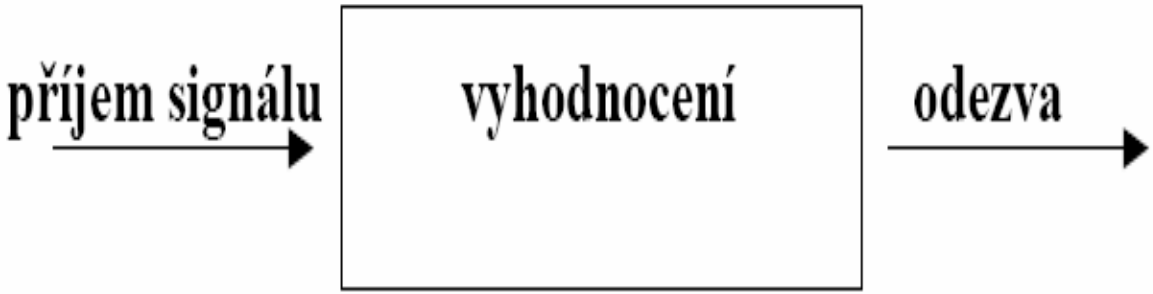
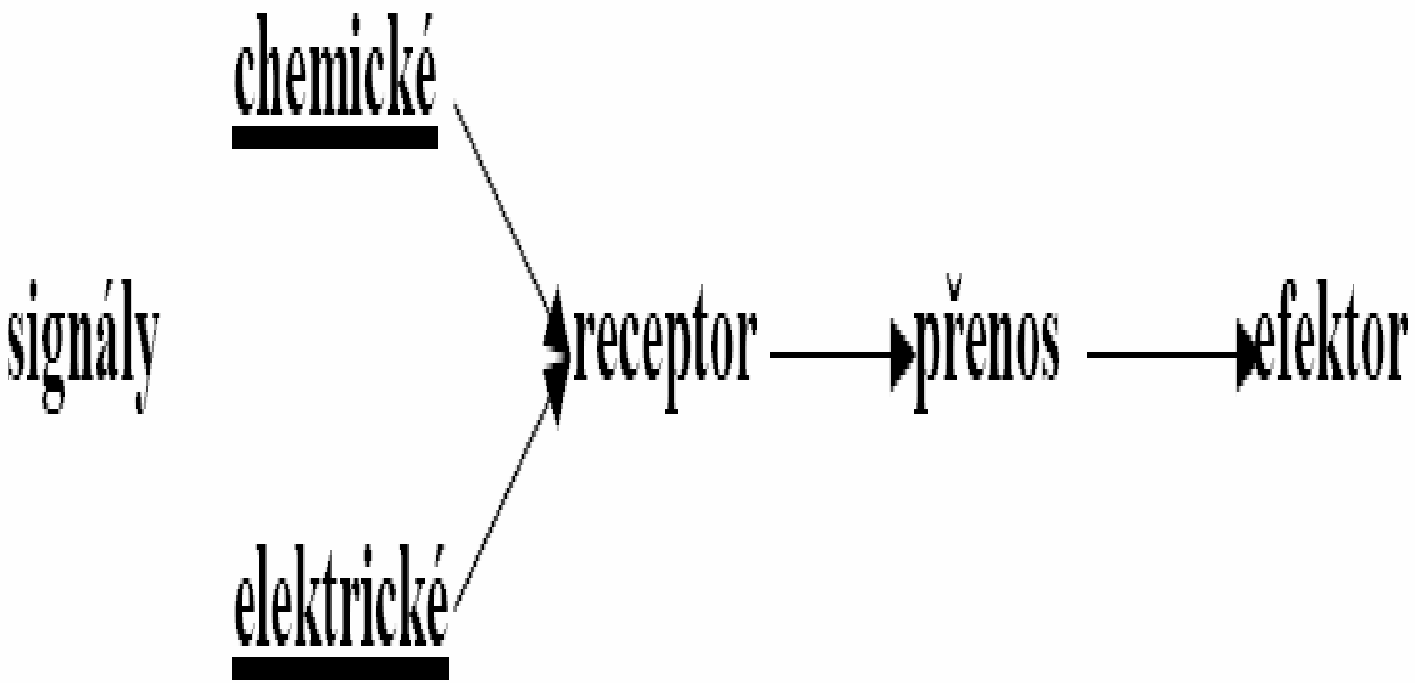
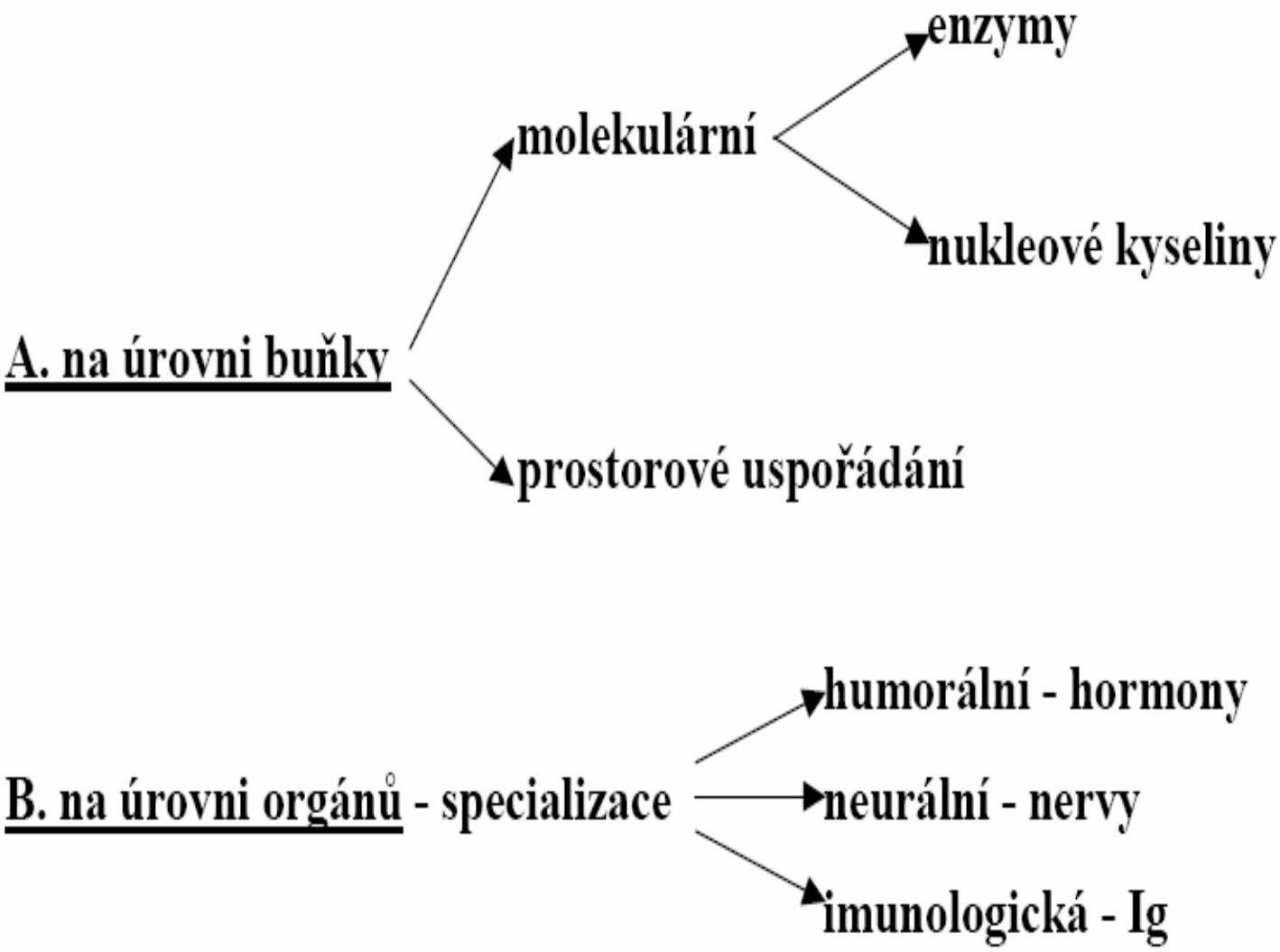
BIOCHEMIE REGULACE

WIENER – kybernetika




chemické
signály
receptor
přenos
efektor
elektrické

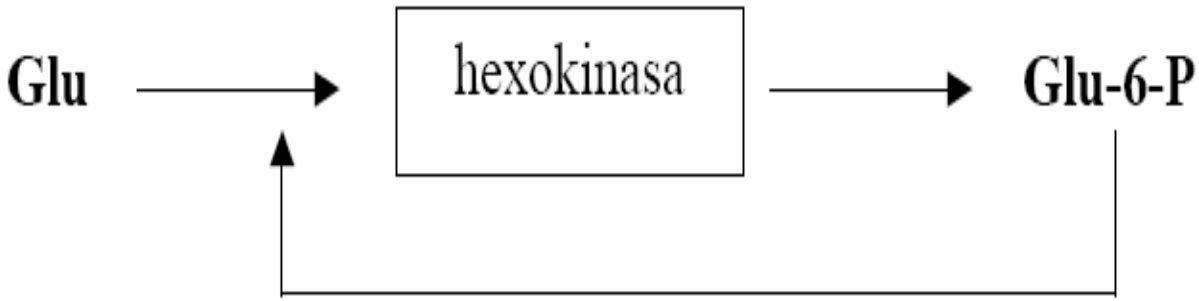
Regulační mechanismy



Regulace na enzymové úrovni – rychlá odezva

- Michaelisovskou kinetikou – hexokinasa Km 10^{-4} M
  – glukokinasa Km 10 mM

- Inhibicí produktem



- Zpětnou vazbou – allosterie negativní x pozitivní

- Řídícími enzymy v cyklech – citrátový cyklus - ICDH

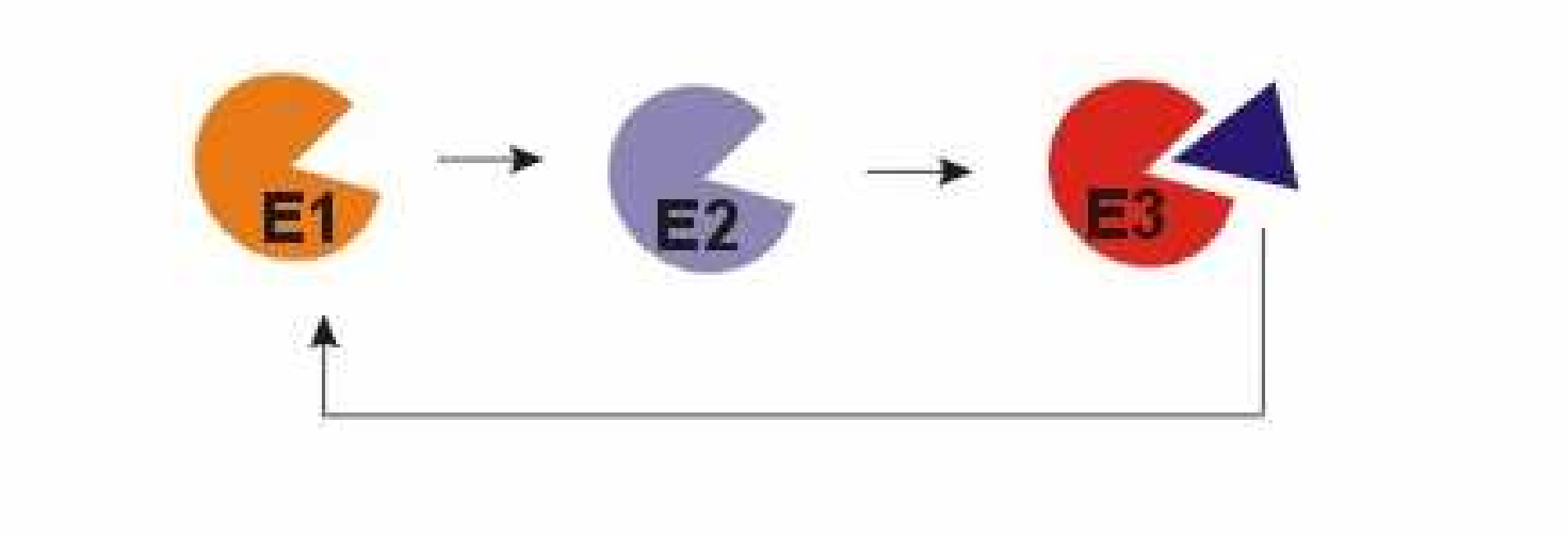
  – glykolysa PFK

- Kovalentí modifikací – proteasy

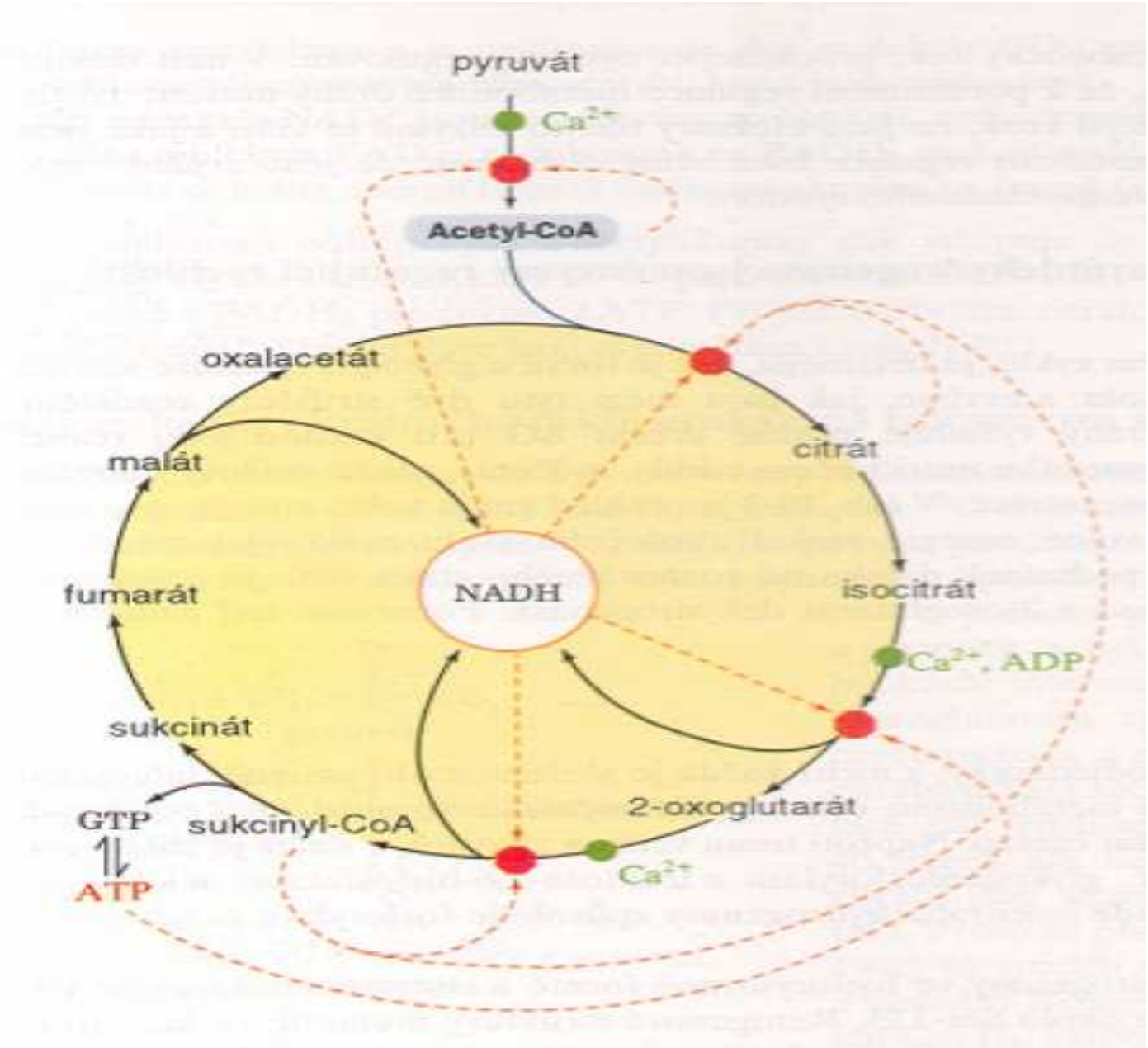
  – fosforylasa A B

  – trombin

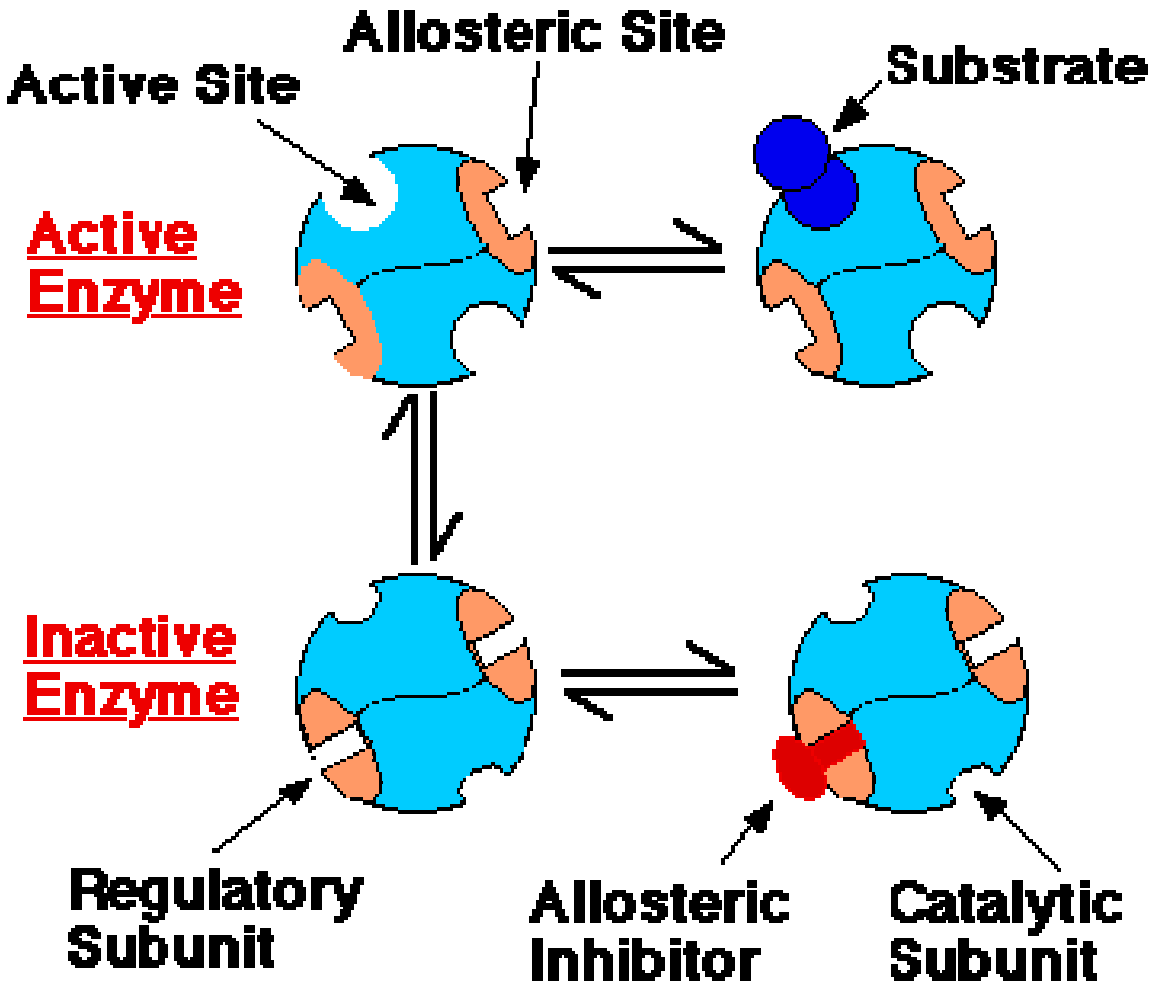
Regulace zpětnou vazbou



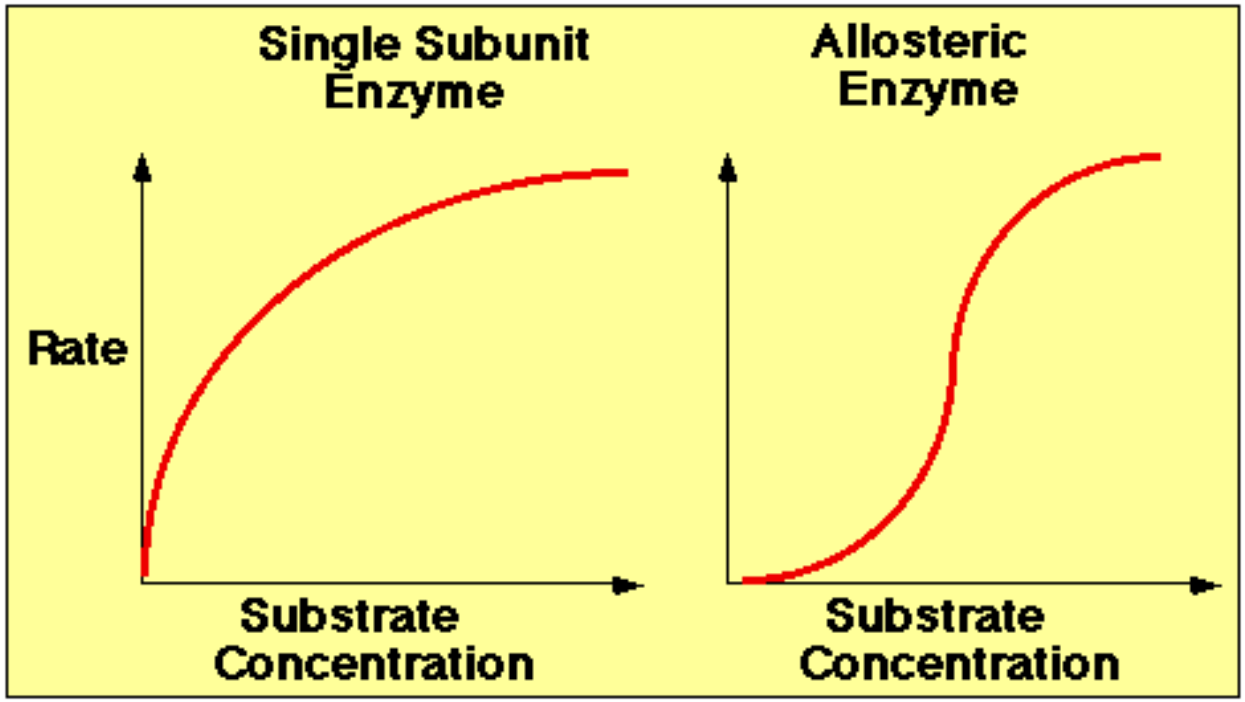
Regulace


pyruvát
Ca^{2+}
Acetyl-CoA
oxalacetát
citrát
malát
NADH
isocitrát
fumarát
Ca^{2+}, ADP
sukcinát
2-oxoglutarát
GTP
sukcinyl-CoA
ATP
Ca^{2+}

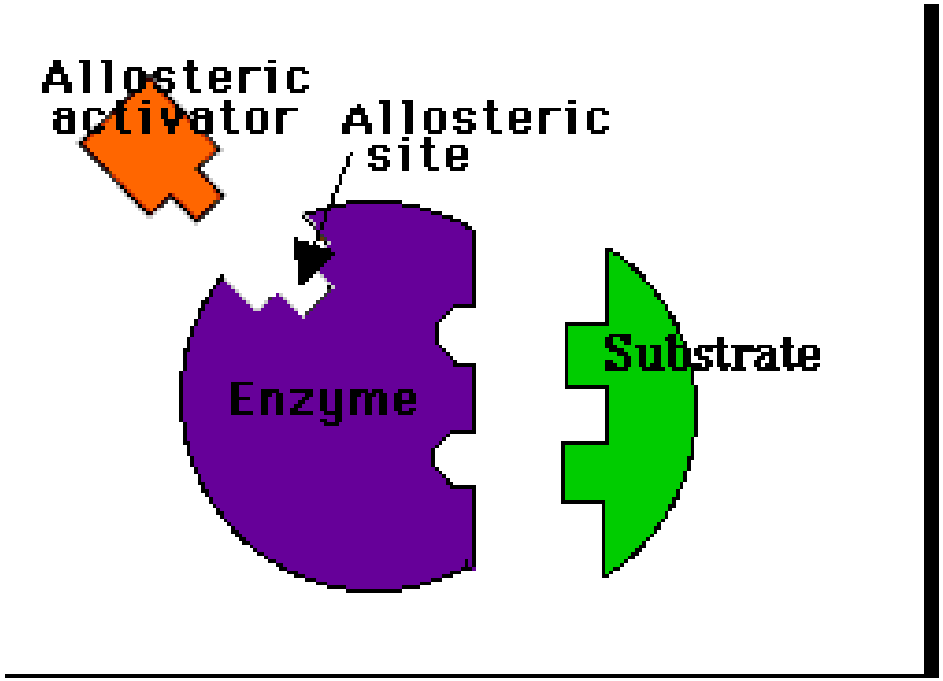
Allosterie


Allosteric Site
Active Site
Substrate
Active Enzyme
Inactive Enzyme
Regulatory Subunit
Allosteric Inhibitor
Catalytic Subunit

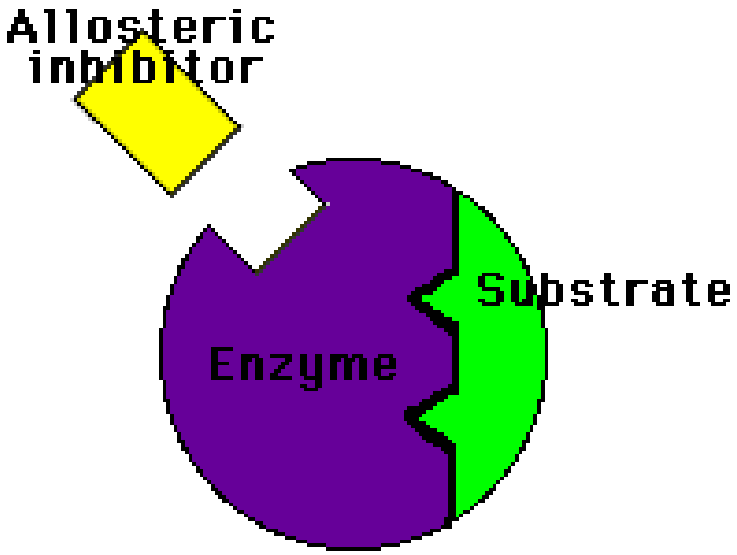
Allosterie


Single Subunit Enzyme
Allosteric Enzyme
Rate
Substrate Concentration
Substrate Concentration

