Medical Pharmacology

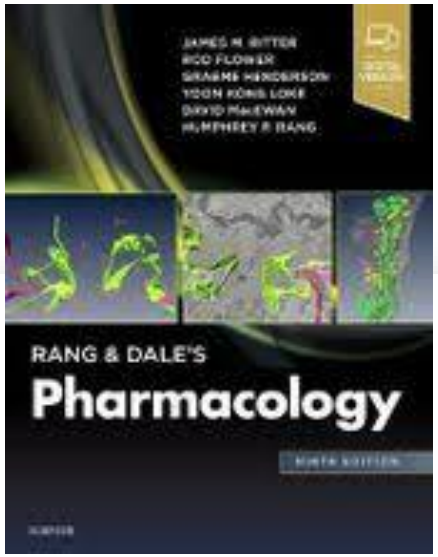
Robiul Islam, PhD

College of Medicine and Dentistry

JAMES COOK UNIVERSITY AUSTRALIA

Celebrating 50 YEARS 1970 - 2020

Endocrine & Bone: Thyroids and Osteoporosis



Rang & Dale's Pharmacology

10th ed 2020

Chap 34, 36

Thyroid gland

- Thyroid gland
  - Located in anterior of neck, over the trachea, below the larynx
  - Bi-lobed & “Butterfly shaped”
  - Endocrine gland producing thyroid hormone (T_3 & T_4)
  - Has four parathyroid glands (producing parathyroid hormone – calcium regulation)

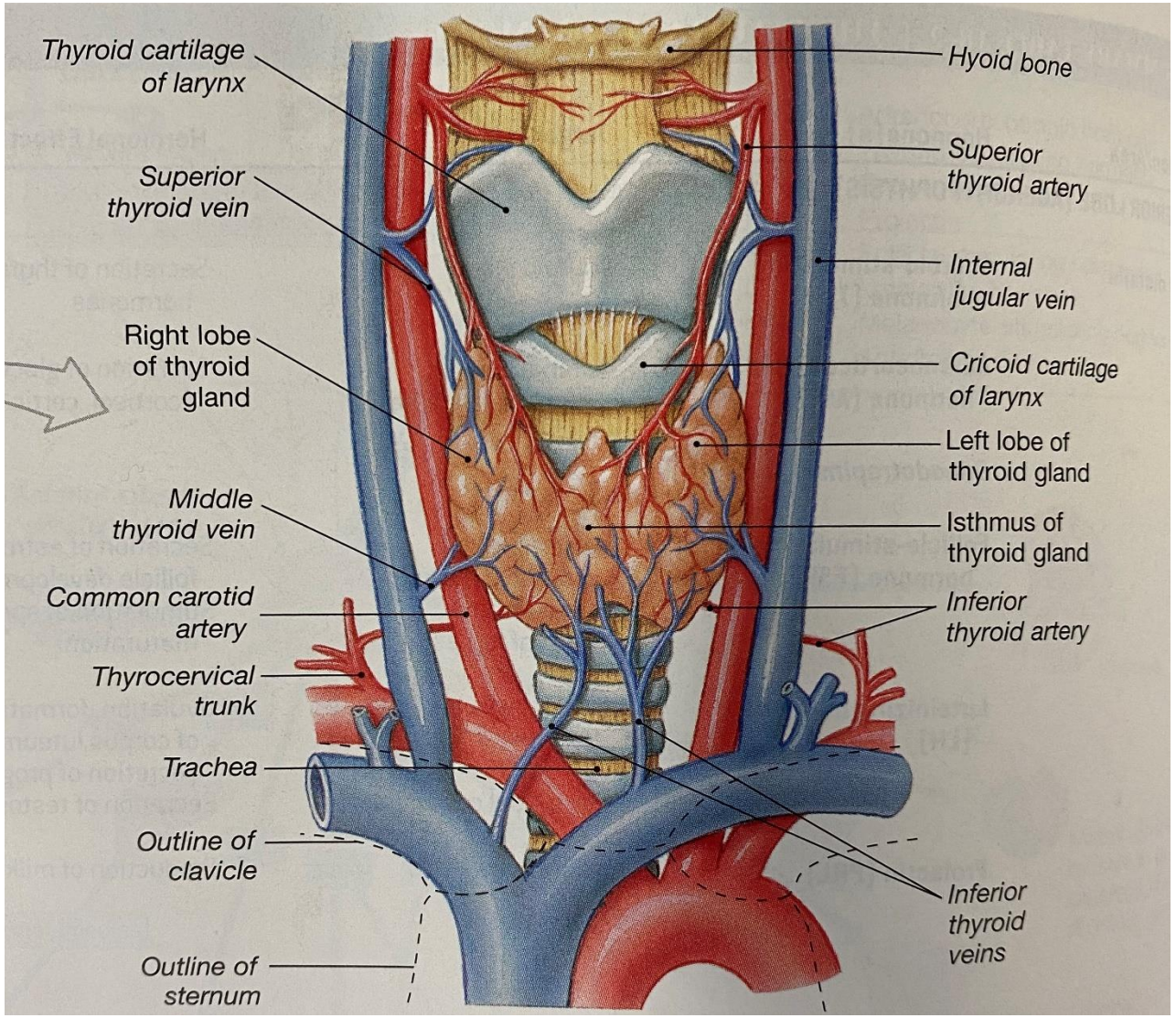
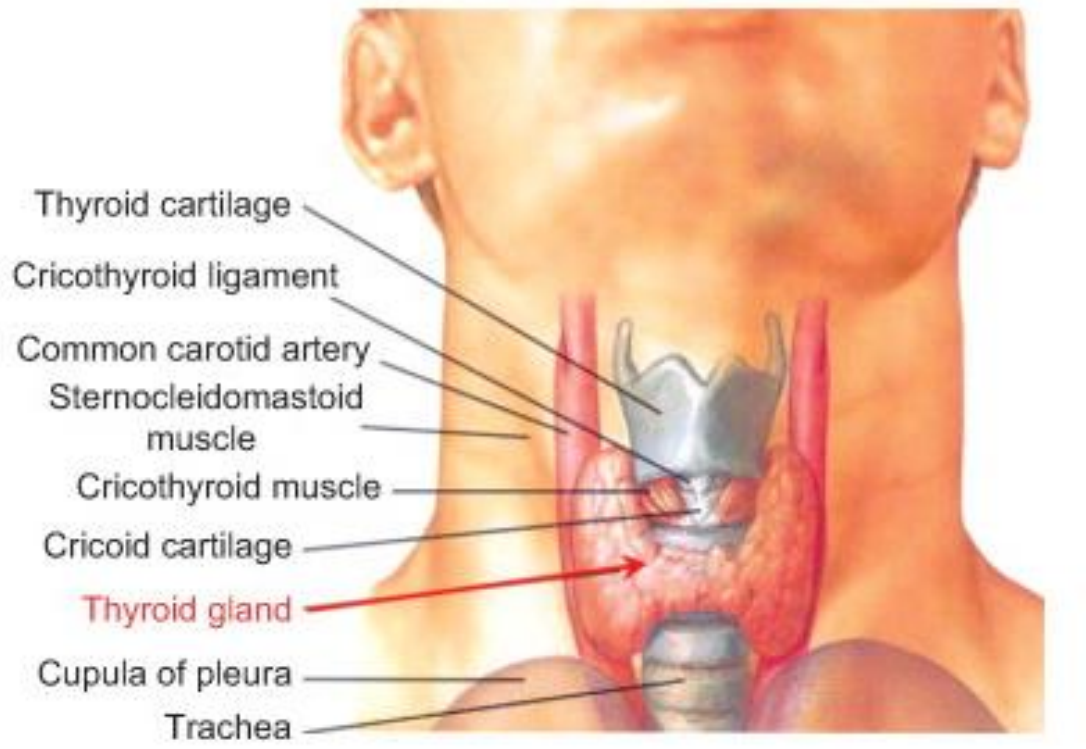


