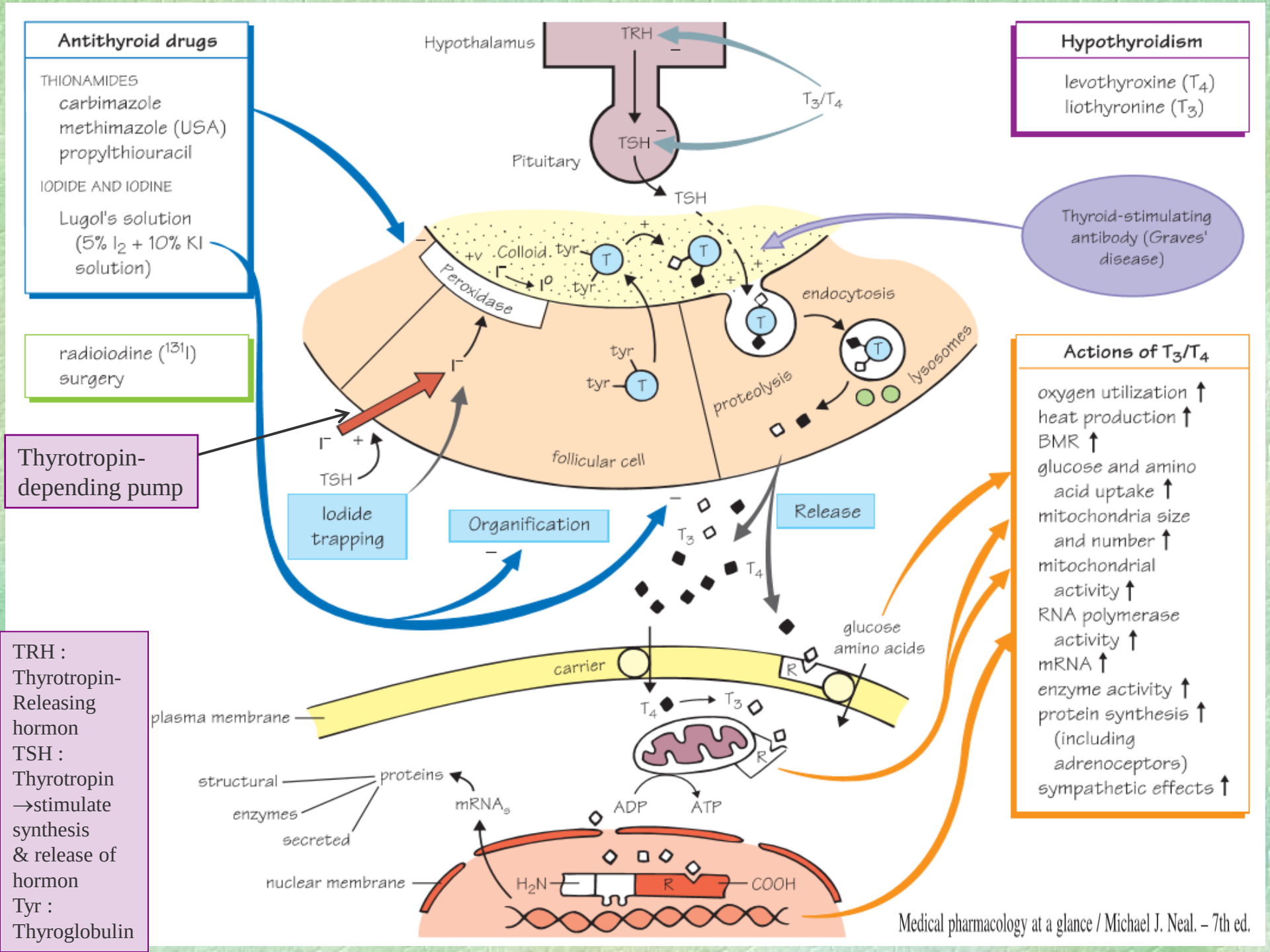
TIROID & ANTITIROID

Kelenjar Tiroid menghasilkan 2 jenis hormon :

1. Utk Pertumbuhan dan Metabolisme Energi : Tiroksin (T_4) dan Triiodotironin (T_3)
2. Utk Pengaturan Mtblsme Kalsium : Kalsitonin


Antithyroid drugs
THIONAMIDES
carbimazole
methimazole (USA)
propylthiouracil
IODIDE AND IODINE
Lugol's solution (5% I_2 + 10% KI solution)
radioiodine (^{131}I)
surgery
Thyrotropin-depending pump
Hypothalamus
TRH
T_3/T_4
Pituitary
TSH
TSH
Thyroid-stimulating antibody (Graves' disease)
Hypothyroidism
levothyroxine (T_4)
liothyronine (T_3)
Colloid
Peroxidase
endocytosis
lysosomes
proteolysis
follicular cell
Iodide trapping
Organification
Release
T_3
T_4
glucose
amino acids
carrier
plasma membrane
structural
enzymes
secreted
proteins
$mRNA_s$
ADP
ATP
nuclear membrane
H_2N
R
COOH
Actions of T_3/T_4
oxygen utilization ↑
heat production ↑
BMR ↑
glucose and amino acid uptake ↑
mitochondria size and number ↑
mitochondrial activity ↑
RNA polymerase activity ↑
mRNA ↑
enzyme activity ↑
protein synthesis ↑ (including adrenoceptors)
sympathetic effects ↑
TRH : Thyrotropin-Releasing hormon
TSH : Thyrotropin →stimulate synthesis & release of hormon
Tyr : Thyroglobulin
Medical pharmacology at a glance / Michael J. Neal. – 7th ed.

