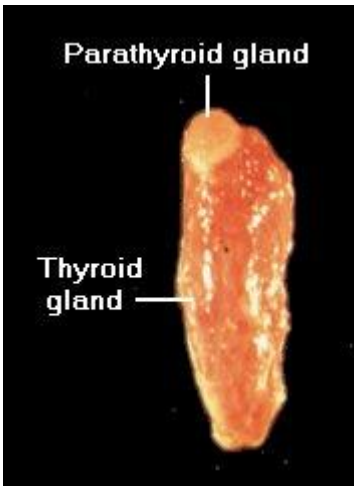
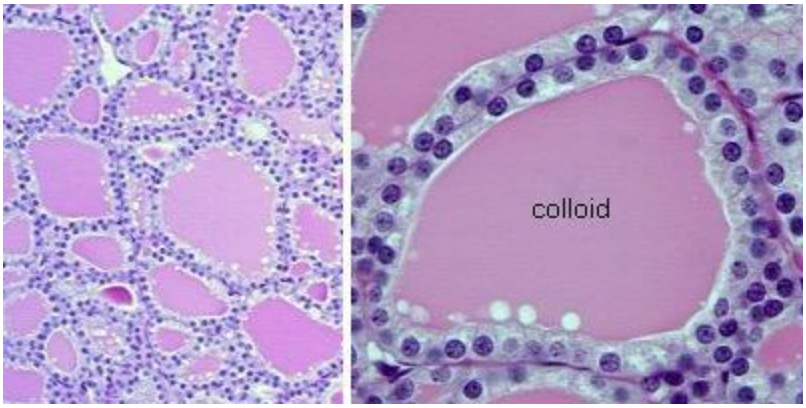
Functional Anatomy of the Thyroid and Parathyroid Glands



Thyroid glands are located in the neck, in close approximation to the first part of the trachea. In humans, the thyroid gland has a "butterfly" shape, with two lateral lobes that are connected by a narrow section called the isthmus. Most animals, however, have two separate glands on either side of the trachea. Thyroid glands are brownish-red in color.

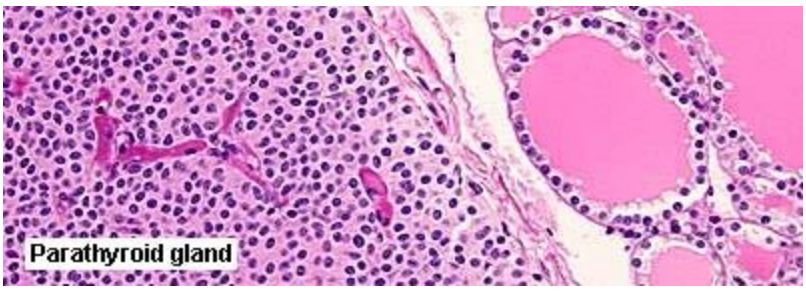
Close examination of a thyroid gland will reveal one or more small, light-colored nodules on or protruding from its surface - these are **parathyroid glands** (meaning "beside the thyroid"). The image to the right shows a canine thyroid gland and one attached parathyroid gland.

The microscopic structure of the thyroid is quite distinctive. Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called **thyroid follicles**. Follicles are filled with **colloid**, a proteinaceous depot of thyroid hormone precursor. In the low (left) and high-magnification (right) images of a cat thyroid below, follicles are cut in cross section at different levels, appearing as roughly circular forms of varying size. In standard histologic preparations such as these, colloid stains pink.



In addition to thyroid epithelial cells, the thyroid gland houses one other important endocrine cell. Nestled in spaces between thyroid follicles are **parafollicular or C cells**, which secrete the hormone calcitonin.

The structure of a parathyroid gland is distinctly different from a thyroid gland. The cells that synthesize and secrete parathyroid hormone are arranged in rather dense cords or nests around abundant capillaries. The image below shows a section of a feline parathyroid gland on the left, associated with thyroid gland (note the follicles) on the right.

