Ingegneria delle tecnologie per la salute

Fondamenti di anatomia e istologia

Sistema Endocrino
When you send a text message to two friends to meet you at six, you’re sending digital signals that (you hope) will affect their behavior—even though they are some distance away. Similarly, certain cells send chemical signals to other cells in the body that influence their behavior. This long-distance intercellular communication, coordination, and control is critical for homeostasis.

In the human body, two major organ systems participate in relatively “long distance” communication:

- the nervous system
- the endocrine system
Nervous system

The nervous system uses two types of intercellular communication—electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters.

Neurotransmitters act **locally** and **rapidly**. When an electrical signal arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap between a sending neuron and a receiving neuron or muscle cell) and neurotransmitters are released. Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response.

The target cell responds within milliseconds and this response ceases very quickly once the neural signaling ends → useful for body functions that involve quick, brief actions, such as movement, sensation, and cognition.
Endocrine system

The endocrine system uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the hormone—into the extracellular fluid → Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response.

Endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones.

For example, the hormones released when you are confronted with a dangerous or frightening situation (epinephrine and norepinephrine) are released within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

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<td>Environment targeted</td>
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Homeostasis

The long-distance intercellular communication, coordination, and control is critical for keeping homeostasis.

1. **Stimulus** produces change in variable.
2. **Receptor** detects change.
3. **Input**: Information sent along afferent pathway to control center.
4. **Output**: Information sent along efferent pathway to effector.
5. **Response** of effector feeds back to reduce the effect of stimulus and returns variable to homeostatic level.
The **endocrine gland** is the major player in endocrine system. The primary function of these ductless glands is to secrete their hormones directly into the surrounding fluid. The interstitial fluid and the blood vessels then transport the hormones throughout the body.

The ductless endocrine glands are not to be confused with the body’s **exocrine system**, whose glands release their secretions through ducts outside the body (e.g. the sebaceous and sweat glands of the skin) or in the lumen of hollow organs (e.g. pancreas secrete pancreatic juice through the pancreatic and accessory ducts to the lumen of the small intestine).
Endocrine System

It is composed of:

- The **endocrine glands**:
  - the pituitary gland (*ipofisi*)
  - the thyroid gland
  - the parathyroid gland
  - the adrenal gland
  - the pineal gland (*epifisi*)

- Some **glands with both endocrine and non-endocrine functions** (exocrine). For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels.

- Some organs (the hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, female ovaries, and male testes are others) that contain **cells with endocrine function**.

- **Adipose tissue and bone tissue** that produce hormones.
Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many other body functions.
Cellular signalling

In **endocrine signaling**, hormones secreted into the extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body.

**Autocrine signaling** takes place within the same cell. An autocrine is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the **paracrine signaling**, that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways. Another example is the neurotransmitters of the nervous system, which act only locally within the synaptic cleft.
Hormones action

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its **target cells**; that is, cells with **receptors** for that particular hormone.

A **hormone receptor** is a protein located either inside the cell or within the cell membrane, that recognize molecules with specific shapes (specific hormones) and respond only to those hormones that are recognized. When a receptor recognize its specific hormone creates a response in the target cell.

The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses → the response triggered by a hormone depends not only on the hormone, but also on the target cell.
Hormones action

The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell’s response.

Once the target cell receives the hormone signal, it can respond in a variety of ways.

The response may include:
• stimulation of protein synthesis
• activation or deactivation of enzymes
• alteration in the permeability of the cell
• altered rates of mitosis and cell growth
• stimulation of the secretion of products
The hormones of the human body can be divided into two major groups on the basis of their chemical structure.

- Hormones derived from amino acids include amines, peptides, and proteins
- Hormones derived from lipids include steroids

These chemical groups affect a hormone’s distribution, the type of receptors it binds to, and other aspects of its function.

According to their solubility, hormones can be divided in:
- **Lipid-soluble hormones**
- **Water-soluble hormones**
Lipid-soluble hormones

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel to their target cell bound to a transport protein.

This more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid–derived hormone epinephrine has a half-life of approximately one minute.

A hormone’s half-life is the time required for half the concentration of the hormone to be degraded.
Lipid-soluble hormones

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane.

**Steroid hormones** are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor.

**Thyroid hormones** are also lipid-soluble and can enter the cell.
Water soluble hormone

Except for thyroid hormones, which are lipid-soluble, all amino acid–derived hormones bind to cell membrane receptors that are located, at least in part, on the extracellular surface of the cell membrane. Therefore, they do not directly affect the transcription of target genes, but instead initiate a signaling cascade that is carried out by a molecule called a second messenger. In this case, the hormone is called a first messenger. The second messenger used by most hormones is cyclic adenosine monophosphate (cAMP).
Several factors influence the target cell response:

- **Downregulation.** The presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that hormone. This allows cells to become less reactive to the excessive hormone levels.