Figure 6.2 from Tortora, GJ., Derrickson, B., Burkett, B., Peoples, G.,Dye, D., Cooke, J., et al. Principles of anatomy and physiology. Second Asia-Pacific ed. Queensland, Australia: John Wiley & Sons; 2019.

Thyroid gland



Source: https://www.sciencedirect.com/topics/immunology-and-microbiology/thyroid-gland. Accessed February 2024

Thyroid hormone synthesis

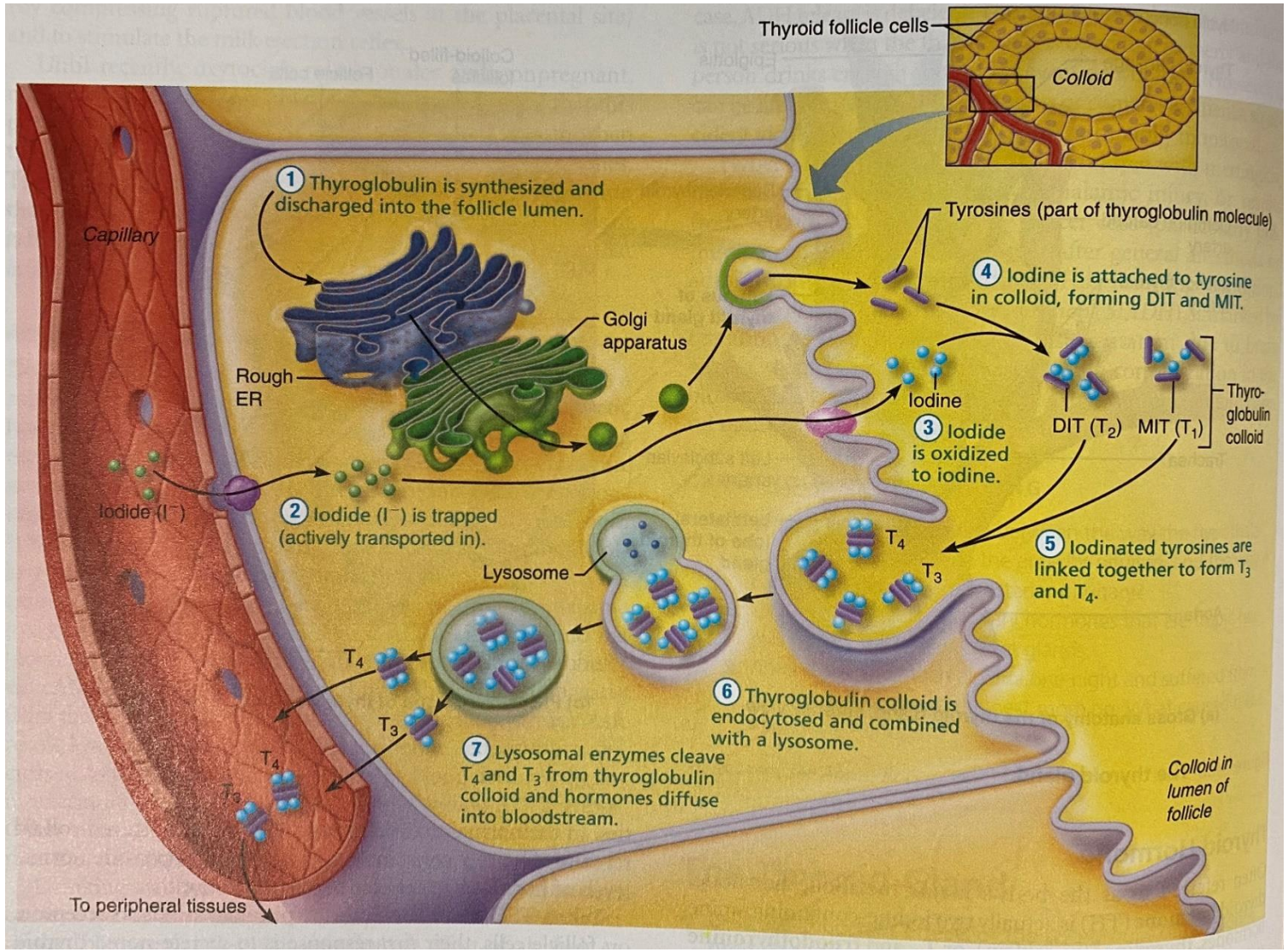
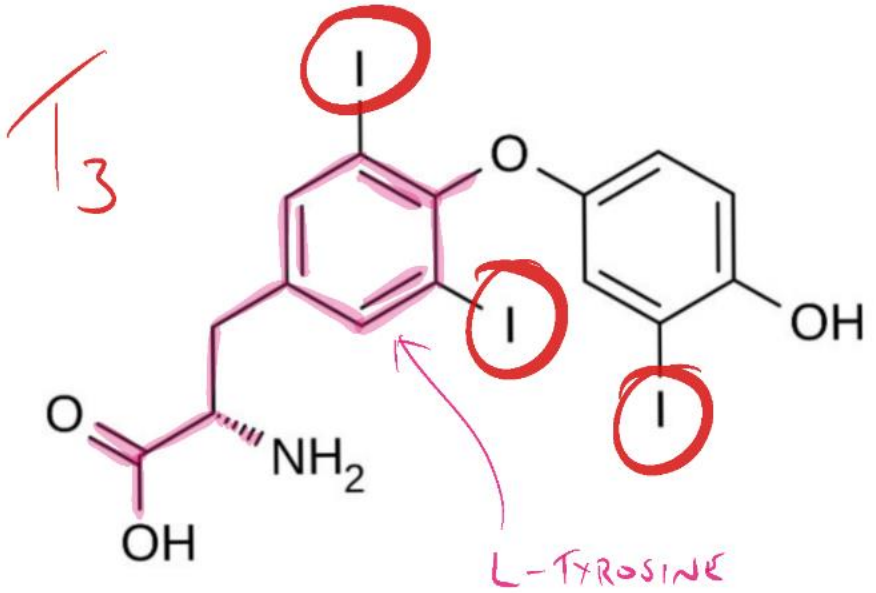


