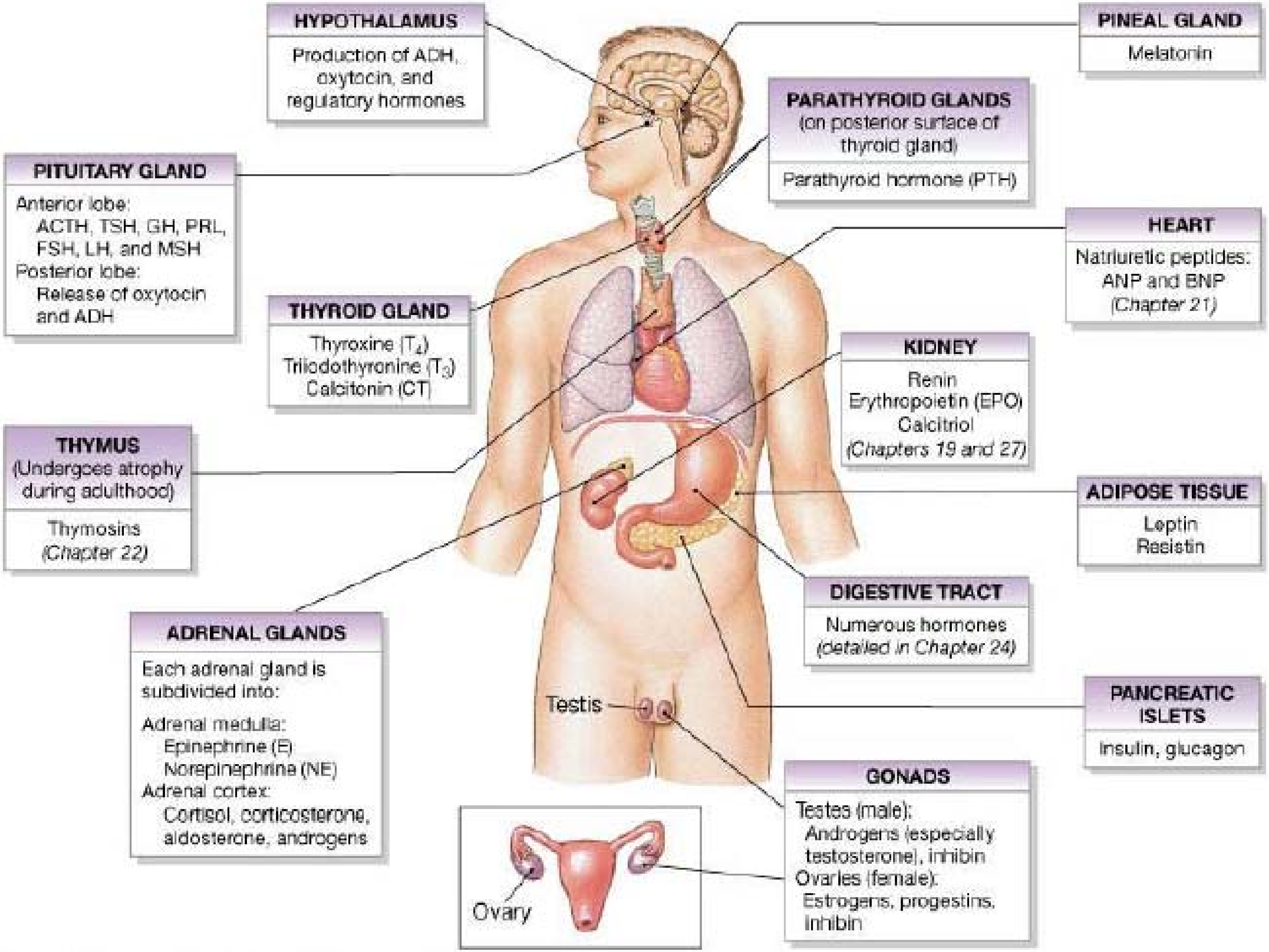
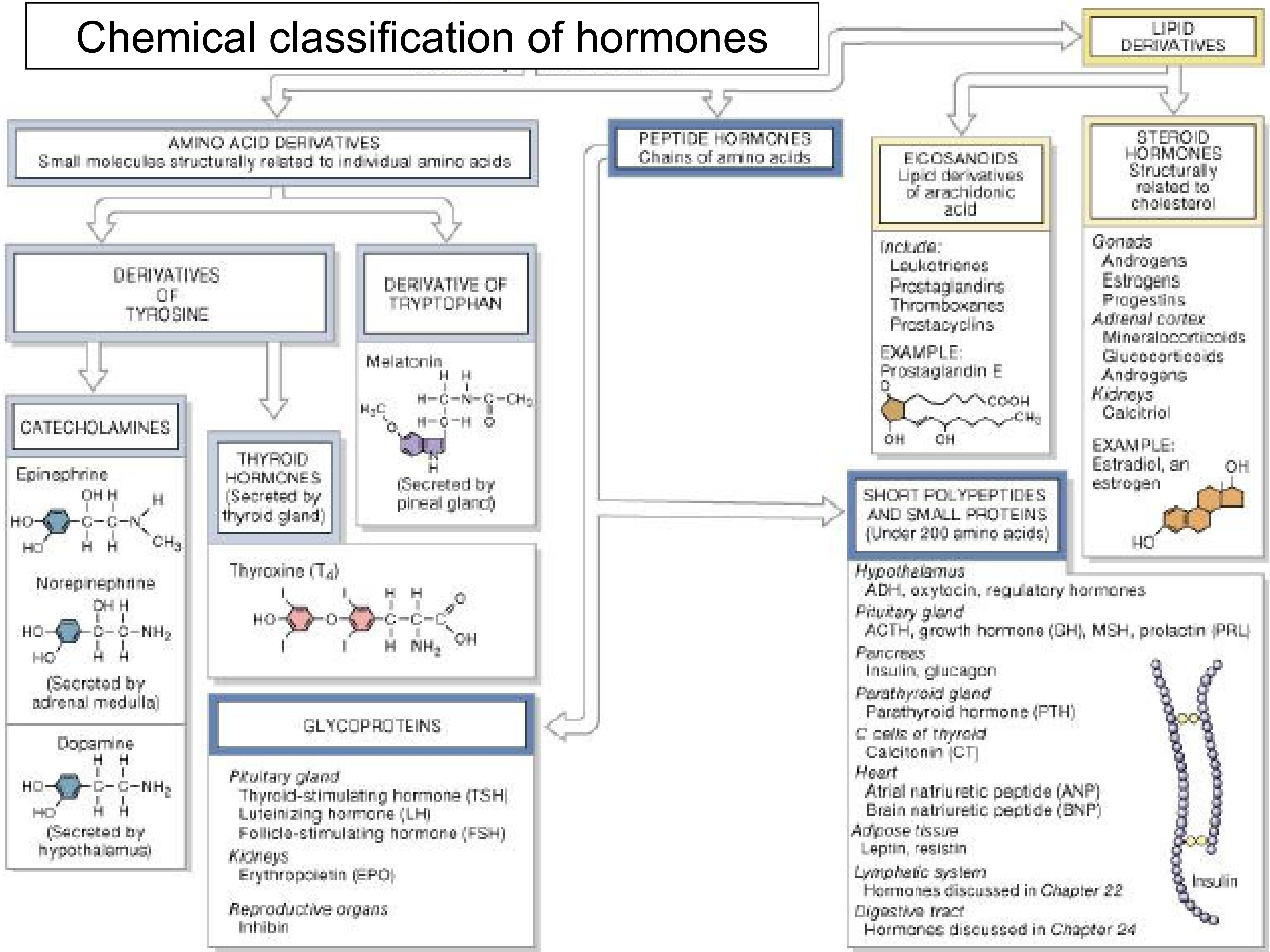
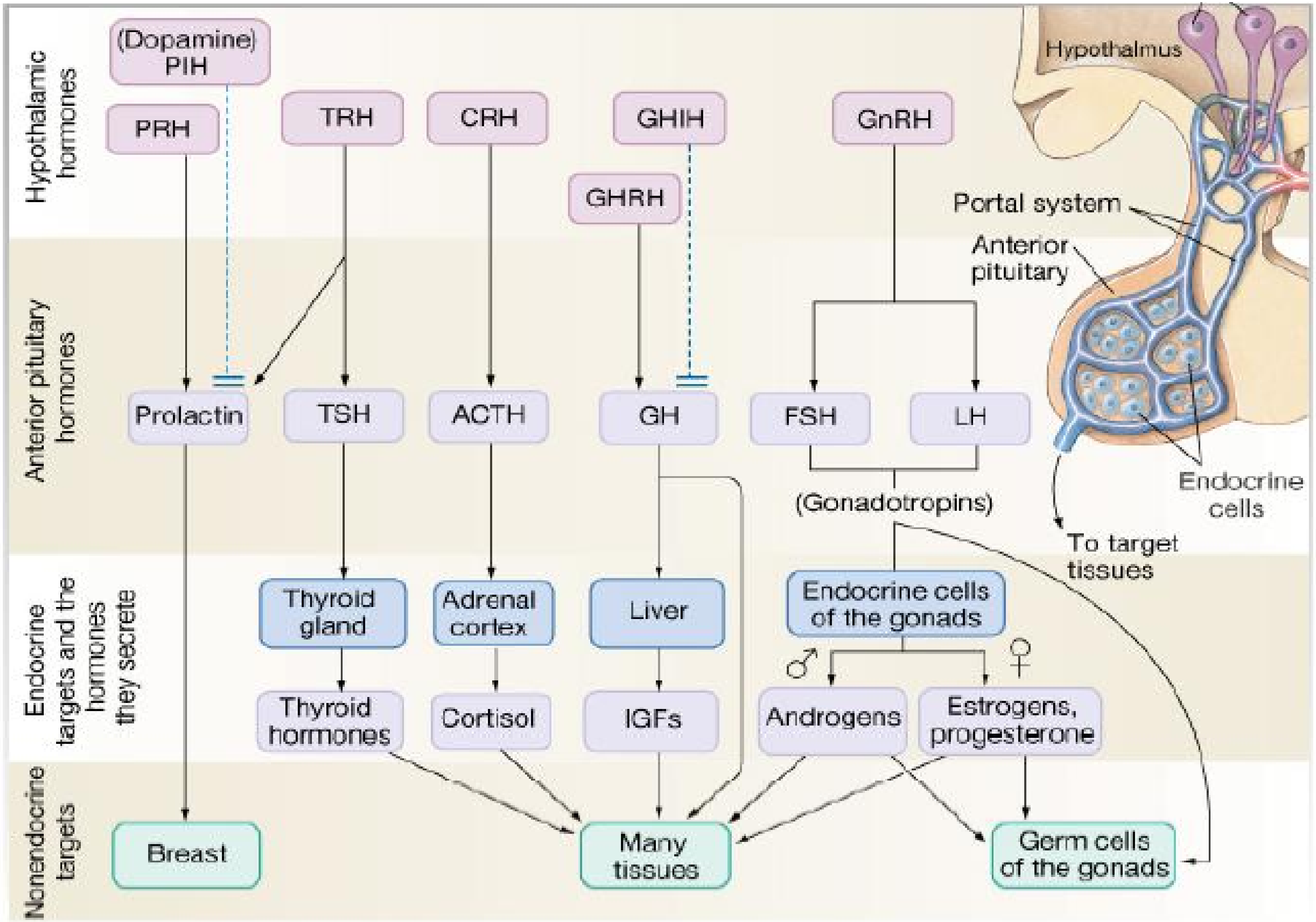
Endocrinology



Chemical classification of hormones



Hypothalamic-pituitary axis - Adenohypophysis



Biochemical classification:

1. Choriosomatomammotrop hormonok:

- Prolatin
- Growth hormone (GF)

2. Glikoproteinek

•Thyroid-stimulating hormone (TSH)
•Gonadotropins- Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH)

GF:

•Increase insulin level

•Iby this inhibit gluconeogenesis

•HYPERFUNCTION

→giantism

→ in older ages:

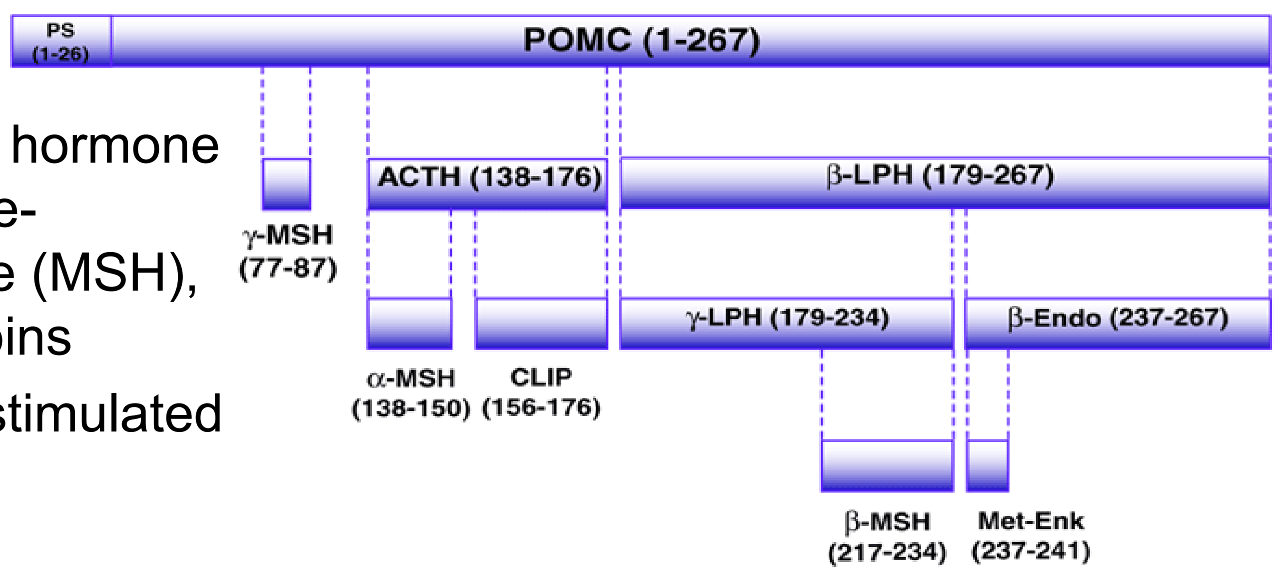
acromegaly

•HYPOFUNCTION:

→short stature

3. POMC (proopiomelanocortin) – derivatives

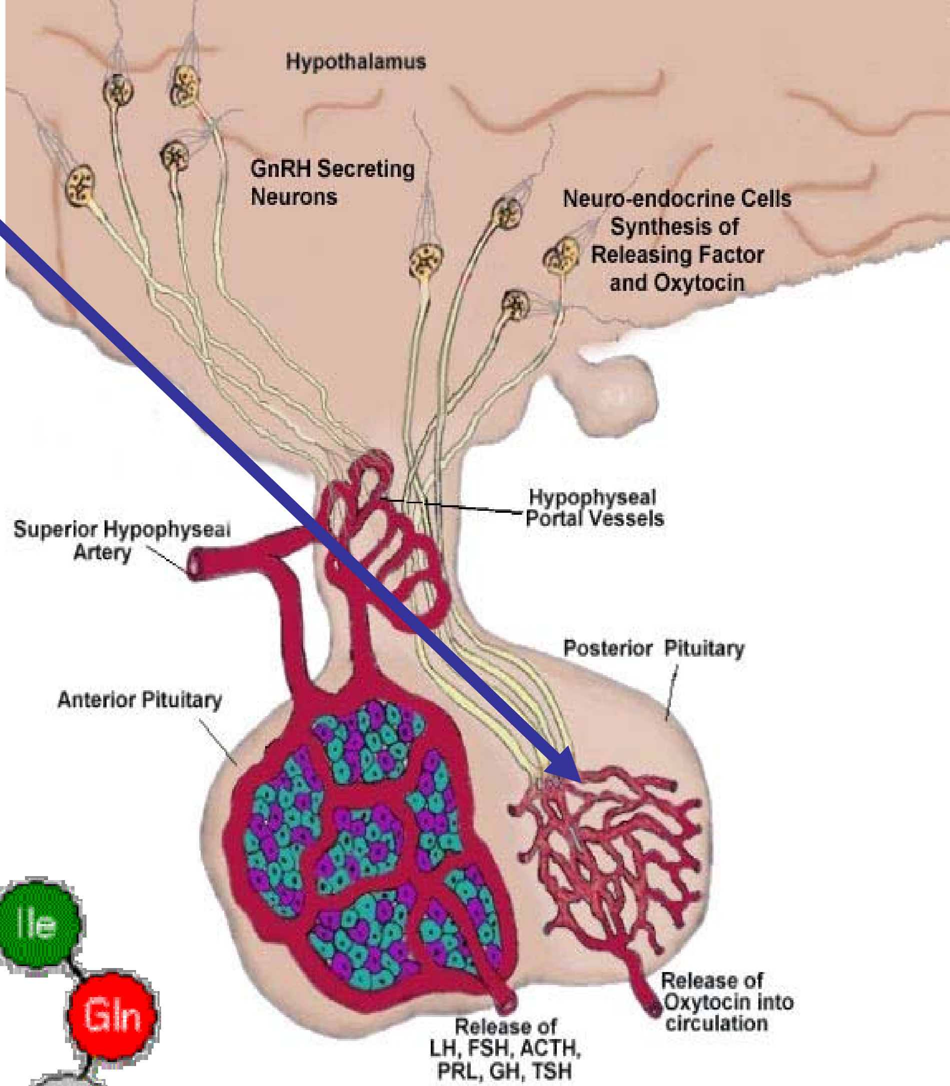
- Adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), endorphins, lipotropins
- Pituitary synthesis stimulated by corticoliberin

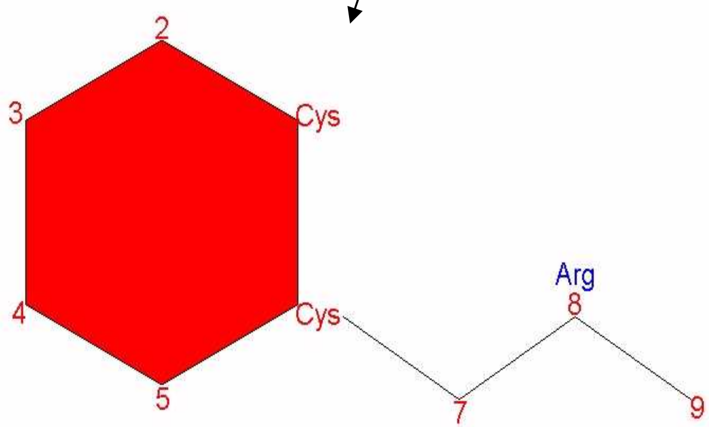


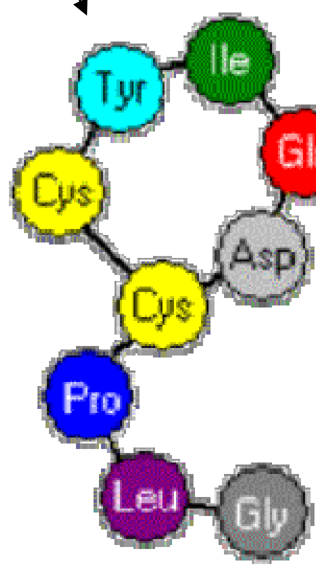
Neurohypophysis

- Not glandular as is the anterior pituitary, just store hormones from the hypothalamus
- Nucl. supraopticus et paraventricularis
- Stimuláció hatására ürít
- Two peptids which contains 9 amino acids

