In the Name of GOD

Thyroid & Antithyroid Drugs

Prepared and summarized by

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Aim:

At the end of this lecture the students should be able to:

1- Explain the biosynthesis, transport and degradation of thyroid hormones
2- Name three mechanisms of thyroid control.
3- Define the pharmacokinetics, mechanism of action, clinical uses and side effects of thyroid preparations.
4- Name three strategies of antithyroid action.
5- Explain the pharmacokinetics, mechanism of action, clinical uses and side effects of each antithyroid drug groups.

THYROID PHYSIOLOGY

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.

Iodide Metabolism

The recommended daily adult iodide (I^-) intake is 150 mcg . The thyroid gland removes about 75 mcg a day from this pool for hormone synthesis, and the balance is excreted in the urine.

BiosBiosynthesis of Thyroid Hormones

1-The first step is the transport of iodide into the thyroid gland
2- iodide is oxidized by thyroidal peroxidase (TPO) to iodine,
3- it rapidly iodinates tyrosine residues within the thyroglobulin molecule to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT).** This process is called **iodide organification.**
4-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.
5- Thyroxine, T3, MIT, and DIT are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin. The ratio of T4 to T3 within thyroglobulin is approximately 5:1,

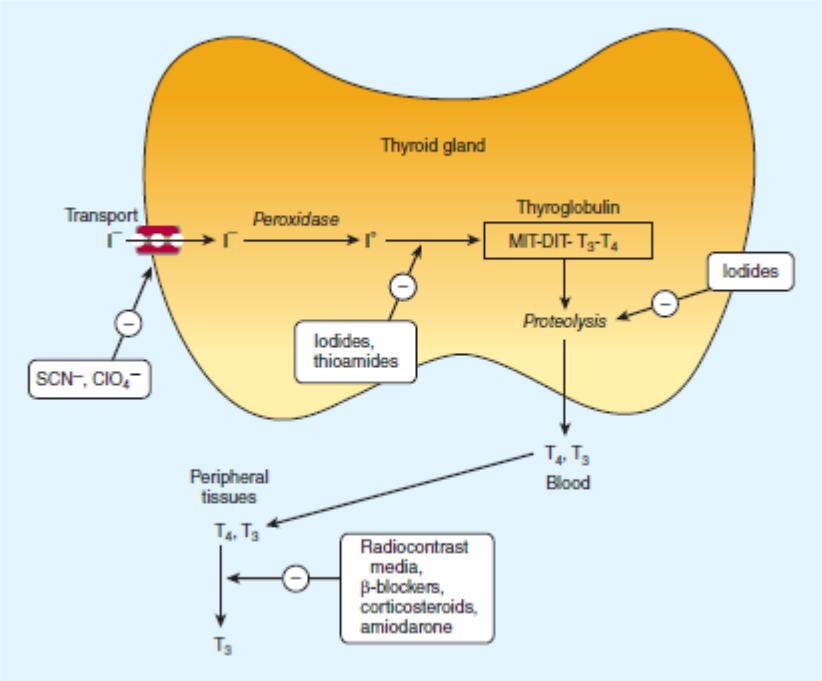

FIGURE 1 Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

Transport of Thyroid Hormones

Thyroxine and T3 in plasma are reversibly bound to protein, primarily thyroxine-binding globulin (TBG). Only about 0.04% of total T4 and 0.4% of T3 exist in the free form.

Peripheral Metabolism of Thyroid Hormones

The primary pathway for the peripheral metabolism of thyroxine is deiodination. Deiodination of T4 may occur by monodeiodination of the outer ring, producing T3, which is three to four times more potent than T4, or by monodeiodination of the inner ring, producing (reverse T3 [rT3]), which is metabolically inactive