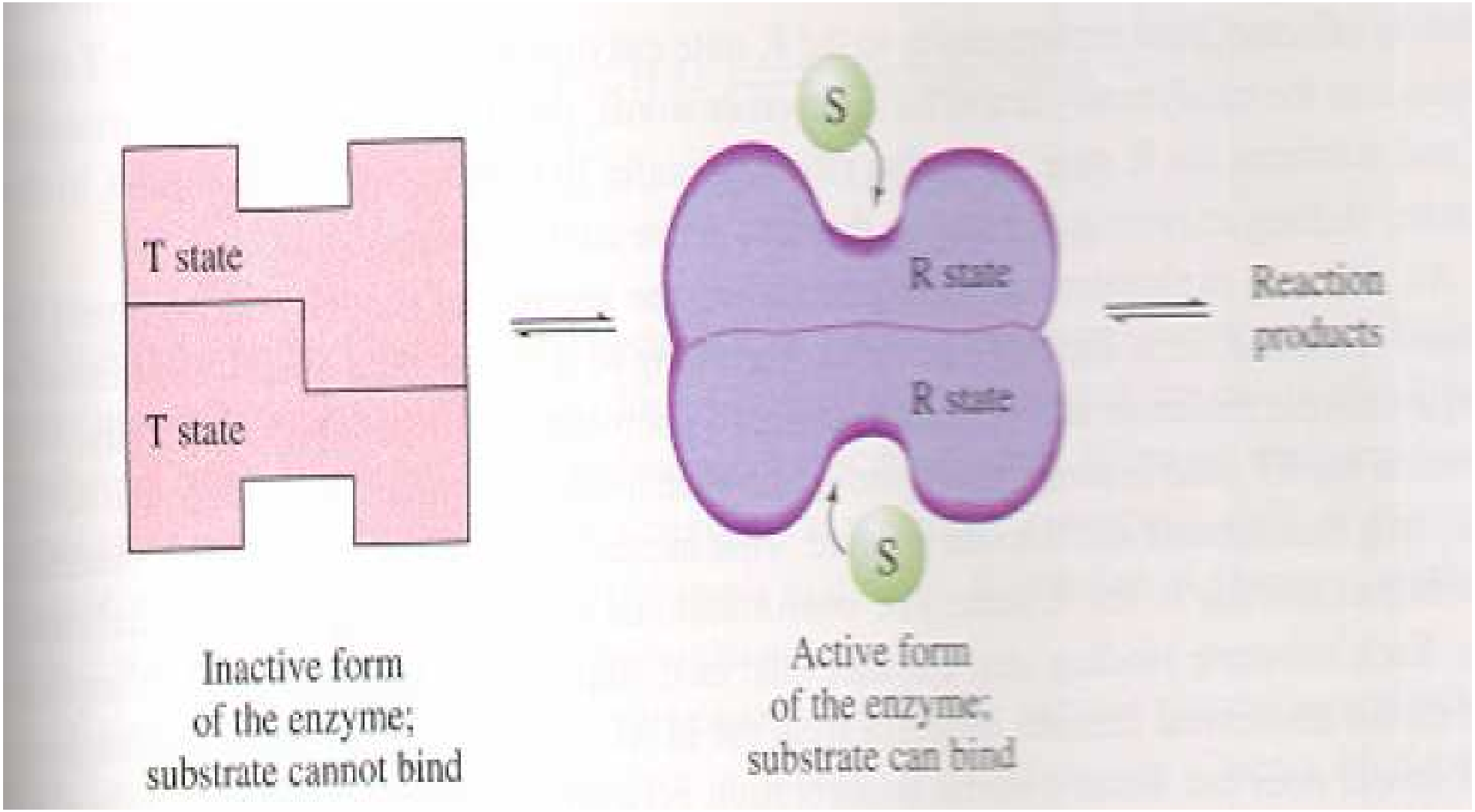
Allosterický aktivátor



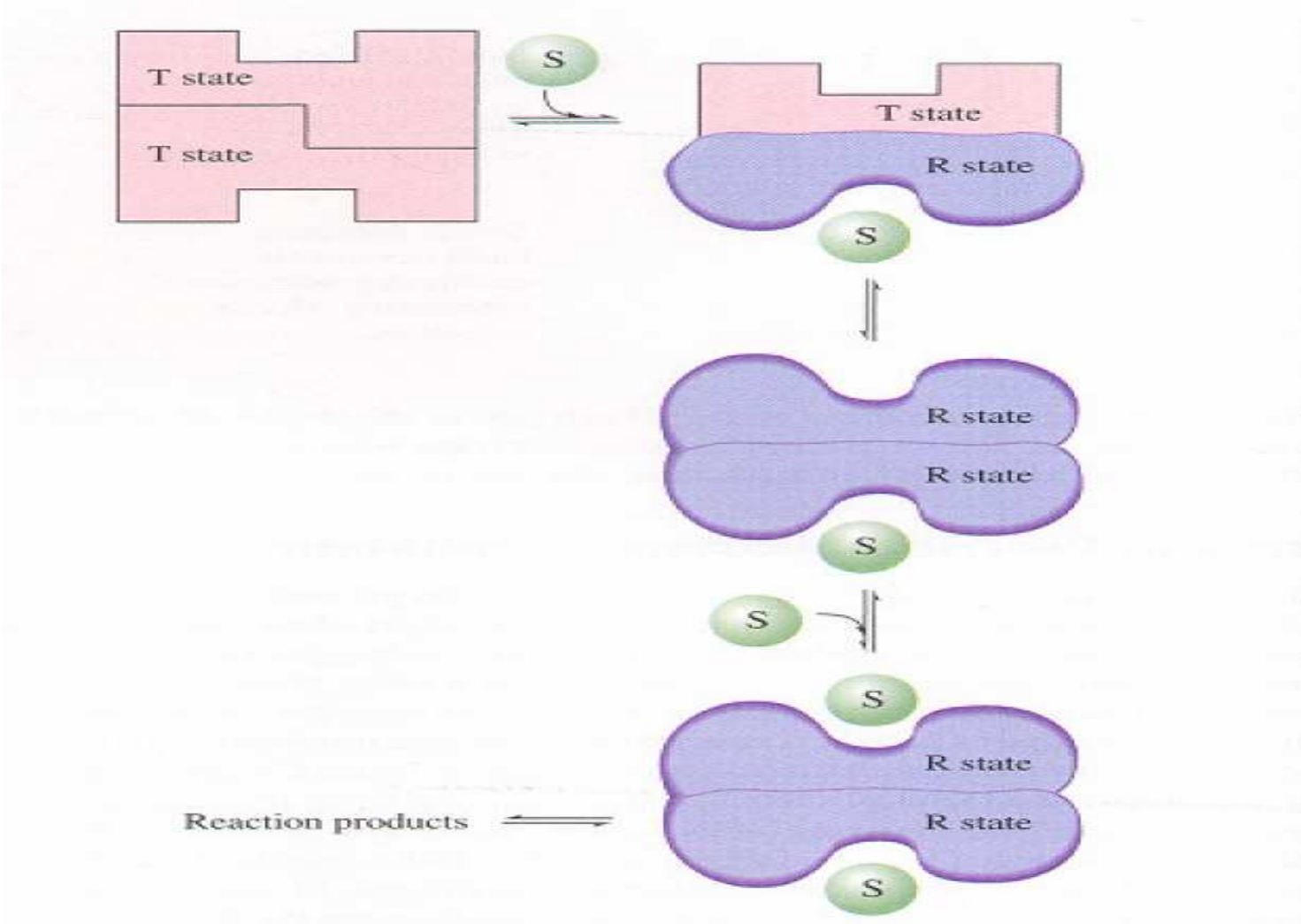
Allosterický inhibitor



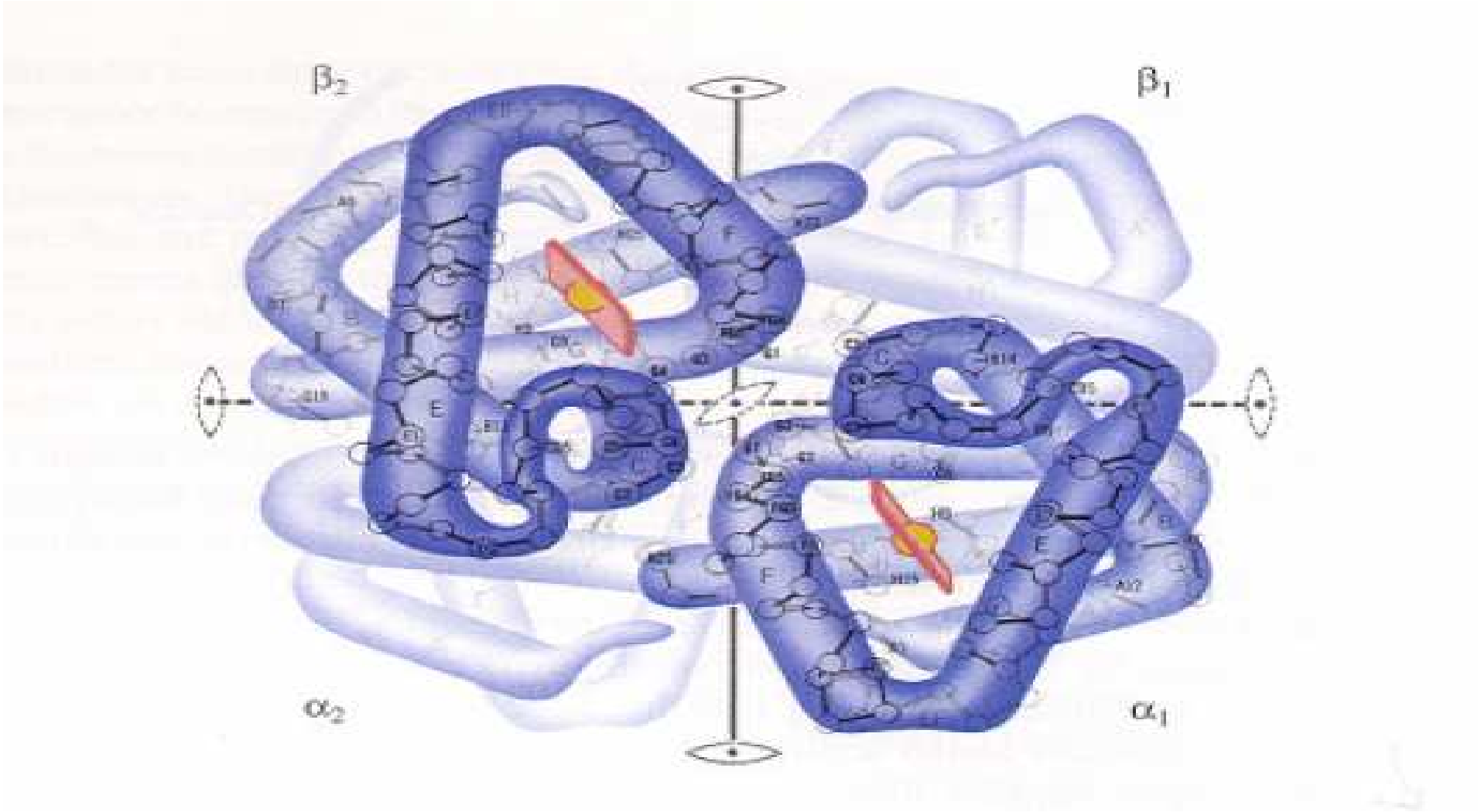
Symetrický model



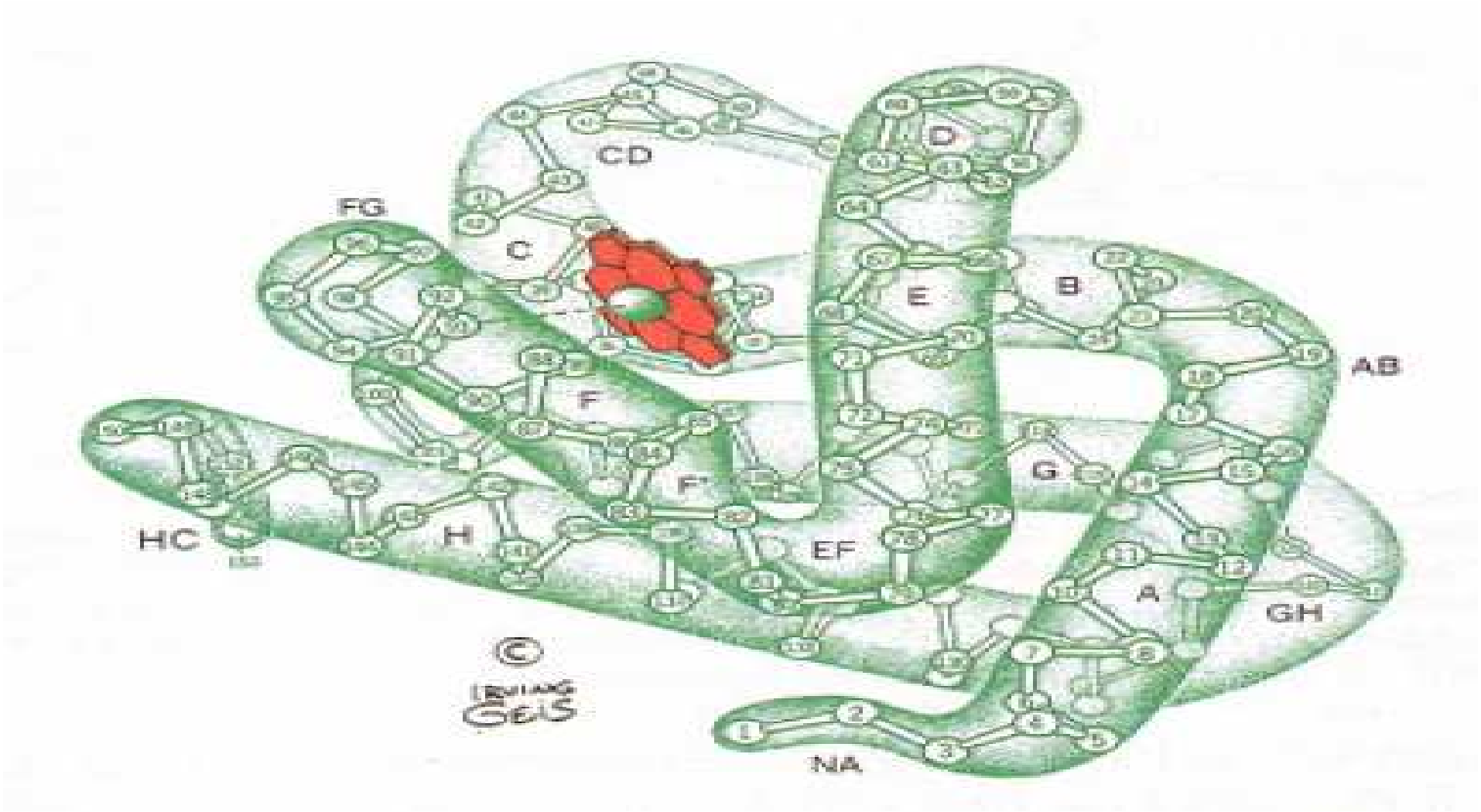
Sekvenční model



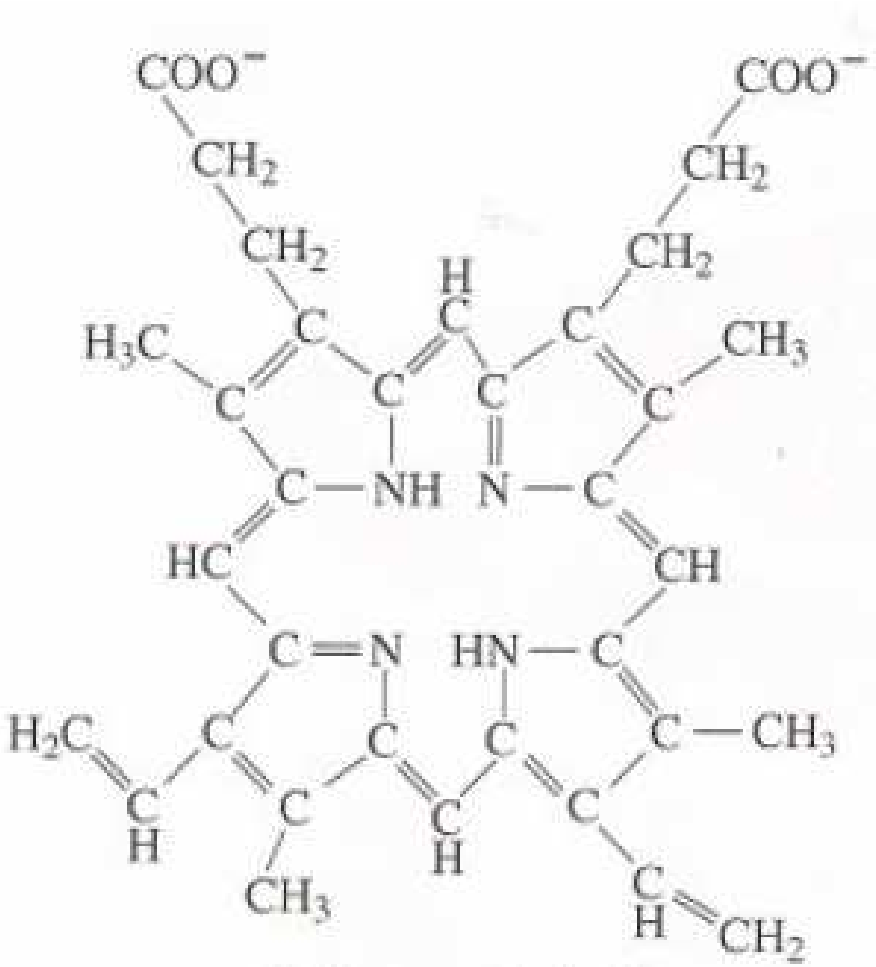
Allosterie hemoglobinu



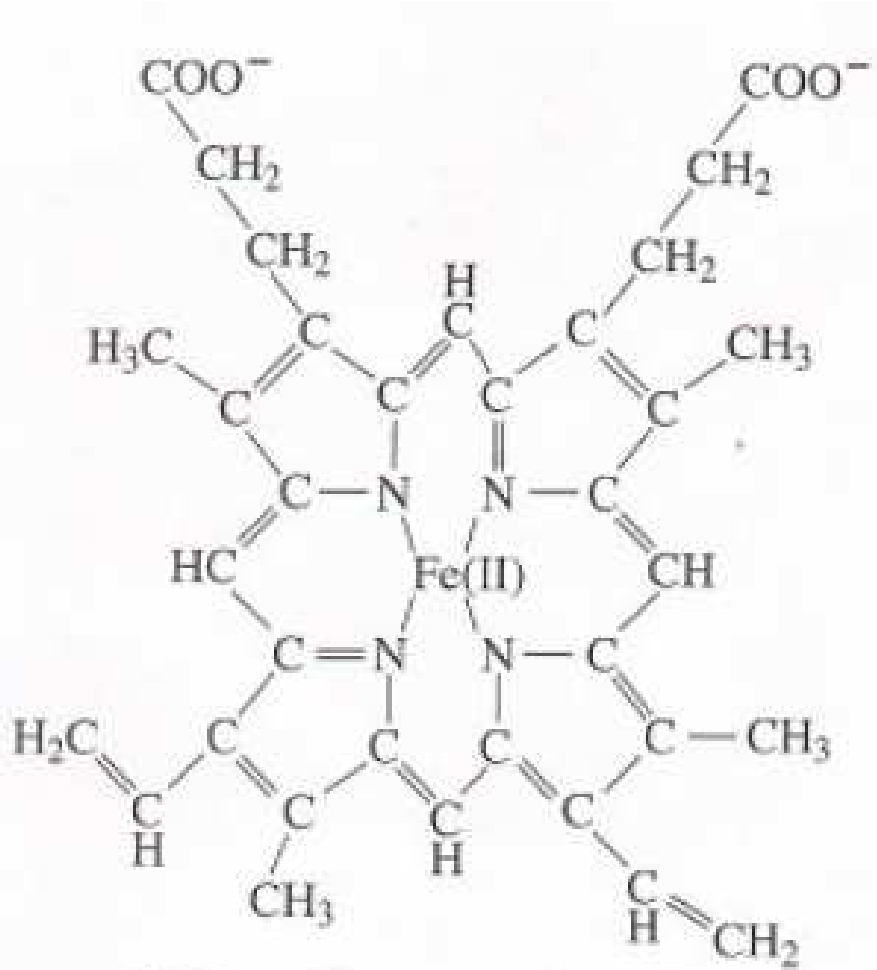
Myoglobin



Hem

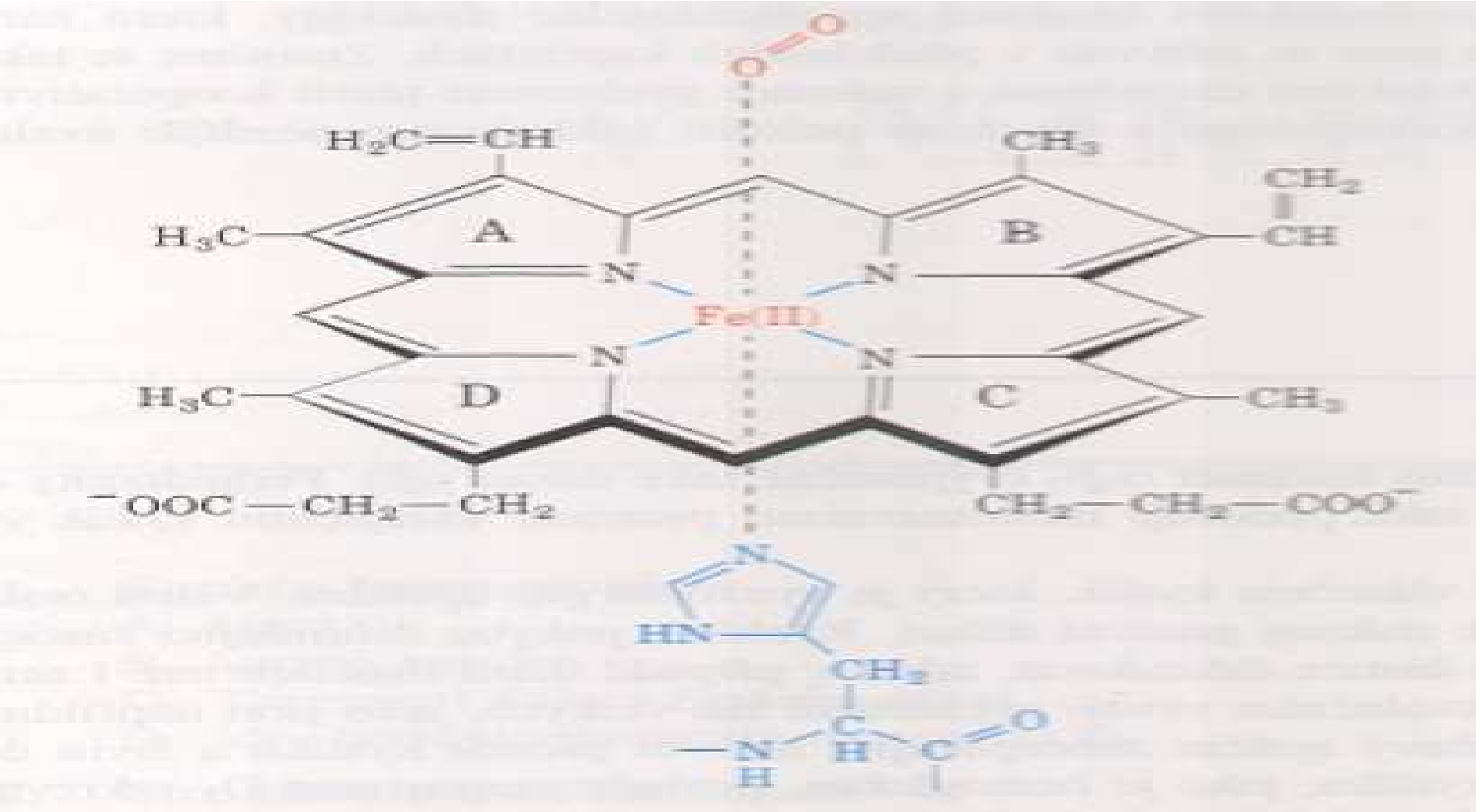


(a) Protoporphyrin IX



(b) Heme (Fe-protoporphyrin IX)

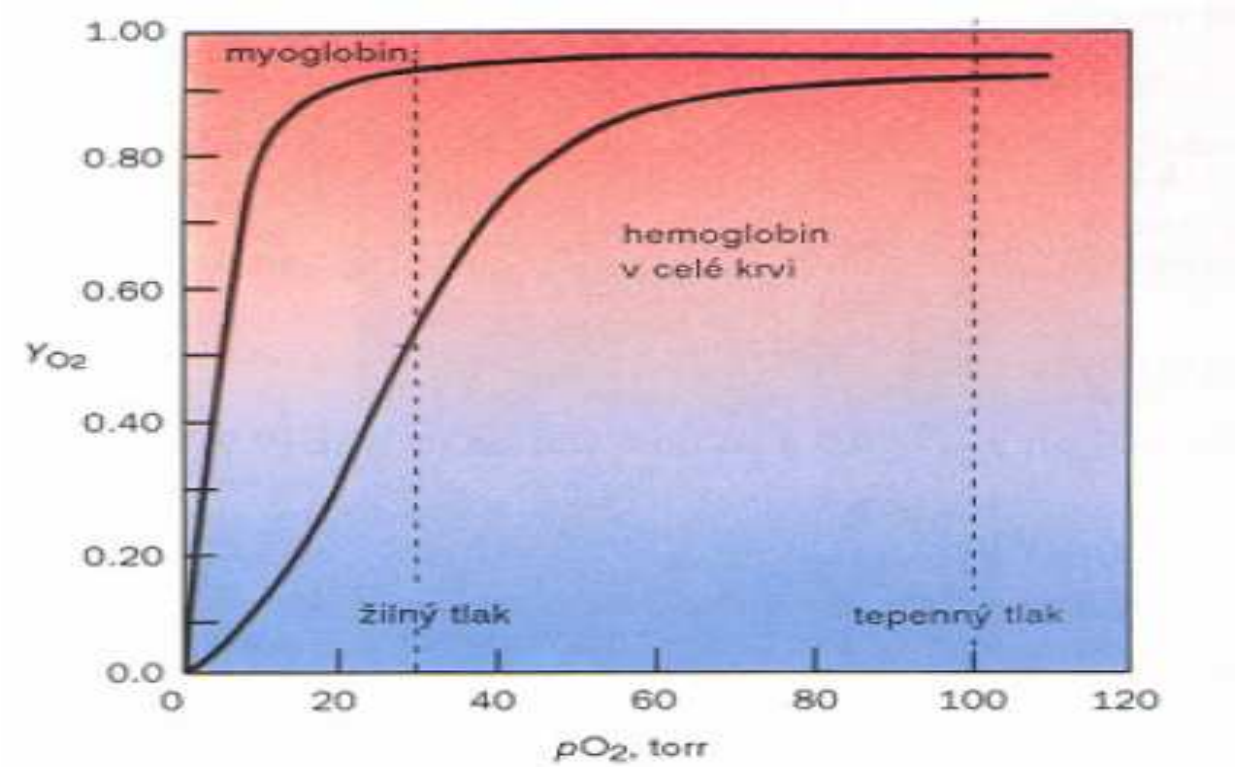
Vazba O_2 na Hb



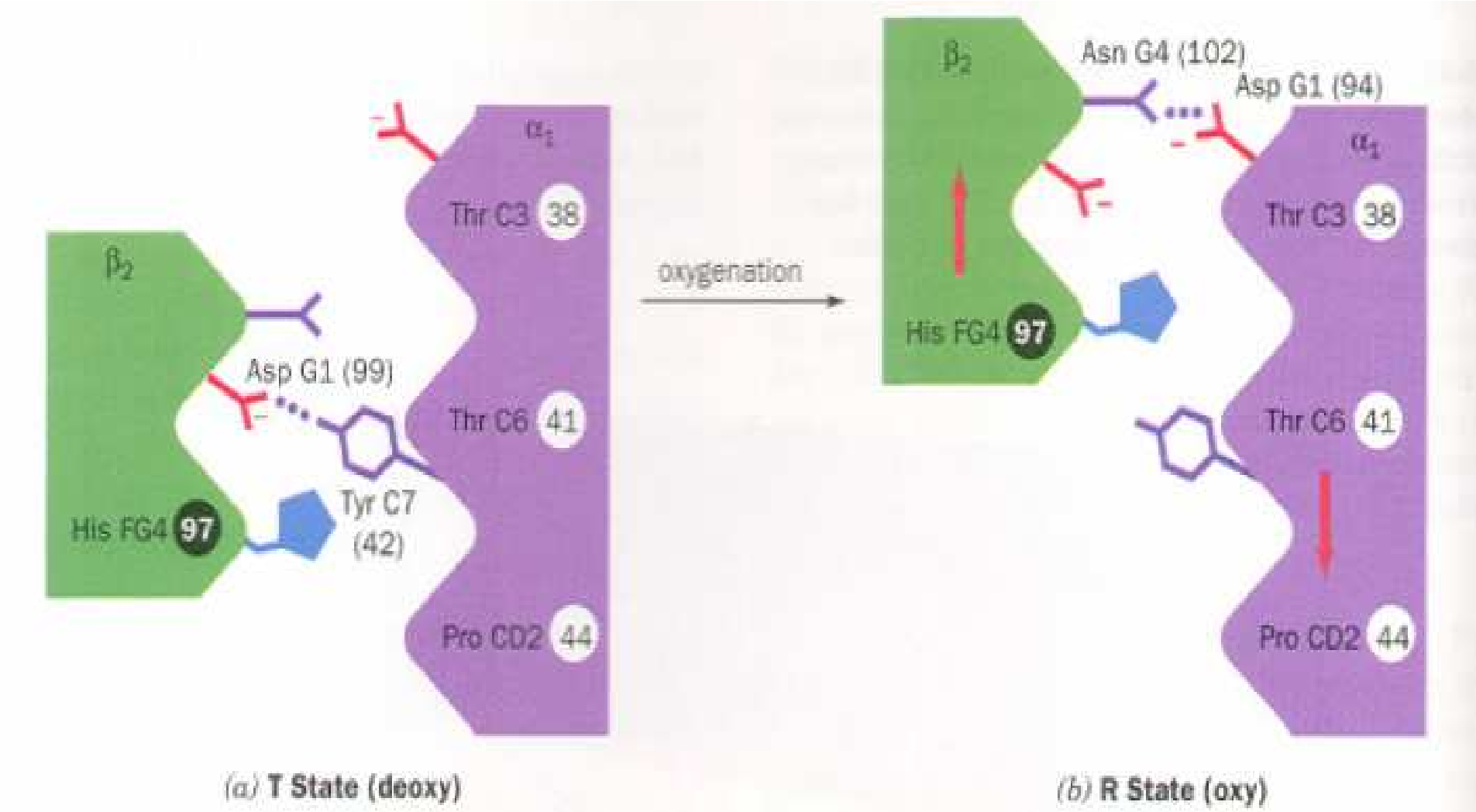
Hb versus Mb

$$Mb + O_2 \rightleftharpoons MbO_2$$

$$Hb + O_2 \rightleftharpoons Hb(O_2)$$
$$Hb(O_2) + O_2 \rightleftharpoons Hb(O_2)_2$$
$$Hb(O_2)_2 + O_2 \rightleftharpoons Hb(O_2)_3$$
$$Hb(O_2)_3 + O_2 \rightleftharpoons Hb(O_2)_4$$