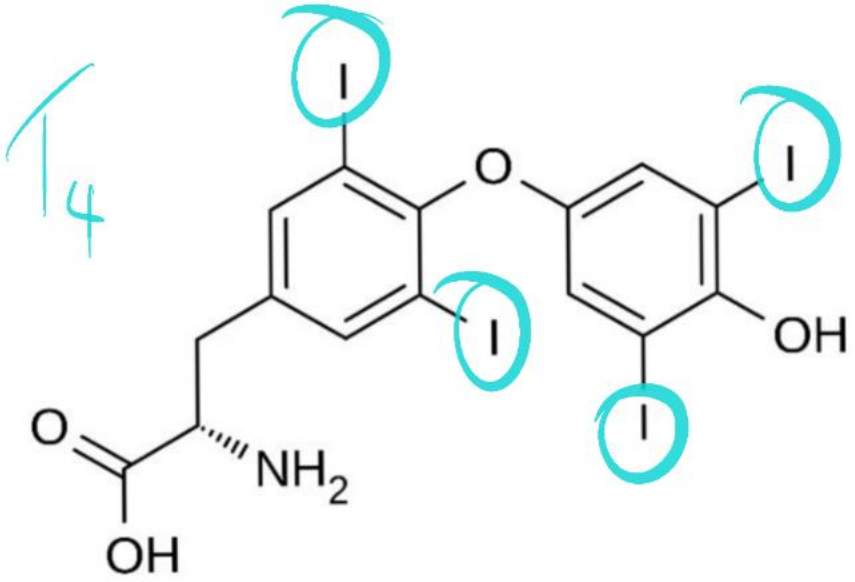
Figure 16.9 Synthesis of thyroid hormone: Marieb, E. and Hoehn, K. Chapter 16 The Endocrine System In: Human Anatomy and Physiology. Eighth edition. San Francisco, USA: Benjamin Cummings; 2010. Pp. 610.

- Iodide (I^-) actively transported into thyroid follicle
- Iodide (I^-) converted to iodine (I)
- Iodine attached to tyrosine to form T1 (monoiodotyrosine (MIT)) OR two iodines attached to a tyrosine to form T2 (diiodotyrosine (DIT))
- Iodinated tyrosines linked together
  - MIT + DIT = T_3
  - DIT + DIT = T_4
- T_3 & T_4 released into blood for biological action

Thyroid Hormone

- Thyroid gland produces 2 thyroid hormones - T_3, and T_4,
- Two types of thyroid hormones: iodine-containing molecules
  - Mostly **levothyroxine (T_4)**
    - Predominant form secreted from the thyroid
    - ~20x more than T3
    - Physiologically “inactive”
  - Some **triiodothyronine (T_3)**
    - “Active” thyroid hormone
    - Mainly generate in periphery following deiodination of T_4 to T_3





M/A: Thyroid hormone effect on target cell

After entering cells, thyroid hormones act primarily at nuclear receptors

Bind to specific DNA sequences in the promotor/regulatory regions of target genes

Transcription of target gene(s) is suppressed if unbound; binding induces gene transcription

Non-genomic effects include vasodilation due to stimulation of NO production by endothelial cells

