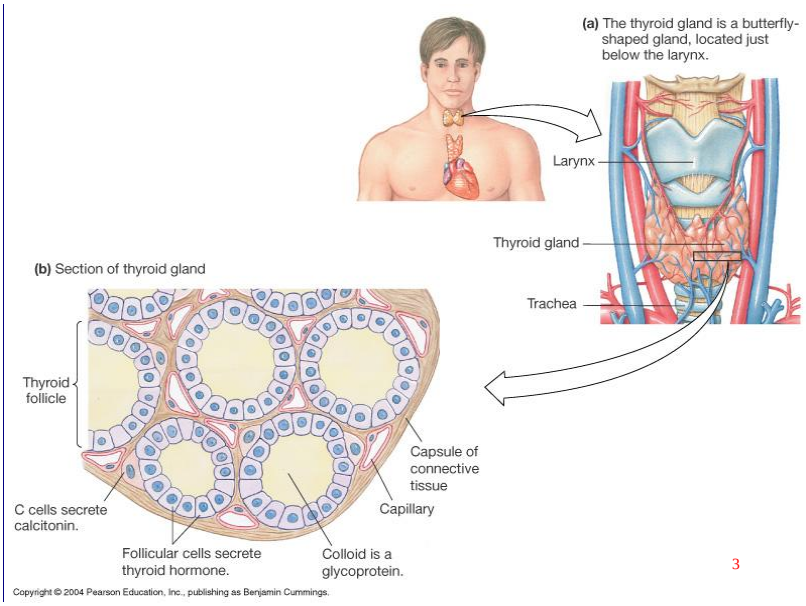
THE THYROID GLAND

The thyroid gland is the largest organ specialized for endocrine function in the human body. The major function of the thyroid follicular cells is to secrete a sufficient amount of the thyroid hormones, primarily 3,5,3',5'-tetraiodothyroine (T_4) and a lesser quantity of 3,5,3'-triiodothyronine (T_3). Thyroid hormones promote normal growth and development and regulate a number of homeostatic functions, including energy and heat production. In addition, the parafollicular cells of the human thyroid secrete calcitonin, which is important in Ca^{++} homeostasis.

The thyroid gland originates in the floor of the pharynx, which grows downward anterior to the trachea. The weight of the gland is ~ 10-20 grams. The thyroid gland consists of a series of follicles of varying sizes that contain the "colloid", and are surrounded by a single layer of thyroid epithelium.

The follicle cells synthesize thyroglobulin, which is extruded into the lumen of the follicle.



The biosynthesis of T_4 and T_3 occurs within thyroglobulin at the cell-colloid interface. Numerous microvilli project from the surface of the follicle into the lumen; these are involved in endocytosis of thyroglobulin, which is then hydrolyzed in the cell to release thyroid hormone (Fig. 7-5). The structures of the thyroid hormones T_4 and T_3 are shown in Fig. 7-6).

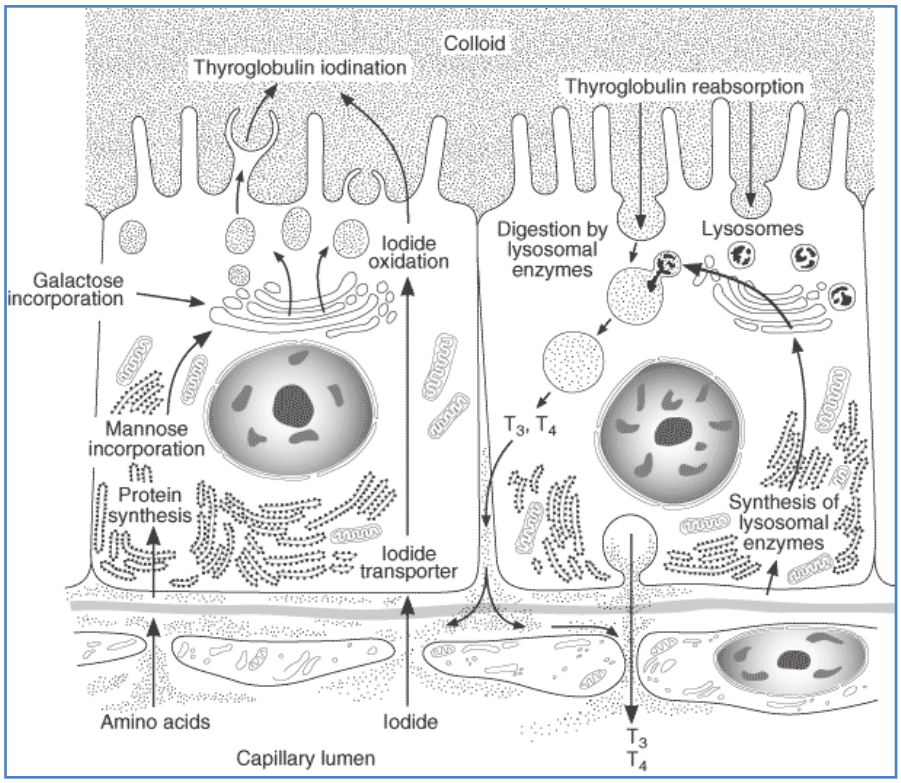
Thyroid Hormones Synthesis and Secretion

The synthesis of T_4 and T_3 by the thyroid gland involves six major steps:

1. active transport of I^- a cross the basement membrane into the thyroid cells (trapping of iodide);
2. oxidation of iodide and iodination of tyrosyl residues in thyroglobulin;
3. coupling of iodotyrosine molecules within thyroglobulin to for m T_3 and T_4;
4. proteolysis of thyroglobulin, with release of free iodothyronines and iodotyrosines;
5. deiodination of iodotyrosines within the thyroid cell with conservation and reuse of the liberated iodide; and
6. under circumstances, intrathyroidal 5'- deiodination of T_4 to T_3.

Thyroid hormone synthesis involves a unique glycoprotein, thyroglobulin, and an essential enzyme, thyroperoxidase (TPO). This process is summarized in Fig. 7-9.

Figure 7-5. Processes of synthesis and iodination of thyroglobulin (left) and its reabsorption and digestion (right). These events occur in the same cell.



Thyroglobulin

Thyroglobulin is a large glycoprotein molecule with al MW of ~ 660,000. It contains about 140 tyrosyl residues and about 10% carbohydrate in the form of mannose N-acetylglucosamine, galactose, fucose, sialic acid, and chondriotin sulfate. It is a dimmer of two identical subunits. The iodine content of the molecule can vary from 0.1% to 1% by weight. The mRNA is translated in the rough ER, and thyroglobulin chains are glycosylated during transport to the Golgi apparatus (Fig. 7-5). In the Golgi apparatus, the thyroglobulin dimmers are incorporated into exocytotic vesicles that fuse with the basement membrane and release the thyroglobulin into the follicular lumen. There, at the apical collioid border, tyrosines within thyroglobulin are iodinated and stored in colloid.

