الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية2

د.رامز ونوس

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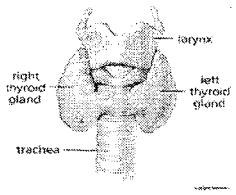
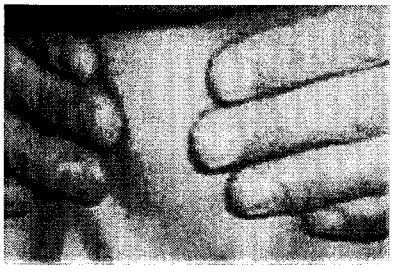
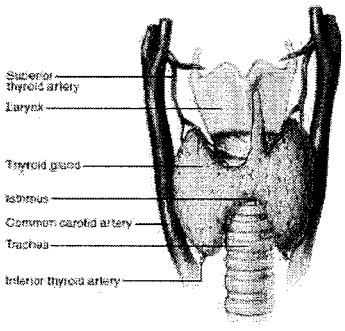


Thyroid Hormone

Anatomy

- Over Trachea
- Two Lobes connected together by an isthmus
- 15 to 20 g

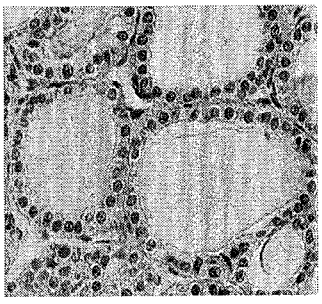


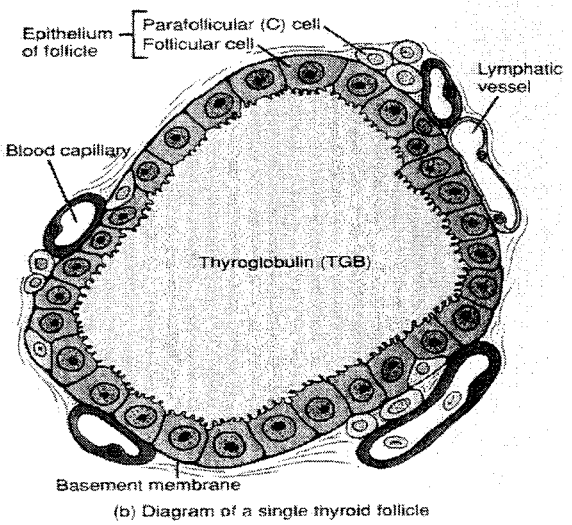


Thyroid gland

- Thyroid gland is composed over a million cluster of follicles
- Follicles are spherical & consists of epithelial cells surrounding a central mass (colloid)
- Normal thyroid gland secretes thyroid hormones
- Natural hormone compounds having biological activity (Iodide containing):
  - T_4 or tetraiodo-L-thyroxine
  - T_3 or triiodo-L-thyronine
- Parafollicular (C) cells produce calcitonin

Follicular Cells – the functional unit





(b) Diagram of a single thyroid follicle

Thyroid Hormone - Biosynthesis

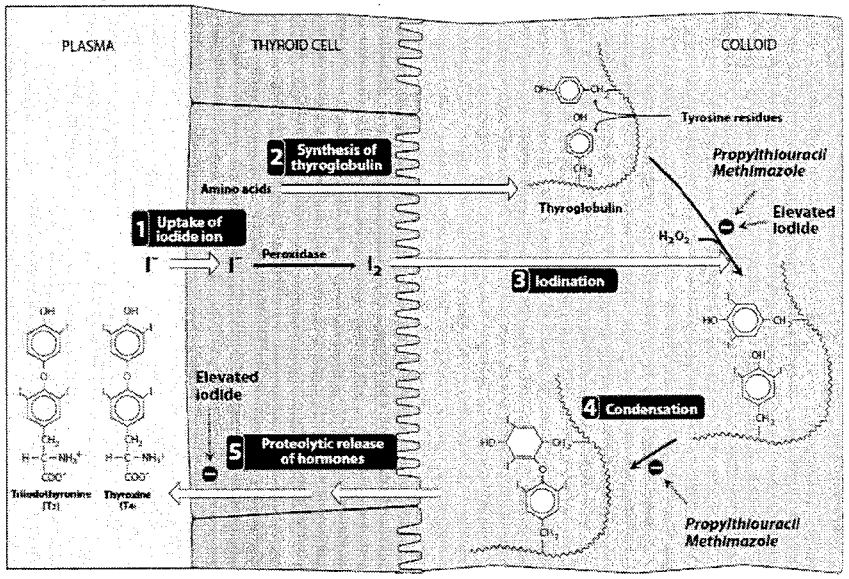


Figure 24.7
Biosynthesis of thyroid hormones.

