

Thyroid and Antithyroid Drugs

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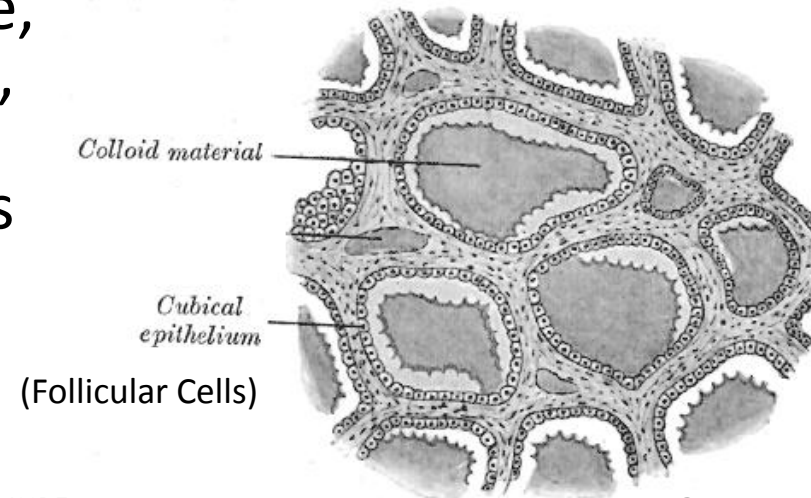
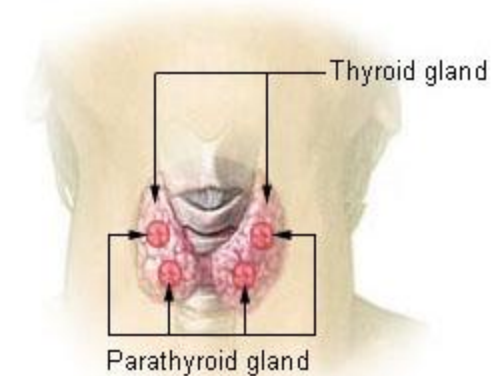
Faculty of Medicine

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Anatomy and histology of the thyroid gland

- Located in neck adjacent to the 5th cervical vertebra (C5).
- Composed of epithelial cells which specialize in the absorption of iodine and, of course, secretion of thyroid hormones.
- Follicles surround a protein core, the colloid, where thyroglobulin, a substrate in thyroid hormone synthesis, and thyroid hormones are stored.

Thyroid and Parathyroid Glands

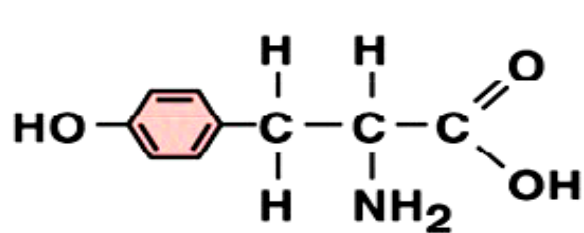


Thyroid Hormones

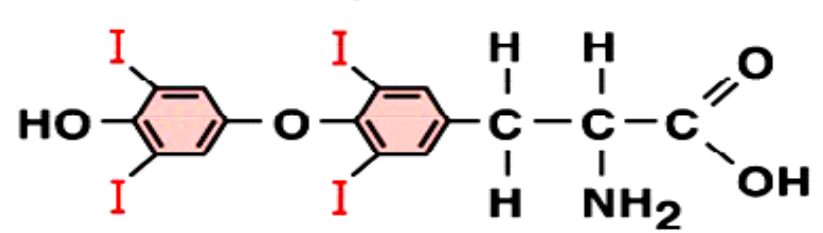
- **3 hormones**
 - **Thyroxin** (3,5,3',5'-tetraiodothyronine) or (**T₄**)
 - **Triiodothyronine** (**T₃**)
 - **Calcitonin**
- T₃ and T₄ are iodine containing amino acid derivatives.
- Every tissue in the body is affected by thyroid hormones.
- There are no discrete target tissue.