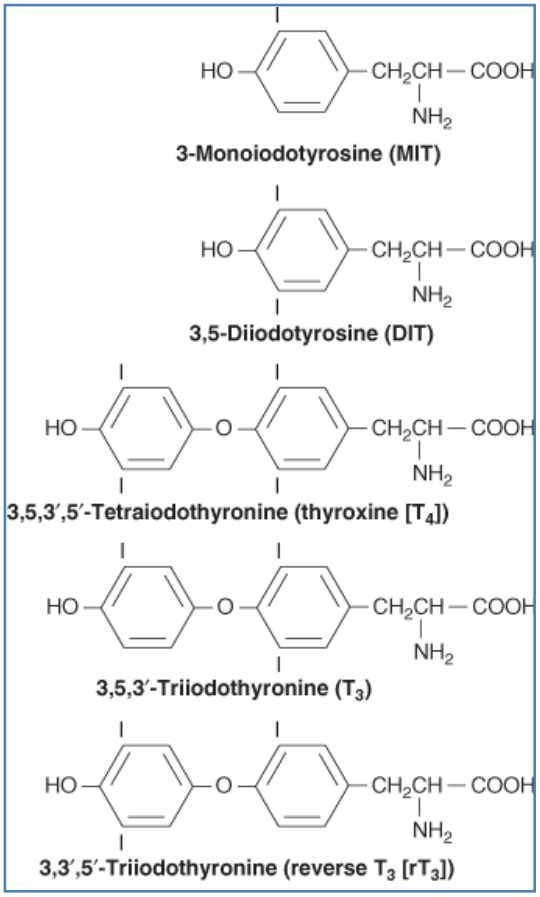
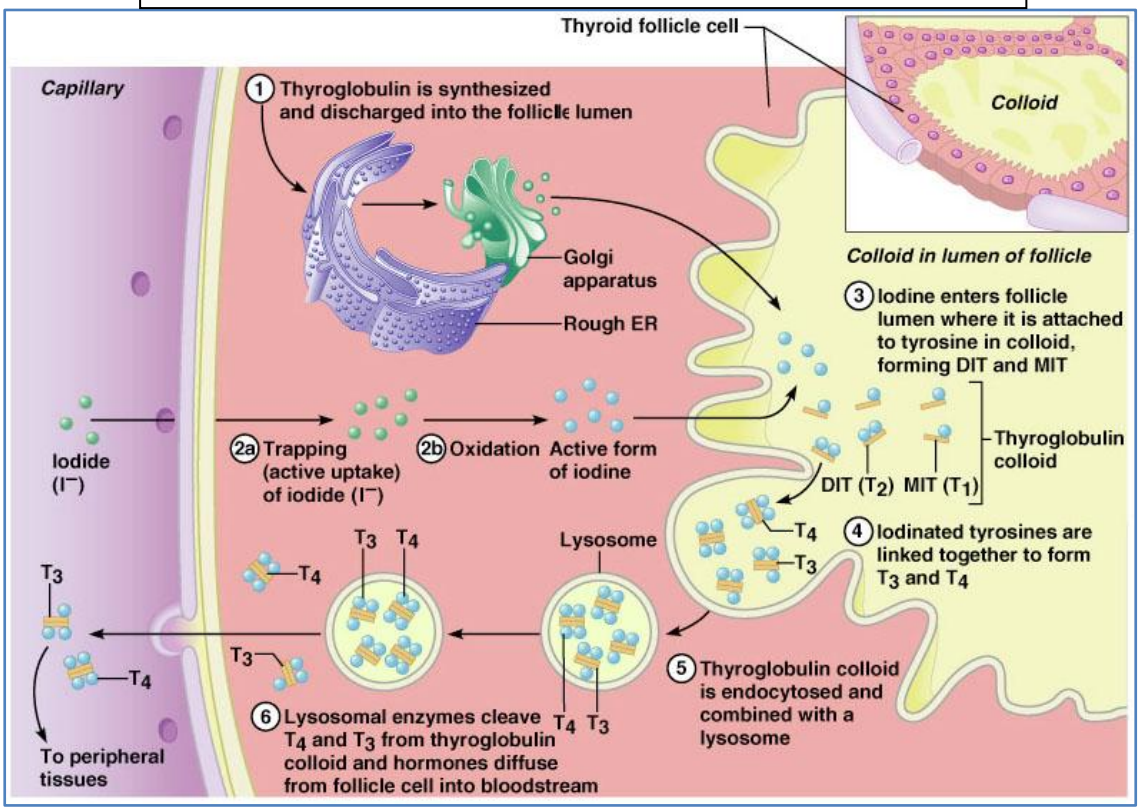


Figure 7-6. Structure of thyroid hormones and related compounds.

Figure 7-9. Thyroid hormone synthesis in the thyroid follicle



Thyroidal Peroxidase

Thyroidal peroxidase is a membrane – bound glycoprotein that mediates both the oxidation of iodide ions and the incorporation of iodine into tyrosine residues of thyroglobulin. Thyroidal peroxidase is synthesized in the rough ER. After insertion into the membrane of RER cisternae, it is transferred to the apical cell surface through Golgi elements and exocytotic vesicles. Here, at the cell colloid interface, it is available for iodination and hormonogenesis in thyroglobulin. Thyroidal peroxidase biosynthesis is stimulated by TSH.

Iodide Transport (The Iodide Trap)

I^- is transported across the basement membrane of thyroid cell by an intrinsic membrane protein called the Na^+/I^- symporter (NIS). At the apical border, a second I^- transport protein called pendrin, moves iodine into the colloid, where it is involved in hormonogenesis (Fig. 7-10).

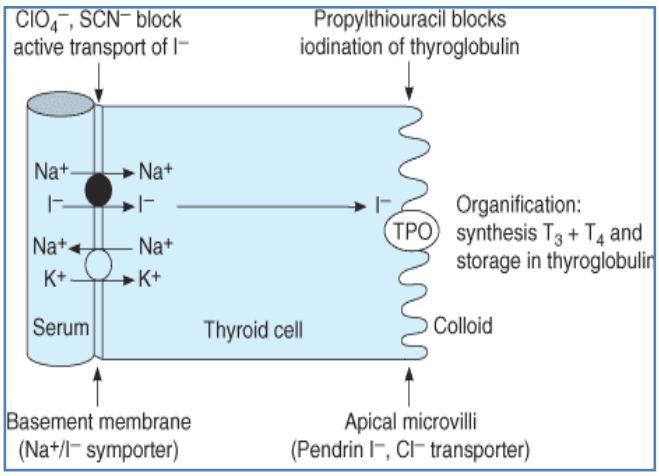


Figure 7-10. The iodide transporter in the thyroid cell. The large solid circle represents the Na^+/I^- symporter actively transporting I^- into the cell; the large open circle represents Na^+-K^+ ATPase supplying the ion gradient which drives the reaction. I^- is transported across the apical membrane by pendrin. Hormone synthesis takes place in the colloid at the colloid-apical membrane, catalyzed by thyroperoxidase (TPO).

The NIS derives its energy from Na^+- K^+ ATPase, which drives the transport process. This active transport system allows the human thyroid gland to maintain a concentration of free iodide 30-40 times that in plasma. The NIS is stimulated by TSH and by the TSH receptor-stimulating antibody found in Grave's disease.

Iodination of Tyrosyl in Thyroglobulin

Within the thyroid cell, at the cell-colloid interface, iodide is rapidly oxidized by H_2O_2, catalyzed by thyroperoxidase, and converted to an active intermediated which is incorporated into tyrosyl residues in thyroglobulin.

Coupling of Iodotyrosyl Residues in Thyroglobulin

The coupling of iodotyrosyl residues in thyroglobulin is also catalyzed by thyroperoxidase. For this process to occur, the dimeric structure of thyroglobulin is essential. Within the thyroglobulin molecule, two molecules of DIT may couple to form T_4, and an MIT and a DIT molecule may couple to form T_3. Thiocarbamide drugs, particularly polythiourcil, methimazole, and carbimazole are potent inhibitors of thyroperoxidase and will block thyroid hormone synthesis. These drugs are clinically useful in the management of hyperthyroidism.

Proteolysis of Thyroglobulin and Thyroid Hormone Secretion

Lysosomal enzymes are synthesized by the RER and packaged by the Golgi apparatus into lysosomes, filled with proteolytic enzymes. At the cell - colloid interface, colloid is engulfed into a colloid vesicle that fuses with lysosomes and hydrolysis of thyroglobulin occurs, releasing T_4, T_3, DIT, MIT, peptide fragments and amino acids. T_3 and T_4 are released into the circulation, while DIT and MIT are deiodinated and the I^- is conserved. Thyroid hormone secretion is stimulated by TSH, which activates adenylate cyclase.

Intrathyroidal Deiodination

MIT and DIT formed during the synthesis of thyroid hormone are deiodinated by intrathyroidal deiodinase (Fig.7-9). It acts on MIT and DIT but not on T_3 and T_4. The iodide released in mostly reutilized for hormone synthesis; a small amount leaks out of the thyroid into the body pool. The 5'- deiodinase that converts T_4 to T_3 in peripheral tissues is also found in the thyroid gland. In situation of iodide deficiency, the activity of this enzyme may increase the amount of T_3 secreted by the thyroid gland, increasing the metabolic efficiency of hormone synthesis.

Abnormalities in Thyroid Hormone Synthesis and Release

Inherited Metabolic Defects (Dyshormonogenesis)

Inherited metabolic defects may involve any phase of hormonal biosynthesis. These result in "dyshormonogenesis" and impaired hormonal synthesis. Patients present with thyroid enlargement, or goiter, mild to severe hypothyroidism, low serum T_3 and T_4, and elevated serum TSH.

