CDL Advances Chemical Studies (ACS)

Metabolic Biochemistry 7 CFU = 6+1

Lecture

Laboratory

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Fatty acid Metabolism

LIPIDS

Lipids of importance metabolic in mammals include

Triglycerides | Phospholipids | Steroids

Metabolism products

Fatty acids (FA) | Glycerol (G) | Ketone bodies

Lipids make up 10-20% of body weight.

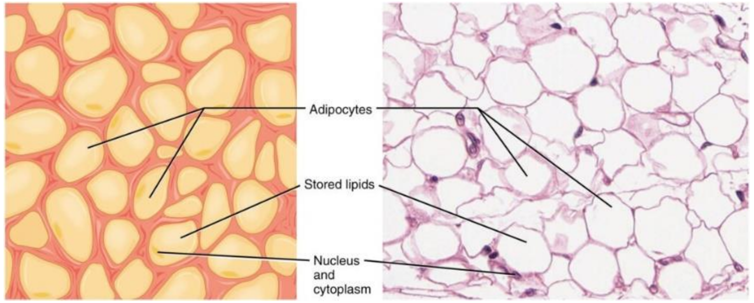
They consist mostly of triglycerides

LIPIDS

They are located in all organs and tissues distributed in varying quantities

The main site of accumulation of triglycerides is the cytoplasm of fat cells (Adipose tissue)

In the adipocytes they form large blood cells that occupy a large part of the cytoplasm



They are the best source of metabolic energy.

1 oxidized gram of triglycerides produces 9.3 kcal while 1 oxidized gram of protein produces 4.1 kcal

WHY ??

Carbon atoms have a lower oxidation state than sugars and proteins

. Therefore they can be more oxidized and produce more energy

Lipids

Cells can obtain fatty acid fuels from:

Fats consumed in the diet

Fats stored in cells as lipid droplets

Fats stored in specialized tissue

Adipose tissue
(adipocytes)

Liver

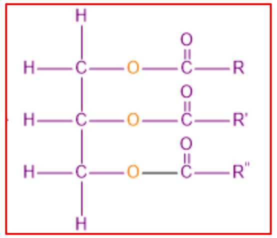
major sites of lipid metabolism

Blood (transport lipids)

Cardiac muscle
Skeletal muscle

major users of fatty acids and ketone bodies

Digestion, Mobilization, and Transport of Fats

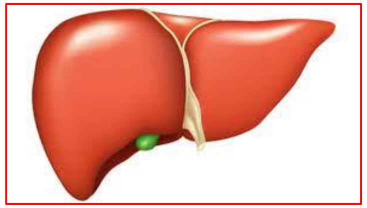


Triacylglycerols

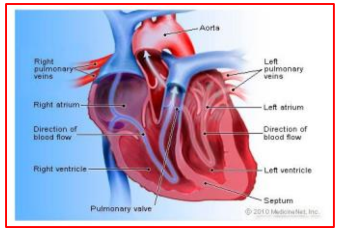
Unique source of energy

provide more than half the energy requirements of some organs,

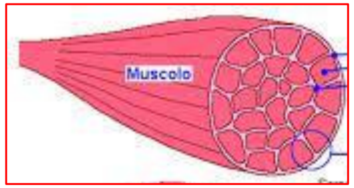
liver



heart



resting skeletal muscle.



Hibernating animals

Migrating birds.

Digestion, absorption and transport of lipids

1

Digestion of lipids begins in the stomach (gastric lipase) and continues in the duodenum.

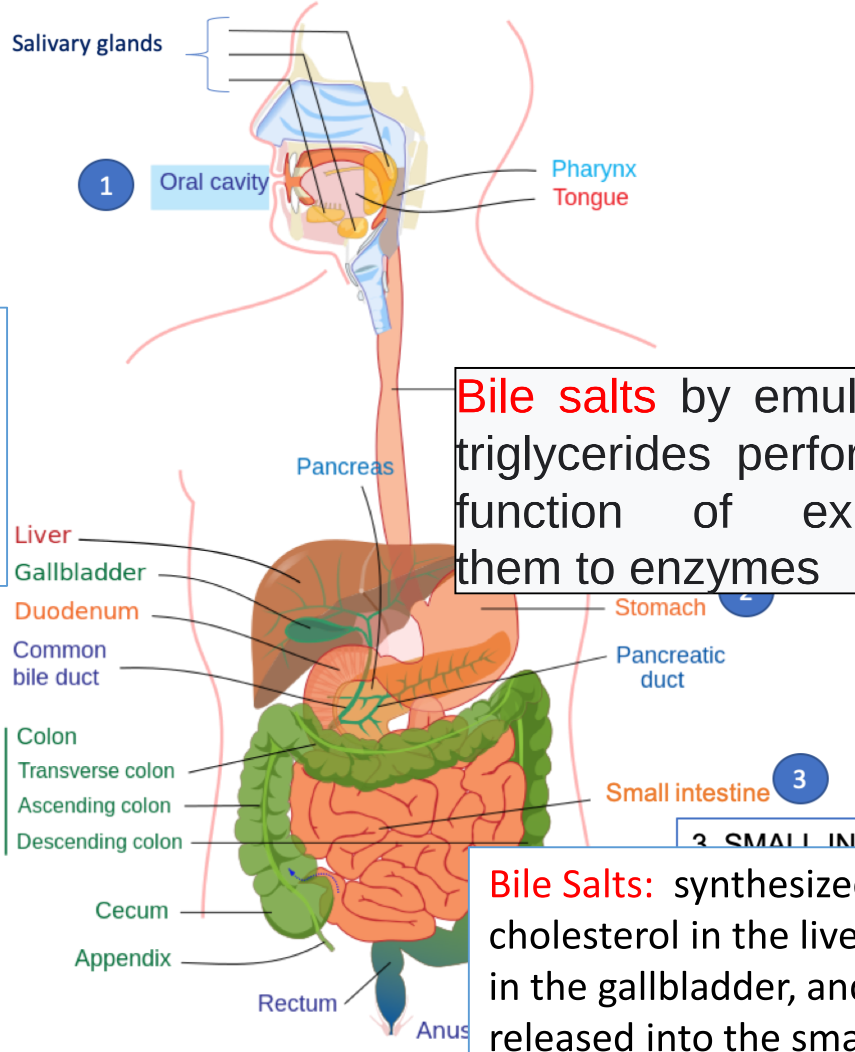
2

Duodenum → Triacylglycerols (TAG) are converted from insoluble macroscopic fat particles to finely dispersed microscopic micelles (by bile salts)

Pancreatic lipases (Ca^{2+} dependent serine esterase) degrade triglycerides into diglycerides (DAG) and monoglycerides (MAG)

Absorbed through the intestinal wall

Reconverted into triacylglycerols.



Bile salts by emulsifying triglycerides perform the function of exposing them to enzymes

Bile Salts: synthesized from cholesterol in the liver, stored in the gallbladder, and released into the small intestine after ingestion of a fatty meal.

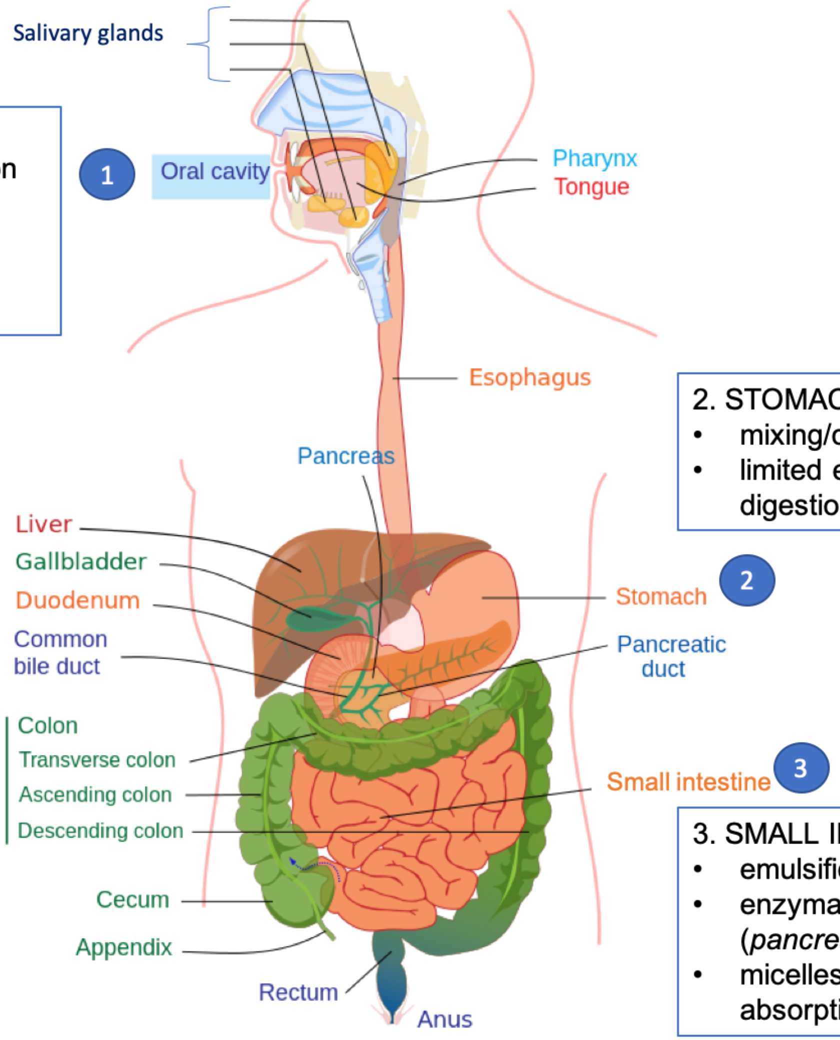
Pancreatic lipase is associated with colipase.

Colipase is produced by the pancreas as a prolipase.

Prolipase is converted into colipase in the small intestine

Release a protein (enterostatin) which signals the sense of satiety to the central nervous system

1. MOUTH
- mechanical digestion
- mixing with saliva
- limited enzymatic digestion (*lingual lipase*)



2. STOMACH
- mixing/churning
- limited enzymatic digestion (*gastric lipase*)

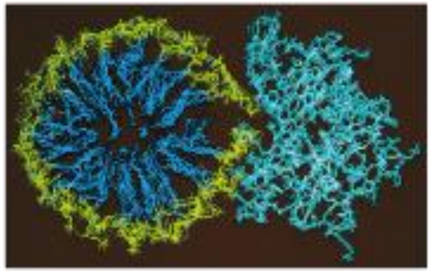
3. SMALL INTESTINE
- emulsification (bile)
- enzymatic digestion (*pancreatic lipases*)
- micelles help with absorption

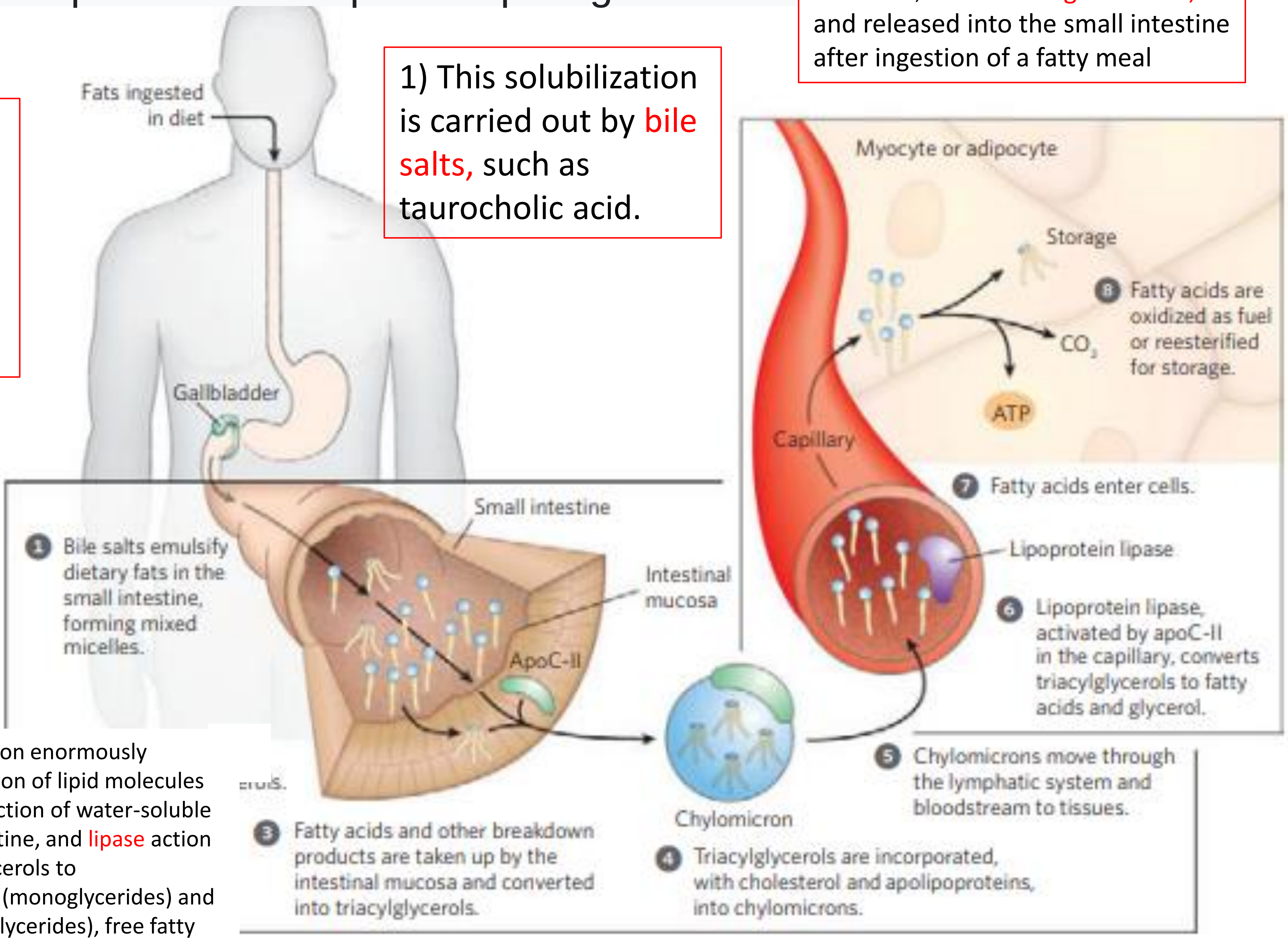
Digestion, absorption and transport of lipids genes.

Bile salts are synthesized from cholesterol in the liver, stored in the gallbladder, and released into the small intestine after ingestion of a fatty meal

Triacylglycerols can be absorbed through the intestinal wall after converting from insoluble macroscopic fat particles to finely dispersed microscopic micelles.

1) This solubilization is carried out by bile salts, such as taurocholic acid.

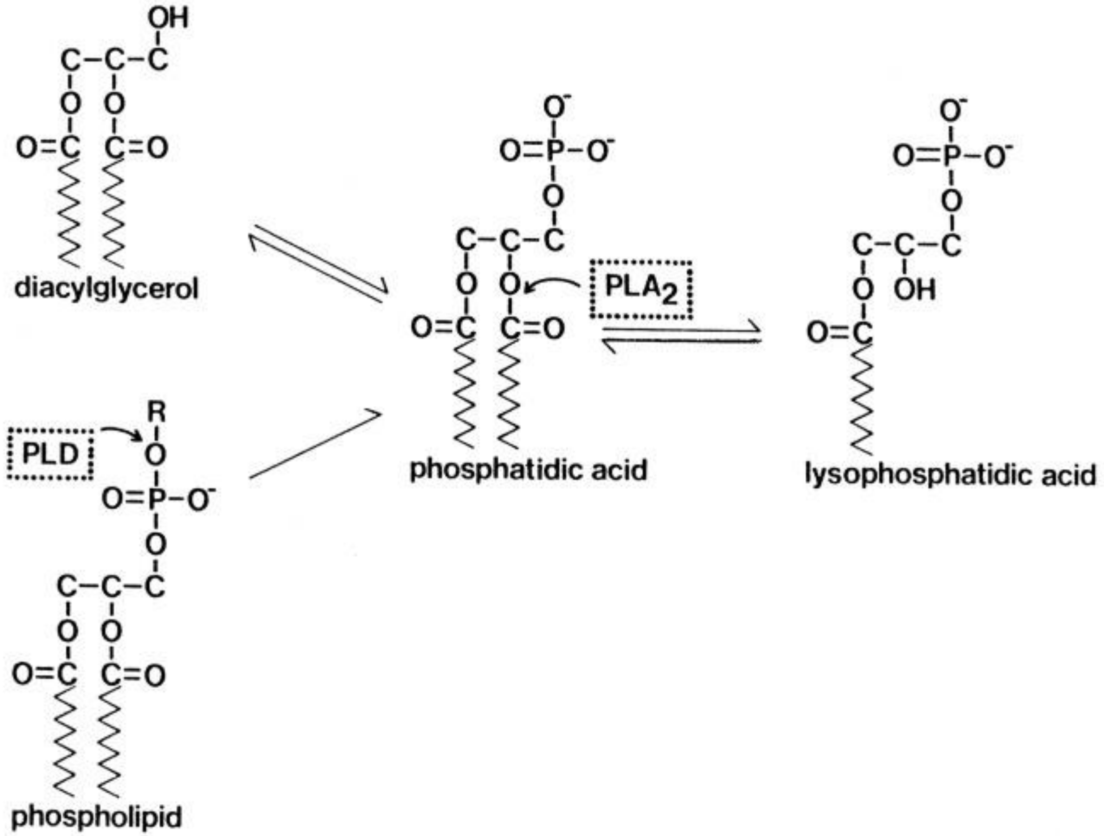




2) Micelles formation enormously increases the fraction of lipid molecules accessible to the action of water-soluble lipases in the intestine, and lipase action converts triacylglycerols to monoacylglycerols (monoglycerides) and diacylglycerols (diglycerides), free fatty acids, and glycerol.

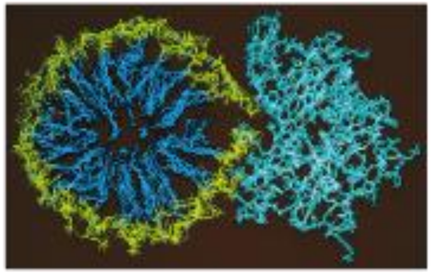
Enterocytes is wetted by an unstirred layer of water.

