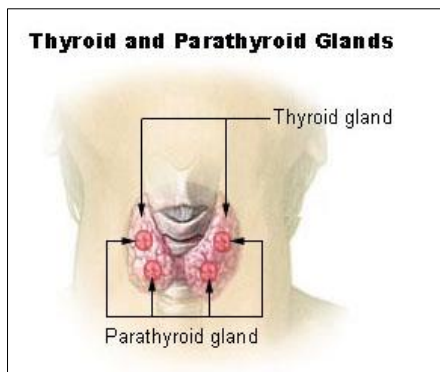


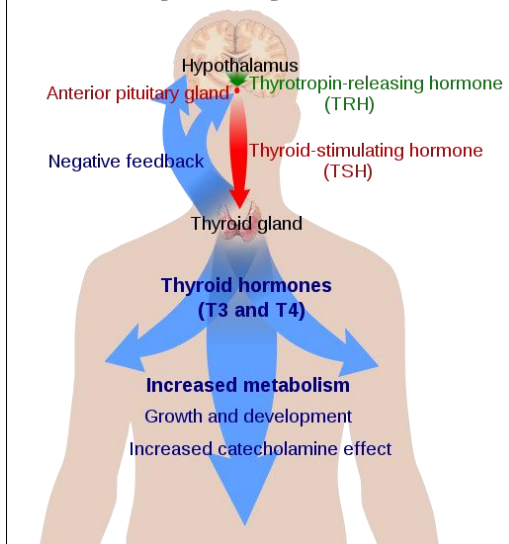
Drugs used for treatment of Thyroid disorders

Anatomical position of thyroid and parathyroid glands



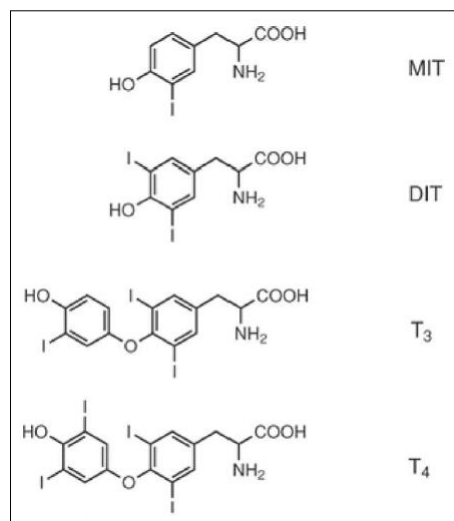
- The thyroid gland is a highly vascular, flat structure located at the upper portion of the trachea, just below the larynx.
- It is composed of two lateral lobes joined by an isthmus across the ventral surface of the trachea.

Thyroid system



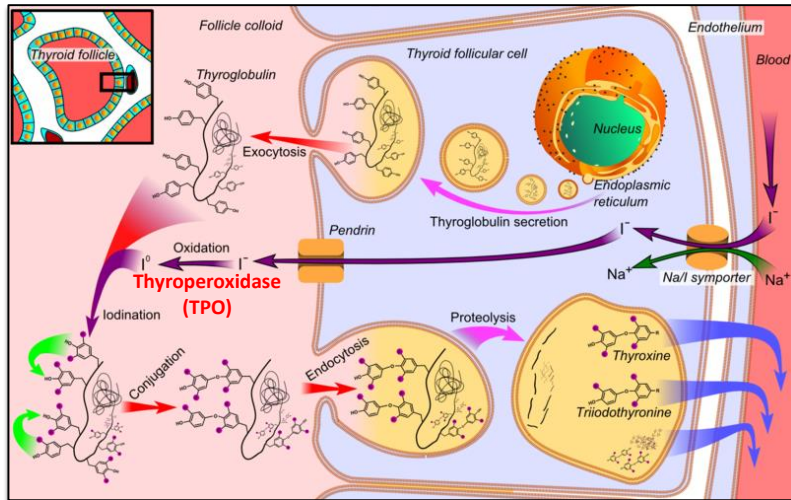
- The gland is the source of two fundamentally different types of hormones, thyroxine (T4) and triiodothyronine (T3) .
- Both hormones are vital for normal growth and development and control essential functions, such as energy metabolism and protein synthesis.

Thyroid hormones



Thyroid hormones

Biosynthesis and secretion



Physiological actions of thyroid hormones

- Exhibit pronounced metabolic control over practically every cell in the body.
- Unlike many other hormones, they exhibit a diffusive effect on the whole organism, not on individual organs.
- By controlling the rate of oxidative cellular processes, these hormones take part in regulation of
 - growth and development (physical, mental) of the organism,
 - formation of bone marrow and bone tissue
 - Increase the BMR
 - metabolism of carbohydrates, fats, and proteins
 - they have an effect on regulation of body temperature,
 - Muscle activity
 - water–electrolyte balance, and
 - Reproduction

Thyroid Disorders

- Hypothyroidism
- Hyperthyroidism

Hypothyroidism

- Hypothyroidism is a disease characterized by a decrease or lack of endogenic thyroid hormone secretion.
- Cretinism
 - Originating in childhood, it can be clinically described as infantile hypothyroidism
- Myxoedema
 - Seen in adults (adult hypothyroidism), which is expressed in a loss of mental or physical ability to work, suppression of metabolic processes in the body, and edema.
- Hypothyroidism
 - Goiter
 - Decrease in metabolic rate
 - Fatigue, mental dullness, lethargy, and inattention.

