Thyroid Hormones

COMPILED BY
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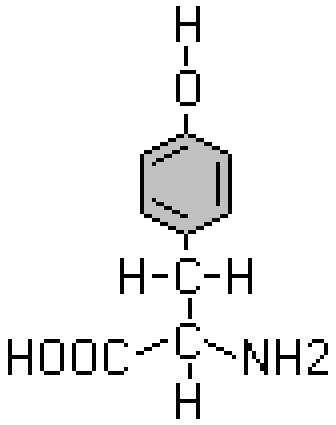
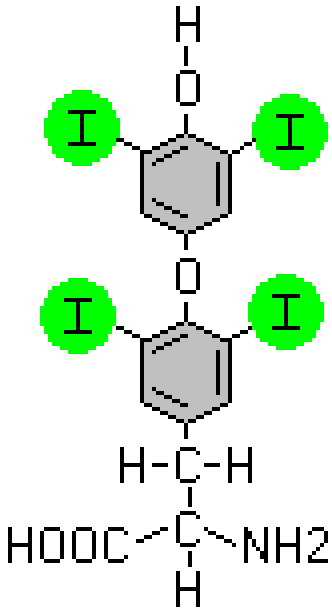
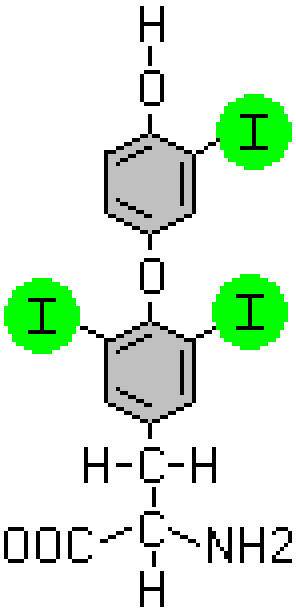
Thyroid hormones derived from two iodinated tyrosine molecules



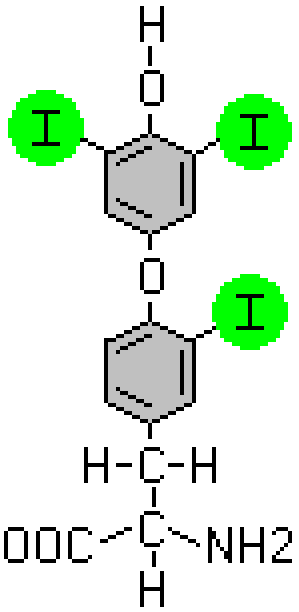
Tyrosine



Thyroxine (T4)

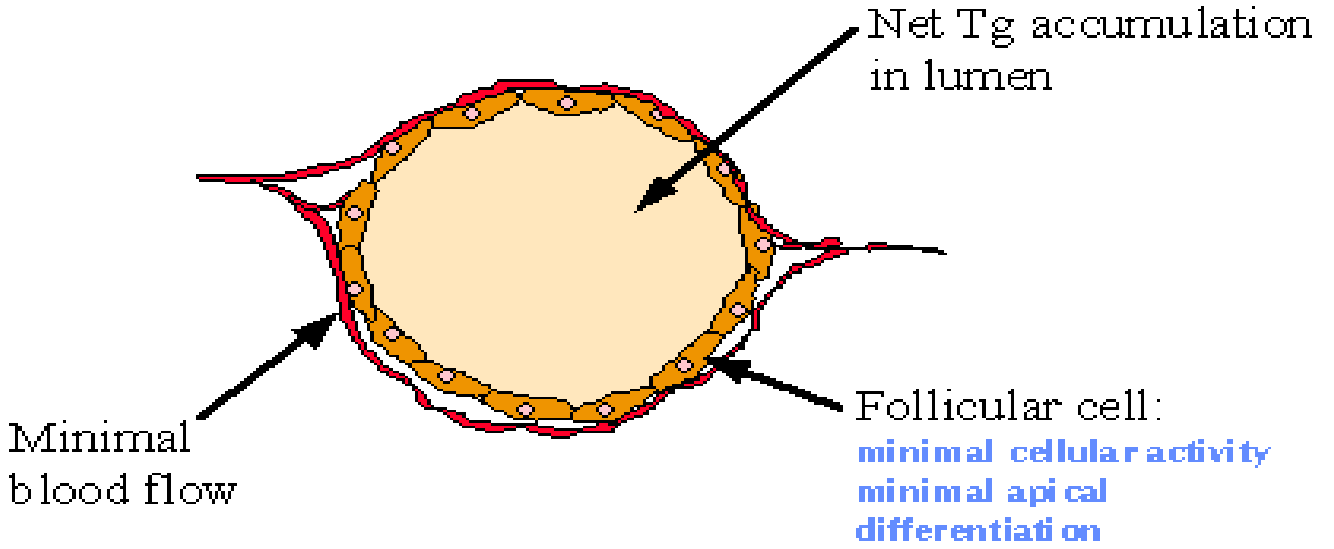


Triiodothyronine (T3)

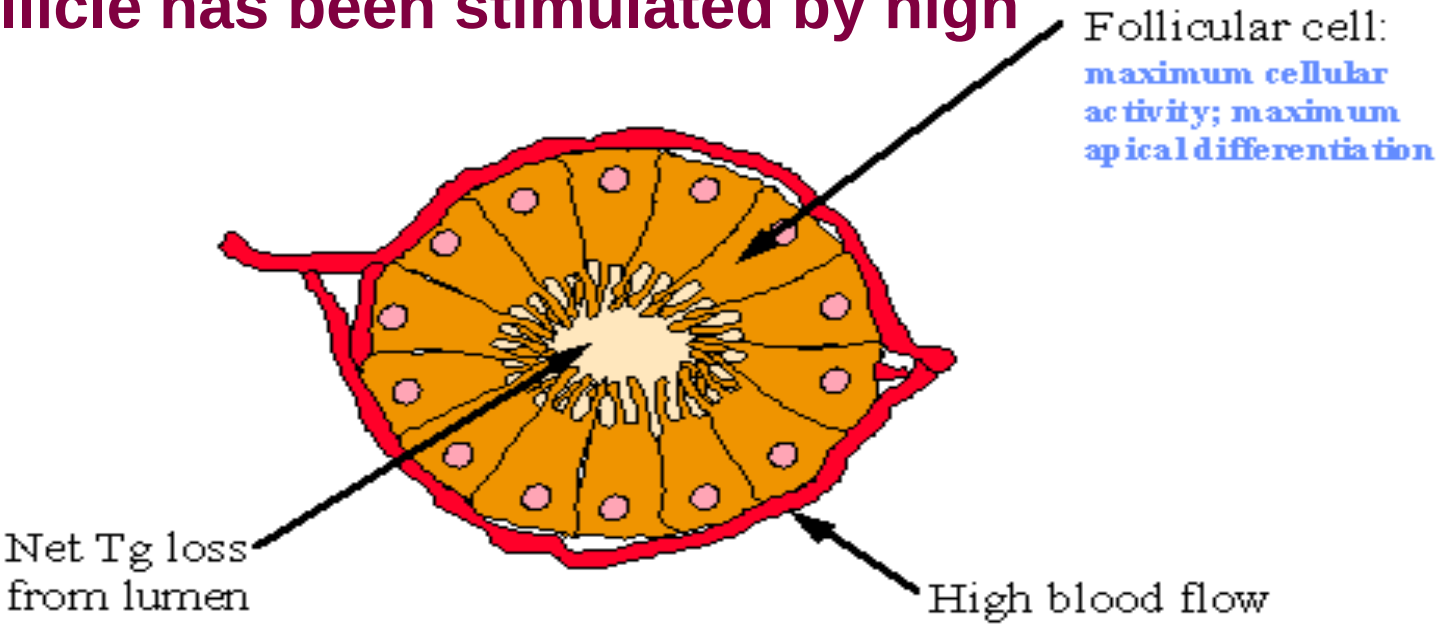


"Reverse T3" (inactive)

This follicle lacks TSH stimulation



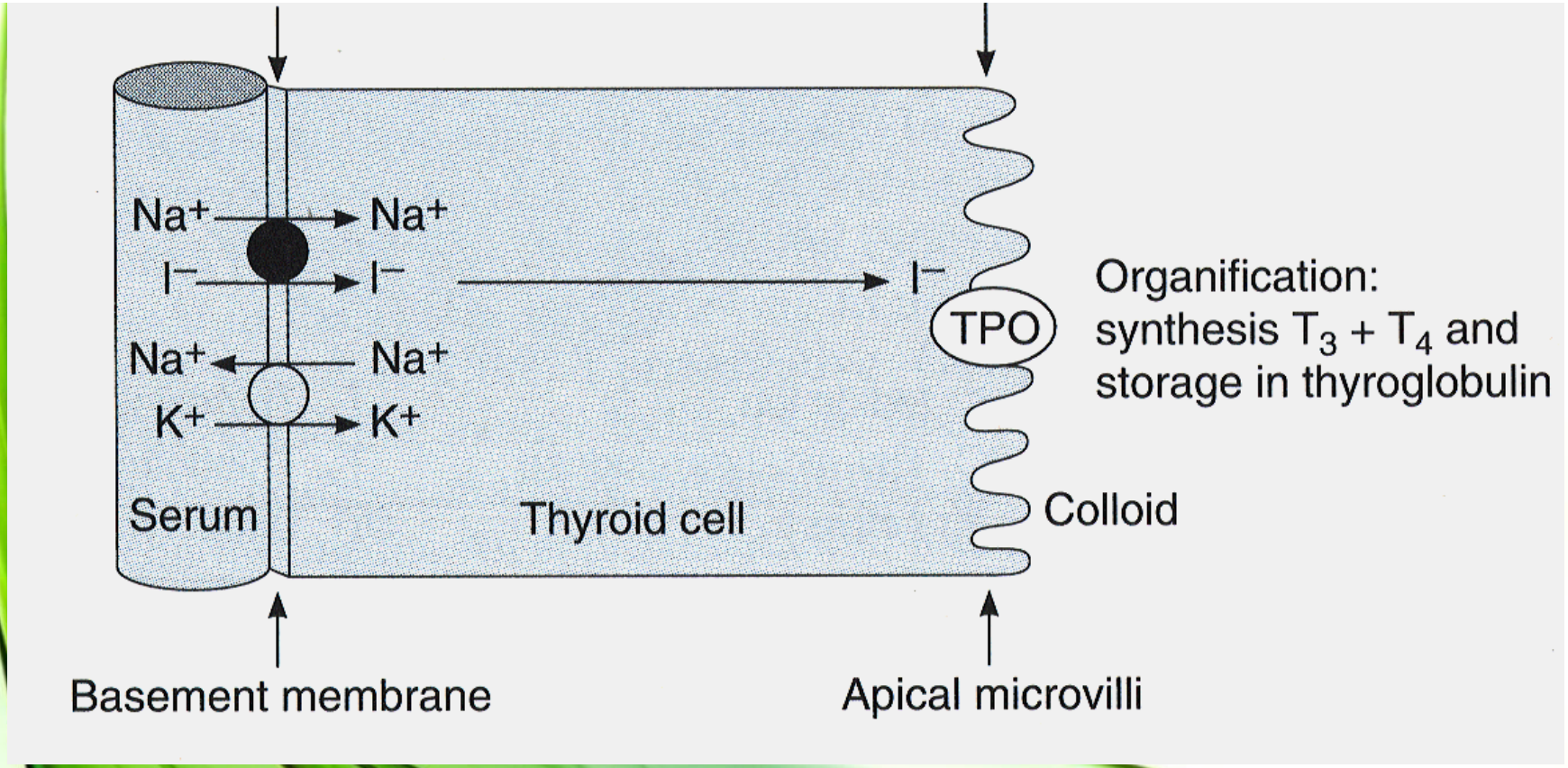
This follicle has been stimulated by high TSH

