Thyroid and Antithyroid Drugs

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

12th edition pp 681-694 , or 13th edition pp 663-677

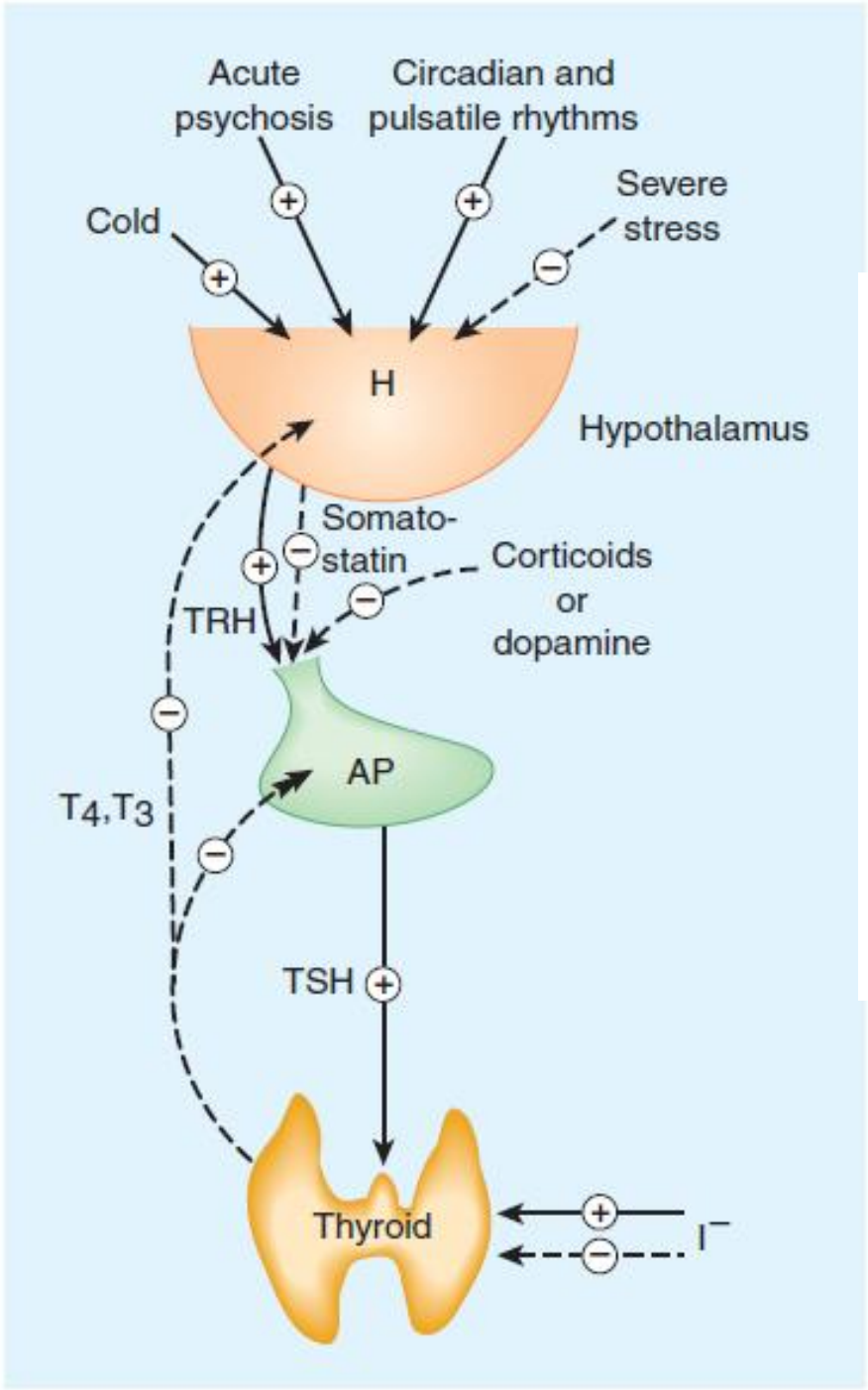

FIGURE 38–3 The hypothalamic-pituitary-thyroid axis. Acute psychosis or prolonged exposure to cold may activate the axis. Hypothalamic thyroid-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH) release, while somatostatin and dopamine inhibit it. TSH stimulates T_4 and T_3 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**

