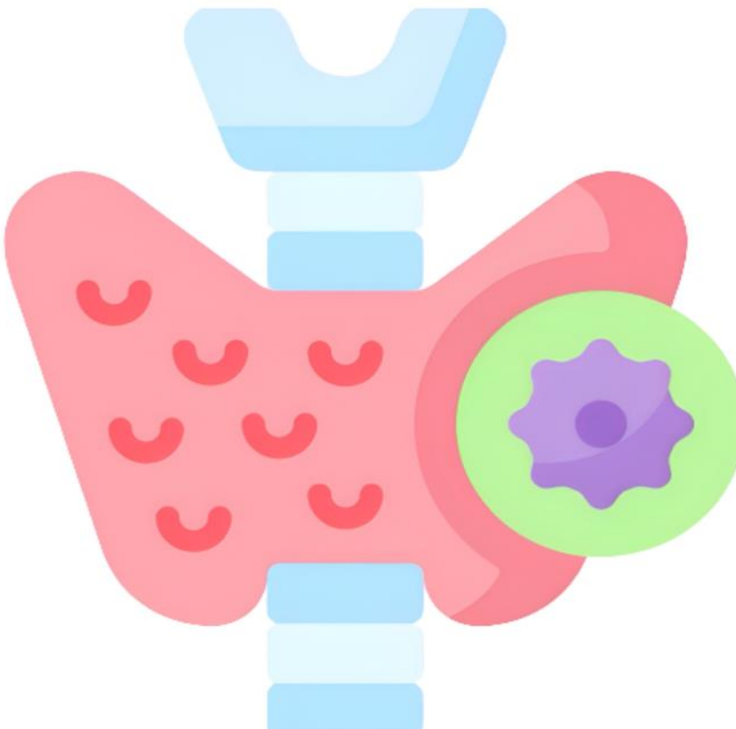
Endocrine system 2

physiology



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Mechanisms of hormone action and second messengers

Remember that hormones are either proteins, amino acid derivatives or steroids according to their chemical composition.

For a hormone to **function** it must first bind its **receptor** and then produce **2nd messengers**, so if a hormone does NOT bind to its own receptor or doesn't produce a 2nd messenger, it won't function.

1- Protein hormones

The mechanism of action for protein hormones is as the following:

①Hormone binds to receptor → ②production of 2nd messenger → ③Hormone Effect/Function

As we mentioned in the previous lecture hormones are mainly proteins that could be (glycoproteins, dipeptides, tripeptides, polypeptides...etc.)

Since proteins are large, water-soluble molecules they cannot penetrate the cell/nuclear membrane and thus, require cell **surface receptors** which are usually **G protein-coupled receptors (GPCR)**

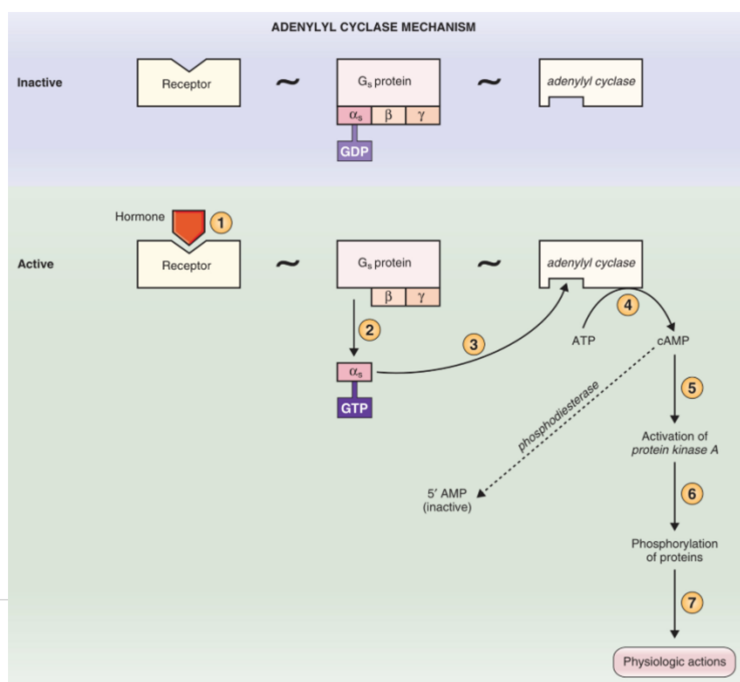
The G protein complex is present on the inner surface of the cell membrane and composed of 3 subunits: α, β, γ *(alpha is the active subunit, beta & gamma are regulatory subunits)*, this complex is inactive when GDP is bound to the alpha subunit.

When a hormone binds to its receptor, a conformational change takes place resulting in the exchange of GDP for GTP on the alpha subunit leading to its activation and dissociation from the beta & gamma subunits.

then the active α-subunit interacts and activates membrane-bound proteins like adenylyl cyclase that initiate intracellular signals by producing **2nd messengers**.

