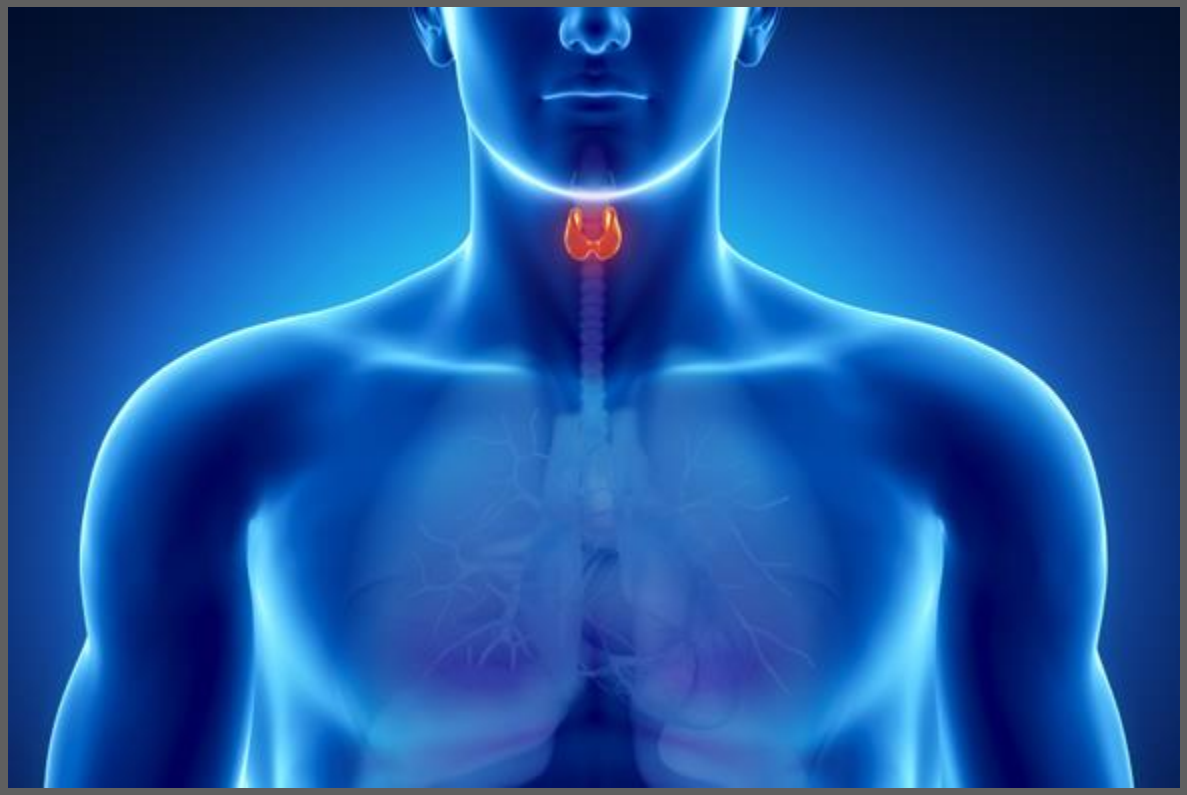
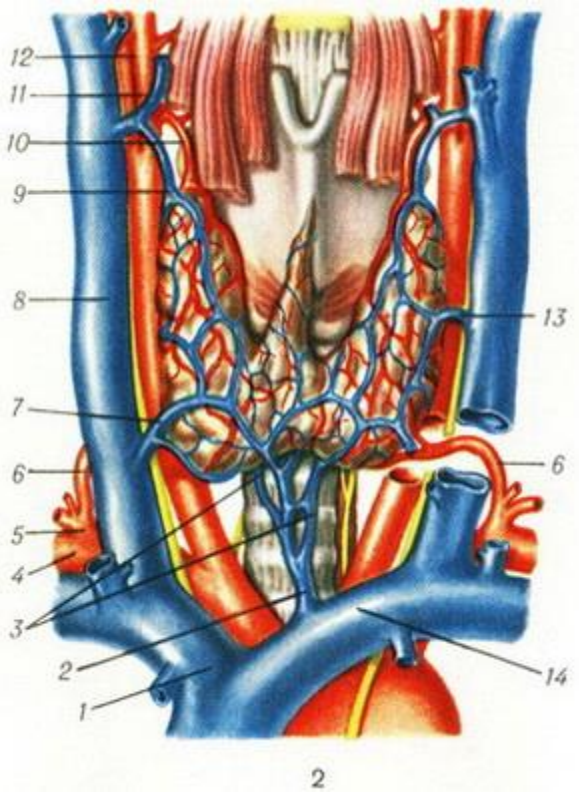
Thyroid gland (*glandula thyreoidea*)



Thyroid gland - anatomy

- frontal side of the neck, attached to the larynx and trachea
- two lobes connected by isthmus; lobus pyramidalis present in some individuals
- larger in women, geographically further from the sea and at higher altitudes
- blood and lymphatic circulation highly developed



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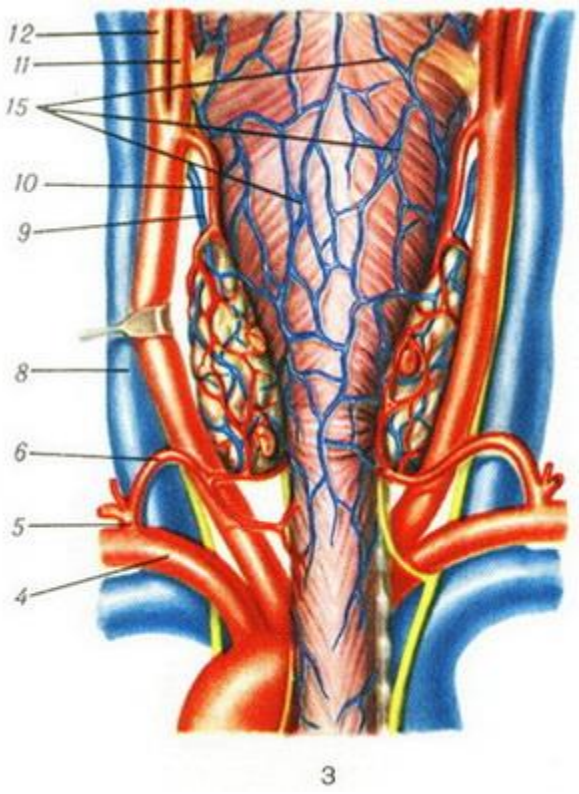

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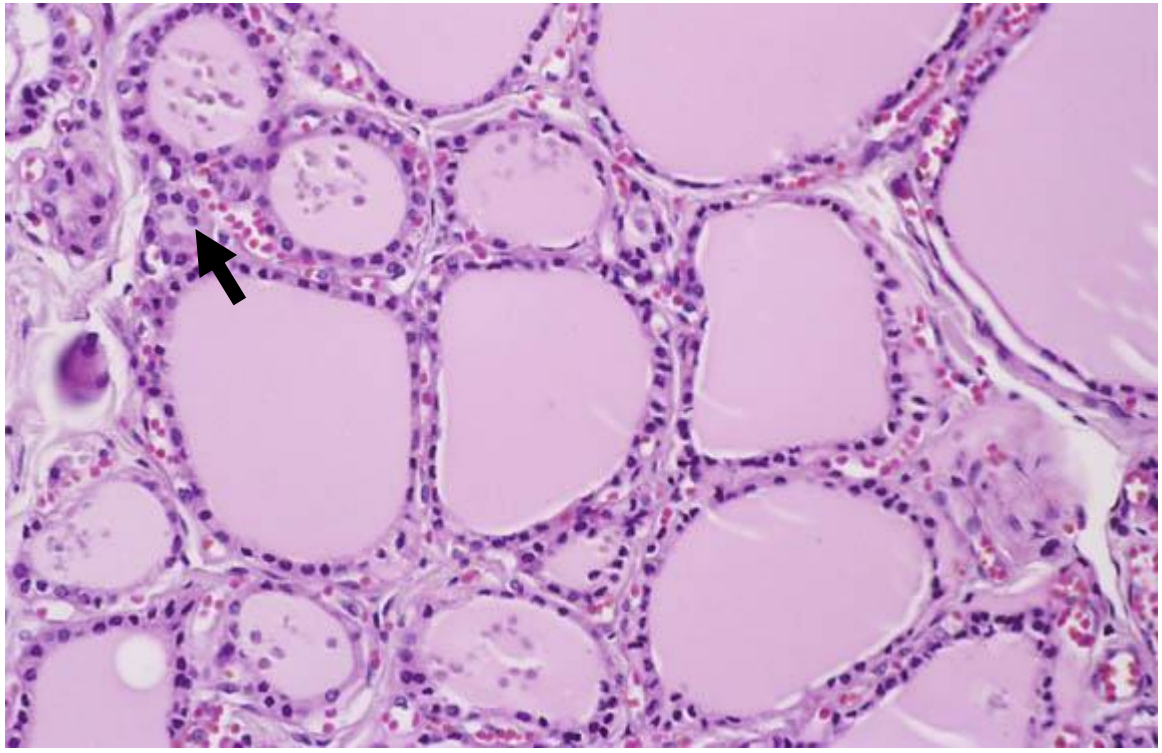
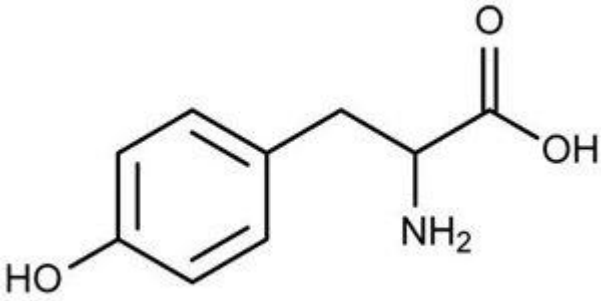
Thyroid gland - microanatomy

