Anti-thyroid drugs

Thyroid physiology

The thyroid gland produces three main hormones: tri-iodothyronine (T3) and thyroxine (T4-tetra-iodothyronine) and calcitonin (involved in the control of plasma calcium).

*T3 is more potent than T4

*Liothyronine is the synthetic T3 and levothyroxine is synthetic T4

Synthesis and fate of thyroid hormones

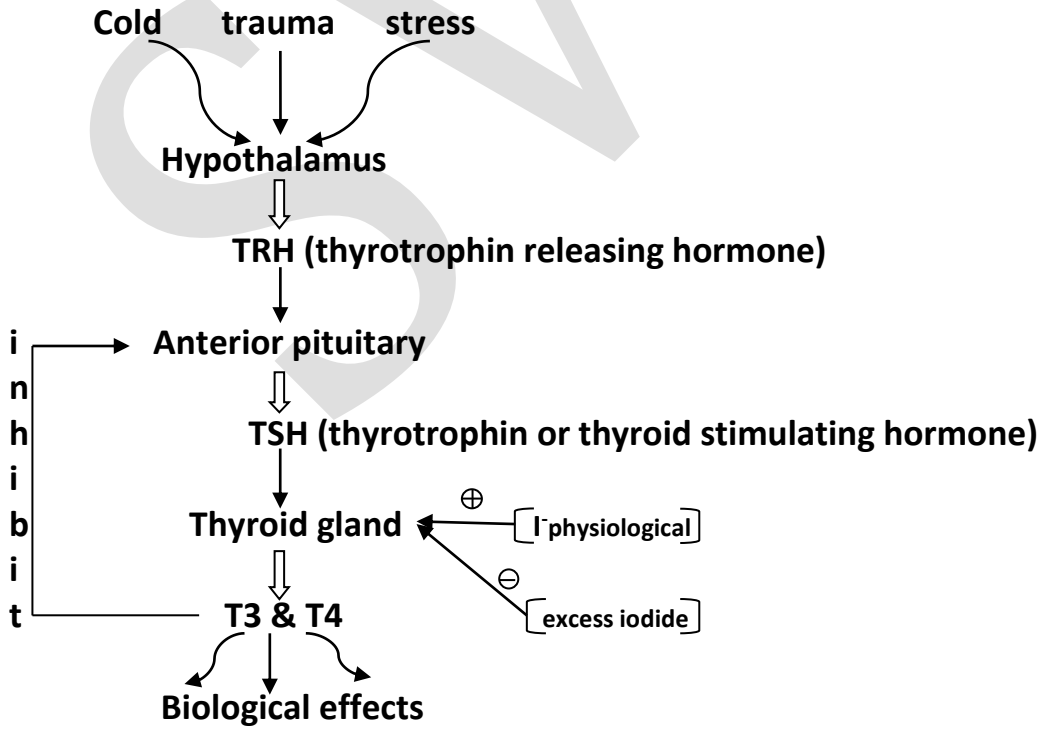
Formation of thyroid hormone begins with:

1. active transport of iodide into thyroid gland
2. oxidation of iodide to iodine (the active form of iodide); which is catalyzed by thyroperoxidase enzyme
3. activated iodine is incorporated into tyrosine residues that are bound to thyroglobulin (a large glycoprotein molecule), resulting in formation of monoiodotyrosine (MIT) and diiodotyrosine(DIT)
4. coupling of iodinated tyrosine molecules takes place.

*coupling of one MIT with DIT ⟶ T3

*coupling of two DIT ⟶ T4

Regulation of thyroid function



Fate Thyroid hormones are released from the thyroid gland by a proteolytic process. The amount of T4 released is greater than the amount of T3. However, much of T4 released undergoes conversion to T3 by enzymes in peripheral tissues.
*About 80% of T3 found in plasma is due to conversion of T4 to T3
*In blood both T3 and T4 are extensively (99.9%) bound to plasma proteins (thyroxine binding globulin TBG and thyroxine binding prealbumin TBPA)
***only the free circulating thyroid hormones produce biological effects**

*Both T3 and T4 are metabolized in liver which is slow, so half lives of these hormones are prolonged, t1/2 of T3 is 1.5 days and t1/2 of T4 s 1 week.

*TSH acts on the thyroid gland causing increase in:
1. Gland size
2. Iodine uptake
3. Synthsis and release of thyroid hormones
*The rising plasma levels of T3 and T4 leads to suppression of TSH release.

Hyperthyroidism (Thyrotoxicosis) either:

1. Diffuse toxic goiter (Grave's disease)
2. Toxic nodular goiter (adenoma)
*The symptoms are due to supra-physiological amounts of thyroid hormones leading to tachycardia, nervousness, tremor, diarrhea, increase in skin temperature and sweating, marked sensitivity to heat (↑BMR), fatigability, increased appetite with weight loss.

