# Hormonal drugs

**GLUCOCORTICOIDS**

**MINERALOCORTICOIDS**

**SEX HORMONES**

**ANABOLIC STEROIDS**

**Hormones** are biologically active substances, produced by the endocrine glands. They regulate various functions of the body.

Hypofunction or hyperfunction leads to the development of diseases. Failure of pancreatic gland leads to the development of diabetes mellitus, parathyroid glands failure causes hypocalcaemia and convulsions. Insufficiency of the antidiuretic hormone of the posterior pituitary lobe leads to diabetes insipidus. Hyperfunction of the thyroid gland causes hyperthyroidism or Basedow’ disease, hyperproduction of the somatotropic hormone leads to acromegaly.

# Types of hormonal therapy

**Specific:**

A. Replacement therapy for the treatment of the failure of endocrine gland. (Insuline for the treatment of diabetes mellitus)

B. Stimulating therapy (adrenocorticotropic hormone stimulates glucocorticoid production)

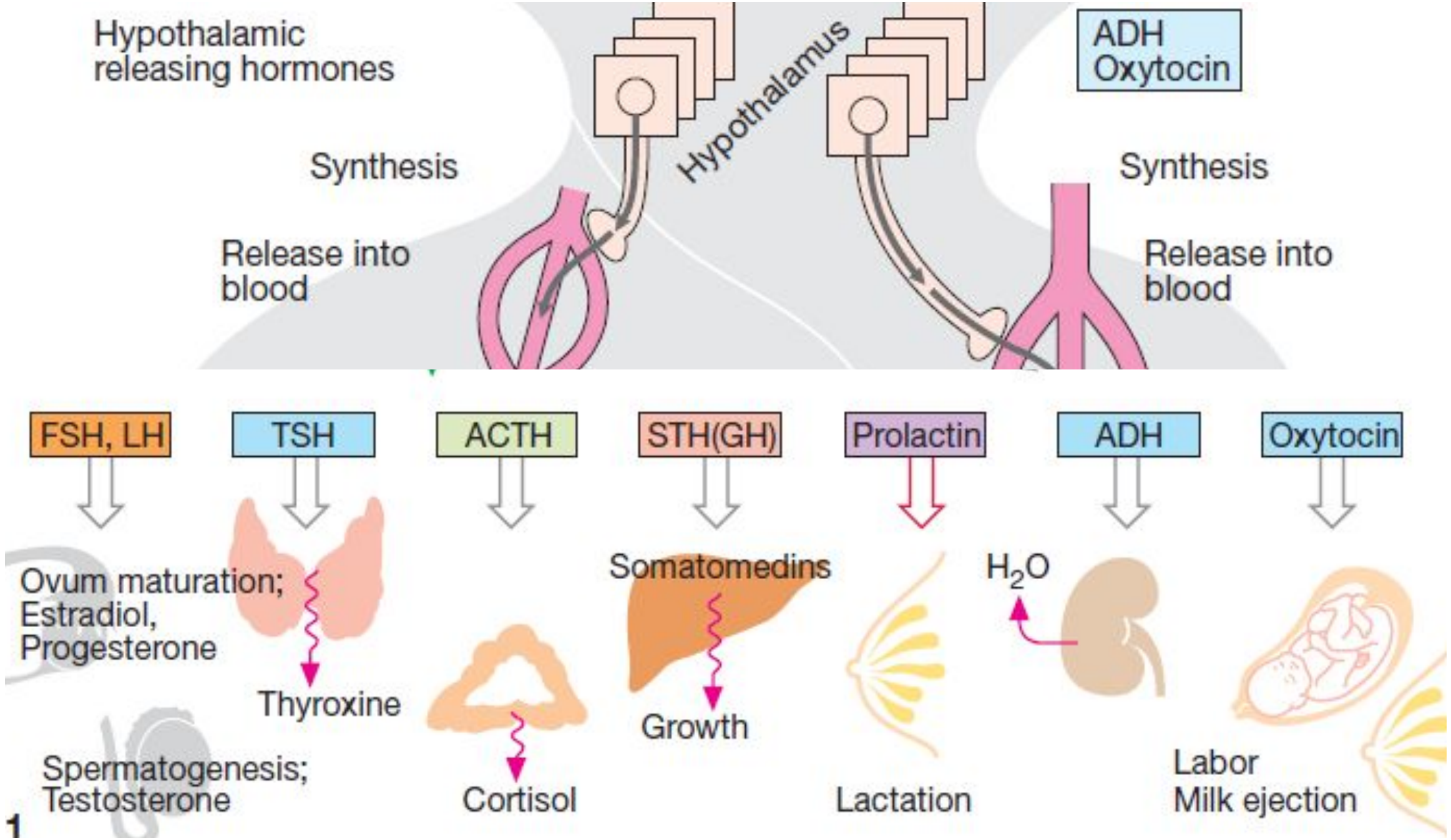
C. Inhibitory or suppressive (oral contraceptives inhibit the production of gonadotropic hormones of the pituitary gland)

**Non-specific:** glucocorticoids as anti-inflammatory and anti-allergic agents

- Hormones drugs are obtained from the organs and urine of animals. In this case the activity of drug is evaluated by biological standardization and measured in action units.
- Genetic engineering methods are widely used to obtained hormones.
- Many hormones and their derivatives are synthesized. Some derivatives are different from the natural hormones in their structure and have additional properties.

# Hypothalamus and pituitary hormones.

- The hypothalamus produces releasing or inhibitory factors. They control the production and release of pituitary hormones.
- The pituitary (hypophysis) consists of three lobes: anterior, posterior, intermediate. The anterior lobe contains glandular cells (adenohypophysis) and produces tropic hormones (adrenocorticotropic, somatotropic, thyrotropic, follicle-stimulating, luteinizing, lactotropic). They regulate work of peripheral glands.
- Synthesis and release of the hypothalamic factors and adenohypophyseal hormones are regulated by the feedback mechanism.


Hypothalamic releasing hormones
Hypothalamus
ADH
Oxytocin
Synthesis
Release into blood
Synthesis
Release into blood
FSH, LH
TSH
ACTH
STH(GH)
Prolactin
ADH
Oxytocin
Ovum maturation;
Estradiol,
Progesterone
Thyroxine
Somatomedins
Growth
$H_2O$
Spermatogenesis;
Testosterone
Cortisol
Lactation
Labor
Milk ejection

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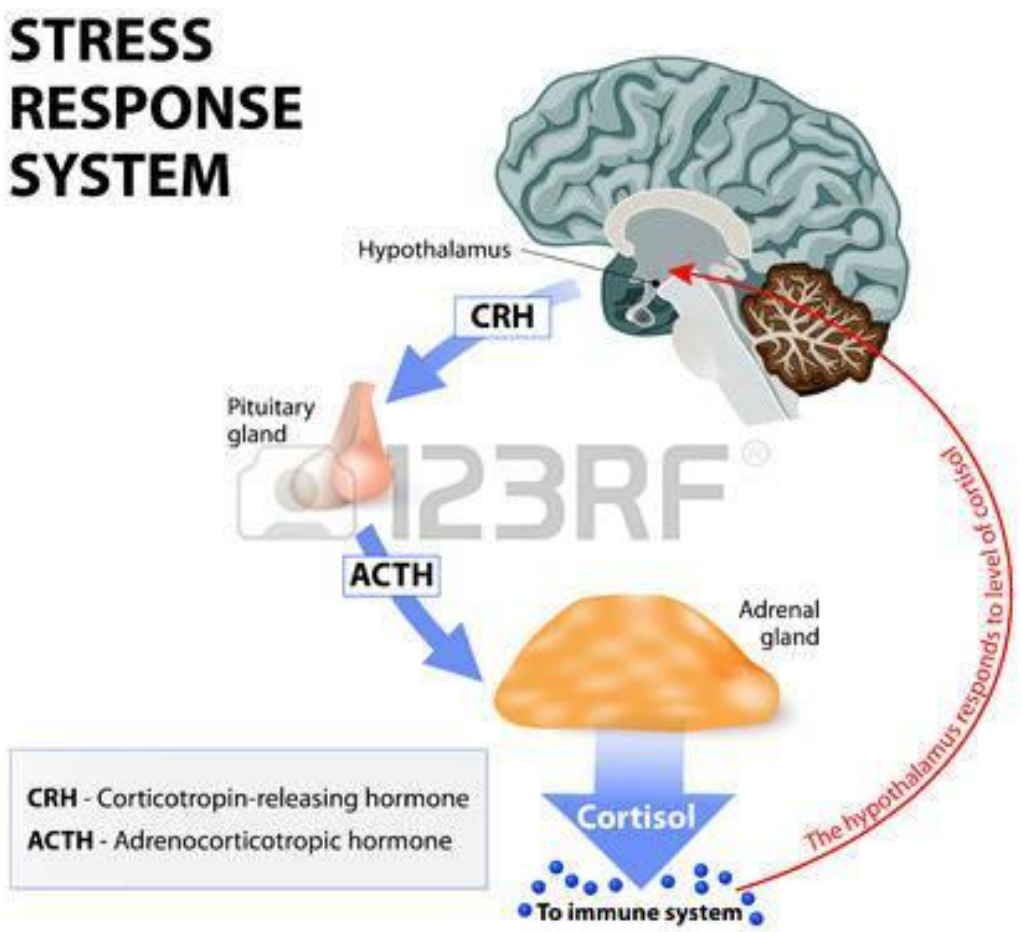
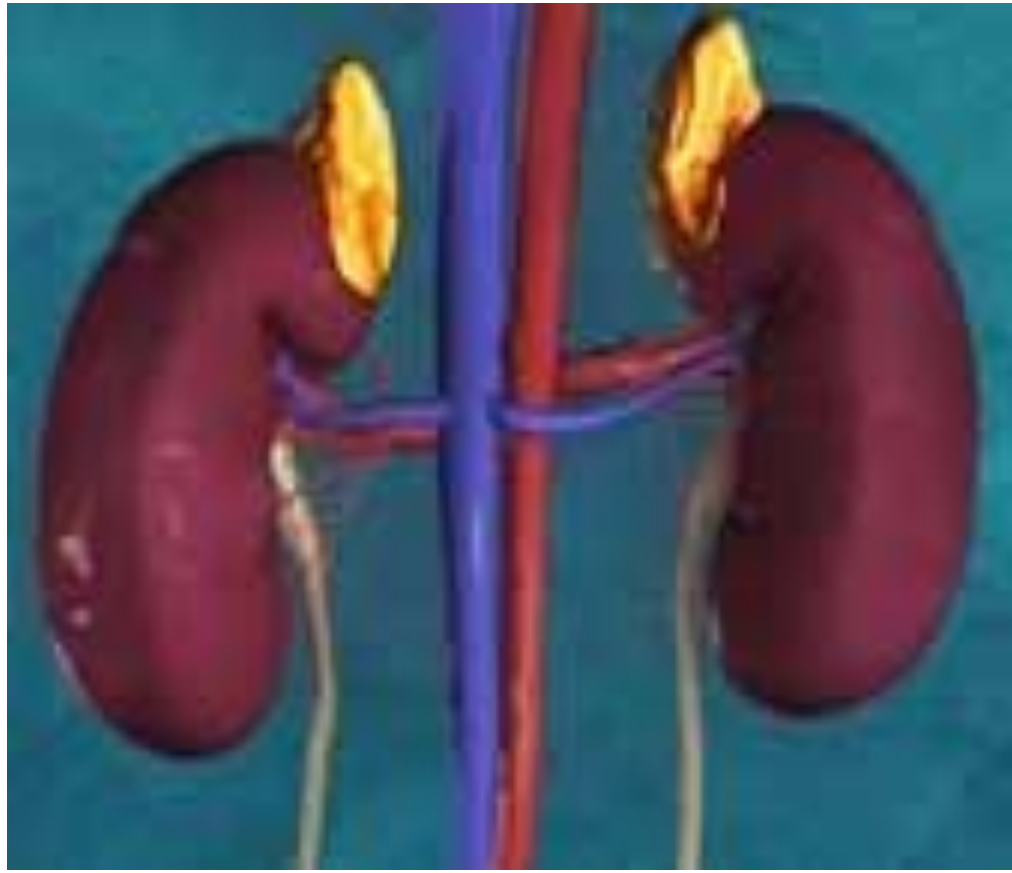
Activity of the hypothalamus and pituitary depends on the concentration of the hormones that circulate in the blood. A reduction in the concentration of hormones in the blood stimulates the hypothalamic – pituitary system, whereas an increase in concentration is associated with an inhibitory effect.



