chapter 18 Thyroid Hormones and Thyroid Inhibitors

THYROID HORMONES

The thyroid gland secretes 3 hormones—thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former two are produced by thyroid follicles, have similar biological activity and the term 'thyroid hormone' is restricted to these only. *Calcitonin* produced by interfollicular 'C' cells is chemically and biologically entirely different. It is considered along with parathormone (*see* Ch. 24) with which it regulates calcium metabolism.

The physiological significance of thyroid gland was recognized only after Graves and Basedow (1835, 1840) associated the clinical features of the 'Graves' disease' with swelling of thyroid gland and Gull (1874) correlated myxoedema with its atrophy. Kendall (1915) obtained crystalline thyroxine and postulated its chemical formula which was confirmed in 1926. Thyroxine was the first hormone to be synthesized in the laboratory. Since T_4 could not account for all the biological activity of thyroid extract, search was made and more potent T_3 was discovered in 1952.

Chemistry and Synthesis

Both T_4 and T_3 are iodine containing derivatives of *thyronine* which is a condensation product of two molecules of the amino acid *tyrosine*. *Thyroxine* is 3, 5, 3′, 5′–tetraiodothyronine while T_3 is 3, 5, 3′ triiodothyronine.

The thyroid hormones are synthesized and stored in the thyroid follicles as part of *thyroglobulin* molecule—which is a glycoprotein synthesized by thyroid cells, MW 660 KDa, contains 10% sugar. The synthesis, storage and release of T_4 and T_3 is summarized in Fig. 18.1 and involves the following processes.

1. *Iodide uptake* The total body content of I_2, obtained from food and water, is 30–50 mg, out of which about 1/5 is present in the thyroid. Concentration of iodide in blood is low (0.2–0.4 µg/dl) but thyroid cells have an active transport process Na^+: *iodide symporter (NIS)* to concentrate this anion; this trapping is stimulated by thyroid stimulating hormone (TSH) to exceed a gradient of more than 100 fold by inducing and activating NIS. The I_2 content of thyroid gland somehow regulates the uptake mechanism: meagre store activating and large store inhibiting it. The iodide concentrating mechanism is not peculiar to thyroid. Skin, salivary glands, gastric mucosa, intestine, mammary glands and placenta also possess it, but uptake in these organs is not stimulated by TSH.

2. *Oxidation and iodination* Iodide trapped by follicular cells is carried across the apical membrane by another transporter termed '*pendrin*' and oxidized by the membrane bound thyroid peroxidase enzyme to iodinium (I^+) ions or hypoiodous acid (HOI) or enzyme-linked hypoiodate (E-OI) with the help of H_2O_2. These forms of iodine combine avidly with tyrosil residues of thyroglobulin, apparently without any enzymatic intervention, to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) while these residues are still attached to the thyroglobulin chains.

3. *Coupling* Pairs of iodinated tyrosil residues couple together (Fig. 18.2) to form T_3 and T_4.

