Endocrine System

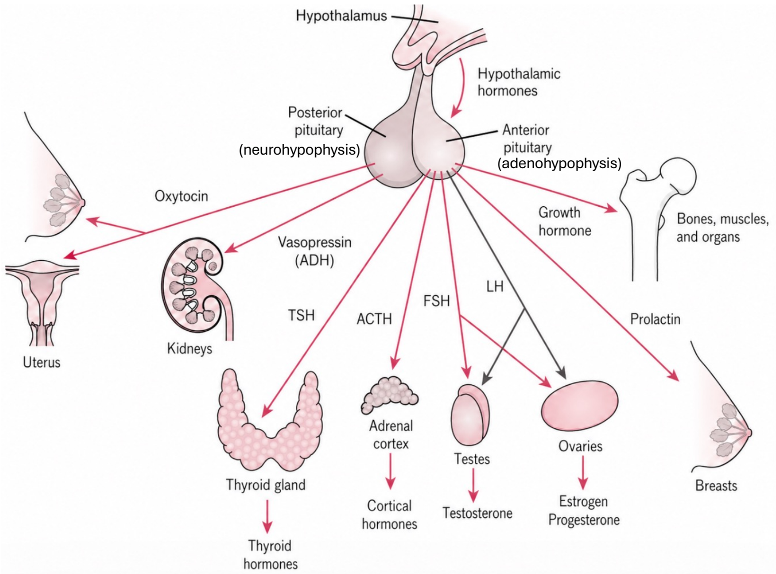
The endocrine system, unlike other systems or apparatuses in our body, is characterized by anatomical and structural discontinuity. In the nervous system, and even more clearly in the gastrointestinal system, there is anatomical continuity between the organs involved. For example, in the digestive tract, the food bolus passes from the oral cavity to the pharynx, then to the esophagus, the stomach, and subsequently to the intestine. This anatomical continuity also reflects a functional continuity.
In the endocrine system, on the other hand, the organs involved are located in different and distant sites within the body.

Endocrine system functions

- Releases hormones through endocrine organs (glands)
- Specific hormone–receptor interaction
- Homeostasis of the organism
- Signaling through feedback mechanisms

To understand this, we first need to define what endocrine organs are.
Endocrine organs are structures that produce and release substances, so they are glands.
Any structure in the body that secretes something is called a gland.
If the secretion is released through a duct into a body cavity or outside the body, it is called an exocrine gland.
Examples of exocrine glands are salivary glands (release saliva into the mouth), sweat glands (release sweat onto the skin), and gastric glands (release gastric juice into the stomach).
If a gland releases its product directly into the blood without a duct, it is called an endocrine gland.
The substances released by endocrine glands are hormones. These hormones travel in the blood and can reach many parts of the body.
However, hormones do not act on all organs. They act only on cells that have the right receptor.
So, the endocrine system is specific because of the hormone–receptor interaction.
Its continuity is functional, not anatomical: a gland releases a hormone, the hormone travels in the blood, and acts only on target organs with the correct receptor.
The main role of the endocrine system is homeostasis (keeping balance).
For example, body temperature: during exercise or heat, temperature rises. The hypothalamus in the brain detects this and activates responses like sweating and vasodilation. These help reduce temperature and bring it back to normal.
If the endocrine system does not work well, body parameters can change.
To keep balance, the system uses feedback mechanisms.
Feedback is a return signal that controls activity.
If gland B stimulates gland C, gland C can then control gland B.
This control can be positive (increase activity) or negative (reduce activity).
Most of the time, the body uses negative feedback.
An exception is the luteinizing hormone peak before ovulation, which is positive feedback.
So, in most cases, the endocrine system works with negative feedback:
a gland stimulates a target organ, the organ responds, and then sends a signal to reduce the initial stimulation. This keeps the body in balance.

Endocrine system organs



Let's now look at the main organs of the endocrine system.
At the center of regulation is the hypothalamus. It is not only involved in body temperature control, but it is also an important endocrine control center. The hypothalamus is in the central nervous system and connects the nervous system with the endocrine system.
This connection happens through a gland located just below it: the pituitary gland.
The pituitary has two main parts: the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis).
The neurohypophysis contains extensions of hypothalamic neurons. These neurons carry two main hormones: vasopressin (antidiuretic hormone) and oxytocin. These hormones are produced in the hypothalamus, transported along the axons, and released into the blood from the neurohypophysis.
The adenohypophysis, instead, is a true endocrine gland.
It is stimulated by hypothalamic hormones called releasing factors, and it produces hormones that control other endocrine glands.
Target organs of the adenohypophysis include the thyroid, adrenal glands, gonads (testes and ovaries), the breast, and also the musculoskeletal system.

Endocrine hormones

GLAND	TYPE OF CELL	HORMONES
(HYPOTHALAMUS)	Supraoptic nucleus Paraventricular nucleus	Antidiuretic hormone (ADH) Oxytocin
HYPOPHYSIS	Neurohypophysis:	Antidiuretic hormone (ADH) Oxytocin
(HYPOTHALAMUS)		Releasing factors (TRH and CRH)
HYPOPHYSIS	Adenohypophysis: - Distal part	Thyrotropin (TSH) " adrenocorticotropic (ACTH) " follicle-stimulating (FSH) " luteinizing (LH) " somatotropin (GH) Prolactin (PRL)
	- Intermediate part	Melanotropin (MSH)

Table with the main hormones involved in the regulation of body homeostasis.
The hypothalamus produces ADH and oxytocin. These hormones are transported along axons to the neurohypophysis, where they are stored and released into the bloodstream.
The hypothalamus also produces several releasing factors, such as TRH (thyrotropin-releasing hormone) and CRH (corticotropin-releasing hormone). These act on the adenohypophysis and stimulate it to produce specific hormones. For example:
TSH stimulates the thyroid
ACTH stimulates the adrenal cortex
FSH and LH (gonadotropins) regulate the activity of the gonads
Other hormones produced by the adenohypophysis are prolactin and growth hormone.
Prolactin acts on the mammary gland and stimulates milk production, while oxytocin helps milk ejection and uterine contraction.
Antidiuretic hormone (ADH) regulates water balance: it increases water reabsorption in the kidneys and allows the production of more concentrated urine.

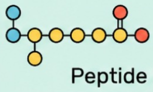
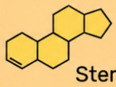
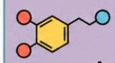
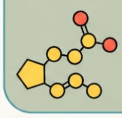
GLAND	TYPE OF CELL	HORMONES
THYROID	Thyrocytes C cells	Thyroxine (T4) Triiodothyronine (T3) Calcitonin
PARATHYROIDS	Chief cells	Parathyroid hormone (PTH)
ADRENAL GLAND	Cortex: - Zona glomerulosa - Zona fasciculata - Zona reticularis Medulla	 Mineralocorticoids Glucocorticoids Androgens Adrenaline (epinephrine) Noradrenaline (norepinephrine)
PANCREAS (Islets of Langerhans)	Alpha cells Beta cells Delta cells F or PP cells	Glucagon Insulin Somatostatin Pancreatic polypeptide

Among the main endocrine glands, we also find the thyroid, parathyroids, adrenal glands, pancreas, ovaries, and testes. Some of these glands are directly controlled by the hypothalamus–pituitary axis, such as the thyroid, adrenal glands, and gonads.
Others, like the pancreas and parathyroids, are not directly controlled by this axis.

GLAND	TYPE OF CELL	HORMONES
OVARY	Follicular cells Corpus luteum	Estrogens Inhibin Progestins Relaxin
TESTIS	Interstitial cells of Leydig Sertoli supporting cells	Androgens Inhibin

Example of negative feedback:
The gonads are regulated by FSH and LH.
In the ovary, these hormones stimulate the production of estrogens, progesterone, and inhibin.
In the testis, they stimulate the production of testosterone (androgens) and inhibin.
Inhibin is a hormone that, once released into the blood, reaches the hypothalamus and the pituitary gland and inhibits their activity, contributing to the negative feedback mechanism.

