Anterior Pituitary hormones

The secretory activity of the hypothalamus and hypophysis is regulated by the negative feedback mechanism.

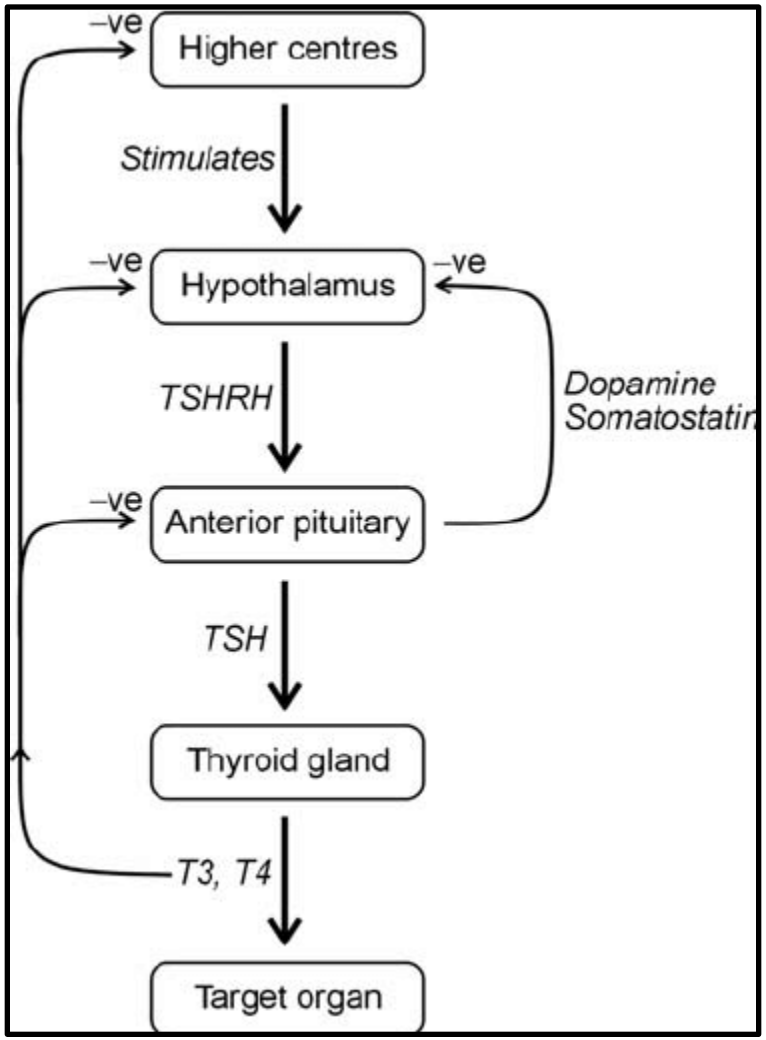
There are two negative feedback loops that affect the hypothalamic-pituitary axis:

Long loop feedback:

When the blood level of hormones from the peripheral glands reaches the homeostatic concentration, those hormones signal to the pituitary and hypothalamus to stop the secretion of releasing and stimulating hormones until the concentration lower again(to reach homeostasis).

Short-loop feedback:

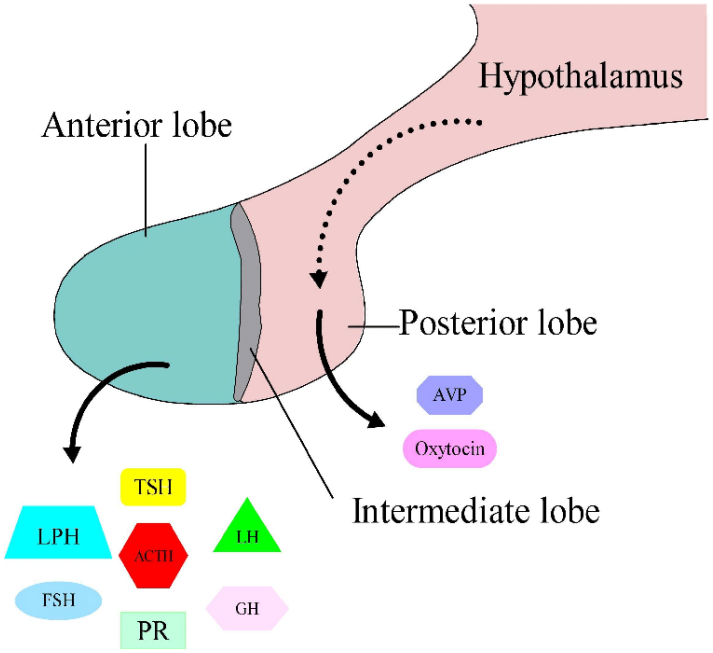
The rise of pituitary hormones blood level inhibits the synthesis and/or release of the related hypothalamic hormones.