# Natural hormones of the adrenal cortex (they have steroid structure)

- **Glucocorticoids:** hydrocortisone, corticosterone
- **Mineralocorticoids:** aldosterone, deoxycorticosterone
- **Sex hormones:** Androsterone, estron, progesterone



**Mineralocorticoids** interact with the receptors that are localized inside the cells. They enhance the synthesis of protein-carriers of sodium in the distal parts of the nephron.

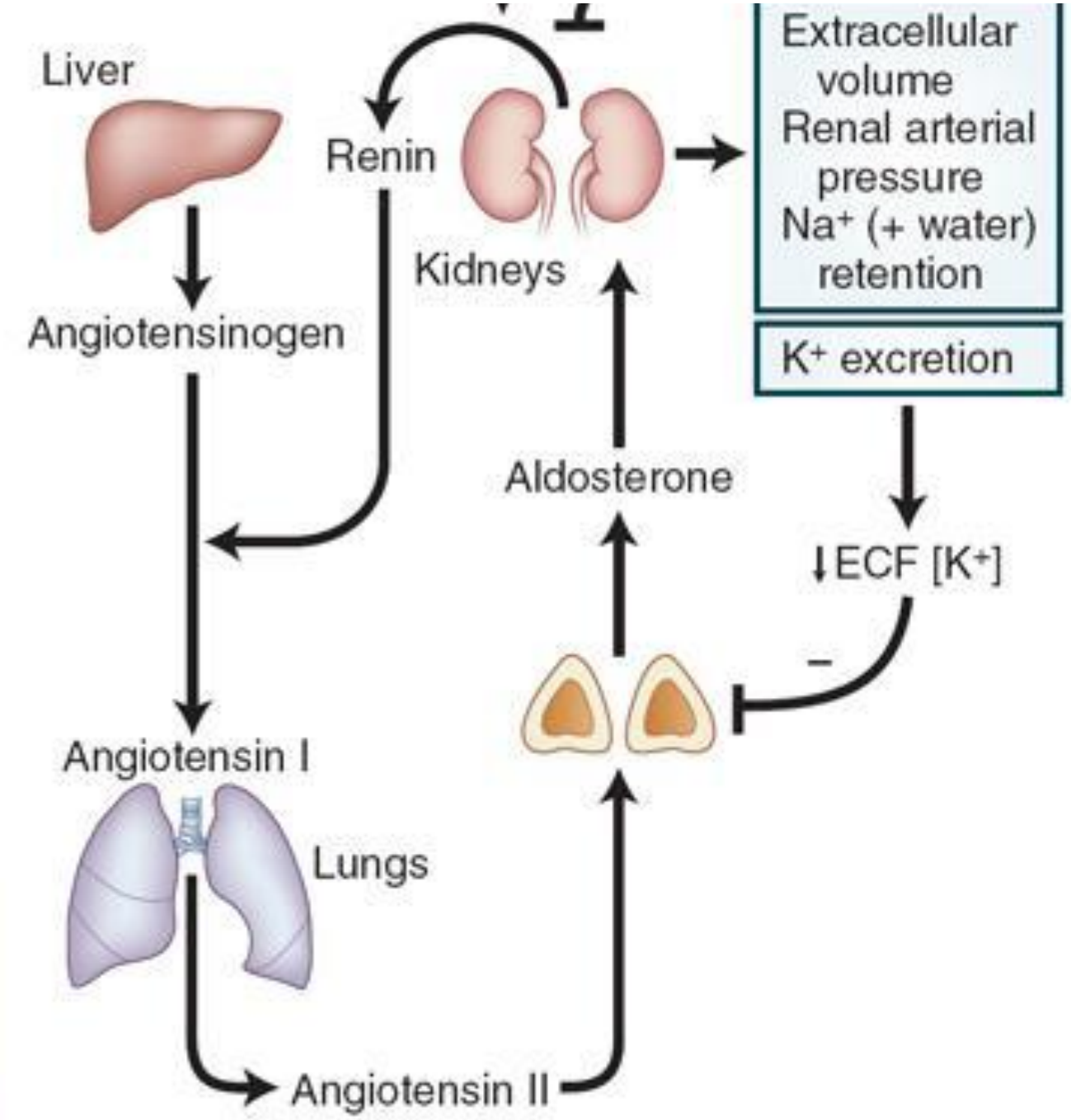
They increase the reabsorption of sodium ions and isosmotic amounts of water, the sensitivity of vessels to catecholamines, the sensitivity of skeletal muscle to acetylcholine, muscular tone and efficiency.

Drugs: Desoxycortone (Deoxycorticosterone acetate) – oil solution, tab. under the tongue; Fluorohydrocortisone acetate is taken orally.

**Indication for use:** chronic failure of the adrenal cortex, myasthenia, adynamia.

**Side effects:** edema, swelling of the body tissues, ascites, hypertension.

**Antagonist:** spironolactone.



# Glucocorticoids

A. Natural: Hydrocortisone

B. Synthetic

- ❖Dehydrated:  Prednisolone, Methylprednisolone
- ❖Fluorinated: Dexamethasone  Triamcinolone
- ❖Difluorinated:  Fluocinolone acetonide (Sinaflan)
- ❖Trifluorinated: Fluticasone
- ❖Chlorinated: Beclomethasone (Becotide)

The introduction of 2 atoms of fluorine or chlorine into the molecules of glucocorticoids reduces their ability to absorb, and they are applied externally or in the form of inhalation.

Glucocorticoids are used in the form of salts. The succinates and hemisuccinates are water-soluble. They are injected IV or IM for emergency indications.

Acetates and acetonides are poorly soluble. They are used in the form of ointments. They can be used intramuscularly or in the joint cavity also.

Glucocorticoids bind to blood proteins.

Hydrocortisone binds to blood proteins (transcortin and albumin) by 90%, the free fraction is 10%.

Synthetic preparations bind to protein by 60-70%, and the free fraction is 40%. It promotes more rapid and complete penetration of GC in tissues and cells, increases the activity and prolongs their action.

Synthetic preparations have less effect on water-salt metabolism. They are more important as drugs of non-specific therapy. They are stronger and more durable.

| **Drug** | **Comparative activity** | **Duration of action** |
|---|---|---|
| Hydrocortisone | 1 | 8-12 h |
| Prednisolone | 4 | 18-36 h |
| Triamcinolone | 5-7.5 | up to 48 hours |
| Dexamethasone | 20-30 | up to 72 hours |

# Effects on metabolism

Glucocorticoids act intracellular. They interact with specific receptors in the cellular cytoplasm. The receptor becomes activated and this leads to its conformational alterations.

The complex “steroid+receptor” penetrates into the nucleus of the cell and binds with the DNA. It stimulates the production of specific mRNA that affects the synthesis of proteins and enzymes.

**Carbohydrate metabolism:** They increase glucose level in blood. They inhibit hexokinase, ↓the utilization of glucose, ↑gluconeogenesis, ↑glycogen deposition in the liver. Glucocorticoids can cause steroid diabetes mellitus

**Protein metabolism.** They accelerate protein catabolism (negative nitrogen balance) and inhibit protein synthesis. They delay the regenerative processes, and growth of children.

They improve protein synthesis in the liver (erythropoietin, surfactant, lipomodulin, insulin, histaminase), antitoxic liver function. Glucocorticoids are used in the treatment of hepatitis, acute poisoning.

**Fat metabolism.** They cause the redistribution of fat (Cushing syndrome): accumulation of a considerable amount of fat on the face (crescent-shaped face), dorsal part of the neck and shoulders .

