Pharmacology - 2

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Thyroid & Antithyroid Agents

Learning outcomes:

After studying this chapter, the student should be able to:

- Differentiate between hypo-and hyperthyroidism depending on observing a list of marks and symptoms.
- Illustrate the mechanisms of action, indications, side effects and contraindications of the thyroid hormones as used in supplemental therapy.
- Numerate and illustrate the most important documented interactions between drugs used in patients with hypothyroidism or hyperthyroidism.
- Summarize the main pharmacokinetic parameters of the indicated drugs.
- List drugs used in hyperthyroidism and thyroid storm specifying the mechanism of action, side effects, precautions and important clinical considerations.

Thyroid and antithyroid drugs

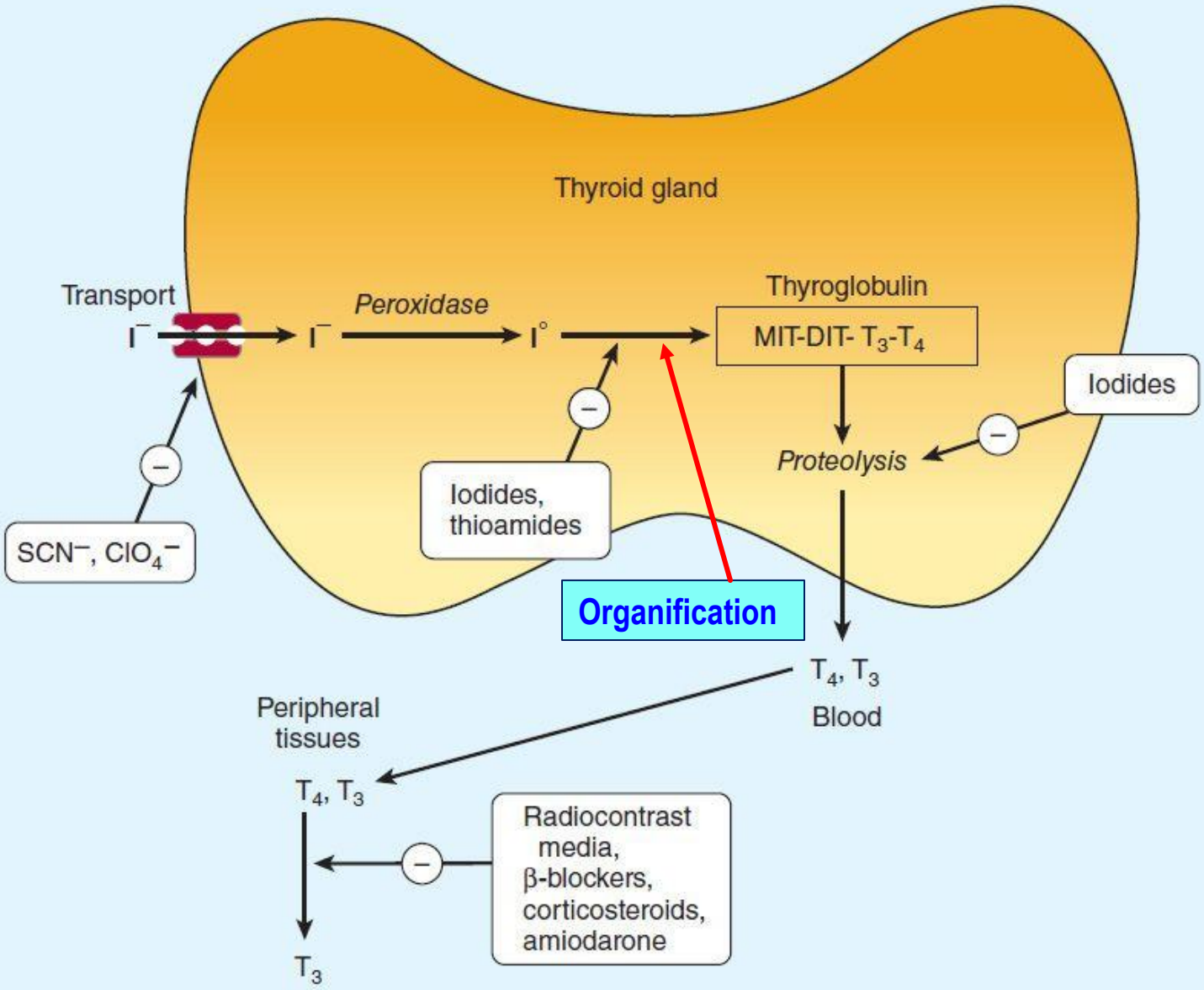
- The normal thyroid gland secretes sufficient amounts of the thyroid hormones; **triiodothyronine (T3)** and **tetraiodothyronine (T4, thyroxine)** to normalize growth and development, body temperature, and energy levels.
- These hormones contain 59% and 65% (respectively) of iodine as an essential part of the molecule.
- **Calcitonin**, the second type of thyroid hormone, is important in the regulation of calcium metabolism (lowers plasma calcium level).
- Iodide, ingested from food, water, or medication, is rapidly absorbed and enters an extracellular fluid pool.
- The thyroid gland removes about 75 mcg a day from this pool for hormone synthesis.