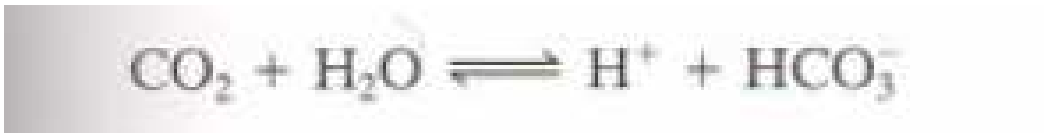


Solné můstky



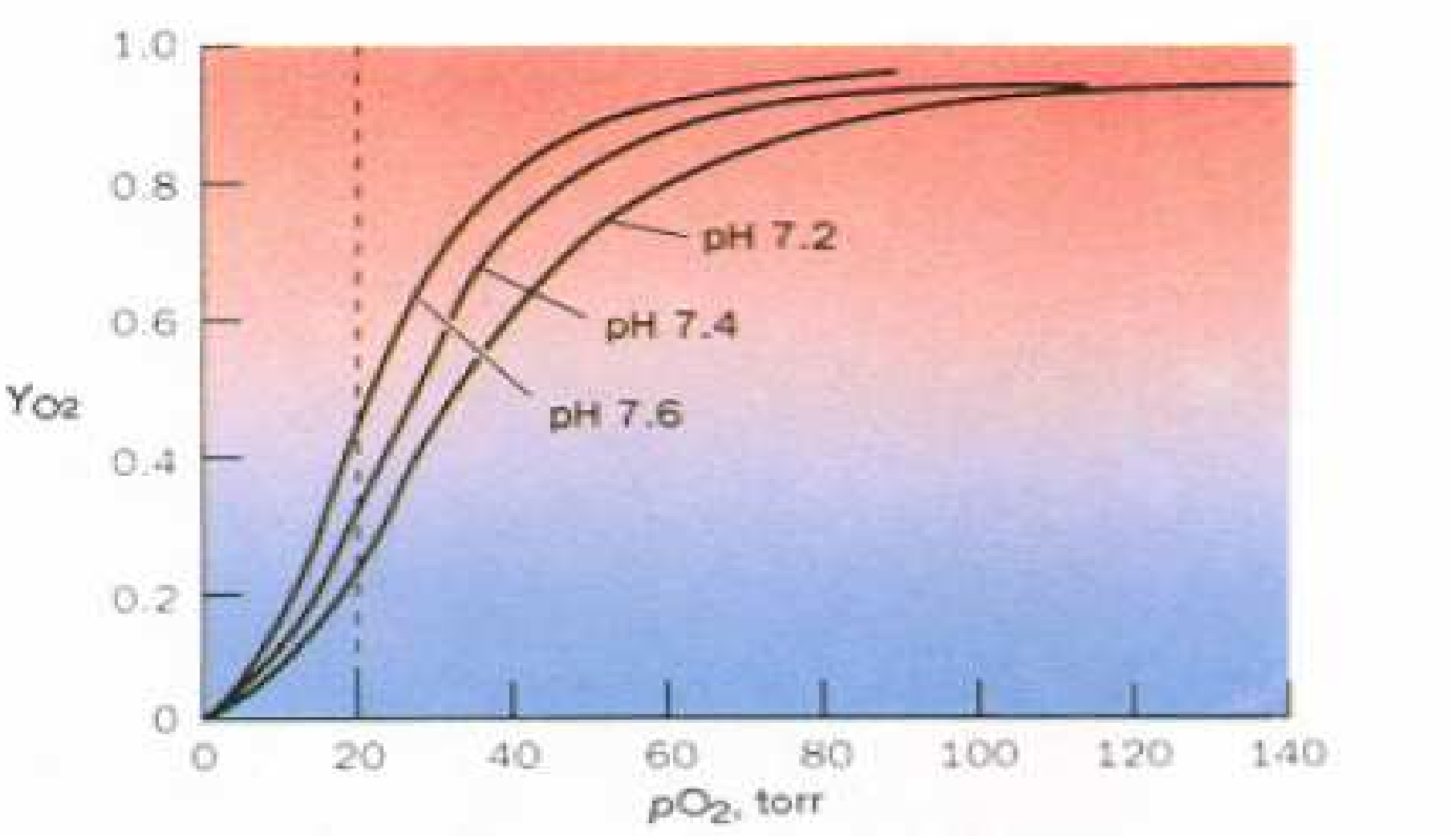
Bohrův effekt – vliv H^+ a CO_2

$$Hb(O_2)_nH_x + O_2 \rightleftharpoons Hb(O_2)_{n+1} + xH^+$$

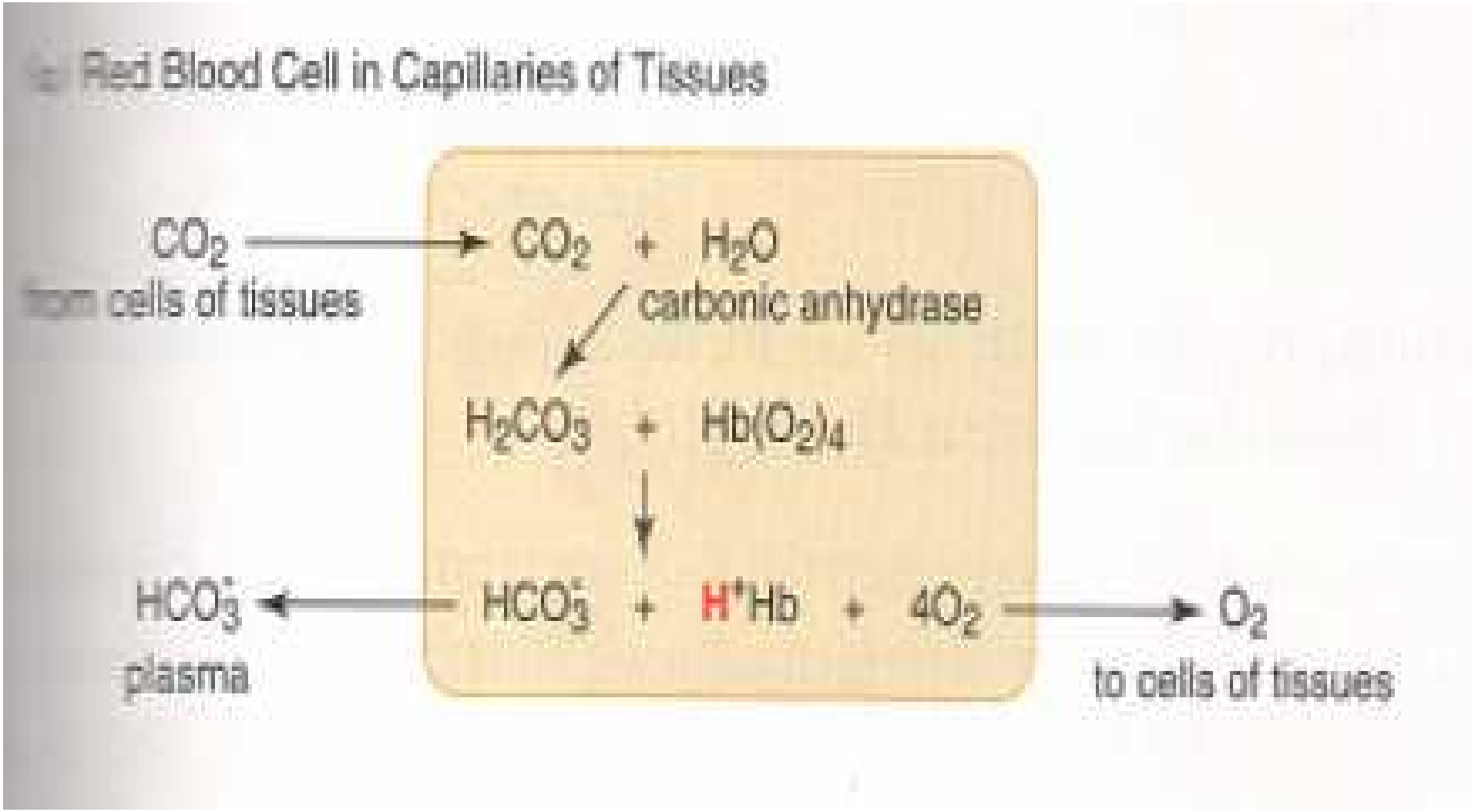


$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

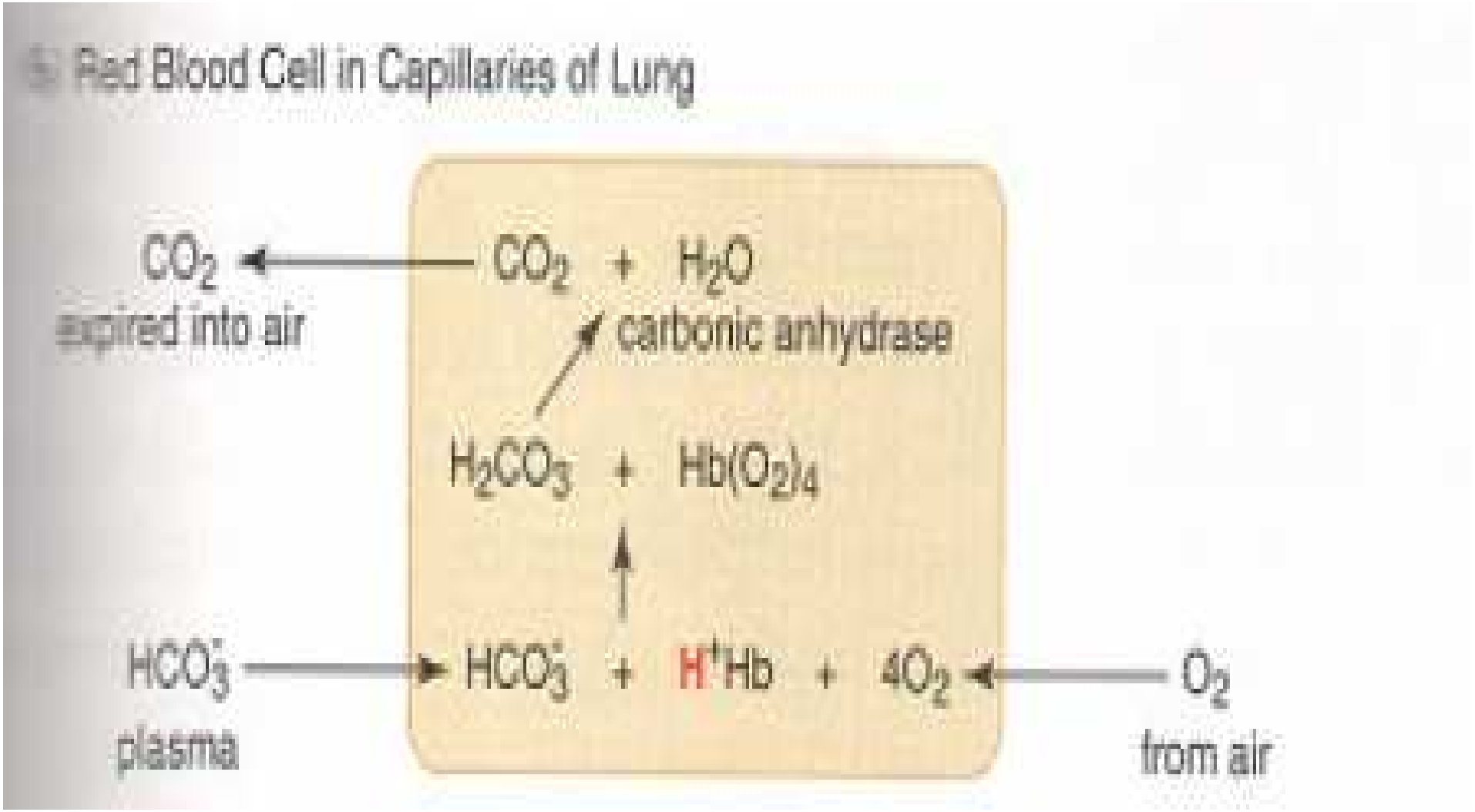
Bohrův effekt – vliv H^+ a CO_2



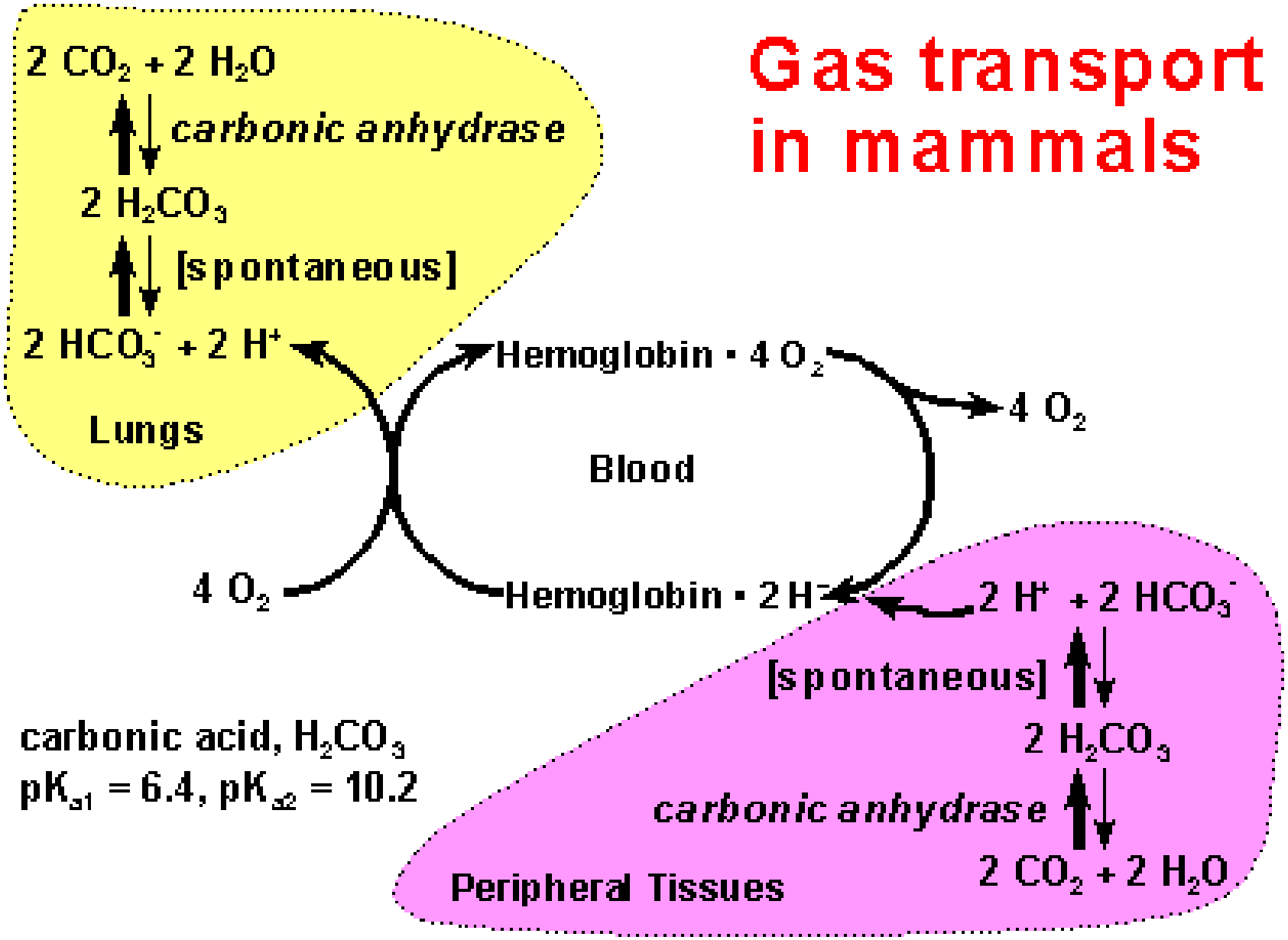
Bohrův effekt – vliv H^+ a CO_2



Bohrův effekt – vliv H^+ a CO_2

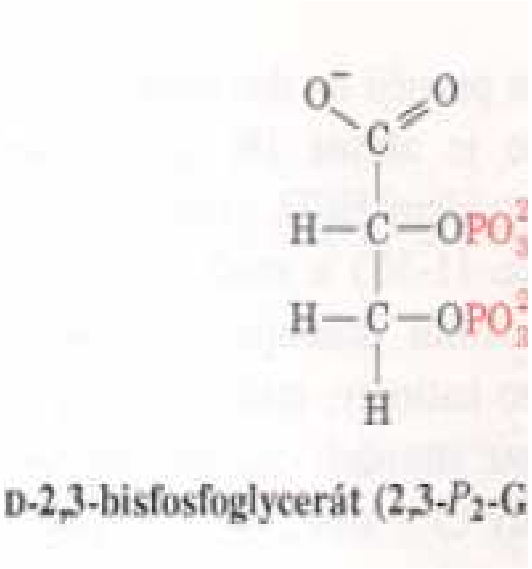


Gas transport in mammals

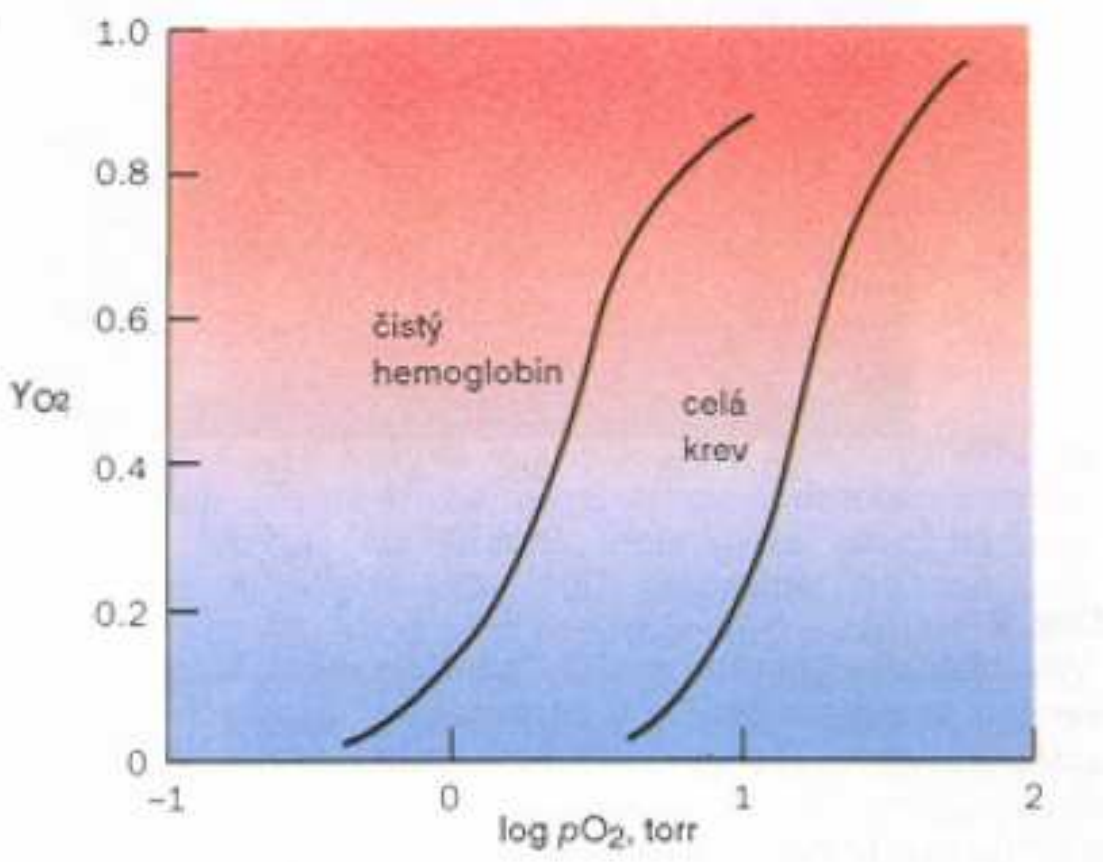


carbonic acid, H_2CO_3
$pK_{a1} = 6.4$, $pK_{a2} = 10.2$

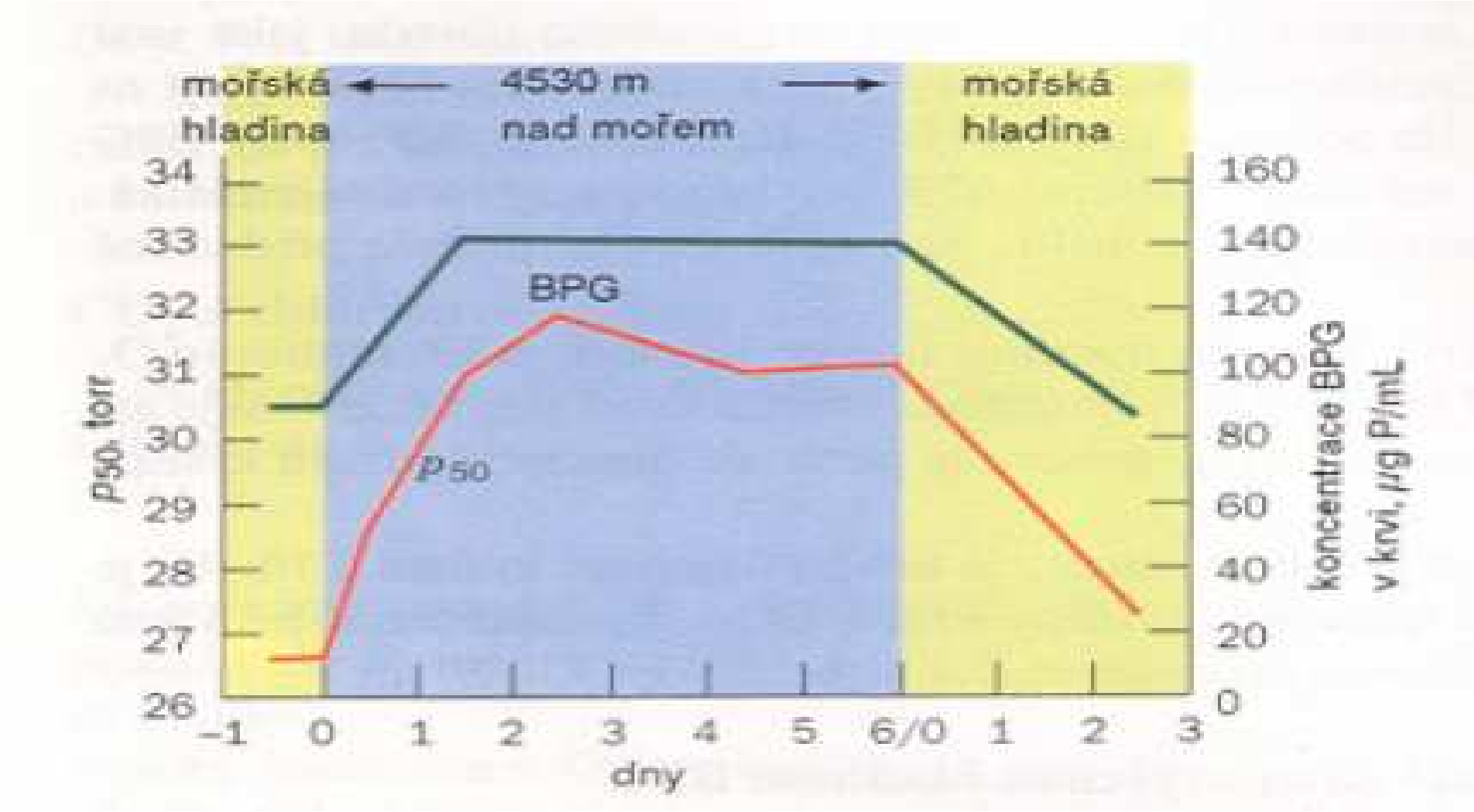
Vliv BPG



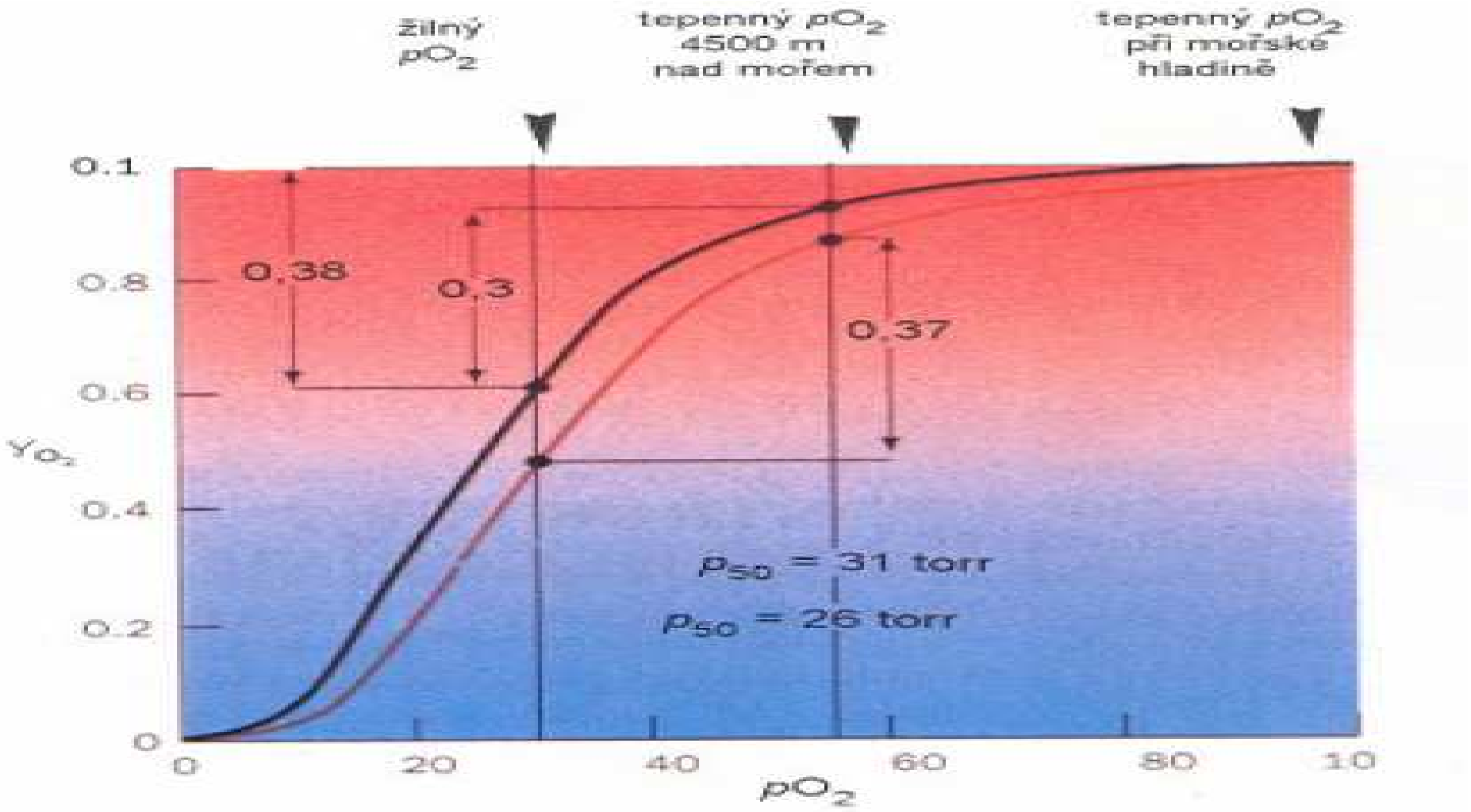
D-2,3-bisfosfoglycerát (2,3-P_2-G



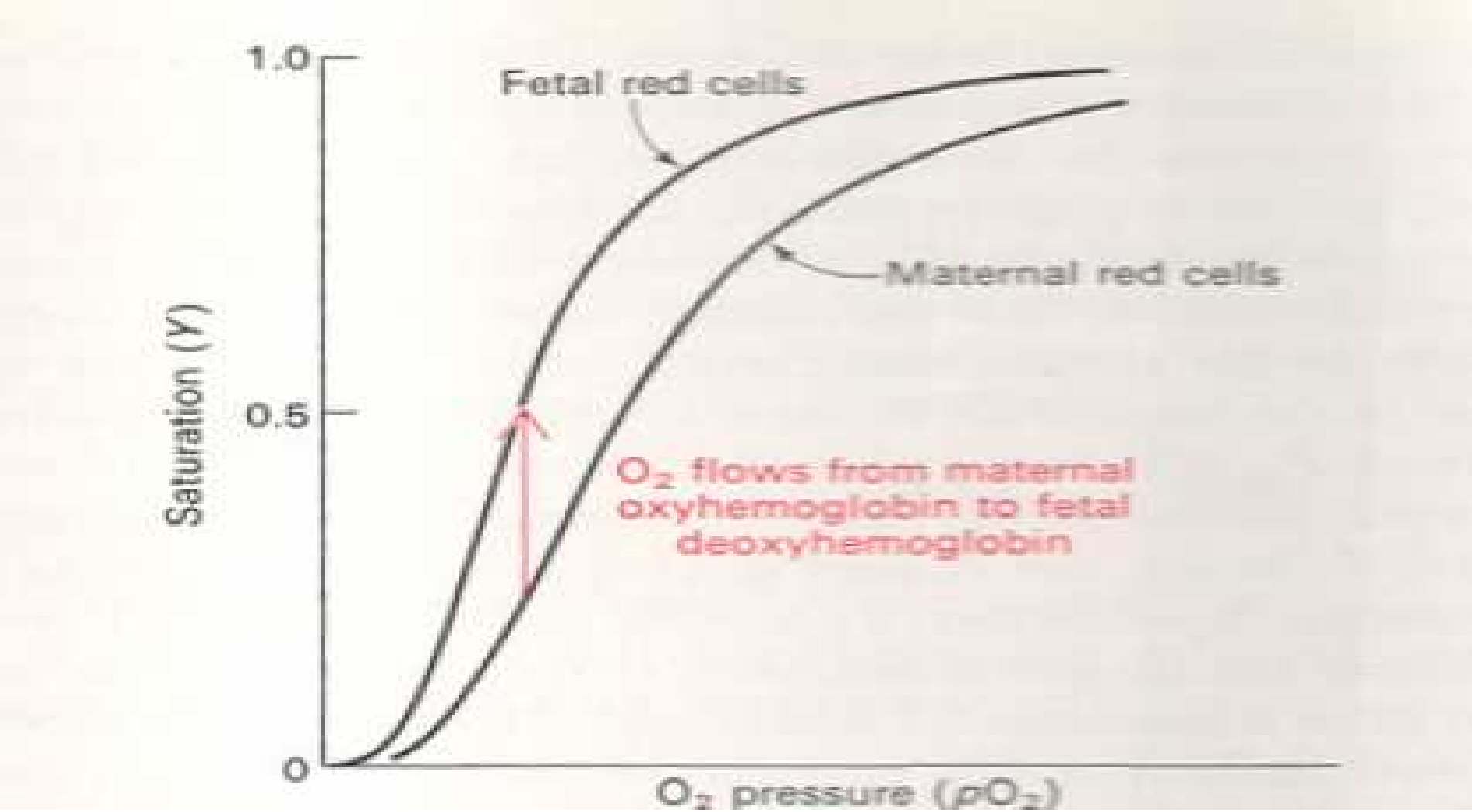
Vliv BPG a nadmořská výška



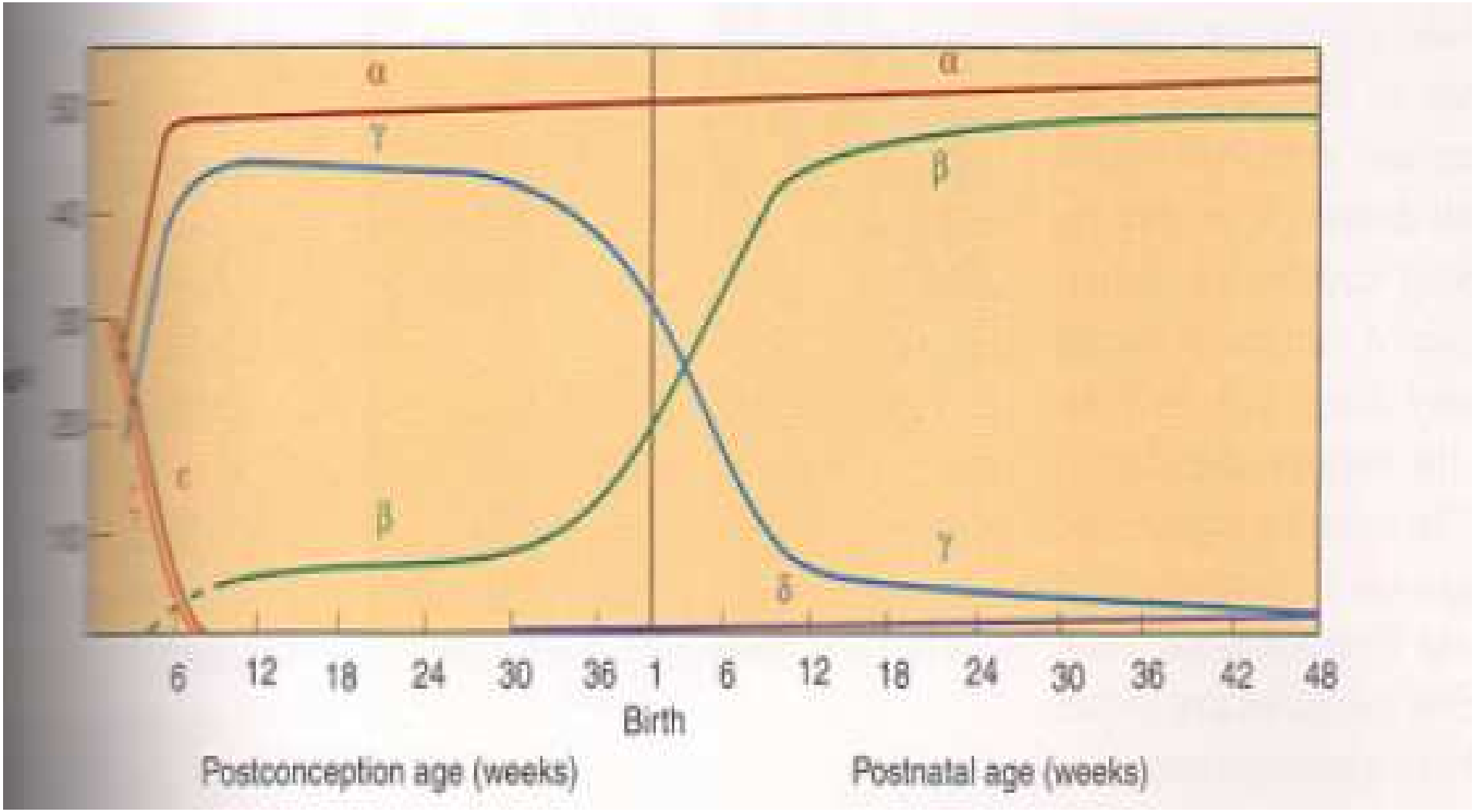
Vliv BPG a nadmořská výška



Fetální versus normální Hb

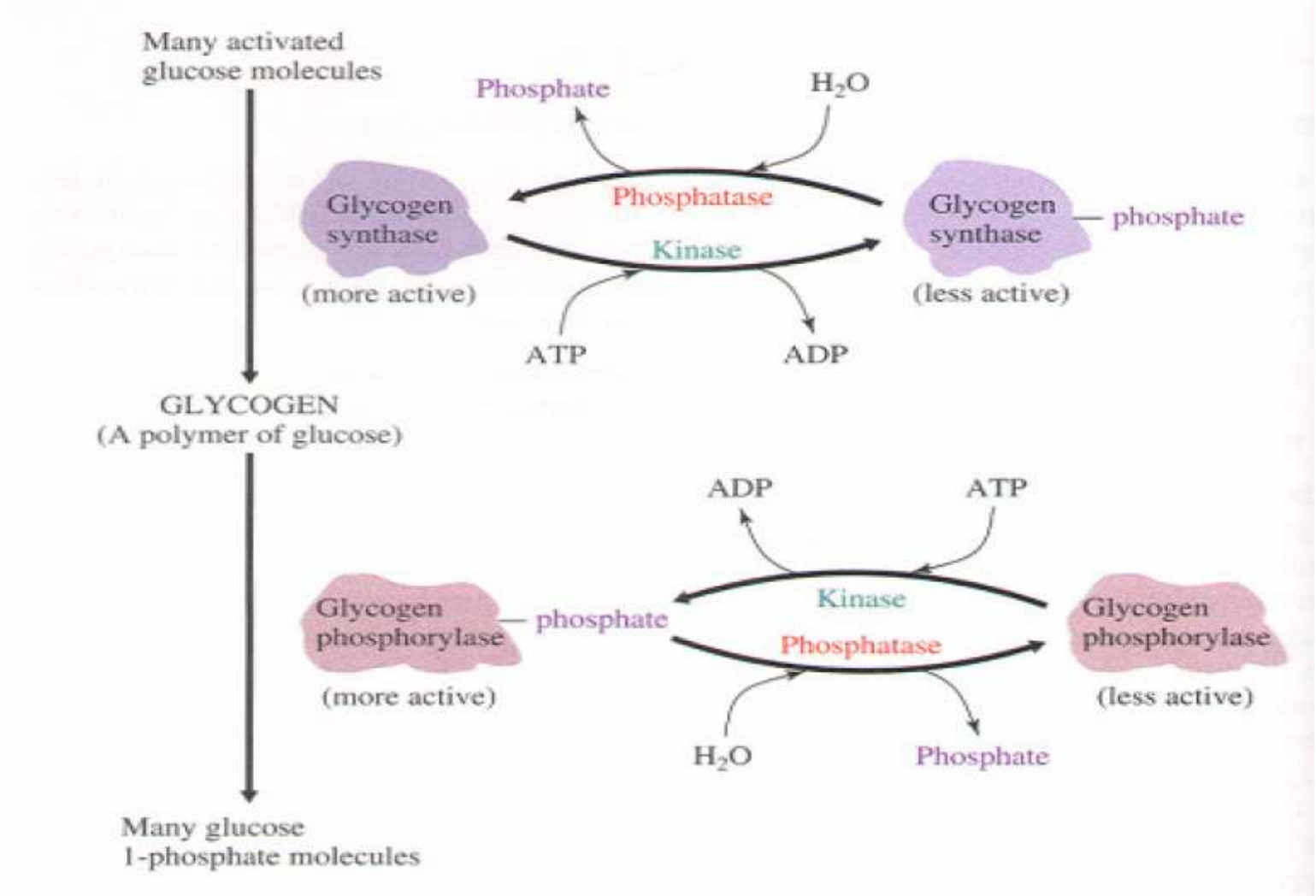


Fetální versus normální Hb



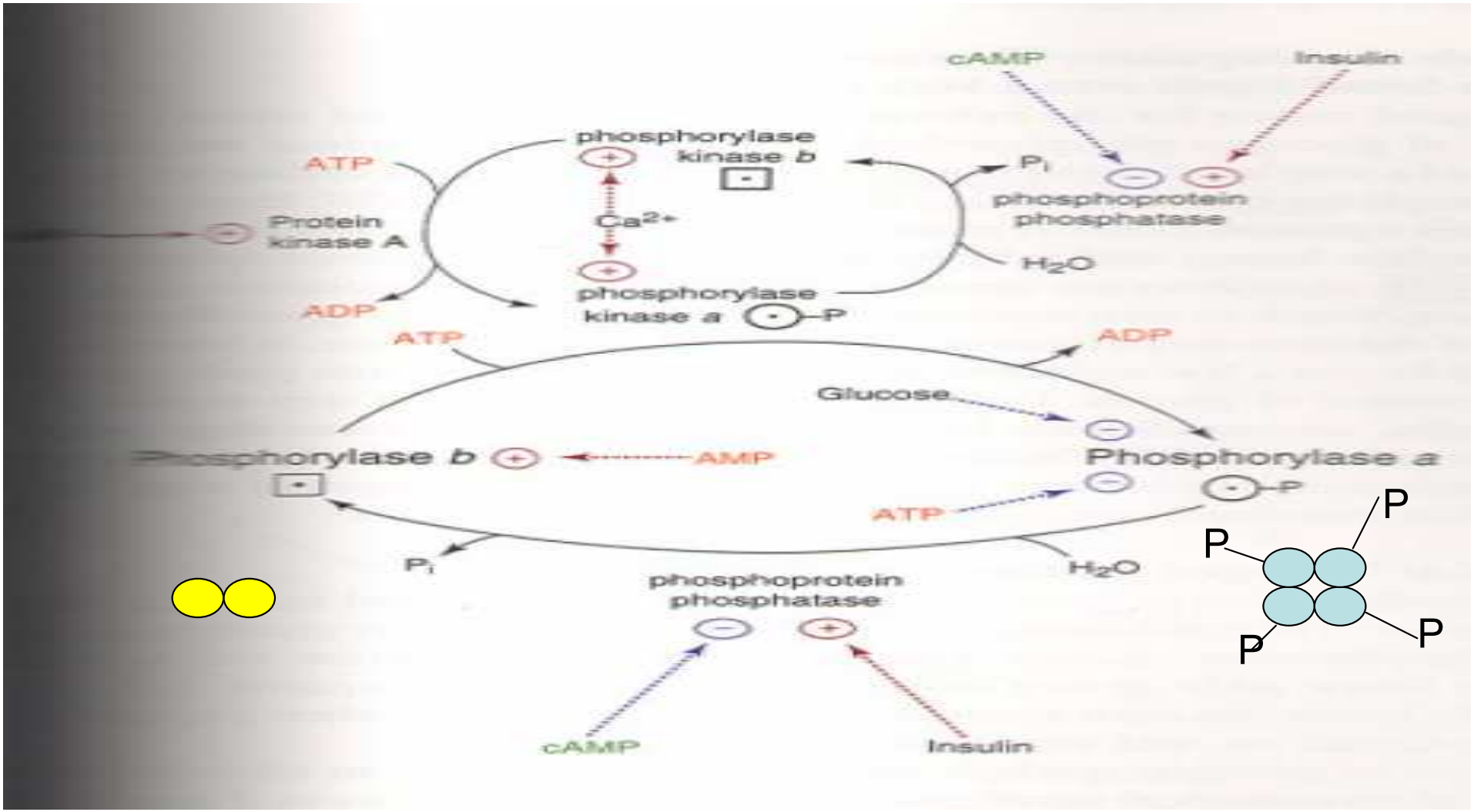
Regulace kovalentní modifikací

glykogenfosforylasa



Regulace kovalentní modifikací

glykogenfosforylasa



Aktivace zymogenů

žaludek

pepsinogen → pepsin

pH

slinivka břišní

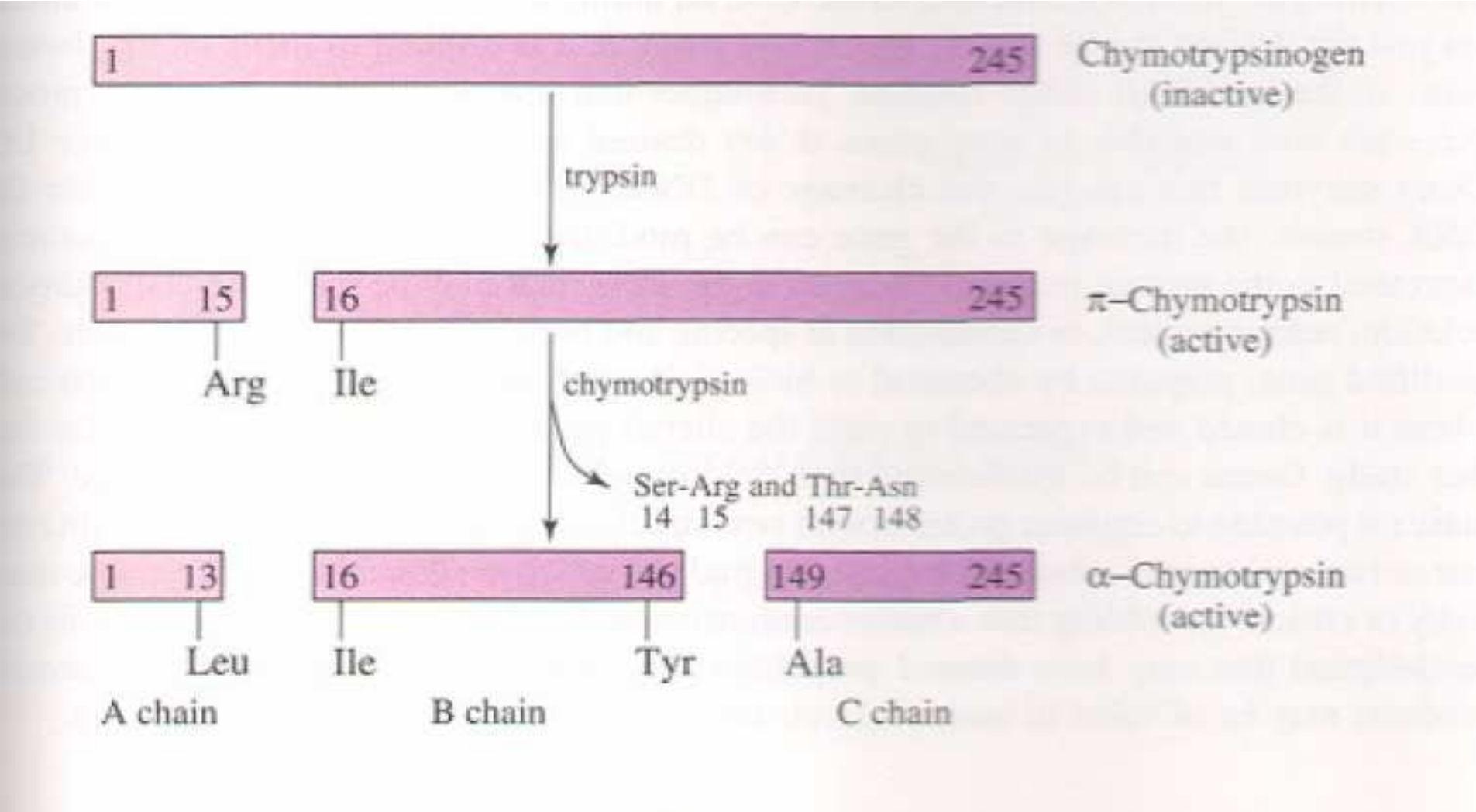
enterokinasa

trypsinogen → trypsin

chymotrypsinogen → chymotrypsin

proelastasa → elastasa

Regulace kovalentní modifikací



Regulace hladiny enzymů v buňce

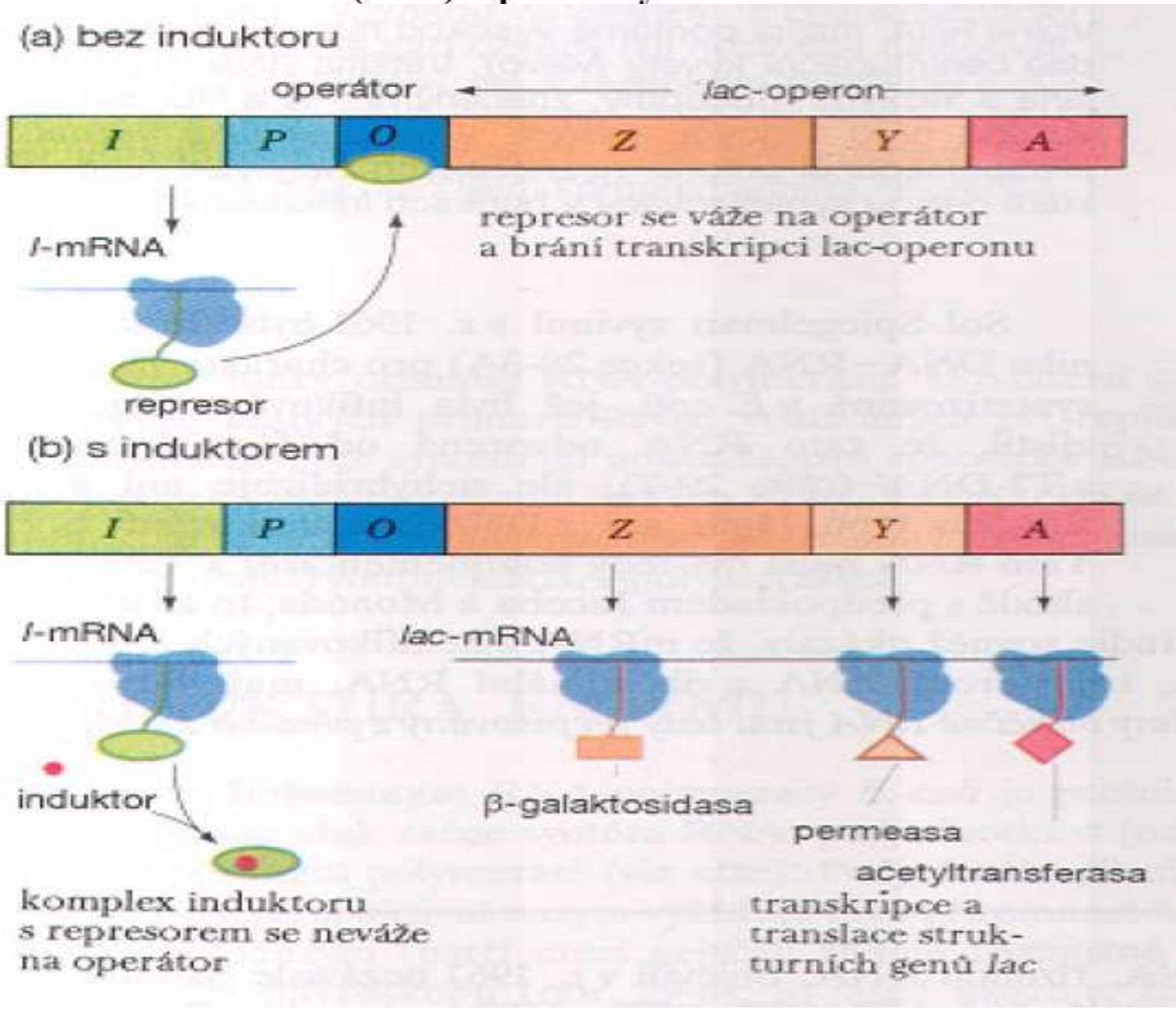
- Operon - skupina strukturních genů
  DNA koordinovaně regulovaných
