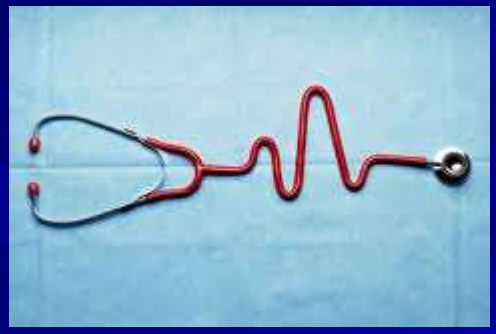
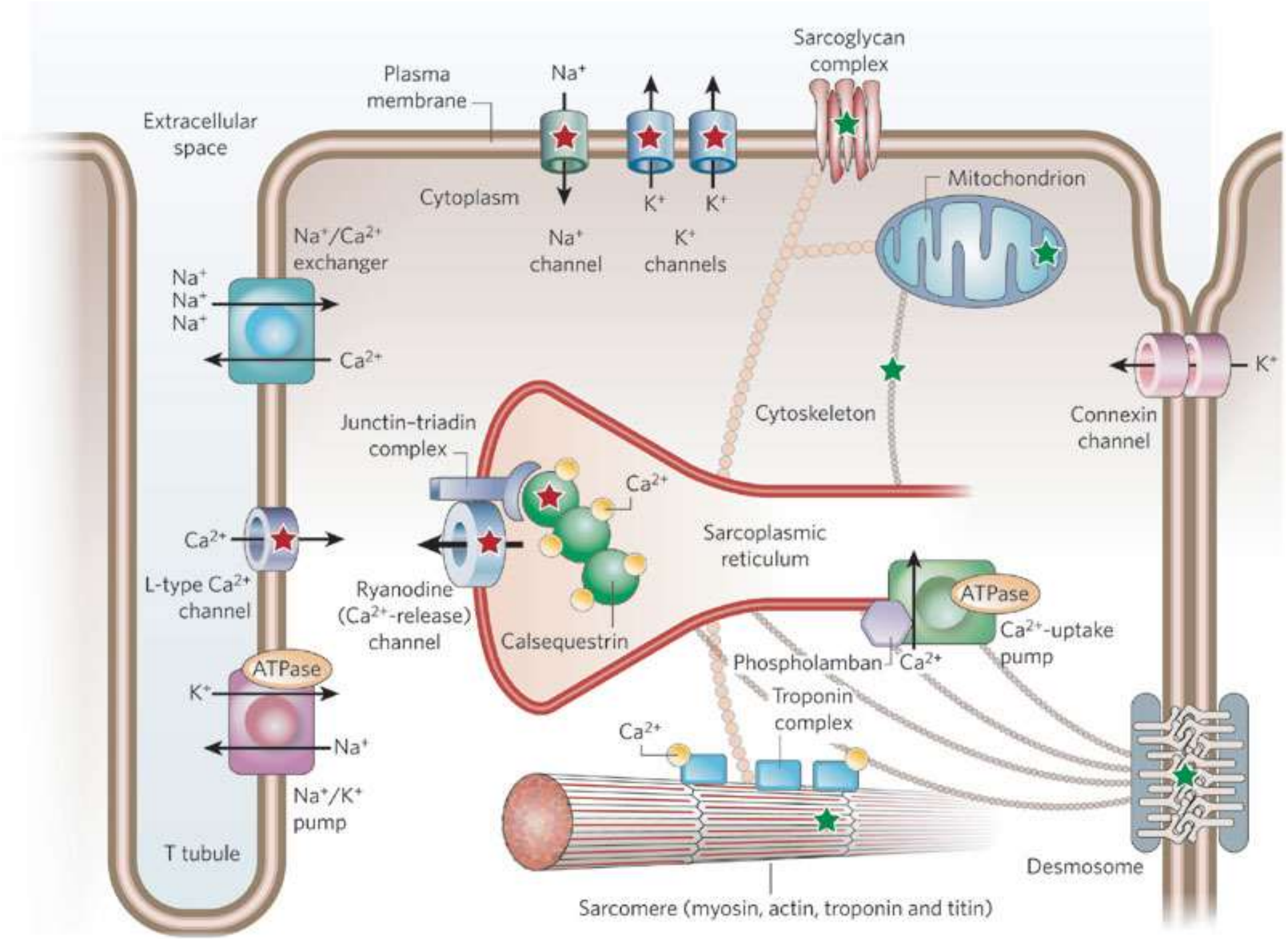
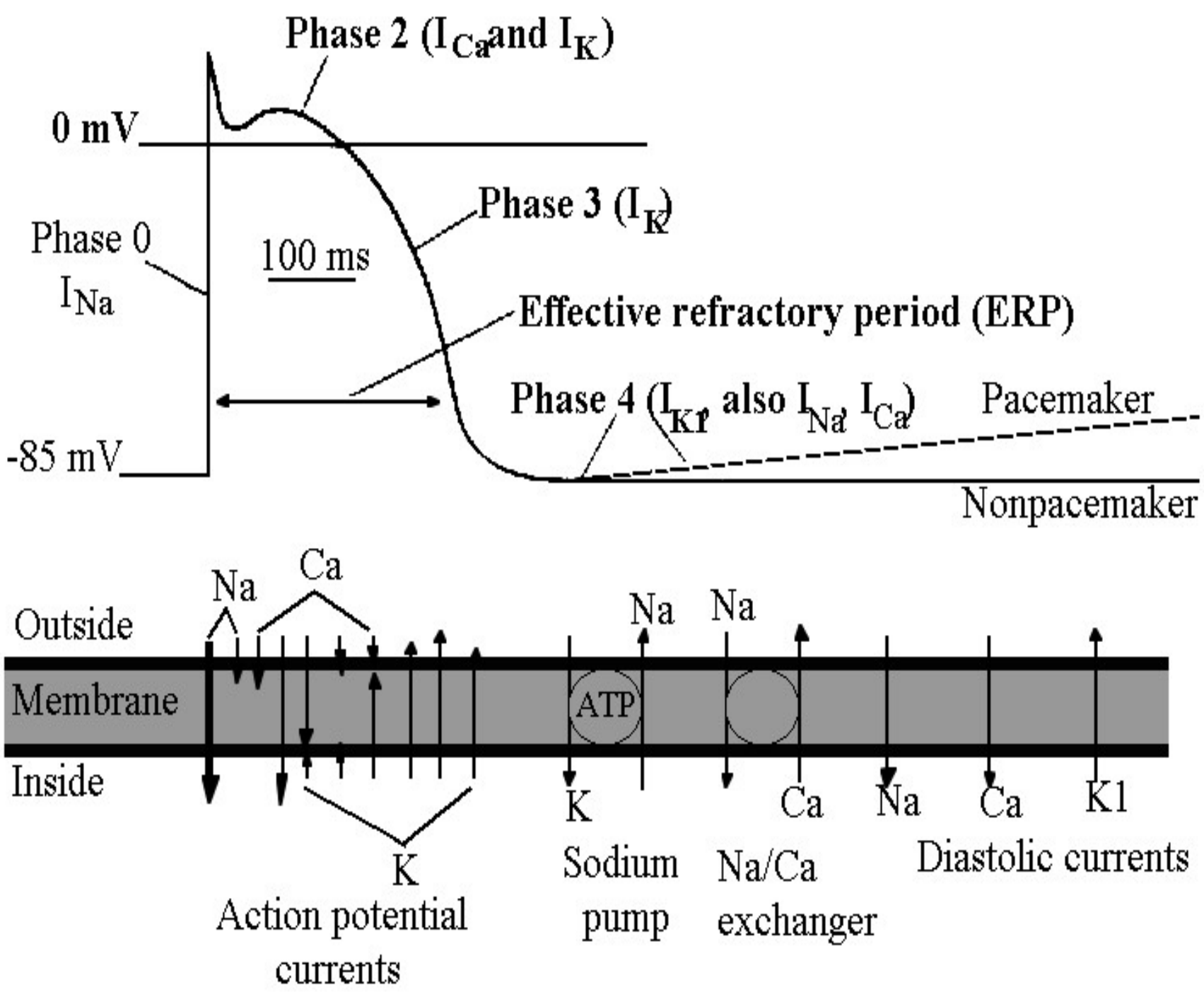
Experimentally induced arrhythmias in rat

