Can the body form new triglycerides?

In the organism:

- Synthesis of FA (excluding essential)
- Synthesis of triglycerides

Synthesis of fatty acids from acetyl-CoA

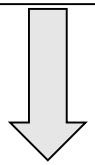
Where does it takes place?

especially in the liver, adipocytes, lactating mammary gland

(not in the intestinal mucosa)

When does it takes place?

if enough of acetyl-CoA,
which is not necessary
to metabolize energy



?

after a meal, when enough glucose,
which is catabolized to acetyl-CoA

Synthesis of fatty acids from acetyl-CoA

(cytoplasm of cells)

cellular localization : **cytoplasm**

That synthesis of FA occurs in the cytoplasm may cause trouble. Most Ac-CoA in the body forms in mitochondria (oxidative decarboxylation of pyruvate formed from starch, glucose, amino acids,...).

It is therefore necessary to provide transport of Ac-CoA from the mitochondria into the cytoplasm.

1. Transport of acetyl-CoA from the **matrix into the cytoplasm**
2. Formation of malonyl-CoA **(+ formation of NADPH+H+)**

3. A series of reactions of fatty acid synthase

Transport of acetyl-CoA from matrix to the cytoplasm

in matrix acetyl-CoA is formed by an oxidative decarboxylation of pyruvate (from glucose and amino acids)

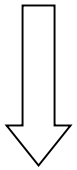
- acetyl-CoA does not pass freely through mitochondrial membrane
- transport as citrate

when does it occur?

unless citrate is required in the citrate cycle

When is citrate not required for CC?

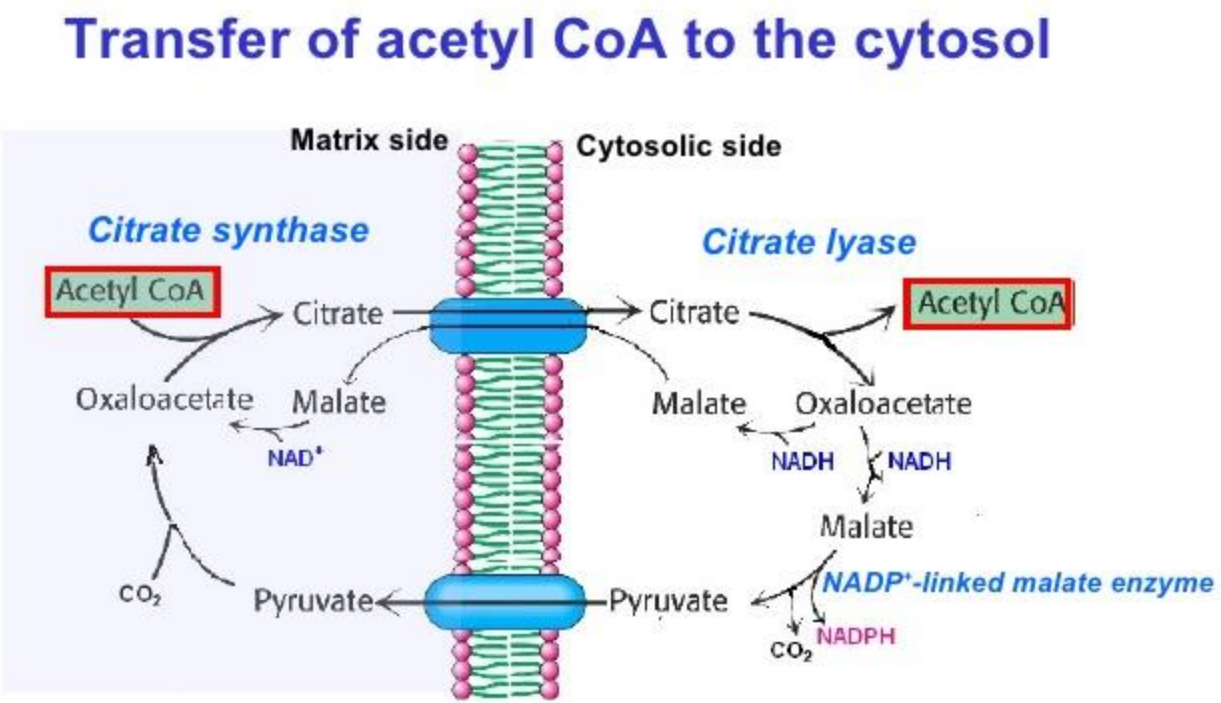
If enough ATP



Synthesis of fatty acids takes place if the cell has enough energy and enough acetyl-CoA

Citrate needed in the TCA cycle if the cell has enough energy (glucose), and can thus build up a stock for a rainy day. The cell is in this state especially after a meal.

Transport of citrate to the cytoplasm

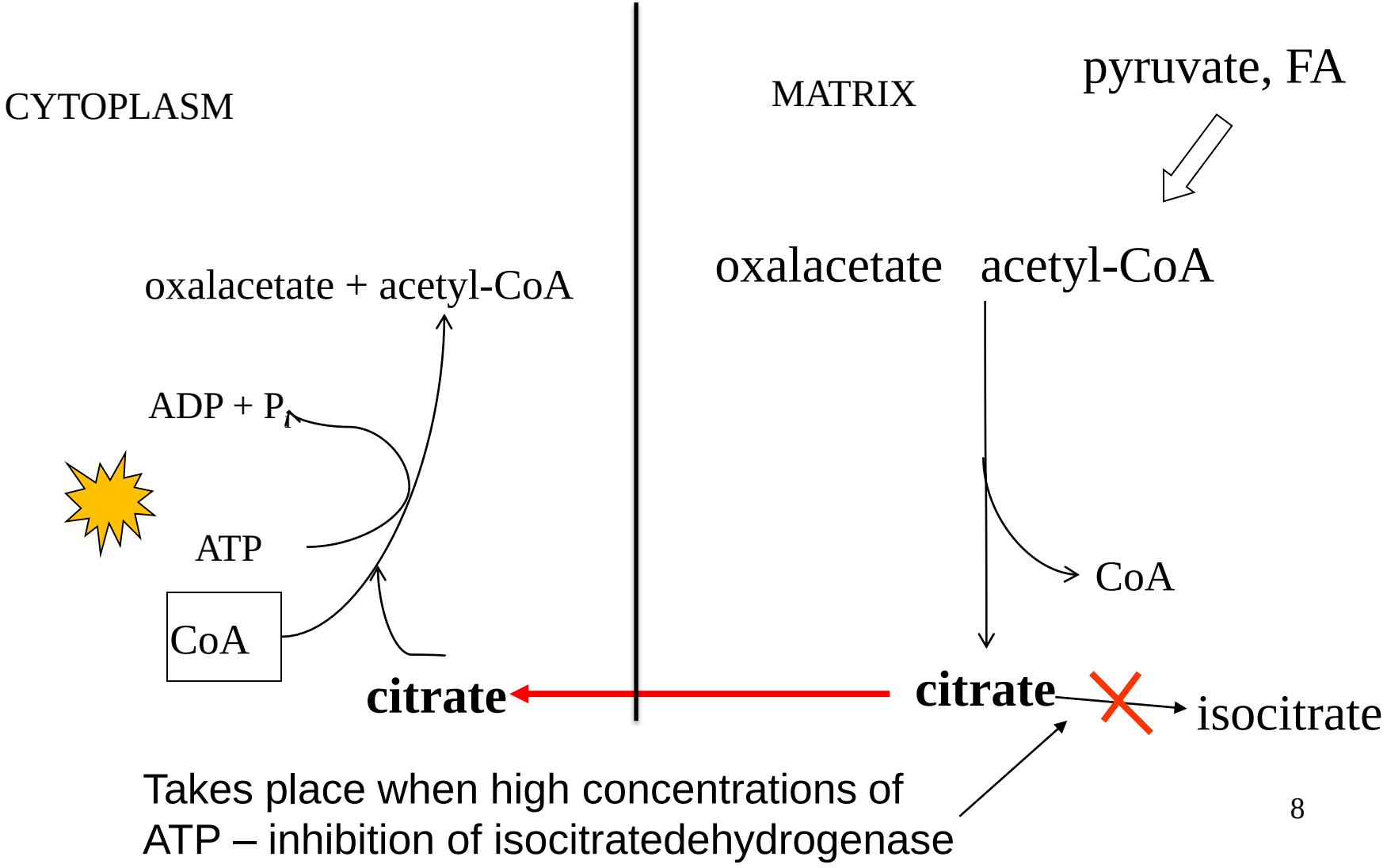


Citrate lyase catalyses the reaction

Citrate + ATP + CoA-SH + H_2O → acetyl-CoA + ADP + P_i + oxaloacetate

50

Transport of citrate into the cytoplasm

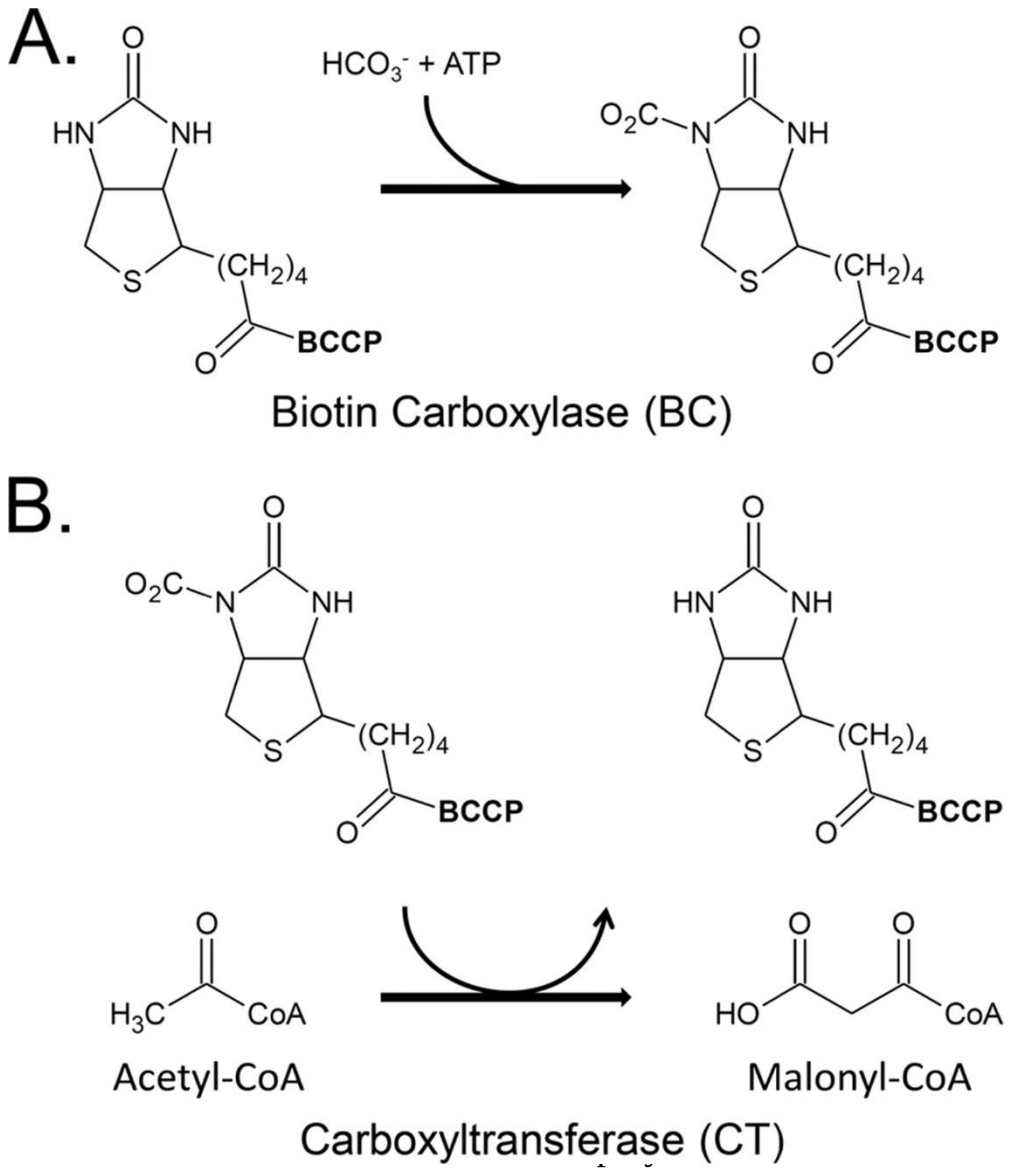


Formation of malonyl-CoA

Acetyl-CoA does not have sufficient energy to enter into synthetic reactions

Carboxylation (cofactor = biotin) catalyzed by acetyl-CoA-carboxylase

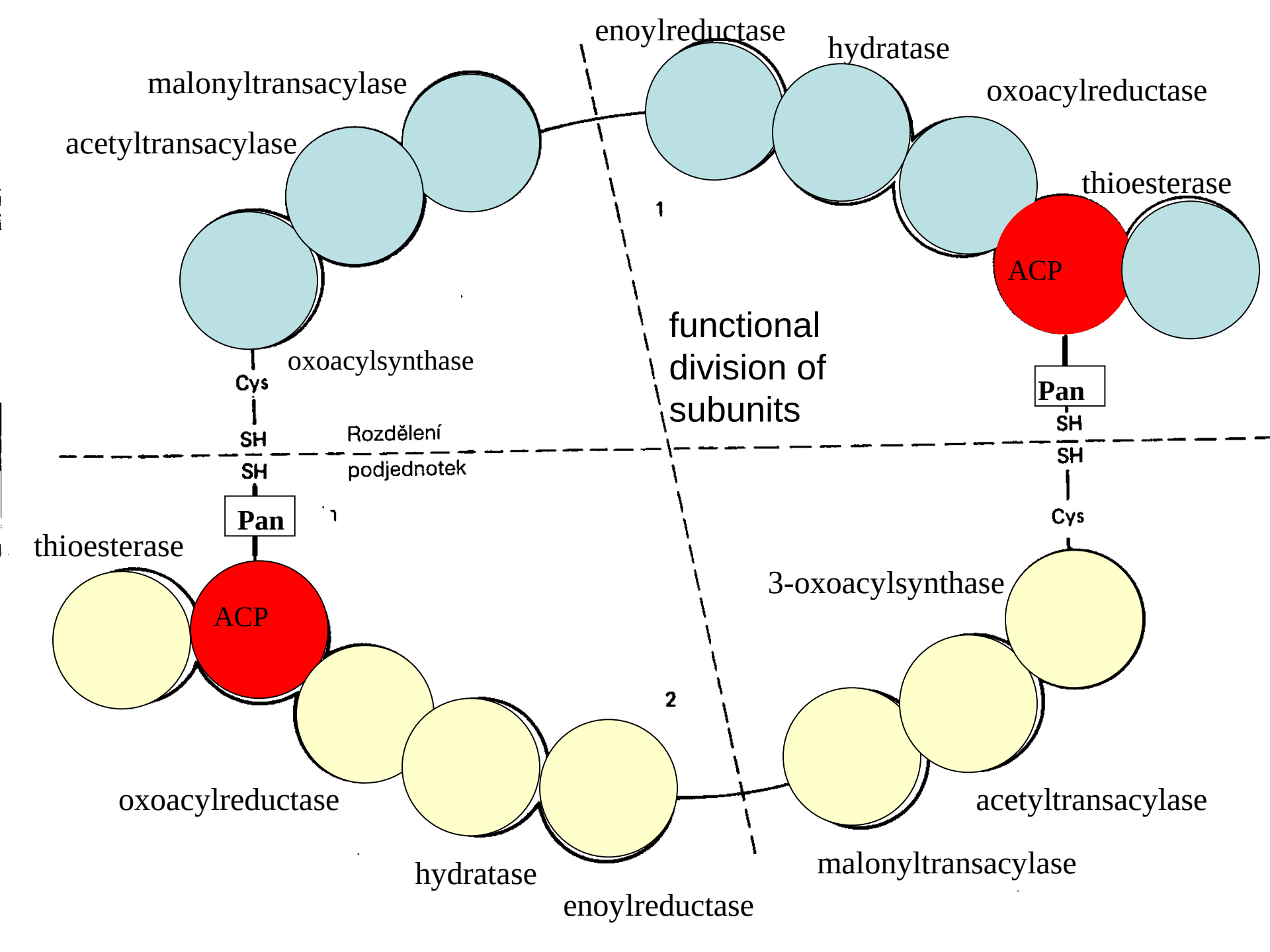
Synthesis of malonyl-CoA



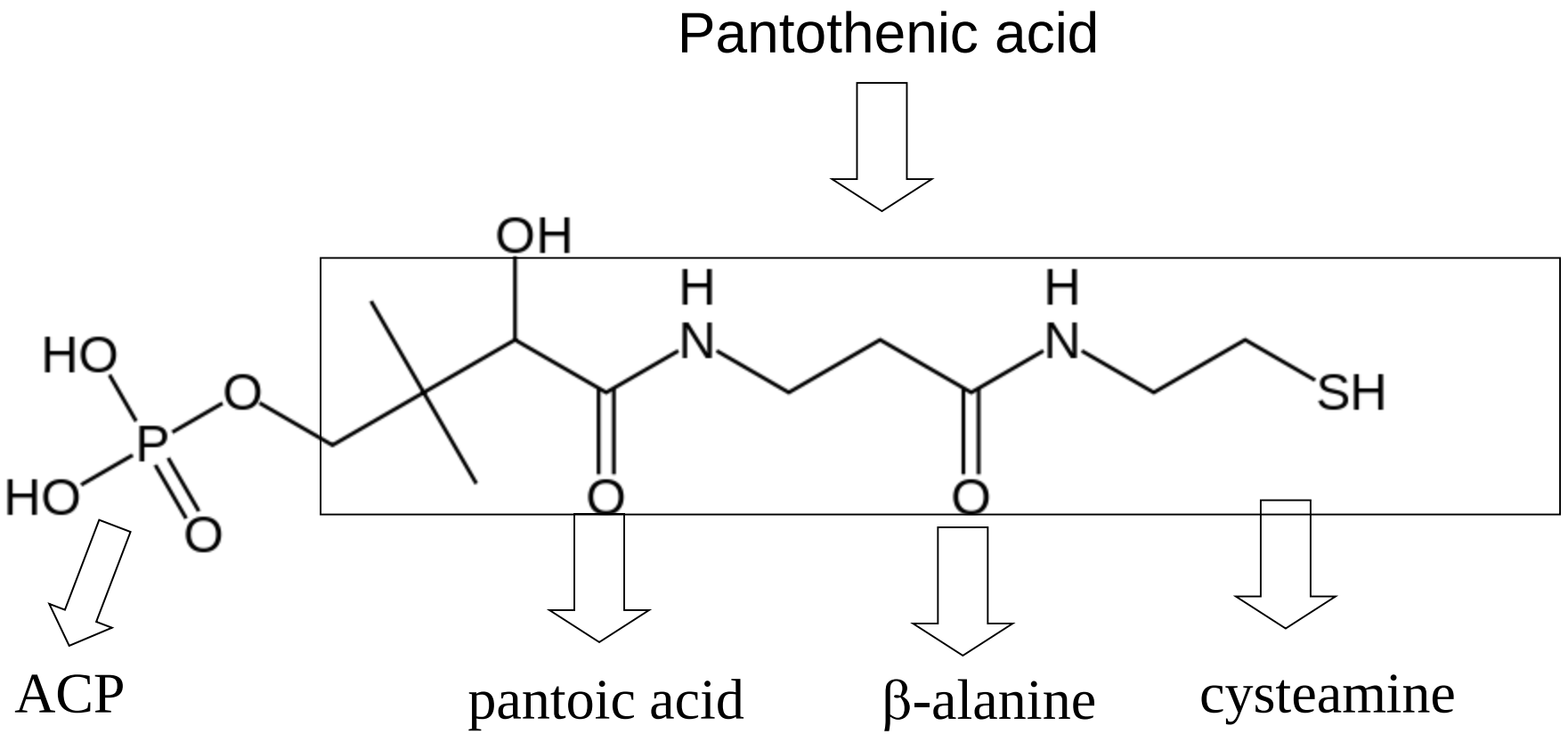
http://jb.asm.org/content/194/1/72/F1.large.jpg

Fatty acid synthase

- multienzyme complex with seven enzymatic activities
- **contains ACP (acyl carrier protein) to which it binds phosphopantetheine**
- mammalian dimeric form comprising two identical complexes
- in parallel two molecules of fatty acids are formed


enoylreductase
hydratase
malonyltransacylase
oxoacylreductase
acetyltransacylase
thioesterase
1
ACP
functional
division of
subunits
oxoacylsynthase
Cys
SH
SH
Pan
Rozdělení
podjednotek
Pan
SH
SH
Cys
thioesterase
ACP
3-oxoacylsynthase
2
oxoacylreductase
acetyltransacylase
hydratase
malonyltransacylase
enoylreductase