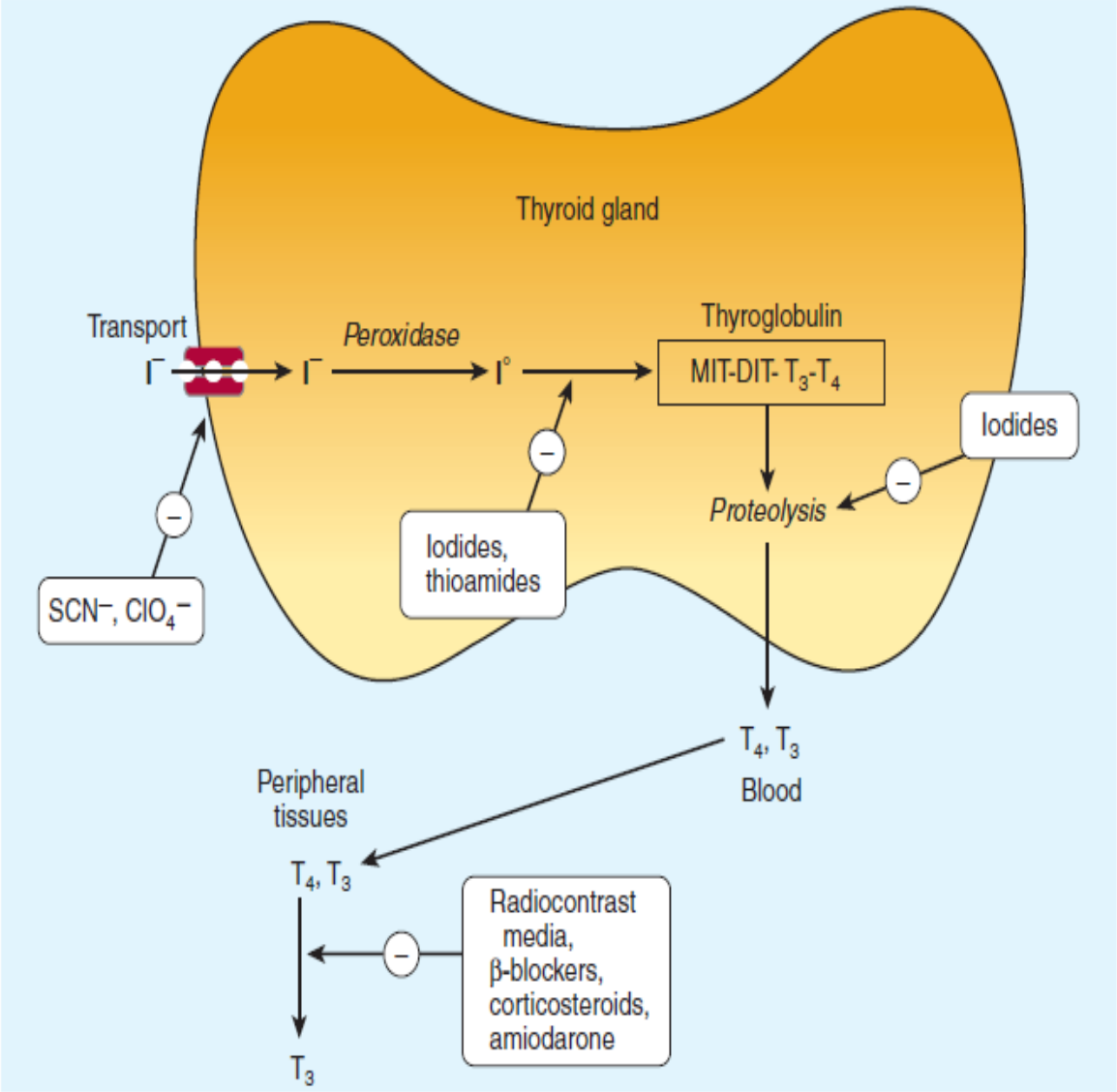

FIGURE 38–1 Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

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).**

Thyroid Hormones (T_4 & T_3)

- **Hepatic metabolism is increased by inducers of hepatic microsomal enzymes: Rifampin, Phenobarbital, phenytoin, carbamazepine, tyrosine kinase inhibitors (imatinib), HIV protease inhibitors.**
- **In this case, normal hormone concentration is maintained in euthyroid patients due to compensatory hyperfunction of the thyroid gland, but patients on thyroid replacement therapy require higher doses.**

Thyroid Hormones (T_4 & T_3)

- **A similar compensation occurs if binding sites are altered:**
- **If TBG sites are increased by pregnancy, estrogens, or oral contraceptives, there is an initial shift of hormone from the free to the bound state and a decrease in its rate of elimination until the normal free hormone concentration is restored.**

Thyroid Hormones (T_4 & T_3)

- **Thus, the concentration of total and bound hormone will increase, but the concentration of free hormone and the steady-state elimination will remain normal.**
- **The reverse occurs when thyroid binding sites are decreased.**

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.

