Odessa National Medical University
Department of general and clinical pharmacology and pharmacognosy

CARDIOTONICS.

CARDIAC GLYCOSIDES.

NON-GLYCOSIDE CARDIOTONICS .

HEART FAILURE

- **Heart failure** occurs when the heart muscle doesn't pump blood as well as it should
- When this happens, blood often backs up and fluid can build up in the lungs, causing shortness of breath.
- Certain heart conditions gradually leave the heart too weak or stiff to fill and pump blood properly.

HEART FAILURE

Causes of congestive heart failure include:

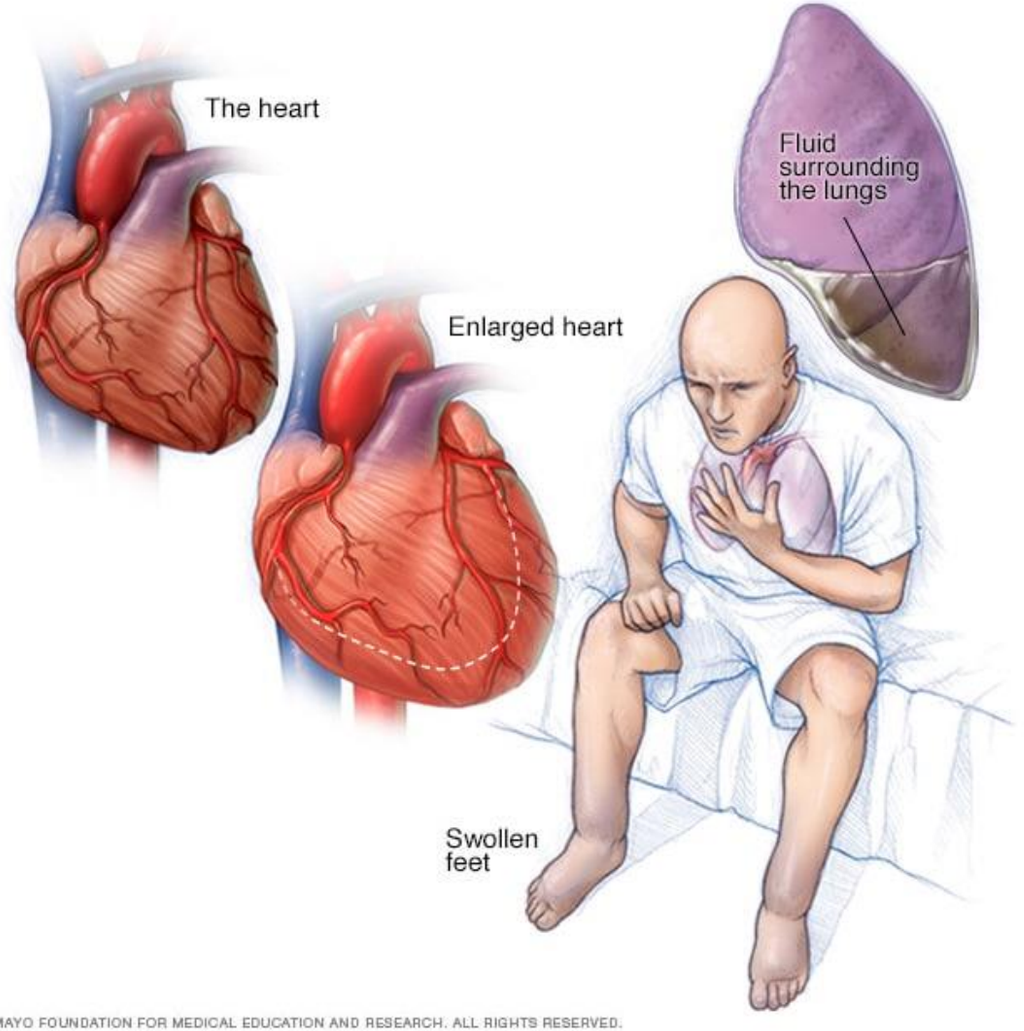
- Coronary artery disease and/or heart attack.
- Cardiomyopathy (genetic or viral).
- Heart issues present at birth (congenital heart disease).
- Diabetes.
- High blood pressure (hypertension).
- Arrhythmia.
- Kidney disease.
- A body mass index (BMI) higher than 30.
- Tobacco and recreational drug use.
- Alcohol use.
- Medications such as cancer drugs (chemotherapy).

