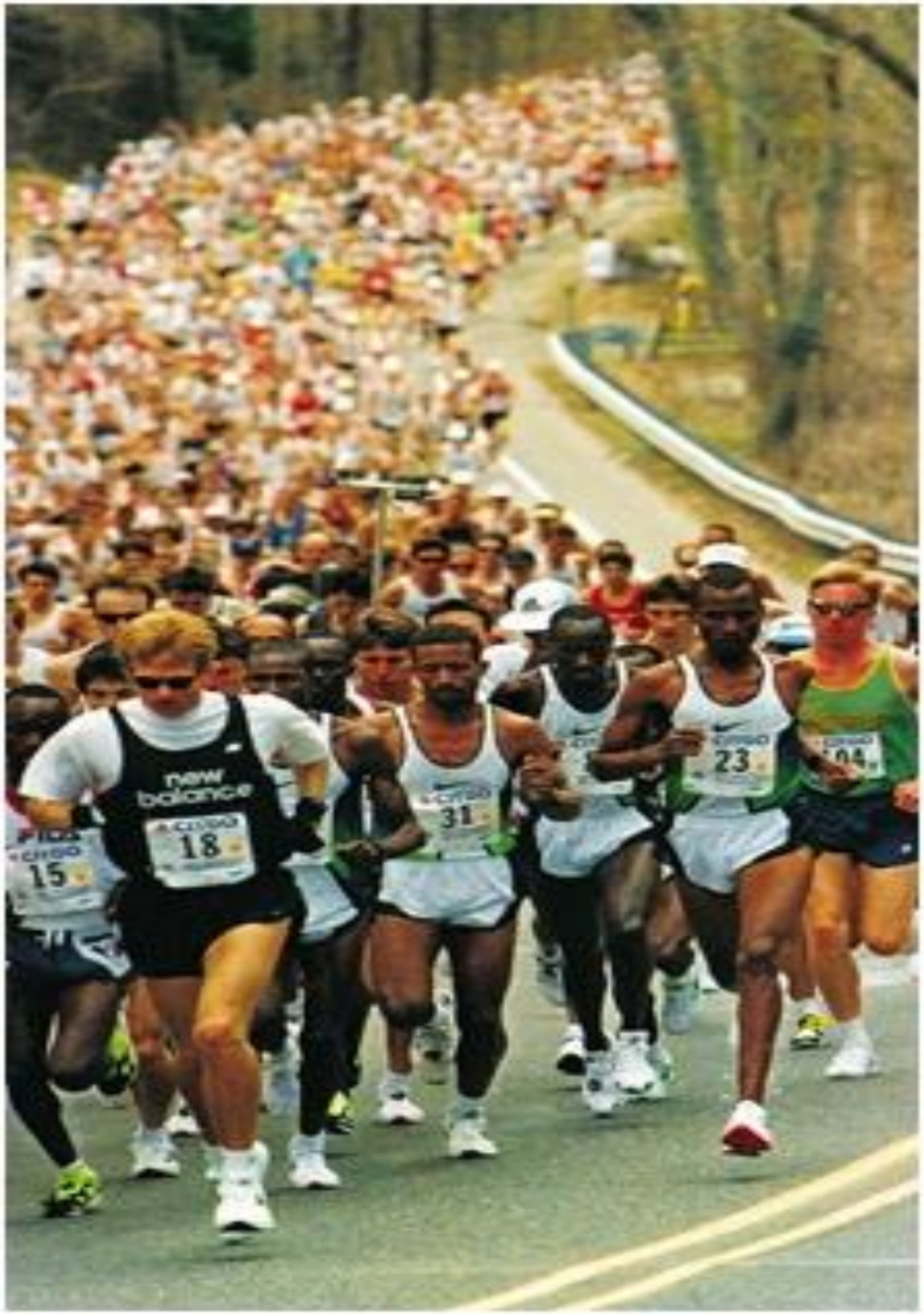
Fatty Acid Oxidation



Cells can obtain fatty acid fuels from 3 sources

1. Fats consumed in the diet

   Digestion & absorption of dietary lipids occur in the small intestine, and the fatty acids released from triglycerols are packaged & delivered to muscle & adipose tissues…

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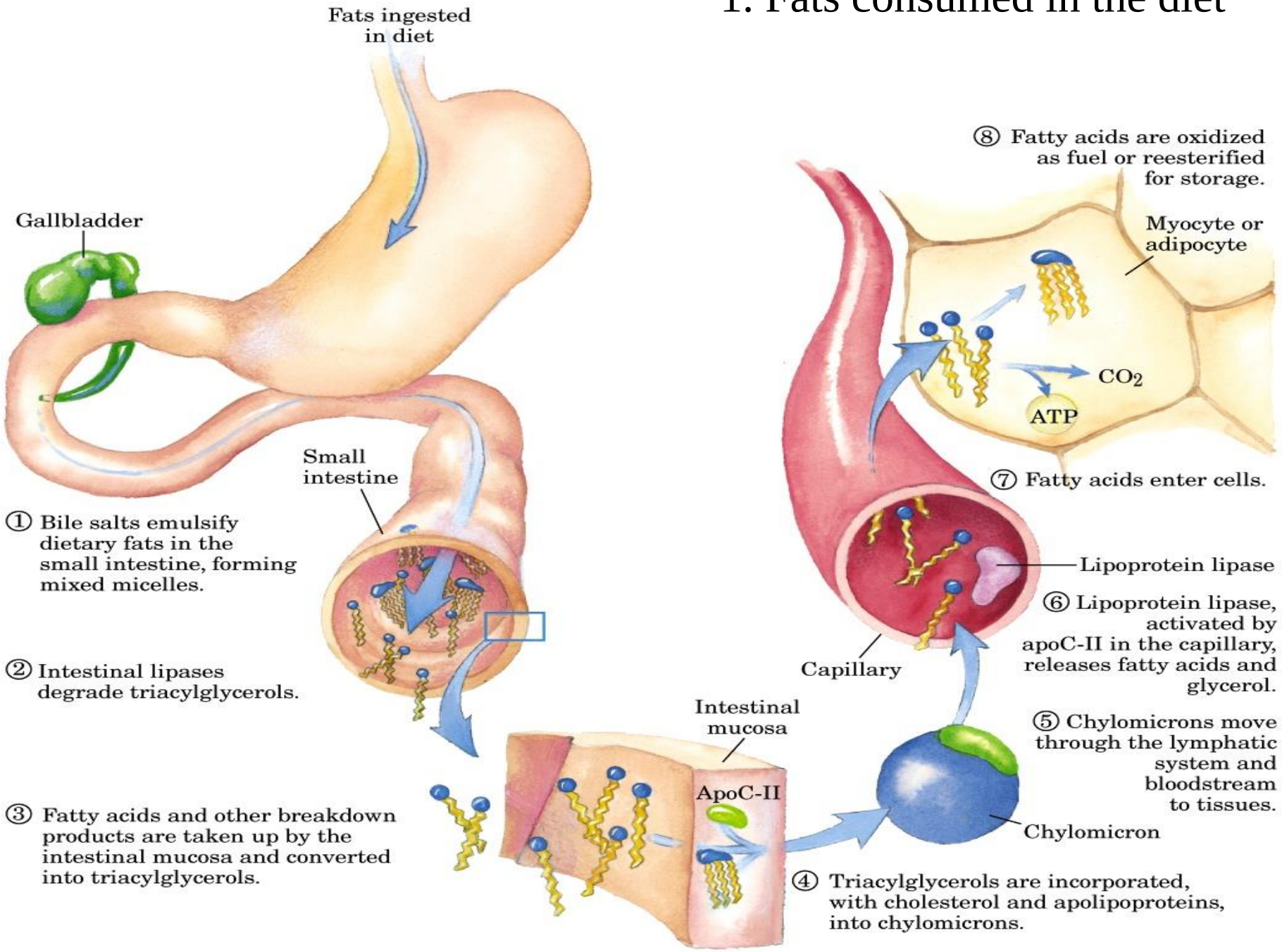

