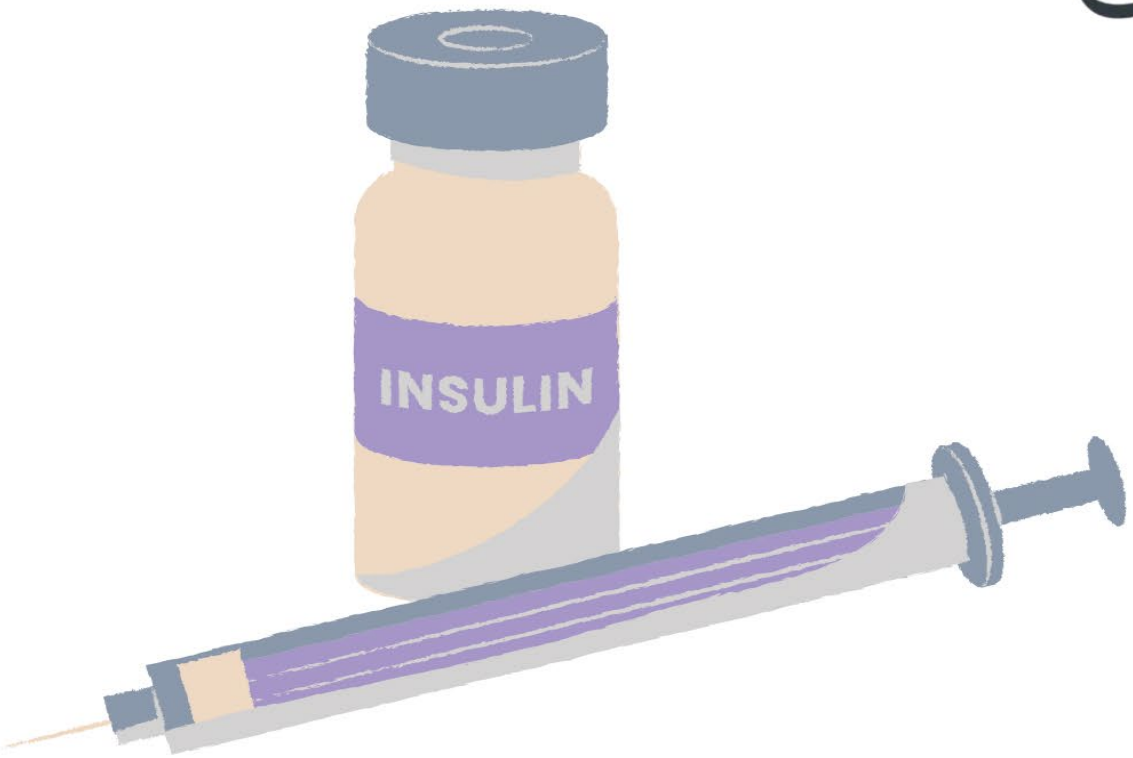
Endocrine system 4

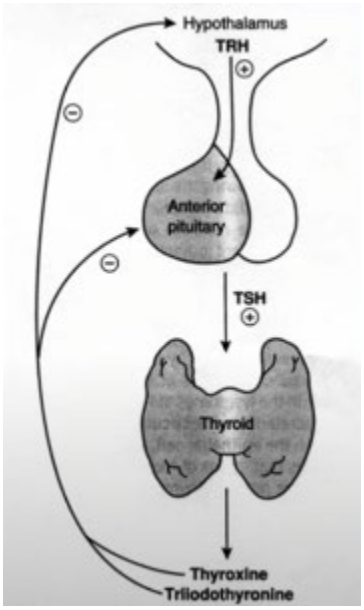
Pharmacology

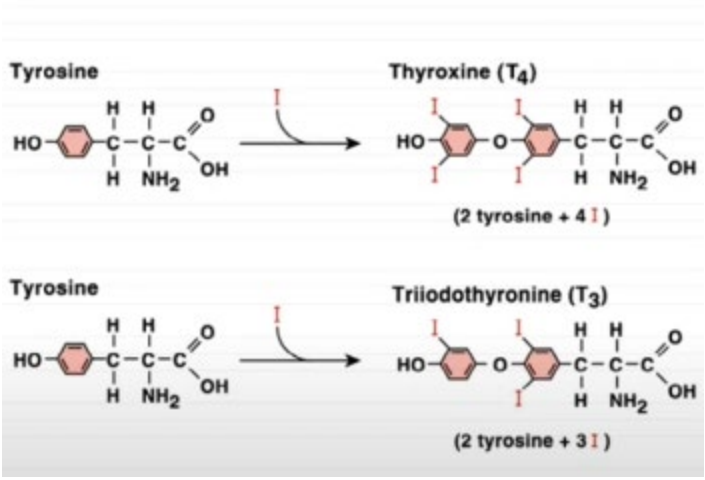


Writer: Ahmad AlHurani
Corrector: Hana Arikat
Doctor: Suheil Zmeili

Thyroid gland hormones

Thyroid hormones are under regulation by the hypothalamus, the hormone TRH reaches the anterior pituitary and stimulates the synthesis and release of TSH, which in turn passes through the blood to the thyroid gland to then interact with it by binding to cell membrane receptors leading to increased synthesis and release of thyroid hormones, T3+T4 then negatively feedback at the level of both, the pituitary and the hypothalamus.





Thyroid hormones are iodinated forms of the amino acid Tyrosine, and in the image above you can see the chemical structure of both.

T4 has 2 tyrosine's with 4 iodides, therefore it's Tetraiodothyronine aka (Thyroxine).

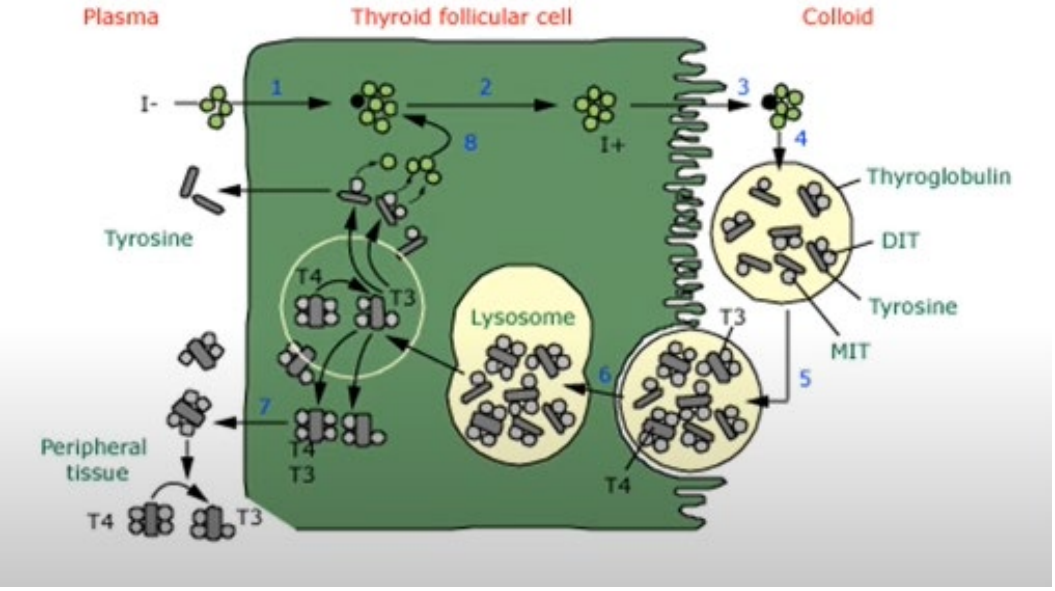
T3 has 2 tyrosine's with 3 iodides, therefore it's triiodothyronine.

These hormones are synthesized in the follicles of the thyroid gland.

Iodide in the body is only used for thyroid hormones synthesis, and it's essential for their synthesis.

1) Iodide is up taken by thyroid follicles.
2) Iodide will be oxidized to iodine.
3) These follicles contain a storage protein known as thyroglobulin, which contains tyrosine residues.
4) An iodination reaction will happen, in which iodine will be added to the tyrosine residues present on the thyroglobulin.
5) Now we formed monoiodotyrosine, if we added 2 iodine's we will form diiodotyrosine.
6) Following that, we have a combination reaction, where 1 monoiodotyrosine combines with 1 diiodotyrosine to form T3.
7) If 2 diiodotyrosine combine, this forms T4

8) Now, Thyroglobulin is usually hydrolyzed by enzymes, to form the free T3, T4, and even some monoiodotyrosine/diiodotyrosine
9) T3+T4 are released from the thyroid follicles, and once they reach the peripheral tissues, most of the T4 is converted to T3 by deiodinase enzymes where there's loss of 1 iodine as if we're saying that the effect of thyroid hormones is mainly due to T3, however T4 is synthesized in excess inside the follicles with a ratio of 4:1, (80% of T3 is formed by deiodination of T4)
10) Thyroid hormones travel in blood while bound to a specific thyroxine binding globulin (TBG) (Mainly, it also binds to albumin & pre-albumin).