Arg-vasopressin(ADH) and oxytocin

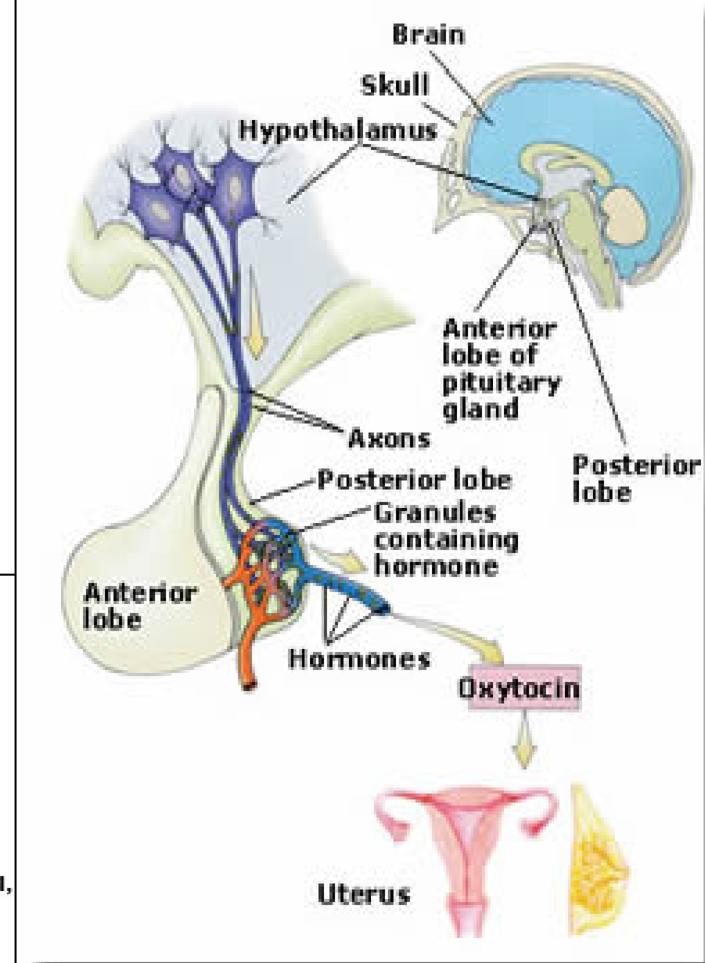


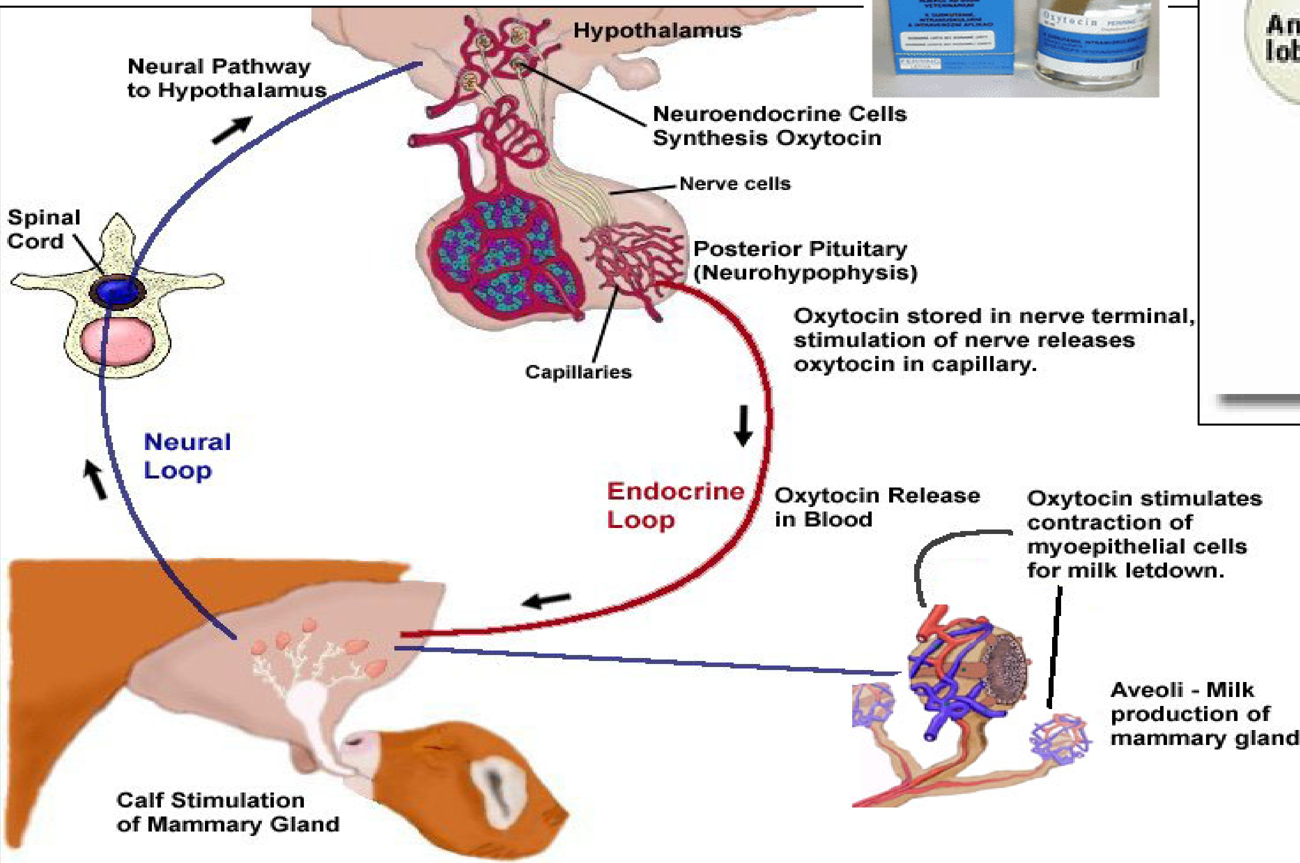


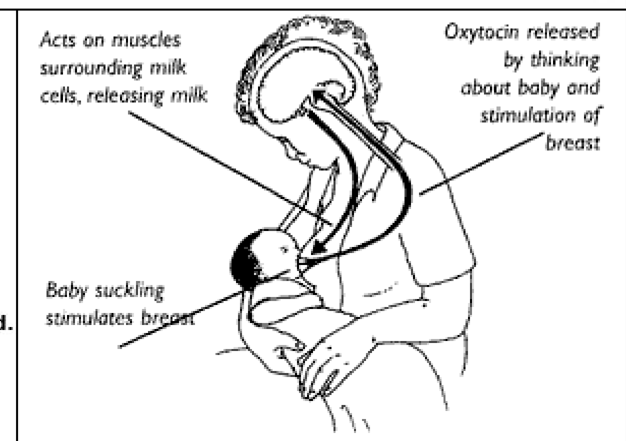


Oxytocin

- Relaesed by mechanical stimulation
- Main function in childbirth and milk ejection
- Oestrogens increase the effect
- Gestagens inhibit – stop abortion
- Labour induction





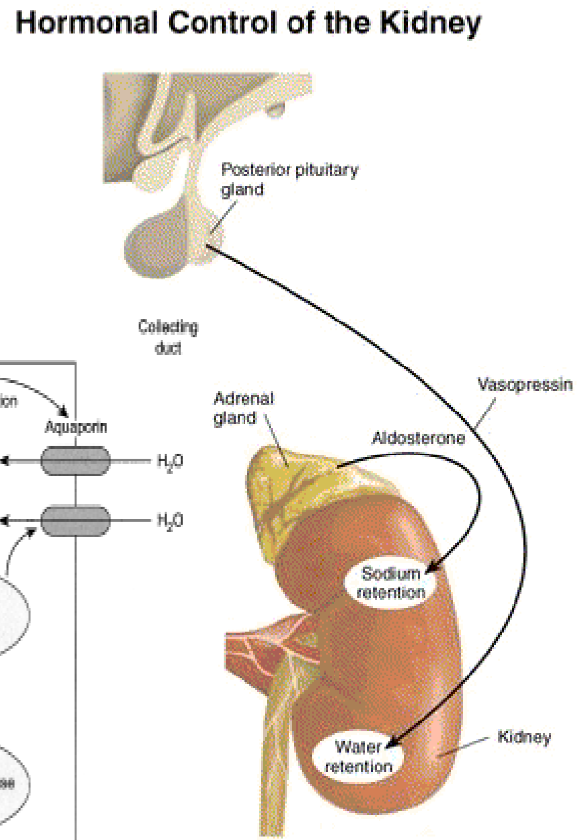


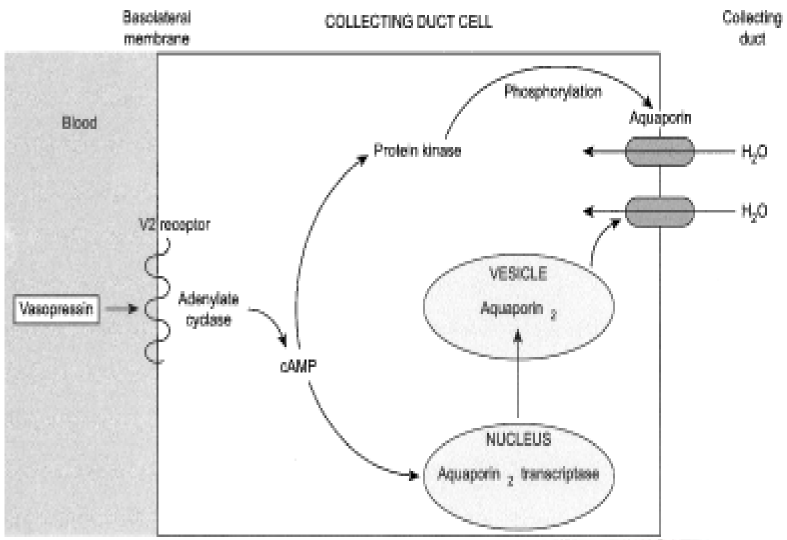
Antidiuretic hormone - ADH

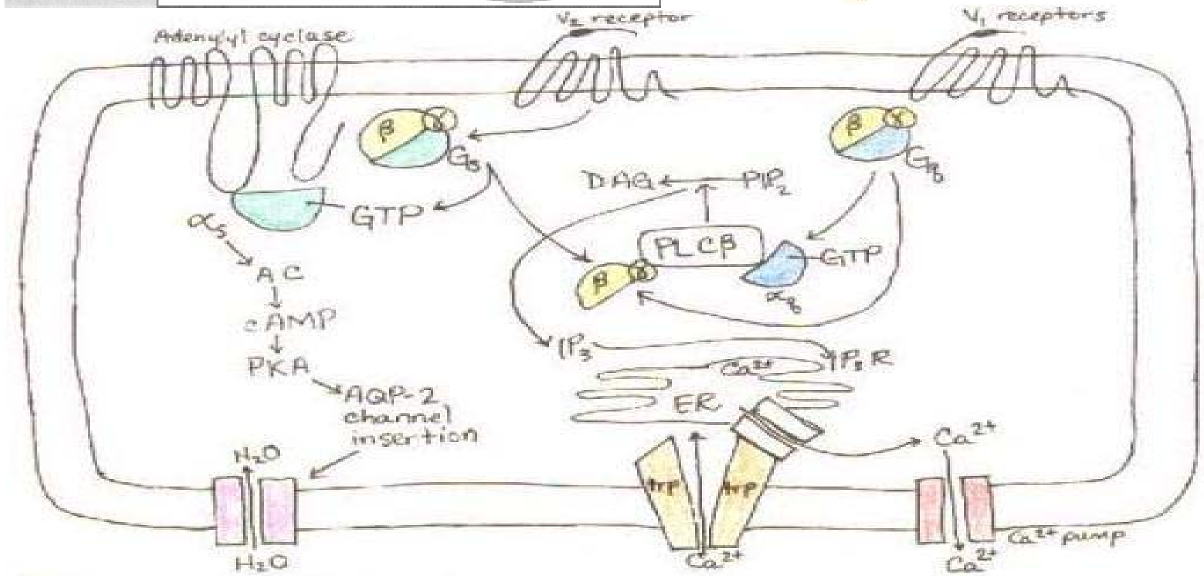
- Main functon in urine contentration
- Isosmosis and isovolaemia
- HYPOFUNCTION

  Diabetes insipidus
- HYPERFUNCTION

Schwartz-Bartter syndrome

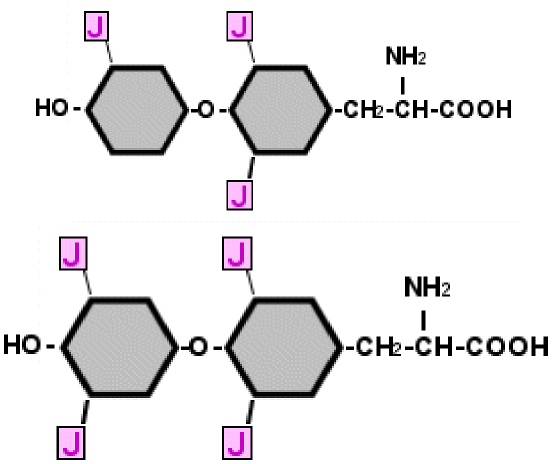






Thyroid horomones

General characteristics



- Chemical derivatives of amino acids
- Intracellular effecting hormones
- Long term responses
  →induction of transcription

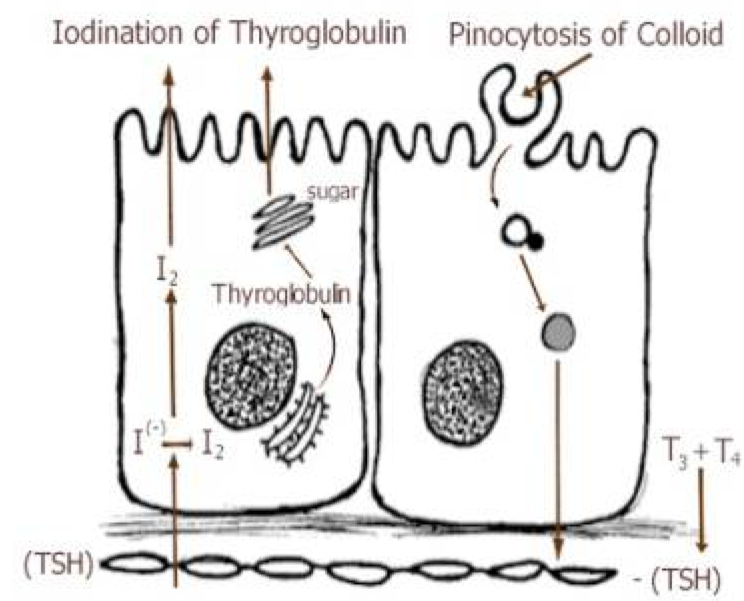
Regulation

- Hypothalamus – thyreoliberin (TRH)
- Adenohypophysis - TSH

•Negative feedback

•Thyroxine inhibit secretion of TRH

Synthesis



- In folliculare space Tyr-thyreoglubulin
- To Tyr sidechains Iodine binding
- One Tyr-ring put to another and Ala remain
- DIT and MIT are created
- 2 DIT= T4 , DIT+MIT=T3
- Above T3 and T4 rT3 are created
- The non active forms (rT3, DIT, MIT) recirculating in the cell
- T3 and T4 relaese in to blood

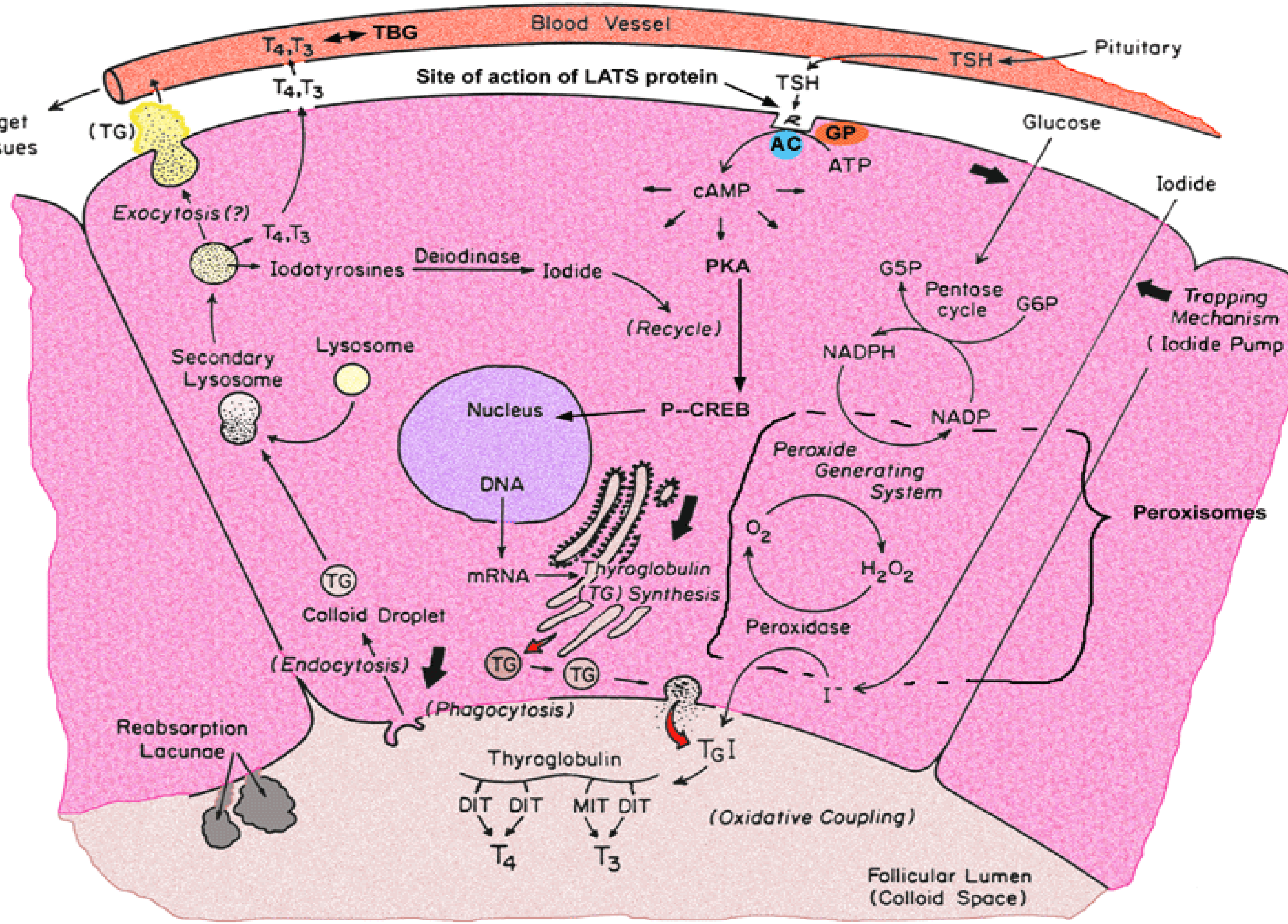
Inhibition of synthesis

- Iodine uptake
- Iodine incorporation:

  tiogracil (sulfurized N-containing compounds)

  in cabbage there are similar materials → hypothyreosis

Thyroid Hormone Synthesis by Thyroid Follicle Epithelial Cells



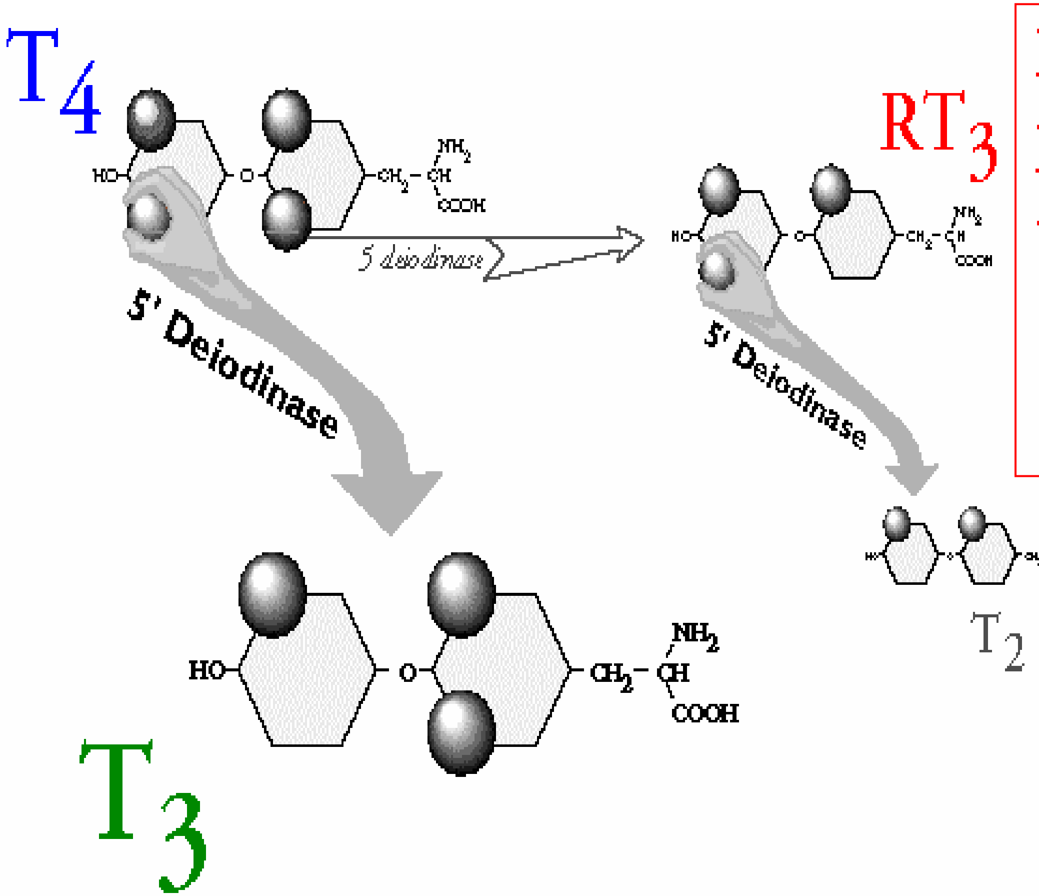
(Modified from Hadley, *Endocrinology, 4th Ed,* Prentice Hall: Upper Saddle River, NJ, 1996.)

Hormones

3hormon:T3 → 4 times stronger effect than T4, mainly created in peripherial by 5'-deiodinase from T4

T4 → total thyroid glang origin

rT3 → no biological effect



TBG: thyroxine binding globulin

TBP: thyroxine binding prealbumin

Transported in blood by binding proteins. Dinamic balance between binding protein and free hormone level. Inhibit the filtration!