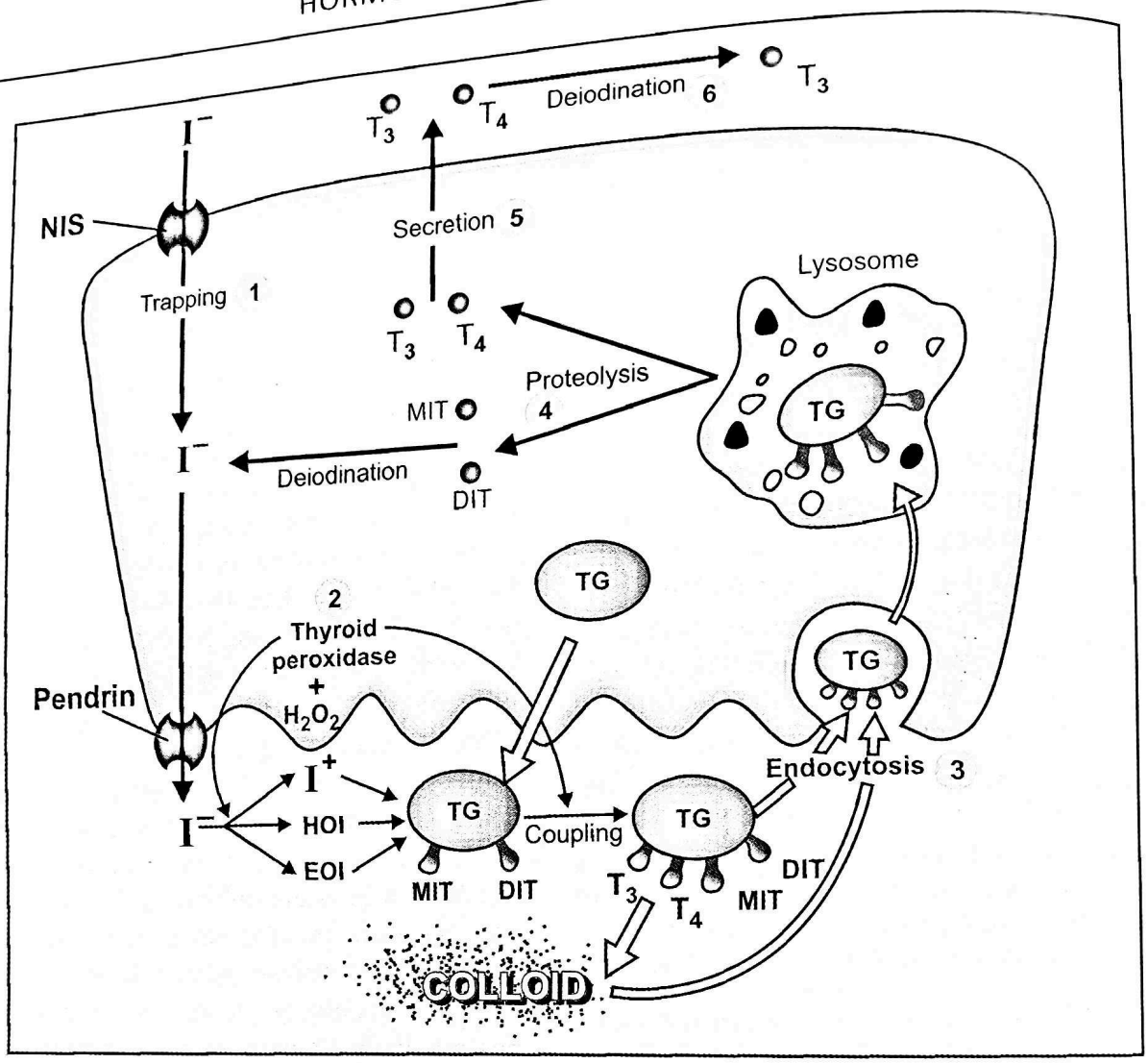


Fig. 18.1: Synthesis, storage and secretion of thyroid hormone
TG—Thyroglobulin; MIT—Monoiodotyrosine; DIT—Diiodotyrosine; T_3—Triiodothyronine; T_4—Thyroxine (Tetraiodothyronine); HOI—Hypoiodous acid; EOI—Enzyme linked hypoiodate; NIS—Na^+-iodide symporter; Thyroid-stimulating hormone (TSH) activates steps 1, 2, 3, 4, and 5; Ionic inhibitors block step 1; Excess iodide interferes with steps 1, 2, 3 and 5 with primary action on step 3 and 5; Propylthiouracil inhibits steps 2 and 6; Carbimazole inhibits step 2 only

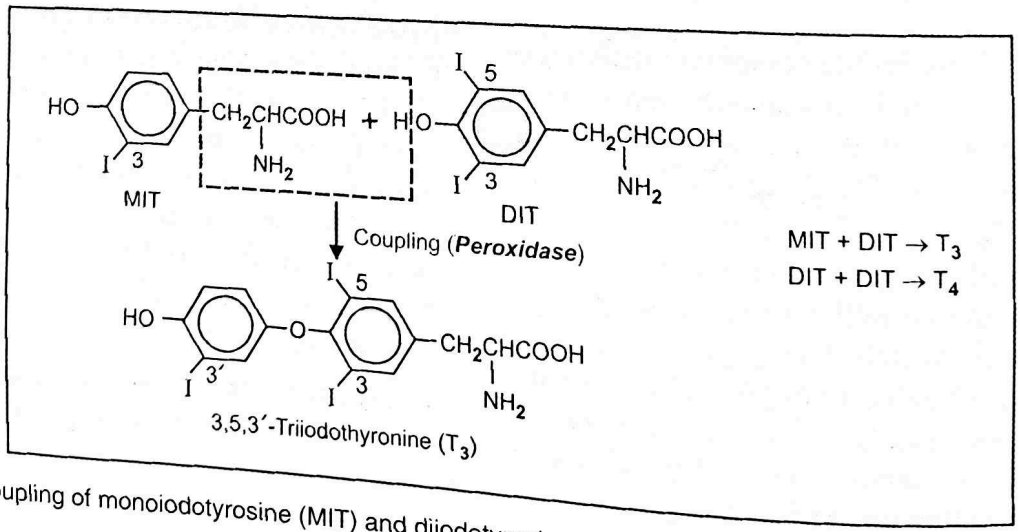


Fig. 18.2: Coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to produce triiodothyronine (T_3)

Normally much more T_4 than T_3 is formed, but during I_2 deficiency relatively more MIT is available and a greater proportion of T_3 is formed. The result is—more active hormone is generated with lesser amount of I_2.

Coupling is an oxidative reaction and is catalysed by the same thyroid peroxidase. Thyroglobulin is the most efficient protein, compared to other similar proteins, in supporting coupling by providing favourable spatial configuration to facilitate the reaction. Oxidation of iodide and coupling are both stimulated by TSH.

4. *Storage and release* Thyroglobulin containing iodinated tyrosil and thyronil residues is transported to the interior of the follicles and remains stored as thyroid colloid till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released is secreted into circulation while MIT and DIT residues are deiodinated and the iodide released is reutilized. The uptake of colloid and proteolysis are stimulated by TSH: the quiscent gland has follicles distended with colloid and cells are flat or cubical, while the TSH stimulated gland has columnar cells and colloid virtually disappears.

Normal human thyroid secretes 60–90 µg of T_4 and 10–30 µg of T_3 daily.

5. *Peripheral conversion of T_4 to T_3* Peripheral tissues, especially liver and kidney, convert T_4 to T_3. About 1/3 of T_4 secreted by thyroid undergoes this change and most of the T_3 in plasma is derived from liver. Target tissues take up T_3 from circulation for their metabolic need, except brain and pituitary which take up T_4 and convert it to T_3 within their own cells. Almost equal amounts of 3, 5, 3′ triiodothyronine (normal T_3 : active) and 3, 3′, 5′ triiodothyronine (reverse T_3 or rT_3: inactive) are produced in the periphery. The T_4 to T_3 conversion is carried out by the enzyme *iodothyronine deiodinase* which exists in 3 forms (D1, D2, D3). These forms differ in their organ and cellular localization as well as in the product formed. Whereas type 2 deiodinase (D2) generates T_3 and D3 generates rT_3, the D1 form generates both T_3 and rT_3. The antithyroid drug propylthiouracil (but not carbimazole) inhibits Type1 deiodinase and the antiarrhythmic amiodarone inhibits both D1 and D2 forms. Propranolol (high dose) and glucocorticoids also inhibit peripheral conversion of T_4 to T_3 (except in brain and in pituitary).

Transport, Metabolism and Excretion

Thyroid hormones are avidly bound to plasma proteins—only 0.03–0.08% of T_4 and 0.2–0.5% of T_3 are in the free form. Almost all protein bound iodine (PBI) in plasma is thyroid hormone, of which 90–95% is T_4 and the rest T_3. Binding occurs to 3 plasma proteins in the following decreasing order of affinity for T_4:

(i) Thyroxine binding globulin (TBG)
(ii) Thyroxine binding prealbumin (trans-thyretin)
(iii) Albumin

The normal concentration of PBI is 4–10 µg/dl; only 0.1–0.2 µg/dl of this is T_3, rest is T_4. During pregnancy thyroxine binding globulin is increased—PBI levels are elevated, but there is no effect on thyroid status because the concentration of free hormone remains unaltered.

Only the free hormone is available for action as well as for metabolism and excretion. Metabolic inactivation of T_4 and T_3 occurs by deiodination and glucuronide or sulfate conjugation of the hormones as well as that of their deiodinated products. Liver is the primary site (also salivary glands and kidneys). The conjugates are excreted in bile, of which a significant fraction is deconjugated in intestines and reabsorbed (enterohepatic circulation) to be finally excreted in urine.

