Lipid metabolism: b-oxidation

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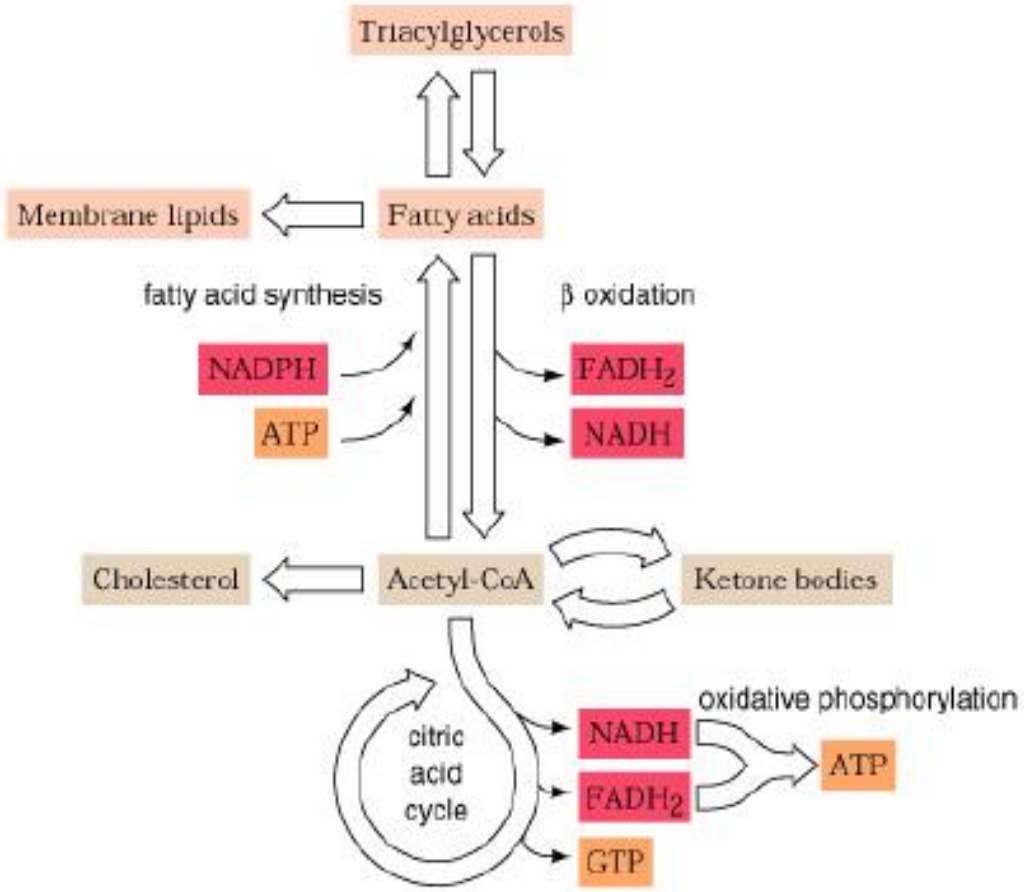
Lipid Metabolism – Summary

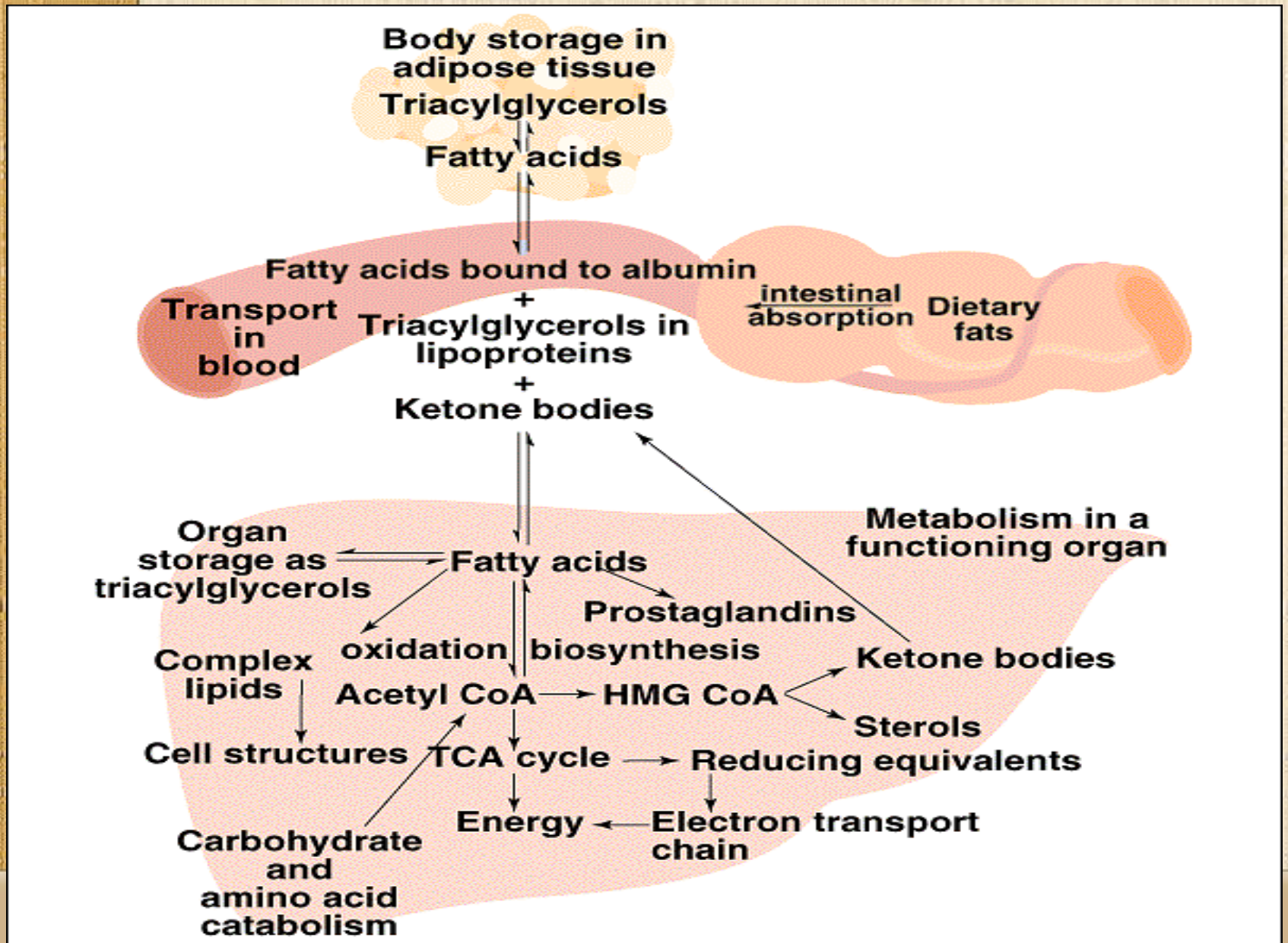


- Remember that triacylglycerols represent a very efficient means of storing energy.
- long alkyl chains are highly reduced, giving a high energy of complete oxidation
- ~38 kJ/g, more than twice that for carbohydrate or protein.
- Oxidation of one gram of fat yields 6 times more ATP molecules than oxidation of one gram of hydrated saccharide.

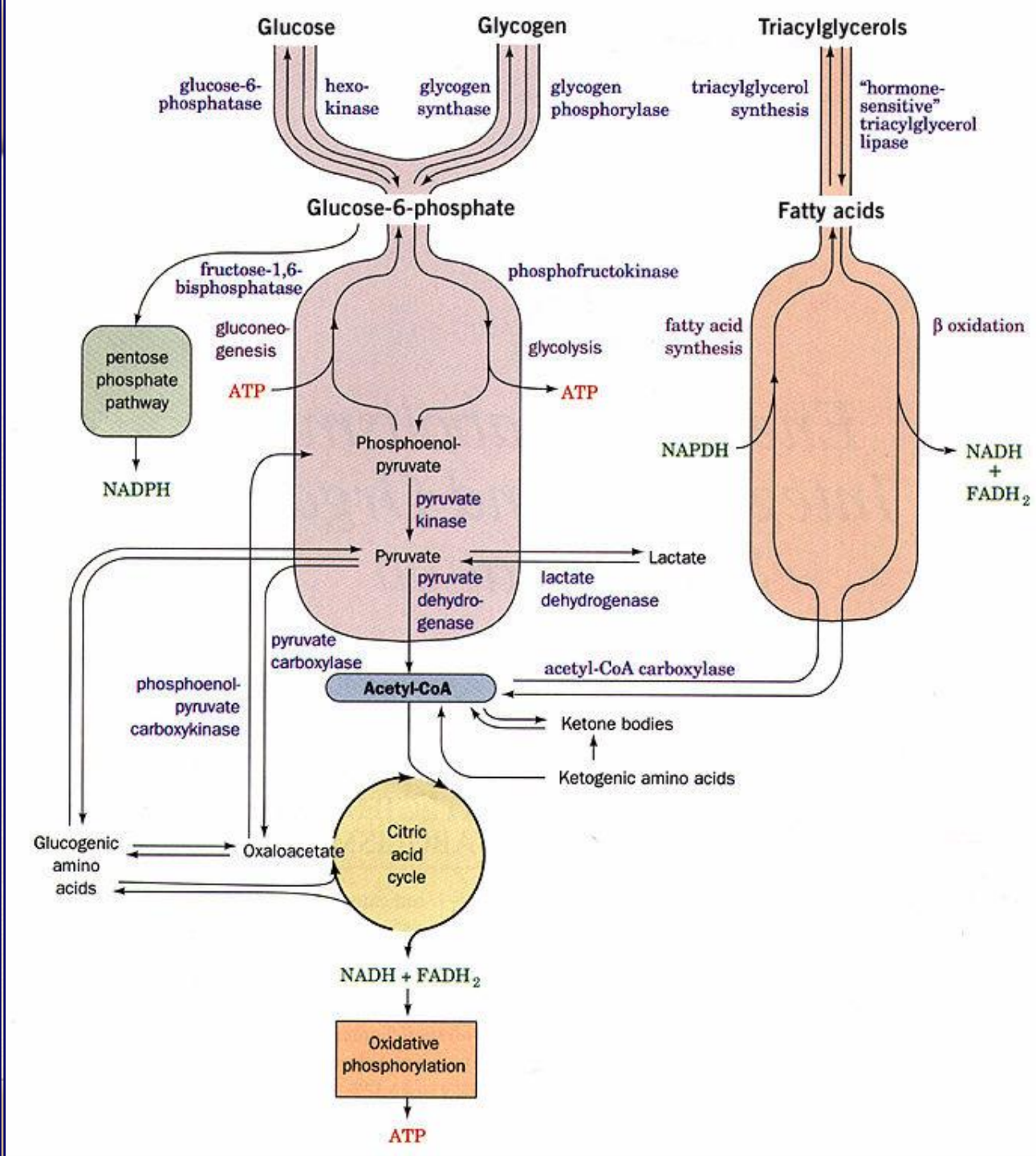
- very insoluble – they aggregate, so they do not raise the osmolarity of the solution in which they are stored.
- Further, they are unsolvated, reducing their mass relative to storage polysaccharides, in which the mass is effectively increased by as much as a factor of 3 because of the associated water.

- Chemically inert – they can be stored for long times without bad things happening.
- Here we examine the metabolic breakdown of fats.
- Two general parts to this process: first the fats are mobilized from their storage locations, then they are broken down in a process called **b-oxidation**.

OVERVIEW OF FATTY ACID AND TRIACYLGLYCEROL METABOLISM



Metabolism of Fatty Acids and Triacylglycerols and Relationship to Carbohydrate Metabolism



Triacylglycerols -- Efficient Energy Storage

- **Highly reduced, giving a very high energy of complete oxidation -- 38 kJ/g**
- **Very insoluble; aggregates do not raise osmolarity and do not have associated water to raise effective mass**
- **Chemically inert**

Mobilization of fat reserves

- In principle, cells can obtain fatty acids for fuel from three sources (and we use all three)

A. directly from fats consumed in the diet

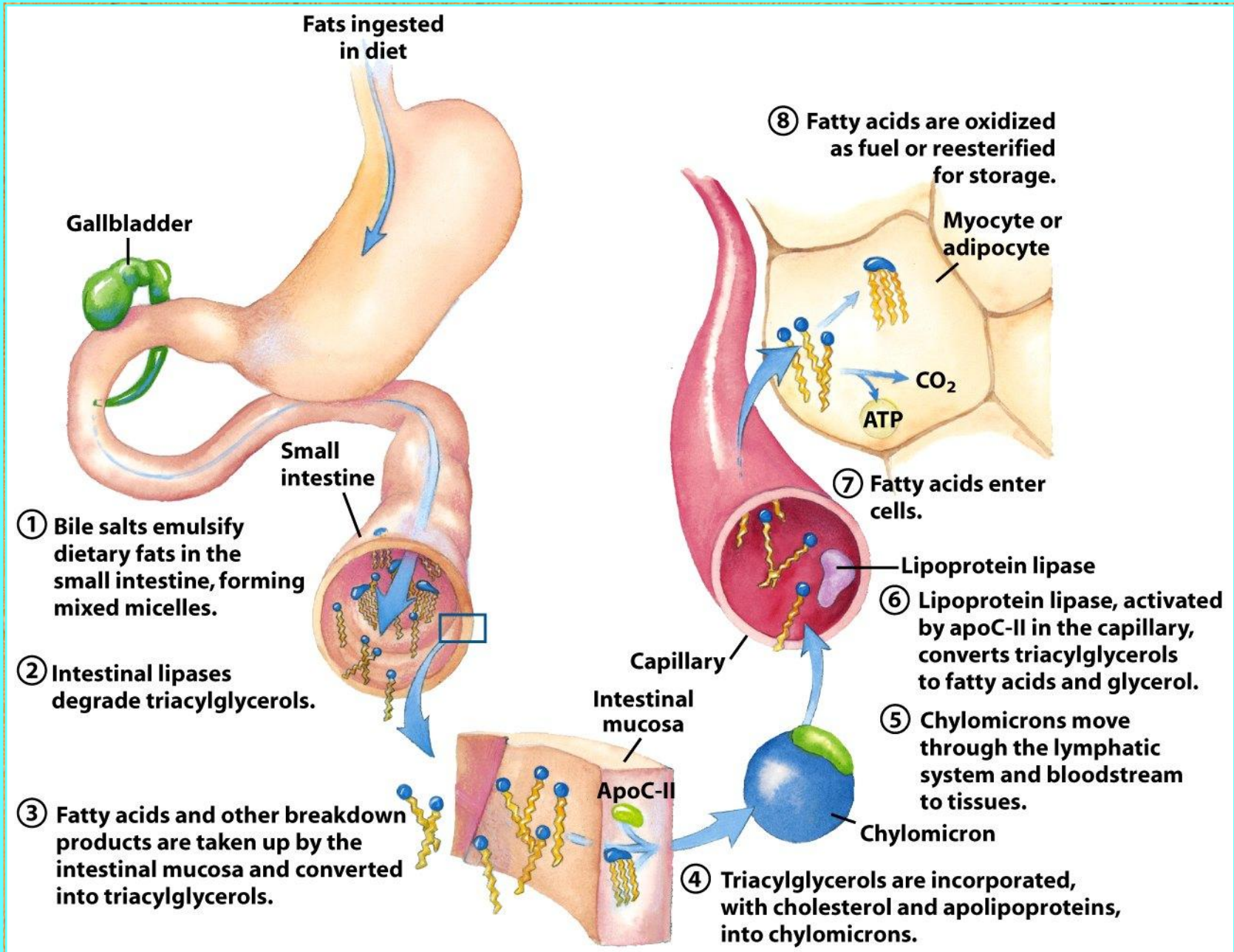
B. fats stored in the cell as lipid droplets

C. fats synthesized in one organ for export to another

Fat storage

- Dietary fats are absorbed in the small intestine.
- They are emulsified by bile acids, digested by lipases, then taken up by intestinal mucosa and reconverted to triacylglycerols .
- They are packaged into aggregates and carried in the blood to muscles, adipose tissue, and to the liver.

