15. THYROID FUNCTION

The thyroid gland consists of two lobes joined by the isthmus and is found over the trachea (Fig. 15-1).

Further, imbedded in the glandular tissue of the thyroid gland is the location of the parathyroid glands (two or four depending on the species), which are responsible for the production of the parathyroid hormone, another regulator of calcium metabolism (Fig. 15-1).

The thyroid gland, therefore, plays an important role in the regulation of the metabolic activity of the body. It is also an important component in the thermoregulatory capacity of the animal and in the regulation of calcium metabolism.

SYNTHESIS OF THYROID HORMONES

The follicles of the thyroid cycle between a colloid synthesis (Figs. 15-3, 15-4) and a colloid degradation mode. The colloid synthesis mode consists of the production of thyroglobulin, the protein containing the TH, by all the cells surrounding that follicle.

The thyroglobulin is continuously emptied into the center of the follicle where it forms the colloid. This mode continues until the follicle becomes distended and filled with colloid. Once a follicle is filled the cells surrounding that follicle produce and exteriorize receptors for the Thyroid Stimulation Hormone (TSH) a glycoprotein hormone consisting of two subunits (Fig. 15-5). When TSH attaches to these receptors it changes the pattern of activities of all the cells in the follicle to the secretory mode (Figs. 15-6, 

The secretory components of the gland are made of quasispherical structures called follicles, which are surrounded by secretory cells. The lumen of the follicles fills with a thick substance called colloid, made out of large proteins containing thyroid hormones. The colloid serves as a reservoir for Thyroid hormones (TH). Within the follicles of the thyroid gland other endocrine cells, called the parafollicular cells or C are located. These are responsible for the production of Calcitonin, a hormone involved in the regulation of calcium metabolism (Fig. 15-2).
Each cell in the follicle starts internalizing, through pinocytosis, small volumes of colloid from the lumen, then digesting the protein and releasing thyroid hormones, through the basal wall of the cells towards circulation.

The amino acids are reused within the cells to form new thyroglobulin when the mode reverts to the synthesis of the colloid. To maintain order in this process all cells in a follicle are synchronized with each other. The follicles, however, are not synchronized thus ensuring the possibility of a continuous supply of thyroid hormone, if required. In a normal animal the reservoir of the thyroid hormone can supply normal needs for up to 2 months. This explains why a deficiency is manifested very slowly.

**Follicular cells**  
**synthesis mode**
- Concentrates iodine from circulation
- Uses active transport system
- Can reach 25-200 times higher than circulation
- Assemble thyroglobulin
- Attaches iodine to tyrosine molecules in thyroglobulin to form:
  - Monoiodotyrosine (MIT)
  - Diiodotyrosine (DIT)
- Iodinated tyrosine moieties combine to form:
  - Tetraiodothyronine (T₄)
  - Triiodothyronine (T₃)
- Or stay as MIT or DIT
- All part of the thyroglobulin stored in the colloid

**Follicular cells**  
**secretion mode**
- Upon stimulation by TSH
- Incorporates thyroglobulin in cell
- Mixes with lysosomes
- Digests protein
- Secretes TH
- Deiodinates MIT and DIT
- Recycles aa and iodine

In the process of synthesizing thyroglobulins, the follicular cells have to uptake and concentrate iodine from circulation. This is done through an active transport mechanism that is capable of pumping iodine against a gradient ranging from 25 times higher in normal animals to as much as 250 times higher in iodine deficient animals. The thyroglobulin is assembled in the ribosome using recycled and circulatory amino acids. A chain of
thyroglobulin has a weight of 335,000 daltons and contains within the chain about 70 molecules of tyrosine. The tyrosin amino acids of the protein are iodized with either one or two iodine molecules as the thyroglobulin molecule leaves the cells through the apical membrane, towards the lumen of the follicle. The enzyme iodinase is responsible for these reactions. The results are thyroglobulins containing MIT or MIT (Fig. 15-9).

As the molecule of thyroglobulin adopts its tertiary and quaternary structure, some of the DIT and MIT can combine to form Tetraiodothyronine (T₄) or Triiodothyronine (T₃). When a molecule of DIT attaches to another DIT they form T₄ while if a MIT molecule moves and attaches to a DIT the result is T₃ (Fig. 15-7). Some DIT and MIT remain in the thyroglobulin as such, without combining. Finally, if a DIT moves and attaches to a MIT residue, the product is reverse triiodothyronine, which is a biologically inactive molecule (Fig. 15-9).

To initiate the process of secretion TSH stimulates the follicular cells. This triggers an internal mechanism leading to the uptake of colloid from the lumen into small vacuoles. These vacuoles containing thyroglobulin move within the follicular cells and are combined with lysosomes to form phagolysosomes. The proteolytic enzymes in the phagolysosomes digest the molecules of thyroglobulin releasing molecules of T₃, T₄, and rT₃ (Fig. 15-10). The rest of the amino acids are either released into circulation or they are internally redirected for use in new protein synthesis within the follicular cells. The MIT and DIT residues are deiodinated and the iodine is recycled to be incorporated into new TH.