Effect of Iodide Deficiency

A diet vary low in iodine reduces intrathyroidal iodine content, increases the intrathyroidal ratio of MIT to DIT, increases the ratio of T_3 to T_4, decreases the secretion of T_4, and increases

serum TSH. In the adult, this results in goiter, with a high iodine uptake and mild to severe hypothyroidism; in the neonate, it may result in cretinism.

Thyroid Hormone Transport

Thyroid hormones are transported in serum bound to carrier protein. Although only 0.04% of T_4 and 0.4% of T_3 are "free", it is the free fraction that is responsible for hormonal activity (Fig. 7-15). There are three major thyroid hormone transport proteins: thyroxine–binding globulin (TBG); thyroxine–binding prealbumin (TBPA), or transthyretin; and albumin.

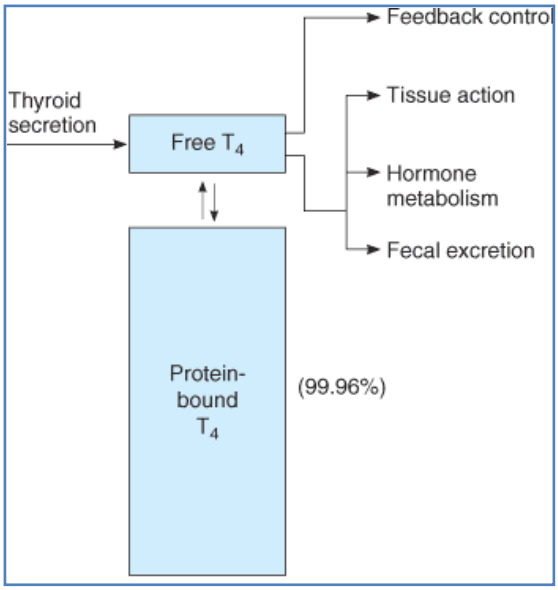


Figure 7-15. Representation of free T_4 (and free T_3) as the biologically active hormones at the level of the pituitary and the peripheral tissues. Most of the thyroid hormones circulating in plasma are protein-bound and have no biologic activity. This pool of bound hormone is in equilibrium with the free hormone pool.

Thyroxine- Binding Globulin (TBG)

TBG, a single 54-KDa polypeptide chain, is synthesized in the liver. It contains four carbohydrate chains, and has homology with α_1-antichymotrypsin and α_1-antitrypsin. Pregnancy or estrogen therapy increases the sialic acid content of the molecule, resulting in decreased metabolic clearance and elevated serum levels of TBG. Each molecule of TBG has a single binding site for T_4 or T_3.

The high affinity for T_3 and T_4 allows TBG to carry about 70% of the circulating hormones. Androgenic steroids and glucocorticoids lower TBG levels. Heparin stimulates lipoprotein lipase, releasing free fatting acids, which displace T_3 and T_4 from TBG, increasing the levels of free T_4 and T_3.

Thyroxine – Binding Prealbumin

Transthyretin, or thyroxin-binding prealbumin (TBPA), is 55-KDa globular polypeptide consisting of four identical subunits. It binds about 10% of circulating T_4. Its affinity for T_3 is about tenfold lower than for T_4, so that it mostly carries T_4.

Albumin

Albumin has one strong binding site for T_4 and T_3 and several weaker ones. Because of its high concentration in serum, albumin carries about 15% of circulating T_4 and T_3. The rapid dissociation rates of T_4 and T_3 from albumin makes this carrier a major source of free hormone to tissues. Hypoalbuminemia, as occurs in nephrosis or in cirrhosis of the liver, is associated with a low total T_4 and T_3, but the free hormone levels are normal.

Metabolism of Thyroid Hormones

The daily secretion of the normal thyroid gland is ~ 100 nmol of T_4, about 5 nmol of T_3, and less than 5nmol of metabolically inactive reverse T_3 (rT_3) (Fig. 7-18). Most of the plasma pool of T_3 is derived from peripheral metabolism (5'-deiodination) of T_4. T_3 is 3-8 times potent than T_4.

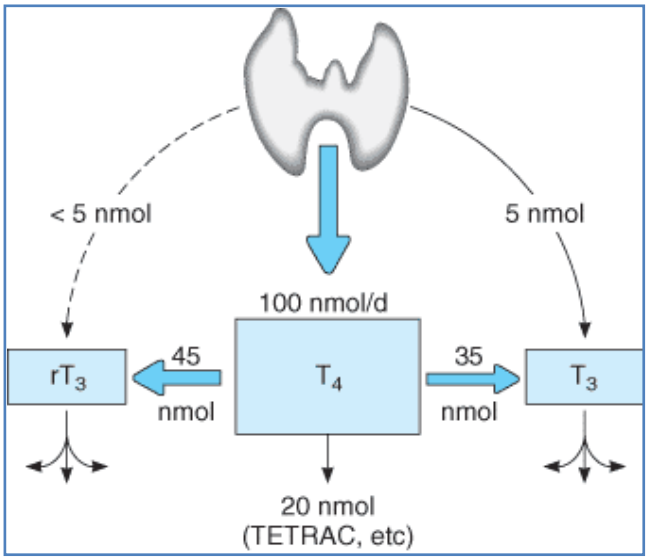


Figure 7-18. Major pathways of thyroxine metabolism in normal adult humans. Rates are expressed in nmol/24 h and are approximations based upon available data. 100 nmol of T_4 is equivalent to approximately 75 µg. (rT_3, reverse T_3; TETRAC, tetraiodothyroacetic acid.)

At least three enzymes catalyze the monodeiodination reactions: type 1 5'-deiodinase; type 5'-deiodinase; and type 3 tyrosyl ring deiodinase, or 5-deiodinase. They differ in tissue localization, substrate specificity, and effect of disease. The properties of these deiodinases are summarized in Table 7-3.

Table 7-3. Iodothyronine Deiodinase Types and Characteristics.

Deiodinase Type	**D1**	**D2**	**D3**
Substrates	$rT_3 > T_4 > T_3$	$T_4 > rT_3$	$T_3 > T_4$
Tissue distribution	Liver, kidney, skeletal muscle, thyroid	Brain, pituitary	Brain, placenta, fetal tissues
Function	Plasma T_3 production	Local T_3 production	T_3 degradation
PTU inhibition (IC50, µM)	5	> 1000	> 1000
Hypothyroidism	Decrease	Increase	Decrease
Hyperthyroidism	Increase	Decrease	Increase

Type 1 5'-deiodinase is the most abundant deiodinase and is found largely in liver and kidney and in lesser quantity in the thyroid gland, skeletal muscle, heart muscle and other tissues. The major function of type 1 5'-diodinace is to provide T_3 to the plasma. It is increased in hyperthyroidism and decreased in hypothyroidism. The enzyme is inhibited by propylthiouracil but not methimazole, which explains why propylthiouracil is more effective than methimazole in reducing T_3 levels in sever hyperthyroidism.

Type 2 5'-deiodinase is found largely in the brain and pituitary gland. It is resistant to polythiouracil but very sensitive to circulating T_4. The major effect of the enzyme is to maintain a constant level of intracellular T_3 in the central nervous system. High levels of serum T_4 reduce type 2 5'-deiodinase, protecting brain cells from excessive T_3. This may be the mechanism whereby the hypothalamus and pituitary monitor the levels of circulating T_4.

Type 3 5-deiodinase, or tyrosyl ring deiodinase, is found in placental chorionic membrane and glial cells in the CNS. It inactivates T_4 by converting it to rT_3 and T_3 to 3,3'-T_2. It is elevated in hyperthyroidism and decreased in hypothyroidism. Then, it may help to protect the fetus and the brain from excess or deficiency of T_4.

Overall, the functions of the deiodinases may be threefold: (1) they may provide a means for local tissue and cellular control of thyroidal activity; (2) they may allow the organism to adapt to changing environmental states such as iodine deficiency or chronic illness; (3) they have an important role in the early development of many vertebrates, including amphibian and mammals.

About 80% of T_4 is metabolized by deiodination, 35% to T_3 and 45% to rT_3 (Fig. 7-18). The remainder is inactivated in the liver or kidney.