SINTESIS&RELEASE

The thyroid gland secretes two iodinated hormones called **triiodothyronine** (T_3) and **thyroxine** (**levothyroxine**, tetraiodothyronine, T_4), which are responsible for the optimal growth, development, function and maintenance of body tissues. Another hormone, **calcitonin**, is produced by the parafollicular cells and is involved in the regulation of calcium metabolism.

The synthesis of T_3 and T_4 requires **iodine**, which is normally ingested (as iodide) in the diet. An active, *thyrotrophin*-dependent pump (➡) concentrates the **iodide** (I^-) in the follicular cells (centre figure) where, at the apical boundary, it is rapidly oxidized by peroxidase to the more reactive **iodine** (I^0). The iodine reacts with tyrosine residues present in thyroglobulin ('organification', Ⓣ), and units of T_3 (◇) and T_4 (◆) are formed. The thyroglobulin containing these iodothyronines is stored in the follicles as colloid (▢).

The release of T_3 and T_4 is controlled by a negative feedback system (top figure). When the circulating levels of T_3 and T_4 fall, **thyrotrophin** (**TSH**) is released from the anterior pituitary gland and

SINTESIS&RELEASE

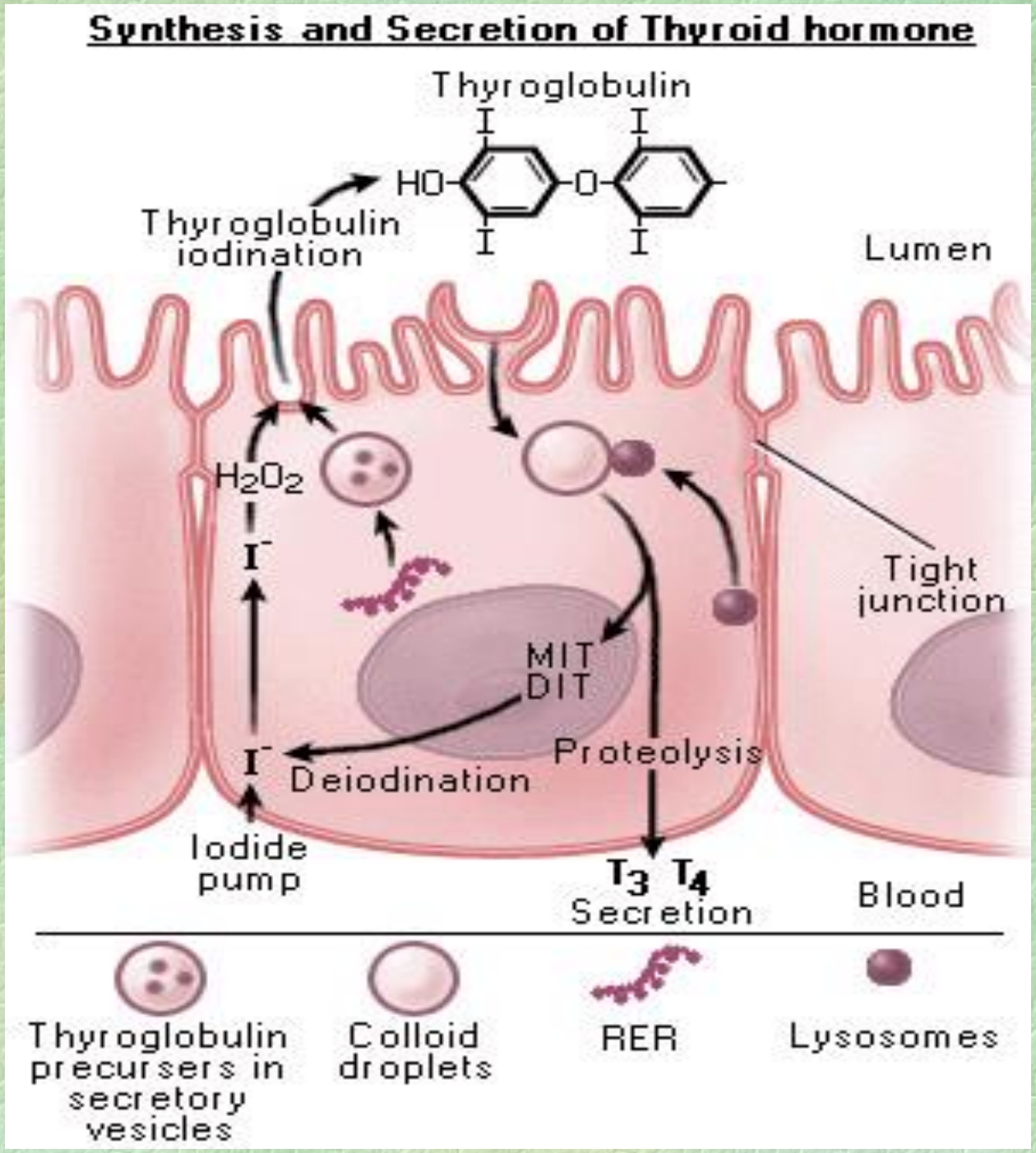
stimulates the transport of colloid (by endocytosis) into the follicular cells. Then, the colloid droplets fuse with lysosomes (●), and protease enzymes degrade the thyroglobulin, releasing T_3 (◇) and T_4 (◆) into the circulation. Both thyroid hormones act on **receptors** (**R**) in the plasma membrane and on intracellular receptors (bottom figure) to produce a variety of actions (right).