Plasma t½ of T_4 is 6–7 days, while that of T_3 is 1–2 days. The half-lives are shortened in hyperthyroidism and prolonged in hypothyroidism due respectively to faster and slower metabolism.

Regulation of Secretion

The secretion of hormones from the thyroid is controlled by anterior pituitary by the elaboration of TSH, while TSH secretion itself is

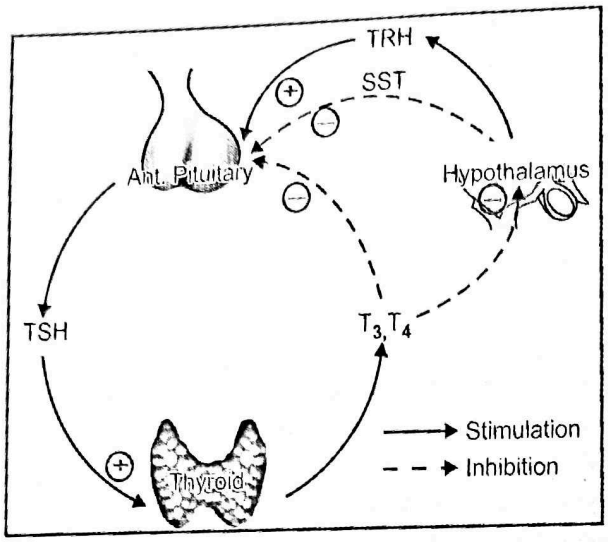


Fig. 18.3: Regulation of thyroid function
TSH—Thyroid stimulating hormone; TRH—Thyrotropin releasing hormone; T_3—Triiodothyronine; T_4—Thyroxine; SST—Somatostatin

regulated by TRH produced in hypothalamus (*see* p. 265). Somatostatin elaborated by hypothalamus inhibits not only GH and prolactin, but also TSH secretion from pituitary. The relation between thyroid, anterior pituitary and hypothalamus is depicted in Fig. 18.3. The negative feedback by the thyroid hormones is exercised directly on the pituitary as well as through hypothalamus. The action of TRH on pituitary and that of TSH on thyroid cells is mediated by enhanced cAMP synthesis. High concentration of TSH also acts *via* IP_3/DAG–increased intracellular Ca^{2+} pathway in the thyroid cells.

The blood iodine level and iodine content of thyroid also regulate thyroid function (*see* p. 277).

Actions

The actions of T_4 and T_3 are qualitatively similar and are nicely depicted in the features of hypo- and hyperthyroidism. They affect the function of practically every body cell.

1. *Growth and development* T_4 and T_3 are essential for normal growth and development. The most remarkable action is metamorphosis of tadpole to frog: the tail is used-up to build lungs, limbs and other organs. The actions cannot be broadly labelled as catabolic or anabolic, and are exerted through a critical control of protein synthesis in the translation of the genetic code. Congenital deficiency of thyroid hormone resulting in cretinism emphasizes its importance. The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system. Retardation and nervous deficit is a consequence of paucity of axonal and dendritic ramification, synapse formation and impaired myelination. In adult hypothyroidism also, intelligence is impaired and movements are slow.

2. *Intermediary metabolism* Thyroid hormones have marked effect on lipid, carbohydrate and protein metabolism.

Lipid T_4 and T_3 indirectly enhance lipolysis by potentiating the action of catecholamines and other lipolytic hormones. As a result plasma free fatty acid levels are elevated. Lipogenesis is also stimulated. All phases of cholesterol metabolism are accelerated, but its conversion to bile acids dominates. Thus, hyperthyroidism is characterized by hypocholesterolemia. Plasma LDL levels are reduced.

Carbohydrate Carbohydrate metabolism is also stimulated. Though utilization of sugar by tissues is increased (mainly secondary to increased BMR), glycogenolysis and gluconeogenesis in liver as well as faster absorption of glucose from intestines more than compensate it producing hyperglycaemia and a diabetic-like state with insulin resistance in hyperthyroidism.

Protein Synthesis of certain proteins is increased, but the overall effect of T_3 is catabolic—increased amounts of protein being used as energy source. Prolonged action results in negative nitrogen balance and tissue wasting. Weight loss is a feature of hyperthyroidism. T_3, T_4 inhibit mucoprotein synthesis which so characteristically accumulates in myxoedema.

3. *Calorigenesis* T_3 and T_4 increase BMR by stimulation of cellular metabolism and resetting of the energystat. This is important

for maintaining body temperature. However, metabolic rate in brain, gonads, uterus, spleen and lymph nodes is not significantly affected. The mechanism of calorigenesis was believed to be uncoupling of oxidative phosphorylation: excess energy being released as heat. However, this occurs only at very high doses and is not involved in mediating the physiological actions of T_3, T_4.

4. *CVS* T_3 and T_4 cause a hyperdynamic state of circulation which is partly secondary to increased peripheral demand and partly due to direct cardiac actions. Heart rate, contractility and output are increased resulting in a fast, bounding pulse. T_3 and T_4 stimulate heart by direct action on contractile elements (increasing the myosin fraction having greater Ca^{2+} ATPase activity) as well as by up regulation of β adrenergic receptors. Atrial fibrillation and other irregularities are common in hyperthyroidism. Thyroid hormones can also precipitate CHF and angina. BP, specially systolic, is often raised. Myocardial O_2 consumption can be markedly reduced by induction of hypothyroidism.

5. *Nervous system* T_3, T_4 have profound functional effect on CNS. Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema. Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

6. *Skeletal muscle* Muscles are flabby and weak in myxoedema, while thyrotoxicosis produces increased muscle tone, tremor and weakness due to myopathy.

7. *GIT* Propulsive activity of gut is increased by T_3/T_4. Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism.

8. *Kidney* T_3 and T_4 do not cause diuresis in euthyroid individuals, but the rate of urine flow is often increased when myxoedematous patients are treated with it.

9. *Haemopoiesis* Hypothyroid patients suffer from some degree of anaemia which is restored only by T_4 treatment. Thus, T_4 appears to be facilitatory to erythropoiesis.

