5.1.5

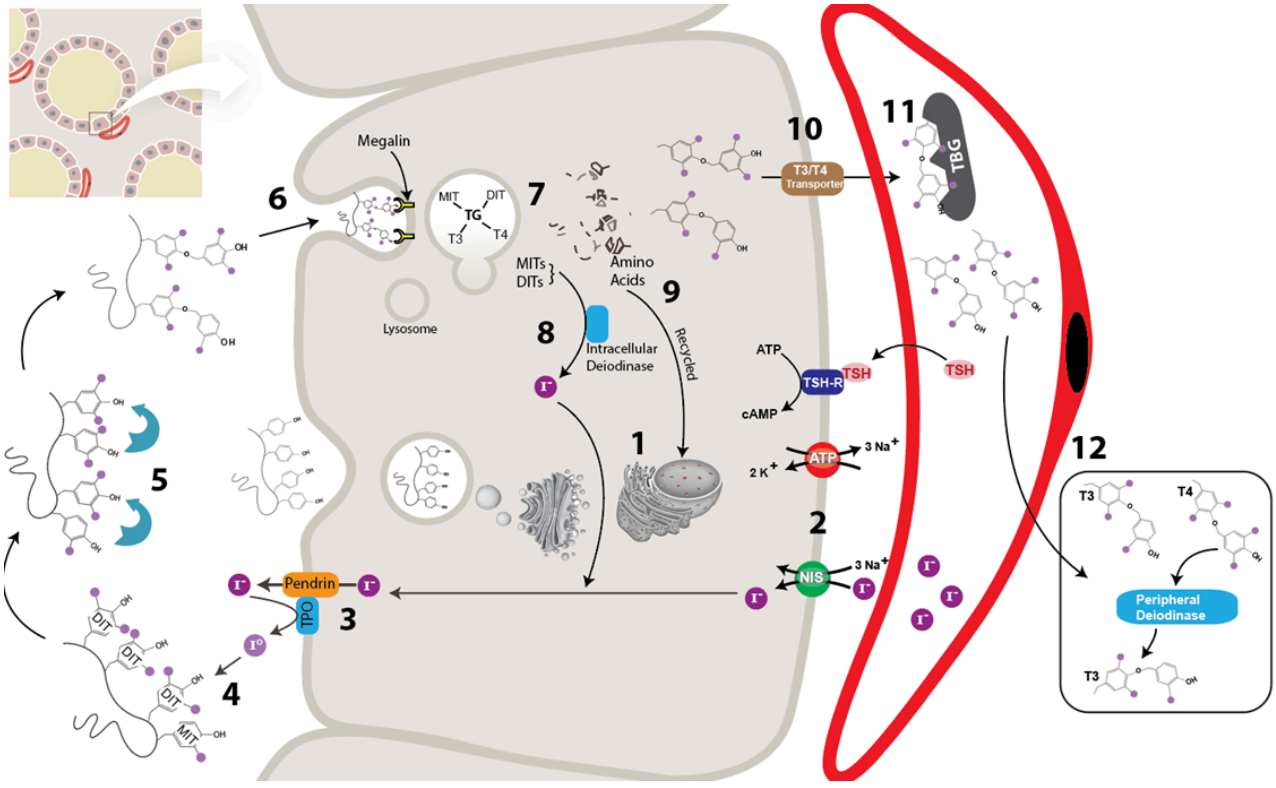
Thyroid Hormone Disorders

Watch the video Thyroid Part 1 - Thyroid Gland Structure and Calcitonin

The thyroid gland is located inferior to the larynx on the anterior side of the body. There are two major types of cells that make up the thyroid gland. The first are the **follicular cells** that produce thyroid hormone or T3/T4 (T4 is commonly called **thyroxine**). The second are **parafollicular cells** (also called C cells because they produce calcitonin). **Calcitonin** inhibits osteoclasts, stimulates osteoblasts, and inhibits renal reabsorption of calcium. In many ways it is the exact opposite of parathyroid hormone (PTH).

Thyroid Hormone Synthesis

Watch the video Thyroid Part 2 - Thyroid Hormone Synthesis



Thyroid Hormone Synthesis *Image by JS BYU-I*

The thyroid hormones T3 and T4 are made by follicular cells in a complex process that we will discuss step by step below. The numbers reference the image above:

1. The glycoprotein **thyroglobulin (TG)** is synthesized in the nucleus and rough endoplasmic reticulum and then packaged into a vesicle by the Golgi apparatus to then be secreted into the follicular lumen by exocytosis.
2. On the basolateral membrane of the follicular cell there are Na^+/K^+ pumps that use ATP to pump 3 Na^+ out of the cell and 2 K^+ in. They create energy and a gradient for the sodium iodide symporter (NIS). The NIS utilizes secondary active transport by using the energy of moving Na^+ from high to low concentration to move iodide (I^-) from low to high concentration into the cell.
3. A protein on the apical membrane called **pendrin** then transports iodide into the lumen. An enzyme called **thyroid peroxidase (TPO)** that is also on the apical membrane then oxidizes iodide into iodine.
4. Iodine then combines with tyrosine amino acid molecules located on the thyroglobulin molecule.