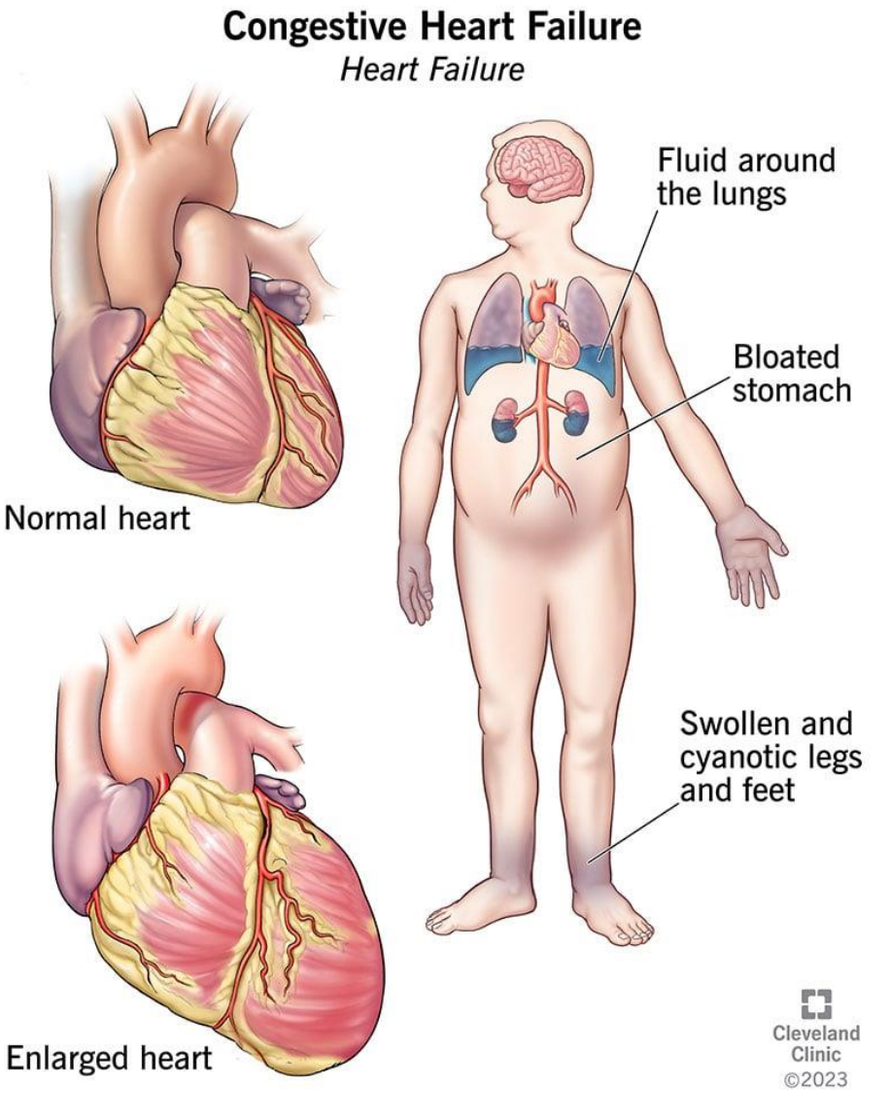
HEART FAILURE

Congestive heart failure symptoms include:

- Shortness of breath.
- Waking up short of breath at night.
- Chest pain.
- Heart palpitations.
- Fatigue when you're active.
- Swelling in your ankles, legs and abdomen.
- Weight gain.
- Need to urinate while resting at night.
- A dry, hacking cough.
- A full (bloated) or hard stomach.
- Loss of appetite or upset stomach (nausea).

