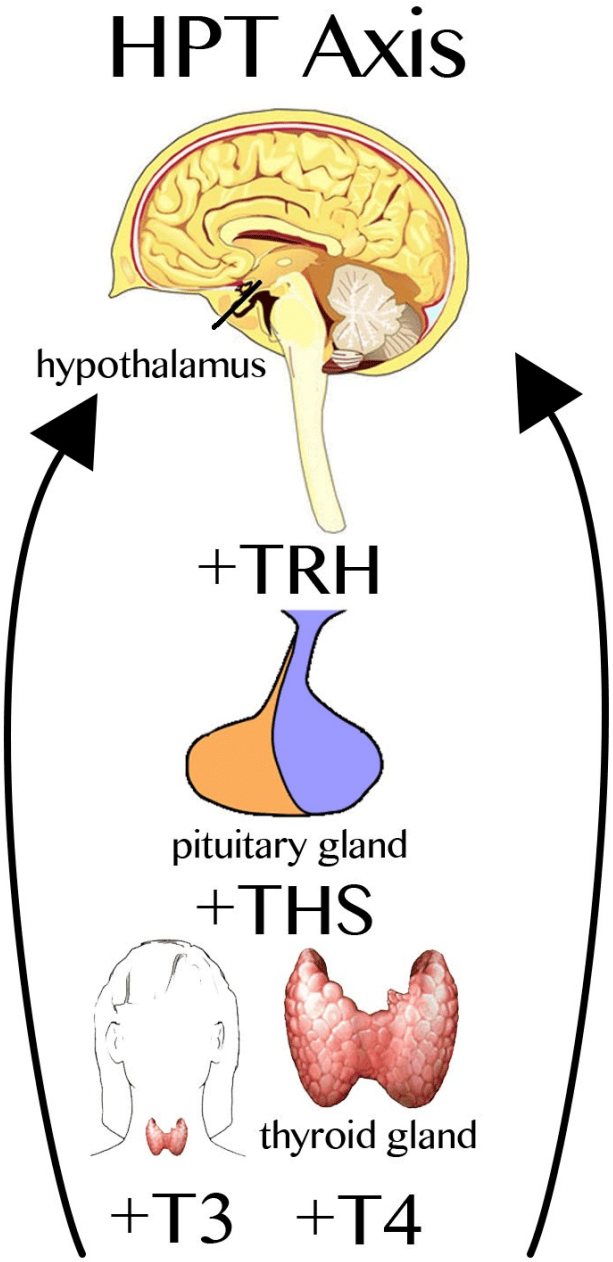
Pituitary and Thyroid

Dr. Qutaiba Ghanim

Department of Pharmacology
College of Medicine
University of Diyala



Hypothalamic and Anterior Pituitary Hormones

- The hormones of the **anterior pituitary** are regulated by *neuropeptides* that are called either ***releasing*** or ***inhibiting*** factors or hormones.

- These are produced in cell bodies in the hypothalamus, and they reach the cells of the pituitary by the **hypophysial portal system**.

- The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors. These are then processed posttranslationally to the hormones and are released into the circulation.

- Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary. The hypothalamic-releasing hormones are primarily used for **diagnostic purposes** (that is, to determine pituitary insufficiency).

- The hypothalamus also synthesizes the precursor proteins of the hormones ***vasopressin*** and ***oxytocin***, which are transported to the posterior pituitary, where they are stored until released.

