The Thyroid Gland 9.3

Learning Objectives

- Indicate the anatomic location of the thyroid gland
- Identify in a histological drawing: thyroid follicle, colloid, parafollicular cell, and identify the state of the gland (normal, stimulated, unstimulated)
- Recognize the chemical structures of T3 and T4
- Describe the mechanism of iodine uptake by the thyroid gland
- List the steps in the synthesis of T4
- Define monoiodotyrosine (MIT) and diiodotyrosine (DIT)
- List the major signals for release of TRH from the hypothalamus
- List the major signals for release of TSH from thyrotrope cells in the anterior pituitary
- Draw appropriate feedback loops for thyroid gland status for the following conditions: normal, central hypothyroidism, iodine deficiency, and thyroid defect hypothyroidism
- Describe T4 and T3 transport in blood
- Describe the major mechanism of T3 action
- Describe the consequence of hypothyroidism in children
- Describe the consequence of hypothyroidism in adults
- Discuss the basis for goiter formation
- Describe the suspected cause of Graves' disease—hyperthyroidism in adults

THE THYROID GLAND IS ONE OF THE LARGEST ENDROCRINE GLANDS

The **thyroid gland** is located in the neck just below the cricoid cartilage (Figure 9.3.1). It consists of two lobes separated by a narrow **isthmus** and is covered by two layers of connective tissue that form its capsule. Normal thyroid glands weigh 25–40 g, but size varies with age, reproductive state, and diet. Its rich blood supply, 4–6 mL min^{-1} g^{-1}, is one of the highest in the body. Two pairs of parathyroid glands are embedded within the thyroid. These glands secrete parathyroid hormone (PTH) that helps regulate plasma [Ca^{2+}] and [H_2 PO_4^-]. PTH will be discussed separately.

THE THYROID GLAND CONSISTS OF THOUSANDS OF *FOLLICLES* THAT STORE *THYROGLOBULIN*

The thyroid gland is made up of thousands of spherical or ovate **follicles**, as shown in Figure 9.3.2. Secretory epithelial cells line the follicles, and the follicle contains a homogeneous, gelatinous **colloid**. The epithelial cells' appearance correlates with their function: inactive thyroid consists of low cuboidal or squamous epithelium; active thyroid consists of columnar epithelial cells with basilar infoldings and numerous apical microvilli (see Figure 9.3.3). Interspersed among the follicles are **parafollicular cells** or **C cells**. These cells secrete another hormone, **calcitonin**, that helps regulate bone resorption and plasma [Ca^{2+}] homeostasis. This hormone is unrelated to the principal hormones of the follicular cells.

THE THYROID FOLLICLE SECRETES *THYROXINE* AND *TRIIODOTHYRONINE*

Upon stimulation, the thyroid follicle secretes thyroxine and triiodothyronine. The chemical structures of these hormones are shown in Figure 9.3.4. Both are iodinated derivatives of the amino acid tyrosine. Because thyroxine contains four iodine atoms per molecule, it is referred to as T4. Triiodothyronine has only three iodine atoms, lacking the second iodine at the 5′ position on the phenyl ring, and it is abbreviated as T3. These hormones are incorporated as part of **thyroglobulin**, the main constituent of the colloid.

FOLLICULAR CELLS SECRETE THYROGLOBULIN PRECURSOR INTO THE FOLLICLE

Follicular cells secrete a glycosylated, 300 kDa thyroglobulin precursor into the follicle that forms a 660-kDa dimer linked by disulfide bonds. Either during its secretion into the follicle or soon after, thyroglobulin is iodinated to form **monoiodotyrosine** (MIT) and **diiodotyrosine** (DIT). Figure 9.3.5 illustrates the cellular processes of synthesis, storage, and secretion of thyroxine.

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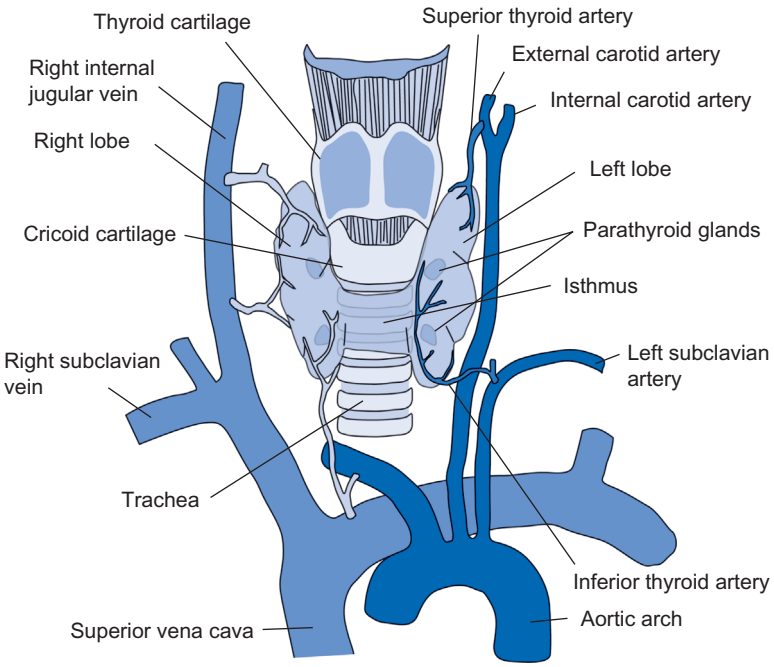

FIGURE 9.3.1 Anatomical position of the thyroid gland. The gland consists of two lobes that are closely affixed to the lateral and anterior aspects of the trachea near the cricoid cartilage. The gland receives rich blood flow through the superior thyroid artery originating from the external carotid artery, and the inferior thyroid artery originating from the left subclavian artery. Blood drains the gland into the superior, middle, and inferior thyroid veins that drain into the internal jugular and innominate veins. The parathyroid glands constitute a separate endocrine function and are considered separately. The parathyroid glands consist of a pair of glands embedded in each lobe of the thyroid gland.

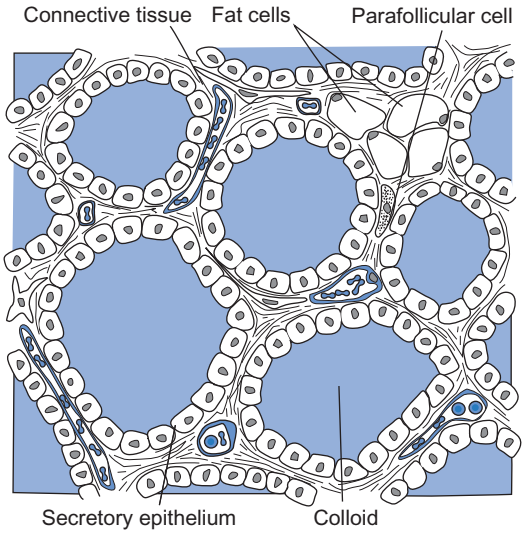

FIGURE 9.3.2 Histological appearance of a section of the thyroid gland. The gland is filled with follicles consisting of an internal colloid surrounded by a single layer of secretory epithelium. Interspersed among the follicles are connective tissue, including fibroblasts and fat cells, and special cells called parafollicular cells that secrete another hormone, calcitonin, that is involved in plasma [Ca^{2+}] regulation. Calcitonin is unrelated to the hormones produced by the follicular cells.

