CHAPTER 33

The Thyroid Gland

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CHAPTER OUTLINE

- FUNCTIONAL ANATOMY OF THE THYROID GLAND
- SYNTHESIS, SECRETION, AND METABOLISM OF THE THYROID HORMONES
- THE MECHANISM OF THYROID HORMONE ACTION
- ROLE OF THE THYROID HORMONES IN DEVELOPMENT, GROWTH, AND METABOLISM
- THYROID HORMONE DEFICIENCY AND EXCESS IN ADULTS

KEY CONCEPTS

1. The thyroid gland consists of two lobes attached to either side of the trachea. Within the lobes of the thyroid gland are spherical follicles surrounded by a single layer of epithelial cells. Parafollicular cells that secrete calcitonin are also present within the walls of the follicles.
2. The major thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3), both of which contain iodine.
3. Thyroid hormones are synthesized by iodination and the coupling of tyrosines in reactions catalyzed by the enzyme thyroid peroxidase.
4. Thyroid hormones are released from the thyroid gland by the degradation of thyroglobulin within the follicular cells.
5. The synthesis and release of thyroid hormones is regulated by thyroid-stimulating hormone (TSH), mainly via cAMP.
6. TSH release from the anterior pituitary is regulated by the concentration of thyroid hormones in the circulation.
7. In peripheral tissues, T_4 is deiodinated to the physiologically active hormone T_3 by 5′- deiodinase.
8. In target tissues, T_3 binds to the thyroid hormone receptor (TR), which then associates with a second TR or other nuclear receptor to regulate transcription.
9. TR regulates transcription by binding to specific thyroid hormone response elements (TRE) in target genes.
10. Thyroid hormones are important regulators of central nervous system development.
11. Thyroid hormones stimulate growth by regulating growth hormone release from the pituitary and by direct actions on target tissues, such as bone.
12. Thyroid hormones regulate the basal metabolic rate and intermediary metabolism through effects on mitochondrial ATP synthesis and the expression of genes encoding metabolic enzymes.
13. An excess of thyroid hormone (hyperthyroidism) is characterized by nervousness and increased metabolic rate, resulting in weight loss.
14. A deficiency of thyroid hormone (hypothyroidism) is characterized by decreased metabolic rate, resulting in weight gain.

The development of the human body, from embryo to adult, is an orderly, programmed process. The timing of developmental events is remarkably constant from one individual to the next, with developmental milestones reached at about the same time in all of us. For example, the early development of motor skills, body growth, the start of puberty, and final sexual and physical maturation occur within rather narrow timeframes during the human life span.

At the level of the individual cell, the timing or rate of metabolic processes is also tightly regulated. For example, energy metabolism occurs at a rate needed to make the amount of ATP required for activities such as excitability, secretion, maintaining osmotic integrity, and countless biosynthetic processes. The cell not only meets its basic metabolic "housekeeping" needs but also remains poised to do its own special work in the body, such as conducting nerve impulses and contracting, absorbing, and secreting. During its life span, the cell continues to make the enzymatic and structural proteins that ensure the maintenance of an appropriate rate of metabolism.

The thyroid hormones, thyroxine and triiodothyronine, play key roles in the regulation of body development and govern the rate at which metabolism occurs in individual cells. Although these hormones are not essential for life, without them, life would lose its orderly nature. Without adequate levels of thyroid hormones, the body fails to develop on time. Cellular housekeeping moves at a slower pace, eventually influencing the ability of individual cells to

carry out their physiological functions. The thyroid hormones exert their regulatory functions by influencing gene expression, affecting the developmental program and the amount of cellular constituents needed for the normal rate of metabolism.

FUNCTIONAL ANATOMY OF THE THYROID GLAND

The human thyroid gland consists of two lobes attached to either side of the trachea by connective tissue. The two lobes are connected by a band of thyroid tissue or isthmus, which lies just below the cricoid cartilage. A normal thyroid gland in a healthy adult weighs about 20 g.

Each lobe of the thyroid receives its arterial blood supply from a superior and an inferior thyroid artery, which arise from the external carotid and subclavian artery, respectively. Blood leaves the lobes of the thyroid by a series of thyroid veins that drain into the external jugular and innominate veins. This circulation provides a rich blood supply to the thyroid gland, giving it a higher rate of blood flow per gram than even that of the kidneys.

The thyroid gland receives adrenergic innervation from the cervical ganglia and cholinergic innervation from the vagus nerves. This innervation regulates vasomotor function to increase the delivery of TSH, iodide, and metabolic substrates to the thyroid gland. The adrenergic system can also affect thyroid function by direct effects on the cells.

Thyroxine and Triiodothyronine Are Synthesized and Secreted by the Thyroid Follicle

The lobes of the thyroid gland consist of aggregates of many spherical **follicles**, lined by a single layer of epithelial cells (Fig. 33.1). The apical membranes of the follicular cells, which face the lumen, are covered with microvilli. Pseudopods formed from the apical membrane extend into the lumen. The lateral membranes of the follicular cells are connected by tight junctions, which provide a seal for the contents of the lumen. The basal membranes of the follicular cells are close to the rich capillary network that penetrates the stroma between the follicles.

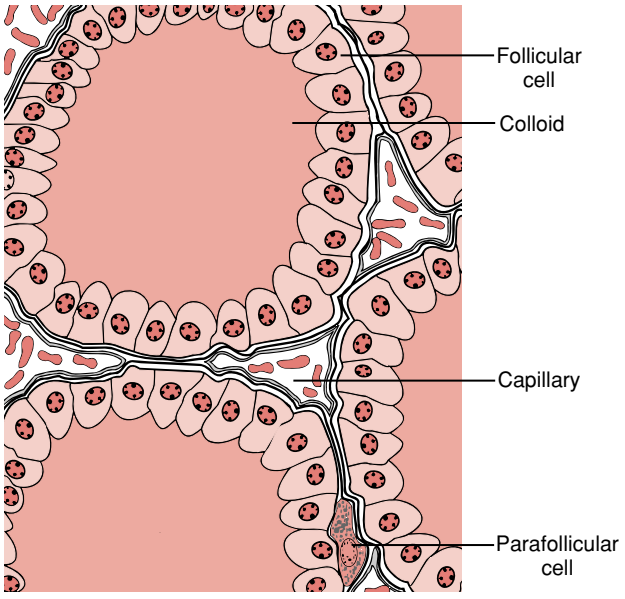

FIGURE 33.1 **A cross-sectional view through a portion of the human thyroid gland.**

The lumen of the follicle contains a thick, gel-like substance called **colloid** (see Fig. 33.1). The colloid is a solution composed primarily of **thyroglobulin**, a large protein that is a storage form of the thyroid hormones. The high viscosity of the colloid is due to the high concentration (10 to 25%) of thyroglobulin.

