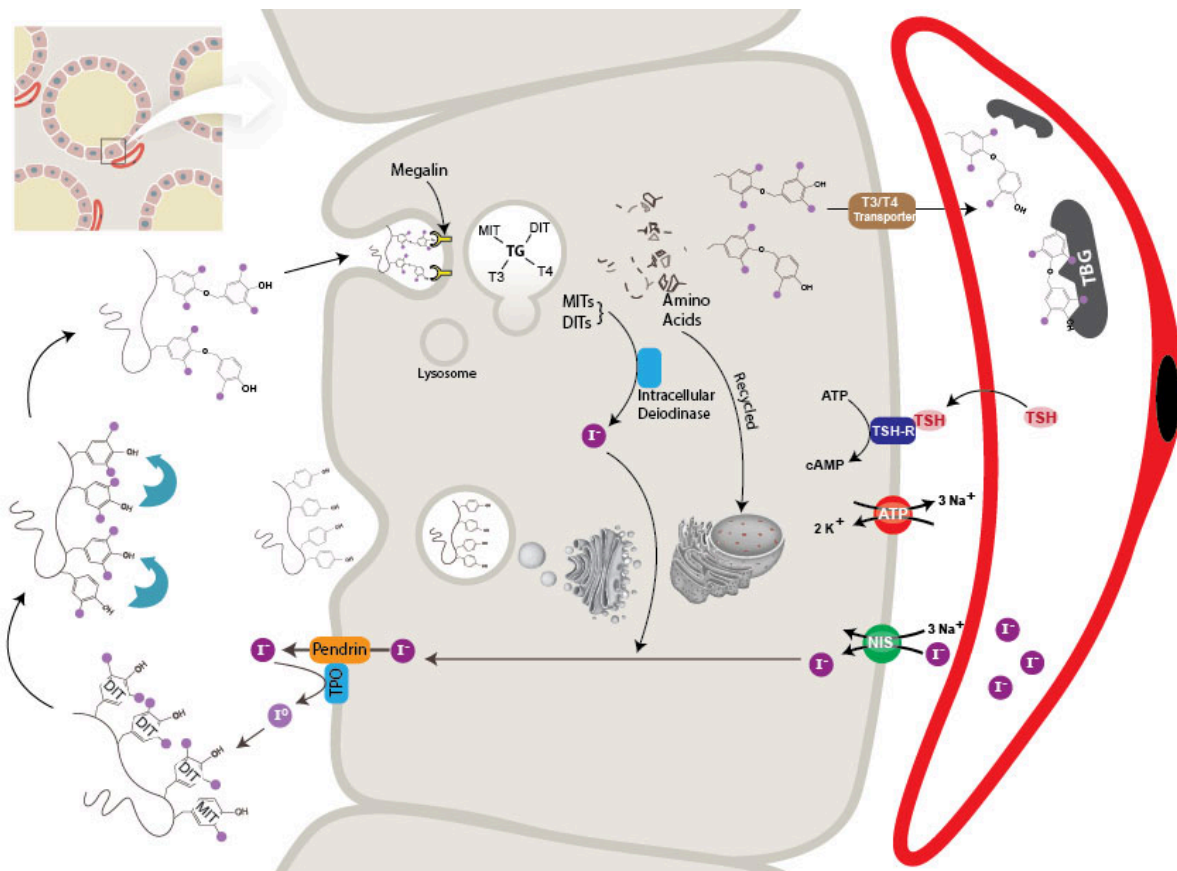


5.5.6

Thyroid Hormones

Ever notice how some people can eat all they want and never gain weight while others eat a peanut and gain a pound. This all has to do with our metabolism and how our bodies burn the calories we eat. The thyroid gland has the primary role of regulating our metabolism through the hormones it secretes. The person who eats and never gains weight, is said to have a high metabolism. What this really means is that a larger portion of the calories that he/she is burning is used to produce heat, making him/her less efficient in handling nutrients. He/she will have an easier time maintaining a lower weight, but in times of famine he/she will need more food to survive (I suppose there is justice in this world!)