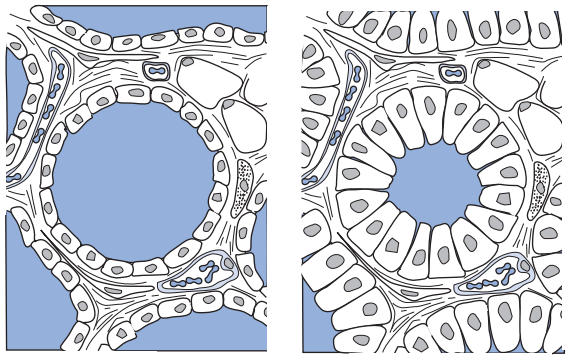

FIGURE 9.3.3 Histological appearance of the thyroid under different physiological states. In the unstimulated state, the cells appear as low cuboidal epithelial cells with abundant colloid. Highly stimulated thyroid follicles have columnar epithelium and their colloid becomes depleted.

SYNTHESIS OF THYROXINE REQUIRES FOUR STEPS

1. Accumulation of iodine
2. Oxidation of I^- to I^0
3. Organification
4. Coupling.

Thyroid secretory cells actively pump I into the cytoplasm through a **2Na:I symport (NIS)** located on the basolateral membrane. The uphill transport of I^- derives its energy from the Na^+ gradient that is maintained by the Na^+–K^+-ATPase. The human NIS gene codes for a protein of 643 amino acids. NIS can concentrate I^- some 25-fold over that in plasma. A second carrier, **pendrin**, carries I^- across the apical membrane.

Thyroid peroxidase on the apical membrane of follicular cells **oxidizes I^- to I^0**. Iodine in this state spontaneously displaces H on the phenyl group of tyrosine residues. The iodination reaction itself is not catalyzed. The process of adding iodine to thyroglobulin is called **organification**. The products of the reaction, MIT and DIT, remain attached to the peptide chain of thyroglobulin.

The final stage in synthesis of the storage form of T4 and T3 is the **coupling** of two molecules of DIT to form

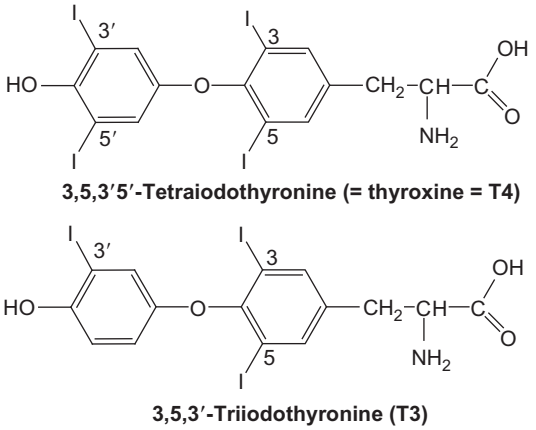

FIGURE 9.3.4 Chemical structures of thyroxine (T4) and triiodothyronine (T3).

T4 or the coupling of one molecule of MIT to DIT to form T3. The exact chemical mechanism by which coupling occurs is not known, but it involves thyroid peroxidase. After coupling, the T3 or T4 remain attached to thyroglobulin's peptide chain. Some of the MIT and DIT remain as MIT or DIT attached to thyroglobulin.

FOLLICULAR CELLS PROTEOLYZE THYROGLOBULIN TO RELEASE T4 AND T3

Thyroid stimulating hormone, or **TSH**, is secreted from the anterior pituitary and acutely stimulates the thyroid follicular cells to extend long strands called **pseudopodia** to surround chunks of colloid and take them into the cell in endocytotic vesicles. These fuse with lysosomes, whose enzymes proteolyze the thyroglobulin and release T4 and T3 that were bound to thyroglobulin's peptide backbone. MIT and DIT are also released. Only T4 and T3 are released into the bloodstream, in the ratio of about 20:1 of T4 and T3, respectively.

The thyroid follicular cells have no mechanism for making T3 or T4 from MIT and DIT in its cytoplasm. **Thyroid deiodinase** located on the endoplasmic reticulum removes iodine from MIT and DIT. The iodine released in this process is recycled into thyroglobulin. Two-thirds of the iodine that gets incorporated into thyroglobulin originates from iodine recycled from MIT and DIT rather than freshly accumulated iodine that enters the cell through the sodium–iodine symport (NIS).

TSH REGULATES STATE OF THE THYROID GLAND

TSH is an N-linked glycoprotein of 28 kDa that is synthesized, stored, and released in basophilic cells, called thyrotrophs, of the anterior pituitary. TSH is also called **thyrotropin** because it is a "trophic" hormone, derived from the Greek "trophos," meaning "to nourish." Anterior pituitary trophic hormones increase the size of their target tissue. Like the other pituitary glycoproteins, FSH, LH, and HCG (human chorionic gonadotrophin), TSH consists of an α and β chain that are not covalently linked. The α subunits of FSH, LH, HCG, and TSH are identical, whereas the β chains confer biological specificity.

TSH binds to specific G_s-coupled receptors on the basolateral membrane of thyroid follicle secretory cells. These receptors link to phosphorylation of cell proteins that regulate thyroid cell metabolism and T3 and T4 synthesis. The short-term effect of TSH on the thyroid is the release of T3 and T4 from already synthesized colloid material. Long-term exposure to TSH increases the size of the thyroid gland by increasing the number of follicular secretory cells (**hyperplasia**) and increasing the size of the cells (**hypertrophy**).

THE HYPOTHALAMUS PARTLY CONTROLS TSH RELEASE

Neurons in the **paraventricular nucleus** of the **hypothalamus** secrete **thyrotropin releasing hormone (TRH)**, a tripeptide, into the portal blood that travels from the hypothalamus down to the anterior pituitary. In the anterior pituitary, TRH binds to G_q-coupled receptors on the surfaces of thyrotrophs to increase release of TSH. The paraventricular nucleus that produces TRH receives inputs from a variety of sources within the brain (see Figure 9.3.6).

T4 AND T3 INHIBIT SECRETION OF TSH

T3 and T4 inhibit TSH secretion and synthesis and decrease the sensitivity of the thyrotrophs to TRH. The effect of T4 and T3 is mediated by T3, as it is in all target tissues, through effects on gene transcription. T3 binds to a thyroid hormone receptor (TR) which then binds to the thyroid hormone response element on the DNA (TRE). These modify genetic expression in the thyrotrophs. T3 decreases the expression of the genes for TSH and for the TRH receptor on the cell membrane. In this way, T3 decreases the release of TSH, completing a negative feedback loop.

ALMOST ALL CIRCULATING T4 AND T3 ARE BOUND TO PLASMA PROTEINS

T4 and T3 are lipophilic and bind to hydrophobic or lipophilic domains of circulating proteins:

- eighty percent to thyroxine-binding globulin (TBG);
- fifteen percent to thyroxine-binding prealbumin;
- five percent to albumin.

These proteins are large enough that they are not filtered by the kidney, and they cannot escape the capillaries to enter target cells. Only 0.03% of the T4 and 0.3% of T3 are free to cross the capillaries and enter cells. This small fraction of the total circulating thyroxine is the biologically active fraction.

