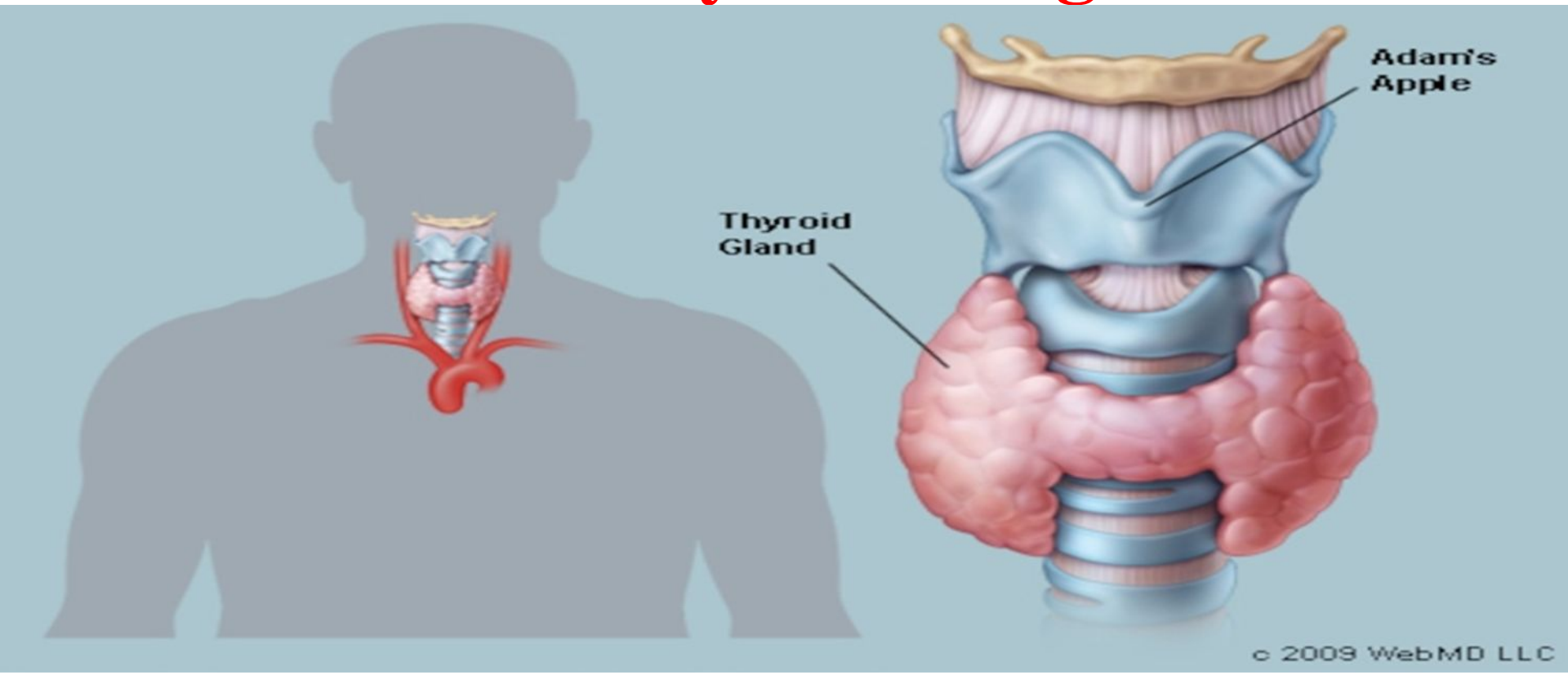
Thyroid Hormones and anti thyroid drugs



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Objectives

Understanding synthesis, pharmacological effects, MOA **-1**
.and kinetics of thyroid hormone

