Thyroid & Anti thyroid drugs

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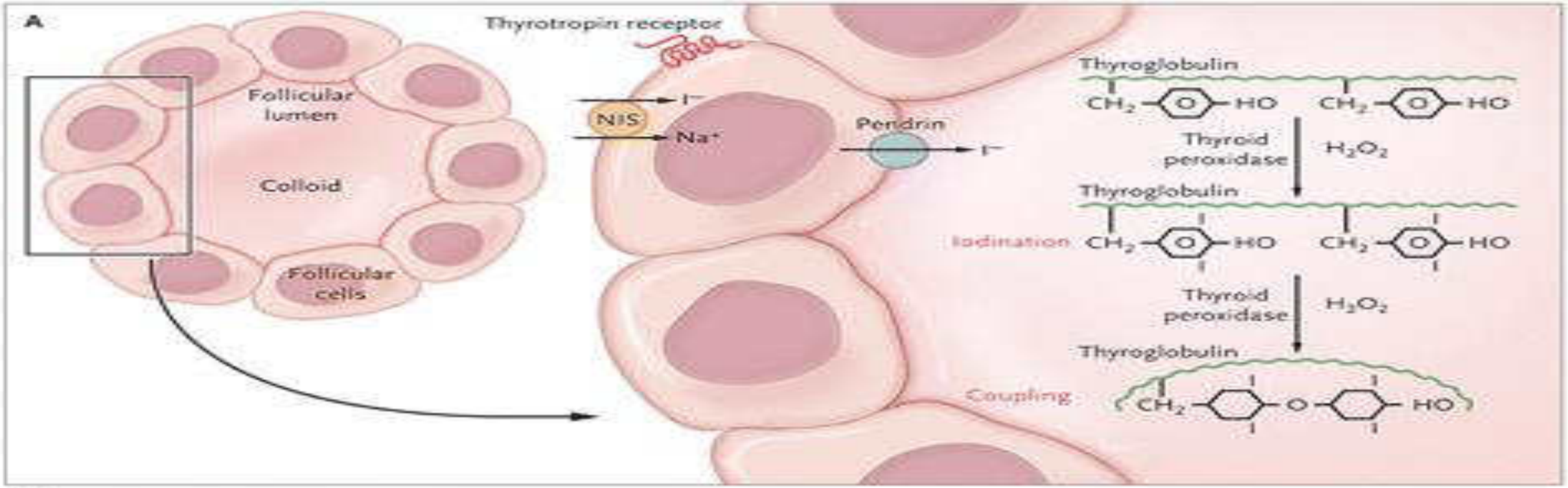
