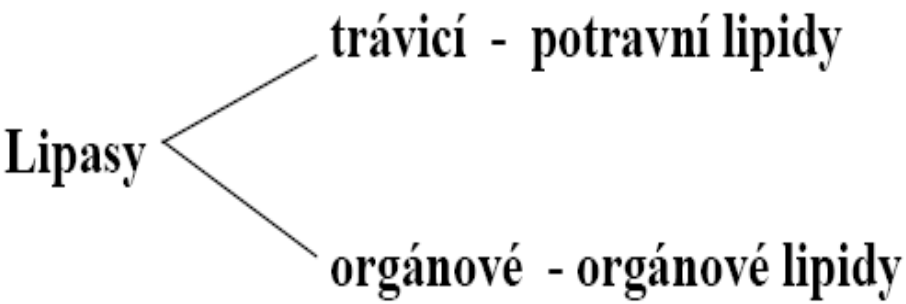
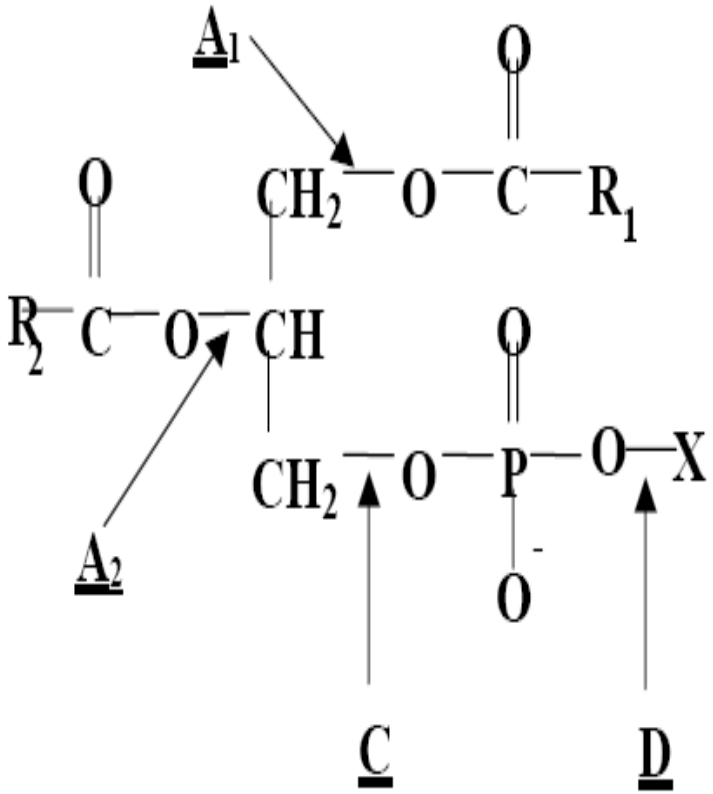
METABOLISMUS LIPIDŮ

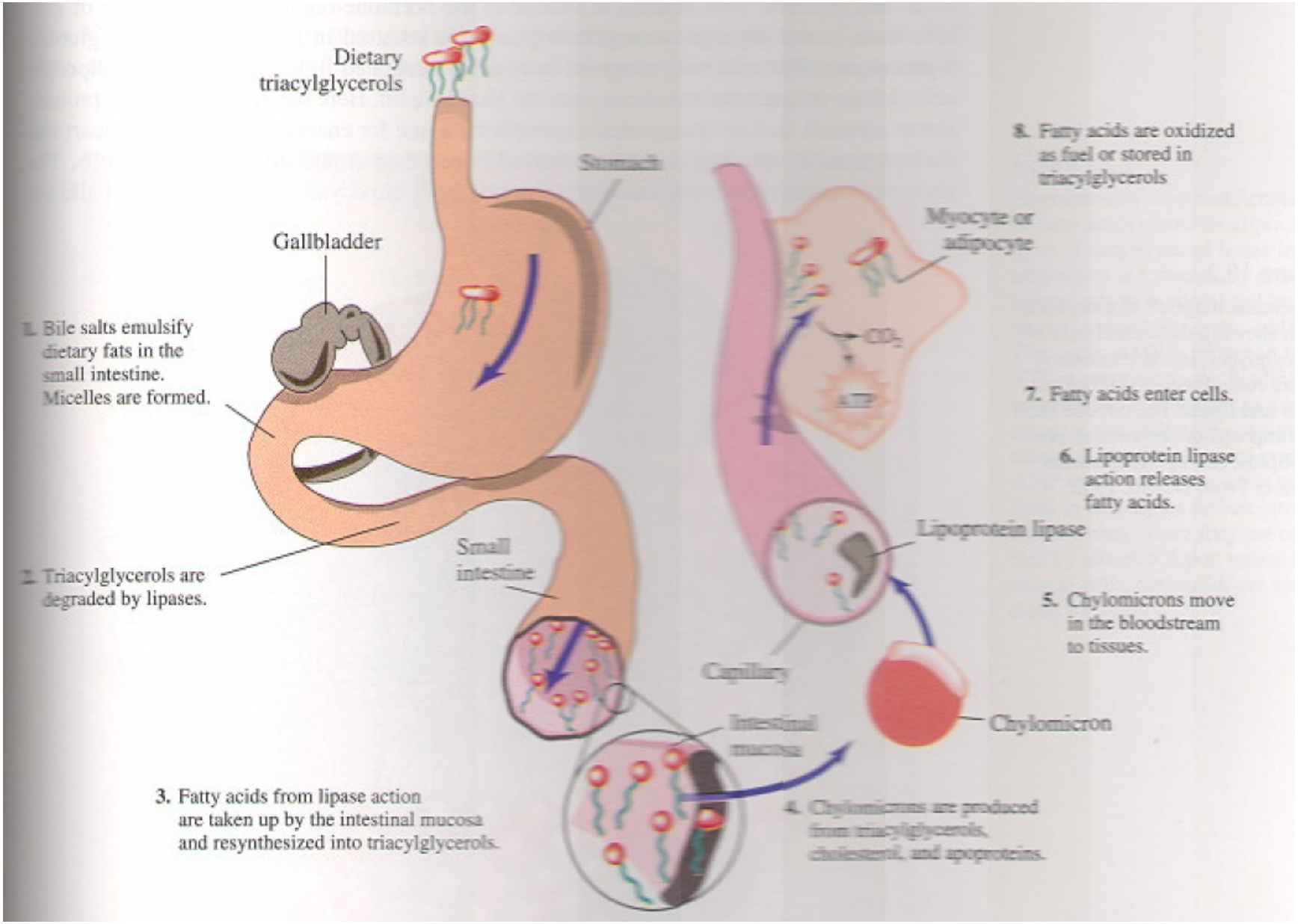
Lipasy - hydrolasy - karboxylesterasy

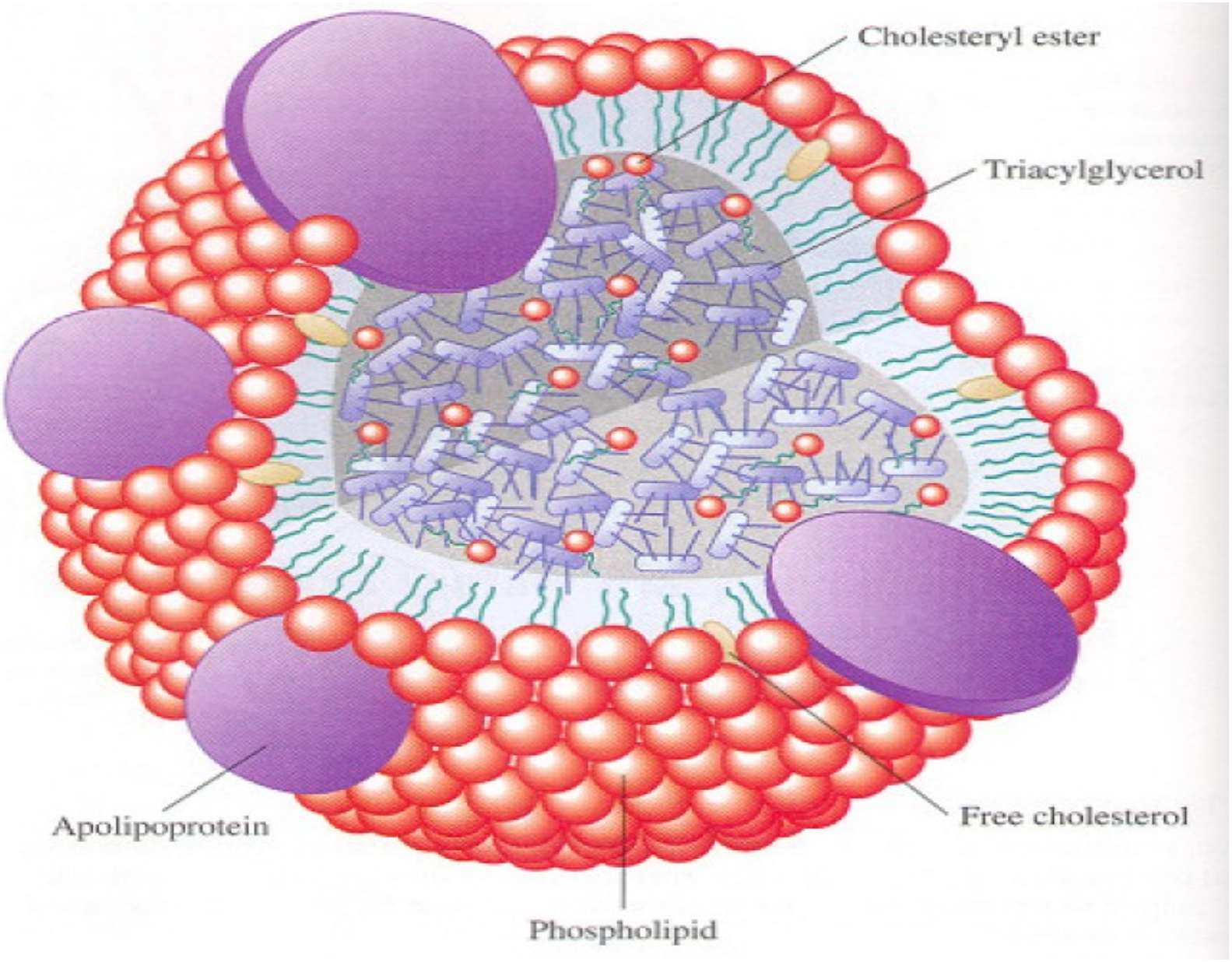
triacylglycerol + H_2O → glycerol + mastné kyseliny

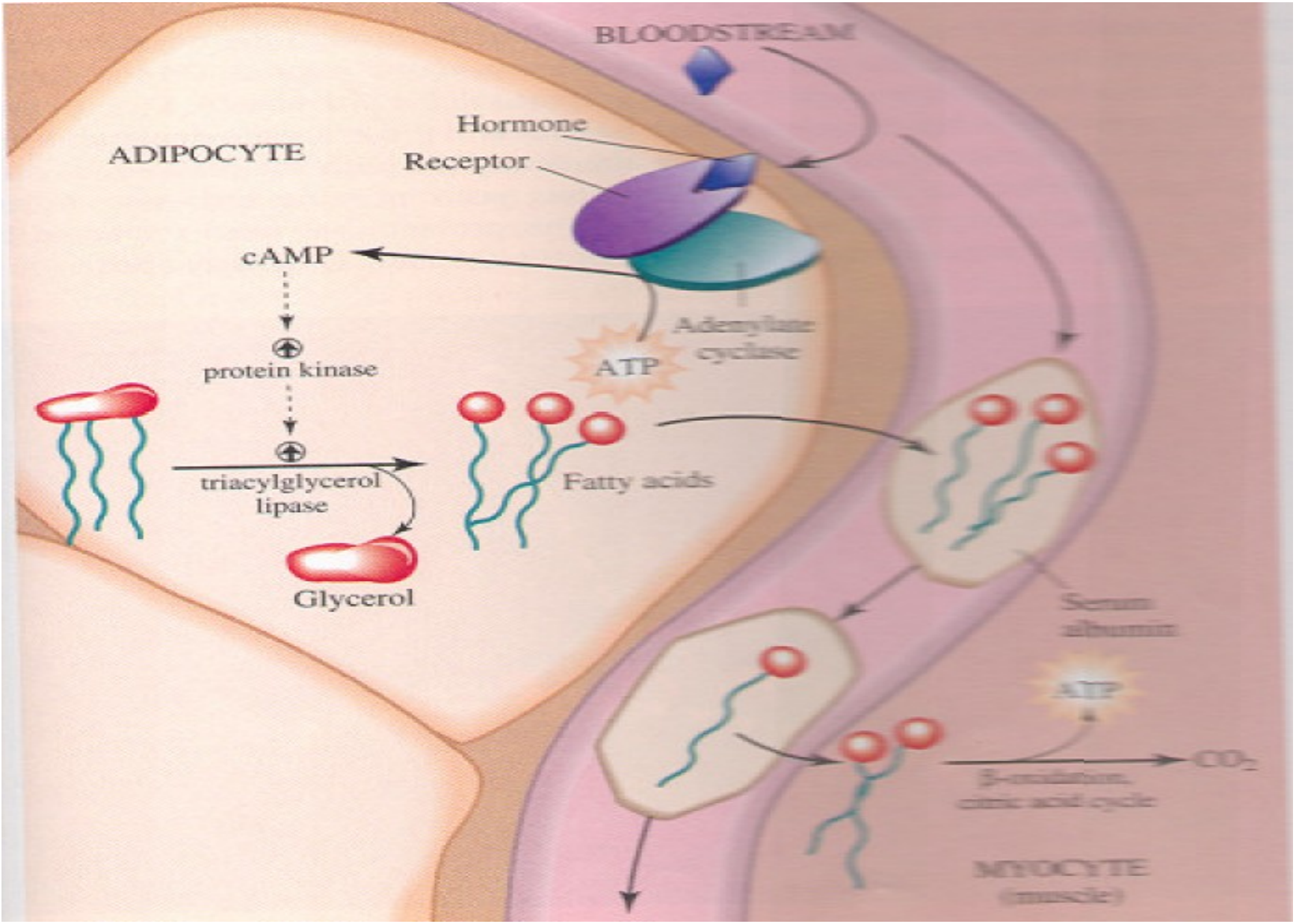


Fosfolipasy




Dietary triacylglycerols
Stomach
Gallbladder
1. Bile salts emulsify dietary fats in the small intestine. Micelles are formed.
2. Triacylglycerols are degraded by lipases.
Small intestine
3. Fatty acids from lipase action are taken up by the intestinal mucosa and resynthesized into triacylglycerols.
Intestinal mucosa
4. Chylomicrons are produced from triacylglycerols, cholesterol, and apoproteins.
Chylomicron
5. Chylomicrons move in the bloodstream to tissues.
Capillary
6. Lipoprotein lipase action releases fatty acids.
Lipoprotein lipase
7. Fatty acids enter cells.
Myocyte or adipocyte
8. Fatty acids are oxidized as fuel or stored in triacylglycerols


Cholesteryl ester
Triacylglycerol
Apolipoprotein
Free cholesterol
Phospholipid

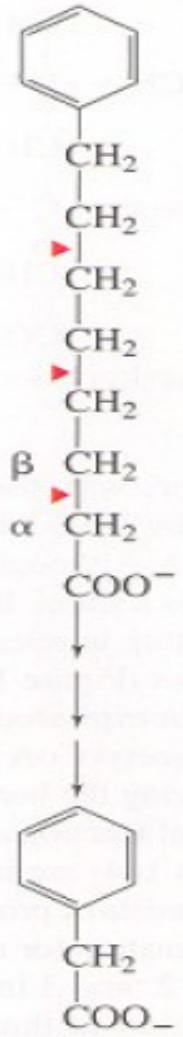

BLOODSTREAM
ADIPOCYTE
Hormone
Receptor
cAMP
Adenylate cyclase
ATP
protein kinase
triacylglycerol lipase
Fatty acids
Glycerol
Serum albumin
ATP
MYOCYTE (muscle)

Odbourávání mastných kyselin

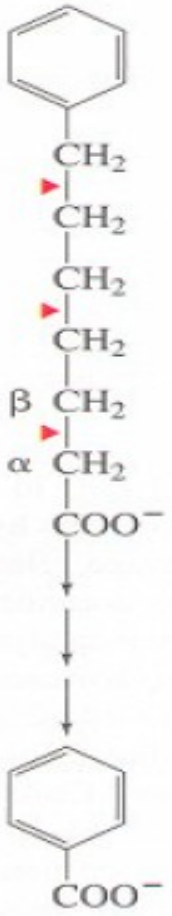
β oxidace

F.KNOOP 1909

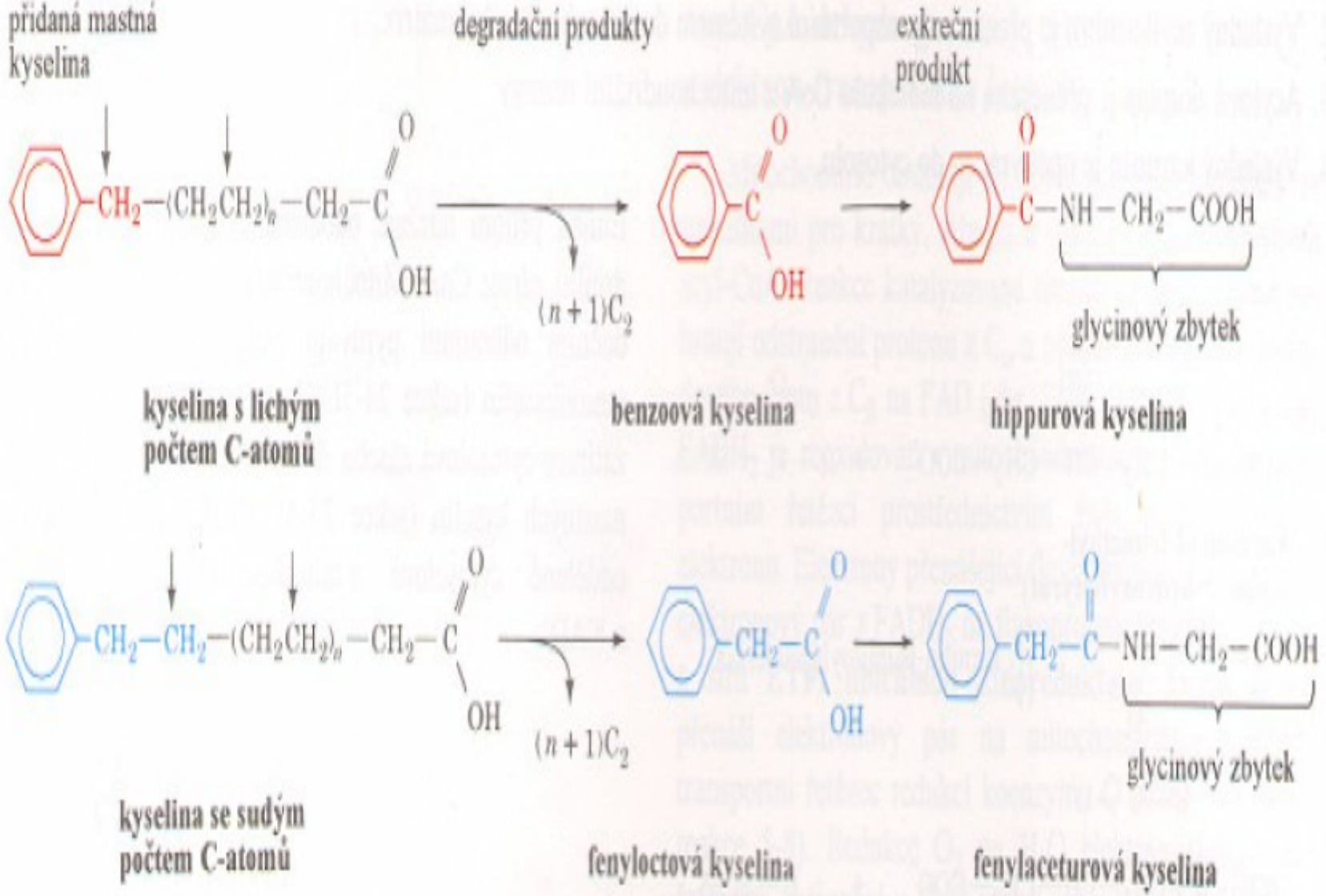
F.LYNEN 1951



Phenylacetate
(from even-numbered carbon chain)



Benzoate
(from odd-numbered carbon chain)


přidaná mastná kyselina
degradační produkty
exkreční produkt
$CH_2-(CH_2CH_2)_n-CH_2-C(=O)-OH$
$(n+1)C_2$
benzoová kyselina
$C(=O)-NH-CH_2-COOH$
glycinový zbytek
kyselina s lichým počtem C-atomů
hippurová kyselina
$CH_2-CH_2-(CH_2CH_2)_n-CH_2-C(=O)-OH$
$(n+1)C_2$
$CH_2-C(=O)-OH$
$CH_2-C(=O)-NH-CH_2-COOH$
glycinový zbytek
kyselina se sudým počtem C-atomů
fenyloctová kyselina
fenylaceturová kyselina

Odbourávání mastných kyselin

β oxidace

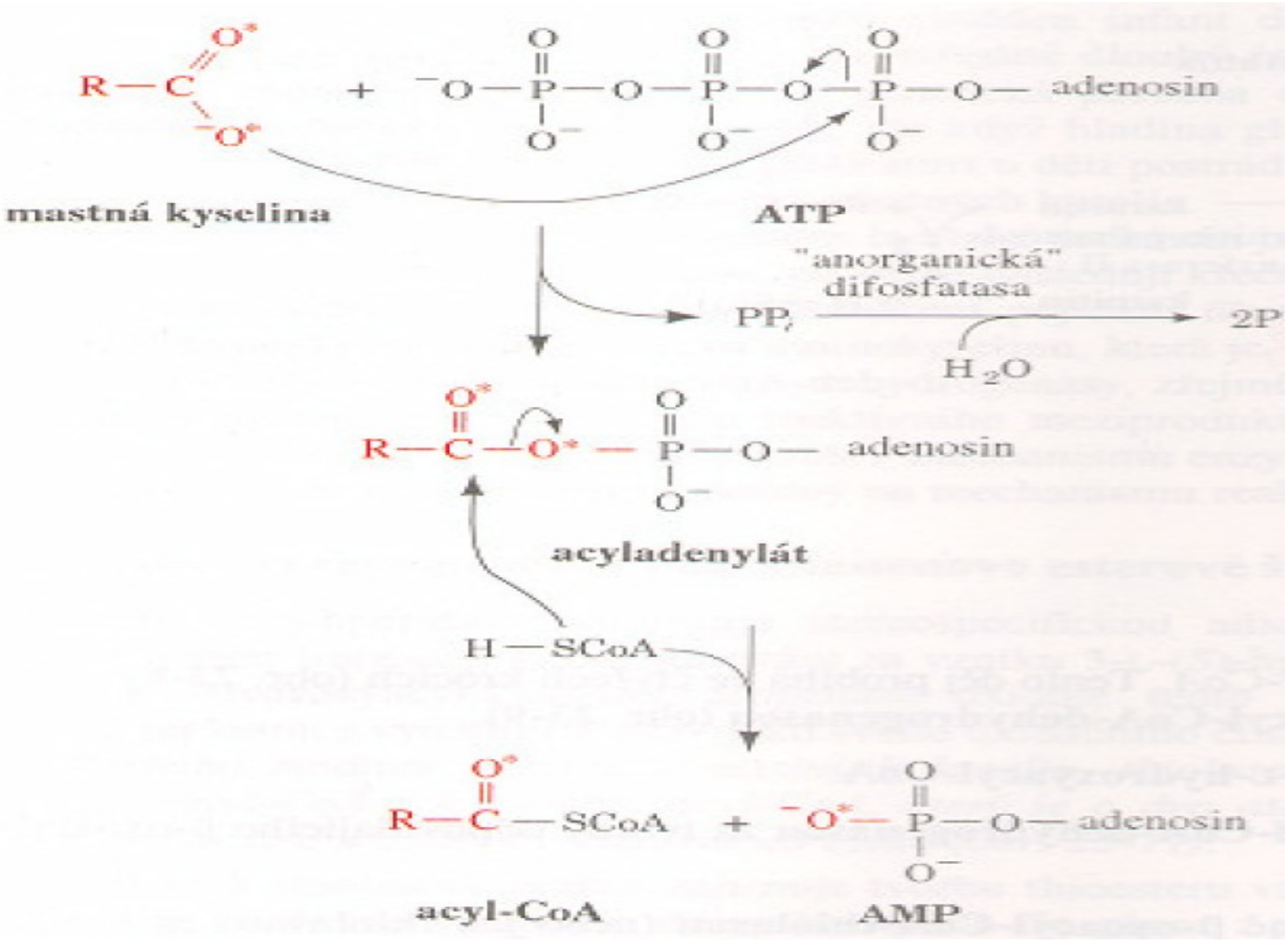
F.KNOOP 1909

F.LYNEN 1951

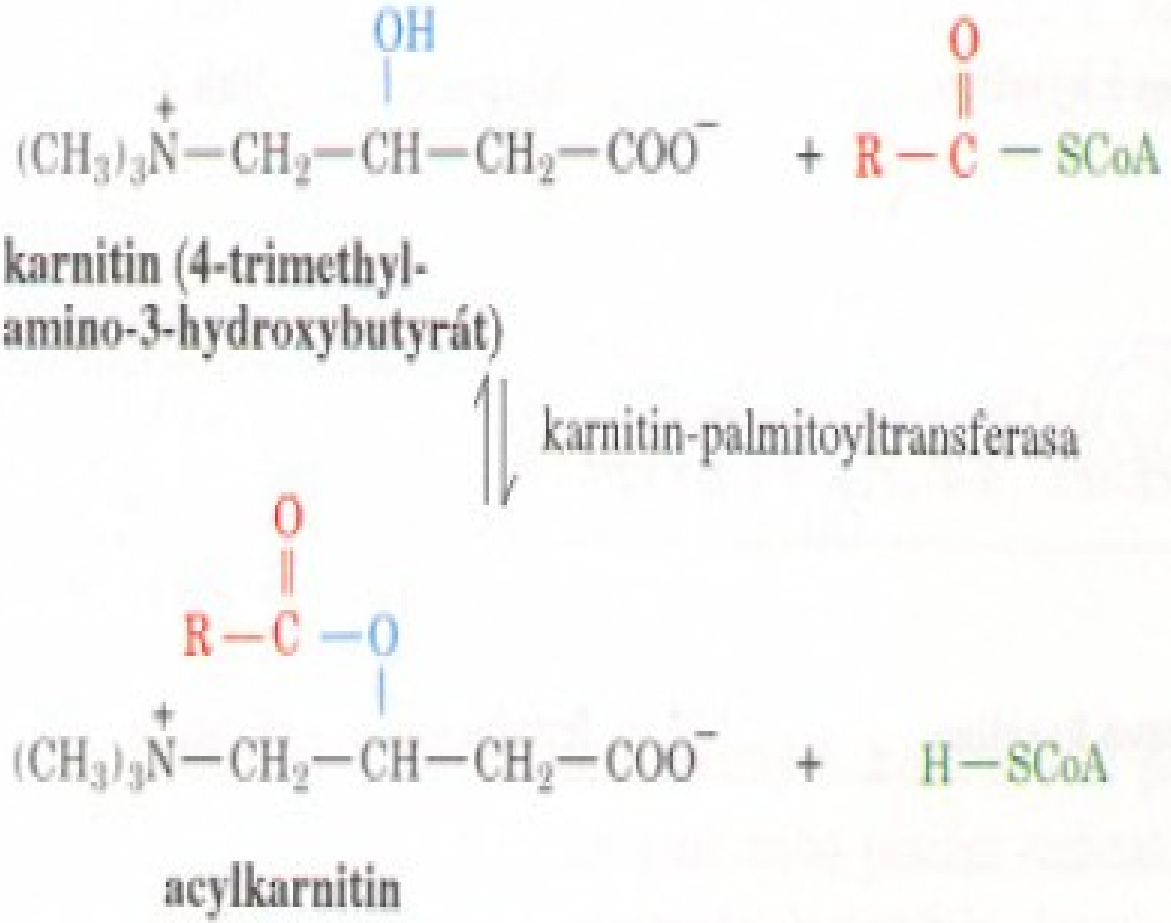
A. Aktivace mastných kyselin

$$RCOO^- + ATP \rightarrow RCOO\text{-}AMP + P\sim P$$

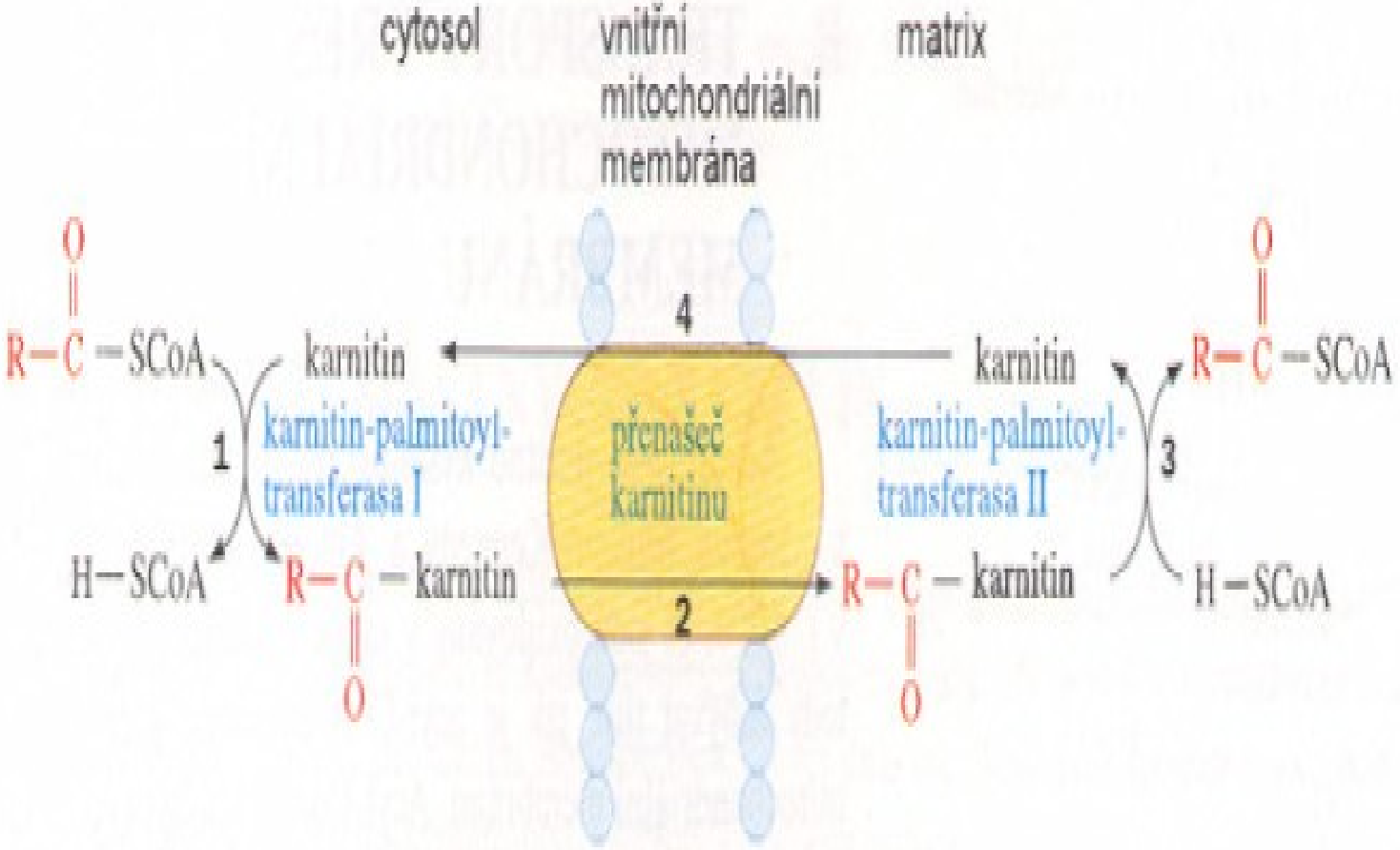
$$RCOO\text{-}AMP + HSCoA \rightarrow RCOSCoA + AMP$$


mastná kyselina
ATP
adenosin
"anorganická"
difosfatasa
PPi
2P
H2O
acyladenylát
H—SCoA
R—C—SCoA
acyl-CoA
AMP

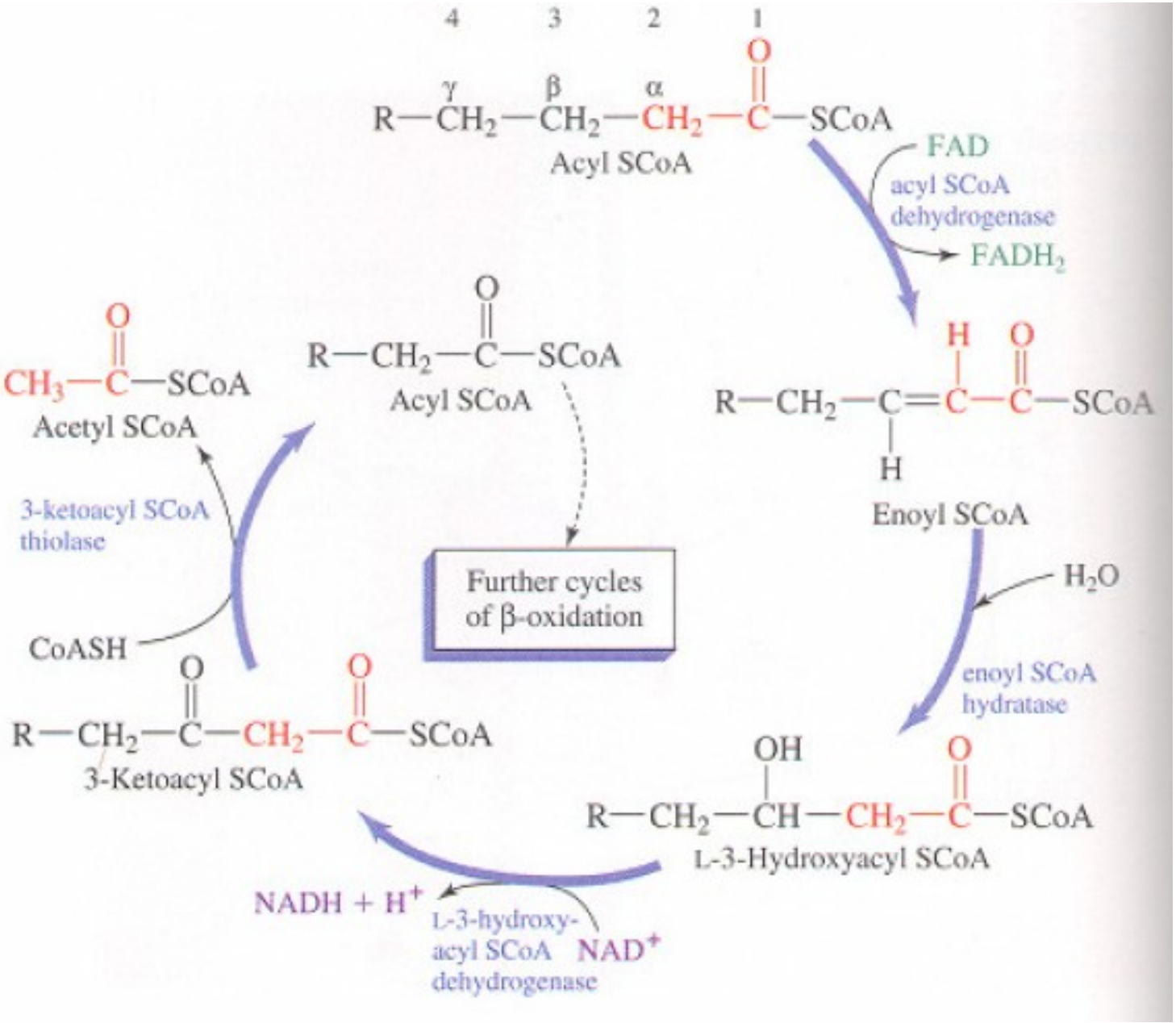
B. Transport RCOSCoA - karnitinový člunek

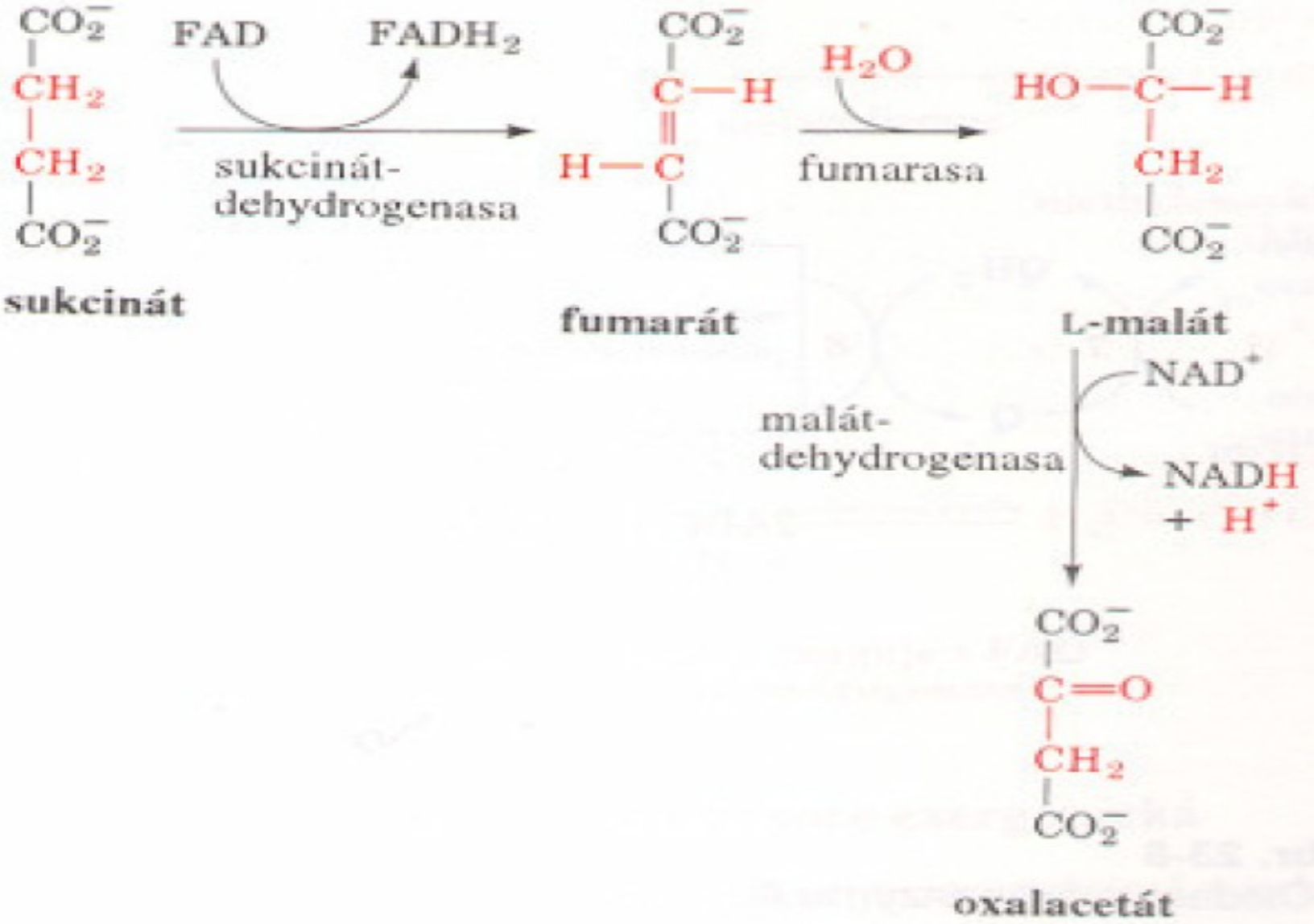


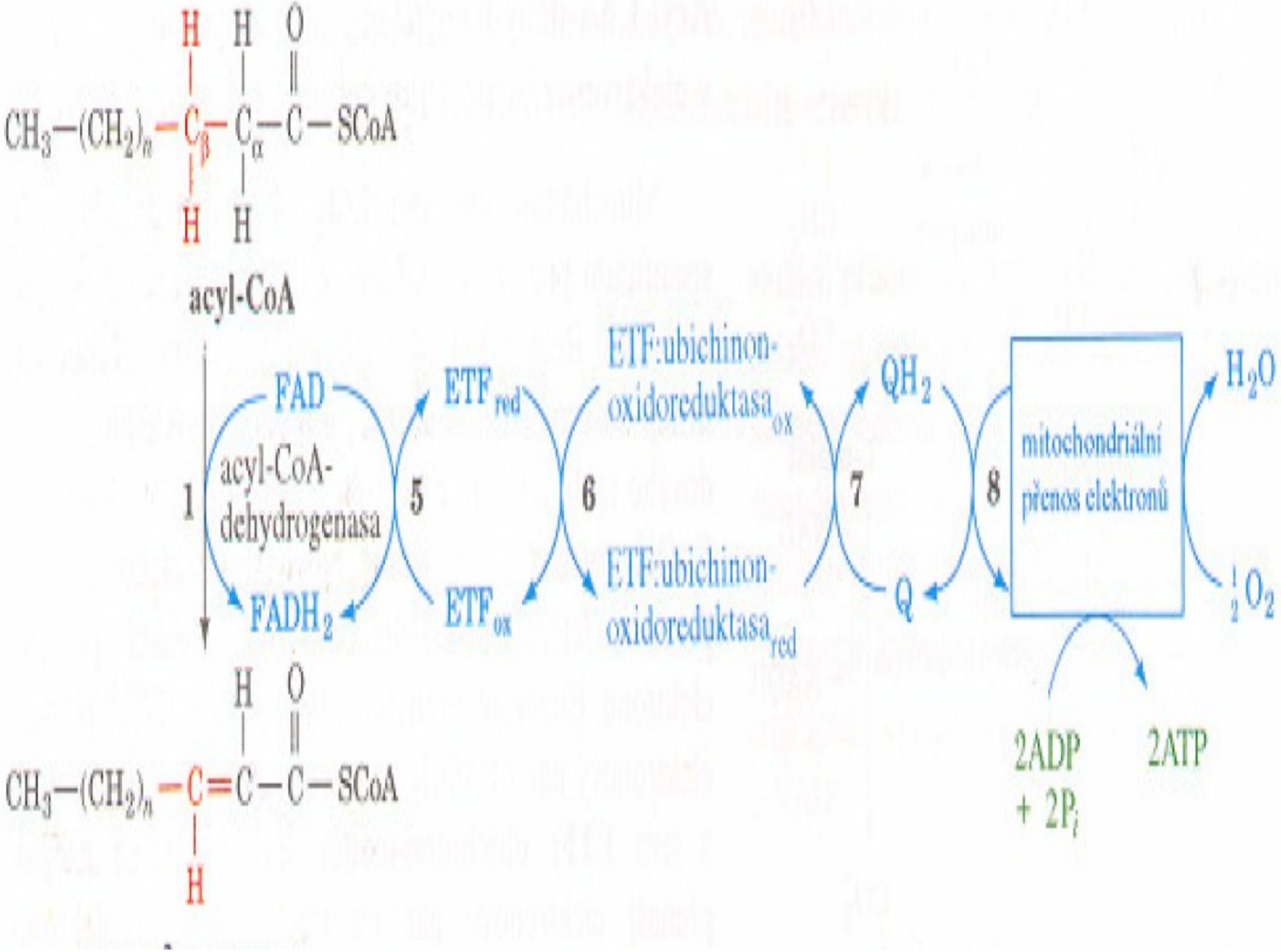
B. Transport RCOSCoA - karnitinový člunek



C. β oxidace


4 3 2 1
γ β α
R—CH2—CH2—CH2—C—SCoA
Acyl SCoA
FAD
acyl SCoA dehydrogenase
FADH2
H O
R—CH2—C=C—C—SCoA
H
Enoyl SCoA
H2O
enoyl SCoA hydratase
OH O
R—CH2—CH—CH2—C—SCoA
L-3-Hydroxyacyl SCoA
NADH + H+
L-3-hydroxy-acyl SCoA dehydrogenase
NAD+
O O
R—CH2—C—CH2—C—SCoA
3-Ketoacyl SCoA
CoASH
3-ketoacyl SCoA thiolase
CH3—C—SCoA
Acetyl SCoA
R—CH2—C—SCoA
Acyl SCoA
Further cycles of β-oxidation

