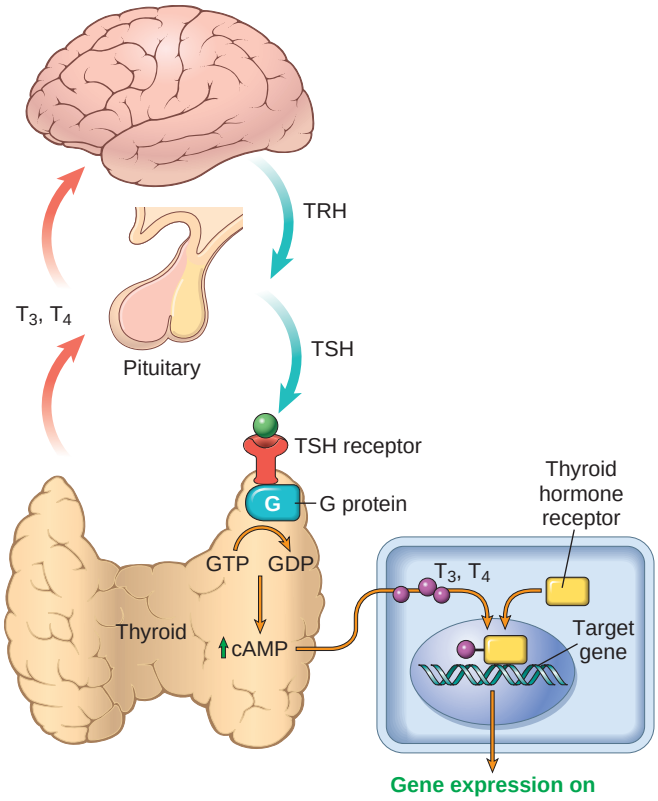

Figure 24-8 Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormones. Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary, causing T_3 and T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, feed back to suppress the secretion of both TRH and TSH. TSH binds to the TSH receptor on the thyroid follicular epithelium, which causes activation of G proteins, and cAMP-mediated synthesis and release of thyroid hormones (T_3 and T_4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes to initiate transcription.

events that result in an increase in intracellular cAMP levels, which stimulates thyroid growth and thyroid hormone synthesis and release via cAMP-dependent protein kinases.

Thyroid follicular epithelial cells convert thyroglobulin into *thyroxine (T_4)* and lesser amounts of *triiodothyronine (T_3)*. T_4 and T_3 are released into the systemic circulation, where most of these peptides are reversibly bound to circulating plasma proteins, such as thyroxine-binding globulin and transthyretin. The binding proteins act as a buffer that maintains the serum unbound ("free") T_3 and T_4 concentrations within narrow limits, while ensuring that the hormones are readily available to the tissues. In the periphery, the majority of free T_4 is deiodinated to T_3; the latter binds to thyroid hormone nuclear receptors in target cells with tenfold greater affinity than does T_4 and has proportionately greater activity. Binding of thyroid hormone to its nuclear thyroid hormone receptor (TR) results in the assembly of a multiprotein hormone-receptor complex on thyroid hormone response elements (TREs) in target genes, up regulating their transcription (Fig. 24-8). Thyroid hormone has diverse cellular effects, including the stimulation of carbohydrate and lipid catabolism and protein synthesis in a wide range of cells. The net result is an increase in the basal metabolic rate. In addition, thyroid hormone has a critical role in brain development in the fetus and neonate (see later).

The function of the thyroid gland can be inhibited by a variety of chemical agents, collectively referred to as *goitrogens*. Because they suppress T_3 and T_4 synthesis, the level of TSH increases, and subsequent hyperplastic enlargement of the gland (*goiter*) follows. The antithyroid agent *propylthiouracil* inhibits the oxidation of iodide and thus blocks the production of thyroid hormones; parenthetically, propylthiouracil also inhibits the peripheral deiodination of circulating T_4 into T_3, thus ameliorating symptoms of thyroid hormone excess (see later). Iodide, when given in large doses to individuals with thyroid hyperfunction, also blocks the release of thyroid hormones by inhibiting the proteolysis of thyroglobulin. Thus, thyroid hormone is synthesized and incorporated into colloid, but it is not released into the blood.

The thyroid gland follicles also contain a population of *parafollicular cells*, or C cells, which synthesize and secrete the hormone *calcitonin*. This hormone promotes the absorption of calcium by the skeletal system and inhibits the resorption of bone by osteoclasts.

Diseases of the thyroid include conditions associated with excessive release of thyroid hormones (hyperthyroidism), thyroid hormone deficiency (hypothyroidism), and mass lesions of the thyroid. We will first consider the clinical consequences of disturbed thyroid function, and then turn to the disorders that generate these problems.

Hyperthyroidism

***Thyrotoxicosis* is a hypermetabolic state caused by elevated circulating levels of free T_3 and T_4.** Because it is caused most commonly by hyperfunction of the thyroid gland, it is often referred to as *hyperthyroidism*. However, in certain conditions the oversupply is related to either excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extrathyroidal source, rather than hyperfunction of the gland (Table 24-3). Thus, strictly speaking, hyperthyroidism is only one (albeit the most common) cause of thyrotoxicosis. The terms *primary* and *secondary hyperthyroidism* are sometimes used to designate hyperthyroidism arising from an intrinsic thyroid abnormality and that arising from processes outside of the thyroid, such as a TSH-secreting pituitary tumor, respectively. With this caveat, we follow the common practice of using the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably. **The three most common causes of thyrotoxicosis are associated with hyperfunction of the gland and include the following:**

- *Diffuse hyperplasia* of the thyroid associated with Graves disease (approximately 85% of cases)
- Hyperfunctional *multinodular goiter*
- Hyperfunctional thyroid *adenoma*

Clinical Course. The clinical manifestations of hyperthyroidism are protean and include changes referable to the