The thyroid follicle produces and secretes two thyroid hormones, **thyroxine** (T_4) and **triiodothyronine** (T_3). Their molecular structures are shown in Figure 33.2. Thyroxine and triiodothyronine are iodinated derivatives of the amino acid tyrosine. They are formed by the coupling of the phenyl rings of two iodinated tyrosine molecules in an ether linkage. The resulting structure is called an **iodothyronine**. The mechanism of this process is discussed in detail later.

Thyroxine contains four iodine atoms on the 3, 5, 3′, and 5′ positions of the thyronine ring structure, whereas triiodothyronine has only three iodine atoms, at ring positions 3, 5, and 3′ (see Fig. 33.2). Consequently, thyroxine is usually abbreviated as T_4 and triiodothyronine as T_3. Because T_4 and T_3 contain the element iodine, their synthesis by the thyroid follicle depends on an adequate supply of iodine in the diet.

Parafollicular Cells Are the Sites of Calcitonin Synthesis

In addition to the epithelial cells that secrete T_4 and T_3, the wall of the thyroid follicle contains small numbers of **parafollicular cells** (see Fig. 33.1). The parafollicular cell is usually embedded in the wall of the follicle, inside the basal lamina surrounding the follicle. However, its plasma membrane does not form part of the wall of the lumen. Parafollicular cells produce and secrete the hormone calcitonin. Calcitonin and its effects on calcium metabolism are discussed in Chapter 36.

SYNTHESIS, SECRETION, AND METABOLISM OF THE THYROID HORMONES

T_4 and T_3 are not directly synthesized by the thyroid follicle in their final form. Instead, they are formed by the chemical modification of tyrosine residues in the peptide structure of thyroglobulin as it is secreted by the follicular cells into the lumen of the follicle. Therefore, the T_4 and T_3 formed by this chemical modification are actually part of the amino acid sequence of thyroglobulin.

The high concentration of thyroglobulin in the colloid provides a large reservoir of stored thyroid hormones for later processing and secretion by the follicle. The synthesis of T_4 and T_3 is completed when thyroglobulin is retrieved through pinocytosis of the colloid by the follicular cells. Thyroglobulin is then hydrolyzed by lysosomal enzymes

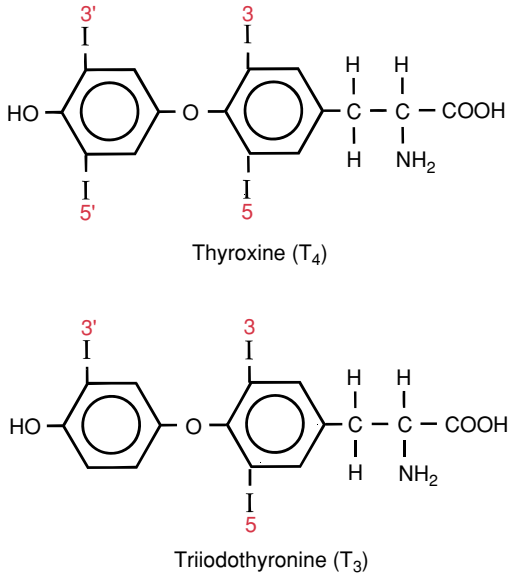

FIGURE 33.2 **The molecular structure of the thyroid hormones.** The numbering of the iodine atoms on the iodothyronine ring structure is shown in red.

to its constituent amino acids, releasing T_4 and T_3 molecules from their peptide linkage. T_4 and T_3 are then secreted into the blood.

Follicular Cells Synthesize Iodinated Thyroglobulin

The steps involved in the synthesis of iodinated thyroglobulin are shown in Figure 33.3. This process involves the synthesis of a thyroglobulin precursor, the uptake of iodide, and the formation of iodothyronine residues.

Synthesis and Secretion of the Thyroglobulin Precursor. The synthesis of the protein precursor for thyroglobulin is the first step in the formation of T_4 and T_3. This substance is a 660-kDa glycoprotein composed of two similar 330-kDa subunits held together by disulfide bridges. The subunits are synthesized by ribosomes on the rough ER and then undergo dimerization and glycosylation in the smooth ER. The completed glycoprotein is packaged into vesicles by the Golgi apparatus. These vesicles migrate to the apical membrane of the follicular cell and fuse with it. The thyroglobulin precursor protein is then extruded onto the apical surface of the cell, where iodination takes place.

Iodide Uptake. The iodide used for iodination of the thyroglobulin precursor protein comes from the blood perfusing the thyroid gland. The basal plasma membranes of follicular cells, which are near the capillaries that supply the follicle, contain **iodide transporters**. These transporters move iodide across the basal membrane and into the cytosol of the follicular cell. The iodide transporter is an active transport mechanism that requires ATP, is saturable, and can also transport certain other anions, such as bromide, thiocyanate, and perchlorate. It enables the follicular cell to concentrate iodide many times over the concentration of iodide present in the blood; therefore, follicular cells are efficient extractors of the small amount of iodide circulating in the blood. Once inside follicular cells, the iodide ions diffuse rapidly to the apical membrane, where they are used for iodination of the thyroglobulin precursor.

Formation of the Iodothyronine Residues. The next step in the formation of thyroglobulin is the addition of one or two iodine atoms to certain tyrosine residues in the precursor protein. The precursor of thyroglobulin contains 134 tyrosine residues, but only a small fraction of these become iodinated. A typical thyroglobulin molecule contains only 20 to 30 atoms of iodine.

The iodination of thyroglobulin is catalyzed by the enzyme **thyroid peroxidase**, which is bound to the apical membranes of follicular cells. Thyroid peroxidase binds an iodide ion and a tyrosine residue in the thyroglobulin precursor, bringing them in close proximity. The enzyme oxidizes the iodide ion and the tyrosine residue to short-lived free radicals, using hydrogen peroxide that has been generated within the mitochondria of follicular cells. The free radicals then undergo addition. The product formed is a **monoiodotyrosine** (MIT) residue, which remains in peptide linkage in the thyroglobulin structure. A second iodine atom may be added to a MIT residue by this same enzymatic process, forming a **diiodotyrosine** (DIT) residue (see Fig. 33.3).

Iodinated tyrosine residues that are close together in the thyroglobulin precursor molecule undergo a **coupling reaction**, which forms the iodothyronine structure. Thyroid peroxidase, the same enzyme that initially oxidizes iodine, is believed to catalyze the coupling reaction through the oxidation of neighboring iodinated tyrosine residues to short-lived free radicals. These free radicals undergo addition, as shown in Figure 33.4. The addition reaction produces an iodothyronine residue and a **dehydroalanine residue**, both of which remain in peptide linkage in the thyroglobulin structure. For example, when two neighboring DIT residues couple by this mechanism, T_4 is formed (see Fig. 33.4). After being iodinated, the thyroglobulin molecule is stored as part of the colloid in the lumen of the follicle.

