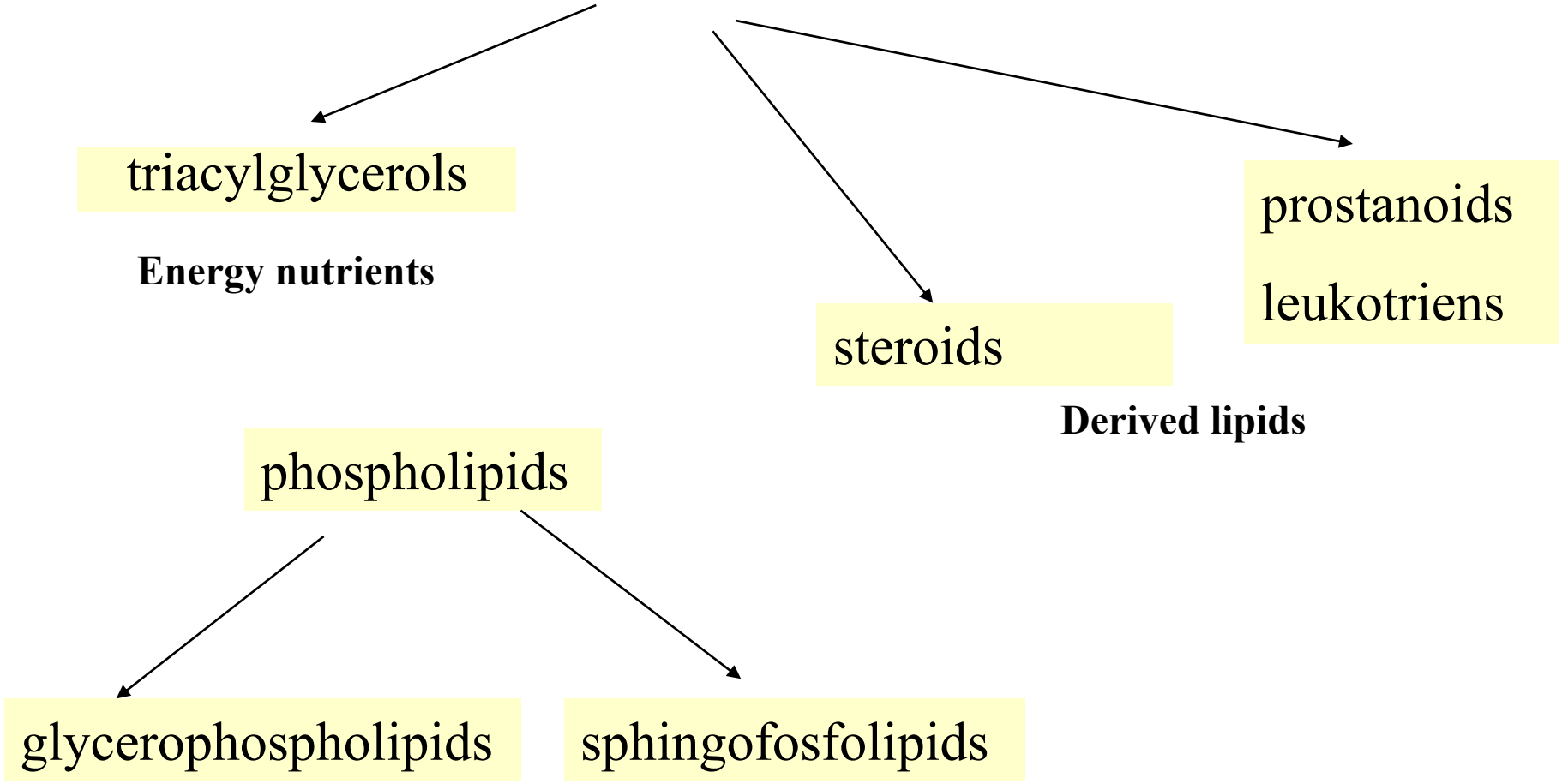
Lipid metabolism I

Biochemistry I
Lecture 8

2013 (E.T.)

Major classes of lipids



Metabolisms of lipids

metabolism of TG a FA

100 g/day

Source of energy

metabolism of structural lipids

2 g/day

Triacylaglycerols are the most effective form of energy deposition.

compound	Heat of combustion (kJ/g)
Glykogen	17
TG	38

Triacylglycerols, fatty acids and esterified cholesterol

are **very hydrophobic**

they are **not soluble in water**

unless they are emulsified or included in micelles in the presence of tensides.

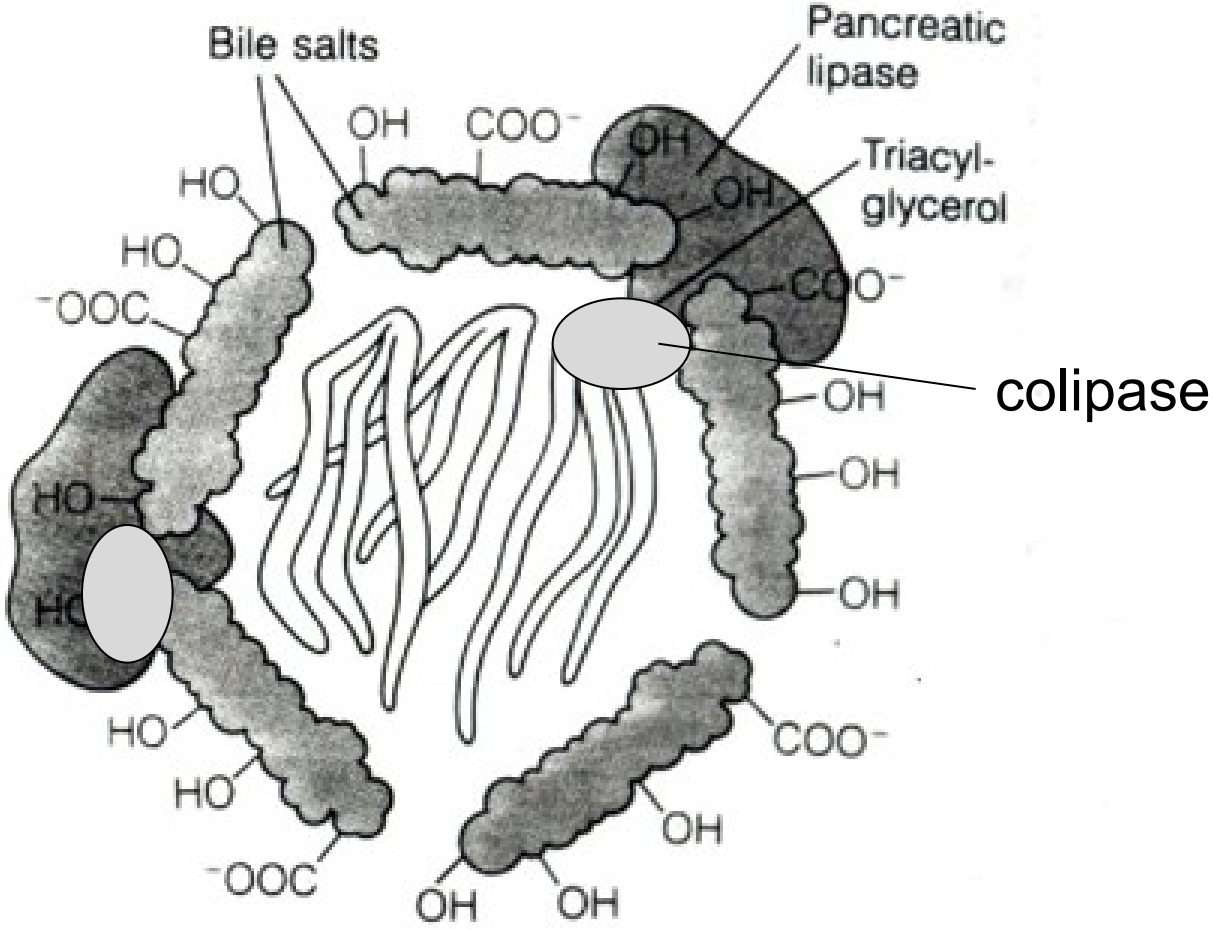
lipids make the upper phase

water

Four natural tensides work in fat digestion

Tenside	Type	Origin
Bile acids	anionic	from cholesterol in liver
2-Acylglycerol	non-ionic	TAG hydrolysis in gut
FA anions	anionic	TAG hydrolysis in gut
Phospholipids	amphoteric	food

Emulsification of lipids in the intestine – formation of micelles



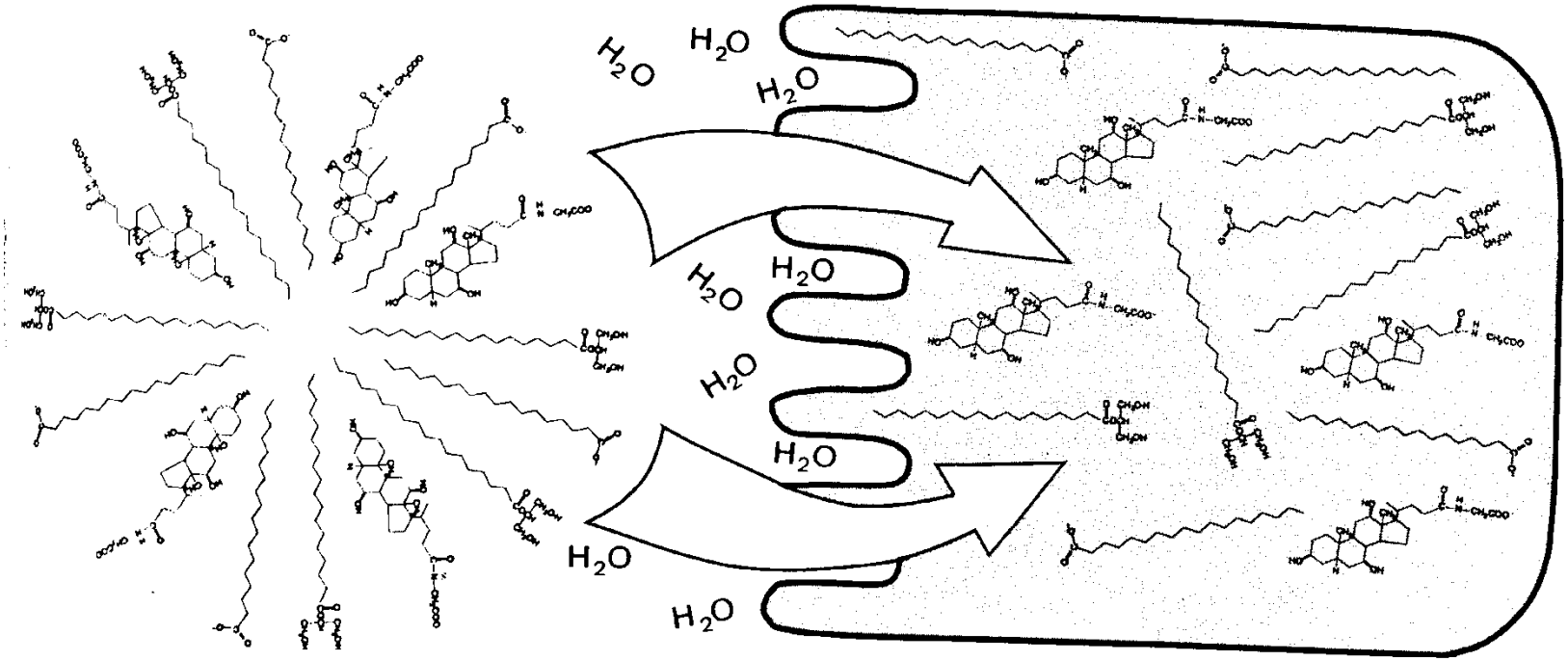
The main tensides are fatty bile acids

Lipid adsorption in the intestine

Formation of mixed micelles from products of digestion

Mixed micelles are composed of fatty acids, mono/diacylglycerols, bile acids, phospholipids and **fat-soluble vitamins**

Bile acids, phospholipids and fatty acids function as tensides



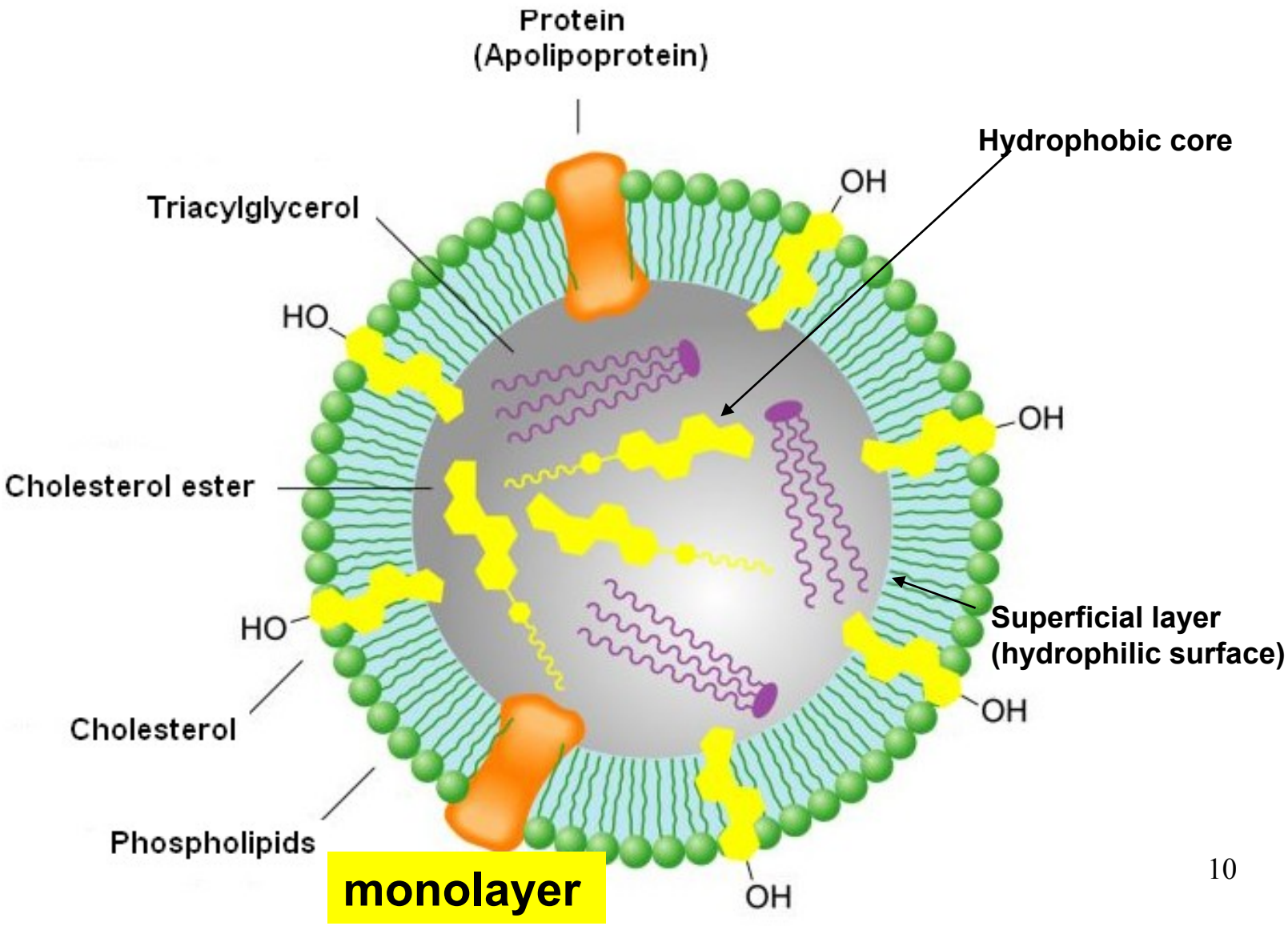
Intestinal lumen **Mucosal cell (enterocyte)**

In the extracellular fluids

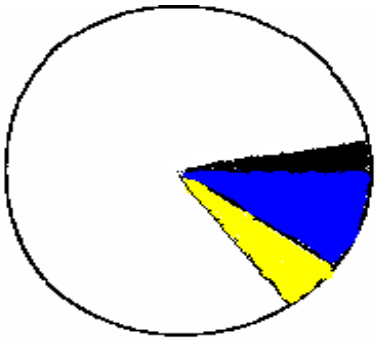
hydrophobic lipids are transported in the

form of **lipoprotein particles**

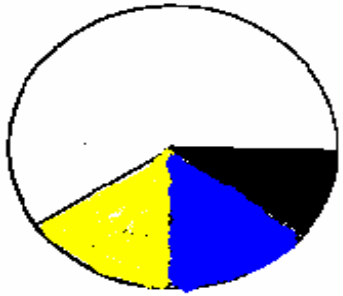
Lipoprotein particles transport triacylglycerols and cholesterol in body fluids



Types of lipoproteins



Chylomikron CM



VLDL (very low density)

LDL (low density

HDL (high density)

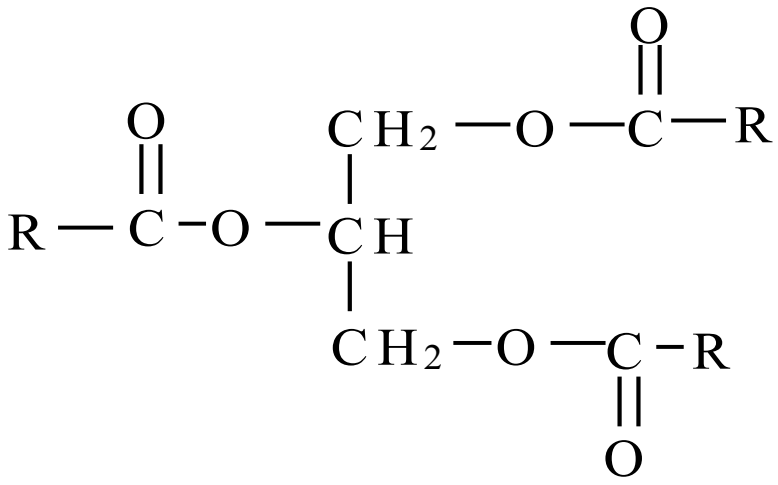
TG

PL

CH

Proteiny

Metabolism of triacylglycerols

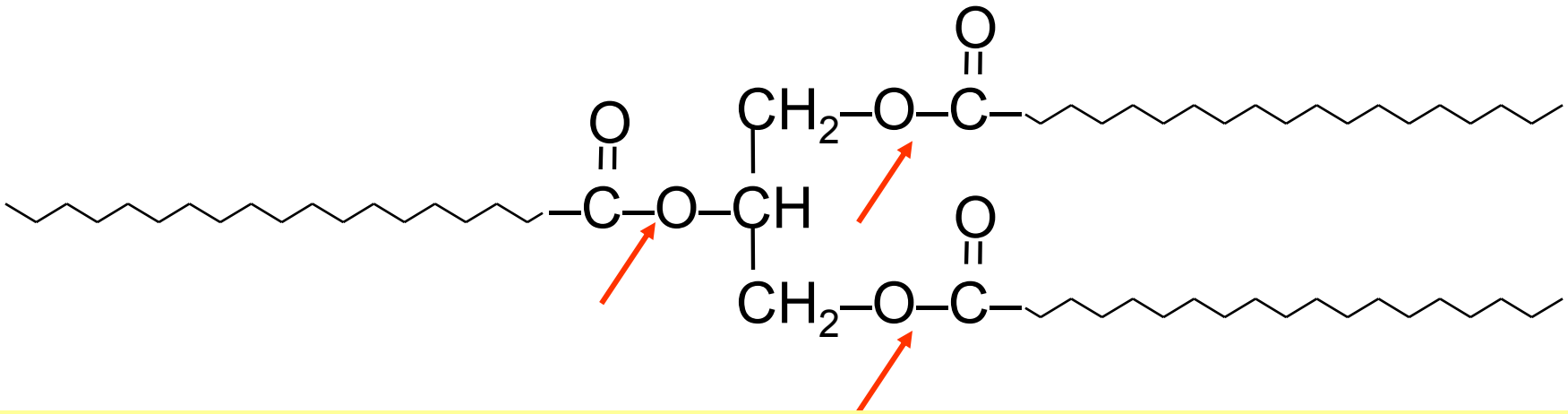


1. Hydrolytic cleavage of ester bonds

2. Metabolism of fatty acids and glycerol

Lipases

are enzymes that catalyse **hydrolysis of ester bonds of triacylglycerols** releasing free fatty acids.