  promotorem a operátorem

Regulace hladiny enzymů v buňce

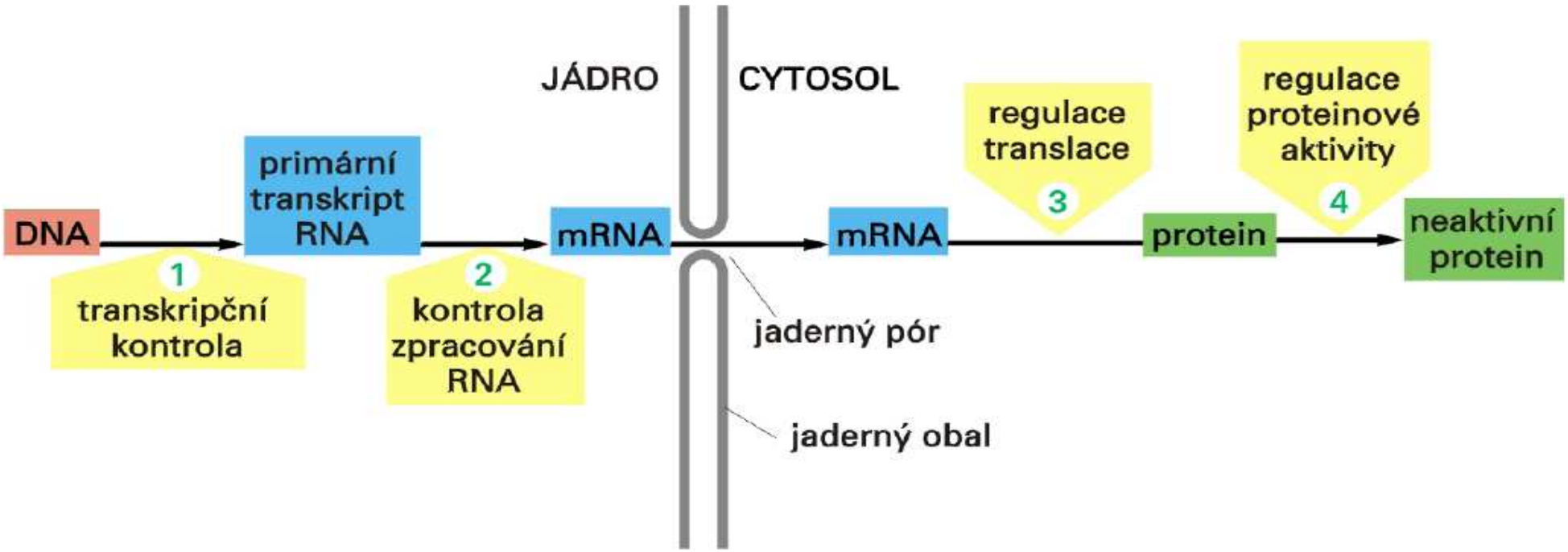
- Promotor - oblast poblíž genu, kde se váže RNApolymerasa
- Regulátorový gen - gen produkující represor
- Operátor - místo vazby represoru

Regulace na úrovni NK – indukce a represe – pomalá odezva

JACOB MONOD (1961) operonový model



Čtyři kroky, ve kterých může být regulována exprese eukaryontních genů



Prostorové uspořádání

- Kompartmentace - mitochondrie – βoxidace, citrátový cyklus, respirace
  - cytoplasma – glykolysa, synthesa mastných kyselin

- Transportní systémy - ATPasa
  - karnitinový cyklus

Humorální regulace

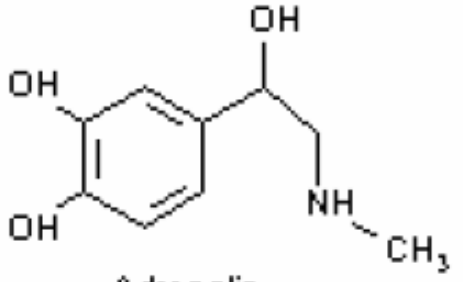
Endokrinní systém – žlázy s vnitřní sekrecí → hormony

BAYLISS, STARLING (1904) - hormony

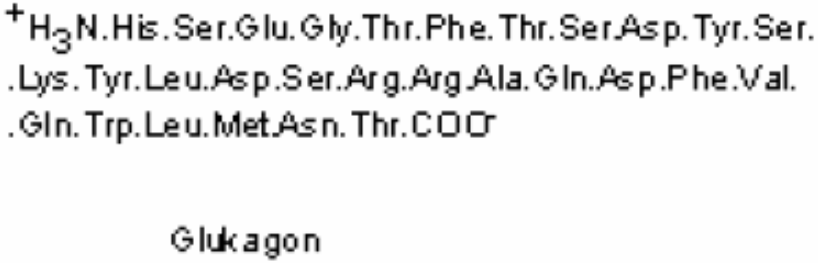
Chemické složení – NO, AMK, peptidy, bílkoviny, steroidy, k.arachidonová

Hormony

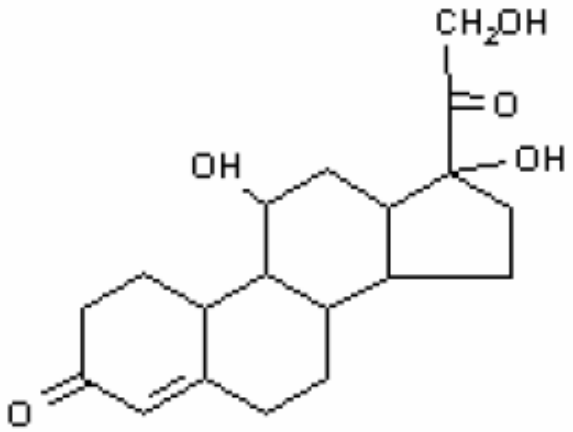
- -aminokyselinové, peptidové, steroidní, pocházející z MK



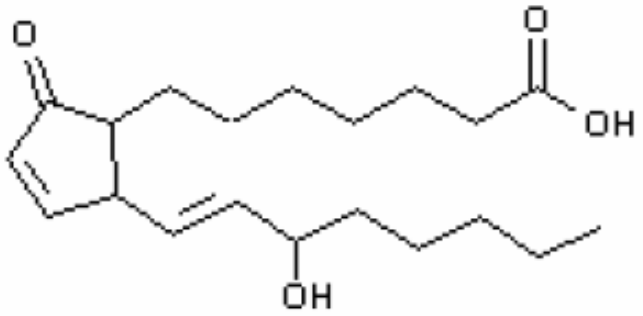
Adrenalin



Glukagon

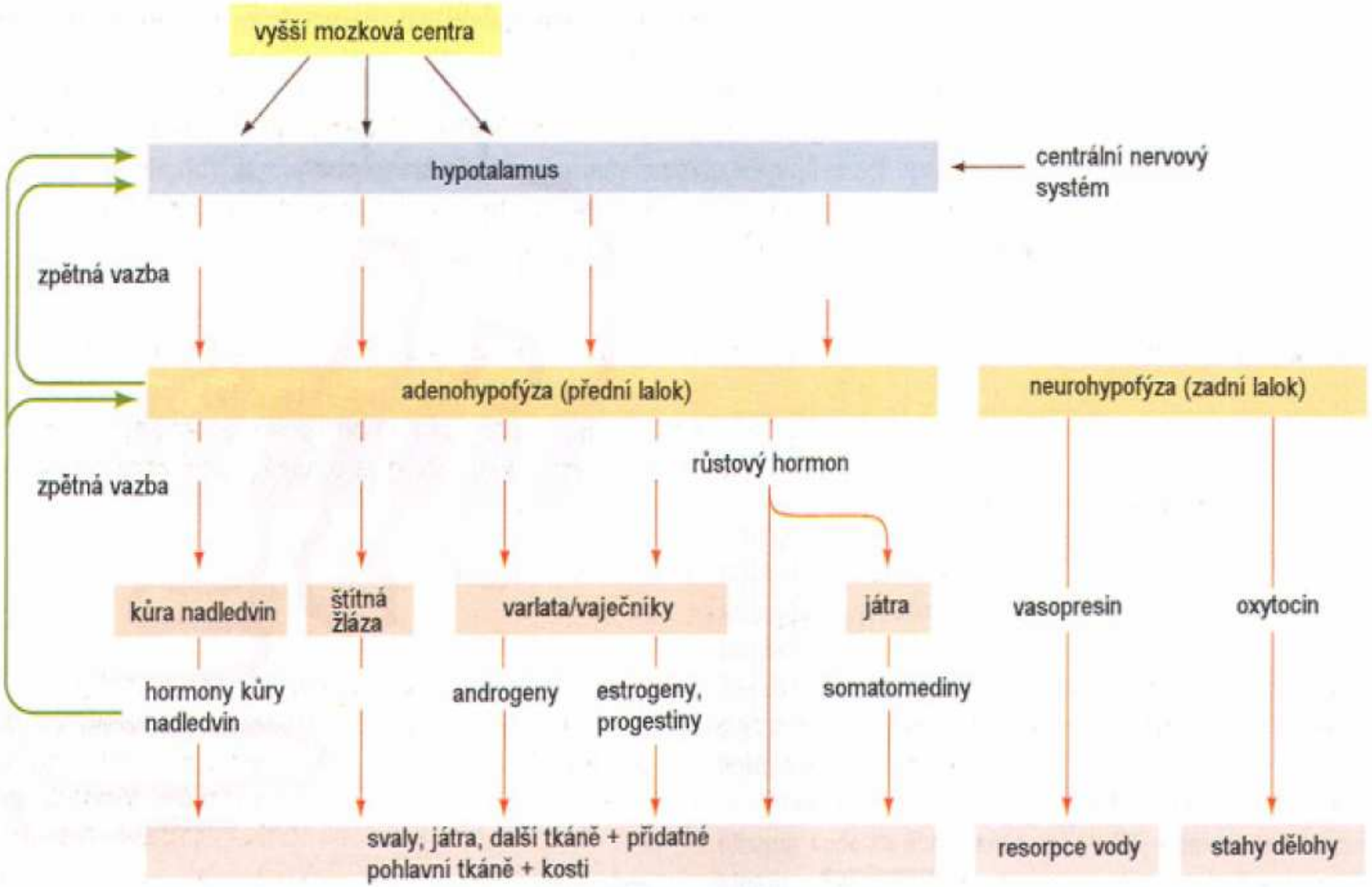


Kortisol



Prostaglandin PGA1

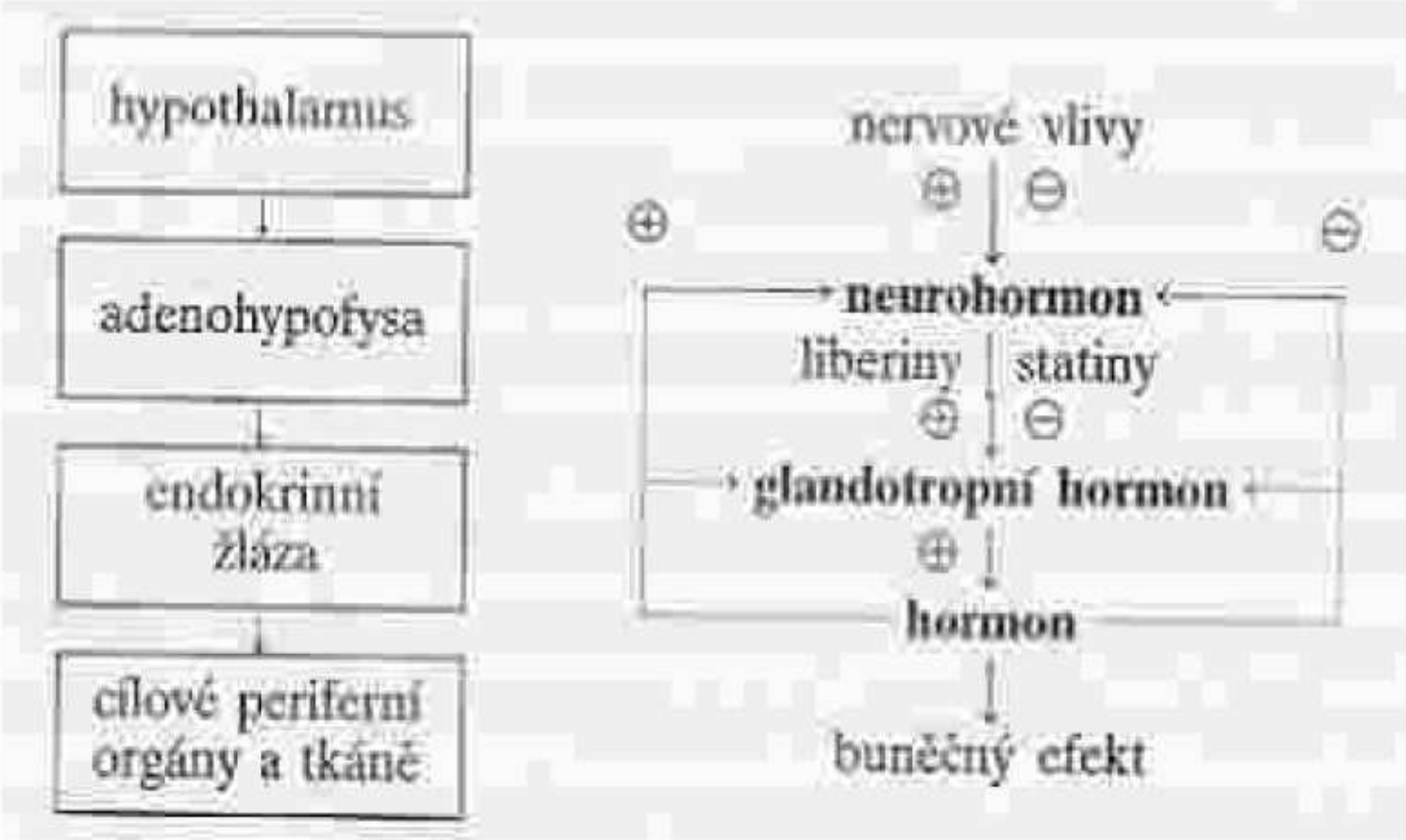
Řízení


vyšší mozková centra
hypotalamus
centrální nervový systém
zpětná vazba
adenohypofýza (přední lalok)
neurohypofýza (zadní lalok)
zpětná vazba
růstový hormon
kůra nadledvin
štítná žláza
varlata/vaječníky
játra
vasopresin
oxytocin
hormony kůry nadledvin
androgeny
estrogeny, progestiny
somatomediny
svaly, játra, další tkáně + přídatné pohlavní tkáně + kosti
resorpce vody
stahy dělohy