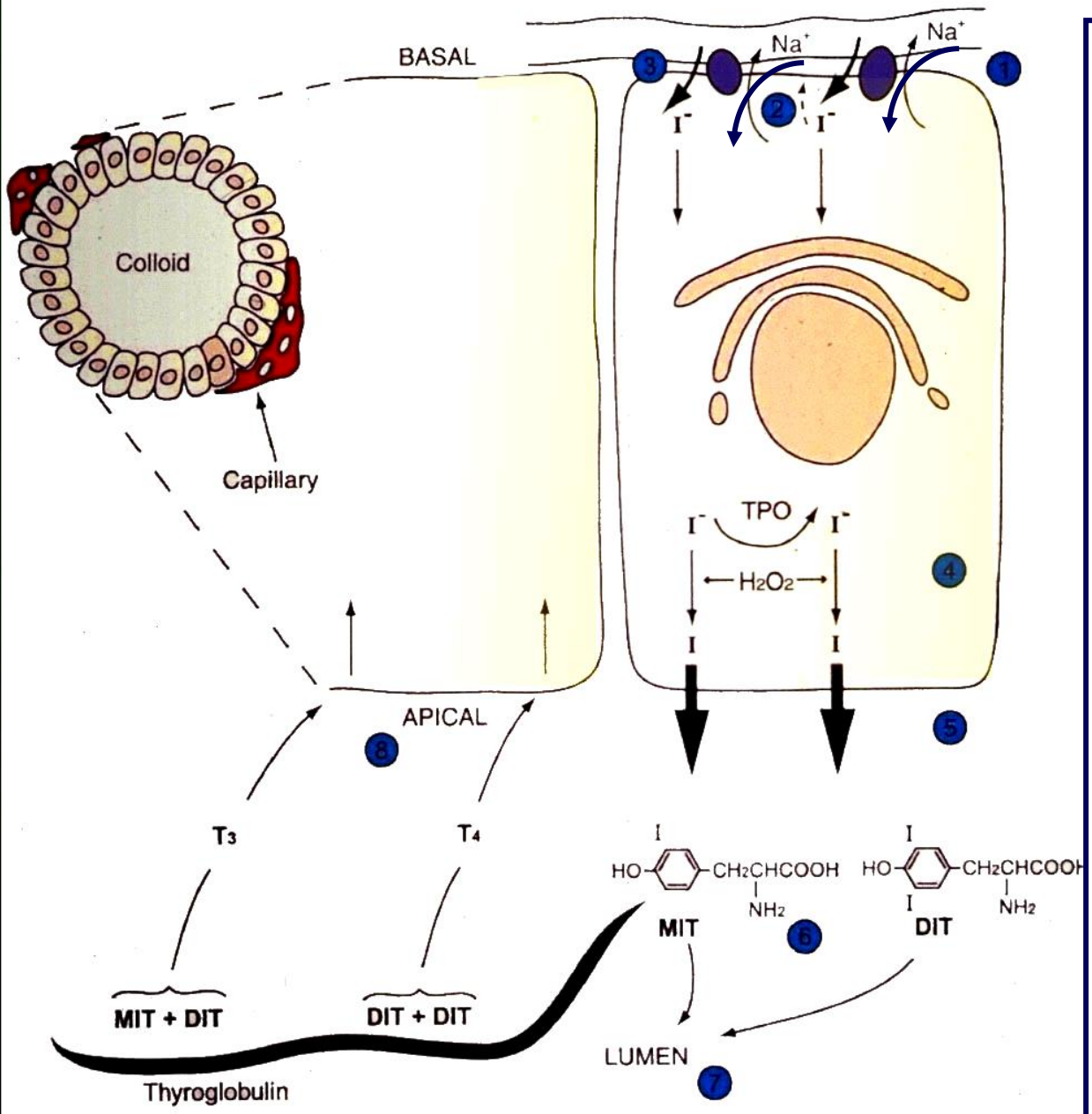


Synthesis of thyroid hormones

- Active uptake of iodide into follicular cell
- Iodide → iodine - H_2O_2 (catalysed by TPO)
- Active uptake of iodine at follicular/ colloid interface
- Incorporation of iodine onto tyrosine residues of thyroglobulin
- Coupling of iodinated tyrosines
- Storage of T_3 and T_4

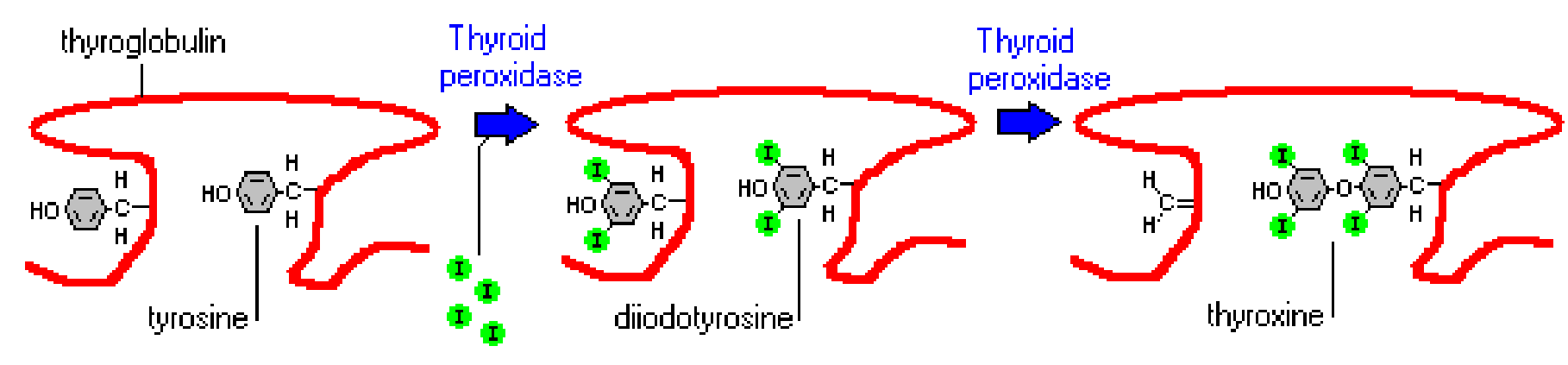
Active transport of iodine (ATP_{ase} dependent) against electrical and chemical gradient - concentration of iodine 30-50 times that of the circulation