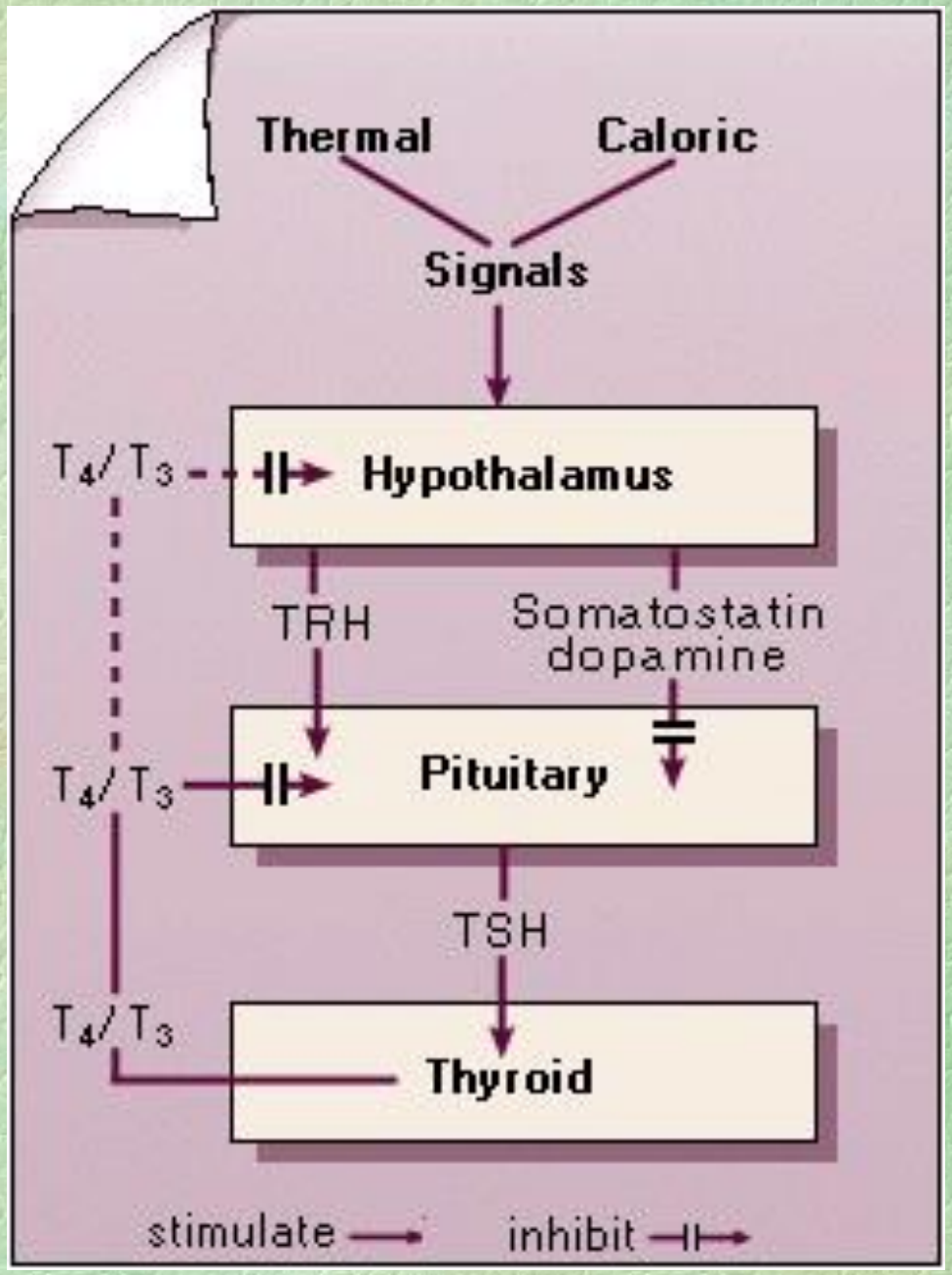
Thyroid hyperfunction and hypofunction occur in about 2% of the population and, together with diabetes mellitus (2–3% of the population), are the most common endocrine disorders. In **Graves' disease**, hyperthyroidism is produced by an IgG antibody that causes prolonged activation of the TSH receptors and results in excessive secretion of T_3 and T_4. Thyroid activity can be reduced with drugs that decrease hormone synthesis (left), or by the destruction of the gland with radiation (using ^{131}I) or surgery. Hyperthyroidism often causes increased sympathetic effects, which can be blocked with β-adrenoceptor antagonists (e.g. propranolol). Graves' disease is often associated with ophthalmopathy, which can be difficult to control, and may be a distinct organ-specific autoimmune disease.

SINTESIS&RELEASE

Primary hypothyroidism (**myxoedema**) probably results in most cases from a cell-mediated immune response directed against the thyroid follicular cells. **Levothyroxine** is the drug of choice for replacement therapy (top right) because it has a longer half-life ($t_{1/2}$) than liothyronine and can be given once daily.

Medical pharmacology at a glance / Michael J. Neal. – 7th ed.


