THYROID HORMONES AND ANTITHYROID DRUGS

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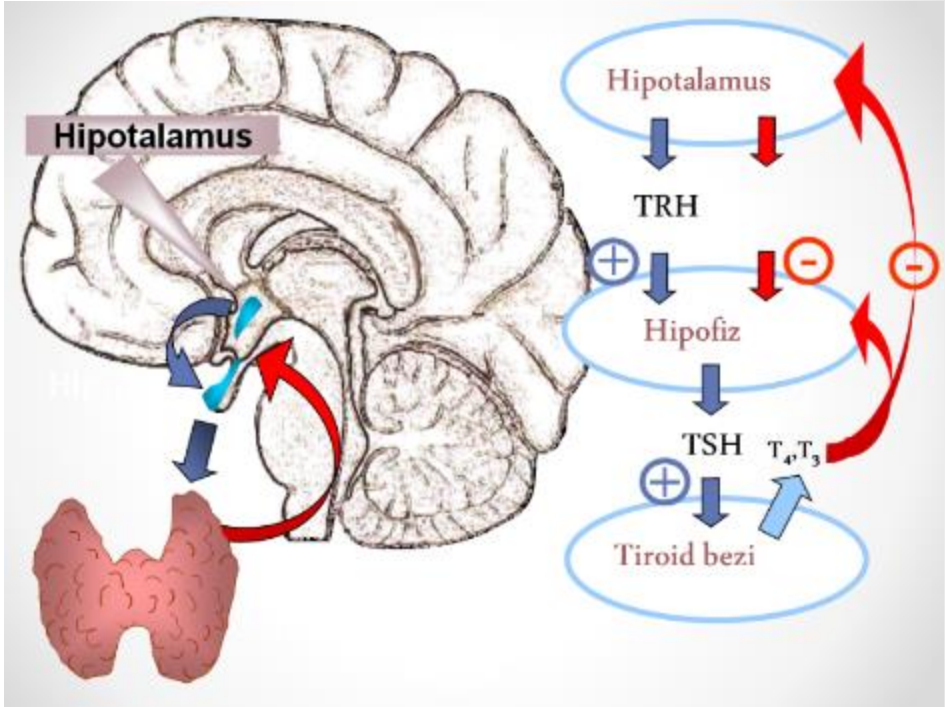
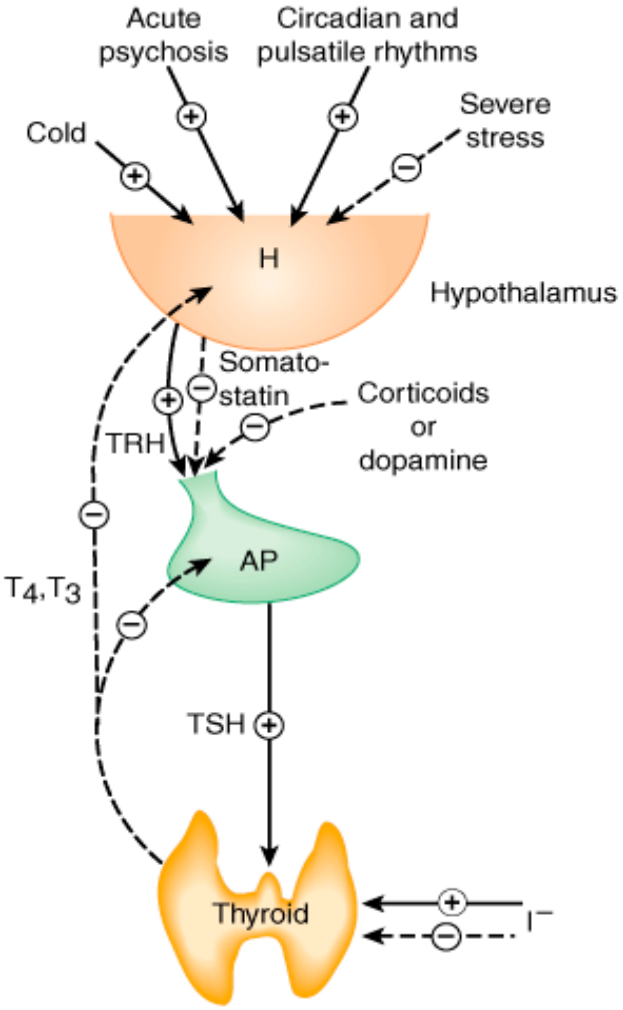
- Thyroid works on a delicate feedback mechanism.
- T3 and T4 synthesis in thyroid is regulated by TSH.
- If the circulation levels of T3 and T4 are high then pituitary gland decreases its sensitivity to TSH
- This entire process make synthesis and release of TSH low by negative feedback mechanism.
- If the T3 and T4 levels are low the Pituitary gland becomes more sensitive to thyroid regulating hormone(TRH), which is secreted by the hypothalamus.
- This stimulates TSH secretion with the release of excess thyroid hormones.