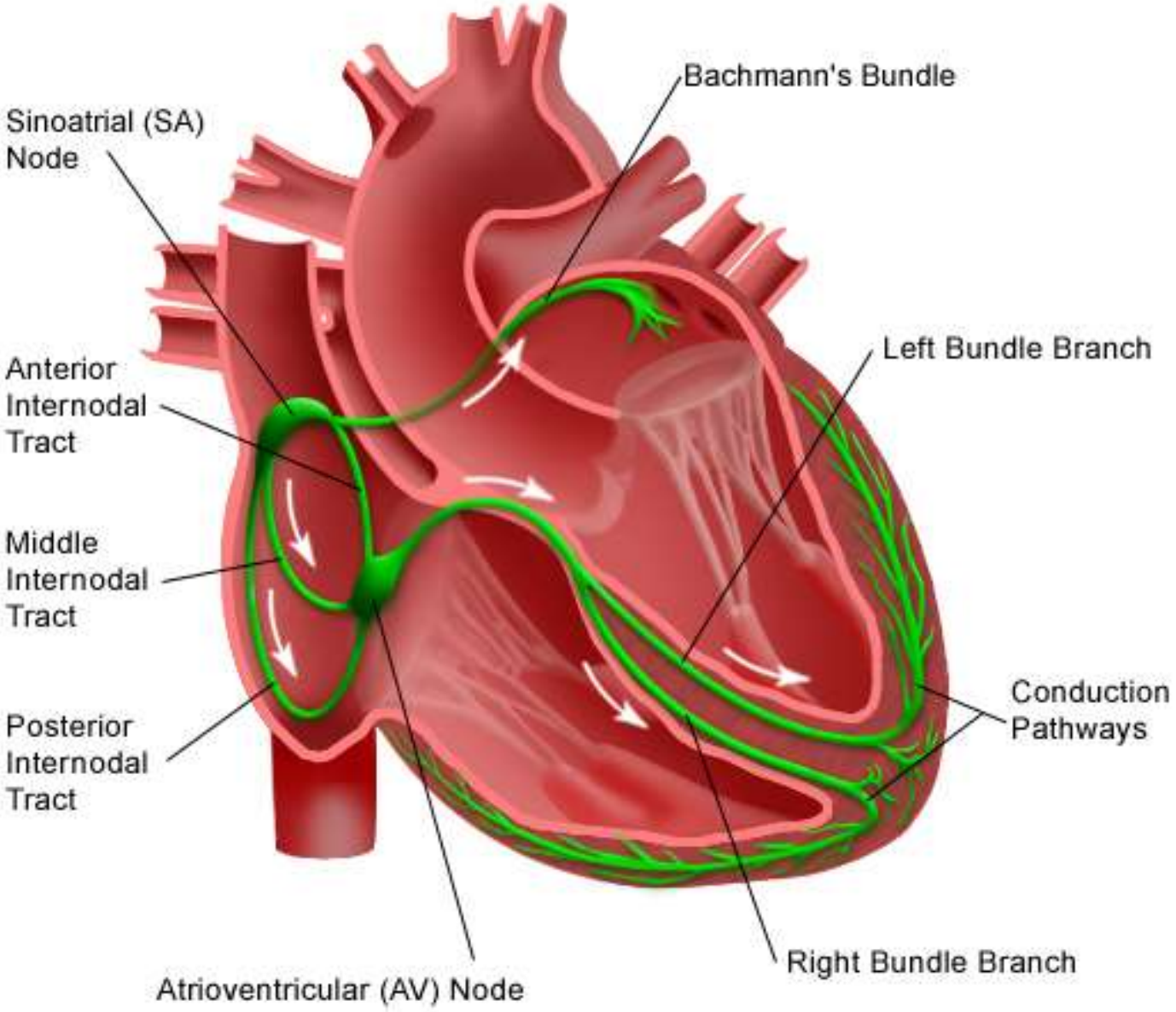


- Adrenergic hyperstimulation
- Hyperkalemia
- Block of cardiac calcium channels

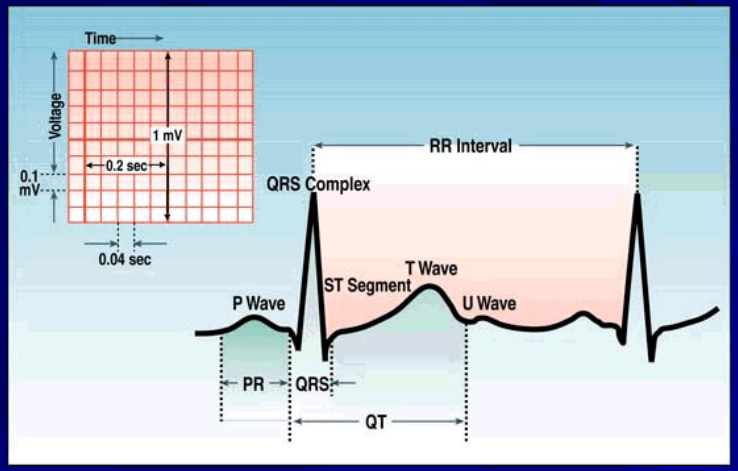

Sarcoglycan complex
Plasma membrane
Na+
Extracellular space
Cytoplasm
K+
K+
Mitochondrion
Na+/Ca2+ exchanger
Na+ channel
K+ channels
Na+
Na+
Na+
Ca2+
Cytoskeleton
K+
Connexin channel
Junctin–triadin complex
Ca2+
Sarcoplasmic reticulum
Ca2+
L-type Ca2+ channel
Ryanodine (Ca2+-release) channel
Calsequestrin
ATPase
Ca2+-uptake pump
Phospholamban
Ca2+
Troponin complex
ATPase
K+
Ca2+
Na+
Na+/K+ pump
T tubule
Desmosome
Sarcomere (myosin, actin, troponin and titin)