Biosynthesis of Thyroid Hormones:

- The first step is the transport of iodide into the thyroid gland by an intrinsic follicle cell basement membrane protein called the sodium/iodide symporter (NIS).
- This can be inhibited by large doses of iodides as well as anions (e.g., thiocyanate (SCN-)).
- At the apical cell membrane a second I^- transport enzyme called pendrin controls the flow of iodide across the membrane.
- Pendrin is also found in the cochlea of the inner ear.
- If pendrin is deficient or absent (a mutation), a hereditary syndrome of goiter and deafness, called Pendred syndrome (PDS), ensues.

- At the apical cell membrane, iodide is oxidized by thyroidal peroxidase (TPO) to iodine.
- Iodine rapidly iodinates tyrosine residues within the thyroglobulin molecule to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT).** This process is called iodide organification.
- Thyroglobulin is a glycoprotein produced by the thyroid follicular cells.
- Thyroidal peroxidase is transiently blocked by high levels of intrathyroidal iodide and blocked more persistently by thioamide drugs.
- Gene expression of TPO is stimulated by thyroid-stimulating hormone (TSH).

Thyroid and antithyroid drugs



- Two molecules of DIT combine within the thyroglobulin molecule to form l-thyroxine (T4). One molecule of MIT and one molecule of DIT combine to form T3.
- Thyroxine, T3, MIT, and DIT are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin at the apical colloid border.
- This process of proteolysis is also blocked by high levels of intrathyroidal iodide.
- The ratio of T4 to T3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine.
- Eighty percent of T3 circulating in the blood is derived from peripheral metabolism of thyroxine and the rest from direct thyroid secretion.

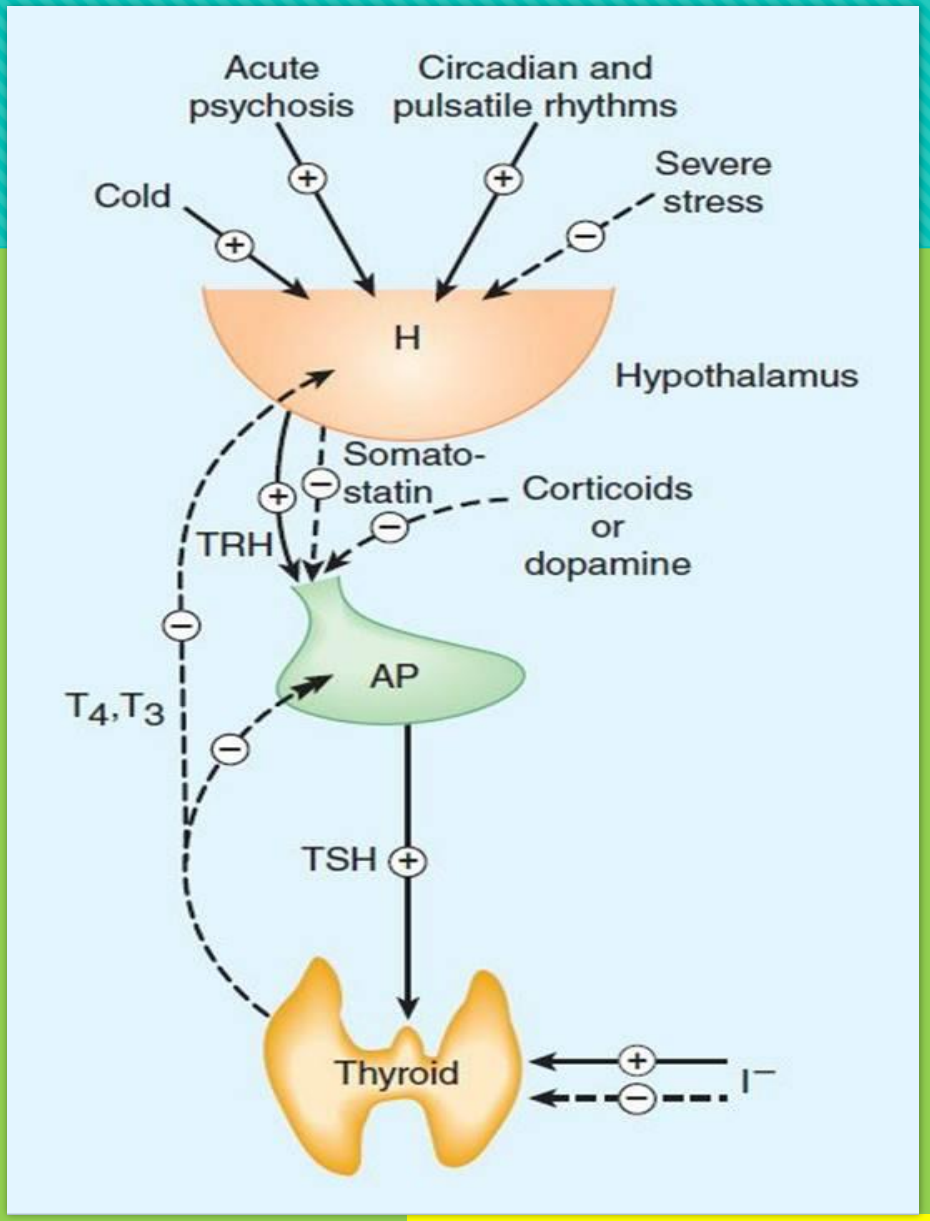
- Deiodination of T4 may occur by monodeiodination of the outer ring, producing 3,5,3′-triiodothyronine (T3), which is three to four times more potent than T4.