Acute psychosis
Circadian and pulsatile rhythms
Cold
Severe stress
H
Hypothalamus
Somato-statin
Corticoids or dopamine
TRH
AP
T_4,T_3
TSH
Thyroid
I^-

Thyroid Hormone - Biosynthesis

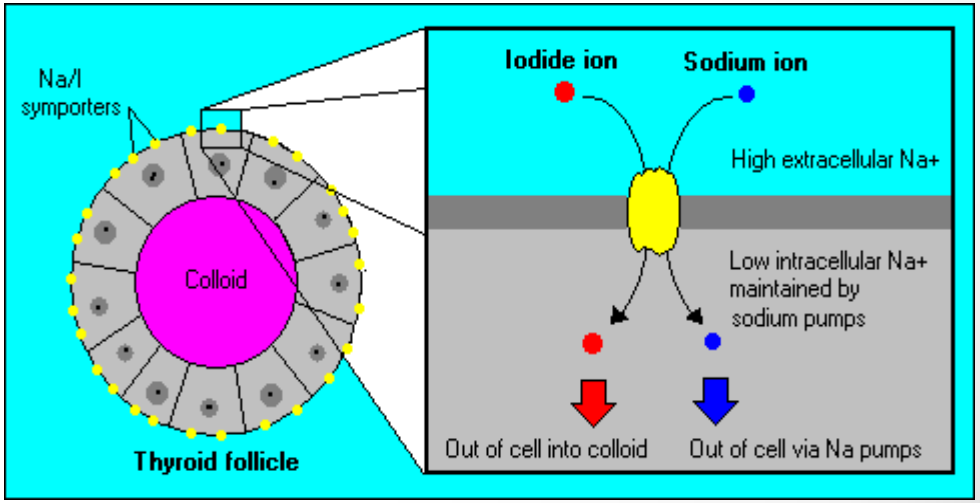
- Thyroid gland is unique in storing large amount of preformed hormone
- Thyroid follicular colloid stores thyroid hormone as amino residues of thyroglobulin
- Iodide is required for synhesis of thyroid hormone
- Sea fish, eggs, milk and water - dietary sources of iodide, carried in plasma as inorganic iodide
- Sources: Food, water or medication
- Daily Requirement for adult: 150 µg (200 µg in pregnancy and lactation)
- Total body content of Iodine 30 – 50 mg (1/5th in thyroid gland)
- Iodine denotes all form of the element and Iodide denotes only the ionic form (I^-)
- 75 µg is utilized daily for hormone synthesis by thyroid gland

Thyroid hormone synthesis

1) Iodide uptake or pump

- the transport of iodide into the thyroid gland by an intrinsic follicle cell basement membrane protein called the sodium/iodide symporter (NIS)

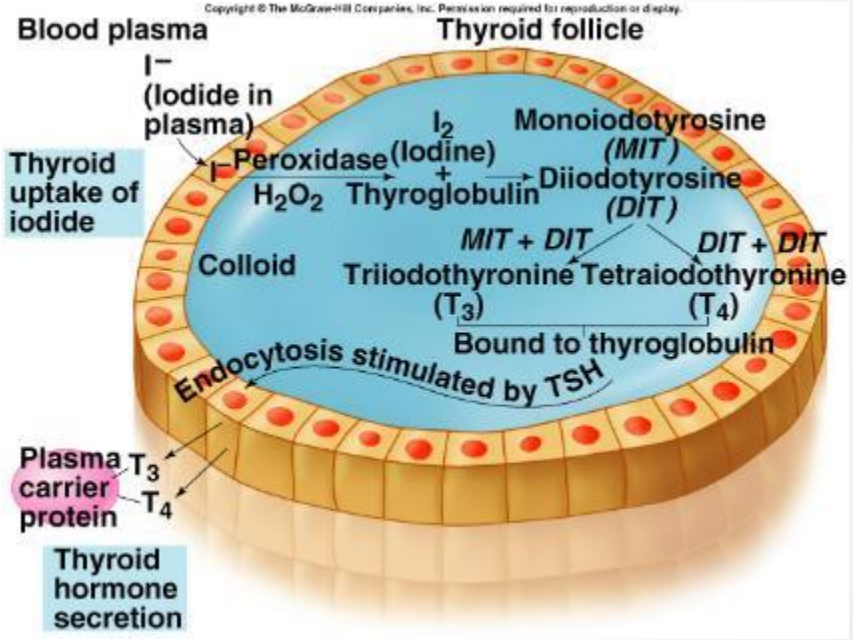
- Normal thyroid: serum iodine is 30-40:1
  - Iodide uptake enhancers:
    - TSH
    - Iodine deficiency
    - TSH receptors antibody
  - Iodide uptake inhibitors
    - Iodide ion
    - Drugs
      - Digoxin
      - Thiocynate
      - perchlorate