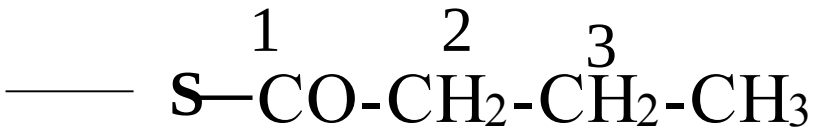
Phosphopantetheine is half of the structure of CoA



http://upload.wikimedia.org/wikipedia/commons/thumb/d/d8/Phosphopantetheine.svg/799px-Phosphopantetheine.svg.png

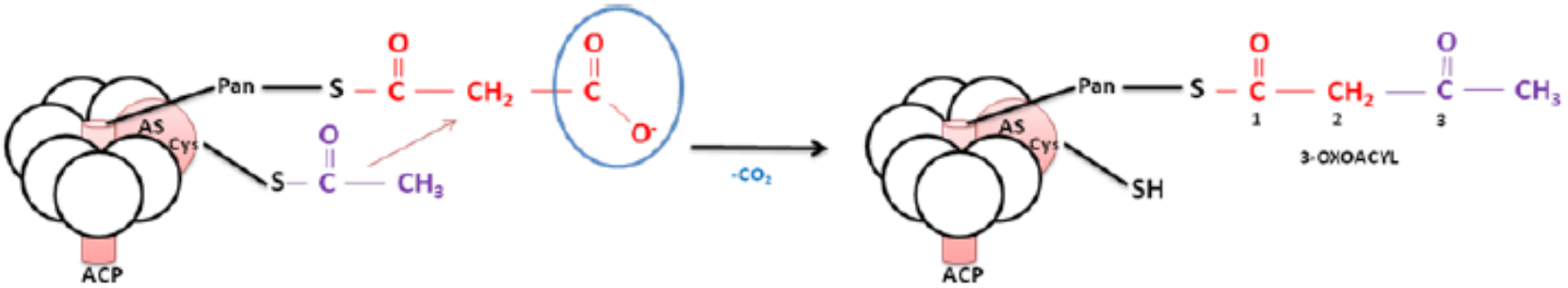
General FA synthesis reaction

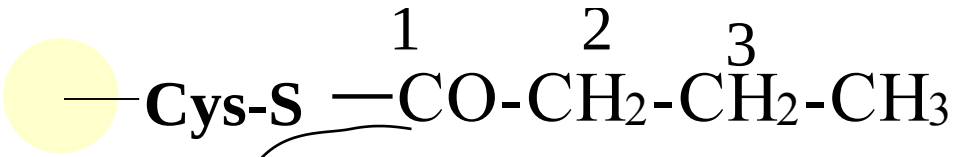
- acyl (acetyl in the first step) is bound to –SH of enzyme

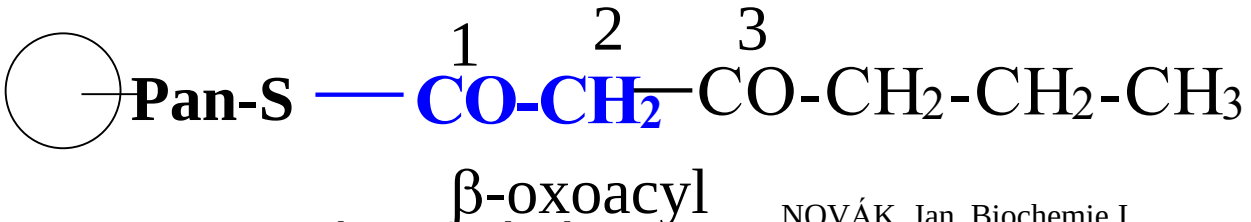


- malonyl bound to the Pan-SH

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 19

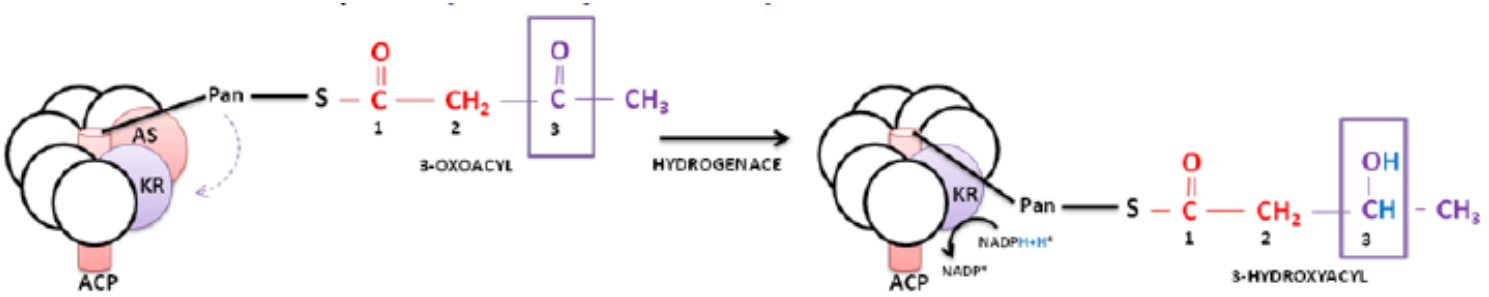




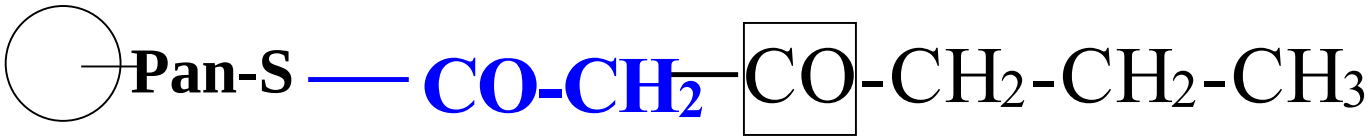


Acyl (acetyl in the first step) is transmitted to the malonyl-CoA, then beta-oxoacyl is formed, releasing CO_2

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 19



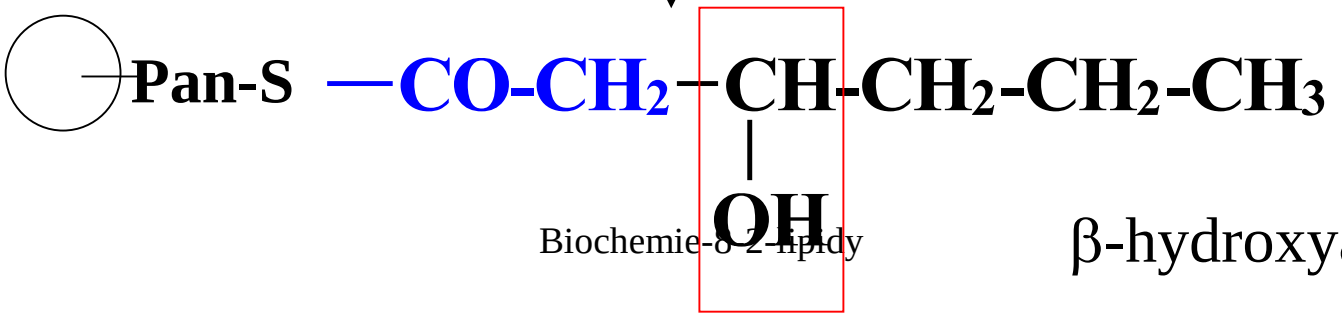
NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 20



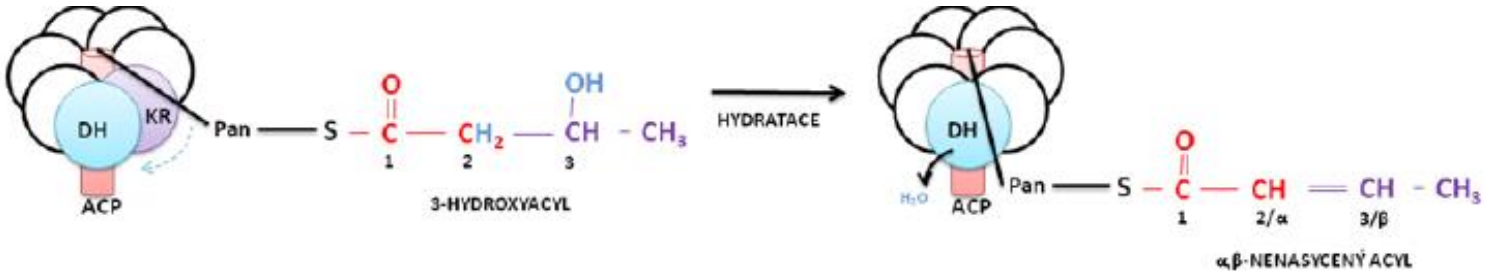
Other reactions take place in relation to fosfopantetein

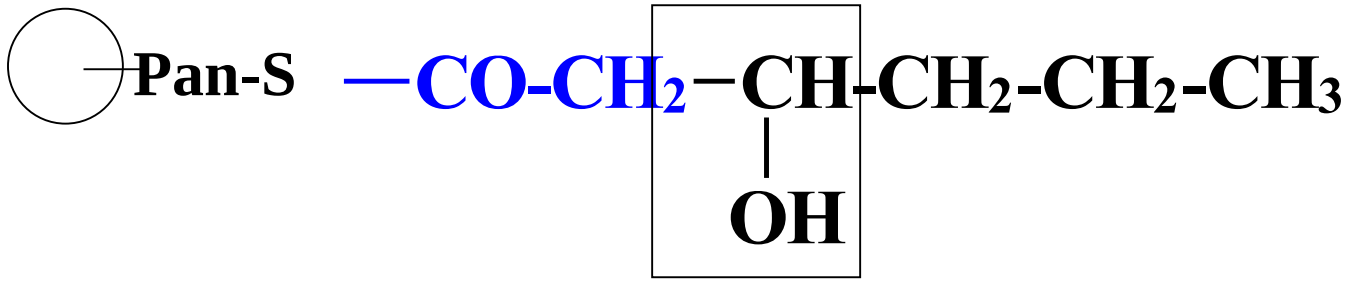
+ 2 H

hydrogenation (NADPH)

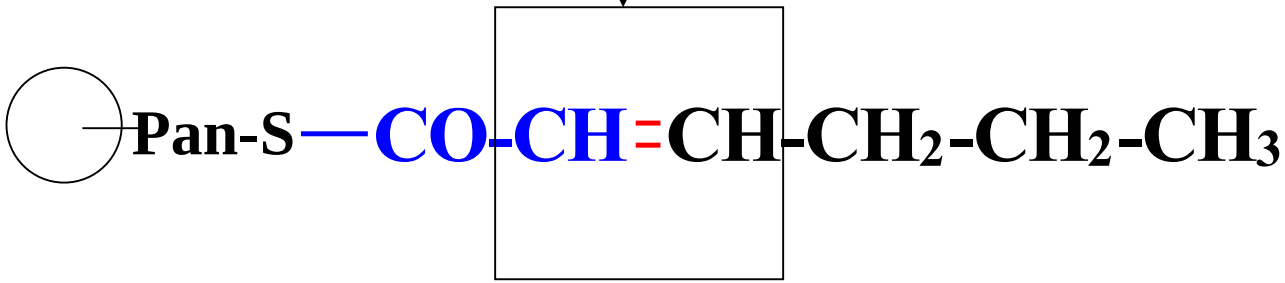


β-hydroxyacyl



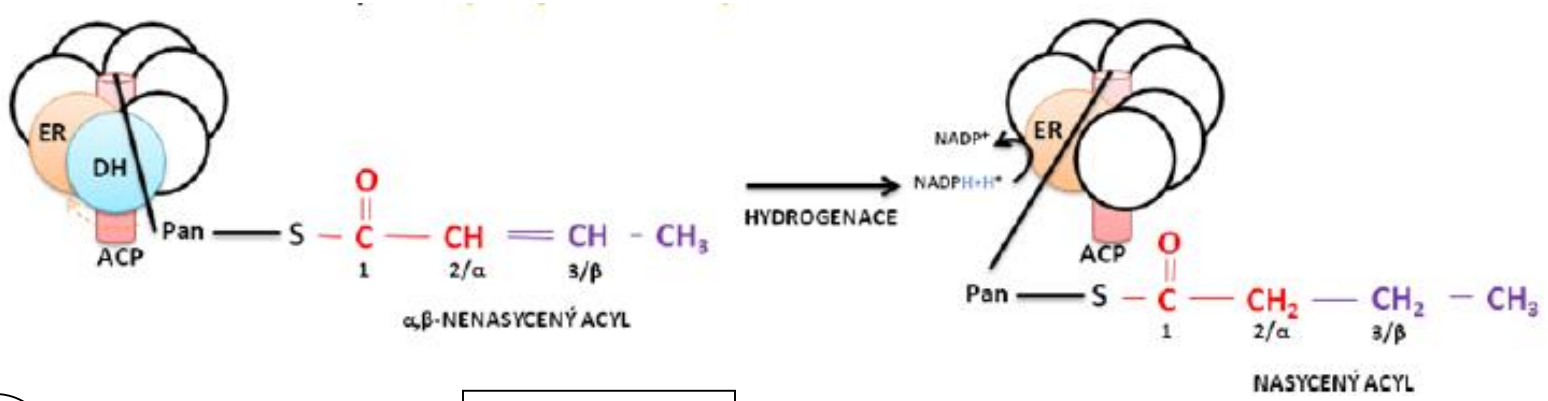


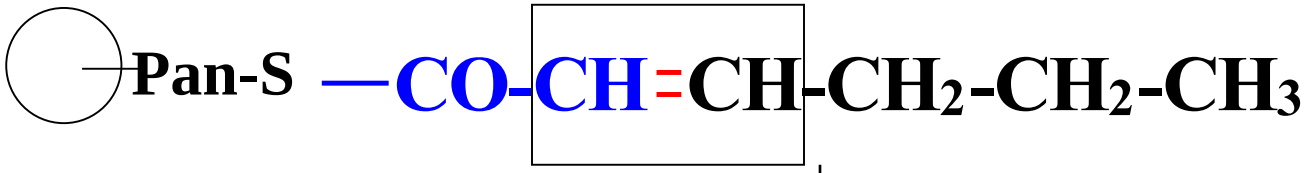
- H_2O dehydratation



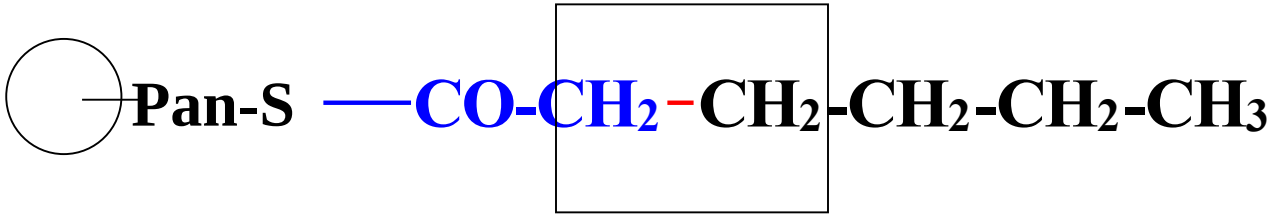
NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 20

α,β-unsaturated acyl





+ 2H hydrogenation (NADPH)



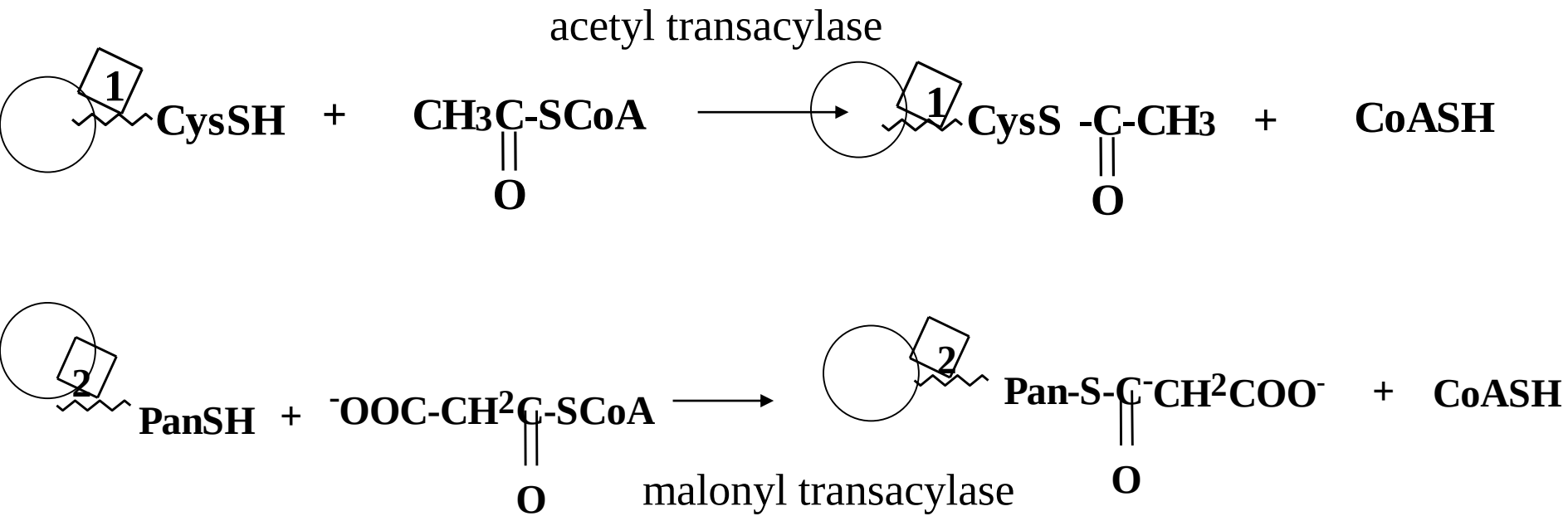
NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 20

saturated acyl longer by 2C

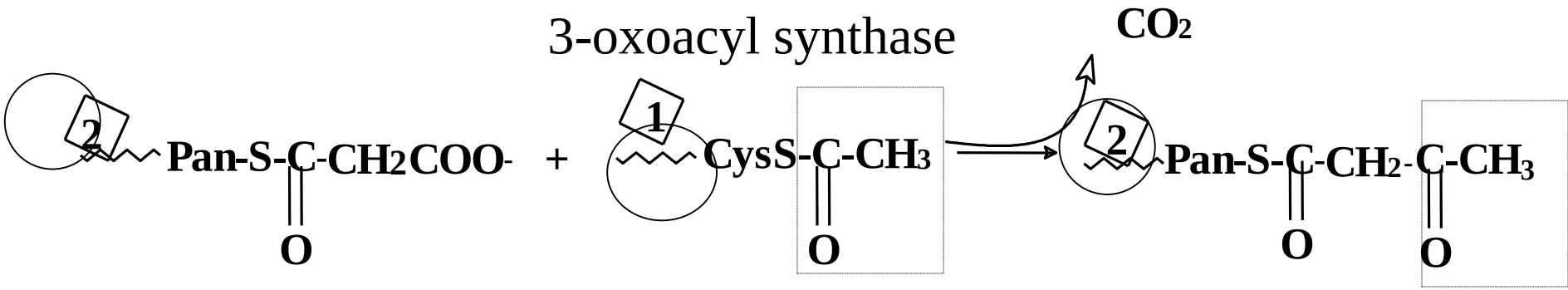
another reaction with malonyl-CoA

Reactions at FA synthase complex

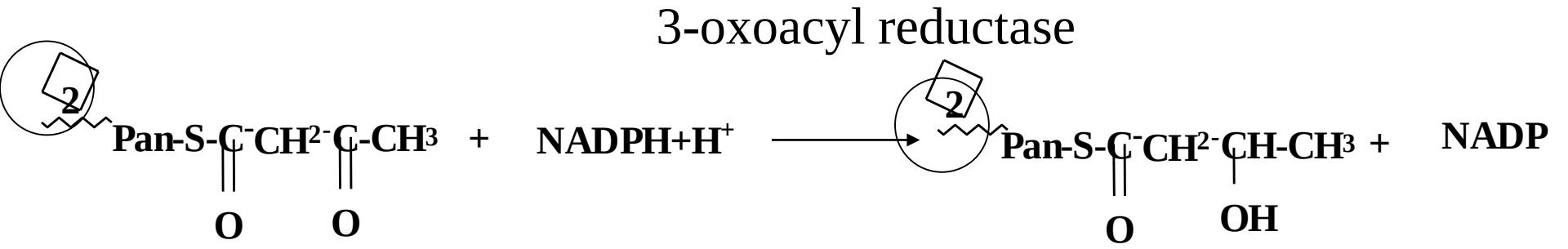
collectively



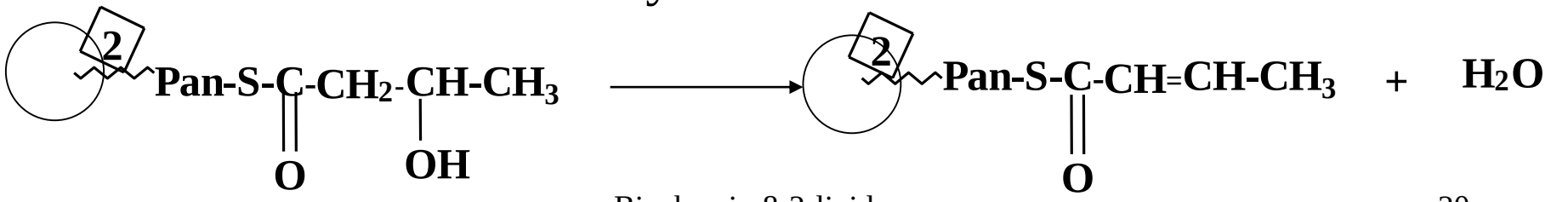
•1


3-oxoacyl synthase
CO2
2
Pan-S-C-CH2COO-
O
+
1
CysS-C-CH3
O
2
Pan-S-C-CH2-C-CH3
O
O

