

08 - 394 Thyroid Gland Physiology and Testing

394 Thyroid Gland Physiology and Testing

as pseudohyponatremia (due to raised lipids or protein) or translocational hyponatremia (due to raised glucose or exogenous effective osmolytes [e.g., mannitol]). SIAD must then be differentiated from other types of hypotonic hyponatremia. Measurement of urinary osmolality helps to distinguish SIAD from primary polydipsia where urinary osmolality is usually $<100\text{--}200$ mosm/L. Measurement of urinary sodium levels are useful to differentiate hyponatremia with low effective arterial blood volume from hyponatremia with normal effective arterial blood volume. In hypovolemic or hypervolemic hyponatremia with low effective blood volume, the mechanisms to conserve sodium remain intact, resulting in low urine sodium excretion, whereas in SIAD, there is ongoing renal sodium loss. According to guidelines, levels of <30 mmol/L argue for low effective arterial blood volume. Assessment of volume status has been used to classify hyponatremia into hypo-, hyper-, or euvolemic hyponatremia, though the accuracy of the clinical examination is poor. Hypervolemic hyponatremia typically occurs in patients with generalized edema due to severe congestive heart failure or cirrhosis. Hypovolemic hyponatremia occurs in patients with loss of sodium and water due to severe vomiting, diarrhea, diuretic use or primary adrenal insufficiency. In case of euvolemic hyponatremia, secondary adrenal insufficiency should be excluded before SIAD is diagnosed. Measurement of plasma AVP or copeptin has no diagnostic value. It is widely recommended to evaluate thyroid function in the workup of hyponatremia. There is, however, limited evidence for hypothyroidism as a significant cause of hyponatremia.

PART 12 Endocrinology and Metabolism **TREATMENT** Syndrome of Inappropriate Antidiuresis The management of SIAD differs depending on the underlying etiology as well as the severity and duration of symptoms. In the presence of severe neurologic symptoms, urgent intervention and treatment with hypertonic saline are indicated, aiming for an initial sodium rise of 4–6 mmol with a 100-mL bolus of hypertonic (3%) sodium chloride administered over ~15 min. An initial dose should be followed by clinical reassessment and a repeat dose if there is no clinical response until this target increment has been achieved. First-line treatment of chronic hyponatremia is fluid restriction, usually in the range of 500 to 1000 mL/d including all liquids, not solely water. However, fluid restriction is often ineffective, especially if urinary osmolality is >500 mosm/L. Second-line treatments when fluid restriction is inadequate are urea or tolvaptan. Urea is a product of hepatic nitrogen metabolism that is renally excreted and exerts an osmotic effect to promote free water excretion. Usually, doses of 30–60 g are sufficient to raise sodium levels. Tolvaptan is an oral vasopressin V₂-receptor antagonist that blocks AVP action in the kidney, inducing a water diuresis and raising sodium levels. Due to the risk of overly rapid correction, low-dose tolvaptan (7.5 mg)

has become more widely prescribed in recent years. Other concerns with tolvaptan include cost and risk of liver function derangement seen with sustained higher-dose therapy as used for autosomal dominant polycystic kidney disease. Demeclocycline is recommended by some as an alternative therapy, but European guidelines do not recommend it due to side effects. Demeclocycline can induce renal AVP resistance, thereby promoting dilute urine excretion. This effect is unpredictable and potential adverse effects include gastrointestinal intolerance, nephrotoxicity, and a photosensitive skin rash. According to a recent study, oral sodium chloride tablets and loop diuretics have a questionable efficacy. SGLT-2 inhibitors act at the sodium-glucose cotransporter in the proximal tubule to reduce resorption of glucose and sodium. SGLT-2 inhibitors induce glycosuria, which is accompanied by increased water excretion due to an osmotic diuresis. This has been shown to increase sodium levels in hospitalized as well as in outpatients with SIAD.

Acknowledgments The authors are grateful to Gary L. Robertson and Daniel G. Bichet for their contributions to this chapter in previous editions of Harrison's. ■ ■ **FURTHER READING** Adrogue HJ, Madias NE: The syndrome of inappropriate antidiuresis. *N Engl J Med* 389:1499, 2023. Christ-Crain M et al: Diabetes insipidus. *Nat Rev Dis Primers* 5:54, 2019. Fenske W et al: A copeptin based approach in the diagnosis of diabetes insipidus. *N Engl J Med* 379:428, 2018. Refardt J et al: Arginine or hypertonic saline-stimulated copeptin to diagnose AVP deficiency. *N Engl J Med* 389:1877, 2023. Tomkins M et al: Diagnosis and management of central diabetes insipidus in adults. *J Clin Endocrinol Metab* 107:2701, 2022. Warren A et al: Syndrome of inappropriate antidiuresis: From pathophysiology to management. *Endocr Rev* 44:819, 2023. J. Larry Jameson, Anthony P. Weetman,