- Drugs such as amiodarone, iodinated contrast media, β blockers, and corticosteroids, as well as severe illness or starvation, inhibit the 5′-deiodinase necessary for the conversion of T4 to T3, resulting in low T3 levels in the serum.

- A polymorphism in the deionase enzyme (D2) gene can reduce T3 activation and impair thyroid hormone response.

Thyroid and antithyroid drugs

- Control of thyroid function is via thyroid-pituitary feedback.
- Hypothalamic cells secrete thyrotropin-releasing hormone (TRH).
- TRH is secreted into capillaries of the pituitary portal venous system, and in the pituitary gland, TRH stimulates the synthesis and release of thyrotropin (thyroid-stimulating hormone, TSH).
- TSH in turn stimulates an adenylyl cyclase–mediated mechanism in the thyroid cell to increase the synthesis and release of T4 and T3. T3, the more active of the two hormones, acts in a negative feedback fashion in the pituitary to block the action of TSH and in the hypothalamus to inhibit the synthesis and secretion of TRH.



Pharmacokinetics of thyroid hormones:

- Thyroxine is absorbed best in the duodenum and ileum.
- Absorption is modified by intraluminal factors such as **food**, **drugs**, **gastric acidity**, and **intestinal flora**.
- Bioavailability: T4 (70-80%), T3 (95%).
- In patients with hyperthyroidism, the metabolic clearances of T4 and T3 are increased and the half-lives decreased; the opposite is true in patients with hypothyroidism.
- Drugs that indsuce hepatic microsomal enzymes (eg, rifampin, phenobarbital, carbamazepine, phenytoin, tyrosine kinase inhibitors (anticancer), HIV protease inhibitors) increase the metabolism of both T4 and T3.

- If Thyroxine-binding globulin 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.
- 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.