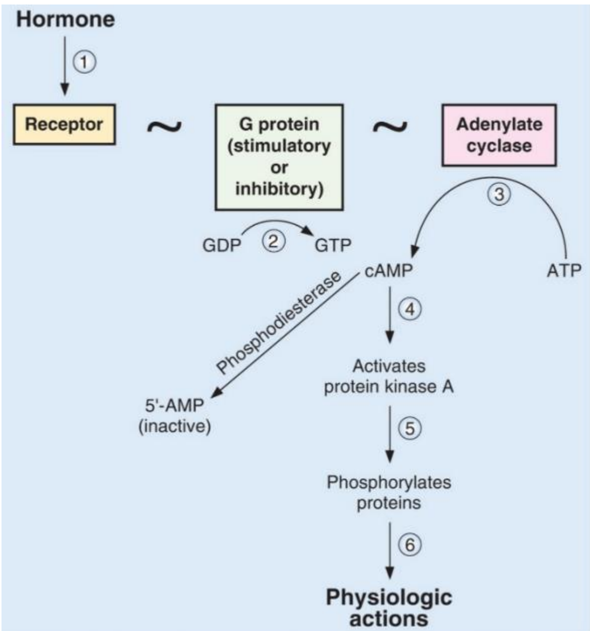
Adenylyl cyclase produces cAMP from ATP, **cAMP** is the 2nd messenger that will carry out the hormone's function.

cAMP then activates protein kinase A (**PKA**) that phosphorylates many proteins either activating or inactivating them resulting in cellular response.



> ***Note:*** *the hormone-receptor complex activates **several** G-proteins; each activating adenylyl cyclase to produce **many** cAMP molecules this is known as **amplification** of the signal. (its not a 1:1 relation but rather one complex activates more than a 100 G-protein and the activated α-subunit activates more than a 1000 adenylyl cyclase and to produce multiple cAMP molecules.*

→ cAMP levels are regulated by **phosphodiesterase** which converts it to **5'AMP,** thereby turning **off** the action of the 2nd messenger when its no longer needed.

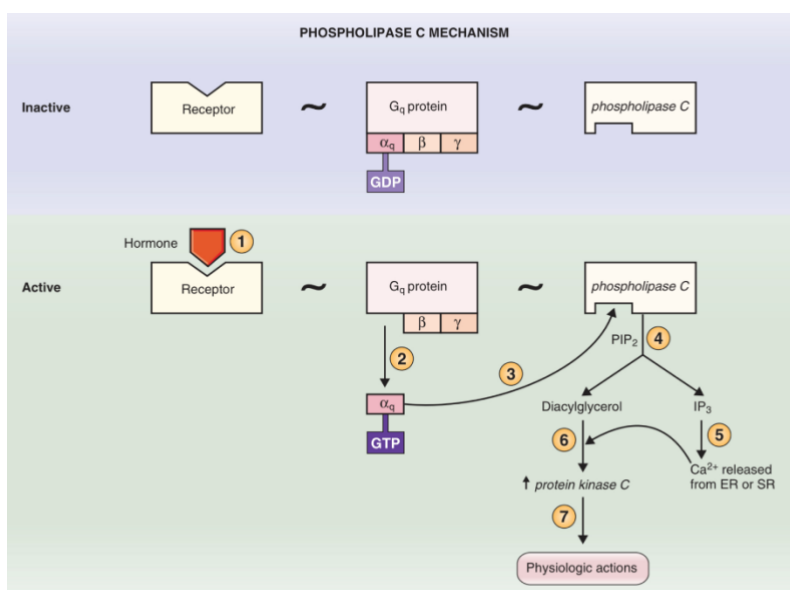


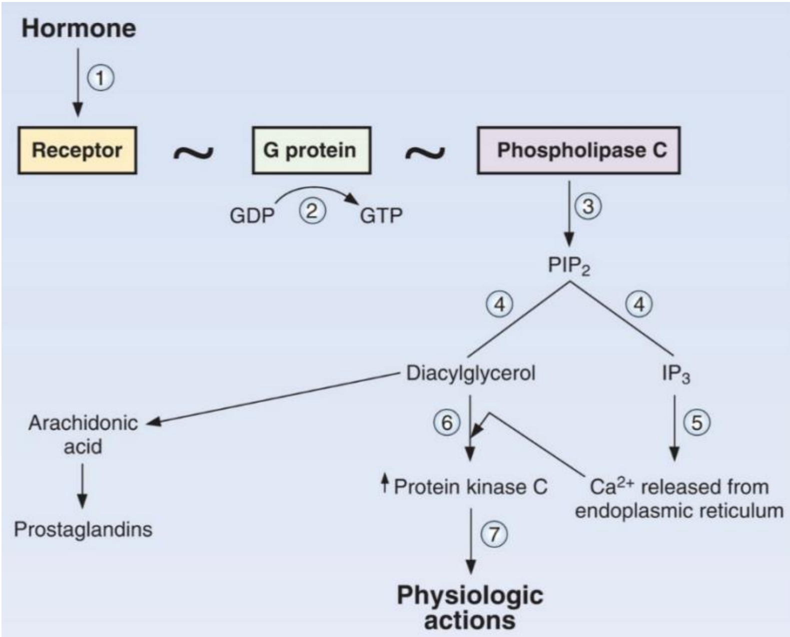
Protein Hormones that use Adenylyl Cyclase-cAMP 2nd messenger pathway

Adrenocorticotropic hormone (ACTH)	Human chorionic gonadotropin (HCG)
Angiotensin II (epithelial cells)	Luteinizing hormone (LH)
Calcitonin	Parathyroid hormone (PTH)
Catecholamines (β receptors)	Secretin
Corticotropin-releasing hormone (CRH)	Somatostatin
Follicle-stimulating hormone (FSH)	Thyroid-stimulating hormone (TSH)
Glucagon	Vasopressin (V2 receptor, epithelial cells)

Other protein hormones produce **two** 2nd messengers, the membrane-bound protein that gets activated by the α-subunit in this pathway is phospholipase C (**PLC**), when activated it produces **two** 2nd messengers: **DAG** and **IP3** from PIP2.

- **IP3 (inositol triphosphate)**
  releases **calcium** from the endoplasmic reticulum, this released calcium leads to the **cellular response**, thus calcium is a must for a specific hormone to function.
- **DAG (diacyl glycerol)** activates protein kinase C (PKC) which also needs calcium for its activation.
  This pathway has two 2nd messengers, with calcium being required to cause a cellular response.





