

# Introduction to Thyroid: Anatomy and Functions

Evren Bursuk  
University of İstanbul  
Turkey

## 1. Introduction

As it is known the endocrine system together with the nervous system enables other systems in the body to work in coordination with each other and protect homeostasis using hormones. Hormones secreted by the endocrine system are carried to target organs and cause affect through receptors.

## 2. Anatomy

The thyroid gland is among the most significant organs of the endocrine system and has a weight of 15-20g. It is soft and its colour is red. This organ is located between the C<sub>5</sub>-T<sub>1</sub> vertebrae of columna vertebralis, in front of the trachea and below the larynx. It is comprised of two lobes (lobus dexter and lobus sinister) and the isthmus that binds them together (Figure 1a). Capsule glandular which is internal and external folium of thyroid

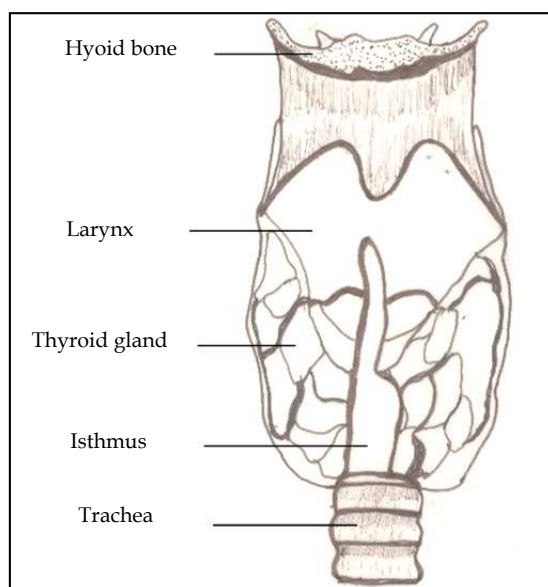


Fig. 1a. The thyroid gland anatomy

gland is wrapped up by a fibrosis capsule named thyroid. The thyroid gland is nourished by a thyroidea superior that is the branch of a. carotis external and a. thyroidea inferior that is the branch of a. subclavia (Figure 1b) (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Snell, 1995; Utiger, 1997).

In addition, there are 4 parathyroid glands in total, two of which are on the right and the other two are on the left in between capsule foliums and behind the thyroid gland lobes (Figure 1b) (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Snell, 1995; Utiger, 1997).

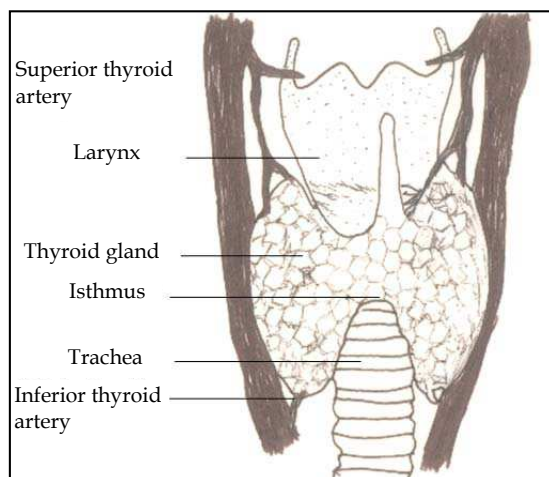


Fig. 1b. The thyroid gland anatomy with vessels

### 3. Embryology and histology

The thyroid gland develops from the endoderm by a merging of the 4th pouch parts of the primitive pharynx and tongue base median line in the 3rd gestational week. By fetus organifying iodine in the 10th gestational week and commencing the thyroid hormone synthesis,  $T_4$  (L-thyroxin) and TSH (thyroid stimulating hormone) can be measured in fetal blood. Due to the fact that hormone and thyroglobulin syntheses in fetal thyroid increase in the 2nd trimester, an increase is also observed in  $T_4$  and TSH amounts. In addition, the development of fetal hypothalamus contributes to the synthesizing of TRH (thyroid releasing hormone) and thus TSH increase. While TRH can be passed from mother to fetus through the placenta, TSH cannot.  $T_3$  (3,5,3'-triiodo-L-thyronine) begins increasing at the end of the 2<sup>nd</sup> trimester and is detected in fetal blood in small amounts. Its synthesis increases after birth.

The development of the thyroid gland is controlled by thyroid transcription factor 1 (TTF-1 or its other name NKX2A), thyroid transcription factor 2 (TTF-2 or FKHL15) and paired homeobox-8 (PAX-8). (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Scanlon, 2001; Snell, 1995; Utiger, 1997).

With these transcription factors working together, follicular cell growth and the development of such thyroid-specific proteins as TSH receptor and thyroglobulin is commenced. If any mutation occurs in these transcription factors, babies are born with hypothyroidism due to thyroid agenesis or insufficient secretion of thyroid hormones. (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Scanlon, 2001; Snell, 1995; Utiger, 1997).