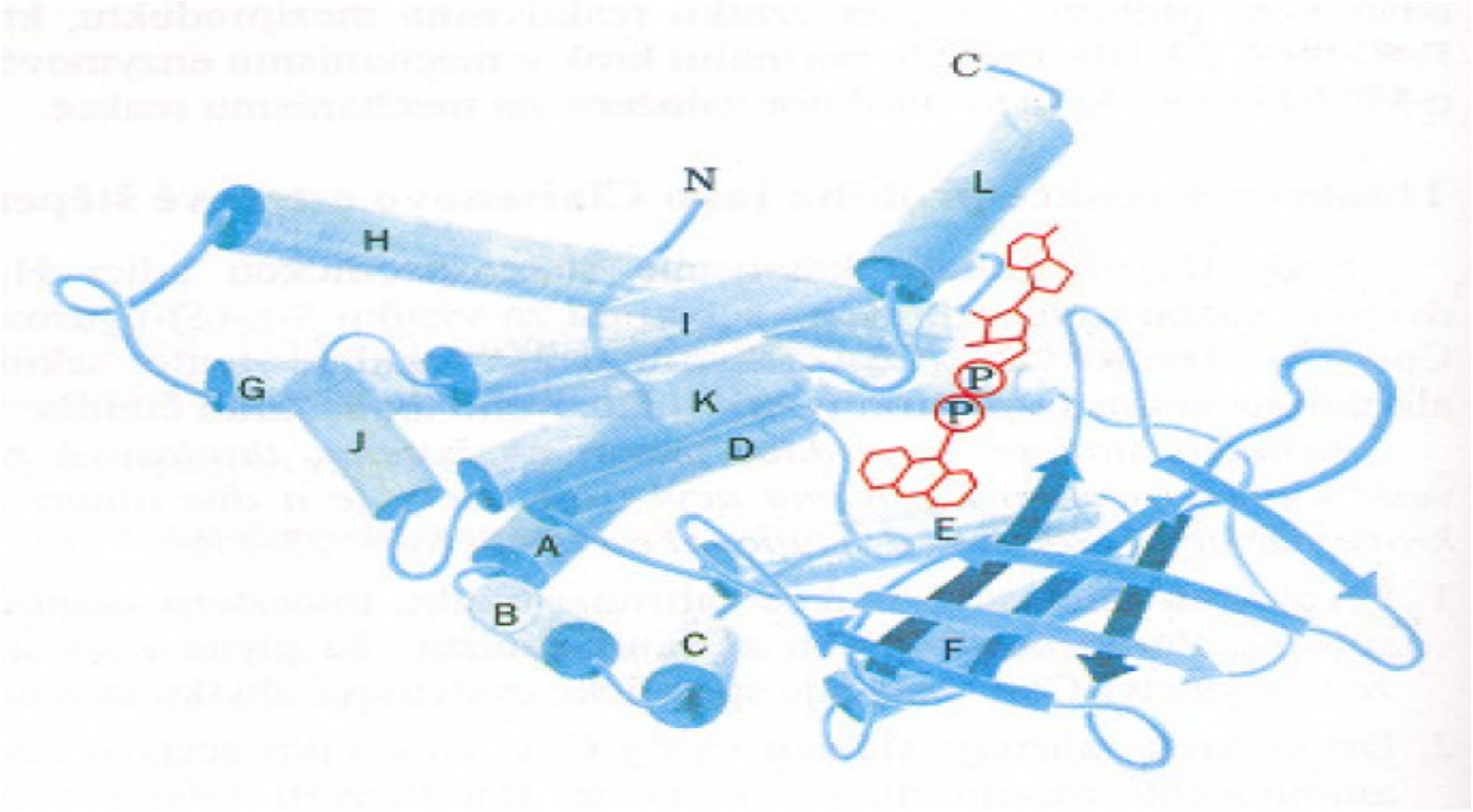

FAD
FADH2
sukcinát-dehydrogenasa
H2O
fumarasa
malát-dehydrogenasa
NAD+
NADH + H+
sukcinát
fumarát
L-malát
oxalacetát

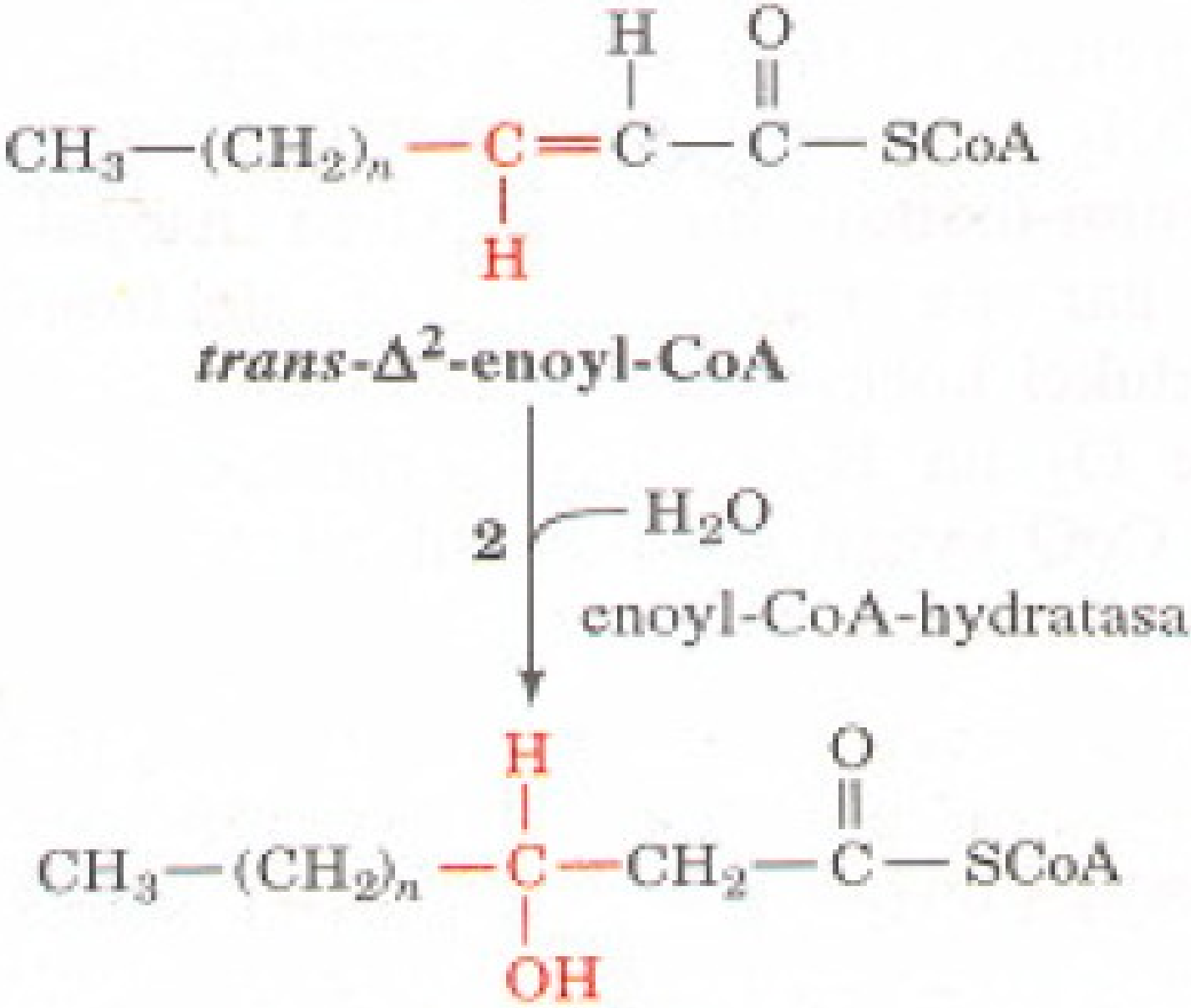

acyl-CoA
1
acyl-CoA-dehydrogenasa
FAD
FADH2
5
ETFred
ETFox
6
ETF:ubichinon-oxidoreduktasaox
ETF:ubichinon-oxidoreduktasared
7
QH2
Q
8
mitochondriální přenos elektronů
H2O
½ O2
2ADP + 2Pi
2ATP

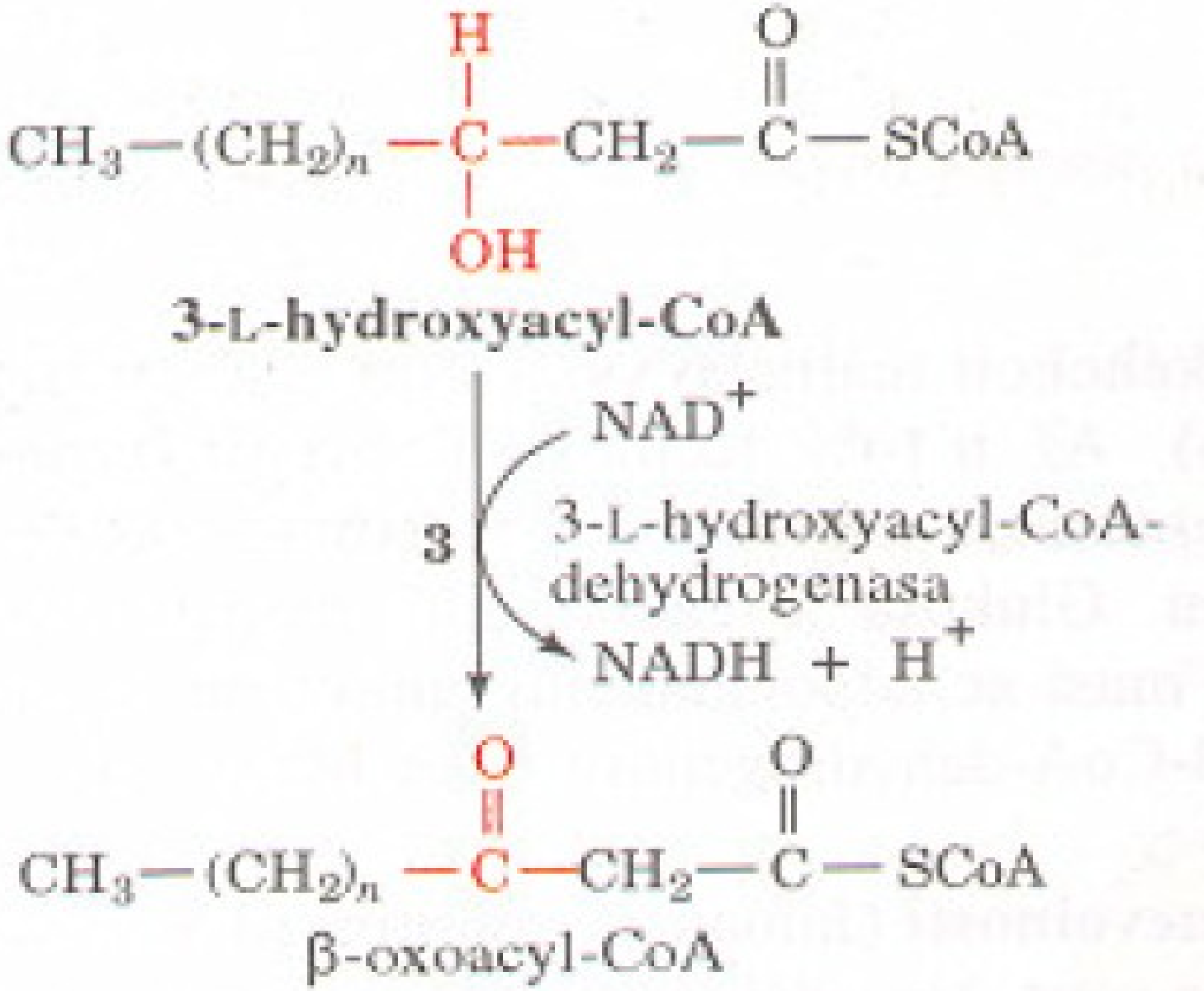
Acyl-CoA DH

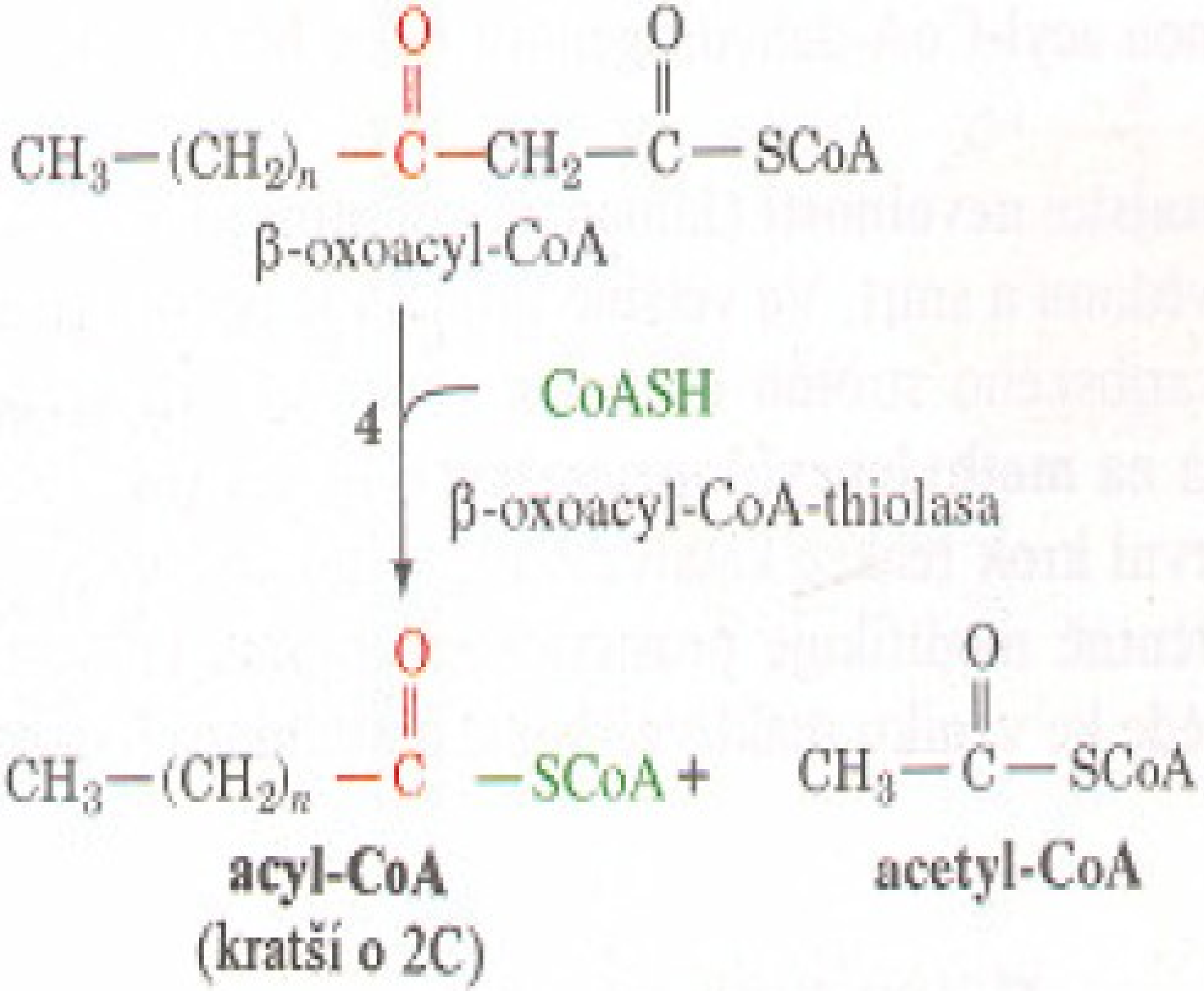
nedostatek

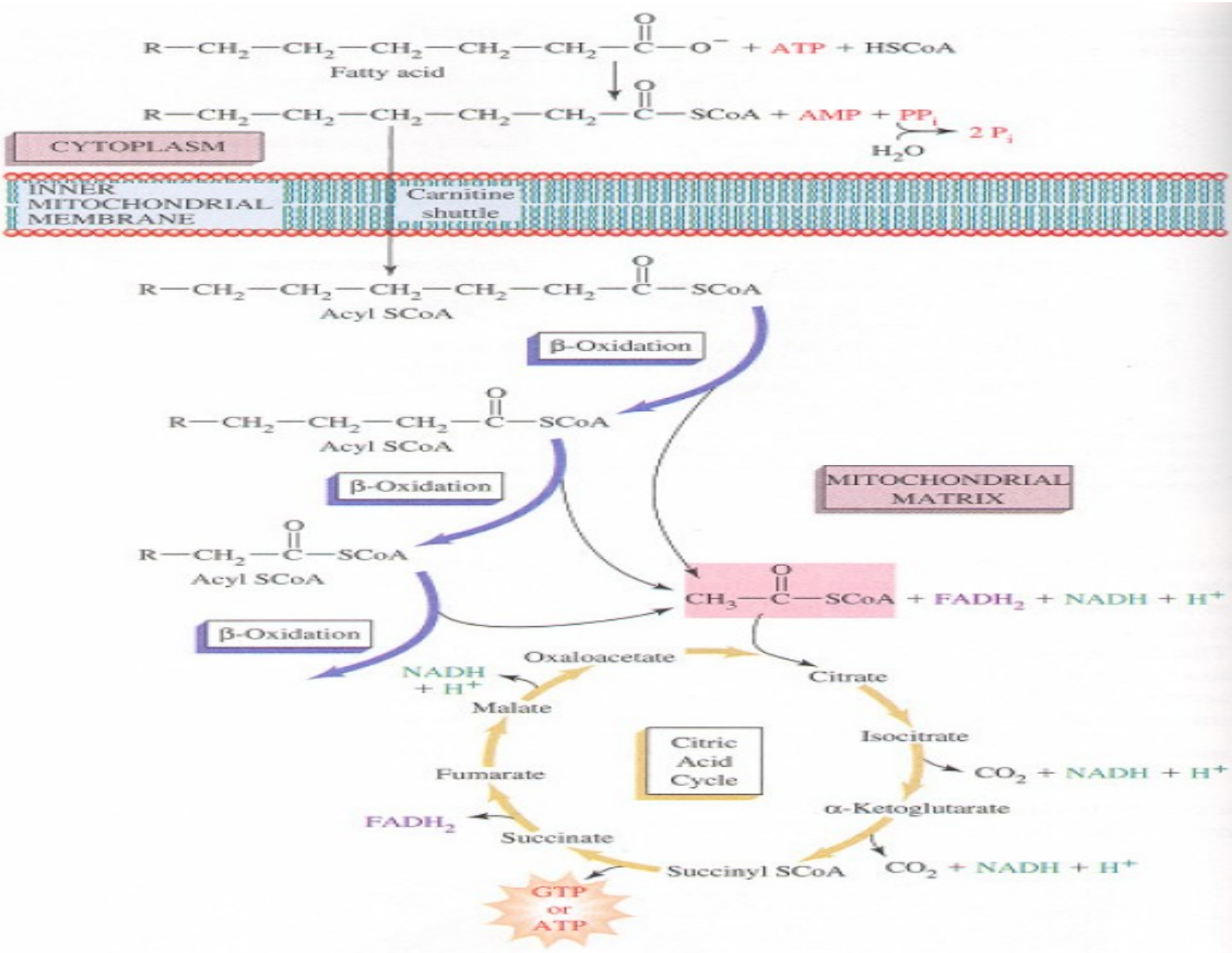
syndrom náhlého dětského úmrtí (sudden infant death syndrome, SIDS)




CH3—(CH2)n—C(H)=C(H)—C(=O)—SCoA
trans-Δ2-enoyl-CoA
2 H2O
enoyl-CoA-hydratasa
CH3—(CH2)n—C(H)(OH)—CH2—C(=O)—SCoA


H
O
CH3—(CH2)n—C—CH2—C—SCoA
OH
3-L-hydroxyacyl-CoA
NAD+
3
3-L-hydroxyacyl-CoA-
dehydrogenasa
NADH + H+
O
O
CH3—(CH2)n—C—CH2—C—SCoA
β-oxoacyl-CoA


CH3—(CH2)n—C—CH2—C—SCoA
β-oxoacyl-CoA
4
CoASH
β-oxoacyl-CoA-thiolasa
CH3—(CH2)n—C—SCoA +
CH3—C—SCoA
acyl-CoA
(kratší o 2C)
acetyl-CoA


R—CH2—CH2—CH2—CH2—CH2—C(=O)—O⁻ + ATP + HSCoA
Fatty acid
R—CH2—CH2—CH2—CH2—CH2—C(=O)—SCoA + AMP + PPi
2 Pi
H2O
CYTOPLASM
INNER MITOCHONDRIAL MEMBRANE
Carnitine shuttle
R—CH2—CH2—CH2—CH2—CH2—C(=O)—SCoA
Acyl SCoA
β-Oxidation
R—CH2—CH2—CH2—C(=O)—SCoA
Acyl SCoA
β-Oxidation
MITOCHONDRIAL MATRIX
R—CH2—C(=O)—SCoA
Acyl SCoA
β-Oxidation
CH3—C(=O)—SCoA + FADH2 + NADH + H+
Oxaloacetate
NADH + H+
Malate
Citrate
Isocitrate
Citric Acid Cycle
CO2 + NADH + H+
Fumarate
α-Ketoglutarate
FADH2
Succinate
Succinyl SCoA
CO2 + NADH + H+
GTP or ATP

Bilance β oxidace :

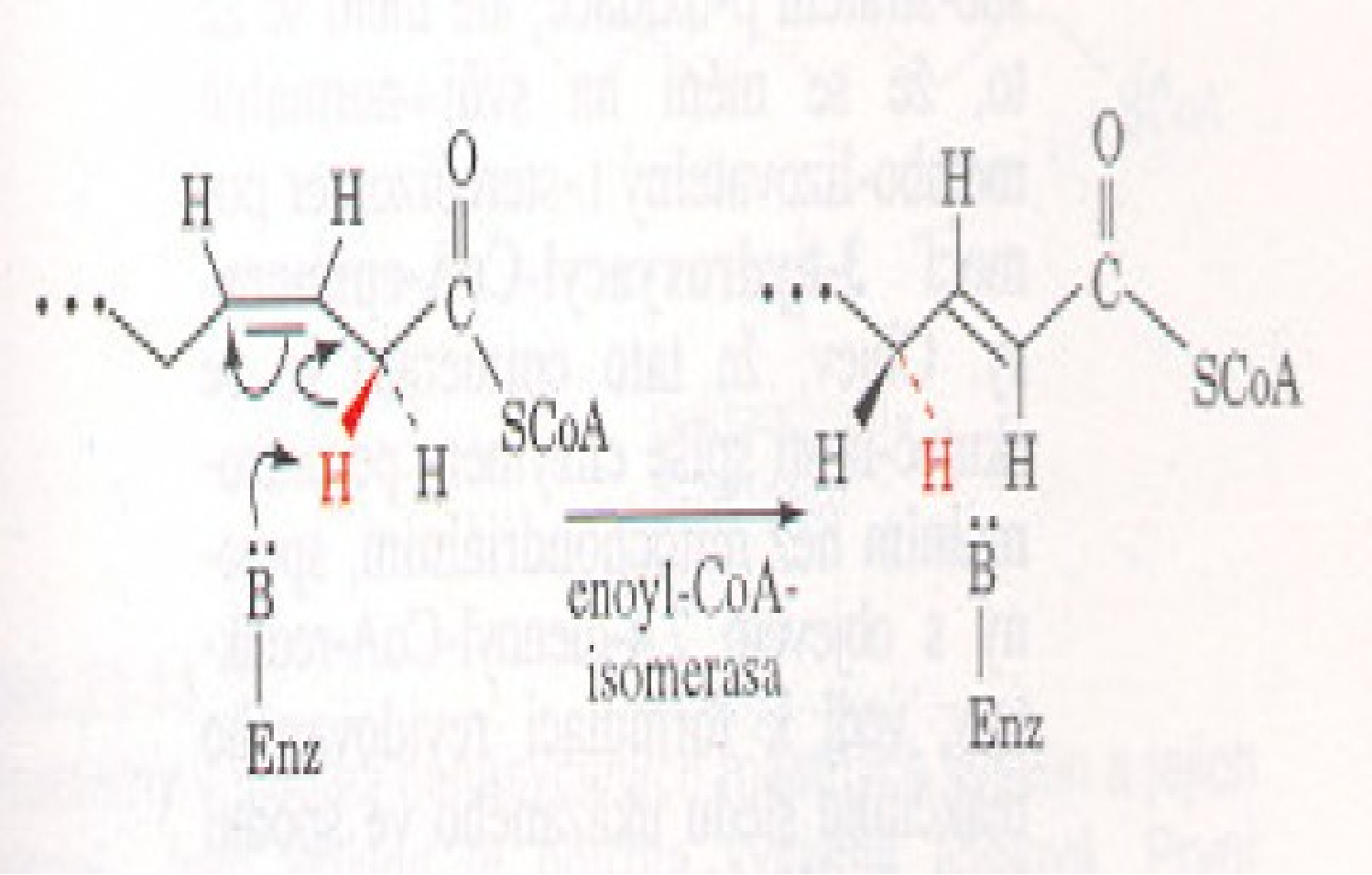
1. cyklus - 1 $FADH_2$ (2 ATP) + 1 NADH (3 ATP) - 5 ATP

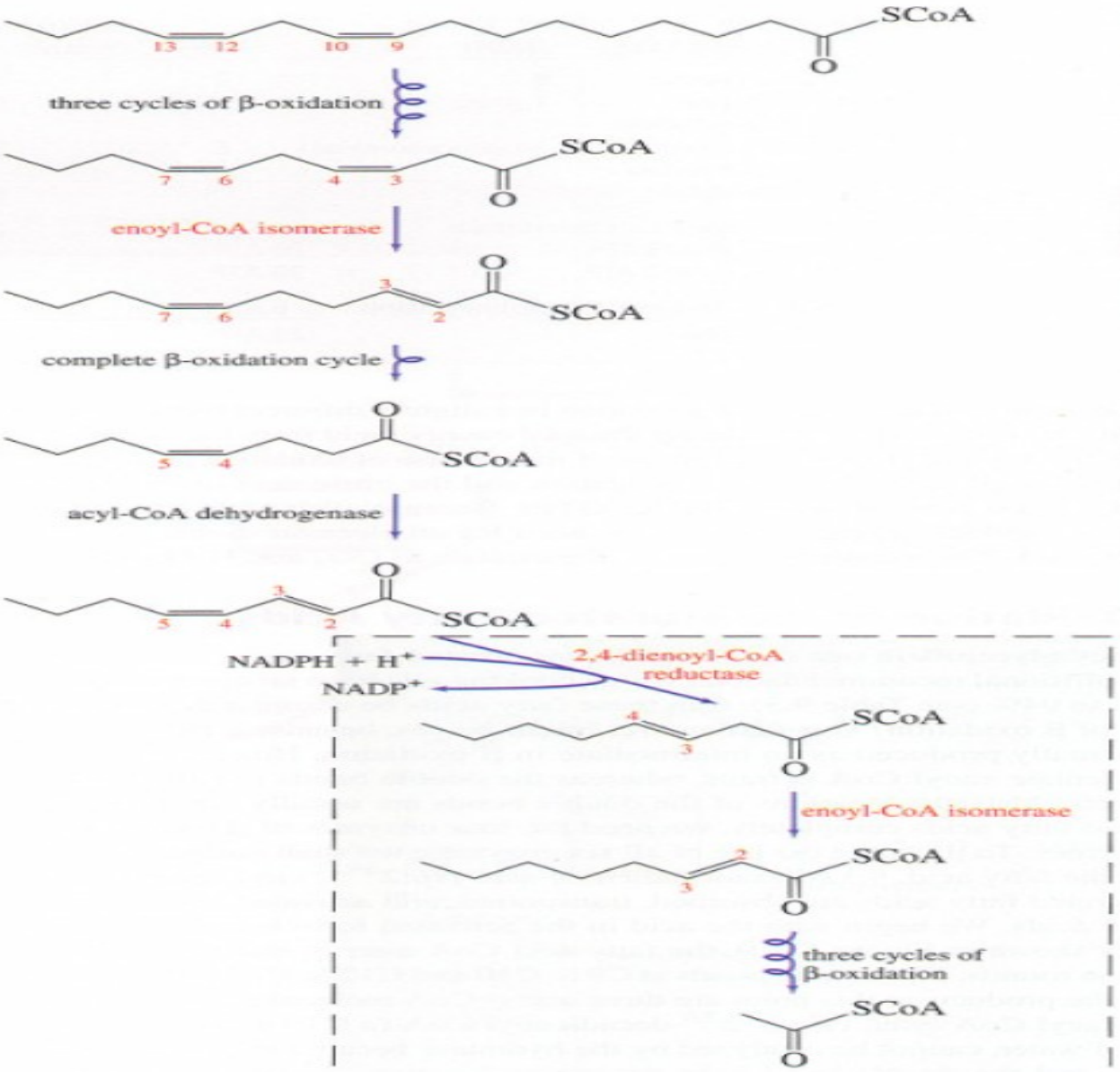
acetylCoA (citrátový cyklus) - 12 ATP

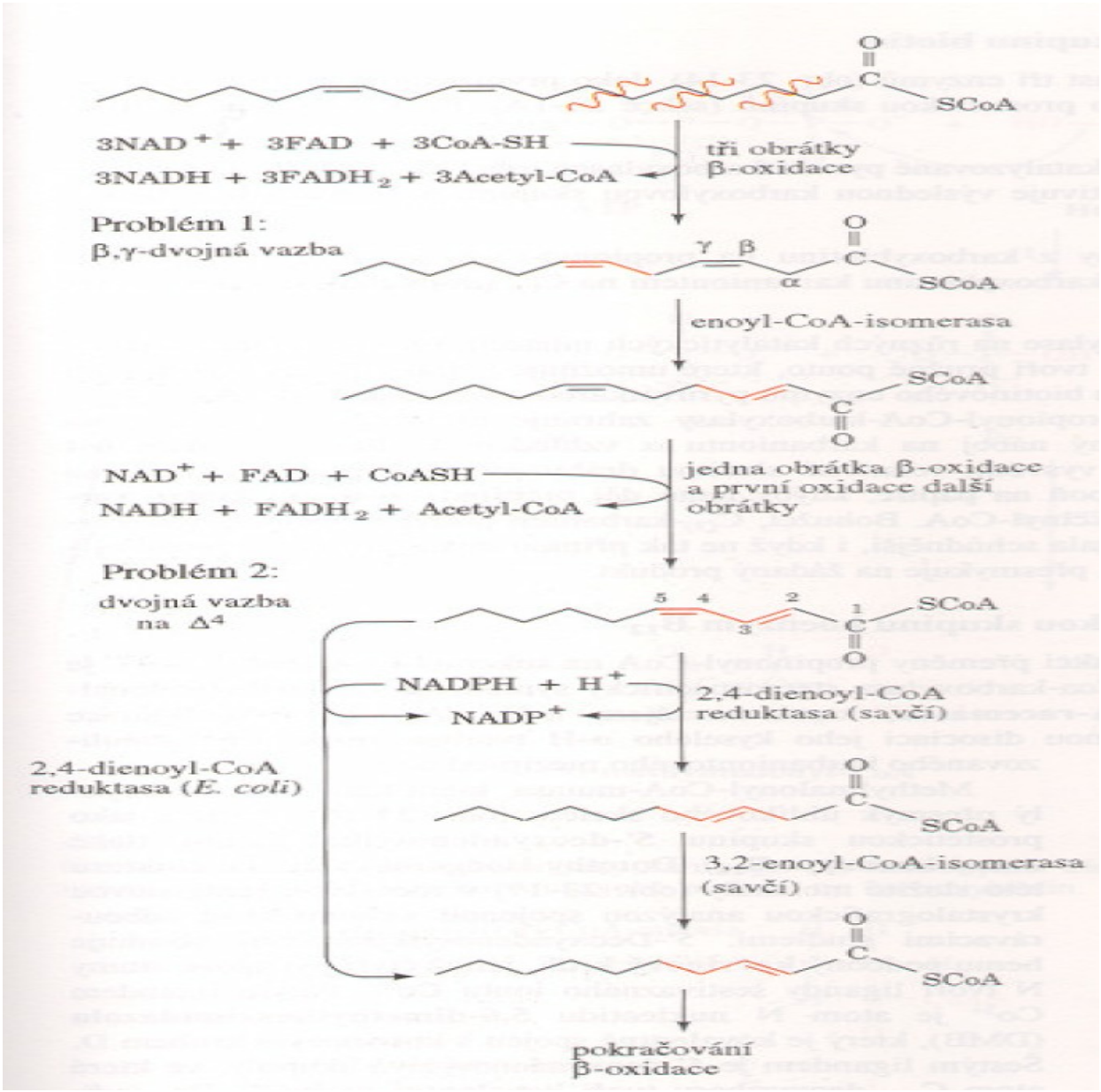
na C_{16} - 7 x β oxidace + 8 x citrátový cyklus - aktivace

(7 x 5) + (8 x 12) - 2 ATP = 129 ATP

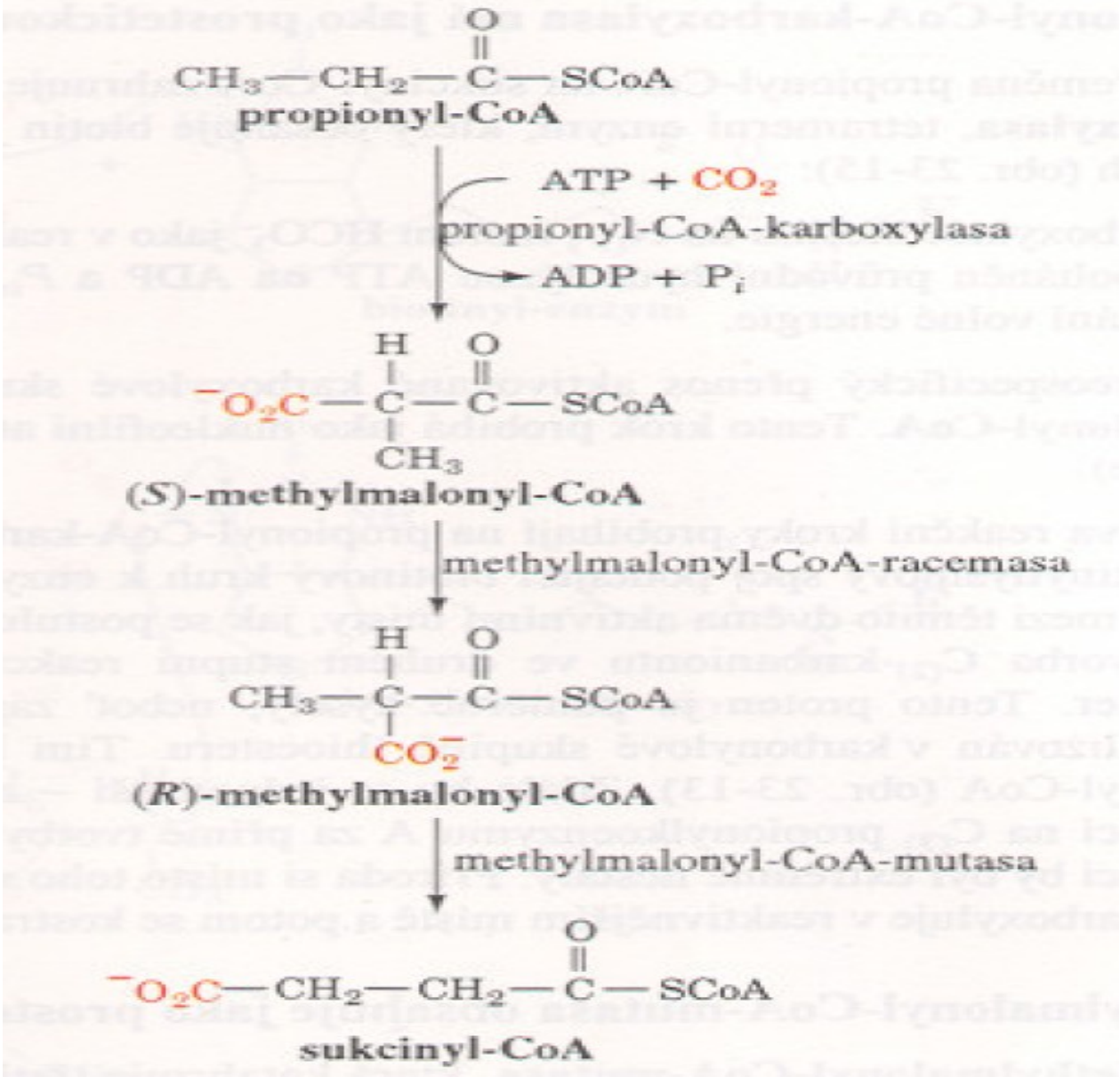
Odbourávání nenasycených mastných kyselin



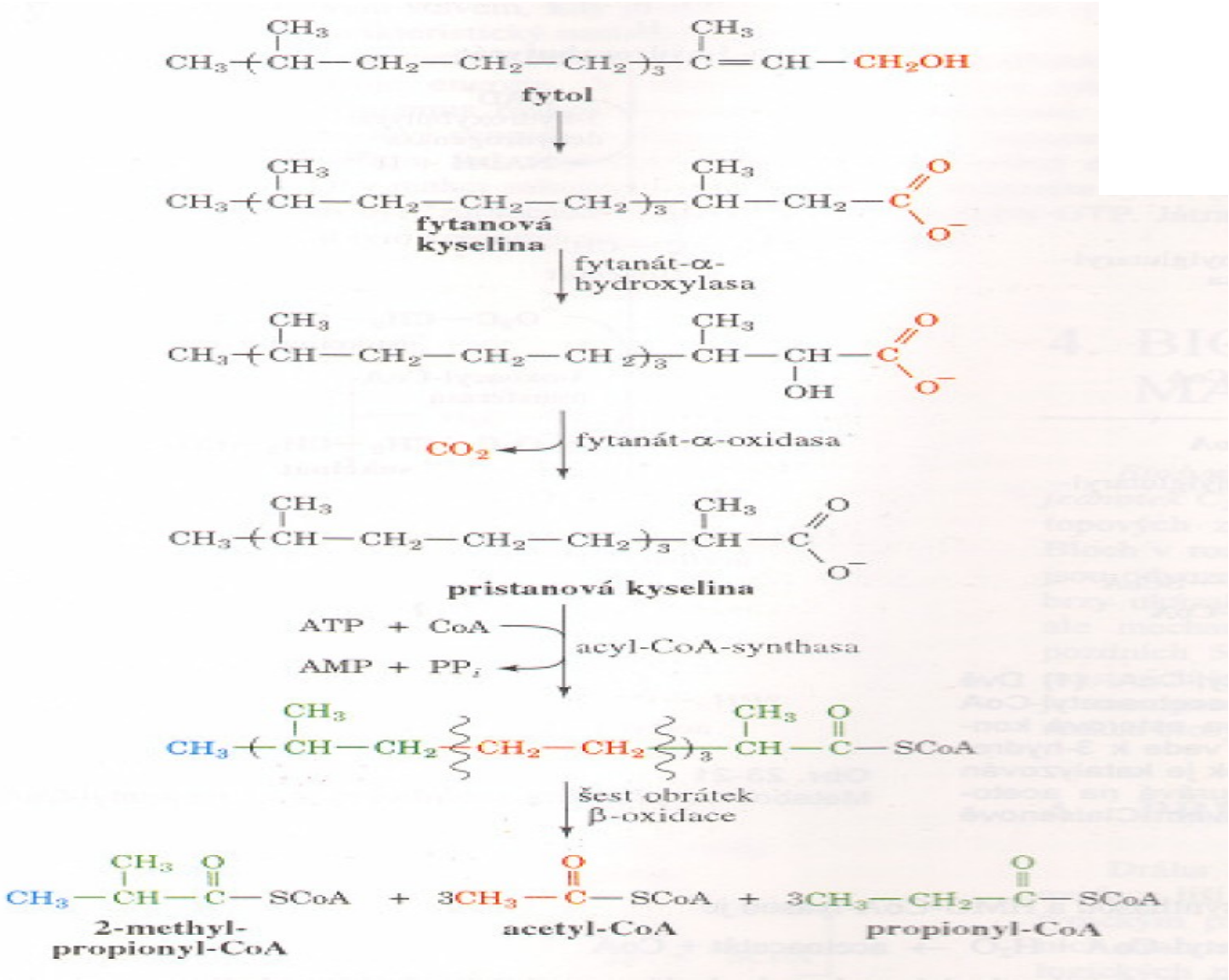

SCoA
13 12 10 9
three cycles of β-oxidation
SCoA
7 6 4 3
enoyl-CoA isomerase
O
3
7 6 2
SCoA
complete β-oxidation cycle
O
5 4
SCoA
acyl-CoA dehydrogenase
O
3
5 4 2
SCoA
NADPH + H+
NADP+
2,4-dienoyl-CoA reductase
4
3
SCoA
enoyl-CoA isomerase
2
3
SCoA
three cycles of β-oxidation
SCoA


SCoA
3NAD+ + 3FAD + 3CoA-SH
3NADH + 3FADH2 + 3Acetyl-CoA
tři obrátky β-oxidace
Problém 1:
β,γ-dvojná vazba
γ β α
enoyl-CoA-isomerasa
NAD+ + FAD + CoASH
NADH + FADH2 + Acetyl-CoA
jedna obrátka β-oxidace a první oxidace další obrátky
Problém 2:
dvojná vazba na Δ4
5 4 3 2 1
NADPH + H+
NADP+
2,4-dienoyl-CoA reduktasa (savčí)
2,4-dienoyl-CoA reduktasa (E. coli)
3,2-enoyl-CoA-isomerasa (savčí)
pokračování β-oxidace

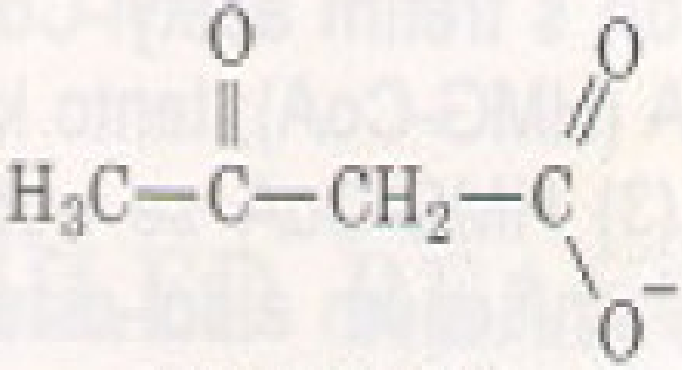
Odbourávání mastných kyselin s lichým počtem C atomů



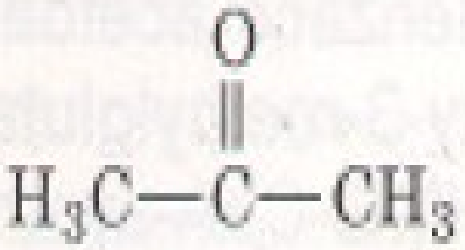
α-oxidace


fytol
fytanová kyselina
fytanát-α-hydroxylasa
CO2
fytanát-α-oxidasa
pristanová kyselina
ATP + CoA
AMP + PPi
acyl-CoA-synthasa
šest obrátek β-oxidace
2-methyl-propionyl-CoA
acetyl-CoA
propionyl-CoA