Anatomy of the Pituitary

3 distinct parts and their functions

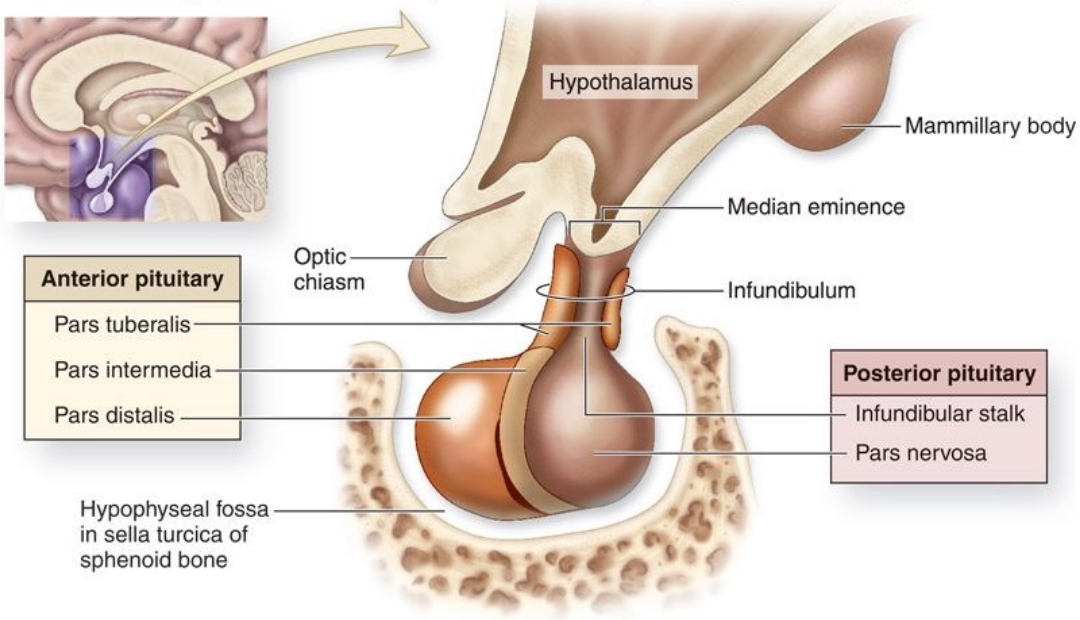
1. Anterior pituitary (adenohypophysis)
2. Intermediate lobe (pars intermedialis)
   Little functional capacity
3. Posterior pituitary (neurohypophysis)
   Stores and releases oxytocin and vasopressin (ADH)



Anatomy of the Pituitary

The pituitary gland is connected to the hypothalamus by the **infundibulum** (pituitary stalk), which is a process that extends inferiorly from the tuber cinereum of the hypothalamus.

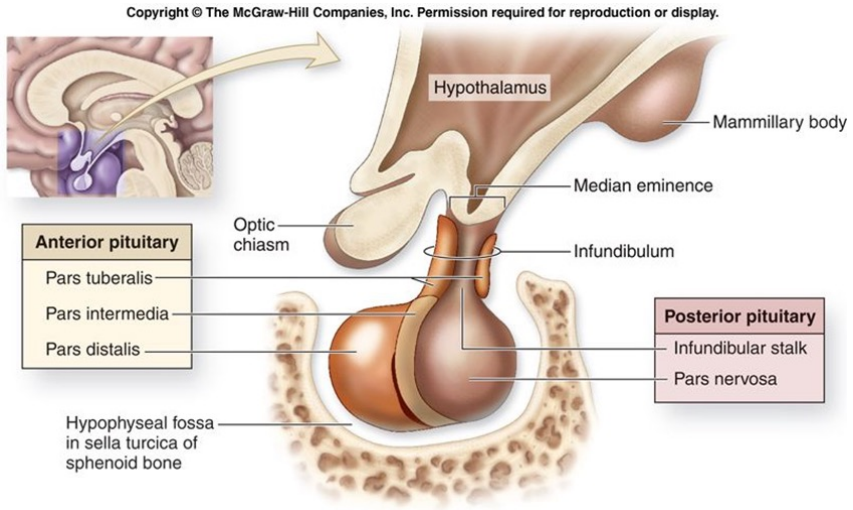
The infundibulum not only connects the two glands physically, but it also enables the passage of the hypothalamic hormones to the hypophysis as it is traversed by the hypophyseal portal system and hypothalamohypophyseal tract



The anterior pituitary (adenohypophysis) is made of three distinctive parts:

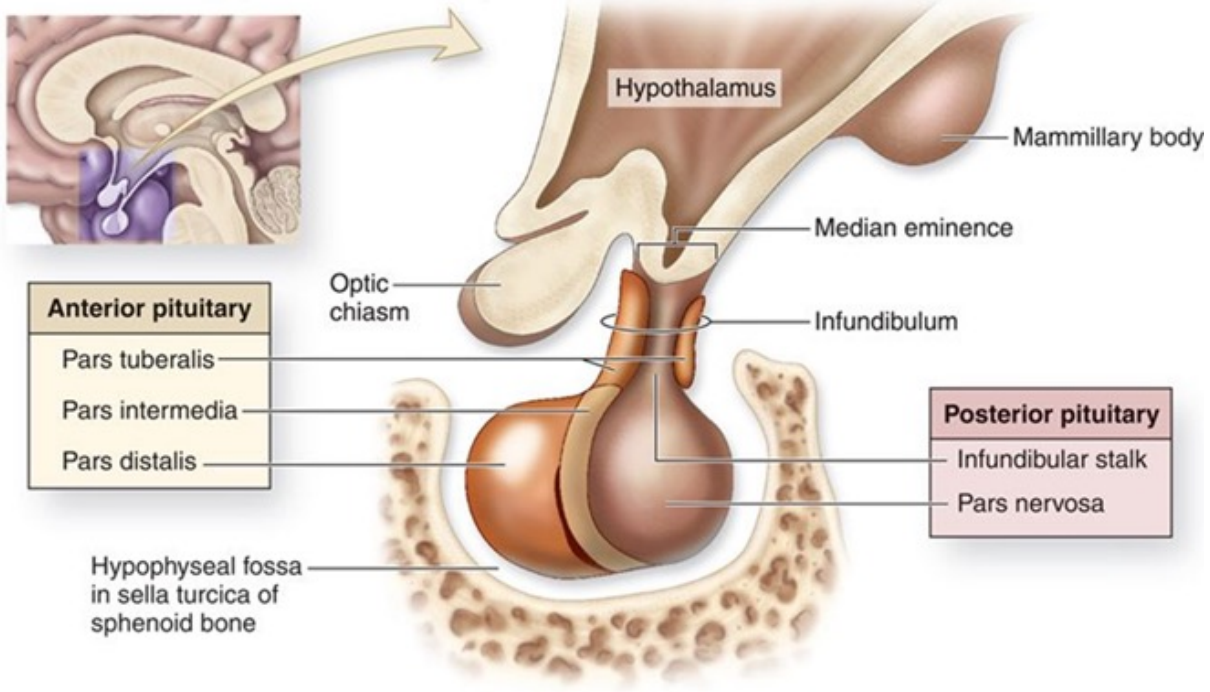
1. **Anterior part (distal or glandular part) is the part with the strongest secretory activity**