Susan J. Mandel

Thyroid Gland

Physiology and Testing The thyroid gland produces two related hormones, thyroxine (T₄) and triiodothyronine (T₃) (Fig. 394-1). Acting through thyroid hormone receptors (TR) α and β , these hormones play a critical role in cell differentiation and organogenesis during development and help maintain thermogenic and metabolic homeostasis in the adult. Autoimmune disorders of the thyroid gland can stimulate overproduction of thyroid hormones (thyrotoxicosis) (Chap. 396) or cause glandular destruction and hormone deficiency (hypothyroidism) (Chap. 395). Benign nodules and various forms of thyroid cancer are relatively common and amenable to detection by physical examination, ultrasound, and other imaging techniques (Chap. 397). **ANATOMY AND DEVELOPMENT** The thyroid (Greek *thyreos*, shield, plus *eidos*, form) consists of two lobes connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12–20 g in size, highly vascular, and soft in consistency. Four parathyroid glands, which produce parathyroid hormone (Chap. 422), are located posterior to each pole of the thyroid. The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid injury and vocal cord paralysis. The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of thyroglossal duct cysts along this developmental tract. Thyroid hormone synthesis begins at about 11 weeks' gestation. Neural crest derivatives from the ultimobranchial

body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the juncture of the upper onethird and lower two-thirds of the gland. Calcitonin plays a minimal role in calcium homeostasis in humans, but the C cells are clinically important because they are the cellular origin of medullary thyroid cancer (Chap. 400).

11 NH2

3' 5' CH HO O CH₂ COOH || Thyroxine (T₄) 3,5,3',5'-Tetraiodothyronine Deiodinase 1 or 2 (5'-Deiodination) Deiodinase 3>2 (5-Deiodination) || || NH₂ O CH₂ CH HO COOH O CH₂ CH HO || Triiodothyronine (T₃) 3,5,3'-Triiodothyronine Reverse T₃ (rT₃) 3,3',5'-Triiodothyronine

FIGURE 394-1 Structures of thyroid hormones. Thyroxine (T₄) contains four iodine atoms. Deiodination leads to production of the potent hormone triiodothyronine (T₃) or the inactive hormone reverse T₃. Thyroid gland development is orchestrated by the coordinated expression of several developmental transcription factors. Thyroid transcription factor genes TTF1, TTF2, NKX2-1, FOXE1, and paired homeobox-8 (PAX8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they dictate thyroid cell development and the induction of thyroid-specific proteins such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na⁺/I⁻, NIS), and the thyroid-stimulating hormone (TSH) receptor (TSH-R). Mutations in these developmental transcription factors or their downstream target genes are rare causes of thyroid agenesis or dysmorphogenesis, although the causes of most forms of congenital hypothyroidism remain unknown (see Chap. 395, Table 395-1). Because congenital hypothyroidism occurs in ~1 in 4000 newborns, neonatal screening is now performed in most industrialized countries. Transplacental passage of maternal thyroid hormone occurs before the fetal thyroid gland begins to function and provides significant hormone support to a fetus with congenital hypothyroidism. Early thyroid hormone replacement in newborns with congenital hypothyroidism prevents potentially severe developmental abnormalities. The thyroid gland consists of numerous spherical follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid containing large amounts of thyroglobulin, the protein precursor of thyroid hormones (Fig. 394-2). The thyroid follicular cells are polarized—the basolateral surface is apposed to the bloodstream and an apical surface faces the follicular lumen. Increased demand for thyroid hormone is regulated by TSH, which binds to its receptor on the basolateral surface of the follicular cells. This binding leads to Tg reabsorption from the follicular lumen and proteolysis within the cytoplasm, yielding thyroid hormones for secretion into the bloodstream.

REGULATION OF THE THYROID AXIS TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. TSH is a 31-kDa hormone composed of α and β subunits; the α subunit is common to the other glycoprotein hormones (luteinizing hormone, folliclestimulating hormone, human chorionic gonadotropin [hCG]), whereas the TSH β subunit is unique to TSH. The extent and nature of carbohydrate modification are modulated by thyrotropin-releasing hormone (TRH) and influence the biologic activity of the hormone. The thyroid axis is a classic example of an endocrine feedback loop (Chap. 389). Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones act via negative feedback predominantly through thyroid hormone receptor β 2 (TR β 2) to inhibit TRH and TSH production (Fig. 394-2). The “set point” in this axis is established by

TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs ~15 min after administration of exogenous TRH. Dopamine, glucocorticoids, and somatostatin suppress TSH but are not of major physiologic importance except when these agents are administered in pharmacologic doses. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH-mediated stimulation of TSH. High thyroid hormone levels rapidly and directly suppress TSH gene expression and inhibit TRH stimulation of TSH secretion, indicating that thyroid hormones are the dominant regulator of TSH production. Like other pituitary hormones, TSH is released in a pulsatile manner and exhibits a diurnal rhythm; its highest levels occur at night. However, these TSH excursions are modest in comparison to those of other pituitary hormones, in part, because TSH has a relatively long plasma half-life (50 min). Consequently, single measurements of TSH are adequate for assessing its circulating level. TSH is measured using immunoradiometric assays that are highly sensitive and specific. These assays readily distinguish between normal and suppressed TSH values; thus, TSH can be used for the diagnosis of primary hyperthyroidism (low TSH) or primary hypothyroidism (high TSH).

