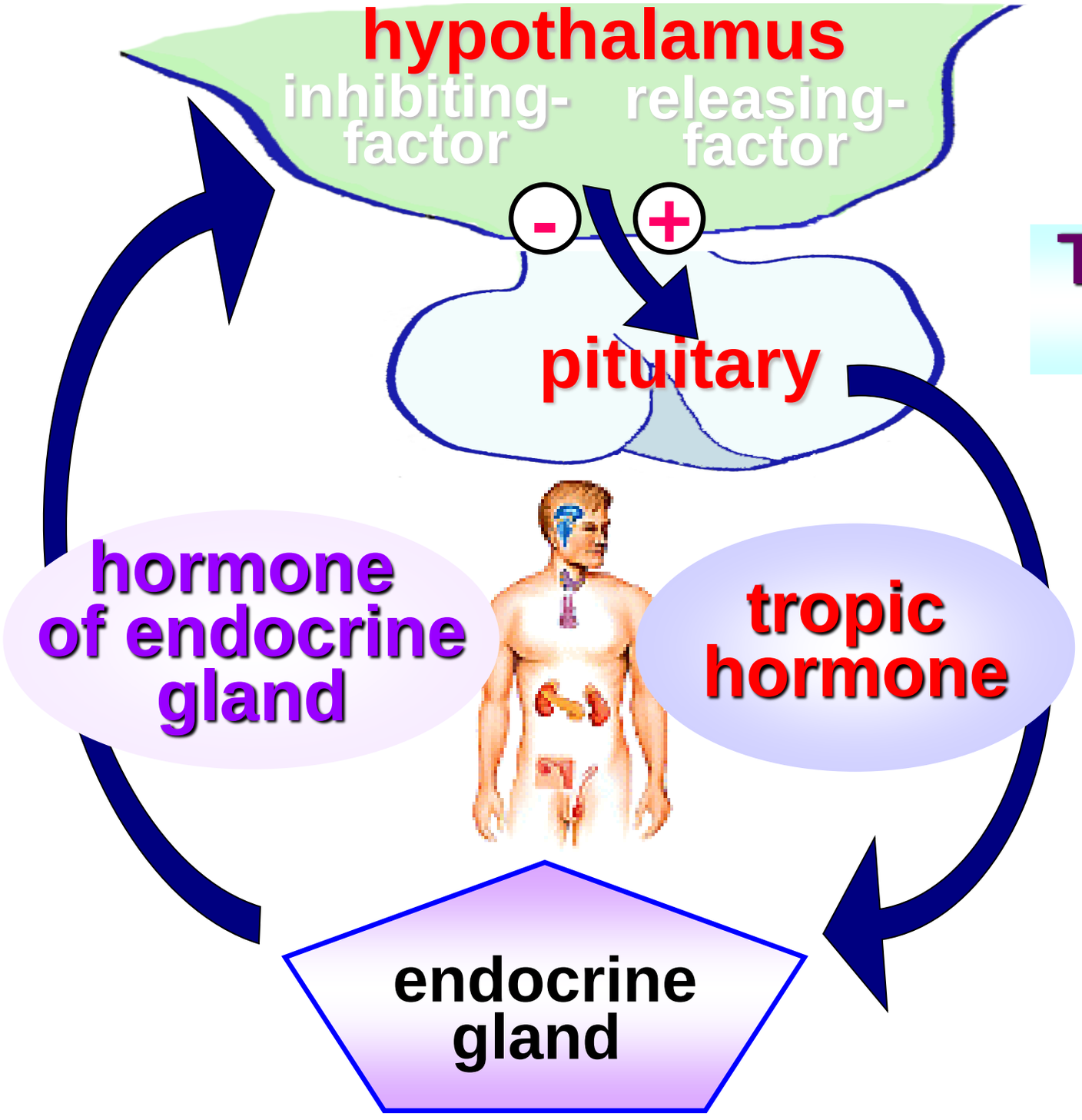
ENDOCRINE AGENTS

NEUROENDOCRINE REGULATION

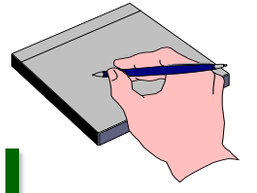


Types of hormonal therapy:

- substitutive
- stimulative
- inhibiting
- pharmacodynamic
- diagnostic

CLASSIFICATION OF HORMONAL AGENTS (according to chemical structure)

- **agents of protein and polypeptide structure – hormonal agents of *hypothalamus, pituitary, epiphysis, parathyroid gland and pancreas***

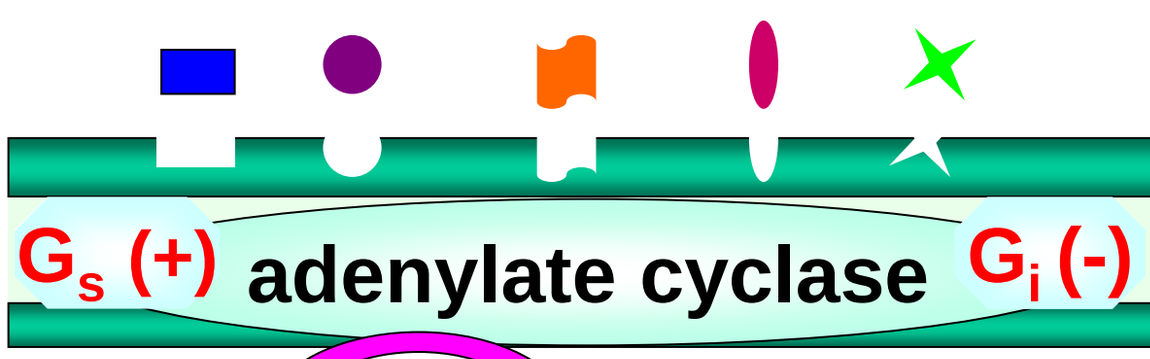


- **derivatives of amino acids – hormonal agents of *thyroid gland, adrenal medulla***

- **steroidal agents – hormonal agents of *adrenal cortex, sexual glands, prostaglandins***