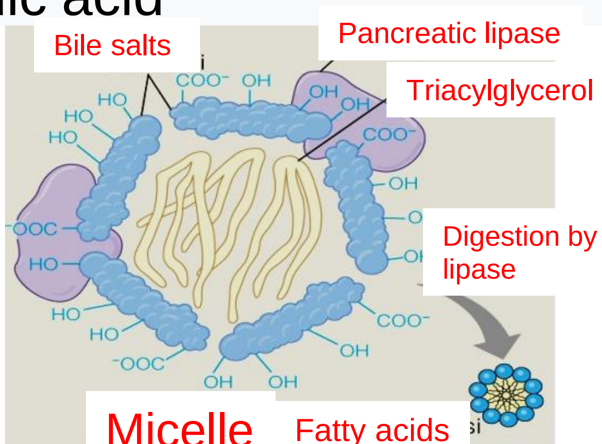
The water barrier is overcome thanks to the formation of mixed micelles formed by bile salts and by the products of digestion of the lipids themselves. .



Mixed micelles are formed from:

- Monoacylglycerols
- Diacylglycerols
- Fatty acids
- Cholesterol
- Lysophosphatidic acid





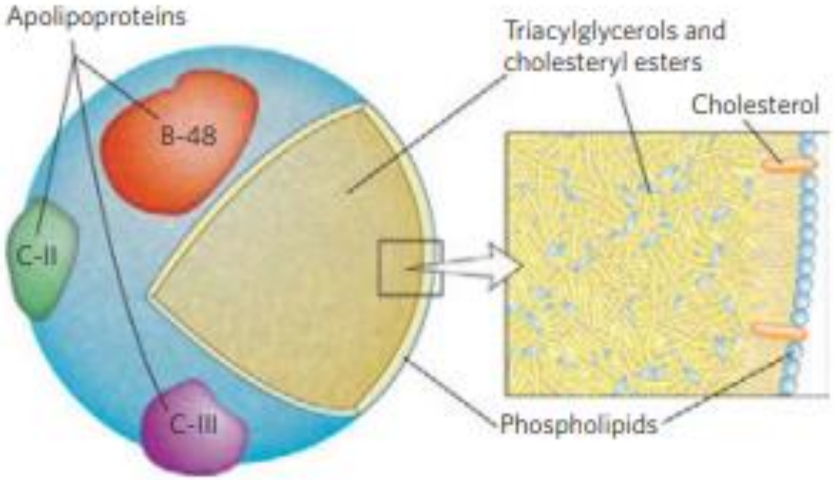
Bile salts by emulsifying triglycerides perform the function of exposing them to enzymes

Chylomicrons Function:

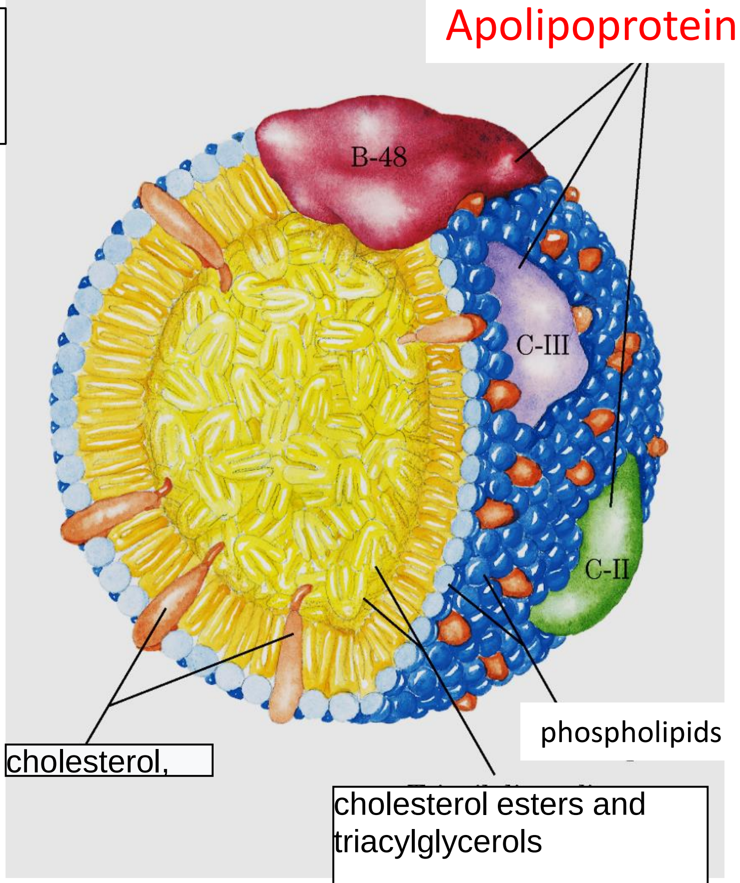
transfer triglycerides from the intestine to the lymphatic and blood circulation

Molecular structure of a chylomicron.

The diameter of chylomicrons ranges from about 100 to 500 nm



Triacylglycerols **sequestered in the interior (yellow)** make up more than 80% of the mass.



The surface is a layer of phospholipids, with head groups facing the aqueous phase.

Several Apolipoproteins protrude from the surface (B-48, C-III, C-II)

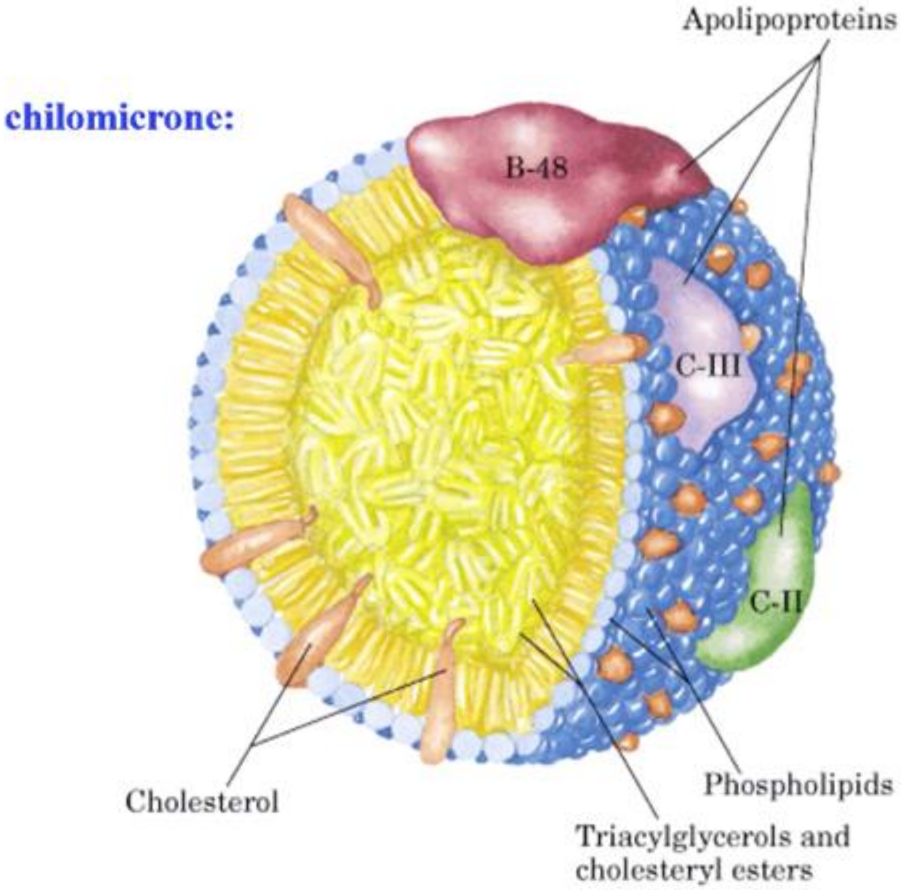
Apolipoproteins act as signals in the uptake and metabolism of chylomicron contents.

Lipoproteins: molecular aggregates of specific carrier proteins called apolipoproteins, which bind different combinations of phospholipids, cholesterol, cholesterol esters and triacylglycerols

Chylomicron.

They move through the lymphatic system
and enter the bloodstream via the left subclavian vein.

ApoC-II activates lipoprotein lipase in the capillaries of adipose, heart, skeletal muscle, and lactating mammary tissues, allowing the release of free fatty acids (FFA) to these tissues.



Molecular structure of a chylomicron.

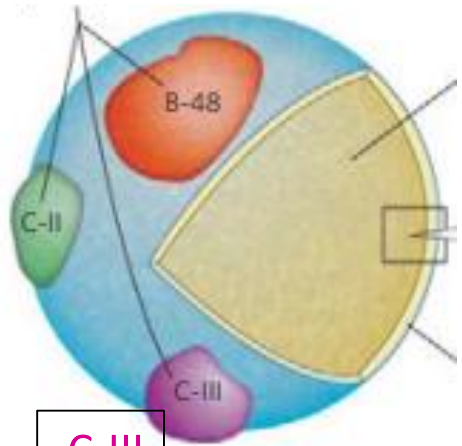
Apolipoproteins ("apo" means "detached" or "separate," designating the protein in its lipid-free form)

Apolipoproteins combine with lipids to form several classes of lipoprotein particles with different densities, ranging from chylomicrons and very-low-density lipoproteins (VLDL) to very-high density lipoproteins (VHDL),

Apolipoproteins

B-48

C-II



C-III

The protein moieties of lipoproteins are recognized by receptors on cell surfaces.

Liver sinthetizes VLDL, VHDL, IDL, LDL, HDL

Each class of lipoprotein has a specific function, determined by its point of synthesis, lipid composition, and apolipoprotein content.

(*Intermediate Density Lipoprotein)*

Transport of lipids

Synthesized in the ER of enterocytes, epithelial cells that line the small intestine.

Plasma lipoproteins are classified as:

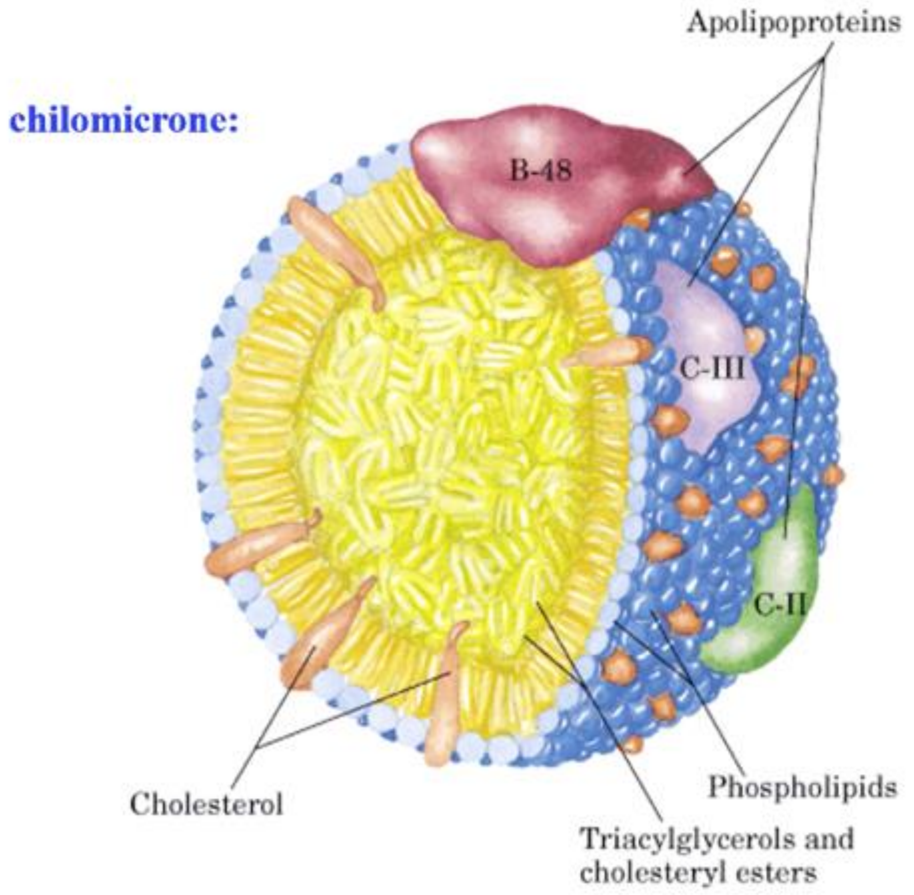
chylomicrons,

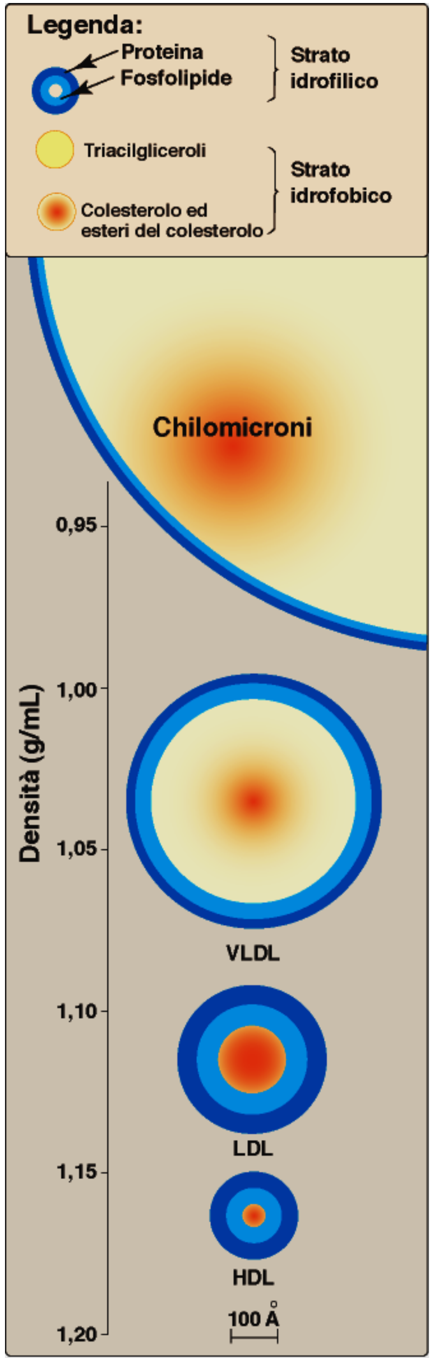
very low-density lipoproteins (VLDL),
very-high density lipoproteins (VHDL),

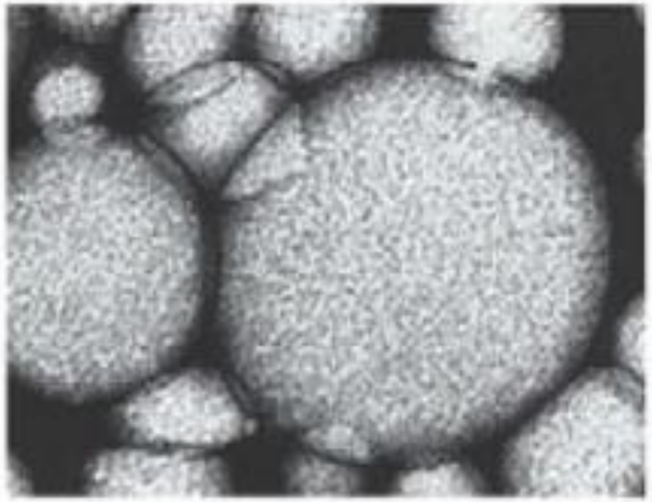
intermediate-density lipoproteins (IDL),

low-density lipoproteins (LDL),

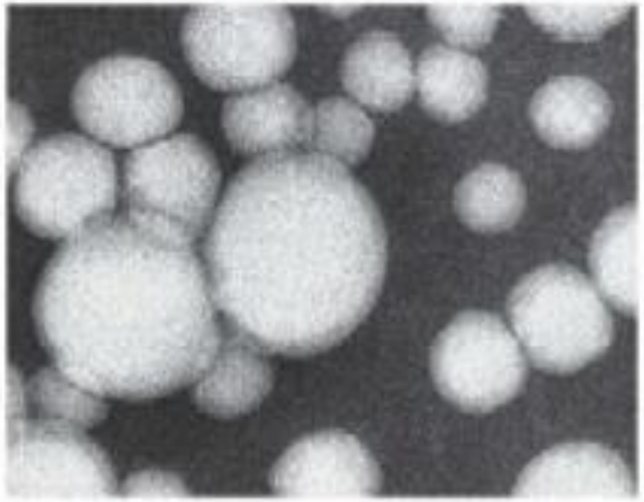
high-density lipoproteins (HDL)



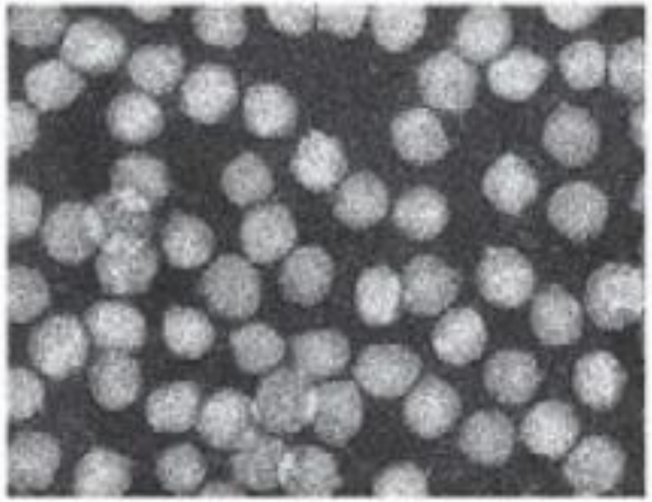




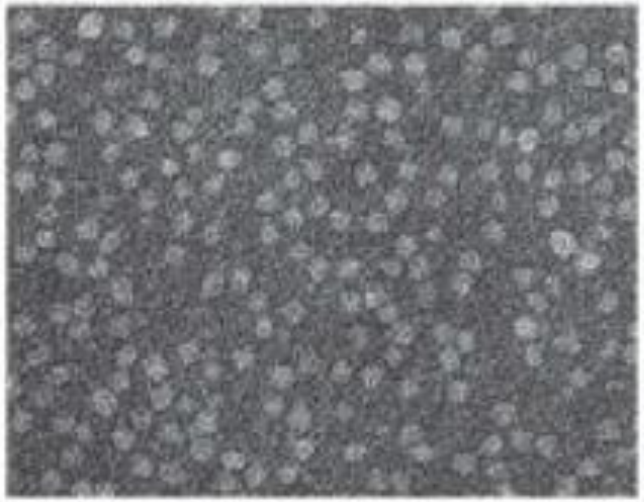
Chylomicrons (×60,000)
50 to 200 nm in diameter;



VLDL (×180,000)
28 to 70 nm



LDL (×180,000)
20 to 25 nm



HDL (×180,000)
8 to 11 nm

They are classified on the basis of the density determined by centrifugation

At least ten distinct apolipoproteins are found in the lipoproteins of human plasma , distinguishable by their size, their reactions with specific antibodies, and their characteristic distribution in the lipoprotein classes.