-T3 is 3-5 times more active than free T4, so it's much more potent.
-T4 binds to proteins more than T3, where 99.7% of T4 are bound, 99.5% of T3 are bound.
-T4 has a longer half-life, where t1/2 of T4 = 1 week | t1/2 of T3 = 1 day only
-The oxidation, iodination, and coupling reactions are catalyzed by iodine peroxidase/ Thyroid peroxidase enzymes.
Lysosomal enzymes hydrolyze thyroglobulin.

Sources of iodide include:
1- Iodized salt
2- Iodinated bread
3- Dairy products
The human body requires a daily intake of 75 micrograms of iodide, that is about 10g iodized salt, and nowadays, we don't have reported cases of hypothyroidism due to iodine deficiency because it's added to our salts.

Thyroid hormones mechanism of action:

-Thyroxine reaches target cells by the aid of the carrier protein.

-Thyroxine easily passes cell membranes (It's highly lipophilic).

-As we mentioned, most of T4 is converted into T3 in target cells, so ONLY the T3 form enters the nucleus and binds nuclear receptor protein.

-The hormone-receptor complex binds specific response elements on DNA leading to a direct effect on the level of transcription.

-The mRNA produced then codes for specific proteins that mediate the effects of thyroid hormones.

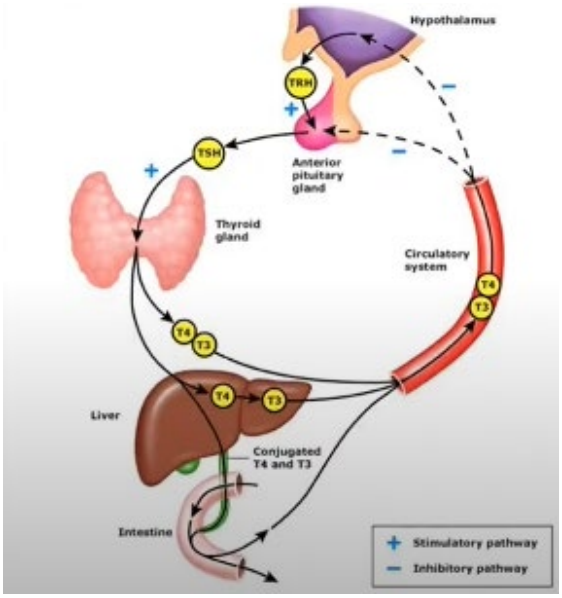
General effects of thyroid hormones:

-Promote growth & development (essential for growth in childhood)

-Calorigenic effect, as they:

1) Increase basal metabolic rate (BMR)
2) Increase O2 consumption
3) Increase general metabolism
4) Increase carbohydrate metabolism (CHO metabolism)
5) Increase lipolysis (lipid breakdown)
6) Decrease cholesterol blood levels
7) Increase beta-adrenergic receptors in most tissues (particularly the cardiovascular system, especially the heart)
8) Increase GI tract motility.

This slide demonstrates the regulation of T3, T4 synthesis and release by the thyroid gland and their metabolism, as they're mainly metabolized by the liver through conjugation.



Disorders affecting the thyroid gland are either deficiency/excess production of thyroid hormones, so starting with deficiency disorders which are more common:

Hypothyroidism:

Leads to:
In children: Cretinism
In adults: Myxedema

Causes of Hypothyroidism include:
1) Surgical removal of thyroid gland, (removed to manage hyperthyroidism/cancer of the thyroid) (After thyroidectomy, a patient has to remain on thyroxine replacement therapy for the rest of his life, so if that patient doesn't follow the prescription or even stops it, that will cause hypothyroidism).
2) Thyroiditis, which could be due to:
- Hashimoto's = chronic lymphocytic thyroiditis (an AI inflammatory disease-causing atrophy of thyroid.
- Infectious thyroiditis
- Transient or subacute thyroiditis
- postpartum hemorrhage
3) Severe deficiency or excess of iodine (discussed below-page 8)
4) Severe deficiency of one or more of the synthesis enzymes
5) Severe pituitary (secondary) or hypothalamic (tertiary) dysfunction
6) Drug induced hypothyroidism (By anti-thyroid drugs)

