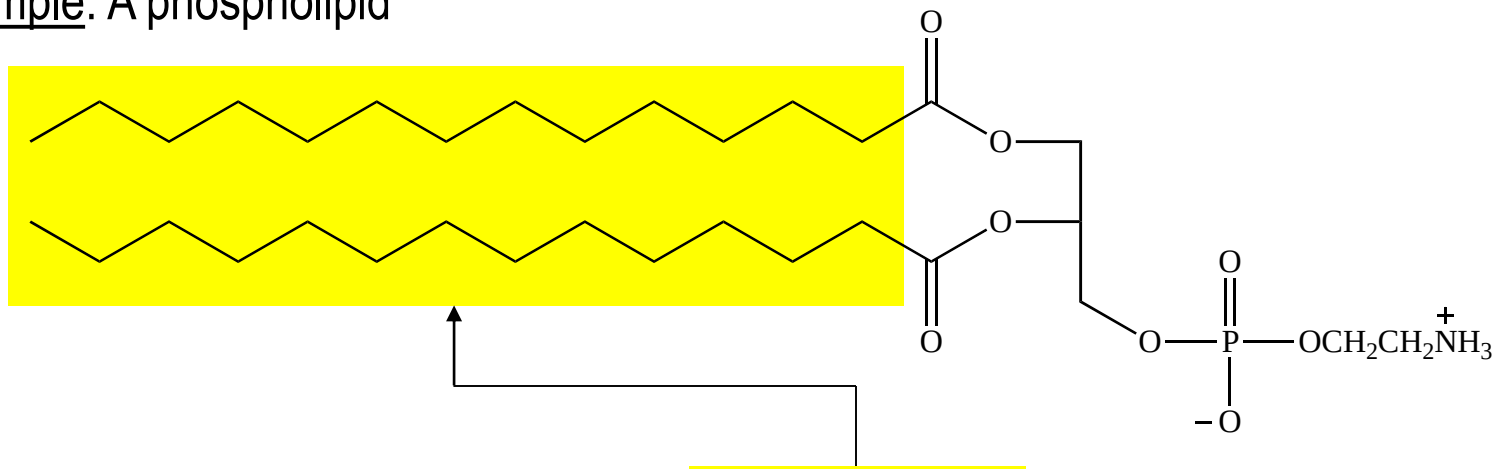
Lipids
Definitions

Lipid (Greek: *lipos*, fat): organic molecule of biological origin that is insoluble in water and soluble in nonpolar solvents (CH_2Cl_2, $CH_3CH_2OCH_2CH_3$, etc.)

Example: A phospholipid



- Lipid solubility properties due to large nonpolar regions
- Found mostly in fatty tissues, membranes, and other nonpolar biological structures
- Nonpolar: **hydrophobic** ("water hating") or **lipophilic** ("fat loving")
- Polar: **hydrophilic** ("water loving") or **lipophobic** ("fat hating")

Lipids

Categories

General Categories of Lipids

Fatty acids

Waxes

Triacylglycerols

Phospholipids

Prostaglandins

Steroids

Lipophilic vitamins

Terpenes •*Produced mostly by plants*

Biological role

1. Fuel

-(adipocytes)

Oxidation in mitochondria

2. Nutrients

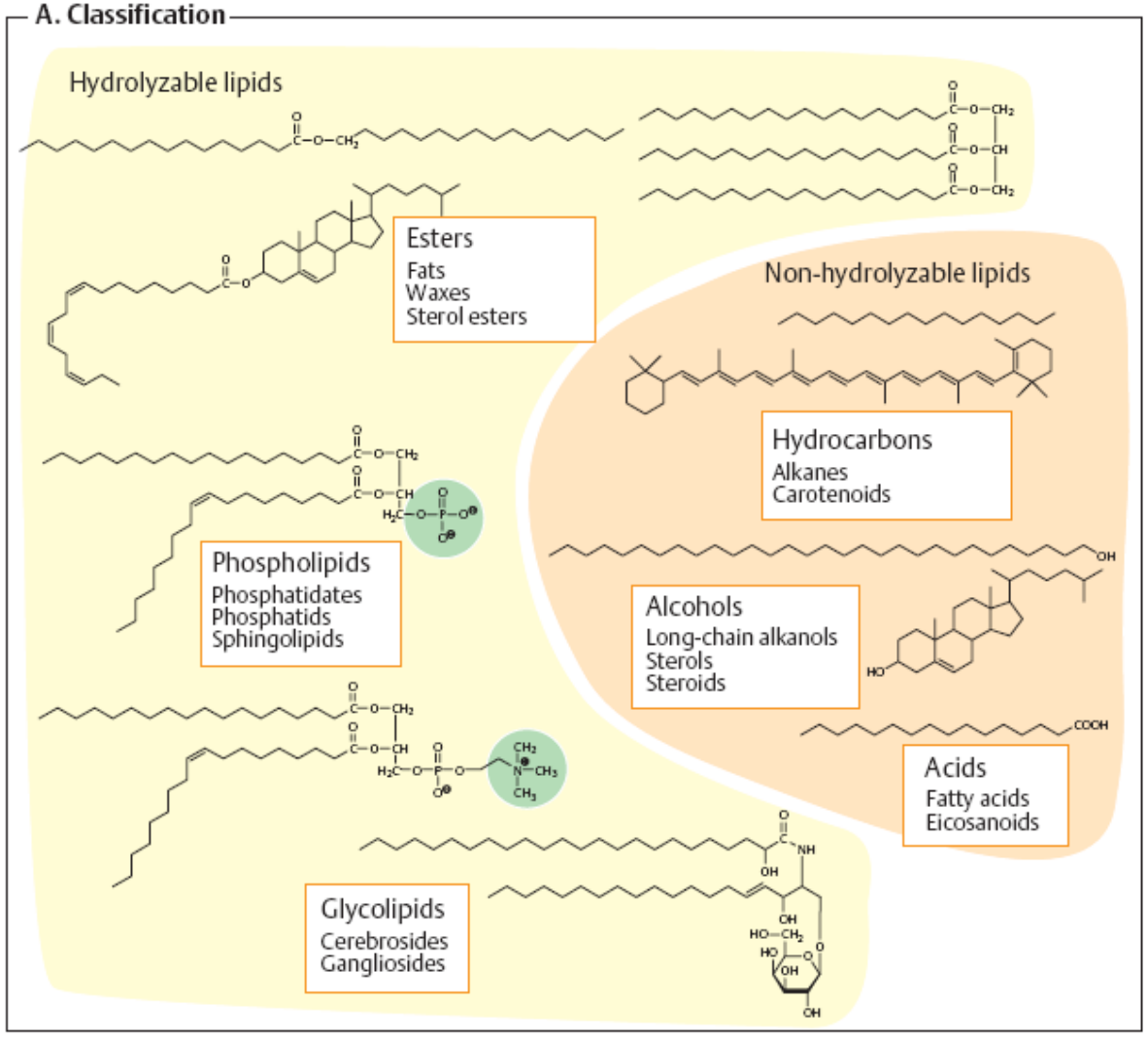
Amphipathic lipids- build cell membrane (ph.l., glycolipids, cholesterol)

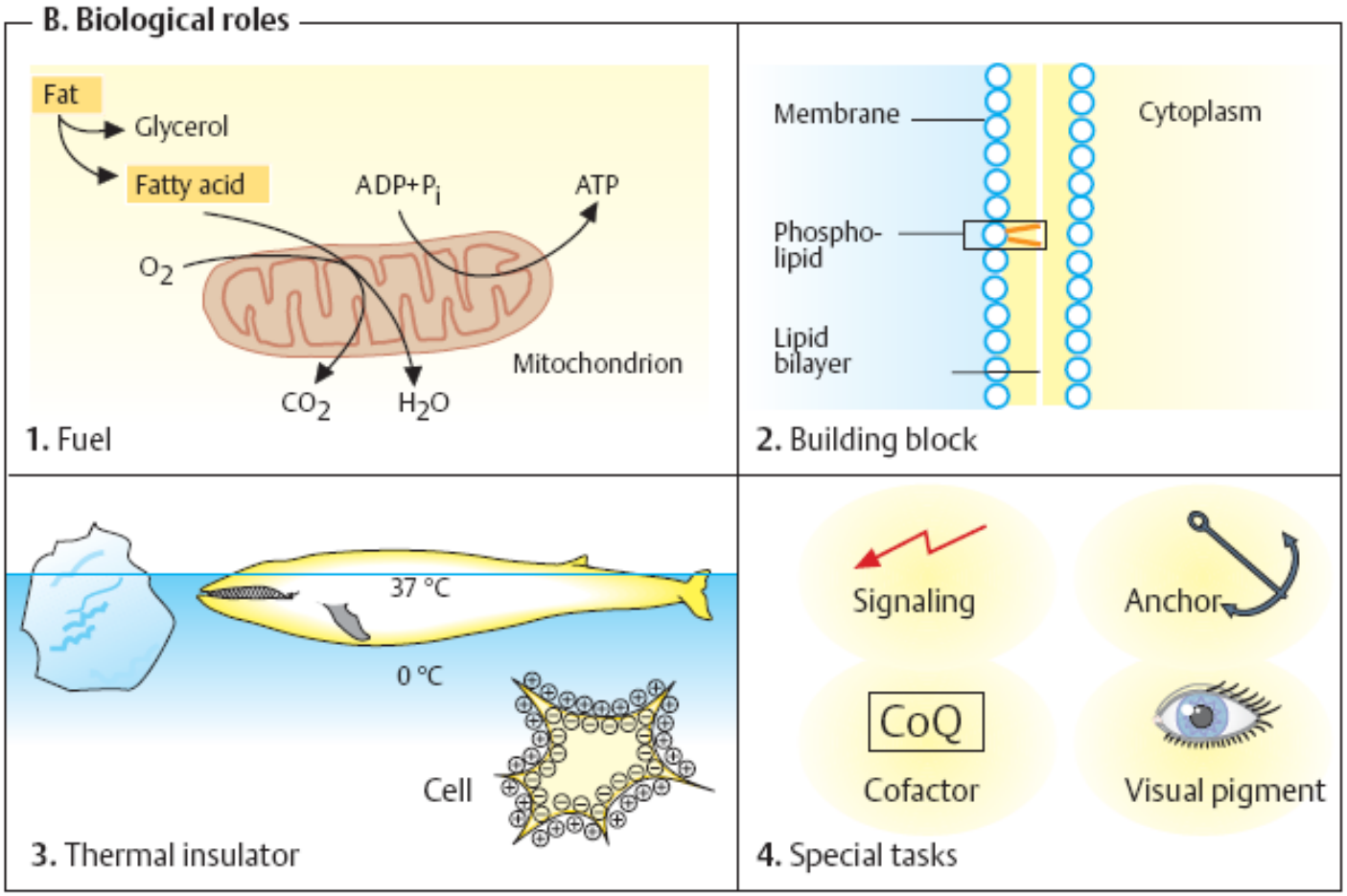
3. Insulation

Mechanical and thermal insulation

4. special task

-signaling function, cofactors


A. Classification
Hydrolyzable lipids
Esters
Fats
Waxes
Sterol esters
Non-hydrolyzable lipids
Hydrocarbons
Alkanes
Carotenoids
Phospholipids
Phosphatidates
Phosphatids
Sphingolipids
Alcohols
Long-chain alkanols
Sterols
Steroids
Acids
Fatty acids
Eicosanoids
Glycolipids
Cerebrosides
Gangliosides


B. Biological roles
Fat
Glycerol
Fatty acid
ADP+P_i
ATP
O_2
Mitochondrion
CO_2
H_2O
1. Fuel
Membrane
Cytoplasm
Phospho-
lipid
Lipid
bilayer
2. Building block
37 °C
0 °C
Cell
3. Thermal insulator
Signaling
Anchor
CoQ
Cofactor
Visual pigment
4. Special tasks

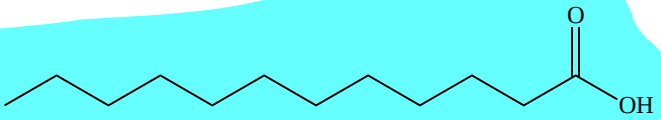
Fatty Acids

Fatty acid: unbranched carboxylic acid

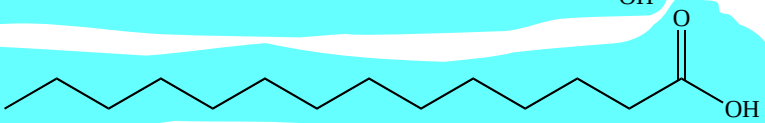
- Most have even number of carbons: two carbons added at a time during biosynthesis
- 12-20 carbons most common
- Most biologically-important fatty acids have 18 carbons: stearic, oleic, and linoleic acids
- Main biological function: component of other lipids
- Categorized by C=C in chain: saturated (no C=C) or unsaturated (one or more C=C)

Saturated fatty acids

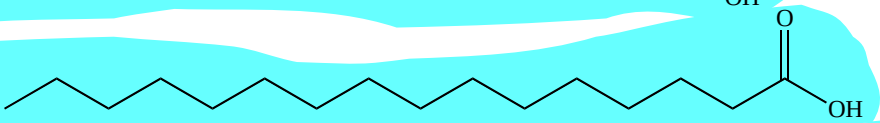
Lauric acid (12 C)



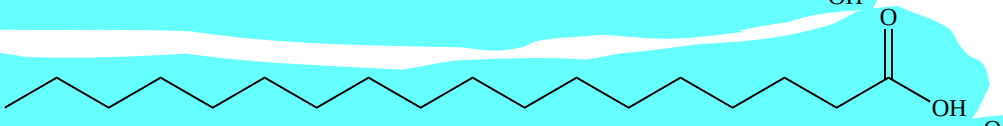
Myristic acid (14 C)



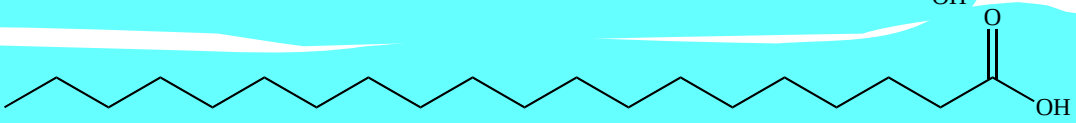
Palmitic acid (16 C)



Stearic acid (18 C)



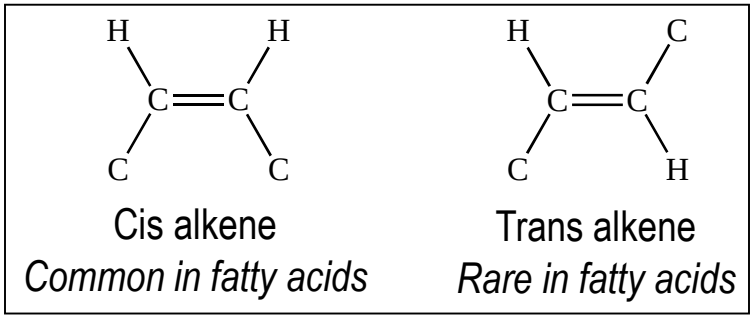
Arachidic acid (20 C)



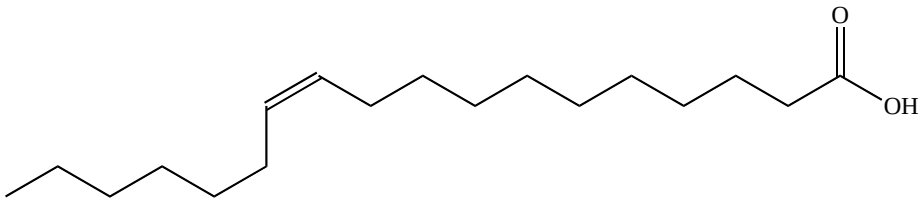
Fatty Acids

Unsaturated fatty acids

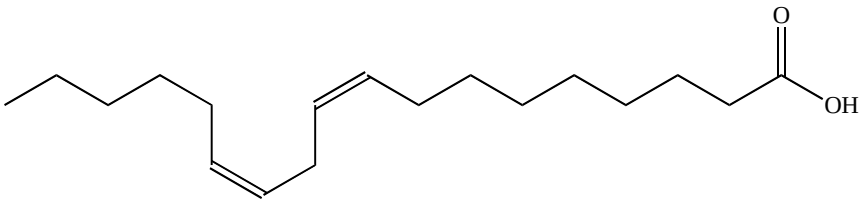
- **Monounsaturated**: contains one C=C
- **Polyunsaturated**: contains more than one C=C
- Cis C=C much more common than trans C=C



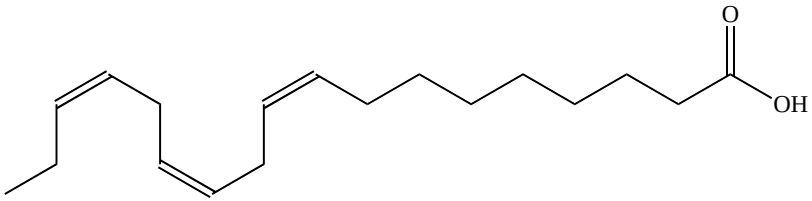
Some important unsaturated fatty acids



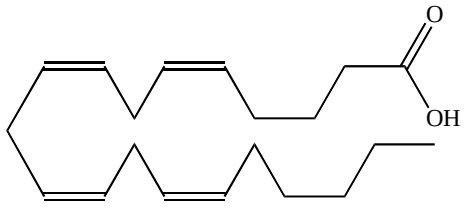
Oleic acid (C_{18})