These protein components act as signals, targeting lipoproteins to specific tissues or activating enzymes that act on the lipoproteins.

They have also been implicated in different diseases;

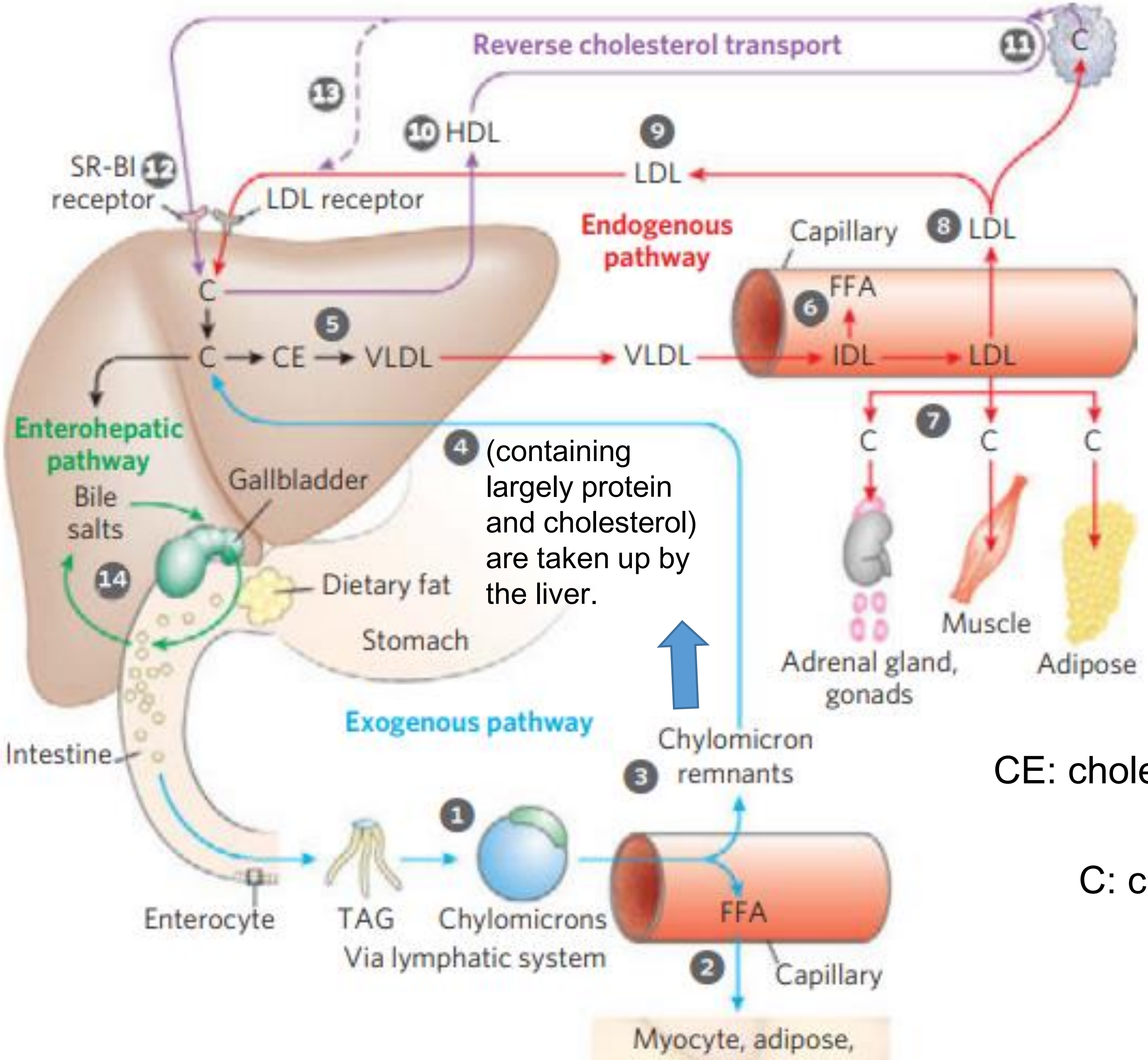
ApoE is implicated in Alzheimer disease.

TABLE 21–2 Apolipoproteins of the Human Plasma Lipoproteins

Apolipoprotein	Polypeptide molecular weight	Lipoprotein association	Function (if known)
ApoA-I	28,100	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,400	HDL	Inhibits LCAT
ApoA-IV	44,500	Chylomicrons, HDL	Activates LCAT; cholesterol transport/clearance
ApoB-48	242,000	Chylomicrons	Cholesterol transport/clearance
ApoB-100	512,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	9,000	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	9,000	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,200	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants

Source: Modified from Vance, D.E. & Vance, J.E. (eds) (2008) *Biochemistry of Lipids and Membranes*, 5th edn, Elsevier Science Publishing.

Bile salts produced in the liver aid in dispersing dietary fats, and are then reabsorbed in the enterohepatic pathway (green arrows).



CE: cholesteryl ester

C: cholesterol;

There are two pathway f the transport of lipids: exogenous (lipids introduced with the diet) endogenous (lipids synthesized in the organism)

Chylomicrons are the largest and least dense lipoproteins synthesized in the smooth endoplasmic reticulum of enterocytes.

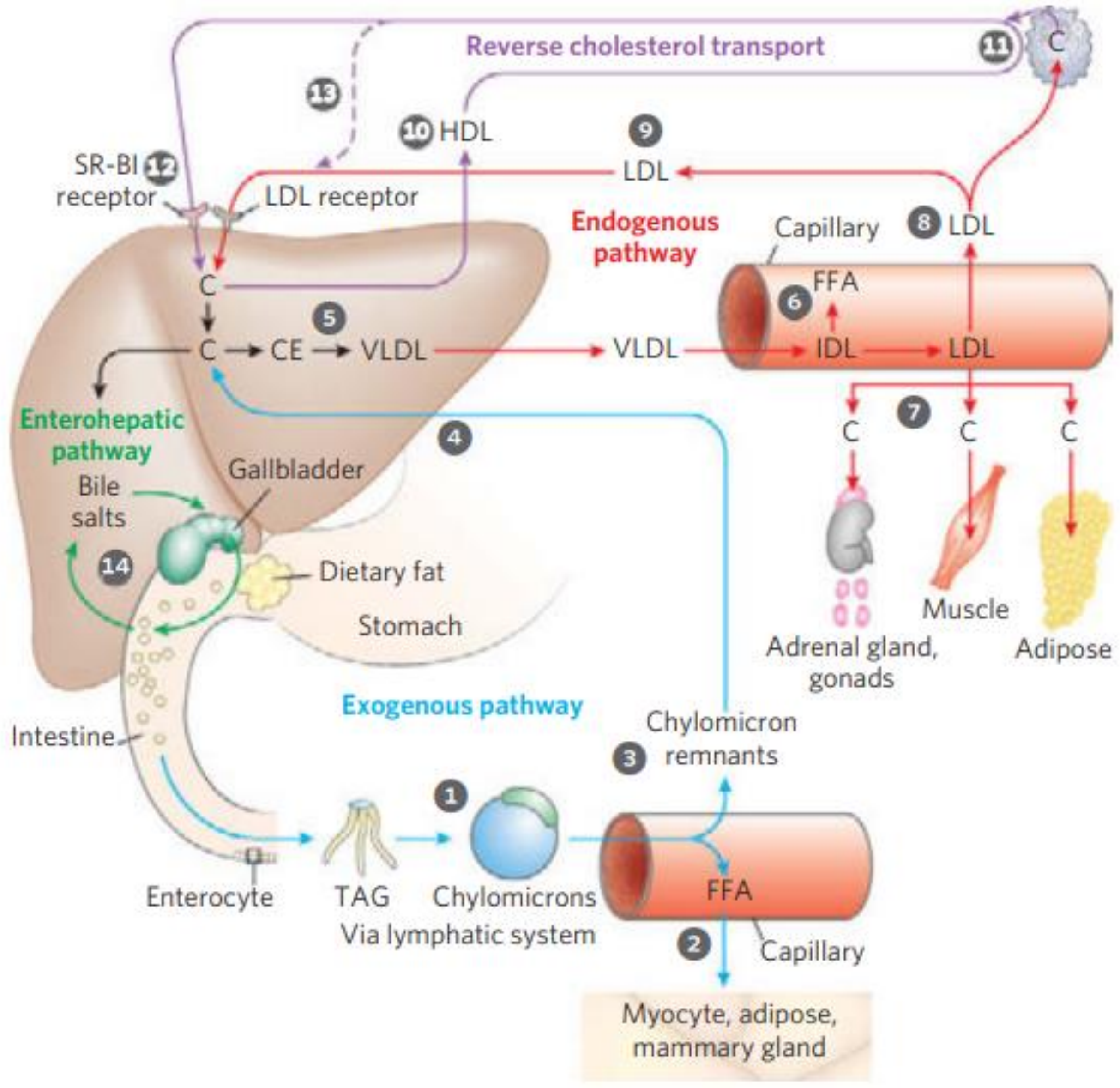
1. **Exogenous pathway** (blue arrows),

TAGs are packaged into chylomicrons;

Tags are released by lipoprotein lipase to adipose and muscle tissues during transport through capillaries.

Apolipoproteins ApoAIV, Apo B48, Apo E , Apo CII and Apo CIII

ApoCII activates lipoprotein lipase in the capillaries of adipose tissue, heart, skeletal muscle, and mammary gland



Chylomicron remnants

In the liver, Apo E receptors capture chylomicrons through endocyto s.

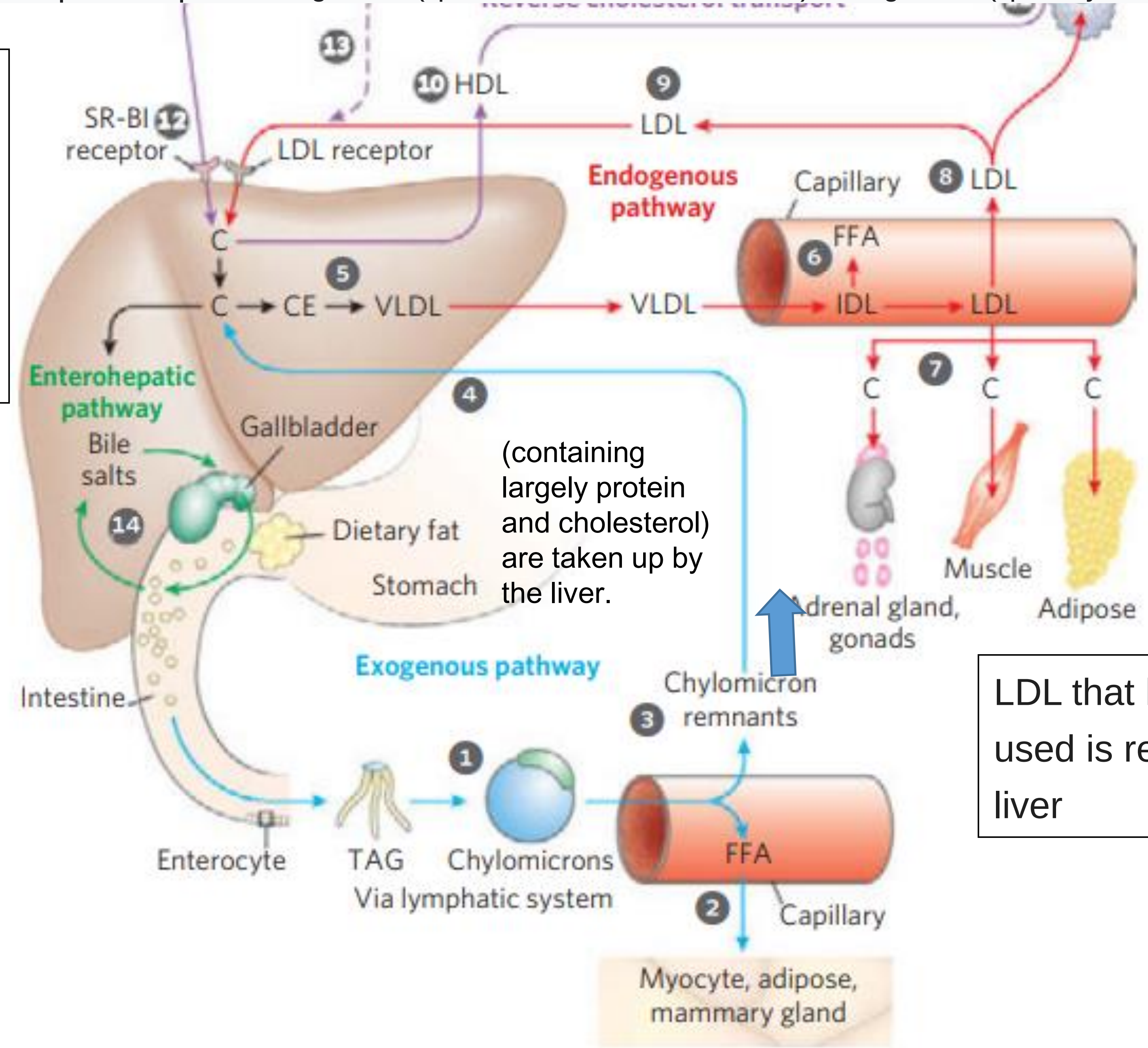
Release cholesterol.

There are two pathway for the transport of lipids: exogenous (lipids introduced with the diet) endogenous (lipids synthesized in the organism)

When the diet contains more fatty acids and cholesterol than are needed as fuel, they are converted into TAGs and cholesteryl esters and transferred to apolipoproteins, forming VLDL.

VLDL :ApoB100, Apo CI, Apo CII, Apo CIII, and Apo E.

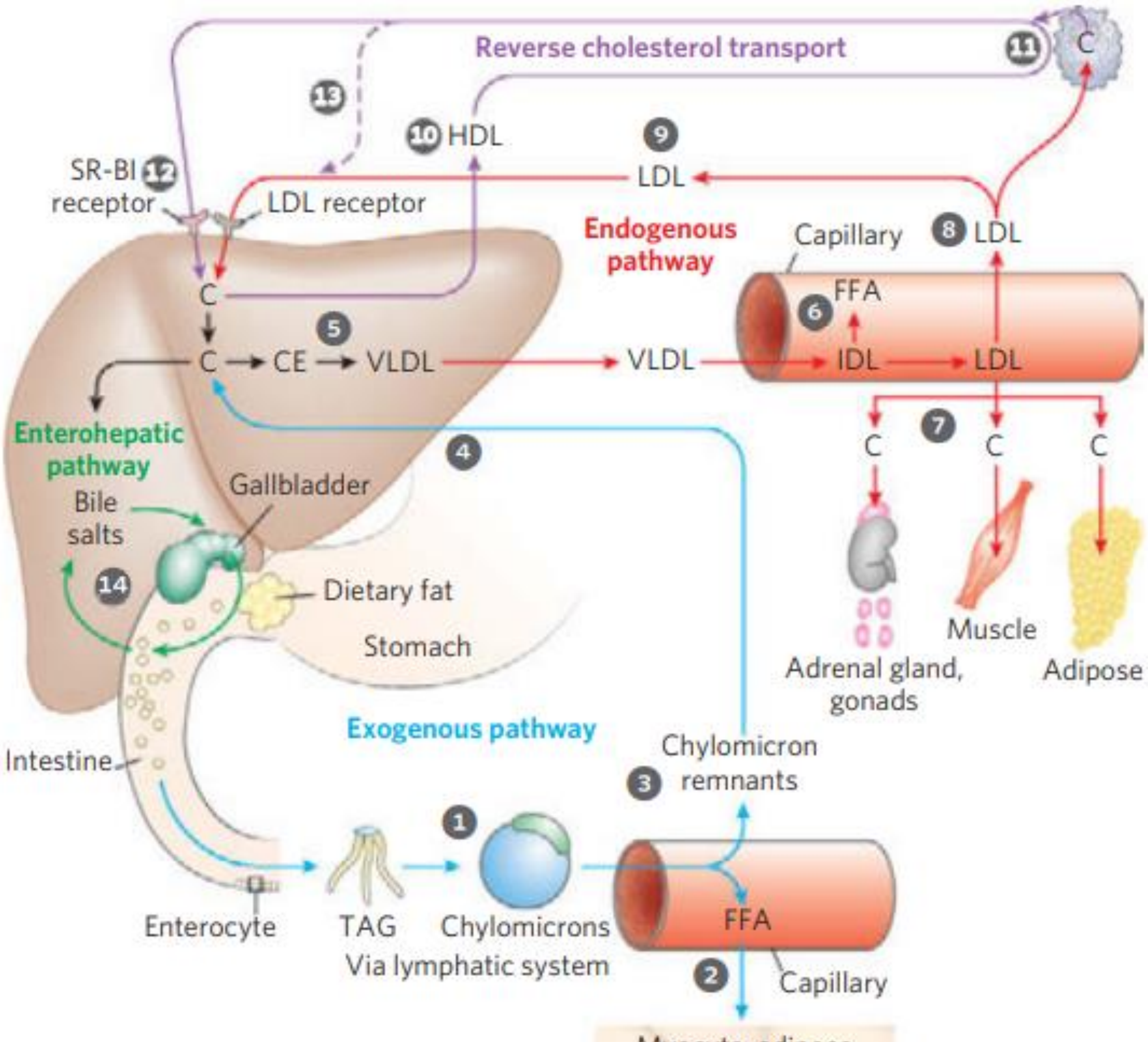
Endogenous pathway (red arrows),
VLDL gradually converts to IDL (*Intermediate Density Lipoprotein) and* LDL. which delivers cholesterol to extrahepatic tissues or returns to the liver.



(containing largely protein and cholesterol) are taken up by the liver.

LDL contains Apo B100, and the tissues contain receptors for cholesterol uptake.

LDL that has not been used is returned to the liver



Excess cholesterol in extrahepatic tissues is transported back to the liver as HDL in reverse cholesterol transport (purple arrows).