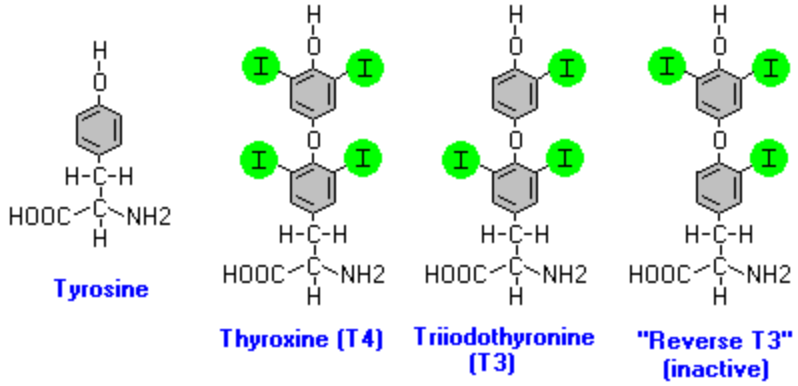


Chemistry of Thyroid Hormones

Thyroid hormones are derivatives of the the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:

- **thyroxine** (also known as T4 or L-3,5,3',5'-tetraiodothyronine)
- **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine)

As shown in the following diagram, the thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3,3',5'-T3) is such an example.



A large majority of the thyroid hormone secreted from the thyroid gland is T4, but T3 is the considerably more active hormone. Although some T3 is also secreted, the bulk of the T3 is derived by deiodination of T4 in peripheral tissues, especially liver and kidney. Deiodination of T4 also yields reverse T3, a molecule with no known metabolic activity.

Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is *thyroxine-binding globulin*, a glycoprotein synthesized in the liver. Two other carriers of import are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.

Synthesis and Secretion of Thyroid Hormones

Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones.

Constructing Thyroid Hormones

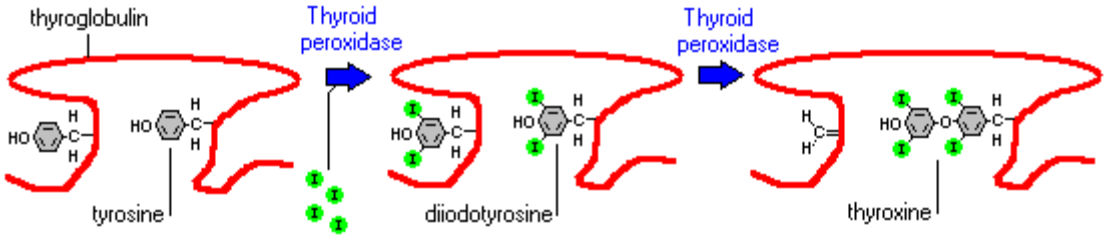
The recipe for making thyroid hormones calls for two principle raw materials:

- *Tyrosines* are provided from a large glycoprotein scaffold called *thyroglobulin*, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.

Iodine, or more accurately iodide (I^-), is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "*iodine trap*". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme *thyroid peroxidase*, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

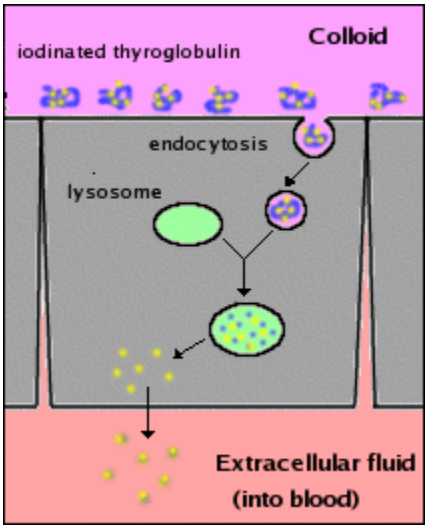
1. Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
2. Synthesis of thyroxine or triiodothyronine from two iodotyrosines.