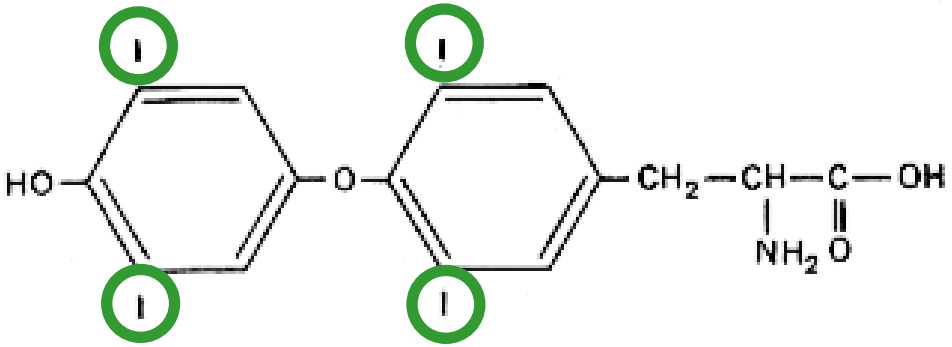
- fibrous septa divides the gland into lobes (lobuli), which consist of follicles, 50 – 500 μm) separated by ligaments and capillary and lymphatic vessels
- follicles composed of one layer of cubic follicular cells and filled with colloid (viscous and homogeneous fluid, thyroglobulin)
- parafollicular cells (C-cells producing **calcitonin**) of neuroectodermal origin (neural crest)



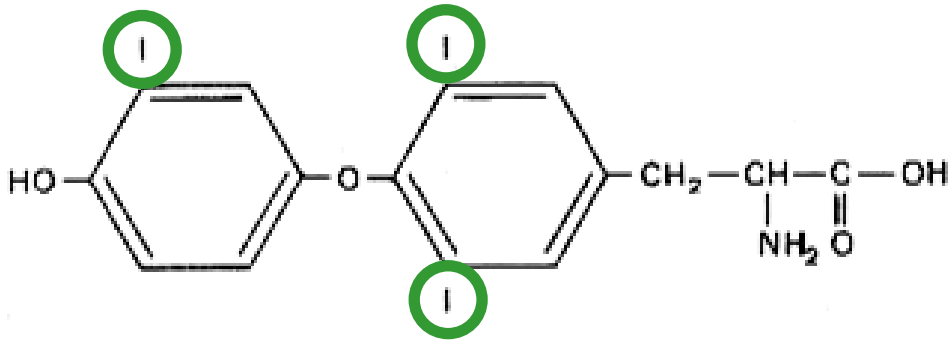
Thyroid hormones: triiodothyronine (T_3), tetraiodothyronine/thyroxine (T_4)

- derived from amino acid tyrosine
- essentially double tyrosine with three or four iodine atoms
- lipid soluble





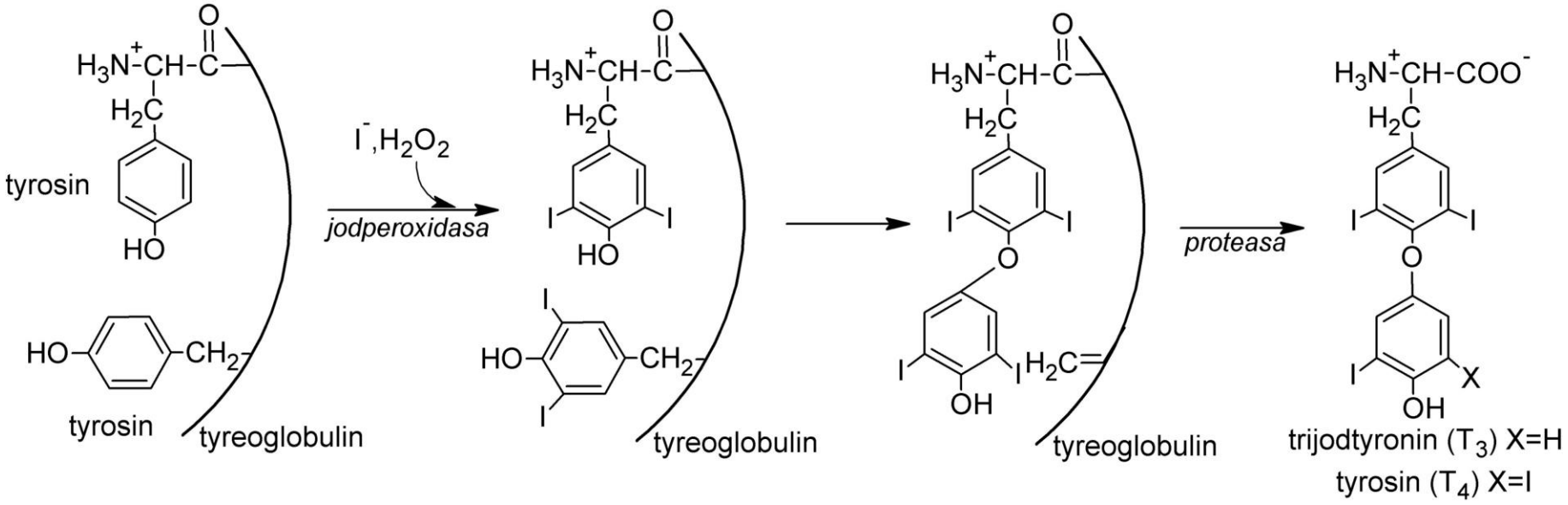
3, 5, 3', 5' - Tetraiodothyronine (thyroxine, T_4)



3, 5, 3'-Triiodothyronine (T_3)

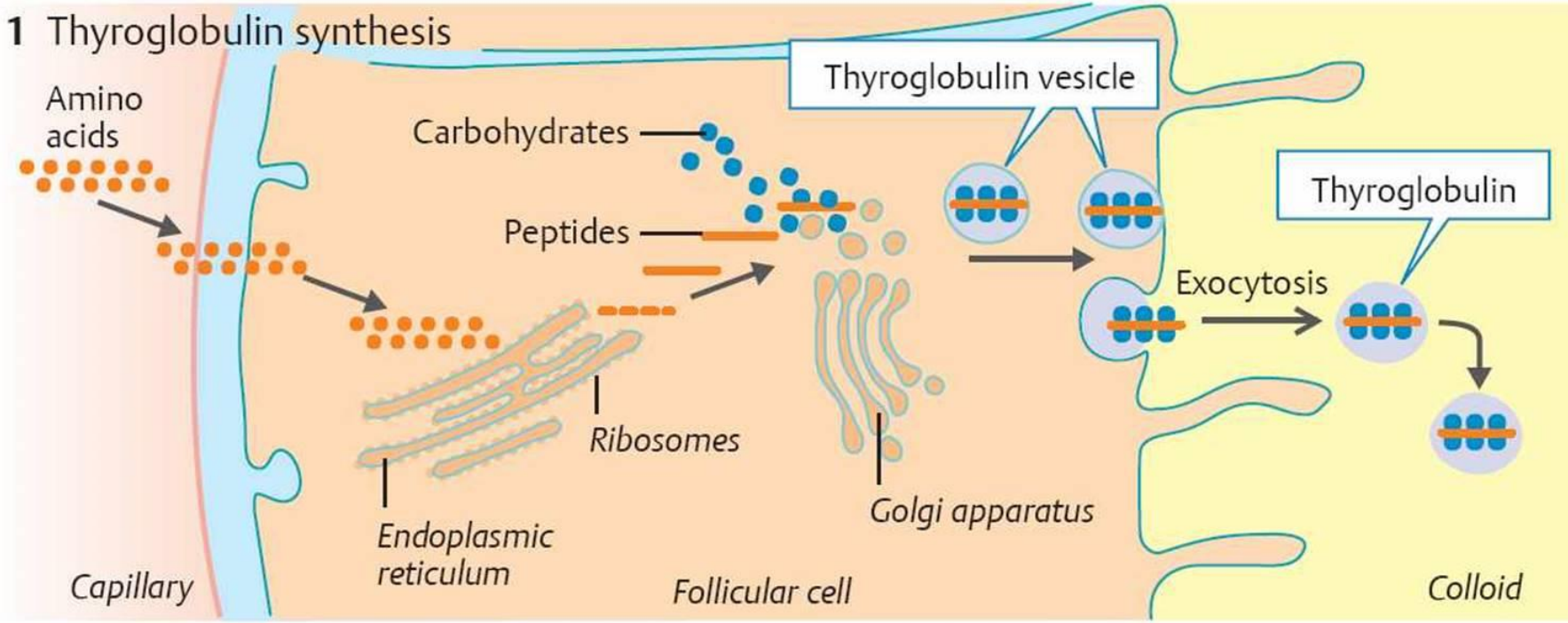
Thyroid hormones - synthesis

- modification of thyroglobulin-bound tyrosines
- posttranslational iodine-binding
- proteolytic cleavage
- released as T_3 or T_4
- binding to globulins and transport