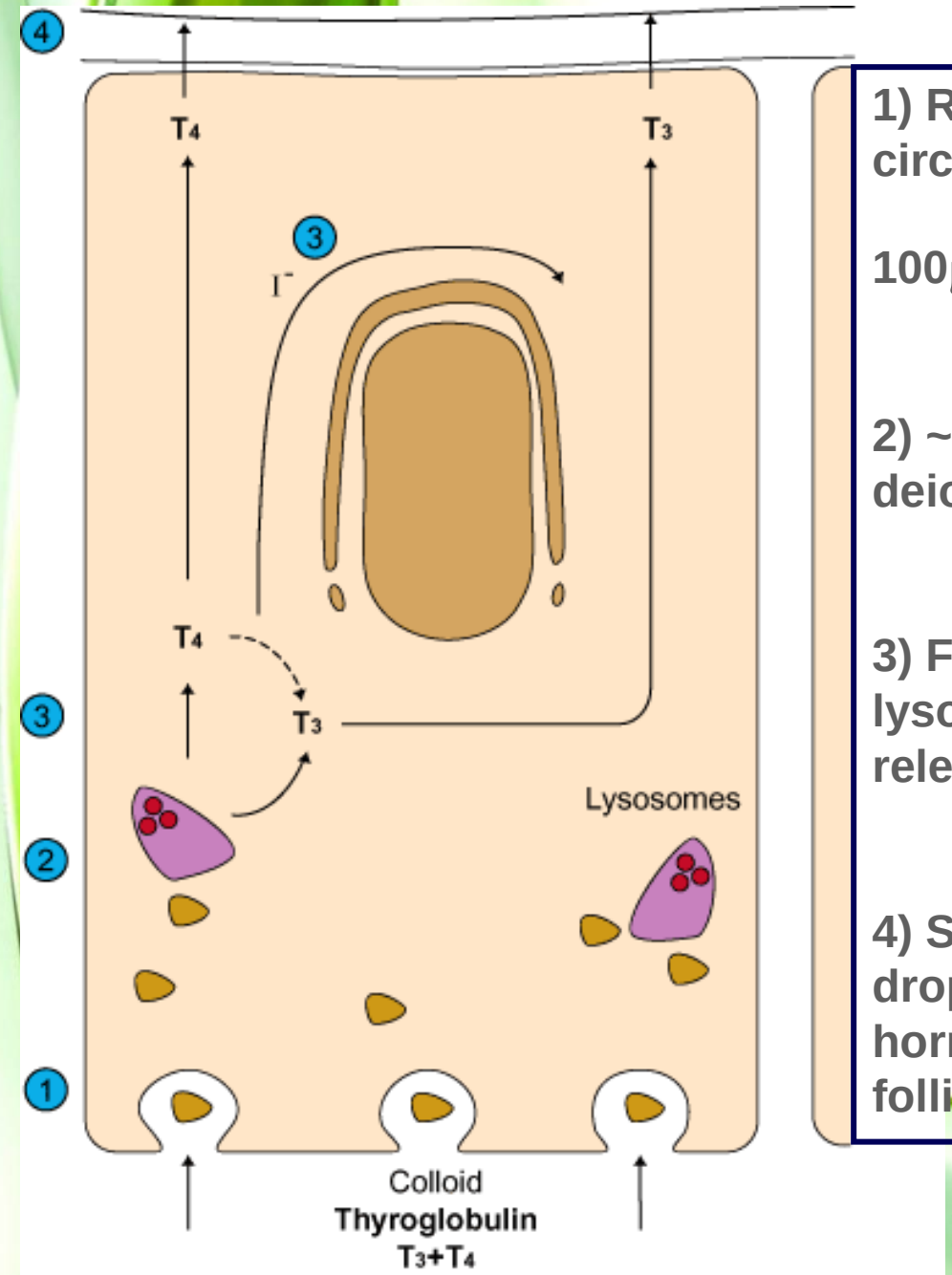




- **Active uptake of iodine by a sodium iodide symporter**
- **Oxidation of iodide to iodine**
- **Iodination of tyrosine residues at apical/colloid interface to form MIT and DIT**
- **Uptake of thyroglobulin into the lumen of the follicle**

Incorporation of iodine onto tyrosine residues on the thyroglobulin molecule





1) Release of T_4 and T_3 into circulation -

100μg T_4 & 10μg T_3/day

2) ~ 10% T_4 undergoes mono-deiodination to T_3 before secretion

3) Fusion of colloid droplets with lysosomes --> hydrolysis and release of thyroid hormones

4) Stimulated by TSH colloid droplets with the bound thyroid hormones are taken back into follicular cells by pinocytosis

Iodine metabolism

Concentration of Iodide (I^-)

- **ACTIVE TRANSPORT BY THYROIDAL (I^-) TRANSPORTER LINKED WITH Na^+/I^+ ATPase**
- **Inhibition**
  - **Perchlorate (ClO^-_4)**
  - **Thiocyanate (SCN^-)**

Oxidation of iodide ($I^- \rightarrow I$)

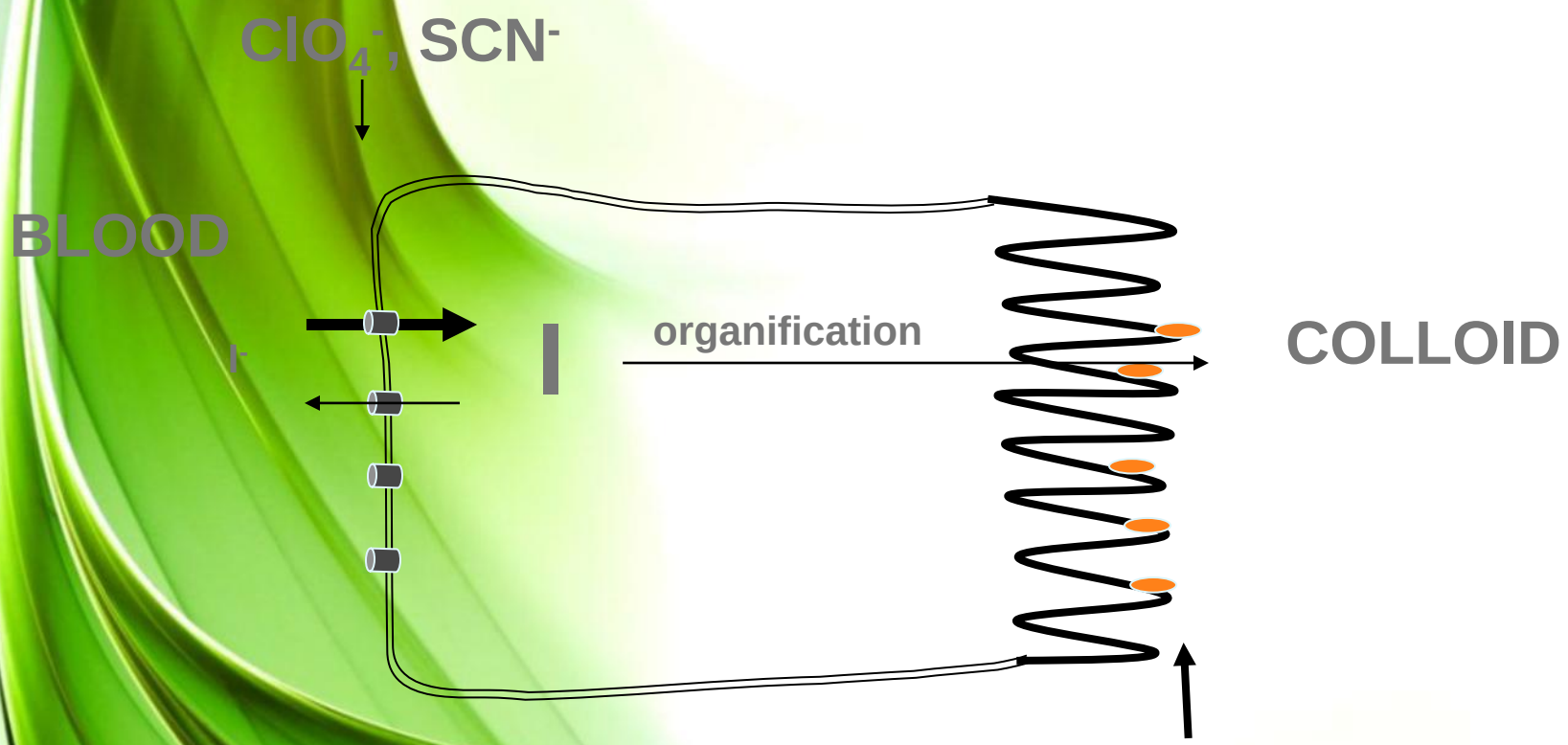
- Iodide ⟶ Iodine

Thyroid peroxidase & H_2O_2

- Inhibitor

Propylthiouracil

Ion transport by the Thyroid follicular cell



- NaI symporter (NIS)
- Thyroid peroxidase (TPO)

Iodination of tyrosine (Organification)

- **Oxidized Iodine + tyrosine residues**

(thyroglobulin) → MIT and DIT

Peroxidase

Inhibitor

Thioureas

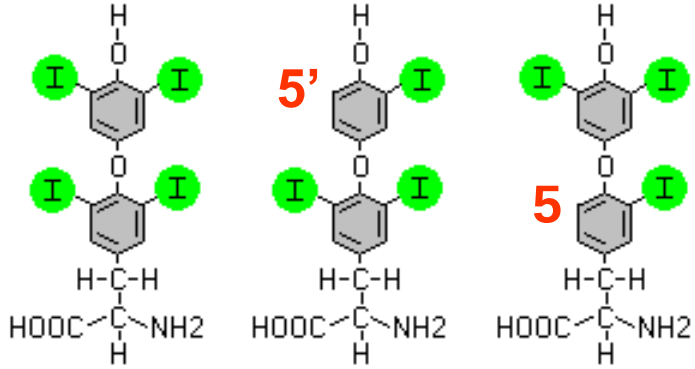
Coupling of Iodotyrosyls

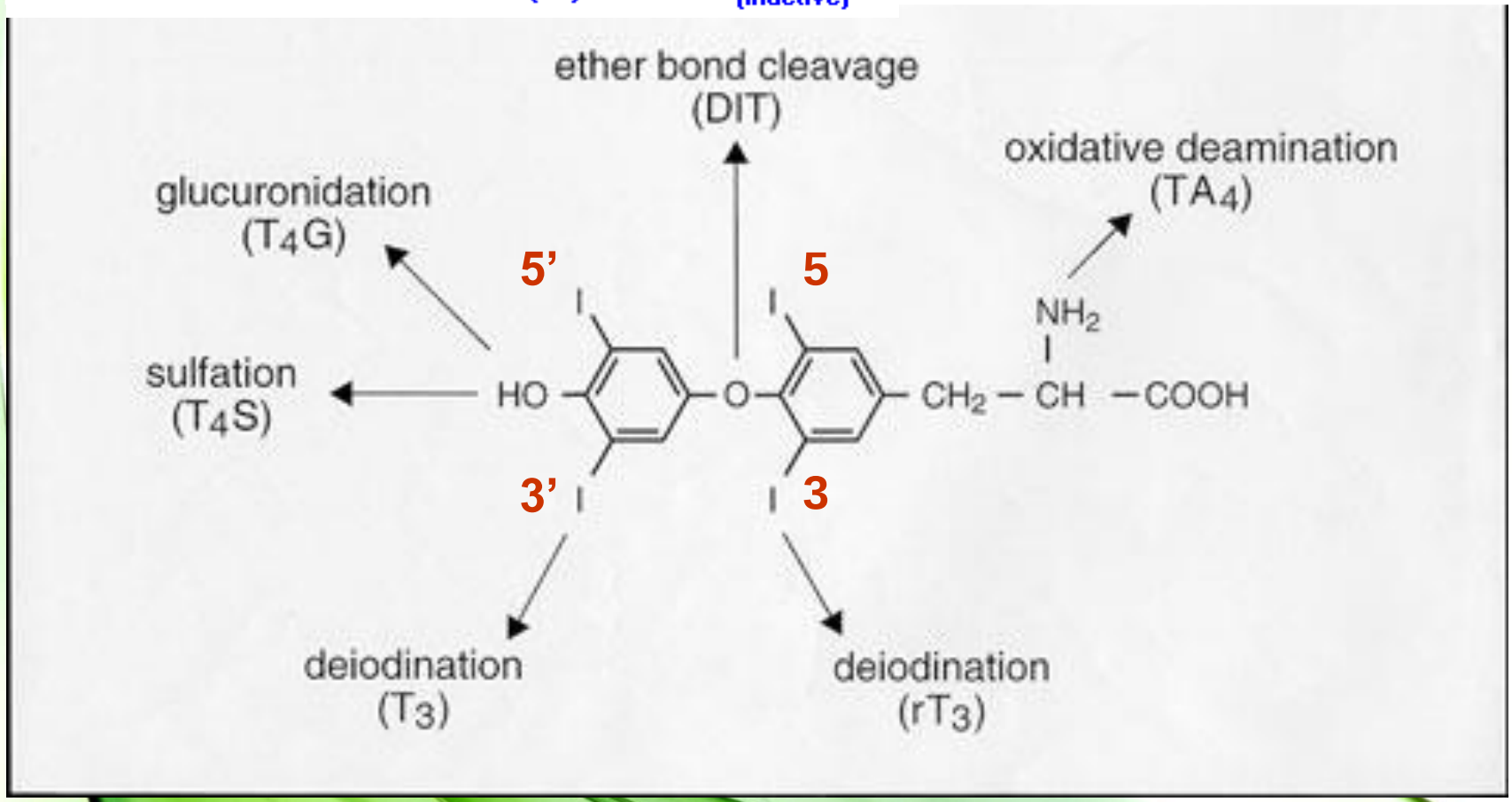
DIT + DIT $\xrightarrow[\text{Thyroperoxidase}]{}$ Thyroxine (T_4)