Thyroid Hormone - Biosynthesis

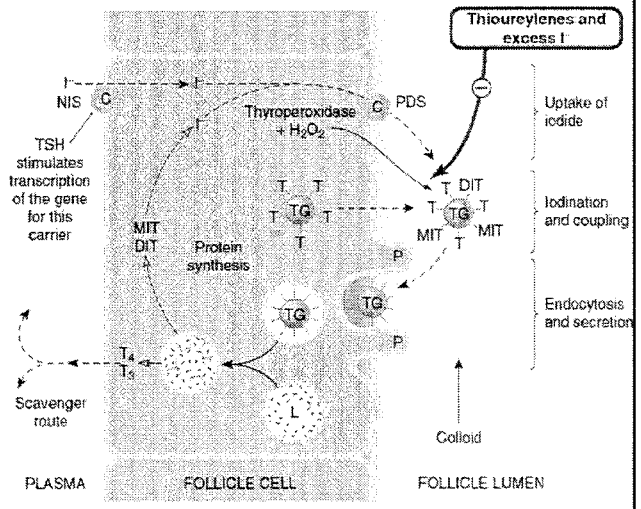


Fig. 33.1 Diagram of thyroid hormone synthesis and secretion, with the sites of action of drugs used in the treatment of thyroid disorders. Iodide in the blood is transported by the carriers NIS and pendrin (PDS) through the follicular cell and into the colloid-rich lumen, where it is incorporated into thyroglobulin under the influence of the thyroperoxidase enzyme (see text for details). The hormones are produced by processing of the endocytosed thyroglobulin and exported into the blood. DIT, di-iodotyrosine; L, lysosome; MIT, monoiodotyrosine; P, pseudopod; T, tyrosine; T_3, tri-iodothyronine; T_4, thyroxine; TG, thyroglobulin; TSH, thyroid-stimulating hormone (thyrotrophin).

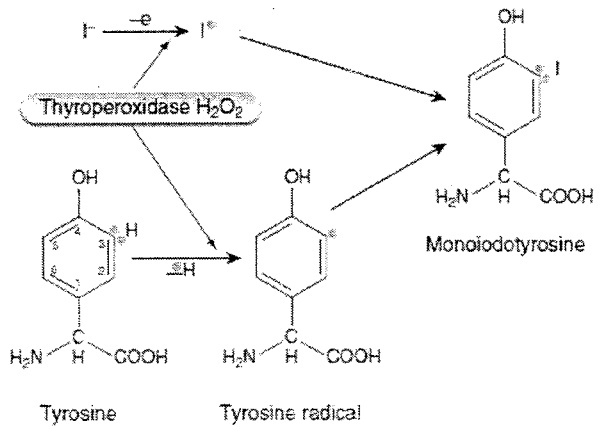


Fig. 33.2 Iodination of tyrosyl residues by the thyroperoxidase–H_2O_2 complex. This probably involves two sites on the enzyme, one of which removes an electron from iodide to give the free radical I•; another removes an electron from tyrosine to give the tyrosyl radical (shown by orange dot). Monoiodotyrosine results from the addition of the two radicals.

Uptake Of Plasma Iodide By The Follicle Cells

•Iodide is captured from the blood and moved to the lumen by two transporters: the Na+/I− symporter (NIS) located at the basolateral surface of the thyrocytes, and *pendrin1 (PDS), an I−/Cl−* porter in the apical membranes.
•(mutations in the *NIS and PDS genes contribute to thyroid disease in some* patients).
•Uptake is very rapid: labelled iodide (^{125}I) is found in the lumen within 40 s of intravenous injection.