TBG is a glycoprotein that is made in the liver and binds one T4 or T3 molecule. Pregnancy and estrogen therapy increase plasma levels of TBG; chronic liver disease such as **cirrhosis** decreases TBG because the rate of

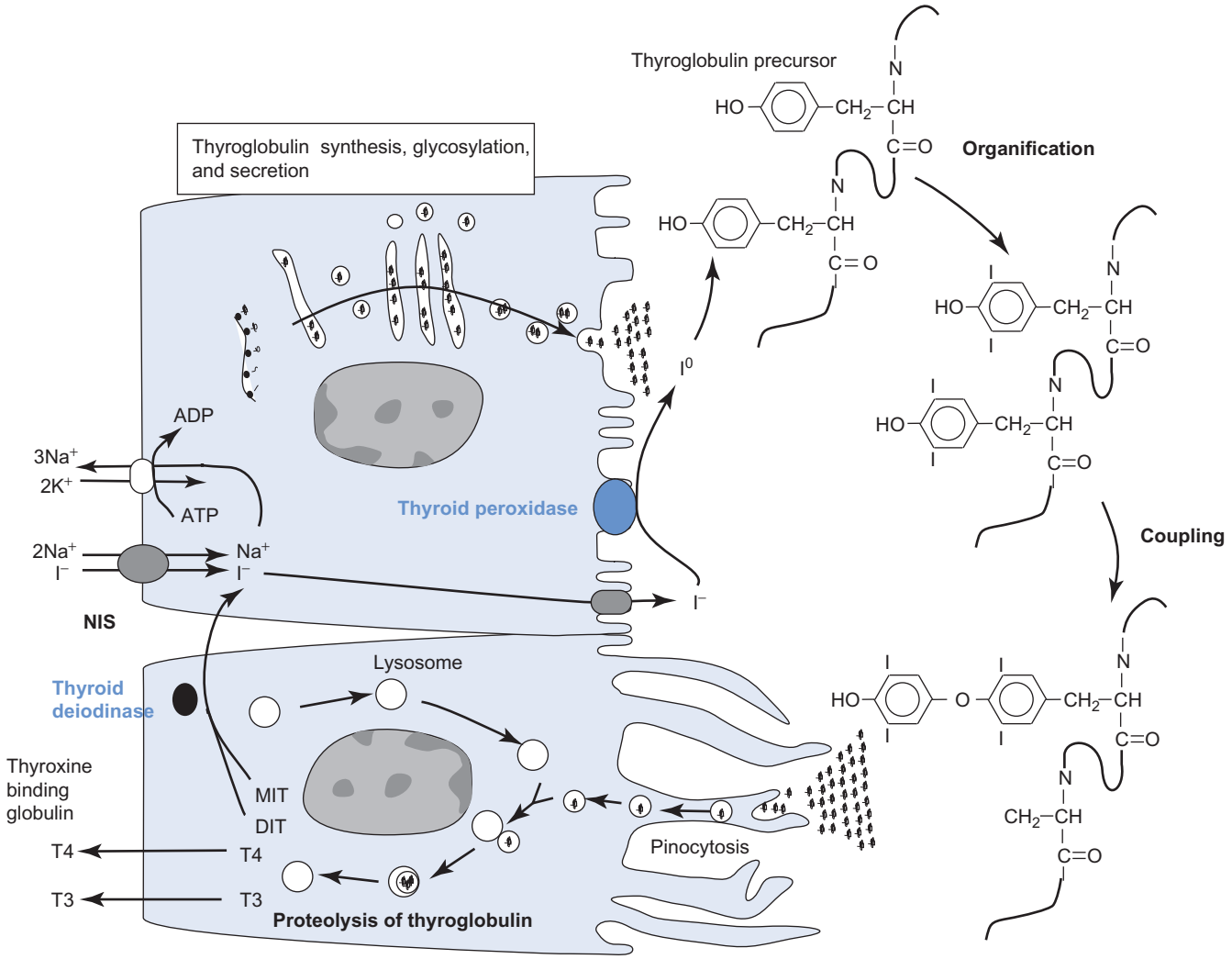

FIGURE 9.3.5 Cellular processes involved in synthesis, storage, and secretion of thyroxine. Thyroglobulin precursor is made on polysomes in the cell, enters the ER, and is transferred to the Golgi apparatus where it is glycosylated and packaged into secretory vesicles that carry the precursor to the apical membrane and secrete it into the follicle. During or soon after exocytosis into the follicle, it is iodinated. The iodine originates from dietary iodine that is absorbed by the gastrointestinal tract. It is actively pumped into the secretory cells by secondary active transport using a Na^+–I^- symport (NIS) on the basolateral membrane of the cell. Iodine is then transported into the follicle, where thyroid peroxidase on the apical membrane oxidizes the iodine. The iodine chemically incorporates itself into tyrosine residues on the thyroglobulin precursor, forming MIT and DIT. In an incompletely understood reaction, thyroid peroxidase helps couple two DITs to form T4 coupled to thyroglobulin, or one MIT and one DIT to form T3. When the cell is stimulated, pseudopodia engulf chunks of the follicle contents, which migrate in endocytotic vesicles toward the base of the cell where they fuse with lysosomes migrating to meet them. The proteases within the lysosomes completely degrade the thyroglobulin, releasing T4 and T3 that are subsequently secreted from the cell into the blood. Thyroid deiodinase liberates iodine from MIT and DIT produced from the proteolysis of thyroglobulin, and the iodine is recycled back into thyroglobulin.

synthesis is decreased; chronic kidney disease such as the **nephrotic syndrome** decreases TBG because it is lost in the urine.

THE TISSUES METABOLIZE T4 TO T3 AND rT3; T3 IS THE ACTIVE METABOLITE

LIVER AND KIDNEY POSSESS 5′ DEIODINASE TYPE I THAT CONVERTS T4 TO T3 AND rT3

The thyroid gland secretes about 80–100 μg of T4 each day. This is the main circulating form of the hormone, with plasma concentrations of about 8 μg dL^{-1}. Injected radioactively labeled T4 has a half-life of about 6 days. T4 is deiodinated by the enzyme **deiodinase Type I**, which is particularly rich in liver and kidney. This enzyme removes iodine at either the outer ring 5′ position to form T3 or at the inner ring 5 position to form reverse T3 (rT3) (Figure 9.3.7).

Brain, anterior pituitary, brown adipose tissue, and placenta have 5′ deiodinase type II that is similar to Type I 5′ deiodinase in that it incorporates a rare amino acid, **selenocysteine** (Sec), and it is an integral membrane protein. It has only outer ring deiodinase activity. Thus, it converts T4 to T3 and rT3 to 3,3′-T2. Most of the T3 in these tissues derives from Type II 5′ deiodinase acting on circulating T4.

