

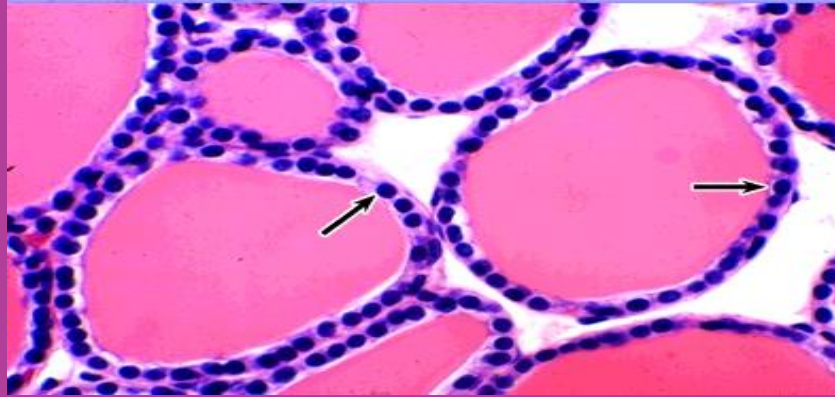
Thyroid & Antithyroid Drugs

Three hormones are secreted by the thyroid gland

- **thyroxine (3,5,3,5-tetraiodothyronine, or T4),**
- **triiodothyronine (3,5,3-triiodothyronine, or T3),**
- **Calcitonin**

• Every tissue in the body is affected in some way by thyroid hormones, and almost all cells appear to require constant optimal amounts for normal operation.

structural of the thyroid gland



- * Thyroid follicles are the structural & functional units of the thyroid gland.
- * Each follicle is surround mainly by simple cuboidal epithelium and is filled with a colloid
- * Thyroid hormones are mainly synthesized in colloid while the simple cuboidal epithelium undertaking thyroglobulin production, iodide intake & thyroid hormones release.

- Thyroglobulin (Tg) is a 660 kDa, dimeric protein produced by the follicular cells of the thyroid and used entirely within the thyroid gland.
- Thyroglobulin protein accounts for approximately half of the protein content of the thyroid gland

● Synthesis of thyroid hormones

Thyroid hormones

triiodothyronine (T3)

tetraiodothyronine (T4, thyroxine)

Materials

iodine & tyrosine

MIT: moniodotyrosine

DIT: diiodotyrosine

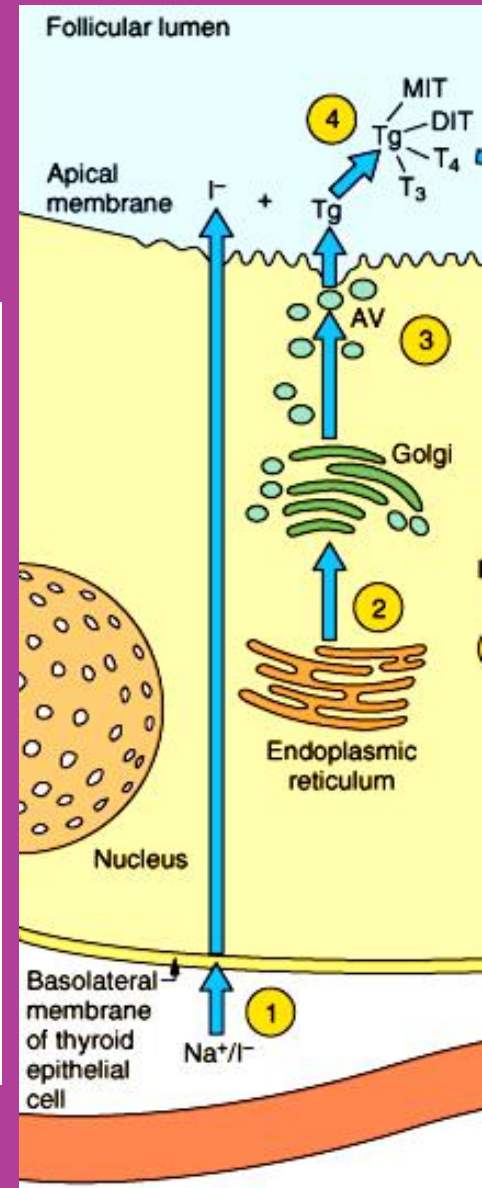
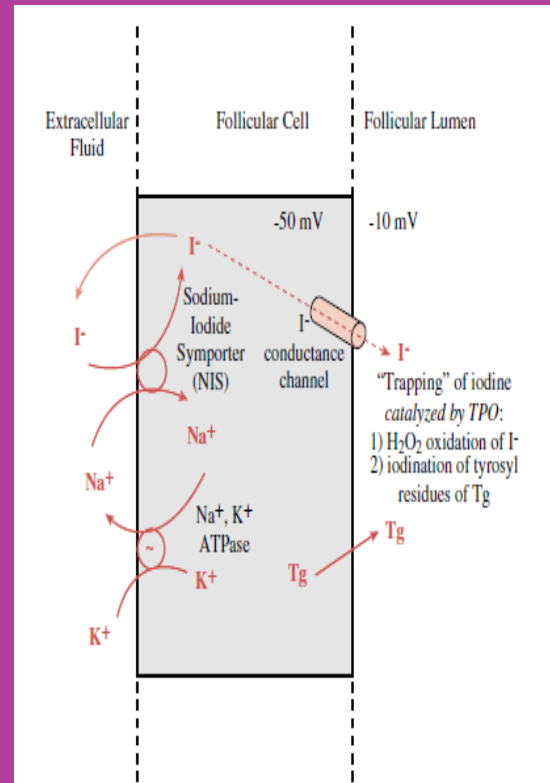
Steps

