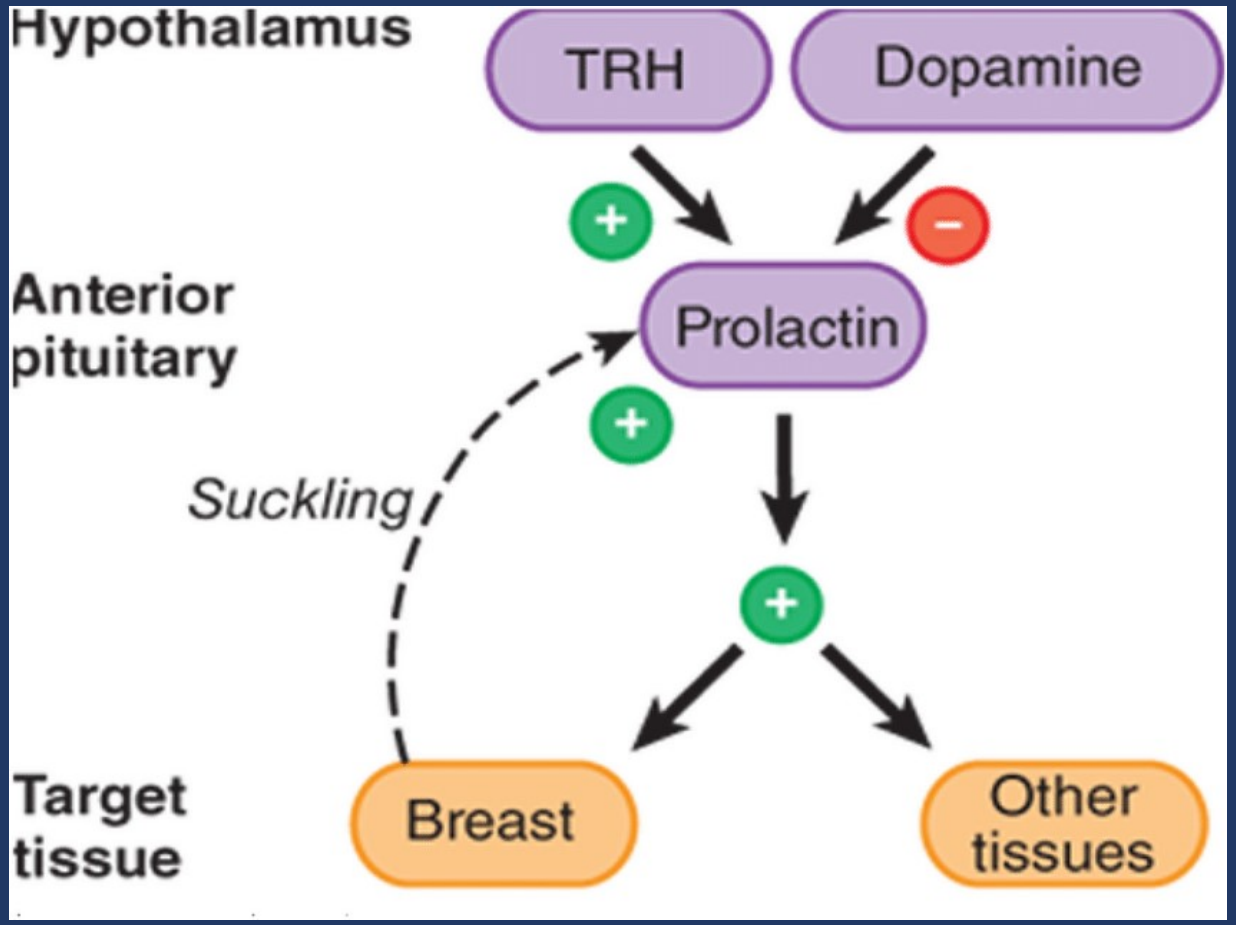
- PRL is a **198-amino-acid polypeptide hormone (MW 22,000) synthesized and secreted from the lactotrophs of the anterior pituitary.** Prolactin functions mainly to **promote lactation but also helps regulate reproduction, metabolism, and the immune system.**
- PRL shares 16% of its residues with GH. PRL and GH are structurally related to members of the cytokinehematopoietin family that include erythropoietin, granulocytemacrophage colony stimulating factor (GM-CSF), and interleukins IL-2 to IL-7.




- **PRL also has a role in immunomodulation;** extrapituitary synthesis of PRL occurs in T lymphocytes (among other sites), and PRL receptors are present on T and B lymphocytes and macrophages.
- **PRL modulates and stimulates both immune cell proliferation and survival.**

# Prolactin- PRL II



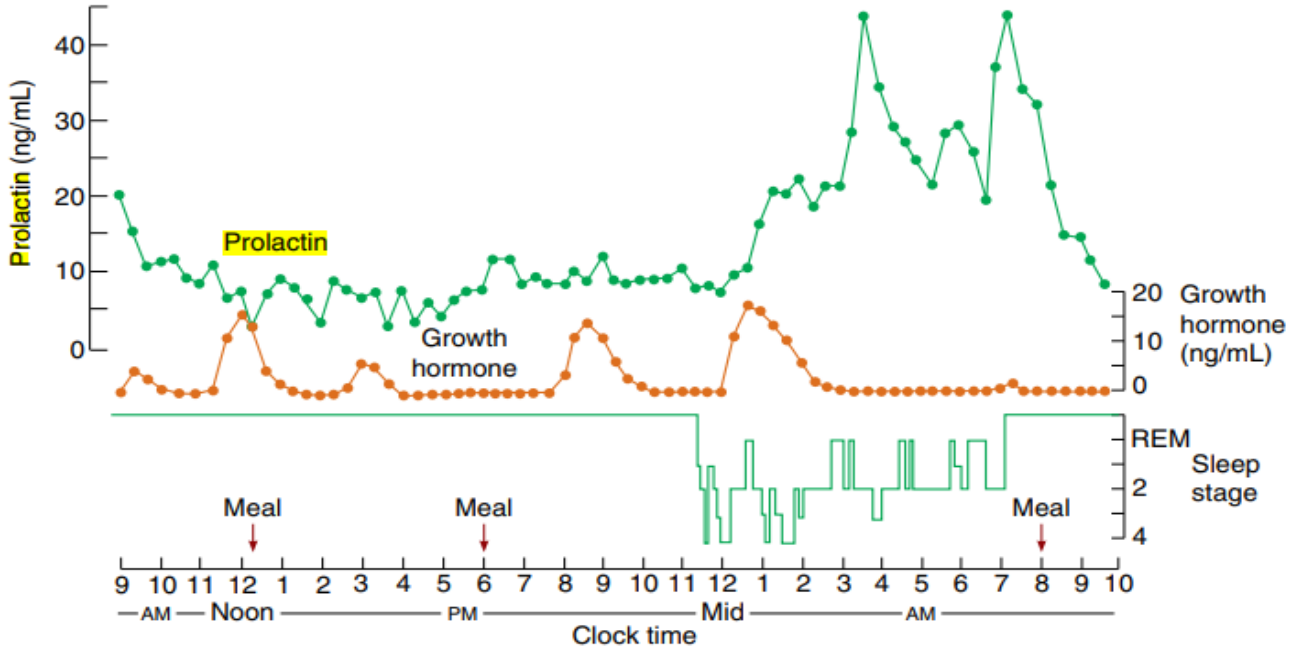



- **Promotes milk production in the mammary glands of the breast.**
- **Starts and maintains lactation**(production milk)
- In **women**, **high levels of prolactin** can **suppress ovulation:** irregular menstruation or amenorrhea (lack of menstruation).
  In **men**, it can **affect testosterone production (sperm mobility and fertility)**
- **Elevated prolactin levels have been associated with autoimmune conditions** and may affect immune responses.
- **Elevated levels of prolactin may lead to skin and hair changes, including acne, hirsutism** (excessive body hair growth), and other dermatological issues.

- **The release of PRL is suspended by: dopamine while stimulated by TRH**

# Prolactin- PRL IV

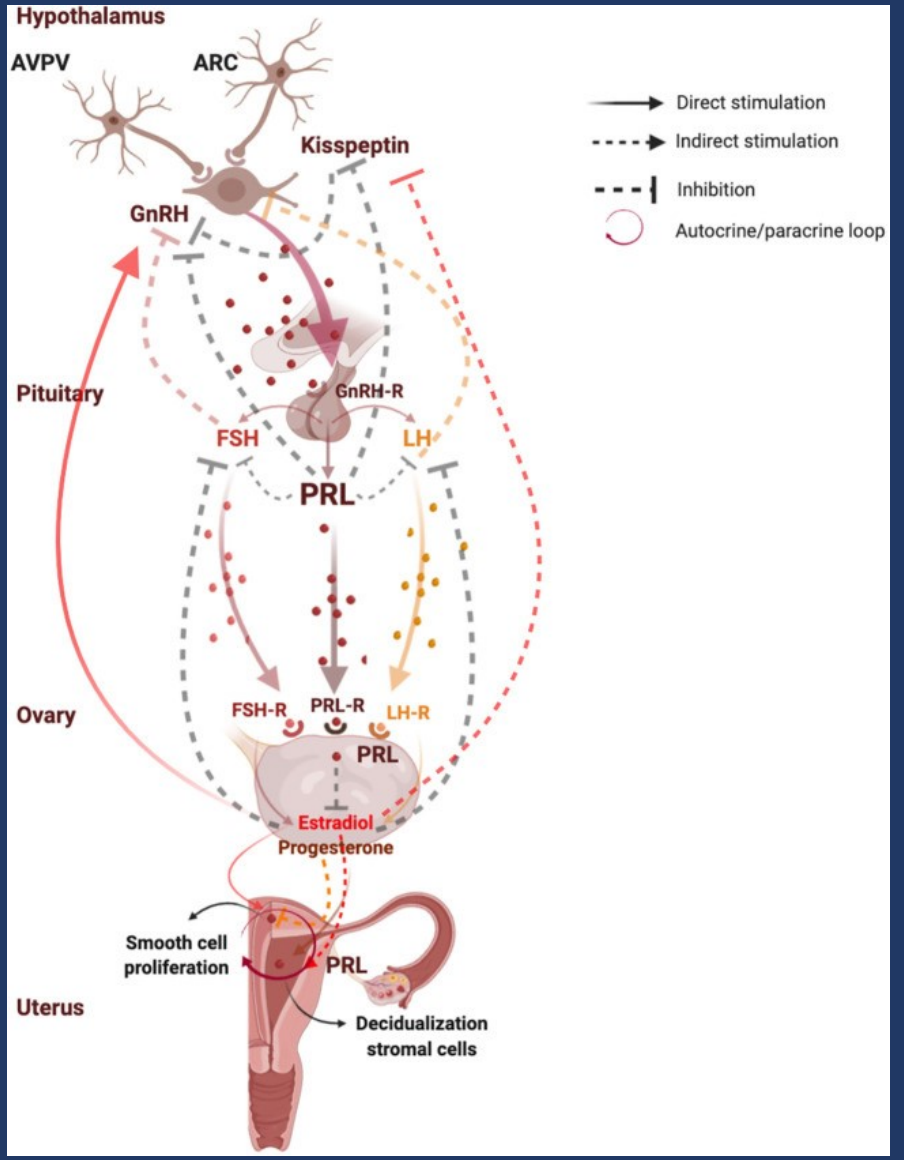
- **Peak levels occur 1 to 4 hours after the onset of sleep (during stages 3 and 4)**
- These nocturnal sleep bursts, which account for nearly 70% of daily GH secretion, are **greater in children and tend to decrease with age.**
- **Deep sleep is what rebuilds the body**




Prolactin-releasing stimuli not only include the nursing stimulus, but light, audition, olfaction, and stress can serve a stimulatory role.

# Prolactin- PRL V

- **PRL plays a key role in the reproductive system.** At peripheral level, PRL plays a direct inhibitory effect on estrogen and progesterone synthesis.
- **Estrogens exert negative feedback on GnRH release on kisspeptin neurons in the ARC**, and a **positive feedback on GnRH release on kisspeptin neurons in the AVPV.**




Auriemma RS, Del Vecchio G, Scairati R, Pirchio R, Liccardi A, Verde N, de Angelis C, Menafra D, Pivonello C, Conforti A, Alviggi C, Pivonello R, Colao A. The Interplay Between Prolactin and Reproductive System: Focus on Uterine Pathophysiology. Front Endocrinol (Lausanne). 2020 Oct 9;11:594370. doi: 10.3389/fendo.2020.594370. PMID: 33162942; PMCID: PMC7581729.

# Prolactin- PRL VI



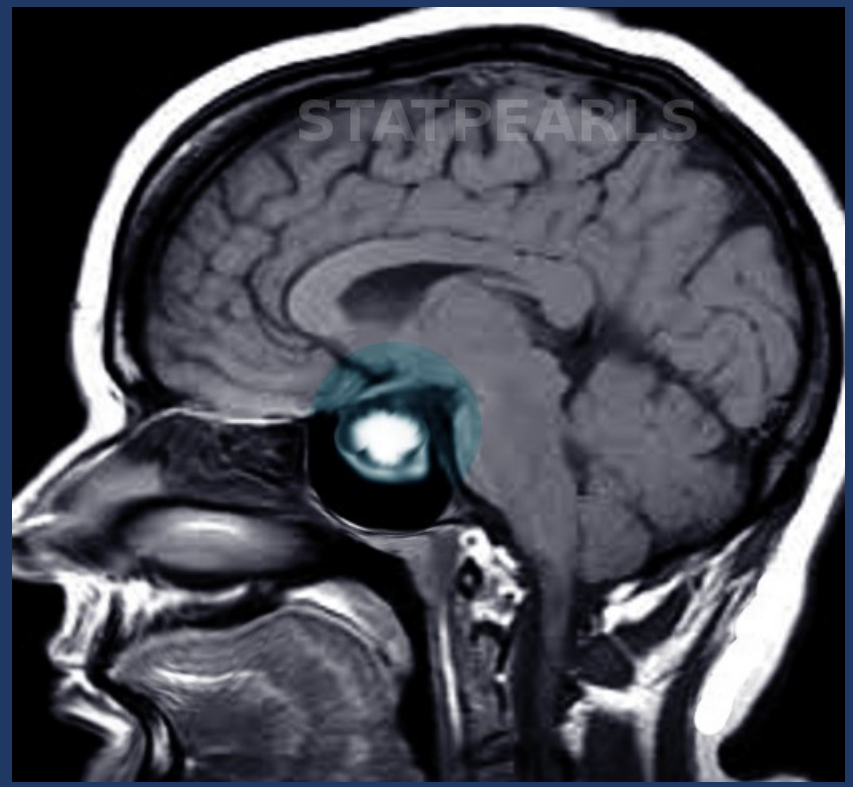
- Although PRL does not appear to play a physiologic role in the regulation of gonadal function, **hyperprolactinemia in humans leads to hypogonadism**.
- The exact mechanisms of **PRL inhibition of gonadal function are unclear, but the principal one appears to be alteration of hypothalamic-pituitary control of gonadotropin secretion.**
- During pregnancy, **PRL secretion increases and, in concert with many other hormones (estrogen, progesterone, hPL, insulin, and cortisol), promotes additional breast development in preparation for milk production.**

| Increase | Decrease |
|---|---|
| **Physiologic** | |
| Pregnancy | |
| Nursing | |
| Nipple stimulation | |
| Exercise | |
| Stress (hypoglycemia) | |
| Sleep | |
| Seizures | |
| Neonatal | |
| **Pharmacologic** | |
| TRH | Dopamine agonists (levodopa, apomorphine, bromocriptine, pergolide) |
| Estrogen | GABA |
| Vasoactive intestinal peptide | |
| Dopamine antagonists (phenothiazines, haloperidol, risperidone, metoclopramide, reserpine, methyldopa, amoxapine, opioids) | |
| Monoamine oxidase inhibitors | |
| Verapamil | |
| Licorice | |
| **Pathologic** | |
| Pituitary tumors | Pseudohypoparathyroidism |
| Hypothalamic/pituitary stalk lesions | Pituitary destruction or removal |
| Neuraxis irradiation | Lymphocytic hypophysitis |
| Chest wall lesions | |
| Spinal cord lesions | |
| Hypothyroidism | |
| Chronic renal failure | |
| Severe liver disease | |

