

THYROID AND ANTI-THYROID DRUGS



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@@= introduction
Imp !!
notes

imp. summary

**@ @Normal thyroid gland secretes
T3 (triiodothyronine)
and
T4 (tetraiodothyronine).**

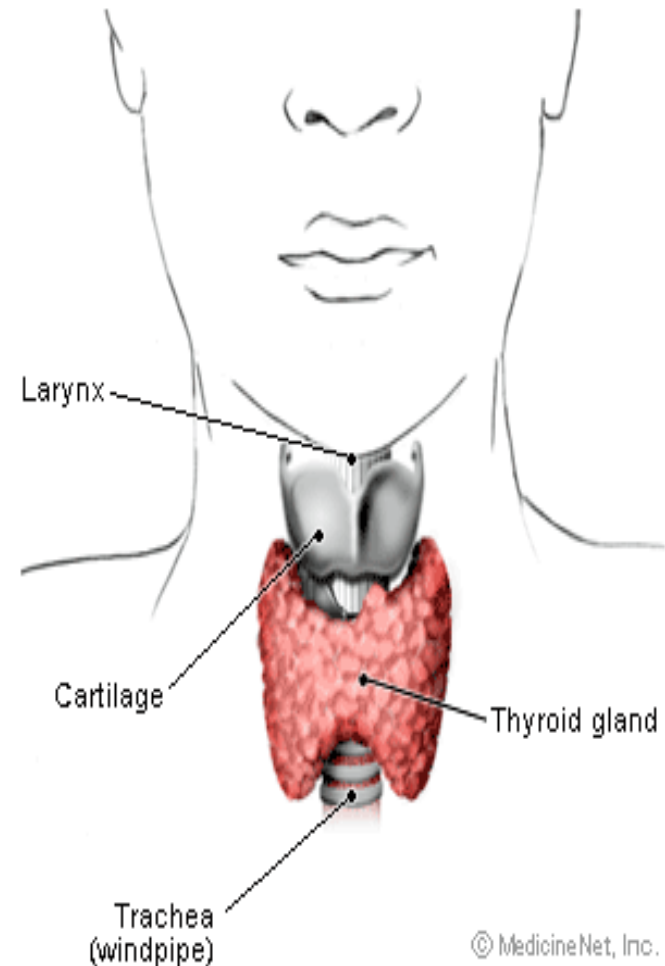
To maintain

Normal growth and development of

- **Nervous**
- **Skeletal**
- **Reproductive systems**

It also controls metabolism of

- **Fats**
- **Carbohydrates**
- **Proteins and**
- **Vitamins**



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@@HYPERTHYROIDISM

- **Over activity of the thyroid gland**

GRAVES' DISEASE

- **Most common cause of hyperthyroidism 60-80%.**
- **It is autoimmune disorder associated with circulating immunoglobulins that bind to and stimulate the thyrotropin (TSH) receptor , resulting in sustained thyroid over activity & it can be familial.**