Only about 20 to 25% of the DIT and MIT residues in the thyroglobulin molecule become coupled to form iodothyronines. For example, a typical thyroglobulin molecule contains five to six uncoupled residues of DIT and two to three residues of T_4. However, T_3 is formed in only about one of three thyroglobulin molecules. As a result, the thyroid secretes substantially more T_4 than T_3.

Thyroid Hormones Are Formed From the Hydrolysis of Thyroglobulin

When the thyroid gland is stimulated to secrete thyroid hormones, vigorous pinocytosis occurs at the apical membranes of follicular cells. Pseudopods from the apical membrane reach into the lumen of the follicle, engulfing bits of the colloid (see Fig. 33.3). Endocytotic vesicles or **colloid droplets** formed by this pinocytotic activity migrate toward the basal region of the follicular cell. Lysosomes, which are mainly located in the basal region of resting fol-

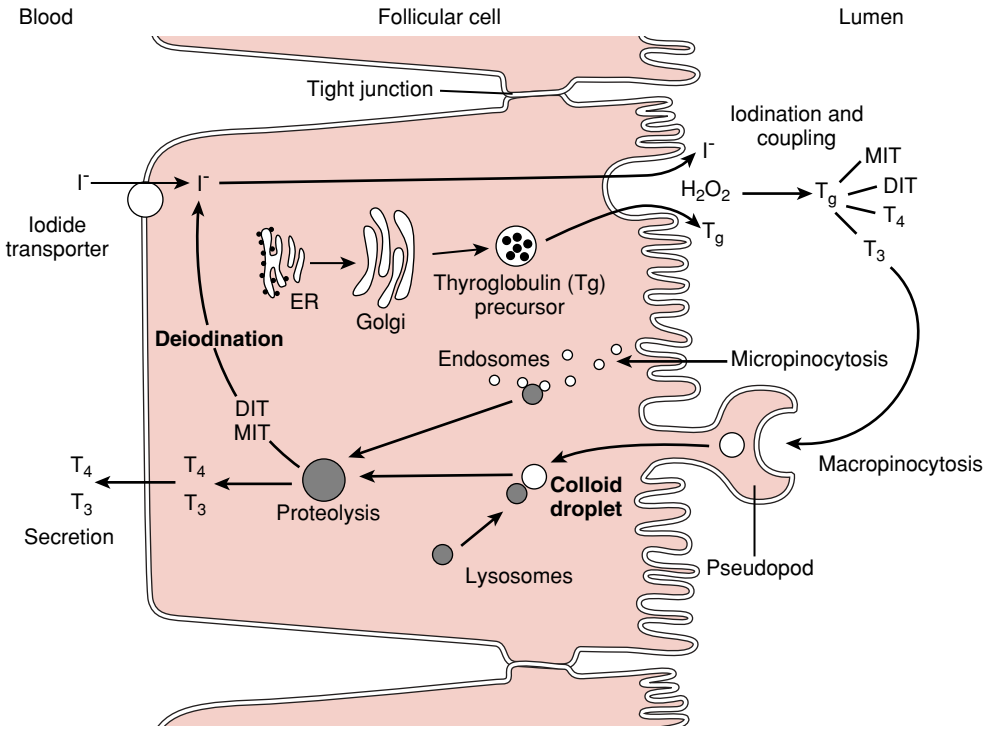

FIGURE 33.3 **Thyroid hormone synthesis and secretion.** (See text for details.) DIT, diiodotyrosine; MIT, monoiodotyrosine.

licular cells, migrate toward the apical region of the stimulated cells. The lysosomes fuse with the colloid droplets and hydrolyze the thyroglobulin to its constituent amino acids. As a result, T_4 and T_3 and the other iodinated amino acids are released into the cytosol.

Secretion of Free T_4 and T_3. T_4 and T_3 formed from the hydrolysis of thyroglobulin are released from the follicular cell and enter the nearby capillary circulation, however, the mechanism of transport of T_4 and T_3 across the basal plasma membrane has not been defined. The DIT and MIT generated by the hydrolysis of thyroglobulin are deiodinated in the follicular cell. The released iodide is then reutilized by the follicular cell for the iodination of thyroglobulin (see Fig. 33.3).

Binding of T_4 and T_3 to Plasma Proteins. Most of the T_4 and T_3 molecules that enter the bloodstream become bound to plasma proteins. About 70% of the T_4 and 80% of the T_3 are noncovalently bound to **thyroxine-binding globulin** (TBG), a 54-kDa glycoprotein that is synthesized and secreted by the liver. Each molecule of TBG has a single binding site for a thyroid hormone molecule. The remaining T_4 and T_3 in the blood are bound to **transthyretin** or to albumin. Less than 1% of the T_4 and T_3 in blood is in the free form, and it is in equilibrium with the large protein-bound fraction. It is this small amount of free thyroid hormone that interacts with target cells.

The protein-bound form of T_4 and T_3 represents a large reservoir of preformed hormone that can replenish the small amount of circulating free hormone as it is cleared from the blood. This reservoir provides the body with a buffer against drastic changes in circulating thyroid hormone levels as a result of sudden changes in the rate of T_4 and T_3 secretion. The protein-bound T_4 and T_3 molecules are also protected from metabolic inactivation and excretion in the urine. As a result of these factors, the thyroid hormones have long half-lives in the bloodstream. The half-life of T_4 is about 7 days; the half-life of T_3 is about 1 day.

Thyroid Hormones Are Metabolized by Peripheral Tissues

Thyroid hormones are both activated and inactivated by deiodination reactions in the peripheral tissues. The enzymes that catalyze the various deiodination reactions are regulated, resulting in different thyroid hormone concentrations in various tissues in different physiological and pathophysiological conditions.

Conversion of T_4 to T_3. As noted earlier, T_4 is the major secretory product of the thyroid gland and is the predominant thyroid hormone in the blood. However, about 40% of the T_4 secreted by the thyroid gland is converted to T_3 by enzymatic removal of the iodine atom at position 5′ of the thyronine ring structure (Fig. 33.5). This reaction is catalyzed by a **5′-deiodinase** (type 1) located in the liver, kidneys, and thyroid gland. The T_3 formed by this deiodination and that secreted by the thyroid react with thyroid hormone receptors in target cells; therefore, T_3 is the physiologically active form of the thyroid hormones. A second 5′-deiodinase (type 2) is