The thyroid gland is located in the neck. It is composed of two lobes on either side of the trachea just below the larynx. The two lobes are connected by a small band of tissue called the isthmus. Histologically, the thyroid is composed of millions of small, spherical follicles, think of tiny tennis balls. The walls of the follicles are composed of simple cuboidal epithelium, **follicular cells**, and the lumens serve as reservoirs for the materials used to produce thyroid hormones. These follicular cells are responsible for the production and secretion of the thyroid hormones. Scattered between the spaces of the follicles are the **parafollicular cells** which secrete the hormone **calcitonin**. Calcitonin acts to reduce blood Ca^{2+} levels. Embedded on the posterior side of the gland are the four small **parathyroid glands**. These glands secrete **parathyroid hormone** whose function is to increase blood Ca^{2+} concentrations.



Thyroid Hormone Synthesis.

Image done by BYU-Idaho Spring 2015

The thyroid follicles produce two hormones, **Thyroxine** or **T₄** and **Triiodothyronine** or **T₃**. They are synthesized from **tyrosine**, an amino acid, and iodine. The designations T₄ and T₃ refer to the number of iodine atoms on the hormone. The synthesis of thyroid hormones by the follicular cells occurs as follows:

1. The protein **thyroglobulin** (TBG) is synthesized in the rough endoplasmic reticulum of the follicular cells and then secreted into the follicular lumen (the colloid space) by exocytosis.
2. At the basal surface of the follicular cell (side opposite the lumen) a sodium-iodine symport pump actively brings iodide (I⁻) into the cell using Na⁺ to move the iodide against its concentration gradient.
3. The iodide moves through the cell and is transported into the colloid space by another transporter called pendrin.
4. As the iodide moves into the lumen of the follicle, it is oxidized to iodine (I⁰) by the enzyme thyroid peroxidase (TPO). In the oxidized state, iodine is very reactive and interacts with tyrosine amino acids located on the thyroglobulin molecule forming an iodinated tyrosine.
5. If one iodine is added to a tyrosine the resultant is **moniodotyrosine** (MIT). If two iodine are added to one tyrosine the result is **diiodotyrosine** (DIT). Tyrosine molecules that are adjacent to each other can combine (conjugation) to create the thyroid hormones. For example, one MIT and one DIT combine to form T₃ whereas two DITs form T₄. The newly synthesized hormones remain attached to the thyroglobulin molecule within the colloidal space in a ratio of 9:1 (T₄:T₃).
6. Thyroid Stimulating Hormone (TSH), a water-soluble hormone, is released from the anterior pituitary gland and binds to the TSH receptors on the thyroid. In response to the binding of thyroid stimulating hormone to its receptor on the follicular cell, the entire thyroglobulin complex is brought back into the cell via endocytosis.