Types of Hormones

Hormone class	Solubility	Receptor location	Examples
 Peptide hormones	Water-soluble	Cell membrane receptors	• Insulin (glucose regulation) • Glucagon (glucose regulation) • Oxytocin (labor & bonding)
 Steroid hormones	Lipid-soluble	Intracellular receptors	• Cortisol (stress) • Estrogen (reproduction) • Testosterone (androgenic)
 Amine hormones	Water-soluble (catecholamines) Lipid-soluble (thyroid hormones)	Water-soluble → Membrane receptors Lipid-soluble → Nuclear receptors	• Epinephrine (water-soluble membrane) • Thyroxine (lipid-soluble nuclear)
 Eicosanoids	Lipid-soluble (local action)	Cell membrane receptors	• Prostaglandins (inflammation) • Leukotrienes (immune response)

The table classifies hormones into four main groups based on their chemical nature, solubility, and type of receptor.

Peptide hormones

They are water-soluble and cannot cross the cell membrane, so they act through membrane receptors.

Examples: insulin, glucagon, oxytocin.

Steroid hormones

They are lipid-soluble (derived from cholesterol), can cross the membrane, and bind to intracellular receptors.

Examples: cortisol, estrogens, testosterone.

Amine hormones

They come from amino acids but behave differently:

Catecholamines are water-soluble → membrane receptors

Thyroid hormones are fat-soluble (thanks to aromatic rings that make them hydrophobic, so they can cross the membrane) → intracellular nuclear receptors

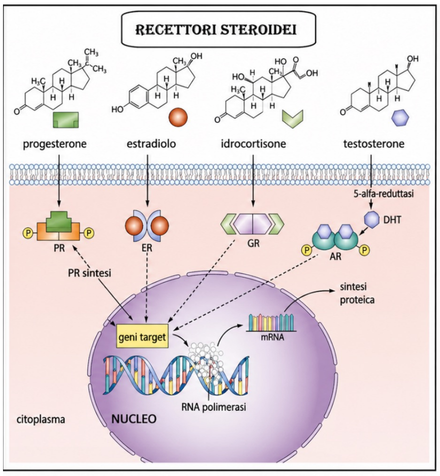
Examples: adrenaline, thyroxine.

Eicosanoids

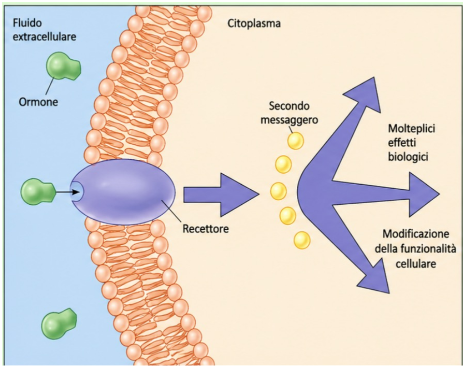
They are lipid-soluble, derived from membrane fatty acids, and act mainly locally through membrane receptors.

Examples: prostaglandins, leukotrienes.

Hormone-receptor interaction



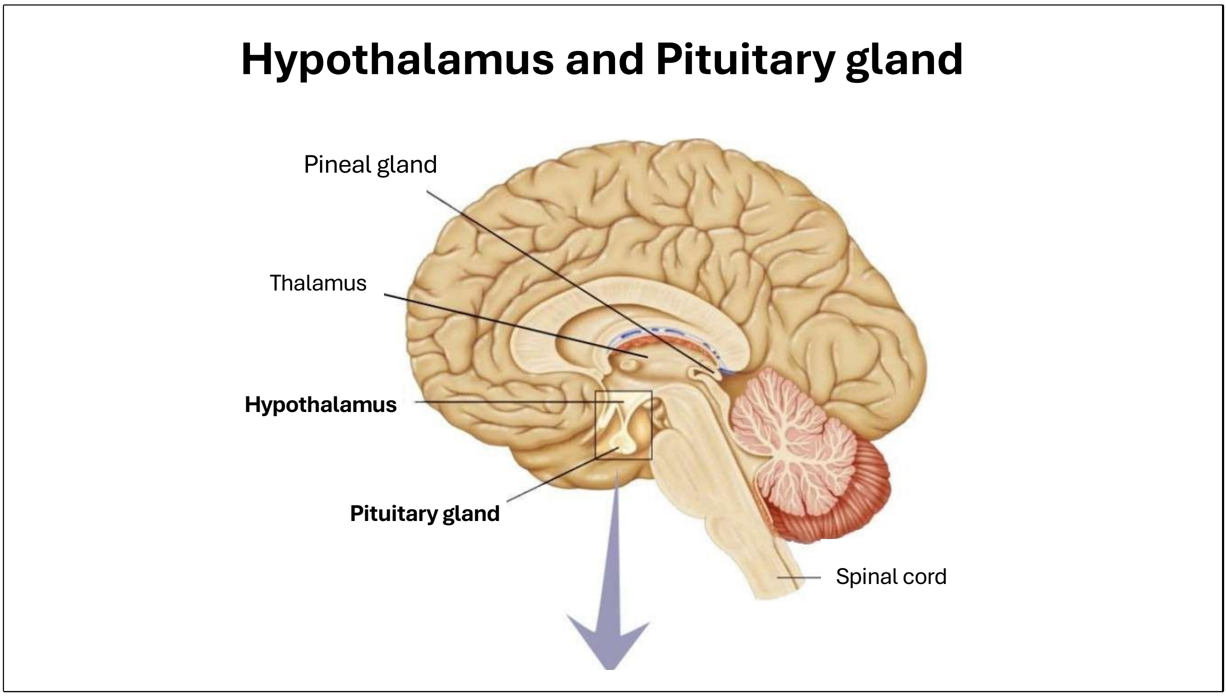
Lipid-soluble



Water-soluble

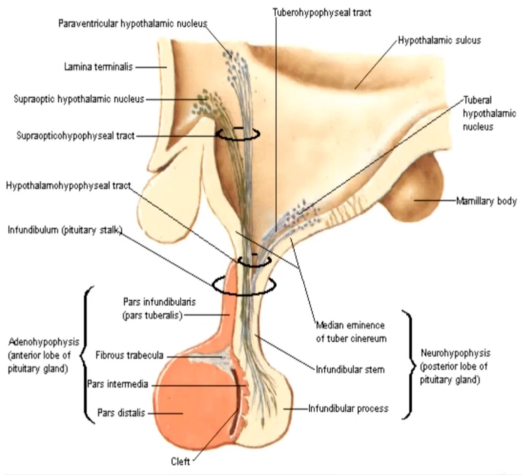
Lipid-soluble hormones can cross the cell membrane and bind to intracellular receptors (in the cytoplasm or nucleus). The hormone–receptor complex acts directly on DNA and regulates gene expression.

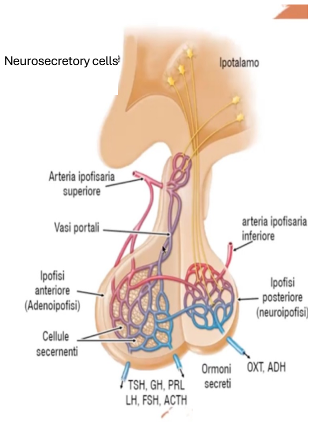
Water-soluble hormones (peptides and some amines) cannot cross the membrane. They bind to receptors on the cell membrane.
This activates a signal transduction cascade with second messengers, leading to functional changes in the cell and sometimes indirectly affecting nuclear activity.

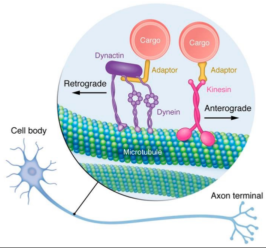


Looking more closely at the anatomy of the hypothalamus and pituitary gland:
The hypothalamus is located inside the skull, is part of the diencephalon, and lies below the thalamus.
Below the hypothalamus is the pituitary gland, connected to it by a stalk.
The pituitary is located in a bony cavity of the sphenoid bone called the sella turcica.
The pituitary is anatomically close to the optic chiasm and optic pathways.
For this reason, pituitary tumors can compress these structures and cause visual problems.
From a histological point of view, the pituitary has two very different parts:
The adenohypophysis has a glandular epithelial nature and produces several hormones.
The neurohypophysis has a nervous nature, because it is made of axons from the hypothalamus and glial cells.

