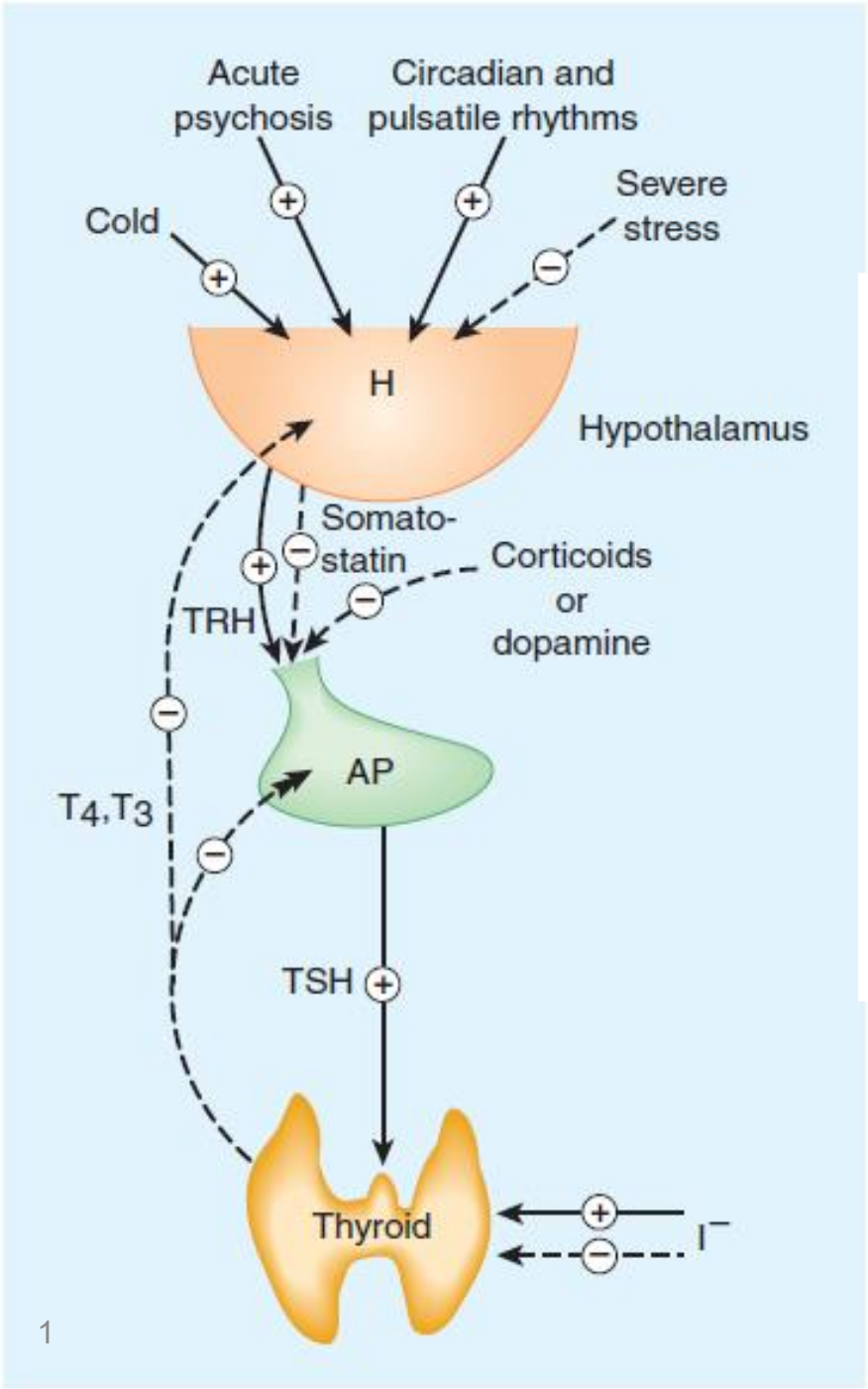


FIGURE 38–3 The hypothalamic-pituitary-thyroid axis. Acute psychosis or prolonged exposure to cold may activate the axis. Hypothalamic thyroid-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH) release, while somatostatin and dopamine inhibit it. TSH stimulates T_4 and T_3 synthesis and release from the thyroid, and they in turn inhibit both TRH and TSH synthesis and release. Small amounts of iodide are necessary for hormone production, but large amounts inhibit T_3 and T_4 production and release. Solid arrows, stimulatory influence; dashed arrows, inhibitory influence. H, hypothalamus; AP, anterior pituitary.

