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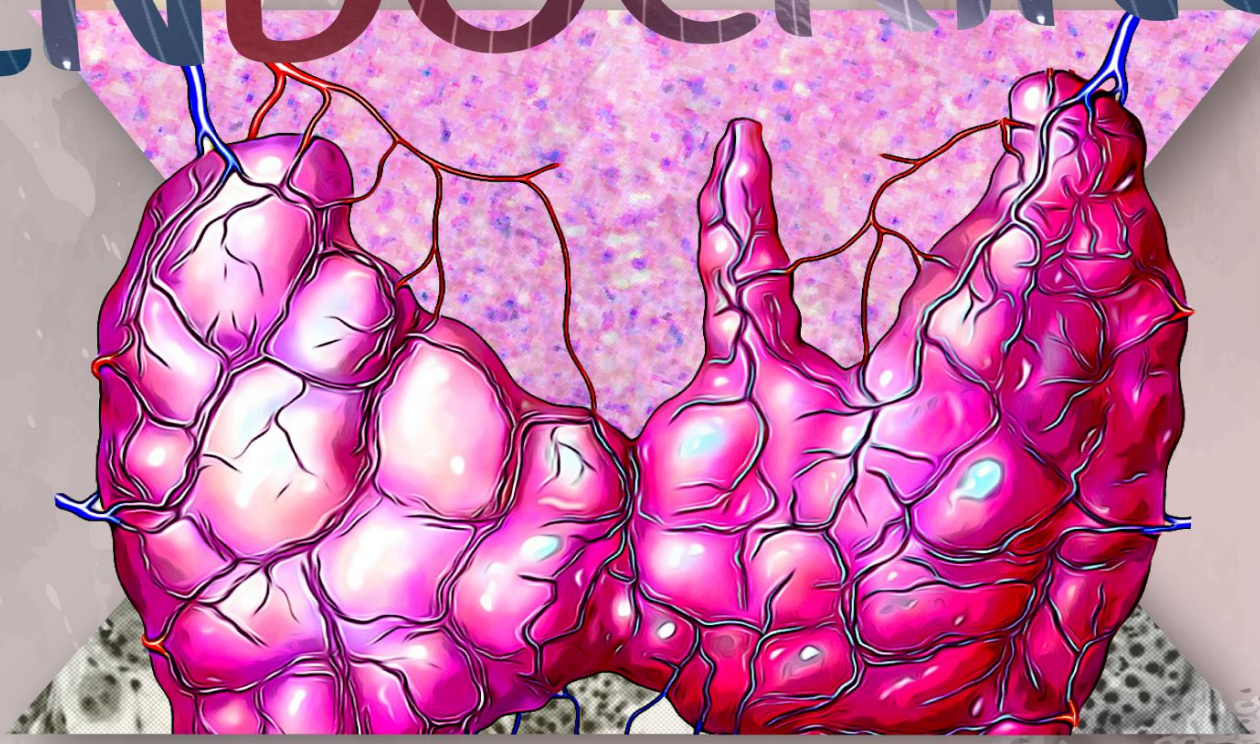

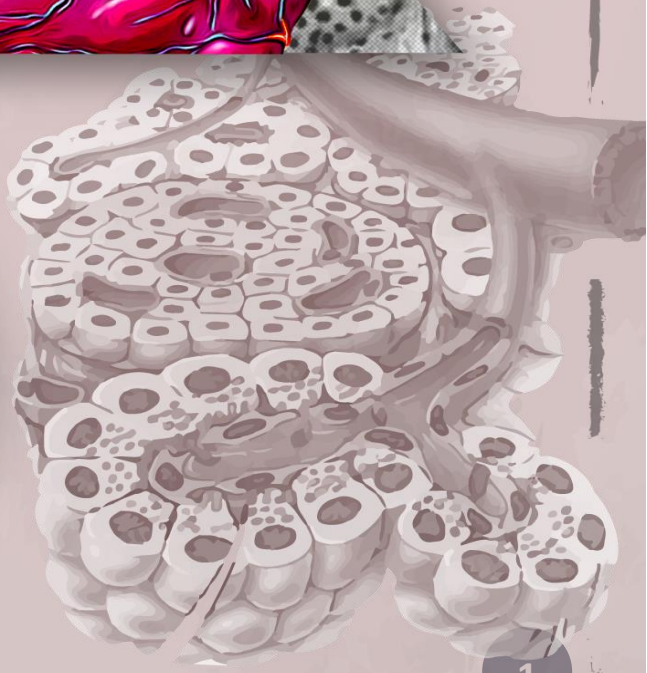

SUBJECT: Pharmacology

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CORRECTED BY: Sarah Jaar

DOCTOR: Malik

Hypothyroids

Today , we will talk about the thyroid hormones and gland , which is the store of iodine within our body. The hormones that are **highly composed of iodine are T3/T4**

RECAP FOR PHYSIOLOGY

Remember that T3/T4 are under the control of anterior pituitary gland which releases **TSH (stimulated by TRH from the hypothalamus)**; as usual there is something that **induces and reduces** the release of TRH :

Inducing factors:

1- Cold
2- Acute psychosis
3- Circadian and pulsation rhythms

Reducing factor:

*Severe stress, then the release of T3/T4 will be inhibited through the inhibition of the hypothalamus then anterior pituitary gland until reaching the thyroid hormones.