Synthesis and Secretion of Thyroid hormone
Thyroglobulin
HO
O
Thyroglobulin iodination
Lumen
H_2O_2
I^-
Tight junction
MIT
DIT
I^- Deiodination
Proteolysis
Iodide pump
T_3 T_4 Secretion
Blood
Thyroglobulin precursers in secretory vesicles
Colloid droplets
RER
Lysosomes


Thermal
Caloric
Signals
T4/T3
Hypothalamus
TRH
Somatostatin
dopamine
T4/T3
Pituitary
TSH
T4/T3
Thyroid
stimulate
inhibit

OBAT^2 TIROID

- Obat^2 tiroid mempunyai mknsme kerja spt hormon^2 tiroid :

  $T_4 \rightarrow$ aktivasi $\rightarrow T_3$

  $\rightarrow$ inaktivasi $\rightarrow rT_3$

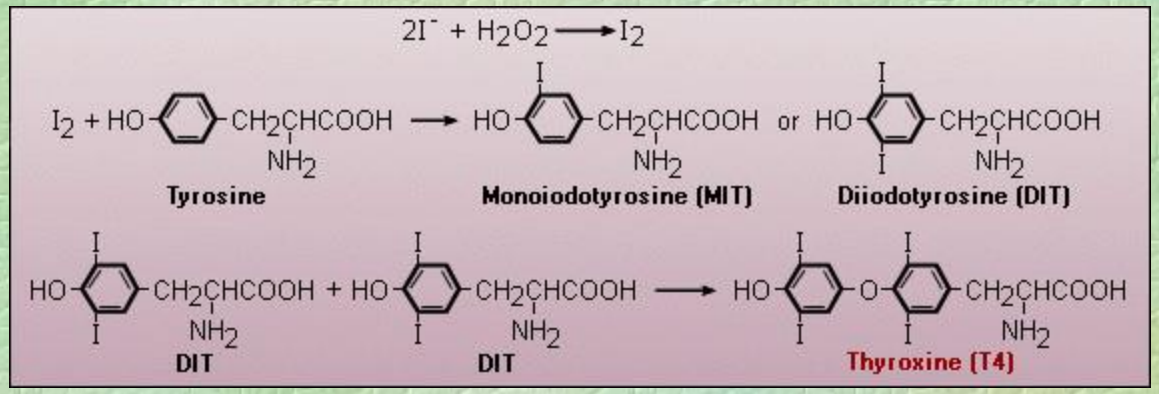
  $\downarrow$

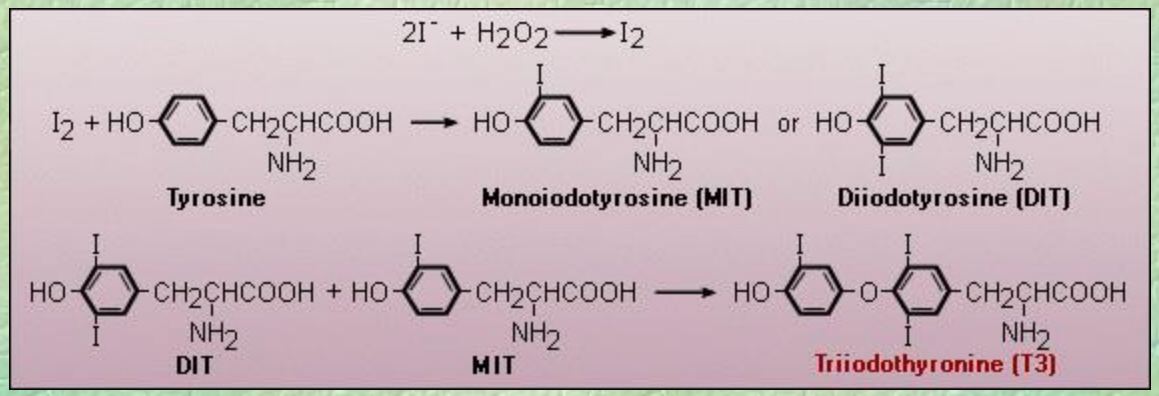
  deaminasi, dekarboksilasi, konjugasi gluku-ronat & sulfat

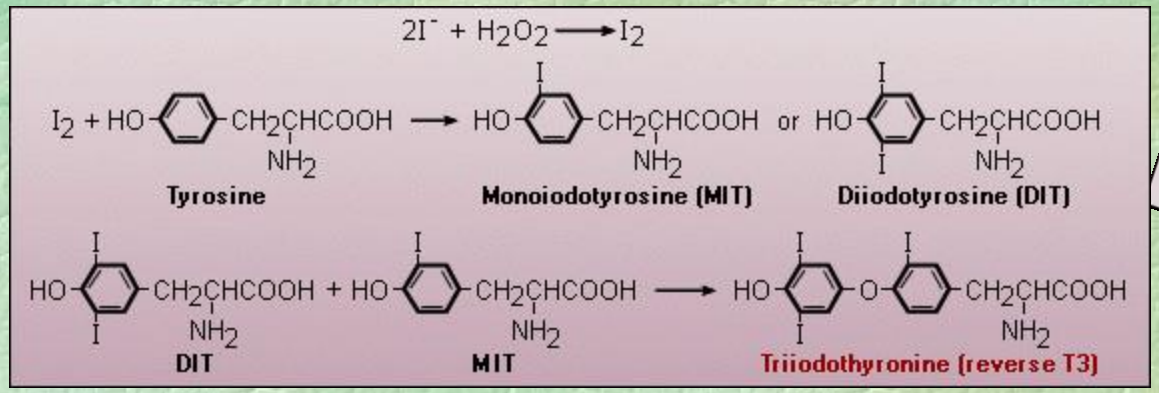
- Mknsme kerja : T_3 berinteraksi dg reseptor pd membran plasma, mitokondria & nukleus. Interaksi hormon-reseptor tsb menghasilkan berbagai efek meliputi peningkatan sintesis prot & mtblsme energi.