•2

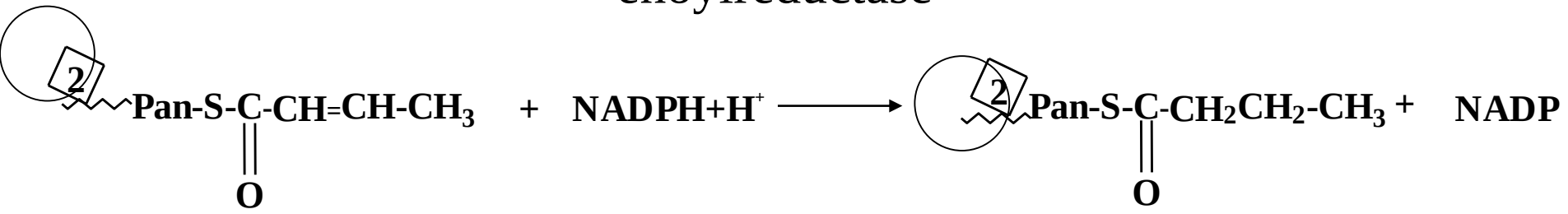

3-oxoacyl reductase
2
Pan-S-C-CH2-C-CH3
O
O
+
NADPH+H+
2
Pan-S-C-CH2-CH-CH3
O
OH
+
NADP

•3

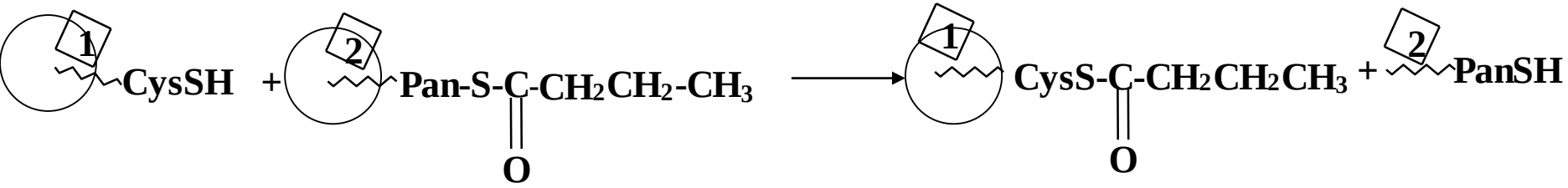

hydratase
2
Pan-S-C-CH2-CH-CH3
O
OH
2
Pan-S-C-CH=CH-CH3
O
+
H2O

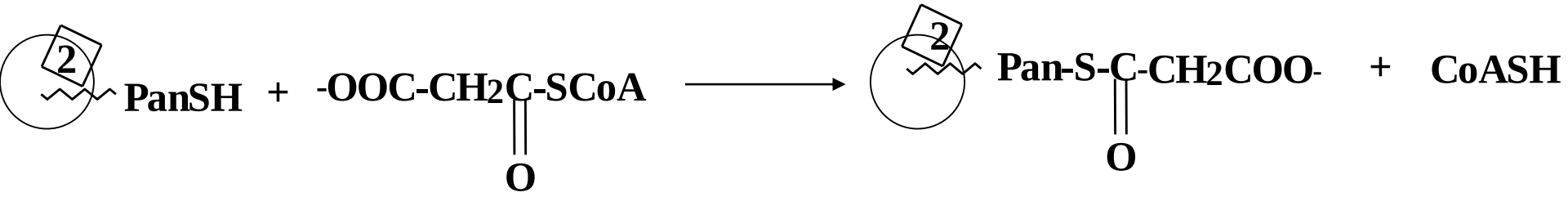
•4

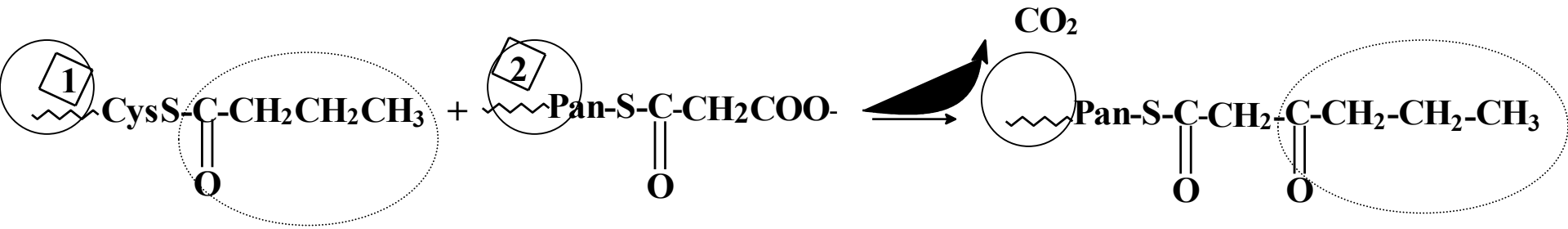
enoylreductase



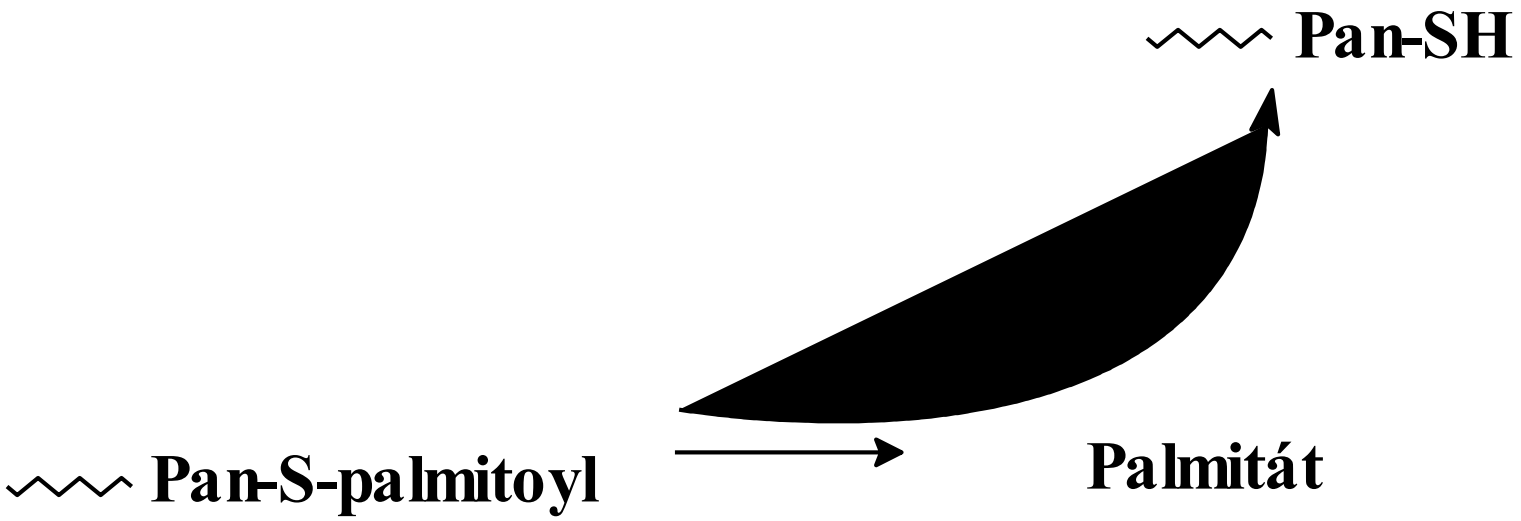
malonyl transacylase




2
PanSH
+
-OOC-CH2C-SCoA
O
2
Pan-S-C-CH2COO-
O
+
CoASH


1
CysS-C-CH2CH2CH3
O
+
2
Pan-S-C-CH2COO-
O
CO2
Pan-S-C-CH2-C-CH2-CH2-CH3
O
O

After passing through steps 1-4 sevenfold …



Balance of synthesis of palmitate (16 C)

$$7\ CH_3CO\text{-}S\text{-}CoA + 7\ ATP + 7\ CO_2$$

$$\mathbf{CH_3CO\text{-}S\text{-}CoA + 7\ HOOC\text{-}CH_2CO\text{-}S\text{-}CoA + 14\ NADPH + 14\ H^+}$$

$$\mathbf{CH_3\text{-}(CH_2)_{14}\text{-}COOH + 7\ CO_2 + 6\ H_2O + 8\ CoASH + 14\ NADP^+}$$

Product of FA synthase in mammals

16:0 (palmitate) (main)

18:0 (stearate) (minor)

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 22

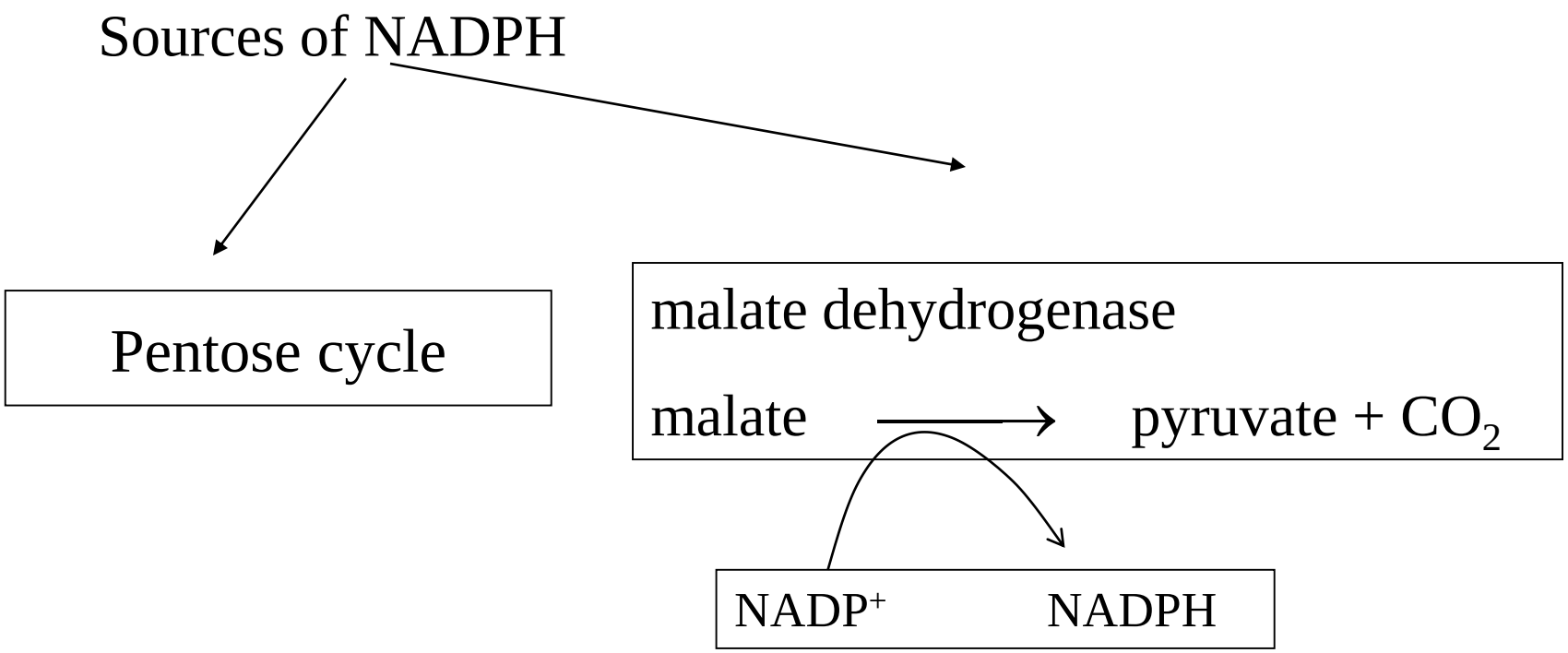
Regulation of the FA synthesis

acetyl-CoA-carboxylase (formation of malonyl-CoA)

Activation	Inhibition
acetyl-CoA	acyl-CoA
insulin	glucagon
	adrenaline

Hormonal regulation provided by insulin (increases the synthesis of FA in the cell if enough glucose - a lot of energy, we can create reserves) and glucagon (reduces the synthesis of FA - the cell has little glucose, can not synthesize FA, it is necessary to carry out their β-oxidation).

NADPH is required for the synthesis of FA



Summary: synthesis and degradation of fatty acids is carried out by two separate tracks

	β-oxidation	**synthesis**
Localization	mitochondria	cytoplasm
Acyl transporter	CoA	ACP
Primary unit	C_2	C_2
Redox cofactors	NAD^+, FAD	NADPH
Enzymes	separately	complex
Hormonal regulation	ratio I/G low	ratio I/G high

I – insulin, G - glucagon

Elongation and desaturation of FA

- On FA synthase complex can be synthesized fatty acids with a maximum length of 18 C, all of which are saturated FA.
- Our body needs for various processes more than 18 C FA and unsaturated FA.
- To receive all via food would be very disadvantageous, therefore in our body are enzymes used for lengthening (elongation) and double bond formation (desaturation) of FA.

Elongation of FA

endoplazmatic reticulum – elongation by malonyl-CoA, cofactor NADPH

mitochondria – reverse of β-oxidation

Elongation of FA is carried out on –COOH end

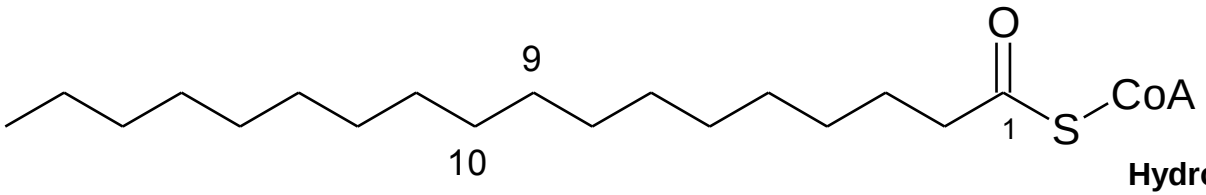
Desaturation

Δ^9, Δ^6, Δ^5 desaturases, plants also Δ^{12}, Δ^{15} desaturases

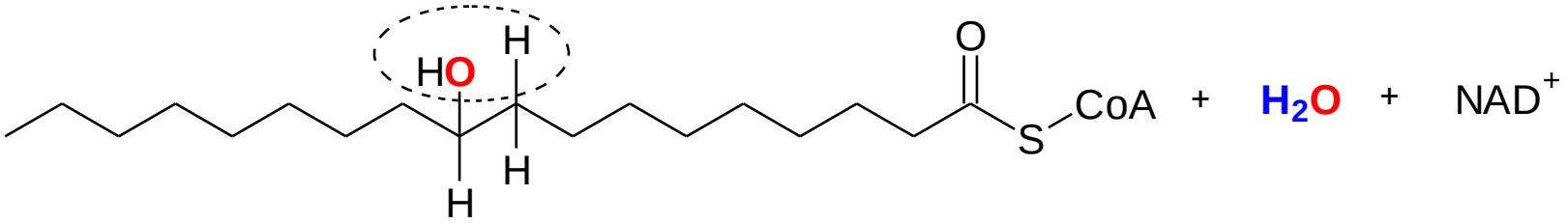
complexes of membrane-bound proteins in the endoplasmic reticulum of the liver cells

- Desaturation of fatty acids is a process which leads to the formation of double bonds. Human (and other animals) are equipped with only a limited number of enzymes (desaturases) that catalyze these reactions, namely **Δ9, Δ6 and Δ5 desaturases.**
- Desaturation process begins by creating a double bond between the **9th and 10th carbon**. We expect to desaturate (ie. dehydrogenation) uses a cofactor FAD and the double bond formed directly, but it is not, desaturation is somewhat more complicated.

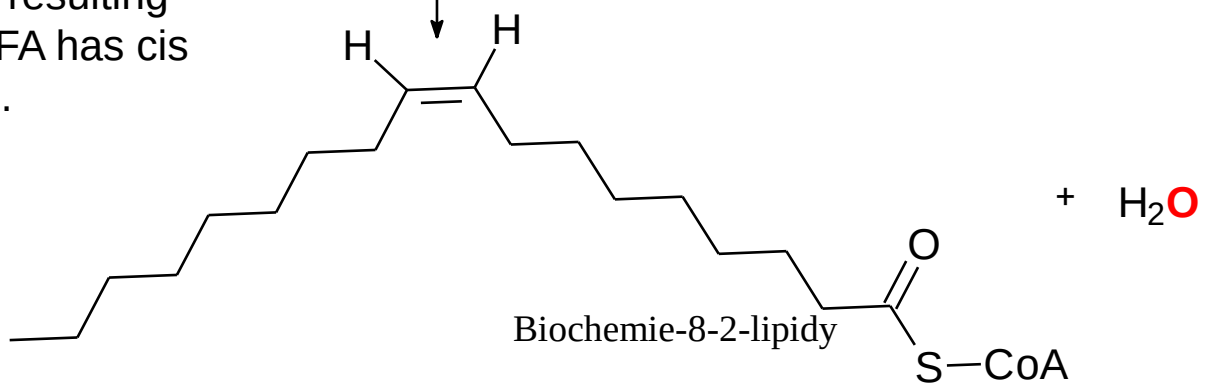
Mechanism of desaturation of fatty acids



Hydroxylation. Oxygen participates the hydroxylation, but only one atom gives rise to the the -OH group on 10th carbon. The second oxygen atom must be reduced to water, which is assisted by NADH + H+.

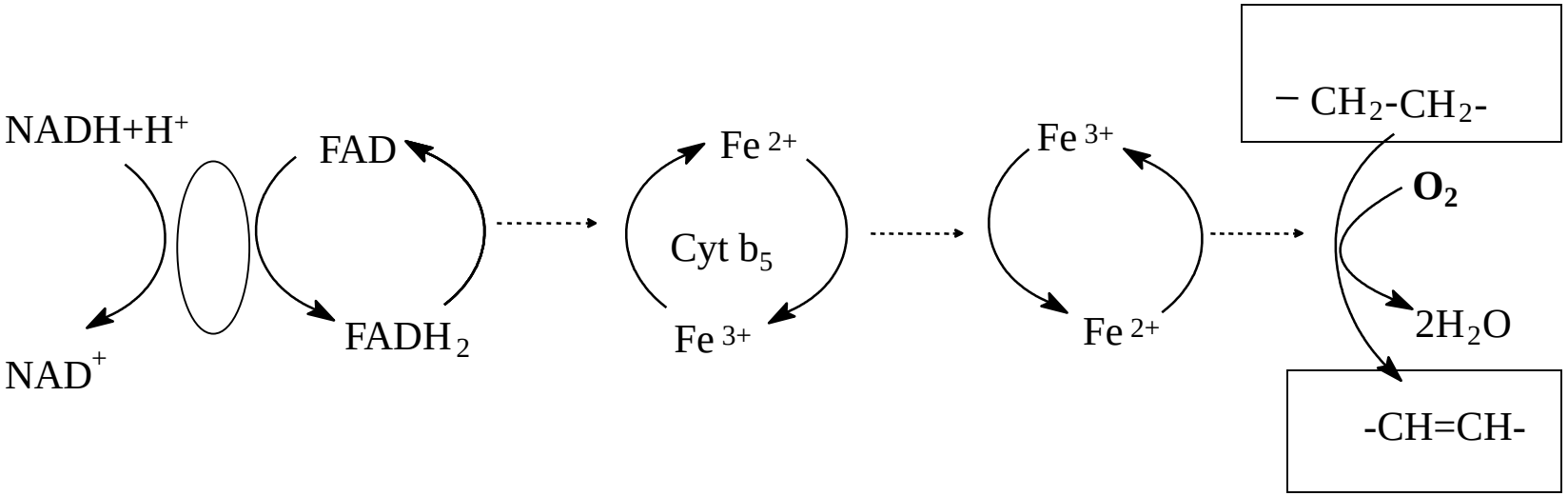


Following dehydration, double bond is created. The resulting unsaturated FA has cis configuration.