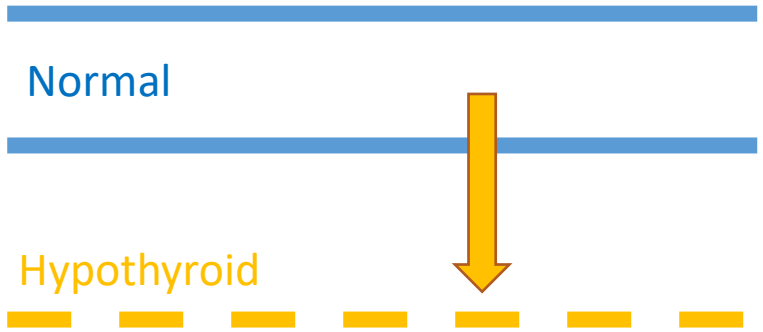
Thyroid hormone function

- Thyroid hormones are ‘permissive’, meaning they allow cells to function normally.
- Thyroid hormone (TH) acts in the developed body to:
  - Maintain **thermogenic and metabolic homeostasis**: makes physiological processes thermodynamically inefficient, promoting heat production
  - **Set basal metabolic rate** (BMR) / **body temperature** – promotes normal oxygen use and BMR, calorigenesis, enhances effect of sympathetic nervous system
  - **Nutrient metabolism and glucose catabolism**, mobilizes fats, necessary for protein synthesis, enhances liver production of cholesterol
  - Skeletal system: **Promotes normal growth** and maturation of skeleton
  - Facilitates normal **cardiovascular, skin and gastrointestinal function**
  - **Promote** increased body **calcium storage**
- Important role in cellular differentiation and CNS development during foetal development
- Critical role in immediate post-partum development of the brain, and general development of the musculoskeletal and reproductive systems

Two broad groups of thyroid disorders

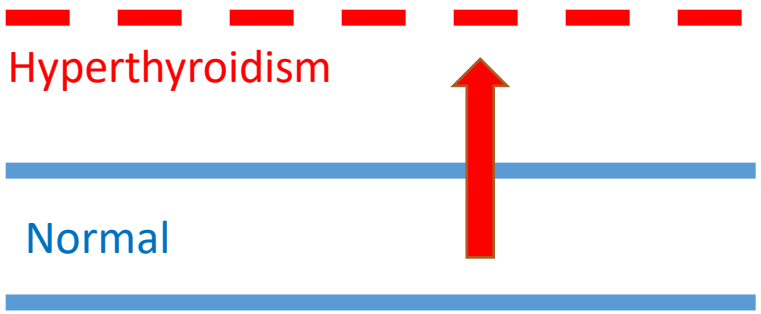
- Low thyroid hormone levels
  - Hypothyroidism
  - **Treated with replacement thyroid hormone**

Hypothyroidism



- Excessive thyroid hormone levels:
  - Hyperthyroidism
  - Treated with thyroid gland suppression medicines

Hyperthyroidism

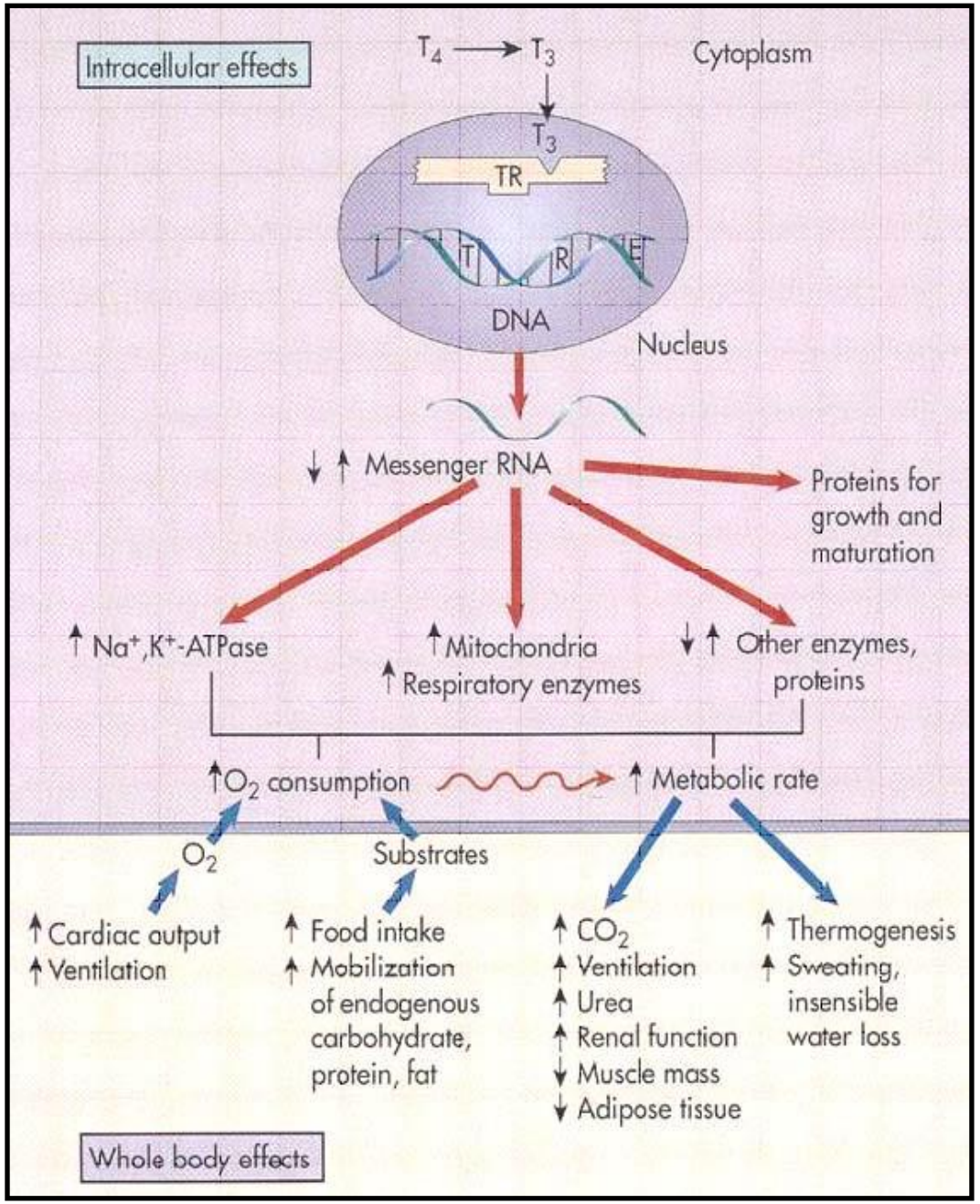


Hypothyroidism

- chronic metabolic disorder characterised by thyroid hormone deficiency
- low serum free thyroxine (T4)
- elevated thyroid stimulating hormone (TSH)
- causes include autoimmune (Hashimoto's), atrophic, congenital, drug-induced, surgery
- treat by replacing T4