GOOD CHOLESTEROL

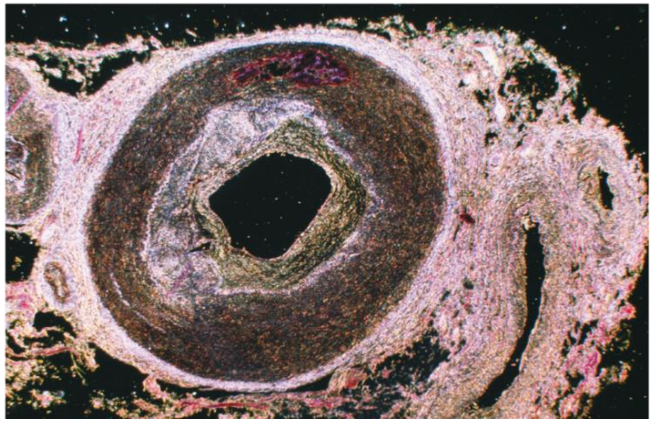
HDL (high density lipoprotein) takes cholesterol from artery walls, hindering the formation of atherosclerotic plaques, therefore it is called "good" cholesterol,

High levels of LDL cholesterol can lower your risk for heart disease and stroke

BAD CHOLESTEROL

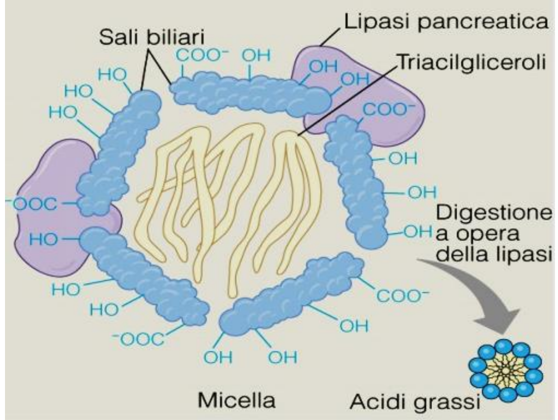
LDL (low density lipoprotein) deposit excess cholesterol on the walls of the arteries, favoring the formation of atherosclerotic

therefore it is called "bad" cholesterol,



Digestion, absorption and transport of lipids genes.

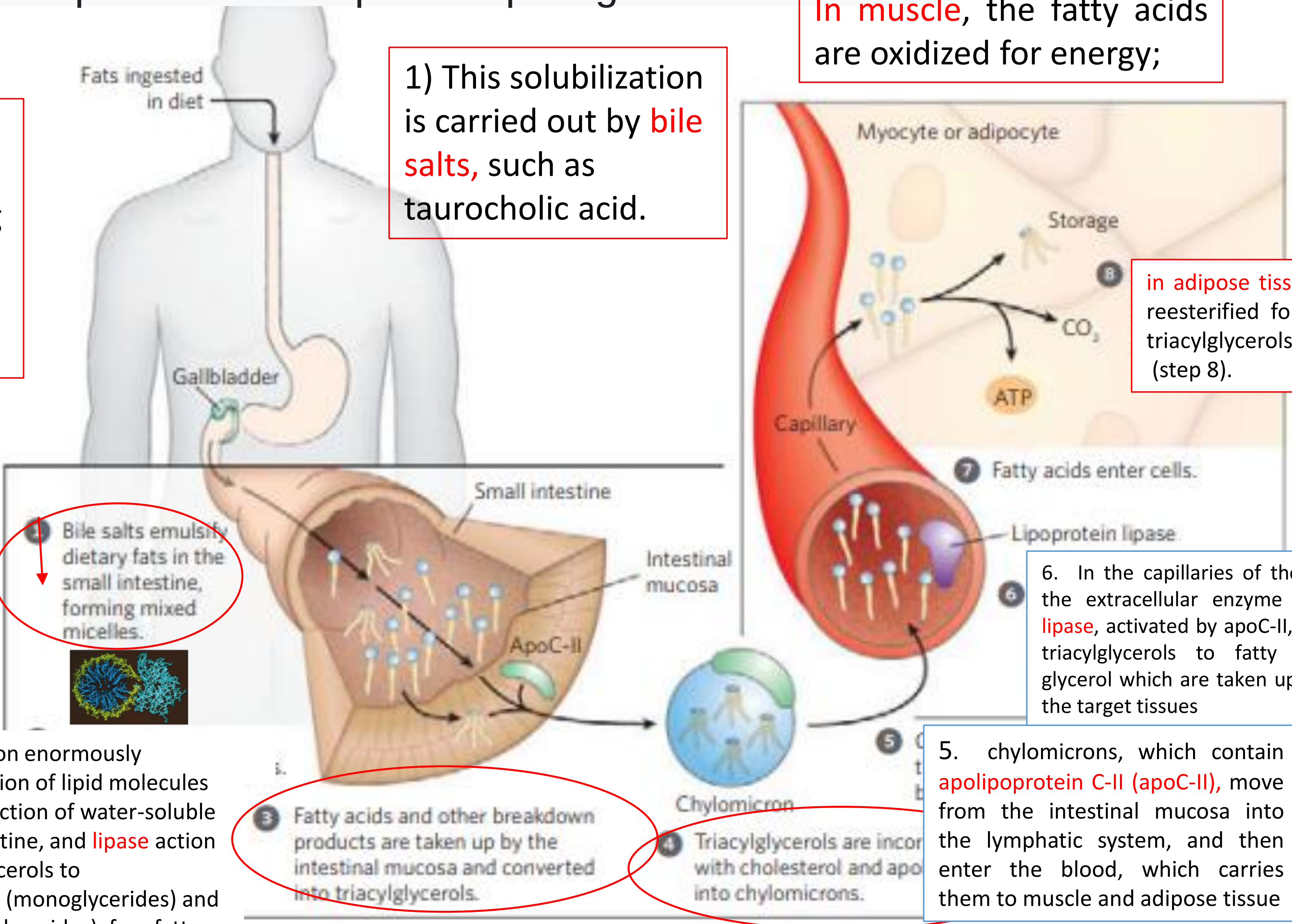
Triacylglycerols can be absorbed through the intestinal wall after converting from insoluble macroscopic fat particles to finely dispersed microscopic micelles.



1) This solubilization is carried out by bile salts, such as taurocholic acid.

In muscle, the fatty acids are oxidized for energy;

in adipose tissue, they are reesterified for storage as triacylglycerols (step 8).



2) Micelle formation enormously increases the fraction of lipid molecules accessible to the action of water-soluble lipases in the intestine, and lipase action converts triacylglycerols to monoacylglycerols (monoglycerides) and diacylglycerols (diglycerides), free fatty acids, and glycerol.

6. In the capillaries of these tissues, the extracellular enzyme lipoprotein lipase, activated by apoC-II, hydrolyzes triacylglycerols to fatty acids and glycerol which are taken up by cells in the target tissues

5. chylomicrons, which contain apolipoprotein C-II (apoC-II), move from the intestinal mucosa into the lymphatic system, and then enter the blood, which carries them to muscle and adipose tissue

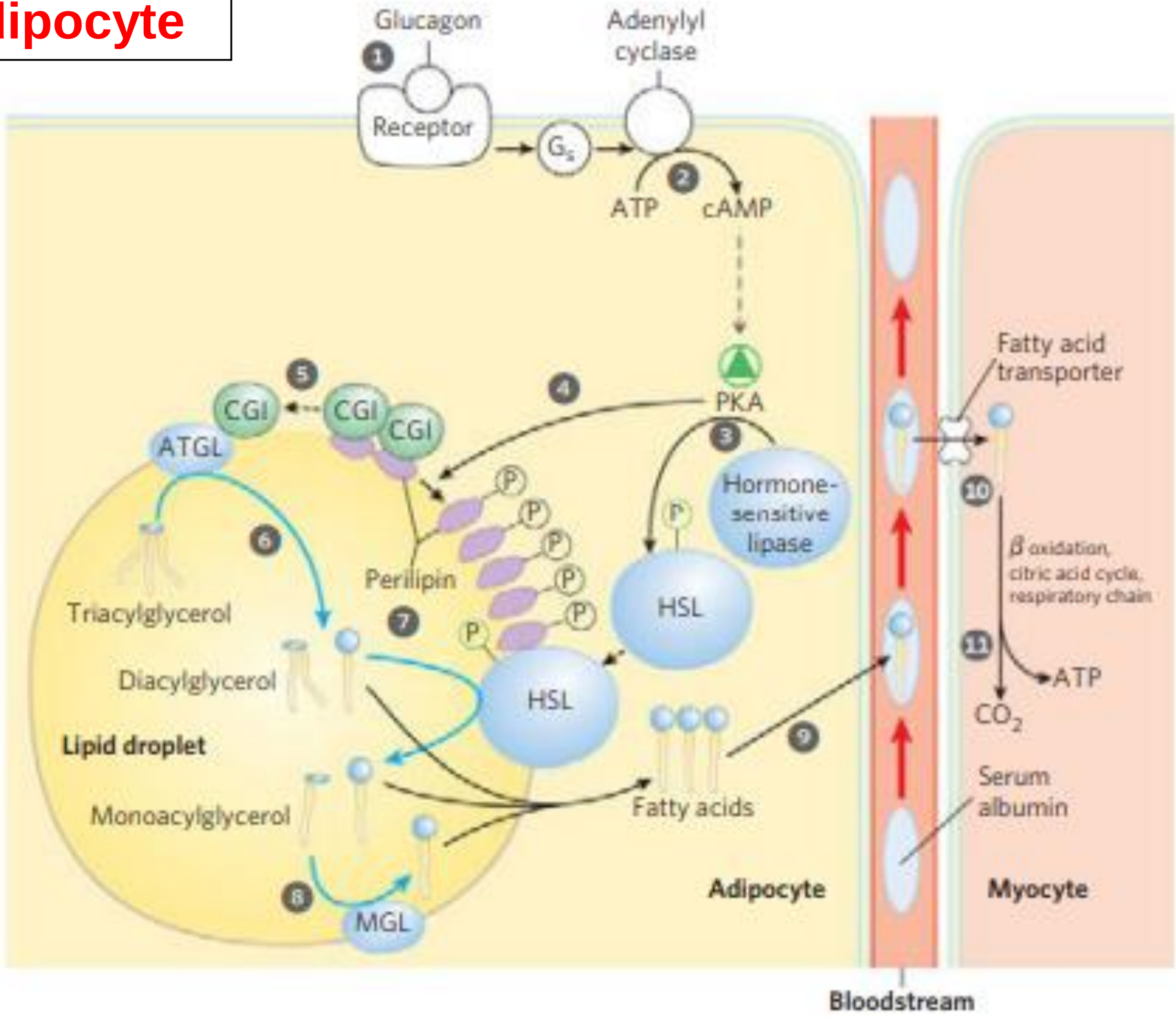
Mobilization of Stored Triacylglycerols from Adipocyte

Neutral lipids are stored in adipocytes in the form of lipid droplets, with a core of sterol esters and triacylglycerols surrounded by a monolayer of phospholipids.

The surface of these droplets is coated with perilipins, a family of proteins that restrict access to lipid droplets, preventing untimely lipid mobilization.

When hormones signal the need for metabolic energy, triacylglycerols stored in adipose tissue are mobilized (brought out of storage) and transported to tissues (skeletal muscle, heart, and renal cortex) in which fatty acids can be oxidized for energy production.

The hormones epinephrine and glucagon, secreted in response to low blood glucose levels or impending activity, stimulate the enzyme adenylyl cyclase in the adipocyte plasma membrane



Hormones Trigger

Low blood glucose levels

The hormones epinephrine and glucagon,

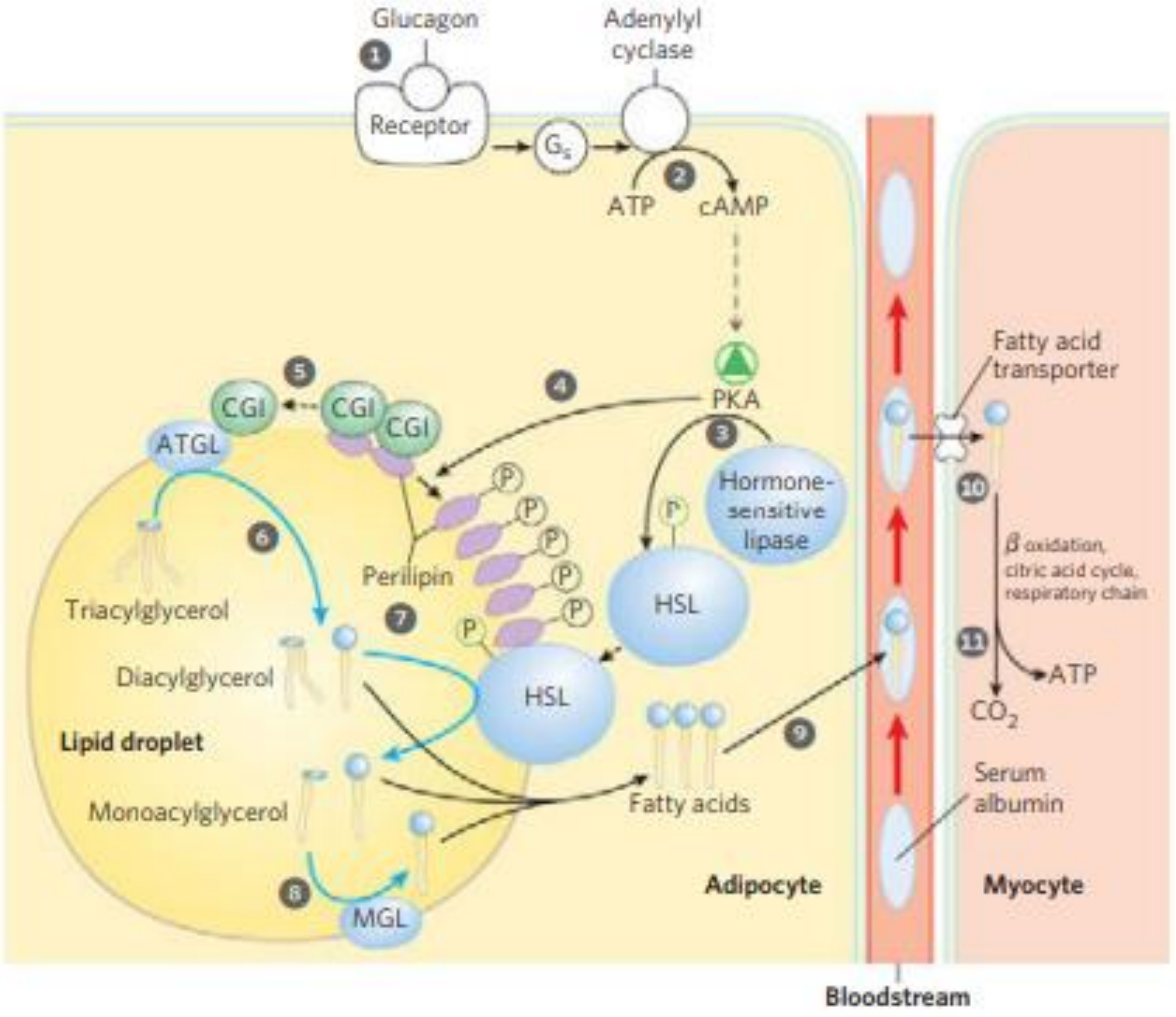
stimulate the enzyme adenylyl cyclase in the adipocyte plasma membrane

via a G protein, to produce cAMP.

cAMP activates PKA

PKA phosphorylates:

- the hormone-sensitive lipase (HSL)
- perilipin molecules on the surface of the lipid droplet.

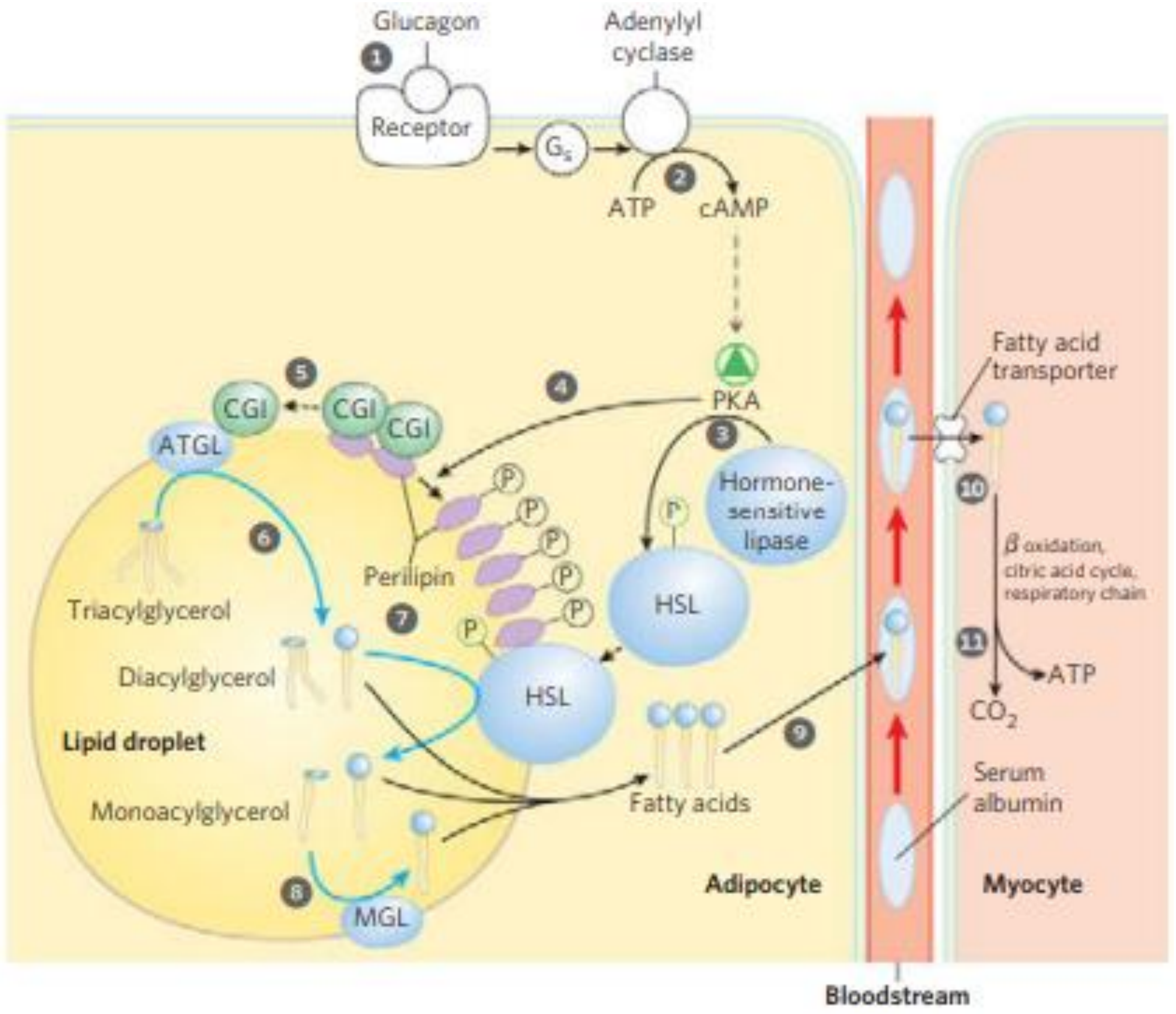


Phosphorylation of perilipin causes

Dissociation of the protein CGI from perilipin.