Mechanism of desaturation of fatty acids

The double bond is thus formed by **hydroxylation and dehydration**. Hydroxylation is performed by oxygen. Its reduction again is somewhat more complicated than that illustrated in the scheme. The electrons needed for the reduction are transferred from NADH + H+ to FADH2 and then to the iron atoms.



1. hydroxylation: $RCH_2CH_2R + O_2 + AH_2 \rightarrow RCH(OH)CH_2R + H_2O + A$

2. dehydration: $RCH(OH)CH_2R \rightarrow RCH{=}CHR + H_2O$

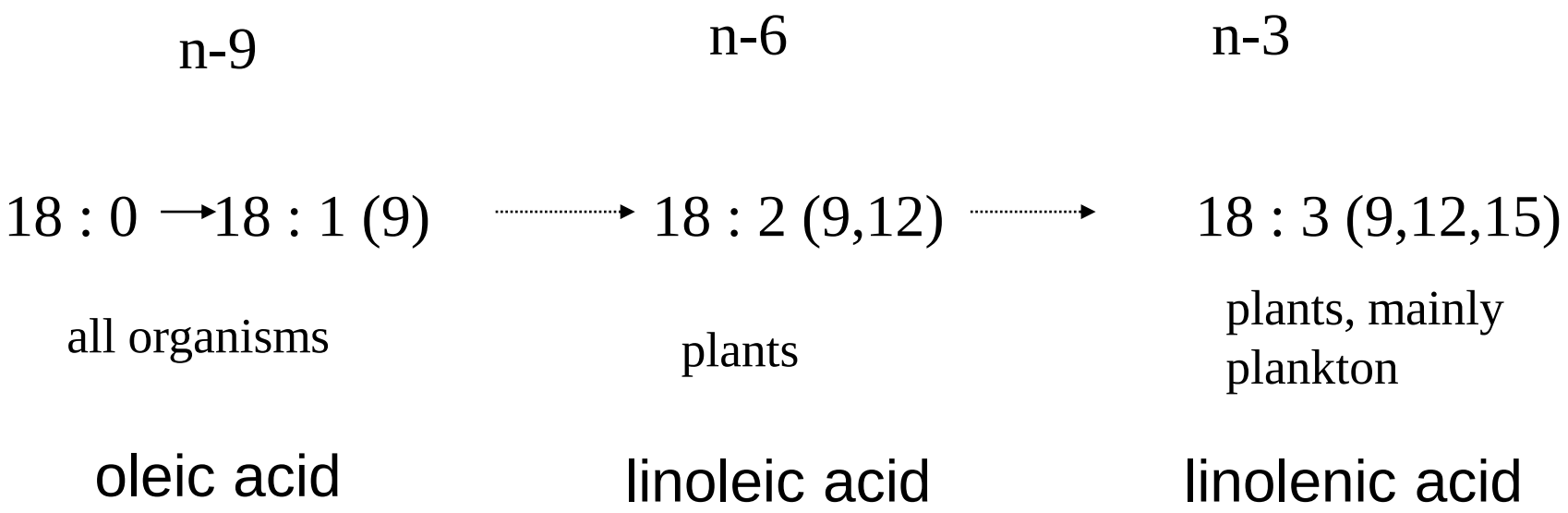
Fatty acids participate in all reactions in the form of acyl-CoA

Desaturation of fatty acids

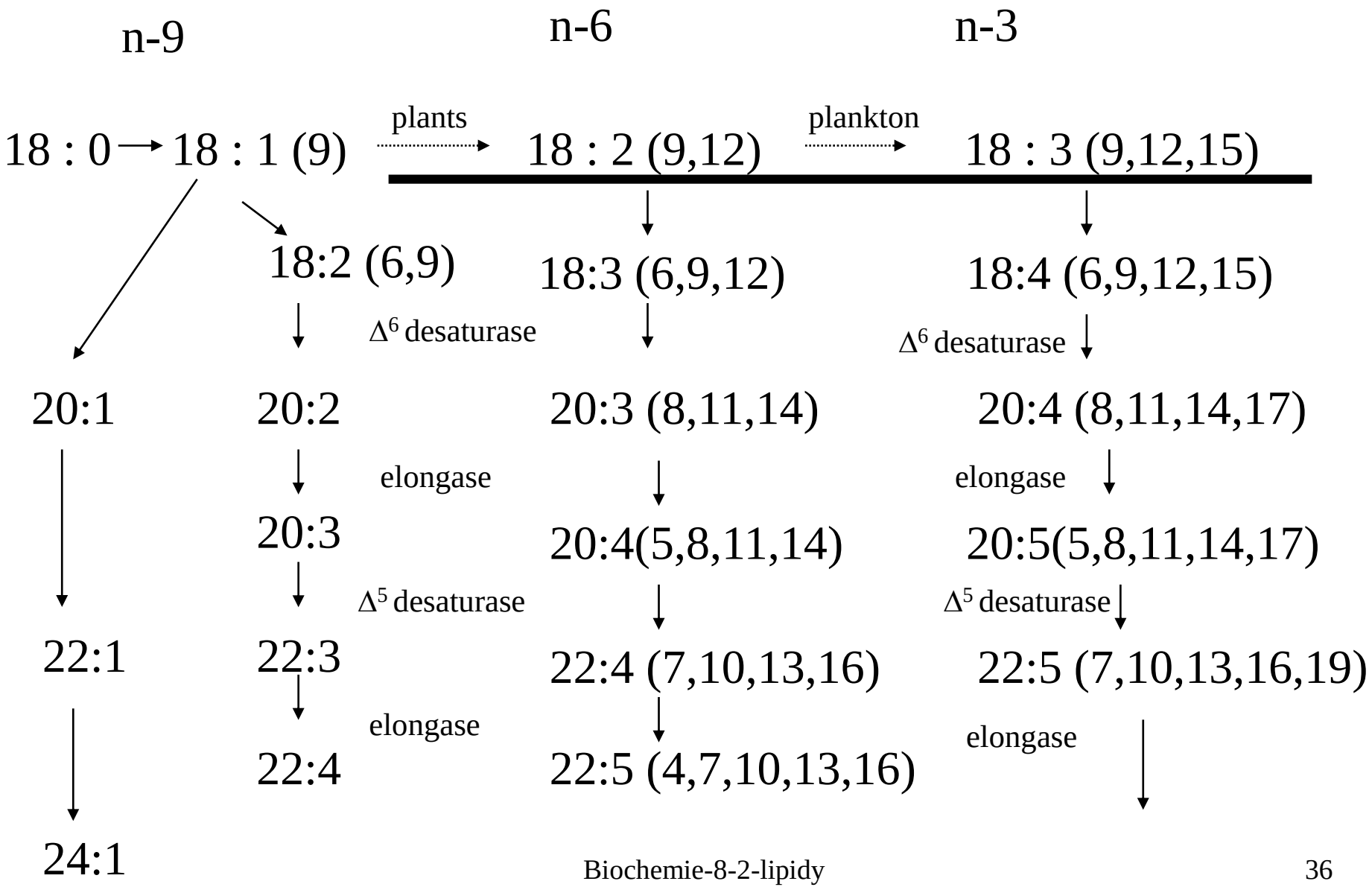
The first step in the desaturation to form a double bond at the ninth carbon of stearic or palmitic acid. Most organisms have Δ9 desaturase.

- Animals form a further double bond only in a region between an existing double bond and the carboxyl terminus (Δ6, Δ5 desaturase)
- Plants also have Δ12 and Δ15 desaturase (found in vegetable oils n-6 and a smaller amount of n-3 unsaturated FA)
- Δ15 desaturase is located in particular in plants vegetating in cold water (algae, plankton)
- The high content of n-3 unsaturated fatty acids in fat of fish (fish feed on plankton, which has the ability to synthesise n-3 fatty acids to a greater extent)

Desaturation of fatty acids



Animals can synthesize more of the FA by combination of elongation and desaturation. They have, however, only available Δ6 and Δ5 desaturases.


n-9
n-6
n-3
18 : 0
18 : 1 (9)
plants
18 : 2 (9,12)
plankton
18 : 3 (9,12,15)
18:2 (6,9)
18:3 (6,9,12)
18:4 (6,9,12,15)
Δ6 desaturase
Δ6 desaturase
20:1
20:2
20:3 (8,11,14)
20:4 (8,11,14,17)
elongase
elongase
20:3
20:4(5,8,11,14)
20:5(5,8,11,14,17)
Δ5 desaturase
Δ5 desaturase
22:1
22:3
22:4 (7,10,13,16)
22:5 (7,10,13,16,19)
elongase
elongase
22:4
22:5 (4,7,10,13,16)
24:1

Linoleic and linolenic acids are essential for humans.

Their food intake is required.

The sources are vegetable oils and fish oil.

Polyunsaturated FA n-3 and n-6 are necessary for the construction of membranes.

Arachidonic acid and eicosapentaenoic acid are necessary for the synthesis of prostanoids.

Deficiency of polyunsaturated FA n-3 and n-6 in experimental animals induces disturbances in permeability of the skin, weight loss, accumulation of cholesterol.

Triglycerides as energy reserves

Triglycerides are the most effective means of saving energy

They are stored without ties of water, while a gram of glycogen binds two grams of water

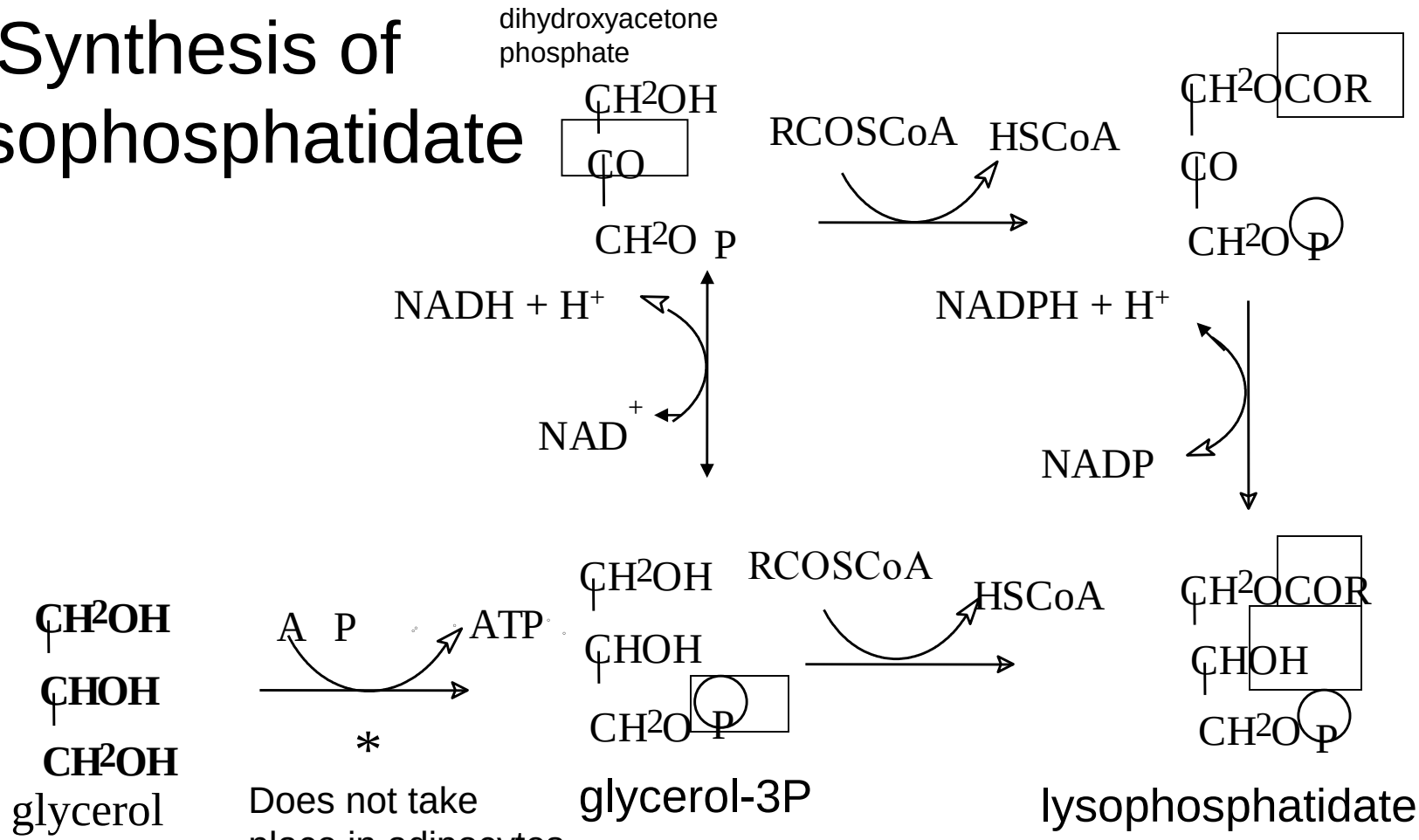
compound	Combustion heat (kJ/g)
Glycogen	17
TG	38

15 kg of fat is equivalent to 100 kg of hydrated glycogen

Synthesis of triglycerides

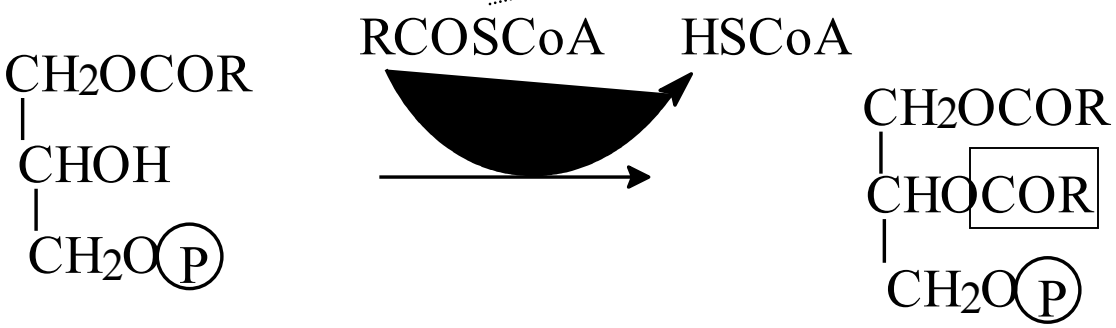
ER - liver, fat cells, intestinal mucosa

1. Synthesis of lysophosphatidate



2. Synthesis of phosphatidate

usually unsaturated

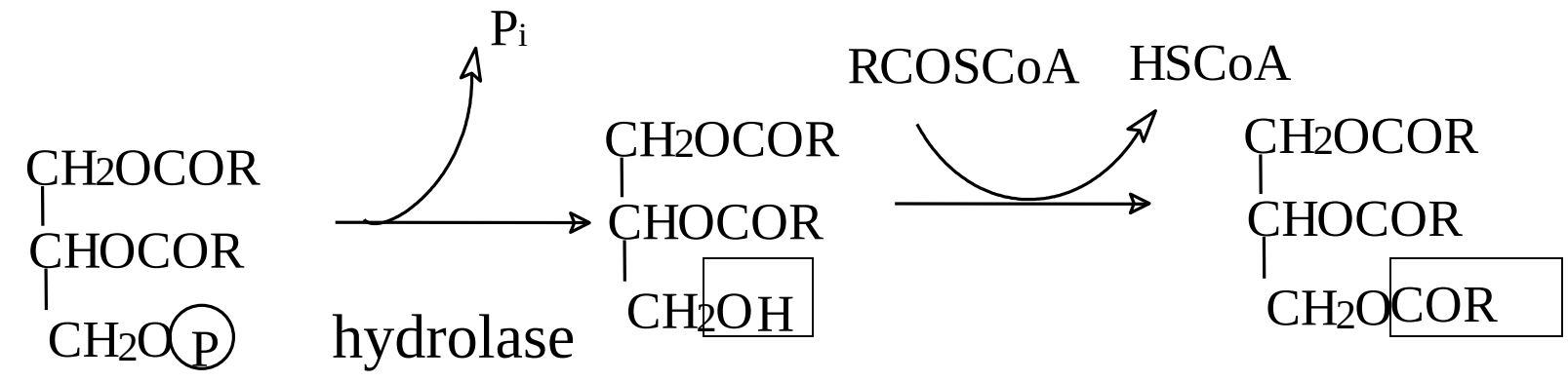


lysophosphatidate

phosphatidate

esterification to carbon 2
usually unsaturated

3. Synthesis of triglycerides



ER

PI (phosphatidylinositol), cardiolipin

PC (phosphatidylcholine),

PE (phosphatidylethanolamine),

PS (Phosphatidylserine)

Small intestine → CM

Liver → VLDL

adipose tissue → storage

Metabolism of phospholipids and glycolipids

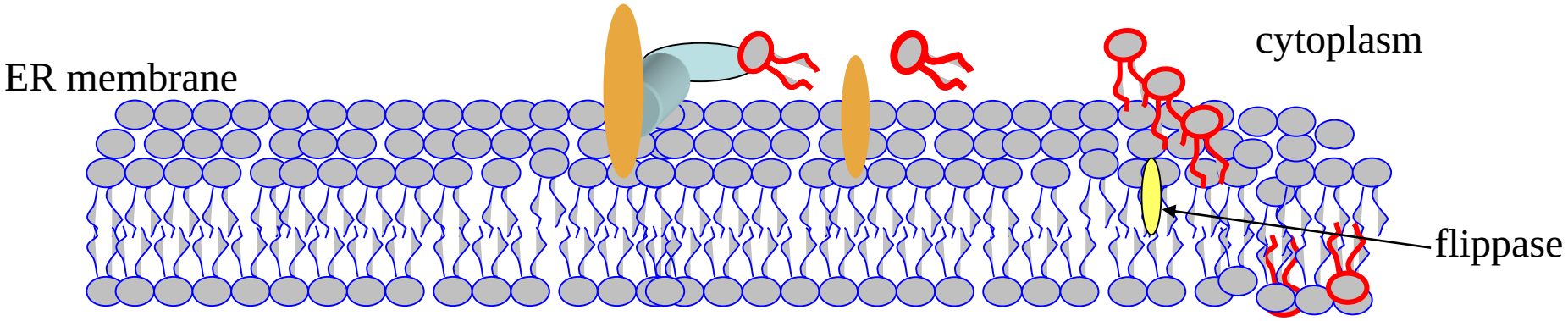
Among the main phospholipids belong :

- **phosphatidylcholine – PC**
- **phosphatidylethanolamine – PE**
- **phosphatidylserine – PS**
- **phosphatidylinositol – PI**
- **cardiolipin – CL**

Biosynthesis of glycerophospholipids

- Occurs in all cells except erythrocytes
- Part of cell membranes
- Some initial reactions are the same as in the synthesis of triglycerides

Localization of synthesis of phospholipids in cell



Synthesis takes place on the phospholipid membranes of the **smooth and rough ER**

Enzymes catalyzing the synthesis are **integral membrane proteins** with active centers facing the cytoplasm

Newly synthesized phospholipids are built into the outer layer membranes

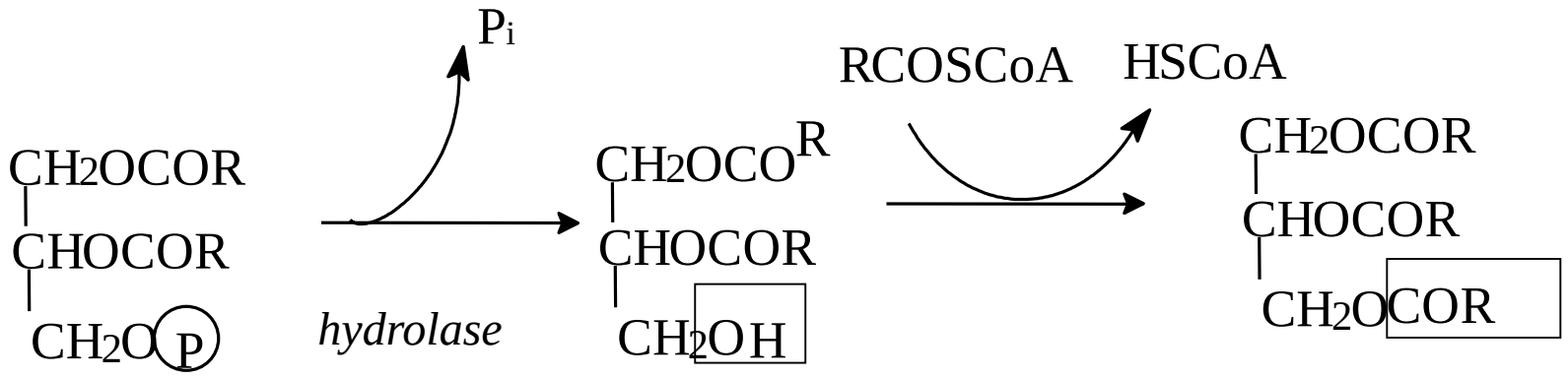
By flippases they are transmitted to the inner layer