# Prolactinoma

- **PRL levels are very high in the fetus and in newborn infants, declining during the first few months of life.**
- Normal PRL is controlled by many stimulatory and inhibitory factors. **PRL secretion is primarily under tonic inhibition by dopamine.**
- **In women, initially there is a shortening of the luteal phase; subsequently, anovulation, oligomenorrhea or amenorrhea, and infertility occur.**
- In men, **PRL excess leads to decreased testosterone synthesis and decreased spermatogenesis, which clinically present as decreased libido, impotence, and infertility.**

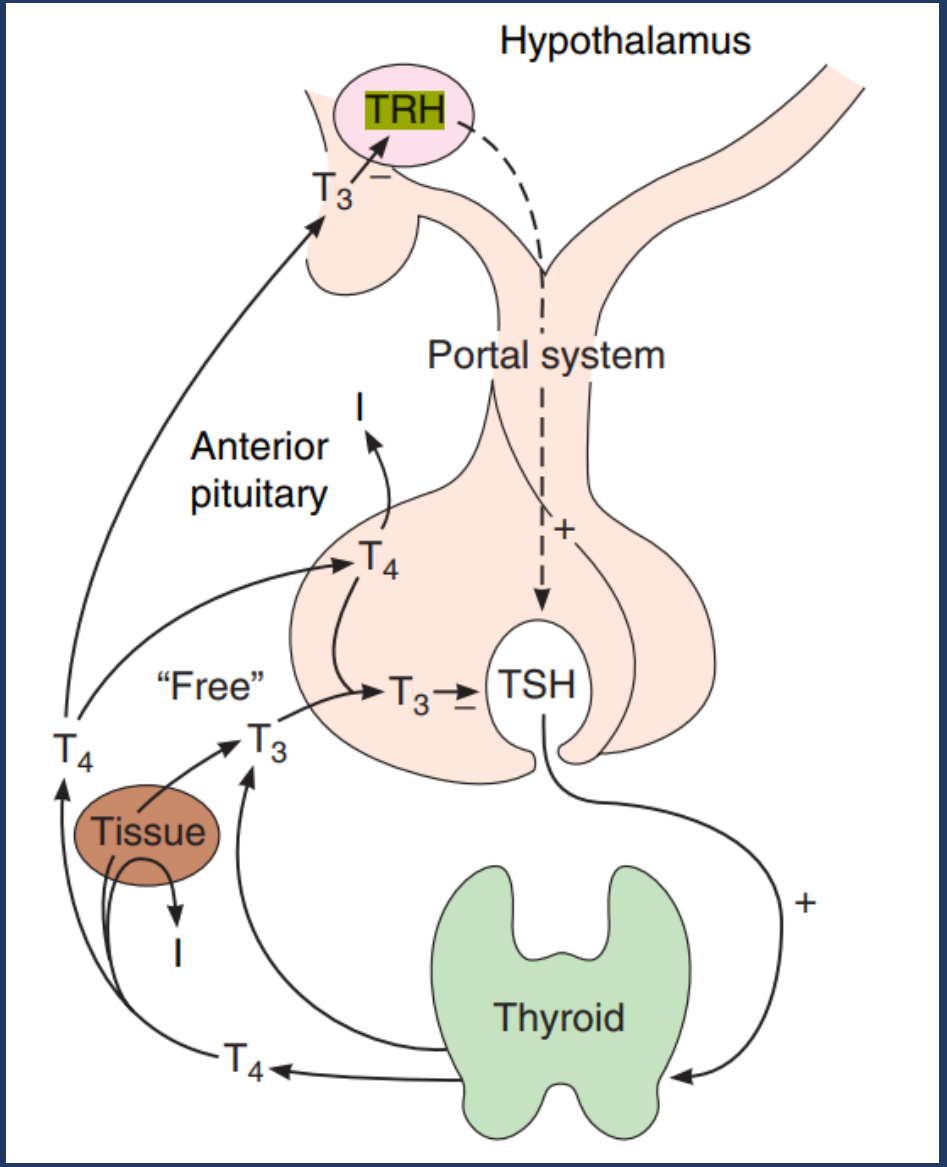
Outside of pregnancy or postpartum lactation, **hyperprolactinemia is almost always associated with a hypothalamic-pituitary disorder that disrupts dopamine synthesis or transport**.




Yatavelli RKR, Bhusal K. Prolactinoma. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459347/

# TRH-TSH

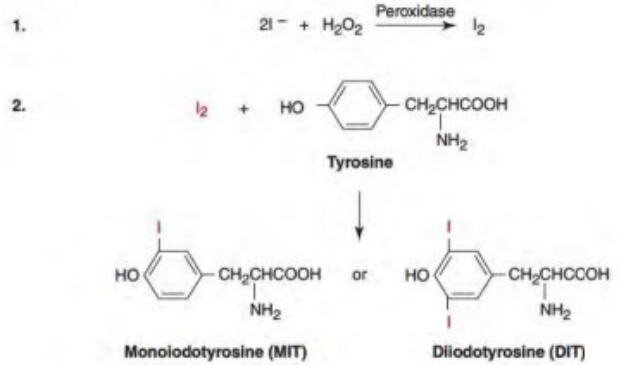
- **TRH, a tripeptide, is the major hypothalamic factor regulating TSH secretion.**
- **TSH synthesis is stimulated in thyrotropic pituitary cells by the action of thyrotropin-releasing hormone (TRH) and (by TRH triggering again) is released into the portal system.**
- TRH stimulates phosphorylation of cAMP reactive elements binding proteins CREB which recruits CREB-binding protein (CBP) which then, in cooperation with P-LIM, activates the TSH-α promoter.

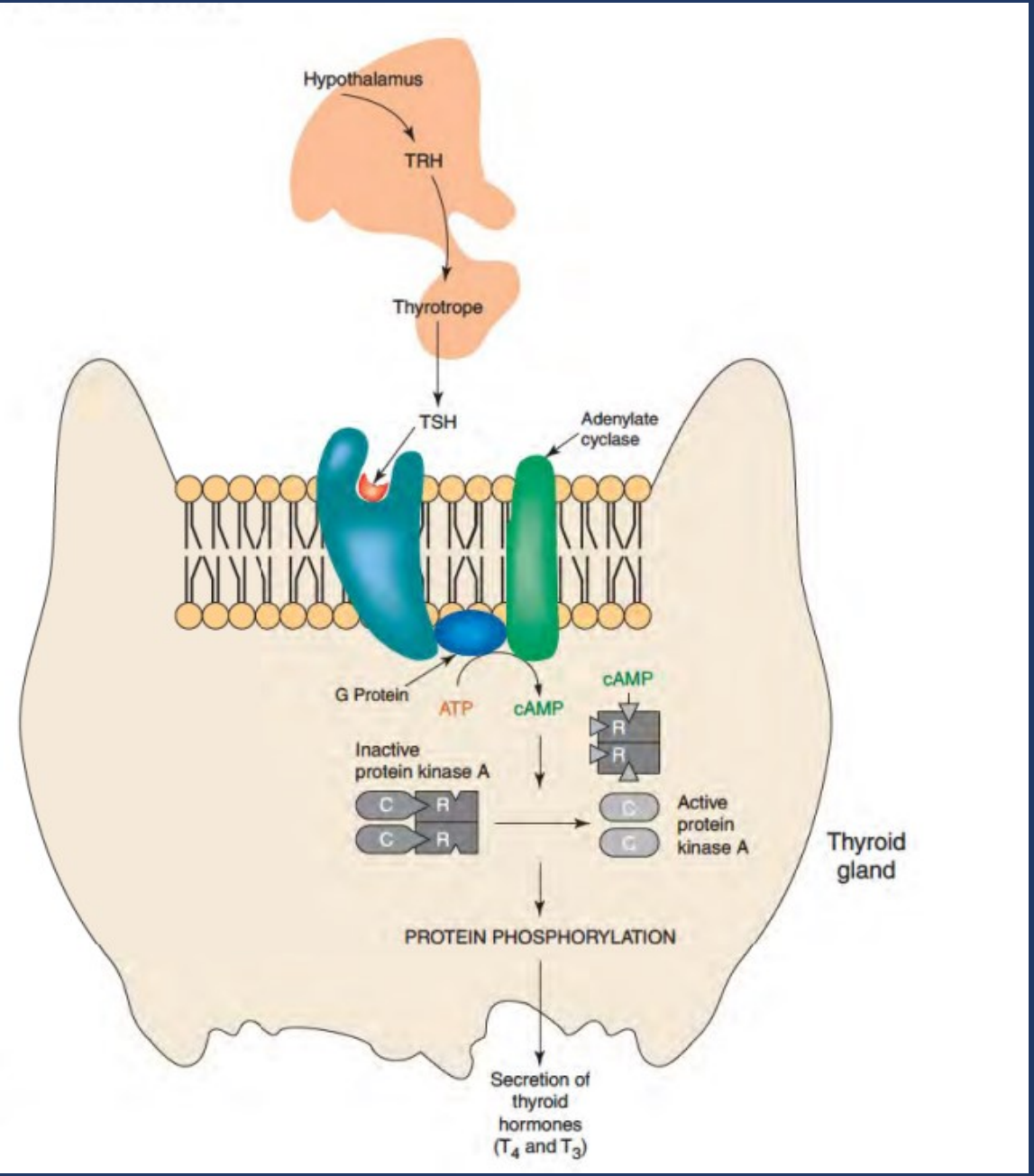


# Thyrotropin-releasing hormone TSH



- **TRH is a tripeptide that stimulates the release of thyroid-stimulating hormone and prolactin from the anterior pituitary gland.**
- **TSH is a glycoprotein (MW 28,000) composed of two noncovalently linked alpha and beta subunits.** The structure of the alpha subunit of TSH is identical to that of the other glycoprotein molecules—FSH, LH, and hCG—but the **beta subunits differ in these glycoproteins and is responsible for their biologic and immunologic specificity.**
- **The beta subunit of TSH attaches to high-affinity receptors in the thyroid, stimulating iodide uptake, hormonogenesis, and release of T4 and T3.**
- **This occurs through activation of adenylyl cyclase and the generation of cAMP**. TSH secretion also causes an increase in gland size and vascularity by promoting mRNA and protein synthesis






**1.** Thyrotropin-releasing hormone-TRH- synthesized by hypothalamic neurons reaches the thyrotropes in the anterior pituitary and stimulates them to synthesize and secrete thyroid-hormone- stimulating hormone (TSH)

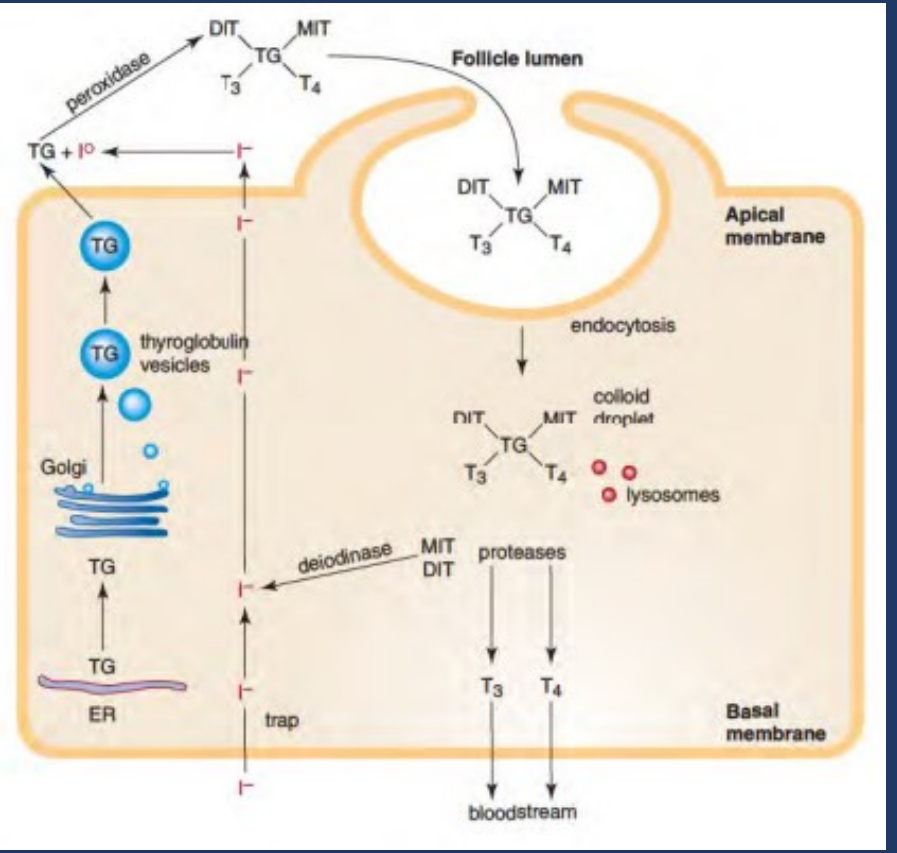
**2.** TSH binds to its G protein-coupled membrane receptors in the thyroid gland and activates adenylate cyclase with generation of cAMP

**3.** cAMP in turn binds to the regulatory subunits in the inactive form of protein kinase A leading to their dissociation from the catalytic subunits, which are fully active

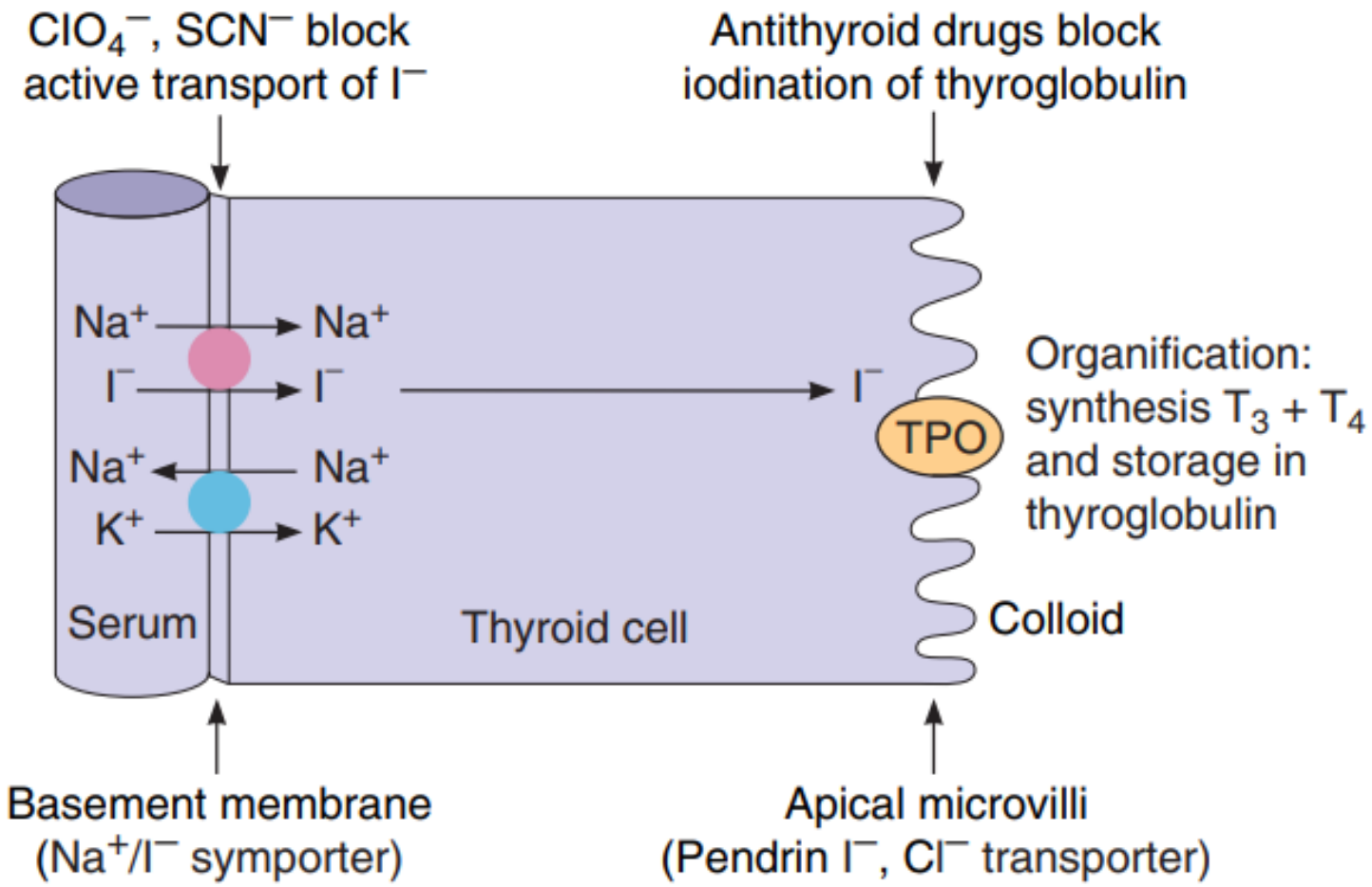
**4.** initiate a cascade of protein phosphorylations that results in secretion of thyroid hormone