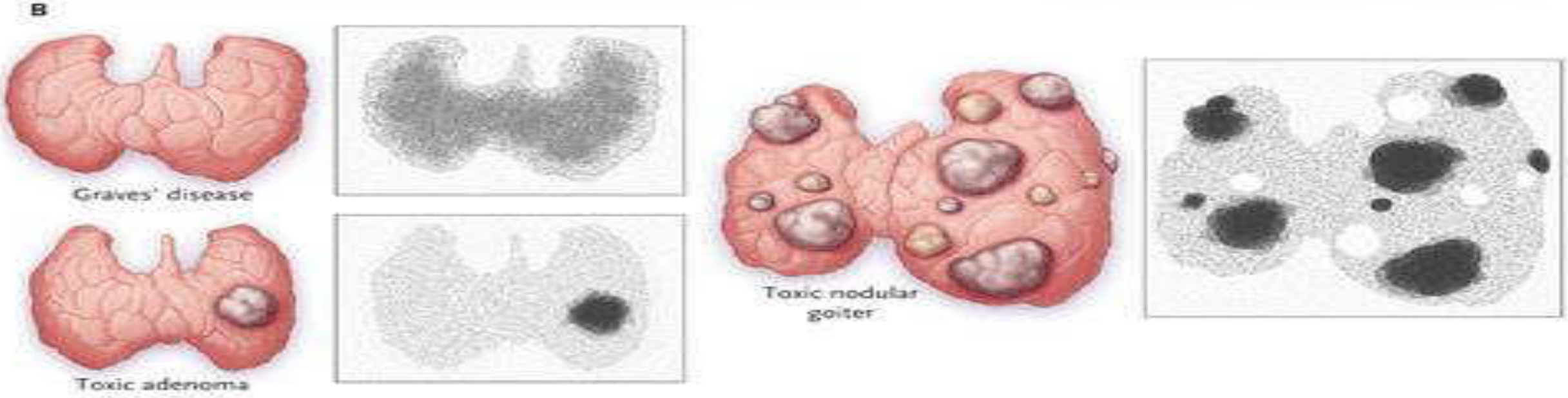
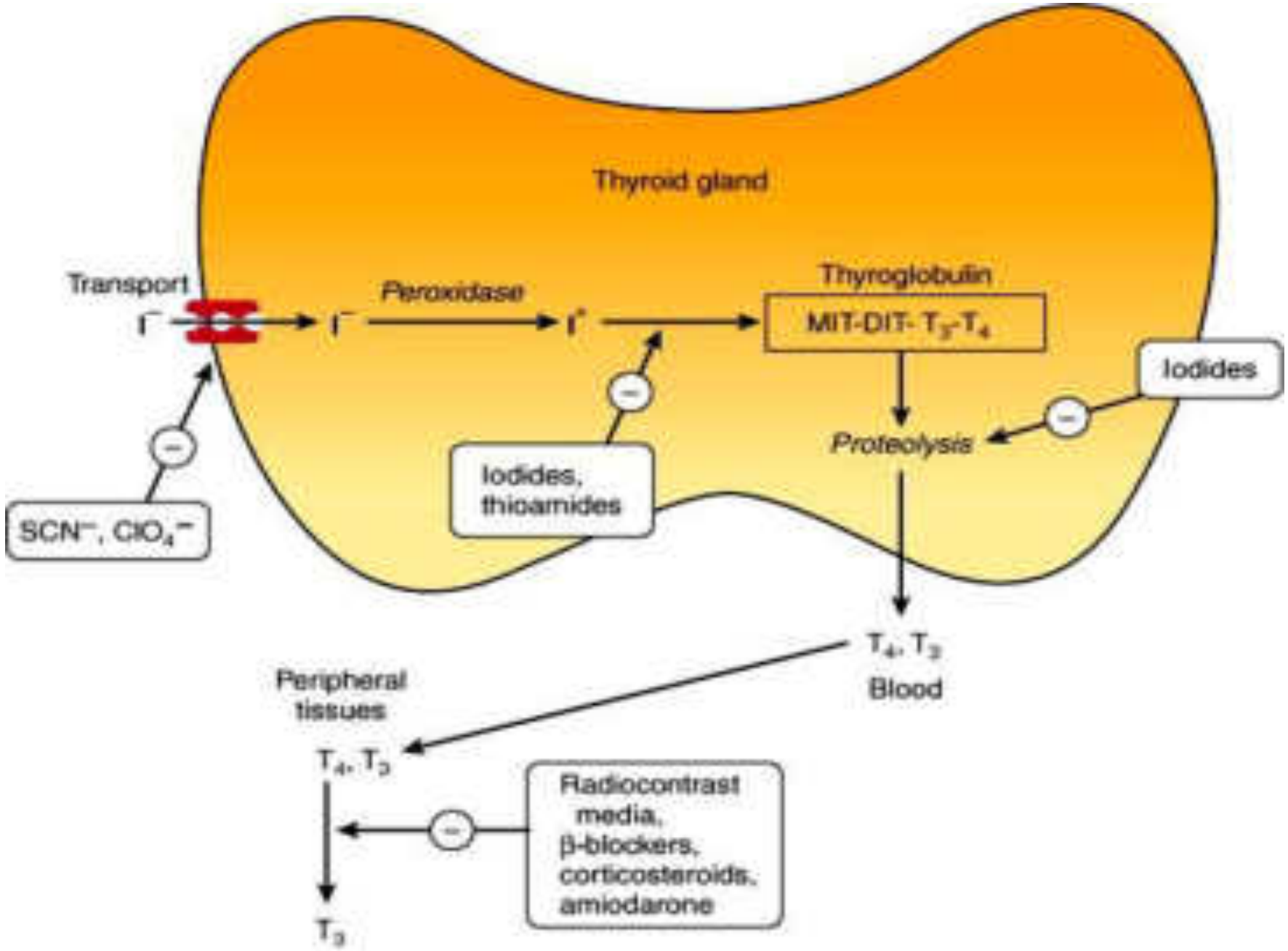