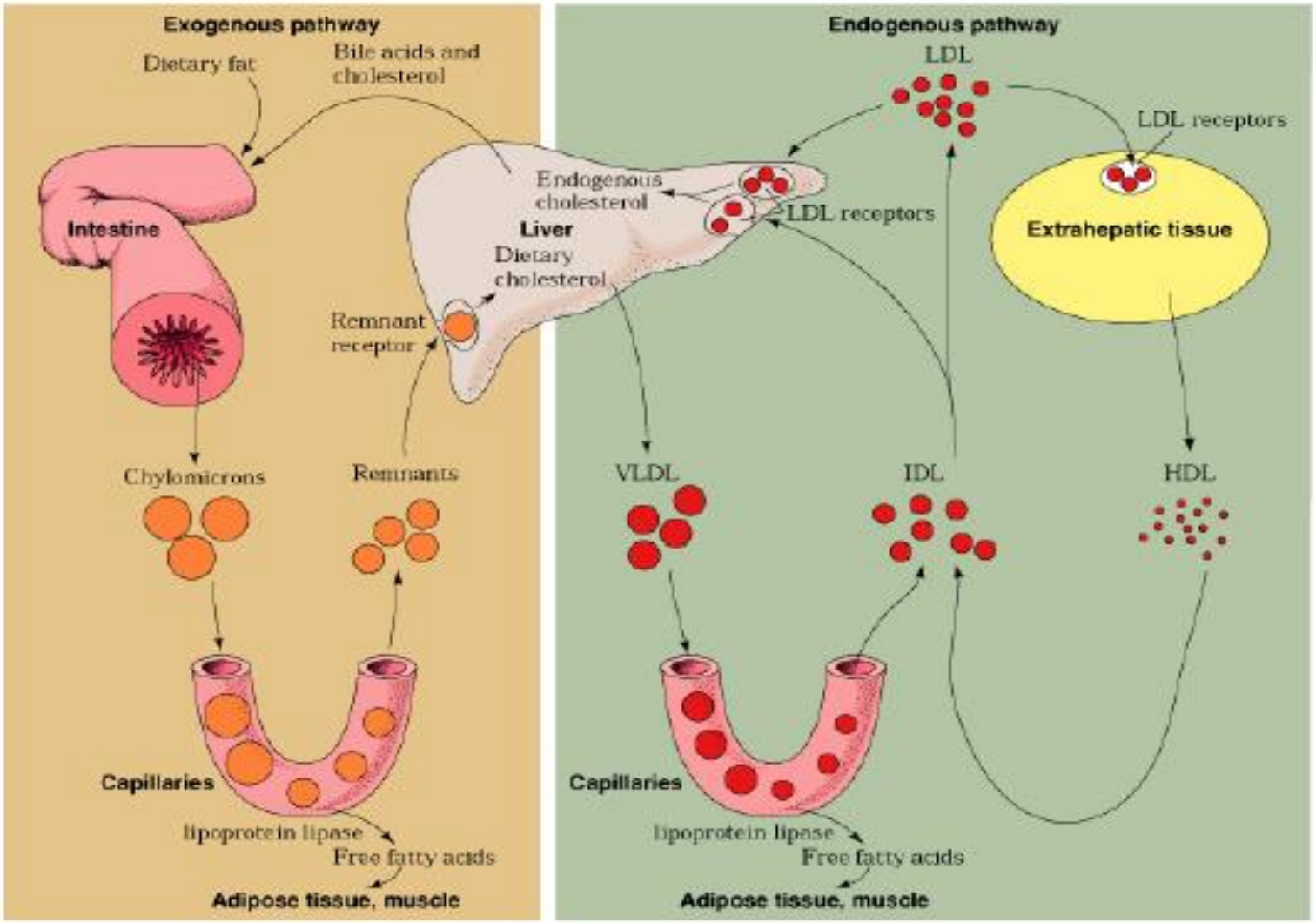
Processing Ingested Lipids



Hormones trigger mobilization

- ✓ Epinephrine and glucagon trigger mobilization of fats from storage (adipose tissue) to muscle (skeletal, heart) where fatty acids are oxidized for energy production .
- ✓ The hormones use a cAMP dependent pathway, which gives phosphorylation and activation of a triacylglycerol lipase.
- ✓ This enzyme catalyzes hydrolysis of the ester linkages, releasing free fatty acids.

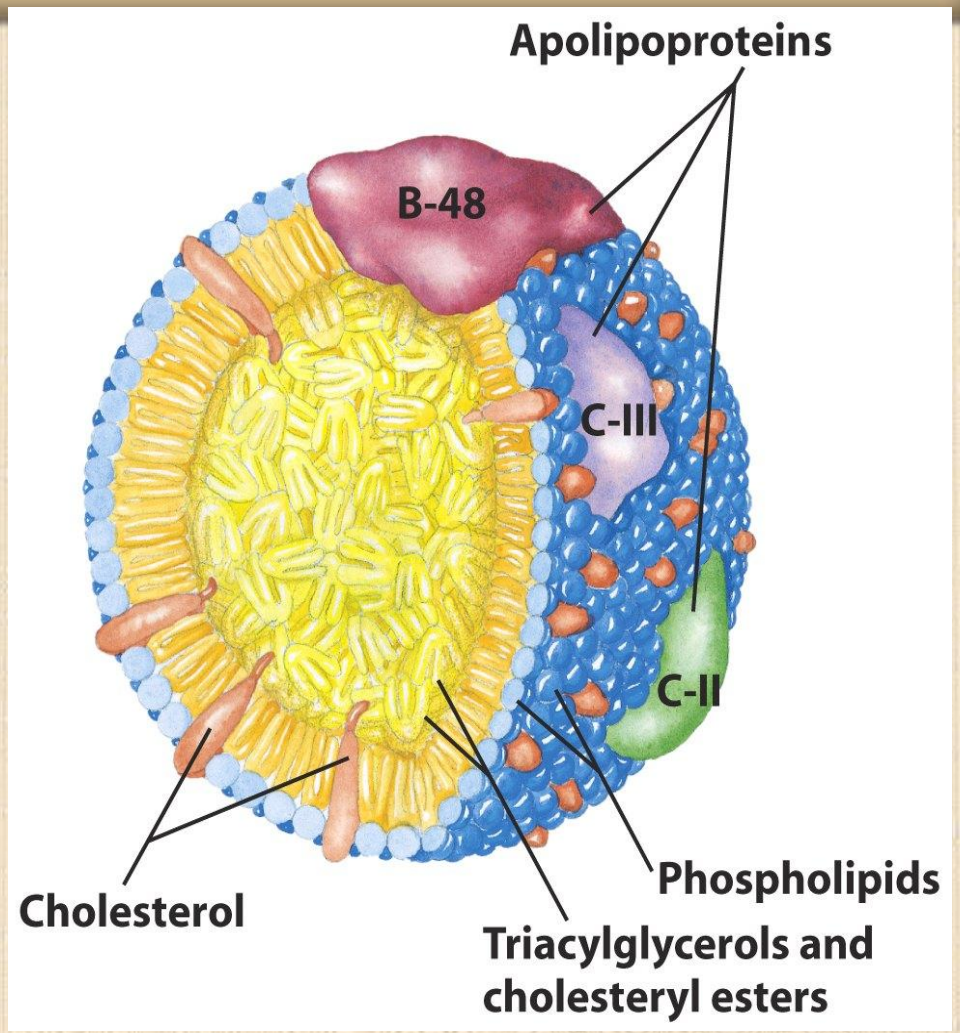
Transport in Blood: The Big Picture



- The fatty acids pass into the blood and bind to a protein called **serum albumin**.
- The binding allows the fatty acids to be effectively increased in solubility so that they can be readily transported to tissues.
- Nearly all of the energy from fats is generated from the alkyl chains, not from the glycerol.
- However, the glycerol generated from cleaving off the alkyl chains can be converted to glycerol 3-phosphate, then to dihydroxyacetone phosphate, and enter into glycolysis .

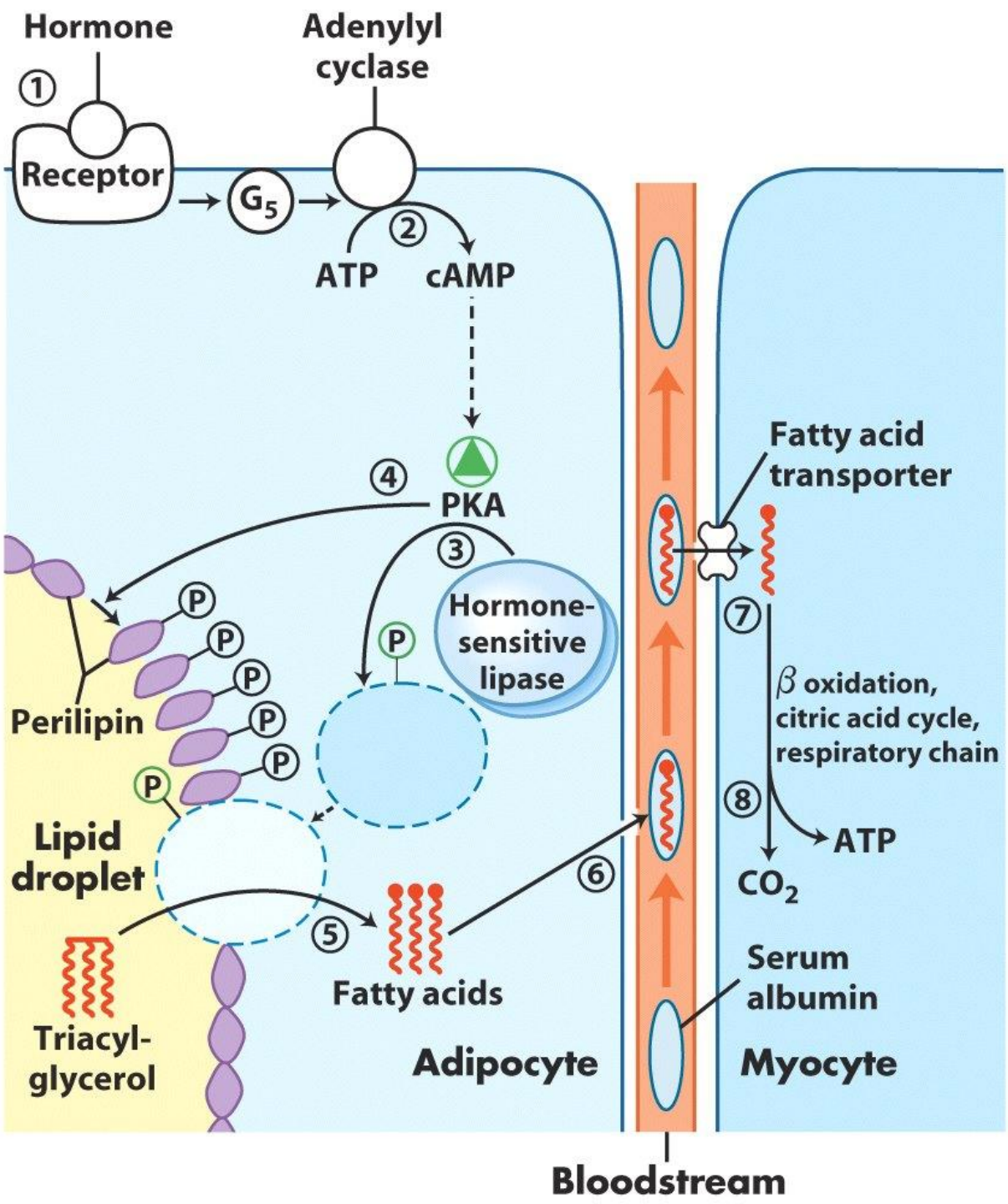
Apolipoproteins are lipid-binding proteins in the blood, responsible for the transport of triacylglycerols, phospholipids, cholesterol, and cholesteryl esters between organs.

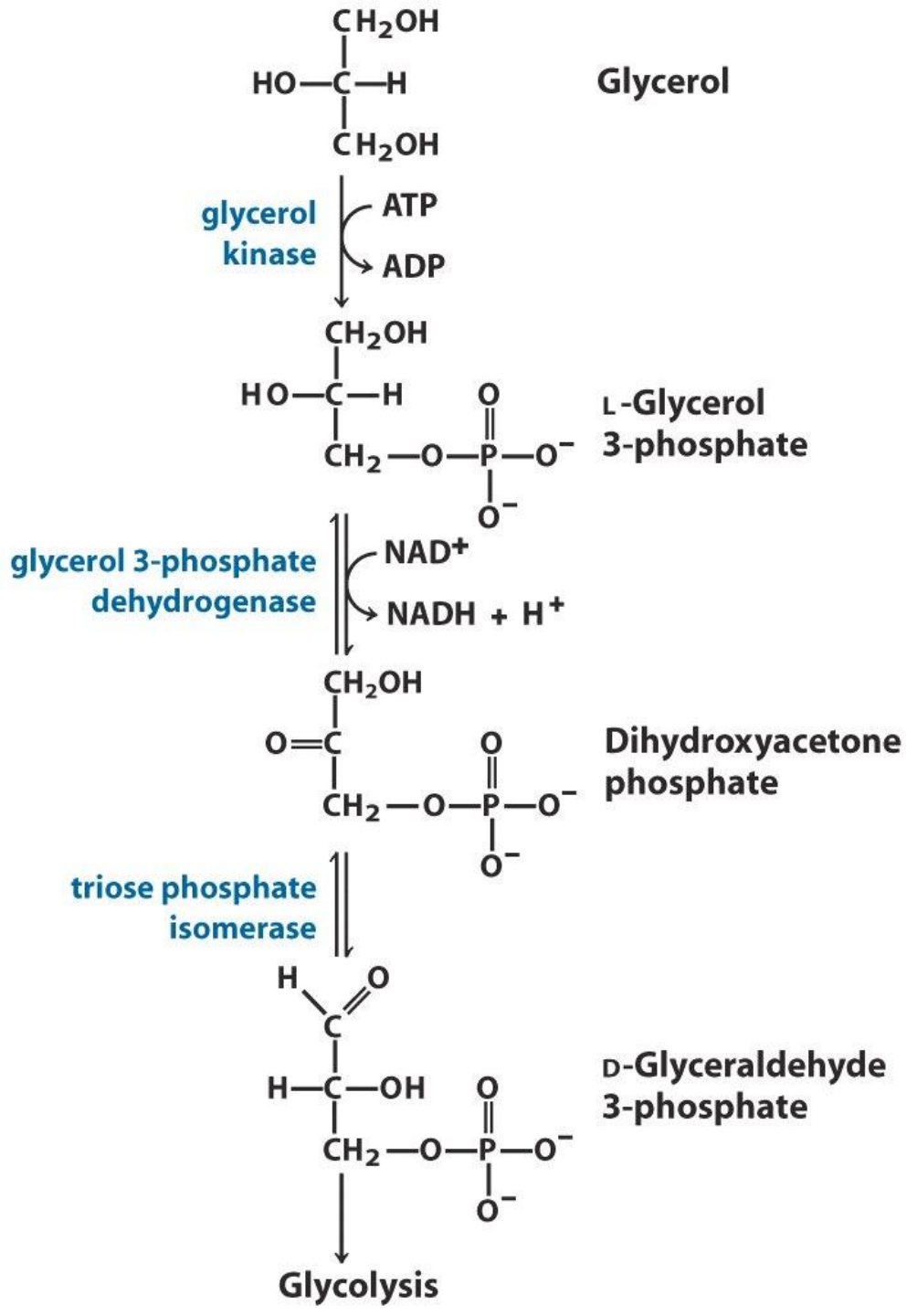
spherical aggregates with hydrophobic lipids at the core and hydrophilic protein side chains and lipid head groups at the surface.