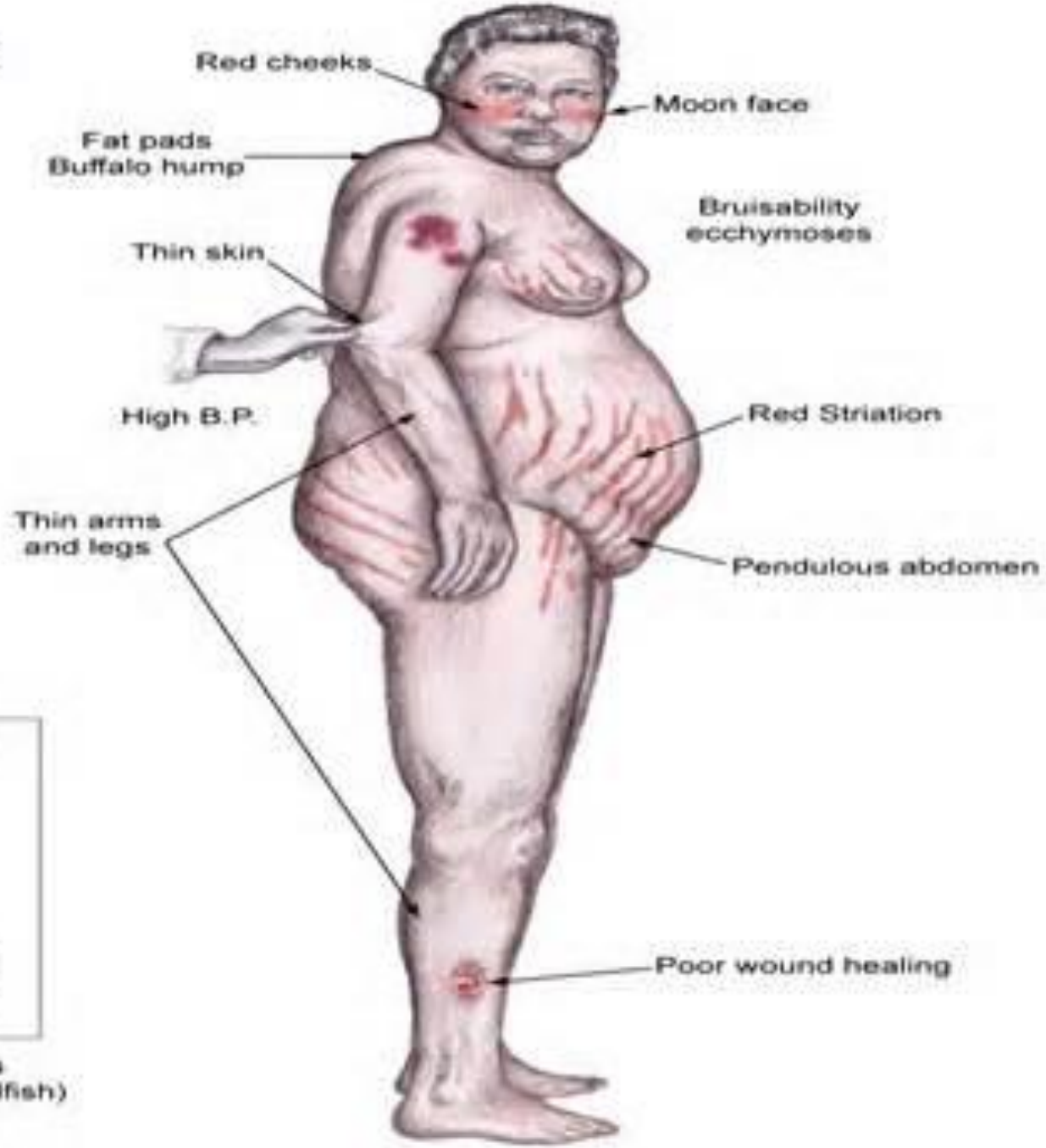
**Water-salt metabolism**. They retain sodium in the body (reabsorption in the renal tubules is increased), increase the secretion of potassium and calcium. Due to the retention of sodium there is an increase in the plasma volume, blood pressure. Osteoporosis can occur.

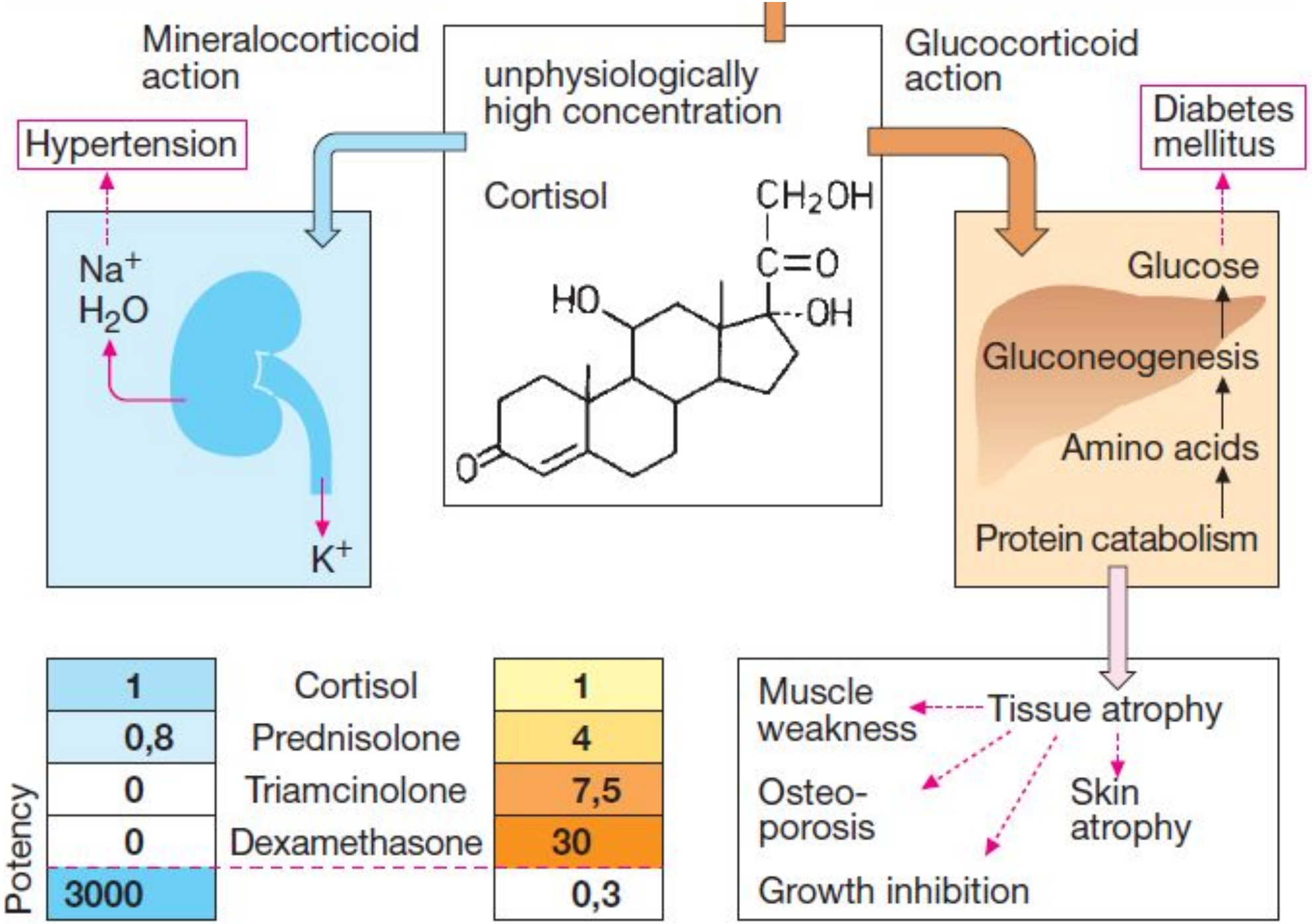
# CUSHING Syndrome

**Background**

Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids

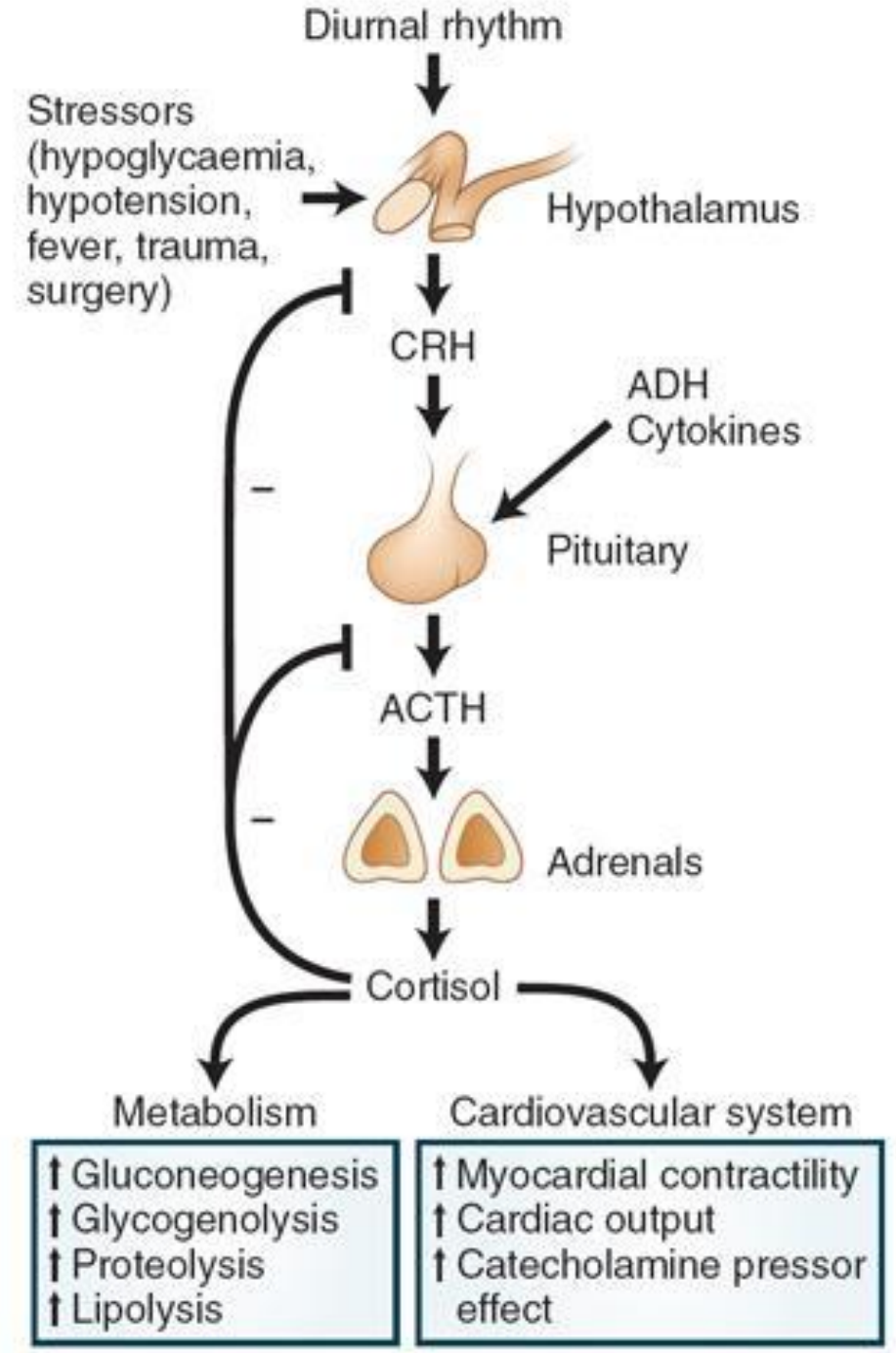
Osteoporosis compressed (codfish) vertebrae