A
Thyrotropin receptor
Follicular lumen
Colloid
Follicular cells
NIS
I⁻
Na⁺
Pendrin
I⁻
Thyroglobulin
Thyroid peroxidase
H2O2
Thyroglobulin
Iodination
Thyroid peroxidase
H2O2
Thyroglobulin
Coupling


B
Graves' disease
Toxic adenoma
Toxic nodular goiter

Biosynthesis of thyroid hormones



Synthesis Of Thyroid hormone

Steps

1. Transport of iodide into the thyroid gland by sodium-iodide symporter
2. Iodide is oxidized by thyroidal **peroxidase** to iodine
3. Tyrosine in thyroglobulin is iodinated and forms MIT & DIT- **iodide organification**
   (MIT- monoiodotyrosine, DIT- Diiodotyrosine)
4. Iodotyrosines condensation within thyroglobulin molecule

   MIT+DIT→T3; DIT+DIT→T4

. T_4, T_3, MIT & DIT - released from thyroglobulin by exocytosis & proteolysis of thyroglobulin .

6. The MIT and DIT are deiodinated within the gland, and the iodine is reutilized.

- T_4 & T_3 ratio within thyroglobulin - 5:1
- Most of the T_3 circulating in the blood is derived from peripheral metabolism of thyroxine.
- T_3 is three to four times more potent than T_4
- receptor affinity of T_3 about ten times higher than T_4

- Pharmacological actions of thyroid hormone
- Metabolic function –
  - CHO metabolism:
    - ↑ glycogenolysis
    - Increase gluconeogensis
    - ↑ glucose absorption from GIT
    - Enhance glycolysis – rapid uptake of glucose by the cell.
  - Net result - ↑ blood glucose level
  - On protein metabolism: ↑ protein catabolism
  - On fat metabolism:
    - ↑mobilization of fat,
    - oxidation of FA → ↑ FFA
  - On BMR: ↑ BMR

- Growth : ↑ growth

- On GIT:
  - ↑ appetite & food intake.
  - ↑ rate of secretion of digestive juice.
  - ↑ motility of GIT → diarrhea often result in hyperthyroidism

- On CVS:
  - Enhance tissue sensitivity to catecholamines
  - ↑cardiac output

- On nervous system:
  - excitable effect.
  - Has role on development of brain in fetal & 1st few weeks of postnatal life

- Muscle weakness due to protein catabolism

THYROID DYSFUNCTION

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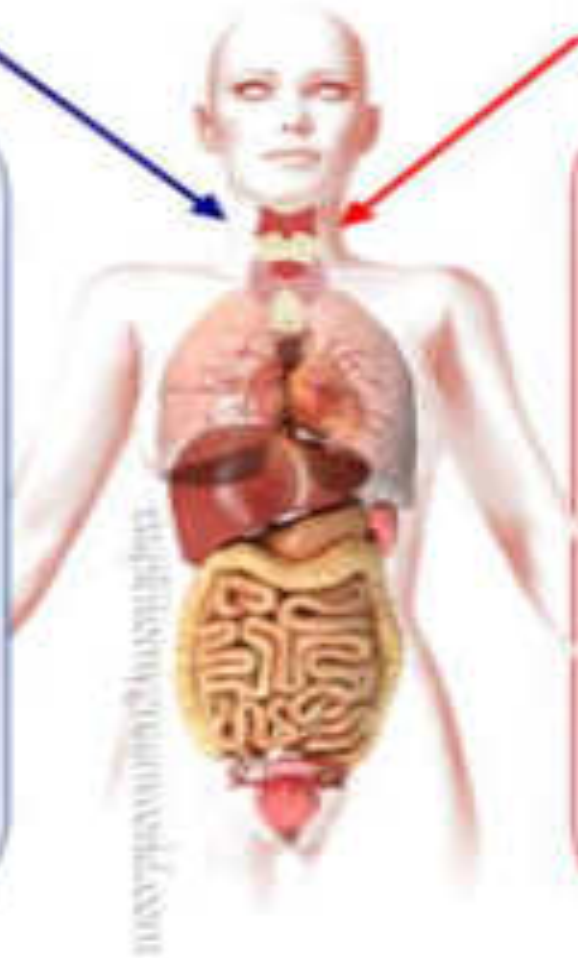
HYPO THYROIDISM

