Al-Mustaqbal University College

Pharmacy Department / Second Stage

PHYSIOLOGY II

ENDOCRINE SYSTEM, L2

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Hormones of the adenohypophysis

The *gonadotropins*, follicle-stimulating hormone and luteinizing hormone, exert their effects on the gonads (ovaries in the female and testes in the male). Taken together, the gonadotropins stimulate the gonads to:

Produce gametes (ova and sperm)

Secrete sex hormones (estrogen, progesterone, and testosterone)

FSH and LH are produced by the same cell type in the adenohypophysis: the gonadotrope. The release of FSH and LH is regulated by the hypothalamic releasing hormone, *gonadotropin-releasing hormone (GnRH)*.

Thyroid-stimulating hormone *(TSH, thyrotropin)* regulates the growth and metabolism of the thyroid gland. The release of TSH from the thyrotrope cells of the adenohypophysis is induced by *thyrotropin-releasing hormone (TRH)*.

Adrenocorticotropic hormone *(ACTH, adrenocorticotropin)* stimulates growth and steroid production in the adrenal cortex. *Corticotropin-releasing hormone (CRH)* from the hypothalamus stimulates the secretion of ACTH.

Prolactin (PRL), produced by the lactotrope cells of the adenohypophysis, is involved with the initiation and maintenance of lactation in females. Its function in males is uncertain. Lactation involves three processes:

Mammogenesis Lactogenesis Galactopoeisis

Mammogenesis is the growth and development of the mammary glands that produce the milk. This process requires the actions of many hormones, including estrogens and progestins, in addition to PRL.
Lactogenesis is the initiation of lactation. During pregnancy, lactation is inhibited by high levels of estrogens and progestins. At delivery, the levels of these two hormones fall, allowing PRL to initiate lactation.
Galactopoeisis is the maintenance of milk production. This process requires PRL and oxytocin.
The release of prolactin from the adenohypophysis is normally inhibited by *prolactin-inhibiting hormone (PIH, dopamine)* from the hypothalamus. Prolactin secretion is also controlled by *prolactin-releasing factor (PRF)*. The release of PRF from the hypothalamus is mediated by reflexes elicited by suckling and breast stimulation.

Growth hormone (GH, somatotropin) is one of the few hormones that exerts its effects on organs and tissues throughout the body. This hormone is essential for normal growth and development of the skeleton as well as visceral, or soft tissues from birth until young adulthood. Growth of the skeleton involves an increase in bone thickness and an increase in bone length. The mechanism of this growth involves stimulation of osteoblast (bone-forming cell) activity and proliferation of the epiphyseal cartilage in the ends of the long bones. The growth of visceral tissues occurs by ***hyperplasia*** (increasing the number of cells) and ***hypertrophy*** (increasing the size of cells). Growth hormone causes hyperplasia by stimulating cell division and by inhibiting apoptosis (programmed cell death) and cellular hypertrophy by promoting protein synthesis and inhibiting protein degradation.

The growth-promoting effects of GH are carried out by ***somatomedins***, which are peptides found in the blood. Two somatomedins have been identified and described. Structurally and functionally similar to insulin, these peptides are referred to as ***insulin-like growth factors I*** **and** ***II*** *(IGF-I* and *IGF-II)*. Growth hormone stimulates the production of IGF-I in the liver, which is the predominant source of that found in the circulation. Local production of IGF-I also occurs in many target tissues.

All the major anterior pituitary hormones, except for GH, exert their principal effects mainly by stimulating target glands, including thyroid gland, adrenal cortex, ovaries, testicles, and mammary glands.

Growth hormone also has many metabolic actions in the body:

Protein metabolism

Increase in tissue amino acid uptake

Stimulation of protein synthesis

Lipid metabolism

Increase in blood fatty acids Stimulation of lipolysis

Inhibition of lipogenesis

Carbohydrate metabolism

Increase in blood glucose

Decrease in glucose uptake by muscle

Increase in the hepatic output of glucose (glycogenolysis)

The net effects of these actions include enhanced growth due to protein synthesis; enhanced availability of fatty acids for use by skeletal muscle as an energy source; and glucose sparing for the brain, which can use only this nutrient molecule as a source of energy.