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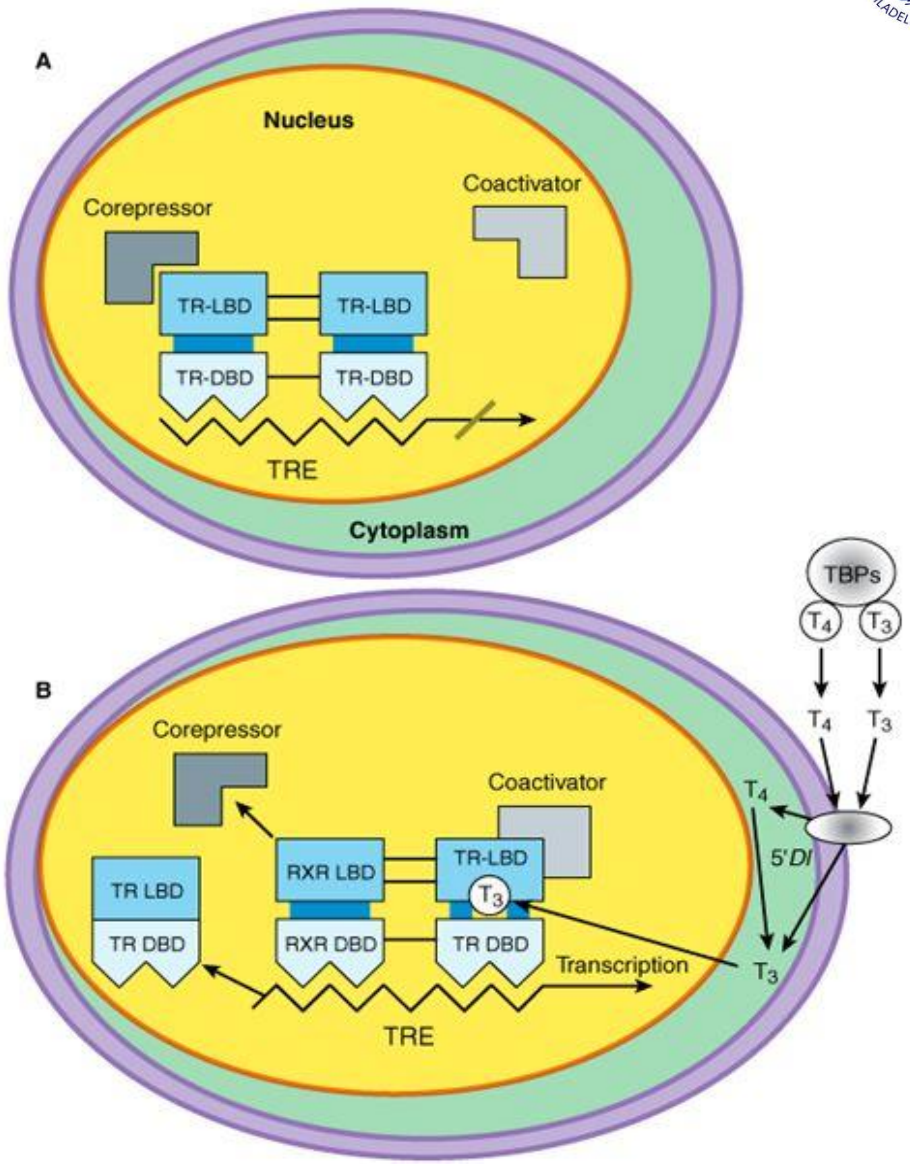
MECHNIMS OF ACTION:

- Most of the effects of thyroid on metabolic processes appear to be mediated by activation of **nuclear receptors** that lead to increased formation of **RNA** and subsequent **protein synthesis**, eg, increased formation of Na+/K+-ATPase.

Thyroid and antithyroid drugs

A: *Inactive phase*—the unliganded T3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription. **B:** *Active phase*—T3 and T4 circulate bound to thyroid-binding proteins (TBPs). The free hormones are transported into the cell by a specific transport system. Within the cytoplasm, T4 is converted to T3 by 5′-deiodinase (5′DI); T3 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, T3 receptor ligand-binding domain; TR-DBD, T3 receptor DNA-binding domain; RXR-LBD, retinoid X receptor ligand-binding domain; RXR-DBD, retinoid X receptor DNA-binding domain; T3, triiodothyronine; T4, tetraiodothyronine, L-thyroxine



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Effects of Thyroid Hormones:

- The thyroid hormones are responsible for optimal growth, development, function, and maintenance of all body tissues.
- Excess or inadequate amounts result in the signs and symptoms of hyperthyroidism or hypothyroidism, respectively.

Thyroid Preparations:

- Levothyroxine (T4) – liothyronine (T3) – Liotrex (a 4:1 mixture of thyroxine and triiodothyronine).
- 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.