Thyroxine Synthesis

Tyrosine

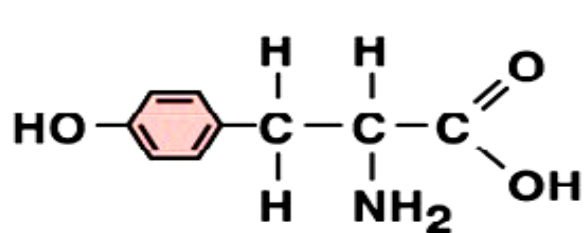


Thyroxine (T₄)

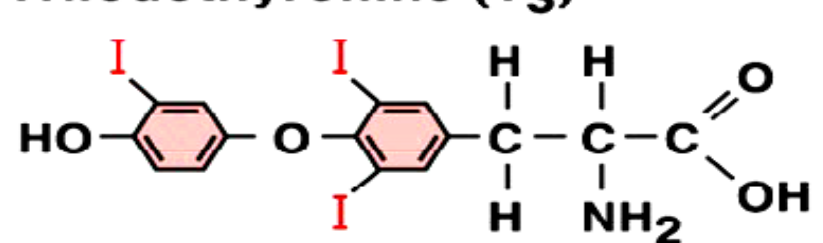


(2 tyrosine + 4 I)

Tyrosine



Triiodothyronine (T₃)



(2 tyrosine + 3 I)

Iodide

- Needed for synthesis of thyroid hormones
- Sources:
 - - Iodized salt, Iodated bread, and Dairy products
- Daily requirement: 75 micrograms.
- Thyroid peroxidase enzyme
- Lysosomal enzymes hydrolyze thyroglobulin
- Most of released T4 is converted in periphery to T3 by deiodinase enzyme
- Thyroid hormones travel in blood bound to a specific thyroxine binding globulin (TBG)

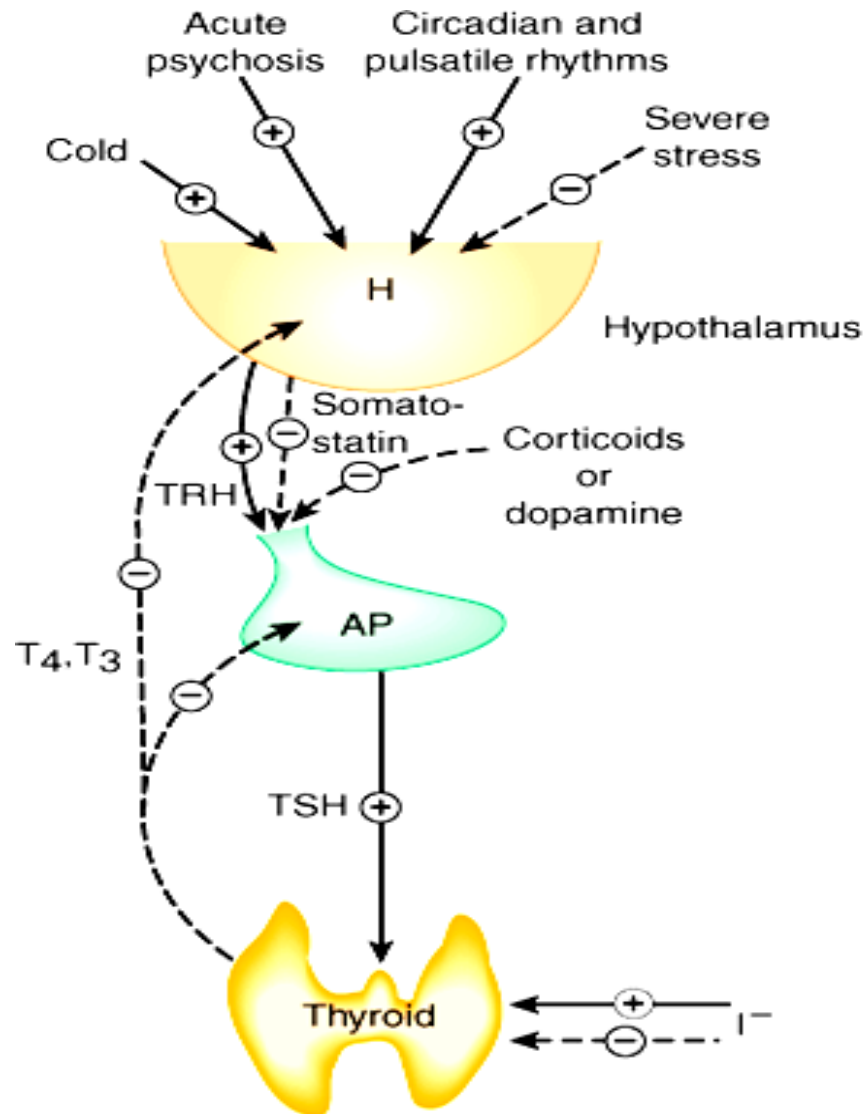
Physiological Actions

- Normalize growth and development, body temperature, and energy levels.
- Influence the metabolism of proteins, carbohydrates, and lipids.
- Constant circulating concentrations of T_3 and T_4 are required for their proper effect.
- Calcitonin is important in the regulation of calcium metabolism