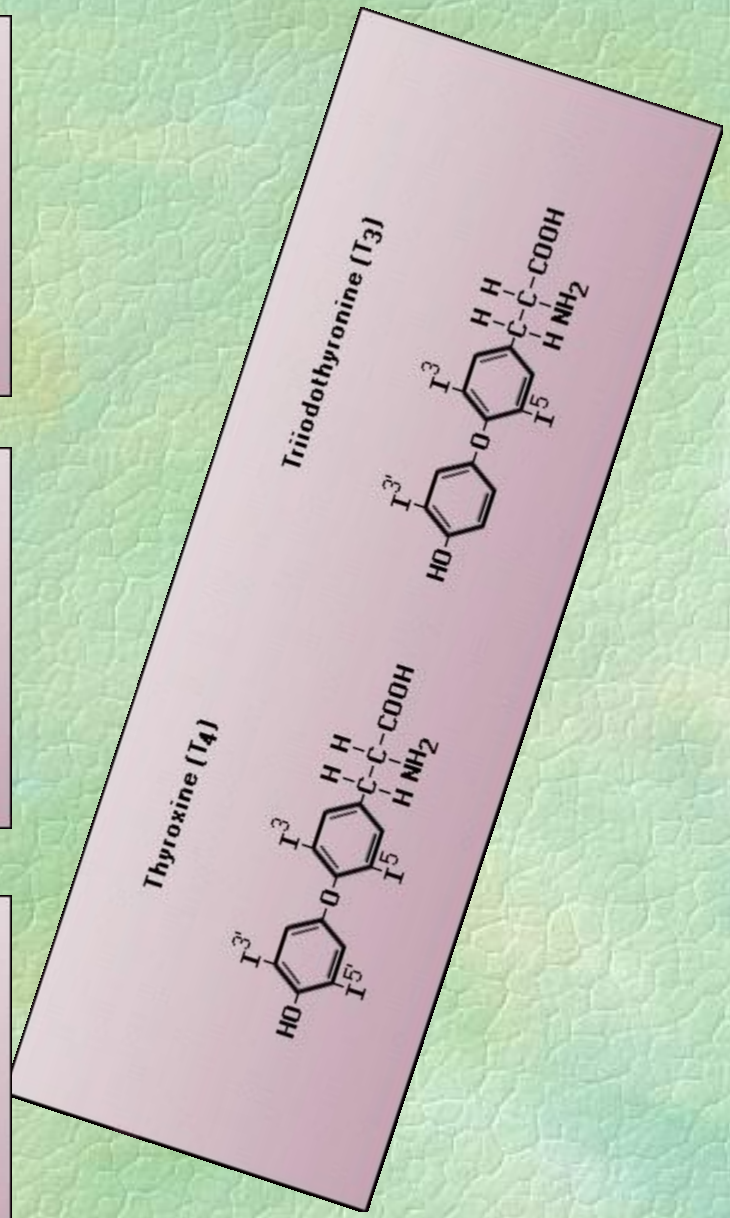
Mekanisme kerjanya melalui inti sel.
→ Bekerja dengan memodulasi transkripsi gen dan sintesis protein.

T4 dan T3 berikatan dengan reseptor yang sama, tapi T4 tidak menyebabkan transkripsi gen, jadi T4 disebut sebagai prohormon.


2I⁻ + H2O2 → I2
I2 + HO-CH2CHCOOH (NH2) → HO-CH2CHCOOH (NH2) or HO-CH2CHCOOH (NH2)
Tyrosine
Monoiodotyrosine (MIT)
Diiodotyrosine (DIT)
HO-CH2CHCOOH (NH2) + HO-CH2CHCOOH (NH2) → HO-O-CH2CHCOOH (NH2)
DIT
DIT
Thyroxine (T4)


2I⁻ + H2O2 → I2
I2 + HO-CH2CHCOOH (NH2) → HO-CH2CHCOOH (NH2) or HO-CH2CHCOOH (NH2)
Tyrosine
Monoiodotyrosine (MIT)
Diiodotyrosine (DIT)
HO-CH2CHCOOH (NH2) + HO-CH2CHCOOH (NH2) → HO-O-CH2CHCOOH (NH2)
DIT
MIT
Triiodothyronine (T3)


2I⁻ + H2O2 → I2
I2 + HO-CH2CHCOOH (NH2) → HO-CH2CHCOOH (NH2) or HO-CH2CHCOOH (NH2)
Tyrosine
Monoiodotyrosine (MIT)
Diiodotyrosine (DIT)
HO-CH2CHCOOH (NH2) + HO-CH2CHCOOH (NH2) → HO-O-CH2CHCOOH (NH2)
DIT
MIT
Triiodothyronine (reverse T3)


Triiodothyronine (T3)
Thyroxine (T4)

PREPARAT TIROID

→Utk terapi pengganti / replacement therapy pd hipotiroidisme

1. Tiroksin / T_4 :

→sintetik : stabil, murah, seragam, tdk alergenik, $T\frac{1}{2}$ panjang, T_4 diubah sebagian mjd T_3 shg keduanya tersedia.

→alami (tiroid kering) : tdk stabil, alergenik.

2. Liotironin / T_3 / Triiodotironin :

lebih aktif, $T\frac{1}{2}$ pendek, mahal, sulit dimonitor, kardiotoksisitas ↑.