Signs:

Hypothyroidism

- Hair loss
- Inability to think clearly
- Goiter (enlarged thyroid)
- Reduced heart rate
- Strong fatigue
- Sensitivity to cold
- Dry skin
- Weight gain
- Puffiness
- Memory problems
- Constipation
- Irregular menstrual periods
- Severe PMS
- Depression, mood swings
- Joint, muscle pain
- High cholesterol

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Hyperthyroidism

- Hair loss
- Bulging eyes
- Goiter (enlarged thyroid)
- Heart palpitations
- Tremors
- Heat intolerance
- Sleep disturbances
- Weight loss
- Shortness of breath
- Diarrhoea
- Increased appetite
- Irregular menstrual periods
- Muscle weakness
- Sweating
- Anxiety, nervousness
- Depression, mood swings

Premenstrual syndrome; depression and anxiety

- In addition, T4 is converted to T3 intracellularly; thus, administration of T4 produces both hormones and T3 administration is unnecessary.
- Although liothyronine (T3) is three to four times more potent than levothyroxine, it is not recommended for routine replacement therapy because of its shorter half-life (24 hours), requiring multiple daily doses, and difficulty in monitoring its adequacy of replacement by conventional laboratory tests.
- **T3** should also be avoided in patients with cardiac disease due to a greater risk of cardiotoxicity.
- Using the more expensive thyroxine and liothyronine fixed-dose combination (**liotrix**) has not been shown to be more effective than T4 administration alone.
- **T3** is best reserved for short-term TSH suppression.

- The use of desiccated thyroid (dried thyroid extract) rather than synthetic preparations is never justified, since the disadvantages of protein antigenicity, product instability, variable hormone concentrations, and difficulty in laboratory monitoring far outweigh the advantage of lower cost.

ANTITHYROID AGENTS:

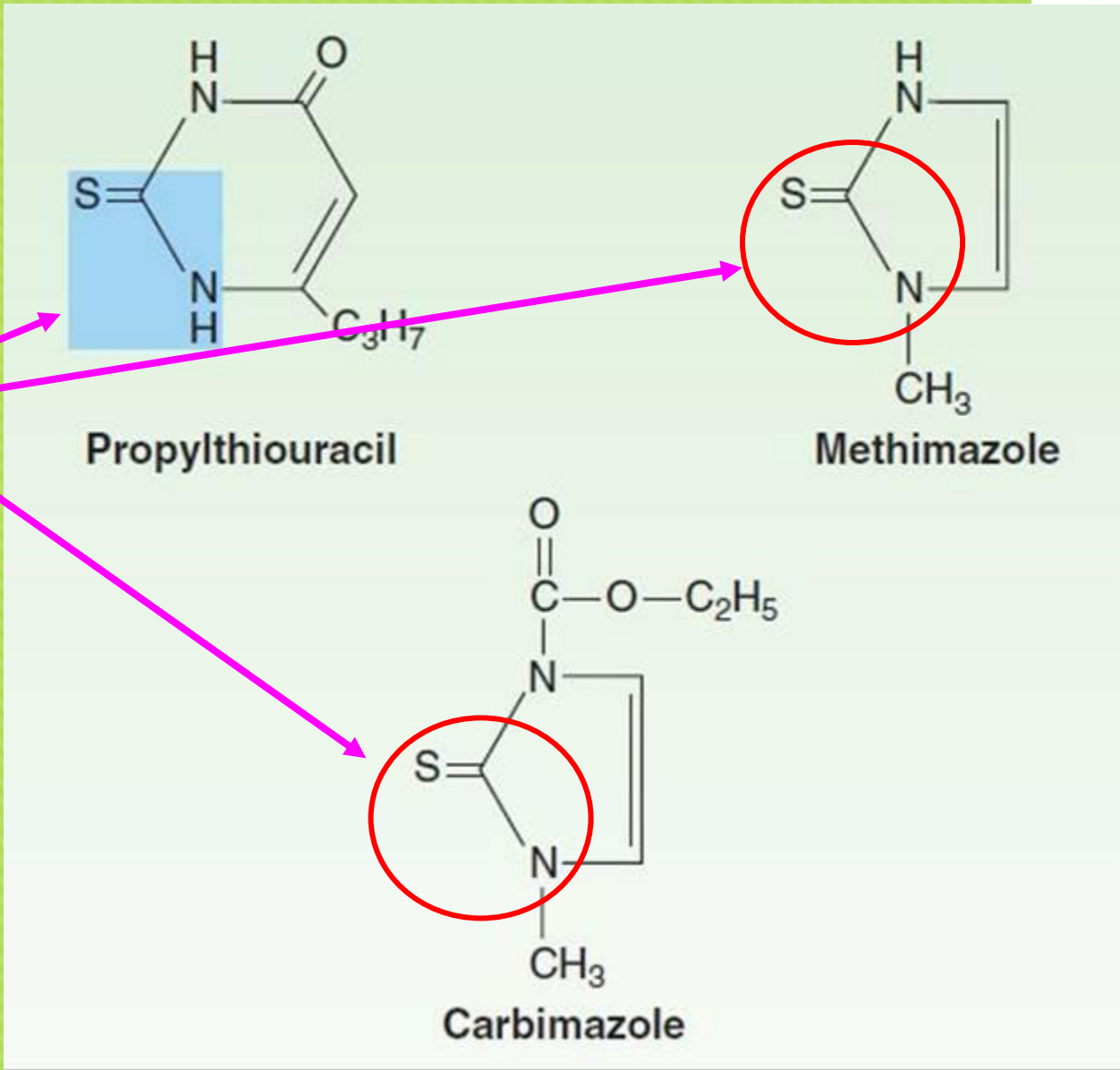
- Reduction of thyroid activity and hormone effects can be accomplished by agents that (1) interfere with the production of thyroid hormones, by agents that (2) modify the tissue response to thyroid hormones, or by (3) glandular destruction with radiation or surgery.
- Goitrogens are agents that suppress secretion of T3 and T4 to subnormal levels and thereby increase TSH, which in turn produces glandular enlargement (goiter).