- Hormones of the anterior and posterior pituitary are administered either ***intramuscularly (IM), subcutaneously, or intranasally***, but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

A. Adrenocorticotropic hormone (corticotropin)

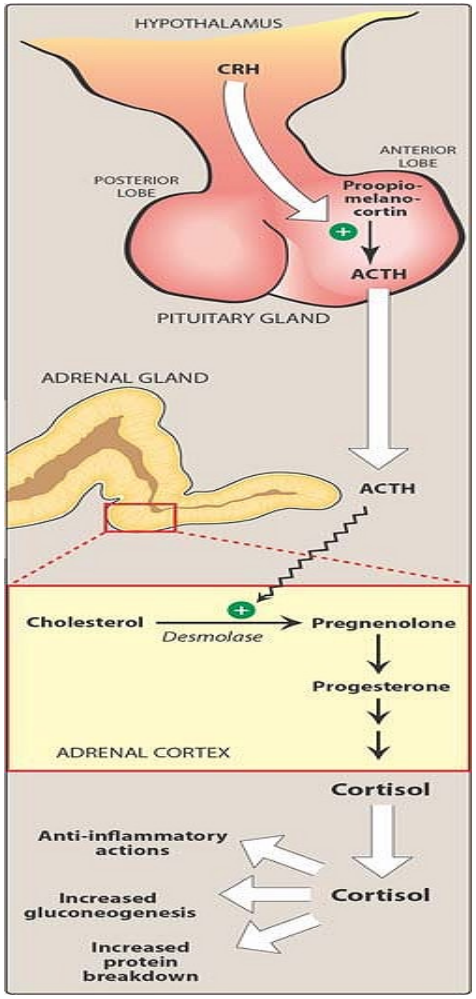
- ***Corticotropin-releasing hormone (CRH)*** is responsible for the synthesis and release of the peptide ***pro-opiomelanocortin*** by the pituitary.

- ***Adrenocorticotropic hormone (ACTH), or corticotropin*** is a product of the posttranslational processing of this precursor polypeptide. It is responsible for cortisol release.

- Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM and the lowest in the evening. Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release.

- CRH is used **diagnostically** to differentiate between Cushing's syndrome and ectopic ACTH-producing cells.

- Other products of proopiomelanocortin are **melanocyte stimulating hormone** and **lipotropin**, the latter being the precursor of the ***endorphins***.



- **Mechanism of action:**

  The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces. The occupied receptors activate G protein-coupled processes to increase cyclic adenosine monophosphate (cAMP), which in turn stimulates the rate-limiting step in the adreno-corticosteroid synthetic pathway (cholesterol to pregnenolone). This pathway ends with the synthesis and release of the ***adrenocorticosteroids*** and the ***adrenal androgens***.

- **Therapeutic uses:**

  Corticotropin is mainly used as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison's disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary).

- ***Cosyntropin*** is preferred for the diagnosis of adrenal insufficiency.

- ACTH is used in the treatment of infantile spasm (West Syndrome).

B. Growth hormone (somatotropin)

- ***Somatotropin*** is a large polypeptide that is released by the anterior pituitary in response to *growth hormone (GH) releasing hormone* produced by the hypothalamus. Secretion of GH is inhibited by another pituitary hormone, ***somatostatin***.

- GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass.

- Somatotropin influences a wide variety of biochemical processes:

1. Stimulation of protein synthetic processes.
2. Cell proliferation and bone growth are promoted.
3. Increased formation of hydroxyproline from proline boosts cartilage synthesis.

Mechanism of action:

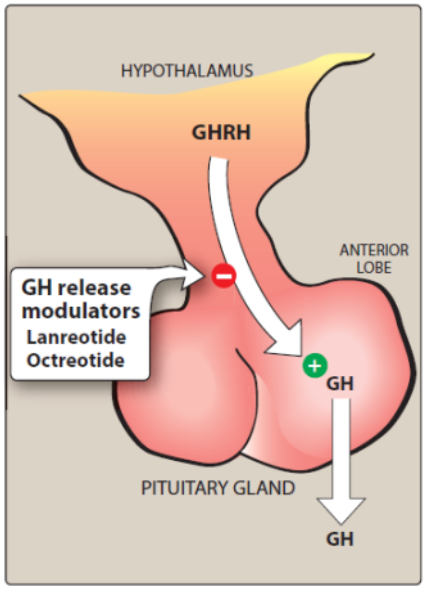
Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins-insulin-like growth factors I and II (IGF-I and IGF-II).