TRANSPORT OF THYROID HORMONES IN CIRCULATION

Once the thyroid hormones are released into circulation, they have to bind to carrier proteins in order to be transported (Fig. 15-11). In humans approximately 99.95% of T₄ and 99.5 of T₃ are bound and the rest circulate freely. The exact amount of free moving hormones depends on several physiological parameters. Most of these parameters result in a change in the concentration of carrier proteins, such as the effect of Es.

The main proteins carrying TH are: Thyroid Binding Globulin (TBG), which has a high affinity for T₄ and can also carry T₃. Although only about 25% of the circulating TBG is carrying thyroid hormones, TBG is responsible for transporting 75% of the total T₄ and 80% of all T₃.
Albumin, carry loosely attached about 12% of $T_4$, and 10% of the $T_3$. Thyroxin-binding prealumln (TBPA), also named transthyretin (TTH), transport 10% of $T_4$ and 5% of $T_3$ and, finally, lipoproteins that carry 3% of the $T_4$ and

**TH transport in circulation**

- Released to circulation
- Binds to carrier proteins
- Very small percentage moves free
  - Humans 0.05% of $T_4$ and 0.5 of $T_3$
  - Dogs 1.0% of $T_4$ and 1.0% of $T_3$
- Balance shifts with physiological changes
  - Es increases TBG synthesis

5% of the $T_3$ have an intermediate carrying capacity (Fig.15-12).

**TH carrier proteins**

- **Thyroxin-binding globulin**
  - High affinity but low capacity for $T_4$
  - Also transports $T_3$
- **Albumin**
  - Low affinity but intermediate capacity for $T_4$ and $T_3$
- **Thyroxine-binding prealbumin** (Transthyretin)
  - Specific for $T_4$
  - Intermediate capacity
- **Lipoproteins**
  - Low capacity

Although both TH are available in circulation, the only biologically active hormone is $T_3$. If a cell requires TH stimulation and a molecule of $T_4$ approaches it, then a deiodinase enzyme in the cell membrane converts it to $T_3$. If the cell does not require TH stimulation, then the deiodinase enzyme converts $T_4$ into $rT_3$, thus sparing the cell from the unnecessary stimulation. Thyroid hormones act through the stimulation of a nuclear receptor (Fig. 15-13). The molecule of $T_3$ freely crosses the plasma membrane and the cytoplasm to reach the nucleus.

There, the receptor-hormone complex activates a hormone response element in the DNA triggering a translation of specific proteins to cause the desired effect (Fig. 15-13).

**BIOLOGICAL EFFECTS**

Usually, the changes initiated by thyroid hormones are related to an increase in oxygen consumption (Fig. 15-14),

- **Biological effects**
  - Exerts through penetration of plasma and nuclear membrane
  - Binds to nuclear receptor
  - Activates hormone response element
  - Triggers protein translation
  - Causes effect
  - Increases oxygen consumption
  - Produces heat
  - “Calorigenic effect” within the mitochondrion

Catabolism of the hormones is delayed because proteins are carrying them. This provides for a relatively long half-life, which varies depending on the species.
which in turn translates into heat production. The chemical reaction associated with the calorigenic effects takes place within the mitochondrion of the cell.

Other effects of TH are part of the regulation of carbohydrate and lipid metabolism (Fig. 15-15). Thyroid hormones facilitate glucose absorption and its transfer into muscle and fat cells. It does this through facilitation of insulin mediated glucose uptake. When the circulatory concentration of TH is low, there is a predominant glyconeogenesis and, when the concentration increases it reverts to predominant glycogenolysis (Fig. 15-15).

**Further TH effects**

- Enhances sympathetic nervous system effects
  - Stimulation of B-adrenergic receptors
- Contributes to normal development of CNS
- In adults maintains alertness
  - Lethargy if hypothyroidism
- Increases heart rate and force of contraction
  - Elevates blood pressure
  - Increases cardiac output

**CATABOLISM OF THYROID HORMONES**

Most of the thyroid hormones are rendered biologically inactive by removing iodine from their structure with the help of deiodinases (Fig. 15-17). The best example is the conversion of T₄ into rT₃, if the cell does not require stimulation. To get rid of the thyronine, the liver conjugates the molecule with a glucoronide or sulphate molecule making it more water soluble, and possible to excrete through the kidney into the urine. Deiodination is usually the first step as a mechanism to conserve and recycle iodine. Deiodination takes place in the liver and the iodine is released into circulation where it then reaches the thyroid gland for further use.