Hyperthyroidism (thyrotoxicosis)

- high synthesis and secretion of thyroid hormone
- causes include Graves' disease (autoimmune), toxic multinodular goitre, adenoma, inflammation, iodine-induced



Low thyroid hormone production

Strategy – Replace thyroid hormone

- **Levothyroxine (T_4) – preferred for replacement therapy**
- Liothyroxine (tri-iodothronine, T_3) – shorter half-life - more potent – used for emergency use

	T_3 Lyothyronine	T_4 Levothyroxine (aka thyroxine)
Physiological effect	Same –active form of T_4. Same effect as exogenous thyroxine	Same – T_4 converted to active T_3
Onset	Short	Longer
Duration of action	2-3 days	2-3 weeks
Use	Severe hypothyroidism, thyroid cancer	Hypothyroidism, suppressive regimen in thyroid cancer (high dose) and euthyroid goiter, thyroidectomy, suppresses TSH suppression
Dose / equivalence	Normal range 20-60 micrograms / day in 2-3 divided doses	1.6 micrograms/kg ideal body weight rounded to nearest 25 micrograms Normal dose 50-200 micrograms/day Dose less for elderly – increased CV risk

Kinetics – thyroid replacement therapy

- Pharmacokinetics – Pharmacodynamics
  - Good absorption from GIT – 50-80%
  - 99.9% protein bound – thyroxine-binding globulin and albumin
  - Half-life of T_4 6-7 days but biological half-life measured in weeks – steady state may take 3-4 weeks to achieve: response to dose and changes can be slow.
  - M/A – Mimics effects of endogenous thyroid hormones
- Excessive dose simulates hyperthyroid state: tachycardia, elevated temperature, diarrhea, tremors irritability, weight loss, insomnia
  - also reduced bone density, arrhythmia, ischaemia
- Sub-therapeutic doses simulate hypothyroid state: cold, dry skin, tiredness, weight gain, muscle aches, drowsiness

Kinetics – thyroid replacement therapy

T_3 versus T_4

	T_4	T_3 (liothyronine)
Potency	1	~5
*f_u (fraction unbound)	0.04%	0.4%
V_d	10L (mostly in blood)	40L (cells)
$T_{½}$	6-8 days	1 day
CL/d	1L	24L
Use	Maintenance	Emergency

* Extensively bound to plasma protein

Excessive thyroid hormone production

Strategy – Block thyroid hormone production and/or activation of pro-hormone T_4 to T_3 in the peripheries

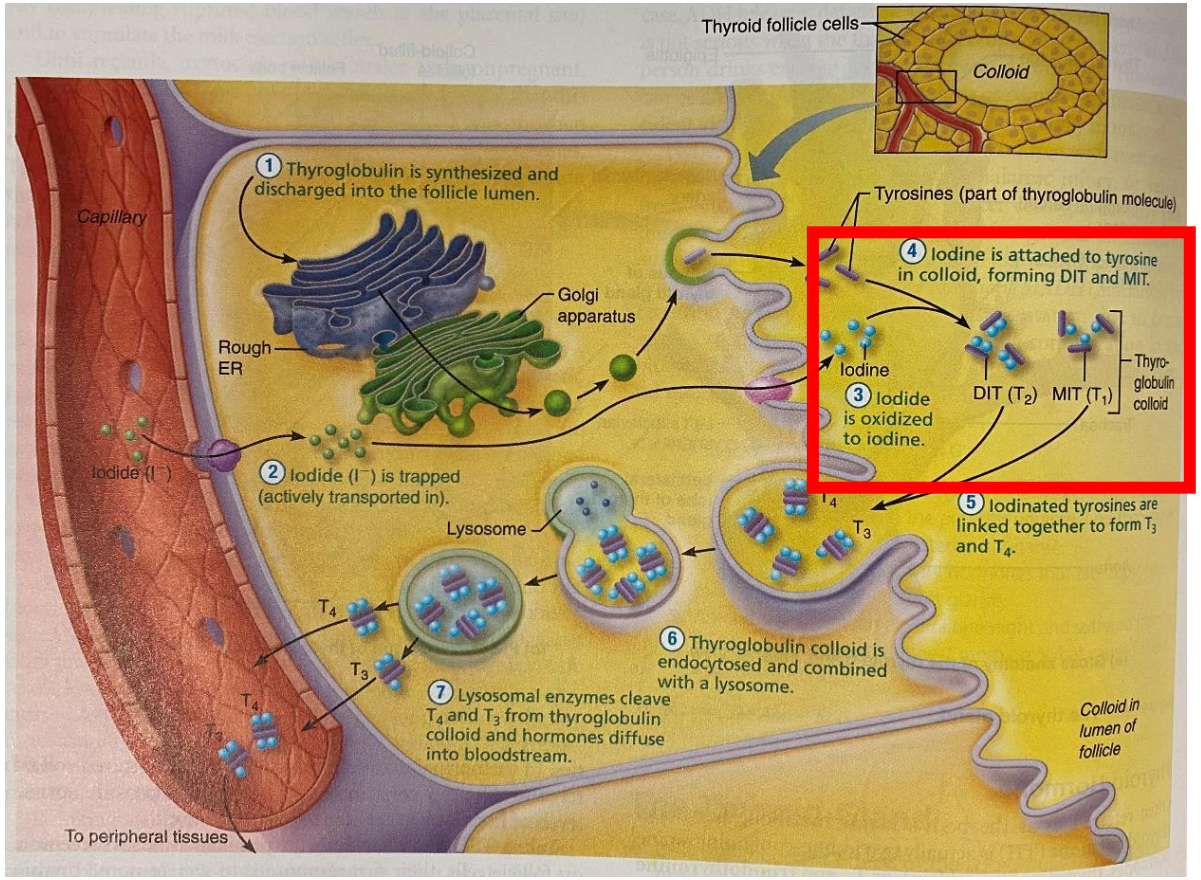
- Carbimazole
- Propylthiouricil (PTU)