- It is composed of follicles that vary in size, but essentially contain three types of cells.
- These cells are classified according to their histological staining and include chromophils (acidophilic and basophilic) and chromophobes.
  - The acidophilic cells further divide into somatotrophs and lactotrophs. The former produces the growth hormone, while the latter produce prolactin.
  - The basophilic cells are divided into gonadotrophs (producing FSH and LH), corticotrophs (ACTH) and thyrotropes (TSH).
  - The chromophobes stain weakly, and they are the progenitor cells.



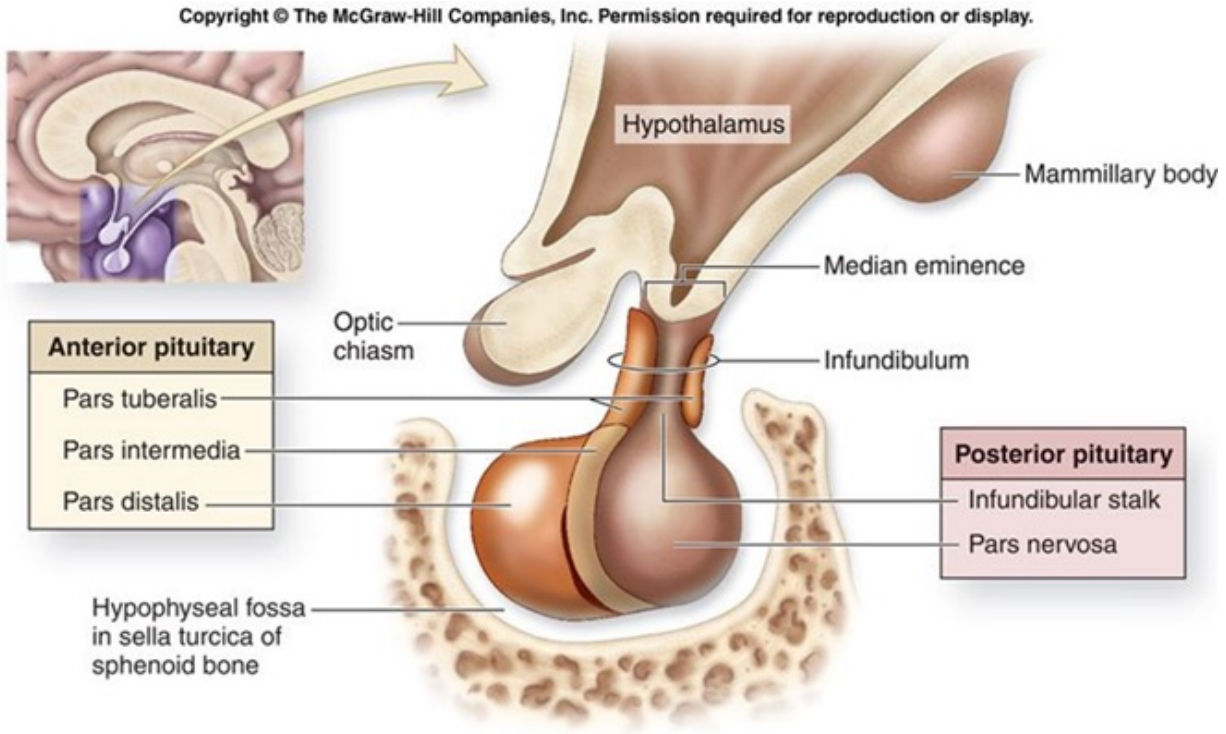
2. Tuberal part extends from the anterior (distal) part of the pituitary gland.

- The majority of its cells are gonadotrophs, with the small remainder being the thyrotrophs.
- The tuberal part surrounds the infundibular stem, a collection of axons that project into the pituitary from the hypothalamus.
- These axons are filled with the accumulated hormones (oxytocin and vasopressin).



3. Intermediate part is located between the anterior part of adenohypophysis and neurohypophysis.

- It contains follicles that are made up of colloidal matrices.
- The majority of the cells in this part are the corticotropic basophils, with less abundant pituitary stem cells.
- These corticotropic cells of this part produce melanocyte-stimulating hormones and endorphins.



Anterior Pituitary Cell Types and Hormones

Each of anterior pituitary hormone is synthesized by a cell population

- Corticotrophs

  - Release Adrenalcorticotrophic (ACTH)

- Gonadotrophs
  - Release Leutinizing Hormone (LH) and Follicle stimulating hormone (FSH)
- Thyrotrophs
  - Release Thyroid Stimulating Hormone (TSH)
- Lactotrophs
  - Release Prolactin
- Somatotrophs
  - Release Growth Hormone (GH)