1. Iodide is trapped by sodium-iodide symporter

2. Iodide is oxidized by thyroidal peroxidase to iodine

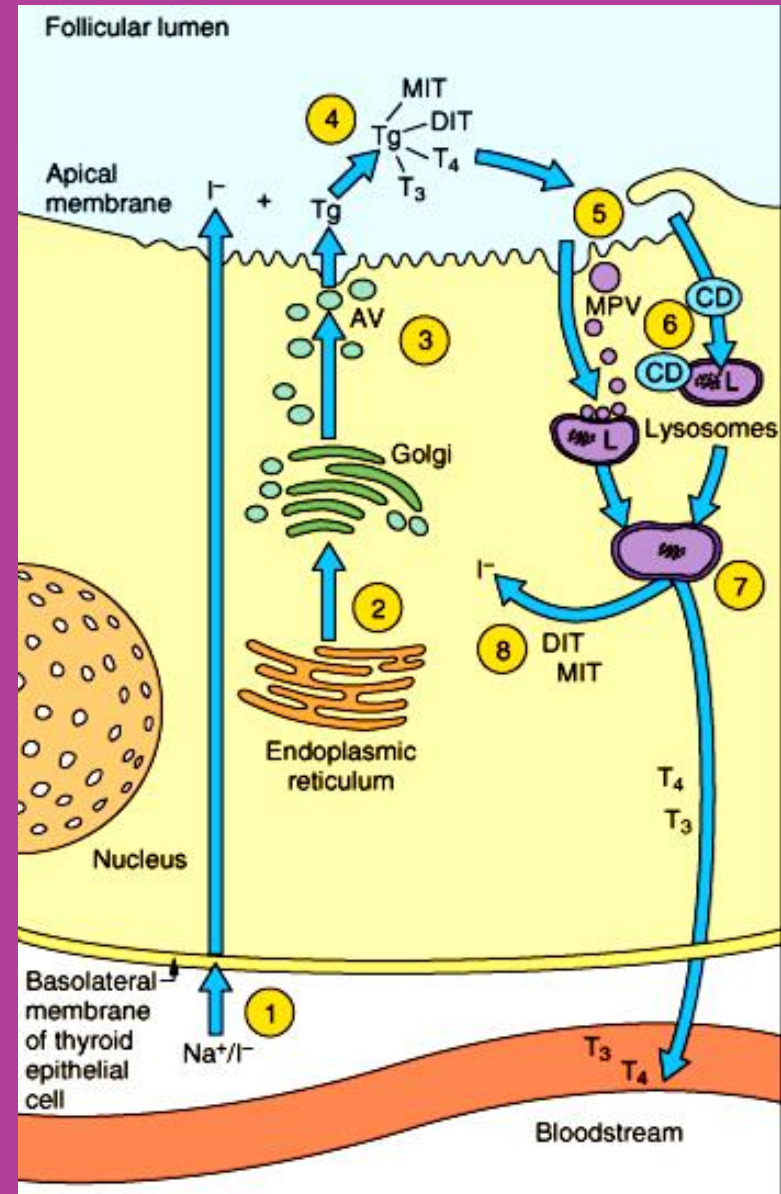
3. Tyrosine in thyroglobulin is iodinated and forms MIT & DIT