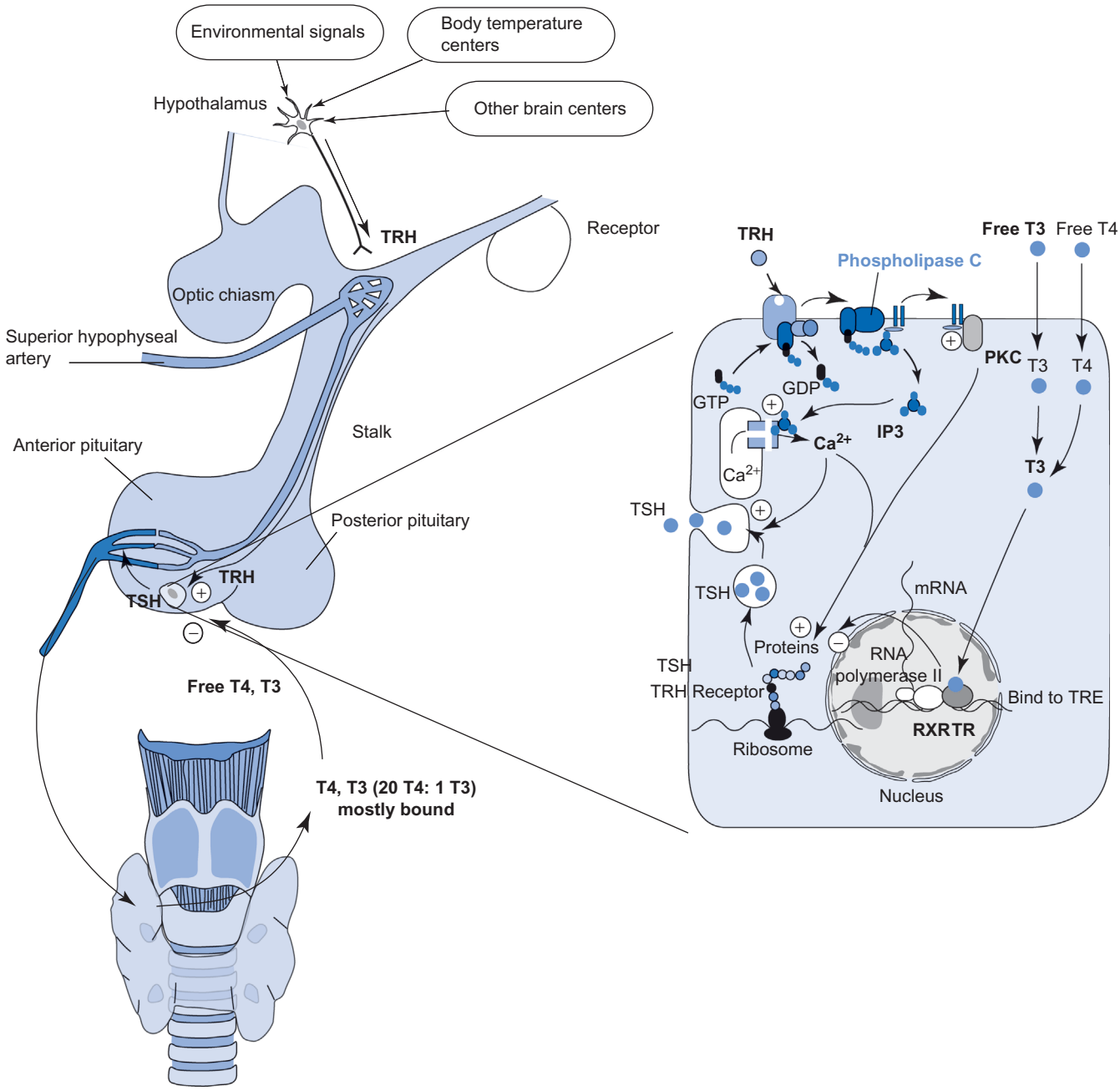

FIGURE 9.3.6 Control of T4 and T3 secretion. T3 and T4 secretion is stimulated solely by TSH, or thyrotropin, which in turn is secreted by the anterior pituitary solely in response to TRH, thyrotropin-releasing hormone. TRH reaches the anterior pituitary through the hypophyseal portal circulation. TRH is synthesized in neurohormonal cells residing in the paraventricular nucleus of the hypothalamus and is secreted in response to environmental stimuli, body temperature, and other inputs from the brain. TRH activates secretion of TSH in thyrotrophs through activation of G_q-coupled receptors. TSH is released into the blood wherein it travels to the thyroid gland where it causes release of T3 and T4 in the short term and causes enlargement of the thyroid and increased synthesis of thyroglobulin in the long term. Over-secretion of T3 and T4 is prevented by a negative feedback of T3 on the anterior pituitary. T3 binds to its nuclear receptor (TR) and modulates gene expression in the thyrotrophs. T3 reduces the number of receptors for TRH, thereby reducing the sensitivity of the thyrotrophs to TRH levels, and reduces the synthesis of TSH within the thyrotrophs.

A type III deiodinase is present in most tissues. It also contains a selenocysteine residue. It removes I from the 5 position on the inner ring. Thus, it converts T4 to rT3 and T3 to 3,3′-T2.

A fraction of the circulating T4 is deaminated and decarboxylated to form tetraiodoacetic acid, or **tetrac**. This compound circulates at about 0.06 μg dL^{-1}. Thyroid sulphotransferases, mainly in the liver, conjugate T4, T3, and rT3 with sulfate. The liver also has iodothyronine UDP-glucuronyltransferase activity, which catalyzes the conjugation of T4 and T3 with glucuronic acid. The liver excretes T4 sulfate and T4 glucuronate in the bile. The normal plasma concentrations, metabolic clearance rate,

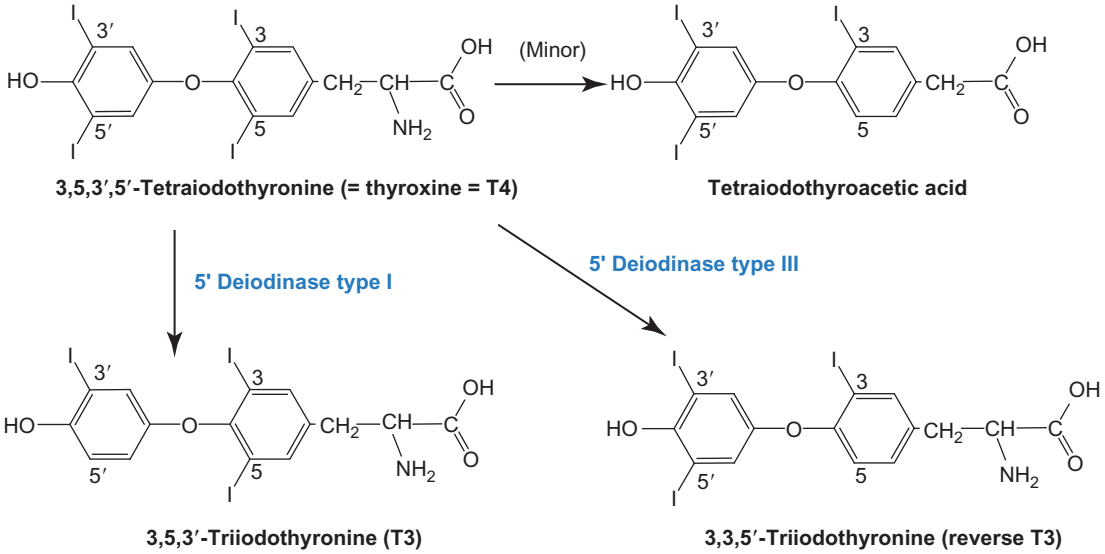

FIGURE 9.3.7 Metabolism of T4. The major circulating hormone is T4. It is deiodinated in peripheral tissues to T3 and rT3, primarily in the kidney and liver. T3 is the active metabolite in tissues. Deiodination to rT3 is the beginning of a degradative pathway.

TABLE 9.3.1 Approximate Values for the Normal Plasma Concentration, Metabolic Clearance Rate, and Production Rate of the Major Thyroid Hormone Derivatives in Normal Adult Humans

Compound	Plasma Total [ ] ($\mu g\ dL^{-1}$)	Metabolic Clearance Rate (L day^{-1}) per 70 kg Body Weight	Production Rate ($\mu g\ day^{-1}$) per 70 kg Body Weight
T4	8.6	1.2	100
T3	0.14	24	31
rT3	0.04	111	39

and production rates for the major thyroid hormone derivatives are summarized in Table 9.3.1.

The estimates shown here are the average mean values of multiple studies. Values can be converted to nmol by using the formula weights: T4, 1 nmol = 777 ng; T3 and rT3, 1 nmol = 651 ng. (Data from I.J. Chopra and L. Sabatino, Nature and sources of circulating thyroid hormones, in L.E. Braverman and R.D. Utger, eds., *The Thyroid, A Fundamental and Clinical Text*, 8th edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2000.)

T3 ALTERS GENE EXPRESSION

Most tissues contain TR in the nucleus of their cells. These 50–55 kDa receptors structurally resemble the nuclear receptors for steroid hormones and vitamin D. Tissues often have all three types: TR-α1, TR-β1, and TR-β2; however, their proportion varies with the tissue.