Thyroid hormones effects on metabolism

- THs serve as a nuclear transcription factor, regulating gene expression in targeted cells to increase metabolism.
 - Increase size and number of mitochondria in the cell.
 - Synthesize cytochromes which feed into the electron transfer chain of cellular respiration, stimulating metabolism through increasing ATP production.
 - Increase ATPase concentration.
 - Increase K^+ and Na^+ concentrations in the cell.
- Increase BMR to maintain electrochemical gradient in the cell.
- Stimulate carbohydrate metabolism and lipolysis.
- Affect protein synthesis.
- Increase the body sensitivity to catecholamines.

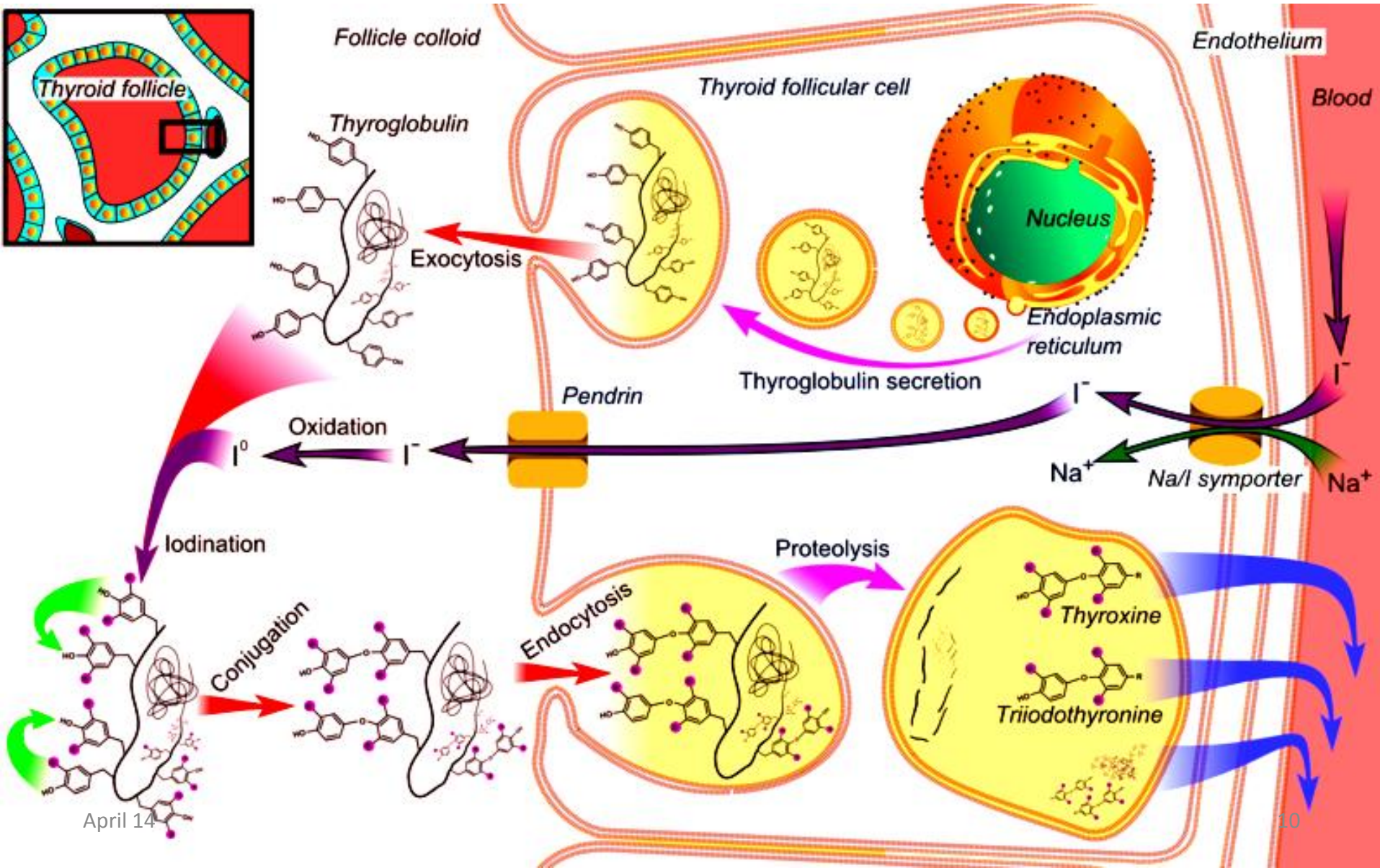
The hypothalamic-pituitary-thyroid axis



The Wolff–Chaikoff effect

- This is a reduction in thyroid hormone levels caused by ingestion of large amounts of iodine.
- Small amounts of iodide are necessary for hormone production, but large amounts inhibit T3 and T4 production and release.
- It is an autoregulatory phenomenon that inhibits organification (oxidation of iodide) in the thyroid gland, the formation of thyroid hormones inside the thyroid follicle, and the release of thyroid hormones into the bloodstream

Synthesis of thyroid hormones



Synthesis of thyroid hormones

- Follicular cells transport iodide across the cell.
- These cells secrete precursor protein thyroglobulin into the follicular lumen.
- An enzyme thyroperoxidase (TPO) catalyzes the conversion of iodide (I_2) to iodine (I^-) using H_2O_2 as a cofactor.
- TPO then catalyzes the addition of iodine to the C-3 and C-5 position of a tyrosine residue of thyroglobulin.
- Two iodinated tyrosine rings condense to form thyroxine, or T4, with four iodine substituents.
- Triiodothyronine, or T3, with three iodine substituents, accounts for about 10% of thyroid hormone

Thyroid Agents:

These are used as supplements in the treatment of hypothyroidism.

- Levothyroxine (T4) (*Eltroxin*)
- Liothyronine (T3)
- Liotrix (a 4:1 ratio of T4: T3)
- Thyroid desiccated

Antithyroid Agents

- Radioactive iodine (^{131}I) sodium
- Methimazole
- Potassium iodide: Oral solution, tablets