The release of GH from the adenohypophysis is regulated by two hypothalamic hormones:

growth hormone-releasing hormone (GHRH) **and**
growth hormone-inhibiting hormone (GHIH, somatostatin)**.**

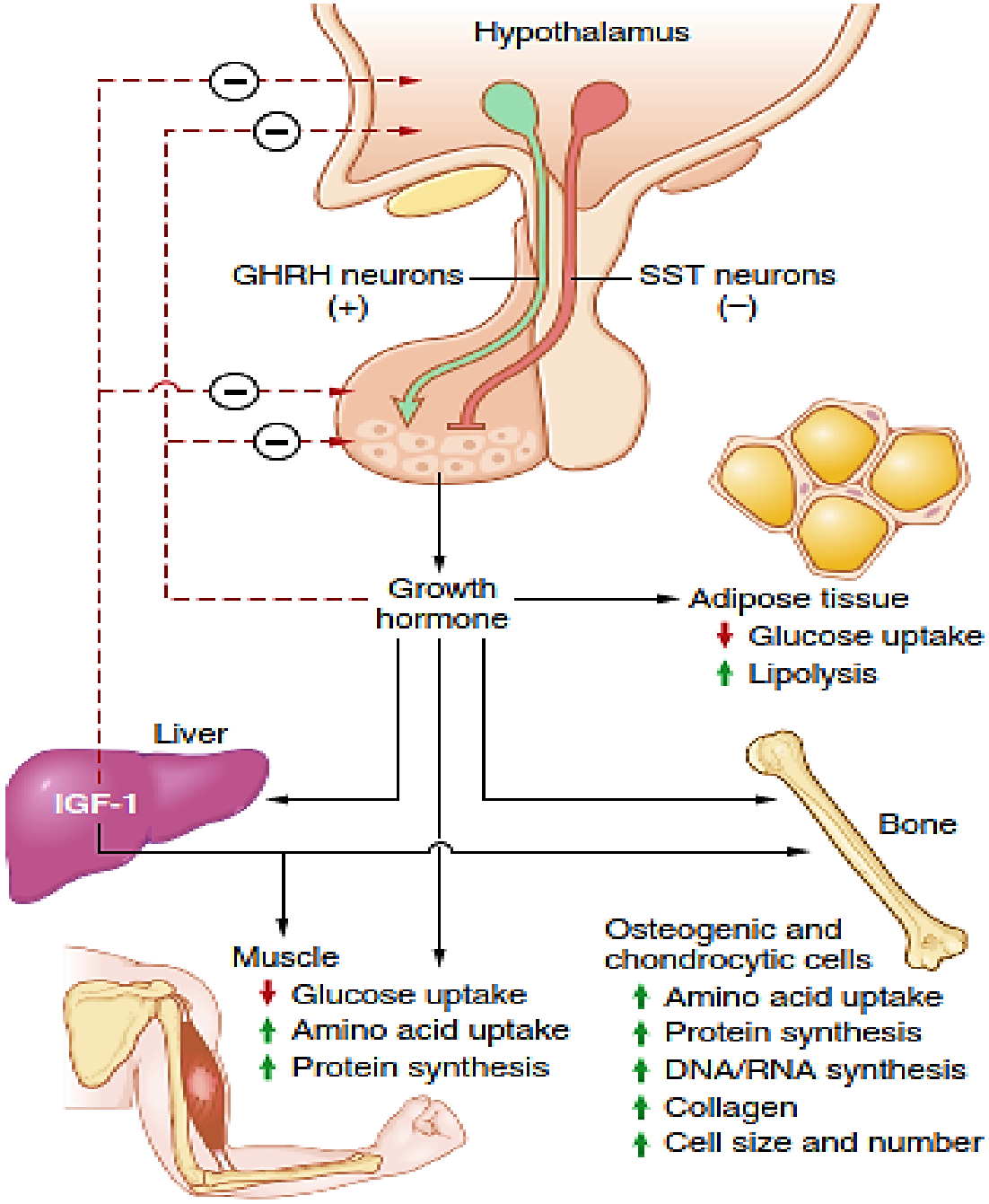
The secretion of GH follows a **diurnal rhythm** with GH levels low and constant throughout the day and with a marked burst of GH secretion approximately one hour following the onset of sleep (deep or stage III and IV sleep).