10. *Reproduction* Thyroid has an indirect effect on reproduction. Fertility is impaired in hypothyroidism and women suffer from oligomenorrhoea. Normal thyroid function is required for maintenance of pregnancy and lactation.

Mechanism of action

Both T_3 and T_4 penetrate cells by active transport and produce majority of their actions by combining with a nuclear thyroid hormone receptor (TR) which belongs to the steroid and retinoid superfamily of intracellular receptors. Two TR isoform families (TRα and TRβ) have been identified. Both bind T_3 and function in similar manner, but their tissue distribution differs, which may account for quantitative differences in the sensitivity of different tissues to T_3.

In contrast to the steroid receptor, the TR resides in the nucleus even in the unliganded inactive state. It is bound to the *'thyroid hormone response element'* (TRE) in the enhancer region of the target genes along with corepressors (Fig. 18.4). This keeps gene transcription suppressed. When T_3 binds to the ligand-binding domain of TR, it heterodimerizes with retinoid X receptor (RXR) and undergoes a conformation change releasing the corepressor and binding the coactivator. This induces gene transcription followed by production of specific mRNA and a specific pattern of protein synthesis which produces the various metabolic and anatomic effects. The expression of certain genes is repressed by T_3. In their case, the unliganded TR allows gene transcription, while binding of T_3 to TR halts the process.

Many of the effects of T_3 e.g. tachycardia, arrhythmias, raised BP, tremor, hyperglycaemia are mediated, at least partly, by sensitization of adrenergic receptors to catecholamines. Induction of adenylyl cyclase, proliferation of β adrenoceptors and a better coupling between these two has been demonstrated.

Apart from the nuclear T_3 receptor, other sites of thyroid hormone action have been described. It acts on cell membrane to enhance amino acid and glucose entry and on mitochondria to increase oxygen consumption. At these sites T_4 appears to be equipotent to T_3, while at the nuclear receptor T_4 has much lower affinity. Moreover, even on binding to the TR, T_4 does not promote gene transcription.

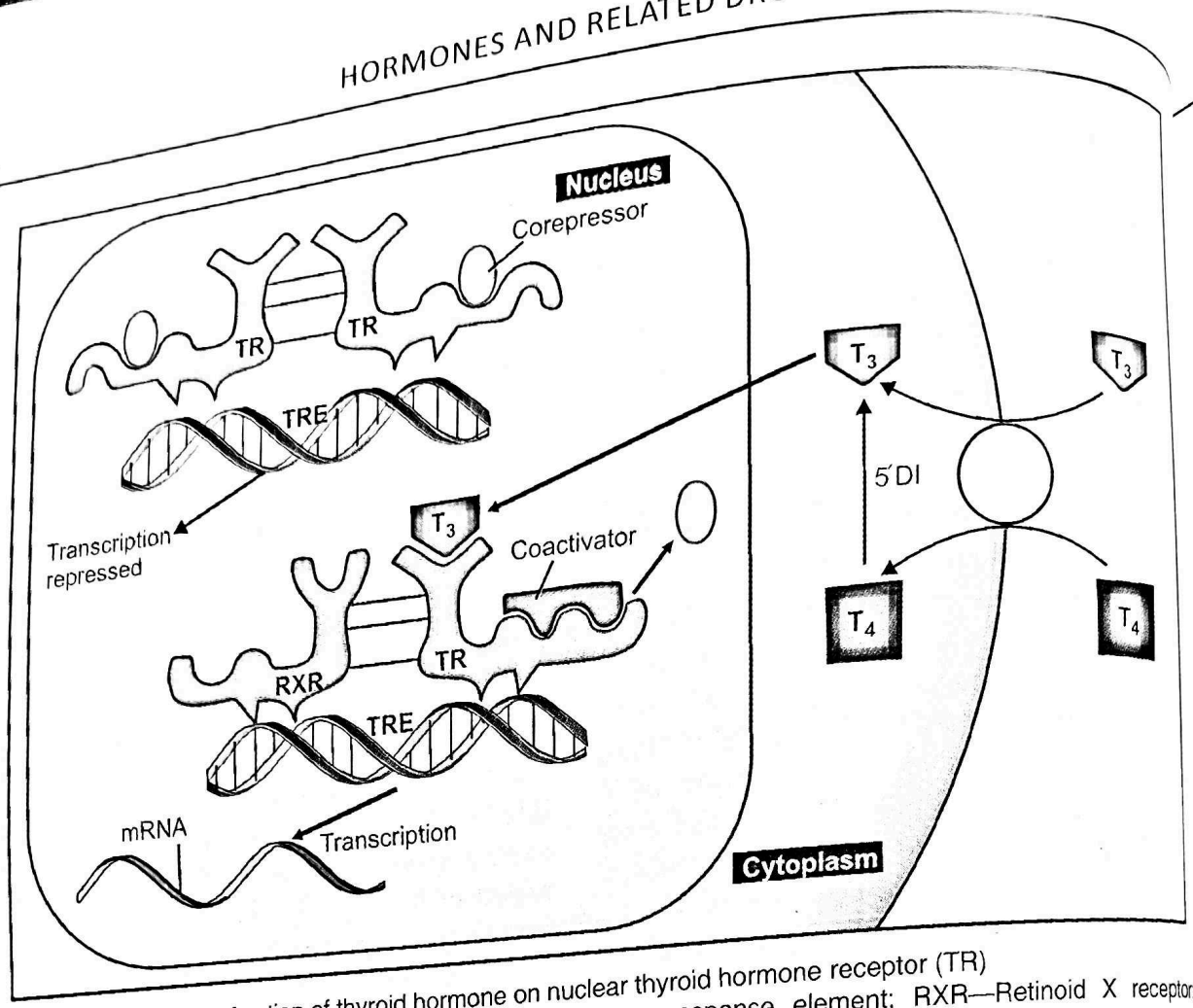


Fig. 18.4: Mechanism of action of thyroid hormone on nuclear thyroid hormone receptor (TR)
T_3—Triiodothyronine; T_4—Thyroxine; TRE—Thyroid hormone response element; RXR—Retinoid X receptor; mRNA—Messenger ribonucleic acid; 5'DI—5'Deiodinase (See text for explanation)

SECTION 5

Relation between T_4 and T_3

- Thyroid secretes more T_4 than T_3, but in iodine deficient state this difference is reduced.
- T_4 is the major circulating hormone because it is 15 times more tightly bound to plasma proteins.
- T_3 is 5 times more potent than T_4 and acts faster. Peak effect of T_3 comes in 1–2 days while that of T_4 takes 6–8 days.
- T_3 is more avidly bound to the nuclear receptor than T_4 and the T_4-receptor complex is unable to activate/derepress gene transcription.
- About 1/3 of T_4 is converted to T_3 in the thyroid cells, liver and kidney by type 1 deiodinase (D1) and released into circulation. In addition, T_3 is generated within the target cells (skeletal muscle, heart, brain, pituitary) by another type (D2) of deiodinase.