Linoleic acid (C_{18})



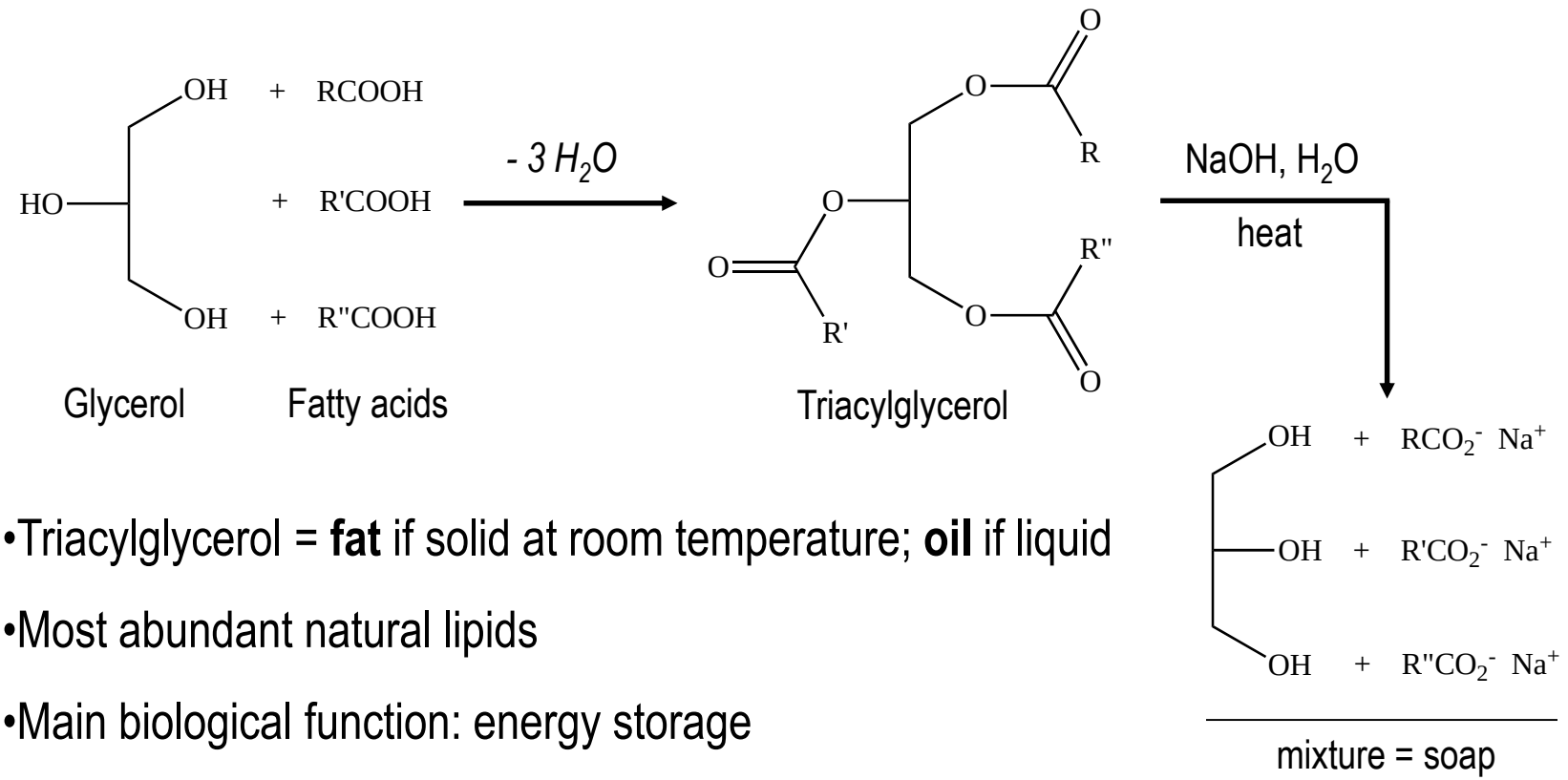
Linolenic acid (C_{18})



Arachidonic acid (C_{20})

Triacylglycerols

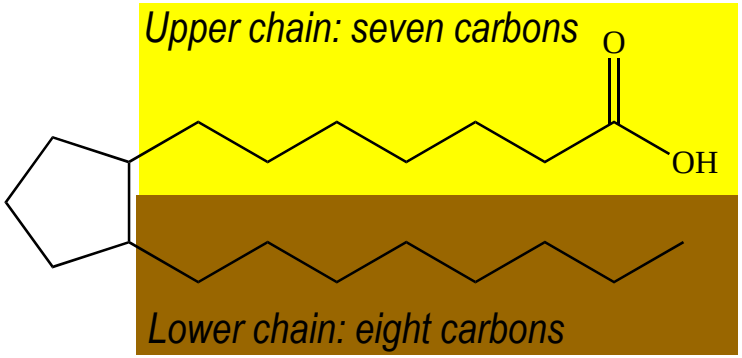
Triacylglycerol (triacylglyceride): fatty acid triester of **glycerol (glycerin)**



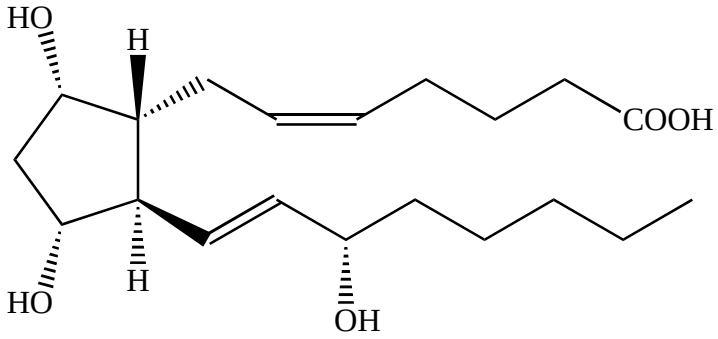
- Triacylglycerol = **fat** if solid at room temperature; **oil** if liquid
- Most abundant natural lipids
- Main biological function: energy storage
- Hydrolysis ("water breaking") of animal fats yields soap

Prostaglandins

Prostaglandin: molecule having the **prostanoic acid** skeleton



Prostanoic acid



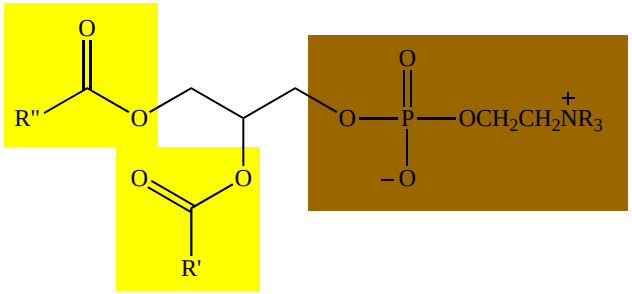
Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

- Nomenclature: based on stereochemistry, number of OH, C=C, C=O groups
- Biological functions: mostly as regulators and signal molecules
  - cause constriction or dilatation in vascular and other smooth muscle cells
  - regulate aggregation and disaggregation of platelets
  - sensitize spinal neurons to pain
  - regulate inflammatory mediation, calcium movement, hormones
  - control cell growth

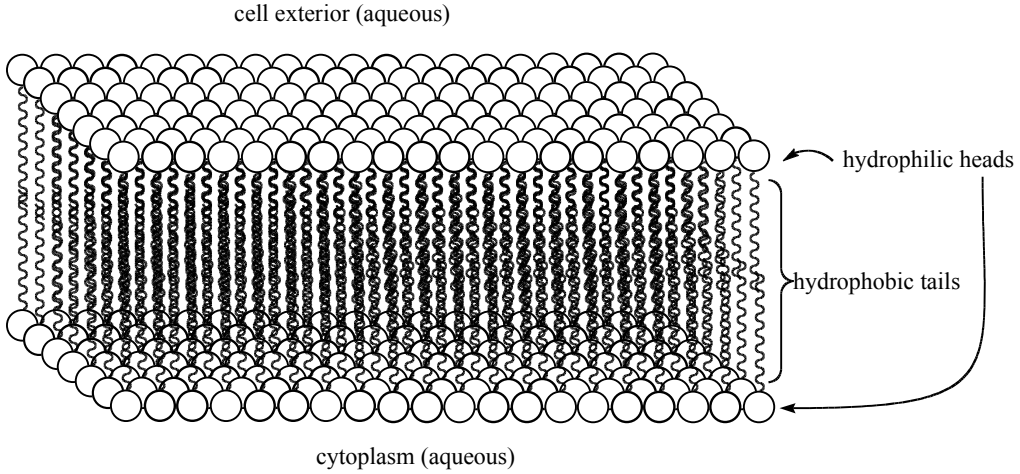
Phospholipids

Phospholipid: Glycerol esterified with two fatty acids and one phosphate group

Fatty acid esters *Phosphate ester*



Generic phospholipid structure

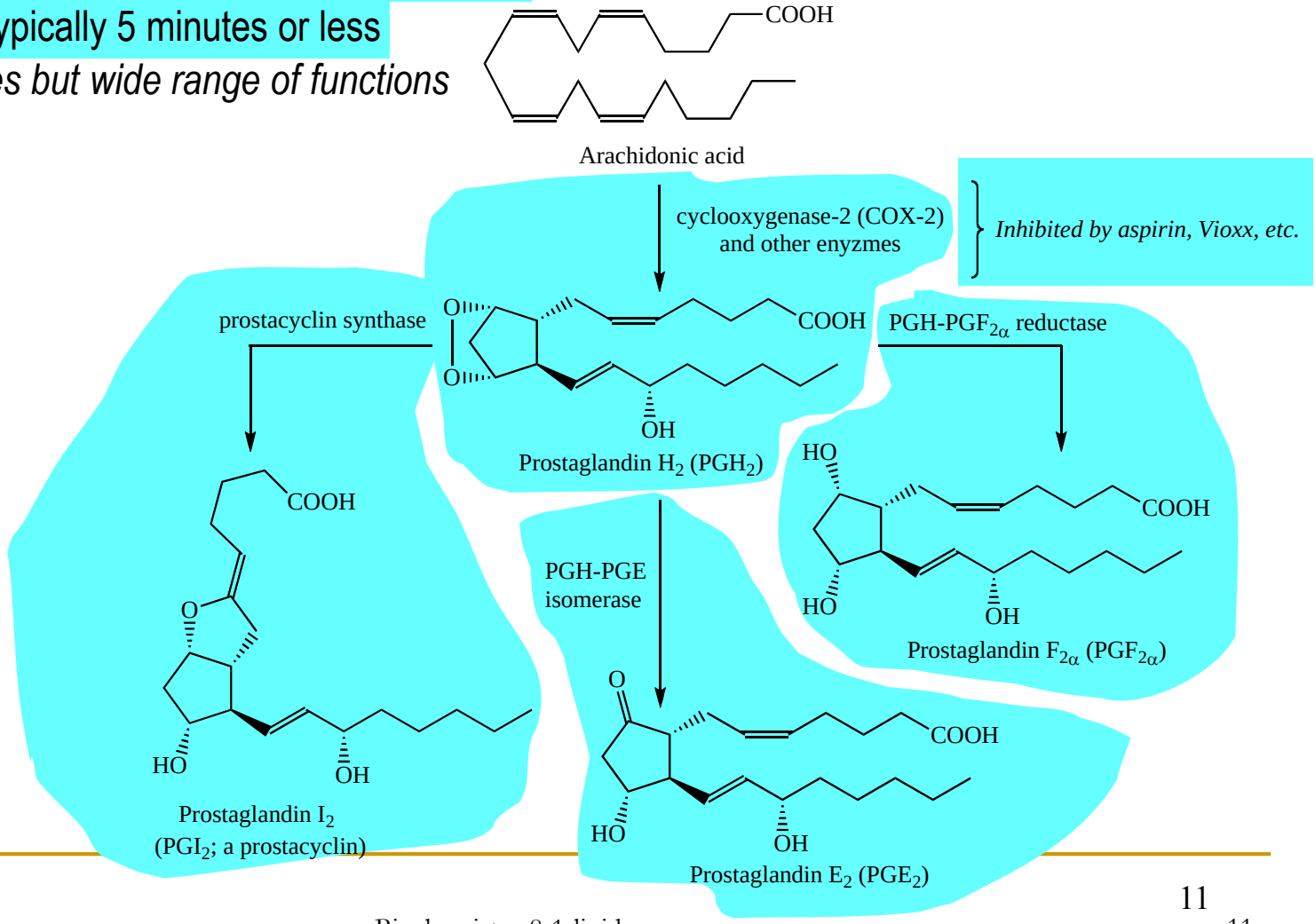


Simplified cell membrane

- Fatty acids are usually palmitic (C_{16}), stearic (C_{18}), and oleic (C_{18})
- Second most abundant group of natural lipids
- Main biological function: cell membranes (phospholipid bilayer)
- **Hydrophobic effect**: hydrophobic tails avoid water

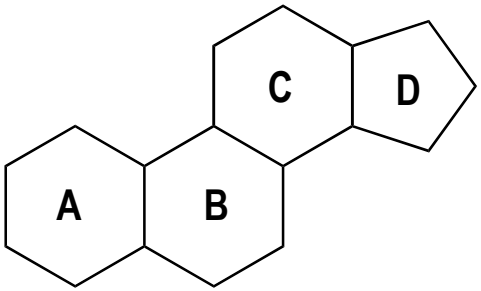
Prostaglandins

- Biological origin: prostaglandin cascade
- May occur at wound site, leading to inflammation
- *in vivo* half-life typically 5 minutes or less
- *Similar structures but wide range of functions*