Therapeutic uses:

1. Treatment of GH deficiency in children.
2. Indicated for growth failure due to Prader-Willi syndrome,
3. Management of AIDS wasting syndrome
4. In adults with confirmed GH deficiency.

C. Growth hormone-inhibiting hormone (somatostatin)

- In the pituitary**,** ***Somatostatin*** binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release.



- Somatostatin not only inhibits the release of *GH* but, also, that of *insulin, glucagon, and gastrin*.

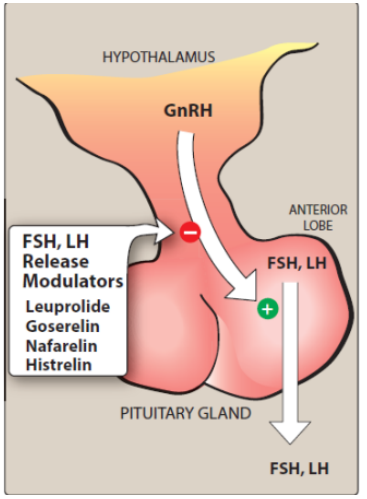
- ***Octreotide*** and ***lanreotide*** are synthetic analog of somatostatin with half-life that is longer than that of the natural compound, and depot forms are also available.

- **Therapeutic uses:**

1. Acromegaly.
2. In diarrhea and flushing associated with carcinoid tumors.

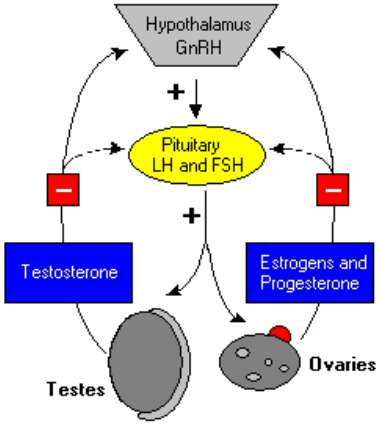
D. Gonadotropin-releasing hormone/luteinizing hormone-releasing hormone

- ***Gonadotropin-releasing hormone (GnRH),*** also called *gonadorelin*, is obtained from the hypothalamus.



- Pulsatile secretion of GnRH is essential for the release of ***follicle-stimulating hormone (FSH***) and ***luteinizing hormone (LH)*** from the pituitary (Both called gonadotropins)

- GnRH is employed to stimulate gonadal hormone production in hypogonadism, while continuous administration inhibits gonadotropin release.



- A number of synthetic analogs, such as ***leuprolide, goserelin, nafarelin, and histrelin***, are effective in suppressing the production of gonadotropins.

- These agents are effective in the treatment of prostatic cancer, endometriosis, and precocious puberty.

E. Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin

- They find use in the **treatment of infertility** in men and women.
- ***Menotropins*** (human menopausal gonadotropins, or hMG) are obtained from the urine of menopausal women and contain FSH and LH.
- ***Human Chorionic gonadotropin (hCG)*** is a placental hormone that is excreted in the urine of pregnant women. Along with choriogonadotropin alfa, hCG is essentially identical to LH.
- ***Urofollitropin*** is FSH obtained from menopausal women and is devoid of LH.
- ***Follitropin alfa and beta*** are human FSH manufactured by recombinant DNA technology.

- All of these hormones are injected IM or SC.

- Injection of hMG or FSH over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of hCG, ovulation occurs.

- In men who are lacking gonadotropins, treatment with hCG causes external sexual maturation, and with the subsequent injection of hMG, spermatogenesis occurs.

- Adverse effects include ovarian enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening.

- Multiple births are not uncommon.

F. Prolactin

- **Prolactin** is a peptide hormone that is secreted by the *anterior pituitary*.

