Thyroid Disorder

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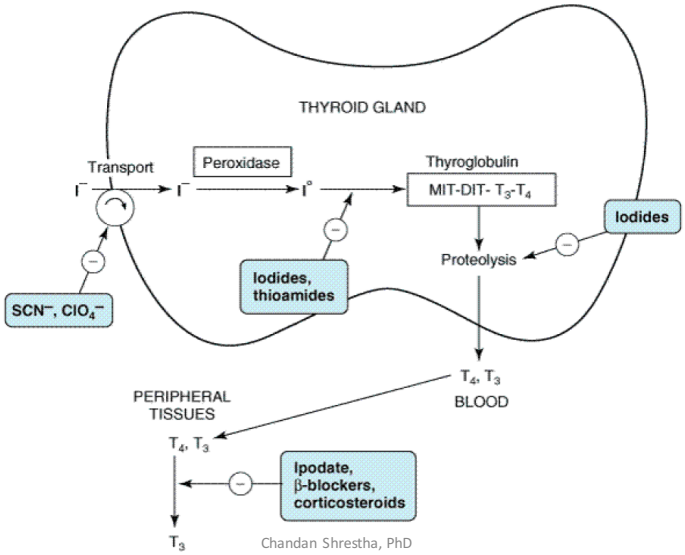
Introduction

- Thyroid gland is a butterfly shaped gland located at the base of the neck and trapped around the lateral sides of the trachea. The thyroid gland produces three major hormones-
  1. Thyroxine (T4)
  2. Triiodothyronine (T3)
  3. Calcitonin
- Triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine) normalize growth and development, body temperature, and energy levels. These hormones contain 59% and 65% (respectively) of iodine as an essential part of the molecule.
- Calcitonin, the second type of thyroid hormone, is important in the regulation of calcium metabolism

Biosynthesis of thyroid hormones

1. Iodide uptake
2. Oxidation and Iodination
3. Coupling
4. Storage and release
5. Peripheral conversion of T4 to T3

Biosynthesis of thyroid hormones



- The first step is the transport of iodide into the thyroid gland by an intrinsic follicle cell basement membrane protein called the sodium/iodide symporter (NIS). This can be inhibited by such anions as SCN– and ClO4.
- Iodide is then oxidized by thyroidal peroxidase to iodine, in which form it rapidly iodinates tyrosine residues within the thyroglobulin molecule to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). This process is called iodide organification. Thyroidal peroxidase is transiently blocked by high levels of intrathyroidal iodide and blocked more persistently by thioamide drugs.

- Two molecules of DIT combine within the thyroglobulin molecule to form L-thyroxine (T4). One molecule of MIT and one molecule of DIT combine to form T3.
- Thyroxine, T3, MIT, and DIT are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin at the apical colloid border. The MIT and DIT are deiodinated within the gland, and the iodine is reutilized. This process of proteolysis is also blocked by high levels of intrathyroidal iodide.
- The ratio of T4 to T3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine.
- Most of the T3 circulating in the blood is derived from peripheral metabolism of thyroxine.

Regulation of secretion

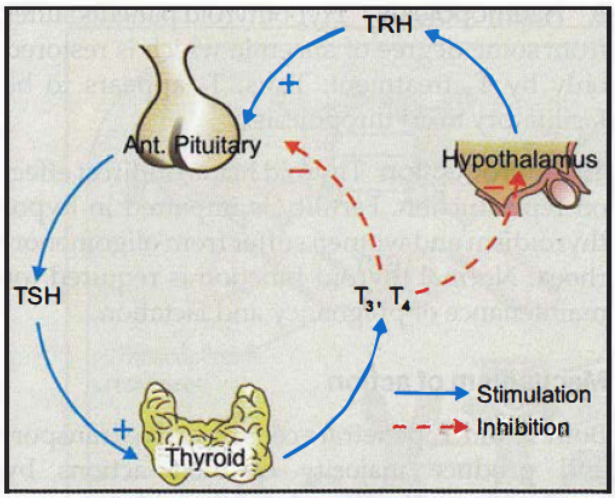


Fig. 18.3: Regulation of thyroid function
TSH—Thyroid stimulating hormone; TRH—Thyrotropin releasing hormone; T_3—Triiodothyronine; T_4—Thyroxine.

