THYROID HORMONES & ANTITHYROID DRUGS

The thyroid secretes 2 types of hormones:

1- Iodine containing amino acids (are important for growth, development and metabolism) and these are: triodothyronine, tetraiodothyronine,( thyroxine)

2- Calcitonin is important in the regulation of calcium level.

BIOSYNTHESIS, TRANSPORT & PERIPHERAL METABOLISM OF THYROID HORMONES:

- The iodine necessary for the synthesis of T3 & T4 is derived from food or iodine supplement. Iodine uptake is an active process. Once taken up by the thyroid gland, iodine undergoes a series of enzymatic reactions that convert it into active hormone.

  1- The 1st step is the transport of the iodine into the gland by intrinsic follicle cell basement membrane protein called sodium/iodine symporter(NIS). This step is inhibited by SCN & CLO$_4^-$

  2- Iodide is oxidized by thyroid peroxidase to iodine.

  3- Iodination of tyrosine residues within the thyroglobulin molecule to form monoiiodotyrosine (MIT) & diodotyrosine (DIT) this process is called iodide organification. Thyroidal peroxidase is transiently blocked by high levels of intrathyroidal iodide & thioamide drugs.

  4- Two molecules of DIT combine within the thyroglobulinto form L-thyroxine (T4)'

  One molecule of MIT & one molecule of DIT combine to form T3

  5- T4, T3, MIT & DIT are released from thyroglobulin by exocytosis & proteolysis of thyroglobulin. The DIT & MIT are deiodinated within the gland & the iodine is reutilized. This process of proteolysis is blocked by high levels of intrathyroidal iodide.

- The ratio of T4 to T3 within the thyroglobulin is 5:1 so that most of the hormone released is thyroxine. Most of circulating T3 in the blood is derived from peripheral metabolism of thyroxine.
TRANSPORT

T3 & T4 in the plasma are reversibly bound to thyroxine binding globulin (TBG) a transport protein in the blood.

PERIPHERAL METABOLISM

The primary pathway of peripheral metabolism is deiodination. Deiodination of T4 may occur by monoiodination of the outer ring producing 3,5,3 triiodothyronine (T3). Alternatively deiodination of the inner ring produces 3,3,5 triiodothyronine (reverse T3 or rT3) which is inactive.

Drugs such as ipodate, beta-blockers & corticosteroids and severe illness or starvation inhibit the 5-deiodinase necessary for the conversion of T4 to T3 resulting in low T3 & high rT3.

CONTROL OF THYROID FUNCTION

- Hypothalamic cells secrete thyrotroin releasing hormone (TRH) into the capillaries of the pituitary portal system. TRH stimulates the synthesis & release of thyroid stimulating hormone (TSH). TSH stimulates an adenylyl cyclase-mediated mechanism in the thyroid gland to increase the synthesis & release of T4 & T3.

- T4 & T3 act in a negative feedback fashion (mechanism) to block the action of TRH on the pituitary gland & on the hypothalamus to inhibit the synthesis & release of TRH. In Grave's disease; lymphocytes secrete a TSH receptor stimulating Ab which binds to the TSH receptor.

- The thyroid gland also regulates its uptake of iodide & thyroid hormone synthesis by intrathyroidal mechanism that are independent of TSH. These mechanisms primarily related to the level of iodine in the blood. High concentration of iodide inhibits iodide organification, and effect that is useful in the treatment of thyroid disease. Inadequate iodine intake results in diffuse enlargement of the thyroid (Goitre)

MECHANISMS OF ACTION OF T4 & T3

T3 is 10 times more potent than T4 and since T4 is converted to T3 in target cells (the liver & kidneys), most of the effect of circulating T4 is probably due to T3.

Thyroid hormone binds to receptors in the nucleus that control the expression of genes responsible for many metabolic processes. These receptors when activated by T3 bind to DNA response elements & control synthesis of RNA which codes for specific proteins that mediate the action of thyroid hormones.
The proteins synthesized differ depending on the tissue involved. These proteins include Na+/K+ ATPase, specific contractile protein in smooth muscles & the heart, enzymes involved in lipid metabolism, important developmental components in the brain ... Etc.

**EFFECTS OF THYROID HORMONE**

- Include normal growth & development of the nervous, skeletal, reproductive systems & control of metabolism of fat, CHO, proteins & also metabolism of drugs.

- Thyroid deprivation in early life results in irreversible mental retardation & dwarfism (congenital cretinism), thyroid hyperactivity results in thyrotoxicosis. Conversely a decrease in thyroid activity results in hypothyroidism (myxedema).

**PHARMACOKINETICS**

- All of the naturally occurring T4 & T3 exist in Levo form (L-isomers), the Dextro form of Thyroxine has only 4% of the biological activity of the L-isomer.

- Thyroxine is well absorbed from the duodenum & ileum when taken orally; oral bioavailability of L-Thyroxine is about 80% absorbed while T3 is almost completely absorbed. T4 & T3 can also be given intravenously.