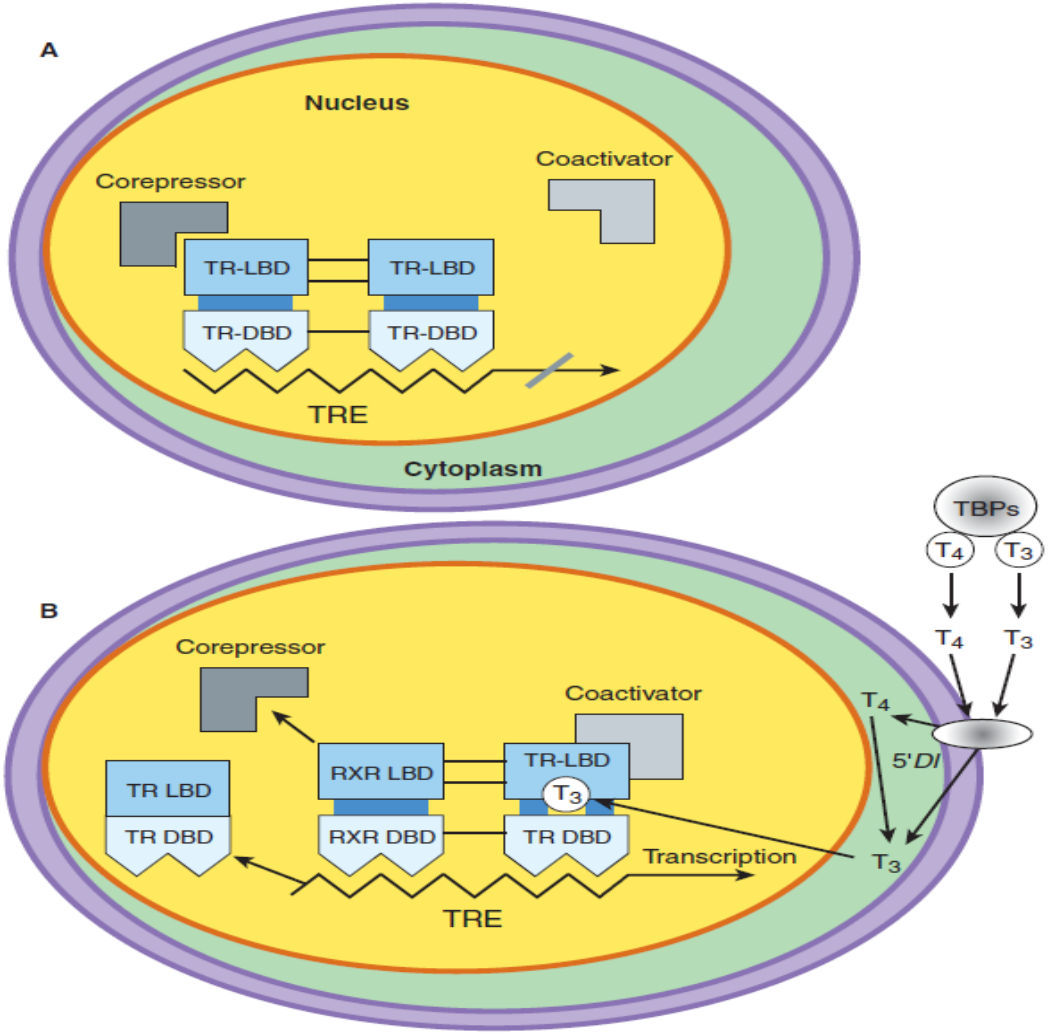

FIGURE 38–4 Model of the interaction of T_3 with the T_3 receptor. **A:** *Inactive phase*—the unliganded T_3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription. **B:** *Active phase*—T_3 and T_4 circulate bound to thyroid-binding 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.**

Antithyroid Drugs

- **Agents which reduce hyperactive thyroid activity interfere with the production of thyroid hormones, or modify the tissue response to thyroid hormones, or cause glandular destruction with radiation or surgery.**

Antithyroid Drugs

1. **Thionamides**
   - **Propylthiouracil (PTU)**
   - **Methimazole**
   - **Carbimazole → methimazole**
2. **Iodides.**
3. **Radioactive iodine**
4. **Iodinated Contrast Media**
5. **β-Adrenergic Blockers**

Thionamides

- Are major drugs for treatment of hyperthyroidism
- Methimazole is ~ 10x more potent than propylthiouracil and is the drug of choice in adults and children.
- Propylthiouracil should be reserved for use during the first trimester of pregnancy, in thyroid storm, and in those experiencing adverse reactions to methimazole (other than agranulocytosis or hepatitis).

Thionamides

Pharmacokinetics:

- **Bioavailability of methimazole is better than PTU.**
- **Both accumulate in thyroid gland**
- **Vd ~ total body water.**
- **PTU is excreted by the kidney as inactive glucuronide.**
- **Methimazole is excreted by the kidney slowly.**

Thionamides

- **t½:**

  PTU 1.5 hours → given every 6-8 hours

  Methimazole 6 hours → given once daily
- **Both can cross placenta and accumulate in fetal thyroid and cause hypothyroidism, but PTU less readily so because of high protein binding.**
- **Not secreted in sufficient quantity in breast milk to preclude breast feeding.**

Thionamides

Pharmacodynamics:

1. **Prevention of thyroid hormone synthesis by inhibiting thyroid peroxidase and blockade of iodine organification.**
2. **Block coupling of iodotyrosines.**
3. **PTU also blocks the peripheral conversion of T_4 into T_3 by 5'-deiodinase.**

- **The effect is slow requiring 3-4 weeks before stores of T_4 are depleted.**

Thionamides

Adverse Effects:

Occur in 3-12% of patients.