Other factors that stimulate GH secretion include exercise, stress, hypoglycemia, and increased serum amino acids.

Factors that inhibit GH secretion include hyperglycemia and aging. In most individuals, production of GH decreases after 30 years of age. This decrease in GH production is likely a critical factor in the loss of lean muscle mass at a rate of 5% per decade and gain of body fat at the same rate after 40 years of age.

Effects of growth hormone and insulin- like growth factor -1 (IGF-1) on growth and metabolism.
Growth hormone secretion is stimulated by growth hormone–releasing hormone (GHRH) and inhibited by somatostatin (SST), as well as negative feedback effects of growth hormone and IGF-1 on the anterior pituitary gland and the hypothalamic neurons.

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose level	Increased blood glucose level
Decreased blood free fatty acid levels	Increased blood free fatty acid levels
Increased blood amino acid levels (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	Growth hormone inhibitory hormone (somatostatin)
Exercise	Growth hormone (exogenous)
Testosterone, estrogen	Insulin-like growth factors (somatomedins)
Deep sleep (stages 2 and 4)	
Growth hormone–releasing hormone	
Ghrelin	



Clinical Relevance : Growth Hormone Deficiency

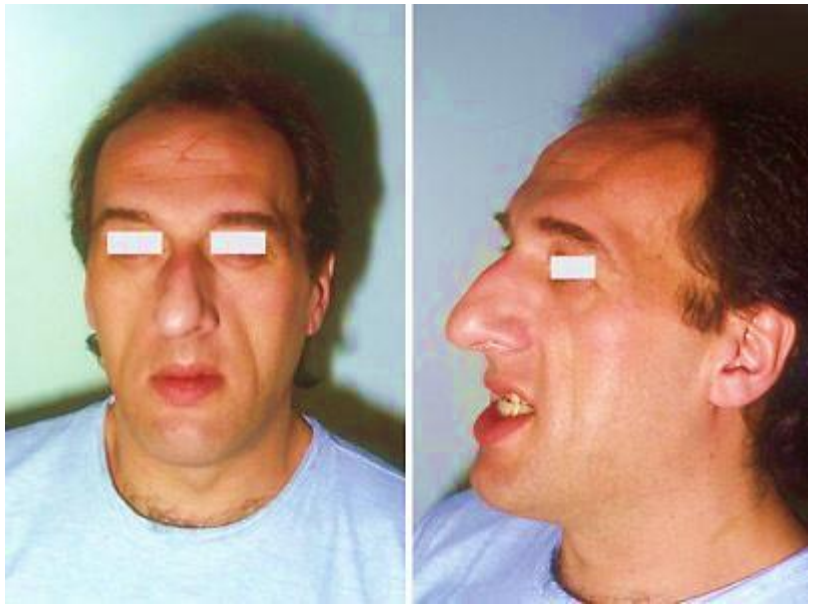
In children, a deficiency of GH could result in short stature (dwarfism) due to slow bone and muscle maturation and delayed puberty. result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood.

Growth Hormone Excess

In children, hypersecretion of GH before the bony epiphyses have fused results in **gigantism**, whereby the child grows very tall.

In adults, excess GH is called **acromegaly** and is mostly caused by a pituitary tumour secreting GH.

Clinical features include: Large extremities with growth of hands, feet and jaw, Paraesthesia in the extremities, amenorrhoea,coarse facial features, wide nose and rounded face, hypertension, cardiomegaly (enlarged heart).