Extracellular lipases

Pancreatic lipase secreted into the duodenum,
Lipoprotein lipase on the surface of the endothelium lining the capillaries

Intracellular lipases

Hormone-sensitive lipase of adipocytes mobilizing fat stores
Lysosomal lipase

Transport of fatty acids in ECT

FA are released mainly from TG in adipocytes by the action of hormon-sensitive lipase (hormonal regulation) or from lipoprotein particles

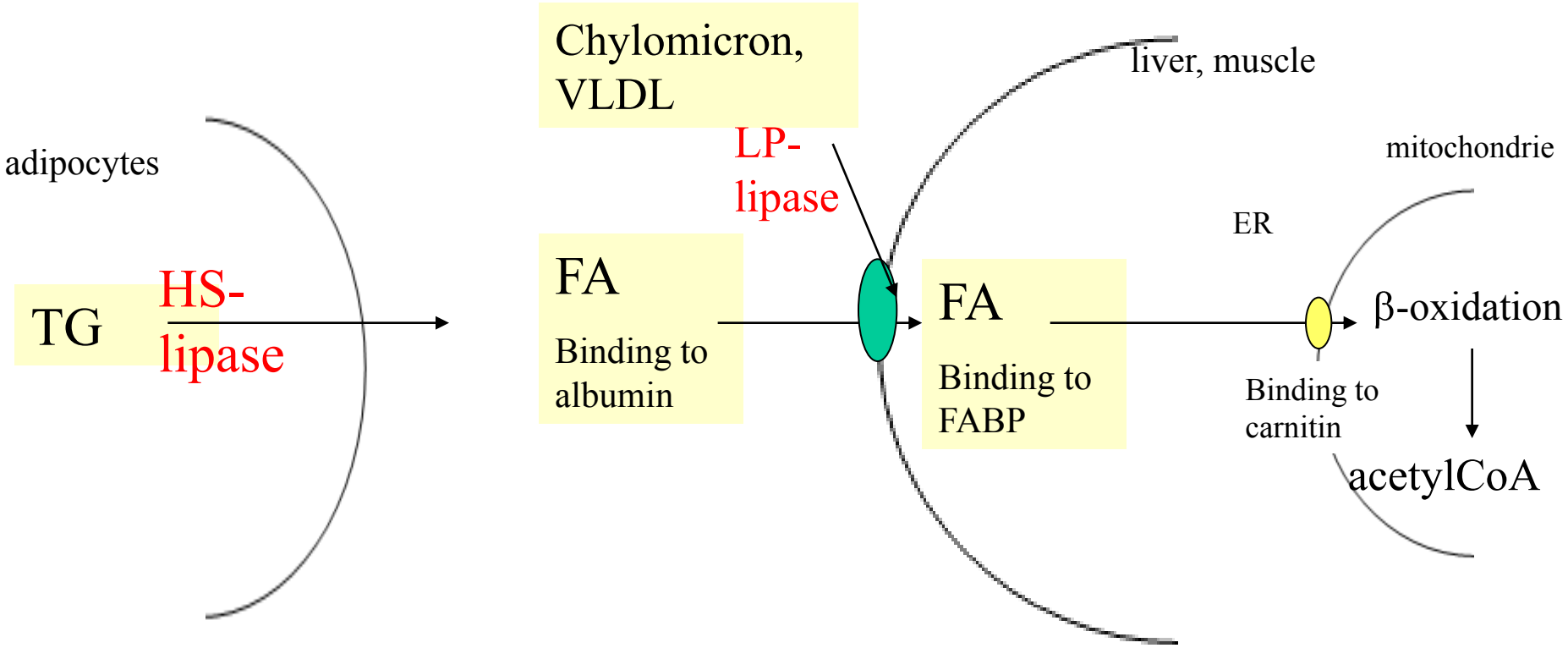
FA in blood – carried by albumin

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

Transport of FA in cells

- special membrane proteins facilitate the transport of FA across cytoplasmatic membrane
- fatty acid binding proteins facilitate the intracellular transport
- carnitine facilitates the transport across mitochondrial membrane

Degradation of lipids in the body



Hormone-sensitive lipase in adipocytes
is an intracellular lipase that through hydrolysis of triacylglycerols **mobilizes the fat energy reserves.**
The activity of this lipase is controlled by hormones:

Glucagon (at low blood glucose)
and **adrenaline/noradrenaline** (in stress)

Degradation of fatty acids: β-oxidation

Fatty acids serve as an **energy source for most of the cells** (not for the nervous system and for red blood cells).

The tissues gain fatty acids

- either from lipoprotein particles after the triacylglycerols have been hydrolysed by lipoprotein lipase,
- or as fatty acids mobilized by the action of hormones on the fat stores in adipose tissue and supplied bound onto albumin.

Location: matrix of mitochondria

The utilization of fatty acids in the cells requires three stages of processing

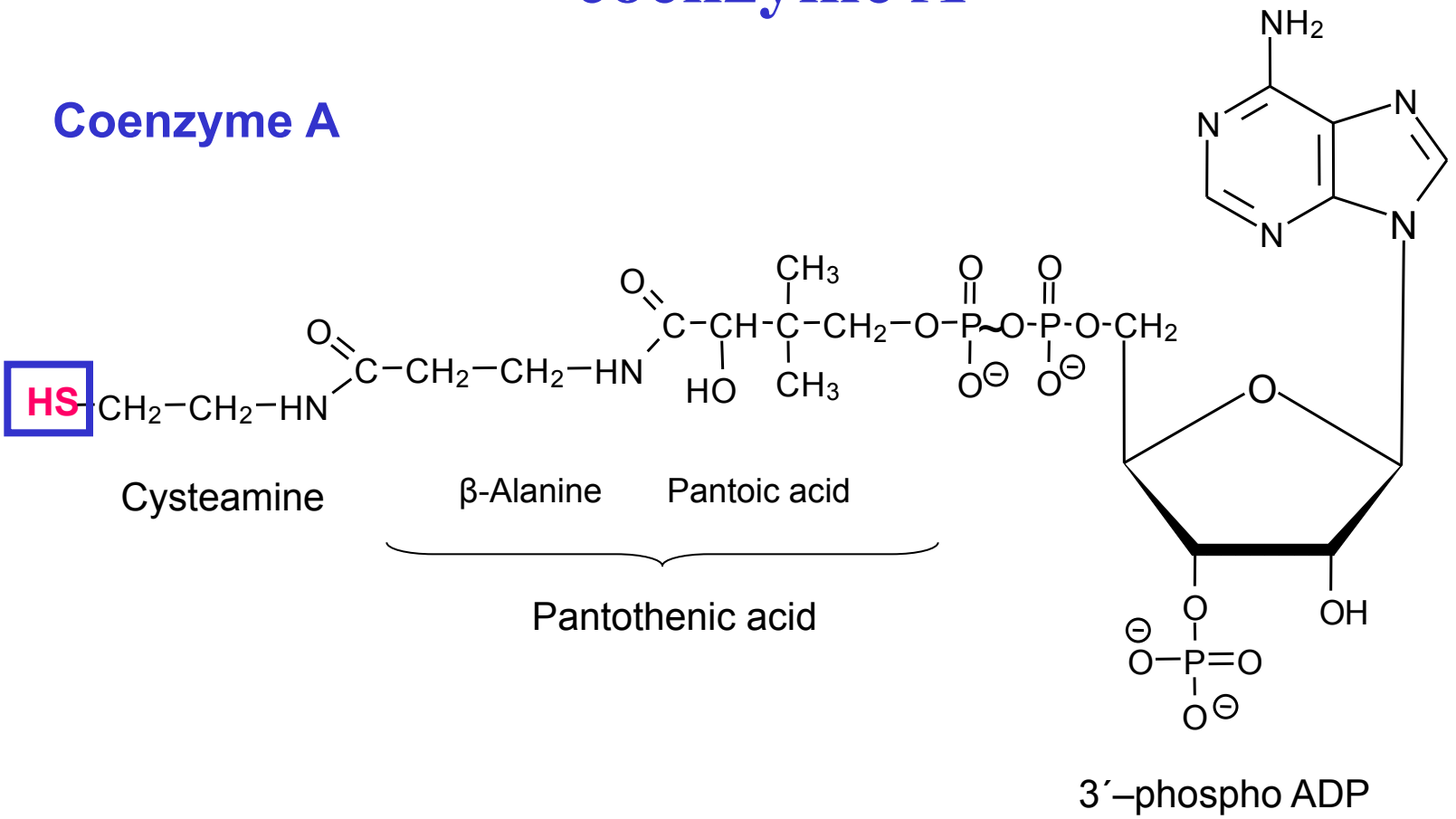
1. **Activation of FA by linking to coenzyme A**

2. **Transport of acyl CoA into the mitochondrial matrix**

3. β-**Oxidation of acyl CoA** in the mitochondrial matrix to acetyl CoA that enters the citrate cycle.

1. Activation of a fatty acid – synthesis of acyl coenzyme A

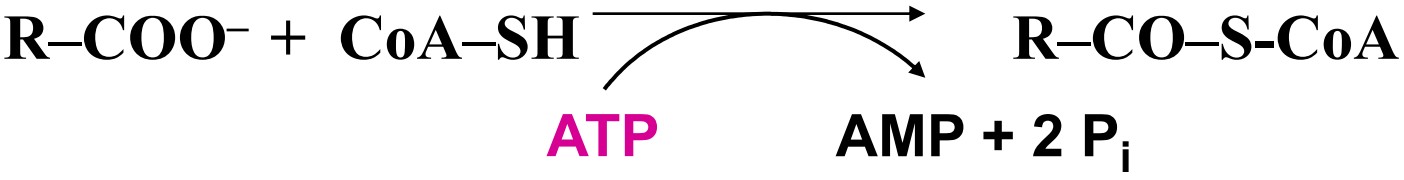
Coenzyme A



Acyls can be attached to the sulfanyl group by means of a **thioester bond**.

Synthesis of acyl-CoA

The synthesis of the high-energy acyl-CoA thioester is catalysed by ***acyl-CoA synthetases***



Acyl-CoA synthetases are located **on the outer mitochondrial membrane.**

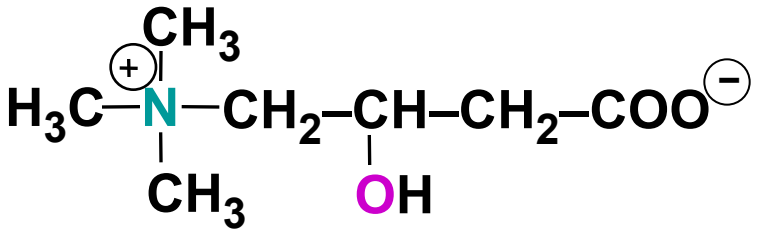
There is a **loss of energy equivalent to 2 molecules of ATP**, because the reaction is made irreversible by the hydrolysis of inorganic diphosphate (AMP + ATP ↔ 2 ADP).

2 Carnitine carries long-chain activated fatty acids into the mitochondrial matrix

Acyl-CoA itself cannot cross the inner mitochondrial membrane; instead, acyl groups are transferred to **carnitine**, transported across the membrane as **acylcarnitine**, and transferred back to CoA within the mitochondrial matrix.

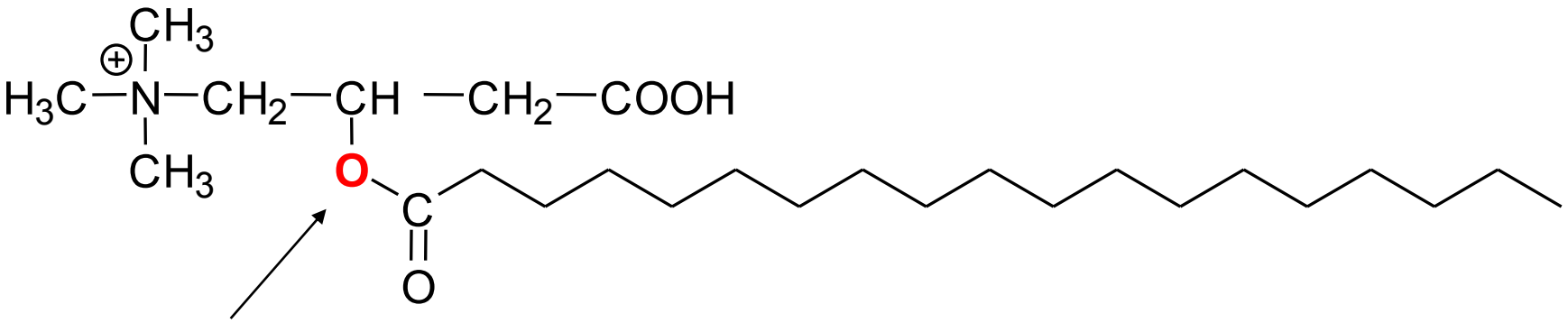
Short-chain fatty acids (4 – 10 carbon atoms) **do not** require the carnitine shuttle, they can cross the inner mitochondrial membrane.