In the other membranes PLs are transmitted either by continuous diffusion between membranes or membrane vesicles

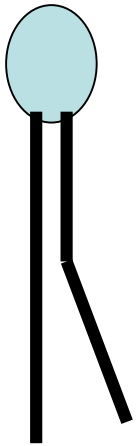
In the cytoplasm PLs are transmitted using **phospholipid transfer proteins**

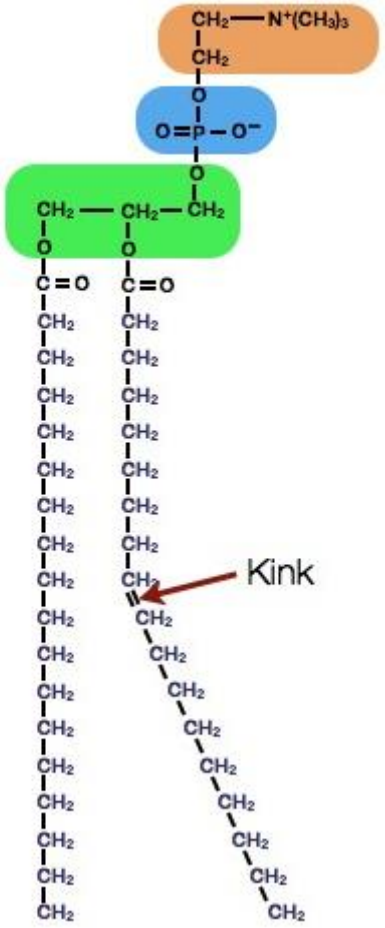
The synthesis of phospholipids is based either on phosphatidate or 1,2-diacylglycerol

Synthesis of triglycerides and glycerophospholipids - following a joint reaction



Glycerophospholipids





Phosphatidylcholine – PC

Phosphatidylethanolamine – PE

Phosphatidylserin – PS

Phosphatidylinositol – PI

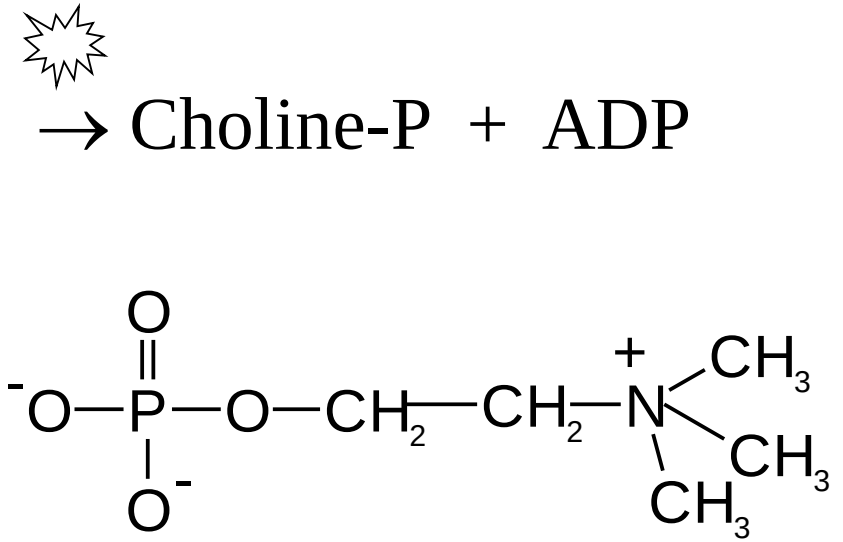
Cardiolipin - CL

http://medcell.med.yale.edu/lectures/images/phospholipid.jpg

A) Synthesis of phosphatidylcholine

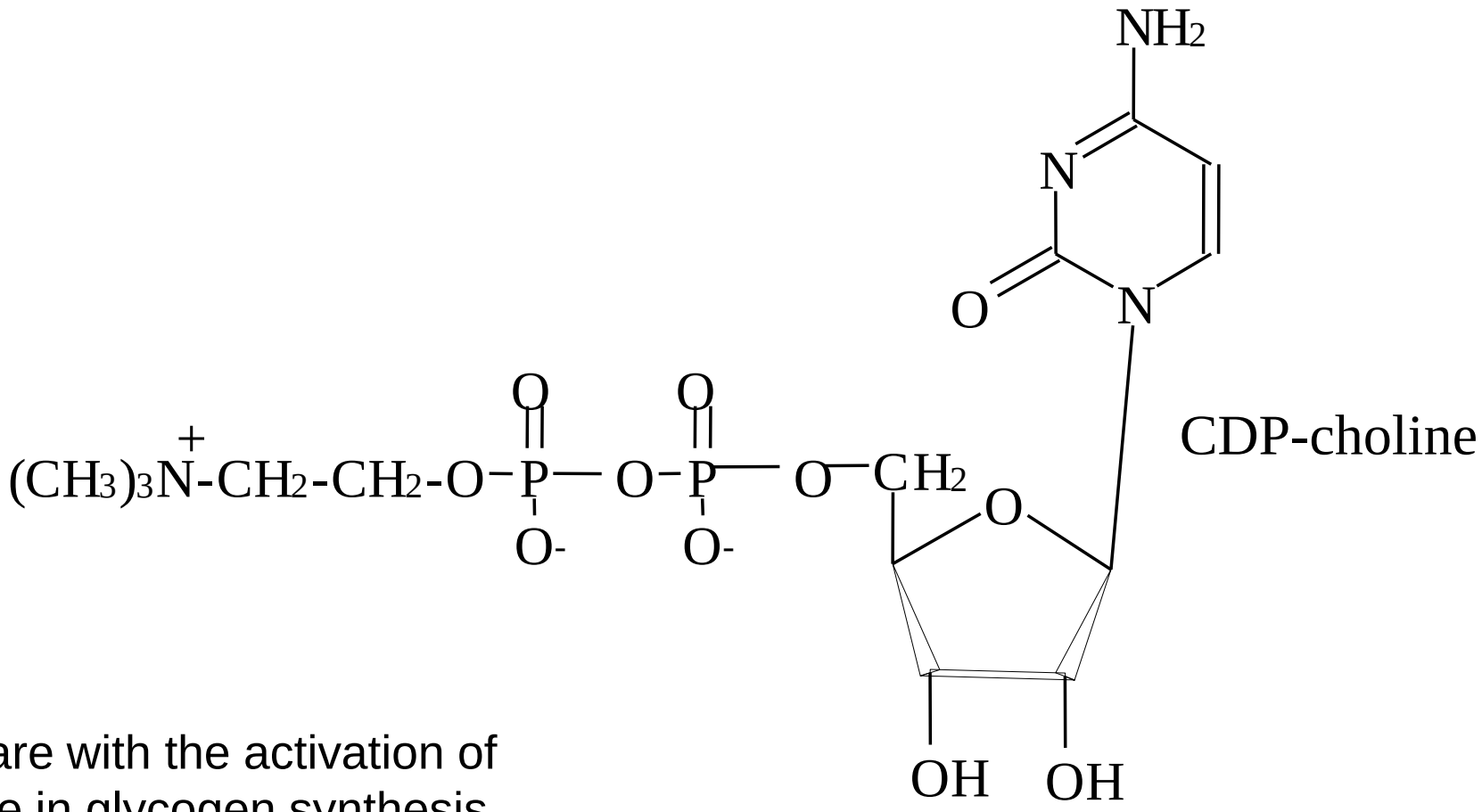
Choline must be activated prior to the synthesis

Activation of choline takes place in two steps



cholinephosphate

2) choline-P + CTP $\rightarrow$ CDP-choline + PP_i



CDP-choline

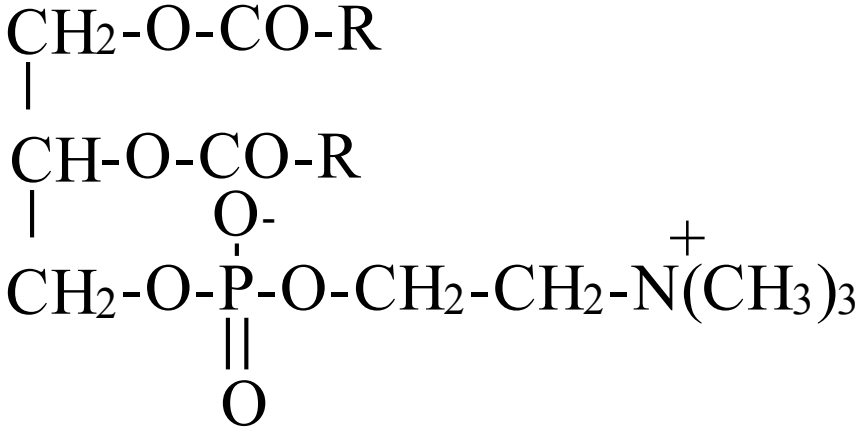
Compare with the activation of glucose in glycogen synthesis

3) Synthesis of activated choline of phosphatidylcholine and 1,2-diacylglycerol

CDP-choline + 1,2-DG → **phosphatidylcholine** + CMP

Besides that we synthesize phosphatidylcholine, we accept it in food and store large part in the intestines

Note the **activation of choline by CTP**, in carbohydrate metabolism glucose is **activated by UDP**.



Functions
A) **Phosphatidylcholine (pulmonary surfactant)**

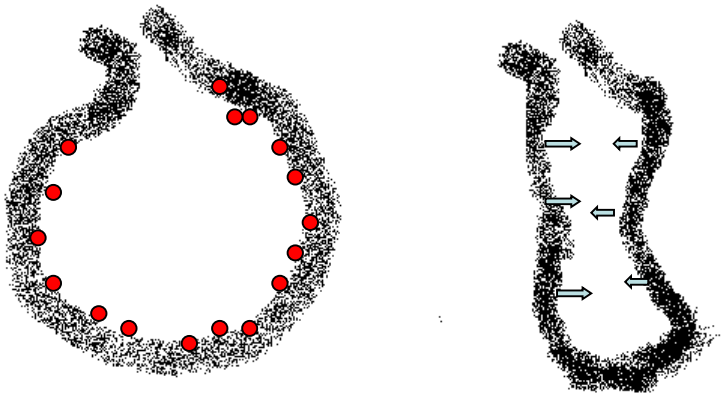
- Pulmonary surfactant generally is a mixture of phospholipids (90%) and protein (10%), the main phospholipid is dipalmitoylphosphatidylcholine.
- The task of pulmonary surfactant is to decrease surface tension at the surface of the alveoli. This makes them easier to open during aspiration (inhaling) and prevent "sticking" their walls (alveolar collapse) during expiratory (exhalation). Deprivation of human lung surfactant means experiencing respiratory distress.

pulmonary surfactant

main component is dipalmitoylphosphatidylcholine

reduces the surface tension on the surface of alveoli, facilitates opening of the alveoli during aspiration

lack of surfactant - respiratory distress

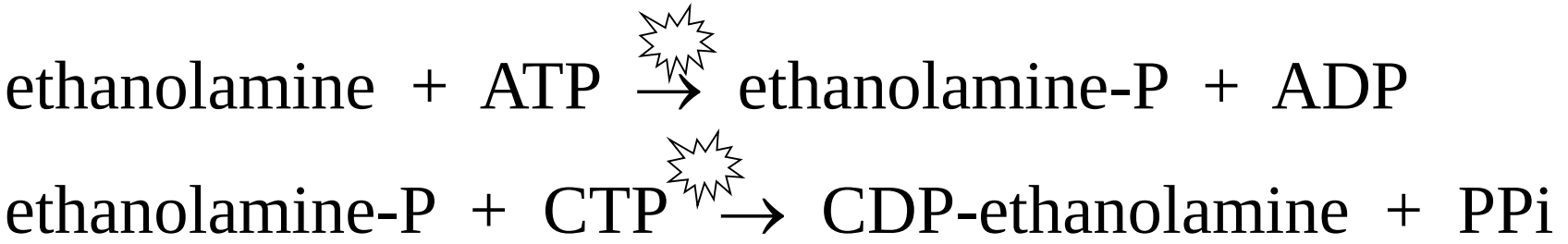


The walls of the alveoli are covered with water molecules, during exhalation the walls go close to each other and bind due to attractive forces, then the expansion may prevent reuse

Pulmonary surfactant eliminates these attractive forces

B) Synthesis of phosphatidylethanolamine

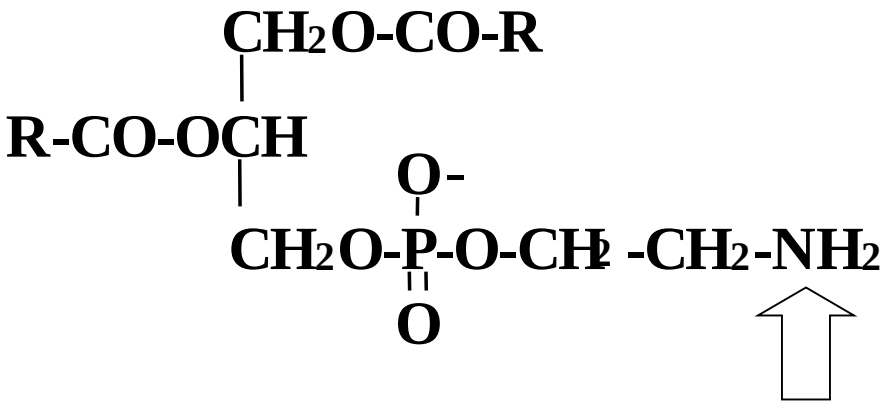
activation of ethanolamine



Synthesis

C) Conversion of phosphatidylethanolamine to phosphatidylcholine

- alternative route of synthesis of phosphatidylcholine



N-methylation using S-adenosylmethionine

→ ph**osphatidylcholine** (in the liver)

Choline in the diet

No disorder has yet been defined related to lack of choline

Choline deficiency in rats induced disorders structures ER membranes and fatty liver

Choline is sometimes classified among the group B vitamins

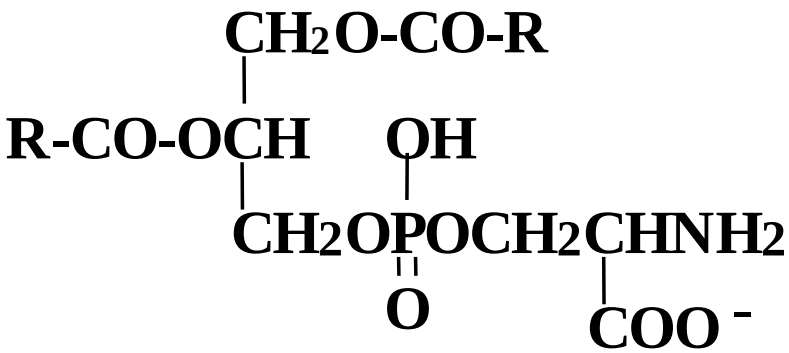
In the US, the recommended daily dose of choline is 500 mg

Foods rich in choline:

liver, meat, nuts, eggs

D) Biosynthesis of phosphatidylserine proceeds differently

phosphatidylethanolamine + serine → **phosphatidylserine** + ethanolamine

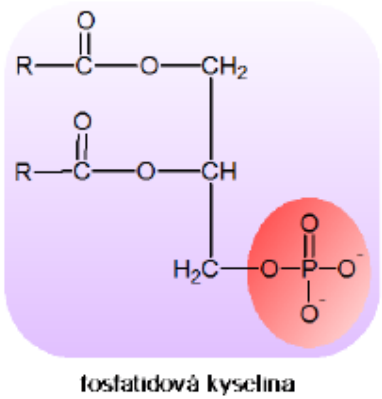


phosphatydylethanolamine may be produced by decarboxylation

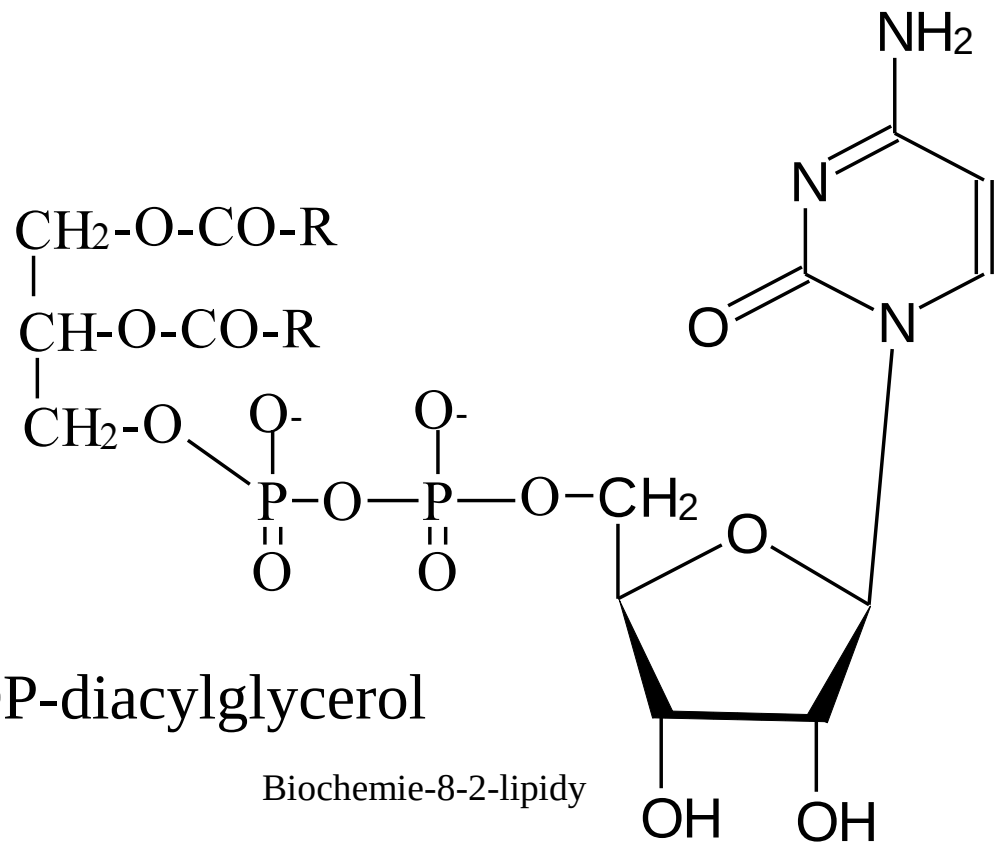
E) biosynthesis of phosphatidylinositol

1) Activation of phosphatidic acid

phosphatidic acid + CTP → CDP-diacylglycerol + PPi



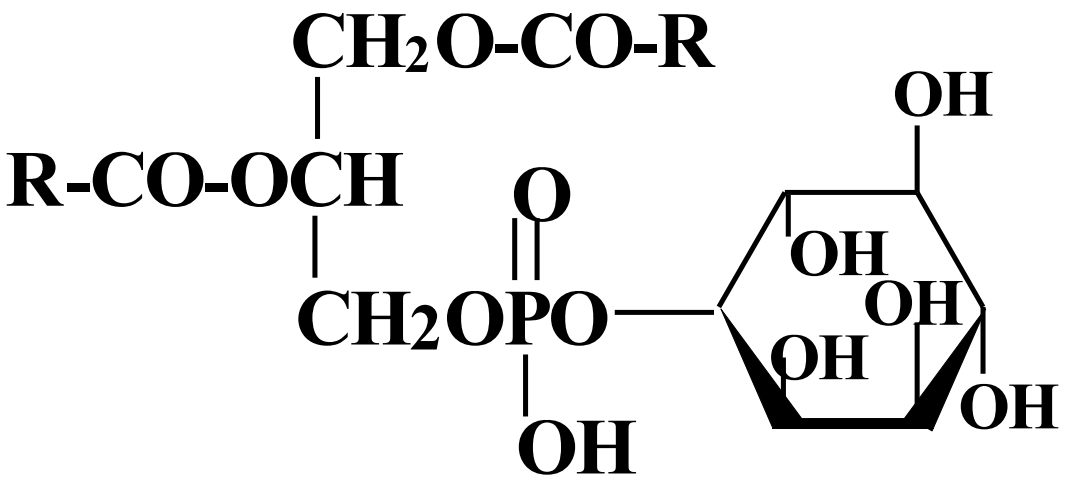
NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 29



