Thyroxine (T₄): An Overview

The most common symptoms include: Skin dryness, hair loss, hand tremors, increased heat rate, changes in weight, anxiety, fatigue, and weakness (“T3” Lab Tests Online”). If you experience some or all of these symptoms, consult your doctor right away as you may have a thyroid disorder.

Background/About the Molecule: The thyroid gland is located in the anterior region of a neck and contains a large network of blood vessels. It consists of two lobes and extends from the region of the 5th cervical to the 1st thoracic vertebrae. The lobes are composed of follicles which are the structural unit of the thyroid gland (“Disease of the Thyroid”). The thyroid gland is environmentally modulated by the availability of iodine, primarily obtained from our diet (in foods such as bread, salt, and seafood) to produce thyroid hormones. Thyroid hormones are amino acid derivatives made up of a group of chemically similar substances with a unique iodine-amino acid structure. Triiodothyronine (T₃) and Thyroxine (T₄) are the hormones produced by the thyroid gland whose functions include regulating metabolism, growth, differentiation, and reproduction (Norris and Carr, Pg 207). Of the two hormones, T₄ is the primary hormone produced by the thyroid gland (“About Your Medicine: Thyroxine”) with a molecular formula C₁₅H₁₁I₄NO₄ and a molecular weight of 776.87. The primary function of T₄ is to stimulate the consumption of oxygen and in turn the metabolism of all cells and tissues in the body (“Thyroxine”). All vertebrates and even some invertebrates, like sea squirts, make thyroid hormones even though they lack a thyroid gland. These hormones are important as the direct seasonal changes such as fur molting in mammals or skin shedding by reptiles. They also initiate hair growth in rodents, sheep, and other mammals and amphibian metamorphosis that transforms tadpoles into frogs (“The Hormones: Thyroid”).

Synthesis (Figure 2): Thyroid Stimulating Hormone, produced by the pituitary gland, binds to G-protein-coupled receptors (GPCRs) present on the membranes of the follicular cells and stimulates cAMP initiating the formation if T₃ and T₄ (“THRβ Thyroid Hormone Receptor, Beta (Homo Sapiens)”). Thyroxine (T₄) is synthesized in the follicular cells of the thyroid gland by the iodonation (addition of iodine) of tyrosine which is found attached, by peptide bonds, to Thyroglobulin (T_gb) (Figure 6). T_gb, a large globular protein found in the lumen of the thyroid
follicles, acts as a substrate for the synthesis of $T_4$ and $T_3$, as well as the inactive forms of thyroid hormone and iodine. The ratio of $T_4$ to $T_3$ produced in the thyroid is 4:1. **Tyrosine** is initially incorporated into the $T_{gb}$ and then **iodinated with** the help of the enzyme thyroid peroxidase (TPO) to form moniodotyrosine (MIT) and diiodotyrosine (DIT). The inactive iodide that is collected in the thyroid via active transport from the blood, is converted to “active iodide” by TPO and is then able to attach to tyrosine. Two DIT form $T_4$; one DIT and one MIT form a slight amount of $T_3$ (Miot, 2012). Thyroxine is released from $T_{gb}$ containing $T_4$ molecules via hydrolysis and enters the blood. $T_4$ is the primary form of circulating thyroid hormone in the blood and is converted to $T_3$ in the periphery by **a type 1 deiodinase (D1) enzyme in the liver or the target cells**. The bulk of the circulating $T_3$ if formed in the liver by the deiodination of $T_4$ but a small portion is formed in the thyroid gland itself by a thyroid D1 deiodinase before the $T_4$ is released into the blood. Thyroid hormones are poorly soluble in blood plasma as they are hydrophobic at normal blood pH (Norris and Carr, Pg 80-81). Maternal thyroid hormone is transferred to the fetus early in pregnancy and is postulated to regulate brain development (“Thyroid Hormone Receptor, Beta; THRBB”).