Control of Thyroid Function

The growth and function of the thyroid gland and the peripheral effects of thyroid hormones are controlled by at least four mechanisms: (1) the classic hypothalamic pituitary–thyroid axis (Fig. 7-20), in which hypothalamic thyrotropin–releasing hormone (TRH) stimulates the synthesis and release of anterior pituitary thyroid–stimulating hormone (TSH), which in turn stimulates growth and hormone secretion by the thyroid gland; (2) the pituitary and peripheral deiodinases, which modify the effects of T_3 and T_4, (3) autoregulation of hormone synthesis by the thyroid gland itself in relationship to its iodine supply; and (4) stimulation or inhibition of thyroid function by TSH receptor auto antibodies.

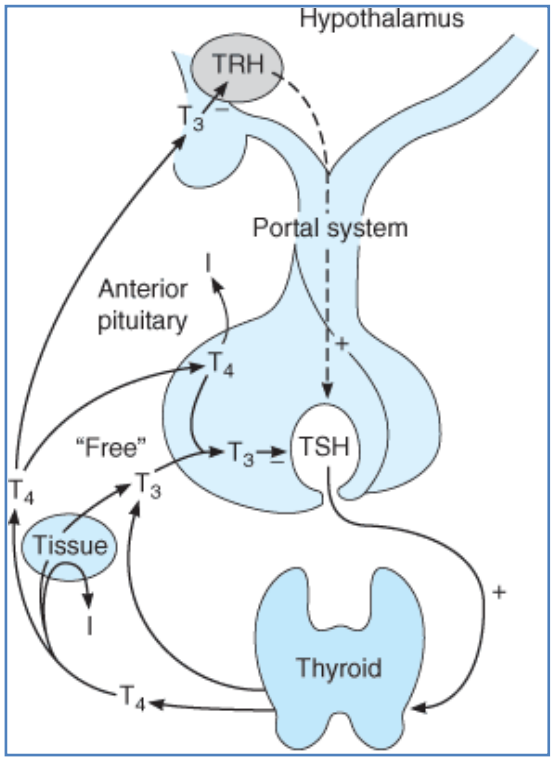


Figure 7-20. The hypothalamic-hypophysial-thyroidal axis. TRH produced in the hypothalamus reaches the thyrotrophs in the anterior pituitary by the hypothalamic-hypophysial-portal system and stimulates the synthesis and release of TSH. In both the hypothalamus and the pituitary, it is primarily T_3 that inhibits TRH and TSH secretion, respectively. T_4 undergoes monodeiodination to T_3 in neural and pituitary as well as in peripheral tissues.

Thyrotropin–Releasing Hormone (TRH)

TRH is a tripeptide synthesized by neurons in the supraoptic and supraventricular nuclei of the hypothalamus (Fig. 7-21). It is stored in the median eminence of the hypothalamus and then transported via the pituitary portal venous system down the pituitary stalk to the anterior pituitary gland. In the anterior pituitary gland, TRH binds to specific membrane receptors on thyrotrophs and prolactin-secreting cells, stimulating synthesis and release of both TSH and prolactin. Thyroid hormones cause a slow depletion of pituitary TRH receptors, diminishing TRH response; estrogen increases TRH receptors, increasing pituitary sensitivity to TRH.

After binding to its receptor on the thyrotroph, TRH activates a G protein, which in turn activates phospholipase C to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5- triphosphate (IP_3). IP_3 stimulates the release of intracellular Ca^{++}, which causes the first burst response of hormone release. Simultaneously, there is generation of 1,2-diacylglycerol, which activates protein kinase C, thought to be responsible for the second and sustained phase of hormone secretion. The increases in intracellular Ca^{++} and in protein Kinase C may be involved in increased transcription of TSH. TRH also stimulates the glycosylation of TSH, which is necessary for full biologic activity of the hormone.

T_3 directly inhibits the transcription of TRH gene and thus the synthesis of TRH in the hypothalamus. Since T_4 is converted to T_3, it is also an effective inhibitor of TRH synthesis and secretion.

Thyrotropin (TSH)

Thyroid–stimulating hormone, or thyrotropin (TSH), is a glycoprotein synthesized and secreted by the thyrotrophs of the anterior pituitary gland. It has a MW of ~ 28,000 and is composed of two noncovalently linked subunits, α and β. The α subunit is common to the two other pituitary glycoproteins, FSH and LH and also to the placental hormone hCG; the β subunit is different for each glycoprotein hormone and confers specific binding properties and biologic activity. Glycosylation takes place in the RER and Golgi of the thyrotrophs. The function of carbohydrate residues added is not entirely clear, but it is likely that they enhance TSH biologic activity and modify its metabolic clearance rate.

TSH is the primary factor controlling thyroid cell growth and thyroid hormone synthesis and secretion. It achieves this effect by binding to a specific TSH receptor (TSH-R) on the thyroid cell membrane and activating both the G-protein-adenylate cyclase–cAMP and the phospholipase C signaling systems. The TSH-R is unique in that it has binding sites not only for TSH but also for TSH receptor–stimulating antibodies, which are found in patients with autoimmune hyperthyroidism (Graves' disease), and also for autoantibodies that bind to the TSH receptors and block the action of TSH, found in patients with severe hypothyroidism due to autoimmune atrophic thyroiditis.

Effects of TSH on the thyroid Cell

TSH rapidly induces pseudopods at the cell-colloid border, accelerating thyroglobulin resorption. Intracellular colloid droplets are formed and lysosomal formation is stimulated, increasing thyroglobulin hydrolysis.

Individual thyroid cell increases in size and vascularity. TSH stimulates all phases of iodide metabolism, from increased iodide uptake and transport to increased iodination of thyroglobulin and increased secretion of thyroid hormones. The increase in cAMP mediates increased iodide transport, while $P1P_2$ hydrolysis and increased intracellular Ca^{++} stimulate the iodination of thyroglobulin.

TSH also increases mRNA for thyroglobulin and peroxidase, with an increase in incorporation of I^- into MIT, DIT, T_3 and T_4; and increases lysosomal activity, with increased secretion of T_4 and T_3 from the gland. There is also increased activity of type 1 5'-deiodinase, conserving intrathyroidal iodine.

TSH also stimulates glucose uptake, O_2 consumption and an increase in glucose oxidation, stimulation of synthesis or purine and pyrimidine precursors, with increased synthesis of DNA and RNA.

Control of Pituitary TSH Secretion

The two major factors controlling the synthesis and release of TSH are the level of intrathyrotroph T_3, which controls mRNA for TSH synthesis and release; and TRH, which controls glycosylation, activation and release of TSH.

TSH synthesis and release are inhibited by high serum levels of T_4 and T_3 (hyperthyroidism) and stimulated by low levels of thyroid hormone (hypothyroidism). In addition, certain drugs and hormones inhibit TSH secretion. These include somatostatin, dopamine, dopamine agonists such as bromocriptine, and glucocorticoids. These drugs suppress serum TSH in contract to hyperthyroidism which turns off TSH secretion entirely.

Thyroidal Autoregulation

Auto regulation may be defined as the capacity of the thyroid gland to modify its function and adapt to changes in the availability of iodine, independent of pituitary TSH. Thus humans can maintain normal thyroid hormone secretion with iodide intake varying from 50 mg to several milligrams per day. The major adaptation to low iodide intake is the preferential synthesis of T_3 rather than T_4, increasing the metabolic effectiveness of the secreted hormone. Iodide excess, on the other hand, inhibits many thyroidal functions, including I^- transport, cAMP formation, H_2O_2 generation, hormone synthesis and secretion, and binding of TSH and TSH-R Ab to the TSH receptor. Some of these effects may be mediated by the formation of intrathyroidal iodinated fatty acids. The ability of the normal thyroid to "escape" from these transient inhibitory effects (wolff–Chaikoff effect) allows the gland to continue to secrete hormone after 10-14 days despite a high dietary iodide intake. This is due to inhibition of H_2O_2 generation by the high intrathyroidal I^- content. Inhibition of the transport of I^- with reduction in intrathyroidal iodide, allows hormonogenesis to proceed.