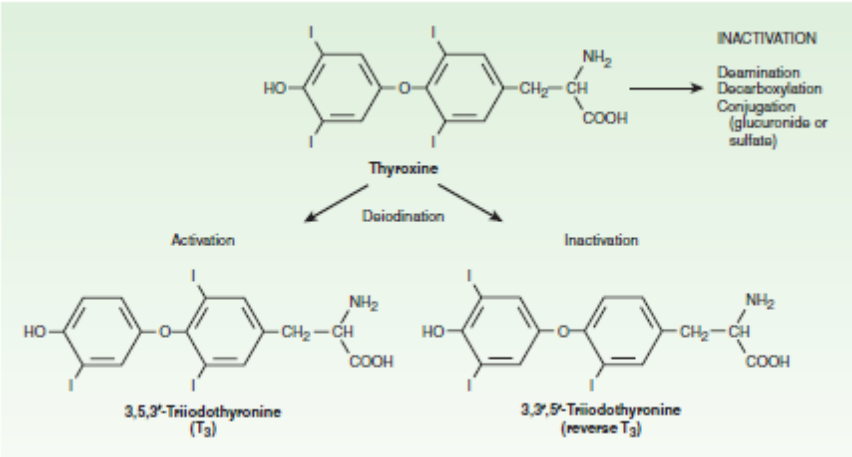

FIGURE 2 Peripheral metabolism of thyroxine.

Evaluation of Thyroid Function

A. Thyroid-Pituitary Relationships

Hypothalamic cells secrete thyrotropinreleasing hormone (TRH) (Figure 3). TRH stimulates the synthesis and release of thyrotropin (thyroid-stimulating hormone, TSH). TSH in turn stimulates synthesis and release of T4 and T3. These thyroid hormones act in a negative feedback fashion in the pituitary to block the action of TSH

B. Autoregulation of the Thyroid Gland

These mechanisms are primarily related to the level of iodine in the blood. Large doses of iodine inhibit iodide organification. In certain disease states (eg, Hashimoto's thyroiditis), this can inhibit thyroid hormone synthesis and result in hypothyroidism.

C. Abnormal Thyroid Stimulators

In Graves' disease, lymphocytes secrete a TSH receptor-stimulating antibody (TSH-R Ab [stim]), also known as thyroid-stimulating immunoglobulin (TSI). This immunoglobulin binds to the TSH receptor and stimulates the gland in the same fashion as TSH itself. The duration of its effect, however, is much longer than that of TSH.

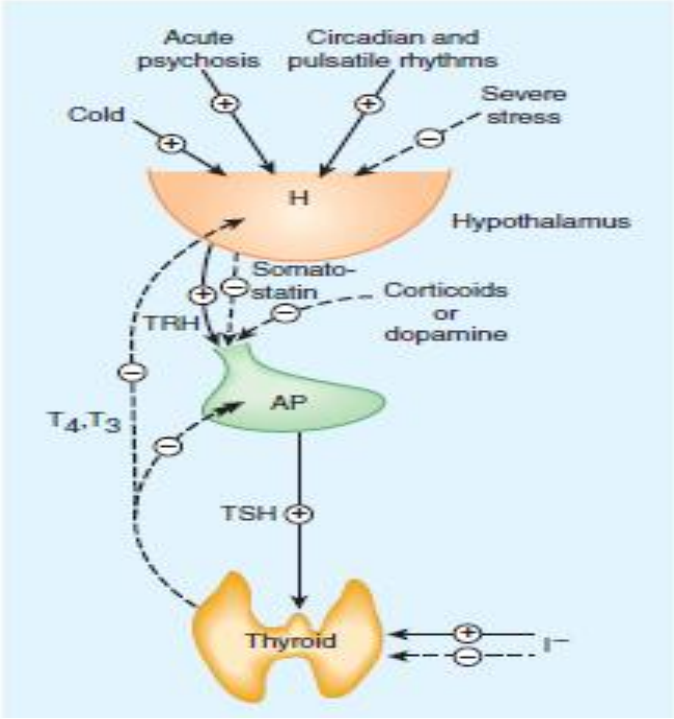

FIGURE 3 The hypothalamic-pituitary-thyroid axis

■ BASIC PHARMACOLOGY OF THYROID & ANTITHYROID DRUGS

THYROID HORMONES

Pharmacokinetics

Thyroxine is absorbed best in the duodenum and ileum;. Oral bioavailability of current preparations of l-thyroxine averages 70%. In contrast, T3 is almost completely absorbed (95%). T4 and T3 absorption appears not to be affected by mild hypothyroidism but may be **impaired** in severe myxedema with ileus. These factors are important
in switching from oral to parenteral therapy. For parenteral use, the intravenous route is preferred for both hormones. In hyperthyroidism, the clearances of T4 and T3 are increased and the half-lives decreased; the opposite is true in patients with hypothyroidism. Drugs that induce hepatic microsomal enzymes increase the metabolism of both T4 and T3. Therefore, patients dependent on T4 replacement medication may require increased dosages to maintain clinical effectiveness

