

BIOC 385: M05.T05-Miesfeld

Assigned Reading: *Biochemistry* Chapter 19.1a





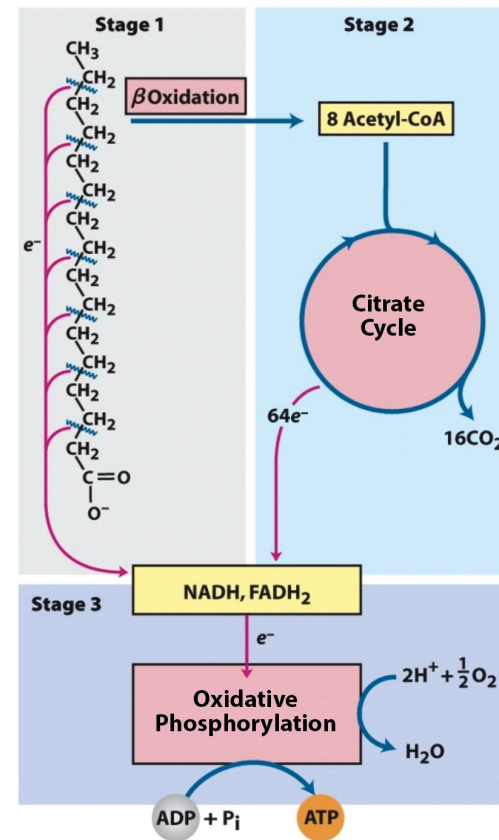
The Fatty Acid Oxidation Pathway in Mitochondria

M05.T05-Miesfeld



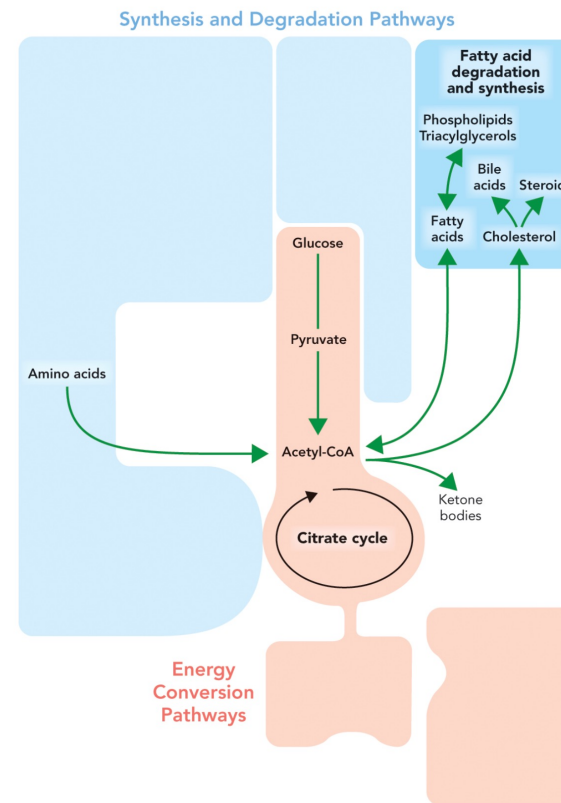
The Big Picture

- Fatty acid oxidation mobilizes long-term energy reserves when glucose is scarce, sustaining metabolism during fasting and exercise.
- The acetyl-CoA that is produced links lipid metabolism to the citrate cycle, ketogenesis, and biosynthesis of cholesterol and steroids.



Acetyl-CoA is a Central Metabolite

- Acetyl-CoA integrates carbohydrate, amino acid, and fatty acid metabolism into a unified network of energy and biosynthetic pathways.
- Acetyl-CoA also serves as the precursor for cholesterol, bile acids, and steroids, coupling fatty acid degradation to essential biosynthesis.