Molecular structure of a chylomicron.

Mobilization of Triacylglycerols





Glycerol goes into the glycolytic pathway

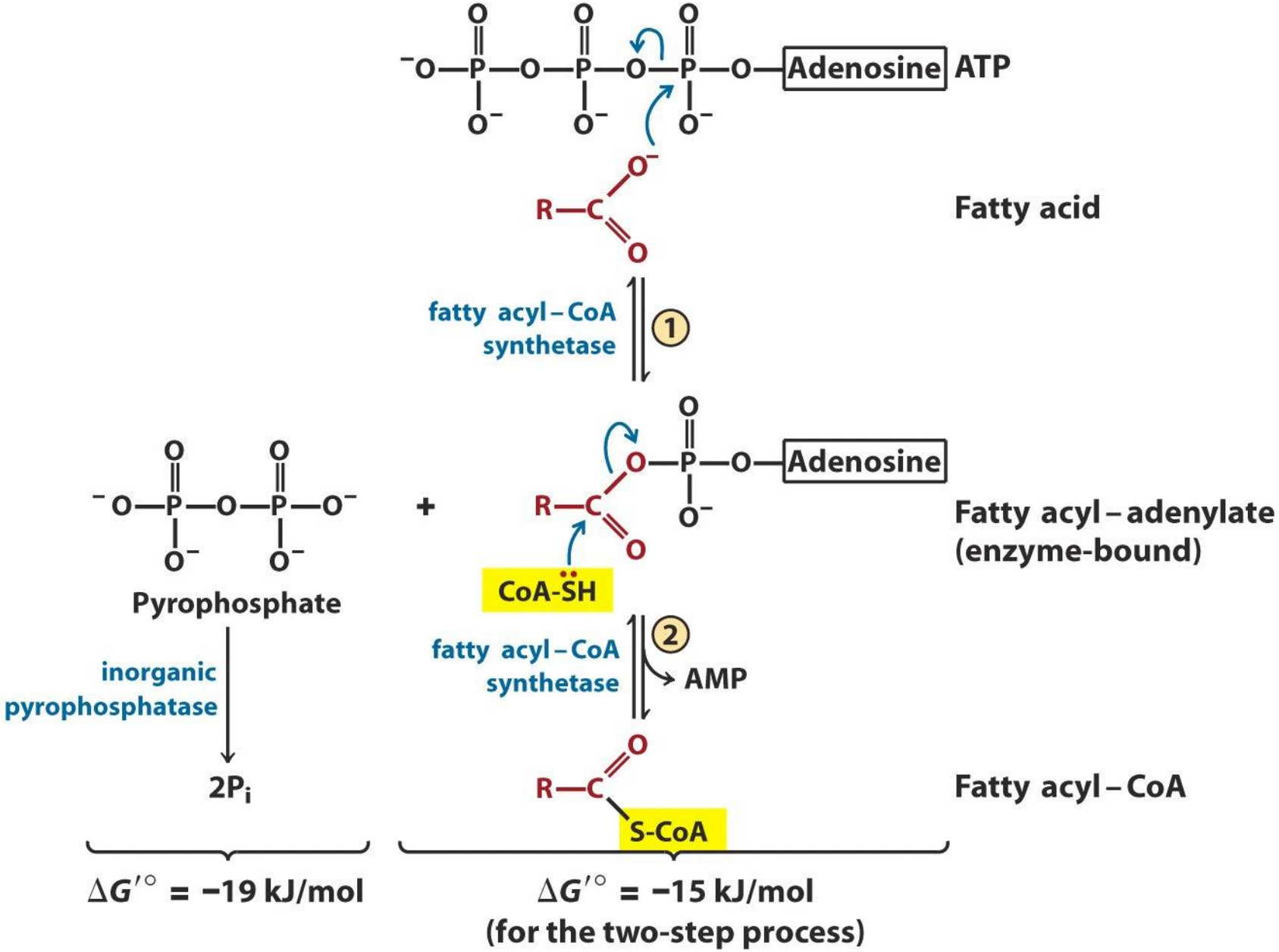
Transport of fatty acids into mitochondria

- Free fatty acids that enter cytoplasm cannot be transported into the mitochondria. They are first activated by a series of three reactions **.**

1. **Acyl-CoA synthetases**, present in outer mitochondrial membrane, catalyze the reaction:

- Fatty acid + CoA + ATP → fatty acyl-CoA + AMP + 2Pi DG = –34 kJ/mol
- Reaction is made favorable by coupling to cleavage of ATP, plus cleavage of pyrophosphate into two molecules of Pi
- Different isozymes for fatty acids with short, medium, or long tails

Conversion to Fatty acyl-CoA



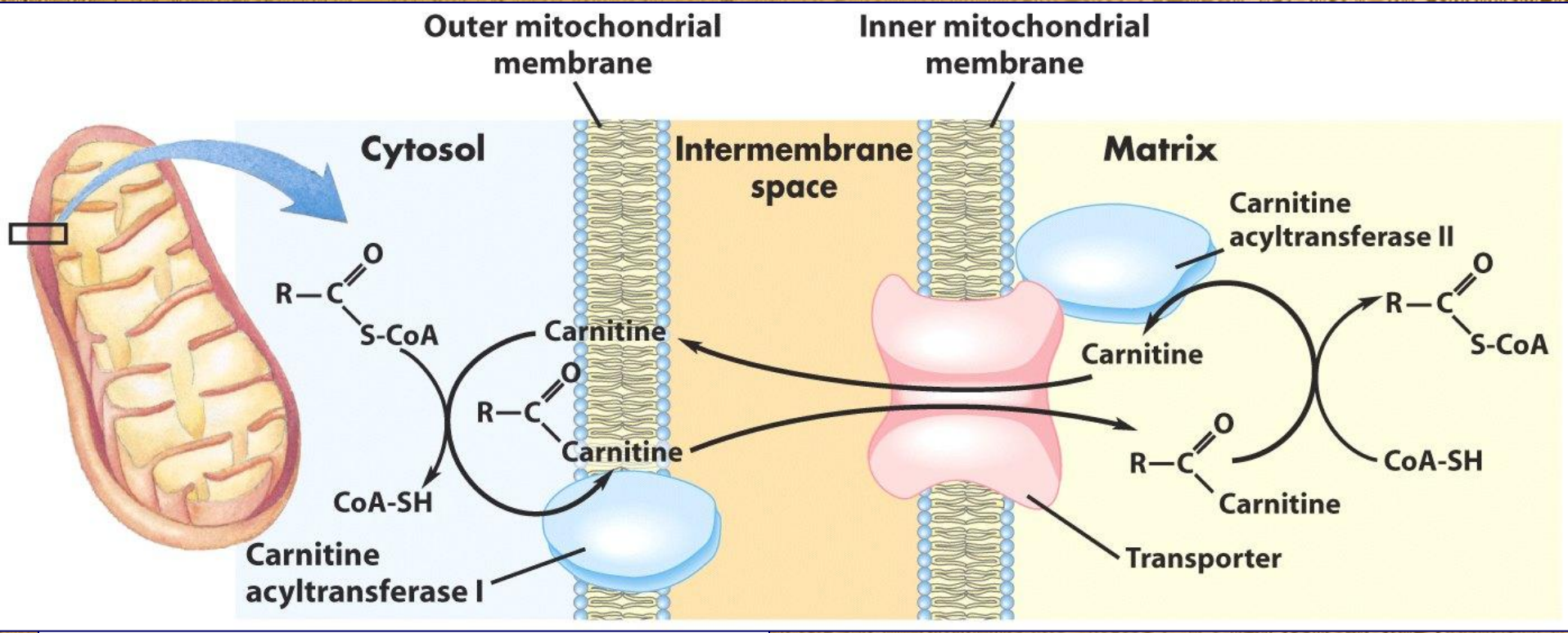
2. **Fatty acyl group transferred to carnitine by carnitine acyl-transferase I .**

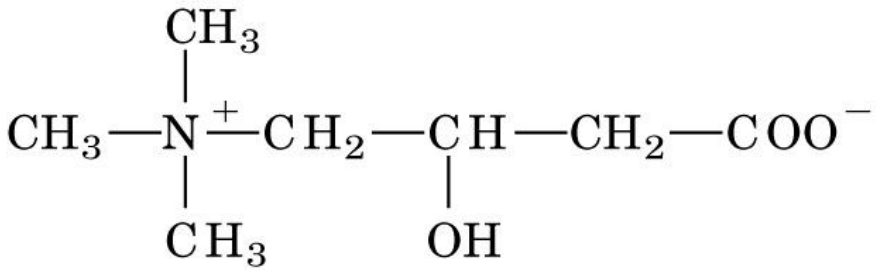
- Reaction is on the outer face of the inner mitochondrial membrane
- Fatty acyl-carnitine ester then enters the matrix by facilitated diffusion through the **acyl-carnitine/carnitine transporter.**

3. **Fatty acyl group is transferred from carnitine back to intramitochondrial CoA by carnitine acyltransferase II.**

- Carnitine then re-enters the space between the membranes
- This three-step, carnitine-mediated entry process is the rate-limiting step for oxidation of fatty acids and is the main point of regulation.

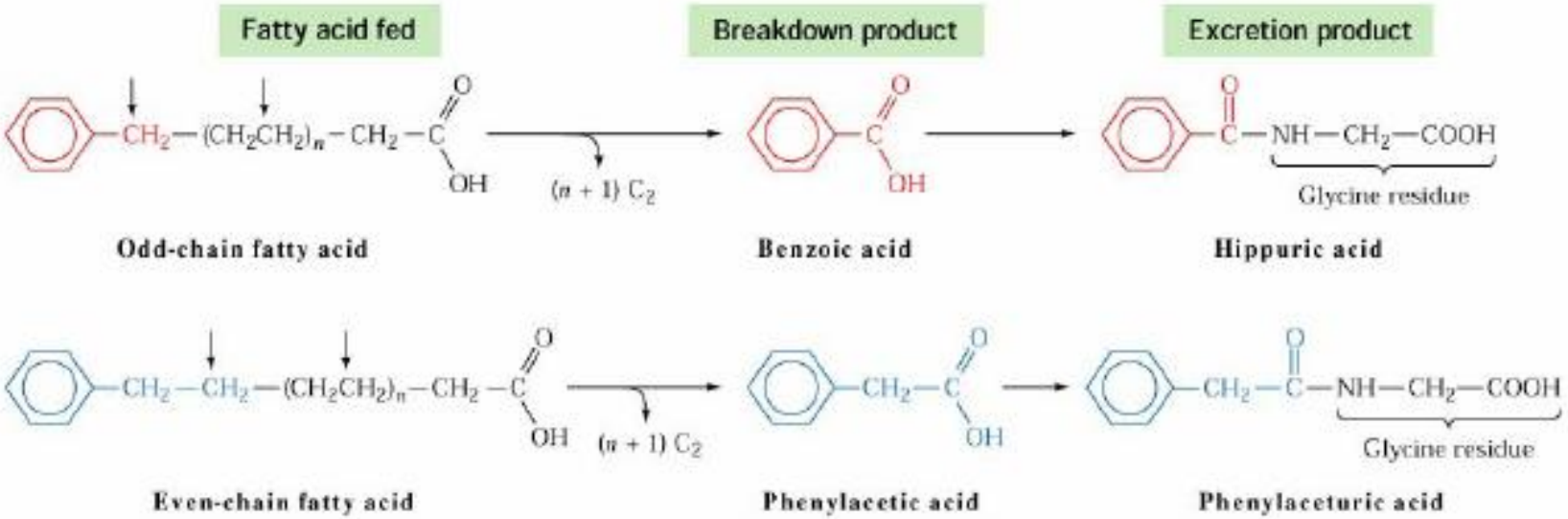
Fatty Acid Entry Into Mitochondria





Carnitine

Fatty Acids are Converted to Acetate by β-Oxidation



Franz Knoop -- 1904

β-oxidation of fatty acids

- There are three stages in the catabolism of fatty acids, and two of them are exactly the same as we already learned for sugars! .

I. Fatty acids undergo oxidative removal of two-carbon units to form acetyl-CoA.

II. Acetyl-CoA goes through the citric acid cycle to generate reduced electron carriers.

III. The electron transport process transfers the electrons to O2 and generates a proton gradient, which is used to synthesize ATP.