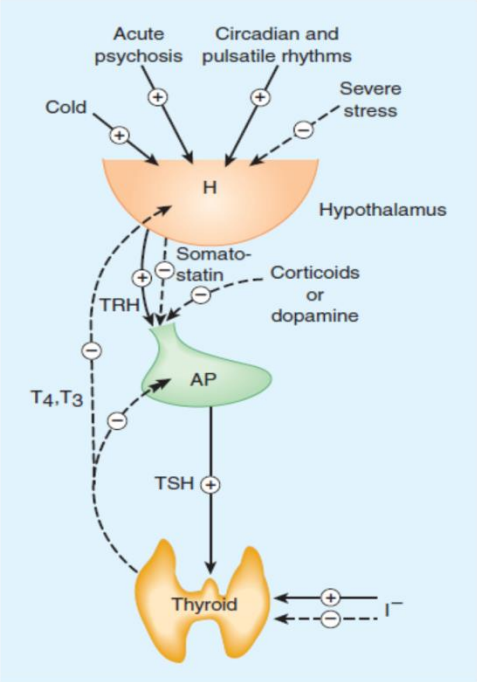

FIGURE 38-3 The hypothalamic-pituitary-thyroid axis. Acute psychosis or prolonged exposure to cold may activate the axis. Hypothalamic thyroid-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH) release, while somatostatin and dopamine inhibit it. TSH stimulates T_4 and T_3 synthesis and release from the thyroid, and they in turn inhibit both TRH and TSH synthesis and release. Small amounts of iodide are necessary for hormone production, but large amounts inhibit T_3 and T_4 production and release. Solid arrows, stimulatory influence; dashed arrows, inhibitory influence. H, hypothalamus; AP, anterior pituitary.

Thyroid hormones (T3/T4)

FUNCTION:

*Normalize growth and development and body temperature, and energy levels. So there is no chance to live without the thyroid hormones.

*Used as thyroid **replacement therapy in hypothyroidism**. The problem in **hypothyroidism** patients: being lazy, and coma in severe states of hypothyroidism. The problem **in hyperthyroidism** patients: hyperactivity, energy and temperature

***Thyroxine (T4) is peripherally metabolized to triiodothyronine (T3)** by **deiodination (thyroxine 5'-deiodinase enzyme).**

Thyroid hormones (T3/T4) " from the slides"

Inhibitors of 5'-deiodinase:

1-Amiodarone

2-Iodinated contrast media
3-Propylthiouracil
4-β-Adrenergic blockers
5-Corticosteroids
6-Severe illness
7-Starvation