The TRs bind to specific sequences in the DNA called thyroid responsive elements, or **TREs**. Each of these regulates the transcription of mRNA that codes for a protein. Binding of the TR to **positive TREs** increases expression of the mRNA and the protein. Binding of TRs to **negative TREs** decreases the mRNA and protein expression. All positive TREs require dimers to activate transcription, but some negative TREs contain only a single binding site for TR. It is currently thought that heterodimer formation with **RXR**, the **9-cis-retinoic acid receptor**, forms the most effective configuration of TR for regulation of transcription (see Figure 9.3.8).

TR proteins bind to the TRE in the presence or absence of T3. In the absence of T3, TRs bind to positive TREs and inhibit or repress the rate of transcription. Binding of T3 to the TR on these positive TREs relieves this inhibition. The repression of gene expression is due to **TR corepressors**, of which there are several varieties. These proteins bind to the TR when the T3 binding site is vacant, and dissociate from the TR when the receptor binds T3.

THYROID HORMONE PLAYS A CRUCIAL ROLE IN GROWTH AND DEVELOPMENT AND IN GENERAL METABOLISM

Thyroid hormone has multiple effects on every tissue in the body. During particular times during development, thyroid hormone plays a crucial role and its insufficiency has devastating consequences. An overview of the effects is shown in Table 9.3.2.

TABLE 9.3.2 Overview of the Physiological Actions of Thyroid Hormone

1 CNS development
- 1.1 Normal T3 is required for proper development and function of the CNS
- 1.2 Low levels of T3 during development cause mental retardation
- 1.3 High levels of T3 increase irritability and excitability
- 1.4 T3 inhibits nerve cell replication
- 1.5 T3 stimulates neuron cell body growth and branching of dendrites
- 1.6 T3 stimulates axon myelination

2 Body growth
- 2.1 T3 stimulates growth hormone synthesis in somatotrophs in the anterior pituitary. Thus hypothyroidism is associated with growth retardation
- 2.2 T3 stimulates synthesis of structural proteins in skeletal muscle, heart, liver, etc.
- 2.3 T3 stimulates calcification of the growth plates of the long bones, limiting linear growth

3 Basal energy expenditure
- 3.1 T3 increases the basal metabolic rate (BMR). This is called the **thermogenic effect**
- 3.2 T3 increases O_2 consumption, energy production, and heat production
- 3.3 T3 promotes mitochondrial growth and replication
- 3.4 T3 increases expression of a variety of respiratory enzymes

4 Intermediary metabolism
- 4.1 T3 promotes protein synthesis in a variety of tissues
- 4.2 T3 potentiates the effects of epinephrine in the liver and increases liver glycogenolysis and gluconeogenesis; thus, it raises blood glucose and decreases liver glycogen
- 4.3 T3 potentiates the effects of insulin on skeletal muscle; it increases uptake, utilization, and storage of glucose
- 4.4 T3 potentiates the effects of insulin on adipose tissue; it increases lipolysis and increases circulating levels of free fatty acids and decreases plasma cholesterol

5 Cardiovascular system
- 5.1 The heart has receptors for T3 which increase transcription of specific genes. Among these are the genes coding for SERCA and for myosin heavy chain α and β
- 5.2 T3 increases cardiac output by increasing both stroke volume and heart rate
- 5.3 T3 increases sensitivity to β-adrenergic stimulation
- 5.4 T3 increases respiratory ventilation secondary to increased CO_2 production

6 TSH secretion
- 6.1 The TSH gene is negatively regulated by T3; T3 decreases the synthesis of mRNAs coding for TSH α and β subunits, thereby decreasing synthesis of TSH

HYPOTHYROIDISM REFERS TO REDUCED CIRCULATING LEVELS OF T4 AND T3

Figures 9.3.5 and 9.3.6 show numerous steps in the synthesis, storage, and secretion of T4 and T3. Defects in any one of these steps can interfere with the secretion of sufficient thyroid hormone. Defects in the thyroid gland itself are classified as **primary hypothyroidism**. Insufficient T4 and T3 production because of lack of stimulation by TSH is called **central hypothyroidism**.

The most common cause of hypothyroidism worldwide is **iodine deficiency**. The iodine required to make T4 and T3 comes from the diet. Insufficient dietary iodine results in primary hypothyroidism. The low circulating levels of T4 and T3 no longer inhibit TSH synthesis and secretion, and TSH levels rise. The increased TSH levels exert a trophic effect on the thyroid, causing hyperplasia and hypertrophy of the cells (see Figure 9.3.3), resulting in an enlarged thyroid gland, called a **goiter**. Goiters are common in primary hypothyroidism (Figure 9.3.9).

There are many causes of hypothyroidism. Defects are known to occur in:

- iodine availability in the diet;
- NIS, the sodium–iodine symport, that traps iodine within the secretory cell;
- pendrin, the protein that transports iodine into the follicle across the apical membrane;
- thyroid peroxidase, the enzyme that oxidizes iodine for organification;
- thyroglobulin synthesis;
- iodine recycling in the thyroid secretory cells;
- the TSH receptor that signals the follicular secretory cells to secrete T4 and T3;
- the $G_{\alpha s}$ subunit that couples the TSH receptor to adenylyl cyclase to turn on secretion;
- the development of the thyroid gland.

These all cause primary hypothyroidism. Central or secondary hypothyroidism can be caused by defects in:

- development of the hypothalamus or pituitary;
- the TRH receptor;
- regulation of TSH synthesis or secretion.