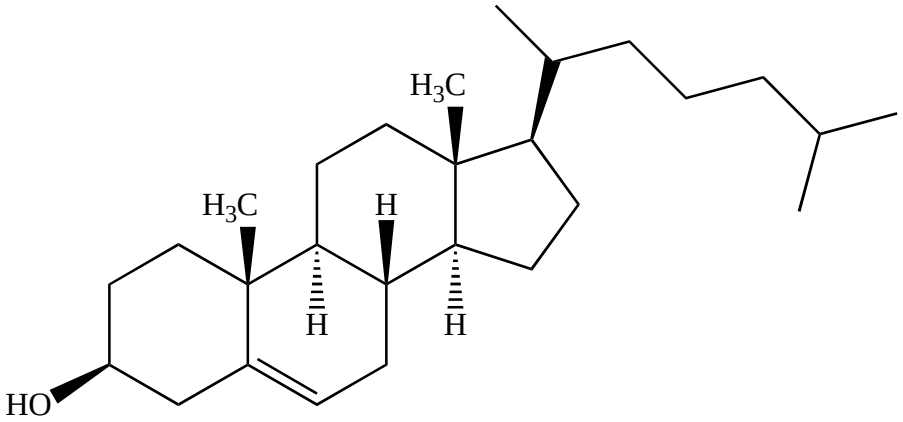


Steroids

Steroid: a molecule having the ring system shown below

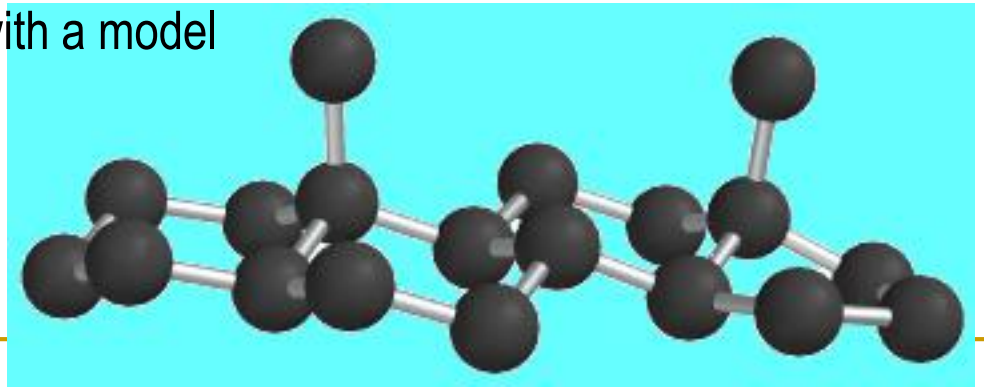


Steroid skeleton



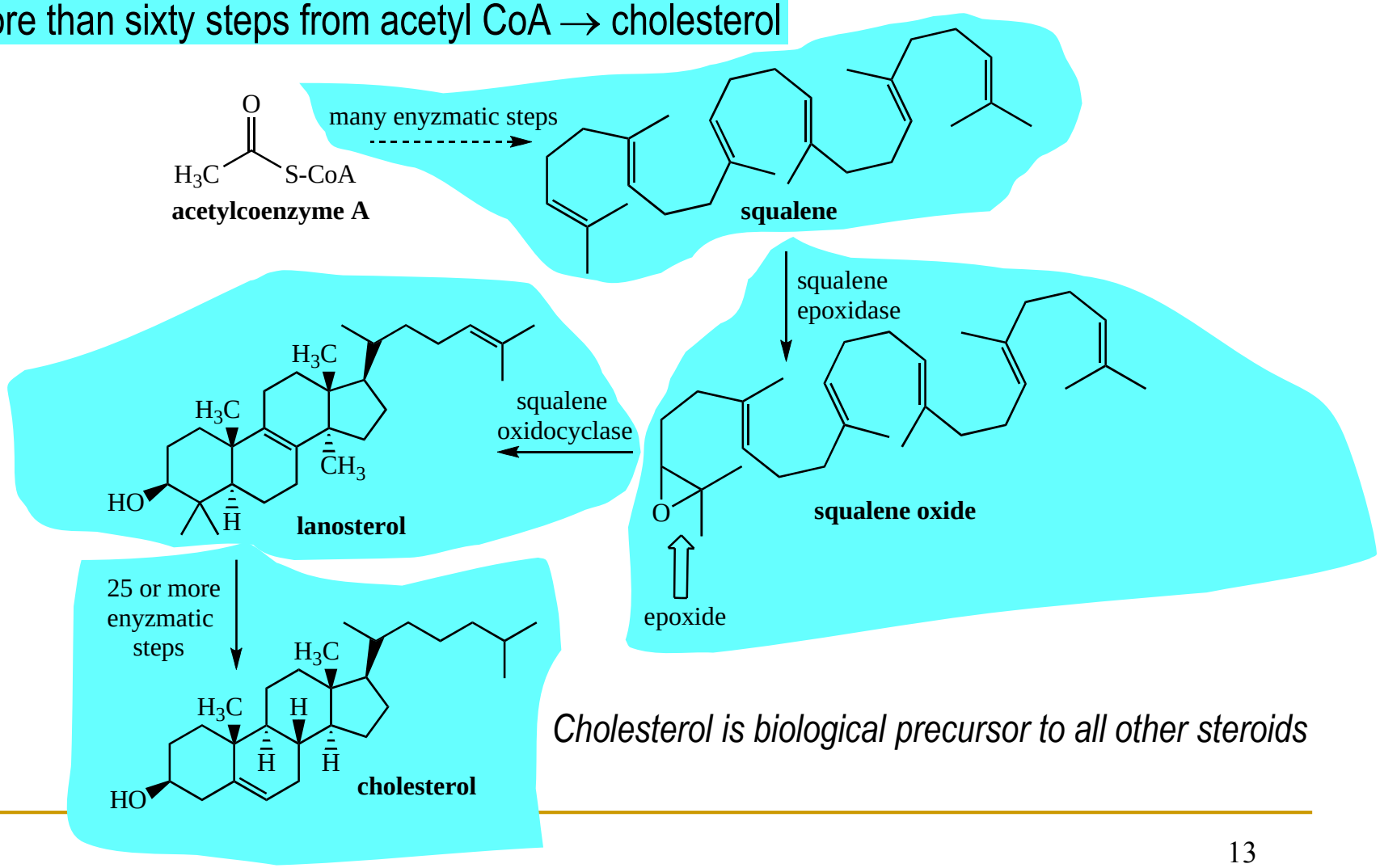
Steroid example: cholesterol

- Shape: fairly flat and fairly rigid
- Verify and explore with a model



Steroid Biosynthesis

•More than sixty steps from acetyl CoA → cholesterol

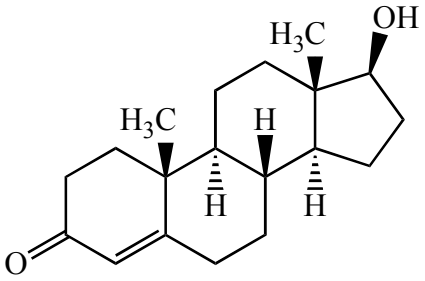


Cholesterol is biological precursor to all other steroids

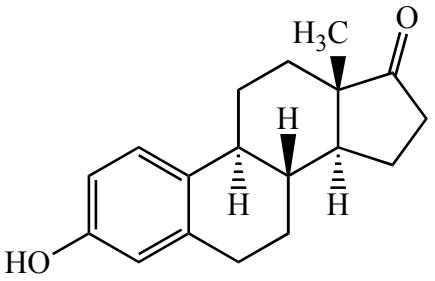
Steroids

Steroid categories and examples

Sex hormones:



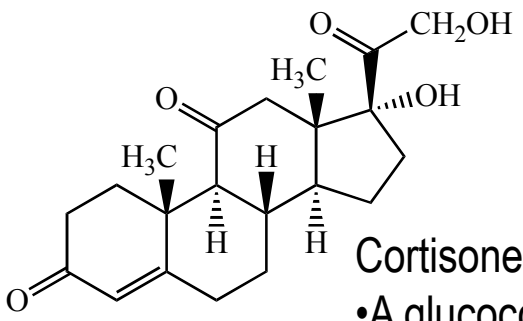
Testosterone *(an androgen)*



Estrone (a*n estrogen)*

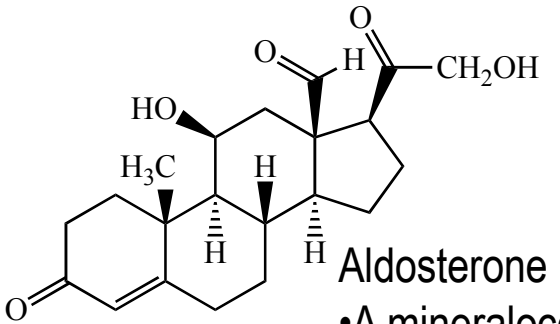
Corticoid hormones:

- Synthesized in the adrenal complex
- Regulate metabolic processes



Cortisone

- A glucocorticoid hormone
- Regulates inflammation
- Regulates glucose metabolism

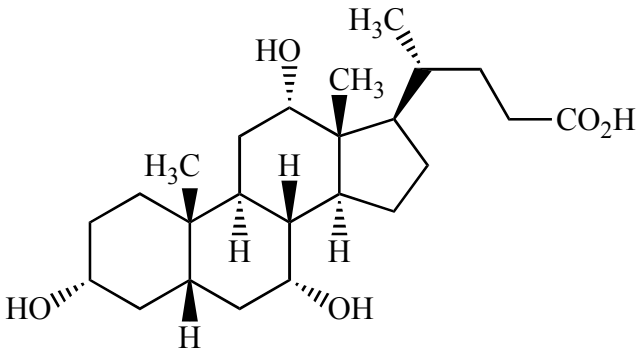


Aldosterone

- A mineralocorticoid hormone
- Regulates Na^+/K^+ balance

Steroids

Steroid categories and examples



Bile acids

- Aid in digestion by emulsifying fats in intestine

Steroids have similar structures but wide range of functions

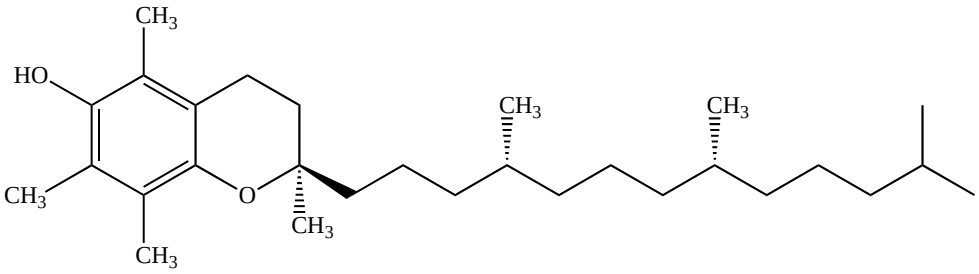
Lipophilic Vitamins

Vitamin: an organic compound, other than fat, protein or carbohydrate, required for the normal growth and maintenance of animals

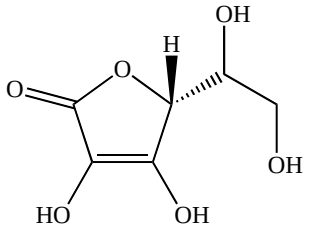
- Very broad range of structures and functions

Vitamin E

- Mixture of isomers; α-tocopherol most important
- Protects against oxidative damage to cells from radicals



α-Tocopherol
Hydrophobic antioxidant vitamin

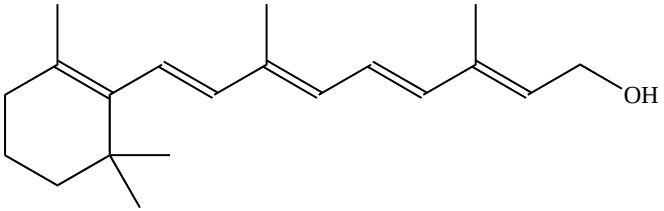


Vitamin C (ascorbic acid)
Hydrophilic antioxidant vitamin

Lipophilic Vitamins

Vitamin A (retinol)

- Essential to vision
- Incorporated into rhodopsin (photon-harvesting protein)



Lipid metabolism

metabolism of TG and FA

100 g/day

energy source

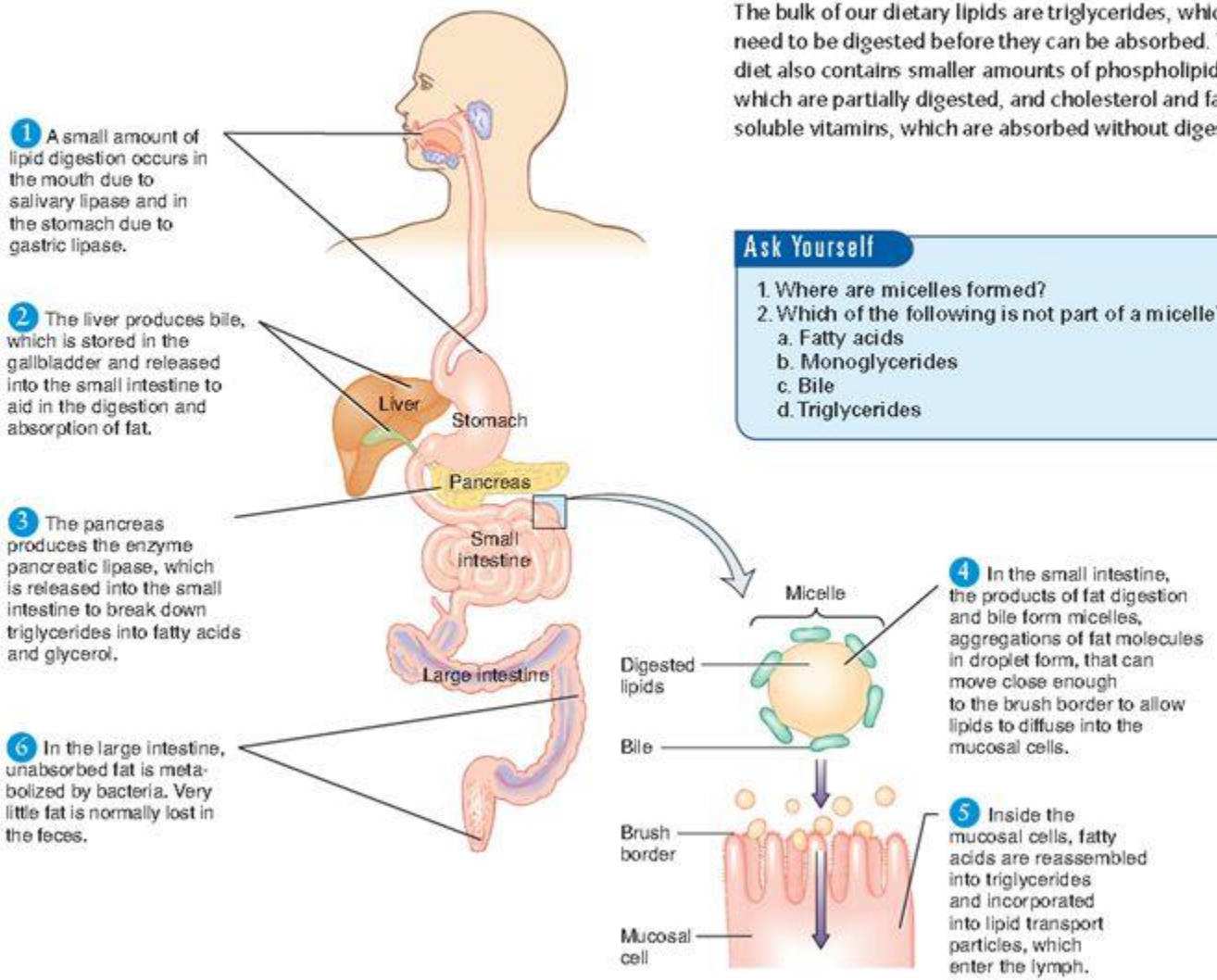
metabolism of structural lipids

2 g/day

Compared to most of the carbohydrates and FA are lipids (mainly TG, FA, esterified cholesterol) hydrophobic (non-polar). However, the environment in which the metabolism of nutrients takes place is filled with water which is polar. Therefore, in the body they are natural surfactants, able to receive, transport and enable the metabolism of lipids.

Lipid digestion and absorption

The bulk of our dietary lipids are triglycerides, which need to be digested before they can be absorbed. The diet also contains smaller amounts of phospholipids, which are partially digested, and cholesterol and fat-soluble vitamins, which are absorbed without digestion.



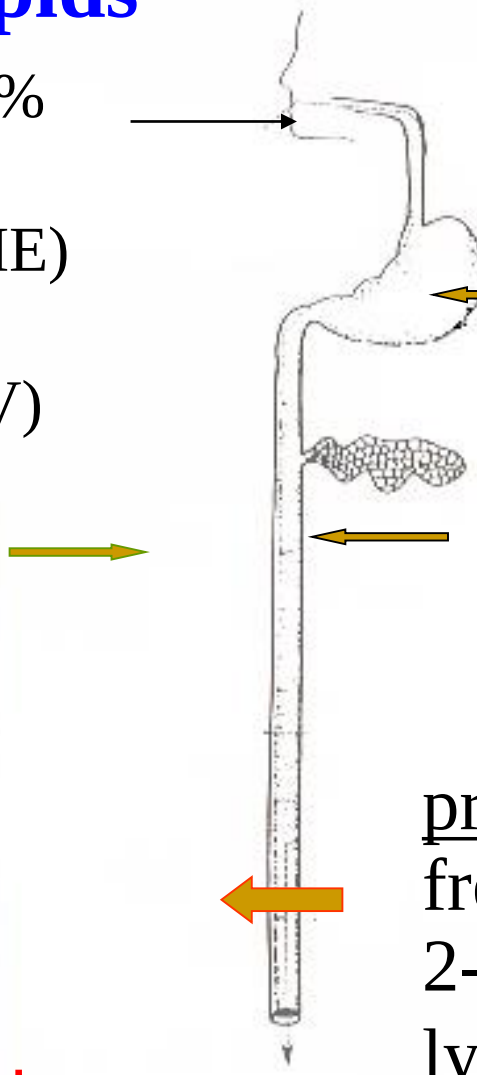
Ask Yourself

1. Where are micelles formed?
2. Which of the following is not part of a micelle?
   a. Fatty acids
   b. Monoglycerides
   c. Bile
   d. Triglycerides

Digestion of lipids

Triglycerides (TG)-90%
phospholipids (PL)
Cholesteryl ester (CHE)
glycolipids (GL)
lipophilic vitamins (LV)

Bile acids



Lingual and
Gastric Lipase

pancreatic lipase
+ colipase

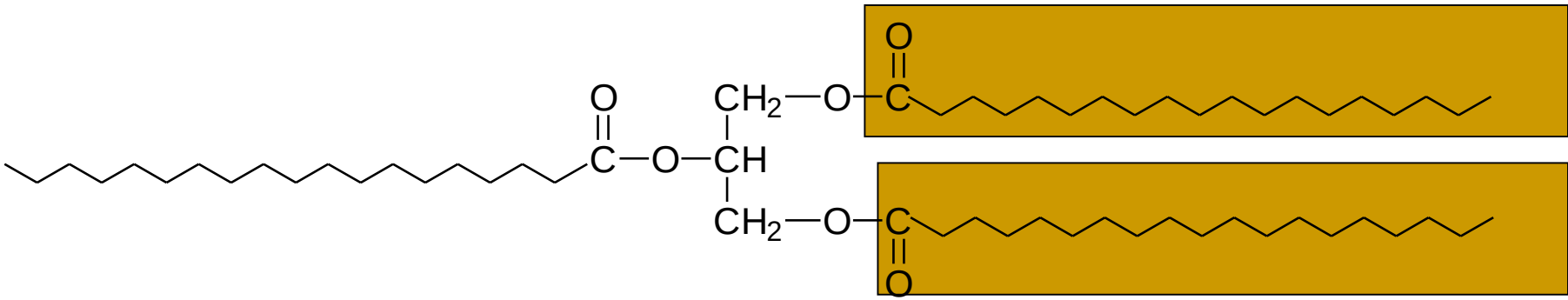
<u>primary products :</u>
free FA
2-monoacylglycerols
lysophospholipids
cholesterol
lipophilic vitamins

Resorption to the
enterocytes
in the form of mixed
micelles (particles <20 nm)

Cleavage of lipids in the intestine by pancreatic enzymes

- **pancreatic lipase**

triacylglycerol → 2-monoacylglycerol + 2 FA



< 1/4 TG

triacylglycerol → glycerol + FA

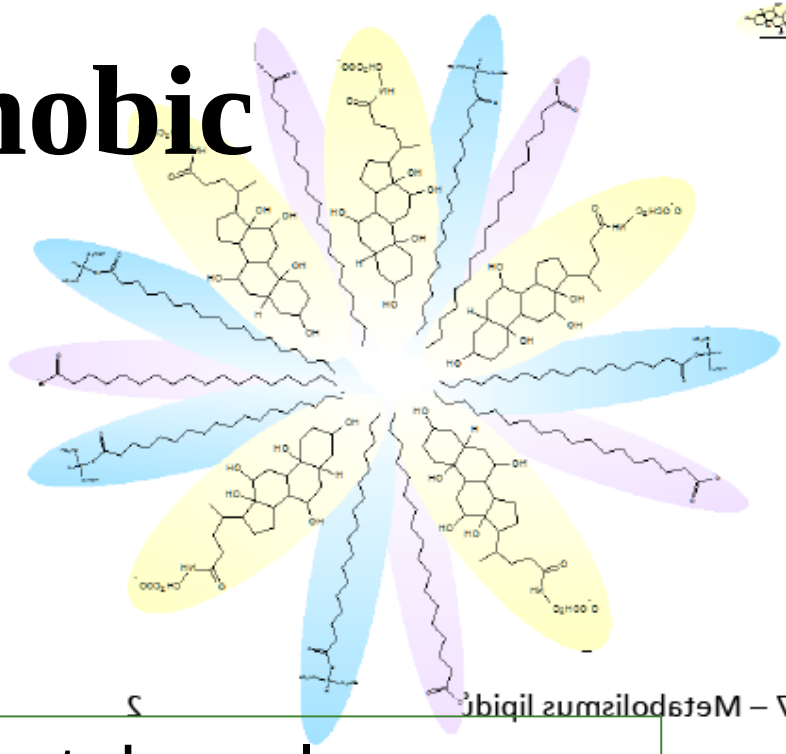
Orlistat – Anti-obesity agent inhibits lipase digestive tract, reduces absorption of about 30% of dietary fat

Lipids are hydrophobic

triacylglycerols

free fatty acids

esterified cholesterol



Their transport and metabolism takes place through various natural surfactants.