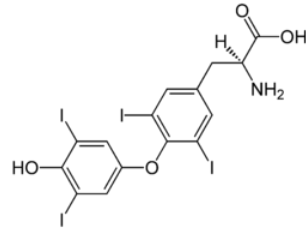
Hypothyroidism

- Symptoms
 - Goiter –
 - An enlarged, palpable thyroid
 - When insufficient thyroid hormone is liberated from the thyroid gland, the breakdown of the thyroid-pituitary-hypothalamic feedback mechanism results in the release of excess TSH and in the formation of a thyroid hypertrophy referred to as a nontoxic goiter
 - The gland enlarges as it tries to take up more iodine, leading to goiter .
 - Goiters most frequently are caused by inadequate intake of dietary iodide in regions not reached by iodide-providing sea mists
 - This condition can be prevented with iodine supplements, and many industrialized countries now iodize salt.
 - Decrease in metabolic rate
 - Fatigue, mental dullness, lethargy, and inattention.

Hypothyroidism

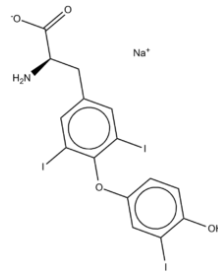
- Treatment – Replacement therapy with T4, T3
 - Since thyroid function cannot be restored, the clinical effect is only visible when using thyroid hormones.
 - Replacement therapy that does not correct the disease itself.
 - Supplementation of T4 with the goal of returning TSH levels to normal.

Levothyroxine (T₄)



- Synthetic form of the thyroid hormone thyroxine
- Marketed as the Levo form
- Typically used to treat hypothyroidism and may also be used to treat goiter
- Effects of this drug depend heavily on dosage.
 - In small doses, levothyroxine exhibits anabolic action.
 - In medium doses, it stimulates growth and development of tissue, metabolism of protein, fats, and carbohydrates, increases functional activity of central nervous and cardiovascular systems, as well as kidneys and liver.
 - In large doses, it slows the thyrotropic activity of the hypophysis and suppresses thyroid gland production.
- Uses
 - Levothyroxine is used for hypothyroidism, myxedema and cretinism.

Levothyronine (T₃)



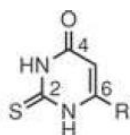
- Costlier
- Short half-life than T₄ hence not preferred
- However it can be used in special situations
 - Severe Myxoedema
 - Myxoedema coma
 - For short term suppression of TSH in patients undergoing surgery of thyroid cancer

Hyperthyroidism

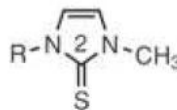
- In a hyperfunctioning of the thyroid gland,
 - secretion of an excess quantity of thyroid hormones leads to a hyperthyroid condition (goiter).
- In this condition, drugs are used that
 - suppress production of thyrotropic hormones in the thyroid gland
 - Thioamides - **propylthiouracil, methylthiouracil, methimazole, carbimazole**
 - drugs that destroy thyroid gland follicles
 - radioactive iodine

Thioamide derivatives

- The most clinically useful thionamides are thioureylenes, which are five- or six-membered heterocyclic derivatives of thiourea and include
 - the thiouracil 6-n-propyl-2- thiouracil (PTU) and
 - the thioimidazole 1-methyl-2-mercaptoimidazole (methimazole) .