CGI associates with the enzyme adipose triacylglycerol lipase (ATGL), activating it.

Active ATGL converts triacylglycerols to diacylglycerols



Phosphorylated perilipin associates with phosphorylated HSL, allowing it access to the surface of the lipid droplet

HSL converts diacylglycerols to monoacylglycerols.

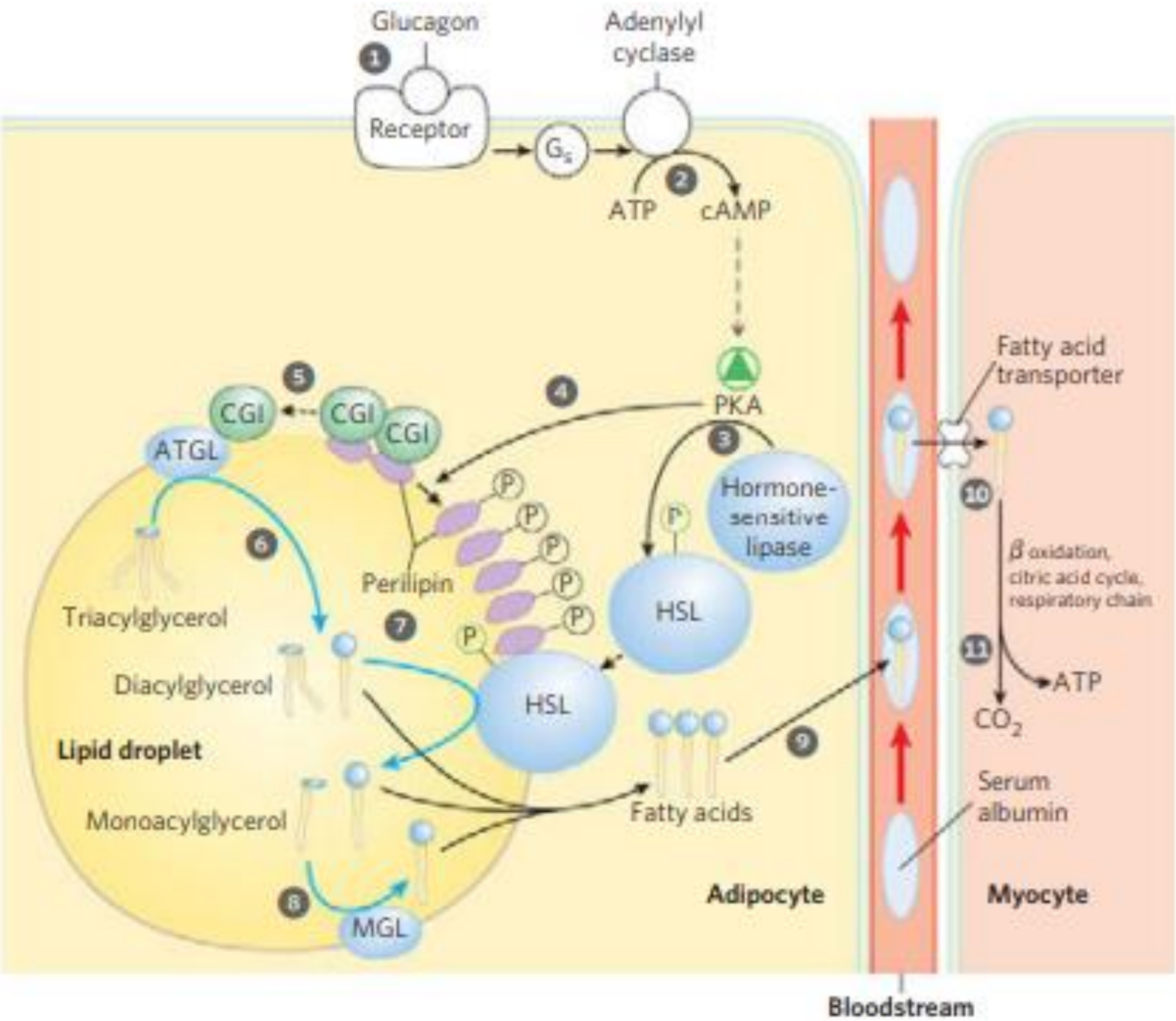
Monoacylglycerol lipase (MGL) hydrolyzes monoacylglycerols

Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood;

They are released from the albumin and enter a myocyte via a specific fatty acid transporter.

The glycerol released by lipase action is phosphorylated

Hormone-sensitive lipase (HSL)



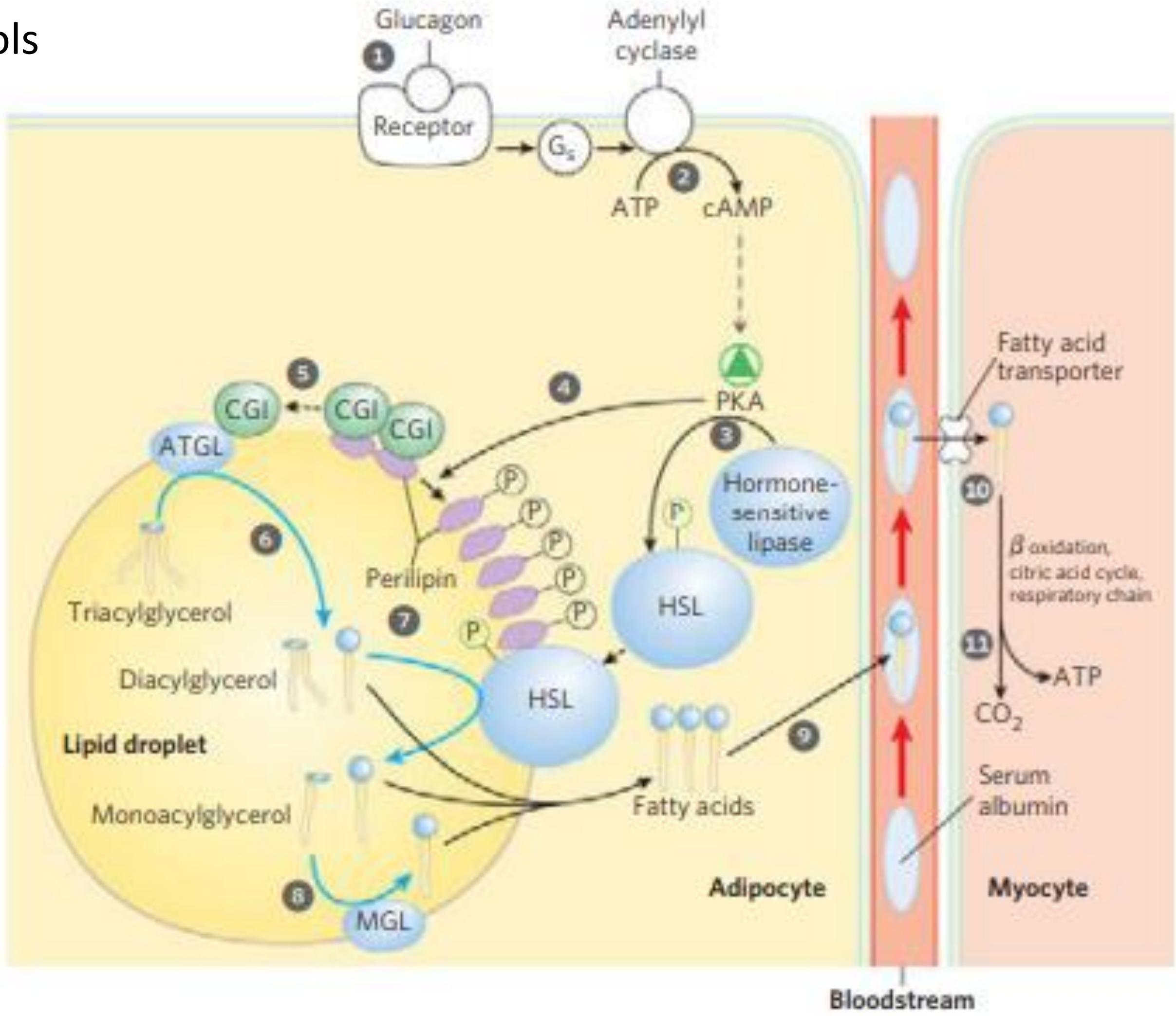
In the myocyte, fatty acids are oxidized to CO_2, and the energy of oxidation is conserved in ATP, which fuels muscle contraction and other energy-requiring metabolism in the myocyte

LIPASES

- Triacylglycerol lipase (ATGL) triacylglycerols to diacylglycerols

- Hormone-sensitive lipase (HSL) converts diacylglycerols to monoacylglycerols.

- Monoacylglycerol lipase (MGL) hydrolyzes monoacylglycerols



Fatty acids (free fatty acids, FFA) leave the adipocyte, bind serum albumin in the blood, and are carried in the blood;

They are released from the albumin and enter a myocyte via a specific fatty acid transporter.

Serum albumin:
(Mr 66,000), which makes up about half of the total serum protein, noncovalently binds as many as 10 fatty acids per protein monomer.

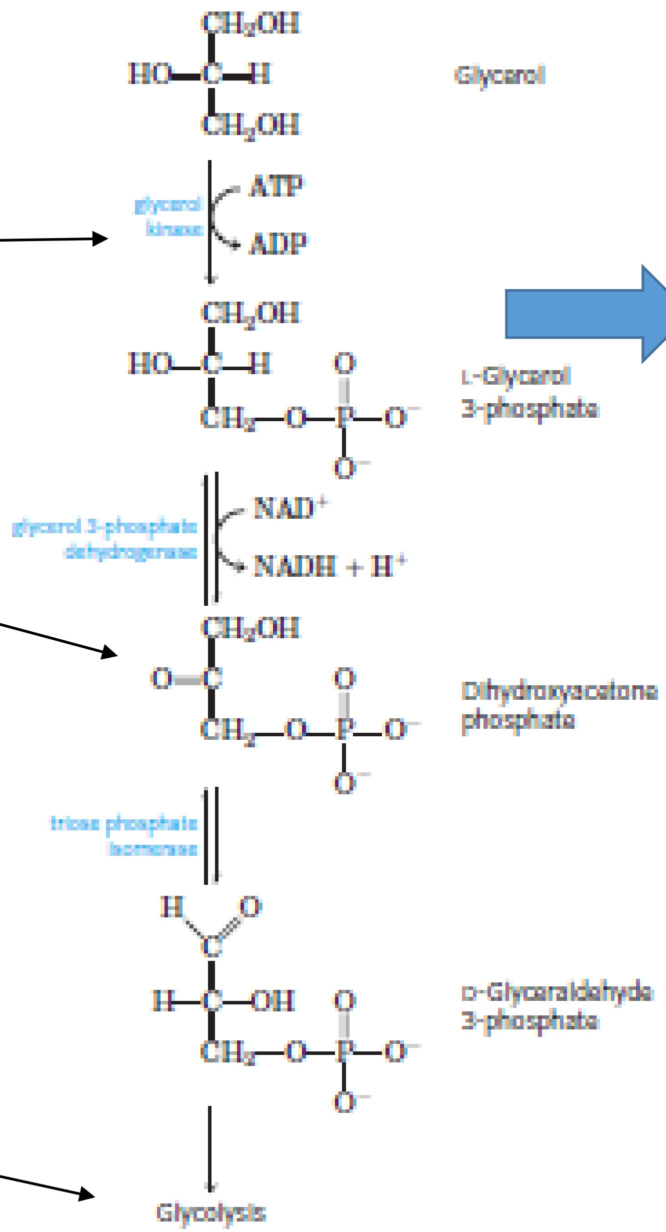
Glycerol released by the lipase undergoes a different pathway

Glycerol is used by the liver to produce glycerol-3-phosphate, which can enter glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate

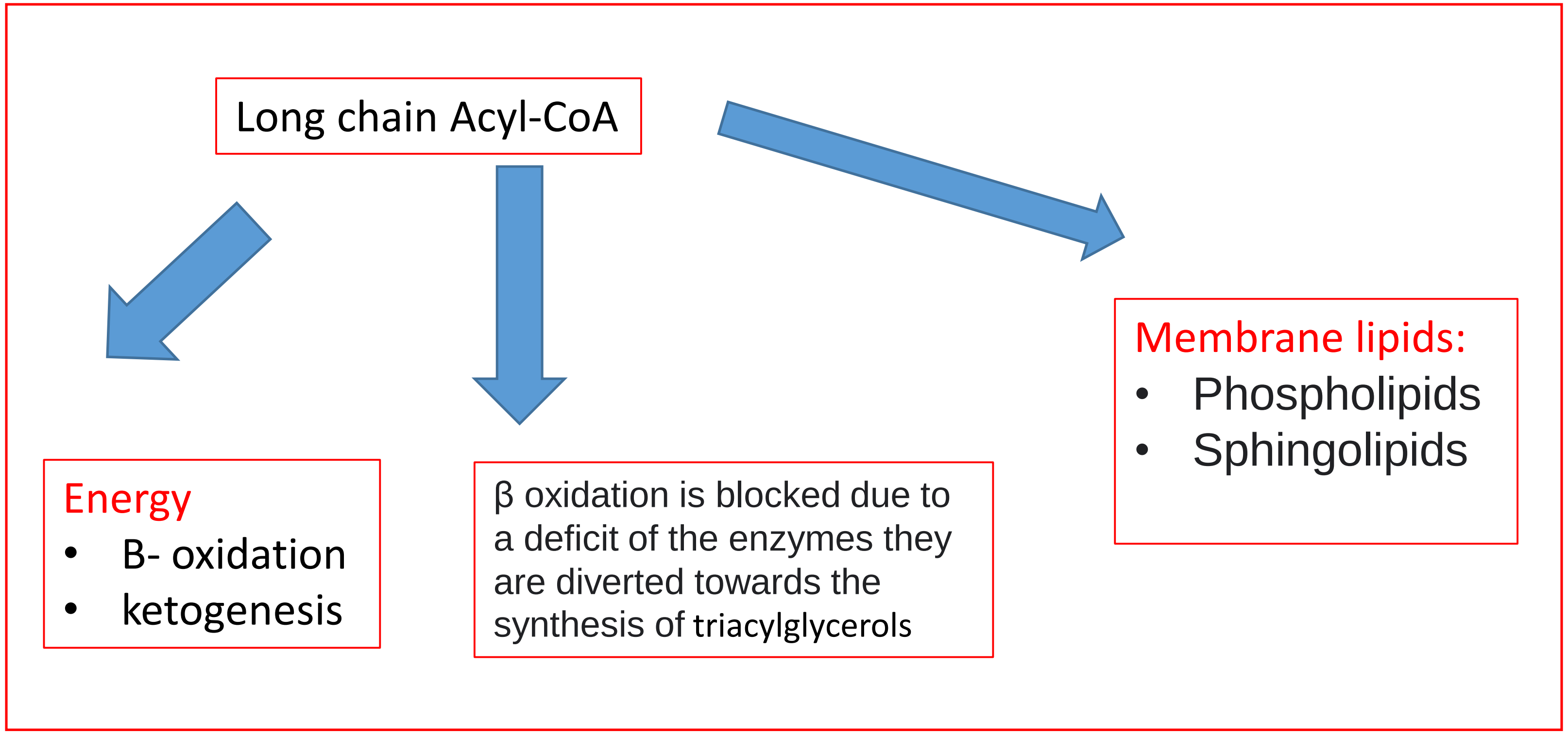
The glycerol released by lipase action is phosphorylated by **glycerol kinase**

glycerol 3-phosphate is oxidized to dihydroxyacetone phosphate.

The glycolytic enzyme triose phosphate isomerase converts this compound to glyceraldehyde 3-phosphate, which is oxidized via glycolysis.



triacylglycerol or phospholipid synthesis.


Long chain Acyl-CoA
Energy
• B- oxidation
• ketogenesis
β oxidation is blocked due to a deficit of the enzymes they are diverted towards the synthesis of triacylglycerols
Membrane lipids:
• Phospholipids
• Sphingolipids

Oxidation of Fatty Acids

The enzymes of fatty acid oxidation in animal cells are located in the mitochondrial matrix,

β oxidation (oxidation at β carbon atom)

Fats consumed in the diet

Fats stored in cells as lipid droplets

Fats synthesized in one organ for export to another.

Energy source for liver, heart, resting skeletal muscle, hibernating animals, migrating birds.

Oxidation of Fatty Acids occurs into mitochondrial matrix:

- fatty acids with chain lengths of 12 carbon atoms enter mitochondria without membrane transporters

- fatty acids with 14 or more carbon atoms are transported by the shuttle system

The fatty acids released to the tissues

entry into mitochondria via the acyl-carnitine/ carnitine transporter.

Fatty acids in the cell must be activated

By binding the CoA (which makes them water-soluble and metabolically active)

Fatty acids destined for mitochondrial oxidation

Carnitine shuttle

-3 enzymatic reactions:

(1) Acyl-CoA sintethase → Conversion of a fatty acid to a fatty acyl–CoA

(2)(3) Carnitine palmitil/Acyltransferase I and II

The first reaction is catalyzed by a family of isozymes (different isozymes specific for fatty acids having short, intermediate, or long carbon chains) present in the outer mitochondrial membrane, the **acyl- CoA synthetases**, which promote the general reaction

Fatty acid + CoA + ATP-> fatty acyl–CoA + AMP + PP_i

(1) Acyl-CoA sintethase

Conversion of a fatty acid to a fatty acyl–CoA.

(outer mitochondrial membrane)

Catalyzed by fatty acyl–CoA synthetase and inorganic pyrophosphatase.