**Catabolism of TH**

- Mainly through deiodination
  - *Deiodinase*
- In liver, muscle and kidney
- Conjugation in liver and kidney with glucoronides and sulphates
- Deiodination more common
- Permits recycling of iodine

Furthermore, TH enhances the effect caused by sympathetic nervous stimulation, such as that of the β-adrenergic receptors. During early development, it contributes to the normal development of the CNS to the extent that deficiencies at this time result in abnormalities such as cretinism. In adults, a normal circulatory concentration of TH maintains a basic degree of alertness, which translates in lethargy under hypothyroid conditions (Fig. 15-16). Thyroid hormones also support cardiac function by increasing heart rate and the force of contraction, which in turn translates to an elevation in blood pressure and an increase in cardiac output (Fig. 15-16).
**REGULATION OF THYROID ACTIVITY**

Two hormones from the hypothalamus and hypophysis respectively are the main regulators of thyroid activity. In response to low temperature the hypothalamus secretes TRH, which reaches the thyrotropes in the hypophysis through the portal system. In the thyrotropes, it stimulates the production of TSH, which through circulation reaches the thyroid gland. There, it stimulates the follicular cells, which in turn are ready to secrete TH and commence the secretory mode of these follicles. The circulatory T₃ and T₄ exert a negative feedback in both the hypothalamus to reduce TRH production, and in the pars distalis to reduce secretion of TSH. TH also exerts a negative feedback directly in the thyroid gland (Fig. 15-18).

**PATHOPHYSIOLOGY**

- Low TH secretion lead to gland enlargement (Goiter)
  - Due to low dietary Iodine
  - Dietary progoitrin or thiocyanates
- Can be counteracted by:
  - Feeding large amounts of iodine
  - Using specific drugs
    - Thiocarbamides, thiourea, thiouracil +...
    - Wait for pharmacology

Hypothyroidism can be corrected by increasing the dietary availability of iodine, and / or, with different drugs. In animals this problem can translate in other visual symptoms, such as loss of hair, myxedematous, and lethargy (Fig. 15-20).

**ABNORMALITIES RELATED TO THYROID FUNCTION**

Two types of problems may appear in relation to thyroid function. One has to do with deficient production of thyroid hormones, hypothyroidism; and the other with an excess stimulation by thyroid hormones, hyperthiroidism. The cause for hypothyroidism can be dietary or pathologic. In the case of a dietary induced hypothyroidism the disease is called Goiter. A deficiency in dietary iodine or the presence of compounds that trap iodine, prevent the normal synthesis of TH; therefore, in an attempt to compensate, the thyroid gland grows disproportionately. This is easily observed as a large mass around the front of the neck (Figs. 15-19, 15-20).

Pathological hypothyroidism could be a congenital problem, or a problem with the iodine transport mechanism; in which case, it is considered primary hypothyroidism (Figs. 15-21, 15-22).

Secondary reasons for hypothyroidism are pituitary tumors, damage to the thyroid as a consequence of exposure to radioactive iodine, which destroys the glandular tissue or an excess of circulatory glucocorticoids. Finally, tertiary causes of hypothyroidism are the presence of tumors in the hypothalamus, a problem with the synthesis of TRH or with its receptors in the pituitary.
The opposite situation, under which an animal is exposed to an excess of thyroid hormones, is hyperthyroidism and the specific disease is called Graves disease. This phenomenon is more common in cats than in dogs and, in most cases, can be traced to hyperplasia of the thyroid gland (Figs. 15-23, 15-24).

The symptoms are hypermetabolism and polyphagia, but at the same time weight loss, polydipsia and polyurea. Physiologically this translates in an elevation of blood urea nitrogen (BUN) and not creatinine, a marked decrease in cholesterol and elevated alanine aminotransferase (ALT).

**Hypothyroidism**

- **Primary / congenital**
  - Dysgenesis, dyshomonogenesis, transport defect, goitrogens or iodine deficiency
- **Secondary**
  - Pituitary tumors, radiation therapy, excess glucocorticoids
- **Tertiary**
  - Hypothalamic tumors, TRH defect in synthesis or its receptors

**Hypothyroidism**

Figure 15-21. Types of hypothyroidism

**CLINICAL SIGNS**

- Develop slowly
  - Lethargy and obesity
  - Symmetrical alopecia
  - Dull and dry hair
  - Thickened skin (myxedematous)

Figure 15-22. Typical clinical signs of hypothyroidism

**HYPERTHYROIDISM**

**Graves disease**

- Most common in cats than dogs
  - Usually caused by hyperplasia of thyroid gland
  - Predominant in mature to old cats

Figure 15-23. Pictorial examples of Graves disease

The symptoms are hypermetabolism and polyphagia, but at the same time weight loss, polydipsia and polyurea. Physiologically this translates in an elevation of blood urea nitrogen (BUN) and not creatinine, a marked decrease in cholesterol and elevated alanine aminotransferase (ALT).

**HYPERTHYROIDISM**

- **CHARACTERIZED BY**
  - Hypermetabolism
  - Polyphagia
  - Weight loss
  - Polydipsia
  - Polyurea
  - Increased BUN, not creatinine
  - Decreased cholesterol
  - Increased ALT

www.marvistavet.com/htm1/body_thyroid.html

Figure 15-24. Characteristics of hyperthyroidism