HEART FAILURE





HEART FAILURE

Risk factors for congestive heart failure include:

- Being older than 65.
- Using tobacco products, cocaine or alcohol.
- Having an inactive (sedentary) lifestyle.
- Eating foods that have a lot of salt and fat.
- Having high blood pressure.
- Having coronary artery disease.
- Having a heart attack.
- Having a family history of congestive heart failure.

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)

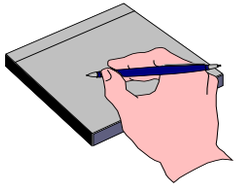
Strophantus
(Strophanthus)

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**

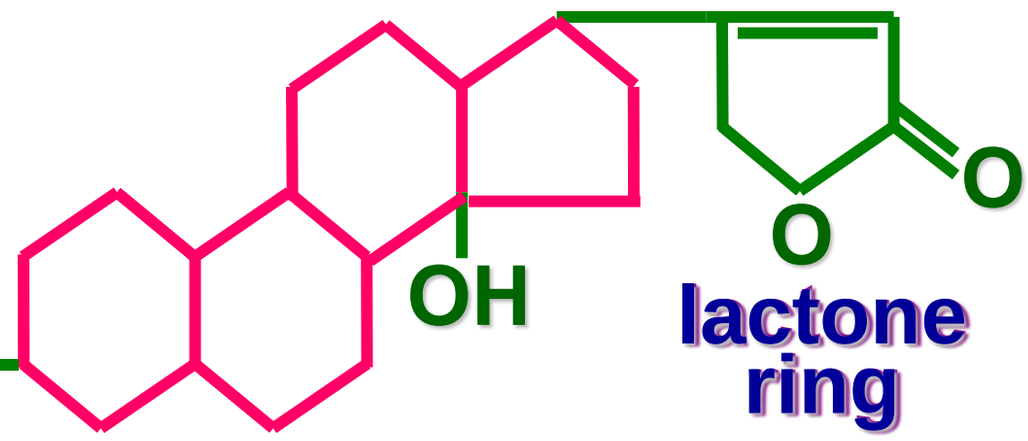
n=1 – monozide
n=2 – diozide
n=3 – thriozide
n=4 – tetrazide

n – number of molecules

Activity

steroid spirit
(der. Cyclopentane perhydrophenantrene

sugary part — O —



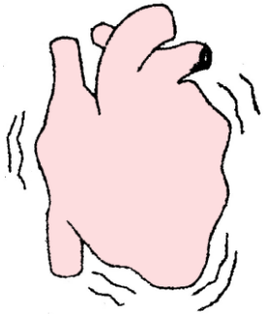
pharmacokinetic and biological activity in general

cardiotonic properties

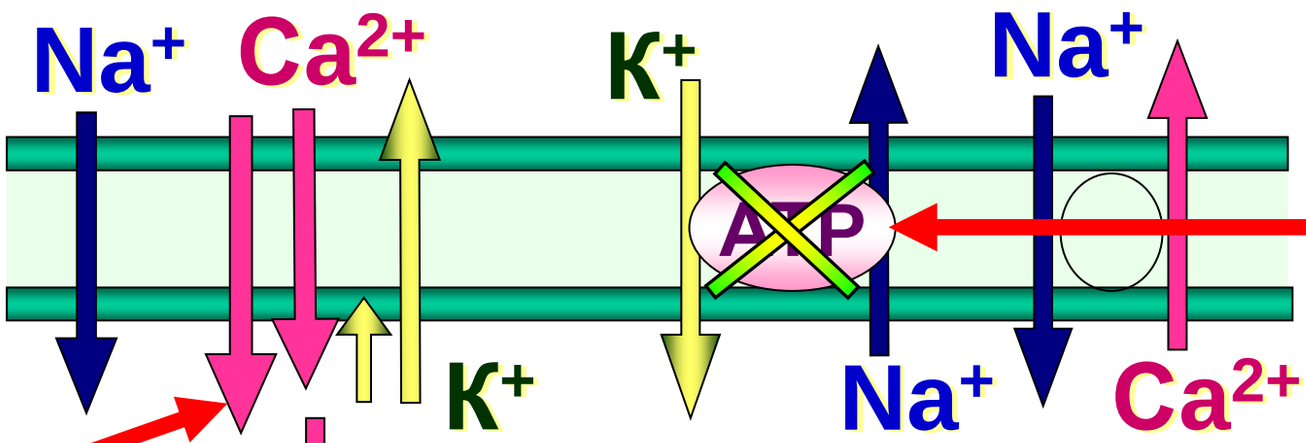
PHARMACODYNAMIC OF CARDIAC GL.