CDP-diacylglycerol

2) **synthesis**

CDP-diacylglycerol + inositol → phosphatidylinositol

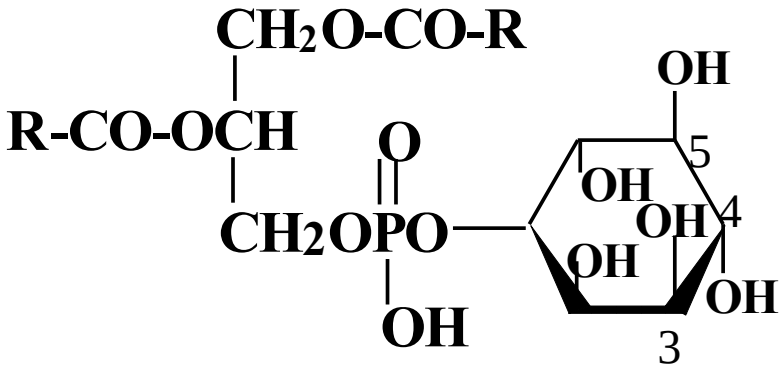


Synthesis of phosphatidylinositol phosphate

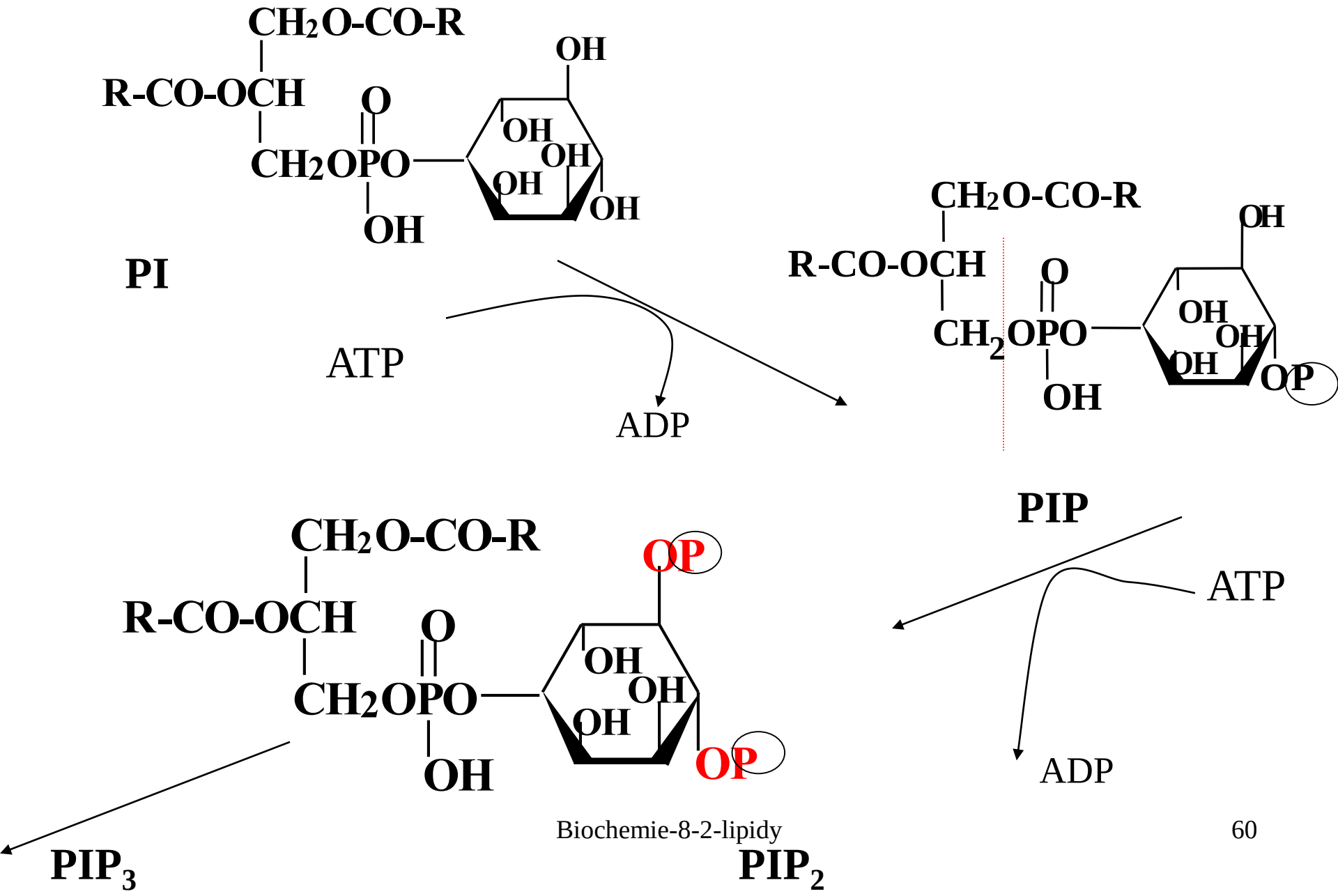
PI + ATP ⟶ PIP + ADP

PIP + ATP ⟶ PIP_2 + ADP

PIP_2 + ATP ⟶ PIP_3 + ADP

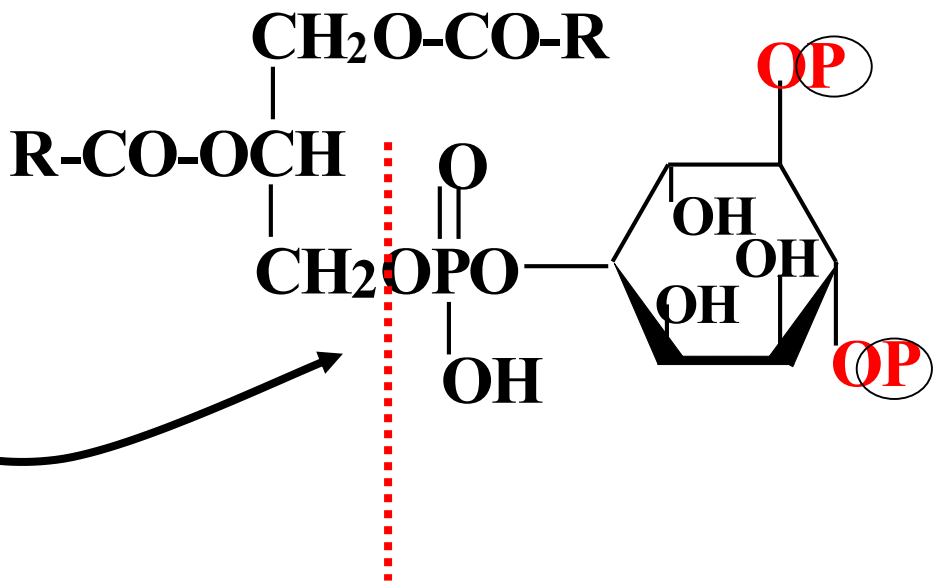


Synthesis of phosphatidylinositol phosphate



The role of PIPs in the transmission of signals across the cytoplasmic membrane

- binding of certain mediators in the cytoplasmic membrane receptor activates **phospholipase C**
- that catalyzes the cleavage of PIP (PIP2 and PIP3) to DG and IP2 (IP3 and IP4)
- these products act as second messengers in the cell



second messenger

substance that is produced in the cell as a result of binding of the hormone or the neurotransmitter to a membrane receptor

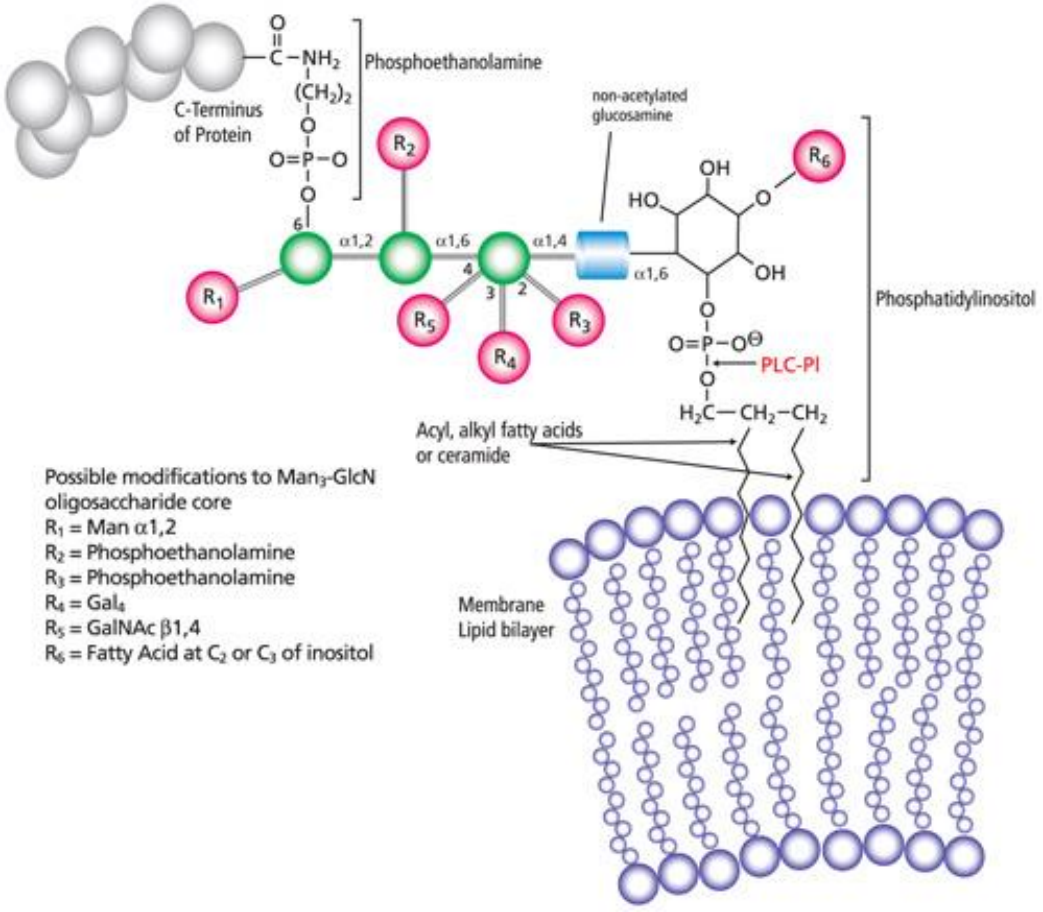
•mediates the effect of the hormone or mediator in cell

• transmits information in a cell on other intracellular systems

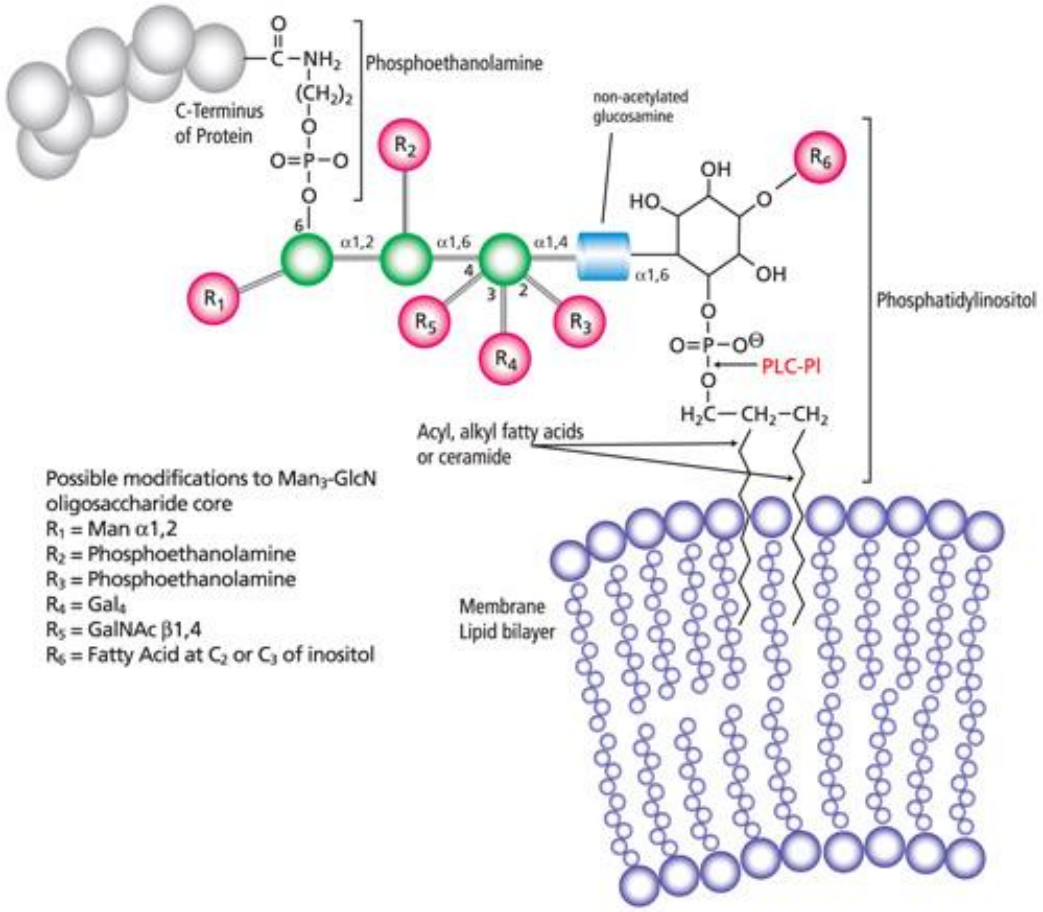
In addition to the functions of the second messenger

PI performs the function of phosphatidylinositol anchor

- Phosphatidylinositol anchored in the membrane with bound **polysaccharide chain**. On this chain can then be bound **proteins** that need to communicate with the environment (e.g. **alkaline phosphatase, acetylcholinesterase, antigens** ...). That they are connected to the "PI anchor“ puts them above the surface of the membrane and thus can perform its functions (they are accessible to other enzymes, hormones)



Phosphatidylinositol anchor

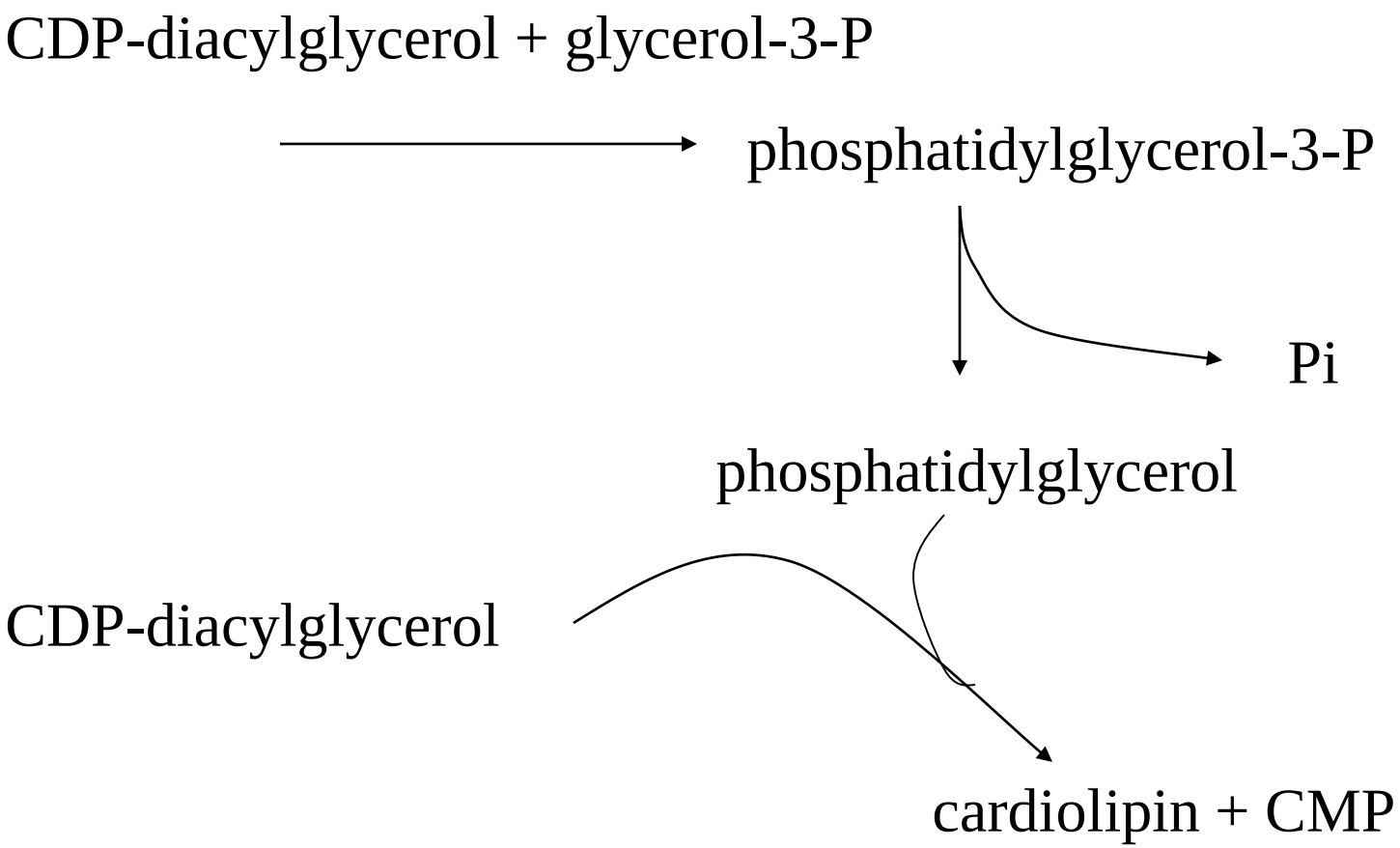


glycosylphosphatidylinositol structure on the cell surface

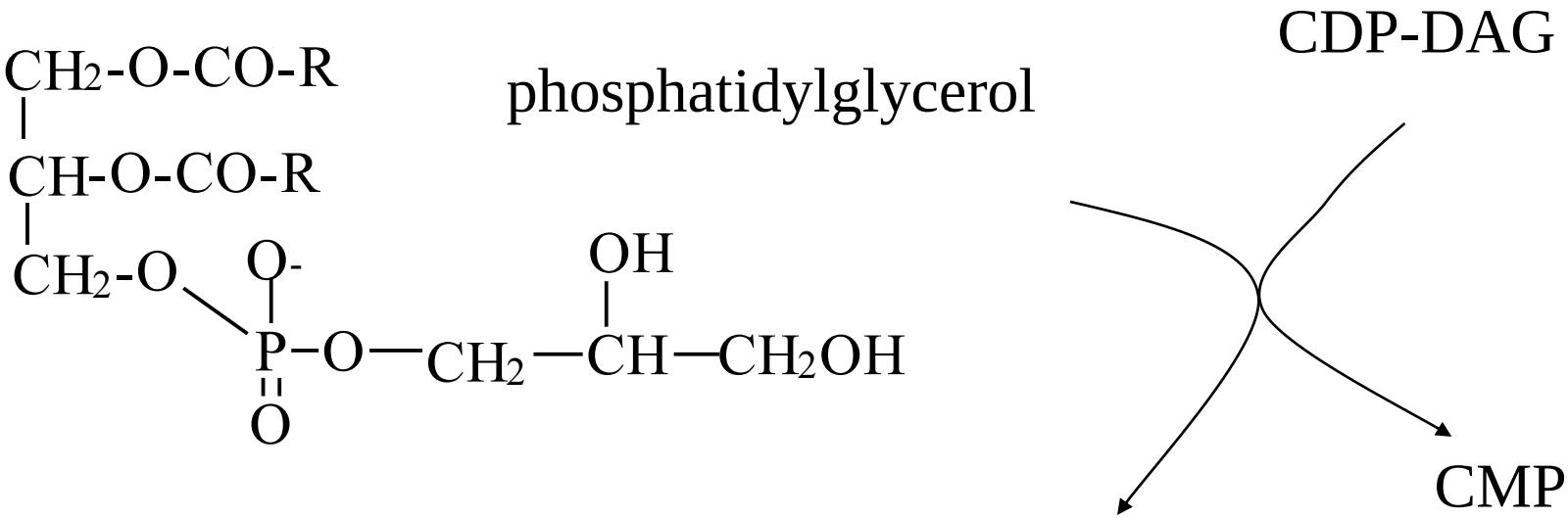
polysaccharide chain is connected on phosphatidylinositol in membrane

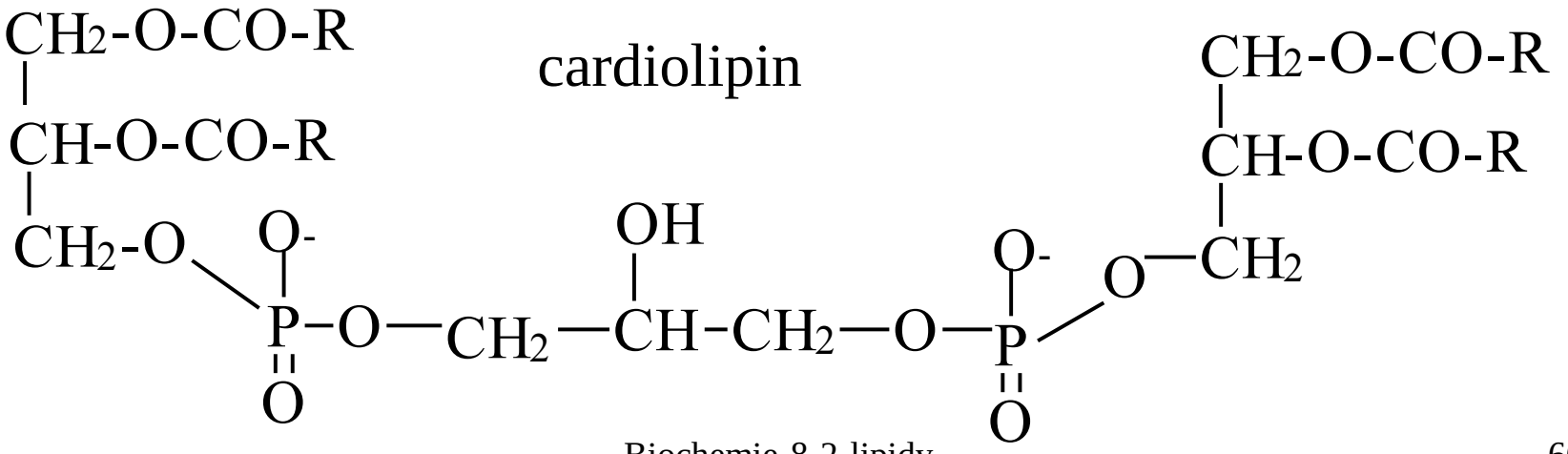
- binding of proteins (alkaline phosphatase, acetylcholinesterase, antigens ...)

