كلية المستقبل الجامعة قسم الصيدلة

المرحلة الثانية

PHYSIOLOGY

ENDOCRINE

THYROID GLAND

(L2)

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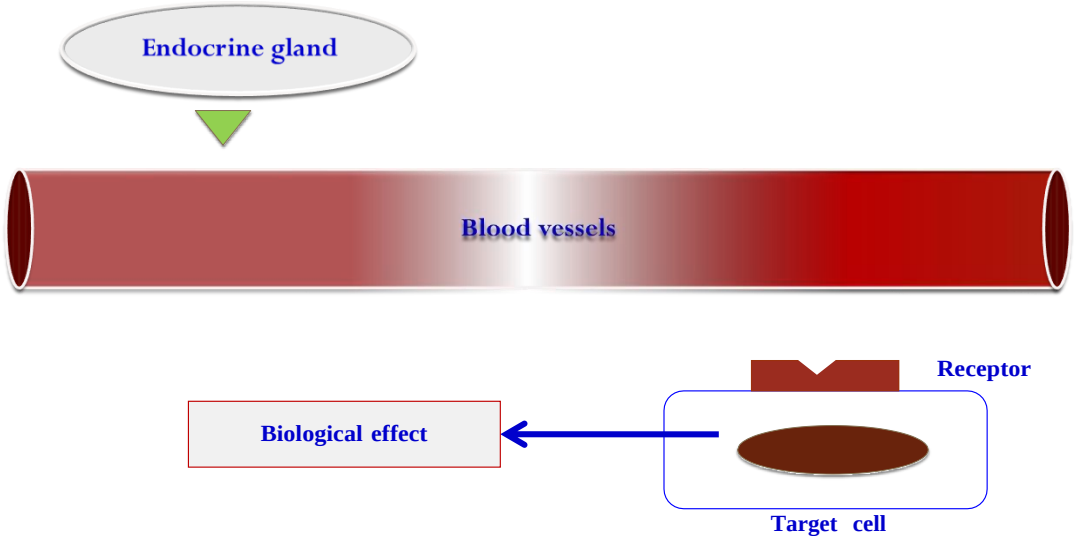
Previous Lecture Summary

Endocrine glands

- **Endocrine glands** are groups of cells that produce **specific chemicals**, called **hormones**, having well **defined effects** on body functions.
- **Endocrine glands** also, called **ductless glands** since their secretion is not conveyed along ducts but pass **directly** into **blood** and **lymphatic vessels.**

Hormones

- **Hormones** are mediators secreted From endocrine glands, which are ductless structures , released directly into the blood.
- They are then transported by the circulation to the tissues.
- The blood carries the hormones to target cells that contain specific protein receptors for the hormones, thus can respond in a specific fashion to them.



The Hypothalamus

The hypothalamus is a small organ, which lies deep within the centre of the brain. It plays an important role in a wide variety of physiological functions, including the regulation of pituitary hormones, regulating

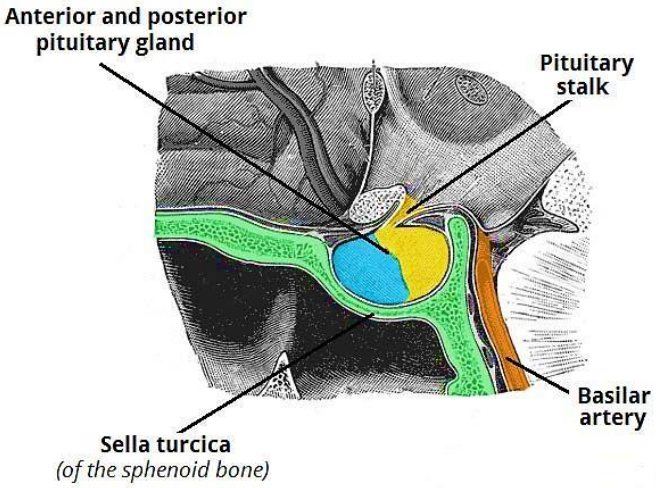
body temperature, and the control of appetite. The hypothalamus is highly interconnected with other parts of the central nervous system, and has a close relationship with the pituitary gland.

The pituitary gland

is a small endocrine organ found in the brain. It consists of two lobes – the **anterior** and **posterior** pituitary. The lobes are embryologically and histologically different and effectively function as two **separate endocrine glands.**

Structure

The pituitary gland (hypophysis) is a **pea-sized**, oval gland suspended from the brain by the pituitary stalk (infundibulum). It is found within the sella turcica of the sphenoid bone. The posterior lobe arises from a down growth of the **diencephalon** – a division of the forebrain – and is essentially an extension of the hypothalamus. This lobe consists of axons of the hypothalamic neurons and neuroglial cells, which support these axons.