Autoimmune Regulation

The ability of B lymphocytes to synthesize TSH receptor antibodies that can either block the action of TSH or mimic TSH activity by binding to different areas on the TSH receptor provides a form of thyroid regulation by the immune system.

The action of Thyroid Hormone

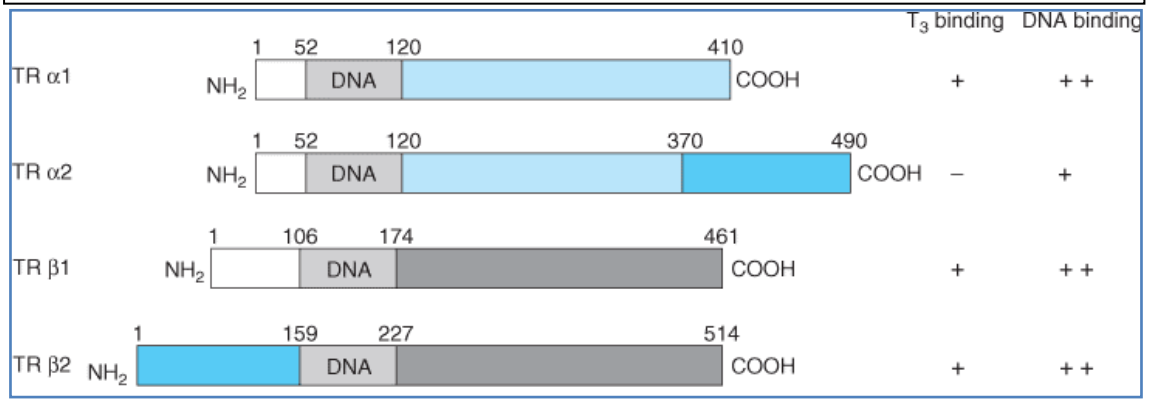
1. Thyroid Hormone Receptor

Thyroid hormones T_3 and T_4, circulate in plasma largely bound to protein but in equilibrium with the free hormone. It is the free hormone that is transported, either by passive diffusion or by specific carriers, through the cell membrane, through the cell cytoplasm, to bind to specific receptors in the nucleus. Within the cell, T_4 in converted to T_3 by 5'-deiodinase. The nuclear receptor for T_3 is one of a family of receptors all similar to the nuclear receptors for glucocorticoids, mineralocorticoids, estrogens, progestins, vitamin D_3 and retinoic acid.

In the human, there are two genes for the thyroid hormone receptor, alpha and beta (TRα and TRβ). Each gene produces at least two products, TRα 1 and 2 and TRβ 1 and 2 (fig. 7-25). Each has three domains: a ligand independent domain at the amino terminal, a centrally located

DNA binding area, and a ligand-binding domain at the carboxyl terminal. $TR\alpha_2$ does not bind T_3 and may actually inhibit T_3 action. The concentration of these receptors in tissue varies with the stage of development and the tissue. For example, the brain contains mostly TRα, the liver mostly TRβ, and cardiac muscle contains both.

Figure 7-25. Deduced protein structure of the thyroid hormone receptor α and β gene products. The receptor protein has three domains: a DNA-binding domain with a high degree of similarity among the different types of receptors, a carboxyl terminal triiodothyronine (T_3) binding domain, and an amino terminal domain that is not required for full function. The numbers above the structures represent amino acid numbers. The properties of the receptors with respect to their ability to bind T_3 and bind to a T_3-response element of DNA are shown on the right. Identical shading of receptor domains indicates identical amino acid sequences. (TR, thyroid hormone receptor.)



The thyroid hormone receptors may bind to the specific thyroid hormone response element (TRE) sites on DNA even in the absence of T_3 (Fig. 7-26) unlike the steroid hormone receptors. The TREs are located near to the promoter where transcription of specific thyroid hormone-responsive genes in initiated. T_3 binding to the receptors results in stimulation – in some cases inhibition – of the transcription of these genes. These receptors often function as heterodimers with other transcription factors such as the retinoid X receptor and the retinoic acid receptor (Fig. 7-26).

2. Physiology Effects of Hormones

The transcriptional effects of T_3 characteristically demonstrate a lag time of hours or days to achieve full effect. These genomic action result in a number of effects including those on tissue growth, brain maturation, and increased heat production and O_2 consumption, which is due in part to increased activity of Na^+-K^+ ATPase and in part to production of increased beta-adrenergic receptors. Some actions of T_3 are not genomic, such as reduction of pituitary type 2 5`-deiodinase and increase in glucose and amino acid transport.

Effects on fetal Development:

The thyroid and the anterior pituitary TSH system begin to function in the human fetus at ~ 11 weeks. The small amount of free hormone from the mother may be important for early fetal brain development. However, after 11 weeks of gestation, the fetus is largely dependent on its own thyroidal secretion. Although some fetal growth occurs in the absence of fetal thyroid hormone secretion, brain development and skeletal maturation are markedly impaired, resulting in cretinism (mental retardation and dwarfism).

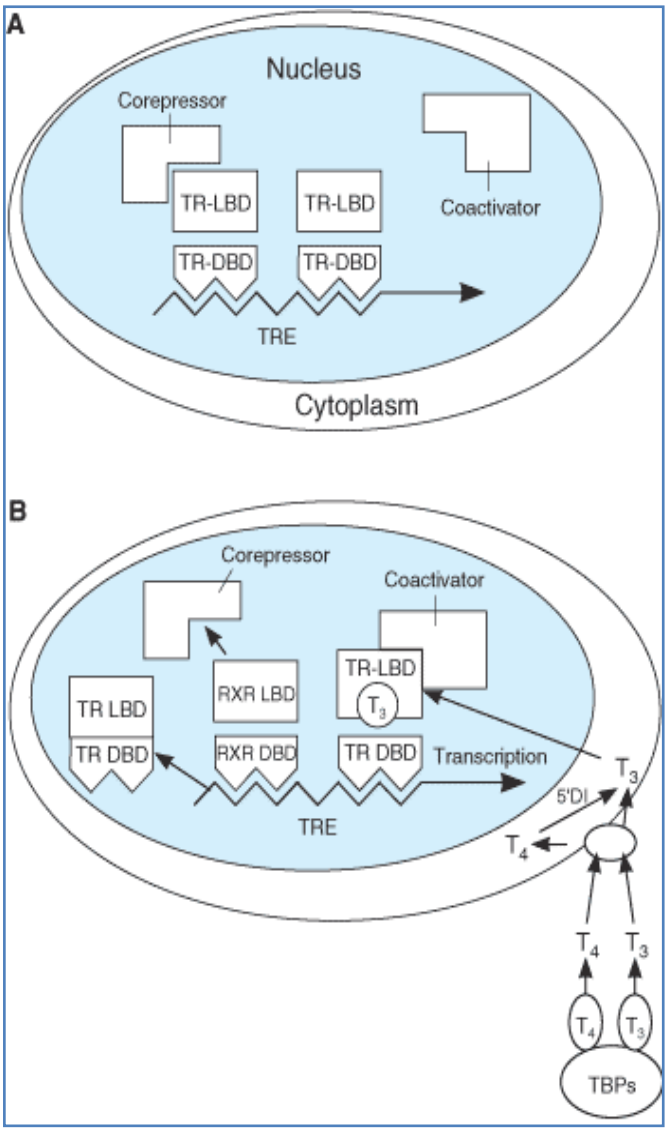


Figure 7-26. Model of the interaction of T_3 with the T_3 receptor. **Panel A, Inactive Phase:** The unliganded T_3 receptor dimer bound to the TRE along with corepressors acts as a suppressor of gene transcription. **Panel B, Active Phase:** T_3 and T_4 circulate bound to thyroid-binding proteins (TBPs). The free hormones are transported into the cell by a specific transport system. Within the cytoplasm, T_4 is converted to T_3 by 5'-deiodinase and T_3 moves into the nucleus. There it binds to the ligand-binding domain of the TR monomer. This promotes disruption of the TR homodimer and heterodimerization with RXR on the TRE, displacement of corepressors, and binding of coactivators. The TR-coactivator complex activates gene transcription, which leads to alteration in protein synthesis and cellular phenotype. TR-LBD, T3 receptor ligand-binding domain; TR-DBD, T_3 receptor DNA-binding domain; RXR-LBD, retinoid X receptor ligand-binding domain; RXR-DBD, retinoid X receptor DNA-binding domain; TRE, thyroid hormone response element; TBPs, thyroxine-binding proteins; T_3, triiodothyronine; T_4, tetraiodothyro-nine, L-thyroxine; 5'DI, 5'-deiodinase.