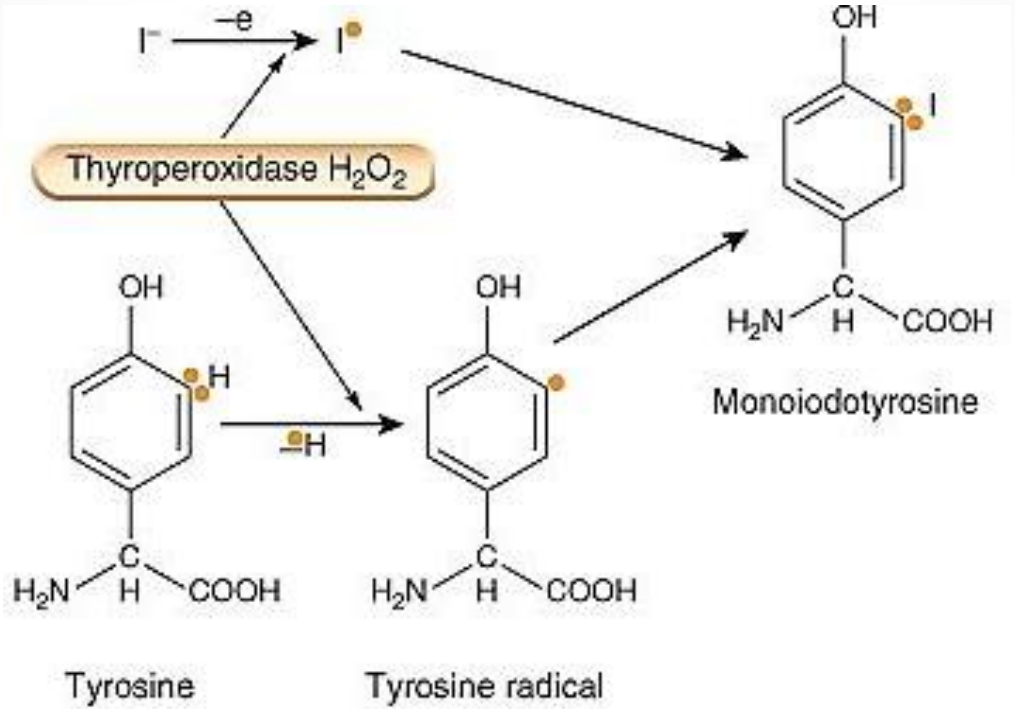


Thyroid hormone synthesis – contd.

2) Iodide oxidation to iodine and Organification

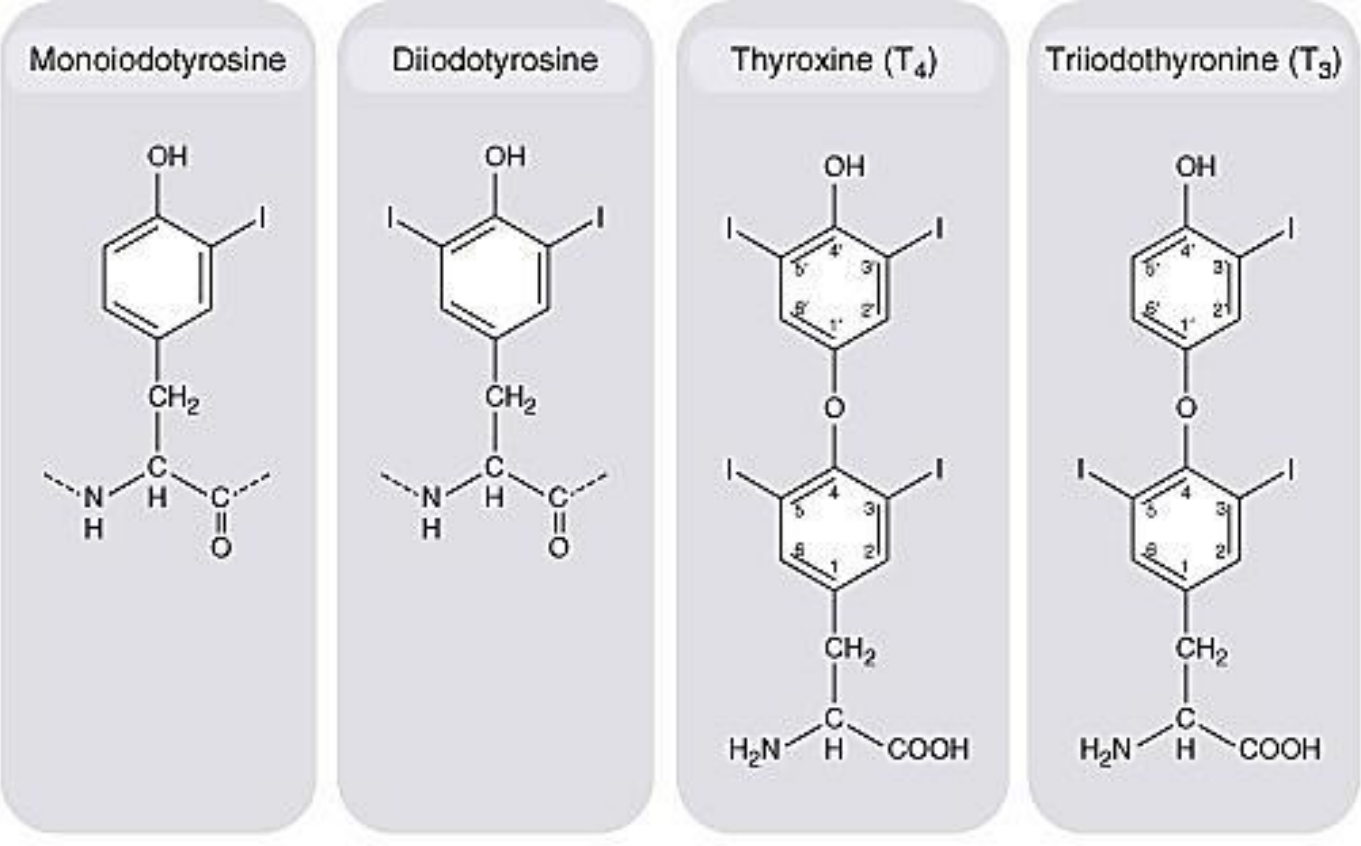
- Inside the cells, iodide is oxidized by membrane bound peroxidase system to more reactive iodine (Iodinium or I+)→ **Iodide oxidation**
- Iodine immediately reacts with tyrosine residue on a thyroid glycoprotein called “thyroglobulin” to form: MIT and DIT→ **iodide organification**
- Both processes are catalyzed by thyroid peroxidase enzyme





- Iodine rapidly iodinates tyrosine residues within the thyroglobulin molecule to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT).** This process is called **iodide organification**

3) Coupling



- Two molecules of DIT combine within the thyroglobulin molecule to form thyroxine (T_4).
- One molecule of MIT and one molecule of DIT combine to form T_3 .