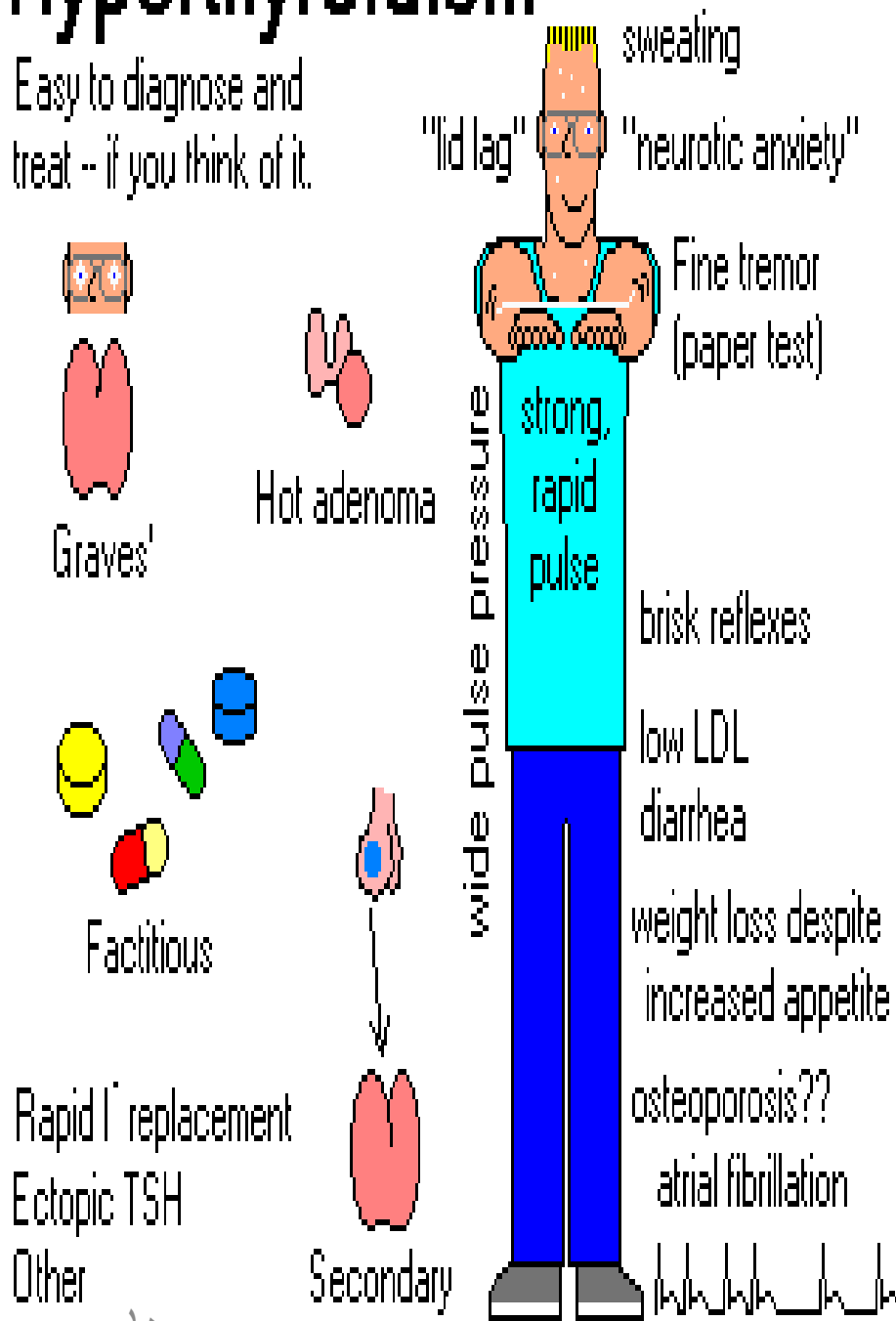
@@Manifestations of Hyperthyroidism

- **Restlessness , nervousness , irritability.**
- **Tremors**
- **palpitation**
- **Weight loss**
- **sweating**
- **Heat intolerance**
- **Diarrhea**
- **short breath**
- **Itching**
- **Light periods**(menstruation distributions)
- **Exophthalmos**

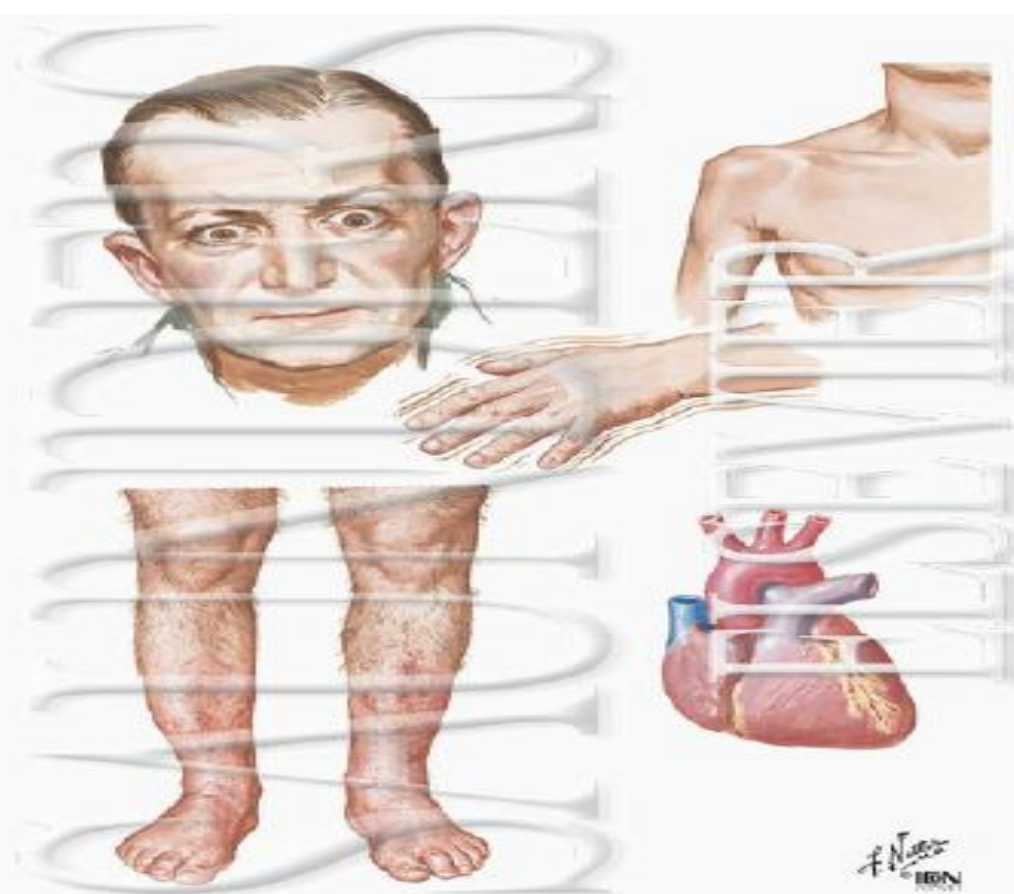
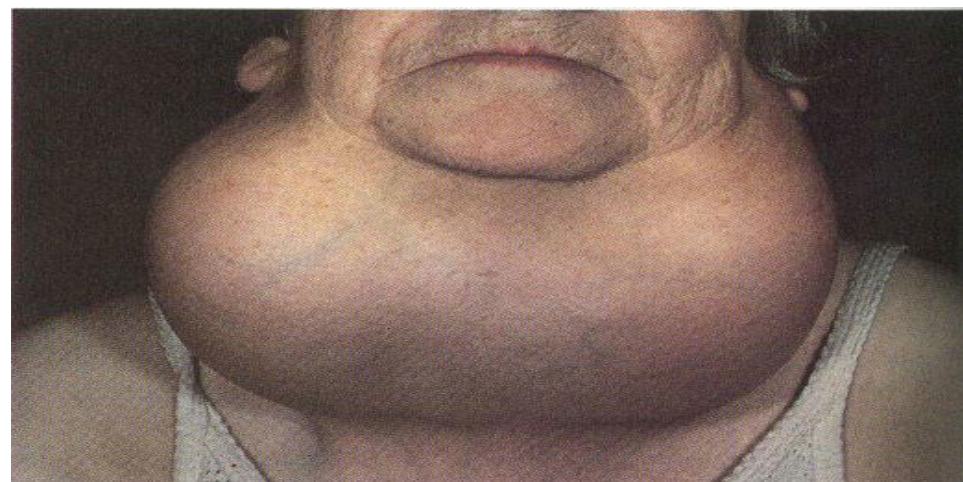
Sympathetic
over activity