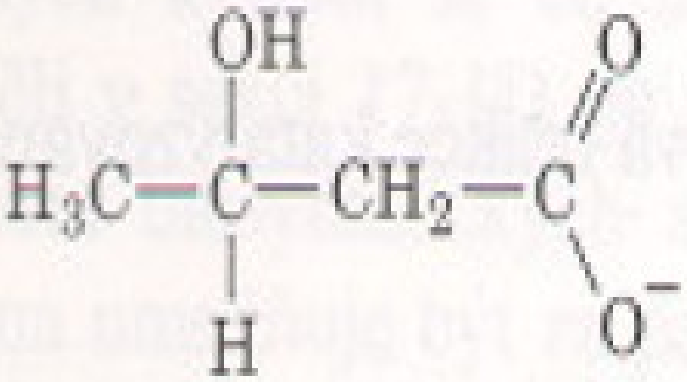
Ketonové látky



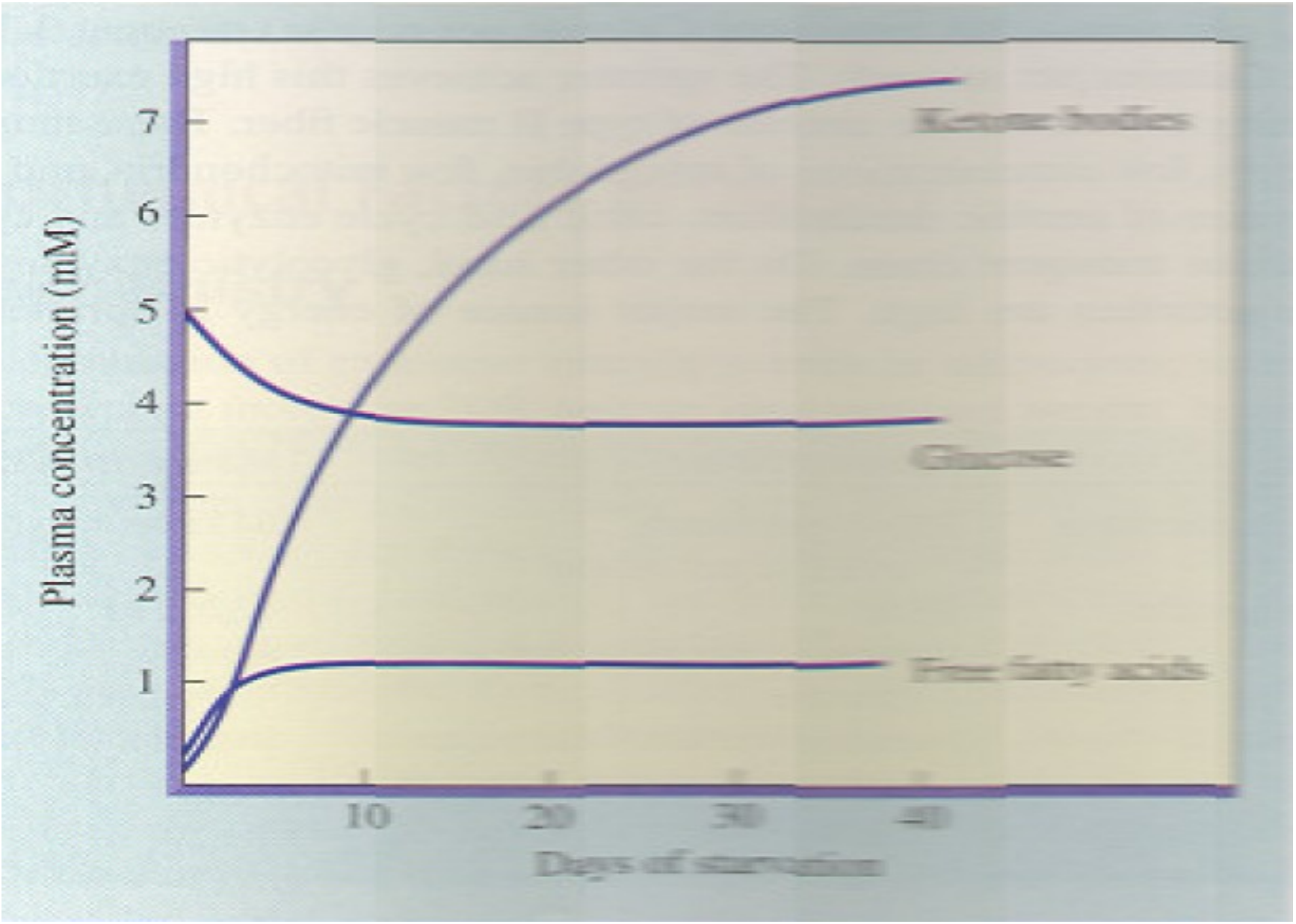
acetoacetát



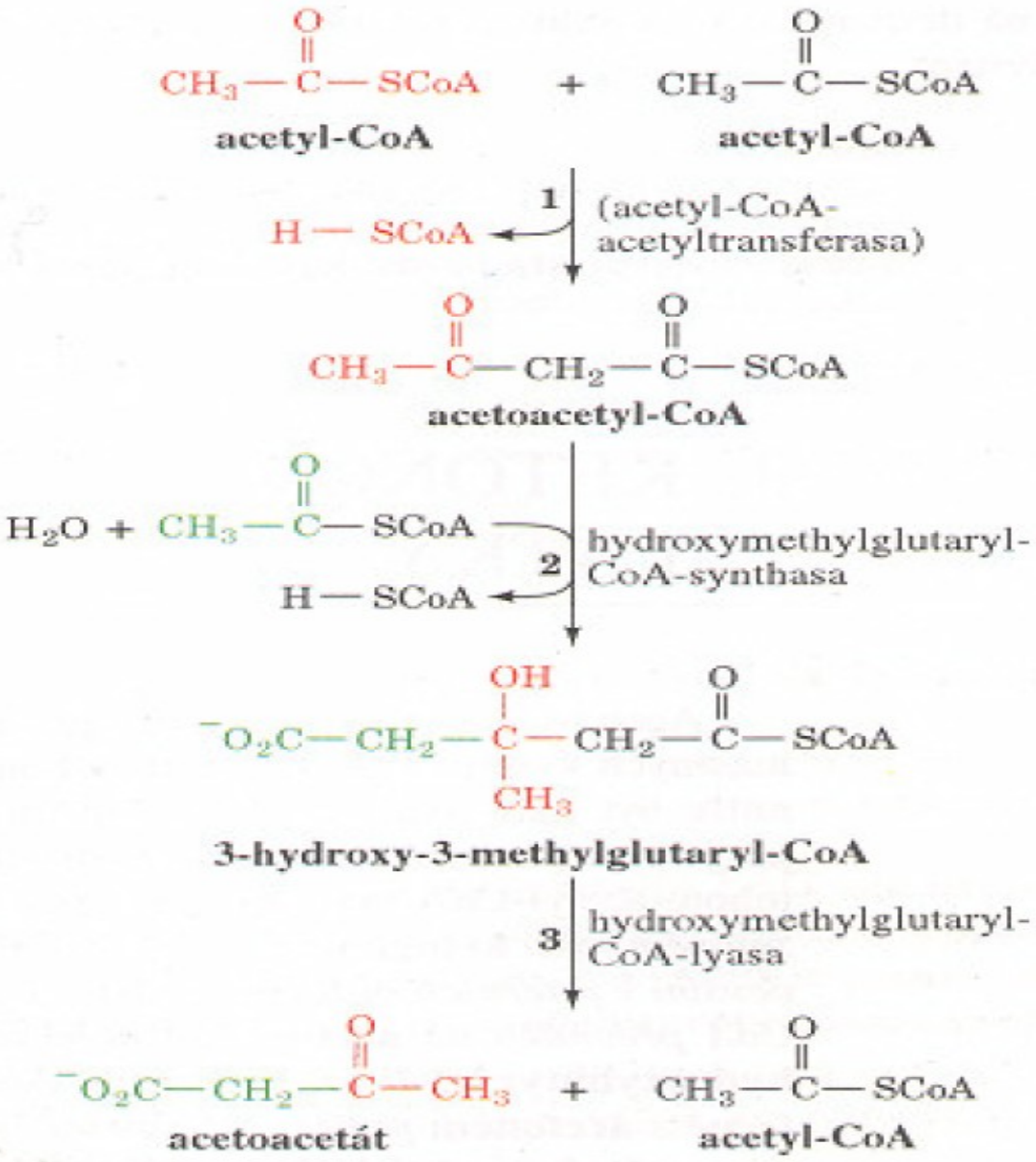
aceton



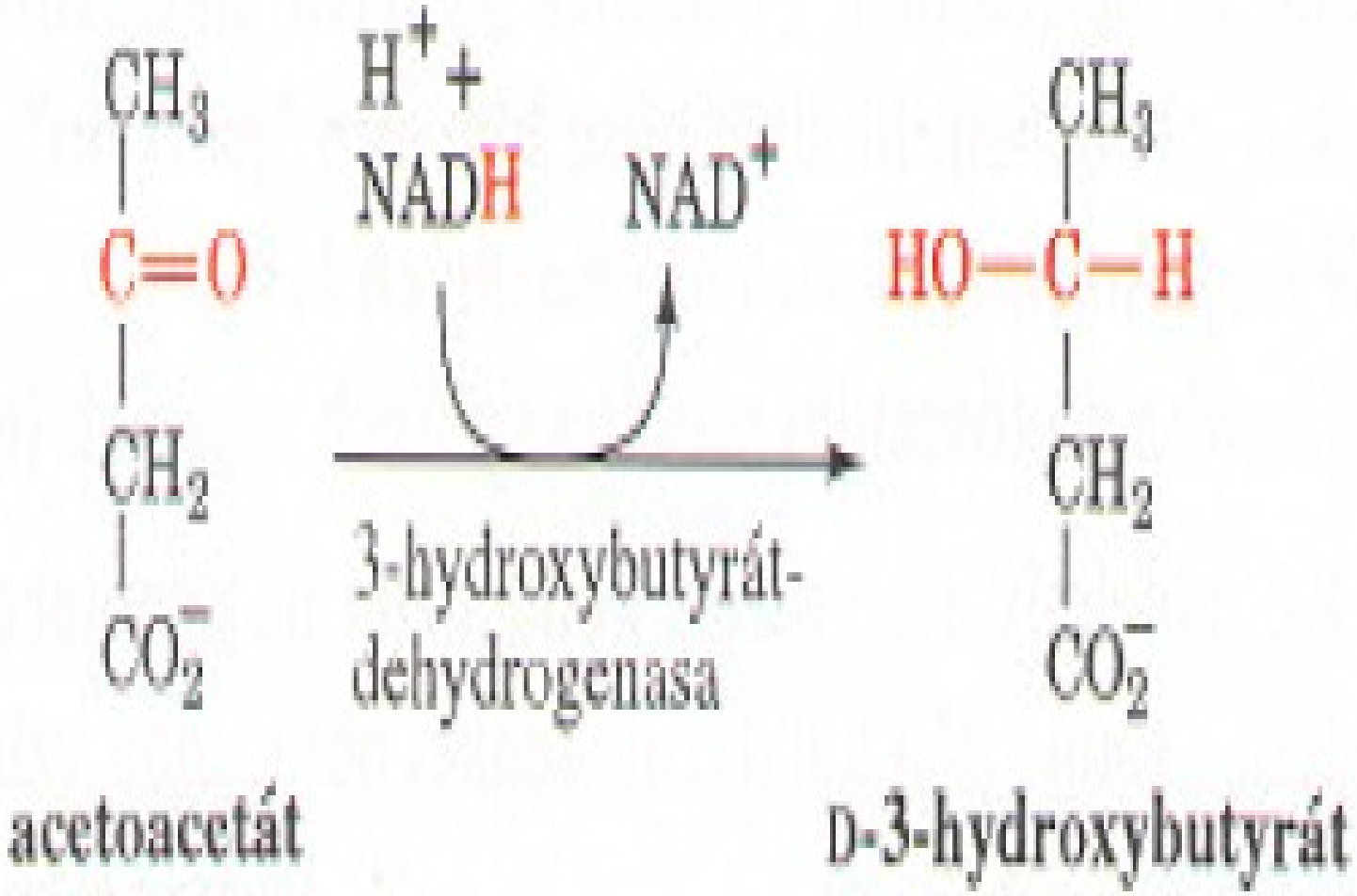
D-3-hydroxybutyrát


Plasma concentration (mM)
7
6
5
4
3
2
1
10
20
30
40

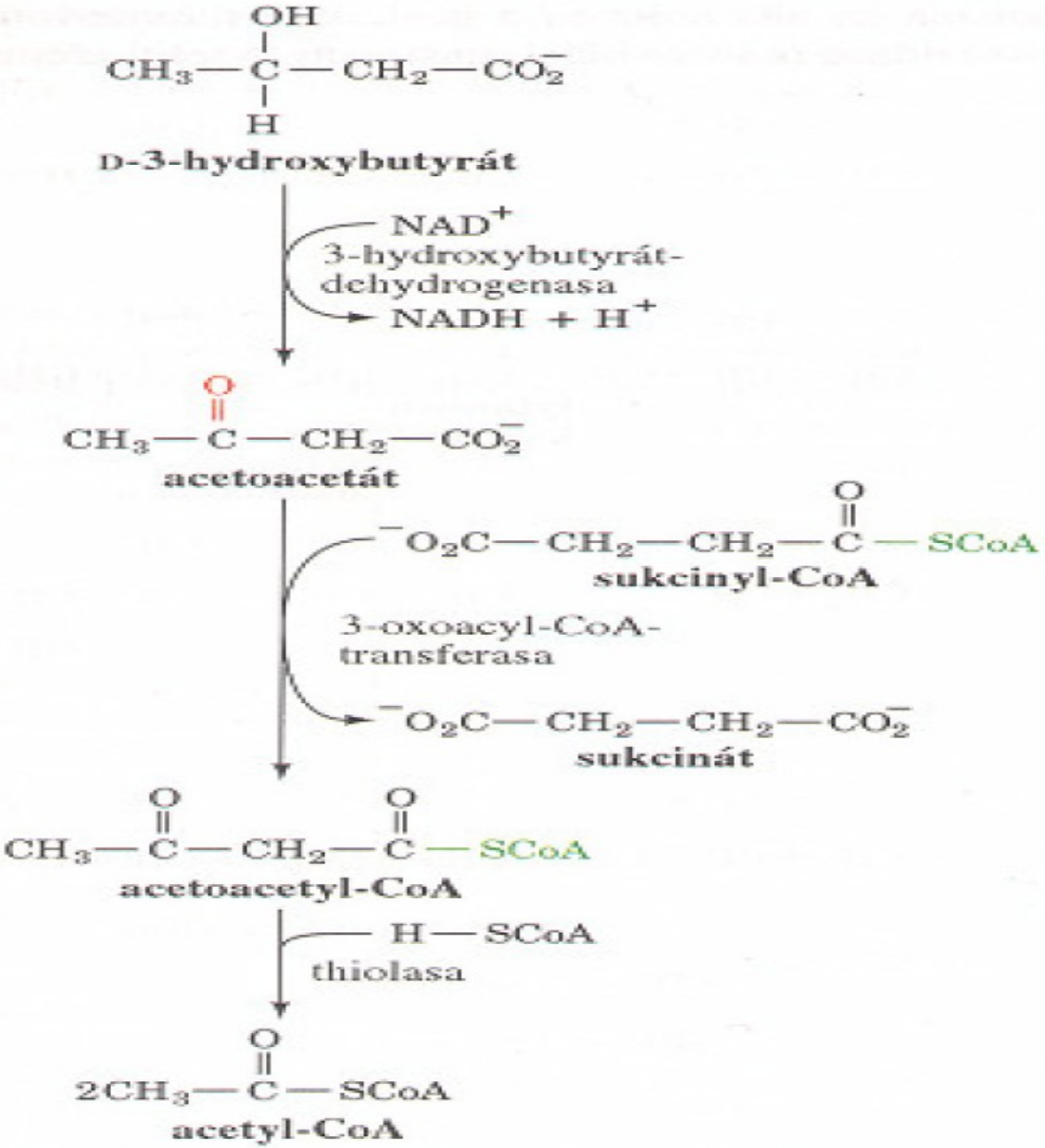
Ketonové látky



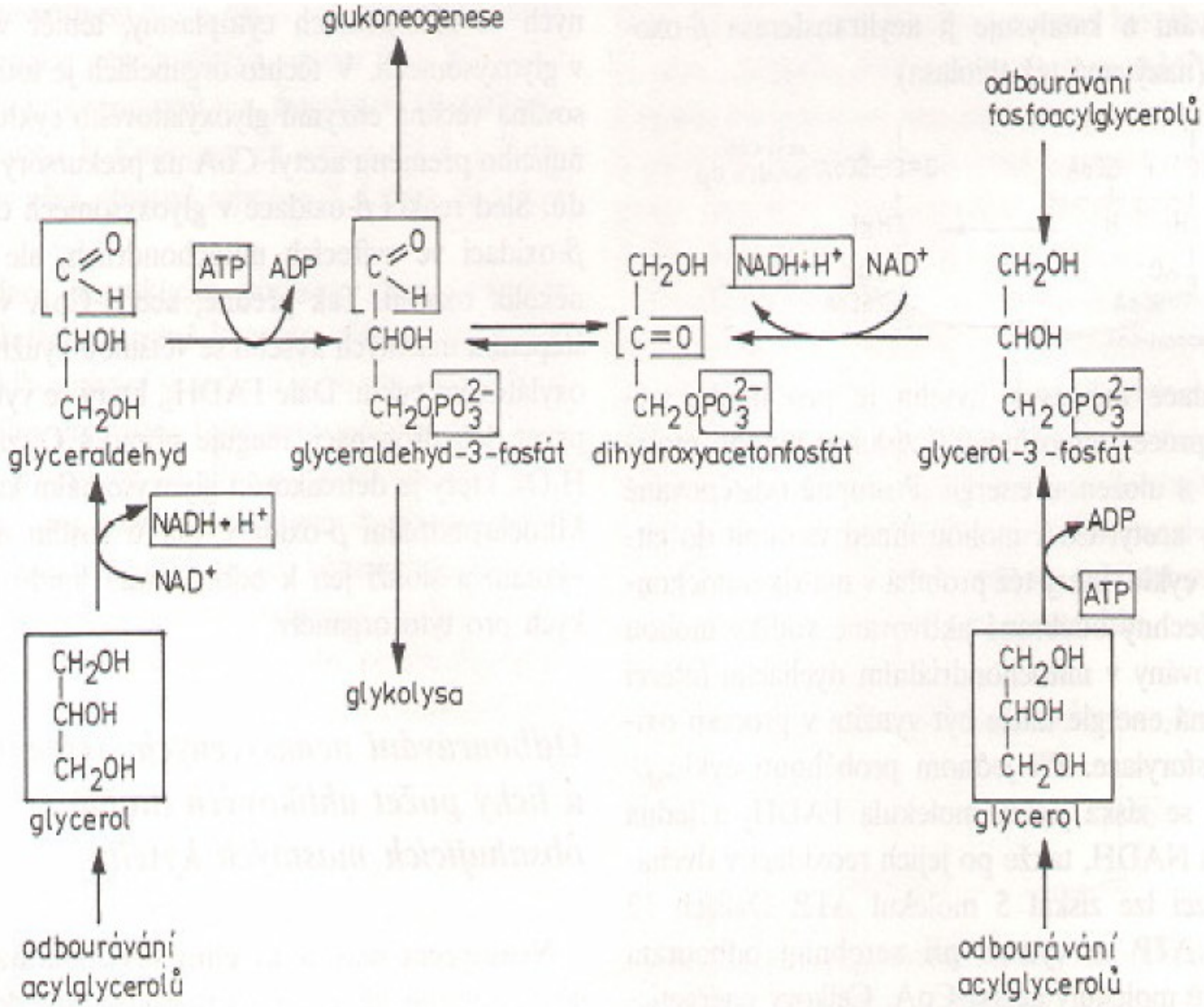
Ketonové látky

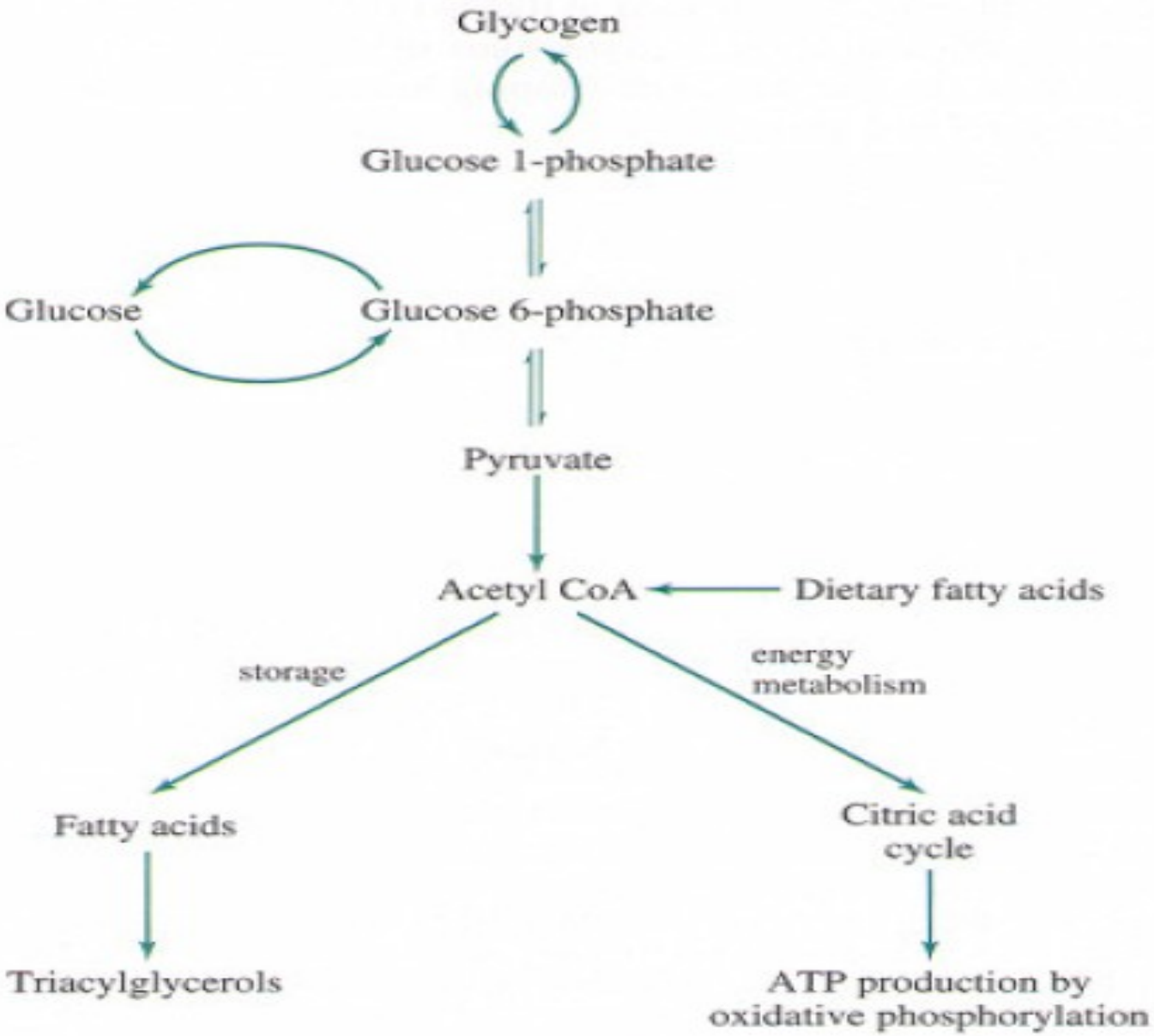


Ketonové látky

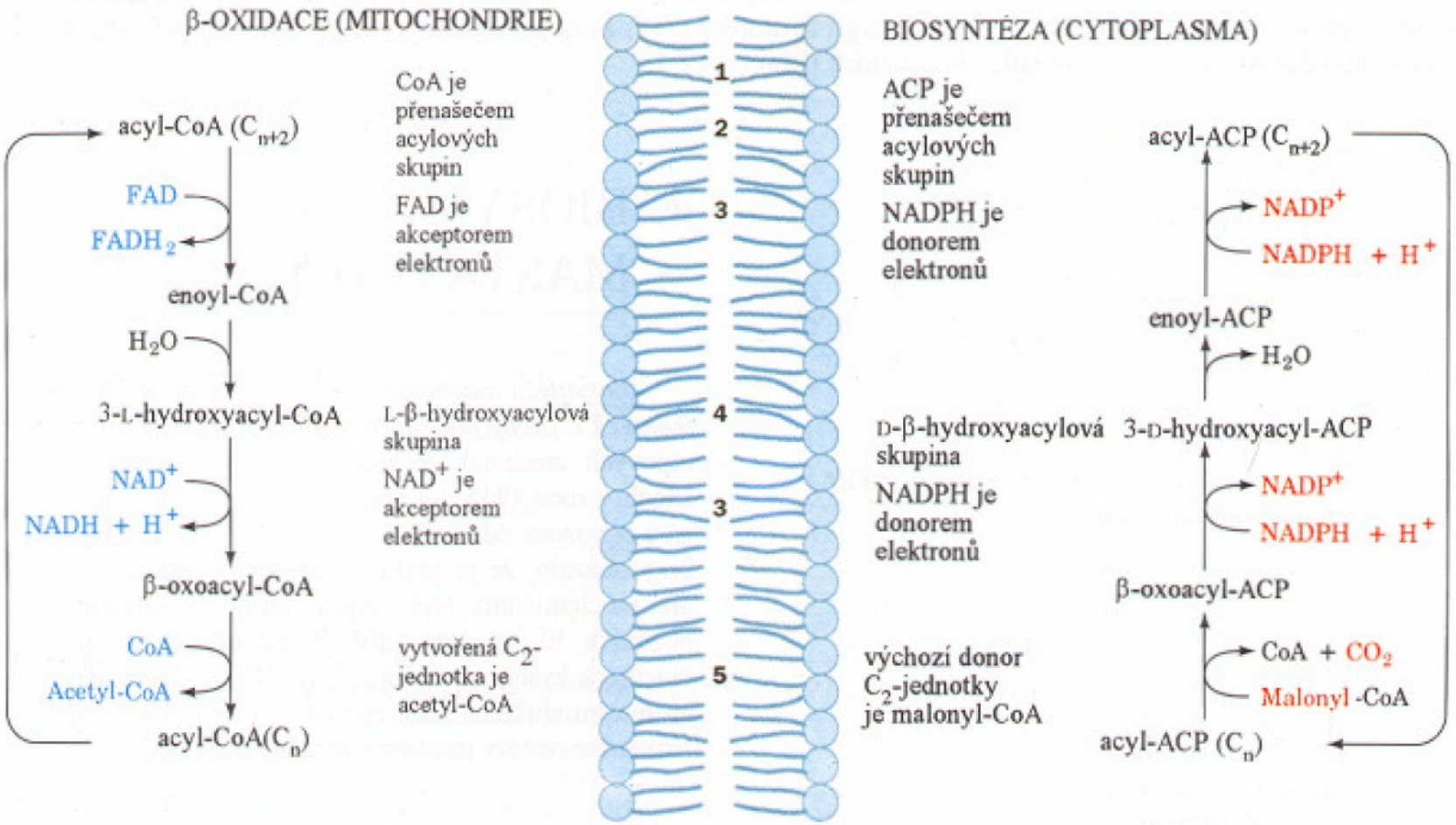


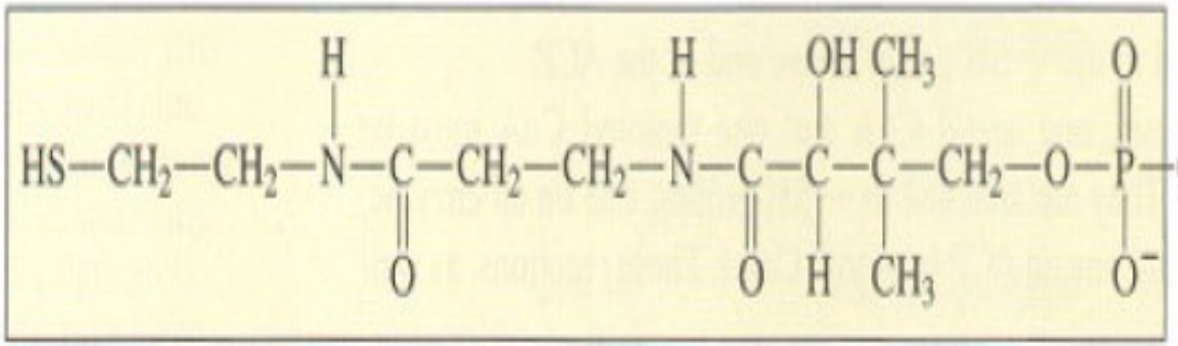
Metabolismus glycerolu



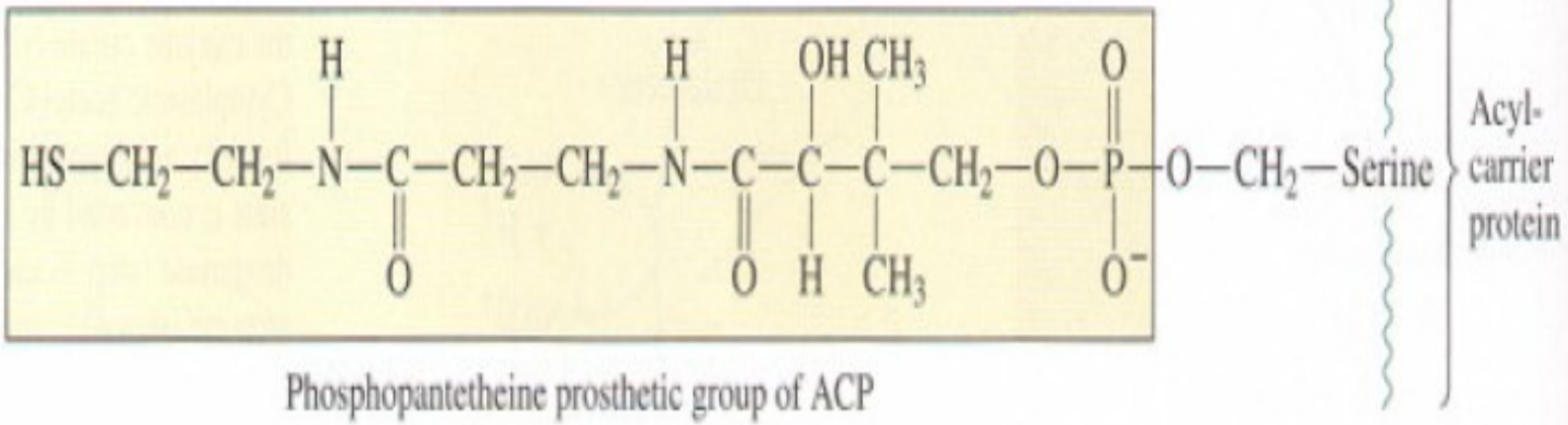

Glycogen
Glucose 1-phosphate
Glucose
Glucose 6-phosphate
Pyruvate
Acetyl CoA
Dietary fatty acids
storage
energy
metabolism
Fatty acids
Citric acid
cycle
Triacylglycerols
ATP production by
oxidative phosphorylation

Metabolismus versus biosyntéza MK





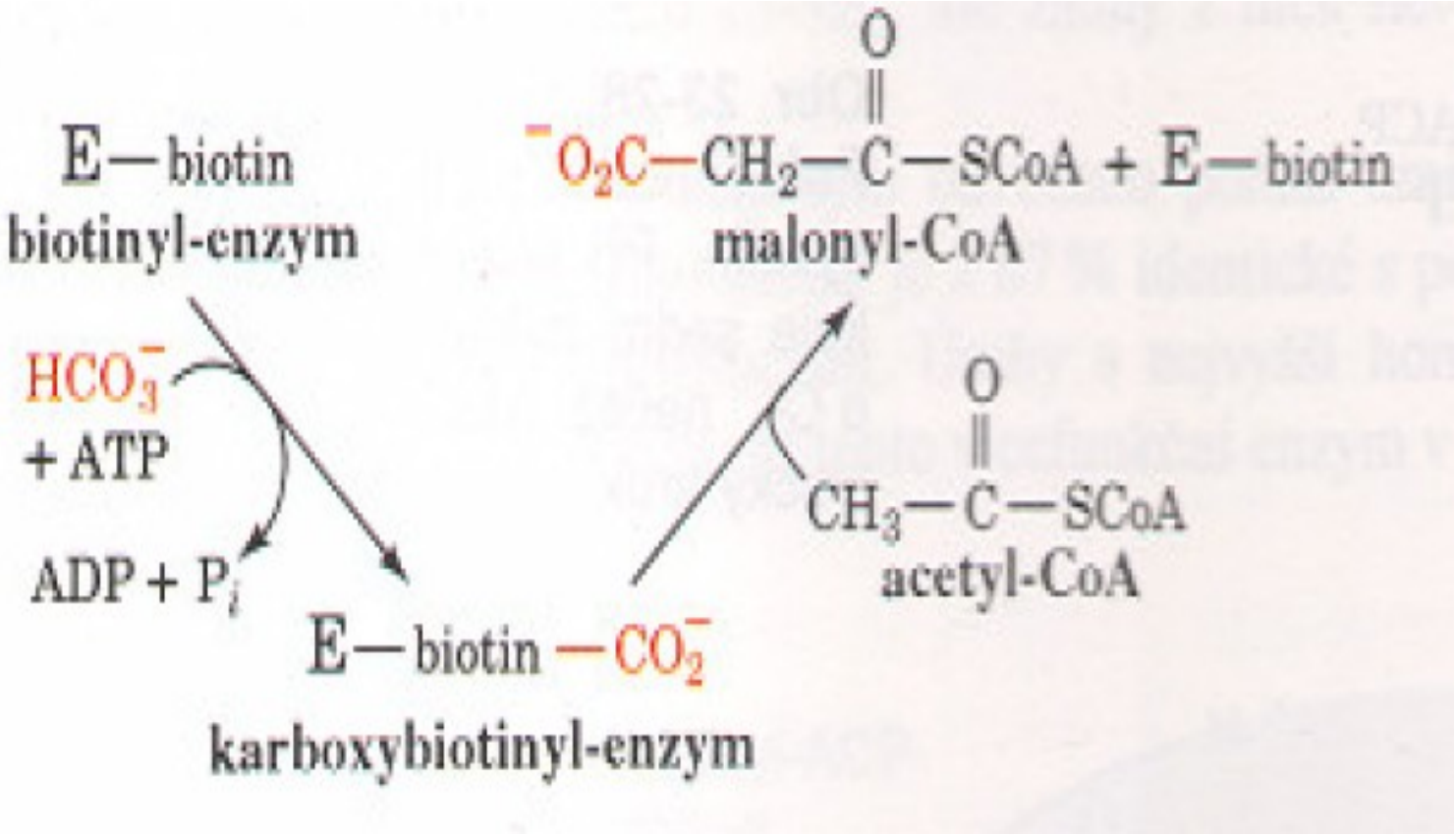
Phosphopantetheine group of CoASH



Phosphopantetheine prosthetic group of ACP

Biosyntéza mastných kyselin

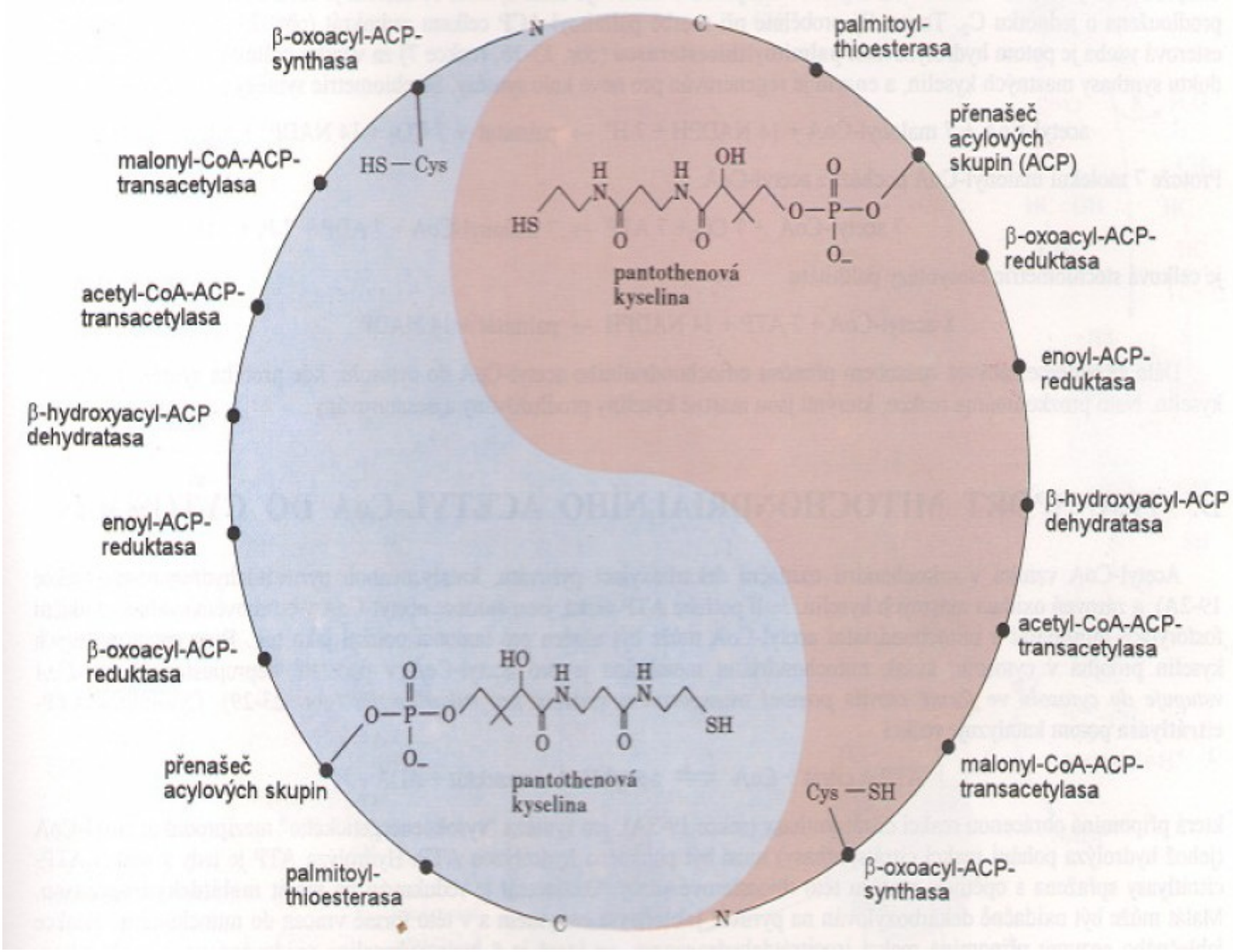
A. Syntéza malonylCoA



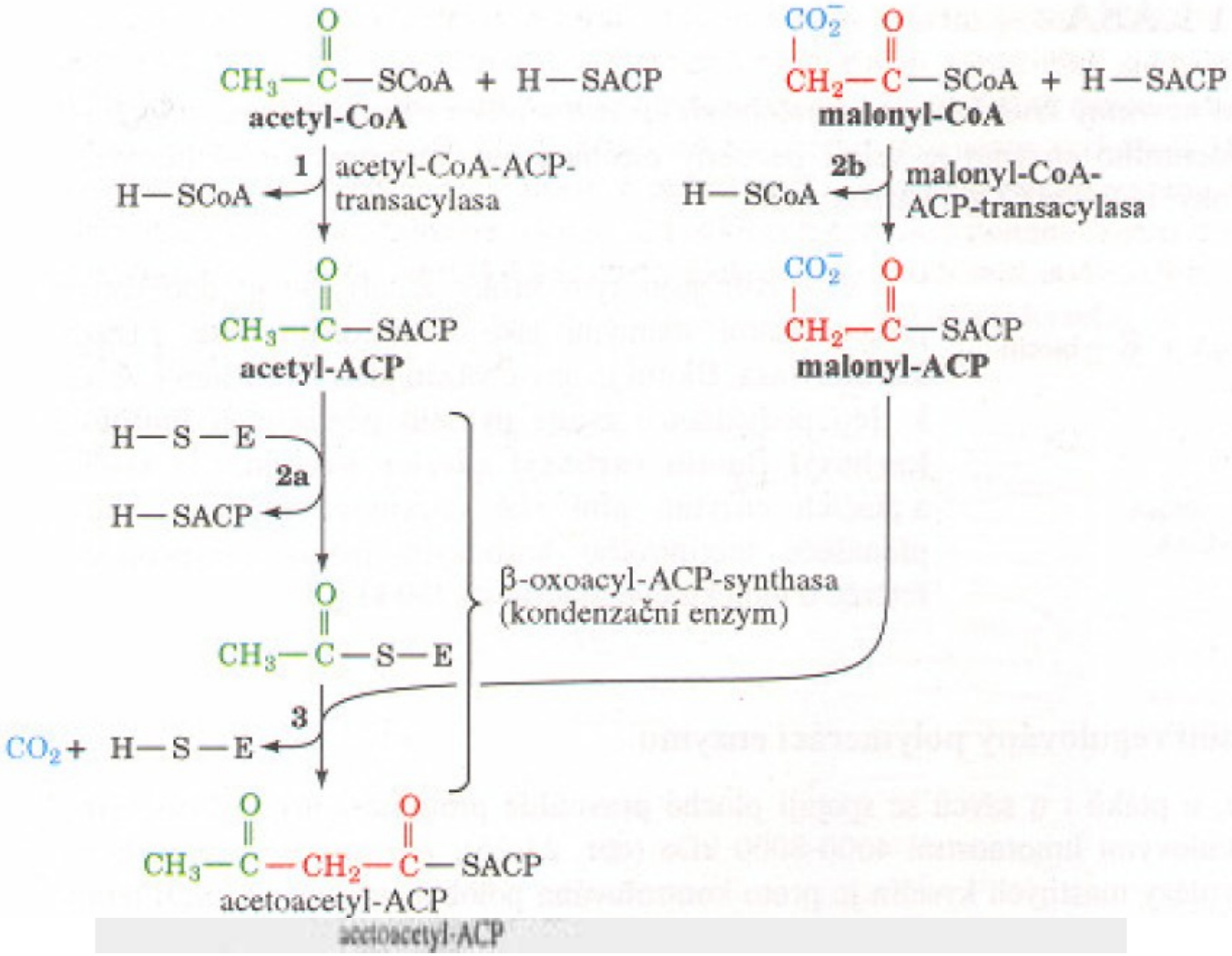
Regulace Acetyl-CoA karboxylasy

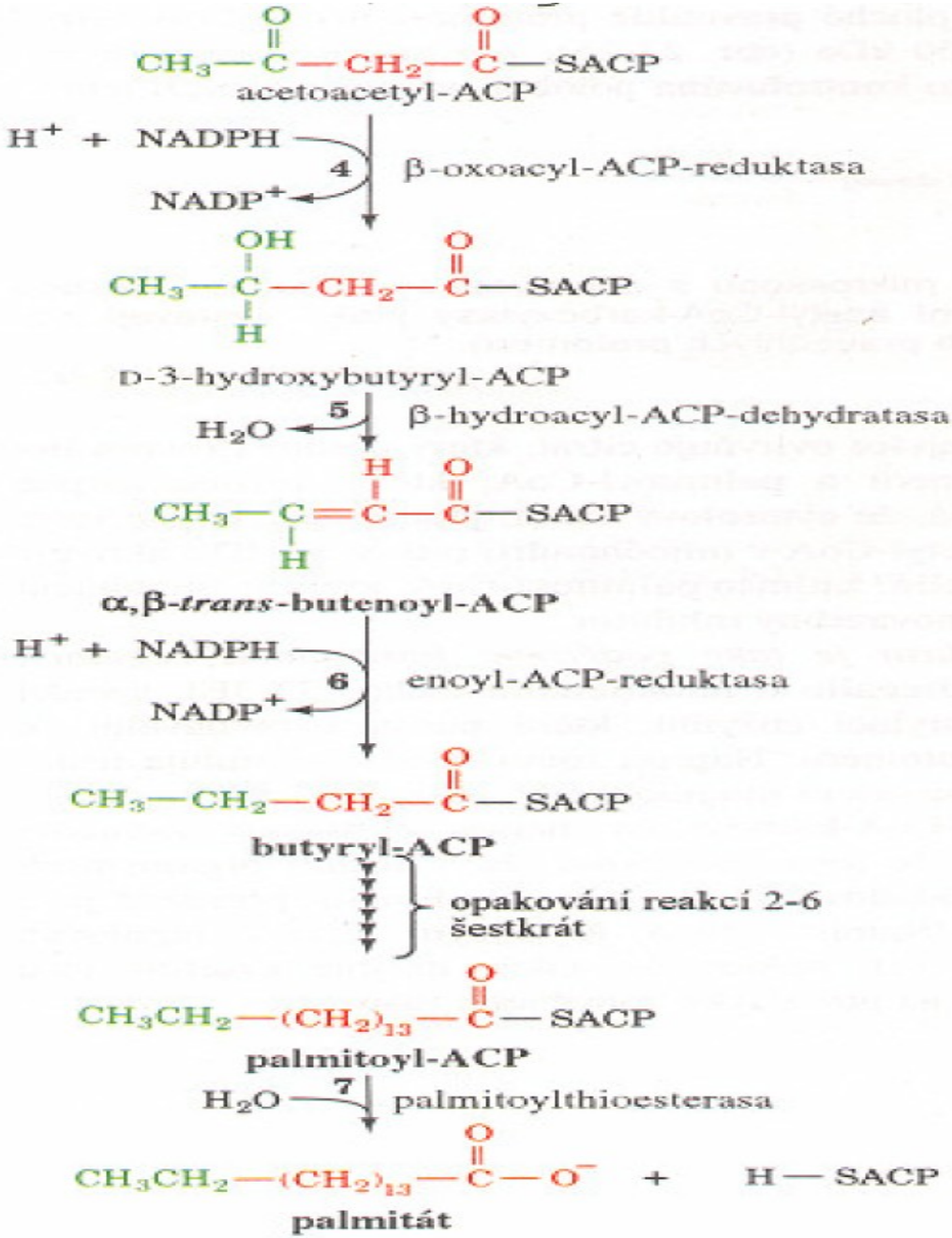
protomer *(neaktivní)* ⇌ polymer *(aktivní)*