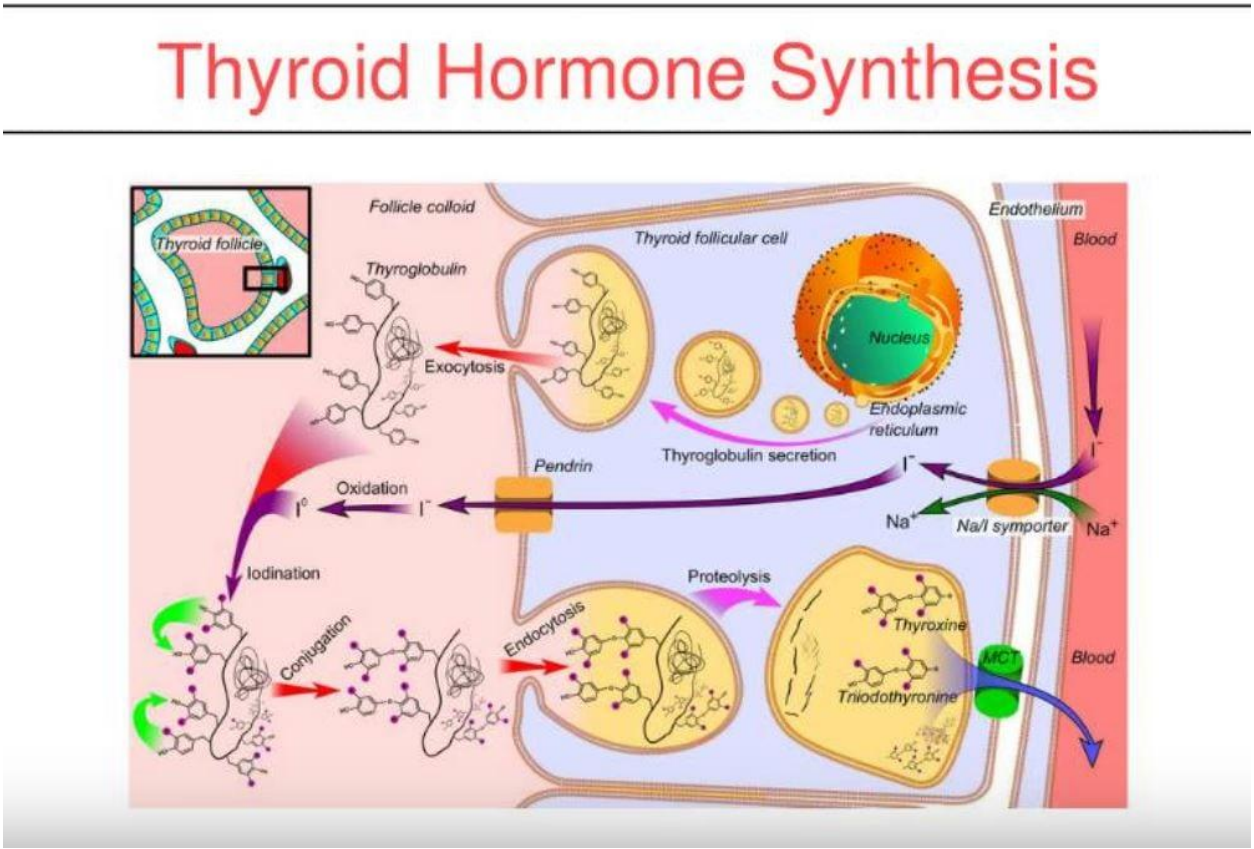


Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.
- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobluin, thereby liberating free thyroid hormones.
- Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.





Control of Thyroid Hormone Synthesis and Secretion

Each of the processes described above appears to be stimulated by thyroid-stimulating hormone from the anterior pituitary gland. Binding of TSH to its receptors on thyroid epithelial cells stimulates synthesis of the iodine transporter, thyroid peroxidase and thyroglobulin.

The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

Mechanism of Action and Physiologic Effects of Thyroid Hormones

Thyroid Hormone Receptors and Mechanism of Action

Receptors for thyroid hormones are intracellular DNA-binding proteins that function as hormone-responsive transcription factors, very similar conceptually to the receptors for steroid hormones.

Thyroid hormones enter cells through membrane transporter proteins. A number of plasma membrane transporters have been identified, some of

which require ATP hydrolysis; the relative importance of different carrier systems is not yet clear and may differ among tissues. Once inside the nucleus, the hormone binds its receptor, and the hormone-receptor complex interacts with specific sequences of DNA in the promoters of responsive genes.

The effect of the hormone-receptor complex binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes.

For the purpose of illustration, consider one mechanism by which thyroid hormones increase the strength of contraction of the heart. Cardiac contractility depends, in part, on the relative ratio of different types of myosin proteins in cardiac muscle. Transcription of some myosin genes is stimulated by thyroid hormones, while transcription of others in inhibited. The net effect is to alter the ratio toward increased contractility.

Physiologic Effects of Thyroid Hormones

It is likely that all cells in the body are targets for thyroid hormones. While not strictly necessary for life, thyroid hormones have profound effects on many "big time" physiologic processes, such as development, growth and metabolism, and deficiency in thyroid hormones is not compatible with normal health. Additionally, many of the effects of thyroid hormone have been delineated by study of deficiency and excess states, as discussed briefly below.

Metabolism: Thyroid hormones stimulate diverse metabolic activities most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is to increase body heat production, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis. By way of analogy, the action of thyroid hormones is akin to blowing on a smouldering fire. A few examples of specific metabolic effects of thyroid hormones include:

- *Lipid metabolism*: Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels - one diagnostic indiction of hypothyroidism is increased blood cholesterol concentration.
- *Carbohydrate metabolism*: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.