- **Upregulation.** When the level of a hormone is chronically reduced, target cells increase their number of receptors. This process allows cells to be more sensitive to the hormone that is present.
Regulation of Hormone Secretion

To prevent abnormal hormone levels and a potential disease state, hormone levels must be tightly controlled. The body maintains this control by balancing hormone production and degradation. Feedback loops govern the initiation and maintenance of most hormone secretion in response to various stimuli.

**Positive feedback loops** are characterized by the release of additional hormone in response to an original hormone release. The release of oxytocin during childbirth is a positive feedback loop. The initial release of oxytocin begins to signal the uterine muscles to contract, which pushes the fetus toward the cervix, causing it to stretch. This, in turn, signals the pituitary gland to release more oxytocin, causing labor contractions to intensify. The release of oxytocin decreases after the birth of the child.

**Negative feedback loops** are characterized by the inhibition of further secretion of a hormone in response to adequate levels of that hormone. This allows blood levels of the hormone to be regulated within a narrow range. As glucocorticoid concentrations in the blood rise, the hypothalamus and pituitary gland reduce their signaling to the adrenal glands to prevent additional glucocorticoid secretion.
Negative feedback

1. Imbalance
   - Hypothalamus perceives low blood concentrations of glucocorticoids via sensors in the blood vessels
   - Blood
2. Hormone release
   - Hypothalamus releases corticotropin-releasing hormone (CRH)
   - Hypothalamus glucocorticoid sensor
3. Correction
   - Blood concentration of glucocorticoids increases
   - Blood
4. Negative feedback
   - CRH release
   - CRH release starts a hormone cascade that triggers the adrenal glands to release glucocorticoid into blood
   - Glucocorticoid release
   - Glucocorticoid levels in the blood increase
   - Homeostasis
   - Hypothalamus perceives normal concentration of glucocorticoid and stops releasing CRH
The hypothalamus–pituitary complex can be thought of as the “command center” of the endocrine system.

This complex:
• secretes several hormones that directly produce responses in target tissues
• secretes hormones that regulate the synthesis and secretion of hormones of other glands
• coordinates the messages of the endocrine and nervous systems → often a stimulus received by the nervous system must pass through the hypothalamus–pituitary complex to be translated into hormones that can initiate a response
The hypothalamus is a structure of the diencephalon of the brain located anterior and inferior to the thalamus. It has both neural and endocrine functions, producing and secreting many hormones. The hypothalamus is anatomically and functionally related to the pituitary gland (or hypophysis), a bean-sized organ suspended from it by a stem called the infundibulum (or pituitary stalk).

The pituitary gland is cradled within the sellaturcica of the sphenoid bone of the skull. It consists of two lobes that arise from distinct parts of embryonic tissue: the posterior pituitary neurohypophysis is neural tissue, whereas the anterior pituitary (also known as the adenohypophysis) is glandular tissue that develops from the primitive digestive tract.
During embryonic development, the epithelium of the pharyngeal roof (oral cavity) forms an outpocketing called the hypophyseal (Rathke) pouch. As development proceeds, the hypophyseal pouch detaches from the oral cavity to become the cellular or glandular portion of the hypophysis or adenohypophysis (anterior pituitary). At the same time, the downgrowth from the developing brain (diencephalon) forms the neural portion of the hypophysis, called the neurohypophysis (posterior pituitary).

The two separately developed structures then unite to form a single pituitary gland, the hypophysis. The hypophysis remains attached to a ventral extension of the brain called the hypothalamus through the infundibulum.
Pituitary gland-hypophysis

Size of a pea, 0.5 g weight
On the basis of the hypothalamus, in the sella turcica (sphenoid bone)
Strictly related with the optic chiasm (bitemporal hemianopsia in pineal adenomas)
The posterior pituitary is actually an extension of the neurons of the paraventricular and supraoptic nuclei of the hypothalamus. The cell bodies of these regions rest in the hypothalamus, but their axons descend as the hypothalamic–hypophyseal tract within the infundibulum, and end in axon terminals that comprise the posterior pituitary.
The neurohypophysis consists of three parts:

- **median eminence**: located at the base of the hypothalamus of the brain from which extends the pituitary stalk, or infundibulum
- **infundibulum** in which is found a multitude of unmyelinated axons that extend from the neurons in the hypothalamus
- **pars nervosa**: this region contains the terminal ends of unmyelinated axons for the storage of hormones that have been secreted by the neurons in the hypothalamus. Surrounding the axons are the nonsecretory pituicytes that support and nourish the axons.

The neurons (cell bodies) of these axons are located in the **supraoptic** and **paraventricular nuclei** (a collection of neurons) in the hypothalamus. The unmyelinated axons that extend from the hypothalamus into the neurohypophysis form the **hypothalamohypophyseal tract** and the bulk of the neurohypophysis. These axons terminate near the fenestrated capillaries in the pars nervosa.