MECHANISM OF ACTION OF HORMONES

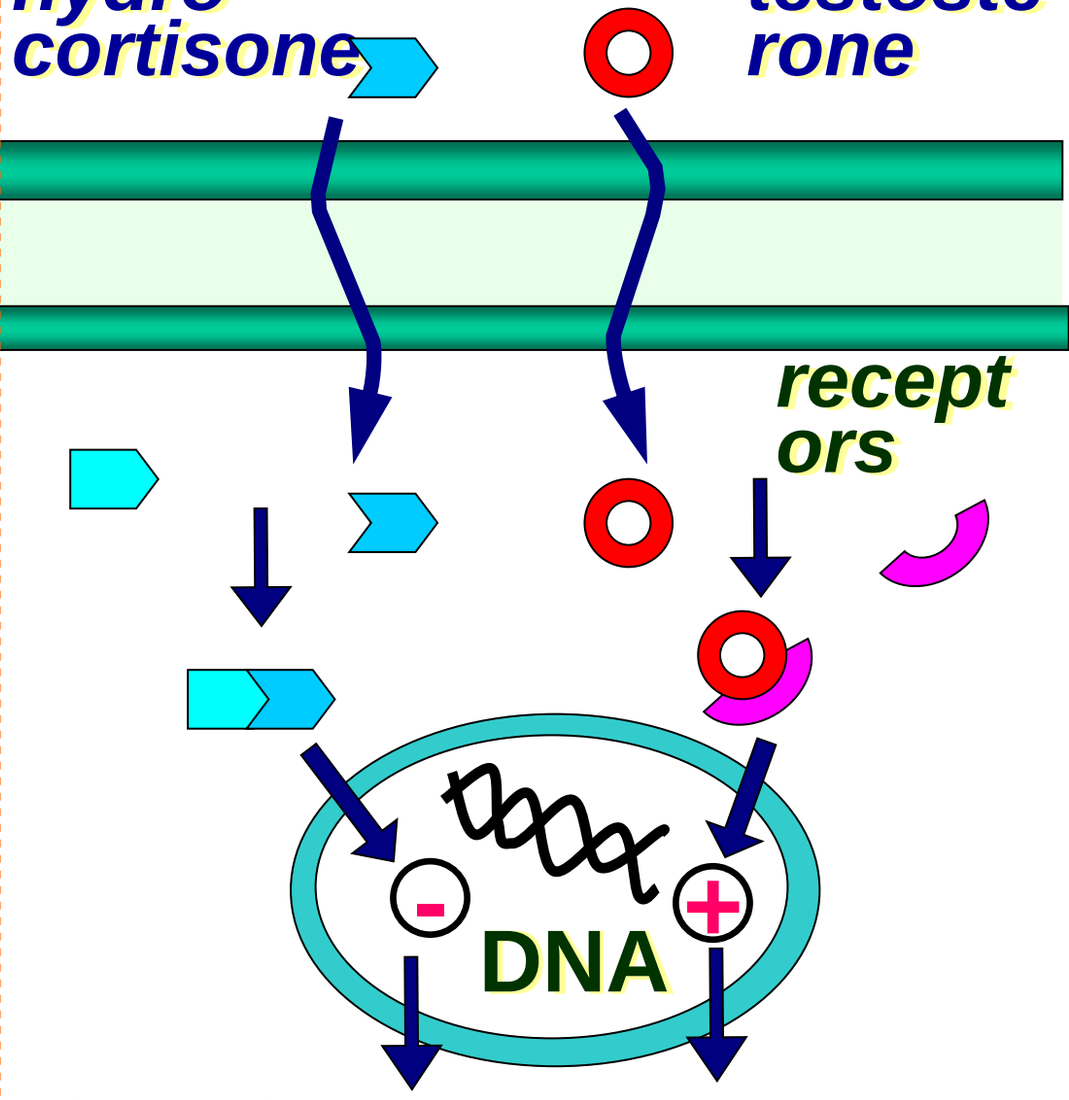
polypeptide and amino acids



ATP → cAMP → protein kinase →

- membrane permeation
- lipolysis
- glucogenolysis
- secretion
- ions flux

steroidal



- ↓ or ↑ mRNA and protein
- metabolism

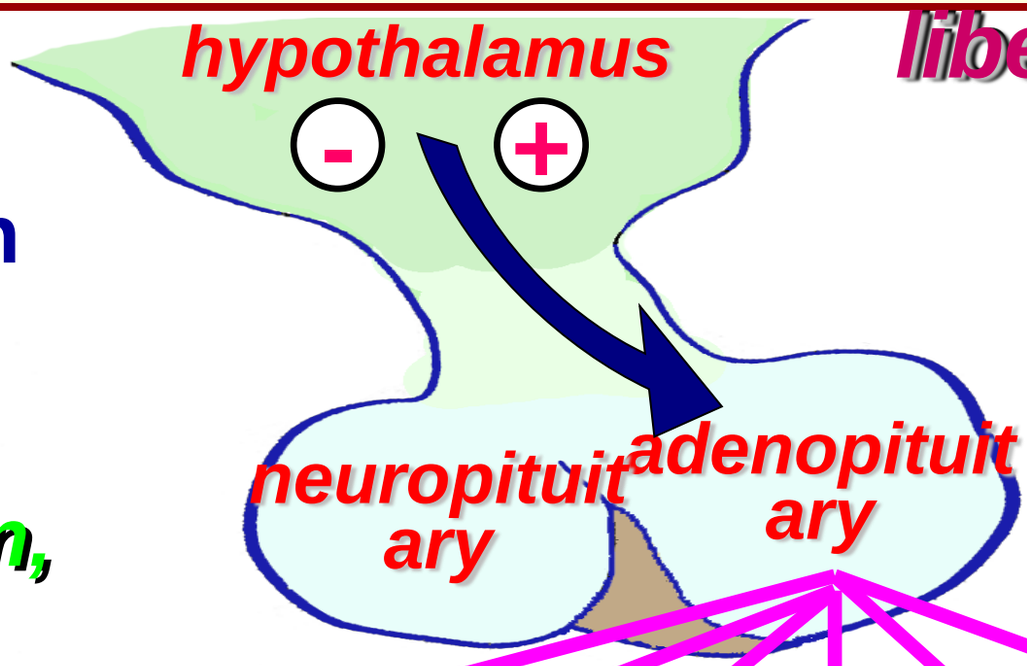
HYPOTHALAMUS AND PITUITARY HORMONES

statins:

prolactostatin
somatostatin
melanostatin

liberins:

corticoliberin
thyroliberin
prolactoliberin
somatoliberin
melanoliberin
gonadorilin



vasopressin,
oxytocin

Melanocyte-stimulating hormone

ACTH → Cortico steroids

Somato tropic → Somato medins

TTH → T_3, T_4

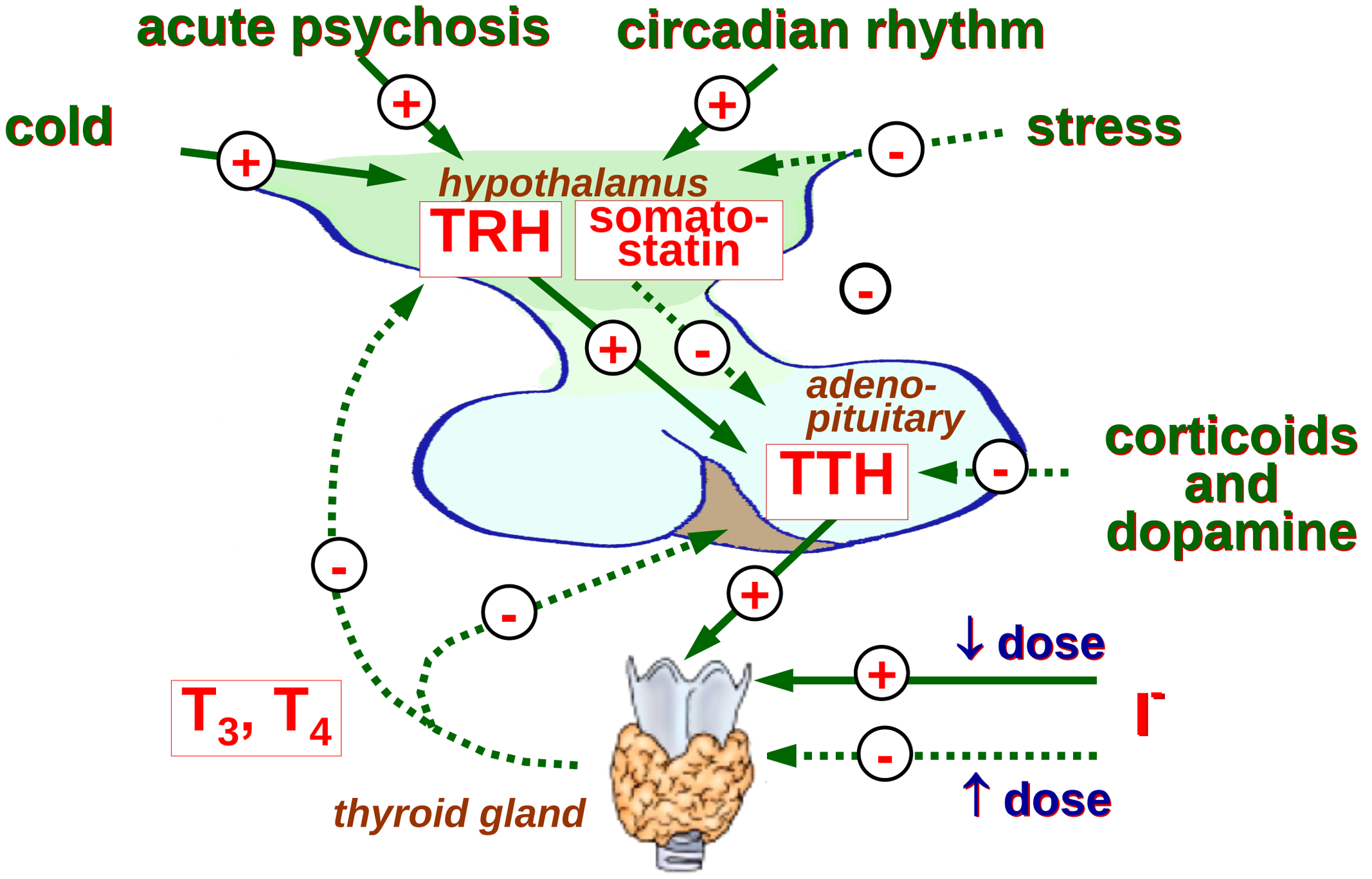
Pro lactin → breast

gonadotropic: follicle-stimulating (FSH), luteinizing (LH) → Sexual glands

PITUITARY HORMONAL AGENTS

hormones	Agents
anterior lobe	
somatotropic	somatotropin
ACTH	corticotropin and its synthetic analogs – cosyntropin
TTH	thyrotropin
gonadotropic	FSH+LH (human menopausal gonadotropins, hMG), resemble with LH from placenta (human chorionic gonadotropins)
prolactin	lactin
intermediate lobe	
melanotropic	Intermedin
posterior lobe	
oxytocin	oxytocin
vasopressin	desmopressin

THYROID GLAND (TG). NEUROHORMONAL REGULATION



THYROID GLAND DYSFUNCTION

hyperthyroidism

(commonly diffuse thyrotoxic goiter (Graves or Basedov disease) –

↑ metabolism and hyperrectivity of organs and systems:

cachexia, ↑ body T, sweating, exophtalm;
CNS: ↑ excitability, hyperkinesis
CVS: ↑ BP, heart rate, arrhythmia
GIT: ↑ appetite, diarrh
breathing: dyspnoe
bone marrow: ↑
kidney: polyuria
reproduction: ↓ fertility

hypothyroidism

children **– cretinism**
(↓ psychical, physical development)

adults **– myxedema:**
↓ metabolism, hypoacivity of organs:

obesity, ↓ body T, dry, edemous skin, ptosis;
CNS: drowsiness, neuropathy
CVS: ↓ BP, heart rate
GIT: constipation
breathing: hypoventilation
bone marrow: ↓
kidney: ↓ filtration
reproduction: infertility, impotence