Occurs in two steps

The overall reaction is highly exergonic:

Fatty acid + CoA + ATP - > fatty acyl–CoA + AMP + PPi

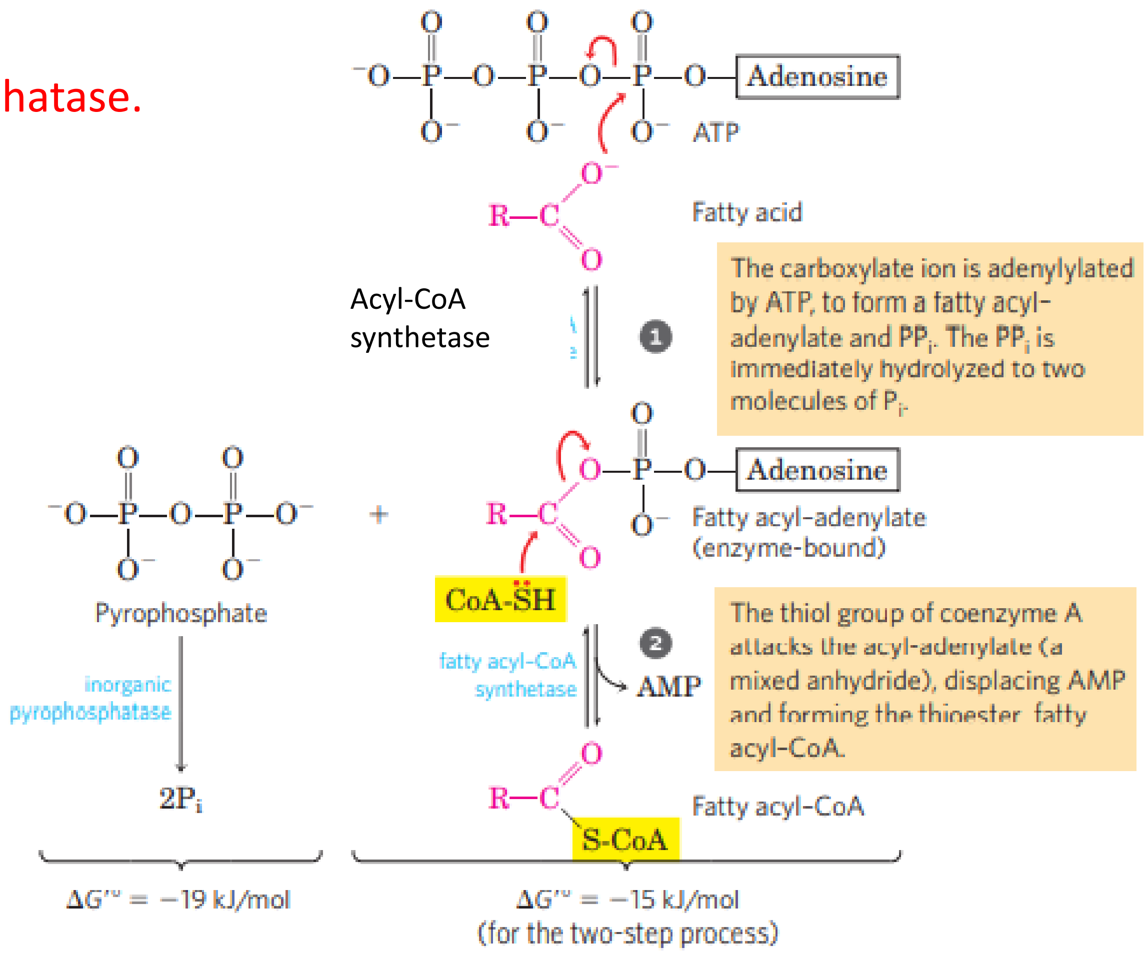
The reaction occurs in two steps and involves a fatty acyl–adenylate intermediate.

Fatty acyl–CoAs are high-energy compounds

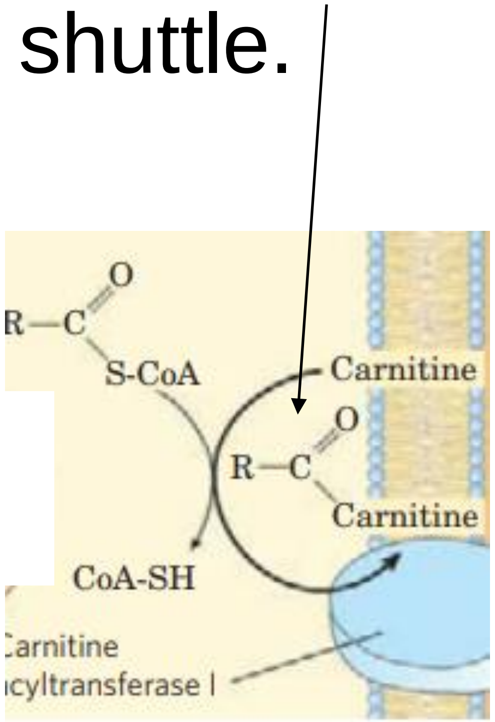
Hydrolysis (-31 kJ/mol).

The formation of a fatty acyl–CoA is made more favorable by the hydrolysis of two high-energy bonds in ATP;

Pyrophosphate formed is immediately hydrolyzed by inorganic pyrophosphatase .



Fatty acyl-CoA destined for mitochondrial oxidation are transiently attached to the hydroxyl group of **carnitine** to form fatty acyl–carnitine—the second reaction of the shuttle.

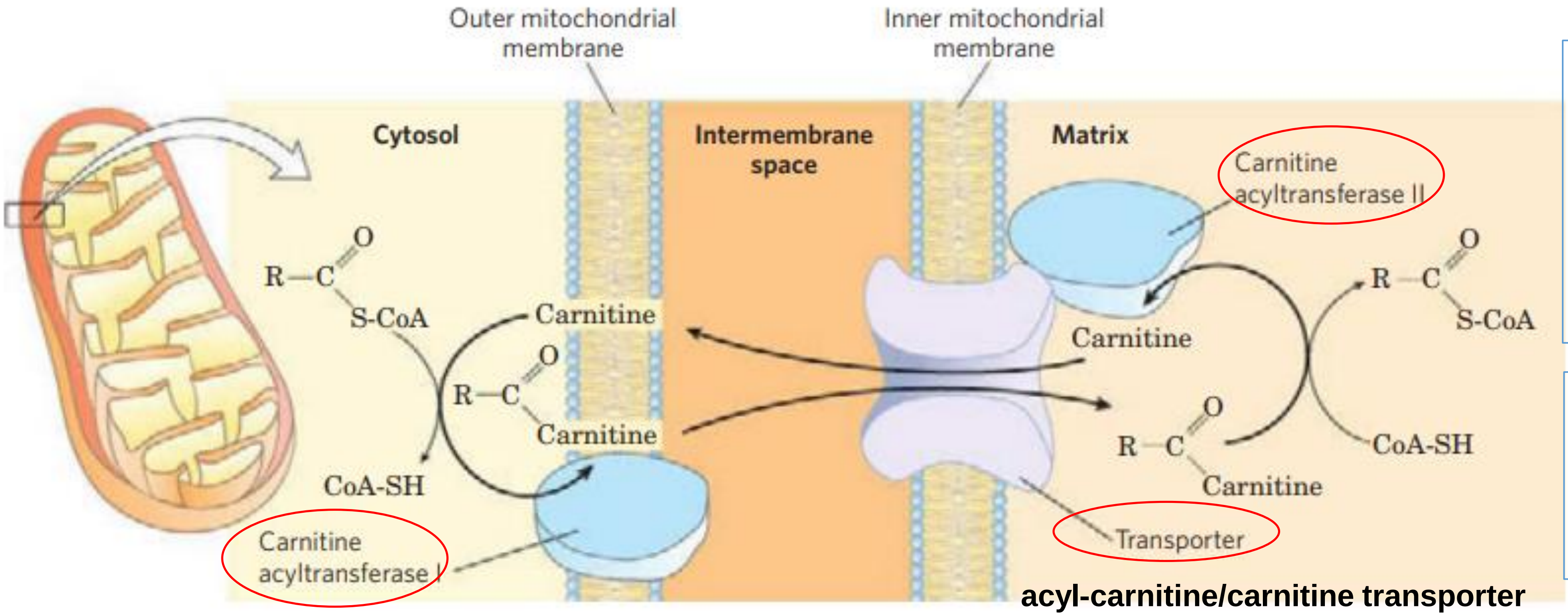


(2)(3) Carnitine palmitil/Acyltransferase I and II

Fatty acids destined for mitochondrial oxidation are transiently attached to the hydroxyl group of **carnitine** to form fatty acyl–carnitine (second reaction).

Acyltransferase I at the outer membrane or in the intermembrane space

Fatty acyl–carnitine moves into the matrix by facilitated diffusion through the transporter in the inner membrane



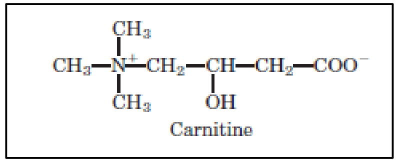
acyl-carnitine/carnitine transporter

In matrix, the acyl group is transferred to mitochondrial coenzyme A By Carnitine Acyltransferase II

Carnitine to return to the intermembrane space through the same transporter

.Acyltransferase I is inhibited by malonyl-CoA, the first intermediate in fatty acid synthesis

IMPORTANT : to prevents the simultaneous synthesis and degradation of fatty acids.



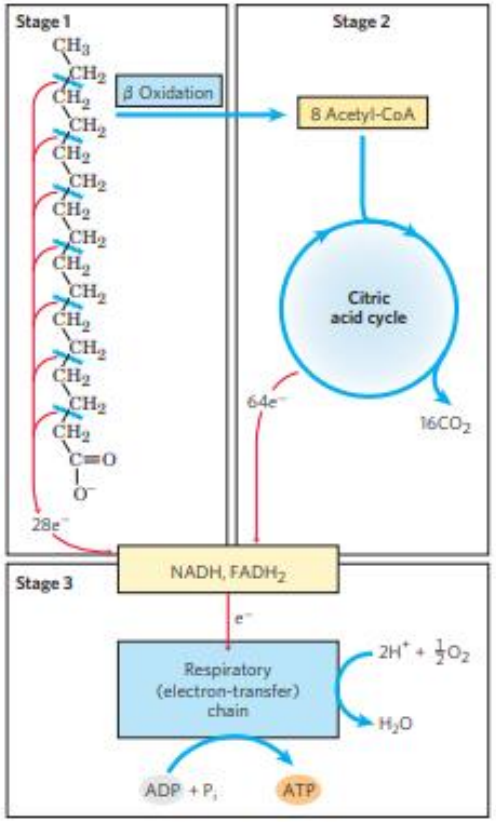
B- Oxidation of Fatty Acids

Mitochondrial oxidation of fatty acids takes place in three stages

First stage:

Oxidative phase: removal of two carbon units as Acetyl-CoA

β oxidation:



Fatty acids undergo oxidative removal of successive two-carbon units in the form of acetyl-CoA, starting from the carboxyl end of the fatty acyl chain.

Palmitic acid (16-carbon atoms) undergoes 7 passes through the oxidative sequence, in each pass losing two carbons as acetyl-CoA.

At the end of seven cycles the last two carbons of palmitate (originally C-15 and C-16) remain as acetyl-CoA.

The overall result is the conversion of the 16-carbon chain of palmitate to **eight two-carbon acetyl groups** of acetyl-CoA molecules.

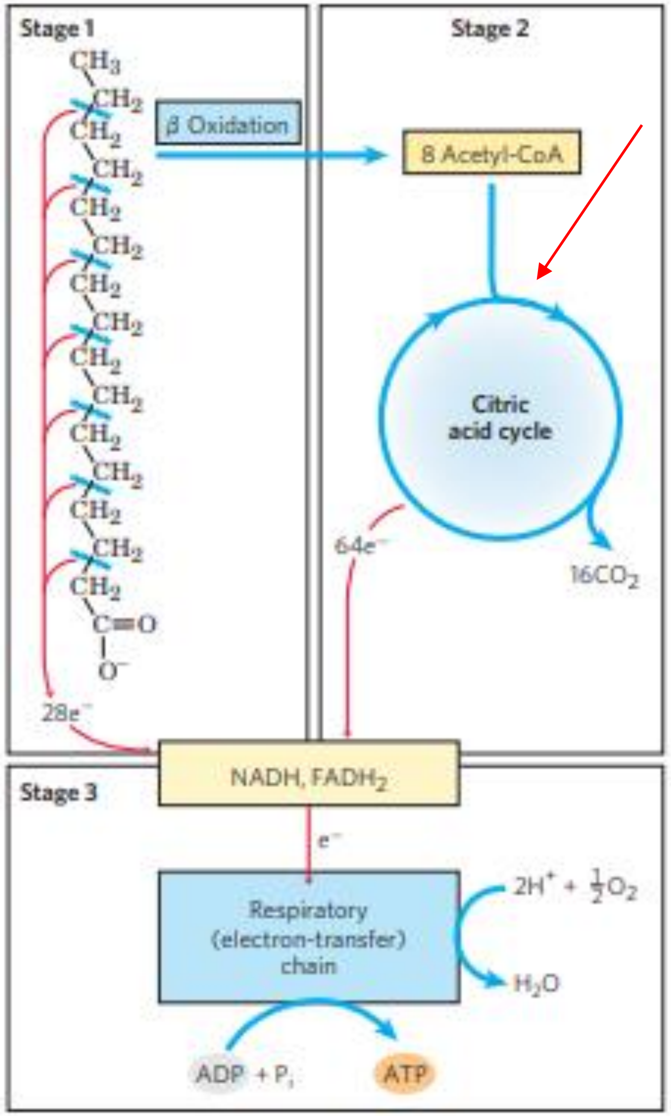
Formation of each acetyl-CoA requires removal of four hydrogen atoms (two pairs of electrons and four H+).

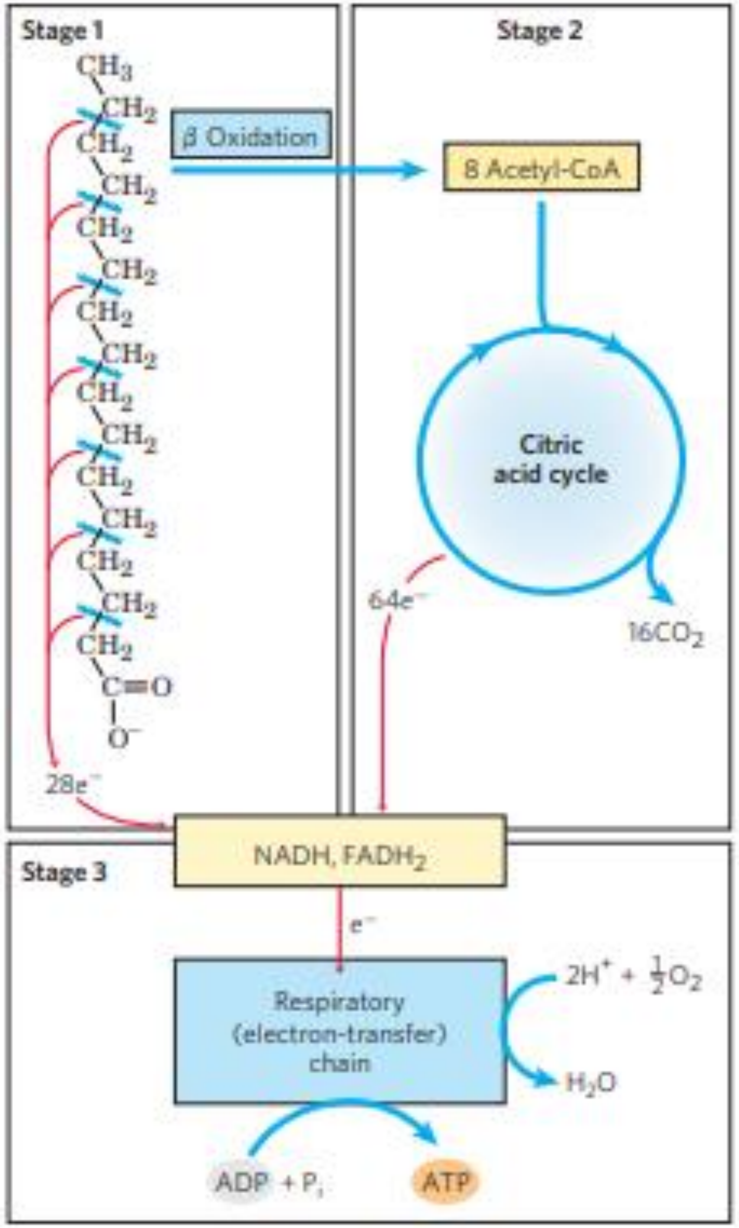
Oxidation of Fatty Acids

Second stage

Acetyl groups of acetyl-CoA are oxidized to CO_2 in the citric acid cycle, which also takes place in the mitochondrial matrix.

- Stage 1 and stage 2 produce the reduced electron carriers NADH and $FADH_2$
- Stage 3 donate electrons to the mitochondrial respiratory chain.
- Electrons pass to oxygen with the concomitant phosphorylation of ADP to ATP
- The energy released by fatty acid oxidation is thus conserved as ATP.





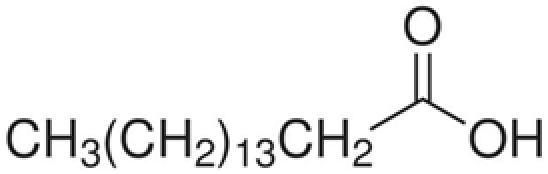
Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA.
This process is called oxidation.

Stage 2: The acetyl groups are oxidized to CO2 via the citric acid cycle.