Anterior pituitary: adenohypophysis

- **Anterior pituitary**: connected to the hypothalamus by the hypothalmoanterior pituitary portal vessels.
- The antererior pituitary is collection of hormone producing glandular cells.
- The anterior pituitary produces six peptide hormones:
  - **Prolactin (PRL) , growth hormone (GH),**
  - **thyroid stimulating hormone (TSH),**
  - **adrenocorticotropic hormone (ACTH),**
  - **follicle-stimulating hormone (FSH),**
  - **luteinizing hormone (LH).**
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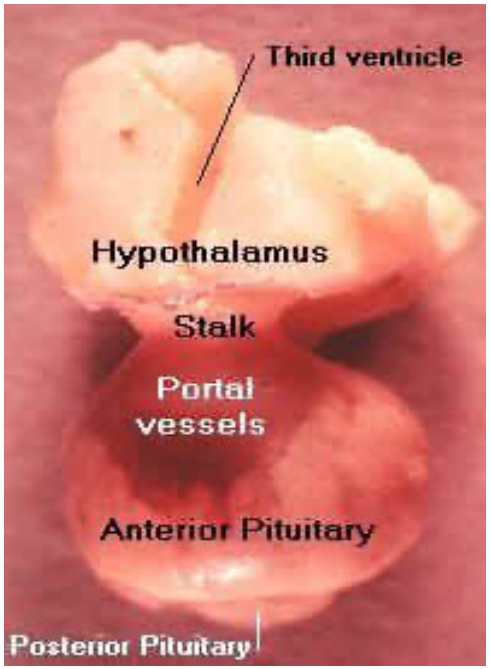


They are Classified into:

1- Somatotropic Hormones

have similar structure and function

1- lactogenic activity (stimulation of lactation and milk secretion)

2- growth promoting effect:

1- Growth Hormone (GH).

2- Prolactin (PRL).

2- Glycoprotein Hormones:

1- Luteinizing Hormone (LH).

2- Follicle-Stimulating Hormone (FSH).

3- Thyroid-Stimulating Hormone (TSH).

3- Pro-Opiomelanocortin (POMC) derived Hormones:

1- Corticotropin: ACTH.

2- Melanocyte-Stimulating Hormones: α-MSH, β-MSH.

3- Lipotropins: β-LPH, γ-LPH

Somatotropic Hormones

Growth Hormone

- Also called **somatotropin**
- **Secreted by Somatotropes of the Anterior Pituitary**
- Peptide with **direct effector** functions
  - **Secretion occurs in pulse ~ every 2-3 hours**
  - **Peaks at the onset of sleep**
- **Level:**

  High in children.

  Maximal during adolescence.

  Lowest during adulthood.

Growth Hormone

Stimulators (Increased secretion)

- Trauma
- Exercise
- Sleep
- Hypoglycemia

Inhibitors (Decreased secretion)

- Glucose loading
- Epinephrine
- Emotional/psychogenic stress
- Nutritional deficiencies
- Insulin deficiency (hyperglycemia)
- Hypothyrodism

Growth hormone

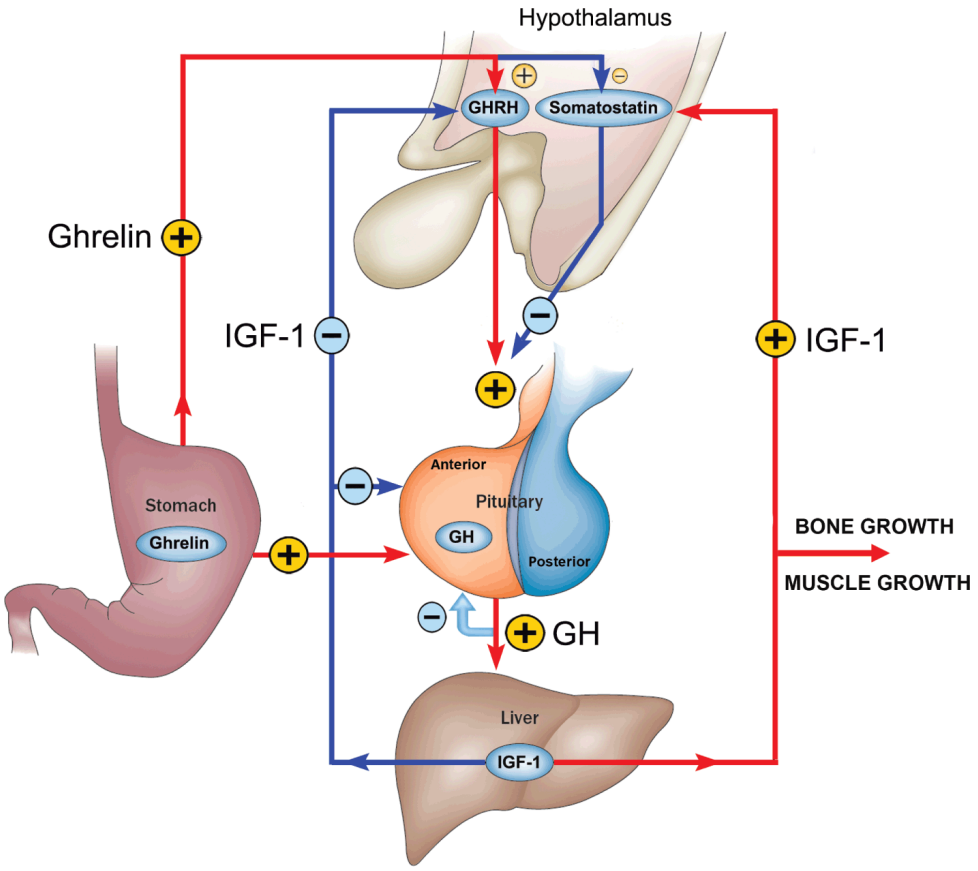
Growth hormone-releasing hormone (GHRH) is a hypothalamic peptide that stimulates both the synthesis and secretion of growth hormone.

Somatostatin (SS) is a peptide produced by several tissues in the body, including the hypothalamus.

- Somatostatin inhibits growth hormone release in response to GHRH and to other stimulatory factors such as low blood glucose concentration.

Ghrelin is a peptide hormone secreted from the stomach.

- Ghrelin binds to receptors on somatotrophs and potently stimulates secretion of growth hormone.

