Odesa National Medical University
Department of Pharmacology and Pharmacognosy

AGENTS ACTING ON ERYTHROPOESIS, LEUCOPOIESIS AND BLOOD COAGULATION. BLOOD SUBSTITUTES

COAGULATION

I stage – activation of the thrombocytes' hemostatsis

trauma, injury

distraction of tissues & vessels

adhesion & aggregation of platelets → release of vasocontrictors → vasocon-striction

formation of thrombocyte fuse

II stage – activation of serum hemostasis

internal path	external path
serum factors + enzyme activity of collagen	serum factors + tissue factor (III)

1 phase

formation of prothrombinase

2 phase

prothrombin → thrombin

thrombin formation

3 phase

fibrinogen → fibrin

formation of fibrin clot

III stage – thrombus retration

retractive enzyme

retraction of thrombus

TYPES OF THE CLOTTING DISTURBANCES

- ↑ coagulation & thrombus formation — hypercoagulation & development of thrombus syndrome
- ↓ coagulation & thrombus formation — hypocoagulation and development of hemorrhagic states
- phased coagulation disturbances – disseminated intravascular coagulation: hypercoagulation phase followed by hypocoagulation

HEMOSTATIC AGENTS

- **coagulants:**
  - ***direct-acting: local* – thrombin, hemostatic collagen sponge, etc; *systemic* – agents of clotting factors (fibrinogen, antihemophilic factors VIII, IX, cryoprecipitate etc.)**
  - ***indirect-acting:* vicasol /menadione/, phytonadione, ethamsilate /dicinone/**
- **inhibitors of fibrinolysis:**
  - ***synthetic:* aminocaproic acid, amben**
  - ***animal origin:* aprotinin (contrycal, gordox)**
- **aggregates: calcium salts, serotonin adipinate**
- **thrombus-formating: decilate**
- **coagulants of animal & plant origin: gelatinol, water pepper, viburnum etc.**
- **heparin antagonist: protamine sulfate**

DIRECT-ACTING COAGULANTS

thrombin, hemostatic sponge

- ***mechanism of action*** **– thrombin is the IIa clotting factor; covert fibrinogen into fibrin**
- ***is used*** **only locally! on bleeding organ during or after operation**

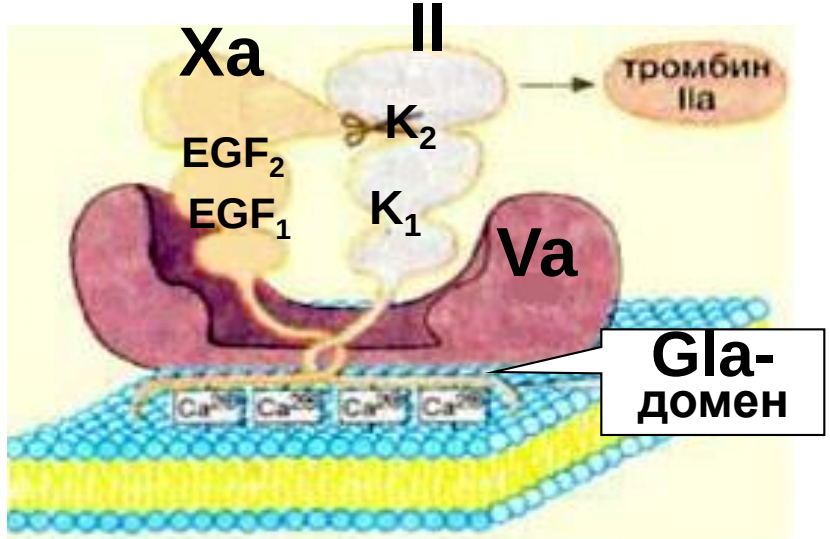
fibrinogen

- ***mechanism of action*****– I clotting factor (glycoprotein)**
- ***is used*** **for the first aid at bleeding related to its lack: acute fibrinolysis during pulmonary, pancreatic, prostate, thyroid surgery; at traumatic, burn shock, late stages of disseminated intravascular coagulation; given as 1-2 % sol. I.V. by drops**
- ***adverse effects*** **– thrombosis, allergic reaction**

INDIRECT-ACTING COAGULANTS

vitamin K – phytonadione (K_1) vicasol /menadione/ (water-soluble K_3)

- ***mechanism of action*** – **lipid-soluble K (daily demand=100 mcg): K_1 – phyloquinone in meal (leafy green vegetables), K_2 – menaquinone is synthesized by intestinal microflora; K_3 – menadione, synthetic water-soluble); participate in decarboxylation glutamate residues in prothrombin (II), proconvertin (VII), factors IX & X. These residues (domens) need for conversion in active condition (bind calcium and attach to phospholipids)**



VITAMIN K AGENTS

phytonadione (K_1), vicasol /menadione/ (K_3)

- ***pharmacokinetics*** – absorption of K_1 take place in small intestine, K_2 – in bowel (bile acids are essential!); 20-30 % vit. K after oral intake are not absorbed and excreted

- ***indications*** – preventive therapy (120 mcg, pregnancy, infancy, aged people, surgery, cancer chemotherapy etc.) & treatment (10-15 mg, hemorrhages and hypoprothrombinemia: liver and GI-tract dysfunction etc; overdosing of indirect-acting anticoagulants. Onset of the therapeutic effect 24 hrs. BVicasol is less effect than phytonadione.

- ***adverse effects*** – ↑ sweating, redness (face), at I.V. – dyspnoe, chest tightness, allergic reaction ⇒ administration is very slow!; vicasol – also methemoglobinemia, RBC hemolysis

INDIRECT-ACTING ANTICOAGULANTS

ethamzilate (dicinone)