Stage 3: Electrons derived from the oxidations of stages 1 and 2 pass to O_2 via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation

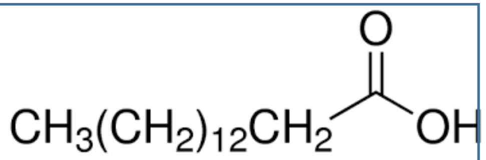
The β Oxidation has different reactions in:

- Saturated Fatty Acids

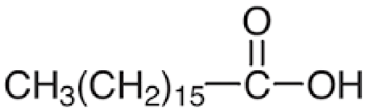


Palmytic acid

- Oxidation of Odd-Number Fatty Acids

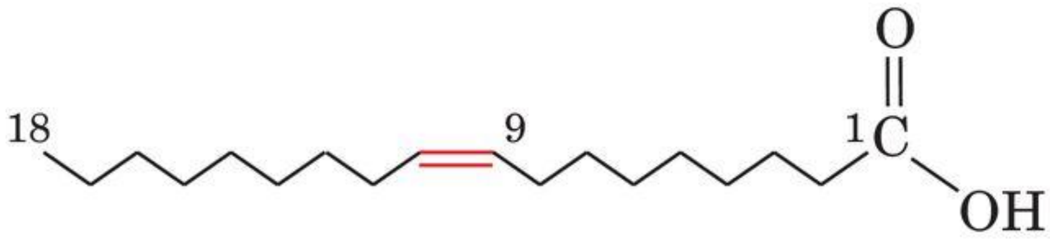


pentadecanoic acid



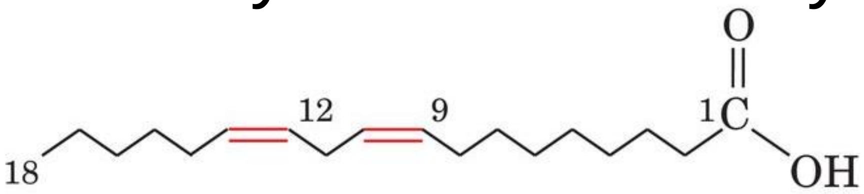
heptadecanoic acid

- Oxidation of Unsaturated fatty acids
- Oxidation of Monounsaturated fatty acids



Oleic acid
(9-*cis*-octadecenoic acid)

- Oxidation of a Polyunsaturated fatty acids



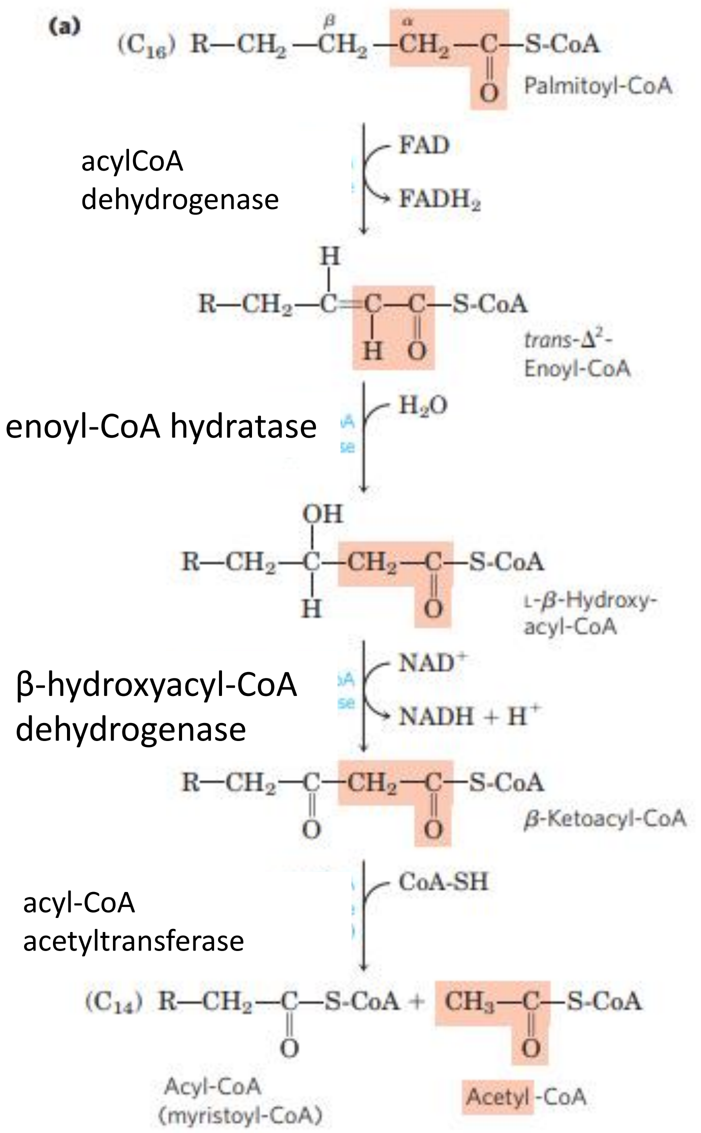
Linoleic acid
(9,12-*cis*-octadecadienoic acid)

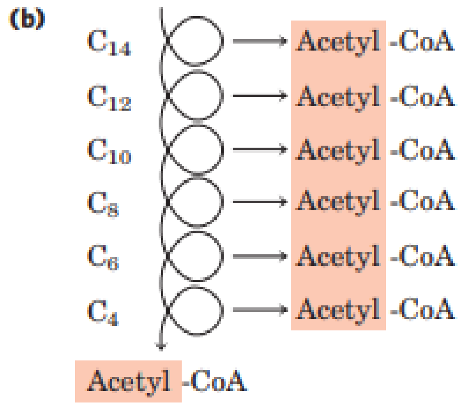
The β Oxidation of Saturated Fatty Acids Has Four Basic Steps

Palmitate (C16), which enters as palmitoyl-CoA.

Four enzyme-catalyzed reactions make up the first stage of fatty acid oxidation

In each pass through this four-step sequence, one acetyl residue (shaded in pink) is removed in the form of acetyl-CoA from the carboxyl end of the fatty acyl chain





(b) Six more passes through the pathway yield seven more molecules of acetylCoA, the seventh arising from the last two carbon atoms of the 16-carbon chain.

8 molecules of acetyl-CoA are formed in all.

Reaction 1

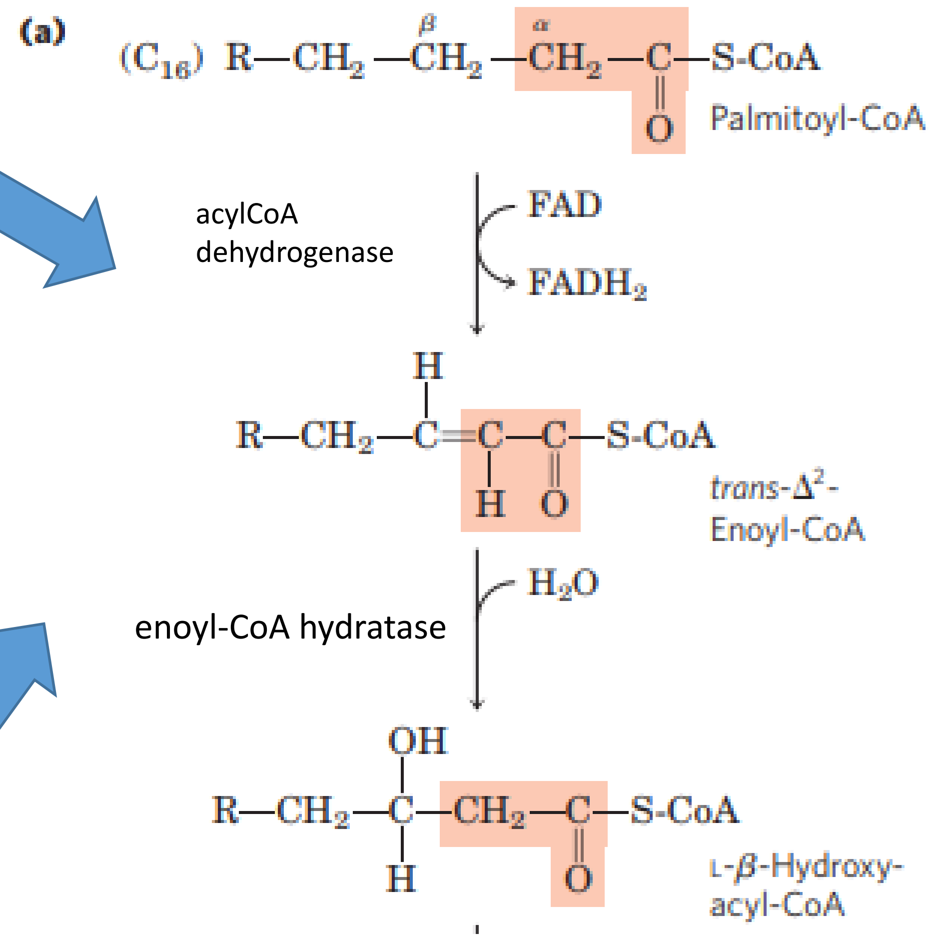
Acyl-CoA dehydrogenase

- Enzyme is bound to the inner membrane
- A double bond is introduced between the α and β carbon atoms
- (C-2 and C-3),
- FAD is the electron acceptor -------→ (1.5 ATP molecules).

Reaction 2

Enoyl-CoA hydratase

- H_2O is added to the double bond of the trans-Δ^2 -enoyl-CoA to form the L stereoisomer of β-hydroxyacyl-CoA (3-hydroxyacyl-CoA).



Reaction 3

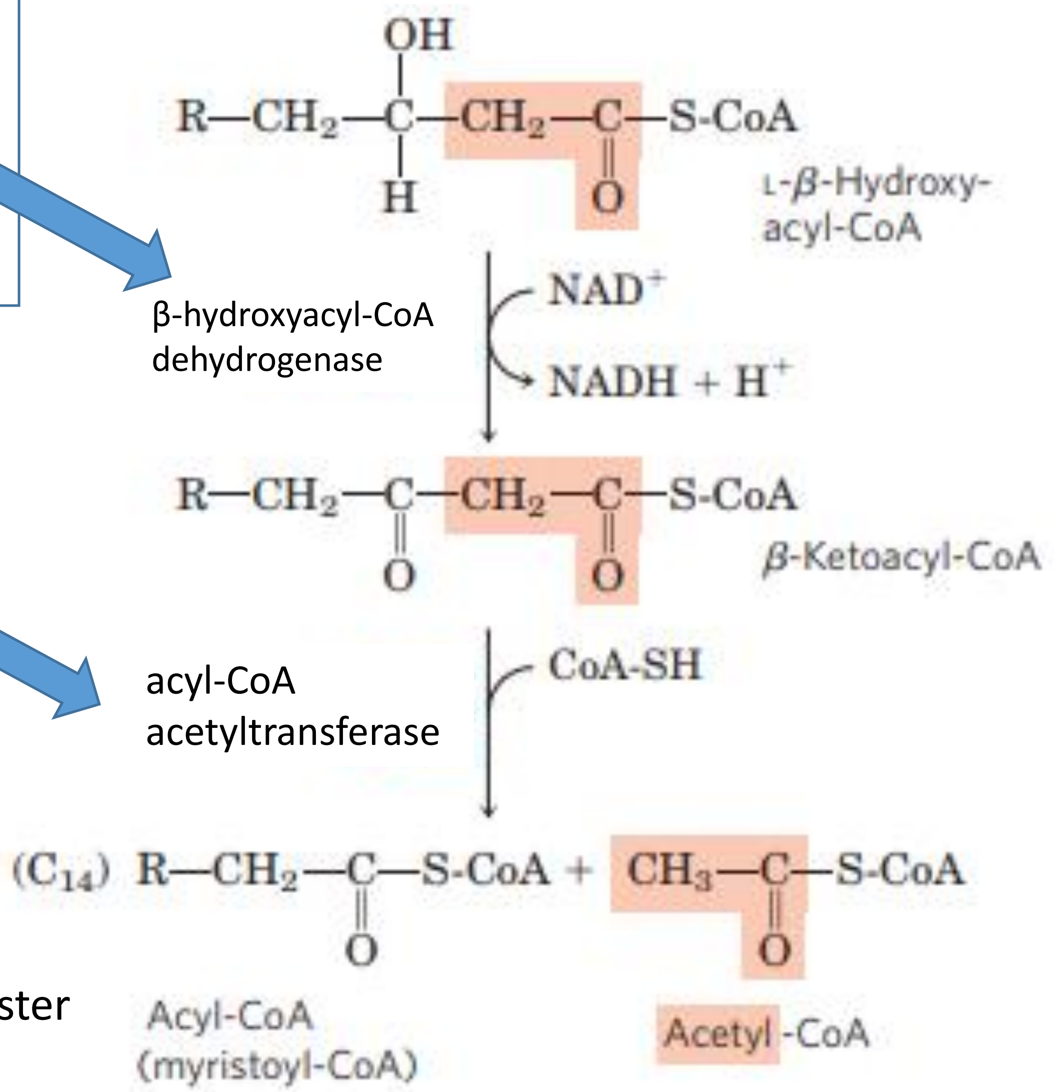
β-hydroxyacyl-CoA dehydrogenase

- Dehydrogenation
- NAD^+ is the electron acceptor --→ (2,5 ATP molucules)

Reaction 4

Acyl-CoA acetyltransferase (thiolase)

- Reaction of β-ketoacyl-CoA with a molecule of free CoA (Thiolysis)

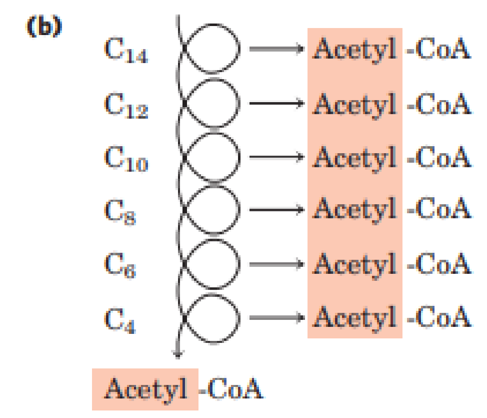


Coenzyme A thioester of the fatty acid

Palmitoyl-CoA + CoA + FAD + NAD^+ + H_2O -> myristoyl-CoA + acetyl-CoA + $FADH_2$ + NADH + H+

Palmitoyl-CoA + CoA + FAD + NAD+ + H2O -> myristoyl-CoA + acetyl-CoA + FADH2 + NADH + H+

Seven passes through the beta-oxidation sequence are required to oxidize one molecule of palmitoyl-CoA to eight molecules of acetyl-CoA:



The overall equation is

Palmitoyl-CoA + 7CoA + 7FAD + 7NAD$^+$ + 7H_2O $\rightarrow$ 8 acetyl-CoA + 7$FADH_2$ + 7NADH + 7H^+

The last three steps of this four-step sequence are catalyzed

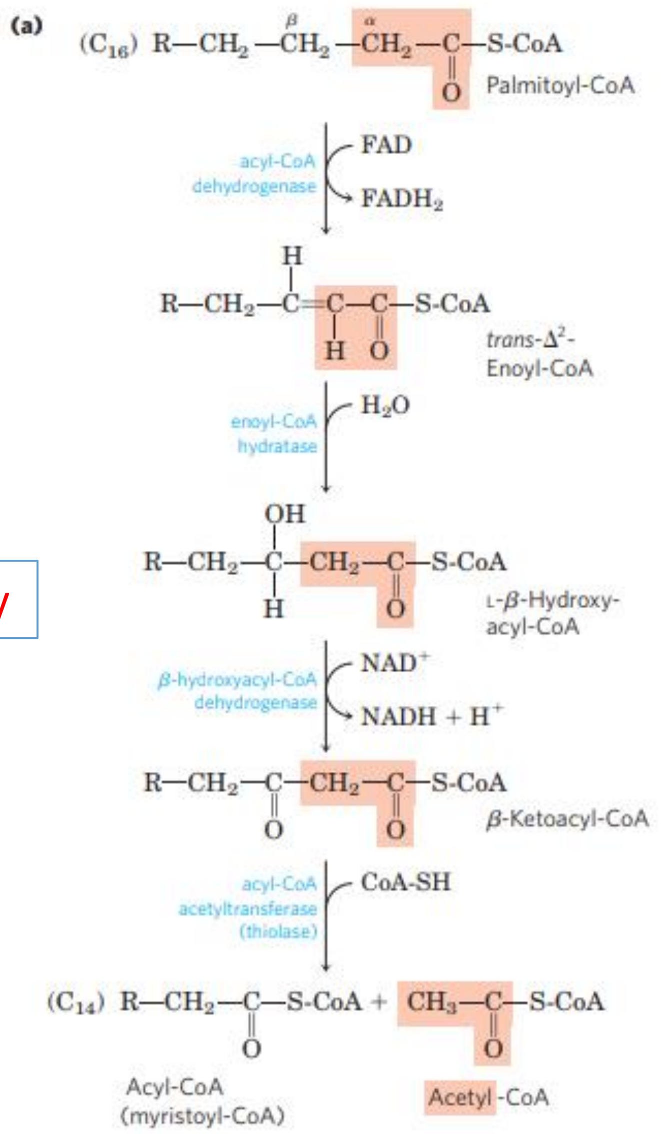
The reactions are catalyzed by a multienzyme complex associated with the inner mitochondrial membrane, the trifunctional protein (TFP).

Heterooctamer of $\alpha_4\beta_4$ subunits.

Each subunit α contains two activities,

Enoyl-CoA hydratase
β-hydroxyacyl-CoA dehydrogenase;

Each subunit β contains thiolase activity



The overall equation is

Palmitoyl-CoA + 7CoA + 7FAD + 7NAD$^+$ + 7H_2O → 8 acetyl-CoA + 7$FADH_2$ + 7NADH + 7H^+

$FADH_2$	1.5 molecules of ATP
NADH	2.5 molecules of ATP.

Thus 4 molecules of ATP are formed for each two-carbon unit removed in one pass through the sequence.

TABLE 17–1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

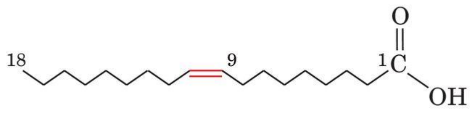
Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed*
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 526).

Oxidation of Monounsaturated Fatty Acids Requires An Additional Reaction

Double bonds in naturally unsaturated fatty acids are normally in the cis configuration.