Synthasa mastných kyselin

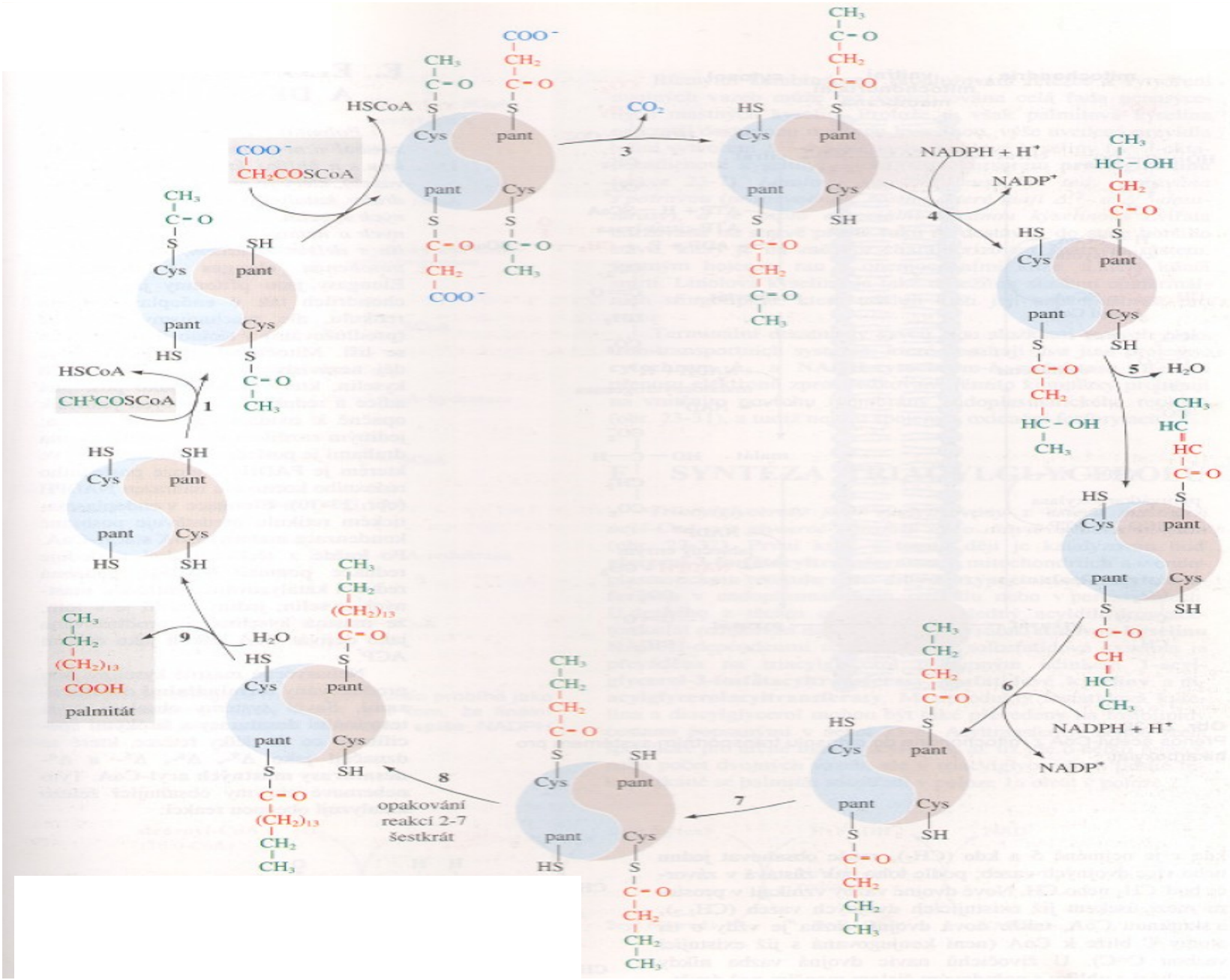


B. Syntéza palmitové kyseliny




CH3—C(=O)—CH2—C(=O)—SACP
acetoacetyl-ACP
H+ + NADPH
4
NADP+
β-oxoacyl-ACP-reduktasa
CH3—C(OH)H—CH2—C(=O)—SACP
D-3-hydroxybutyryl-ACP
H2O
5
β-hydroacyl-ACP-dehydratasa
CH3—C(H)=C(H)—C(=O)—SACP
α,β-trans-butenoyl-ACP
H+ + NADPH
6
NADP+
enoyl-ACP-reduktasa
CH3—CH2—CH2—C(=O)—SACP
butyryl-ACP
opakování reakcí 2-6
šestkrát
CH3CH2—(CH2)13—C(=O)—SACP
palmitoyl-ACP
H2O
7
palmitoylthioesterasa
CH3CH2—(CH2)13—C(=O)—O−
+
H—SACP
palmitát

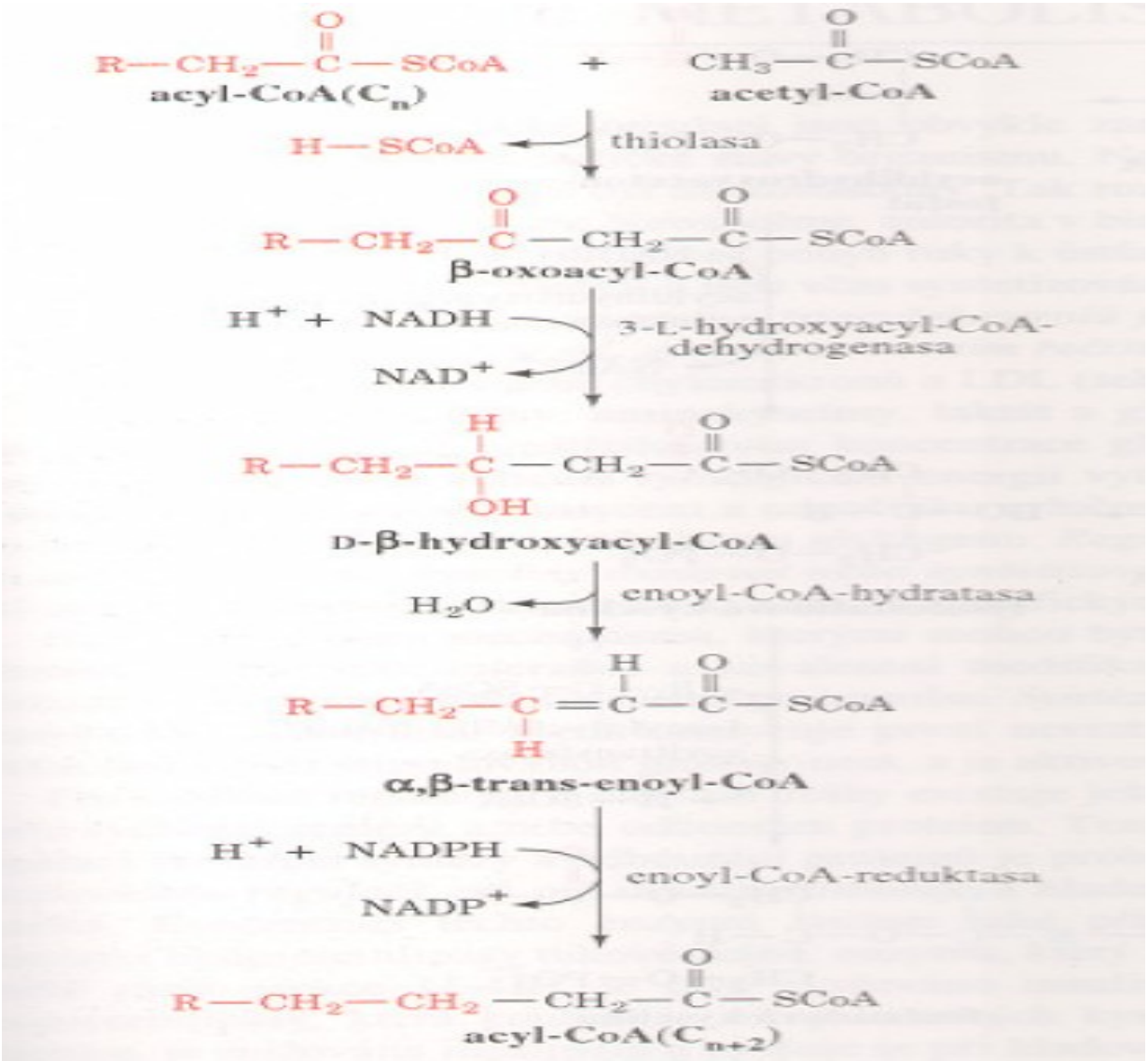
Synthasa mastných kyselin



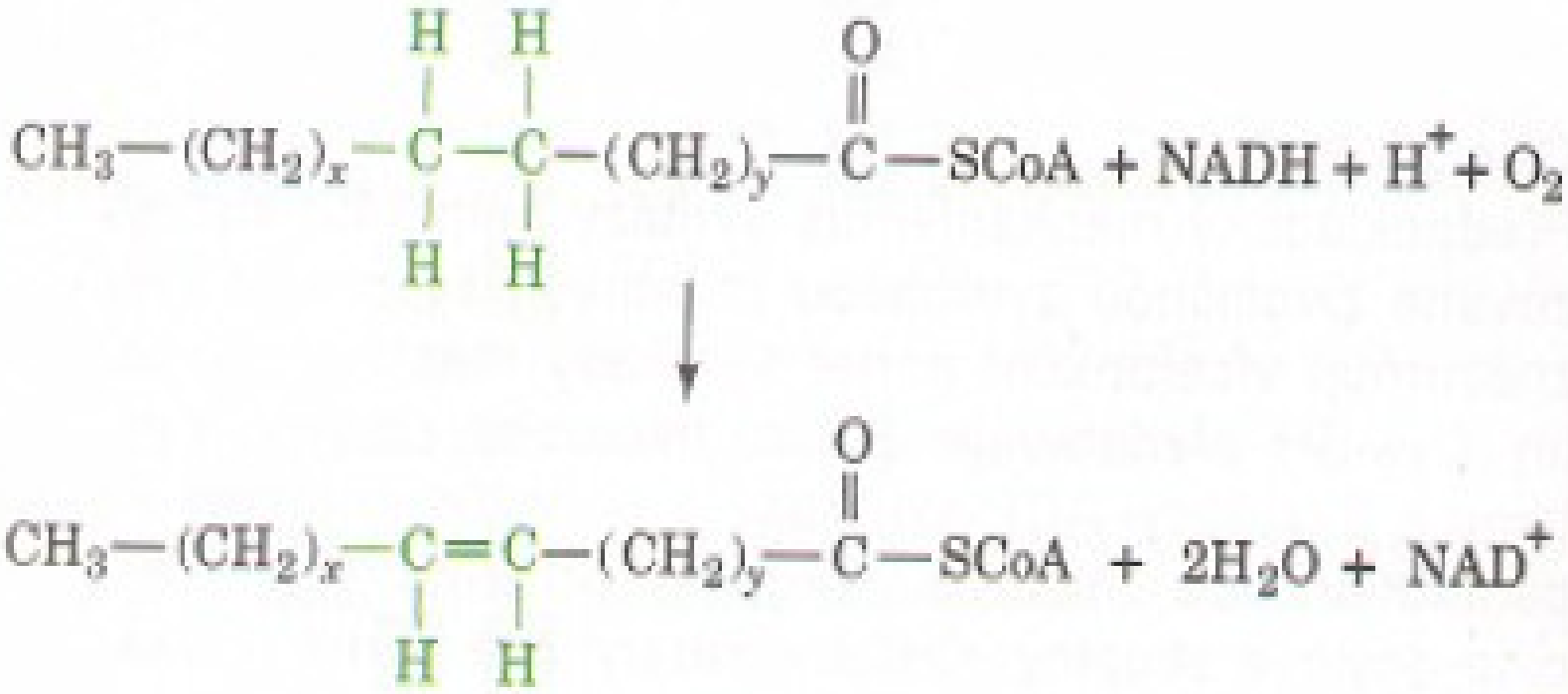
C. Další přeměny palmitové kyseliny

- prodlužování řetězce - elongace - elongasy
- dehydrogenace - desaturece - desaturasy

Elongace


R—CH2—C(=O)—SCoA
acyl-CoA(Cn)
+
CH3—C(=O)—SCoA
acetyl-CoA
H—SCoA
thiolasa
R—CH2—C(=O)—CH2—C(=O)—SCoA
β-oxoacyl-CoA
H+ + NADH
NAD+
3-L-hydroxyacyl-CoA-dehydrogenasa
R—CH2—C(H)(OH)—CH2—C(=O)—SCoA
D-β-hydroxyacyl-CoA
H2O
enoyl-CoA-hydratasa
R—CH2—C(H)=C(H)—C(=O)—SCoA
α,β-trans-enoyl-CoA
H+ + NADPH
NADP+
enoyl-CoA-reduktasa
R—CH2—CH2—CH2—C(=O)—SCoA
acyl-CoA(Cn+2)

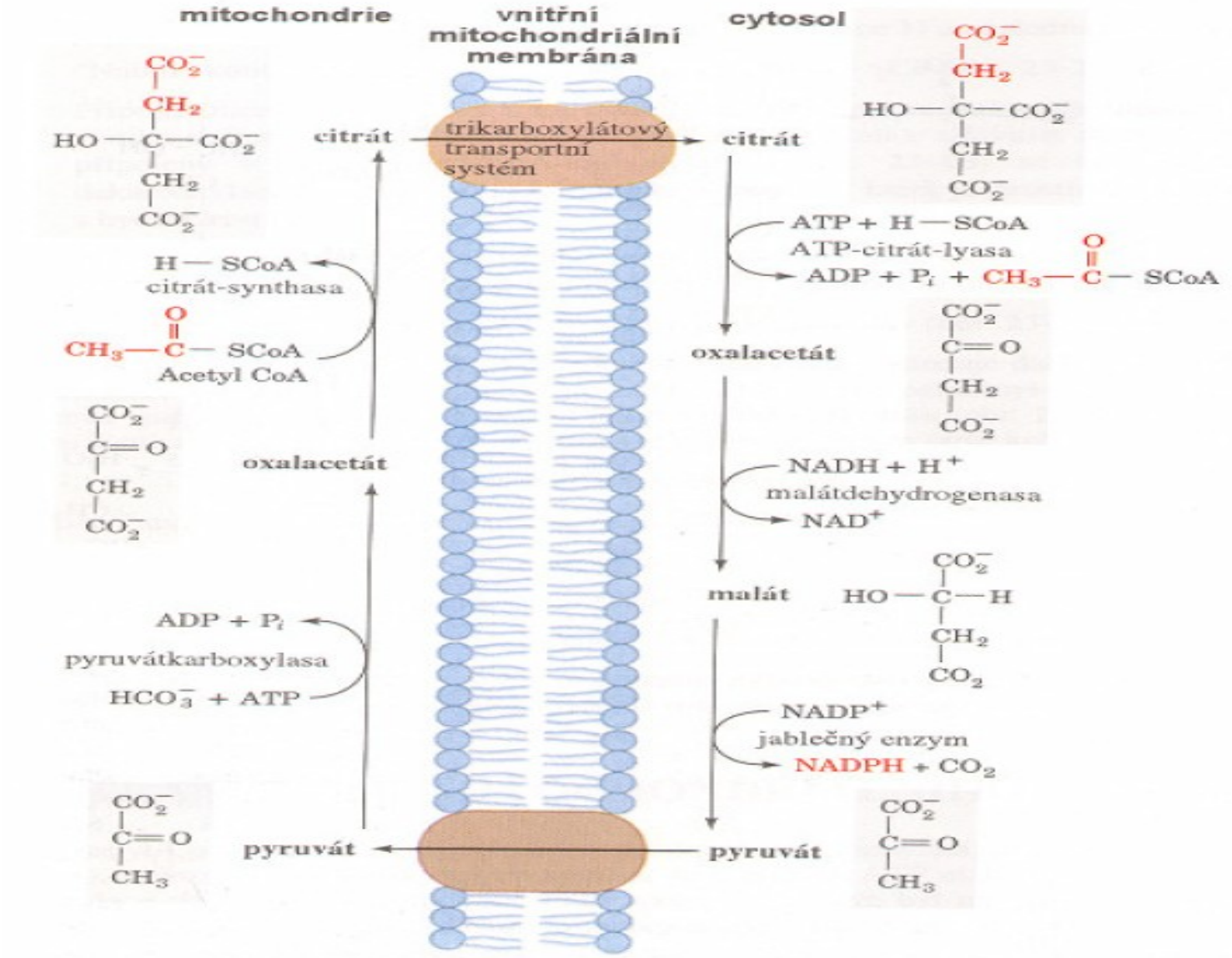
Desaturace


CH3—(CH2)x—CH—CH—(CH2)y—C—SCoA + NADH + H+ + O2
CH3—(CH2)x—C=C—(CH2)y—C—SCoA + 2H2O + NAD+

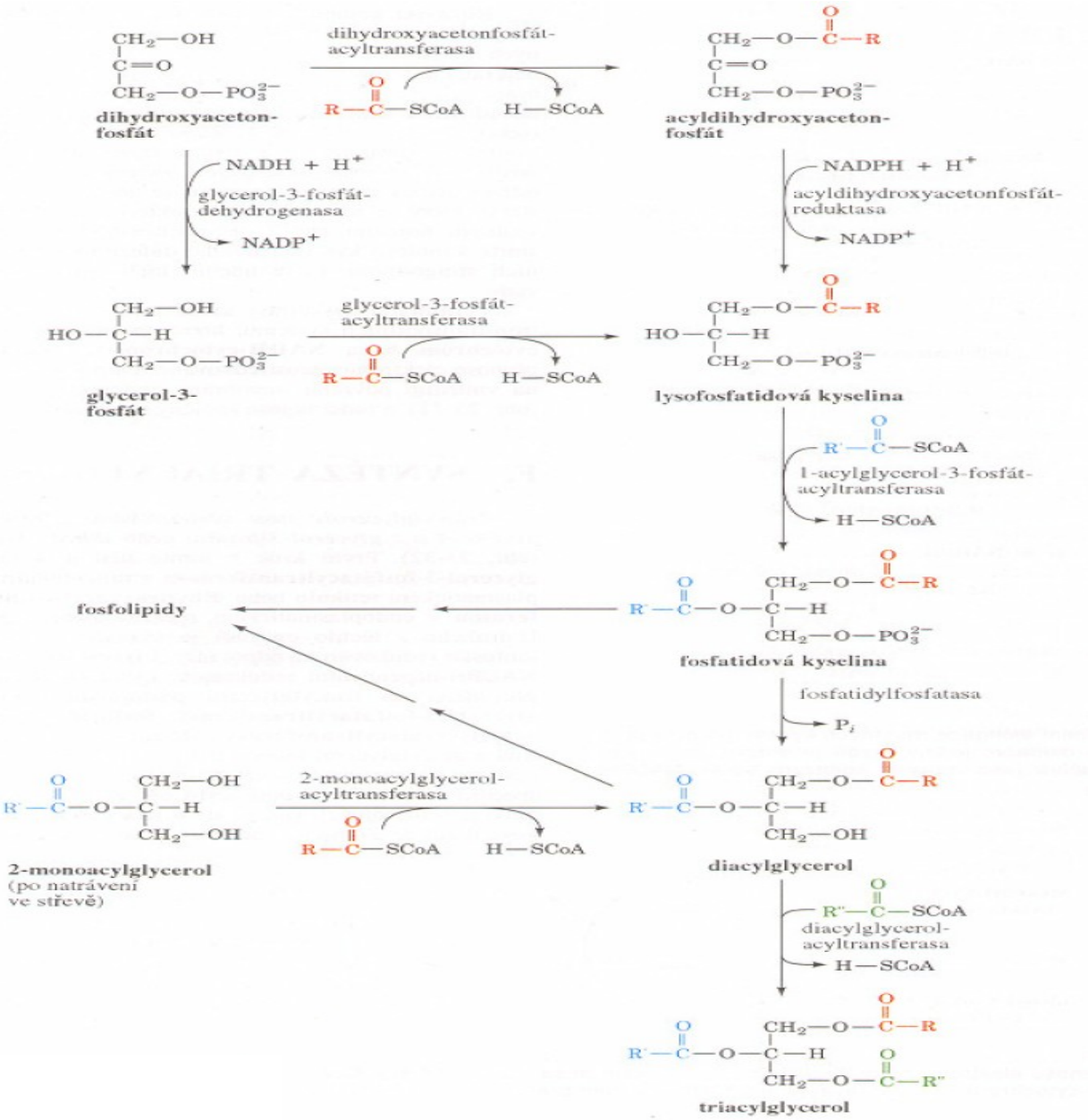
Bilance biosyntézy mastných kyselin :

1. cyklus	syntéza malonylCoA	1 ATP
	2 NADPH na redukci	6 ATP
na C_{16}	$7 \times ({}^{16}/_{2} - 1)$	49 ATP

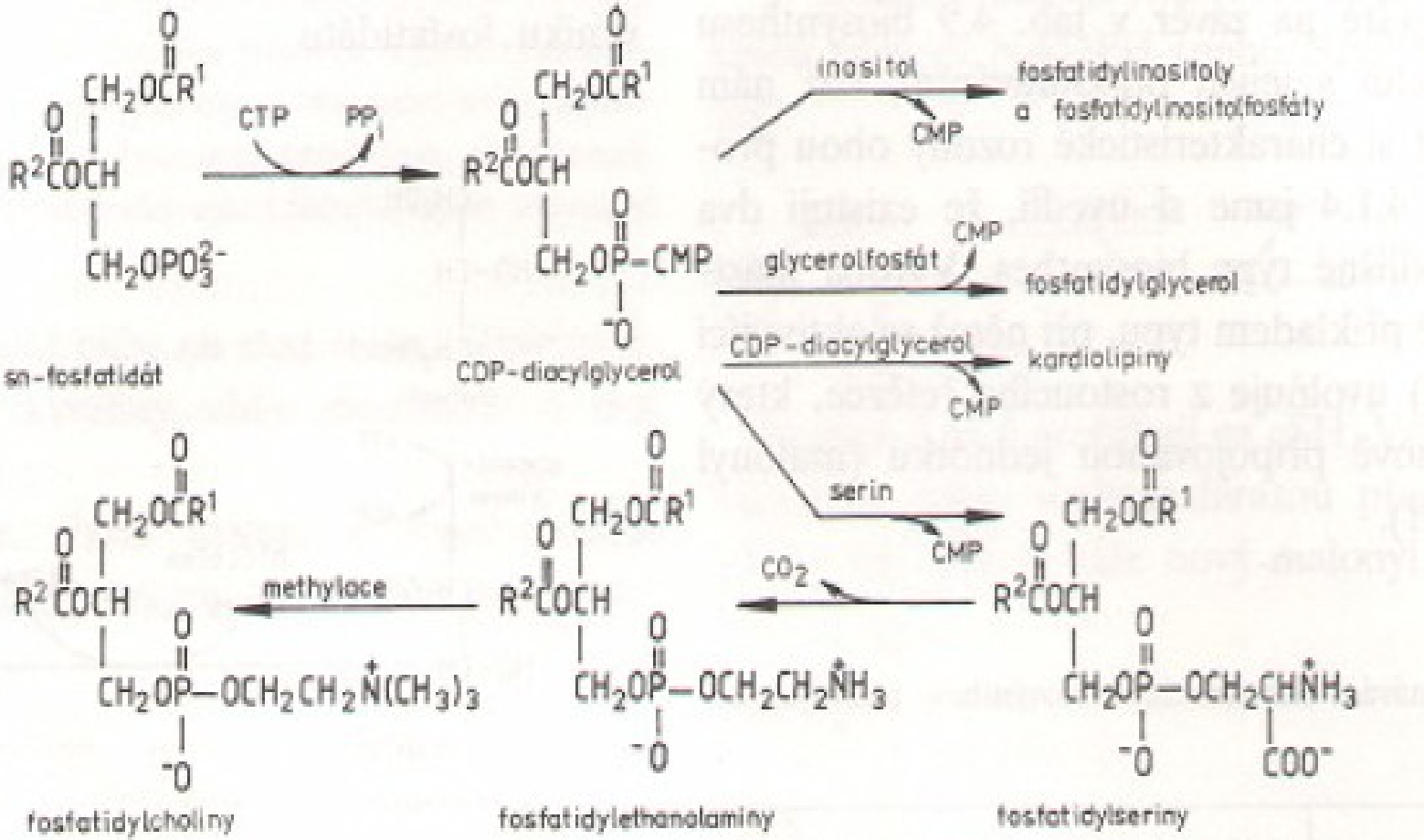
Přenos AcetCoA vně mitochondrie



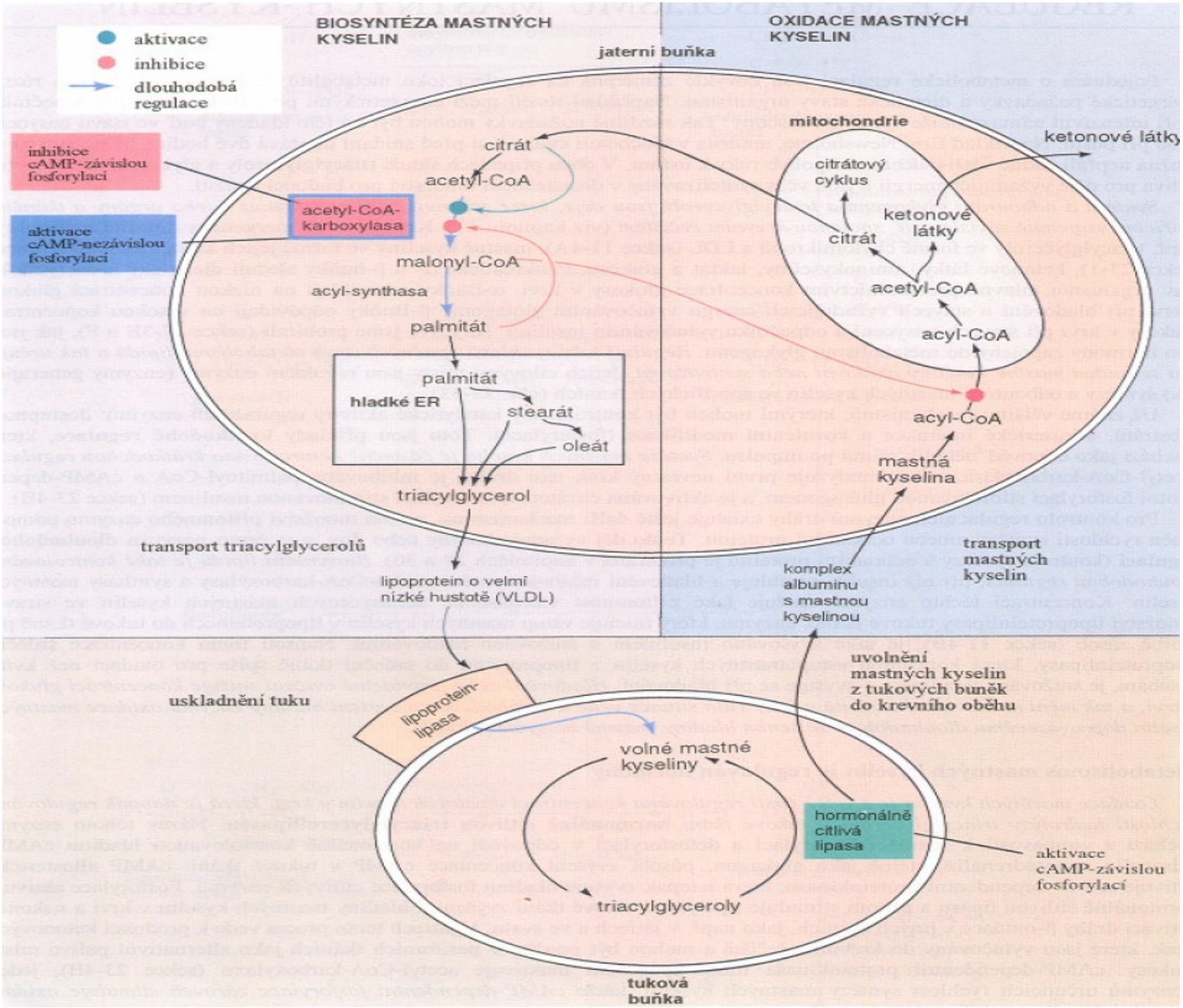
Biosyntéza triacylglycerolů



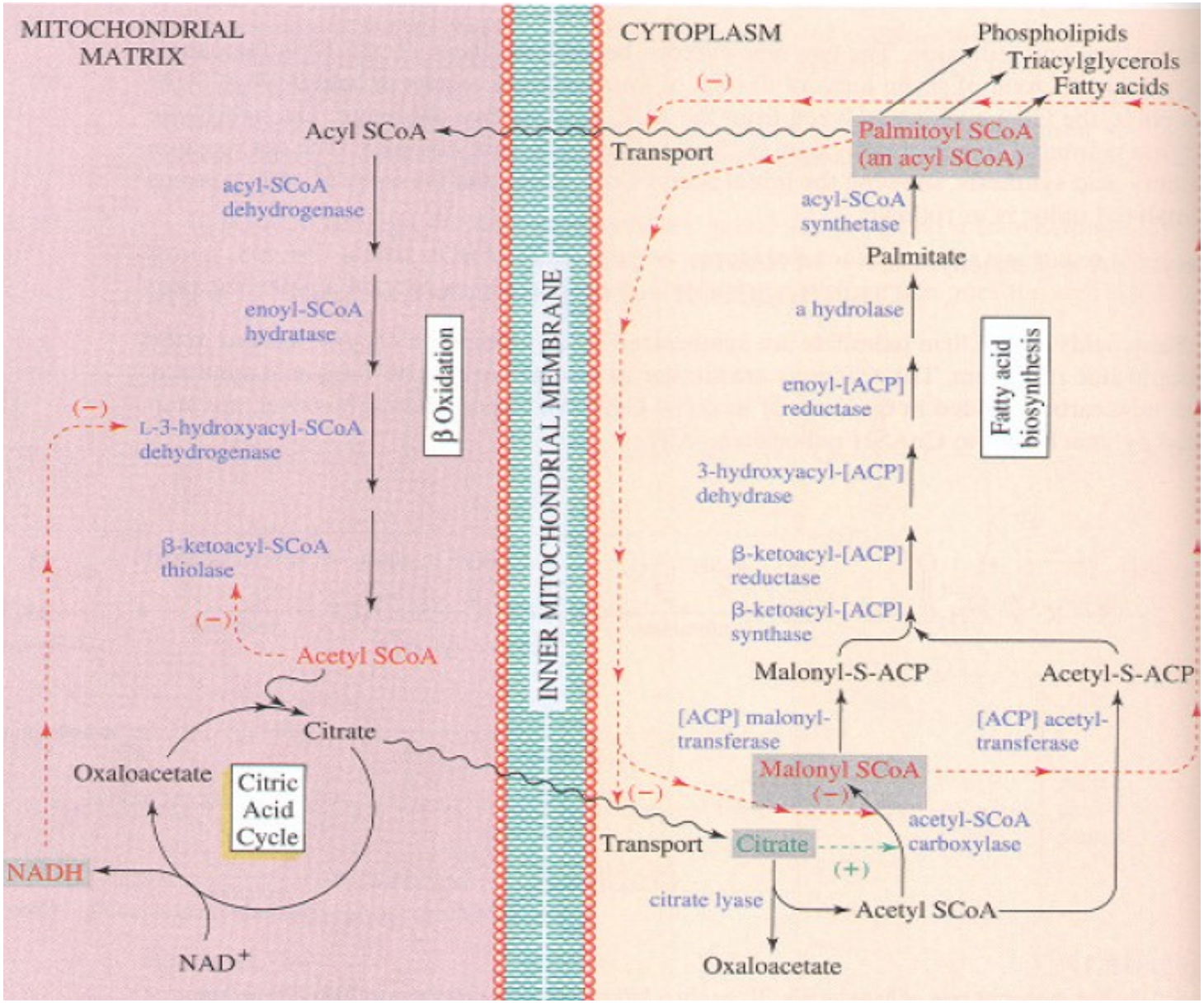
Biosyntéza fosfolipidů

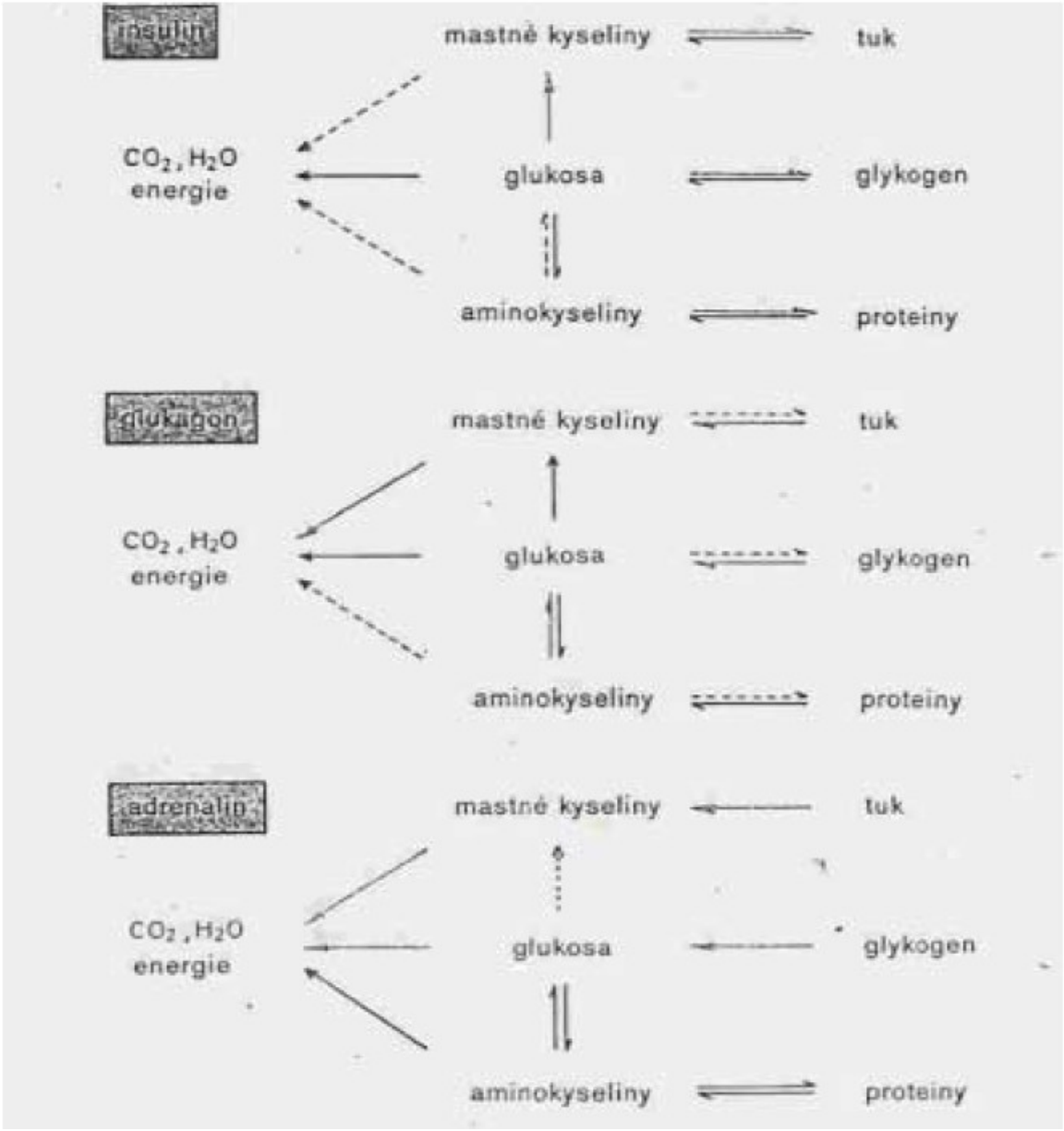


Regulace metabolismu triacylglytcerolů

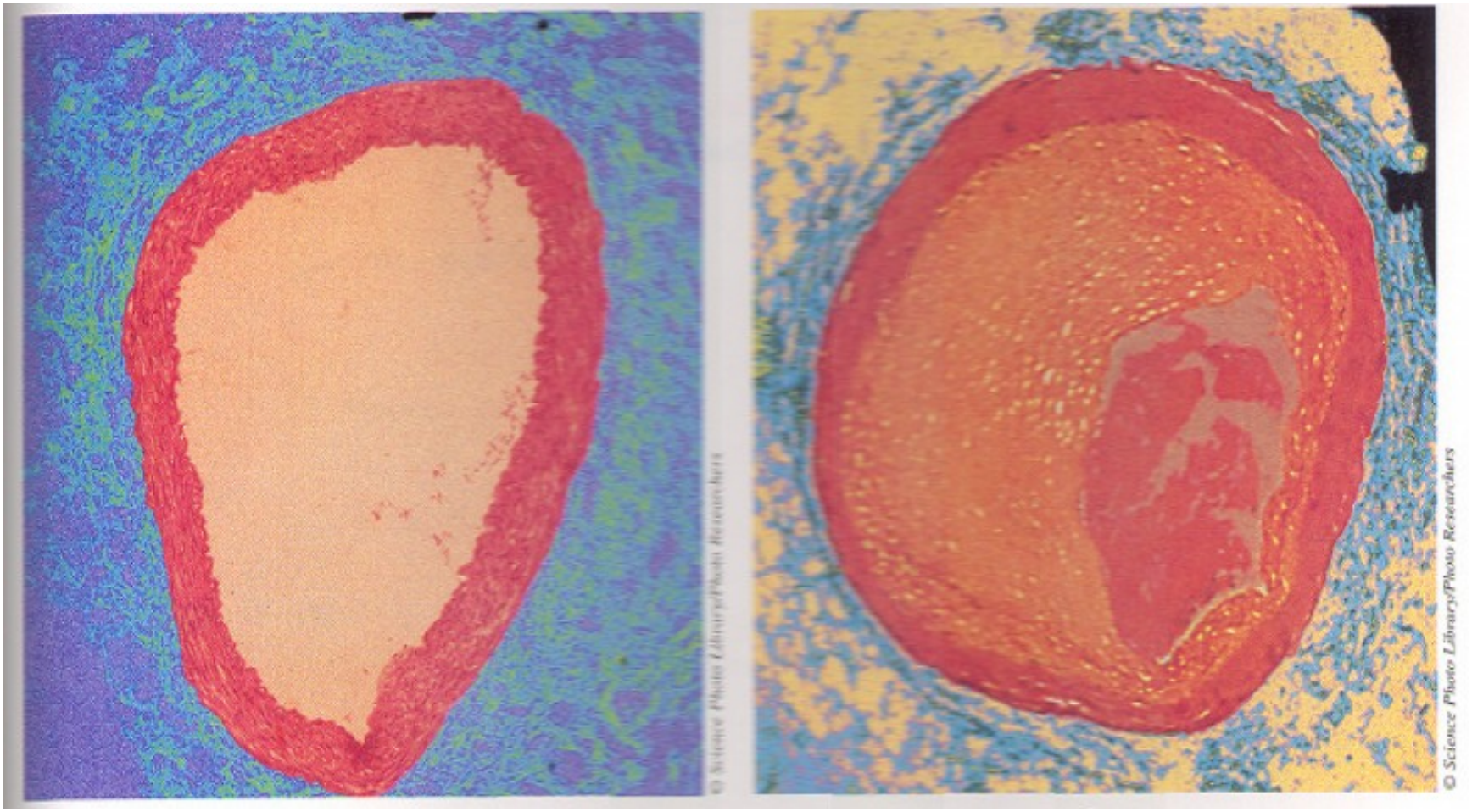


Regulace metabolismu triacylglytcerolů

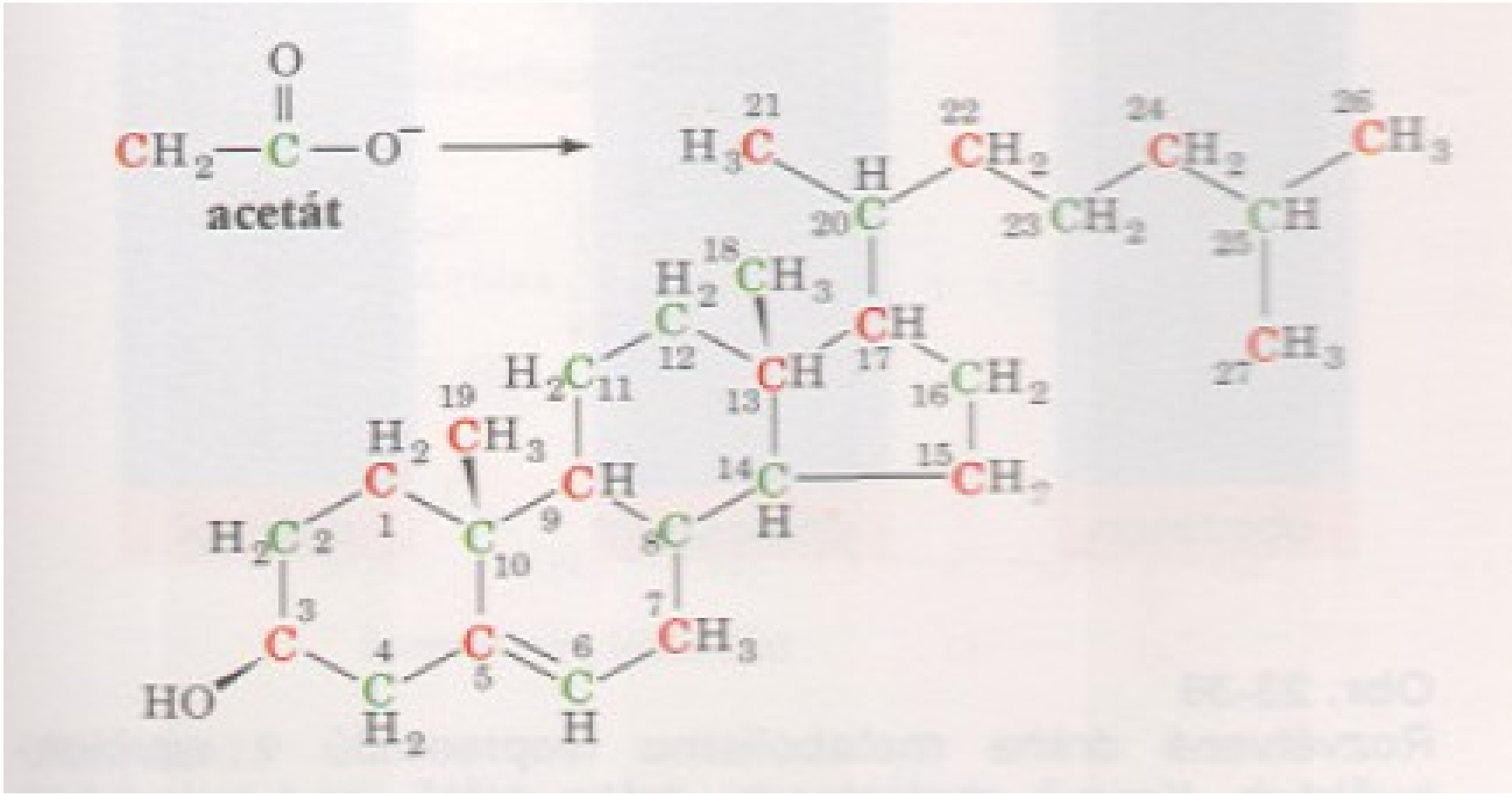



inzulín
mastné kyseliny
tuk
CO_2, H_2O
energie
glukosa
glykogen
aminokyseliny
proteiny
glukagon
mastné kyseliny
tuk
CO_2, H_2O
energie
glukosa
glykogen
aminokyseliny
proteiny
adrenalín
mastné kyseliny
tuk
CO_2, H_2O
energie
glukosa
glykogen
aminokyseliny
proteiny