Carnitine



Trimethyl(2-hydroxy-3-carboxypropyl)ammonium

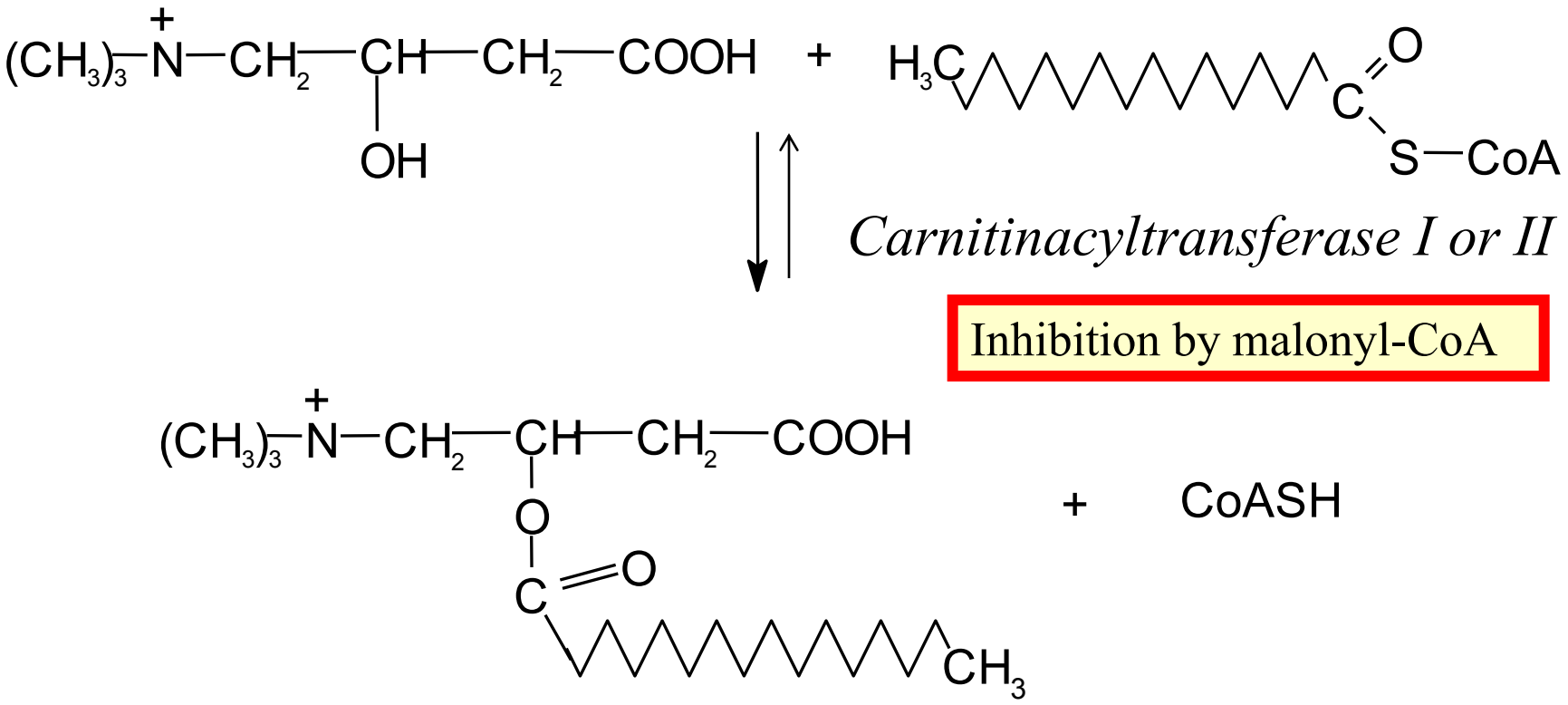
The transfers of acyls from acyl-CoA to carnitine and from acylcarnitines to CoA are catalysed by ***carnitine acyltransferases I and II***.
*(*also named carnitinpalmitoyltransferase CPT1 and 2)



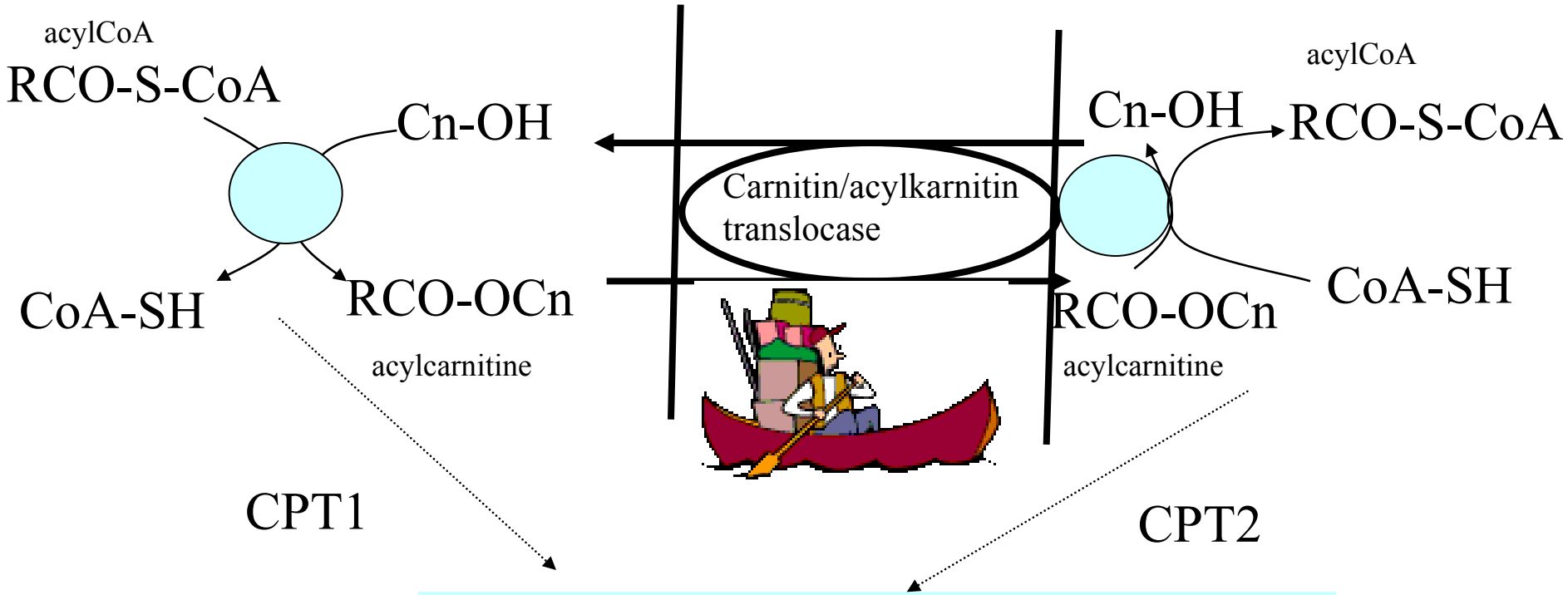
Ester bond

Formation of acylcarnitine

Intermembrane space



Transport of fatty acid into mitochondria – carnitine shuttle

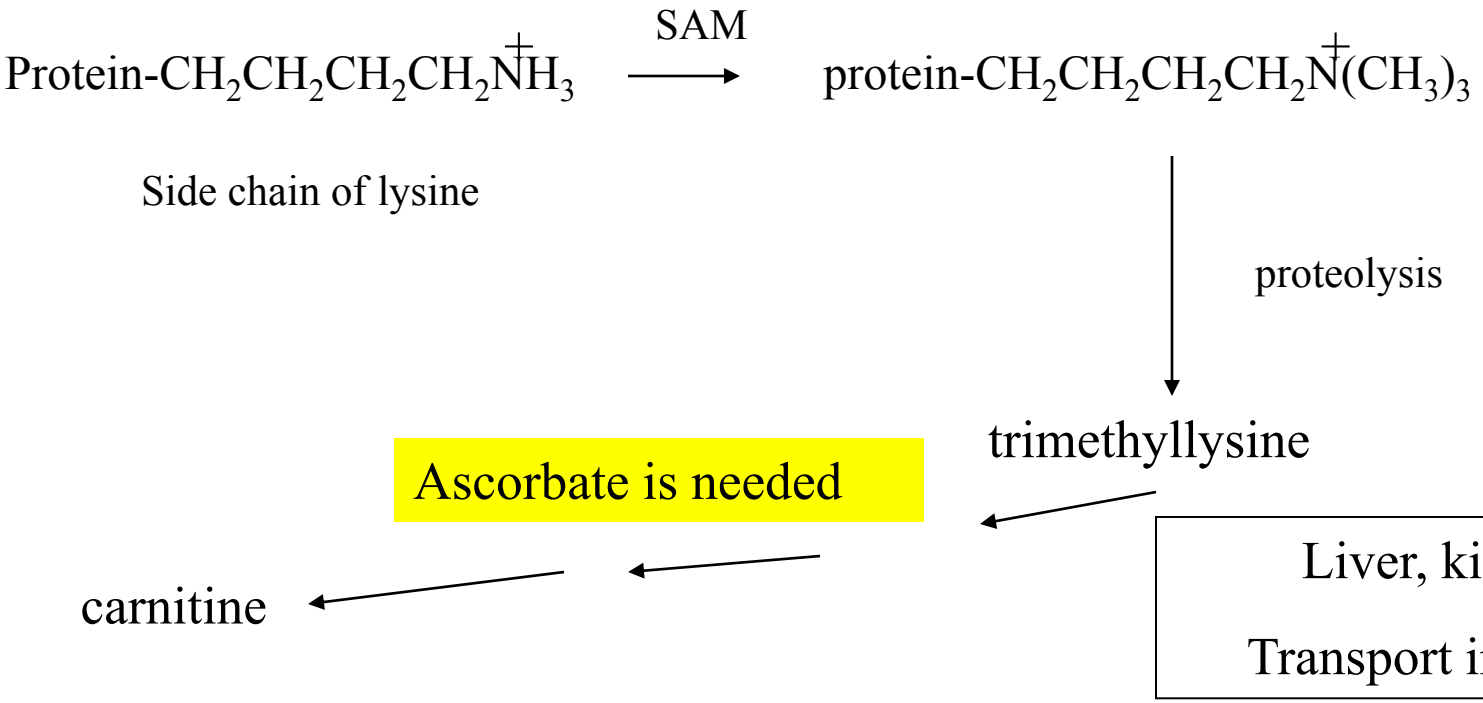


Two forms of carnitinacyltransferase

(also named carnitinpalmitoyltransferase CPT)

Sources and need of carnitine

Synthesis in organism (10-20 mg/day) **Carnitine pool** ~ 20g



Intake in food: cca 100 mg/day (meat, milk, also plant sources).
Bioavailability - ~ 75%

Resorption in kidneys – 98-99% is resorbed in tubuli

Carnitine deficiences

- Liver diseases $\rightarrow$ decreased synthesis
- Malnutrition, vegetarian diet
- Increased requirements for carnitine (pregnancy, burns, trauma)
- Enzyme deficiency (transferases, translocase)

Decreased ability of tissues to use long chain fatty acids as a metabolic fuel.

Carnitine supplementation is necessary

Consequences of carnitine deficiency

The ability to use fatty acids as a source of energy is reduced

- Deficiency in liver – nonketotic hypoykemia during fasting

  during fasting β-oxidation is necessary for provision of acetylCoA for ketogenesis and ATP production in citric acid cycle

- Deficiency in liver – muscle weakness, cramps during work

Inborn deficiency in carnitine transport

Autosomal recesive deficiency of Na^+-dependent carnitine transporter in muscle and kidney

- Carnitine deficiency in muscle and heart

- typically appear during infancy or early childhood and can include severe brain dysfunction (encephalopathy), a weakened and enlarged heart (cardiomyopathy), confusion, vomiting, muscle weakness, and low blood sugar (hypoglycemia). All individuals with this disorder are at risk for heart failure, liver problems, coma, and sudden death.

Can be detected by expanded newborn screening by tandem mass spectrometry.
Therapy: lifelong use of L-carnitine

FA-transport enzyme deficiency

Inborn errors in fatty acids metabolism are components of newborn screening

•**CPT-I deficiency** — affects the liver; severe hypoglycemia, total c**arnitine 150–200 % of** normal value.

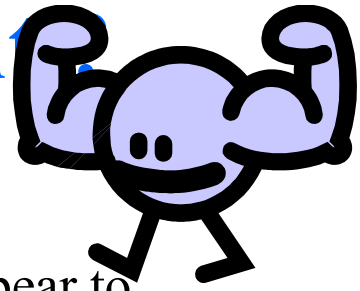
•**CPT-II deficiency**— cardiac and skeletal muscle, carnitine cca 25–50 %

mild (adult form) — rhabdomyolysis after prolonged exercise,starvation or at exposure to cold;

severe (neonatal form) — cardiomyopathy, muscle weakness, congenital malformation.

•**Carnitin acylkarnitin translocase deficiency** — hypoketotic hypoglycemia at fasting, arythmia, apnoe. Often death in infancy.

Carnitine as dietary supplement



- The available research on L-carnitine supplementation does not appear to support claims of enhanced aerobic or anaerobic exercise performance.
- Carnitine supplementation with supraphysiological doses above and beyond that which the body requires, does not result in increased fat oxidation at rest or during exercise in well-nourished individuals;
- thus, it appears that we can synthesize the necessary amounts from a diet adequate in its precursors.
- Athletes wishing to explore carnitine's purported benefits must be aware that the dietary supplement industry is not regulated and, therefore, product safety is not guaranteed. The bioavailability is 5-10%
- High doses (5 or more grams per day) may cause diarrhea. Other rare side effects include increased appetite, body odor, and rash.

Transport of fatty acids with the short chain

Fatty acids with the chains shorter than 12 carbons do not require carnitine for their transport into the mitochondria.

They freely cross the mitochondrial membrane.

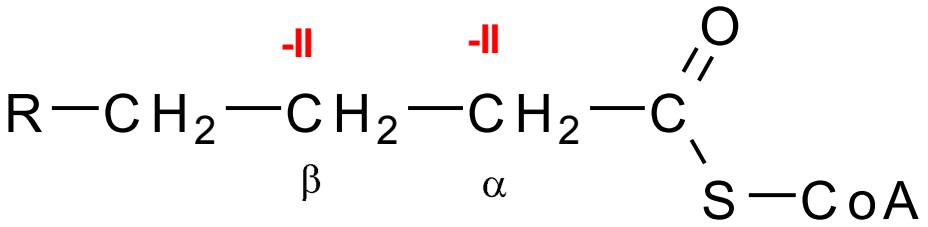
3. β-Oxidation of fatty acids

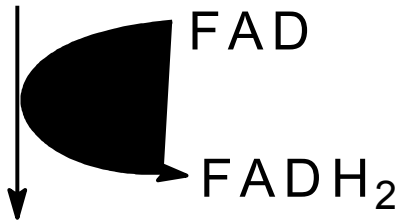
- Main way of FA degradation
- Fatty acid is enters the process in form of acyl-CoA
- β-carbon is oxidized (C-3)
- repetition of **four reactions** :

dehydrogenation → hydration → dehydrogenation → thiolysis by CoA (fatty acid is shortened by two carbons and acetyl-CoA is released)

(1) First dehydrogenation

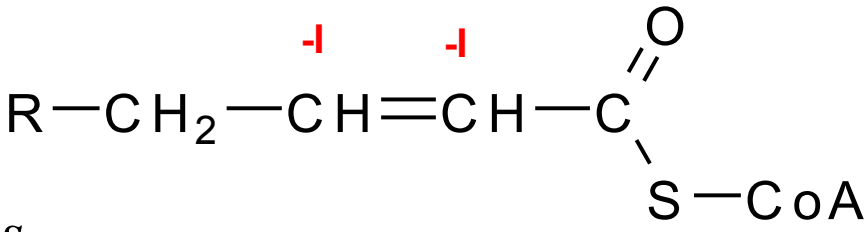
Saturated acyl CoA





α,β-Unsaturated acyl CoA

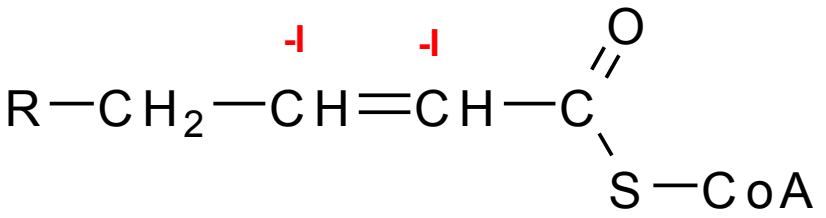
(2,3-unsaturated)



configuration trans

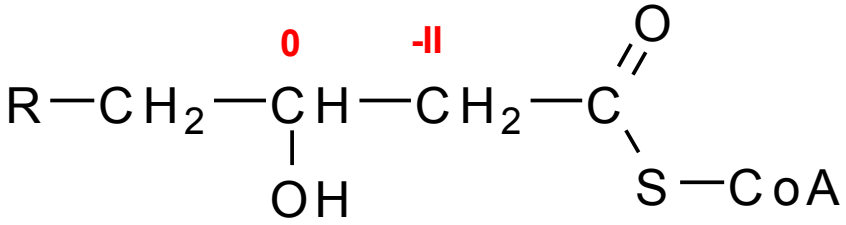
(2) Hydration of double bond

α,β-Unsaturated acyl CoA



H_2O

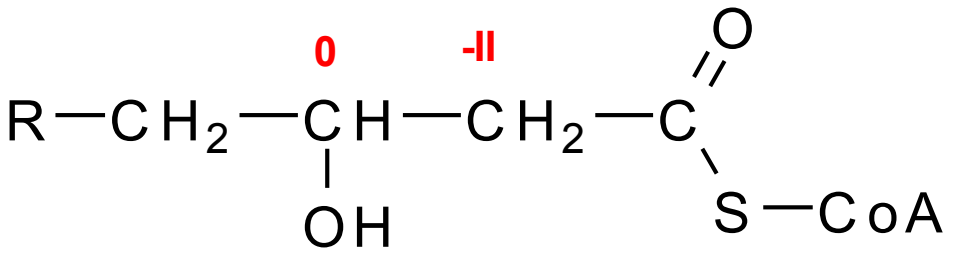
β-Hydroxyacyl CoA
(L-3-Hydroxy)



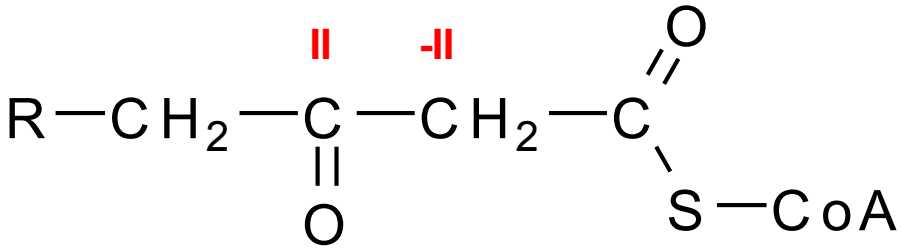
Hydration is **not a redox reaction**, by addition of water to a double bond the sum of the oxidation numbers of both carbon atoms remain the same.