Thyroid Gland Physiology and Testing CHAPTER 394 NH₂ COOH THYROID HORMONE SYNTHESIS, METABOLISM, AND ACTION ■ ■ THYROID HORMONE SYNTHESIS Thyroid hormones are derived from Tg, a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on tyrosine T3 T4 Hypothalamus – TSH-R Basal NIS II- cAMP TRH + – Tg Pituitary Apical TPO DIT Follicular cell Tg-MIT

- Iodination Tg C TSH o u p l i n g
-

Thyroid Thyroid follicle T3 T4 Peripheral actions FIGURE 394-2 Regulation of thyroid hormone synthesis. Left. Thyroid hormones T4 and T3 feed back to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH). TSH stimulates thyroid gland production of T4 and T3. Right. Thyroid follicles are formed by thyroid epithelial cells surrounding proteinaceous colloid, which contains thyroglobulin. Follicular cells, which are polarized, synthesize thyroglobulin and carry out thyroid hormone biosynthesis (see text for details). DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium iodide symporter; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH-R, thyroid-stimulating hormone receptor.

residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T3.

Iodine Metabolism and Transport Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner. For example, 10–25% of radioactive tracer (e.g., ¹²³I) is taken up by the normal thyroid gland over 24 h in an iodine-replete state; this value can rise to 70–90% in Graves' disease. Iodide uptake is mediated by NIS, which is expressed at the basolateral membrane of thyroid follicular cells. NIS is most highly expressed in the thyroid gland, but low levels are present in the salivary glands, lactating breast, and placenta. The iodide transport mechanism is highly regulated, allowing adaptation to variations in dietary supply. Low iodine levels increase the amount of NIS and stimulate uptake, whereas high iodine levels suppress NIS expression and uptake. The selective expression of NIS in the thyroid allows isotopic scanning, treatment of hyperthyroidism, and

ablation of thyroid cancer with radioisotopes of iodine, without significant effects on other organs. Mutation of the NIS gene is a rare cause of congenital hypothyroidism, underscoring its importance in thyroid hormone synthesis. Another iodine transporter, pendrin, is located on the apical surface of thyroid cells and mediates PART 12 Endocrinology and Metabolism Global scorecard of iodine nutrition in 2021 Iodine intake in the general population assessed by median urinary iodine concentration (mUIC) in school-age children (SAC)a Studies conducted in 2005–2020 Insufficient mUIC <100 µg/L

National data

Sub-national data No recent data

FIGURE 394-3 Worldwide iodine nutrition. aIn population monitoring of iodine status using urinary iodine concentration (UIC), school-age children (SAC) serve as a proxy for the general population; therefore, preference has been given to studies carried out in SAC. The UIC data have been selected for each country in the following order of priority: data from the most recent known nationally representative survey carried out between 2005 and 2020 in (1) SAC, (2) SAC and adolescents, (3) adolescents, (4) women of reproductive age, (5) other adults (excluding pregnant or lactating women), and (6) other eligible populations. In the absence of recent national surveys, subnational data were used in the same order of priority. Subnational UIC surveys are commonly carried out to provide a rapid assessment of population iodine status, but due to a lack of sampling rigor, they may over- or underestimate the iodine status at the national level and should be interpreted with caution. bAdequate iodine intake in SAC corresponds to median UIC values in the range of 100–299 µg/L and includes categories previously referred to as “adequate” (100–199 µg/L) and “more than adequate” (200–299 µg/L). (Reproduced with permission from The Iodine Global Network. Global scorecard of iodine nutrition in 2021 in the general population based on data in schoolage children (SAC). IGN: Ottawa, Canada. 2021.)

iodine efflux into the lumen. Mutation of the pendrin gene causes Pendred syndrome, a disorder characterized by defective organification of iodine, goiter, and sensorineural deafness. Iodine deficiency is prevalent in many mountainous regions and in central Africa, central South America, and northern Asia (Fig. 394-3). Europe remains mildly iodine-deficient, and health surveys indicate that iodine intake has been falling in the United States and Australia. The World Health Organization (WHO) estimates that about 2 billion people are iodine-deficient, based on urinary excretion data. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. Cretinism is characterized by intellectual disability and growth retardation and occurs when children who live in iodine-deficient regions are not treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early life. These children are often born to mothers with iodine deficiency, and it is likely that maternal thyroid hormone deficiency worsens the condition. The physiologic iodine requirement is higher in lactating women, and iodine turnover is high in infants. Concomitant selenium deficiency may also contribute to the neurologic manifestations of cretinism. Iodine supplementation of salt, bread, and other food substances has markedly reduced the prevalence of cretinism. Unfortunately, however, iodine deficiency remains a common cause of preventable intellectual disability, often because of societal resistance to food additives or the cost of supplementation. In Iodine intake Adequateb mUIC 100–299 µg/L Excess mUIC ≥300 µg/L

addition to overt cretinism, mild iodine deficiency can lead to subtle reduction of IQ. Oversupply of iodine, through supplements or foods enriched in iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The Recommended Dietary Allowance (RDA) is 220 µg iodine per day for pregnant women and 290 µg iodine per day for breastfeeding women. Because the effects of iodine deficiency are most severe in pregnant women and their babies, the American Thyroid Association has recommended that all pregnant and breastfeeding women in the United States and Canada take a pre natal multivitamin containing 150 µg iodine per day. Urinary iodine is