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

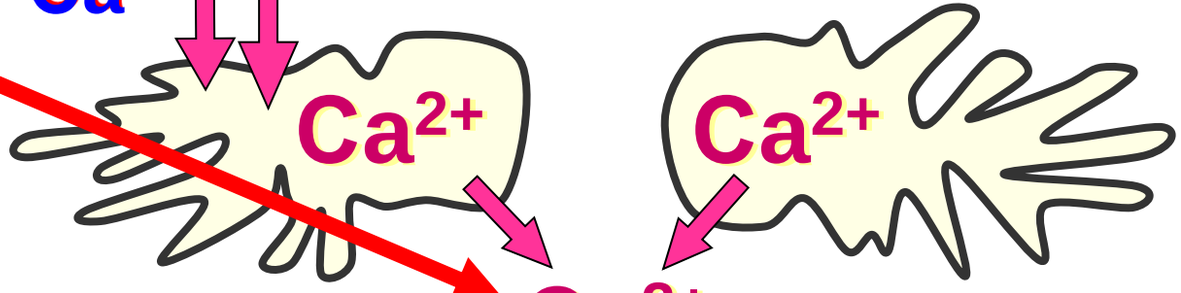


I – membrane excitation

CG

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

CG ↑ Ca^{2+}



II – coupling of excitation and contraction

ATP

actin G

CG

myosin

+

actin F

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

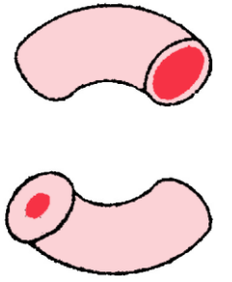
after glycosides

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 %)	weak (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 up to 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 (panangin, "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.)

ANTIANGINAL AGENTS

General definitions

Angina pectoris is the principal symptom of ischemic heart disease. The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels.

In classic angina, the imbalance occurs when the myocardial oxygen requirement increases, as during exercise, emotion, and coronary blood flow does not increase proportionately.

The resulting ischemia usually leads to sudden, severe, pressing substernal pain that often radiates to the left shoulder and arm and is often associated with depression of the S-T segment of the ECG.

Classic angina is therefore **"angina of effort."** In **variant angina**, oxygen delivery decreases as a result of reversible coronary vasospasm (usually superimposed on chronic obstruction). The underlying pathological process is usually advanced atherosclerosis of the coronary vasculature. In contrast, variant angina is caused by vasospasm of the coronary vessels and may not by associated with severe atherosclerosis.

In theory, the imbalance between oxygen delivery and myocardial oxygen demand can be corrected by

- **increasing delivery** (by increasing coronary flow);
- **decreasing oxygen demand** (by decreasing cardiac work).

Both measures are used in clinical practice.