Thiouracil; R = H
Methylthiouracil; R = CH₃
Propylthiouracil (PTU); R = n-C₃H₇

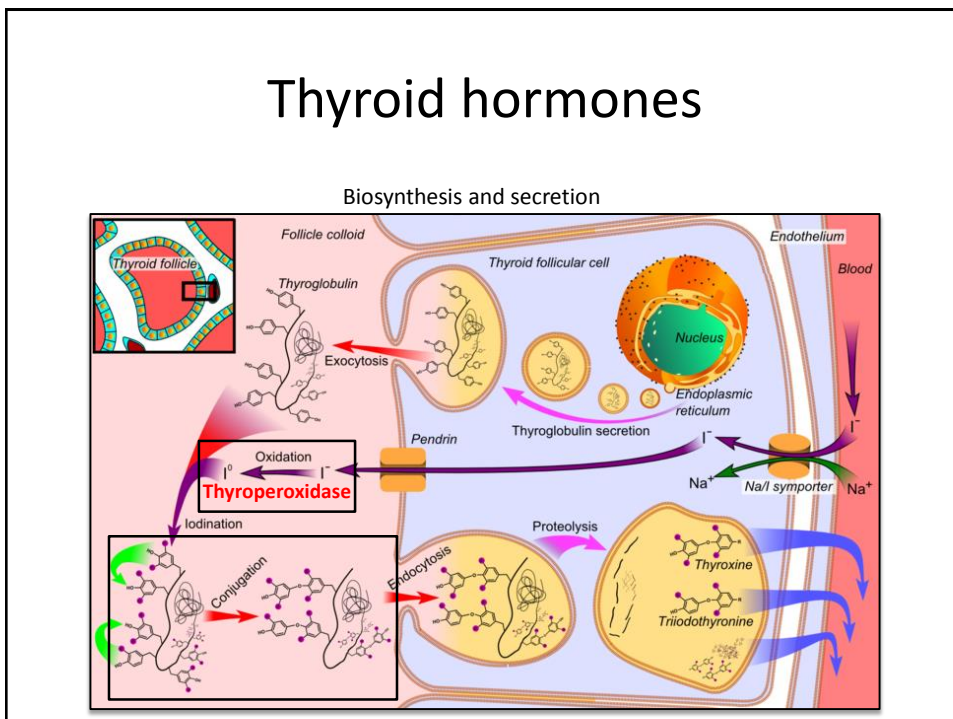


Methimazole (MMI, R = H)
Carbimazole (R = C₂H₅OCO)

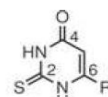
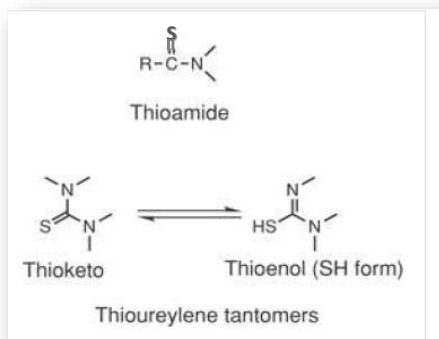
Mechanism of action

- Thioamides are reducing agents.
- They inhibit thyroid hormone synthesis by inhibiting the peroxidase enzymatic system, which catalyzes oxidation of iodide ions and iodine that are consumed in food, which is necessary for iodination of tyrosine derivatives.
- Thus they reduce the concentration of free iodine necessary to react with tyrosine derivatives,
- They can also block oxidative coupling reactions of mono- and diiodotyrosines, which form L-thyroxine and L-triiodothyronine

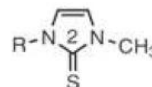
Thyroid hormones



- Chemically, the grouping R-CS-N- as been referred to as thioamide, thionamide, thiocarbamide,
- or if R is N, as it is in thiouracil, PTU, and MMI, it is called a thioureylene. This structure may exist in either the thioketo or thioenol tautomeric forms.
- For tautomerism stabilisation, formation of the thioenol form, one of the nitrogens must be unsubstituted.



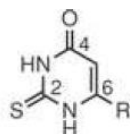
Thiouracil; R = H
Methylthiouracil; R = CH₃
Propylthiouracil (PTU); R = n-C₃H₇



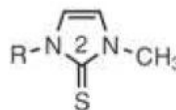
Methimazole(MMI, R = H)
Carbimazole (R = C₂H₅OCO)

SAR

- The C2 thioketo/ thioenol group and an unsubstituted N1 position are essential for activity
- Carbimazole with a substituted N1 position is a prodrug of methimazole
- The enolic hydroxyl group at C4 in PTU and the presence of alkyl group at C6 enhance the inhibitory potency.
- Methimazole has more peroxidase inhibitory activity and is longer -acting than PTU



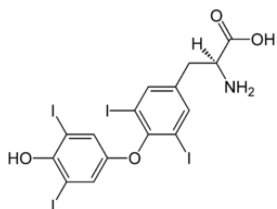
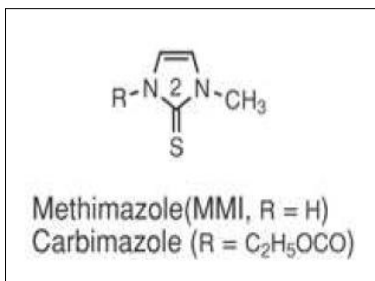
Thiouracil; R = H
Methylthiouracil; R = CH₃
Propylthiouracil (PTU); R = n-C₃H₇



Methimazole(MMI, R = H)
Carbimazole (R = C₂H₅OCO)

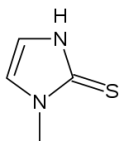
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- Efforts to improve the taste and decrease the rate of release of Methimazole led to the development of Carbimazole
- Carbimazole, the pro-drug derivative of methimazole, gives rise to methimazole in vivo



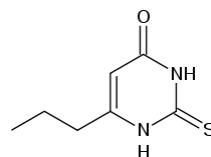
Levothyroxine

(S)-2-Amino-3-[4-(4-hydroxy-3,5- diiodo phenoxy)-3,5-diiodophenyl]propanoic acid



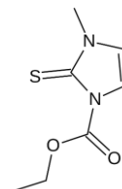
Methimazole

1-methyl-3*H*-imidazole-2-thione



Propylthiouracil

6-propyl-2-sulfanyl pyrimidin-4-one



Carbimazole

Ethyl 3-methyl-2-sulfanylidene-imidazole-1-carboxylate