Aim of treatment

To reduce excessive secretion of thyroid hormones by:
1. Subtotal thyroidectomy or radioactive iodine (^{131}I) to reduce amount of functioning thyroid tissue
2. Antithyroid drugs to decrease secretion of thyroid hormones
3. Symptomatic treatment with beta-blockers

Anti-thyroid drugs

A. Thionamides (Thiourea derivatives)

Carbimazole, Methimazole & Propylthiouracil

Methimazole is the chief metabolite of carbimazole.

Mechanism of action

1. Block thyroid hormone synthesis by:
   a) preventing oxidation of iodide, so inhibiting incorporation of iodine into tyrosine
   b) prevents iodinated tyrosine from coupling
*Both these effects due to inhibiting thyroperoxidase enzyme
2. Propylthiouracil also acts peripherally to suppress conversion of T4 to T3.

Note: although these drugs prevent thyroid hormone synthesis, they do not destroy existing stores of thyroid hormone, so once therapy begun, it may take 1-2 weeks for existing stores to become depleted.

Therapeutic uses

1. alone in Grave's disease
2. as an adjunct to radiation therapy
3. in preparation for thyroid surgery
4. propylthiouracil for thyrotoxic crisis (by inhibiting hormone synthesis and preventing conversion of T4 to T3).

Adverse effects are relatively rare; however severe adverse effects can occur:

a. Agranulocytosis is the most serious toxicity, usually occurs during first 2 months of therapy. Sore throat and fever may be the earliest symptoms, so patients should be instructed to report these immediately and repeated blood counts should be done.

If agranulocytosis occurs, the drug should be discontinued and treatment with granulocyte-colony stimulating factor may accelerate recovery.

b. Hypothyroidism due to excessive dosing

c. Others rash, nausea, arthralgia, headache, dizziness and parasthesia.

Thionamides in pregnancy & lactation

If a pregnant woman has hyperthyroidism, she should be treated with the smallest possible amount of these drugs because they cross the placenta, overtreatment causes fetal goiter.

*Surgery in the second trimester may be preferred to continued drug therapy.

*They are safe in lactating woman but because of the risk of hepatotoxicity caused by propylthiouracil, carbimazole is preferred.

B. Radioactive iodine (^{131}I)

*Is the first line treatment particularly in USA.

Is concentrated in thyroid gland. Destruction of thyroid tissue is produced primarily by emission of beta particles. Since beta particles have a very limited ability to penetrate any type of physical barrier, these particles do not travel outside the thyroid, so damage to surrounding tissue is minimal.

*Reduction of thyroid function is gradual. Initial effects become apparent in days or weeks. Full effects develop in 2-3 months.

Uses is usually given for middle-aged and elderly patients

1. In Grave's disease
2. In thyroid cancer- high doses are required
3. For diagnosis of a variety of thyroid disorders

Advantages

*Easy administration (orally in solution as sodium ^{131}I, given as one single dose)

*Low cost

*Patients are spared the risks, discomfort and expense of thyroid surgery

*Death due to ^{131}I had never occurred

*No tissue other than thyroid is injured

Disadvantages

* Delayed effect (for 1-2 months)

*Delayed hypothyroidism

*Theoretical risk of thyroid cancer

Contraindications

1. Children-risk of delayed hypothyroidism is higher than in adults
2. Pregnancy-after first trimester, it may damage the immature thyroid
   -during whole pregnancy, it causes generalized developmental harm
3. Breast feeding

C. Iodide products (Non-radioactive) include:

1. Strong iodine solution (lugol's solution)
2. Sodium iodide
3. Potassium iodide

*All have same mechanism of action and similar pharmacological effects.

Lugol's solution

Is a mixture of elemental iodine and potassium iodide

Mechanism of action it suppresses thyroid function by:

1. Decreasing iodine uptake, suppressing both the iodination of tyrosine and coupling of iodinated tyrosine
2. Inhibiting release of thyroid hormone into blood stream

*With long term iodide administration, suppressant effects become weaker, so iodide is rarely used alone to produce thyroid suppression.

Therapeutic uses

1. In preparation for surgery
2. Thyrotoxic crisis
3. As antiseptic
4. As expectorant
5. As contrast media in radiology

Adverse effects

Chronic ingestion of iodine causes iodism characterized by: metallic taste, burning sensation in mouth & throat, soreness of teeth & gums, frontal headache, coryza (nasal inflammation & sneezing), various skin eruptions, excessive salivation with painful salivary gland.

Overdose

Iodine is corrosive and overdose will injure GIT, causing abdominal pain, vomiting & diarrhea.

D. Beta- blockers

β-blockers without intrinsic sympathomimetic effect (ISA) like propranolol, cause clinical improvement of hyperthyroid symptoms but do not alter thyroid hormones level, so they are not used as a sole therapy.

Uses

1. in patients on long wait for effect of antithyroid drugs
2. in preparation for surgery
3. as apart of treatment of acute hyperthyroid crisis