Hypothalamic–pituitary portal system







The hypothalamus is made of groups of neurons (called nuclei).
Some of these neurons produce oxytocin and vasopressin. These hormones travel along axons by an anterograde mechanisms involving kinesin and micortubules of the neurosecretory cells) to the neurohypophysis.
The neurohypophysis has many blood vessels and releases these hormones into the blood.
The adenohypophysis works differently.
The hypothalamus produces releasing factors that enter a special blood system called the hypothalamic–pituitary portal system.
This system has:
one capillary network in the hypothalamus
portal vessels
a second capillary network in the adenohypophysis
Normally, blood goes from an artery to capillaries, then to a vein.
In the portal system, two capillary networks are directly connected.
This allows hypothalamic hormones to go straight to the adenohypophysis and stimulate it.

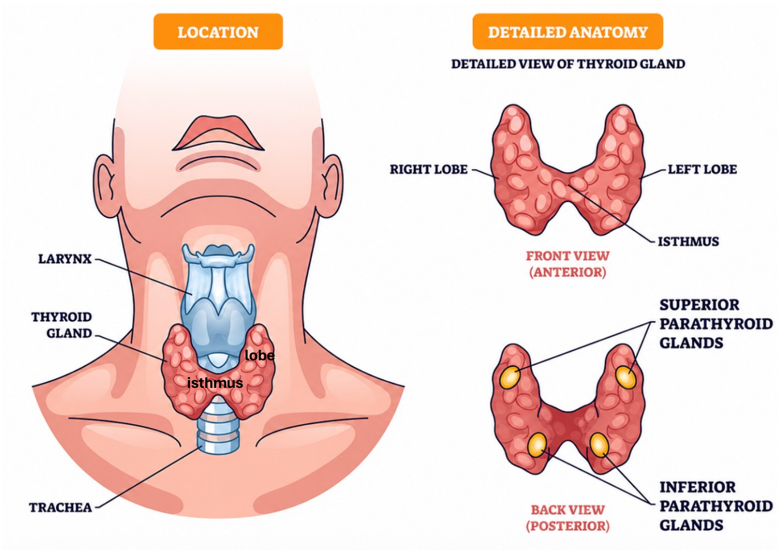
In simple words:
The hypothalamus sends a message to the pituitary using the blood.
It uses a "direct route" (portal vessels) that connects them, so the message arrives quickly.

In summary:
The hypothalamus–pituitary axis is the main control system of the endocrine system.
The hypothalamus controls the pituitary.
The pituitary controls many glands.
These glands produce hormones that act on target tissues and also send negative feedback to the hypothalamus and pituitary.

Note about the axonal transport of secretory vescicles.

A classic example involves the hormones vasopressin and oxytocin, which are synthesized in neurons of the hypothalamus. After synthesis, these hormones are packaged into secretory vesicles and transported along the axon to the posterior pituitary, where they are released into the bloodstream.
This movement occurs through axonal transport, which relies on the neuronal cytoskeleton and specific motor proteins. In particular:
kinesins mediate anterograde transport, from the cell body to the axon terminal;
dyneins are involved in retrograde transport, from the periphery back to the soma.
In the case of hormones such as vasopressin and oxytocin, transport is anterograde, because the vesicles must reach the axon terminal to be secreted.

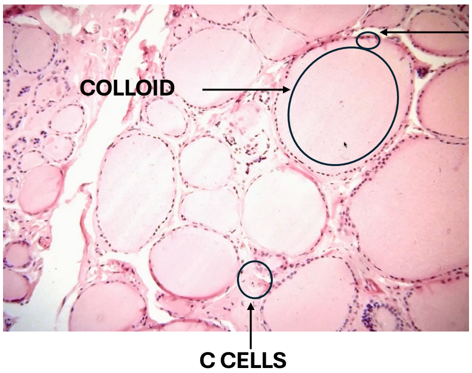
Thyroid



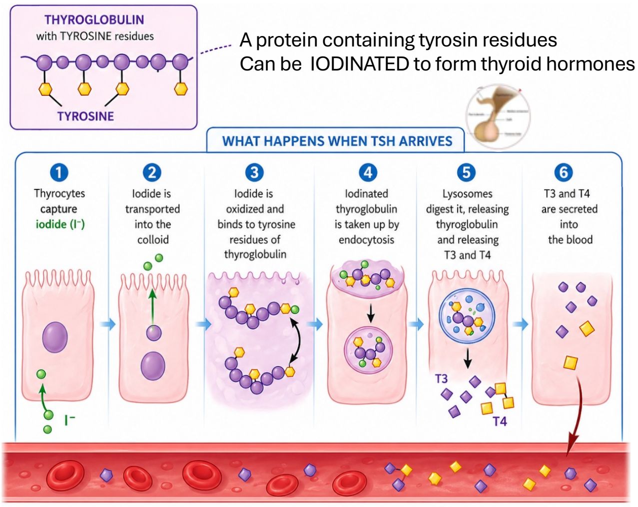
The thyroid is controlled by the hypothalamus–pituitary axis, while the parathyroids are directly regulated by calcium levels in the blood.
The thyroid is located at the base of the neck, attached to the trachea and the laryngeal cartilage.
On the sides, it is close to the jugular veins and carotid arteries.
It has a butterfly shape, with two lobes connected by an isthmus, and it is a single, central organ.

Thyroid

- *organized into follicles*

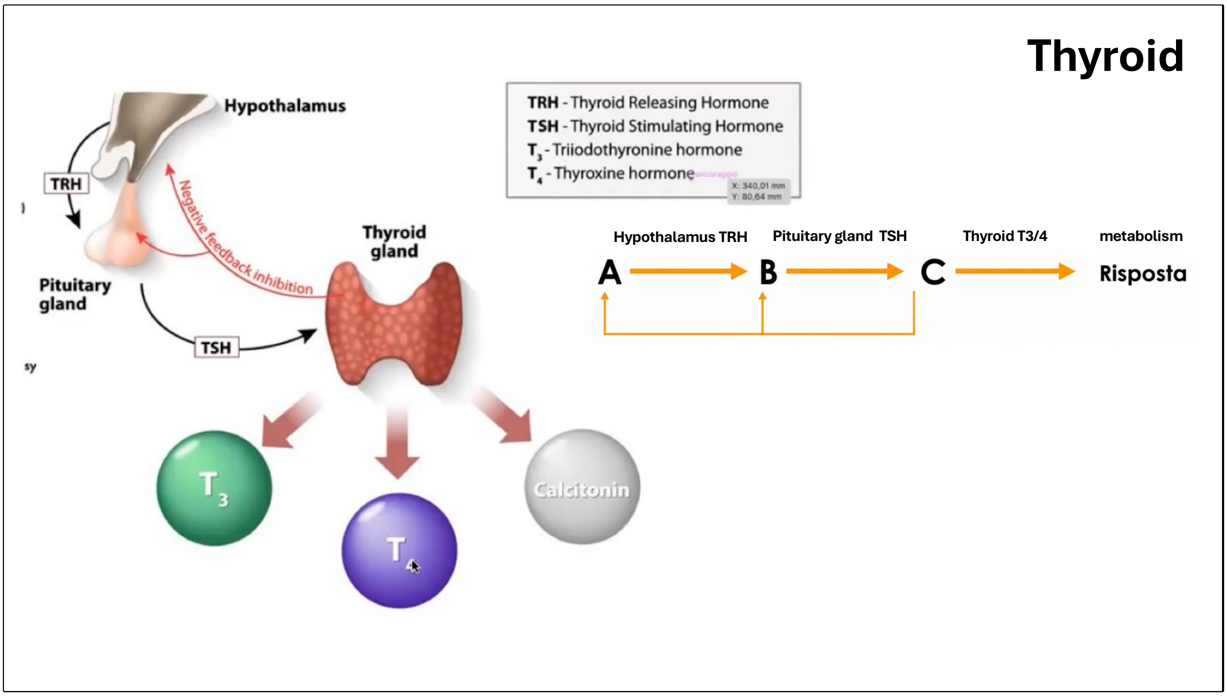


Thyrocytes
They surround a substance called colloid, rich in thyroglobulin.