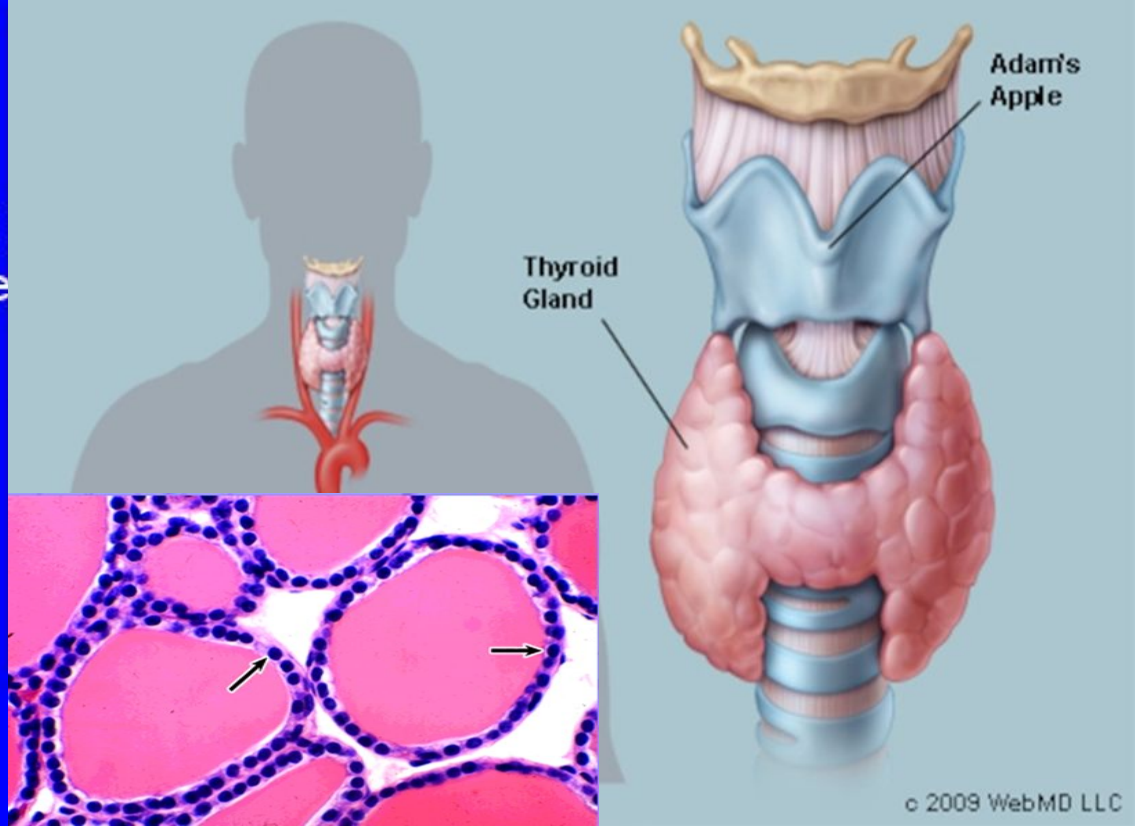
Know drugs used in treatment of hyperthyroidism, **-2**
MOA, kinetics, important caution and contraindications of
.some drugs

.Take informations about treatment of thyroid crisis **-3**

Thyroid gland:

is a **butterfly-shaped gland** located in the **front** of the **neck** just **above** the trachea.

It **weighs** approximately **15 to 20 grams** in the adult human.



.Thyroid **follicles** are the **structural** & **functional** units of the thyroid gland

Each follicle is **surround** mainly by simple **cuboidal** epithelium

.and is **filled** with a **colloid** which mainly **composed** of **thyroglobulin**

Thyroid **hormones** are mainly **synthesized** in **colloid** while the simple **cuboidal** epithelium undertaking **thyroglobulin production**, **iodide intake** & .thyroid hormones **release**

:Thyroid hormone synthesis and releasing

The 1st step is the **transport of the iodide into the gland** by intrinsic follicle cell -1 .basement membrane protein called sodium/iodine symporter(NIS)