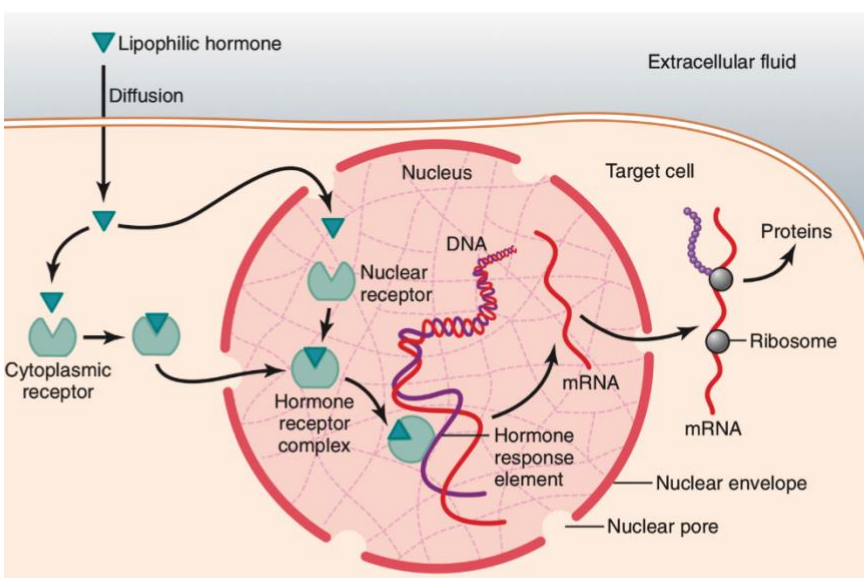
Protein Hormones that use the PLC 2nd messenger pathway

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Goadotropin-releasing hormone(GnRH)
Growth hormone-releasing hormone(GHRH)
Oxytocin
Thyrotropin releasing hormone(TRH)
Vasopressin (v1 receptor, vascular smooth muscle)

2- Amino acid derived hormones

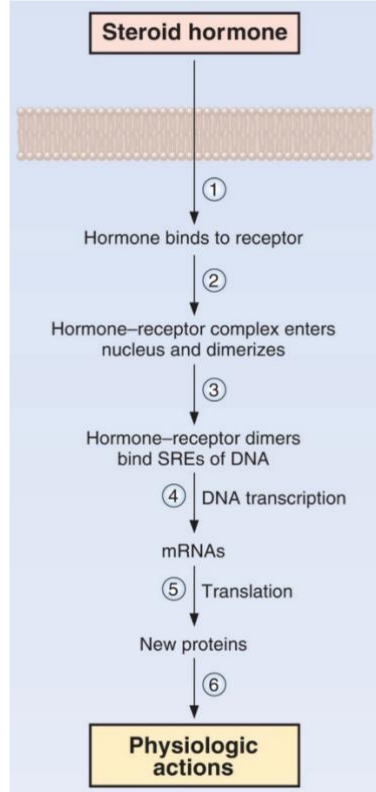
A. Catecholamines *(Epinephrine, norepinephrine, and dopamine)* have **cell surface receptors,** although they're small and made of only one amino acid (one tyrosine) they cannot penetrate the cell membrane.

B. Thyroid hormones *(lipophilic)* either have **intracellular** receptors that are then transported to the nucleus or **nuclear receptors** directly.
Thyroid hormones enter the cell by diffusion.



3- Steroid hormones

These hormones are **lipophilic** and can enter the membrane **passively** *(without ATP)* to bind with **cytoplasmic** receptors then nuclear receptors, or they just bind to nuclear receptors **directly**.



⇨ Binding of these hormones *(steroid hormones and thyroid hormones)* to their nuclear receptors leads to **increased or decreased** transcription of DNA to mRNA and protein synthesis, thus eliciting a response.

⇨ Remember from the previous lecture that steroid hormones are: male & female sex hormones, adrenal cortex hormone & vitamin D.

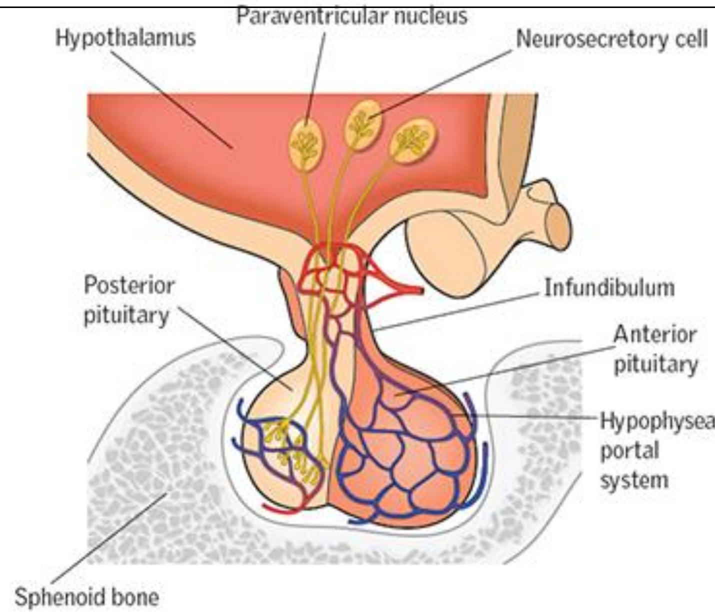
> ***Note:*** *Sometimes for **rapid action and quick response** sex hormones (especially female sex hormones: estrogens and progesterone) bind to receptors on the **cell membrane** rather than **intracellular** receptors.*

4- Other examples

Hormones that follow Tyrosine kinase mechanism, e.g. Insulin, and others following cGMP mechanism, e.g. NO and ANP receptors.