Cholesterol

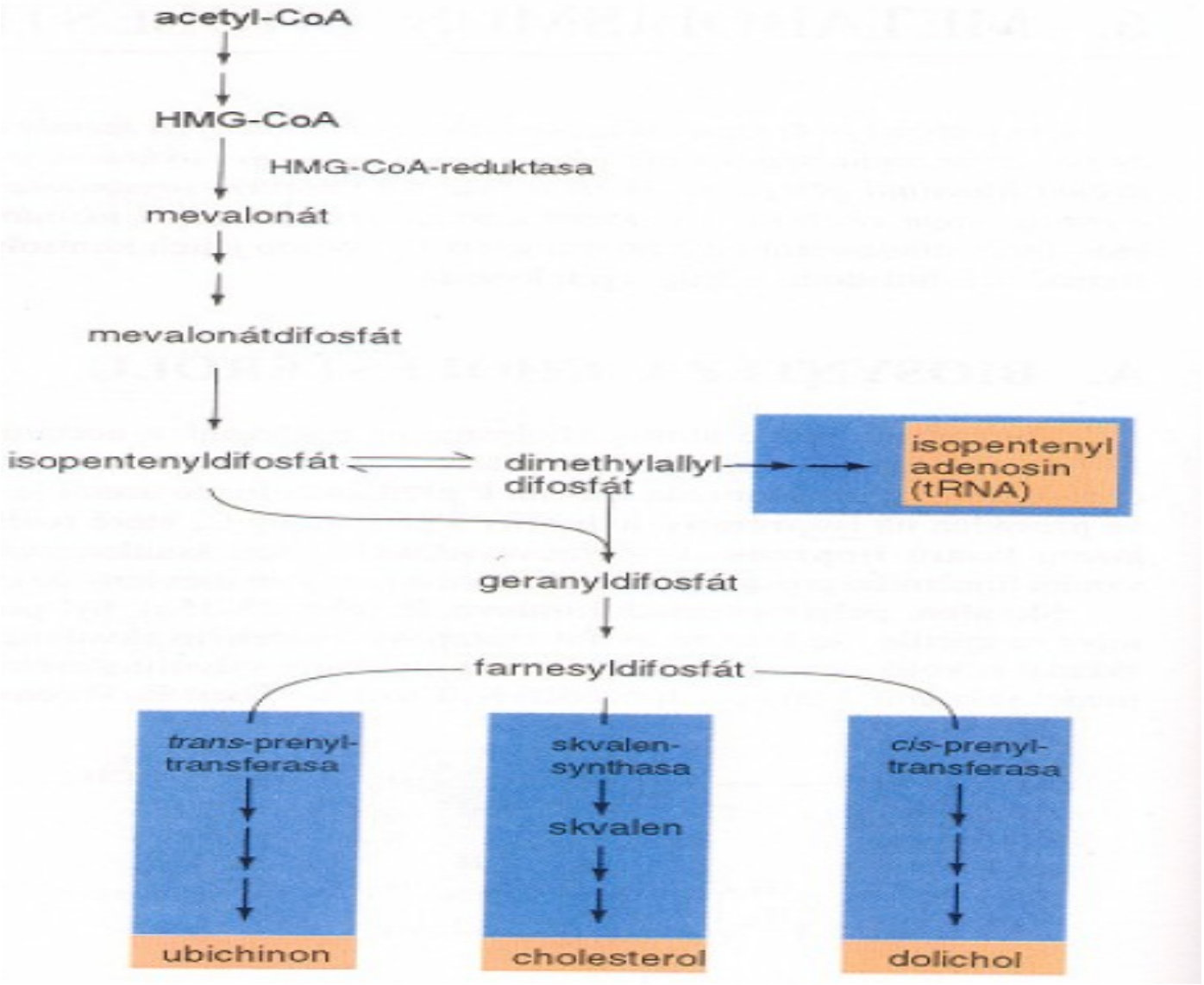


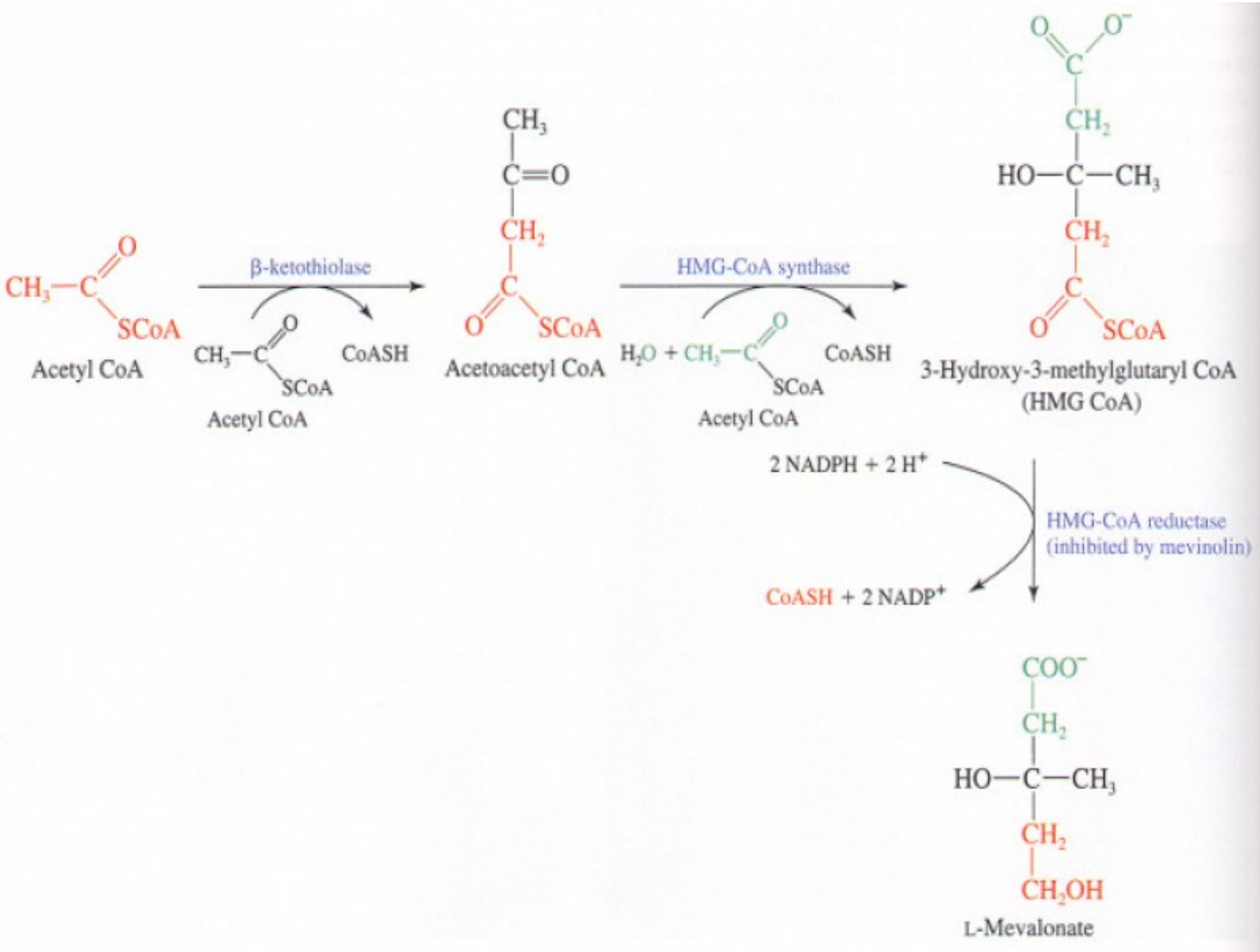
Biosyntéza cholesterolu

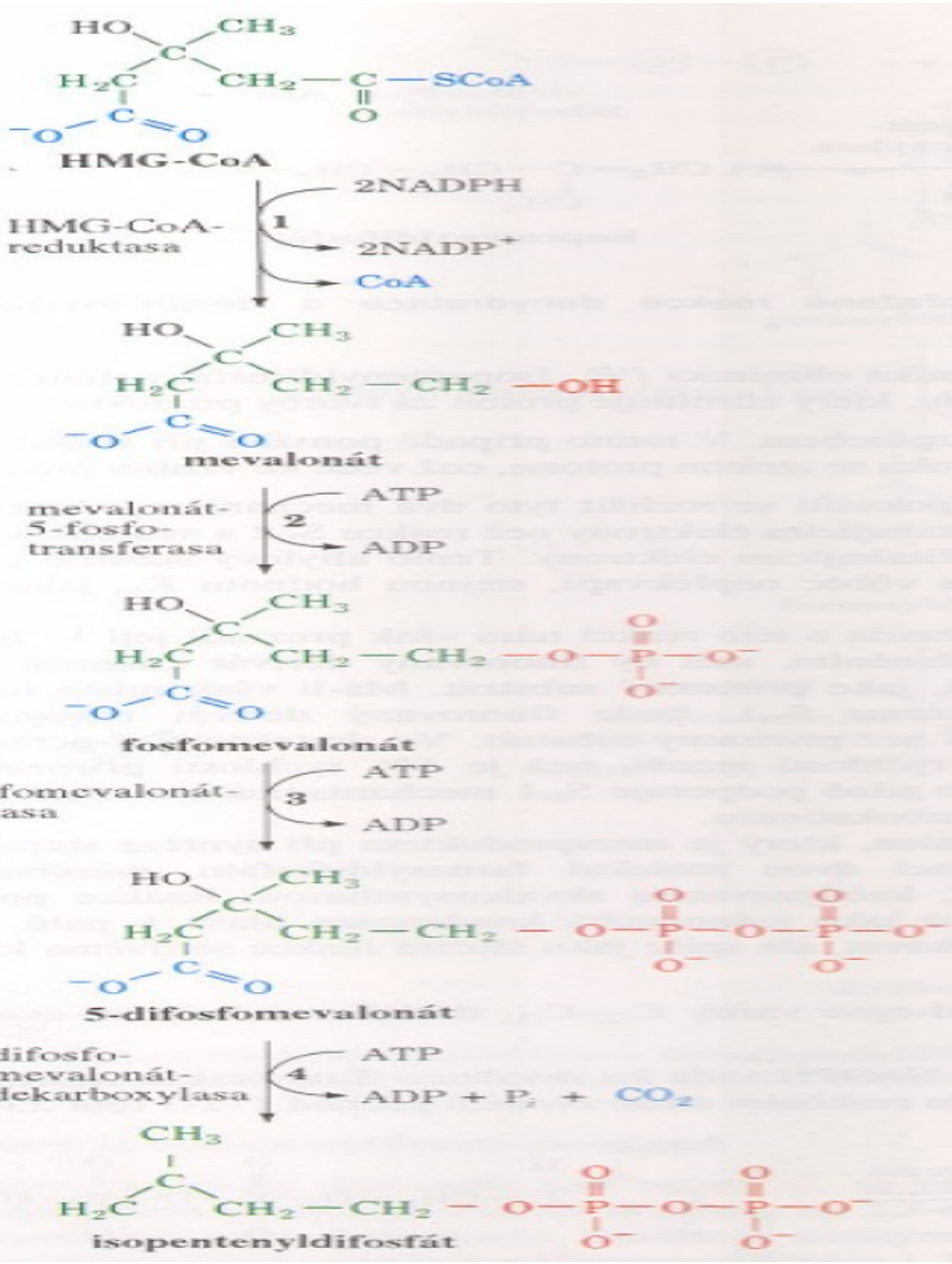


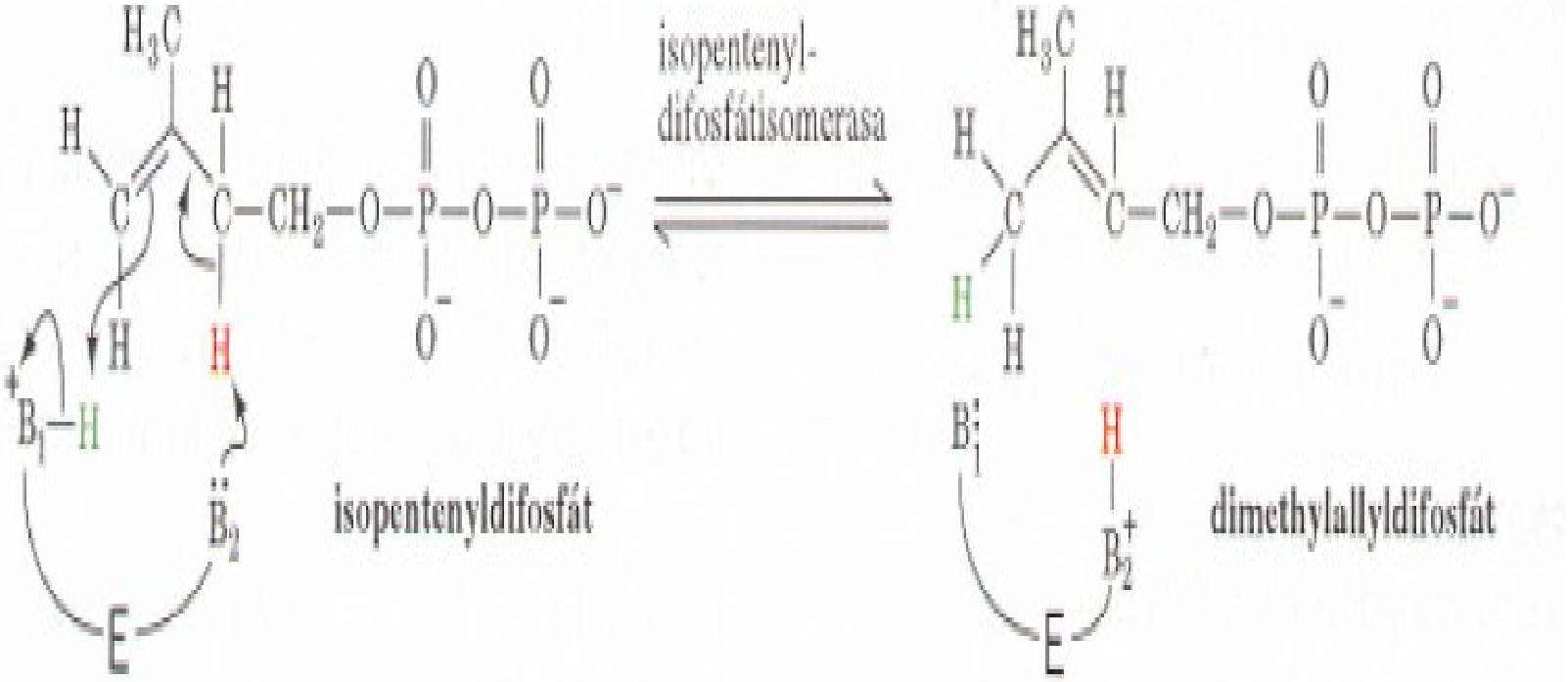
acetát → isopprenoidní intermediát → skvalen
→ produkt cyklizace → cholesterol

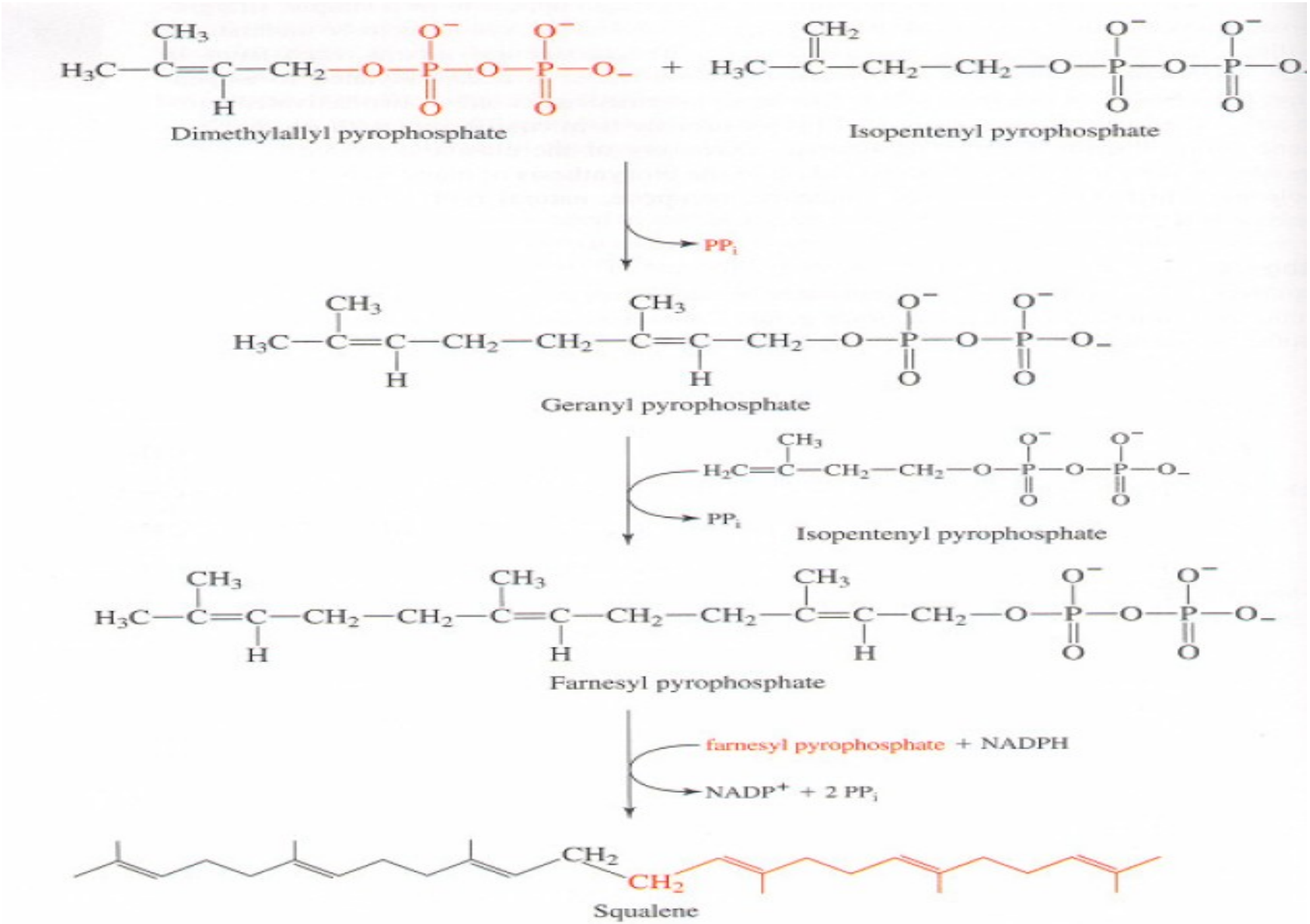
Biosyntéza cholesterolu

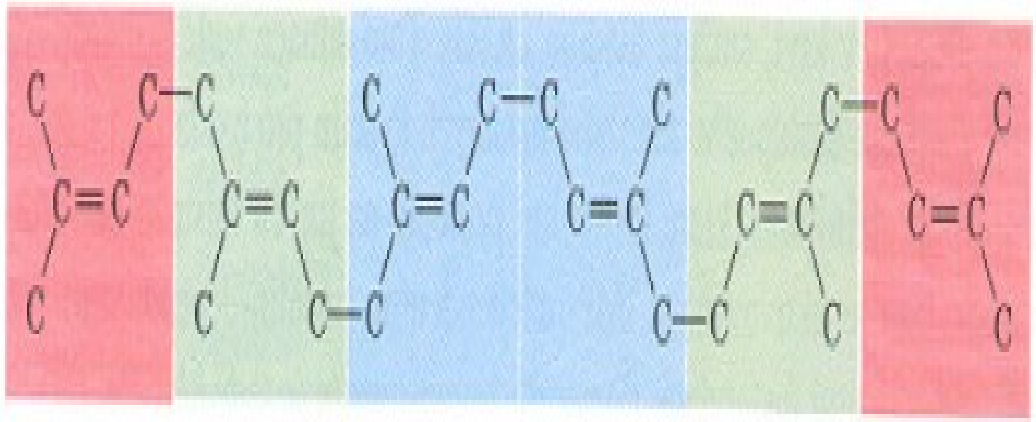


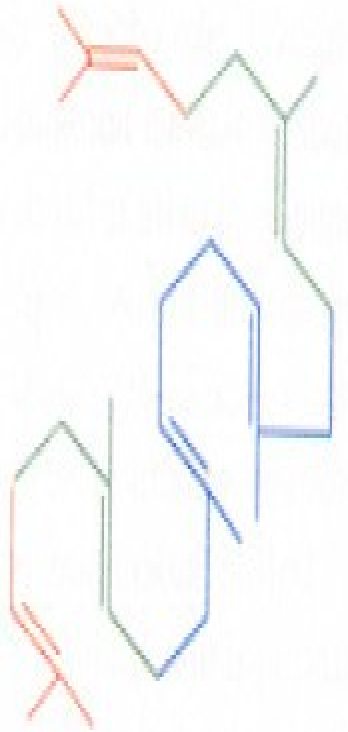

Acetyl CoA
β-ketothiolase
CoASH
Acetyl CoA
Acetoacetyl CoA
HMG-CoA synthase
CoASH
Acetyl CoA
3-Hydroxy-3-methylglutaryl CoA
(HMG CoA)
2 NADPH + 2 H+
HMG-CoA reductase
(inhibited by mevinolin)
CoASH + 2 NADP+
L-Mevalonate

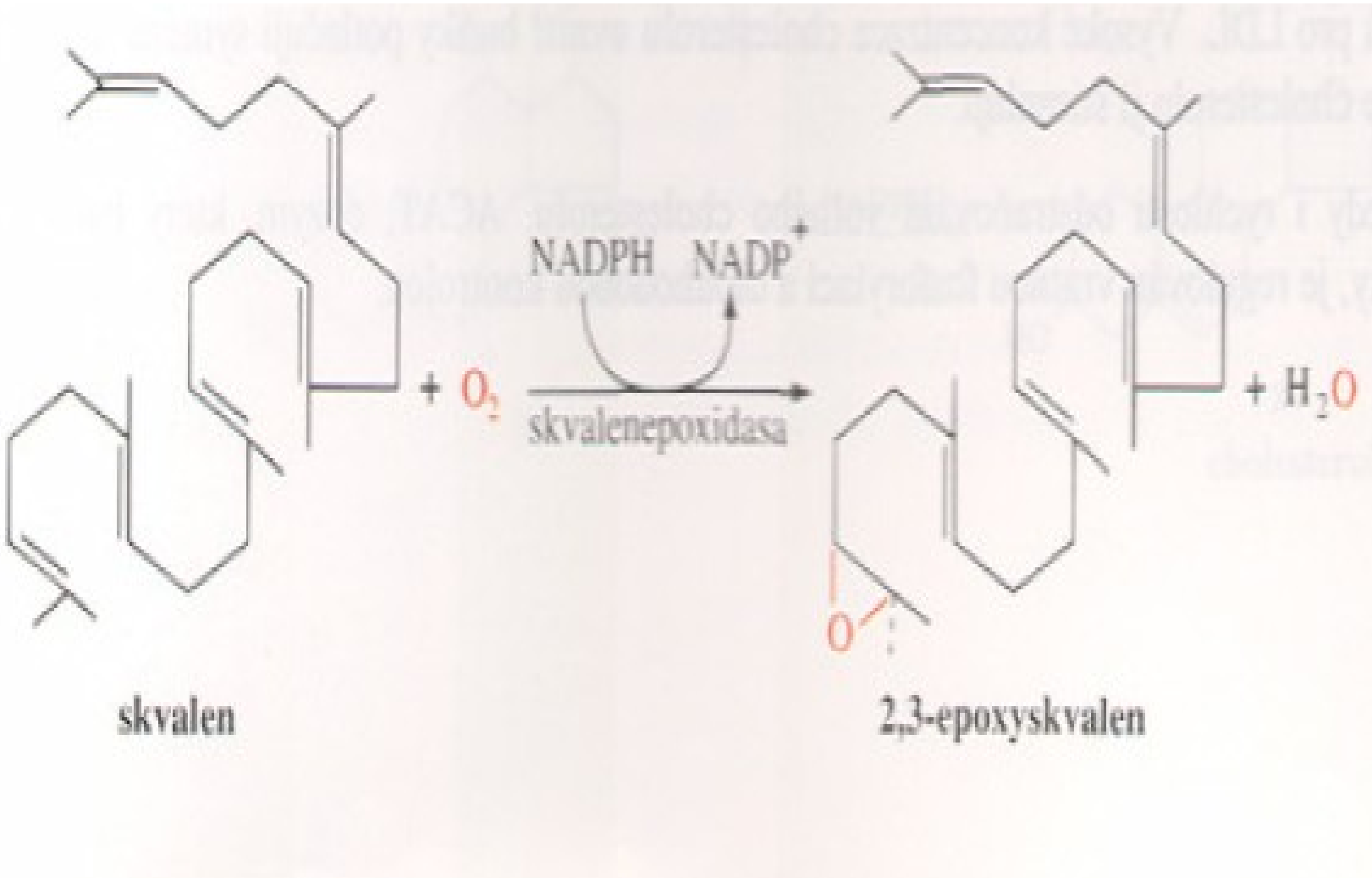

HMG-CoA
HMG-CoA-reduktasa
2NADPH
2NADP+
CoA
mevalonát
mevalonát-5-fosfo-transferasa
ATP
ADP
fosfomevalonát
fosfomevalonát-kinasa
ATP
ADP
5-difosfomevalonát
difosfo-mevalonát-dekarboxylasa
ATP
ADP + Pi + CO2
isopentenyldifosfát

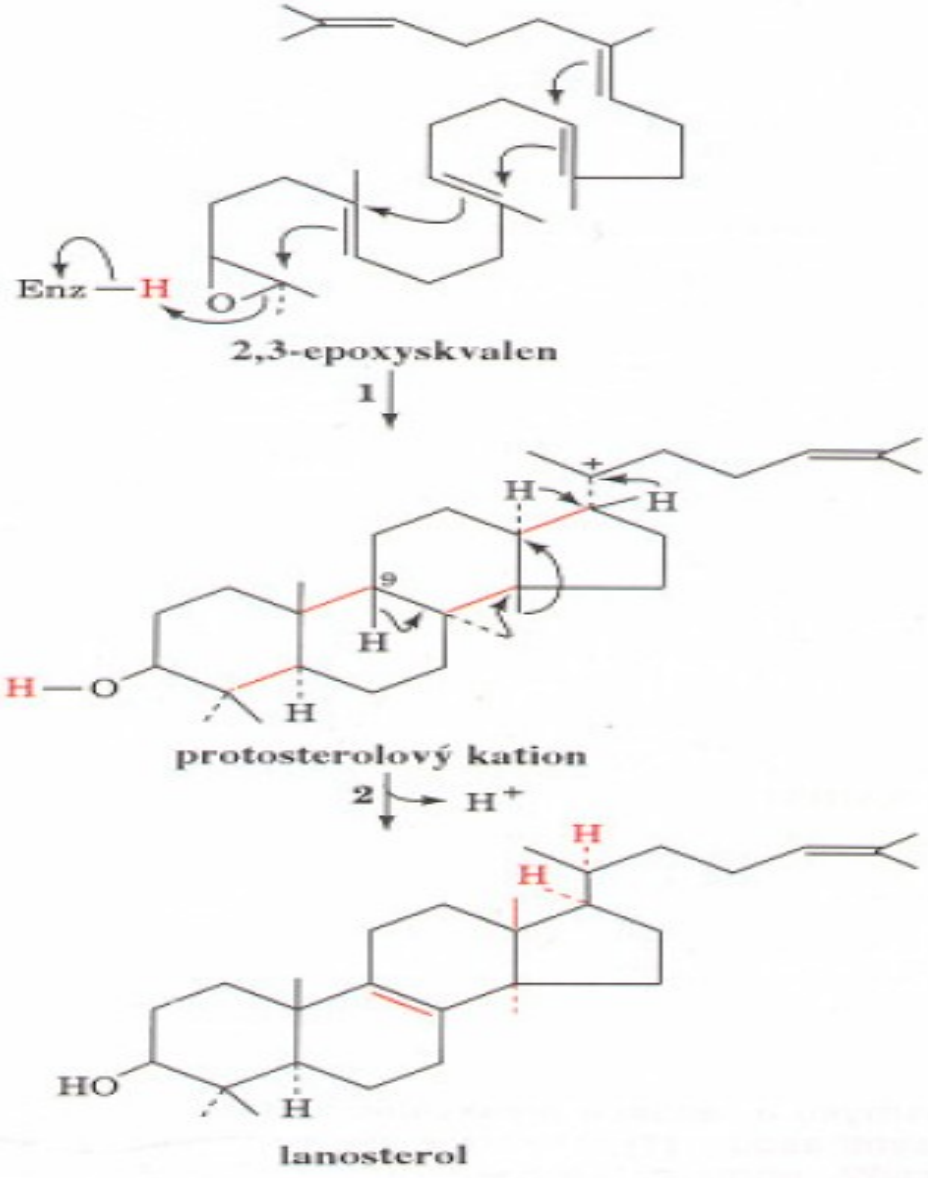

isopentenyl-
difosfátisomerasa
isopentenyldifosfát
dimethylallyldifosfát

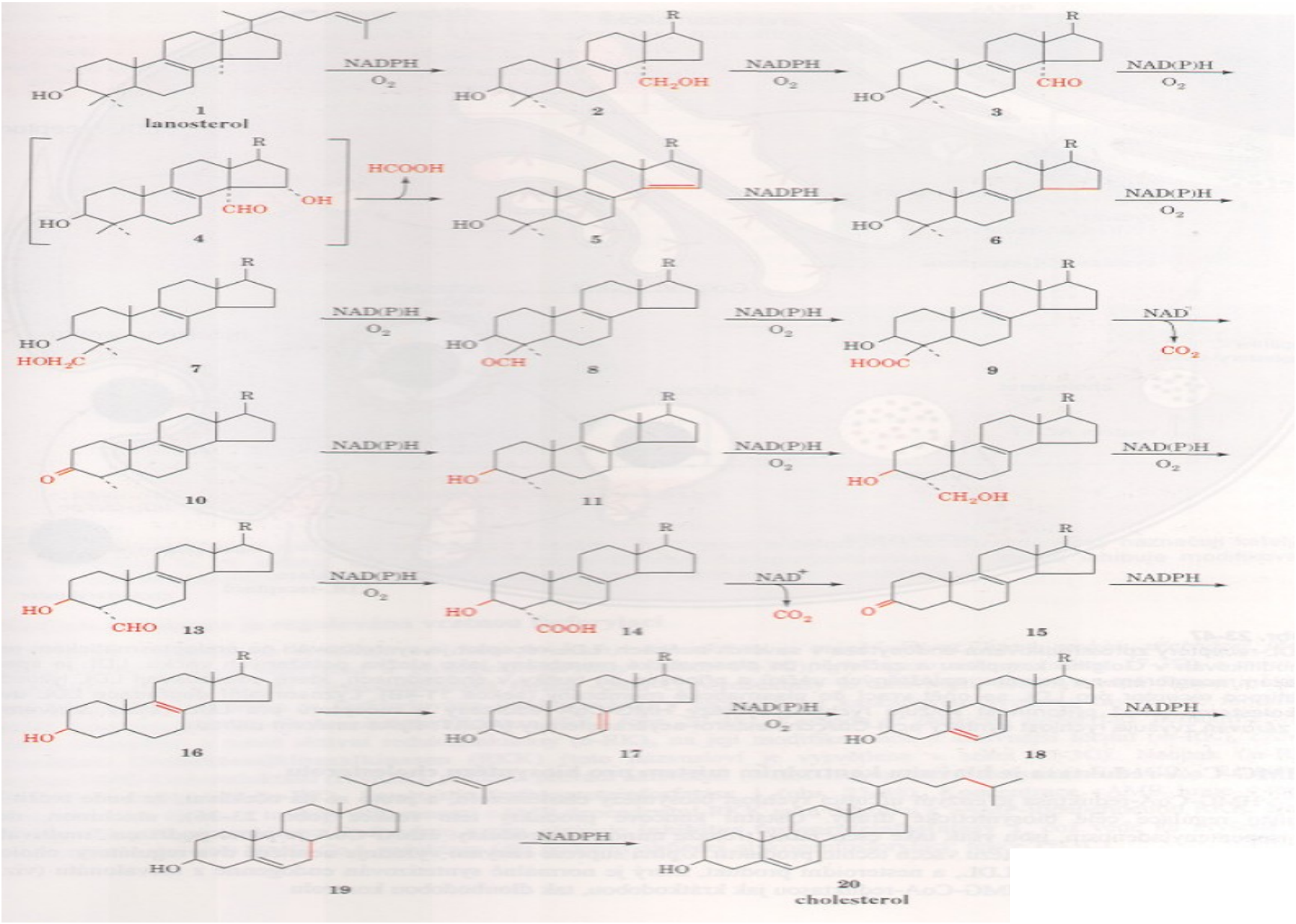

Dimethylallyl pyrophosphate
+
Isopentenyl pyrophosphate
PPi
Geranyl pyrophosphate
PPi
Isopentenyl pyrophosphate
Farnesyl pyrophosphate
farnesyl pyrophosphate + NADPH
NADP+ + 2 PPi
Squalene





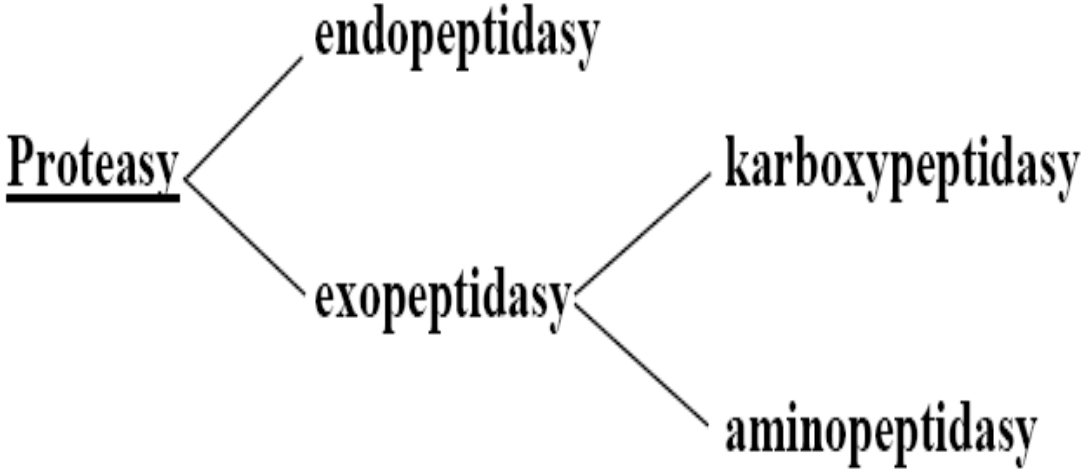

NADPH
NADP+
+ O2
skvalenepoxidasa
+ H2O
O
skvalen
2,3-epoxyskvalen


Enz—H
O
2,3-epoxyskvalen
1
+
H
H
9
H
H—O
H
protosterolový kation
2
H+
H
H
HO
H
lanosterol


NADPH
O2
HCOOH
NAD(P)H
NAD+
CO2
1
lanosterol
2
3
4
5
6
7
8
9
10
11
13
14
15
16
17
18
19
20
cholesterol

METABOLISMUS BÍLKOVIN

Proteolýza



Proteasy -

- serinové
- cysteinové
- metaloproteasy
- kyselé - aspartátové

1. Žaludeční proteasy

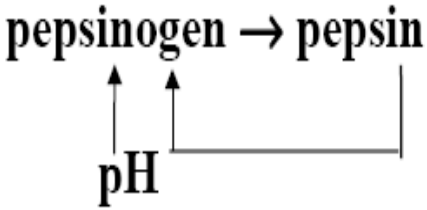
- pepsin
- chymosin (renin, sýřidlo)

2. Pankreatické proteasy

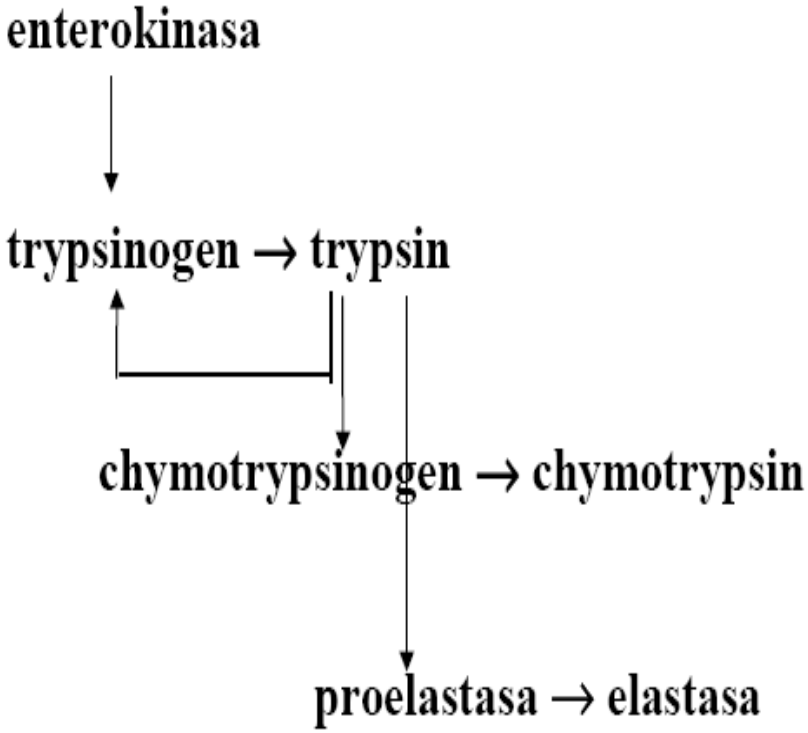
- trypsin
- chymotrypsin
- elastasa
- karboxypeptidasa A,B

Aktivace zymogenů

žaludek



slinivka břišní



3. Proteasy střevní šťávy

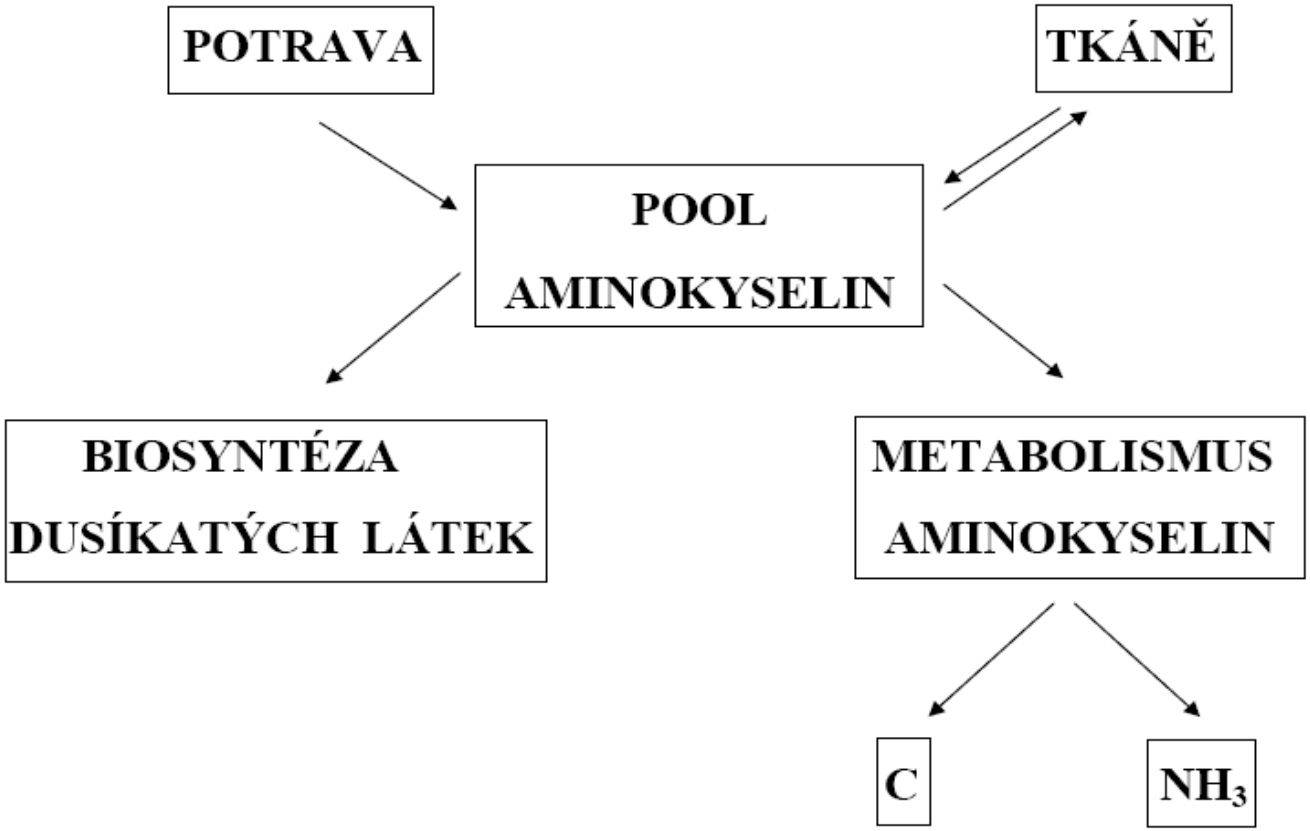
- aminopeptidasy
- dipeptidasy

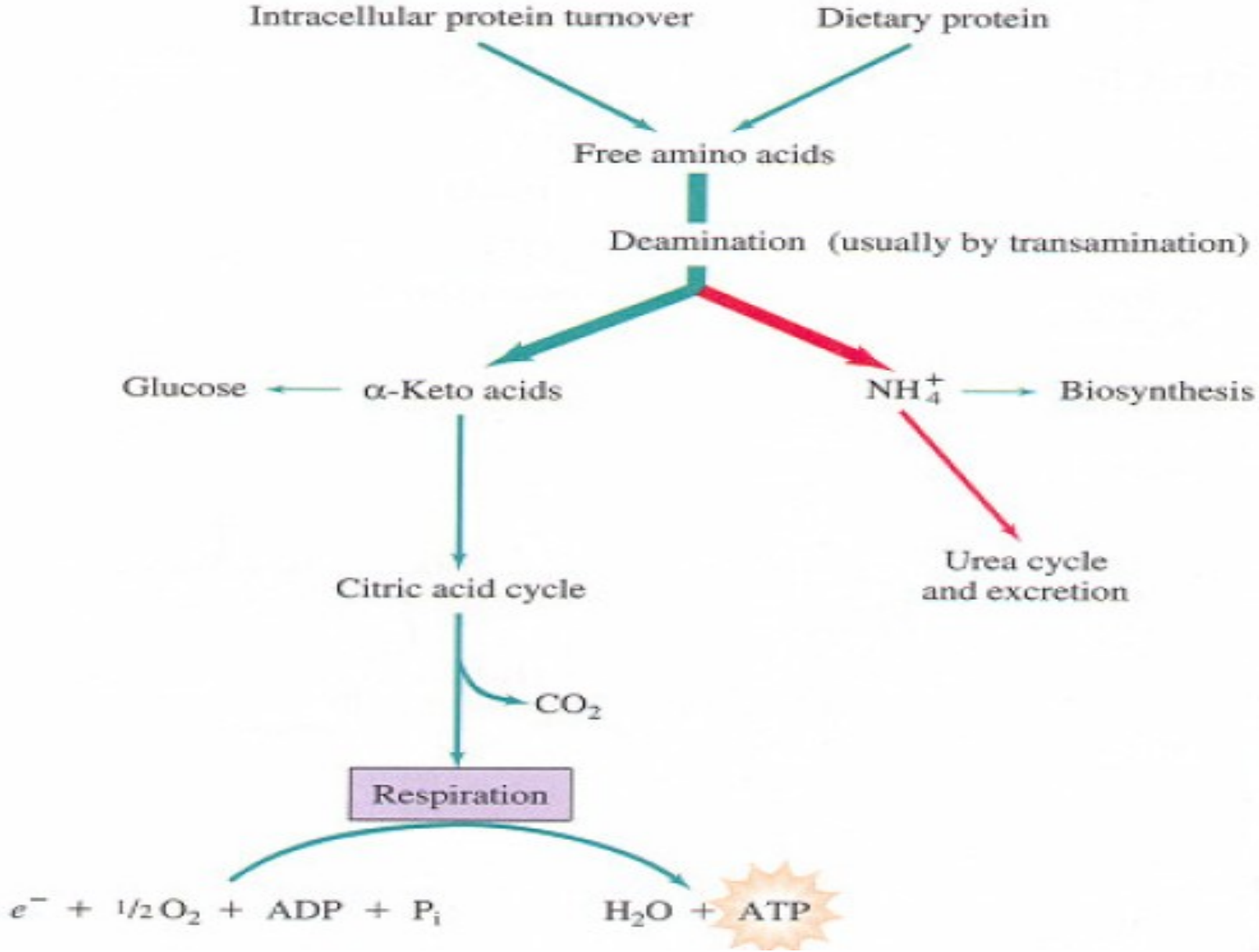
4. Buněčné proteasy

- živočichové - kathepsiny B, D, L, H, M, S a T
- rostliny - papain
- bakterie - subtilisin, pronasa