The fundamental functional unit of the thyroid gland is the follicle cells and their diameter is in the range of 100-300  $\mu\text{m}$ . Follicle cells in the thyroid gland create a lumen, and there exists a protein named thyroglobulin that they synthesize in the colloid in this lumen (Figure 2a-b). The apical part of these follicle cells make contact with colloidal lumen and its basal part with blood circulation through rich capillaries. Thus, thyroid hormones easily pass into circulation and can reach target tissues. Parafollicular-c cells secreting a hormone called calcitonin that affects the calcium metabolism also exist in this gland (Di Lauro & De

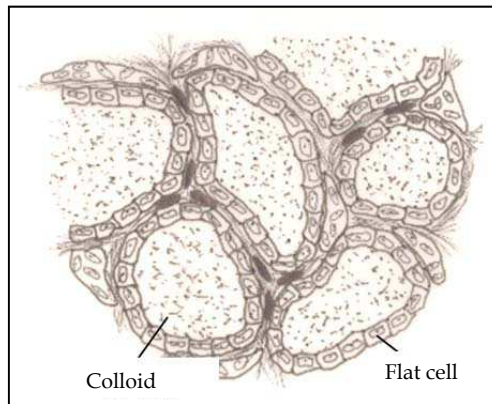


Fig. 2a. Thyroid follicle cell in the inactive state

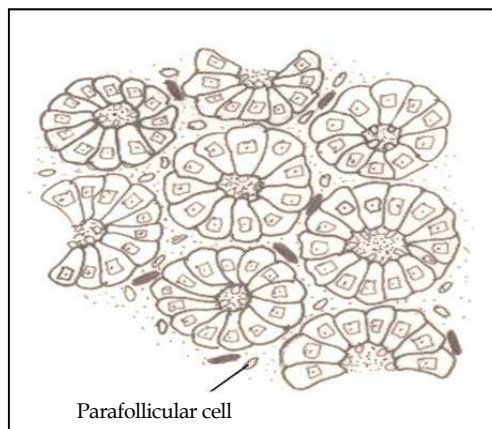


Fig. 2b. Thyroid follicle cell in the active state

Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Scanlon, 2001; Snell, 1995; Utiger, 1997).

## 4. Physiology

The thyroid gland synthesizes and secretes  $T_3$  and  $T_4$  hormones and these hormones play an important role in the functioning of the body.

### 4.1 Iodine metabolism

Chemicals in the organism are divided into two as organic and inorganic according to their carbon contents. Organic compounds always contain carbon and have covalent bonds. Carbohydrates, fats, proteins, nucleic acids, enzymes, and adenosine triphosphate (ATP) are the organic compounds. Inorganic compounds have simple structures and do not contain carbons except for carbon dioxide ( $CO_2$ ) and bicarbonate ion ( $HCO_3^{-1}$ ). They contain ionic and covalent bonds in their structures. Water, acid, base, salt, and minerals are the inorganic forms. Iodine that is a trace element important for life is among these minerals and is the fundamental substance for thyroid hormones ( $T_3$  and  $T_4$ ) synthesis. Iodine exists in 3 forms in the circulation. The first one is inorganic iodine (I<sup>-</sup>) and is about 2-10  $\mu\text{g/L}$ . Secondly, it exists sparingly in organic compounds before going into the thyroid hormone structure. And the third is the most important one and it is present as bound to protein in thyroid hormones (35-80  $\mu\text{g/L}$ ). About 59% and 65%, respectively, of the molecular weights of  $T_3$  and  $T_4$  hormones are comprised of iodine. This accounts for 30% of iodine in the body. The remaining iodine (approximately 70%) exists in a way disseminated to other tissues such as mammary glands, eyes, gastric mucosa, cervix, and salivary glands, and it bears great importance for the functioning of these tissues (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

The daily intake is recommended by the United States Institute of Medicine as in the range of 110-130  $\mu\text{g}$  for babies up to 12 months, 150  $\mu\text{g}$  for adults, 220  $\mu\text{g}$  for pregnant women, and 290  $\mu\text{g}$  for women in lactation (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Iodine is taken into the body oral. Among the foods that contain iodine are seafood, iodine-rich vegetables grown in soil, and iodized salt. For this reason, iodine intake geographically differs in the world. Places that are seen predominantly to have iodine deficiency are icy mountainous areas and daily iodine intake in these places is less than 25  $\mu\text{g}$ . Hence, diseases due to iodine deficiency are more common in these geographies. Cretinism in which mental retardation is significant was first identified in the Western Alps (Di Lauro & De Felice, 2001; Dillmann, 2004; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

### 4.2 Thyroid hormone synthesis

Iodine absorbed from the gastrointestinal system immediately diffuses in extracellular fluid.  $T_3$  and  $T_4$  hormones are fundamentally formed by the addition of iodine to tyrosine

aminoacids. While the most synthesized hormone in thyroid gland is  $T_4$ , the most efficient hormone is  $T_3$ . (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997). Basely, thyroid hormone synthesis occurs in 4 stages:

*1<sup>st</sup> stage* is the obtaining of iodine by active transport to thyroid follicle cells by utilizing  $Na^+/I^-$  symporter pump. Starting and acceleration of this transport is under the control of TSH. Organification increases as the iodine concentration of the cell rises, however, this pump slows down and stops after a point. For this reason, it is believed that a concentration-dependent autocontrol mechanism exists at this level. This stage of the synthesis that is the iodine transport can be inhibited by single-value anions such as perchlorate, pertechnetate, and thiocyanate. Pertechnetate ( $^{99m}Tc$ ) is also used in thyroid gland imaging due to its characteristic of being radioactive (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

*2<sup>nd</sup> stage* is oxidation of iodine by NADPH dependent thyroperoxidase enzyme in the presence of  $H_2O_2$  which, at this stage, occurs in follicular lumen. The drugs propylthiouracil and methimazole inhibit this step (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

*3<sup>rd</sup> stage* is the binding of oxidized iodine with thyroglobulin tyrosine residues. This is called iodization of tyrosine or organification. Thus, monoiodotyrosine (MIT) or diiodotyrosine (DIT) is synthesized. These are the inactive thyroid hormone forms (Figure 3) (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