Mechanism of Action

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

Large numbers of thyroid hormone receptors are found in the most hormone-responsive tissues (pituitary, liver, kidney, heart, skeletal muscle, lung, and intestine), while few receptor sites occur in hormone-unresponsive tissues (spleen, testes).
The affinity of the receptor site for T4 is about ten times lower than that for T3. Under some conditions, the number of nuclear receptors may be altered to preserve body homeostasis. For example, starvation lowers both circulating T3 hormone and cellular T3 receptors.

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 hormone is critical for the development and functioning of nervous, skeletal, and reproductive tissues. Thyroid deprivation in early life results in irreversible mental retardation and dwarfism.
The secretion and degradation rates of virtually all other hormones, including catecholamines, cortisol, estrogens, testosterone, and insulin, are affected by thyroid status.
Many of the manifestations of thyroid hyperactivity are similar to sympathetic nervous system overactivity (especially in the cardiovascular system), although catecholamine levels are not increased.
Thyroid hormone increases the numbers of β receptors and enhances amplification of the β-receptor signal. Other clinical symptoms reminiscent of excessive epinephrine activity (and partially alleviated by adrenoceptor antagonists) include lid lag and retraction, tremor, excessive sweating, anxiety, and nervousness. The opposite effects is seen in hypothyroidism

Thyroid Preparations

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. T3 is best reserved for short-term TSH suppression.
The use of desiccated thyroid rather than synthetic preparations is never justified,

ANTITHYROID AGENTS

Reduction of thyroid activity and hormone effects can be accomplished By: **1**- agents that interfere with the production of thyroid hormones, **2**- by agents that modify the tissue response to thyroid hormones, **3**- or by glandular destruction with radiation or surgery. The antithyroid compounds used clinically include the thioamides, iodides, and radioactive iodine.

THIOAMIDES

The thioamides **methimazole** and **propylthiouracil** are major drugs for treatment of thyrotoxicosis. Methimazole is about ten times more potent than propylthiouracil and is the drug of choice in adults and children. Due to a warning about severe hepatitis, 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).

Pharmacokinetics

Methimazole is completely absorbed but at variable rates. It is readily accumulated by the thyroid gland and has a volume of distribution similar to that of propylthiouracil. Excretion is slower than with propylthiouracil; 65–70% of a dose is recovered in the urine in 48 hours.
In contrast, propylthiouracil is rapidly absorbed, reaching peak serum levels after 1 hour. The bioavailability is 50–80% . The volume of distribution approximates total body water with accumulation in the thyroid gland. Most of an ingested dose of propylthiouracil is excreted by the kidney as the inactive glucuronide within 24 hours. The plasma half-life of these agents are (1.5 hours for propylthiouracil and 6 hours for methimazole) .
Both agents are accumulated by the thyroid gland. For propylthiouracil, intetvals of 6–8 hours is reasonable. For methimazole, a single daily dose is effective in the management of mild to severe hyperthyroidism.
Both thioamides cross the placental barrier and are concentrated by the fetal thyroid,
Of the two, propylthiouracil is preferable during the first trimester of pregnancy because it is more strongly protein-bound and, therefore, crosses the placenta less readily. In addition, methimazole has been (rarely,) associated with congenital malformations. Both thioamides are secreted in low concentrations in breast milk but are considered safe for the nursing infant.

Pharmacodynamics

The thioamides act by multiple mechanisms. The major action is to **prevent hormone synthesis** by inhibiting the thyroid peroxidase and blocking iodine organification. In addition, they block coupling of the iodotyrosines. Propylthiouracil but not methimazole inhibits the peripheral deiodination of T4 and T3 (Figure 1). Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T4 are depleted.