- ***mechanism of action*** – **hemostatic (↑ tissue thromboplastin level + ↑ level of platelets & their release from bone marrow); angioprotective (inhibit hyaluronidase activity, ↑ capillaries resistance, ↓ their permeability)**
- ***therapeutic uses*** – **parenchyma and capillary hemorrhages, thrombocytopenia, prevention of postsurgery bleeding, diabetic micro angiopathy**
- ***adverse effects*** – **dyspepsia, redness of face, paresthesia, ↓ BP**

desmopressin

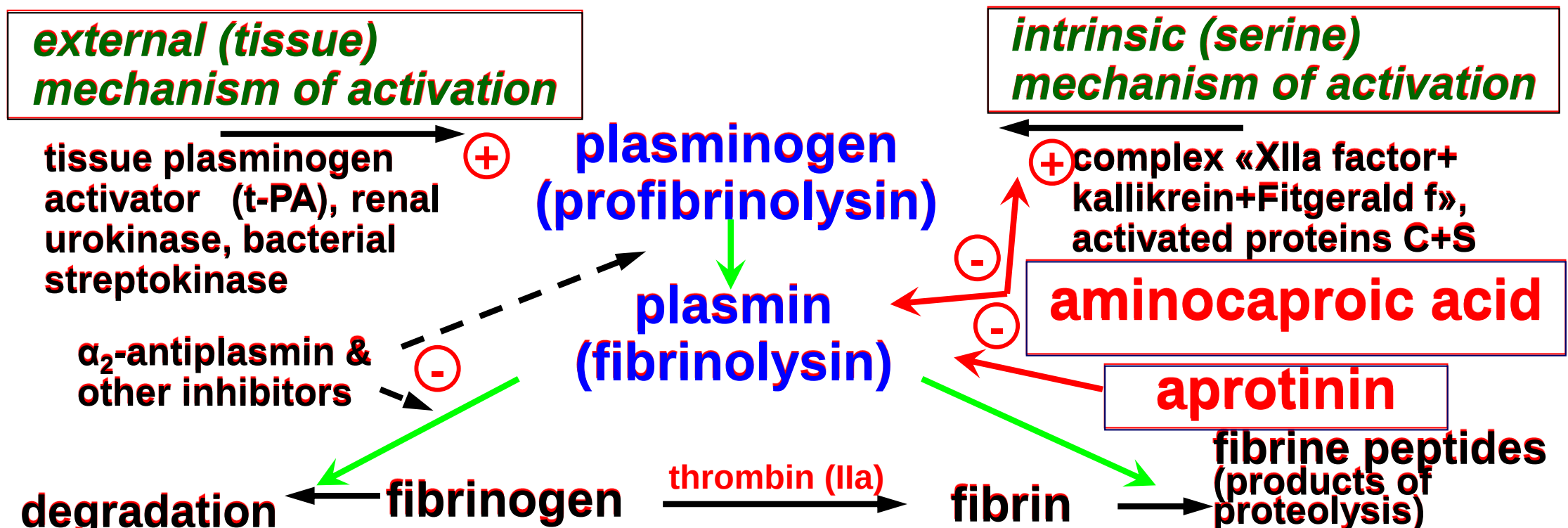
- ***mechanism of hemostatic action*** – **↑ synthesis of Willebrands factors & VIII**

INHIBITORS OF FIBRINOLYSIS

- *synthetic* – aminocaproic acid, amben
- *animal origin* – aprotinin (contrycal, gordox, trasilol)

reasons of generalized fibrinolysis

- hyperactivity of fibrinolysis in response to ↑bloodcoagulation
- releasing of tissue proteases at massive tissue damage of lungs, pancreas, thyroid gland etc
- septicemia with ↑ toxins & enzymes like streptokinase



INHIBITORS OF FIBRINOLYSIS

synthetic (acids relative to lysine) – aminocaproic acid, amben

- ***mode of action:***
  - ✓ ↓ **fibrinolysis** due to ↓ plasminogen conversion into plasmin **thanks to competitive block** aof active center of **plasminogen activator** + ↓ **plasmin**
  - ✓ **kinines' inhibition (bradykinine)** and some factors of complement system (produced at hypoxia, tissue damage, inflammation, allergic reactions)
  - ✓ **anti-shock** (↓ proteolytic enzymes and ↑ liver detoxification)

INHIBITORS OF FIBRINOLYSIS

synthetic

- ***indications:*** **excessive fibrinolysis associated with intensive bleeding:**
  - ✓ **overdosing of fibrinolytics**
  - ✓ **massive blood transfusion**
  - ✓ **traumas (operations) of organs rich in plasminogen activator (lungs, brain, prostate, pancreas, thyroid gland)**
  - ✓ **placenta exfoliation, sepsis**
  - ✓ **extracorporeal circulation etc**

- ***adverse effects:*** **low-toxicity; возможно dizziness, nausea, diarrhea**

INHIBITORS OF FIBRINOLYSIS

animal origin (polypeptides from cattle tissues) – aprotinin (contrycal, gordox)

- ***mechanism of action:*** **inhibition of serum and tissue (plasmin, kallikrrein, trypsin), through formation of non-active complex, also ↓ its production from proactivators ⇒ ↓ blood fibrinolysis and tissue proteolysis in inflammation area, massive injure**
- ***indications*** **(treatment & prevention):**
  - ✓ **bleeding, caused by hyperfibrinolysis (prostate and pulmonary surgery, pulmonary and lipid embolism etc.)**
  - ✓ **acute pancreatitis**
  - ✓ **shock (endotoxic, burning, hemorrhagic)**

INHIBITORS OF FIBRINOLYSIS

animal origin **(polypeptides from cattle tissues) –**
aprotinin (contrycal, gordox)

- ***adverse effects*:**
  - ✓ **CVS: hypertension and/or tachycardia**
  - ✓ **allergic reaction: skin rash, rhinitis, bronchospasm, anaphylactic shock**
  - ✓ **CNS: psychosis, mental confusion**
  - ✓ **GIT: rapid infusion – nausea, vomiting**
  - ✓ **local reaction: prolonged infusion – thrombophlebitis**
  - ✓ **embriotoxicity**

AGGREGANTS

calcium chloride and gluconate

- ***mechanism of action:*** **calcium directly stimulates aggregation and adhesion thrombocytes, promotes formation of thrombin and fibrin**
- ***indications:***
  - ✓ **for decreasing of vascular permeability (at hemorrhagic vasculitis)**
  - ✓ **as hemostatic for pulmonary, gastric, nasal bleeding;**
  - ✓ **transfusion of citrated blood, blood substitutes**
- ***adverse effects:*** **during rapid I.V. injection there can sensation of warmth (“hot injection"); cardiac arrest, ↓BP; s.c. injection – tissue necrosis**

AGENTS THAT INCREASE COAGULATION & DECREASE FIBRINOLYSIS

- **anticoagulants:**
  - ***direct-acting:*** **heparin, enoxaparin, hirudin, sodium citrate**
  - ***indirect-acting:*** **пneodicumarin, syncumar, phenylin, warfarin**
- **fibirinolytics:**
  - ***direct-acting:*** **fibrinolysin, heparin, trypsin**
  - ***indirect-acting:*** **streptokinase, streptodecase, urokinase, alteplase**
- **antiaggregants:** **aspirin, dipyridamol, pentoxyphyllin, ticlopidine, lamifiban**