Neurons in the hypothalamus first synthesize the hormones that are released from the neurohypophysis → transported from the hypothalamus down the axons by **axonal transport** to the neurohypophysis. → Here, the hormones accumulate and are stored in the distended terminal ends of unmyelinated axons as **Herring bodies**. When needed, hormones from the neurohypophysis are directly released into the fenestrated capillaries of the pars nervosa by nerve impulses from the hypothalamus.
Posterior pituitary

1 Connective tissue capsule
2 Basophils
3 Capillaries
4 Acidophils
5 Pars distalis
6 Infundibulum
7 Pars tuberalis
8 Blood vessels
9 Pars intermedia a. Colloid vesicles
10 Connective tissue capsule
11 Pars nervosa
The posterior pituitary gland does not produce hormones, but rather stores and secretes hormones produced by the hypothalamus.

The paraventricular nuclei produce oxytocin (OT)
The supraoptic nuclei produce antidiuretic hormone (ADH)

These hormones travel along the axons into storage sites in the axon terminals of the posterior pituitary. In response to signals from the same hypothalamic neurons, the hormones are released from the axon terminals into the bloodstream.

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<tbody>
<tr>
<td>Posterior</td>
<td>Antidiuretic hormone (ADH)</td>
<td>Peptide</td>
<td>Stimulates water reabsorption by kidneys</td>
</tr>
<tr>
<td>Posterior</td>
<td>Oxytocin</td>
<td>Peptide</td>
<td>Stimulates uterine contractions during childbirth</td>
</tr>
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</table>
ADH

In response to high blood osmolarity, which can occur during dehydration or following a very salty meal, the **osmoreceptors** signal the posterior pituitary to release ADH → The target cells of ADH are located in the **tubular cells of the kidneys**: it increases epithelial permeability to **water**, allowing increased water reabsorption. The more water reabsorbed from the filtrate, the greater the amount of water that is returned to the blood and the less that is excreted in the urine.

ADH is also known as **vasopressin** because, in very high concentrations, it causes **constriction of blood vessels**, which increases blood pressure by increasing peripheral resistance.

**Negative feedback loop**: As blood osmolarity decreases, the hypothalamic osmoreceptors sense the change and prompt a corresponding decrease in the secretion of ADH→less water is reabsorbed from the urine filtrate.

**No ADH Present-** Collecting Duct is NOT permeable to water and large volume of urine is produced

**ADH Present-** Collecting Duct is permeable to water and a small volume of urine is produced

Alcohol consumption inhibits the release of ADH, resulting in increased urine production that can eventually lead to dehydration and a hangover.
When fetal development is complete, the peptide-derived hormone **oxytocin** stimulates uterine contractions and dilation of the cervix. Oxytocin is continually released throughout childbirth through a **positive feedback mechanism**.

Oxytocin prompts uterine contractions that push the fetal head toward the cervix. In response, cervical stretching stimulates additional oxytocin to be synthesized by the hypothalamus and released from the pituitary. This increases the intensity and effectiveness of uterine contractions and prompts additional dilation of the cervix. The feedback loop continues until birth.

OT continues to play a role in maternal and newborn health. First, oxytocin is necessary for the milk ejection reflex in breastfeeding women. As the newborn begins suckling, sensory receptors in the nipples transmit signals to the hypothalamus. In response, oxytocin is secreted and released into the bloodstream. Within seconds, cells in the mother’s milk ducts contract, ejecting milk into the infant’s mouth.
Posterior Pituitary

Releasing hormone (hypothalamus)

ADH

Posterior Pituitary Hormones

Pituitary hormone

Stores ADH

Target

Kidneys, sweat glands, circulatory system

Effects

Water balance

OT

Female reproductive system

Triggers uterine contractions during childbirth
The epithelial-derived adenohypophysis has three subdivisions:

- The **pars distalis** is the largest part of the hypophysis.
- The **pars tuberalis** surrounds the neural stalk, or infundibulum.
- The **pars intermedia** is a thin cell layer between the pars distalis and the neurohypophysis. It represents the remnant of the hypophyseal (Rathke) pouch that becomes rudimentary in humans but prominent in other mammals.
The anterior pituitary does manufacture hormones. However, the secretion of hormones from the anterior pituitary is regulated by two classes of hormones secreted by the hypothalamus:

- the **releasing hormones** that stimulate the secretion of hormones from the anterior pituitary
- the **inhibiting hormones** that inhibit secretion.

Because the adenohypophysis does not develop from the neural tissue, its connection to the **hypothalamus** of the brain is via a rich vascular network made of **fenestrated** capillaries.
Anterior Pituitary

Hypothalamic hormones are secreted by neurons, but enter the anterior pituitary through blood vessels: the hypophyseal portal system in the infundibulum. It allows hypothalamic hormones to be transported to the anterior pituitary without entering the systemic circulation. The system originates from the superior hypophyseal artery, which branches off the carotid arteries. Hypothalamic releasing and inhibiting hormones travel through a primary capillary plexus to the portal veins, which carry them into the anterior pituitary. Hormones produced by the anterior pituitary (in response to releasing hormones) enter a secondary capillary plexus, and from there drain into the circulation.
Anterior Pituitary

The cells of the adenohypophysis were initially classified as **chromophobes** and **chromophils** based on the affinity of their cytoplasmic granules for specific stains. The pale-staining chromophobes are believed to be either degranulated chromophils with few granules or undifferentiated stem cells. The chromophils were further subdivided into **acidophils** and **basophils** because of their staining properties.

