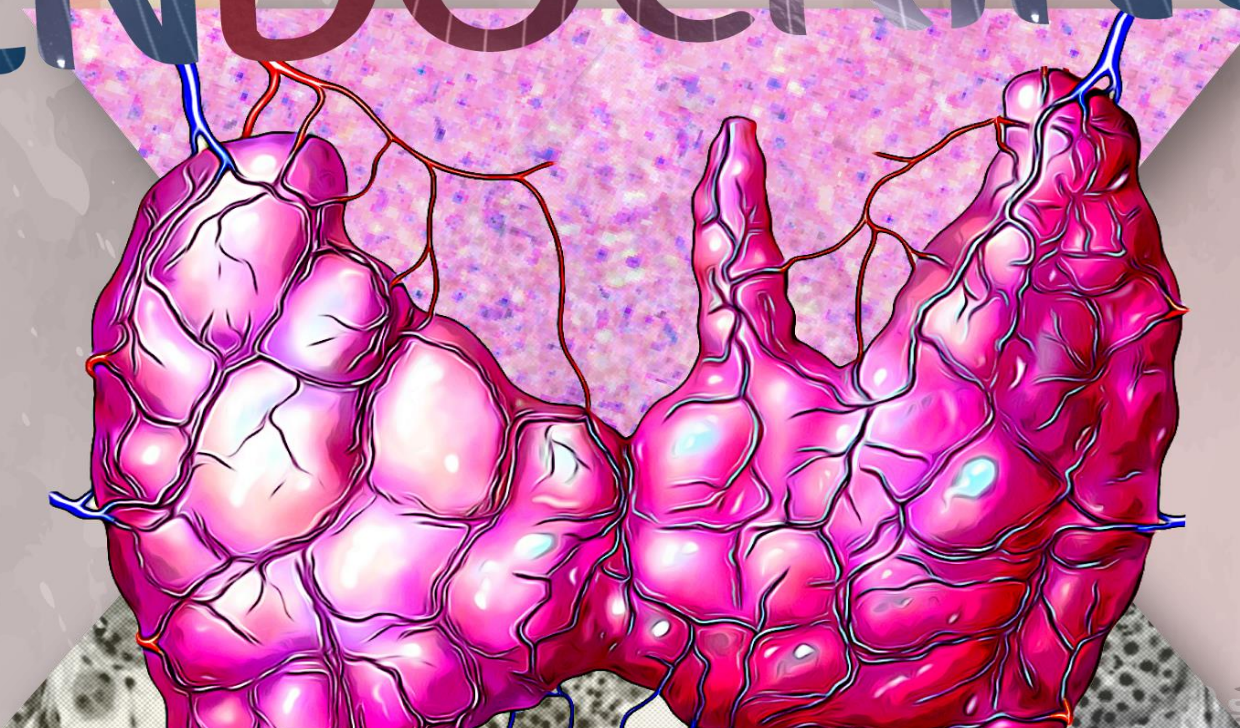
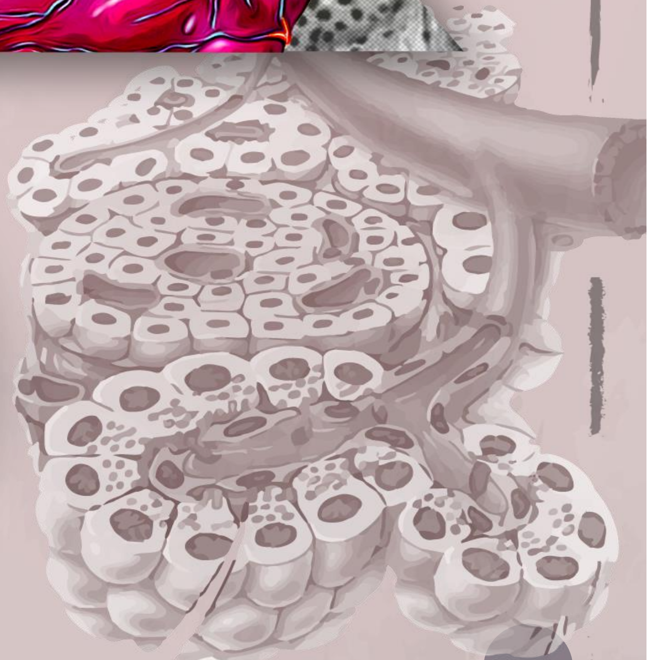
ENDOCRINE