Mineralocorticoid action
Hypertension
Na+
H2O
K+
unphysiologically high concentration
Cortisol
CH2OH
C=O
HO
OH
O
Glucocorticoid action
Diabetes mellitus
Glucose
Gluconeogenesis
Amino acids
Protein catabolism
Potency
1
0,8
0
0
3000
Cortisol
Prednisolone
Triamcinolone
Dexamethasone
1
4
7,5
30
0,3
Muscle weakness
Tissue atrophy
Osteo-porosis
Skin atrophy
Growth inhibition

# «Non-specific» effects of glucocorticoids

- ❑Anti-inflammatory (SAID)
- ❑Anti-allergic and immunosuppressive
- ❑Antitoxic
- ❑Anticancer (leukemia)
- ❑Effect on the cardiovascular system



## Effects on the cardiovascular system:

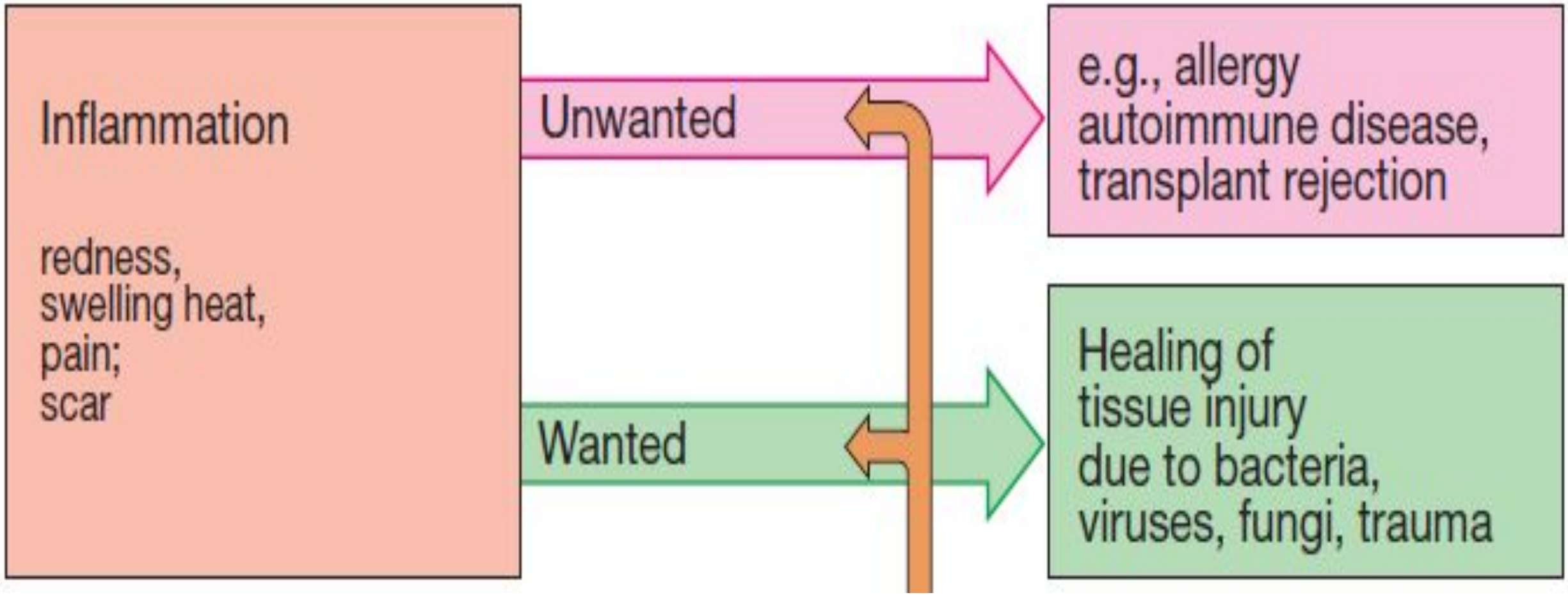
- ↑blood volume;
- reduce release, but increase the breakdown of histamine;
- ↑the sensitivity of receptors to catecholamines;
- Normalize microcirculation; improve AV conduction, ↑ heart rate. ↑blood pressure.

Glucocorticoids are applied in shock of any origin, sepsis, hypoxia, cerebral edema, intracranial hemorrhages, intoxication, hepatitis and cirrhosis.

Natural glucocorticoids are used in acute and chronic adrenal insufficiency (Addison's disease).

## Effects on hematopoiesis

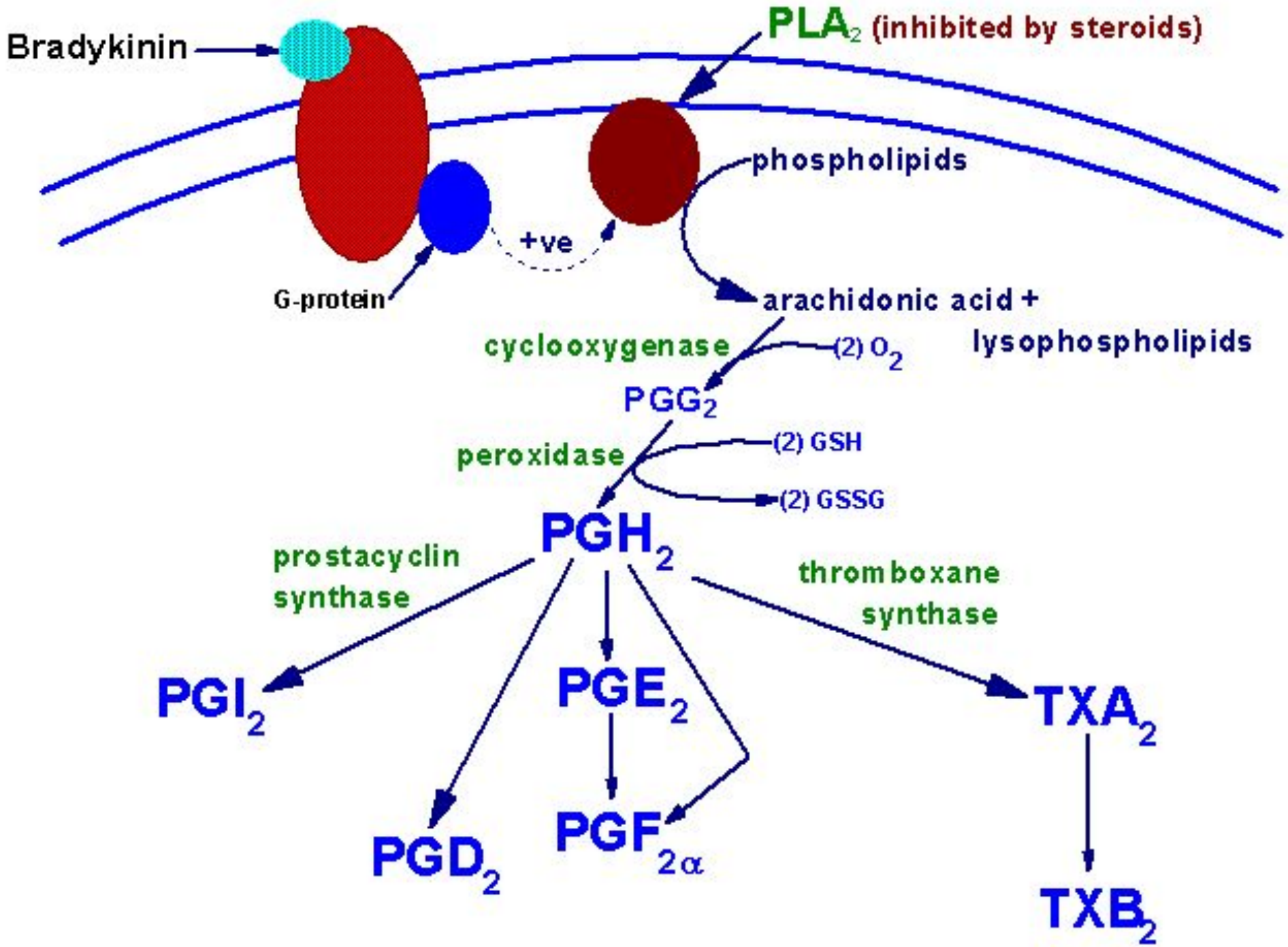
- Glucocorticoids increase the amount of reticulocytes and erythrocytes. They are used for the treatment of hypo - and aplastic anemia, hemolytic anemia.
- They increase the number of neutrophils, reduce the amount of eosinophils, lower the number of lymphocytes, mass of thymus, lymphadens. They are used in the treatment of leukemia.