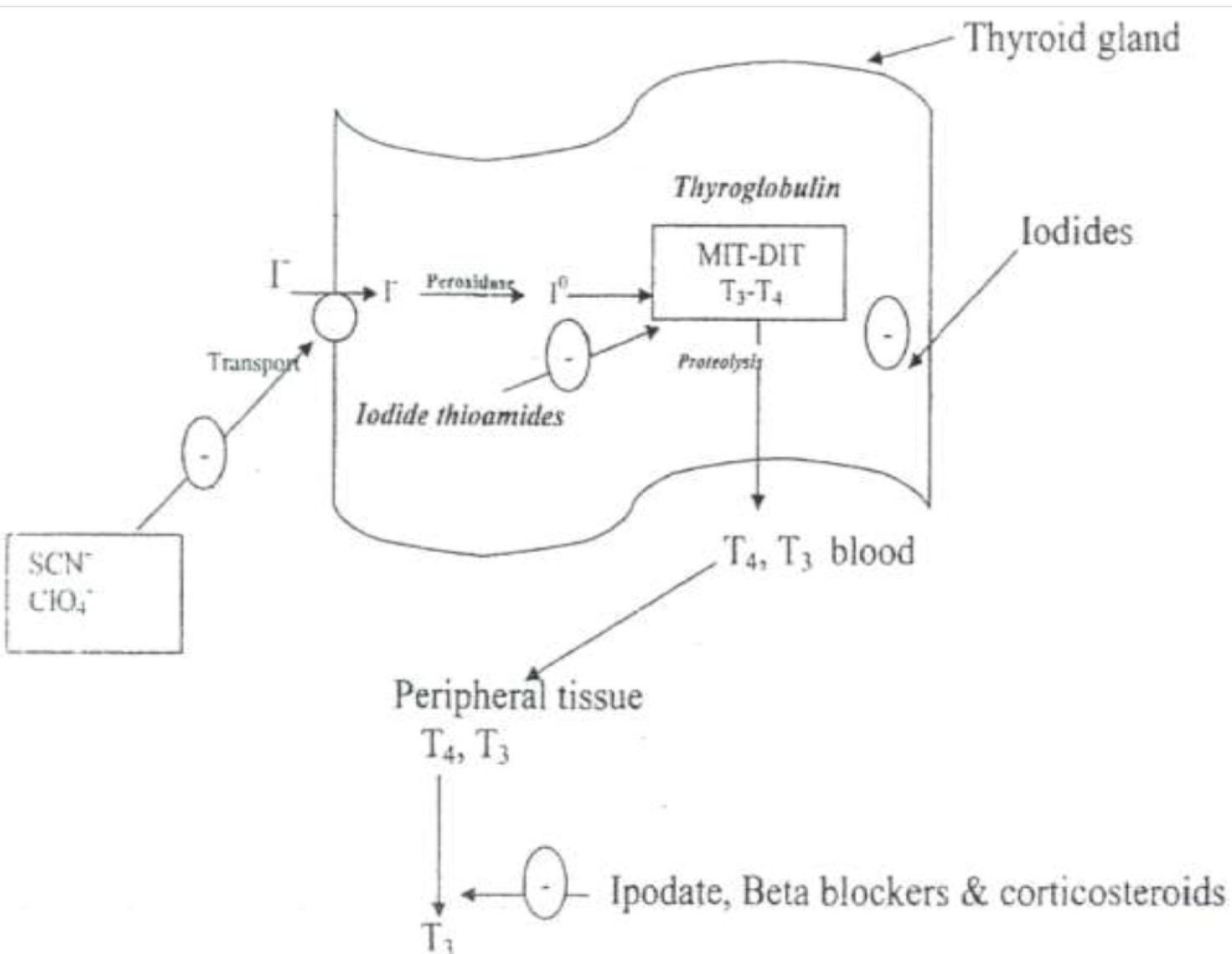
.Iodide is **oxidized** by thyroid peroxidase to **iodine** -2

Iodination of tyrosine residues within the thyroglobulin molecule to form -3 monoiodotyrosine (MIT) & diodotyrosine (DIT) this process is called **iodide .Organifaction**

Two molecules of **DIT** combine within the thyroglobulin to form L-thyroxine **(T4)** -4
One molecule of **MIT** & **one** molecule of **DIT** combine to form **T3 (condensation)**