- Propylthiouracil
- Thyrotropin, recombinant human TSH.

Hypothyroidism

- A syndrome resulting from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body functions.
- In infants and children, there is striking retardation of growth and development that results in growth and mental retardation, which could be irreversible(**Cretinism**).

Hypothyroidism

- In Children → Cretinism
- In adults → Myxedema
- Causes:
 - Surgical removal of thyroid
 - Thyroiditis (Hashimoto's= an AI
 - Inflammatory disease causing atrophy of thyroid.
 - Infectious; transient; postpartum;
 - Severe deficiency or excess of iodine
 - Severe deficiency of one or more of the synthesis enzymes
 - Severe pituitary or hypothalamic dysfunction
 - Drug induced...

Hypothyroidism

- Causes lethargy and weight gain, among other symptoms.
- Primary hypothyroidism is typically caused by Hashimoto's Disease, an auto-immune disorder in which the thyroid is destroyed by antibodies.
- Impaired hypothalamus and pituitary function, typically due to a tumor, can inhibit the secretion of TSH, causing secondary hypothyroidism.
- A diet insufficient in iodine causes hypothyroidism as well.

The etiology and pathogenesis of hypothyroidism

Cause	Pathogenesis	Goiter	Degree of Hypothyroidism
Hashimoto's thyroiditis	Autoimmune destruction of thyroid	Present early, absent later	Mild to severe
Drug-induced ¹	Blocked hormone formation ²	Present	Mild to moderate
Dyshormonogenesis	Impaired synthesis of T₄ due to enzyme deficiency	Present	Mild to severe
Radiation, ¹³¹ I, x-ray, thyroidectomy	Destruction or removal of gland	Absent	Severe
Congenital (cretinism)	Athyreosis or ectopic thyroid, iodine deficiency; TSH receptor-blocking antibodies	Absent or present	Severe
Secondary (TSH deficit)	Pituitary or hypothalamic disease	Absent	Mild

Symptoms of thyroid dysfunction: Goiter



- Goiter simply means an enlargement of the thyroid gland, from any cause.
- Worldwide, over 90% cases of goiter are caused by iodine deficiency.
- Can be associated with a functional or dysfunctional gland.
- Can be associated with either hypothyroidism or hyperthyroidism.