MIT +DIT = T3 (Tri-iodothyronine)

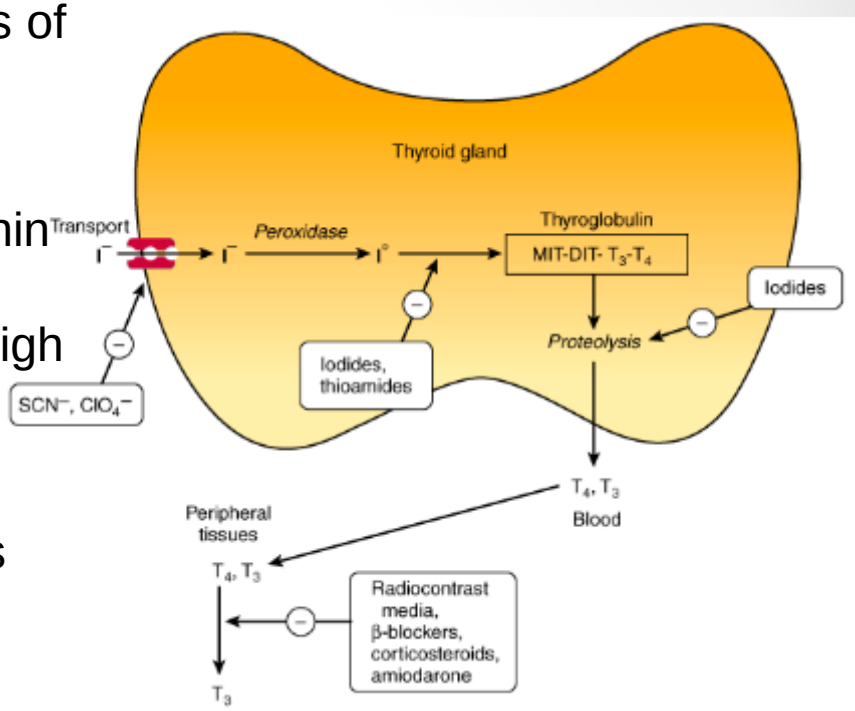
DIT + DIT = T4 (Thyroxine)

4) Release of T3 and T4 by proteolysis of thyroglobulin.

- Thyroxine, T3, MIT and DIT are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin at the apical colloid border.

- The MIT and DIT are then deiodinated within the gland, and the iodine is reutilized. This process of proteolysis is also blocked by high levels of intrathyroidal iodide.

- The ratio of T4 to T3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine.



5) Conversion of T4 to T3

- Most of the T3 circulating in the blood is derived from peripheral metabolism of thyroxine

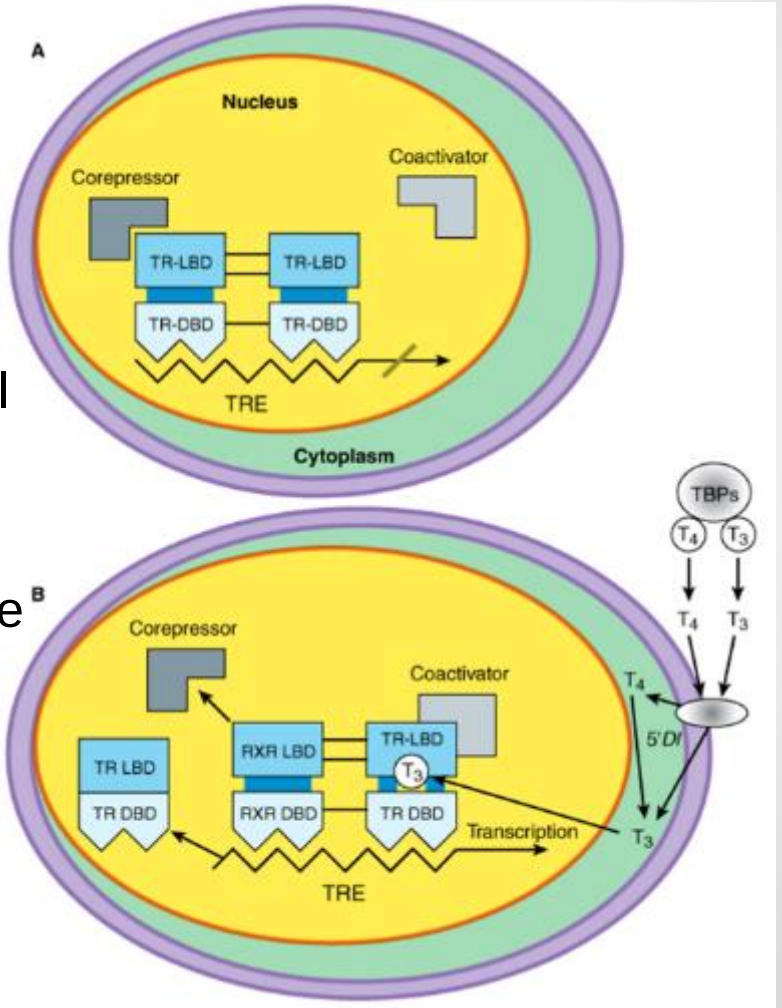
Mechanism/mode of action

- **A:** ***Inactive phase*** —the unliganded T_3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription.