Immunocytochemical techniques now identify these cells on the basis of their specific hormones. The adenohypophysis includes two types of acidophils, the **somatotrophs** (producing GH) and **mammatrophs** (producing PRL), as well as three types of basophils: **gonadotrophs** (producing FSH and LH), **thyrotrophs** (producing TRH), and **corticotrophs** (producing ACTH).
Anterior Pituitary

Pars distalis

1. Basophils
2. Acidophils
3. Blood vessels
4. Chromophobes
5. Capillaries
6. Connective tissue fibers
Anterior Pituitary

Sections of pars distalis, pars intermedia, and pars nervosa. Stain: hematoxylin and eosin.
Anterior Pituitary

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<tr>
<td>Anterior</td>
<td>Growth hormone (GH)</td>
<td>Protein</td>
<td>Promotes growth of body tissues</td>
</tr>
<tr>
<td>Anterior</td>
<td>Prolactin (PRL)</td>
<td>Peptide</td>
<td>Promotes milk production from mammary glands</td>
</tr>
<tr>
<td>Anterior</td>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Glycoprotein</td>
<td>Stimulates thyroid hormone release from thyroid</td>
</tr>
<tr>
<td>Anterior</td>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Peptide</td>
<td>Stimulates hormone release by adrenal cortex</td>
</tr>
<tr>
<td>Anterior</td>
<td>Follicle-stimulating hormone (FSH)</td>
<td>Glycoprotein</td>
<td>Stimulates gamete production in gonads</td>
</tr>
<tr>
<td>Anterior</td>
<td>Luteinizing hormone (LH)</td>
<td>Glycoprotein</td>
<td>Stimulates androgen production by gonads</td>
</tr>
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Of the hormones of the anterior pituitary, TSH, ACTH, FSH, and LH are collectively referred to as tropic hormones (trope- = “turning”) because they turn on or off the function of other endocrine glands.
Growth Hormone (GH)

1) Release of growth hormone:
   - Hypothalamus releases growth hormone–releasing hormone (GHRH)
   - GHRH stimulates the anterior pituitary to release growth hormone (GH)

2a) Glucose-sparing effect:
   - Stimulates adipose cells to break down stored fat, fueling growth effects

2b) Growth effects:
   - Increases uptake of amino acids from the blood
   - Enhances cellular proliferation and reduces apoptosis

Targets:
- Bone cells
- Muscle cells
- Nervous system cells
- Immune system cells

3) Inhibition of growth hormone:
   - High IGF-1 levels perceived by hypothalamus
   - Growth hormone–inhibiting hormone (GHIH) is released to inhibit GH release
   - GHIH inhibits GH release in the anterior pituitary

GH stimulates lipolysis, releasing fatty acids into the blood. Many tissues switch from glucose to fatty acids as their main energy source. Less glucose is taken up from the bloodstream.

Its primary function is anabolic; it promotes protein synthesis and tissue building through direct and indirect mechanisms.

GH levels are controlled by the release of GHRH and GHIH (also known as somatostatin) from the hypothalamus.
Dysfunction of the endocrine system’s control of growth can result in several disorders. For example, **gigantism** is a disorder in children that is caused by the secretion of abnormally large amounts of GH, resulting in excessive growth.
A similar condition in adults is **acromegaly**, a disorder that results in the growth of bones in the face, hands, and feet in response to excessive levels of GH in individuals who have stopped growing.
Growth Hormone (GH) disorders

Abnormally low levels of GH in children can cause growth impairment—a disorder called pituitary dwarfism (also known as growth hormone deficiency). It is an harmonic dwarfism.
Anterior Pituitary Hormones

- **GnRH**: Stimulates production of sex hormones by gonads
- **FSH**: Stimulates production of sperm and eggs
- **TRH**: Stimulates the release of thyroid hormone (TH). TH regulates metabolism.
- **PRL**: Promotes milk production
- **GHRH**: Induces targets to produce insulin-like growth factors (IGFs). IGFs stimulate body growth and a higher metabolic rate.
- **CRH**: Induces targets to produce glucocorticoids, which regulate metabolism and the stress response
Intermediate Pituitary

The cells in the zone between the pituitary lobes secrete a hormone known as melanocyte-stimulating hormone (MSH). Local production of MSH in the skin is responsible for melanin production in response to UV light exposure. The role of MSH made by the pituitary is more complicated. For instance, people with lighter skin generally have the same amount of MSH as people with darker skin. Nevertheless, this hormone is capable of darkening of the skin by inducing melanin production in the skin’s melanocytes. Women also show increased MSH production during pregnancy; in combination with estrogens, it can lead to darker skin pigmentation, especially the skin of the areolas and labia minora.