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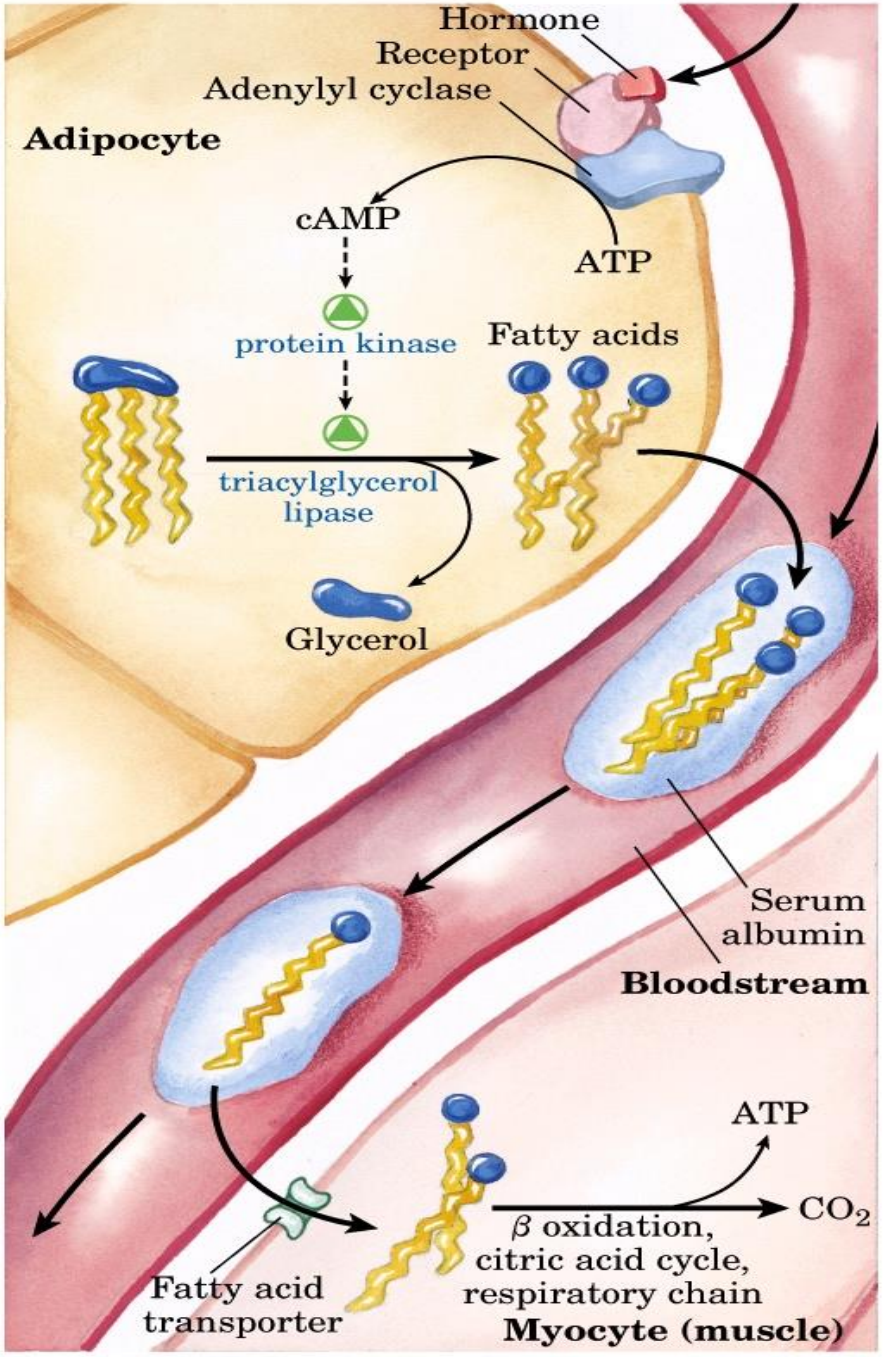
   Digestion & absorption of dietary lipids occur in the small intestine, and the fatty acids released from triglycerols are packaged & delivered to muscle & adipose tissues…

2. Fats stored in cells as lipid droplets



Mobilization of Triglycerides stored in adipose tissues

- **Low blood glucose levels** trigger the secretion of **Epinephrine** & **Glucagon**
- Activate adenylate cyclase in adipocytes to produce cAMP
- Activates protein kinase then glycerol lipase that hydrolyzes triglycerides to Fatty acids & Glycerol
- **Fatty acids** pass into blood (bind to serum albumin), carried to tissues (skeletal muscles, heart, renal cortex), dissociates from albumin, transported into cells… mitochondria… β-oxidation
- **Glycerol** (phosphorylation) …Glycerol-3-P …Glyceraldehyde-3-P … Glycolysis