Effects on O_2 consumption, Heat production and Free Radical Formation:

T_3 increases O_2 consumption and heat production in part by stimulation of Na^+-K^+ ATPase in all tissues except the brain, spleen and testis. This contributes to the increased basal metabolic rate and the increased sensitivity to heat in hyperthyroidism and the converse in hypothyroidism. Thyroid hormones also decrease superoxide dismutase levels, resulting in increased superoxide anion free radical formation. This may contribute to the deleterious effects of chronic hyperthyroidism.

Cardiovascular Effects:

T_3 improve cardiac muscle contractibility. T_3 also increases transcription of Ca^{++} ATPase in the sarcoplasmic reticulum, increasing diastolic tone of the heart; increases β-adrenergic receptors and the concentration of G proteins. This accounts for the increased cardiac output and marked increases in heart rate in hyperthyroidism and the reverse in hypothyroidism.

Hematopoietic Effects:

The increased cellular demand for O_2 in hyperthyroidism leads to increased production of erythropoietin and increased erythropoiesis. Thyroid hormones increase the 2,3-diphosphoglycerate content of erythrocytes, allowing increased O_2 dissociation from hemoglobin and increasing O_2 availability to tissues. The reverse occurs in hypothyroidism.

Gastrointestinal Effects:

Thyroid hormone stimulates gut motility, which can result in increased motility and diarrhea in hyperthyroidism and slowed bowel transit and constipation in hypothyroidism. This may also contribute to the modest weight loss in hyperthyroidism and weight gain in hypothyroidism.

Neuromuscular Effects

Although thyroid hormones stimulate increased synthesis of many structural proteins, in hyperthyroidism there is increased protein turnover and loss of muscle tissue, or myopathy. This may be associated with spontaneous creatinuria. There is also an increase in the speed of muscle contraction and relaxation (hyperflexia of hyperthyroidism). Thyroid hormones are essential for normal development and function of the CNS and failure of fetal thyroid function results in severe mental retardation.

Effects on Lipid and Carbohydrate Metabolism

Hyperthyroidism increases hepatic gluconeogenesis and glycogenolysis as well as intestinal glucose absorption. Cholesterol synthesis and degradation are both increased by thyroid hormones. The latter effect is due largely to an increase in the hepatic LDL receptors, so that cholesterol levels decline with thyroid over activity. Lipolysis is also increased, releasing fatty acids and glycerol. Conversely, cholesterol levels are elevated in hypothyroidism.

Endocrine Effects

Thyroid hormones increase the metabolic turnover of many hormones. Ovulation may be impaired in both hyperthyroidism and hypothyroidism, resulting in infertility.

Thyroid Autoimmunity

Autoimmune mechanisms are involved in the pathogenesis of many thyroid diseases, including the hyperthyroidism, opthalmopathy, and dermopathy associated with Graves' disease; the nontoxic goiter or atrophic hypothyroidism associated with Hashimoto's thyroiditis; and postpartum hyperthyroidism or hypothyroidism.

There are three major thyroidal autoantigens: Thyroglobulin (Tg), thyroperoxidase (TPO) and the TSH receptor (TSH-R).

Autoantibodies to these antigens are useful as markers for the presence of autoimmune thyroid disease. Thyroid cells have the capacity to ingest antigen (e.g. HLA–DR4) to present these antigens to T lymphocytes. Whereas the presence of both the antigen and the class II molecule may be required for autoimmune thyroid disease to develop, other unknown factors also are critical. Both genetic and environmental factors are now known to be associated with autoimmune thyroid disease.

Genetic factors play a large role in the autoimmune process. HLA typing in patients with Graves' disease reveals high incidence of HLA-B8 and HLA-DR3 in Caucasians, HLA-Bw46 and HLA-B5 in Chinese…

Environmental factors may also play a role in the pathogenesis of autoimmune thyroid disease. Viruses infecting human thyroid cell cultures induce the expression of HLA-DR4 or the follicle cell surface. The increased incidence of autoimmune thyroid disease in post pubertal and premenopausal women, as well as the occurrence of postpartum thyroiditis, implies a role for sex hormones in the pathogenesis of autoimmune thyroid disease. Antibodies against Y. *enterocolitica* could cross-react with the TSH-R on the thyroid cell membrane and trigger an episode of Graves' disease. A high iodine intake may result in more highly iodinated thyroglobulin, which is more immunogenic and would favor the development of autoimmune thyroid disease.

Tests of Thyroid Function

The function of the thyroid gland may be evaluated in many different ways:

1. Tests of thyroid hormones in blood.
2. Evaluation of the hypothalamic-pituitary-thyroid axis.
3. Assessment of iodine metabolism.
4. Estimation of gland size.
5. Thyroid biopsy.
6. Observation of the effects of thyroid hormones on peripheral tissues.
7. Measurement of thyroid autoantibodies.

Tests of thyroid hormones in blood

The total serum T_4 and total serum T_3 are measured by radioimmunoassay or immunofluorescent assay. If the concentration of the serum thyroid hormone binding proteins is normal, these measurements provide a reasonable reliable index of thyroid gland activity. However, changes in serum concentration of thyroid binding proteins or the presence of drugs that modify the binding of T_4 or T_3 to TBP will modify the total T_4 and T_3 but not the amount of free hormone. Thus, further tests must be performed to assess the free hormone level that determines biological activity (Fig. 7-15).

Serum free thyroxine (FT_4) can be estimated using the free thyroxine index (FT_4I). This is the product of the total T_4 multiplied by the percentage of free T_4 as estimated by the amount of T_4 which binds to resin or charcoal added to the system. Note that FT_4 does not measure T_3, so that patients receiving high oral doses of T_3 or with T_3 hyperthyroidism (early Graves' disease or toxic nodular goiter), FT_4 may be low despite the hyperthyroid state (T_3 toxicosis).
Total T_3 can be measured in serum by immunoassay with specific T_3 antisera. The normal range in adults is 70-132 ng/dL (1.1-2 nmol/L). The measurement of total T_3 is most useful in the differential diagnosis of hyperthyroidism, because T_3 is preferentially secreted in early Graves' disease or toxic nodular goiter.

Reverse T_3 (rT_3) can be measured by radioimmunoassay and is used to differentiate chronic illness from hypothyroidism because rT_3 levels are elevated in chronic illness and low in hypothyroidism. However, this differential diagnosis can be made by determination of TSH, so it is rarely necessary to measure rT_3.

Thyroglobulin (Tg) can be measured in serum by double antibody radioimmunoassay and is elevated in situation of thyroid overactivity such as Graves' disease and toxic multinodular goiter; in chronic thyroiditis, where it is released as a consequence of tissue damage, and in patients with large goiters.