“ 100 µg/L in iodine-sufficient populations. **Organification, Coupling, Storage, and Release** After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide produced by dual oxidase (DUOX) and DUOX maturation factor (DUOXA). The reactive iodine atom is added to specific tyrosyl residues within Tg, a large (660 kDa) dimeric protein that consists of 2769 amino acids. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T4 and T3. Uncoupled mono- and diiodotyrosines (MIT, DIT) can be deiodinated by the enzyme iodotyrosine deiodinase, thereby recycling any iodide that is not converted into thyroid hormones. Disorders of thyroid hormone synthesis are rare causes of congenital hypothyroidism (Chap. 395). The vast majority of these disorders are due to recessive mutations in TPO or Tg, but defects have also been identified in the TSH-R, NIS, pendrin, hydrogen peroxide generation, and iodotyrosine deiodinase, as well as genes involved in thyroid gland development. In the case of biosynthetic defects, the gland is incapable of synthesizing adequate amounts of hormone, leading to increased TSH and a large goiter. **TSH Action** TSH regulates thyroid gland function through the TSH-R, a seven-transmembrane G protein-coupled receptor (GPCR). The TSH-R is coupled to the α subunit of stimulatory G protein (G_sα), which activates adenylyl cyclase, leading to increased production of cyclic adenosine monophosphate (cAMP). TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. Recessive loss-of-function TSH-R mutations cause thyroid hypoplasia and congenital hypothyroidism. Dominant gain-of-function mutations are rare causes of sporadic or familial hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function (Chap. 396). Most of these activating mutations occur in the transmembrane domain of the receptor. They mimic the conformational changes induced by TSH binding or the interactions of thyroid-stimulating immunoglobulins (TSIs) in Graves' disease. Activating TSH-R mutations also occur as somatic events, leading to clonal selection and expansion of the affected thyroid follicular cell and autonomously functioning thyroid nodules. **Other Factors That Influence Hormone Synthesis and Release**

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland, also influence thyroid hormone synthesis. These include insulin-like growth factor 1 (IGF-1), epidermal growth factor, transforming growth factor β (TGF- β), endothelins, and various cytokines. The quantitative roles of these factors are not well understood, but they are important in selected disease states. In acromegaly, for example, increased levels of growth hormone and IGF-1 are associated with goiter and predisposition to multinodular goiter (MNG). Certain cytokines and interleukins (ILs) produced in association with autoimmune thyroid disease induce thyroid growth, whereas others lead to apoptosis. Iodine deficiency increases thyroid blood flow and upregulates the NIS, stimulating more efficient iodine uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the Wolff-Chaikoff effect. In individuals with

a normal thyroid, the gland escapes from this inhibitory effect and iodide organification resumes; the suppressive action of high iodide may persist, however, in patients with underlying autoimmune thyroid disease.

THYROID FUNCTION IN PREGNANCY Five factors alter thyroid function in pregnancy: (1) the transient increase in hCG during the first trimester, which weakly stimulates the TSH-R; (2) the estrogen-induced rise in thyroxine-binding globulin (TBG) during the first trimester, which is sustained during pregnancy; (3) alterations in the immune system, leading to the onset, exacerbation, or amelioration of an underlying autoimmune thyroid disease; (4) increased thyroid hormone metabolism by the placental type III deiodinase; and (5) increased urinary iodide excretion, which can cause impaired thyroid hormone production in areas of marginal iodine sufficiency. Women with a precarious iodine intake ($<50 \mu\text{g/d}$) are most at risk of developing a goiter during pregnancy or giving birth to an infant with a goiter and hypothyroidism. The WHO recommends a daily iodine intake of $250 \mu\text{g}$ during pregnancy and lactation, and prenatal vitamins should contain $150 \mu\text{g}$ per tablet.

Thyroid Gland Physiology and Testing **CHAPTER 394** The rise in circulating hCG levels during the first trimester is accompanied by a reciprocal fall in TSH that persists into the middle of pregnancy. This reflects the weak binding of hCG, which is present at very high levels, to the TSH-R. Rare individuals have variant TSH-R sequences that enhance hCG binding and TSH-R activation. hCG-induced changes in thyroid function can result in transient gestational hyperthyroidism that may be associated with hyperemesis gravidarum, a condition characterized by severe nausea and vomiting and risk of volume depletion. However, antithyroid drugs are not indicated unless concomitant Graves' disease is suspected. Parenteral fluid replacement usually suffices until the condition resolves. Normative values for most thyroid function tests differ during pregnancy, and if available, trimester-specific reference ranges should be used when diagnosing thyroid dysfunction during pregnancy. TSH levels decrease at the end of the first trimester and then rise as gestation progresses so that the nonpregnant reference ranges can be used from mid-gestation to delivery. Total T4 and T3 levels are $\sim 1.5\times$ higher throughout pregnancy, but the free T4, which is the same or slightly higher at the end of the first trimester, progressively decreases so that by the third trimester, values are often below the nonpregnant lower reference cutoff. During

pregnancy, subclinical hypothyroidism occurs in 2% of women, but overt hypothyroidism is present in only 1 in 500. Prospective randomized controlled trials have not shown a benefit for universal thyroid disease screening in pregnancy. Targeted TSH testing for hypothyroidism is recommended for women planning a pregnancy if they have a strong family history of autoimmune thyroid disease, other autoimmune disorders (e.g., type 1 diabetes), infertility, prior preterm delivery or recurrent miscarriage, or signs or symptoms of thyroid disease, or are older than 30 years. Thyroid hormone requirements are increased by up to 45% during pregnancy in levothyroxine-treated hypothyroid women.