The first problem with the fact that they are non-polar lipids and internal environment of our bodies is polar occurs in the small intestine.
Solution to the problem is the formation of mixed micelles, which is provided by surfactants of the small intestine as bile acids, phospholipids, salts of free FA (soaps) and 2-glycerides. Nonpolar lipids "hide" between polar surfactants and in this polar packaging can be transported into the cells of the intestinal mucosa.

Natural surfactants in the absorption of fat

Surfactant	Type	Origin
Bile acids	anionic	from cholesterol in the liver
2-Acylglycerol	nonionic	TAG hydrolysis in the intestine
Anionts of FA	anionic	TAG hydrolysis in the intestine
Phospholipids	amphoteric	food

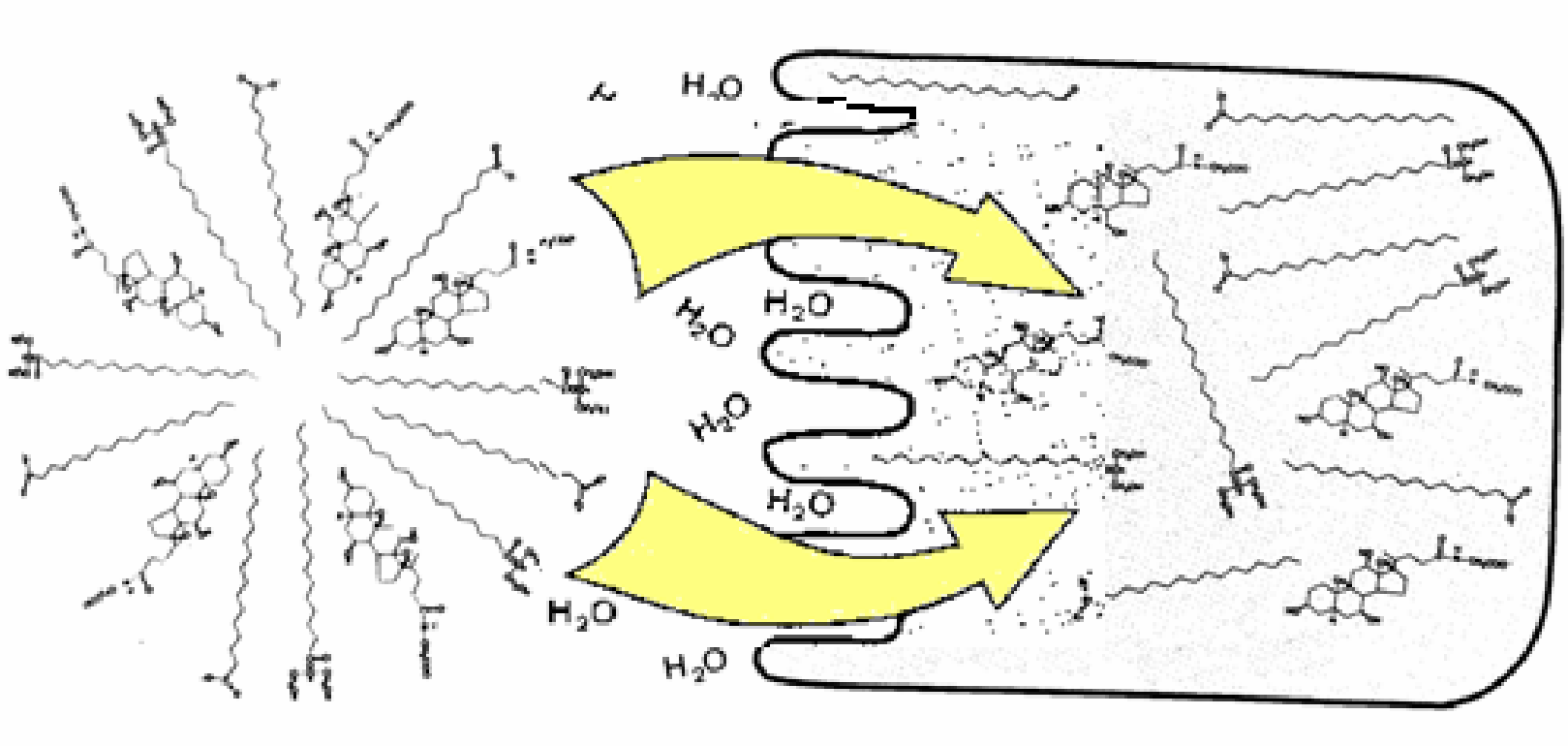
Form a micelle, which enters into the enterocytes

Resorption of lipid cells of the intestinal mucosa (Mostly in the jejunum, bile acids to the ileum)

mixed micelles

brush border

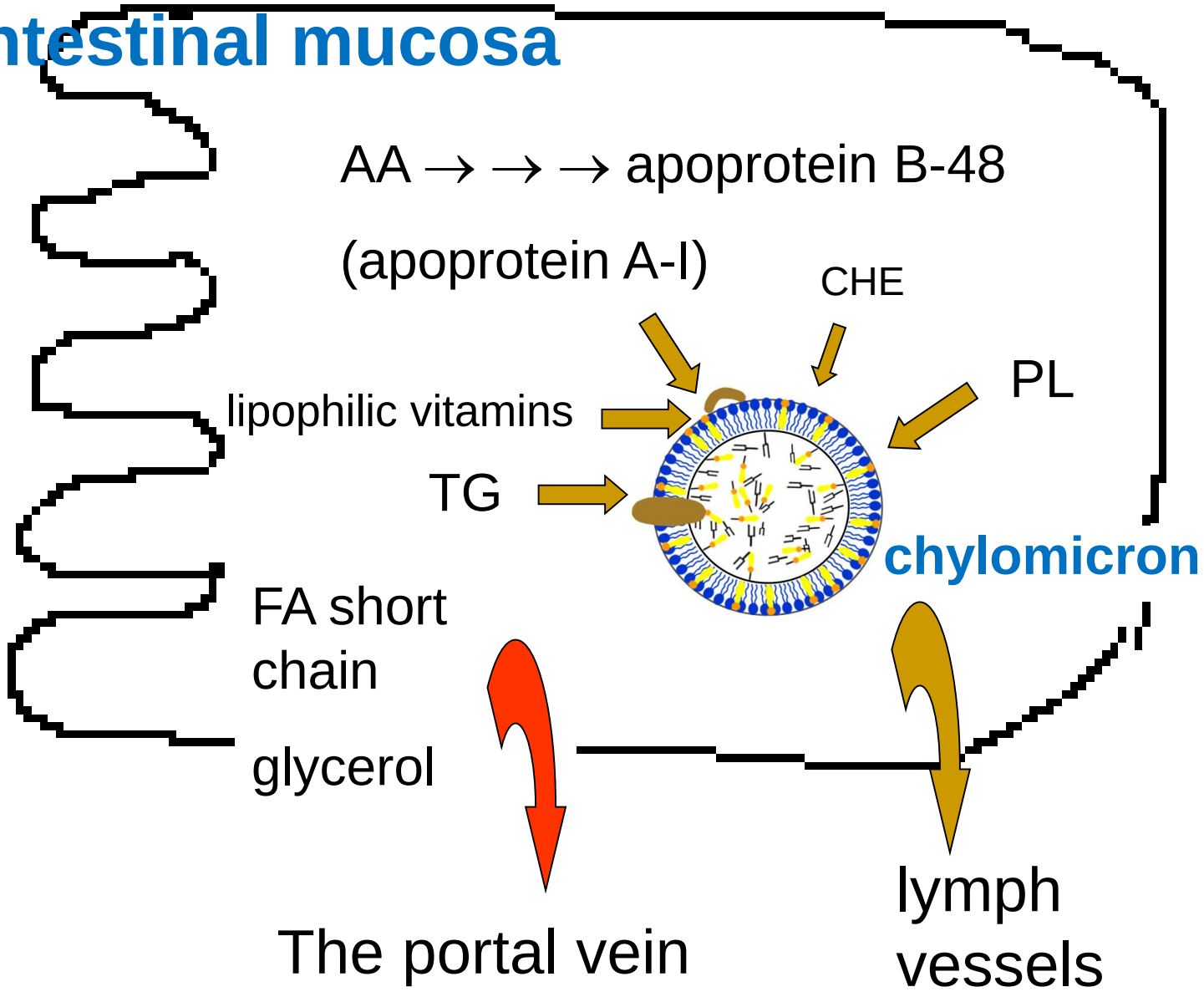
epithelial cells



The diameter of <20 nm

Passive diffusion of monoglycerides and FA

Transport of lipids from cells of the intestinal mucosa



Blood plasma

transport of triacylglycerols in the form of lipoproteins

fatty acids bound to albumin.

Lipoproteins are the transport form of non-polar lipids in blood

More specifically, we will focus on lipoproteins, which we can say that they are a "transport form" otherwise non-polar lipids in the blood.

Lipoprotein is composed of a core and cover. At the core we find transmitted lipids (TAG, cholesterol esters), the packaging is made of phospholipids, cholesterol, and various proteins (integral and peripheral).

Lipoprotein size for most types does not exceed the size of the colloidal particles (ie the 500 mm), only one type (chylomicrons) has a diameter greater than 500 microns.

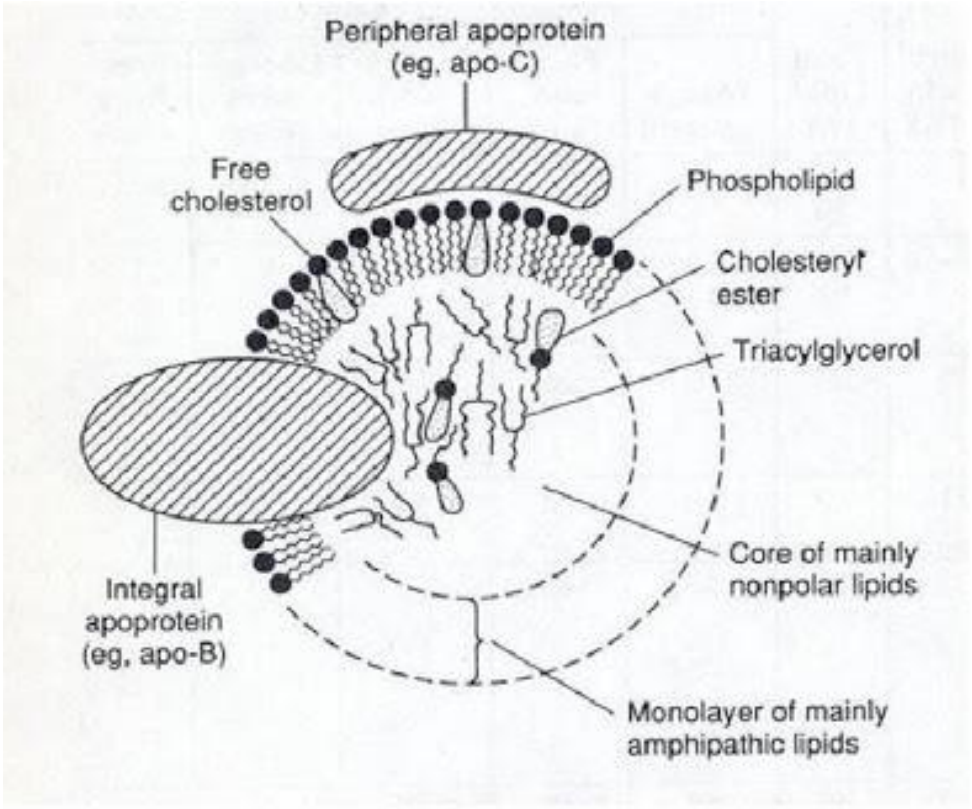
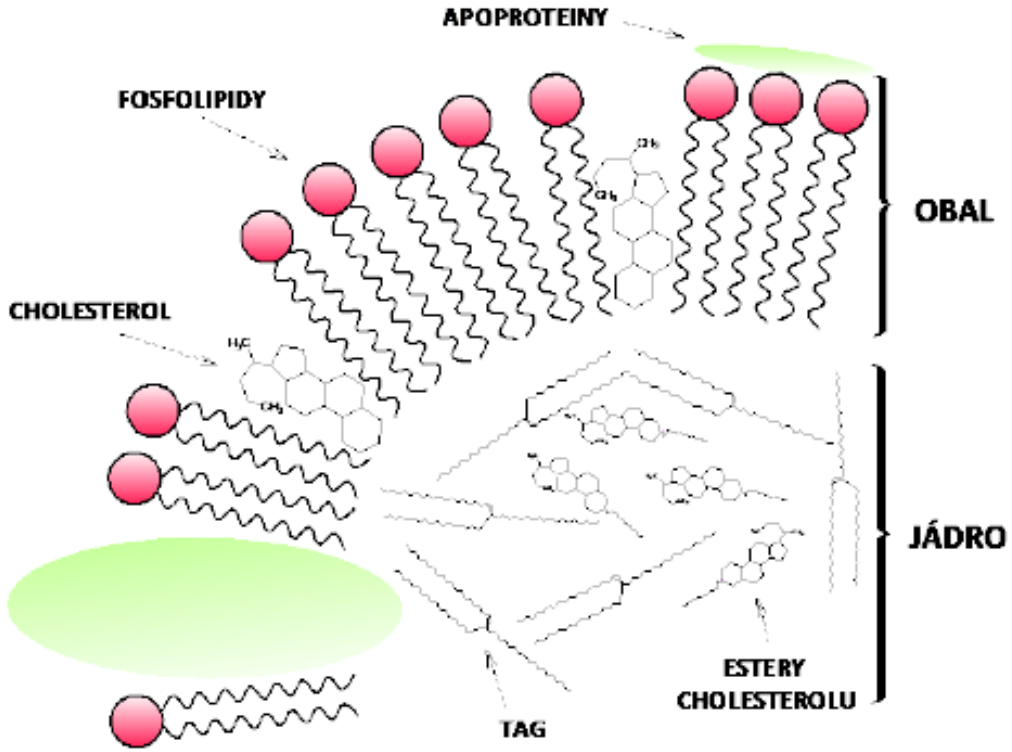


Figure : LIPOPROTEIN STRUCTURE www.toosogie-lipid-diagnostic.blogspot.com/

http://1.bp.blogspot.com/_fS2Wvz7uGBo/SxyYjpj0ApI/AAAAAAAAALI/fyof6TlCCnY/s400/lipoprotein+structure.JPG



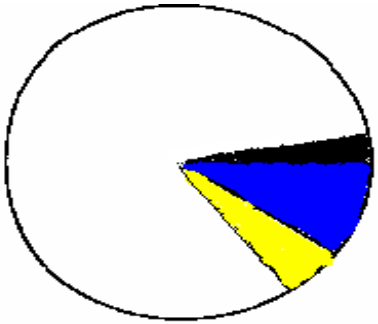
Podle **různé hustoty** rozdělujeme lipoproteiny do 4 typů:

Název	Hustota	Typ přenášených lipidů
Chylomikrony (CM)	nejnižší hustota	lipidy přijaté potravou
VLDL	very low density lipoprotein	lipidy vzniklé v játrech určené na export
LDL	low density lipoprotein	transport cholesterolu
HDL	high denstiy lipoprotein	transport cholesterolu

NOVÁK, Jan. Biochemie I. Brno: Muni, 2009, Metabolismus lipidů s. 3

Types of lipoproteins

Density of lipoprotein is determined by its composition. If we focus on the 4 basic structural components of lipoprotein (TAG - triacylgylcetroly CH - cholesterol, PL - phospholipids, P - proteins), the percentage of these components can be expressed by the following graphs.