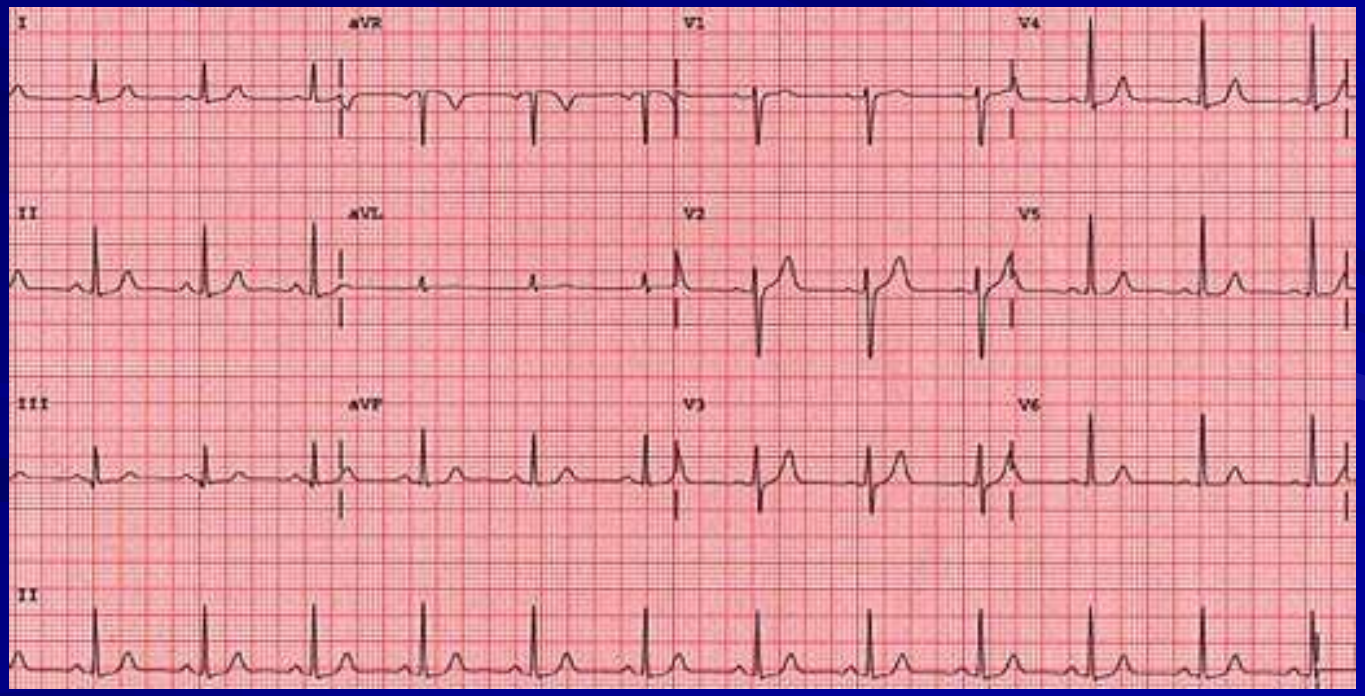

Phase 2 (I_{Ca} and I_K)
0 mV
Phase 3 (I_K)
Phase 0
I_{Na}
100 ms
Effective refractory period (ERP)
Phase 4 (I_{K1} also I_{Na}, I_{Ca})
Pacemaker
-85 mV
Nonpacemaker
Na
Ca
Outside
Membrane
Inside
ATP
Na
Na
K
Ca
Na
Ca
K1
K
Action potential currents
Sodium pump
Na/Ca exchanger
Diastolic currents

Electrical System of the Heart

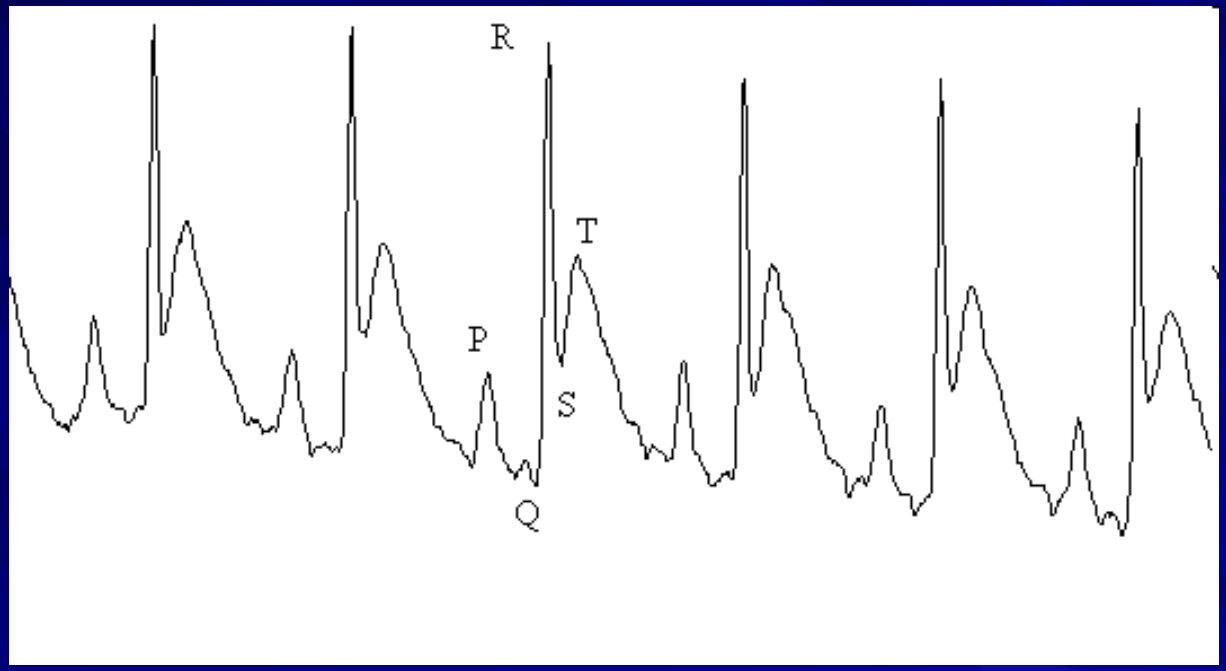


Normal ECG curve in human…





…and in rat heart



Note the missing ST segment (phase 2 = plateau of the ventricles)
SA nodal rate about 300/min

Vegetative nervous system and the heart

Receptors:

- Sympathetic nervous system:

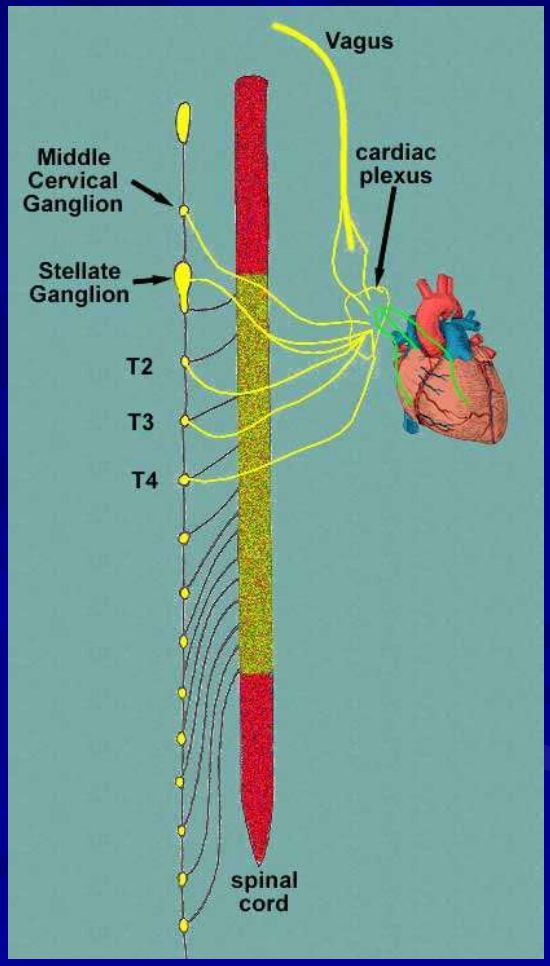
  β1 - positively inotropic, dromotropic and chronotropic (mainly through opening of pacemaker F-channels and Ca^{2+} channels in SA node, AV node and working myocardium)