DIT + MIT $\xrightarrow[\text{Thyroperoxidase}]{}$ Triiodothyronineine (T_3)

- **Inhibitor**
  Propylthiouracil

Thyroid hormone metabolism





Metabolism of thyroid hormones

Series of deiodinations by deiodinases

- **Type 1 - liver, kidney, thyroid, pituitary gland, CNS: 5’ and 5 positions**
- **Type 2 - brain, brown fat, placenta, pituitary gland: 5’ position only: $T_4 \rightarrow T_3$ only: intracellular concentrations of T_3**
- **Type 3 - brain, placenta: 5 position only**

$T_4 \not\rightarrow T_3$

- **Other metabolic pathways: sulphation, decarboxylation, conjugated with glucuronide**

Thyroid Hormone Transport

- **Thyroxine binding prealbumin (TBPA)** (transthyretin), binds 10% of circulating thyroxine, increased level may be familial (high total T4, but normal fT4)
- **Albumin**-binds about 15%of circulating T4 and T3

Thyroid Hormone transport

- Thyroid hormones are transported in the blood bound to protein carriers
- Only 0.04% of T4, and 0.4% of T3 are free
- The free fraction is responsible for hormone action
- About 99% of T3 is derived from peripheral conversion of T4

Factors affecting Thyroxine binding Globulin level (TBG)-Increase level

- Hereditary
- Pregnancy
- Estrogen therapy
- Hypothyroidism
- Phenothiazines
- Acute viral hepatitis

Factors that decrease

- Hereditary
- Androgens
- Corticosteroids
- Thyrotoxicosis
- Nephrotic syndrome
- malnutrition
- ’major illness

Thyroid function in pregnancy

- Rise in Total Binding globulin (due to estrogen) →inc. total T4 and T3, due to estrogen
- Free T4 and T3 are normal
- HCG has weak TSH agonist activity, and responsible for the slight thyroid enlargement during pregnancy
- Anti thyroid drugs like carbimazole and

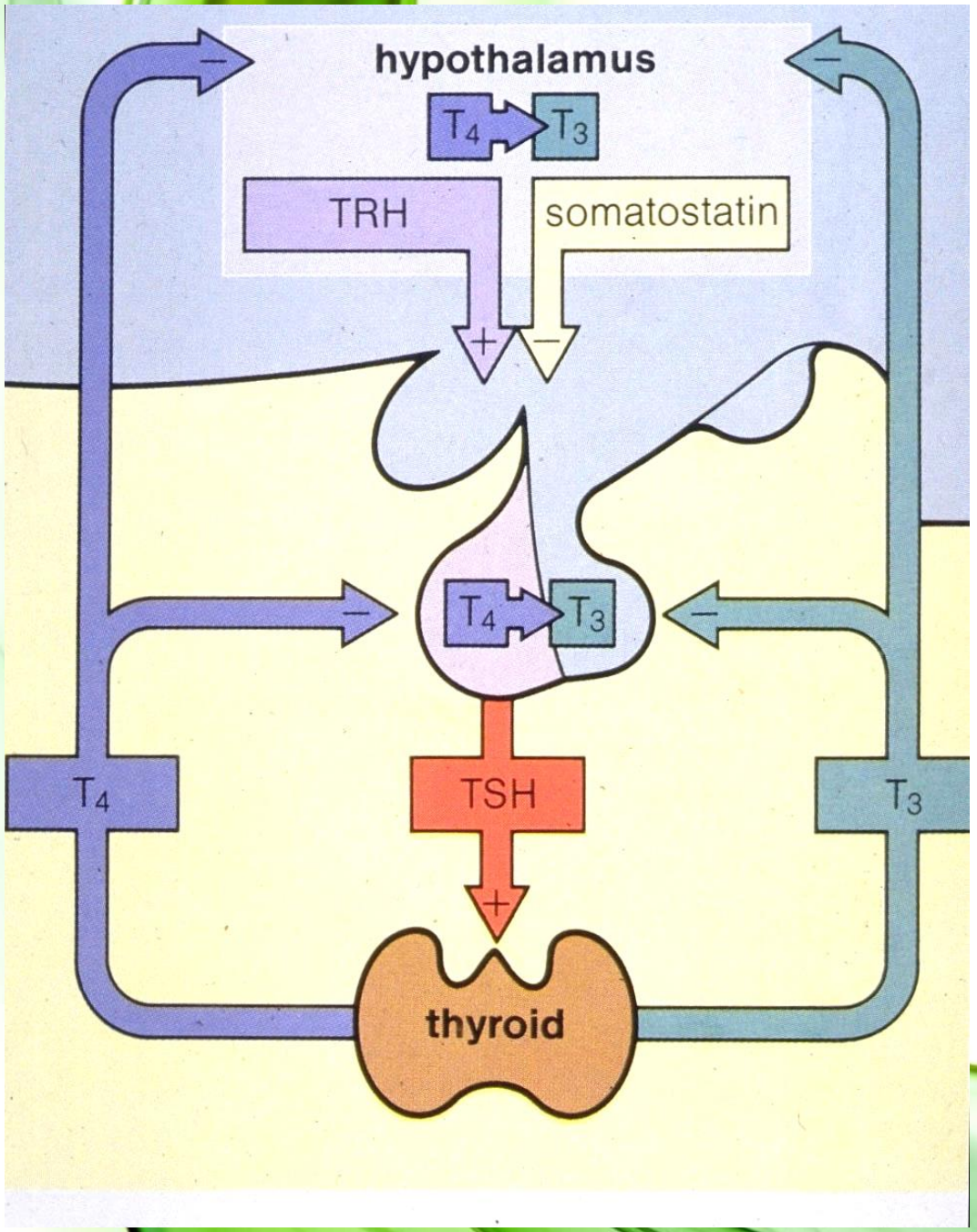
Propylthiouracil (**PTU**) is a medication used to treat hyperthyroidism cross the placenta to varying degrees.

Thyroid hormone in various disorders

condition	TSH	Free T4	Free T3
Primary hyperthyroid	Undetectable	V.high	High
T3 thyrotoxicosis	Undetectable	Normal	v.High
Secondary hyperthyroidism	Increased	High	High
Subclinical hyperthyroidism	Low	N	N

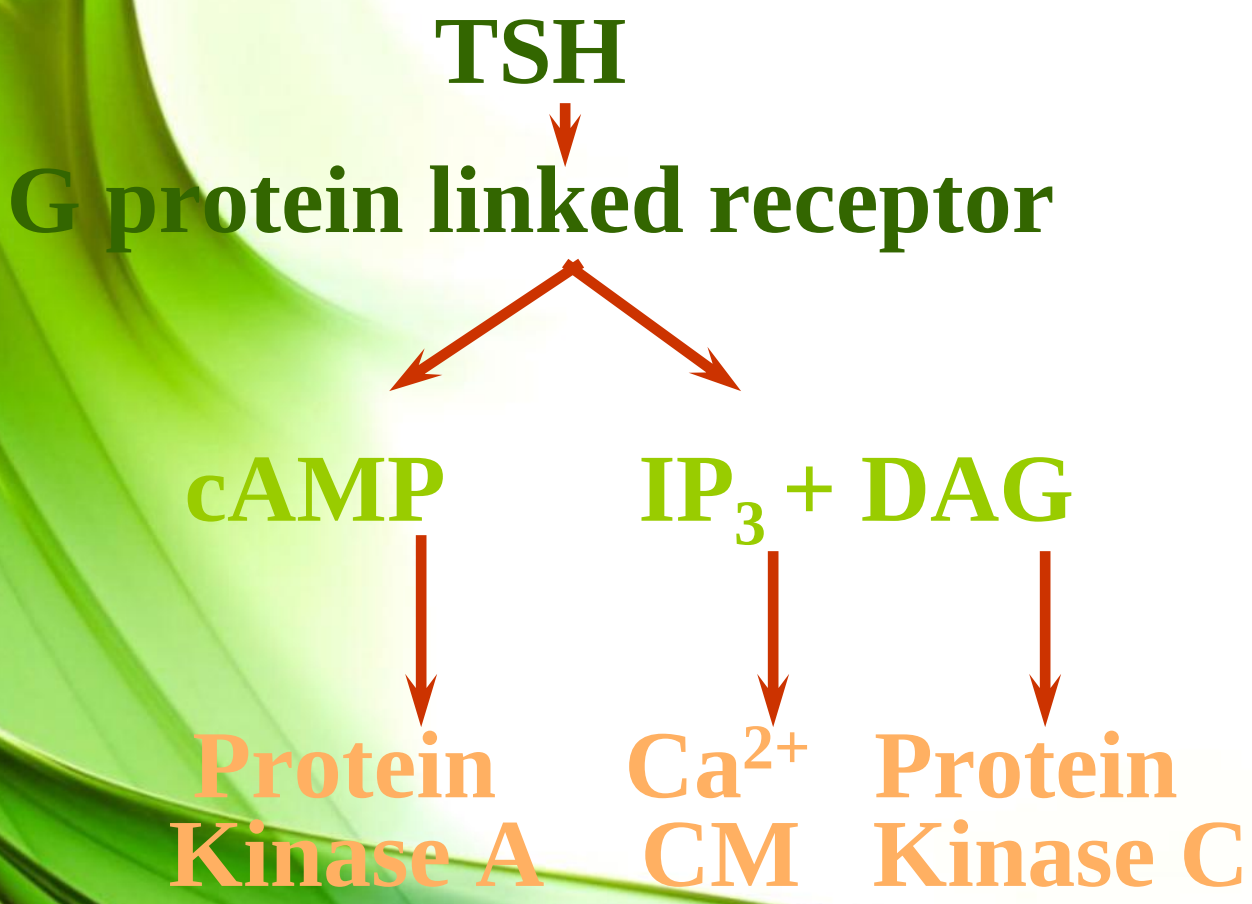
Thyroid hormone conc. In various Disorders