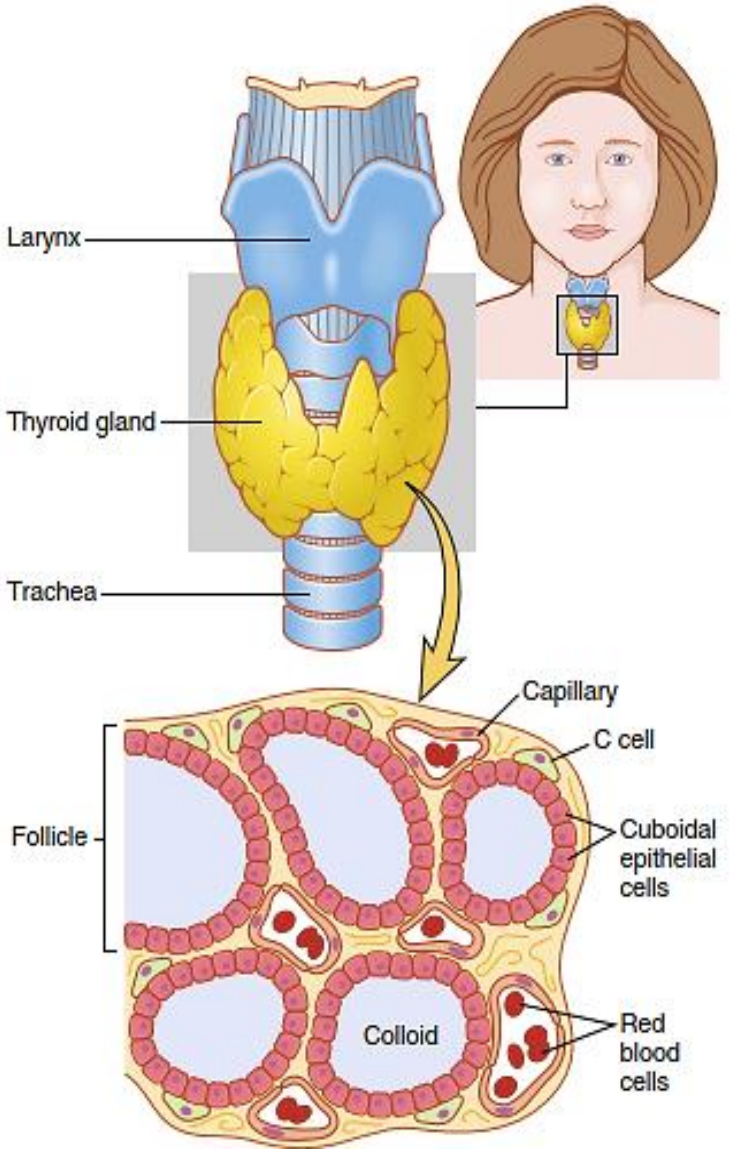
Thyroid gland

The thyroid gland is a butterfly-shaped structure lying over the ventral surface of the trachea just below the larynx. This gland produces two classes of hormones synthesized by two distinct cell types:

Thyroid hormones:(T^3 and T^4) synthesized by follicular cells

Calcitonin: synthesized by parafollicular cells

Thyroid hormones. Internally, the thyroid consists of *follicles*, which are spherical structures with walls formed by a single layer of epithelial cells called *follicular cells*. The center of each follicle contains a homogenous gel referred to as ***colloid***. Thyroid hormones are stored here as a component of the larger molecule, ***thyroglobulin***. The amount of thyroid hormones stored within the colloid is enough to supply the body for 2 to 3 months.



Derived from the amino acid **tyrosine**, thyroid hormones are unique because they contain **iodine**. At this time, its incorporation into thyroid hormones is the only known use for iodine in the body.
There are two thyroid hormones, named for the number of iodides added to the tyrosine residues of the thyroglobulin: **triiodothyronine** (T3) and **tetraiodothyronine** (T4, thyroxine).

Although significantly more T4 is synthesized by the thyroid gland, T3 is the active hormone. At the target tissue, T4 is deiodoninated to form the more potent T3.

- T_3 has a shorter half-life than T4 and that its action on the tissues is much more rapid.