SUBJECT: Physiology

DONE BY: Ahmad Massad

CORRECTED BY: Tala Saleh

DOCTOR: Salim Khraisha

Regulation of Hormone Secretion

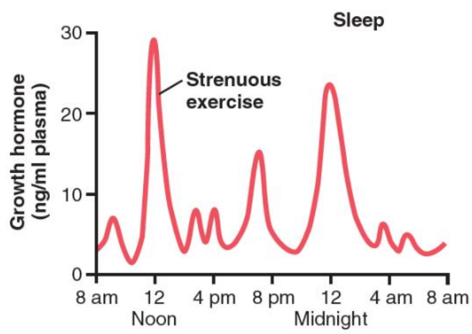
Hormones are needed within certain levels in the body requiring constant regulation:

1- **Neural control:** Pain, emotion, sexual excitement, fright, injury, and stress can all modulate hormone secretion through neural mechanisms. These neural mechanisms include Adrenergic, Cholinergic, Dopaminergic, Serotonergic, endorphinergic and enkephalinergic mechanisms *(one or more can be activated)*. Here usually there's an increase in hormone production. In stress, adrenalin and Ach are mainly increased.

2- **Chronotropic control:** This control mechanism is related to **time**. So being at a specific time whether during different times of the day or different seasons of the year can affect the level of hormones. Chronotropic control has many rhythms, such as:

   a- **Diurnal rhythm:** is the rhythm during day and night, **growth hormone** secretion is controlled by this mechanism.

   Looking at the figure to the right, you can see that the level of hormone secretion variations at different times throughout the day.



   b- **Sleep-wake cycle:** the level of secretion of some hormones changes during **sleep and wake**.

   c- **Menstrual rhythm:** the level of some hormones changes during the **menstrual cycle**.

   d- **Seasonal rhythm:** one example is the increase of **sex hormone** levels in mammals during breeding seasons.

   e- **Developmental rhythm:** Different levels of the hormone during different **developmental stages**. An example is the **growth hormone** level.

> ***Note:*** *Hormones are released either in a* ***regular manner****, increasing and decreasing* ***(Oscillating)*** *or in* ***pulses (Pulsatiles)****.*

3- **Feedback control:** Almost all hormones are regulated by this mechanism. The relationship between the response and the stimulus is called feedback control.

When the response decreases the stimulus, decreasing the release of the hormone, this is called negative feedback control. When the response increases the stimulus, increasing the release of the hormone, this is called positive feedback control.

> ***Note:*** *Regulation may occur in **gene transcription** and **translation** of the **hormone**, or in the **processing** and **release** of the hormone.*

Feedback control may occur on a:

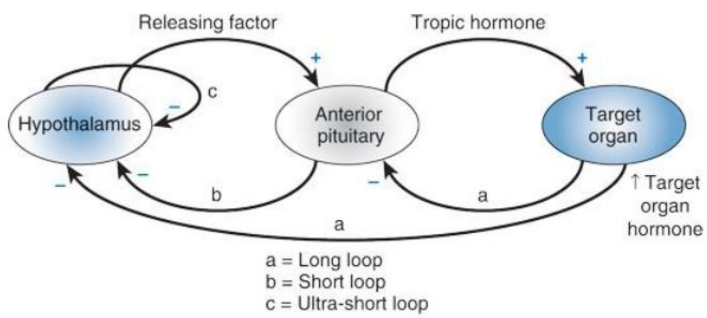
a- **Hormone-hormone level:** One hormone causing the release or the inhibition of the release of **another hormone**, e.g. increase in **thyroxin level** inhibits the release of thyroxin-releasing hormone from the hypothalamus *(negative feedback control).*

b- **Substrate-hormone level:** **Glucose** causes the release of **insulin**, while **hypoglycemia** causes **glucagon** release.

c- **Mineral-hormone level:** **Hypocalcaemia** causes the release of **parathyroid hormone** as a response.

Negative Feedback Loops:

Negative feedback usually occurs in loops, an important example of these loops is the hypothalamus-pituitary-peripheral gland axis.



1- **Ultra-short loop 'c':** Regulation in an **autocrine** manner, e.g. the hypothalamus produces a hormone, this hormone affects the hypothalamus **itself** altering the secretion of this hormone.

2- **Short loop 'b':** Regulation by an **intermediate product**, e.g. the hypothalamus produces a hormone (releasing factor), which affects the pituitary gland causing the release of another hormone, this is an example of **Hormone-Hormone** feedback mechanism. Consequently, the hormone released by the pituitary affects the hypothalamus altering hormone levels.

3- **Long loop 'a':** Regulation by the hormone produced by the **end product**, e.g. the hypothalamus produces a hormone, which affects the pituitary gland causing the release of another hormone. This pituitary hormone affects the thyroid gland for example, and the thyroid gland responds by releasing another hormone affecting either the pituitary gland or the hypothalamus in a long loop.