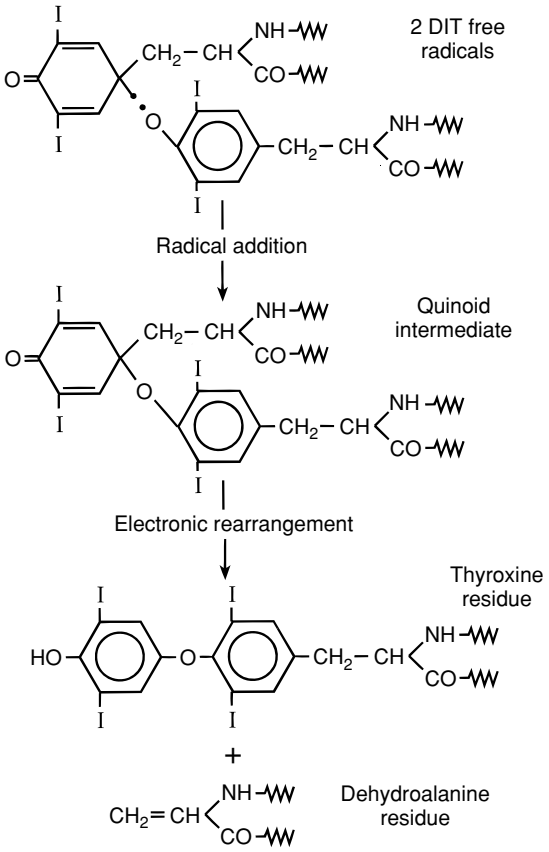

FIGURE 33.4 Theoretical model for the coupling reaction between two diiodotyrosine (DIT) residues in iodinated thyroglobulin. This model is based on free radical formation catalyzed by thyroid peroxidase. (Adapted from Taurog AM. Hormone synthesis: Thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. 8th Ed. Philadelphia: Lippincott Williams & Wilkins, 2000;61–85.)

present in skeletal muscle, the CNS, the pituitary gland, and the placenta. Type 2 deiodinase is believed to function primarily to maintain intracellular T_3 in target tissues, but it may also contribute to the generation of circulating T_3. All of the deiodinases contain **selenocysteine** in the active center. This rare amino acid has properties that make it ideal to catalyze deiodination reactions.

Deiodinations That Inactivate T_4 and T_3. Whereas the 5′-deiodination of T_4 to produce T_3 can be viewed as a metabolic activation process, both T_4 and T_3 undergo enzymatic deiodinations, particularly in the liver and kidneys, which inactivate them. For example, about 40% of the T_4 secreted by the human thyroid gland is deiodinated at the 5 position on the thyronine ring structure by a 5-deiodinase. This produces reverse T_3 (see Fig. 33.5). Since reverse T_3 has little or no thyroid hormone activity, this deiodination reaction is a major pathway for the metabolic inactivation or disposal of T_4. Triiodothyronine and reverse T_3 also undergo deiodination to yield 3,3′-diiodothyronine. This inactivate metabolite may be further deiodinated before being excreted.

Regulation of 5′-Deiodination. The 5′-deiodination reaction is a regulated process influenced by certain physiological and pathological factors. The result is a change in the relative amounts of T_3 and reverse T_3 produced from T_4. For example, a human fetus produces less T_3 from T_4 than a child or adult because the 5′-deiodination reaction is less active in the fetus. Also, 5′-deiodination is inhibited during fasting, particularly in response to carbohydrate restriction, but it can be restored to normal when the individual is fed again. Trauma, as well as most acute and chronic illnesses, also suppresses the 5′-deiodination reaction. Under all of these circumstances, the amount of T_3 produced from T_4 is reduced and its blood concentration falls. However, the amount of reverse T_3 rises in the circulation, mainly because its conversion to 3,3′-diiodothyronine by 5′-deiodination is reduced. A rise in reverse T_3 in the blood may signal that the 5′-deiodination reaction is suppressed.

Note that during fasting or in the disease states mentioned above, the secretion of T_4 is usually not increased, despite the decrease of T_3 in the circulation. This response indicates that, under these circumstances, a T_3 decrease in the blood does not stimulate the hypothalamic-pituitary-thyroid axis.

Minor Degradative Pathways. T_4 and, to a lesser extent, T_3 are also metabolized by conjugation with glucuronic acid in the liver. The conjugated hormones are secreted into the bile and eliminated in the feces. Many tissues also metabolize thyroid hormones by modifying the three-carbon side chain of the iodothyronine structure. These modifications include decarboxylation and deamination. The derivatives formed from T_4, such as **tetraiodoacetic acid** (tetrac), may also undergo deiodinations before being excreted (see Fig. 33.5).

TSH Regulates Thyroid Hormone Synthesis and Secretion

When the concentrations of free T_4 and T_3 fall in the blood, the anterior pituitary gland is stimulated to secrete **thyroid-stimulating hormone** (TSH), raising the concentration of TSH in the blood. This action results in increased interactions between TSH and its receptors on thyroid follicular cells.

TSH Receptors and Second Messengers. The receptor for TSH is a transmembrane glycoprotein thought to be located on the basal plasma membrane of the follicular cell. These receptors are coupled by G_s proteins, mainly to the adenylyl cyclase-cAMP-protein kinase A pathway, however, there is also evidence for effects via phospholipase C (PLC), inositol trisphosphate, and diacylglycerol (see Chapter 1). The physiological importance of TSH-stimulated phospholipid metabolism in human follicular cells is unclear, since very high concentrations of TSH are needed to activate PLC.

TSH and Thyroid Hormone Formation and Secretion. TSH stimulates most of the processes involved in thyroid hormone synthesis and secretion by follicular cells. The rise in cAMP produced by TSH is believed to cause many of these effects. TSH stimulates the uptake of iodide by follicular cells, usually after a short interval during which io-

