Odesa National Medical University
Department of General and Clinical Pharmacology and Pharmacognosy

AGENTS ACTING ON CARDIOVASCULAR SYSTEM.

CARDIOTONICS.

ANTIARRYTHMIC AGENTS

CARDIAC GLYCOSIDES (CG) –

(greek. “glikis” - sweat)

Substances of plant origin that consist of 2 parts: nitrous-free (aglycon) and sugary (glycon), which possesses the cardiotonic and cardiotrophic actions, used for the treatment of heart failure

Foxglove
(Digitalis)

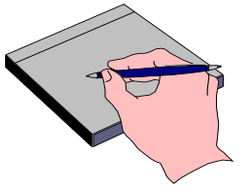
Strophantus
(Strophanthus)

Adonis
(Adonis vernalis)

Lily of the valley
(*Convallaria*)

CLASSIFICATION OF CARDIAC GLYCOSIDES

- **Long-acting agents with significant cumulation :**
  - **Ladyfingers *(Digitalis purpurea)* – digitoxin, cordigit**
- **Intermediate-acting agents with middle cumulative properties :**
  - **Woolly foxglove *(Digitalis lanata)* – digoxin, celanide, lantoside**
  - **Adonis spring *(Adonis vernalis)* – adoniside**
- **Short-acting agents with insignificant cumulation:**
  - **Strophantin *(Strophanthus)* – strophantin**
  - **Lily of the valley *(Convallaria majalis)* – corgylcon, tincture of convallaria**



STRUCTURE OF CARDIAC GLYCOSIDES

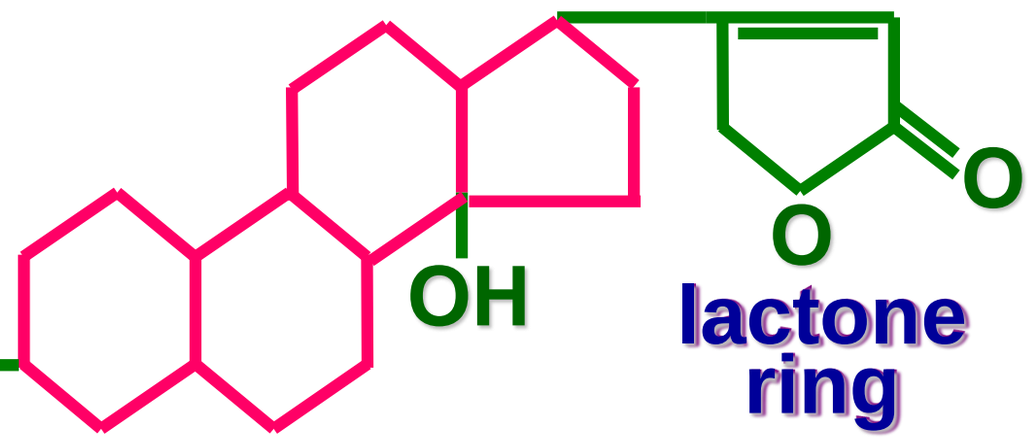
glycon — **O** — **aglycon**

n=1 – monozide
n=2 – diozide
n=3 – thriozide
n=4 – tetrazide

n – number of molecules

Activity

steroid spirit
(der. Cyclopentane perhydrophenantrene



sugary part — **O** —

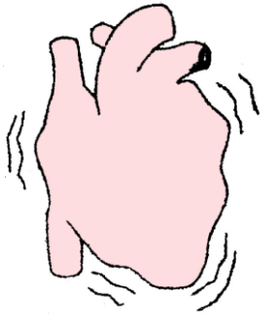
pharmacokinetic and biological activity in general

cardiotonic properties

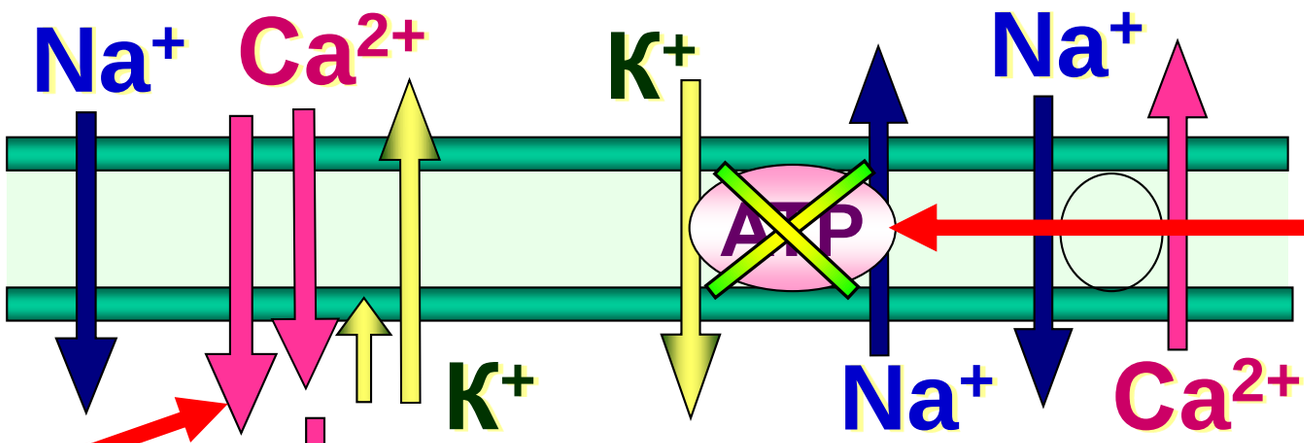
PHARMACODYNAMIC OF CARDIAC GL.

cardiac glycosides:

- «+» inotropic (systolic) – increasing and shortening of systole
- «+» tonotropic – ↑ myocardial tonus
- «–» chronotropic (diastolic) – ↓ heart rate
- «–» dromotropic – ↓ conductivity
- «+» bathmotropic – ↑ excitability



MECHANISM OF THE CARDIOTONIC ACTION OF CARDIAC GLYCOSIDES

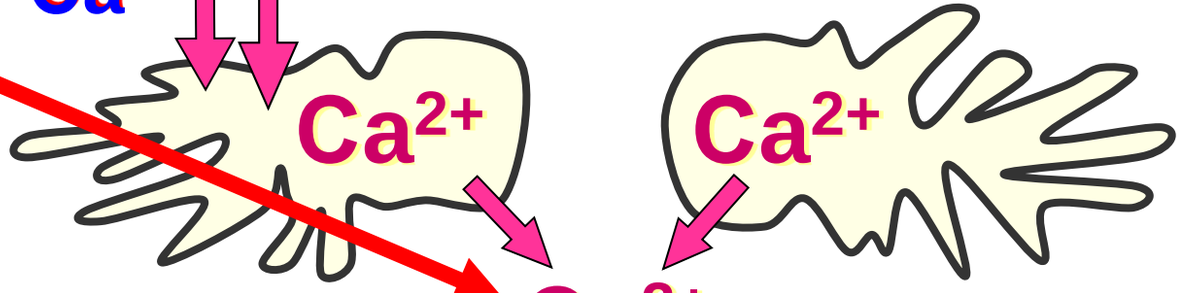


I – membrane excitation

CG

block SH-group of ATP-ase Na^+, K^+-pump, ↓ K^+, ↑ Na^+, Ca^{2+}

CG ↑ Ca^{2+}



II – coupling of excitation and contraction

ATP → myosin

actin G → actin F

CG

III – contraction

↑ Ca^{2+}, conversion of globular actin (G) into fibrillar (F), ATP-activity of myosin

actinomyosin

PHARMACODYNAMICS OF CG

according to «+» inotropic effect:

- Ca^{2+} –CG enhancer
- K^{+} and SH-group donators (unithiol etc) – CG antagonists

- «+» tonotropic: ↓ size of previously dilated heart
- «–» chronotropic (diastolic):
  - ✓↑ vagus influence in reflex way from baroreceptors of sinocarotid zone and myocardium – «vagal factor»;
  - ✓↓ reflex tachycardia because of direct anti-adrenergic impact –«extra-vagal factor»
- cardiotrophic: restoring energy, lipid balance, ↓ O_2 consumption, liposomal stabilization, ↓ tissue hypoxia

ECG CHANGES

inborn valve abnormality

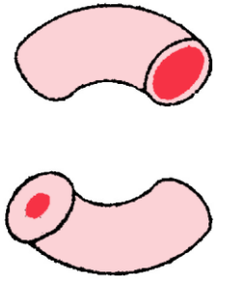
after glycosides

In the therapeutic doses:

- ↓ T wave (early symptom - ↑ tissue metabolism), ↓ ST down from isoelectric line, ↓ QRST (sign of «+» inotropic effect);
- ↑ PP interval («-» chronotropic effect),
- modest ↑ PQ («-» dromotropic effect)

PHARMACODYNAMICS OF CG

non-cardiac effects:



- **hemodynamics:**
  - ↑ cardiac output
  - Arterial BP may ↓ or ↑ (become normal)
  - ↓ venous pressure (unloading of venous compartment of systemic circulation)
  - ↓ diastolic pressure in the ventricles
    ↑ sub-endocardiac bloodflow
  - ↓ of pressure in pulmonary circulation (improvement of gases exchange → decreasing of cyanosis, dyspnoea, tissue hypoxia, metabolic acidosis)
  - ↑ systemic and cerebral blood circulation

PHARMACODYNAMICS OF CG

non-cardiac effects:

- **kidneys: diuretic effect *via*:**
  - **↑ renal blood flow and glomerular filtration**
  - **↓ reabsorption of water, Na^+, and Cl^-:**
- **blood coagulation: ↓ blood coagulation (corglycon), ↑ blood coagulation (foxgloves' agents, strophantin)**
- **CNS: sedation (medicines of Lily of valley and Adonis)**

PHARMACOKINETICS CG

Indexes	Foxgloves' group	Strophantin group
GIT asborption	70-96 % (lipid-soluble),	3-8 % (water-soluble)
route of administrat. and onset of action	oral (0,5-2 hrs), I.V. (5-30 min)	I.V. ! (after 2-5 min)
plasma protein binding	tight (20-97 %)	слабая (10-20 %)
T ½	digoxin – 40 hrs digitoxin – 168 hrs	20-25 hrs
cumulation	significant !	low

INDICATIONS FOR CARDIAC GLYCOSIDES

- **acute heart failure** (corglycon, strophantin, digoxin I.V., diluted with **sodium chloride solution!**)
- **chronic heart failure :** decompensated heart valve abnormalities, cardiosclerosis, overloading of myocardium at arterial hypertension etc. (for oral intake)
- **supraventricular tachycardia (!):** paroxysmal tachycardia, atrial flutter, and atrial fibrillation

MANAGEMENT OF CG DOSING

principles of digitalization:

- **saturation phase:**
  - **rapid (during 1 day - 100 % of full-dose)**
  - **intermediate (3-4 days; at 1-st day – 1/2 of full-dose)**
  - **slow (5-7 days; at 1-st day – 1/4 of full-dose)**
- **maintaining phase (long-lasting): maintaining dose = full-dose x elimination (%) / 100 %**

Symptoms of the therapeutic level of digitalization:

- **normal heart rate instead of tachycardia**
- **transformation of tachysystolic form of atrial fibrillation into bradysystolic, elimination of pulse deficit**
- **↓ clinical symptoms of heart failure (dyspnoe, cyanosis, oedema, ↑ daily diuresis), ↓ liver size**

INTOXICATION BY CG

- «–» dromotropic – suppression of AV-conductivity (↓ PQ, dropping-out of QRS):
- «+» bathmotropic – alteration of conductivity + automacity ⇒ ectopic areas (around 20 types of arrhythmia, especially ventricular)

cardiac symptoms (50-90 %):

→ initially – bradycardia with ectopic beats

→ followed by tachycardia with sharp ↑ BP

→ then ventricular tachyarrhythmia upto ventricular fibrillation and death !

INTOXICATION BY CG

extra-cardiac effects:

- **GIT-disturbances (75-90 %):** anorexia, vomiting spasm of intestine, diarrhea (↑ vagal tonus), intestinal necrosis (spasm of splanchical vessels) – as the rule, develop before cardiac symptoms!
- **neurological (30-90 %):** xantopsia (95 %), headache, insomnia, neuralgia of n.trigeminis and n.facialis
- **others (rare) –** bronchospasm, allergy, thrombocytopenia, gynecomastia

TREATMENT OF GC INTOXICATION

- at the beginning – lowering of dose; at the advanced stage – agents withdrawal and usage of charcoal (50-100 gr) or cholestiramine (4-8 gr)
- K+ containing agents (panagin, "polarizing combination" – solution of KCl in 5 % glucose sol. with insulin and ascorbic acid)
- donators of SH-group (unithiol,acetylcystein)
- chelators (EDTA)
- anti-arrhythmics (lidocaine, phenytoin)
- ascorbic and panthotenic acid
- digibind (antibodies to foxgloves' medicines)

NON-GLYCOSIDE CARDIOTONICS

classfication

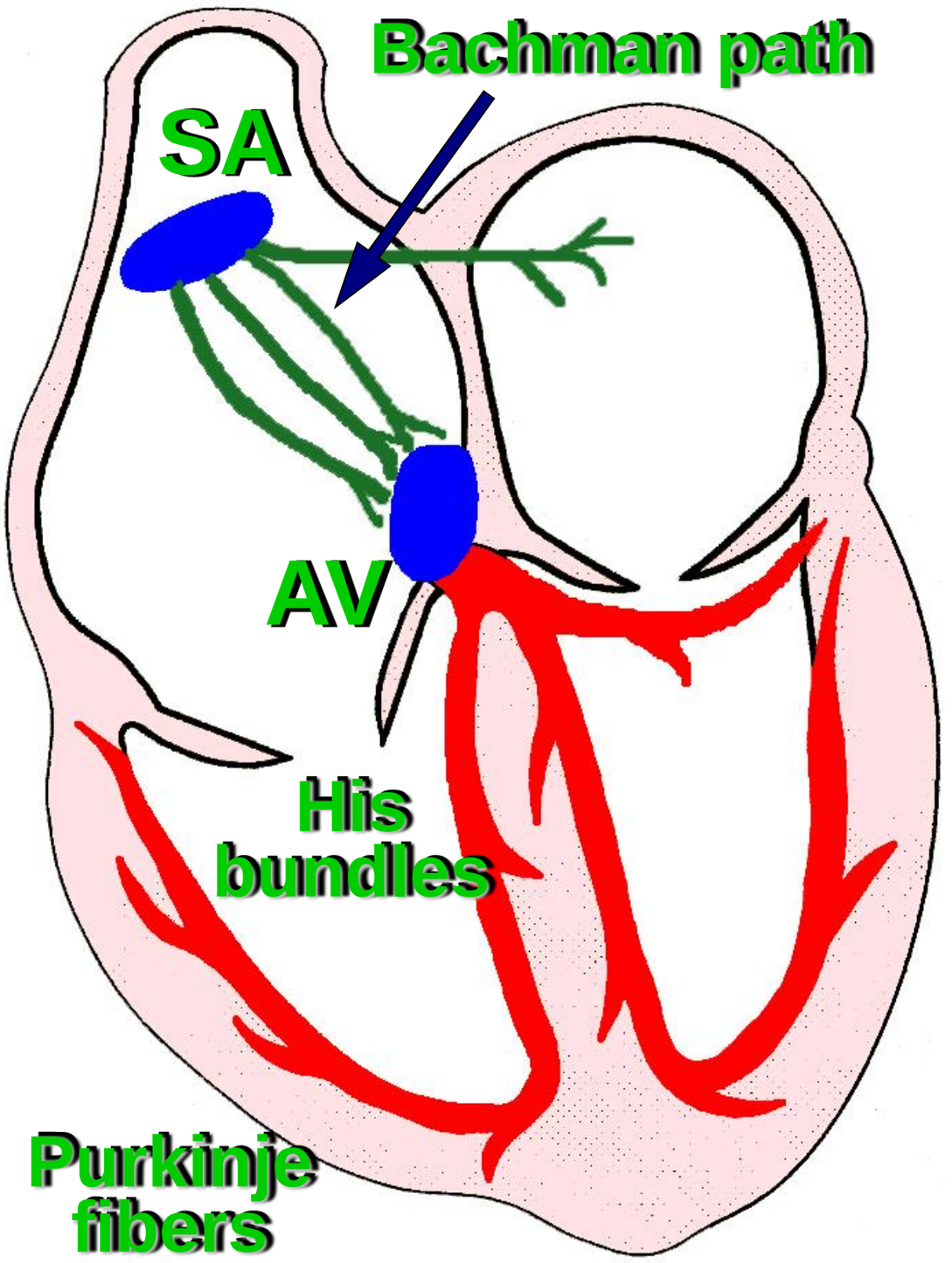
- adrenomimetics* – dopamine, dobutamine etc.
- phosphodiesterase inhibitors* – amrinone, milrinone
- calcium sensitizators* – levosimendan
- metabolic agents – glucagon, riboxin, glutamic acid etc.