Treatment: Titrated thioureylenes

- Carbimazole is a pro-drug, converted to active methimazole.
- Methimazole binds to thyroid peroxidase enzyme so inhibits it from coupling iodine to thyroglobulin and forming MIT or DIT.
- This reduces the production of T_3 and T_4. Competitively inhibit the iodination of tyrosine residues in thyroglobulin

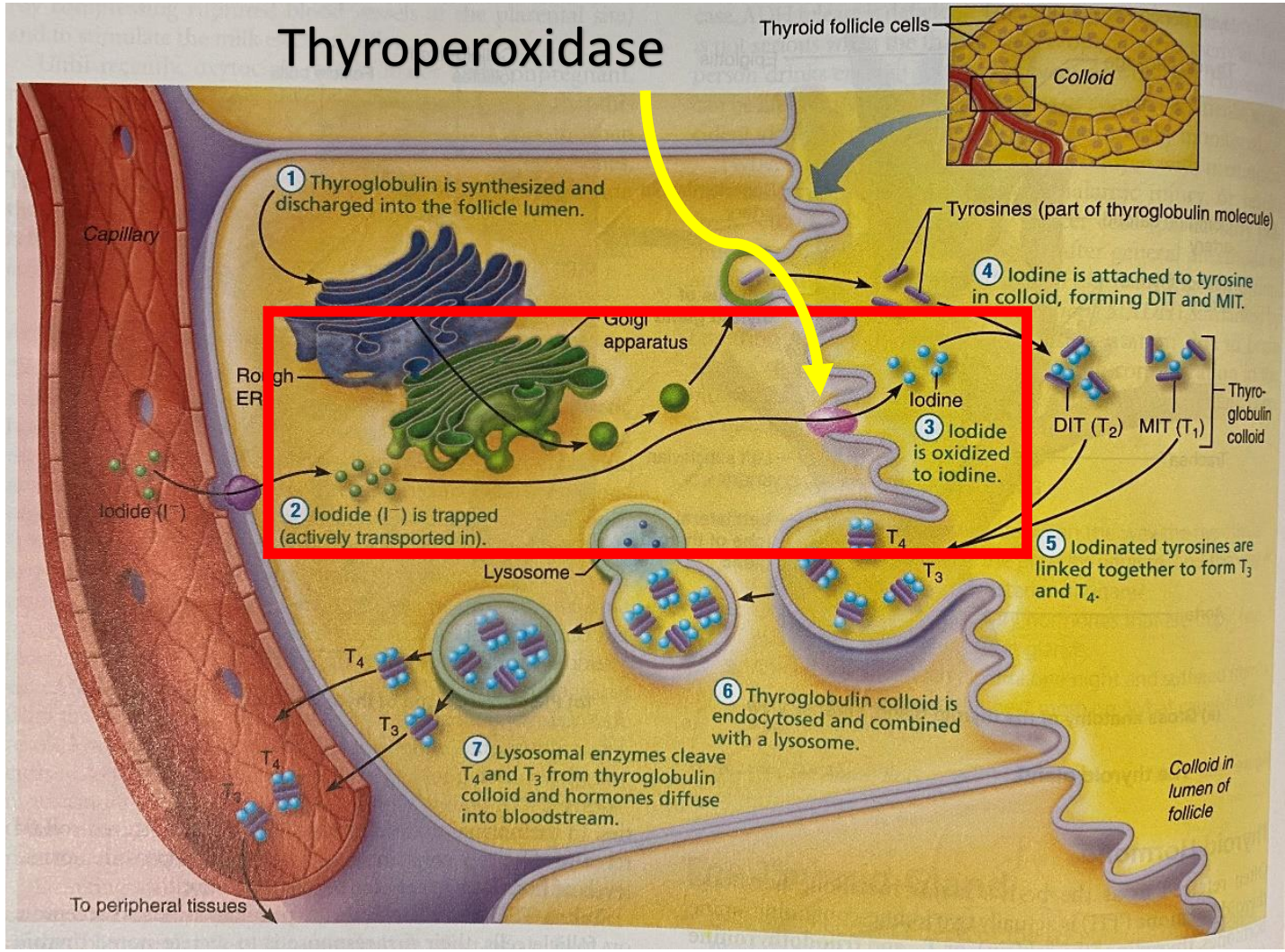
Adverse effects / Precautions / Interactions

- itching, rash, leucopenia, GI disturbances
- agranulocytosis (rare)