- In patients with hyperthyroidism, the clearance of T4 & T3 is ↑ & the opposite is true in hypothyroidism. Drugs that induce hepatic microsomal enzymes (e.g. rifampicin phenytoin & Phenobarbital) ↑ the metabolism of T4 & T3 & patients receiving T4 replacement therapy may require modification (↑dosage) to maintain clinical effectiveness.

- If TBC binding sites are increased (this is caused by pregnancy, estrogens, oral contraceptives) there is an initial shift of the hormone from the free to the bond state & α ↓ in the rate of elimination until the normal hormone concentration is restored thus the total & bound hormone will increase but the concentration of free hormone will remain normal. The reverse occurs when TBG sites are ↓
THYROID PREPARATION

- These preparations are synthetic
  1. Levothyroxine (is the best which is T4).
  2. Liothyronine (T3, is faster acting but has shorter half-life & more expensive).
  3. Liotrix (is a mixture of Thyroxine & liothyronine. It is never required).

ANTI-THYROID DRUGS

Reduction of thyroid & hormone effects can be accomplished by agents that interfere with the production of thyroid hormones, by agents that modify the tissue response to thyroid hormones or by glandular destruction with radiation or surgery. The anti-thyroid compounds used clinically include the thioamides, iodides & radioactive iodine.

THIOAMIDES

- Methimazole (carbimazole)
- Propyl thiouracil (PTU)

- These 2 are the major drugs used in the treatment of thyrotoxicosis {Carbimazole converted to methimazole in vivo).
- The most important effect of these drugs is to block iodination of tyrosine. Also these drugs may block the coupling of DIT & MIT.
- These drugs are given by oral route. Since the synthesis of thyroid hormones rather than release is inhibited, the onset of activity of these drugs is usually slow requiring 3-4 weeks for full effect.
<table>
<thead>
<tr>
<th>Carbimazole</th>
<th>Propyl thiouracil (PTU)</th>
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<tbody>
<tr>
<td>1- More potent given in a single daily dose.</td>
<td>Does is 10 times that of Carbimazole given every 6-8 hrs.</td>
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<tr>
<td>2-Completely absorbed &amp; readily accumulated in thyroid gland.</td>
<td>Rapidly absorbed with a bioavailability of 50-80%</td>
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<tr>
<td>3-Excreted in urine but slower than PTU.</td>
<td>Excreted in urine within 24 hrs</td>
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<td>4-Has some immunosuppressive action leading to decrease in serum TSH receptor antibodies.</td>
<td>No such effect</td>
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<tr>
<td>5-Has little effect on conversion of T4 to T3.</td>
<td>It inhibits the peripheral conversion of T4 to T3•</td>
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<tr>
<td>6-Crosses placenta.</td>
<td>Crosses placenta less readily Preferable in pregnancy</td>
</tr>
<tr>
<td>7-Sufficient quantity is excreted in breast milk.</td>
<td>Not excreted in sufficient quantities to preclude breast feeding.</td>
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**ADVERSE EFFECTS OF THIOAMIDES** occur in 3-12% of treated patients.

Most reactions occur early. The most common adverse effect is maculopapular pruritic rash, sometimes accompanied by fever.

**RARE ADVERSE EFFECTS INCLUDE:**

1. Urticarial rash.
2. Vasculitis.
3. Arthralgia.
4. A lupus like reaction
5. Cholestatic jaundice.
7. Hyperprothrombinemia, aplastic anemia & agranulocytosis the most dangerous complication)
8. All these adverse effects are reversible.
IODIDE SALTS AND IODINE:

- Iodide salts inhibit organification (iodination of tyrosine) and thyroid hormone release. These salts also decrease the size & vascularity of the hyperplastic thyroid 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. However the effect is transient because the thyroid gland escapes from iodide block after several weeks of treatment.

- Iodide salts are used in thyroid storm (severe thyrotoxicosis) & to prepare the patient for surgical resections of the hyperactive thyroid. The usual forms of this drug are lugol's solution (iodine & potassium iodide) and saturated solution of potassium iodide.

IODINATED CONTRAST MEDIA (IPODATE):

- It suppresses the conversion of T4 to T3 via 5 deiodinase in the liver, kidney and other peripheral tissues. Inhibition of hormone release from thyroid gland may also play a part.

- Ipodate has proved very useful in rapidly reducing T3 concentration in thyrotoxicosis (in thyroid storm)

RADIOACTIVE IODINE 1\( ^{131} \) (ADMINISTERED ORALLY)

- It is taken up & concentrated in the thyroid gland. A dose large enough to severely damage the gland can be given without endangering other tissues.

An effective dose of \( 1^{131} \) (single) can produce permanent cure of thyrotoxicosis without surgery. \( 1^{131} \) shouldn't be used in pregnancy or nursing mother.

β-blockers:

Propranolol is used as an effective therapeutic adjuvant in the management of thyrotoxicosis. Since many of these symptoms mimic those associated with sympathetic stimulation (particularly tachycardia) propranolol inhibits 5-deiodinase (the conversion of T4 to T3).
Thyroid gland

Thyroglobulin

Iodides

MIT-DIT

T3, T4

Protease

T3, T3 blood

Peripheral tissue

T4, T3

Iopodate, Beta blockers & corticosteroids

Transport

Iodide thioamides

SCN−

ClO₄⁻