■ ■ THYROID HORMONE TRANSPORT AND METABOLISM

Serum-Binding Proteins T4 is secreted from the thyroid gland in about 15-fold excess over T3 (Table 394-1). Both hormones are bound to plasma proteins, including TBG, transthyretin (TTR, formerly known as thyroxine-binding prealbumin [TBPA]), and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones ($T4 > T3$), it carries ~80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (~3.5 g/dL), and it binds up to 10% of T4 and 30% of T3. TTR carries ~10% of T4 but little T3. When the effects of the various binding proteins are combined, ~99.98% of T4 and 99.7% of T3 are protein-bound. Because T3 is less

TABLE 394-1 Characteristics of Circulating T4 and T3

	T4	T3
Serum concentrations	8 µg/dL	0.14 µg/dL
Fraction of total hormone in the unbound form	0.02%	0.3%
Unbound (free) hormone	21×10^{-12} M	6×10^{-12} M
Serum half-life	7 d	2 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 µg/d	32 µg/d
PART	12	Endocrinology and Metabolism
Intracellular hormone fraction	~20%	~70%
Relative metabolic potency	0.3	

Receptor binding 10^{-10} – 10^{-11} M 10^{-10} – 10^{-11} M tightly bound than T4, the fraction of unbound T3 is greater than unbound T4, but there is less unbound T3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T4. The unbound or “free” concentrations of the hormones are $\sim 2 \times 10^{-11}$ M for T4 and $\sim 6 \times 10^{-12}$ M for T3, which roughly correspond to the thyroid hormone receptor-binding constants for these hormones (see below). The unbound hormone is thought to be biologically available to tissues. The homeostatic mechanisms that regulate the thyroid axis are directed toward maintenance of normal concentrations of unbound hormones.

Abnormalities of Thyroid Hormone-Binding Proteins A number of inherited and acquired abnormalities affect thyroid hormone-binding proteins. X-linked TBG deficiency is associated with very low levels of total T4 and T3. However, because unbound hormone levels are normal, patients are euthyroid and TSH levels are normal. It is important to recognize this disorder to avoid efforts to normalize total T4 levels, because this leads to thyrotoxicosis and is futile because of rapid hormone clearance in the absence of TBG. TBG levels are elevated by estrogen, which increases sialylation and delays TBG clearance. Consequently, in women who are pregnant or taking estrogen-containing contraceptives, elevated TBG increases total T4 and T3 levels; however, unbound T4 and T3 levels are normal. These features are part of the explanation for why women with hypothyroidism require increased amounts of L-thyroxine replacement as TBG levels are increased by pregnancy or estrogen treatment. Mutations in TBG, TTR, and albumin may increase the binding affinity for T4 and/ or T3 and cause disorders known as euthyroid hyperthyroxinemia or familial dysalbuminemic hyperthyroxinemia (FDH) (Table 394-2). These disorders result in

increased total T4 and/or T3, but unbound hormone levels are normal. The familial nature of the disorders, and the fact that TSH levels are normal rather than suppressed, should suggest this diagnosis. Unbound hormone levels (ideally measured by dialysis) are normal in FDH. The diagnosis can be confirmed by using tests that measure the affinities of radiolabeled hormone binding to specific transport proteins or by performing DNA sequence analyses of the abnormal transport protein genes.

TABLE 394-2 Conditions Associated with Euthyroid Hyperthyroxinemia

DISORDER	CAUSE	TRANSMISSION	CHARACTERISTICS
Familial dysalbuminemic hyperthyroxinemia (FDH)	AD	Increased T4	Normal unbound T4
Rarely increased T3	TBG	Familial excess	Increased TBG production
XL	Increased total T4, T3	Normal unbound T4, T3	Acquired excess
Medications (estrogen), pregnancy, cirrhosis, hepatitis	Acquired	Increased total T4, T3	Normal unbound T4, T3
Transthyretin	Excess	Islet tumors	Acquired
Usually normal T4, T3	Mutations	Increased affinity for T4 or T3	AD
Increased total T4, T3	Normal unbound T4, T3	Medications: propranolol, ipodate, iopanoic acid, amiodarone	Certain medications, such as salicylates and salicylate, can displace thyroid hormones from circulating binding proteins. Although these drugs transiently perturb the thyroid axis by increasing free thyroid hormone levels, TSH is suppressed until a new steady state is reached, thereby restoring euthyroidism. Circulating factors associated with acute illness may also displace thyroid hormone from binding proteins (Chap. 396). Resistance to thyroid hormone (RTH)

Also known as thyroxine-binding prealbumin (TBPA). Abbreviations: AD, autosomal dominant; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; XL, X-linked.