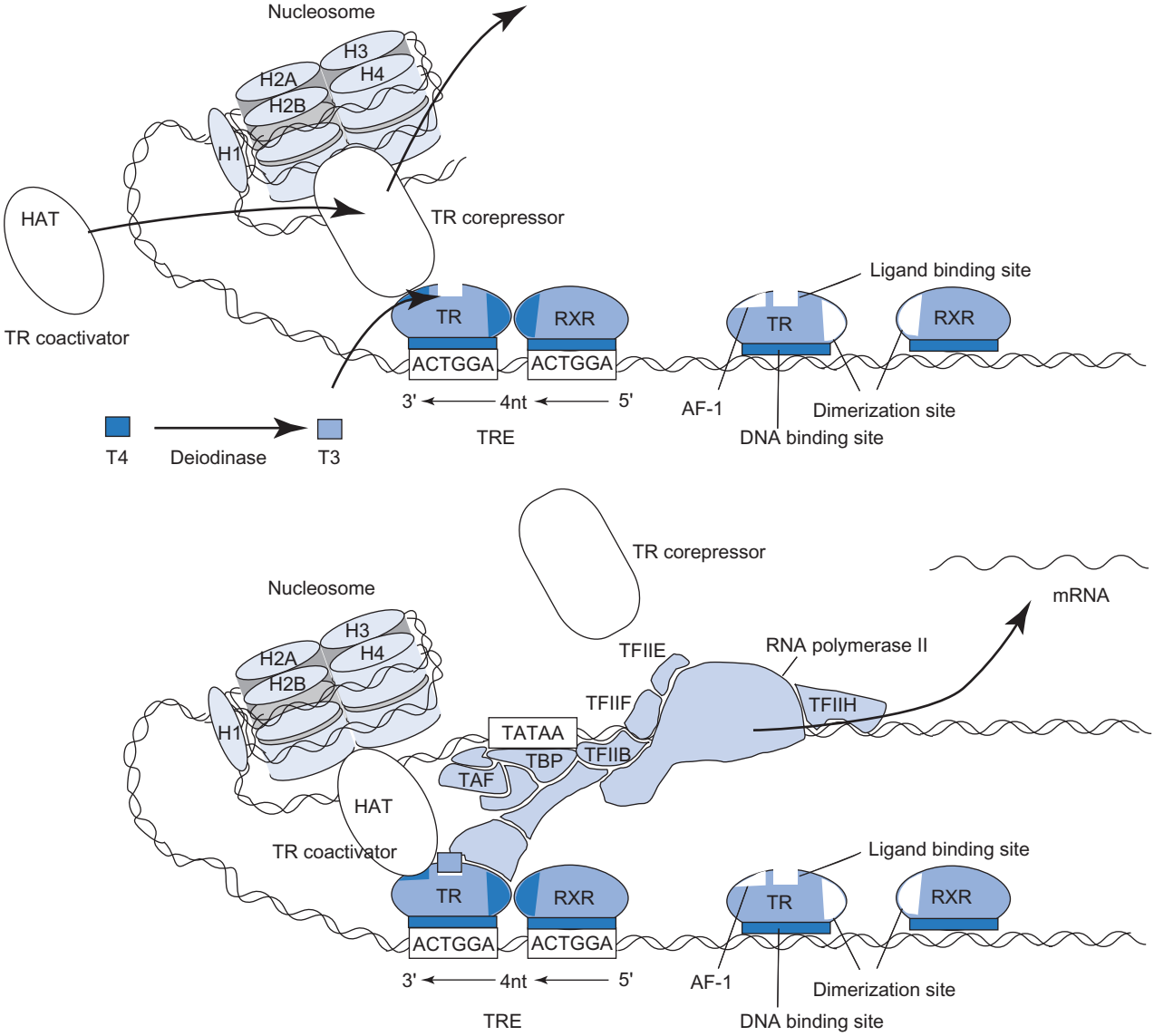

FIGURE 9.3.8 Action of T3 on gene expression at positive TREs. The TR binds to a TRE, which consists of specific nucleotide sequences. The one shown is called a **direct repeat**, consisting of two sets of six nucleotides separated by four nucleotides of variable composition. The TR binds to one half-site in the TRE on its DNA-binding domain. The second half-site is occupied by a retinoid X receptor (RXR), which forms a heterodimer with the TR. This binding occurs in the absence of T3. In this case, the TR binds one of a variety of TR corepressors that inhibits transcription, probably through histone deacetylase activity. In the hypoacetylated state, DNA is compact and provides poor access for transcription. When T3 binds to the TR, a TR coactivator displaces the corepressor. There are several varieties of coactivator. Many of these activators have histone acetyl transferase activity (HAT). The unraveling of the DNA and exposure of the TATA box recruits a variety of proteins, culminating in the stabilization of the preinitiation complex and activation of RNA polymerase II to transcribe mRNA from the DNA template.

Hypothyroidism can also be caused by:

- goitrogens, environmental compounds that interfere with iodine transport;
- infammation of the thyroid gland (**thyroiditis**);
- autoimmune destruction of the thyroid gland, such as in **Hashimoto's thyroiditis**.

Many of these disorders are exceedingly rare (see Clinical Applications: Pendred Syndrome), whereas primary hypothyroidism due to iodine deficiency is quite common. The prevalence of hypothyroidism increases with age. For most of those patients, the cause is unidentified because the diagnosis and treatment, exogenous replacement therapy with T4, does not require detailed knowledge of its etiology. The regulatory mechanisms leading to goiter are summarized diagrammatically in Figure 9.3.9.

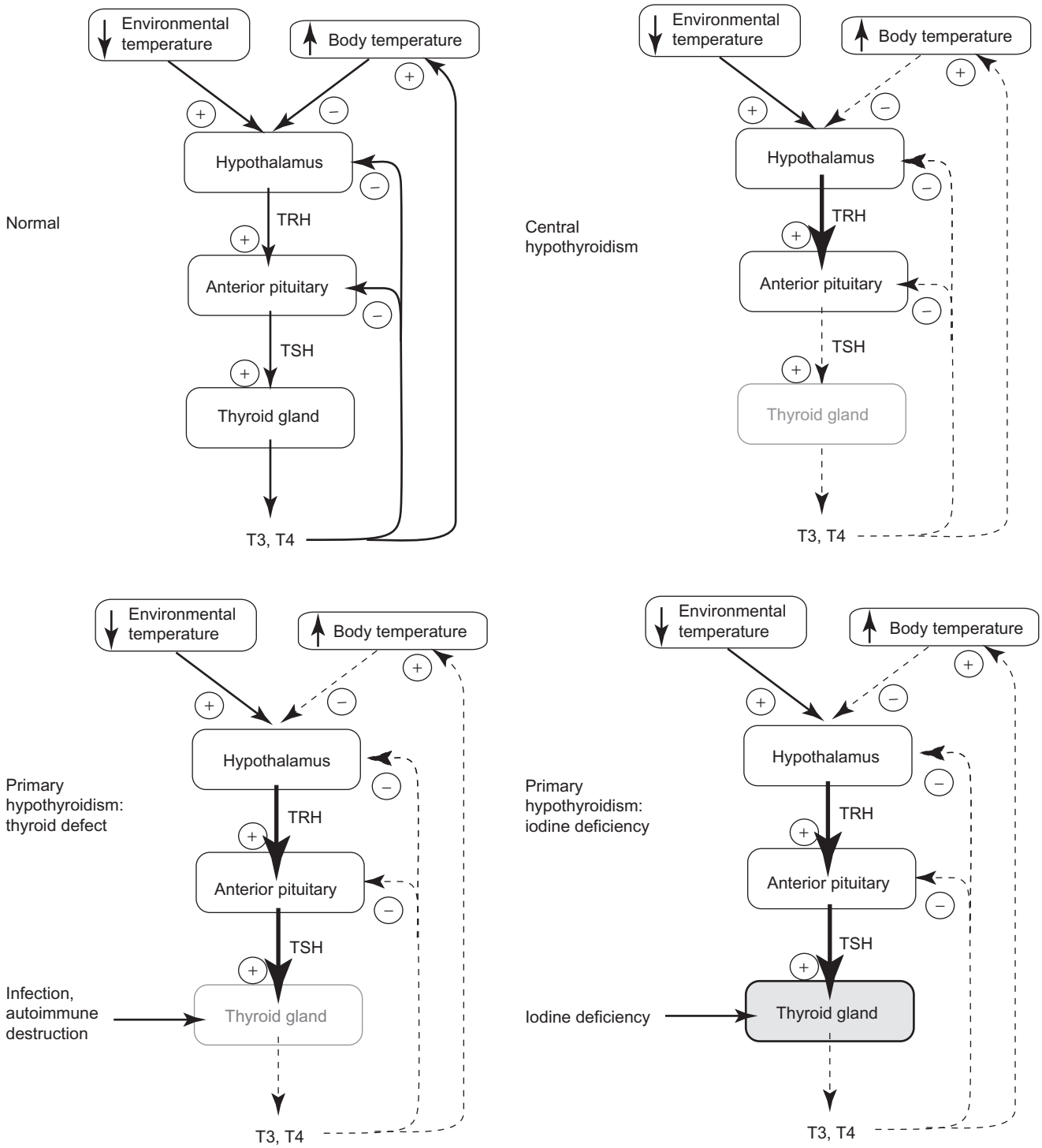

FIGURE 9.3.9 Control mechanisms in various states of thyroidism. In the normal state, the neurons in the hypothalamus release TRH to the portal circulation leading to the anterior pituitary gland in response to integrated signals from the environment and the body, mostly dealing with temperature and energy production. Decreases in environmental temperature stimulate TRH release, whereas rises in body temperature or energy production decrease it. TRH releases TSH from the anterior pituitary, which then stimulates T3 and T4 release from the thyroid. T3 and T4 feed back directly on TSH synthesis and secretion and indirectly through body energy production on the release of TRH. In persons with thyroid defects, TSH is ineffective in increasing T3 and T4 secretion because the thyroid cannot respond. The thyroid may or may not enlarge because it is simultaneously being stimulated by TSH and destroyed by autoimmune or inflammatory processes. In central hypothyroidism, TRH may fail to elicit TSH secretion. Thus, TRH remains high and T3 and T4 levels do not rise. In iodine deficiency, the thyroid also cannot make sufficient T3 and T4. There is no feedback inhibition of TRH or TSH secretion and so both remain high. The high TSH levels stimulate thyroid growth, producing a goiter.