Hyperthyroidism

Easy to diagnose and treat - if you think of it.



"Depression?" "Dementia?"
Rule out "apathetic" hyperthyroidism!



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Treatment of Hyperthyroidism

- 1) Thioamides (antithyroid drugs)**
- 2) Iodides**
- 3) Radioactive iodine**
- 4) Beta blockers**
- 5) Surgery (last option)**

1-THIOAMIDES

e.g:

- **Methimazole**
- **Propyl thiouracil**

***the commonest drugs which used in hyperthyroidism**

Q of this category can be written about :

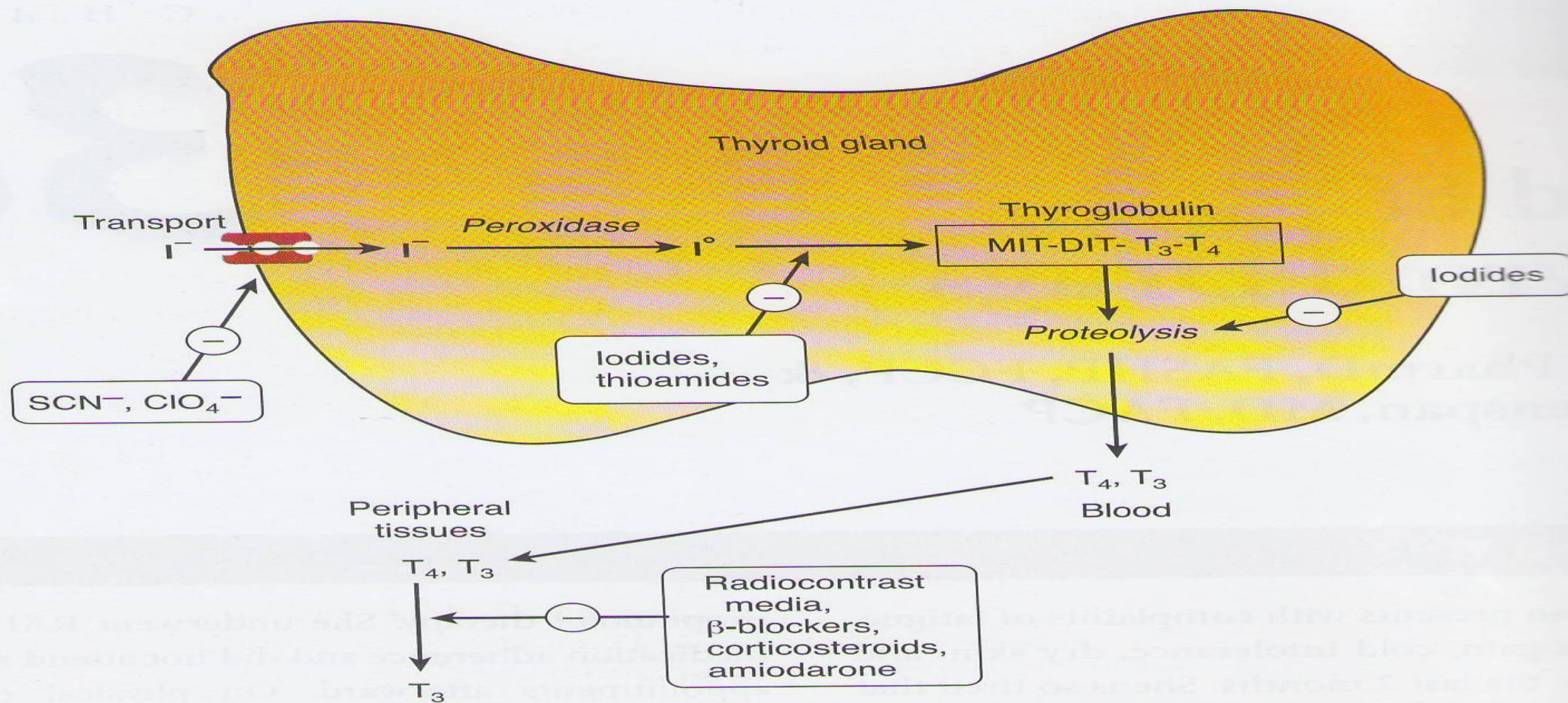
**Methimazole OR
Propyl thiouracil OR
antithyroid drugs OR
THIOAMIDES**