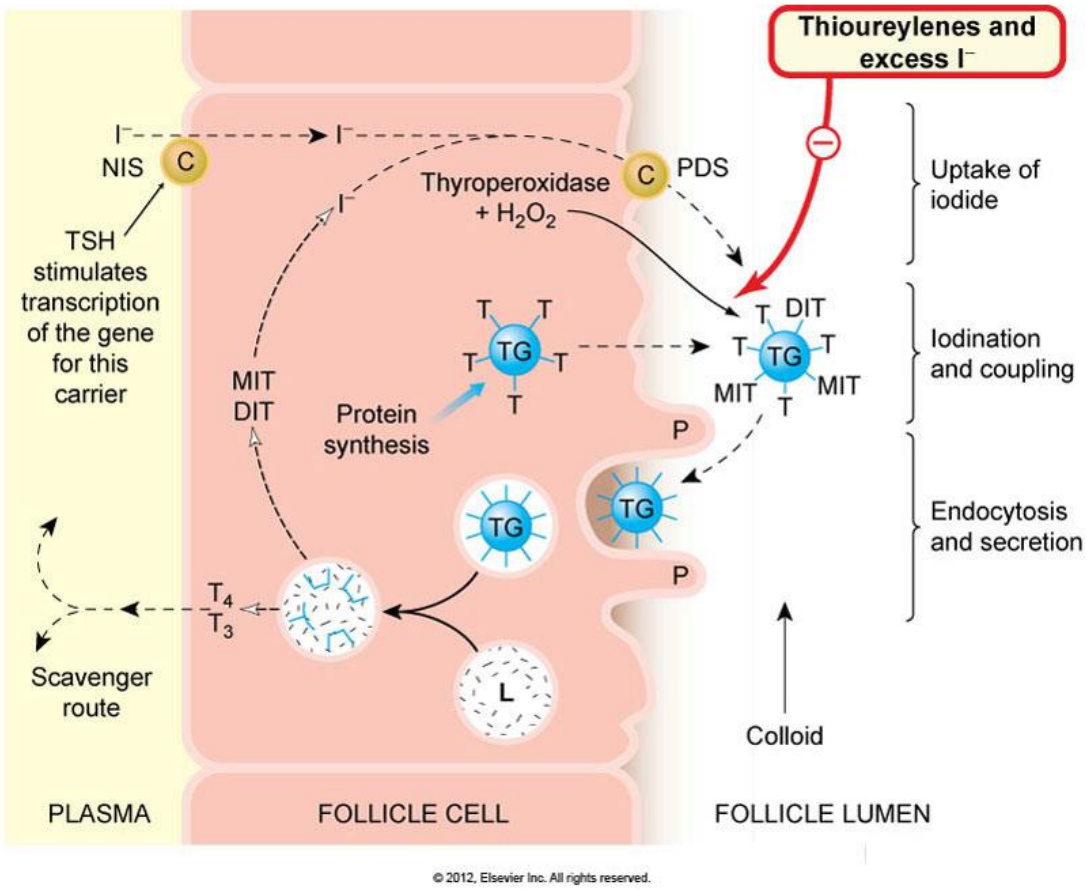
Treatment: Titrated thioureylenes

- Propylthiouracil (PTU) inhibits thyroperoxidase, the enzyme that oxidises iodide to iodine. The reduction of available iodine reduces the production of T_3 and T_4 in the thyroid gland.
- Propylthiouracil also inhibits the conversion of T_4 to T_3 in the peripheral tissues



Treatment: Titrated thioureylenes

- Propylthiouracil (PTU) inhibits thyroperoxidase, the enzyme that oxidises iodide to iodine. The reduction of available iodine reduces the production of T_3 and T_4 in the thyroid gland.
- Propylthiouracil also inhibits the conversion of T_4 to T_3 in the peripheral tissues



Drug induced changes in thyroid function / interactions etc

- drugs can induce hypo or hyperthyroidism
- drug interactions with thyroxine
- drugs can interfere with thyroid function testing
- metabolism of some drugs is affected by hypo / hyperthyroidism

Table 1. Classification of Drug Effects on the Thyroid.*

Interference with endogenous thyroid function
Disruption of hypothalamic–pituitary control
Decreased thyroid hormone production or release
Increased thyroid hormone production
Enhanced thyroid autoimmunity
Destructive thyroiditis
Changes in thyroid hormone–binding proteins
Inhibition of thyroid hormone activation (T_4-to-T_3 conversion)
Displacement of thyroid hormone from binding proteins
Increased thyroid hormone metabolism or elimination
Interference with thyroid hormone therapy
Decreased pill dissolution
Decreased thyroid hormone absorption
Decreased free thyroid hormone levels
Increased thyroid hormone metabolism or elimination
Interference with thyroid laboratory testing in euthyroid persons

Osteoporosis

- systemic condition characterised by decreased bone mass and deterioration in bone microstructure
- leads to increased bone fragility and increased fracture risk
- major public health concern
    - large numbers of undiagnosed / untreated

- causes – female gender, post menopause
- vit D, calcium deficiency
- endocrine and malabsorption disorders
- drug-induced, physical inactivity

Osteoporosis - Management

Strategies to reduce the risk and treatment

- prevent falls
- increase weight-bearing exercise and balance training
- ensure adequate calcium intake and vitamin D
- stop smoking and limit alcohol intake
- maintain ideal body weight

Two types of agents are currently used for treatment of osteoporosis

- Antiresorptive drugs that decrease bone loss, e.g. bisphosphonates, calcitonin, selective [o]estrogen receptor modulators (SERMs), denosumab
- Anabolic agents that increase bone formation, e.g. PTH, teriparatide

Bisphosphonates

Exemplar

- alendronic acid (alendronate)

Mechanisms of action

- form strong complexes with calcium in bone matrix
- taken up into osteoclasts during bone resorption and inhibit several enzymes in the mevalonate biosynthetic pathway
- decreases prenylation of proteins required for osteoclast function and survival and inhibits osteoclast bone resorption

Adverse effects / Precautions / Interactions

- increased risk of upper GIT adverse effects
- caution in renal impairment, dental complications
- nausea, diarrhoea, headache, hypocalcaemia, MSK pain
- food, drinks etc affect absorption

Denosumab

indications

- recommended for the treatment of osteoporosis in postmenopausal women at increased risk of minimal trauma fracture