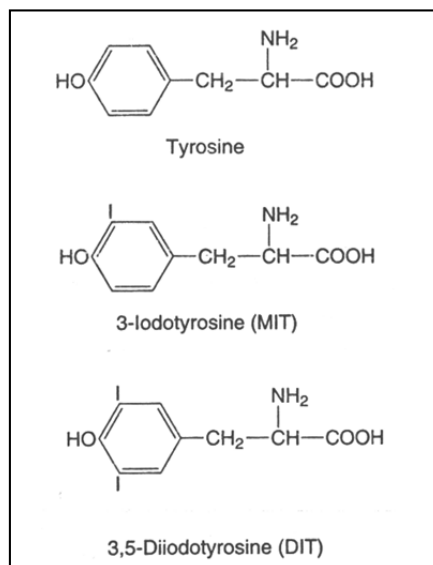


Fig. 3. Chemical structures of tyrosine, monoiodothyronine, and diiodothyronine

4<sup>th</sup> stage is the coupling and T<sub>3</sub> and T<sub>4</sub> are synthesized from MIT and DIT (Figure 4).

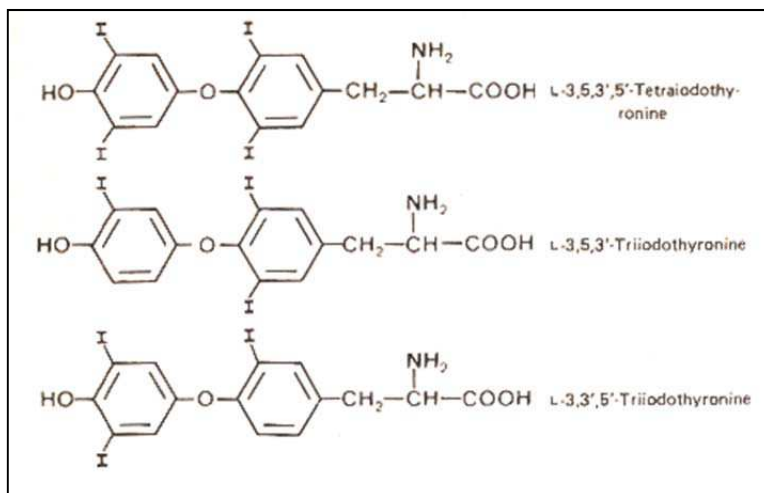


Fig. 4. Chemical structures of triiodothyronine, thyroxine, and reverse T<sub>3</sub>

In addition to synthesizing this way, the T<sub>3</sub> hormone is also created by the metabolism of T<sub>4</sub>.

Almost the entire colloid found in each thyroid follicle lumen is thyroglobulin. Thyroglobulin that contains 70% of thyroid protein content is a glycoprotein with a molecular weight of 660 kDa. Each thyroglobulin molecule has 70 tyrosine aminoacids and contains 6 MIT, 4 DIT, 2 T<sub>4</sub>, and 0.2 T<sub>3</sub> residues. Thyroglobulin synthesis is TSH-dependent and occurs in the granule endoplasmic reticulum of the follicle cells of the thyroid gland. The synthesized thyroglobulin is transported to the apical section of the cell and passes to the follicular lumen through exocytosis, and then joins thyroid hormone synthesis (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

### 4.3 Thyroid hormone secretion

Thyroid hormones are stocked in the colloid of follicle cells lumen in a manner bound to thyroglobulin. With TSH secretion, apical microvillus count increases and colloid droplet is caught by microtubules and taken back to the apex of the follicular cell through pinocytosis. Lysosomes approach these colloidal pinocytic vesicles containing thyroglobulin and thyroid hormones. These vesicles bind with lysosomes and form fagolysosomes. Lysosomal proteases are activated while these fagolysosomes move towards the basal cell, and thus, thyroglobulin is hydrolyzed. Tyrosine formed as a result of this reaction is excreted by T<sub>3</sub>

and  $T_4$  facilitated diffusion (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Not all hormones separated from thyroglobulin can pass to the blood. Such iodotyronines as MIT and DIT cannot leave the cell and are reused as deiodonized. In addition,  $T_3$  is formed from a certain amount of  $T_4$  again by deiodonization. These reactions occur in the thyroid follicular cell and the enzyme catalyzing these reactions, in other words, deiodinizations is dehalogenase. Through this deiodonization, about 50% of iodine in the thyroglobulin structure is taken back and can be reused. Iodine deficiency in individuals lacking this enzyme, and correspondingly, hypothyroid goiter is observed. Such patients are given iodine replacement treatment (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

#### 4.4 Thyroid hormone transport

When thyroid hormones pass into circulation, all become inactive by reversibly binding to carrier proteins that are synthesized in the liver. While those being bound to proteins prevent a vast amount of hormones to be excreted in the urine, it also acts as a depository. Thus, free, in other words, active hormone exists in blood only as much as is needed. The main carrier proteins are thyroxin-binding globulin (TBG), thyroxin-binding prealbumin (transthyretin, TTR) and serum albumin (Table 1) (Benvenega, 2005; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

TBG is the most bound protein by thyroid hormones. Its molecular weight is 54 kDa and is has the least concentration among others in circulations. The hormone that binds to this protein the most is  $T_4$  and is about 75% of  $T_4$  hormone. This is responsible for the diffusion of  $T_4$  hormone in extracellular fluid in large amounts. However,  $T_3$  is bound in fewer amounts. While TBG rise increases total  $T_3$  and total  $T_4$ , it does not affect free  $T_3$  and  $T_4$  (Benvenega, 2005; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