Fatty Acid Metabolism: Key Questions

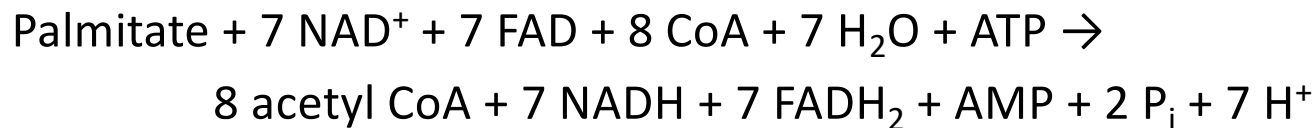
1. What **purpose does fatty acid metabolism** serve in animals?
 - Fatty acid oxidation in mitochondria is responsible for providing energy to cells when glucose levels are low.
 - Most humans store enough triacylglycerols in their adipose tissue to supply energy to the body for ~3 months during starvation. Liver and adipose cells convert excess acetyl-CoA into fatty acids that can be stored or exported as triacylglycerols.



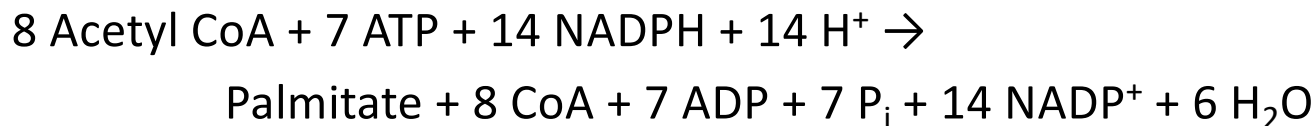
Fatty Acid Metabolism: Key Questions

2. What are the **net reactions** of fatty acid oxidation and fatty acid synthesis for the C₁₆ fatty acid palmitate?

Fatty acid oxidation:



Fatty acid synthesis:



Fatty Acid Metabolism: Key Questions

3. What are the **key enzymes** in fatty acid metabolism?

Fatty acyl-CoA synthetase catalyzes the “priming” reaction in fatty acid oxidation, converting free fatty acids in the cytosol into fatty acyl-CoA using ATP.

Carnitine acyltransferase I catalyzes the commitment step in fatty acid oxidation, which links fatty acyl-CoA molecules to carnitine for transport into the matrix.

Acetyl-CoA carboxylase catalyzes the commitment step in fatty acid synthesis by using acetyl-CoA to form the C₃ compound malonyl-CoA.

Fatty acid synthase is responsible for catalyzing a series of reactions that sequentially adds C₂ units to a growing fatty acid chain.



Fatty Acid Metabolism: Key Questions

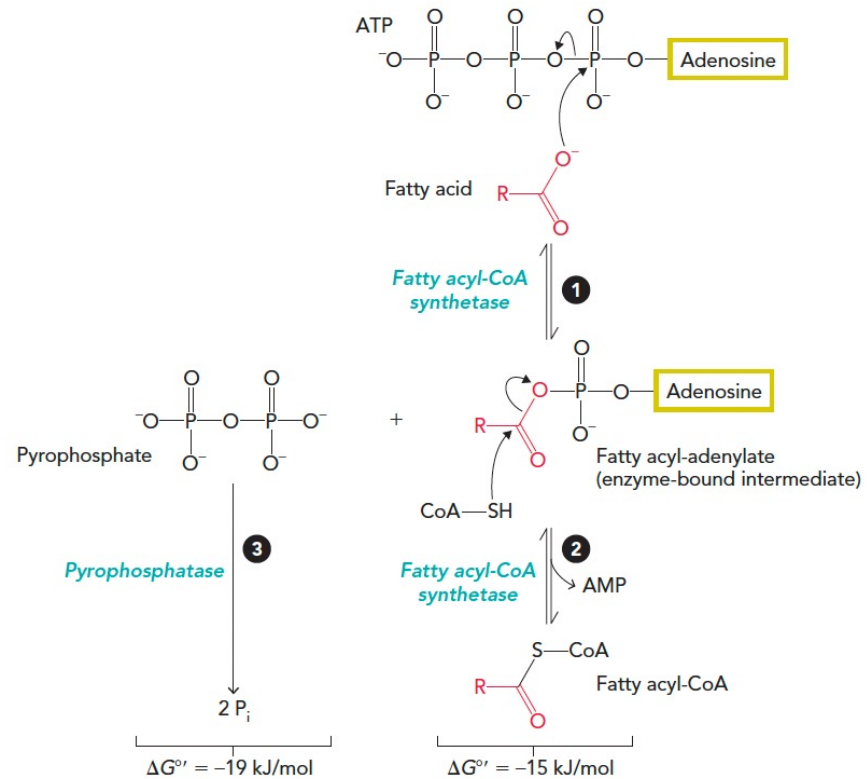
4. What are examples of fatty acid metabolism in **everyday biochemistry**?