Positive Feedback Loops:

As for positive feedback loops, there are 2 main examples:

1- **Neural-hormonal positive feedback loop**: The sucking of an infant stimulates receptors in the mammary gland, neural signals travel to the hypothalamus stimulating the release of **oxytocin** from the neurohypophysis (posterior pituitary), i.e. more sucking = more oxytocin release until the baby is full.

2- **Uterine contractions** push the fetus against the cervix, this causes **oxytocin** release through neuroendocrine reflexes. Oxytocin increases uterine contraction either directly or indirectly by increasing the production of prostaglandins, this continues until the baby is delivered.

Regulation of Receptor Number

Hormones determine the sensitivity of the target tissue by regulating the number or activity of receptors.

1- **Down-regulation of receptors**: A hormone decreases the number or affinity of receptors for itself or for another hormone. Down-regulation may occur when exposing cells to an **excess** of hormone for a **sustained** period of time (chronically) causing a decreased number of receptors for this hormone on the cell, as well as decreased affinity.

> ***Note:*** *Down-regulation of receptors found on the cell membrane is done by* ***endocytosis*** *of these receptors to the inside of the cell followed by their* ***destruction by lysosomes****.*

2- **Up-regulation of receptors**: A hormone increases the number or affinity of receptors for itself or for another hormone.

Hormones can not only change the number of receptors but can also affect their function. For example, in many old, obese individuals, the insulin level is normal or high, but the insulin **doesn't function properly** because of the **decreased** number and **activity** of its receptors. Glucose level, therefore, remains **higher than normal** resulting in **diabetes mellitus type II**. This could also happen in young, obese or **inactive** persons of normal weight.

These individuals are advised to exercise and stick to a healthy diet. If that is applied, their weight may return to normal (if they were obese), thereby insulin returns to its **normal** function. This is due to an increase in the **number** and **affinity** of insulin receptors, in a process called upregulation.

Interactions Between Hormones

Most hormones do not function separately, rather, they function together. This is called hormonal interaction.

1- **Permissive effect (Permissiveness):** In this type of hormonal interaction the effect of one hormone on a target cell requires **previous** or simultaneous **exposure** to **another** hormone(s). Such previous exposure **enhances** the response of a target cell or **increases** the activity of another hormone. (0+1=2)

   Example:

   - Fat cells affected by thyroid hormone alone result in no fatty acid release.
   - Fat cells affected by adrenalin (epinephrine) alone result in a small amount of fatty acid release.
   - Fat cells affected by thyroxine first then adrenaline result in increased fatty acid release (optimal effect).

   ⇨ In the third case, adrenalin functions properly only when the cells are previously exposed to thyroxine first.

   i.e. Thyroxine alone =0, adrenalin alone =1 , both together =2

   - Another example is the exposure of the uterus first to estrogens and then to progesterone to prepare the organ for implantation.

2- **Synergistic effect (Synergism):** The effects of two or more hormones complement each other in such a way that the target cell responds effectively to the **sum of the hormones** involved. (1+1>2)

   Example:

   The production and secretion of milk by the mammary glands requires, among others, the **synergistic effects** of estrogen, progesterone, prolactin (PRL), and oxytocin (OT). Mammogenic hormones (promote cell proliferation) function together. Lactogenic hormones (promote milk production) function together. Galactokinetic hormones (promote milk ejection) function together.

   In these cases, each hormone functions in **different degrees** compared to other hormones, but when more than one of them function simultaneously a **better response** can be achieved.

3- **Antagonistic effect (Antagonism):** The effect of **one hormone** on a target cell is **opposed** by **another** hormone. **Example**: calcitonin (CT), lowers blood calcium level, and parathyroid hormone (PTH), raises blood calcium level. Insulin reduces blood glucose level, and Glucagon increases blood glucose level.

Mechanisms of hormone action and second messengers

We said earlier that hormones are either proteins, amino acid derivatives or steroids according to their chemical composition. For a hormone to function it must first bind its receptor and then produce 2nd messengers, otherwise, it won't function.

1- **Protein hormones:** Proteins are large molecules that cannot penetrate the cell membrane and thus require cell surface receptors, these receptors are usually G protein-coupled receptors (**GPCR**).
The G protein complex is composed of α, β, γ subunits *(alpha is the active subunit, beta and gamma are regulatory subunits)*, this complex is inactive when GDP is bound to the alpha subunit. When the hormone binds to the receptor, a conformational change takes place resulting in the exchange of GDP for GTP on the alpha subunit leading to its activation and dissociation from the beta and gamma subunits and then its interaction and activation of membrane-bound proteins like adenylyl cyclase that initiate intracellular signals by producing 2nd messengers.
Adenylyl cyclase produces cAMP from ATP, **cAMP** is the 2nd messenger. cAMP then activates protein kinase A (**PKA**) that phosphorylates many proteins either activating or inactivating them resulting in cellular response.