Mechanism of Action imp!!

Inhibit synthesis of thyroid hormones

- By inhibiting thyroid peroxidase- mediated iodination of tyrosine residues in thyroglobulin
- They block coupling of iodotyrosine
- They block the conversion of T4 to T3 within the thyroid & in peripheral tissues

to remember☺ **Propylthiouracil (PTU): mechanism It inhibits** **PTU:**
Peroxidase/ Peripheral deiodination
Tyrosine iodination
Union (coupling)



Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone

1-inhibit thyroid peroxidase which mediate oxidation of iodide to iodine (active form) which leads to iodination of tyrosin to form MIT & DIT >>so it inhibit synthesis by inhibiting the first step

2-inhibit coupling (which normally $2 \text{ DIT} = T_4$ / $\text{DIT} + \text{MIT} = T_3$) >>so it inhibit synthesis

3-it also inhibits the conversion of T_4 to T_3 (In thyroid and peripherally especially liver)

Pharmacokinetic comparison between Propylthiouracil and Methimazole

	Propylthiouracil	Methimazole
Absorption	Rapidly absorbed from GIT	Same
Protein binding	80-90% is bound > high protein binding >> less amount can cross placenta and excreted with milk >> SO it is <u>more safe</u> in pregnancy and breast feeding ...	Most of drug is free SO it is <u>NOT safe</u> in pregnancy and breast feeding ...
accumulation	In thyroid	Similar
Excretion	Kidneys as inactive metabolite within 24 hrs	Excretion slow, 60- 70% of drug is recovered in urine in 48 hrs

Pharmacokinetic comparison between Propylthiouracil and Methimazole

	Propylthiouracil	Methimazole
Half life	1.5 hrs (short half-life)	6 hrs (long half-life)
Administration	Every 6-8 hrs	As a single dose
Pregnancy	Preferred , though cross placenta and is conc .in fetal thyroid but is highly protein bound , <u>crossing placenta is less readily</u>	Cross placenta and concentrated by fetal thyroid Not recommended
Breastfeeding	Less secreted in breast milk Recommended	secreted Not recommended

The imp points in PK : 1- both Taken orally .

2- the drug of choice hyperthyroidism in pregnant or lactating women is **Propylthiouracil.**

3-Propylthiouracil should be taken more than one (short half life) (opposite to Methimazole)

Adverse Effects

- Cutaneous reactions (urticaria , maculopapular rash)

>> **most** common ADRs

is a type of rash characterized by a flat, red area on the skin that is covered with small confluent bumps

- Arthralgia (antithyroid arthritis syndrome)

>> 😊 المفاصل توجع الواحد ، ، مابيتخافش منه

- GI upset , **Hepatotoxicity** (cholestatic jaundice mainly with **methimazole**) ➤

- **Most dangerous complication is agranulocytosis** (low white cell) **occur within 90 days of treatment.**