β-Oxidation Occurs in Three Stages

Activation

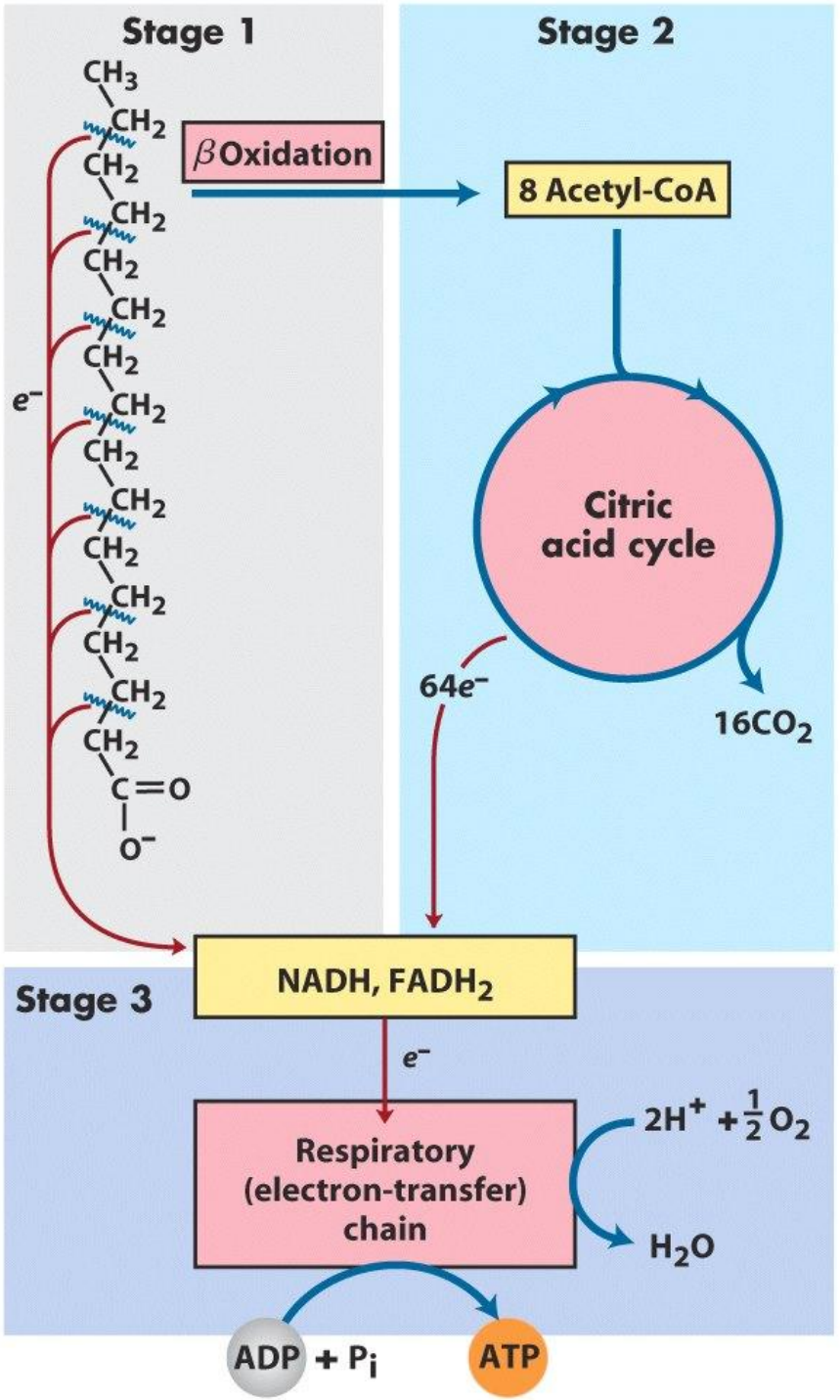
FA's are converted to the CoA ester

Transport

FACoA's are moved across the mitochondrial membrane

β-Oxidation

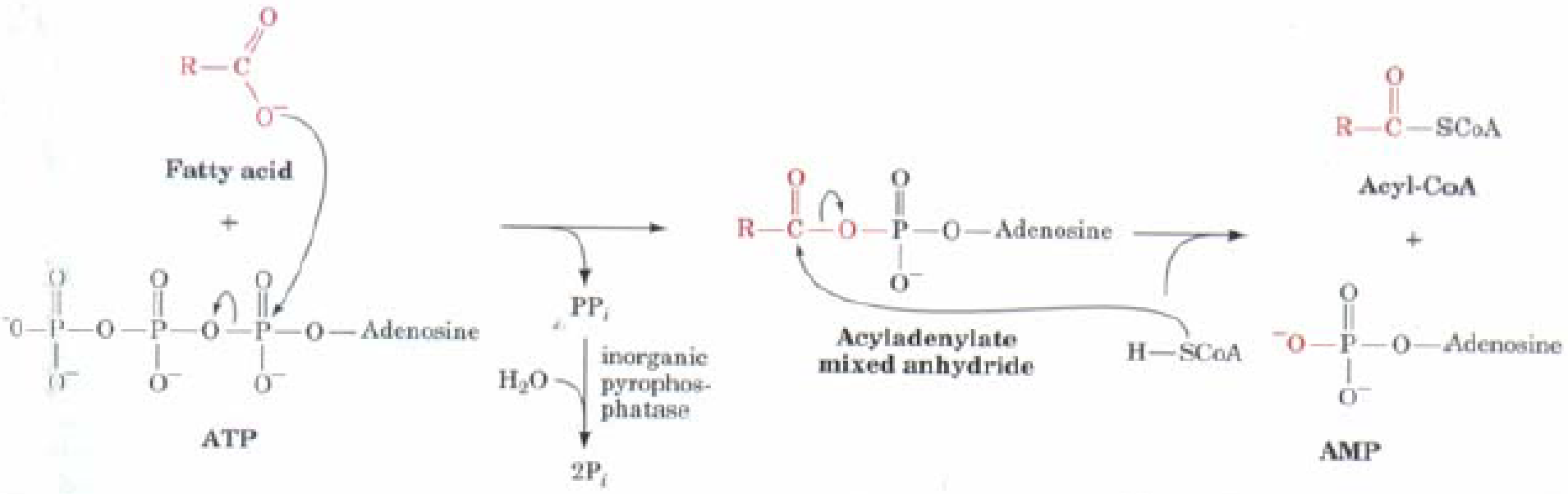
FACoA's are degraded into acetate in a stepwise manner



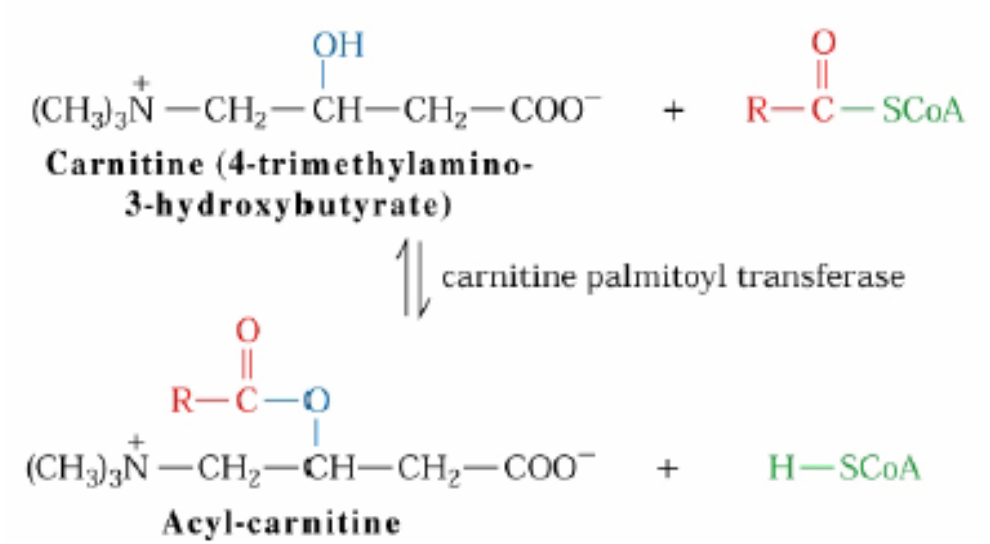
Stages of Fatty Acid Oxidation

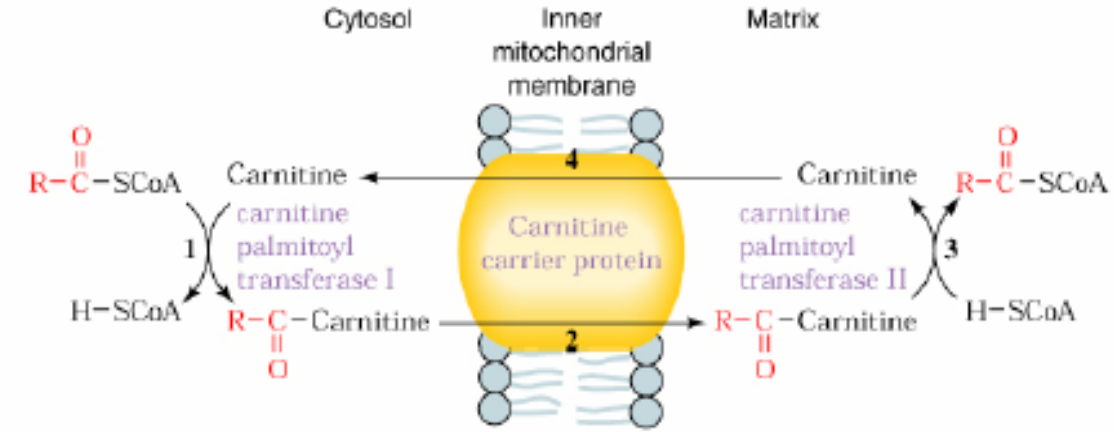
Activation –

Fatty Acid + CoA + ATP ⟶ FA-CoA + AMP + PP_i



Transport –


OH
$(CH_3)_3\overset{+}{N}-CH_2-CH-CH_2-COO^-$
+
O
R—C—SCoA
Carnitine (4-trimethylamino-3-hydroxybutyrate)
carnitine palmitoyl transferase
O
R—C—O
$(CH_3)_3\overset{+}{N}-CH_2-CH-CH_2-COO^-$
+
H—SCoA
Acyl-carnitine


Cytosol
Inner mitochondrial membrane
Matrix
R–C–SCoA
Carnitine
carnitine palmitoyl transferase I
1
H–SCoA
R–C–Carnitine
O
4
Carnitine carrier protein
2
Carnitine
carnitine palmitoyl transferase II
3
R–C–SCoA
H–SCoA
R–C–Carnitine
O

β Oxidation –

Four Reactions

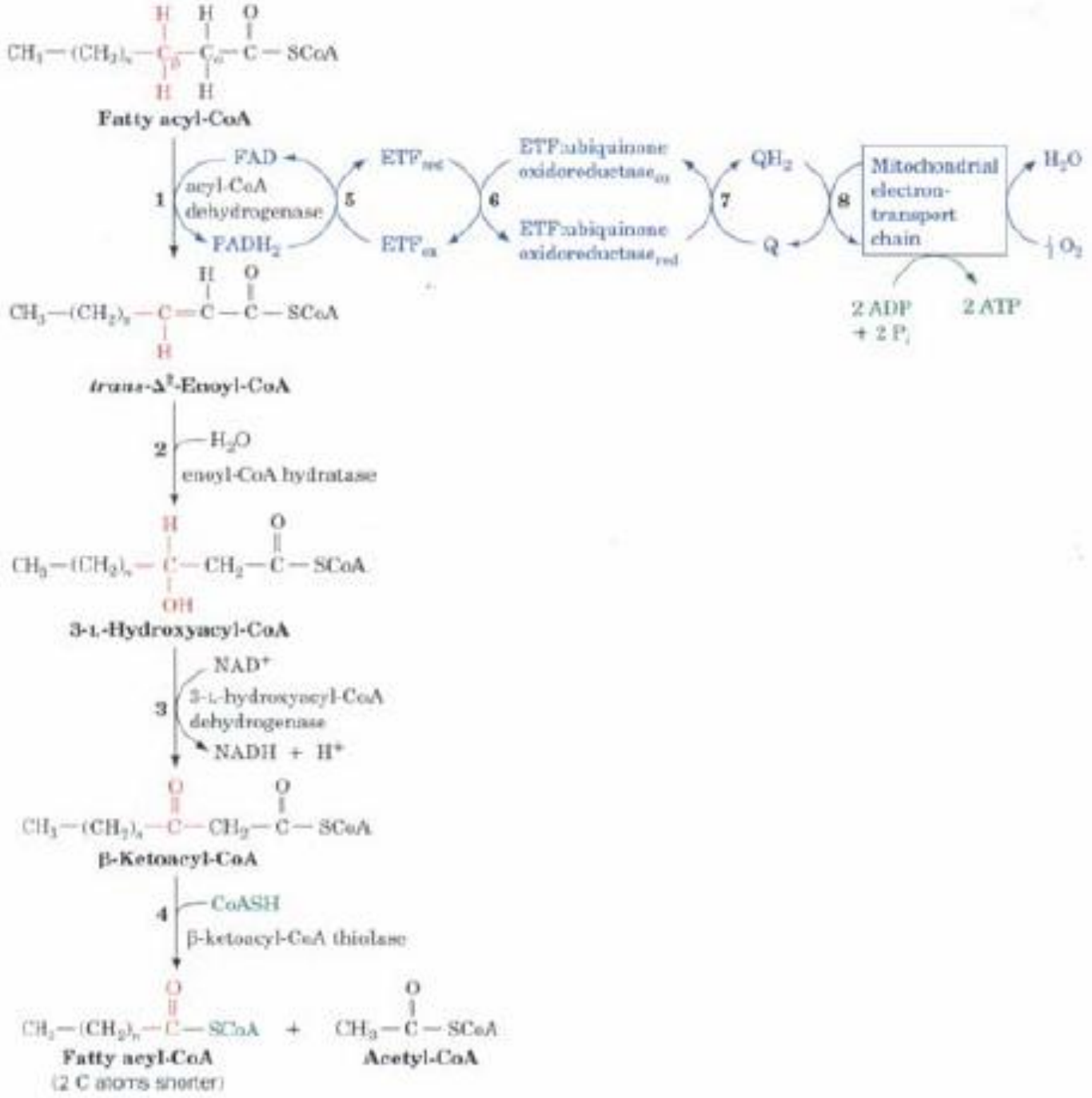
Acyl-CoA Dehydrogenase – introduces a trans α,β C=C
(FAD as electron acceptor)

Enol-CoA Hydratase – adds a water

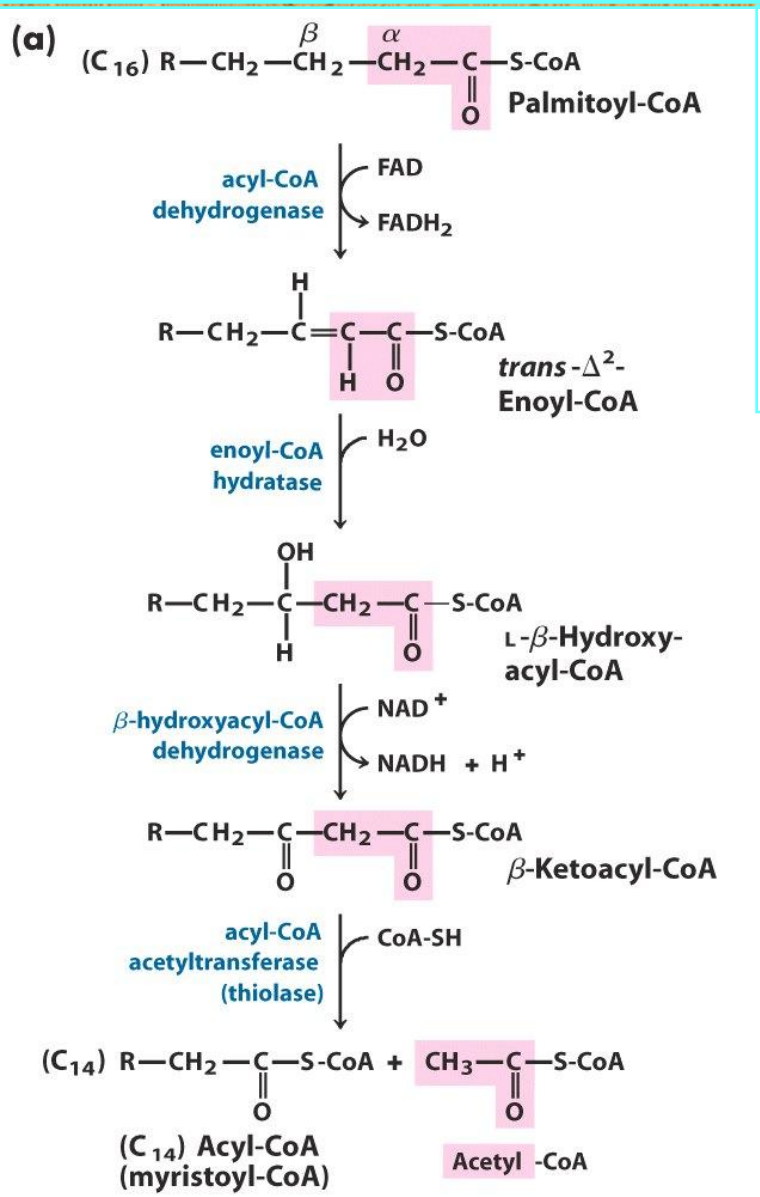
3-Hydroxylacyl-CoA Dehydrogenase – makes a carbonyl group
(NAD^+ as electron acceptor)