Thus, it may be concluded that T_3 is the active hormone, while T_4 is mainly a transport form which functions as a prohormone of T_3. However, it may directly produce some non-genomic actions.

Preparations

l-thyroxine sod. (synthetic levothyroxine sod.): ELTROXIN 25 µg, 50 µg, 100 µg tabs, ROXIN 100 µg tab, THYRONORM 12.5 µg, 25 µg, 50 µg, 62.5 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg tabs, THYROX 25 µg, 50 µg, 75 µg, 100 µg tabs. An injectable preparation for i.v. use is available elsewhere.

Triiodothyronine (Liothyronine) is not freely available in India. It is occasionally used i.v. along with l-thyroxine in myxoedema coma.

Clinically, l-thyroxine is preferred over liothyronine for routine as well as urgent indications, because of more sustained and uniform action as well as lower risk of cardiac arrhythmias.

Pharmacokinetics and interactions

Oral bioavailability of l-thyroxine is ~ 75%, but severe hypothyroidism can reduce oral absorption. It should be administered in empty stomach to avoid interference by food. Sucralfate, iron, calcium and proton pump inhibitors also reduce l-thyroxine absorption. CYP3A4 inducers like rifampin, phenytoin and carbamazepine

accelerate metabolism of T_4; dose of l-thyroxine may need enhancement.

Uses

The most important use of thyroid hormone is for *replacement therapy* in deficiency states. Synthetic l-thyroxine is the preparation of choice:

1. *Cretinism* It is either due to failure of thyroid development or a defect in hormone synthesis (sporadic cretinism) or due to extreme iodine deficiency (endemic cretinism). Cretinism is usually detected during infancy or childhood; but screening of neonates is the best preventive strategy. Treatment with thyroxine (8–12 µg/kg) daily should be started as early as possible, because mental retardation that has already ensued is only partially reversible. Response is dramatic: physical growth and development are restored and further mental retardation is prevented.

2. *Adult hypothyroidism* (Myxoedema) This is one of the commonest endocrine disorders which develops as a consequence of autoimmune thyroiditis or thyroidectomy. It may accompany simple goiter if iodine deficiency is severe. Antibodies against thyroid peroxidase or thyroglobulin are responsible for majority of cases of adult hypothyroidism. Important drugs that can cause hypothyroidism are ^{131}I, iodides, lithium and amiodarone.

Treatment with T_4 is most gratifying. Though in younger patients, full replacement doses may be started from the beginning, in those >50 years it is wise to start with a lower dose (50 µg/day), while in the elderly or in those with heart disease, the initial dose should be 12.5–25 µg/day. Doses may be increased every 2–3 weeks to an optimum of 100–150 µg/day (adjusted by clinical response as well as serum TSH and free T_4 levels). Further dose adjustments are made at 4–6 week intervals needed for reaching steady-state. Individualization of proper dose is critical, aiming at normalization of serum TSH levels. Increase in dose is mostly needed during pregnancy.

Subclinical hypothyroidism characterized by euthyroid status and normal free serum thyroxine (FT_4) level (≥ 9 pmol/L) but raised TSH level (>10 mU/L) should be treated with T_4. For TSH level between 6–10 mU/L, replacement therapy is optional. Replacement is preferable if patient has other cardiovascular risk factors.

3. *Myxoedema coma* It is an emergency; characterized by progressive mental deterioration due to acute hypothyroidism: carries significant mortality. Rapid thyroid replacement is crucial. Though liothyronine (T_3) acts faster, its use is attended by higher risk of cardiac arrhythmias, angina, etc. Drug of choice is l-thyroxine (T_4) 200–500 µg i.v. followed by 100 µg i.v. OD till oral therapy can be instituted. Some authorities recommend adding low dose i.v. T_3 10 µg 8 hourly in younger patients with no arrhythmia or ischaemia. Alternatively oral T_4 500 µg loading dose followed by 100–300 µg daily may be used, but in severe hypothyroidism, oral absorption is delayed and inconsistent.

Other essential measures needed are—warming the patient, i.v. corticosteroids to cover attendant adrenal insufficiency, ventilatory and cardiovascular support, correction of hyponatraemia and hypoglycaemia.

4. *Nontoxic goiter* This is characterized by enlargement of thyroid with euthyroid status. It may be endemic or sporadic. Endemic is due to iodine deficiency which may be accentuated by factors present in water (excess calcium), food or milk (goitrin, thiocyanates). A defect in hormone synthesis may be responsible for sporadic cases. In both types, deficient production of thyroid hormone leads to excess TSH → thyroid enlarges, more efficient trapping of iodide occurs and probably greater proportion of T_3 is synthesized → enough hormone to meet peripheral demands is produced so that the patient is clinically euthyroid. Thus, treatment with T_4 is in fact replacement therapy in this condition as well, despite no overt hypothyroidism. Full maintenance doses must be given. Most cases of recent diffuse enlargement of thyroid regress. Long-standing goiter with degenerative

and fibrotic changes and nodular goiter regress little or not at all. Thyroxine therapy may be withdrawn after a year or so in some cases if adequate iodine intake is ensured. Others need life-long therapy.

Endemic goiter and cretinism due to iodine deficiency in pregnant mother is preventable by ensuring daily ingestion of 150–200 µg of iodine. This is best achieved by iodizing edible salt by adding iodate (preferred over iodide). In India iodization of table salt (100 µg iodine/g salt) is required under the National Programme, but recently mandatory iodization rule has been withdrawn.