And TTR has a weight of 55kDa and has a lower rate of binding although its plasma concentration is less than TBG, and this value is more or less around 1/100 (Benvenega, 2005; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Serum albumin is a protein with a molecule weight of 65kDa and has a lower rate of binding even though its plasma concentration is the highest (Benvenega, 2005; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Due to the fact that  $T_3$  binds to fewer proteins, it is more active in intracellular region. While they become free when needed because of the fact that the affinity of carrier proteins is more to  $T_4$ , the half-life of  $T_4$  is about six days, whereas the half-life of  $T_3$  is less than one day.  $T_3$  is

more active since  $T_4$  binds to cytoplasmic proteins when they enter the cell are going to affect (Benvenega, 2005; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Proteins	Molecular weight (kDa)	Plasma concentration	Levels of binding
thyroxin-binding (TBG)	54	Lowest	Highest
thyroxin-binding prealbumin ( TTR)	55	Higher	Lower
Albumin	65	Highest	Lowest

Table 1. Comparison of the binding of thyroid hormones to carrier proteins

#### 4.5 Thyroid hormone metabolism

A 100  $\mu\text{g}$  thyroid hormone is secreted from the thyroid gland and most of these hormones are  $T_4$ . About 40% of  $T_4$  turn into  $T_3$  which is 3 times stronger in periphery, especially in the liver and kidney with deiodinase enzymes (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

Metabolically, in order for active  $T_3$  to form, deiodination needs to occur in region 5' of tyrosine. Instead, if it occurs in the 5<sup>th</sup> atom of inner circle, metabolically inactive reverse triiodothyronine ( $rT_3$ ) is formed. Three types of enzymes that are Selenoenzyme 5'-deiodinase type I (5'-DI), the type II 5' iodothyronine deiodinase (5'-DII) and the 5, or inner circle deiodinase type III (5-DIII) catalyze these deiodinations (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997).

5'-DI enzyme is especially found in the liver, kidneys, and thyroid, and 5'-DII enzyme exists in the brain, hypophysis, placenta, and keratinocytes. 5'-DIII is found in the brain, placenta, and epidermis. Both 5'-DI and 5'DII enzymes allow  $T_4$  to transform into active  $T_3$ ; but with one difference, that is, while 5'- DI enzyme provides the formed  $T_3$  to plasma,  $T_3$  formed by 5'-DII enzyme stays in the tissue and regulates local concentration. This enzyme is regulated by increases and decreases in thyroid hormones. For instance, hyperthyroidism inhibits enzyme and blocks the transformation from  $T_4$  to  $T_3$  in such tissues as the brain and hypophysis. Transformation from  $T_4$  to  $T_3$  is affected by such changes in the organism as hunger, systemic disease, acute stress, iodine contrating agents, and drugs such as propiltiourasil, propranolol, amiodaron, and glicocortikoid, but is not affected by metrmazol. 5'-DIII enzyme transforms  $T_4$  into metabolically inactive reverse  $T_3$  ( $rT_3$ ) (Figure 5) (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997). As mentioned earlier, 40% of  $T_4$  is used for the formation of  $T_3$ . This constitutes 90% of  $T_3$ . Only 10% of  $T_3$  is formed directly. Also, 40% of  $T_4$  is used for the formation of reverse  $T_3$  ( $rT_3$ ). The remaining 20% is excreted with urine or feces.



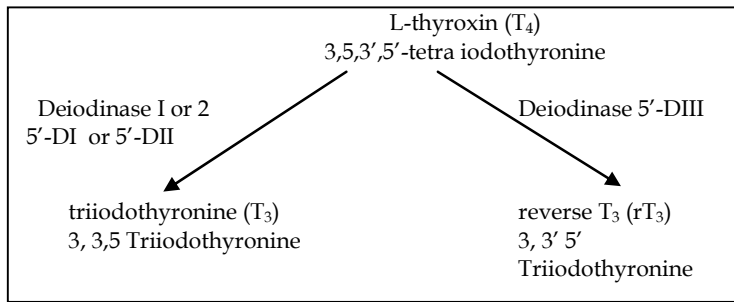


Fig. 5. Effects of deiodinase enzymes

#### 4.6 Controlling the thyroid hormone synthesis and secretion

Synthesis and secretions need to be kept at a certain level in order for the liveliness of thyroid hormones to be maintained. In this respect, the most important mechanism in controlling the synthesis and secretion of thyroid hormones is the hypothalamus-hypophysis-thyroid axis. Another one is the autocontrol mechanism that is dependent on iodine concentration as noted earlier (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Utiger, 1997).

##### 4.6.1 Hypothalamus-hypophysis-thyroid axe

Hormone synthesis and secretion of the thyroid gland is under the strict control of this axis. This event begins with TRH synthesis in the hypothalamus. TRH is carried from the hypothalamus to the hypophysis through portal circulation, and TSH hormone is secreted here following the interaction with TRH receptors in the hypophysis front lobe. TSH is then transferred by blood and stimulates the thyroid gland, and thus, thyroid hormone synthesis and secretion begins. However, if thyroid hormone and synthesis is too large an amount, the feedback system is activated and TSH and TRH are suppressed (Figure 6) (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

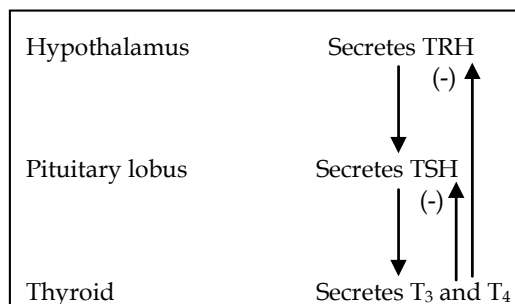


Fig. 6. Controlling of thyroid hormone secretion by the hypothalamus-hypothyroidism-thyroid axis