DIRECT-ACTING ANTICOAGULANTS

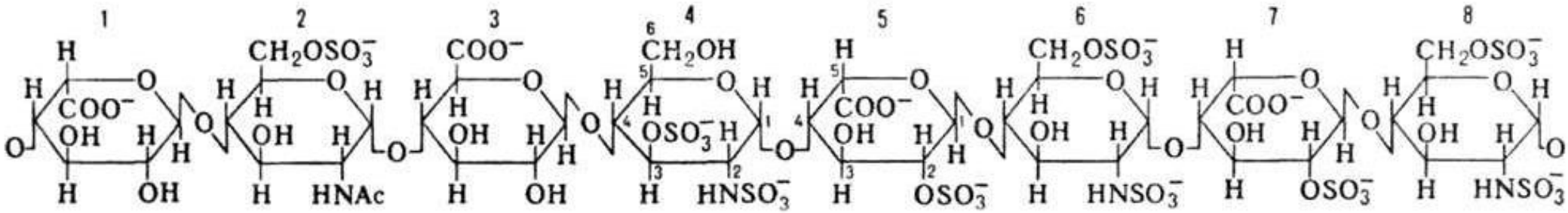
heparin and low-molecular weight heparins (fraxiparin, enoxaparin); hirudin; sodium citrate etc.

classification according to mechanism of action

Thrombin inhibitors (IIa factor):

- **direct-acting - don't need antithrombin III (bind with thrombin active centre: hirudin (from the leech)**
- **indirect-acting (in complex with antithrombin III): heparin and its derivatives**

HEPARIN



– anionic glycosaminoglycan, mixture of sulfated mucopolysaccharides, with different molecular weight – from 3000 to 40000 Da (высокомолекулярных); it possesses strong acid properties due to sulfuric acid residues Present in mast cells

source

- **from porcine intestinal mucosa or bovine lung tissue; the first Is more active; sodium and calcium salts are equal in activity (**
- **lo-molecular weight heparins are obtained after depolymerization of unfractionated heparin**

ACTIONS OF HEPARIN

- bind with antithrombin III (ATIII), greatly ↑ its activity ⇒ inactivation of thrombin (IIa), prothrombinase (Xa), IXa, XIa, XIIa;
- bind to the receptors of vascular intima and platelets ⇒ ↓ platelets' aggregation
- heparin only catalyze reaction of antithrombin-protease, remaining unchanged: after termination of the reaction it is released from "IIa+ATIII+heaprin" complex and could be used once more, while "IIa+ATIII" complex is eliminated by endothelial system
- for ↓ of thrombin high-molecular weight fractions are required ⇒ unfractioned heparin has antithrombotic and anticoagulant actions; for ↓ Xa factor – low-molecular weight fractions needed ⇒ low-molecular weight heparins possess antithrombotic and almost have no action on coagulation

ACTIONS OF HEPARIN

Diversity of the heparin's effects are linked with its high reactive abiities as polyanion: ↓plenty of enzymes (trypsin, phosphotase etc.), stabilization of endothelium etc.

- **anti-atherosclerotic – «lightening effect», ↓atherogenic agents:**
  - ✓ ↑ **lipoprotein lipase (triglycerides hydrolysis in VLDLP);**
  - ✓ ↓ **proliferation and migration of endothelial and smooth muscle cells into vascular wall**
- **hypoglycemic, immunosuppressive (affect T- & B-lymphocytes cooperation, ↓ complement system)**
- **anti-inflammatory, analgesic, wound-closing (↓ hyaluronidase, ↓ vascular permeability)**
- **potassium-sparing diuretic (↓ aldosteron synthesis)**
- **vasodilative, angioprotective**

HEPARIN'S PHARMACOKINETICS

Administration: **I.V. (bolus and infusion – for treatment), S.C. (umbilical area – prevention), also by inhalation, transdermal; in GIT – undergo inactivation**

Bioavailability: **s.c. heparin – 15-20 %; LMWH – 90 %**

Onset of action: **I.V. – immediately, S.C. – 30 min;**
duration of action **2-6 hrs; LMWH – 8-12 hrs**

Distribution: **quickly (especially I.V.) is reversibly uptaken by vascular endothelium, macrophages; after S.C. bind more strongly ⇒ plasma level is more stable; LMWH poorly bind with plasma protein, endothelium**

Biotransformation: **in endothelial cells & macrophages, then in liver by heparinase**

Excretion: **unchanged and depolymerased via kidney, T1/2 ≈ 1 hr (LMWH ≈ 1,5-4,5 hrs)**

HEPARIN'S USES

- **treatment** acute thrombosis and embolism (acute myocardial infarction, pulmonary, cerebral thrombosis,hypercoagulation phase during disseminated intravascular coagulation etc.) – bolus I.V. 5000-10000 IU, than by drops 900 IU/hr
- **prevention** of thrombosis (surgery, diagnostic manipulation on vessels, heart etc; hemodialysis, extracorporeal circulation; angina pectoris; traumatic shock etc.) – S.C. 5000-10000 IU every 8 or 12 hrs
- **locally:** thrombophlebitis of superficial veins, (heparin as ointment)
- **in complex therapy** atherosclerosis, bronchial asthma, rheumatic fever

HEPARIN USE

optimal therapy

- active partial thromboplastin time – can exceed ↑ N (27-35 sec) in 1,5-2 times
- clotting time – ↑ N (5-7 min) in 2-2,5 times

peculiarity of LMWH

- possess antithrombotic action (less action on coagulation); antiaggregative action
- ⇒ prevention venous thrombosis in orthopedic, surgical, neurological patients
- advantage of pharmacokinetic (higher bioavailability, longer duration) ⇒ is given 1-2 times a day S.C. with no blood clotting control
- rare bleeding and thrombocytopenia

ADVERSE EFFECTS OF HEPARIN

- **hemorrhages** (10-30 % patients), **thrombocyopenia** (6-16 % patients; because of autoimmune reaction; rare arterial thrombosis)
- **allergic reactions** (anaphylaxis, fever)
- prolong use (more than 5 months) **alopecia, osteoporosis** (↑ parathormone), **nausea, diarrhea**

at intensive bleeding I.V. immediately should be given antidote – protamine sulfate (protein obtained from sperm of salmon); 1 mg neutralize 100 IU heparin

INDIRECT-ACTING ANTICOAGULANTS

- coumarin derivative – neodicumarin, syncumar, warfarin
- indandione derivative – phenylin

pharmacodynamic

- alter reduction of vitamin K epoxide in liver microsomes ⇒ ↓ carboxylation of II VII, IX, X factors, and proteins C & S
- ⇒ active *in vivo* only