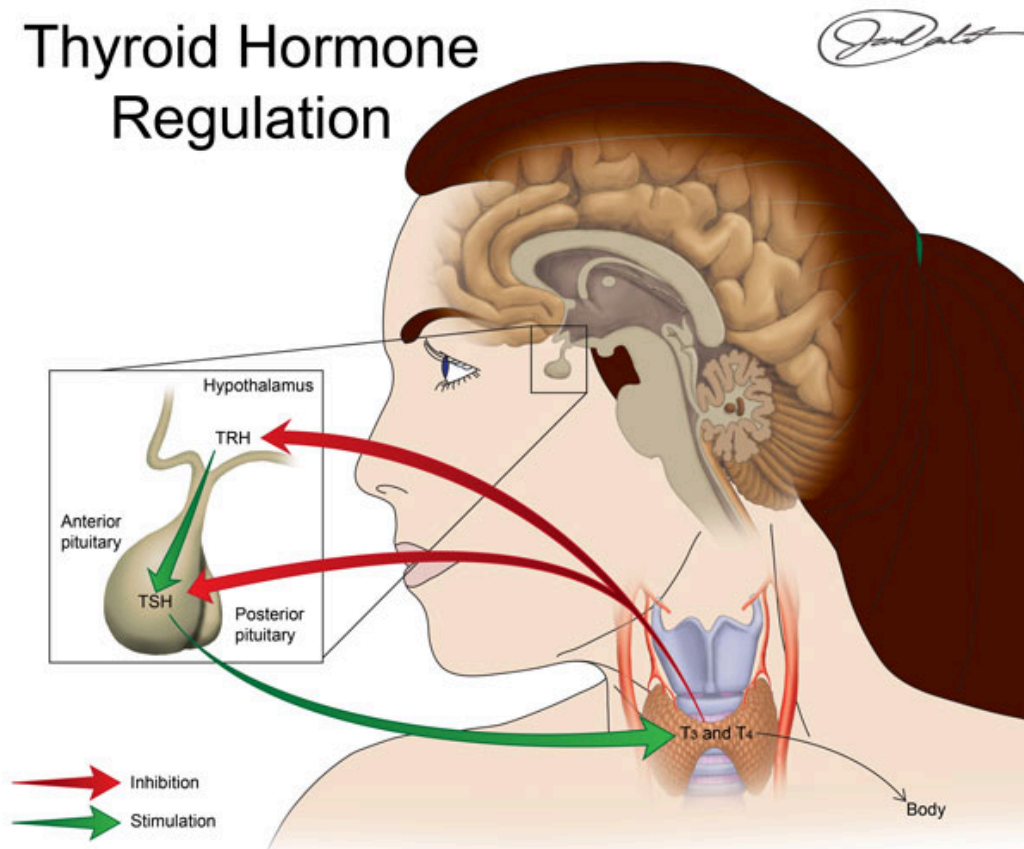
7. Once inside the cell, the newly formed vesicle is fused with a lysosome which cleaves the thyroglobulin protein, liberating the T_3 and T_4
8. The T_3 and T_4 molecules are then transported out of the cell and into the blood via plasma protein carriers and are immediately bound to thyroid binding proteins, mostly thyroxine binding globulin. However, albumin may also be used. Indeed 99.98% of T_4 and 99.5% of T_3 are bound to carrier proteins in the blood.

Ninety percent the thyroid hormones are in the form of T_4 , which is the less active form. In the target tissues T_4 can be converted to the more active form, T_3 , by the enzyme **deiodinase**. This enzyme removes an iodine from T_4 , producing T_3 . The impact of this mechanism is twofold. First, the bound hormones act as a reservoir for the thyroid hormones greatly increasing their half-lives (days). Indeed, thyroid hormone concentrations in the blood remain relatively constant and fluctuate little. Second, it provides another level of control. By increasing deiodinase activity, the action of thyroid hormones can be increased without the necessity of increased production and release. Once in the cell, thyroid hormones interact with nuclear receptors that induce the expression of proteins directly involved in metabolism and oxygen utilization. In short, thyroid hormones increase the metabolic activity of tissue throughout the body.

Clinical Pearl - Deiodinase

There are actually three forms of deiodinase, D1, D2, and D3. Both the D1 and D2 enzymes convert the inactive T_4 hormone to the active T_3 hormone, but the D3 enzyme converts T_4 to reverse T_3 (rT3). This rT3 will bind to the T_3 receptor but not activate it, so in essence it behaves like an antagonist to the T_3 receptor reducing the effects of T_3 . However, the rT3 will still act in a negative feedback function so that measuring TSH will not show any abnormality but the individual will still be experiencing symptoms of hypothyroidism. It has been suggested that the D3 enzyme is upregulated in diabetes type II and in metabolic syndrome (ie., obesity). This could explain why it is so difficult to lose excess weight. Thus, only measuring TSH for a thyroid panel is grossly inadequate, instead, blood tests should be run on TSH, T_3 , T_4 , and rT3.