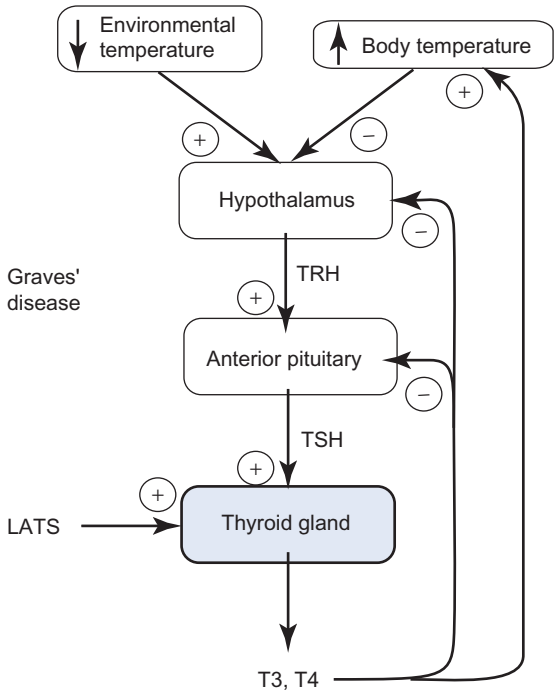

FIGURE 9.3.10 Mechanism of hyperthyroidism in Graves' disease. Persons with Graves' disease produce antibodies against their TSH receptors on the thyroid gland. These antibodies bind to the receptor and stimulate the thyroid gland inappropriately and regardless of the thyroid hormone status of the blood. The result is a hyperactive thyroid and high circulating T3 and T4 levels.

THE CLINICAL SYMPTOMS OF HYPOTHYROIDISM ARE MANIFOLD

Table 9.3.2 shows that thyroid hormone exerts many physiological effects. The sensitivity of these effects to hypothyroidism varies according to the age of onset of the hypothyroidism. Hypothyroidism in utero and in early postnatal life causes **cretinism**, marked by severe mental retardation, deaf-mutism, spastic gait and lack of motor control, and poor growth. Early recognition and treatment of this condition is crucial because the untreated condition leads to permanent damage that cannot be reversed by later return to a euthyroid state.

Hypothyroidism in the juvenile leads to delayed growth and sexual maturation with symptoms intermediate between those of the infant and the adult. Hypothyroidism in the adult is characterized by **myxedema**. Accumulation of hyaluronic acid in the dermis absorbs water and it swells to one-thousand times its weight, resulting in a puffy thickening of the skin. Part of the edema is due to albumin escape from the capillaries. Other symptoms in the adult include the following:

- Sluggish mental functions including memory defects, lethargy, and somnolence
- Slow myotatic reflexes
- Decreased BMR and appetite
- Cold intolerance
- Decreased cardiac output due to bradycardia and decreased stroke volume

Clinical Applications: Goitrogens

Some plants produce natural **goitrogens**, compounds that produce goiters in humans in the absence of dietary iodine deficiency. Broccoli, brussel sprouts, cauliflower, and cabbage are all varieties of the species *Brassica oleracea*. These plants all produce thioglucosides which, after digestion, produce thiocyanate and isothiocyanate. Both of these compounds interfere with the NIS in the thyroid gland. In sufficient amounts, they can cause primary hypothyroidism, increased TSH secretion, and hypertrophy of the thyroid gland, or goiter.

Cassava or **manioc**, is a basic food staple in certain areas of the tropics. It is a starchy root that people grind up to make flour or meal. This plant contains cyanoglucosides that are converted to cyanide, which is then detoxified to thiocyanate. The **thiocyanate is a potent goitrogen**. These cyanoglucosides are also found in bamboo shoots, sweet potatoes, and lima beans. The determining factor in the development of goiter is the ratio of dietary iodine to thiocyanate. Goiter develops when the urinary iodine/thiocyanate ratio drops below about 3 μg iodine per mg of thiocyanate.

Clinical Application: Pendred Syndrome

In 1896, Vaughan Pendred (1869–1946) described a syndrome of deafness associated with goiter, an enlargement of the thyroid gland, in two members of a large family. Its etiology was further illuminated in 1958 when it was found that that Pendred syndrome is accompanied by a positive perchlorate discharge test. In this test, the thyroid is first loaded with radiolabeled iodine by i.v. injection. Two hours later, further uptake is inhibited by injecting 100 mg sodium perchlorate, which blocks the iodine uptake mechanism. If the radiolabeled iodine is already incorporated into thyroglobulin, it will not be released. In Pendred syndrome, a larger fraction of the radiolabeled iodine is released because it has not been transferred to the follicle. It is now known that the Pendred gene, PDS, codes for a protein called Pendrin that is probably involved in transporting iodine into the follicle across the apical membrane. The prevalence of Pendred syndrome is between 1:15,000 and 1:100,000. Some 35 different mutations of pendrin have been identified. The function of pendrin in the inner ear is not yet understood.

- Pale and cool skin due to cutaneous vasoconstriction
- Dry and coarse skin due to reduced sweat and oil secretions
- Myxedematous skin.

THE MOST IMPORTANT CLINICAL ABNORMALITY OF HYPERTHYROIDISM IS *GRAVES' DISEASE*

In 1835, R.J. Graves described women who had goiter and palpitations and included one with **exophthalamos**, a protrusion of the eyeballs. Graves thought that the disease derived from defects in the heart, and it was not until the 1890s that surgeons discovered the thyroid origin of the disease. The etiology of the disease was clarified in 1956 when it was found that serum from persons with Graves' disease could cause release of radiolabeled thyroid hormone when injected into guinea pigs, but its action was more prolonged than that of TSH. (The circulating half-life of TSH is 1 h.) The active substance was termed **long-acting thyroid stimulator**, or **LATS**. This substance is an immunoglobulin directed against the TSH receptor. Some of these antibodies stimulate the TSH receptor, whereas others bind and block TSH stimulation. Graves' hyperthyroidism is caused by autoantibodies that stimulate the TSH receptor but this is not subject to the normal negative feedback loops for control of blood T3 and T4 levels. The etiology of Graves' disease is illustrated in Figure 9.3.10.

Hyperthyroidism in Graves' disease causes the following:

- Diffuse goiter from extended stimulation of the gland through its TSH receptors
- Exophthalamos, protrusion of the eyeballs

Clinical Applications: Iodine Deficiency Disorders

One of the four major public health problems relating to nutrition is iodine deficiency. The thyroid requires iodine to make thyroid hormone, and this iodine is obtained from the diet. Historically, the major natural source of iodine is from seafood. Sea water contains about 50–60 μg of iodide per liter. Iodide is oxidized by sunlight to elemental iodine, which is volatile. Every year some 400,000 tons of iodine escapes from the sea. Air contains about 0.7 μg m^{-3}. The iodine returns to the soil in rain, but this is insufficient to replenish the leaching of iodine from deficient soils. Thus, plants raised in iodine-deficient areas, particularly mountainous regions that have experienced glaciation, and inland areas, are low in iodine. People indigenous to these regions are at risk of developing iodine deficiency disorders (IDDs).