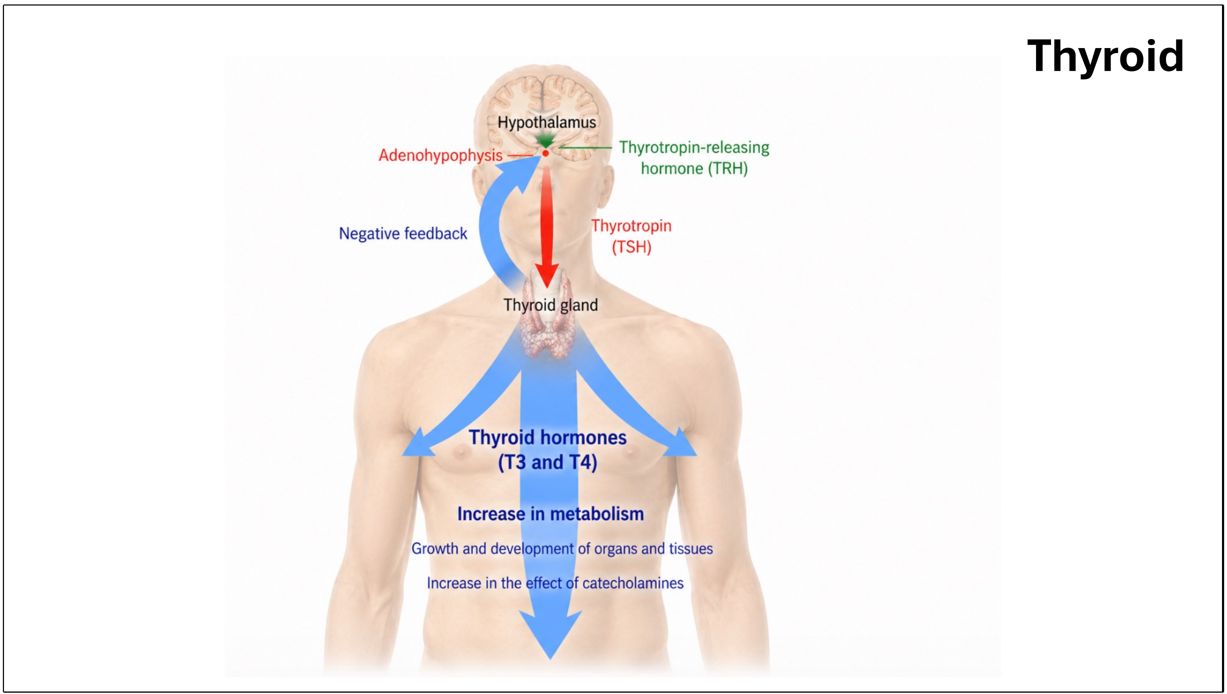


From a histological point of view, the thyroid is organized into follicles, which are the functional units.
Follicles are made of cells called thyrocytes and contain a substance called colloid, rich in thyroglobulin.
This protein contains tyrosine residues that are iodinated to form thyroid hormones.

When the signal from the pituitary (TSH) arrives, thyrocytes start producing thyroid hormones:
T3 (triiodothyronine)
T4 (thyroxine)



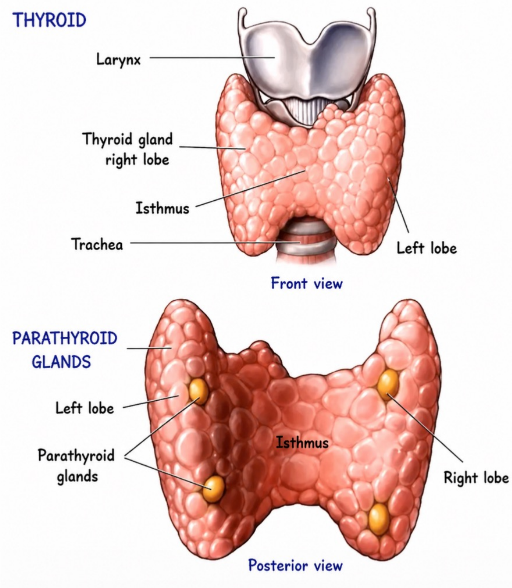
Iodine atoms attached to tyrosine can be 3 (T3) or 4 (T4).
Their secretion is controlled by negative feedback: T3 and T4 inhibit the hypothalamus and the pituitary.
In the thyroid, there are also C cells.
These are interstitial (between follicles) cells that produce calcitonin, which helps regulate calcium levels.

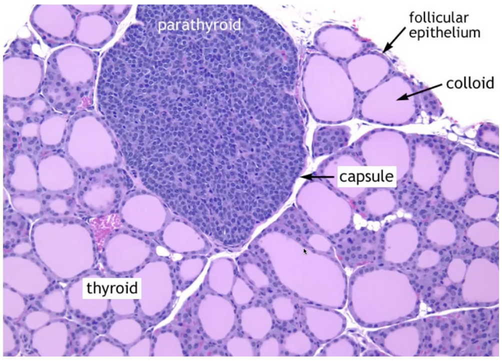


These hormones increase basal metabolism by stimulating catabolic processes.
They stimulate glycolysis and lipolysis, produce heat, and enhance the action of catecholamines (adrenaline, noradrenaline, and dopamine).
They are also essential for growth and development.
They are especially important during pregnancy for the development of the nervous system and bones.
If they are lacking at this stage, the newborn may have cognitive deficits and delayed growth.

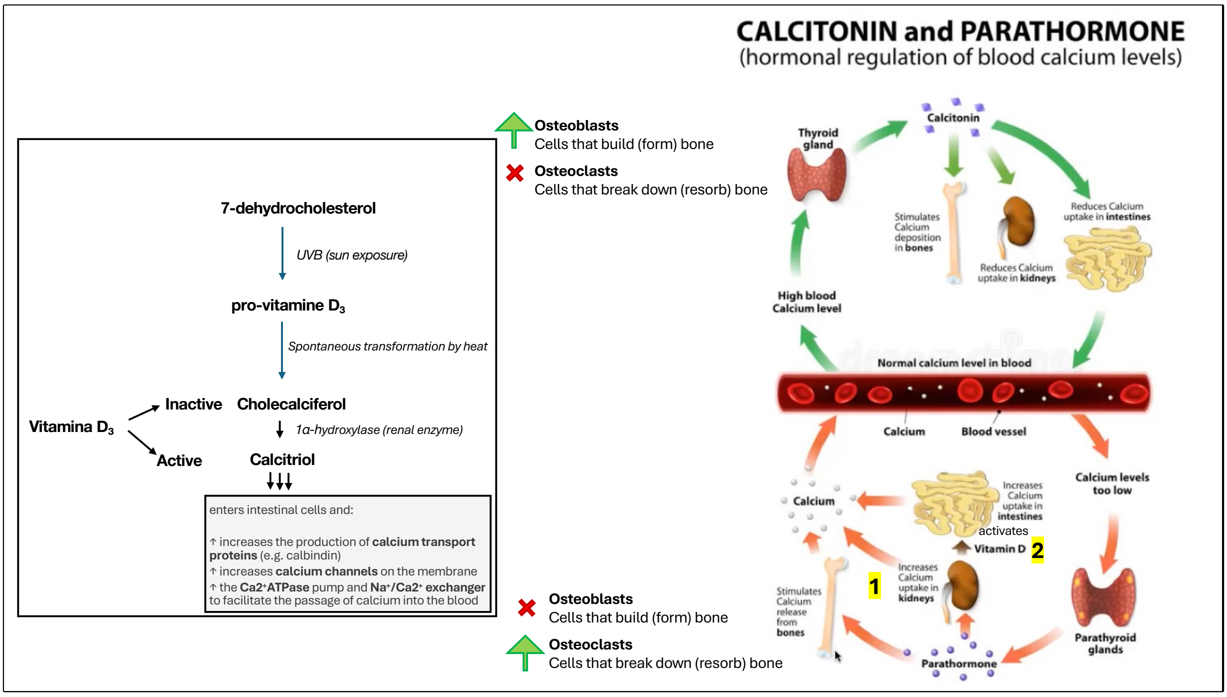
Catecholamines (mainly produced by the adrenal medulla and the sympathetic nervous system):
They have fast and widespread effects:
Increase heart rate and strength of contraction
Increase blood pressure
Stimulate the release of glucose into the blood
Prepare muscles for action (more oxygen and nutrients)

Paratiroidi





The parathyroids are small glands located on the back of the thyroid.
They produce parathyroid hormone (PTH), which is released when calcium levels in the blood are low.