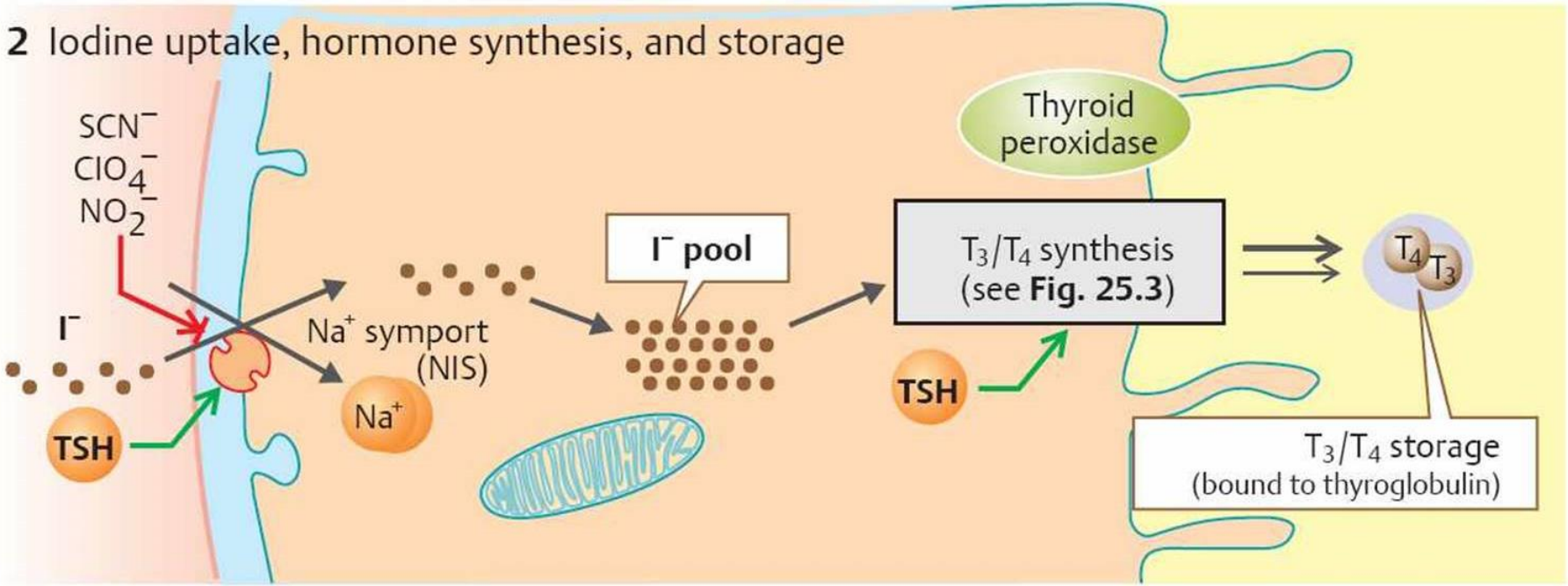
Thyroid hormones - synthesis of thyroglobulin

- protein 660kDa
- synthesis on follicular cell ribosomes
- glycated in the Golgi apparatus
- packed in granules
- exocytosis from follicular cells to colloid



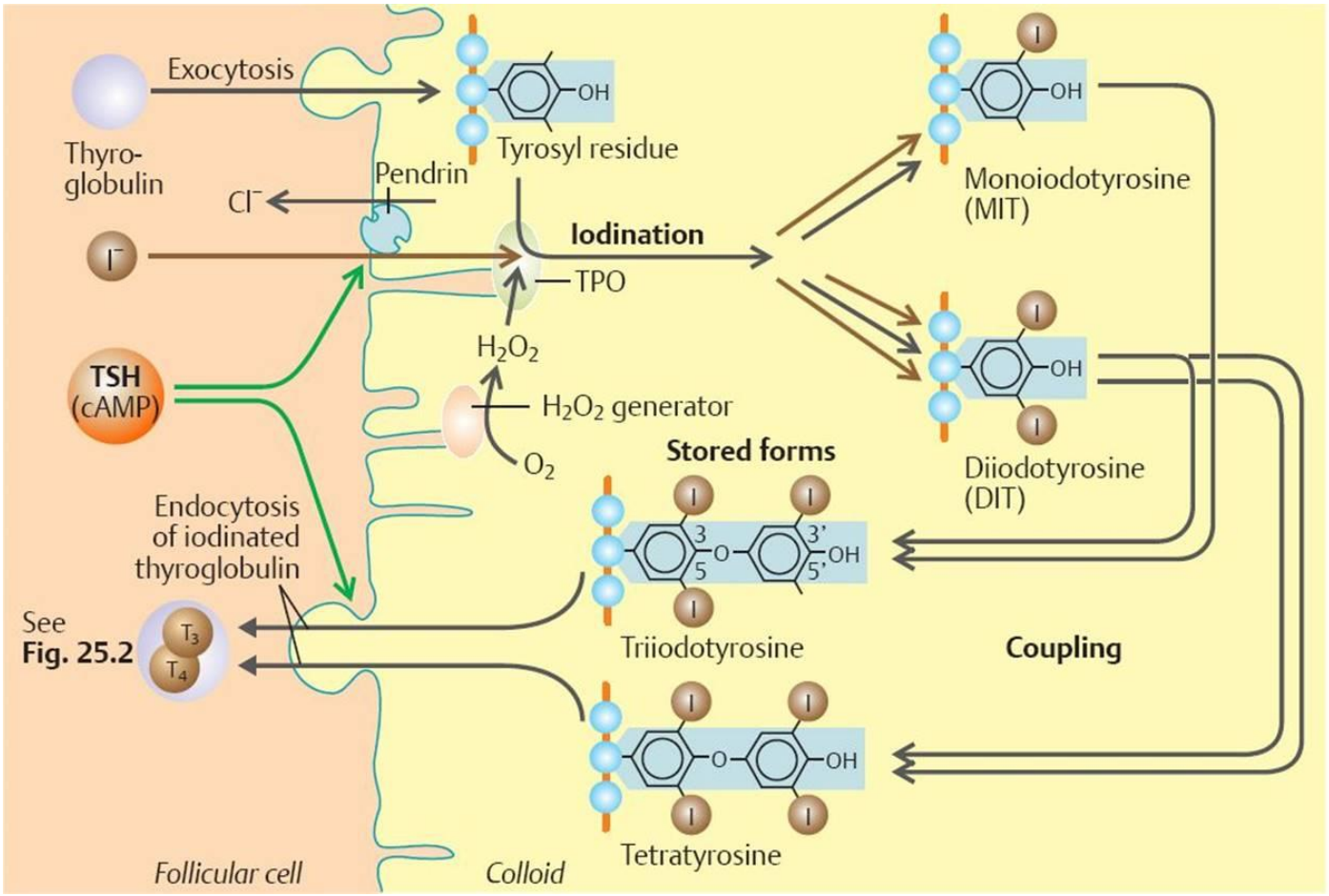
Thyroid hormones - synthesis

- secondary active iodine transport into follicular cells (two Na^+ to one I^-)
- concentrated app. 25x (TSH stimulation via cAMP > 250x concentrated)
- competition with other anions
- transported to colloid by pendrin protein (transported against Cl^-)
- further processing by **iodine peroxidase/thyroperoxidase** on microvilli of follicular cells (oxidation of I^- to I^0)