Inflammation
redness,
swelling heat,
pain;
scar
Unwanted
Wanted
e.g., allergy
autoimmune disease,
transplant rejection
Healing of
tissue injury
due to bacteria,
viruses, fungi, trauma

# Anti-inflammatory effect

Glucocorticoids induce biosynthesis of special proteins – lipocortins. They inhibit phospholipase A2. The production of prostanoids, leucotriens and the platelet-activating factor (PAF) is reduced. They suppress all stages of inflammation and they are active in hyperergic inflammation also.

Influence on stages of inflammation: **1. Alteration.** They reduce tissue damage, ↓the formation of free radicals, stabilize the cell membrane (membranes of lysosomes), ↓ the release of lisosomal enzymes (collagenase, elastase). They decrease the formation of antibodies and immune complexes, their deposition on cell membranes.


Bradykinin
PLA2 (inhibited by steroids)
phospholipids
+ve
G-protein
arachidonic acid +
lysophospholipids
cyclooxygenase
(2) O2
PGG2
peroxidase
(2) GSH
(2) GSSG
PGH2
prostacyclin
synthase
thromboxane
synthase
PGI2
PGE2
TXA2
PGD2
PGF2α
TXB2

**Exudation.** Glucocorticoids:

- ❖ reduce the development of edema;
- ❖↓the formation of mediators of inflammation,
- ❖↓ degranulation of mast cells, release of inflammatory mediators;
- ❖ Inhibits hyaluronidase, ↑ hyaluronic acid content.
- ❖Normalize microcirculation by reducing the formation of PG, thromboxane and prostacycline, leukotrienes.

**Proliferation.** The drugs reduce scar formation because they:

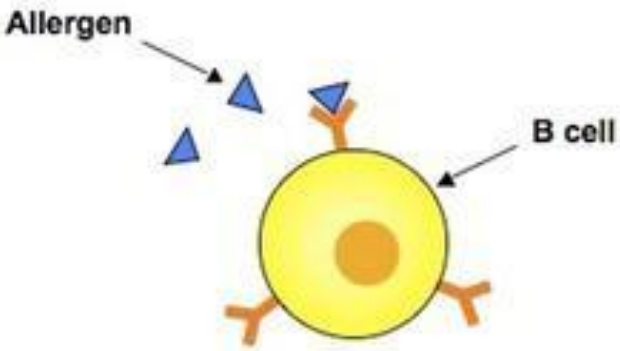
- ❖inhibit the synthesis of proteins;
- ❖↓migration of cellular elements into foci ;
- ❖inhibit the division of fibroblasts;
- ❖↓ synthesis of acidic mucopolysaccharides, ↓ fibrinoid swelling, development of hyalinosis;
- ❖↓ the formation of granulomas;
- ❖prevent the development of hyperergic inflammation.

**Immunosuppressive action. GCs:**

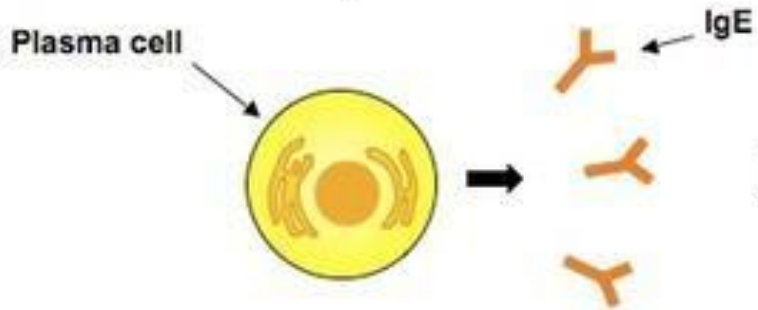
- ↓ migration of stem cells, ↓production of T and B lymphocytes, their development and activity;
- ↓the migration of monocytes, their transformation into macrophages, inhibit phagocytosis; ↓ formation of interleukin 1, ↓ activity of lymphocytes, ↓ the formation of cytokines;
- ↓ formation and activity of B- lymphocytes, production of antibodies;
- ↓ proliferation and activity of T-lymphocytes, ↓ the production of interleukin 2, ↓ the ability of T-killers to produce proteolytic enzymes and cause tissue destruction.

**Anti-allergic effects. Glucocorticoids:**

- ↓synthesis and block the Fc receptors on the surface of mast cells;
- ↓ connection of antibodies to these receptors;
- ↓ the degranulation of mast cells, ↓ histamine release, ↑ its decay;
- ↓ the formation of leukotrienes;
- ↓ the formation of complement;
- ↓inflammation, destruction of tissue;
- ↓manifestation of allergy.

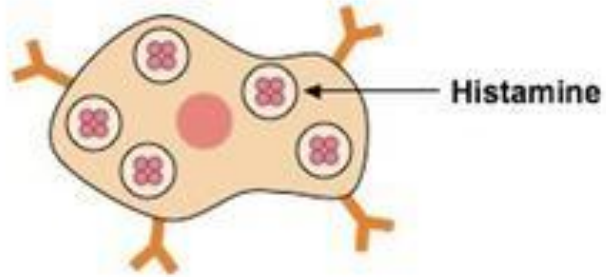



**1.** Initial allergen exposure

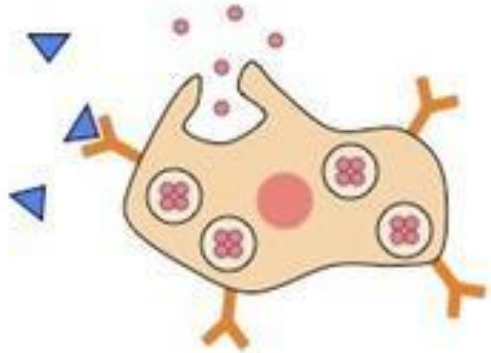



**2.** Antibody (IgE) production


**3.** Histamine-producing mast cell




**4.** IgE bound mast cell (‘*primed*’)



**5.** Allergen re-exposure

# ALLERGIC REACTION

**Hypersensitive Inflammatory Response**

# Types of therapy with steroid anti-inflammatory drugs

- ❑ Substitutional therapy (adrenal insufficiency)
- ❑ Inhibiting therapy (adrenogenital syndrome)
- ❑ Pharmacodynamic therapy:
  - ❖ local (ointments, intra-articular administration, inhalations, nasal and eye drops)
  - ❖ Systemic therapy

1. intense (short period, high doses, parenteral)
2. limited (weeks and months, average doses, tab.)
3. long-term (long-term, low doses, tab.)

## Intensive care:

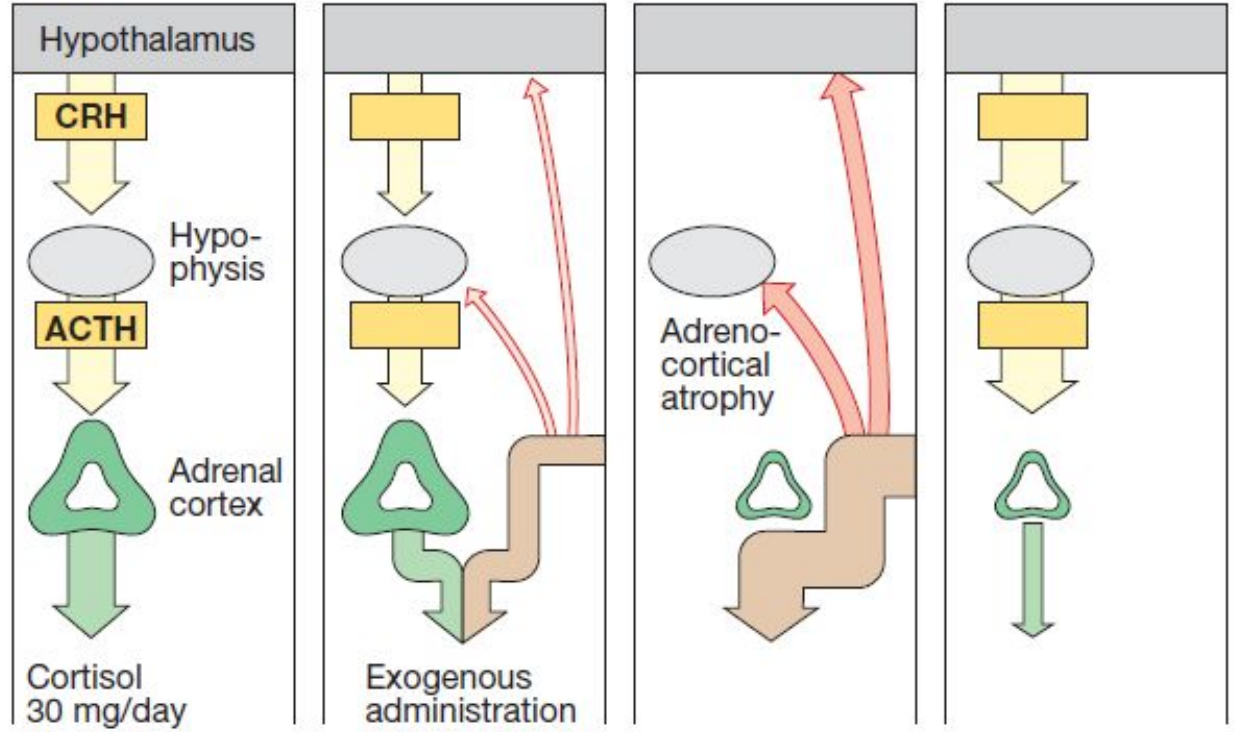
- All kinds of shock
- Swelling of the brain and lungs
- Sepsis
- Asthmatic status
- Serum sickness
- Quincke Edema