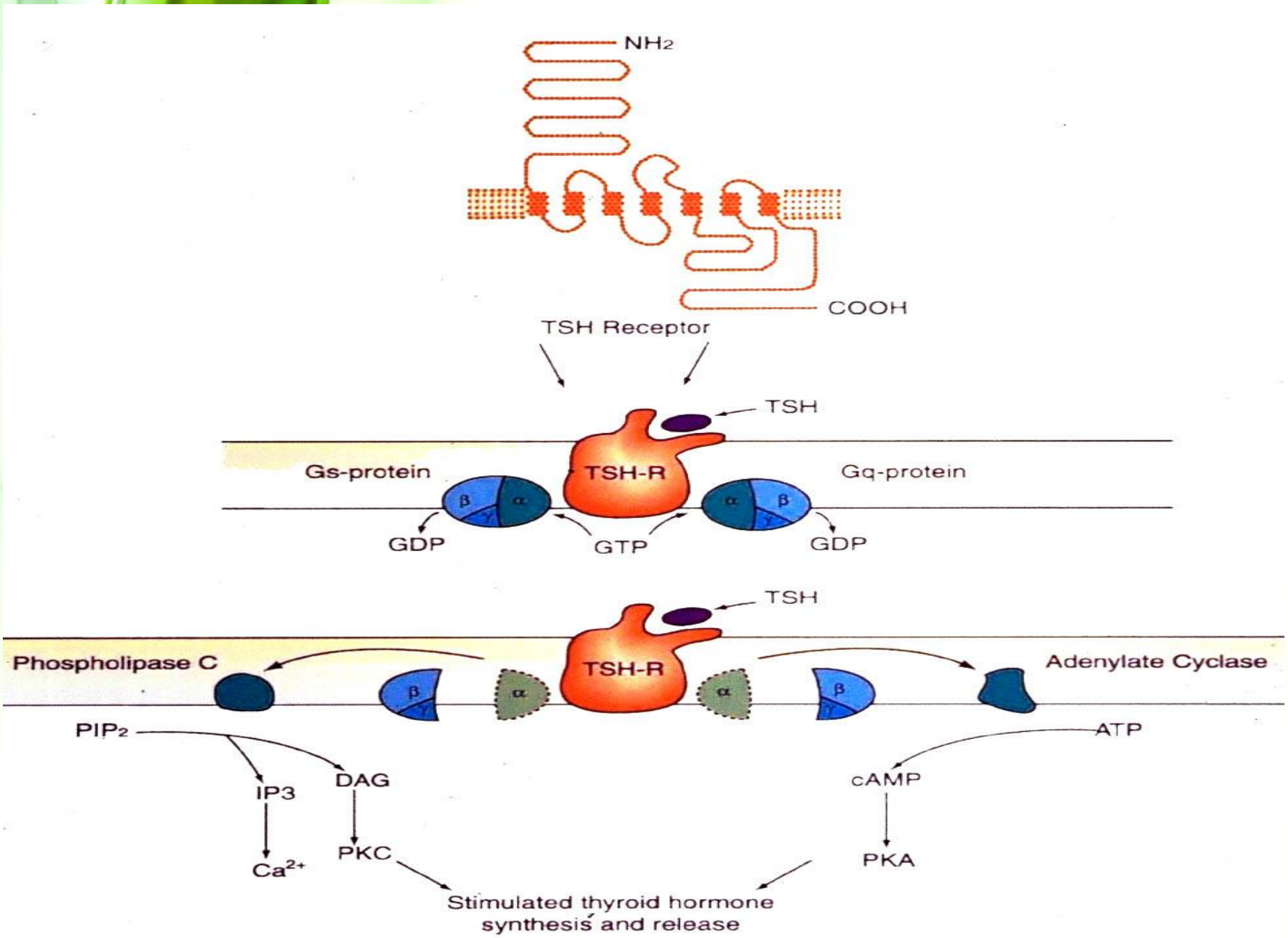
Condition	TSH	Free T4	Free T3
Thyroid H Resistance	↑ or N	↑	↑
Prim hypothyroidism	↑	↓	↓ or N
Secondary hypothyroidism	↓ or N	↓	↓ or N



Control of thyroid hormone synthesis and release and feedback control

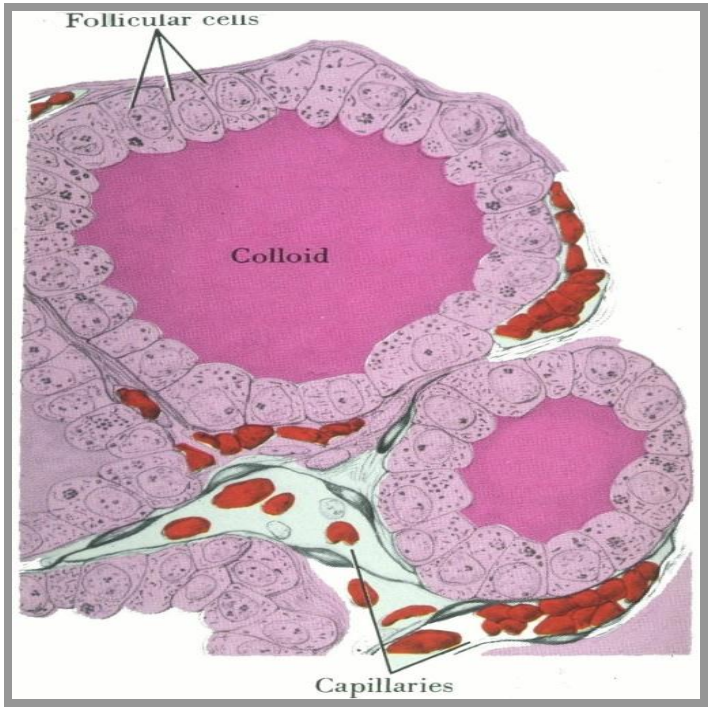
TSH Receptors

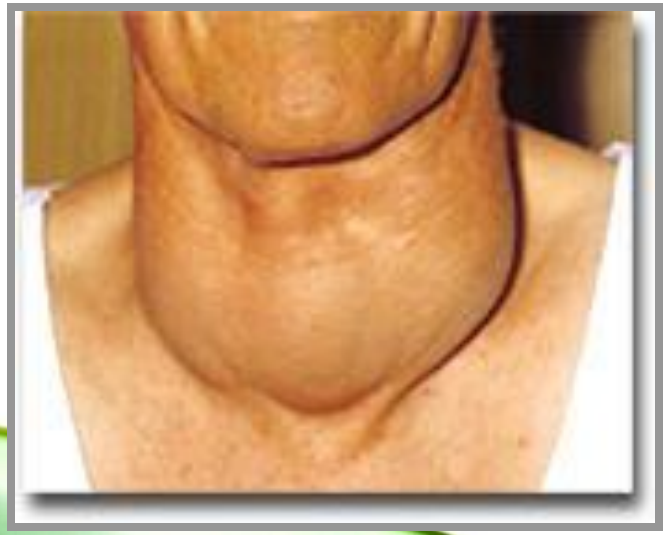



NH2
COOH
TSH Receptor
TSH
Gs-protein
TSH-R
Gq-protein
β
α
γ
GDP
GTP
GDP
TSH
Phospholipase C
TSH-R
Adenylate Cyclase
PIP2
ATP
IP3
DAG
cAMP
Ca2+
PKC
PKA
Stimulated thyroid hormone
synthesis and release