(3) Dehydrogenation of hydroxyacyl

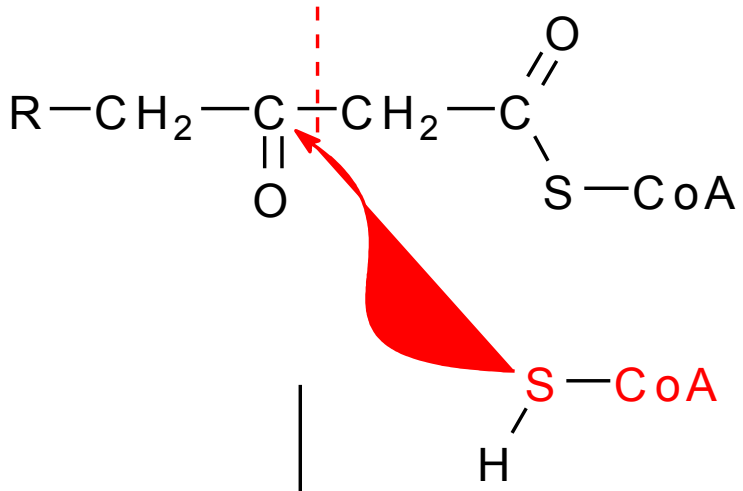
β-hydroxyacyl-CoA



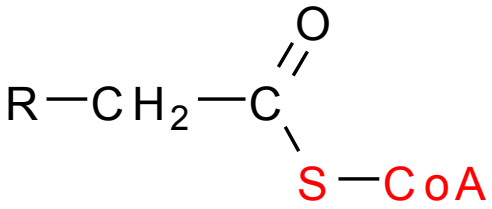
β-oxoacyl-CoA



(4) The final step:
the thiolysis of 3-oxoacyl-CoA by CoA-SH

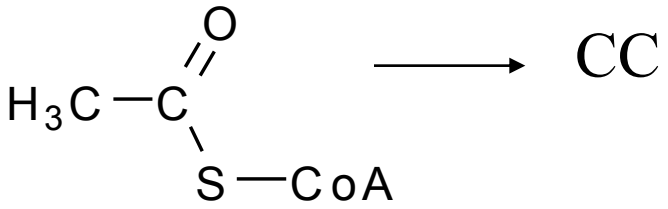


thiolase



ACYL CoA

Shortened by two carbons



Acetyl CoA

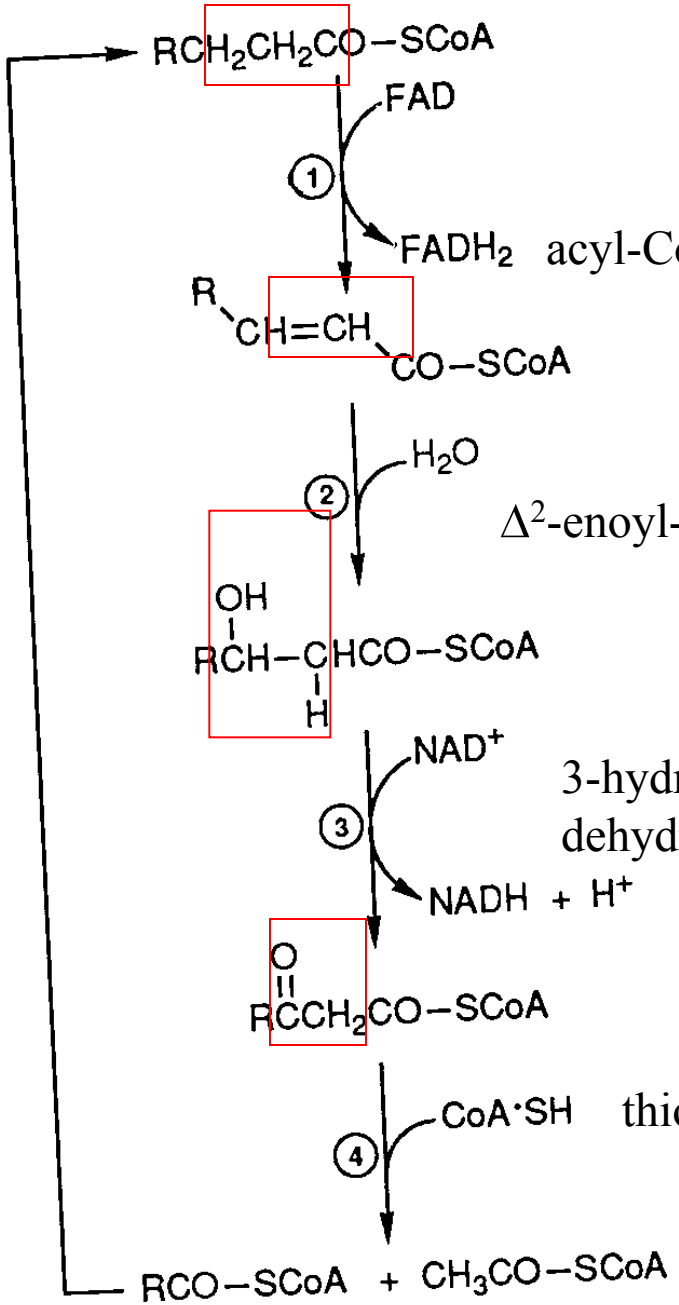
Substrate for the citrate cycle

Distinguish: three types of lysis !

Hydrolysis	cleavage of substrate with **water**: sucrose + H_2O → glucose + fructose $(starch)_n + H_2O \rightarrow$ maltose + $(starch)_{n-2}$
Phosphorolysis	cleavage of *O*-glycosidic bond by **phosphate**: $(glycogen)_n + P_i \rightarrow (glycogen)_{n-1}$ + glucose-1-P
Thiolysis	cleavage of C-C bond by **sulfur** of CoA–SH β-oxidation of FA or utilization of KB, $RCH_2COCH_2CO\text{-}SCoA + CoA\text{-}SH \rightarrow RCH_2CO\text{-}SCoA + CH_3CO\text{-}SCoA$

β-oxidation

- 1.dehydrogenation (FAD)
- 2.hydration
- 3 dehydrogenation (NAD^+)
- 4 thiolytic cleavage and transfer of acyl to CoASH



FA oxidase

Acyl-CoA dehydrogenases (first reaction in β-o.)

4 main types

for FA with short chain (SCAD)

mediate chain (MCAD)

long chain (LCAD)

very long chain (VLCAD)

Examination of MCAD, LCAD and VLCAD deficiency is a component of newborn screening.

MCAD deficiency

One of the most common inborn errors of fatty acid metabolism. Under conditions of health this may not cause significant problems. However, when such individuals do not eat for prolonged periods or have increased energy requirements, the impairment of fatty acid oxidation may lead to fatty acid buildup, hypoglycemia, hyperammonemia and, possibly, sudden death.

The energetic yield of β-oxidation of palmitate

– to 8 acetyl coenzymes A

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

⟶ **8 acetyl CoA** + **7 $FADH_2$** + **7 NADH + 7 H^+**

14 ATP + 21 ATP – 2 ATP (activation of palmitate)

– and 8 acetyl CoA in the citrate cycle

8 × 12 ATP = 96 ATP

Net yield of complete palmitate oxidation to CO_2

14 ATP + 21 ATP – 2 ATP + 96 ATP = **129 ATP/palmitate**

Net yield of the aerobic breakdown of glucose is

38 mol ATP / mol glucose (M = 180 g / mol; 6 mol C),

i.e. 0.21 mol ATP / g glucose, or

6.3 mol ATP / mol C.

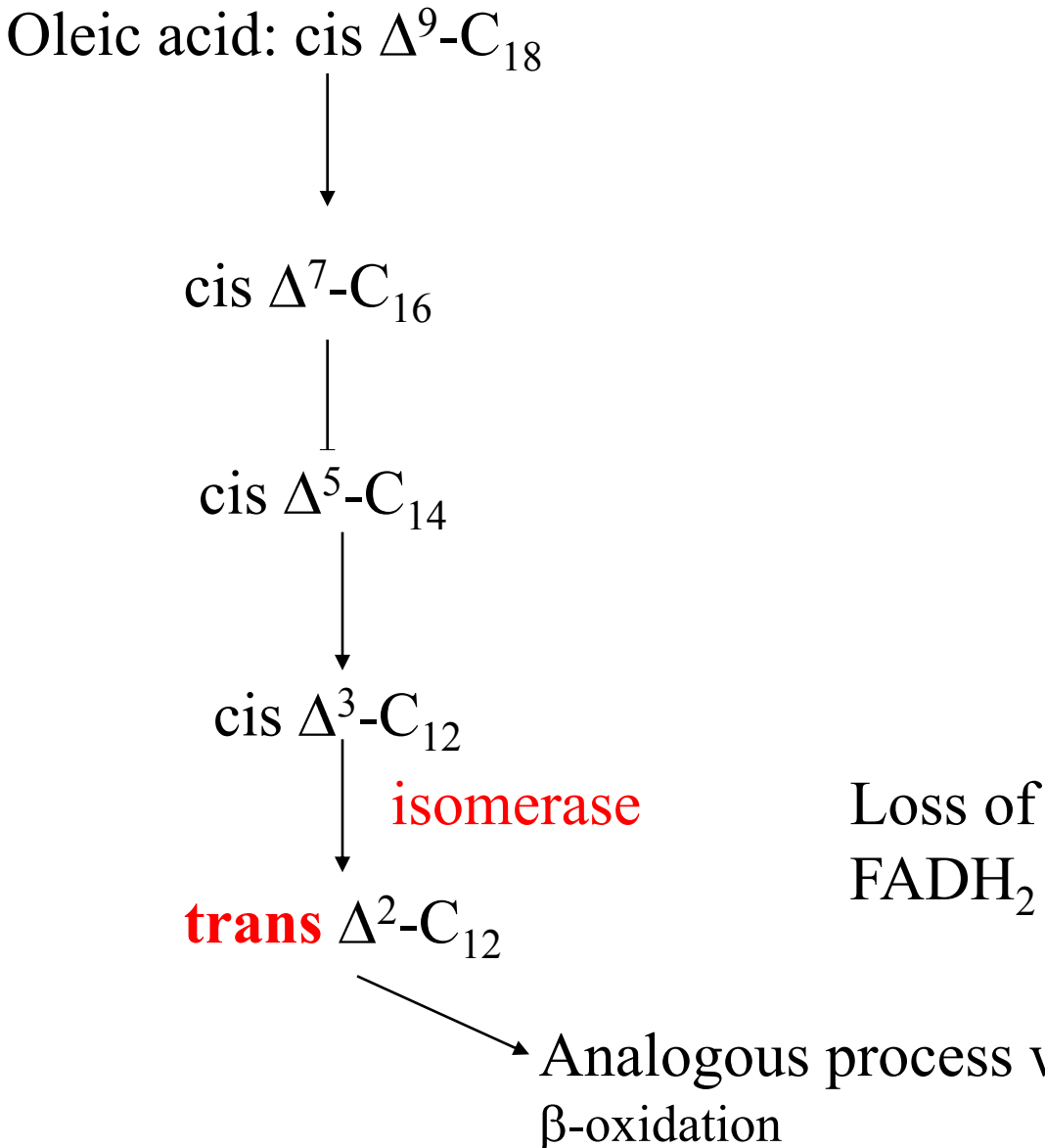
Net yield of complete oxidation of palmitate is

129 mol ATP / mol palmitate (M = 256 g / mol; 16 mol C),

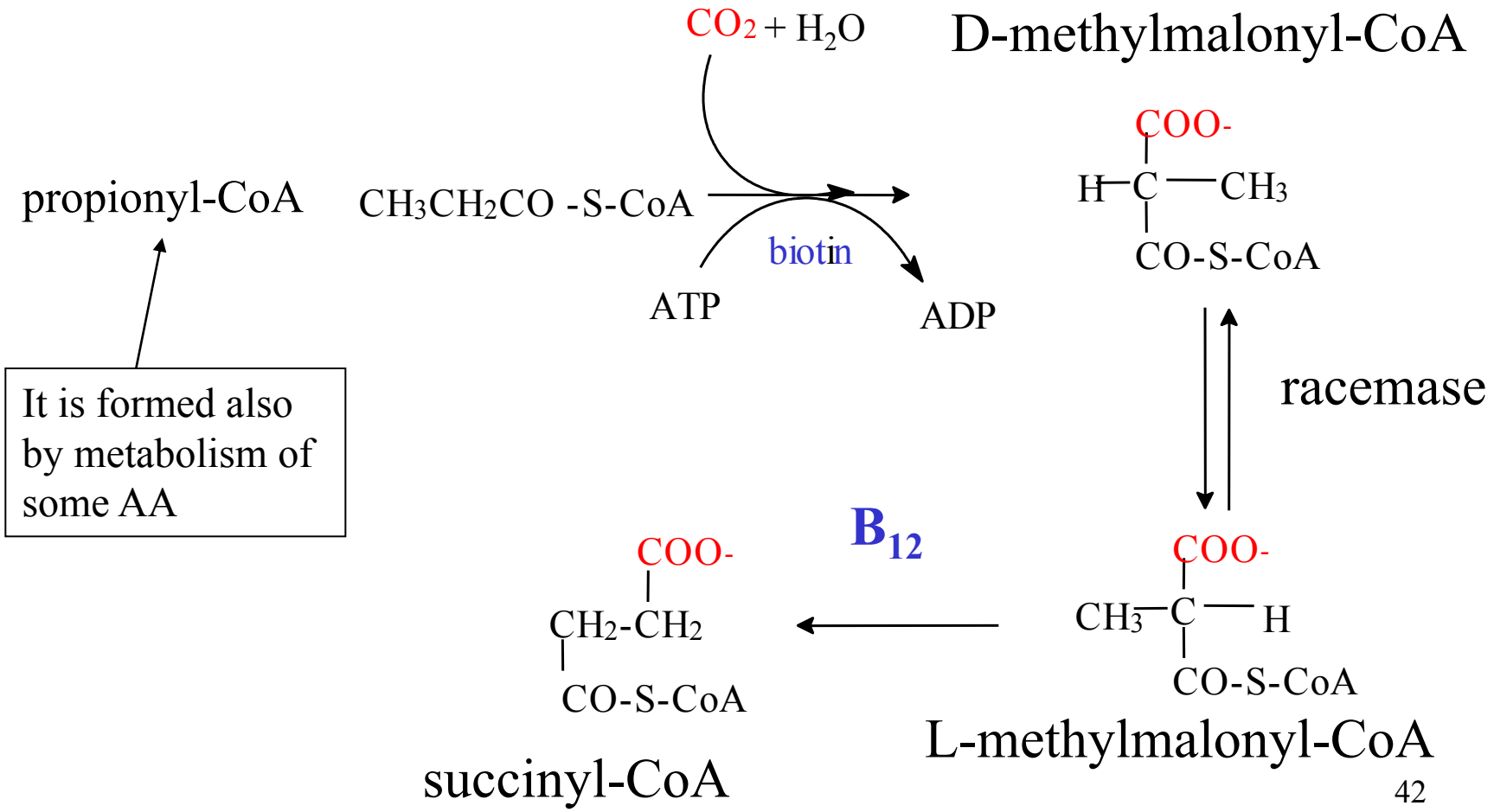
i.e. 0.50 mol ATP / g palmitate, or

8.1 mol ATP / mol C.

Oxidation of unsaturated FA



FA with odd number of C provide propionyl-CoA



β-oxidation in the peroxisome

Very-long-chain fatty acids (20 C or longer)

- preliminary β-oxidation in peroxisomes
- shortening of the chain
- shortened FA is transferred to a mitochondrion

FAD is the cofactor of β-oxidation in peroxisome

It is oxidized by molecular oxygen

$$FADH_2 + O_2 \rightarrow FAD + H_2O_2$$

Energy is not obtained

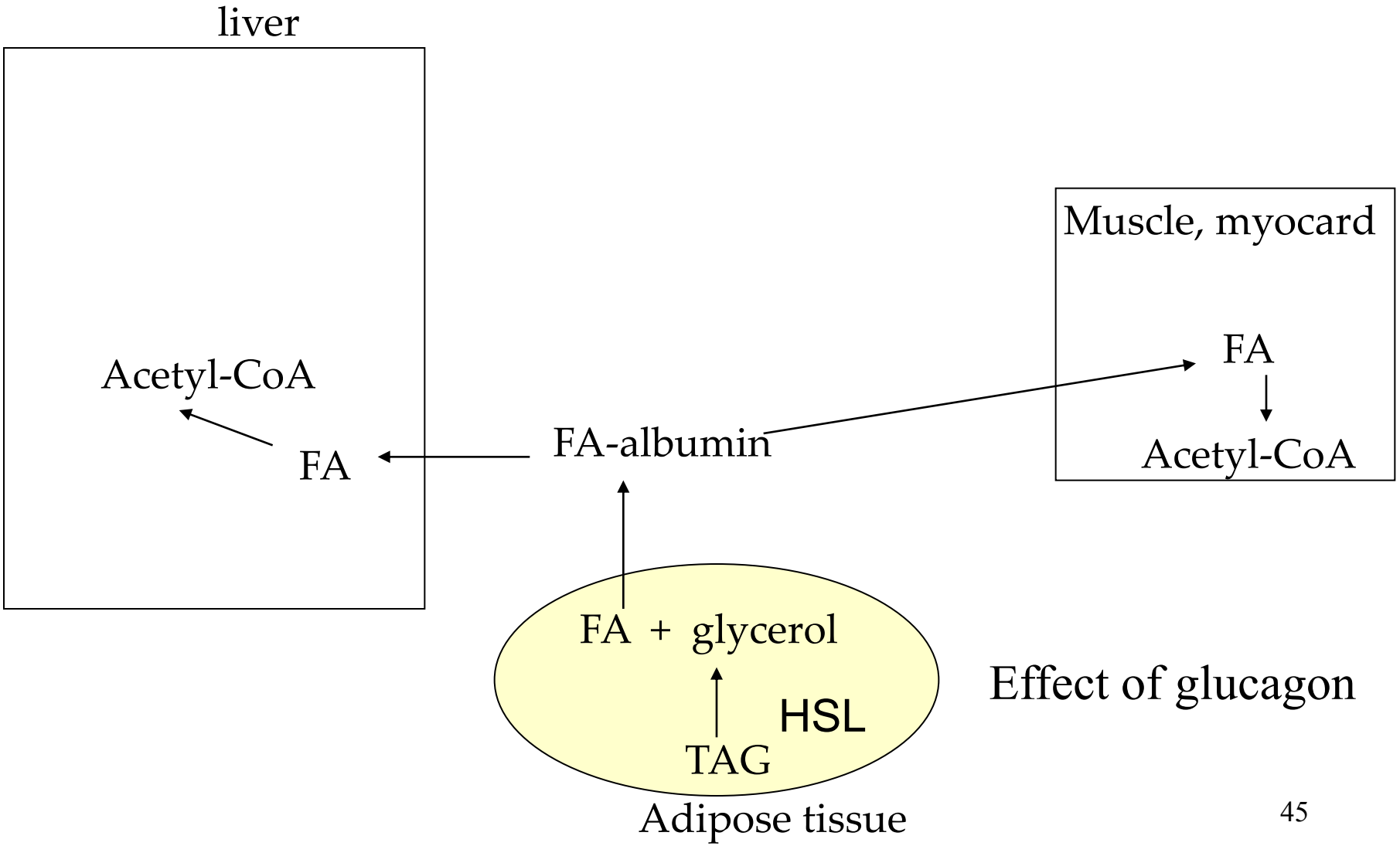
β-oxidation of FA is powerfull source of energy

When does it take place?