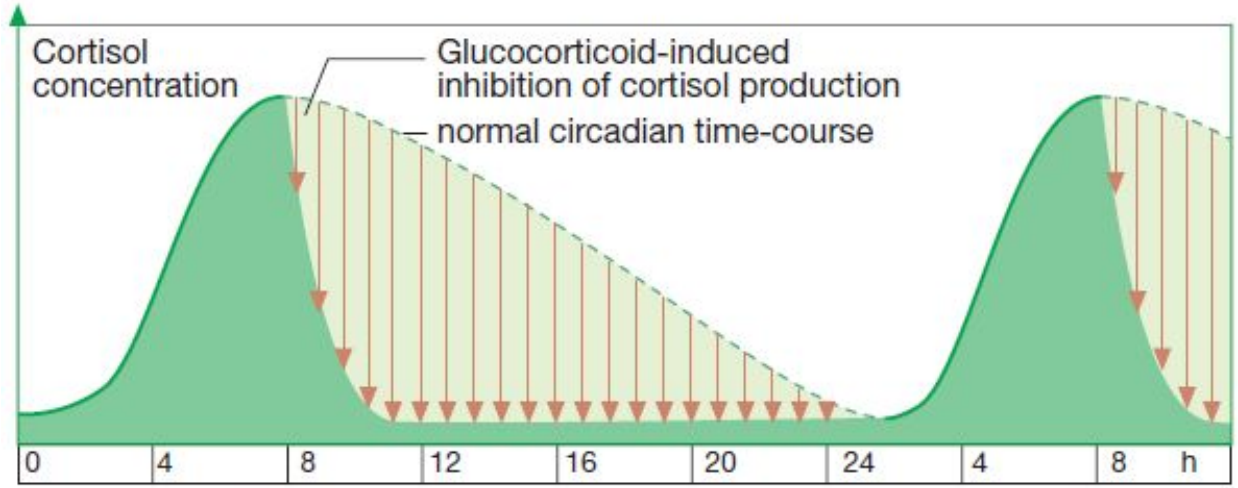
## Limited and long-term therapy:

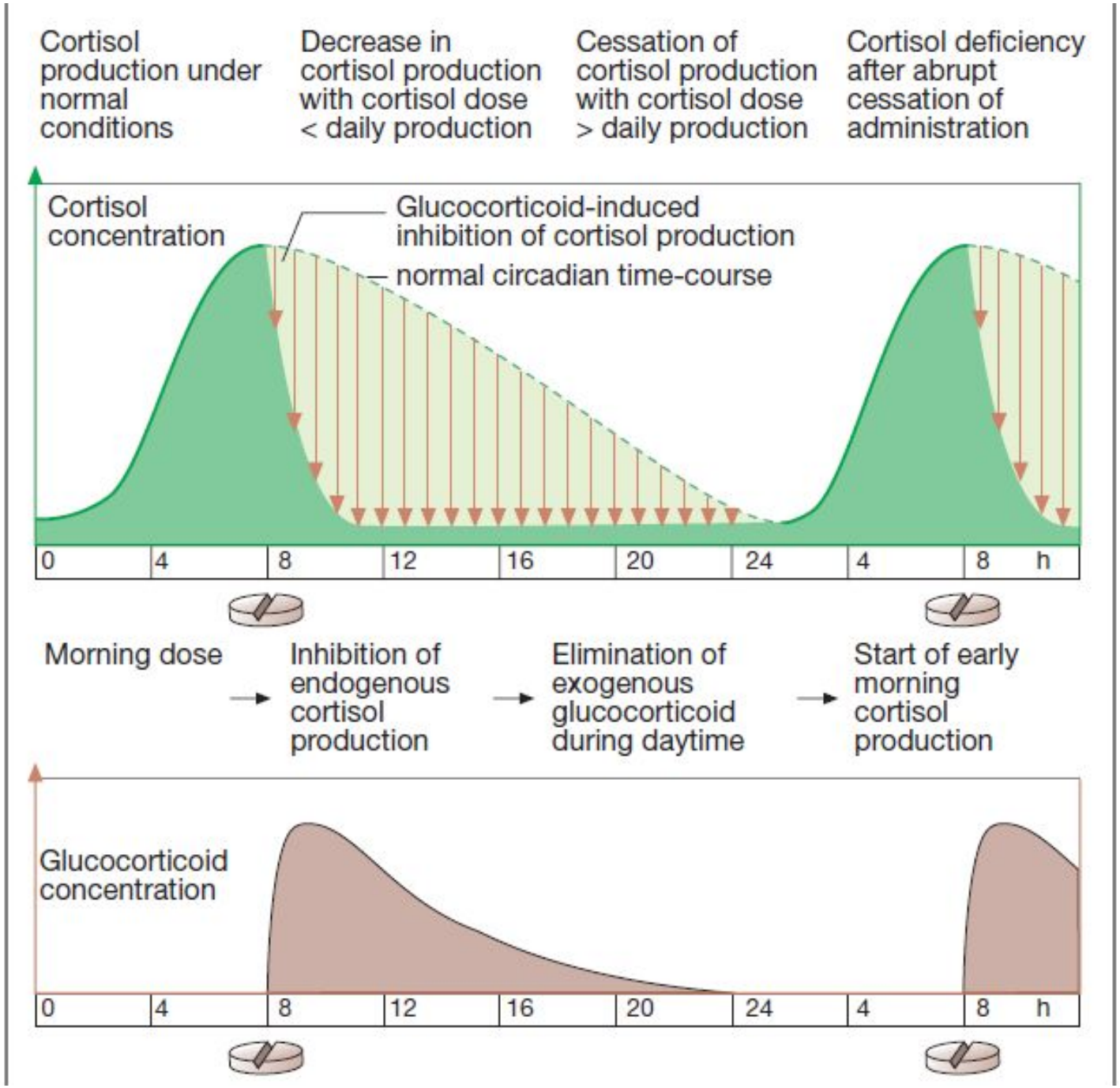
- The connective tissue diseases (rheumatism, systemic lupus erythematosus)
- Bronchial asthma, chronic pneumonia
- Hepatitis, cirrhosis. Nephritis
- Eczema, psoriasis
- Transplant rejection syndrome
- Leukaemias

## Adverse effects:

- acute adrenal insufficiency; the Cushing syndrome; steroid diabetes mellitus;
- ulcerogenicity; slowing of wound's regeneration, growth in children; osteoporosis;
- increase in blood pressure, swelling; thromboses;
- glaucoma, cataracts, exophthalmoses;
- reduced immunity, generalization of infection;
- unstable mood, psychosis; sexual dysfunction;
- teratogenic effect.


Hypothalamus
CRH
Hypo-
physis
ACTH
Adrenal
cortex
Cortisol
30 mg/day
Exogenous
administration
Adreno-
cortical
atrophy
Cortisol
production under
normal
conditions
Decrease in
cortisol production
with cortisol dose
< daily production
Cessation of
cortisol production
with cortisol dose
> daily production
Cortisol deficiency
after abrupt
cessation of
administration


Cortisol
concentration
Glucocorticoid-induced
inhibition of cortisol production
normal circadian time-course
0
4
8
12
16
20
24
4
8
h


Cortisol production under normal conditions
Decrease in cortisol production with cortisol dose < daily production
Cessation of cortisol production with cortisol dose > daily production
Cortisol deficiency after abrupt cessation of administration
Cortisol concentration
Glucocorticoid-induced inhibition of cortisol production
normal circadian time-course
0
4
8
12
16
20
24
4
8
h
Morning dose
Inhibition of endogenous cortisol production
Elimination of exogenous glucocorticoid during daytime
Start of early morning cortisol production
Glucocorticoid concentration
0
4
8
12
16
20
24
4
8
h

# Anabolic steroids

preparations created on the basis of male sex hormones, but have minimal androgenic activity.

**Nandrolone phenylpropionate** acts 7-15 days,

**Nandrolone decanoate** acts 3 weeks. They are administered intramuscularly.

**Methandienone** is administered by tablets 1-2 times a day.

**Effects: Anabolic steroids** increase protein synthesis, improve appetite, increase muscle and body mass, accelerate growth (in children) and bone calcification, accelerate healing of wounds, ulcers, bone fractures.

**Indications:** Cachexia, asthenia, sluggish healing wounds and ulcers, bone fractures, osteoporosis, long-term glucocorticoid therapy, radiation therapy.

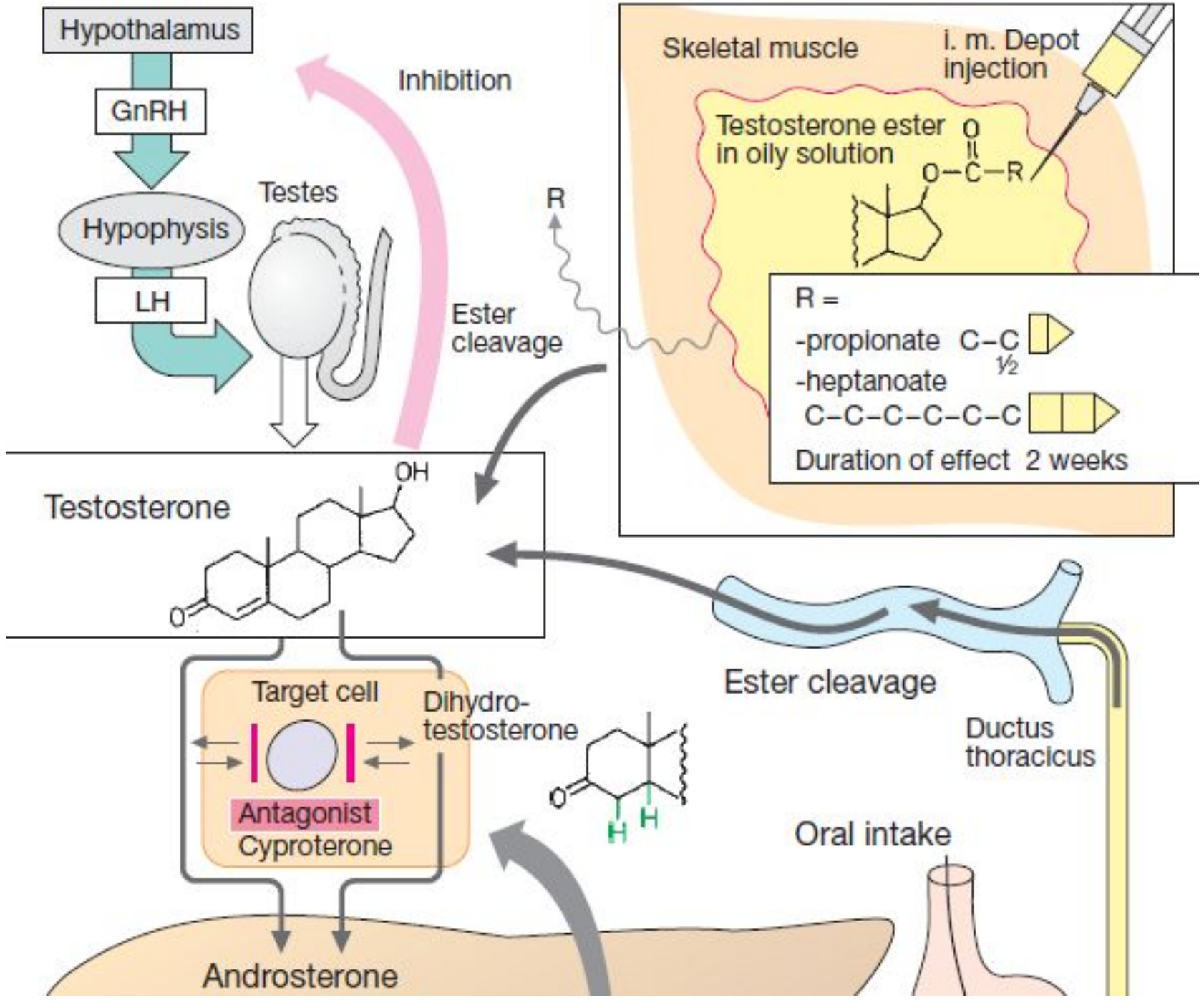
**Side effects:** Hormonal: menstrual disorders, masculinization, impotence; swelling, jaundice, liver failure, excessive storage of calcium in the bone tissue.