- DRY HAIR
- PUFFY FACE
- SLOW HEARTBEAT
- WEIGHT GAIN
- CONSTIPATION
- BRITTLE NAILS
- ARTHRITIS
- COLD INTOLEREANCE
- DEPRESSION
- DRY SKIN
- FATIGUE
- MEMORY LOSS
- HEAVY MENSTRUAL PERIODS
- MUSCLE ACHES



HYPER THYROIDISM

- HAIR LOSS
- BULGING EYES
- SWEATING
- RAPID HEARTBEAT
- WEIGHT LOSS
- REGULAR GAS
- SOFT NAILS
- SLEEPING DIFFICULTIES
- HEAT INTOLERANCE
- INFERTILITY
- IRRITABILITY
- MUSCLE WEAKNESS
- NERVOUSNESS
- SCANT MENSTRUAL PERIODS

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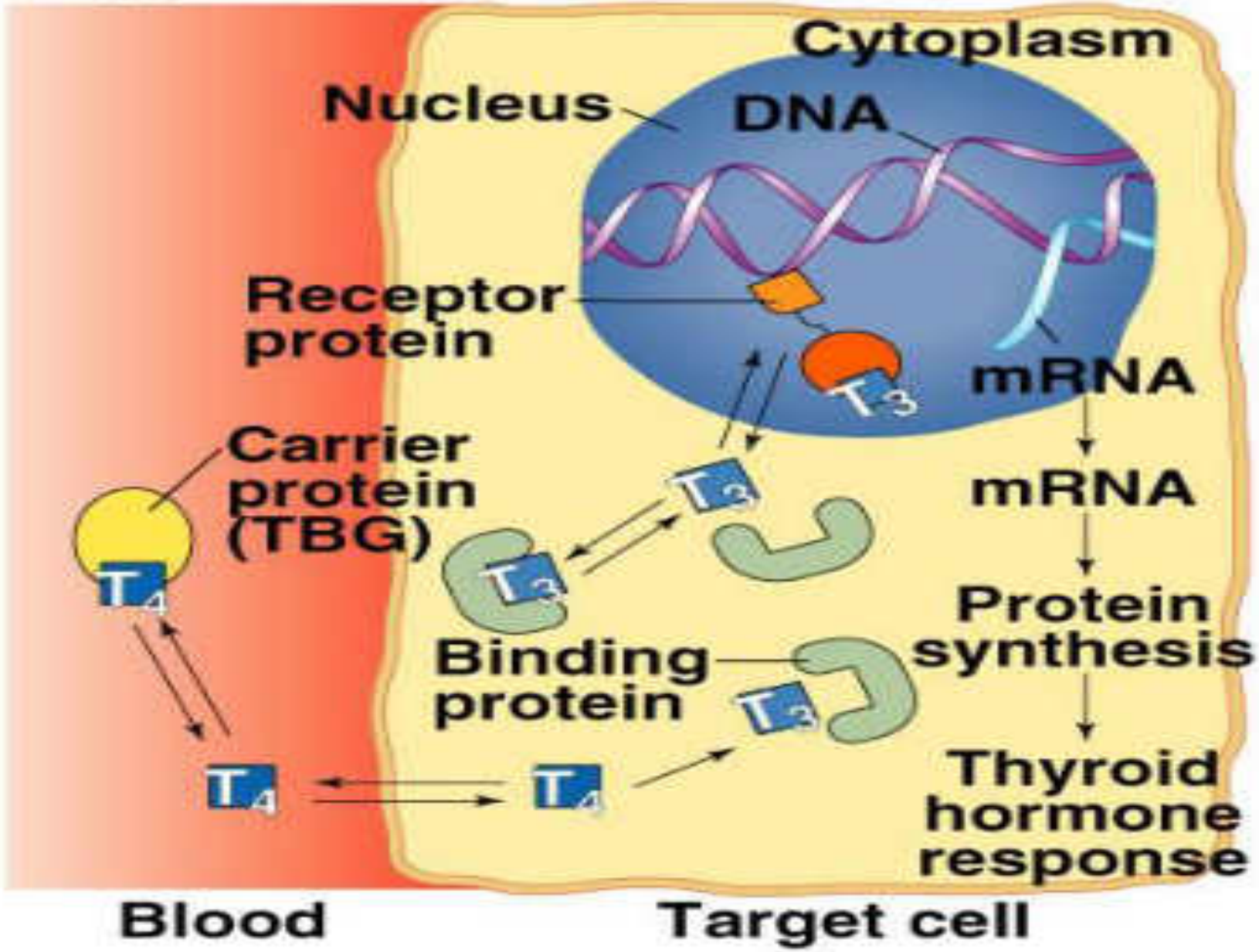
- Hypothyroidism
  - Primary hypothyroidism- Caused by Hashimoto's Disease, an auto-immune disorder in which the thyroid is destroyed by antibodies.
  - Secondary hypothyroidism-Caused by impaired hypothalamus and pituitary function, typically due to a tumor, can inhibit the secretion of THS, causing.
  - Due to iodine deficiency
- Enlarged thyroid, symptom of hypothyroidism.
- Goiters form for different reasons depending on the cause of hypothyroidism
  - Hashimoto's disease- Causes goiters due to the accumulation of lymphocytes.
  - Iodine deficiency-Increase the surface area of the thyroid and aid in its absorption of iodine.