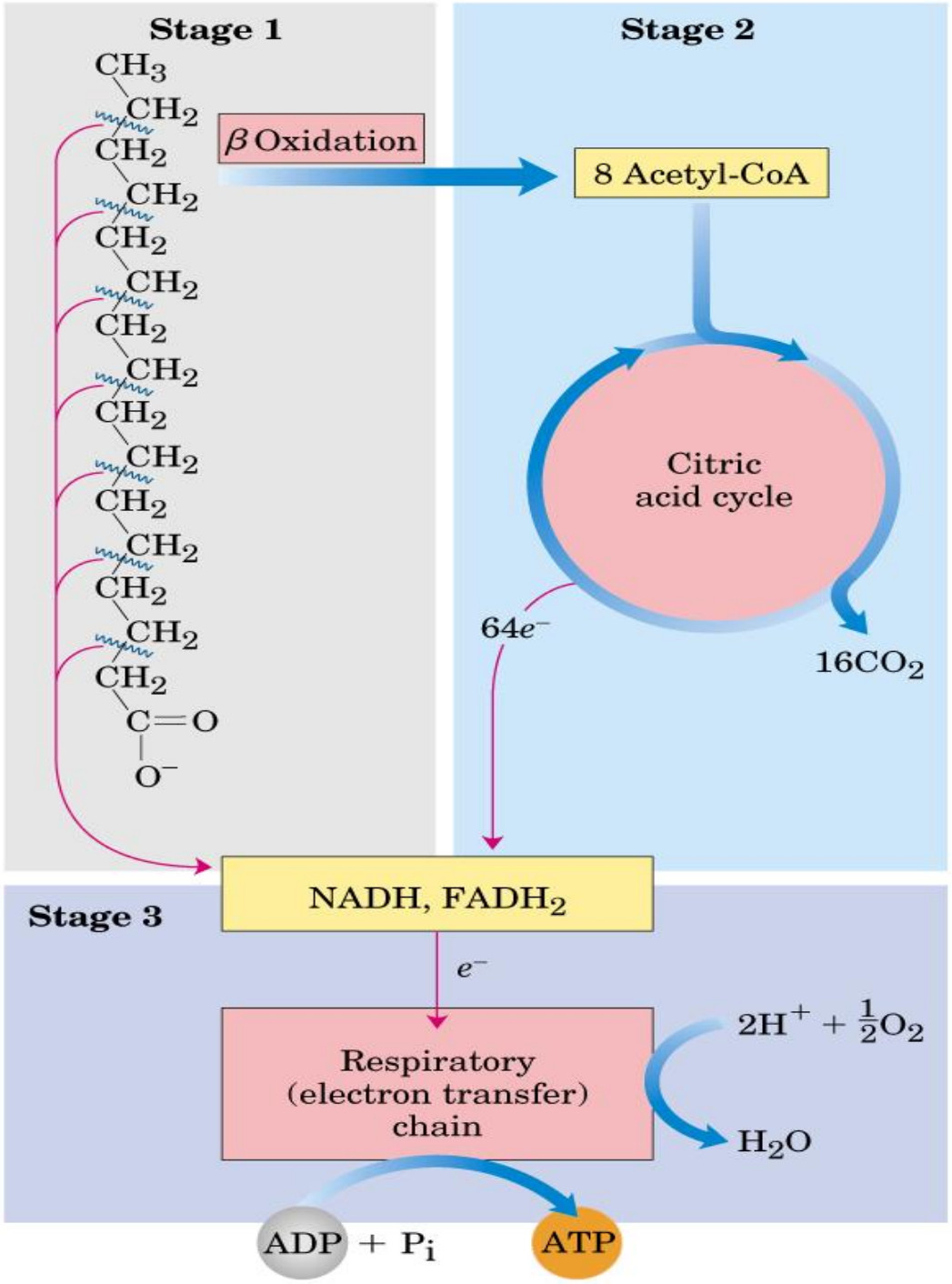
Cells can obtain fatty acid fuels from 3 sources

1. Fats consumed in the diet
2. Fats stored in cells as lipid droplets

3. Fats synthesized in one organ for export to another

   liver converts excess dietary carbohydrates to fats for export to other tissues.

Stages of fatty acid oxidation



- **Stage 1** (β-oxidation): long chain fatty acid is oxidized to acetyl-CoA
- **Stage 2**: the acetyl groups are oxidized to CO_2 via TCA cycle
- **Stage 3**: Electrons are transported to O_2 (respiratory chain) & energy (ATP) is synthesized in oxidative phosphorylation.

Fatty acids are activated and transported into mitochondria

1. Fatty acid activation:

Fatty acids must be **esterified to Coenzyme A** before they can undergo oxidative degradation, be utilized for synthesis of complex lipids, or be attached to proteins as lipid anchors.

Acyl-CoA Synthases (Thiokinases) of **ER** & **outer mitochondrial membranes** catalyze activation of **long chain fatty acids**, esterifying them to coenzyme A.

This process is **ATP-dependent**, & occurs in 2 steps.

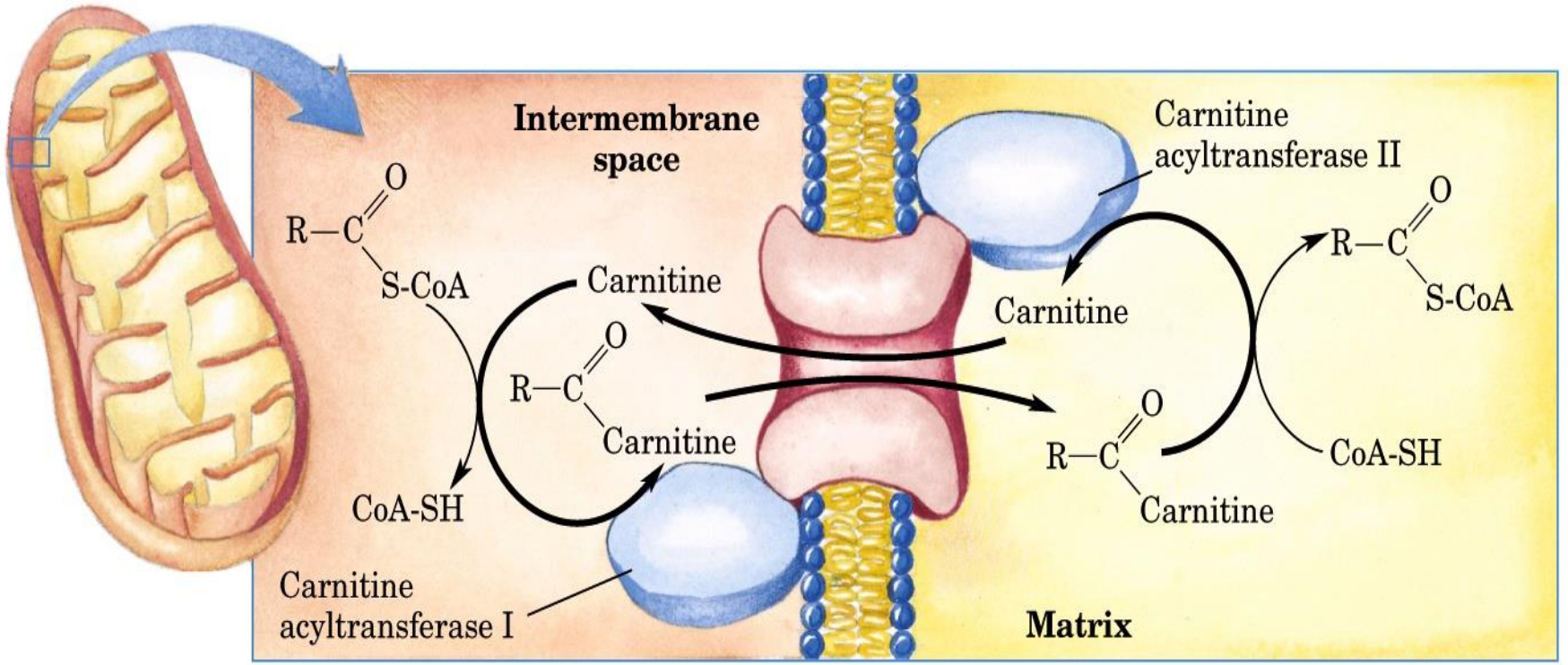
Overall:

fatty acid + ATP + HS-CoA → acyl-CoA + AMP + 2 P_i

2. Fatty acid entry into mitochondria

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

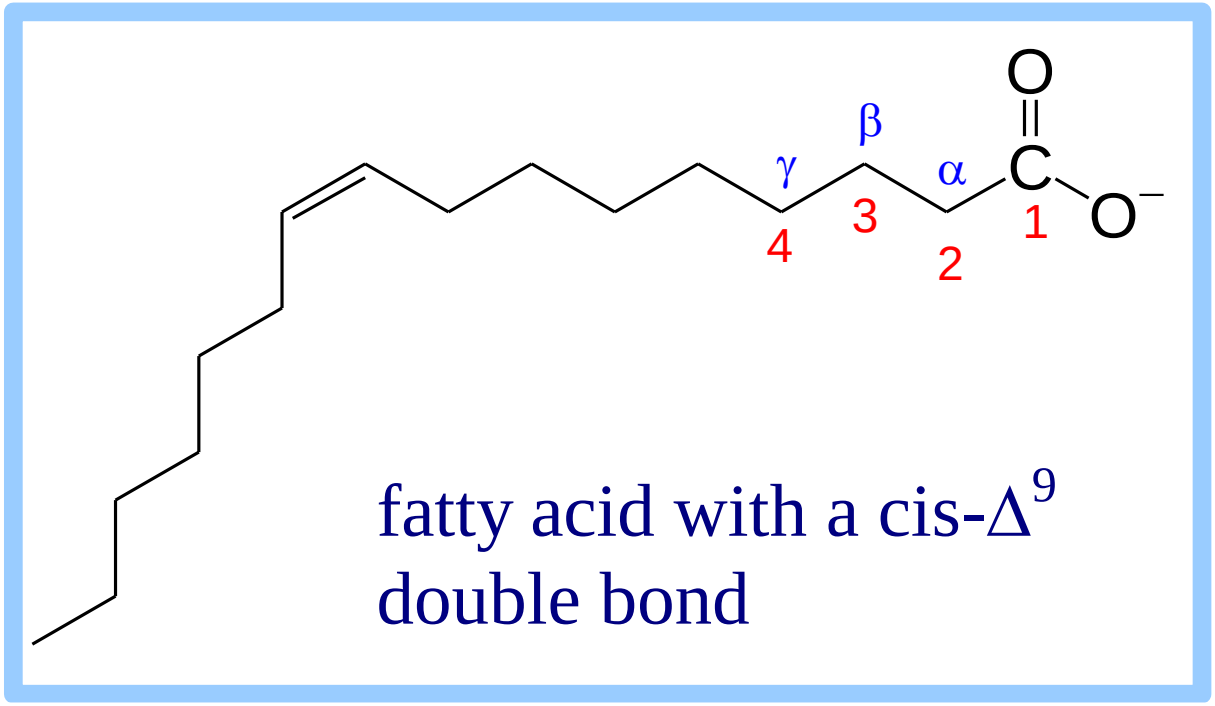
The free fatty acids that enter the cytosol from the blood can't pass directly through the mitochondrial membranes but must undergo a series of enzymatic reactions.



3. β-oxidation

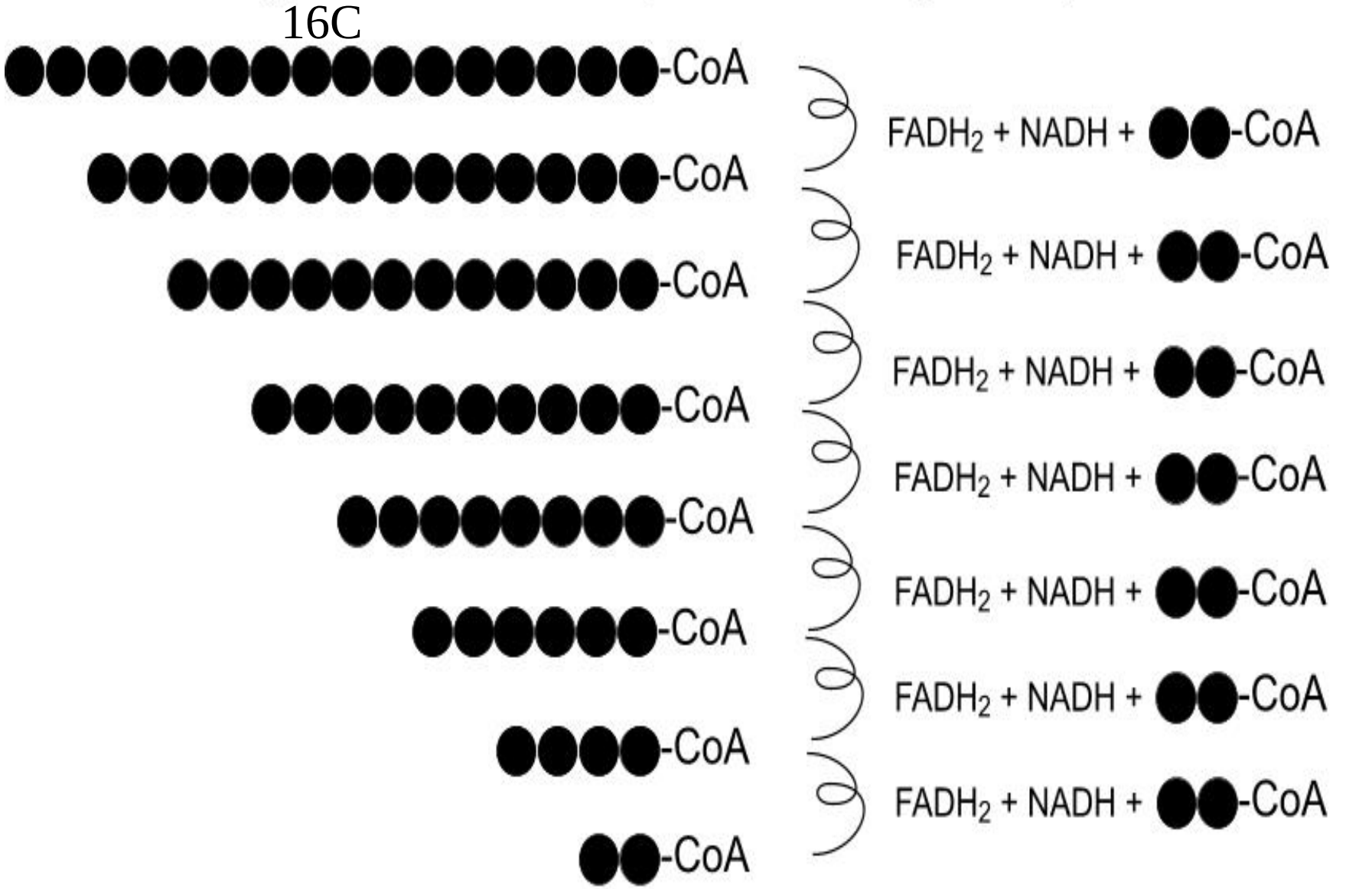
The pathway for catabolism of fatty acids is referred to as the **β-oxidation** pathway, because oxidation occurs at the **β-carbon (C-3).**

β-oxidation: fatty acids undergo oxidative removal of successive 2-C units in the form of acetyl-CoA, starting from the carboxyl end of the fatty acyl chain.



fatty acid with a cis-Δ^9 double bond

Energy Production from β-oxidation of palmitoyl-CoA



Total: palmitoyl-CoA ------> 7 FADH2 + 7 NADH + 8 AcCoA

Summary of one round of the β-oxidation pathway:

fatty acyl-CoA + FAD + NAD^+ + HS-CoA →

fatty acyl-CoA (2 C less) **+ $FADH_2$ + NADH + H^+ + acetyl-CoA**

- The β-oxidation pathway is **cyclic**.