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<td>Intermediate zone</td>
<td>Melanocyte-stimulating hormone</td>
<td>Peptide</td>
<td>Stimulates melanin formation in melanocytes</td>
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Pituitary gland: overview
A butterfly-shaped organ, the **thyroid gland** is located anterior to the trachea, just inferior to the larynx. The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces.

Endodermic origin.
Anterior: platisma and skin

Posterior: trachea, superior and inferior laringeal nerves, parathyroids

Lateral: great vessel of the neck
Thyroid gland

In thyroid gland cells are arranged into spherical structures, called **follicles**, where the hormones are stored. Each follicle is lined with a single layer of follicular cells and surrounded by reticular fibers. The adjacent vascular network of capillaries surrounds the follicles for the easy entrance of thyroid hormones from the follicles into the bloodstream. The follicular epithelium can be simple squamous, cuboidal, or low columnar, depending on the state of activity of the thyroid gland.

**Follicles are the structural and functional units of the thyroid gland.**
Thyroid gland

The cells that surround the follicles, the **follicular cells**, also called principal cells, synthesize, release, and store their product in the lumen of the follicles as a gelatinous substance called **colloid**. Colloid is composed of **thyroglobulin**, an iodinated glycoprotein that is the inactive storage form of the thyroid hormones. In addition to follicular cells, the thyroid gland also contains larger, pale-staining **parafollicular cells**. These cells are found either peripherally in the follicular epithelium or within the follicle.

Thyroid hormones production is dependent on the hormones’ essential and unique component: **iodine**.
Thyroid gland

c) Thyroid follicle cells

- Parafollicular cell
- Colloid-containing follicle
- Follicle cells (cuboidal epithelium)
Thyroid gland

1. Retracted, distorted colloid
2. Follicular cells
3. Parafollicular cells
4. Capillary
5. Blood vessel
6. Follicular cells (tangential section)
7. Follicles with colloid
8. Capillary
9. Interfollicular connective tissue
10. Follicular cells
11. Parafollicular cells
Synthesis and Release of Thyroid Hormones

The secretory functions of **follicular cells**, which are responsible for the production of thyroid hormones in the thyroid gland, are controlled by **thyroid-stimulating hormone (TSH)** released from the adenohypophysis. **Iodide** is an essential element for the production of the active thyroid hormones **triiodothyronine (T3)** and **tetraiodothyronine**, or **thyroxine (T4)**, that are released into the bloodstream by the thyroid gland.

1. Low levels of thyroid hormones in the blood stimulate the release of TSH from the adenohypophysis.
2. In response to TSH stimulus, the follicular cells in the thyroid gland take up **iodide** into their cytoplasm from the circulation via the iodide pump located in the follicular basal cell membrane.
3. Iodide is oxidized to **iodine** in the follicular cells and transported into the follicular lumen that contains colloid material.
4. In the follicular lumen, iodine combines with amino acid tyrosine groups to form **iodinated thyroglobulin**, of which the hormones (T3 and T4) are the principal products.
5. T3 and T4 remain bound to the iodinated thyroglobulin in thyroid follicles in an inactive form until needed. TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T3 and T4, which diffuse across the follicle cell membrane and enter the bloodstream.
Synthesis and Release of Thyroid Hormones

**Thyroid Hormone Synthesis**

1. Provide Iodine

2. Iodine Uptake

3. Thyroid Hormone Production
The release of T3 and T4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). Low blood levels of T3 and T4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus → TRH triggers secretion of TSH from the anterior pituitary → TSH stimulates the thyroid gland to secrete T3 and T4. The levels of TRH, TSH, T3, and T4 are regulated by a negative feedback system.
Thyroid Hormones

✓ The thyroid hormones, T3 and T4, are \textit{metabolic hormones} because their levels influence the body’s basal metabolic rate, the amount of energy used by the body at rest. When T3 and T4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions → \textit{calorigenic effect} (raises body temperature).

✓ Adequate levels of thyroid hormones are also required for protein synthesis and for \textit{fetal and childhood tissue development and growth} → Critical for normal development of the nervous system both in utero and in early childhood.

✓ Thyroid hormones have a complex \textit{interrelationship with reproductive hormones}, and deficiencies can influence libido, fertility, and other aspects of reproductive function.

✓ Thyroid hormones increase the \textit{body’s sensitivity to catecholamines} (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T3 and T4 hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure.
Thyroid Hormones disorders

Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

**Hypothyroidism**
- Hair loss
- Inability to think clearly
- Goiter (enlarged thyroid)
- Reduced heart rate
- Strong fatigue
- Sensitivity to cold
- Dry skin
- Weight gain
- Puffiness
- Memory problems
- Constipation
- Irregular menstrual periods
- Severe PMS
- Depression, mood swings
- Joint, muscle pain
- High cholesterol

**Hyperthyroidism**
- Hair loss
- Bulging eyes
- Goiter (enlarged thyroid)
- Heart palpitations
- Tremors
- Heat intolerance
- Sleep disturbances
- Weight loss
- Shortness of breath
- Diarrhoea
- Increased appetite
- Irregular menstrual periods
- Muscle weakness
- Sweating
- Anxiety, nervousness
- Depression, mood swings
Thyroid Hormones disorders

Dietary iodine is required for the synthesis of T3 and T4. But for much of the world’s population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world’s poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T3 and T4 → When T3 and T4 cannot be produced, TSH is secreted in increasing amounts → Thyroid hyperstimulation → thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid → increase in the overall size of the thyroid gland, a condition called a goiter.

Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death.
Iodine deficiency is the primary cause of preventable mental retardation worldwide. **Neonatal hypothyroidism** (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodinedeficient during pregnancy.
Calcitonin

The thyroid gland also secretes a hormone called **calcitonin** that is produced by the **parafollicular cells** (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium levels.

It appears to have a function in decreasing blood calcium concentrations by:

- Inhibiting the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix
- Increasing osteoblastic activity
- Decreasing calcium absorption in the intestines
- Increasing calcium loss in the urine

### Thyroid Hormones

<table>
<thead>
<tr>
<th>Associated hormones</th>
<th>Chemical class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxine (T₄), triiodothyronine (T₃)</td>
<td>Amine</td>
<td>Stimulate basal metabolic rate</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Peptide</td>
<td>Reduces blood Ca²⁺ levels</td>
</tr>
</tbody>
</table>
Parathyroids

The parathyroid glands are tiny, round structures usually found embedded in the posterior surface of the thyroid gland. A thick connective tissue capsule separates the glands from the thyroid tissue. Most people have four parathyroid glands, but occasionally there are more in tissues of the neck or chest. Normally, one parathyroid gland is located on the superior pole and one on the inferior pole of each lobe of the thyroid gland.
The primary functional cells of the parathyroid glands are the chief cells. These epithelial cells produce and secrete the parathyroid hormone (PTH), the major hormone involved in the regulation of blood calcium levels.
Parathyroids

In contrast to the thyroid gland, the cells of the parathyroid glands are arranged into cords or clumps, surrounded by a rich network of capillaries and normally they do not exhibit follicles that are seen in the adjacent thyroid gland.

There are two types of cells in the parathyroid glands: functional principal, or chief, cells and oxyphil cells.

Oxyphil cells are larger, are found singly or in small groups, and are less numerous than the principal (chief cells). In routine histologic sections, these cells stain deeply acidophilic. On rare occasions, small colloid-filled follicles may be seen in the parathyroid glands.
Parathyroids

1. Follicles with colloid
2. Follicular cells
3. Connective tissue trabecular
4. Chief cells
5. Capillaries
6. Oxyphil cells
7. Thyroid gland
8. Connective tissue
9. Parathyroid gland

1. Follicles with colloid
2. Follicular cells
3. Connective tissue septum
4. Chief cells
5. Oxyphil cells
6. Blood vessels
Parathyroid hormone (PTH)

The parathyroid glands produce and secrete PTH, a peptide hormone, in response to low blood calcium levels.

PTH secretion:
1. causes the release of calcium from the bones by stimulating osteoclasts, which secrete enzymes that degrade bone and release calcium into the interstitial fluid.
2. inhibits osteoblasts, the cells involved in bone deposition, thereby sparing blood calcium.
3. causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate.
4. initiates the production of the steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D), which is the active form of vitamin D3, in the kidneys. Calcitriol then stimulates increased absorption of dietary calcium by the intestines.

A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting further release of PTH.
Parathyroid hormone (PTH)

3a) Effects of PTH on bone:
- Inhibits osteoblasts
- Stimulates osteoclasts
- Bone is broken down, releasing calcium ions into bloodstream

3b) Effects of PTH on kidneys:
- PTH stimulates kidney tubule cells to recover waste calcium from the urine.
- PTH stimulates kidney tubule cells to release calcitriol.

3c) Effects of calcitriol on intestine:
- Stimulates intestines to absorb calcium from digesting food

![Diagram showing the effects of PTH on bone, kidneys, and intestine]
1) Blood calcium concentration drops

2) Release of PTH:
   - Chief cells of the parathyroid gland release parathyroid hormone (PTH).

5) Calcitonin release:
   - High concentrations of calcium stimulate parafollicular cells in the thyroid to release calcitonin.

4) Blood calcium levels increase

6) Effects of calcitonin on bone:
   - Stimulates osteoblasts
   - Inhibits osteoclasts
   - Calcium is removed from blood and used to build bone

Calcium Homeostasis
Abnormally high activity of the parathyroid gland can cause hyperparathyroidism, a disorder caused by an overproduction of PTH that results in excessive calcium reabsorption from bone. Hyperparathyroidism can significantly decrease bone density (osteoporosis), leading to spontaneous fractures or deformities. At the same time, calcium deposits may collect in the body’s tissues and organs, impairing their functioning (renal and ureteral lithiasis).
The adrenal glands are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule. The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body.