>> the pt will complain of sore throat , mouth ulcer , general weakness

2-IODIDES:

- **MOA** :Block the peripheral conversion of T4 to T3 & inhibit hormone release. Imp!!
- Used as adjunctive therapy before surgery for Graves' disease to reduce gland vascularity , and makes the gland more firm >> decrease the chance of bleeding in operation . It also used as adjunctive with antithyroid
- Iodides are not used in the routine treatment of hyperthyroidism because of paradoxical ((abnormal)) increase in hormone release with prolonged use >> it works temporally because with long time use it will do many side effects.
- Organic iodides as iopanoic acid or ipodate are used commonly

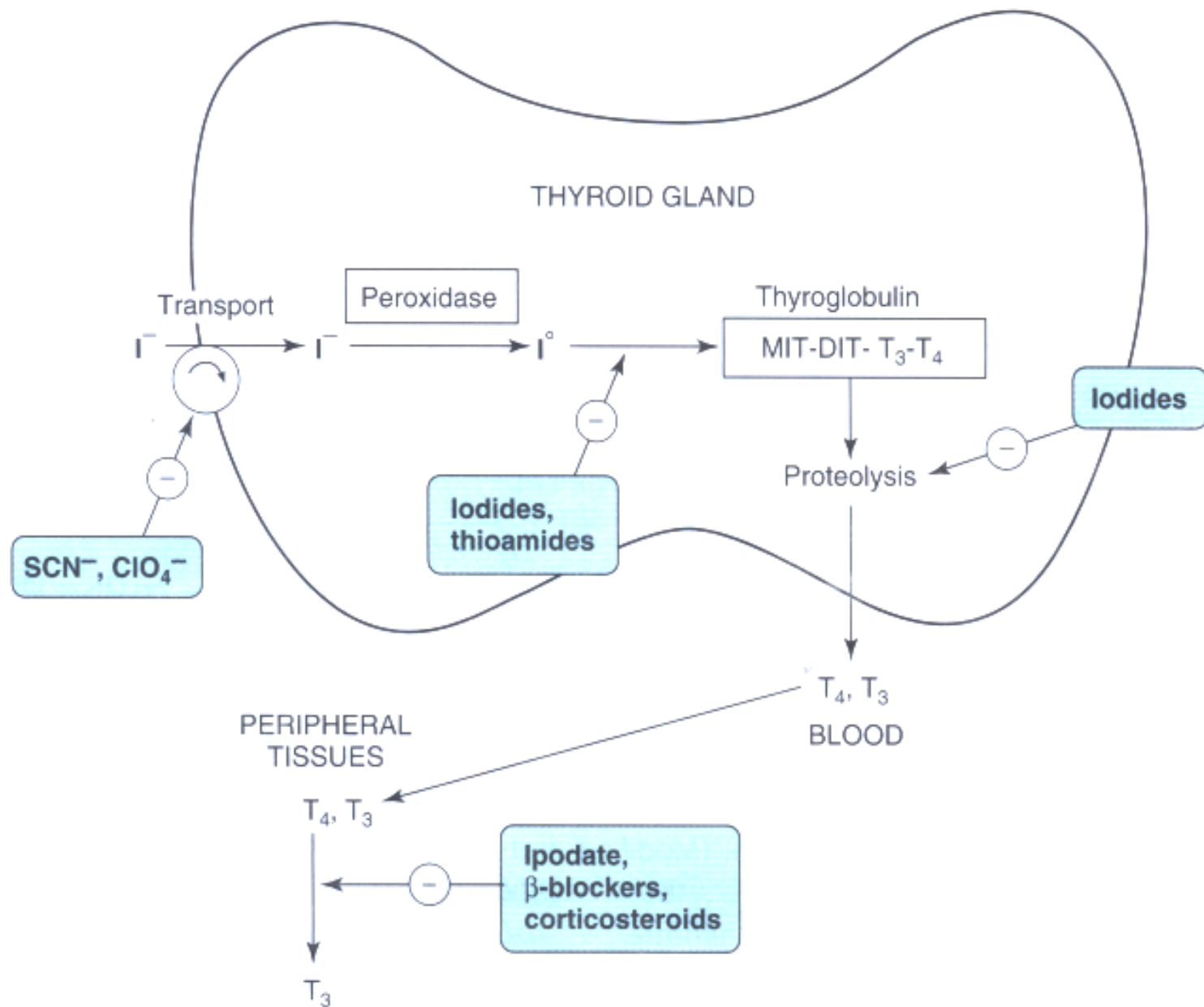


Figure 38–1. Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

Precautions /toxicity:

- Should not be used as a single therapy
- Should not be used in pregnancy
- May produce **iodism** (acniform rash, swelling of salivary glands, mucous membrane ulceration, **metallic taste** > طعام اليود > **bleeding disorders** and rarely **anaphylaxis**).
بالفم

3-RADIOACTIVE IODINE

- **^{131}I isotope (therapeutic effect due to emission of β rays)**
In Dx of the disease>> ^{123}I isotope, ^{127}I isotope (emission Gama rays)
- **Rapidly absorbed, concentrated in thyroid gland and stored in follicles. (MOA>> destruction of the gland cells)**
- **Half -life 5 days**
- **Cross placenta & excreted in breast milk > not used in pregnant, lactating women**
- **Easy to administer ,effective , painless and less expensive**

Radioactive Iodine (con.)