  β2 – apical myocardium, vessels – vasodilatation

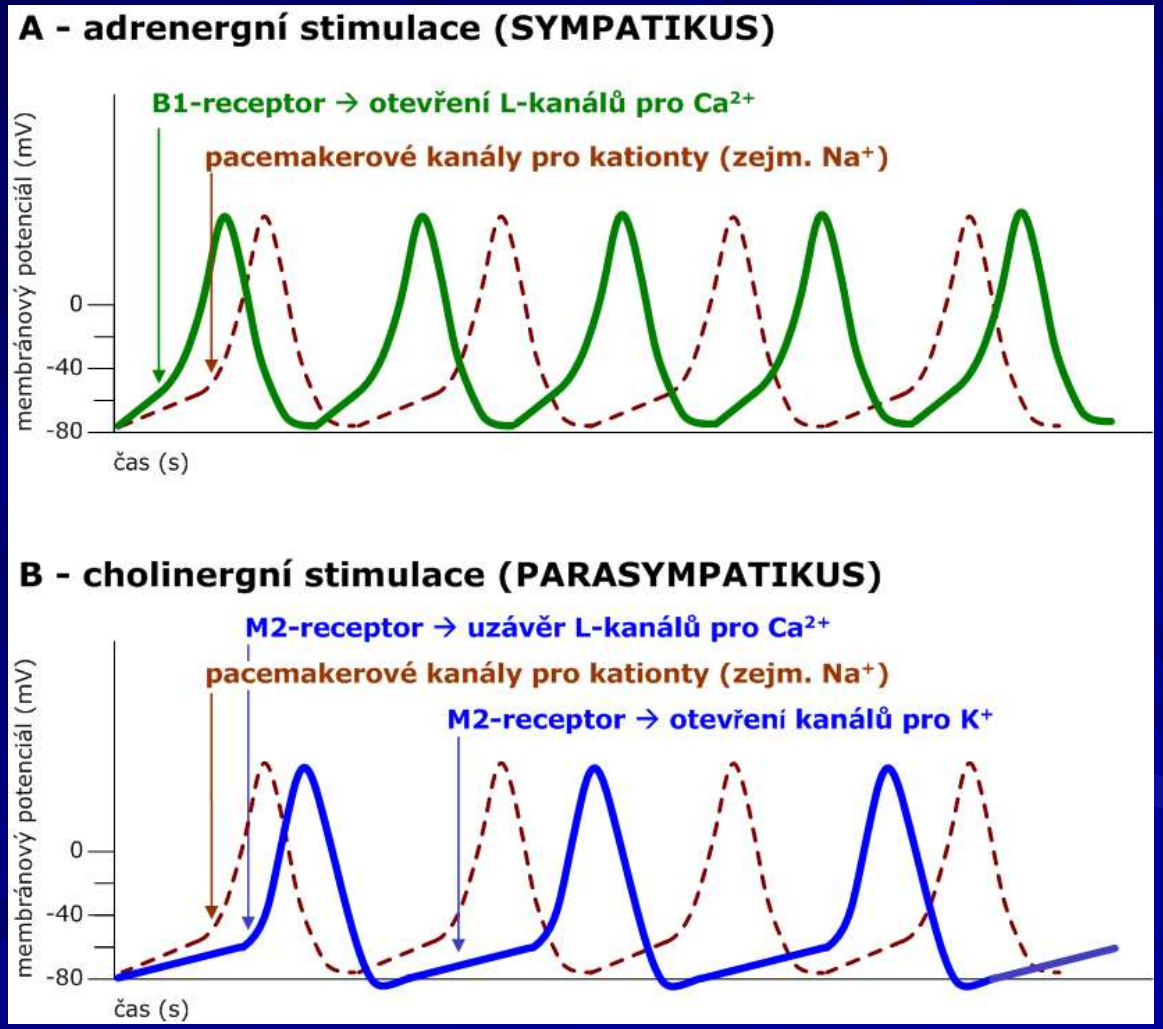
  α1, α2 – vasoconstriction (lower effect in coronary vessels, norepinephrine effect)

- Parasympathetic:

  M2 – negatively chronotropic (inhibits opening of Ca^{2+} channels, opens K_{Ach} channels)

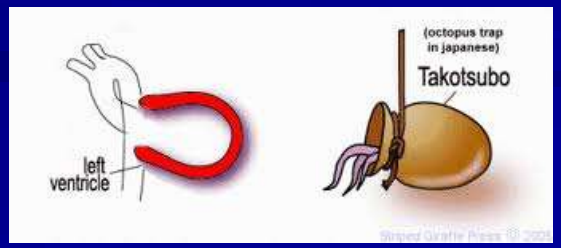


Effects of vegetative nervous system on pacemaker cells



Heart during catecholamine overload

- ↑ heart rate
- ↑ contractility
  - Increase systolic function at the expense of diastolic dysfunction
- Calcium overload of cardiomyocytes
  - DAD → premature beats
  - ↑ oxygene consumption → ischemia
- β2-receptor phosphorylation – transition from G_s to G_i signalization → decreased contractility in the apex
  - but it acts against Ca overload and necrosis
- Vasoconstriction?