Hypothyroidism symptoms include:

Cold intolerance, lethargy, constipation, slowing of mental function and motor activity, weight gain despite decreased appetite, abnormal menses, dry/thick skin, hair loss, hoarse voice.
Stroke volume and heart rate decrease, especially in adults where they complain of non-pitting edema (when you put pressure on it, it doesn't move), unlike the edema of heart failure or liver failure.
And of course as we said before, the therapy for any deficiency of hormones is HRT or hormonal replacement therapy, where we replace what's deficient.

Thyroid hormones preparations:

1) Thyroid USP, - Bovine, Ovine, Porcine - of animal source (sheep, cows, pigs), where thyroid gland of animals is taken and dried to make tablets out of them, and they are effective orally.

Allergic reactions are frequent, as such preparation are not that clean, because they take the whole gland to dry it and make those tablets.
USP here is an abbreviation for united states pharmacopeia, and we mean by adding it next to "thyroid" is the usage of such techniques according to the regulations of united states pharmacopeia, or we can say BP, British pharmacopeia.
because we need this technique to be highly regulated as the iodide content of such tablets shouldn't exceed a specific percentage, as iodine is very dangerous element, and it could cause severe allergic reactions, and before the administration of iodine for whatever reason, one has to test for hypersensitivity reaction (Lewis triple response) as we mentioned before.
The percentage of iodine content should be around 0.3% of the weight of tablet.

2) Thyroid extract (Thyroglobulin), taken orally, a little bit cleaner compared to thyroid USP, what they do is they extract thyroglobulin which has T3, T4 on the polypeptide of its chain (Thyroglobulin is taken from animals).
Less frequent allergic reactions compared to thyroid USP.

-As the structure of thyroid hormones is pretty simple, we can synthesize them.

3) L-thyroxine sodium; synthetic T4, orally.

4) Liothyronine sodium, synthetic T3, orally and I.V

5) Liotrix, synthetic T4 & T3 in a 4:1 ratio (as they're present in the thyroid) , orally

-All of these have a t1/2 of 1 week except Liothyronine (synthetic T3) which has a t1/2 of 1 day, just like T3 itself.
-Animal preparations are cheaper but have more allergic reactions.
(Synthetic preparations are not that expensive too)
-Most widely used preparation is synthetic T4, sodium L-thyroxine.
-In severe acute cases of hypothyroidism, we can use the I.V preparation of T3

Clinical uses of these Thyroid hormones: - HRT -

1) Hypothyroidism
2) Thyroid cancer (we can treat these by thyroid hormones, which shows how important negative feedback mechanisms are, as these cancers depend on TSH for their growth, giving T3&T4 from outside inhibits TSH dependent thyroid cancers)
3) Weight reduction (this is a form of abuse, in the past they used to use it, since thyroid hormones decrease blood cholesterol levels).

D-isomer compared to L-isomer of thyroid hormones:

-Both D and L are equipotent (have the same potency) to their effect on blood cholesterol levels.
-L has 4 times the potency with respect to other effects.
-So, in the past they used D isomer to manage hypercholesterolemia, but nowadays, we have much better options and they're no longer used, As even using the D isomer with ¼ the potency on CVS still will have a burden on the heart

Side effects to thyroid hormones:

-Hyperthyroidism
-Allergic reactions (more frequent with animal preparations)

Hyperthyroidism - thyrotoxicosis:

Grave's disease includes these manifestations:
1) Hyperthyroidism
2) Hyperplasia of thyroid
3) Exophthalmos

Hyperthyroidism symptoms:

Heat intolerance, nervousness, irritability, emotional instability, fatigue, weight loss but increased food ingestion and appetite, increased bowel movements (diarrhea), abnormal menses, Tachycardia, atrial arrythmias (atrial fibrillation).
-In hyperthyroidism we have over activity of sympathetic nervous system, thus increasing the beta receptors activity especially in the CVS.