Deiodinases T4 may be thought of as a precursor for the more potent T3. T4 is converted to T3 by the deiodinase enzymes (Fig. 394-1). Type I deiodinase, which is located primarily in thyroid, liver, and kidneys, has a relatively low affinity for T4. Type II deiodinase has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type II deiodinase allows it to regulate T3 concentrations locally, a property that may be important in the context of levothyroxine (T4) replacement. Type II deiodinase is also regulated by thyroid hormone; hypothyroidism induces the enzyme, resulting in enhanced T4 → T3 conversion in tissues such as brain and pituitary. T4 → T3 conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g., propylthiouracil, propranolol, amiodarone, glucocorticoids). Type III deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3), including in the sick euthyroid syndrome. This enzyme is expressed in the human placenta but is not active in healthy individuals. In the sick euthyroid syndrome, especially with hypoperfusion, the type III deiodinase is activated in muscle and liver. Massive hemangiomas and other tumors that express type III deiodinase are a rare cause of consumptive hypothyroidism. ■

■ **THYROID HORMONE ACTION** Thyroid Hormone Transport Circulating thyroid hormones enter cells by passive diffusion and via specific transporters such as the monocarboxylate 8 transporter (MCT8), MCT10, and organic aniontransporting polypeptide 1C1. Mutations in the MCT8 gene have been identified in patients with X-linked psychomotor retardation and thyroid function abnormalities (low T4, high T3, and high TSH). After entering cells, thyroid hormones act primarily through nuclear receptors, although they also have nongenomic actions through stimulating mitochondrial enzymatic responses and may act directly on blood vessels and the heart through integrin receptors.

Nuclear Thyroid Hormone Receptors Thyroid hormones bind with high affinity to nuclear TRs α and β . Both TR α and TR β are expressed in most tissues, but their relative expression levels vary among organs; TR α is particularly abundant in brain, kidneys, gonads, muscle, and heart, whereas TR β expression is relatively high in the pituitary and liver. Both receptors are variably spliced to form unique isoforms. The TR β 2 isoform, which has a unique amino terminus, is

selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis (see above). The TR α 2 Albumin mutations, usually R218H Decreased T4 $\rightarrow$ T3 conversion Acquired Increased T4 Decreased T3 Normal or increased TSH AD Increased unbound T4, T3 Normal or increased TSH Some patients clinically thyrotoxic Thyroid hormone receptor β mutations

Nucleus T3 T3 T4 CoR

CoA T3 CoA

RXR TR Cytoplasm Gene TRE

Gene expression FIGURE 394-4 Mechanism of thyroid hormone receptor action. The thyroid hormone receptor (TR) and retinoid X receptor (RXR) form heterodimers that bind specifically to thyroid hormone response elements (TRE) in the promoter regions of target genes. In the absence of hormone, TR binds co-repressor (CoR) proteins that silence gene expression. The numbers refer to a series of ordered reactions that occur in response to thyroid hormone: (1) T4 or T3 enters the nucleus; (2) T3 binding dissociates CoR from TR; (3) co-activators (CoA) are recruited to the T3-bound receptor; and (4) gene expression is altered. isoform contains a unique carboxy terminus that precludes thyroid hormone binding. The TRs contain a central DNA-binding domain and a C-terminal ligand-binding domain. They bind to specific DNA sequences, termed thyroid response elements (TREs), in target genes (Fig. 394-4). The receptors bind as homodimers or, more commonly, as heterodimers with retinoic acid X receptors (RXRs) (Chap. 389). The activated receptor can either stimulate gene transcription (e.g., myosin heavy chain α) or inhibit transcription (e.g., TSH β -subunit gene), depending on the nature of the regulatory elements in the target gene. Thyroid hormones (T3 and T4) bind with similar affinities to TR α and TR β . However, structural differences in the ligand-binding domains provide the potential for developing receptor-selective agonists or antagonists, and these are under investigation. T3 is bound with 10–15 times greater affinity than T4, which explains its increased potency. Although T4 is produced in excess of T3, receptors are occupied mainly by T3, reflecting T4 $\rightarrow$ T3 conversion by peripheral tissues, T3 bioavailability in the plasma, and the greater affinity of receptors for T3. After binding to TRs, thyroid hormone induces conformational changes in the receptors that modify its interactions with accessory transcription factors. Importantly, in the absence of thyroid hormone binding, the aporeceptors bind to co-repressor proteins that inhibit gene transcription. Hormone binding dissociates the co-repressors and allows the recruitment of co-activators that enhance transcription. The discovery of TR interactions with co-repressors explains the fact that TR silences gene expression in the absence of hormone binding. Consequently, hormone deficiency has a profound effect on gene expression because it causes gene repression as well as loss of hormone-induced stimulation. This concept has been corroborated by the finding that targeted deletion of the TR genes in mice has a less pronounced phenotypic effect than hormone deficiency. Thyroid Hormone Resistance Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by elevated thyroid hormone levels and inappropriately normal or elevated TSH. Individuals with RTH do not, in general, exhibit signs and symptoms that are typical of hypothyroidism because hormone resistance is partial and is compensated by increased levels of thyroid hormone. The clinical features of RTH can include goiter, attention deficit disorder, mild reduction in IQ, delayed skeletal maturation, tachycardia, and impaired metabolic responses to

thyroid hormone.