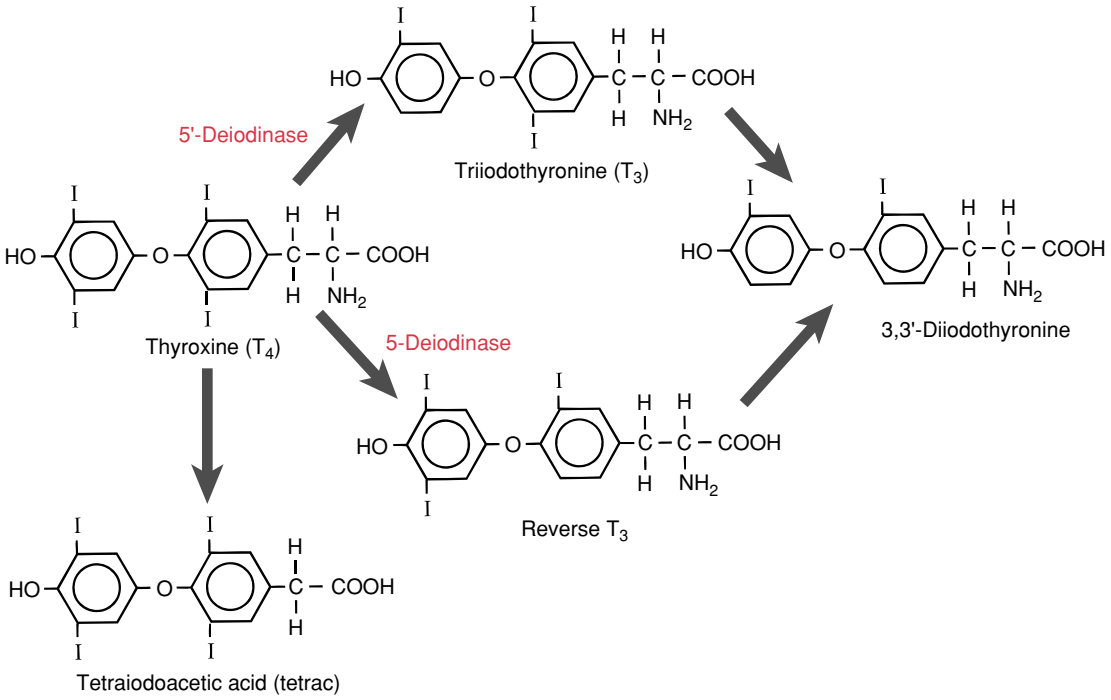

FIGURE 33.5 **The metabolism of thyroxine.** Thyroxine is deiodinated by 5′-deiodinase to form T_3, the physiologically active thyroid hormone. Some T_4 is also enzymatically deiodinated at the 5 position to form the inactive metabolite, reverse T_3. T_3 and reverse T_3 undergo additional deiodinations (e.g., to 3,3′-diiodothyronine) before being excreted. A small amount of T_4 is also decarboxylated and deaminated to form the metabolite, tetraiodoacetic acid (tetrac). Tetrac may then be deiodinated before being excreted.

dide transport is actually depressed. TSH also stimulates the iodination of tyrosine residues in the thyroglobulin precursor and the coupling of iodinated tyrosines to form iodothyronines. Moreover, it stimulates the pinocytosis of colloid by the apical membranes, resulting in a great increase in endocytosis of thyroglobulin and its hydrolysis. The overall result of these effects of TSH is an increased release of T_4 and T_3 into the blood. In addition to its effects on thyroid hormone synthesis and secretion, TSH rapidly increases energy metabolism in the thyroid follicular cell.

TSH and Thyroid Size. Over the long term, TSH promotes protein synthesis in thyroid follicular cells, maintaining their size and structural integrity. Evidence of this **trophic effect** of TSH is seen in a hypophysectomized patient, whose thyroid gland atrophies, largely as a result of a reduction in the height of follicular cells. However, the chronic exposure of an individual to excessive amounts of TSH causes the thyroid gland to increase in size. This enlargement is due to an increase in follicular cell height and number. Such an enlarged thyroid gland is called a **goiter**. These trophic and proliferative effects of TSH on the thyroid are primarily mediated by cAMP.

Dietary Iodide Is Essential for the Synthesis of Thyroid Hormones

Because iodine atoms are constituent parts of the T_4 and T_3 molecules, a continual supply of iodide is required for the synthesis of these hormones. If an individual's diet is severely deficient in iodide, as in some parts of the world, T_4 and T_3 synthesis is limited by the amount of iodide available to the thyroid gland. As a result, the concentrations of T_4 and T_3 in the blood fall, causing a chronic stimulation of TSH secretion, which, in turn, produces a goiter. Enlargement of the thyroid gland increases its capacity to accumulate iodide from the blood and to synthesize T_4 and T_3. However, the degree to which the enlarged gland can produce thyroid hormones to compensate for their deficiency in the blood depends on the severity of the deficiency of iodide in the diet. To prevent iodide deficiency and the consequent goiter formation in the human population, iodide is added to the table salt (iodized salt) sold in most developed countries.

THE MECHANISM OF THYROID HORMONE ACTION

Most cells of the body are targets for the action of thyroid hormones. The sensitivity or responsiveness of a particular cell to thyroid hormones correlates to some degree with the number of receptors for these hormones. The cells of the CNS appear to be an exception. As is discussed later, the thyroid hormones play an important role in CNS development during fetal and neonatal life, and developing nerve cells in the brain are important targets for thyroid hormones. In the adult, however, brain cells show little responsiveness to the metabolic regulatory action of thyroid hormones, although they have numerous receptors for these hormones. The reason for this discrepancy is unclear.

Thyroid hormone receptors (TR) are located in the nuclei of target cells bound to **thyroid hormone response elements** (TRE) in the DNA. TRs are protein molecules of about 50 kDa that are structurally similar to the nuclear receptors for steroid hormones and vitamin D. Thyroid receptors bound to the TRE in the absence of T_3 generally act to repress gene expression.

The free forms of T_3 and T_4 are taken up by target cells from the blood through a carrier-mediated process that requires ATP. Once inside the cell, T_4 is deiodinated to T_3, which enters the nucleus of the cell and binds to its receptor in the chromatin. The TR with bound T_3 forms a complex with other nuclear receptors (called a heterodimer) or with another TR (homodimer) to activate transcription. Other transcription factors may also complex with the TR heterodimer or homodimer. As a result, the production of mRNA for certain proteins is either increased or decreased, changing the cell's capacity to make these proteins (Fig. 33.6). T_3 can influence differentiation by regulating the kinds of proteins produced by its target cells and can influence growth and metabolism by changing the amounts of structural and enzymatic proteins present in the cells. The mechanisms by which T_3 alters gene expression continue to be investigated.

The gene expression response to T_3 is slow to appear. When T_3 is given to an animal or human, several hours elapse before its physiological effects can be detected. This delayed action undoubtedly reflects the time required for changes in gene expression and consequent changes in the synthesis of key proteins to occur. When T_4 is administered, its course of action is usually slower than that of T_3 because of the additional time required for the body to convert T_4 to T_3.

Thyroid hormones also have effects on cells that occur much faster and do not appear to be mediated by nuclear TR receptors, including effects on signal transduction pathways that alter cellular respiration, cell morphology, vascular tone, and ion homeostasis. The physiological relevance of these effects is currently being investigated.

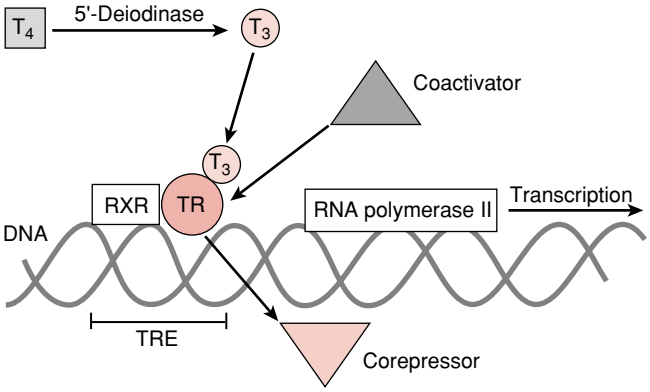

FIGURE 33.6 **The activation of transcription by thyroid hormone.** T_4 is taken up by the cell and deiodinated to T_3, which then binds to the thyroid hormone receptor (TR). The activated TR heterodimerizes with a second transcription factor, 9-*cis* retinoic acid receptor (RXR), and binds to the thyroid hormone response element (TRE). The binding of TR/RXR to the TRE displaces repressors of transcription and recruits additional coactivators. The final result is the activation of RNA polymerase II and the transcription of the target gene.