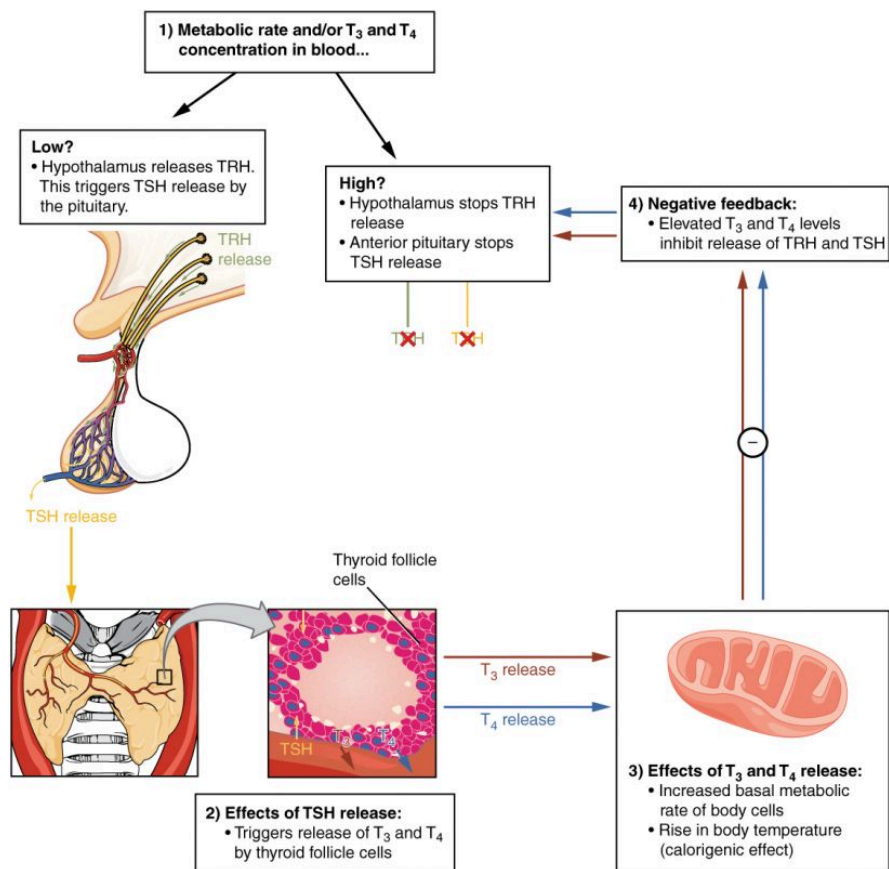
Thyroid Hormone Regulation



Regulation of Thyroid Hormone Secretion: Image by BYU-Idaho Winter 2015

Image by BYU-Idaho Jared C. Winter 2015

Regulation of thyroid hormone secretion begins at the hypothalamus (see the image above). Recall that the hypothalamus secretes the hormone **thyrotropin-releasing hormone** (TRH) into the hypothalamo hypophyseal portal system. TRH stimulates cells in the anterior pituitary to secrete the hormone **thyroid-stimulating hormone** (TSH). TSH then stimulates the thyroid gland to secrete thyroid hormones, Thyroxine (T₄) and T₃. Proper levels of thyroid hormones in the blood are regulated by a classic negative feedback system. If thyroxine and T₃ levels are high, they feed back on the hypothalamus and the pituitary to decrease TSH release. At the level of the hypothalamus, the thyroid hormones inhibit TRH production. In the anterior pituitary, they reduce the number of TRH receptors and inhibit TSH synthesis. The overall effect is to reduce TSH levels, which in turn lowers thyroid hormone synthesis and release. If thyroid hormone levels are low the inhibition is removed and more TSH is secreted to stimulate production and release of more thyroid hormones. Since the thyroid hormones have long half-lives, their concentrations in the blood remain relatively constant and do not tend to fluctuate.



Negative Feedback Loop regulating Thyroid Hormone Levels

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Another level of control of thyroid hormone activity occurs at the level of the target tissues. T_3 is much more biologically active than thyroxine. At the target tissue thyroxine can be deiodinated (one of the iodine is removed) to produce T_3 . By increasing or decreasing the activity of deiodinase thyroid hormone activity can be modulated.

Another factor that can impact thyroid hormone secretion is caloric intake. If caloric intake is greatly elevated (particularly increased carbohydrate consumption), T_3 levels go up and metabolism is increased. On the other hand, if caloric intake is drastically reduced as would happen during starvation or a strict diet, T_3 levels decrease and metabolism goes down. These mechanisms are thought to be regulated at the level of the target tissues rather than in the thyroid gland, hence they are mediated by changes in the activity of the deiodinase enzyme.