1. The thyroid gland is specialized to concentrate iodide from the blood
2. Thyroglobulin is a large glycoprotein that is synthesized and secreted by the thyroid epithelial cells and is stored in the lumen of the thyroid follicles.
3. The coupling of an MIT and DIT or two DIT molecules can occur within the same thyroglobulin molecule or between two adjacent thyroglobulin molecules.
4. Secretion of T3 and larger amounts of T4 into the bloodstream requires endocytosis of the thyroglobulin by follicular epithelial cells and its proteolysis by lysosomal enzymes.
5. The DIT and MIT released within the epithelial cell are then deiodinated and the released iodide ions are recycled and reutilized for thyroid hormone synthesis.
6. This recycling of iodine ions is extremely important, and mutations resulting in inactivation of the deiodinase enzyme can result in an iodide deficiency.

## Cellular mechanisms for T3 and T4 release into bloodstream

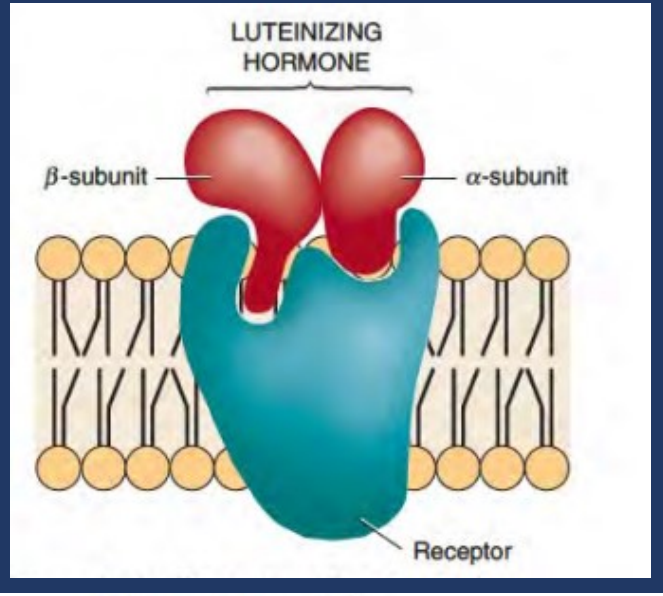


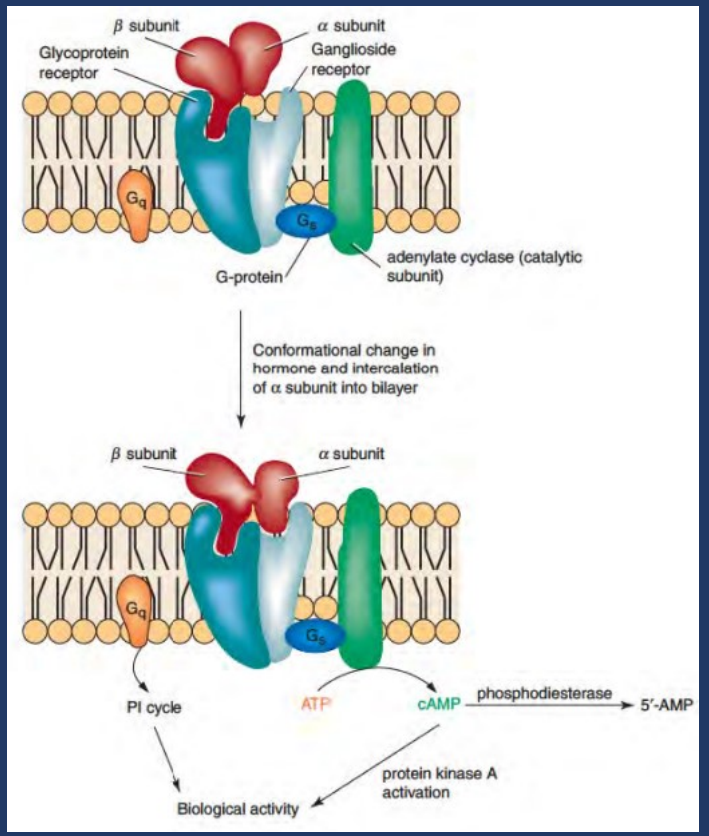
# The iodide transporter in the thyroid cell



# GnRH-FSH-LH-CG

- **LH, FSH, CG Two of the human three gonadotropins are made and released from the pituitary, luteinizing hormone (LH) and follicle stimulating hormone (FSH);** the **third, choriogonadotropin (CG)** is of placental origin and the sign of pregnancy
- **Luteinizing hormone (LH), and follicle -stimulating hormone (FSH)** each contain an a and a β-subunit. **The a-subunits for all three hormones are similar or identical.**
- **The LH receptor recognizes both subunits of the hormone , but the β-subunit is specifically recognized by the receptor to elicit a hormonal response.** The TSH - receptor complex stimulates adenylate cyclase and the phosphatidylinositol pathway. The preferred model is one in which there is a single receptor whose interaction with hormone activates both the adenylate cyclase and the phospho-lipid second messenger systems.



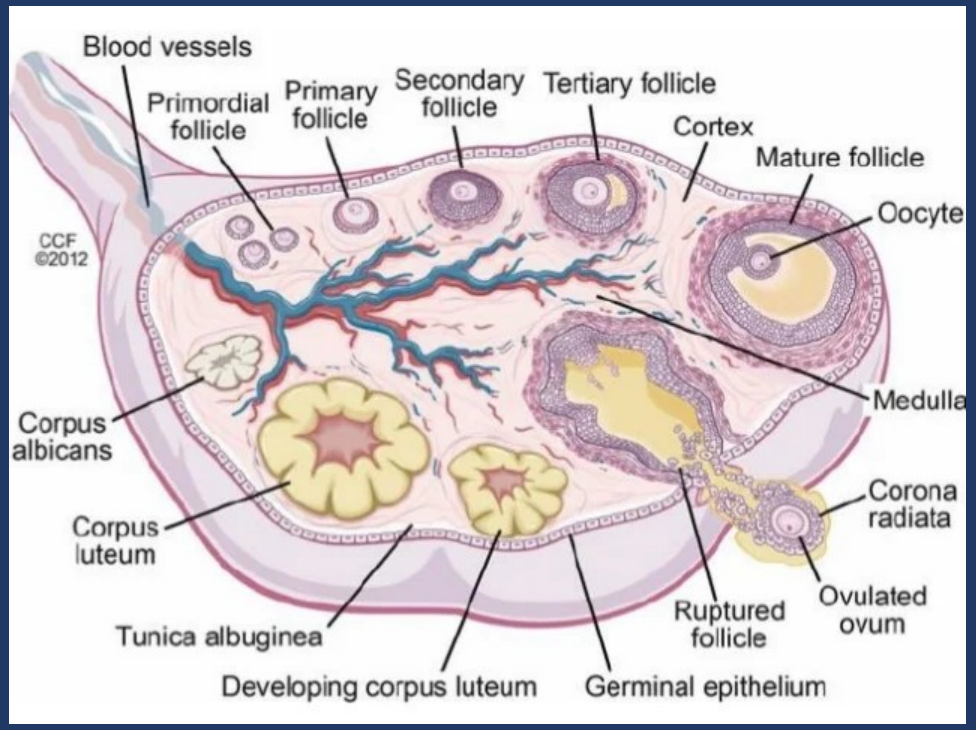



- **Regulation of the female menstrual cycle occurs in four organs: in the hypothalamus, in the pituitary, in the ovaries, and in the uterus. The hypothalamic– pituitary–gonadal axis.**
- The first essential variable indispensable to reproduction is pulsatile release of GnRH in the hypothalamus.
- Without pulsatile release—that is, with continuously elevated or missing GnRH levels—LH/FSH release is efficiently blocked.
- **GnRH stimulates FSH (follicle-stimulating hormone) release. The hypothalamus produces GnRH, and it is released into the hypophyseal portal circulation to act on G-protein-coupled receptors at gonadotropic cells of the anterior pituitary. Those gonadotropic cells produce FSH and luteinizing hormone (LH) and release them into the peripheral circulation.**

**In the ovary FSH (follitropin) induces follicle maturation.**
**In testes FSH stimulates sperm-forming Sertoli cells.**

**Target of LH/CG is the common LH-receptor on cells in the gonads: for men the Leydig cells and for women theca cells.**

# OVARIES



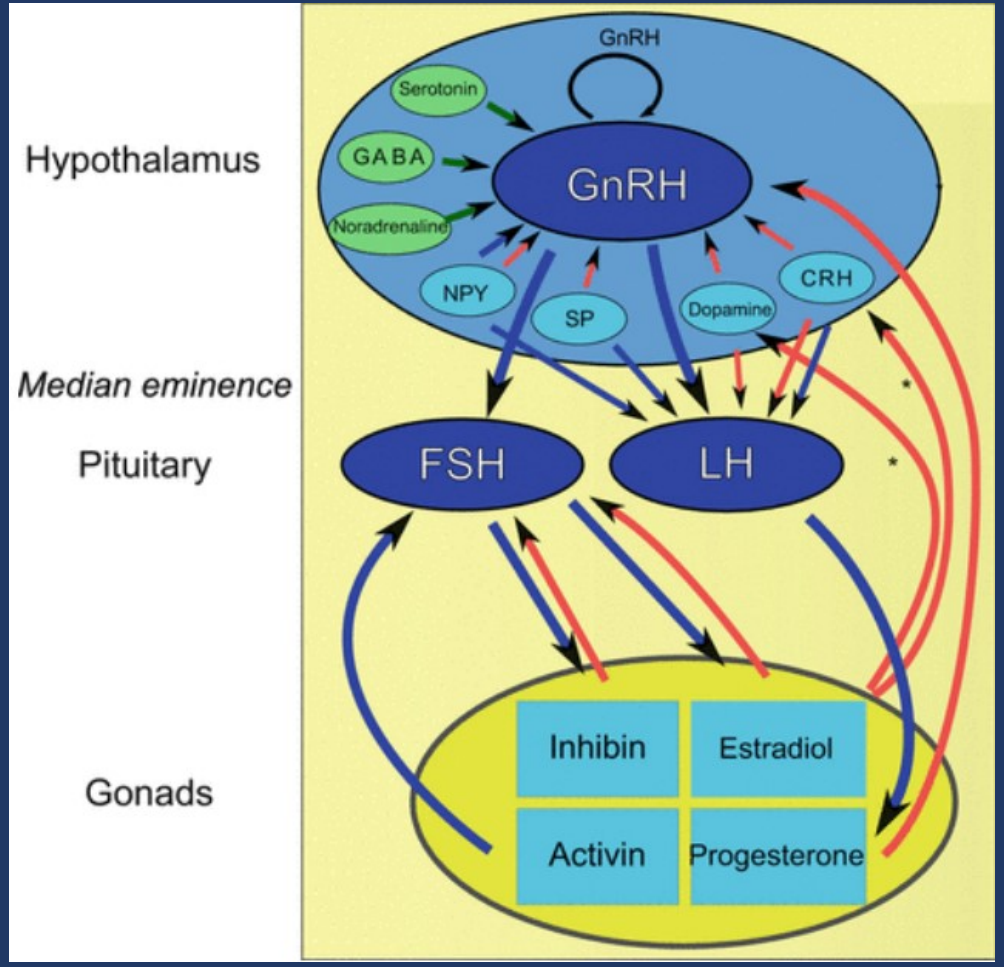

The ovaries consist of the medulla and the cortex, where ovarian follicles are found in various stages of development.

They are mixed glands:

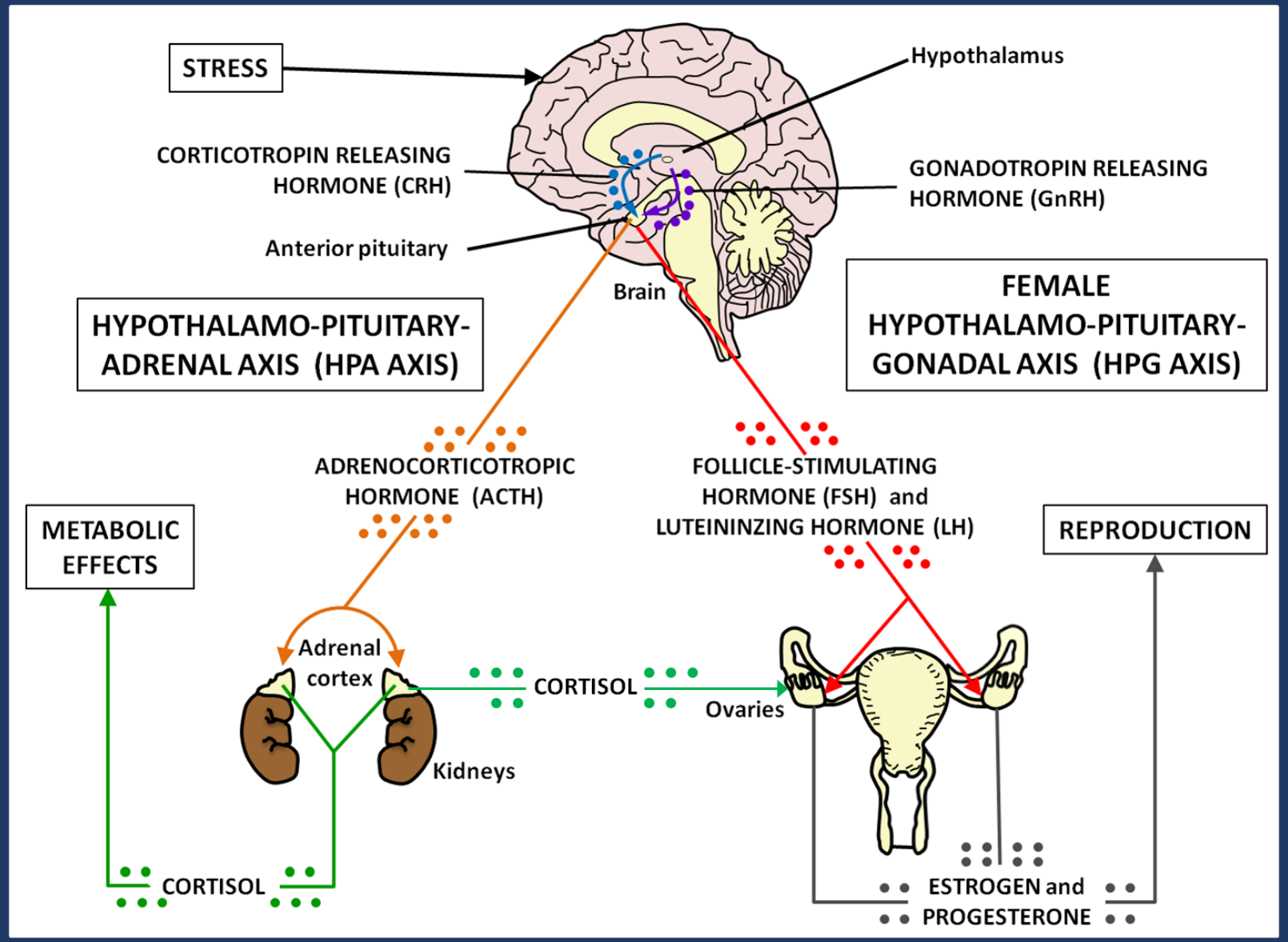
- Reproductive function with the release of ova (exocrine portion)
- Synthesis and secretion of hormones (endocrine portion)