Classical forms of RTH are caused by mutations in the TR β gene. These mutations, located in restricted regions of the ligand-binding domain, cause loss of receptor function. However, because the mutant receptors retain the capacity to dimerize with RXRs, bind to DNA, and recruit co-repressor proteins, they function as antagonists of the remaining normal TR β and TR α receptors. This property, referred to as “dominant negative” activity, explains the autosomal dominant mode of transmission. The diagnosis is suspected when unbound thyroid hormone levels are increased without suppression of TSH. Similar hormonal abnormalities are found in other affected family members, although the TR β mutation arises de novo in ~20% of patients. DNA sequence analysis of the TR β gene provides a definitive diagnosis. RTH must be distinguished from other causes of euthyroid hyperthyroxinemia (e.g., FDH) and inappropriate secretion of TSH by TSH-secreting pituitary adenomas (Chap. 392). In most patients, no treatment is indicated; the importance of making the diagnosis is to avoid inappropriate treatment of mistaken hyperthyroidism and to provide genetic counseling.

Thyroid Gland Physiology and Testing CHAPTER 394 A distinct form of RTH is caused by mutations in the TR α gene. Affected patients have many clinical features of congenital hypothyroidism including growth retardation, skeletal dysplasia, severe constipation, and delayed neurocognitive development. In contrast to RTH caused by mutations in TR β , thyroid function tests include normal TSH, low or normal T₄, and normal or elevated T₃ levels. These distinct clinical and laboratory features underscore the different tissue distribution and functional roles of TR β and TR α . Thyroxine treatment appears to alleviate some of the clinical manifestations of patients with RTH caused by TR α mutations. ■ ■ **PHYSICAL EXAMINATION** In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of ophthalmopathy and dermopathy (Chap. 396). Examination of the neck begins by inspecting the seated patient from the front and side and noting any surgical scars, obvious masses, or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when nodules are small. The patient’s neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus, which is attached to the lower one-third of the thyroid lobes, can be identified and then followed laterally to locate either lobe (normally, the right lobe is slightly larger than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner’s fingers. Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12–20 g) should be made, and a drawing is often the best way to record findings. Ultrasound imaging provides the most accurate measurement of thyroid volume and nodularity and is useful for assessment of goiter prevalence in iodine-deficient regions. However, ultrasound is not indicated if the thyroid physical examination is normal. The size, location, and consistency of any nodules should also be defined. A bruit or thrill over the gland, located over the insertion of the superior and inferior thyroid arteries (superior or inferolaterally), indicates increased vascularity, associated with turbulent rather than laminar blood flow, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton’s sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward.

The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck. ■ ■LABORATORY EVALUATION Measurement of Thyroid Hormones The enhanced sensitivity and specificity of TSH assays have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically

in response to alterations of T4 and T3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. With rare exceptions (see below), a normal TSH level excludes a primary abnormality of thyroid function. This strategy depends on the use of assays for TSH that are sensitive enough to discriminate between the lower limit of the reference interval and the suppressed values that occur with thyrotoxicosis. Extremely sensitive assays can detect TSH levels ≤ 0.004 mIU/L, but, for practical purposes, assays sensitive to ≤ 0.01 mIU/L are sufficient. The widespread availability of sensitive TSH assays has rendered the TRH stimulation test obsolete, because the failure of TSH to rise after an intravenous bolus of 200–400 μ g TRH has the same implications as a suppressed basal TSH. Because the antibodies used in many TSH assays are biotinylated, biotin supplements containing 1000 μ g or more, including biotin in some multivitamins, can interfere with TSH measurements, resulting in falsely low TSH values and falsely high T4 or T3 levels. Therefore, patients should be advised to stop taking biotin for at least 2 days prior to thyroid function testing.

PART 12 Endocrinology and Metabolism The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Automated immunoassays are widely available for serum total T4 and total T3. T4 and T3 are highly protein-bound, and numerous factors (illness, medications, genetic factors) can influence protein binding. It is useful, therefore, to measure the free, or unbound, hormone levels, which correspond to the biologically available hormone pool. Two direct methods are used to measure unbound thyroid hormones: (1) unbound thyroid hormone competition with radiolabeled T4 (or an analogue) for binding to a solid-phase antibody, and (2) physical separation of the unbound hormone fraction by ultracentrifugation or equilibrium dialysis. Although early unbound hormone immunoassays suffered from artifacts, newer assays correlate well with the results of the more technically demanding and expensive physical separation methods. An indirect method that is now less commonly used to estimate unbound thyroid hormone levels is to calculate the free T3 or free T4 index from the total T4 or T3 concentration and the thyroid hormone binding ratio (THBR). The latter is derived from the T3-resin uptake test, which determines the distribution of radiolabeled T3 between an absorbent resin and the unoccupied thyroid hormone-binding proteins in the sample. The binding of the labeled T3 to the resin is increased when there is reduced unoccupied protein binding sites (e.g., TBG deficiency) or increased total thyroid hormone in the sample; it is decreased under the opposite circumstances. The product of THBR and total T3 or T4 provides the free T3 or T4 index. In effect, the index corrects for anomalous total hormone values caused by variations in hormone-protein binding. Total thyroid hormone levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone therapy, tamoxifen, selective estrogen receptor modulators, inflammatory liver disease) and decreased when TBG binding is reduced (androgens, nephrotic syndrome). Genetic disorders and acute illness can also cause abnormalities in thyroid hormone-binding proteins, and various drugs (phenytoin, carbamazepine, salicylates, and nonsteroidal antiinflammatory drugs [NSAIDs]) can interfere with thyroid hormone binding. Because unbound thyroid hormone levels are normal and the patient is euthyroid in all of these