Řízení

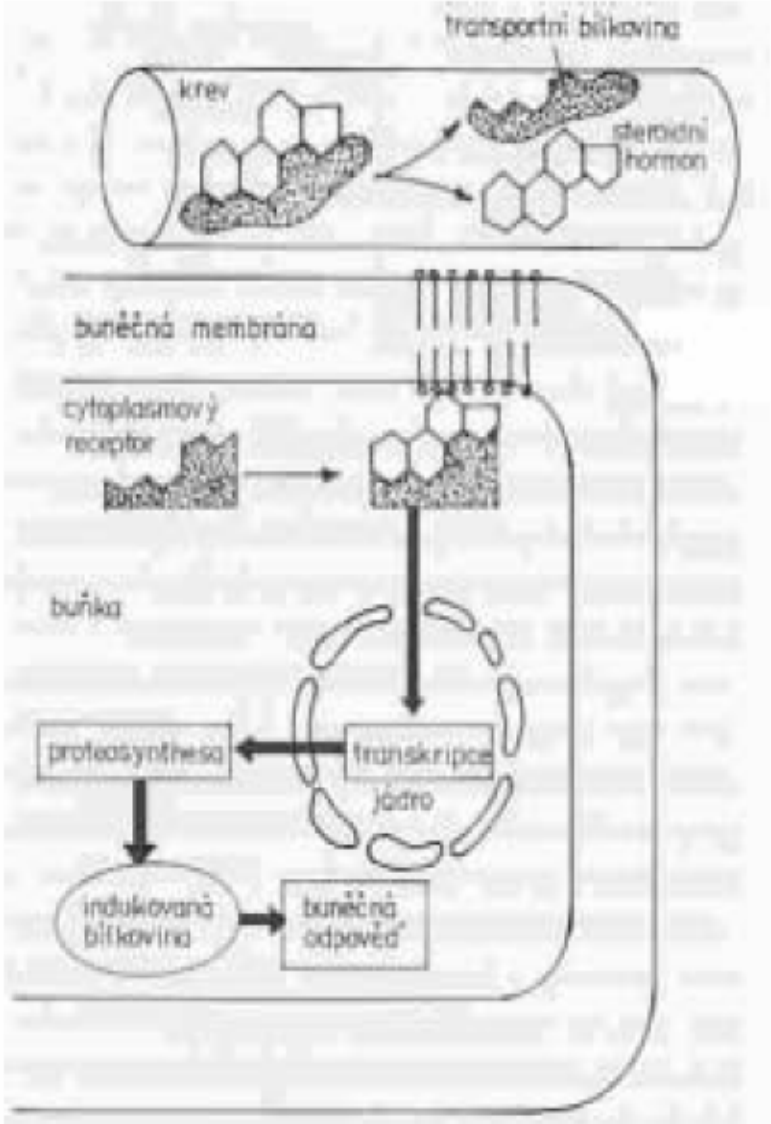
CNS

↓

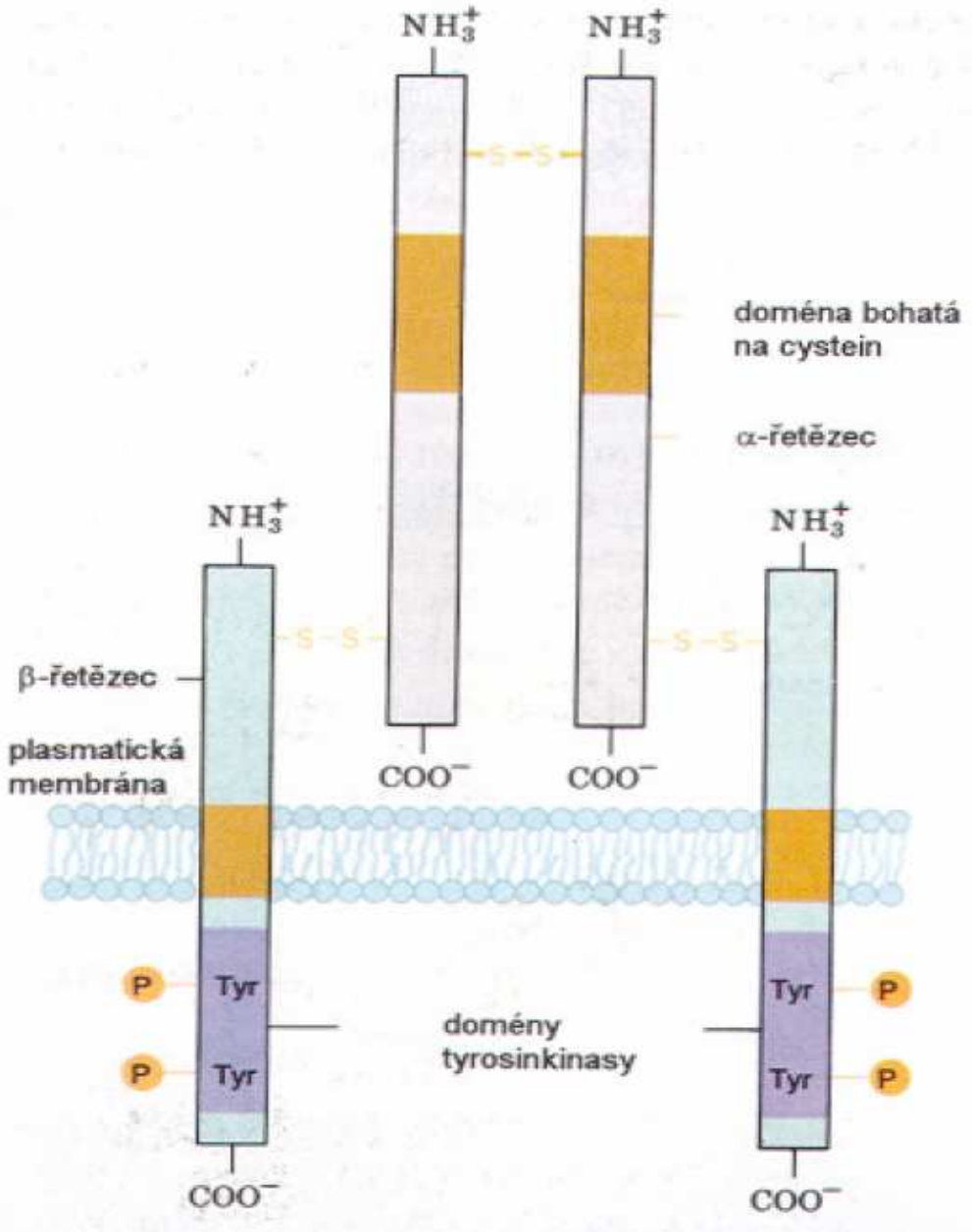

hypothalamus
adenohypofysa
endokrinní žláza
cílové periferní orgány a tkáně
nervové vlivy
⊕
⊖
⊕
⊖
neurohormon
liberiny
statiny
⊕
⊖
glandotropní hormon
⊕
hormon
buněčný efekt

Receptory pro hormony

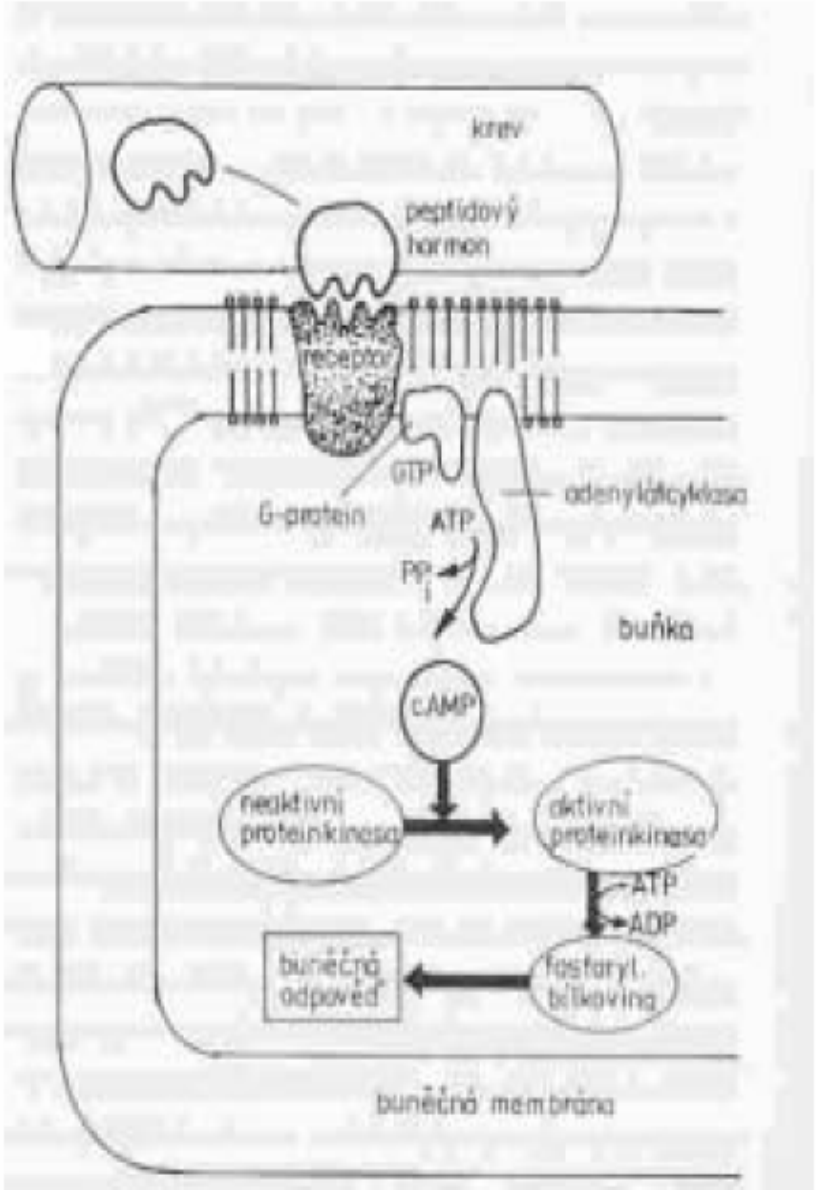
Steroidy-tyroidní hormony



Inzulín

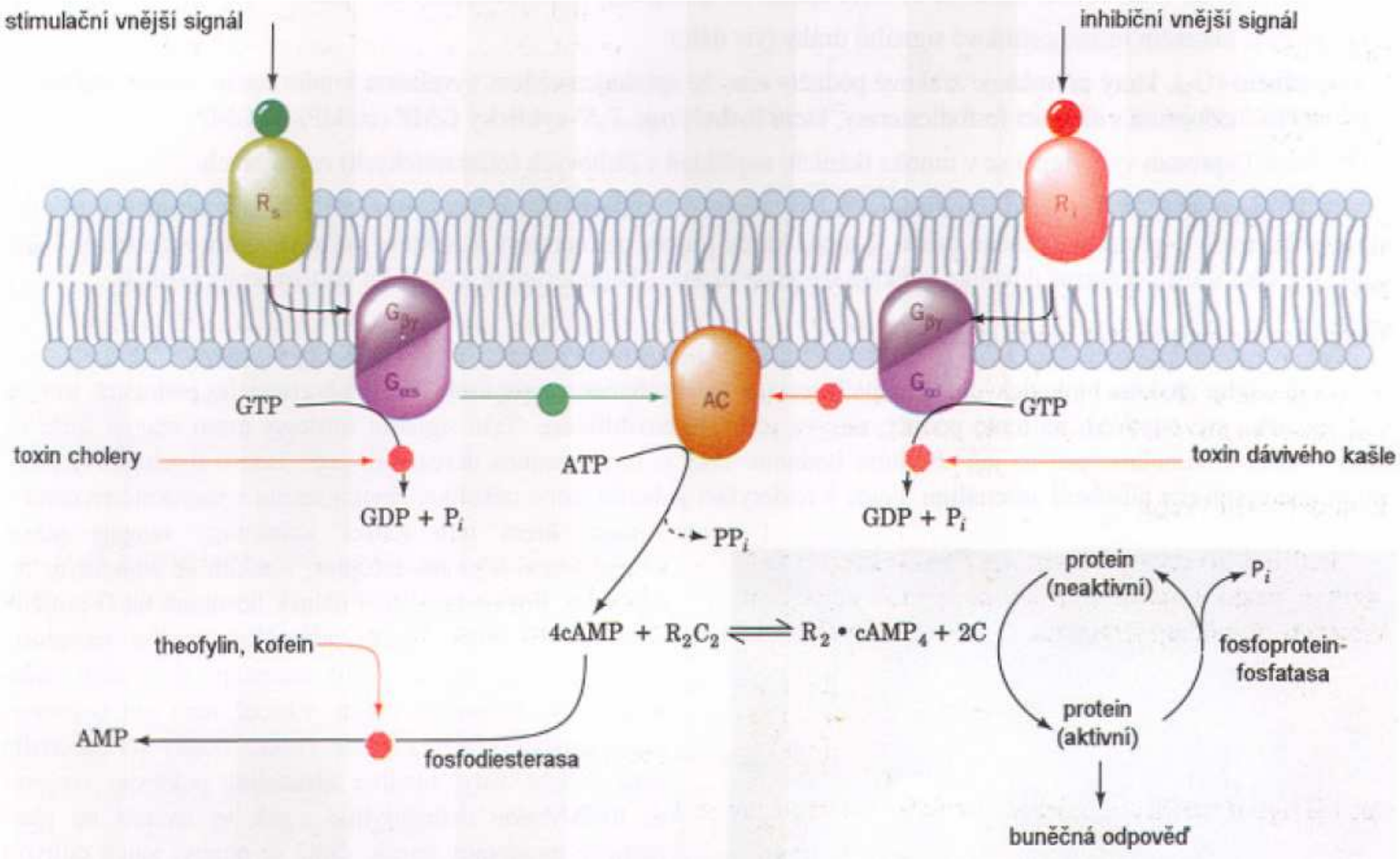

NH_3^+
NH_3^+
doména bohatá na cystein
α-řetězec
NH_3^+
NH_3^+
β-řetězec
plasmatická membrána
COO^-
COO^-
P
Tyr
P
Tyr
domény tyrosinkinasy
Tyr
P
Tyr
P
COO^-
COO^-

Peptidy


krev
peptidový hormon
receptor
GTP
G-protein
ATP
adenylátcykláza
PP
i
buňka
cAMP
neaktivní proteinkináza
aktivní proteinkináza
ATP
ADP
buněčná odpověď
fosforyl. bílkoviny
buněčná membrána

Druzí poslové

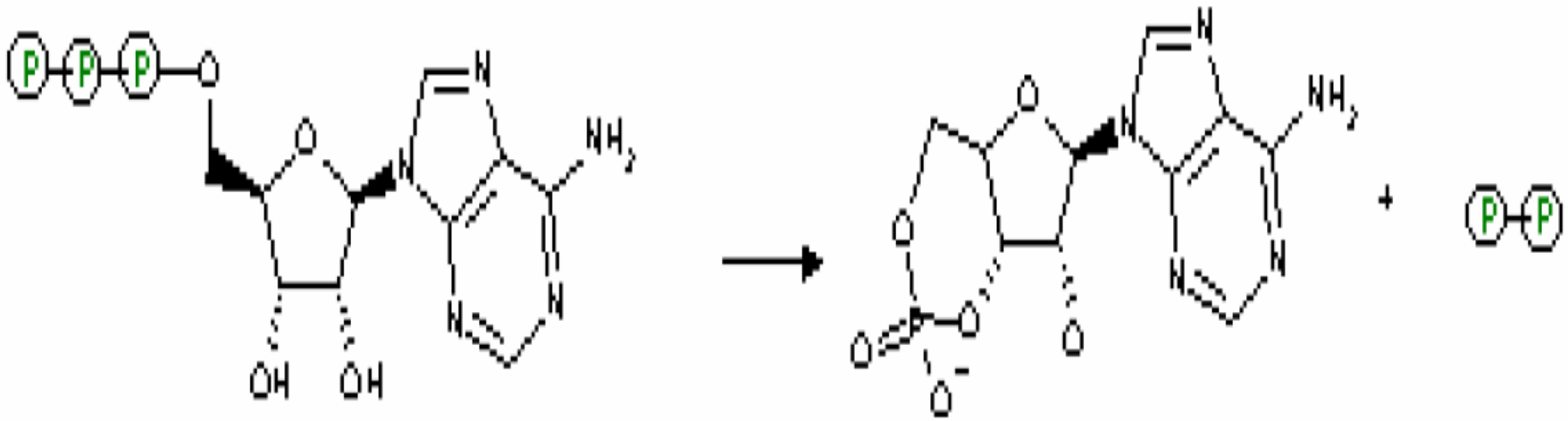
cAMP



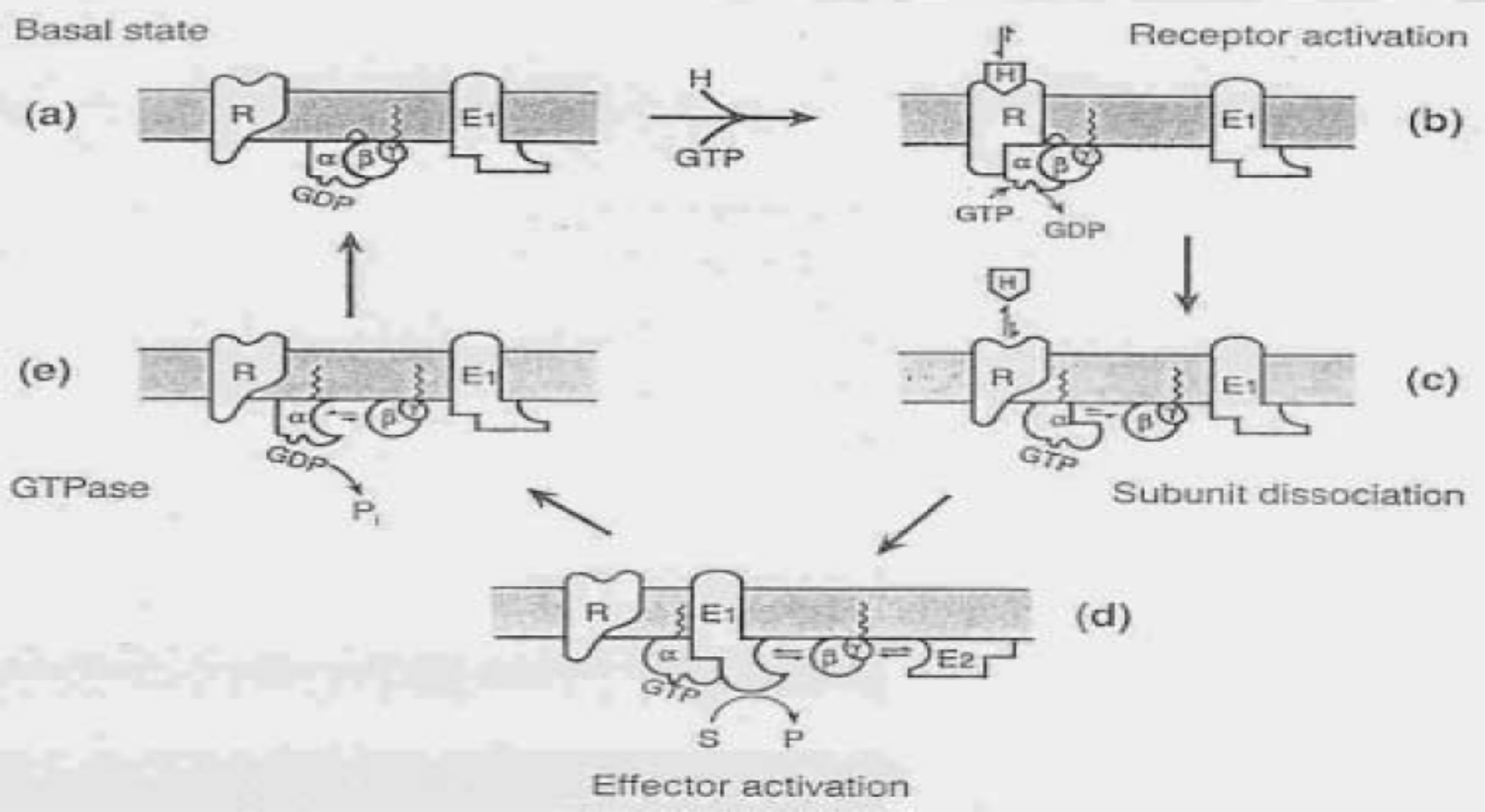
ATP → c-AMP

↓

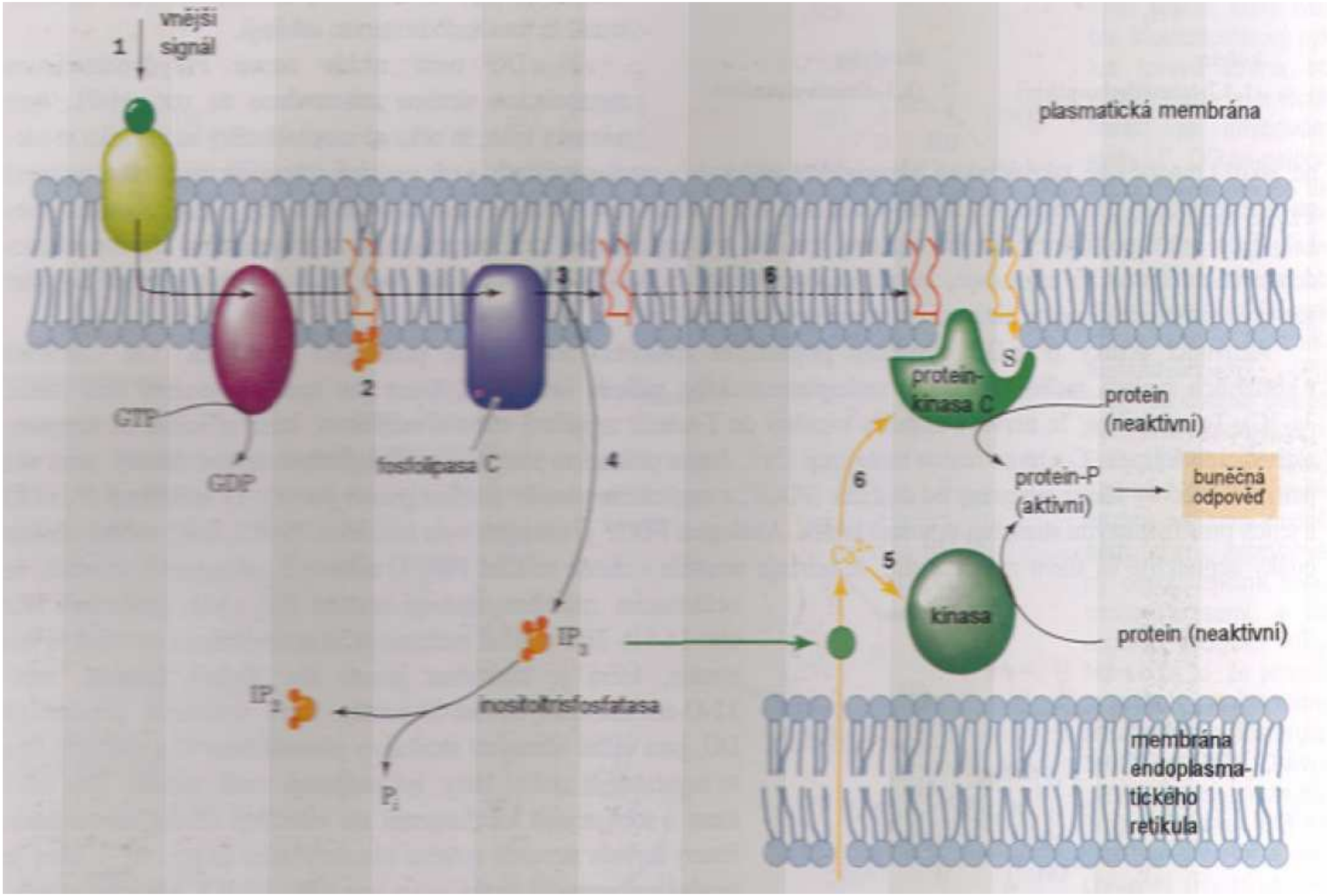
Cílový enzym: aktivace proteinkinasy A



G-proteiny

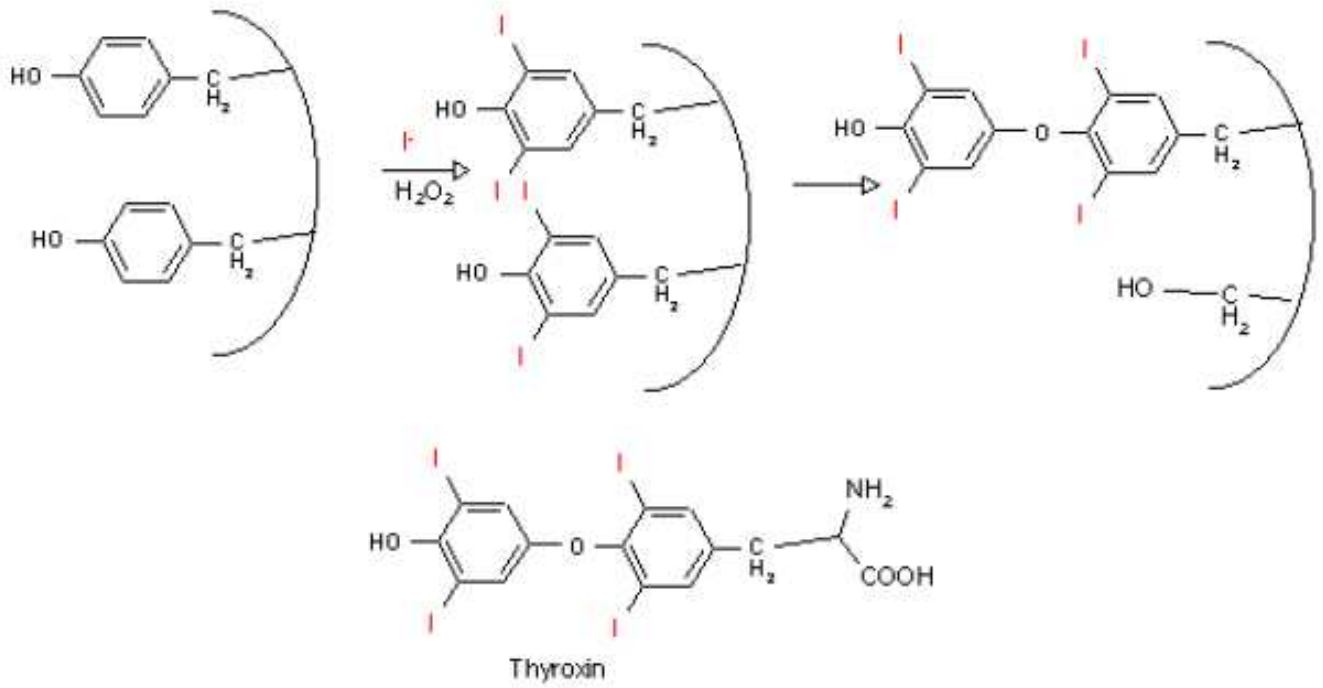

Basal state
(a)
R
E1
α
β
γ
GDP
H
GTP
Receptor activation
(b)
GTP
GDP
(c)
Subunit dissociation
(d)
E2
S
P
Effector activation
(e)
GTPase
P_i

Fosfatidylinositol-4,5-bisfosfát



Hormony

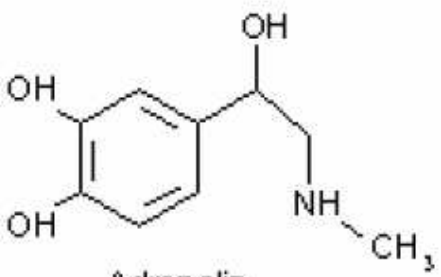
- Thyroxin - celková stimulace metabolismu



Thyroxin

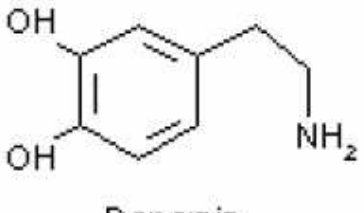
Hormony

- adrenalin, noradrenalin (regulace odbourávání glykogenu ve svalech)
- Tyr → DOPA → dopamin → noradrenalin → adrenalin

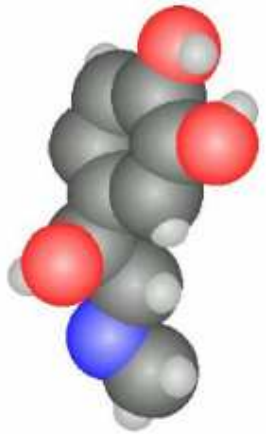


Adrenalin

Noradrenalin

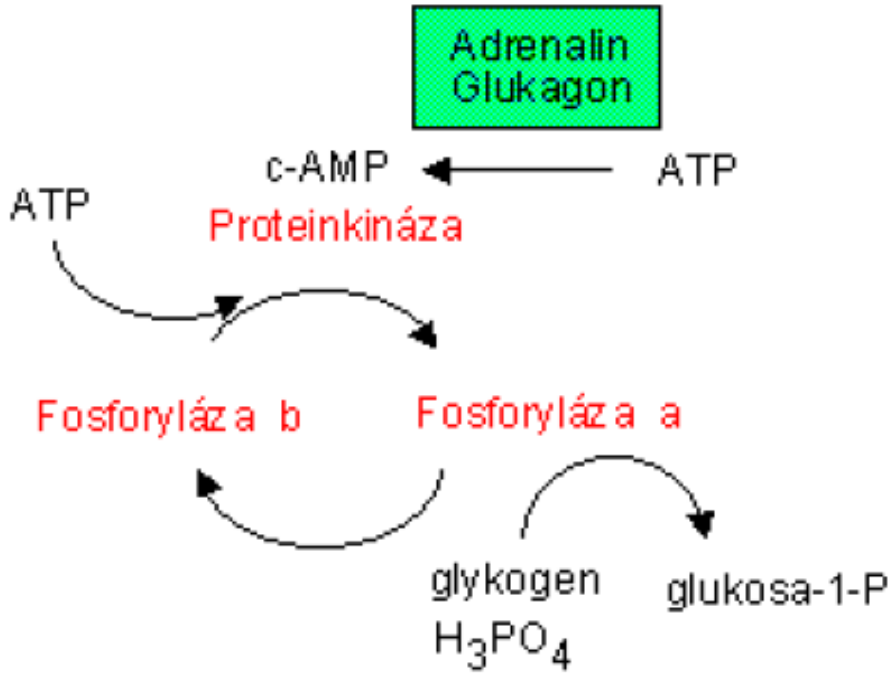


Dopamin



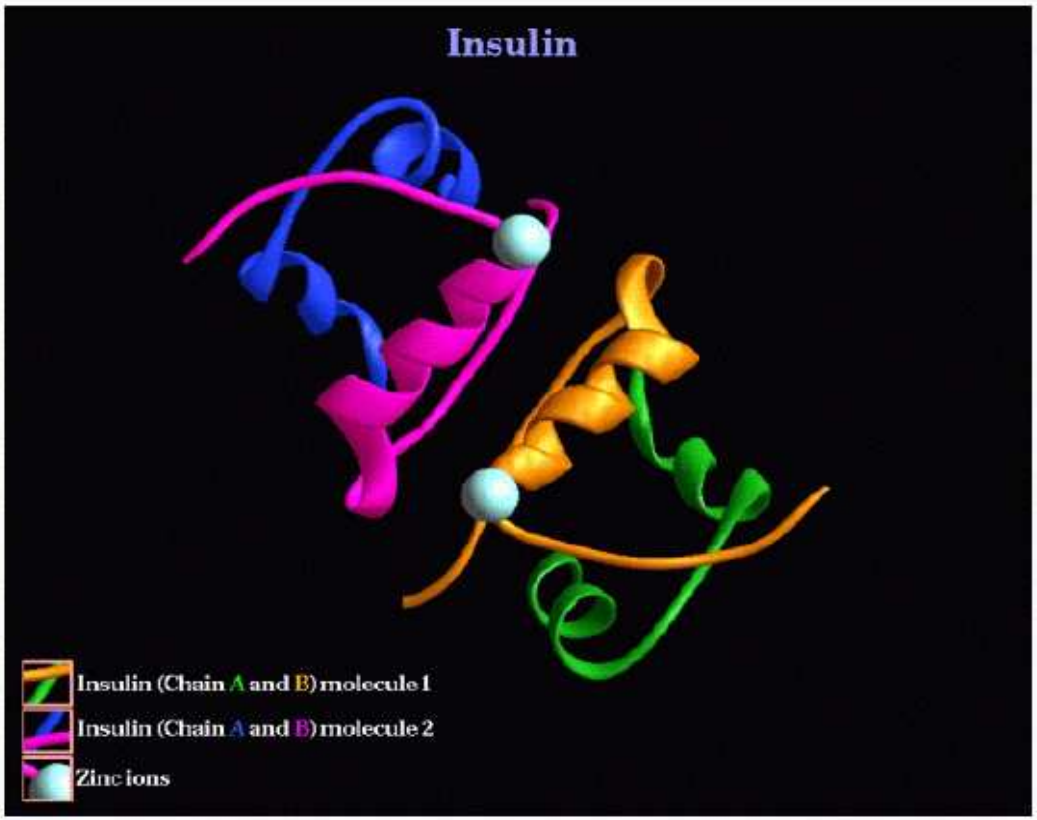
Metabolismus sacharidů

- Regulace syntézy a odbourávání glykogenu
  - adrenalin (sval), glukagon (játra)