Thyroid Hormones (T_4 & T_3)

- **Normalize growth and development, body temperature, and energy levels.**
- **Used as thyroid replacement therapy in hypothyroidism.**
- **Thyroxine (T_4) is peripherally metabolized to triiodothyronine (T_3) by deiodination (5'-deiodinase).**

Thyroid Hormones (T_4 & T_3)

Inhibitors of 5'-deiodinase:

1. Amiodarone
2. Iodinated contrast media
3. Propylthiouracil
4. β-Adrenergic blockers
5. Corticosteroids
6. Severe illness
7. Starvation

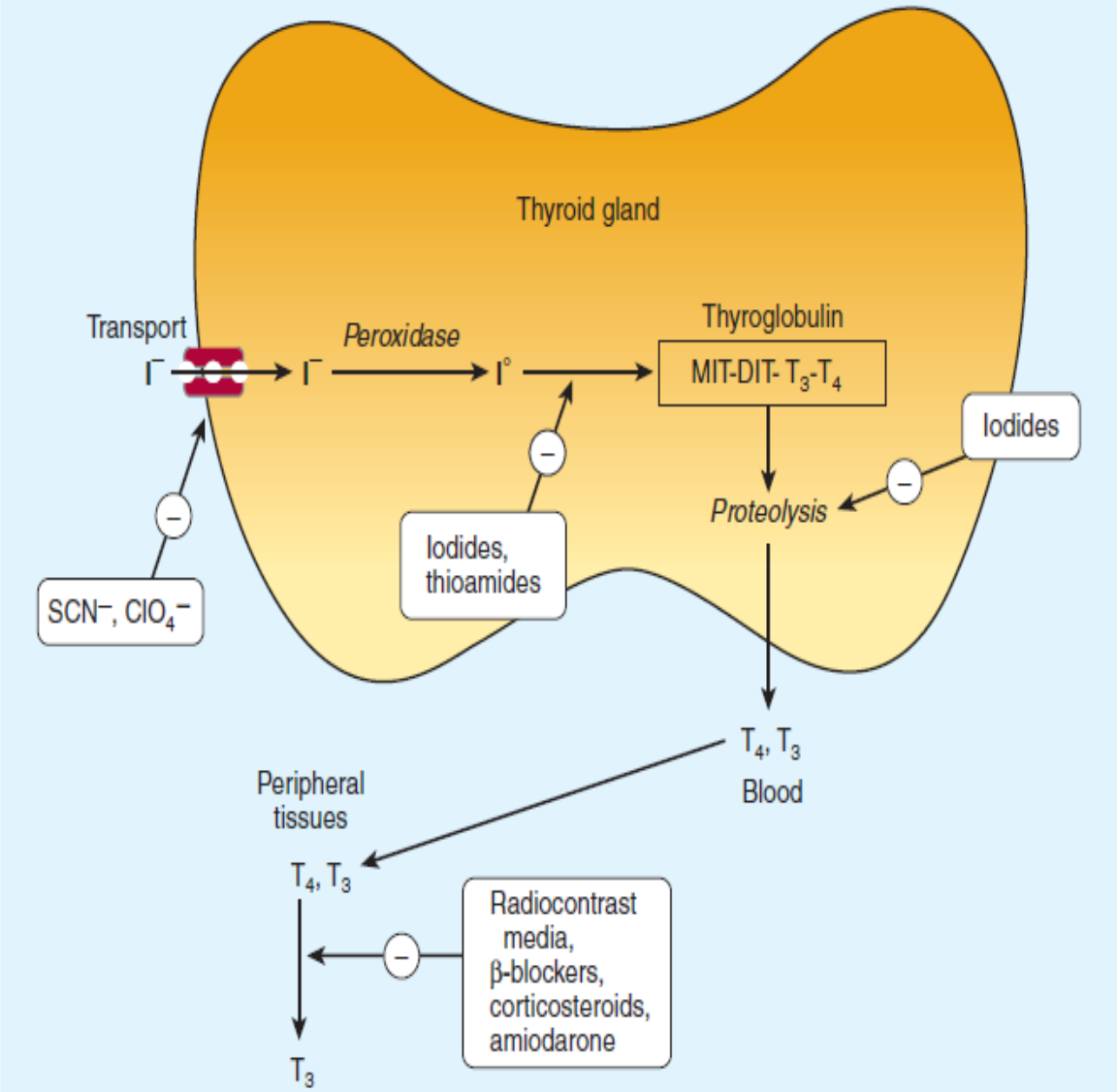


FIGURE 38–1 Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

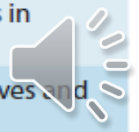
Thyroid Hormones (T_4 & T_3)

Pharmacokinetics:

- **Absorption occurs mainly in the duodenum and ileum.**
- **Absorption is modified by food, drugs, gastric acidity and intestinal flora.**
- **Absorption is reduced by cholestyramine, ciprofloxacin and aluminum hydroxide..**

TABLE 38–3 Drug effects and thyroid function.