- The kangaroo rat and the camel are two animals that survive in desert environments for long periods of time without drinking water, which they accomplish this by generating H_2O internally through the complete oxidation of fatty acids. The kangaroo rat obtains fatty acids from oils in seeds, whereas camels store triacylglycerols in the adipose tissue of their humps.



Fatty Acyl-CoA Synthetase: Fatty Acid Activation

- Fatty acyl-CoA synthetase catalyzes a two-step adenylation and thioesterification reaction that converts fatty acids to fatty acyl-CoA at the cost of 2 ATP.
- Hydrolysis of pyrophosphate helps drive this highly exergonic reaction, committing fatty acids to mitochondrial import; the energetics of the coupled reaction are -34 kJ/mol.



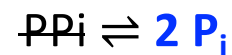
Fatty Acyl-CoA Synthetase: 2 ATP Equivalents

- The ATP-coupled fatty acyl-CoA synthetase reaction requires 2 ATP equivalents considering the nucleoside diphosphate kinase and adenylate kinase reactions.

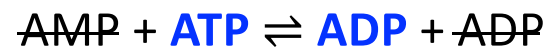
Fatty acyl-CoA synthetase:



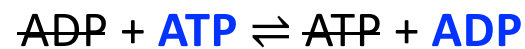
Pyrophosphatase:



Adenylate kinase:



Nucleoside diphosphate kinase:

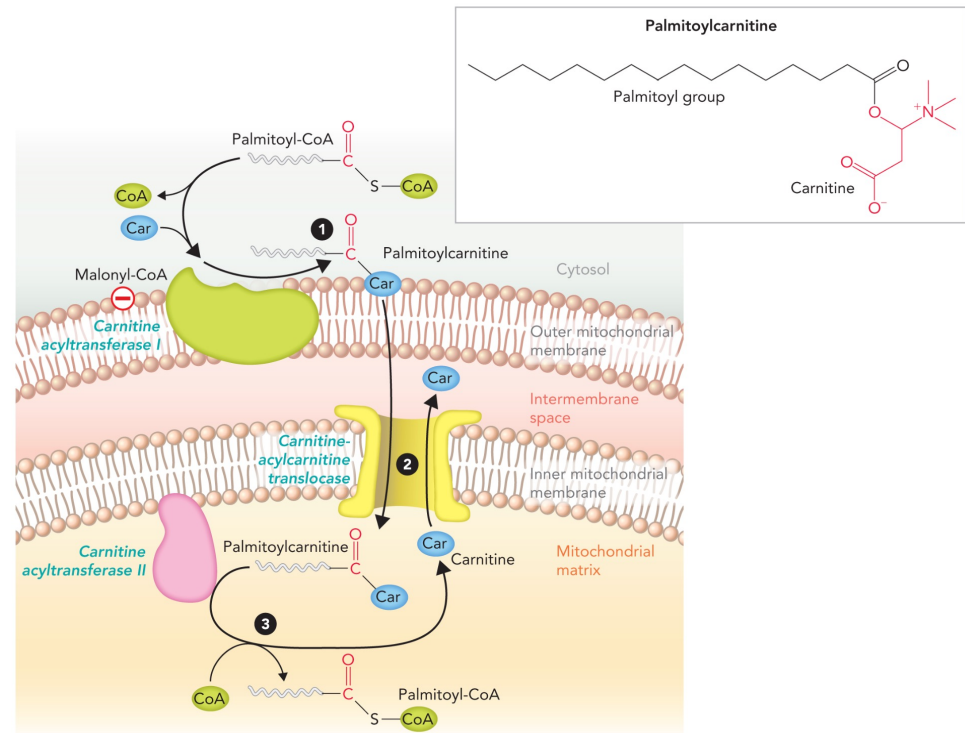


Net reaction:



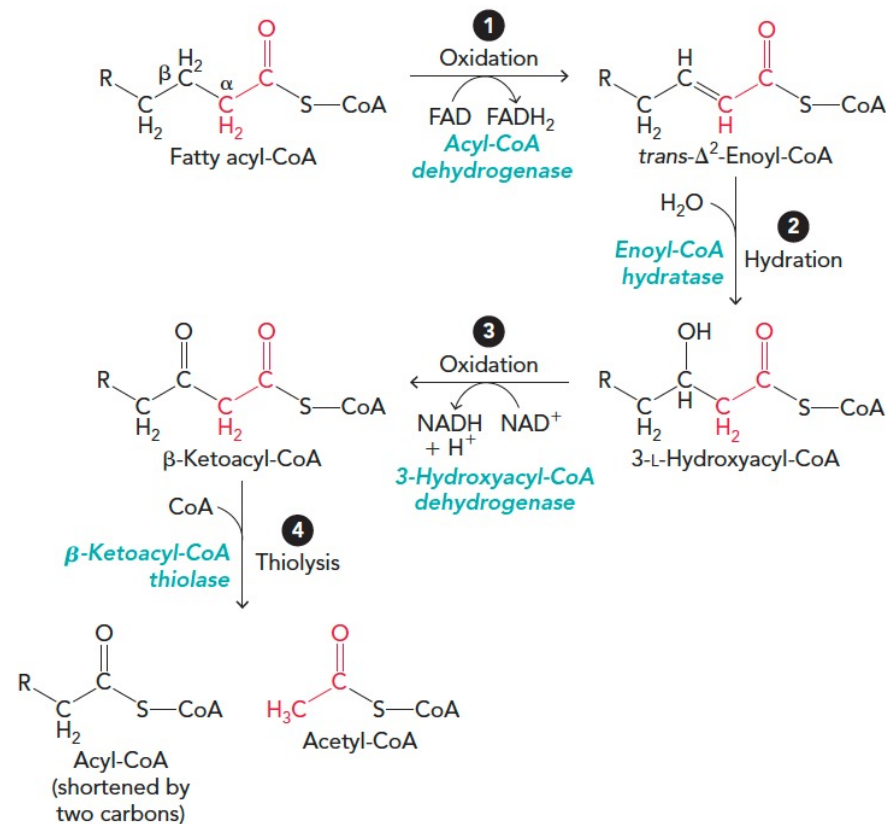
The Carnitine Transport Cycle

- Carnitine acyltransferase I forms acyl-carnitine, which is translocated into mitochondria and reconverted to acyl-CoA by carnitine acyltransferase II.
- Malonyl-CoA blocks this step during synthesis, ensuring β -oxidation does not compete with fatty acid biosynthesis.



Four Reactions in the β -Oxidation Cycle

- Acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and thiolase sequentially oxidize and shorten fatty acyl chains by 2 carbons (C_2).
- Each round releases acetyl-CoA, NADH, and $FADH_2$, progressively extracting energy until the fatty acid is fully degraded.