T4, T3, MIT & DIT are released form thyroglobulin by **exocytosis** & **proteolysis** of -5 thyroglobulin. The **DIT & MIT are deiodinated** within the gland & **the iodine is .reutilized**

- **Note**: The **majority** of our T3 however comes from a process called **deiodination**, which takes place in our **peripheral tissues** (such as the liver and kidney) via the activity of two **enzymes called deiodinase 1 and 2**. During this process, an iodine molecule is removed from the hormone T4, converting it into its active form T3


Thyroid gland
Thyroglobulin
MIT-DIT
T3-T4
Iodides
I⁻
I⁻
Peroxidase
I⁰
Transport
Proteolysis
Iodide thioamides
SCN⁻
ClO4⁻
T4, T3 blood
Peripheral tissue
T4, T3
Ipodate, Beta blockers & corticosteroids
T3

Function of thyroid gland : The thyroid gland facilitates **normal growth and maturation** by maintaining a **level of metabolism** in the tissues that .is optimal for their normal function

:The thyroid secretes 2 types of hormones

Iodine containing amino acids (important for **growth**, -1 **development** and **metabolism**) and these are

a- **T3(triiodothyronine)** the most **active** form

.**b- T4 (thyroxin)**

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

Pharmacological effect of thyroid hormone :

1- **Protein** synthesis during **growth**.

2-Increase **metabolic rate** with raised **oxygen** consumption.

3-Increase sensitivity to **catecholeamines** with proliferation of β-adrenoceptors

4-Thyroid hormones affect the **dilation of blood** vessels, which in turn **affects the rate** at which **heat can escape** the body. The **more** dilated blood vessels are, the **faster** heat can escape.