Table 9–3 Mechanisms of Hormone Action

Adenylyl Cyclase Mechanism (cAMP)	Phospholipase C Mechanism (IP_3/Ca^{2+})	Steroid Hormone Mechanism	Tyrosine Kinase Mechanism	Guanylate Cyclase Mechanism (cGMP)
ACTH	GnRH	Glucocorticoids	Insulin	Atrial natriuretic peptide (ANP)
LH	TRH	Estrogen	IGF-1	Nitric oxide (NO)
FSH	GHRH	Progesterone	Growth hormone	
TSH	Angiotensin II	Testosterone	Prolactin	
ADH (V_2 receptor)	ADH (V_1 receptor)	Aldosterone		
HCG	Oxytocin	1,25-Dihydroxycholecalciferol		
MSH	α_1 Receptors	Thyroid hormones		
CRH				
Calcitonin				
PTH				
Glucagon				
β_1 and β_2 receptors				



The Pituitary Gland

- It is a **small gland** *(less than 1g, less than 1cm in diameter)* that **controls** the secretion of many hormones.
  It is located in a cavity at the base of the brain called **Sella Turcica.**
- It's also called the **hypophysis gland**; physis = growth, hypophysis-cerebri = outgrowth under the brain.

The pituitary gland is composed of two lobes that are connected to the hypothalamus by hypophyseal stalk:

1- **Anterior pituitary (adenohypophysis)**
indirectly connected with the hypothalamus, is truly **glandular**.
It produces its **own** hormones and releases them into the circulation.

2- **Posterior pituitary (neurohypophysis)**
directly connected with the hypothalamus
neurons of the hypothalamus and extend down in the posterior pituitary gland.
the posterior pituitary contains nerve endings **storing** secretory granules filled with **hormones** that are synthesized & originate from the **cell bodies** of the **hypothalamus** neurons.

These two parts are different in their embryology, histology, and physiology.

The Posterior pituitary lobe

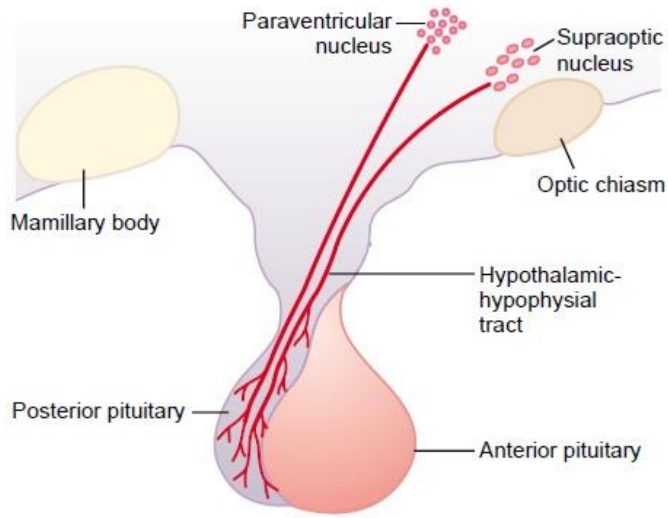
- It has a **direct** connection with the hypothalamus.
- **Neurons** (magnocellular neurons) **extend** from the **hypothalamus** down to the posterior pituitary gland; these neurons are called neuroendocrine glands that synthesize neuroendocrine hormones in their cell bodies, then the hormones are packed in secretory granules and transported down the axons to the nerve endings located in the posterior pituitary gland, they remain there and are released upon stimulation.

You can conclude that → The **function** of the **posterior pituitary** gland is to **store hormones** that are synthesized by the hypothalamus.
Remember neurohormones means → produced by nerve cell bodies.

Two types of nuclei present in the hypothalamus:

1- **The Paraventricular nucleus** mainly produces <u>**Oxytocin**</u> and a little bit of ADH.
2- **The Supraoptic nucleus** which produces <u>**ADH**</u> and a little bit of oxytocin.

Each nucleus secretes one of the two hormones mainly and a little bit of the other. there are similarities in the structure and function between these two hormones.



→ADH and Oxytocin are stored in the **posterior pituitary** and released into the blood in response to signals coming from the **hypothalamus**. This type of secretion is **neuroendocrine.**

The Posterior pituitary hormones: Oxytocin and ADH (vasopressin)

- ADH and Oxytocin are cyclic peptides due to a disulfide bond.
- Both are composed of **nine amino acids** having an amide group at the c-terminal end.

They differ from each other in just **two** amino acids:

NH3-Gly-Tyr- **X** -Gln-Asn-Cys-Pro- **Y** -Gly-N

In Oxytocin → X represents Ile // Y represents Leu

In ADH → X represents Phe // Y represents Arg

the doctor only mentioned in 2022 lecture that they are similar in function, and this is extra↑

They have a similar structure & also have <u>little</u> similarities in function:

1- Both increase **water reabsorption** in the kidneys, but ADH is 200 times more potent than Oxytocin, so ADH <u>mainly</u> increases water reabsorption with (200:1) potency

2- Both increase **milk ejection**, but Oxytocin is 100 times more potent.