5. *Thyroid nodule* Certain benign functioning nodules regress when TSH is suppressed by T_4 therapy. Nonfunctional nodules and those non-responsive to TSH (that are associated with low TSH levels) do not respond and should not be treated with levothyroxine. T_4 therapy should be stopped if the nodule does not decrease in size within 6 months, as well as when it stops regressing after the initial response.

6. *Papillary carcinoma of thyroid* This type of cancer is often responsive to TSH. In nonresectable cases, full doses of T_4 suppress endogenous TSH production and may induce temporary regression.

7. *Empirical uses* T_4 has been sometimes used in the following conditions without any rationale; response is unpredictable.

Refractory anaemias.
Mental depression.
Menstrual disorders, infertility not corrected by usual treatment.
Chronic/non-healing ulcers.
Obstinate constipation.

Thyroxine is not to be used for obesity and as a hypocholesterolemic agent.

THYROID INHIBITORS

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

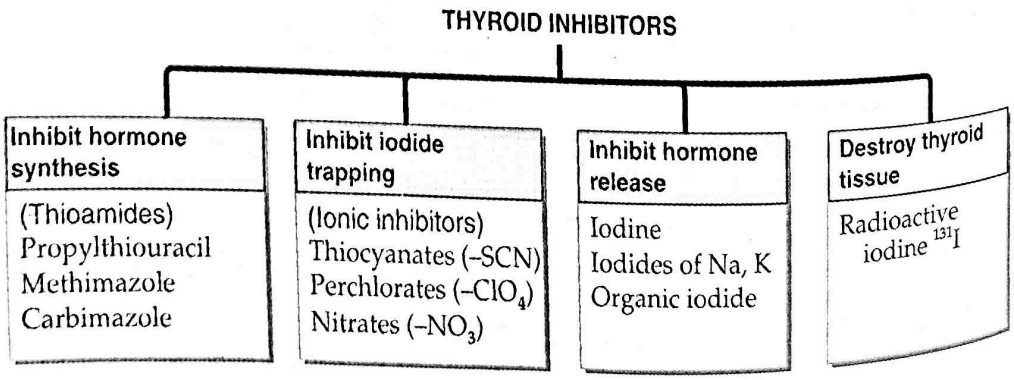
Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are *Graves' disease* and *toxic nodular goiter*. Graves' disease is an autoimmune disorder due to production of an IgG class of antibody called 'thyroid stimulating immunoglobulin'. It binds to the TSH receptor and causes long lasting stimulation of the thyroid cells. The exophthalmos of Graves' disease appears to be due to stimulation of TSH receptors on the periorbital tissues. Due to feed-back inhibition, TSH levels are low.

Toxic nodular goiter, which produces thyroid hormone independent of TSH, is less common and mostly supervenes on old nontoxic goiters. It is more common in the elderly; ocular changes are generally absent.

The thioamide antithyroid drugs and ionic inhibitors are also called *goitrogens* because, if given in excess, they cause enlargement of thyroid by feedback release of TSH.

In addition, certain drugs used in high doses for prolonged periods cause hypothyroidism/goiter as a side effect:

- Lithium: inhibits thyroid hormone release.
- Amiodarone: inhibits peripheral conversion of T_4 to T_3; also interferes with thyroid hormone action.
- Sulfonamides, paraaminosalicylic acid: inhibit thyroglobulin iodination and coupling reaction.
- Phenobarbitone, phenytoin, carbamazepine, rifampin: induce metabolic degradation of T_4/T_3.



Goitrin—found in plants (cabbage, turnip, mustard, etc.), is the cause of goiter in cattle who feed on these plants. Goitring may contribute to endemic goiter in certain iodine deficient regions.

THIOAMIDES (Antithyroid drugs)

By convention, only the thioamide hormone synthesis inhibitors are called '*antithyroid drugs*', though this term has also been applied to all thyroid inhibitors.

Thiourea derivatives were found to produce goiter and hypothyroidism in rats in the 1940s. Open chain thiourea compounds were found to be toxic. Subsequently, methyl and propyl thiouracil and thioimidazole derivatives methimazole and carbimazole were found to be safe and effective.

Thioamides bind to the thyroid peroxidase and prevent oxidation of iodide and iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin

(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

Action (ii) has been observed at lower concentration of antithyroid drugs than action (i). Thyroid colloid is depleted over time and blood levels of T_3/T_4 are progressively lowered.

Thioamides do not interfere with trapping of iodide and do not modify the action of T_3 and T_4 on peripheral tissues or on pituitary. Goiter that occurs with higher doses is not the result of potentiation of TSH action on thyroid, but is due to increased TSH release as a consequence of reduction in feedback inhibition. No goiter occurs if antithyroid drugs are given to hypophysectomised animals or if T_4 is given along with them. Antithyroid drugs do not affect release of T_3 and T_4—their effects are not apparent till thyroid is depleted of its hormone content.

Propylthiouracil also inhibits peripheral conversion of T_4 to T_3 by D1 type of 5-DI, but not by D2 type. This may partly contribute to its antithyroid effects. Methimazole and carbimazole do not have this action (Table 18.1).

Pharmacokinetics The antithyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta; are metabolized in liver and excreted in urine primarily as metabolites. All are concentrated in thyroid; the intrathyroid t½ is longer: effect of a single dose lasts longer than would be expected from the plasma t½. Carbimazole acts largely by getting converted to methimazole in the body and is longer acting than propythiouracil.

Adverse effects Hypothyroidism and goiter can occur due to overtreatment, but this is reversible on stopping the drug. Enlargement of thyroid is an indication of hypothyroidism and is due to excess feedback TSH production. Goiter does not develop with appropriate doses which restore T_4 concentration to normal so that feedback TSH inhibition is maintained.

Important side effects are: g.i. intolerance, skin rashes and joint pain. Liver damage can occur, especially with propylthiouracil.

Loss or graying of hair, loss of taste and fever are infrequent.

Table 18.1: Differences between propylthiouracil and carbimazole

Propylthiouracil	*Carbimazole*
1. Dose to dose less potent	About 5 × more potent
2. Highly plasma protein bound	Less bound
3. Less transferred across placenta and in milk	Larger amounts cross to foetus and in milk
4. Plasma t½ 1–2 hours	6–10 hours
5. Single dose acts for 4–8 hours	12–24 hours
6. No active metabolite	Produces active metabolite—methimazole
7. Multiple (2–3) daily doses needed	Mostly single daily dose
8. Inhibits peripheral conversion of T_4 to T_3	Does not inhibit T_4 to T_3 conversion

A rare but serious adverse effect is agranulocytosis (1 in 500 to 1000 cases); It is mostly reversible. There is partial cross reactivity between propylthiouracil and carbimazole.

