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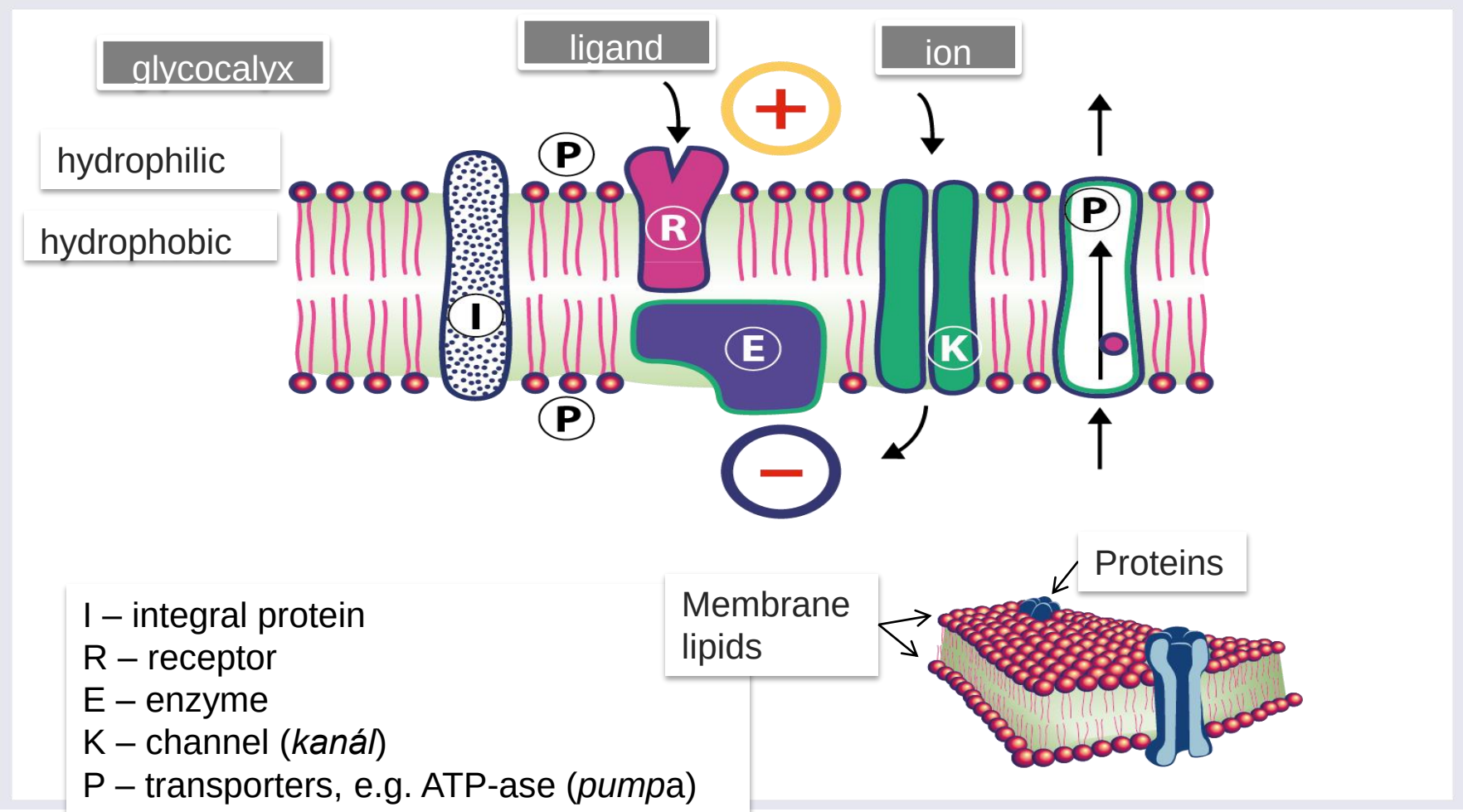
PHYSIOLOGY OF THE CELL

Seminar I.