ANTIANGINAL AGENTS

Agents, that diminish oxygen demand of myocardium

β-adrenergic antagonists

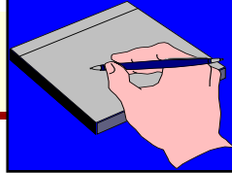
Agents, that decrease myocardial oxygen consumption and increase oxygen income to myocardium

- **Organic nitrates**
- **Calcium channels blockers**
- **Agents, prolonging repolarization**

Agents, that increase oxygen income to myocardium

Coronaro-dilators

ORGANIC NITRATES



Organic nitrates (and nitrites) are simple nitric and nitrous acid esters of alcohols. They differ in their volatility; for example, isosorbide dinitrate is solid at room temperature, nitroglycerin (glyceryl trinitrate) is moderately volatile, whereas amyl nitrate is extremely volatile.

Mechanism of action:

Release of nitric oxide (NO) → **Increasing of cGMP** → **Vascular smooth muscle relaxation**

Effects on cardiovascular system:

i. At therapeutic doses, nitroglycerin causes dilation of the large veins, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart).

ii. Dilation of large arteries decreases arterial pressure. This result in diminished afterload. Decreased pre- and afterload causes decreased myocardial oxygen requirement.

iii. Nitrates dilate the epicardial coronary arteries. Nitrates benefit patients with variant angina by relieving coronary artery spasm.

Pharmacokinetics: Significant first pass metabolism of organic nitrates occurs in the liver. Their bioavailability is very low (typically < 10-20%). The sublingual route, which avoids the first-pass effect, is therefore preferred for achieving a therapeutic blood level rapidly (in a few minutes). Therefore, it is common to give the drug either sublingually or via a patch.

The major **adverse effects** of organic nitrates is a direct extension of therapeutic vasodilation: orthostatic hypotension, tachycardia, throbbing headache, and elevation of intracranial pressure.

Tolerance: Tolerance to the action of nitrates develops rapidly. It can be overcome by provision of a daily " nitrate-free interval " to restore sensitivity to the drug. This interval is typically 6 to 8 hours, usually at night because there is decreased demand on the heart at that time.

Organic nitrates

Agents	Route of administration	Onset (min)	Duration	Uses	
				attack	course
Nitroglycerin (tab., caps., sol.)	Sublingual	1-2	10-30 min	+	-
Nitroderm (patch)	Trans Dermal	15-30	upto 24 hrs	-	+
Isosorbide dinitrate	Sublingual, Oral	3-10 20-60	1-12 hrs	+-	+
Isosorbide mononitrate	Oral	30 min - 2 hrs	4-14 hrs	-	+

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»