The thyrotrophin-releasing hormone (TRH) is a tripeptide synthesized in periventricular nucleus in the hypothalamus. The structure of TRH formed by the repetition of -Glu-H<sub>5</sub>-Pro-Gly- series 6 times in the beginning turns into pyroglutamyl histidylprolinamide at the end of synthesis. As noted earlier, TRH is carried to the front hypophysis through hypophyseal portal system and provides the secretion of TSH from thyrotrope cells (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

There are receptors specific to TRH on the surfaces of these cells. When TRH makes contact with these receptors, G<sub>q</sub> protein is activated, and it then activates the phospholipase C enzyme, fractionates membrane phospholipids and forms diacylglycerol (DAG) and inositol triphosphate (IP<sub>3</sub>). These are secondary messengers and cause the secretion of Ca<sup>+2</sup> via IP<sub>3</sub> from endoplasmic reticulum, and DAG activates protein kinase C. The effect of TRH on TSH is provided through these secondary messengers (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

TRH also increases the secretions of growth hormone (GH), follicle stimulating hormone (FSH), and prolactin (PRL). While the TRH secretion is increased by noradrenaline, somatostatin and serotonin inhibits it. (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

The thyrotropin-stimulating hormone (TSH) is a hormone that has a glycoprotein structure comprised of  $\alpha$  and  $\beta$  subunits and synthesized in 5% basophilic thyrotrope cells of frontal hypophysis.  $\alpha$  subunit is almost the same as that found in such hormones as human chorionic gonadotropin (HCG), luteinizing hormone (LH), and follicle stimulating hormone (FSH). It is believed that the task of this subunit is the stimulation of adenylate cyclase that provides the formation of cAMP secondary precursor.  $\beta$  subunit is completely different to other hormones and is related with receptor specificity. Therefore, TSH is active when it possesses both subunits (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

TSH activates G<sub>s</sub> protein when it merges with the receptor in the membrane of thyroid gland follicle cell, and thus, the adenylate cyclase enzyme is activated as well. When this enzyme becomes activated, it increases the secondary messenger cAMP. Along with stimulating protein kinase A enzymes, it causes the development of thyroid follicular cell and the synthesis of thyroid hormone (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

TSH is metabolized in kidneys and liver. It is released as pulsatile and demonstrates circadian rhythm, which means that the secretion begins at night, reaches a maximum at midnight, and decreases all day long (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

The effects of TSH may be divided into three.

- a. **Effects occurring within minutes;**
  - Binding of iodine,
  - T<sub>3</sub> and T<sub>4</sub> hormone synthesis
  - Secretion of thyroglobulin into colloid
  - Taking colloid back into the cell with endocytosis,
- b. **Effects occurring within hours;**
  - Trapping iodine into the cell by active transport
  - Increase in blood flow
- c. **Chronic effects,**
  - Hypertrophy and hyperplasia occurring in cells
  - Gland weight increases.

Despite these effects, TSH does not affect the transformation from T<sub>4</sub> to T<sub>3</sub> in the periphery.

Although TSH secretion is stimulated by TRH and estradiol, it is inhibited by somatostatin, dopamine, T<sub>3</sub>, T<sub>4</sub>, and glucocorticoids. While  $\alpha_1$  adrenergics demonstrate inhibiting effects,  $\alpha_2$  adrenergics are stimulators (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

#### 4.6.2 Autoregulation of the thyroid

Changes in iodine concentrations in follicular cells of thyroid gland affect the iodine transport and form an autoregulation (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997). Thyroid hormone synthesis is inhibited as the iodine amount increases in follicles, however, synthesis increases as the amount decreases. Wolf Chaikoff effect in which excessive iodine stops the thyroid hormone synthesis may also be mentioned. This effect is especially observed when individuals with hyperthyroidism take antithyroid along with iodine and become euthyroid (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

In addition, the sensitivity of the thyroid gland also increases through a development of a response to TSH, although TSH does not have a stimulating effect in iodine deficiency. Along with the increase in sensitivity, follicular cells in the gland reach hypertrophy and hyperplasia, and increase the weight of the gland and create goiter. The effects of TSH decrease as the response to TSH decreases with the rise in iodine (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997). In this case, all of the effects, such as binding of iodine, thyroid hormone synthesis, secretion of thyroglobulin into colloid, taking colloid back to cell by endocytosis, entrapment of iodine, and cell hypertrophy are decreased. However, blood flow to the thyroid glands is reduced. Iodine supplement before thyroid surgery is for the purpose of reducing the blood flow in the thyroid gland. (Dillmann, 2004; Dunn,

2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Santiseban, 2005; Scanlon, 2001; Utiger, 1997).