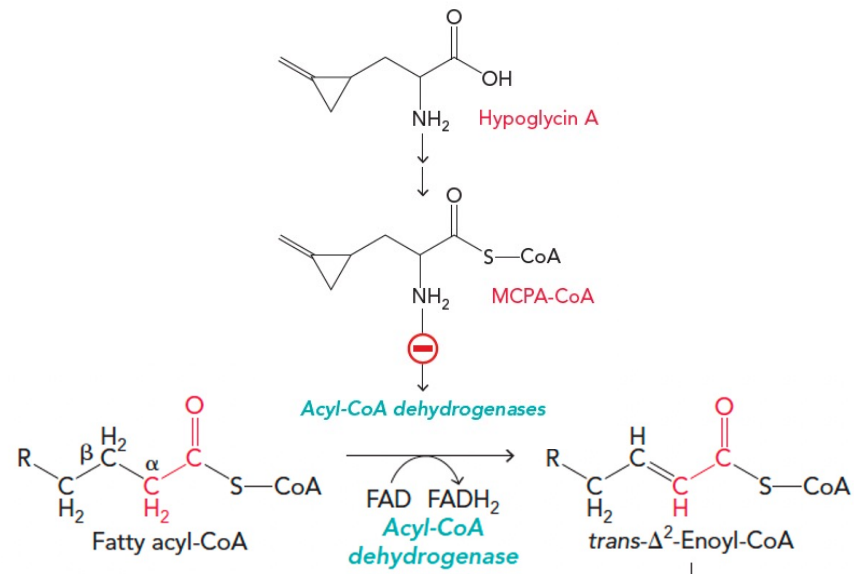


Hypoglycin A: Toxin from Unripe Ackee Fruit

- Hypoglycin A from unripe ackee fruit is converted to MCPA-CoA, which irreversibly inhibits acyl-CoA dehydrogenases.
- This block in β -oxidation leads to hypoglycemia and liver dysfunction, resulting in Jamaican vomiting sickness.