Evaluation of the Hypothalamic-Pituitary-Thyroid Axis

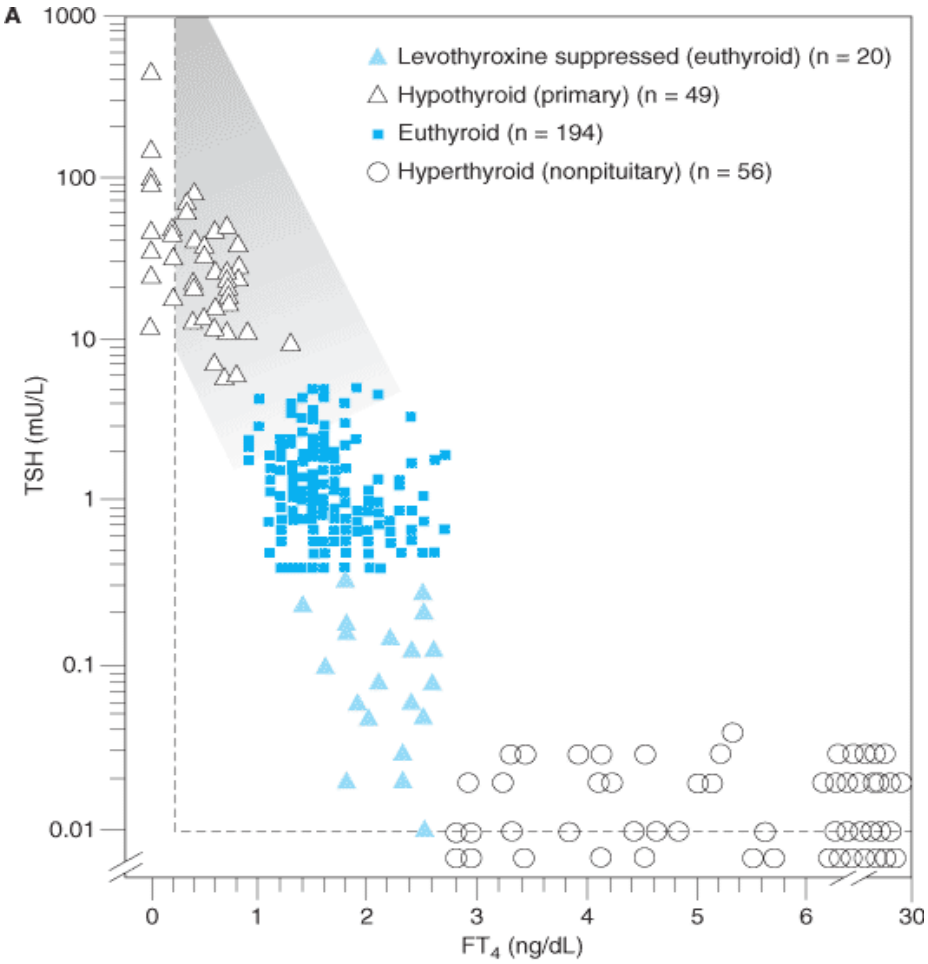


Figure 7-28. Relationship between serum free thyroxine by dialysis (FT_4) ng/dL and log_{10}TSH in euthyroid, hyperthyroid, hypothyroid, and T_4-suppressed euthyroid individuals. Note that for each unit change in T_4 there is a logarithmic change in TSH.

The level of FT_4 is inversely related to the logarithm of the TSH concentration (Fig. 7-28). Serum TSH below 0.1 µU/mL and an elevated FT_4 or FT_4I is indicative of hyperthyroidism. This may be due to Graves' disease, toxic nodular goiter, or high-dose thyroxine therapy. In the rare case of hyperthyroidism due to a TSH-secreting pituitary tumor, FT_4I or FT_4 will be elevated and TSH will not be suppressed but will actually be normal or slightly elevated. An elevated TSH (> 10 µU/mL) and a low FT_4 or FT_4I is diagnostic of hypothyroidism. In patients with hypothyroidism due to a pituitary or hypothalamic tumor (central hypothyroidism), FT_4I or FT_4 will be low and TSH will not be elevated. This diagnosis can be confirmed by demonstrating the failure of serum TSH to increase following an injection of TRH.

Serum TSH levels reflect the anterior pituitary gland sensing the level of circulating FT_4. High FT_4 levels suppress TSH and low FT_4 levels increase TSH release. Thus, the ultrasensitive

measurement of TSH has become the most sensitive, most convenient, and most specific test for the diagnosis of both hyperthyroidism and hypothyroidism.

Disorders of the Thyroid

Patients with thyroid disease will usually complain of:

1. Thyroid enlargement, which may be diffuse or nodular;
2. Symptoms of thyroid deficiency, or hypothyroidism;
3. Symptoms of thyroid hormone excess, or hyperthyroidism, or;
4. Complications of a specific form of hyperthyroidism –Graves' disease- which may present with striking prominence of the eyes (exophthalmos).

Hypothyroidism

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones, which in turn results in a generalized slowing down of metabolic processes. Hypothyroidism in infants and children results in marked slowing of growth and development, with serious permanent consequences including mental retardation. Hypothyroidism with onset in adulthood causes a generalized slowing down of the organism, with deposition of glycosaminoglycans in intracellular spaces, particularly in skin and muscle, producing the clinical picture of **myxedema.** The symptoms of hypothyroidism in adults are largely reversible with therapy.

Etiology

Hypothyroidism may be classified as (1) primary (thyroid failure), (2) secondary (due to pituitary TSH deficit) or (3) tertiary (due to hypothalamic deficiency of TRH) or may be due to (4) peripheral resistance to the action of thyroid hormones. Hypothyroidism can also be classified as goitrous or nongiotrous, but this classification is probably unsatisfactory, since Hashimoto's thyroiditis (autoimmune thyroiditis) may produce hypothyroidism with or without goiter (Table 7-7).

Hashimoto's thyroiditis is probably the most common cause of hypothyroidism. In younger patients, it is more likely to be associated with goiter; in older patients, the gland may be totally destroyed by the immunologic process. Similarly, the end stage of Graves' disease may be hypothyroidism. This is accelerated by destructive therapy such as administration of radioactive iodine or subtotal thyroidectomy. Thyroid glands involved in autoimmune disease are particularly susceptible to excessive iodide intake. The large amount of iodide blocks thyroid hormone synthesis, producing hypothyroidism with goiter in the patients with an abnormal thyroid gland; the normal gland usually "escapes" from the iodide block. Iodide deficiency causes hypothyroidism in developing countries.

Certain drugs can block hormone synthesis and produce hypothyroidism with goiter such as lithium carbonate, used for the treatment of manic-depressing states. Chronic therapy with the antithyroid drugs propylthiouracil and methimazole will do the same. Inborn errors of thyroid hormone synthesis result in severe hypothyroidism if the block in hormone synthesis is complete or mild hypothyroidism if the block is partial.

Table 7–7. Etiology of Hypothyroidism.
Primary: 1. Hashimoto's thyroiditis: a. With goiter. b. "Idiopathic" thyroid atrophy, presumably end-stage autoimmune thyroid disease, following either Hashimoto's thyroiditis or Graves' disease. c. Neonatal hypothyroidism due to placental transmission of TSH-R blocking antibodies.
2. Radioactive iodine therapy for Graves' disease.
3. Subtotal thyroidectomy for Graves' disease, nodular goiter, or thyroid cancer.
4. Excessive iodide intake (kelp, radiocontrast dyes).
5. Subacute thyroiditis (usually transient).
6. Iodide deficiency (rare in North America)
7. Inborn errors of thyroid hormone synthesis.
8. Drugs a. Lithium b. Interferon-alfa c. Amiodarone
Secondary: Hypopituitarism due to pituitary adenoma, pituitary ablative therapy, or pituitary destruction.
Tertiary: Hypothalamic dysfunction (rare).
Peripheral resistance to the action of thyroid hormone.

Pathogenesis

Thyroid hormone deficiency affects every tissue in the body, so that the symptoms are multiple. Pathologically, the most characteristic finding is the accumulation of glycosaminoglycans – mostly hyaluronic acid – in interstitial tissues. Accumulation of this hydrophilic substance, and increased capillary permeability to albumin, account for the interstitial edema that is particularly evident in the skin, heart muscle, and striated muscle. The accumulation is due not to excessive synthesis but to decreased destruction of glycosaminoglycans.

a. Newborn Infants (Cretinism):

Neonatal hypothyroidism may result from failure of the thyroid to descend during embryonic development, which results in an "ectopic thyroid" gland that functions poorly or placental transfer to the embryo of TSH-R Ab [block] from mother with Hashimoto's thyroiditis.

Inherited defects in thyroid hormone biosynthesis induce neonatal hypothyroidism and goiter. Rare causes of neonatal hypothyroidism include administration during pregnancy of iodides, anti thyroidal drugs, or radioactive iodine for thyrotoxicosis.

The symptoms of hypothyroidism in newborns include respiratory difficulty, jaundice, umbilical hernia, and marked retardation of bone maturation. The introduction of routine screening of newborns for TSH or T_4 has been a major achievement in the early diagnosis of neonatal hypothyroidism. Note that euthyroid infants born to hypothyroid mother inadequately treated during pregnancy may have symptoms of mild mental retardation later in life – emphasizing the importance of maintaining the mother in a euthyroid state throughout pregnancy.

b. Children

Hypothyroidism in children is characterized by retarded growth and evidence of mental retardation. In the adolescent, precocious puberty may occur in addition to short stature as a result of binding of TSH to FSH receptors.

c. Adult

In adult, the common features of hypothyroidism include easy fatigability, coldness, weight gain, constipation, menstrual irregularities, and muscle cramps. Physical findings include a cool, rough dry skin, puffy face and hands and slow reflexes.