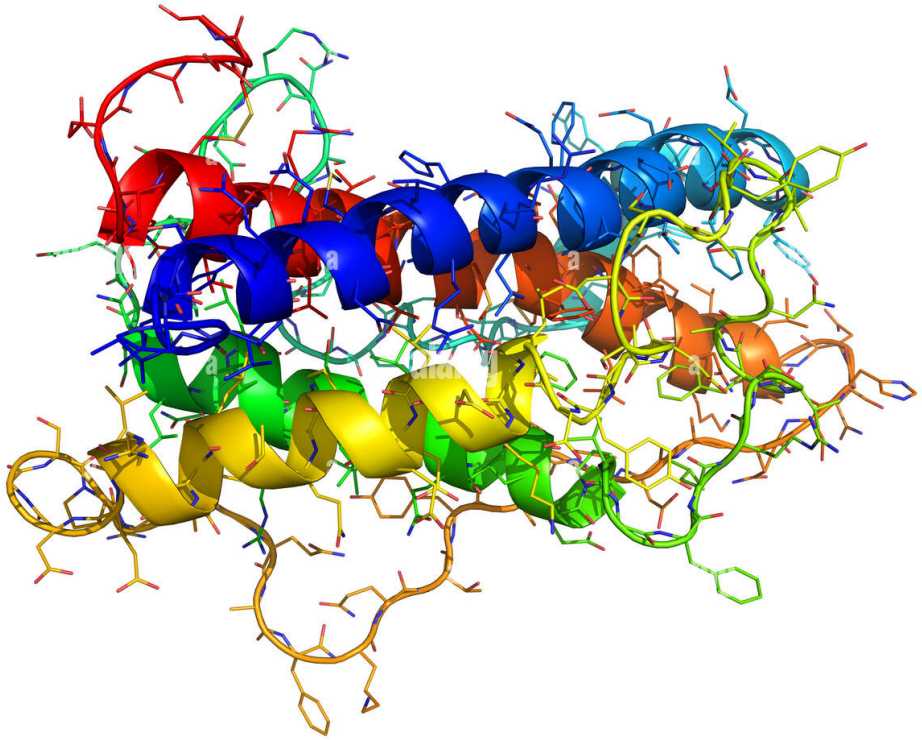


Note: Insulin-like growth factor 1 (IGF-1)

Human growth hormone structure

Structure: It is a single polypeptide chain composed of 191 amino acid residues. It has two disulfide bonds

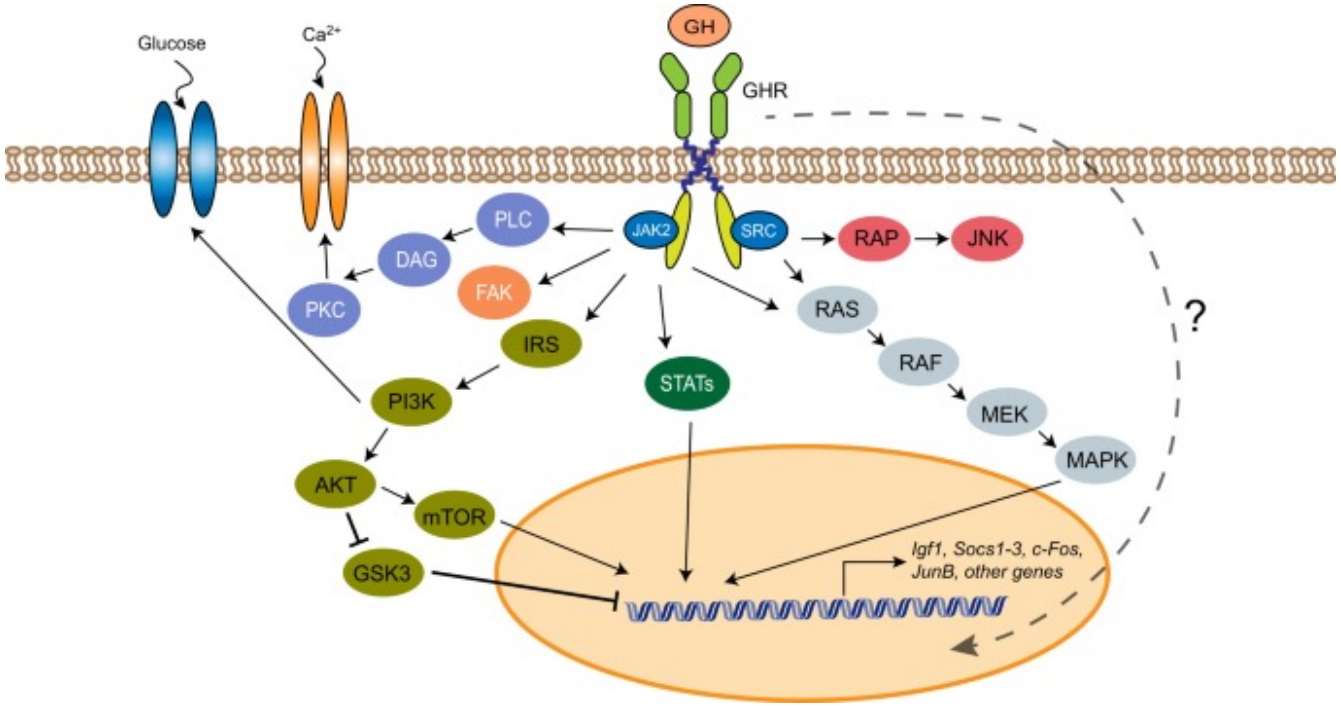
Human growth hormone forms a four-helix bundle