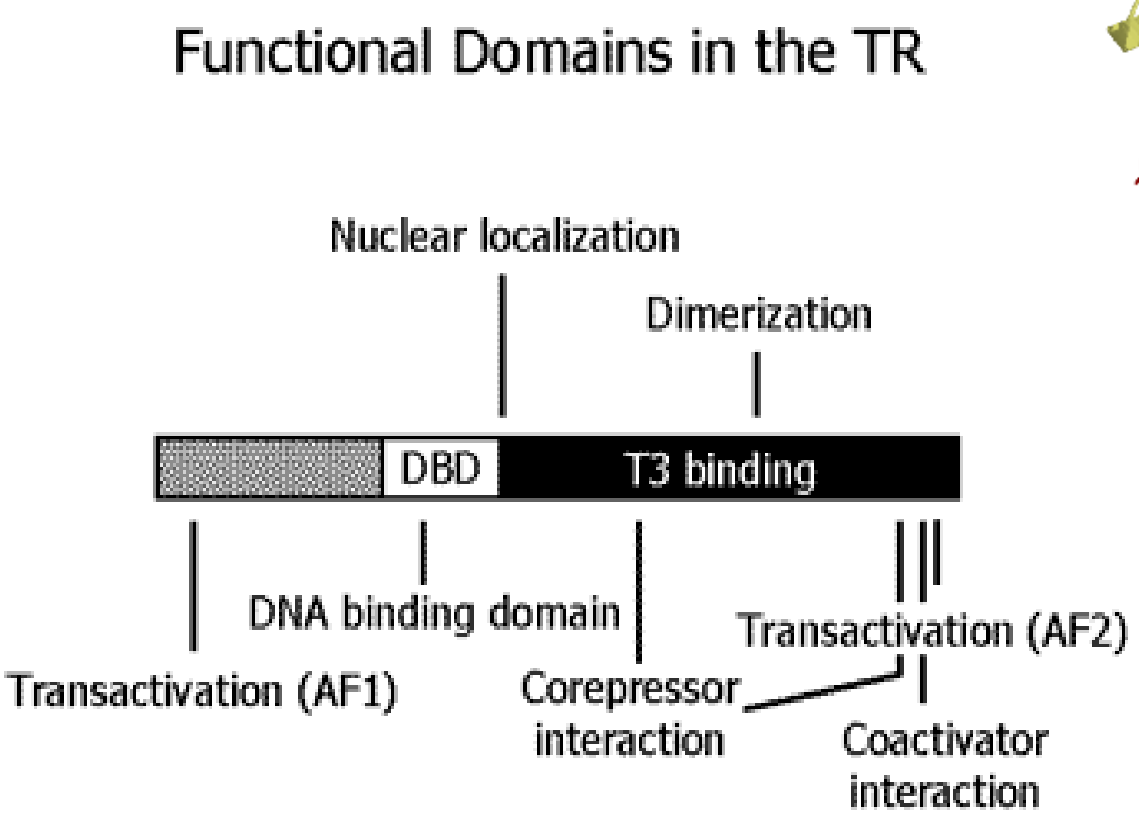
Actions of TSH

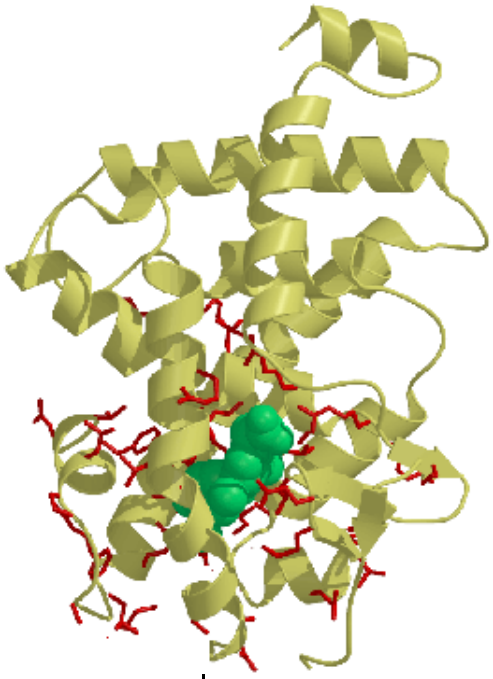
- Active uptake of iodine*
- Stimulates other reactions involved in thyroid hormone synthesis
- Stimulates the uptake of colloid
- Induces growth of the thyroid gland





Thyroid hormone receptors

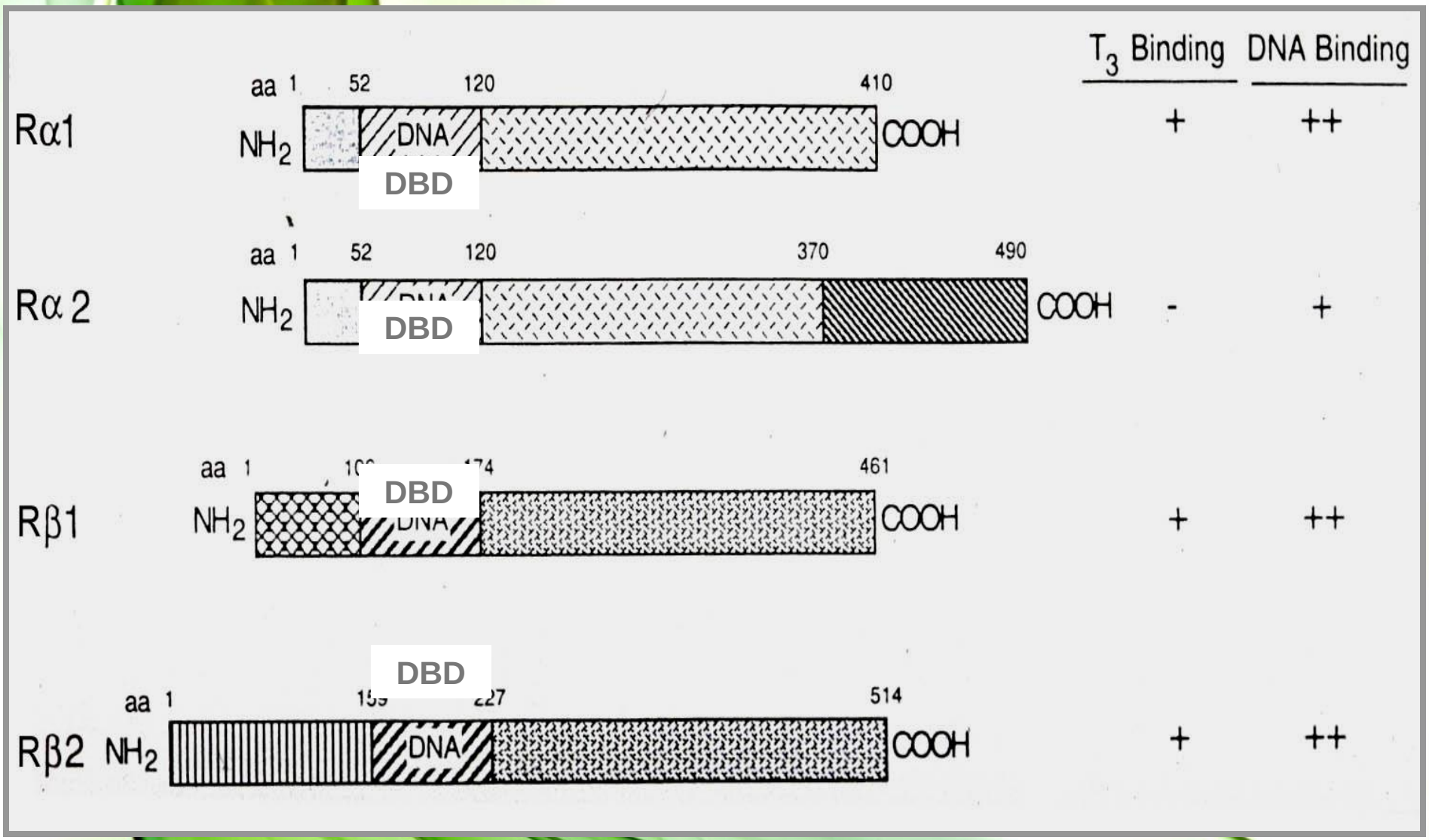




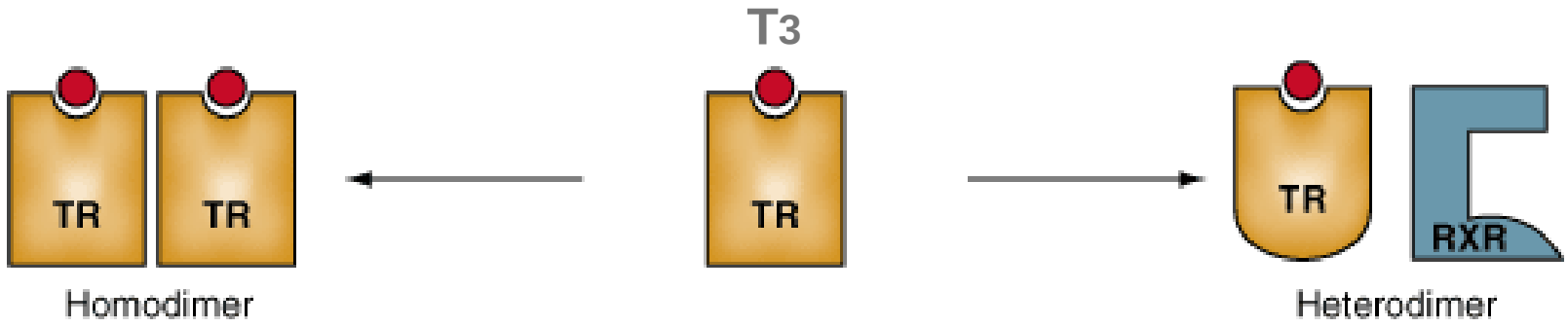
Thyroid hormone receptors

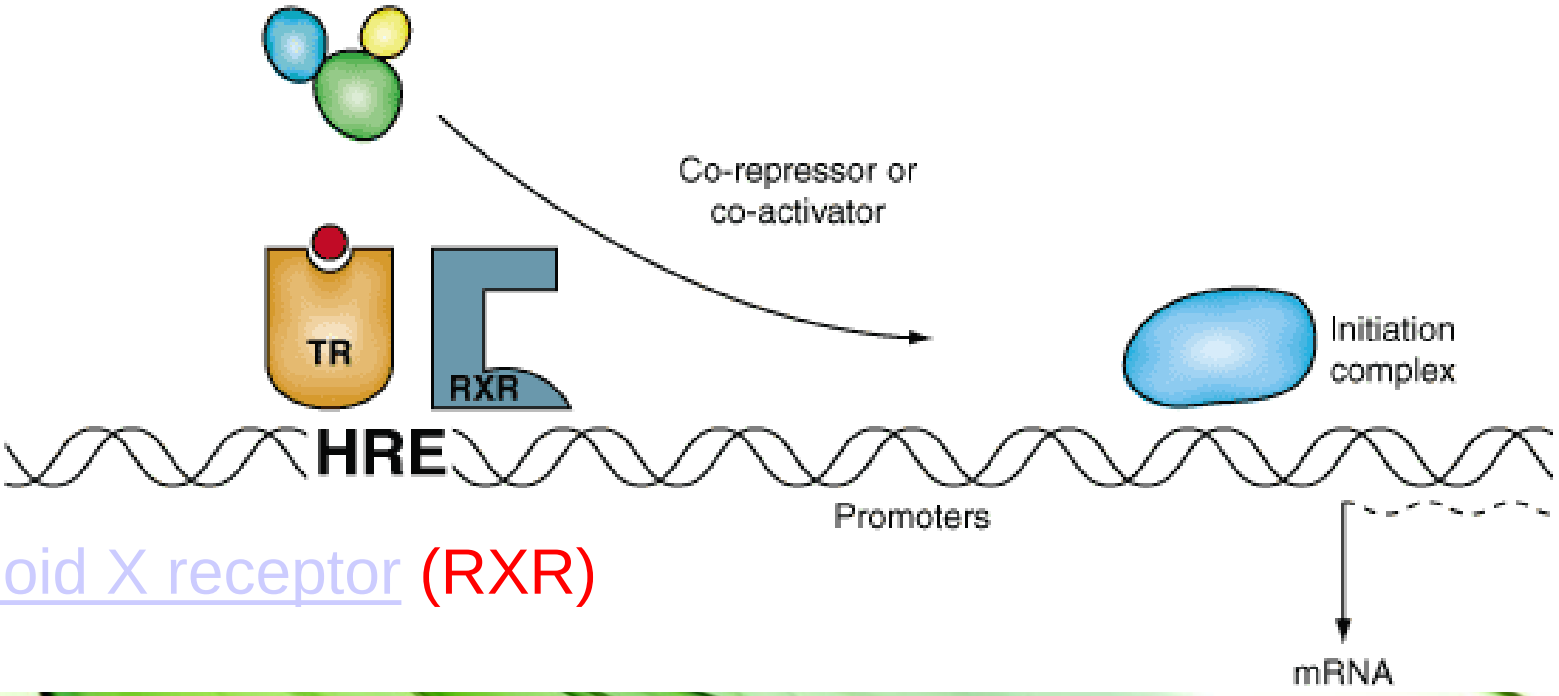
- Type 2 receptors in nucleus - high affinity for T_3
- Dimerize with another T_3 receptor (homodimer) or retinoic acid receptor (heterodimer)
- Dimerized receptor + other transcription factors → gene transcription
- Membrane receptors? Ion movements