- 1 iodine + 1 tyrosine = **monoiodotyrosine (MIT)**

- 2 iodine + 1 tyrosine = **diiodotyrosine (DIT)**

5. As well as oxidizing iodide to iodine, TPO is the enzyme that catalyzes the reaction that binds MITs with DITs together to create T3 and T4.

- 1 MIT + 1 DIT = **T3** (active form of thyroid hormone that makes up 10% of amount synthesized)

- 2 DITs = **T4** (inactive form of thyroid hormone that makes up 90% of amount synthesized)

6. The newly formed thyroid hormone is then taken into the cell through receptor mediated endocytosis via a receptor called **megalin**.
7. Once the thyroglobulin complex is in the cell, a lysosome will fuse with the vesicle and begin to break it down into MITs, DITs, amino acids, T3, and T4.
8. In the cytoplasm of the cell there is **intracellular deiodinase** which removes the iodine from the MITs and DITs and recycles it.
9. The amino acids are also recycled to make more thyroglobulin.
10. On the basolateral membrane there is a T3/T4 transporter that moves the newly synthesized thyroid hormones across the membrane to the blood.
11. Inside the capillary, T3 and T4 bind to **thyroid binding globulin (TBG)** for transport in the circulatory system.
12. In the peripheral tissue, inactive T4 is converted to active T3 by **peripheral deiodinase**. T3 then binds to its receptors and exerts its action to increase growth and metabolism.

The process discussed above is regulated by thyroid stimulating hormone (TSH) that is released from the anterior pituitary. TSH has a receptor on the basolateral membrane of the follicular cell. The binding of TSH to this receptor results in an increased production of cyclic AMP from ATP. cAMP acts as an intracellular second messenger to cause the stimulation of Na^+/K^+ pumps, NIS, TPO, pendrin, thyroglobulin, megalin, and the T3/T4 transporter. All of these processes being turned on works together to increase production and release of more T3 and T4 into the blood.

Role of Thyroid Hormone and Thyroid Blood Tests

T3/T4 increase the rate of metabolism in most tissues. One of the most important physiological consequences of these thyroid hormones is the overall effect they have on the heart to increase cardiac output. They accomplish this by several mechanisms.

- Thyroid hormone inhibits the expression of $3Na^+/Ca^{2+}$ antiporters in the cardiac myocyte membrane. This increases myocellular levels of Ca^{2+} and thus increases heart contractile strength.
- Thyroid hormone increases the expression of ryanodine channels in the sarcoplasmic reticular membrane and thus promotes the release of calcium from the SR during systole. This also increases contractile strength.
- Thyroid hormone also increases the expression of SERCA which in turn increases the sequestration of Ca^{2+} during diastole to cause a shortened relaxation time so the heart can beat faster.
- Thyroid hormone increases beta adrenergic receptor expression on cardiomyocytes which makes the heart more sensitive to excitation through the sympathetic nervous system.

Thyroid hormone will also increase GI motility and appetite. Despite increased appetite, weight loss with excess thyroid hormone occurs because of increased metabolic rate. Thyroid hormone is also absolutely essential for normal brain development. There is a strong interaction between thyroid hormone and the autonomic nervous system (ANS). Because of this interaction, signs of hyperthyroidism include tachycardia, sweating, tremors, anxiety, and diarrhea.

There are several blood tests that can be done to measure thyroid function. Looking at blood levels of different hormones can give an insight into where a problem is and whether it is a primary, secondary or tertiary endocrine dysfunction. For example: T3 and T4 levels are low in primary hypothyroidism even though the TRH and TSH levels are elevated. Anti-TPO antibodies can sometimes be measured in the blood as well and are important in the diagnosis of Hashimoto's disease. Thyroid stimulating immunoglobulin (TSI) is an antibody that is important for diagnosis of Graves' Disease, a form of hyperthyroidism.

Hypothyroidism

Hypothyroidism occurs when the thyroid gland does not produce sufficient amounts of thyroid hormone. There are many different reasons that hypothyroidism can occur, some of which we will discuss.

Congenital hypothyroidism, also known as **cretinism**, occurs when an infant does not produce enough thyroid hormone after birth. When it was in the womb, the fetus got plenty of thyroid hormone from the placenta. The thyroid deficiency becomes a problem after the child is born and loses access to maternal T3/T4. If left untreated, hypothyroidism can lead to mental retardation and impaired physical growth. Blood tests for thyroid hormone levels for an infant with cretinism would reveal low T3 and T4 but high TRH and TSH. Can you explain why?