The product, **2 carbons shorter**, is the input to another round of the pathway.

Fatty acid oxidation is a major source of cell ATP.

Compare energy yield oxidizing a **12-C fatty acid**.
Assume:

- **1.5 ATP** produced per **$FADH_2$** reoxidized in the respiratory chain.
- **2.5 ATP** produced per **NADH** reoxidized in the respiratory chain.

table 17–1

Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

16 C = 8 Acetyl CoA

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

β-oxidation:

Palmitoyl-CoA + 7CoA + 7O2 + 28Pi+ 28ADP → 8 acetyl-CoA + 28ATP + 7H2O

Full oxidation:

Palmitoyl-CoA + 23O2 + 108Pi+ 108ADP → CoA + 108ATP + 16CO2 + 23H2O

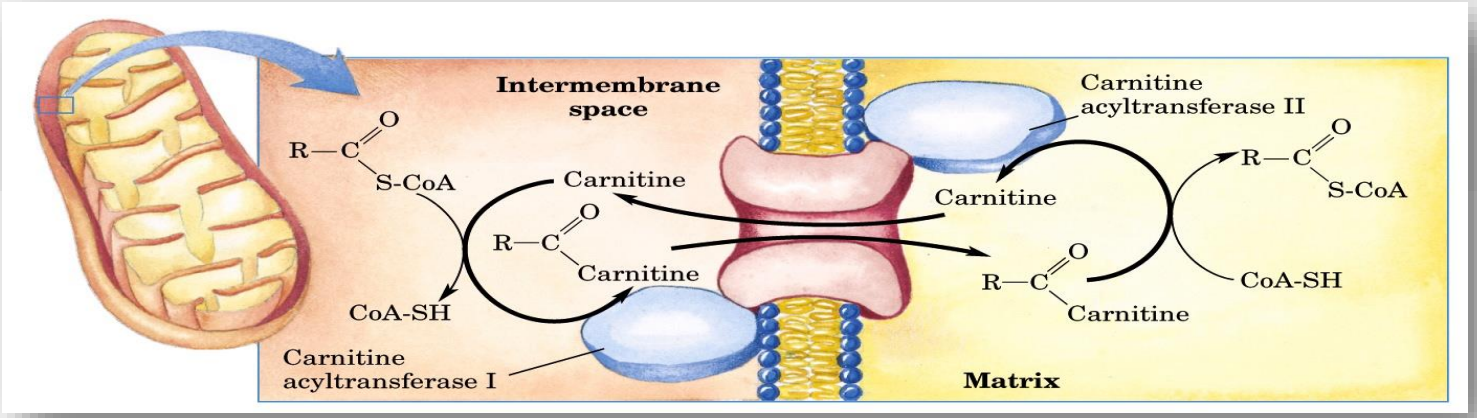
Regulation of fatty acid oxidation

- **In liver**

1. β-oxidation
2. triacylglycerols & phospholipids

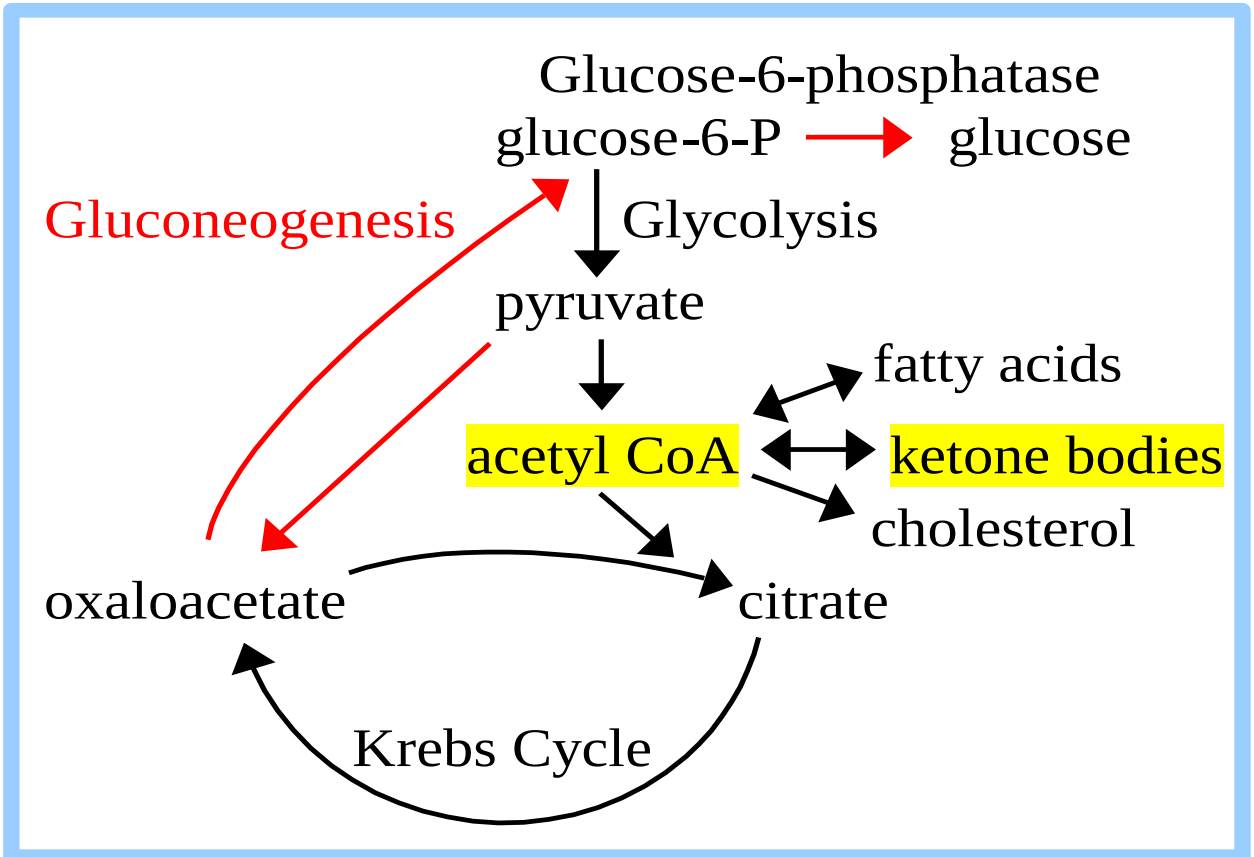
- **<u>A rate limiting step</u> ….** three step process:

➢ fatty acyl groups are carried from **cytosolic** fatty acyl CoA into the **mitochondrial** matrix.