Effects

- General activating effect – stimuli of the metabolisation
- R/R ↑, heartrate ↑, body temperature ↑, bowel peristaltic ↑, neuronal nervous irritability ↑, →HYPERTHYIREOSIS mild signs
- HYPOTHYREOSIS: contrary to the previous one

HYPOTHYREOSIS:

Primer: the synthesis of the hormone is inhibited

Secunder: inadequacy of the control center (hypothalamus-hypophysis)

→

DISCRIMINATION:

TSH level measurement

Primer – TSH high level

Secunder – TSH low level

Hyperthyreosis

Autoantibodies against TSH receptor activateing receptros→stimulation of thyroid gland→T3, T4↑ → no control of the H-H axis

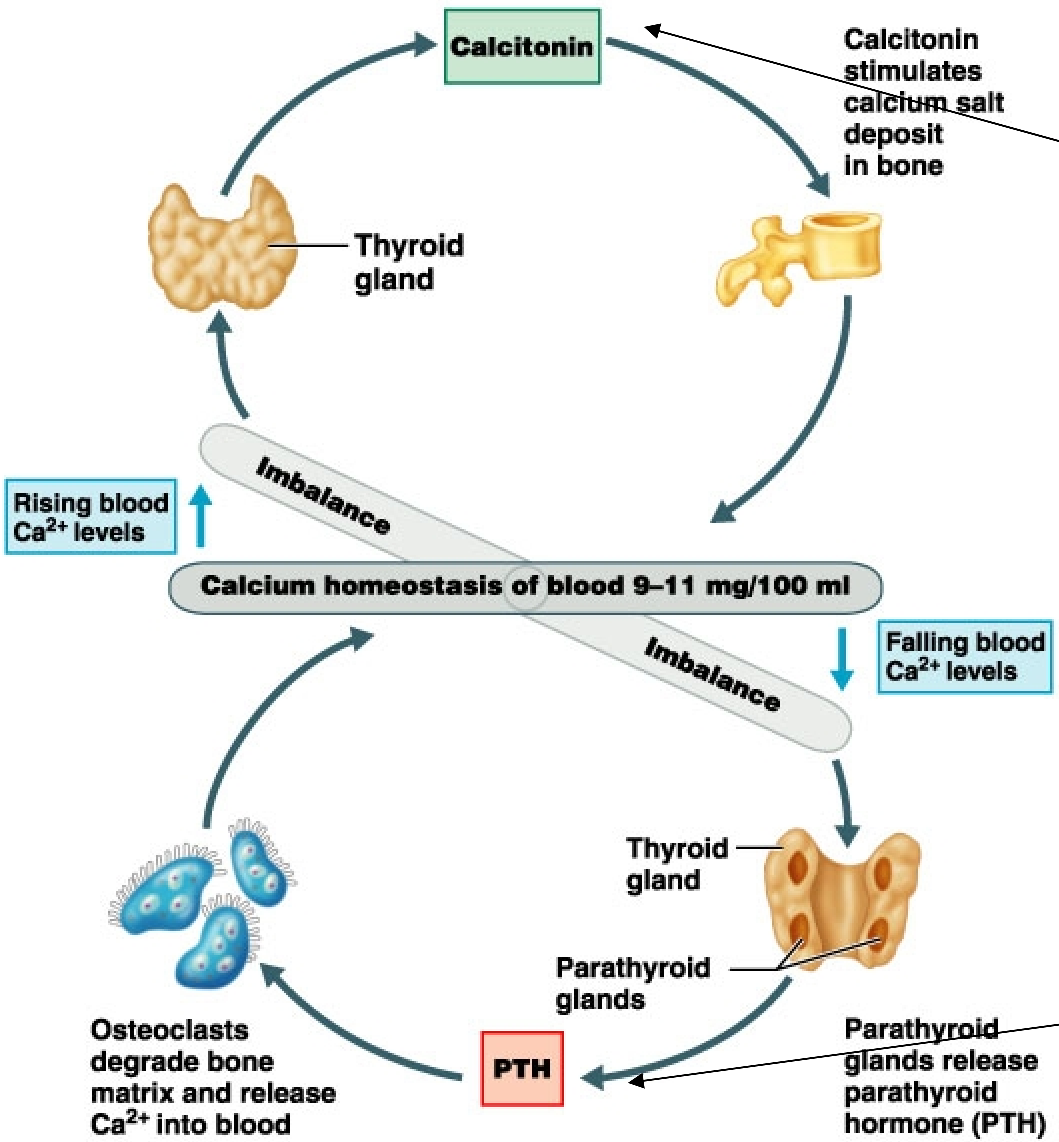
Symptones: restlessness, warm moist skin, tremor, palpitations, atrial fibrillation, rapid pulse, exophthalmos, heat intolerance, muscle weakness & atrophy, osteoporosis, weight loss, increased appetite, emotional lability / hyperkinesis, diarrhea, menstrual abnormalities

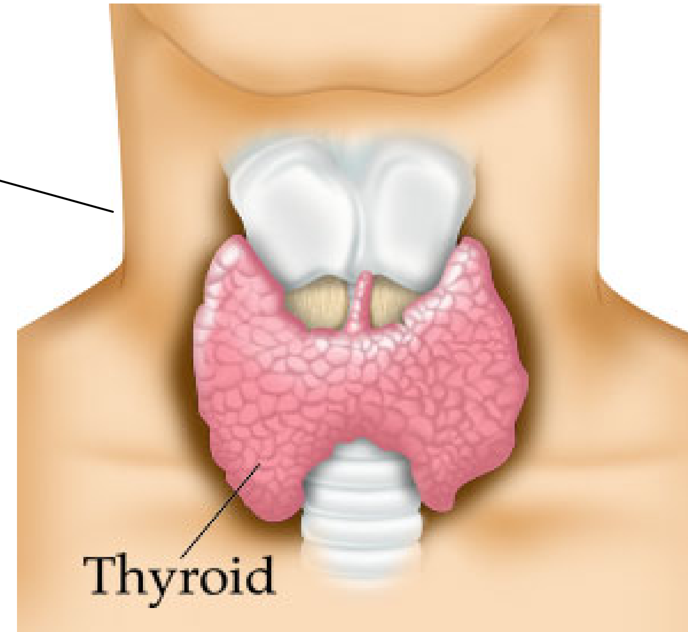
Hypotyreosis

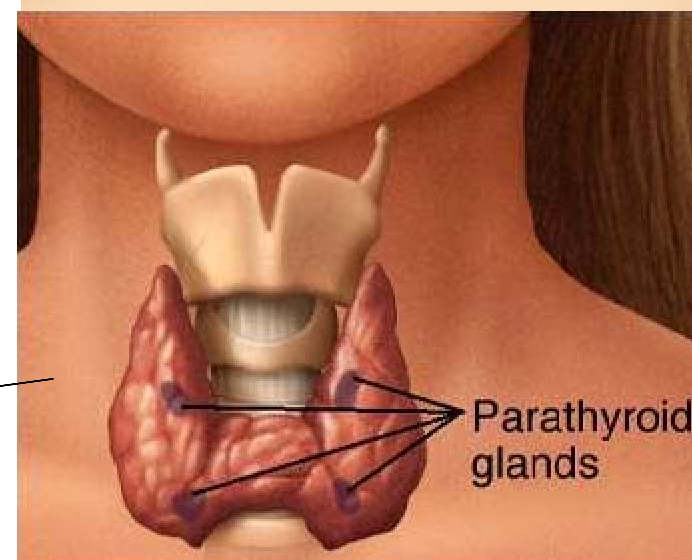
Due to lack of T3 & T4 emerging hypometabolic state

1. Gland dysfunction (malformations after radioactive therapy)
2. Congenital biochemical disorders - disorders of the hormone biosynthesis
3. Cretinism
   - Sporadic cretinism: congenital - no thyroid gland or small
   - Endemic cretinism in maternal iodine deficiency - goitre is present at birth, severe mental retardation, short stature, coarse facial features, language, deafness possible
4. myxedema: adult hypothyroidism (fatigue, lethargy, slow speech, mental slowing, poor reflexes cold intolerance, weight gain, constipation, ⇓ sweating, bradycardia, glycosaminoglycanok accumulation of pitting does not hold edema (myxedema), facial features coarsening, menstrual abnormalities

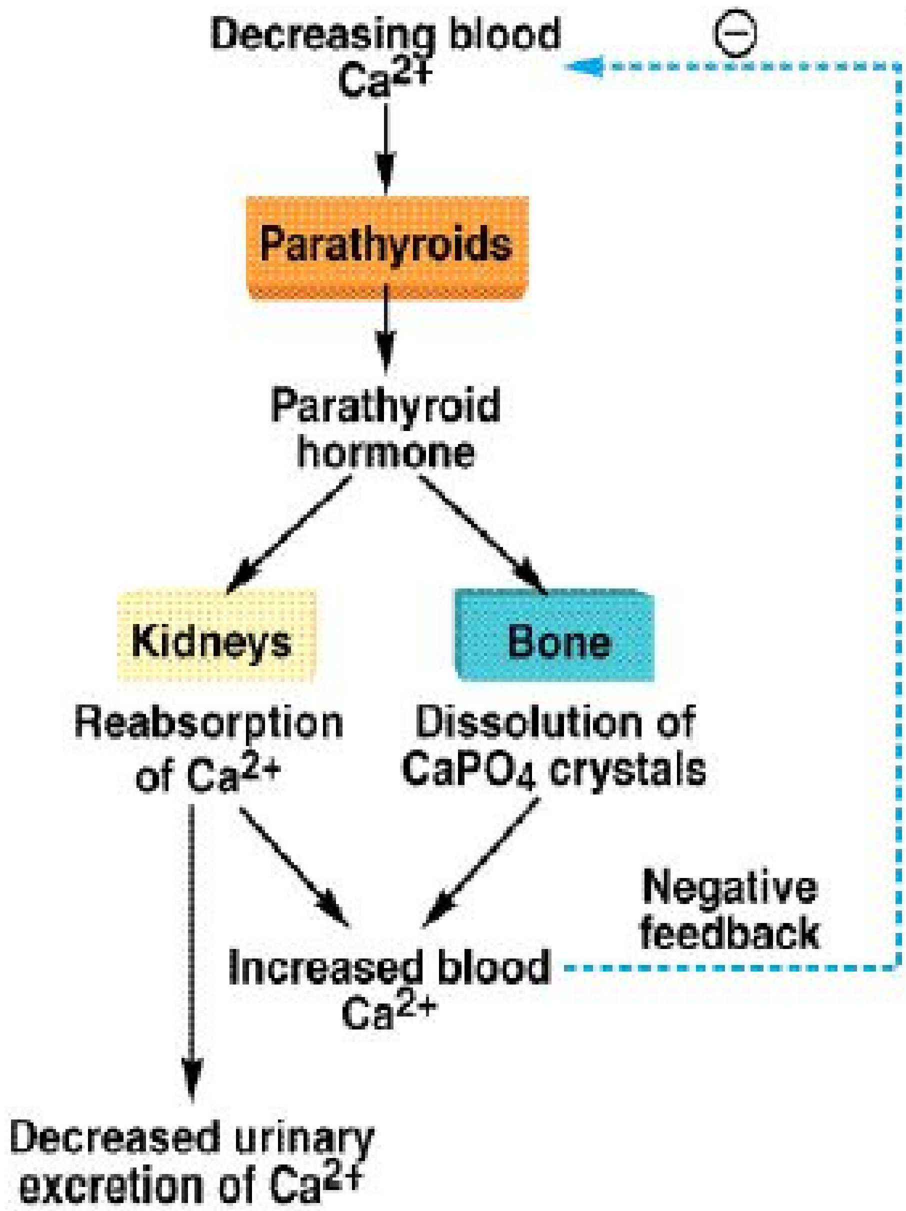
Hormonal regulation of blood Ca2 + level

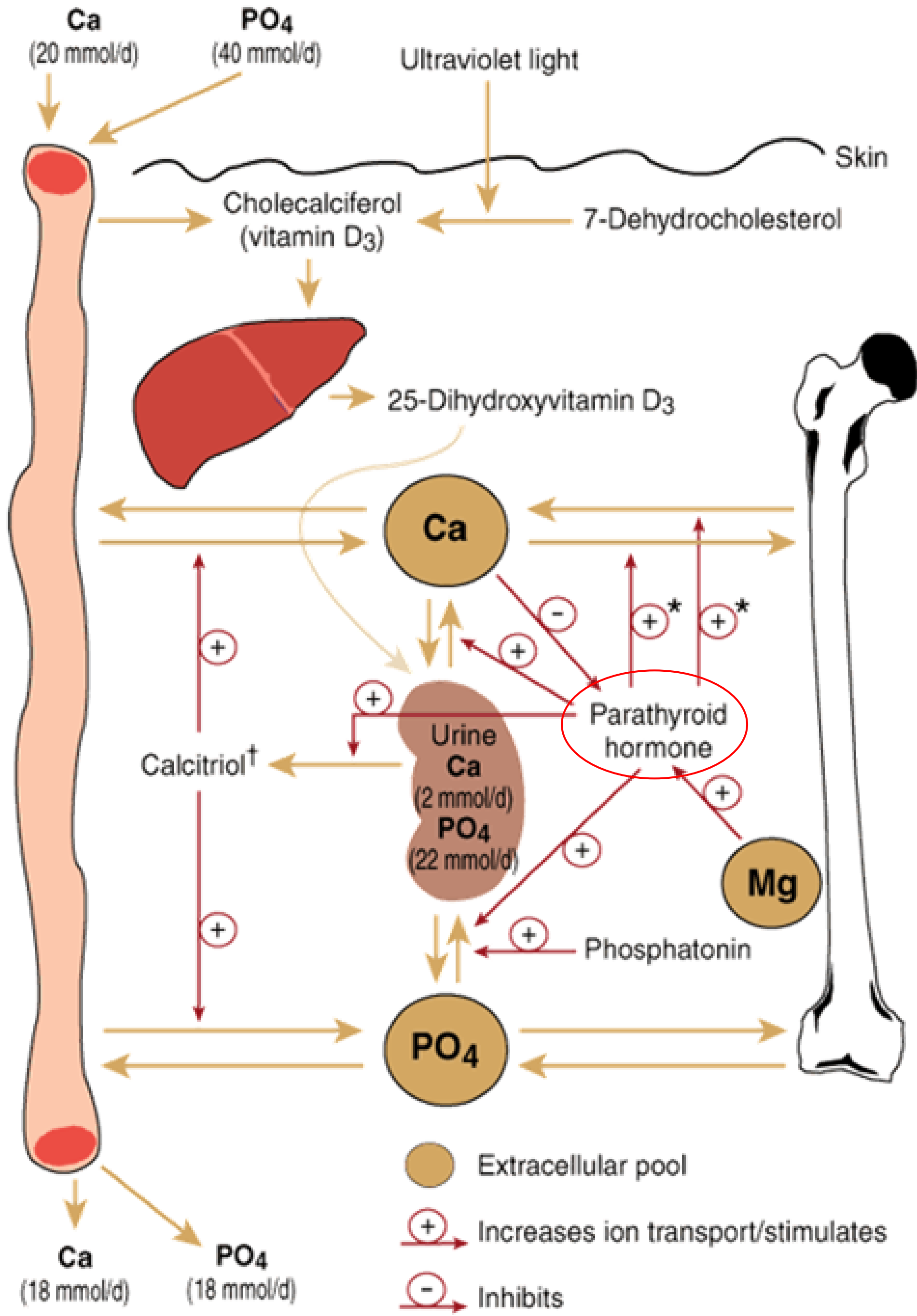


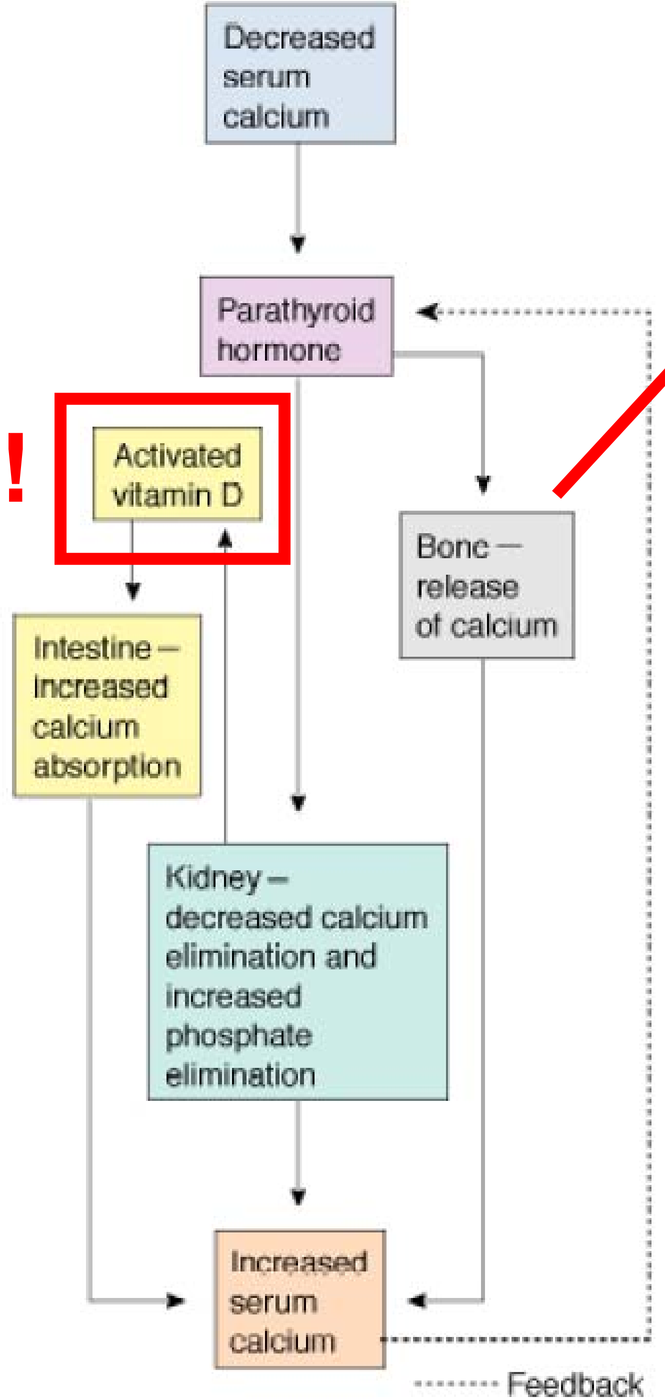


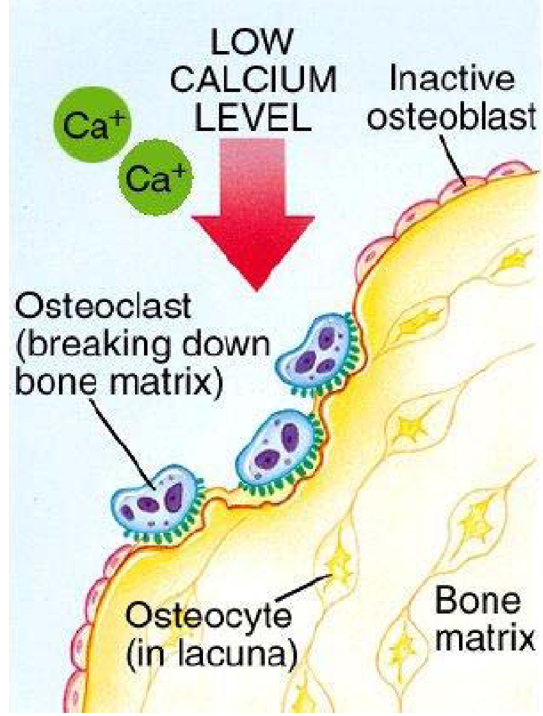


Effects of parathormone







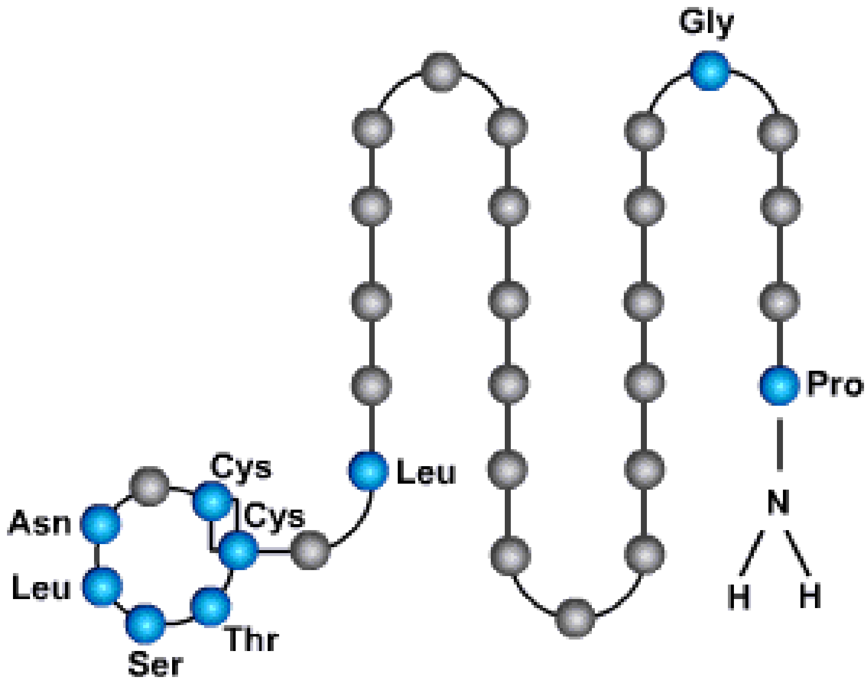


Summerize:

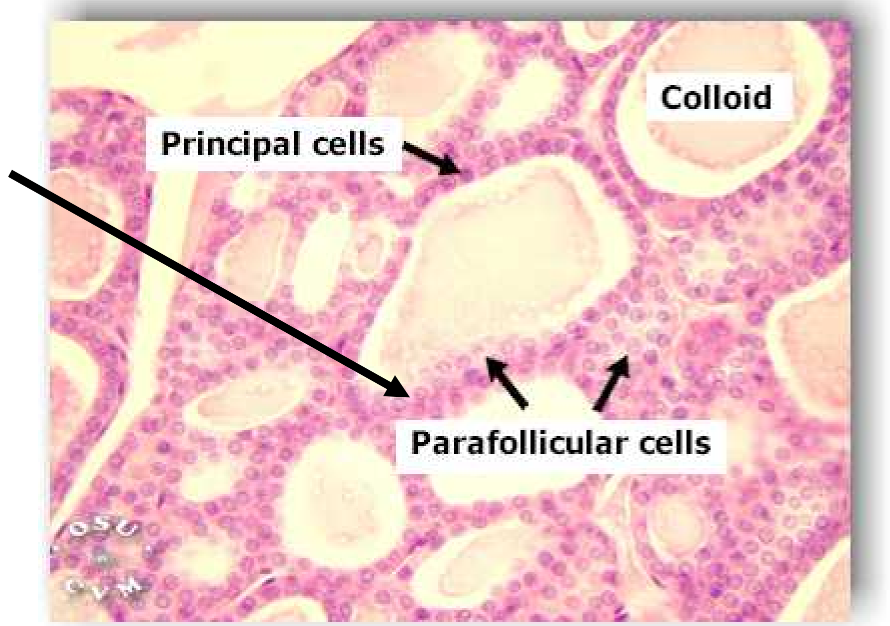
1. **Increasing Ca 2+ reabsorption in kidney**
2. **Increasing osteoclast activity**
3. **Increasing the activity of 1α-hidroxilase, thus enhancing the 1, 25-dihydroxy vitamin D levels and intestinal absorption of Ca 2 +**