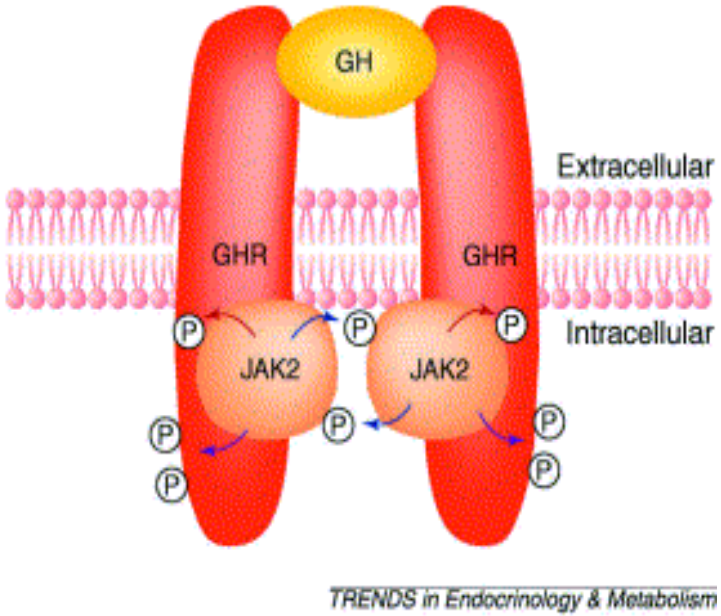


Growth hormone receptor signal transduction

- The GHR is a type I cytokine receptor that lacks intrinsic kinase activity and requires recruitment of the nonreceptor tyrosine kinase, Janus kinase 2 (JAK2), for activation.
- A predimerized GHR homodimer interacts with the GH ligand through two binding sites, which have different affinities for the receptor. Binding leads to a rotational change in the receptor transmembrane domain, which leads to transphosphorylation and activation of two JAK2 molecules that are associated with the cytoplasmic domain of the receptor.
- Phosphorylated JAK2 then phosphorylates tyrosines in the cytoplasmic domain of GHR, and this facilitates recruitment of signaling molecules to the receptor.

- The primary signaling pathway activated by GH is the JAK-STAT (signal transducer and activator of transcription) pathway.
- The STAT molecules that are activated by GH signaling are STAT1, 3, 5a, and 5b. Other key signaling pathways that are utilized are the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathways, as well as SH2B1β, a scaffold protein that interacts with JAK2 and mediates GH-induced changes in the cytoskeleton.
- The GHR has also been observed to rapidly translocate to the nucleus following activation, but its role there remains unclear





- Mechanism of action takes place by binding of GH molecule in between the receptor molecules.
- This binding occurs in the extracellular region leading to receptor dimerization.
- phosphorylation of the JAK2 protein which causes physiologic effects.

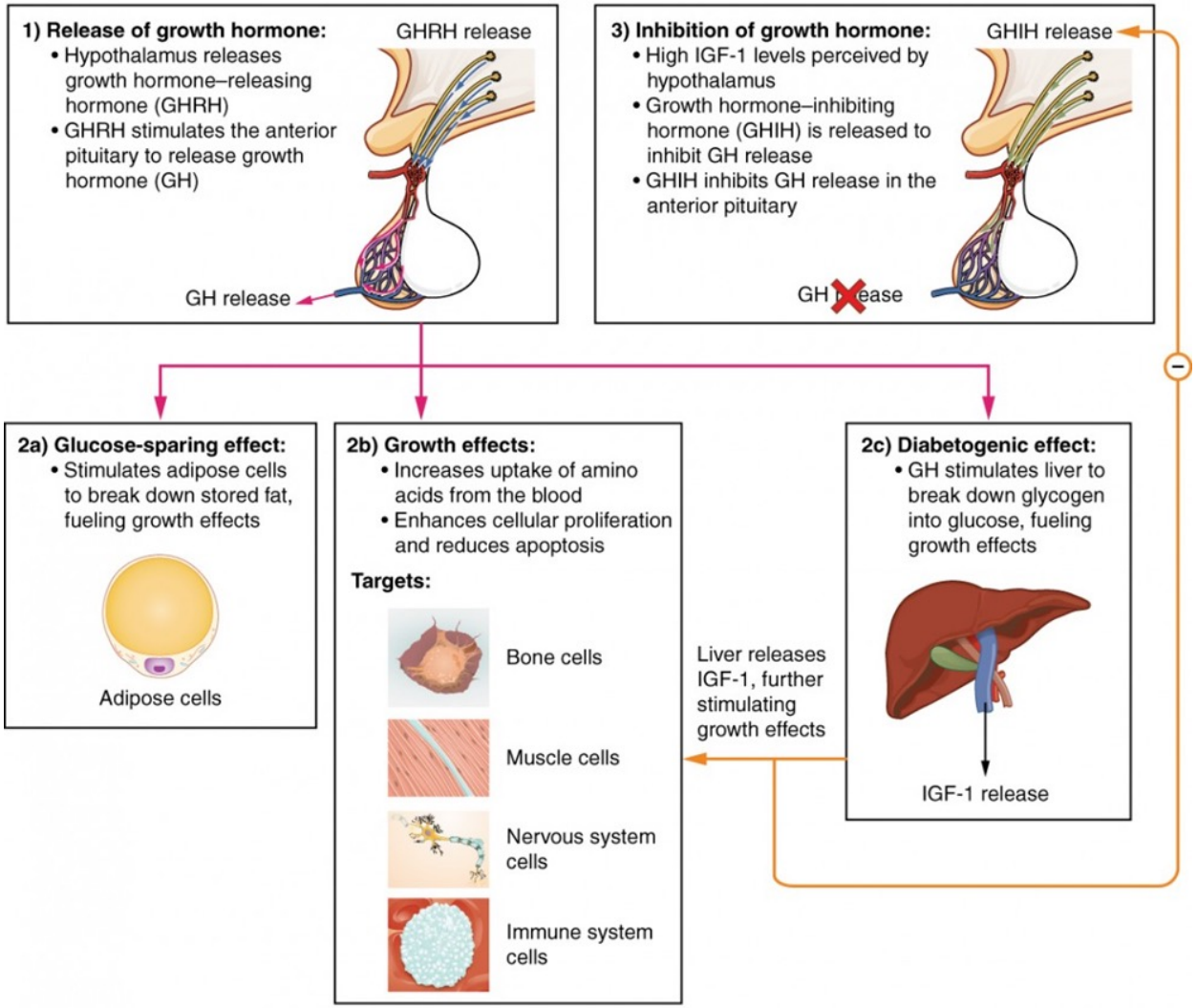
GHR signal transduction downregulation

- Once activated, GHR signal transduction is downregulated by suppressor of cytokine signaling proteins 1–3 (SOCS1–3); these are negative regulators that facilitate the ubiquitination and degradation of the receptor.
- Downregulation of the receptor also occurs through dephosphorylation by several protein tyrosine phosphatases and protein inhibitor of activated STATs (PIAS)

Growth Hormone (GH)

- Its function varies during the age & mainly in the cell growth proliferation
- Produces somatomedians or insulin-like growth factor-1

(IGF-I) that act as secondary messengers from the liver.