PLASMATIC MEMBRANE



I – integral protein
R – receptor
E – enzyme
K – channel (*kanál*)
P – transporters, e.g. ATP-ase (*pumpa*)

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INTER-CELLULAR CONTACT

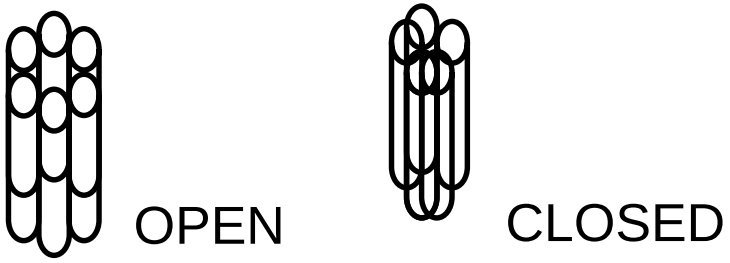
MECHANICAL COUPLING

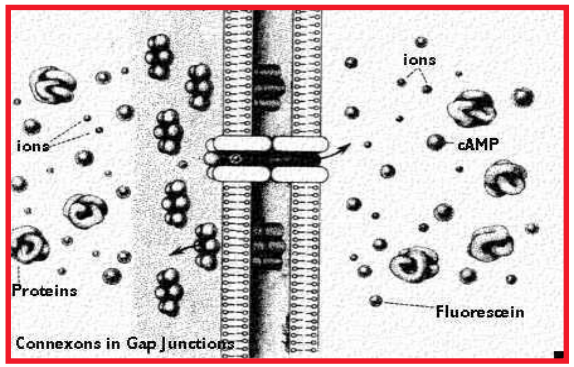
• desmosomes (macula adherens; cell adhesion and mechanical stability of tissues) – epidermis, liver, myocardium

ELECTRICAL COUPLING

• gap junction (nexus), consists of two connexons, forms s.-c. electrical synapse (neuron)

CONNEXON 6 subunits, connexin
1-2 nm central channel





Marie Nováková, 2020-2021

HUMORAL COUPLING (REGULATION)

autocrine

paracrine (neurocrine)

endocrine (neuroendocrine)

juxtacrine

NERVOUS COUPLING (REGULATION)

Integration of humoral and nervous regulations in organism

Receptor, ligand, second messenger.

Neurotransmitters *vs.* tissue „hormones“ *vs.* „classic“ hormones

1. Number of receptors
2. Number of ligands
3. Subtypes of receptors
4. Competition on receptors
5. Endogenous ligands, exogenous ligands
6. Orphan receptors
7. Placement of receptors
8. Convergence and divergence of the effects
9. Transmission of information intracellularly

SECOND MESSENGER SYSTEMS

cAMP, cGMP, IP_3, DAG, Ca^{2+}-calmodulin

cAMP

H-R complex binds to G-protein – stimulatory or inhibitory
(α, β and γ subunits)
Mg^{2+}, HR β–γ
Activation or inhibition of adenylcyclase ↑ ↓ cAMP
Activation of proteinkinases ⟶ protein phosphorylation

Direct regulation of ionic channels and exchangers (K^+, Ca^{2+})

G_s: glucagon, oxytocin, histamine, dopamine, ADH, FSH, TSH, AD ($\beta_{1,2}$)