4. Iodotyrosines condensation



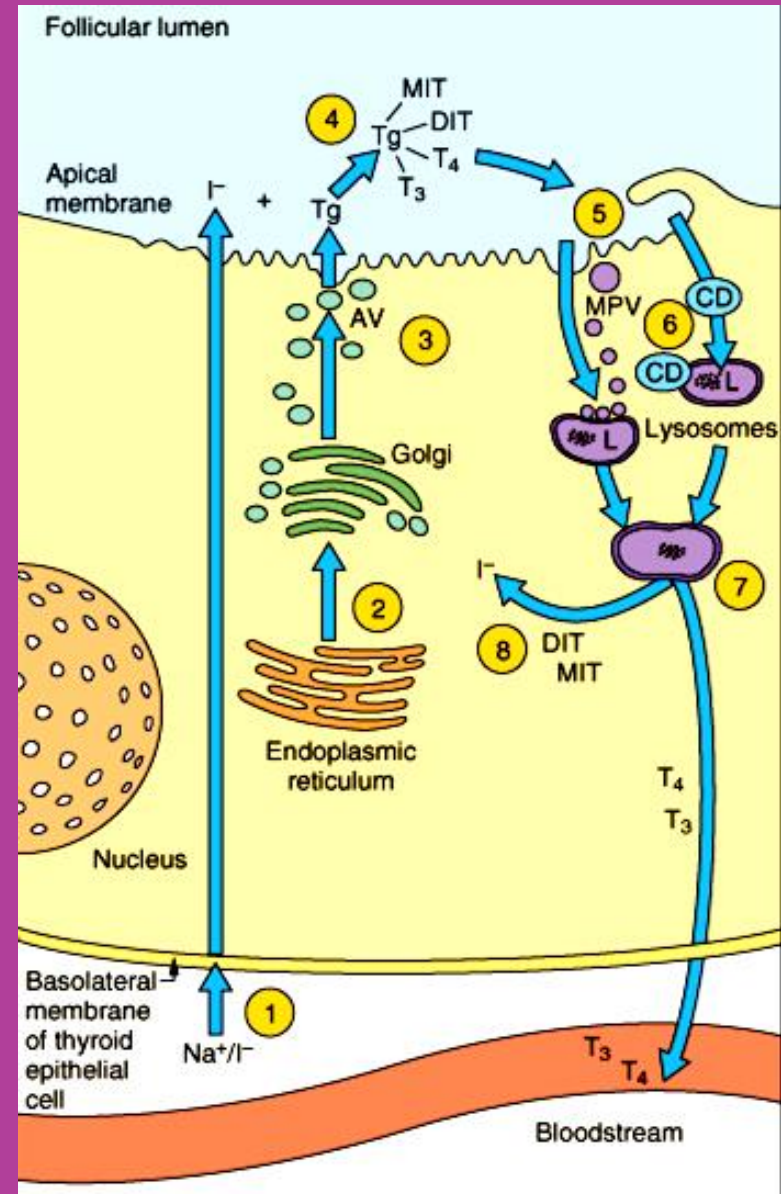
synthesis of thyroidal hormones

1. **Iodide** is taken up at the basolateral cell membrane and transported to the apical membrane
2. Polypeptide chains of **Tg** (thyroglobulin) are synthesized in the rough endoplasmic reticulum, and posttranslational modifications take place in the Golgi
3. Newly formed **Tg** is transported to the cell surface in small apical vesicles (**AV**)
4. Within the follicular lumen, **iodide** is activated and iodinates tyrosyl residues on **Tg**, producing fully iodinated Tg containing **MIT**, **DIT**, **T4** and a small amount of **T3** (organification and coupling), which is stored as colloid in the follicular lumen