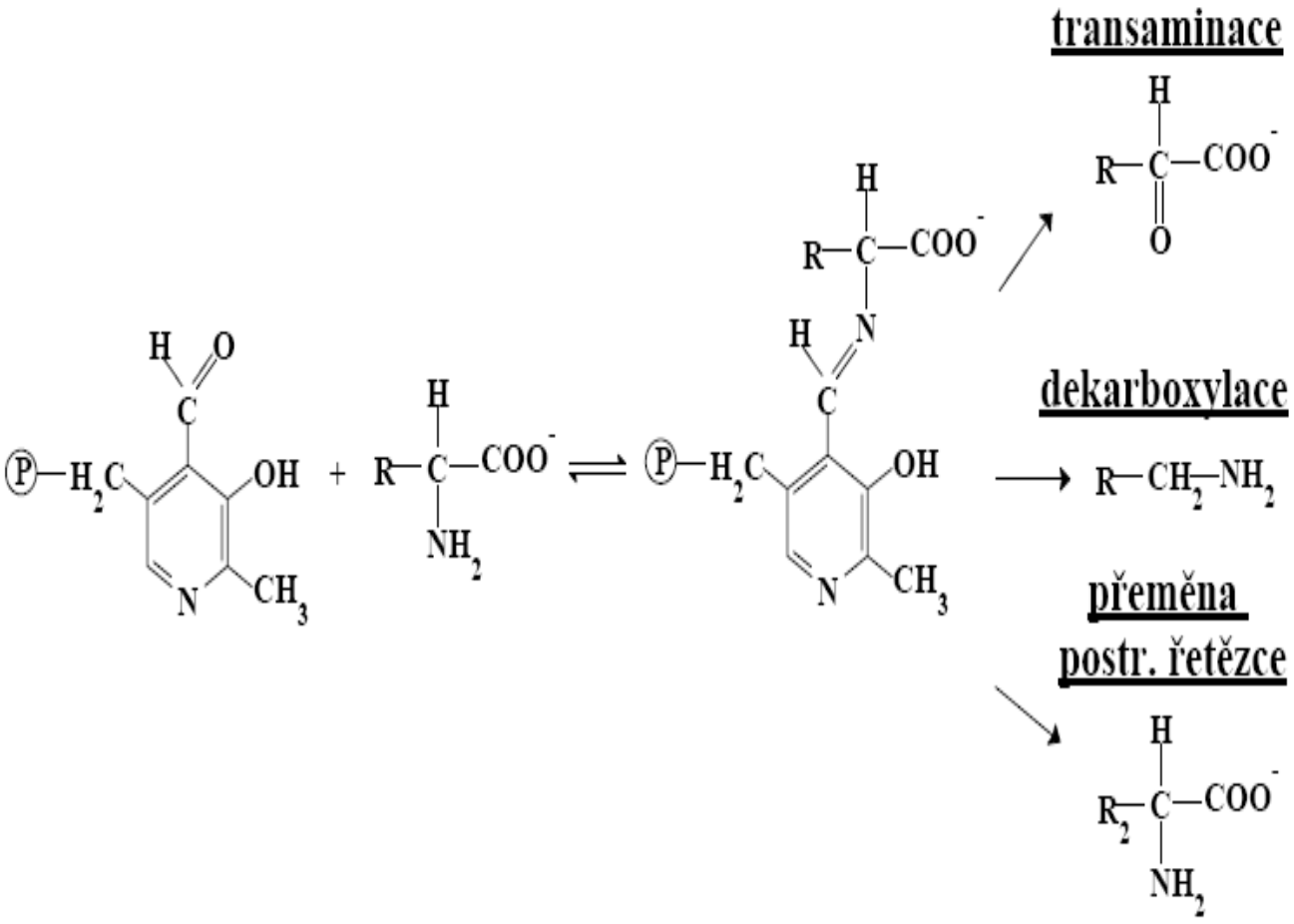
- Proteasy s jinou funkcí
- enterokinasa - aktivace zymogenů
- trombin - sráženi krve

Hotovost - pool aminokyselin




Intracellular protein turnover
Dietary protein
Free amino acids
Deamination (usually by transamination)
Glucose
α-Keto acids
NH_4^+
Biosynthesis
Urea cycle and excretion
Citric acid cycle
CO_2
Respiration
$e^- + {}^1/_2 O_2 + ADP + P_i$
$H_2O + ATP$

METABOLISMUS AMINOKYSELIN



Transaminace

$$\text{aminokyselina}_1 + \alpha\text{-oxokyselina}_1 \leftrightarrow \text{aminokyselina}_2 + \alpha\text{-oxokyselina}_2$$

Oxidační deaminace

savci

$$\text{glutamát} + NAD^+ + H_2O \leftrightarrow \text{2-oxoglutarát} + NH_3 + NADH + H^+$$

vejcorodí

$$\text{aminokyselina} + FAD + H_2O \leftrightarrow \alpha\text{-oxokyselina} + NH_3 + FADH_2$$

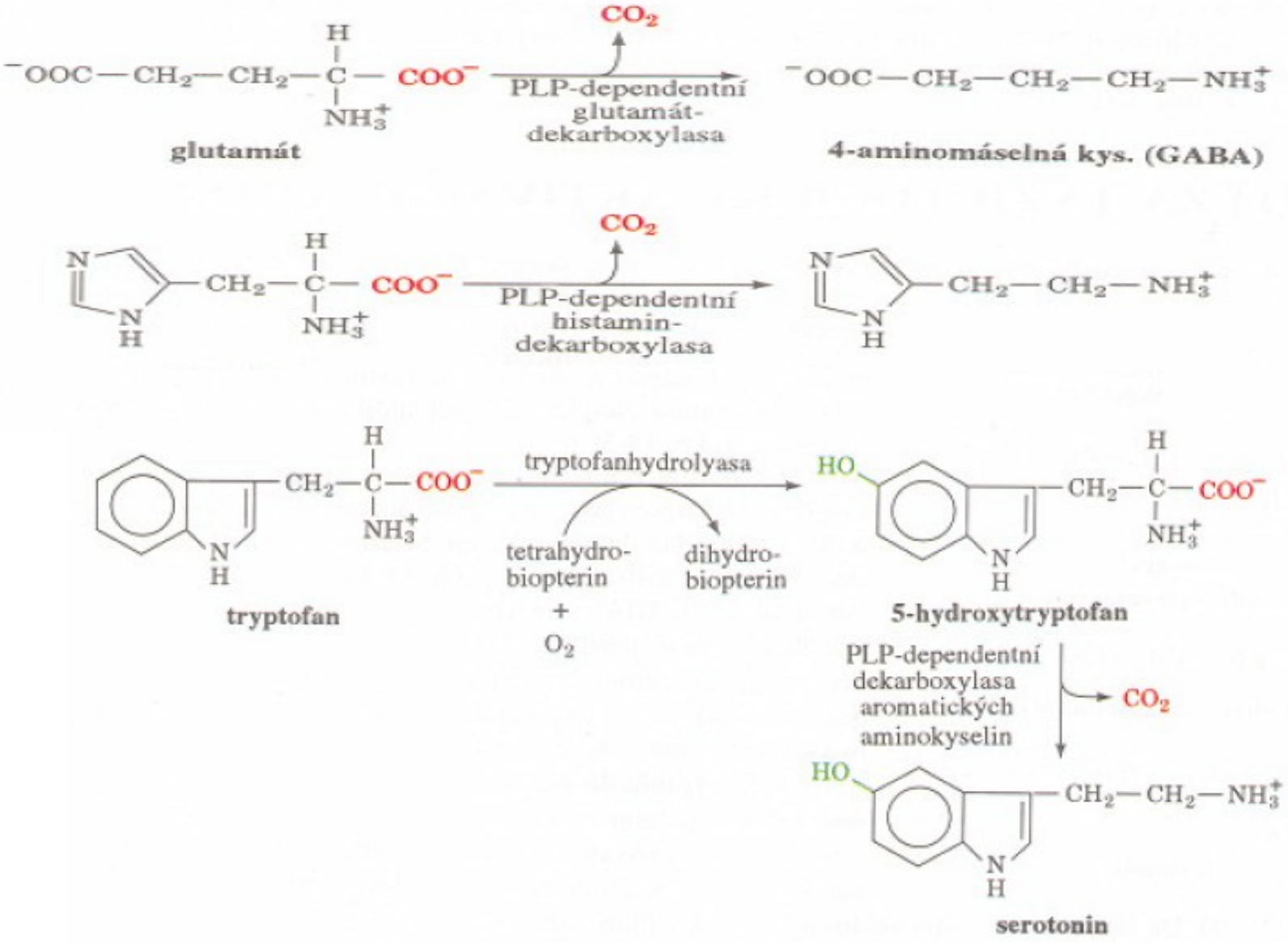
$$FADH_2 + O_2 \leftrightarrow FAD + H_2O_2$$

Dekarboxylace

aminokyselina ↔ amin + CO_2

Biogenní aminy

cystein	cystamin	CoA
k.asparagová	β alanin	„
tyrosin	tyramin	tkáňový hormon
DOPA	dopamin	„
histidin	histamin	„
hydroxytryptofan	serotonin	„
k.glutamová	k.γ-aminomáselná	neuromodulátor
serin	ethanolamin	fosfolipidy
methionin	spermin, spermidin	sperma


CO2
PLP-dependentní glutamát-dekarboxylasa
glutamát
4-aminomáselná kys. (GABA)
CO2
PLP-dependentní histamin-dekarboxylasa
tryptofanhydrolyasa
tetrahydro-biopterin
+
O2
dihydro-biopterin
tryptofan
5-hydroxytryptofan
PLP-dependentní dekarboxylasa aromatických aminokyselin
CO2
serotonin

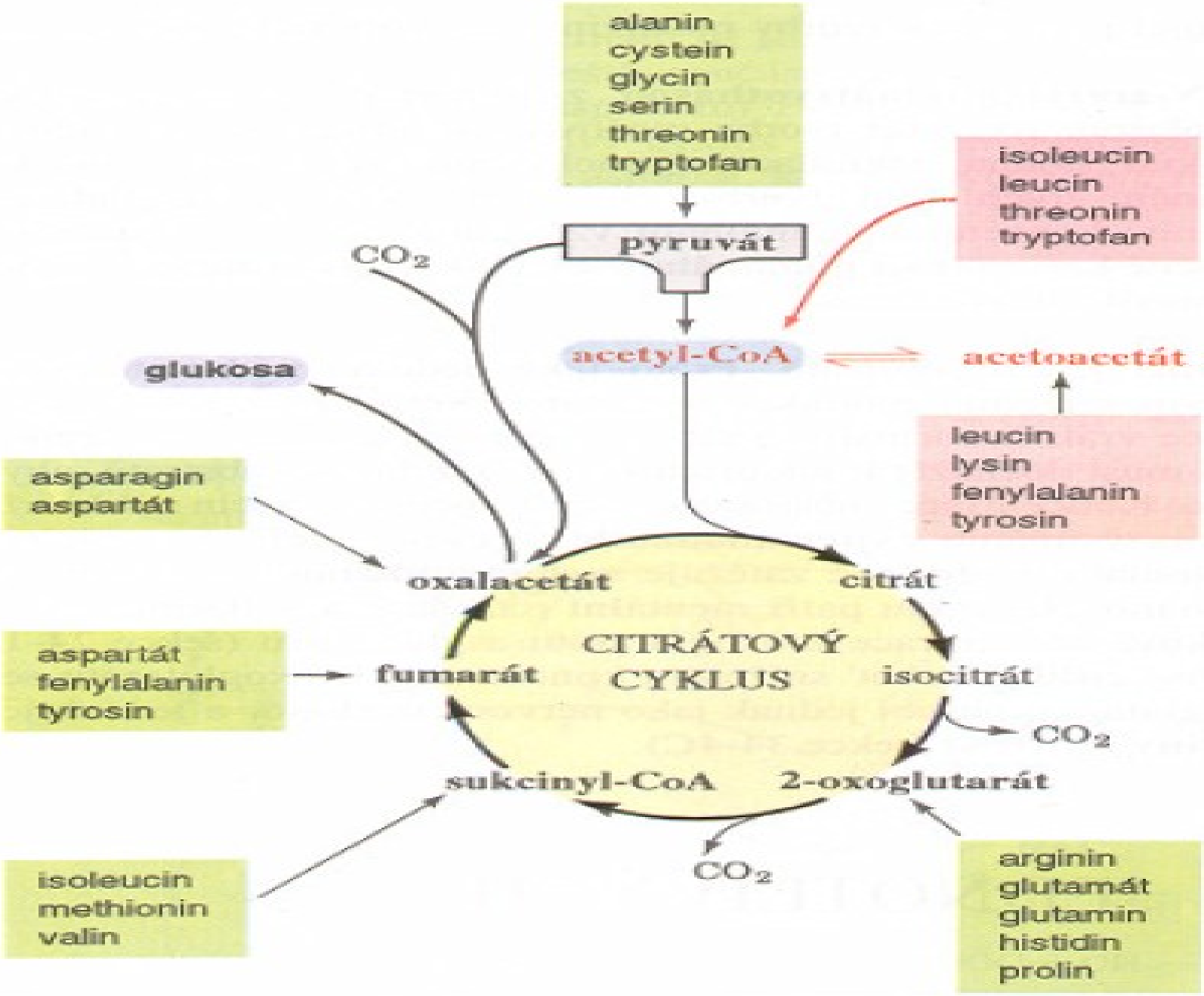
Degradace uhlíkových koster aminokyselin

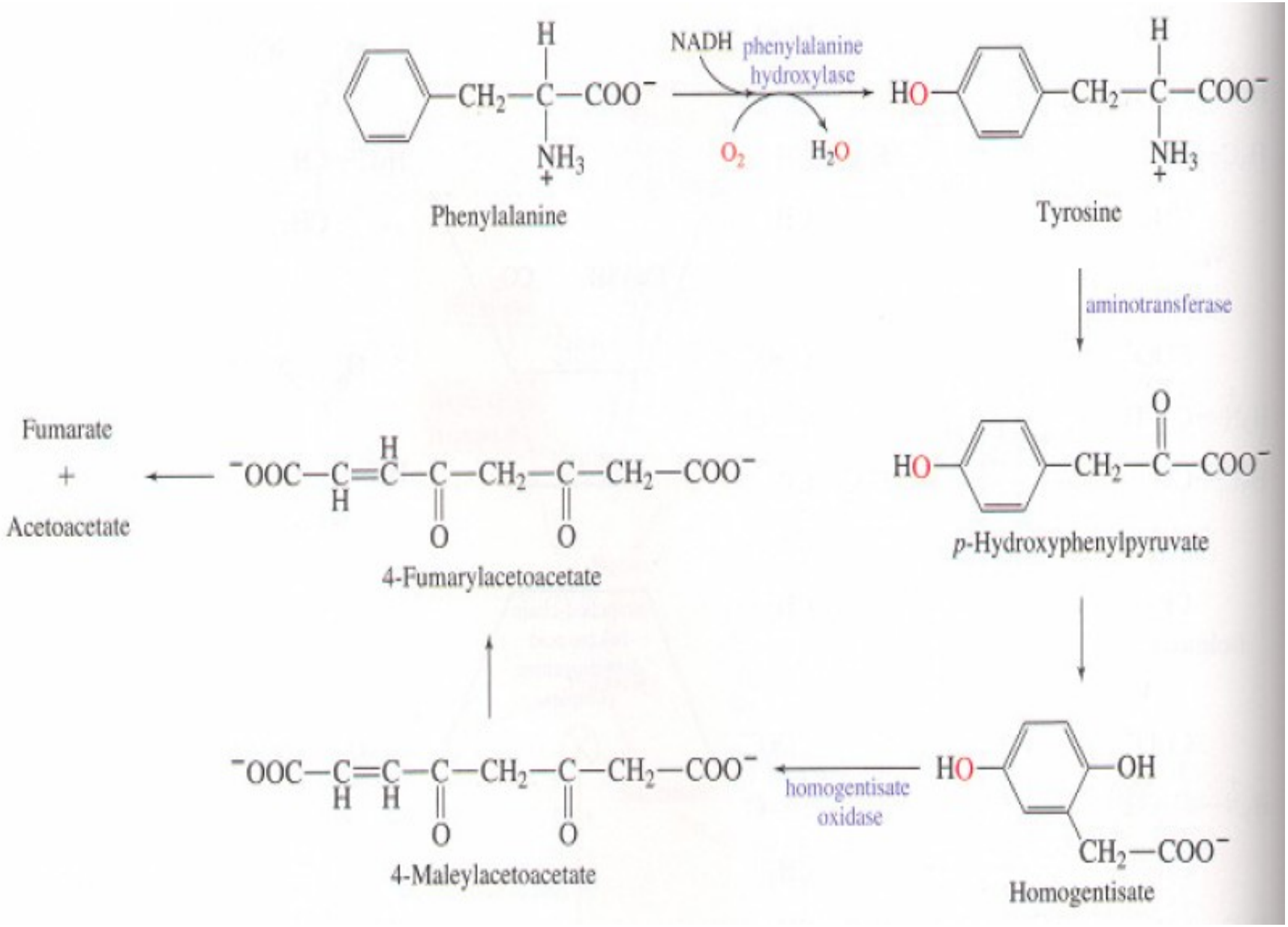
1. Glukogenní aminokyseliny - prekurzory sacharidů

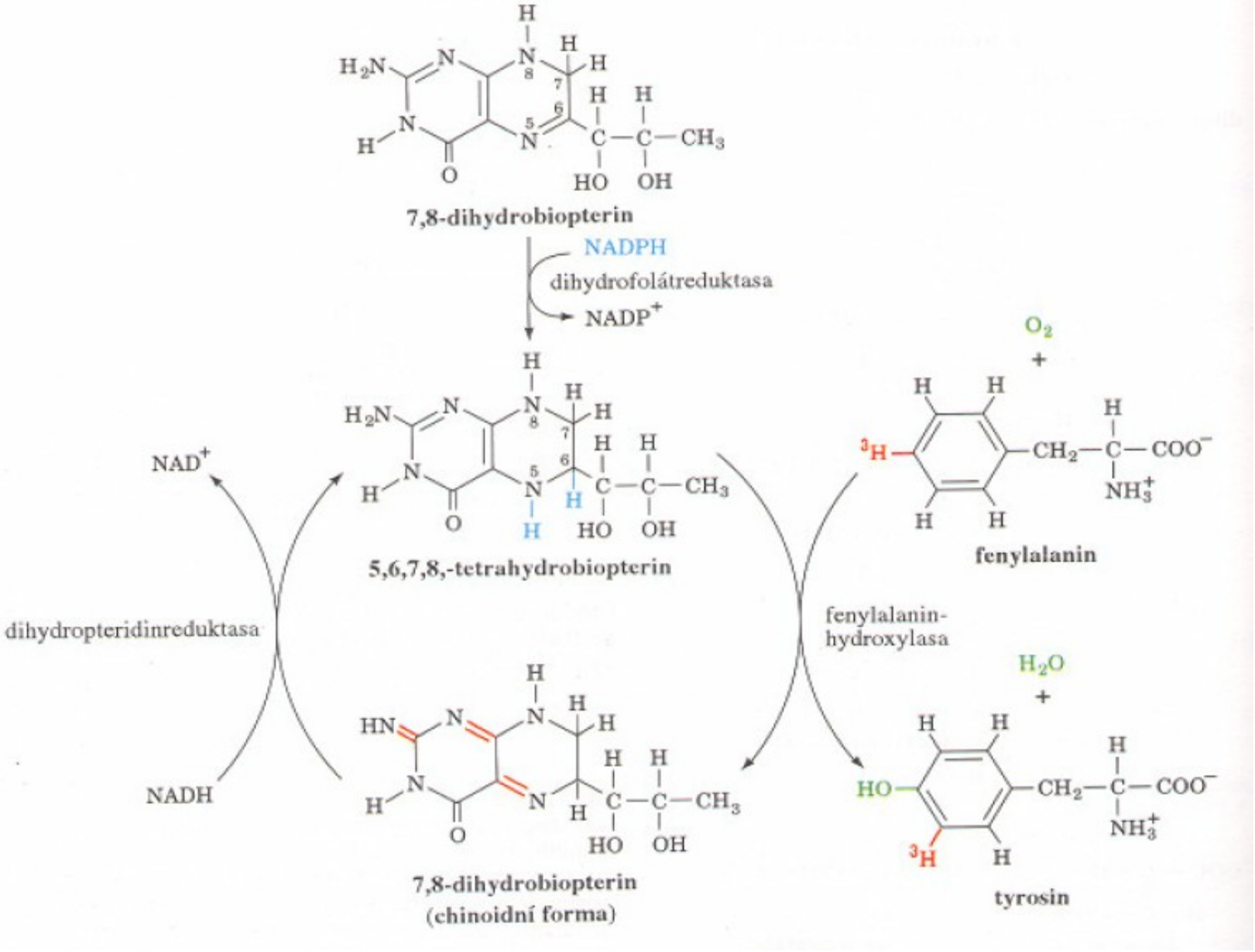
pyruvát	-	Ser, Ala, Cys, Gly, Thr, Met, Trp
2-oxoglutarát	-	Glu, Gln, Arg, Pro, His
oxalacetát	-	Asp, Asn
fumarát	-	Phe, Tyr
sukcinyl-CoA	-	Val, Ile, Met, Thr

2. Ketogenní aminokyseliny - prekurzory mastných kyselin

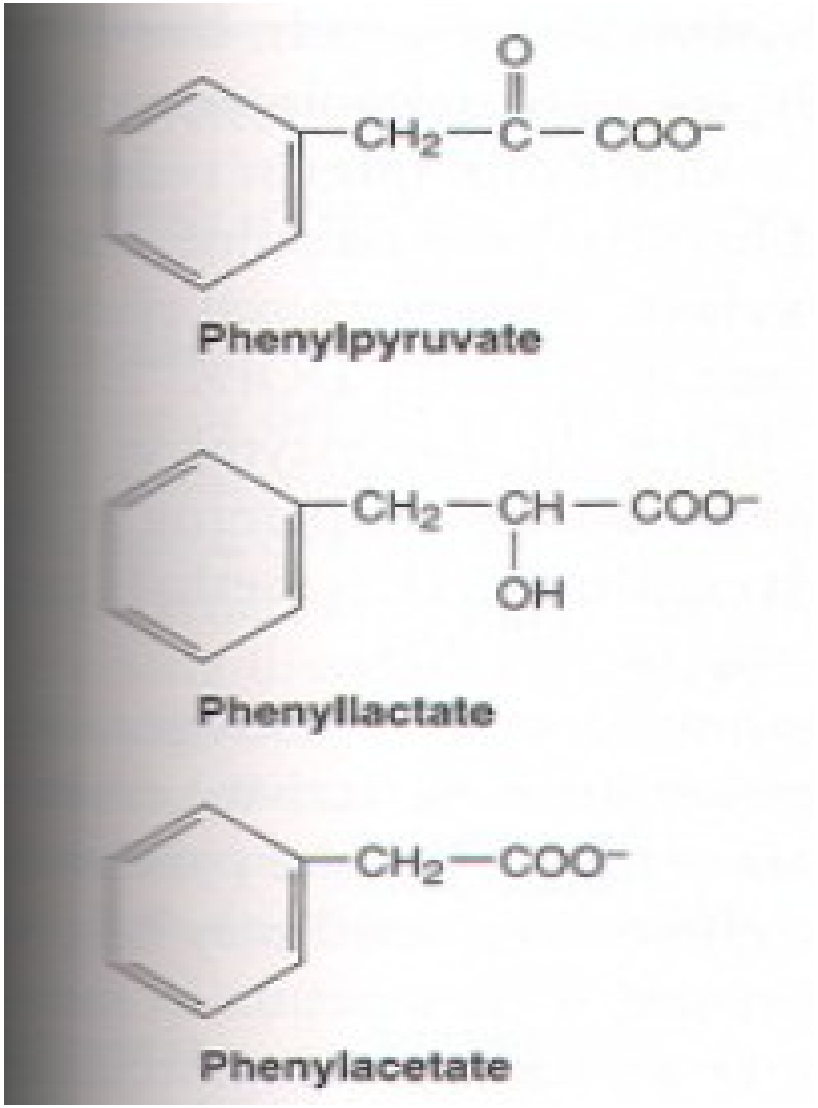
acetoacetát	-	Leu, Phe, Tyr, Lys, Trp
acetyl-CoA	-	Leu, Ile, Trp


alanin
cystein
glycin
serin
threonin
tryptofan
isoleucin
leucin
threonin
tryptofan
pyruvát
CO_2
acetyl-CoA
acetoacetát
glukosa
leucin
lysin
fenylalanin
tyrosin
asparagin
aspartát
oxalacetát
citrát
aspartát
fenylalanin
tyrosin
CITRÁTOVÝ CYKLUS
fumarát
isocitrát
CO_2
sukcinyl-CoA
2-oxoglutarát
CO_2
isoleucin
methionin
valin
arginin
glutamát
glutamin
histidin
prolin


NADH
phenylalanine hydroxylase
O_2
H_2O
Phenylalanine
Tyrosine
aminotransferase
p-Hydroxyphenylpyruvate
Homogentisate
homogentisate oxidase
4-Maleylacetoacetate
4-Fumarylacetoacetate
Fumarate
+
Acetoacetate


7,8-dihydrobiopterin
NADPH
dihydrofolátreduktasa
NADP+
O2
+
5,6,7,8,-tetrahydrobiopterin
fenylalanin
NAD+
dihydropteridinreduktasa
fenylalanin-
hydroxylasa
H2O
+
NADH
7,8-dihydrobiopterin
(chinoidní forma)
tyrosin

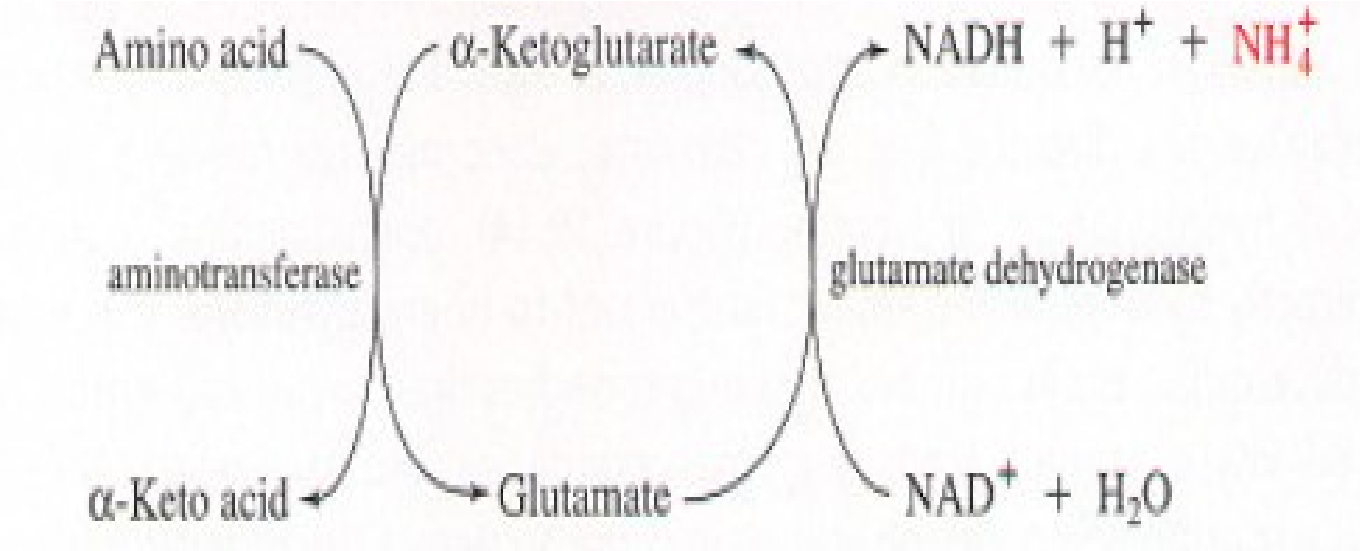
Fenylketonurie



Metabolismus amoniaku

NH_3 — biosyntéza dusíkatých látek - AMK, puriny, pyrimidiny

NH_3 — detoxikace



Metabolismus amoniaku

NH_3 → biosyntéza dusíkatých látek - AMK, puriny, pyrimidiny

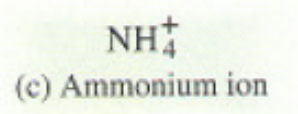
NH_3 → detoxikace

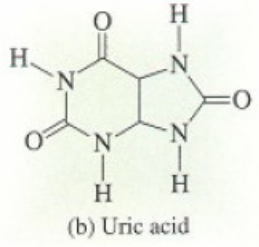
Živočichové - amonotelní - NH_3 - vodní živočichové

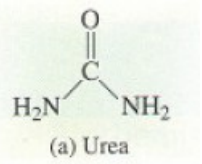
- urikotelní - k.močová - vejcorodí

- ureotelní - močovina - placentálové

Rostliny - nevylučují NH_3

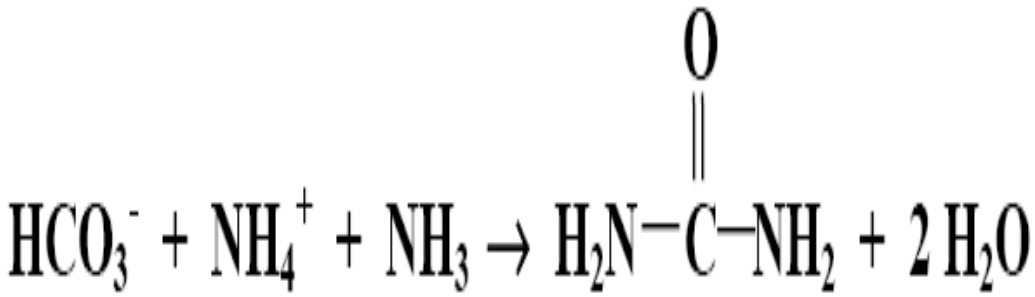


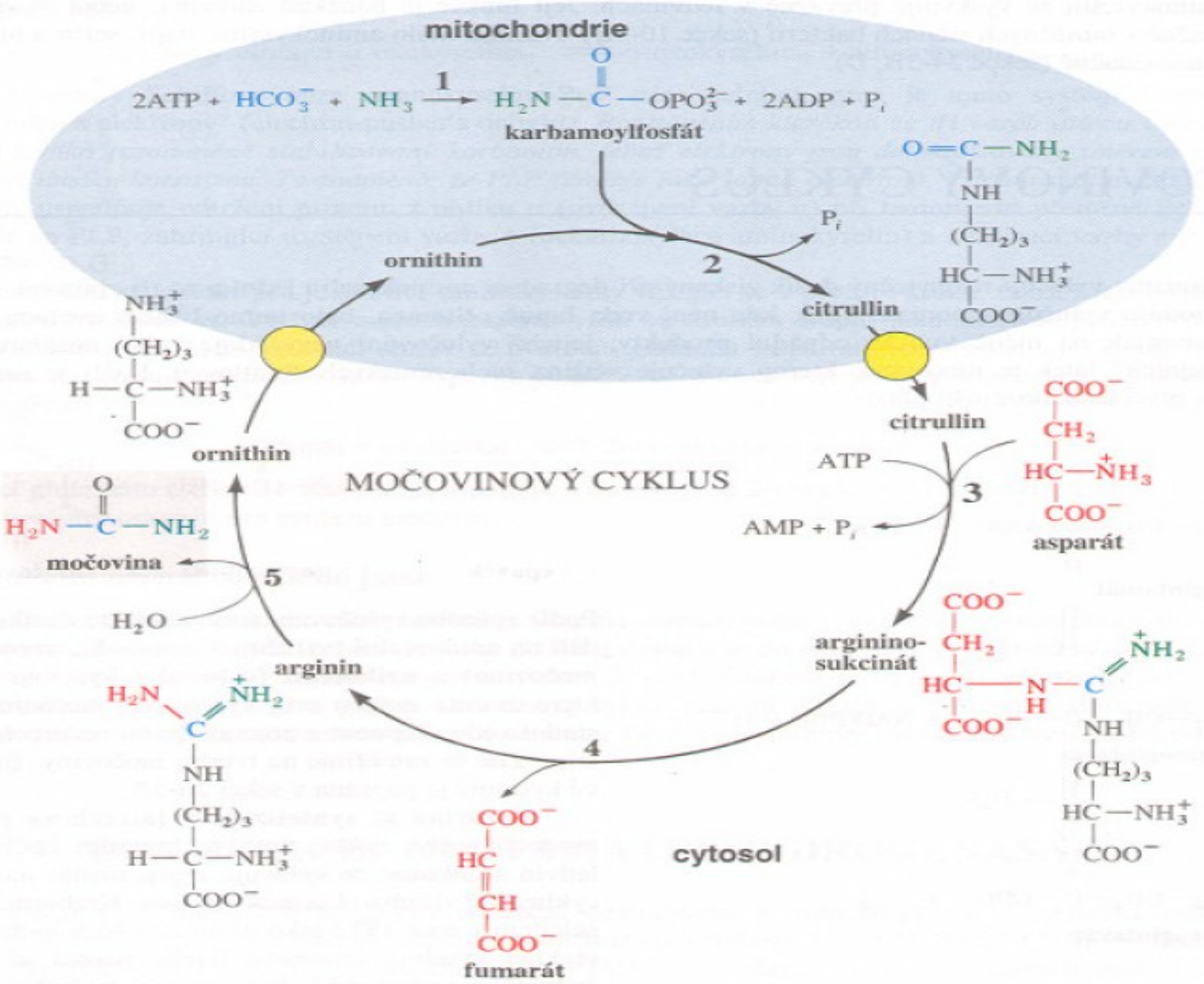


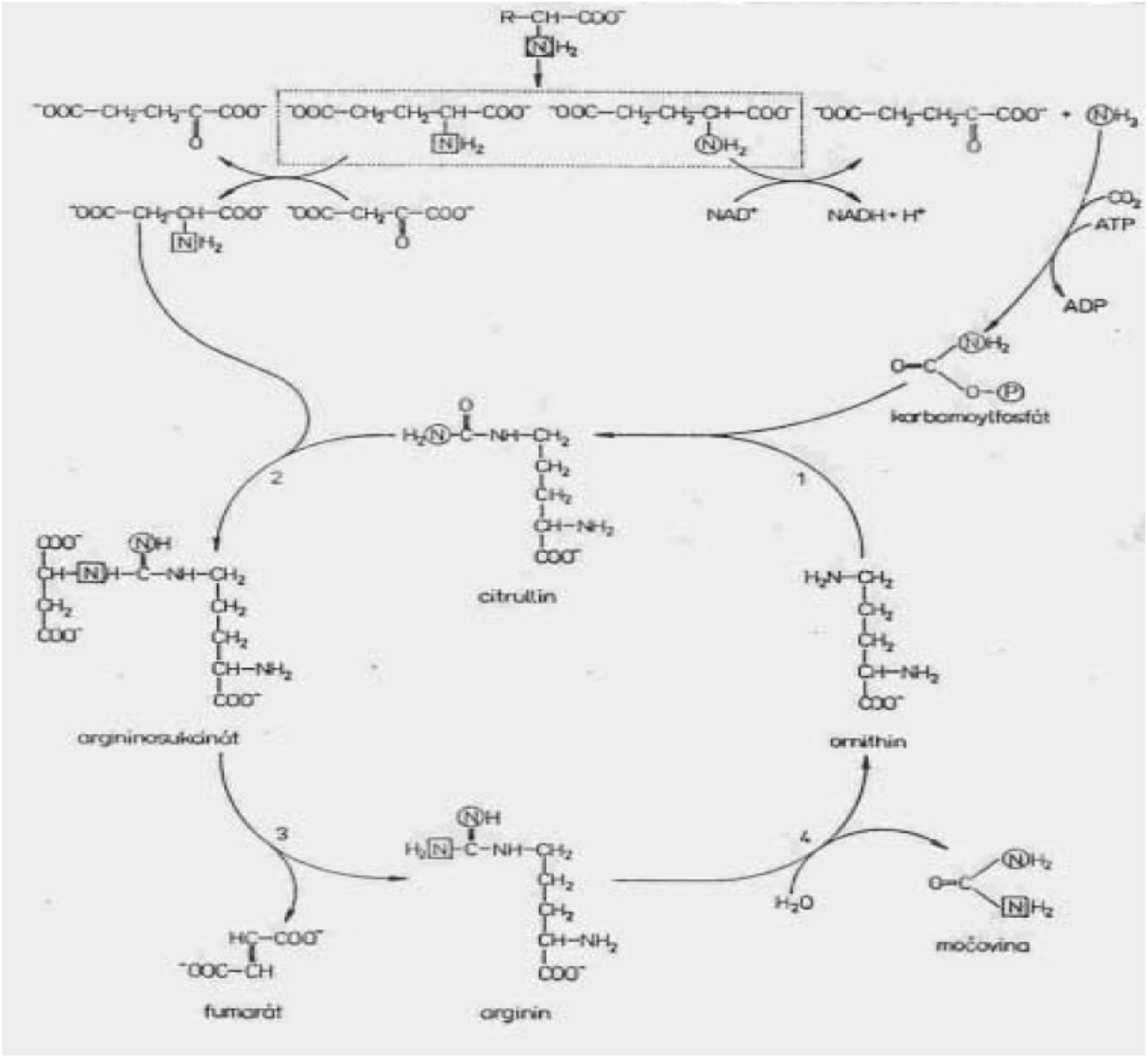


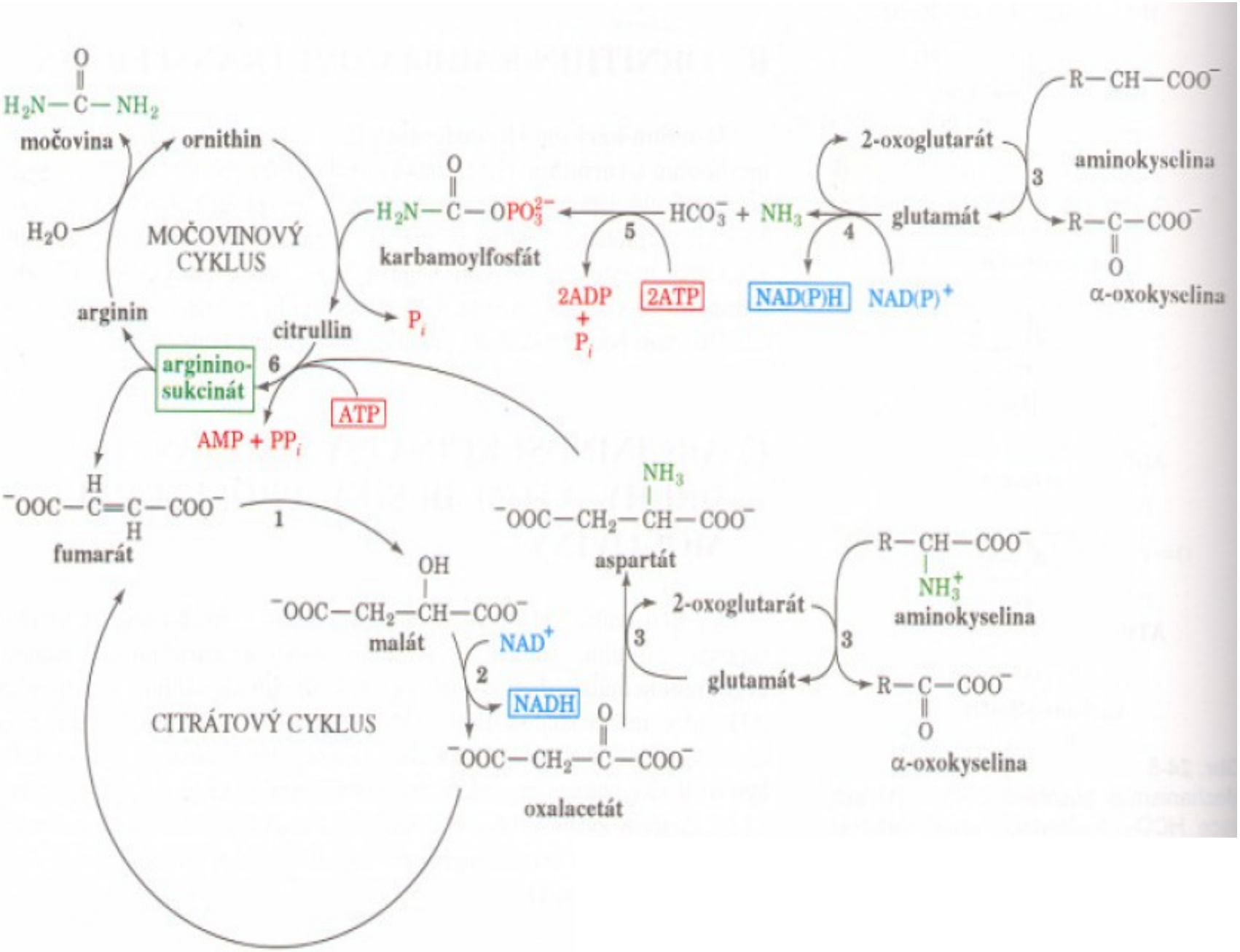
Tvorba močoviny - ornitinový cyklus

H. KREBS, K. HENSELEIT - 1932

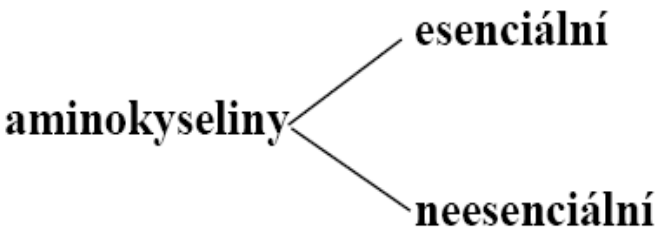



mitochondrie
2ATP + HCO3− + NH3
1
karbamoylfosfát
2ADP + Pi
ornithin
Pi
2
citrullin
ornithin
MOČOVINOVÝ CYKLUS
citrullin
ATP
AMP + Pi
3
asparát
močovina
5
H2O
arginin
arginino-
sukcinát
4
fumarát
cytosol

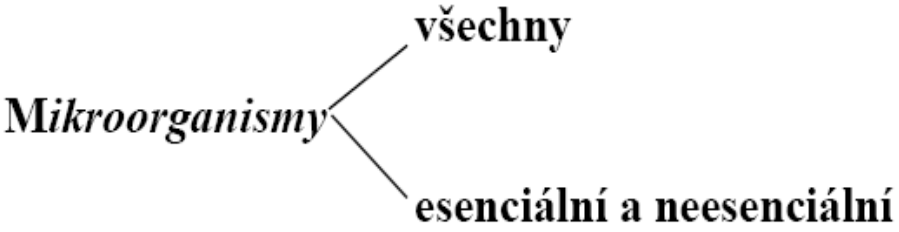

NAD+
NADH + H+
CO2
ATP
ADP
karbamoyltrasfát
citrulin
ornithin
argininosukcinát
arginin
fumarát
močovina
H2O
1
2
3
4


močovina
ornithin
H_2O
MOČOVINOVÝ CYKLUS
arginin
citrullin
P_i
arginino-sukcinát
6
ATP
AMP + PP_i
karbamoylfosfát
5
2ADP + P_i
2ATP
HCO_3^- + NH_3
4
NAD(P)H
$NAD(P)^+$
glutamát
2-oxoglutarát
3
aminokyselina
α-oxokyselina
fumarát
1
malát
NAD+
2
NADH
oxalacetát
aspartát
NH_3
3
2-oxoglutarát
glutamát
aminokyselina
α-oxokyselina
CITRÁTOVÝ CYKLUS