These inhibitors weren't mentioned by the doctor

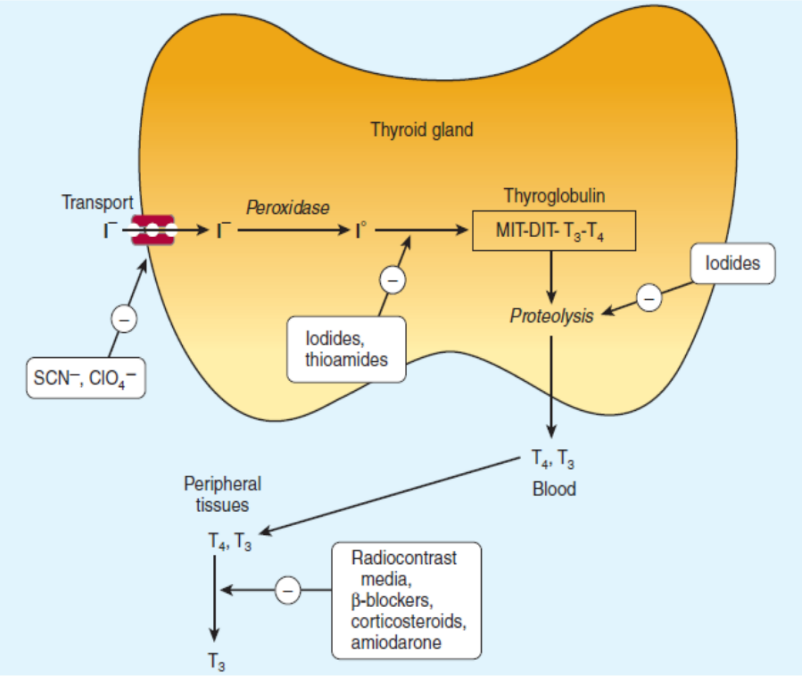

FIGURE 38–1 Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

- This picture shows from where Iodine gets inside the thyroid gland. there'll be an enzyme called "Peroxidase" that converts I^- TO I^O (Iodine organic). Then incorporation of tyrosine and iodine to form: (MIT-DIT-T3-T4); all these will be released by something called proteolysis to the blood ------ then to the peripheral tissues ---- at this step T4 will be converted to the active form T3
- There is a drug that can inhibit peroxidase in the case of hyperthyroidism
- When there is **deficiency** in thyroid hormone :
  1- We can give the patient T4 then it will be converted to T3
  2- But if the body can't produce T3, **HERE WE MUST GIVE THE PATIENT EXOGENOUS THYROID HORMONES**

*****Pharmacokinetics: "note from the slide"**

-Absorption occurs mainly in the **duodenum and ileum**.

-Absorption is modified by **food, drugs, gastric acidity and intestinal flora**

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TABLE 38–3 Drug effects and thyroid function.

Drug Effect	Drugs
Change in thyroid hormone synthesis	
Inhibition of TRH or TSH secretion without induction of hypothyroidism or hyperthyroidism	Dopamine, bromocriptine, levodopa, corticosteroids, somatostatin, metformin
Inhibition of thyroid hormone synthesis or release with the induction of hypothyroidism (or occasionally hyperthyroidism)	Iodides (including amiodarone), lithium, aminoglutethimide, thioamides, ethionamide, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib), HIV protease inhibitors
Alteration of thyroid hormone transport and serum total T_3 and T_4 levels, but usually no modification of FT_4 or TSH	
Increased TBG	Estrogens, tamoxifen, heroin, methadone, mitotane, fluorouracil
Decreased TBG	Androgens, glucocorticoids
Displacement of T_3 and T_4 from TBG with transient hyperthyroxinemia	Salicylates, fenclofenac, mefenamic acid, furosemide
Alteration of T_4 and T_3 metabolism with modified serum T_3 and T_4 levels but not TSH levels (unless receiving thyroxine replacement therapy)	
Increased hepatic metabolism, enhanced degradation of thyroid hormone	Nicardipine, bexarotene, phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Inhibition of 5′-deiodinase with decreased T_3, increased rT_3	Iopanoic acid, ipodate, amiodarone, β blockers, corticosteroids, propylthiouracil, flavonoids
Other interactions	
Interference with T_4 absorption	Cholestyramine, chromium picolinate, colestipol, ciprofloxacin, proton pump inhibitors, sucralfate, sodium polystyrene sulfonate, raloxifene, sevelamer hydrochloride, aluminum hydroxide, ferrous sulfate, calcium carbonate, bran, soy, coffee
Induction of autoimmune thyroid disease with hypothyroidism or hyperthyroidism	Interferon-α, interleukin-2, interferon-β, lithium, amiodarone, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Effect of thyroid function on drug effects	
Anticoagulation	Lower doses of warfarin required in hyperthyroidism, higher doses in hypothyroidism
Glucose control	Increased hepatic glucose production and glucose intolerance in hyperthyroidism; impaired insulin action and glucose disposal in hypothyroidism
Cardiac drugs	Higher doses of digoxin required in hyperthyroidism; lower doses in hypothyroidism
Sedatives; analgesics	Increased sedative and respiratory depressant effects from sedatives and opioids in hypothyroidism; converse in hyperthyroidism

Absorption **is reduced by cholestyramine, ciprofloxacin and aluminum hydroxide.**

Thyroid function and drug effects (things mentioned by the doctor)

1- **Anticoagulation: lower doses of Warfarin are required in patients with hyperthyroidism, and higher doses of Warfarin in those with hypothyroidism ----- when a patient has hyperthyroidism, their blood moves more/is less viscous which increases its response to Warfarin, so we need to give low doses of Warfarin**

2- **Glucose control: increased hepatic glucose production and glucose intolerance in hyperthyroidism , impaired insulin action and glucose disposal in hypothyroidism**
3- **Cardiac drugs: higher doses of Digoxin required in hyperthyroidism , lower doses in hypothyroidism**
4- **Sedatives, analgesics: increased sedative and respiratory depressed effects from sedative opioids in hypothyroidism, and the opposite in hyperthyroidism**