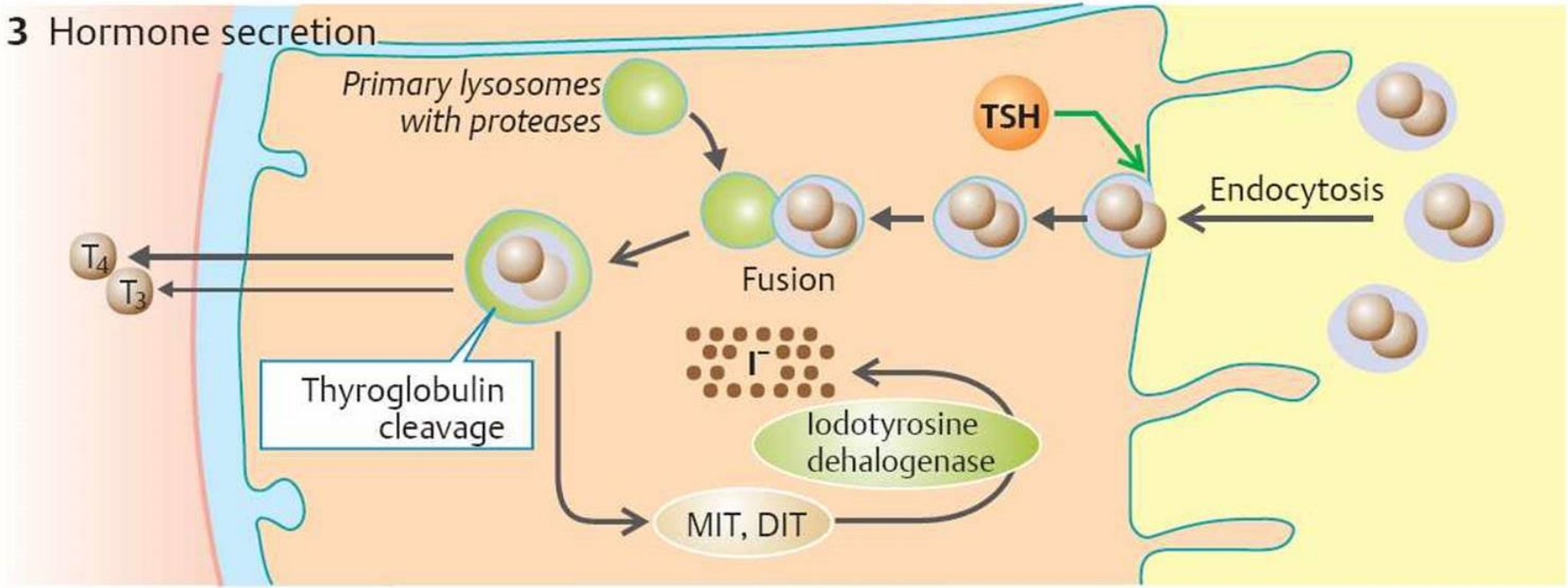
Thyroid hormones - synthesis

- thyroglobulin iodination stimulated by TSH via IP_3
- iodinated tyrosines on thyroglobulin react with each other > T_3/ T_4
- stored in the colloid (in the form of T_3 and T_4)

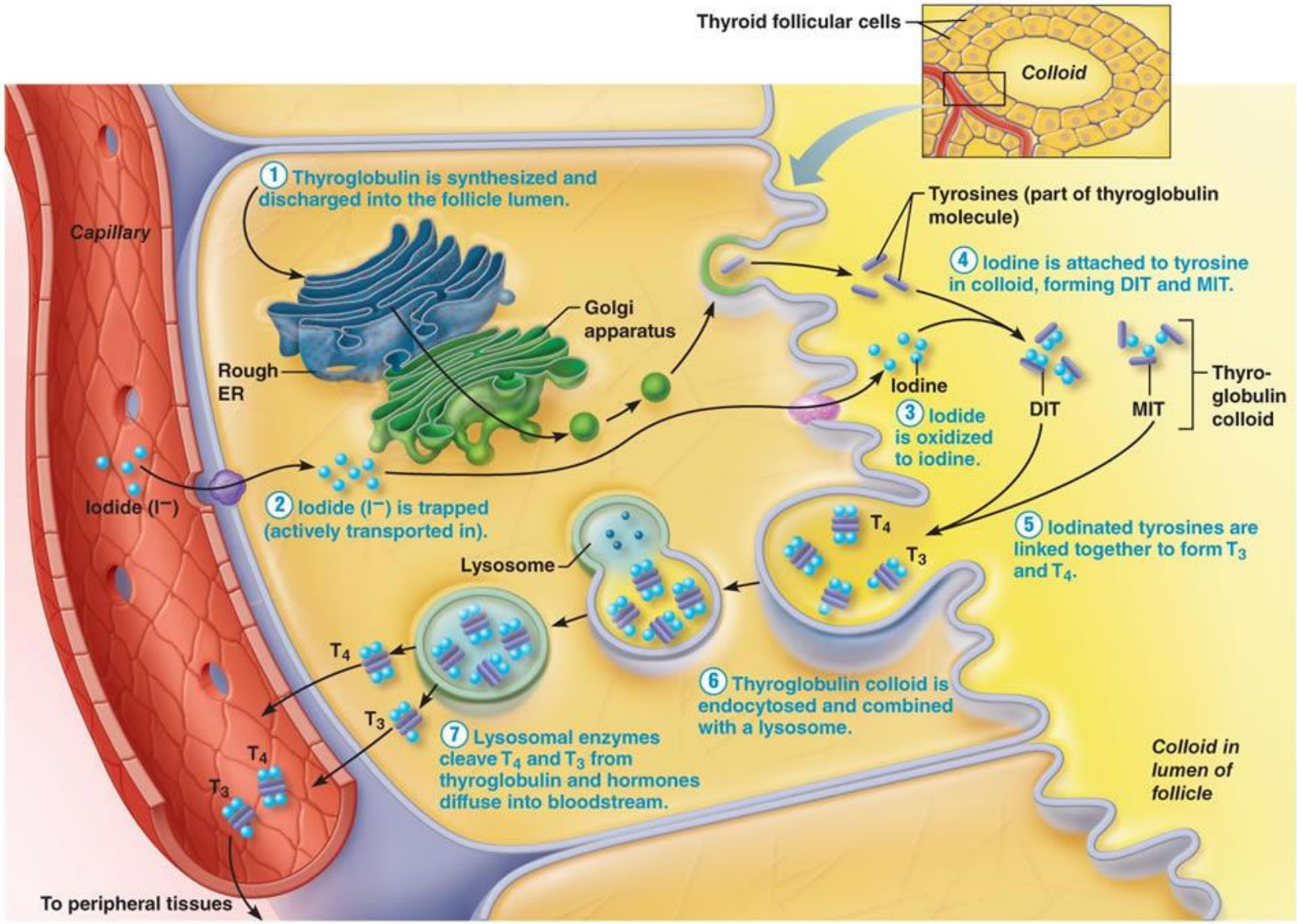


Thyroid hormones - secretion

- thyroglobulin transferred to follicular cells by endocytosis
- forming of phagolysosomes
- T_3 and T_4 cleaved from thyroglobulin by proteases
- T_3 and T_4 released to the blood
- monoiodotyrosine (MIT) and diiodothyrosine (DIT) residues used for iodine recycling