G_i: Ach, opioids, AGII, AD (α_2), dopamine

IP_3 / DAG

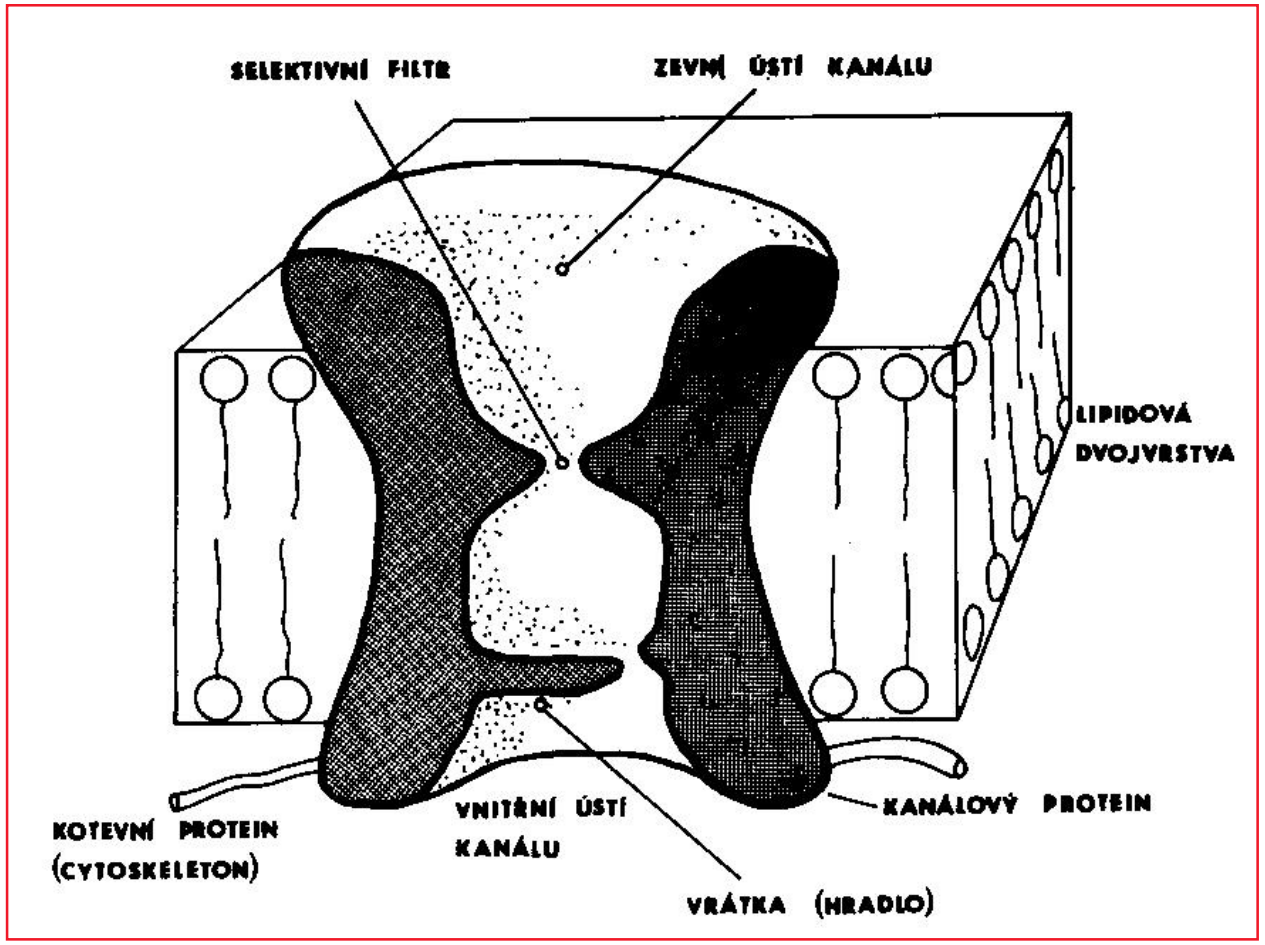
H-R complex binds to G-protein – G_q
Activation of phospholipase C ⟶ PIP_2 ⟶ IP_3 and DAG

DAG: activates proteinkinase C
Phosphorylation of Na^+/H^+ pump ↓ pH_i
Effect of prostaglandins and prostacyclin

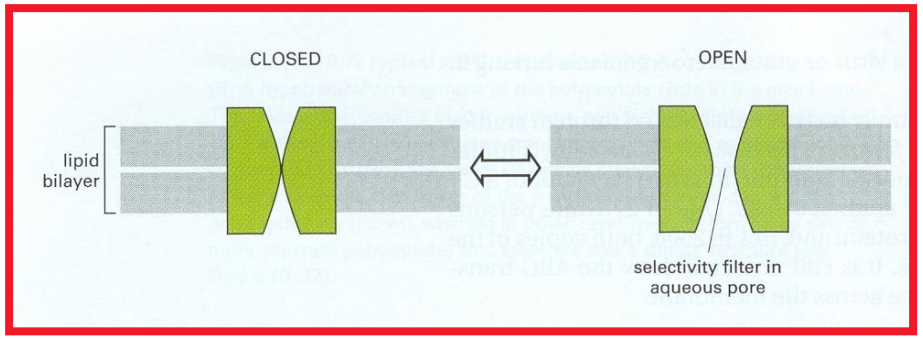
IP_3: translocation to endoplasmic reticulum
IP_3 receptor (subtypes), opening of calcium channels
Increase in cytoplasmic availability of calcium - „**third messenger**“