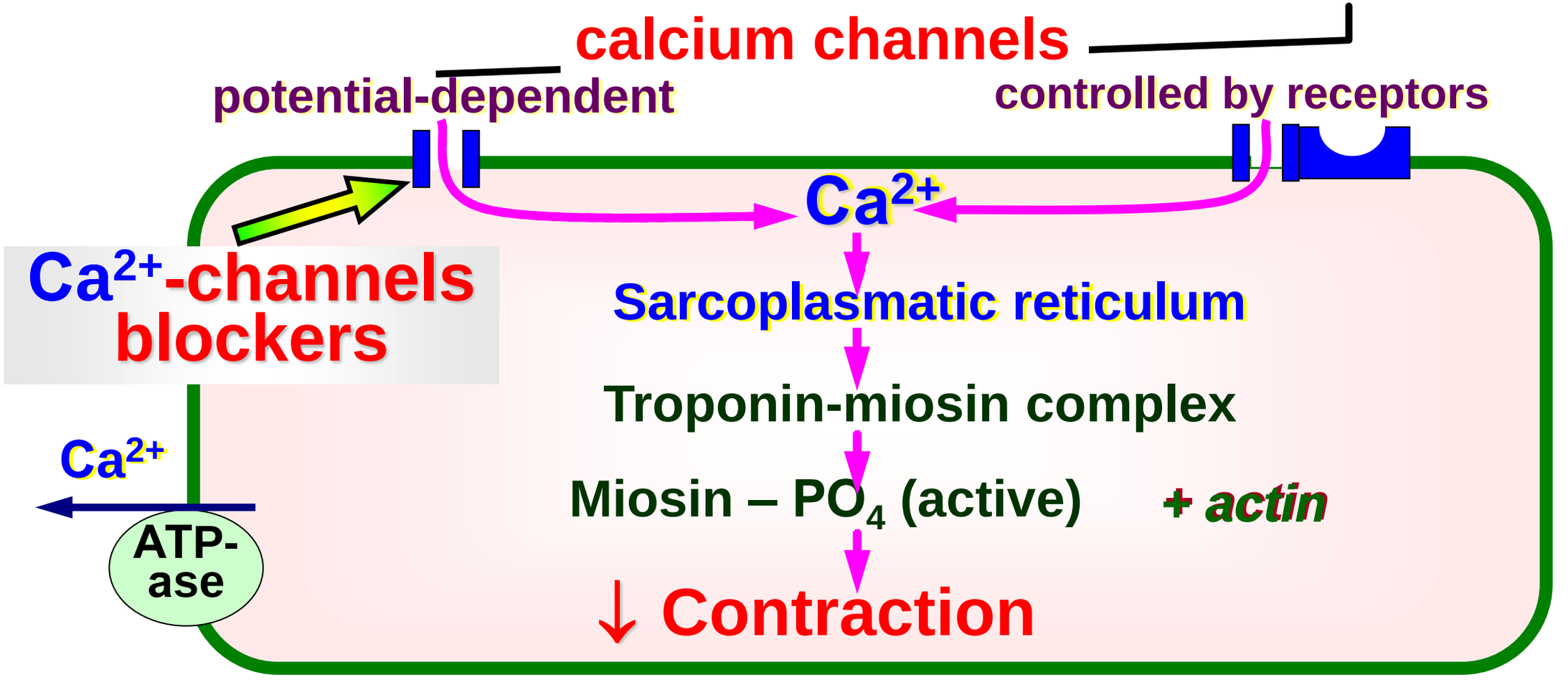
1966 and 1971 yy. **nifedipine** and **dilthiazem** (correspondently) were got

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 hypo-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, cinnarizin) ⇒ 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

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

CALCIUM CHANNELS BLOCKERS

Mechanism of action and effects on cardiovascular system.

inhibit the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. The result is a marked decrease in transmembrane calcium current associated

- in smooth muscle with a long-lasting relaxation (decreased arteriolar tone and systemic vascular resistance, resulting in decreased arterial and intraventricular pressure);
- in cardiac muscle
  - with a reduction in contractility throughout the heart which in turn reduces myocardial oxygen requirements;
  - decreases in sinus node pacemaker rate and in atrioventricular node conduction velocity.

CALCIUM CHANNELS BLOCKERS

As a result of all of these effects, left ventricular wall stress declines, which reduces myocardial oxygen requirements. Calcium channel-blocking agents also relieve and prevent focal coronary artery spasms - the primary mechanism of variant angina.

Pharmacokinetics: The calcium channel blockers are orally active agents. Verapamil and diltiazem are used by the intravenous route as well. They are characterized by high first-pass effect, high plasma protein binding, and extensive metabolism.

COMPARATIVE CHARACTERISTICS OF CALCIUM CHANNELS BLOCKERS

Function	Verapamil	Nifedipine
Coronary blood flow	↑	↑↑
Arterial BP	↓	↓↓
Heart rate	↓	↑
AV-conductivity	↓	-

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

CALCIUM CHANNELS BLOCKERS

Adverse effects

Recent reports suggest that prompt-acting nifedipine may increase the incidence of myocardial infarction.

Patients receiving beta-adrenoceptor-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers.

The most important adverse effects reported for the calcium channel blockers are direct extensions of their therapeutic action - serious cardiac depression, including cardiac arrest, bradycardia, atrioventricular block, and congestive heart failure. These effects have been rare in clinical use.

Minor toxicity (not usually requiring discontinuance of therapy) includes flushing, edema, dizziness, nausea, and constipation.