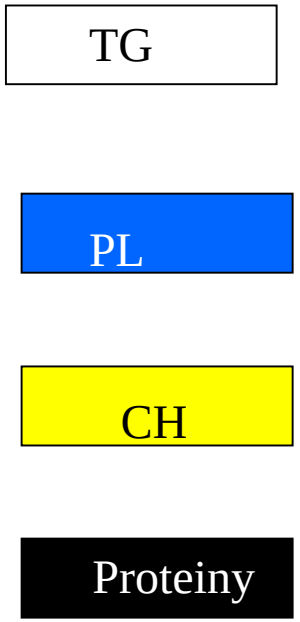


Chylomikron CM

VLDL

LDL

HDL



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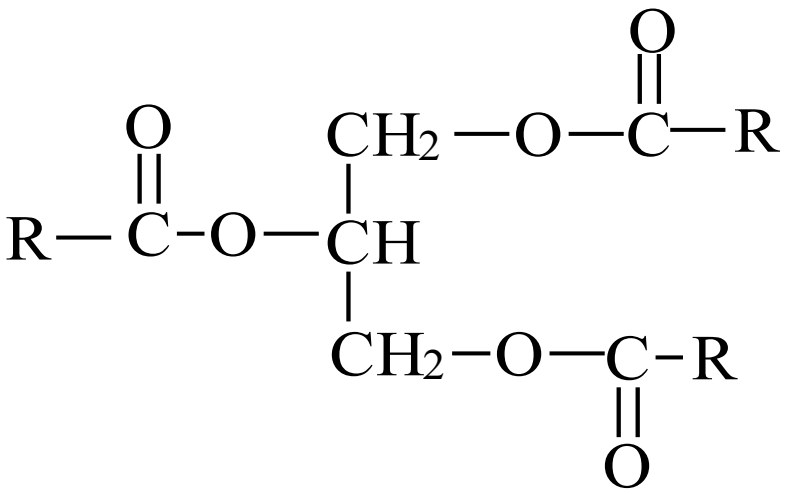
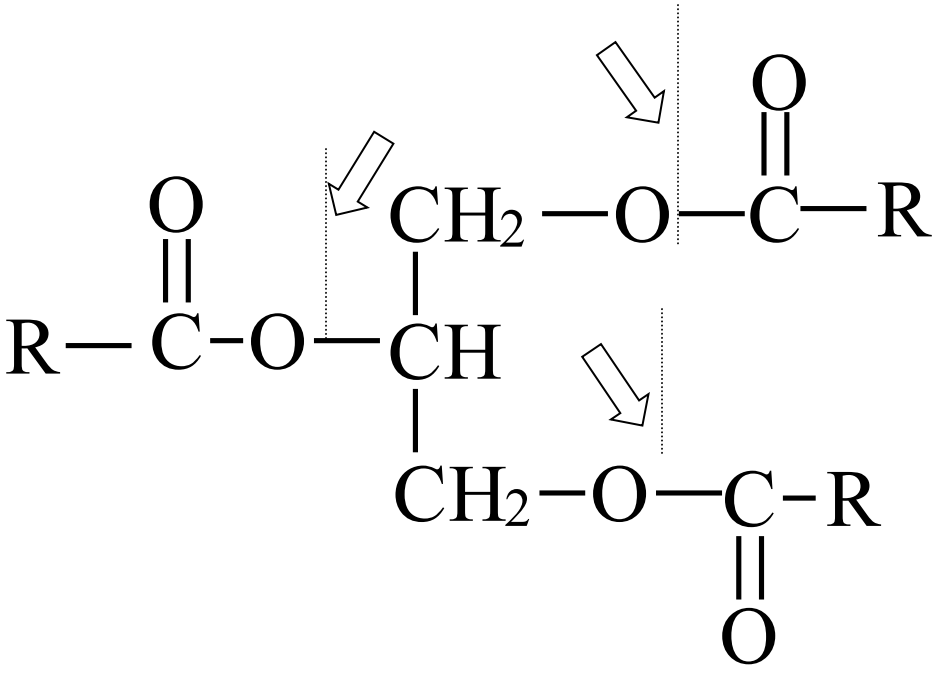
Metabolism of triglycerides

The most commonly accepted dietary triglycerides, which are esters of glycerol and fatty acids. Their metabolism begins by hydrolysis to glycerol and FA. FA and glycerol then go through a completely different metabolic pathways.
Decomposition of TAG into glycerol and FA by enzymes called lipases (enzymes from the group of hydrolases) which cleave the ester bond between the glycerol and the chain of FA.



1. Hydrolytic cleavage of fatty acids
2. Metabolism of fatty acids and glycerol

Lipases catalyze the hydrolysis of triacylglycerols



Cleave the ester bond between the glycerol and FA

Lipases

Extracellular

pancreatic lipase (small intestine)

- lipoprotein lipase (blood)
- hepatic lipase (surface of sinusoid)

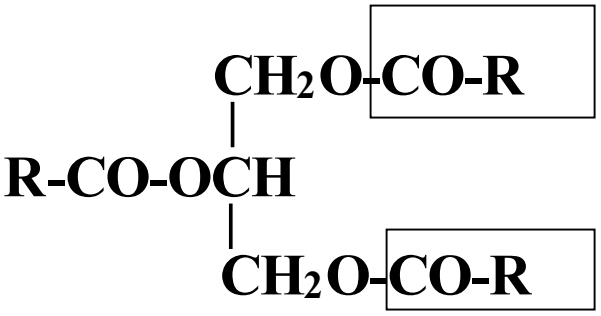
Intracellular

- hormone-sensitive (adipocytes - fat cells)
- acidic lipase (lysosomes)

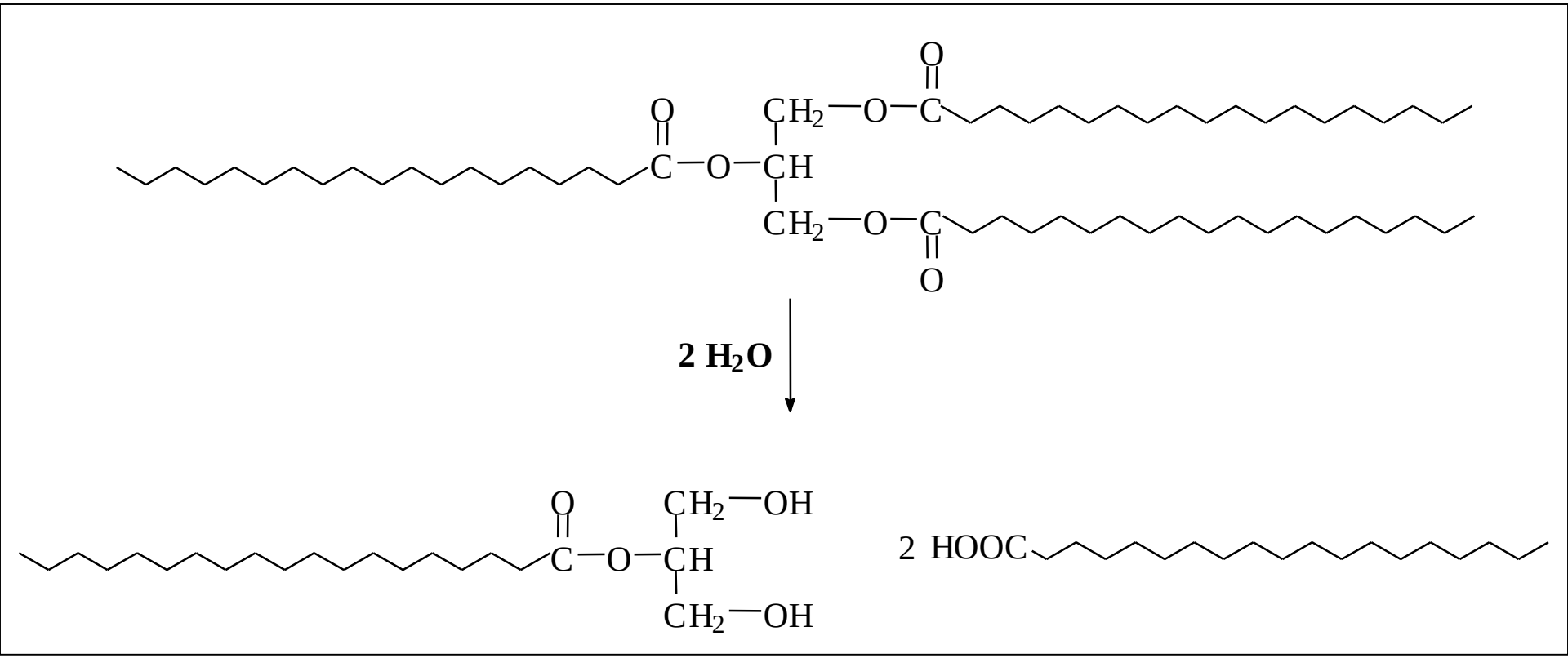
Pancreatic lipase

(+ colipase)

- operates in the small intestine, splits fats ingested
- triacylglycerol $\rightarrow$ 2-monoacylglycerol + 2 FA



Effect of pancreatic lipase

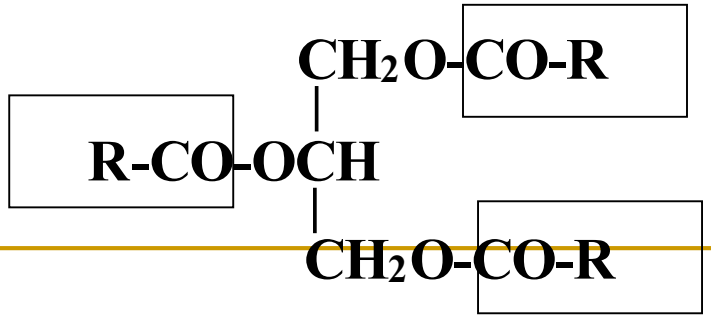


Lipoprotein lipase

• acts on chylomicrons and VLDL in blood

cleaves triglycerides contained therein

triacylglycerol $\rightarrow$ glycerol + 3 FA



Adipocytal lipase (hormone sensitive)

active in adipocytes

- depends on hormone action
  (glucagon - starvation, adrenaline, noradrenaline - stress)
- releases fatty acids into the blood

triglyceride $\rightarrow$ glycerol + 3 FA

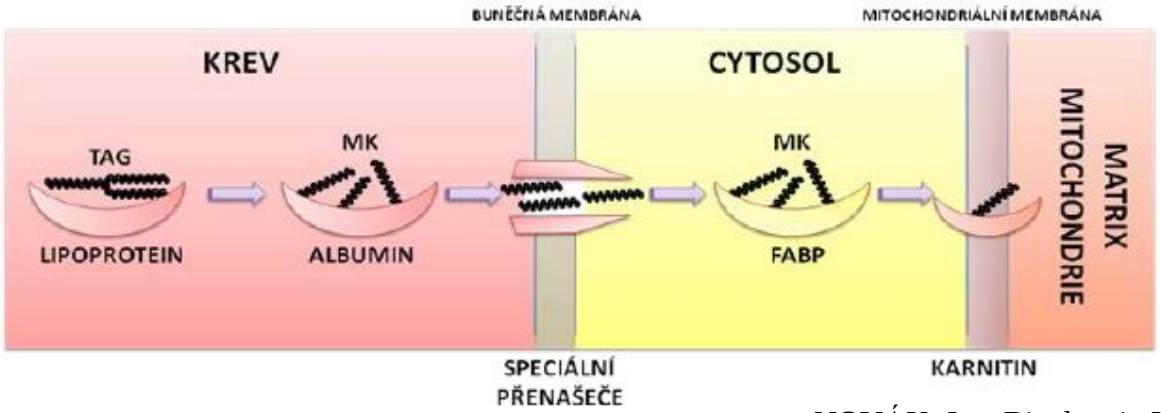
Transport of fatty acids in ECT

TAG release of the ECT (CM, VLDL)

Release of TG in adipocytes, hormonsensitive action of lipase (Hormonal regulation)

FA in blood - albumin binding

(1 mmol/l, half-life 2 min)



Biochemie-8-1-lipidy

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Transport of fatty acids in the cells

• specific membrane proteins facilitate transportation of FA in cells

transport in cells using FABP (fatty acid binding protein)

• across the mitochondrial membrane by **carnitine**

β-Oxidation of fatty acids

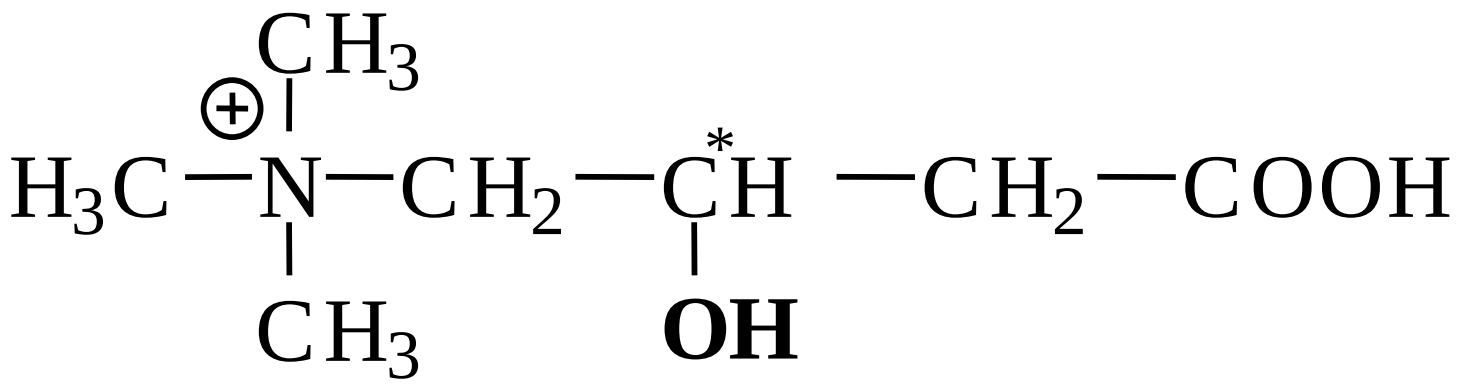
- Meaning: energy source

In virtually all cells

- Location: mitochondrial matrix

Progress: stepwise removal of acetyl-CoA

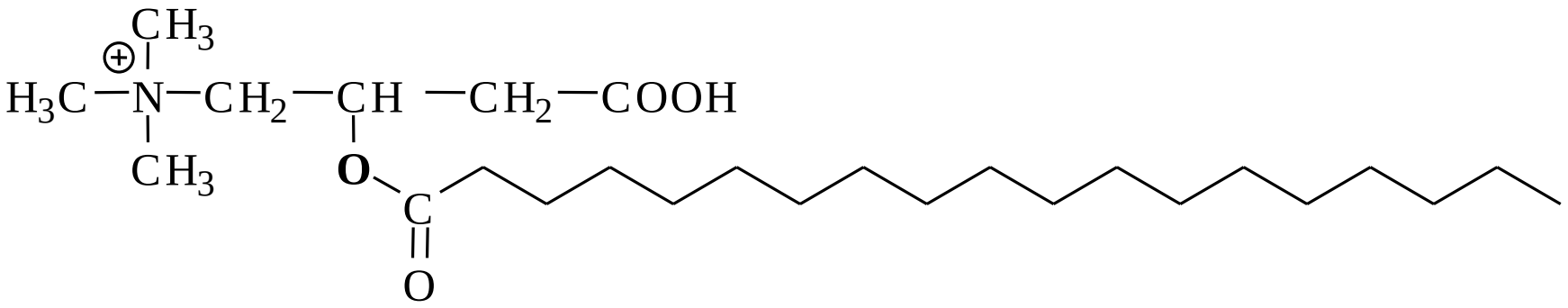
For transport of FA into mitochondria **carnitine** is needed



(2-hydroxy-3-carboxypropyl)trimethylammonium

short chain FA do not require carnitine

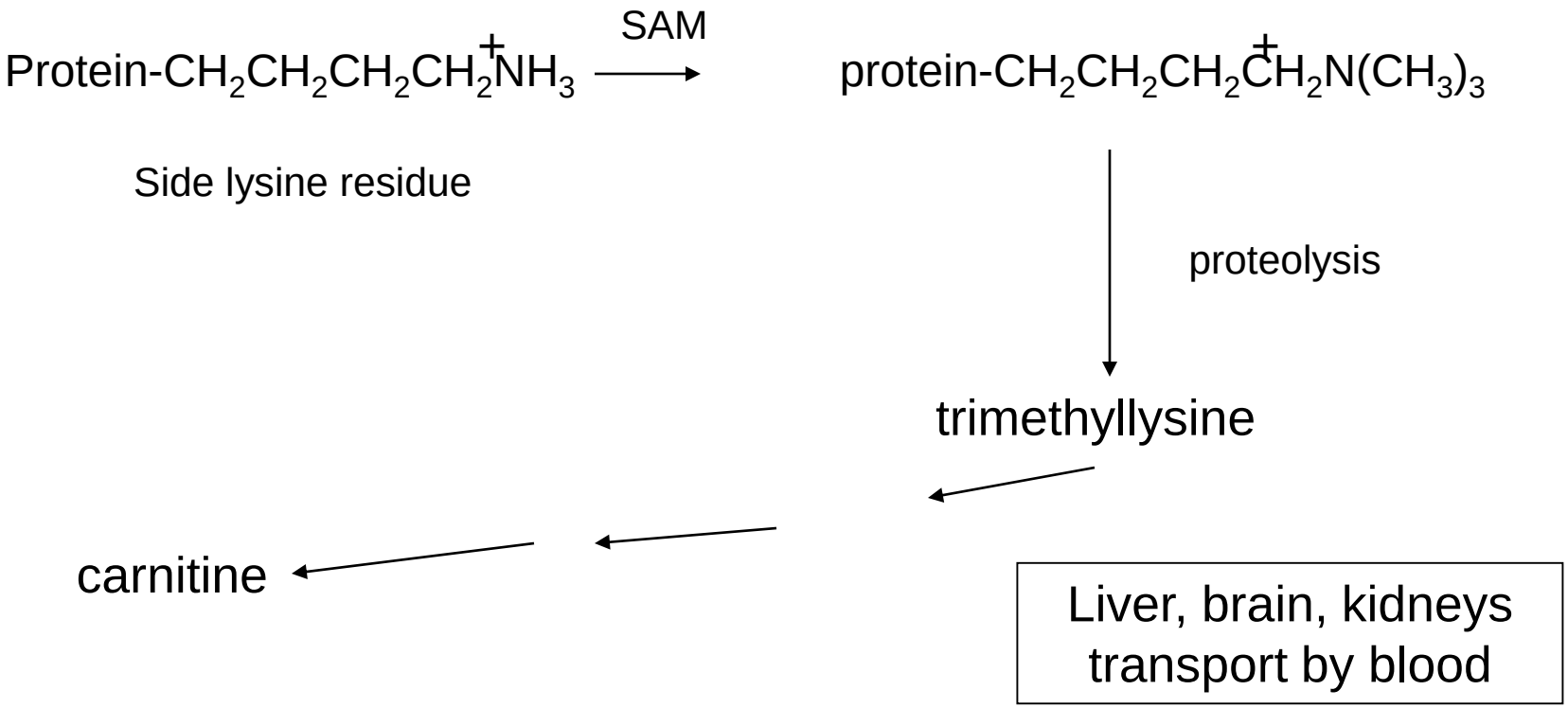
FA is transmitted in the form of acylcarnitine



ester bond

Sources of carnitine

Synthesis in an organism



Dietary intake: about 100 mg / day (Animal sources: meat, milk. It is also found in plant sources.)

carnitine deficiency

- congenital disorder of carnitine transport
- in certain diseases (especially organs that can synthesize it)
- large losses (diarrhea, hemodialysis, burns ...)
- inhibition of transport into the cell by some drugs (doxorubicin, cisplatin, lidocaine)

decreased biosynthesis (malnutrition)

Carnitine supplementation in these disorders is required.