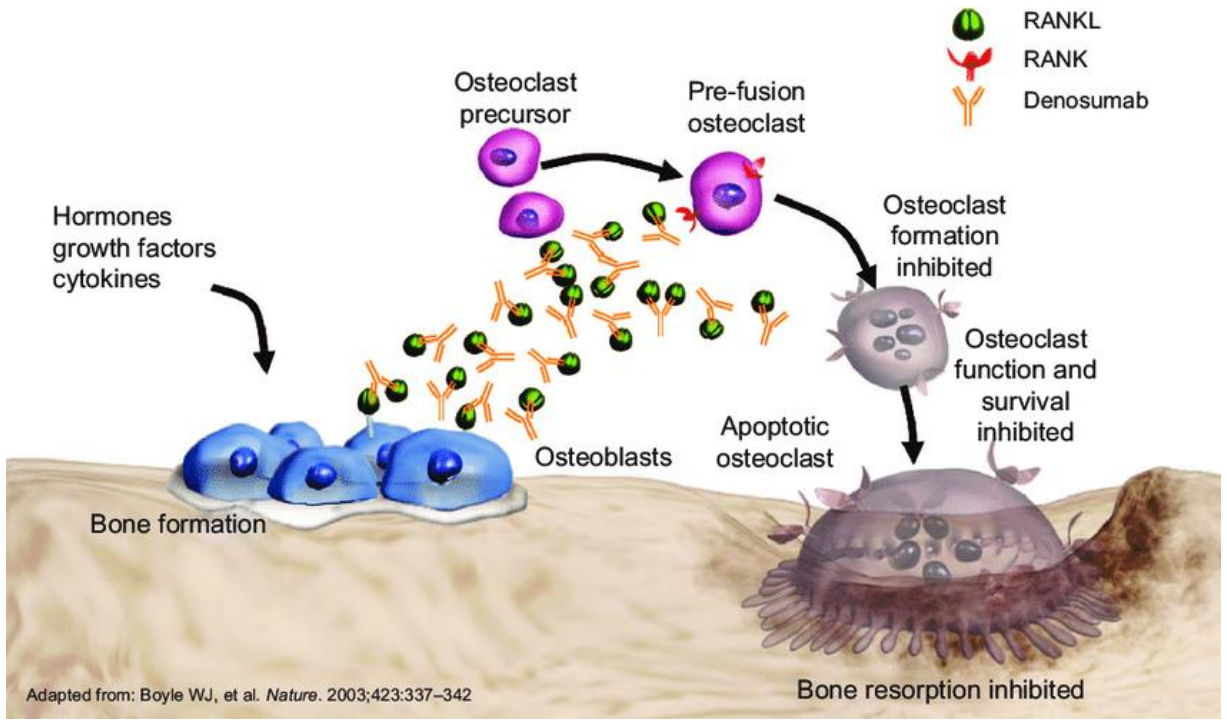
Mechanisms of action

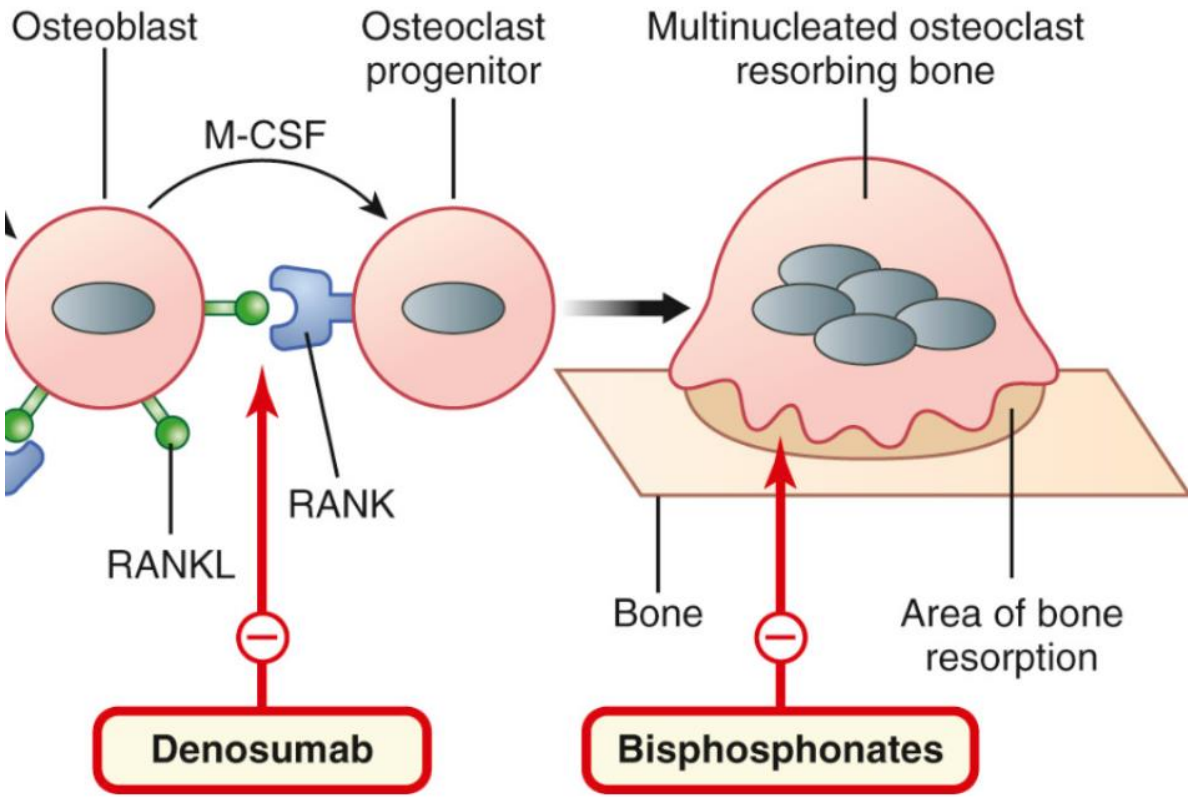
- monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL)
- important regulator of osteoclast development and activity
- Denosumab prevents RANKL binding to its receptor (RANK) on osteoclasts surface reducing osteoclast formation, function and survival
- Results in decreased bone resorption and increased mass and strength

Adverse effects / Precautions / Interactions

- subcutaneous admin
- hypocalcemia in renal impairment

Denosumab


RANKL
RANK
Denosumab
Osteoclast precursor
Pre-fusion osteoclast
Hormones growth factors cytokines
Osteoclast formation inhibited
Osteoclast function and survival inhibited
Osteoblasts
Apoptotic osteoclast
Bone formation
Bone resorption inhibited
Adapted from: Boyle WJ, et al. Nature. 2003;423:337–342


Osteoblast
Osteoclast progenitor
Multinucleated osteoclast resorbing bone
M-CSF
RANK
RANKL
Bone
Area of bone resorption
Denosumab
Bisphosphonates