Toxicity

Adverse reactions to the thioamides occur in 3–12% of treated patients. Most reactions occur early, especially nausea and gastrointestinal distress. The **most common** adverse effect is a **maculopapular pruritic rash** (4–6%). **Rare** adverse effects include an urticarial rash, vasculitis, a lupus-like reaction, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, and acute arthralgia.
The **most dangerous** complication is **agranulocytosis**. It occurs in 0.1–0.5% of patients taking thioamides. The reaction is usually rapidly reversible when the drug is discontinued. The **cross-sensitivity** between ropylthiouracil and methimazole is about **50%;** therefore, switching drugs in patients with severe reactions is not recommended.

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. 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.

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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.

Pharmacodynamics

Iodides have several actions on the thyroid. They **inhibit organification** and hormone release and **decrease** the size and vascularity of the hyperplastic gland. In pharmacologic doses (> 6 mg/d), the major action of iodides is to inhibit hormone release, possibly through inhibition of thyroglobulin proteolysis. In addition, iodides decrease the vascularity, size, and fragility of a hyperplastic gland, making the drugs valuable as **preoperative preparation** for surgery.

Clinical Use of Iodide

. In radiation emergencies involving release of radioactive iodine isotopes, the thyroid blocking effects of potassium iodide can protect the gland from subsequent damage if administered before radiation exposure.

Toxicity

Adverse reactions to iodine (iodism) are uncommon and in most cases reversible upon discontinuance. They include **acneiform rash** (similar to that of bromism), **swollen salivary glands, mucous membrane ulcerations, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding disorders**, and rarely, anaphylactoid reactions.

RADIOACTIVE IODINE

131I is the only isotope used for treatment of thyrotoxicosis. Administered orally in solution as sodium 131I.

It is rapidly absorbed, concentrated by the thyroid, and incorporated into storage follicles. Its therapeutic effect depends on emission of β rays with an effective half-life of 5 days. 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. 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. Beta blockers cause clinical improvement of hyperthyroid symptoms but do not typically alter thyroid hormone levels.

■ CLINICAL PHARMACOLOGY OF THYROID & ANTITHYROID DRUGS

HYPOTHYROIDISM

Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body functions (Table 38–4). In infants and children, there is striking retardation of growth and development that results in dwarfism and irreversible mental retardation. The etiology and pathogenesis of hypothyroidism are outlined in Table 38–5. 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 (Table 38–2). The most common cause of hypothyroidism in the USA at this time is probably Hashimoto's thyroiditis, an immunologic disorder in genetically predisposed individuals. In this condition, there is evidence of humoral immunity in the presence of antithyroid antibodies and lymphocyte sensitization to thyroid antigens. Genetic mutations as discussed previously and certain medications can also cause hypothyroidism (Table 38–5).

TABLE 38–5 Etiology and pathogenesis of hypothyroidism.

Cause	Pathogenesis	Goiter	Degree of Hypothyroidism
Hashimoto's thyroiditis	Autoimmune destruction of thyroid	Present early, absent later	Mild to severe
Drug-induced[1]	Blocked hormone formation[2]	Present	Mild to moderate
Dyshormonogenesis	Impaired synthesis of T_4 due to enzyme deficiency	Present	Mild to severe
Radiation, ^{131}I, X-ray, thyroidectomy	Destruction or removal of gland	Absent	Severe
Congenital (cretinism)	Athyreosis or ectopic thyroid, iodine deficiency; TSH receptor-blocking antibodies	Absent or present	Severe
Secondary (TSH deficit)	Pituitary or hypothalamic disease	Absent	Mild

[1]Iodides, lithium, fluoride, thioamides, aminosalicylic acid, phenylbutazone, amiodarone, perchlorate, ethionamide, thiocyanate, cytokines (interferons, interleukins), bexarotene, tyrosine kinase inhibitors, etc. See Table 38–3.

[2]See Table 38–3 for specific pathogenesis.

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**, 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. Since interactions with certain foods 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). Its long half-life of 7 days permits once-daily dosing. Children should be monitored for normal growth and development.

In younger patients or those with very mild disease, full replacement therapy may be started immediately. In older patients (> 50 years) without cardiac disease, levothyroxine can be started at a lower dose. In long-standing hypothyroidism and in older patients with underlying cardiac disease, it is imperative to start with reduced dosages of levothyroxine, for 2 weeks, before increasing every 2 weeks until euthyroidism or drug toxicity is observed.