Calcitonin

Excreated by parafollicular C-cells



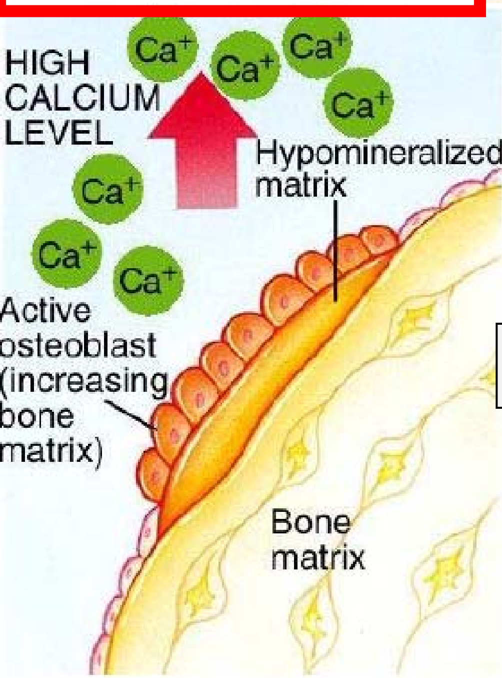
Calcitonin

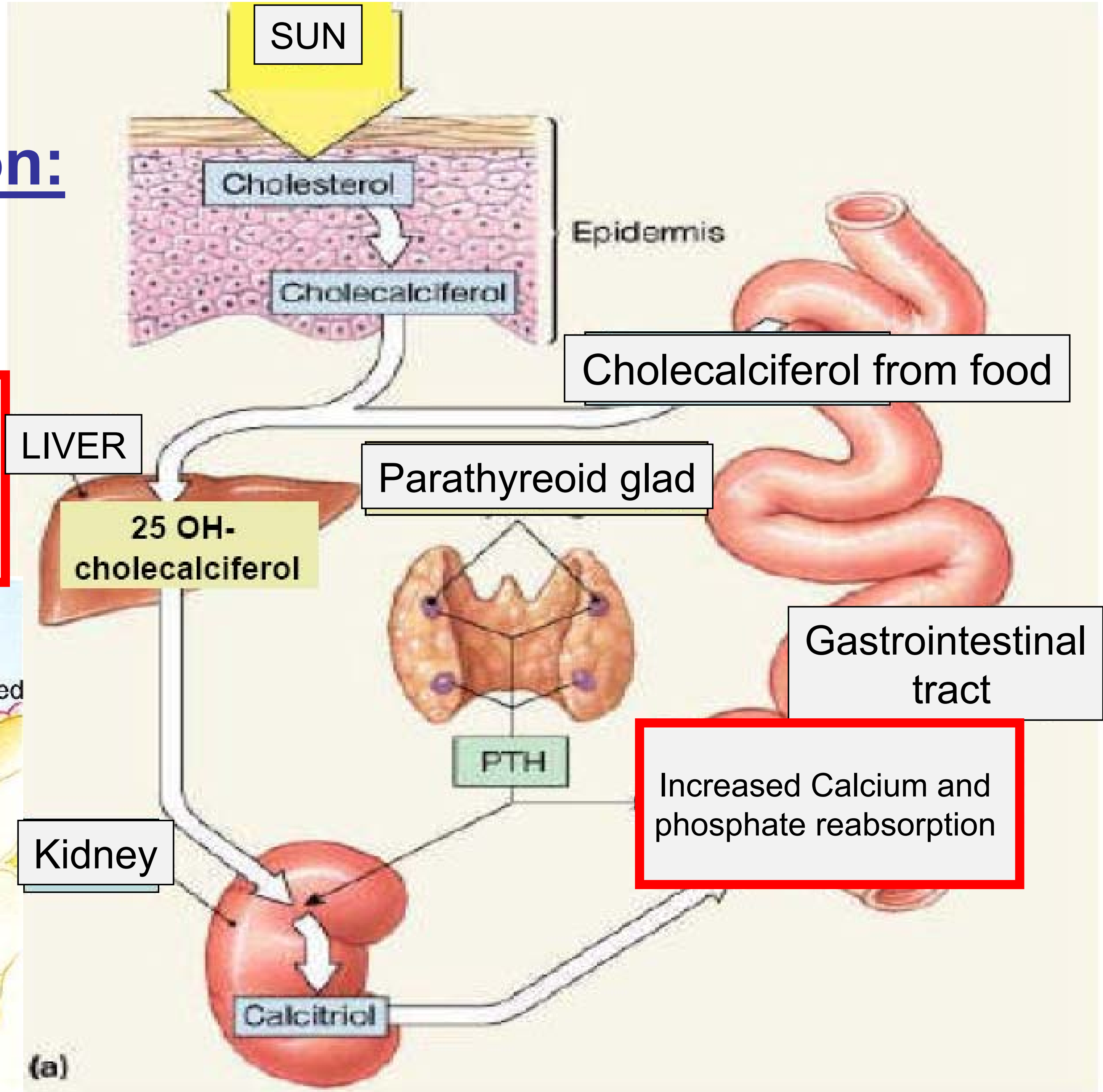


1. Csökkenti a Ca 2+ visszaszívást a vesében
2. Csökkenti az osteoclast aktiválást – fokozza az osteoblast aktivitást

Vitamin D and function:

Increased osteoblast activity





Hormonal regulation of blood glucose

- One of the most delicate system regulated
- complex regulation
- Balance of blood glucose lowering and increasing effects :

INCREASING:

- glucagon

-thyroid hormons

-glucocorticoids

-growth hormon

-hormons of suprarenal cortex
(NE,E)

-eating of carbohydrate

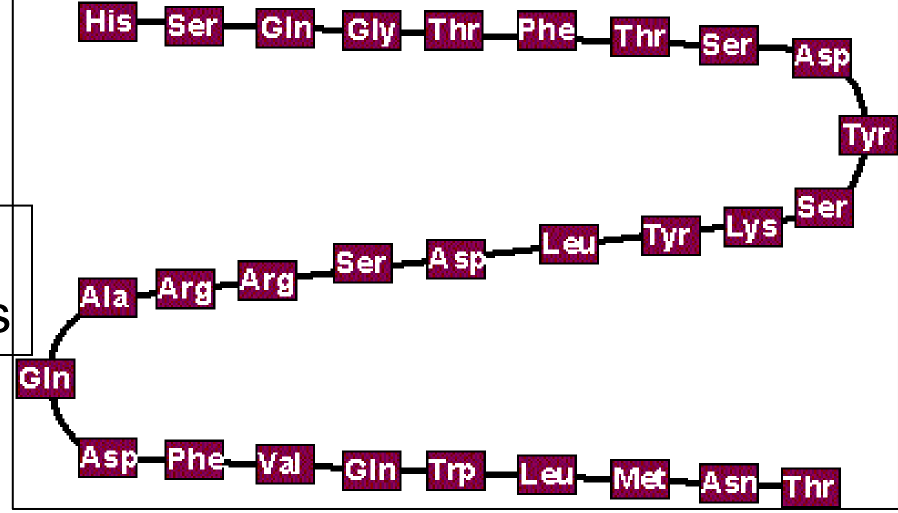
DECREASING:

-insulin

-starving

-physical activity

Glucagon

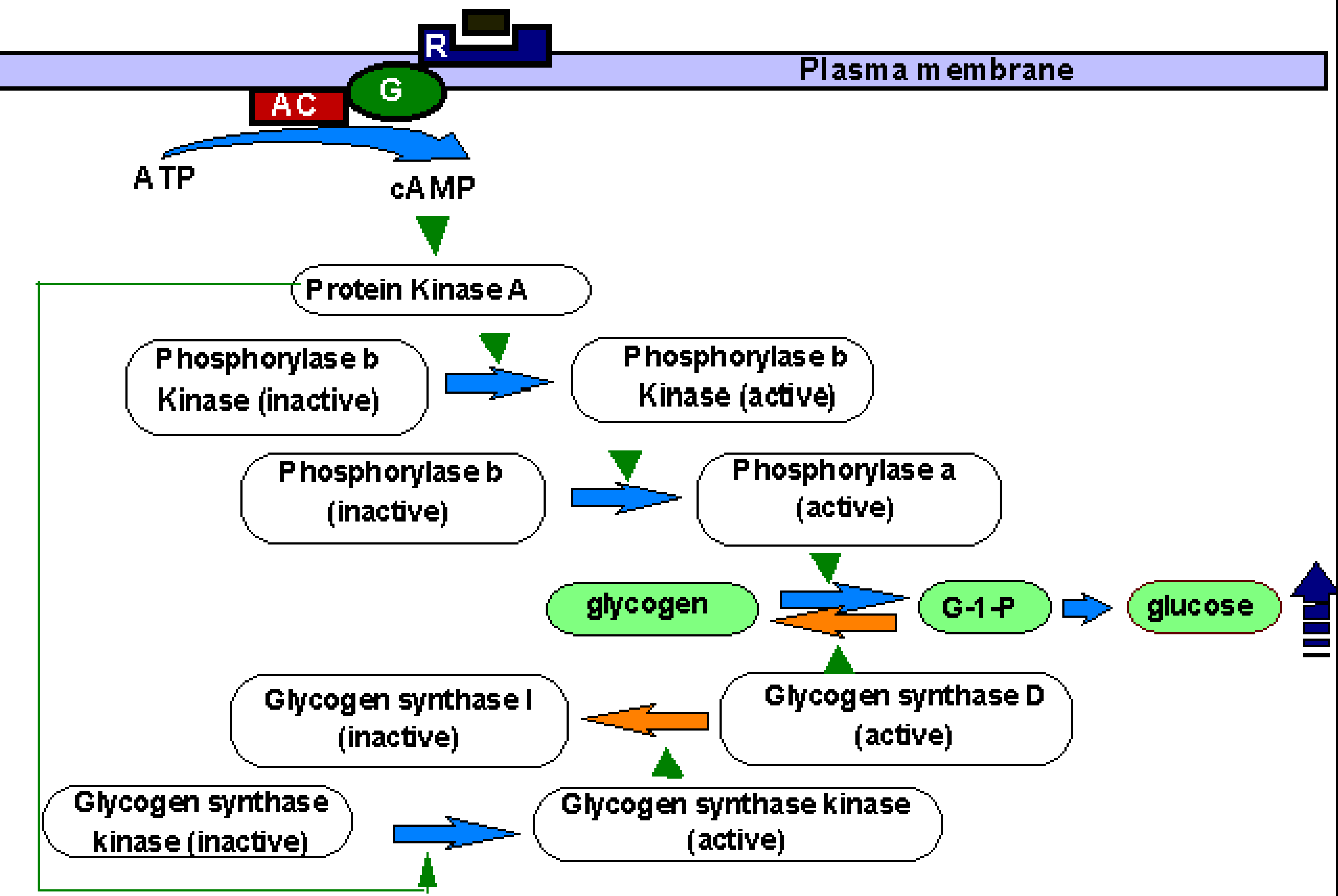


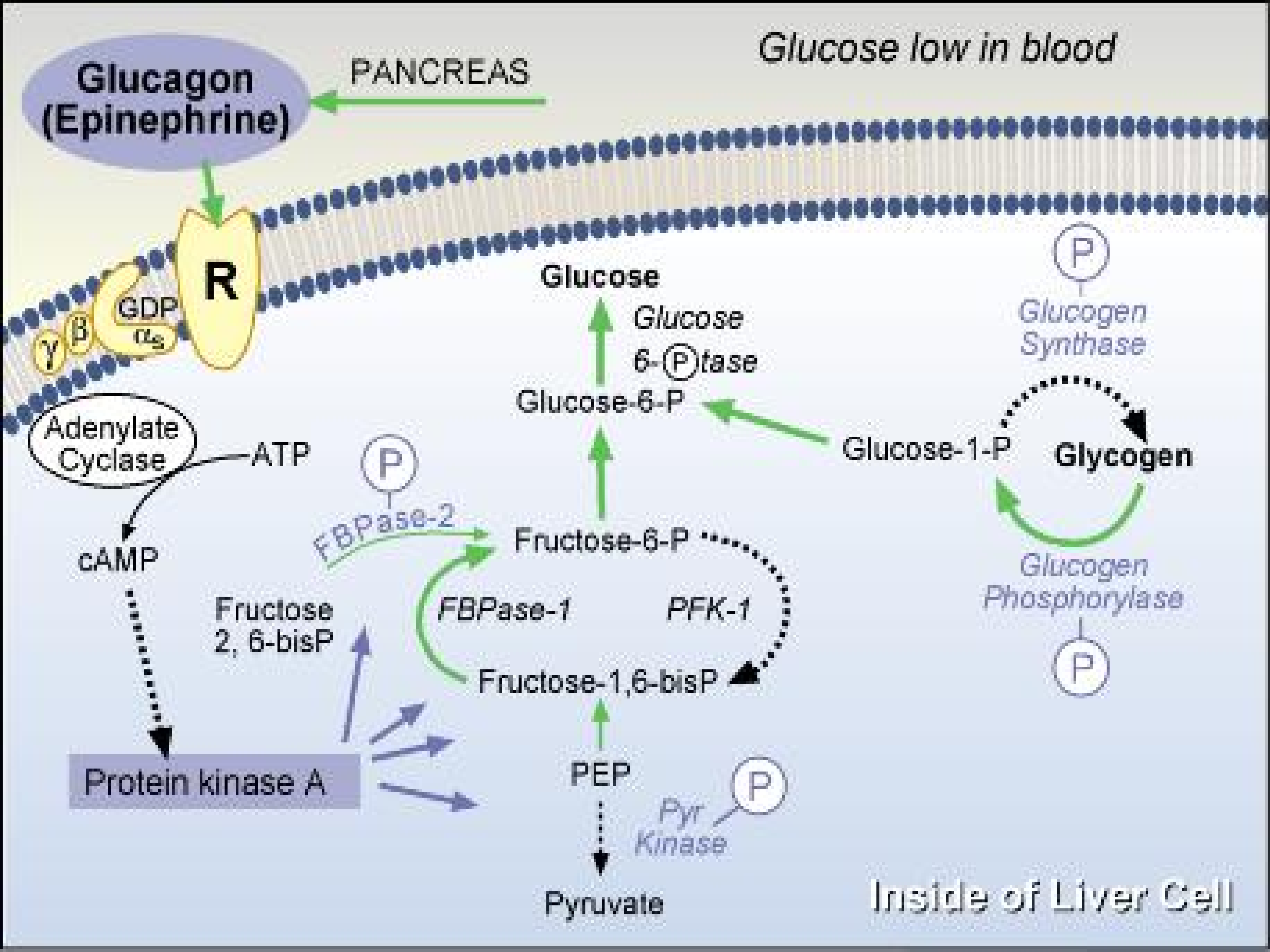
- 29 amino acids
- produced by alpha cells of the pancreas

Secretion

- transport nutrients levels in the blood, hormones and paracrine mediators regulate level of glucagon
- Glucose below 3.8 mmol/l is the separation threshold
- Potent inhibitor of insulin secretion → reduces proglucagon mRNA transcription
- Termination of insulin secretion leads to overproduction of glucagon (fasting, DM)
- Insulin reaches in high conc the α-cells
- Stress Hormones increase secretion → stress hyperglycaemia

Glucagon signal transduction

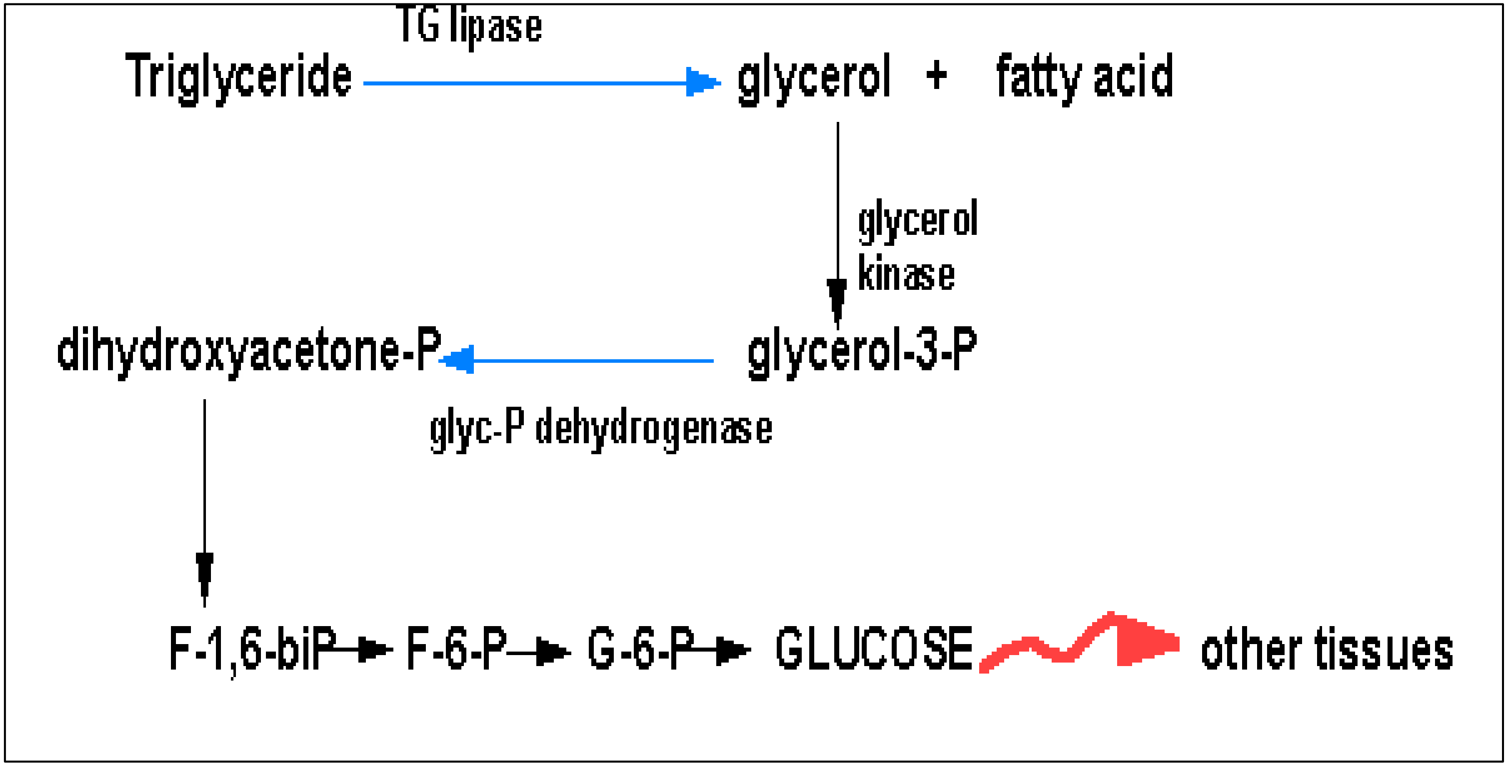



Glucose low in blood
Glucagon (Epinephrine)
PANCREAS
R
GDP
αs
γ
β
Adenylate Cyclase
ATP
cAMP
Protein kinase A
Fructose 2, 6-bisP
FBPase-2
P
Glucose
Glucose 6-P tase
Glucose-6-P
Glucose-1-P
Glycogen
Glucogen Synthase
Glucogen Phosphorylase
Fructose-6-P
FBPase-1
PFK-1
Fructose-1,6-bisP
PEP
Pyr Kinase
Pyruvate
Inside of Liver Cell

It works through the liver cells

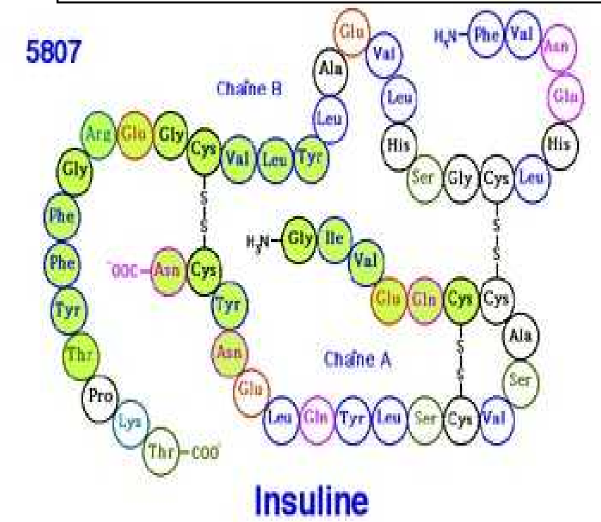
- Increase glycogenolysis
- Increase glyconeogenesis
- Increase ketogenesis

- Increase lipolysis
- Increase glycerine usage
- Decrease triglycerol synthesis



Insulin

- Peptide
- Good antigene (potent immunchemical measurement– as C-peptide)
- Halflife 7-15 min – difficult to administer
- Effect on surface receptor Tyr-kinase

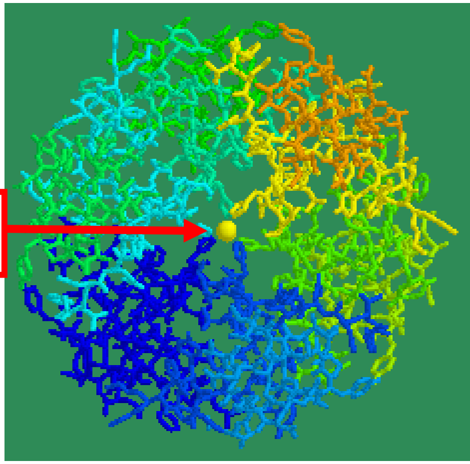


•**A-chain:** 21 amino acids

1 disulfide bridge inside the chain

•**B-lánc:** 30 amino acids

Between the two chains 2 disulfide bridge



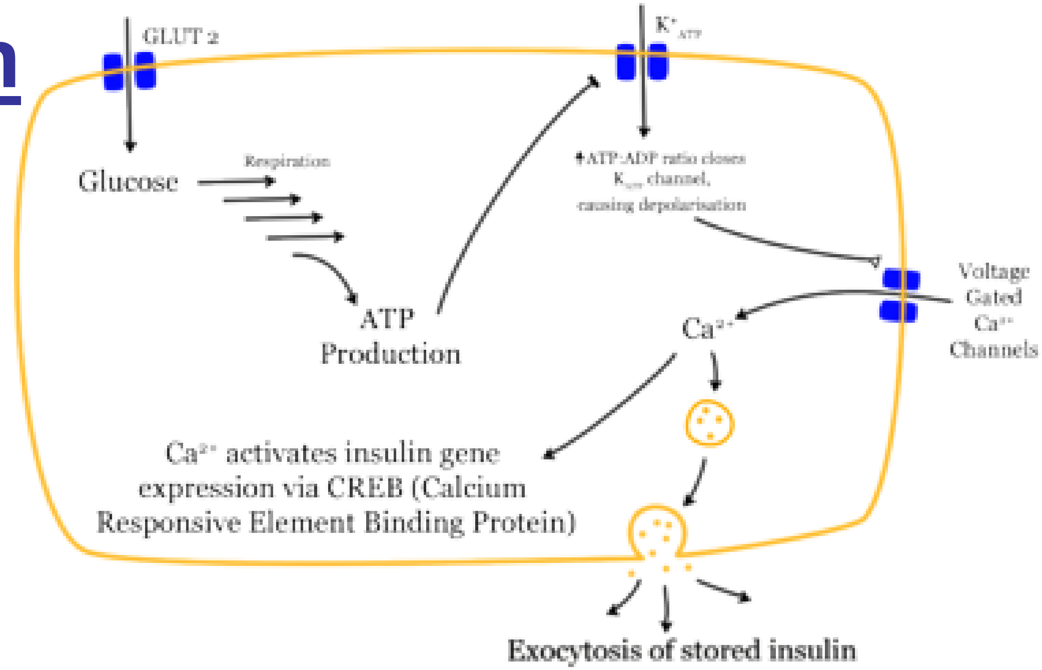
Production of insulin

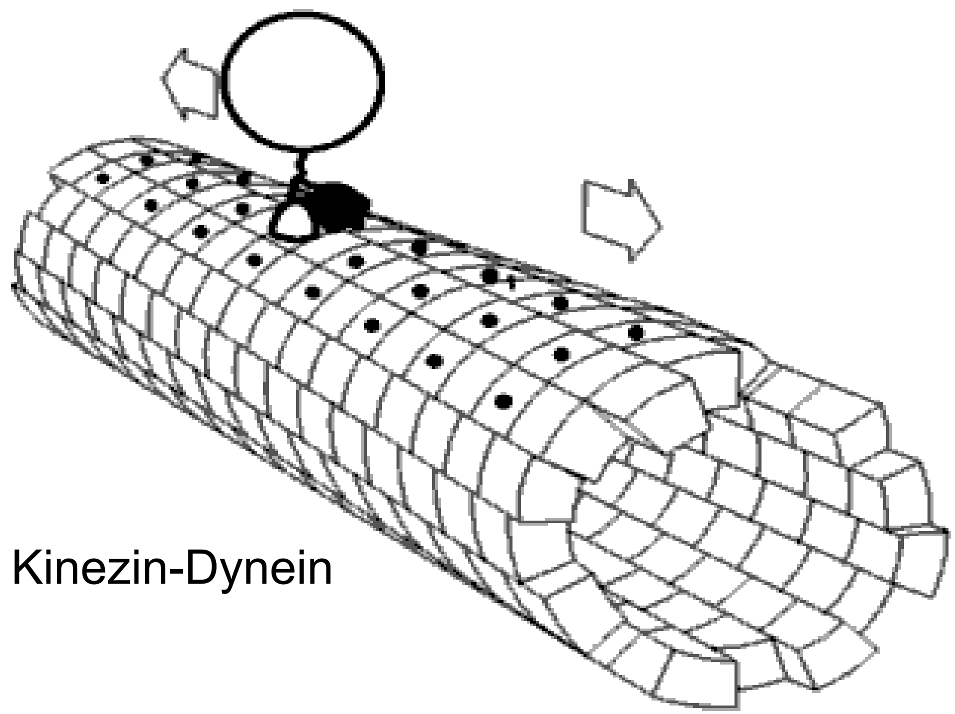
- There is no known factor, which is produced by the hypothalamic-hypophisealis system, and have effect on the direct production of insulin
- The control of blood sugar