- The ovarian reserve, constituted by the size of the ovarian follicle pool and the quality of the oocytes declines with increasing age, resulting in the decrease of a woman's reproductive function
- A primordial follicle pool of 300.000–500.000 follicles at menarche

- **Reproductive rhythms are controlled via GnRH.**
- **Pulsatile GnRH release induces pulsatile release of gonadotropins, which in turn regulate gonadal activity.**
- Suppression of reproductive activity as a consequence of stress : The central and peripheral stress systems are thought to play the prominent role: **CRH directly suppresses GnRH release via synaptic contact of CRH axons to dendrites of GnRH neurons in the medial preoptic nucleus**



# The hypothalamo-pituitary-adrenal axis (HPAA) and the female hypothalamo-pituitary-gonadal axis (HPGA)



# Ovarian Cycle Is Controlled by Pulsatile and Cyclic Secretion of Gonadotropin-Releasing Hormone

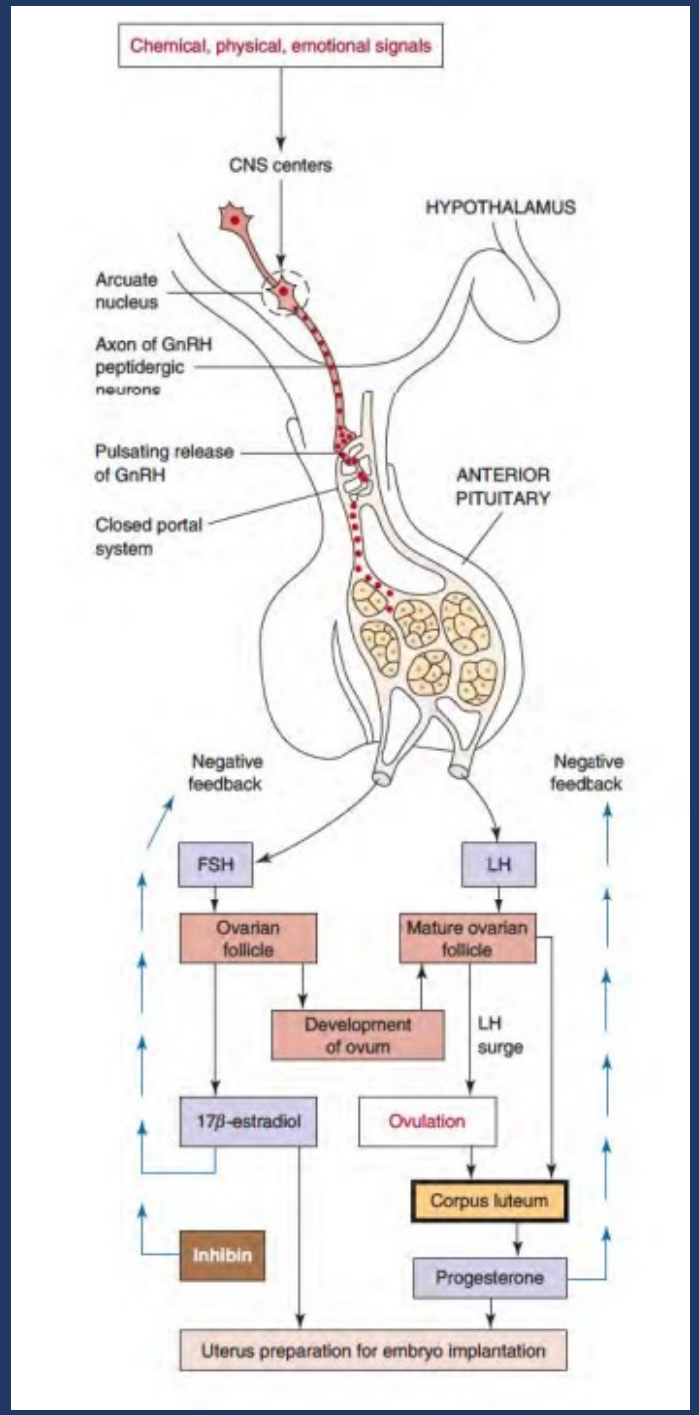
1. GnRH is secreted from hypothalamic neuroendocrine cells in pulses.

2. Entry of GnRH into the portal system is through fenestrations in the blood vessels to reach the gonadotropes located in the anterior pituitary.

3. GnRH binds to its membrane receptors and mediates its effects via the phosphatidylinositol second messenger system with release of FSH and LH from the same gonadotrope

4. FSH operating through protein kinase A via cAMP elevation , stimulates synthesis and secretion of 17 /3-estradiol, and matures the ovarian follicle and ovum.

5. Inhibin , a disulfide-linked dimeric glycoprotein hormone , is also synthesized and secreted by the granulosa cells of the ovarian follicle.



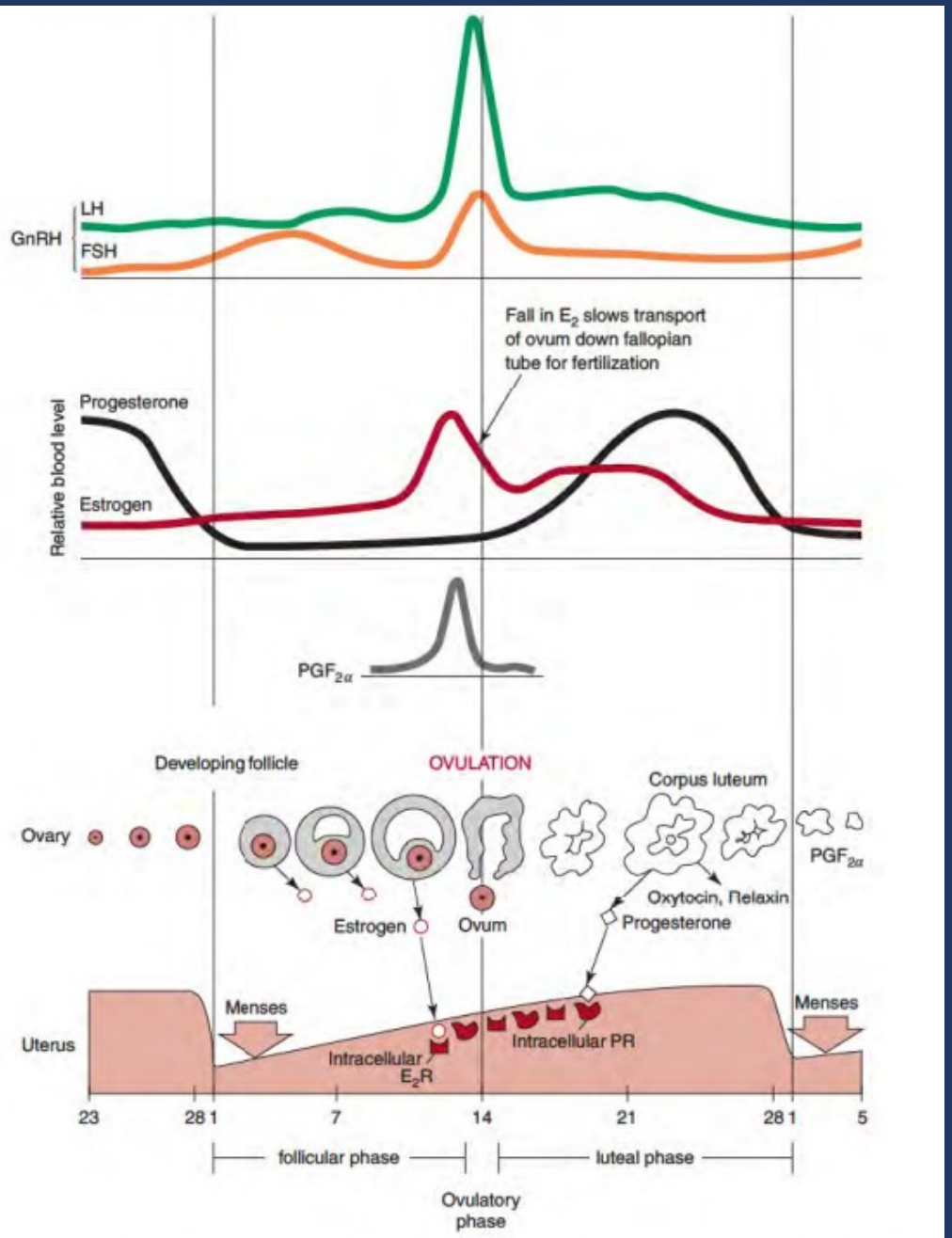

6. When a follicle reaches maturity , a surge of LH and prostaglandin $F_{2a}$ triggers ovulation.

7. The residual follicle under primary control by LH becomes the functional corpus luteum.

8. LH binds to its cognate receptors in the corpus luteum and through stimulation of protein kinase A increases synthesis of progesterone.

9. Estradiol and progesterone bind to specific intracellular receptors in the uterine endometrium and promote thickening of the wall, vascularization, and increased secretory activity in preparation for implantation of the fertilized egg.

# Absence of Fertilization




**If fertilization does not occur, the corpus luteum involutes or degenerates because of diminished LH supply, and progesterone and estrogen levels fall sharply.**

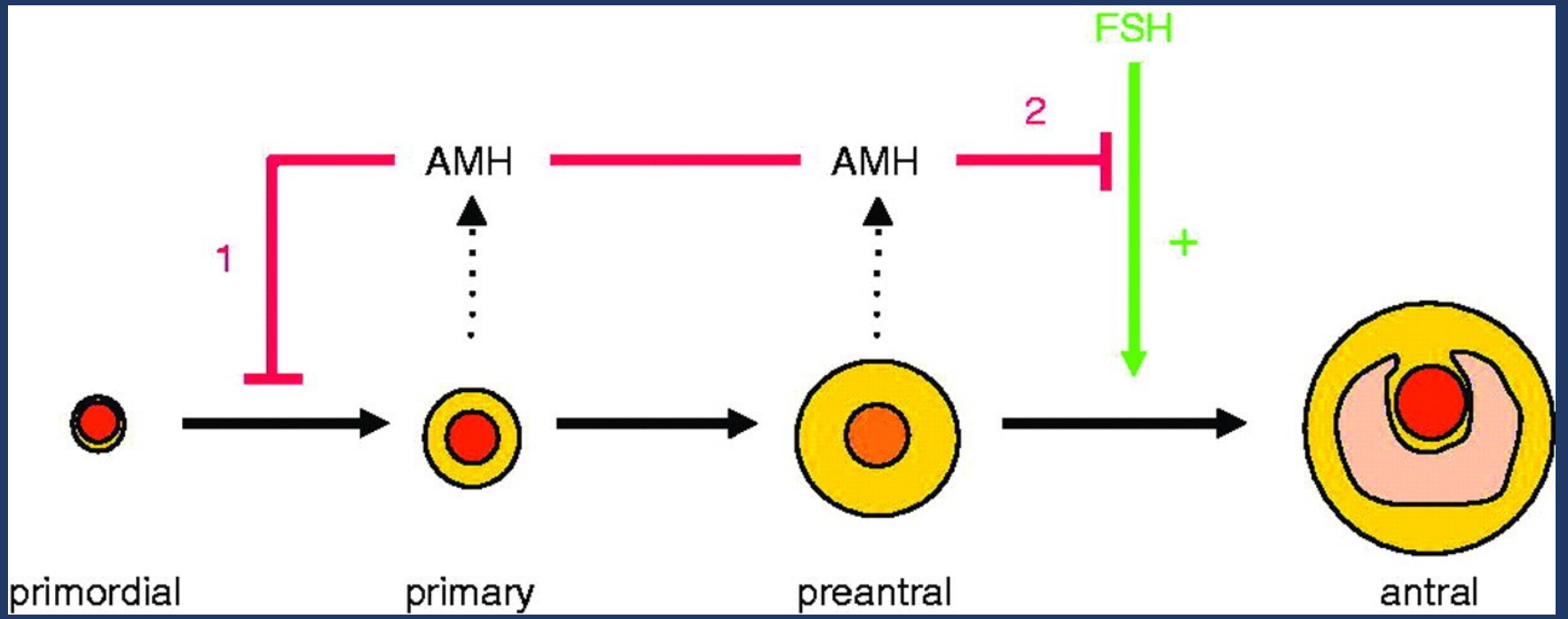
**The hormonal stimuli for a thickened and vascularized uterine endometrial wall are thus lost and menstruation occurs as a consequence of cellular necrosis.**

**The fall in blood steroid levels releases the feedback inhibition on the gonadotropes and hypothalamus and the cycle starts again.**

The first monthly cycle occurs at the time of puberty when GnRH secretion begins to increase.

GnRH is released in a pulsatile fashion, causing the gonadotrope to release FSH and LH, and the blood concentrations of these hormones gradually increase in subsequent days.

# Stages of folliculogenesis




**Anti-Müllerian hormone: a new marker for ovarian function**

Visser JA, de Jong FH, Laven JS, Themmen AP. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction. 2006 Jan;131(1):1-9. doi: 10.1530/rep.1.00529. PMID: 16388003.