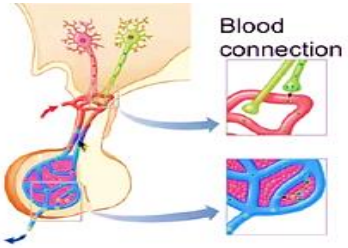


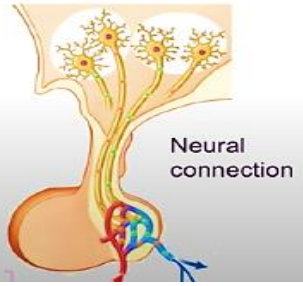
Pituitary Gland

- The Pituitary Gland has 2 lobes, anterior and posterior that are related only by location
- Anterior Pituitary (adenohypophysis):
  - glandular tissue
  - produces and secretes 6 hormones
- Posterior Pituitary (neurohypophysis):
  - neural tissue
  - NO hormone production
  - stores and secretes 2 hormones

Hypothalamus – Pituitary: Anatomical Connections

- **<u>Hypothalamus → Anterior Pituitary</u>**
  - Hypothalamic-Hypophyseal Portal System
  - ***Blood connection***: The Hypothalamus is connected to the anterior pituitary by a network of capillaries called the Hypothalamic-Hypophyseal Portal System
- **<u>Hypothalamus→ Posterior Pituitary</u>**
  - ***Neural connection***: a direct neural connection, cell bodies of neurons are located in hypothalamus, axons and axon terminals in posterior pituitary





Hypothalamus – Pituitary: Functional Connections

- **<u>Hypothalamus → Anterior Pituitary</u>**
  - The Hypothalamus secretes hormones which regulate the anterior pituitary
    - **<u>Releasing Hormones</u>**: increase release/secretion of anterior pituitary hormones
    - **<u>Inhibiting Hormones</u>**: decrease release/secretion of anterior pituitary hormones
- **<u>Hypothalamus→ Posterior Pituitary</u>**
  - The Hypothalamus produces hormones that are stored and released by the posterior pituitary

Anterior Pituitary Gland

The anterior pituitary releases hormones in response to hormones secreted from the hypothalamus. The hypothalamus releases hormones into its surrounding interstitial fluid, which permeate into nearby fenestrated capillaries. These capillaries form the hypophyseal portal system that extends into the anterior pituitary. They are histologically similar to veins. However, they connect to each other, rather than to arteries and veins, and provide a rich supply to the pituitary endocrine cells. The hormones released by the hypothalamus into the anterior pituitary are either releasing hormones (RH) that stimulate the secretion/synthesis of hormones, or inhibiting hormones (IH) that inhibit the synthesis/secretion of hormones.

In response, the anterior pituitary releases hormones into the blood. They have a tropic ("turning on") effect on another endocrine organ in the body. This means they stimulate another endocrine organ to release a third hormone in the pathway, known as a peripheral hormone. This peripheral hormone travels in the blood stream to exert metabolic actions at different tissues in the body.

Note that in some cases, the hormone secreted by the anterior pituitary hormone may itself be the peripheral hormone in the pathway. Or, it may have dual actions to act directly on tissues, in addition to stimulating a target endocrine gland to release a peripheral hormone.

The peripheral hormone will usually have a positive and/or negative feedback effect on the pituitary and hypothalamus. In other words, it will stimulate or inhibit further release of hypothalamic and/or pituitary hormones. This circuit between the hypothalamus, anterior pituitary and third endocrine gland is known as an axis. A general framework for an axis is depicted below