Oxidation Of Iodide And Iodination Of Tyrosine Residues

•The oxidation of iodide and its incorporation into thyroglobulin (termed the *organification of iodide) is catalysed* by *thyroperoxidase, an enzyme situated at the inner surface* of the cell at the interface with the colloid.
•The reaction requires the presence of hydrogen peroxide (H_2O_2) as an oxidising agent.
•Tyrosine residues are iodinated first at position 3 on the ring, forming *monoiodotyrosine (MIT) and then, in some* molecules, on position 5 as well, forming *di-iodotyrosine* (DIT).
•While still incorporated into thyroglobulin, these molecules are then coupled in pairs, either MIT with DIT to form T3, or two DIT molecules to form T4.
•The iodinated thyroglobulin of the thyroid forms a large store of thyroid hormone within the gland, with a relatively slow turnover.

Secretion Of Thyroid Hormone

• Thyroglobulin molecule is taken up into the follicle cell by endocytosis
• Endocytotic vesicles fuse with lysosomes, and proteolytic enzymes act on thyroglobulin, releasing T4 and T3 to be secreted into the plasma
• Surplus MIT and DIT, which are released at the same time, are scavenged by the cell, where the iodide is removed enzymatically and reused

Transport, Metabolism and Excretion - Kinetics

- Highly bound to plasma protein
- Main Plasma proteins for T4 are – TBG and albumin
- Only 0.04% of T3 and 0.2% T4 are in free form
- Only free form of hormone is available for action and metabolism
- Metabolism occurs by deiodination and conjugation, mainly in liver and kidneys
- T4 is deiodinated to T3 (active) or rT3 (inactive) by deiodination
- Conjugated products are excreted in bile – enterohepatic circulation
- Finally excreted in urine

T_3 vs T_4

- The term thyroid hormone is used to comprise both T4 plus T3
- T4 is the major circulating hormone – bound more to plasma proteins
- T4 is less active and a precursor of T3 - the major mediator of physiological effects
- T4 is 5 times less potent than T3
- Half life of T4 is 6-7 days and T3 is 1-2 days –
- T4 deiodination to T3 or reverse T3
- T3 & reverse T3 deiodination to di-iodothyronines, deiodinated to two monoiodothyronines - (inactive)

Thyroid Regulation

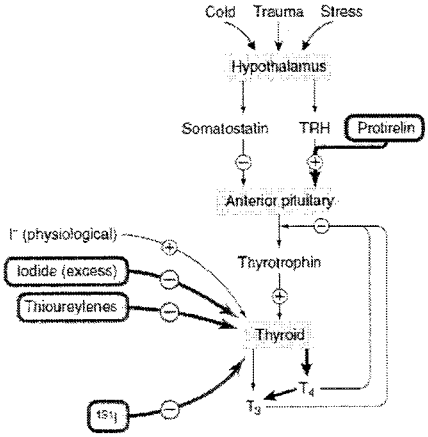
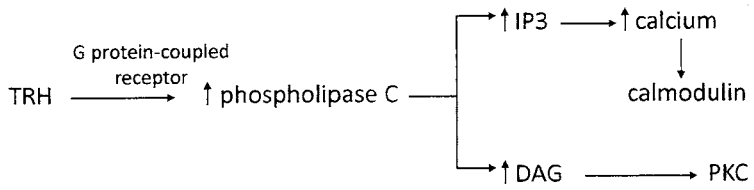


Fig. 33.3 Regulation of thyroid hormone secretion. Iodide (I^-) is essential for thyroid hormone synthesis, but excess of endogenous or exogenous iodide (30 times the daily requirement of iodine) actually inhibits the increased thyroid hormone production, which occurs in thyrotoxicosis. Protirelin as well as recombinant thyrotrophin-releasing hormone (TRH) is sometimes used to stimulate the system for diagnostic purposes, as is the administration of ^{131}I (see text for details). T_3, tri-iodothyronine; T_4, thyroxine.