OBAT^2 ANTITIROID

(Utk terapi hipertiroidisme)

1. **Gol. Tioamida / Thionamides**

→Propiltiourasil, Metimazol, Karbimazol
(gugus aktif : Tiokarbamida S=C-N)

→Mencegah sint hormon tiroid dg mknsme :

-scr kompetitif menghambat rx katalisis peroksidase tiroid shg menghambat organifikasi Iodium.

-Memblok penggabungan Iodotirosin (terutama DIT)

→Propiltiourasil (PTU) bekerja menghambat proses inkorporasi yodium pada residu tirosil dari tiroglobulin, dan juga menghambat yodium membentuk yodotironin.

→Propiltiourasil utk pasien intolerant thd karbimazol

→Karbimazol diubah mjd metimazol invivo

Farmakokinetik	Propiltiourasil	Metimazol
Ikatan protein plasma	75 %	-
Waktu paruh	75'	4 - 6 jam
Terdistribusi	20 L	40 L
Pada gangguan hati	-	Metabolisme turun
Pada gangguan ginjal	-	-
Dosis	1 - 4 kali/hari	1 - 2 kali/hari
Daya tembus plasenta	Rendah	Rendah
Sekresi pada ASI	Rendah	Rendah

Propiltiourasil 100mg bekerja 6-8jam
Metimazol dosis 30-40mg bekerja 24jam.
Sebaiknya diberikan selama 12 minggu, setelah itu dosis dikurangi / dilihat perkembangannya. Pemberian tidak langsung dihentikan

Contoh preparat /sediaan merek dagang :

1. Neo Mercazole

   Karbimazol 5 mg

Efek antitiroid kuat & paling sering digunakan.

F'kinetik : resorpsi dari usus cepat & langsung diubah scr lengkap mjd metabolit aktifnya, tiamazol.

10 mg Karbimazol -> 6-7 mg tiamazol.
T1/2 plasma 9 jam.

Indikasi : tirotoksikosis primer & sekunder, terapi definitif/kausatif dan persiapan sebelum tiroidektomi, sebelum dan sesudah terapi dengan iodium radioaktif.

KI : kerusakan trakhea, ibu menyusui.

Dosis :

dosis awal kasus ringan/sedang/parah : 3-4/6/8-9 tab sehari dlm dosis terbagi.

dosis pemeliharaan : 1-3 tab sehari

2.Thyrozol

Tiamazol (metimazol) 5, 10, 20 mg

In : hipertiroidisme terutama pasien usia muda,persiapan operasi,yang akan diobati dengan radioiodin.

KI : hipersensitif

Ds :

a.Untuk pemblokiran total prod tiroid :

25-40 mg / hari

Kasus ringan : 2x sehari 1 tab 10 mg

Kasus berat : 2x sehari 1 tab 20 mg

Setelah fungsi tiroid normal (3-8 mgg) dosis diturunkan perlahan hingga dosis pemeliharaan (5-20 mg sehari)

(Lanjutan)

Ds :

b. Dosis disesuaikan aktivitas metabolik tiap pasien dg mempertimbangkan nilai TSH, dosis : 2,5 dan 10 mg

F'kinetik : T1/2 plasma 2-6 jam ttp afinitasnya pada tiroid besar, padahal lama kerja berkorelasi dg kadar di tiroid.Shg dapat aktif selama 24 jam & dpt diberikan sbg single dose

2. Gol. Penghambat Anion

→ClO_4^-, SCN^-, TcO_4^- (tektenat)

→Menghambat uptake Iodida melalui mknsme : scr kompetitif menghambat transpor Iodida.

3. Gol. Iodida

→Larutan lugol, larutan KI

→Menghambat organifikasi Iodida & pembebasan hormon (m'hambat proteolisis tiroglobulin).

→Mengurangi ukuran & vaskularitas kel. Tiroid yg hiperplastik (preparat preoperatif utk pembedahan)

→Pd indvdu sensitif justru hipo/hipertir ↑

4. Iodium radioaktif (I^{131})

→ Emisi sinar β akan merusak jaringan kel. Tiroid shg prod hormon berkurang.

→ Penggunaan dibatasi utk pasien diatas 40 th (krn ada kekhawatiran pd efek kerusakan genetik).

5. Penghambat adrenoreseptor (simpatolitik)

→ Mengurangi gejala tirotoksikosis yg mirip dg gejala perangsangan simpatik.

→ cth : propanolol

SUMMARY Drugs Used in the Management of Thyroid Disease

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
THYROID PREPARATIONS			
• Levothyroxine (T_4) • Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	See Table 38–1 • maximum effect seen after 6–8 weeks of therapy • *Toxicity*: See Table 38–4 for symptoms of thyroid excess
ANTITHYROID AGENTS			
THIOAMIDES			
• Methimazole • Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions • block iodine organification • inhibit peripheral deiodination of T_4 and T_3 (primarily PTU)	Hyperthyroidism	Oral • duration of action: 24 h (methimazole), 6–8 h (PTU) • delayed onset of action • *Toxicity*: Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis (PTU black box), hypothyroidism
IODIDES			
• Lugol's solution • Potassium iodide	Inhibit organification and hormone release • reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral • acute onset within 2–7 days • *Toxicity*: Rare (see text)
BETA BLOCKERS			
• Propranolol, other β blockers lacking partial agonist activity	Inhibition of β adrenoreceptors • inhibit T_4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm • adjunct to control tachycardia, hypertension, and atrial fibrillation	Onset within hours • duration of 4–6 h (oral propranolol) • *Toxicity:* Asthma, AV blockade, hypotension, bradycardia
RADIOACTIVE IODINE ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism • patients should be euthyroid or on β blockers before RAI • avoid in pregnancy and in nursing mothers	Oral • half-life 5 days • onset in 6–12 weeks • maximum effect in 3–6 months • *Toxicity:* Sore throat, sialitis, hypothyroidism