ROLE OF THE THYROID HORMONES IN DEVELOPMENT, GROWTH, AND METABOLISM

Thyroid hormones play a critical role in the development of the central nervous system (CNS). They are also essential for normal body growth during childhood, and in basal energy metabolism.

Thyroid Hormones Are Essential for Development of the Central Nervous System

The human brain undergoes its most active phase of growth during the last 6 months of fetal life and the first 6 months of postnatal life. During the second trimester of pregnancy, the multiplication of neuroblasts in the fetal brain reaches a peak and then declines. As pregnancy progresses and the rate of neuroblast division drops, neuroblasts differentiate into neurons and begin the process of synapse formation that extends into postnatal life.

Thyroid hormones first appear in the fetal blood during the second trimester of pregnancy, and levels continue to rise during the remaining months of fetal life. Thyroid hormone receptors increase about 10-fold in the fetal brain at about the time the concentrations of T_4 and T_3 begin to rise in the blood. These events are critical for normal brain development because thyroid hormones are essential for timing the decline in nerve cell division and the initiation of differentiation and maturation of these cells.

If thyroid hormones are deficient during these prenatal and postnatal periods of differentiation and maturation of the brain, mental retardation occurs. The cause is thought to be inadequate development of the neuronal circuitry of the CNS. Thyroid hormone therapy must be given to a thyroid hormone-deficient child during the first few months of postnatal life to prevent mental retardation. Starting thyroid hormone therapy after behavioral deficits have occurred cannot reverse the mental retardation (i.e., thyroid hormone must be present when differentiation normally occurs). Thyroid hormone deficiency during infancy causes both mental retardation and growth impairment, as discussed below. Fortunately, this occurs rarely today because thyroid hormone deficiency is usually detected in newborn infants and hormone therapy is given at the proper time.

The exact mechanism by which thyroid hormones influence differentiation of the CNS is unknown. Animal studies have demonstrated that thyroid hormones inhibit nerve cell replication in the brain and stimulate the growth of nerve cell bodies, the branching of dendrites, and the rate of myelinization of axons. These effects of thyroid hormones are presumably due to their ability to regulate the expression of genes involved in nerve cell replication and differentiation. However, the details, particularly in the human, are unclear.

Thyroid Hormones Are Essential for Normal Body Growth

The thyroid hormones are important factors regulating the growth of the entire body. For example, an individual who is deficient in thyroid hormones, who does not receive thyroid hormone therapy during childhood, will not grow to a normal adult height.

Thyroid Hormones and the Gene for GH. A major way thyroid hormones promote normal body growth is by stimulating the expression of the gene for **growth hormone** (GH) in the somatotrophs of the anterior pituitary gland. In a thyroid hormone-deficient individual, GH synthesis by the somatotrophs is greatly reduced and consequently GH secretion is impaired; therefore, a thyroid hormone-deficient individual will also be GH-deficient. If this condition occurs in a child, it will cause growth retardation, largely a result of the lack of the growth-promoting action of GH (see Chapter 32).

Other Effects of Thyroid Hormones on Growth. The thyroid hormones have additional effects on growth. In tissues such as skeletal muscle, the heart, and the liver, thyroid hormones have direct effects on the synthesis of a variety of structural and enzymatic proteins. For example, they stimulate the synthesis of structural proteins of mitochondria, as well as the formation of many enzymes involved in intermediary metabolism and oxidative phosphorylation.

Thyroid hormones also promote the calcification and, hence, the closure, of the cartilaginous growth plates of the bones of the skeleton. This action limits further linear body growth. How the thyroid hormones promote calcification of the growth plates of bones is not understood.

Thyroid Hormones Regulate the Basal Energy Economy of the Body

When the body is at rest, about half of the ATP produced by its cells is used to drive energy-requiring membrane transport processes. The remainder is used in involuntary muscular activity, such as respiratory movements, peristalsis, contraction of the heart, and in many metabolic reactions requiring ATP, such as protein synthesis. The energy required to do this work is eventually released as body heat.

Basal Oxygen Consumption and Body Heat Production. The major site of ATP production is the mitochondria, where the oxidative phosphorylation of ADP to ATP takes place. The rate of oxidative phosphorylation depends on the supply of ADP for electron transport. The ADP supply is, in turn, a function of the amount of ATP used to do work. For example, when more work is done per unit time, more ATP is used and more ADP is generated, increasing the rate of oxidative phosphorylation. The rate at which oxidative phosphorylation occurs is reflected in the amount of oxygen consumed by the body because oxygen is the final electron acceptor at the end of the electron transport chain.

Activities that occur when the body is not at rest, such as voluntary movements, use additional ATP for the work involved; the amounts of oxygen consumed and body heat produced depend on total body activity.

Thermogenic Action of the Thyroid Hormones. Thyroid hormones regulate the basal rate at which oxidative phosphorylation takes place in cells. As a result, they set the basal rate of body heat production and of oxygen consumed by the body. This is called the **thermogenic action** of thyroid hormones.

Thyroid hormone levels in the blood must be within normal limits for basal metabolism to proceed at the rate needed for a balanced energy economy of the body. For example, if thyroid hormones are present in excess, oxidative phosphorylation is accelerated, and body heat production and oxygen consumption are abnormally high. The converse occurs when the blood concentrations of T_4 and T_3 are lower than normal. The fact that thyroid hormones affect the amount of oxygen consumed by the body has been used clinically to assess the status of thyroid function. Oxygen consumption is measured under resting conditions and compared with the rate expected of a similar individual with normal thyroid function. This measurement is the **basal metabolic rate** (BMR) test.

Tissues Affected by the Thermogenic Action of Thyroid Hormones. Not all tissues are sensitive to the thermogenic action of thyroid hormones. Tissues and organs that give this response include skeletal muscle, the heart, the liver, and the kidneys. These are also tissues in which thyroid hormone receptors are abundant. The adult brain, skin, lymphoid organs, and gonads show little thermogenic response to thyroid hormones. With the exception of the adult brain, these tissues contain few thyroid hormone receptors, which may explain their poor response.

Molecular and Cellular Mechanisms. The thermogenic action of the thyroid hormones is poorly understood at the molecular level. The thermogenic effect takes many hours to appear after the administration of thyroid hormones to a human or animal, probably because of the time required for changes in the expression of genes involved. T_3 is known to stimulate the synthesis of cytochromes, cytochrome oxidase, and Na^+/K^+-ATPase in certain cells. This action suggests that T_3 may regulate the number of respiratory units in these cells, affecting their capacity to carry out oxidative phosphorylation. A greater rate of oxidative phosphorylation would result in greater heat production.