Preparations and dose

Propylthiouracil: 50–150 mg TDS followed by 25–50 mg BD–TDS for maintenance. PTU 50 mg tab.
Methimazole: 5–10 mg TDS initially, maintenance dose 5–15 mg daily in 1–2 doses.
Carbimazole: 5–15 mg TDS initially, maintenance dose 2.5–10 mg daily in 1–2 divided doses, NEO MERCAZOLE, THYROZOLE, ANTITHYROX 5, 10, 20 mg tab.

Carbimazole is used in India while methimazole is not marketed. Since popylthiouracil has shorter duration of action and carries risk of severe hepatitis, it should be reserved for use in early pregnancy (due to less placental transfer than carbimazole) and in thyroid storm for its inhibitory action on peripheral conversion of T_4 to more active T_3. It may be tried in patients developing adverse effects with carbimazole.

Use Antithyroid drugs control thyrotoxicosis in both Graves' disease and toxic nodular goiter. Clinical improvement starts after 1–2 weeks or more (depending on hormone content of thyroid gland). Iodide loaded patients (who have received iodide containing contrast media/cough mixtures, amiodarone) are less responsive. Maintenance doses are titrated on the basis of clinical status of the patient. The following strategies are adopted.

(i) *As definitive therapy* (a) Remission may occur in upto half of the patients of Graves' disease after 1–2 years of treatment: the drug can then be withdrawn. If symptoms recur—treatment is reinstituted. This is preferred in young patients with a short history of Graves' disease and a small goiter.

(b) Remissions are rare in toxic nodular goiter; surgery (or ^{131}I) is preferred. However, in frail elderly patients with multinodular goiter who may be less responsive to ^{131}I, permanent maintenance therapy with antithyroid drugs can be employed.

(ii) *Preoperatively* Surgery in thyrotoxic patients is risky. Young patients with florid hyperthyroidism and substantial goiter are rendered euthyroid with carbimazole before performing subtotal thyroidectomy.

(iii) *Along with ^{131}I* Initial control with antithyroid drug—1 to 2 weeks gap—radioiodine dosing—resume antithyroid drug after 5–7 days and gradually withdraw over 3 months as the response to ^{131}I develops. This approach is preferred in older patients and in those with heart disease who are to be treated with ^{131}I, but require prompt control of severe hyperthyroidism. This will also prevent initial disease flare-up following ^{131}I due to release of stored T_4.

Advantages of antithyroid drugs over surgery and ^{131}I are:

(a) No surgical risk, scar or chances of injury to parathyroid glands or recurrent laryngeal nerve.
(b) Hypothyroidism, if induced, is reversible.
(c) Can be used even in children and young adults.

Disadvantages are:

(a) Prolonged (often life-long) treatment is needed because relapse rate is high.
(b) Not practicable in uncooperative/unintelligent patient.
(c) Drug toxicity.

Thyroidectomy and ^{131}I are contraindicated during pregnancy. With antithyroid drugs risk of foetal hypothyroidism and goiter is there. However, low doses of propylthiouracil may be used: its greater protein binding allows less transfer to the foetus. However, methimazole has also now been found safe during pregnancy.

Propylthiouracil is used in thyroid storm as well (*see* p. 279).

IONIC INHIBITORS

Certain monovalent anions inhibit iodide trapping by NIS into the thyroid. Consequently, T_4/T_3 cannot be synthesized. Perchlorate is 10 times more potent than thiocyanate in blocking NIS, while nitrate is very weak.
These ions are toxic and not clinically used.

IODINE AND IODIDES

Though iodine is a constituent of thyroid hormones, it is the fastest acting thyroid inhibitor. In Graves' disease the gland, if enlarged, shrinks,

becomes firm and less vascular. The thyroid status starts returning to normal at a rate commensurate with complete stoppage of hormone release from the gland. The thyroid gland involutes and colloid is restored. The response to iodine and iodides is identical, because elemental iodine is reduced to iodide in the intestines. With daily administration, peak effects are seen in 10–15 days, after which 'thyroid escape' occurs and thyrotoxicosis may return with greater vengeance. Worsening of hyperthyroidism occurs, especially in multinodular goiter.

All facets of thyroid function seem to be affected, but the most important action is inhibition of hormone release—'thyroid constipation'. Endocytosis of colloid and proteolysis of thyroglobulin comes to a halt. The mechanism of action is not clear. Excess iodide inhibits its own transport into thyroid cells by interfering with expression of NIS on the cell membrane. In addition, it attenuates TSH and cAMP induced thyroid stimulation. Excess iodide rapidly and briefly interferes with iodination of tyrosil and thyronil residues of thyroglobulin (probably by altering redox potential of thyroid cells) resulting in reduced T_3/T_4 synthesis (Wolff-Chaikoff effect). However, within a few days, the gland 'escapes' from this effect and hormone synthesis resumes.

Preparations and dose Lugol's solution (5% iodine in 10% Pot. iodide solution): LUGOL'S SOLUTION, COLLOID IODINE 10%: 5–10 drops/day. COLLOSOL 8 mg iodine/5 ml liq.
Iodide (Sod./Pot.) 100–300 mg/day before thyroidectomy, 5–10 mg/day (prophylactic) for endemic goiter.

Uses

1. *Preoperative preparation* for thyroidectomy in Graves' disease: Iodine is generally given for 10 days just preceding surgery. The aim is to make the gland firm, less vascular and easier to operate on. Though iodide itself will lower the thyroid status, it cannot be relied upon to attain euthyroidism which is done by use of carbimazole before starting iodide. Propranolol may be given additionally for rapid control of symptoms.

2. *Thyroid storm* Lugol's iodine (6–10 drops) or iodine containing radiocontrast media (iopanoic acid/ipodate) orally are used to stop any further release of T_3/T_4 from the thyroid and to decrease T_4 to T_3 conversion.

3. *Prophylaxis of endemic goiter* It is generally used as "iodized salt"(*see* p. 274).

4. *Antiseptic* As tincture iodine, povidone iodine, etc. (*see* Ch. 67).