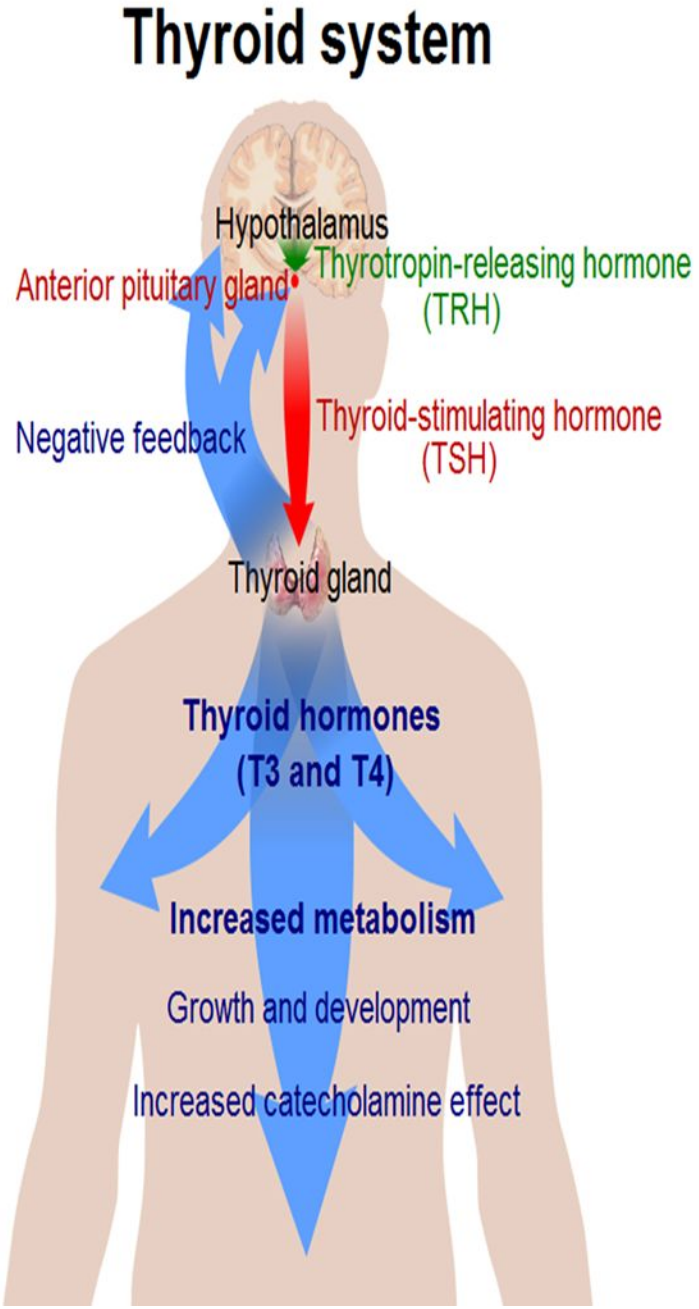
CONTROL OF THYROID FUNCTION

Hypothalamic cells **secrete** thyroid releasing hormone (**TRH**) **into** the .**pituitary**

TRH stimulates the **synthesis** & **release** of thyroid stimulating hormone (**TSH**) from anterior pituitary

TSH (=thyrotropin) stimulates uptake of Iodide by thyroid cell(from blood) and then .the synthesis & release of T4 & T3

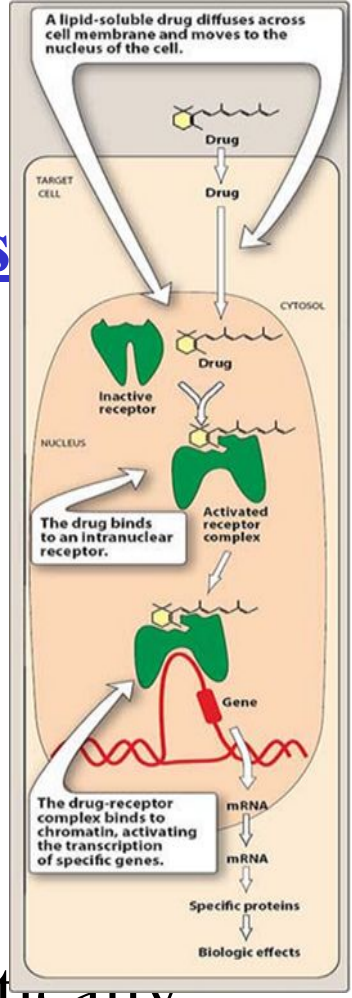
Feedback inhibition of **TRH** occurs with **high** levels of circulating **thyroid hormone**. T4 .T3 act in **a negative feedback mechanism** & **At pharmacologic doses**, dopamine, somatostatin, or .glucocorticoids can also **suppress TSH secretion**



:Mechanism of action

(all cell in body have receptor to T3 and T4)

Thyroid hormone **binds to receptors** in the **nucleus** that **control** the **expression of genes** responsible .for many metabolic processes



:This mechanism started as follow

-Most circulating T3 and T4 is **bound** to thyroxine binding globulin in the plasma. The hormones must **dissociate** from thyroxine-binding globulin prior to entry into peripheral cells. In the cell, **T4** is enzymatically **deiodinated to T3**, which **enters** the nucleus and **attaches** to specific **receptors**. The activation of these receptors promotes the formation of **RNA** and subsequent **protein** .**synthesis**, which is responsible for the **effects** of hormone

:Pharmacokinetics

.**Both** T3 and T4 are **absorbed after oral** administration **-1**

Bioavailability of **Thyroxin is about 80%** absorbed while-2

. **T3 is almost completely (95%)** absorbed

Food, aluminum containing **antacids, Ca** preparations and -3 **iron** salt can **decrease** the absorption of **T4**

Metabolized by **CYP P450** system (thus, they affected by -4 drug affect this enzyme like phenytoin, phenobarbital and rifampin which **accelerate** enz. activity)

Most of the hormone (T3 and T4) is **bound** to -5

.**thyroxin-binding globulin** in the plasma

.**excreted** into **bile** -6

inadequate secretion of thyroid hormone leads to **hypothyroidism** , results in

,Bradycardia, over weight (bs of decrease metabolism)

poor resistance to cold

mental and physical slowing (in children, this can cause **,mental retardation** and **dwarfism**)

Thick skin bs of increase extracellular matrix like .collagen → **accumulated in skin**

TSH is increased → *

An **excess of thyroid** hormones is secreted leads to **hyperthyroidism**, which characterized by

Tachycardia

,Cardiac arrhythmias

Body wasting

Nervousness (bs change the chemistry of brain)

Tremor

.Excess heat production

TSH is reduced *

Note :The **normal range** of **TSH** levels is **0.4 - 4.0** micro-international units per liter.