THYROID PREPARATIONS

tetraiodothyronine (thyroxine), triiodothyronine hydrochloride, thyreoidine

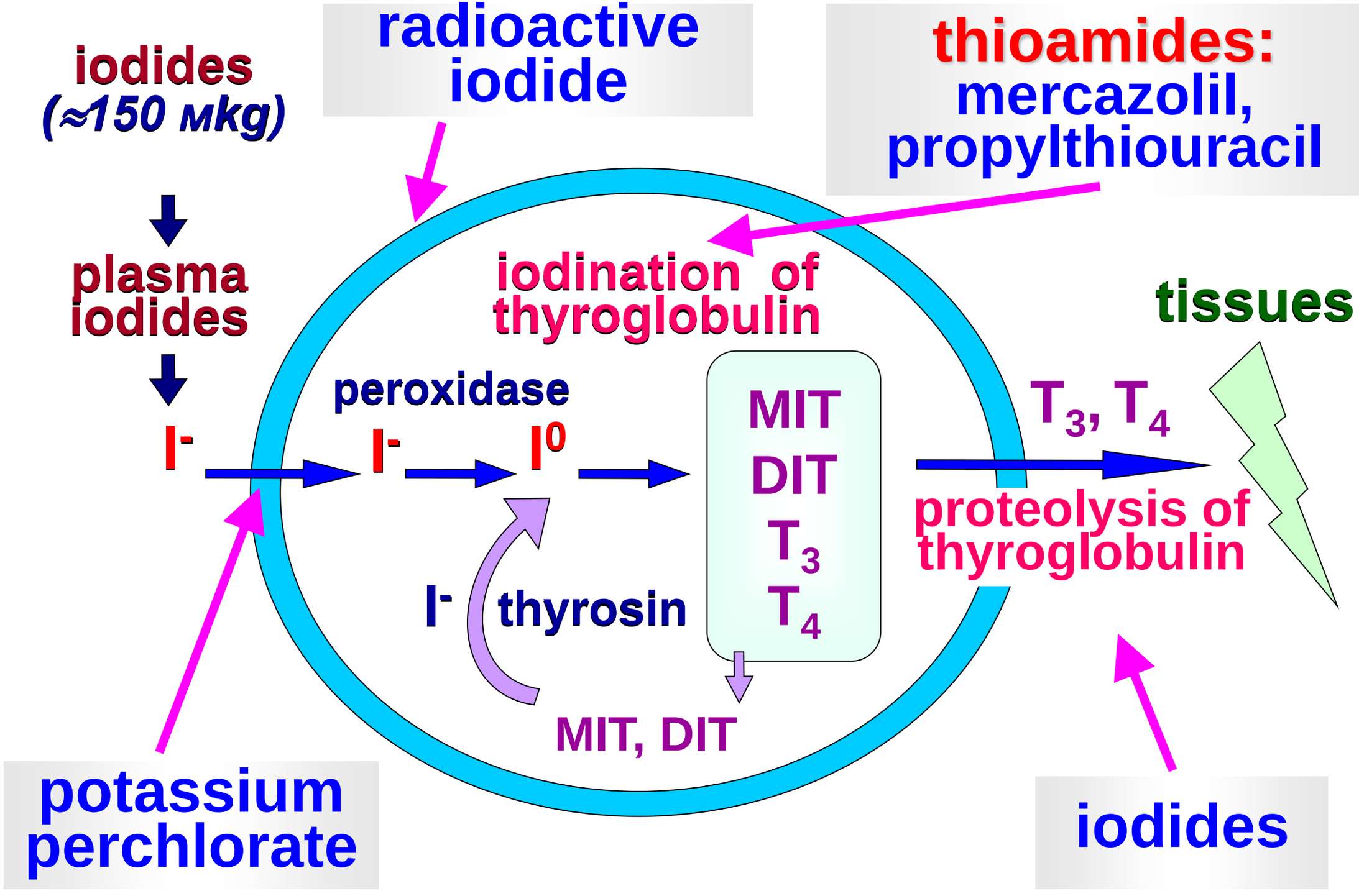
therapeutic uses

- **substitutive:** hypothyroidism – long-term therapy (L-thyroxine), myxedema coma (triiodothyronine hydrochloride)
- **inhibiting** (cancer of thyroid gland)

adverse effects

- overdosing (symptoms of hyperthyroidism)

ANTITHYROID AGENTS



ANTITHYROID AGENTS

thioamides: mercazolil (methimazole) propylthiouracil

indications

- hyperthyroidism
- hyperthyroid crisis

adverse effects

- ↓ bone marrow (leucopenia, anemia)
- goiter (↑ TTH in negative feedback)
- allergic reactions
- rare: headache, neuritis etc

ANTITHYROID AGENTS

iodides: potassium and sodium iodides

indications

- hyperthyroid crisis (↓ symptoms in 2-7 days)
- preoperative preparation for surgery(↓ size and vascularization of thyroid gland)
- prevention of endemic goiter
- prevention of relapse after thyroid resection

adverse effects

- ↑ storage of iodide in gland ⇒ can delay effect of thiomides and radioactive iodide; “rebound” syndrome (↑ thyrotoxicosis)
- iodism (skin rashes, rhinorhea, cough, conjunctivitis, etc)

OTHER THYROID HORMONES

calcitonin (calcitrin, miacalcic)

pharmacodynamic

- ↓ osteoclastic bone resorption, ↑ capturing Ca^{2+} by bones ⇒ ↑ formation of bones (prolong therapy ↓ osteogenesis !)
- ↓ reabsorption Ca^{2+} and phosphates in small intestine
- ↓ renal reabsorption Ca^{2+} and phosphates in kidneys, as well as Na^{+}, K^{+}, Mg^{2+} ⇒ ↑ their excretion ⇒ ↓ level of Ca^{2+} and phosphates in blood

indications

- hypercalciemia
- osteoporosis
- nephrocalcinosis

PARATHYROID GLAND AGENTS

parathormone (parathyroid hormone, PTH)

pharmacodynamic

- ↑ osteoclastic bone resorption, ↓ osteoblasts, ↓ Ca^{2+} capturing by bones ⇒ ↓ bones formation
- ↑ Ca^{2+} and phosphates absorption in small intestine
- ↑ renal reabsorption of Ca^{2+} in kidneys
- ⇒ in blood ↑ level Ca^{2+}, ↓ phosphates

indications for use

- **substitutive therapy:** hypoparathyroidism
  (permanent control of calcium level in blood)

DIABETES MELLITUS

- **I type – insulin-dependent (IDDM):**
  - ✓ severe form, untreated IDDM leads to ketoacidosis
  - ✓ common in young age (juvenile)
  - ✓ absence of insulin in blood
  - ✓ administration of insulin is essential
- **II type – non-insulin-dependent (NIDDM):**
  - ✓ mild form
  - ✓ common after 40 years, associated with obesity
  - ✓ Insulin resistance in tissues
  - ✓ needs diet therapy, ↓ body weight, prescription of oral antidiabetic agents, and finally administration of insulin

CLASSIFICATION OF INSULINS

according to origin:

- **animal – badly purified; moderately- (monopeak – MP) and highly purified (monocomponent – MC):**
  - ✓ **pork (actrapid);**
  - ✓ **bovine (insulin lente);**
- **human (recombinant):**
  - ✓ **recombinant: actrapid HM, humulin regular etc.**
  - ✓ **analogs of insulin: humalog (insulin lispro), epaidra (insulin glylisin), lantus (insulin glargin) etc**

INSULINS

according to duration of action:

insulins	onset	peak	duration
ultrashort			
analogs of insulin: **insulin glylisin, insulin lispro**	**5-10 min**	**0,5-2 h**	**3-4 h**
short			
regular insulin	**15-30 min**	**2 h**	**5-8 h**
intermediate			
insulin zinc-suspension amorphic and protamin insulin	**2-4 h**	**6-8 h**	**12-14 h**
long			
insulin zinc-suspension crystal*; *analog of insulin: **lantus etc.**	**4-5 h**	**8-12 h**	**24-36 h**

INSULINS

combinations

for achievement of permanent therapeutic concentration :

- **combining of insulins in one syringe short-acting and intermediate-acting (NPH-insulin only) in ratio from 10:90 % to 50:50 %**
- **ready-to-use combination – 30% regular and 70% NPH-insulin**

biological activity:

- **40 U (U-40) and 100 U (U-100) insulin in 1 ml**

AVAILABLE INSULINS

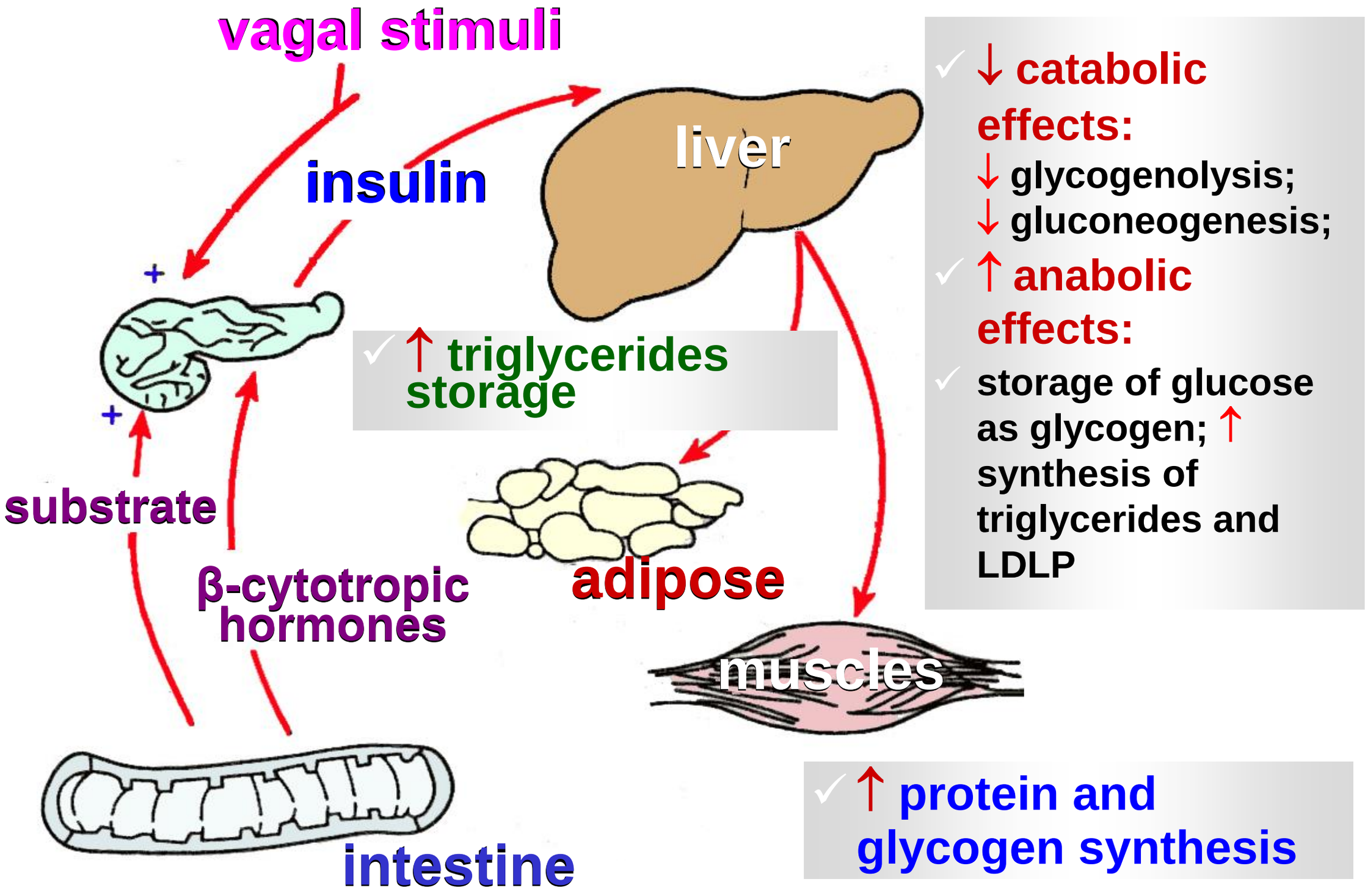
drug form and delivery systems:

- **powder for injections:** S.C. – for daily use, I.V. and intraperitoneal – in case of coma
- **solution for injection:**
  - ✓ **pen-like injector** (for repetitive S.C. injections)
  - ✓ **systems with «close circle»** (infusive system that control glucose level in blood; in diabetic coma only)
  - ✓ **systems with «open circle»** (insulin pump – reservoir and pump with programmed administration of insulin with calculated speed without measurement of glucose level; S.C., I.V., intra-peritoneal
- **aerosol for inhalation**

EFFECTS OF INSULIN

- **stimuli (glucose, arginin, leicin, vagal activity) ⇒ ↑ intra-cellular level of ATP ⇒ closing of ATP-depending K^+-channels ⇒ depolarization of β-cells and opening of Ca^{2+}-channels ⇒ ↑ intra-cellular level of Ca^{2+}, launch secretion of insulin from pro-insulin**
- **insulin → blood ⇒ insulin + specific receptors (consist of α- and β-subunits) on cellular surface; through endocytosis enter the cell + activation of β- subunit with tyrosin kinase activity**
- **primary effect – facilitation of glucose permeation through membrane in target tissues (liver, muscles, adipose and lymphoid tissues) ⇒ ↑ its amount in 2,5 times and >; ↑ their utilization and conversion in glycogen**

PHARMACODYNAMIC OF INSULIN



✓ ↓ catabolic effects:
↓ glycogenolysis;
↓ gluconeogenesis;

✓ ↑ anabolic effects:

✓ storage of glucose as glycogen; ↑ synthesis of triglycerides and LDLP

✓ ↑ triglycerides storage

✓ ↑ protein and glycogen synthesis

PHARMACOKINETICS OF INSULINS

Absorption: **in GIT destruction ⇒ S.C., inhalation, if needs I.V. and intra-peritoneal injection (regular insulin!)**

Plasma protein binding: **2-25 %**

Elimination **from blood by liver (60 %) and kidneys (35-40 %) under action of insulinase (T ½ - 3-5 min, after S.C. upto 40 min)**

INSULIN PRODUCTION

- ✓ in healthy human 23-60 ED of insulin produced or 0,6-1,0 ED/kg body weight
- ✓ insulin secretion is divided into basal and prandial (bolus): basal need ≈ upto 1,0 U/hrs, or = 24 ED/day; meal-stimulated = from 1,0 to 1,5 U insulin for every 10-12 g of carbohydrates
- ✓ requirement in insulin ↑ in the morning, but sensitivity to it ↑ in the evening
- ✓ In healthy fasting glucose level in blood 3,3–5,5 mmol/l and up to 7,8 mmol/l after meal

INDICATIONS FOR INSULIN

- IDDM
- ketoacidosis
- comas: diabetic (hyperglycemic, kettoacidic) – I.V., intra-peritoneum (regular insulin only!)
- DM with concomitant severe pathology (myocardial infarction, brain stroke, surgical operation)
- resistance to oral hypoglycemic agents at DM Type 2
- pregnancy in diabetic patient
- exhaustion and rapid weight loss
- severe liver pathology (hepatitis, cirrhosis)

PRINCIPLES OF INSULIN THERAPY

intensifyed

- **basis-bolus therapy, means continuous substitution of insulin: administration of small amount of long-acting insulin 1-2 times per day (basal) and regular insulin 20 min before meal; 2/3 dose – during day, 1/3 – at bed time**
- **following of diet instructions**
- **self-control (continuous glucose monitoring)**
- **physical activity**
- **changing of insulin dose if need change**

PRINCIPLES OF INSULIN THERAPY

dose is selected under level of glucose in blood & urine

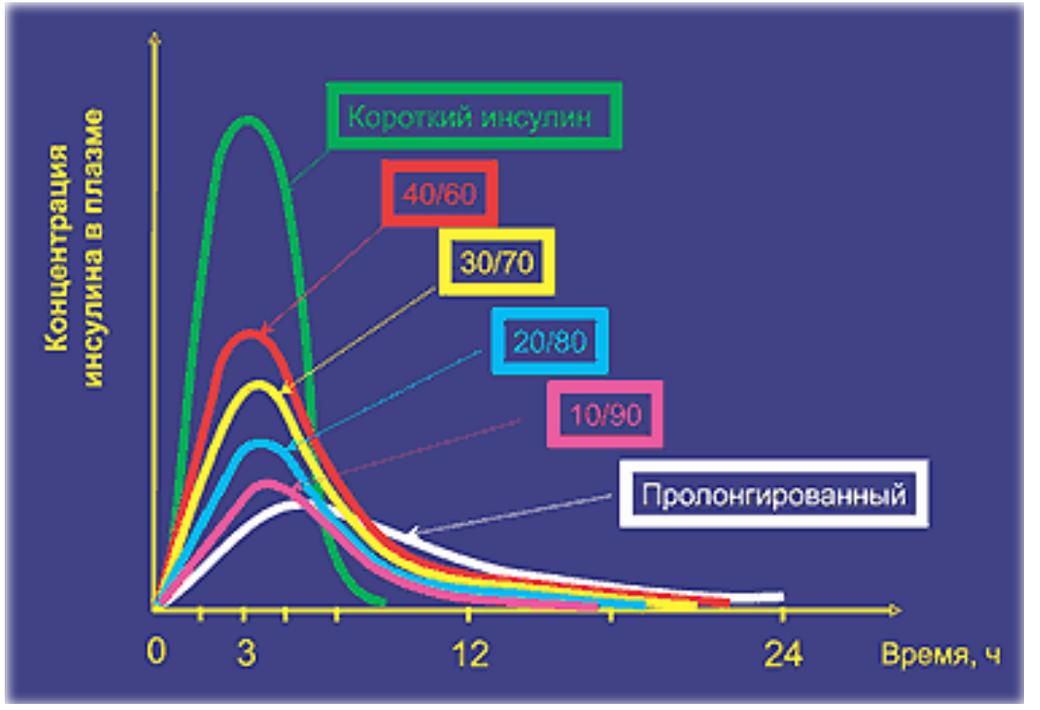
ways of counting:

1. **1 U of insulin for 4-5 g glucose in urine;** before breakfast – 35%, before dinner – 25%, before supper – 30% and before sleep –10% daily need
2. **if glycemia more than 8,33 mmol/l for every following 0,22 mmol/l let it give 1 U of regular insulin every 6-8 hrs**
3. **DM depends on body weight of patient and termin of disease:** for “fresh” patients with DM-1 should be give insulin 0,5 U/kg/day; during remission – 0,4 U/kg, for patients with bad compensation – 0,7-0,8 U/kg/day

PRINCIPLES OF INSULIN THERAPY

ways of counting (continuation):

5. Counting for basis-bolus therapy:



✓ for formation of basal concentration one can use long-acting insulin (around 1 U/hr ⇒ per day ≈ 24-26 U)

✓ For regulation of post-prandial glucose one can use regular insulin 1-1,5 U for 10-12 g carbohydrates (1 bread unit)

✓ At healthy person 1U of insulin ↓ glucose level in blood on 2,22 mmol/l and 12 g of carbhydrates (1 bread unit) ↑ it on 2,77 mmol/l

ADVERSE EFFECTS OF INSULIN THERAPY

- **immunologic** (antibodies production: IgA, IgD, IgT, IgG, IgM):
  - ✓ **insulin allergy** (bovine, pork insulin)
  - ✓ **Immunoresistance to insulin**
- **lipodystrophy** at injection sites
- **hypoglycemia** (20-40 ml 40 % sol. glucose, S.C. 0,5 ml 0,1 % sol. adrenaline)

ADVERSE EFFECTS OF INSULIN THERAPY

- **hyperglycemic (diabetic) coma:**
  - ✓**correction of dehydration with blood expanders (I.V. by drops 1-2 l saline solution)**
  - ✓**↓ insulin level up to normal**
  - ✓**acidosis corrections if pH < 7,2 (sodium bicarbonate)**
  - ✓**Maintaining of potassium level**
  - ✓**treatment of concomitant diseases**

SYNTHETIC ANTIDIABETIC AGENTS

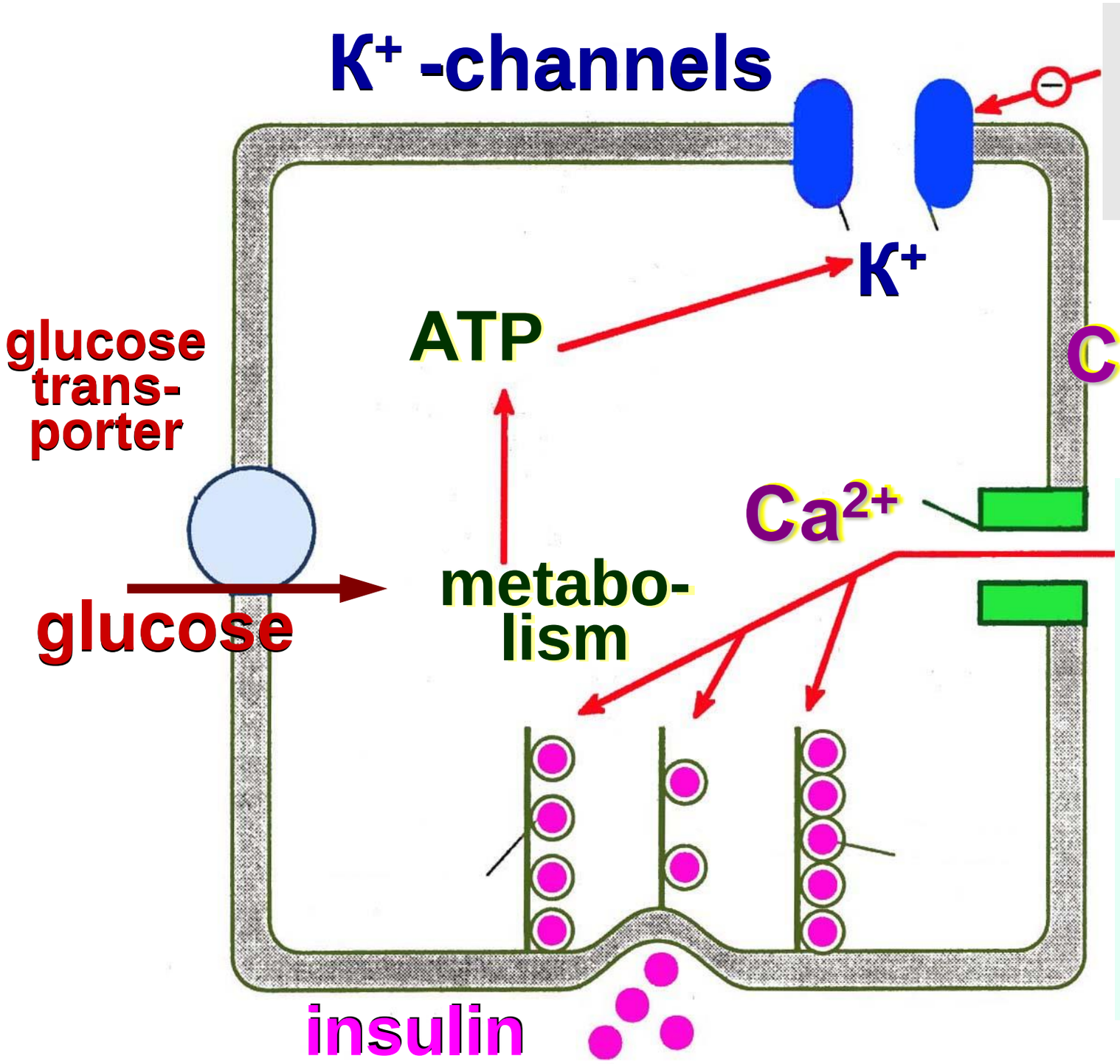
classificaton:

- **Sulfonurea derivatives:**
  - 1 generation – butamine
  - 2 generation – chlorpropamide, glibenclamide
  - 3 generation – glimepiride
- **Biguanides:** metformin
- **Thioglitazones:** pioglitazone
- **Glinides:** repaglinide

indications:

- NIDDM (> 40 yrs and not longer 5 yrs) – sulfonurea derivative
- NIDDM with obesity – biguanides

ANTIDIABETIC AGENTS



- ✓ ↑ insulin release from β-cells
- ✓ ↓ glucagon in blood
- ✓ extra-pancreatic effects (↑ insulin action on target tissues)

ADVERSE EFFECTS OF ORAL ANTIDIABETIC AGENTS

sulfonureas:

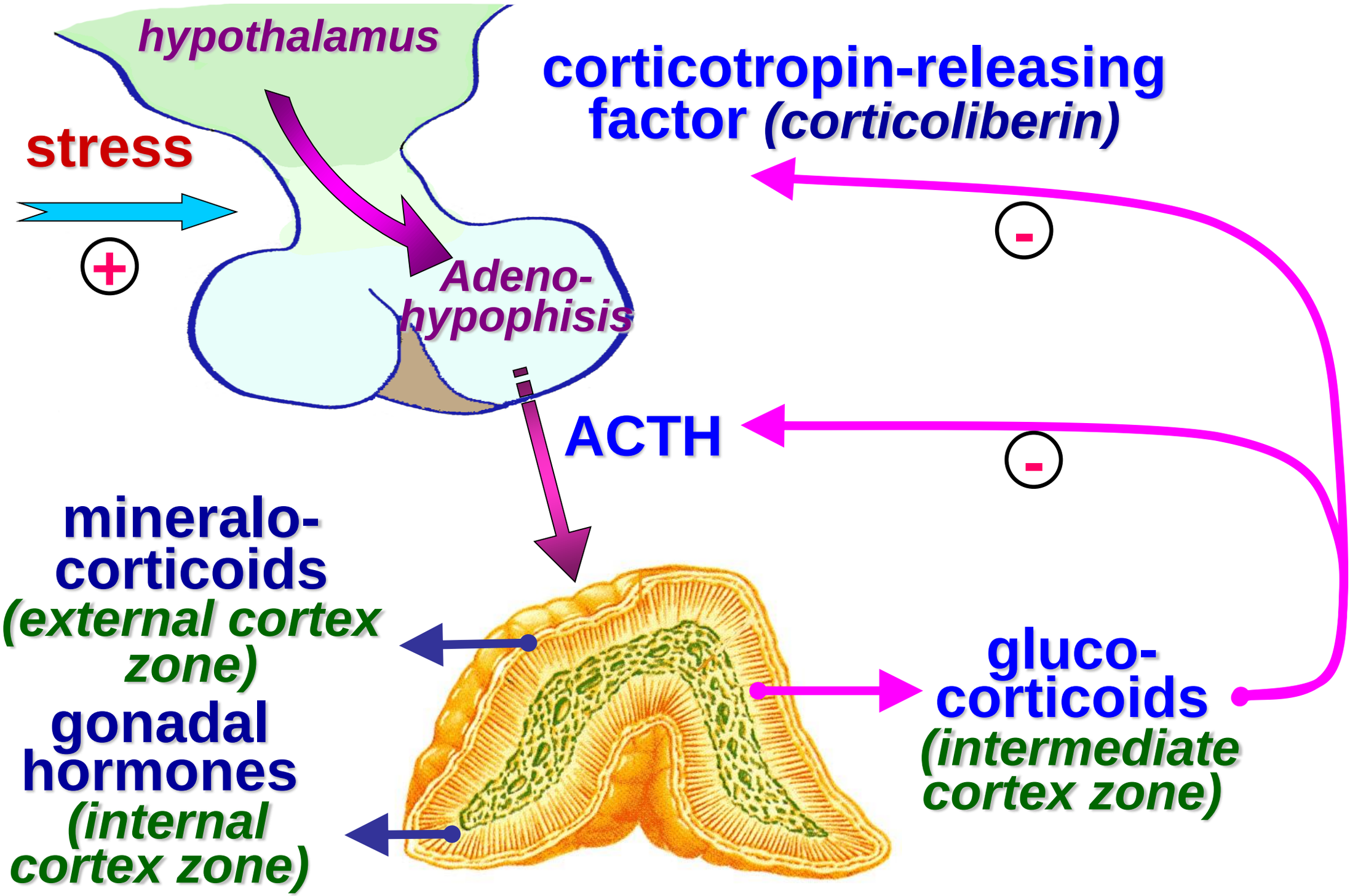
- allergic reactions (leucopenia, dermatitis)
- cardio-vascular disturbances (↑ risk of angina pectoris)
- gastrointestinal disturbances (needs ↓ dose)

biguanides:

- lactic acidosis up to coma
- metallic taste in mouth, heartburn, nausea, vomiting, anorexia (↓ dose or withdraw)

ADRENOCORTICOIDS AND GONADAL HORMONES

ADRENOCORTICTOIDS



MINERALOCORTICOIDS (aldosterone, desoxycorticosterone)

desoxycorticosterone acetate (DOCSA) and fludrocortisone acetate

pharmacodynamics

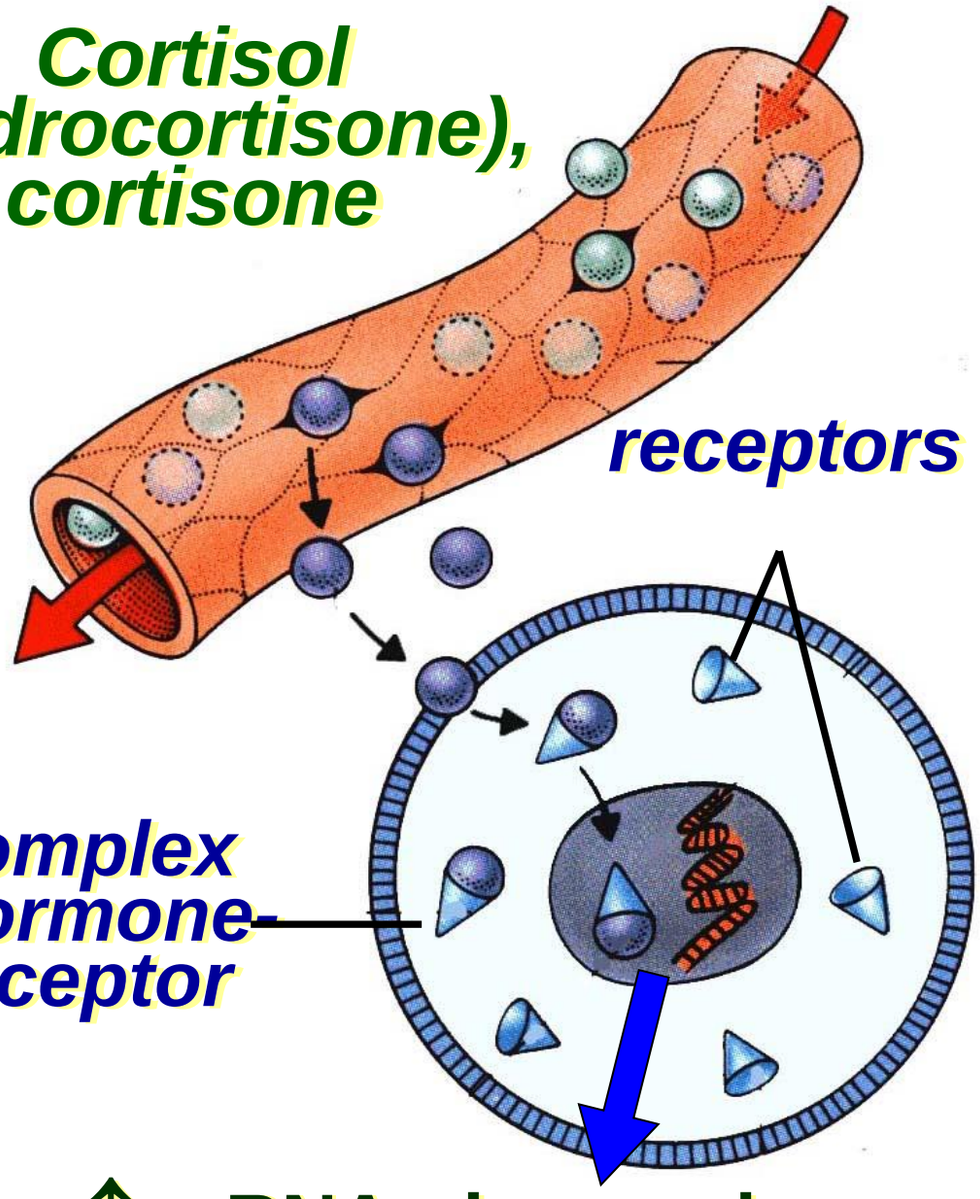
- water-electrolite balance (via target-organs: kidneys, intestine, salivary and sweat glands) – hypernatriemia, hypokaliemia, metabolic alkalosis, ↑ plasma volume, hypertension (↑ reabsorption of Na^+, Cl^-, HCO_3^-, and secretion of K^+ and H^+)
- anabolic action

indications

- adrenal cortex insufficiency (including Addison's disease)
- adynamia, myasthenia

GLUCOCORTICOIDS AGENTS

- **natural:** cortisone acetate, hydrocortisone acetate and hemisucinate
- **synthetic:** prednisolone, prednisone, triamcinolone, dexamethasone, betamethasone etc.



- ↓ or ↑ mRNA, depression or regression of the genes
- ↓ or ↑ enzymes, numerous biological effects

GLUCOCORTICOIDS' PHARMACODYNAMICS

- **carbohydrates metabolism** – ↑ hepatic gluconeogenesis and an antagonism for insulin
- **protein metabolism** – «-» nitrogen balance, **catabolism** in lymphatic nodes, thymus, spleen, skin, adipose and connective tissues, muscles (their involution, worsening of the wound healing), in bones (osteoporosis), **anabolism** in the liver (↑ size)
- **lipid metabolism** – ↑ fatty acids level, redistribution of adipose tissues (on extremities - lipolysis, while on chest, neck, face, trunk - lipogenesis)
- **water-electrolyte balance** – ↑ Na^+, H^+, H_2O reabsortion and increase Ca^{2+}, K^+ excretion (demineralization, osteoporosis)

GLUCOCORTICOIDS' PHARMACODYNAMICS (continuation)

- **CVS** – «+» inotropic effect, ↑ susceptibility of the blood vessels for catecholamines, ↑ angiotensin action
- **peripheral blood** – lymphocytopenia, eosinopenia, ↑ erythrocytes, thrombocytes, granulocytes
- **CNS** – ↑ mood, euphoria, hyposomnia
- **GIT** – ↑ pepsin and hydrochloric acid
- **endocrinic system** – ↓ hypothalamus-pituitary-suprarenal system, TTH, FSH, gonadal hormones
- **organism development** – ↑ surfactant

GLUCOCORTICOIDS' PHARMACODYNAMICS (continuation)

- **anti-inflammatory (all phases):**
  - ✓ ↓ phospholipase A_2 ⇒ ↓ prostaglandins and leukotrienes
  - ✓ ↑ neutrophils, ↓ lympho-, monocytes, eosinophils
  - ✓ ↓ release of histamine and kinins, capillaries permeability ⇒ stabilizing of cellular membrane, ↓ edema
  - ✓ ↓ function of neutrophils and macrophages (interleukin 1, 6, 8, tumor necrosis factor etc.) ⇒ ↓ cellular reaction of inflammation
  - ✓ ↓ proliferation of fibroblasts, collagen synthesis ⇒ ↓ proliferation phase, scar formation, wound healing

GLUCOCORTICOIDS' PHARMACODYNAMICS (ending)

- **immunosupressive:**
  - ✓ antagonists of immuno-stimulating hormones (growth hormones, thymus factors, androgens)
  - ✓ ↓ lymphoid tissue proliferation; in large doses – involution of immuno-competent organs
  - ✓ ↓ cellular immunity – ↓ migration into the blood of stem cells of T- and B-lymphocytes from bone marrow and thymus; ↓ activity of T- and partially B-lymphocytes ⇒ ↓ production of antibodies
- **anti-allergic:** ↓ histamine release, desensibilization of H_1-receptors
- **anti-shock and anti-toxic:** ↑ metabolic activity of the liver, ↓ permeabiligy of BBB for toxins etc.