When the cells requires energy and availability of glucose is limited

β-oxidation is initiated by hormones in post-absorptive state or starvation, particularly in liver, muscle and myocardium

Lipids in postresorption phase (glucagon)



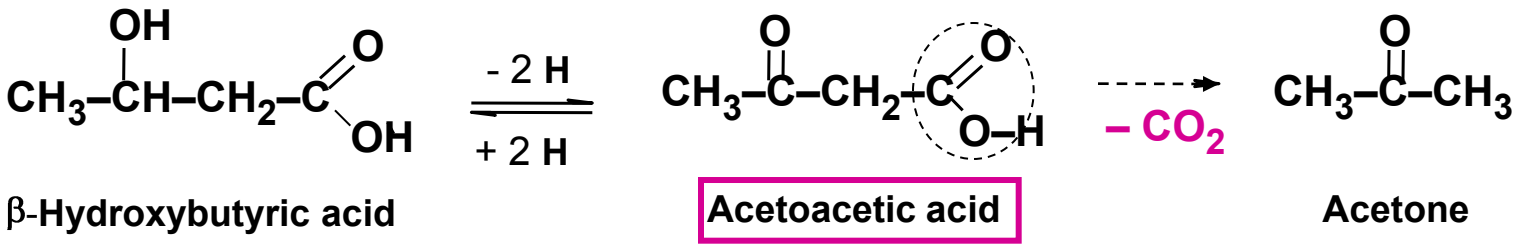
Effect of glucagon

Mobilization of fat stores in post-absorptive phase (glucagon)

Glucagon (or **adrenaline)** activate hormone sensitive lipase in adipose tissue

- HSL cleaves triacylglycerols to fatty acids and glycerol
- Fatty acids are released into the blood
- the plasma level of free fatty acids increases
- FA are taken up by the liver and other peripheral tissues (esp. muscle, myocard and kidney) at the rates proportional to the plasma concentration.

Formation of ketone bodies - ketogenesis



β-Hydroxybutyric acid

Acetoacetic acid

Acetone

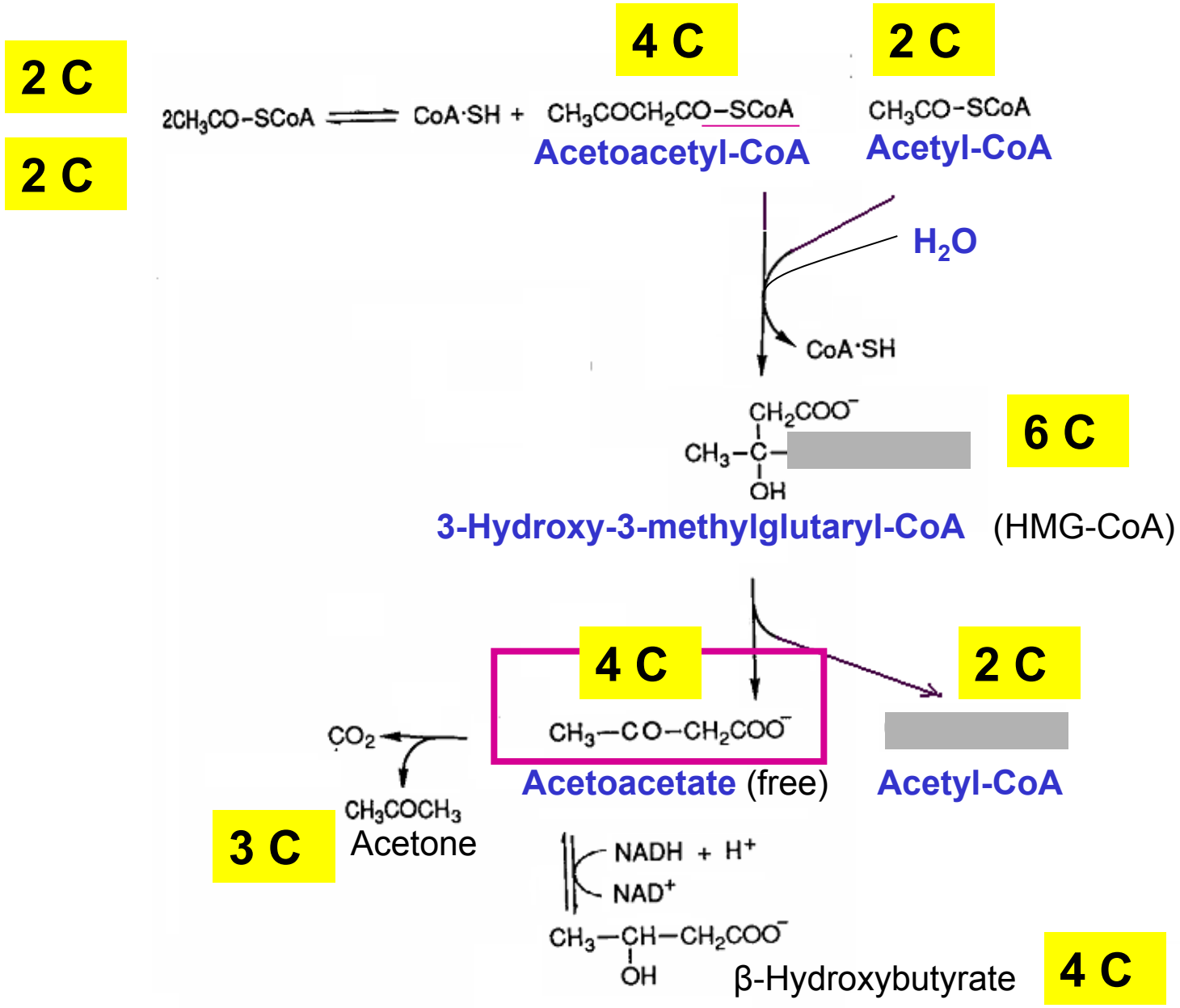
Ketone bodies are formed in the **liver mitochondria** and released into blood plasma.

The two acids are detectable in plasma at any time, the usual ratio β-hydroxybutyrate to acetoacetate is 3 – 6 (it reflects the intramitochondrial $NADH/NAD^+$ ratio).

There are always traces of ketone bodies in urine, since there is no renal threshold for the two acids.

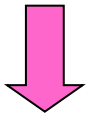
Ketone bodies are readily metabolised in **non-hepatic tissues.**

Ketogenesis in liver mitochondria



The causes of increased keton bodies formation

During fasting fatty acids are mobilized from adipose tissue and part of them is transported into the liver



→increased production of acetyl-CoA by β-oxidation

→ capacity of citric cycle is overloaded (lack of oxalacetate)

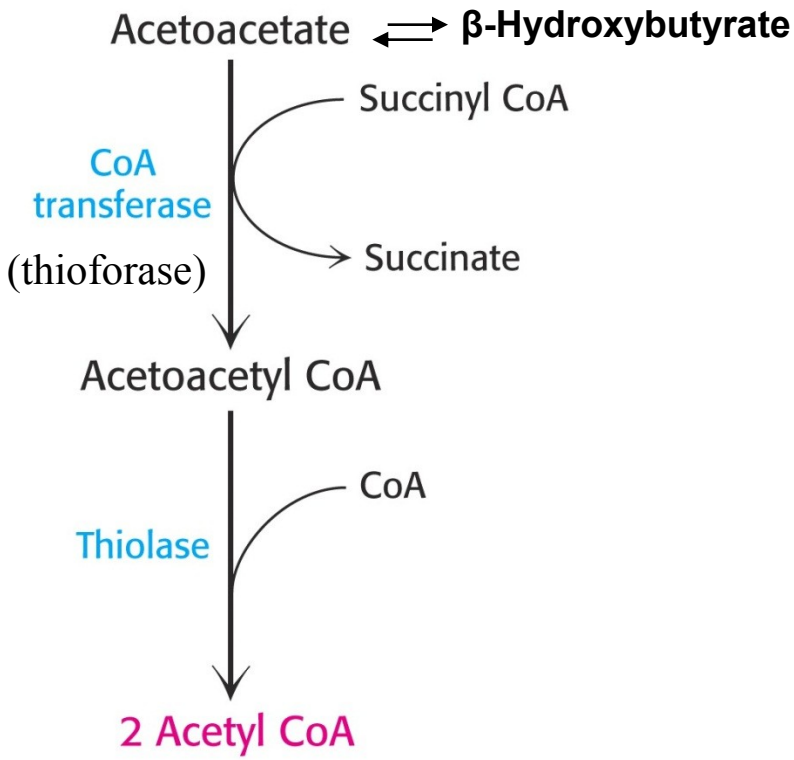
→ synthesis of keton bodies

Utilization of ketone bodies in non-hepatic tissues

β-Hydroxybutyrate and **acetoacetate** are important in providing energy for peripheral tissues.

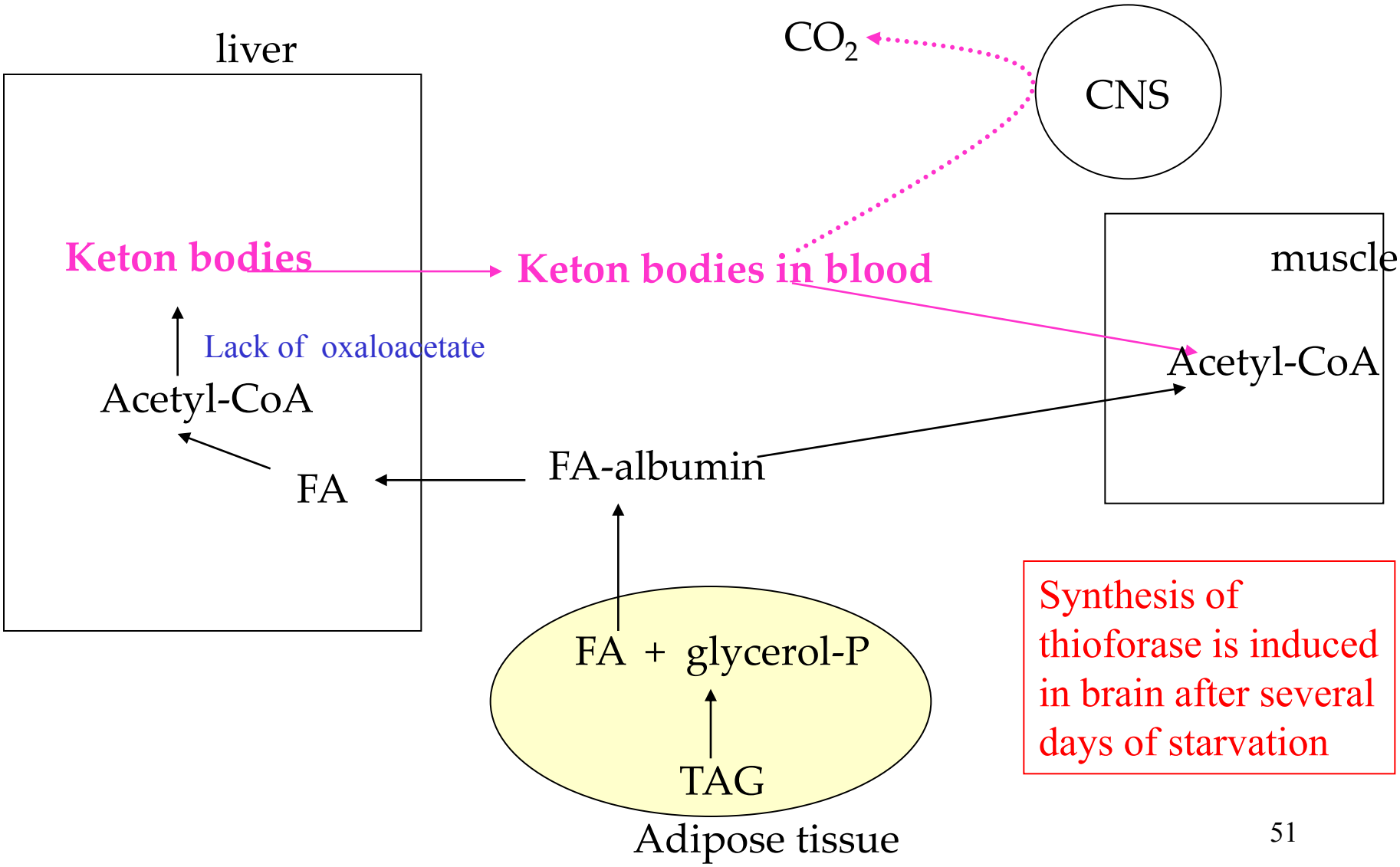
Acetone is a waste product, eliminated by the kidney or expired, it can be smelt on the breath.

Acetoacetate is reactivated to acetoacetyl-CoA through the transfer of CoA from succinyl-CoA.



are broken down in the **citrate cycle**

Formation and utilization of keton bodies



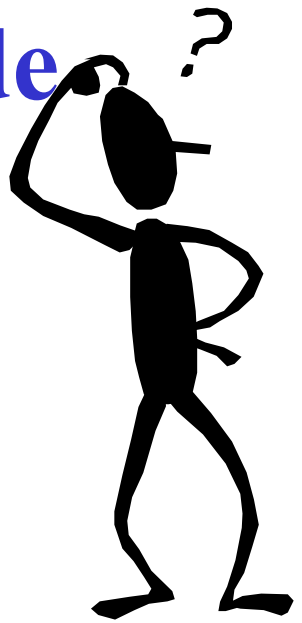
Synthesis of thioforase is induced in brain after several days of starvation

The production of ketone bodies increases at high ratio glucagon/insulin, when fat stores are mobilized (prolonged fasting, starvation, uncontrolled diabetes mellitus type I).

An extreme production of ketone bodies (**ketosis**) is very dangerous, because ketogenesis is a proton-producing process that disturbs acid-base balance (evoking **ketoacidosis**) and, through excretion of the two acids into urine, is a cause of serious loss of cations.

Acetoacetic acid	$pK_a = 3.52$
β-Hydroxybutyric acid	$pK_a = 4.70$

Can be triacylglycerols formed de novo in the body?



In human:

fatty acids (except the essential)

triacylglycerols

can be synthesized

Fatty acids synthesis

Location:

Mainly liver, lactating mammary gland, in lesser extent adipocytes,brain

When?

sufficient amounts of acetylCoA, that need not be utilized for production of energy

?

After the meal, when sufficient amounts of glucose are available for production of **acetyl CoA**,

Steps in fatty acid synthesis

(cytoplasma)

1. Transport of acetyl-CoA from matrix to cytoplasma

2. Malonyl-CoA formation

3. Serie of reactions on fatty acid synthase enzyme complex

Transfer of acetyl CoA to the cytosol

acetyl-CoA is formed in matrix of mitochondria mainly by oxidative decarboxylation of pyruvate (from glucose, amino acids)

- acetyl-CoA cannot freely penetrate the mitochondrial membrane
- it is transported in form of citrate

When it does occur?

In case that citrate is not necessary for citric acid cycle

When the citrate is not necessary for citric acid cycle?

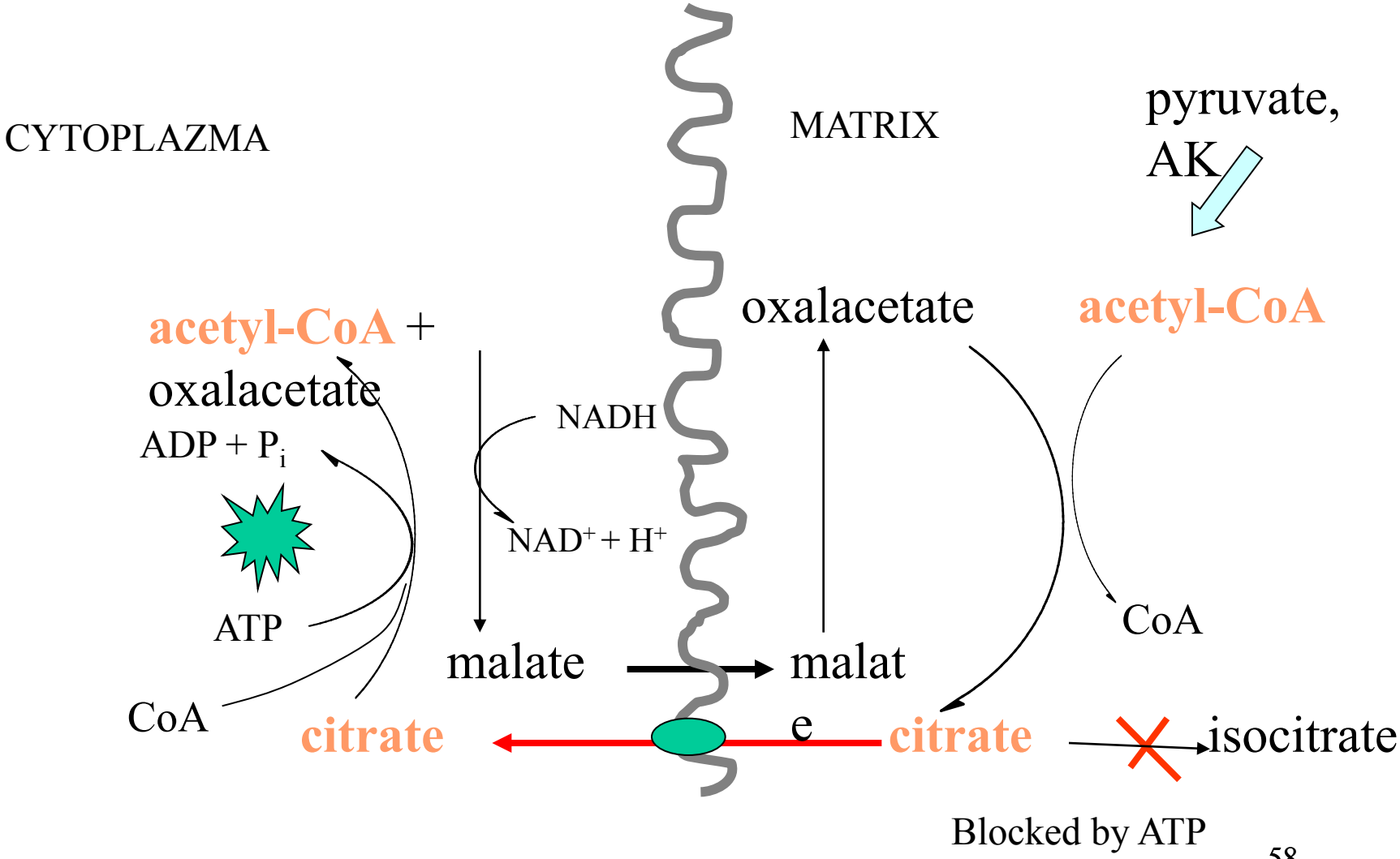
-the well fed state

– sufficient amounts of glucose are available producing **acetyl CoA**,

– **low energy expenditure** – high **ATP** concentrations within the cells inhibit degradation of acetyl CoA in the citrate cycle,

– absence of stress that activates mobilization of fat stores, free fatty acids released through the action of catecholamines inhibit fatty acid synthesis.