Biosyntéza aminokyselin

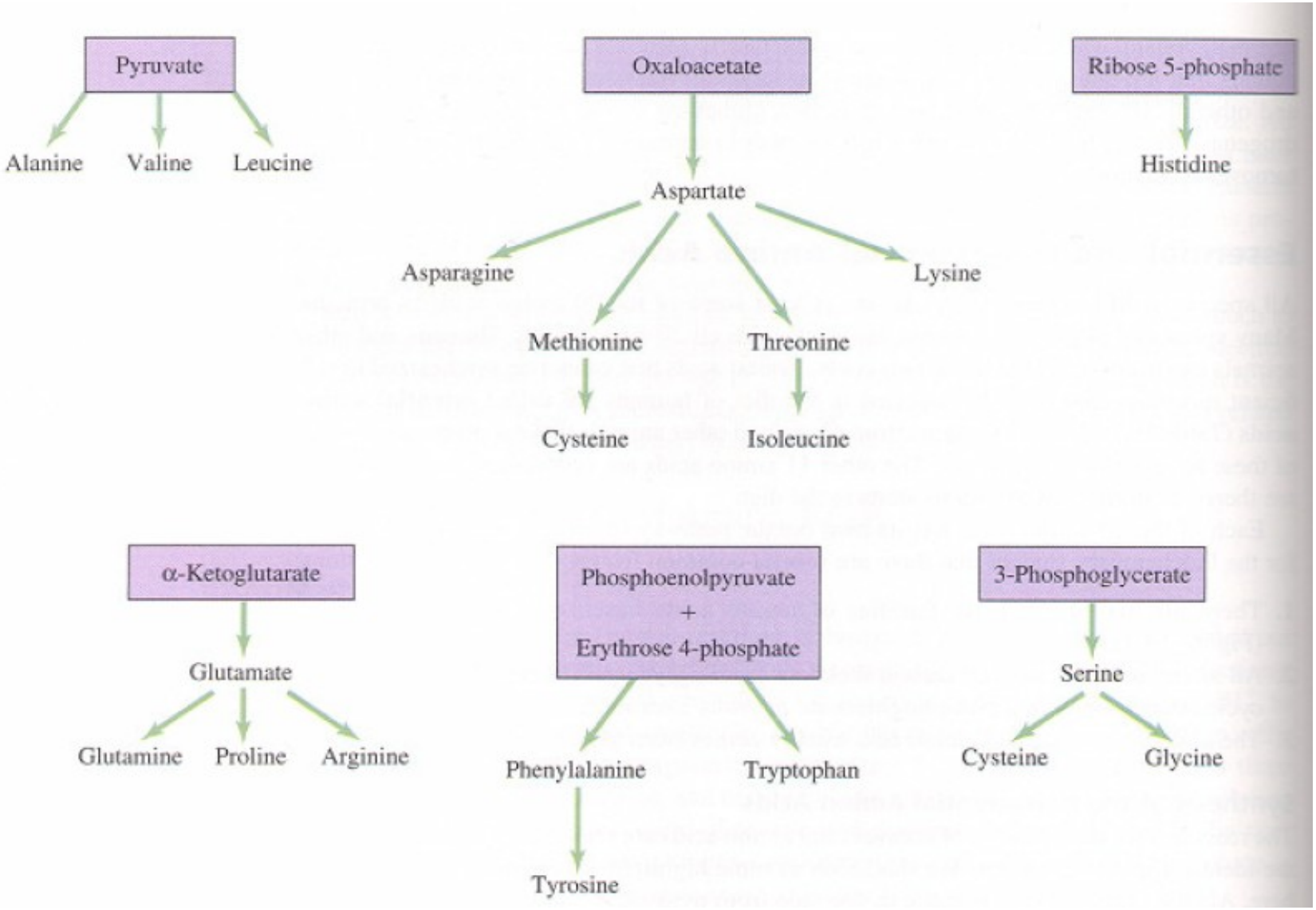


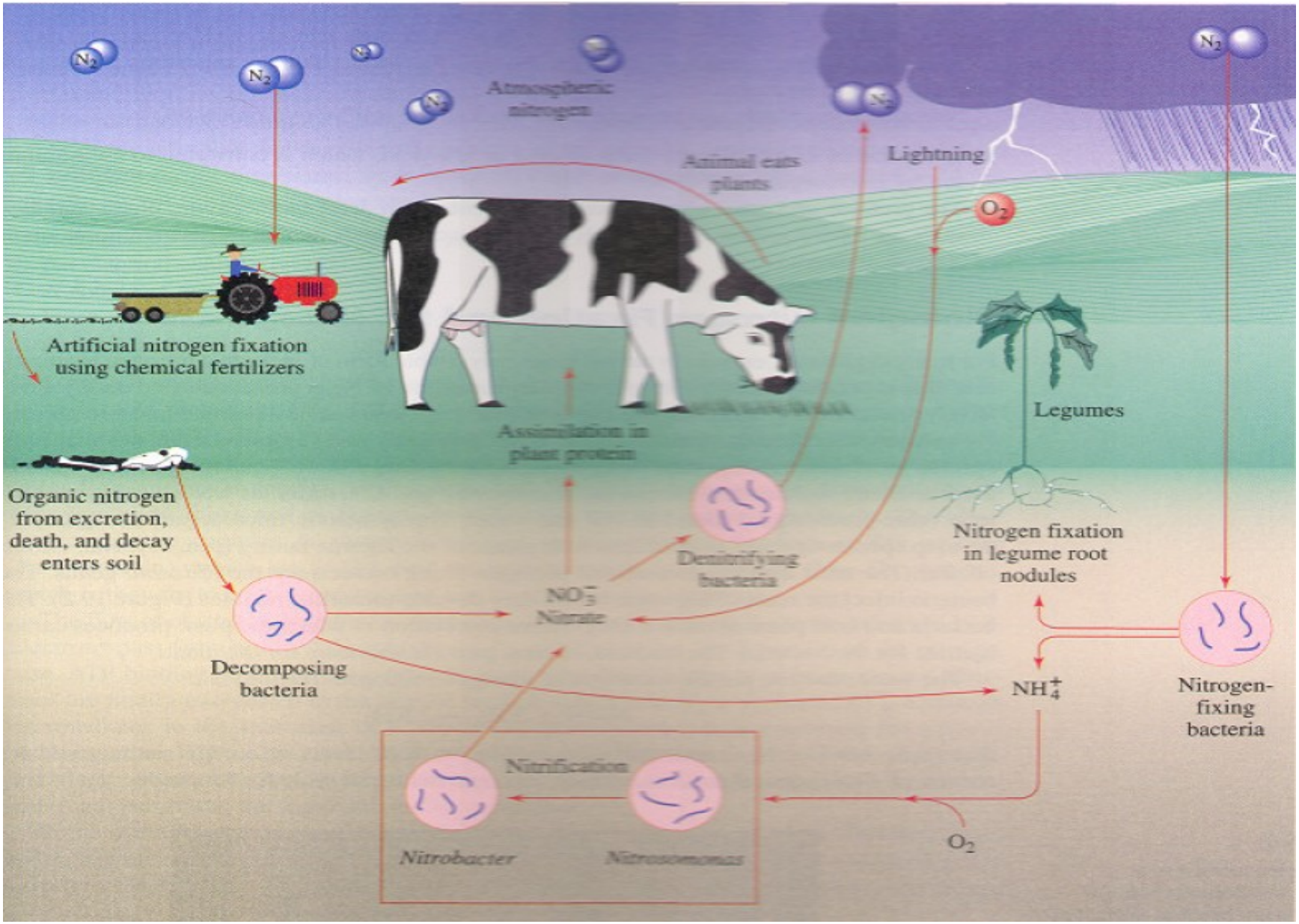
Rostliny **- všechny**



Živočichové **- esenciální a neesenciální**

Biosyntéza aminokyselin




N_2
Atmospheric nitrogen
Animal eats plants
Lightning
O_2
Artificial nitrogen fixation using chemical fertilizers
Assimilation in plant protein
Legumes
Organic nitrogen from excretion, death, and decay enters soil
Denitrifying bacteria
Nitrogen fixation in legume root nodules
NO_3^- Nitrate
Decomposing bacteria
NH_4^+
Nitrogen-fixing bacteria
Nitrification
Nitrobacter
Nitrosomonas
O_2

Fixace N_2

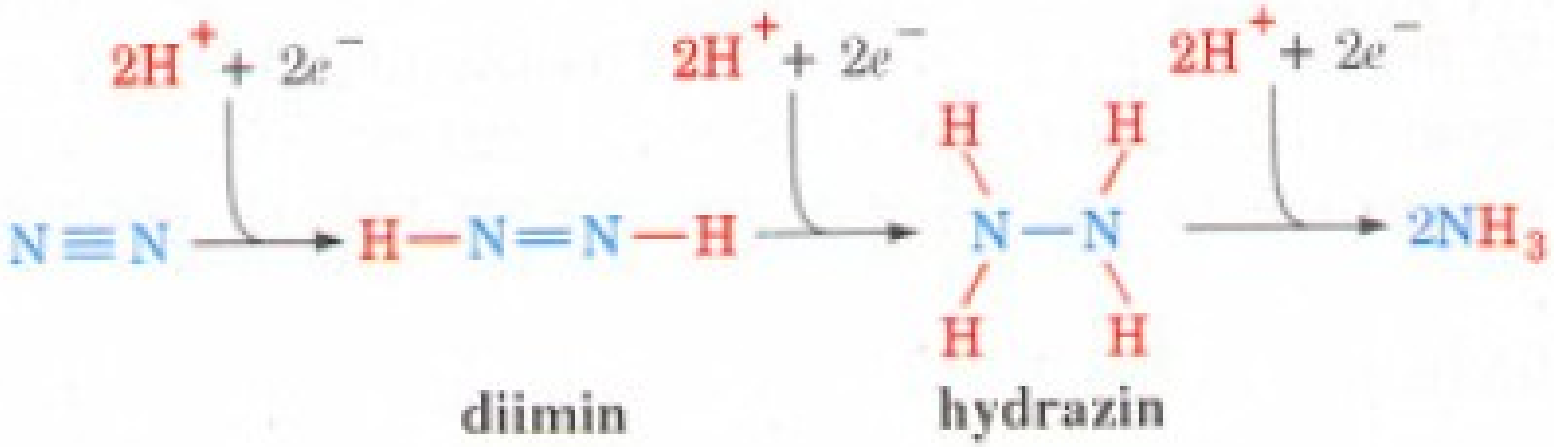
Chemická syntéza - Haber Bosch (500 °C, 300 atm, kat – Fe)

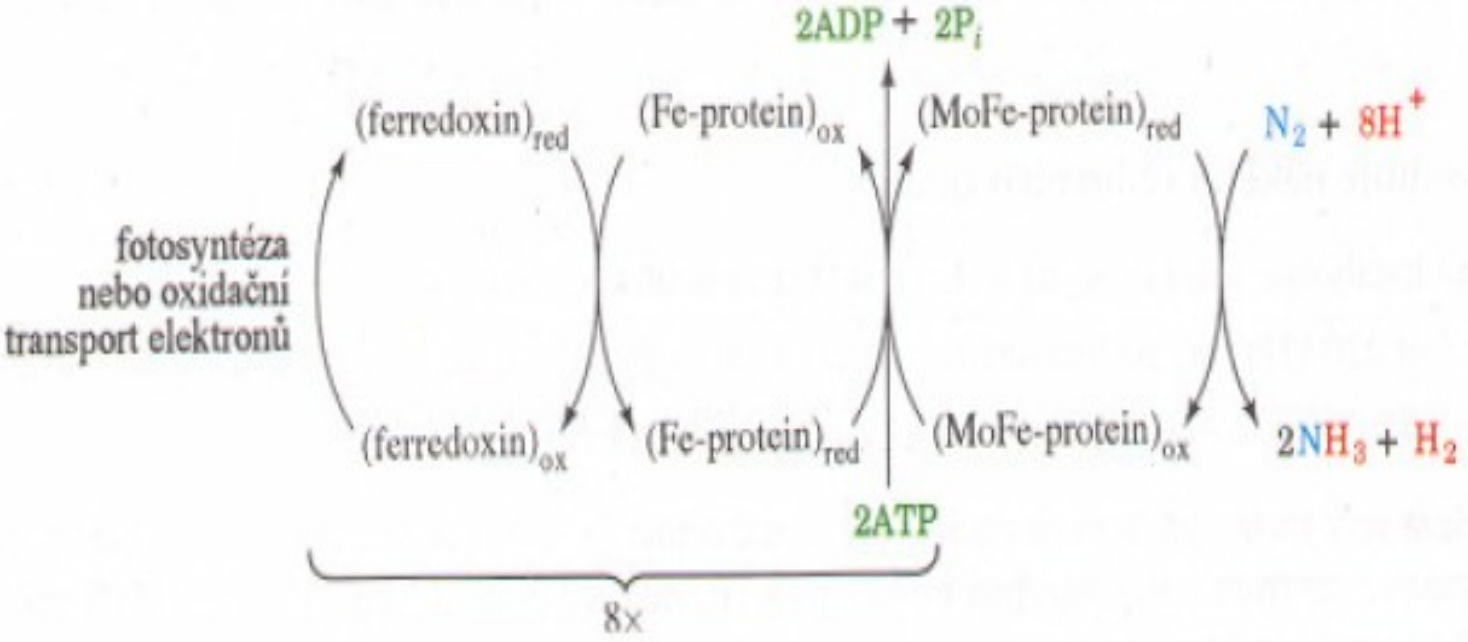
$$N_2 + 3\,H_2 \rightarrow 2\,NH_3$$

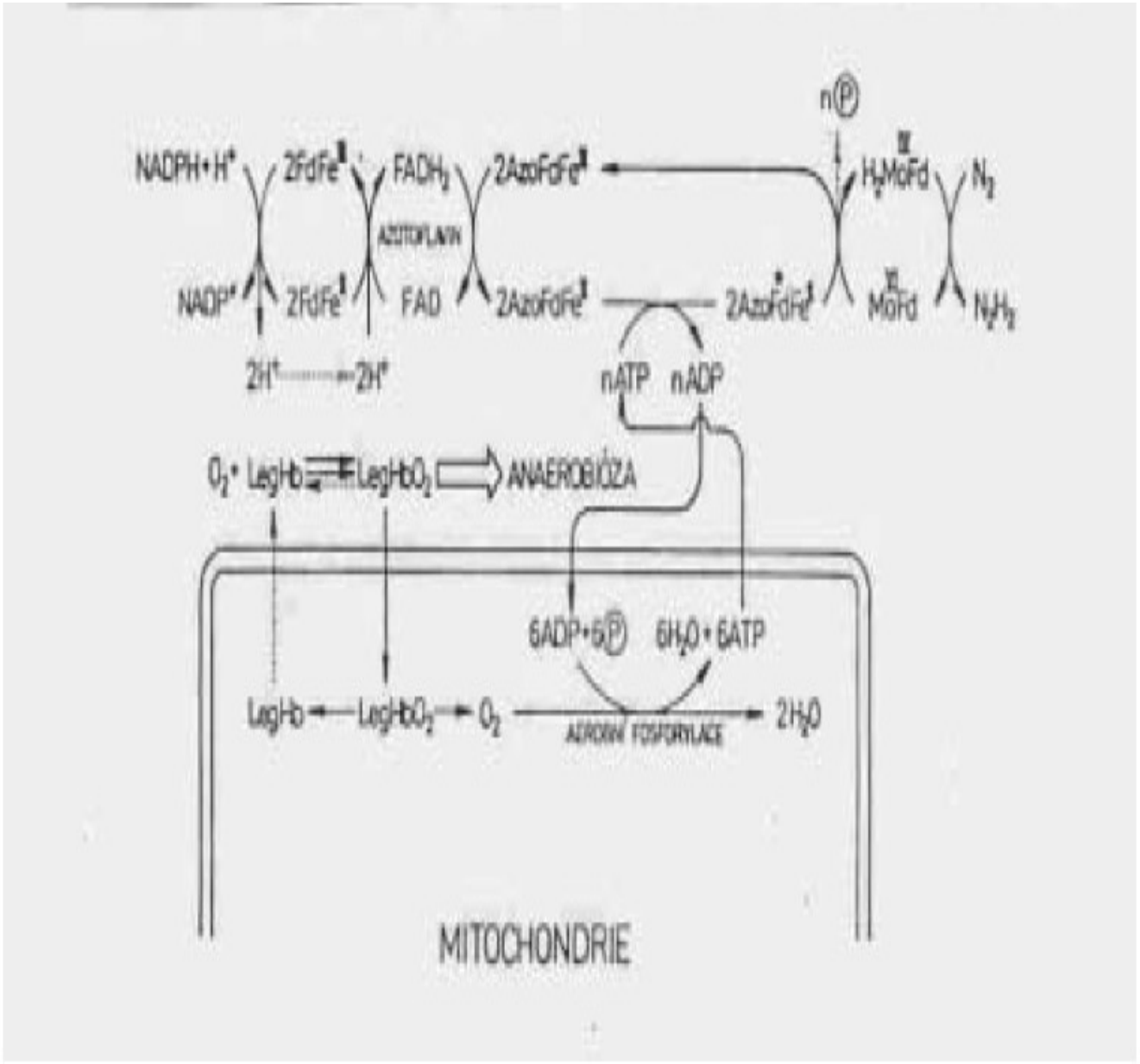
Biosyntéza – sinice, bakterie - *Rhizobium*, *Azotobacter*

$$N_2 + 8\,H^+ + 8\,e^- + 16\,ATP \rightarrow 2\,NH_3 + H_2 + 16\,ADP + 16\,P_i$$

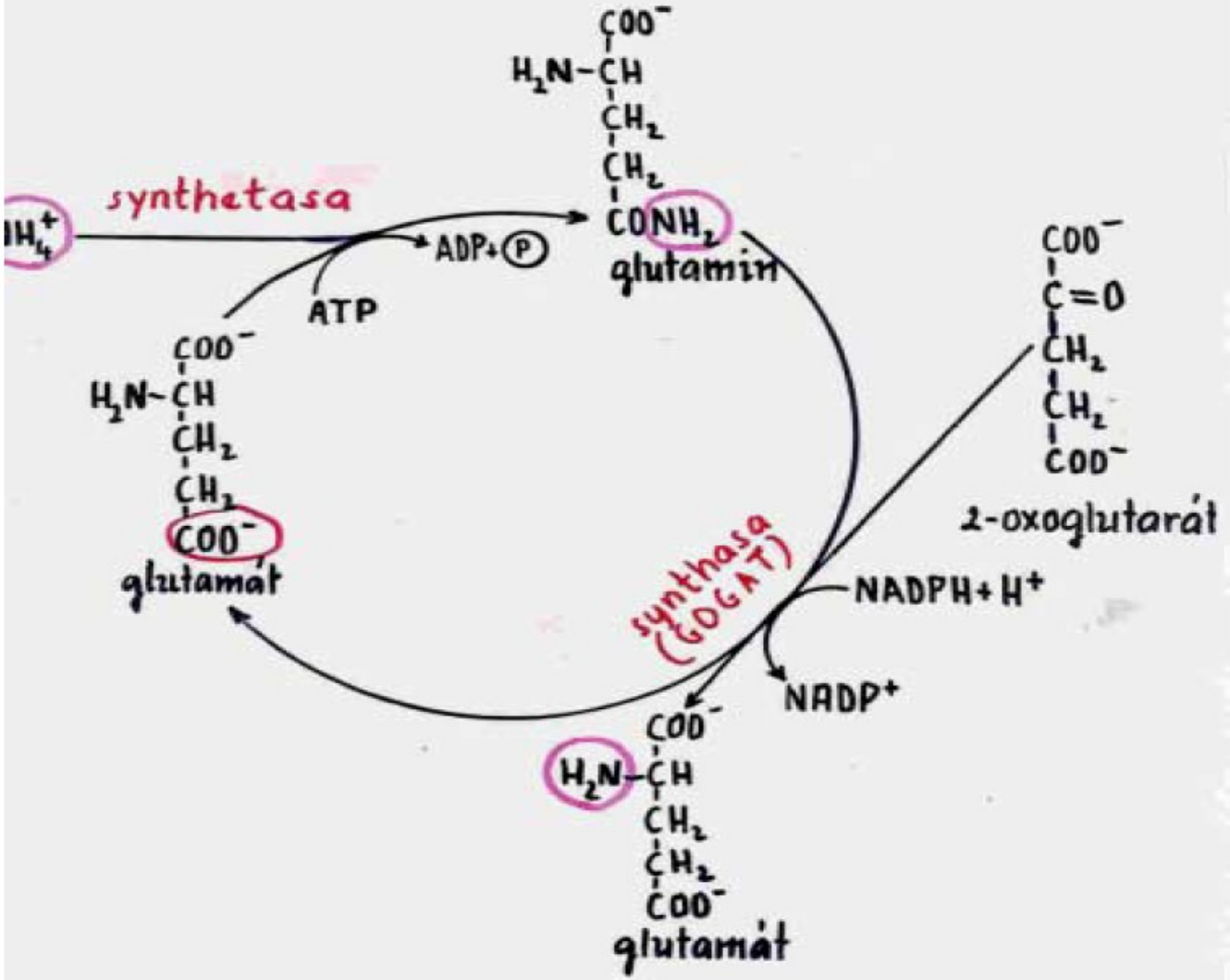
Nitrogenasa : 1. protein Fe
2. protein MoFe


2H+ + 2e−
2H+ + 2e−
2H+ + 2e−
N≡N
H−N=N−H
N−N
2NH3
diimin
hydrazin


2ADP + 2Pi
(ferredoxin)red
(Fe-protein)ox
(MoFe-protein)red
N2 + 8H+
fotosyntéza
nebo oxidační
transport elektronů
(ferredoxin)ox
(Fe-protein)red
(MoFe-protein)ox
2NH3 + H2
2ATP
8×


NADPH + H+
2FdFe3+
FADH2
AZOTOFLAVIN
2AzoFdFe3+
n Ⓟ
H2MoFd
N2
NADP+
2FdFe3+
FAD
2AzoFdFe3+
2AzoFdFe2+
MoFd
N2H2
2H+
2H+
nATP
nADP
O2 + LegHb
LegHbO2
ANAEROBIÓZA
6ADP + 6Ⓟ
6H2O + 6ATP
LegHb
LegHbO2
O2
AERÓBNÍ FOSFORYLACE
2H2O
MITOCHONDRIE

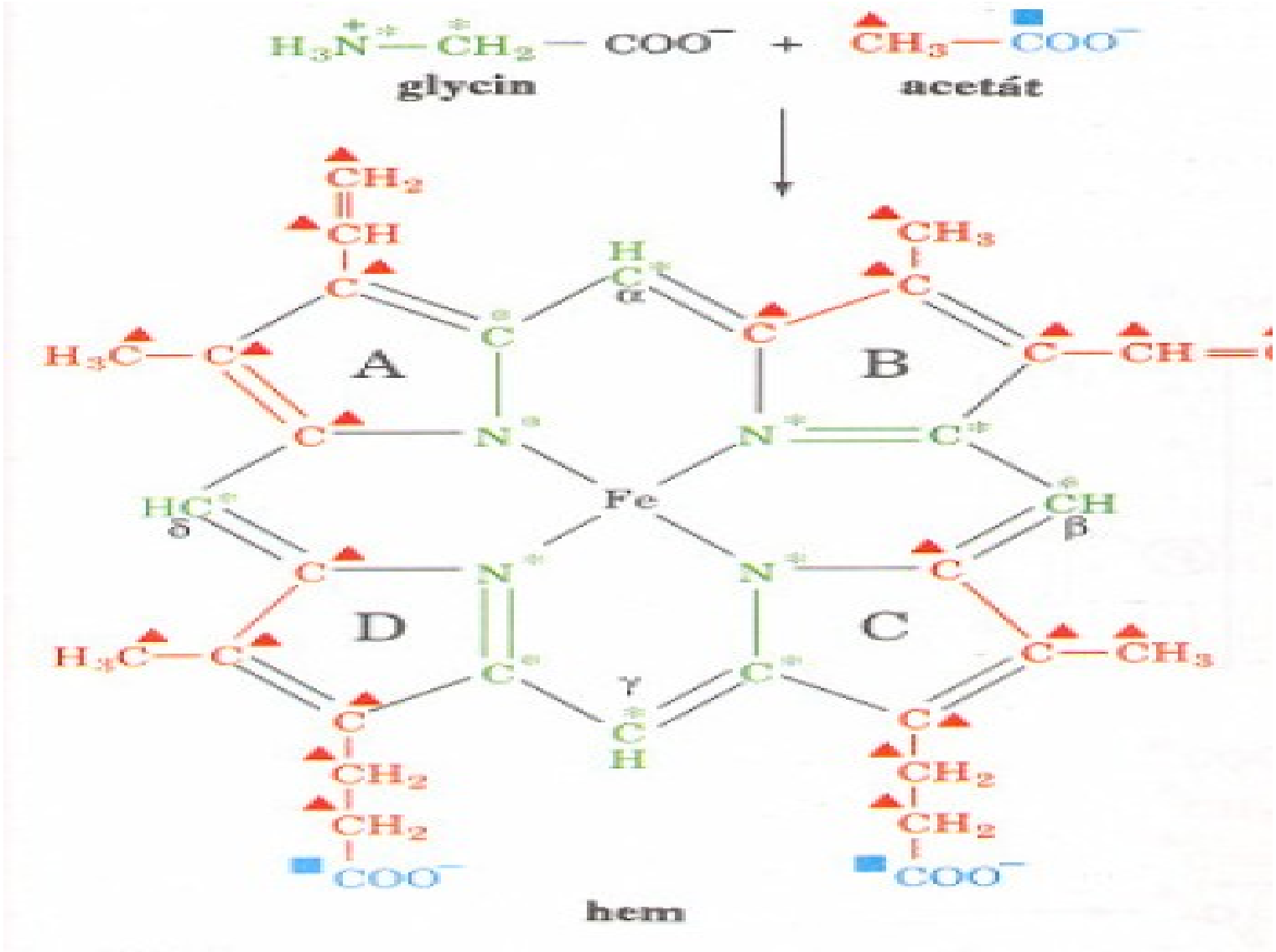
INKORPORACE NH_3 U PROKARYOT



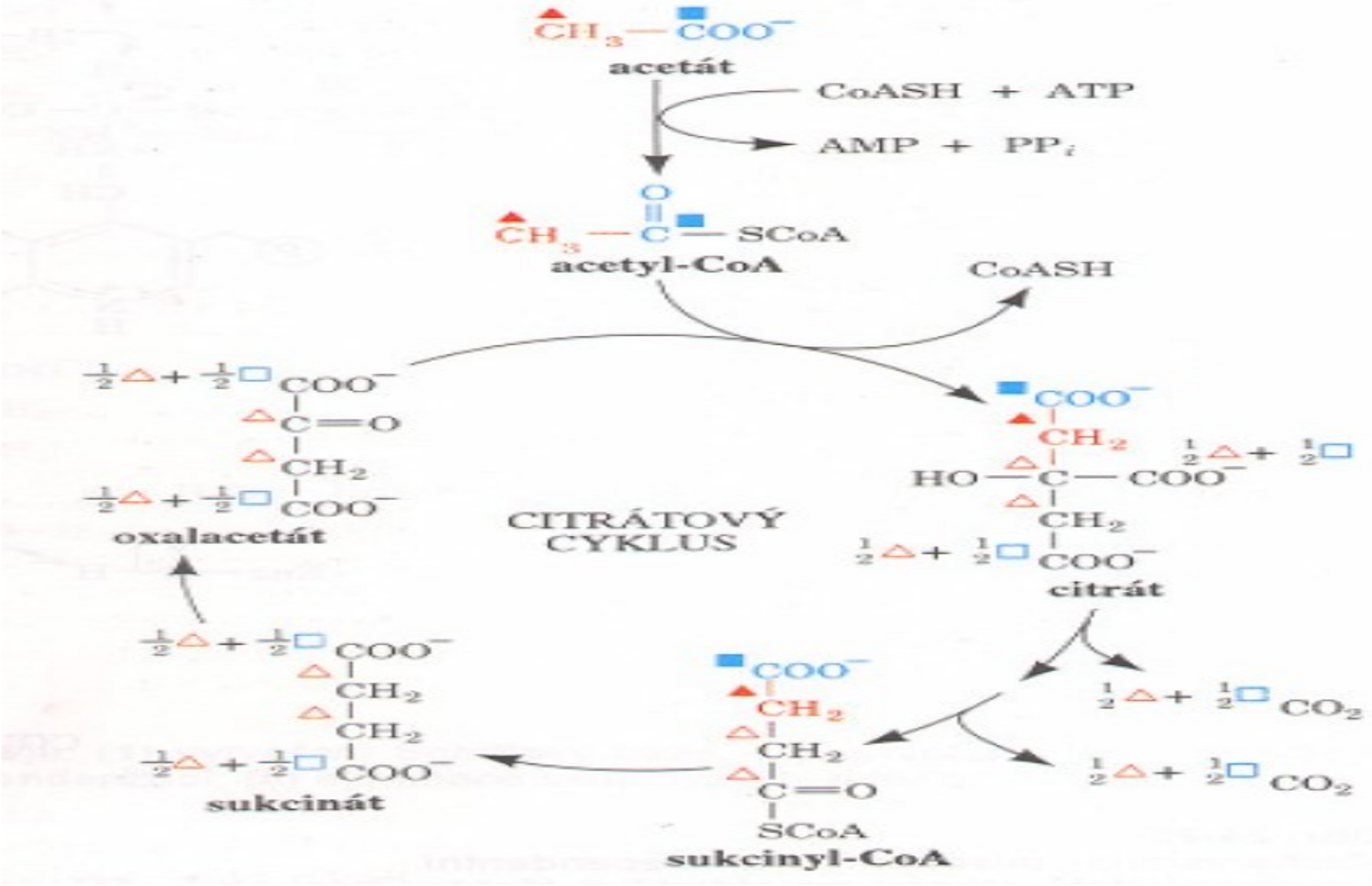
AMK jako prekurzory

Bioactive Product	Biological Function	Amino Acid Precursor(s)
Alkaloids	Nitrogen bases in plants	Ornithine, Asp, Lys, Tyr, Trp, Phe, His
γ-Aminobutyric acid (GABA)	Inhibitory neurotransmitter	Glu
Auxin	Plant growth hormone	Trp
Catecholamines	Neurotransmitters, hormones	Tyr, Phe
Glutathione	Redox tripeptide	Gly, Glu, Cys
Histamine	Allergic response, stomach acid secretion	His
Melanin	Skin pigments	Tyr, Phe
Melatonin	Regulates sleep cycles	Trp
Nitric oxide	Cell messenger	Arg
Phosphocreatine	Energy molecule in muscle	Gly, Arg, Met
Porphyrin	Heme and chlorophyll	Gly
Purine bases	RNA, DNA, cofactors	Asp, Gly, Gln
Pyrimidine bases	RNA, DNA, cofactors	Asp
Serotonin	Neurotransmitter (hormone)	Trp
Spermine, spermidine	DNA packaging	Met, ornithine
Thyroxine	Hormone	Tyr

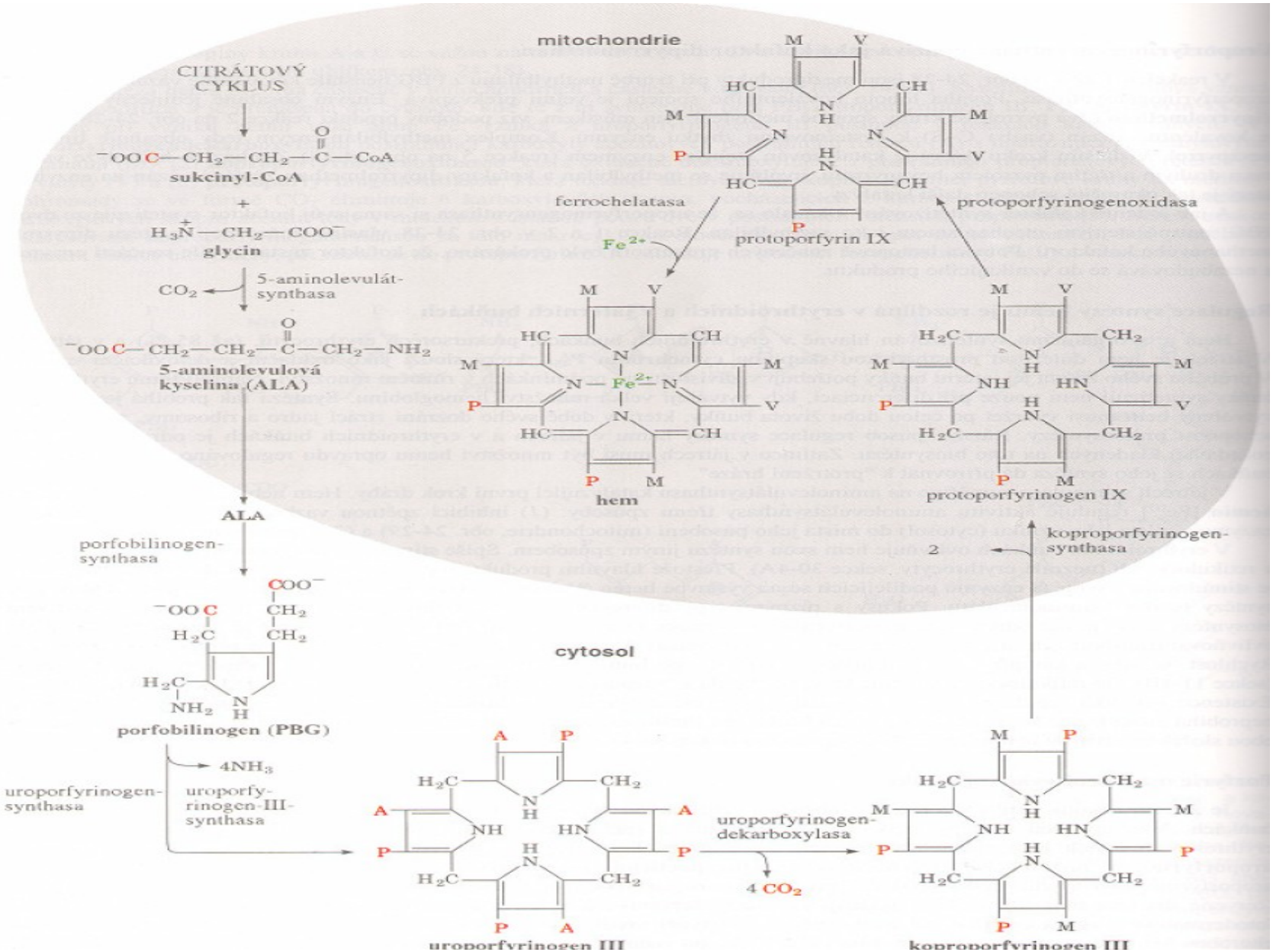
Hem



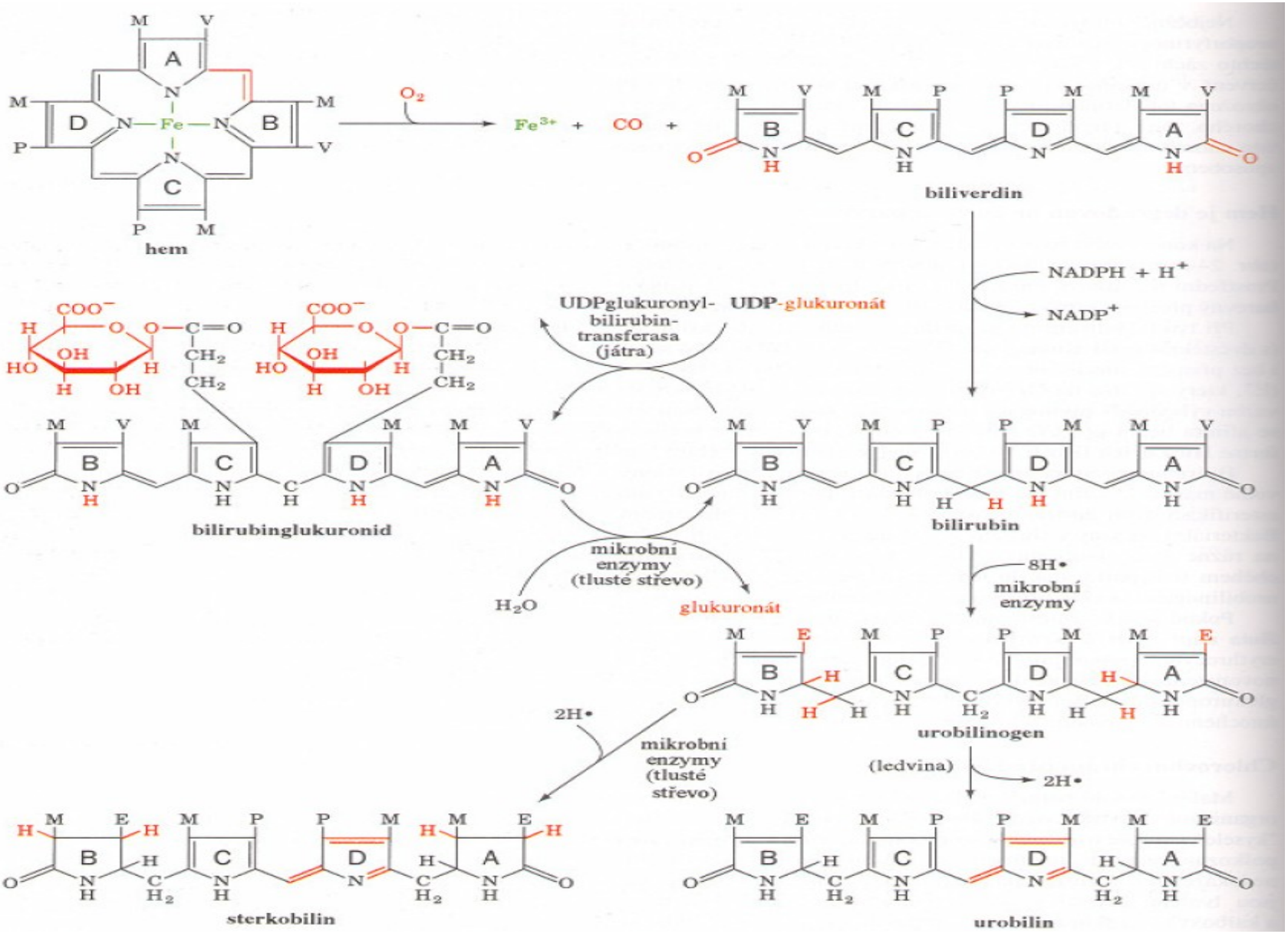
Hem


acetát
CoASH + ATP
AMP + PPi
acetyl-CoA
SCoA
CoASH
oxalacetát
CITRÁTOVÝ CYKLUS
citrát
sukcinát
sukcinyl-CoA
CO2
CO2

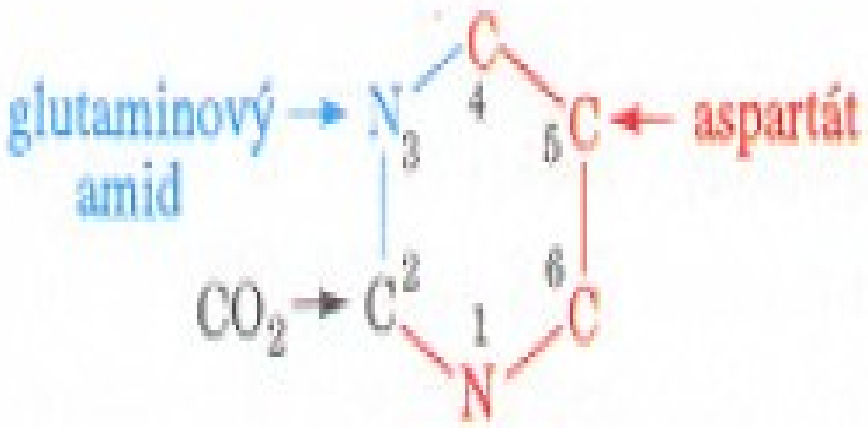
Biosyntéza hemu

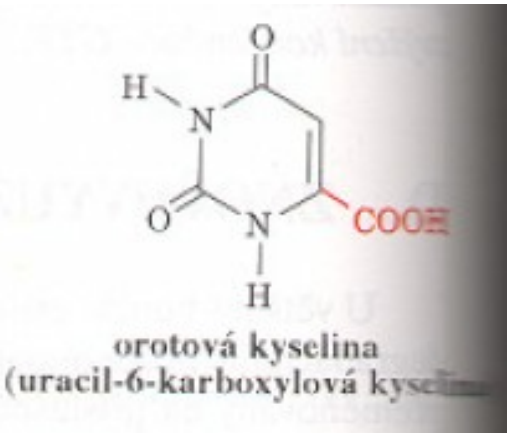


Degradace hemu



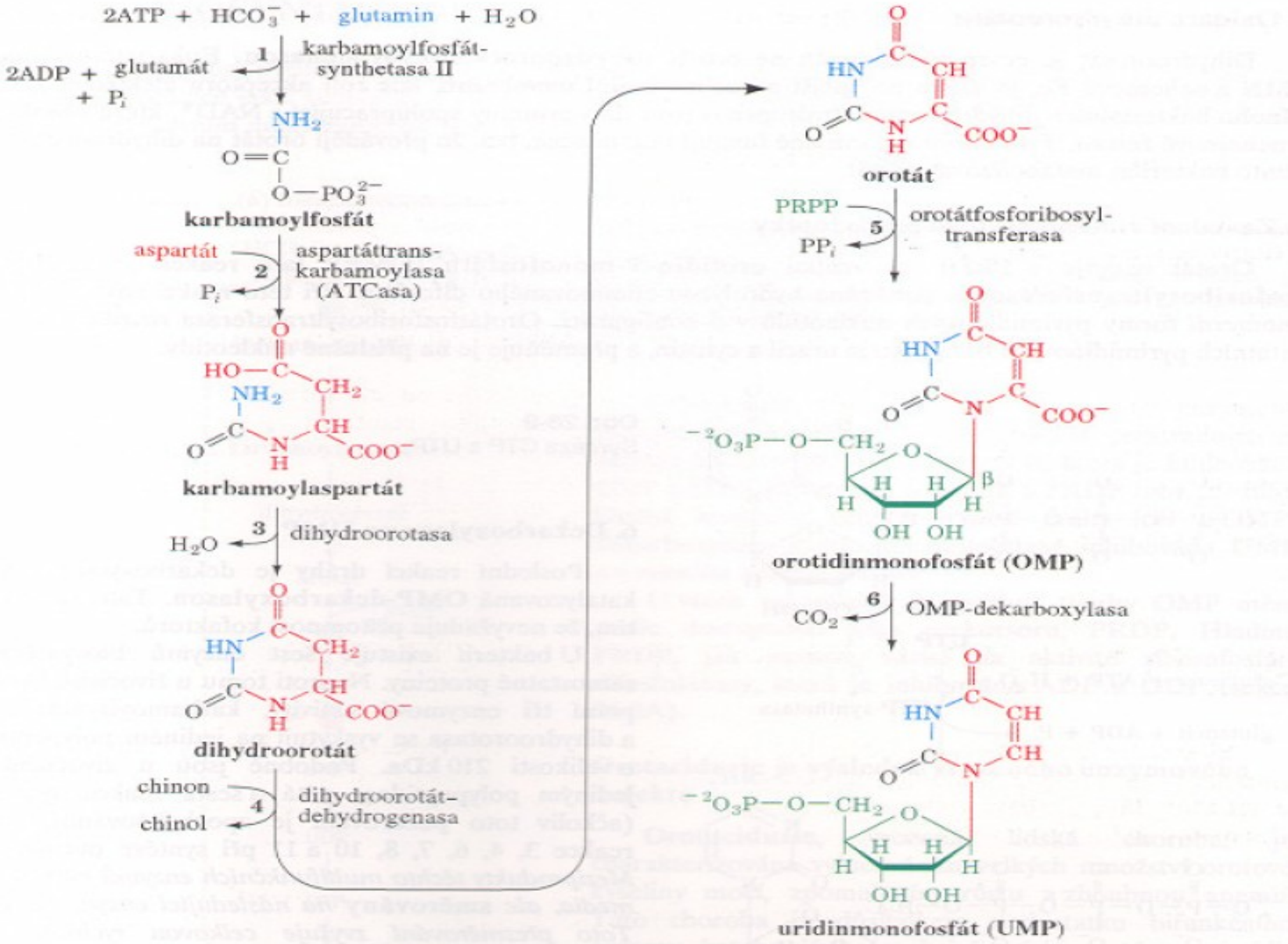
Biosyntéza pyrimidinových bází



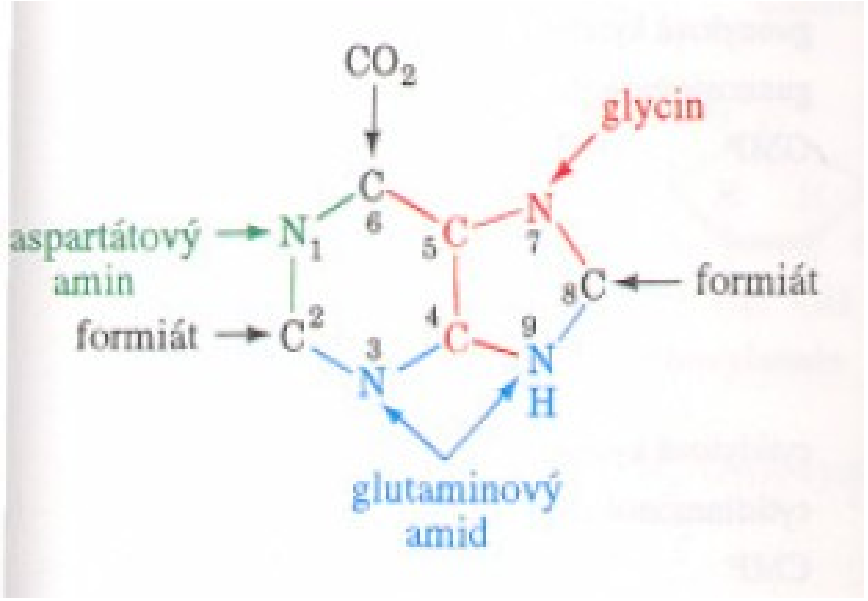


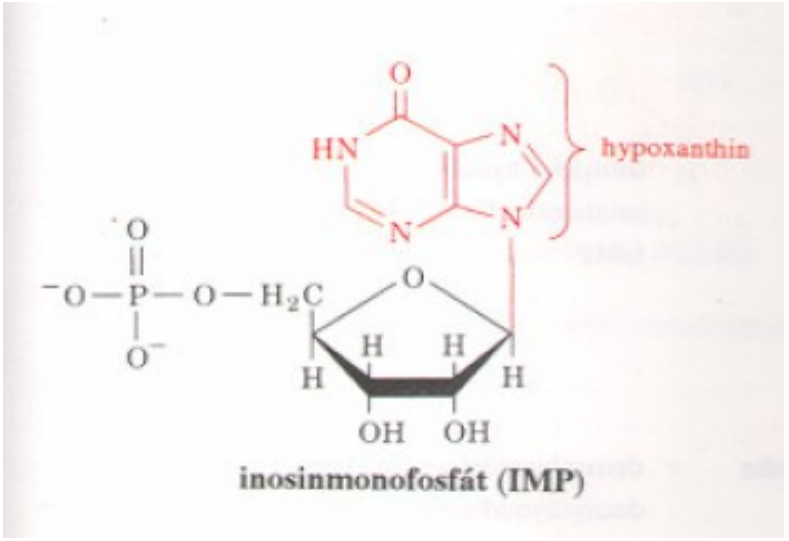
orotová kyselina
(uracil-6-karboxylová kyselina)