Thyroid and antithyroid drugs

- The thioamides **methimazole** and **propylthiouracil** are major drugs for treatment of thyrotoxicosis.
- In UK, **carbimazole** which is converted to methimazole in vivo, is widely used.
- Methimazole is about ten times more potent than propylthiouracil and is the drug of choice in adults and children.
- Due to a black box warning about **severe hepatitis**, propylthiouracil should be reserved for use during the (1) first trimester of pregnancy, (2) in thyroid storm, and (3) in those experiencing adverse reactions to methimazole (other than agranulocytosis or hepatitis).
- The thiocarbamide group is essential for antithyroid activity.

Anti-thyroid drugs:

Thiocarbamide moiety



Pharmacokinetics:

- Methimazole is completely absorbed after an oral dose, and accumulated in the thyroid.
- The bioavailability of propylthiouracil is 50–80%; may be due to incomplete absorption or a large first-pass effect in the liver.
- Methimazole is more slowly exerted than propylthiouracil.
- The short plasma half-life of these agents (**1.5** hours for propylthiouracil and **6** hours for methimazole) has little influence on the duration of the antithyroid action or the dosing interval because both agents are **accumulated by the thyroid gland.**
- Both thioamides cross the placental barrier and are concentrated by the fetal thyroid, so that caution must be employed when using these drugs in pregnancy. Because of the risk of fetal hypothyroidism, both thioamides are classified as FDA pregnancy category D (fetal risk due to an adverse effect).

- Of the two, propylthiouracil is preferable during the first trimester of pregnancy because it is (1) more strongly protein-bound and, therefore, crosses the placenta less readily.
- In addition, methimazole has been, albeit rarely, associated with (2) congenital malformations.
- Both thioamides are secreted in low concentrations in breast milk but are considered safe for the nursing infant.

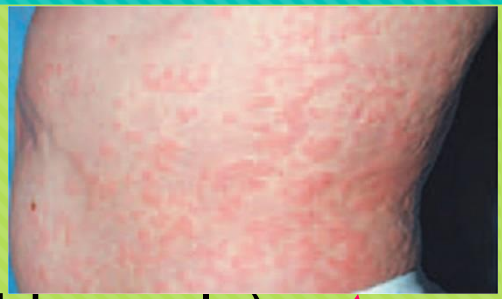
Thioamides act by multiple mechanisms:

(1) Inhibiting the thyroid peroxidase-catalyzed reactions.

(2) Blocking iodine organification.

(3) Blocking iodotyrosine coupling.

(4) Propylthiouracil but not methimazole also inhibits the peripheral deiodination of T4 and T3.



Toxicity and adverse reactions:

- GIT-related.
- Altered sense of taste or smell may occur (methimazole).
- The most common adverse effect is a maculopapular pruritic rash.
- Rare: several skin adverse reactions.
- Rare: acute arthralgia.
- Severe hepatitis, sometimes deadly, with propylthiouracil.
- Cholestatic jaundice with both drugs.
- The most dangerous complication is agranulocytosis (granulocyte count < 500 cells/mm3), an infrequent but potentially fatal adverse reaction.
  - ✓ This side effect is rapidly reversible. A broad-spectrum antibiotic use may be necessary .