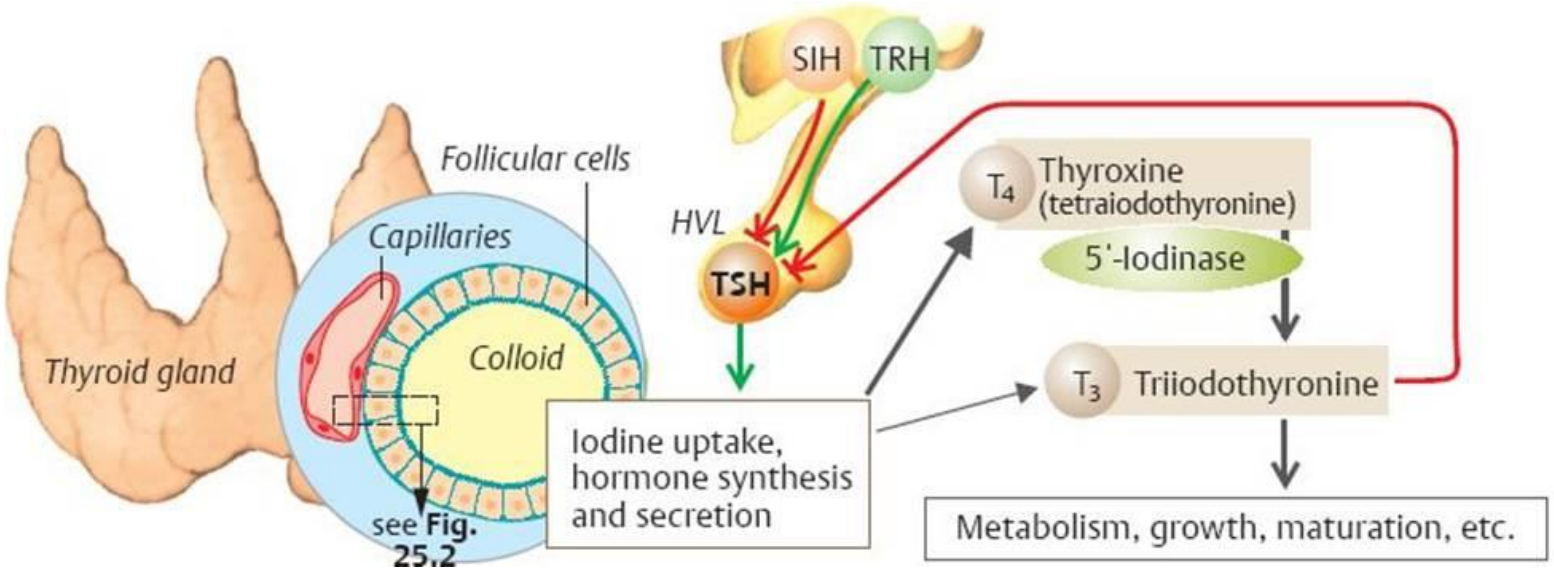


Thyroid Hormones:
Summary of the synthesis and secretion



Thyroid hormones - regulation and transport

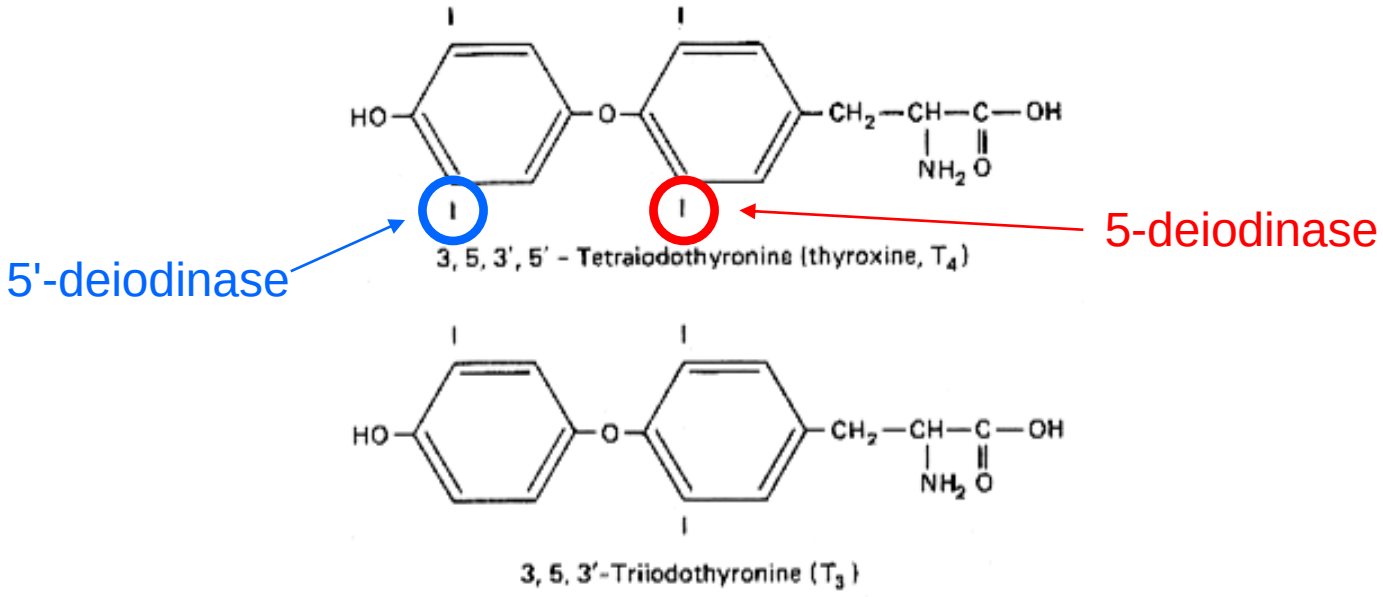
- hypothalamic-pituitary axis (stimulation by **thyroliberin-thyrotropin, TRH-TSH;** inhibition by **somatostatin, SIH**)
- stimulated by a decrease in thyroxine (T_4 deiodinated to T_3 in target cells), decreased BMR, hypothermia
- negative feedback (exercise > increase in body temperature > inhibition)



- globulin binding (thyroxine-binding globulin, TBG - primarily T_4); in smaller quantities bound to prealbumin and serum albumin
- free T_3 and T_4 transported in trace amounts (0.3 %), however, they are active

Thyroid hormones - action

- T_3 3x - 8x more efficient than T_4 which is considered a storage form
- T_3 acts faster
- half-life 1 day (T_3) and 7 days (T_4)
- 80 % of T_3 is formed by cleaving iodine from T_4 in the liver, kidneys and other tissues (brain, pituitary gland, placenta, brown adipose): **5'-deiodinase**
- **5-deiodinase** produces inactive **reverse T_3** by cleaving out iodine on the inner ring > regulation of TSH production during starvation
- **active transport to target cells (ATP) and binding to nuclear receptors**



Thyroid hormones - activity

- hormone + nuclear receptor (monomer or dimer TR/RXR) > binding to DNA response elements (co-activator, RNA polymerase) > gene expression

- increase basal metabolism (increase the number of mitochondria, cristae, stimulates cholesterol processing)
- ↑ **energy metabolism - ↑ oxygen consumption - ↑ heat production** (moreover supports lipolysis of brown fat by regulating the expression of necessary enzymes)
- synergy with growth hormone
- T_3 stimulates growth (skeleton, brain) and maturation, increases heart rate and activity, supports catabolism of proteins and carbohydrates, increases sensitivity to other hormones and their effects (insulin, glucagon, somatotropin, adrenaline)

Thyroid hormones - pathophysiology

- the disorder can occur in any of the steps of T_3 and T_4 synthesis or at the level of their transporters and receptors
- disorders may be manifested by the enlarged thyroid gland (**goitre**) - release T_3 and T_4 may be both increased (e.g. thyroid proliferation due to autoantibody binding) and decreased (e.g. iodine deficiency > decreased T_3 and T_4 > increased TSH production > proliferation of follicular cells)

Thyroid hormones - hyperthyroidism

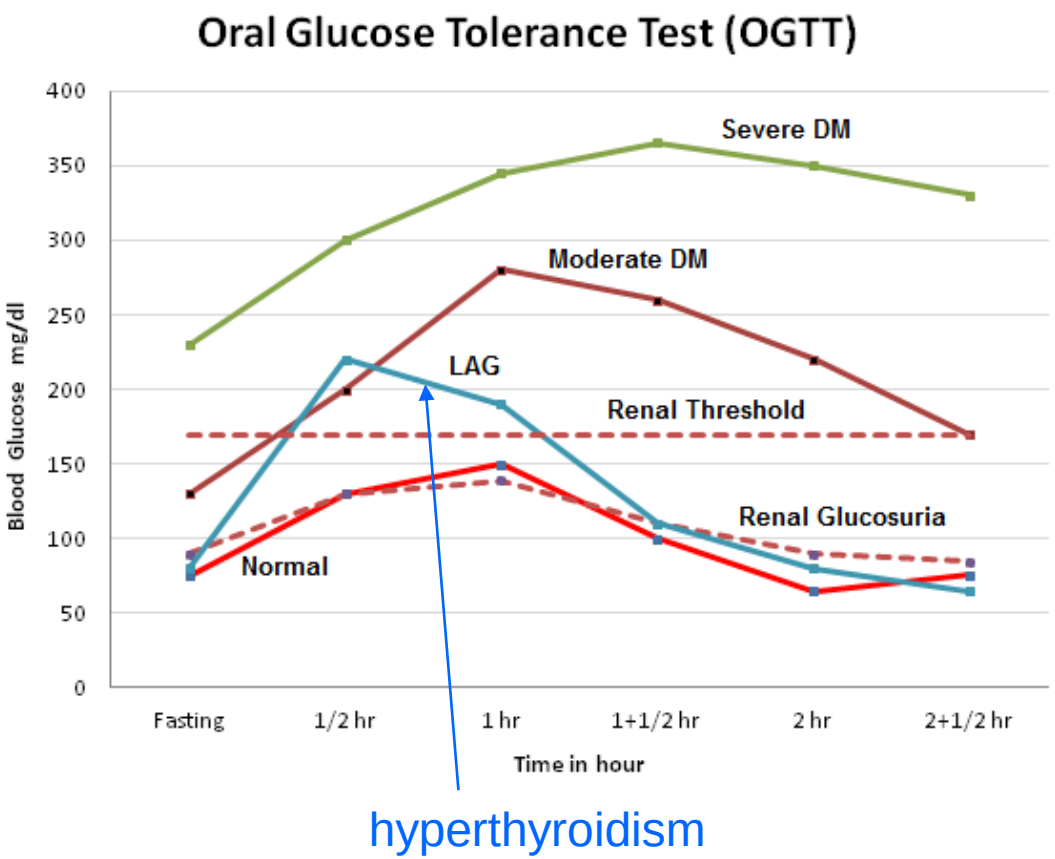
Causes:

- tumors
- inflammation of the thyroid gland (*thyroiditis*)
- increased TSH secretion (for instance its release increases under stress)
- autoantibodies that bind to TSH receptors (**Graves-Basedow disease**)

Symptoms:

- increased metabolism (weight loss, hyperventilation)
- increased heat production (increase in basal metabolism up to 2x)
- patients experience heat intolerance and increased sweating
- increased lipolysis and proteolysis (muscle degradation and osteoporosis)
- saccharide metabolism > reversible *diabetes mellitus* (hyperglycemia)
- growth can be accelerated in children
- increased cardiac output and systolic blood pressure
- increased glomerular filtration in the kidneys and intestinal muscle function (diarrhea)
- increased neuromuscular irritability (tremor, muscle weakness, insomnia)