Consequences of lack of carnitine

• Lack of carnitine in liver : hypoketotic hypoglycemia during starvation

β-oxidation is required during fasting for the production of acetyl-CoA for ketogenesis and ATP production for gluconeogesis

Lack in muscle - muscle weakness and cramps

Carnitine as a dietary supplement?

The importance of increased intake of carnitine especially for athletes leads to numerous disputes. Although many findings about the function and dynamics of carnitine in the body suggests beneficial effects of increased intake of dietary supplement in particular, excessive physical exertion, no convincing and reliable evidence for this assumption so far been filed.

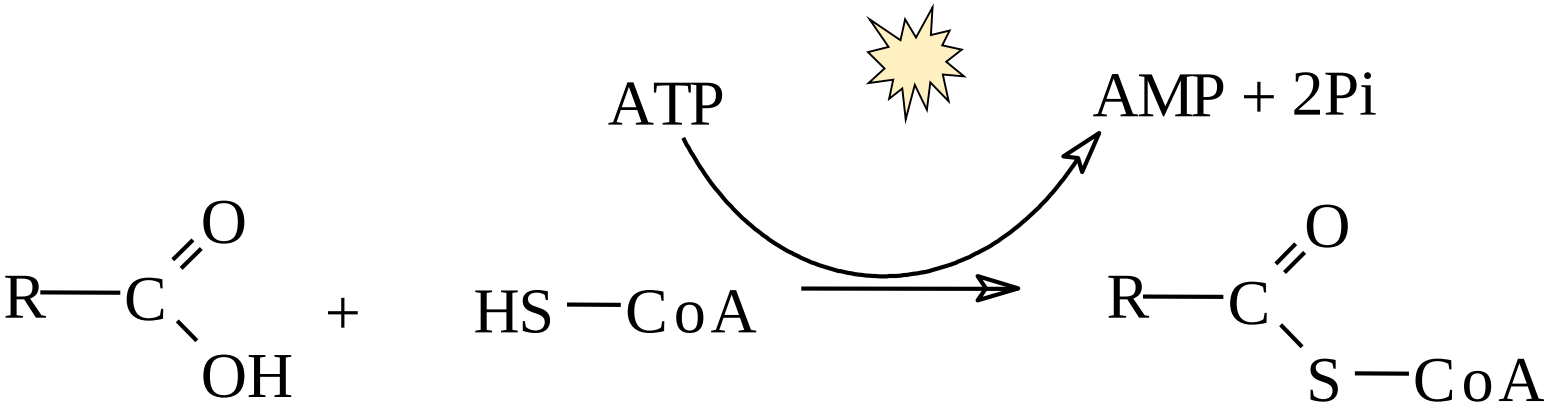
Carnitine from food is poorly absorbed, intestinal bacteria can metabolize to form trimethylamine.

The administration can be only L-carnitine. D-carnitine and racemate are officially banned.

Activation of FA before binding to carnitine

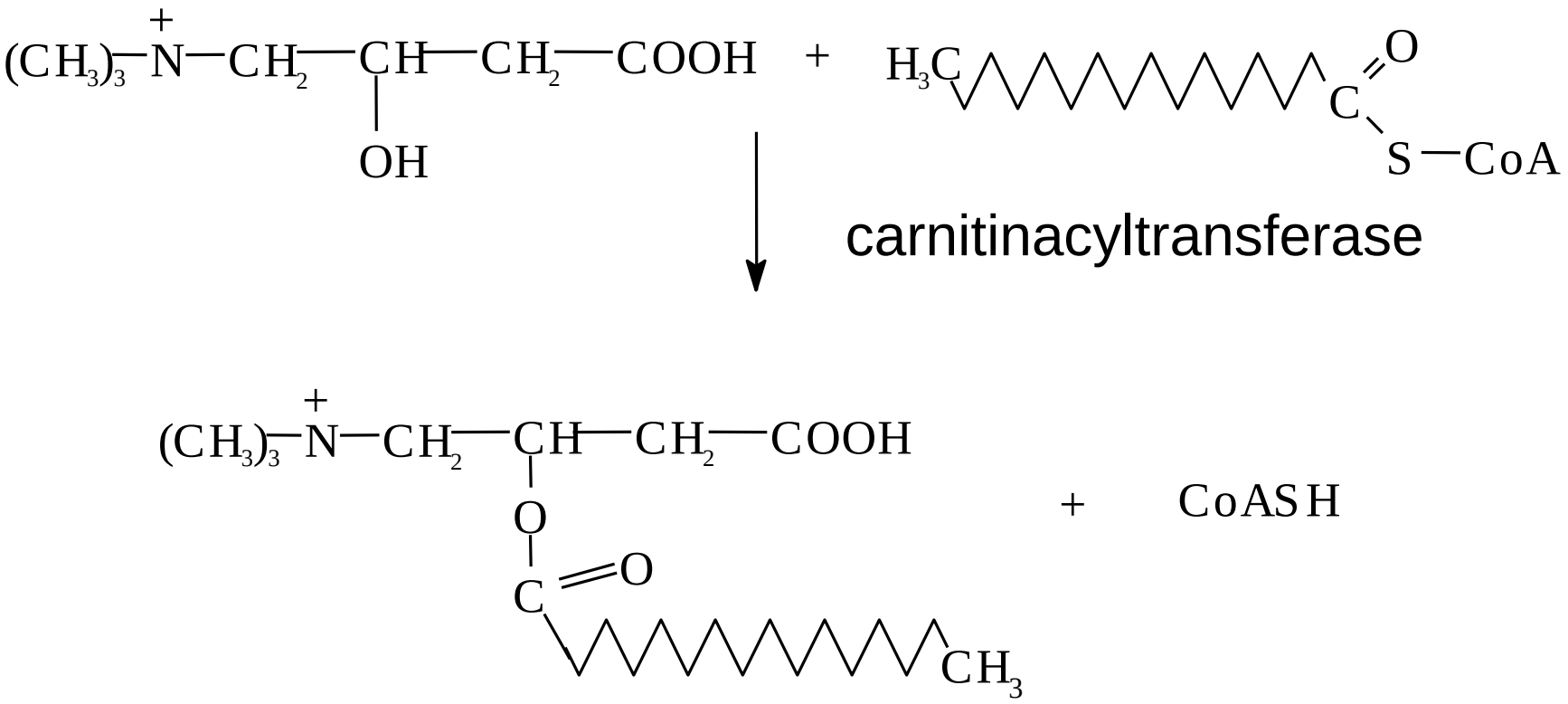
Cytoplasm

Loss of energy equivalent to 2 ATP

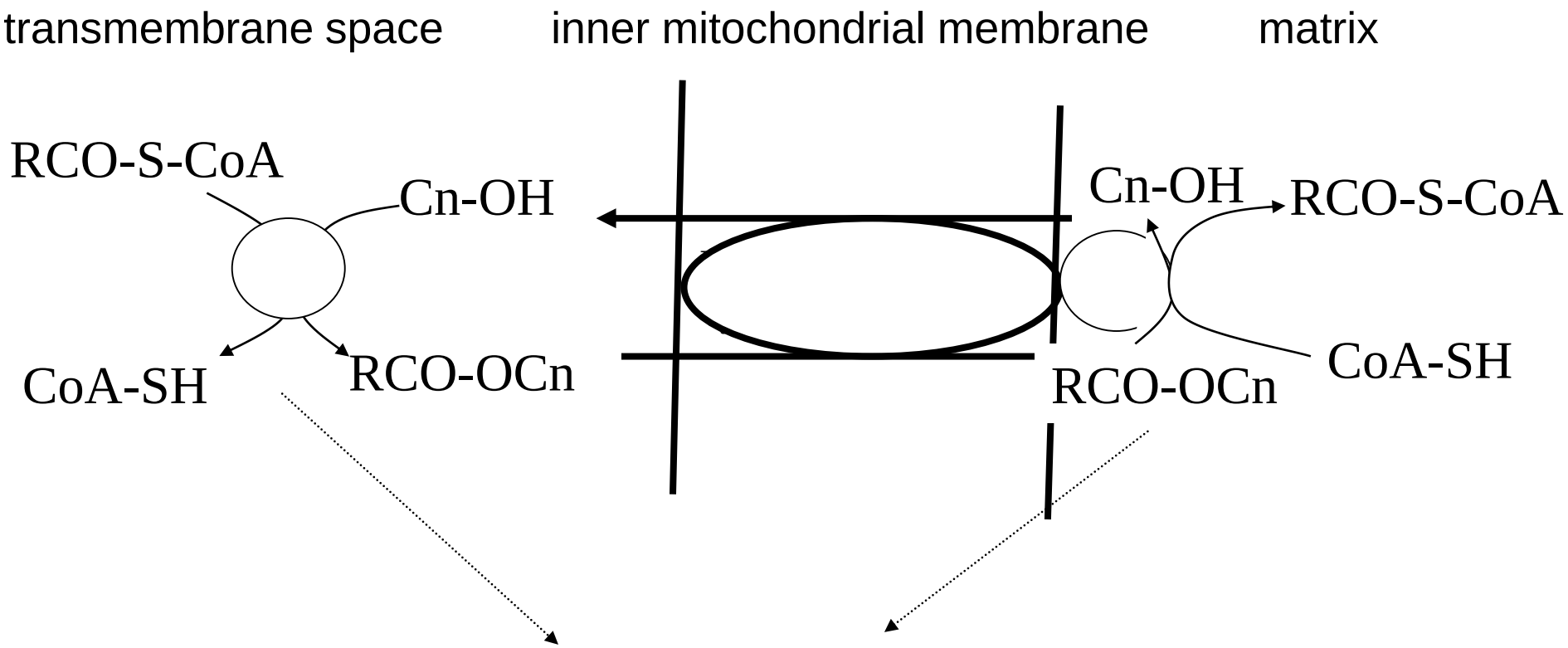


Formation of acyl-carnitine

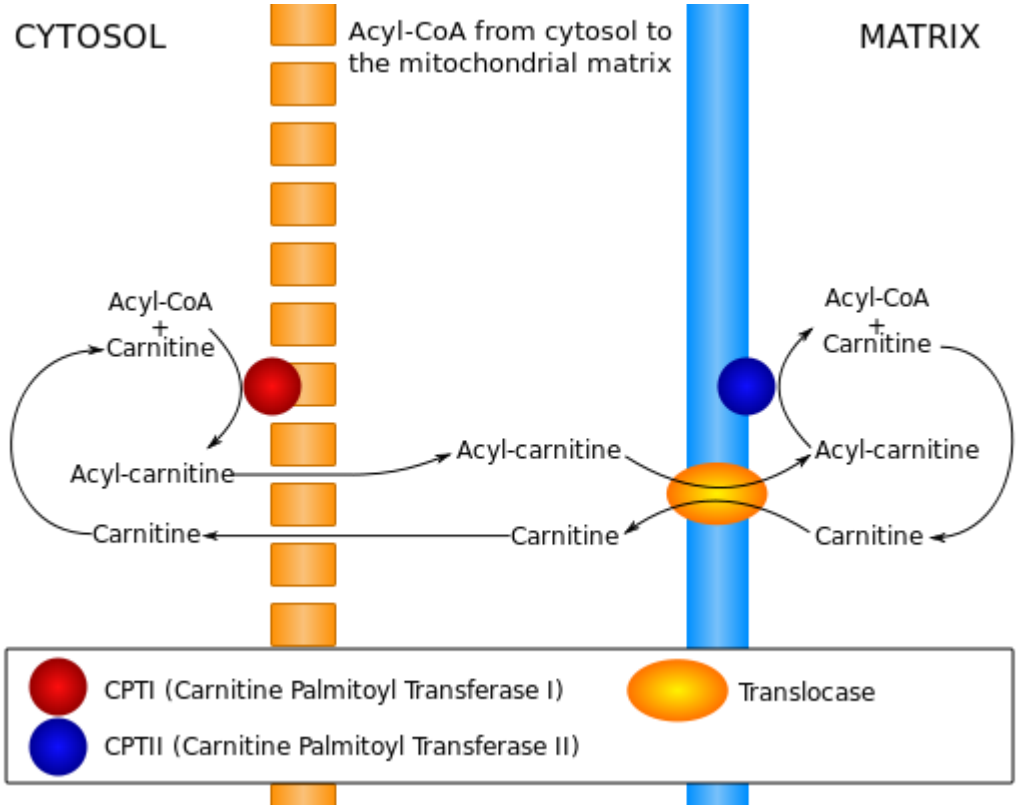
Takes place in the mitochondria transmembrane space



Transport of fatty acids into mitochondria



Two forms of carnitin-acyltransferase



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β-Oxidation of fatty acids

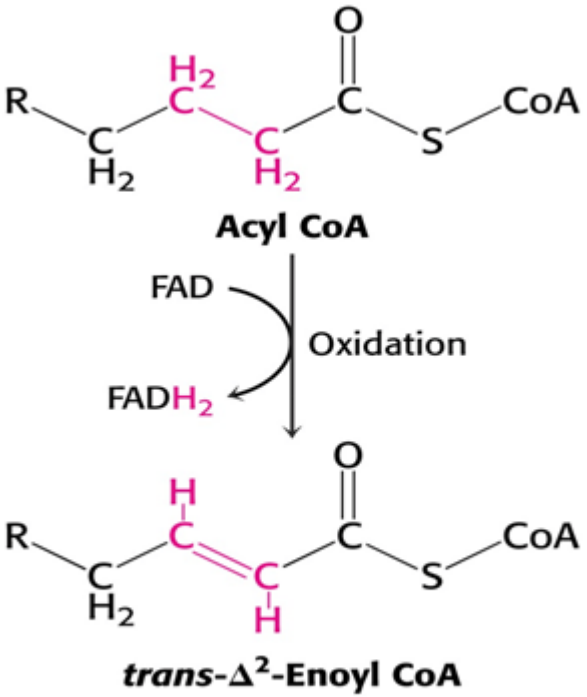
- the main FA degradation pathway
- acyl-CoA enters the reaction
- carbon (C-3) is oxidized
- general mechanism - the repetition of four steps:

  dehydrogenation → hydratation →

  dehydrogenation → cleavage of acetyl-CoA

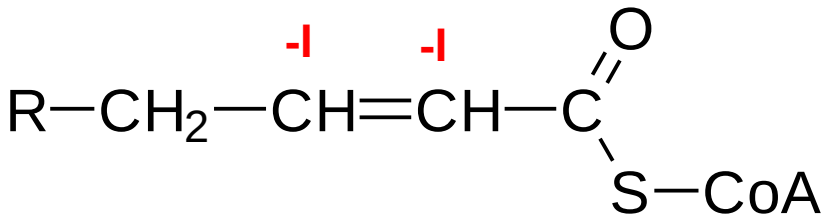
(1) Dehydrogenation of acyl-CoA

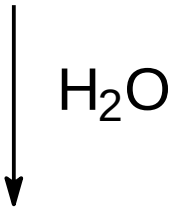
trans configuration



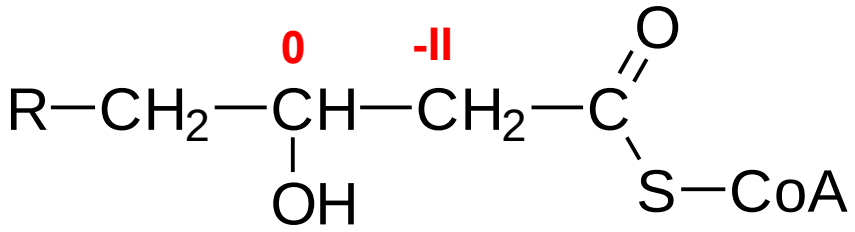
(2) Hydration of the double bond

α,β-nenasycený acyl-CoA





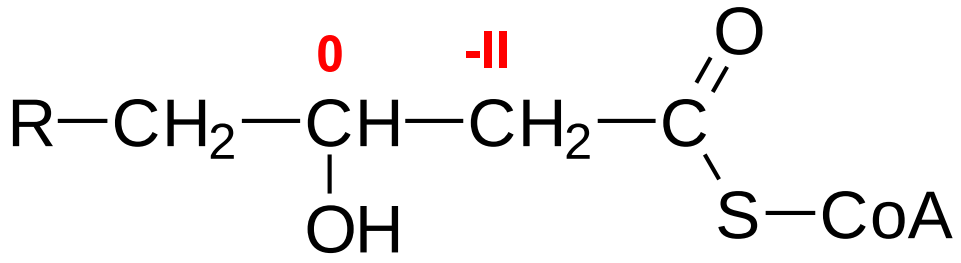
β-hydroxyacyl-CoA



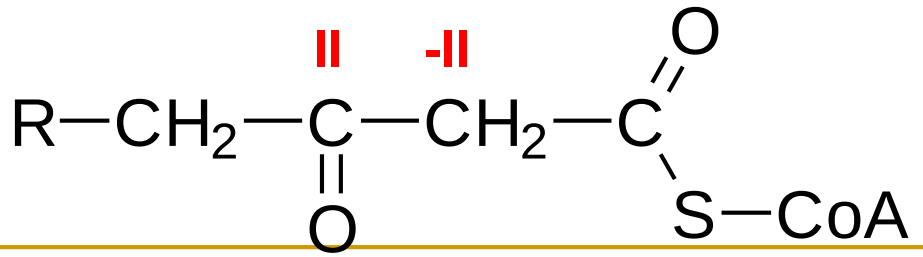
Hydration is not a redox reaction, one C was reduced, the second C oxidized, but the sum of carbon oxidation numbers is the same