Influence of TRH on TSH Release

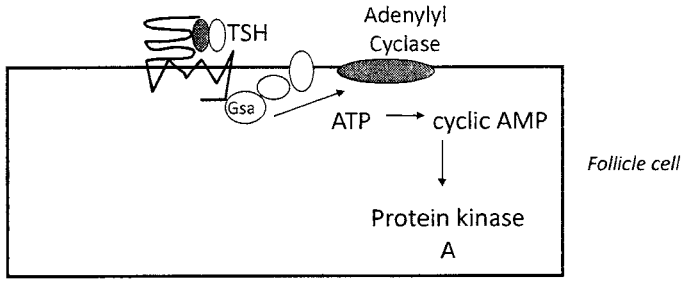
- Thyrotropin-releasing hormone (TRH) is a hypothalamic releasing factor which travels through the pituitary portal system to act on anterior pituitary Thyrotroph cells.
- TRH acts through G protein-coupled receptors, activating the IP3 (Ca^{2+}) and DAG (PKC) pathways to cause increased production and release of TSH.



- Thyroid hormones also inhibit TRH synthesis.

Mechanism of Action of TSH

- TSH binds to G protein-coupled receptor on thyroid follicular cells.
- Specifically, it activates a Gs-coupled receptor which leads to activation of Adenyl cyclase resulting in increased c-AMP production and PKA (Protein Kinase-A) activation.



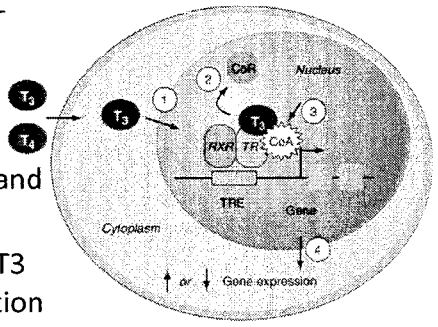
Action of TSH on the Thyroid

TSH has a trophic action on thyroid cells and controls all aspects of thyroid hormone synthesis, including:

- *uptake of iodide by follicle cells, by stimulating* transcription of the iodide transporter genes
- *synthesis and secretion of thyroglobulin*
- *generation of H_2O_2 and the iodination of tyrosine*
- *endocytosis and proteolysis of thyroglobulin*
- actual *secretion of T3 and T4*
- *blood flow through the gland*

MOA - thyroid hormones

- T3 binds to high affinity receptors
- Three thyroid hormone receptor:- TR α1, TRβ1, TRβ2
- TRα1, binds to DNA sequence in specific genes
- T3 modulates gene transcription and protein synthesis
- T4 binds with lower affinity than T3 but does not alter gene transcription
- T3 causes all actions of thyroid hormones at transcriptional level



Actions

Effects On Growth And Development

- directly: on cells
- Indirectly: by influencing *growth hormone production and potentiating its* effects on its target tissues
- important for a normal response to parathormone and calcitonin as well as for skeletal development
- essential for normal growth and maturation of the central nervous system
- Irreversible mental retardation (cretinism) in absence of thyroid hormones during active neurogenesis (upto 6 month postpartum). Supplementation during first 2 weeks of life prevent development of brain changes

Actions – contd.

Metabolism:

- Lipid: Induce lipolysis (catecholamines), ↑ free plasma fatty acid and all phases of cholesterol metabolism enhanced (bile acid more)
  - Hyperthyroidism – hypercholesterolemia
- Carbohydrate:Stimulation of carbohydrate metbolism, glycogenolysis, gluconeogenesis
  - Hyperthyroidism – diabetes-like state
- Protein: Certain protein synthesis increased but overall catabolic action – negative nitrogen balance
  - Hyperthyroidism – Weight loss and wasting

Abnormalities Of Thyroid Function

- Abnormalities of thyroid function include:

– hyperthyroidism (thyrotoxicosis); either diffuse toxic goitre or toxic nodular goitre

– simple non-toxic goitre caused by dietary iodine deficiency, usually with normal thyroid function

– hypothyroidism; in adults this causes myxoedema, in infants cretinism(*congenital hypothyroidism)*

Abnormalities Of Thyroid Function

1- Hyperthyroidism

a) Thyrotoxicosis

excessive activity of the thyroid hormones, resulting in

- high metabolic rate
- Increase in skin temperature
- heat sensitivity
- Sweating
- Nervousness
- Tremor
- Tachycardia
- increased appetite associated with loss of weight