- **B:** ***Active phase —*** T_3 and T4 circulate bound to thyroid-binding proteins (TBPs).
- The free hormones are transported into the cell by a specific transport system.

- Within the cytoplasm, T_4 is converted to T_3 by 5'-deiodinase; T_3 , which has high affinity for the thyroid receptors, then moves into the nucleus.

- The receptors undergo a change in their conformation ,which stimulates transcription, results in the synthesis of proteins,
  ultimately stimulating function of T3 and T4



Relation of Iodine to Thyroid Function

- Iodine essential for thyroid hormone
- Adult hypothyroidism and cretinism occurs in severe iodine deficiency
- Daily adult require 1 to 2 µg / Kg / day.
- Iodine used for iodine-deficiency goiter
- Iodine or iodate added to salt (iodized salt) 100 µg of iodine per gram

WHO/UNICEF Recommended daily iodine

Age group	Iodine requirement(µg)
• Infants (0 -11mth)	50
• Children (12 mnth - 59 mnth)	90
• School age child (6-12 year)	120
• Adults (above 12 year)	150
• Pregnant & lactating women	200

Functions of Tyhroid Hormones

Growth and development

- Normal growth and development of organism
- DNA transcription, critical control of protein synthesis and translation of genetic code
- Brain development
- Irreversible mental retardation (cretinism) in absence of thyroid hormones during active neurogenesis (upto 6 month postpartum)
  - Severe morphological alteration in brain
  - Supplementation during first 2 weeks of life prevent development of brain changes

Functions of Tyhroid Hormones

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 metabolism, glycogenolysis, gluconeogenesis
  - Hyperthyroidism – diabetes-like state

- Protein: Certain protein synthesis increased but overall catabolic action – negative nitrogen balance
  - Hyperthyroidism – Weight loss and wasting

Functions of Tyhroid Hormones

Calorigenic & CVS(Cardio Vascular System) Effects

- T3 and T4 increases basal metabolic rate (BMR) by stimulation of cellular metabolism – maintenance of body temperature

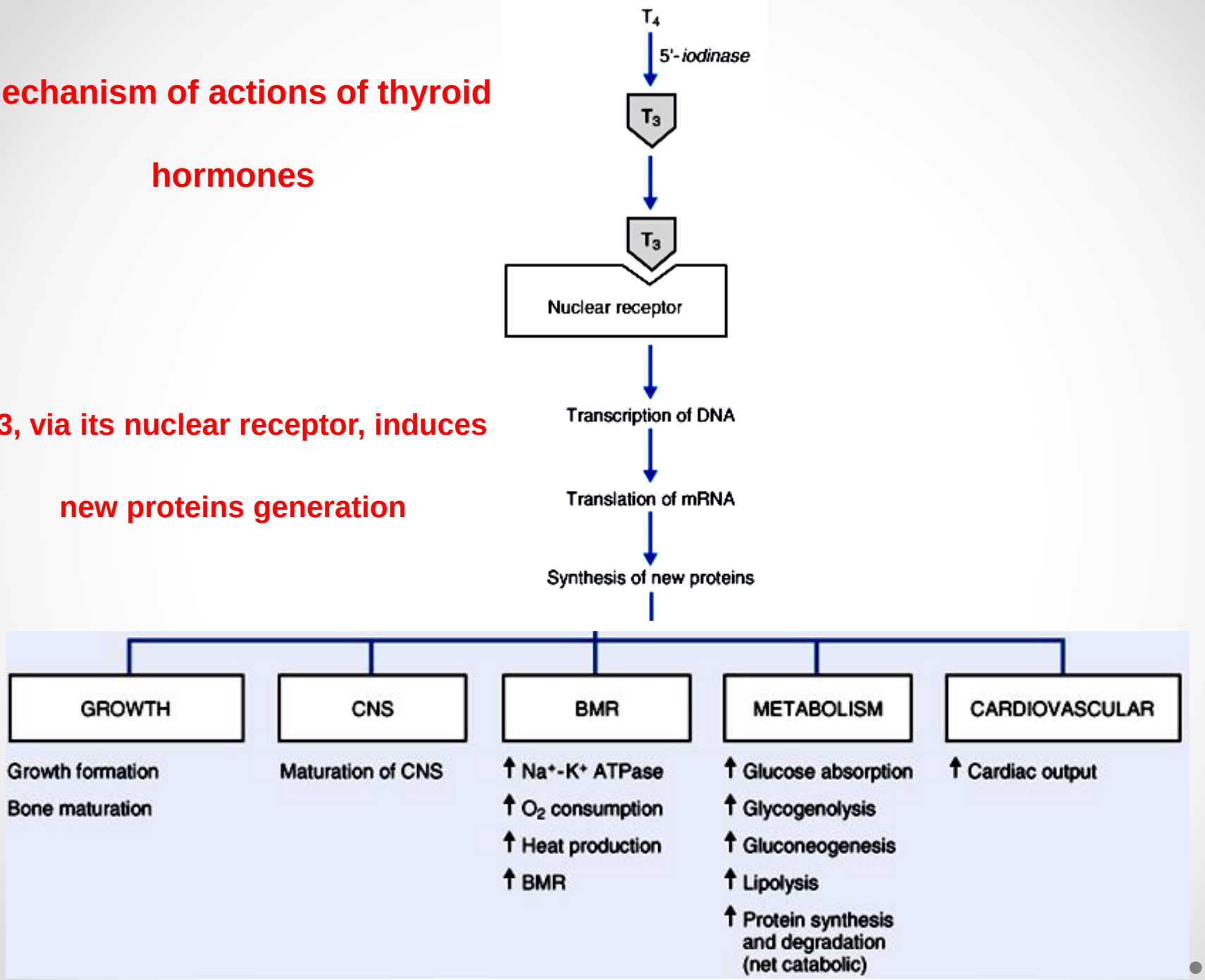
- Hyperdynamic state of circulation - due to direct CVS action and ↑ peripheral demand
  - Hyperthyroidism: tachycardia, ↑ Total Periferic Resistance (TPR)
  - Hypothyrodism: bradycardia, ↓ cardic index, ↓ TPR