**Transport:** As thyroid hormones are not easily soluble in blood, they **bind to plasma proteins** in order **to facilitate transport** and reduce elimination as waste from the kidneys. There are several different protein chaperones that bind and transport these thyroid hormones. In **humans**, **75%** of the **bound hormones are linked to** the $\alpha_2$-globulins called **Thyroid-binding globulin (TBG)**, and the remaining is bound to **prealbumin/transthyretin (TTR)** - **15%** and **albumin (TBA)** - **10%** (Norris and Carr, Pg 82). **TBG** is **synthesized in the liver** as a single polypeptide chain of 415 amino acids and keeps the thyroid hormones in constant circulation in the blood for immediate use when required. The protein is very stable when stored in serum, but rapidly loses its hormone binding properties by denaturation at temperatures above 55°C and pH below 4 (Miot, 2012). The transporter for $T_4$ is much more energy dependent than the transporter for $T_3$ in the case of transporting these hormones to peripheral target cells. The pituitary hormone transporters, however, are different from those throughout the body, are not energy dependent, and will take up $T_4$ and $T_3$ at low energy states. An increase in TBG may result in an increase in total T4 and T3 without an increase in hormone activity in the body (Liess, 2014).
**Signal Transduction → Target Cells → Receptor** (Figure 3): Thyroid hormones enter target cells and the liver by active transport and migrate to the nucleus where they bind to specific nuclear receptor proteins. In the target cells, enzymes remove one of thyroxine's four iodine atoms converting the hormone into the highly active triiodothyronine. Thyroid hormone receptors (TRs) are nuclear receptors that mediate gene regulation by thyroid hormone (“Thyroid Hormone Receptor, Beta; THRβ”). “These receptors are identified by specific gene sequences, similar to steroids” (Norris and Carr, Pg 82). They act by regulating gene expression. There are two major isoforms of mammalian thyroid hormone receptors coded by two genes, Thyroid Hormone Receptor Alpha (THRA) and Thyroid Hormone Receptor Beta (THRβ) (“THRβ Thyroid Hormone Receptor, Beta (Homo Sapiens)”). These hormone receptor monomer unit binds to a binding partner called the Retinoid X Receptor (RXR), to form a heterodimer which provides maximal stimulation of transcription. These receptors develop special loops from the deposition of Zn$^{2+}$ residues, forming zinc fingers which interact with DNA and allow the transcription of mRNA. The zinc fingers of the receptor bind specifically to short, repeated sequences of target DNA called thyroid or T$_3$ response elements (TREs), a type of hormone response element that occurs only on certain genes (Bowen 2000; Norris and Carr, Pg 74-76). The region where the zinc fingers bind to the DNA is known as the DNA binding region. When the thyroid hormone binds to this receptor protein, chemical processes are activated and protein producing genes that control the energy and metabolic processes of the cell are formed (“The Hormones: Thyroid”).

**Regulation of Hormone** (Figure 4): The thyroid, and the production of its hormones are regulated by the interaction between two other glands in the body, namely, the pituitary gland and the hypothalamus located at the base of the brain. The amount of thyroxine that is released is regulated by a Hypothalamus- Pituitary feedback loop. The hypothalamus releases a hormone called Thyrotropin Releasing Hormone (TRH) which in turn sends a signal to the pituitary, through the hypophyseal portal system, to stimulate the production of Thyroid Stimulating Hormone (TSH) from the anterior lobe of the gland (Figure 5). The TSH in turn signals the production of thyroid hormones in the thyroid gland (inkling.com).
If there isn’t a sufficient amount of thyroid hormone circulating through the body at any given point of time, the rate of release for TRH by the hypothalamus, and in turn the release of TSH by the pituitary, is increased to stimulate thyroid hormone production. This process also works as a negative feedback system when there are excessive amounts of thyroid hormone in the blood, suppressing or lowering its production. A person with continuously decreased levels of circulating thyroid hormone is said to have **Hypothyroidism** and a person with increased thyroid hormone levels has **Hyperthyroidism** (Mather).