- Treatment for Hypothyroidism
- Hormone replacement therapy
  - Levothyroxine—Synthetic T4, tabs- 25µg, 50µg, 100µg: inj. Preferred over liothyronine (bec of more sustained and uniform action & lower risk of cardiac arrhythmias)
  - Liothyronine—Synthetic T3, limited availability, occasionally used i.v. along with l-thyroxine in myxedema coma.
  - Liotrix—Combination of synthetic T4 and T3
  - Natural Thyroid Hormones—Thyroid hormones derived from pigs, contains T4 and T3

➢ Older patients, heart patients: T4, the inactive form, is preferred (Because thyroid hormones serve to increase heart rate)

➢ Younger patients: Synthetic T3 is preferred

- Dosage specific to individual and is determined by their TSH serum levels. Typically 1.5µg T4 per kg body weight.
- Dosage for individuals suffering from secondary hypothyroidism determined by the amount of free T4 and T3 circulating in their system.



- **Therapeutic uses**

1. replacement therapy
   - Cretinism:
     - ➢ Must be started soon after birth
     - ➢ Physical development will be normal with some degree of mental retardation
     - ➢ Must be continued lifelong
   - Hypothyroidism in adults (myxedema)

     Occurs due to- Autoimmune thyroiditis
     Thyroidectomy
     Drug induced-iodides, radioiodine,lithium, amidarone
     - ➢ Mild-treatment for few months
     - ➢ Severe –life long
   - Myxedeme coma
2. Nontoxic goitre
3. Thyroid carcinoma

larger doses of thyroxine ⟶ keeps low levels of TSH ⟶ used to control small well differentiated carcinomas

❖ First choice-surgery

❖ Second choice-radioiodine therapy

- Side effects of levothyroxine

➢ Common side effects: headache, mental/mood changes (e.g., nervousness, irritability), shaking, sweating, sensitivity to heat, diarrhea, weight loss, trouble sleeping, tiredness.