G_q: AD (α_1), Ach, thyreoliberin, ADH, thromboxane

IONIC CHANNELS



Membránová elektrofyziologie myokardu, P. Pučelík, Avicenum, 1990



Molecular biology of the cell. B. Alberts et al., Garland Science 2002

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CHANNELS WITHOUT GATES

GATED CHANNELS

1. **VOLTAGE** GATED CHANNELS

- One-gate channels (activation vs. deactivation)
- Two-gates channels (activation vs. inactivation vs. recovery from inactivation)

2. **LIGAND** GATED CHANNELS (nicotinic cholinergic receptor; ATP-sensitive K^+ channel)
3. **G-PROTEIN** GATED CHANNELS (Ach-sensitive K^+ channel of SA node – muscarinic receptor)
4. **MECHANICALLY** GATED CHANNELS – „stretch receptors“ (K^+ , Ca^{2+})

RESTING MEMBRANE POTENTIAL

= difference between electrical potential of intra- and extracellular solution (at rest).

Different composition of IC and EC environment is kept by membrane transport mechanisms.

DIFUSSION CURRENTS: ionic currents across the membrane (in both directions) through open ionic channels (specific channels) = simple diffusion according to concentration gradient

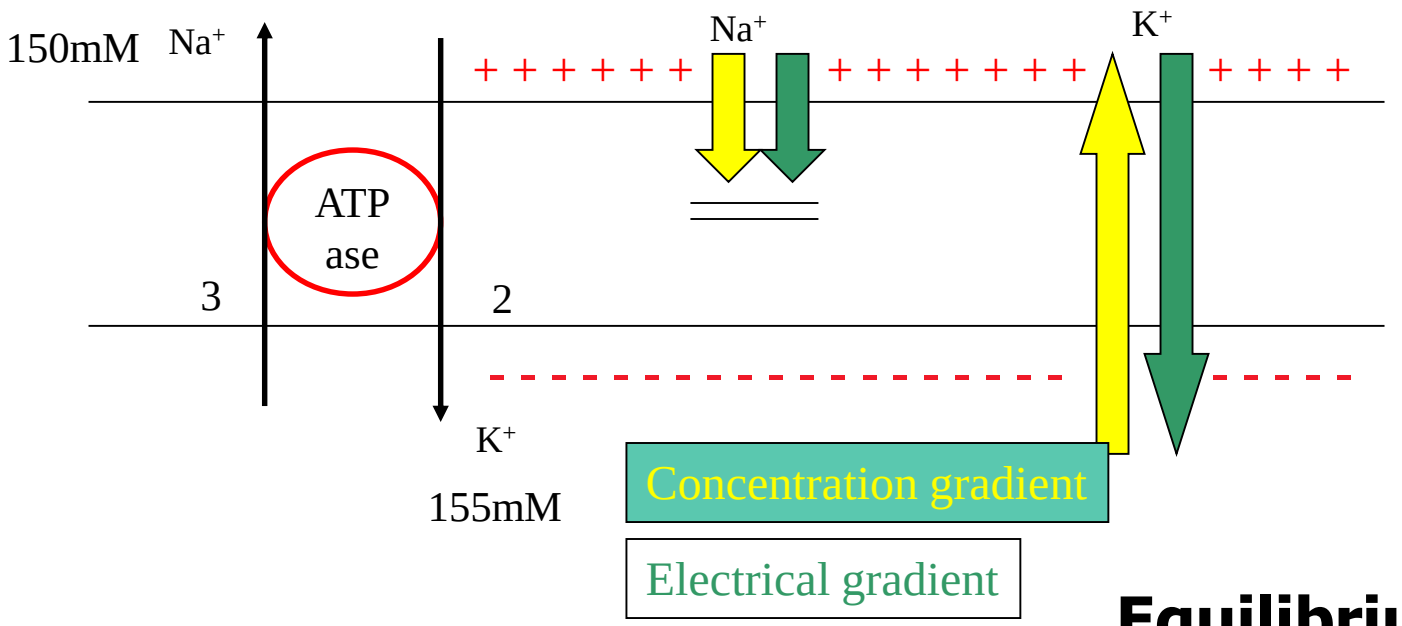
ELECTROCHEMICAL GRADIENT

- semipermeable membrane
- different conductivity for ions
- the force given by concentration gradient equals to the force given by electrical gradient

DONNAN EQUILIBRIUM (D. PHENOMENON)

Concentration of anions multiplied by concentration of cations on one side of membrane equals to concentration of anions multiplied by concentration of cations on the other side of membrane.