- Available as a solution or in capsules
- **Clinical uses**
 - ❖ Hyperthyroidism mainly in old patients (above 40)
>> not prefer to be given in young people , may cause infertility
 - ❖ Graves' disease
 - ❖ Patients with toxic nodular goiter
 - ❖ Diagnostic uses

Disadvantages

- **High incidence of delayed hypothyroidism**> because it works by destruction of thyroid follicles (this the most common side effect)
- Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis)
- May cause genetic damage
- May cause leukemia & neoplasia (carcinogenic)

The last 3 side effects related mostly to the dose

* لو الدكتور مش شاطر وما ضبط الجرعة /:

4-ADRENOCEPTOR BLOCKING AGENTS (Beta blockers)

- **Relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness. (because most of the clinical manifestation caused by sympathetic over activity)**

Propranolol is widely used(10-20mg/6hrs).

- **Contraindicated in asthmatic patients..imp!!**

Propranolol is non selective beta blocker > so it cause bronchospasm.

5-THYROIDECTOMY

Thyroidectomy has to types either total or sub-total (most used)

- A near-total thyroidectomy is the treatment of choice in very large gland or multinodular goiter
- In case of large or multinodular goiter and to simplify surgery (to diminish vascularity) saturated solution of potassium iodide 5 drops twice daily for two weeks prior to surgery

Management of Grave's disease

- 1st choice Drug therapy
- 2nd choice surgical thyroidectomy
- Destruction of the gland with radioactive iodine >>
this is mostly used when the pt treatment with drugs is unsuccessful and he refuses to have thyroidectomy (مثل ما كان مع أم كلثوم ^_^)

- **In young patient with small gland and mild disease:**
- **Methimazole / propylthiouracil** (start with first line antithyroid) **until disease undergoes spontaneous remission.**
- **this may take 1-2 years .with 60-70 % relapse.**

- **therapy is started with large divided doses ,then shifted to maintenance therapy with single daily dose.**
- **Propylthiouracil is better than methimazole.**
- **Reactivation of the autoimmune process may occur lead to increase in TSH and stimulation of thyroid, this can be prevented by addition of levothyroxine.**

THYROID STORM:

- It is sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome. *Emergency*
- There is hyper metabolism, and excessive adrenergic activity, death may occur due to heart failure and shock.

- Vigorous management is mandatory. Propranolol 1-2mg slows I/v or 40-80 mg orally every 6 hours
(Vigorous management = use all the lines of treatment ,, *whatever can help use it *)
- Potassium iodide 10 drops orally daily or
- Propylthiouracil 250 mg orally every six hours or 400 mg every six hours rectally.
- Hydrocortisone 50 mg I/V every 6 hours to prevent shock.
Imp!!
- If above methods fail peritoneal dialysis >> to decrease hormone percentage in the body

Thyrotoxicosis during pregnancy

- **Definitive therapy with ^{131}I or subtotal thyroidectomy prior to pregnancy to avoid acute exacerbation during pregnancy or after delivery**
- **During pregnancy radioiodine is contraindicated.**
- **Propylthiouracil is better choice during pregnancy.!!**
- **Dose must be kept minimum i.e., <300 mg daily**
(minimal therapeutic dose)

Quick Revision Qs

- Drug of choice in pregnant women has hyperthyroidism?

Propylthiouracil

- Pt has thyroidectomy , what he should be given before the operation?

Iodides

- Pt treated from hyperthyroidism and developed maculopapular rash which drug he used?

Propylthiouracil, methimazole

- High incidence of delayed hypothyroidism associate with?