The parathyroid produces parathyroid hormone (PTH) when blood calcium is low.

PTH acts in two main places:

BONE

It inhibits osteoblasts (cells that build bone)

It activates osteoclasts (cells that break down bone)

→ This releases calcium from the bone into the blood

KIDNEY

PTH has two roles:

It increases calcium reabsorption

Calcium is normally filtered by the kidneys and could be lost in urine

PTH helps the kidneys keep more calcium

It activates vitamin D

Vitamin D arrives in the kidney in an inactive form (hydroxylated cholecalciferol)

It is converted into the active form, calcitriol, by a renal enzyme (hydroxylase)

Active vitamin D acts mainly in the intestine, increasing calcium absorption

Without vitamin D, the intestine absorbs little calcium

PTH works in opposition to another hormone: **calcitonin** (produced by thyroid C cells).

When calcium is high, calcitonin acts

It has opposite effects to PTH

Vitamin D3 metabolism (simple):

Cholecalciferol comes from cholesterol

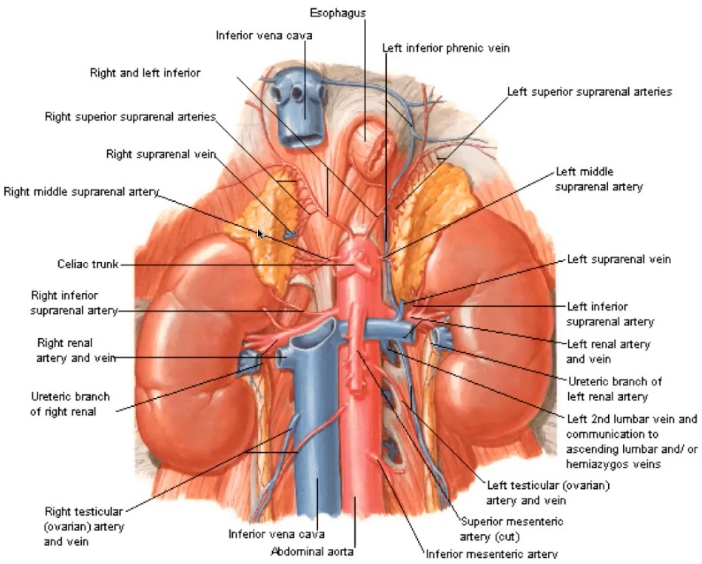
In the skin, 7-dehydrocholesterol + UVB sunlight → pre-vitamin D3

Heat converts it into cholecalciferol (inactive form)

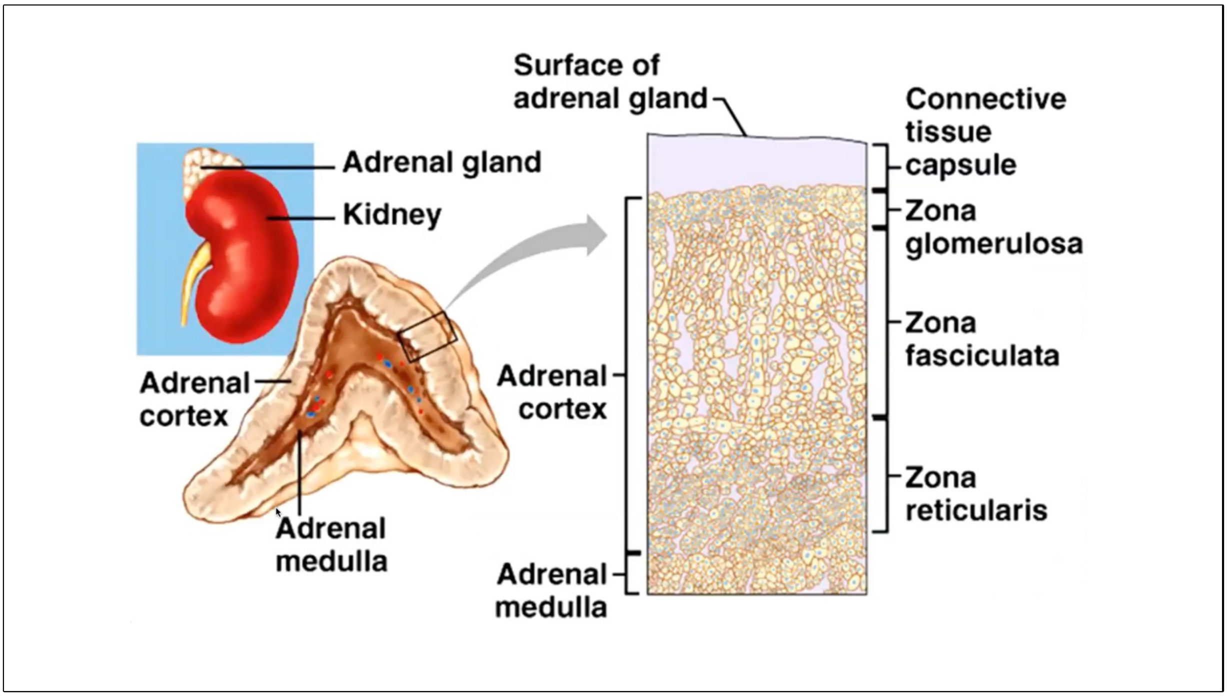
In the kidney, it is activated by the enzyme 1α-hydroxylase → calcitriol

→ Sun exposure is important to increase calcium availability in the blood.