The **normal range for** the **T4** is **100–200** ng/dl. **T3** = **5-12** ng/dl

:SYNTHETIC THYROID PREPARATION

Levothyroxine: (= **T4**, the **better tolerated, longer t1/2.1** .= **6-7 days,** given **once daily,** part of it **converted to T3**)

Liothyronine: (=**T3**, **faster** acting, **shorter** half-life **.2** .=1day , more **expensive** and **more cardiotoxic**)

T_3 is **not** use in **routine** treatment of hypothyroidism **because** its **rapid** onset of effect and can induce **heart failure (more cardiotoxic).**

T3 main uses are **myxedema coma**.

.**Liotrix** (is a mixture of Levothyroxine & liothyronine) **.3**

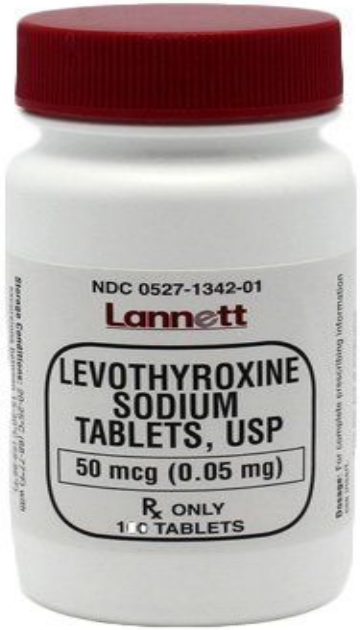
.Thus T4 is better used in Rx**


L-Thyroxin 100
Berlin-Chemie
100 micrograms tablets
Levothyroxine sodium
100 tablets · Oral use
BERLIN-CHEMIE
MENARINI


L-Тироксин 100
Берлин-Хеми


Tefor
Duotab
tiroid hormonu
Schering-Plough


NDC 0527-1350-01
Lannett
LEVOTHYROXINE
SODIUM
TABLETS, USP
175 mcg (0.175 mg)
℞ ONLY
100 TABLETS


NDC 0527-1342-01
Lannett
LEVOTHYROXINE
SODIUM
TABLETS, USP
50 mcg (0.05 mg)
℞ ONLY

Treatment of hypothyroidism

Iodide containing food-1

Levothyroxine (T4) once daily**-2**

:Side effect of levothyroxine

A- Nervousness

B- Tachycardia

C- heat intolerance

.D- weight loss

Symptoms of **myocardial problem** like atrial fibrillation **when occur**, drug is **discontinued** for at least a **week** and begin again later at **lower dosage**.

Note :

- The **initial oral dose** of levothyroxine is **50-100** microgram daily but in **old patients** with **cardiac** or hypertensive diseases should start with **12.5-25** microgram daily for the **first two weeks** and **increase** by **12.5** microgram **monthly**.
- **Adult dose** is **constant** and annul monitoring is needed.
- More **monitoring** is needed in **children** as they are **growing** and the dose is changing

- **Early treatment** of **neonatal** hypothyroidism is important to **avoid mental defect** and the treatment is **lifelong**.