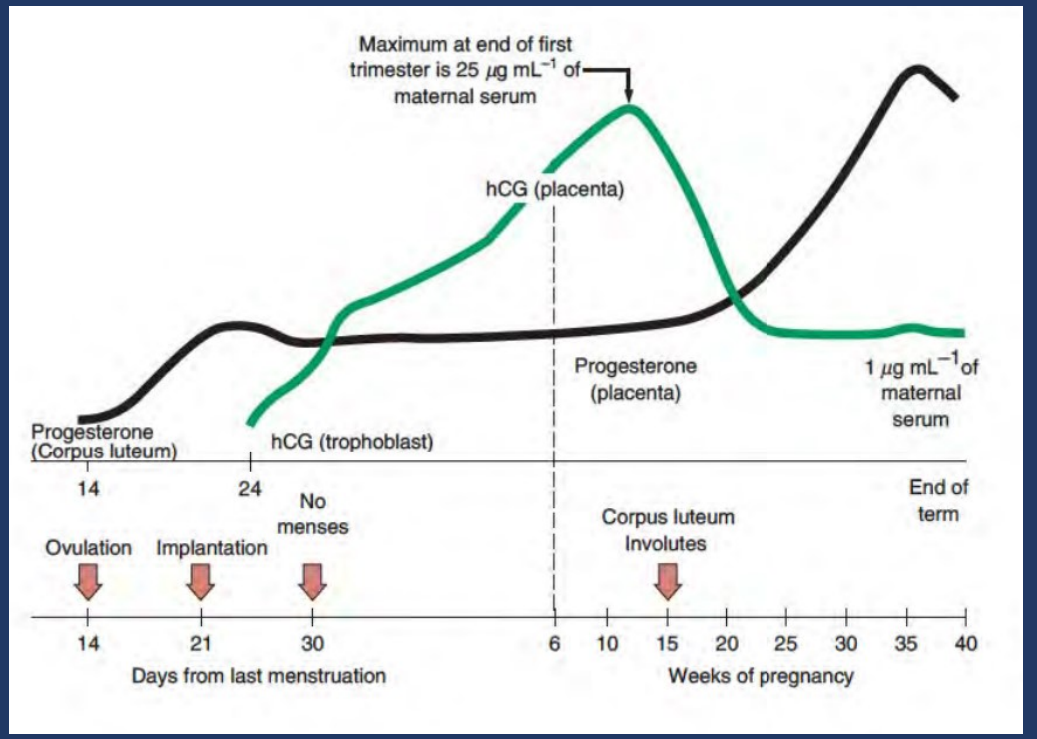
**Model of AMH action in the ovary.**
AMH is produced by the small growing (primary and preantral) follicles in the postnatal ovary and has two sites of action.
It inhibits initial follicle recruitment (1) and inhibits FSH-dependent growth and selection of preantral and small antral follicles

# Fertilization



- **The corpus luteum remains viable because of production of chorionic gonadotropin (CG), which resembles and acts like LH, from the trophoblast cells.**
- The secretion of CG reaches a peak about 80 days after the last menstrual period.
- It then declines very rapidly and is produced by the placenta at a relatively low level for the remainder of pregnancy.
- **Once CG levels fall, the corpus luteum begins to involute, and by about 12 weeks of pregnancy, the placenta takes over production and secretion of progesterone and estrogens (primarily estriol).**

**secretion of progesterone and human chorionic gonadotropin {hCG)**



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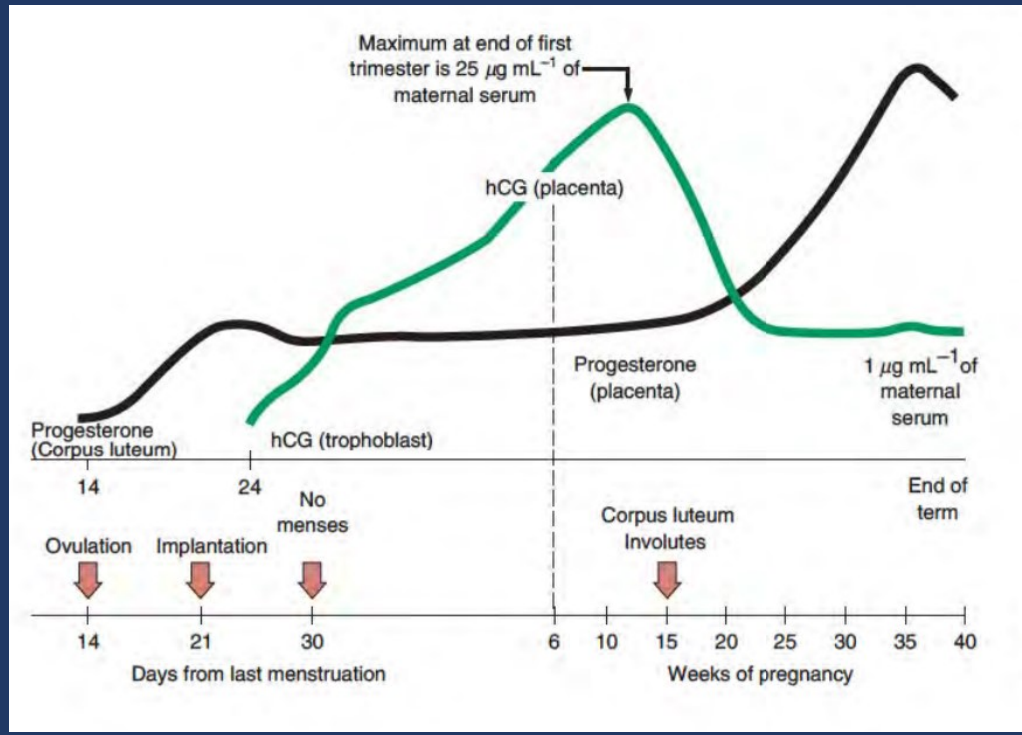
# Fertilization

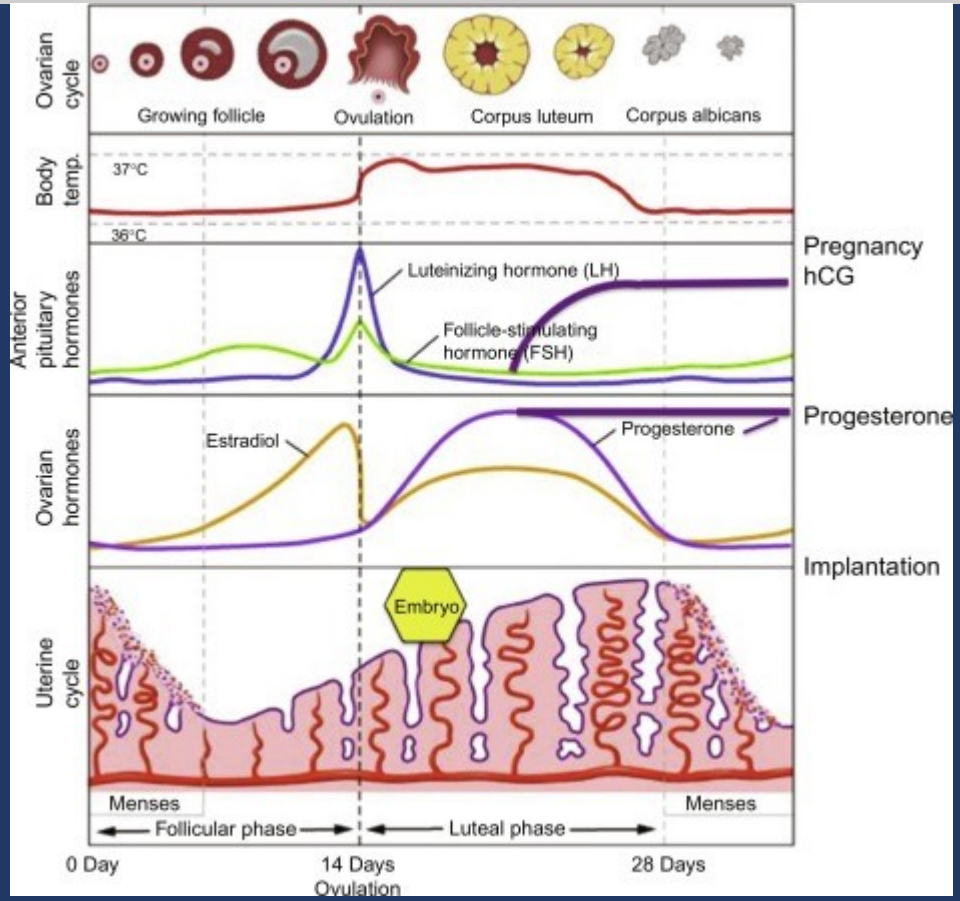
- From the seventh month onward estrogen secretion continues to increase while progesterone secretion remains constant or may even decrease slightly.
- **The estrogen/progesterone ratio increases toward the end of pregnancy and may be partly responsible for increased uterine contractions.**
- **Oxytocin from the posterior pituitary contributes to these uterine contractions.**
- The fetal membranes release prostaglandins (PGF2a) at the time of parturition , which increases the intensity of uterine contractions.
- Finally, the fetal adrenal cortex secretes cortisol, which stimulates fetal lung maturation by inducing the synthesis of surfactant-associated proteins.



# Progesterone

- An intermediate of testosterone, estrogen, cortisol, and aldosterone synthesis. **As a hormone it is indispensable for ovulation, nidation of the fertilized egg, and for the maintenance of pregnancy**
- **Increased concentrations of progesterone which are made in the corpus luteum block LH formation.**
- **PRG inhibits the secretion of GnRH**.
- Maintenance of corpus luteum function. **Preparation of the endometrium for the reception, implantation, and development of the fertilized ovum**

- **Higher levels of PRG are found between the 19th and 23rd day, with a peak on the 21st day.**
- **The corpus luteum, without LH, regresses, and PRG decreases, resulting in the shedding of the endometrium and the onset of bleeding.**
- **Estrogen levels decrease, and FSH levels begin to rise, initiating a new cycle.**




Richards JS. The Ovarian Cycle. Vitam Horm. 2018;107:1-25. doi: 10.1016/bs.vh.2018.01.009. Epub 2018 Feb 23. PMID: 29544627.

# Oral Contraception

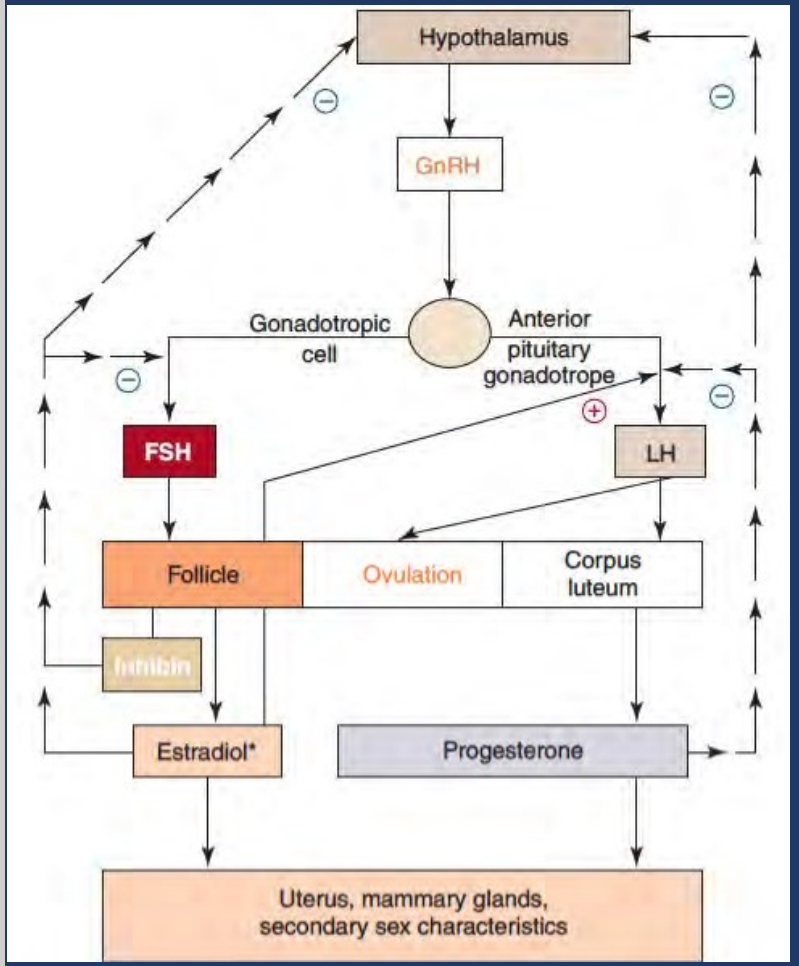
- **Estrogens and progesterone can inhibit pituitary secretion of FSH and LH : no maturation of the ovarian follicle and ovulation.**
- Are a combination of a synthetic estrogen and a progesterone-like substance or progestin.

**This combination of steroids blocks the LH surge required for ovulation and results in thickening and increased vascularization of the uterine endometrium.**

Pills that lack any steroids (placebos) are usually inserted in the regimen at about the 28th day, causing blood levels of estrogens and progestins to fall dramatically and menstruation to occur.

When the combination oral contraceptives are resumed, the blood levels of estrogen and progestin increase again and the uterine endometrium thickens.

**This creates a false cycling because of the occurrence of menstruation at the expected time point in the cycle.**

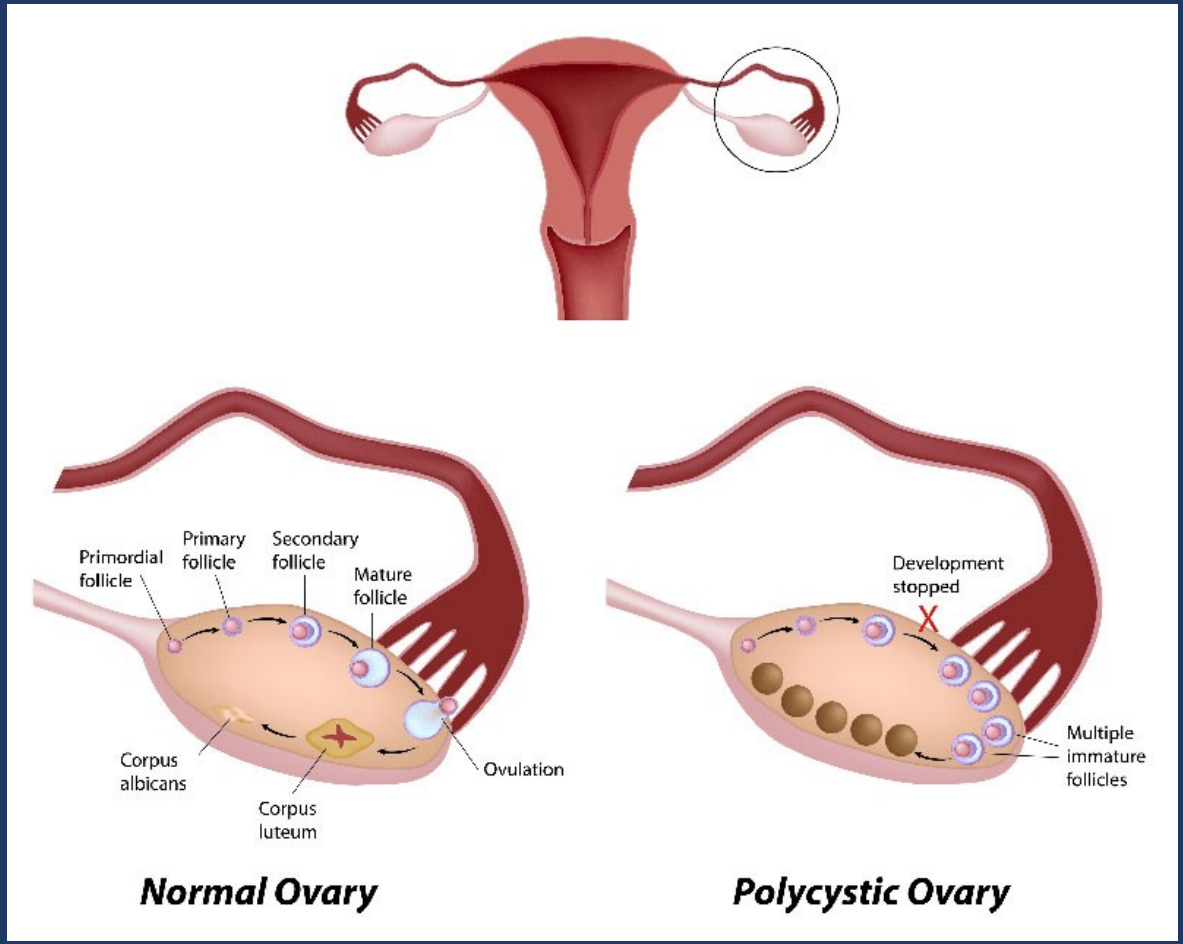


# Morning after pill

- **Two common types of morning-after pills are levonorgestrel (Plan B One-Step) and ulipristal acetate (ella)**
- The morning-after pill **contains synthetic hormones or hormone-like substances that mimic the hormones involved in the menstrual cycle.**
- **These hormones primarily include progestin (levonorgestrel) or a selective progesterone receptor modulator (ulipristal acetate).**
- **One of the primary mechanisms of action is to prevent or delay ovulation (the release of an egg from the ovary).**
- The hormones in the pill can interfere with the hormonal signals responsible for triggering ovulation.
- **The morning-after pill may also affect the cervical mucus, making it thicker and less receptive to sperm penetration.**
- **This change in cervical mucus can hinder sperm movement through the reproductive tract, reducing the chances of fertilization.**