➢ Serious & rare side effects : chest pain, shortness of breath, fast/pounding/irregular heartbeat, swelling of the hands/feet, seizures.

➢ A very serious allergic reaction to this drug is rare: serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

- **Hyperthyroidism**

➢Thyrotoxicosis - Occurs due to excessive secretion of thyroid hormones in the circulation

- Causes

❖Graves' disease (diffuse toxic goiter)

Autoimmune disorder ➡ Formation of IgG antibodies to TSH ➡ Stimulate thyroid gland

⬇

Excess thyroid hormones

- Autoimmune inflammation of periorbital tissues (exophthalmos)

❖Toxic nodular goiter

- Produce thyroid hormones independent of TSH
- Common in elderly
- No ocular changes

- Choices of Rx Hyperthyroidism
  - Medical treatment
  - Radioiodine treatment
  - Combined medical & RAI Rx
  - Surgical treatment

WHAT IS RADIOIODINE?

- Used to treat disorders of the thyroid gland
  - Hyperthyroidism
  - Thyroid cancer

- Delivered as oral capsule or solution
- Active isotope I^{131}
- Uptake by thyroid gland
- β particle release
- Destruction of follicular cells

- Thyroid inhibitors
  - Drugs used to lower functional capacity of hyperactive thyroid gland

Classification

- Thioamides (Inhibitors of thyroxine synthesis)

  propylthiouracil, methylthiouracil, methimazole, carbimazole
- Anion inhibitors
  - Inhibitors of iodide trapping

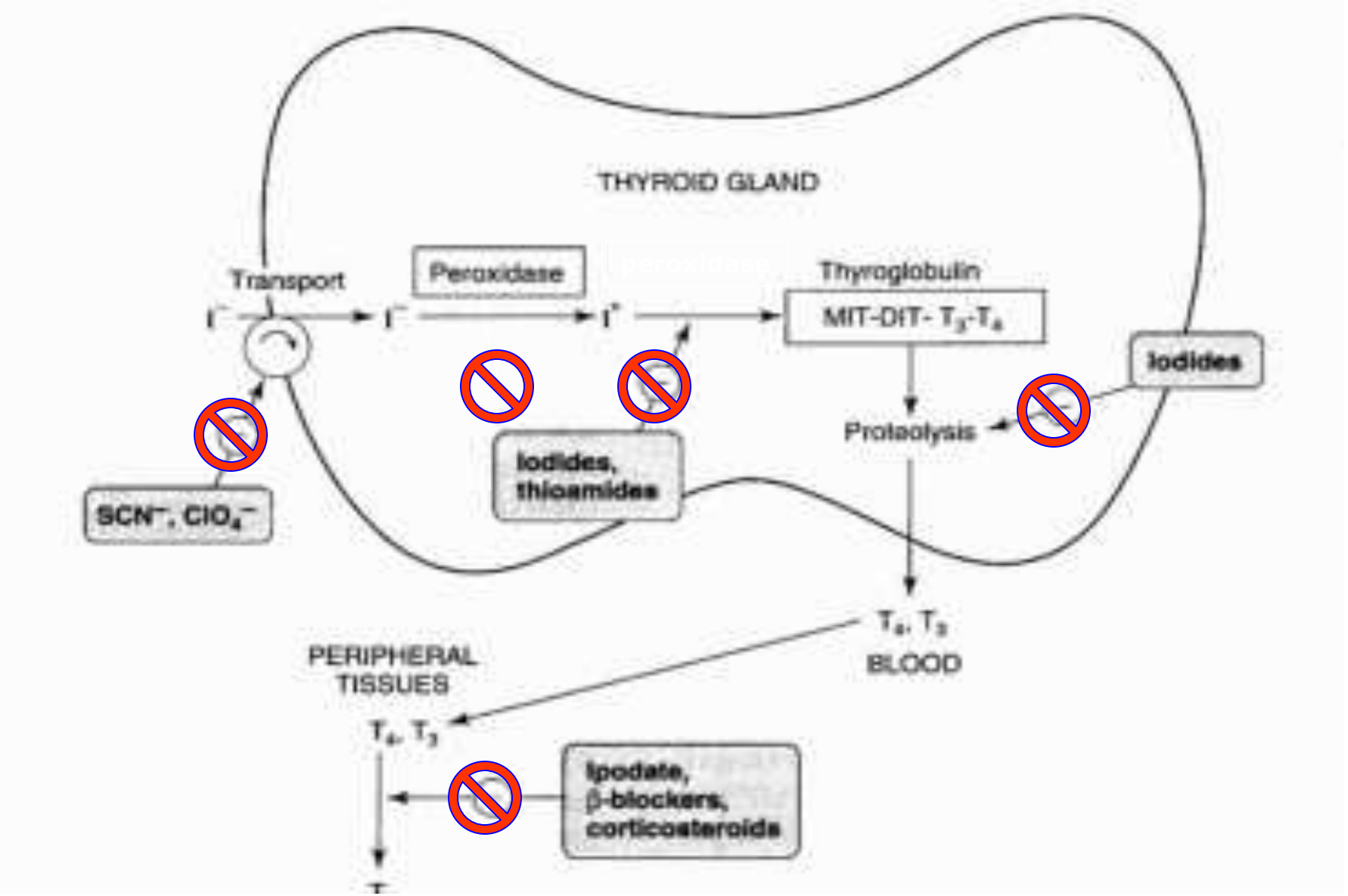
    perchlorate, Thiocyanate,
  - Iodinated contrast media