#### **4.7 Occurrence of the thyroid hormone effect**

Thyroid hormone receptors exist within the cell. Most of these receptors are in the nucleus and show more affinity to  $T_3$ . Due to the fact that  $T_4$  binds more to carrier proteins and exists more in extracellular region, it passes inside the cell, in other words, intracellular amount of  $T_4$  is lesser. When they pass to the intracellular section, very few of them are free for receptors after they are bound to proteins. However,  $T_3$  already exists more in intracellular section due to it binding to fewer amount of carrier proteins and receptors show more affinity to  $T_3$  due to being free. As a result,  $T_3$  is 3-8 times more potent compared to  $T_4$ . The reason for this difference in effect is that  $T_4$  transforms into  $T_3$  while  $T_4$  exists in high amounts; the actual efficient one is  $T_3$  (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones easily pass through the cell membrane due to being lipid soluble and  $T_3$  immediately binds to thyroid hormone receptor in nucleus. Thyroid hormone receptors are of two types as  $\alpha$  (TR  $\alpha$ ) and  $\beta$  (TR $\beta$ ). Although these receptors generally exist in all tissues, they differ in effects. While TR  $\alpha$  is more efficient in the brain, kidneys, heart, muscles and gonads, TR $\beta$  is more efficient in liver and hypophysis. TR  $\alpha$  and  $\beta$  are bind to a special DNA sequence that has thyroid response elements (TRE<sub>s</sub>). Receptors bind and activate by retinoic acid X (RXR<sub>s</sub>) receptors. They either stimulate transcription or inhibit it due to regulatory mechanisms in the target gene. When the transcription starts, various mRNAs are synthesized, and various proteins are synthesized by going through translation in ribosomes that are present in cell cytoplasm. Also, enzymes in the protein structure are synthesized and some of these play an active role in the formation of thyroid hormone effects (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

#### **4.8 Effects of thyroid hormones**

The effects of thyroid hormones are varying. It can be divided into 4 as cellular level, and effects on growth, metabolism, and on systems.

##### **4.8.1 Effects of thyroid hormones at the cellular level**

The general cellular effect is the aforementioned  $T_3$  synthesizing various proteins in which enzymes are also included by transcription and then translation in ribosomes in cytoplasm after interacting with receptor in nucleus. While, on one hand, protein synthesis increases, and on the other, a rise occurs in catabolism, and thus basal metabolism increases. Cell metabolism shows an increase of 60-100% when thyroid hormones are oversecreted (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones accelerate mRNA synthesis in mitochondria by acting with intrinsic receptors in mitochondria inner and outer membranes and increases protein production. Due to these proteins produced here in mitochondria being respiratory chain proteins such as NADPH dehydrogenase, cytochrome-c-oxidase, and cytochrome reductase, the respiratory chain accelerates as the synthesis of these enzymes increases, and thus, ATP synthesis and oxygen consumption also increases. Therefore, it may be noted that ATP synthesis is dependent on thyroid hormone stimulation. In addition, the number of mitochondria increases due to the increase in mitochondria activity parallel to mitochondria protein synthesis (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Protein synthesis causes an increase in enzyme synthesis by increasing with the effect of thyroid hormones, and this affects the passage by increasing the production of transport enzymes in the cell membrane. Among these enzymes, the  $\text{Na}^+ \cdot \text{K}^+$  ATPase pump provides  $\text{Na}^+$  to exit and  $\text{K}^+$  to enter by using ATP, thus, the rate of metabolism also increases (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Another membrane enzyme  $\text{Ca}^{+2}$  ATPase acts more in the circulation system as intracellular  $\text{Ca}^{+2}$  decreases when this enzyme operates (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

#### 4.8.2 Effects on growth

Among the effects of thyroid is the effect it has on growth. This hormone has both specific and general effects on growth. Thyroid hormones are necessary for normal growth and muscle development. While children with hypothyroidism are shorter due to early epiphysis closure, children with hyperthyroidism are taller compared to their peers. Another important effect of the thyroid hormone is its contribution to the pre- and post-natal development of the brain. When in the mother's uterus, if the fetus cannot synthesize and secrete sufficient thyroid hormone and it is not replaced, growth and development retardation occurs in both pre- and post-natal periods (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995). Normal serum levels are Total  $\text{T}_4$  5-12 $\mu\text{g}/\text{dl}$ , Total  $\text{T}_3$  80-200 $\text{ng}/\text{dl}$ , Free  $\text{T}_4$  0,9-2 $\text{ng}/\text{dl}$  and free  $\text{T}_3$  0,2-0,5 $\text{ng}/\text{dl}$ , respectively. If a thyroid hormone test is conducted on the baby after birth and hormone treatment is started immediately, a completely normal child is developed and a dramatic difference between early and late detection of the disease is clearly observed.

#### 4.8.3 Metabolic effects

Thyroid hormones carry out their metabolic effects by carbohydrates, fat and protein metabolisms, vitamins, basal metabolic rate and its effect on body weight.

When the effects of thyroid hormones on carbohydrate metabolism are observed, it is established that it is both anabolic and catabolic. As a result of thyroid hormones increasing

the enzyme synthesis due to protein synthesis in cells, enzymes in carbohydrate metabolism also increase their activities. Thus, thyroid hormones increase the entrance of glucose into the cell, absorption of glucose from the gastrointestinal system, both glycolysis and gluconeogenesis, and secondarily, insulin secretion (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

The effect of thyroid hormone on fat metabolism are both anabolic and catabolic. Thyroid hormones have an especially lipolysis effect on adipose tissue, and free fatty acid concentrations in plasma increase with the said effect, and in addition, fatty acid oxidation also increases (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995). While, as a result of these effects, an increase is expected in the amounts of cholesterol and triglyceride, in contrast, their levels in blood are established to be low. This occurs due to two reasons. Firstly, thyroid hormones (especially  $T_3$ ) cause an increase in receptor synthesis specific to LDL and cholesterol in liver, bind to lipoproteins, and decrease the triglyceride level in blood. Secondly, thyroid hormones accelerate the transformation of triglyceride to cholesterol with their effect. Cholesterol reaching the liver is used in the production of bile and the produced bile is excreted from the intestines with feces. Consequently, there occurs a decrease in adipose tissue, cholesterol and triglyceride in blood, and an increase in free fatty acids when thyroid hormone is oversecreted. The opposite occurs in individuals with hyperthyroidism. In a study by Bursuk et al., it was established by comparing the body composition in control, hypothyroidism, and hyperthyroidism groups with the bioelectrical impedance analysis method that body fat percentage and the amount decreased in cases with hyperthyroidism while they increased in cases with hypothyroidism (Bursuk et al., 2010; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