- **Adequate treatment** is indicated by **reducing** plasma **TSH** to **normal** concentration

Treatment of hyperthyroidism (thyrotoxicosis)

The goal of therapy is to decrease thyroid hormone by: 1.Surgery

Drug.2

Surgery: **Removal** part (subtotal) or all of the gland -1

Drugs: act by **inhibiting certain step(s)** in pathway of -2 .hormone synthesis (as in table below)

Drugs for hyperthyroidism

Thioamides: Propylthiouracil, Methimazole	Inhibit hormone synthesis
Iodide salts: KI, Lugol's solution	Blocks hormone release
Iodinated contrast media: Ipodate	Inhibition of peripheral T4 to T3 conversion; inhibits hormone release
Anion inhibitors: Perchlorate, thiocyanate	block uptake of iodide by thyroid
Radioactive iodine (^{131}I)	destruction of thyroid tissue
Beta-blocker: Propranolol, esmolol	Controls heart rate

: The thioamides drugs -1

All of them inhibit step 2, 3 and 4 in hormone synthesis

Carbimazole is a **pro-drug**, after absorption it -1 converted to **active** form (methimazole)

Propylthiouracil (PTU) :**also** blocks the peripheral -2 conversion of T4 to T3. (plasma **t ½**=1.5 hr, **rapid** acting)

Methimazole (t1/2 = 6-8 hrs, **less rapid** acting than PTU) ·

:Adverse effect

Agranulocytosis (bone marrow suppression), rash, edema. immune suppression effect.

Uses:- They are used in **hyperthyroidism** as:

1-**Principle** therapy.

2-**Adjuvant** to radioiodine to control the disease until radiation achieve its effect.

3-To **prepare** patients for **surgery**

The differances between carbimazole and PTU

Carbimazole	Propyl thiouracil (PTU)
More **potent** given in a **single** daily	-**Dose** is **10 times** that of Carbimazole -1 .dose. given every 6-8 hrs
Completely absorbed & readily	-Rapidly absorbed with a **bioavailability** **-2** **% of 50-80 .**
Excreted in **urine** but **slower** than PTU	-**Excreted** in **urine** within **24 hrs** **-3**
No such effect	4-Has some **immunosuppressive** action- leading to **decrease** in serum **TSH receptor antibody**
Has **little** effect on **conversion** of T4 toT3	- It **inhibits** the-5 peripheral **conversion** of T4 to T3
.**Crosses placenta** (more **teratogenic**) -6	Crosses placenta **less** readily(**Preferable**- **(**in 1st trimester **pregnancy**
Sufficient quantity is **excreted** in **breast**	-**Not excreted** in sufficient quantities to-7 .**milk**. So used in breast feeding
less affinity to plasma protein	- more bound to pl.protein&**hepatotoxic** -8

Iodide salt (like potassium iodide KI) :characterized by -2

Selective **accumulation** in **thyroid** gland -1

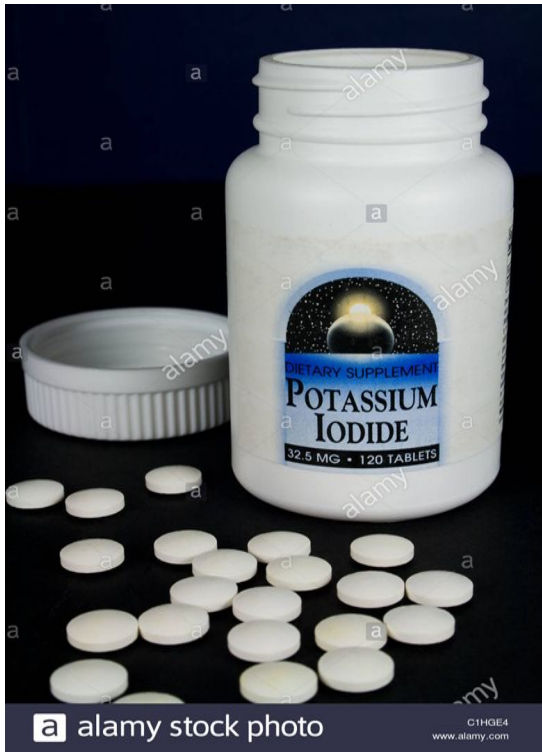
Prevent iodination and **release** of T3 and T4 -2

: Used only in

.A-**fatal** (thyrotoxic crisis or thyroid storm)