Treatment of hyperthyroidism:

-Propranolol, a beta blocker, #1 drug used to treat manifestations of hyperthyroidism, and it controls all the manifestation of the over activity of the sympathetic nervous system. (Propranolol has no antithyroid activity)
-Antithyroid drugs, discussed below
-Surgery, removal of the thyroid gland, subtotal thyroidectomy is used to preserve at least 1 parathyroid gland, as removing the thyroid without parathyroid is very difficult (parathyroid glands are embedded inside the thyroid). But as the left-over thyroid tissue can still cause hyperthyroidism, we just remove the whole gland.

Antithyroid drugs: (Thiourea derivatives (Thionamides))

1) Methimazole
2) Carbimazole (A pro-drug) that's converted to methimazole
3) Propylthiouracil

Potency wise:
Methimazole > Carbimazole > Propylthiouracil
Mechanism of action: (They have **no effect on thyroid hormones release** from the glands)
-They inhibit thyroid peroxidase enzyme, and interfere with oxidation, iodination, and coupling reactions.
-Propylthiouracil has an **EXTRA** mechanism which is that it inhibits peripheral deiodination of T4 (prevents T4 conversion to T3).
-all effective orally

Side effects to thionamides:

-Allergy
-Hepatic dysfunction
-Agranulocytosis (also an absolute contraindication to their use)
-Methimazole is teratogenic (Causes a rare condition (Aplasia cutis congenita) which causes loss of part of the skin especially the scalp)
**Propylthiouracil is not teratogenic (It's the drug of choice to manage hyperthyroidism during pregnancy.

Disadvantages of thionamides:

-Delayed onset of actions (12-18hrs) (As they work by inhibiting the synthesis not the release, not effective on managing the acute cases)
-Prolonged treatment required (12-18 months)
-Side effects
-High relapse rate (Once you stop the drug, hyperthyroidism reoccurs) (patient must be kept on it for life)

Iodide potassium/sodium:

-available as solution/oral tablets
-MOA:
Inhibits oxidation, Release of T3, T4 (so it acts on both, synthesis, and release) by:
The Wolff-Chaikoff effect: an autoregulatory phenomenon, whereby a large amount of ingested iodine inhibits thyroid hormone synthesis within the follicular cells)
-Major side effects:
1) Allergy (as we said we must test for iodide hypersensitivity)
2) Widely used before thyroid surgeries to inhibit vascularity of the thyroid gland

Radioactive iodine=RAI (^{131}I):

-given as solutions, capsules.
-used as a diagnostic tool when given in **small doses,** this dose will be up taken by the thyroid, and you'll see radioactivity in the neck, to assess whether the thyroid gland is functioning or not.
-Treatment and management of hyperthyroidism and grave's disease when given in **Intermediate doses.**
-Treatment of thyroid cancer in **large doses** and it's efficient

- In the US, over 60% of endocrinologists select radioiodine as first-line therapy for grave's disease.
- It is the preferred therapy for women desiring pregnancy soon. But a woman must wait 4-6 months after stopping RAI therapy, before conceiving.
  (RAI is very teratogenic)

- Advantages: higher remission rates – 10% will fail first treatment and require a second dose of ^{131}**I**
- Disadvantages: hypothyroidism – but it's dose dependent
- Contraindications: pregnancy (absolute contraindication), ophthalmopathy (relative RAI therapy may cause/worsen this condition)

Side effects of RAI:
-Pulmonary fibrosis (may appear 5-6 years after stopping RAI therapy!)
-Teratogenicity and carcinogenicity

Lithium carbonate:
-Oral and S.R tablets (Sustained release)
-Similar MOA to iodide (remember, inhibition of oxidation and release of thyroid hormones)
-Narrow therapeutic window (accurate dosing required)
-It's the **drug of choice** to treat **manic depressive psychosis** (Changing in between schizophrenia and depression)

Side effects of Lithium carbonate:
Nausea, diarrhea, drowsiness, blurred vision, ataxia, tinnitus, diabetes insipidus.

Iodinated contrast media:
like: Ipodate
-Given orally
-Contain iodine (so it inhibits oxidation and release), and in addition to that mechanism, it causes inhibition of peripheral conversion of T4 to T3.
-Similar side effects to iodide, which are mainly **allergic reactions.**

You'll figure it out, you always do