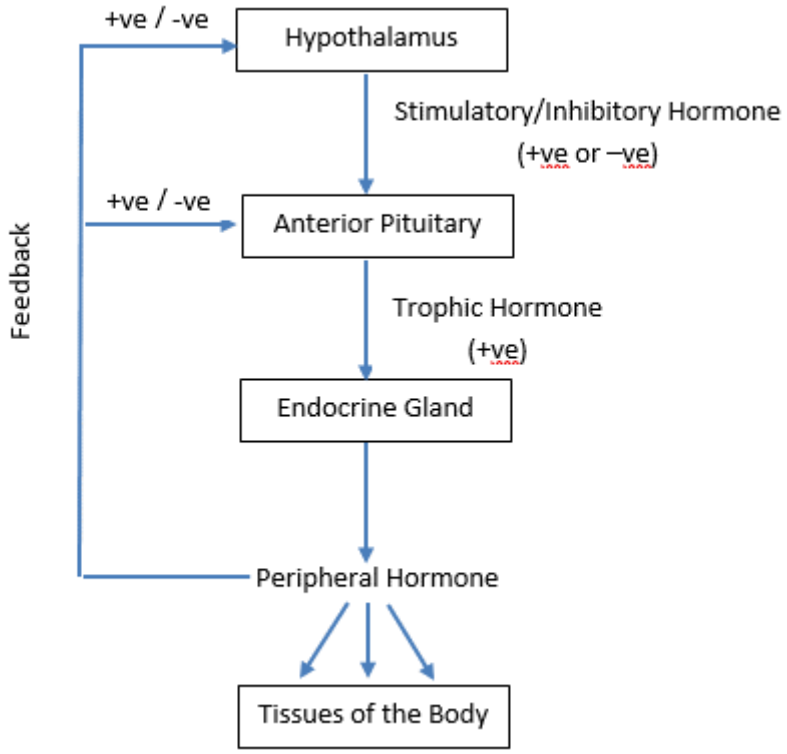


Diagram showing the general mechanism for a hypothalamic – anterior pituitary – endocrine axis

There are 5 anterior pituitary axes summarised below:

Hypothalamic-Pituitary-Adrenal Axis *Involving Adrenocorticotrophic Hormone (ACTH).*

Growth Hormone Axis *Involving Growth Hormone (GH)*

Hypothalamic-Pituitary-Thyroid Axis *Involving Thyroid Stimulating Hormone (TSH)*

Hypothalamic-Pituitary-Gonadal Axis *Involving Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH)*

Prolactin Axis *Involving Prolactin (PRL)*

Features of Endocrine Axes

Their activity is maintained within a normal range around a set point, determined by levels of stimulatory and inhibitory hormones in the blood. This means that if the level of the peripheral hormone drops too much, then hypothalamic and pituitary hormones will rise to bring

peripheral hormone levels up. Similarly, if the peripheral hormone levels increase, then hypothalamic and pituitary hormone levels will decrease.

Hypothalamic hormones are secreted in a pulsatile manner, governed by internal rhythms. However, they can be regulated by a variety of inputs, including stress, infections and even onset of puberty.

Clinical Relevance - Endocrine Disorders

Endocrine disorders are commonly referred to as being **primary, secondary** or **tertiary** diseases. This relates to which organ in the axis is affected.

A primary endocrine disease refers to a disease that affects hormone secretion in the organ that produces the hormone. An example of this would be Addison's disease, which is where the disease affects the adrenal gland directly and cortisol production. This is sometimes referred to as primary **hypoadrenalism.**

A secondary endocrine disease affects the endocrine organ that releases tropic hormones, which indirectly affects peripheral hormone secretion. An example here would be Cushing's disease – a tumour in the pituitary secreting ACTH, resulting in increased adrenal gland activity and raised cortisol production. This would be known as secondary **hyperadrenalism.**

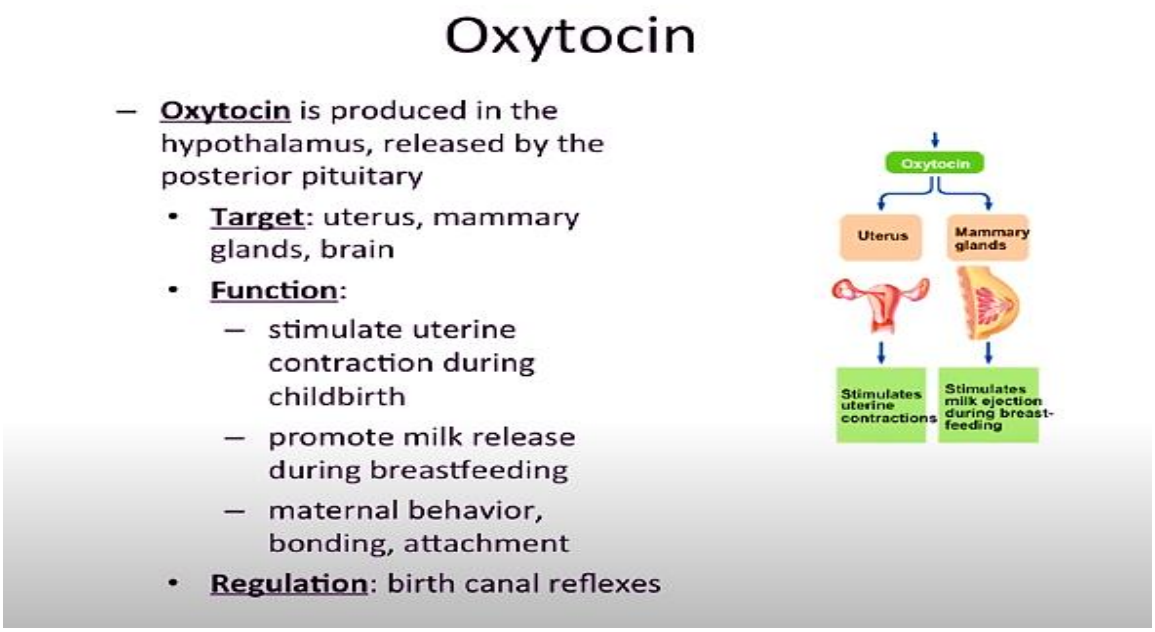
A tertiary endocrine disease affects the initial endocrine organ in an axis. This is usually a disease of the hypothalamus. Indirectly, it affects a second endocrine organ and then a third endocrine organ, ultimately affecting peripheral hormone levels. Tertiary adrenal insufficiency is a disease of low cortisol caused by a **dysfunctional hypothalamus** and decreased CRH production.