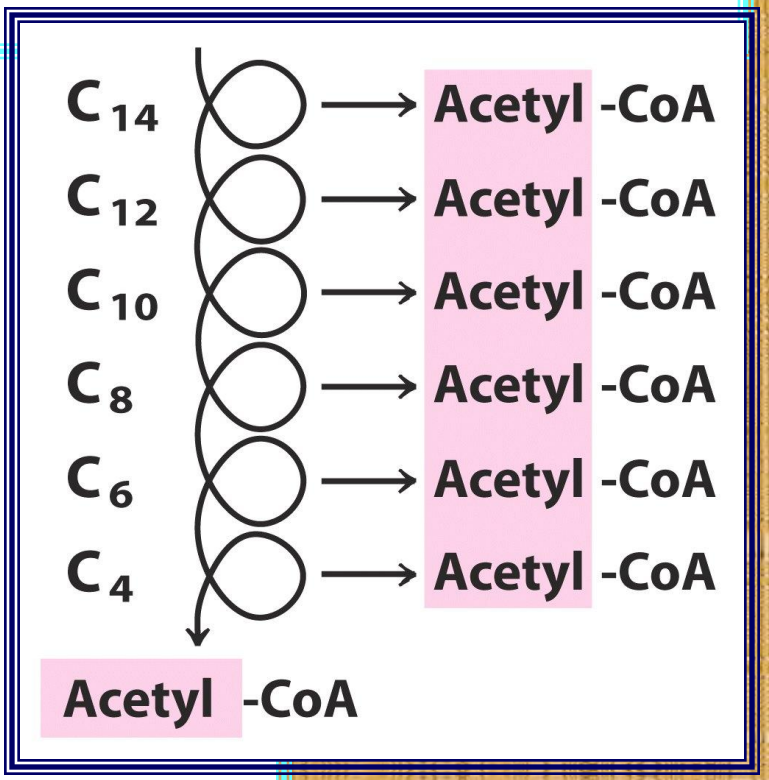
β-ketoacyl-CoA Thiolase – "splits out" an Acetyl-CoA

β Oxidation –

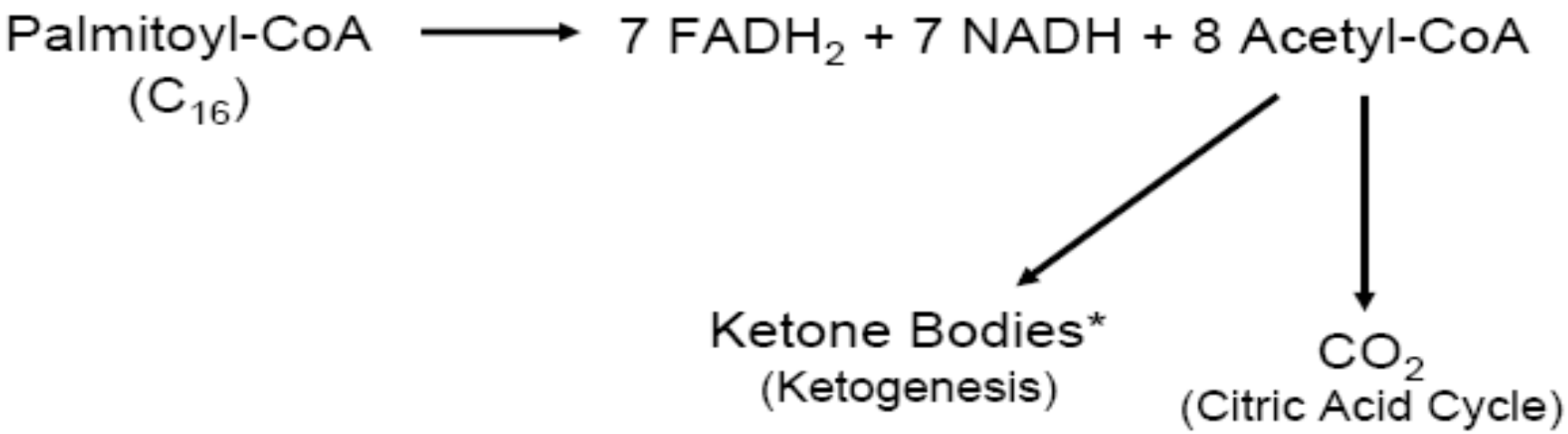

Fatty acyl-CoA
FAD
acyl-CoA dehydrogenase
FADH2
1
5
ETFox
ETFred
6
ETF:ubiquinone oxidoreductaseox
ETF:ubiquinone oxidoreductasered
7
QH2
Q
8
Mitochondrial electron-transport chain
H2O
½ O2
2 ADP + 2 Pi
2 ATP
trans-Δ2-Enoyl-CoA
2
H2O
enoyl-CoA hydratase
3-L-Hydroxyacyl-CoA
3
NAD+
3-L-hydroxyacyl-CoA dehydrogenase
NADH + H+
β-Ketoacyl-CoA
4
CoASH
β-ketoacyl-CoA thiolase
Fatty acyl-CoA
(2 C atoms shorter)
+
Acetyl-CoA

Four steps of b-oxidation





β-Oxidation -- Overall Reaction



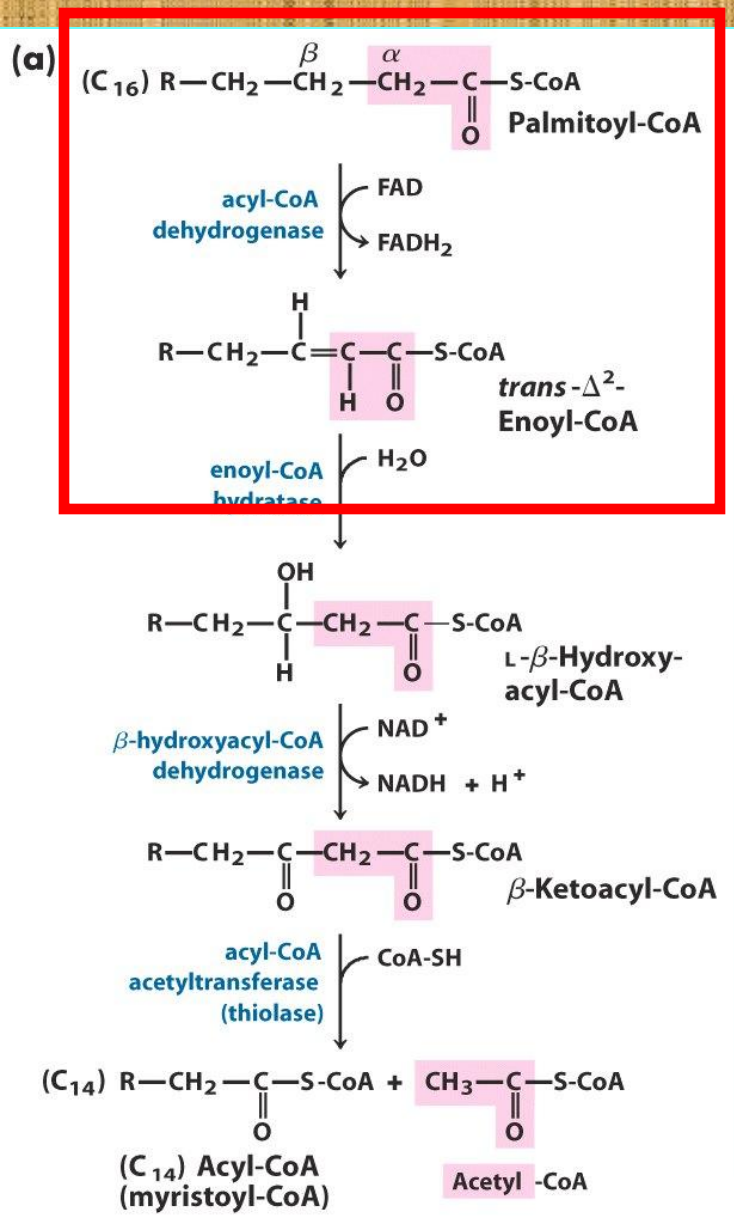
*Acetoacetate, Acetone, b-Hydroxyburyrate

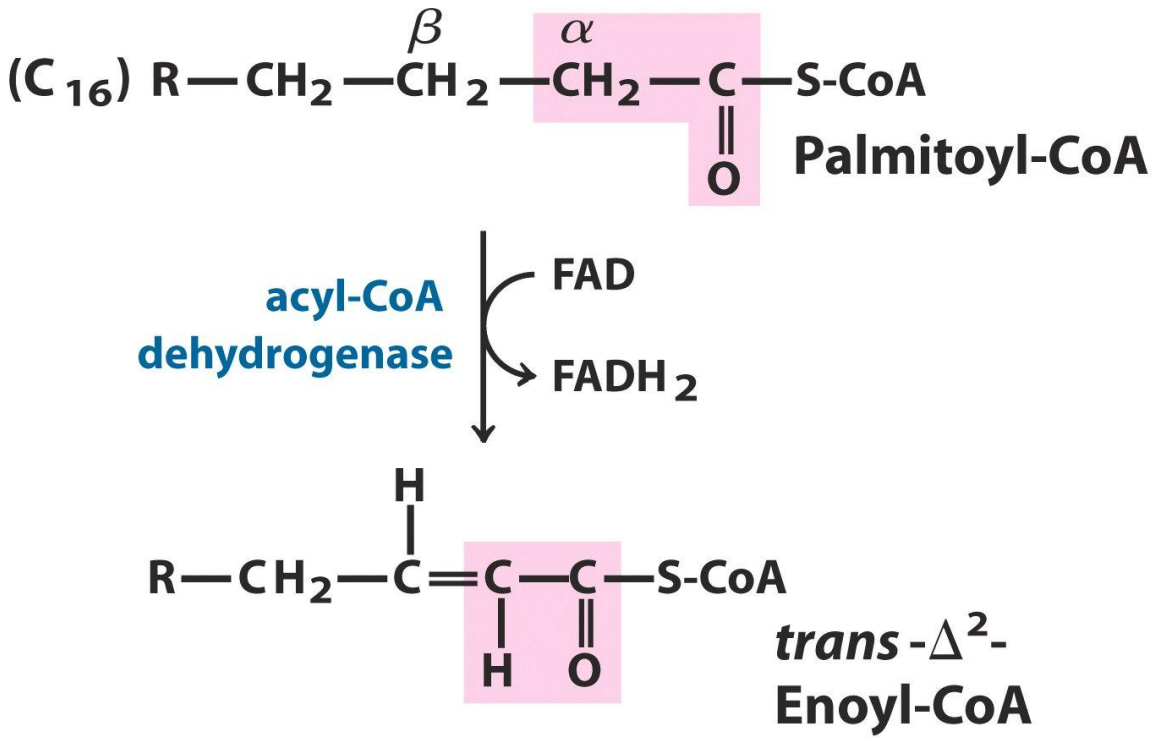
- The first stage, b-oxidation, has four basic steps**:**

1. Dehydrogenation of fatty acyl-CoA.

- Catalyzed by **acyl-CoA dehydrogenase** in the inner mitochondrial membrane
- Produces a double bond between a and b carbons (C-2 and C-3). The double bond is always *trans*, so this gives a **trans-D2-enoyl-CoA** intermediate.
- Three isozymes of **acyl-CoA dehydrogenase**, for short (4–8), medium (4-14), and long (12-18) carbon chains
- Electrons removed from the fatty acid chain are transferred to FAD, and they pass immediately into the mitochondrial respiratory chain.

Four steps of b-oxidation





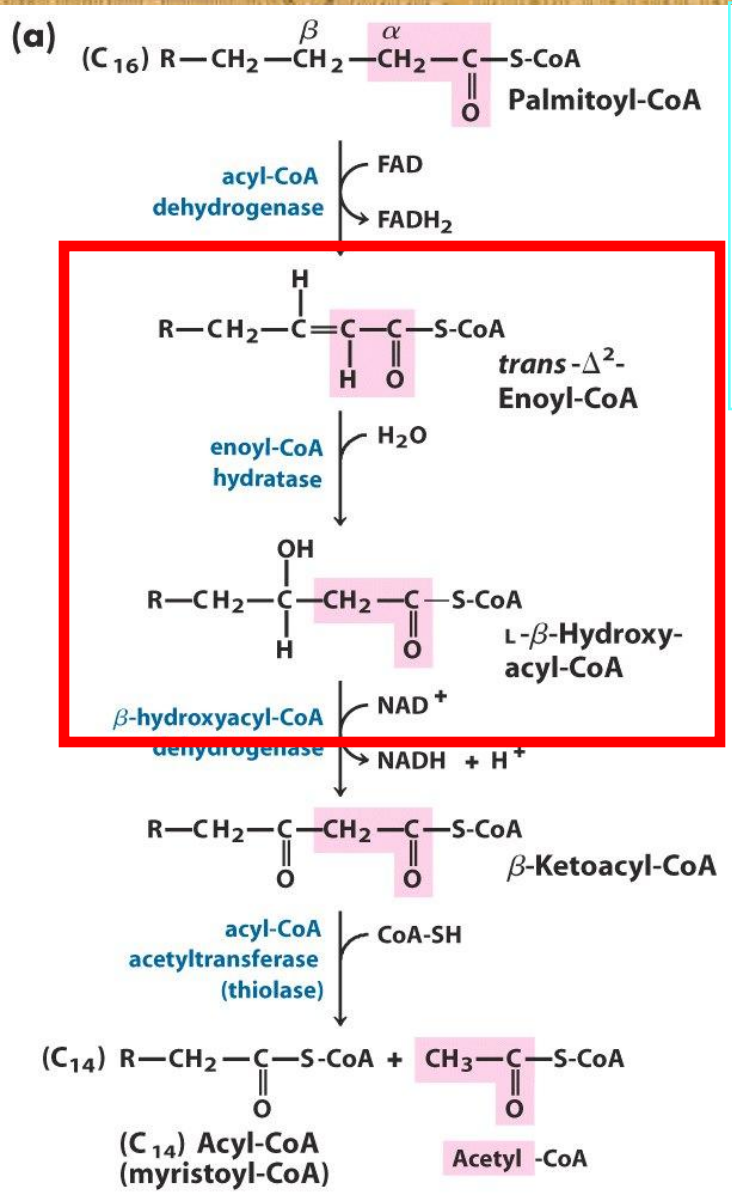
2. **Hydration to yield b-hydroxy derivative (L stereoisomer)**

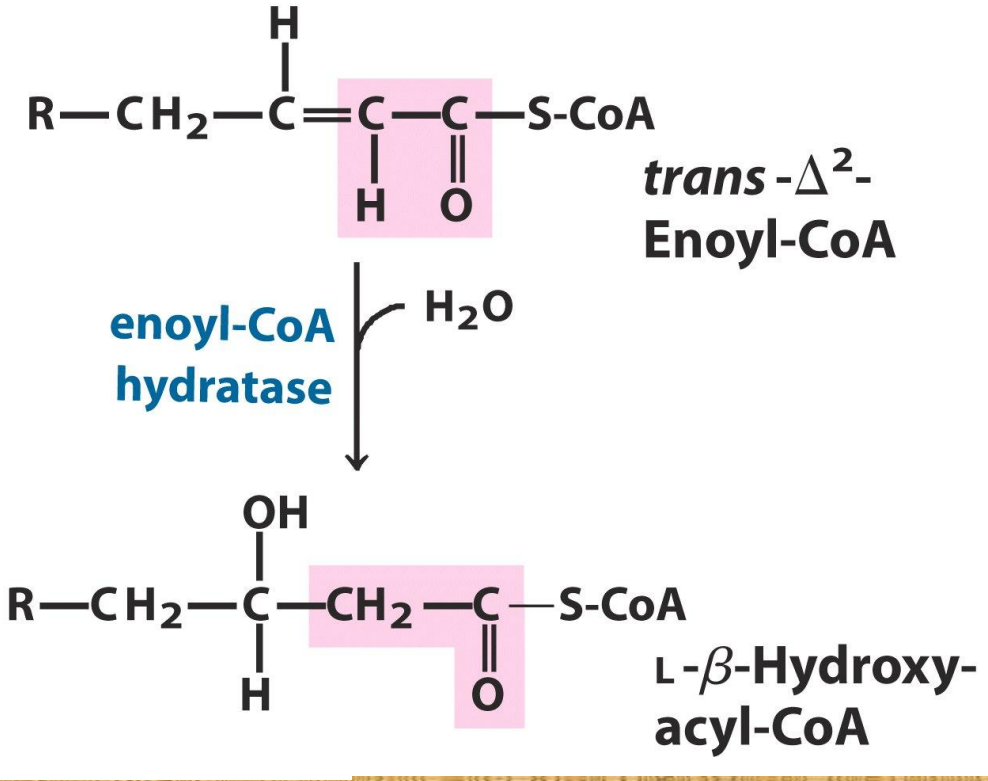
- Catalyzed by **enoyl-CoA hydratase**
- Reaction is analogous to fumarase reaction in CAC, where water adds across an a-b double bond.