Physiological Effects:

- **Direct Effects:**

1- Stimulation of Lipolysis (Hydrolyses of Triglycerides) (**catabolic**) that Increases plasma free fatty acids (FFA) - source of energy for muscle tissue

2- Stimulation of Hepatic glucose output (**hepatic gluconeogenesis**)

3- Directly **antagonizes effect of insulin on glucose metabolism**(GH causes inhibition of glucose uptake and utilization)

4- Production of Insulin-like growth factors (IGF's, Somatomedins)

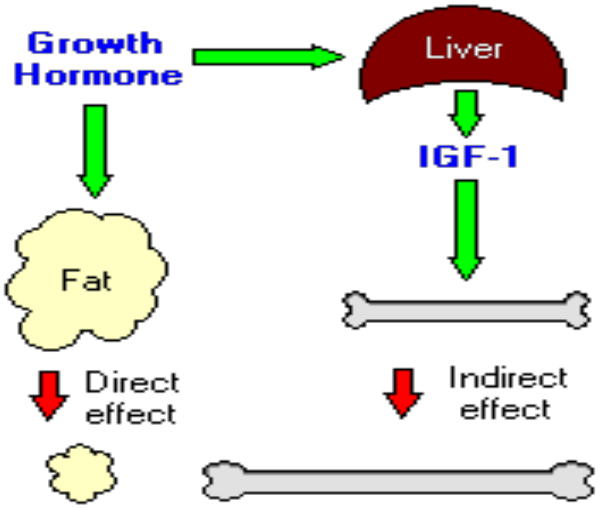
- **Indirect Effects:**

Mediated by IGF-1:

1- Increase cell numbers.

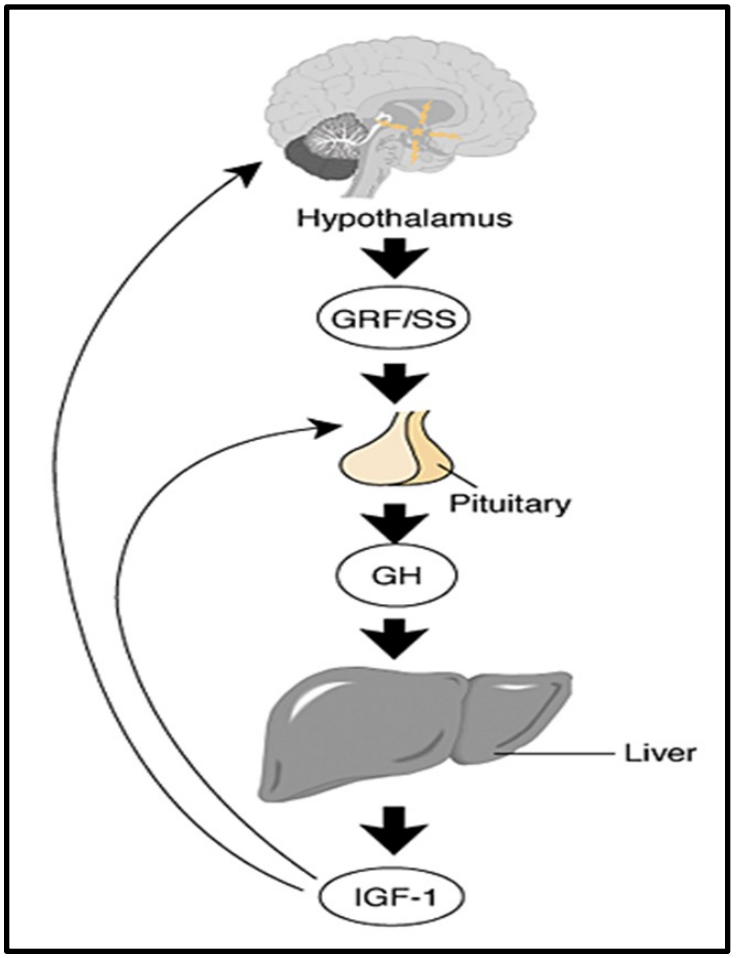
2- Positive Nitrogen balance.

3- Increase Protein synthesis.



Growth Hormones

- GH primary job is to stimulate the liver to secrete IGF-1 (Insulin Growth Factor)
- GH exerts its **growth-promoting** mainly through induction of Insulin-like Growth Factor I (IGF-I).
- **IGF-1**
  - stimulates proliferation of chondrocytes (cartilage cells), resulting in bone growth.
  - differentiation and proliferation of myoblasts
  - Stimulates amino acid uptake and protein synthesis in muscle and other tissues (**anabolic**)



NB:-GH is Amphibolic; influences both anabolic & catabolic processes

Disease Conditions Related to GH:

- **Deficiency:**

  * **Dwarfism:**

More serious in infancy, the affected infants fail to grow properly **.**

Due to deficiency in growth hormone or defects in its binding to receptor

- Excessive GH during childhood

- **Excessive Secretion:**

1. Gigantism :

Due to tumor in somatotrpes in young children or adolescents (**Before puberty**), rapid growth of long bones.