Posterior Pituitary Endocrine Function

Oxytocin : Maternal oxytocin plasma levels gradually increase during pregnancy, and oestrogen increases the number of oxytocin receptors present in the myometrium. Oxytocin is an essential stimulator of myometrial contraction during labour, and uterine contraction

perpetrates a positive feedback loop on oxytocin release to help maintain labour.

The release of oxytocin is also triggered by the suckling of a baby on the breast. Afferent input from the nipple triggers oxytocin production and release from the posterior pituitary into the bloodstream. Oxytocin then travels to the myoepithelial cells of the breast to induce contraction, leading to milk expression. This is known as the milk ejection reflex .



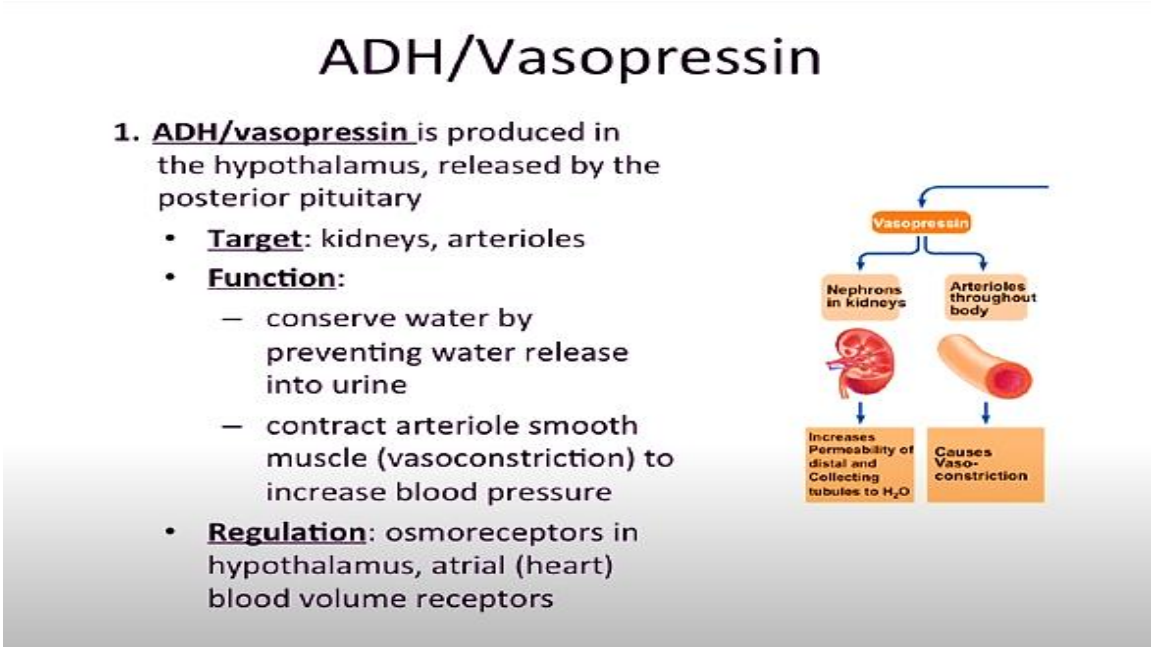
Antidiuretic Hormone

ADH (also called arginine vasopressin, AVP) is a neuropeptide hormone that acts on the kidney's collecting ducts to increase water reabsorption. Various factors control ADH release, but its most important factors are changes in plasma **osmotic pressure** and **volume status**.