***Absorption is reduced in** severe hypothyroidism (myxedema with ileus) --→ switch from oral to parenteral therapy.

***Clearance is** increased and half life is decreased in hyperthyroidism**, and the opposite is true in hypothyroidism.**

***Thyroid hormones bound in the plasma by** thyroid binding globulin (TBG).

TABLE 38–1 Summary of thyroid hormone kinetics.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL	60–181 ng/dL
	(62–134 nmol/L)	(0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL	230–420 pg/dL
	(10.3–34.7 pmol/L)	(3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	80%	95%

In the previous table , all the categories have been mentioned by the doctor

***depending on the previous table:**

-We have T3 more than T4 because T3 will enter the cells and tissues

But T4 will be in the blood and extracellular areas

-Oral absorption can be affected by drugs and GI motility

Mechanism of Action:

***The free forms of thyroid hormones, T4 and T3, dissociate from thyroid-binding proteins, enter the cell by the active transporters.**

***Within the cell T4 is converted to T3 by 5'-deiodinase.**

***T3 enters the nucleus where it binds to a specific T3 receptor protein, then there'll be gene transcription**

***The T3 receptor exists in two forms, α and β.**

***While there is no T3/T4 there is something called corepressors to suppress the gene transcription**

***Activation of nuclear receptor leads to increased formation of mRNA and subsequent protein synthesis (delay in onset of action hours-days).**

***Affinity of the receptor for T4 is about 10 times lower than T3.**

***The number of nuclear receptors may be altered to preserve body homeostasis**

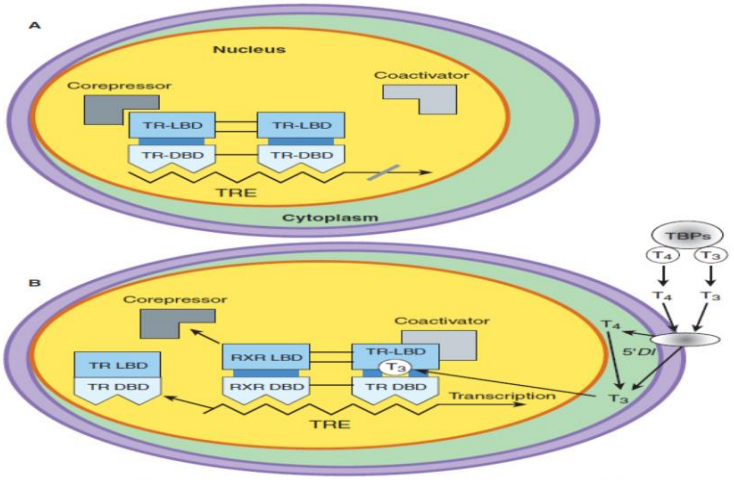

FIGURE 38–4 Model of the interaction of T_3 with the T_3 receptor. **A:** *Inactive phase*—the unliganded T_3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription. **B:** *Active phase*—T_3 and T_4 circulate bound to thyroid-binding proteins (TBPs). The free hormones are transported into the cell by a specific transport system. Within the cytoplasm, T_4 is converted to T_3 by 5′-deiodinase (5′DI); T_3 then moves into the nucleus. There it binds to the ligand-binding domain of the thyroid receptor (TR) monomer. This promotes disruption of the TR homodimer and heterodimerization with retinoid X receptor (RXR) on the TRE, displacement of corepressors, and binding of coactivators. The TR-coactivator complex activates gene transcription, which leads to alteration in protein synthesis and cellular phenotype. TR-LBD, T_3 receptor ligand-binding domain; TR-DBD, T_3 receptor DNA-binding domain; RXR-LBD, retinoid X receptor ligand-binding domain; RXR-DBD, retinoid X receptor DNA-binding domain; T_3, triiodothyronine; T_4, tetraiodothyronine, L-thyroxine. (Modified and reproduced, with permission, from Gardner DG, Shoback D [editors]: *Greenspan's Basic & Clinical Endocrinology*, 8th ed. McGraw-Hill, 2007.)

***Starvation lowers both circulating T3 hormone and cellular T3 receptors.**

***T4 & T3 are available for replacement therapy as levothyroxine and liothyronine, respectively.**

***T3 is not recommended for routine replacement therapy (usual question: why T3 is not recommended for replacement therapy?) because of its shorter half-life (24 hours), requiring multiple daily doses, and difficulty in its monitoring by conventional laboratory tests. It is also more cardiotoxic the most important reason , too potant to the heat and can cause rythmia**

***Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity, low cost, lack of allergenic foreign protein, easy laboratory measurement of serum levels, and long half-life (7 days), which permits once-daily to weekly administration.**

Good Luck