Potassium

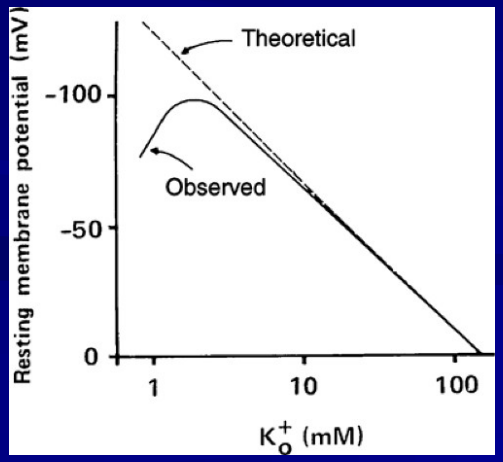
- The most abundant intracellular cation (98% intracellulary)
- Most willingly passes cellular membrane
- Concentration gradient is maintained by Na+/K+ ATPase
- The extra/intracellular distribution is regulated by hormones (insulin, adrenaline, aldosterone) and pH
- Its total body content depends mainly on renal functions
- Both hyper- and hypokalemia are frequent conditions in clinical practice and both are proarrhythmogenic

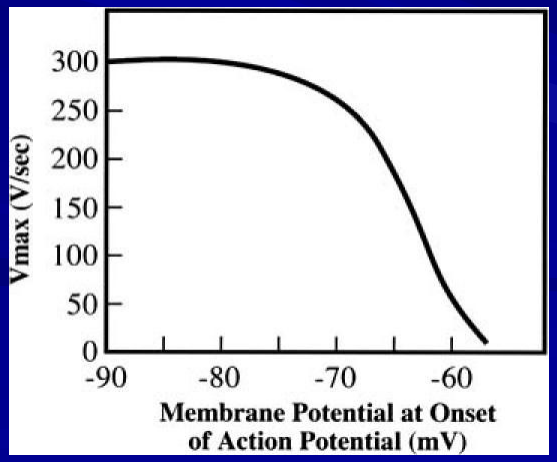
Potassium and the membrane potential

- Positively charged, intracellular ion: ↑ concentration → lowering of membrane polarity (analogy of a small and a large basin connected by a hose)
- Various functionally different K^+ channels
- By various mechanisms, potassium increases the permeability of K^+ channels
  - direct binding
  - competion with Mg^{2+} that closes the K^+ channels
  - changes in expression and translocation

Effect on sodium channels

- Mild hyperkalemia – easier excitation
- Severe hyperkalemia – block of a portion of Na^+ channel
  - Slower conduction
  - Finally the threshold voltage „runs away“ from baseline voltage and the depolarization is no longer possible
- Mild hypokalemia – hyperpolarization
- Severe hypokalemia – lack of substrate for the Na/K ATP-ase → lower polarity, easier excitation