Thyroid hormone also stimulates the synthesis of **uncoupling protein-1** (UCP-1) in brown adipose tissue. ATP is synthesized by ATP synthase in the mitochondria when protons flow down their electrochemical gradient. UCP-1 acts as a channel in the mitochondrial membrane to dissipate the ion gradient without making ATP. As the protons move down their electrochemical gradient *uncoupled* from ATP synthesis, energy is released as heat. Adult humans have little brown adipose tissue, so it is not likely that UCP-1 makes a significant contribution to nutrient oxidation or body heat production. However, several uncoupling proteins (UCP-2 and UCP-3) have recently been discovered in many tissues, and their expression is regulated by thyroid hormones.

These novel uncoupling proteins may be involved in the thermogenic action of thyroid hormones.

Thyroid Hormones Stimulate Intermediary Metabolism

In addition to their ability to regulate the rate of basal energy metabolism, thyroid hormones influence the rate at which most of the pathways of intermediary metabolism operate in their target cells. When thyroid hormones are deficient, pathways of carbohydrate, lipid, and protein metabolism are slowed, and their responsiveness to other regulatory factors, such as other hormones, is decreased. However, these same metabolic pathways run at an abnormally high rate when thyroid hormones are present in excess. Thyroid hormones, therefore, can be viewed as amplifiers of cellular metabolic activity. The amplifying effect of thyroid hormones on intermediary metabolism is mediated through the activation of genes encoding enzymes involved in these metabolic pathways.

Thyroid Hormones Regulate Their Own Secretion

An important action of the thyroid hormones is the ability to regulate their own secretion. As discussed in Chapter 32, T_3 exerts an inhibitory effect on TSH secretion by thyrotrophs in the anterior pituitary gland by decreasing thyrotroph sensitivity to thyrotropin-releasing hormone (TRH). Consequently, when the circulating concentration of free thyroid hormones is high, thyrotrophs are relatively insensitive to TRH, and the rate of TSH secretion decreases. The resulting fall of TSH levels in the blood reduces the rate of thyroid hormone release from the follicular cells in the thyroid. When the free thyroid hormone level falls in the blood, however, the negative-feedback effect of T_3 on thyrotrophs is reduced, and the rate of TSH secretion increases. The rise in TSH in the blood stimulates the thyroid gland to secrete thyroid hormones at a greater rate. This action of T_3 on thyrotrophs is thought to be due to changes in gene expression in these cells.

The physiological actions of the thyroid hormones described above are summarized in Table 33.1.

TABLE 33.1 The Physiological Actions of Thyroid Hormones

Development of CNS	Inhibit nerve cell replication Stimulate growth of nerve cell bodies Stimulate branching of dendrites Stimulate rate of axon myelinization
Body growth	Stimulate expression of gene for GH in somatotrophs Stimulate synthesis of many structural and enzymatic proteins Promote calcification of growth plates of bones
Basal energy economy of the body	Regulate basal rates of oxidative phosphorylation, body heat production, and oxygen consumption (thermogenic effect)
Intermediary metabolism	Stimulate synthetic and degradative pathways of carbohydrate, lipid, and protein metabolism
Thyroid-stimulating hormone (TSH) secretion	Inhibit TSH secretion by decreasing sensitivity of thyrotrophs to thyrotropin-releasing hormone (TRH)

THYROID HORMONE DEFICIENCY AND EXCESS IN ADULTS

A deficiency or an excess of thyroid hormones produces characteristic changes in the body. These changes result from dysregulation of nervous system function and altered metabolism.

Thyroid Hormone Deficiency Causes Nervous and Metabolic Disorders

Thyroid hormone deficiency in humans has a variety of causes. For example, iodide deficiency may result in a reduction in thyroid hormone production. Autoimmune diseases, such as **Hashimoto's disease**, impair thyroid hormone synthesis (see Clinical Focus Box 33.1). Other causes of thyroid hormone deficiency include heritable diseases that affect certain steps in the biosynthesis of thyroid hormones and hypothalamic or pituitary diseases that interfere with TRH or TSH secretion. Obviously, radioiodine ablation or surgical removal of the thyroid gland also causes thyroid hormone deficiency. **Hypothyroidism** is the disease state that results from thyroid hormone deficiency.

Thyroid hormone deficiency impairs the functioning of most tissues in the body. As described earlier, a deficiency of thyroid hormones at birth that is not treated during the first few months of postnatal life causes irreversible mental retardation. Thyroid hormone deficiency later in life also influences the function of the nervous system. For example, all cognitive functions, including speech and memory, are slowed and body movements may be clumsy. These changes can usually be reversed with thyroid hormone therapy.

Metabolism is also reduced in thyroid hormone-deficient individuals. Basal metabolic rate is reduced, resulting in impaired body heat production. Vasoconstriction occurs in the skin as a compensatory mechanism to conserve body heat. Heart rate and cardiac output are reduced. Food intake is reduced, and the synthetic and degradative processes of intermediary metabolism are slowed. In severe hypothyroidism, a substance consisting of hyaluronic acid and chondroitin sulfate complexed with protein is deposited in the extracellular spaces of the skin, causing water to accumulate osmotically. This effect gives a puffy appearance to the face, hands, and feet called **myxedema**. All of the above disorders can be normalized with thyroid hormone therapy.

An Excess of Thyroid Hormone Produces Nervous and Other Disorders

The most common cause of excessive thyroid hormone production in humans is **Graves' disease**, an autoimmune

CLINICAL FOCUS BOX 33.1

Autoimmune Thyroid Disease—Postpartum Thyroiditis

Certain diseases affecting the function of the thyroid gland occur when an individual's immune system fails to recognize particular thyroid proteins as "self" and reacts to the proteins as if they were foreign. This usually triggers both humoral and cellular immune responses. As a result, antibodies to these proteins are generated, which then alter thyroid function. Two common autoimmune diseases with opposite effects on thyroid function are Hashimoto's disease and Graves' disease. In Hashimoto's disease, the thyroid gland is infiltrated by lymphocytes, and elevated levels of antibodies against several components of thyroid tissue (e.g., antithyroid peroxidase and antithyroglobulin antibodies) are found in the serum. The thyroid gland is destroyed, resulting in hypothyroidism. In Graves' disease, stimulatory antibodies to the TSH receptor activate thyroid hormone synthesis, resulting in hyperthyroidism (see text for details).

A third, fairly common autoimmune disease is postpartum thyroiditis, which usually occurs within 3 to 12 months after delivery. The disease is characterized by a transient thyrotoxicosis (hyperthyroidism) often followed by a period of hypothyroidism lasting several months. Many patients eventually return to the euthyroid state. Often only the hypothyroid phase of the disease may be observed, occurring in more than 30% of women with antibodies to thyroid peroxidase detectable preconception. The disease is also observed in patients known to have Graves' disease. The postpartum occurrence of the disorder is likely due to increased immune system function following the suppression of its activity during pregnancy.