Adverse effects

1. *Acute reaction* It occurs only in rare individuals sensitive to iodine, and can be triggered even by a minute quantity. Manifestations are swelling of lips, eyelids, angioedema of larynx (may be dangerous), fever, joint pain, petechial haemorrhages, thrombocytopenia, lymphadenopathy. Further exposure to iodine should be stopped immediately.

2. *Chronic overdose (iodism)* Inflammation of mucous membranes, salivation, rhinorrhoea, sneezing, lacrimation, swelling of eyelids, burning sensation in mouth, headache, rashes, g.i. symptoms, etc. The symptoms regress on stopping iodide ingestion.

Long-term use of high doses can cause hypothyroidism and goiter.

Iodide may cause flaring of acne in adolescents. Given to pregnant or nursing mothers, it may be responsible for foetal/infantile goiter and hypothyroidism. Thyrotoxicosis may be aggravated in multinodular goiter.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I. Its radioactive isotope of medicinal importance is:

^{131}I: physical half-life 8 days.

The chemical behaviour of ^{131}I is similar to that of the stable isotope.

^{131}I emits γ-rays (higher energy X-rays emitted by atomic nuclei), as well as β particles (electrons). The former are useful in tracer studies, because they traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells. ^{131}I is concentrated by thyroid and incorporated in the colloid. Thus, it emits radiation from within the

follicles. The β particles penetrate only 0.5–2 mm of tissue. The thyroid follicular cells are affected from within, undergo pyknosis and necrosis followed by fibrosis when a sufficiently large dose has been administered, without damage to neighbouring tissues. With carefully selected doses, it is possible to achieve partial ablation of thyroid.

Radioactive iodine is administered as sodium salt of ^{131}I dissolved in water and taken orally.

Diagnostic 25–100 μ curie is given; counting or scanning is done at intervals. No damage to thyroid cells occurs at this dose.

Therapeutic The most common indication is *hyperthyroidism* due to Graves' disease or toxic nodular goiter. The average therapeutic dose is 3–6 m curie—calculated on the basis of previous tracer studies and thyroid size. Higher doses are generally required for toxic multinodular goiter than for Graves' disease. The clinical response is slow—starts after 2 weeks and gradually increases, reaching peak at 3 months or so. Thyroid status is evaluated after 3 months, and a repeat dose, if needed, is given. About 20–40% patients require one or more repeat doses.

Advantages

1. Treatment with ^{131}I is simple, conveniently given on outpatient basis and inexpensive.
2. No surgical risk, scar or injury to parathyroid glands/recurrent laryngeal nerves.
3. Once hyperthyroidism is controlled, cure is permanent.

Disadvantages

1. Hypothyroidism: About 5–10% patients of Graves' disease treated with ^{131}I become hypothyroid every year (upto 50% or more patients may ultimately require supplemental thyroxine treatment). This probably reflects the natural history of Graves' disease, because only few patients of toxic nodular goiter treated with ^{131}I develop hypothyroidism. Moreover, eventual hypothyroidism is a complication of subtotal thyroidectomy/ prolonged carbimazole therapy as well.
2. Long latent period of response.
3. Contraindicated during pregnancy—foetal thyroid will also be destroyed resulting in cretinism, other abnormalities if given during first trimester.
4. Not suitable for young patients: they are more likely to develop hypothyroidism later and would then require life-long T_4 treatment.

^{131}I is the treatment of choice after 25 years of age and if CHF, angina or any other contraindication to surgery is present.

Metastatic carcinoma of thyroid (especially papillary or those cases of follicular carcinoma which concentrate iodine), ^{131}I may be used as palliative therapy after thyroidectomy. Much higher doses are required and prior stimulation with TSH is recommended.

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity, *viz.* palpitation, tremor, nervousness, severe myopathy, sweating. They have little effect on thyroid function and the hypermetabolic state. They are used in hyperthyroidism in the following situations.

(a) While awaiting response to carbimazole or ^{131}I.

(b) Along with iodide for preoperative preparation before subtotal thyroidectomy.

(c) *Thyroid storm (thyrotoxic crisis)*: This is an emergency due to decompensated hyperthyroidism. Vigorous treatment with the following is indicated:

Nonselective β blockers (e.g. propranolol) are the most valuable measure. They afford dramatic symptomatic relief. In addition, higher doses reduce peripheral conversion of T_4 to T_3. Propranolol 1–2 mg slow i.v. may be followed by 40–80 mg oral every

6 hours. It may be withdrawn gradually when T_4 levels normalise.

- Propylthiouracil 200–300 mg oral 6 hourly: reduces hormone synthesis as well as peripheral T_4 to T_3 conversion.
- Iopanoic acid (0.5–1 g OD oral one hour after propylthiouracil) or ipodate are iodine containing radiocontrast media. They are potent inhibitors of thyroid hormone release from thyroid, as well as of peripheral T_4 to T_3 conversion.
- Corticosteroids (hydrocortisone 100 mg i.v. 8 hourly followed by oral prednisolone): help to tide over crisis, cover any adrenal insufficiency and reduce conversion of T_4 to T_3 in periphery.
- Diltiazem 60–120 mg BD oral may be added if tachycardia is not controlled by propranolol alone, or when it is contraindicated.
- Rehydration, anxiolytics, external cooling and appropriate antibiotics are the other measures.

PROBLEM DIRECTED STUDY

18.1 A 20-year girl was diagnosed as a case of recent onset Graves' disease with mild diffuse pulsatile thyroid enlargement. She was treated with tab. Carbimazole 5 mg 2 tab 3 times a day. Her symptoms started subsiding after 2 weeks and were fully controlled after 3 months. The thyroid swelling also subsided and she was maintained on a dose of carbimazole 5 mg twice daily. After one year she noticed that the neck swelling was reappearing and her body weight increased by 2 kg in the last one month, but without recurrence of her earlier symptoms. She rather felt dull, sleepy and depressed. The serum TSH was 12 μU/ml and free thyroxine (FT_4) was 9 pmol/L.

(a) Why was the initial response to carbimazole delayed? Could any additional medicine be given to her initially to afford more rapid symptomatic relief?

(b) What was the cause of reappearance of the neck swelling and her condition after 1 year? What measures need to be taken at this stage?

(see Appendix-1 for solution)