Secretion ofInsulin

1. Glucose transported by GLUT-2 to the β-cell
2. Metabolisation and ATP is generated
3. The ATP closes ATP-sensitive K + channels – depolarization
4. Ca2+ influx:

- Geneexpression changes (CREB)
- cytoskeletal rearrangement
- excretion of insulin vesicles





Kinezin-Dynein

Regulating mechanisms of secretion

- Forward in time puts the insulin
- The degree of alimnetare hyperglycaemia
- Reflex parasympathetic effect (n.vagus) - a sweet taste, due to food intake activates
- Incretins - GI hormones that are released from the effect of nutrients and stimulate insulin secretion

  -GIP (glucose-dependent insulinotropic peptide)

  -GLP-1 (glucagon like peptide 1)
- Damping Mechanism: Somatostatin – after diet reduces hypoglycaemia
- Catecholamines – due stress reduce the insulin secretion by α2-receptors

Structure of Insulin

PREPROINSULIN

Some amino acids is cleaved

↓

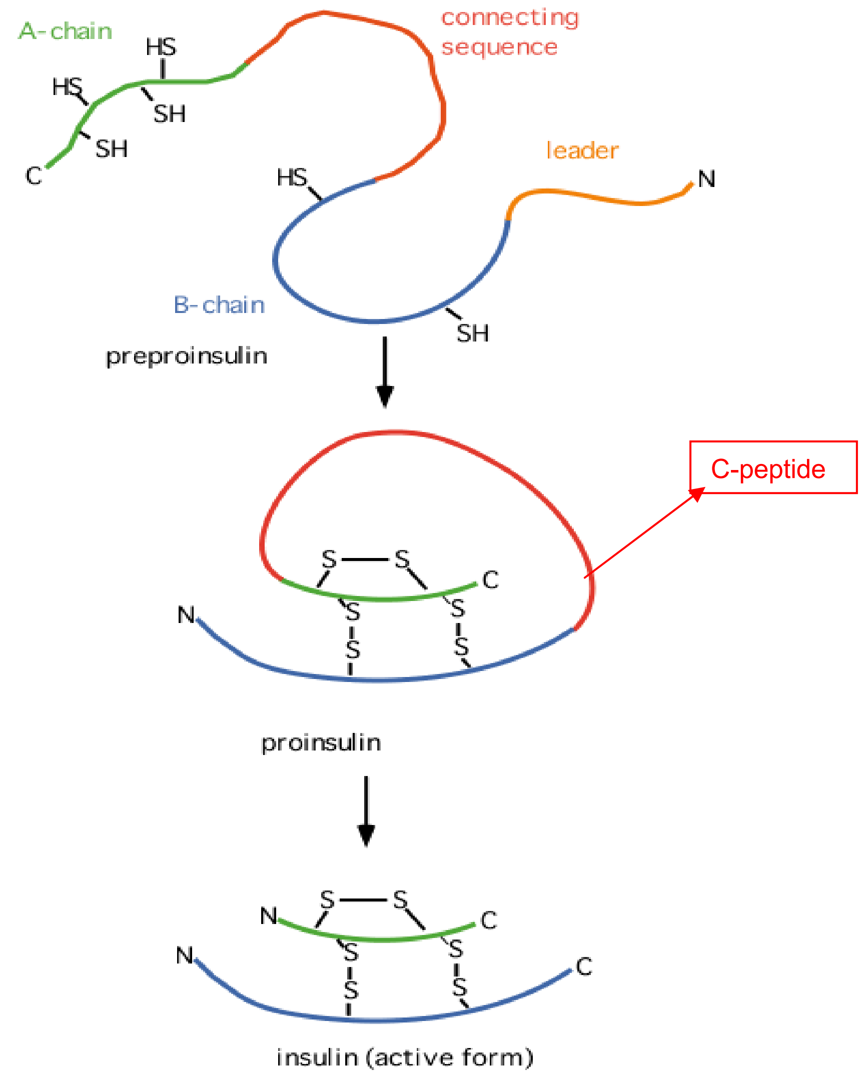
PROINSULIN

secreted by the β-cells, forming a loop-related peptide

↓

INSULIN

After cleavage of the C-peptide



C-peptide:

- Provides information of endogenous insulin formation
- In Type II. diabetes there is insulin secretion (C-peptide ratio of 1:1)
- Synthetic insulin does not contain C-peptide
- opportunity to set specifically, management

Effects on carbohydrate metabolism

- Decrease blood sugar levels
- Stimulate the uptake of glucose in cells where insulin dependent facilitative glucose transporter (GLUT-4) is located - fat, skeletal muscle
- GLUT-4 translocation from endosomes to the plasmamembrane
- It promotes the further development of glucose :
  - glycogen synthesis
  - -inhibiting gluconeogenesis
  - -stimulation of glycolysis
  - fatty acid and triglycerol synthesis

On potassium metabolism

- It stimulates the uptake of K + into cells
- Insulin administration may cause hypokalaemia

On geneexpression

- Through complex cascades effect the cell transcription.
- Best known genes it regulates glucagon: decrease expression of the proglucagon gene.
- Insulin like proteins are known, but their effect is mainly on growth.
- IGF1 and IGF2 (IGF1 in szomatomedinC) - produced by the liver, but from a lot of tissue can be detected.

On amino acid-protein metabolism

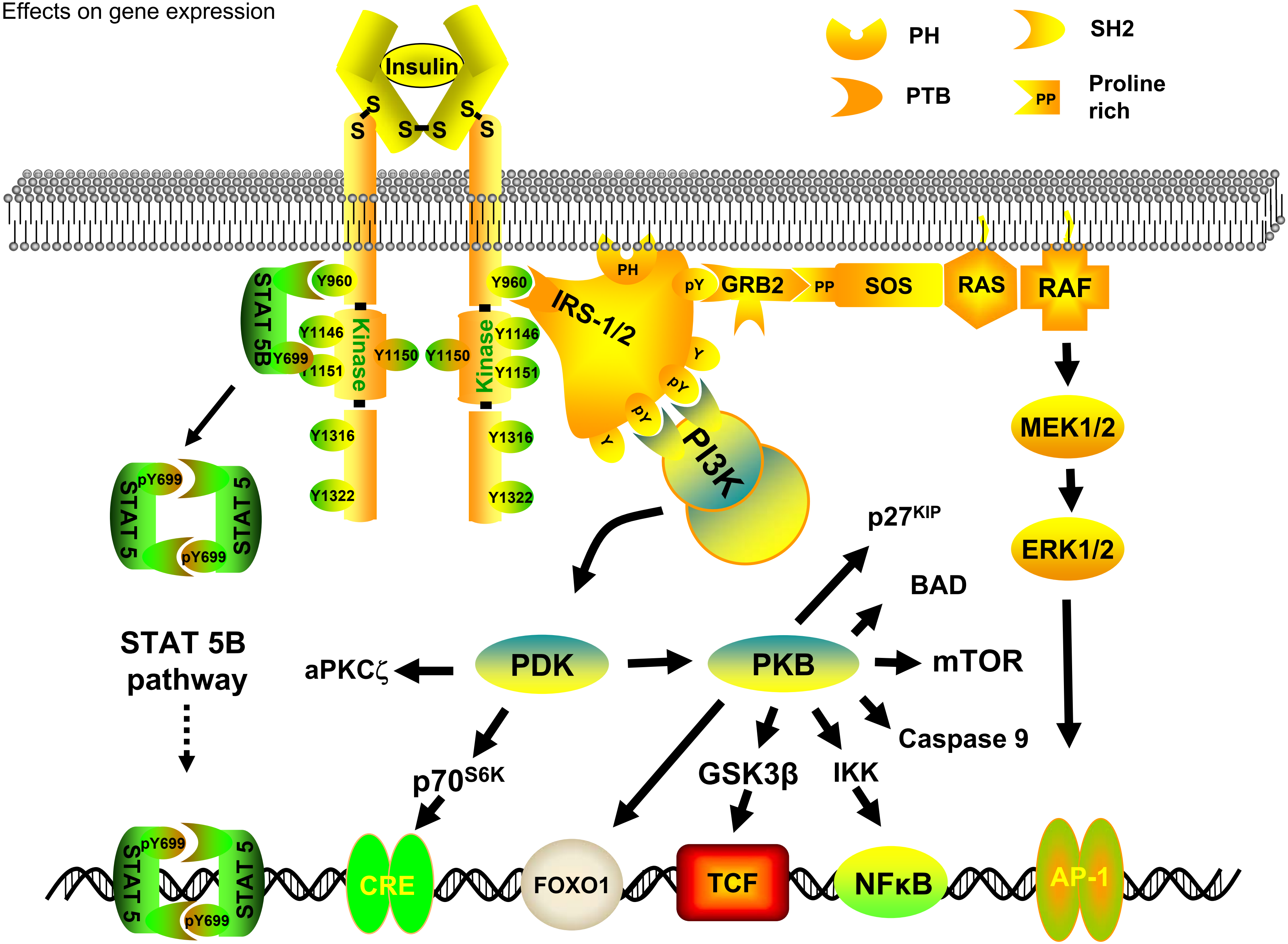
- It stimulates the incorporation of amino acids into proteins
- This reduces gluconeogenesis substrates and thereby inhibits

On lipid mezabolism

- Stimulates triglyceride synthesis
- inhibits lipolysis
- antiketogenic

Insulin Receptor Signaling

Effects on gene expression



Diabetes mellitus

- Conditions associated with polyuria
- polyuria also occurs in the absence of ADH diabetes insipidus
- There are two types:
  - Type I.: juvenile, insulin-dependent DM (IDDM)
  - Type II.: adult, non-insulin-dependent DM (NIDDM)
- Also occur temporarily in connection with pregnancy

- IDDM: -start at the age of -6-10

  of the pancreas release insulin production or inhibited

  - to keeping them alive immediate administration of insulin required (can not given orally because digested in the GI tract)
- NIDDM: -In age of 50 and obese people insulin sensitivity reduced of the target cells (high levels of insulin receptor cause downregul)

  -Also, it is necessary lifestyle changes:

  -Reducing carbohydrate intake + exercise

Pathomechanism

- Hyperglycaemia: high blood sugar, but the cells are starving because of the absence of insulin can not absorb the glucose
- protein catabolism start → the formation of amino acids utilized by gluconeogenesis → glucose levels continue to increase (circulus vitiosus)
- Enhanced lipolysis → ketone bodies are formed → metabolic acidosis → Cusmaul breathing
- increased tubular glucose load →glucose appears in the urine →osmotic diuresis

Hypoglycemic Vs. hyperglycemic coma

Hypoglycemic	Hyperglycemic
• In case of excessive insulin administration or normal insulin administration with increased muscle work or fever • Cool moist skin, no acetone breath, pale, abnormal reflexes • Occurs acutely and after a few minutes, permanent damage occur	• Develops in the absence of insulin • Hot, dry flushed skin • acetone breath

should be considered BOTH as Hypoglycaemia! SUGAR TRANSMISSION

Consequences of hyperglycaemia

- Non-enzymatic glycosylation of proteins
- Part of normal aging processes
- AGE = advanced glicosilation end products
- Angiopathy, nephropathy retinopathy
- Collagen glycosylation - thrombogénebb
- Angiopathy pronounced in the lower limb - amputations
- Susceptibility to infection
- Used for diagnostic purposes in HbA1c

•Extent of glycosylation can be examined

•60 days back to the status of your blood sugar

Biochemistry of Steroid Hormones

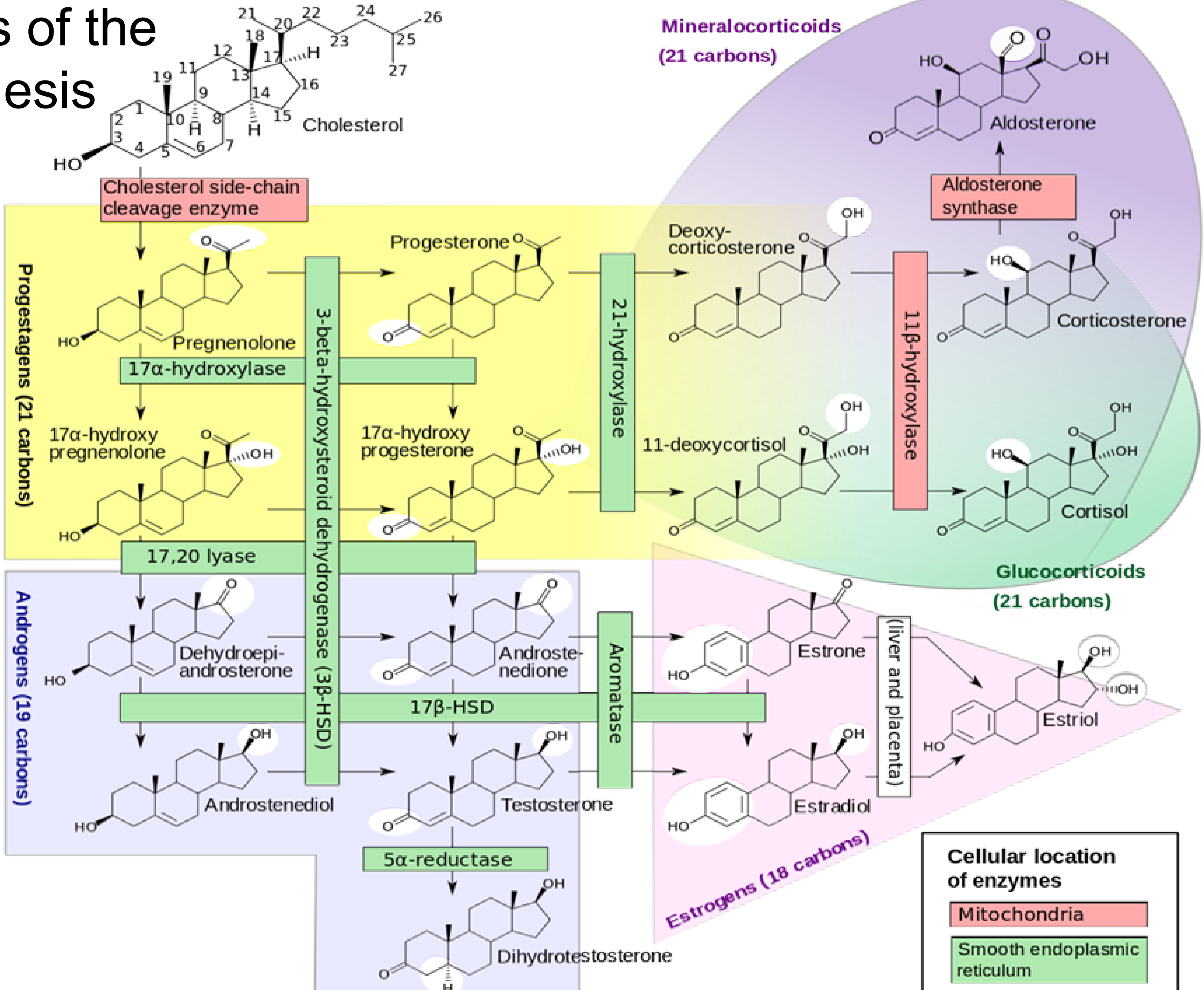
Origins:

- All steroid hormones from cholesterol develops
- Common compound: cyclopentanoperhidrophenantrene (sterane structure)
- Difference: the number of substitutions, the number, position and configuration of double bonds,
- C18 and C19 methyl groups:
  - Before → same ring plane orientation β-position
  - Behind the plane of the ring → α-position
- Δ denotes number of double bonds
- Glucocorticoids contain 21 C-atoms, androgens19, gestagens 18

Synthesis in the adrenal cortex

- Mineralocorticosteroids - zona glomerulosa
- Glucocorticoids and androgens (dehydroepiandrosterone) - zona fasciculata and reticularis

Steps of the synthesis



Steps of the Synthesis :

- In cells of Zona fasciculata 17α-hydroxylase causes the synthesis direction of glucocorticoids
- in Both directions of the synthesis 21-hydroxylase and 11β-hydroxylase are involved - Cortisol
- Zona glomerulosaban lack this enzyme – production of mineralocorticosteroids
- In zona glomerulosa multifunctional 11β-hydroxylase (18 hidroxilase and oxidase activity, too!) - The final step in aldosterone synthesis
- DHEA is produced in small quantities

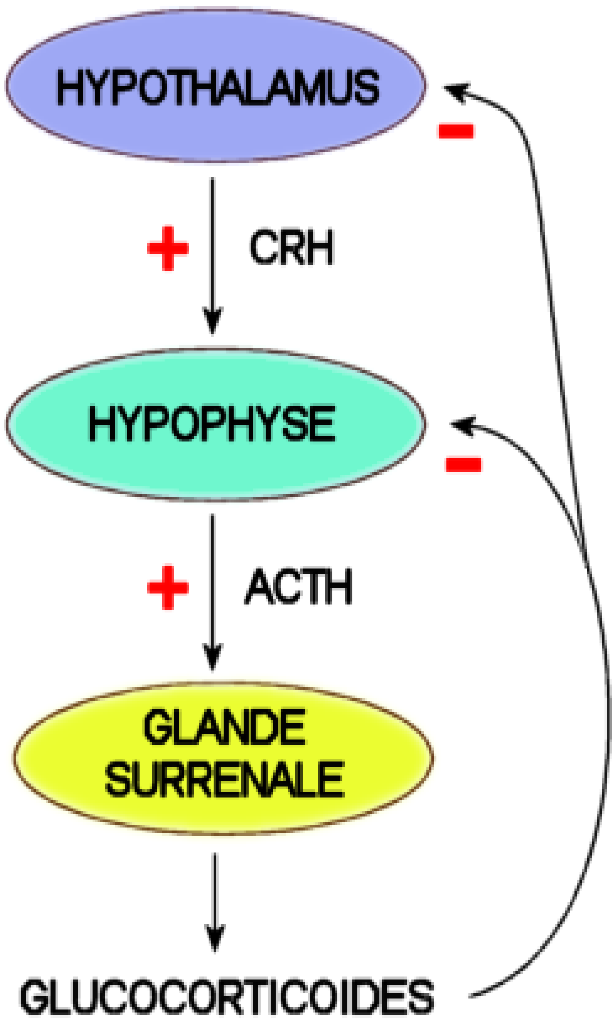
Enzyme deficiency:

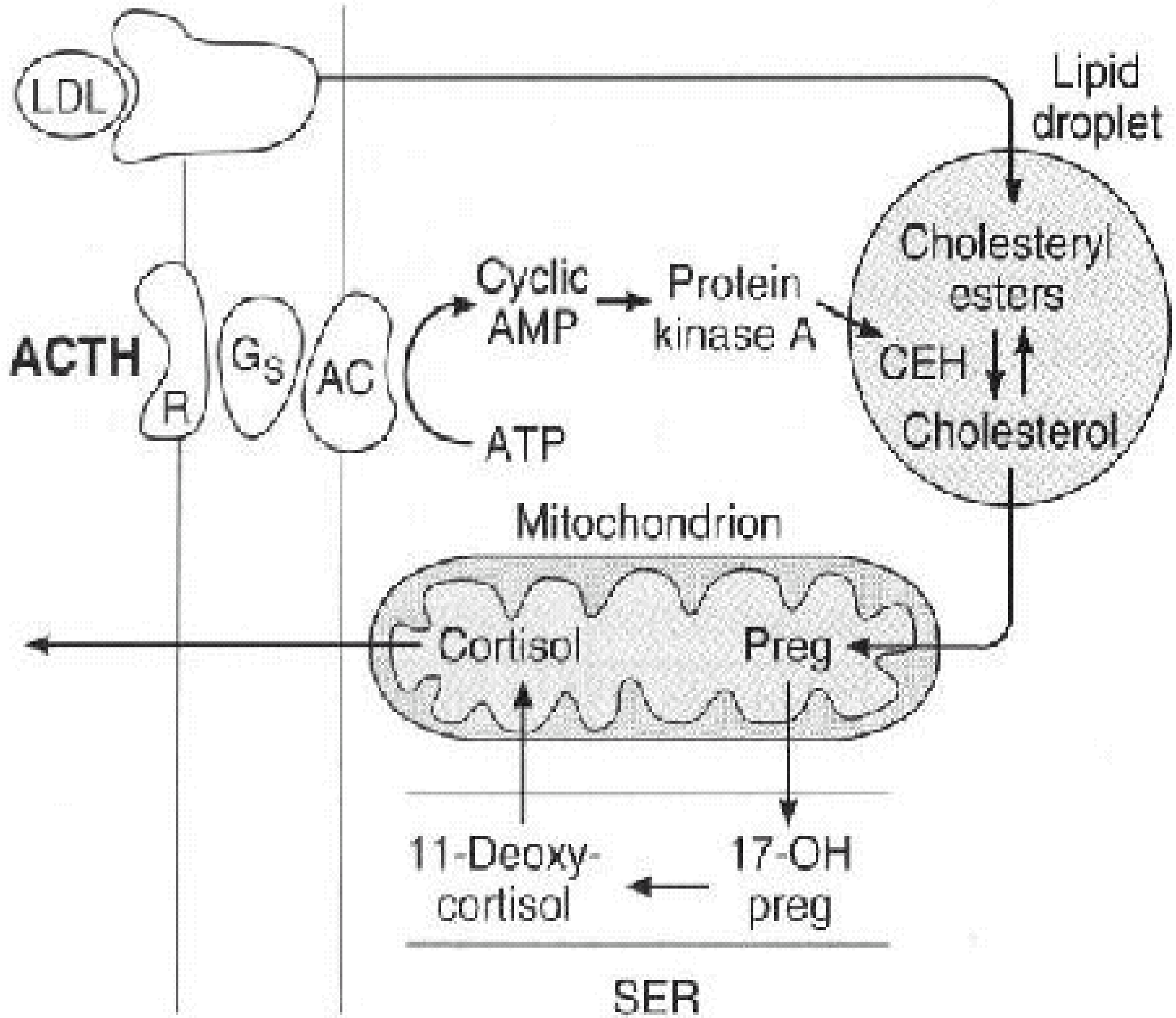
21 hydroxylase deficiency:

- Insufficient cortisol synthesis - insufficient cortisol - Feedback - ACTH overproduction - congenital adrenal hyperplasia
- Due to insufficient enzyme decreased cortisol and aldosterone level
- Due to increased ACTH increased cholesterol - pregnenolone conversion - no other way - towards androgens turn on - early sexual maturation, in women masculine nature
- Adrenogenital syndrome: virilismus, hirsutism, alopecia, small breasts, etc., due to the lack of aldosterone significant salt loss.