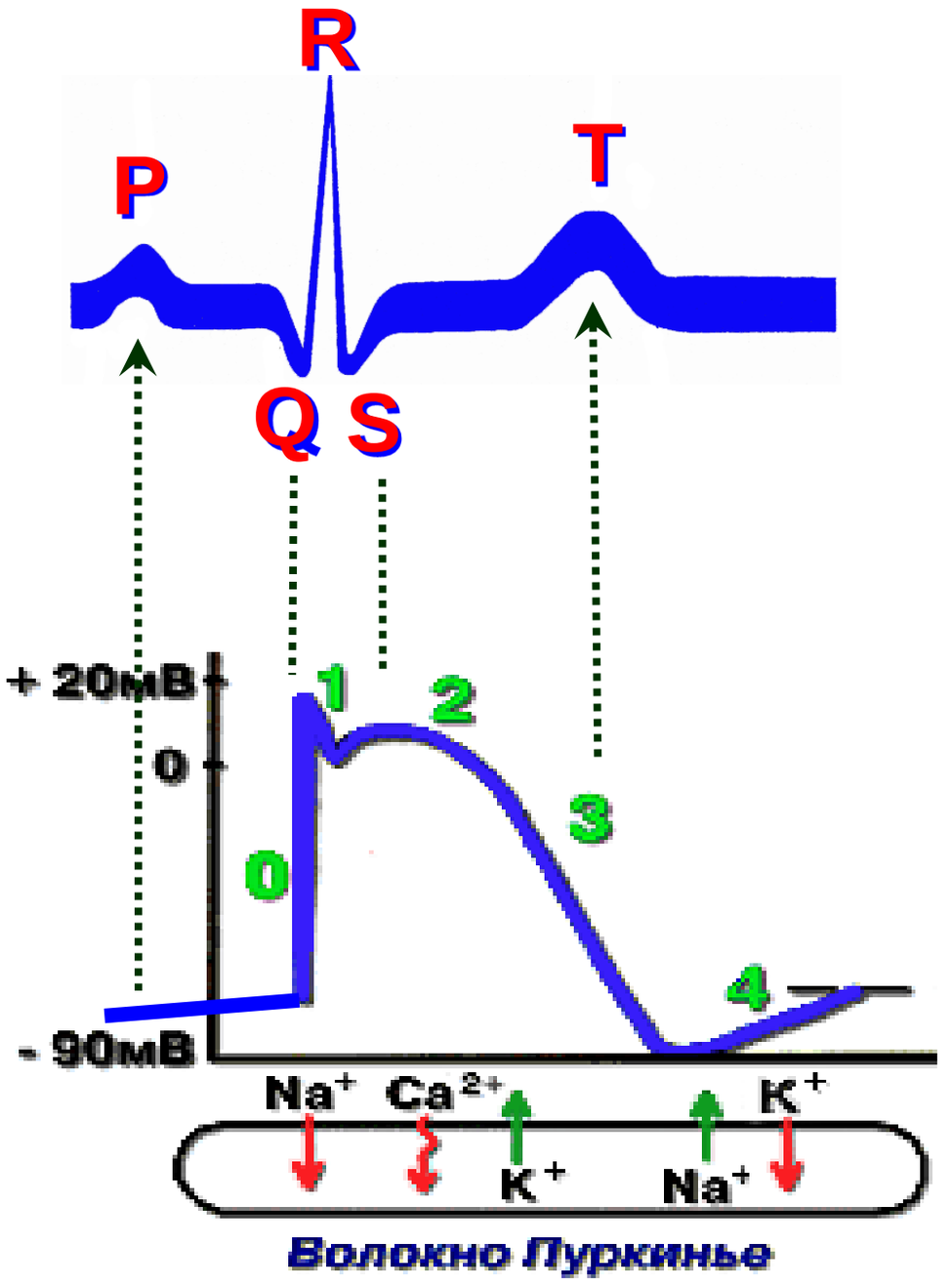
*indications

- cardiogenic shock (dopamine, dobutamine)
- advanced heart failure of III-IV classes that resistant to glycoside therapy (dobutamine, milrinone etc.)

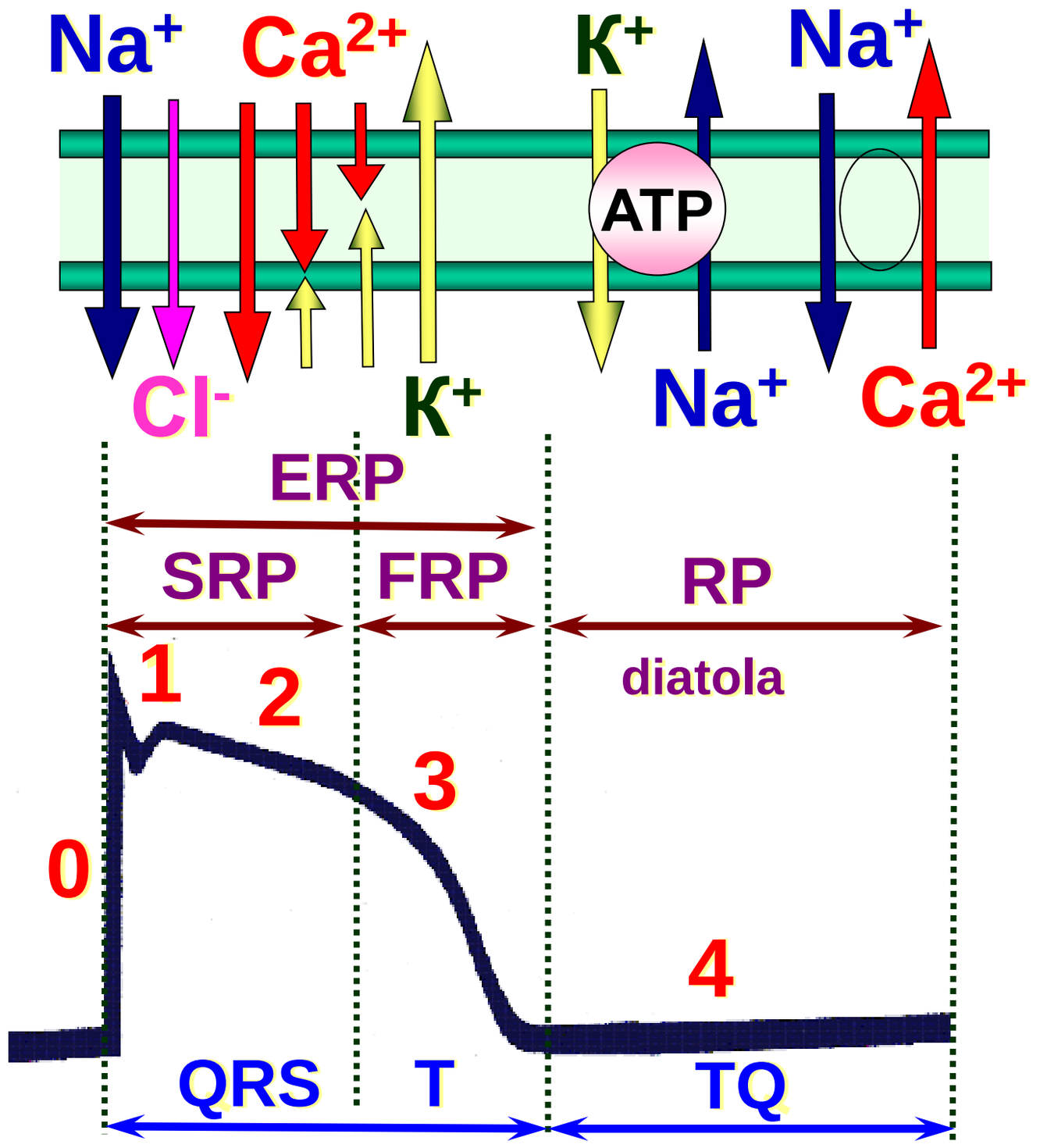
ANTI-ARRHYTHMIC AGENTS

CARDIAC CONDUCTIVE SYSTEM





CARDIAC ELECTROPHYSIOLOGY



Phases of action potential (AP):

0 – rapid depolarization (rapid influx of Na^+)

1 – starting rapid repolarisation (influx of Cl^-)

2 – plateau (influx of Ca^{2+})

3 – final rapid repolarisation (outflux of K^+)

4 – diastolic depolarization (Na^+, K^+-pump)