Isoforms of the thyroid hormone receptor



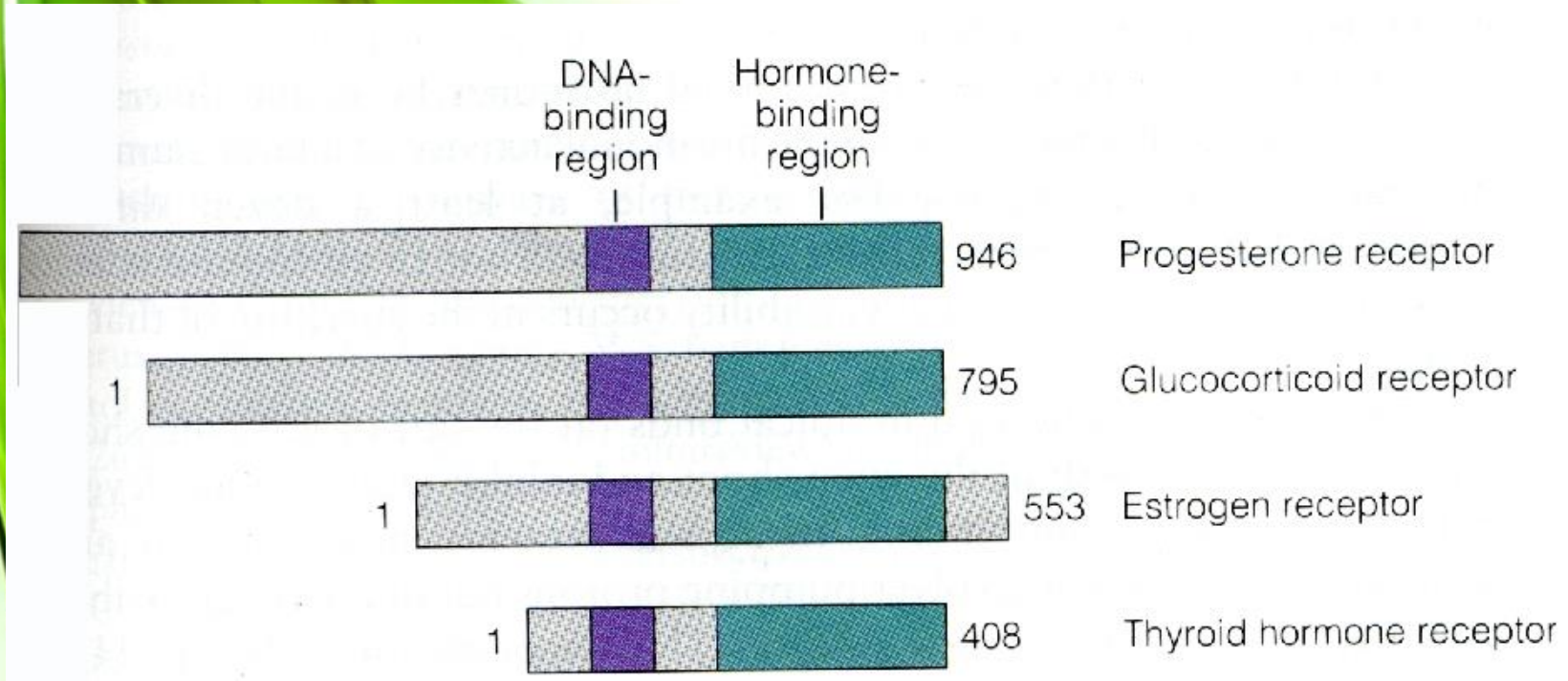
Dimerization of thyroid hormone receptors and gene activation/inactivation





retinoid X receptor (RXR)

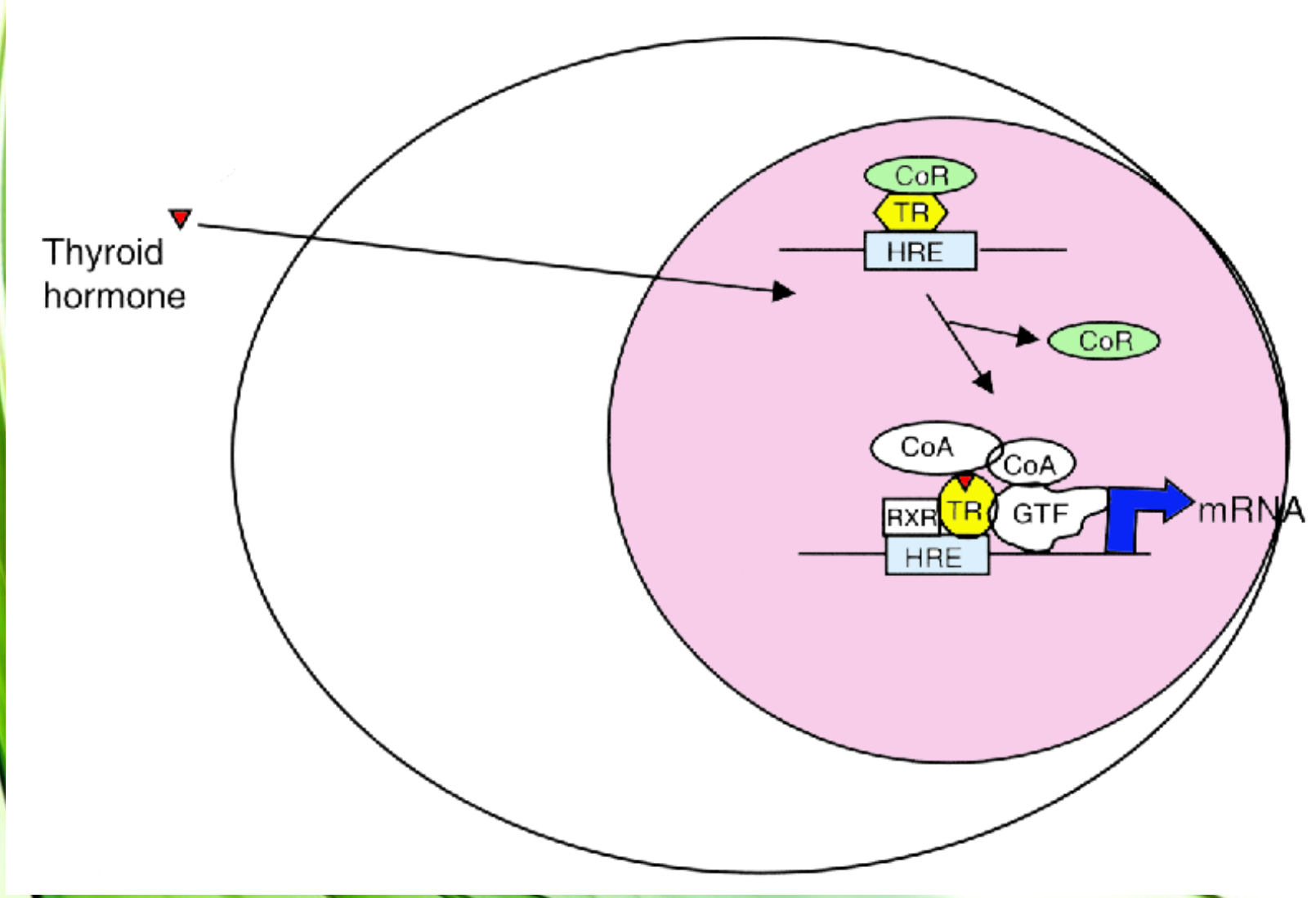
Structural similarities among receptors for steroid and thyroid hormones



Mechanism of thyroid hormone action

- Receptors for thyroid h
  is ten times higher for T
- Four variants of nuclear rec
  mitochondrial receptor fo
- Free thyroid hormone
  hormone is bound to h
  (HRE) and corepresso

Mechanism of thyroid hormone action



Increased expression of proteins by thyroid hormones

- **Glycerol 3-phospha**
  component of glycerol
  mitochondria (one of tra
  mitochondria)
- **Cytochrome c oxidase**
  enzyme in the electr
  cytochrome c to oxyg
- **ATPases** – (eg. Ca A
- **Carbamyl phosphat**
  cycle
- **Growth hormone**

Increased respiration during hyperthyroidism

Increased synthesis of
- synthesis of cytoch
- increased oxidative p
- the increased con
- increased produc

Increased consumpt
- synthesis of vari
- dependent in mus
- of store of ATP

Mechanisms increasing body temperature during hyperthyroidism

Reducing efficiency of A
synthesis of glycerol
increased transport NA
malate/aspartate sh