The secretory portion of each adrenal gland consists of an outer cortex and an inner medulla. Although these two regions of the adrenal gland are located in one organ and are linked by a common blood supply, they have separate and distinct embryologic origins, structures, and functions.

They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.
Adrenal glands

Medial to the kidney, 5x3 cm
Two different components: medulla and cortex.

Medulla: ectodermal origin
(nervous system)
Cortex: mesodermic origin
Adrenal glands

The cortex itself is divided into three zones: the **zona glomerulosa**, the **zona fasciculata**, and the **zona reticularis**. Each region secretes its own set of hormones.

The **adrenal cortex**, as a component of the **hypothalamic-pituitary-adrenal (HPA) axis**, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation.

The HPA axis involves the stimulation of release of adrenocorticotrophic hormone (ACTH) from the pituitary by the hypothalamus → ACTH then stimulates the adrenal cortex to produce the hormone cortisol.
Adrenal glands

The adrenal medulla is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress (physical or psychological). Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the general adaptation syndrome (GAS).
**General adaptation syndrome (GAS)**

**Stage 1:** alarm reaction. This is short-term stress, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal.

**Stage 2:** If the stress is not soon relieved, the body adapts to the stress in the *stage of resistance*. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

**Stage 3:** During the *stage of exhaustion*, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.
Adrenal glands

Corticoids hormones: all derived from cholestherol, lipid hormones

**Mineralcorticoids**: produced by zona glomerulosa. Effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance. **Aldosterone** is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. Aldosterone regulates blood volume or blood pressure.

**Glucocorticoids**: produced by zona fasciculata. Role in glucose metabolism. The most important of these is **cortisol**, some of which the liver converts to cortisone. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose for use as body fuels.

**Androgens**: produced by zona reticularis. Steroid sex hormones. The androgens produced in the zona reticularis supplement the gonadal androgens.
**Adrenal glands**

Cortex: under the control of CRH and ACTH secreted by hypothalamus and hypophysis

- **Zona glomerulosa** (adrenal cortex) - Mineralcorticoids (regulate mineral balance)
- **Zona fasciculata** (adrenal cortex) - Glucocorticoids (regulate glucose metabolism)
- **Zona reticularis** (adrenal cortex) - Androgens (stimulate masculinization)
- **Adrenal medulla** - Stress hormones (stimulate sympathetic ANS)

Examples:
- Aldosterone
- Cortisol
- Corticosterone
- Cortisone
- Dehydroepiandrosterone
- Epinephrine
- Norepinephrine

Medulla: driven by autonomous nervous system, it can be considered a special sympathetic ganglion
Adrenal glands

Regulation of adrenal gland secretion
Adrenal glands

The **zona glomerulosa** is a thin zone inferior to the adrenal gland capsule. It consists of cells arranged in small clumps.

The **zona fasciculata** is intermediate and the thickest zone of the adrenal cortex, exhibits vertical columns of one-cell thickness adjacent to straight capillaries. This layer is characterized by pale-staining cells owing to the increased presence of numerous lipid droplets.

The **zona reticularis** is the innermost zone that is adjacent to the adrenal medulla. The cells in this zone are arranged in cords or clumps.

In all three zones, the secretory cells are adjacent to fenestrated capillaries.
The cells of the adrenal **medulla**, also arranged in small cords, are modified postganglionic sympathetic neurons that have lost their axons and dendrites during development. Preganglionic axons of the sympathetic neurons innervate the adrenal medulla cells, which are surrounded by an extensive capillary network.

The release of epinephrine and norepinephrine from the adrenal medulla is very efficient and under the direct control of the sympathetic division of the **autonomic nervous system**.
Inferior but somewhat posterior to the thalamus is the **pineal gland**, a tiny endocrine gland whose functions are not entirely clear. The **pinealocyte** cells that make up the pineal gland are known to produce and secrete the amine hormone **melatonin**.

The secretion of melatonin varies according to the level of light received from the environment. When photons of light stimulate the retinas of the eyes, a nerve impulse is sent to hypothalamus → the nerve signal is carried to the pineal gland, where the production of melatonin is inhibited → blood levels of melatonin fall, promoting wakefulness.

In contrast, as light levels decline—such as during the evening—melatonin production increases, boosting blood levels and causing drowsiness.

The secretion of melatonin may influence the body’s circadian rhythms.
Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag.