RESTING MEMBRANE VOLTAGE



Nernst equation:

$$E_x = \frac{R \cdot T}{F} \ln \frac{(Cx_{out})}{(Cx_{in})}$$

$$I_x = g_x \cdot (E - E_x)$$

Equilibrium potential

E_{Na} = +40 mV

E_K = -90 mV

E_{Cl} = -70 mV

E_{Ca} = +60 mV

E_r = -85 mV

I – current, E – voltage, g – specific voltage and time-dependent conductance

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GOLDMAN (HODGKIN-KATZ) EQUATION

$$MP = g_K \cdot E_K + g_{Na} \cdot E_{Na} + g_{Cl} \cdot E_{Cl} / g_K + g_{Na} + g_{Cl}$$

Respects the fact that even at rest there are membrane currents present –

background current (inward, outward).

PHYSIOLOGICAL SIGNIFICANCE OF RESTING MEMBRANE POTENTIAL

Possibility to code and transmit information in living systems (excitable tissues) – in the form of **action potential**

Triggering of muscle contraction by action potential!

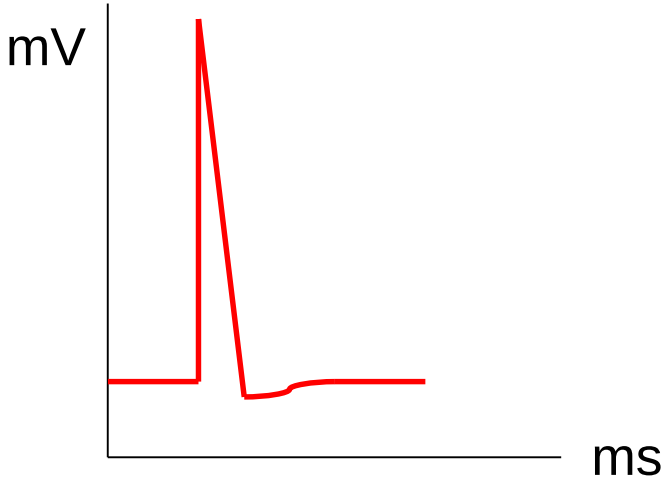
ACTION POTENTIAL

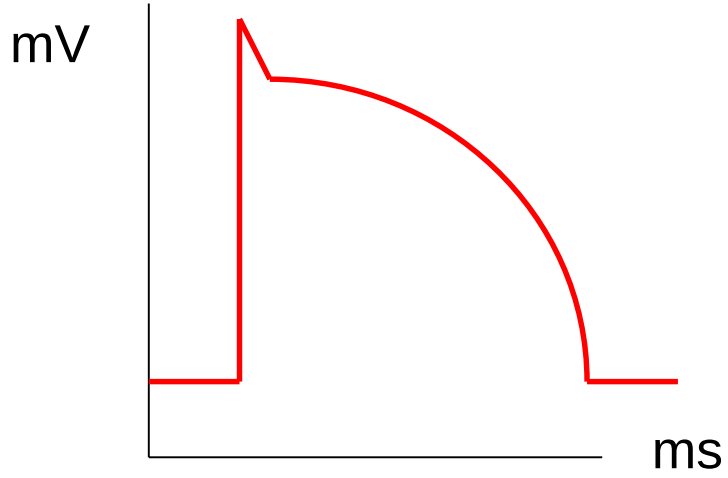
LOCAL RESPONSE

Changes of conductivity of the membrane for particular ions
(opening the ion-specific channels)

Depolarization, transpolarization, repolarization. **REFRACTERITY.**

Inward currents x outward currents.