Drug Effect	Drugs
Change in thyroid hormone synthesis	
Inhibition of TRH or TSH secretion without induction of hypothyroidism or hyperthyroidism	Dopamine, bromocriptine, levodopa, corticosteroids, somatostatin, metformin
Inhibition of thyroid hormone synthesis or release with the induction of hypothyroidism (or occasionally hyperthyroidism)	Iodides (including amiodarone), lithium, aminoglutethimide, thioamides, ethionamide, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib), HIV protease inhibitors
Alteration of thyroid hormone transport and serum total T_3 and T_4 levels, but usually no modification of FT_4 or TSH	
Increased TBG	Estrogens, tamoxifen, heroin, methadone, mitotane, fluorouracil
Decreased TBG	Androgens, glucocorticoids
Displacement of T_3 and T_4 from TBG with transient hyperthyroxinemia	Salicylates, fenclofenac, mefenamic acid, furosemide
Alteration of T_4 and T_3 metabolism with modified serum T_3 and T_4 levels but not TSH levels (unless receiving thyroxine replacement therapy)	
Increased hepatic metabolism, enhanced degradation of thyroid hormone	Nicardipine, bexarotene, phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Inhibition of 5'-deiodinase with decreased T_3, increased rT_3	Iopanoic acid, ipodate, amiodarone, β blockers, corticosteroids, propylthiouracil, flavonoids
Other interactions	
Interference with T_4 absorption	Cholestyramine, chromium picolinate, colestipol, ciprofloxacin, proton pump inhibitors, sucralfate, sodium polystyrene sulfonate, raloxifene, sevelamer hydrochloride, aluminum hydroxide, ferrous sulfate, calcium carbonate, bran, soy, coffee
Induction of autoimmune thyroid disease with hypothyroidism or hyperthyroidism	Interferon-α, interleukin-2, interferon-β, lithium, amiodarone, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Effect of thyroid function on drug effects	
Anticoagulation	Lower doses of warfarin required in hyperthyroidism, higher doses in hypothyroidism
Glucose control	Increased hepatic glucose production and glucose intolerance in hyperthyroidism; impaired insulin action and glucose disposal in hypothyroidism
Cardiac drugs	Higher doses of digoxin required in hyperthyroidism; lower doses in hypothyroidism
Sedatives; analgesics	Increased sedative and respiratory depressant effects from sedatives and opioids in hypothyroidism; converse in hyperthyroidism



Thyroid Hormones (T_4 & T_3)

- **Absorption is reduced in severe hypothyroidism (myxedema with ileus) → switch from oral to pareneteral therapy.**
- **Clearance is increased and half life is decreased in hyperthyroidism, and the opposite is true in hypothyroidism.**
- **Bound in the plasma by thyroid binding globulin (TBG).**

TABLE 38–1 Summary of thyroid hormone kinetics.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL	60–181 ng/dL
	(62–134 nmol/L)	(0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL	230–420 pg/dL
	(10.3–34.7 pmol/L)	(3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	80%	95%

70%

Thyroid Hormones (T_4 & T_3)

Mechanism of Action:

- The free forms of thyroid hormones, T_4 and T_3, dissociate from thyroid-binding proteins, enter the cell by the active transporters.
- Within the cell T_4 is converted to T_3 by 5'-deiodinase.
- T_3 enters the nucleus where it binds to a specific T_3 receptor protein.
- The T_3 receptor exists in two forms, α and β.