The control of synthesis :

- Glucocorticoids - adrenocorticotropic hormone (ACTH)

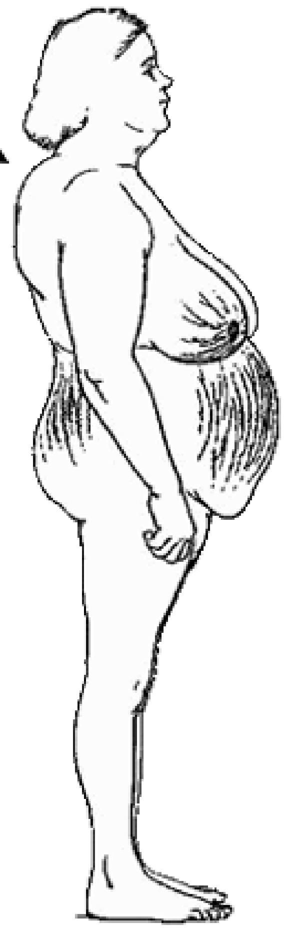




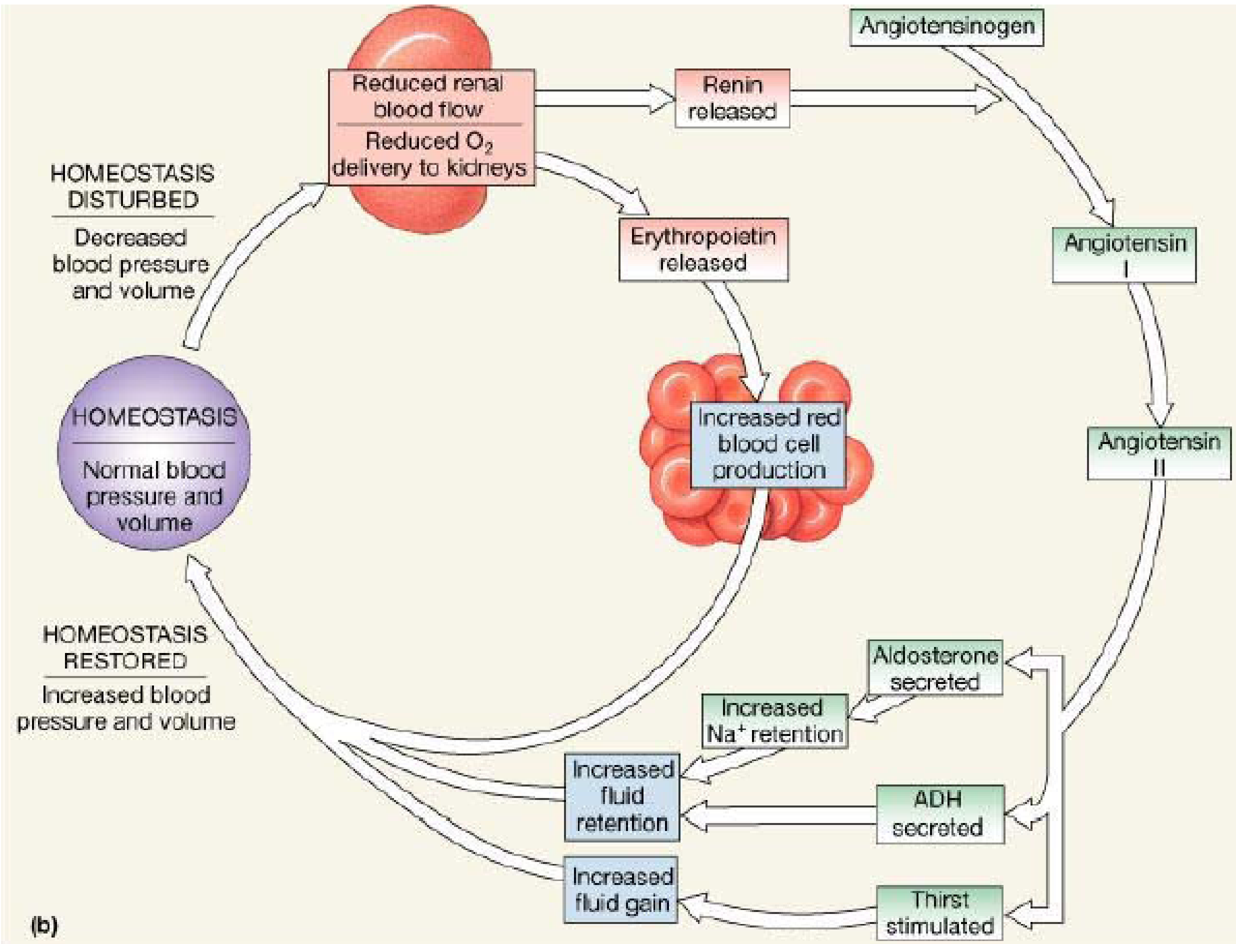
Cushing disease:

- Ectopic ACTH production is the most common reason (adrenal and pituitary can too)
- Example. paraneoplasic syndrome - small cell lung cancer

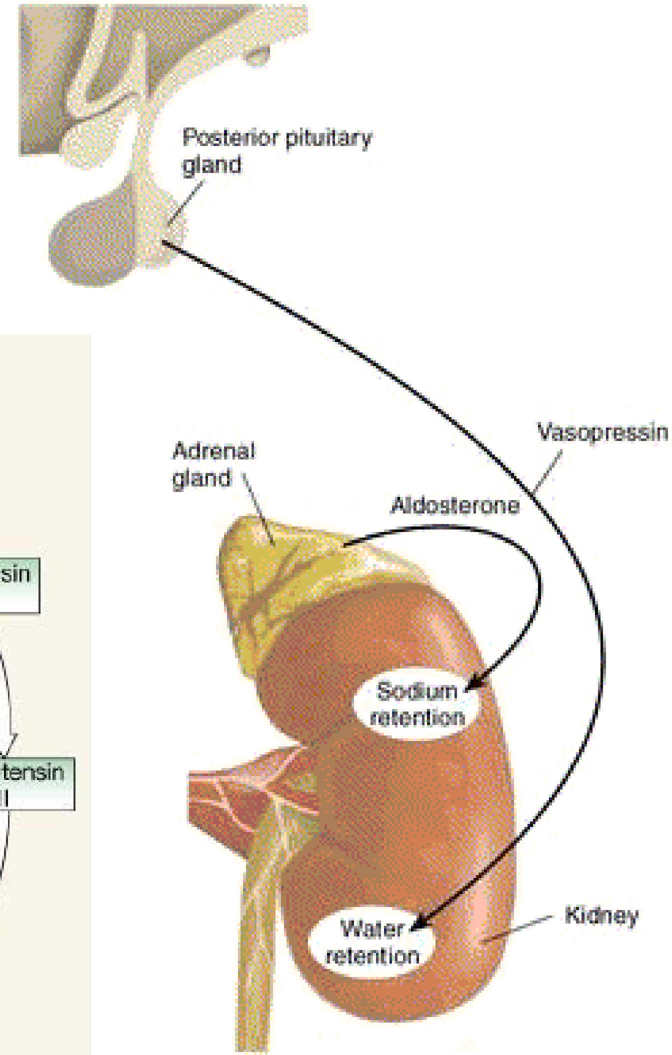
- Upper body obesity with thin arms and legs
- Buffalo Hump
- Red, Round Face
- High Blood Sugar
- High Blood Pressure
- Vertigo
- Blurry Vision
- Acne
- Female Balding
- Water Retention
- Menstrual Irregularities
- Thin Skin and Bruising
- Purple Striae
- Poor Wound Healing
- Hirsutism
- Severe Depression
- Cognitive Difficulties
- Emotional Instability
- Sleep Disorders
- Fatigue



Normal renal function

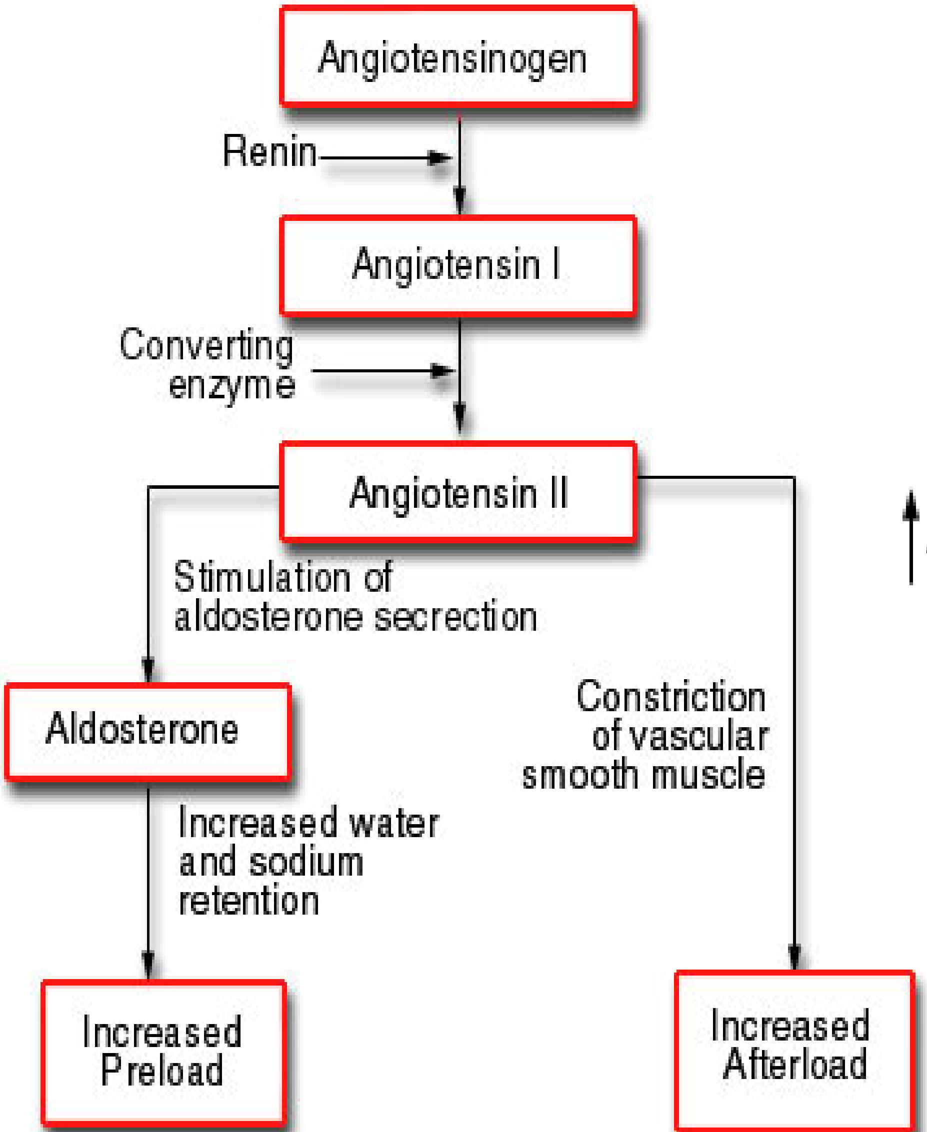


Hormonal Control of the Kidney



The regulation of the synthesis:

- Mineralocorticosteroids - Angiotensin II. (RATA



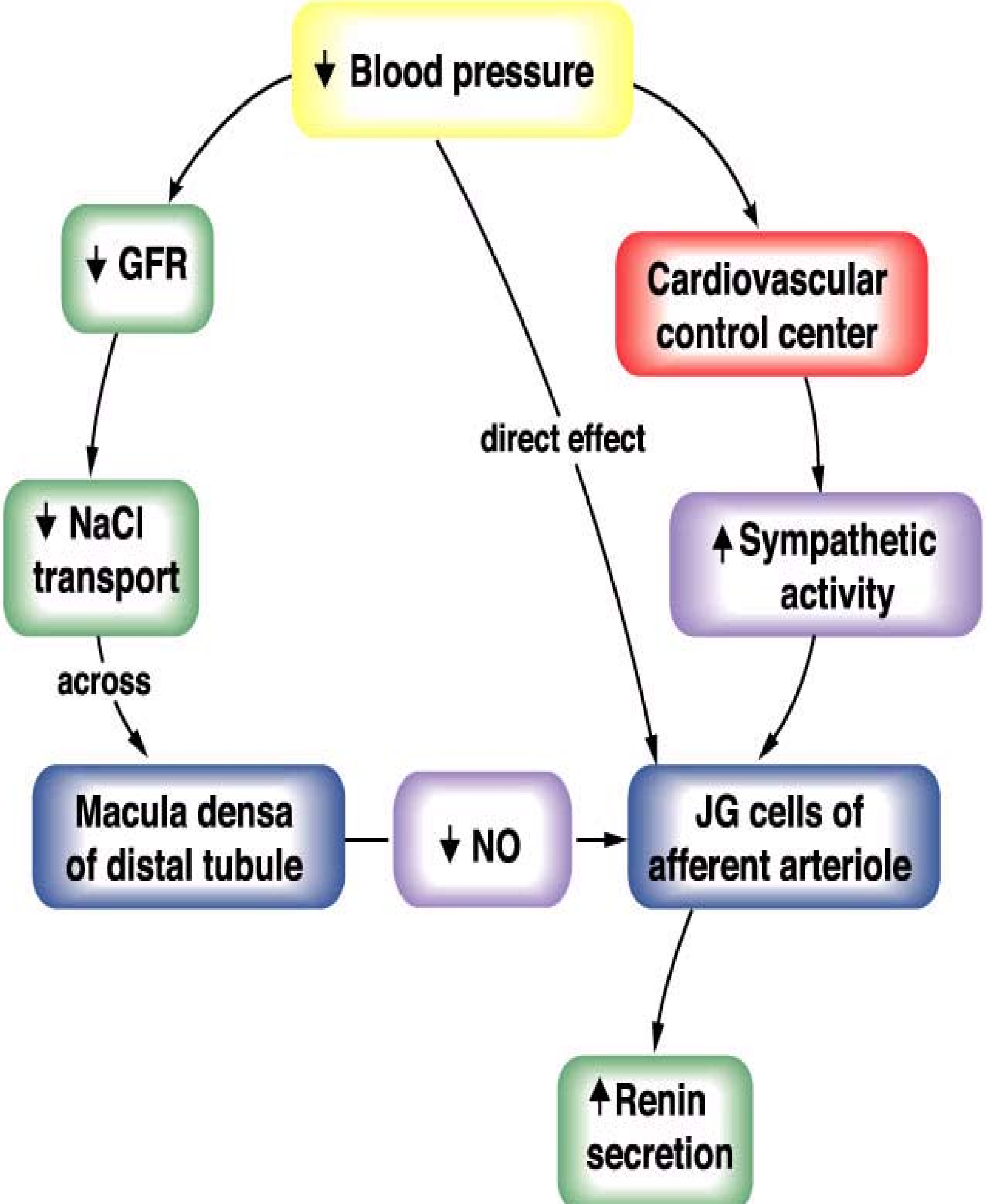
Role of cardiac decompensation :

↓ Cardiac Output

↑ Afterload

Vasoconstriction

↑ Systemic vascular resistance



In hypertension possible to lower blood pressure:

1 ACE inhibition (problem: bradykinin decomposition is inhibited)

2 Angiotenzin II. receptor blocking

Synthesis in genitals - Sex hormones

1. **Testosterone:**

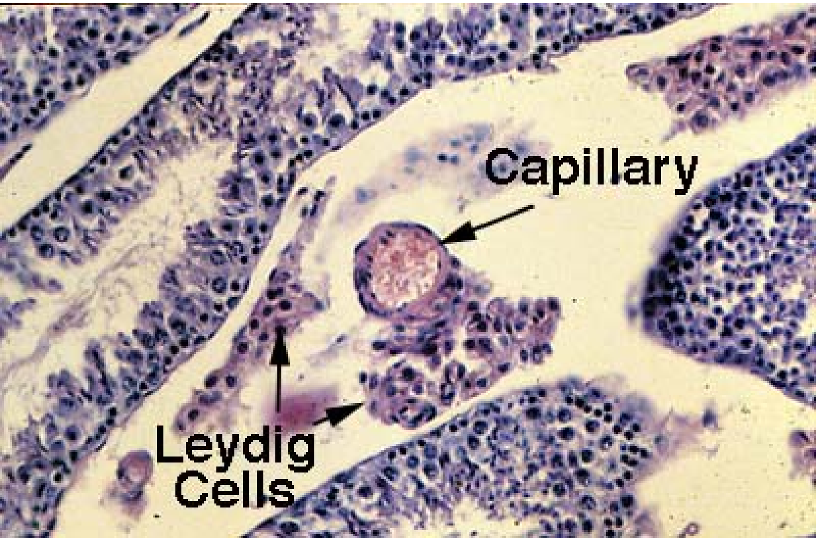
Testicular Leydig cells is synthesized from cholesterolin by two routes:

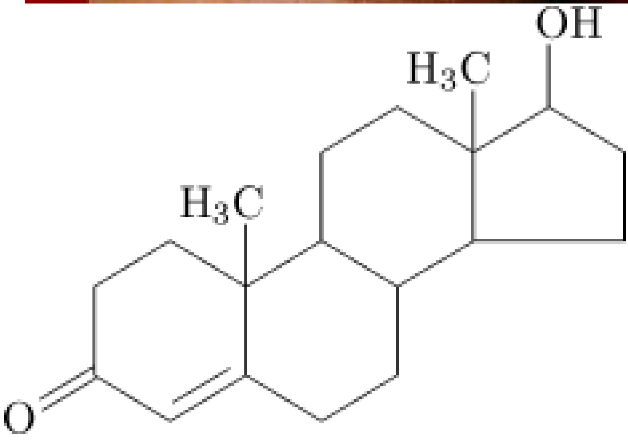
Cholesterol - pregnenolone - Progesterone - Testosterone

Pregnenolone - Dehydroepiandrosterone - androstenedione - testosterone

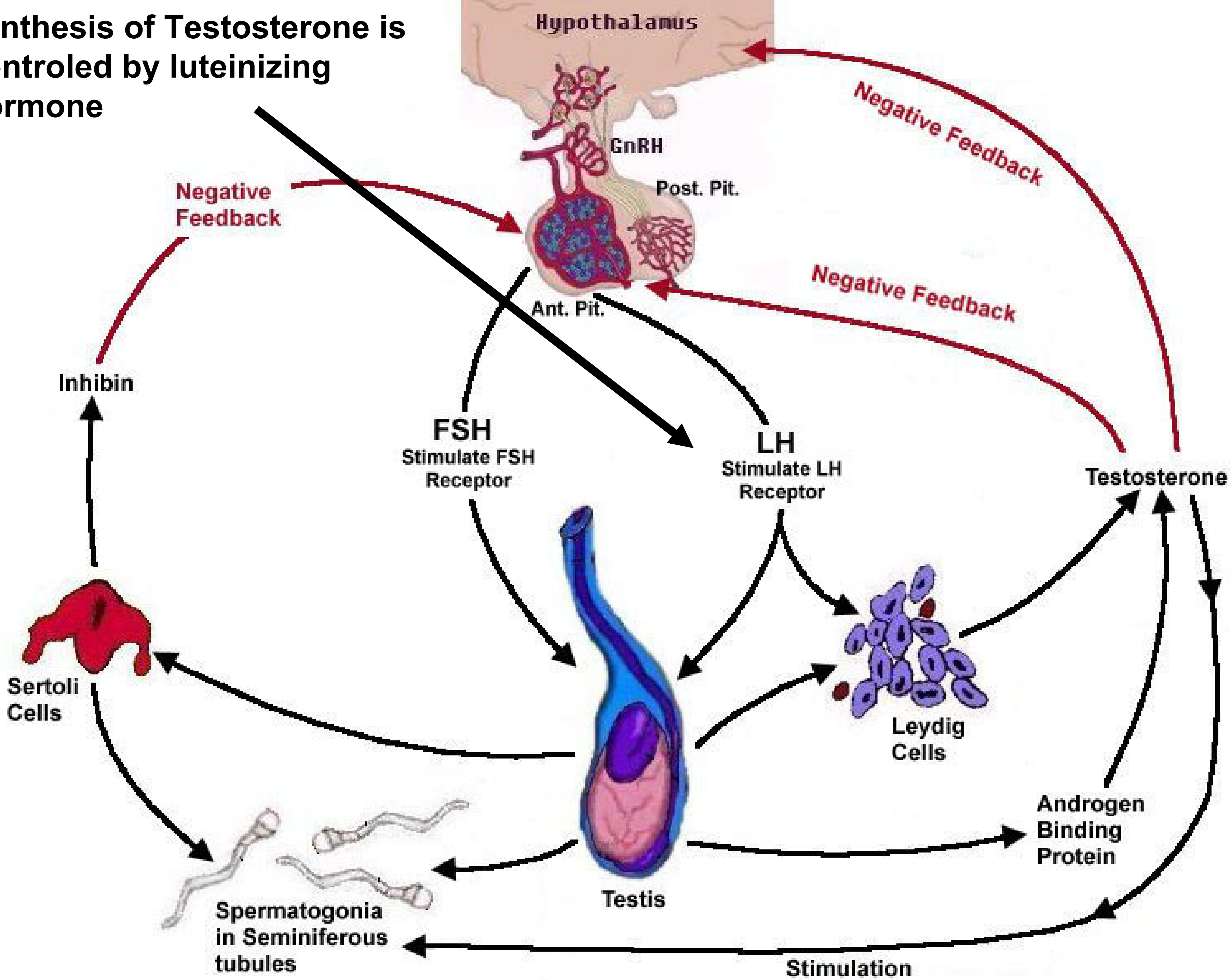
Testosteron in target cells (seminal vesicle, prostate, external genitalia) is formed to 5α-dihydrotestosterone, it is the active metabolite of testosterone