Oleic acid
(9-*cis*-octadecenoic acid)

18 carbon atoms

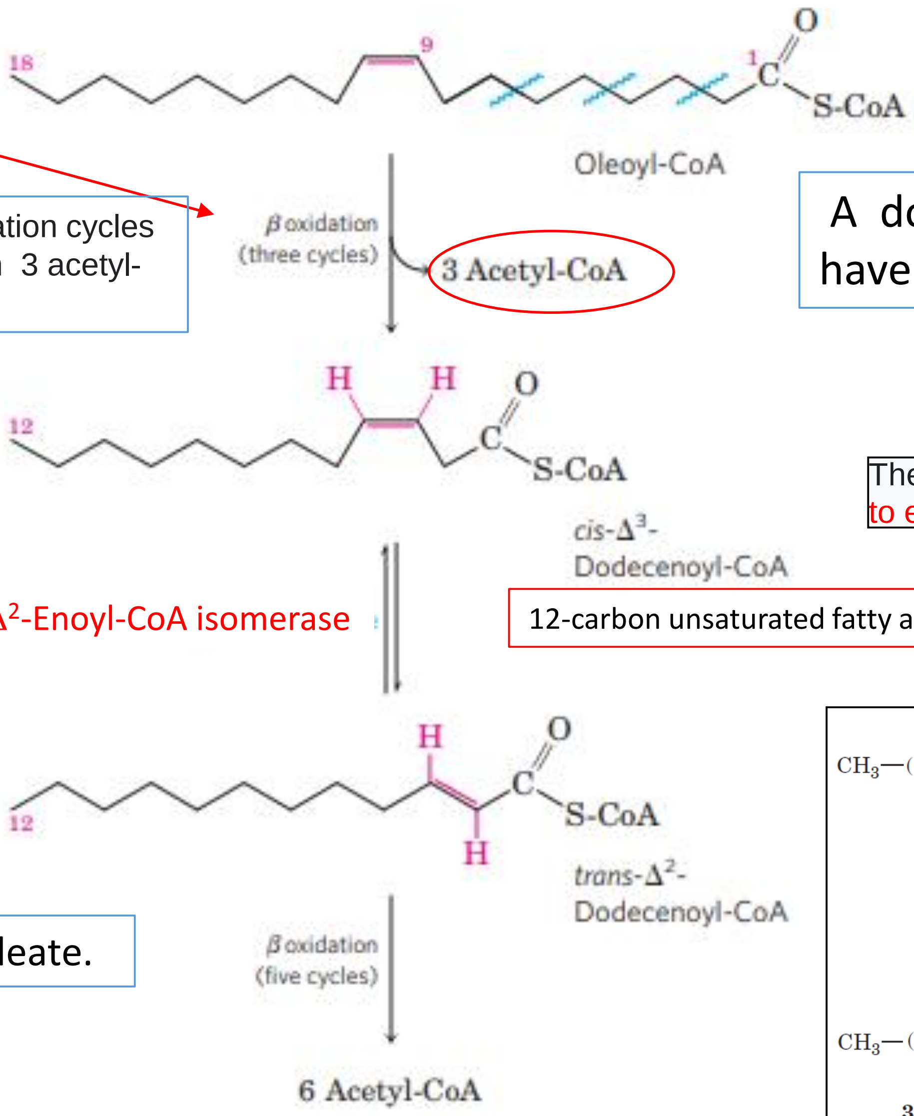
Oleic acid, as oleoyl-CoA (Δ^9)

Oxidation requires an additional enzyme:

Δ^3- Δ^2-Enoyl-CoA isomerase

Converted the cis isomer to a trans isomer (normal intermediate in β-oxidation)

- 3 oxidation cycles to form 3 acetyl-CoA

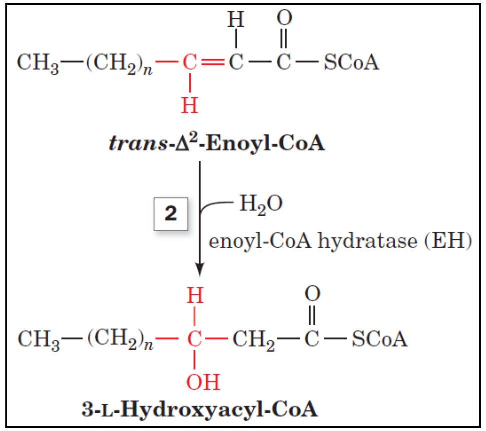


Δ^3- Δ^2-Enoyl-CoA isomerase

A double bond must have trans configuration

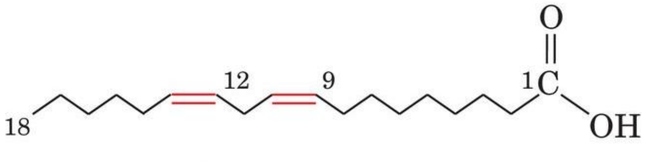
The cis double bond is resistant to enoyl-CoA hydratase

12-carbon unsaturated fatty acid,



9 acetyl-CoAs are produced from one molecule of the 18-carbon oleate.

Oxidation of a polyunsaturated fatty acid



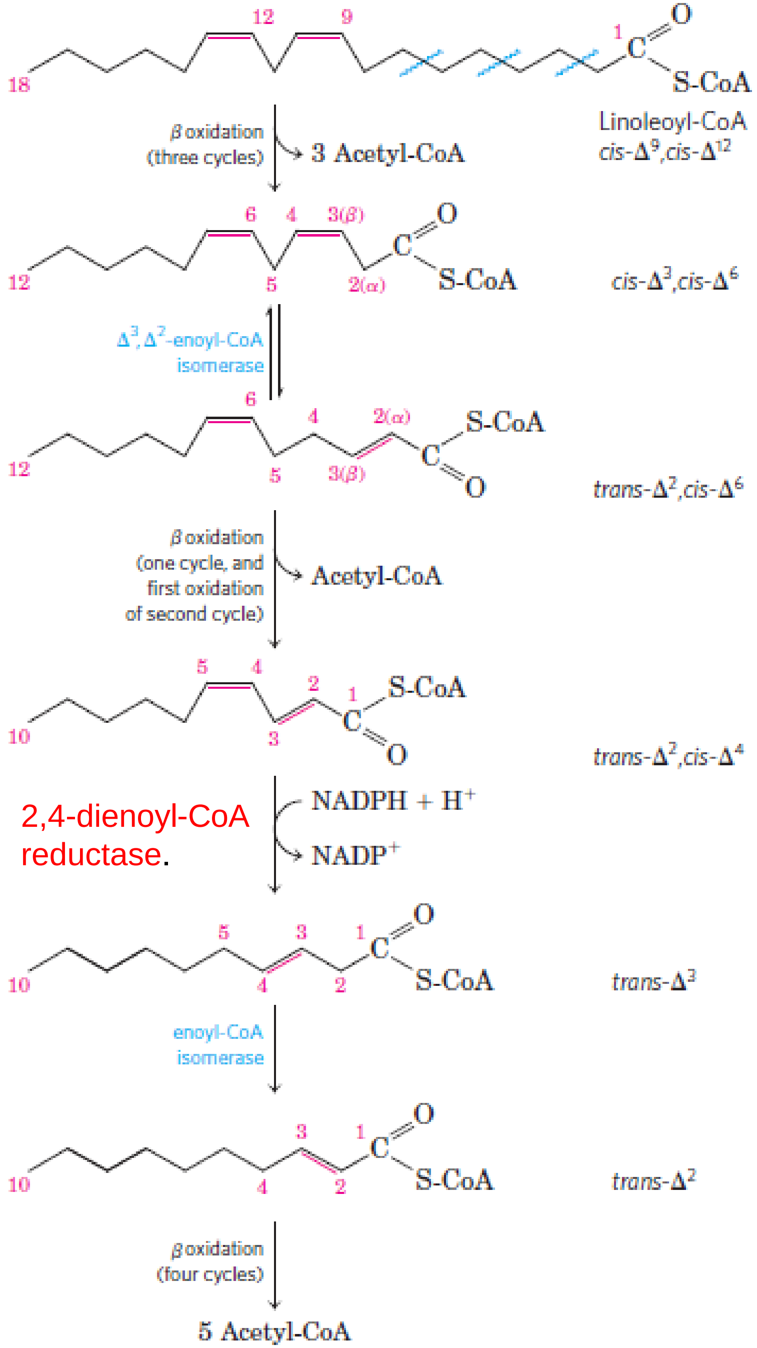
Linoleic acid
(9,12-*cis*-octadecadienoic acid)

Linoleoyl-CoA cis ($\Delta_{9,12}$).

Oxidation requires an enzyme in addition to enoyl-CoA isomerase:

NADPH-dependent 2,4-dienoyl-CoA reductase.

The combined action of these two enzymes converts a *trans*-Δ_2,*cis*-Δ_4-dienoyl-CoA intermediate to the *trans*-Δ_2-enoyl-CoA substrate necessary for oxidation.



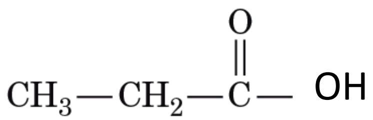
Oxidation of Odd-Number Fatty Acids

Most naturally lipids contain fatty acids with an even number of carbon atoms,

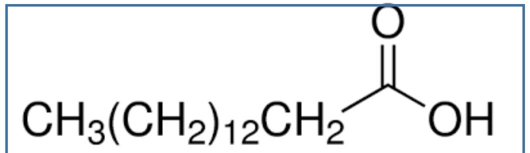
Fatty acids with an odd number of carbons are common in the lipids of many plants and some marine organisms.

Cattle and other ruminants form large amounts of the three-carbon during fermentation of carbohydrates in the rumen.

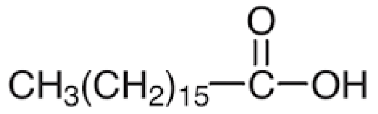
Small quantities of propionate are added as a mold inhibitor to some breads and cereals, thus entering the human diet



The propionate is absorbed into the blood and oxidized by the liver and other tissues.



pentadecanoic acid



heptadecanoic acid

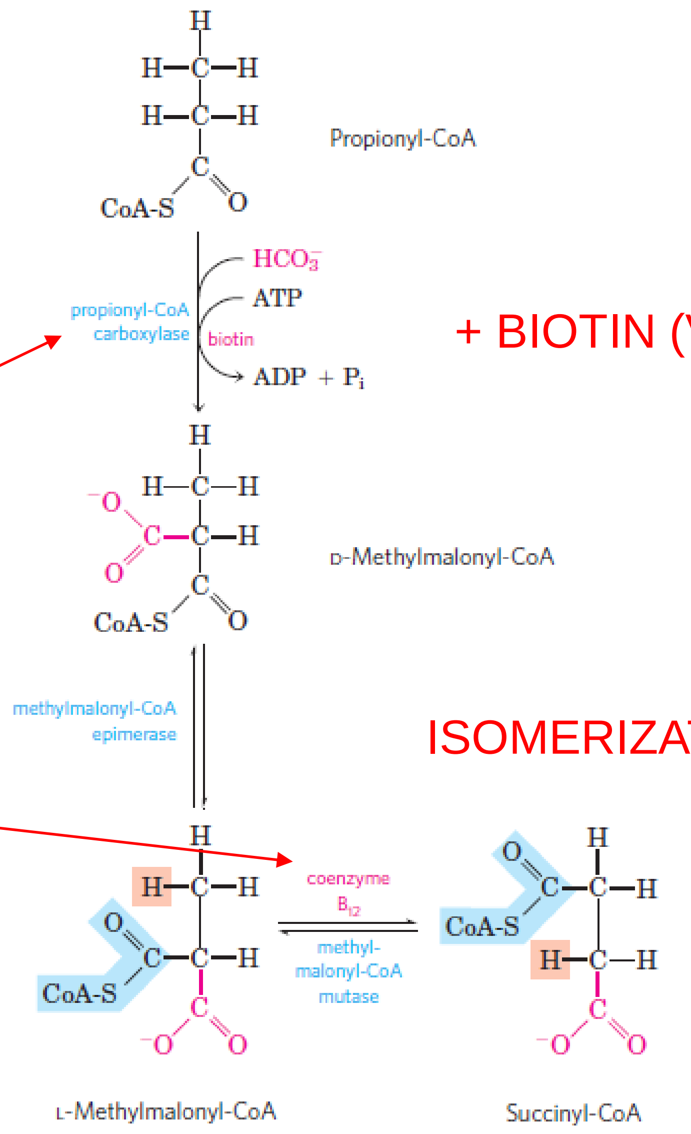
Oxidation of Odd-Number Fatty Acids

The last product of beta oxidation has 3 carbon atoms

Propionyl-CoA

Requires Three Enzyme:

- 1. propionyl-CoA carboxylase
- 2. methylmalonylCoA epimerase
- 3. methylmalonyl-CoA mutase



+ BIOTIN (Vitamin B8)

ISOMERIZATION

+ coenzyme B12

Krebs cycle,

Fatty Acid Oxidation Is Tightly Regulated

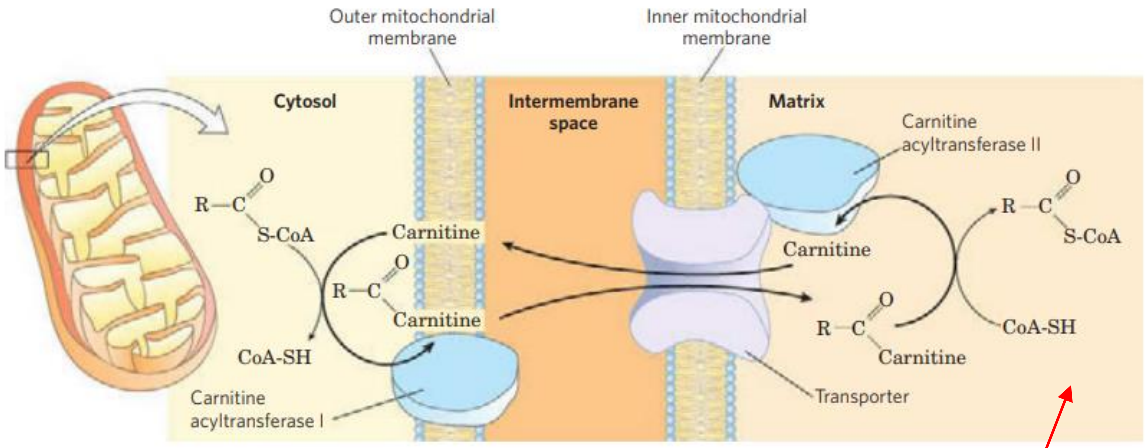
Oxidation of fatty acids is regulated so as to occur only when the need for energy requires it.

Fatty acyl–CoA formed in the cytosol has two major pathways open to it:

(1) β-oxidation by enzymes in mitochondria

(2) Conversion into triacylglycerols and phospholipids by enzymes in the cytosol.

Excess glucose that cannot be oxidized or stored as glycogen is converted in the cytosol into fatty acids for storage as triacylglycerol.



Acyltransferase I is inhibited by malonyl-CoA, the first intermediate in fatty acid synthesis

CoA into the mitochondrial matrix is rate limiting for fatty acid oxidation and is an important point of regulation

The inhibition of carnitine acyltransferase I by malonyl-CoA

Inhibits oxidation of fatty acids

Produce triacylglycerols from excess glucose

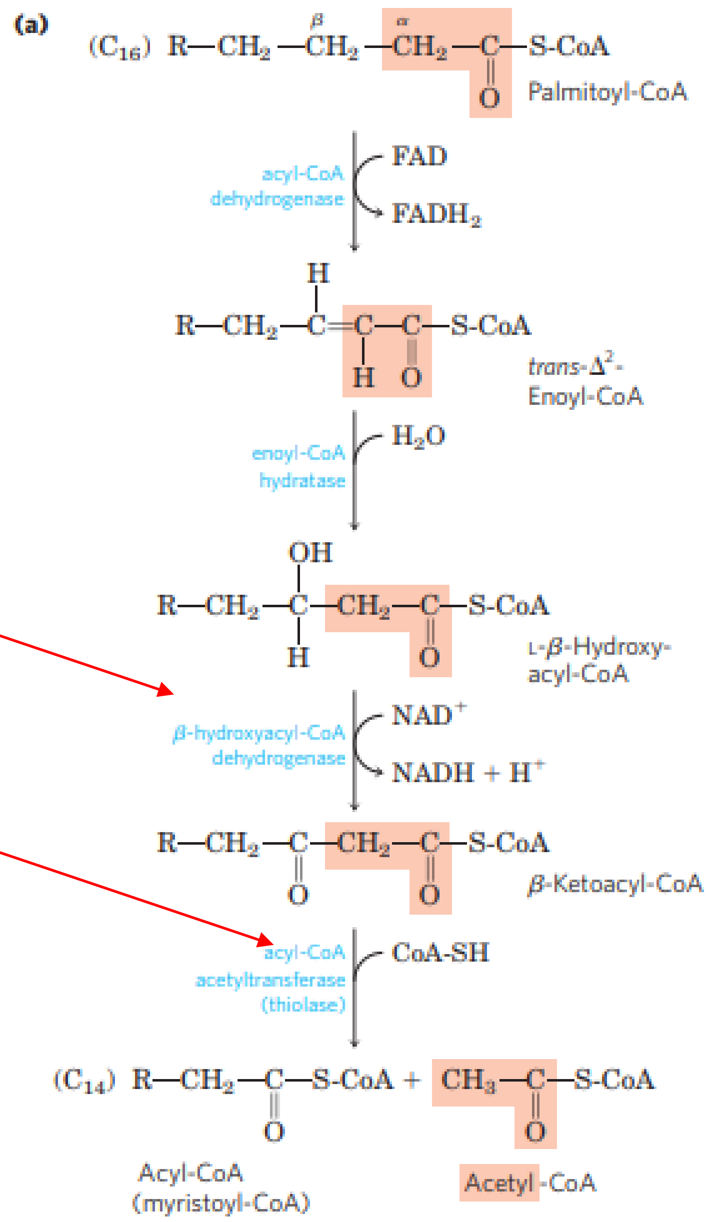
Two of the enzymes of β-oxidation are also regulated by metabolites that signal energy sufficiency.

[NADH]/[NAD+] ratio is high

↓

inhibited β- hydroxyacyl-CoA dehydrogenase

Acetyl-CoA is high → inhibited thiolase.



Coordinated regulation of fatty acid synthesis and breakdown

When the diet provides a ready source of carbohydrate as fuel, oxidation of fatty acids is unnecessary and is therefore downregulated.

Two enzymes are key to the coordination of fatty acid metabolism:

- acetyl-CoA carboxylase (ACC), the first enzyme in the synthesis of fatty acids
- -carnitine acyltransferase I, which limits the transport of fatty acids into the mitochondrial matrix for oxidation

Ingestion of a high-carbohydrate meal

raises the blood glucose level

When blood glucose levels drop between meals

Glucagon also triggers the mobilization of fatty acids in adipose tissue, a supply of fatty acids begins arriving in the blood.

triggers the release of insulin

Activates cAMP-dependent protein kinase (PKA),

Insulindependent protein phosphatase dephosphorylates ACC

PKA phosphorylates and inactivates ACC

Fatty acids enter the mitochondrial matrix and become the major fuel.

ACC catalyzes the formation of malonyl-CoA

Malonyl-CoA inhibits carnitine acyltransferase I, thereby preventing fatty acid entry into the mitochondrial matrix.