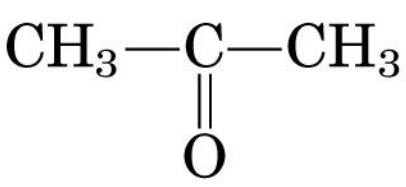


Formation of Ketone Bodies

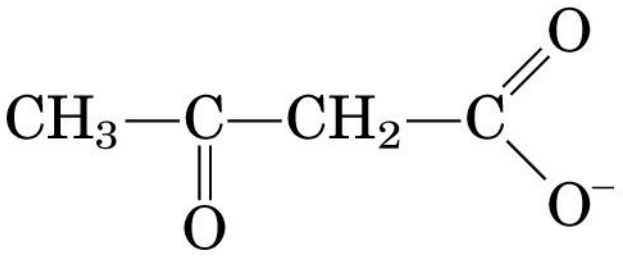
- During **fasting** or carbohydrate starvation, oxaloacetate is depleted in **liver** due to gluconeogenesis.
- This impedes entry of acetyl-CoA into Krebs cycle.
- Acetyl-CoA in liver mitochondria is converted then to **ketone bodies**: **acetoacetate & b-hydroxybutyrate**.



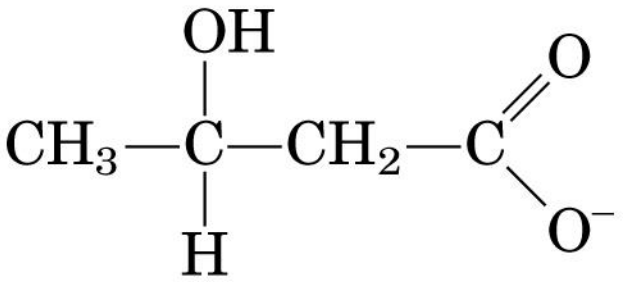
Ketone bodies



Acetone

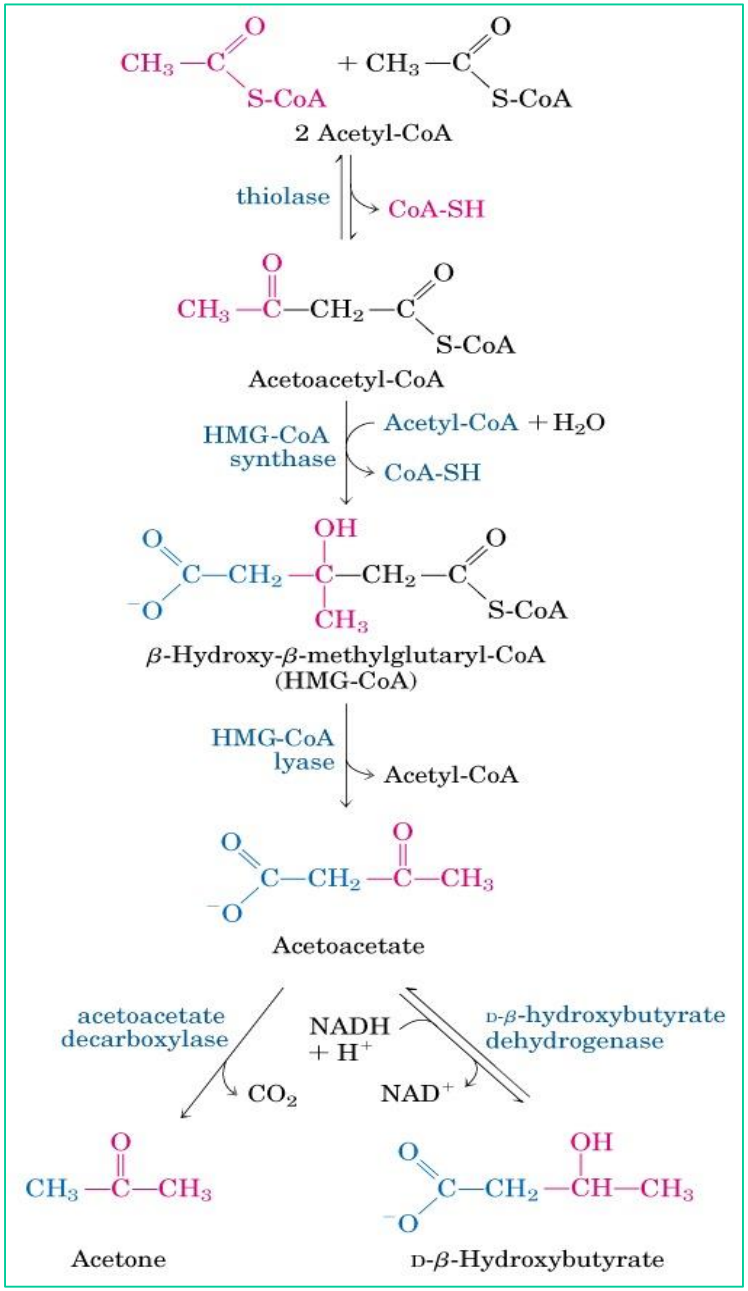


Acetoacetate

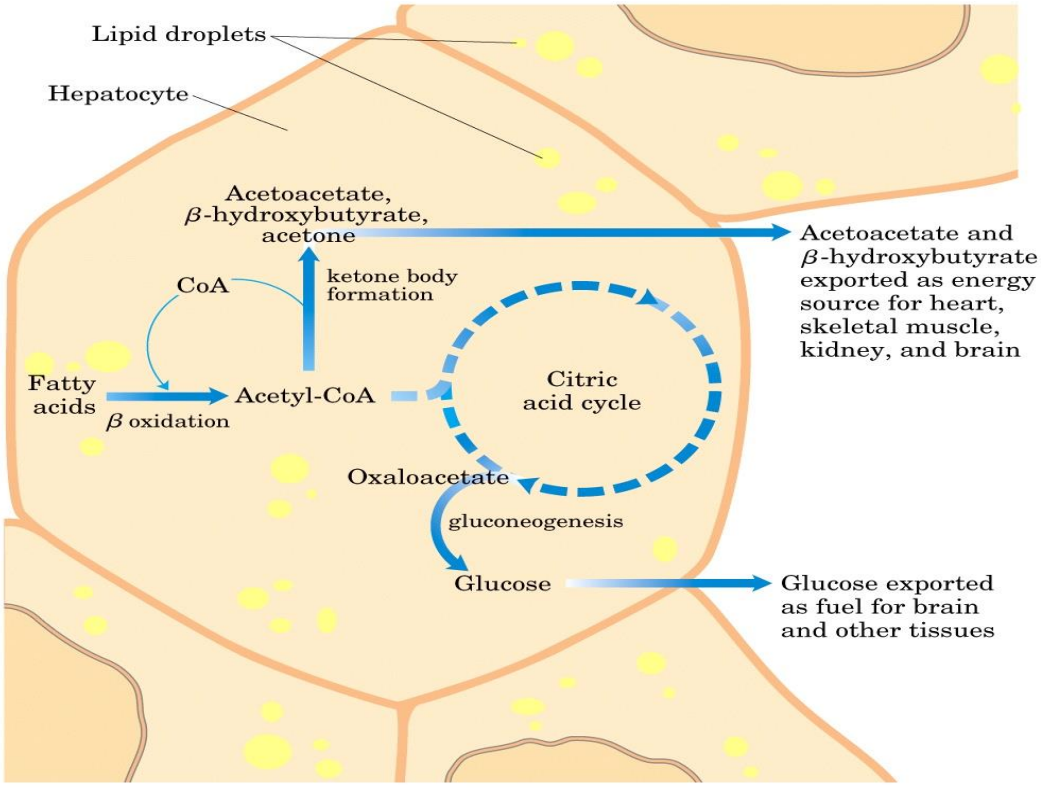


D-β-Hydroxybutyrate

Formation of ketone bodies from acetyl-CoA



Formation of Ketone Bodies



- **ketone bodies function as an alternative fuel:**

✓ **Ketone bodies** are transported in the blood to other cells, where they are converted back to **acetyl-CoA** for catabolism in Krebs cycle, to generate ATP.