Osmoreceptors in the hypothalamus regulate ADH release by detecting and responding to changes in plasma osmotic pressure:

- If osmolarity increases, i.e. following a fall in plasma volume, this stimulates osmoreceptor cells to contract. This sends afferent signals from the hypothalamus to the posterior pituitary to increase the release of ADH.

- If osmolarity is decreased, i.e. following an increase in total body volume, osmoreceptors will expand. This sends afferent signals to the posterior pituitary to decrease the release of ADH.

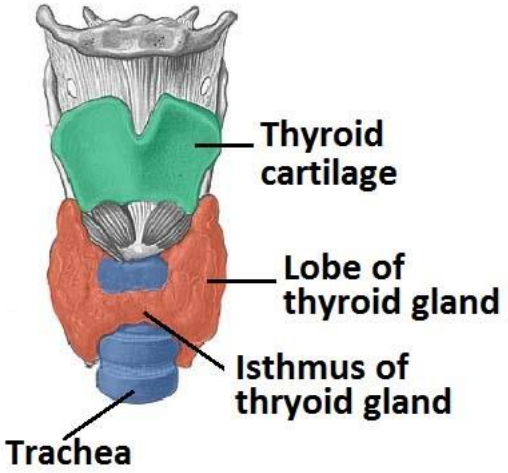


Thyroid Gland

The thyroid gland is an **endocrine** organ found in the neck, it is responsible for regulating the body's metabolic rate via hormones it produces.

Anatomy

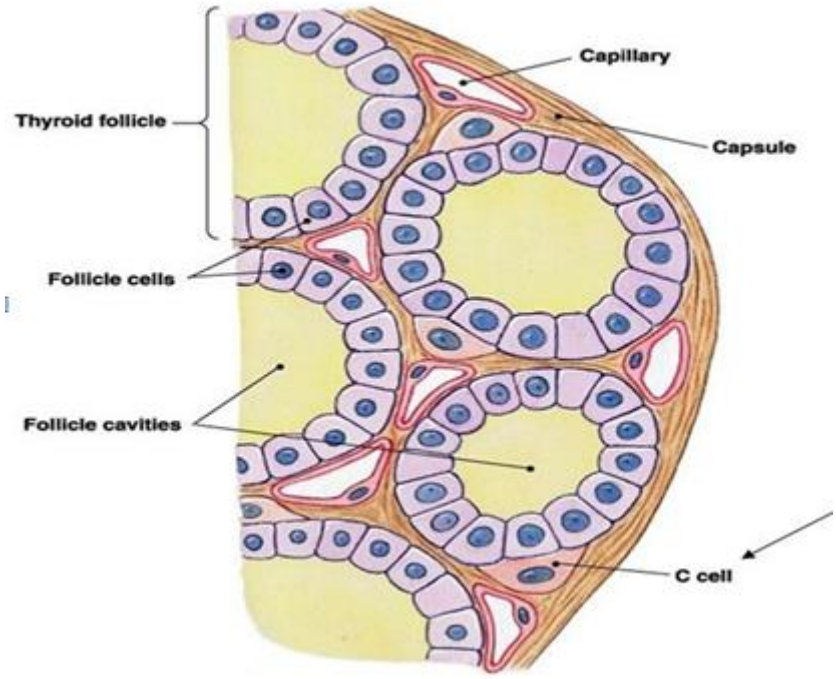
The thyroid gland is a ductless alveolar gland found in the anterior neck, just below the laryngeal prominence (Adam's apple). It is roughly butterfly-shaped, with two lobes wrapping around the trachea and connected in the middle by an isthmus. The thyroid gland is not usually palpable.



Cellular Structure

The function of the Thyroid gland is to produce and store thyroid hormones. Thyroid epithelia form follicles filled with colloid – a protein-rich reservoir of the materials needed for thyroid hormone production. These follicles range in size from 0.02-0.3mm and the epithelium may be simple cuboidal or simple columnar.

In the spaces between the follicles, parafollicular cells can be found. These cells secrete calcitonin, which is involved in the regulation of calcium metabolism in the body



Function

- Thyroid gland has two primary functions. The first is to secrete the thyroid hormones, which maintain the level of metabolism in the tissues , and help in regulating lipid and carbohydrate metabolism, thereby influence body mass and mental body state .

- Consequences of thyroid gland dysfunction (its absence or hypofunction) during fetal and neonatal life results in severe mental retardation and dwarfism.

