382-1). Type I deiodinase, which is located primarily in thyroid, liver, and kidneys, has a relatively low affinity for T_4. Type II deiodinase has a higher affinity for T_4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type II deiodinase allows it to regulate T_3 concentrations locally, a property that may be important in the context of levothyroxine (T_4) replacement. Type II deiodinase is also regulated by thyroid hormone; hypothyroidism induces the enzyme, resulting in enhanced $T_4 \rightarrow T_3$ conversion in tissues such as brain and pituitary. $T_4 \rightarrow T_3$ 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 T_4 and T_3 and is the most important source of reverse T_3 (rT_3), 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 anion-transporting polypeptide 1C1. Mutations in the *MCT8* gene have been identified in patients with X-linked psychomotor retardation and thyroid function abnormalities (low T_4, high T_3, 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 TRα and TRβ are expressed in most tissues, but their relative expression levels vary among organs; TRα is particularly abundant in brain, kidneys,