# Male sex hormones (androgens)

In male sex organs interstitial Leydig cells produce **testosterone**. It is converted into dihydrotestosterone, which has the highest affinity to androgen receptors.

**Effects:** 1. Testosterone controls the development of genital organs and secondary sex characteristics.

2. Testosterone has anabolic activity. It increase reabsorption water of Ca, Cl, Na, K, N, P in kidneys. It has a marked effect on protein synthesis, catabolism of amino acids. It improves growth of skeletal muscles, myocardium, bone growth and calcification, regeneration of tissues, erythropoiesis.


Hypothalamus
GnRH
Hypophysis
LH
Testes
Inhibition
Ester cleavage
R
Skeletal muscle
i. m. Depot injection
Testosterone ester in oily solution
O
O–C–R
R =
-propionate C–C ½
-heptanoate
C–C–C–C–C–C
Duration of effect 2 weeks
Testosterone
OH
O
Target cell
Dihydro-testosterone
Antagonist
Cyproterone
H
H
Ester cleavage
Ductus thoracicus
Oral intake
Androsterone

## Drugs:

**Testosterone propionatis** and **testenate** are produced in oil for muscular injections.

Testosterone propionatis is administered once every two days,  testenate – once every 2-4 weeks.

**Methyltestosterone** is administered orally or placed under tongue.

## Indications for use

Men: treatment of male sex organs dysfunction (delayed sexual development, impotence, castration),

Female: breast and ovarian cancer (females under 60 years old), dysmenorrhoea, climacteric disorders.

## Adverse effects

Females: a musculinizing effect (hoarseness of voice, male pattern hair growth)

Retention of water and sodium ions in the body, jaundice.

# Antagonists

1. 5α-reductase inhibitors that supress testosterone conversion to dihydrotestosterone

**Finasteride** blocks 5α-reductase and reduces the conversion of testosterone into the active form. It is used for the treatment of benign prostatic hyperplasia, reduces its size, normalizes urination.

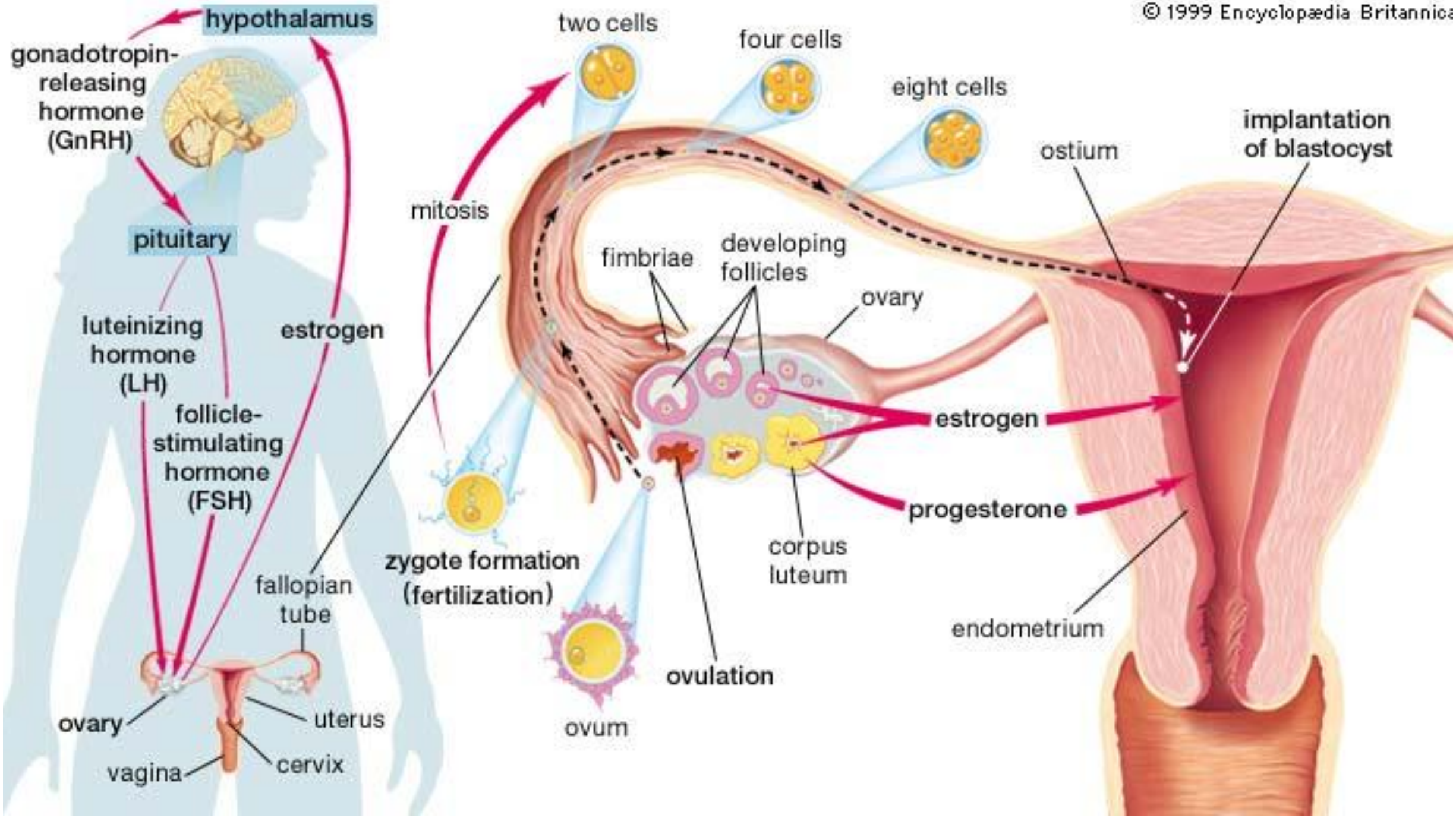
2.Androgen receptors blockers

- **Cyproterone**
- **Flutamide**

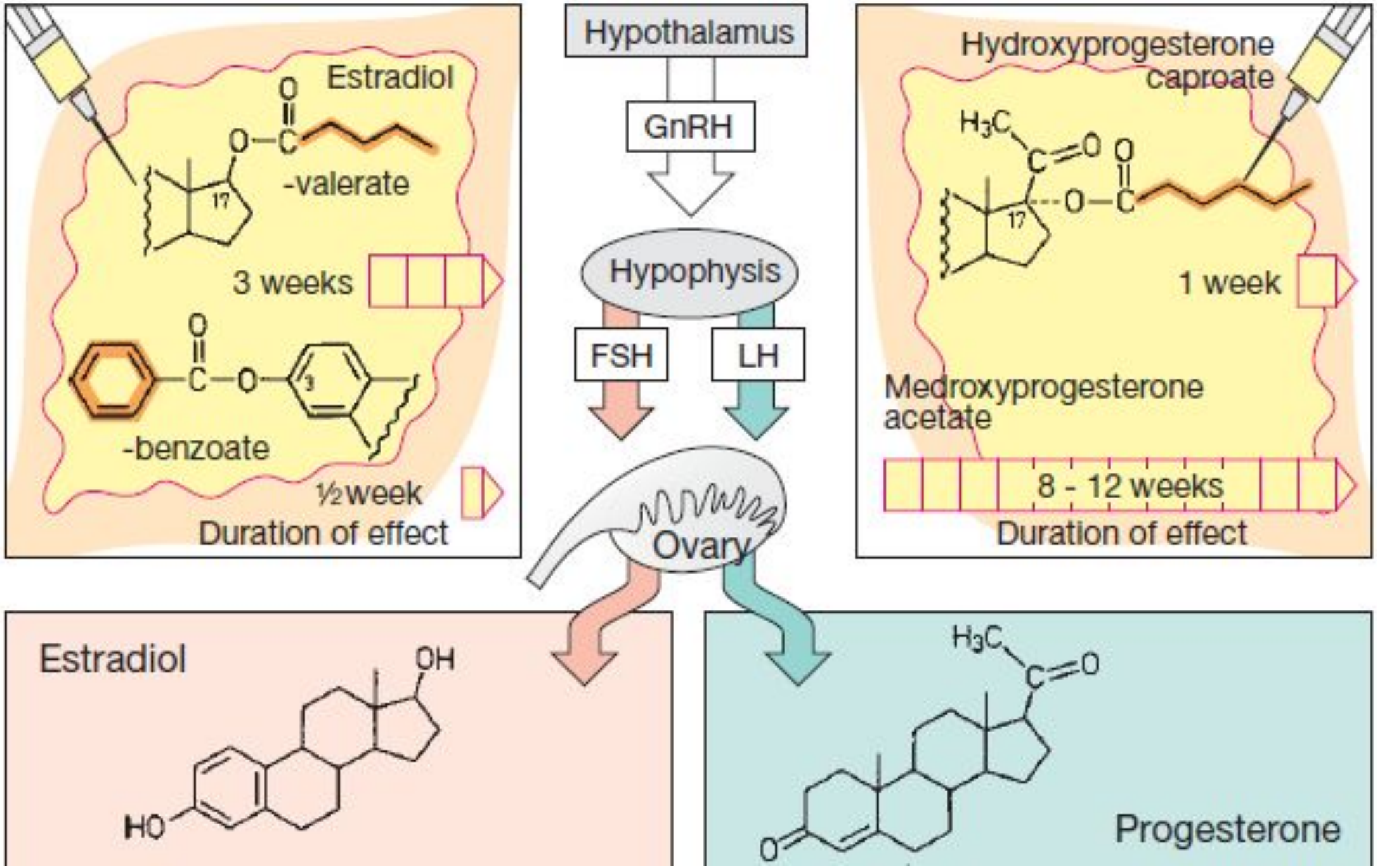
- The drugs block the testosterone – sensitive androgen receptors in the peripheral target tissues, suppresses spermatogenesis. They block androgen receptors in the CNS and reduce sexual desire, can cause impotence.
- They suppress gonadotropic hormones production, reduce plasma levels of testosterone, luteinizing, follicle-stimulating hormones.
- They are used for the treatment of severe hirsutism in females, acne, benign prostatic hyperplasia, hypersexuality in males.

