Biochemistry and Disorder of Hormones of the Thyroid Gland

Objectives:
1. to describe the structure and function of the thyroid gland
2. to list the hormones synthesized by the thyroid gland and state their functions
3. to describe synthesis, regulation, and metabolism of thyroid hormones
4. to state the effects of increased and decreased concentrations of thyroid hormones on TSH concentrations.
5. to understand the disorders of the thyroid and the associated diseases such as:
   a. Hashimoto disease
   b. Graves disease
   c. Secondary hypothyroidism
   d. Thyroid antibodies

The Thyroid Gland
The thyroid gland (Greek thyros “shield”) is shaped like a shield and lies just below the Adam’s apple in the front of the neck.
The thyroid gland secretes thyroxine and smaller amounts of triiodothyronine (T3), which stimulate oxidative respiration in most cells in the body and, in so doing, help set the body’s basal metabolic rate. In children, these thyroid hormones also promote growth and stimulate maturation of the central nervous system. Children with underactive thyroid glands are therefore stunted in their growth and suffer severe mental retardation, a condition called cretinism. This differs from pituitary dwarfism, which results from inadequate GH and is not associated with abnormal intellectual development.
People who are hypothyroid (whose secretion of thyroxine is too low) can take thyroxine orally, as pills. Only thyroxine and the steroid hormones (as in contraceptive pills), can be taken orally because they are nonpolar and can pass through the plasma membranes of intestinal epithelial cells without being digested.
The thyroid gland also secretes calcitonin, a peptide hormone that plays a role in maintaining proper levels of calcium (Ca++) in the blood. When the blood Ca++ concentration rises too high, calcitonin stimulates the uptake of Ca++ into bones, thus lowering its level in the blood.
Thyroid Hormones

1. Thyroxin (T4) and triiodotyronine T3

Biochemistry of Thyroid Hormones

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

- **thyroxine** (T₄ or L-3,5,3',5'-tetraiodothyronine)
- **triiodothyronine** (T₃ or L-3,5,3'-triiodothyronine).

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".

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. Another carrier is albumin.
Quick quiz: The characteristic features of active form of thyroid hormone are all except:
1. T3 is 4 times active than T4
2. T4 acts as a pro-hormone to T3
3. 80% of T3 is converted in circulation to T4
4. T3 is 10 times active at binding of receptors

Synthesis and Secretion of Thyroid Hormones
The entire synthetic process occurs in three major steps:
- Production and accumulation of the raw materials
- Fabrication or synthesis of the hormones on a backbone or scaffold of precursor
- Release of the free hormones from the scaffold and secretion into blood

Raw materials:
- Tyrosines are provided from a large glycoprotein scaffold called thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T<sub>4</sub> and T<sub>3</sub>.
- Iodine, or more accurately iodide (I<sup>-</sup>), is taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane an "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.
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.

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. 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.

Quick quiz: Which of the following statement is true regarding thyroid peroxidase?
1. Free tyrosine in thyroid gland
2. It iodinates tyrosine residues in thyroxin binding globulin
3. It iodinates tyrosine residues in thyroxin binding prealbumin;
4. It iodinates tyrosine residues in thyroglobulin

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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. When TSH levels are low, rates of thyroid hormone synthesis and release diminish.

The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback.

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.

Metabolic Effects of Thyroid Hormones

Thyroid hormones have profound effects on many physiologic processes, such as development, growth and metabolism. They 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. 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 indication 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.

**Other Effects**: A few additional, effects of thyroid hormones include:

- **On muscle**: T3 increases glucose uptake by muscle cells it also stimulate protein synthesis and therefore growth of muscle through its stimulatory actions on gene expression. Thyroid hormone sensitizes the muscle cell to the glycogenolytic actions of epinephrine. Glycolysis in muscle is increased by this action of T₃.

- **On the pancreas**: thyroid hormone increases the sensitivity of the β cells of the pancreas to those stimuli that normally promote insulin release and is required for optimal insulin secretion

- **On 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.

- **On 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.

- **On 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

1. Hypothyroidism: a deficiency in thyroid hormone secretion and action
   a. Primary: the synthesis of T4 and T3 is impaired due to one or more of the following:
      i. Loss of functional tissue
      ii. Infiltrative disease of the thyroid
      iii. Defects in the thyroid hormone synthesis
      iv. Idiopathic (TSH receptor defect)
      v. Thyroditis with auto-antibodies
   b. Secondary: (central) occurs as a result of pituitary or hypothalamic disease that produce a deficiency in TSH, TRH or both.