ARRHYTHMIAS –

abnormal processes of depolarisation in myocardium:

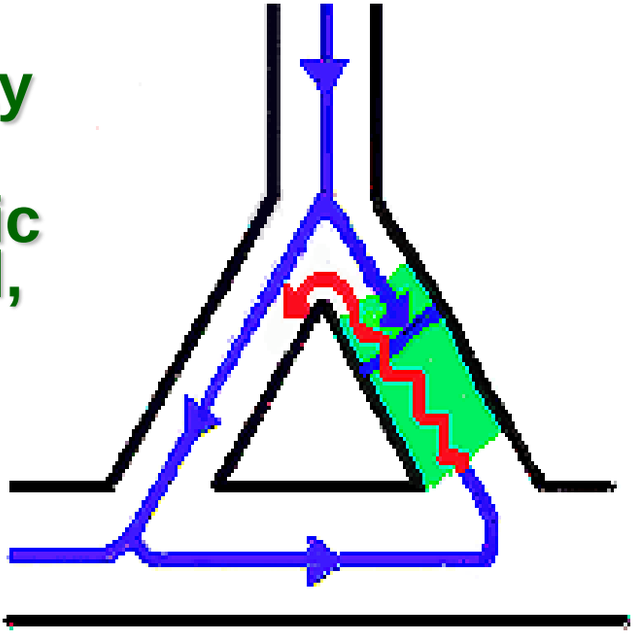
- ✓ ***according to loci of impulse appearance (any non-sinus rhythm)***
- ✓ ***their frequency (< or > 60-90 per min)***
- ✓ ***regularity (incorrect)***
- ✓ ***way of transmission***

types:

- **tachyarrhythmia**
- **bradyarrhythmia**
- **supra-ventricular**
- **ventricular**

pathogenesis:

- **upset of impulse generation – automaticity of SA-node, pathologic automaticity (ectopic areas), early and late depolarisation**
- **upset of conductivity – simple physiologic refractiveness, it's prolongation, ↓ rest potential, fading impulse transmission, n re-entry phenomenon, disturbance of trans-cellular electrotonic interaction etc**



ARRHYTHMIA

principles of pharmacotherapy:

- **ethiotropic** – correction of:
  - neurogenic and endocrinic disturbances (угнетающие ЦНС, антитиреоидные)
  - inflammation of myocardium (NSAIDs, glucocorticoids)
  - acute and chronic ischemia of myocardium (angioprotectors, coronarodilators etc.)
- **pathogenetic** – removing of disturbances of:
  - electrolyte balance in different phases of cardiac cycle and associated abnormalities of automaticity and excitability (membrane-stabilizing, Ca^{2+} and K^{+} channels blockers, potassium-containing agents)
  - neural regulation of cardiac functioning (conductivity) – for tachyarrhythmias (beta-adrenergic blockers), for bradyarrhythmias (M-cholinergic blockers, beta-adrenomimetics)

SITES OF ACTION OF ANTI-ARRHYTHMIC AGENTS

I. Influence of heart:

I. refractive period (↑ non-susceptibility)

- automacity (↓ diastole, depolarisation, ↑ excitability threshold)
- conductivity (↑ P-R, ↑ R-R)
- excitability (↓)
- contractility (↓)

II. Influence on efferent innervation:

- in tachyarrhythmia disturbances (↓ sympathetic and ↑ cholinergic innervations)
- in bradyarrhythmia disturbances (↓ cholinergic and ↑ sympathetic innervations)

DEMANDS FOR THE IDEAL ANTI-ARHYTHMICT AGENT

- effectiveness at different types of arrhythmia
- absence of negative impact on cardiac contractility and coronary blood flow (especially at myocardial infarction and heart failure)
- broad wideness of therapeutic action (!)
- possibility of long-lasting usage (for years)
- long-lasting anti-arrhythmic effect (at least 12-24 hrs)

CLASSIFICATION OF ANTI-ARRHYTHMICS

for tachyarrhythmias:

⇒ **I class – sodium channels blockers (membrane-stabilizing agnets):**

- **I A –** ***those that prolong effective refractive period (ERP):*** **quinidine, novocainamide, disopyramide etc.**
- **I B –** ***those that shorten ERP:*** **lidocaine, diphenin etc.**
- **I C –** ***those with different influence on ERP:*** **propafenon, etacizin etc.**

⇒ **II class – β-adrenoblockers: propranolol, atenolol, metoprolol etc.**

⇒ **III class – potassium channels blockers: amiodarone, sotalol, ibutilide etc.**

⇒ **IV class – calcium channels blockers: verapamil, halopamil, diltiazem**

⇒ **V class – those that normalize electrolytes equilibrium: panangin, potassium chloride etc.**

SODIUM CHANNELS BLOCKERS

(membrane-stabilizing)

I A – quinidine, novocainamide, disopyramide etc.

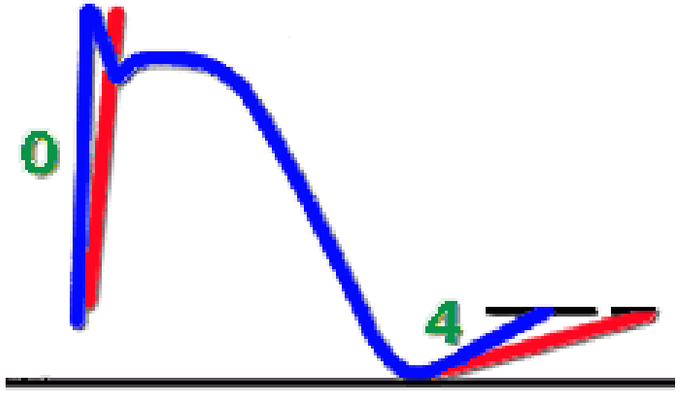
I B – lidocaine, diphenin etc.

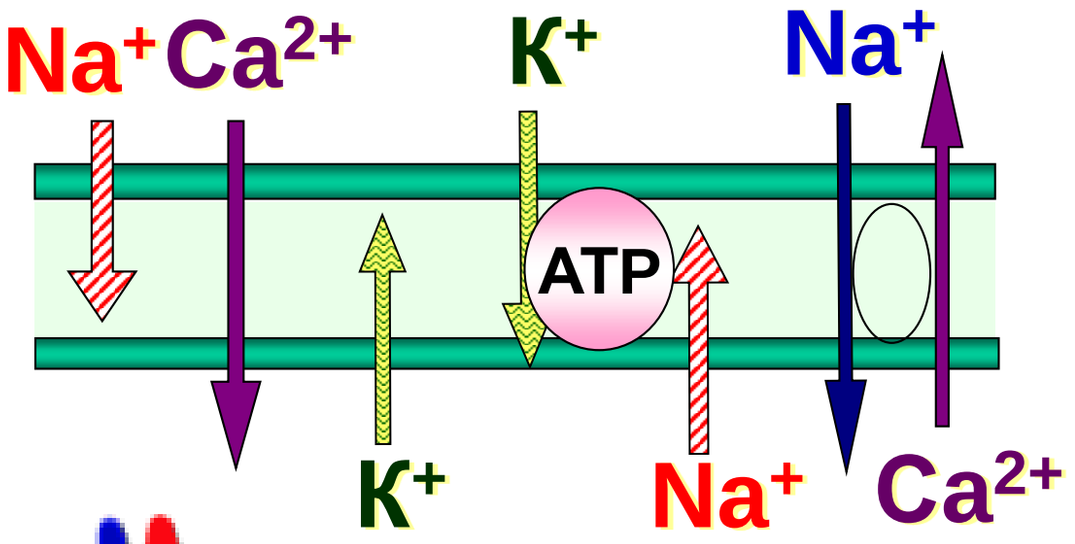
I C – propafenone, etazicin etc.