In some cell 17β-estradiol can be generated





synthesis of Testosterone is controled by luteinizing hormone

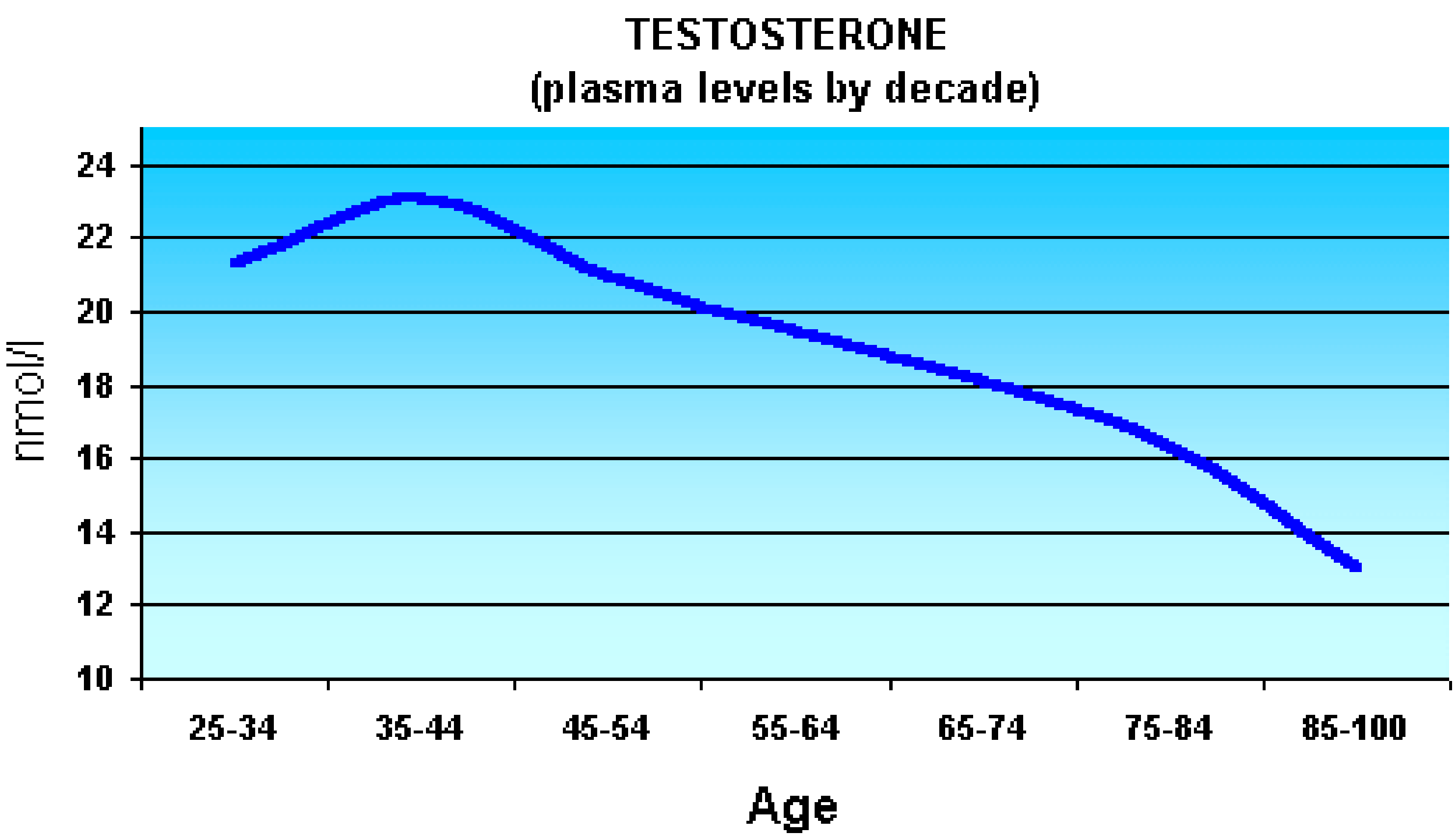


In circulation transported by albumin and sex hormone-binding globulin.

97-99% of the total amount of protein are bounden, and the remaining free fraction is the biologically active hormone.

Degradation and inactivation are in the liver, the oxidation of17 C atoms are formed 17-ketosteroids.

Receptors are located intracellularly, affect spermatogenesis, sexual maturation, the development of secondary sexual characteristics, sexual behavior and anabolic effects.

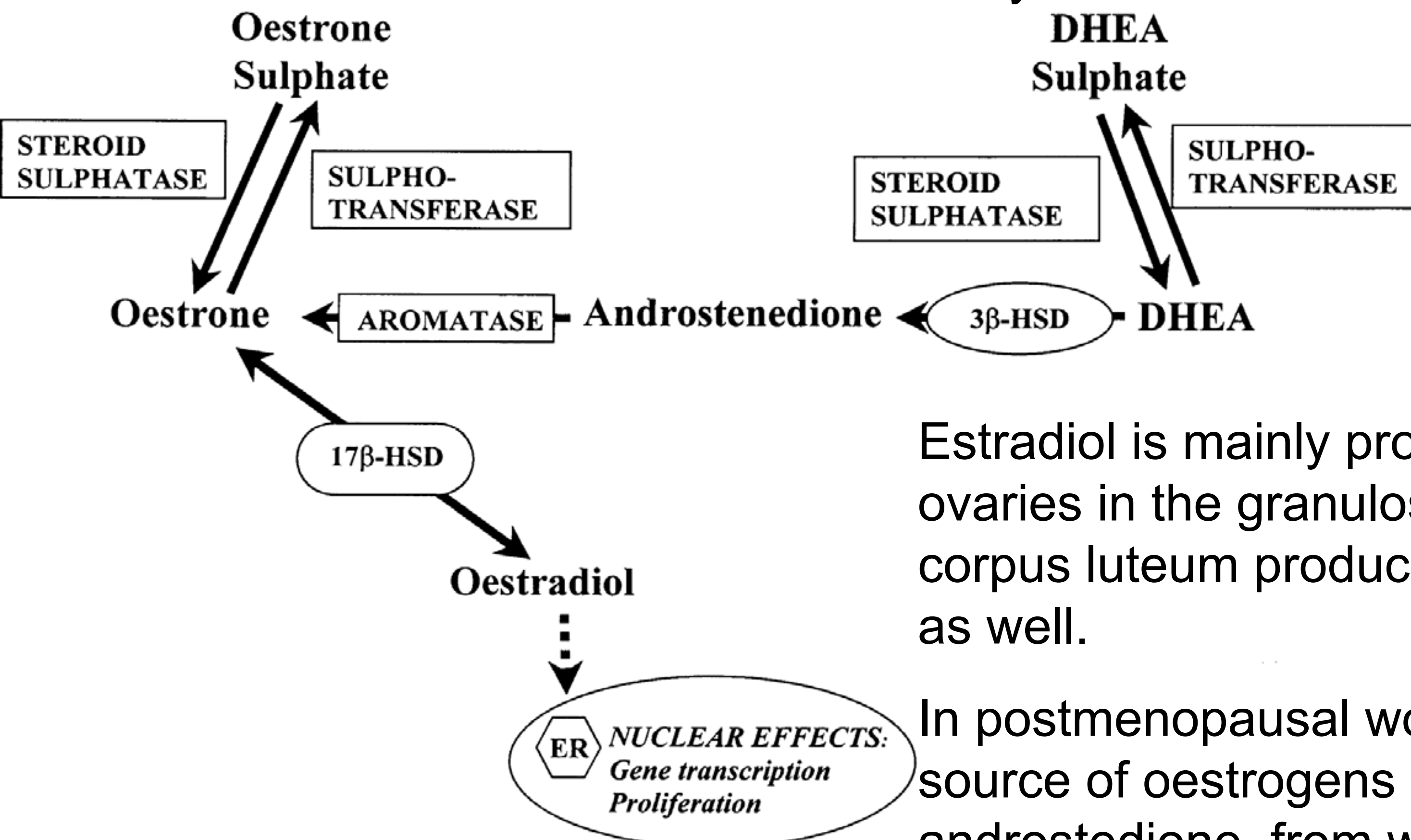


2. Female sex hormones:

The main female sex hormone 17β-estradiol are generated in the ovaries.

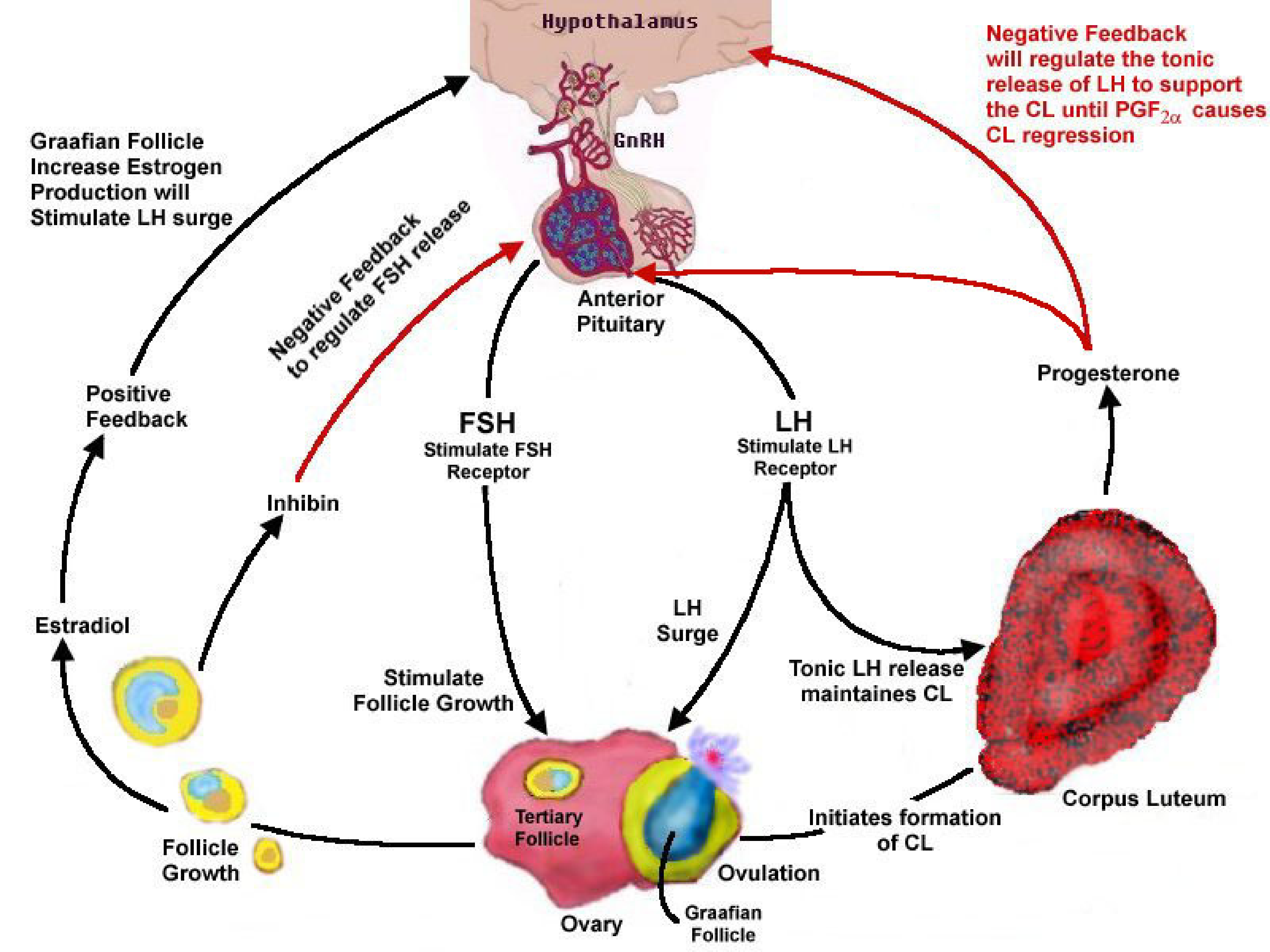
Other estrogens are formed in other organs (placenta, skin, adipose tissue, liver)

The initial steps of the synthesis from cholesterol are similar with the adrenal steroid synthesis..



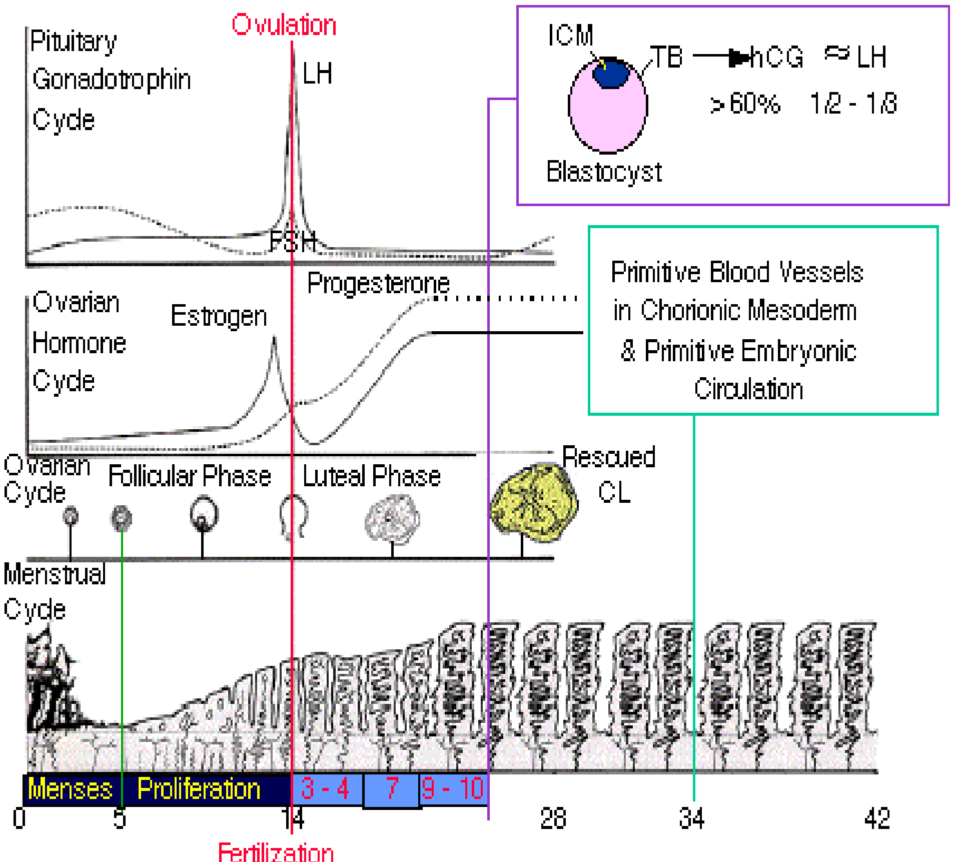
Estradiol is mainly produced in the ovaries in the granulosa cells, the corpus luteum produce lesser amount as well.

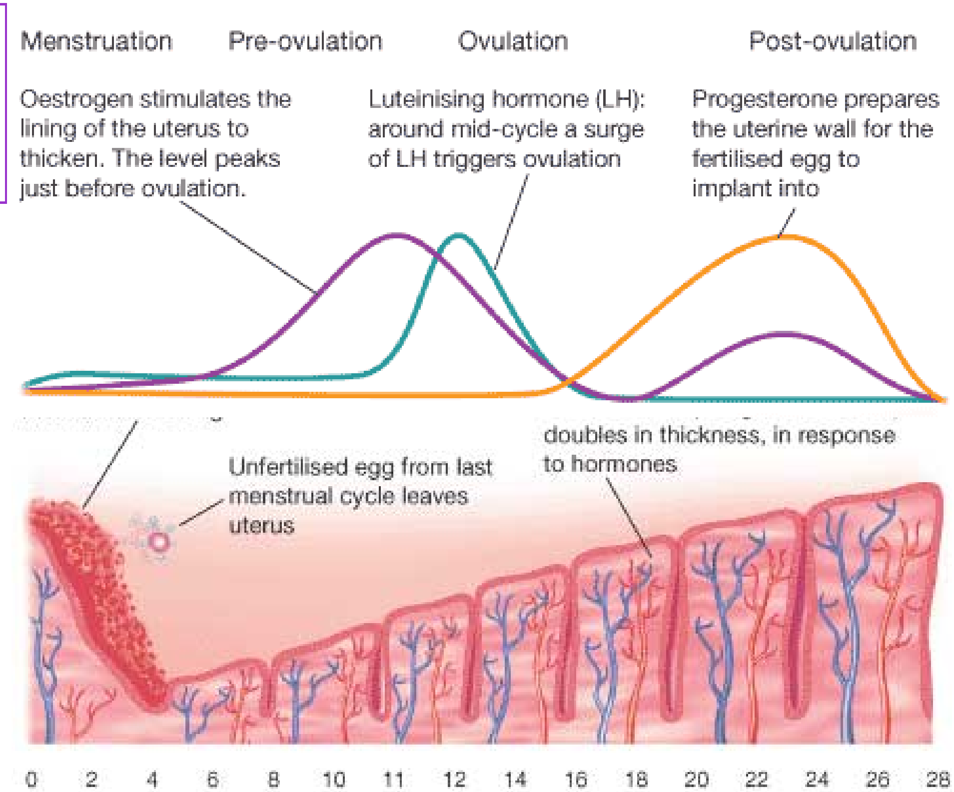
In postmenopausal women major source of oestrogens is adrenal androstedione, from what estrone created by aromatase.



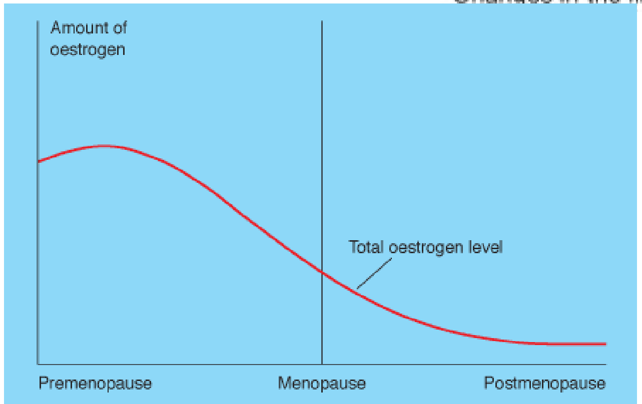
Hypothalamus
Negative Feedback will regulate the tonic release of LH to support the CL until $PGF_{2\alpha}$ causes CL regression
GnRH
Graafian Follicle Increase Estrogen Production will Stimulate LH surge
Negative Feedback to regulate FSH release
Anterior Pituitary
Progesterone
Positive Feedback
FSH
Stimulate FSH Receptor
LH
Stimulate LH Receptor
Inhibin
LH Surge
Estradiol
Stimulate Follicle Growth
Tonic LH release maintaines CL
Corpus Luteum
Tertiary Follicle
Initiates formation of CL
Follicle Growth
Ovulation
Ovary
Graafian Follicle

Menstrual cycle





Changes in the lining of the uterus during the menstrual cycle



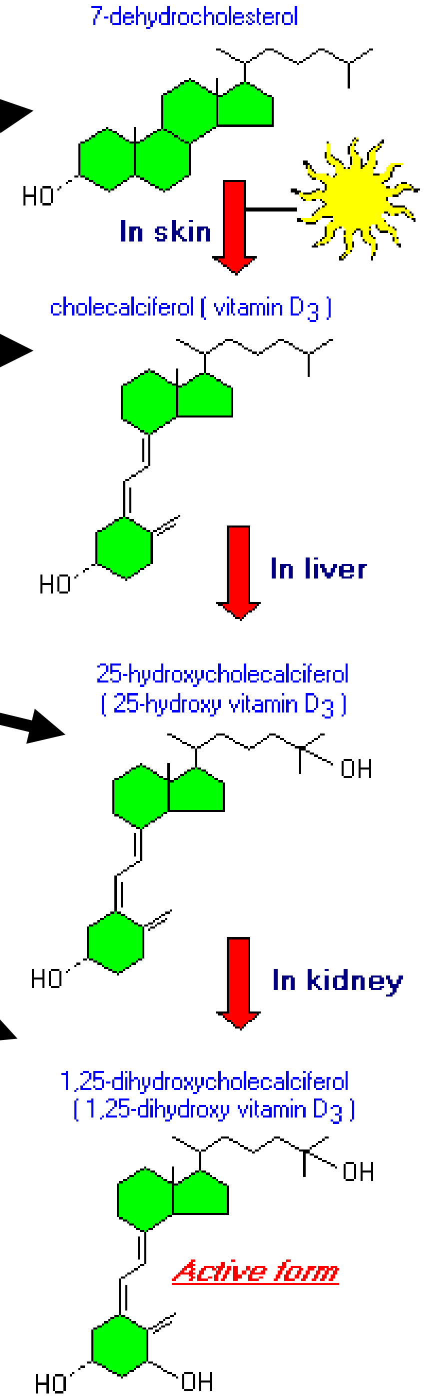
Synthesis of vitamin D3

From cholesterol, the direct precursor is 7 dehidrocholesterol.