Thyroid hormones - excess



hyperthyroidism

Graves-Basedow disease (disease Basedowi)

- swelling of the soft tissues behind the bulb causes exophthalmos, double vision, tearing
- increased serum T_3, T_4, **reduced TSH levels**, antibodies against TSH-receptors

Thyroid hormones - hypothyroidism

Causes:

- iodine deficient in the diet
- inflammatory damage or thyroid removal
- less often due to insufficient action of the TRH-TSH axis
- thyroid suppressors: thiouracil, thiocyanate, glutathione and others

Symptoms:

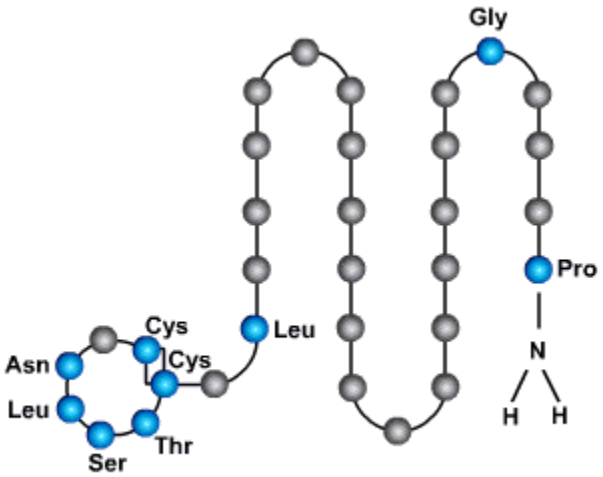
- opposite to hyperthyroidism: decreased basal metabolism, cold intolerance, lipolysis, kidney function (swelling), anemia, hypoglycemia etc.
- **irreversible brain damage in newborns!**

Calcitonin (thyrocalcitonin, CT)

- 32 amino acids
- calcitonin-like protein family (alternative splicing of the gene product; for instance to calcitonin gene-related peptide > vasodilatory effect)
- parafollicular thyroid cells (C-cells) with Ca $^{2+}$ receptors

Regulation:

- hypercalcemia > induction of CT production; hypocalcemia > inhibition of CT production
- stimulating effect of gastrin and other gastrointestinal hormones on CT secretion



Calcitonin

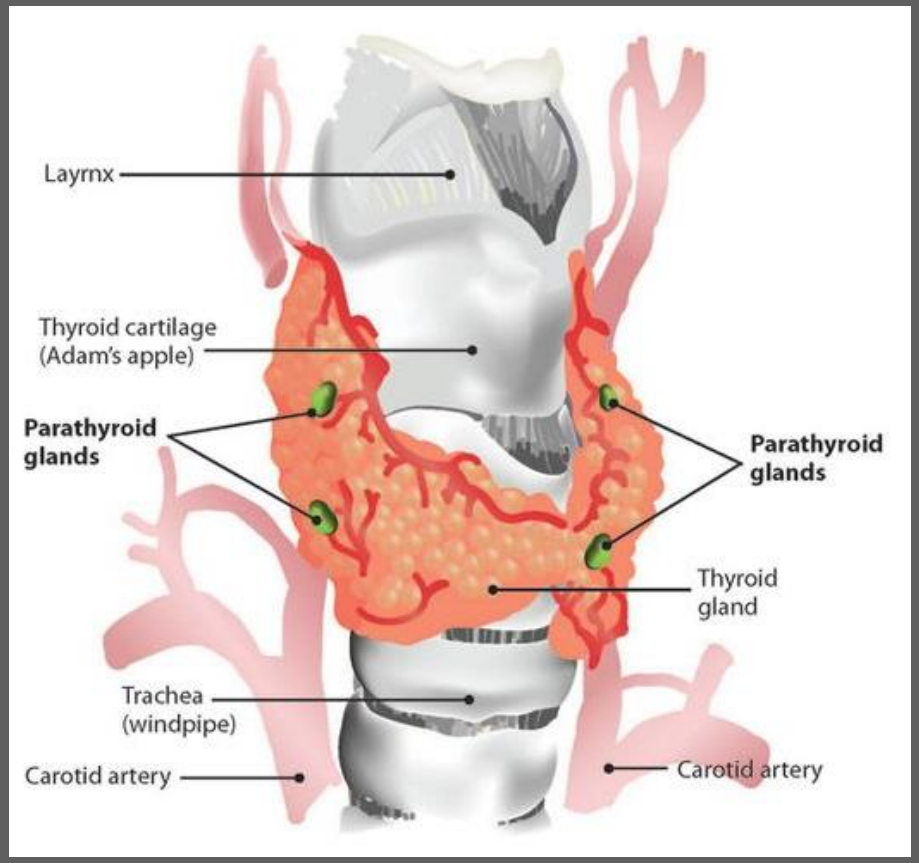
Calcitonin (thyrocalcitonin, CT)

- G protein > adenylate cyclase > cAMP
- **reduces increased Ca^{2+} concentration in the blood** (antagonist of the parathyroid hormone)

- 99 % of Ca^{2+} in the bones; 1% in body fluids (60 % diffusible and 40 % bound to albumins and other plasma proteins)
- total calcium in serum 2.1-2.6 mmol/l; normal concentration of ionized Ca^{2+} is 1.25 mmol/l
- Ca^{2+} for neuronal transmission, muscle contraction and blood clotting
- calcium regulated together with phosphate > precipitate in high concentrations
- regulation through the intestine, kidneys and bones

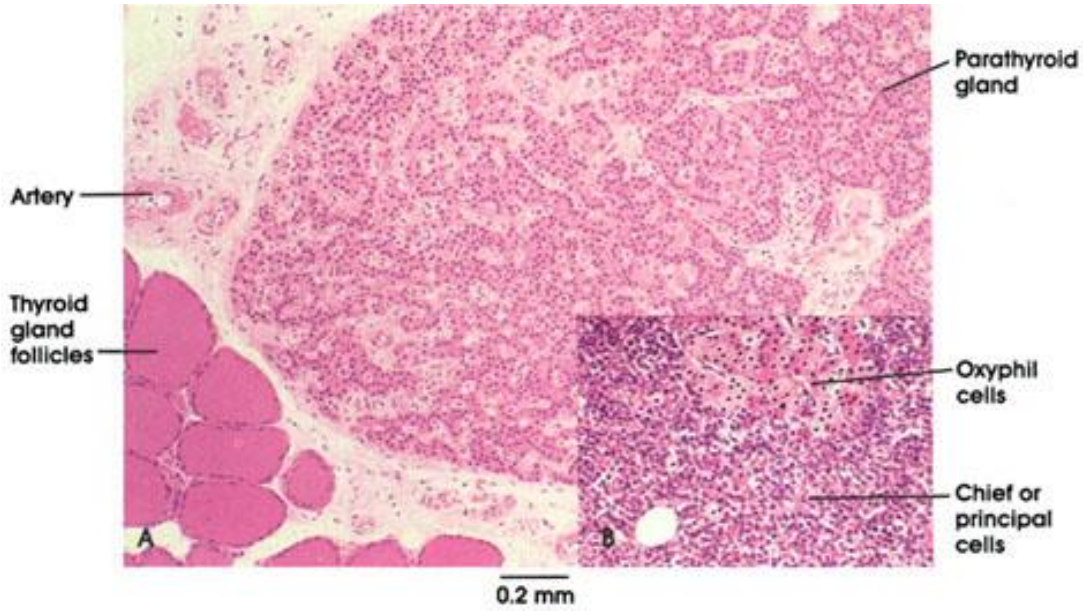
- suppresses osteoclasts in bones
- reduces Ca^{2+} absorption in the intestine
- increased Ca^{2+} deposition in the bones
- increases Ca^{2+} and phosphates secretion by the kidneys
- prevents hypercalcemia after eating
- acts to protect bones during pregnancy and lactation

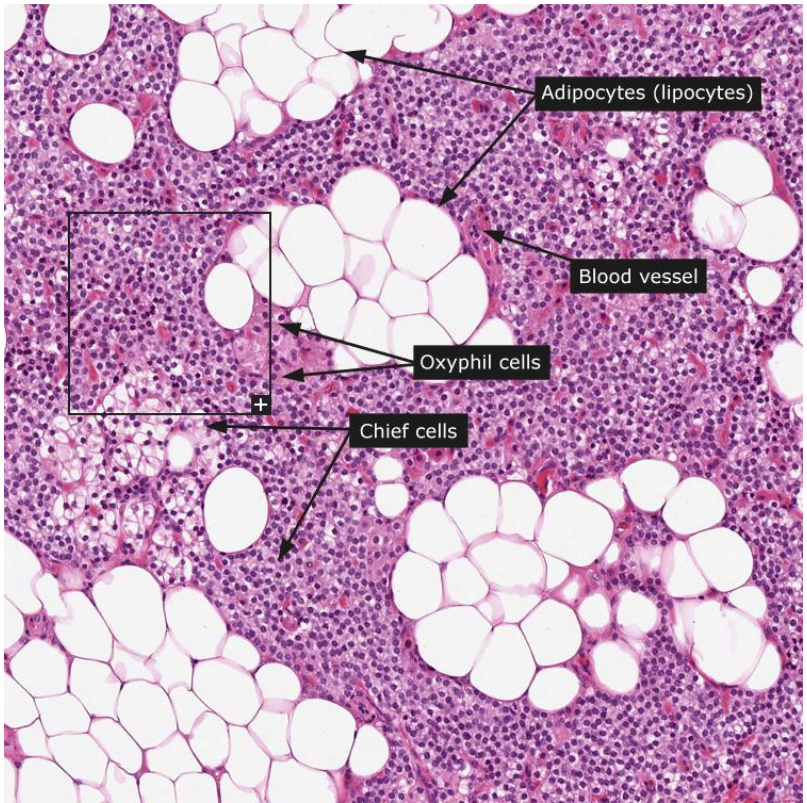
Parathyroid glands (*glandulae parathyroideae*)