Goiter

- Decreased levels of thyroid hormone, from any cause, signal increased production of TSH which accumulates in the thyroid causing a characteristic goiter.
- Also, goiter results from insufficient amounts of ingested iodine, this serves to increase the surface area of the thyroid to increase the absorption of iodine.

Treatment of Hypothyroidism

- Hormone replacement therapy.
- Thyroxine can be administered orally with a bioavailability ranging from 48%-80%.
 - Levothyroxine—Synthetic T4
 - Liothyronine—Synthetic T3
 - Liotrix—Combination of synthetic T4 and T3 in a ratio of 4:1.
 - Desiccated natural thyroid hormone—derived from pigs, contains T4 and T3.

Treatment of hypothyroidism

- Dosage specific to individual and is determined by their TSH serum levels.
- Because thyroid hormones increase heart rate, T4, the inactive form, is typically administered to older patients who have an increased risk for heart attack.
- Synthetic T3 is reserved for younger patients, who do not have a history of heart problems and individuals non-responsive to T4 treatment.
 - Some patients are inefficient in the conversion of T4 to T3, making combination drugs like Liotrix and desiccated thyroid ideal treatment options.
- Dosage for individuals suffering from secondary hypothyroidism is determined by the amount of free T4 and T3 circulating in their system.
- Administering too high of a dosage leads to hyperthyroid symptoms.

Hyperthyroidism

- Symptoms include fatigue, weight loss, rapid heart beat, anxiety, swollen eyes, and sensitivity to hot temperatures.
- Causes:
 - Grave's disease**, an autoimmune disorder in which antibodies serve as agonists to the TSH receptors on the thyroid's surface, causing thyroid growth and activation of hormone synthesis and secretion.
 - Thyroid tumors** which cause the uncontrolled synthesis and secretion of thyroid hormones.
 - Thyroiditis**, inflammation of the thyroid typically caused by infection.

Treatment of Hyperthyroidism

- **Anti-thyroid drugs (Thiourea derivatives or Thionamides):**
 - Propylthiouracil
 - Methimazole
 - Carbamazepine
 - Interfere with oxidation, iodination, and coupling reactions.
 - Inhibit 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.
- **Side effects:**
 - Allergy, Hepatic dysfunction, Agranulocytosis, Teratogenicity.
- **Disadvantages:**
 - Prolonged Rx, Delayed onset of action (12-18 hrs), Side effects, - High relapse rate.

Treatment of Hyperthyroidism

- **Anti-thyroid drugs.**
- **Iodide (K⁺ or Na⁺):**
 - Solution and oral tab.
 - ↓ oxidation ↓ release of T4, T3 ? ↓ uptake
 - Can cause allergy.
 - Widely used before thyroid surgeries to ↓ vascularity of the thyroid gland
- **Beta Blockers**
- **Radioactive Iodine**
- **Thyroidectomy**

Treatment of Hyperthyroidism

- **Anti-thyroid drugs.**
- **Iodide (K⁺ or Na⁺):**
- **Beta Blockers:**
 - **Only control the symptoms.**
- **Radioactive Iodine**
- **Thyroidectomy**

Treatment of Hyperthyroidism

- **Anti-thyroid drugs.**
- **Iodide (K⁺ or Na⁺)**
- **Beta Blockers:**
- **Radioactive Iodine:**
 - Higher remission rates , 10% will fail first treatment and require a second dose of ¹³¹I.
 - Cause hypothyroidism, dose dependent
 - Contraindications: pregnancy (absolute), ophthalmopathy (relative) , may cause or worsen this condition.
 - Side effects: Pulmonary fibrosis, Teratogenicity
- **Thyroidectomy**

Grave's Ophthalmopathy



Protrusion of one or both eyes, caused by inflammation of the eye muscles by attacking autoantibodies

Thyroid treatment: Potential drug interactions

- **Drugs that reduce thyroid hormone production**
 - Lithium
 - Iodine-containing medications
 - Amiodarone
- **Drugs that reduce thyroid hormone absorption**
 - Sucralfate
 - Ferrous sulfate
 - Cholestyramine
 - Colestipol
 - Aluminum-containing antacids
 - Calcium products
- **Drugs that increase metabolism of thyroxine**
 - Rifampin
 - Phenobarbital
 - Carbamazepine
 - Warfarin
 - Oral hypoglycemic agents
- **Drugs that displace thyroid hormone from protein binding**
 - Furosemide
 - Mefenamic acid
 - Salicylates