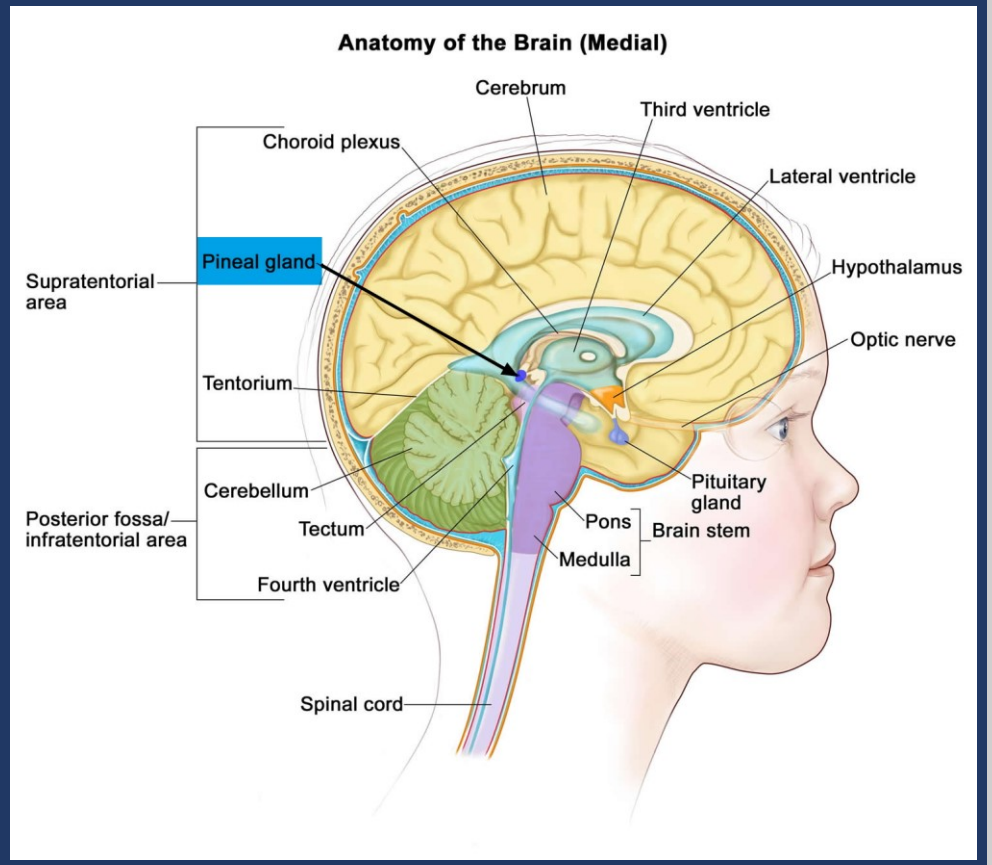
# Polycystic Ovarian Syndrome

- **Polycystic ovarian syndrome (PCOS) is a syndrome characterized by elevated androgens, polycystic ovaries, and anovulation.** Patients with PCOS often present with **hirsutism, obesity, insulin resistance, menstrual irregularity, and infertility.**
- In PCOS, the LH:FSH ratio is skewed due to **persistently rapid GnRH pulses.** These GnRH pulses lead to an increased LH: FSH ratio.
- This skewed ratio leads to the theca cells of **the ovaries producing excess androgen** while the granulosa cells do not produce enough aromatase to convert the androgens to estradiol.



# Pineal Gland

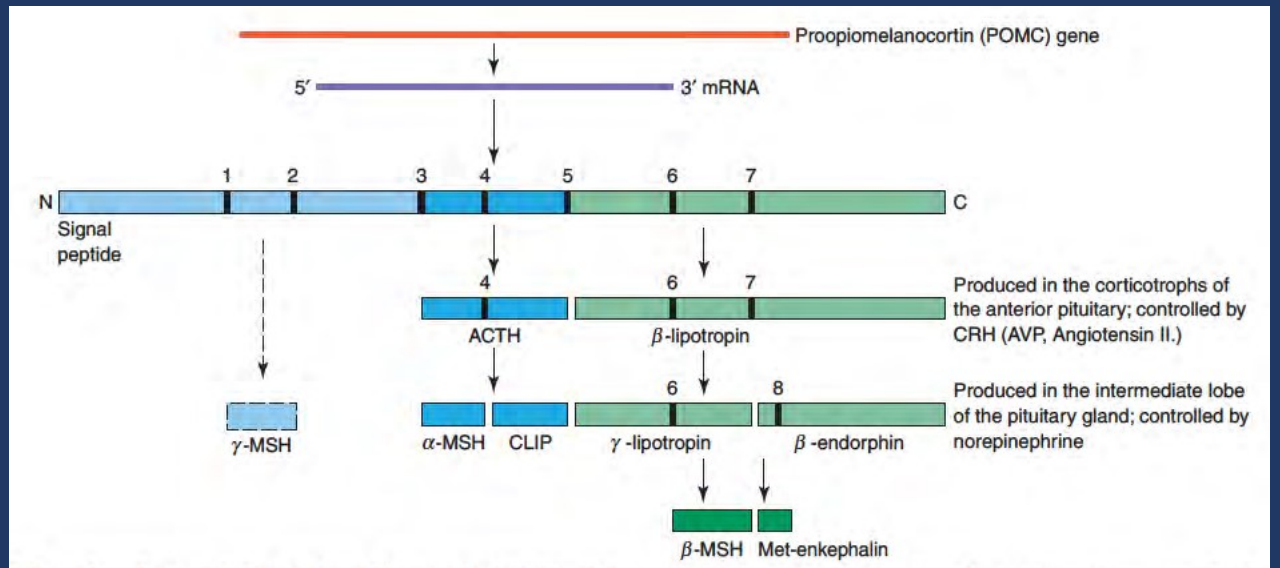





- 'The seat of the soul', 'the pineal body', 'third eye,' or the epiphysis cerebri/ Located at the roof of the posterior portion of the third ventricle.
- **No direct neural connections with the brain except for sympathetic innervation via the superior cervical ganglion. The pineal gland secretes melatonin and releases melatonin into the general circulation and into the cerebrospinal fluid**.
- The pineal also contains other bioactive peptides and amines including TRH, somatostatin, GnRH, and norepinephrine.
- **The physiologic roles of the pineal appear to involve regulation of gonadal function and development and chronobiologic rhythms**
- **Pineal gland is also directly photosensitive. This sensitivity promotes and demotes the synthesis of melatonin.**

# Melatonin

- **Relatively small doses of melatonin can induce sleep and basically reset the daily rhythm.**
- This physiological response could benefit workers whose shifts alternate between daylight and nighttime hours.
- **Melatonin is also a potent antioxidant and may provide some protection against damaging oxygen free radicals.**
- Although melatonin inhibits reproductive functions in animals that breed during specific seasons, there is no proof that it influences human reproductive functions.



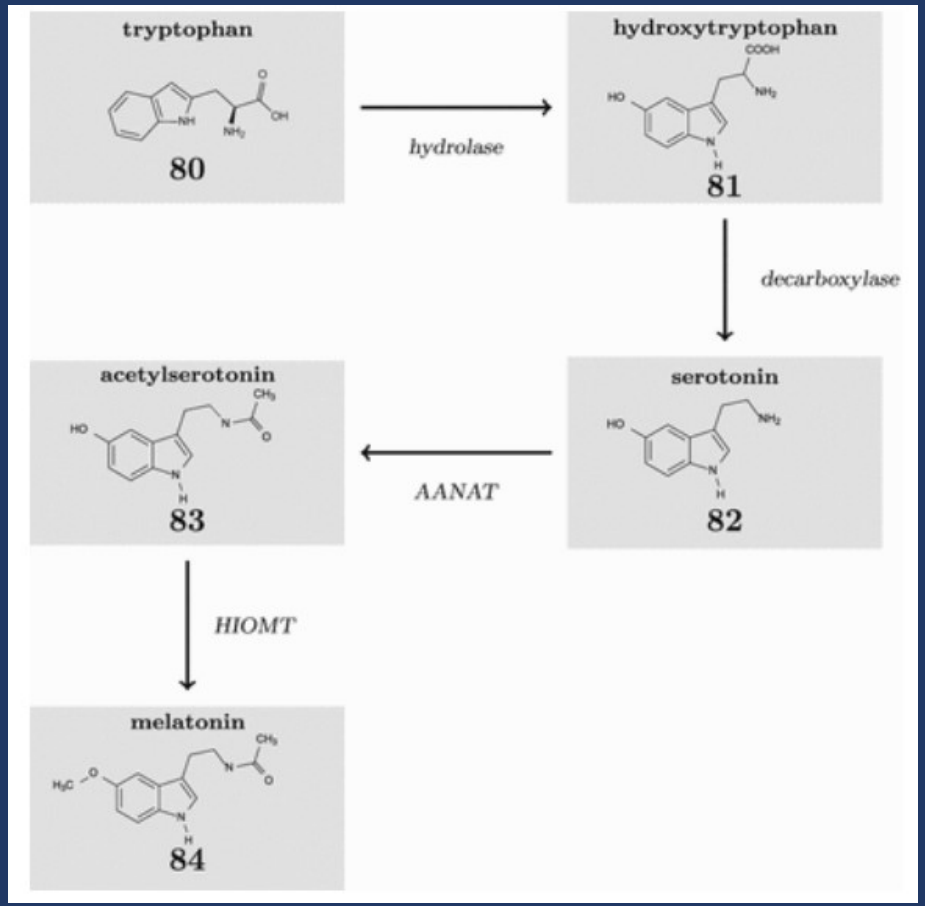

**Proopiomelanocortin is a polypeptide encoded by one gene.**

# Melatonin

- Melatonin secretion is regulated by the sympathetic nervous system and is increased in response to hypoglycemia and darkness.
- Melatonin is responsible for initiating and maintaining the sleep-wake cycle, better known as the circadian rhythm. The light-dark control acts by way of the suprachiasmatic nuclei.
- Its biosynthetic intermediate serotonin is an important neurotransmitter in the central nervous system.
- Melatonin biosynthesis is controlled by the suprachiasmatic nucleus (SCN)

Formation of melatonin occurs in a light–dark cycle: in the dark, tenfold more melatonin is released than in brightness.

## A REGULATOR OF SLEEP



# Circadian Rhythm

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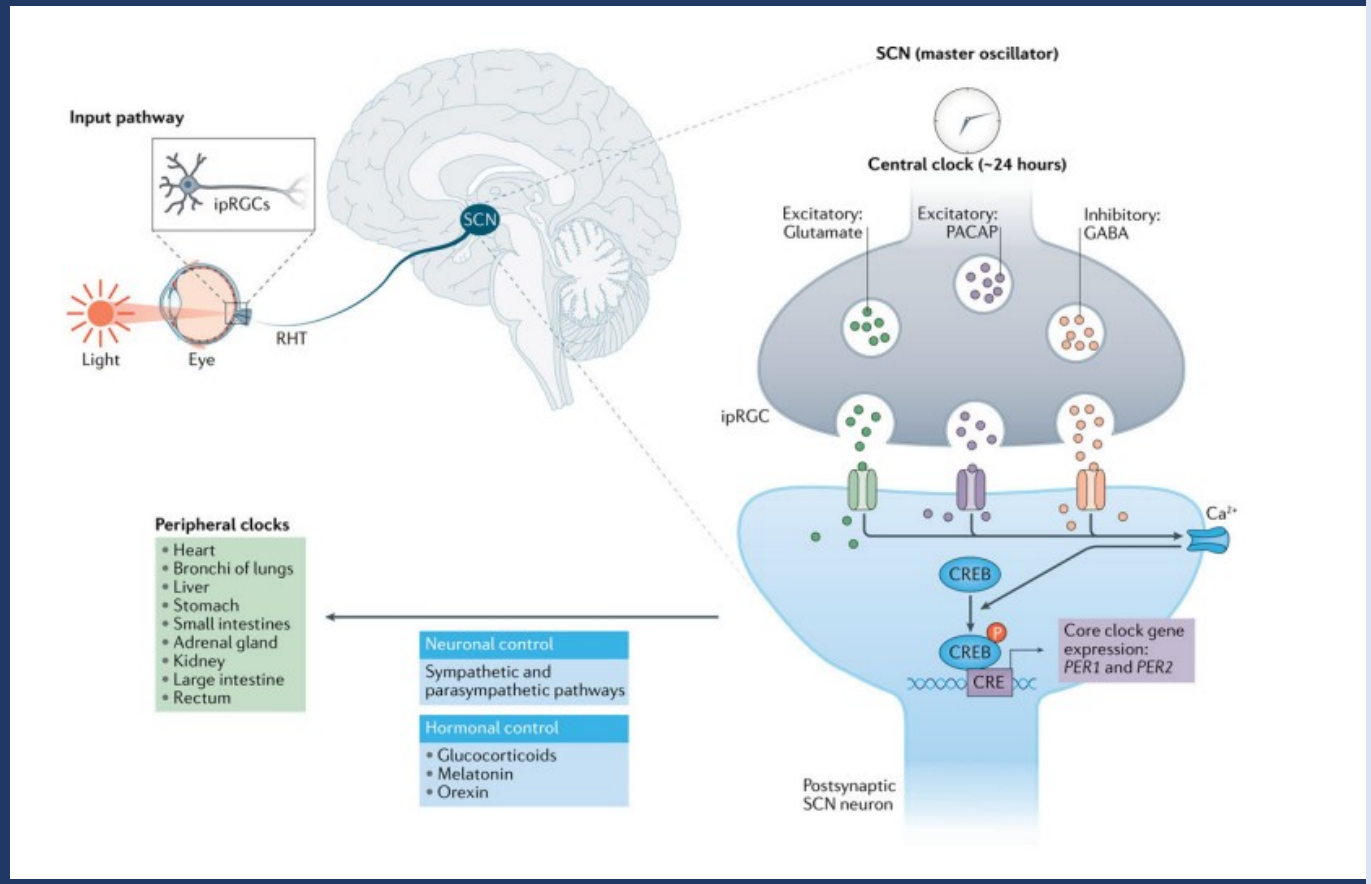
A circadian system consists of three components: inputs, the oscillator and outputs. **This basic design principle operates at two levels, systemic and cellular.**

Light is a major input signal for the circadian system and resets the master pacemaker, the SCN

**morning peak of myocardial infarction and stroke (due to rapid rise of blood pressure)**
**night-time exacerbation of asthma and other inflammatory diseases**

**SCN**

- Coordinates other brain areas and peripheral tissues throughout the body by neural and hormonal signals.
- Regulates the circadian secretion of diffusible endocrine signals via HPA axis:, such as melatonin from the pineal gland, and glucocorticoids and catecholamines from the adrenal cortex