- Amino acids must be degraded to supply input to gluconeogenesis when hypoglycemia occurs, since acetate cannot be converted to glucose.

Formation of Ketone Bodies

Ketone Body Accumulation in Diabetic Ketosis

	Urinary excretion (mg/24 h)	Blood concentration (mg/100 mL)
Normal	≤125	<3
Extreme ketosis (untreated diabetes)	5,000	90

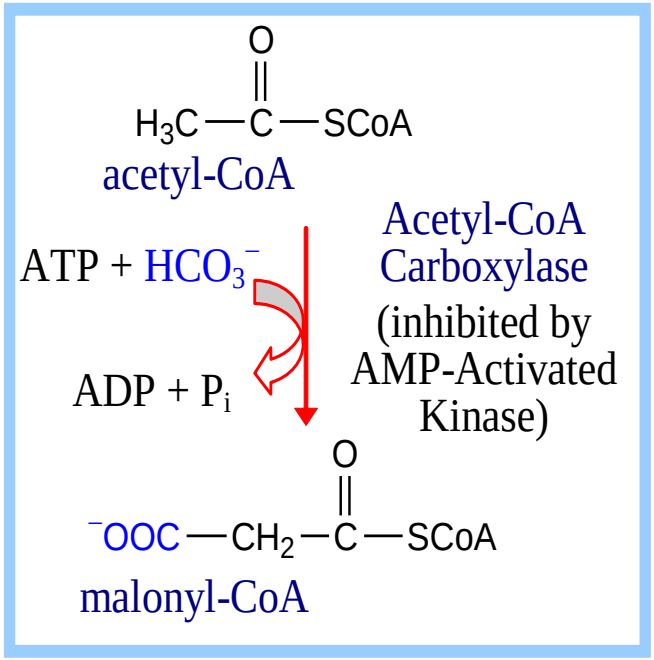
Acidosis:

In untreated diabetes, the concentration of ketone bodies (two of which are acids) in blood increases so much that it decreases the pH of blood. This condition is called "acidosis" which can lead to coma or death.

Ketosis:

High concentration of ketone bodies in blood and urine is referred as "ketosis". Due to high concentration of acetoacetate, which is converted to acetone, the breath and urine of the untreated diabetic patients smells like acetone.

Anabolism of fatty acids



- Occurs in cytosol in animals.
- Requires:

✓ **acetyl-CoA** and **malonyl-CoA**

➢ Malonyl-CoA is formed from acetyl-CoA and bicarbonate catalyzed by acetyl-CoA carboxylase.

✓ reducing power from **NADPH**

- Activation of fatty acids by 2 different –SH groups on protein
- Fatty acids are built in several passes, processing one acetate unit at a time.
- The acetate is coming from malonyl-CoA (activated malonate).
- Each pass involves reduction of a carbonyl carbon to a methylene carbon.

Anabolism of fatty acids

- Synthesis of fatty acids is catalyzed by **fatty acid synthase**.

- FAS system:

✓ Elongates the fatty acyl chain by two carbons at each step

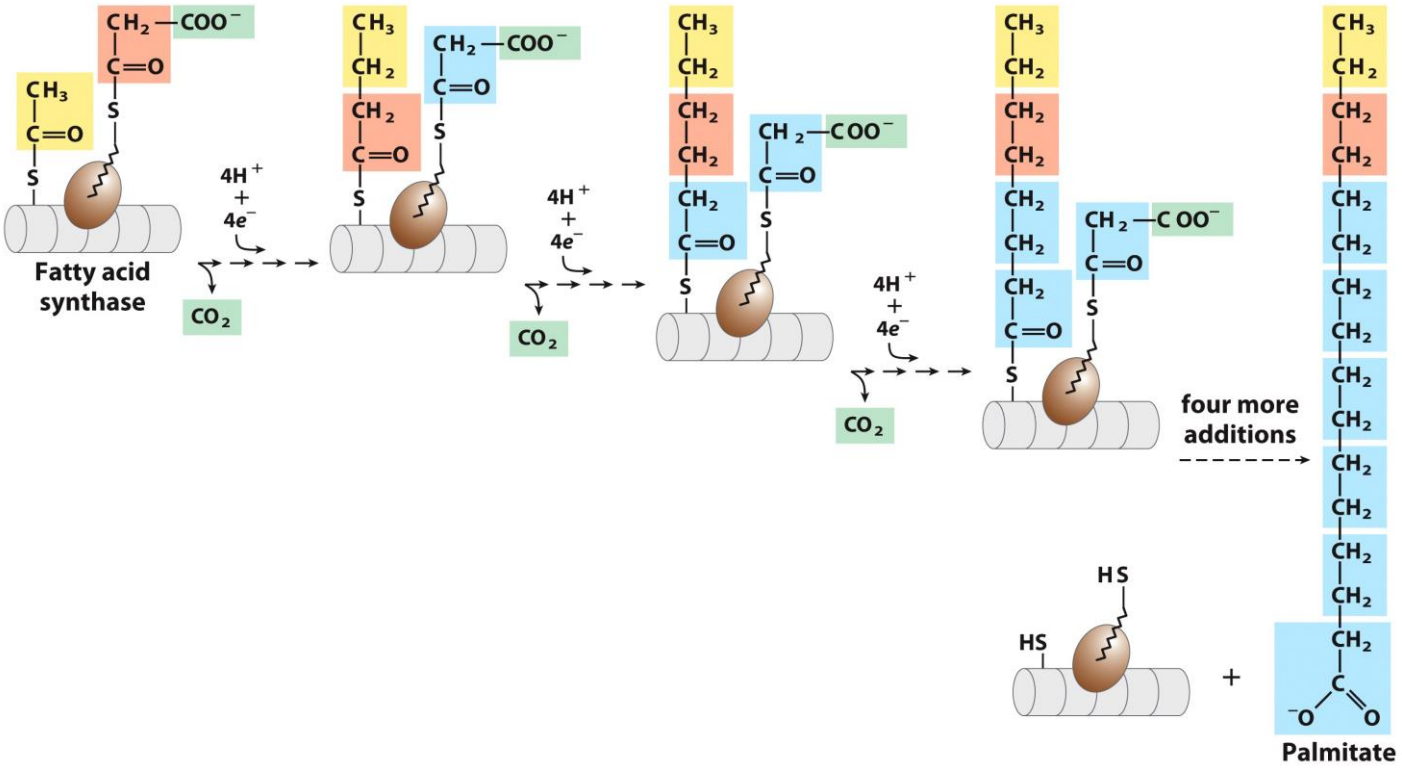
✓ Uses NADPH as the electron donor

✓ Uses two enzyme-bound -SH groups as activating groups

Synthesis of Palmitate

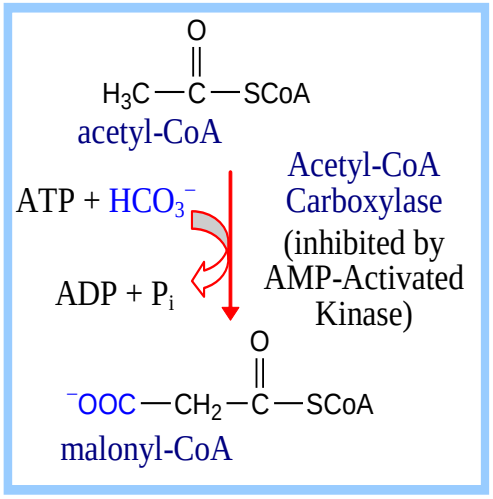
7 Acetyl-CoA + 7 CO_2 + 7 ATP → 7 mal-CoA + 7 ADP + 7 Pi

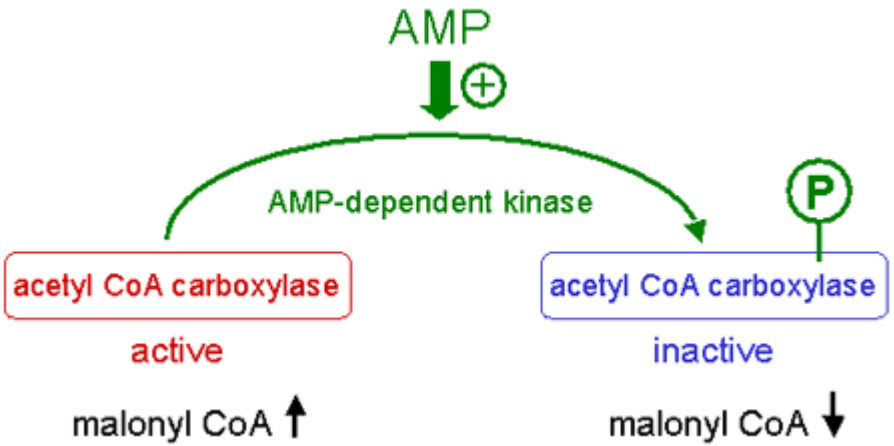
Acetyl-CoA + 7 mal-CoA + 14 NADPH + 14 H^+ → Palmitate + 7 CO_2 + 8 CoA + 14 NADP+ + 6 H_2O



Regulation of fatty acid metabolism

- **AMP-Activated Kinase** is allosterically activated by **AMP**.
- **Acetyl-CoA Carboxylase** is inhibited when phosphorylated by AMP-Activated Kinase, leading to decreased malonyl-CoA.

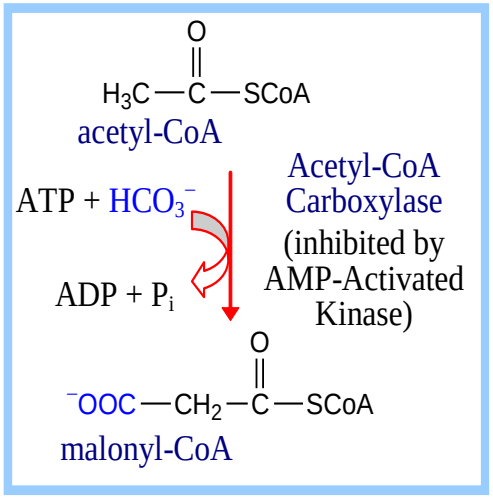


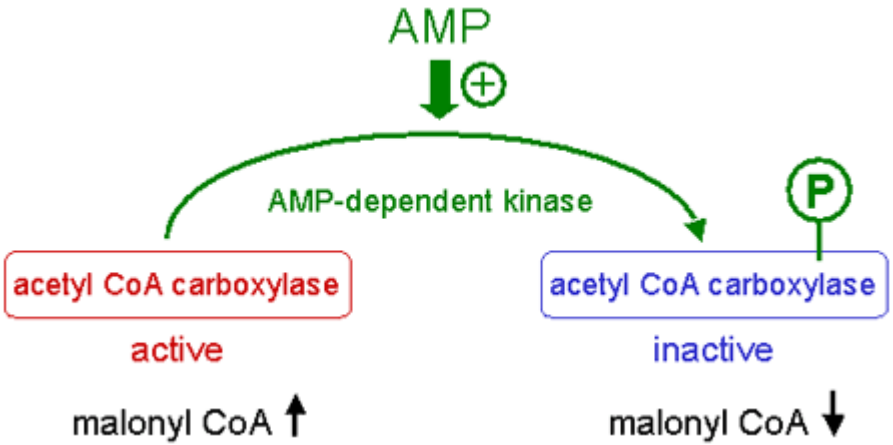


- Malonyl-CoA:
  - ✓ precursor for fatty acid synthesis
  - ✓ inhibits Carnitine Palmitoyl Transferase I
    - → Inhibits fatty acid oxidation

Regulation of fatty acid metabolism

- The decrease in malonyl-CoA concentration leads to:
  - ➢ increased activity of Carnitine Palmitoyl Transferase I
  - ➢ Increased fatty acid oxidation
- generates acetyl-CoA, for entry into Krebs cycle with associated ATP production.

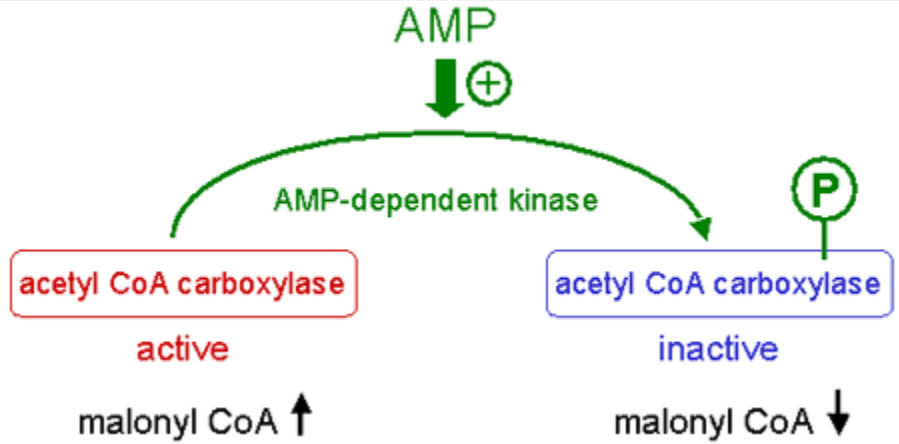




Acetyl-CoA

AMP-Activated Kinase

Acetyl-CoA ⇌ Carboxylase.



Malonyl-CoA ⇌→ FA oxidation

Fatty acid synthesis