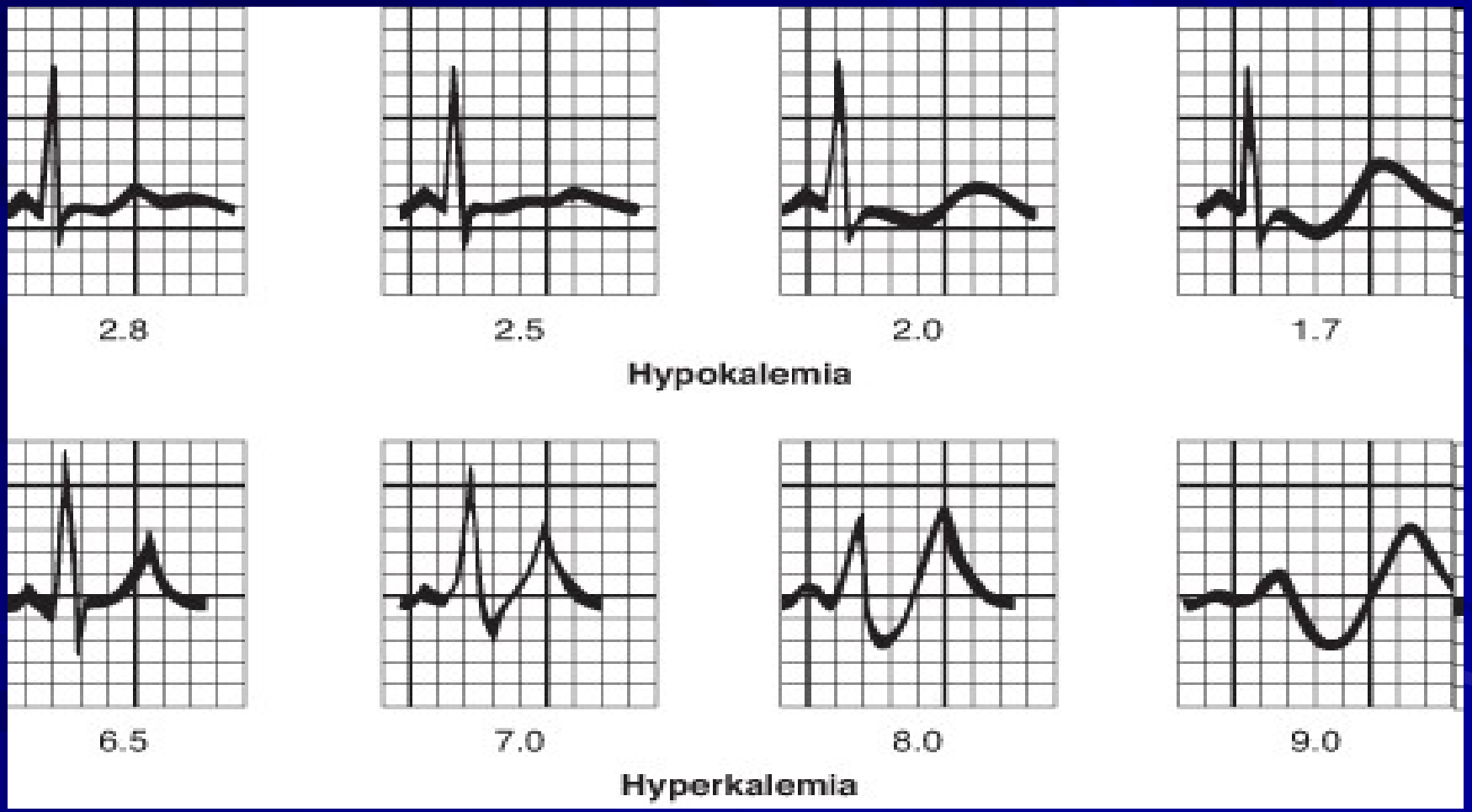




Potassium – main effects

- Hyperkalemia
  - Peaked T wave (dif. dg. hyperacute phase of MI)
  - Wide QRS (may merge into sinusoid wave with T)
  - Widening, flattening and event. disappearing of the P wave (but sinus rhythm remains for a long time)
  - Higher excitability at the beginning, then lower, diastolic arrest in the end (heart is depolarized compared to the normal state)
  - ↑ risk of re-entry (↑ differences in conduction velocities)
- Hypokalemia
  - Flat, wide T-wave
  - Pathologic U wave (delayed repolarization), lengthening of QT (QU) interval
  - EAD, torsades de pointes
  - Sometimes, peaked P is present
  - ↑ risk of re-entry (↑ differences in refraktory periods)
  - First lower excitability (hyperpolarization), then higher

Changes of ECG in hyper-/hypokalemia



Calcium

- Ion that is necessary for muscle contraction
- Intracellulary, it is present in very low concentration (making high gradient between cytoplasm and cell)