MOA

- Free form of T4 and T3 enter cell by diffusion or by active transport.
- T4 is converted into T3 with the cell
- T3 enter the nucleus and binds to specific T3 receptor protein (Thyroid hormone receptor element)→ regulate gene transcription.

Action

Growth and development
T4 and T3 regulates optimal growth and development of all body tissues.

Metabolic effect
Marked effect on lipid, carbohydrate and protein metabolism
Lipid- enhance lipolysis
Carbohydrate- increase carbohydrate metabolism
Protein- increase protein synthesis

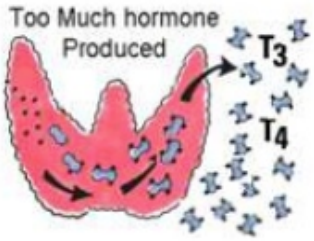
Calorigenesis
Increase basal metabolic rate (BMR)
Mainly maintain body temperature (increase body temperature)

CVS- increase HR, contractility and CO

Hyperthyroidism

Hyperthyroidism

- **Hyperthyroidism** is the condition that occurs due to excessive production of thyroid hormone by the thyroid gland.
- Refers to the clinical manisfestation associated with elevation in serum level of T3 and T4. Or Excessive secretion of thyroid hormones.



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Hyperthyroidism

Causes

Major causes: Graves disease, toxic nodular goiter

others

Medication: lithium , amiodarone

stress;; pregnancy, infection , surgery

Excess iodine intake

Sign and symptoms

Nervousness, Restlessness, tremors, heat intolerance, tiredness, Increased sweating, Fatigue, Weakness, Muscle cramp, Weight loss, Insomnia, weight loss, diarrhea

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Diagnosis

- Thyroid function test (T3, T4 and TSH)
- USG of neck
- MRI of the thyroid gland

Drugs used in the treatment of thyrotoxicosis

1. Inhibit hormone synthesis (antithyroid drugs): Propylthiouracil, methimazole, Carbimazole
2. Inhibit iodide trapping (Ionic Inhibitor): Thiocyanates, Perchlorates, Nitrates
3. Inhibit hormone release: Iodine and Iodide
4. Destroy thyroid tissue: Radioactive iodide (^{131}I, ^{125}I, ^{123}I)
5. Inhibit peripheral conversion of T4 to T3: beta blocker, Ipodate

Antithyroid drugs

- Propylthiouracil and methimazole are the major drugs for the treatment of thyrotoxicosis.
- Methimazole is 10 times more potent than propylthiouracil.

Antithyroid drugs

MOA

- Prevent hormone synthesis by inhibiting the thyroid peroxidase catalyzed reaction (ie. Oxidation of iodide) and thereby –

  i) inhibit iodination of tyrosine residues in thyroglobulin and

  ii) inhibit coupling of iodotyrosine residue to form T3 and T4.

- Propylthiouracil and (to much lesser extent) methimazole inhibit the peripheral deiodination of T4 to T3.

Antithyroid drugs

A/E

- GI intolerance, skin rashes and joint pain
- A less common but serious A/E is agranulocytosis (1 in 500~1000 cases)

Uses: thyrotoxicosis in both grave's disease and toxic nodular goiter

C/I: hypersensitivity, pregnancy and nursing mother

Ionic inhibitor

- Some monovalent anions can block the uptake of iodide by the gland through competitive inhibition of the iodide transport mechanism. Therefore, T3 and T4 can not be synthesized.
- They are toxic and not used now.

1. Thiocyanates (-SCN): can cause liver, kidney, bone marrow and brain toxicity.
2. Perchlorates ($-ClO_4$): produce rashes, fever, aplastic anaemia, agranulocytosis.
3. Nitrates ($-NO_3$): are weak drugs, can induce methemoglobinaemia and vascular effects.