circumstances, assays that measure unbound hormone are preferable to those for total thyroid hormones. For most purposes, the unbound T4 level is sufficient to confirm thyrotoxicosis, but 2-5% of patients have only an elevated T3 level (T3 toxicosis). Thus, unbound T3 levels should be measured in patients with a suppressed TSH but normal unbound T4 levels. There are several clinical conditions in which the use of TSH as a screening test may be misleading, particularly without simultaneous unbound T4 determinations. Any severe nonthyroidal illness can cause abnormal TSH levels. Although hypothyroidism is the most common cause of an elevated TSH level, rare causes include a TSH-secreting pituitary tumor (Chap. 392), thyroid hormone resistance, and assay artifact. Conversely, a suppressed TSH level, particularly <0.01 mIU/L, usually indicates thyrotoxicosis. However, subnormal TSH levels between 0.01 and 0.1 mIU/L may be seen during the first trimester of

pregnancy (due to hCG secretion), after treatment of hyperthyroidism (because TSH can remain suppressed for several months), and in response to certain medications (e.g., high doses of glucocorticoids or dopamine). As above, biotin supplements, generally those containing more than 1000 ug, taken <18 h prior to a blood draw can interfere with biotinylated TSH antibodies and the subsequent streptavidin capture. Importantly, secondary hypothyroidism, caused by hypothalamic-pituitary disease, is associated with a variable (low to high-normal) TSH level, which is inappropriate for the low T4 level. Thus, TSH should not be used as an isolated laboratory test to assess thyroid function in patients with suspected or known hypothalamic or pituitary disease. Tests for the end-organ effects of thyroid hormone excess or depletion, such as estimation of basal metabolic rate, tendon reflex relaxation rates, or serum cholesterol, are relatively insensitive and are not useful as clinical determinants of thyroid function. Tests to Determine the Etiology of Thyroid Dysfunction

Autoimmune thyroid disease is detected most easily by measuring circulating antibodies against TPO and Tg. Because antibodies to Tg alone are less common, it is reasonable to measure only TPO antibodies. About 5-15% of euthyroid women and up to 2% of euthyroid men have thyroid antibodies; such individuals are at increased risk of developing thyroid dysfunction. Almost all patients with autoimmune hypothyroidism, and up to 80% of those with Graves' disease, have TPO antibodies, usually at high levels. TSIs are antibodies that stimulate the TSH-R in Graves' disease. They are most commonly measured by commercially available tracer displacement assays called TRAb (TSH receptor antibody) with the assumption that elevated levels in the setting of clinical hyperthyroidism reflect stimulatory effects on the TSH receptor. A bioassay is less commonly used. Remission rates in patients with Graves' disease after antithyroid drug cessation are higher in patients with disappearance TRAb. Furthermore, the TRAb assay is used to predict both fetal and neonatal thyrotoxicosis caused by transplacental passage of high maternal levels of TRAb or TSI ($>3\times$ upper limit of normal) in the last trimester of pregnancy. Serum Tg levels are increased in all types of thyrotoxicosis except thyrotoxicosis factitia caused by self-administration of thyroid hormone. Tg levels are particularly increased in thyroiditis, reflecting thyroid tissue destruction and release of Tg. The main role for Tg measurement, however, is in the follow-up of thyroid cancer patients. After total thyroidectomy and radioablation for patients with thyroid cancer, Tg levels should be <0.2 ng/mL in the absence of anti-Tg antibodies; measurable levels indicate incomplete ablation or recurrent cancer. Radioiodine Uptake and Thyroid Scanning The thyroid gland selectively transports and organifies radioisotopes of iodine (^{123}I , ^{125}I , ^{131}I) and transports $^{99\text{m}}\text{Tc}$ pertechnetate, allowing thyroid imaging for all these isotopes, but quantitation of

radioactive tracer fractional uptake for iodine isotopes only. Nuclear imaging of Graves' disease is characterized by an enlarged gland and increased tracer uptake that is distributed homogeneously. Toxic adenomas appear as focal areas of increased uptake, with suppressed tracer uptake in the remainder of the gland (reflecting suppressed TSH). In toxic MNG, the gland is enlarged—often with distorted architecture—and there are multiple areas of relatively increased (functioning nodules) or decreased tracer uptake (suppressed thyroid parenchyma or nonfunctioning nodules). Subacute, viral, and postpartum thyroiditis are associated with very low uptake because of follicular cell damage and TSH suppression. Thyrotoxicosis factitia is also associated with low uptake because exogenous hormone suppresses TSH. In addition, excessive circulating exogenous iodine (e.g., from dietary sources of iodinated contrast dye) reduces radionuclide uptake even in the presence of increased thyroid hormone production. Thyroid scintigraphy is not used in the routine evaluation of patients with thyroid nodules but should be performed if the serum TSH level is subnormal to determine if functioning thyroid nodules are present. Functioning or “hot” nodules are almost never malignant, and fine-needle aspiration (FNA) biopsy is not indicated (see Chap. 397,

Fig. 397-3B). The vast majority of thyroid nodules do not produce thyroid

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