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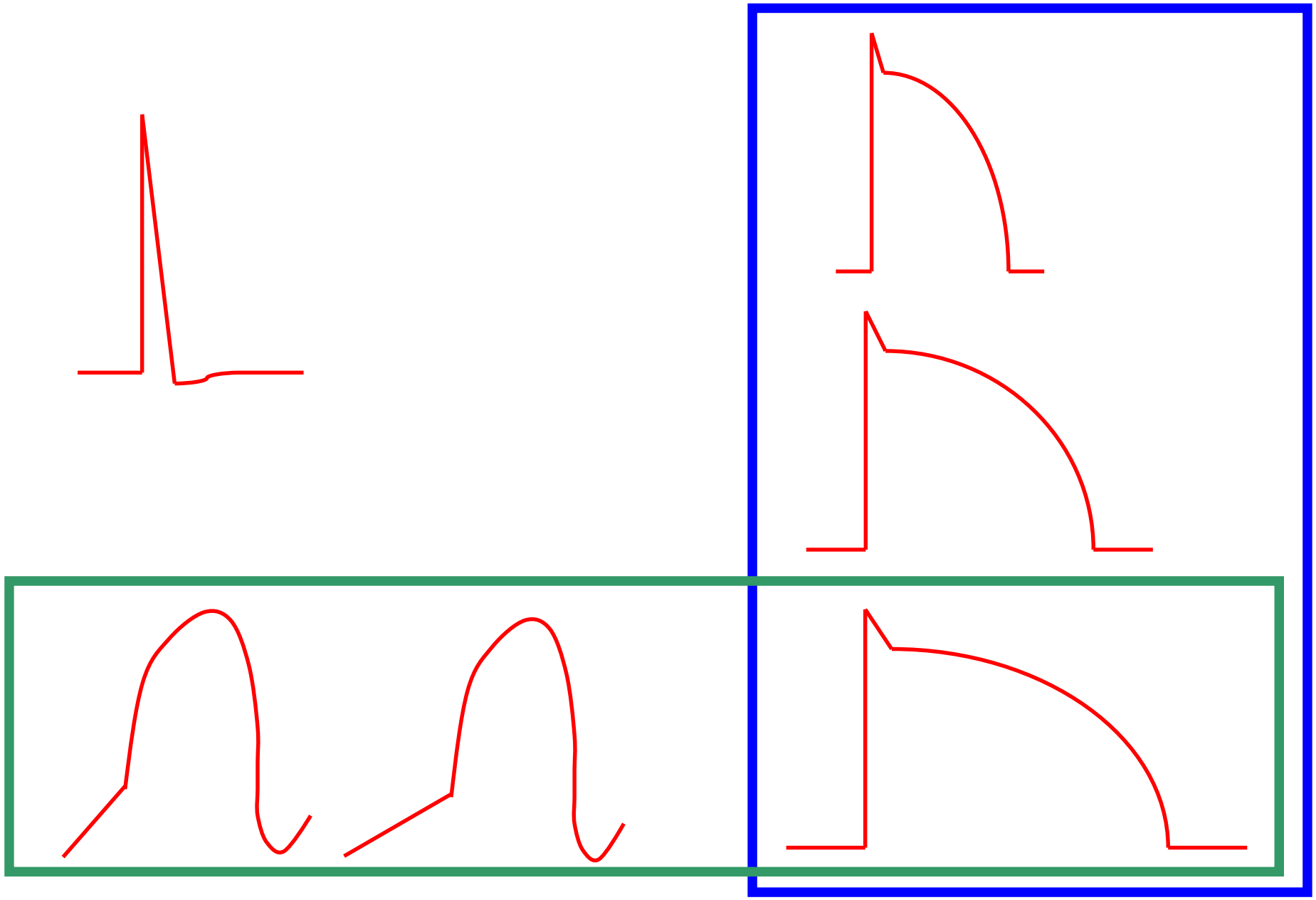

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MUSCLE CONTRACTION AND RELAXATION

CONTRACTILE PROTEINS

ACTIN – globular, 400 molecules = chain = F-actin; 2 chains in spiral = filament

MYOSIN – „thick“ filaments, head with ATP-ase activity, filament = 150 – 360 molecules of myosin (head + neck = heavy meromyosin, light meromyosin)