Hormones that use cAMP pathway are shown in the figure to the right.

Adrenocorticotropic hormone (ACTH)	Human chorionic gonadotropin (HCG)
Angiotensin II (epithelial cells)	Luteinizing hormone (LH)
Calcitonin	Parathyroid hormone (PTH)
Catecholamines (β receptors)	Secretin
Corticotropin-releasing hormone (CRH)	Somatostatin
Follicle-stimulating hormone (FSH)	Thyroid-stimulating hormone (TSH)
Glucagon	Vasopressin (V_2 receptor, epithelial cells)

Note: *When the hormone binds to its receptor, several G-proteins are activated; each activating adenylyl cyclase to produce many cAMP molecules, which means that there is amplification of the signal. cAMP levels are regulated by **phosphodiesterase** which converts it to **5'AMP** thereby turning **off** the action of the 2nd messenger.*

Another membrane-bound protein that can be activated by the alpha subunit is phospholipase C (**PLC**), when activated it produces **two** 2^{nd} messengers; **DAG** and **IP3** from PIP2.

- ⇨ **IP3** releases **calcium** from the endoplasmic reticulum, this released calcium leads to the **cellular response**, thus calcium is a must for a specific hormone to function.
- ⇨ **DAG** activates protein kinase C (PKC) which also needs calcium for its activation.

This pathway has two 2nd messengers, with calcium being required to cause a cellular response. Hormones following this mechanism are shown to the right.

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

2- **Amino acid derivatives hormones:** Catecholamines *(Epinephrine, norepinephrine, and dopamine)* have **cell surface receptors**, while thyroid hormones *(lipophilic)* either have **intracellular** receptors that are then transported to the nucleus or **nuclear receptors** directly. Thyroid hormones enter the cell via **carrier-mediated** transport which is **ATP dependent** and **not** passive, despite being lipophilic.

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

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

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

4- **Other examples:** Hormones that follow Tyrosine kinase mechanism, e.g. Insulin, and others following cGMP mechanism, e.g. NO and ANP receptors.

The Pituitary Gland

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

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

2- Posterior pituitary: also called **neurohypophysis**, **directly** connected with the hypothalamus. it contains nerve endings **storing** secretory granules filled with **hormones** synthesized in the **cells bodies** that lie in the **hypothalamus**.

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

The Posterior pituitary lobe

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

⇨ The **function** of the **posterior pituitary** gland is to **store hormones** synthesized by the hypothalamus. These hormones are called **neurohormones** because they are produced by nerve cell bodies present in **two types of nuclei**:

1- The Paraventricular nucleus, which produces **oxytocin** and a little bit of ADH.

2- The Supraoptic nucleus, which produces **ADH** and a little bit of oxytocin.

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

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

The Posterior pituitary hormones: Oxytocin and ADH (vasopressin)

- ADH and Oxytocin are cyclic peptides due to a disulfide bond.
- Both are composed of **nine amino acids** having an amide group at the c-terminal end. They differ from each other in just **two** amino acids:

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

In Oxytocin → X represents Ile // Y represents Leu

In ADH → X represents Phe // Y represents Arg

- As they have a similar structure, they also have little similarities in function:

1- Both increase **water reabsorption** in the kidneys, but ADH is 200 times more potent than Oxytocin.

2- Both increase **milk ejection**, but Oxytocin is 100 times more potent. ADH mainly increases water reabsorption.

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

The Antidiuretic hormone (ADH // Vasopressin)

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

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

2- **Vasoconstriction** of the blood vessels.

⇨ Notice how it may either work on nephrons *(ADH)*, or on blood vessels *(vasopressin)*. Both names are for the same hormone, only differing in the **receptors** they work on.

ADH → Decreases diuresis (production of urine) → **V2** receptors in **nephrons**.

Vasopressin → Constriction of blood vessels → **V1** receptors in **blood vessels**.

3- **Increases sweating.**

- **Stimulators of ADH:**

1- Increased serum osmolarity
2- Decreased extracellular fluid volume

3- Stress-related factors: nausea, pain, vomiting, nicotine, opiates (analgesic drugs like morphine), and hypoglycemia.
4- Anti-neoplastic drugs.

- **Inhibitors of ADH:**

1- Ethanol.
2- α-Adrenergic Agonists.
3- Atrial natriuretic peptide (the hormone from the atria of the heart).
4- Decreased serum osmolarity.