INDIRECT-ACTING ANTICOAGULANTS

pharmacokinetics

Absorption: **well absorbed in intestive (80-90 %) ⇒ oral intake**

Plasma-protein binding: **90 % !**

Onset of action: **half-life of suppressed clotting factors is long ⇒ delayed onset 24-72 hrs, duration of action 24-72 hrs!**

Biotransformation: **liver microsomal oxidation (P450); some undergo entero-hepatic circulation**

Excretion: **via kidney, T1/2 is different: 2 hrs (neodicumarin), 42 hrs (warfarin)**

Cumulation: **majority is significant**

INDIRECT-ACTING ANTICOAGULANTS

indications

prolong therapy for prevention and treatment of venous thrombosis

- **thrombophlebitis of deep veins;**
- **synthetic cardiac valves;**
- **atrial flutter/fibrillation;**
- **severe CHF;**
- **treatment of acute embolism of pulmonary artery**

INDIRECT-ACTING ANTICOAGULANTS

adverse effects

Treatment under control of prothrombin ratio = 40-50

- hemorrhages (0,9-2,7 %)
- diarrhea, hepatitis, vasculitis, skin necrosis, alopecia
- hereditary resistance to coumarins
- teratogenic

Antidote – vit. K, blood transfusion

principles of therapy

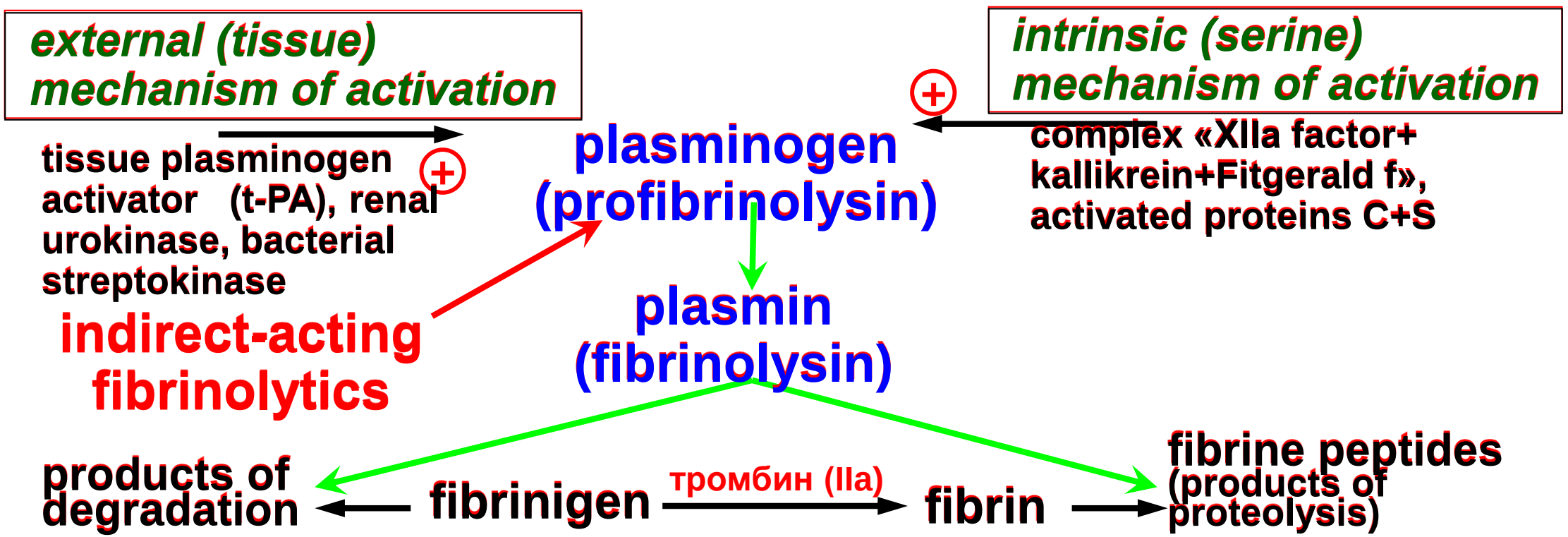
- immediate results – direct-acting anticoagulants
- prolong therapy – indirect-acting anticoagulants
- combination: for 2-4 days after – only indirect-acting anticoagulants

FIBRINOLYTICS

- **direct – fibrinolysin, heparin, trypsin**
- **indirect – streptokinase, streptodecase, urokinase, alteplase**

pharmacodynamics

promote lysis of fibrin thrombus – thrombolysis
(venous better than arterial)



FIBRINOLYTICS

Agent	Source	Molecular weight	Affinity to fibrin	Footnote
Fibrinolysin	Human blood	75 000-120 000	+	Rarely used, remove only fresh v. thrombus
Streptokinase	beta-hemolytic streptococcus	47 000	-	Allergic reactions, teratogenic
Urokinase	Human kidney tissue culture	33 000	+	No antigenic properties
Alteplase	Recombinant tissue plasminogen activator	70 000	+	-»-

FIBRINOLYTICS

indications

- acute myocardial infarction (first 4-6 hrs)
- pulmonary thromboembolism (5-14 days)
- peripheral arterial thrombosis
- thrombosis of vascular by-pass, prosthesis of cardiac valves

adverse effects

- hemorrhages ⇒ control of prothrombin time, fibrinogen level, platelets level
- allergic reactions: reactions of alien proteint (redness of face, chest pain, abdominal pain), fever, angioedema
- hypotension

ANTIAGGREGATE AGENTS

Inducers of platelets' aggregation	Inhibitors of platelets' aggregation
collagen	-
ADP	adenosin
noradrenalin (via α_2)	α_2-adrenolytics
serotonin	Anti-seroton agents
histamine	антигистаминовые средства
thrombin	heparin
Ca^{2+}	Ca^{2+}- channel blockers
cGMP and its inducers	cAMP (via β-receptors and PDE inhibition
arachidonic acid	dextran, albumin
thromboxane A_2	prostacyclin I_2

ANTIAGGREGATE AGENTS

- ✓ ↓ inhibition of thromboxane A_2: COX-inhibitors (aspirin)
- ✓ blockers of receptors on platelets: ADP (ticlopidine); factors that activate platelets (ketotifen, tanacan); serotonin (ketanserin), glycoprotein receptors IIb/IIIa (lamifiban, thyrofiban etc.)
- ✓ inhibitors of PDE + adenosine deaminase (↑cAMP level, cAMP & adenosine in platelets): dipyridamol, pentoxyphyllin
- ✓ ↑ activator of prostacyclin system (↑ prostacyclinic receptors): epoprostenol