MODULATORY PROTEINS

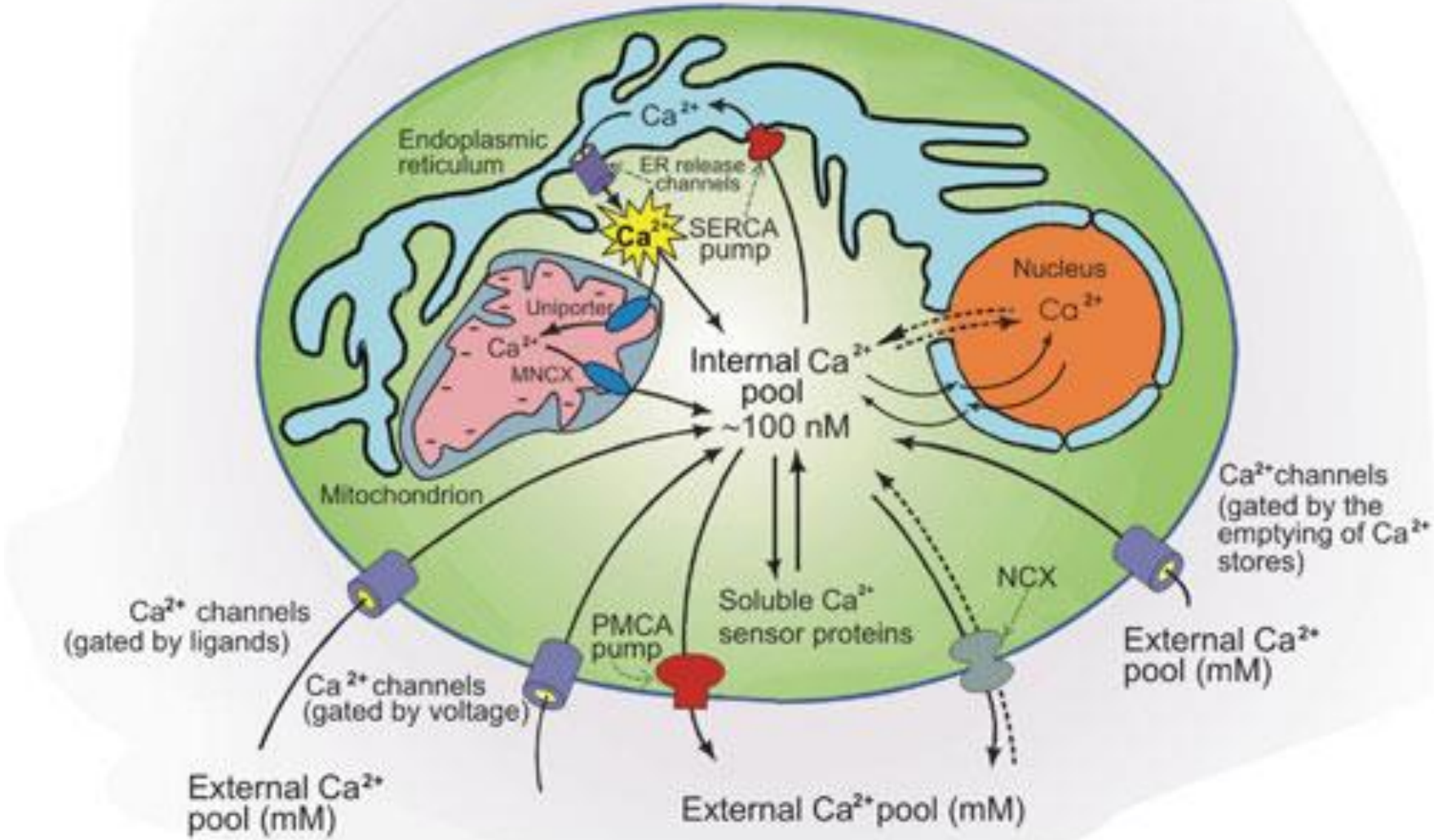
TROPONIN – C, I, T

TROPOMYOSIN

PHYSIOLOGICAL ROLE OF CALCIUM

PRINCIPLE OF MUSCLE RELAXATION

Removal of calcium from cytoplasm


Endoplasmic reticulum
Ca2+
ER release channels
Ca2+
SERCA pump
Nucleus
Ca2+
Uniporter
Ca2+
MNCX
Internal Ca2+ pool ~100 nM
Mitochondrion
Ca2+channels (gated by the emptying of Ca2+ stores)
Ca2+ channels (gated by ligands)
Soluble Ca2+ sensor proteins
NCX
PMCA pump
External Ca2+ pool (mM)
Ca2+ channels (gated by voltage)
External Ca2+ pool (mM)
External Ca2+pool (mM)