- In cardiomyocyte and skeletal muscle, it is also present in sarcoplasmic reticulum
- Cardiomyocyte (and smooth muscle cell) bears specific Ca^{2+}-channels, that are necessary for phase 2 (plateau), pacemaker function and conduction through slow cells
- They can be blocked by specific agents to slow the heart rate and enhance vasodilatation by smooth muscle relaxation

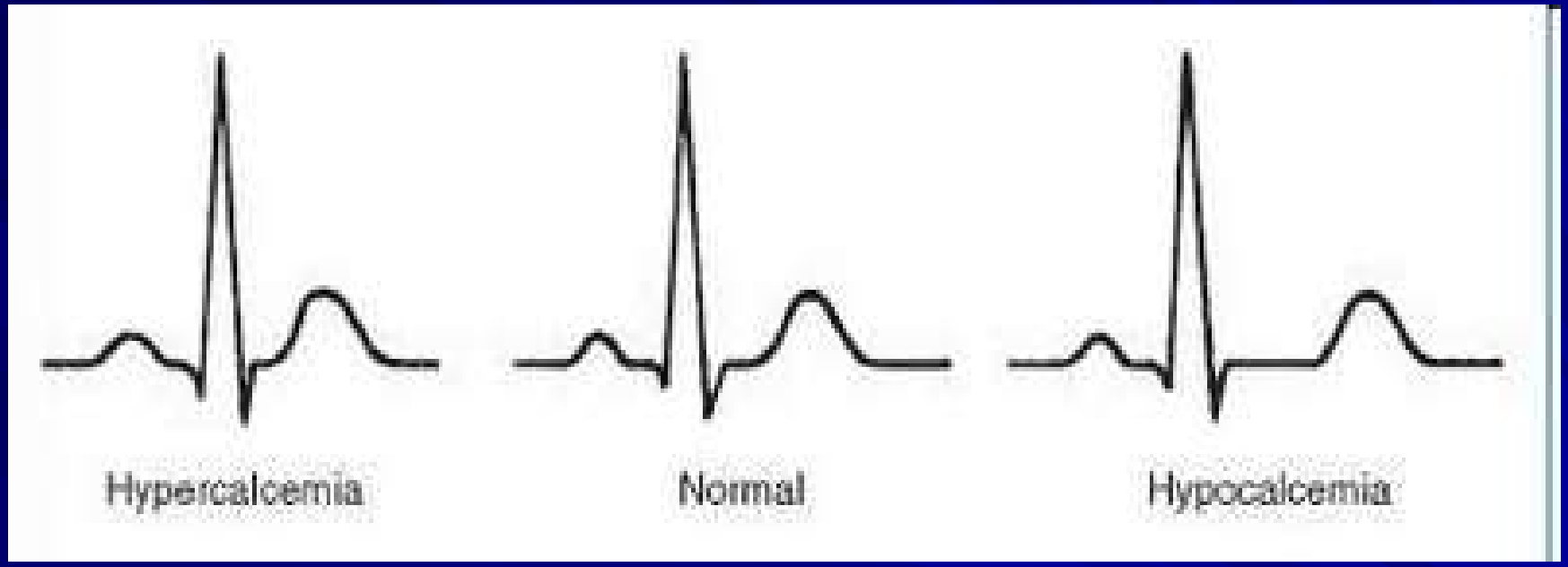
Calcium and the membrane potential

- Extracellular ion – Membrane potential gets into more negative values
- During the action potential, Ca^{2+} activate potassium (and chloride) channels, which shortens the phase 2 → repolarization leads into the closing of Ca^{2+} L-channels
  - the proces is impostant for maintaining the calcium homeostasis in the cell
  - in extreme hypercalcemia, phase 2 may be missing
  - opposite effect may be present in hypocalcemia
- Mechanical effects
  - Extreme hypercalcemia: triggered activity (DAD), systolic arrest (very rare)
  - Extreme hypocalcemia: triggered activity (EAD), hypocalcemic cardiomyopathy, heart failure