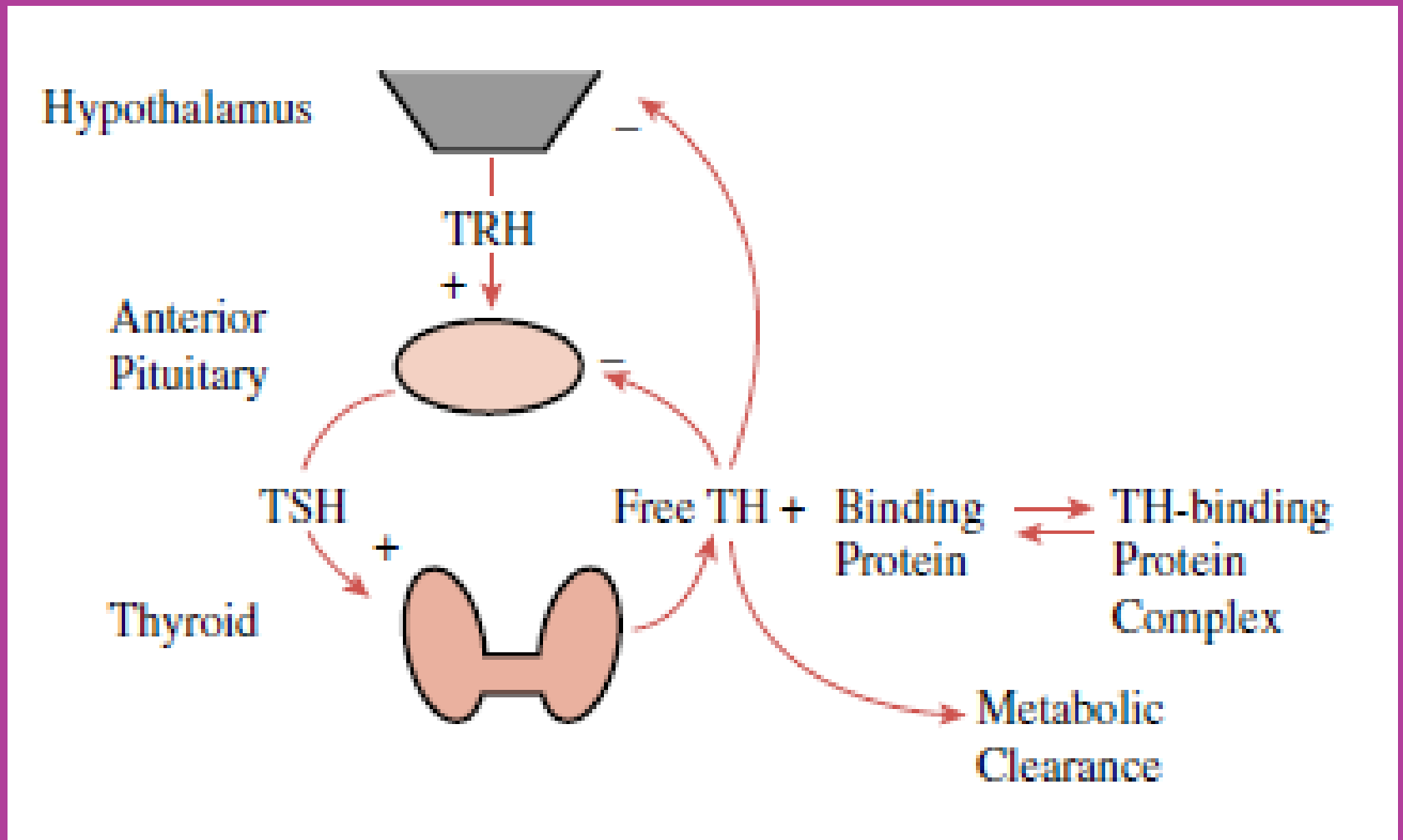


synthesis of thyroidal hormones

5. Upon **TSH** stimulation, villi at the apical membrane engulf the colloid and endocytose the iodinated Tg as either colloid droplets (CD) or small vesicles (MPV)
6. Lysosomal proteolysis of the droplets or vesicles hydrolyzes **Tg** to release its iodinated amino acids and carbohydrates
7. **T4** and **T3** are released into the circulation
8. **DIT** and **MIT** are deiodinated, and the **iodide** and **tyrosine** are recycled



● Regulation of thyroid function



TRH: thyrotropin-releasing hormone
TSH: thyroid-stimulating hormone

● Physiological actions of thyroid hormones

- To normalize growth and development, body temperature, and energy levels
- To enhance CNS excitability

T3 is 3 to 4 times more potent than T4 in heat production;

T4 in colloid is about 4 times more numerous than T3 ;

▲ Insufficiency of thyroid hormones result in *Primary hypothyroidism* which results from an inability of the thyroid gland itself to produce and secrete sufficient quantities of T4 and T3

→ cretinism (infant & child),
a condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones (congenital hypothyroidism)

myxedema (adult);

Myxedema or myxoedema is a term used synonymously with severe hypothyroidism. It is also used to describe a dermatological change that can occur in hypothyroidism, and some forms of hyperthyroidism.