- The second function involves calcitonin hormone secretion that aid in regulating Ca level in the blood .

The thyroid gland is one of the main regulators of metabolism. T3 and T4 typically act via nuclear receptors in target tissues and initiate a variety of metabolic pathways. High levels of them typically cause these processes to occur faster or more frequently. Metabolic processes increased by thyroid hormones include:

Basal Metabolic Rate	Gluconeogenesis
Glycogenolysis	Protein synthesis
Lipogenesis	Thermogenesis

Thyroid Hormone Synthesis

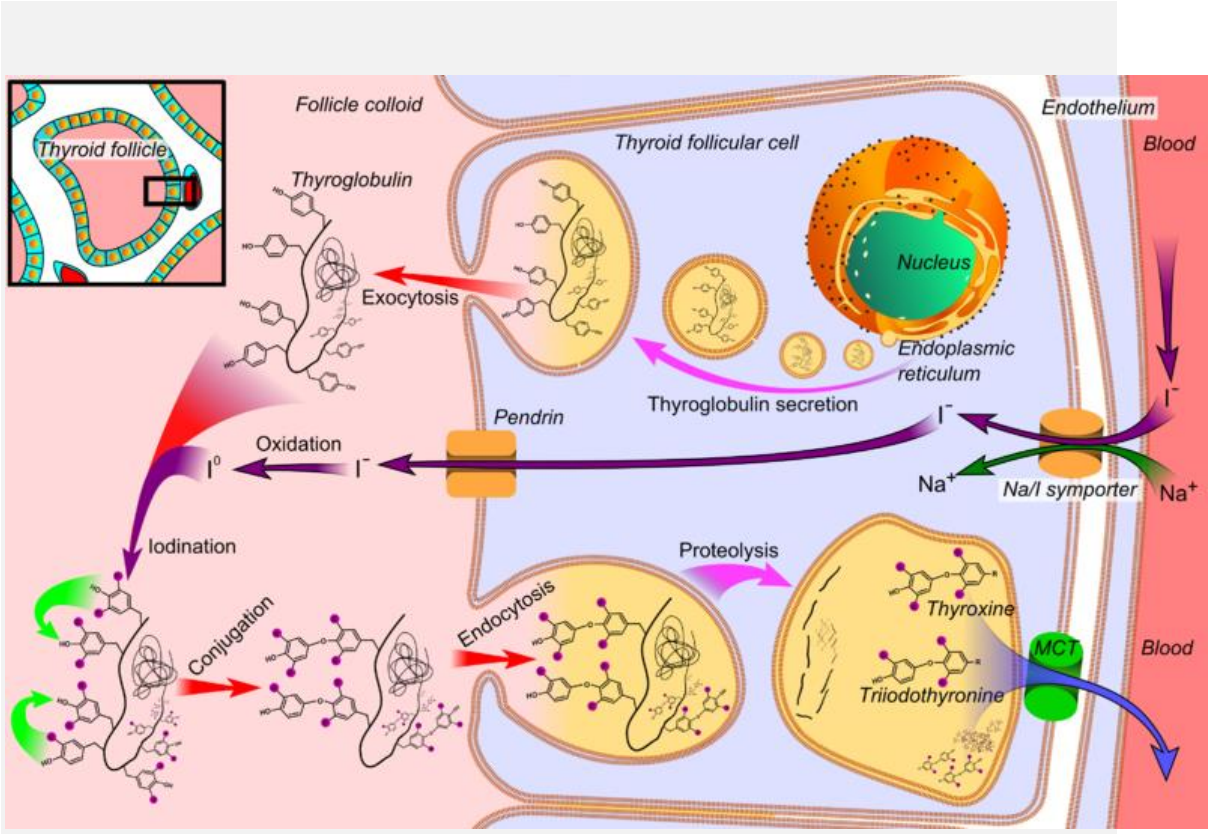
There are six steps in the synthesis of thyroid hormone, and we can remember them using the mnemonic ATE ICE:

- **Active transport** of Iodide into the follicular cell via the Sodium-Iodide Symporter (NIS). This is actually secondary active transport.
- **Thyroglobulin** (Tg), a large protein rich in Tyrosine, is formed in follicular ribosomes and placed into secretory vesicles.
- **Exocytosis** of Thyroglobulin into the follicle lumen, where it is stored as colloid. Thyroglobulin is the scaffold upon which thyroid hormone is synthesised.
- **Iodination** of the Thyroglobulin. Iodide is made reactive by the enzyme **thyroid peroxidase**. Iodide binds to the benzene ring on Tyrosine residues of Thyroglobulin, forming monoiodotyrosine (MIT) then diiodotyrosine (DIT).