ANTIAGGREGATE AGENTS

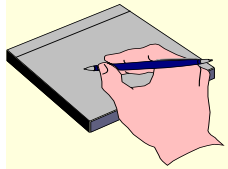
indications

- prevention of thrombosis, hemodialysis
- coronary shunting, cardiac valve surgery,
- angina pectoris, disturbances of peripheral blood flow
- prevention of disseminated intravascular coagulation at intoxications, sepsis (shock)

adverse effects

- hemorrhages, lack of platelets, RBC, WBC
- dyspepsia, ulcerogenic, hepatitis (aspirin, ticlopidine, pentoxyphyllin)
- redness of face, dizziness, headache
- allergic reactions

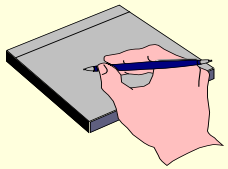
AGENTS, ACTING ON ERYTHROPOIESIS. BLOOD SUBSTITUTES.



CLASSIFICATION OF AGENTS, ACTING ON ERYTHROPIESIS

- **stimulators of erythropoiesis:**
  - **for hypochromic (microcytic) anemia – iron-containing agent for oral and parenteral administration**
  - **for hyperchromic (megaloblastic) anemia– cyanocobalamine, folic acid**
  - **for anemias of different origin (cancer, AIDS, renal failure etc.) – hemopoietic factors of growth: *erythropoietin* (epoetin-alfa), *colony-stimulating factors of granulocyt* (filgrastim) & *of granulocytes-macropha* (molgramostim)**

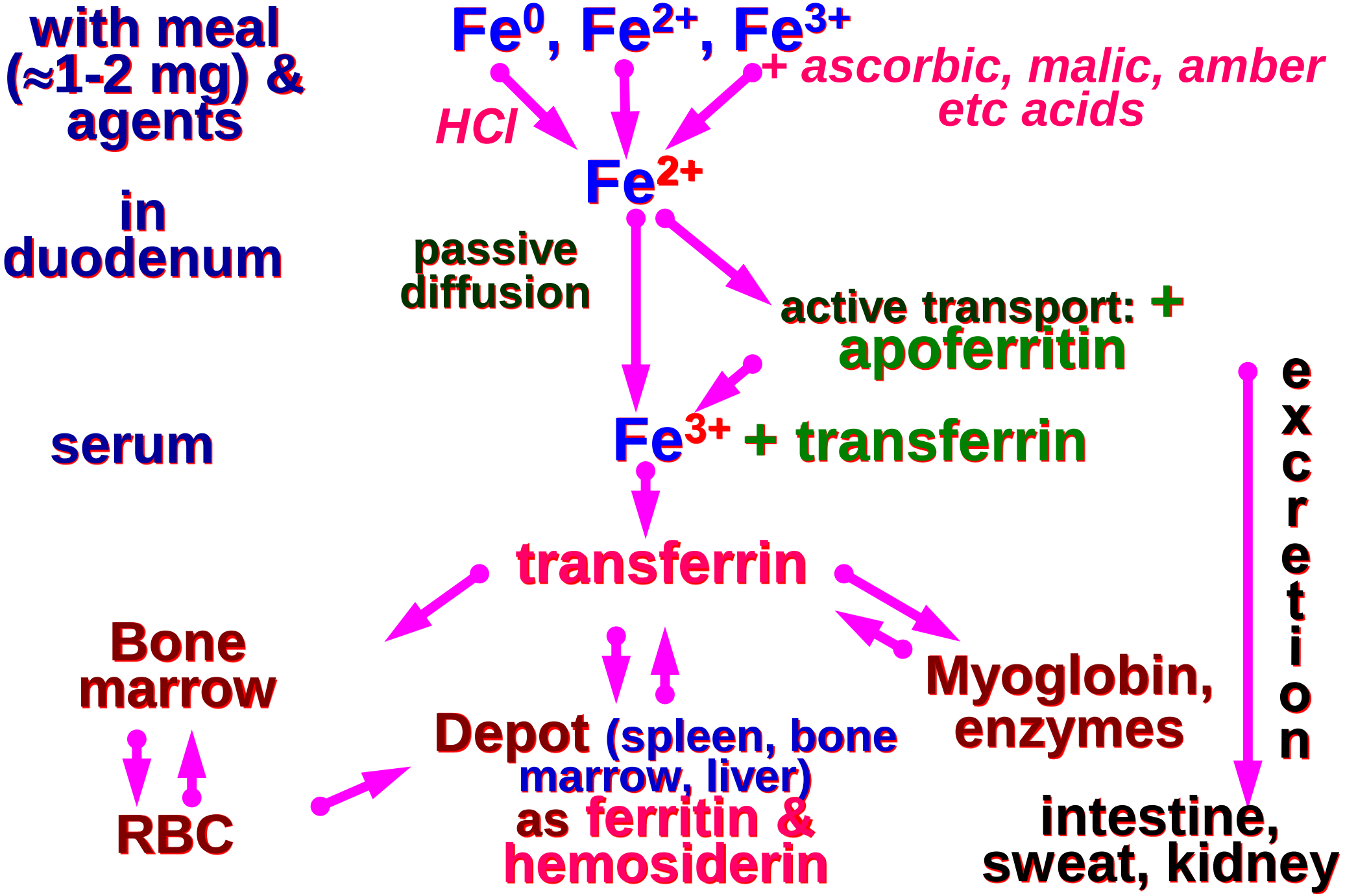
- **inhibitors of erythropoiesis : radioactive phosphorus-32 isotope (^{32}P)**



IRON-CONTAINING AGENTS

- **for oral intake:**
  - ✓ **mono-compound:** **ferronal** ***(ferrous gluconate)***, **actiferrin** ***(ferrous sulfate)***, **heferol** ***(ferrous fumarate)***, **hemofer** ***(ferrous chloride)*** **etc;**
  - ✓ **complex:** **ferroplex** ***(+ascorbic acid),*** **hemostimulin** ***(+copper),*** **multiferrol** ***(+folic acid) etc*****.**
- **for parenteral usage:** **ferbitol** ***(ferric-sorbitol complex),*** **fercoven, ferum-lek** ***(ferric saccharate),*** **coamide** ***(+cobalt)***