    diatrizoate, iohexol
- Iodides (Inhibition of hormone release)

  KI, NaI
- Radioactive iodine ^{131}I
- β-R blockers propranolol
- Miscellaneous

  sulphonamides, phenylbutazone, thiopental sodium, lithium, amiodarone, domarcaprol

Anti-thyroid drugs



- Thioamides
- Methimazole (carbimazole)
- Propylthiouracil (PTU)

✓These 2 are the major drugs used in the treatment of thyrotoxicosis (Carbimazoles converted to methimazole *in vivo*).

MOA: These drug inhibit thyroid hormone production by

a) Inhibiting thyroid peroxidase which is required in intrathyroidal oxidation of Iodide.

b) By inhibiting the iodination of tyrosine

c) By inhibiting coupling of MIT and DIT to form thyroid hormones

d) Propylthiouracil also inhibits peripheral conversion of T4 to T3

- Slow in onset ~ 4 weeks-Since the synthesis of hormones is affected, their effect requires 4 weeks.
- Orally absorbed
- Metabolized in liver
- Excreted in urine as metabolites
- Propyl thiouracil is short acting (t1/2-1-2hrs)
- Methimazole long acting (t1/2-1-2hrs).
- Propylthiouracil is preferable in pregnancy:
    - It crosses the placenta less readily
    - Is not secreted in breast milk

Adverse reactions

- Nausea & GI distress
- An altered sense of taste or smell may occur with methimazole
- Maculopapular pruritic rash, arthralgia and vasculitis – most common
- Hepatitis & cholestatic jaundice can be fatal
- The most dangerous – agranulocytosis (granulocyte count < 500 cells/mm^2).
- Propylthiouracil : 50-150mg TDS followed by 25-50 mg BD-TDS for maintenance
- Carbimazole: 5-15 mg TDS initially
- Maintenance dose is 2.5-10mg daily in 1-2 divided doses

- Uses:

1. Graves' disease
   - ➢ Initially larger doses-till reaches to euthyroid state
   - ➢ Later-smaller maintainance doses

2.Toxic nodular goiter
   - ➢ First choice-surgery
   - ➢ Second choice-antithyroid drugs (thioamides)

3.Preoperatively(First choice-carbimazole)
   - ➢ To bring euthyroid state before surgery
     (decrease the size & vascularity of the hyperplastic gland)