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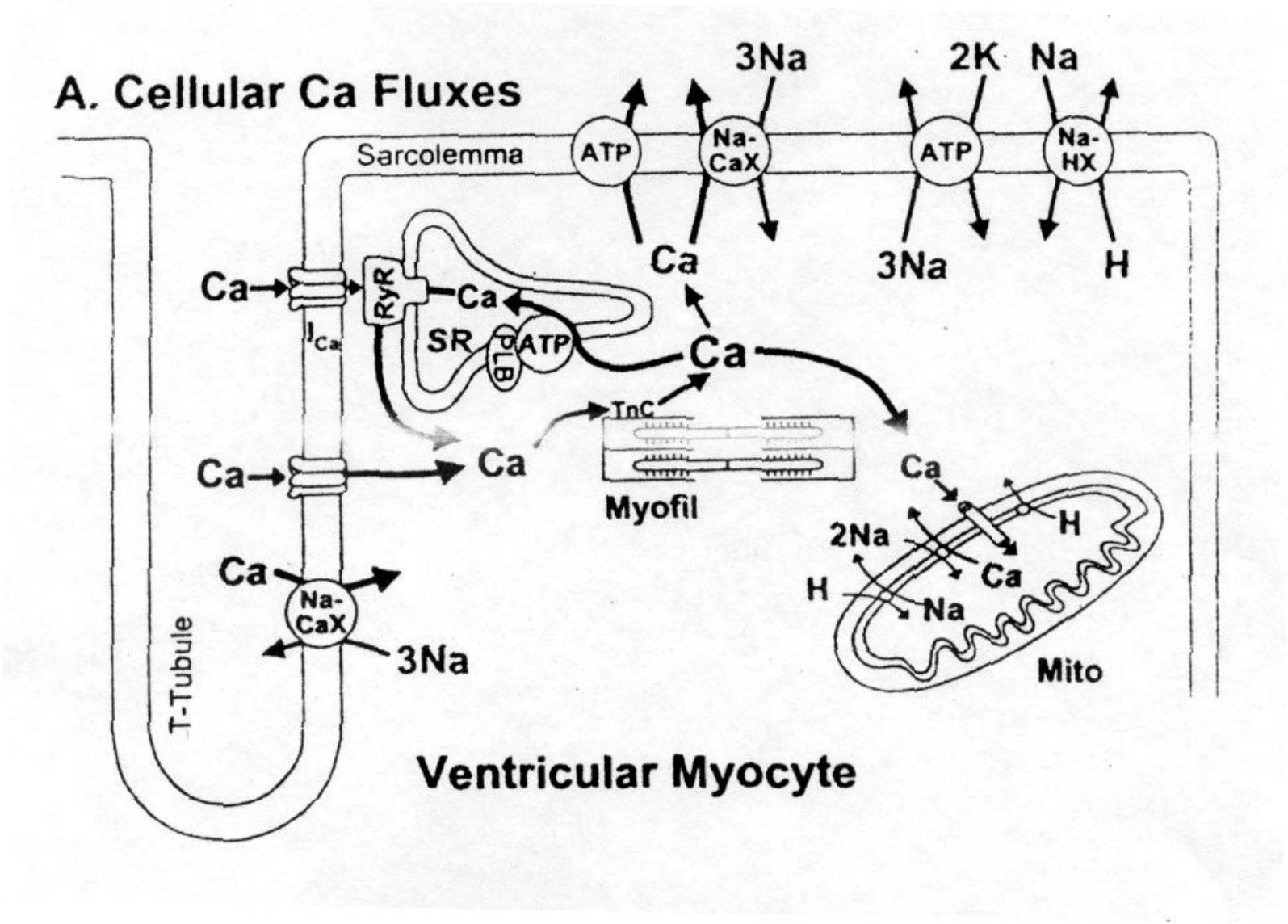
A. Cellular Ca Fluxes
3Na
2K
Na
Sarcolemma
ATP
Na-CaX
ATP
Na-HX
Ca
3Na
H
Ca
RyR
Ca
SR
PLB
ATP
Ca
I_{Ca}
TnC
Ca
Ca
Myofil
Ca
H
2Na
Ca
H
Na
Ca
Na-CaX
3Na
T-Tubule
Mito
Ventricular Myocyte

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