Others:

- Nervous system – mental retardation
- GIT – Increased gut motility

Mechanism of actions of thyroid hormones

T3, via its nuclear receptor, induces new proteins generation



Synthesis and Functions of Thyroid Hormones

- Steps of Thyroid Hormone Synthesis
  1. Iodide uptake or pump
  2. Iodide oxidation to iodine and Organification
  3. Coupling
  4. Storage and release
  5. Peripheral conversion

- Functions of Thyroid Hormones
  - Growth and development
  - Metabolism – lipid, carbohydrate and protein
  - Calorigenic & CVS Effects

Differences between T3 and T4

T_3	T_4
Four time more potent than T_4	Less potent
Peak effect reaches with in 24-48 hrs.	Peak effect reaches in 6-8 hrs
Plasma protein binding capacity is less	It bind more tightly to plasma proteins
It is active in vitro	It is inactive invitro
Thyroid gland produce 20% of T_3	Thyroid gland produces 80% of T_4
T_3 is the active form	T_4 is less active than T_3

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL	60–181 ng/dL
	(62–134 nmol/L)	(0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL	230–420 pg/dL
	(10.3–34.7 pmol/L)	(3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	80%	95%

Transport, Metabolism and Excretion - Kinetics

- Highly reversibly bound to plasma protein primarily thyroxine-binding globulin (TBG)
- 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

THYROID DISORDERS

- Thyroid dysfunctioning results in many unwanted changes in metabolisum of proteins, carbohydrates,lipids .

- It also exerts adverse effect on reproductive, Gastro-intestinal, central nervous system ,and cardiovascular system.

Two types of thyroid disorders are:

- Hypothyroidism
- Hyperthyroidism

Thyroid Drugs

Thyroid drugs

- Levothyroxine sodium: The synthetic Na salt of levo (L) isomer of thyroxine (T4)
- Liothyronine (T3)
- Liotrix (T4 plus T3)

Pharmacokinetics

Orally easily absorbed; the bioavalibility of T4 is 80%, and T3 is 95%.

Drugs that induce hepatic microsomal enzymes (e.g., rifampin, phenbarbital, phenytoin, and etc) improve their metabolism.

Levothyroxine sodium (T_4)

Use: thyroid replacement and suppression therapy.

Advantages:

-high stability

-uniform

-low cost

-lack of allergenic foreign protein

-easy laboratory measurement of serum levels

-long half-life -7 days (once-daily administration)

-In addition, T_4 is converted to T_3 intracellularly; thus, administration of T_4 produces both hormones.

Liothyronine (T_3) is 3 to 4 times more potent than levothyroxine.

- Use:

  short-term suppression of TSH.

- Disadv:

  - Shorter half-life -24 hours (not recommended for routine replacement therapy which requires multiple daily doses)
  - Higher cost
  - Difficulty of monitoring.
  - Its greater hormone activity and consequent greater risk of cardiotoxicity- avoided in patients with cardiac disease.

Liotrix - Mixture of thyroxine and liothyronine

- Expensive

Clinical use

- Hypothyroidism: cretinism & myxedema
  - Cretinism: Decrease in the levels of thyroid hormone in infants or during foetal stage is known as cretinism
  - Myxedema: a condition in which hypothyroidism results in accumulation of mucopolysaccharide in the intercellular spaces of muscle and skin

Adverse reactions

- Overmuch leads to thyrotoxicosis
- Angina or myocardial infarction usually appears in aged

Treatment for Hyperthyroidism

- Anti-thyroid drugs—Inhibits thyroid hormone synthesis by irreversibly binding to TPO inhibiting its ability to break down iodine ($I_2 \rightarrow I^-$) and covalently attach it to the tyrosine residue of thyroglobulin.
  - Propylthiouracil
  - Methimazole
  - Carbamizole—Degraded to methimazole in the body.
- Radioactive Iodine.
- Thyroidectomy.
- β-Blockers used in the treatment of thyroiditis to treat symptoms.

