9.3.1

Thyroid Hormone Synthesis

The thyroid follicles produce two hormones, **Thyroxine** or **T_4** and **Triiodothyronine** or **T_3**. They are synthesized from **tyrosine,** an amino acid, and iodine. The designations T_4 and T_3 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** (TG) 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 (I^0) 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 **monoidotyrosine (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 T_3 whereas two DITs form T_4. The newly synthesized hormones remain attached to the thyroglobulin molecule within the colloidal space in a ratio of 9:1 (T_4:T_3).
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 molecules.
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 (TBG). 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 of the thyroid hormones are in the form of T_4, which is the less active form. In the target tissues T_4 can 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.