Types of Thyrotoxicosis

diffuse toxic goitre *(Graves' disease or exophthalmic goitre)*

- an organ-specific autoimmune disease caused by autoantibodies to the TSH receptor (which actually stimulate it, increasing thyroxine secretion)
- mutations of the TRH receptor
- As is indicated by the name, patients with exophthalmic goitre have protrusion of the eyeballs (and enhanced sensitivity to catecholamines)

toxic nodular goitre.

does not usually have concomitant exophthalmos

caused by:

- a benign neoplasm or adenoma
- Drugs iodine-containing :

Amiodarone (antidysrhythmic drug can cause either hyperthyroidism or hypothyroidism)

iopanoic acid (used as imaging agents used to visualise the gall bladder)

2- Simple, Non-toxic Goitre

- A dietary deficiency of iodine
- if prolonged, causes a rise in plasma TRH and eventually an increase in the size of the gland
- The enlarged thyroid usually manages to produce normal amounts of thyroid hormone
- if the iodine deficiency is very severe, hypothyroidism may supervene

3- Hypothyroidism

- A decreased activity of the thyroid results in hypothyroidism
- manifestations include:
  - low metabolic rate
  - slow speech
  - deep hoarse voice
  - Lethargy
  - Bradycardia
  - sensitivity to cold
  - Mental impairment
  - a characteristic thickening of the skin (myxoedema) in adults
- Thyroid deficiency during development, causes *congenital hypothyroidism,* characterised by gross retardation of growth (dwarfism) and mental deficiency

Hypothyroidism

- ***Hashimoto's thyroiditis**, a chronic **autoimmune** disease in* which there is an immune reaction against ***thyroid peroxidase or thyroglobulin***
- Impaired hypothalamus and pituitary function, can inhibit the secretion of TSH, causing secondary hypothyroidism.
- A diet insufficient in iodine causes hypothyroidism as well.

Drugs Used In Diseases Of The Thyroid

Drugs for hypothyroidism

1. HRT

- **Levothyroxine** has all the actions of endogenous thyroxine; it is given **orally**.
- **Liothyronine** has all the actions of endogenous tri-iodothyronine; it is given **IV**.

Drugs for hyperthyroidism

1. Removal of part or all of the thyroid:
surgically or by radioactive iodine ^{131}I

2. Inhibition of thyroid hormone synthesis:
thioamides, propylthiouracil, iodide

3. Blockade of hormone release
iodide

Treatment of Hypothyroidism

There are no drugs that specifically augment the synthesis or release of thyroid hormones. The only effective treatment for hypothyroidism, unless it is caused by iodine deficiency (which is treated with iodide), is to administer the thyroid hormones themselves as replacement therapy.

Thyroxine (official name: levothyroxine)

tri-iodothyronine (official name: liothyronine)

- synthetic compounds, identical to the natural hormones, and are given orally.
- Thyroxine as the sodium salt in doses of 50–100 μg/day is the usual first-line drug of choice
- Liothyronine has a faster onset but a shorter duration of action, and is generally reserved for acute emergencies such as the rare condition of myxoedema coma, where these properties are an advantage

Unwanted effects

- signs and symptoms of hyperthyroidism
- angina pectoris
- cardiac dysrhythmias
- cardiac failure
- osteoporosis

Drugs Used In Diseases Of The Thyroid

Hyperthyroidism

- Surgery (when there are mechanical problems resulting from compression of the trachea, and it is usual to remove only part of the organ).
- Drugs (do not alter the underlying autoimmune mechanisms or improve the exophthalmos associated with Graves' disease).

Treatment of Hyperthyroidism

Radioiodine ^{131}I

- first-line treatment for hyperthyroidism
  - The isotope used is ^{131}I (usually as the sodium salt)
  - Dose: orally single dose 5–15 millicuries
  - ^{131}I has a half-life of 8 days, its cytotoxic effect on the gland is delayed for 1–2 months and does not reach its maximum for a further 2 months
- used diagnostically as a test of thyroid function (A tracer dose of the isotope is given orally or intravenously, and the amount accumulated by the thyroid is measured by a γ-scintillation counter placed over the gland
- treatment of thyroid cancer

Treatment of Hyperthyroidism

Radioiodine

- Hypothyroidism will eventually occur after treatment with radioiodine, particularly in patients with Graves' disease, but is easily managed by replacement therapy with T4.
- avoided in children and also in pregnant patients because of potential damage to the fetus.
- theoretically : increases risk of thyroid cancer but this has not been seen following the therapeutic treatment.