Biosynthesis of cardiolipinu



Biosynthesis of cardiolipinu (in detail)





With the biggest amount of cardiolipin?

the inner mitochondrial membrane

Replacement of acyl groups at C-2 of phospholipids:

diacylglycerols: on C-2 of oleic acid

phospholipids: on C-2 of polyunsaturated acid (usually arachidic)

The exchange takes place through transacylation reactions

meaning of glycerophospholipids

- structural component of membranes
- component of lipoproteins
- special features

  source of polyunsaturated FA for synthesis and exchange

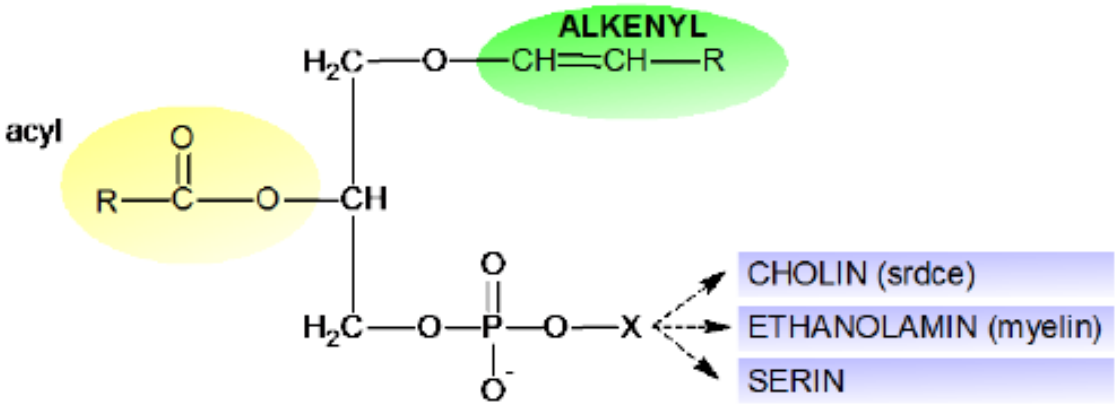
  "Anchoring proteins in membranes"

Modified phospholipids

- plasmalogens
- Platelet activating factor (PAF)

glycerolphosphoether lipids

U plazmalogenů je **acyl na C1 nahrazen <u>alkenylem</u>**. Alkenyl vznikne tak, že je acyl nahrazen alkylem pocházejícím z alkoholu, přičemž –OH skupina je následně eliminována (dehydratace) za vzniku dvojné vazby (desaturace).



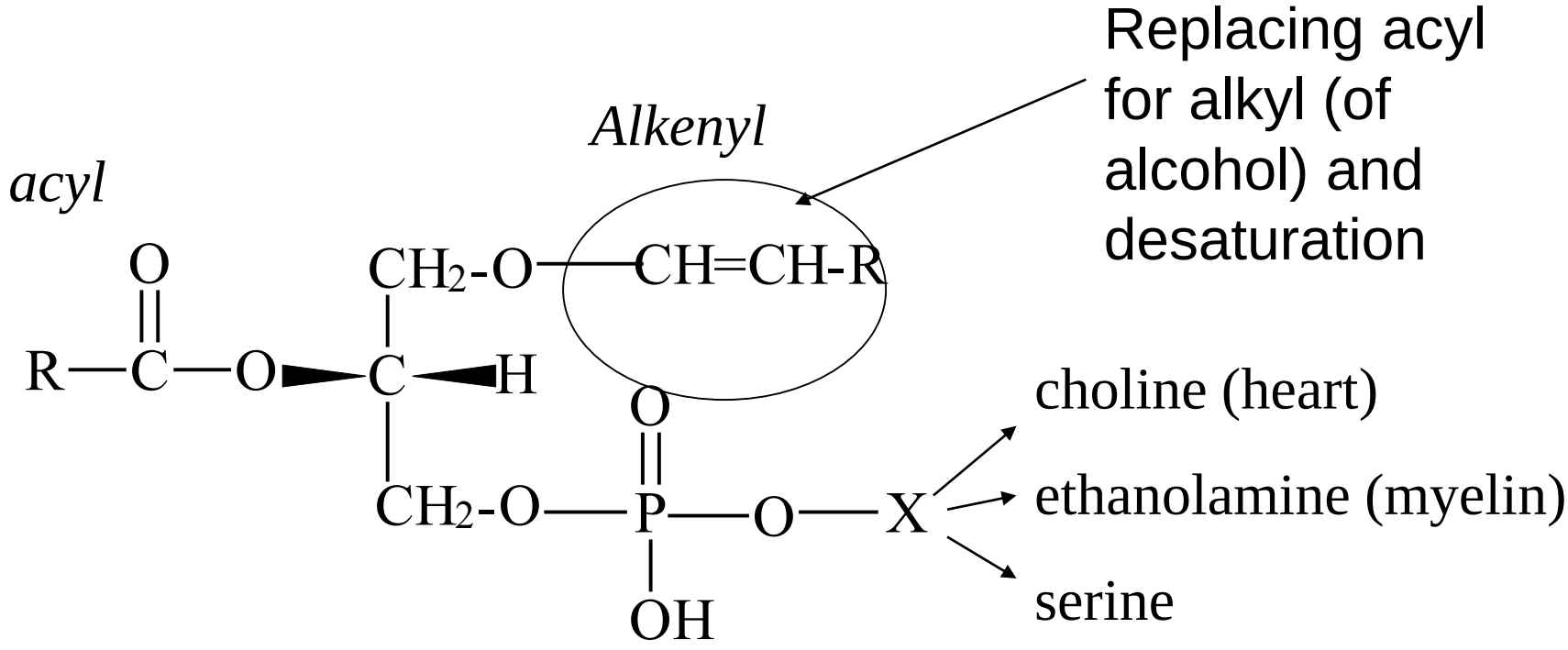
Nachází se především v srdeční tkáni (50% fosfolipidů tvoří plazmalogeny), myelinové pochvě neuronů a mitochodrniálních lipidech.

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 32

Plasmalogens

nerve and muscle tissue (myocardium - 50% of phospholipids)

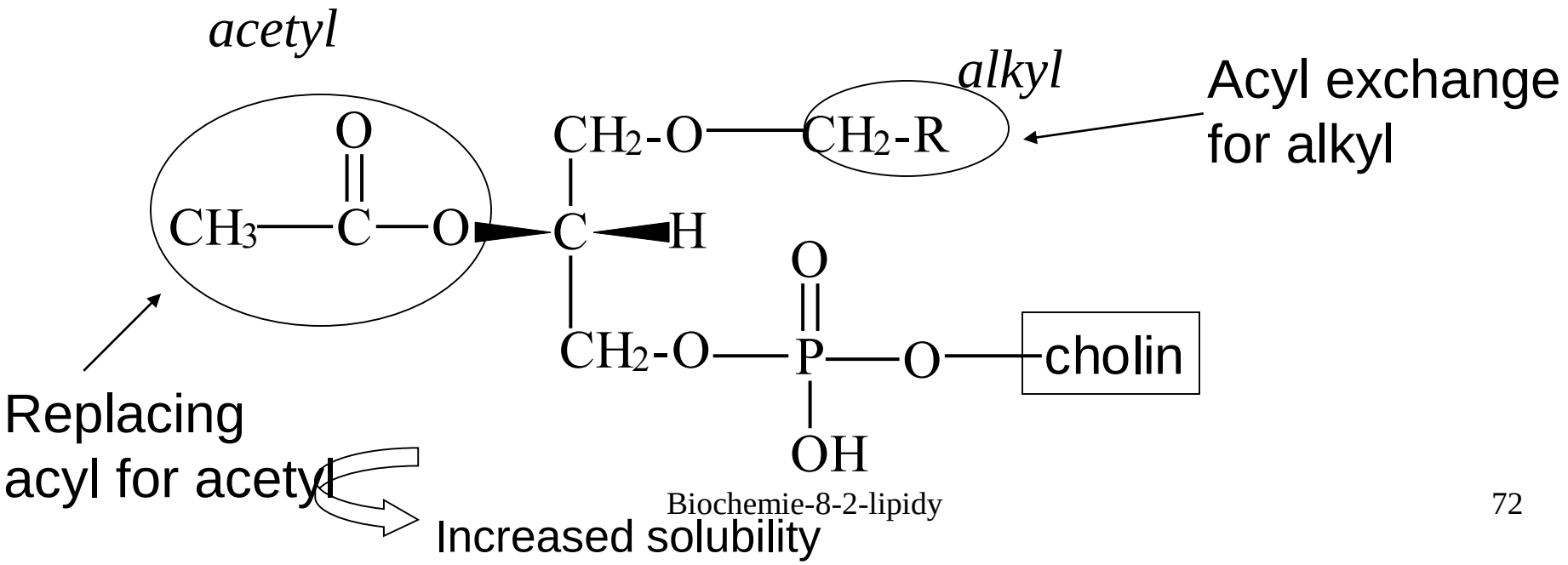
mitochondrial lipids



PAF (platelet activating factor)

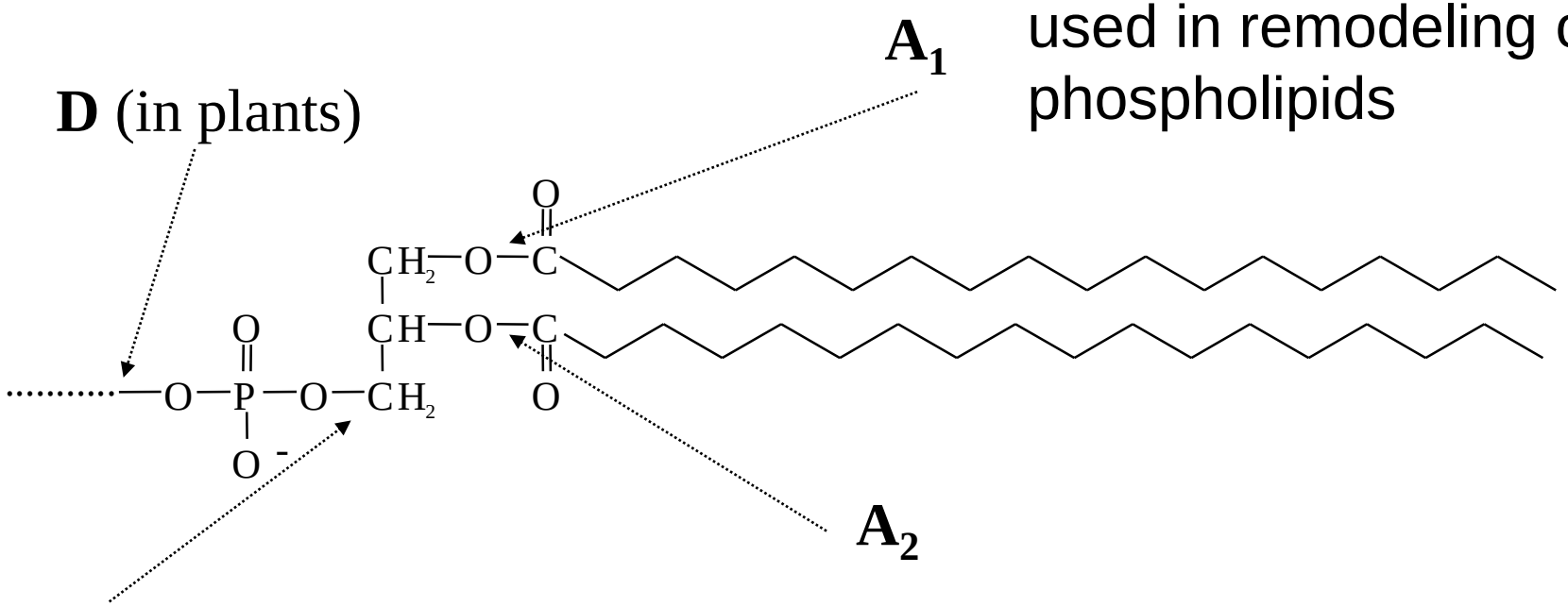
The main mediator of hypersensitivity, anaphylactic shock, acute inflammation.
It is produced in leukocytes.

aggregates platelets, acting as vasodilator and has a number of other physiological effects



Cleavage of phospholipids - phospholipase

Phospholipases are also used in remodeling of phospholipids



several types

PI-system

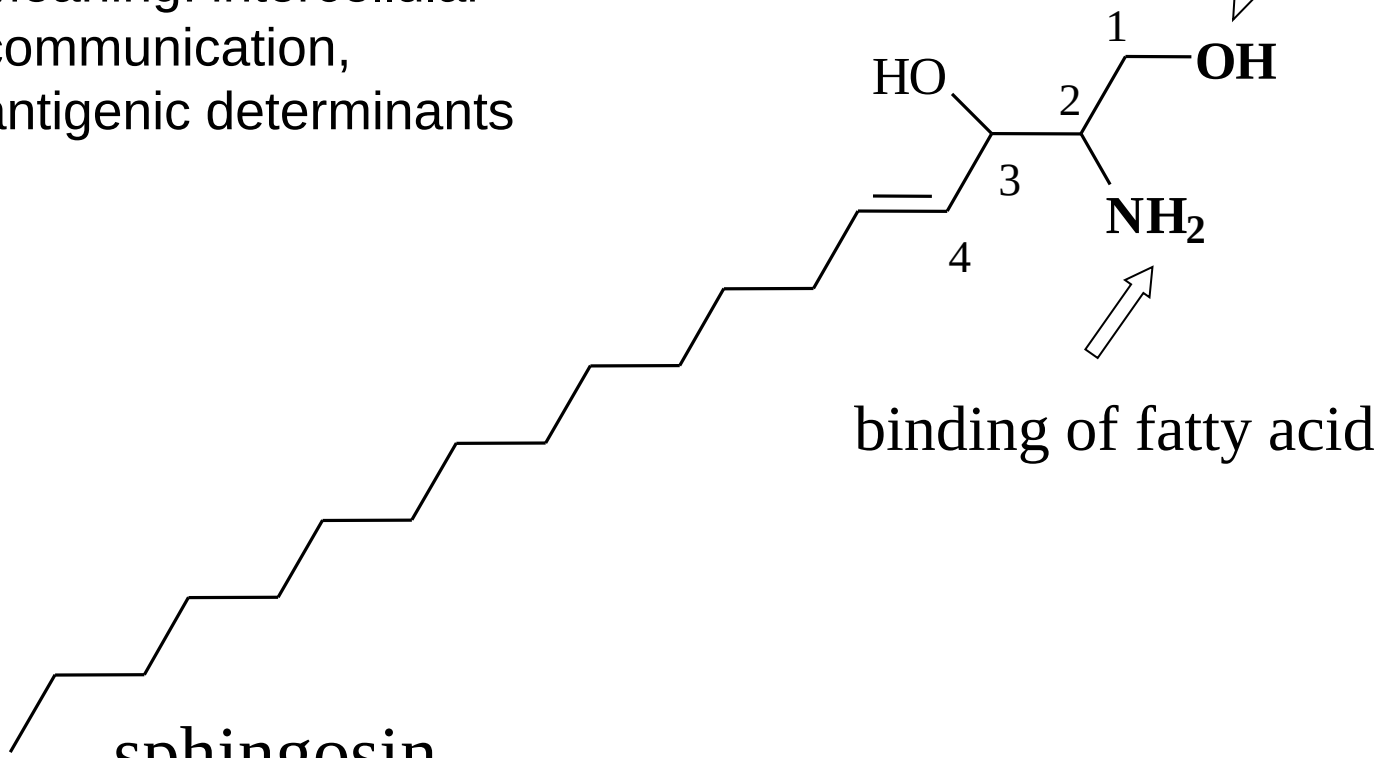
- A1 cleaves acyl at **first carbon**
- A2 cleaves acyl at **second carbon,** is used e.g. in remodeling of phospholipids (e.g. substitution of oleic acid for PUFA) and cleavage of PUFAs, which are then involved in the metabolism of eicosanoids
- C cleaves the bond between the phosphate and glycerol on third carbon; the phospholipase is used in **phosphatidylinositol system** (when an "IPs" of „PIPs")
- D cleaves phosphoester bond between the phosphate and the other structure attached to the phosphate (e.g. ethanolamine, choline, ...); phospholipase is featured only in plants