Thyroxine toxicity is directly related to the hormone level. In children, restlessness, insomnia, and accelerated bone maturation and growth may be signs of thyroxine toxicity. In adults, increased nervousness, heat intolerance, episodes of palpitation and tachycardia, or unexplained weight loss may be the presenting symptoms. Chronic overtreatment with T4, particularly in elderly patients, can increase the risk of atrial fibrillation and accelerated osteoporosis.

Special Problems in Management of Hypothyroidism

A. Myxedema and Coronary Artery Disease

Since myxedema frequently occurs in older persons, it is often associated with underlying coronary artery disease. In this situation, the low levels of circulating thyroid hormone actually protect the heart against increasing demands that could result in angina pectoris, atrial fibrillation, or myocardial infarction. If coronary artery surgery is indicated, it should be done first, prior to correction of the myxedema by thyroxine administration.

B. Myxedema Coma

Myxedema coma is an end state of untreated hypothyroidism. Myxedema coma is a medical emergency. The patient should be treated in the intensive care unit. It is important to give all preparations intravenously, because patients with myxedema coma absorb drugs poorly from other routes.The treatment of choice in myxedema coma is to give a loading dose of levothyroxine intravenously. Intravenous T3 can also be used but may be more cardiotoxic and more difficult to monitor. Opioids and sedatives must be used with extreme caution.

C. Hypothyroidism and Pregnancy

In a pregnant hypothyroid patient receiving thyroxine, it is extremely important that the daily dose of thyroxine be adequate because early development of the fetal brain depends on maternal thyroxine. In many hypothyroid patients, an increase in the thyroxine dose (about 25–30%) is required to normalize the serum TSH level during pregnancy

D. Drug-Induced Hypothyroidism

Drug-induced hypothyroidism can be satisfactorily managed with levothyroxine therapy if the offending agent cannot be stopped. In the case of amiodarone-induced hypothyroidism, levothyroxine therapy may be necessary even after discontinuance because of amiodarone's very long half-life.

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.

Pathophysiology

Graves' disease is considered to be an autoimmune disorder. The antibody described previously (TSH-R Ab [stim], TSI) stimulates growth and biosynthetic activity of the thyroid cell. Spontaneous remission occurs but some patients require years of antithyroid therapy.

Management of Graves' Disease

The three primary methods for controlling hyperthyroidism are antithyroid drug therapy, surgical thyroidectomy, and destruction of the gland with radioactive iodine.

A. Antithyroid Drug Therapy

Drug therapy is most useful in young patients with small glands and mild disease. Methimazole (preferred) or propylthiouracil is administered until the disease undergoes spontaneous remission. This is the only therapy that leaves an intact thyroid gland, but it does require a long period of treatment and observation (12–18 months), and there is a 50–70% incidence of relapse.

B. Thyroidectomy

A near-total thyroidectomy is the treatment of choice for patients with very large glands or multinodular goiters. About 80–90% of patients will require thyroid supplementation following near-total thyroidectomy.

C. Radioactive Iodine

Radioiodine therapy (RAI) utilizing 131I is the preferred treatment for most patients over 21 years of age. In patients without heart disease, the therapeutic dose may be given immediately In patients with underlying heart disease or severe thyrotoxicosis and in elderly patients, it is desirable to treat with antithyroid drugs (preferably methimazole) until the patient is euthyroid. When hypothyroidism develops, prompt replacement with oral Levothyroxine should be instituted.

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 intravenous propranolol, or **esmolol**, is helpful to control the severe cardiovascular manifestations. Hormone synthesis is blocked by the administration of propylthiouracil. Methimazole may also be prepared for rectal administration. Hydrocortisone will protect the patient against shock and will block the conversion of T4 to T3, rapidly reducing the level of thyroactive material in the blood. Supportive therapy is essential to control fever, heart failure, and other diseases.

NONTOXIC GOITER

Nontoxic goiter is a syndrome of thyroid enlargement without excessive thyroid hormone production. Enlargement of the thyroid gland is often due to TSH stimulation from inadequate thyroid hormone synthesis. The most common cause of nontoxic goiter worldwide is iodide deficiency, Goiter due to iodide deficiency is best managed by prophylactic administration of iodide.