As previously noted, thyroid hormones show an anabolic effect by increasing the protein syntheses and a catabolic effect by increasing the destruction when oversecreted. Thyroid hormones also regulate aminoacid transport due to the need for aminoacids in order to increase the protein synthesis. They also provide the synthesis for proteins specific to cell growth. Thyroid hormones provide a normal growth of the baby by increasing the syntheses of insulin-like factors in fetal period (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Hormones that provide growth and development are also under the control of thyroid hormones. As mentioned before, hypothyroidism causes growth-development retardation and can be reversed by hormone replacement treatment when diagnosed early. In hyperthyroidism in which thyroid hormones are oversecreted, muscle atrophies are observed as a result of an increase in protein catabolism (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Most of the enzymes need vitamins as co-factors in order to produce an effect. The need for the co-factor of thyroid hormones increases parallel to enzyme synthesis. Thiamine,

riboflavin, B<sub>12</sub>, folic acid and ascorbic acid (vitamin C) are predominantly used as co-factors. Therefore, deficiencies of these vitamins are common in cases with hyperthyroidism. In addition, vitamin D deficiency is also observed in these individuals due to an increase in excessive consumption and clearance. Also, thyroid hormones are necessary for carotene from food to be transformed into vitamin A. Vitamin A transformation does not occur in cases with hypothyroidism due to thyroid hormone deficiency and carotene is deposited under the skin giving it a yellow color. (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995). Vitamin D deficiency is present in these cases due to a problem in A, E, and cholesterol metabolism. Thus, vitamin supplement is necessary in both hypothyroidism and hyperthyroidism cases.

Another effect of thyroid hormones is the acceleration of basal metabolism. As noted before, thyroid hormones increase the oxygen consumption and thus ATP synthesis by rising the count and activity of mitochondria. Thyroid hormones increase oxygen consumption except for the adult brain, testicles, uterus, lymph nodes, spleen, and front hypophysis. In addition, the increase of such enzymes as Na<sup>+</sup>. K<sup>+</sup>. ATPase, and Ca<sup>+</sup>. ATPase contribute to it. Also, lipid catabolism lends to it. A high level of temperature is produced as a result (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

A protein called thermogenin in brown adipose tissue is uncoupled, that is, ATP production and e<sup>-</sup> transport chain are separated from each other. An excessive temperature occurs as a result. All these effects provide acceleration of basal metabolism. The overworking thyroid gland increases the basal metabolism by 60-100% (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Due to the increase in basal metabolism, a decrease is observed in body weight. Thyroid hormones greatly reduce the fat deposit. Weight loss is observed in cases with hyperthyroidism although appetite increases in cases with hyperthyroidism. However, in cases with hypothyroidism, basal metabolism deceleration and weight gain occur in cases with hypothyroidism (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

#### **4.8.4 Effect of thyroid hormones on systems**

The effect of thyroid hormones on circulation systems is predominantly through catecholamine. Thyroid hormones increase the  $\beta$  adrenergic receptor count without affecting catecholamine secretion. This causes an increase in heart rate, cardiac output, stroke volume, and peripheral vasodilation. Peripheral vasodilation causes the skin to be warm and humid. Warm and humid skin, sweating, and restlessness due to increased sympathetic activity are observed in cases with hyperthyroidism. However, the opposite is seen in hypothyroidism. The  $\beta$  adrenergic receptor count is decreased. In relation to this, heart rate, cardiac output, and stroke volume is also decreased and cold, dry skin is observed due to peripheral vasoconstriction. In a study by Bursuk et al., it was established

by measuring and comparing the stroke volume, cardiac output, heart index, and blood flow in control, hypothyroidism, and hyperthyroidism groups with the bioelectrical impedance analysis method that these parameters significantly increased in cases with hyperthyroidism while they decreased in cases with hypothyroidism (Bursuk et al., 2010; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

In addition, as metabolism products also increase due to an increase in oxygen consumption when thyroid hormones are oversecreted, vasodilation occurs in periphery. Thus, blood flow increases, and cardiac output can be observed to be 60% more than normal. The thyroid hormone also raises the heart rate due to its direct increasing effect on heart stimulation (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones increase the contraction of heart muscles only when they raise it in small amounts. When thyroid hormones are oversecreted, a significant decrease occurs in muscle strength, and even myocardial infarction is observed in severely thyrotoxic patients (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Due to large amounts of oxygen thyroid hormones use during their increasing protein synthesis, hence the enzyme synthesis, and ATP synthesis as well, carbon dioxide amount is also increased. As a result of the carbon dioxide increase affecting the respiratory center of the brain, hyperventilation, that is, the rise in inhalation frequency and deepening of respiration is observed (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

While appetite and food consumption increases, an increase has also been observed in digestive system fluids, secretions, and movements. Frequently, diarrhea occurs when the thyroid hormone is excessively secreted. In contrast, constipation is observed in the case of hypothyroidism (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

When the effects of thyroid hormones on the skeletal system are checked, the first thing that needs to be examined is their effect on bones. The activities of osteoblast and osteoclast that are the main cells of bone structure increase parallel to thyroid hormones. In normal individuals, thyroid hormones possess direct proliferative effect on osteoblasts. In cases with hyperthyroidism, a decrease develops in the cortex of the bones due to increase in osteoclastic activities. Thus, the risk of post-menopausal osteoporosis development increases in these patients. While, in physiological cases, thyroid hormone creates an osteoblastic effect, it produces an osteoporotic effect in hyperthyroidism (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).