2. Hyperthyroidism (thyrotoxicosis): a hyper-metabolic condition caused by excessive production of thyroid hormones. Causes are divided into:
   a. Those that are associated with clinically evident hyperthyroidism and increased production and secretion of thyroid hormones from the gland:
      i. Graves's disease: development of IgG antibody against the thyroid TSH receptor resulting in overproduction of T4 and T3.
      ii. Autonomous production by thyroid nodules
      iii. A toxic solitary edema
      iv. Excessive TSH secretion (rare)
   b. Those that are not:
      i. Exogenous intake
      ii. Iodine ingestion in excess
      iii. Thyroid carcinoma
      iv. Drug induced thyrotoxicosis with iodine containing medication
**Quick quiz:** A patient has an elevated serum T3 and free T4 and a very low serum TSH. What is the most likely cause of these results?

1. primary hyperthyroidism  
2. secondary hyperthyroidism  
3. euthyroid with increased throxine-binding proteins  
4. euthyroid sick syndrome

**Euthyroid sick syndrome:** condition of abnormal thyroid hormone and TSH concentrations in the severely ill opposing normal thyroid function. Often stimulates hypothyroidism in euthyroid patients that suffer another illness, such as, DM of liver cirrhosis.

Conclusions:
1. The thyroid gland is shaped like a shield and secretes hormones that help set the body’s basal metabolic rate.
2. The thyroid gland secretes Thyroxin (T4) and triiodothyronine T3 which stimulate oxidative respiration and calcitonin which stimulates the uptake of Ca++ into bones.
3. Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine.
4. The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback.
5. Thyroid Disease States might be hyper or hypo, and might be primary or secondary autoimmune or other.
Clinical Correlations
A 48-year-old woman was admitted to the hospital because of weight loss, palpitation, weakness, and exophthalmos. She stated that a goiter, which had been present for years, had recently begun to enlarge. She was extremely irritable, could not tolerate heat and was short of breath. Physical examination revealed bilateral eyelid lag. The thyroid gland was diffusely enlarged, and a bruit was audible over the right lobe. Her heart was enlarged, a prominent apical thrust was noted, and there was a soft systolic heart murmur along the left sternal border. Laboratory examination revealed that the hemoglobin was 1.8 mmol/L and that the hematocrit was 38%. The basal metabolic rate was 145% of normal. Plasma T4 and T3 were grossly elevated, and the $^{131}$I uptake by the thyroid gland was very high (18% in 4 hr). A diagnosis of hyperthyroidism was made.

Biochemical questions:
1. What are T3 and T4, and how are they related to the thyroid gland?
2. How are TRH and TSH involved in the regulation of thyroid hormone production and secretion?
3. What is the mechanism of increased $^{131}$I uptake in hyperthyroidism?

T3 and T4, are the thyroid hormones, triiodothyronine and thyroxine, respectively. Both are tyrosine derivatives. Although lesser amounts of T3 are released by the thyroid gland, it has a more potent effect than T4 in producing the hyper metabolic effects of the thyroid hormones. T4 is converted to T3 in the target cells, and it is likely that T3, actually is the metabolically active form of the thyroid hormone. In this sense, T4 may be considered as a prohormone.

TSH is released from the anterior pituitary and stimulates T3 and T4 production and release. In turn, TSH release is stimulated by TRH, which is made in the hypothalamus. When the plasma T3 and T4 concentrations are elevated, TRH production and release are inhibited. This leads to decreased T3 and T4 release from the thyroid gland.

T3 and T4 contain iodine atoms attached to their phenolic rings. Thyroglobulin, the protein precursor of these hormones that is contained in the thyroid cells, has many iodinated tyrosine residues. The iodine is obtained from iodide ions in the blood plasma, and the thyroid-cells have the capacity to take up and concentrate iodide ions.
In hyperthyroidism the thyroid gland is more active than normal. It synthesizes more thyroglobulin, T3, and T4 and takes up much larger amounts of iodine than in the euthyroid (normal) state. Therefore, when $^{131}$I is administered to a hyperthyroid patient, a larger fraction of the dose is concentrated within the thyroid gland than in a euthyroid subject. This is useful clinically in two ways.

1. Small quantities of $^{131}$I can be administered as a diagnostic test of thyroid function. After administration, the radiation emanating from the thyroid gland can be measured at various times by placing a scanning device over the neck. Greater than normal uptakes occur in hyperthyroidism, and less than normal uptakes occur if the thyroid gland is hypo functioning (hypothyroidism).

2. The enhanced iodine uptake can be used to treat hyperthyroidism. If larger amounts of $^{131}$I are administered, enough $^{131}$I will concentrate in the thyroid to provide intense but localized radiation to the glandular cells. This will destroy many of the T3- and T4-producing cells, reducing the excessive function of the thyroid and correcting the hyperthyroidism.

As compared with the thyroid, other tissues take up very little iodine. Consequently, most of the $^{131}$I that is not taken up by the thyroid is rapidly excreted in the urine, and there is comparatively little radiation exposure in other tissues. In some respects this is a safer form of treatment than surgical removal of a large portion of the hyperactive gland. It is not without some danger, however, for $^{131}$I treatment can lead in some cases to either hypothyroidism or even thyroid cancer.