3. **Dehydrogenation of L-b-hydroxylacyl-CoA**

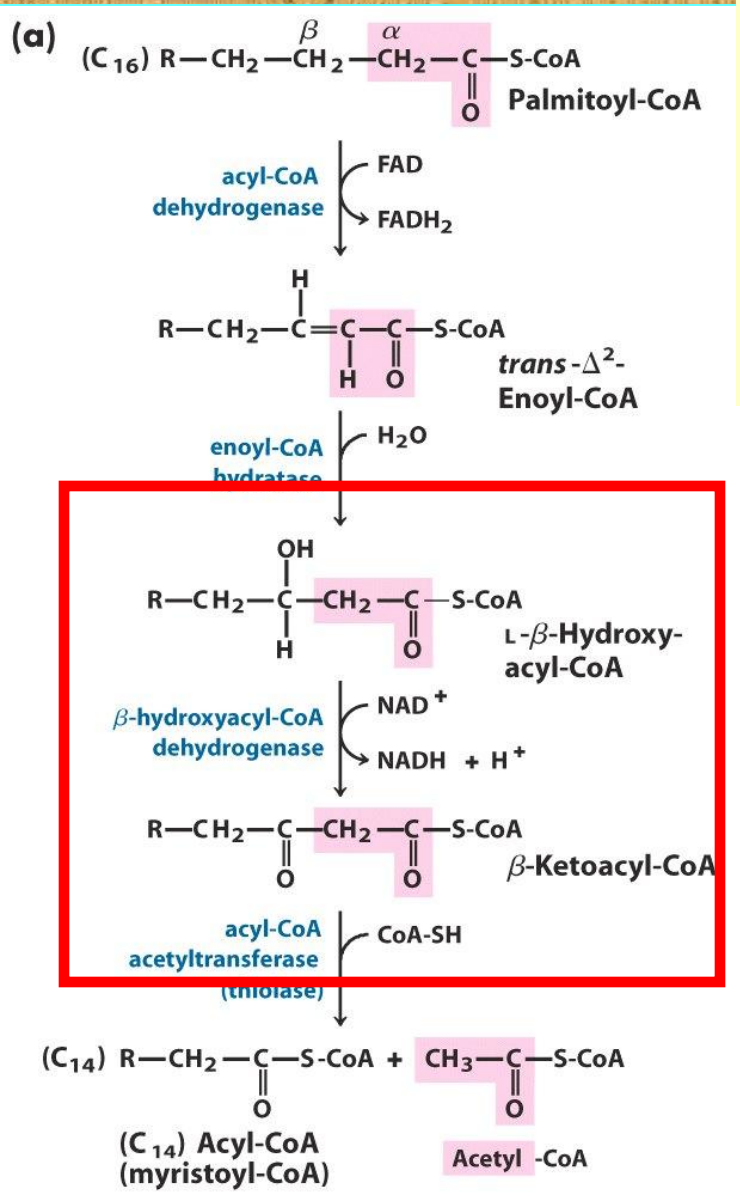
- Catalyzed by **b-hydroxylacyl-CoA dehydrogenase**
- Electrons are transferred to NAD+, then to respiratory chain via NADH dehydrogenase
- Reaction is closely analogous to malate dehydrogenase reaction of CAC

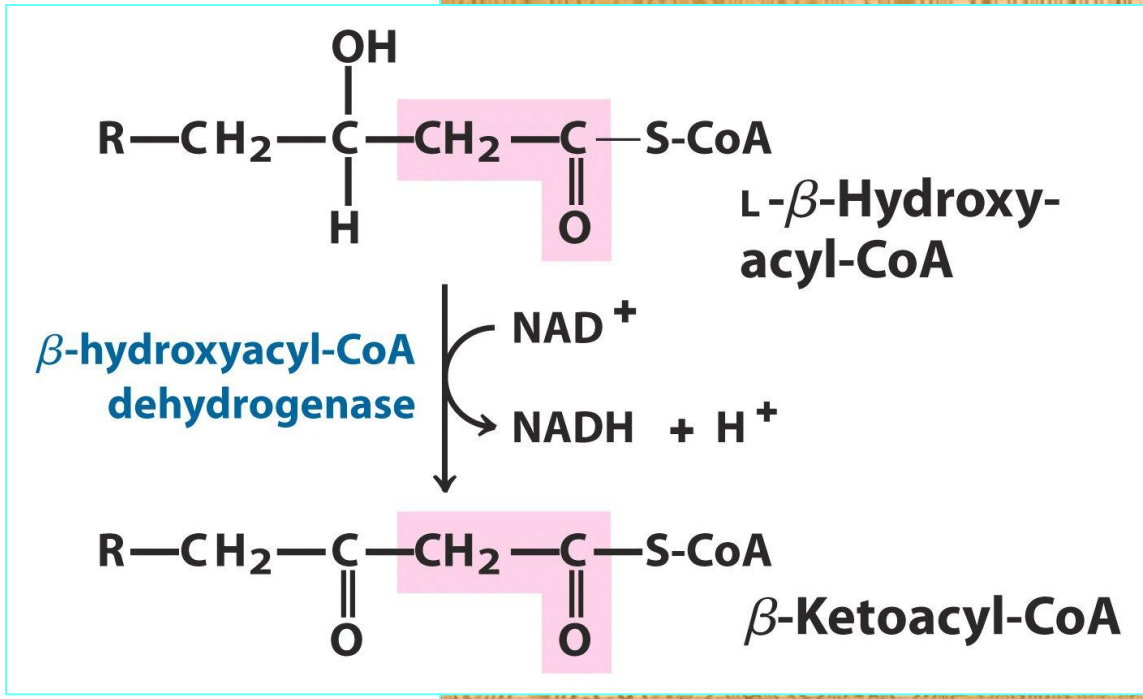
Four steps of b-oxidation





Four steps of b-oxidation



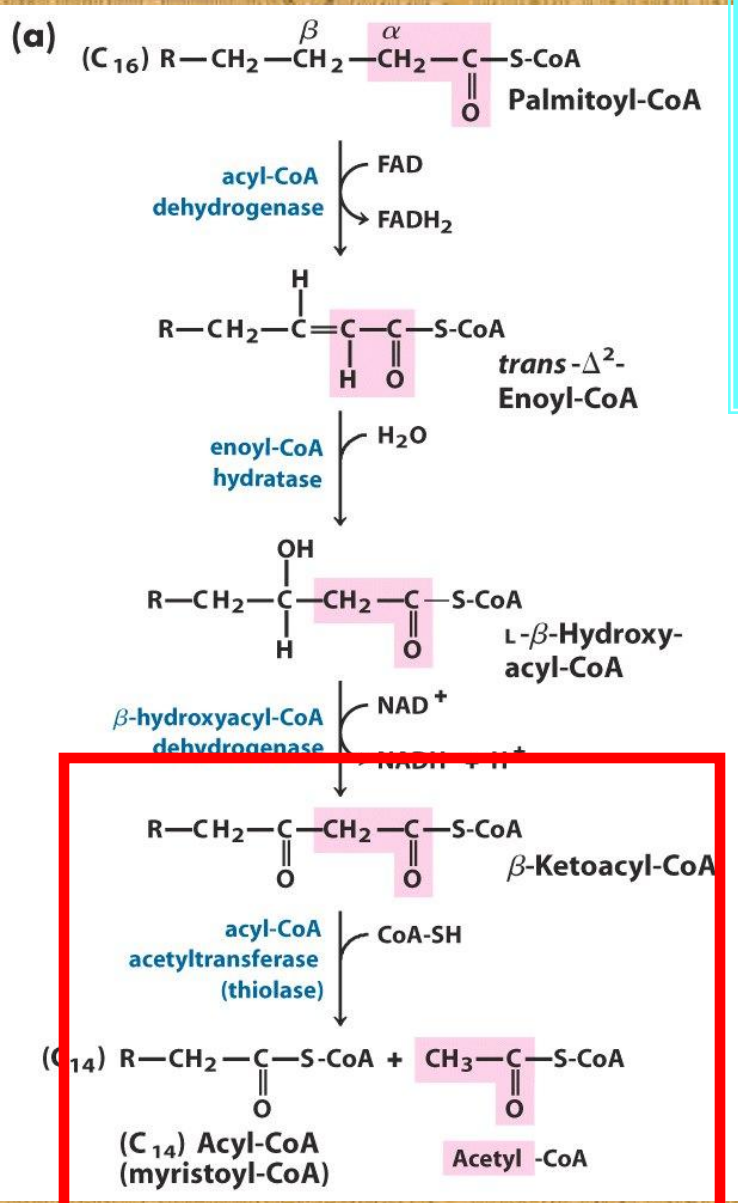


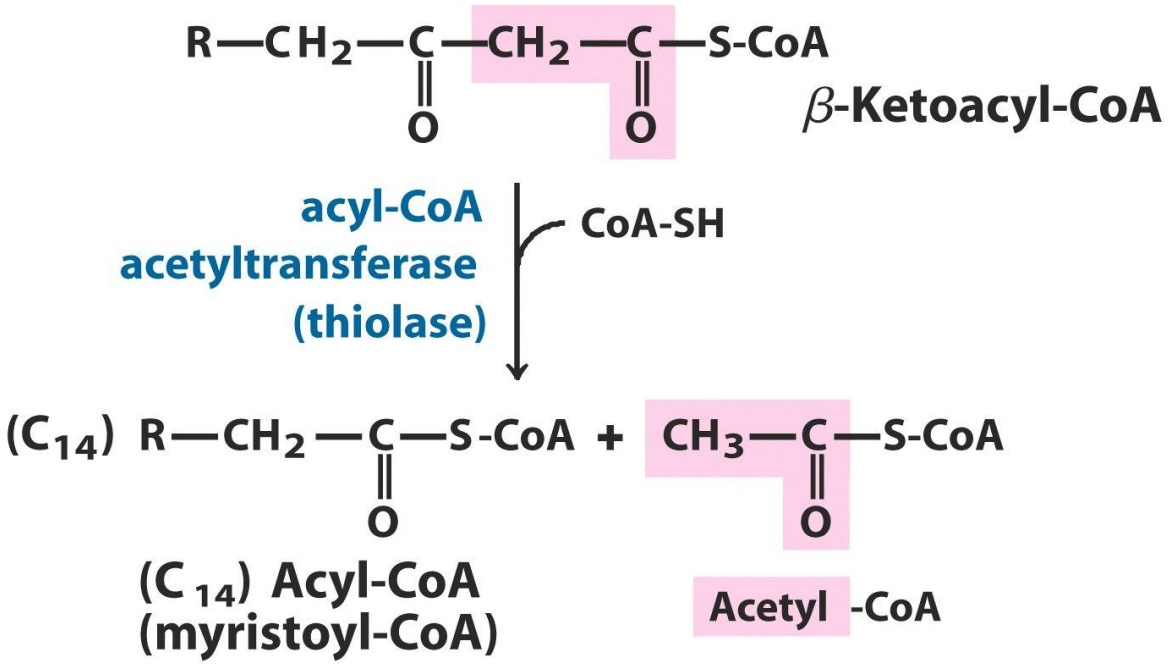
4. Transfer of chain (C-3 and up) to new molecule of CoA

- Catalyzed by **thiolase**
- Reaction involves attack by CoA-SH on carbonyl (C-3), with acetyl-CoA (C-1 and C-2) as leaving group
- This reaction sequence is a very clever way of breaking the bond between C-2 and C-3, which is very stable as a single bond between methylenes.

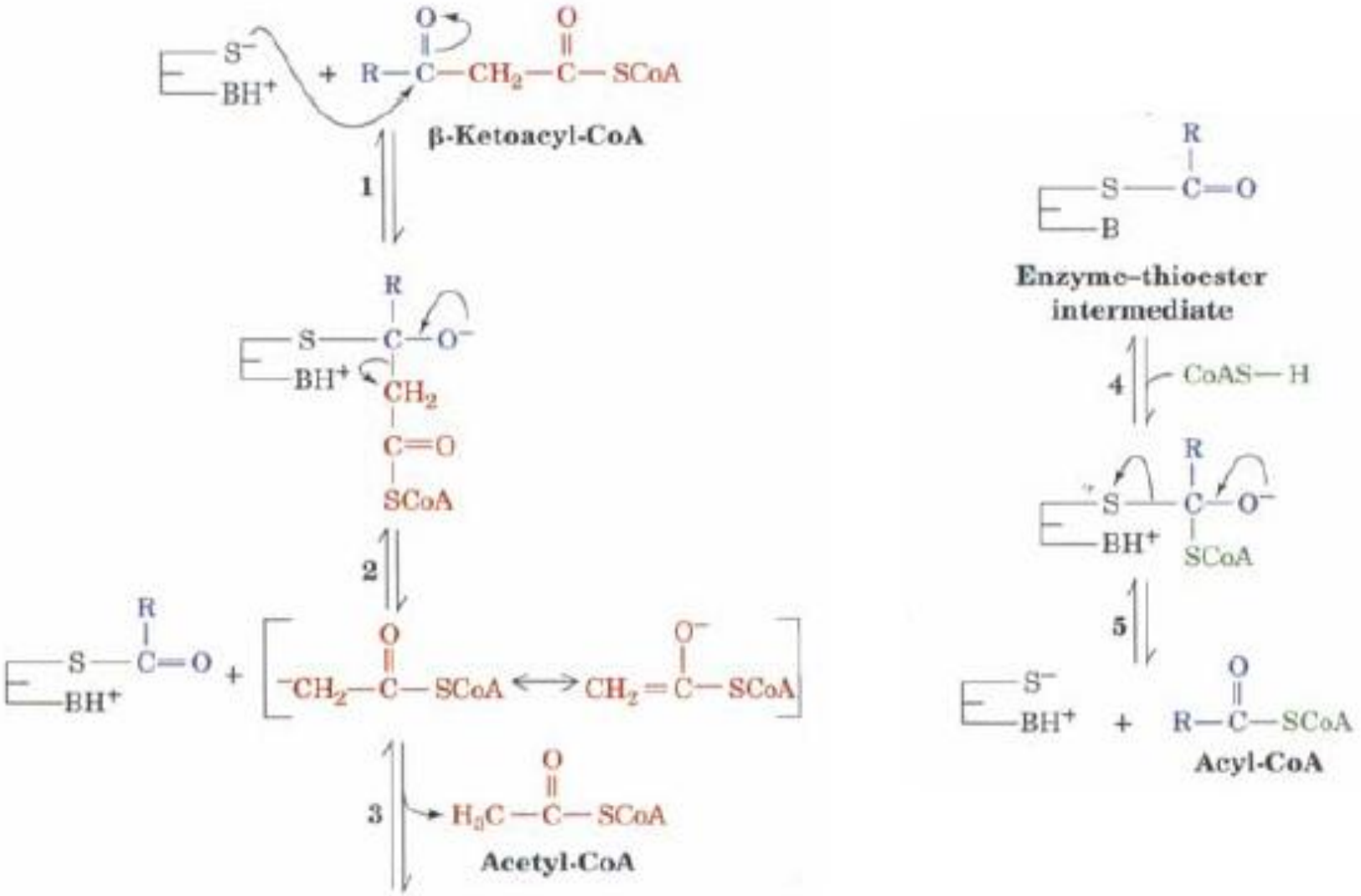
- The bond is activated by oxidizing C-3 to a carbonyl, so it is now electrophilic.
- The bond between C-2 and C-3 is also more easily broken because C-2 is bonded to two carbonyl groups
- The carbon chain is now shorter by two carbon atoms, again in the form of an fatty acyl-CoA.