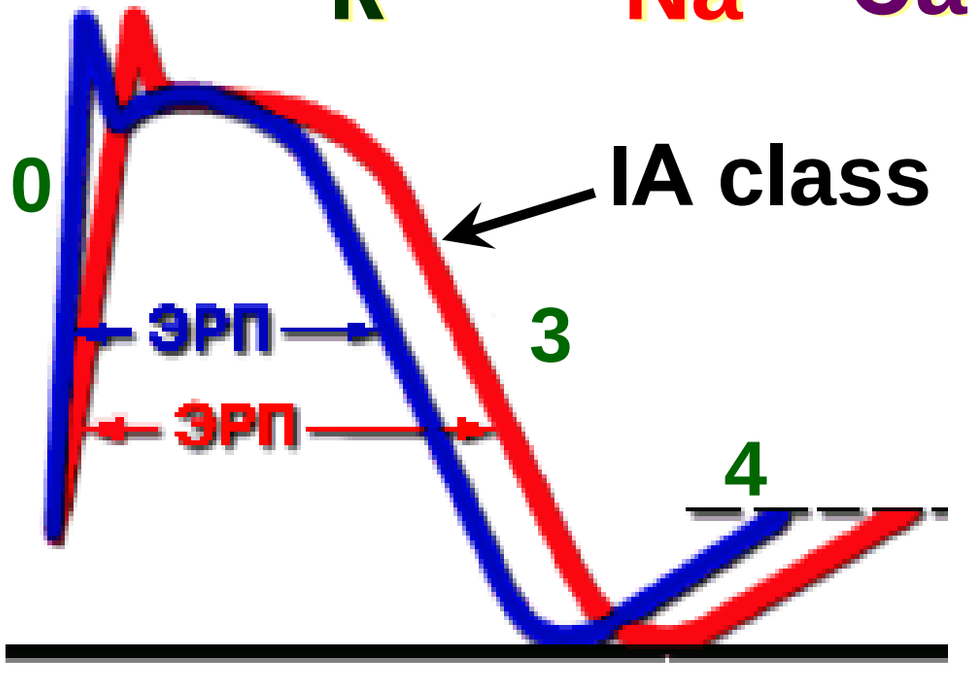
Subgroup	↓ speed of rapid depolarization	duration of action potential
I A	++	↑
I B	+	↓
I C	+++	-

IA SUBGROUP (quinidine-like)

- ✓ block Na^+-channals and slow-down depolarization (phase 0 – excitability and 4 – automaticity)





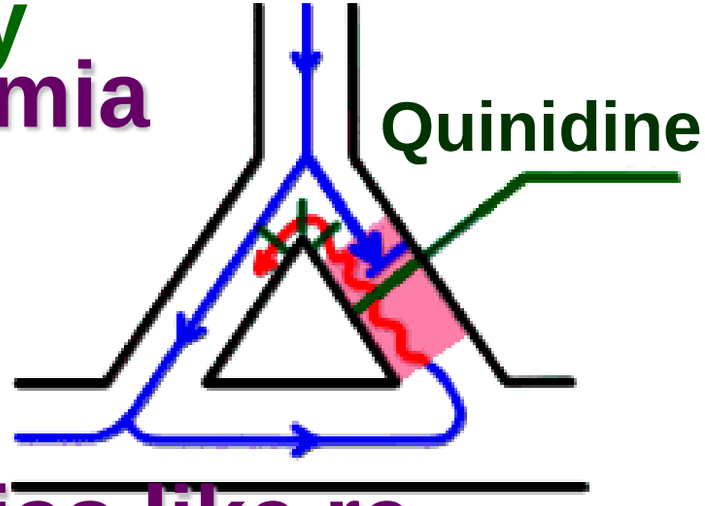


- ✓ block K^+ -channels and slow-down repolarisation (phase 3)
- ✓ ⇒ ↑ AP and ↑ ERP

- ➢ ↓ automaticity, excitability, and conductivity
- ➢ vagolytic action on SA and AV-nodes

IA SUBGROUP (quinidine-like)

- on SA-node: ↓ automaticity, ↑ vagolytic effect ⇒ insignificant tachycardia
- on AV-node: ↓ automaticity and conductivity, ↑ vagolytic effect ⇒ in case of supraventricular tachyarrhythmia
- on Purkinje fibers:
  - ↓ automaticity and excitability ⇒ in ventricular tachyarrhythmia
  - ↑ ERP ⇒ in tachyarrhythmia resulted from impulses circulated in closed chains



  - ↓ conductivity ⇒ in arrhythmias like re-entry (transformation one-way block into complete block)

IA SUBGROUP

Quinidine

- «-» inotropic action
- peripheral vasodilation (α-adrenolytic action)
- ↓ BP (↓ cardiac output and peripheral vascular resistance)

indications:

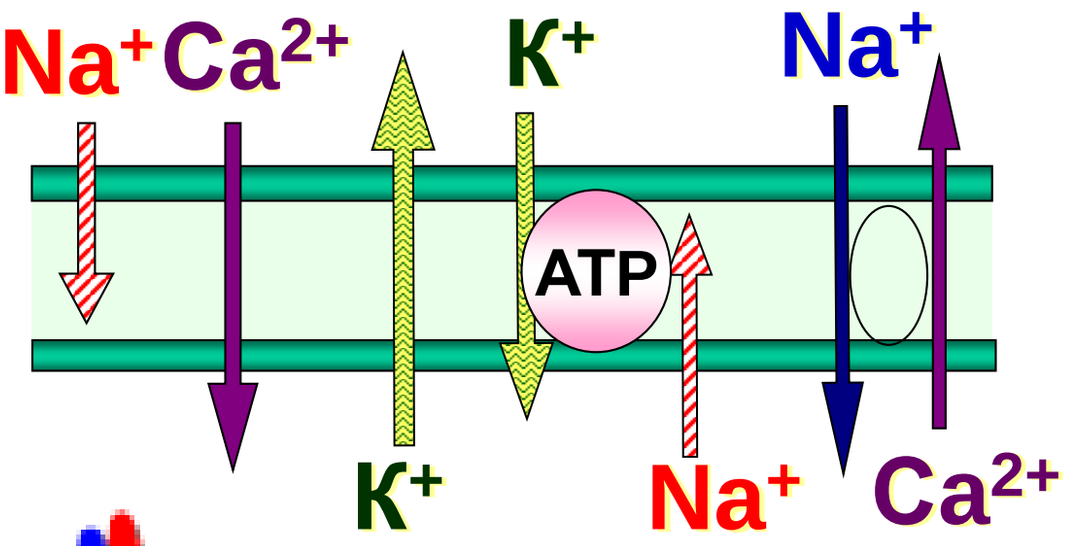
- atrial fibrillation
- supra-ventricular and ventricular paroxysmal tachycardia
- supra-ventricular and ventricular extrasystoles

adverse effects:

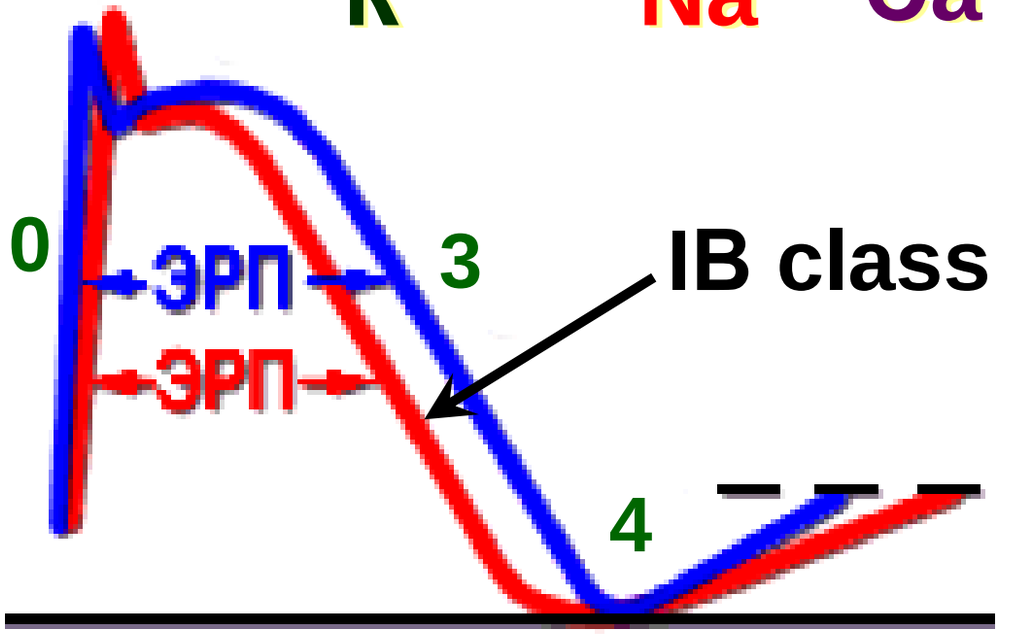
- ↓ contractility, ↓ BP, AV-block
- hearing and visual disturbances, dyspepsia, allergic reactions etc.