The clinical manifestations of IDDs are **hypothyroidism**, **goiter**, **dwarfism**, **impaired neurological development**, **myxedema**, and **cretinism**. Goiter is an enlargement of the thyroid gland, for whatever reason. In iodine deficiency, the deficit in T4 and T3 removes negative feedback on TSH synthesis and secretion in the thyrotrophs of the anterior pituitary. As a result, TSH levels rise and exert trophic effects on the thyroid gland, causing its enlargement. Goiter in areas of iodine deficiency is called **endemic goiter**. The dwarfism arises from the lack of stimulation by T3 of GH synthesis and secretion in somatotrophs in the anterior pituitary. Hypothyroidism leads to impaired neurological function in the adult. Hypothyroidism in the fetus and early postnatal life leads to cretinism. Cretinism is a polymorphous collection of abnormalities of intellectual and physical development. **Neurological cretins** are extremely mentally retarded, deaf-mutes with spastic gaits and impaired motor abilities. **Myxedematous cretins** are less severely retarded but have retarded growth and sexual development, myxedema, retarded maturation of body proportions, dry skin, and sparse development of nails and hair. These two forms comprise the extreme limits of a spectrum of abnormalities caused by fetal iodine deficiency. The evidence that cretinism is an IDD is largely epidemiological: its frequency correlates with the degree of iodine deficiency; iodine treatment of a population reduces its incidence; it appears together with iodine deficiency of recent onset. The prevalence of goiters in the persons with neurological cretinism is about the same as in the noncretin population, whereas goiters in persons with myxedematous cretinism are relatively rare. Nevertheless, myxedematous cretins have hypothyroidism with high TSH levels. Neurological cretinism is the more prevalent form.

These IDDs are a huge public health problem. In 1986, the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) was formed at a meeting in Kathmandu, Nepal. This organization consists of a global interdisciplinary network of experts who work closely with the WHO and UNICEF and a number of governments in efforts to eradicate IDDs. According to the ICCIDD (www.ICCIDD.org), as much as 30% of the world's population is at risk of IDDs; 750 million people suffer from some degree of goiter, 43 million have IDD-related brain damage, and some 5.7 million are afflicted with cretinism.

Prevention of IDDs in populations can be as simple as iodination of ordinary table salt. The dietary requirements for iodine scale with age: 40 μg day^{-1} from 0 to 6 months; 50 μg day^{-1} from 6 to 12 months; 60–120 μg day^{-1} from 1 to 10 years; and 120–150 μg day^{-1} from 11 years onward. The US standard for iodized salt is 0.006% by weight as KI, which is equivalent to 45 μg iodine g^{-1}. One teaspoon of salt weighs 6 g, and so this degree of iodination provides 270 μg of iodine, more than enough for the needs of most people. Iodized salt has a definite shelf-life because the iodine becomes volatilized. Heating the salt in solution removes the iodine.

Despite our collective scientific knowledge, IDDs continue to be a veritable scourge, both medically and socially. Eradication is hampered by lack of education, lack of infrastructure, and cultural resistance to new dietary products.

- Increased CNS excitability, nervousness, emotional lability, hyperkinesia, tremor, insomnia
- Increased BMR
- Increased appetite
- Heat intolerance
- Increased cardiac output caused by tachycardia and increased stroke volume
- Increased sensitivity to adrenergic stimulation
- Peripheral vasodilation
- Cutaneous vasodilation and excessive sweating.

SUMMARY

The thyroid gland is found in the neck surrounding the trachea. It secretes thyroxine and triiodothyronine when stimulated by TSH, a glycoprotein hormone secreted by the anterior pituitary. The gland itself consists of spherical or oblate follicles lined by an epithelium and containing a colloid made up of thyroglobulin. Tyrosine residues in the thyroglobulin are iodinated by the gland. Iodine is taken up by the gland through secondary active transport at the basolateral membrane (facing the blood) through a Na–I symport (NIS). The I^- is carried across the apical membrane by another carrier, probably pendrin. The I^- in the follicle is converted to I^0 by thyroid peroxidase. The I^0 forms covalent bonds with tyrosine residues in a process called organification. MIT and DIT residues are coupled to form thyroxine (T4—four I atoms on two phenyl groups) or triiodothyronine (T3), still bound to thyroglobulin. Release of T4 or T3 occurs when the gland is stimulated by TSH. Thyroid cells endocytose the thyroglobulin and release T3 or T4 after proteolytic digestion of the colloid.

TSH is a glycoprotein hormone secreted by thyrotrophs in the anterior pituitary, when these cells are stimulated by TRH. There are two basic controls of these cells: TRH released from nerve cells in the paraventricular nucleus of the hypothalamus and negative feedback inhibition by T3 and T4. The signals for secretion of TRH are neuronal and derive from environmental temperature, body core temperature, and other brain centers. TRH stimulates TSH secretion through a G_q mechanism.

Circulating T3 and T4 are largely carried by proteins that cannot leave the circulation. Only a small fraction of free T3 is active. It enters cells and binds to multiple nuclear receptors called TR. These bind to TREs. Positive TREs increase mRNA expression in response to T3; negative TREs decrease mRNA synthesis and expression. TR alone binds to TRE and inhibits mRNA expression; binding of T3 to the TR relieves this inhibition. The circulating T3 and T4 are degraded by deiodination followed by deamination and decarboxylation.

Hypothyroidism in infancy and childhood produces devastating dysfunction. Cretinism is marked by severe mental retardation, short stature, deaf-mutism, and lack of motor control. Hypothyroidism in the adult causes myxedema, caused by buildup of dermal hyaluronic acid and its swelling with fluid. This is accompanied by sluggish mental function, decreased metabolic rate, and cold intolerance. Hypothyroidism has many causes. The most common is iodine deficiency, which is readily treated with iodized salt.

Goiters are hyperplastic and hypertrophied thyroid glands, for whatever reason. In iodine deficiency, lack of T3 and T4 output by the gland relieves negative feedback inhibition of TSH secretion so that TSH remains high and the thyroid gland is stimulated. Goiters also occur in Graves' disease, which is a hyperthyroid condition caused by antibodies to the TSH receptor. These persons make a long-acting thyroid stimulator that stimulates the thyroid gland inappropriately. In this case, TSH secretion is inhibited by the high circulating T3 and T4 levels.

REVIEW QUESTIONS

1. Describe the hypothalamic control of TSH release. What is TRF? What stimulates its release? How does it cause TSH release?
2. What is TSH? Where is it released? What stimulates its release? What inhibits it? What does it do? What mechanism does it use to stimulate thyroid secretion?
3. What is thyroid hormone? List the four steps involved in iodination of thyroglobulin. Where does the iodine come from? How does it get into the follicle? How does it combine with tyrosine? How are T3 and T4 formed? How are they released? Which is the predominant secreted form? Which is most active biologically?
4. How are T3 and T4 carried in blood? What physiological effects do they have? What diseases result from hypothyroidism? What is the most common cause of hypothyroidism? How can you cure it?
5. How are T4 and T3 metabolized? Where is T3 formed? What is the mode of action of T3?
6. What diseases result from hyperthyroidism? What is the most common cause of hyperthyroidism?
7. What is a goiter? How can the goiter be enlarged in both hypothyroid or hyperthyroid states?