# Female sex hormones, their drugs and antagonists

Hypothalamic-pituitary-ovarian system functions in the body of women. In the ovaries hormones are being secreted cyclically. Estrogens are secreted into the 1st phase of the menstrual cycle. The release of follicle stimulating hormone from the pituitary gland decreases, and the release of luteinizing hormone increases. Ovulation occurs. Phase 2 begins. The secretion of gestogens is increased, and the secretion of estrogens decreases. If pregnancy does not occur, menstruation begins. The cycle is repeated.


hypothalamus
gonadotropin-releasing hormone (GnRH)
pituitary
luteinizing hormone (LH)
follicle-stimulating hormone (FSH)
estrogen
fallopian tube
ovary
uterus
vagina
cervix
mitosis
two cells
four cells
eight cells
fimbriae
developing follicles
ovary
zygote formation (fertilization)
ovum
ovulation
corpus luteum
estrogen
progesterone
ostium
implantation of blastocyst
endometrium
© 1999 Encyclopædia Britannica

| Drug | Source of origin | Structure | Route of administration | Duration of action |
|---|---|---|---|---|
| **Estrone** | Natural | Steroid | Intramuscularly | 24 h |
| **Estradiol** | Natural | Steroid | Intramuscularly | 2-4 days |
| **Ethinylestradiole (50 times more effective)** | Semisynthetic | Steroid | Orally tabl. | 12-24 h |
| **Hexestrole** | Synthetic | Nonsteroid | Intramuscularly and orally | 12-24 h |

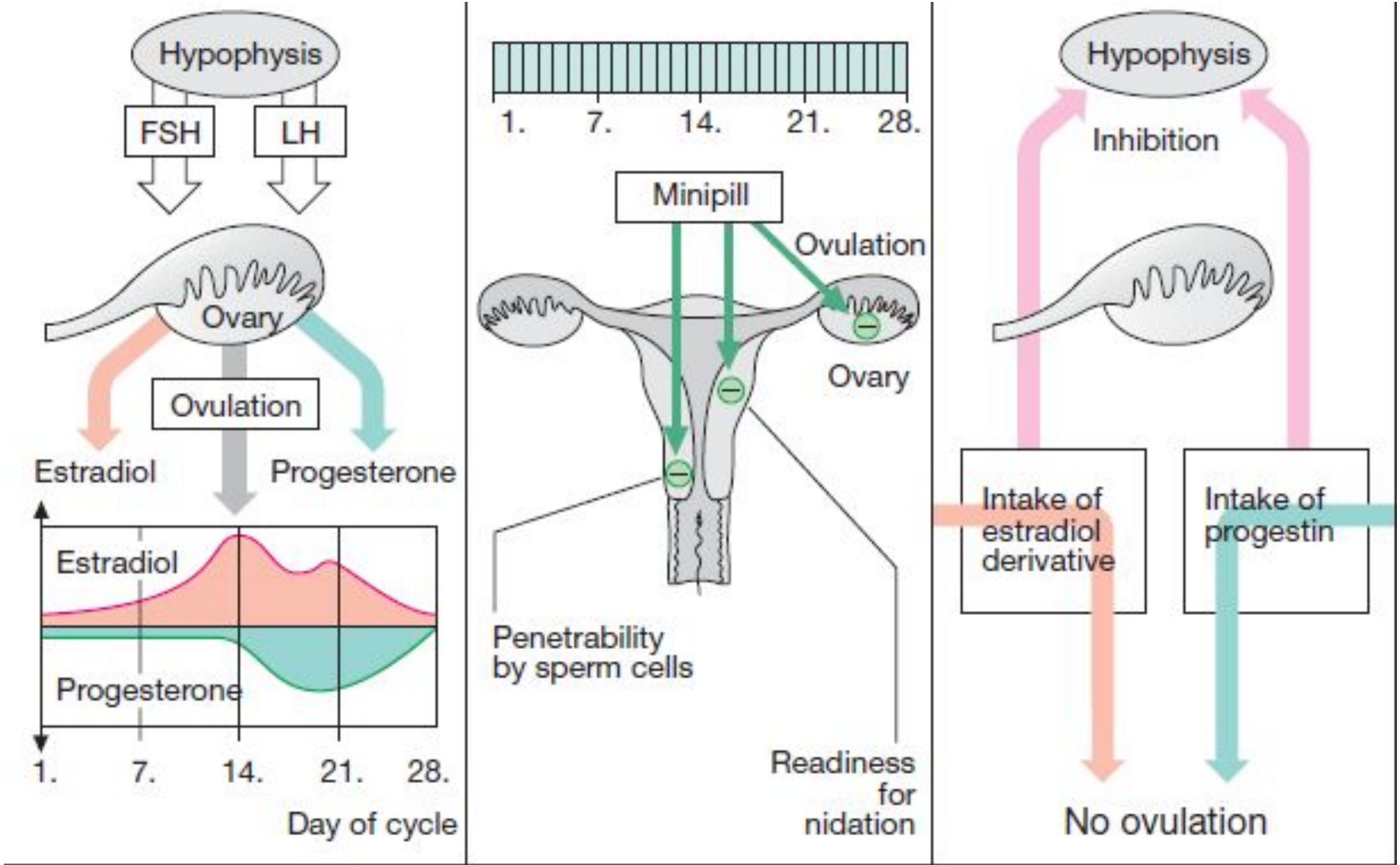

Estradiol
-valerate
3 weeks
-benzoate
½week
Duration of effect
Hypothalamus
GnRH
Hypophysis
FSH
LH
Ovary
Hydroxyprogesterone caproate
1 week
Medroxyprogesterone acetate
8 - 12 weeks
Duration of effect
Estradiol
Progesterone

- Drugs interact with specific estrogen receptors in the target organs (uterus, vagina, fallopian tubes, mammary glands, hypothalamus).
- They normalize the development of sex organs, appearance of secondary sexual characteristics. They cause proliferation of the endometrial epithelium. They increase the sensitivity of the uterus to oxytocin.
- They lower the concentrations of glucose and cholesterol in the blood; promote bone calcification; causing the delay of water and salts; improve mood.

# Indications for use

- drugs of substitution therapy: sexual underdevelopment, amenorrhea, dysmenorrhea, infertility, early menopause, surgical removal of the ovaries;
- weakness of labor, suppression of lactation;
- Contraception (birth control);
- inhibitory therapy (testicular cancer, prostate cancer in men, breast cancer in women over 60 years).

**Side effects:** coagulation disorders (bleeding, thrombosis), swelling, nausea, vomiting, diarrhea, feminization in men.


Hypophysis
FSH
LH
Ovary
Ovulation
Estradiol
Progesterone
Estradiol
Progesterone
1.
7.
14.
21.
28.
Day of cycle
1.
7.
14.
21.
28.
Minipill
Ovulation
Ovary
Penetrability by sperm cells
Readiness for nidation
Hypophysis
Inhibition
Intake of estradiol derivative
Intake of progestin
No ovulation

**Clomiphene** is antiestrogen.

- It passes through the BBB, interacts with the estrogenic receptors of the hypothalamus, disrupts the functioning of the feedback system; increased secretion of FSH and LH;  increase the size of ovaries, their function.
- It is used to treat infertility of Central origin.

**Tamoxifen** is used to treat breast cancer.

# Gestagens and antigestagens

| Drug (gestagens) | Route of administration | Duration of action |
|---|---|---|
| Progesteron | Intramuscularly. | 24 h |
| Hydroxyprogesterone caproate | Intramuscularly | 7-14 days |
| Medroxyprogesterone | Intramuscularly, orally | 14 days |

## Effects:

- They prepare the uterus for implantation.
- They promotes the development of the placenta, reduces the sensitivity of myometrium to hormone oxytocin, prostaglandins, catecholamines during pregnancy.
- They promote the development of glandular tissue in mammary glands .
- They lower aldosterone activity, increase the release of NaCl and H2O.

**Indications for use:**

- Violation of menstrual cycle, dysmenorrhea, dysfunctional uterine bleeding.
- The threat of miscarriage in the first half of pregnancy.
- Cancer of the uterine body, endometrial hyperplasia.
- With the purpose of contraception.

**Side effects:** reduction of libido, depression, insomnia, acne.

**Mifepristone** is antigestagen.

- ✔It interacts with gestagen receptors and prevents the action of gestagens. It increases the tone of the uterus. It is used to induce abortion.
- ✔ It can be used together with prostaglandins because mifepristone increases the sensitivity of myomethrium to prostaglandins.

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