- Its primary function is to:

1. Stimulate and maintain lactation.
2. It decreases sexual drive and reproductive function.

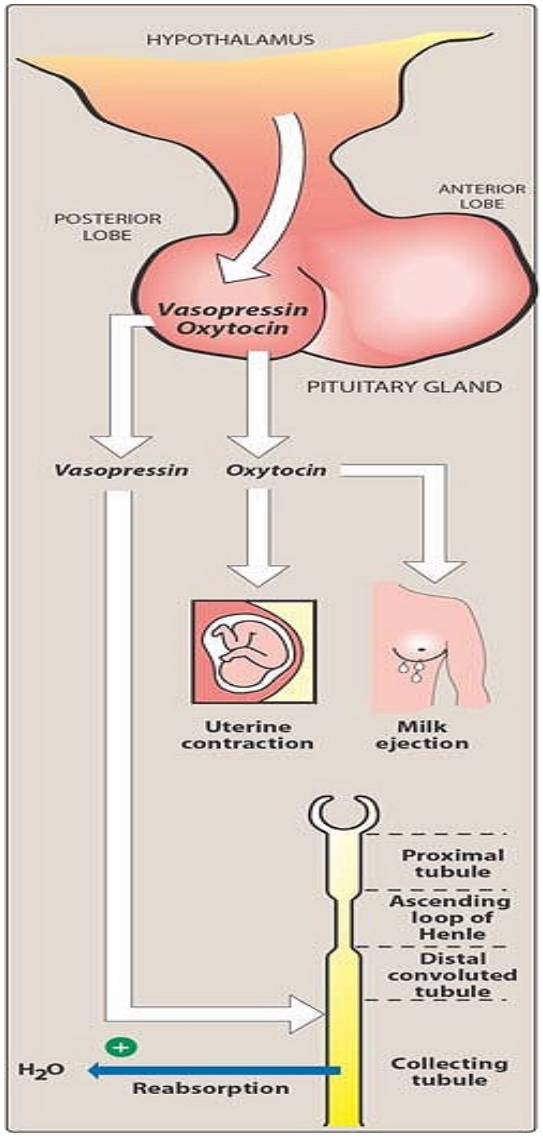
- Its secretion is inhibited by dopamine acting at D_2 receptors.

- Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D2 receptor agonists, such as bromocriptine and cabergoline.

III. Hormones of the Posterior Pituitary

- In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, ***Vasopressin*** and ***Oxytocin***, are not regulated by releasing hormones.

- They are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition.



A. Oxytocin

- Its only use is in obstetrics, where it is employed *to stimulate uterine contraction to induce or reinforce labor or to promote ejection of breast milk*.

- Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.

B. Vasopressin

- Vasopressin has both ***antidiuretic*** and ***vasopressor effects***.
- In the kidney, it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus.
- It is also used in controlling bleeding due to esophageal varices or colonic diverticula.
- ***Desmopressin*** has minimal activity at the V_1 receptor, *making it largely free of pressor effects*.
- This analog is now **preferred** for *diabetes insipidus and nocturnal enuresis.*
- It has longer-acting than vasopressin.
- Desmopressin is conveniently administered **orally and intranasally**. However, local irritation may occur.