(3) Dehydrogenation of hydroxyacyl

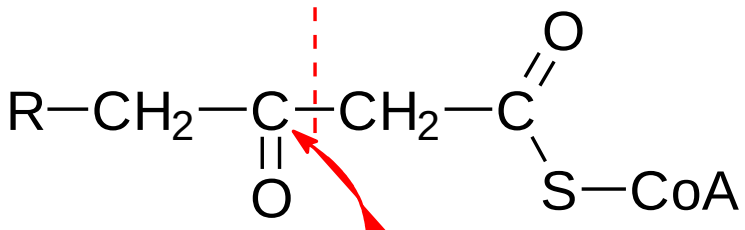
β-hydroxyacyl-CoA

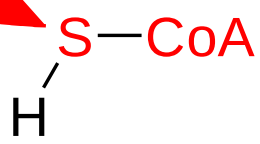


β-oxoacyl-CoA

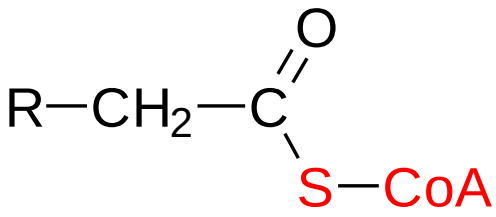


(4) Thiolysis of oxoacyl and cleavage of acetyl-CoA

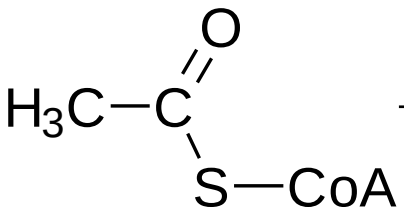




thiolase



acyl-CoA
(2 C shorter)

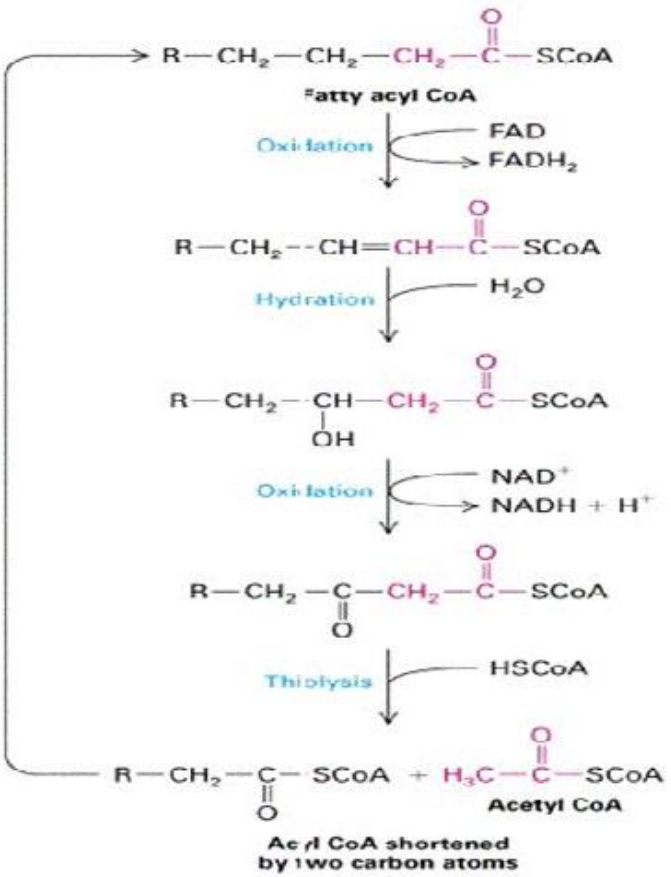


CC

acetyl-CoA

The overall progress of β-oxidation

- 1.dehydrogenation (FAD)
- 2. hydratation
- 3. dehydrogenation (NAD^+)
- 4. transfer of acyl to CoASH



acyl-CoA dehydrogenase

Δ^2-enoyl-CoA hydratase

3-hydroxyacyl-CoA dehydrogenase

thiolase

http://classes.kumc.edu/som/cellbiology/processes/atp/images/nr39.jpg

Acyl-CoA dehydrogenases

3 main types

for FA with short

medium

long chain

Dehydrogenase deficiency for FA with medium chain

congenital disorder - intolerance to prolonged starvation associated with hypoglycaemic coma (extended in northwest Europe - up to 90 % of population)

The energy yield of the oxidation of palmitoyl-CoA (16 C)

Palmitoyl-CoA + 7 FAD + 7 NAD^+ + 7 H_2O + 7 CoA

⇩

8 acetyl-CoA + 7 $FADH_2$ + 7 NADH + 7 H^+

⇩ ⇩ ⇩

8 x 12 ATP = 96 ATP | 14 ATP | 21 ATP

Equivalent to 2 ATP is consumed during formation of acyl-CoA

Overall 131 – 2 = 129 ATP / palmitate

Comparison of energy-yield of β-oxidation and glycolysis:

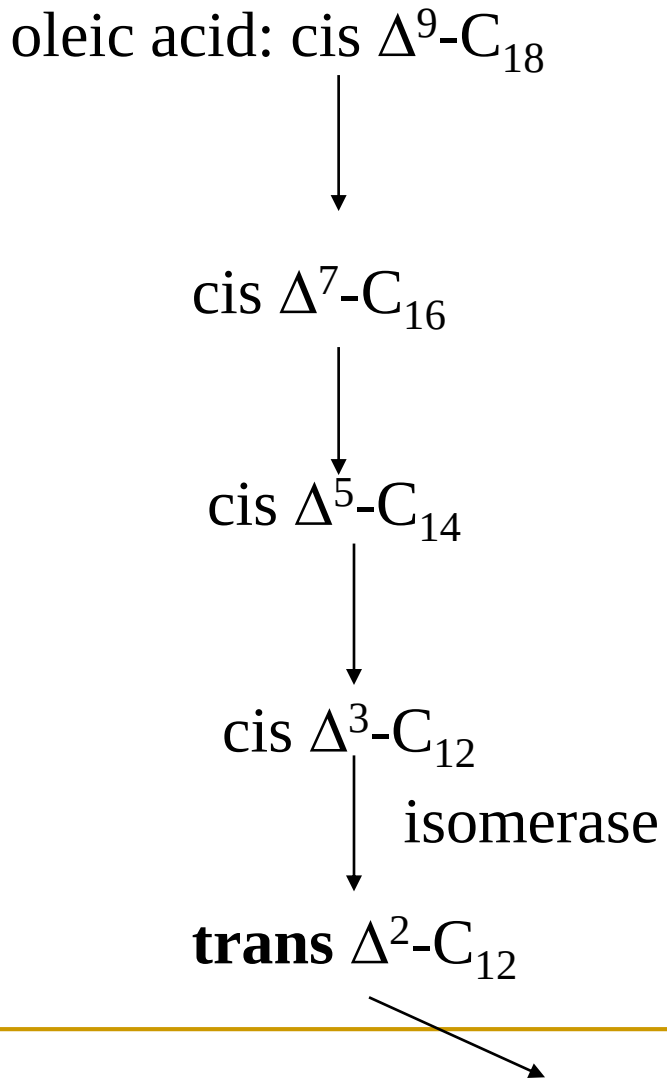
Gain of ATP from glucose (6C)

38 ATP	on 1 C of glucose	38/6 = 6,3 ATP
	from FA (16 C)	129 ATP
	on 1 C of FA	129/16 = 8,1 ATP

From 1 C of FA the average yield is 1.3 times more ATP

Why?

Oxidation of unsaturated fatty acids



loss of $FADH_2$

the same course with β-oxidation

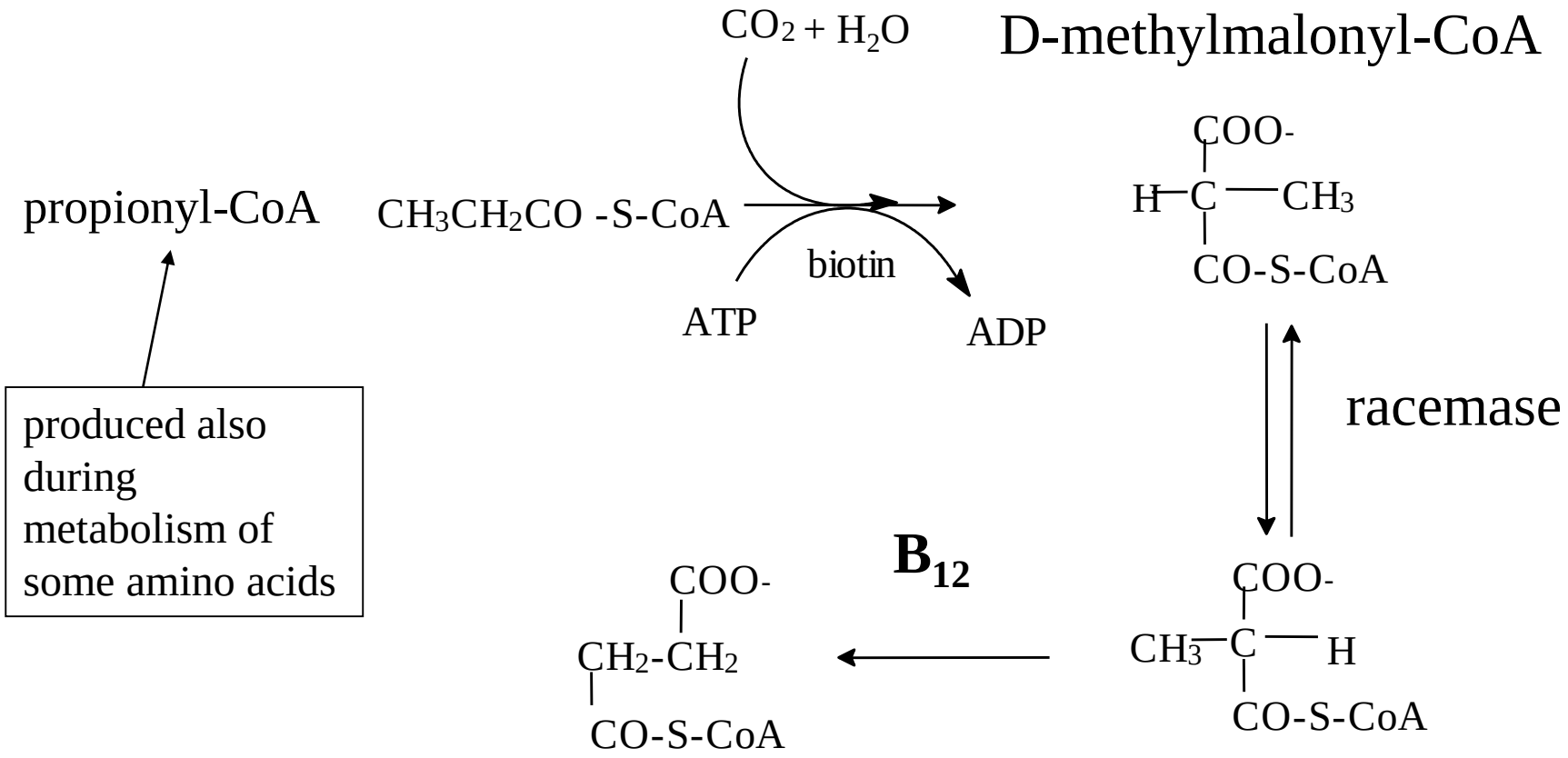
Polyunsaturated FA

linoleic acid: $\Delta^{9,12}$-C_{18}

Δ^{2}-C_{8} cis

Other enzymes allow complete oxidation

FA with an odd number C provide propionyl



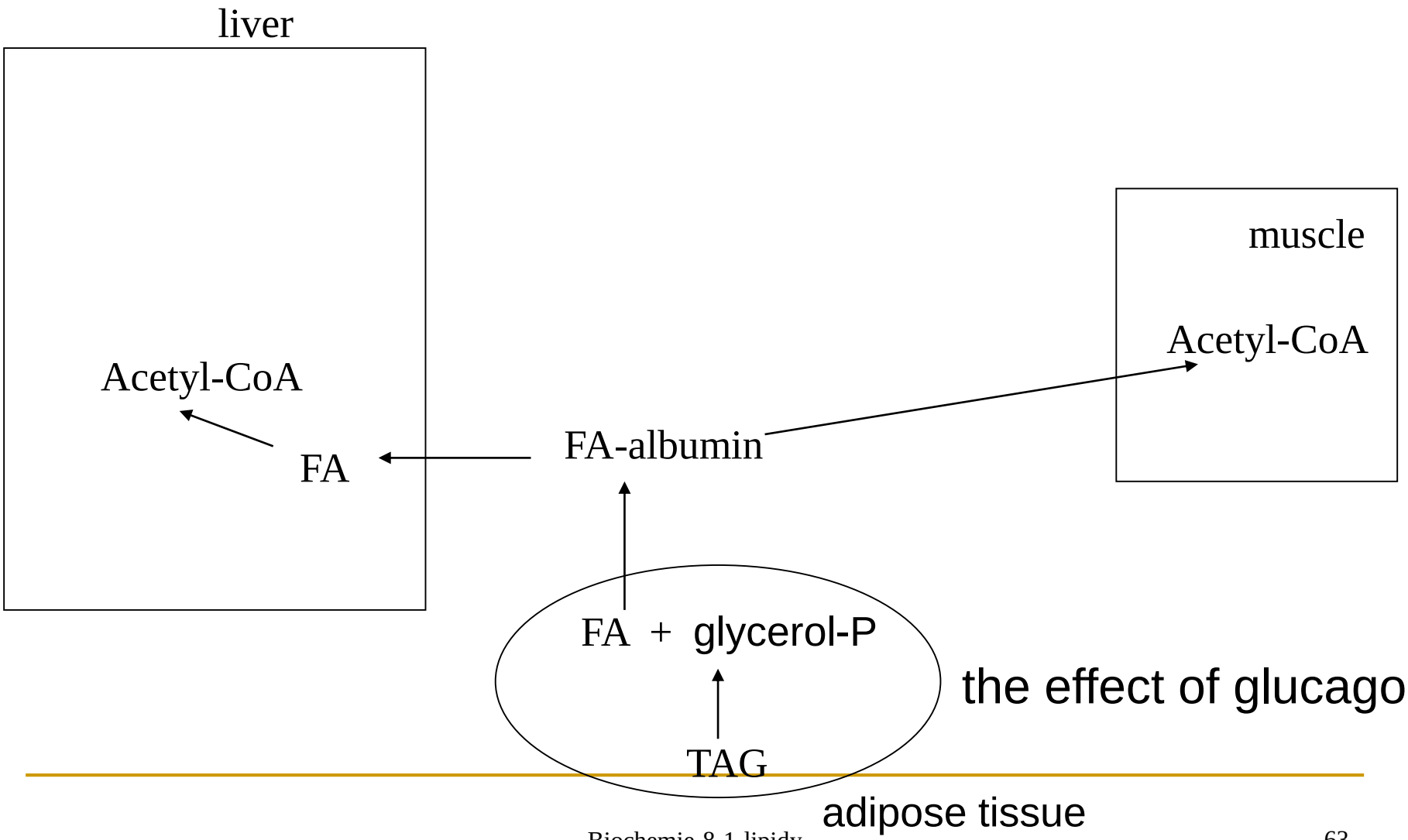
β -oxidation of FA is an important source of energy