ANION INHIBITORS:

- Monovalent anions such as perchlorate (ClO_4^-), pertechnetate (TcO_4^-), and thiocyanate (SCN^-) can block uptake of iodide by the gland through competitive inhibition of the iodide transport mechanism.
- Since these effects can be overcome by large doses of iodides, their effectiveness is somewhat unpredictable.
- The major clinical use for **potassium perchlorate** is to block thyroidal reuptake of I^- in patients with iodide-induced hyperthyroidism (eg, **amiodarone-induced hyperthyroidism**).
- However, potassium perchlorate is rarely used clinically because it is associated with aplastic anemia.

IODIDES:

- Prior to the introduction of the thioamides in the 1940s, iodides were the major antithyroid agents; today they are rarely used as sole therapy.
- Mechanisms of action:
  - ✓ They inhibit organification and hormone release.
  - ✓ Decrease the size and vascularity of the hyperplastic gland; a preoperative (before surgery).
- In susceptible individuals, iodides can induce hyperthyroidism (Jod-Basedow phenomenon) or precipitate hypothyroidism.
- In pharmacologic doses (>6 mg/d), the major action of iodides is to inhibit hormone release, possibly through inhibition of thyroglobulin proteolysis.

Clinical use of iodide:

- Iodide therapy results in an increase in intraglandular stores of iodine, which may delay onset of thioamide therapy or prevent use of radioactive iodine therapy for several weeks.
- Accordingly, iodides should be initiated after onset of thioamide therapy and avoided if treatment with radioactive iodine seems likely.
- Iodide should not be used alone, because the gland (1) will escape from the iodide block in 2–8 weeks, and (2) its withdrawal may produce severe exacerbation of thyrotoxicosis in an iodine-enriched gland.
- Chronic use of iodides in pregnancy should be avoided, since they cross the placenta and can cause fetal goiter.

Toxicity:

- Adverse reactions to iodine (iodism) are uncommon and in most cases reversible upon discontinuance.
- They include:
  - Acneiform rash (similar to that of bromism).
  - Mucous membrane ulcerations.
  - Conjunctivitis
  - Rhinorrhea.
  - Metallic taste.
  - Bleeding disorders.

RADIOACTIVE IODINE:

- ^{131}I is the only isotope used for treatment of thyrotoxicosis. (Others are used in diagnosis – iodine element: $^{126.9}I$.)
- Administered orally in solution as sodium ^{131}I, it is rapidly absorbed, concentrated by the thyroid.
- Its therapeutic effect depends on emission of β rays.
- Within a few weeks after administration, destruction of the thyroid parenchyma is evidenced by epithelial swelling and necrosis, follicular disruption, edema, and leukocyte infiltration.
- Advantages of radioiodine include easy administration, effectiveness, low expense, and absence of pain.
- Fears of radiation-induced genetic damage, leukemia, and neoplasia have not been realized after more than 50 years of clinical experience with radioiodine therapy for hyperthyroidism.

- Radioactive iodine **should not** be administered to **pregnant** women or **nursing** mothers, since it crosses the placenta to destroy the fetal thyroid gland and it is excreted in breast milk.

ADRENOCEPTOR-BLOCKING AGENTS:

- **Beta blockers** without intrinsic sympathomimetic activity (eg, metoprolol, propranolol, atenolol) are effective therapeutic adjuncts in the management of thyrotoxicosis since many of these symptoms mimic those associated with sympathetic stimulation.
- Propranolol has been the β blocker most widely studied and used in the therapy of thyrotoxicosis.
- Propranolol at doses greater than 160 mg/d may also **reduce T3** levels approximately 20% by inhibiting the peripheral conversion of T4 to T3.