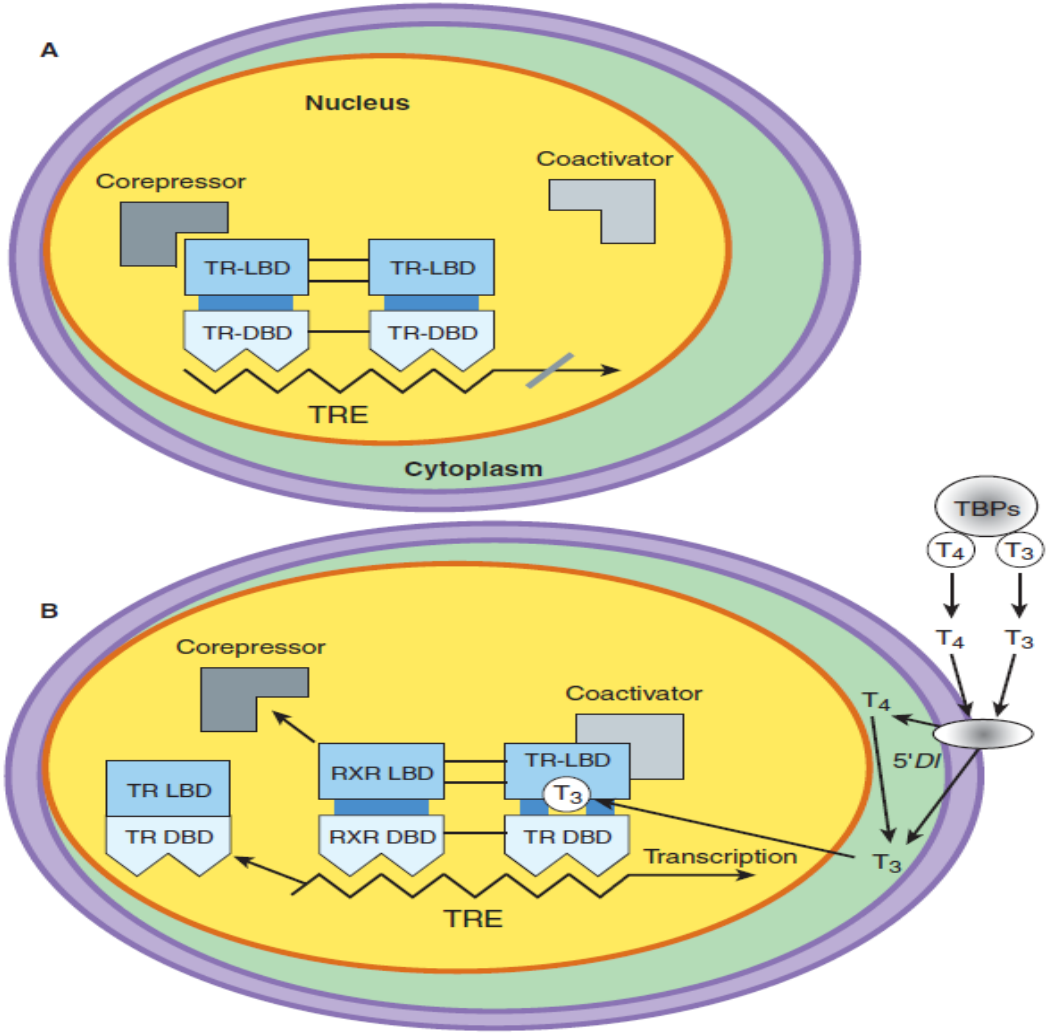


FIGURE 38–4 Model of the interaction of T_3 with the T_3 receptor. **A:** *Inactive phase*—the unliganded T_3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription. **B:** *Active phase*—T_3 and T_4 circulate bound to thyroid-binding proteins (TBPs). The free hormones are transported into the cell by a specific transport system. Within the cytoplasm, T_4 is converted to T_3 by 5′-deiodinase (5′DI); T_3 then moves into the nucleus. There it binds to the ligand-binding domain of the thyroid receptor (TR) monomer. This promotes disruption of the TR homodimer and heterodimerization with retinoid X receptor (RXR) on the TRE, displacement of corepressors, and binding of coactivators. The TR-coactivator complex activates gene transcription, which leads to alteration in protein synthesis and cellular phenotype. TR-LBD, T_3 receptor ligand-binding domain; TR-DBD, T_3 receptor DNA-binding domain; RXR-LBD, retinoid X receptor ligand-binding domain; RXR-DBD, retinoid X receptor DNA-binding domain; T_3, triiodothyronine; T_4, tetraiodothyronine, L-thyroxine. (Modified and reproduced, with permission, from Gardner DG, Shoback D [editors]: *Greenspan's Basic & Clinical Endocrinology,* 8th ed. McGraw-Hill, 2007.)

Thyroid Hormones (T_4 & T_3)

- **Activation of nuclear receptor leads to increased formation of mRNA and subsequent protein synthesis (delay in onset of action hours-days).**
- **Affinity of the receptor for T_4 is about 10 times lower than T_3.**
- **The number of nuclear receptors may be altered to preserve body homeostasis.**

Thyroid Hormones (T_4 & T_3)

- **Starvation lowers both circulating T_3 hormone and cellular T_3 receptors.**
- **T_4 & T_3 are available for replacement therapy as levothyroxine and liothyronine, respectively.**
- **T_3 is not recommended for routine replacement therapy because of its shorter half-life (24 hours), requiring multiple daily doses, and difficulty in its monitoring by conventional laboratory tests. It is also more cardiotoxic.**

Thyroid Hormones (T_4 & T_3)

- **Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity, low cost, lack of allergenic foreign protein, easy laboratory measurement of serum levels, and long half-life (7 days), which permits once-daily to weekly administration.**