Growth: Thyroid hormones are clearly necessary for normal growth in children and young animals, as evidenced by the growth-retardation observed in thyroid deficiency. Not surprisingly, the growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indiction that complex physiologic processes like growth depend upon multiple endocrine controls.

Development: A classical experiment in endocrinology was the demonstration that tadpoles deprived of thyroid hormone failed to undergo metamorphosis into frogs. Of critical importance in mammals is the fact that **normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.**

Other Effects: As mentioned above, there do not seem to be organs and tissues that are not affected by thyroid hormones. A few additional, well-documented effects of thyroid hormones include:

- *Cardiovascular system*: Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs.
- *Central nervous system*: Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone, and the individual tends to feel mentally sluggish, while too much induces anxiety and nervousness.
- *Reproductive system*: Normal reproductive behavior and physiology is dependent on having essentially normal levels of thyroid hormone. Hypothyroidism in particular is commonly associated with infertility.

Thyroid Disease States

Disease is associated with both inadequate production and overproduction of thyroid hormones. Both types of disease are relatively common afflictions of man and animals.

Hypothyroidism is the result from any condition that results in thyroid hormone deficiency. Two well-known examples include:

- *Iodine deficiency*: Iodide is absolutely necessary for production of thyroid hormones; without adequate iodine intake, thyroid hormones cannot be synthesized. Historically, this problem was seen particularly in areas with iodine-deficient soils, and frank iodine deficiency has been virtually eliminated by iodine supplementation of salt.
- *Primary thyroid disease*: Inflammatory diseases of the thyroid that destroy parts of the gland are clearly an important cause of hypothyroidism.

Common symptoms of hypothyroidism arising after early childhood include lethargy, fatigue, cold-intolerance, weakness, hair loss and reproductive failure. If these signs are severe, the clinical condition is called *myxedema*. In the case of iodide deficiency, the thyroid becomes inordinantly large and is called a *goiter*.

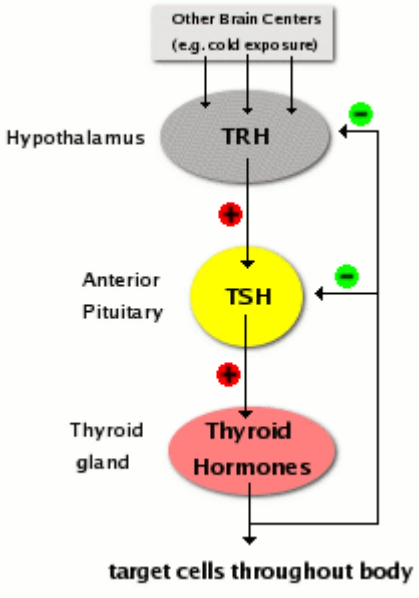
The most severe and devestating form of hypothyroidism is seen in young children with congenital thyroid deficiency. If that condition is not corrected by supplemental therapy soon after birth, the child will suffer from cretinism, a form of irreversible growth and mental retardation.

Most cases of hypothyroidism are readily treated by oral administration of synthetic thyroid hormone. In times past, consumption of dessicated animal thyroid gland was used for the same purpose.

Hyperthyroidism results from secretion of thyroid hormones. In most species, this condition is less common than hypothyroidism. In humans the most common form of hyperthyroidism is *Graves disease*, an immune disease in which autoantibodies bind to and activate the thyroid-stimulating hormone receptor, leading to continual stimulation of thyroid hormone synthesis. Common signs of hyperthyroidism are basically the opposite of those seen in hypothyroidism, and include nervousness, insomnia, high heart rate, eye disease and anxiety. Graves disease is commonly treated with anti-thyroid drugs (e.g. propylthiourea, methimazole), which suppress synthesis of thyroid hormones primarily by interfering with iodination of thyroglobulin by thyroid peroxidase.

Control of Thyroid Hormone Synthesis and Secretion

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormone from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells seems to enhance all of the processes necessary for synthesis of thyroid hormones, including synthesis of the iodide transporter, thyroid peroxidase and thyroglobulin.



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The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback, as depicted in the diagram. Thyroid-releasing hormone (TRH) from the hypothalamus

stimulates TSH from the pituitary, which stimulates thyroid hormone release. As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to "shutdown" of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again.

A number of other factors have been shown to influence thyroid hormone secretion. In rodents and young children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release. This makes sense considering the known ability of thyroid hormones to spark body heat production.