TABLE 405-1 GENETIC CAUSES OF CONGENITAL HYPOTHYROIDISM

Defective Gene Protein	Inheritance	Consequences
PROP-1	Autosomal recessive	Combined pituitary hormone deficiencies with preservation of adrenocorticotropic hormone
PIT-1	Autosomal recessive Autosomal dominant	Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)
TSHβ	Autosomal recessive	TSH deficiency
TTF-1 (TITF-1)	Autosomal dominant	Variable thyroid hypoplasia, choreoathetosis, pulmonary problems
TTF-2 (FOXE-1)	Autosomal recessive	Thyroid agenesis, choanal atresia, spiky hair
PAX-8	Autosomal dominant	Thyroid dysgenesis
TSH-receptor	Autosomal recessive	Resistance to TSH
$G_{s\alpha}$ (Albright hereditary osteodystrophy)	Autosomal dominant	Resistance to TSH
Na^+/I^- symporter	Autosomal recessive	Inability to transport iodide
DUOX2 (THOX2)	Autosomal dominant	Organification defect
DUOXA2	Autosomal recessive	Organification defect
Thyroid peroxidase	Autosomal recessive	Defective organification of iodide
Thyroglobulin	Autosomal recessive	Defective synthesis of thyroid hormone
Pendrin	Autosomal recessive	Pendred syndrome: sensorineural deafness and partial organification defect in thyroid
Dehalogenase 1	Autosomal recessive	Loss of iodide reutilization

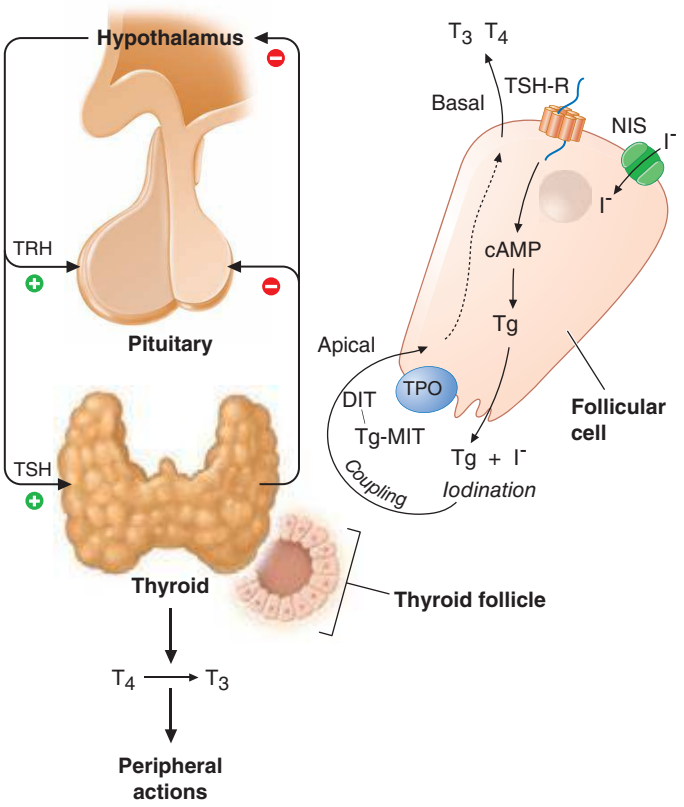

FIGURE 405-2 Regulation of thyroid hormone synthesis. ***Left.*** Thyroid hormones T_4 and T_3 feed back to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH). TSH stimulates thyroid gland production of T_4 and T_3. ***Right.*** 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.

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, follicle-stimulating 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) stimulation and influence the biologic activity of the hormone.

The thyroid axis is a classic example of an endocrine feedback loop. 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 β2 (TRβ2) to inhibit TRH and TSH production (Fig. 405-2). 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 secretion and inhibit TRH stimulation of TSH, 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 hyperthyroidism (low TSH) as well as hypothyroidism (high TSH).

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 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 T_4 and T_3.

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., ^{123}I) is taken up by the normal thyroid gland over 24 h; 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 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.