4.Hyperthyroidism in pregnancy
   - ➢ Propylthiouracil is preferred
   - ❖ Thyroidectomy and ^{131}I are contraindicated during pregnancy

5. Thyroid storm (Thyrotoxic crisis)

6.Prophylaxis in endemic goiter(iodides)

- Ionic inhibitors
- Monovalent anions like perchlorate, pertechnetate, thiocyanate
- MOA: Block uptake of iodine by the gland through competitive inhibition of the iodide transport (NIS) mechanism.
- Anion inhibitors are not clinically used because of their toxicity
- Potassium iodide- block thyroidal reuptake of I^- in patients with iodide-induced hyperthyroidism-so effective in iodide induced hyperthyroidism

- Iodine and Iodides – Inhibitors of hormone release
- The response to iodine or iodides is identical, because elemental iodine is reduced to iodide in the intestine

MOA: Inhibit all phases of thyroid function

❑ Primary mechanism inhibition of Hormone release (thyroid constipation)

➢ Inhibit iodide transport, gland response to TSH, iodination of tyrosine residues

➢ Decrease the size & vascularity of the hyperplastic gland.

- Since iodide salts inhibit the release as well as the synthesis of the hormone, their **onset of action occurs rapidly** within 2-7 days.
- This effect is **transient** because the thyroid gland escapes from iodide block after several weeks of treatment (**thyroid escape**).

- Preparations and dose
- Lugol's solution: 5% iodine in 10% KI solution : 5-10drops/day
- Iodide salts (sod/pot) 100-300 mg/day **(therapeutics),** 5-10mg/day **(prophylactic for endemic goiter)**
- **Uses**

1. Preoperatively

Along with carbimazole (first choice) iodine is given for 10 days for thyroidectomy in Graves' disease

- To bring euthyroid state before surgery

  (decrease the size & vascularity of the hyperplastic gland)

2. Thyroid storm (Lugol's solution)

- Prevents further release of T3/T4
- Decreases T4 to T3 conversion

3. Prophylaxis for endemic goiter (given as iodised salt)

4. Antiseptic-tincture of iodine, povidone iodine

- Adverse effects:
  - Acute : swelling of lip, eye lid, face, angioneurotic edema of larynx, fever, joint pain, lymphadenopathy, thrombocytopenia
  - Chronic : ulceration of mucous membrane of mouth, salivation, lacrimation, burning sensation in the mouth, rhinorrhoea, GI intolerance
- Iodinated contrast media (Ipodate)
- These drugs rapidly inhibit the conversion of T_4 to T_3 in the liver, kidney, pituitary gland, & brain.
- Relatively nontoxic.
- Adjunctive therapy in the treatment of thyroid storm
- Used as alternatives when iodides or thioamides are contraindicated.

- Radioactive iodine
- ^{131}I - is used for treatment of thyrotoxicosis
- Administered orally in solution as sodium ^{131}I, it is rapidly absorbed, concentrated by the thyroid, & incorporated into storage follicles → emits β particles & X rays → β particles damage the thyroid cells → thyroid tissue destroyed by pyknosis → replaced by fibrosis
- Uses
- Graves' disease
- Toxic nodular goiter
  - Diagnostic purpose → 25-100μ curies in thyroid function test
  - Therapeutic use → 3-6 milli curies in toxic nodular goiter, Graves' disease, thyroid carcinoma .

- Adjuncts to Antithyroid Therapy

➢ Hyperthyroidism resembles sympathetic overactivity

➢ Propranolol, will control tachycardia, hypertension, and atrial fibrillation

➢ 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 storm (Thyrotoxic crisis)
- Usually occurs in a severely hyperthyroid patient caused by a precipitating event such as:
  - Infection
  - Surgical stress
  - Stopping antithyroid medication in Graves' disease
- Clinical clues
  - fever→ hyperthermia
  - marked anxiety or agitation→ coma
  - Anorexia
  - tachycardia→ tachyarrhythmias
  - pulmonary edema/cardiac failure
  - hypotension→ shock
  - confusion