Radioactive iodine

@ @ Hypothyroidism

- Thyroid gland does not produce enough hormone
- Can be caused by :
 - ❖ Autoimmune disorder Hashimotos thyroiditis
 - ❖ Irradiation
 - ❖ Surgical removal of thyroid gland
 - ❖ Medications that reduce thyroid hormone levels

@ @ HYPOTHYROIDISM:

- **People who are most at risk include those over age 50 & females**
- **Infants and children suffer severely ,results in dwarfism and irreversible mental retardation**
- **Diagnosed by low free thyroxine and elevated serum TSH**
- **For treatment replacement therapy is appropriate**

@ @ Manifestations of Hypothyroidism

- Fatigue and lack of energy
- weight gain
- Dry and cold skin
- Dry hairs
- Constipation
- Slowed thinking
- Bradycardia
- Heavy menses

Hypothyroidism

Easy to diagnose and treat -- if you think of it.

slowing of mind and body

weak heartbeat

constipation

myxedema

high LDL

slow reflexes

hair thinning

depression
"schizophrenia"
irritability

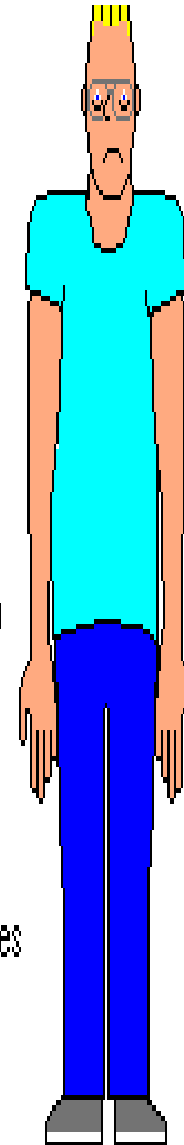
big tongue

croaky voice

dry skin

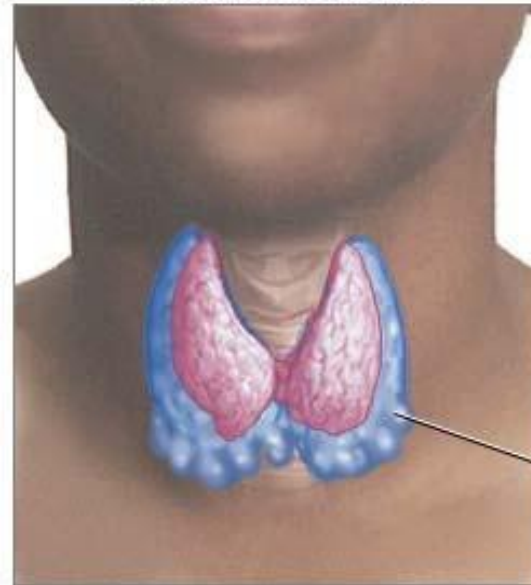
cold skin

cold intolerance





Hashimoto's disease



Enlarged, inflamed
hypofunctioning
thyroid (goiter)

Treatment

- Daily dose of a synthetic thyroid hormone preparations
- Serum TSH is the reliable guide to adjust thyroxine (thyroid hormone) dose
- Infants and children requires more T4 per kilogram of body weight than adults

Thyroid preparations

1) LEVOTHYROXINE:(T4\ thyroxine)

- This is the preparation of choice for thyroid replacement and suppression therapy → because it is stable ,not expensive and has a long (7 days) half life, to be administered once daily.
 - Oral preparations available are from 0.025 to 0.3 mg tablets (common route of administration is orally)
- Absorption is increased when hormone is given on empty stomach (b\c food interfere with absorption of the drug)
- For parenteral use 200-500µg (100µg/ml when reconstituted) for injection (when oral isn't available or severe conditions).

- In long standing condition, in **old patients** and in patients with **cardiac disease**, treatment is started with reduced dosage.
- Can restore normal thyroid levels within 2-3 weeks.
- levothyroxine is given in a dose of 12.5 – 25 µg/day for two weeks and then increasing it after every two weeks.

قاعدة عامة في الـ HRT

Start with low dose then increase it gradually
especially in old and cardiac disease patients

❖ ADRs that is caused by hypothyroidism therapy could be due to over dose or under dose :

- ✓ If over dose → side effects will be similar to HYPERthyroidism manifestations
- ✓ If under dose → side effect will be as HYPOthyroidism manifestations

- **ADVERSE EFFECTS OF OVER DOSE**
- **CHILDREN** : Restlessness, insomnia ,accelerated bone maturation.
- **ADULTS** :
 - Agitation , heat intolerance , pain (headache, muscle pain)
 - Intestinal & metabolic symptoms (change in appetite, diarrhea, weight loss)

Adverse effects of under-dosing

- **Sluggishness** (slow movement)
- **Mental dullness** (بطيء الإستيعاب)
- **Feeling cold**
- **Muscle cramps**

2) Liothyronine(T3) for short term or as adjunctive therapy.

More potent (3-4 times) and rapid than levothyroxine but has a short half life is **not** recommended for routine replacement therapy, it requires multiple daily doses.