In the skin due to the UV component of solar radiation cholecalciferol is formed , which is not biological active. (10-15 minutes a day of direct sunlight should reach the skin)

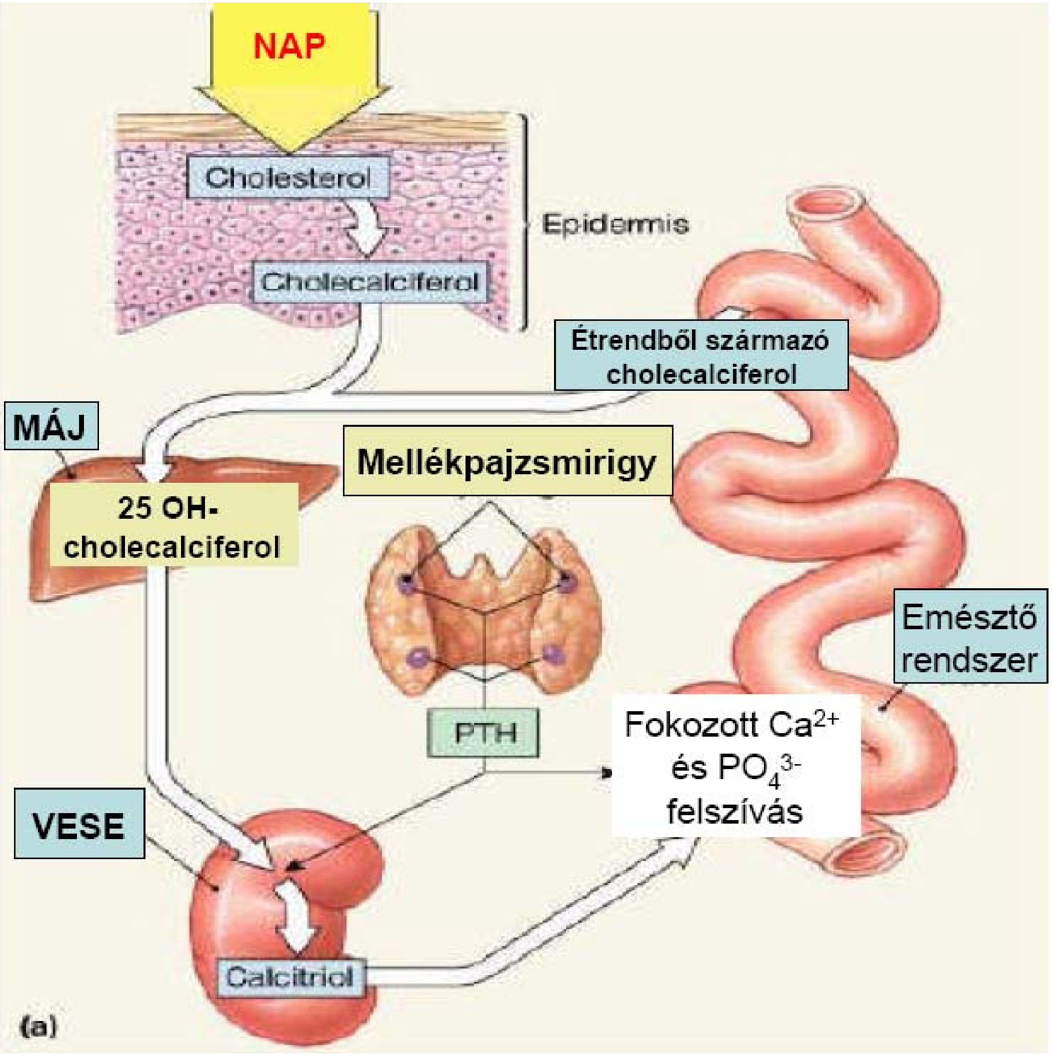
In the liver the formation of 25-hydroxy-cholecalciferol

In the renal proximal tubules develop the effective metabolite, 1,25-dihydroxy-cholecalciferol, PTH regulates the synthesis



Effects of Vitamin D3

- Increases intestinal epithelial absorption of Ca2 +
- In Bone the Ca 2 + release and deposition is in equilibrium
- enhances the renal tubules Ca2 + reabsorption



Intracellular mechanism of steroid hormones - nuclear receptors

- Transcriptional regulation - by way of cis-acting DNA sequences (promoter, enhancer, silencer) or trans-acting regulatory proteins
- transcription factors in the nucleus, are binding to the regulated genes encoding proteins specific parts of DNA, and accelerate or slow down the RNA synthesis.
- Their effects can affect several things:
  - Adherent proteins
  - Post-translational modifications (phosphorilation-dephosphorilation)
  - Binding of ligands
- Those transcription factors that are regulate low molecular weight, easily nucleusaccessing, lipophilic molecules, called nuclear receptors.

Properties

•Steroids, thyroids, retinoids and vitamin D have effect in the nucleus, regulated the transcription.

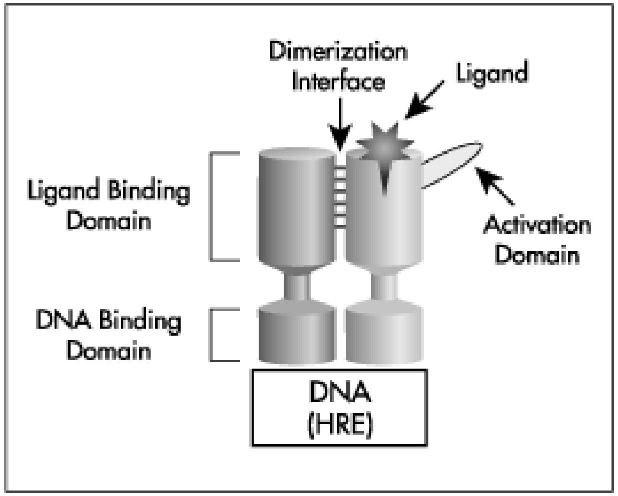
•Nuclear receptors are similar in structure, each have DNA-binding domain →can bind to hormone respondents element (HRE)

•The DNA-binding domain characterized by two highly conserved zinc finger-containing (one of the binding, the second corresponds dimerisation).

•Inverted repeat (palindrome)

•Or directly repeated sequences

•In C-terminal located the ligand binding domain, which is responsible for recognition of specific hormones, provides the specificity and selectivity.



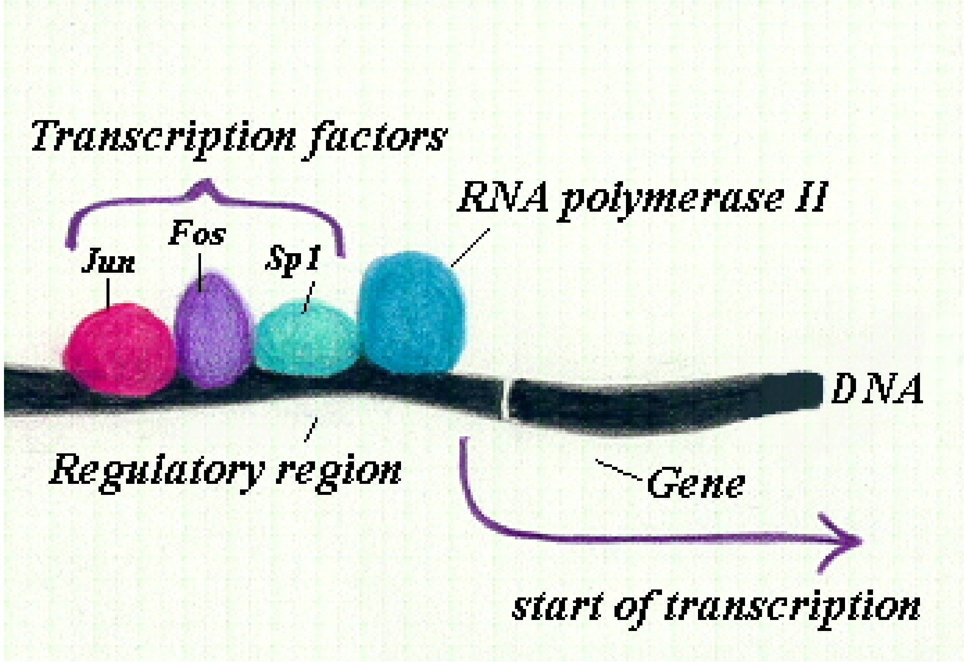
Explanation of the molecular mechanism of cortisol

To our knowledge achieved in two ways:

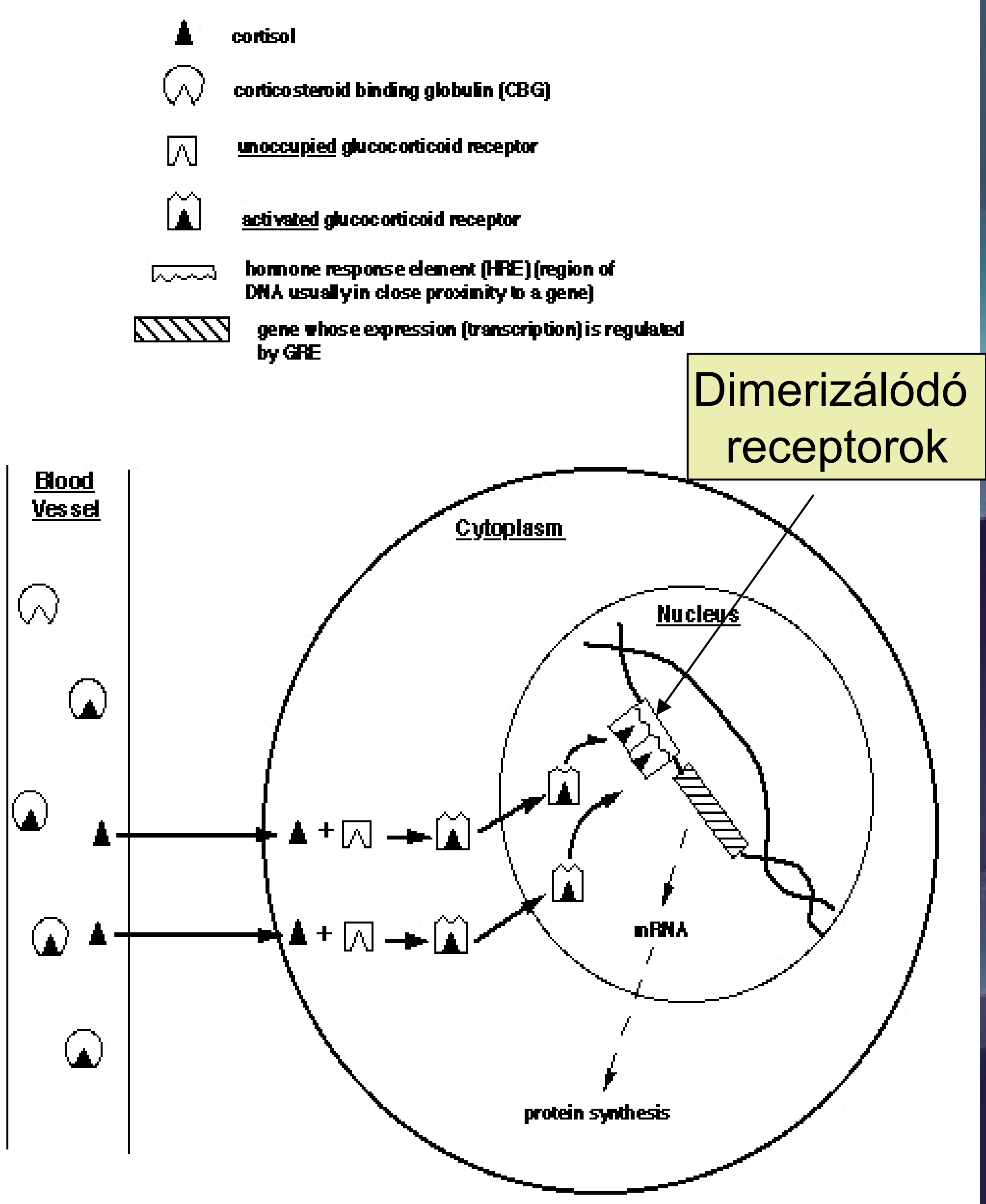
1. Direct transcriptional effect

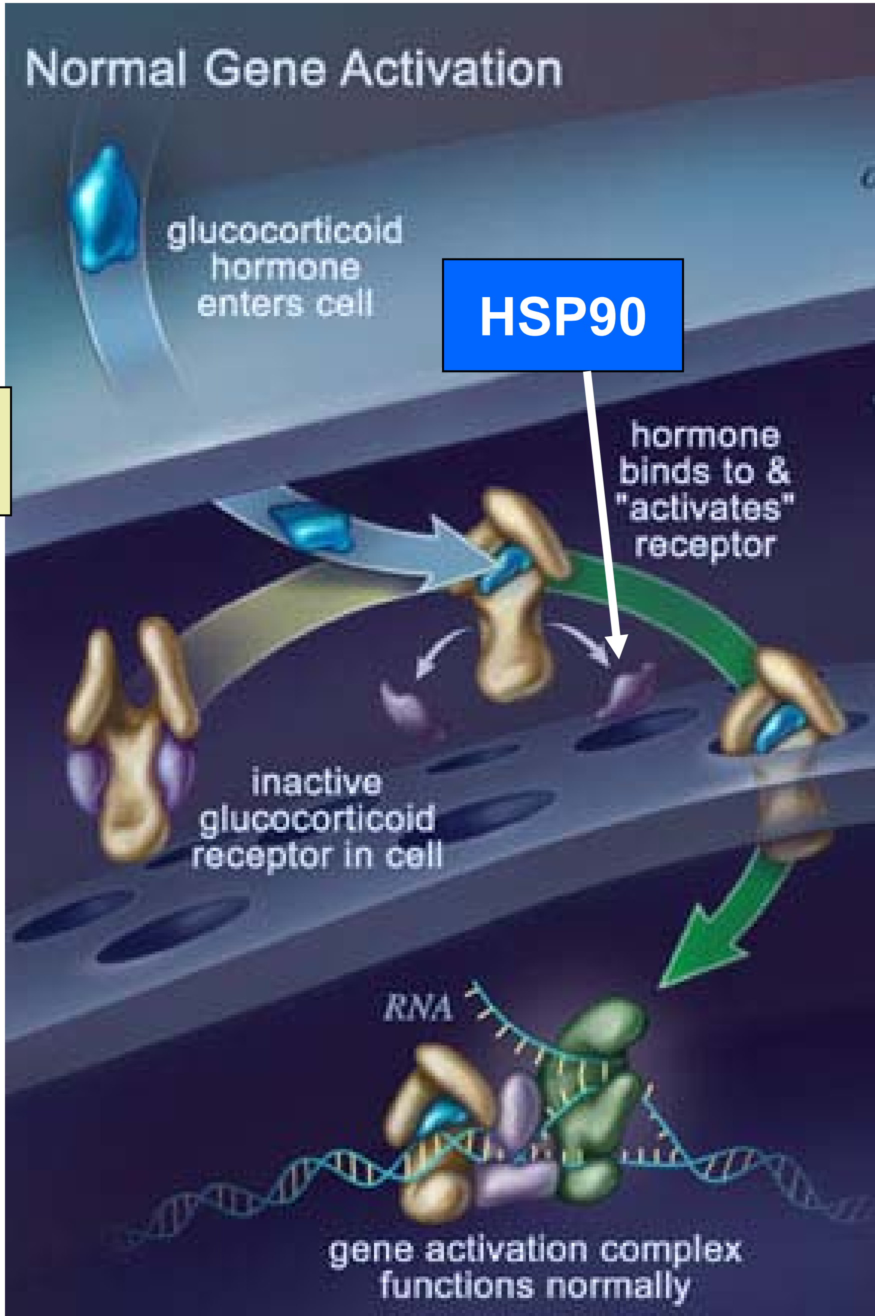
2. Transcriptional interference :

It means that after binding of the ligand the receptor in active conformation state affects the activity of other transcription factors. The diverse effects of cortisol are well explained, because they do not require some of receptor-DNA binding, these are primarily inhibitory processes.



Direct transcriptional effect ofCortisol





The receptor families

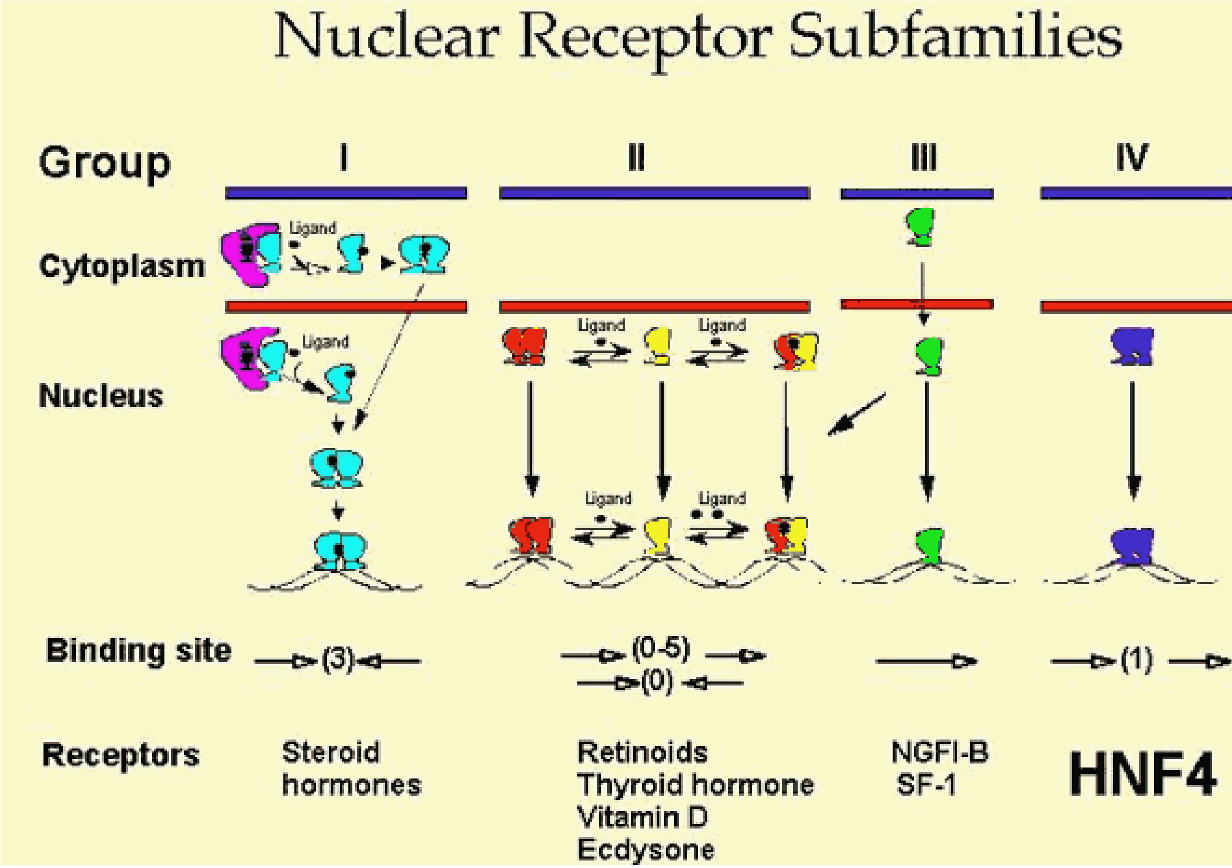
More than 150 kinds of nuclear receptor are known, among which there are also the ligand itself is not yet known. This subgroup is called "orphan" nuclear receptors.

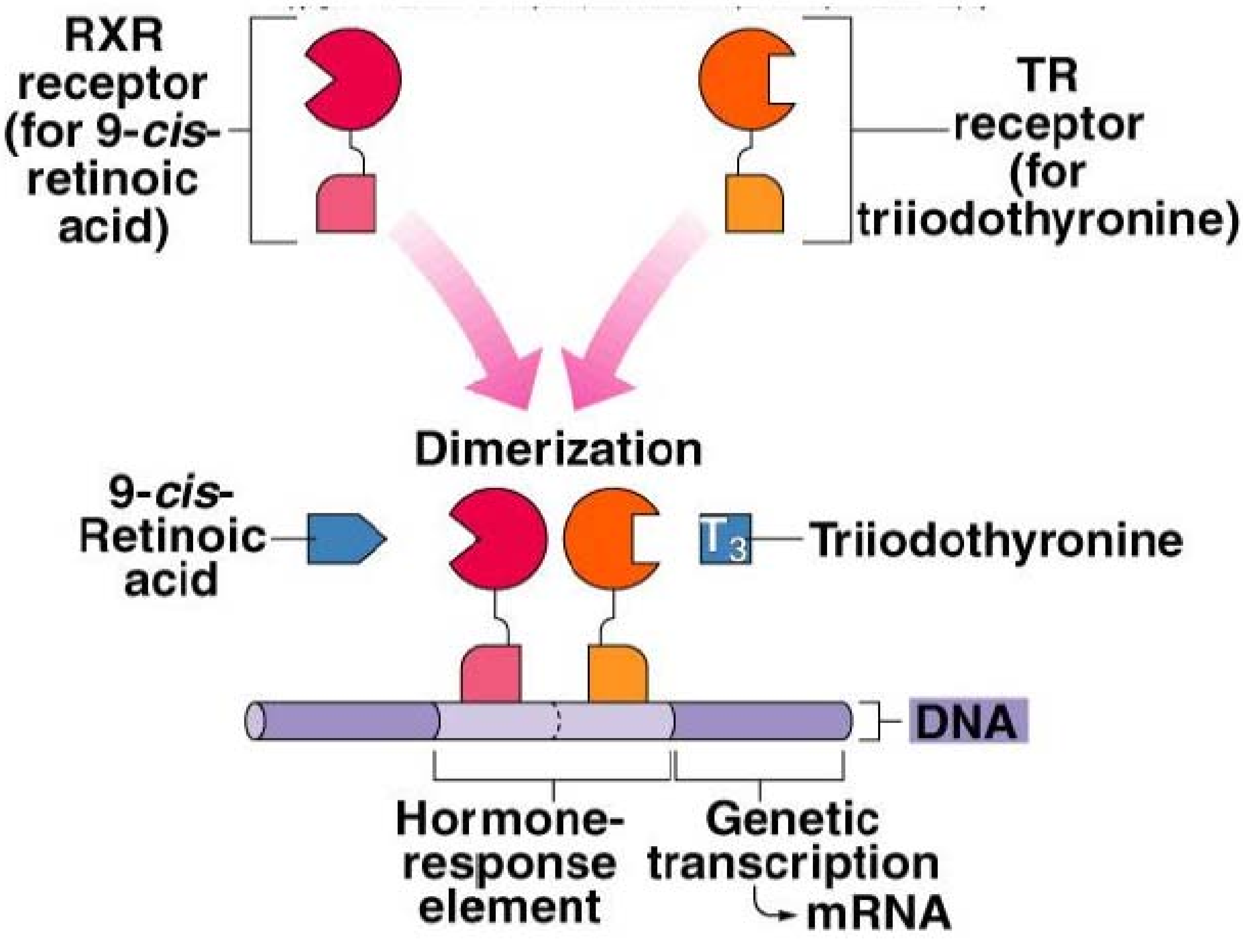
I. group: steroid receptors

II. group: Normally in the nucleus, and without ligand they have inhibitory activity, heterodimerization with 9-cis retinoic acid receptor (RXR)

III. group: monomer orphan receptors

IV. csoport: orphan homodimer receptors





RXR receptor (for 9-*cis*-retinoic acid)
TR receptor (for triiodothyronine)
Dimerization
9-*cis*-Retinoic acid
T_3
Triiodothyronine
DNA
Hormone-response element
Genetic transcription
mRNA

Inactivation of steroid hormones

Mainly in the liver

Eg. progesterone metabolism is fast process, the ring is cleaved, the 3 - and 20-keto group is reduced and conjugated with glucuronic acid

! For Oral contraception are used progesterons which are less metabolized by the liver

Estrogen is conjugated with glucuronic acid and sulfate and excreted into the bile.