It has been estimated that 5 to 10% of women develop postpartum thyroiditis. Of these women, about 50% have transient thyrotoxicosis alone, 25% have transient hypothyroidism alone, and the remaining 25% have both phases of the disease. The prevalence of the disease has prompted a clinical recommendation suggesting that thyroid function (serum T_4, T_3, and TSH levels) be surveyed postpartum at 2, 4, 6, and 12 months in all women with thyroid peroxidase antibodies or symptoms suggestive of thyroid dysfunction. Patients who have experienced one episode of postpartum thyroiditis should also be considered at risk for recurrence after pregnancy.

Treatment for thyrotoxicosis commonly involves inhibiting thyroid hormone synthesis and secretion. Thionamides are a class of drugs that inhibit the oxidation and organic binding of thyroid iodide to reduce thyroid hormone production. Some drugs in this class also inhibit the conversion of T_4 to T_3 in the peripheral tissues. Thyroid hormone replacement is required to treat hypothyroidism.

disorder caused by antibodies directed against the TSH receptor in the plasma membranes of thyroid follicular cells. These antibodies bind to the TSH receptor, resulting in an increase in the activity of adenylyl cyclase. The consequent rise in cAMP in follicular cells produces effects similar to those caused by the action of TSH. The thyroid gland enlarges to form a **diffuse toxic goiter**, which synthesizes and secretes thyroid hormones at an accelerated rate, causing thyroid hormones to be chronically elevated in the blood. Feedback inhibition of thyroid hormone production by the thyroid hormones is also lost.

Less common conditions that cause chronic elevations in circulating thyroid hormones include adenomas of the thyroid gland that secrete thyroid hormones and excessive TSH secretion caused by malfunctions of the hypothalamic-pituitary-thyroid axis. The disease state that develops in response to excessive thyroid hormone secretion, called **hyperthyroidism** or **thyrotoxicosis**, is characterized by many changes in the functioning of the body that are the opposite of those caused by thyroid hormone deficiency.

Hyperthyroid individuals are nervous and emotionally irritable, with a compulsion to be constantly moving around. However, they also experience physical weakness and fatigue. Basal metabolic rate is increased and, as a result, body heat production is increased. Vasodilation in the skin and sweating occur as compensatory mechanisms to dissipate excessive body heat. Heart rate and cardiac output are increased. Energy metabolism increases, as does appetite. However, despite the increase in food intake, a net degradation of protein and lipid stores occurs, resulting in weight loss. All of these changes can be reversed by reducing the rate of thyroid hormone secretion with drugs or by removal of the thyroid gland by radioactive ablation or surgery.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is the BEST in each case.

1. The effects of TSH on thyroid follicular cells include
   (A) Stimulation of endocytosis of thyroglobulin stored in the colloid
   (B) Release of a large pool of T_4 and T_3 stored in secretory vesicles in the cell
   (C) Stimulation of the uptake of iodide from the thyroglobulin stored in the colloid
   (D) Increase in perfusion by the blood
   (E) Stimulation of the binding of T_4 and T_3 to thyroxine-binding globulin
   (F) Increased cAMP hydrolysis
2. A child is born with a rare disorder in which the thyroid gland does not respond to TSH. What would be the predicted effects on mental ability, body growth rate, and thyroid gland size when the child reaches 6 years of age?

(continued)

(A) Mental ability would be impaired, body growth rate would be slowed, and thyroid gland size would be larger than normal
(B) Mental ability would be unaffected, body growth rate would be slowed, and thyroid gland size would be smaller than normal
(C) Mental ability would be impaired, body growth rate would be slowed, and thyroid gland size would be smaller than normal
(D) Mental ability would be unaffected, body growth rate would be unaffected, and thyroid gland size would be smaller than normal
(E) Mental ability would be impaired, body growth rate would be slowed, and thyroid gland size would be normal
(F) Mental ability would be unaffected, body growth rate would be unaffected, and thyroid gland size would be unaffected

3. If the 6-year-old child described in the previous question is now treated with thyroid hormones, how would mental ability, body growth rate, and thyroid gland size be affected?
(A) Mental ability would remain impaired, body growth rate would be improved, and thyroid gland size would be smaller than normal
(B) Mental ability would be improved, body growth rate would be improved, and thyroid gland size would be normal
(C) Mental ability would remain impaired, body growth rate would be improved, and thyroid gland size would be normal
(D) Mental ability would remain impaired, body growth rate would be improved, and thyroid gland size would be larger than normal
(E) Mental ability would be improved, body growth rate would remain slowed, and thyroid gland size would be normal
(F) Mental ability would be improved, body growth rate would remain slowed, and thyroid gland size would larger than normal
4. Uncoupling proteins
(A) Utilize the proton gradient across the mitochondrial membrane to facilitate ATP synthesis
(B) Are decreased by thyroid hormones
(C) Dissipate the proton gradient across the mitochondrial membrane to generate heat
(D) Are present exclusively in brown fat
(E) Uncouple fatty acid oxidation from glucose oxidation in mitochondria
(F) Are essential for maintaining body temperature in mammals
5. Triiodothyronine (T_3)
(A) Is produced in greater amounts by the thyroid gland than T_4
(B) Is bound by the thyroid receptor present in the cytosol of target cells
(C) Is formed from T_4 through the action of a 5-deiodinase
(D) Has a half-life of a few minutes in the bloodstream
(E) Is released from thyroglobulin through the action of thyroid peroxidase
(F) Can be produced by the deiodination of T_4 in pituitary thyrotrophs
6. A 40-year-old man complains of chronic fatigue, aching muscles, and occasional numbness in his fingers. Physical examination reveals a modest weight gain but no goiter is detected. Laboratory findings include TSH > 10 μU/L (normal range, 0.5 to 5 μU/L); free T_4, low to low-normal. These findings are most consistent with a diagnosis of
(A) Hypothyroidism secondary to a hypothalamic-pituitary defect
(B) Hyperthyroidism secondary to a hypothalamic-pituitary defect
(C) Hyperthyroidism as a result of iodine excess
(D) Hypothyroidism as a result of autoimmune thyroid disease
(E) Hypothyroidism as a result of iodine deficiency
(F) Hyperthyroidism as a result of autoimmune thyroid disease
7. The reaction catalyzed by thyroid peroxidase
(A) Produces hydrogen peroxide as an end-product
(B) Couples two iodotyrosine residues to form an iodothyronine residue
(C) Occurs on the basal membrane of the follicular cell
(D) Catalyzes the release of thyroid hormones into the circulation
(E) Couples MIT and DIT to thyroglobulin
(F) Couples dehydroalanine with a thyroxine residue
8. A 25-year-old woman complains of weight loss, heat intolerance, excessive sweating, and weakness. TSH and thyroid hormones are elevated, goiter is present, but no antithyroid antibodies are detected. Which of the following diagnoses is consistent with these symptoms?
(A) Graves' disease
(B) Resistance to thyroid hormone action
(C) Plummer's disease (thyroid gland adenoma)
(D) A 5′-deiodinase deficiency
(E) Acute Hashimoto's disease
(F) TSH-secreting pituitary tumor

SUGGESTED READING

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