Basic & Clinical Pharmacology
Edited by Bertram G. Katzung, MD, PhD

PREPARATIONS AVAILABLE

GENERIC NAME	AVAILABLE AS
THYROID AGENTS	
Levothyroxine (T_4)	Generic, Levoxyl, Levo-T, Levothroid, Levolet*, Novothyrox, Synthroid, Tirosint (capsule), Unithroid
Liothyronine (T_3)	Generic, Cytomel, Triostat (IV)
Liotrix (a 4:1 ratio of T_4: T_3)	Thyrolar
Thyroid desiccated (USP)	Generic, Armour, Nature-Throid, Westhroid
ANTITHYROID AGENTS	
Radioactive iodine (^{131}I) sodium	Iodotope, Sodium Iodide I 131 Therapeutic
Methimazole	Generic, Tapazole
Potassium iodide	
Oral solution (SSKI)	ThyroShield
Oral solution (Lugol's solution)	Lugol's solution
Oral potassium iodide tablets	IOSAT, Thyro-Block, Thyro-Safe
Propylthiouracil [PTU]	Generic
DIAGNOSTIC AGENT	
Thyrotropin; recombinant human TSH	Thyrogen

*Not available in United States.

REFERENCES

General

American Thyroid Association: Professional Guidelines. Available at: *www.thyroid.org/professionals/ata-professional-guidelines/*.

American Thyroid Association Task Force on Radiation Safety et al: Radiation safety in the treatment of patients with thyroid diseases by radioiodine ^{131}I: Practice recommendations of the American Thyroid Association. Thyroid 2011;21:335.

Chen AY et al: American Thyroid Association Statement on Optimal Surgical Management of Goiter. Thyroid 2014;24:181.

Cooper DS, Ladenson PW: The thyroid gland. In: Gardner DG, Shoback D (editors): *Greenspan's Basic & Clinical Endocrinology*, 9th ed. McGraw-Hill, 2011.

Haugen BR et al: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1.

Rugge JB, Bougatsos C, Chou R: Screening and treatment of thyroid dysfunction: An evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162:35.

U.S. Department of Health and Human Services: Potassium iodide as a thyroid blocking agent in radiation emergencies. Available at: *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080542.pdf*.

Thyroid Hormone Action

Chatterjee VK et al: Thyroid in 2012: Advances in thyroid development, hormone action and neoplasia. Nat Rev Endocrinol 2013;9:74.

Galli E, Pingitore A, Iervasi G: The role of thyroid hormone in the pathophysiology of heart failure: Clinical evidence. Heart Fail Rev 2010;15:155.

Contoh Resep → ?

Rumah Sakit Setia Budi
Jl. Pemuda No 13 Surakarta 57555
Telp. (0271) 611644

R/ Propiltiourasil (PTU)
S.3 dd 1 no.XXI
R/ Propanolol
S.3 dd 1 no.XXI

Prp : Ny. Ank

Tgl : 27 February 2013
Dokter : dr. Muhammad Dodi

PARATIROID

Kelenjar paratiroid memproduksi hormon :

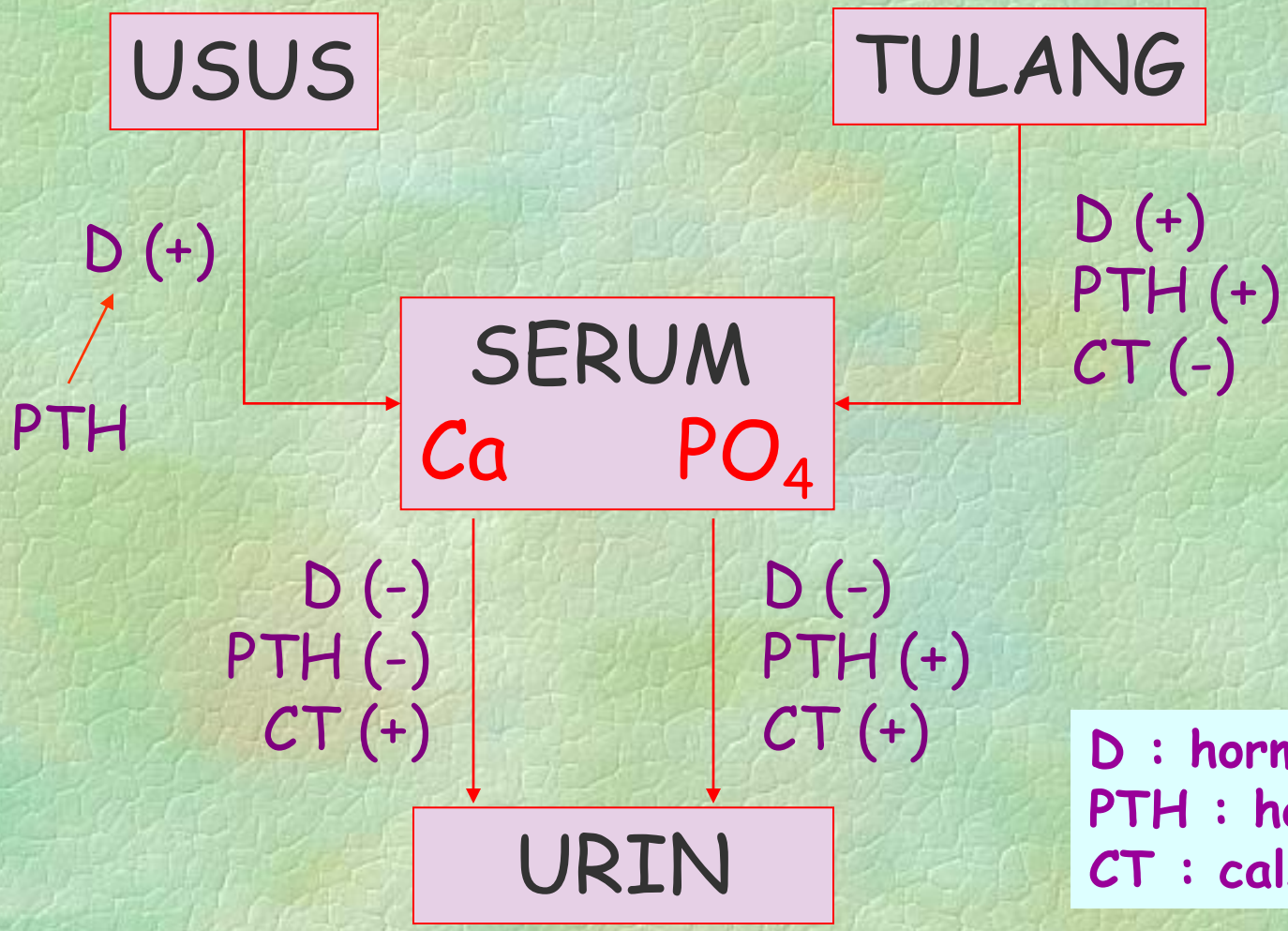
- Parathormon / Paratirin / PTH
  → fungsi : mengatur kesetimbangan kalsium & fosfat