Hormony

- Inzulin
- Mr 11,5 kDa



Hormony

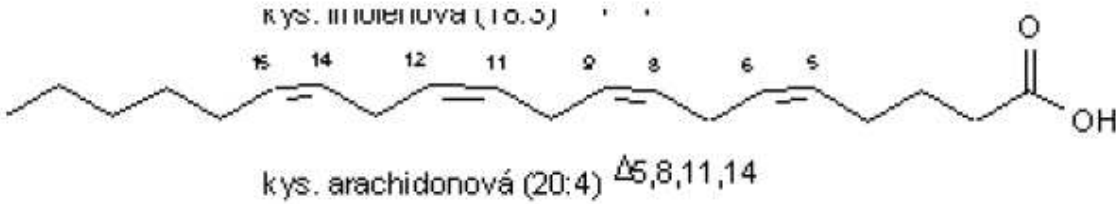
- Efekt inzulinu
  - Játra: hromadění glukosy uvnitř buněk - syntéza glykogenu
- Efekt glukagonu
  - regulace odbourávání glykogenu v játrech (nízká hladina glukosy stimuluje sekreci glukagonu - fosforolýza, stimulace lipas adipocytů))

Hormony

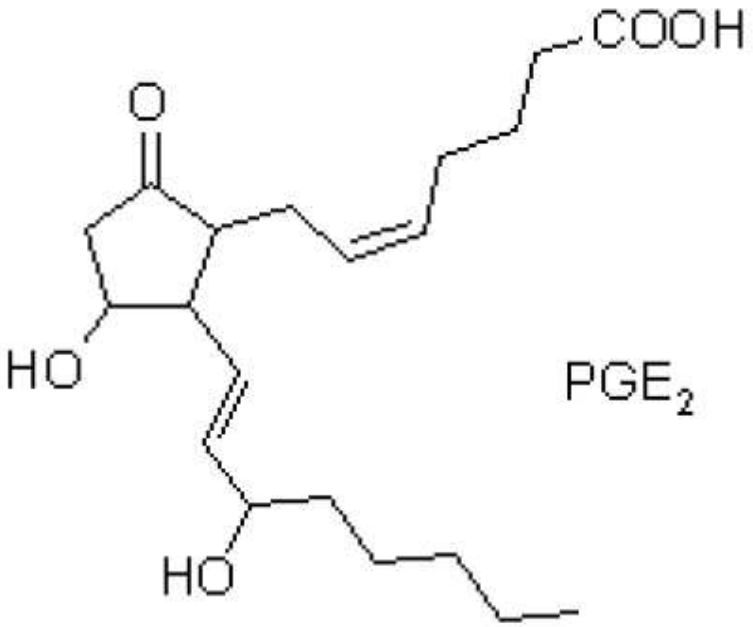
- Diabetes mellitus
  - nízký poměr inzulin/glukagon, hladina glukosy 15 mM, vylučování močí
  - blokování an. glykolýzy, stimulace glukoneogeneze
  - mobilizace tuků, tvorba ketolátek

Hormony

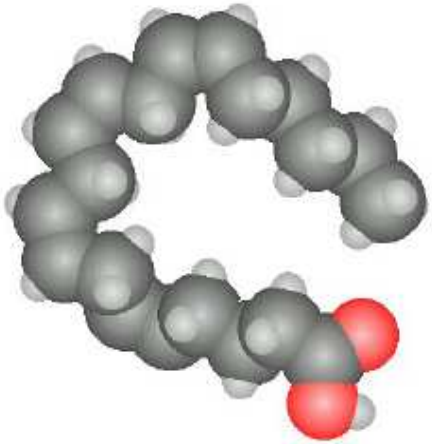
- Prostaglandiny



kys. arachidonová (20:4) Δ5,8,11,14



PGE_2

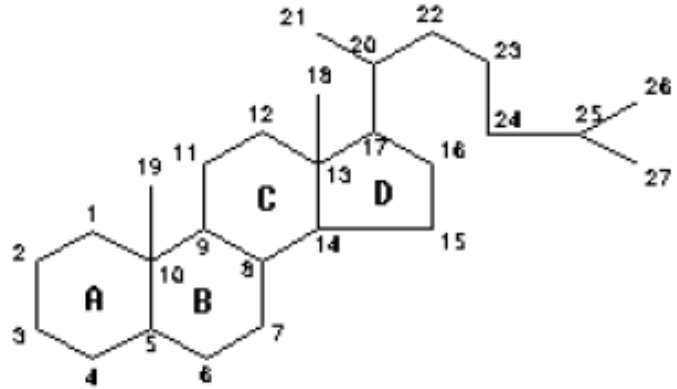


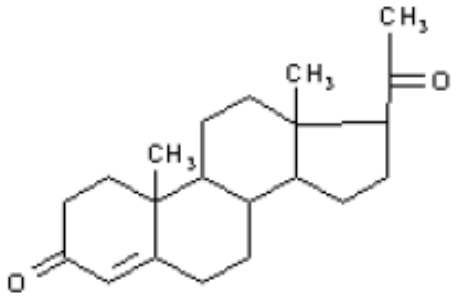
Hormony

- Steroidní hormony
  - cholesterol → pregnenolon (monooxygenasy mitochondrií)
    - kůra nadledvinek (aldosteron, kortisol)
    - pohlavní žlázy, placenta (progesteron, testosteron, etstradiol)

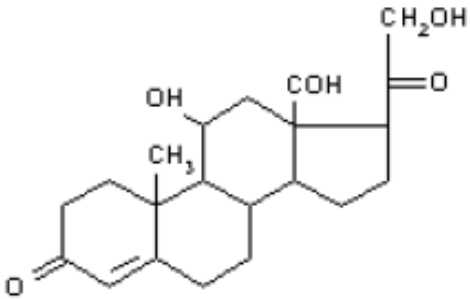
Hormony

- Steroidní hormony

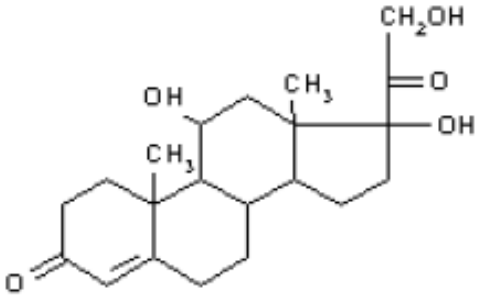




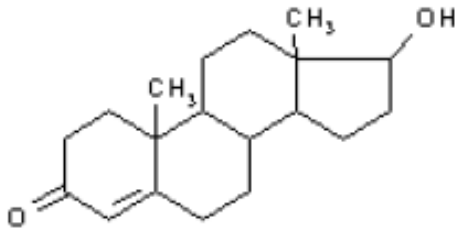
Progesteron



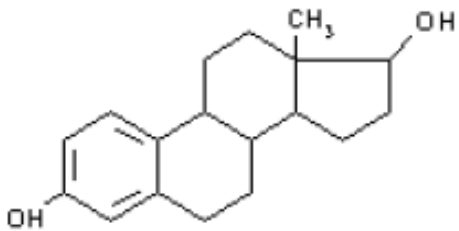
Aldosteron



Kortisol



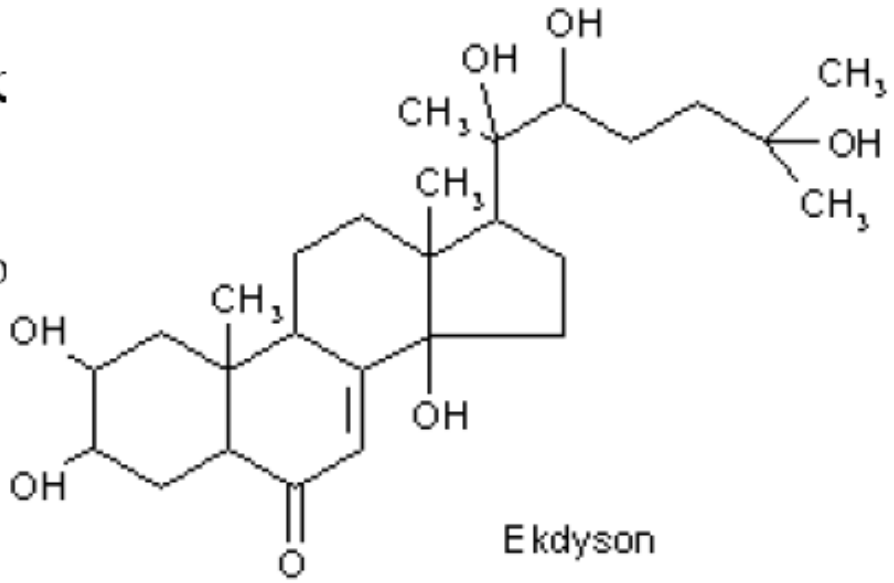
Testosteron



Estradiol

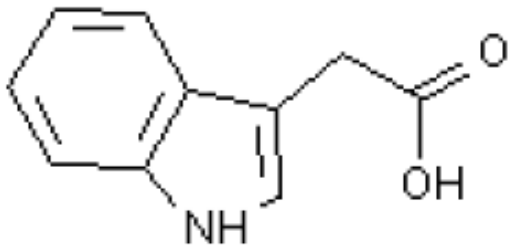
Hormony

- Hormony bezobratlýc
- (ekdyson + juvenilní hormon)
- Regulace svlékání a metamo hmyzu

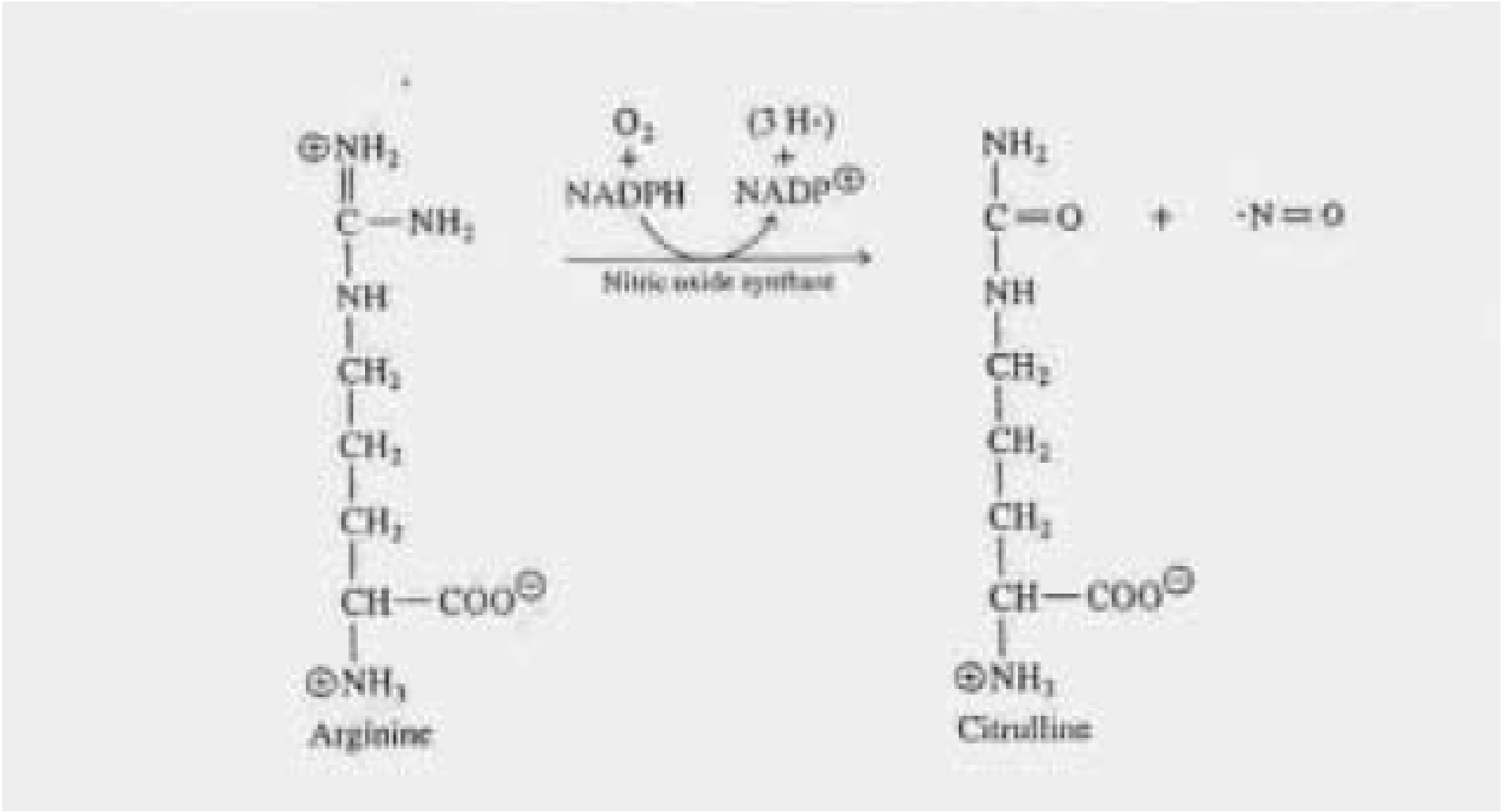


Ekdyson

- rostlinné hormony
- Mechanismus – aktivace plasmatické H+-ATPasy

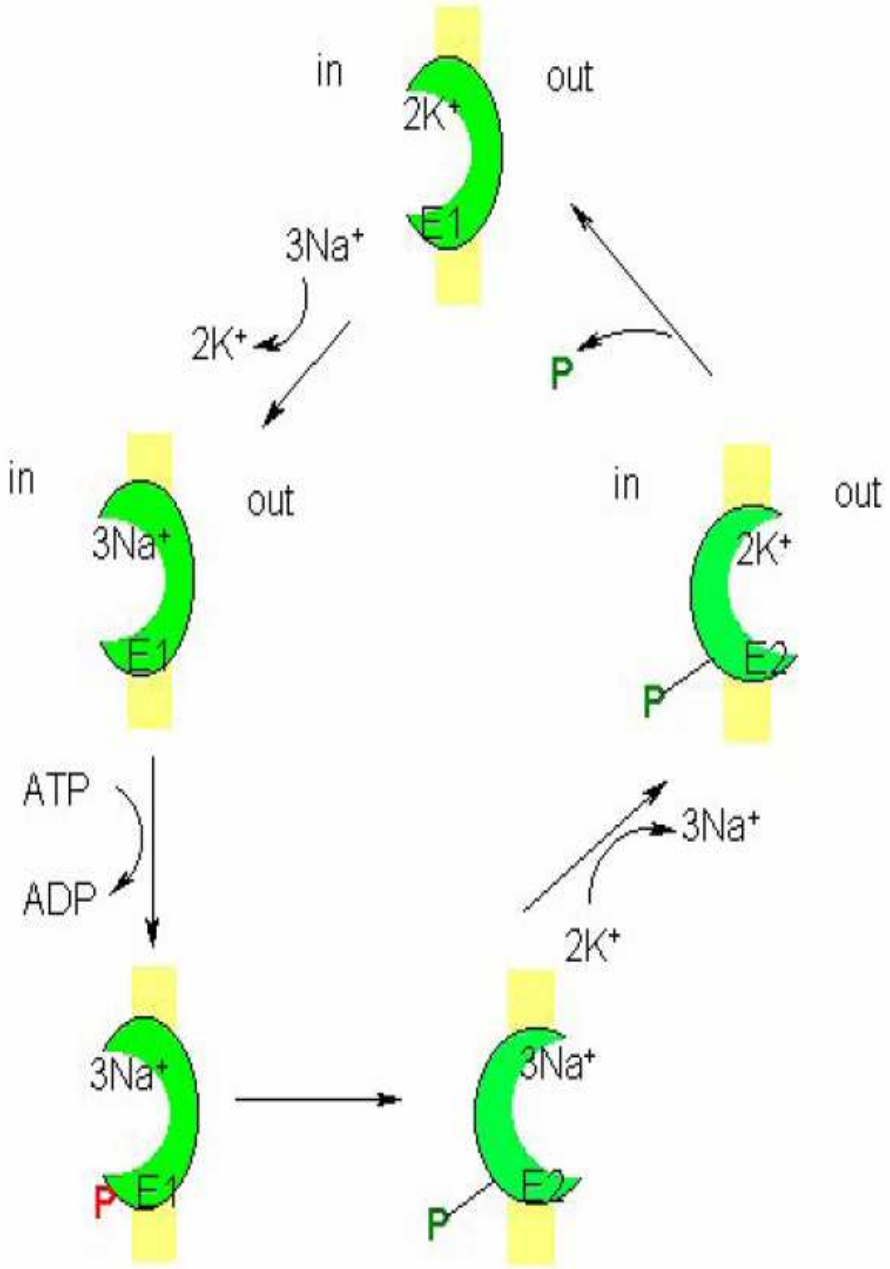


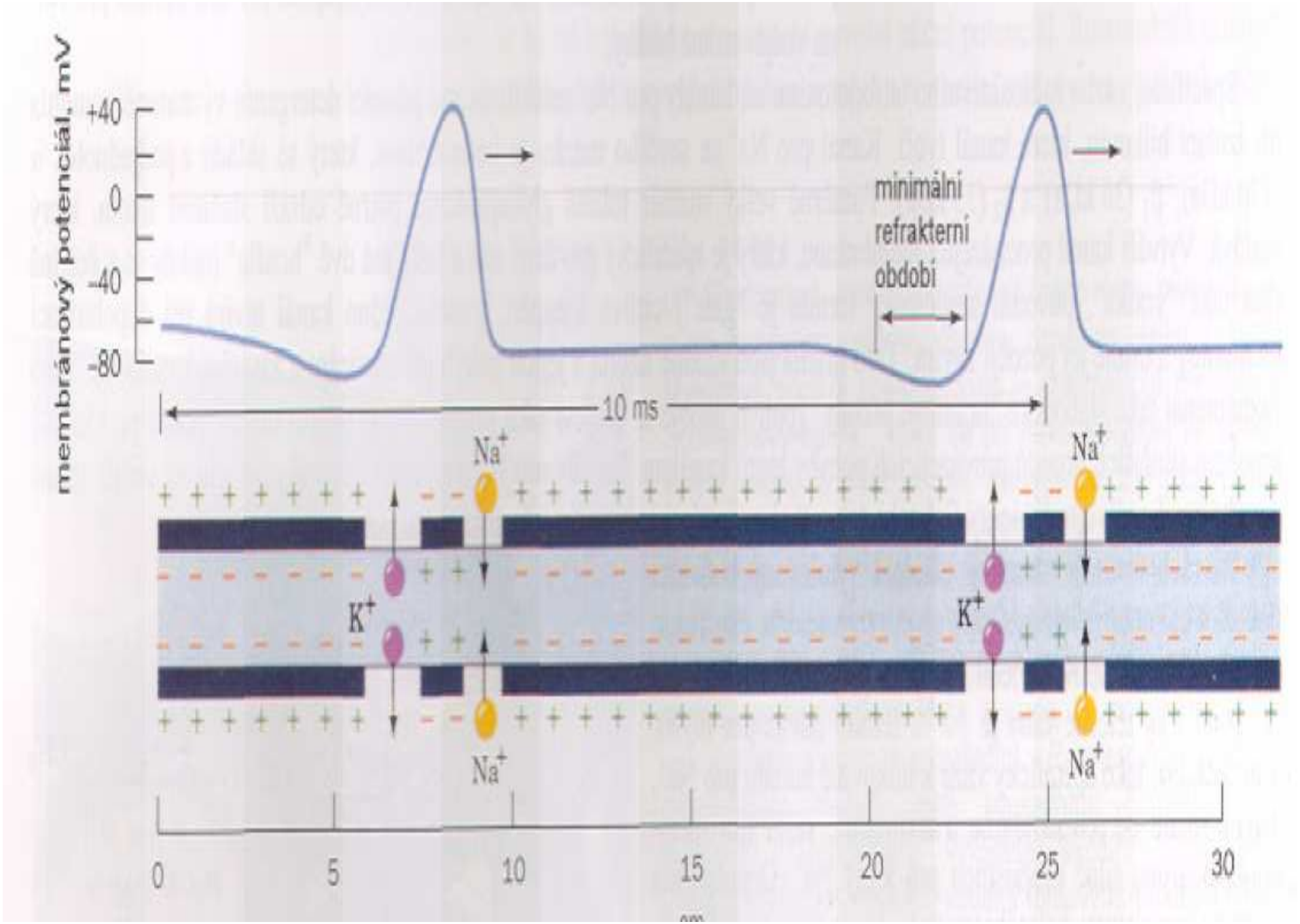
NO jako hormon

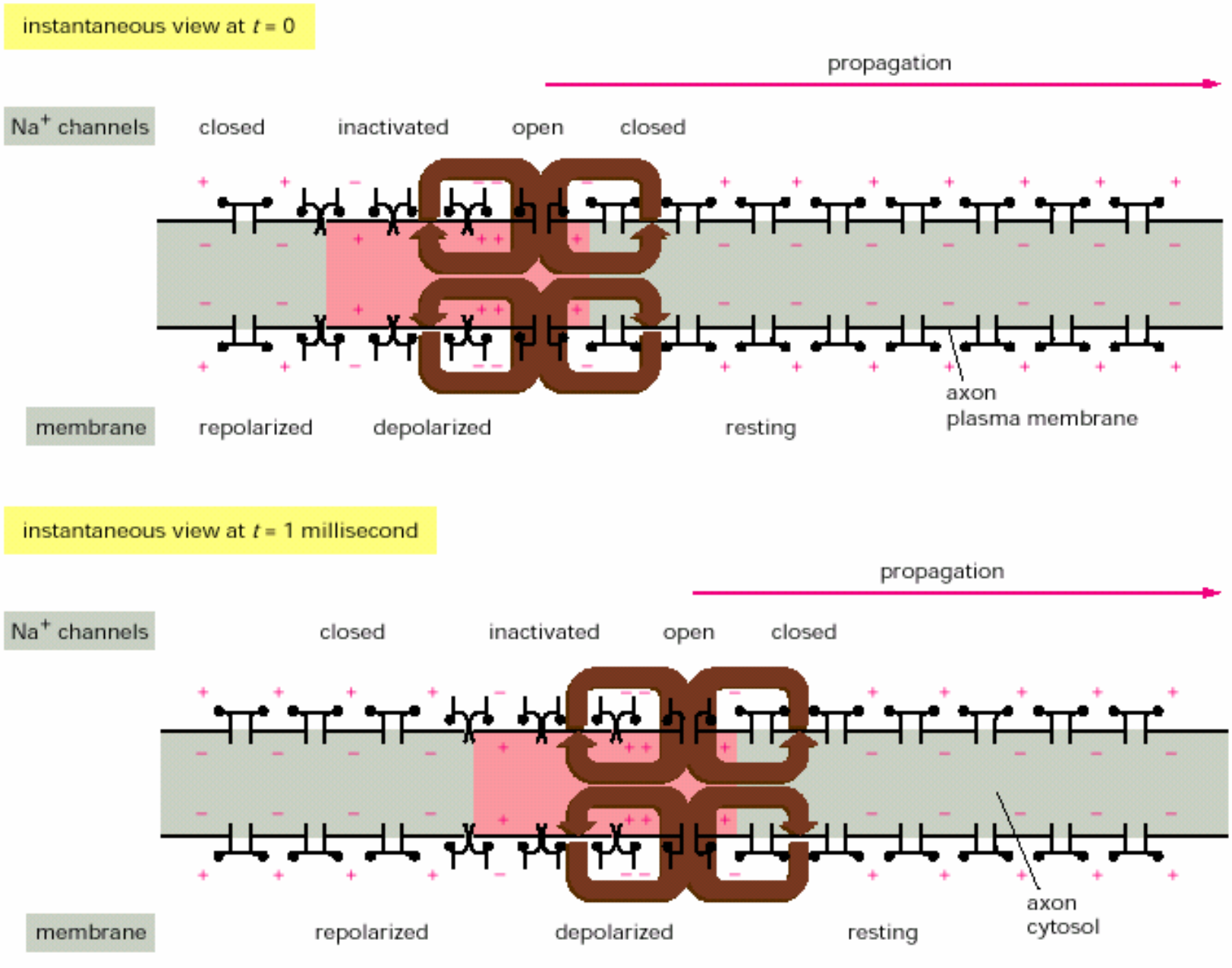


Nervový vzruch

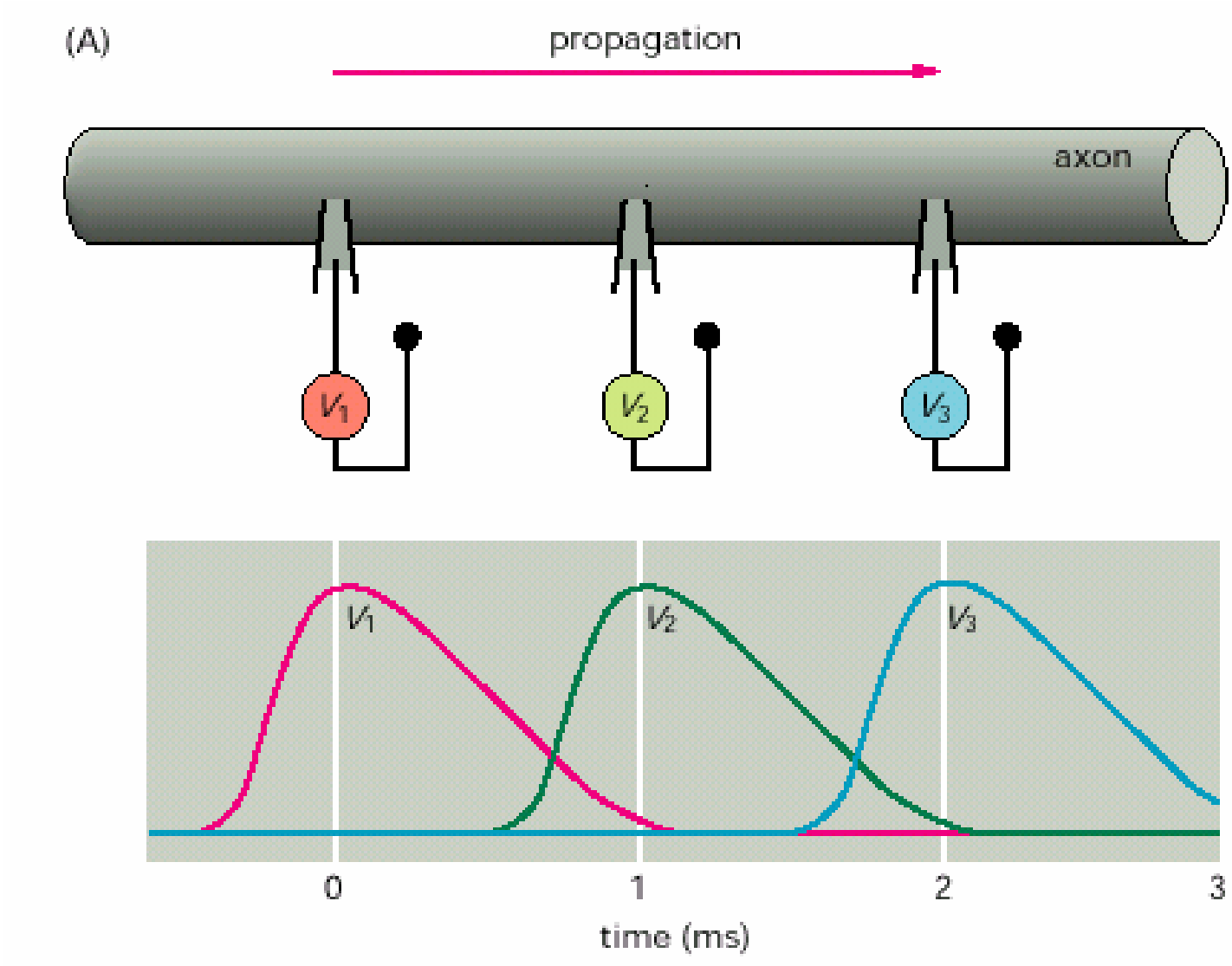
- ATPasa, Na^+-K^+

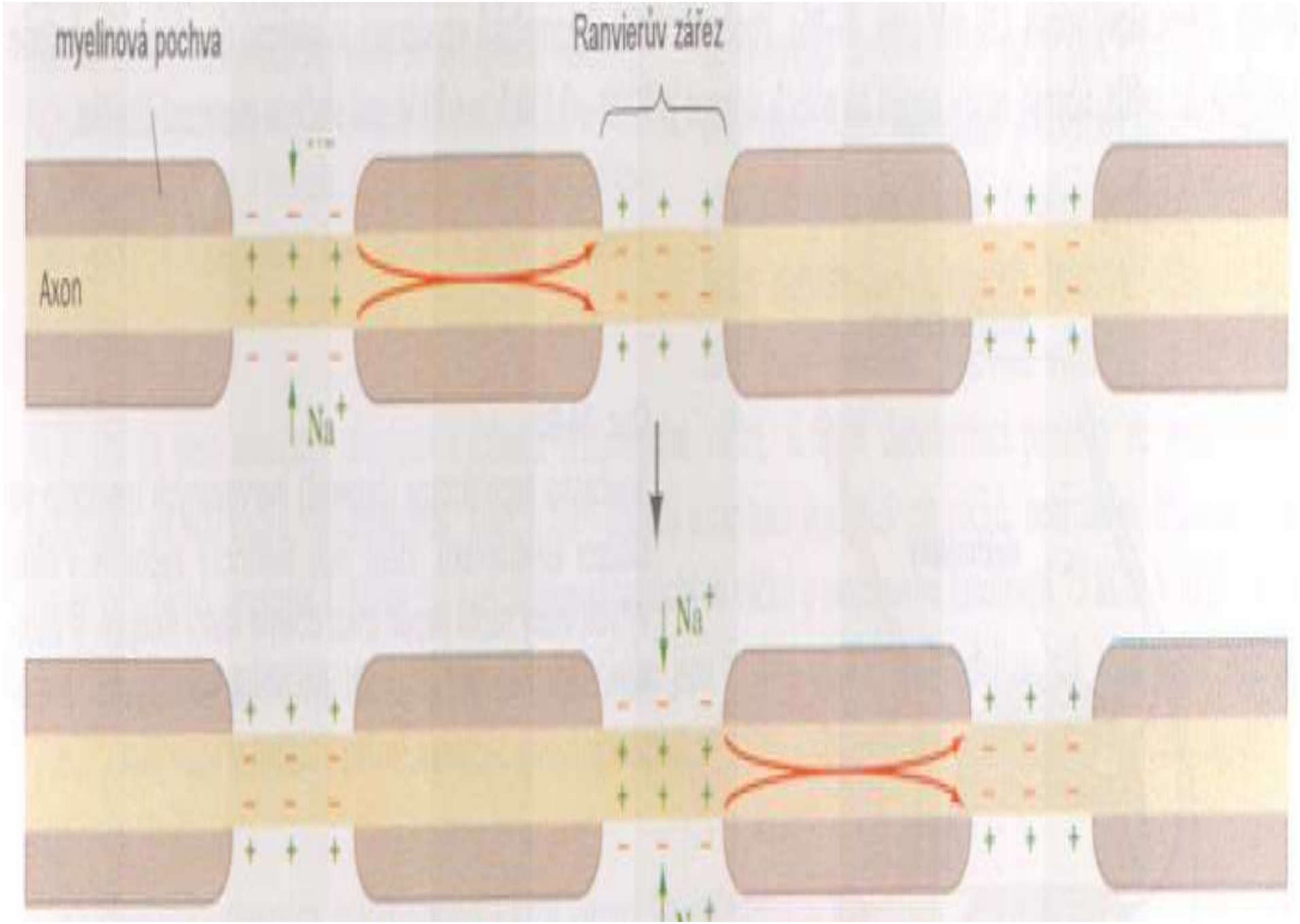

in
out
2K+
E1
3Na+
2K+
P
in
out
3Na+
E1
in
out
2K+
E2
P
ATP
ADP
3Na+
2K+
3Na+
E1
P
3Na+
E2
P