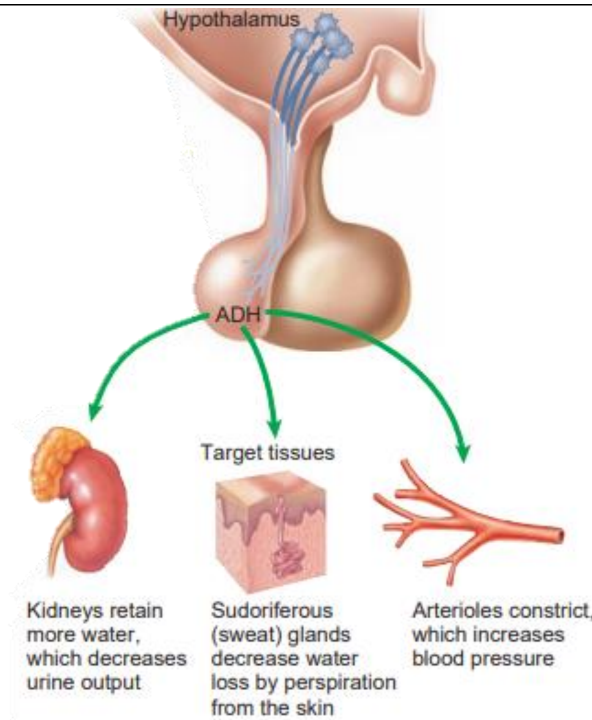
⇨ So, **Oxytocin** mainly increases **milk ejection** and induces **contraction** of the pregnant uterus.

Table 24.21 Relative potencies of oxytocin and vasopressin

Action	Oxytocin	Vasopressin
Antidiuretic potency	1	200
Milk ejection activity	100	1

The Antidiuretic hormone (ADH // Vasopressin)

- **ADH** is also called arginine **vasopressin**.
- It's a hormone **made** by the **hypothalamus** in the brain and **stored** in the **posterior pituitary gland** & secreted from there.



Functions

1- **Regulates serum osmolarity**: it normalizes the blood volume as well as body fluid volume by **increasing the reabsorption of water in the renal tubules.**

2- **Vasoconstriction** of the blood vessels.
(that's why its called vasopressin)
The **receptors** on the renal tubules are different from the receptors on blood vessels that ADH works on.
ADH → Decreases diuresis (production of urine) → binds to **V2** receptors in **distal tubules and collecting ducts of the kidney**.
Vasopressin → Constriction of blood vessels → binds to **V1** receptors in **blood vessels**.

Factors affecting ADH secretion

1. Stimulators of ADH

- **A.** Increased serum osmolarity.
- **B.** Decreased extracellular fluid (ECF) volume.
- **C.** Stress-related factors: nausea, pain, vomiting, nicotine, opiates (analgesic drugs like morphine), and hypoglycemia.
- **D.** Anti-neoplastic drugs.

2. Inhibitors of ADH

- A. Ethanol.
- B. α-Adrenergic Agonists.
- C. (ANP) Atrial natriuretic peptide—hormone secreted from the atria of the heart.
- D. Decreased serum osmolarity.

Anterior Pituitary lobe

- **Indirectly connected** with the Hypothalamus by the Hypothalamic-Hypophyseal **portal system**.
- It is embryonically derived from ***Rathke's pouch*** which is an embryonic invagination of the pharyngeal epithelium. This explains the **epithelioid nature** of its cells compared to the posterior lobe.

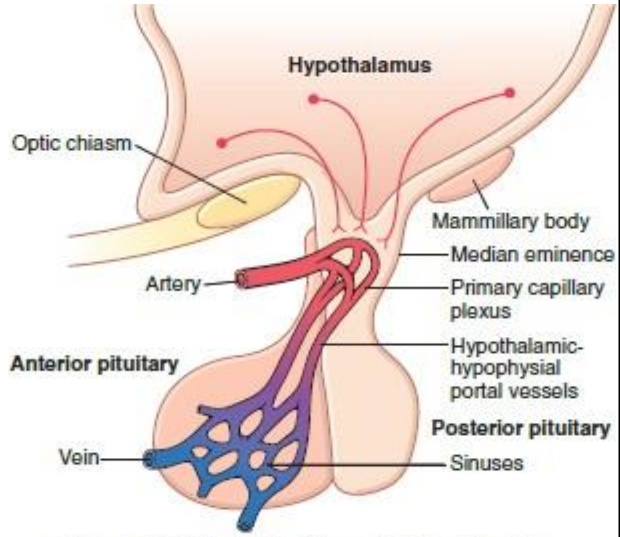


Figure 76-4. Hypothalamic-hypophysial portal system.

- It is highly vascularized with extensive ***capillary sinuses*** between the glandular cells. Blood first passes through ***the primary capillary plexus*** in ***the median eminence*** (the lowermost portion of the hypothalamus) and then blood flows through the portal blood vessels to supply the anterior lobe of the pituitary gland.
- The neuronal cell bodies in the hypothalamus produce hormones to be stored in the nerves ending located in the median eminence. When the neurons of the hypothalamus are stimulated, the nerves endings release the hormones into the blood vessels of the median eminence, from there they are transported to the anterior pituitary to stimulate or inhibit its secretion.