Transfer of acetyl CoA to the cytosol



2. Synthesis of malonyl CoA

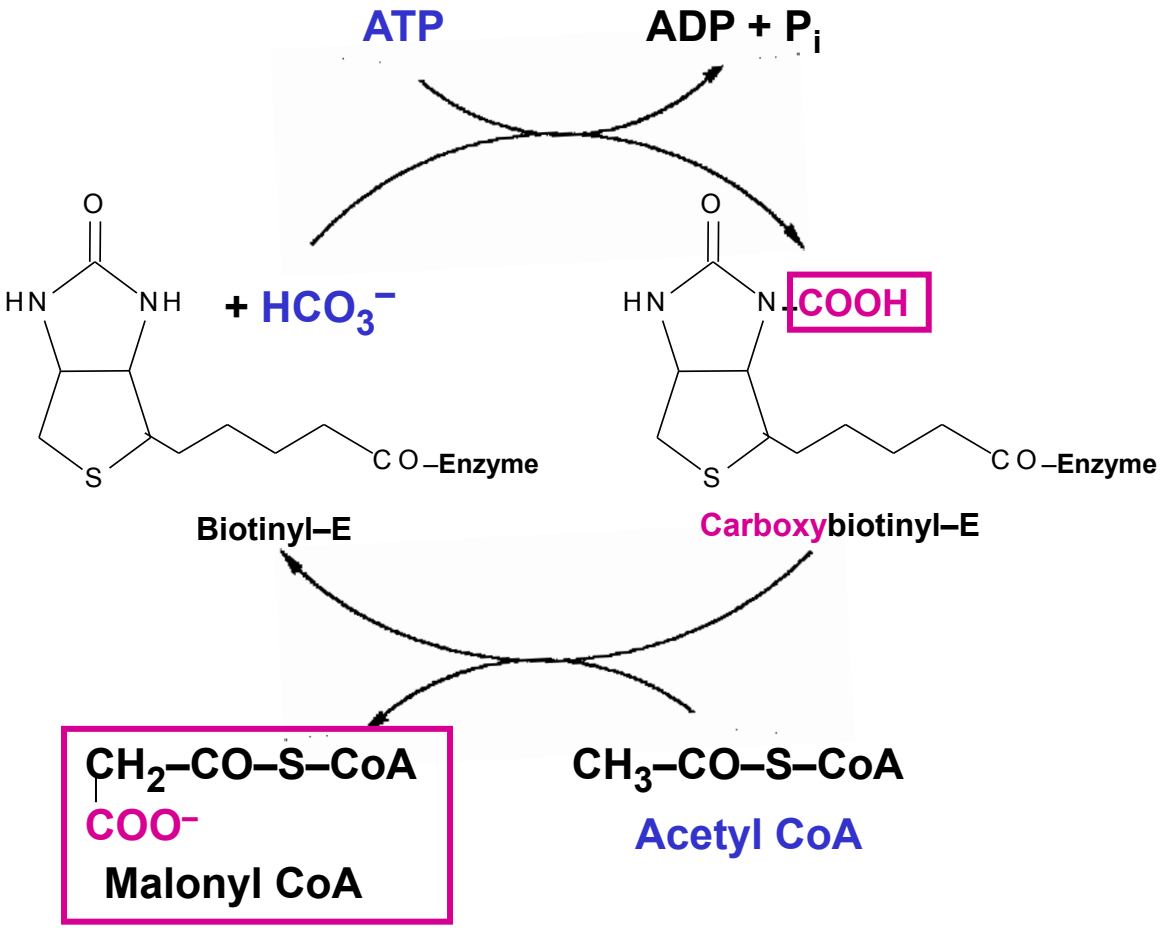
AcetylCoA does not have energy enough to enter the synthesis of fatty acids

Principle of carboxylation and decarboxylation

Formation of malonylCoA by carboxylation and its decarboxylation in the next step

Synthesis of malonyl CoA

is the rate-limiting step in fatty acid synthesis, catalysed by ***acetyl-CoA carboxylase***:



Regulation of acetyl-CoA carboxylase

Activation by citrate

Inhibition by acyl-CoA with long chains (palmitate)

Hormonal regulation:

insulin ↑

glucagon, adrenalin ↓

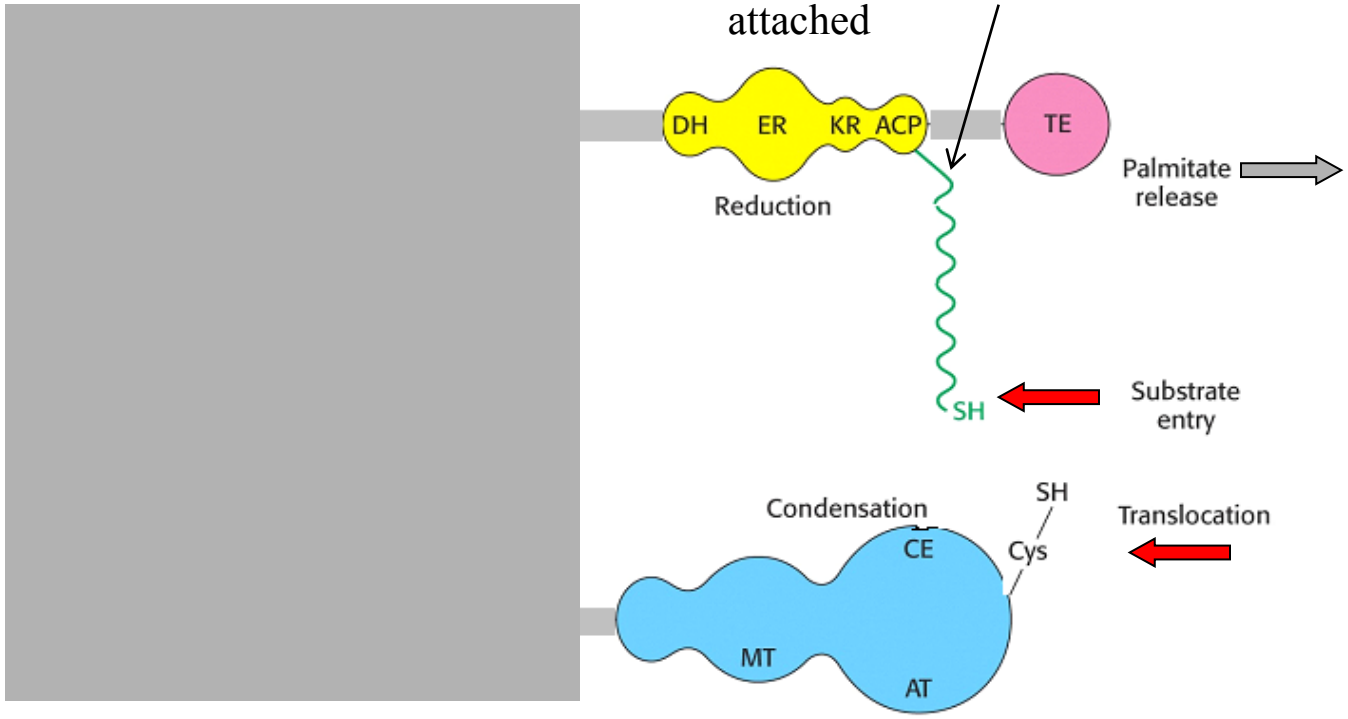
The fatty acyl synthase complex

In mammals, the complex is a **homodimer**

One domain in both monomers includes the **acyl carrier protein (ACP)** area to which the **phosphopantethein** "arm" is attached

Each monomer is arranged in three domains carrying the seven catalytic activities.

One of the two functional units



Two proteins with –SH group bind intermediates of the synthesis

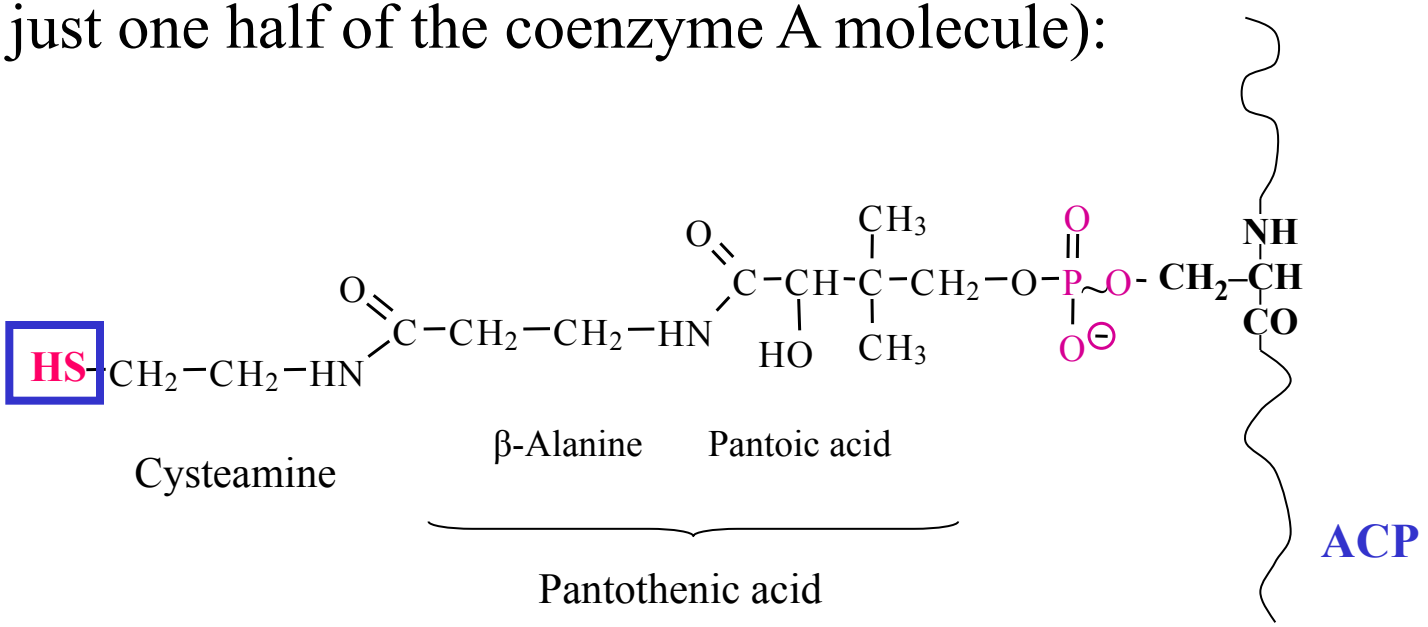
Seven enzyme activities:

AT
Acetyl/acyl-CoA transacylase
MT
Malonyl transacylase
CE
Condensing enzyme (Oxoacyl-PPt synthase)
KR
Oxoacyl reductase
DH
Hydroxyacyl dehydratase
ER
Enoyl reductase
TE
Palmitoyl thioesterase

Both monomers cooperate so that each of them takes part on the synthesis of <u>two</u> fatty acids processed simultaneously,

The flexible phosphopantethein "arm" of the synthase

linked to a serine residue of acyl carrier protein ACP
is found also in coenzyme A
(as just one half of the coenzyme A molecule):

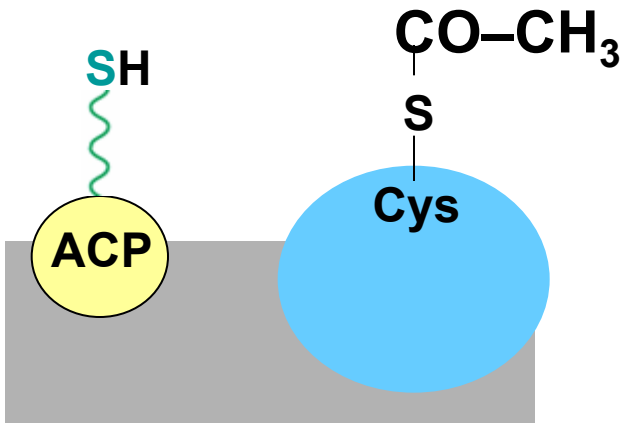


The processed acyls attached to the sulfanyl group are carried from one active site of the synthase complex to another.

Reactions of fatty acid synthesis

1

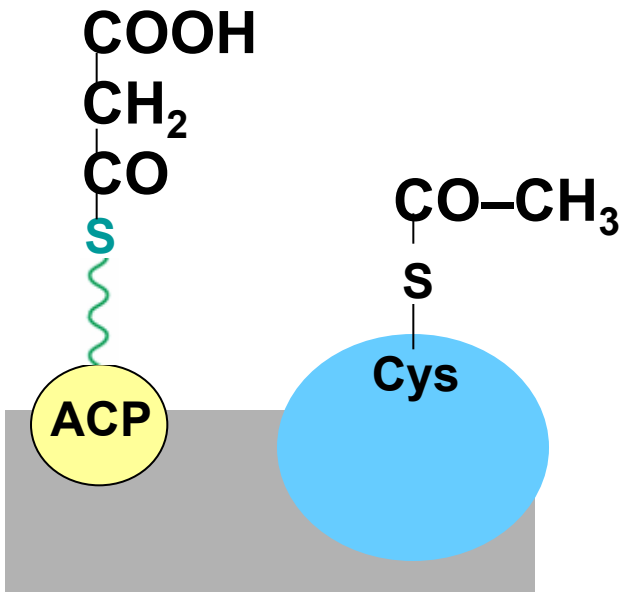
Transfer of the **acetyl group** of acetyl CoA **to the sulfur of a cystein residue** of the condensing enzyme.
The reaction is catalysed by ***acetyl transacylase*****.**



2

The malonyl group is transferred to the **sulphur atom of the phosphopantetheine** attached to ACP.

The reaction is catalysed by ***malonyl transacylase*****.**



3

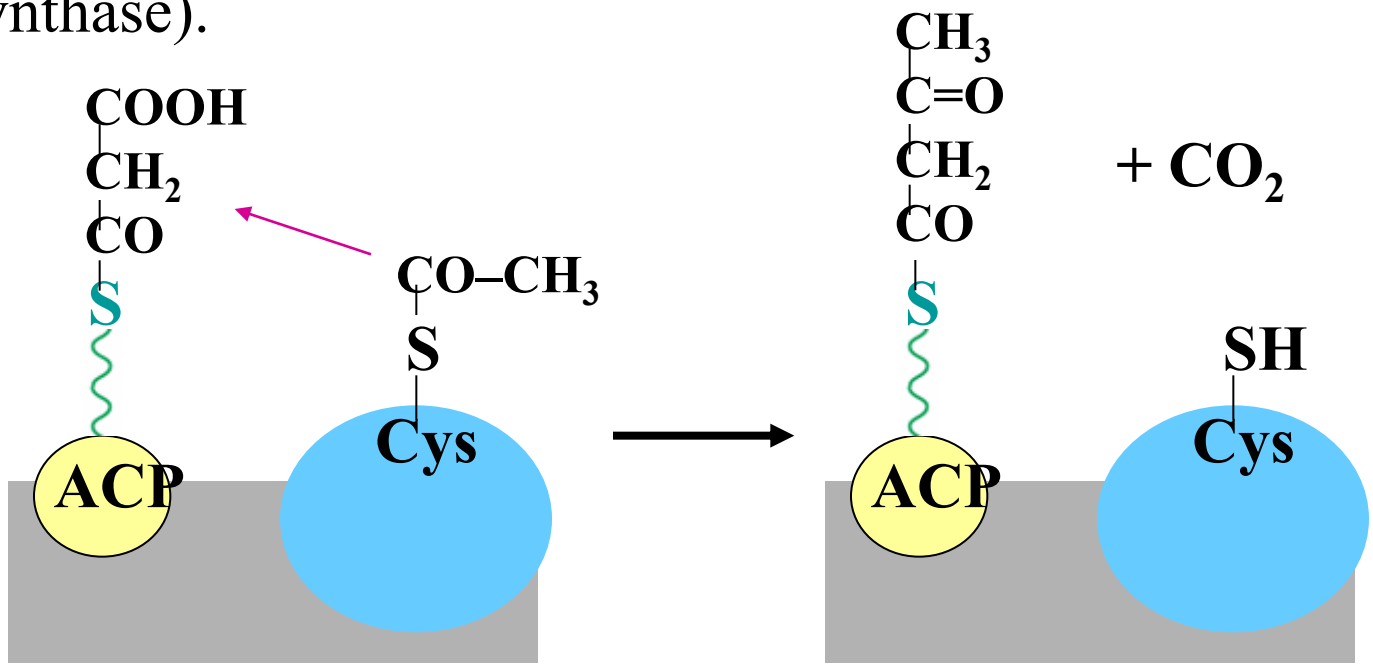
Condensation

joining acetyl unit to a two-carbon part of the **malonyl unit** on phosphopantetheine.