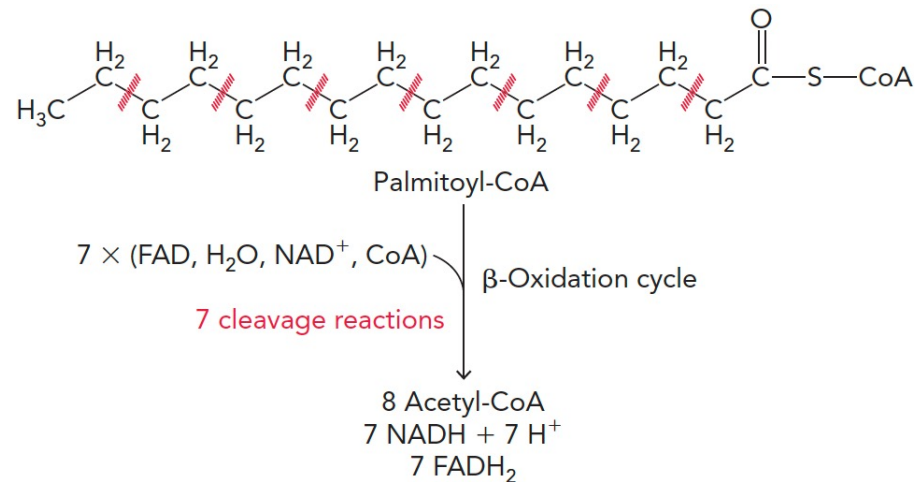


Unripe ackee fruit



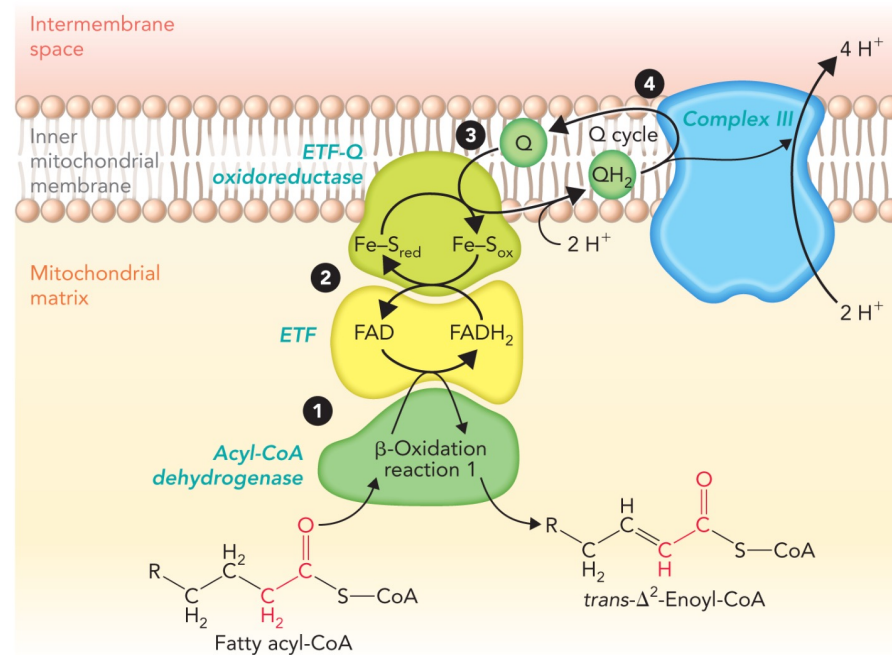
Complete β -Oxidation of Palmitoyl-CoA

- Seven β -oxidation cycles convert palmitoyl-CoA into 8 acetyl-CoA, 7 NADH, and 7 FADH₂.
- This illustrates the high energy potential stored in long-chain fatty acids.



Electron Transfer During β -Oxidation

- Electrons from FADH_2 reduce ETF and ETF-Q oxidoreductase before entering coenzyme Q.
- This pathway yields ~ 1.5 ATP per FADH_2 , paralleling succinate dehydrogenase in the citrate cycle.



ATP Yield: Palmitoyl-CoA

- Complete oxidation of palmitoyl-CoA yields 108 ATP; net yield from free palmitate is 106 ATP after activation costs.
- This high energy density underscores the efficiency of lipid reserves compared with carbohydrates.

Fatty acyl-CoA synthetase: Fatty acid + CoA + **ATP** \rightleftharpoons Fatty acyl-CoA + ~~AMP~~ + **PP_i**

Pyrophosphatase: **PP_i** \rightleftharpoons **2 P_i**

Adenylate kinase: ~~AMP~~ + **ATP** \rightleftharpoons **ADP** + ~~ADP~~

Nucleoside diphosphate kinase: ~~ADP~~ + **ATP** \rightleftharpoons **ATP** + ~~ADP~~

Net reaction: Fatty acid + CoA + **2 ATP** \rightleftharpoons Fatty acyl-CoA + **2 ADP** + **2 P_i**

108 ATP – 2 ATP = **106 ATP** from palmitate

β Oxidation of palmitoyl-CoA	Citrate cycle	ATP generated by oxidative phosphorylation
7 NADH →		17.5 ATP
7 FADH ₂ →		10.5 ATP
	24 NADH →	60 ATP
8 Acetyl-CoA →	8 FADH ₂ →	12 ATP
	8 GTP →	8 ATP
	Total	108 ATP per palmitoyl-CoA

Note: Values for the ATP currency exchange ratio are 2.5 ATP per NADH and 1.5 ATP per FADH₂.



Metabolic Water from β -Oxidation

- Palmitate oxidation generates ~ 130 moles of H_2O , sustaining desert animals and hibernators without external water intake.
- This illustrates the critical role of β -oxidation in both energy and water balance.

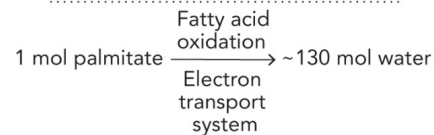


Arabian camel



Desert kangaroo rat

Water production from fatty acid oxidation is a survival mechanism in animals when water is scarce



Hibernating grizzly bear



Key Concepts to Guide Your Learning

- Fatty acids destined for mitochondrial degradation are activated by coenzyme A on the cytosolic side of the outer mitochondrial membrane and then transported into the mitochondrial matrix by the carnitine transport cycle.
- Fatty acid degradation converts redox energy available in electron-rich fatty acids into ATP by producing acetyl-CoA, which is oxidized by the citrate cycle, as well as FADH_2 and NADH , which are oxidized by the electron transport system.
- Each cycle of the β -oxidation pathway requires four reactions: (1) oxidation by acyl-CoA dehydrogenase, (2) hydration by enoyl-CoA hydratase, (3) oxidation by 3-hydroxyacyl-CoA dehydrogenase, and (4) thiolysis by β -ketoacyl-CoA thiolase.
- β -Oxidation of the C_{16} fatty acid palmitate generates 8 acetyl-CoA, 7 FADH_2 , and 7 NADH , which are then oxidized by the citrate cycle and electron transport system; overall yield is 106 net ATP per palmitate after subtracting the 2 ATP equivalents.