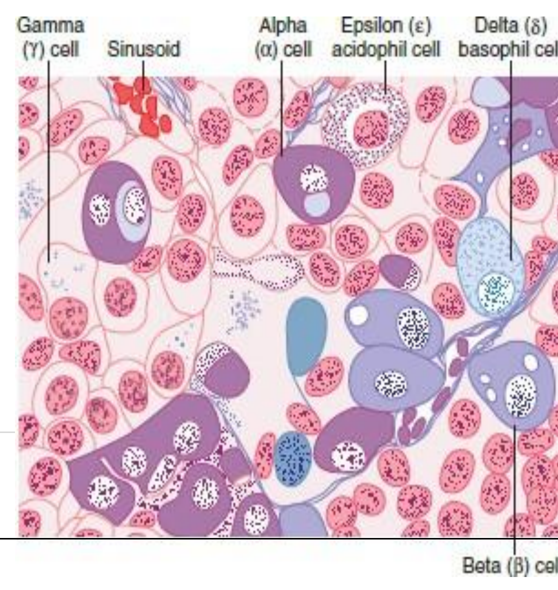
Secretion of anterior pituitary hormones is regulated by two pathways:

✓ ***The short pathway:*** Hormones that are packed in ***secretory granules*** at the Hypothalamus extend down through neurons to the posterior pituitary. From there, they are released into ***Hypothalamic-Hypophyseal short portal vessels***, then to the anterior pituitary to stimulate or inhibit it, this pathway is needed for immediate stimulation

✓ ***The long pathway:*** Hormones from the hypothalamus are released in ***the median eminence***, then through ***Hypothalamic-Hypophyseal long portal vessels*** to the anterior pituitary, useful in long stimulation.

Note: it is not precisely known which pathway is taken by a particular hormone but is believed that each hormone may take either the long or the short pathway depending on the body's need.

when taking a histological section, at least **5 cell types** can be identified in the anterior pituitary glands each one -usually- produces one major distinctive hormone .



Cells of Anterior Pituitary

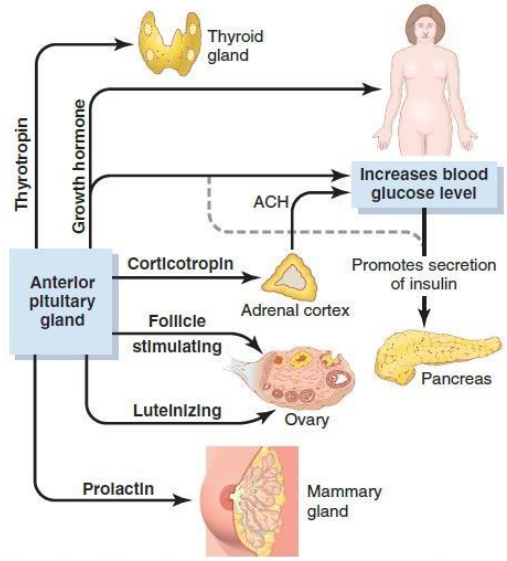


Figure 76-2. Metabolic functions of the anterior pituitary hormones. ACH, adrenal corticosteroid hormones.

1. Cells that release Tropic hormones (hormones that affect other endocrine glands), these cells stain basophilic.

- ✓ **Corticotropes:** cells release **Adrenocorticotropic hormone ACTH** (corticotropin)
  About 20% of all anterior pituitary gland cells.
- ✓ **Thyrotropes:** cells release **Thyroid stimulating hormones TSH.**
- ✓ **Gonadotropes**: cells release both **Follicle-stimulating hormones FSH** and **Luteinizing hormones LH.** A few separate cell types in both normal and abnormal conditions can only produce FSH/LH alone.

2. Cells that release non-tropic hormones

- ✓ **Somatotropes**: cells release **somatotropin (**also known as **growth hormones GH)**, those cells stain acidophilic.
- ✓ **Lacotropes (mammotropes):** cells release **Prolactin.** The mammary glands are exocrine glands not endocrine which are the target of prolactin, so it is a non-tropic hormone.

→ GH is a single chain polypeptide that is homologous with prolactin.
Normally GH and Prolactin are secreted by separate cells. In some cases (maybe normally or abnormally (tumor cells) they are released from the same cell, this indicates that these hormones are relatives (similar in function/structure)

→About 30-40% of all anterior pituitary gland cells are somatotropes, and about 20% are corticoropes, each of the other cell types (thyrotropes, Gonadotropes and Lacotropes) account for only 3-5%, despite this low percentage they produce powerful hormones for controlling thyroid function, sexual function, and milk secretion.

The Hypothalamic Hormones that stimulate or inhibit the secretion of the pituitary hormones:

- ✓ ***Corticotropin Releasing Hormone (CRH)*** that stimulate corticotropes to release ACTH.
- ✓ ***Thyrotropin Releasing Hormone (TRH***) -a polypeptide of 3 amino acids- that stimulate thyrotropes to release TSH.
- ✓ ***Growth Hormone Releasing Hormone (GHRH)*** that stimulate Somatotropes to release GH. has the longest amino acids sequence (44).
- ✓ ***Gonadotropin Releasing Hormone (GnRH)*** that stimulate Gonadotropes to release LH and FSH.
- ✓ ***Growth Hormone Inhibitory Hormone (GHIH/Somatostatin)*** that inhibit the release of GH from Somatotropes.

✓ ***Prolactin inhibiting hormone (PIH/Dopamine)***

All the hypothalamus hormones are peptides except dopamine (a catecholamine).

** For most of these hormones, simulation is more important than inhibition except for the prolactin hormone because it is not needed always in the females and it is not needed at all in males. There may be a stimulatory hormone for prolactin but the inhibitory hormone exerts **more function** & control.

** Growth hormone has stimulatory and inhibitory hormones, while other hormones have only stimulatory hormone as they are regulated by a feedback mechanism.

** The Hypothalamus is affected by all the CNS centers and since the Pituitary gland is regulated by the Hypothalamus, this means that both the Hypothalamus and the Pituitary gland are controlled by the centers of the CNS.