Hypothyroidism can also be acquired at some point in a person's life. As an acquired condition, primary hypothyroidism is more common than secondary or tertiary hypothyroidism. Some causes of primary hypothyroidism include iodine insufficiency, side effects of some drugs, or a viral infection of the thyroid tissue. However, the main cause for primary hypothyroidism is **Hashimoto's Disease**. Hashimoto's disease is characterized by autoantibodies against thyroglobulin and/or thyroid peroxidase that lead to autoimmune destruction of the thyroid and decreased hormone production. Hashimoto's disease is more common in women. It manifests with low levels of T3/T4 but high levels of TRH and TSH.

Some common symptoms and manifestations of hypothyroidism include decreased oxygen use, decreased sweating, decreased heart rate and BP, decreased appetite, a reduced metabolic rate resulting in weight gain, cold intolerance, and tiredness. Low thyroid hormone can lead to hypothermia due to decreased non-shivering (metabolic) thermogenesis. Hyponatremia is another possible symptom and is due to the impairment of free water excretion brought about by increased release of vasopressin and decreased kidney function. Neurological manifestations may also occur that include confusion and lethargy that may progress to a condition called a **myxedematous coma**. This condition occurs due to the decreased function of multiple organs from low thyroid hormone levels. Carbon dioxide retention and hypoxemia come about because of central depression of the respiratory drive. This hypoventilation leads to a state of acidosis because of CO_2 retention leading to increased H^+ and decreased oxygen delivery leading to poor glucose utilization and lactic acidosis. Acidosis contributes to the decrease in nervous system function. Another possible symptom of hypothyroidism is **myxedema**. Myxedema is edema due to an increase of mucopolysaccharide deposition in connective tissue, especially around the face, hands and feet. Mucopolysaccharides are long, linear polysaccharides that when deposited in connective tissue attract and bind water because of their very polar nature. Excessive mucopolysaccharide results in a buildup of water that leads to edema. It is not known for certain how hypothyroidism can lead to myxedema, but one theory involves the idea that the fibroblasts that make these polysaccharides may have TSH or TSH-like receptors that can be stimulated by the higher levels of TSH seen with hypothyroidism.

A common treatment for hypothyroidism is administration of synthetic T4. This medication can supplement T4 levels in the blood which can then be turned to the active form of thyroid hormone in body cells by deiodinase enzymes. One reason for taking T4 instead of T3 is that T4 has a longer half-life in the body, lasting 7 days instead of the 24 hours seen with T3. This longer half-life leads to a more consistent level of thyroid hormone.

Hyperthyroidism

Hyperthyroidism occurs when the thyroid gland produces too much thyroid hormone. Primary hyperthyroidism is most commonly caused by **Graves' disease**. Someone with Graves' has **thyroid stimulating immunoglobulin (TSI)**. This is an autoimmune antibody that binds to the TSH-receptor on follicular cells and activates it just as TSH would. This binding increases the production and release of T3 and T4 and leads to hyperplasia and hypertrophy of the gland, possibly even forming a goiter. TSI is not subject to negative feedback as TSH is, so it will not be reduced as T3/T4 levels increase and will continue to stimulate the thyroid. **Exophthalmos** (pressure pushing on the eyes to the point that they bulge) and a type of myxedema called **pretibial myxedema (PTM)** occur in Graves' disease. Similar to the edema in hypothyroidism, the edema in Grave's disease appears to involve the stimulation of fibroblasts by TSIs (not TSH). It is not understood why fibroblasts in specific areas like the pretibial area are preferentially activated.

Primary hyperthyroidism can also be caused by a **toxic multinodular goiter**. This develops when the thyroid gland is stimulated to create areas of growth and activity beyond the normal glandular tissue in areas called nodules. A multinodular goiter contains areas of hyper-stimulated and hyperactive thyroid cells that are genetically normal. Primary hyperthyroidism can also result from a **solitary toxic adenoma**. A solitary toxic adenoma is distinguished from a multinodular goiter by the fact that areas of hyperactivity are generally caused by a precursor cell that has experienced a genetic mutation that results in abnormal, uncontrolled growth and activity.

Most of the manifestations of hyperthyroidism are due to an increase in metabolic activity in tissues and increased activity of the sympathetic nervous system. In many ways its symptoms are the reverse of hypothyroidism (see the table).

HYPERTHYROIDISM	HYPOTHYROIDISM
↑ Oxygen Use	↓ Oxygen Use
↑ Sweating	↓ Sweating
↑ Heart Rate	↓ Heart Rate
↑ Blood Pressure	↓ Blood Pressure
↑ Appetite	↓ Appetite
Weight Loss	Weight Gain
Heat Intolerance	Cold Intolerance
Insomnia	Sleepiness/Fatigue
Hyperexcitable	Apathy
Irritable	Dry Skin
Muscle Catabolism	Myxedema

There are three main ways to reduce the amount of thyroid hormone: the use of radioactive iodine which damages the thyroid cells, use of drugs that decrease thyroid hormone production, or surgical removal. Methimazole and propylthiouracil are drugs that inhibit TPO and thus decrease thyroid hormone synthesis. Propylthiouracil has an additional action in that it also inhibits peripheral deiodinase.