Increased synthesis

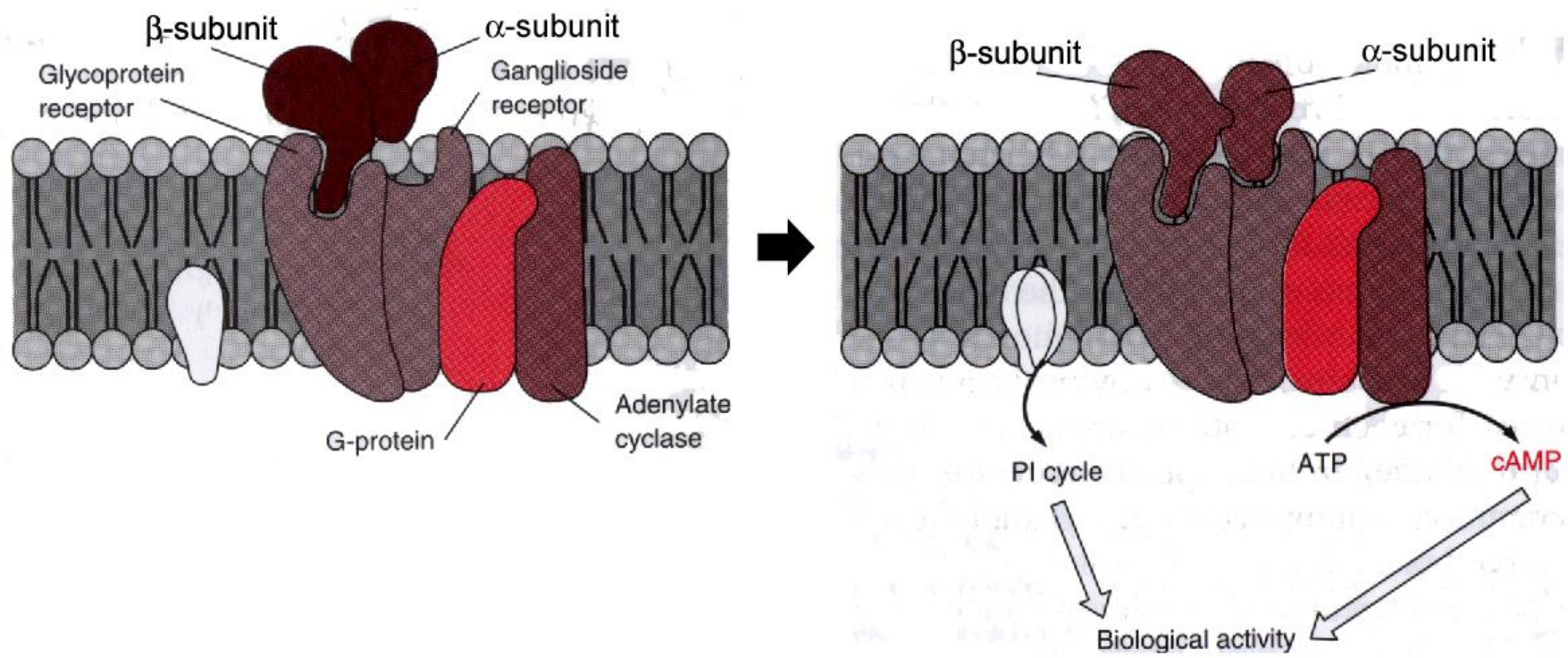
Increased consumpti

Uncoupling of phosp
mitochondria

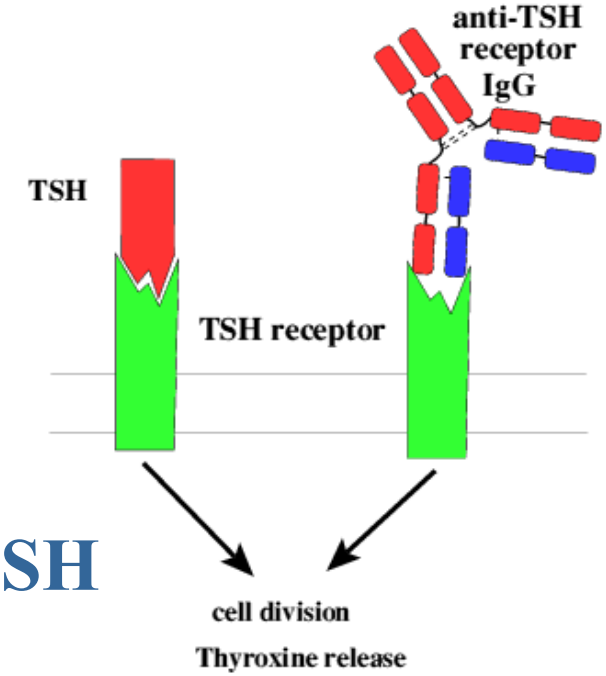
Control of thyroid hormone synthesis and secretion

- Pituitary hormone thy
  activity of iodide pump
  gland
- Endocytosis of iodinat
  following secretion
  upregulated by TSH
- Production of TSH
  controled by thyroi
  feedback

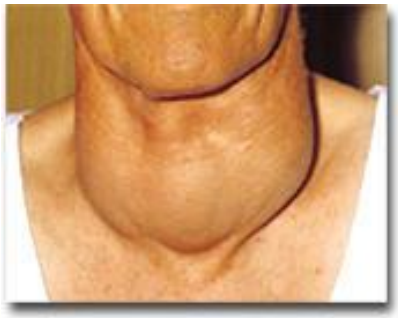
Model of TSH receptor

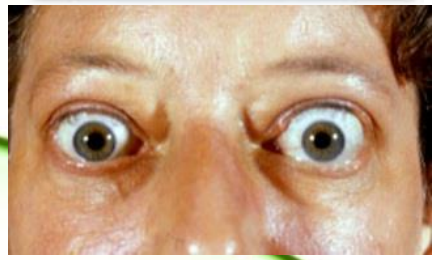


Grave's disease (1^0)



- Autoimmune - activating AB's to TSH receptor
- High concentrations of circulating thyroid hormones
- Weight loss, tachycardia, tiredness
- Diffuse goitre - TSH stimulating growth
- Opthalmopathy and dermopathy





Exophthalmos

- bilateral
  - marker
  - (hypethyre
- Thyroid-stimul
  - action of
  - thyrotropin
  - thyroid
  - through
  - with the
- Subset of
  - membra
- After stimulat
  - capable of differentiating int
  - thus increase orbital adipose tissue

Symptoms and signs of hyperthyroidism

Symptoms	Signs
Common	
Anxiety and irritability (~ >90%)	Tachycardia (~ 100%)
Palpitations (~ 90%)	Tremor (~ 95%)
Increased perspiration and heat intolerance (~ 90%)	Goiter (~ 100%)
Fatigability (~ 80%)	Warm moist skin (~ 95%)
Weakness (~ 70%)	
Increased appetite and weight loss (~ 85%)	
Less common	
Dyspnoea (~ 65%)	Atrial fibrillation (~ 10%)
Increased bowel frequency (~ 30%)	Onycholysis (~ <5%)
Anorexia (~ 10%)	'Liver palms' (~ 5%)
Weight gain (~ <5%)	Heart failure (~ 5%)
Oligomenorrhea (~ 25%)	
Rare	
Pruritus (~ <1%)	
Periodic paralysis (~ <1%)	

Hashimoto's (1º)

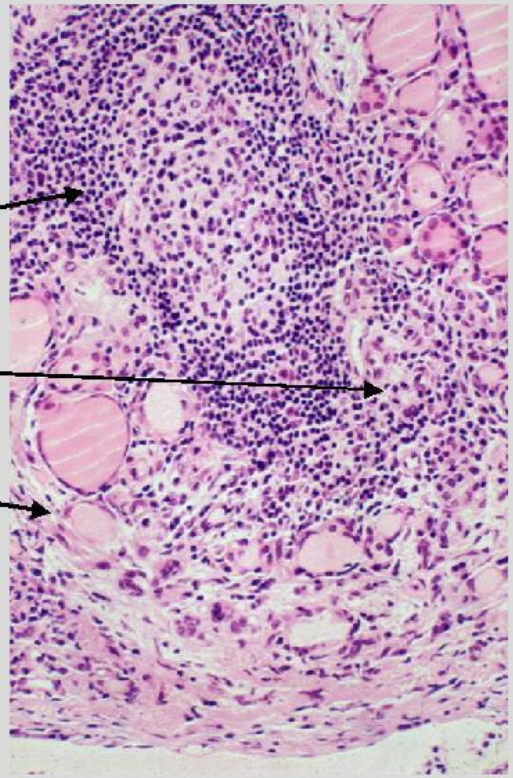
- Autoimmune - AB's destruction of thyroid gland
- Low concentrations of thyroid hormones
- Lethargy, intolerance to cold
- Lack of growth and development
- Diffuse goitre - lymphocytic infiltration of gland + TSH stimulated growth

Hashimoto's Autoimmune Thyroiditis

Histologic features:

Lymphoid follicles

Destruction of Thyroid Cells and Follicles by T Lymphocyes



Myxedema (myxoedema)

- Hypothyroid myxedema is specific form of skin edema
- Increased activity of connective tissues leads to increased deposition of components of extracellular matrix (mainly glycosaminoglycans, proteoglycans) which retains large amounts of sodium ions and water
- Stimulation of fibroblasts is caused by increased amount of TSH which is able to bind to some membrane receptors and by this way it activates biosynthesis of extracellular matrix

Symptoms and signs of hypothyroidism

Clinical features of hypothyroidism

Symptoms	Signs
Common	
Fatigue (~ 90%)	Dry, scaly skin (~ 90%)
Cold intolerance (~ 80%)	Coarse, brittle thinning hair (~ 60%)
Depression (~ 70%)	Bradycardia (~ 40%)
Poor concentration (~ 65%)	Hair loss or dryness (~ 70%)
Musculoskeletal aches and pains (~ 25%)	Anemia
Carpal tunnel syndrome (~ 15%)	Puffy eyes (~ 90%)
Less common	
Constipation (~ 50%)	Edema (~ 30%)
Hoarse voice (~ 40%)	Cerebellar signs*
Menorrhagia (~ 30%)	Deafness*
	Psychiatric*

References

- Concise Medical Biochemistry by Sucheta Dandekar (2019)
- Coneptual review of biochemistry by S.P. Pahwa(2018)
- Biochemistry by Lubert & Stryer(2017)