Blocking the calcium channels

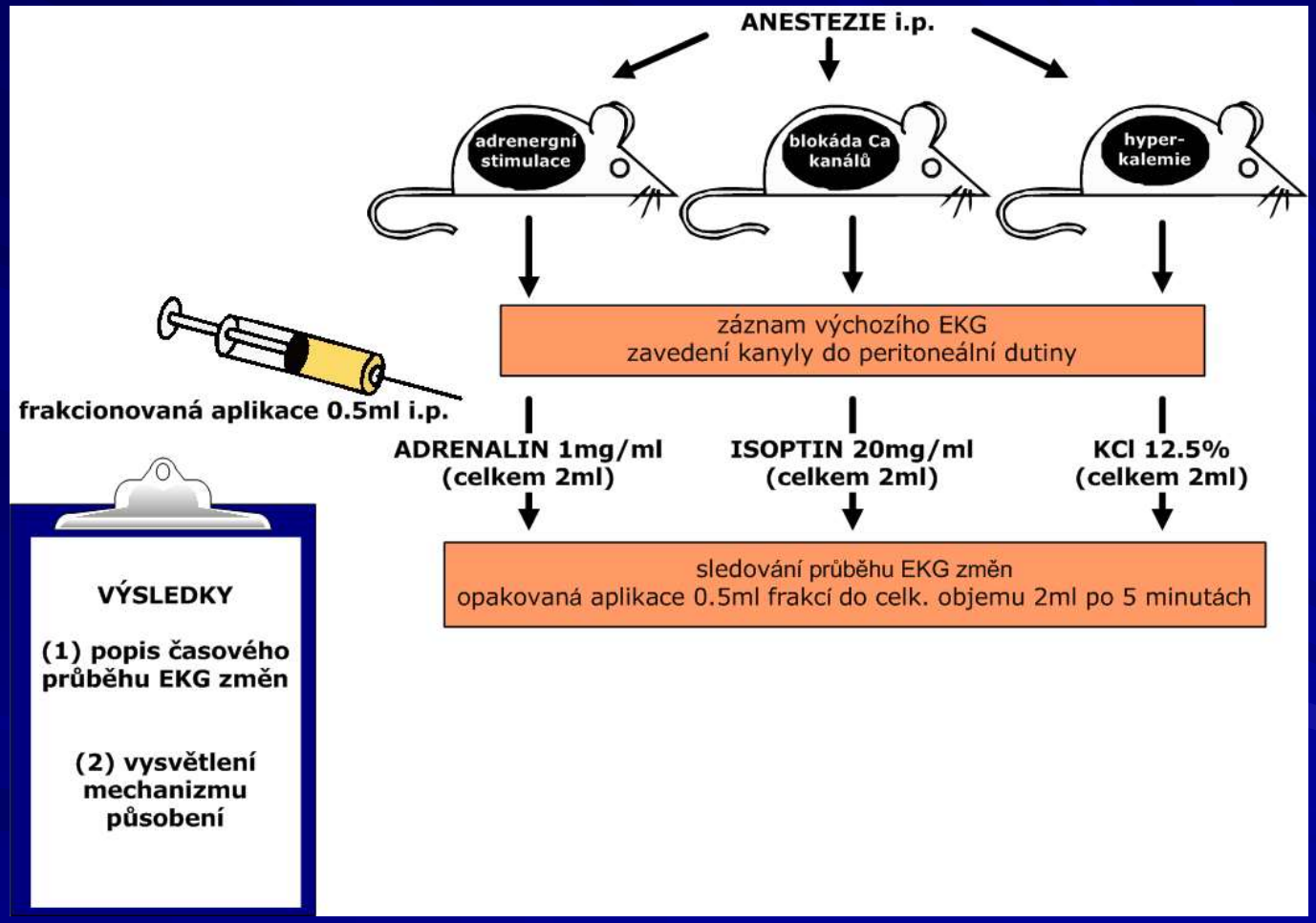
- Verapamil – class IV antiarrhythmic drug
- Tissue distribution roughly symmetrically in the heart and smooth muscle
- Indikace: antiarrhythmic, antihypertenzive (rather rarely), local vasodilatant
- Overdose – effect mainly on the slow cells
  - SA arrest and block
  - AV block
  - Low contractility
  - Long QT may sometimes be present

ECG in calcium levels changes



- The Ca2+ channels-blockers mainly induce the conduction (SA or AV) node blocks and slower pacemaker function

Practical


ANESTEZIE i.p.
adrenergní stimulace
blokáda Ca kanálů
hyper-kalemie
záznam výchozího EKG
zavedení kanyly do peritoneální dutiny
frakcionovaná aplikace 0.5ml i.p.
ADRENALIN 1mg/ml (celkem 2ml)
ISOPTIN 20mg/ml (celkem 2ml)
KCl 12.5% (celkem 2ml)
sledování průběhu EKG změn
opakovaná aplikace 0.5ml frakcí do celk. objemu 2ml po 5 minutách
VÝSLEDKY
(1) popis časového průběhu EKG změn
(2) vysvětlení mechanizmu působení