Iodine and Iodide

- Iodine is a constituent of thyroid hormones and is fasted acting thyroid inhibitor.
- Iodine is reduced to iodide in intestine.
- Iodide inhibit organification of iodine and hormone release and decrease the size and vascularity of the hyperplastic gland.

Iodine and Iodide

Uses

- Preoperative preparation for thyroidectomy: generally given for 10 days just preceding surgery. The aim is to make the gland firm, less vascular and easier to operate on.
- Thyroid storm - is a rare but severe and potentially life-threatening complication of hyperthyroidism
- Prophylaxis of endemic goiter
- Antiseptic

A/E

Acute reaction: swelling of lips, eyelids, fever, joint pain

Chronic reaction: inflammation of mucus membrane, salivation, lacrimation, rhinorrhea

Radioactive Iodine

- The stable isotope of iodine is ^{127}I.
- Its radioactive isotopes of medicinal importance are-
  ^{131}I: half-life of 8 days; most commonly used
  ^{125}I: half-life of 13 days
  ^{123}I: half-life of 60 days
- ^{131}I is the only isotopes used for treatment of thyrotoxicosis.
- Excellent method of destroying overactive thyroid tissue.
- Absorbed rapidly, concentrated in thyroid→emits beta radiation destruction of thyroid glands.

C/I: pregnant women and nursing mothers

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Hypothyroidism

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Hypothyroidism

- Result from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body function
- It can occur with or without thyroid enlargement (goiter)
- The laboratory diagnosis- reduces T3, T4 but increased serum TSH

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Causes

A. Primary

- Hashimoto's thyroiditis
  - Autoimmune disease in which thyroid gland is attacked by a variety of cell and Ab mediated immune
  - Hakura hashimoto in 1912
- Over use of antithyroid drugs
- Iodine deficiency
- Radioactive iodide
- Post thyroidectomy

B. Secondary

Hypothalamic disease
Pituitary disease

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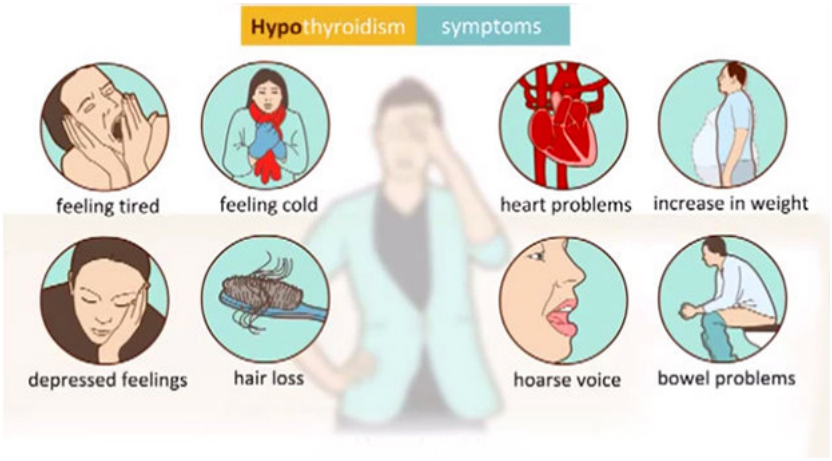

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Hypothyroidism

Drug used in hypothyroidism

- TH replacement therapy: Thyroid hormone preparations includes synthetic preparations of ***T4 (Levo-thyroxine), T3 (Liothyronine)***

  T4 (L-thyroxin) is preferred. T3 is rapidly metabolized and has rapid effect.

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Levo-thyroxine

Indication

- Hypothyroidism
- myxodema coma: It is an emergency; characterized by progressive mental deterioration due to acute hypothyroidism: carries significant mortality.
- Critinism: retarded physical and mental growth due to untreated congenital deficiency of TH.

A/E: usually seen at high dose

- Nervousness, insomnia, chest pain, palpitation, muscle cramp, diarrhea, vomiting, tremor, excessive loss of weight, sweating

C/I: cardiovascular disorder, nursing mother, hypersensitivity, thryrotoxicosis, adrenal insufficiency.