PHARMACOKINETICS OF IRON



PRINCIPLES OF IRON-CONTAINING AGENTS THERAPY

- **it isn't wise to treat iron-containing anemia with diet only** (hem iron has the best absorption: 10-30 %; for non-organic iron: 1-10 %)
- **improve absorption:** organic acids, cysteine, proteins; **decrease absorption:** ingestion during or just after meal, milk, eggs, cereal grains, calcium salts, phosphates, antacids, tetracyclines, etc. Better absorption have fumarate, sulfate; worse – gluconate
- **for hemoglobin synthesis daily required 50-100 mg of iron**
- **prescribed iron 1 hr before** (better absorption) **or 2 hrs** (better tolerance) **after meal**
- **the treatment is successful at hemoglobin growth on 1-2 g/l daily**
- **the therapeutic effect – after 2-4 weeks, restoring of iron depot – after 2-3 months**

TOXICITY OF IRON-CONTAINING AGENTS

- **oral forms:** loss of appetite, nausea, vomiting, diarrhea, constipation (binding with hydrogen sulfide); teeth discoloration (powder), dark discoloration of stool (binding with hydrogen sulfide)
- **parenteral forms:**
  - I.M. – headache, painful infiltrates
  - I.V. – phlebitis, dizziness, metallic taste, arthralgia, fever, anaphylactic shock, leukocytosis, nephrotoxicity, hemolysis
- **at prolong us :** hemosiderosis

the treatment should be proved by real iron deficiency!

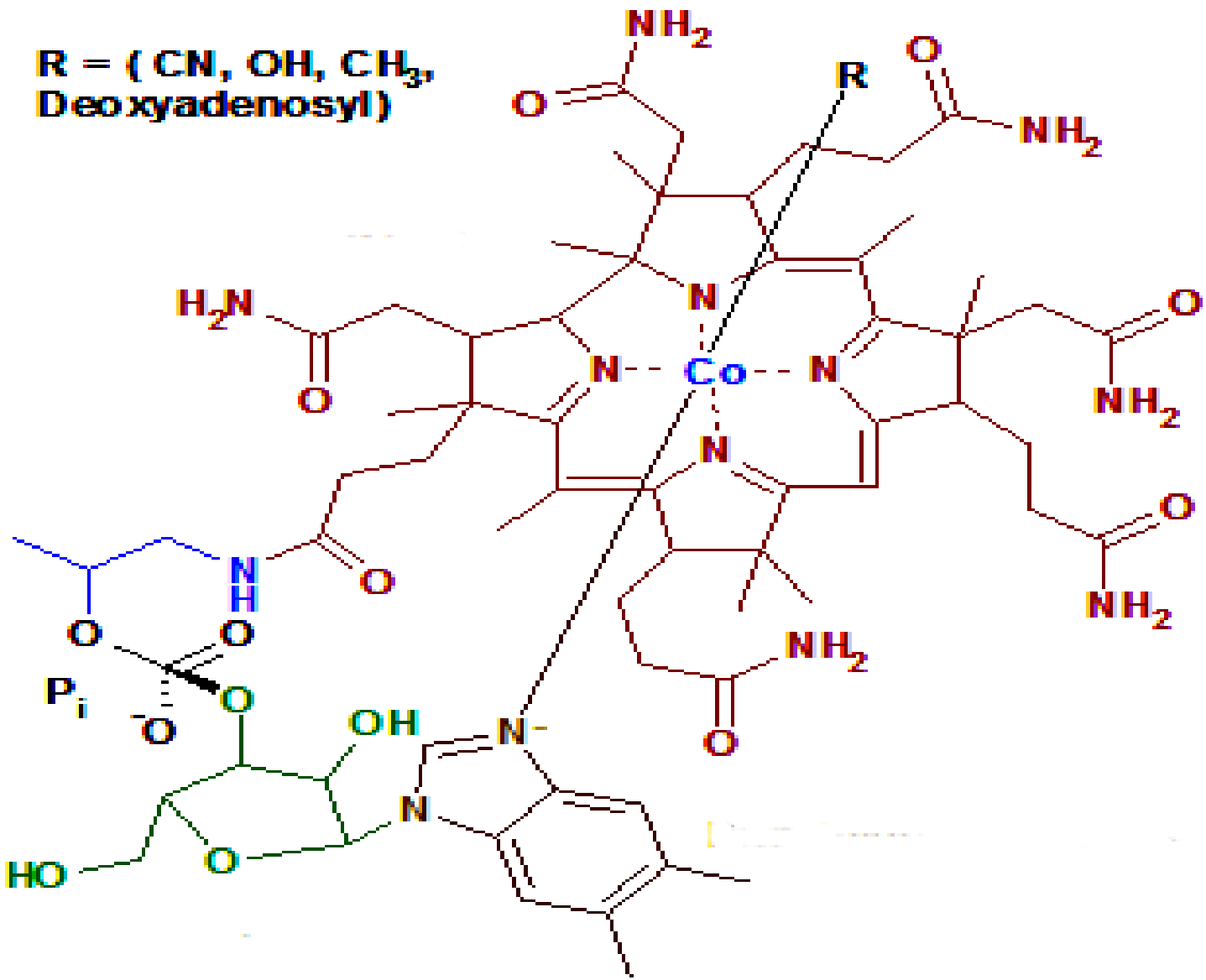
TOXICITY OF IRON-CONTAINING AGENTS

treatment:

- antidote – deferoxamine I.M. or I.V.
- stomach washing with sodium bicarbonate
- correction of collapse, dehydration and acidosis

VITAMIN B_{12}

cyanocobalamin, hydroxycobalamin



Present **– in meat, milk, liver, fish**

synthesized **by intestinal microflora.**

Daily demand **– 2-5 mcg**

CYANOCOBALAMIN

pharmacokinetics

Absorption **– in small intestine and distal part of cecum after binding with intrinsic Castle's factor (intestinal transport is maintained by folic acid)**

Distribution **– transported in blood by plasma protein**

Deposition **– in liver 1-10 mg (store for 2-5 years), in bone marrow etc., daily used 0,5-8 mcg.**

Excretion **with bile into intestine daily 3 mcg; enterohepatic circulation (50-60 % absorbed back); also via kidney (especially at excess)**

CYANOCOBALAMIN

pharmacodynamics

basic reactions:

1. **catalyze conversion of methylmalonic acid into amber acid ⇒ at B_{12} deficiency ↑ content of methylmalonic acid that inhibits myelin synthesis ⇒ neurologic disturbances**