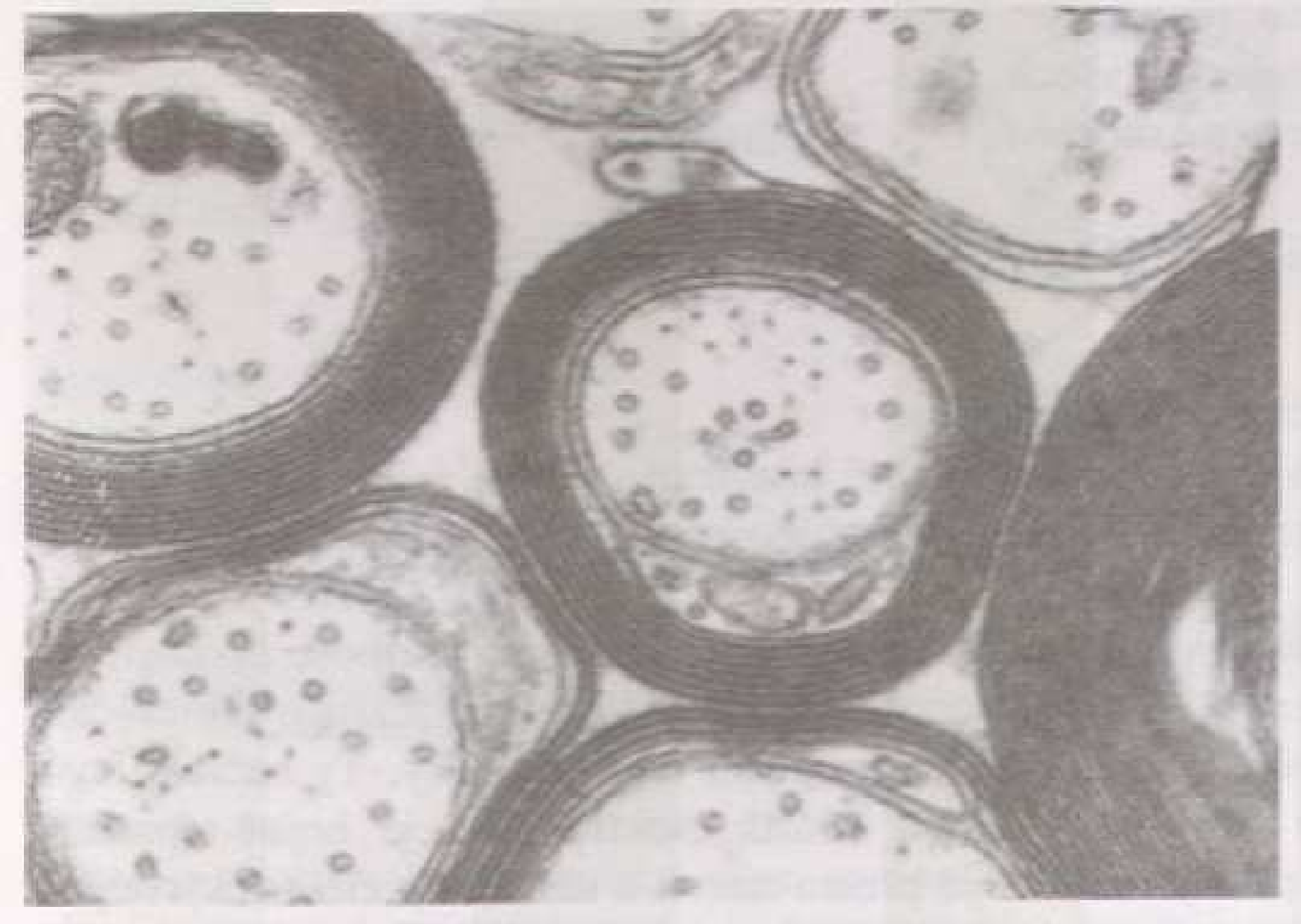

membránový potenciál, mV
+40
0
-40
-80
minimální
refrakterní
období
10 ms
Na+
Na+
K+
K+
Na+
Na+
0
5
10
15
20
25
30


instantaneous view at t = 0
propagation
Na+ channels
closed
inactivated
open
closed
axon
plasma membrane
membrane
repolarized
depolarized
resting
instantaneous view at t = 1 millisecond
propagation
Na+ channels
closed
inactivated
open
closed
axon
cytosol
membrane
repolarized
depolarized
resting

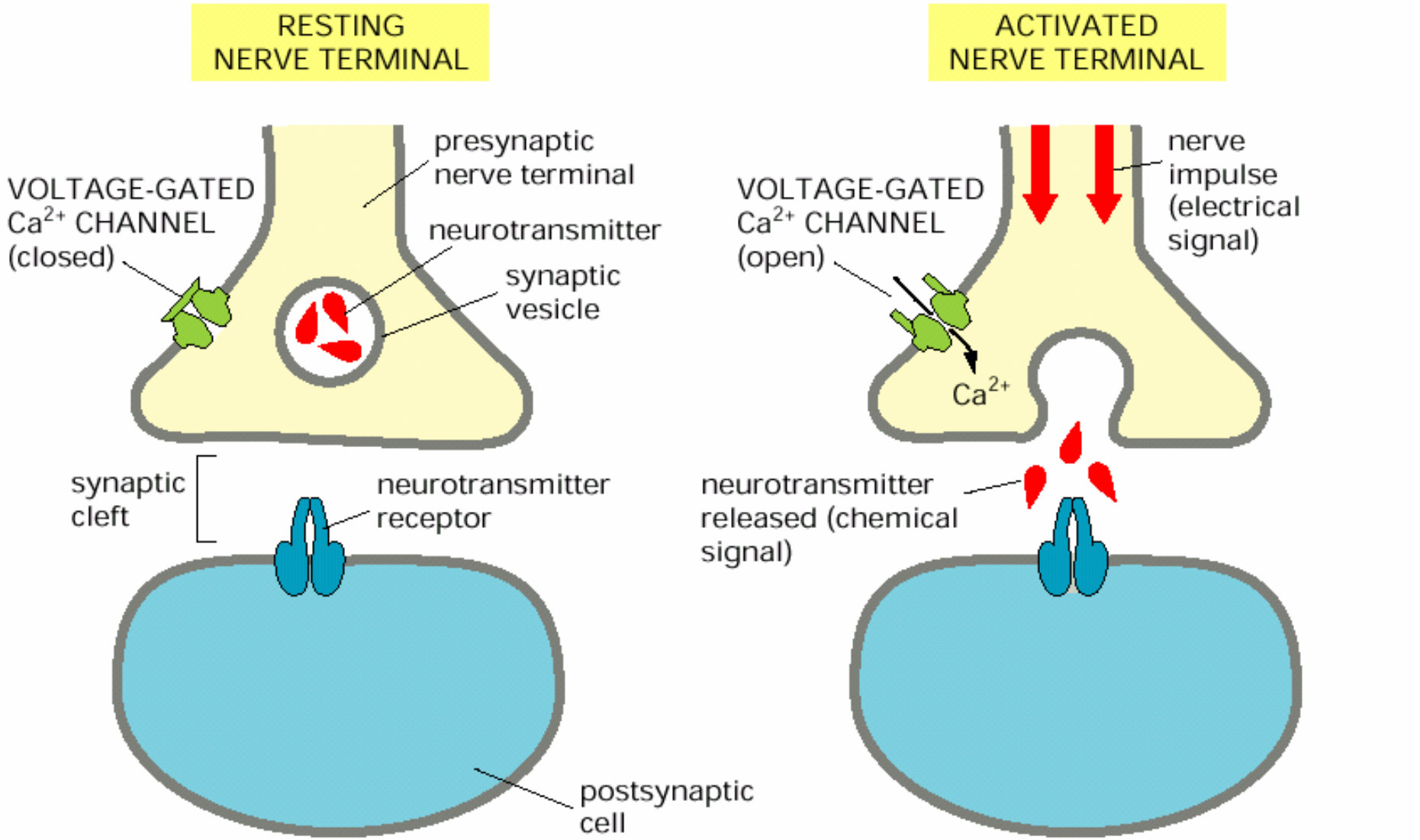
Vedení nervového vzruchu

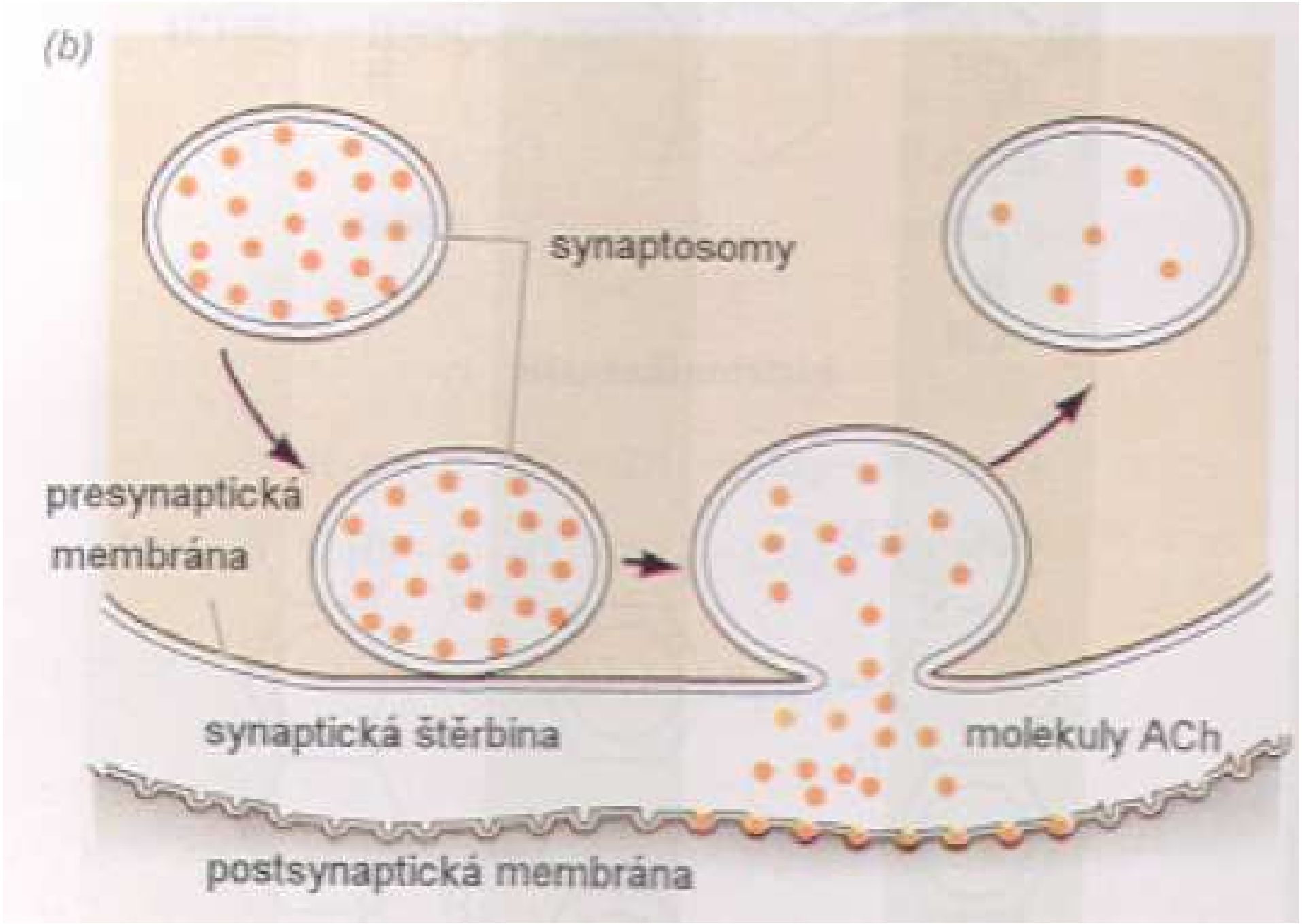



myelinová pochva
Ranvierův zářez
Axon
Na+
Na+

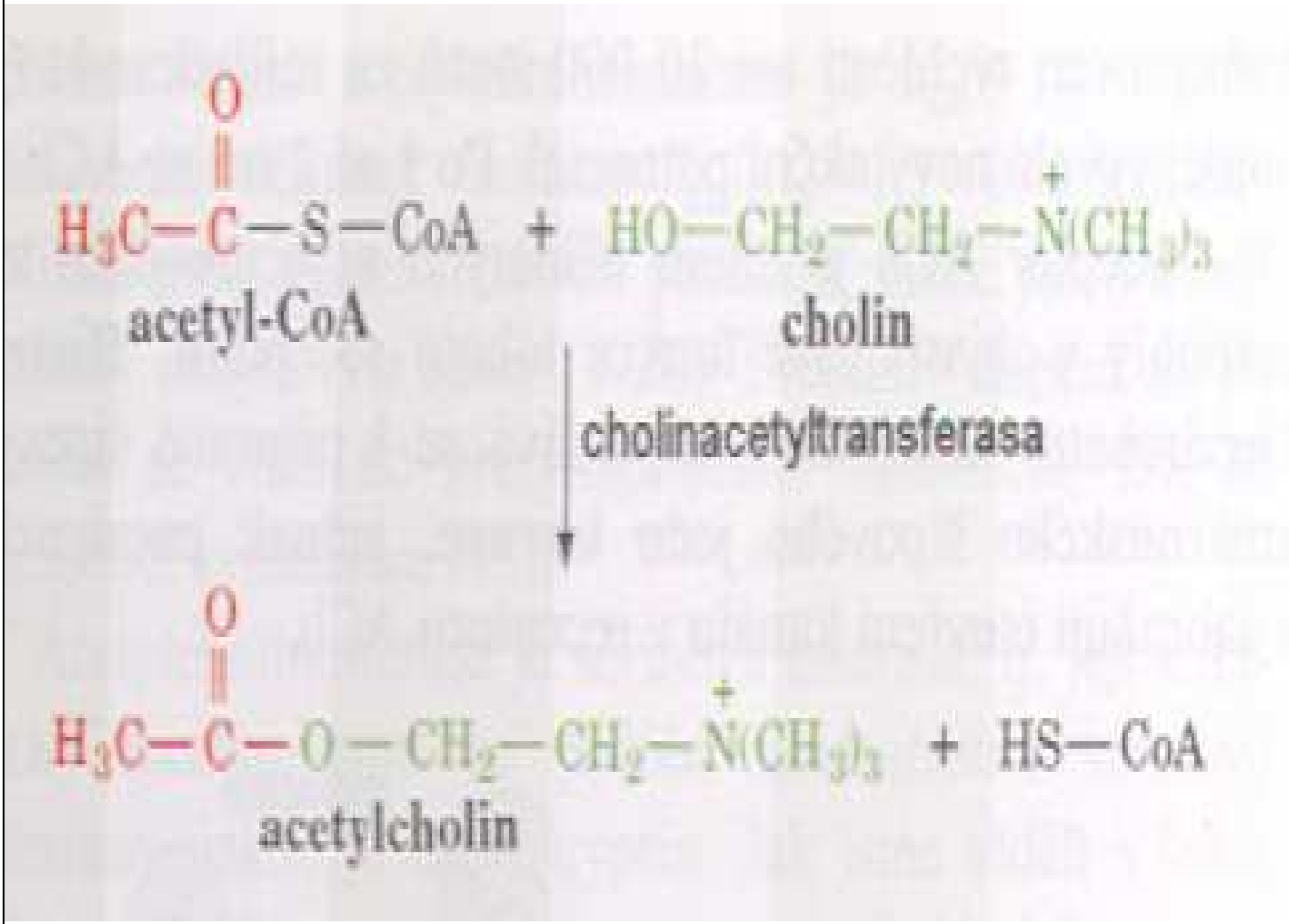


Synapse


RESTING
NERVE TERMINAL
ACTIVATED
NERVE TERMINAL
presynaptic
nerve terminal
VOLTAGE-GATED
Ca2+ CHANNEL
(closed)
neurotransmitter
synaptic
vesicle
synaptic
cleft
neurotransmitter
receptor
postsynaptic
cell
nerve
impulse
(electrical
signal)
VOLTAGE-GATED
Ca2+ CHANNEL
(open)
Ca2+
neurotransmitter
released (chemical
signal)


(b)
synaptosomy
presynaptická membrána
synaptická štěrbina
molekuly ACh
postsynaptická membrána


(a)


acetyl-CoA
cholin
cholinacetyltransferasa
acetylcholin

Imunochemie

ZÁKLADNÍ ÚKOLY IMUNITNÍHO SYSTÉMU

- OBRANA PROTI PATOGENŮ
- ODSTRAŇOVÁNÍ ABNORMÁLNÍCH BUNĚK (NÁDOROVÝCH, POŠKOZENÝCH, INFIKOVANÝCH…)

BUŇKY IMUNITNÍHO SYSTÉMU:

RŮZNÉ TYPY BÍLÝCH KRVINEK (LEUKOCYTŮ):

MONOCYTY, MAKROFÁGY, GRANULOCYTY, LYMFOCYTY…

ZBRANĚ IMUNITNÍHO SYSTÉMU:

Fagocyty (požírají mikroby)
Komplement
Protilátky
NK-buňky (zabíjejí infikované a nádorové buňky)
T-lymfocyty (několik typů)

Imunitní odpověď

- Buněčná imunita – T-lymfocyty
- Humorální imunita – B-lymfocyty

Spuštěna interakcí s antigenem

T- LYMFOCYTY:

VZNIKAJÍ V BRZLÍKU (THYMU)

ROZEZNÁVAJÍ HLAVNĚ FRAGMENTY (VNITROBUNĚČNÝCH) PROTEINŮ NA POVRCHU JINÝCH BUNĚK

ÚČEL: DETEKCE BUNĚK INFIKOVANÝCH "SKRYTÝMI" INTRACELULÁRNÍMI PARAZITY (např. VIRY)

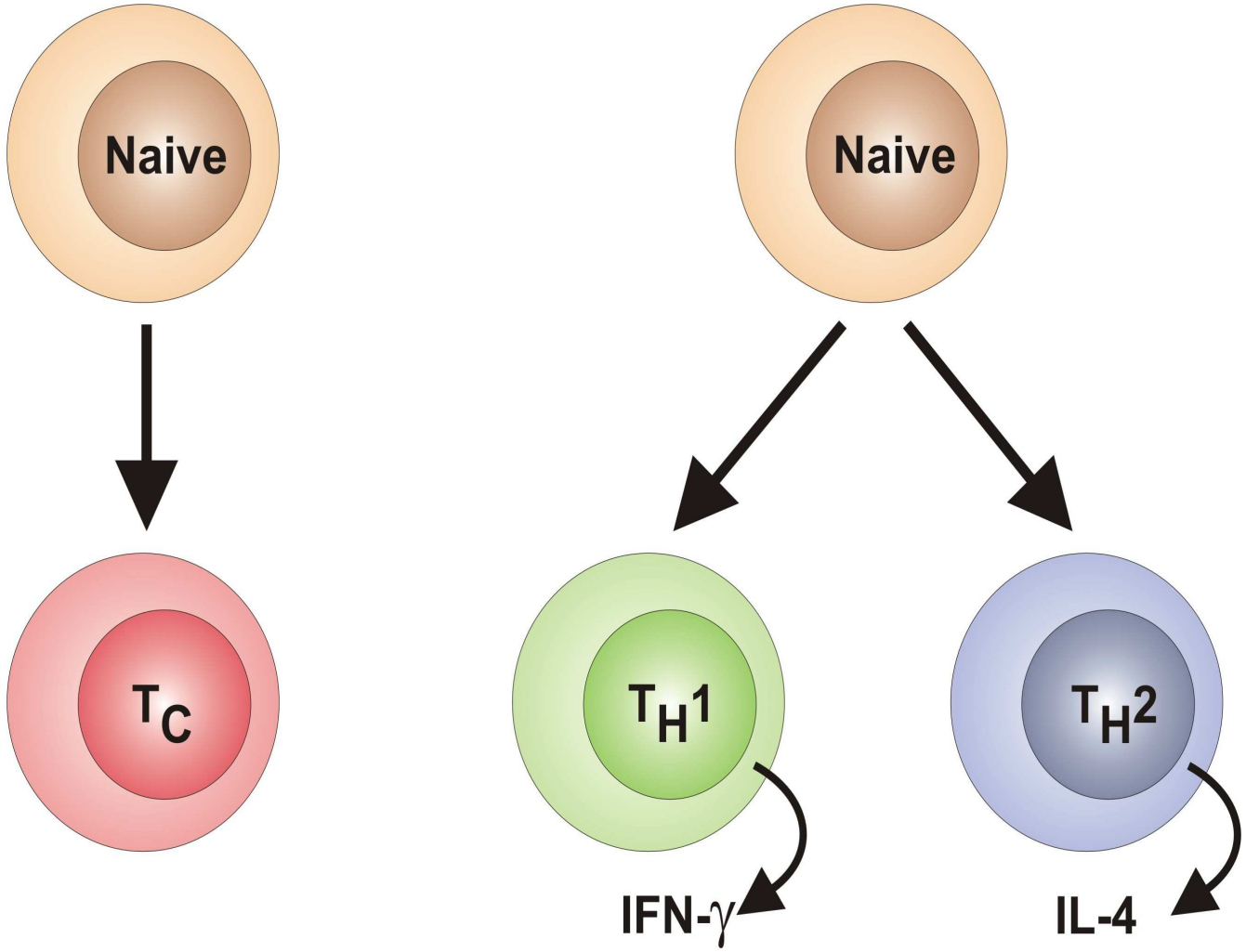
T LYMFOCYTY:

POMOCNÉ TYPU 1 (POMÁHAJÍ VYVOLÁVAT ZÁNĚT)

POMOCNÉ TYPU 2 (POMÁHAJÍ JINÝM BUŇKÁM (B LYMFOCYTŮM) DĚLAT PROTILÁTKY)

CYTOTOXICKÉ (ZABÍJEJÍ INFIKOVANÉ BUŇKY, ABY SE NESTALY ZDROJEM INFEKCE)

T LYMFOCYTY:
DŮLEŽITÉ FUNKČNÍ SUBPOPULACE



B- LYMFOCYTY:

VZNIKAJÍ V KOSTNÍ DŘENI

VYRÁBĚJÍ PROTILÁTKY (VĚTŠINOU ZA VYDATNÉ POMOCI T-LYMFOCYTŮ)

VZNIK REPERTOÁRU B LYMFOCYTŮ

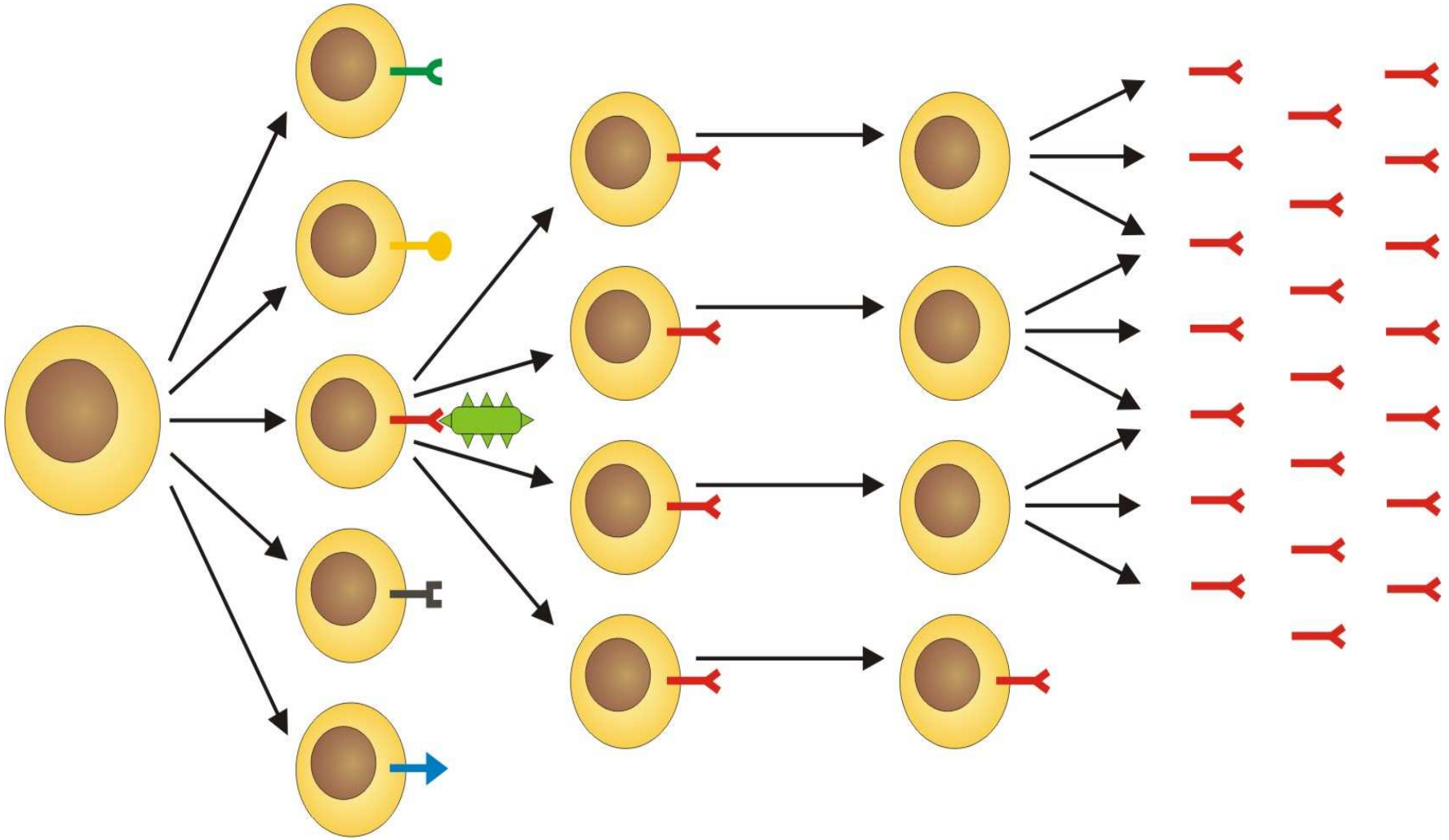


TABLE 35-2 Isotypes of Human Immunoglobulins

Class	Heavy Chain	Light Chain	Subunit Structure	Molecular Mass (kD)
IgA[b]	α	κ or λ	$(\alpha_2\kappa_2)_nJ$[a]	360–720
			$(\alpha_2\lambda_2)_nJ$[a]	
IgD	δ	κ or λ	$\delta_2\kappa_2$	160
			$\delta_2\lambda_2$	
IgE	ε	κ or λ	$\varepsilon_2\kappa_2$	190
			$\varepsilon_2\lambda_2$	
IgG[b]	γ	κ or λ	$\gamma_2\kappa_2$	150
			$\gamma_2\lambda_2$	
IgM	μ	κ or λ	$(\mu_2\kappa_2)_5J$	950
			$(\mu_2\lambda_2)_5J$	

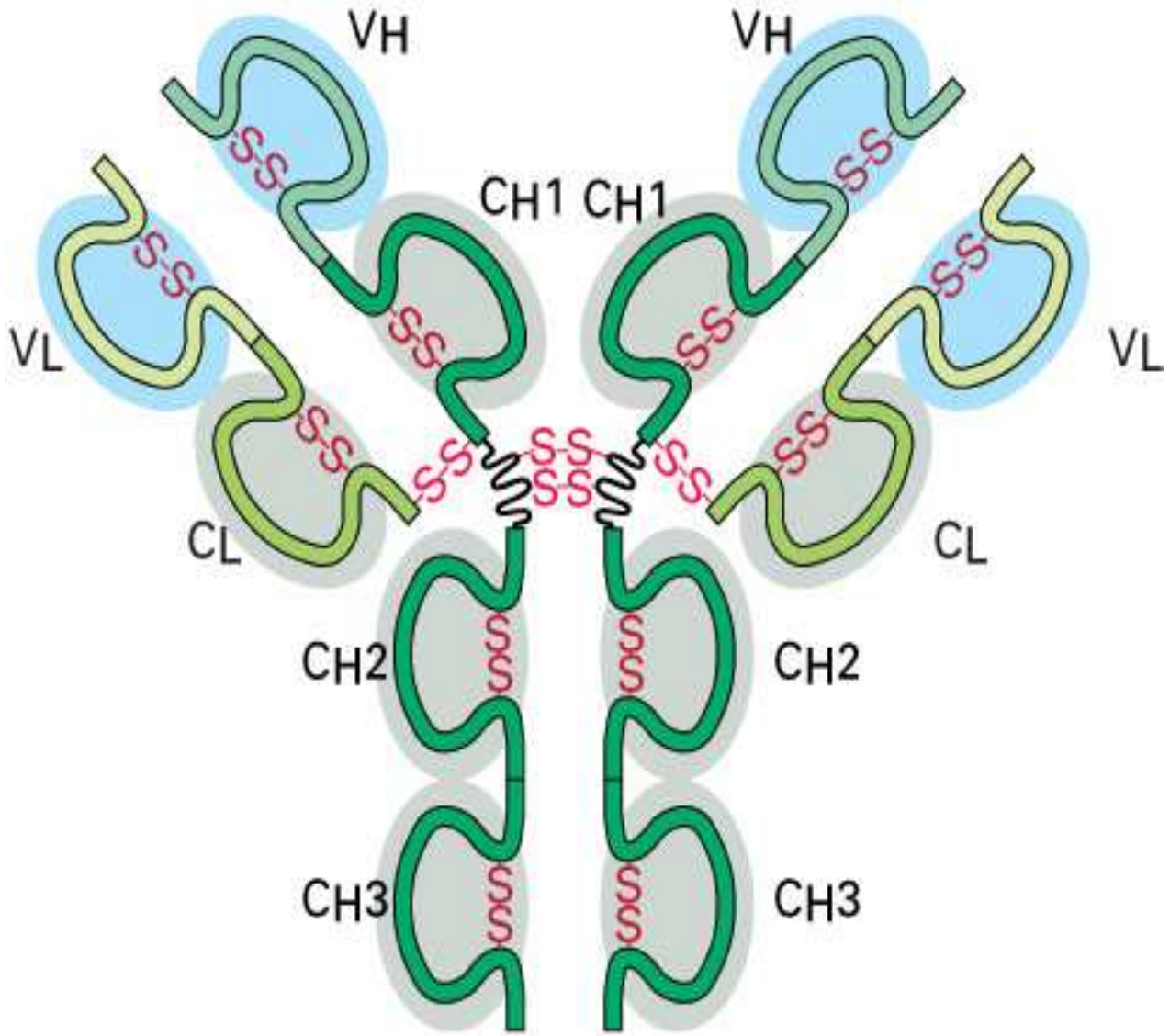


Figure 24–32. Molecular Biology of the Cell, 4th Edition.