1. Cardiovascular Signs:

Hypothyroidism is manifested by impaired muscular contraction, bradycardia, and diminished cardiac output. Cardiac enlargement may occur. There is controversy about whether myxedema induced coronary artery disease, but coronary artery disease is more common in patients with hypothyroidism, particularly in older patients.

2. Pulmonary Function

In the adult, hypothyroidism is characterized by shallow, slow respiration and impaired ventilatory responses to hypoxia. Respiratory failure is a major problem in patients with myxedema coma.

3. Intestinal Peristalsis

Peristalsis is markedly slowed resulting in chronic constipation and occasionally severe fecal impaction.

4. Renal Function

Renal function is impaired with decreased glomerular filtration rate (GFR) and impaired ability to excrete a water load. This predisposes the myxedematous patient to water intoxication if excessive free water is administered.

5. Anemia

There are at least four mechanisms that may contribute to anemia in patients with hypothyroidism:

a. Impaired hemoglobin synthesis as a result of thyroxine deficiency;
b. Iron deficiency from increased iron loss as well as impaired intestinal absorption of iron;
c. Folate deficiency from impaired intestinal absorption of folic acid; and
d. Pernicious anemia, with vitamin B_{12}-deficient megaloblastic anemia.

6. Neuromuscular System

Severe muscle cramps, paresthesias, and muscle weakness.

7. Central Nervous System

Symptoms include chronic fatigue, and inability to concentrate. Hypothyroidism impairs the conversion of estrogen precursors to estrogens, resulting in altered FSH and LH secretion and in anovulatory cycles and infertility. This may be associated with severe menorrhagia. Patients with myxedema can be severely depressed or even extremely agitated ("myxedema madness").

Complications

A. Myxedema Coma

Myxedema coma is the end stage of untreated hypothyroidism. It is characterized by progressive weakness, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock and death. The pathophysiology of myxedema coma involves three major aspects: (1) CO_2 retention and hypoxia, (2) fluid and electrolyte imbalance, and (3) hypothermia.

B. Myxedema and Heart Disease

Patients with myxedema and coronary artery disease can be treated surgically first, and more rapid thyroxine replacement therapy will then be tolerated (levothyroxine replacement before surgery is frequently associated with exacerbation of angina, heart failure, or myocardial infarction).

C. Hypothyroidism and Neuropsychiatric Disease

Hypothyroidism is often associated with depression, which may be quite severe, confused, paranoid or even manic “myxedema madness”.

Treatment

Hypothyroidism is treated with levothyroxine (T_4), which is converted to T_3, so that both hormones become available even though only one is administered. T_3 is unsatisfactory because of its rapid absorption, short-half-life, and transient effects. The half-life of T_4 is ~ 7 days. Myxedema coma is an acute medical emergency and should be treated in the intensive care unit.

Hyperthyroidism and Thyrotoxicosis

Thyrotoxicosis is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone. In most instances, thyrotoxicosis may is due to hyperactivity of the thyroid gland, or hyperthyroidism. Occasionally, thyrotoxicosis may be due to other causes such as excessive ingestion of thyroid hormone or excessive secretion of thyroid hormone from ectopic site.

Diffuse Toxic Goiter (Graves' Disease)

Graves' disease is the most common form of thyrotoxicosis and may occur at any age, more commonly in females than in males. The syndrome consists of one or more of the following features: (1) thyrotoxicosis, (2) goiter, (3) opthalmopathy (exophthalmos), and (4) dermopathy (peritibial myxedema).

Etiology

Graves' disease is currently viewed as an autoimmune disease of unknown cause. There is a strong familial predisposition. Females are involved about five times more commonly then males.

Pathogenesis

In Graves' disease T lymphocytes become sensitized to antigens within the thyroid gland and stimulate B lymphocytes to synthesize antibodies to these antigens. One such antibody is directed against the TSH receptor site in the thyroid cell membrane and has the capacity to stimulate the thyroid cell to increase growth and function (TSH-R Ab [stim]). Some factors that may incite the immune response of Graves' disease are:

1. pregnancy, particularly the postpartum period;
2. iodide excess;
3. lithium therapy;
4. viral or bacterial infections; and
5. glucocorticoid withdrawal.

The pathogenenisis of opthalmopathy may involve cytotoxic lymphocytes (killer cells) and cytotoxic antibodies sensitized to a common antigen such as the TSH-R found in orbital fibroblasts, orbital muscles, and thyroid tissue. Cytokines from these sensitized lymphocytes would cause inflammation of orbital fibroblasts and orbital myositis, resulting in swollen orbital muscles, proptosis of the globes as well as redness, congestion and conjuctival and periorbital edema.

The pathogenesis of thyroid dermopathy (peritibial myxedema) may also involve lymphocyte cytokine stimulation of fibroblasts in these locations.

Many symptoms of thyrotoxicosis suggest of catecholamine excess, including tachycardia, tremor, sweating, and stare. Circulating levels of epinephrine are normal; the hyperreactivity appears to be due to a thyroid-hormone-mediated increase in cardiac catecholamine receptors.

In younger individuals, common manifestations include palpitations, nervousness, easy fatigability, diarrhea, excessive sweating intolerance to heat, and preference for cold. There is often marked weight loss without loss of appetite. Thyroid enlargement, thyrotoxic eye signs, and mild tachycardia commonly occur. Muscle weakness and loss of muscle mass may be so severe that the patient cannot rise from a chair without assistance. In children, rapid growth with accelerated bone maturation occurs. In patients over age 60, cardiovascular and myopathic manifestations predominate.

Thyroid Hormone Resistance Syndromes

Some forms of resistance to thyroid hormones have been reported :(1) generalized resistance to thyroid hormones, (2) selective pituitary resistance to thyroid hormones, and possibly (3) a selective peripheral resistance to thyroid hormone.

Generalized resistance to thyroid hormones is a familial syndrome with abnormally high thyroid hormone levels with normal FSH. This is due to a mutation of human thyroid receptor β-gene, which produces a defective receptor that fails to bind T_3 but retains the ability to bind to DNA. In most patients with generalized resistance to thyroid hormones, the increased levels of T_3 and T_4 will compensate in part of the receptor defect.

In selective pituitary resistance to thyroid hormones, serum T_3 and T_4 levels are elevated with normal or elevated levels of serum TSH. In this syndrome, T_3 receptors in peripheral tissues are normal, but there is a failure of T_3 to inhibit pituitary TSH secretion. This syndrome may be

due in part to some abnormality in pituitary type 2 5'-deiodinace with failure to convert intrapituitary T_4 to T_3. A case of suspected selective peripheral resistance to T_3 has been reported.

Nontoxic Goiter

Nontoxic goiter usually represents enlargement of the thyroid gland from TSH stimulation, which results from inadequate thyroid hormone synthesis. Iodine deficiency was the most common cause of nontoxic goiter. The most common cause of thyroid enlargement in developed countries is chronic thyroiditis (Hashimoto's thyroiditis). Nontoxic goiter may be due to impaired hormone synthesis. This results in TSH release and goiter formation.

Thyroiditis

1. **Subacute Thyroiditis**:

It is an acute inflammatory disorder of the thyroid gland most likely due to viral infection. A number of viruses, including mumps virus and adenoviruses have been implicated. Pathologic examination reveals moderate thyroid enlargement and a mild inflammatory reaction.

2. **Chronic Thyroiditis**:

Chronic thyroiditis (Hashimoto's thyroiditis, lymphocytic thyroiditis) is probably the most common cause of hypothyroidism and goiter. It is certainly the major cause of goiter in children and young adults and is probably the major cause of "idiopathic myxedema" which represents an end stage of Hashimoto's thyroiditis, with total destruction of the gland.

Hashimoto's thyroiditis is thought to be an immunologic disorder in which lymphocytes become sensitized to thyroid antigens and autoantibodies are formed that react with these antigens (thyroglobulin, thyroperoxidase, and TSH receptor inducing TSH-R blocking antibody).