Some air travelers take melatonin supplements to induce sleep.
Endocrine pancreas

The pancreas is a long, slender organ, most of which is located posterior to the bottom half of the stomach. Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its pancreatic islets—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).
Pancreatic islets

About 3,000,000, 0.1 mm diameter 4.5% of the pancreatic volume

Endodermic origin

The pancreatic islets each contain four varieties of cells:

- The **alpha cell** (20% percent of each islet) produces the hormone **glucagon**. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** (75 % of each islet) produces the hormone **insulin**. Elevated blood glucose levels stimulate the release of insulin.
- The **delta cell** (4% of the islet cells) secretes the peptide hormone **somatostatin**. It is also released by the hypothalamus, the stomach and intestines. Pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The **PP cell** (1% of islet cells) secretes the **pancreatic polypeptide hormone**. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

**Paracrine function**: glucagon inhibits beta cell, insulin inhibits alpha cell, somatostatin inhibits alpha and beta.
Pancreatic islets

A photomicrograph of the pancreas shows a mixed gland with both endocrine and exocrine portions. The exocrine pancreas consists of numerous secretory acini that deliver their secretory material into the excretory duct, which is lined by simple cuboidal epithelium and surrounded by a layer of connective tissue. The endocrine pancreas is called the pancreatic islet because it is separated from the cells of the exocrine pancreas by a thin connective tissue capsule. The endocrine pancreatic islet does not contain excretory ducts. Instead, it is highly vascularized, and all of the secretory products leave the pancreatic islet via numerous blood vessels (capillaries).
Pancreatic islets

1. Interlobular connective tissue
2. Blood vessel
3. Cells of pancreatic islet
4. Intercalated duct
6. Interlobular duct
7. Centroacinar cell
8. Pacinian corpuscle
9. Centroacinar cell
10. Blood vessel
11. Capillaries in pancreatic islet
Pancreatic islets

In routine histologic preparations, the cells that secrete different hormones from the pancreatic islet cannot be identified. However, using different staining techniques, the hormone-secreting cells can be identified.

This pancreas has been prepared with a special stain to distinguish the glucagon-secreting alpha cells (1) from the insulin-secreting beta cells (3). The cytoplasm of alpha cells (1) stains pink, whereas the cytoplasm of beta cells (70% of each islets) (3) stains blue.
Pancreatic islets

With immunohistochemical preparation, it is possible to differentiate the major cell types in a pancreatic islet. This high-magnification image shows a more precise distribution of the two major cell types in the pancreatic islet. The glucagon-producing cells, the A cells, are stained bright red; they line the periphery of the islet. The insulin-producing cells, the B cells, are stained bright green. They are located on the inside of the islet and are surrounded by the peripheral A cells.
Homeostatic Regulation of Blood Glucose Levels

**Insulin effects:**
- Triggers body cells to take up glucose from the blood and utilize it in cellular respiration.
- Inhibits glycogenolysis - glucose is removed from the blood and stored as glycogen in the liver.
- Inhibits gluconeogenesis - amino acids and free glycerol are NOT converted to glucose in the ER.

**Glucagon effects:**
- Inhibits body cells from taking up glucose from the blood and utilizing it in cellular respiration.
- Stimulates glycogenolysis - glycogen in the liver is broken down into glucose and released into the blood.
- Stimulates gluconeogenesis - amino acids and free glycerol are converted to glucose in the ER and released into the blood.

**Blood glucose concentration decreases**

- Hyperglycemia (elevated blood glucose)
- Hypoglycemia (low blood glucose)

**START: Homeostasis (70–110 mg/dL)**

- Insulin release: Beta cells of pancreas release insulin
- Glucagon release: Alpha cells of pancreas release glucagon
## Organs with Secondary Endocrine Functions

<table>
<thead>
<tr>
<th>Organ</th>
<th>Major hormones</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Atrial natriuretic peptide (ANP)</td>
<td>Reduces blood volume, blood pressure, and Na(^+) concentration</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Gastrin, secretin, and cholecystokinin</td>
<td>Aid digestion of food and buffering of stomach acids</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Glucose-dependent insulino-tropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)</td>
<td>Stimulate beta cells of the pancreas to release insulin</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renin</td>
<td>Stimulates release of aldosterone</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Calcitriol</td>
<td>Aids in the absorption of Ca(^{2+})</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Erythropoietin</td>
<td>Triggers the formation of red blood cells in the bone marrow</td>
</tr>
<tr>
<td>Skeleton</td>
<td>FGF23</td>
<td>Inhibits production of calcitriol and increases phosphate excretion</td>
</tr>
<tr>
<td>Skeleton</td>
<td>Osteocalcin</td>
<td>Increases insulin production</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Leptin</td>
<td>Promotes satiety signals in the brain</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Adiponectin</td>
<td>Reduces insulin resistance</td>
</tr>
<tr>
<td>Skin</td>
<td>Cholecalciferol</td>
<td>Modified to form vitamin D</td>
</tr>
</tbody>
</table>
## Organs with Secondary Endocrine Functions

<table>
<thead>
<tr>
<th>Organ</th>
<th>Major hormones</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus (and other organs)</td>
<td>Thymosins</td>
<td>Among other things, aids in the development of T lymphocytes of the immune system</td>
</tr>
<tr>
<td>Liver</td>
<td>Insulin-like growth factor-1</td>
<td>Stimulates bodily growth</td>
</tr>
<tr>
<td>Liver</td>
<td>Angiotensinogen</td>
<td>Raises blood pressure</td>
</tr>
<tr>
<td>Liver</td>
<td>Thrombopoietin</td>
<td>Causes increase in platelets</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepcidin</td>
<td>Blocks release of iron into body fluids</td>
</tr>
</tbody>
</table>