**Conditions Associated with Thyroid Hormone Levels** (Figure 1):

**Hypothyroidism**- This is when there are decreased levels of thyroid hormones circulating in blood and is also known as an underactive or inactive thyroid. Congenital hypothyroidism is caused by lack of or abnormal development of the thyroid gland in utero. The major cause for this acquired condition is due to chronic autoimmune thyroiditis (inflammation of the gland). Some other secondary causes can be due to treatment for hyperthyroidism, removal of thyroid gland, and some radiation treatments for certain cancers. There are two types of non-infectious types of thyroiditis:

1) **Hashimoto’s Disease** – An autoimmune disorder who’s onset is initiated by gradual enlargement of the gland and increased thyroxin production. In patients with this disease the immune system mistakenly attacks the thyroid by creating antibodies against several components of the thyroid tissue itself. Among these antibodies are those against the enzyme thyroid peroxidase and thyroglobulin. This attack damages the thyroid so that it does not make enough hormones and decreases the levels in the body.

2) **Central Congenital Hypothyroidism (CCH)** - Caused by a deficiency in thyrotropin (also known as TSH).

The symptoms can vary from person to person. They may include joint and muscle pain, dry skin, dry thinning hair, constipation, puffy face, decrease in sweating, slowed heart rate, fatigue, depression, weight gain, constipation, intolerance to cold, heavy or irregular menstrual periods, and fertility problems (Mather).
**Hyperthyroidism** – A disorder caused due to the excess secretion of thyroid hormone levels in the body. It is often also known as Thyrotoxicosis and is more common in women, people with other thyroid problems, and older people over 60 years of age. There are several disorders that give rise to this condition:

1. **Simple Goiter** – Is displayed when there is a non-cancerous enlargement of the thyroid gland. This can occur without a known reason. It can occur when the thyroid gland is not able to make enough thyroid hormone to meet the body's needs.

2. **Graves Disease/ Exophthalmic Goiter** – This is an autoimmune disease where there is over activity of the thyroid gland, which in turn causes excessive thyroid hormone secretion. There is also diffused enlargement of the gland over time.

3. **Plummers Disease/ Toxic Multinodular Goiter** – It involves an enlarged thyroid gland that contains rounded growths called nodules. These nodules produce too much thyroid hormone and develop from a preexisting simple goiter.

4. **Inflammation of Thyroid Gland** - Could be a response triggered by some damage done to living tissues.

In this case too, different people experience a wide variety of symptoms, including but not limited to: Mood swings, hand tremors, weight loss, diarrhea, Goiter can cause the neck to look swollen, fatigue or muscle weakness, heat intolerance, and being nervous or irritable (Mather).

**Similarities to other Hormones Studied in Class:**

1. It is made up of amino acid derivatives, similar to Serotonin.
2. Thyroid hormones are lipophilic (lipid soluble) and steroid hormones such as Testosterone, and Corticosteroid.
3. Thyroxine stimulates metamorphosis in amphibians and Ecdysone stimulates metamorphosis and molting in invertebrates.
4. In some frog species, additional cortisol will be produced in response to an external environmental stressor which will stimulate quick metamorphosis and conversion of T<sub>4</sub> to T<sub>3</sub>. 
5. Produced in the Thyroid gland like Calcitonin. Calcitonin is found in the parafollicular cells of the Thyroid. **Parafollicular cells** may be found as single cells in the epithelial lining of the follicular cells of the thyroid, or in groups in the connective tissue between follicles.

6. Regulated by the Hypothalamus – Pituitary Axis via +ve and –ve feedback loops like FSH and Oxytocin.

7. Binds to a nuclear receptor in the target cell like PPAR, Estrogen, Corticosteroid, and Ecdysone.

8. The hormone receptors are Heterodimers similar to hormones like T₃, PPAR, and Ecdysone.
Figures

Figure 1:

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<thead>
<tr>
<th>TSH</th>
<th>T4</th>
<th>T3</th>
<th>INTERPRETATION</th>
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<td>Non-thyroidal illness; rare pituitary (secondary) hypothyroidism</td>
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(“T3”Lab Tests Online”)

Figure 2:

![Diagram of thyroid hormones]

Figure 3:

![Diagram of thyroid hormone metabolism]
Figure 4:

![Hypothalamus and Pituitary Regulation](image)

Figure 5:

![Anterior and Posterior Pituitary](image)

Figure 6:

![Thyroid Peroxidase Reaction](image)
Works Cited