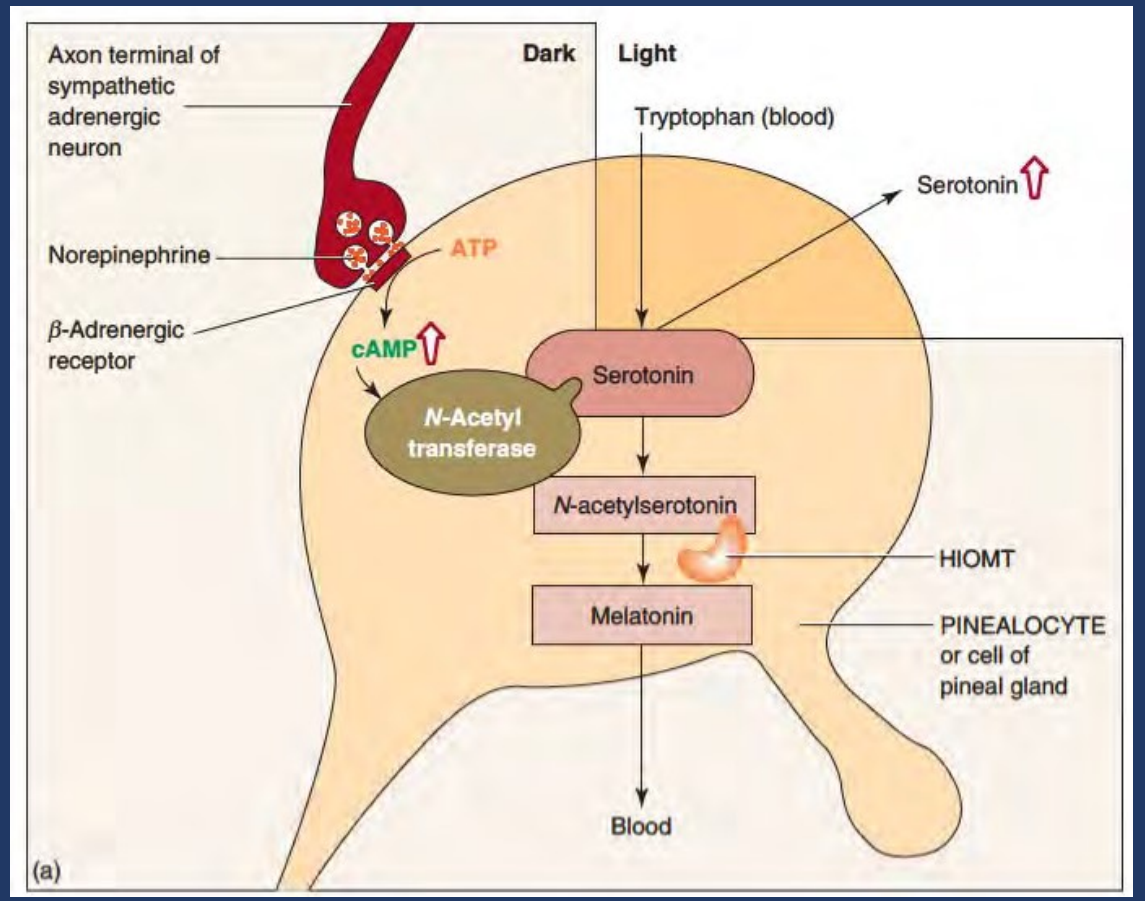

**Phase dissociation**
Jet Lag

**Disrupted Circadian rhythms**
Ageing
neurodegenerative diseases
metabolic disease

Ruan W, Yuan X, Eltzschig HK. Circadian rhythm as a therapeutic target. Nat Rev Drug Discov. 2021 Apr;20(4):287-307. doi: 10.1038/s41573-020-00109-w. Epub 2021 Feb 15. PMID: 33589815; PMCID: PMC8525418.

# Melatonin and Serotonin Synthesis Are Controlled by Light/Dark Cycles

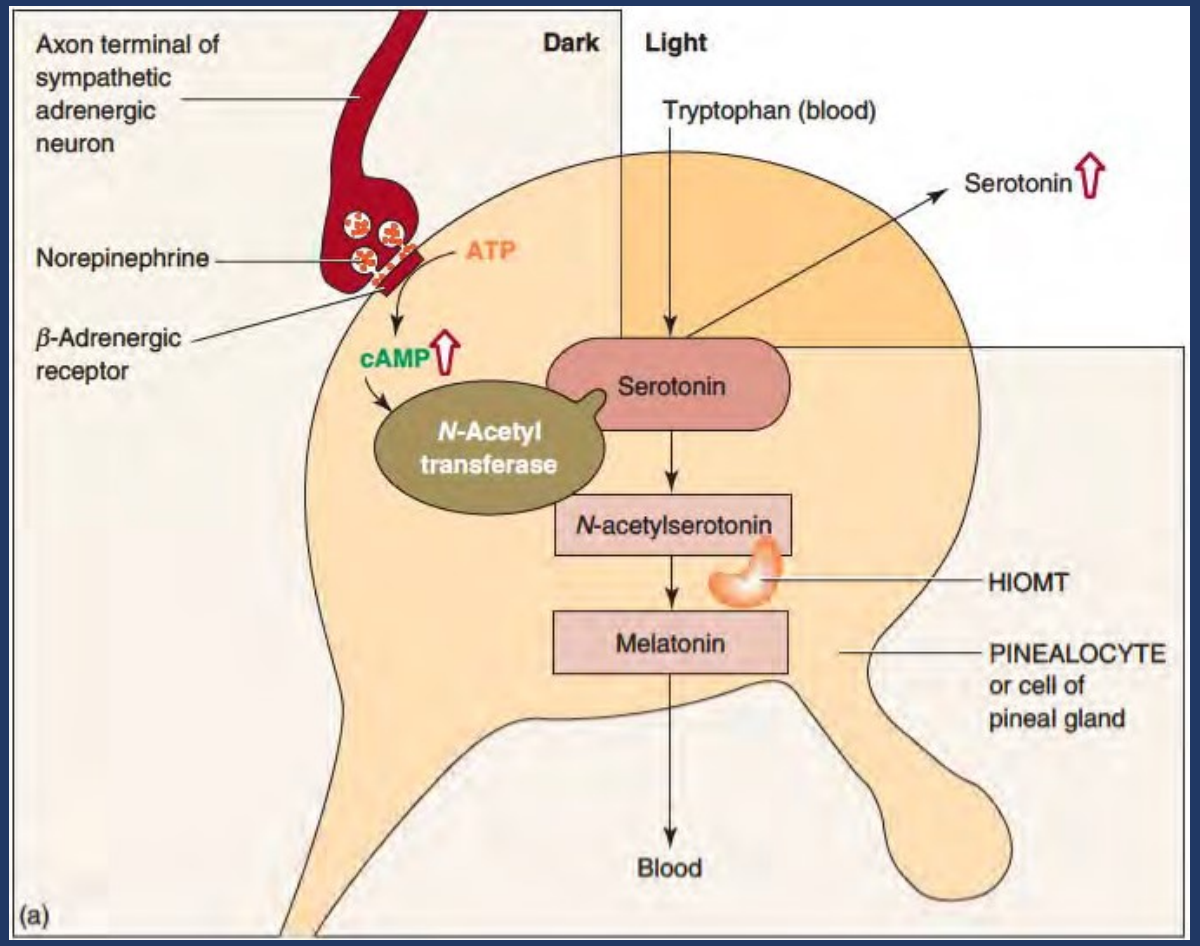
- **In the release of melatonin from the pineal gland the internal signal is provided by norepinephrine released by an adrenergic neuron .**
- Control is exerted by light entering the eyes, which inhibits the pineal gland and hence the release of melatonin.
- **Norepinephrine released in the dark stimulates cAMP formation through a β receptor in the pinealocyte membrane .**
- Increased activity of PKA enhances synthesis of N-acetyltransferase and **conversion of serotonin , synthesized from tryptophan, to N-acetylserotonin, and this is the rate-limiting step that dictates the circadian rhythm of melatonin.**
- Hydroxyindole- 0-methyltransferase (HIOMT) then converts **N-acetylserotonin to melatonin which is secreted during the dark hours**.



# Cyclic Hormonal Systems

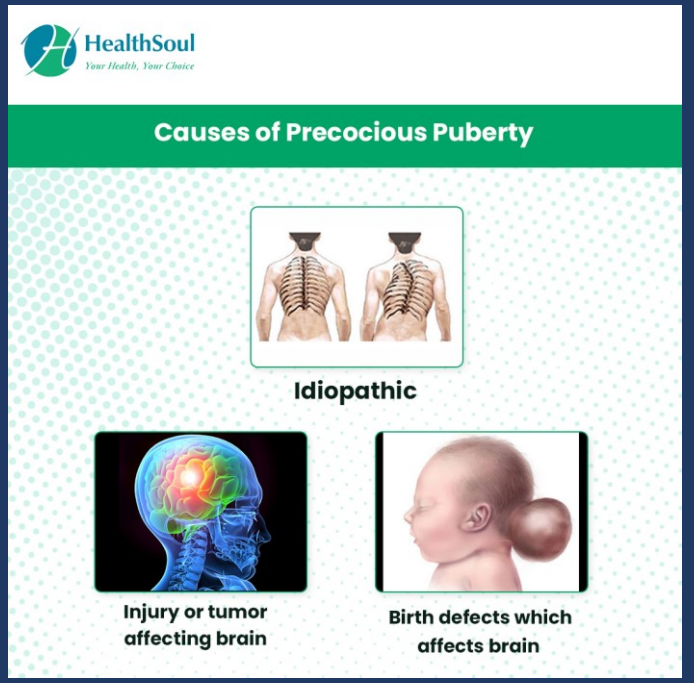


- **The diurnal variation in the secretion of cortisol from the adrenal cortex is regulated by the sleep/wake transition**
- Secretion of melatonin from the pineal gland is dictated by daylight and darkness.
- **The female ovarian cycle also operates on a cyclic basis dictated by the central nervous system.**
- **Example of chronotropic control of hormone secretion.**

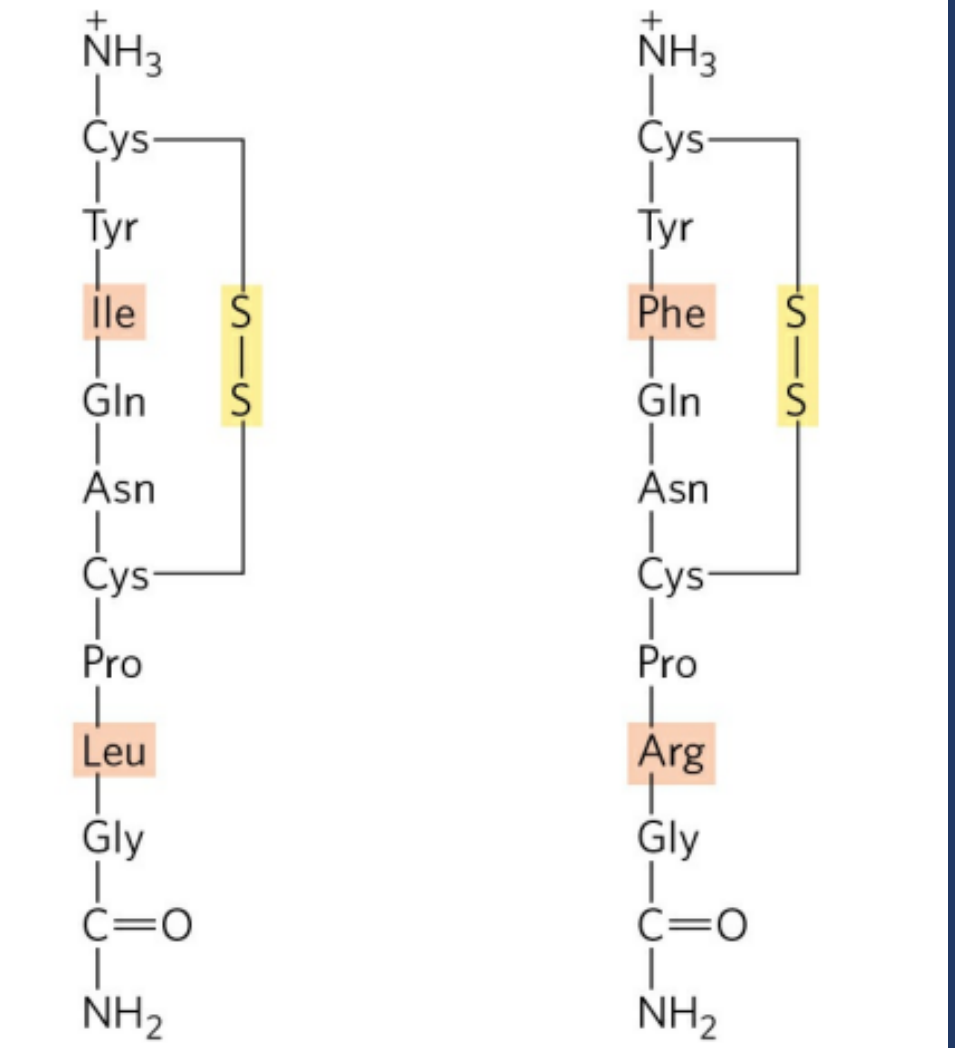


# Precocious Puberty

- **Children with brain tumors or other hypothalamic lesions**
- **Sexual maturation occurs at a very early age due to premature secretion of large amounts of GnRH.**
- **In young boys the testes usually enlarge under gonadotropin stimulation before any other signs of puberty are seen.**
- **In young girls an increased growth rate, breast development, an increase in the size of ovaries and uterus, and changes in the vaginal mucosa along with a rise in estrogen synthesis and secretion: increased growth hormone secretion.**
- Spermatogenesis in males and ovulation in females may occur, and fertility is certainly possible.
- Drugs: Medroxyprogesterone inhibits gonadotropin secretion and also functions as a competitive inhibitor of a specific enzyme involved in steroidogenesis.



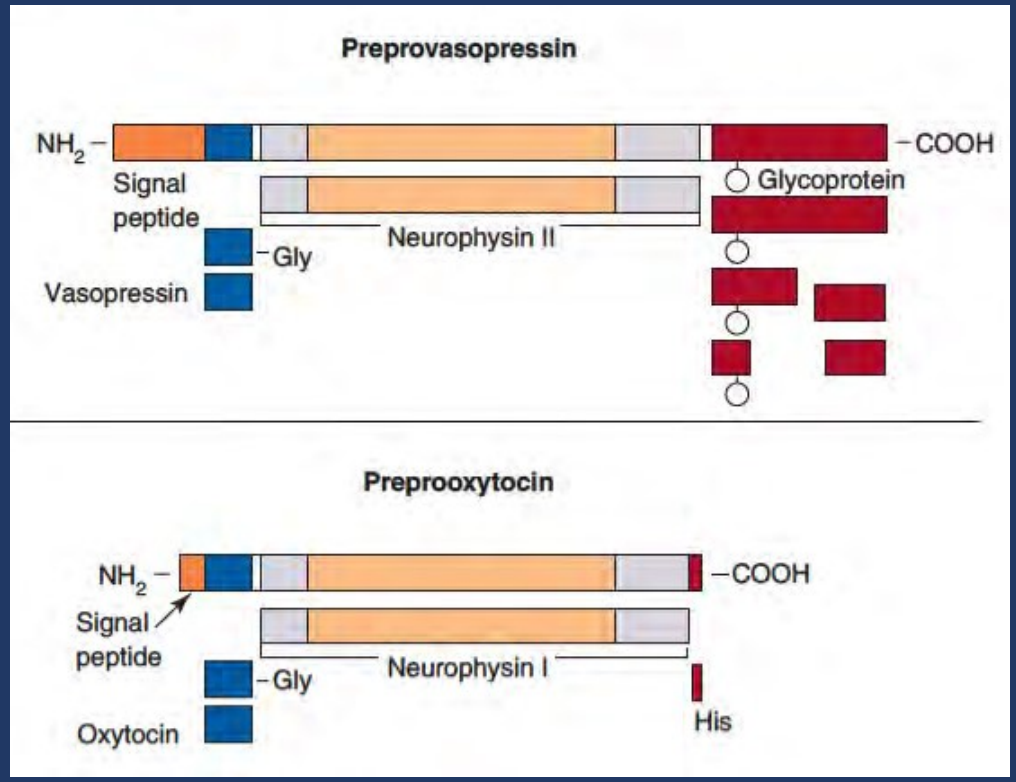
# Posterior pituitary gland- OXYTOCIN- VASOPRESSIN