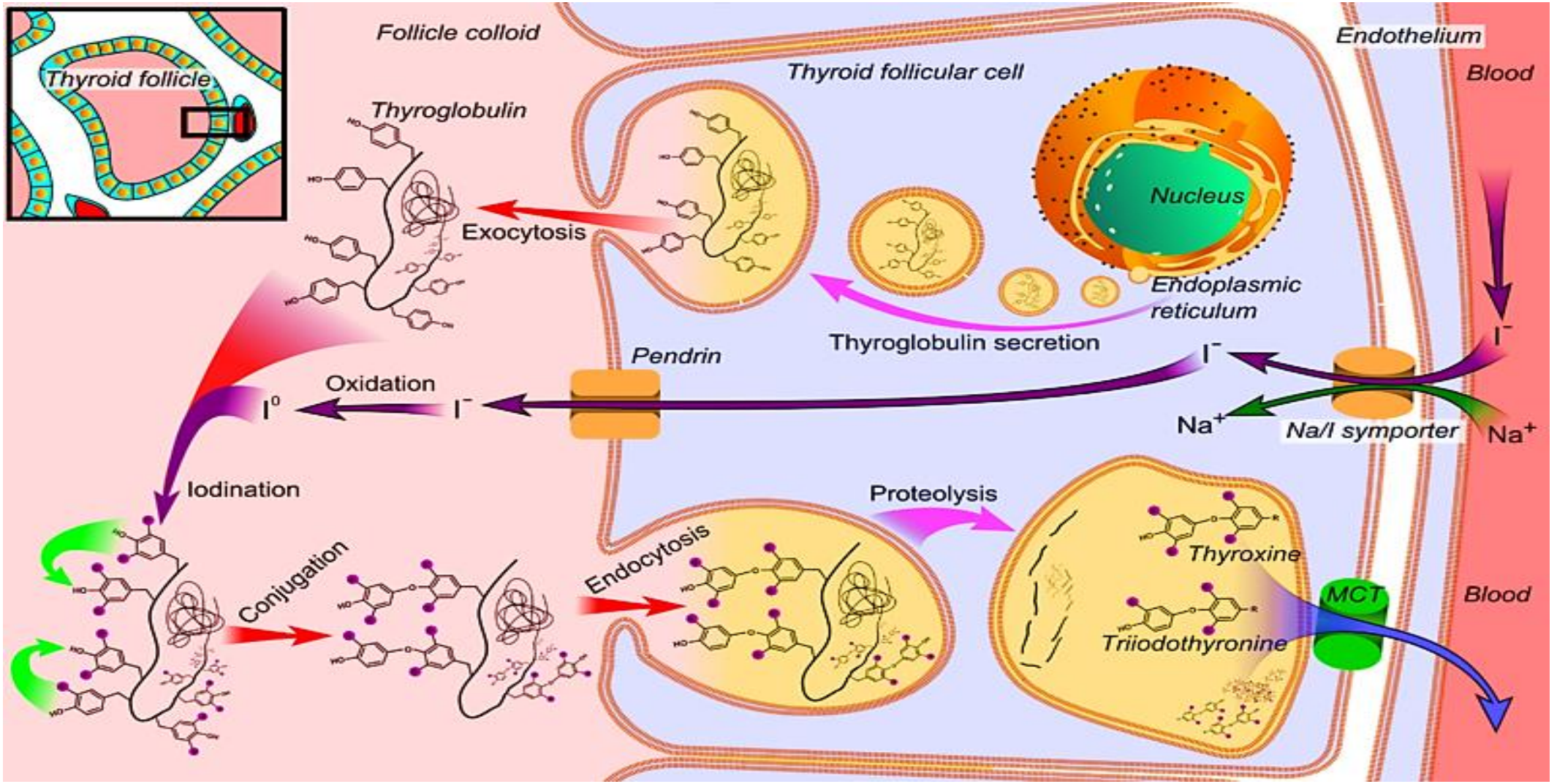
The thyroid hormones are lipophilic and relatively insoluble in the plasma. Therefore, they are transported throughout the circulation bound to plasma proteins such as thyroxine-binding globulin (75%) and albumins (25%).

Approximately 99.96% of circulating thyroxine is protein bound. Bound hormone is not available to cause any physiological effects; however, it is in equilibrium with the remaining 0.04% that is unbound. This free form of the hormone is able to bind to receptors on target tissues and cause its effects.

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 synthesized.
- **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.