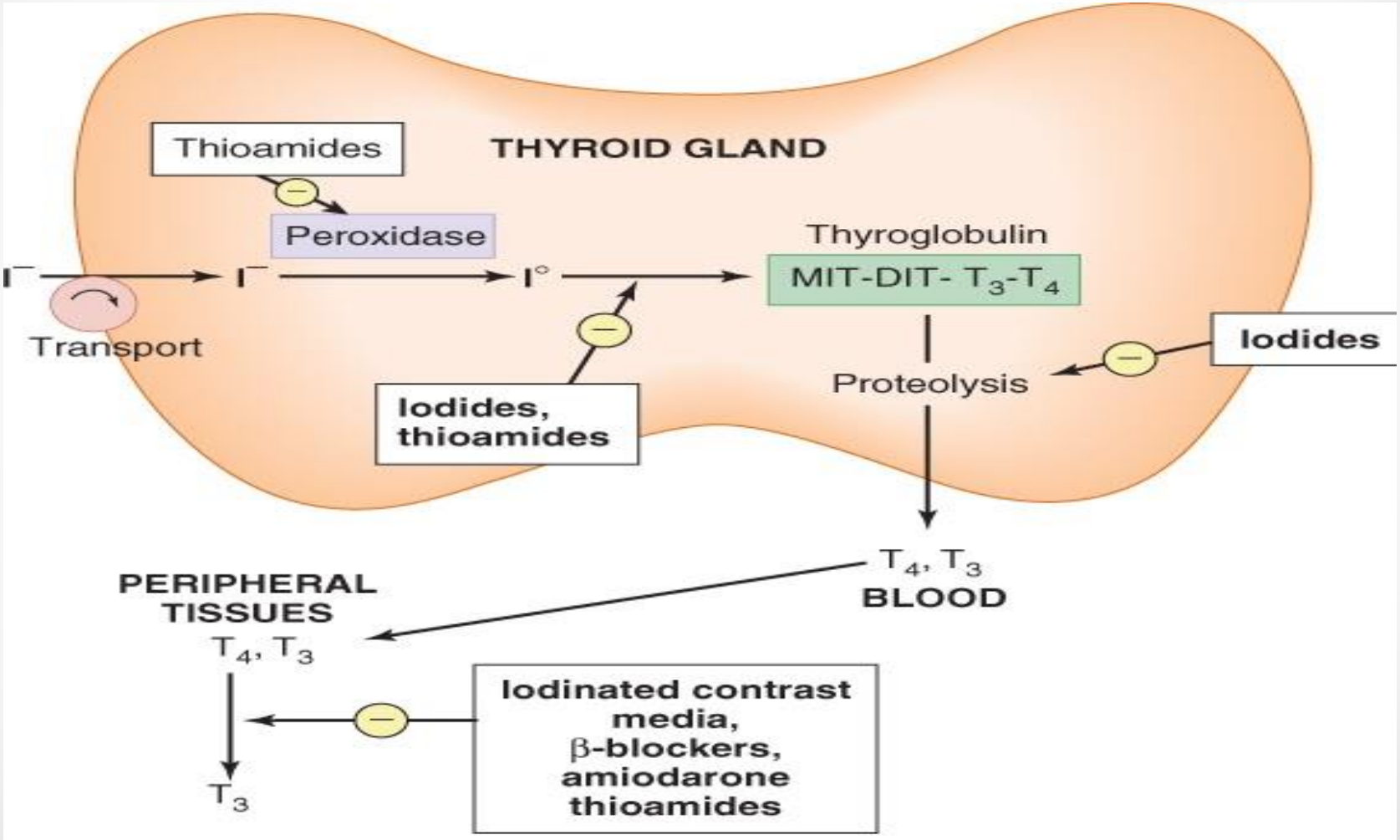
Anti-thyroid Drugs

- Effective in the long-term treatment of hyperthyroidism.
- 6-8 weeks before maximum effect of the drug achieved. Drug inhibits hormone synthesis, so hormones synthesized prior to drug use will continue to cause hyperthyroid condition.
- Typical side effects include headache, nausea, vomiting, itchy skin and rash, and muscle aches and pains.
- Serious liver damage, decreased red and white blood cell synthesis, as well as decreased platelet production have been reported in a few cases. The drug's interaction with other enzymes responsible for clotting factor synthesis accounts for some of these serious side effects.
- Administering too high a dosage of anti-thyroid drugs can cause hypothyroidism.

Antithyroid drugs

Class	Representative	
Thioamides	propylthiouracil	Inhibitors of thyroxine synthesis
	methylthiouracil	
	methimazole	
	carbimazole	
Anion inhibitors	perchlorate Thiocyanate	inhibitors of iodide trapping
Iodinated contrast media	diatrizoate, iohexol	
Iodides	KI, NaI	inhibition of hormone release
Radioactive iodine β-R blockers	^{131}I propranolol	
Miscellaneous	sulphonamides, phenylbutazone, thiopental sodium, lithium, amiodarone, domarcaprol	

Mechanism of action of anti thyroid drugs



Thioamides

- Methimazole
- Propylthiouracil (PTU)
- Carbimazole
- **Mechanism of Action:**

✓ Prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification.

✓ Block coupling of the iodotyrosines.

✓ Blocks peripheral conversion of T_4 to T_3 (PTU)

✓ Since the synthesis of hormones is affected, their effect requires 4 weeks.