HYPOTHYROIDISM:

- In infants and children, there is striking retardation of growth and development that results in **dwarfism** and irreversible **mental retardation.**
- Hypothyroidism can occur with or without thyroid enlargement (goiter).
- The laboratory diagnosis of hypothyroidism in the adult is easily made by the combination of **low free thyroxine** and **elevated serum TSH levels**.
- The **most common** cause of hypothyroidism in the US is probably **Hashimoto's thyroiditis**, an immunologic disorder.
- In this condition, there is evidence of humoral immunity in the presence of **antithyroid antibodies** and **lymphocyte sensitization to thyroid antigens.**

MANAGEMENT OF HYPOTHYROIDISM:

- Except for hypothyroidism caused by drugs, which can be treated in some cases by simply removing the depressant agent, the general strategy of replacement therapy is appropriate.
- The most satisfactory preparation is **levothyroxine**.
- Combination of levothyroxine plus liothyronine is not superior to levothyroxine alone (although some patients remain unwell on thyroxine alone).
- **Genetic variations** in deiodinases or hormone transporters may account for some of this lack of efficacy.
- There is some variability in the absorption of thyroxine; dosage will also vary depending on **age** and **weight**.
- Infants and children require more T4 per kilogram of body weight than adults.

- Higher thyroxine requirements have also been reported in patients with celiac disease {an immune disease in which people can't eat gluten because it will damage their small intestine} and Helicobacter pylori gastritis.
- Since interactions with certain foods (eg, bran, soy, coffee) and drugs can impair its absorption, thyroxine should be administered on an empty stomach (eg, 60 minutes before meals, 4 hours after meals, or at bedtime).
- In long-standing hypothyroidism and in older patients with underlying cardiac disease, it is essential to start with reduced dosages of levothyroxine, start with lower doses and increase until euthyroidism (normal function of the gland) or drug toxicity is observed.
- In cardiac patients, the heart is very sensitive to the level of circulating thyroxine, and if angina pectoris or cardiac arrhythmia develops, it is essential to stop or reduce the thyroxine dosage immediately.

HYPERTHYROIDISM:

- Hyperthyroidism (thyrotoxicosis) is the clinical syndrome that results when tissues are exposed to high levels of thyroid hormone.

GRAVES' DISEASE:

- The most common form of hyperthyroidism is Graves' disease, or diffuse toxic goiter (check the previous table for symptoms).
- Graves' disease is an autoimmune disorder in which a defect in suppressor T lymphocytes stimulates B lymphocytes to synthesize antibodies to thyroidal antigens.
- The Ab is directed against the TSH receptor in the thyroid cell membrane and **stimulates growth and biosynthetic activity of the thyroid cell.**

- (1) Genetics, (2) the postpartum state, (3) cigarette smoking, and (4) physical and emotional stress increase Ab development.
- Lab diagnosis: In most patients with hyperthyroidism, T3 and T4 are elevated and TSH is suppressed.

Management of Graves' Disease:

1. Antithyroid drug therapy.
2. Thyroidectomy.
3. Radioactive Iodine.
4. Adjuncts to antithyroid therapy: β-adrenoceptor–blocking agents without intrinsic sympathomimetic activity are appropriate in symptomatic patients aged 60 years or more, in those with heart rates greater than 90 beats/min, and in those with cardiovascular disease.

- **Propranolol** or **metoprolol** will control tachycardia, hypertension, and atrial fibrillation.
- **Diltiazem** can be used to control tachycardia in patients in whom β blockers are contraindicated, eg, those with asthma.
- Dihydropyridine calcium channel blockers may not be as effective as diltiazem or verapamil.
- Adequate nutrition and vitamin supplements are essential.
- **Barbiturates** accelerate T4 breakdown (by hepatic enzyme induction) and may be helpful both as sedatives and to lower T4 levels.
- **Bile acid sequestrants** (eg, cholestyramine) can also rapidly lower T4 levels by increasing the fecal excretion of T4.

SPECIAL PROBLEMS:

Thyroid Storm:

- Thyroid storm, or thyrotoxic crisis, is sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life-threatening syndrome.
- Vigorous management is mandatory. Propranolol or esmolol with large doses is helpful to control sever cardiovascular manifestations.
- If β blockers are contraindicated by the presence of severe heart failure or asthma, hypertension and tachycardia may be controlled with diltiazem.
- Potassium iodide to retard the release of the hormones from the gland.
- Thioamides and supportive treatment.

Ophthalmopathy:

- Although severe ophthalmopathy is rare, it is difficult to treat.
- The emergence and aggravation of the eye disease especially in those who smoke.
- Management requires effective treatment of the thyroid disease, usually by total surgical excision or ^{131}I ablation (removal) of the gland plus oral prednisone therapy.
- Artificial tears to relieve corneal drying due to exophthalmos.
- Smoking cessation should be advised to prevent progression of the ophthalmopathy.
- In more severe case, X-therapy and surgical intervention may be carried out.

THE END

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