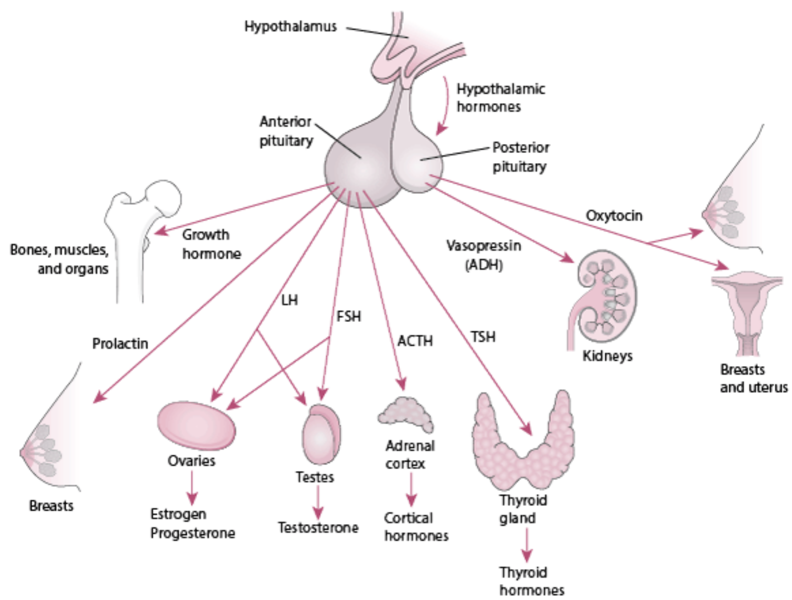


Table 76-1 Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH) (somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of insulin-like growth factor-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH) (corticotropin)	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 (TSH) (thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing (LH) hormone	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes-Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

Growth hormone (somatotropin)

- Small protein molecule that contains 191 amino acids in a single chain with a molecular weight of 22,005.
- It causes growth of almost **all tissues of the body** that are capable of growing & dividing. It promotes increase in size of the cells and increased mitosis (number).
- Notice the increase of a rat's body weight when injected daily with growth hormone.

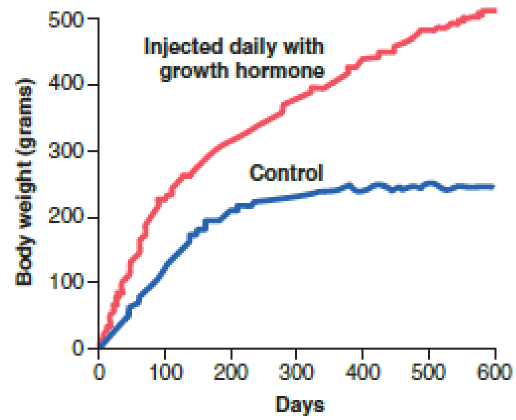


Figure 76-5. Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

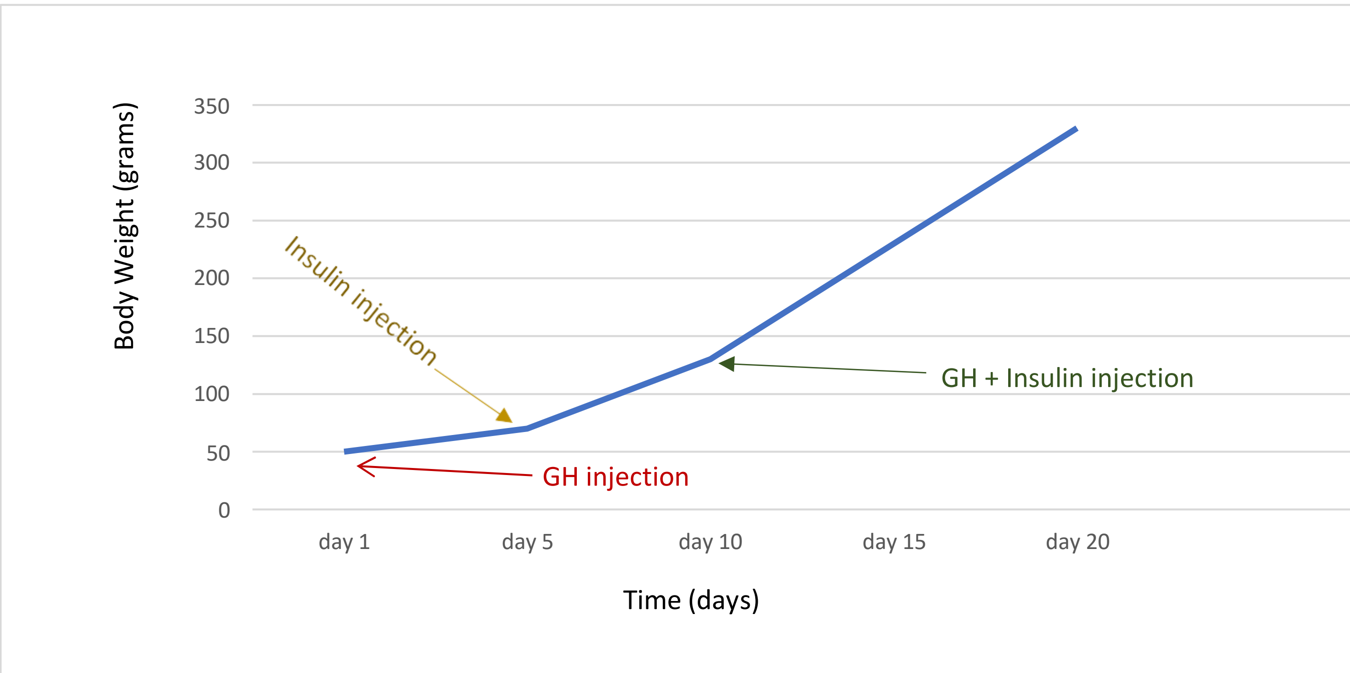
Hormonal interactions

- ***Permissive***: the presence of one hormone is required for other hormone to exert or enhance its effect.
- ***Synergism***: when many hormones complement each other and function together to produce effects greater than sum of their individual effects.
  effect(x+y) > effect(x) + effect(y)
- ***Antagonism***: when a hormone opposes the action of another. *e.g. insulin- glucagon*
- Growth hormone is not the only hormone that stimulate growth in the body. Many hormones stimulate growth ***synergistically:***
  - ✓ Insulin like growth factor-1 [IGF-1] (also called somatomedin).
  - ✓ Androgen
  - ✓ Insulin
  - ✓ Thyroid Hormone
  - ✓ Glucocorticoid hormone (cortisol)
  - ✓ Estrogen

Growth hormone and insulin-like growth factor have been identified as the major determinants of the growth in the normal post-uterine life. However, the deficiency or absence of each of the other hormones seriously affect the normal growth of the musculoskeletal system as well as growth and maturation of other tissues in varying degrees.