Four steps of b-oxidation





Mechanism of Thiolase –



**The four steps are repeated to yield multiple molecules of acetyl-CoA

- In each pass through this cycle the chain is shortened by two carbons. For example:
- Palmitoyl-CoA (16 carbons) + CoA + FAD + NAD+ + H2O →

  Myristoyl-CoA (14 carbons) + acetyl-CoA + FADH2 + NADH + H+
- The cycle is repeated and each time the carbon chain is shortened by 2 .

- Palmitoyl-CoA + 7CoA + 7FAD + 7NAD+ + 7H2O →
- 8 acetyl-CoA + 7FADH2 + 7NADH + 7H+
- Each FADH2 molecule donates a pair of electrons to the respiratory chain, generating ~1.5 ATP.
- Each NADH molecule also donates a pair of electrons, generating ~2.5 ATP.
- Therefore, 4ATP molecules are generated for each two-carbon unit (and this is before all the acetyl-CoAs go through the citric acid cycle).

**When all the energy produced from the b-oxidation and the citric acid cycling of the acetyl-CoA molecules is considered, we arrive at the following overall equation:

- Palmitoyl-CoA + 23O2 + 108Pi + 108ADP →

  CoA + 108ATP + 16CO2 + 23H2O

- • Hopefully you can see from this that fat is a very efficient form of energy storage!

Energy from b-oxidation

In one turn of the cycle

- **Palmitoyl-CoA (16C) + CoA + FAD + NAD^+ + H_2O --> Myristoyl-CoA (14C) + acetyl-CoA + $FADH_2$ + NADH + H^+**

Completion of b-oxidation

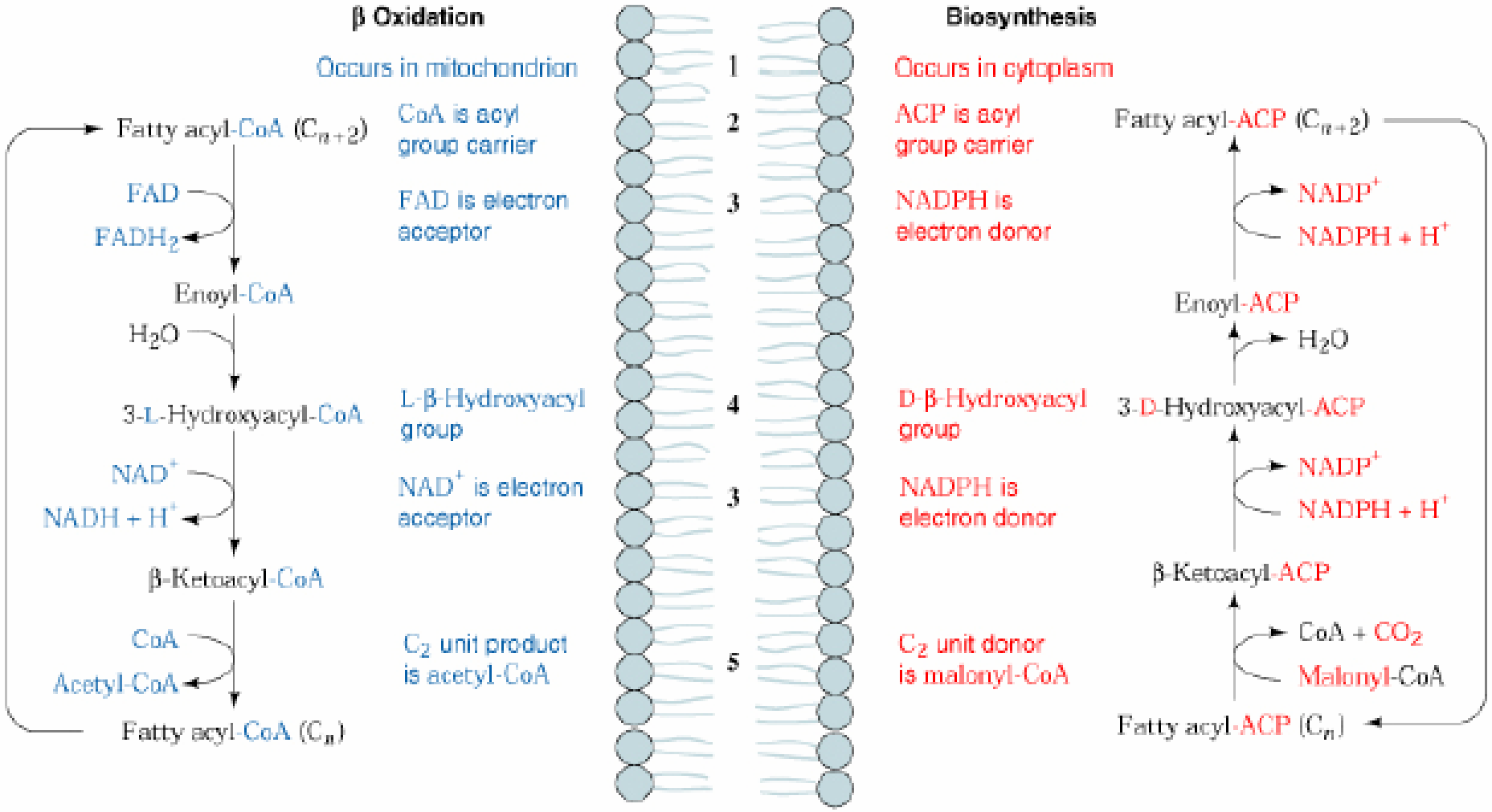
- **Palmitoyl-CoA (16C) + 7CoA + 7FAD + $7NAD^+$ + $7H_2O$ --> 8Acetyl-CoA + $7FADH_2$ + 7NADH + $7H^+$**

Energy from b-oxidation

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

Compare Breakdown and Synthesis of Fatty Acids



Oxidation of Fats Can Sustain an Animal For a Long Time

**Oxidation of unsaturated fatty acids: two additional reactions

- *cis* double bonds cannot be acted on by enoyl-CoA hydratase, so the double bonds must be converted to the *trans* conformation

1) Oxidation of oleate – 18:1(DC9). Cycles proceed normally until double bond is between C-3 and C-4.

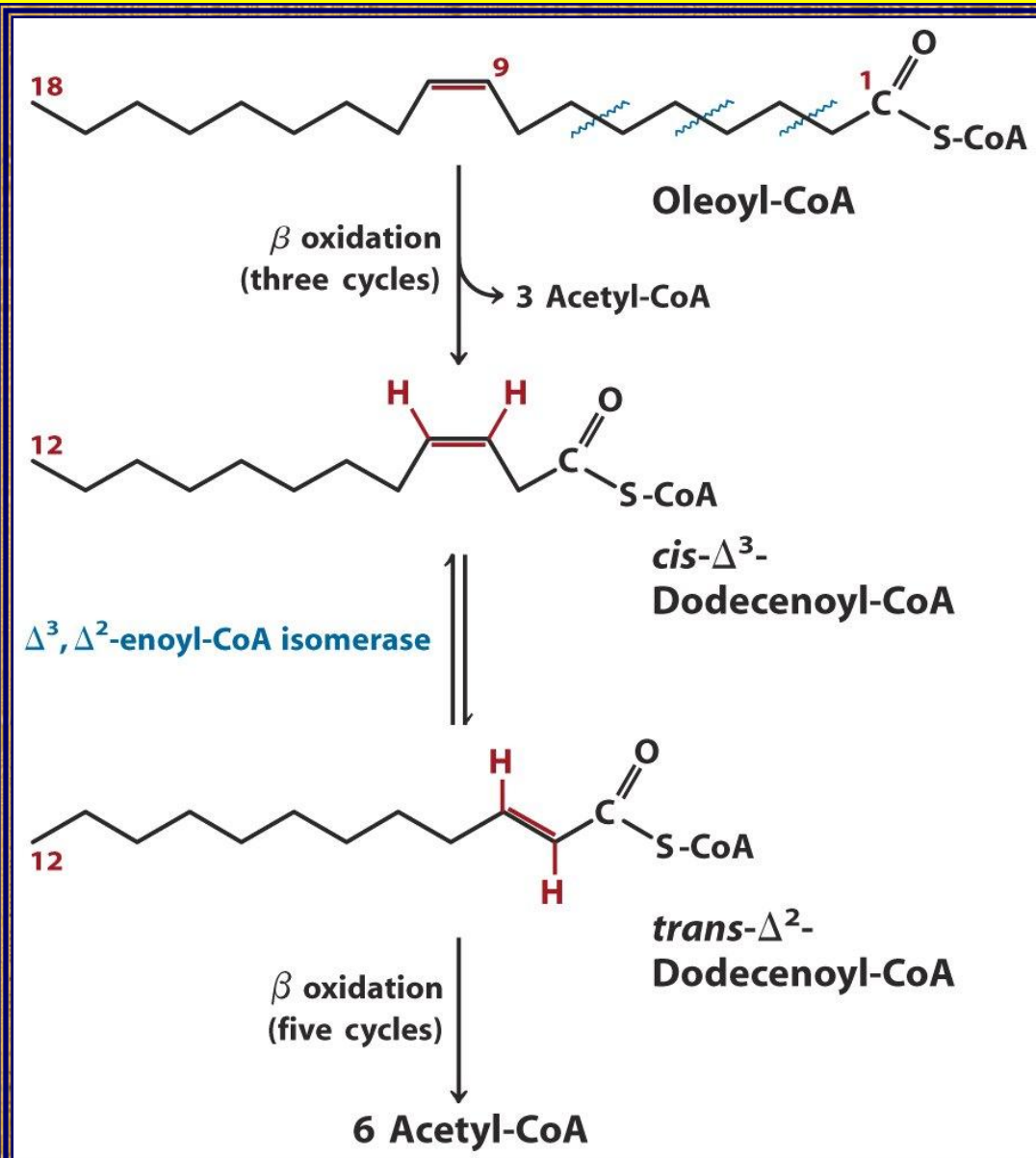
- Then **enoyl-CoA isomerase** repositions bond to C-2-C-3 and converts it to the *trans* isomer .

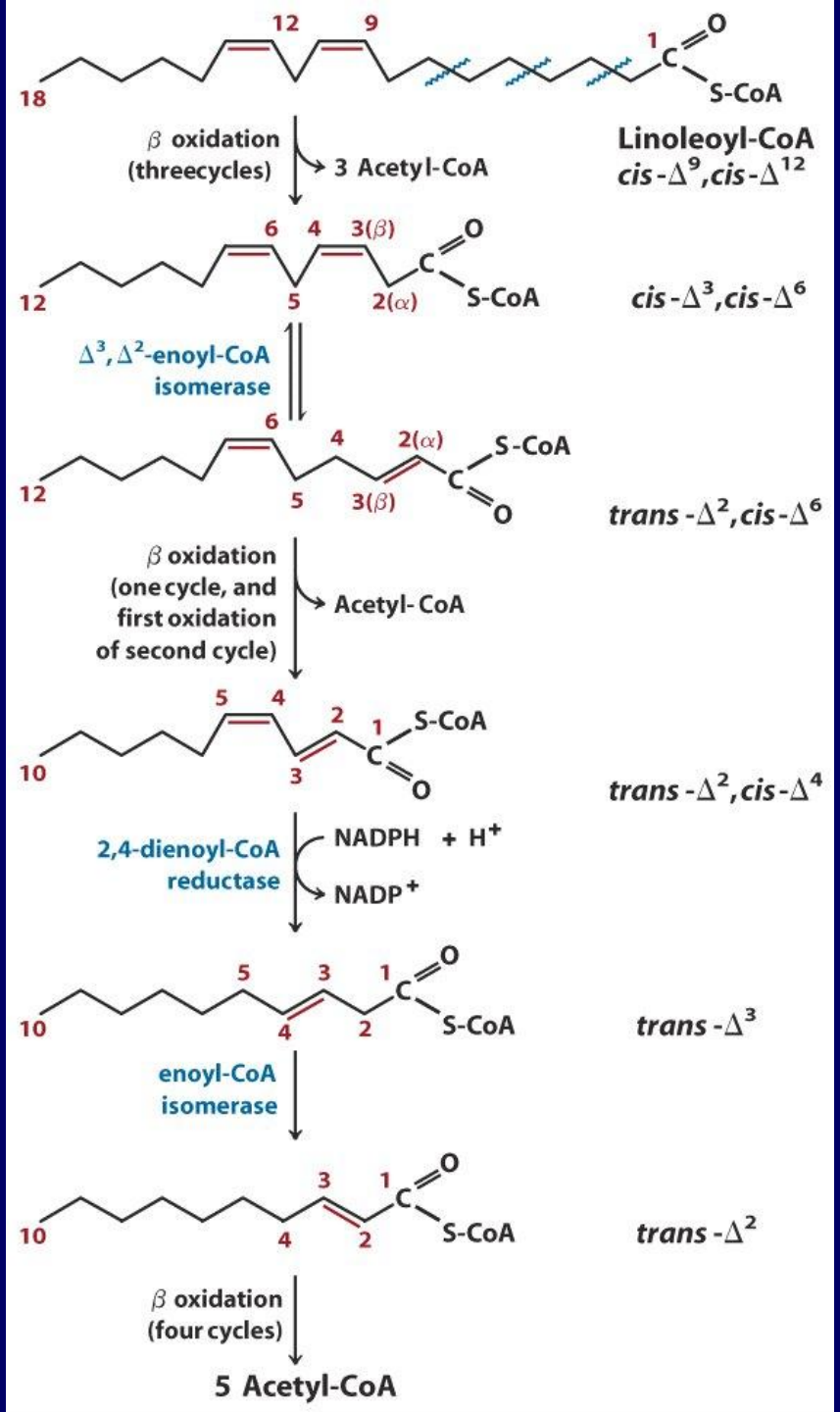
- Then the acyl-CoA can proceed via the normal pathway starting from enoyl-CoA hydratase.

2)A second enzyme, **2,4-dienoyl-CoA reductase**, is required for fatty acids that have two double bonds spaced by three carbons (*e.g.* linoleate, 18:2(D9,12)) .

- It converts them to *trans* isomers and repositions the double bonds so that they are conjugated – *i.e.* D2,4.
- Then they are processed normally.