Overview of the synthesis of thyroid hormones

- **Thyroid hormone** has many metabolic effects in the body:

Growth and maturation

Perinatal lung maturation

Normal skeletal growth

Neurological

Normal fetal and neonatal brain development

Regulation of neuronal proliferation and differentiation, myelinogenesis, neuronal outgrowth, and synapse formation

Normal CNS function in adults

Sympathetic nervous system function

Increase in the number of β-adrenergic receptors, Increase in heart rate,

Tremor

Sweating

Cardiovascular system

Increase in heart rate, Increase in myocardial contractility, Increase in cardiac output

Metabolism

Increase in basal metabolic rate, Stimulation of all metabolic pathways, both anabolic and catabolic
Increase in carbohydrate utilization, Increase in oxygen consumption, Increase in heat production

The secretion of hormones from the thyroid gland is regulated by negative feedback in 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.

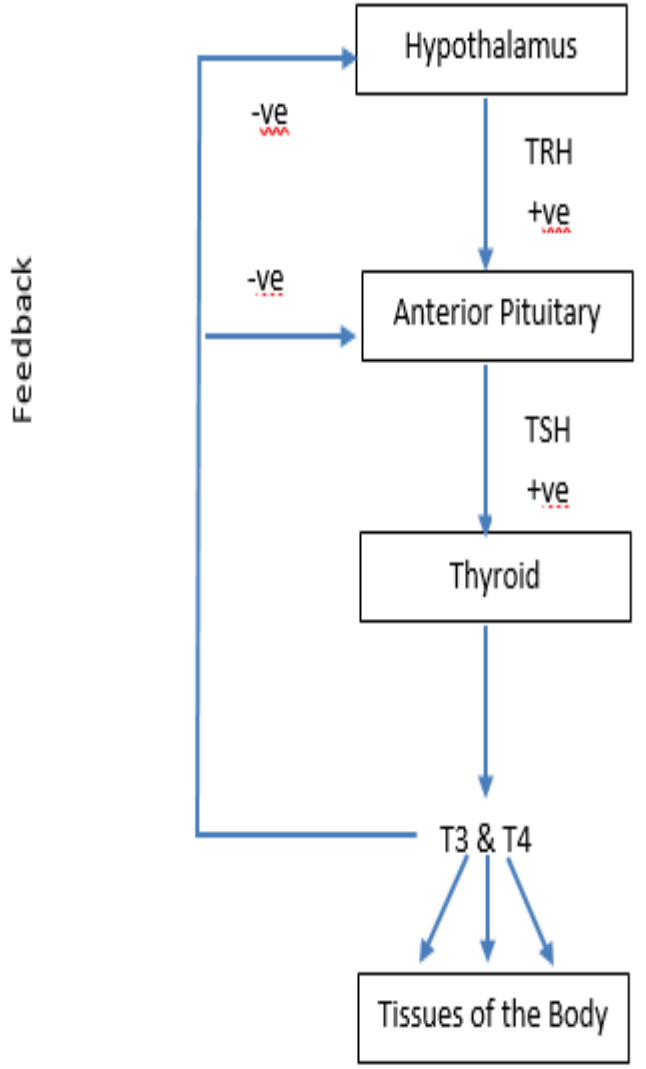
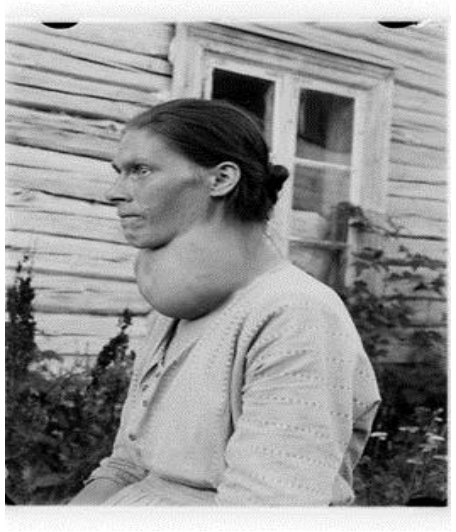


Diagram showing the HPT axis

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.



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. The term **myxedema** is often used interchangeably with hypothyroidism

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 and thick skin), some hair loss and constipation. **Cretinism** is a type of hypothyroidism that affects youngsters. In young people, thyroid secretion failure causes growth retardation of all kinds (physical, mental, and sexual).

Hypothyroidism can be treated with oral T4 tablets (100-200 µg/day), to replace the hormone that is not being produced by the body.