GLUCOCORTICOIDS' PHARMACOKINETICS

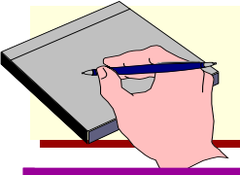
Absorption:

- **at oral intake – quickly and almost completely in the small intestine; K_{max} In the blood through 0,5-1,5 h**
- **injection: I.M. and I.V. – water-soluble (hemisucinate and phosphates); C_{max} I.M. after 1-2 hrs; I.M. – suspension (acetates), absorption is slow (hrs) and prolong (weeks)**

Protein binding: **by albuminates; natural – 90 %; synthetic – 40-60 %**

Biotransformation: **by hepatic microsomal enzymes with production of glucuronides and sulfates. $T_{1/2}$ natural < synthetic. Cortisone and prednisone undergo presystemic metabolism with formation of active metabolites (hydrocortisone, prednisolone). Fluorinated glucocorticoids (triamcinolon, dexamethasone, betamethasone) are metabolized slower, than others ($T_{1/2}$ > in 2-3 times)**

Excretion: **via kidneys**

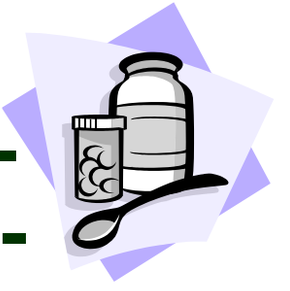


GLUCOCORTICOIDS

agents	glucocorticoid activity	mineralocorti-coid activity	Equivalent doses (mg)
short-acting			
hydrocortisone	1	1	20
cortisone	0,8	1	25
prednisone	4	0,8	5
prednisolone	4	0,8	5
intermediate-acting			
triamcinolone	5	-	4
long-acting			
dexamethasone	30	-	0,75
betamethasone	30	-	0,6

INDICATIONS FOR GLUCOCORTICOIDS

- **substitutive therapy** in adrenal cortex insufficiency (Addison disease, tumor, organs' transplantation etc.) – 10-25 mg of hydrocortisone or another glucocorticoid agent (2/3 daily doses in the morning (!) and 1/3 – in the evening or once a day in the morning);
- **inhibitory therapy** in adrenogenital syndrome for suppression of ACTH (in therapeutic doses 3 times a day or 1/3 – in the morning, 2/3 of doses – in the evening);
- **pharmacodynamic therapy** (as sympto-matic or pathogenetic treatment for the anti-inflammatory, anti-allergic or immunosuppressant effects)



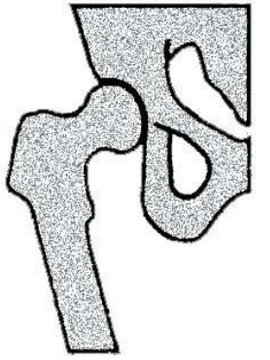
PHARMACODYNAMIC THERAPY BY GLUCOCORTICOIDS

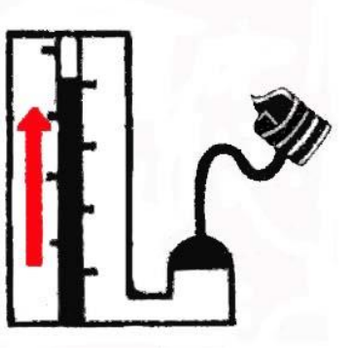
- collagenosis (SLE, polyarthritis etc.)
- allergic diseases (angioedema, hey fever, anaphylactic shock etc.)
- diseases of kidneys (glomerulonephritis etc.)
- disease of blood (auto-immune hemolytic anemia, thrombocytopenic purpura etc.)
- pulmonary diseases (bronchial asthma)
- gastro-intestinal tract diseases (Crohn's disease, some forms of liver cirrhosis etc.)
- neurological disturbances (cerebral edema, multiple sclerosis)
- ophthalmic diseases (allergic keratitis, conjunctivitis etc.)
- dermal diseases (nodal erythema, eczema etc.)
- cancer (leukemia and lympho-proliferative diseases)
- Inflammation of the bones and joints (arthritis etc.)
- infection's diseases (tuberculosis pericarditis etc.)
- severe shock conditions

GLUCOCORTICOIDS' ADVERSE EFFECTS

suppression of hypothalamo-pituitary-suprarenal axis (iatrogenic Cushing's syndrome) !

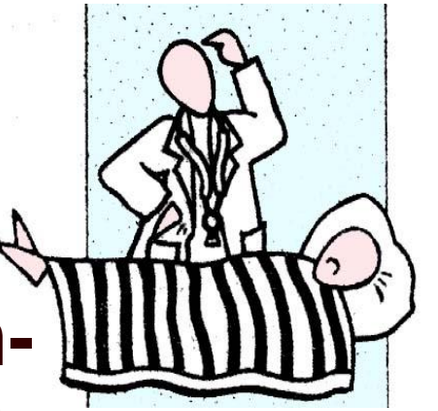
- **endocrinic system** (hyperglycemia, growth retardation in children, dysmenorrhea)
- **locomotor system** (miopathy, osteoporosis, pathologic bone fractures, aseptic necrosis)
- **gastro-intestinal tract** (peptic ulcers of stomach and duodenum)
- **CVS** (hypertension)
- **skin** (thinning of the skin, striae, moon-like face)
- **regeneration** (↓ wound healing)

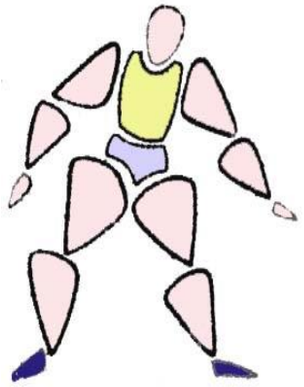


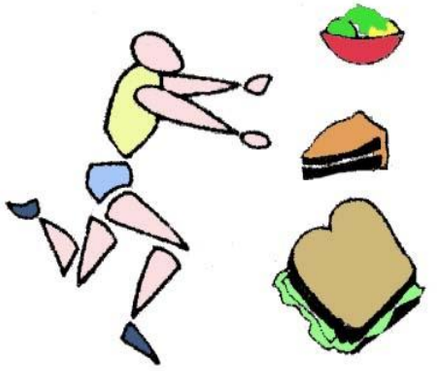


GLUCOCORTICOIDS' ADVERSE EFFECTS (continuation)

- CNS (insomnia, mood disturbances, psychosis)
- water-electrolyte balance (edema, hypokaliemia)
- eyes (glaucoma, cataract)
- immunity ("blunting" of the symptoms of infectional diseases)
- metabolic (hyperglycemia, hyperlipidemia, raising of appetite, adipose tissue redistribution (moon-like face etc.), negative nitrogenous balance)
- blood (↑ coagulation etc.)
- withdrawal syndrome





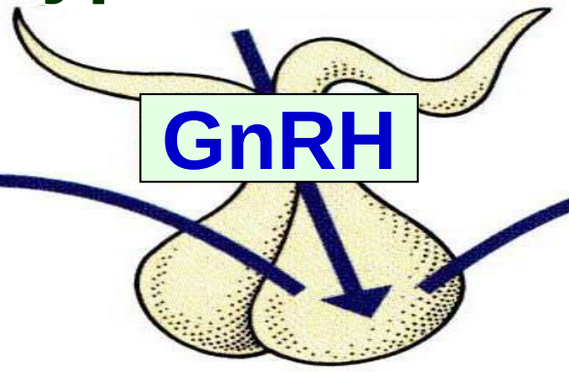


RULES OF THE GLUCOCORTICOIDS' PRESCRIPTION

- individual dosage adjustment !
- single enormous doses are harmless
- short-course therapy (2-3 days) by moderate doses is safe
- treatment that last > 1 month with moderate doses could cause serious adverse effects
- in the case of long-lasting treatment drugs' withdrawal should be step-wise (adrenal cortex recovery take up to 9 months)

FEMALE GONADAL HORMONES

hypothalamus



GnRH

FSH

LH

follicle development

ovulation

development of corpus luteum

estrogens (estradiol, estrone, estriol)

progesterone

development of female sexual organ, endometrium proliferation, functioning of skin, blood vessels, bones, ↑ blood coagulation etc.

preparation for pregnancy

CLASSIFICATION OF FEMALE GONADAL HORMONES

- **estrogens (follicles' hormones):**
  - **steroidal structure:** ***estrone, estriol, estradiol benzoate and dipropionate, ethinyl estradiol;***
  - **non-steroidal structure :** ***synestrol, diethylstilbestrol propionate etc.***
- **gestagens or progestins (hormones of corpus luteum) –** ***progesterone, oxyprogesterone, levonorgestrel, norcolut, pregnin etc.***
- **combined (estrogen-gestagen, estrogen-gestagen-antiandrogen) – oral contracep anti-climax agents** ***(clinorm etc.)***

ESTROGENS AND ANTI-ESTROGENS

indications for estrogens

- primary hypogonadism
- amenorrhea, dysmenorrhea
- climax, osteoporosis
- uterus bleeding
- breast cancer (> 60 yrs)
- prostate cancer

adverse effect of estrogens

- ↑ blood coagulation, thromboembolism, edema
- liver disturbances, nausea, vomiting
- post-menopausal uterus bleeding
- breast tenderness, hyperpigmentation
- in men can be feminization, ↓ libido, potency
- cancerogenic

anti-estrogens

- breast cancer (tamoxifen)
- Infertility (clomifen)
- for ovarium suppression (danasol)