CO_2 is released.

An **acetoacetyl unit** is formed.

The reaction is catalysed by **condensing enzyme** (3-oxoacyl synthase).

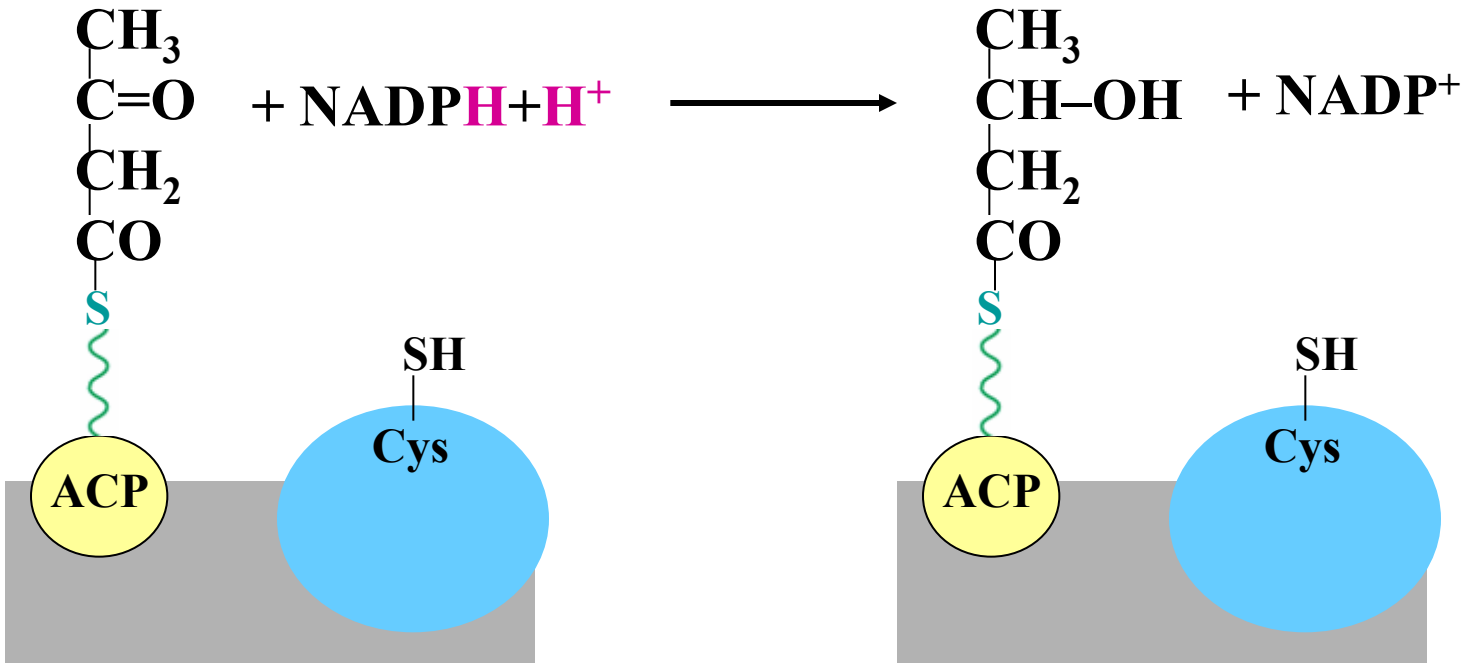


4

The first reduction

catalysed by ***β-ketoacyl reductase*** with **NADPH**.

The product is **3-hydroxyacyl** unit.

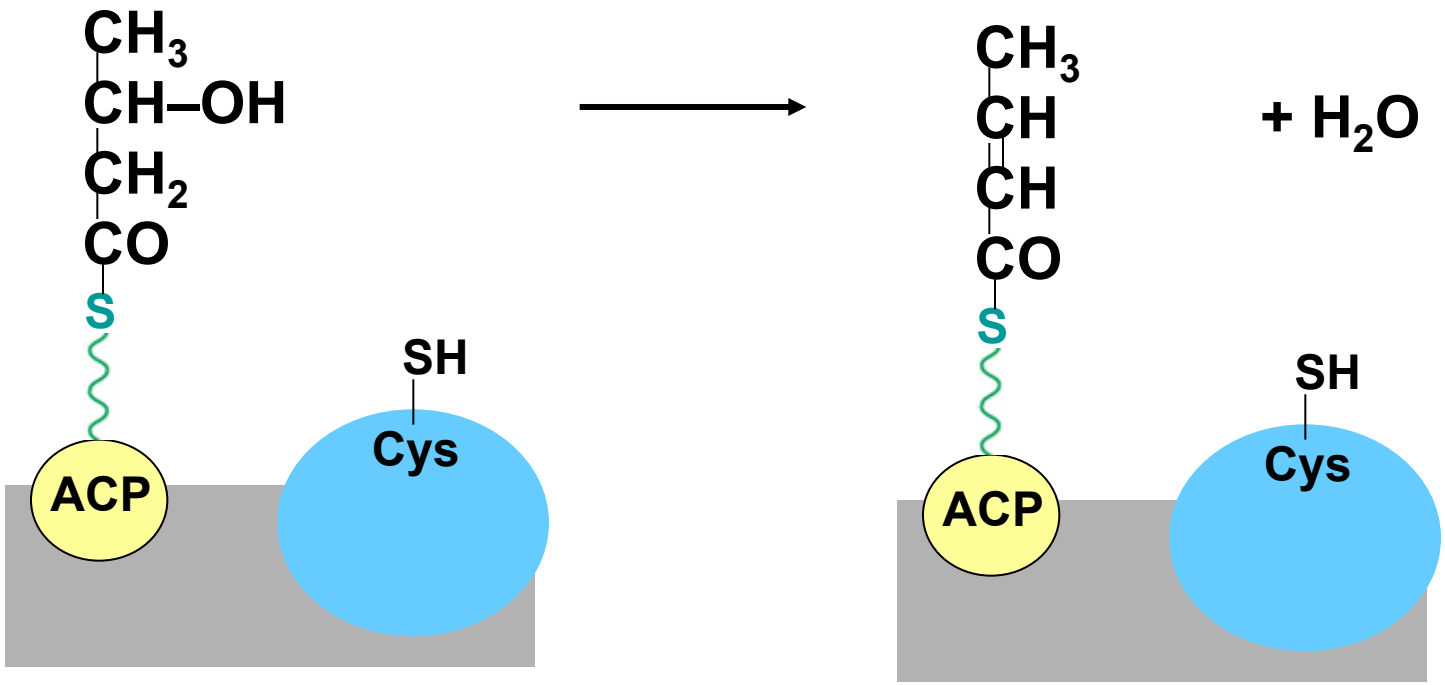


5

Dehydration

catalysed by **3-hydroxyacyl dehydratase**.

The product is ***trans–2–enoyl*** (named crotonyl) unit.



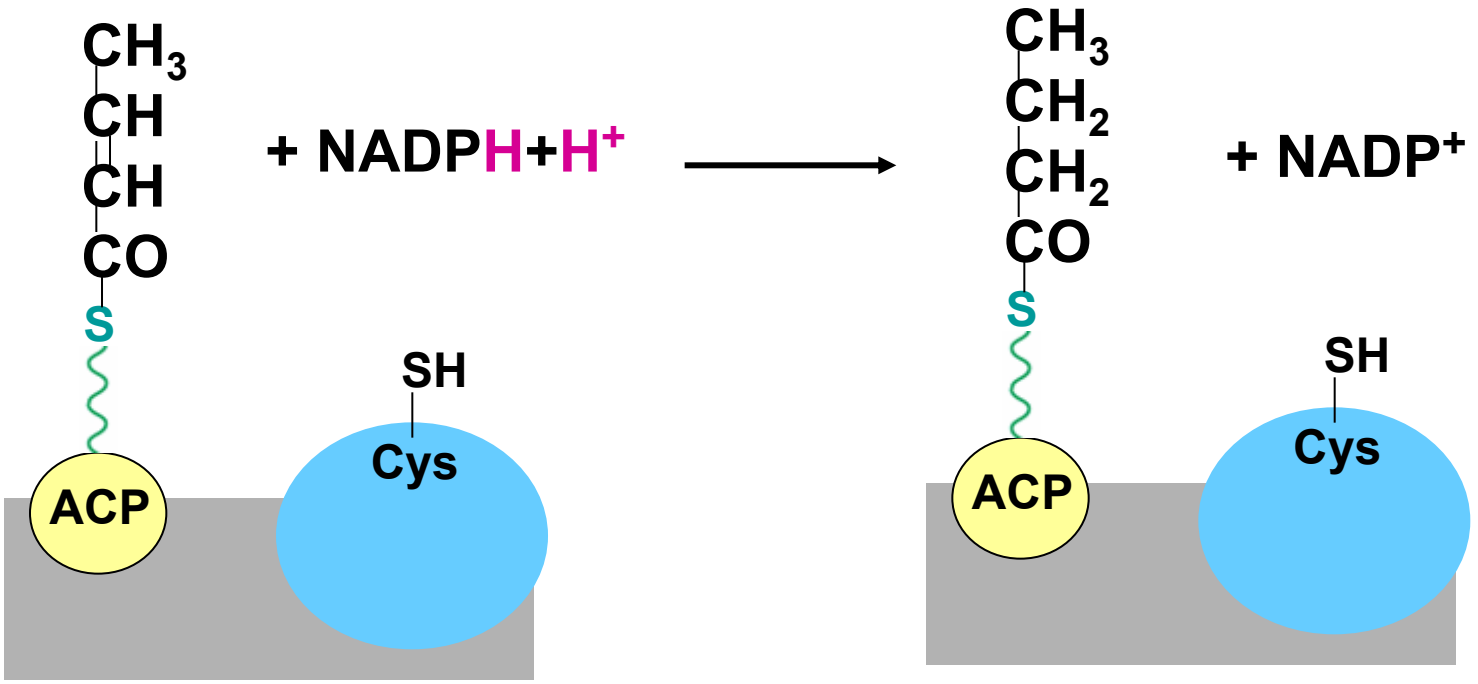
6

The second reduction

catalysed by ***enoyl reductase*** with **NADPH**.

The product is **saturated acyl** (now butyryl) unit.

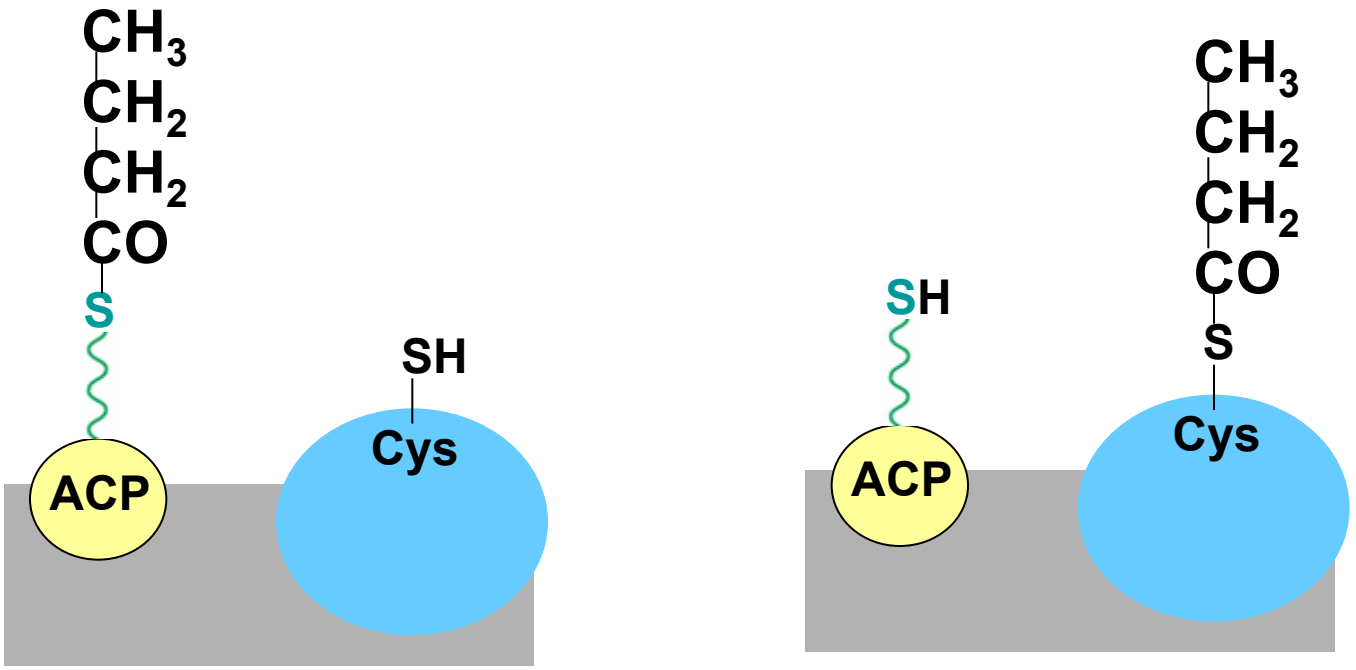
Initial acetyl was elongated by two carbon atoms.



7

The saturated **acyl is transferred to the cysteine sulfur** atom on the condensing enzyme.

The synthase is now ready for another round of elongation



After the completion of the first elongating cycle, **new malonyl is "loaded“** on the sulfanyl group of PPt.

In the second round of fatty acid synthesis, butyryl unit condenses with malonyl to form a C_6-acyl, ……

The elongation cycles continue until C_{16}-acyl unit (palmitoyl) is formed.

Palmitoyl unit is a good substrate for **thioesterase** that hydrolyses palmitoyl-PPt to yield **palmitate** (16:0).

In mammals, palmitate is the major product of FA synthesis.

A minor saturated product is stearate (18:0).

Further elongation of fatty acids is provided by similar mechanisms, but the elongating system is located on the membranes of endoplasmic reticulum

NADPH is required in the reductive steps of FA synthesis

The main source of NADPH is the **pentose phosphate pathway**

.

A certain part of NADPH is supplied by the reaction catalysed by **$NADP^+$–linked malate enzyme** ("malic enzyme"):

$$\text{Malate} + NADP^+ \rightarrow \text{pyruvate} + CO_2 + NADPH$$

The reaction takes part on the transport of acetyl-CoA (in the form of citrate) across the inner mitochondrial membrane.

The stoichiometry of fatty acid synthesis

The synthesis of palmitate (C_{16}):

The synthesis of malonyl CoA

7 Acetyl CoA + 7 CO_2 + 7 ATP → 7 malonyl CoA + 7 ADP + 7 P_i + 14 H^+

The synthesis catalysed by the fatty acid synthase complex

Acetyl CoA + 7 malonyl CoA + 14 NADPH + 20 H^+ →

→ palmitate + 7 CO_2 + 14 $NADP^+$ + 8 CoA + 6 H_2O

The overall stoichiometry for the synthesis of palmitate is

8 Acetyl CoA + 7 ATP + 14 NADPH + 6 H^+ →

→ palmitate + 14 $NADP^+$ + 8 CoA + 6 H_2O + 7 ADP + 7 P_i

Compare

Feature	FA β-oxidation	FA synthesis
Localization	mitochondria	cytoplasm
Acyl attached to	CoA-SH	ACP
Basic unit	acetyl (C_2)	acetyl (C_2)
Redox cofactors	NAD^+, FAD	NADPH
Enzymes	separated	dimer / complex
Stimulated by	glucagon	insulin

Elongation of fatty acids

Although **palmitate (C_{16}) is the major product** of the fatty acid synthase complex, and is the chief saturated fatty acid in human fat,

stearate and oleate (C_{18}) are common and longer-chain fatty acids,
arachidate (C_{20}),
behenate (C_{22}) and
lignocerate (C_{24}) occur in phospholipids.

Elongation by enzymes bound to the endoplasmic reticulum:

– Activation of palmitate by conversion to palmitoyl CoA,
– activation of acetyl CoA by its carboxylation to malonyl CoA,
– elongation *similar* to synthesis catalysed by FA synthase complex,

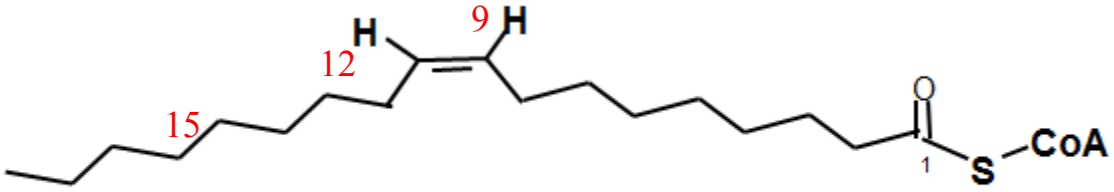
but the **intermediates are CoA-thioesters**, not enzyme-bound acyls. The reductant is also NADPH.

Elongation process in mitochondria (for the synthesis of fatty acids incorporated into mitochondrial lipids):

– Reversal of the β-oxidation.

Desaturation of fatty acids

In higher animals, only the desaturases are known which generate double bonds at carbons 9, 6, 5, and 4.