The thyroid also affects response to stimulants. When this hormone is excessively secreted, muscle fatigue occurs due to protein catabolism increase. The most typical symptom of hyperthyroidism is a faint muscle tremor. Such a tremor happening 10-15 times per second, occurs due to increase in activity of neuronal synapses in medulla spinalis regions that control muscle tone, and differs from tremors in Parkinson's disease. This tremor demonstrates the effects of thyroid hormones on central nervous system (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

As mentioned above, muscle fatigue is observed in hyperthyroidism due to the accelerating effect of the thyroid hormone on protein catabolism. However, the excessive stimulant effect of this hormone on synapses leads to sleeplessness. In hypothyroidism, a sleepy state exists (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995)..

Thyroid hormones play an important role in the development of the central nervous system. They are also responsible for the myelination of the nerves. If there is thyroid hormone deficiency in fetus, it causes neuronal developmental disorders in the brain, myelination retardation, decrease in vascularization, retardation in deep tendon reflexes, cerebral hypoxia due to decrease in cerebral blood flow, mental retardation, and lethargy. In cases with hyperthyroidism, the opposite occurs and hyperirritability, anxiety, and sleeplessness are observed in these children (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones produce an effect by merging with their specific receptors in membrane and nuclei of hemopoietic stem cells. After  $T_3$  and  $T_4$  hormones bind with a receptor, erythroid stem cells go through mitosis and accelerate erythropoiesis. With the protein synthesis they caused to occur in these precursor cells, they provide the synthesis of enzymes at the beginning and at the end of hemoglobin synthesis (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

In addition, when tissues are left without oxygen with the consumption of oxygen thanks to thyroid hormone effect, they stimulate the kidney and increase erythropoietin synthesis and secretion. Erythropoietin then stimulates the bone marrow and accelerates erythropoiesis. While polycythemia is not observed in patients with hyperthyroidism, anemia is quite prevalent among cases with hypothyroidism. Blood levels of cases with hyperthyroidism are generally within normal limits (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

In a study by Bursuk et al., it has been established by measuring and comparing blood parameters and blood viscosity in control, hypothyroidism, and hyperthyroidism groups that blood viscosity was increased in cases with hypothyroidism due to blood count parameters being higher compared to cases with hyperthyroidism, blood lipids and fibrinogen were higher in cases with hypothyroidism, and in addition, blood viscosity

was increased in cases with hypothyroidism due to high plasma viscosity (Bursuk et al., 2010; Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones regulate the actions of other endocrine hormones in order to accelerate basal metabolism. These hormones increase the absorption of glucose in gastrointestinal system, glucose reception into cells, and both glycolysis and gluconeogenesis by producing an effect on insulin and glucagon. Thyroid hormones enable the increase of insulin through secondary mechanism by occasionally rising blood sugar (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Due to the fact that both thyroid hormones and growth hormones are necessary for normal somatic growth, thyroid hormones increase the synthesis and secretion of growth hormone and growth factors (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Also, another effect is produced on prolactin. During hypothyroidism, TRH secretion stimulates prolactin secretion, and while galactorrhea and amenorrhea is observed in females, gynecomastia and impotence is found in males. The inhibiting effect of dopamine is of utmost importance in regulating the secretion of prolactin secretion (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Due to the fact that thyroid hormones regulate the secretion and use of all steroid hormones adrenal gland deficiency with such findings as lack of libido, impotence, amenorrhea, menorrhagia, and polymenorrhea is observed in cases with hypothyroidism. Another cause for findings related to these sex steroids may be excessive prolactin (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

Thyroid hormones affect bone metabolism in parallel with parathormone. Estrogen, vitamin D<sub>3</sub>, TGF- $\beta$ , PGE<sub>2</sub>, parathormone (PTH), and all of the thyroid hormones are necessary for osteoblastic activity (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

As noted earlier, thyroid hormones increase  $\beta$  adrenergic receptor count. Adrenaline and noradrenaline interact with these receptors and accelerates basal metabolism, stimulates the nervous system, and speeds up the circulation system just as in the effect of thyroid hormones (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

For a normal sexual development and life, thyroid hormones are necessary. The reason for this is that thyroid hormones increase the use and secretion of sex steroids, and in addition, affect prolactin secretion. Lack of libido, impotence, gynecomastia, amenorrhea,

menorrhagia, and polymenorrhea are observed due to sex steroid deficiency and excessive prolactin in cases with hypothyroidism (Dillmann, 2004; Dunn, 2001; Ganong, 1997; Guyton & Hall, 1997; Jameson & Weetman, 2010; Larsen et al., 2003; Lo Presti & Singer, 1997; Mc Gregor, 1996; Reed & Pangaro, 1995; Utiger, 1997; Usala, 1995).

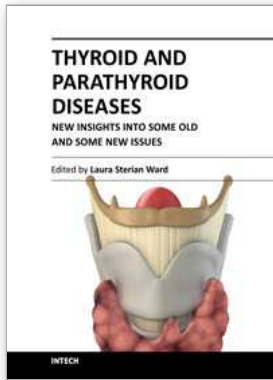
## 5. Conclusion

Anatomy, histology and physiology of thyroid have been addressed in this chapter. In its physiology, its hormone synthesis, metabolism, effect generation mechanism and effects on the body has been explained. While mentioning these effects, the relationship between thyroid diseases and blood hemorheology has also been referred and relationship between disease groups (hyperthyroids and hypothyroids) has been analysed comparatively with these parameters.

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This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

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Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
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### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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