Adrenal glands

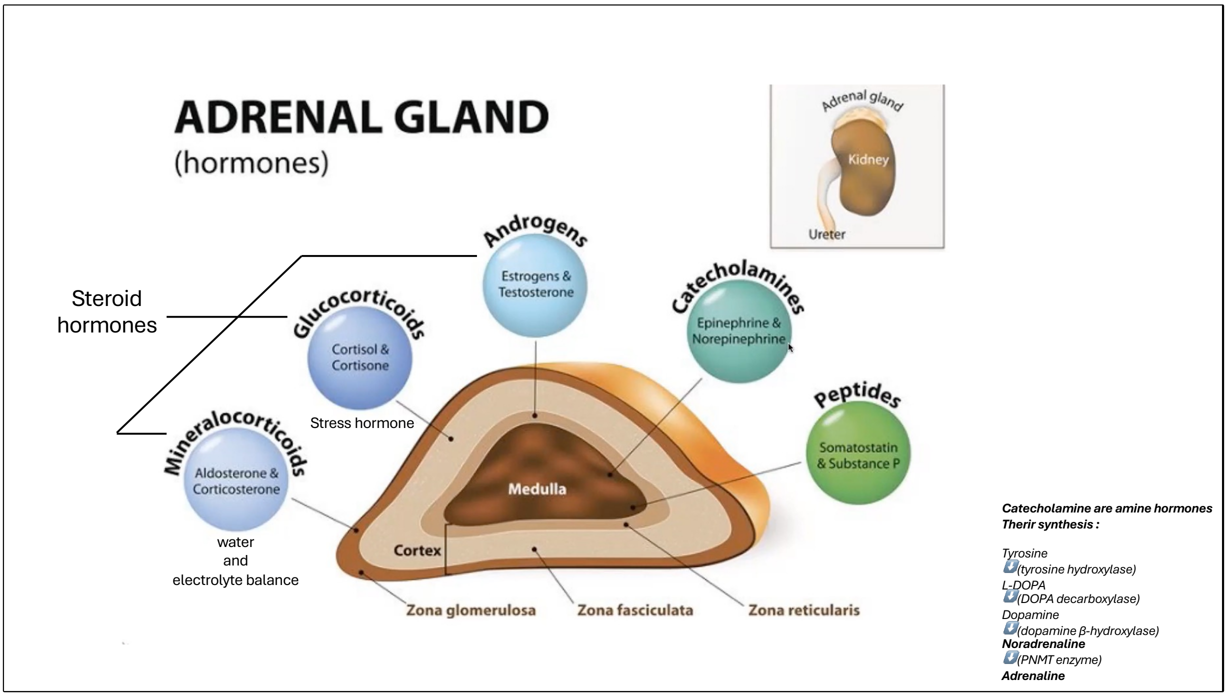


The adrenal glands are located above the kidneys.
They are highly vascularized because they must receive hormones from the pituitary that stimulate them and, at the same time, quickly release their own hormones into the blood through the venous system.



If we look at this organ in cross-section (cut in half), we can see two areas:
Cortex (outer part)
Medulla (inner part)

The cortex is divided into different zones:
Zona glomerulosa
Zona fasciculata
Zona reticularis

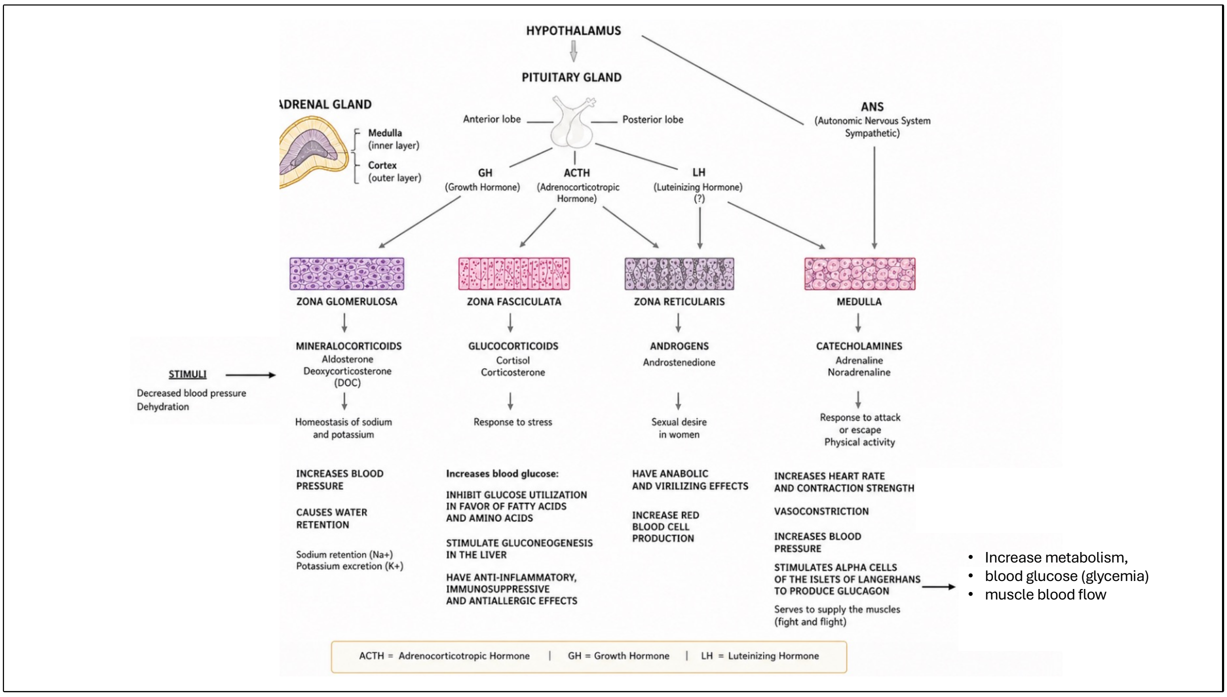


In the **medulla** are produced:
Catecholamines (adrenaline, also called epinephrine, and noradrenaline, also called norepinephrine).
The medulla can be considered part of the sympathetic autonomic nervous system because it produces these hormones when stimulated by it.

Focus:
The sympathetic nervous system sends a direct signal to the adrenal medulla
Nerve fibers release acetylcholine
This activates the medulla cells (chromaffin cells)
Chromaffin cells respond by releasing:
adrenaline
noradrenaline
directly into the blood

Adrenaline and noradrenaline are amine hormones.
They come from tyrosine through a series of enzymatic reactions (hydroxylation, decarboxylation, and methylation).

In the **cortex** are produced steroid hormones:
The zona glomerulosa produces mineralocorticoids, involved in water and electrolyte balance (especially sodium, potassium, and water)
The zona fasciculata produces glucocorticoids, including cortisol, a stress hormone
The zona reticularis produces sex hormones, mainly androgens such as androstenedione and DHEA (dehydroepiandrosterone)

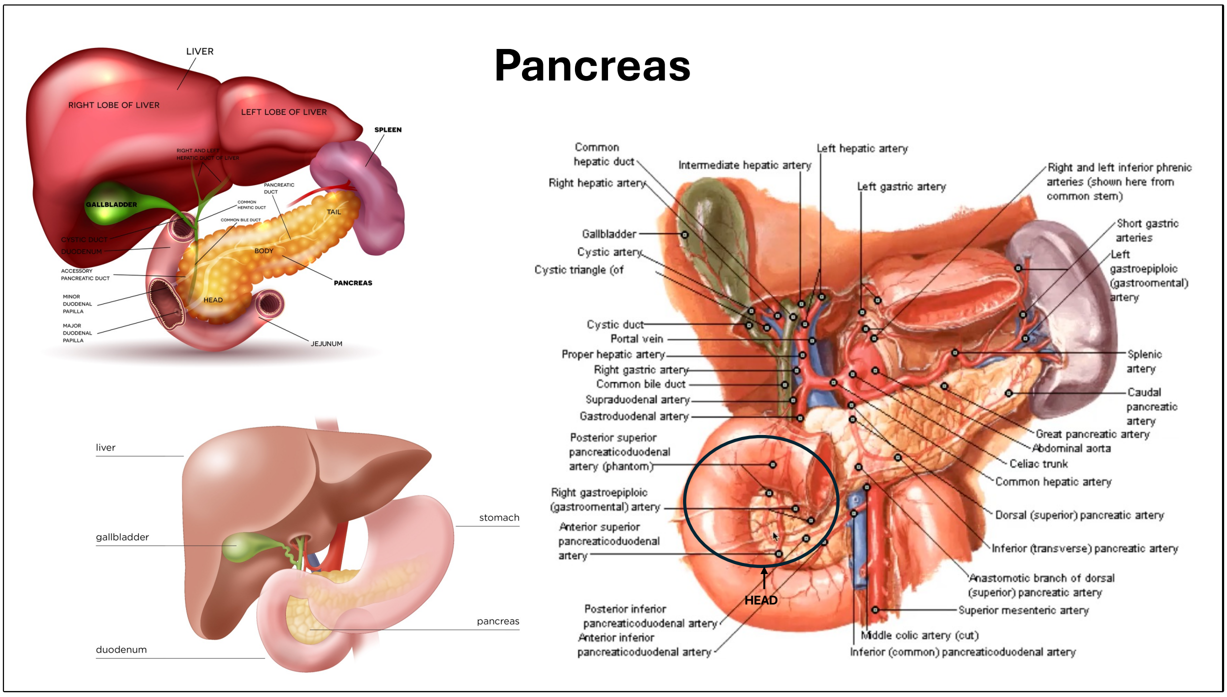


The zona fasciculata and zona reticularis are mainly under the control of the hypothalamic–pituitary axis, therefore:

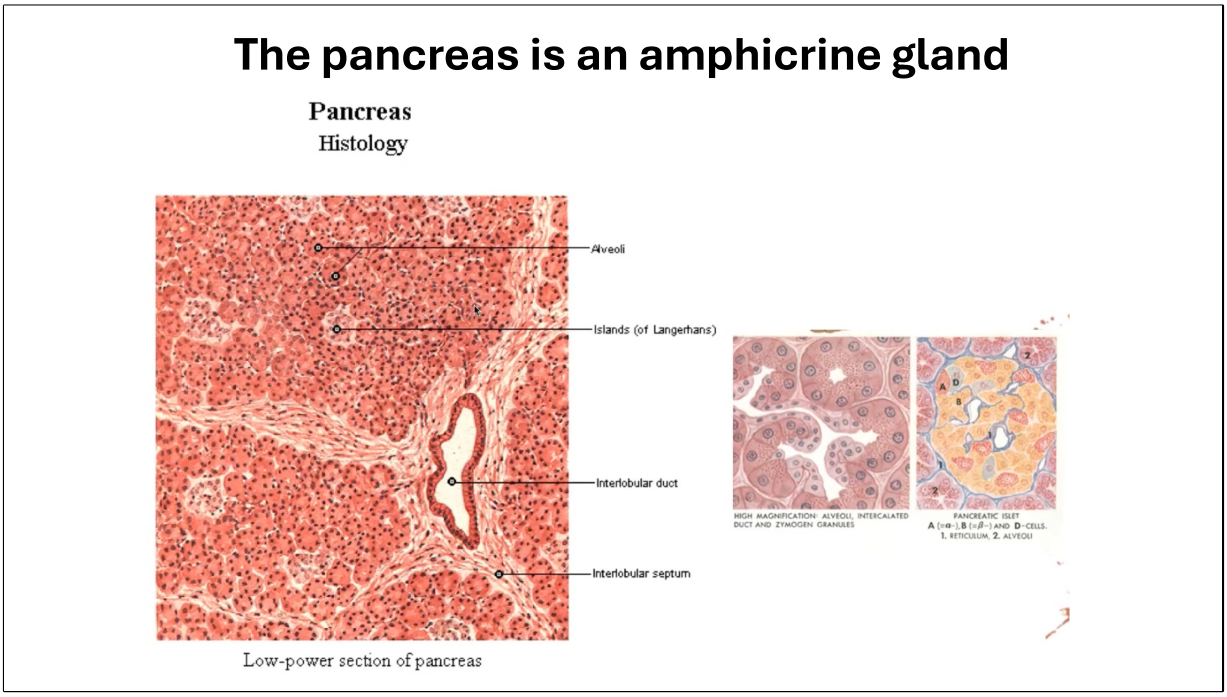
Hypothalamus
produces CRH (Corticotropin-Releasing Hormone)
its function is to “activate” the pituitary gland

Pituitary gland (anterior pituitary / adenohypophysis)
releases ACTH (corticotropin)
this hormone travels through the bloodstream to the adrenal gland

Adrenal gland (cortex, zona fasciculata)
produces cortisol (a glucocorticoid)



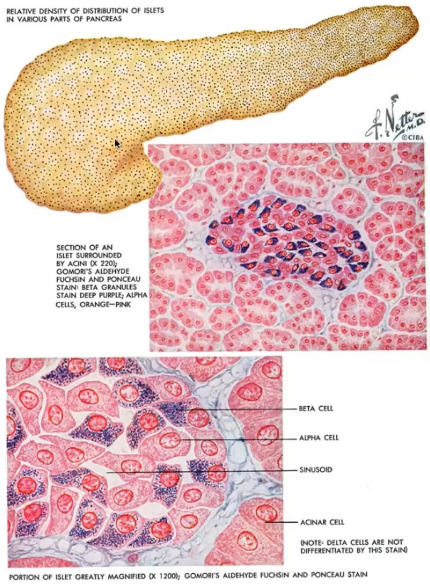
The pancreas is a gland that is not under the direct control of the hypothalamic–pituitary axis.
It is a median organ, located behind the intestinal loops and the main organs of the abdominal cavity, and it is composed of three parts:
a head,
a body,
and a tail.
The head is in very close relation with the duodenum, so much so that they are supplied by the same blood vessels.



If we observe pancreatic tissue at the microscopic (histological) level, we can see that it is composed of two components:

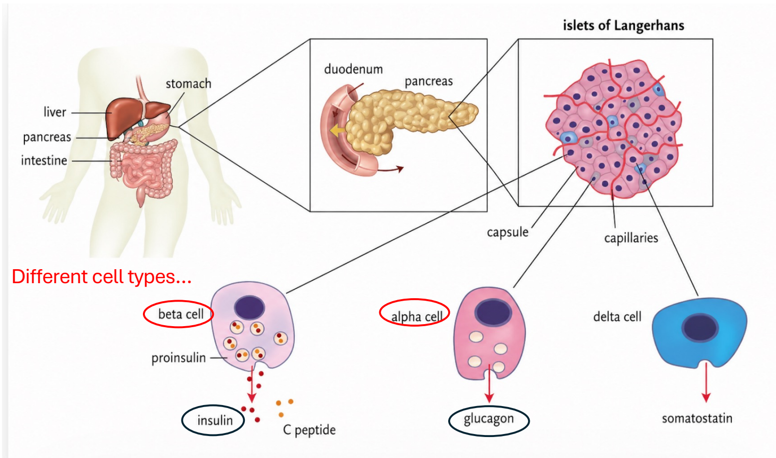
Acini (alveoli), which produce enzymes involved in digestion. These enzymes are released into the pancreatic ducts, which are channels that carry them to the duodenum. Therefore, the acini have an exocrine function. An exocrine gland is a gland that releases its secretion through ducts into a body cavity.

Islets of Langerhans, which are endocrine structures, because they produce hormones that are released directly into the bloodstream.
Therefore, the pancreas has both an exocrine and an endocrine function, and for this reason it is defined as a mixed gland (amphicrine gland).

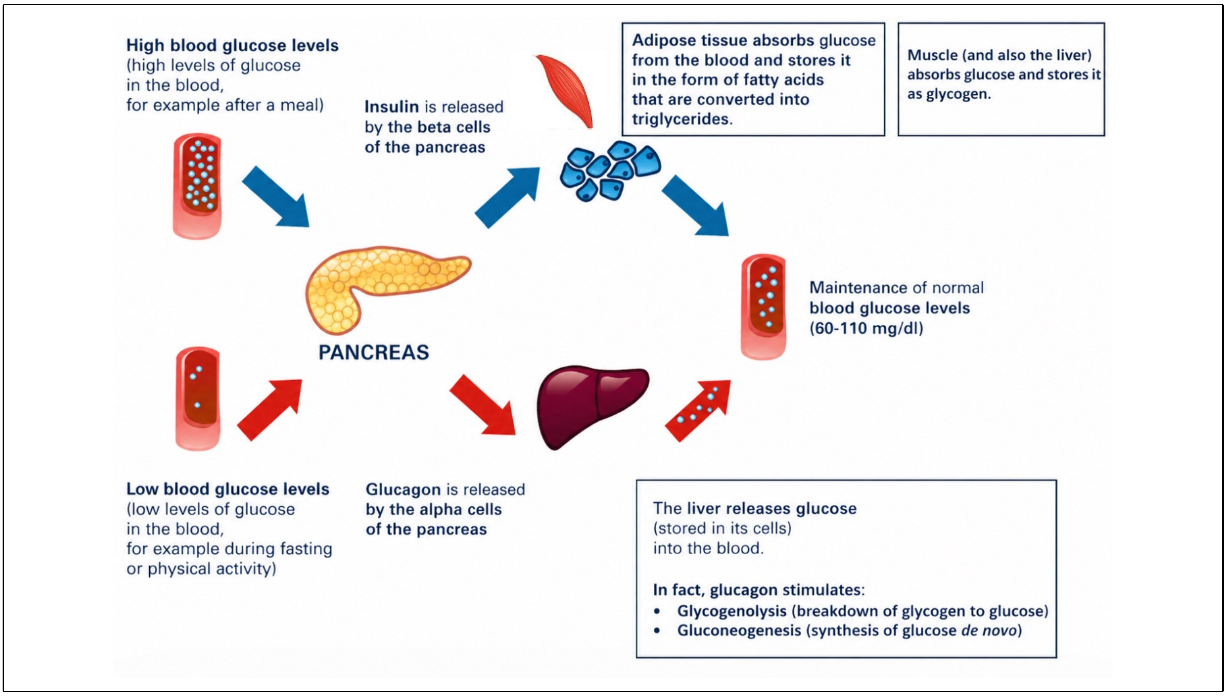


The **Islets of Langerhans** account for about **10% of the total volume of the pancreas** and are more concentrated in the **tail region**.