2. **demethylate of tetrahydrofolic acid and regulate:**
   - ✓ **DNA (nucleoproteins) synthesis ⇒ at deficiency there is disturbances of hemopoiesis (DNA replication, maturation of RBC nuclei ⇒ megaloblasts)**
   - ✓ **methionine synthesis: ⇒ synthesis of proteins, phospholipids, choline, betain**

3. **maintaining sulfhydryl (SH) groups in the reduced form**

CYANOCOBALAMIN

pharmacodynamics

- **anabolic action: ↑ protein and nucleic acid synthesis**
- **metabolism: ↑ fat & carbohydrate metamolism, ↓ cholesterol level in blood**
- **activate erythropoiesis (with B_c): DNA replication, maturation of RBC and prevention of their hemolysis**
- **↑ immunity, ↑ blood coagulation**
- **hepatoprotective & neuroprotective actio (cognitive function)**

- **reproduction (↑ spermatozoids level)**

Deficit at: **↓ content of Castle's factor (chronic gastritis), enteritis, pancreatitis, helmenthiasis etc**

CYANOCOBALAMIN

inidcations:

- **substitutive: hypovitaminosis – anemia megaloblastic (pernicious, B_{12}-deficient, Addison-Birmer), neurologic disturbances: myelosis; gait disturbances, dementia etc; glossitis – treatment (with B_c) 100 mcg daily during 1 week, than once a week during 1 month and than once a month during all live; prophylaxis (once a month) at vegetarians, stomach resection etc.**

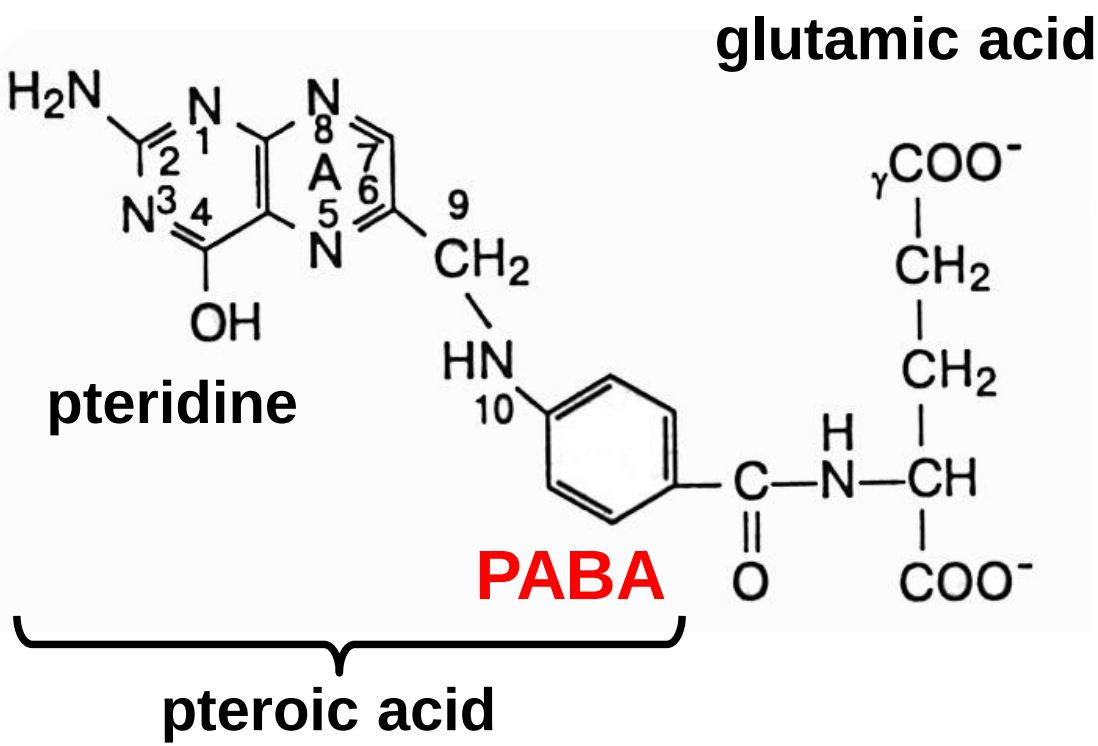
- **pharmacodynamic:**
  - ✓ **anemia (posthemorrhagic, aplastic etc.)**
  - ✓ **polyneuritis, paresis**
  - ✓ **hepatitis, liver cirrhosis**
  - ✓ **myocardiodystrophy**
  - ✓ **skin diseases (psoriasis)**

CYANOCOBALAMIN

adverse effects

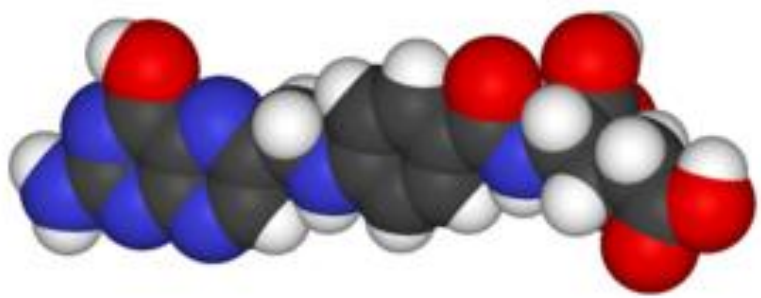
- psychical excitement
- chest pain, tachycardia, arrhythmia (↓ K^+)
- ↑ blood coagulation, ↑ thrombocytes, leucocytes, erythrocytes
- anaphylactic shock (rarely)

FOLIC ACID (B_c)



structure

pteridine heterocycle, PABA, glutaminic acid



Present **– yeast, liver, kidney, cheese, green vegetable, *synthesized* by intestinal microflora**

Daily demand **– 50 mcg, during pregnancy – 400-800 mcg, children 2-12 years – 200mcg**

FOLIC ACID

pharmacokinetics

Absorption: **mainly in form of monoglutamate tetrahydrofolate (THF); alcoholism, spru decrease its absorption; absorption take place in proximal тонкого small intestine кишечника; the best absorption from liver, beer yeast, eggs**

Plasma protein binding **– 60-70 %**

Distribution **– in liver, CSF is the highest concentration; total content – 5-10 мг; actively transported through placenta**