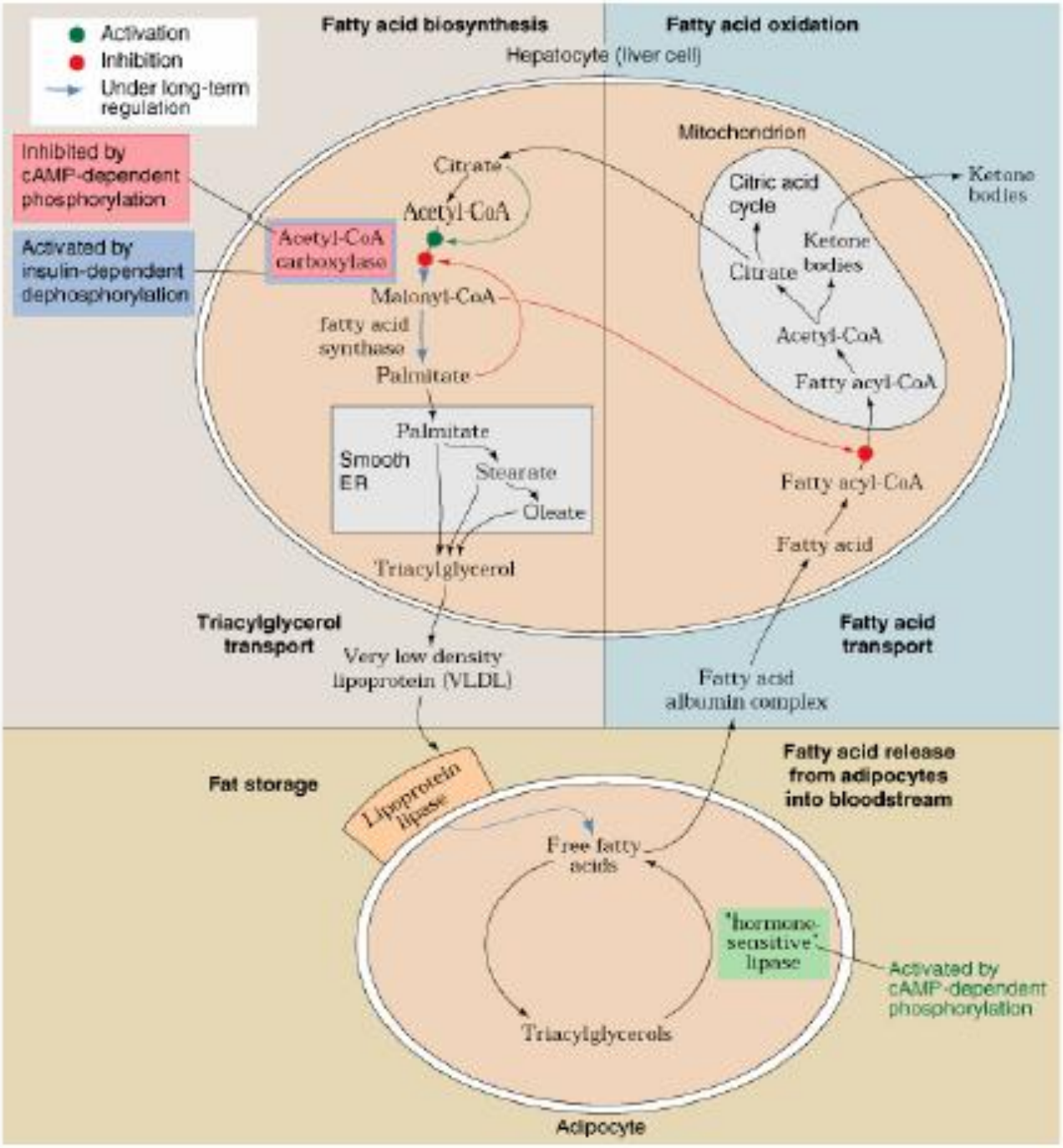
Oxidation of an Unsaturated Fatty Acid





Oxidation of a poly-unsaturated fatty acid

Fatty Acid Metabolism – Summary & Regulation

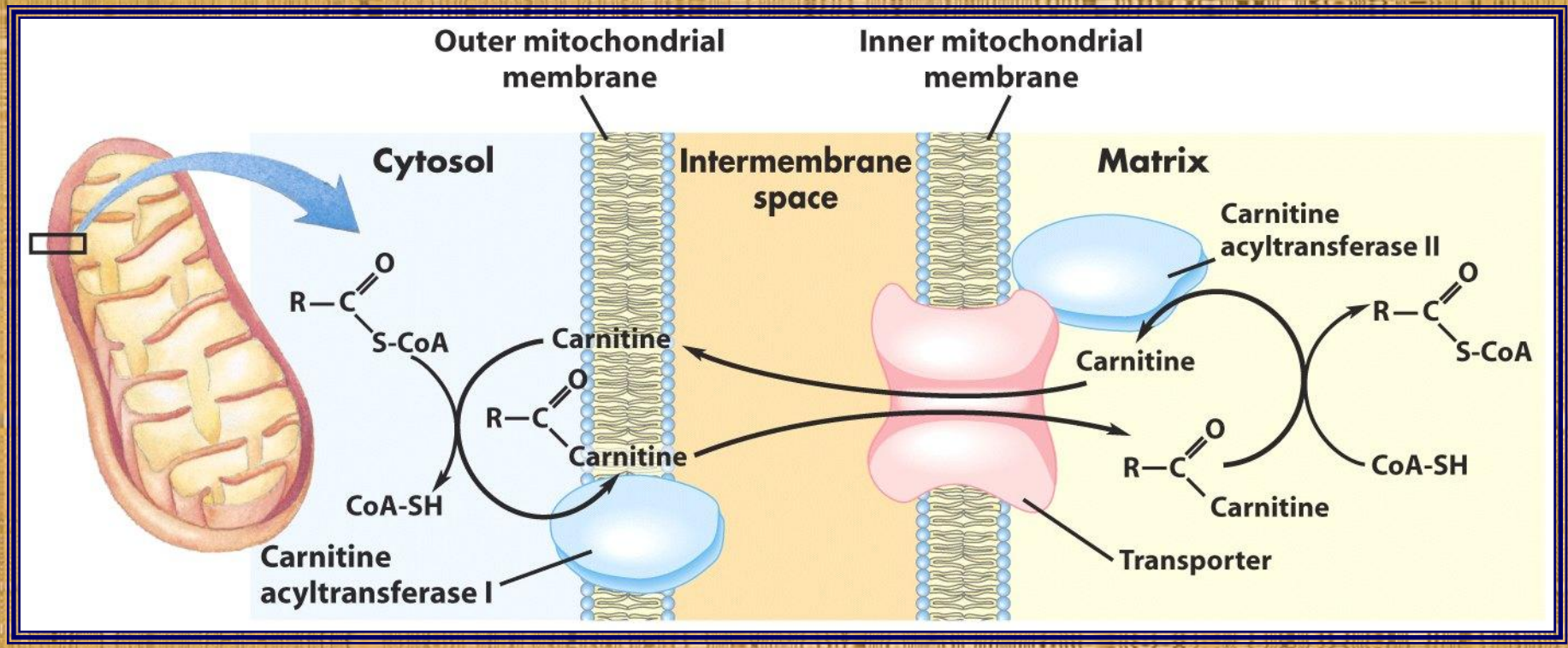


Regulation of fatty acid oxidation

- In the liver, fatty acyl-CoA in the cytosol can enter two pathways: it can be oxidized in the mitochondria or it can be converted into triacylglycerols in the cytosol and destined for storage.
- Which pathway predominates depends on the rate of import into the mitochondria.
- If carbohydrates are plentiful, acetyl-CoA does not enter the citric acid cycle.

- Instead it is converted to malonyl-CoA, the first precursor in fatty acid synthesis.
- Malonyl-CoA inhibits carnitine acyltransferase I, and therefore inhibits mitochondrial import and oxidation.
- This ensures that oxidation of fatty acids is inhibited when the liver is well-supplied with glucose.

Transport into Mitochondria is the Commitment Point for Oxidation of Fatty Acids



Summary

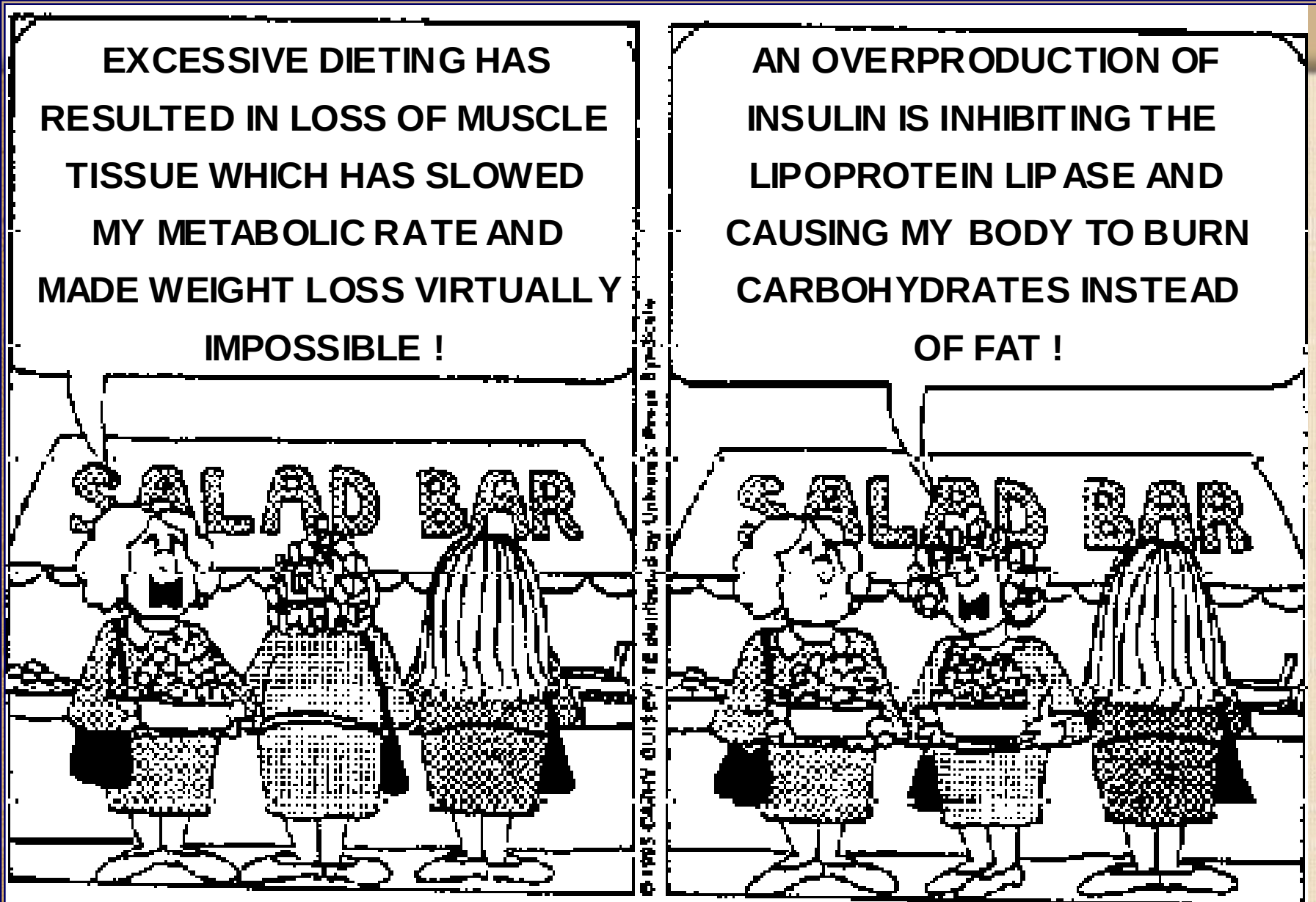
1. Triacylglycerols are mobilized from adipose tissue by hormones.

2. When they reach their target tissues they are first imported into the cell, then imported into the mitochondria to be oxidized.

3. The oxidation reactions yield acetyl-CoA, which then enters the citric acid cycle.

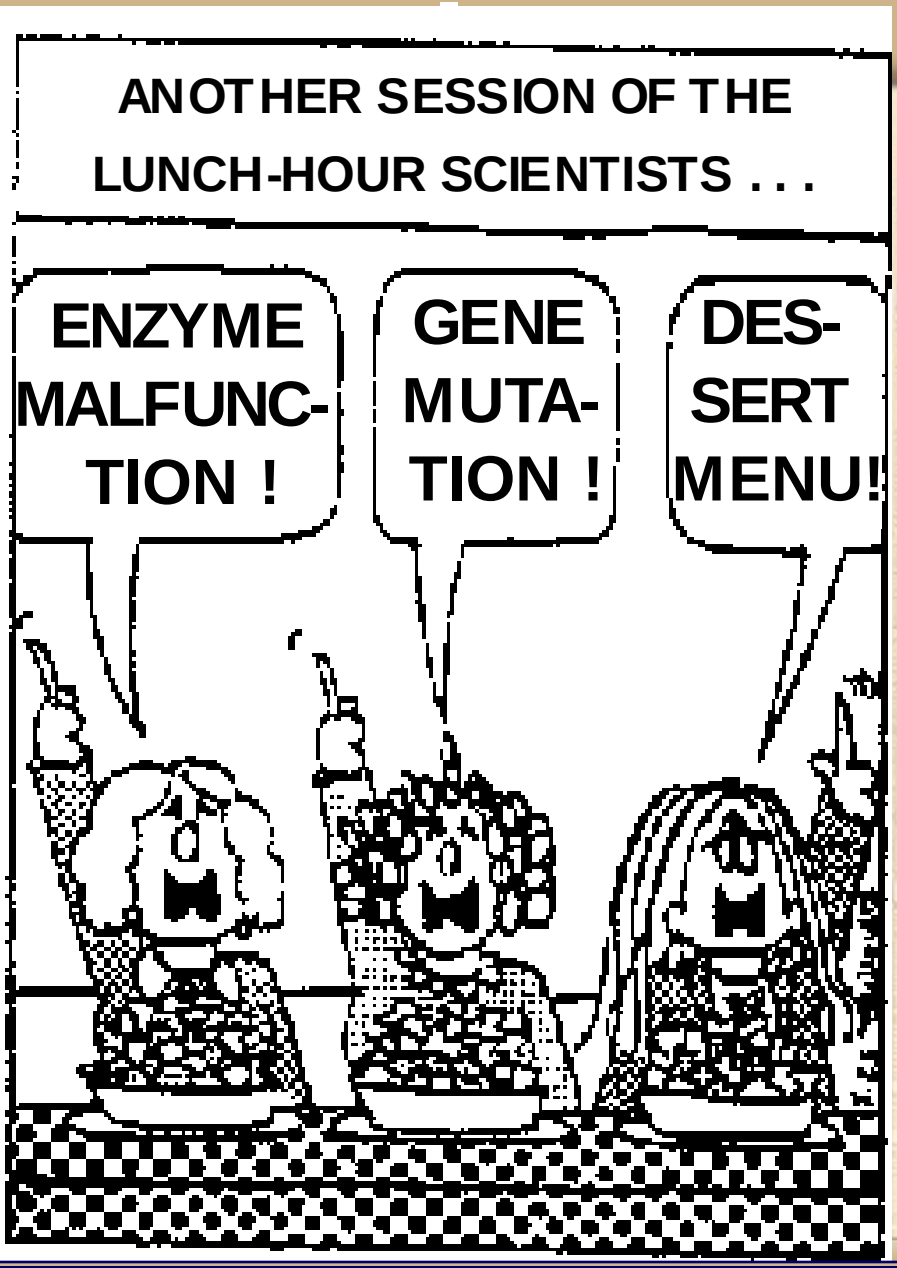
4. Oxidation of fatty acids produces a large yield of ATP.

CATHY


EXCESSIVE DIETING HAS RESULTED IN LOSS OF MUSCLE TISSUE WHICH HAS SLOWED MY METABOLIC RATE AND MADE WEIGHT LOSS VIRTUALLY IMPOSSIBLE !
AN OVERPRODUCTION OF INSULIN IS INHIBITING THE LIPOPROTEIN LIPASE AND CAUSING MY BODY TO BURN CARBOHYDRATES INSTEAD OF FAT !
SALAD BAR
SALAD BAR

CATHY


A BIOCHEMICAL IMBALANCE OF THE NEUROTRANSMITTER SERTONIN IS CREATING UNCONTROLLABLE CRAVINGS AND APPETITE !
BAR


ANOTHER SESSION OF THE LUNCH-HOUR SCIENTISTS . . .
ENZYME MALFUNC-TION !
GENE MUTA-TION !
DES-SERT MENU!