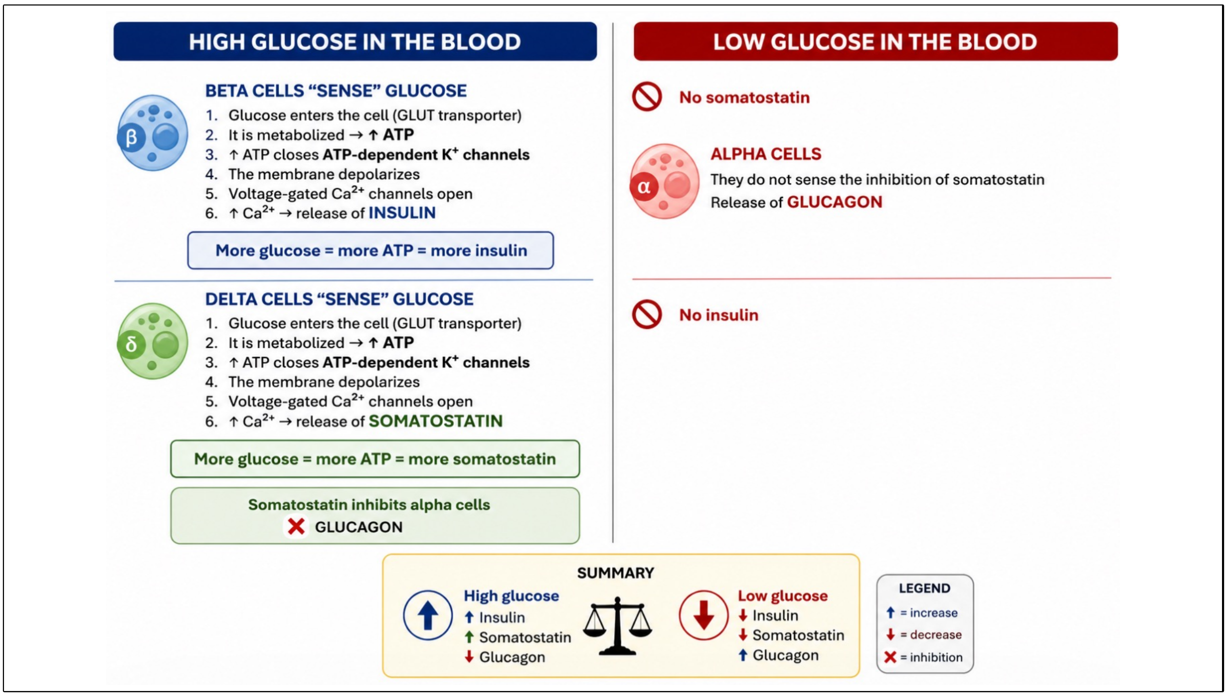
Insuline e Glucagon



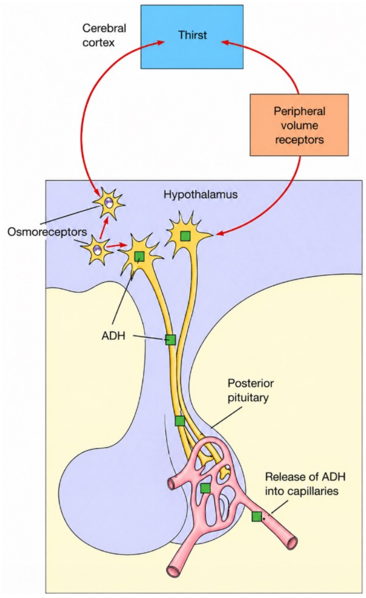
In the Islets of Langerhans, there are different cell types, including alpha and beta cells: one produces insulin and the other glucagon.
These two hormones are involved in the regulation of blood glucose levels (glycemia), that is, the concentration of glucose in the blood, and they act as counter-regulatory hormones.
When, after a meal rich in sugars, blood glucose levels rise, the beta cells of the pancreas detect this increase and produce insulin, releasing it into the bloodstream. Insulin exerts its effects by promoting the uptake of glucose into tissues and by inhibiting the activity of alpha cells.
When, on the other hand, blood glucose levels decrease (for example during fasting), the alpha cells release glucagon. This hormone enters the circulation and reaches the liver, where it binds to specific receptors on hepatic cells. This binding activates a cascade of intracellular signals that leads to glycogenolysis (breakdown of glycogen, the storage form of glucose) and gluconeogenesis (production of new glucose).
In this way, glucagon contributes to increasing blood glucose levels.



Overview of the coordinated regulation between insulin and glucagon


HIGH GLUCOSE IN THE BLOOD
BETA CELLS "SENSE" GLUCOSE
β
1. Glucose enters the cell (GLUT transporter)
2. It is metabolized → ↑ ATP
3. ↑ ATP closes ATP-dependent K^+ channels
4. The membrane depolarizes
5. Voltage-gated Ca^{2+} channels open
6. ↑ Ca^{2+} → release of INSULIN
More glucose = more ATP = more insulin
DELTA CELLS "SENSE" GLUCOSE
δ
1. Glucose enters the cell (GLUT transporter)
2. It is metabolized → ↑ ATP
3. ↑ ATP closes ATP-dependent K^+ channels
4. The membrane depolarizes
5. Voltage-gated Ca^{2+} channels open
6. ↑ Ca^{2+} → release of SOMATOSTATIN
More glucose = more ATP = more somatostatin
Somatostatin inhibits alpha cells
✕ GLUCAGON
LOW GLUCOSE IN THE BLOOD
No somatostatin
α
ALPHA CELLS
They do not sense the inhibition of somatostatin
Release of GLUCAGON
No insulin
SUMMARY
High glucose
↑ Insulin
↑ Somatostatin
↓ Glucagon
Low glucose
↓ Insulin
↓ Somatostatin
↑ Glucagon
LEGEND
↑ = increase
↓ = decrease
✕ = inhibition

Antidiuretic hormone (ADH)



Origin
Hypothalamus → Posterior pituitary

Function
↓ Diuresis
↑ Water reabsorption (kidney, collecting duct)
Inserts aquaporins

Stimuli
Dehydration
↑ Osmolarity (increased solute concentration in the blood)
↓ Blood volume

Effect
↓ Urine volume
More concentrated urine
Water conservation

Antidiuretic hormone (ADH), or vasopressin, is produced by the hypothalamus and released by the posterior pituitary. Its main function is to reduce urine production, helping the body conserve water.
ADH secretion increases during dehydration, low blood volume (e.g., hemorrhage), or high plasma osmolarity (high concentration of solutes in the blood). In these conditions, the body tries to prevent further fluid loss.
Once released into the bloodstream, ADH reaches the kidney, where it acts on the collecting duct. It promotes the insertion of proteins called aquaporins into the cell membrane, allowing water reabsorption.
Because the renal medulla is hyperosmotic, water moves by osmosis from the urine into the blood. As a result, urine becomes less abundant and more concentrated, helping maintain water balance.

Note:
Aquaporins are stored in intracellular vesicles
Without ADH → aquaporins stay inside the cell
With ADH → aquaporins are inserted into the collecting duct membrane