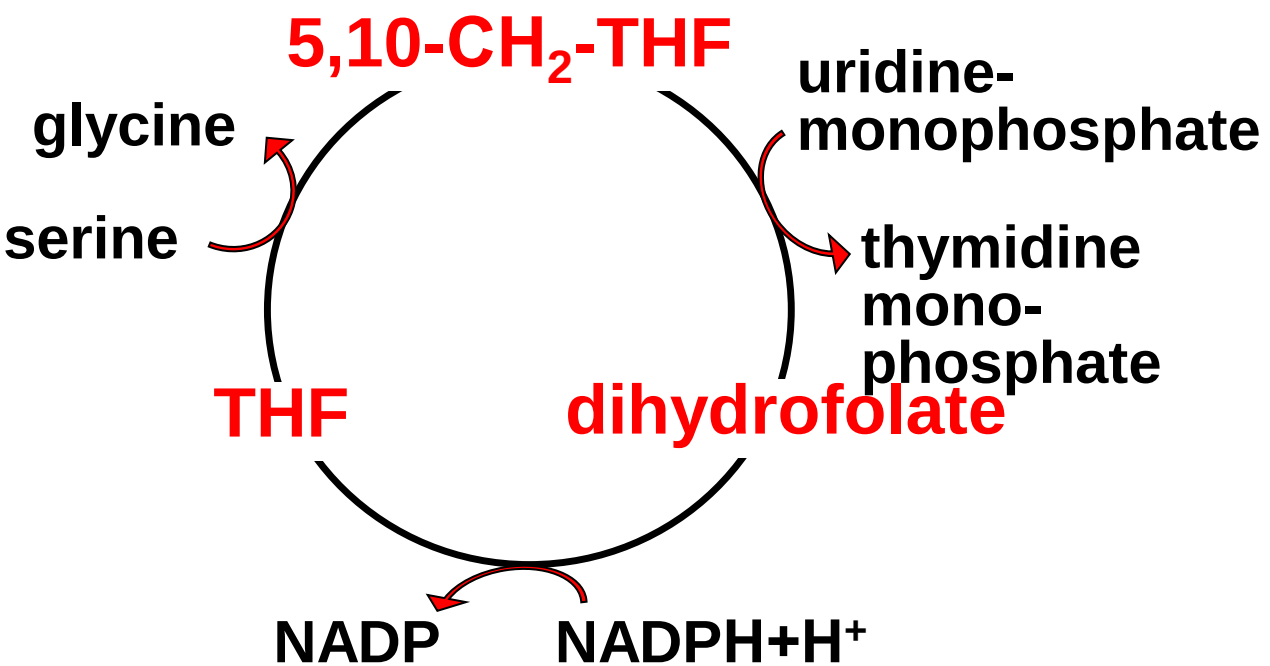
Excretion **via kidney, also with breast milk**

фармакодинамика

main function tetrahydrofolic acid & its derivatives — carrier (acceptor) of monocarbon groups, i.e., methyl from one organic compounds to another

FOLIC ACID

pharmacodynamics



1. conversion of serine into glycine
2. histidine metabolism
3. inclusion of carbon atoms into purine base circle
4. conversion of homocysteine into methionine with B_{12}, as co-factor

↑ erythro-, leuco-, thrombocytosis, plastic and regenerative processes in all organism

FOLIC ACID

indications

- **substitutive: hypovitaminosis** – at chronic alcoholism, liver and intestinal diseases, antibiotics therapy, malabsorption, vit. B_{12}-deficient anemia; for treatment – 15 mg I.M. or orally once a day, for prophylaxis – daily demand
- **adaptative** (pregnancy, breast-feeding, premature infants)
- **pharmacodynamic:**
  - ✓ hypochromic, hypoplastic etc anemias
  - ✓ for stimulation of regenerative processes at peptic ulcer of stomach & duodenum, burns, wounds

adverse effects

- dyspepsia, allergic reaction
- in high doses ↑ CNS excitement up to seizers, ↓ renal function

ERYTHROPOIETIN (α, β, ω)

recombinant human erythropoietin – epoetin-alpha

pharmacodynamics

glucoproteid hormone (synthesized in kidney):

↑ **erythrocytes & reticulocytes, hemoglobin, hem synthesis (after 3-4 weeks of regular use)**

indications

- **anemia of different etiology (chronic renal failure, chemotherapy of cancer, AIDS)**

adverse effects

- ***initial:*** **ifluenza-like symptoms (at the beginning), hypetension, thrombosis, myocardial infarction**
- ***delayed:*** **immune disturbances, tumor of bone marrow**

CLASSIFICATION OF BLOOD SUBSTITUTES according to content

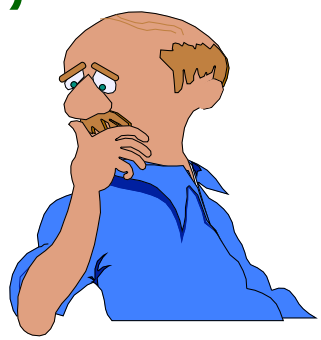
- **protein:** ***from blood cells*** **– erythrocyte, thrombocyte mass ;** ***from plasma*** **– serum, antihemophilic plasma**
- **protein hydrolysate – casein hydrolysate, hydrolysine, aminocrovin etc.; aminoacids derivatives – polyamine**
- **lipid emulsion – lipofundin**
- **colloid:** ***animal origin*** **– gelatinol;** ***plant origin*** **– gumiarabic;** ***synthetic*** **– dextrans (polyglucin, reopolyglycin), polyvinylpyrrolidone derivative (neohemodes)**
- **crystalloid:** ***salt*** **– 0,9 % sodium chloride solution, Ringer's solution, potassium chloride, quantasol, acesol etc; buffer – sodium bicarbonate;** ***solutions of polyatomic alcohols*** **- glucose, fructose, sorbitol**

CLASSIFICATION OF BLOOD SUBSTITUTES according to application

- **hemodynamic *(antishock)* – polyglucin** (T1/2≈3-4 days), **reopolyglucin** (T1/2≈1 day), **geltinol**
- **detoxification – neohemodes, enterodes, repolyglucin, gelatinol**
- **correctors of acid-alkaline and water-salt balance – crystalloid, buffer solutions**
- **for parenteral nutrition – protein hydrolysate, aminoacids' solutions, sugars, lipid emulsion**
- **agents that has oxygen-transport system – perftoran**
- **multifunctional – polyfer** (hemodynamic, hemopoietic), **reogluman** (hemodynamic, hemopoietic, detoxification, diuretic)

ADVERSE EFFECTS OF TRANSFUSION

- **immediate:**
  - ***volume-independent:*** **anaphylaxia, hemolysis, fever, hypercaliemia,**
  - ***at massive transfusion:*** **hypokaliemia, fever, ↓ coagulation**



- **delayed: hypokaliemia, hypothermia, ↓ coagulation**