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

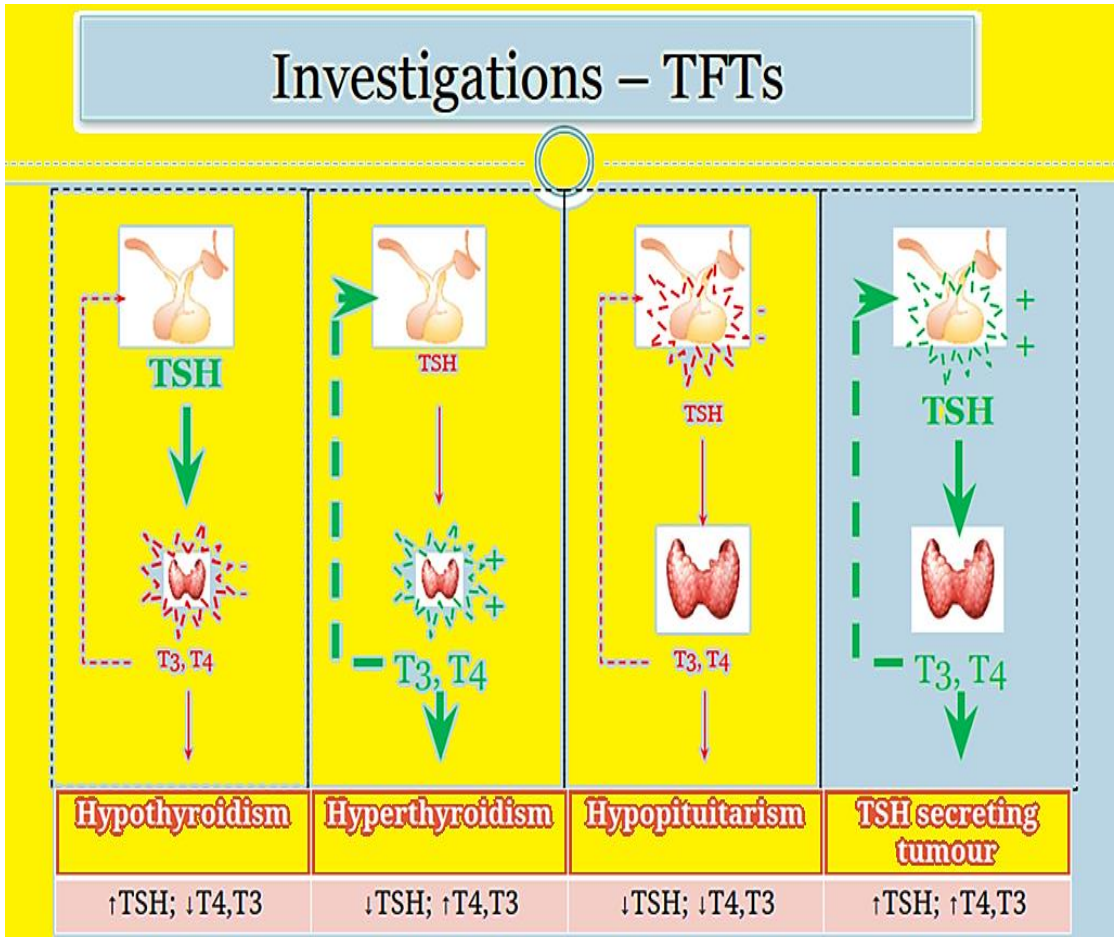
Thyroid Hormone Syndromes

- **Hyperthyroidism**: excess T3 and T4 due to autoimmune disease, tumors. In adults causes high metabolism, sweating, tachycardia, irregular heartbeat, anxiety, protruding eyeballs
  - Grave's disease (autoimmune)

bulging eyes

- **Hypothyroidism**: low T3 and T4 due to lack of iodine in diet, TRH/TSH deficiency, thyroid gland disease in adults causes low metabolism, cold, sluggish, dry skin, puffy eyes, edema
  - myxedema, cretinism (mental disability)
  - goiter: enlarged thyroid gland due to iodine deficiency

goiter: enlarged thyroid




Thank you.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