- It should be avoided in cardiac patients.
- It is best used for short –term suppression of TSH.
- Oral preparation available are 5-50µg tablets
- For parenteral use 10µg/ml

- ✓ Liothyronine is used mainly for mental retardation.
- ✓ Avoided in cardiac patient b\c it cause cardiotoxicity (chest pain "angina" , irregular pulse rate "atrial fibrillation")

MYXEDEMA COMA:

- It is an end state of untreated hypothyroidism (life threatening as thyroid storm).
- It develops quite and progress slowly to : stupor (state of unconsciousness) , coma and death.
- The treatment of choice is loading dose (high) of levothyroxine intravenously 300-400µg initially followed by 50µg daily.
- I.V T3 can be used but it may provoke cardiotoxicity.
- I.V hydrocortisone may be used in case of complicated adrenal and pituitary insufficiency.

HYPOTHYROIDISM AND PREGNANCY.

- In pregnant hypothyroid patient 20-30 % increase in thyroxine is required because of elevated maternal TBG induced by estrogen and because of early development of fetal brain which depends on maternal thyroxine

✓ Pregnant hypothyroidism should be treated otherwise the neonate will have dwarfism and mental retardation.

Conditions affecting thyroid hormone replacement requirements

- Because thyroid hormone is highly **plasma** protein bound, any medical conditions or drugs that alter amount of binding hormones may affect the level of free hormones :

✓الـ thyroid hormones لما تشم ريحة الـ plasma proteins تسبب كل حاقة في الدنيا وتروح ماسكة فيها (=)
So this will lead to decrease free thyroid hormones (the active form) ✓

1- Conditions that cause an increase in serum binding proteins

- High estrogen states (pregnancy, oral contraceptive use, postmenopausal estrogen replacement)
- The dosage of levothyroxin must be increased

In Contrast

2- Conditions that cause a decrease in serum binding proteins

- Androgens decrease levels of thyroid binding proteins
- Old patients also, have lower serum protein levels
- Nephrosis , Cirrhosis

All previous conditions need reduction of hormone replacement dosages

لو عطيناهاهم الجرعة العادية كأننا عطيناهاهم
overdose وبالتالي راح يكون عندنا
ADRs

- **A)Medications that reduce the absorption of thyroid hormone from intestine , such as :**

✓ we need to increase the dose

- **Cholestyramine** (it plays an imp. Role in decreasing the toxicity caused by other drugs by ↓ absorption)
- **Aluminum containing antacids** (مضادات الحموضة)
- **Calcium preparations**
- **Ferrous preparations**

✓ giving space between these drugs and the hormones (at least 4 hrs) >> decrease the chance of interaction.

✓ we need to increase the dose

- **B) Medications that accelerate metabolism of thyroid hormones (enzyme inducer) such as :**
 - Rifampin (antibiotics used mainly in TB)
 - Phenytoin (antiepileptic)
 - Phenobarbital (antiepileptic)
 - Oral hypoglycemic drugs

Summary

1- hyperthyroidism

- the drug of choice hyperthyroidism in pregnant or lactating women is Propylthiouracil
- ADRs of Antithyroid :
 - most common >> rash
 - more dangerous >> Agranulocytosis
 - hepatotoxicity >> Methimazole
- IODIDES :
 - adjunctive therapy before surgery ,
 - Should *not* be used in pregnancy
 - most common ADRs metallic taste
- THYROID STORM:
 - sudden acute & a life threatening syndrome
 - **Propranolol** (for reliving cardiac manifestations) **Hydrocortisone I.V** (for reliving stress)
 - In case of treatment failure **peritoneal dialysis** is used
- Beta blockers (Propranolol) >> to reduce sympathetic over activity ,
Contraindicated in asthmatic patients)
- Radioactive Iodine: MOA>> destruction of the gland cells , **given to pt above 40** , most common ADRs >> **delayed hypothyroidism,**

Summary

2- hypothyroidism

- * the drug of choice in hypothyroidism ? **Levothyroxine**
- * the main side effect caused by **Liothyronine** ? **Cardiotoxicity**
- * The drug of choice in **MYXEDEMA COMA** ? **loading dose of levothyroxine (i.v)**
- * we need to increase the dose of the hormone therapy ?

A) In High **estrogen** states

B) Medications that **reduce the absorption** of thyroid hormone

C) Drugs that **accelerate metabolism** of thyroid hormones

- * we need to decrease the dose of the hormone therapy ?

In Old pt + Nephrosis + Cirrhosis + androgens

Drugs that reduce the absorption of thyroid hormone	Drugs that accelerate metabolism of thyroid hormones	High estrogen states
Cholestyramine	Rifampin	pregnancy
Aluminum containing antacids	Phenytoin	Postmenopausal estrogen therapy
Calcium preparations	Phenobarbital	Oral contraceptive
Ferrous preparations	Oral hypoglycemic drugs	