- **Coupling** of MIT and DIT gives the Triiodothyronine (T3) hormone and coupling of DIT and DIT gives the Tetraiodothyronine (T4) hormone, also known as **Thyroxine**.
- **Endocytosis** of iodinated thyroglobulin back into the follicular cell. Thyroglobulin undergoes proteolysis in lysosomes to cleave the iodinated tyrosine residues from the larger protein. Free T3 or T4 is then released, and the Thyroglobulin scaffold is recycled.

T3 and T4 are the active thyroid hormones. They are **fat soluble** and mostly carried by plasma proteins – Thyronine Binding Globulin and Albumin. While T3 is the more potent form, it also has a shorter half-life due to its lower affinity for the binding proteins. Less than **1%** of T3 and T4 is unbound free hormone. At the peripheries, T4 is deiodinated to the more active T3.

T3 and T4 are deactivated by removing iodine. This happens in the liver and kidney. As T4 has a longer half-life, it is used in the treatment of hypothyroidism over T3 as its plasma concentrations are easier to manage.



Overview of the synthesis of thyroid hormones

Thyroid Hormone Release

Hypothalamic-Pituitary-Thyroid Axis Regulation, Hypothalamic Control

The hypothalamus produces thyrotrophin releasing hormone (TRH). TRH acts on the anterior pituitary, stimulating the production of thyroid stimulating hormone (TSH), also known as thyrotropin.

TSH enters the blood and binds to receptors on follicular cells of the thyroid gland, stimulating the production of thyroid hormones: triiodothyronine (T3) and tetraiodothyronine (T4), also known as thyroxine. Control of this system is via negative feedback: high levels of T3 and T4 inhibit TRH and TSH production by the hypothalamus and anterior pituitary gland, respectively.

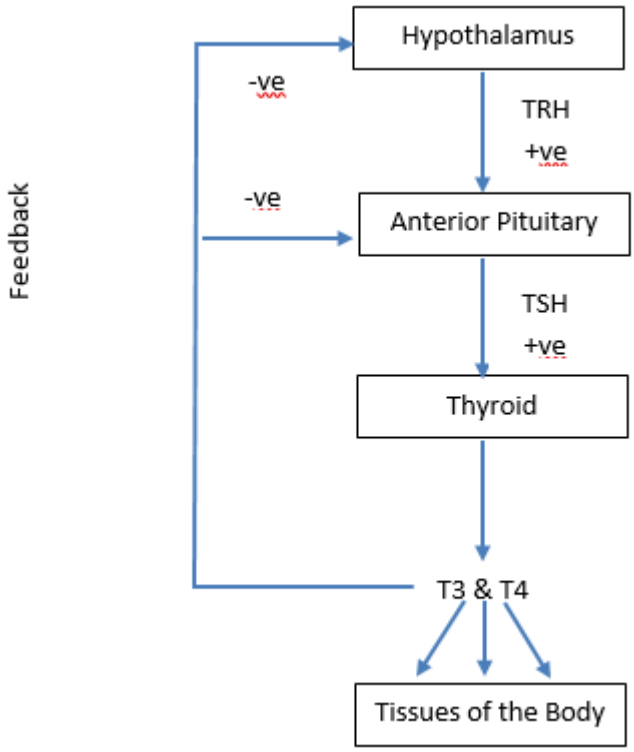


Diagram showing the HPT axis

Thyroid hormones are released as part of the hypothalamic-pituitary-thyroid axis. The Hypothalamus detects a low plasma concentration of thyroid hormone and releases Thyrotropin-Releasing Hormone (TRH) into the hypophyseal portal system. TRH binds to receptors found on thyrotrophic cells of the anterior pituitary gland, causing them to

release Thyroid Stimulating Hormone (TSH) into the systemic circulation. TSH binds to TSH receptors on the basolateral membrane of thyroid follicular cells and induces the synthesis and release of thyroid hormone.

- The thyroid hormones are lipophilic and relatively insoluble in the plasma. Therefore, they are transported throughout the circulation bound to plasma proteins such as thyroxine-binding globulin (TBG) (75%) and albumins (25%).
- T_3 has a shorter half-life than T4 and that its action on the tissues is much more rapid.