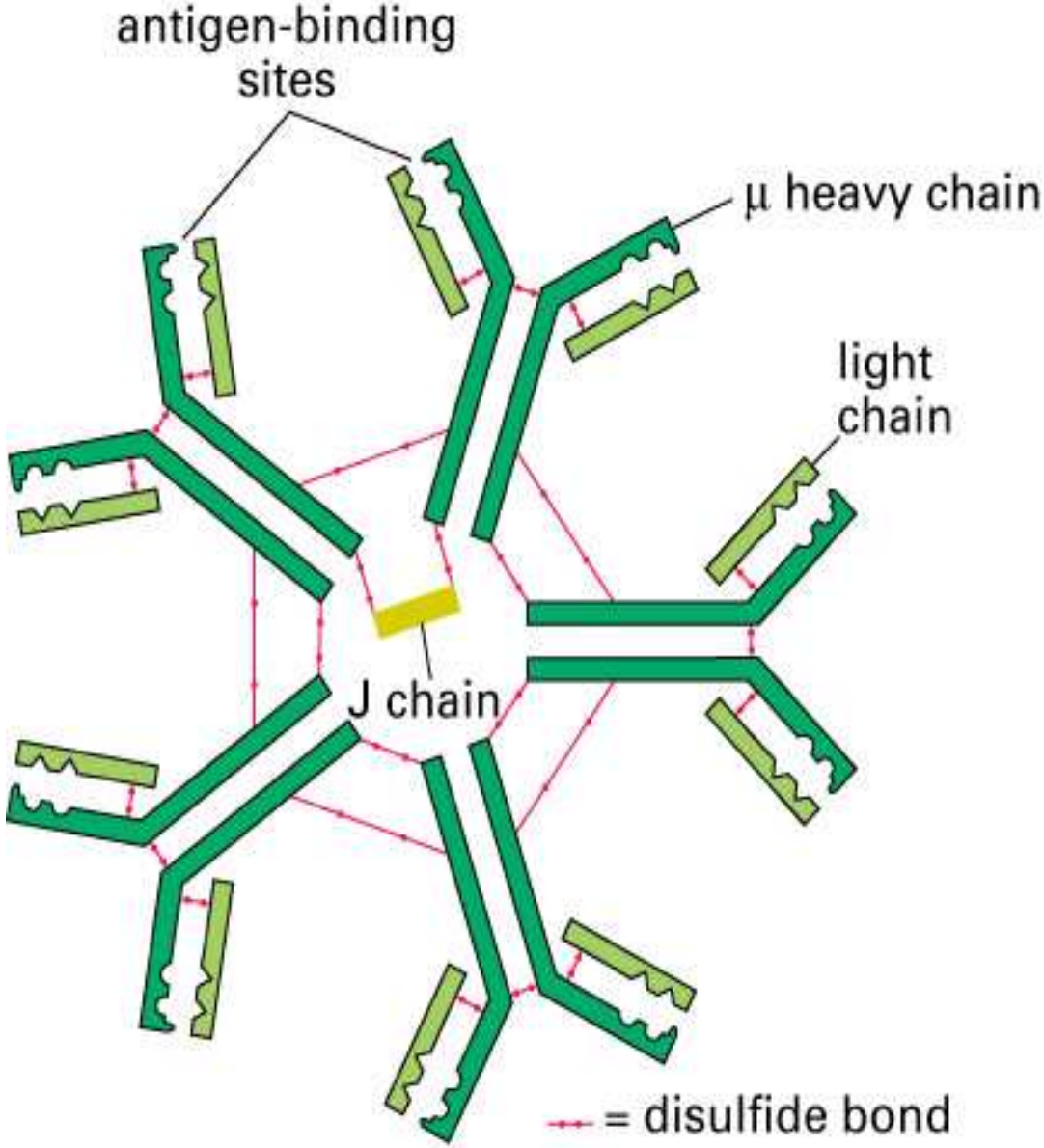
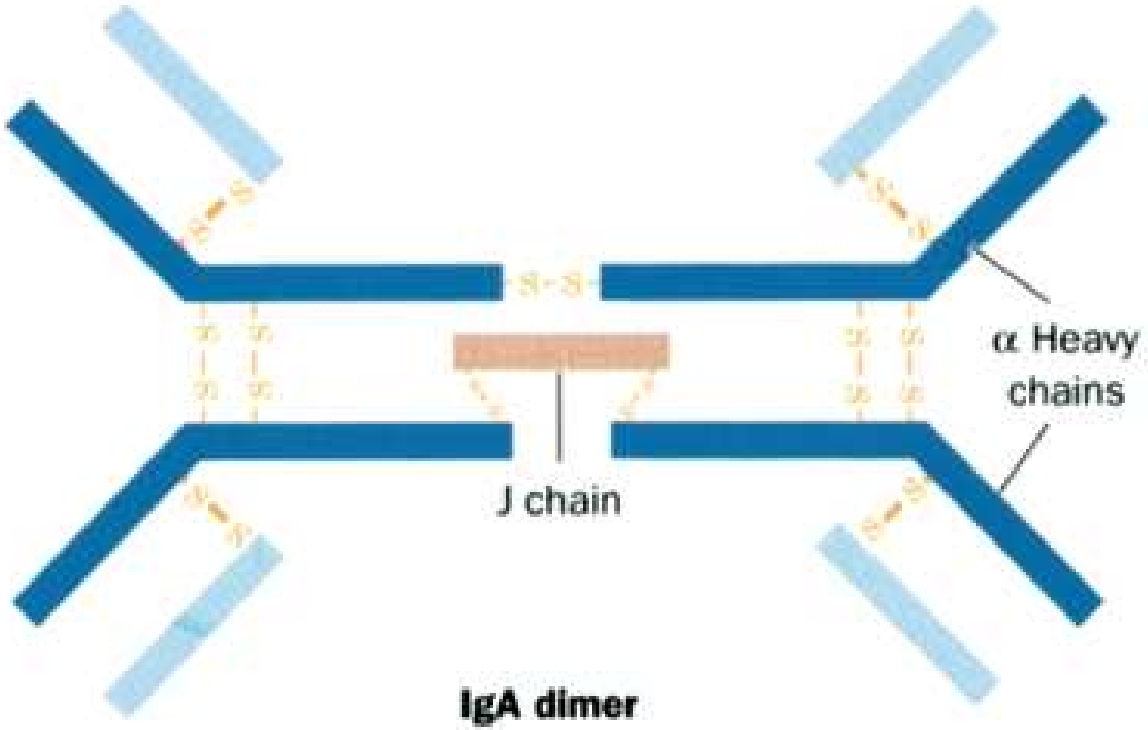


Figure 24–23. Molecular Biology of the Cell, 4th Edition.

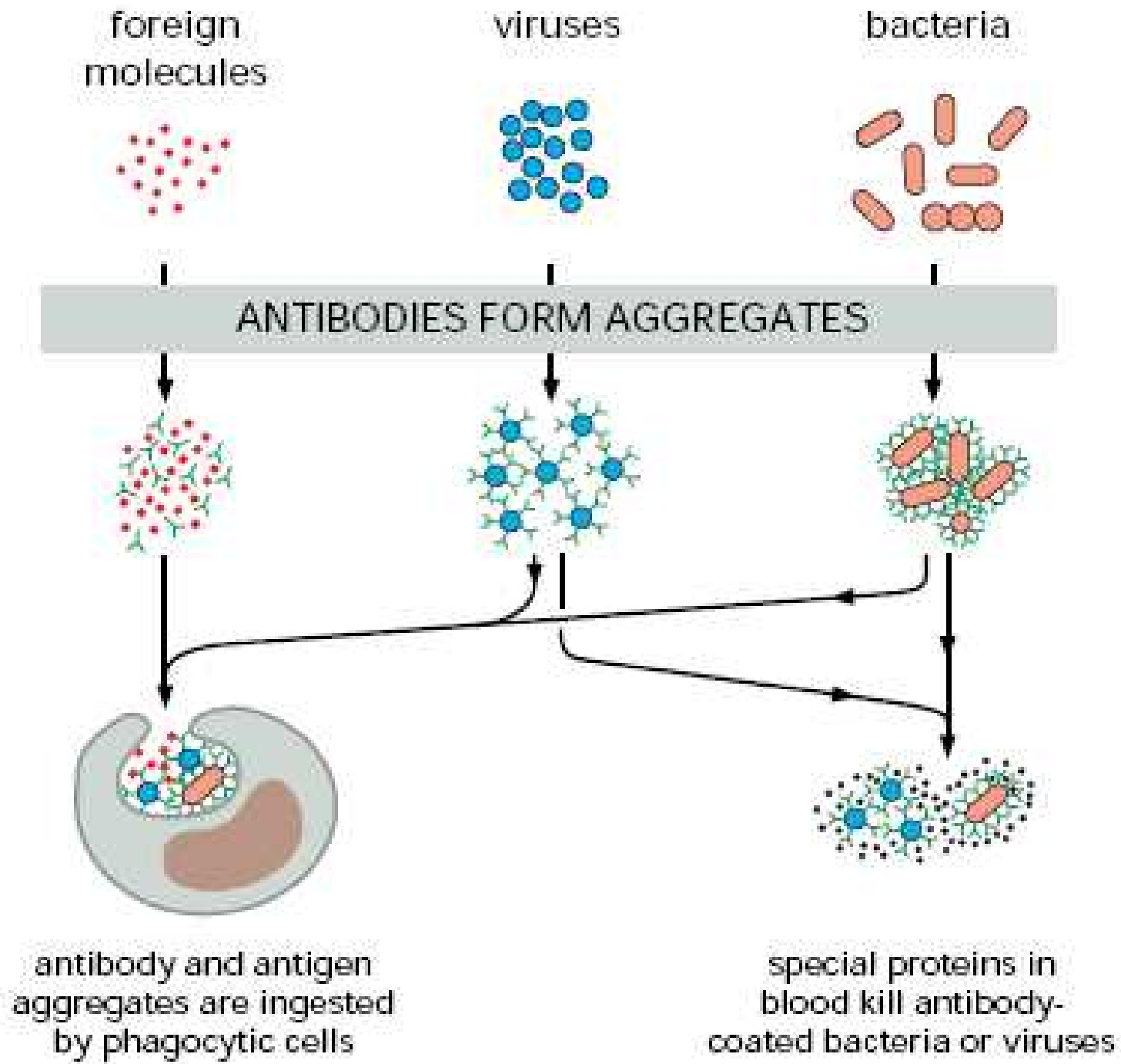


IgA dimer

PROTILÁTKY:

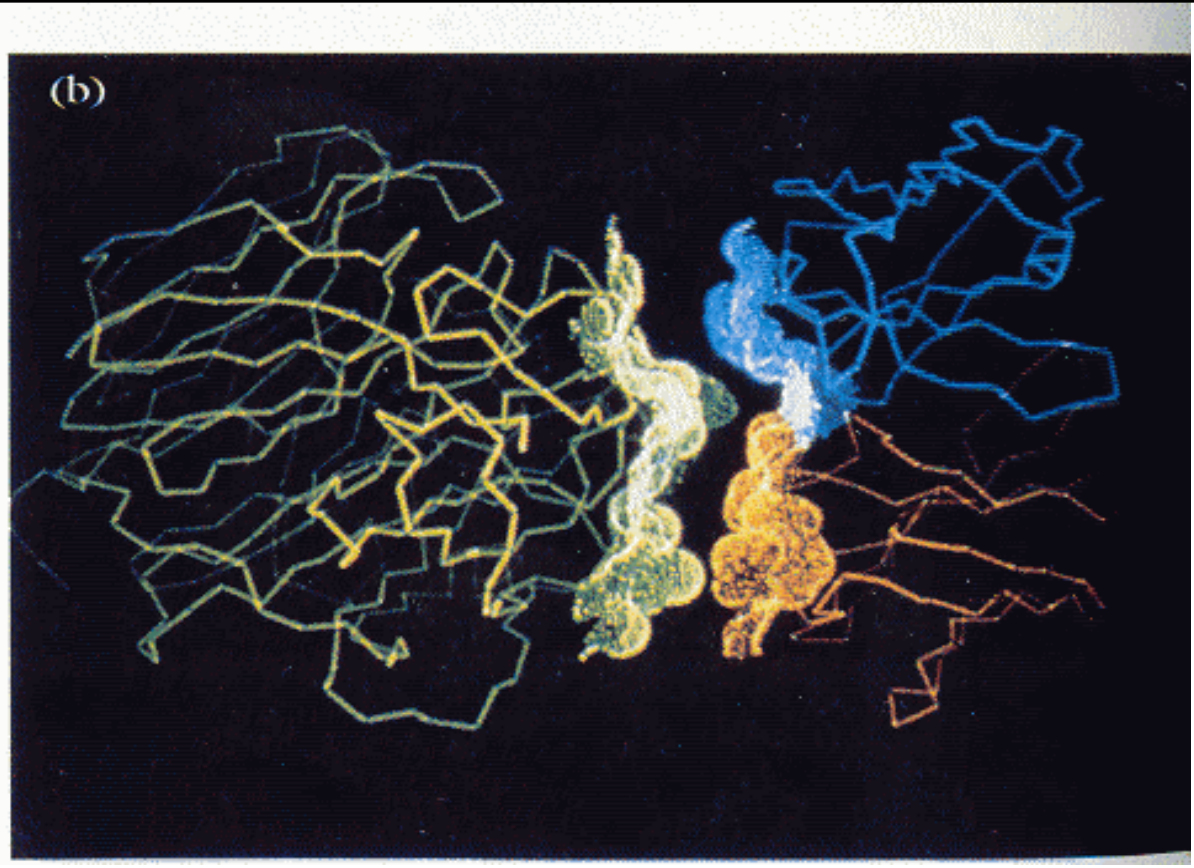
OBALÍ MIKROORGANISMY A ZNEMOŽNÍ JIM NASEDNOUT NA BUŇKY

OBALENÉ MIKROORGANISMY JSOU „CHUTNĚJŠÍ“ PRO FAGOCYTY (POŽÍRAČE MIKROBŮ)


foreign molecules
viruses
bacteria
ANTIBODIES FORM AGGREGATES
antibody and antigen aggregates are ingested by phagocytic cells
special proteins in blood kill antibody-coated bacteria or viruses

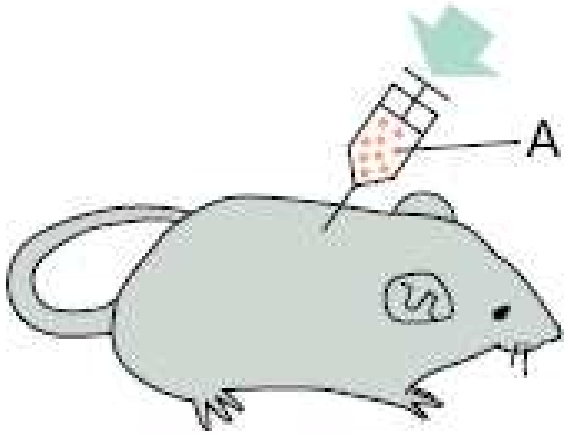
ANTIGENY

Anti = proti (řecky)
gen = od *gegnomai* tvořit

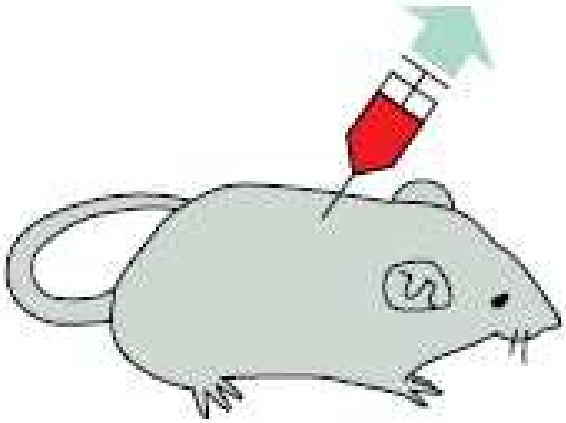


Makromolekulární látky přirozeného nebo umělého původu, které organismus rozpozná jako cizí (nevlastní).
Po vpravení do vhodného (komplementárního) organismu, antigeny stimulují tvorbu protilátek, lymfokinů, regulačních a výkonných T-lymfocytů, čímž se navodí imunitní odpověď.

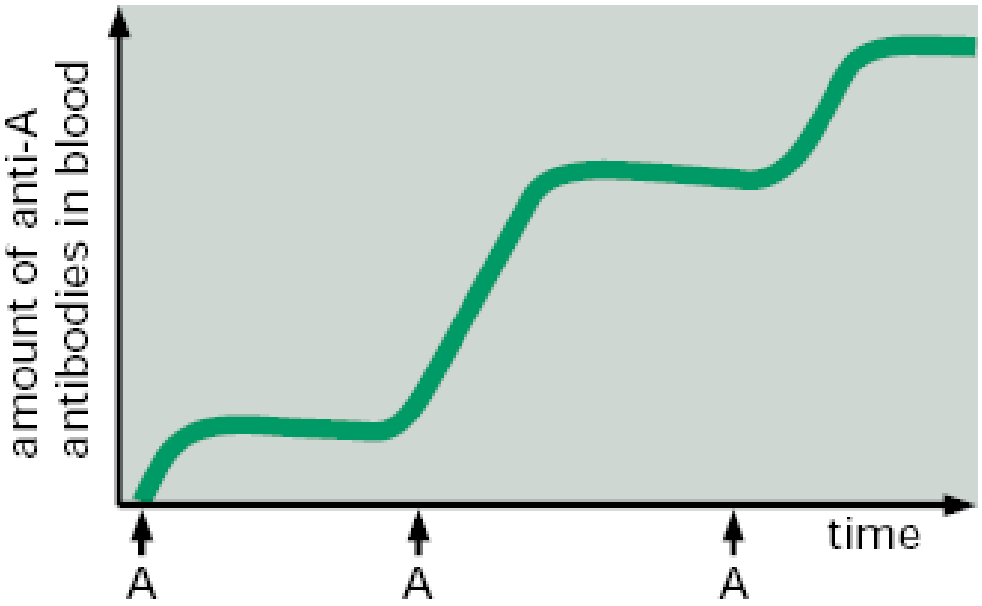
Příprava polyklonálních protilátek



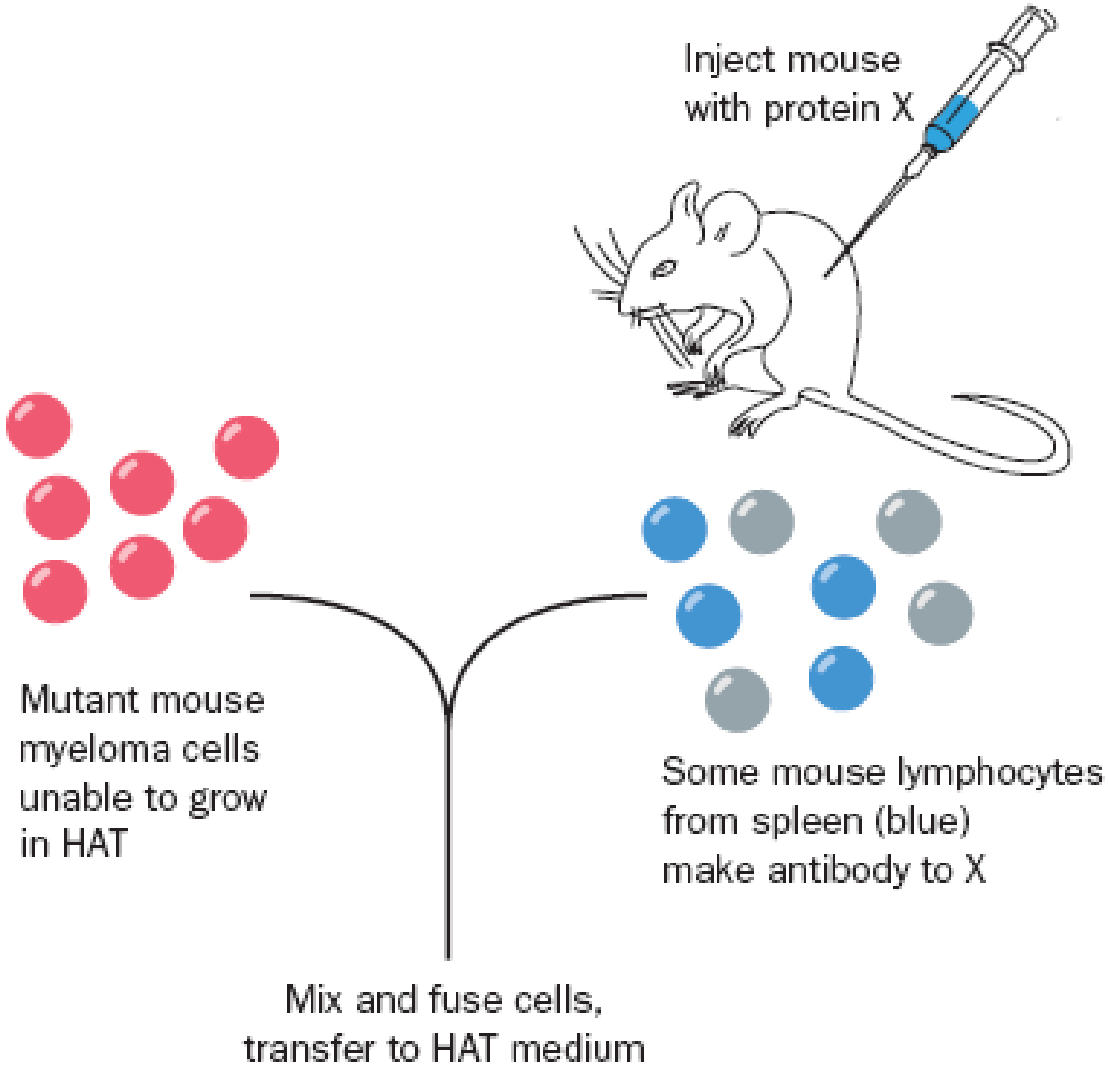
inject antigen A



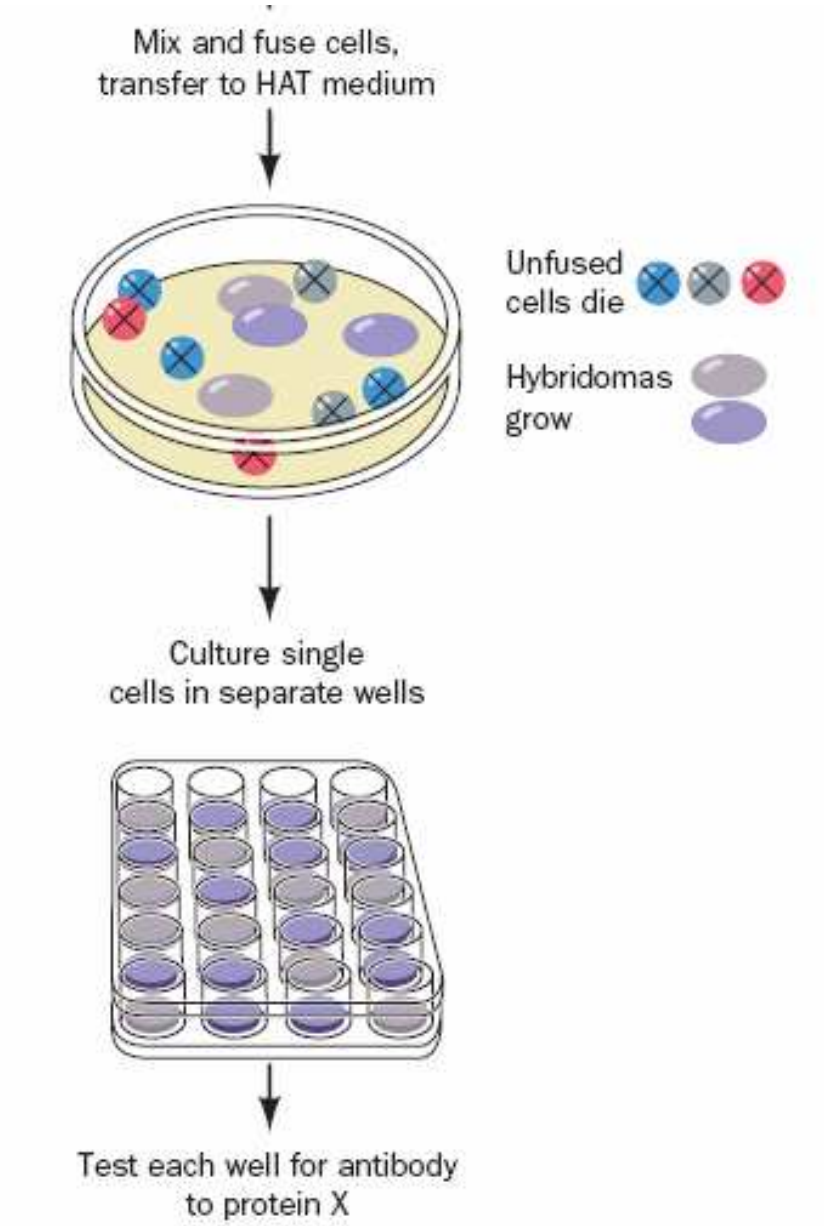
take blood later



Příprava monoklonálních protilátek

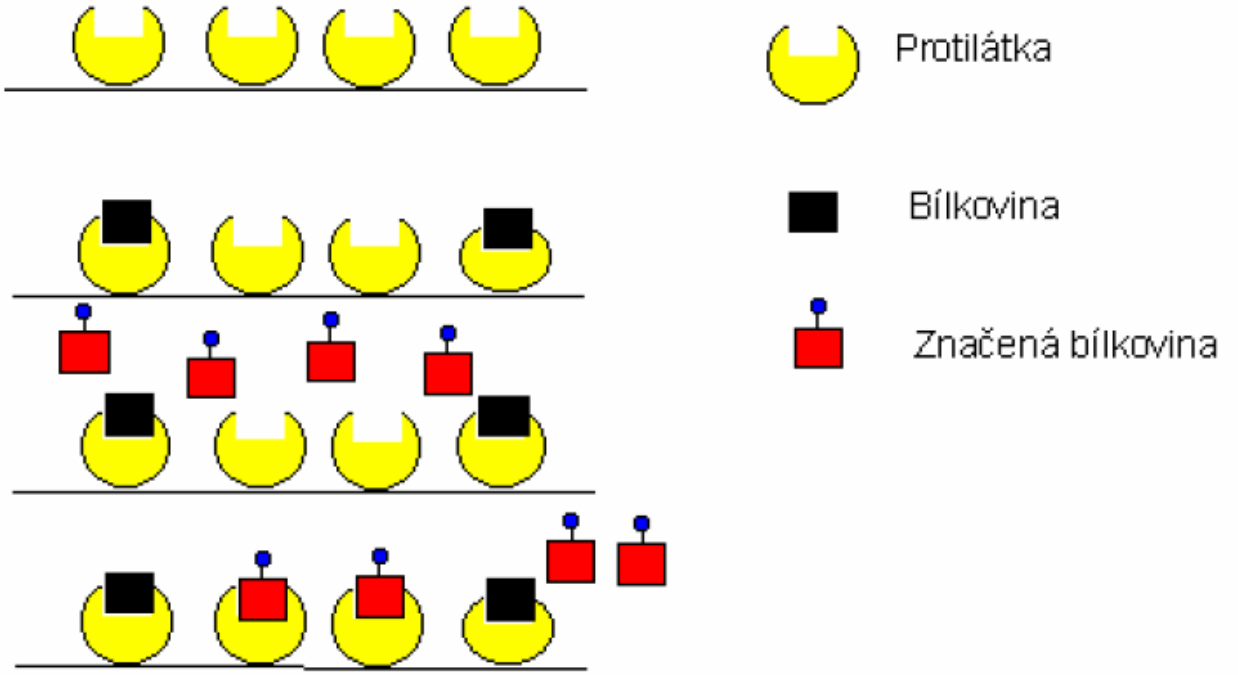


Příprava monoklonálních protilátek



Imunochemické metody

- RIA
  (radioimunoanalýza)



Imunochemické metody

- (ELISA- enzyme linked immunosorbent assay)