MOA:

- it is taken up and processed by the thyroid in the same way as the stable form of iodide, eventually becoming incorporated into thyroglobulin. The isotope emits both β and γ radiation. the β particles have a very short range; they are absorbed by the tissue and exert a powerful cytotoxic action that is restricted to the cells of the thyroid follicles, resulting in significant destruction of the tissue.

- **Thioureylenes**

- comprises **carbimazole, methimazole and propylthiouracil.** Chemically, they are related to thiourea, and the thiocarbamide (S–C–N) group is essential for antithyroid activity.

Mechanism of action

- inhibit the iodination of tyrosyl residues in thyroglobulin
  inhibit the thyroperoxidase-catalysed oxidation reactions by acting as substrates for the postulated peroxidase–iodinium complex, thus competitively inhibiting the interaction with tyrosine.
- inhibit the condansation
- Propylthiouracil has the additional effect of reducing the deiodination of T4 to T3 in peripheral tissues

Pharmacokinetic aspects

- Thioureylenes are given orally.
- Carbimazole is rapidly converted to its active metabilite methimazole,
- An average dose of carbimazole produces more than 90% inhibition of thyroid incorporation of iodine within 12 h.
- The clinical response may take several weeks (because T4 has a longer half-life and because the thyroid large stores, which need to be depleted before the drug's action can be fully manifest)
- Propylthiouracil acts more rapidly because of its additional effect as an inhibitor of the peripheral conversion of T4 to T3.
- Both methimazole and propylthiouracil cross the placenta and also appear in the milk, but this effect is less pronounced with propylthiouracil, because it is more strongly bound to plasma protein.
- metabolites are excreted in the urine
- propylthiouracil being excreted more rapidly than methimazole

- **Unwanted effects**

- neutropenia and agranulocytosis, reversible on cessation of treatment (blood count)
- sore throat
- Rashes
- Headaches
- nausea
- jaundice
- pain in the joints

Iodine/Iodide

- Iodine is converted in vivo to iodide (I−
- When high doses of iodine are given to thyrotoxic patients:
  - Symptoms subside within 1–2 days
  - inhibition of the secretion of thyroid hormones
  - over a period of 10–14 days, a marked reduction in vascularity of the gland, which becomes smaller and firmer.
- orally in a solution with potassium iodide

- **uses of iodine/iodide**

  - the preparation of hyperthyroid subjects for surgical resection of the gland as part of the treatment of severe thyrotoxic crisis (*thyroid storm).*

Mechanism of action

- A pharmacologic dose of *iodide* inhibits the iodination of tyrosines (but this effect lasts only a few days)
- More importantly, *iodide inhibits the* release of thyroid hormones from thyroglobulin by mechanisms not yet understood
- *Iodide is not useful for long-term therapy, because the* thyroid ceases to respond to the drug after a few weeks

Side effects:

- *Allergic reactions (*angio-oedema, rashes and drug fever)
- Conjunctivitis
- cold-like syndrome
- ulcerations of mucous membranes
- metallic taste in the mouth
- pain in the salivary glands
- Lacrimation (by transport mechanisms in tears and saliva)

Other Drugs Used

- **Propranolol** (β-adrenoceptor antagonists) , not as antithyroid agents, but
  - useful for decreasing many of the signs and symptoms of hyperthyroidism—the tachycardia, dysrhythmias, tremor and agitation.
  - preparation of thyrotoxic patients for surgery
  - in most hyperthyroid patients during the initial treatment period while the thioureylenes or radioiodine take effect
  - as part of the treatment of acute hyperthyroid crisis.
- Eye drops containing **guanethidine, a noradrenergic-blocking agent**, are used to ameliorate the exophthalmos of hyperthyroidism (which is not relieved by antithyroid drugs); it acts by relaxing the sympathetically innervated smooth muscle that causes eyelid retraction.
- Glucocorticoids (e.g. **prednisolone or hydrocortisone) or surgical decompression** may be needed to mitigate severe exophthalmia in Graves' disease.