IB SUBGROUP (lidocaine)

- ✓ blocks Na^+-channels and slows down the depolarization (phase 0 – excitability and 4 – automaticity)



- ✓ ↑ permeabiity of K^+ and ⇒ speeds up the repolarization (phase 3)
- ✓ ⇒ ↓ AP and ↓ ЭРП (ERP)



- ➢ ↓ automaticity, excitability and conductivity (<, than IA subgroup)
- ➢ causes weak suppressive action on AV-node

IB SUBGROUP

indications:

- ventricular extra-systoles, for example in myocardial infarction (lidocaine – 2 % sol. I.V. by drops, 10 % sol. I.M.; mexilethin – I.V., oral), cardioversion
- arrhythmia cause by cardiac glycosides (diphenin, lidocaine)

adverse effects:

- arrhythmia (AV-block etc.)
- neurological (paresthesia, tremor, impairment of hearing, convulsions)

II class – BETA-ADRENOBLOCKERS

- ***non-selective (β_1+ β_2):*** **propranolol (anaprilin), nadolol, timolol**
- ***selective (β_1):*** **metoprolol, atenolol, bisoprolol, acebutolol, celiprolol**
- ***with intrinsic sympathomimetic activity:*** **oxprenolol, pindolol**

cardiac effects

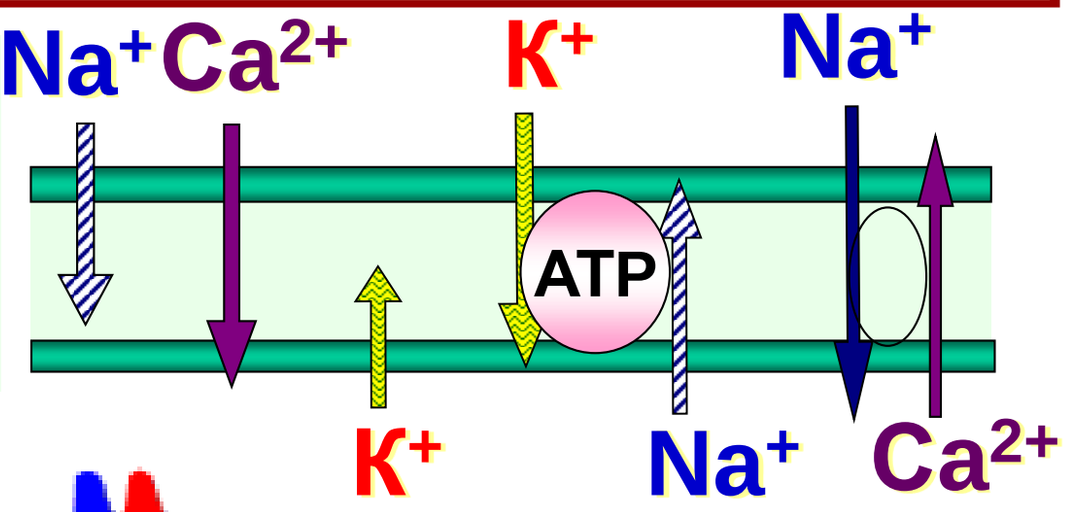
- ↓ automaticity of SA-node
- ↓ automaticity and conductivity of AV-node
- ↓ automaticity of Purkinje fibers
- «-» ino- and chronotropic effects
- ↓ oxygen consumption of myocardium

indications

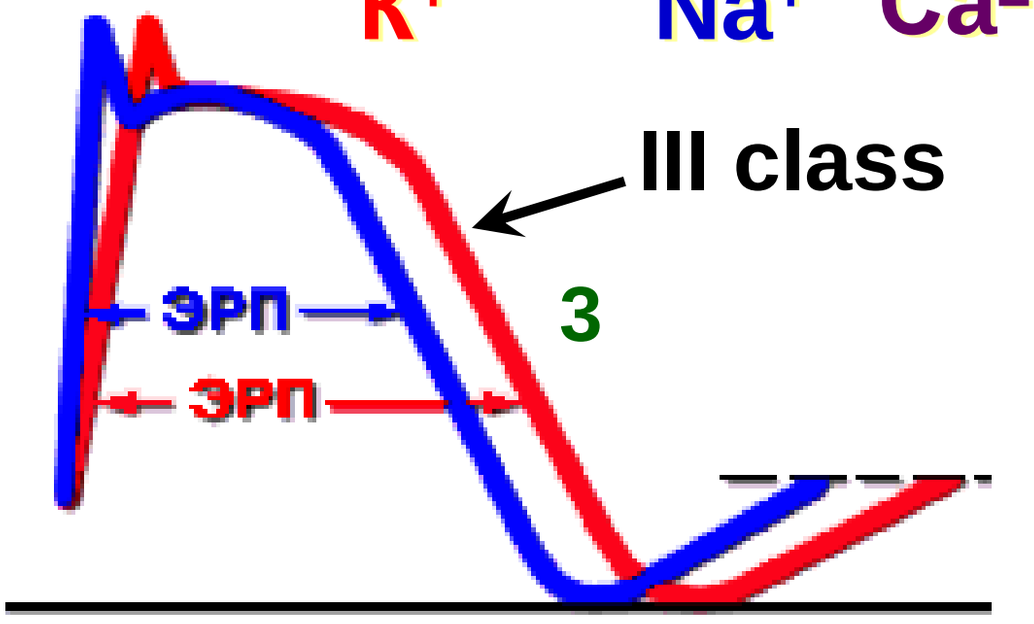
- supra-ventricular tachyarrhythmia and extrasystoles
- ventricular extrasystoles caused by raising of automaticity

III class – POTASSIUM CHANNEL BLOCKERS (amiodarone)

- ✓ blocks K^+-channels and ↓ repolarization (phase 3)
- ✓ ⇒ ↑ AP and ↑ ЭРП (ERP)



- ✓ blocks Na^+- and Ca^{2+}-channels
- ✓ β-adrenolytic effect



- ➢ shares activity IA, II, and IV classes as well

- ➢ «-» ino-, chronotropic effects
- ➢ ↓ AV-conductivity

III class – POTASSIUM CHANNEL BLOCKERS (amiodarone)

indications

- different types of tachyarrhythmias and extrasystoles, including those that are drug-resistant
- angina pectoris, stenocardia

adverse effects

- arrhythmia (AV-block, bradycardia etc.), hypotension
- at long-lasting therapy (cumulate, T1/2 upto 100 days!):
  - ✓ tremor, ataxia, paresthesia
  - ✓ hypo- or hyperthyroidism
  - ✓ pulmonary fibrosis
  - ✓ liver dysfunction, constipation
  - ✓ yellow-brownish precipitates in cornea, visual impairment
  - ✓ photodermatitis (grey-blue skin discolouration), photosensibilization etc.

IV class – CALCIUM CHANNEL BLOCKERS (CCB)

General characteristics

Calcium channels blockers (CCB) — are the agents that decrease the influx of calcium ions predominantly via L-type potential-dependent («slow») calcium channels

History of inventions

1961 y. Dr. F. Dengel synthesized **verapamil** when he was trying to create synthetic analogues of papaverin

1967 y. A. Flekenstein unveiled the mechanism of its action and proposed the name «calcium antagonists»