Growth hormone and Insulin

- GH and Insulin affect growth **synergistically**, but separately insulin has more effect than growth hormone.
- The following graph represents the growth curve of a rat without a pituitary gland & pancreas. At first the rat was only injected with GH which showed a mild increase in weight, but when it was injected with insulin, the growth had increased more. However, the **most** increase was noticed when the rat was injected with **both hormones**. This means neither GH nor insulin can function separately, and insulin is the most needed hormone for growth.



Growth hormone effects:

GH has both ***direct and indirect effects***

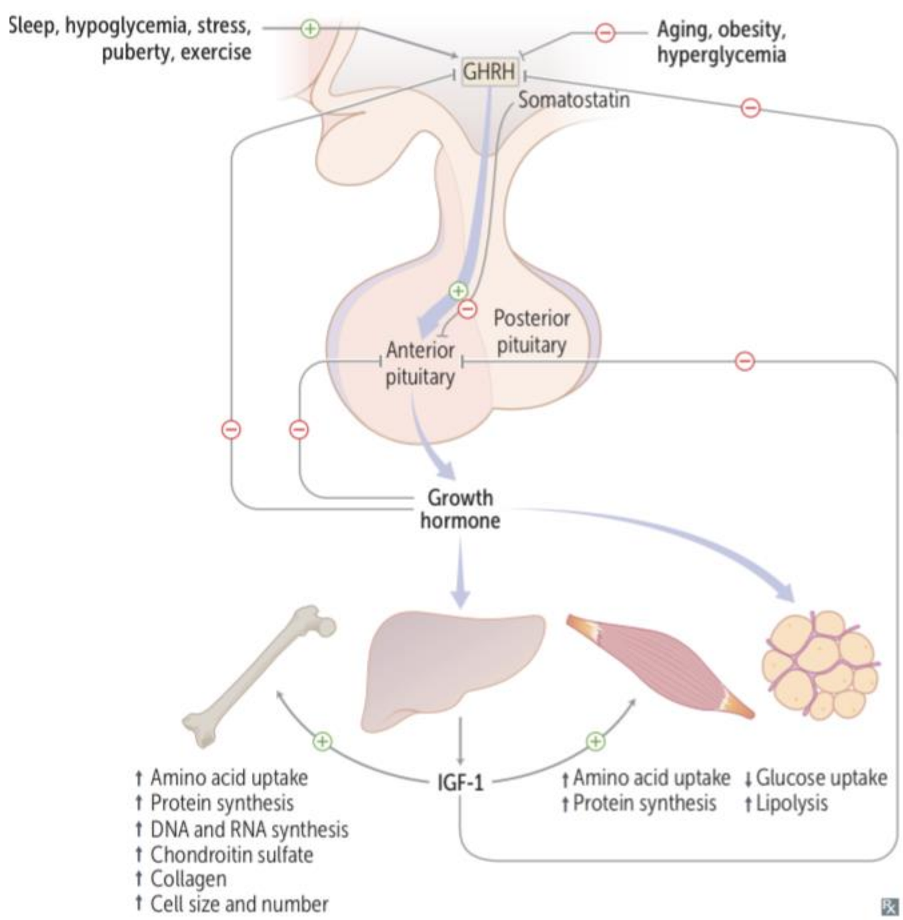
- ***Direct effects of GH on***:
- ✓ ***Adipose tissue:*** it decreases the adiposity, by increasing lipolysis and decreasing glucose uptake by tissues. (increase blood concentration of free fatty acids and glucose)
- ✓ ***Liver cells:*** it increases RNA synthesis, the rate of protein synthesis, promotes Gluconeogenesis (production of glucose from non-carbohydrate sources), and **promotes production of somatomedins**.
- ✓ ***Muscle cells:*** It decreases glucose uptake (glucose levels remain normal in the blood), increase amino acid uptake by the tissues and increase protein synthesis.

*So, it directly **decreases** **glucose uptake**, **increases** **lipolysis**, **increases** **protein synthesis** in muscles (which increases the lean body mass) and **increases** **production of somatomedin**.*

- ***Indirect effects of GH:***
  Growth hormone exerts much of its effect indirectly through intermediate substances called somatomedins (insulin like growth factor-1, IGF-1)

Somatomedins are small proteins hormones produced by the liver under the stimulation of GH, there are 5-6 types of somatomedins that differ in structure & potency. they have potent effect of increasing all aspects of bone growth. They also act on heart, kidneys, intestines, lungs, pancreas, parathyroid glands, skin, connective tissue and **chondrocytes** to increase organ size and they all **function similarly to GH**.

When growth hormone is supplied directly to cartilage chondrocytes cultured outside the body, proliferation or enlargement of the chondrocytes usually fails to occur.
yet, when growth hormone is injected into the intact animal proliferation and growth of the same cells actually occurs.



GOOD LUCK ☺