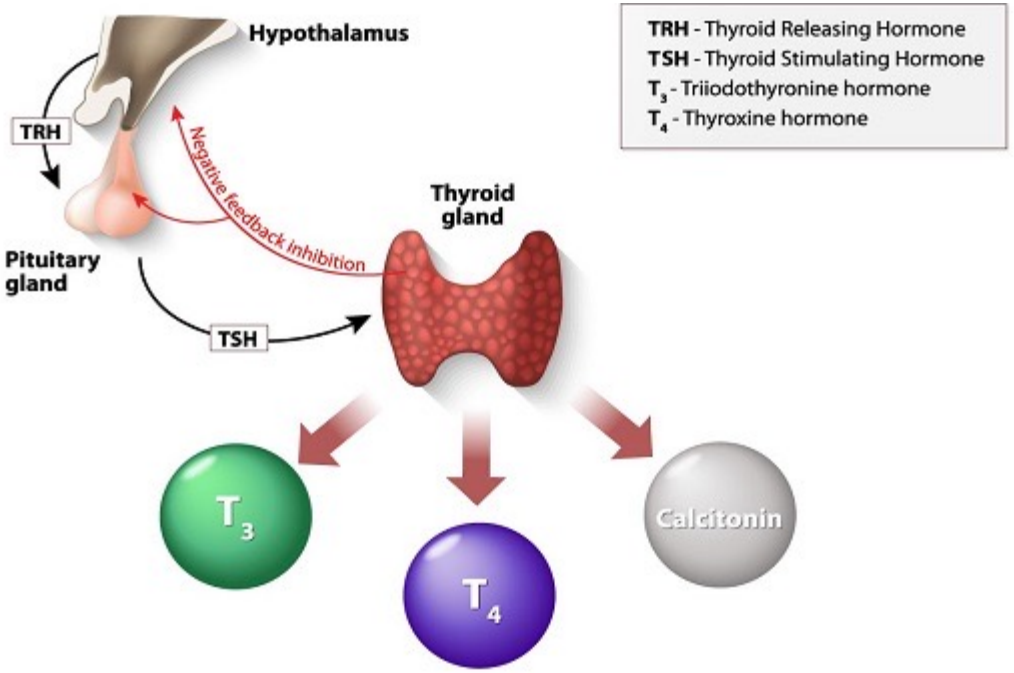
IV. Thyroid Hormones

- The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function.

- The two major thyroid hormones are triiodothyronine (T_3; the most active form) and thyroxine (T_4).

- Inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing (in children, this can cause mental retardation and dwarfism).

- Excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess heat production can occur.



- **<u>Regulation of synthesis:</u>**
- Thyroid function is controlled by *thyroid-stimulating hormone (TSH; thyrotropin)*.

- TSH is synthesized by the anterior pituitary. TSH generation is governed by the hypothalamic ***thyrotropin-releasing hormone (TRH)***.

D. Treatment of hypothyroidism

- Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase and is ***diagnosed by elevated TSH***.

- It is treated with ***levothyroxine (T_4)*** is preferred over T_3 (liothyronine) or T_3/T_4 combination products (liotrix) for the treatment of hypothyroidism.

- It is better tolerated than T3 preparations and has a longer half-life.

- Levothyroxine is dosed once daily, and steady state is achieved in 6 to 8 weeks.

- Toxicity is directly related to T4 levels and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss.

E. Treatment of hyperthyroidism (thyrotoxicosis)

- Graves disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism.

- In these situations, TSH levels are reduced due to negative feedback.

- The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of the hormones from the follicle.

1. Removal of part or all of the thyroid:

- This can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells.

- Most patients become hypothyroid as a result of this drug and require treatment with levothyroxine.

2. Inhibition of thyroid hormone synthesis:

- ***Propylthiouracil (PTU) and methimazole***, are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T_3 and T_4.

- PTU can also block the conversion of T_4 to T_3.

- They are well absorbed from the gastrointestinal tract, but they have short half-lives.

- Several doses of PTU are required per day, whereas a single dose of methimazole suffices due to the duration of its antithyroid effect.

- The effects of these drugs are slow in onset; thus, they are not effective in the treatment of thyroid storm. Relapse may occur.

Thyroid storm

- It presents with extreme symptoms of hyperthyroidism.

- B_2-Blockers that lack sympathomimetic activity, such as ***Metoprolol*** ***Propranolol***, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.

3. Blockade of hormone release:

- A pharmacologic dose of iodide inhibits the iodination of tyrosines (“ Acute Wolff-Chaikoff effect”), but this effect lasts only a few days.

- Iodide also inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood.

- It is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland.

- Iodide is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks.

- Iodide is administered orally.


Thank
you