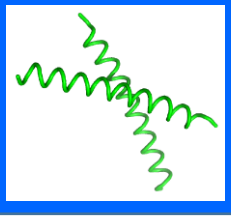
Parathyroid glands - structure

- usually 4 lenticular bodies on the back of the thyroid gland (common blood and lymphatic supply)
- collagen ligaments, septa with adipocytes appearing with increasing age)
- Ca^{2+} receptors
- **chief cells** silver stainable (secretory granules, produce parathyroid hormone) and **oxyphil cells** (without secretory granules, a lot of mitochindria and glycogen > paracrine regulation)

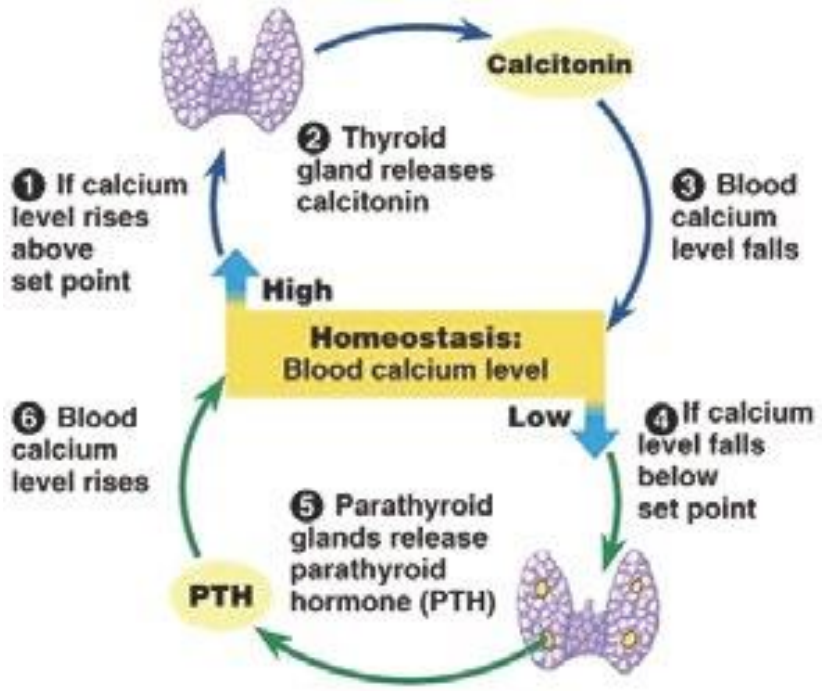




Parathyroid hormone (PTH)



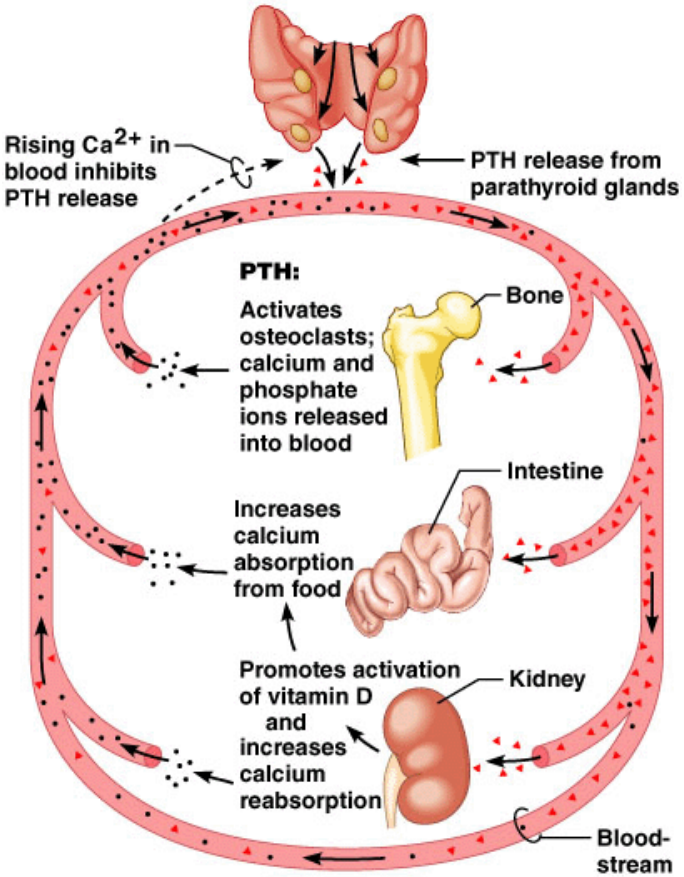
- 84 amino acids, dimer with helical structure
- synthesis and release are controlled by Ca^{2+} concentration in parathyroid glands (↑ Ca^{2+} > ↓ PTH)
- half-life approximately 4 minutes
- target organs: mainly bone, kidney and intestine (*parathyroid hormone 1 receptor*), CNS, pancreas, testes, placenta *(parathyroid hormone 2 receptor)*



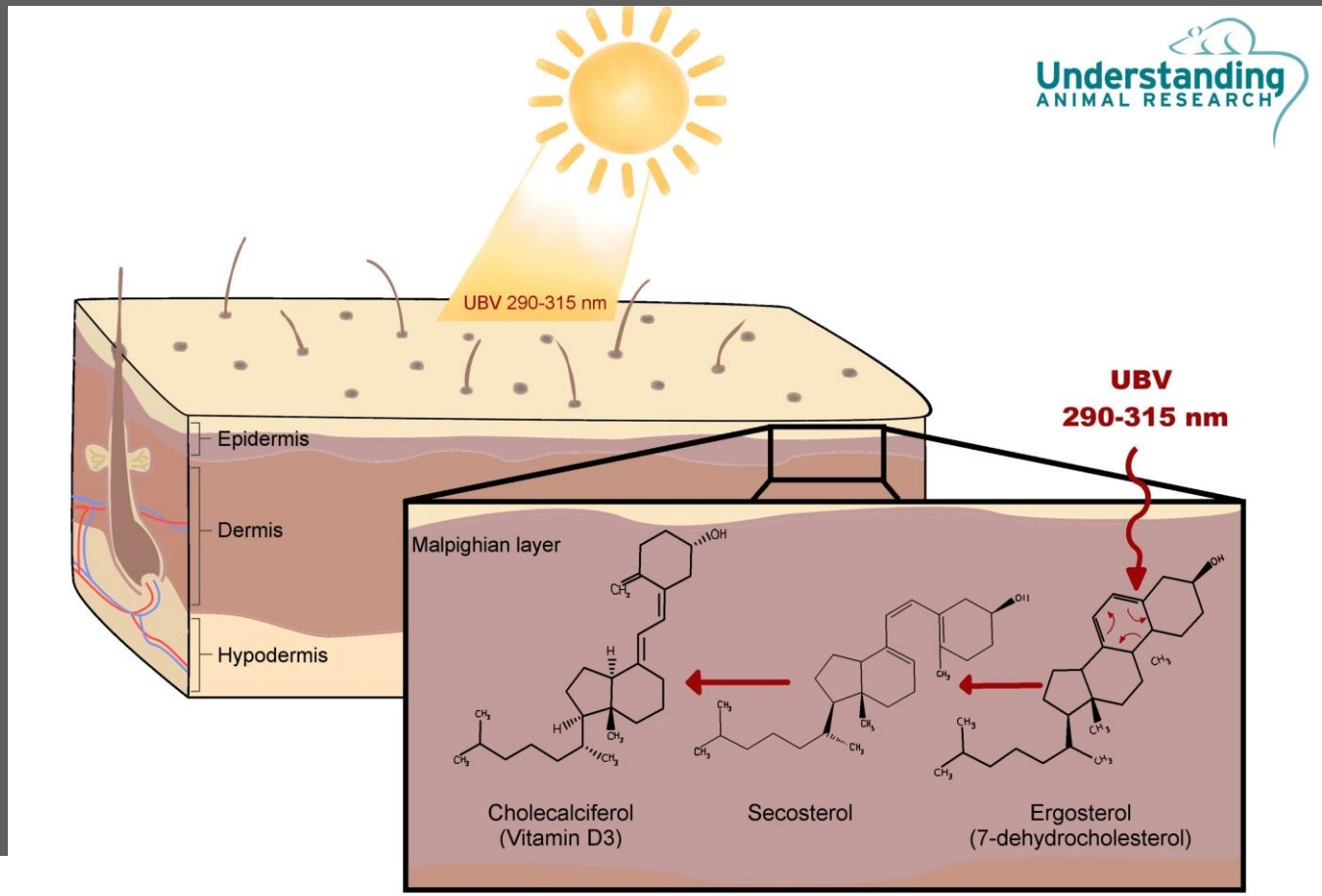
Parathyroid hormone (PTH)