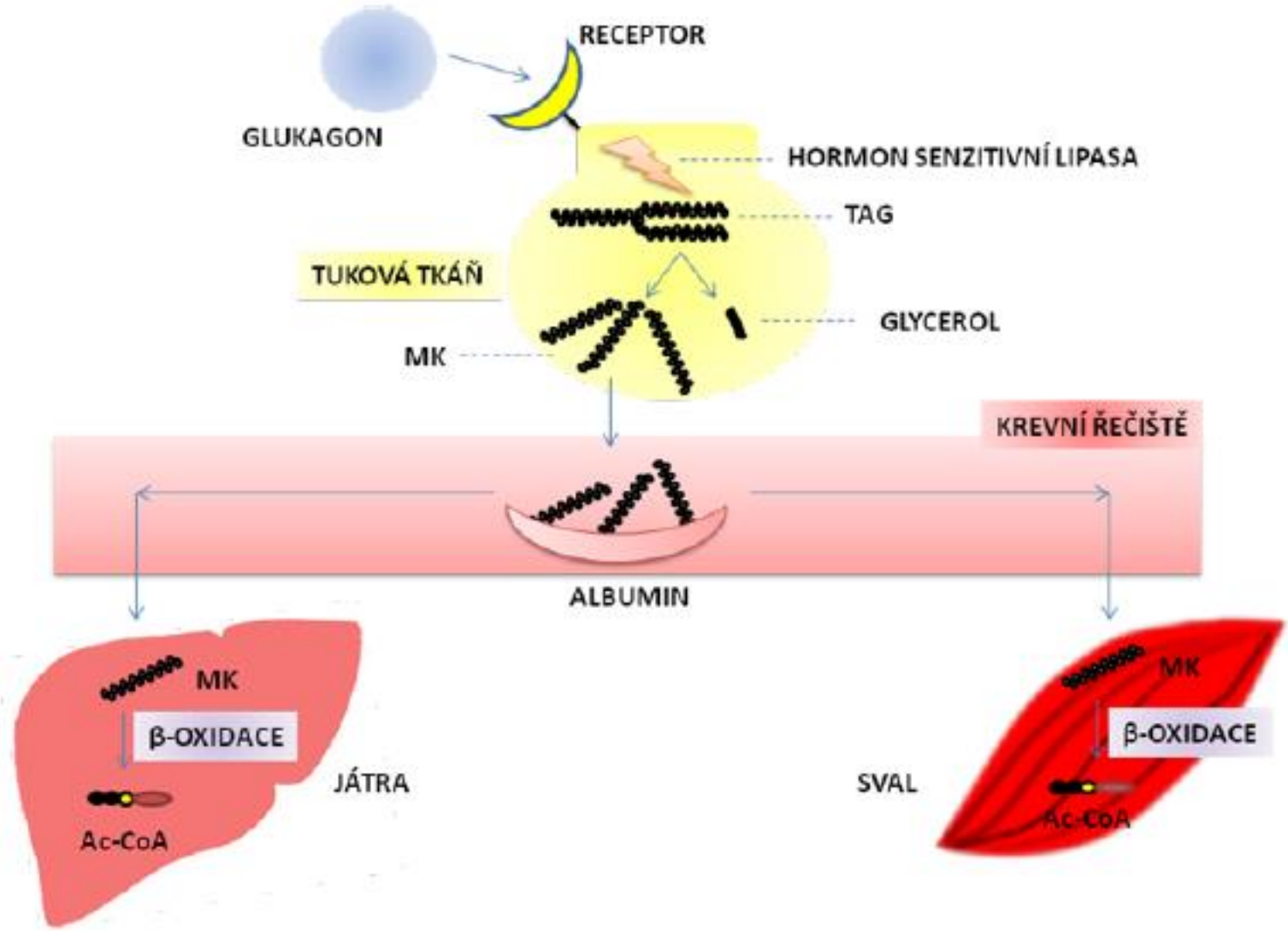
When does it take place?

If a cell needs energy and
does not have enough glucose

β-oxidation takes place in postresorption phase and in starvation especially in the muscles, myocardium and liver

Lipids in postresorption phase (glucagon)





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Lipids in postresorption phase

- In adipose tissue lipolysis occurs (hormone sensitive lipase)
- FA are transported in the ECF bound to albumin
- FA are the source of energy for muscles and myocardium

Ketone bodies

Acetocetate, 3-hydroxybutyrate - metabolically usable

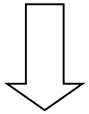
acetone - waste product

produced by the liver

- pass into the blood
- they are processed by extrahepatic tissues
- level increased during fasting, diabetes
- the ratio of glucagon / insulin >>> 1

Causes of ketone bodies

Increased FA mobilization from adipose tissue → transport to the liver



→ Increased production of acetyl-CoA by β-oxidation

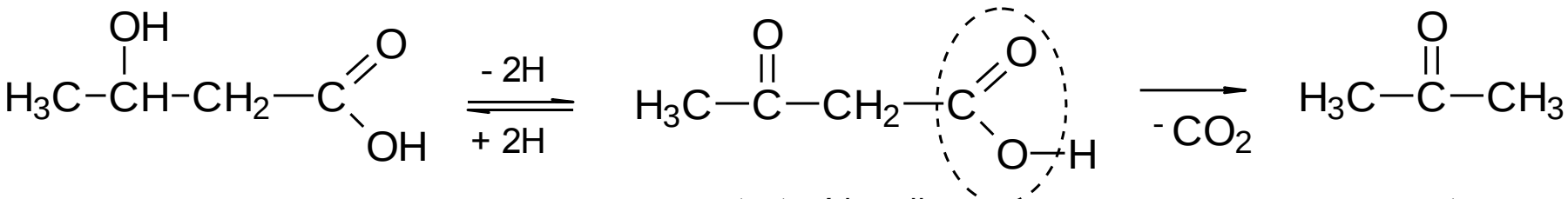
→ capacity exceeded in the citric acid cycle (lack of oxalacetate)

→ → synthesis of ketone bodies

Extrahepatically they are metabolized for energy gains ☺

Increased production is associated with ketoacidosis ☹

Interrelationship of ketone bodies



β-hydroxymáselná kyselina

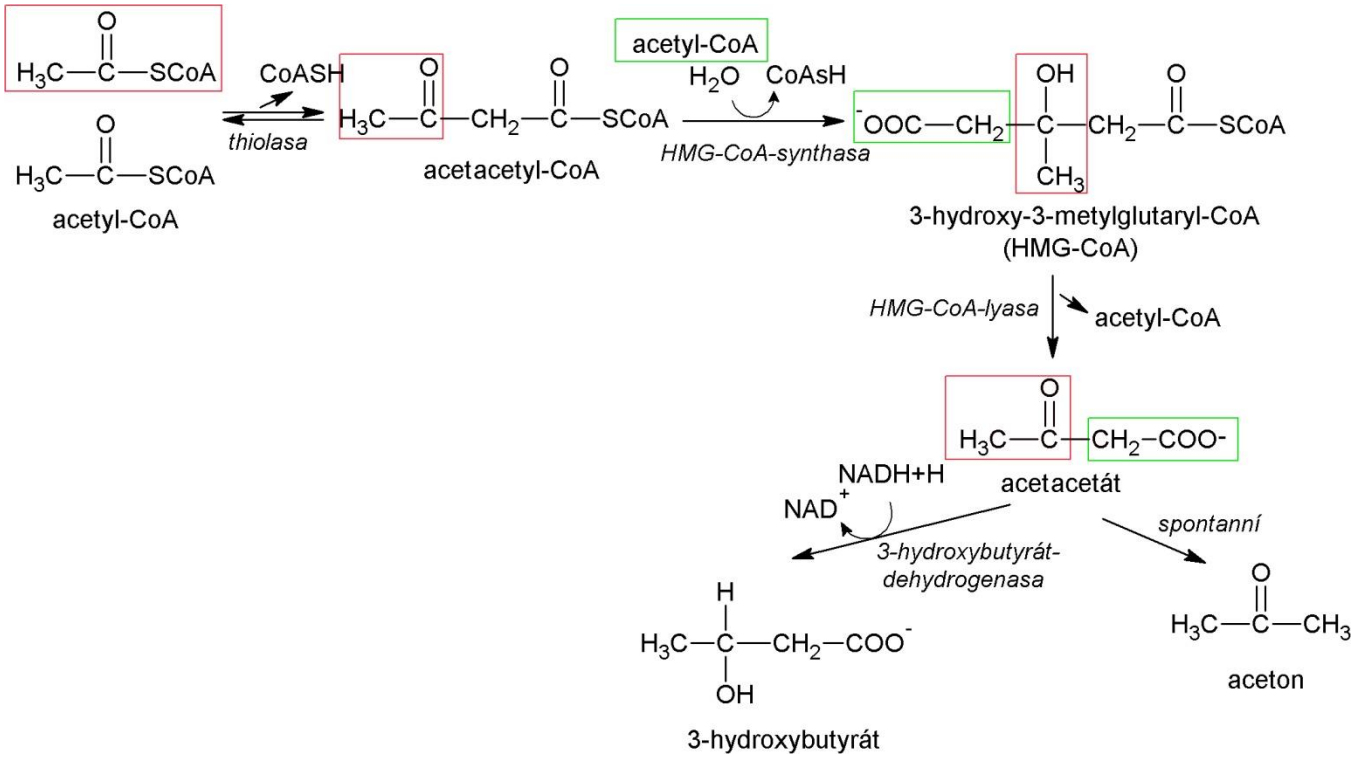
acetoctová kyselina

aceton

Acid	pK_A
Acetoacetic	3,52
β-hydroxybutyric	4,70

Synthesis of ketone bodies

matrix of mitochondria
of liver cells



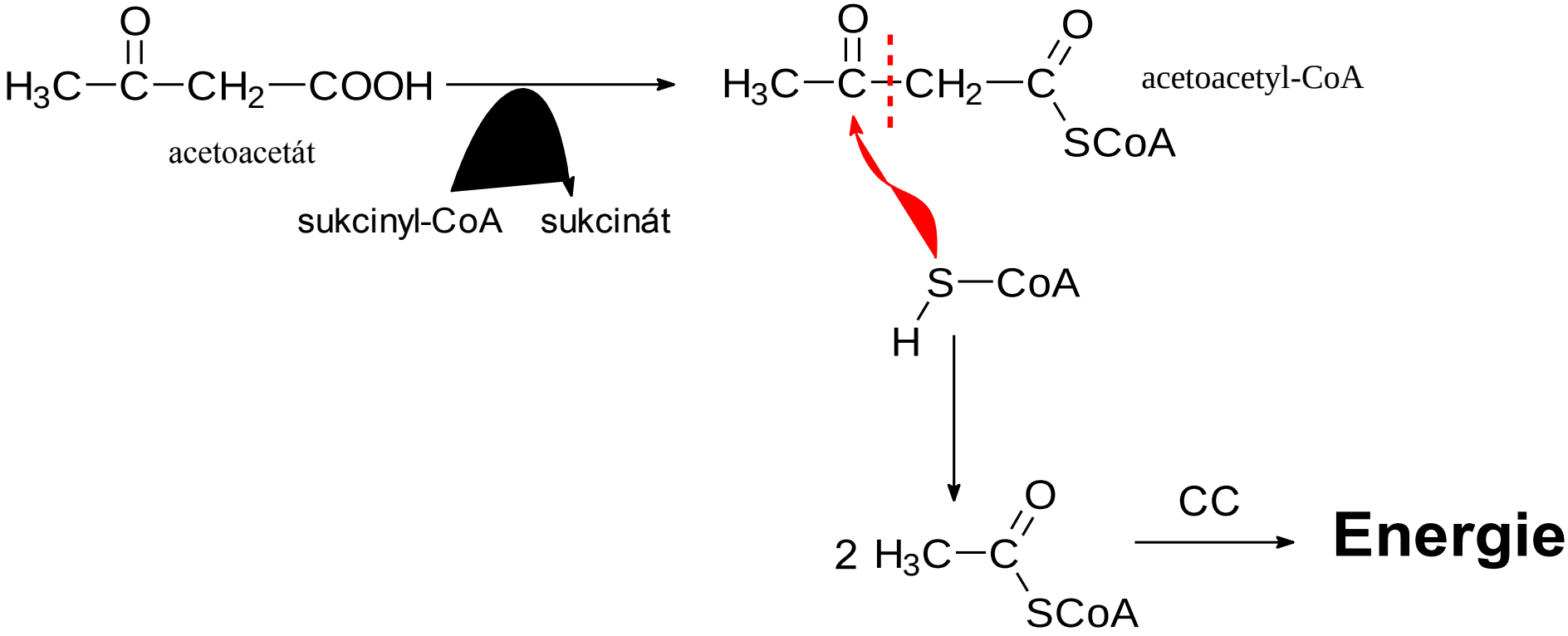
transport via blood to
the extrahepatic tissues

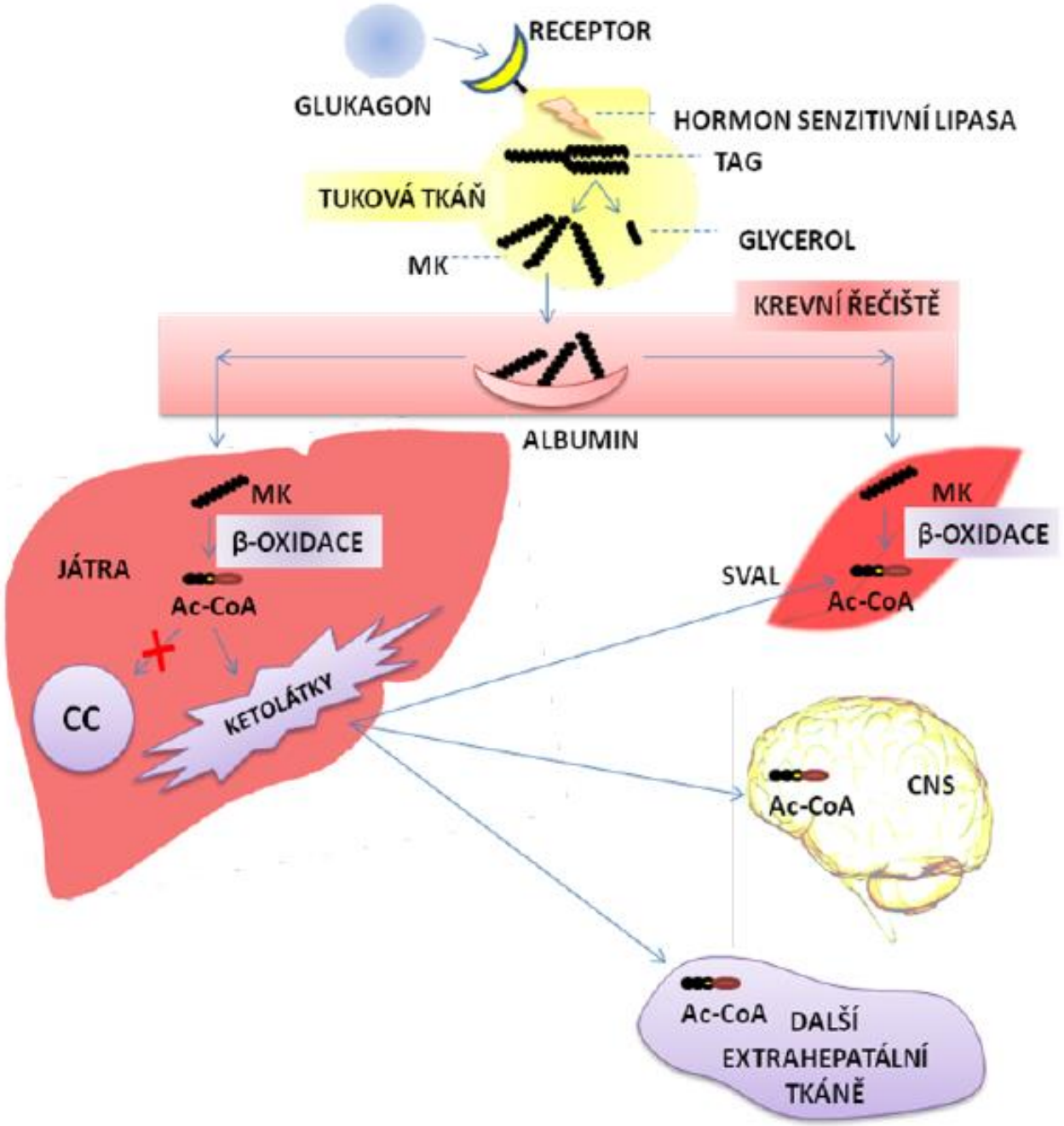
http://dl1.cuni.cz/pluginfile.php/241144/mod_page/content/4/ketola%CC%81tky-schema.jpg

Formation of ketone bodies

- In blood there is always a trace concentration of ketone bodies
- their levels rise during fasting or uncompensated diabetes
- unused acetyl-CoA from degradation of fatty acids in the liver is used to gain energy in extrahepatic tissues

Ketone bodies as an energy source in extrahepatic tissues





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Causes and utilization of ketone bodies