▲Excess→hyperthyroid

Thyroid hormone mechanisms of action can be classified

into two types:

(1) genomic or nuclear and

(2) nongenomic, including effects at the plasma membrane and mitochondria.

Genomic Actions of Thyroid Hormones

the lipophilic T3 binds to a protein receptor to form a complex and the hormone–receptor complex binds to an appropriate hormone response element on DNA to alter the transcription of specific gene

Nongenomic Actions of Thyroid Hormone

The nongenomic actions of thyroid hormone are increasingly recognized as physiologically significant.

- Nongenomic actions may be observed within minutes of stimulation and respond to a range of thyroid hormone**

metabolites (T4, T3, rT3, T2).

- The magnitude of nongenomic actions is usually only a few fold in contrast to the multifold genomic actions.**

DRUGS USED IN THE TREATMENT OF HYPOTHYROIDISM

Liothyronine Sodium

- Liothyronine sodium (*Cytomel*) is the sodium salt of the naturally occurring levorotatory isomer of T3.
- generally not used for maintenance thyroid hormone replacement therapy because of its short plasma half-life and duration of action.
- The use of T3 alone is recommended only in special situations, such as
in the initial therapy of myxedema and myxedema coma and the short-term suppression of TSH in patients undergoing surgery for thyroid cancer

Levothyroxine Sodium

is the sodium salt of the naturally occurring levorotatory isomer of T4. It is the preparation of choice for maintenance of plasma T4 and T3 concentrations for thyroid hormone replacement therapy in hypothyroid patients.

Liotrix

Liotrix (*Euthroid, Thyrolar*) is a 4:1 mixture of levothyroxine sodium and liothyronine sodium. the idea of combining T4 and T3 in replacement therapy so as to mimic the normal ratio secreted by the thyroid

DRUGS USED IN THE TREATMENT OF HYPERTHYROIDISM

- **Treatment of hyperthyroidism is directed at reducing the excessive synthesis and secretion of thyroid hormones.**
- **This may be accomplished by inhibiting thyroidal synthesis and secretion with antithyroid drugs, by reducing the amount of functional thyroid tissue**

Thionamides

- **Propylthiouracil and methylthiouracil (methimazole; Tapazole) are the most commonly used preparations in the United States**
- **Thionamides are the primary drugs used to decrease thyroid hormone production. They do not inhibit secretion of stored thyroid hormone, and therefore, when they are used alone, their clinical effects are not apparent until the preexisting intrathyroidal store of thyroid hormone is depleted**

Clinical use

- the management of hyperthyroidism and thyrotoxic crisis and in the preparation of patients for surgical subtotal thyroidectomy

Adverse reactions

- If given in excessive amounts over a long period,
- Agranulocytosis
severe and dangerous leukopenia (lowered white blood cell count) causing a neutropenia in the circulating blood
- rash.
- cholestatic jaundice,
- drug fever
- psychosis

Iodides (NaI, KI)

Pharmacological action

Inhibition of T3 & T4 release and synthesis

Decrease of size & vascularity of the hyperplastic gland

Clinical use

treatment of hyperthyroid

1. Operation preparation;
2. Thyroid crisis.

Adverse reactions

1. rash
2. Swollen salivary glands, mucous membrane ulcerations

Thyroid storm, also referred to as thyrotoxic crisis, is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones (THs) in individuals with thyrotoxicosis.

Radioactive iodine (^{131}I)

^{131}I is the only **isotope** for treatment of **thyrotoxicosis**.

Its therapeutic effect depends on emission of **β rays** with an effective half-life of 5 days & a penetration range of 0.4-2 mm.

Woman in pregnancy or lactation is forbidden!

β -adrenoceptor blockers

β blockers are effective in treatment of **thyrotoxicosis**.

Propranolol is the most widely studied and used.