Clinical Relevance - Goitre

A Goitre is the medical term for an **enlarged thyroid gland.** The organ swells up to a palpable, and often visible, size within the neck. This may be due to an over or under active thyroid, iodine deficiency and in rare cases thyroid cancer

A thyroid goiter

Hyperthyroidism

Hyperthyroidism is the medical term for an overactive thyroid gland. One common cause of Hyperthyroidism is Grave's Disease – an autoimmune condition where antibodies are produced that stimulate

the TSH receptors on follicular cells. It affects roughly 1% of the population and is 10 times more common in women than in men.

Patients may present with heat intolerance, weight loss, tachycardia, nervousness, increased sweating, exophthalmos and increased bowel movements. Hyperthyroidism can be treated with Carbimazole which inhibits iodine binding to thyroglobulin.

Hypothyroidism

Hypothyroidism is an underactive thyroid gland. One common cause of Hypothyroidism is Hashimoto's Disease – an autoimmune condition where thyroid follicles are destroyed or antibodies are produced that block the TSH receptor on follicle cells.

Like hyperthyroidism, roughly 1% of the population is affected with it being 10 times more common in women than in men. In the developing world, the most common cause of Hypothyroidism is iodine deficiency.

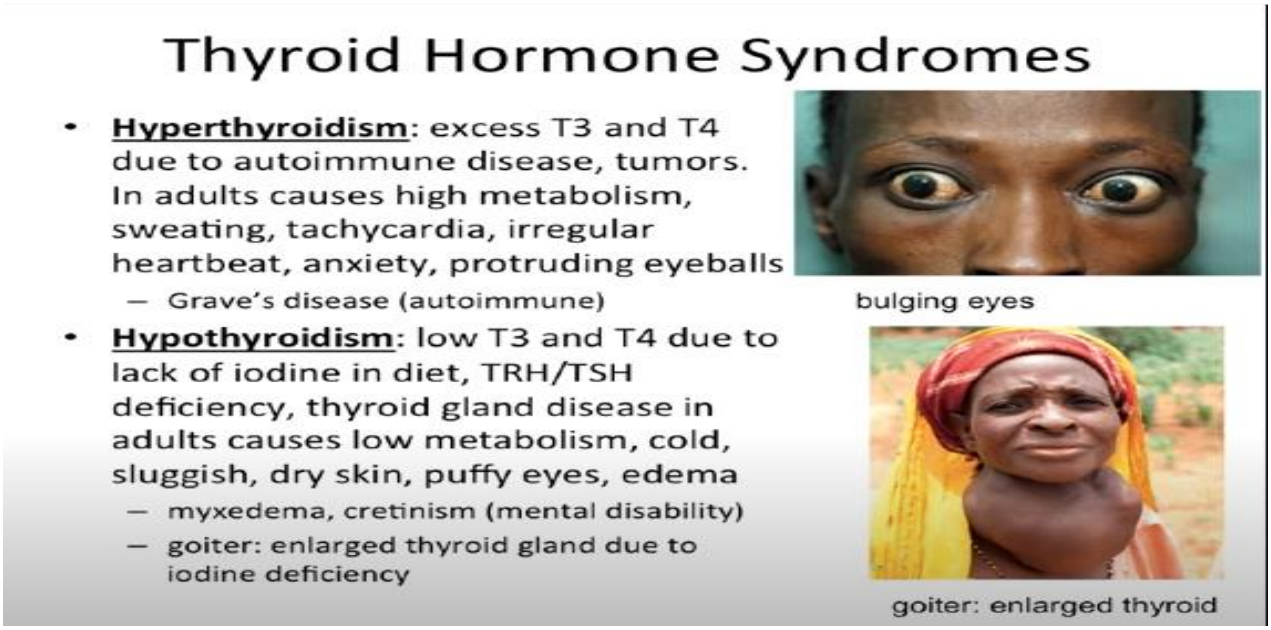
Patients can present with cold intolerance, weight gain, bradycardia, poor concentration, myxoedema, dry skin, some hair loss and constipation. Hypothyroidism can be treated with oral T4 tablets (100-200 µg/day), to replace the hormone that is not being produced by the body.

One way to remember the associated diseases with hyperthyroidism and hypothyroidism is to look at the prominent vowels in each: hypErthyroidism is caused by gravE's disease, whereas hypOthyroidism is caused by hashimOtO's disease.

Table – Clinical features of hyperthyroidism and hypothyroidism

Hyperthyroidism	Hypothyroidism
Anxiety	Depression
Restlessness	Fatigue
Tachycardia	Bradycardia
Weight loss	Weight gain
Thinning skin	Dry, itchy skin
Heat intolerance	Cold intolerance
Frequent bowel movements	Constipation

Goitre possible	Goitre possible
Low TSH	High TSH
High T3/T4	Low T3/T4



Thyroid Function Tests