Sphingolipids
- general structure

binding of choline

binding of phosphate

Meaning: intercellular communication, antigenic determinants

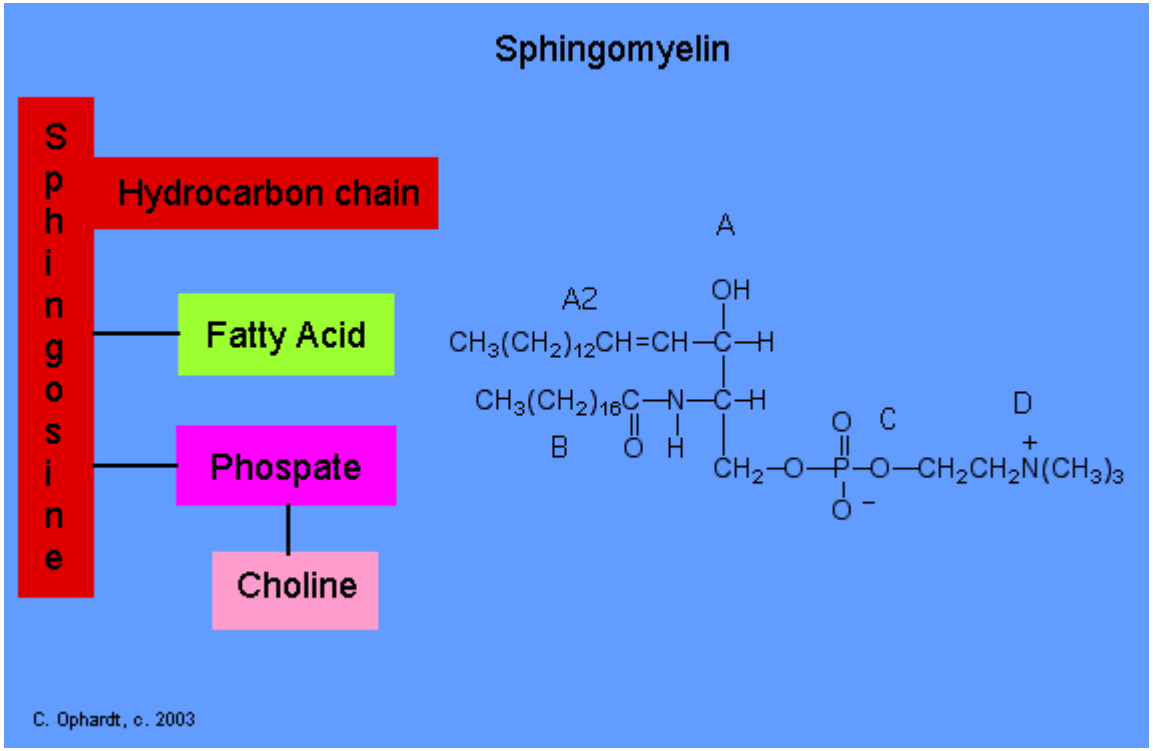


binding of fatty acid

sphingosin

Sphinx of Thebes

Sphingomyelin



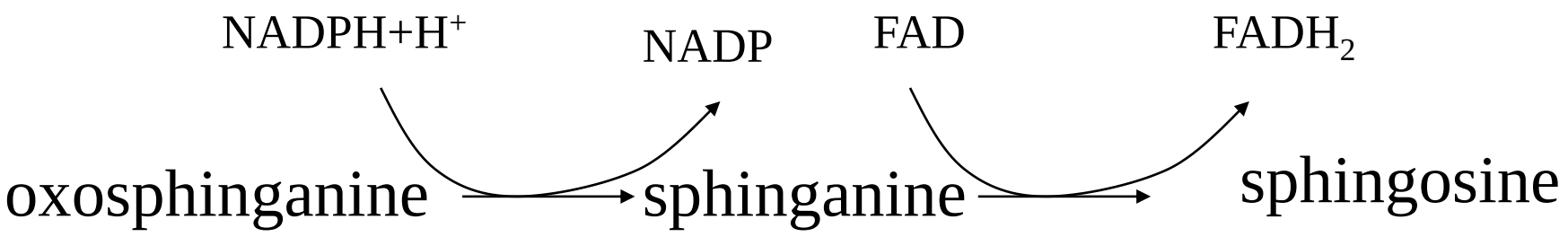
Sphingolipid biosynthesis

- **Biosynthesis of sphingosine (sphinganine)**

- summarily

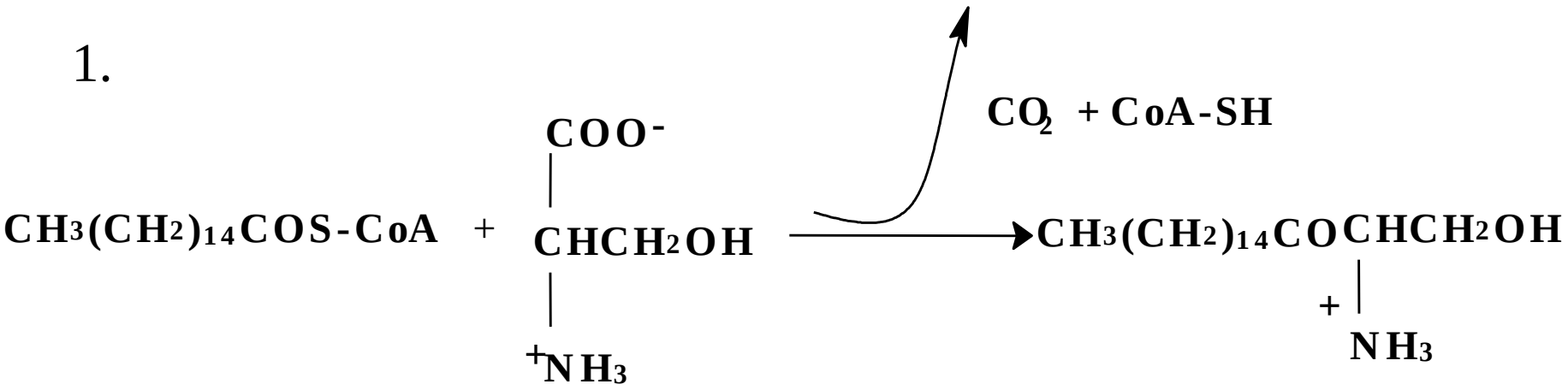
palmitate + **serine** → CO_2 + oxosphinganine

16 C **3 C** **1C** **18 C**



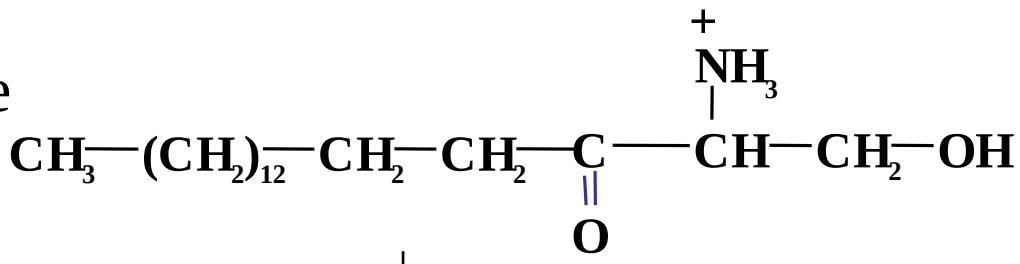
Biosynthesis of sphingosine (sphingenine)

1.



oxosphinganine

oxosphinganine

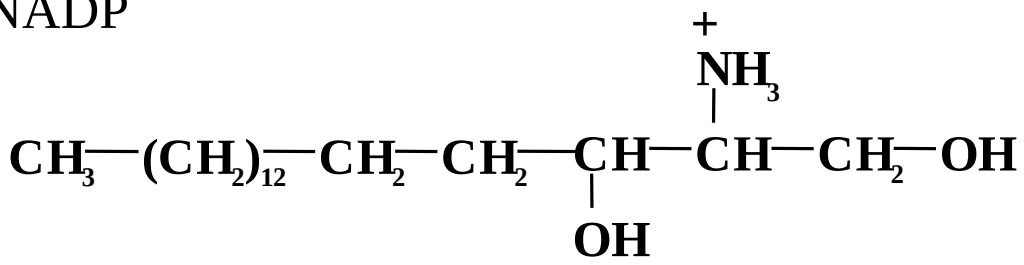


2.

NADPH + H^+

NADP

sphinganine

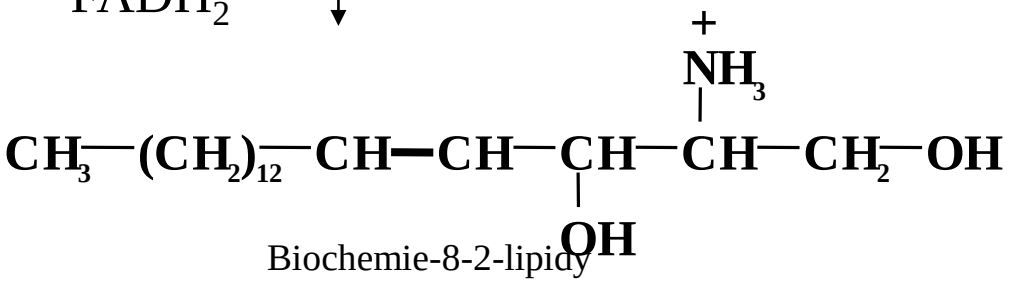


3.

FAD

$FADH_2$

sphingosine

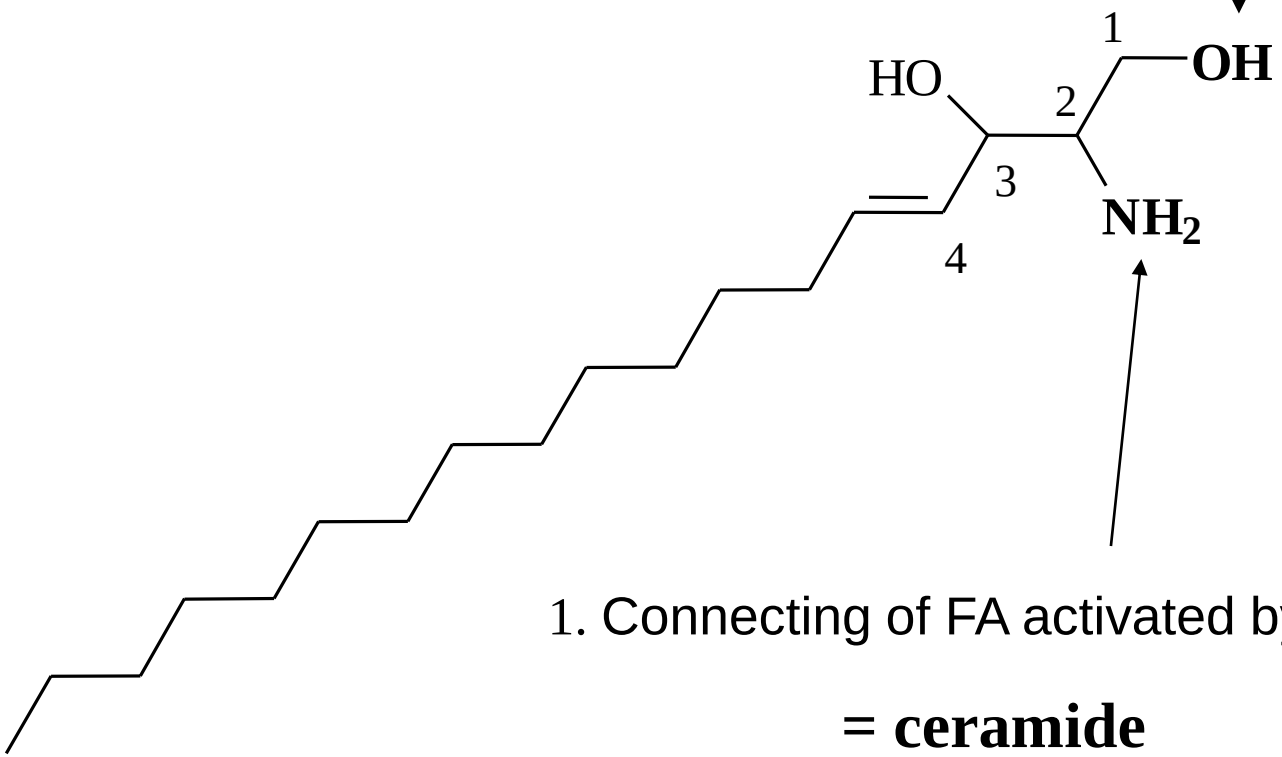


4.

Biosynthesis of sphingomyelin

2. Reaction with CDP-choline: CH_2OH binds with phosphocholine

= **sphingomyelin**

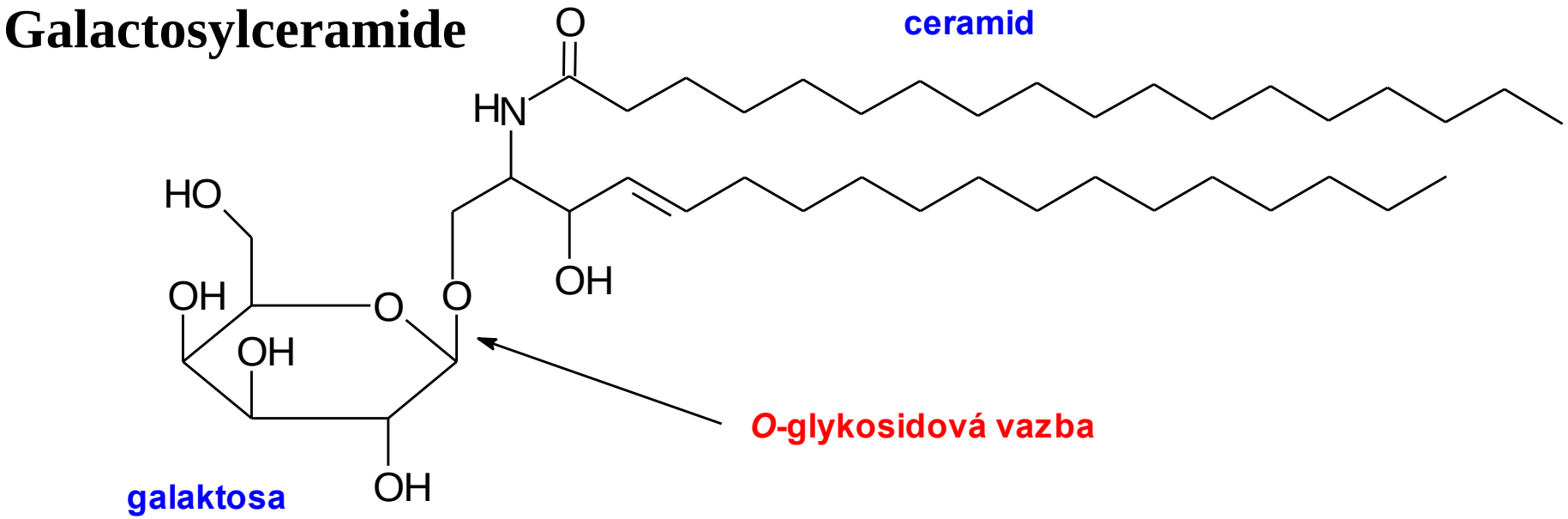


1. Connecting of FA activated by amide bond

= ceramide

glycosphingolipids

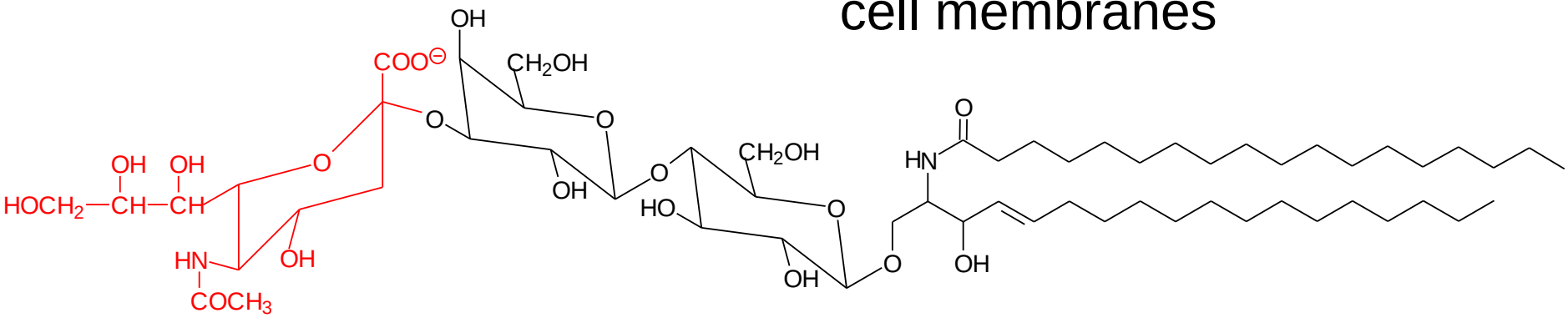
- oligosaccharide component attached by O-glycosidic linkage to ceramide (via CH2OH of sphingosine)



Cerebrosides: more molecules of monosaccharides attached via glycosidic linkage

Structure of ganglioside

Occurrence: mainly ganglion cell membranes



sialic acid is bound to the oligosaccharide

Synthesis of cerebrosides:

ceramide + UDP-gal → ceramide-gal + UDP

…… + Binding of other UDP-monosaccharides

Synthesis of sulphatides:

sulfation of cerebrosides using PAPS

Synthesis of gangliosides:

ceramide + UDP-hexose + CMP-NeuAc (CMP-N-acetylneuraminic acid)

Degradation of sphingoglycolipids and sphingosine

• Takes place in lysosomes

• Enzyme catalyzed hydrolytic reactions (galactosidase enzymes, hexosaminidase, gangliosidneuraminidase, glucocerebrosidase)

• Each of the enzymes is specific for one monosaccharide which it eliminates a type of glycoside bond that is cleaved.

• Lack of any of these enzymes leads to the accumulation of substrates in lysosomes - disease called **sphigolipidosis**

• Sphingomyelin cleaved by sphigomyelinase to ceramide and fatty acid

Sphigolipidosis

Lipid accumulation in the tissues due to congenital deficiency of degradative enzymes

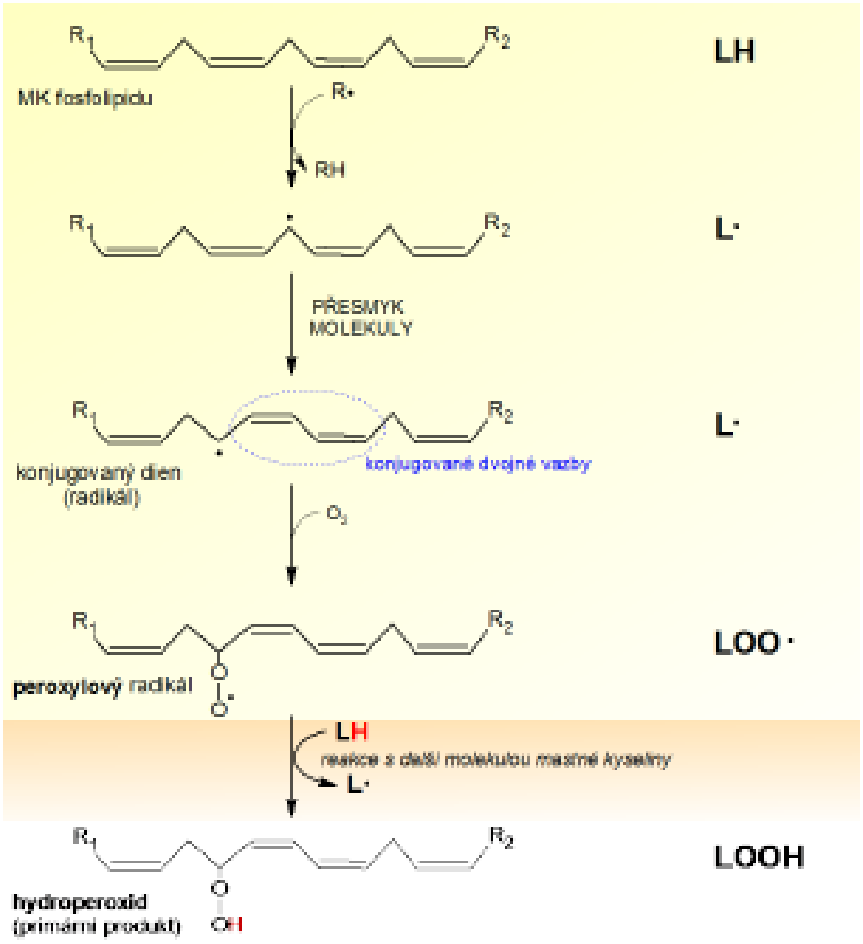
Mainly affected by CNS

Examples:

Tay-Sachs disease: hexoaminidase A deficiency, accumulation of GM2 ganglioside, mental retardation, blindness, hepatosplenomegaly, baby dying within 3 years of life

Gaucher disease: reduction in activity beta-glucosidase at 10-20%, the onset of adulthood, thrombocytopenia, splenomegaly, psychomotor disturbances, rigidity and half of the cases develop epilepsy

Lipid peroxidation is similar to the radical substitution of alkanes - we can distinguish three phases called **initiation, propagation and termination.**



- At **initiation** (yellow-colored) molecule is a fatty acid radical is attacked, most often a hydroxyl radical. The radical attacks the most sensitive point of the fatty acid, which is -CH2- between two double bonds (see chart). Radical torn away from hydrogen, whereby the fatty acids creates radical, which is referred to as L •. In the thus formed radical reshuffle will double bonds (from isolated become conjugated, because we are talking about the creation of a conjugated diene). Conjugated diene is highly reactive and reacts with oxygen molecules to form lipoperoxylového radical LOO •. Lipoperoxylo radical is extremely reactive and can react with another molecule of the fatty acid to form the radical of the L • and of themselves create hydroperoxide LOOH.
- This (the emergence of radical L •) to begin the process of **propagation** (orange-colored).
- In propagation - producing free radicals until:
  - two different radicals meet
  - radical and antioxidant meet, which is most commonly **tocopherol**
- If one of the above cases, we are talking about **termination**.

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 38

- The primary products of lipid peroxidation are **hydroperoxides LOOH**. Greater danger for the organism present the secondary products. They can attack other biomolecules (not only fatty acids), or are directly toxic to the organism (the most dangerous are dialdehydes, e.g. **malondialdehyde**, 4-hydroxynonenal).

Antioxidants

- These are substances which prevent lipid peroxidation. We distinguish between:
- **preventive antioxidants** (prevent the formation of free radicals and so do not even start lipid peroxidation)
- **catalase / peroxidases** (decompose hydrogen peroxide and prevent its conversion to hydroxyl radicals)
- **superoxide dismutase** (scavenges superoxide anion radical)
- **transferrin, ferritin, ceruloplasmin** (substances which sequester ions of copper and iron, and do not allow them to enter the Fenton reaction)

- **antioxidants stopping promotion** (these are substances that have the ability to react with radicals to form stable products, thereby preventing a chain reaction and must have a **lipophilic** character)
- **tocopherol** (vitamin E)
- **carotenoids**
- **ubiquinol** (located on the mitochondrial membrane)
- **flavonoids**