CALCIUM CHANNELS BLOCKERS

Recent reports suggest that prompt-acting nifedipine may increase the incidence of myocardial infarction.

Patients receiving beta-adrenoceptor-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers.

Minor toxicity (not usually requiring discontinuance of therapy) includes flushing, edema, dizziness, nausea, and constipation.

β-ADRENERGIC BLOCKERS

Mechanism of action

Beta blockers, are a class of drugs that works by **blocking the neurotransmitters norepinephrine** and epinephrine from binding to receptors. There are three known types of beta receptors, known as beta1 (β1), beta2 (β2) and beta3 (β3).

β1-adrenergic receptors are located commonly in the heart and kidneys.

β2-adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle.

β3- adrenergic receptors are located in fat cells.

When the neurotransmitters are prevented from binding to the receptors, it in turn causes the effects of adrenaline (epinephrine) to be blocked. This action allows the heart to relax and beat more slowly thereby reducing the amount of blood that the heart must pump. Over time, this action improves the pumping mechanism of the heart.

β-ADRENERGIC BLOCKERS

Mechanism of action

These agent by blocking β1 receptors decrease heart rate and contractility, blood pressure, which decrease myocardial oxygen requirements at rest and during exercise.

Propranolol is the prototype of this class of compounds, but other β-blockers, such as **metoprolol** and **atenolol** are equally effective. However, agents with intrinsic sympathomimetic activity (for example, **pindolol**, and **acebutolol**) are less effective in angina and should be avoided.

The β-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction, because they reduce reinfarction and mortality in patients. The β-blockers can be used with nitrates to increase exercise duration and tolerance.

β-ADRENERGIC BLOCKERS

cardiac arrhythmias,
heart failure,
high coronary artery disease risk,
diabetes,
post heart attack (myocardial infarction),
angina pectoris due to coronary atherosclerosis,
hypertension (high blood pressure).
migraine headaches,
glaucoma,
hyperthyroidism,
fibromyalgia,
generalized anxiety disorder,
parkinsonian tremor,
atrial fibrillation.

β-ADRENERGIC BLOCKERS

side effects

diarrhea, stomach cramps, nausea and vomiting. Rash, blurred vision, muscle cramps, fatigue, hypoglycemia or hyperglycemia mask the symptoms of hypoglycemia in diabetic patients.

bradycardia, hypotension, heart failure or heart block in patients with heart problems, cold extremities due to reduced circulation, chest pain and cause heart attacks or sudden death.

Effects on the central nervous system - headache, depression, confusion, dizziness, nightmares, and hallucinations. Beta blockers may cause shortness of breath in asthmatics. Sexual dysfunction may also occur.

β-ADRENERGIC BLOCKERS

They are, however, contraindicated in patients with diabetes, peripheral vascular disease, or chronic obstructive pulmonary disease.

K^+ -channel blockers (amiodaron)

- ✓ block of K^+-channels
- ✓ block of Na^+- and Ca^{2+}-channels
- ✓ β- and α-adrenolytic action

⇒

- ➢ «-» chrono-, dromo-, batmotropic effects
- ➢ preservation of myocardial energetic resources (↑ creatinin sulfate, adenosin and glycogen)
- ➢ ↓ O_2 demand of myocardium
- ➢ ↓ peripheral vascular resistance and BP (moderate)
- ➢ dilation of the coronary vessels

K^+ -channel blockers (amiodaron)

Therapeutic uses

- stenocardia
- tachyarrhythmia

Adverse effects

- cardiac arrhythmia (disturbances of AV-conductivity, bradicardia etc.)
- tremor, ataxia, paresthesia
- thyroid gland disfunction
- pulmonary fibrosis
- liver disturbances
- drug's accumulation in cornea, skin
- photosensibilization etc.

Miscellaneous

- agents, that improve myocardial O_2 supply : miotropic (papavarin, dipyridamol etc.) and reflective action (validol)
- agents, that increase myocardial resistance to hypoxia: antihypoxants, antioxidants, anabolics etc.