- **increase in Ca^{2+} concentration after its decline:**

→ activation of osteoclasts (release of calcium and phosphates from bones)
→ increases calcitriol synthesis in kidneys > Ca^{2+} resorption in kidneys and intestine
→ inhibits phosphate resorption > hypophosphataemia > Ca^{2+} released from bones

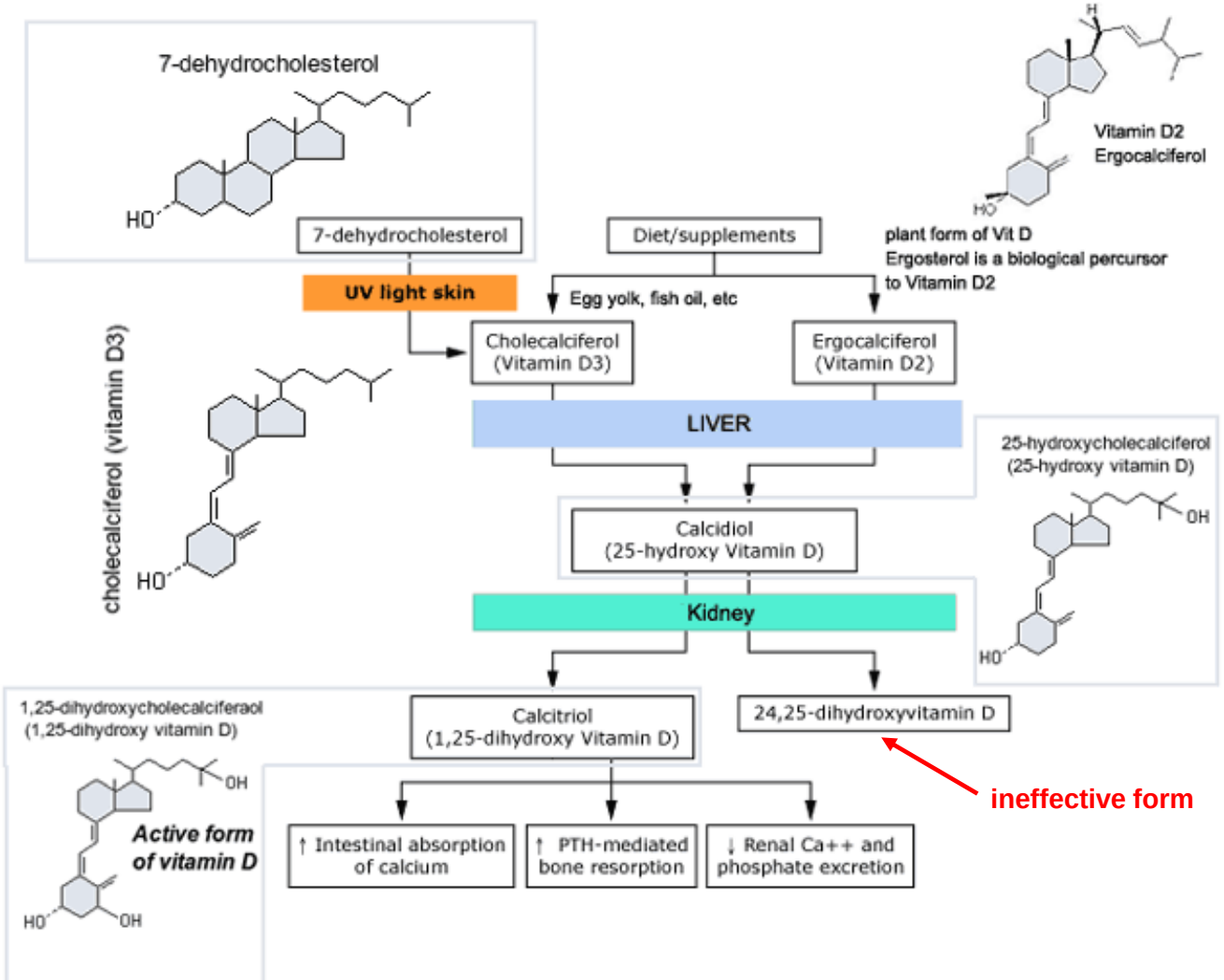


Calcium management in other tissues



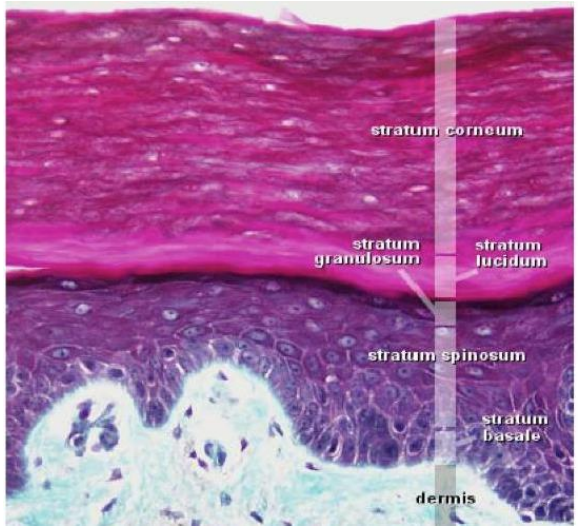
Calcitriol (1,25-$(OH)_2$-cholecalciferol)

- steroid, the active form of vitamin D
- multi-organ dependent synthesis (skin, liver, kidneys)



Calcitriol (1,25-$(OH)_2$-cholecalciferol)

- synthesis in the skin from **7-dehydrocholesterol** after irradiation by UVB (270-300 nm)
- via provitamin D, which is converted to **vitamin D_3**
- vitamin D_3 (cholecalciferol) in animals, vitamin D_2 (ergocalciferol) in plants
- in the liver conversion to 25-OH-cholecalciferol (**calcidiol**; storage form with a half-life of about 15 days)
- in the kidneys (and placenta) conversion to 1,25-$(OH)_2$-cholecalciferol (**calcitriol**; catalysed by **1-α-hydroxylase**)
- 24-hydroxylase produces an inactive form of the hormone
- regulation via enzymes catalyzing synthesis in the kidneys

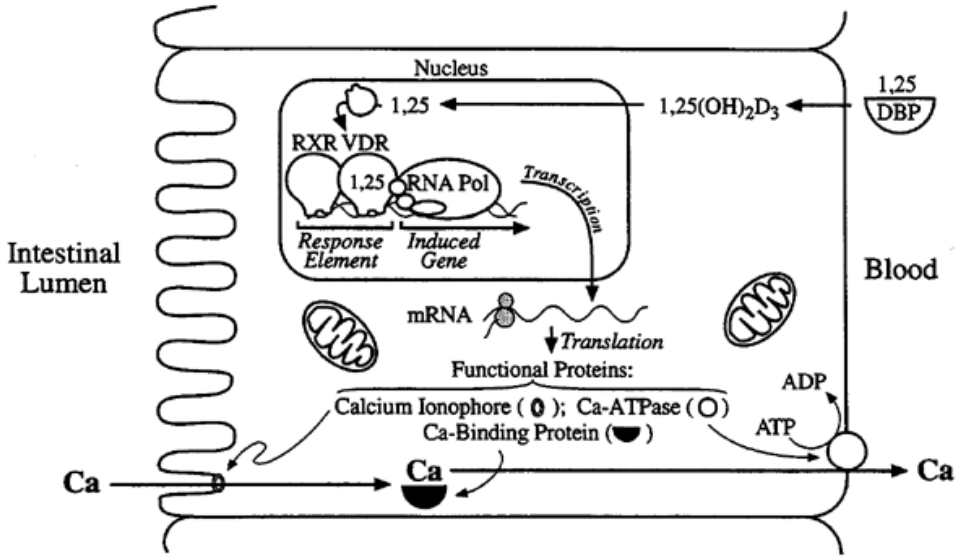


stratum spinosum

stratum basale

Calcitriol (1,25-$(OH)_2$-cholecalciferol)

- targets primarily intestine, bones, kidneys, placenta, mammary glands (prolactin > lactation), skin and more
- binding to nuclear receptors (VDR > transcription factor)
- induced expression of calcium-binding protein and Ca^{2+}-ATPases



- stimulates Ca^{2+} resorption in the intestine
- Ca^{2+} resorption in the kidneys
- promotes bone mineralization
- calcitriol is also produced by monocytes/macrophages, where it acts as a cytokine and thus stimulates the innate immune system