- Carbimazole cross the placental barrier & are concentrated by the fetal thyroid - caution in pregnancy
- Methimazole associated with congenital malformations
- Secreted in low concentrations in breast milk- safe for the nursing infant.
- Propylthiouracil is preferable in pregnancy:
  - ✓It crosses the placenta less readily
  - ✓Is not secreted in breast milk

Thioamides

- Pharmacokinetics:
  - almost completely absorbed in the GIS
  - serum half life: 90mins(PTU) ; 6 hours (methimazole)
  - excretion: kidney – 24 hours (PTU) ; 48 hours (Methimazole)
  - can cross placental barrier (lesser with PTU)
  - Methimazole 10x more potent than PTU
  - PTU more protein-bound

- Uses

Definitive therapy

- Graves disease
- Toxic nodular goitre

Preoperatively

- In thyrotoxic patients
- Along with RAI

Thioamides

- Adverse Effects:
  - ✓Nausea & GI distress
  - ✓An altered sense of taste or smell may occur with methimazole
  - ✓Maculopapular pruritic rash – most common
  - ✓benign transient leukopenia
  - ✓The most dangerous – agranulocytosis (granulocyte count < 500 cells/mm2).
  - ✓hepatitis (PTU) ; cholestatic jaundice (Methimazole) can be fatal
  - ✓vasculitis
  - ✓lupus-like syndrome

Radyoactive Iodine (Iodine^{131})

- Preparations: sodium iodide ^{131}
- Mechanism of Action: trapped within the gland and enter intracellularly and delivers **strong beta radiations** destroying follicular cells
- Clinical uses:
  - ✓Diagnostic purpose → 25-100μ curies in thyroid function test
  - ✓Therapeutic use → 3-6 milli curies in toxic nodular goiter, graves disease, thyroid Ca.
- Contraindication: pregnancy
- Advantages
  - ✓ Easy administration
  - ✓ Effectiveness
  - ✓ Low expense
  - ✓ Absence of pain

Radyoactive Iodine (Iodine^{131})

Adverse effects

- ✓permanent hypothyroidism
- ✓potential for genetic damage
- ✓may precipitate thyroid crisis

Anion Inhibitors

- **Monovalent anions** such as perchlorates, pertechnetate and thiocyanate can block uptake of iodide by the gland by competitive inhibition

Mechanism of Action (MOA):

- ✓ They inhibit organification
- ✓ Hormone release
- ✓ Decrease the size & vascularity of the hyperplastic gland

- can be overcome by large doses of iodides
- useful for iodide-induced hyperthyroidism (amiodarone-induced hyperthyroidism)
- rarely used due to its association with aplastic anemia

Iodinated Contrast Media

- Iodinated contrast media
  - Ipodate (oral)
  - Iopanoic acid (oral)
  - Diatrizoate (intravenous)

valuable in hyperthyroidism (but is not labeled for this indication)

- **Mechanism of Action (MOA):** inhibits conversion of T4 to T3 in the liver, kidney, brain and pituitary

  Another MOA is due to inhibition of hormone release secondary to iodide levels in blood
- **Useful in thyroid storms** (adjunctive therapy)

Adjuncts to Antithyroid Therapy

- Hyperthyroidism resembles sympathetic overactivity
- Propranolol, will control tachycardia, hypertension, and atrial fibrillation, inhibits T_4 to T_3
- Diltiazem, can control tachycardia in patients in whom beta-blockers are contraindicated
- Barbiturates accelerate T_4 breakdown (by enzyme induction) and are also sedative

Thyroid Malfunction and Pregnancy

In a pregnant hypothyroid patient- dose of thyroxine should be adequate.

- This is because early development of the fetal brain depends on maternal thyroxine

In hyperthyroid patient: Ideal situation- treat before pregnancy

- Pregnancy-Radioactive iodine→ contrindicate

- Propylthiouracil (fewer teratogenic risks than methimazole) can be given in the first trimester, and then methimazole can be given for the remainder of the pregnancy in order to avoid potential liver damage.
  - Dose limitation≤ 300mgs/day

- If thyrotoxicosis occurs, propylthiouracil is used and an elective subtotal thyroidectomy performed.

- Methimazole alternative- fetal scalp defects

TSH Replacement Drug

- Thyrotropin alpha—A synthetic form of TSH. Administered intravenously.

- Used in thyroid cancer treatment.
  - Tumors of the hypothalamus or pituitary gland can cause the uncontrolled release of TSH, which accumulates in the thyroid and can cause subsequent follicular or papillary cancer of the thyroid. Partial or total thyroidectomy typical.

  - Following thyroidectomy, the individual is dependent on exogenous thyroid hormones to regulate metabolism, but thyrotropin alpha is also used to suppress the release of endogenous TSH, which could trigger cancerous growth again.

  - Used as a diagnostic tool to determine the reoccurrence of cancer.

Class	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
Antithyroid Agents			
Thioamides			
Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions block iodine organification inhibit peripheral deiodination of T4 and T_3	Hyperthyroidism	Oral duration of action: 6–8 h delayed onset of action *Toxicity:* Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis,hypothyroidism
Iodides			
Lugol solution Potassium iodide	Inhibit organification and hormone release reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral acute onset within 2–7 days *Toxicity:* Rare (see text)
Beta blockers			
Propranolol	Inhibition of adrenoreceptors inhibit T4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm adjunct to control tachycardia, hypertension, and atrial fibrillation	Onset within hours duration of 4–6 h (oral propranolol) *Toxicity:* Asthma, AV blockade, hypotension, bradycardia
Radioactive iodine ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism patients should be euthyroid or on blockers before RAI avoid in pregnancy or in nursing mothers	Oral half-life 5 days onset of 6–12 weeks maximum effect in 3–6 months *Toxicity:* Sore throat, sialitis, hypothyroidism

Class	Mechanism of Action	Indications	Pharmacokinetics, Toxicities, Interactions
Thyroid Preparations			
Levothyroxine (T_4) Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	maximum effect seen after 6–8 weeks of therapy

Thank you for your attention