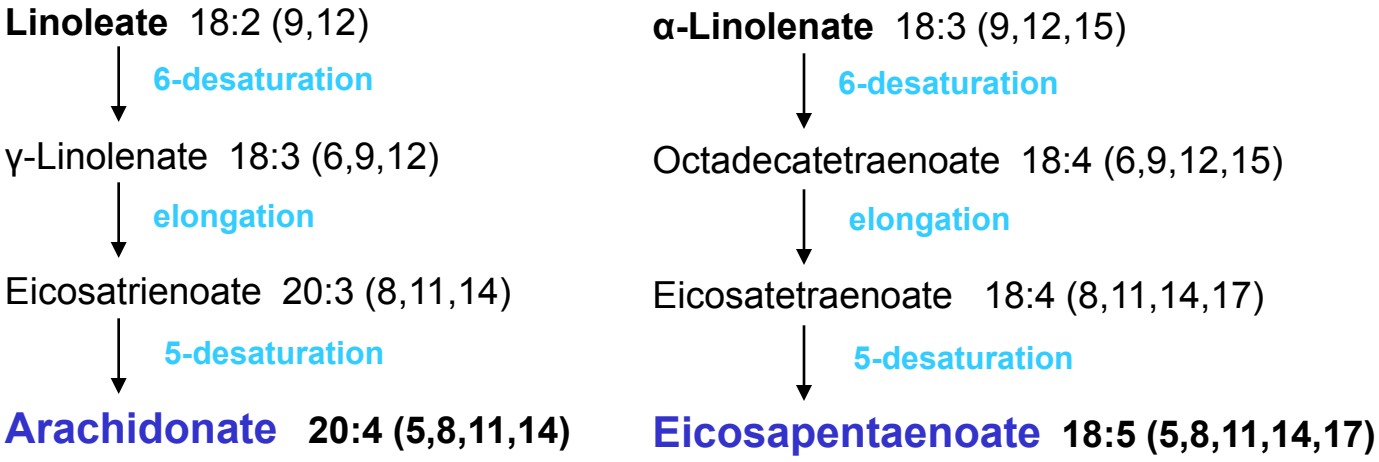
Mammals lack the enzymes to introduce double bonds at carbon atoms beyond C-9. Fatty acids containing double bonds beyond C-9 are synthesized by **plants**, they contain also **12- and 15-desaturase**.

Unsaturated fatty acids of the series *n-6* are comprised in all plant oils (olive oil, sunflower oil etc.).
15-Desaturase is present predominantly in plants growing in cold water (algae, phytoplankton), then a high concentration of polyunsaturated fatty acyls of the series *n*-3 is in fish oils (fish feeds phytoplankton).

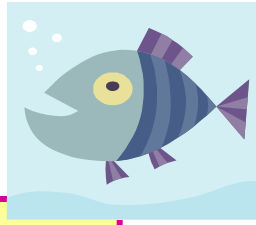
Polyunsaturated fatty acids n-3 and n-6 are essential for animals

They serve as **precursors of eicosanoids** (prostanoids and leukotrienes).

If food intake is sufficient (vegetable oils, fish),
linoleate (linoleic acid) and **α-linolenate (linolenic ac.)** are precursors of other PUFA as **arachidonate** (n-6) and **eicosapentaenoate** *(n*-3), from which eicosanoids are formed.



Elongation and desaturation of FA



n-9 series *n*-6 series *n*-3 series

18:0 → 18:1 (9) ⋯plants⋯▸ **18:2 (9,12)** ⋯phytoplankton⋯▸ **18:3 (9,12,15)**

↓ *6-desaturase*

18:2 (**6**,9) → 18:3 (**6**,9,12) → 18:4 (**6**,9,12,15)

↓ elongation

20:2 (8.11) → 20:3 (8,11,14) → 20:4 (8,11,14,17)

↓ *5-desaturase*

20:3 (**5**,8,11) → 20:4(**5**,8,11,14) → 20:5(**5**,8,11,14,17)

↓ elongation

22:3 (7,10,13) → 22:4 (7,10,13,16) → 22:5 (7,10,13,16,19)

Mechanism of long-chain fatty acyl-CoAs desaturation

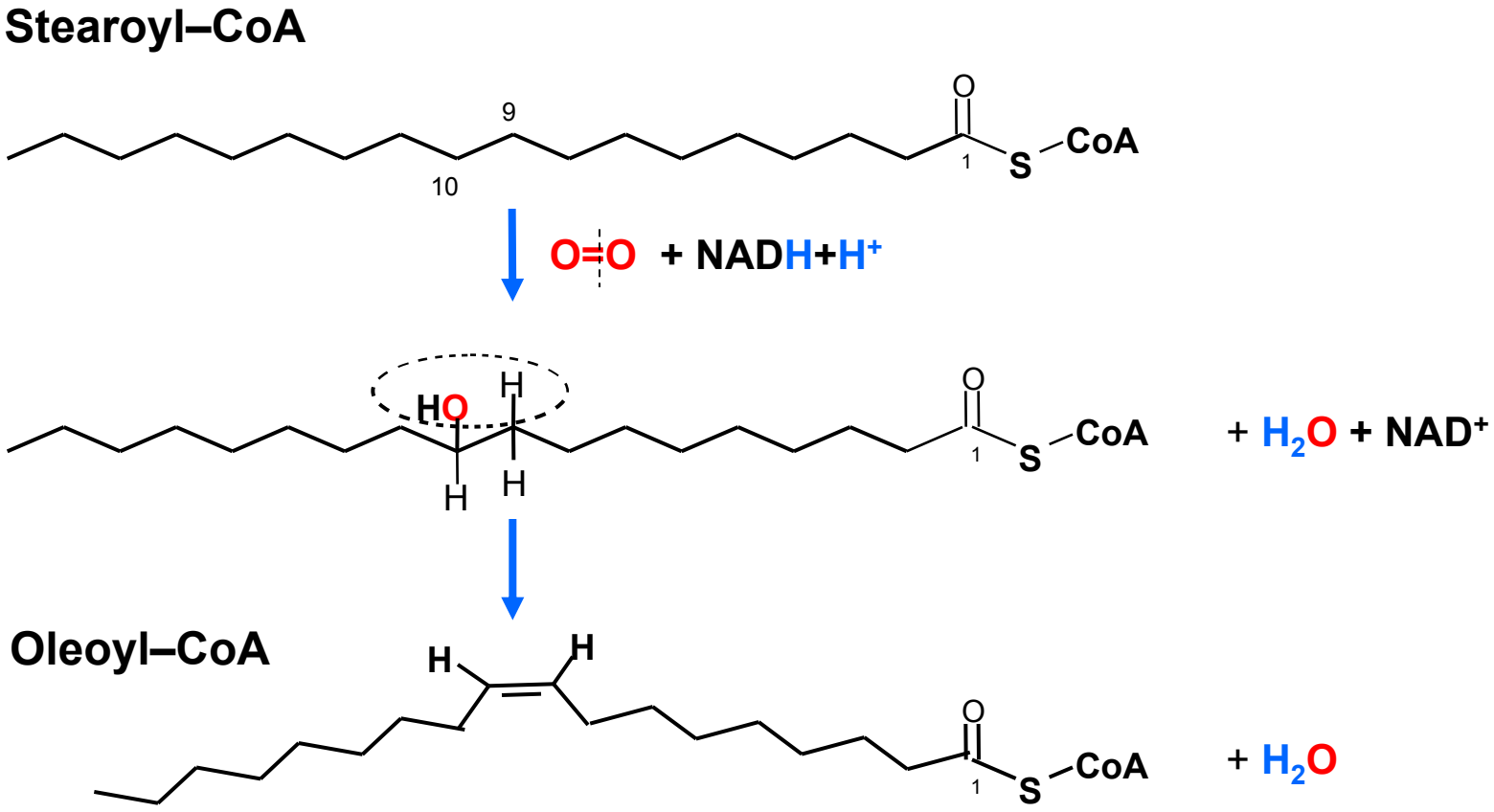
Location: smooth **endoplasmic reticulum** of liver cells.

Desaturases are **hydroxylating monooxygenases.** The substrate is hydroxylated and after it water is eliminated from the hydroxylated product with the formation of the double bond.

The reductant is **NADH+H+**, from which the electrons are carried by the flavine enzyme and the cytochrome *b*5 to a desaturase.

Mechanism of long-chain fatty acyl-CoA desaturation

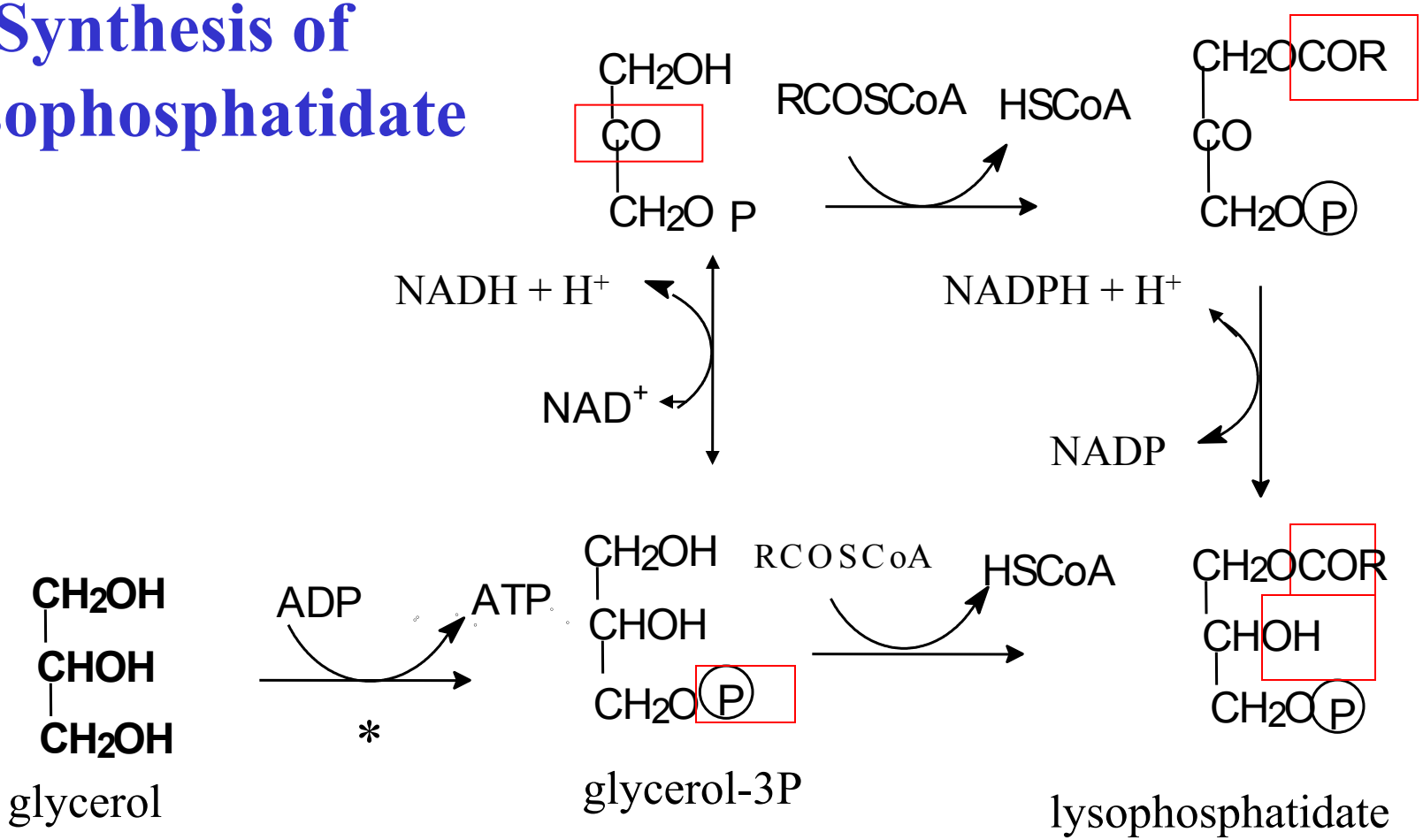
Example:



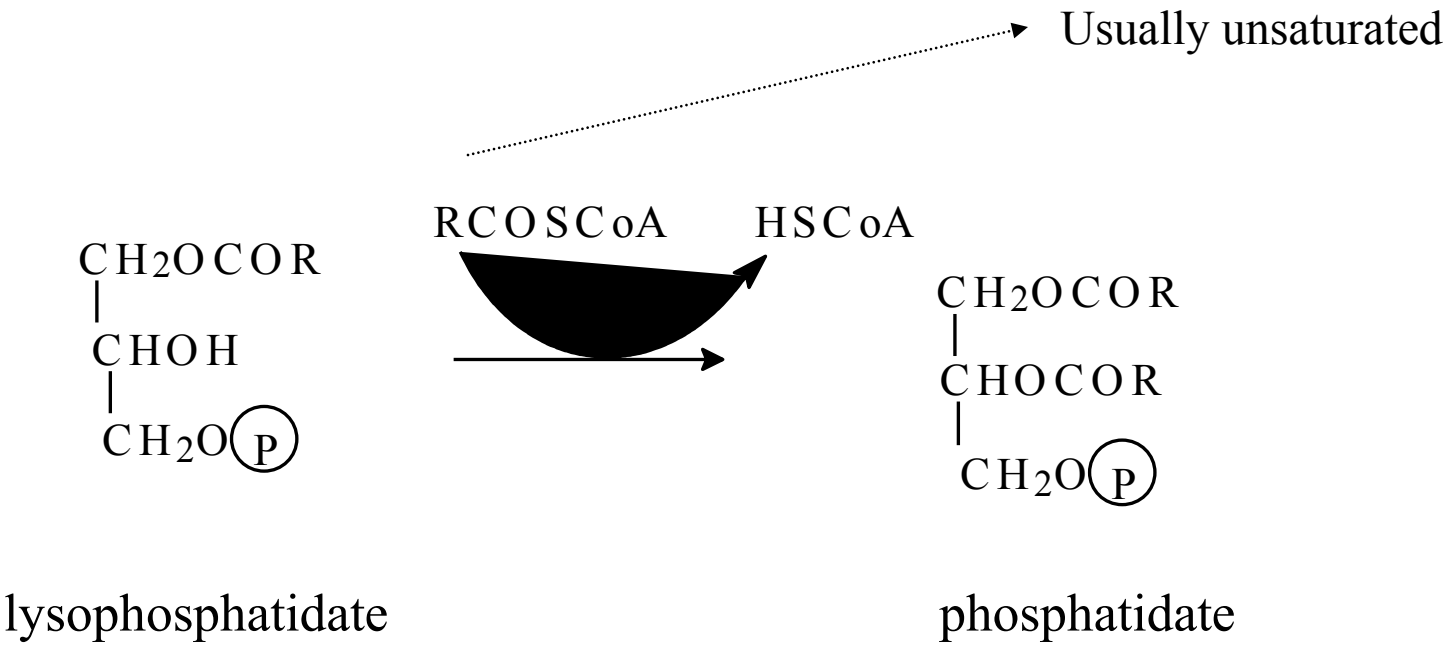
Synthesis of triacylglycerols

ER –liver, adipocytes, enterocytes

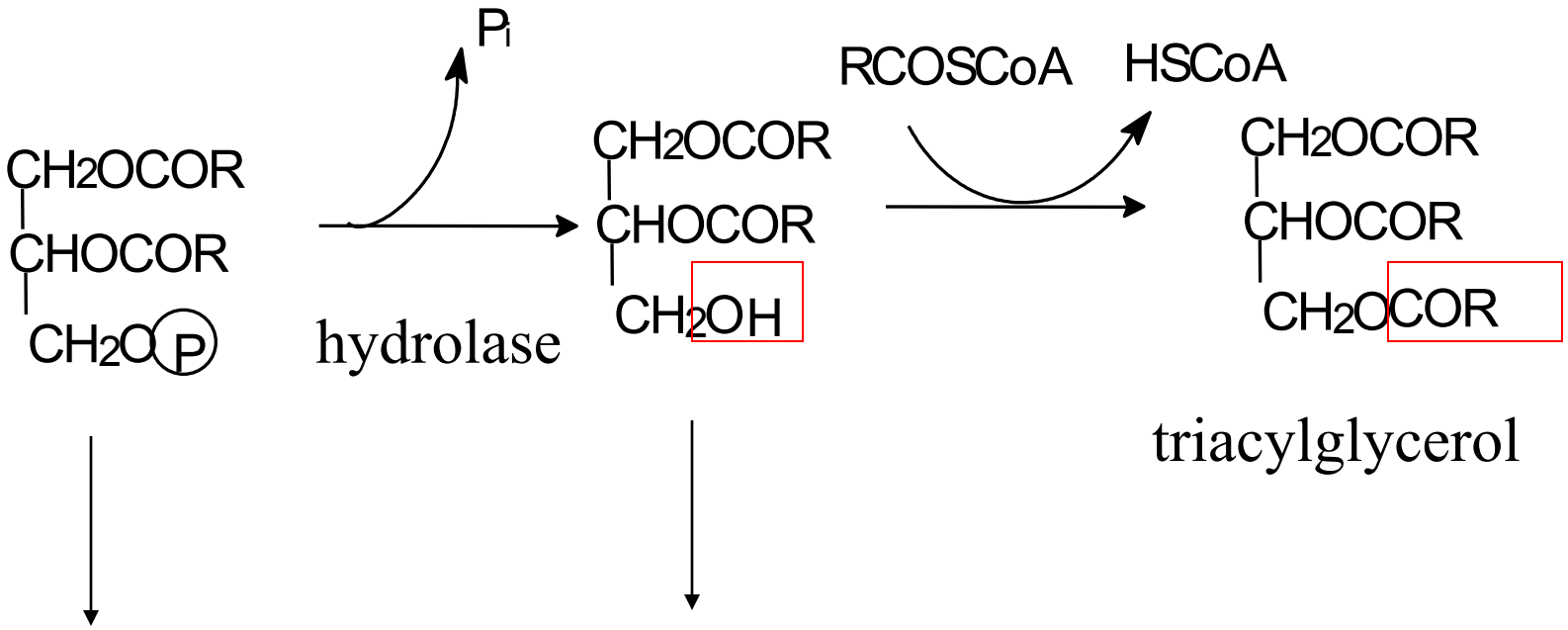
1. Synthesis of lysophosphatidate



2. Synthesis of phosphatidate



3. Synthesis of triacylglycerols



Intestine → CM

Lier → VLDL

Adipocytes → deposition