GESTAGENS (PROGESTINS) AND ANTIPROGESTINS

indications for gestagens

- as contraceptives
- for suppression of ovarium function (endometriosis, dysmenorrhea, hirsutism, bleeding)

adverse effects of gestagens

- ↑ BP, risk of the myocardial infarction
- allergic reactions
- dyspepsia
- ↓ libido, dysmenorrhea

Antigestagens

- for termination of early pregnancies (mifepristone)

CONTRACEPTIVES

- **combinations of estrogens and progestins:**
  - **monophasic – rigevidon, non-ovlon, minisistone, diane-35 etc.**
  - **biphasic – anteovin**
  - **triphasic – trisiston, tri-regol etc.**
- **monocomponent – *microdoses of progestins* (mini-pills): continuin, norgestrel, microlut etc.;**
- **postcoital progestins: levonorgestrel /postinor/;**
- **depo-contraceptives : *by injection* (depo-provera /medroxyprogesterone acetate/), *by implantation* (levonorgestrel /norplast/);**
- **vaginal contraceptives (spermicides): benzalkonium chloride, nonoxynol etc.**

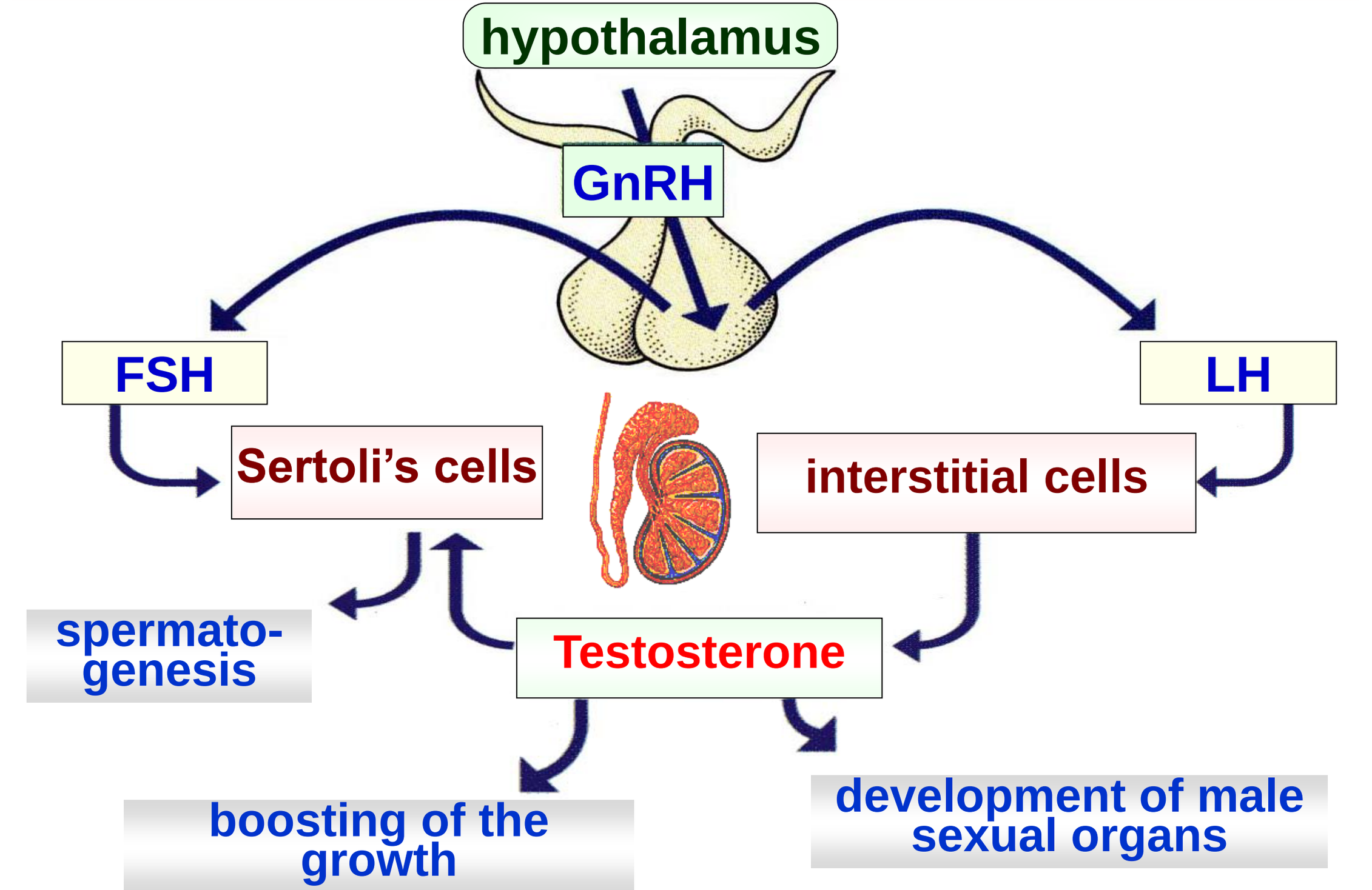
ADVERSE EFFECTS OF THE CONTRACEPTIVES

- **insignificant (need drug's change or ↓ dosage):**
  - ✓ **nausea, breast tenderness, bleeding and oedema (estrogens)**
  - ✓ **headache**
  - ✓ **disturbances of serum proteins, thyroid gland, suprarenal gland**
- **mild degree (need to cancel):**
  - ✓ **intensive bleeding (25 % of the patients)**
  - ✓ **↑ body weight, hirsutism, acnea (those that include androgen-like agents)**
  - ✓ **hyperpigmentation (after 8 yrs in 40 %)**
  - ✓ **vaginal infection, urethra dilation**
  - ✓ **amenorrhea after the cancellation of administration**

ADVERSE EFFECTS OF THE CONTRACEPTIVES (continuation)

- **heavy:**
  - ✓ **vascular:**
    - **venous thromboembolism (in 3 times more often) – *estrogens***
    - **myocardial infarction**
    - **cerebrovascular disturbances (stroke)**
    - **hypertension (in 3-6 times more often)**
  - ✓ **disturbance of gastro-intestinal tract: cholestatic jaundice, cholecystitis**
  - ✓ **depression (in 6 % of the patients)**
  - ✓ **cancerogenic**

MALE GONADAL HORMONES



ANDROGENIC AND ANTIANDROGENIC AGENTS

indications for androgens

- androgen substitutive therapy (hypogonadism, impotence)
- breast cancer
- climax, uterus bleeding

adverse effects of androgens

- disturbances of spermatogenesis , atrophy of testis
- ↑ body temperature, oedema, hepatotoxicity
- in the women – masculinization

Androgens

- for suppression of androgens' production (prostate cancer) – analogues of gonadotropin-releasing hormones (leuprolid etc.) and antiandrogens (finasteride, cyproterone, flutamide)

ANABOLIC STEROIDS

- **steroidal – retabolil, phenoboline, methandrostenolone etc.**
- **non-steroidal – riboxin, potassium orotate, pentoxyl, methyluracil etc.**

indications

- **exhaustion states with protein loss (cachexia, hypotrophy after burn wounds, surgery, infections etc.)**
- **in traumas for hastening of bones recovery, osteoporosis**
- **angina pectoris, myocarditis and other cardiac diseases**
- **hepatic and renal diseases with hypoproteinemia, stomach ulcer**
- **post-hemorrhagic and aplastic anemia, leucopoenia**

ANABOLIC STEROIDS

– testosterone analogues with reduction of their androgenic properties comparatively with testosterone and retention of their anabolic features

pharmacodynamics

- **protein metabolism (glucocorticoids' antagonists):**
  - ✓ **↑ utilization of meal proteins ⇒ ↓ their excretion, nitrogen retention**
  - ✓ **↑ protein synthesis, including skeletal muscles, ↑ their size and strength; ↑ bloodflow**
  - ✓ **↑ protein synthesis in myocardium and kidneys**
  - ✓ **↑ anti-toxic and protein-synthesized function of the liver**
  - ✓ **↑ erythropoiesis, hyperplasia of the bone marrow**
  - ✓ **↑ bone tissue synthesis**
- **carbohydrate and lipid metabolism: hypolipidemia, ↓ lipoproteids and phospholipids level**

ADVERSE EFFECTS OF ANABOLIC STEROIDS

- **endocrinic system and metabolism:**
  - ✓ ↑ insulin, hypoglycemia, risk of diabetes mellitus development
  - ✓ alopecia
  - ✓ in men – testis atrophy, ↓ spermatogenesis, libido, gynecomastia (reversible if not longer than 6 months and irreversible if longer)
  - ✓ in women – acnea, virilism, uterus atrophy, infertility etc. (some are irreversible)
- **liver:** cholestatic hepatitis, tumor (in 80 % persons who misuse)
- **urogenital system:** urolithiasis, renal tumor
- **CNS:** nervousness, mood disturbances, insomnia
- **CVS:** ↑ BP, oedema, arrhythmia
- **musculature, skin:** ruptures of ligaments, degeneration of tendons, arthritis etc.