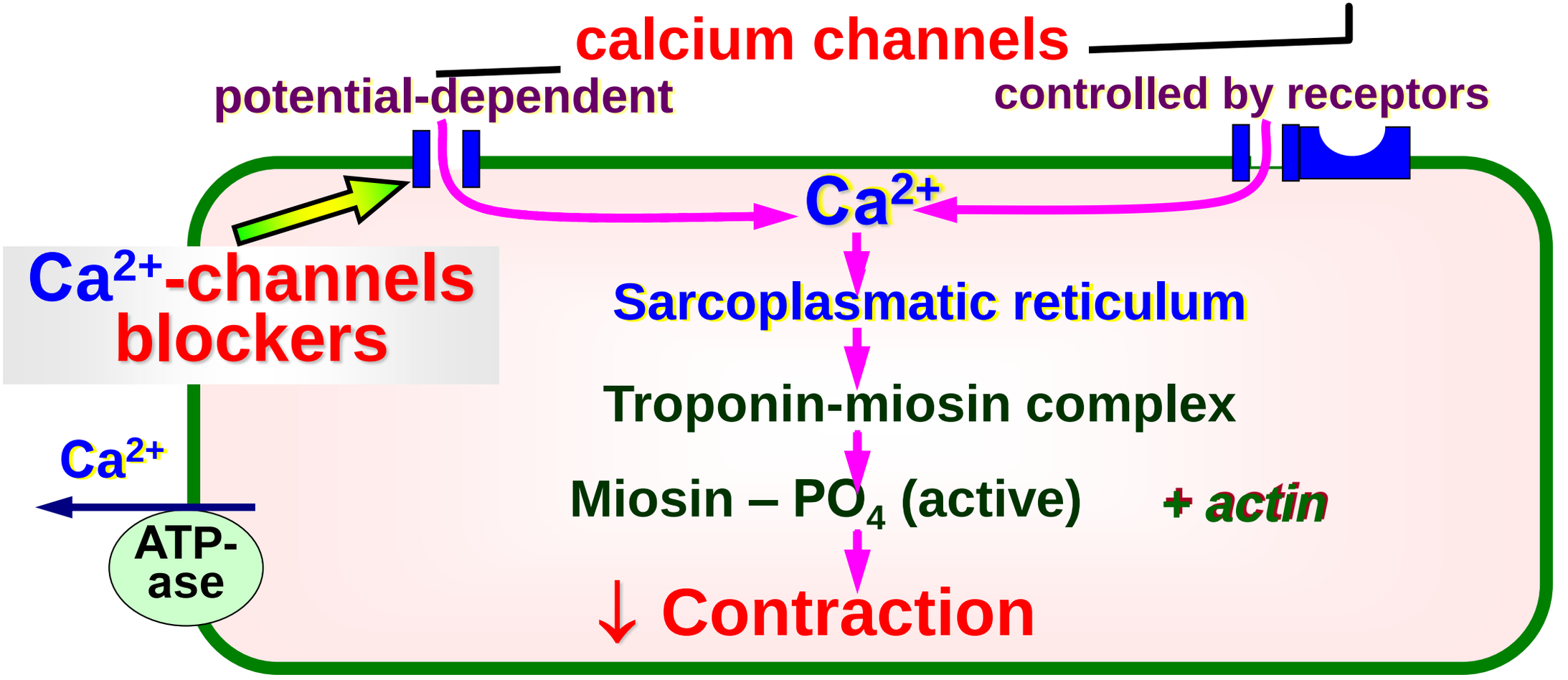
1966 and 1971 yy. **nifedipine** and **dilthiazem** (correspondently) were got

CLASSIFICTION OF CALCIUM CHANNEL BLOCKERS

- **I type – cardio-tropic *(phenylalkylamine derivatives):* *1 generation* – verapamil, *2 generation* – hallopamil etc.**
- **II type (vaso-tropic):**
  - ✓ **systemic action: *dihydro-pyridine derivatives (DCCB): 1 generation* – nifedipine, *2 generation* – nifedipin-GITS, amlodipine, isradipine, nicardipine, nimodipine* etc.**
  - ✓ **cerebro-vaso-tropic –*diphenyl-piperasine derivatives: 1 generation* – cinnarisine, *2 generation* – flunarisine as well as certain dihydro-pyridine derivatives* (nimodipine)**
- **III type – mixed *(benzothiazine derivatives): 1 generation* – dilthiazem, *2 generation* – clenthiazem**

MECHANISM OF ACTION OF CCB

↓ intracellular influx of Ca^{2+} through L–type potential-dependent calcium («slow») channels (myocardium, smooth muscles of blood vessels, bronchi, GIT, myometrium, and thrombocytes) by binding with them and changing their modality (↑ and/or ↓ duration of different phases), but not by blockage of that channels or antagonism to Ca^{2+} (!)



PHARMACODYNAMICS OF CCB

differ by:

- ✓ chemical structure
- ✓ sites of binding at calcium channels
- ✓ tissue specificity

The selectivity of DCCB nifedipine and amlodipine concerning blood vessels 10 times, felodipine — 100 times, nisoldipine — 1000 times more comparatively to verapamil and dilthiazem, nimodipine has selectivity for cerebral vessels, nisoldipine — for coronary vessels, felodipine — both for coronary and peripheral arteries

⇒ Difference in influencing on cardio-vascular system:

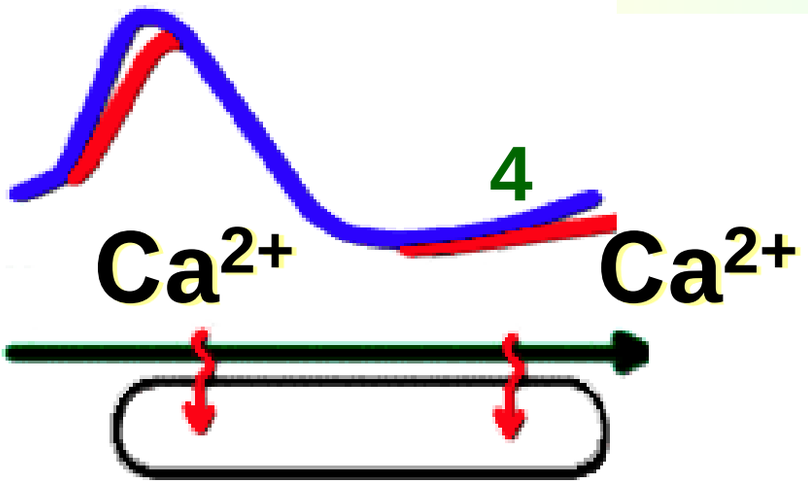
- **vasotropic (DCCB):** prominant vasodilation, weak influence on contractility and absence of action on conductivity ⇒ **hypo-tensive and anti-anginal actions**
- **cardio-tropic (verapamil) and mixed (dilthiazem):** вsignificant impact on contractility, conductivity, and automaticity of myocardium, moderate vasodilation ⇒ **anti-anginal, anti-arrhythmic, and hyp-tensive actions**

PHARMACODYNAMICS OF CCB

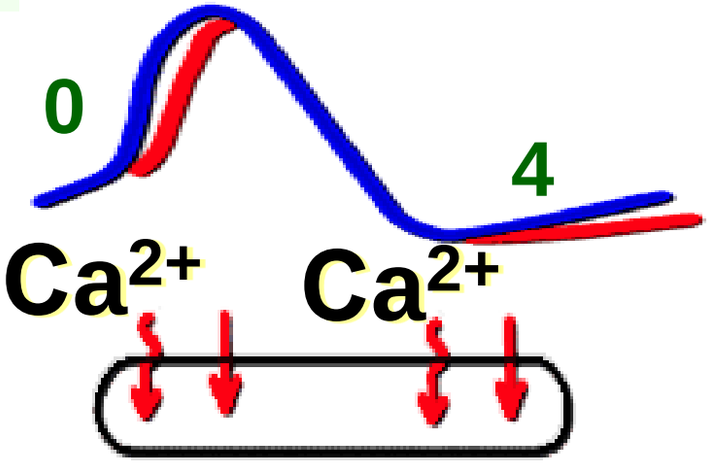
- **blood vessels (basicely in DCCB) – vasodilation (predominantly of vessels) ⇒**
  - ↓ peripheral resistance ⇒ ↓ ABP ⇒ hypotensive action
  - ↓ peripheral resistance results in ↓ cardiac after-load ⇒ ↓ O_2 consumption of myocardium + ↓ coronary spasm ⇒ ↑ coronary blood flow into ischemic zones ⇒ ↑ O_2 supply of myocardium ⇒ anti-anginal action
  - ↓ cerebral vasoconstriction and consequences of brain stroke (nimodipine, cinnariциннаризин) ⇒ cerebro-protection
- **heart (verapamil, dilthiazem):**
  - «-» ino- and chronotropic effects, ↓ cardiac output ⇒ ↓ O_2 consumption of myocardium ⇒ anti-anginal action
  - ↓ SA-node automaticity, ↓ ectopic areas in atrium, ↓ AV-conductivity ⇒ «-» bathmo- and dromo-tropic effects ⇒ anti-arrhythmic action
  - cardio-protective action ⇒ regress of left ventricular hypertrophy