- Tumor of somatotrophs

Excessive Secretion:

2- Acromegaly:

(After puberty, stop of long bone growth),

Rapid growth of acral bones, protruding jaws, enlarged nose, enlargement of hands, feet& skull

Rare disease (3/Million).

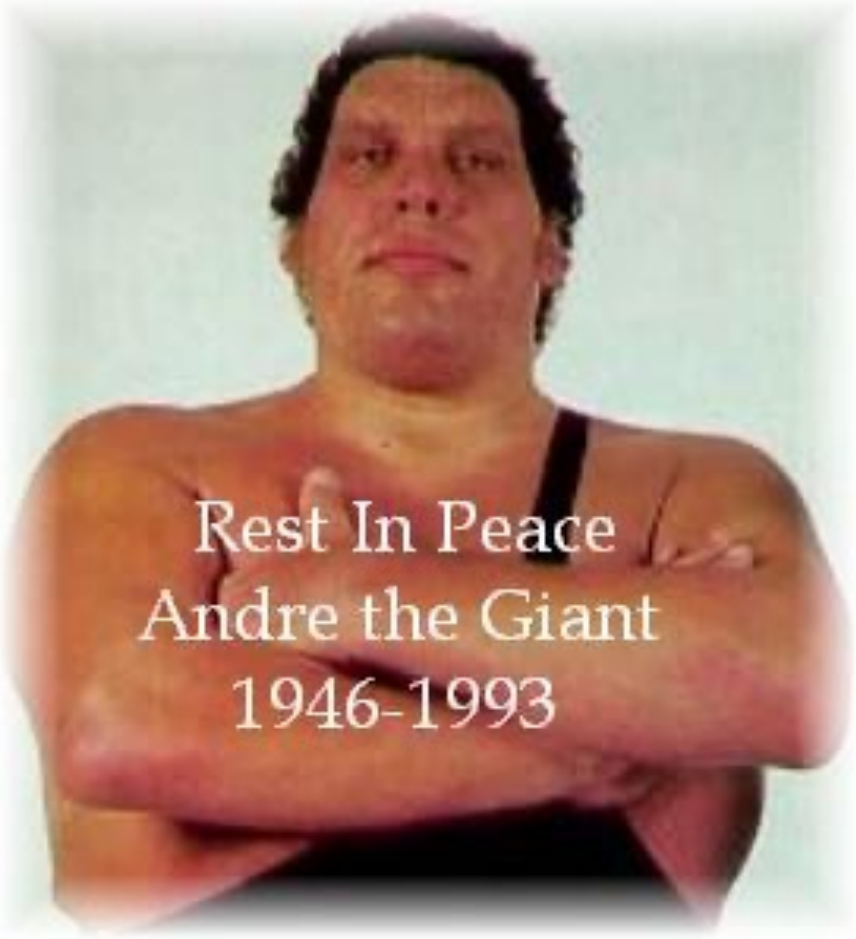
Causes: Benign tumor of Pituitary gland (90%).

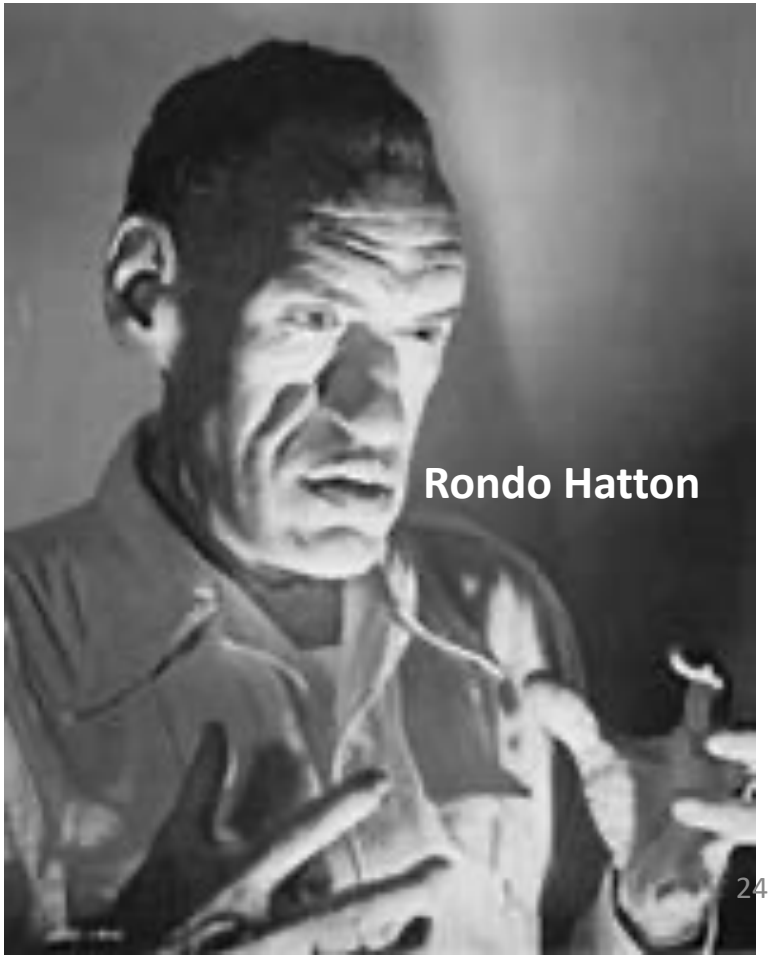
Symptoms:

- Enlargements of extremities. , soft-tissue swelling
- abnormalities in jaw structure and cardiac disease. - The excessive growth hormone and IGF-I
- a number of metabolic derangements, including hyperglycemia

Acromegaly

- GH late in life
- Causes excessive growth of flat bones





Uses of Growth Hormone:

* Replacement therapy for children with GH deficiency.

* Administered by intramuscular or subcutaneous.

- **Sources:**

* Recombinant DNA technology