1. **Most reactions occur early, especially nausea and gastrointestinal distress.**
2. **Altered sense of taste or smell may occur with methimazole.**
3. **Maculopapular pruritic rash with or without fever – most common (4-6%).**

Thionamides

4. **Rare adverse effects include an urticarial rash, vasculitis, a lupus-like reaction, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, and acute arthralgia.**
5. **Severe may be fatal hepatitis reported with propylthiouracil, so it should be avoided in children and adults**
6. **Cholestatic jaundice is more common with methimazole than propylthiouracil.**

Thionamides

7. **Agranulocytosis (< 500 cells/mm^3) – most dangerous:**

- **Infrequent (0.1 – 0.5 % of patients) but potentially fatal, but rapidly Reversible.**
- **More frequent in the elderly and at doses more than 40 mg.**
- **G-CSF may speed recovery of granulocytes.**
- **Cross-sensitivity between PTU and methimazole is ~ 50%**

Iodides

- **At pharmacological doses (> 6 mg/day), the major action is inhibition of organification and thyroid hormone release, possibly by inhibition of thyroglobulin proteolysis → rapid improvement in 2-7 days.**
- **Reduces vascularity, size, fragility of the hyperplastic thyroid glands → useful for preoperative preparation for surgery.**

Iodides

Disadvantages:

1. **Increased intraglandular stores of iodine:**

   A. Delay the onset of thionamide therapy.

   B. Prevent use of radioactive iodine therapy for several weeks.

- **Should be initiated after onset of thionamide therapy.**
- **Should be avoided if treatment with ^{131}I is planned.**

Iodides

2. **Should not be used alone for treatment of hyperthyroidism, because the gland will escape from iodine block in 2-8 weeks.**
3. **Its withdrawal may precipitate thyrotoxicosis because the gland is iodine- enriched.**
4. **Should be avoided during pregnancy, because it may produce fetal goiter and hypo- or hyperthyroidism.**

Iodides

Toxicity:

- **Iodism: uncommon, reversible:**

  Acneiform rash, swollen salivary glands, mucus membrane ulceration, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding, anaphylactoid reactions.

Radioactive Iodine (^{131}I)

- **Administered orally as $Na^{131}I$ solution.**
- **Rapidly absorbed, concentrated by the thyroid gland and incorporated into storage follicles.**
- **Its effect is due to emission of β-rays (t½ ~ 5 days, penetration 400-2000 µm).**
- **The thyroid parenchyma is destroyed within 6-12 weeks.**

Radioactive Iodine (^{131}I)

Advantages:

1. **Easy administration**
2. **Effectiveness**
3. **Low expense**
4. **Painless**

Radioactive Iodine (^{131}I)

Disadvantages:

1. **Major complication is hypothyroidism (80% of patients) which requires T_4 replacement.**
2. **Fears of radiation-induced genetic damage, leukemia and neoplasia which made some clinics to restrict its use for patients < 40 years of age. (No evidence over 50 years of use).**
3. **Should not be administered to pregnant women or nursing mothers.**

Iodinated Contrast Media

Ipodate and Iopanoic acid → PO

Diatrizoate → PO , Iohexol → PO & IV

- **Provide useful adjunctive therapy in the treatment of thyroid storm.**
- **Valuable alternatives when iodides or thionamides are contraindicated.**
- **Relatively nontoxic, toxicity is similar to iodides.**

Iodinated Contrast Media

- **Rapidly inhibit the conversion of T_4 into T_3 → within 3 days they decrease heart rate and normalize T_3.**
- **Also inhibit hormone release.**
- **Safety in pregnancy is undocumented.**

β-Adrenergic Blockers

- Those without intrinsic sympathomimetic activity such as propranolol.
- Many manifestations of thyrotoxicosis are due to hyperactivity of the sympathetic nervous system, which may be due to increased number of β-adrenergic receptors or amplification of β-adrenergic receptor signal (cAMP).
- Do not typically alter thyroid hormone levels.

β-Adrenergic Blockers

- **They also inhibit 5'-deiodinase which converts T_4 into T_3.**
- **Control tachycardia, hypertension and atrial fibrillation associated with hyperthyroidism.**
- **In patients with bronchial asthma or when β-adrenergic blockers are contraindicated, diltiazem is an alternative.**