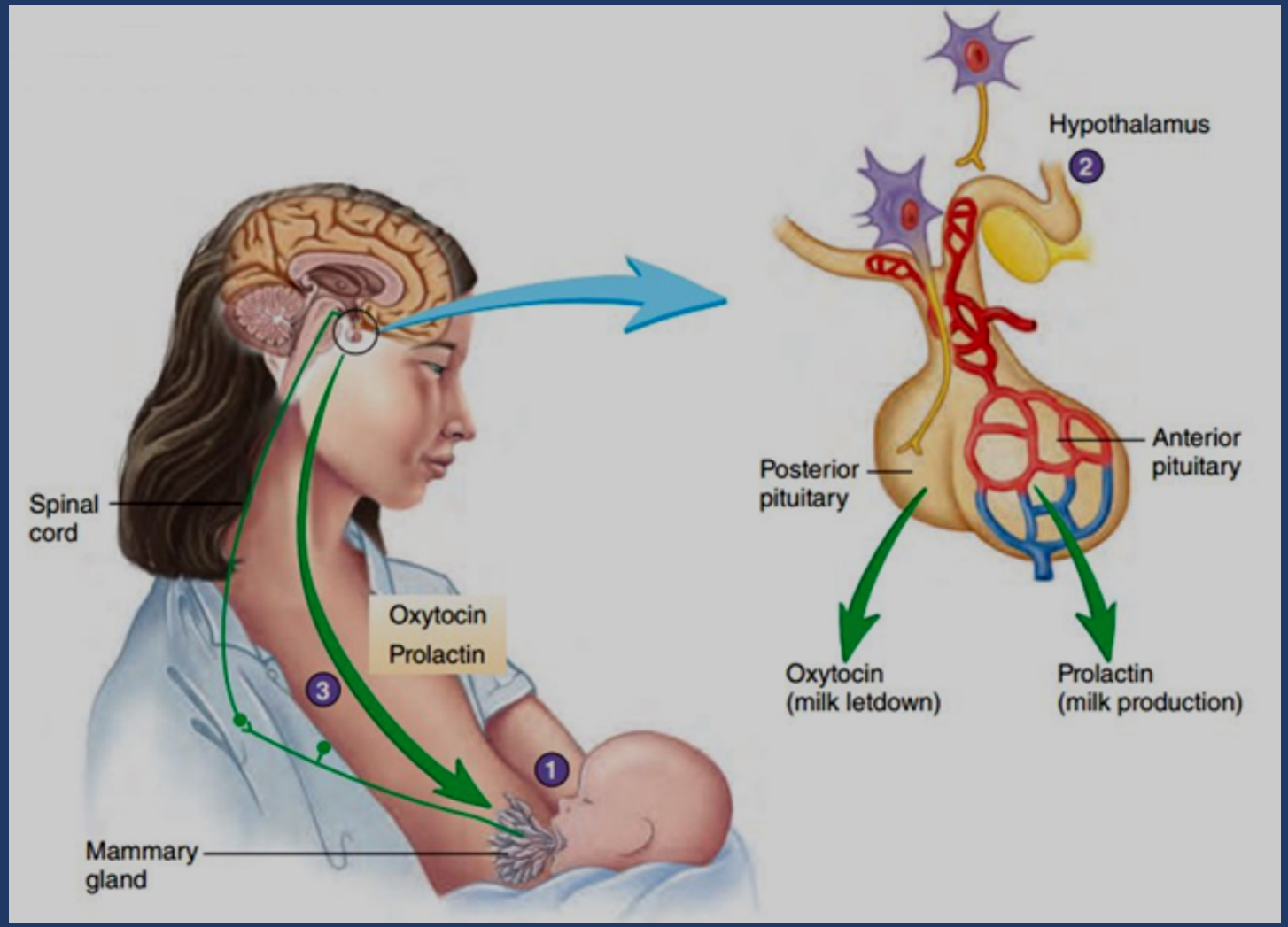

- The carboxyl-terminal residue of both peptides is glycinamide, -NH-CH2-
- These two hormones, identical in all but two residues (shaded light red), have very different biological effects.

# Genes for polypeptide hormones: more than one hormone can be encoded in a gene

- **As seen in protein hormones both antidiuretic hormone (ADH , vasopressin) and oxytocin are synthesized as preprohormones.**
- The prohormones that are generated contain **segments called neurophysin**, which are **cleaved during transport to the posterior pituitary.**
- When secretion occurs equal amounts of the hormone and its neurophysin enter the circulation. These neurophysin have no known physiological function.

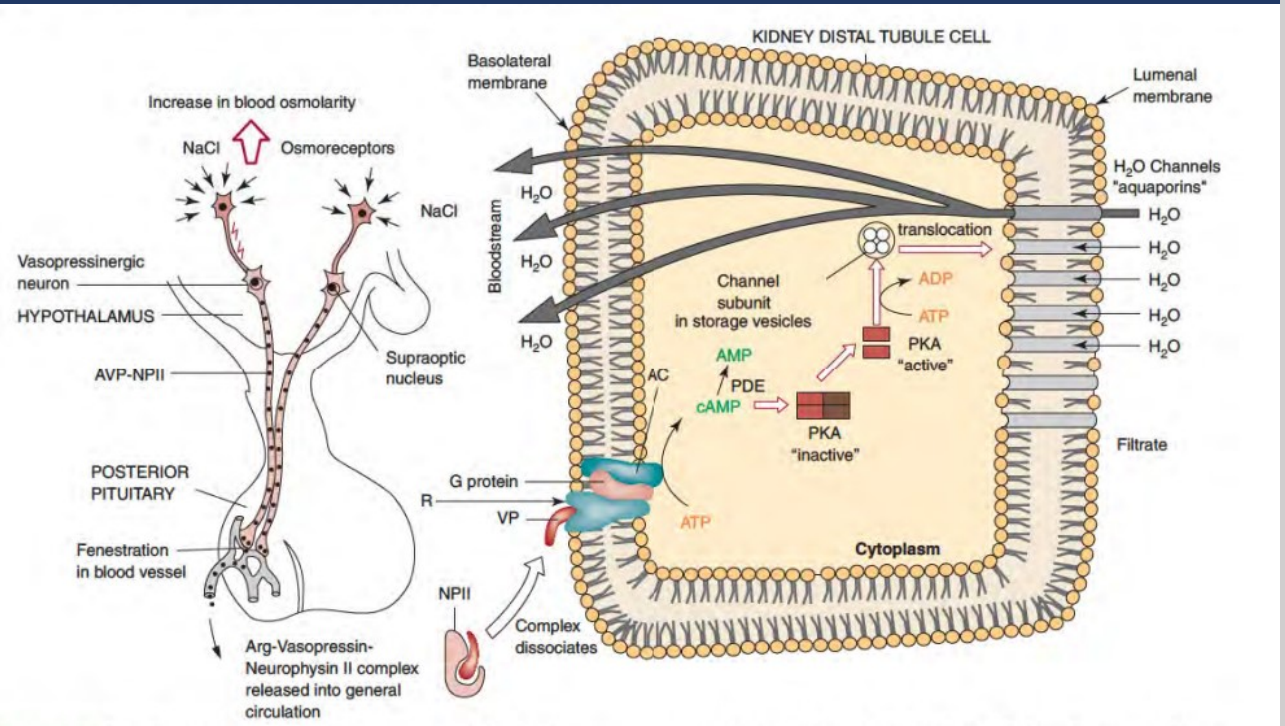


# Lactation Hormones




- Prolactin and Oxytocin
- Oxytocin is released by the suckling response in lactating females or as part of a conditioned reflex, such as a mother hearing her infant cry.
- Oxytocin is well known for its milk "let-down" action in the lactating female.
- Oxytocin acts on the smooth muscle of the uterus and mammary glands, causing uterine contractions during labor and promoting milk release during lactation.

**Vasopressin (also called antidiuretic hormone ADH) increases water reabsorption in the kidney and promotes the constriction of blood vessels, thereby increasing blood pressure**




1. Release of arginine vasopressin : triggered by osmoreceptors or baroreceptors.
2. This signal is transmitted down a vasopressinergic neuron and promotes the release of a VP-neurophysin complex from the posterior pituitary gland
3. The neurophysin bound to the VP eventually dissociates the posterior pituitary hormone binds to cognate membrane receptors on the kidney distal tubule cell.
4. Through this G protein-coupled receptor, adenylate cyclase is stimulated to increase levels of cAMP from ATP.
5. Cyclic-AMP-dependent protein kinase A is then activated and it phosphorylates various proteins including subunits of the aquaporin channels.
6. The phosphorylated subunits aggregate and functional water channels (aquaporins) are inserted in the lumenal plasma membrane, thus increasing the reabsorption of water

# LEARNING OBJECTIVES



- What is the difference between peptide and steroid hormones in terms of signaling.
- Define hypothalamus, pituitary gland and pineal gland.
- Define the hormones of the hypothalamus and the pituitary gland.
- What is the molecular mechanism of action of hypothalamic-pituitary hormone? Describe the HPA axis.
- Explain hypopituitarism.
- Which pituitary hormones are glycoproteins and what is their structure?
- What is the role of the growth hormone? What do you know about IGF-1?

- Explain acromegaly.
- What are lactation hormones? Where are they produced and what are their actions? Explain prolactin's role.
- Which hormones play an important role in spermatogenesis?
- Explain prolactinoma.
- Describe the cellular mechanisms for T3 and T4 release into bloodstream.
- How FSH/LH secretion is regulated in women and in men?
- On which hormones does the ovarian cycle depend?
- Where is progesterone produced and what are its effects?
- Explain oral contraception and the polycystic ovarian syndrome.
- Where is melatonin biosynthesized and produced? Explain its functions.
- Explain circadian rhythm
- Explain precocious puberty.

# SUGGESTED BIBLIOGRAPHY

HELLENIC REPUBLIC
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**Williams "Textbook of Endocrinology"**

**Chapter 15**

**Devlin "Textbook of Biochemistry with clinical correlations"**

**Chapters 22.1-22.5**

**Greenspans "Basic and Clinical Endocrinology",**

**Chapter 4 material covered in lecture only**

**slides**

# SAMPLE QUESTIONS

# QUESTION 1

Hypothalamus is:

A. composed of different nuclei with distinct functions that synthesize different hormones in response to physiological changes
B. an organ
C. a gland
D. lies at the base of the skull in a portion of the sphenoid bone called the sella turcica

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# QUESTION 2

If the stalk between the hypothalamus and anterior pituitary is severed, the pituitary would fail to cause the ultimate release of all of the following hormones except

A. ACTH
B. Estradiol
C. Oxytocin
D. Testosterone
E. Thyroxine

# QUESTION 2

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A. ACTH

B. Estradiol

C. Oxytocin: C Oxytocin is released from the posterior pituitary. A, B, D, and E all require releasing hormones from the hypothalamus for the anterior pituitary to release them.

D. Testosterone

E. Thyroxine

# QUESTION 3

In hypopituitarism the ovarian cycle would be affected because

A. FSH and LH are synthesized in the anterior pituitary
B. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of FSH and LH
C. Inhibins would be secreted in much larger than normal amounts.
D. The corpus luteum would be maintained
E. GnRH would bind to receptors to activate protein kinase A

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# QUESTION 4

Autocrine hormones are

A. secreted by a cell that is also the target for that hormone (neighboring cells may also be targets).
B. produced in one tissue or gland and travel through the general circulation to reach distant target cells that express cognate receptors.
C. secreted by a cell and travel a relatively short distance to interact with cognate receptors on a neighboring cell.

# QUESTION 4

Autocrine hormones are

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C. secreted by a cell and travel a relatively short distance to interact with cognate receptors on a neighboring cell

# QUESTION 5

Release of Anterior Pituitary hormones is regulated by the hormones secreted from the hypothalamus. **Which of the following hormone is not released from the hypothalamus**?

A. Growth hormone-releasing hormone
B. Thyroid Stimulating hormone
C. Gonadotropin-releasing hormone
D. Corticotrophin-releasing hormone

# QUESTION 5

Release of Anterior Pituitary hormones is regulated by the hormones secreted from the hypothalamus. **Which of the following hormone is not released from the hypothalamus**?

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C. Gonadotropin-releasing hormone

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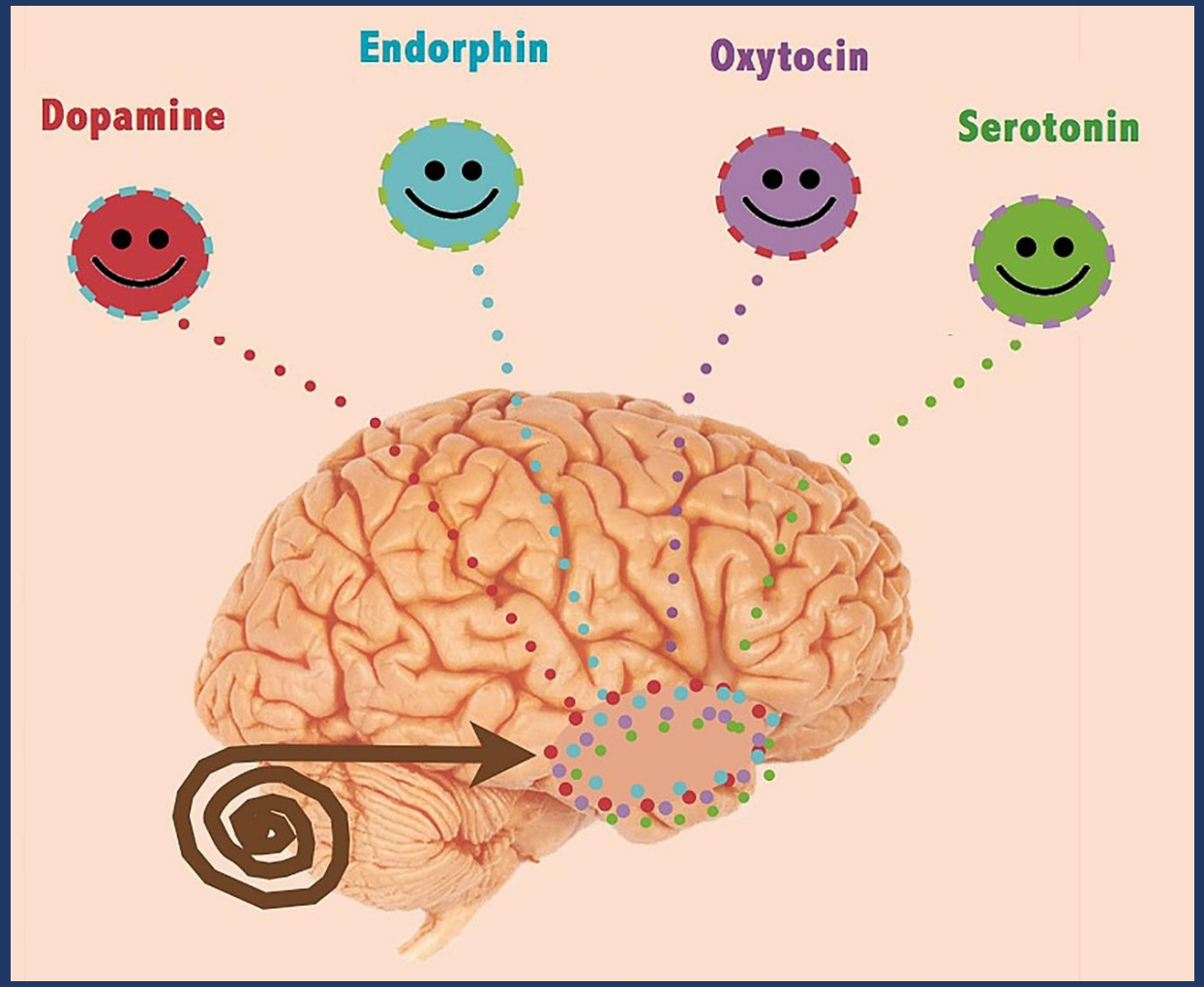


# THANK YOU!