- Tempat Aksi :
  1. Usus → Absorbsi Ca^{2+} ↑, PO_4 ↑
     (melalui pbtkn 1,25-di-OH-vit D_3)
  2. Ginjal → reabsorbsi Ca^{2+} ↑, Mg ↑, PO_4 ↓
     → sekresi PO_4 ↑
  3. Tulang → mobilisasi Ca^{2+} ↑, PO_4 ↑

- Hasil kerja :
  Kadar dalam darah Ca^{2+} ↑, PO_4 ↓

CALSITONIN

- Hormon kelenjar tiroid
- Menghambat pembebasan Ca^{2+} , PO_4 dari tulang
  $\rightarrow$ kadar Ca^{2+} darah turun
- Menaikkan ekskresi Ca^{2+} , PO_4 , Na^{+}, Mg^{2+}
- Reabsobsi PO_4 ginjal turun



D : hormon $1,25(OH)_2D_3$
PTH : hormon paratiroid
CT : calsitonin

Aktivitas PTH, Vit D dan Calsitonin

	PTH	Vit D	CT
Intestinal	**Peningkatan absorbsi Ca & PO4 dg me ↑ prod Vit D**	**Peningkatan absorbsi Ca & PO4**	
Ginjal	**Penurunan ekskresi Ca, peningkatan ekskresi PO4**	**Ekskresi Ca & PO4 menurun**	**Ekskresi Ca & PO4 meningkat**
Tulang	**Dosis tinggi : resorpsi Ca & PO4 me ↑** **Dosis rendah : pbtkn tulang me ↑**	**Resopsi Ca dan PO4 me ↑** **Pbtkn tulang me ↑**	**Resorpsi Ca & PO4 dihambat**
Efek bersih Kadar serum	**Ca me ↑** **PO_4 me ↓**	**Ca me ↑** **PO_4 me ↑**	**Ca me ↓** **PO_4 me ↓**

GANGGUAN FUNGSI KELENJAR PARATIROID

1. **Hipoparatiroidisme**

kekurangan parathormon :

→ **Hipokalsemia**

→ tetani-neuromuskular, spasme laring, kejang otot & konvulsi.

Terapi :

Kalsium

iv → Ca gluseptat, Ca glukonat (lbh disukai karena tdk tll mengiritasi vena), Ca klorida

Utk hipokalsemia berat dg infus lambat Ca glukonat

oral → Ca karbonat (preparat pilihan), Ca laktat, Ca fosfat, Ca sitrat.

Vit D

Metabolit vit D pilihan 1,25(OH)2D3 / Kalsitriol

→ Hiperfosfatemia

Terapi : Dialisis

Infus glukosa & insulin

Antasida $Al(OH)_3$ + Ca^{2+}

{The treatment for acute hyperphosphatemia is administration of phosphate binding salts – calcium, magnesium and aluminum. The latter is avoided in renal failure, as aluminum can accumulate (calcium is preferred)}.

2. Hiperparatiroidisme

hiperfungsi paratiroid :

→ **Hiperkalsemia**

depresi SSP, koma, sampai kematian

Terapi :

Diuresis garam – furosemid

kondisi dehidrasi mencegah ginjal mengkompensasi kelebihan Ca shg di-rehidrasi dg lar. grm → aliran urin membaik, Ca bisa turun. Furosemid akan me ↑ kan aliran urin & mencegah reabsorbsi Ca di pers aferen ansa henle.

Bifosfonat (Etidronat, Pamidronat)

Secara selektif menghambat resorpsi tulang, menghambat prod $1,25(OH)_2D$ & menghambat transport Ca intestinal.

Calsitonin
Galium nitrat
Fosfat

→ Hipofosfatemia
Terapi : Fosfat p.o