Biosyntéza pyrimidinových bází

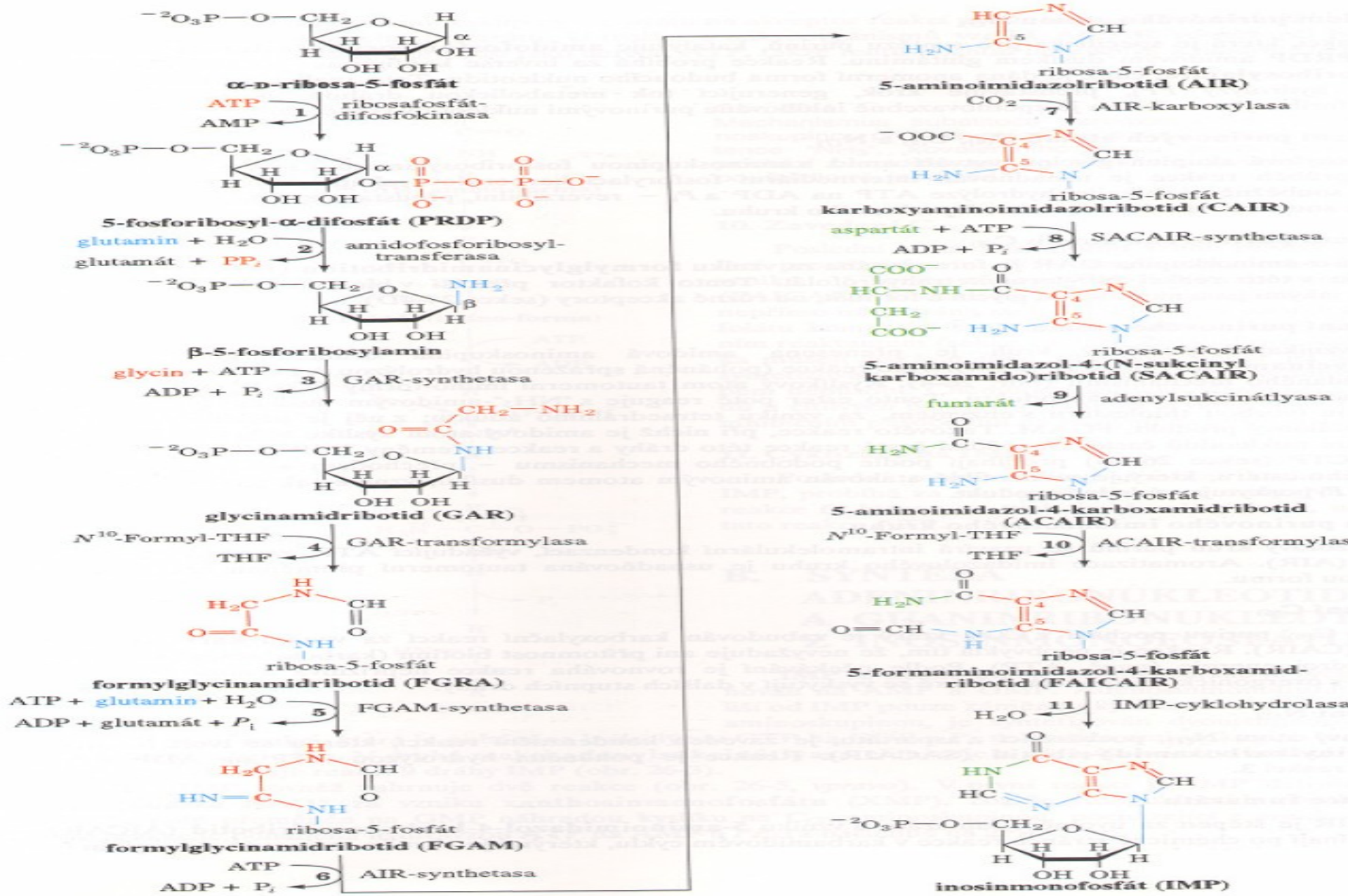


Biosyntéza purinových bází

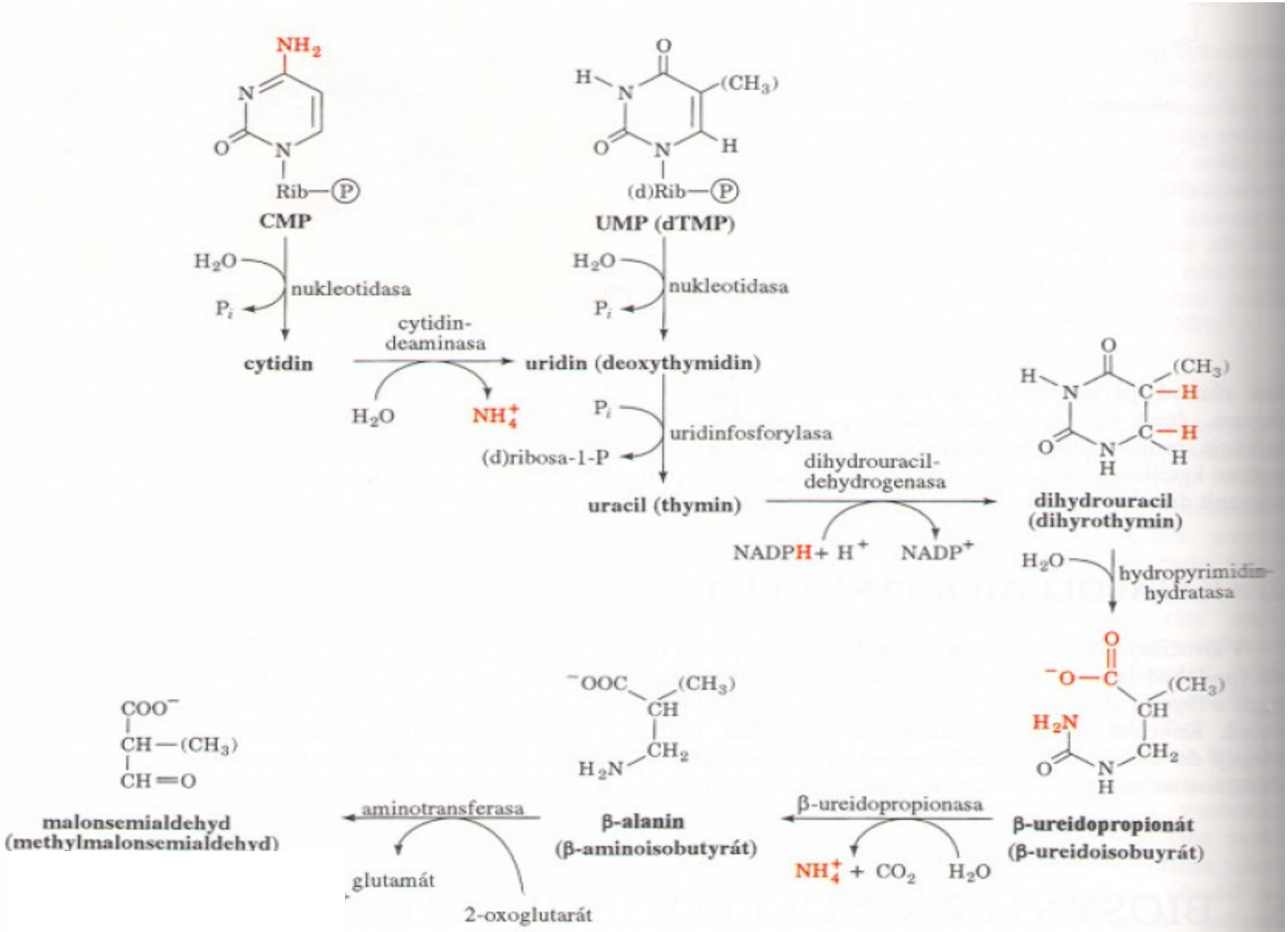




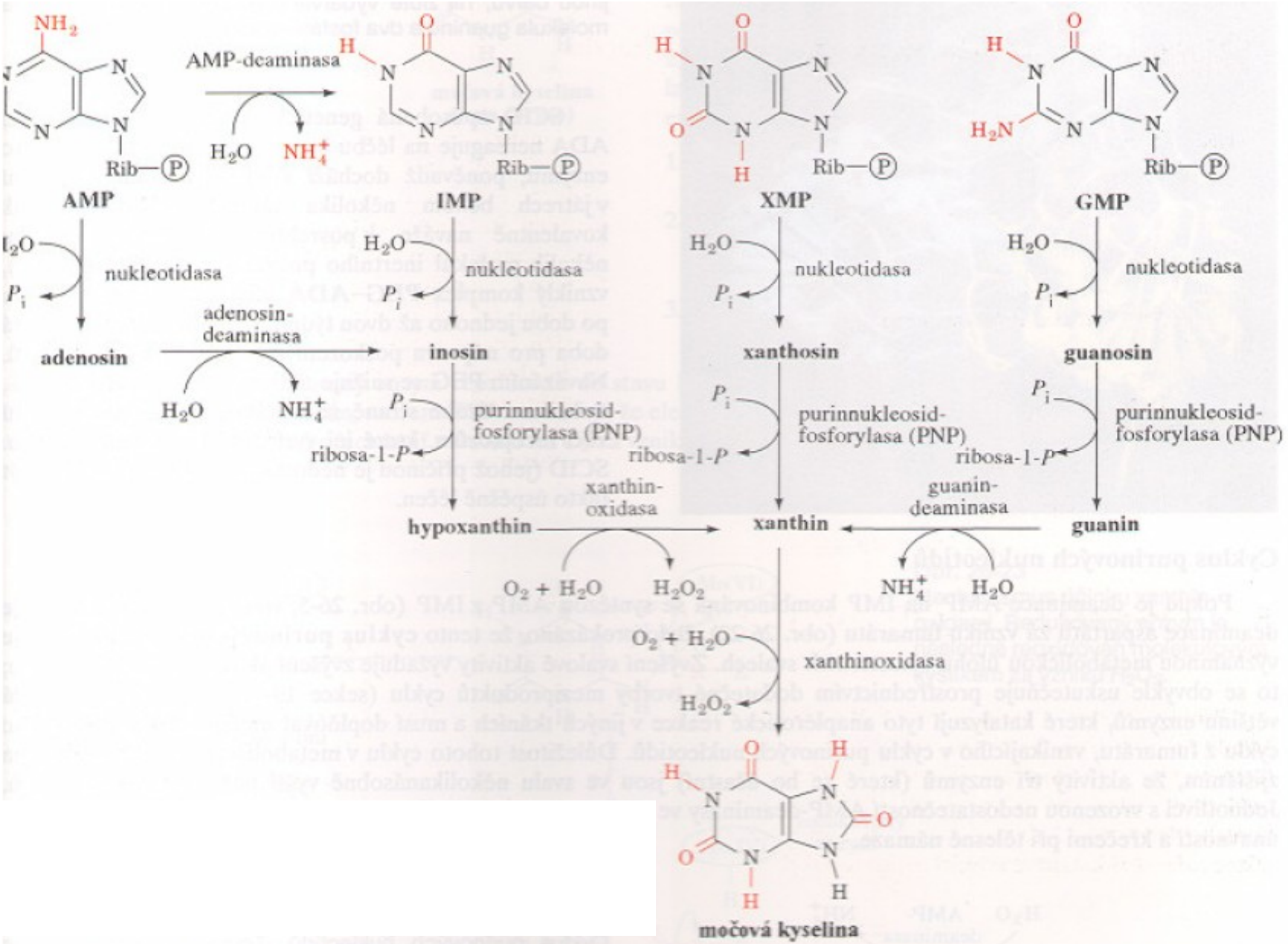
Biosyntéza purinových bází



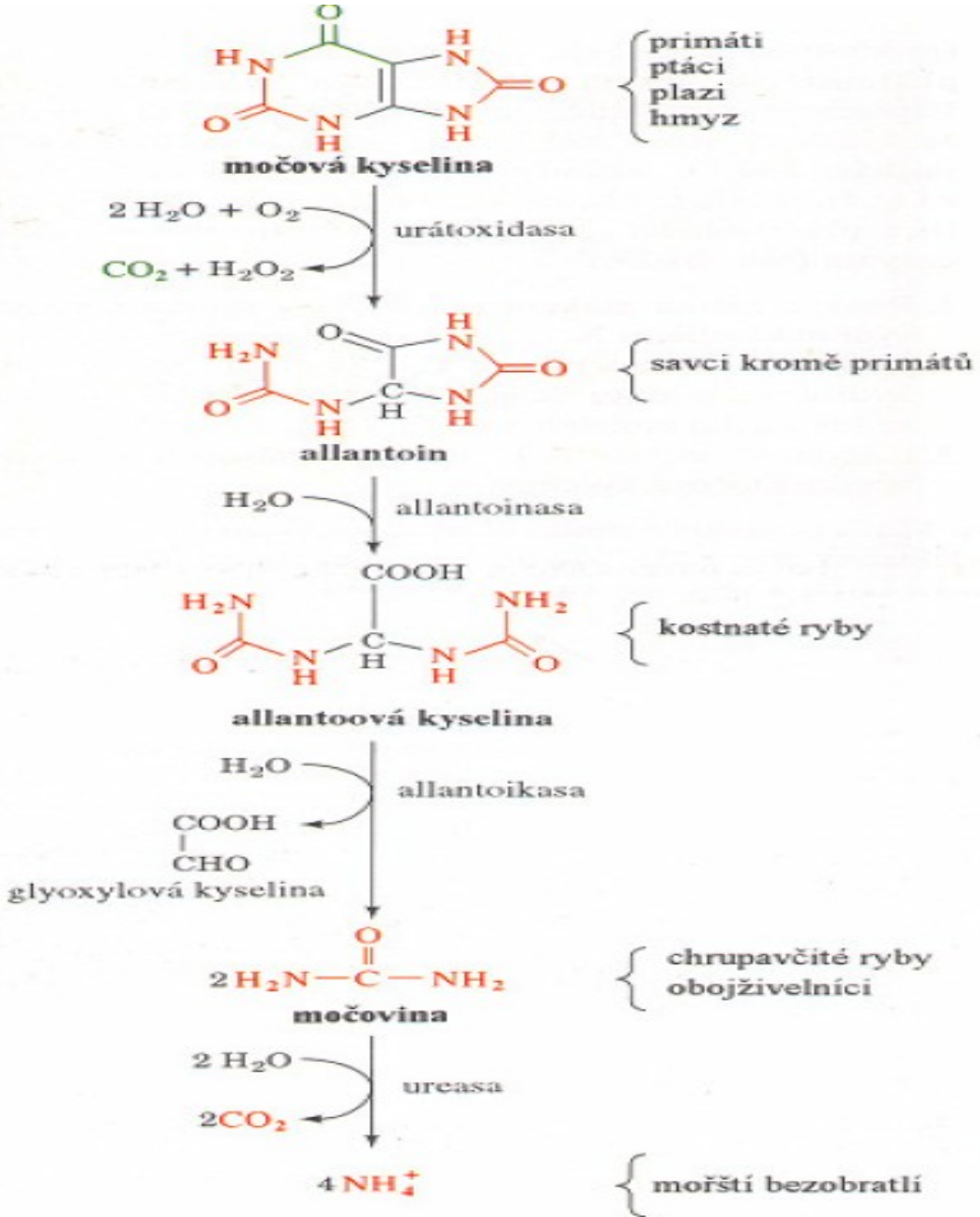
Degradace pyrimidinových bází



Degradace purinových bází



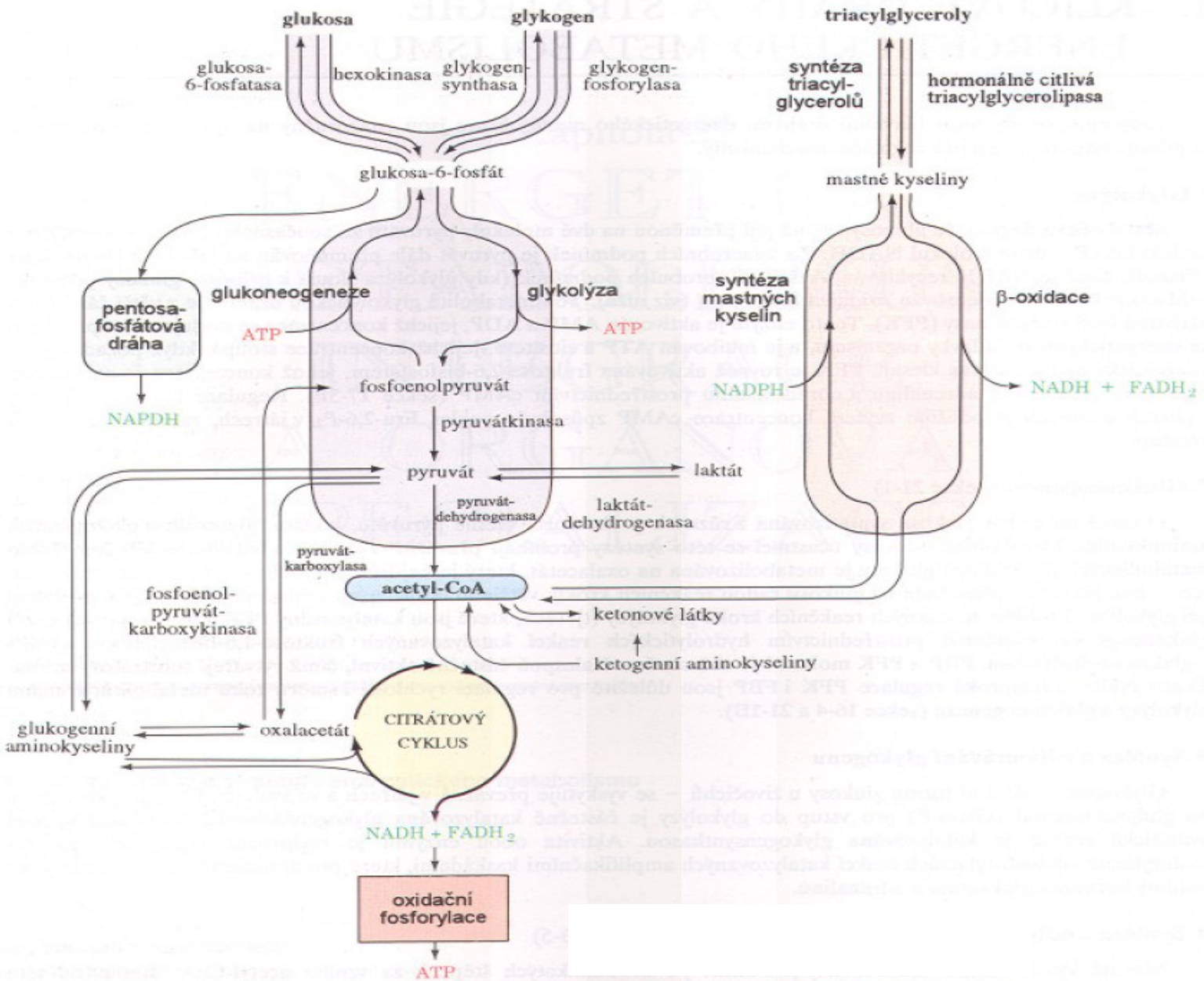
Degradace purinových bází



Metabolismus NK

- Žaludek – odštěpení proteinů pomocí HCl
- Nukleasa (fosfodiesterasa) – štěpení na oligo- a mononukletidy
- Mononukleotidasa – nukleosid + H_3PO_4
- Nukleosidada – cukr + basa

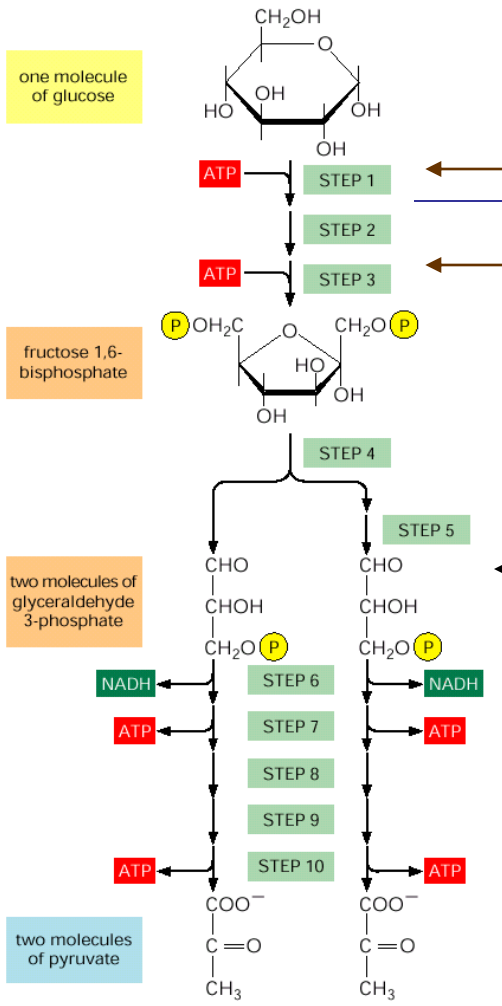
Hlavní dráhy energetického metabolismu



Glykolysa

glykogen

glukosa | monosacharidy



hexokinasa

fosfofruktokinasa

\+

AMP, ADP

G6P

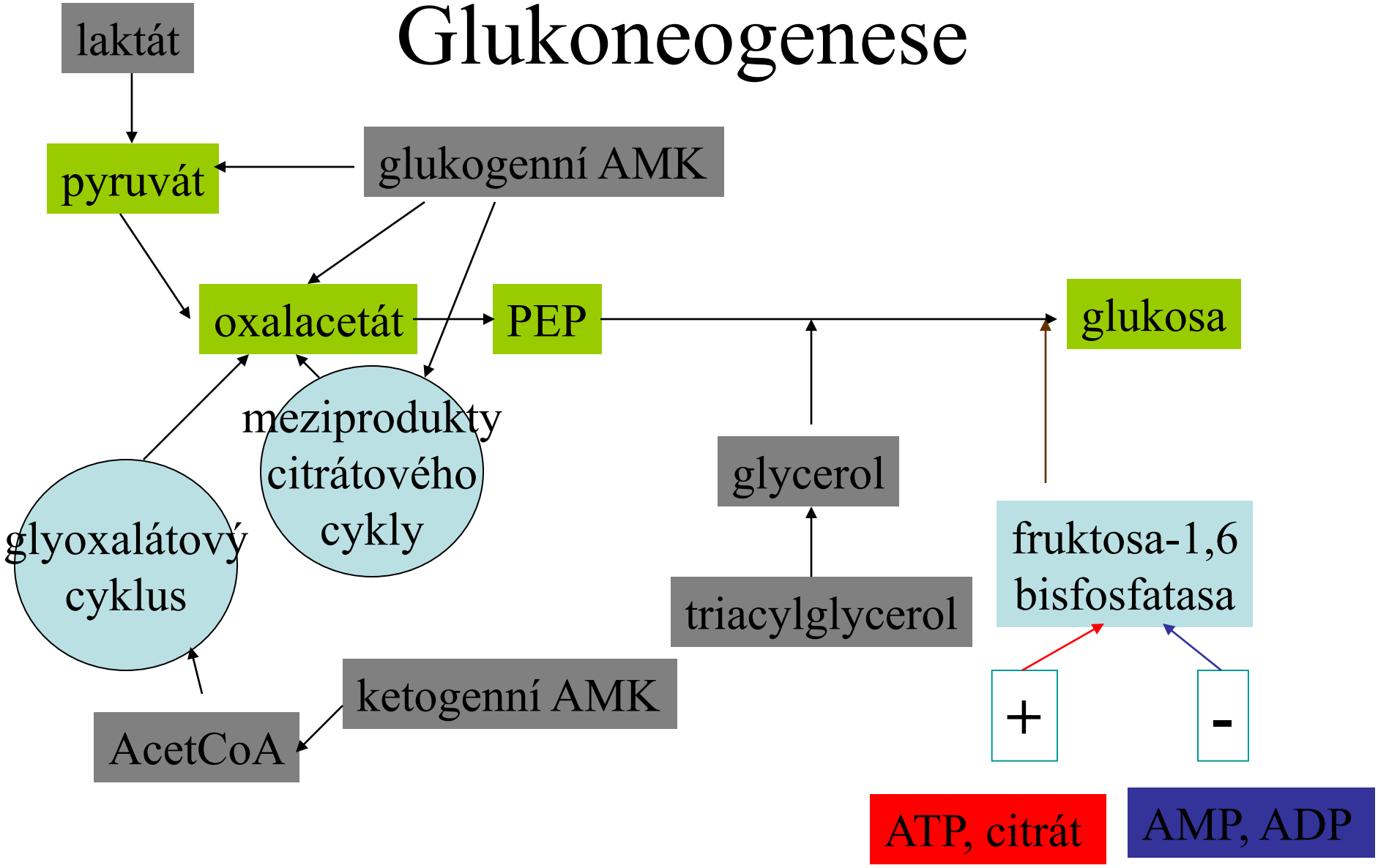
\-

ATP, citrát

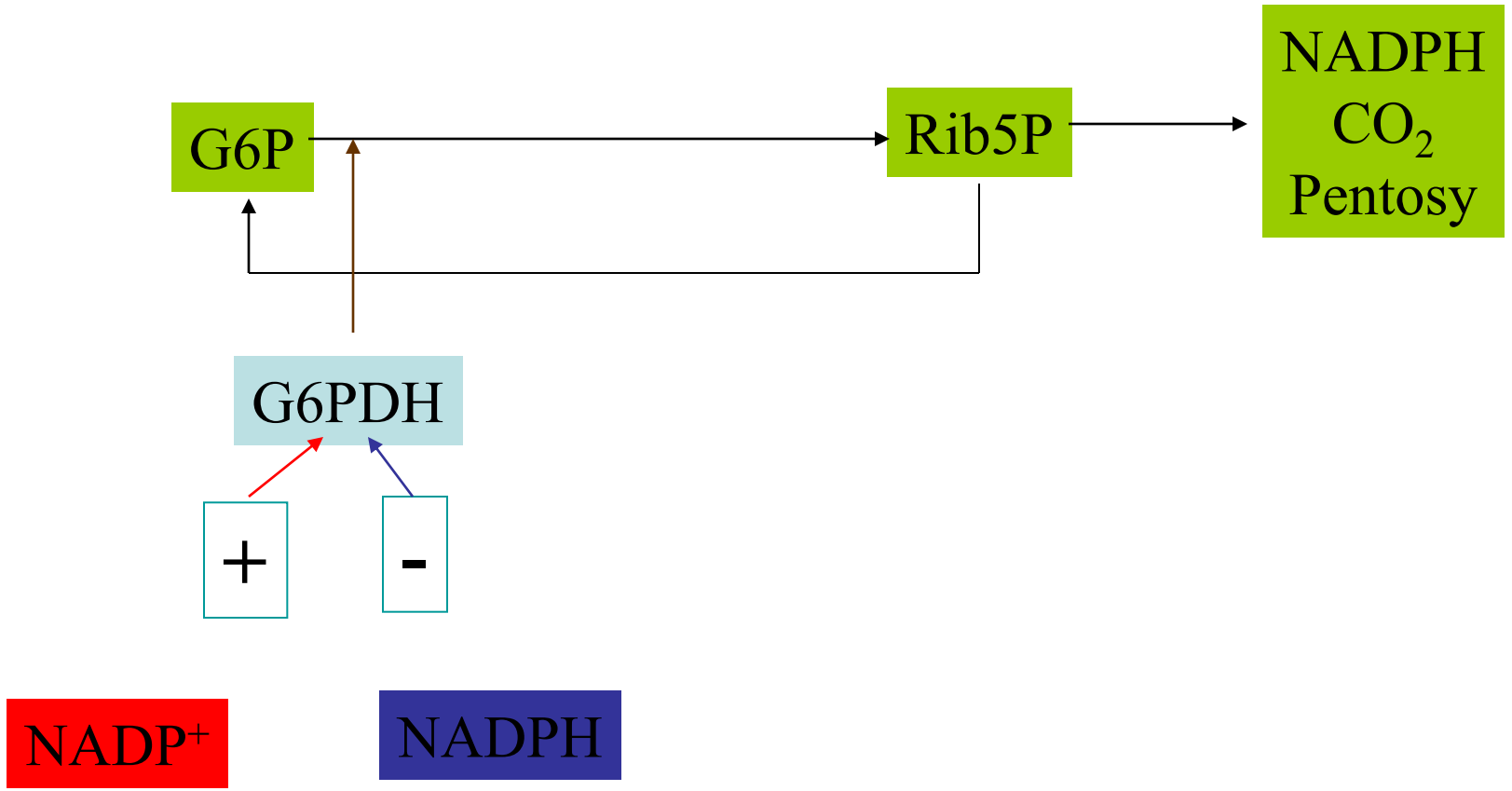
glycerol

triacylglycerol

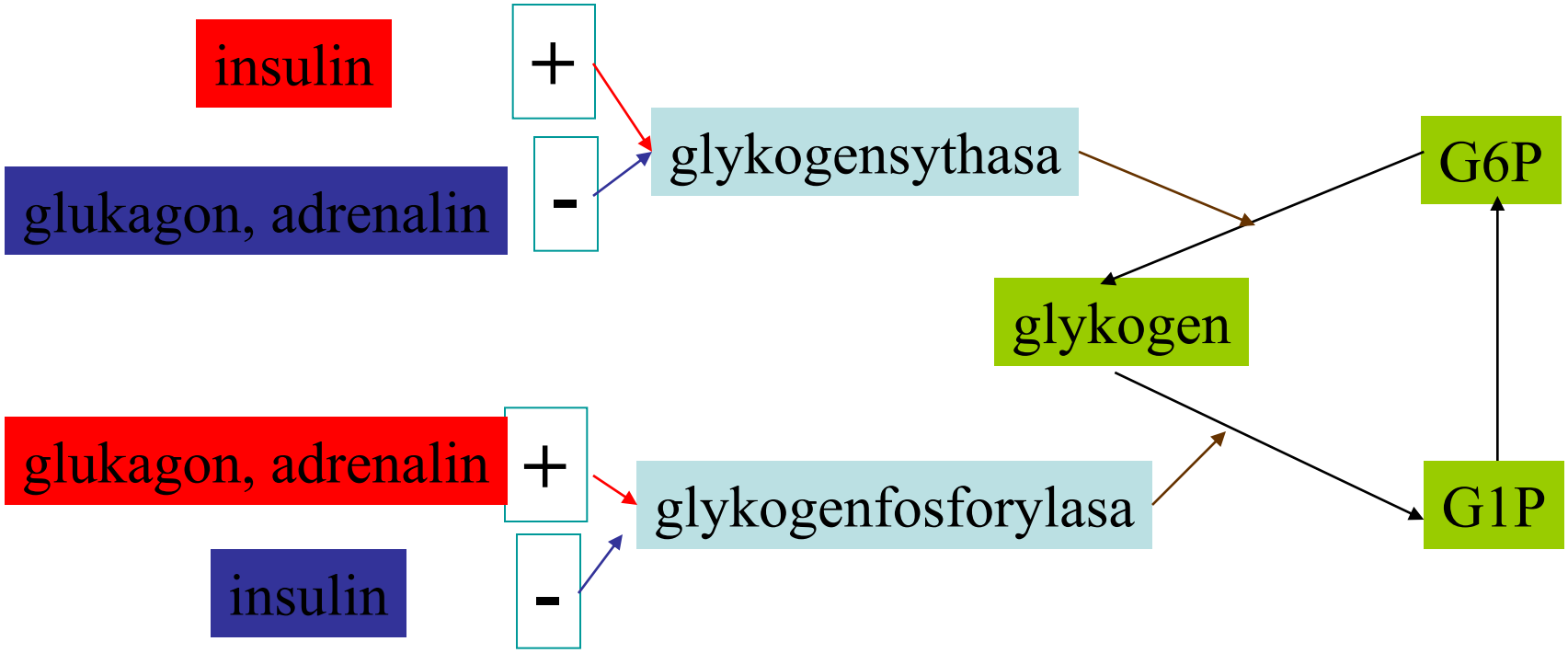
Glukoneogenese



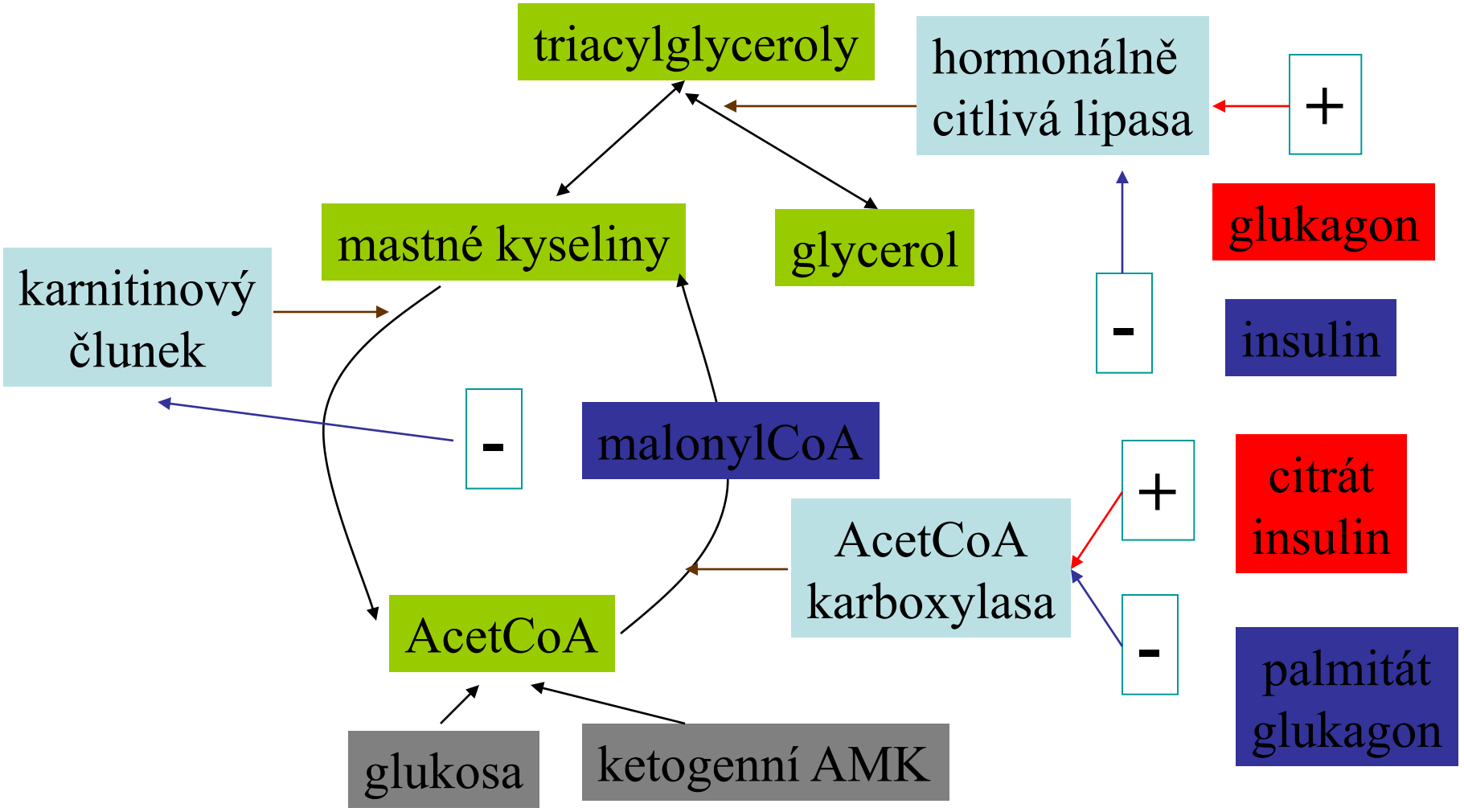
Pentosový cyklus



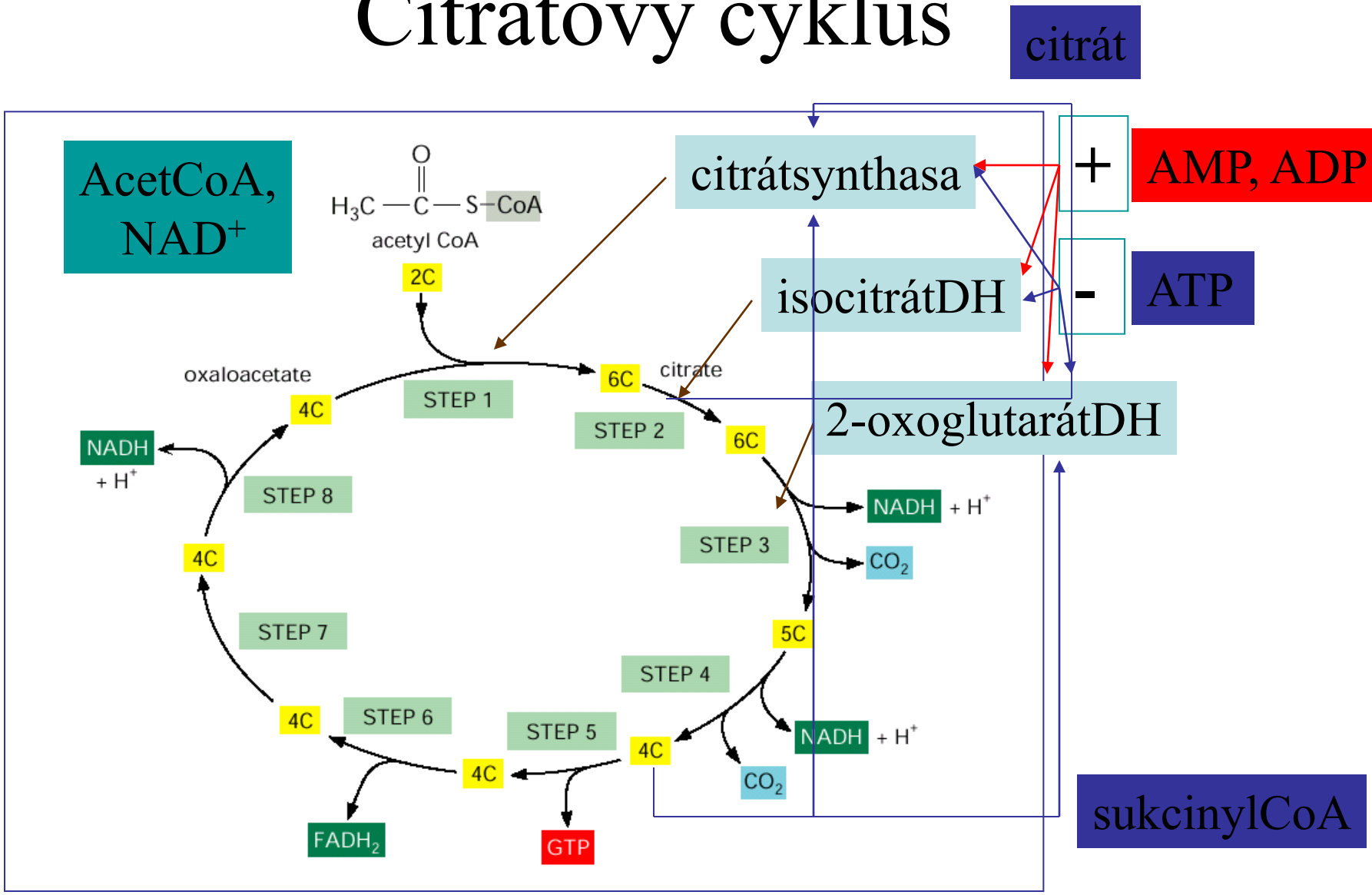
Syntesa a odbourávání glykogenu



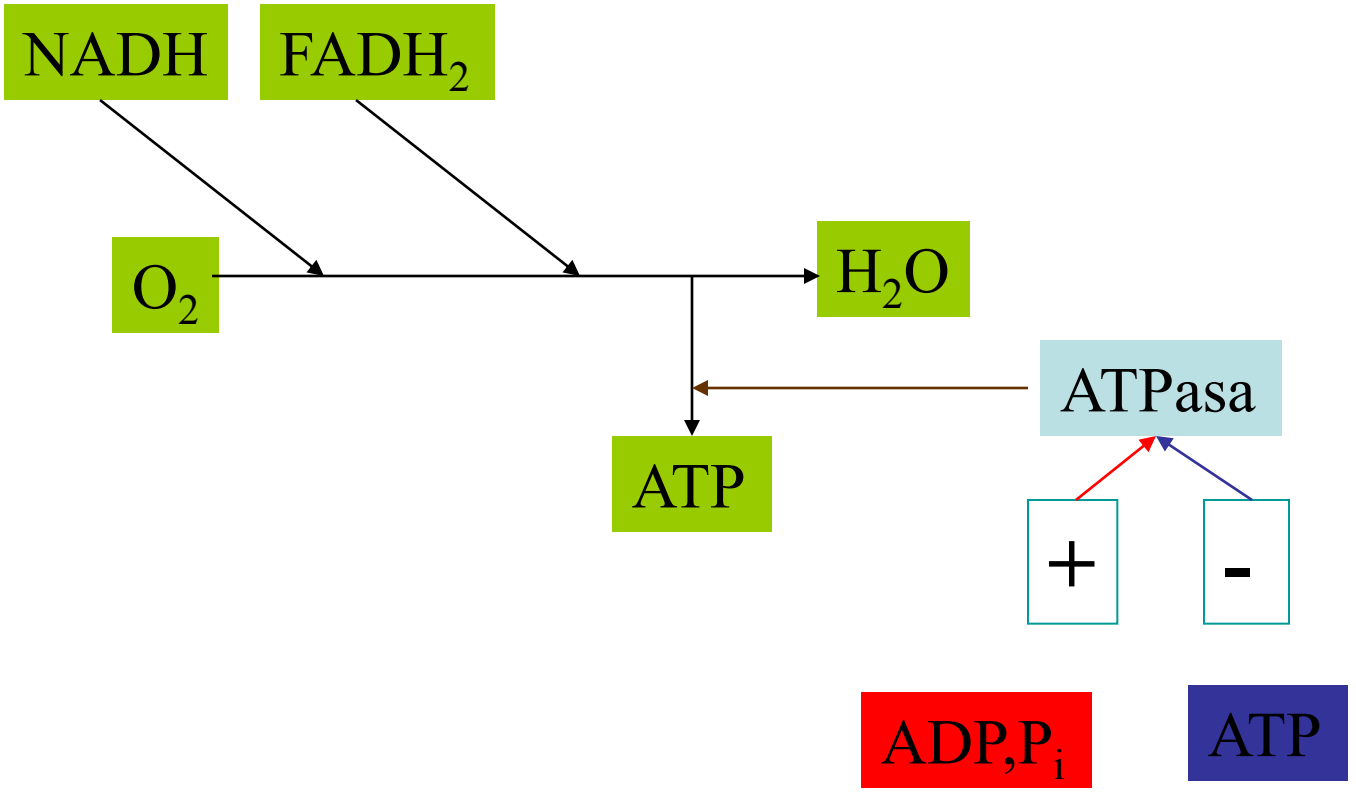
Metabolismus triacylglycerolů



Citrátový cyklus



Oxidační fosforylace



Orgánová specializace