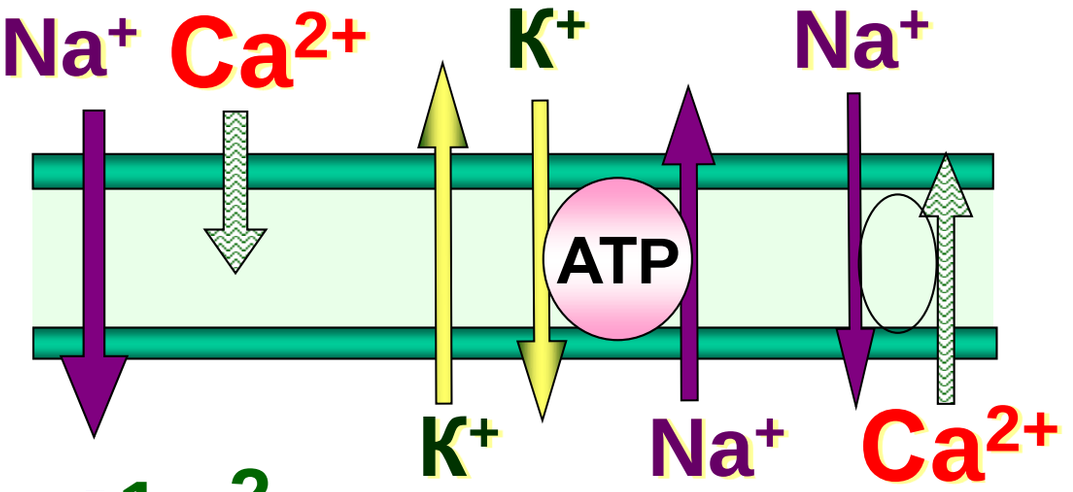
IV class – CALCIUM CHANNELS BLOCKERS (verapamil, dilthiazem)

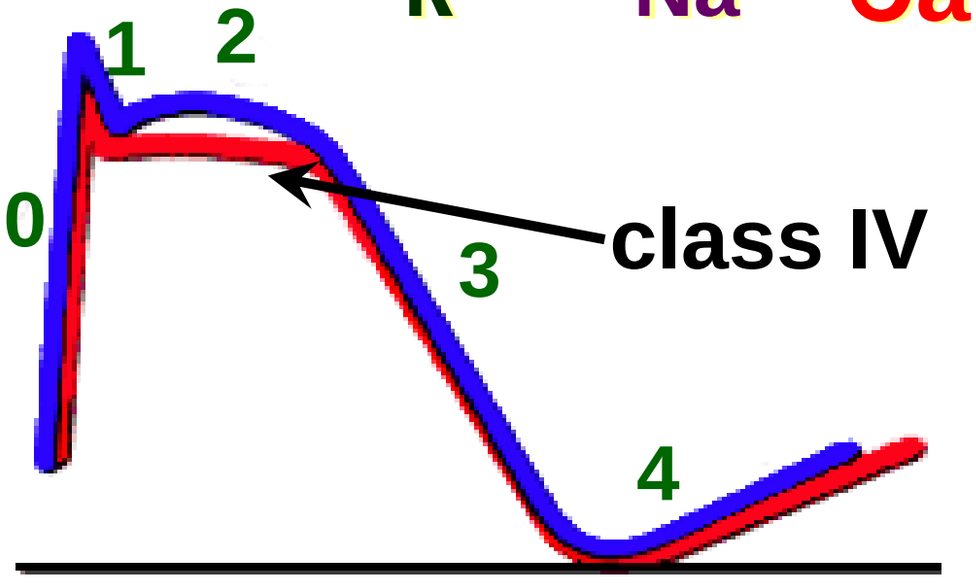
↓ automaticity of SA-node (phase 4)



↓ conductivity (phase 0) and automaticity (phase 4) of AV-node







PHARMACODYNAMICS OF CCB

- **kidneys:**
  - ↓ vasoconstriction of renal vessels, ↑ renal blood flow ⇒ **nephroprotective** effect
  - ↑ rate of glomerular filtration + ↓ sodium reabsorption ⇒ **diuretic** effect (contribute into hypotensive effect)
- **smooth muscles of internal organs:**

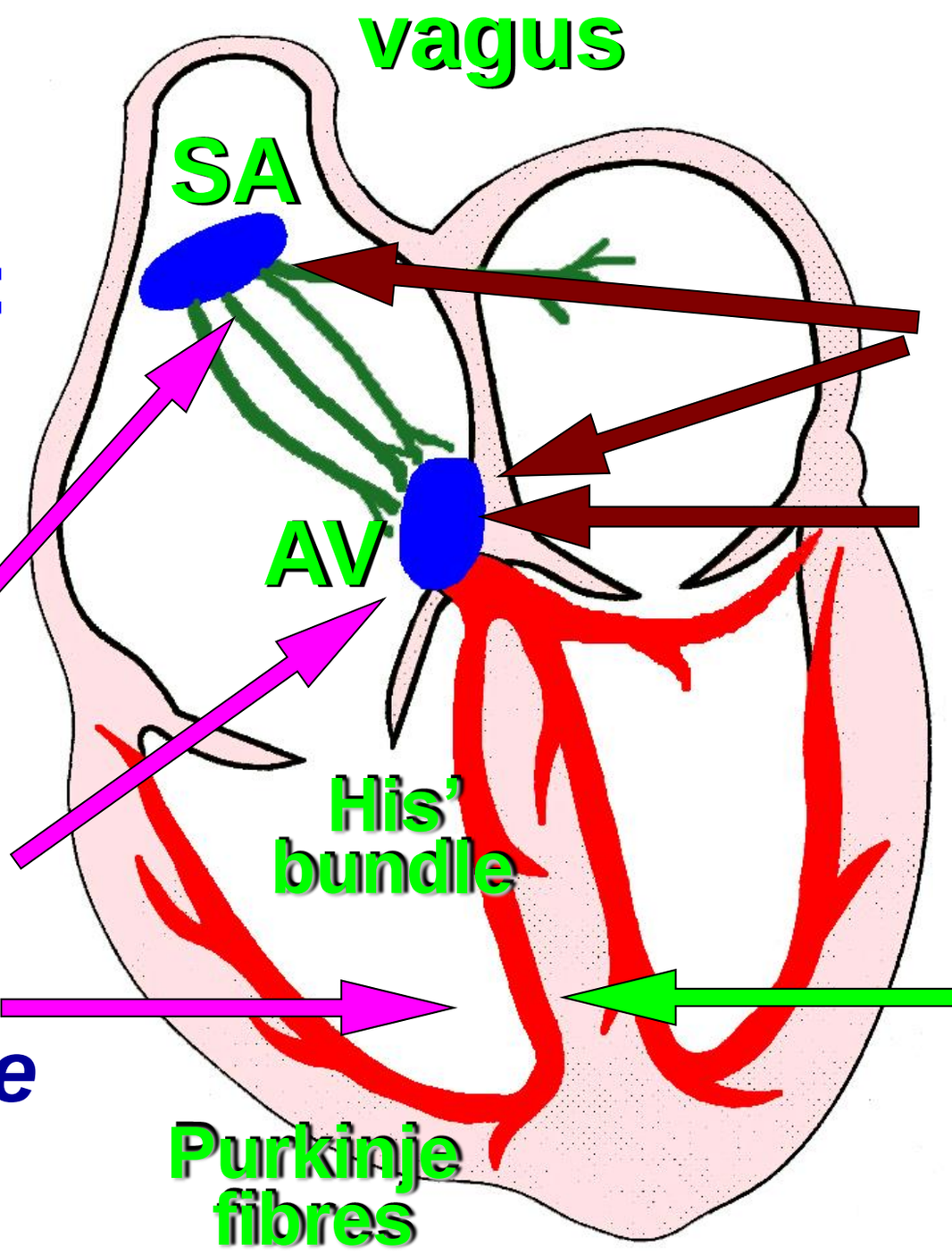
  relaxation ⇒
  - ↓ bronchospasm ⇒ **broncholytic** effect
  - ↓ GIT tonus ⇒ **spasmolytic** effect
  - ↓ uterus tonus ⇒ **tocolytic** effect
- **blood:** ↓ platelets aggregation and thromboxane A_2 и ⇒ **anti-aggregative** action
- **metabolism:**
  - ↓ development of atherosclerosis ⇒ **anti-atherosclerosis** action
  - ↓ lipids peroxydation, that prevent formation of free radicals

INDICATIONS FOR CCB

- supra-ventricular extra-systoles and tachyarrhythmia, atrial flutter and fibrillation (verapamil, dilthiazem)
- angina pectoris: efforts angina, vasospastic angina) (verapamil, dilthiazem, DCCB of II generation)
- arterial hypertension
- disturbance of cerebral blood flow, migraine (nimodipine, cinnarizin)
- impairment of peripheral blood flow, Reyno disease (amlodipine)
- in complex therapy of CNS disorders: Alzheimer disease, dementia, alcoholism, vestibulopathy (nimodipine)
- for prevention of cold air-caused bronchospasm

SITES OF ACTION OF ANTI-ARRHYTHMICS

At supra-ventricular and ventricular:



quinidine-like

beta-adreno-blockers

amiodarone

At supra-ventricular only:

verapamil

cardiac glycosides

At ventricular only:

lidocaine

diphenin