Thyroid Hormone Actions

Thyroid hormones act on virtually every cell of the body. They easily cross the plasma membrane and bind to nuclear receptors where they stimulate transcription of various genes (especially genes involved in cell metabolism), resulting in the production of new proteins. The end result is that the thyroid hormones have a major role in regulating metabolism. In terms of metabolism they play a key role in the metabolism of carbohydrates, lipids and proteins, the overall effect is to increase oxygen utilization. In addition, thyroid hormones are essential for normal growth and development. During development, thyroid hormones are essential for normal growth of long bones, hair and nervous tissue. Indeed, lack of thyroid hormones during early development results in short stature and mental retardation, a condition known as Cretinism. Perhaps the best way to gain an appreciation for the actions of thyroid hormones is to see what happens when they are in excess or when they are lacking. The next section will address common thyroid disorders.

Thyroid Disorders

Next to diabetes, thyroid disorders are the most common endocrine problems. Most thyroid disorders fall into one of two categories, hyperthyroidism (increased thyroid activity) or hypothyroidism (decrease thyroid activity).

Hyperthyroidism

Hyperthyroidism is the result of overproduction of thyroid hormones. Listed below are possible problems associated with excess thyroid hormone levels. As you examine the list try to relate the problems with the normal actions of the hormones.

1. Increased oxygen consumption (increased metabolic rate)
2. Sweating, warm flushed skin
3. Increased heart rate and increased blood pressure
4. Heat intolerance
5. Increased appetite and weight loss
6. Insomnia
7. Increased nervous system activity, hyper-excitability, irritability, insomnia
8. Increased muscle protein catabolism resulting in muscle weakness and weight loss.

One common form of hyperthyroidism is **Graves' disease**. This condition is caused by antibodies called **thyroid-stimulating immunoglobulins** (TSI). For unknown reasons, the body produces TSIs which then circulate in the blood and bind to the TSH receptor on the follicular cells of the thyroid. The TSIs are agonists and therefore induce thyroid hormone release and enlargement of the gland (**goiter**). The TSIs are not subject to the same negative feedback mechanisms as TSH and as a result constantly stimulate the gland. Some Graves' disease sufferers exhibit a condition known as **exophthalmos**. This is an immune-mediated infiltration of the tissues behind the eye, including the extrinsic eye muscles, resulting in double vision as well as protrusion of the eyeballs from the sockets.

Treatments for hyperthyroidism include the use of beta blockers to decrease heart rate, **propylthiouracil** (inactivates thyroid peroxidase) to reduce the production of thyroid hormones, radioactive iodine to destroy some of the thyroid cells and thus reduce the amount of hormones produced, and surgical removal of the thyroid gland (followed by hormone replacement therapy).

Hypothyroidism

Hypothyroidism results from the underproduction of thyroid hormones. The reduction in thyroid hormones has almost the reverse effects of hyperthyroidism.

1. Decreased oxygen consumption (decreased metabolic rate)
2. Decreased heart rate and decreased blood pressure
3. Decreased sweating, cold skin
4. Intolerance to cold
5. Decreased appetite and weight gain
6. Apathy, sleepiness
7. Decreased protein synthesis causing brittle hair and nails, and dry skin.
8. Accumulation of mucoproteins in subcutaneous skin resulting puffy appearance (**myxedema**).
9. Reduced nervous system activity resulting in fatigue and slower processing.

In underdeveloped countries, the most common cause of hypothyroidism is a lack of iodine in the diet. Without iodine, thyroid hormone production is incomplete which results in a lack of negative feedback. Thus, TRH and TSH levels increase causing the gland to increase activity, which results in a goiter. In the United States, the most common cause of hypothyroidism is an autoimmune destruction of the thyroid gland (**Hashimoto's disease**). Approximately 1-2% of all

adults in the U.S. will suffer from hypothyroidism at some time in their lives, with women being at a higher risk than men. The treatment for hypothyroidism is administration of Synthroid, a synthetic form of thyroxine.



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