B- **Prior to surgery** (bs decrease the vascularity of the gland) **not** useful for **long** term therapy(bs the **responses** to drug is **ceased** after 10days .of treatment& the gland start to resynthesis hormone)

.Given **orally**



:Side effect

sore throat and sneezing. **2-** rashes **-1**

. ulceration of mucous membrane **-3**

.metallic taste in the mouth **5-** lacrimation **-4**

All the adverse effect bs iodide **excreted** in

.saliva, tears and nose

** Note: Iodide has complex action!!

- Iodide is **well absorbed** from the **intestine**, **selectively** taken up and **concentrated** by thyroid gland.
- A **deficiency** of iodide **reduces** the amount of thyroid **hormone** which **stimulate pituitary** to secrete **TSH** resulting in **hyperplasia** of the gland and **goiter** formation.

- **Iodide** in **hyperthyroid** subject with **moderate** excess of it may **enhance hormone production** by providing fuel for hormone synthesis. **More** excess iodide **inhibit hormone release** and **promote storage** of hormone and involution of the gland making it **firmer** and **less vascular** and so that **surgery** is **easier**.

- Iodide in **euthyroid** subjects with **normal gland**, excess of it causes **goiter** (with or without hyperthyroidism) e.g. iodide containing **cough medicines**, iodine containing radio **contrast** media, **amiodaron**.

3-Radioiodine ^{131}I:-

After ^{131}I is **swallowed** , it **concentrated** in the gland and **emits β radiation** which **penetrate** the tissue **only** in thyroid gland (0.5 mm distance).
$t_{1/2}$ **= 8 days**.

contraindicated in **children**, **pregnancy** and **breast fed** patient.

Used in **combination** with **surgery**.

Important Note: destruction of thyroid gland by **radioactive iodine isotope ^{131}I drug** has **selectively** to .the thyroid follicles

: **Advantage**

Easy administration –

Effectiveness –

Low expense –

Absence of **pain** –

Indicated in **patient** who have indication for operation but – want to **avoid operation**

: **Disadvantage**

Hypothyroidism – **Latent** period of getting **response** (**8-12** – weeks)

anion inhibitor: not used now a days bs of severe **-4** .agranulocytosis and severe adverse effects

:Beta blockers-5

As there is **increased tissue sensitivity** to catecholamine in hyperthyroidism with an increase in **number of β-adrenoceptors, so** that **β–adrenoceptor blockers** can **relief** such increase, and **heart rate** is the main **check** of their effects.

Also B-blocker (**propranolol)** act by **decrease conversion** of T4 to T3.

But they should **not** be **use alone**.

intravenous administration of b-blocker is **effective** in the .treatment of thyroid **storm** (**symptomatic** treatment)

But If the patient is **asthmatic** or **HF**. so we give Ca channel .blockers (**Diltiazim**)

Thyroid crisis : severe surge(increase) of thyroid

: **hormone:** may occur bs of

infection (unknown cause) -1

vigrous **palpation** to thyroid(obsessive female) -2

patient **not prepared for surgery** (crisis during operation) -3

:RX

I.V fluid (bs of excessive sweating) -1

Antipyretic other than aspirin (bs aspirin cause **displacement** to -2 hormone and more crisis)

propranolol (to treat tachycardia and prevent conversion of T4 to T3) -3

PTU (to prevent formation of T3 and T4, and prevent conversion of -4 T4 to T3)

KI(usually given after 1.5 hr of PUT) .5

Hydrocortisone !! bs : **1-** hypotension due to sweating **2-** patient .6 take beta blocker **3-** degradation of cortisone wn T4 and T3 released .prevent conversion of T3 to T4 **-4**

: Case

yrs old male, was presented to Emergency Care Unite with loss of 38 consciousness. Full history was taken from his family and proper investigation were done. It has been found that TSH was highly increased, T3 and T4 was highly reduced with normal other investigations. on examination, he was over weight, depressed face, .bradycardia and cold extremities

?Q1- What do you think the disease was

?Q2- Why these sign and symptoms appeared

?Q3- How you can overcome bradycardia

?Q4- What are the proper treatment to this case ? why

Thank you