BI/CH 422/622

OUTLINE:

Lipid Degradation (Catabolism)
- FOUR stages in the catabolism of lipids:
  - Mobilization from tissues (mostly adipose)
    - hormone regulated
    - specific lipases
    - glycerol
  - Activation of fatty acids
    - Fatty-acyl CoA Synthetase
  - Transport into mitochondria
    - carnitine
  - Oxidation
    - rationale
    - Saturated FA
    - 4 steps
      - dehydrogenation
      - hydration
      - oxidation
      - thiolase
    - energetics
    - Unsaturated FA
    - Odd-chain FA
    - Ketone Bodies
  - Other organelles

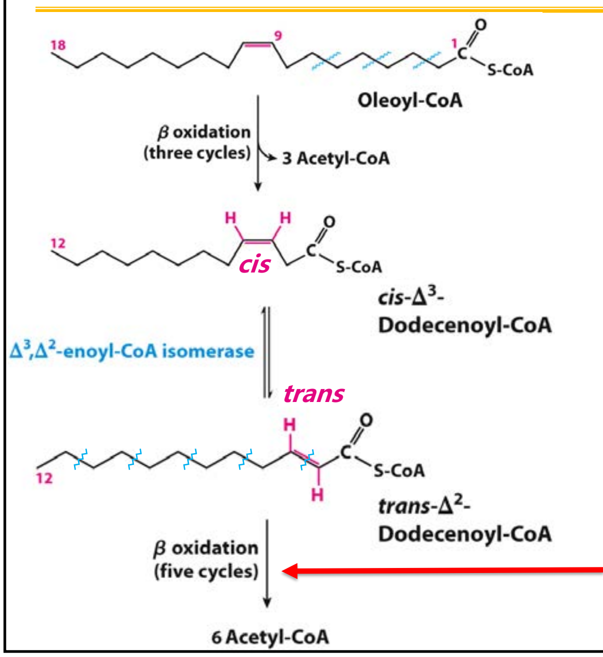
OUTLINE:

Protein Degradation (Catabolism)
- Digestion
- Inside of cells
- Protein turnover
  - Ubiquitin
  - Proteosome

Amino-Acid Degradation

Fatty Acid Degradation

Monounsaturated Fatty Acids



During first of five remaining cycles, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer $FADH_2$.

Fatty Acid Degradation

Energy from Fatty Acid Catabolism

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

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed[a]
***β* Oxidation**		
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	8 NADH	20
Citric acid cycle	35	→87.5 ATP
Isocitrate dehydrogenase	9 NADH	22.5
α-Ketoglutarate dehydrogenase	9 NADH	22.5
Succinyl-CoA synthetase 16		9[b]
Succinate dehydrogenase →24 ATP	9 $FADH_2$	13.5
Malate dehydrogenase	9 NADH	22.5
Total		120.5 – 2 = 118.5*

[a]These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.
[b]GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 516).

*These 2 "ATP" equivalents were expended in the activation by Fatty acyl–CoA synthetase.

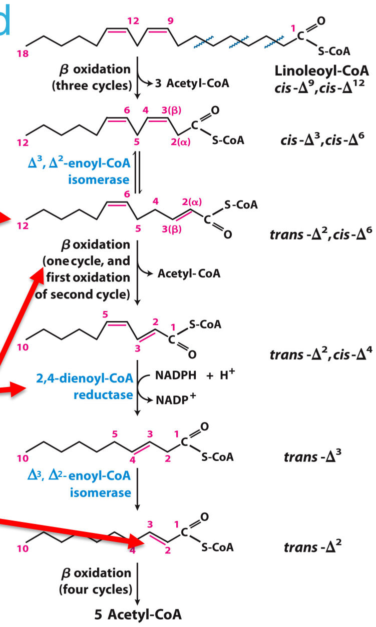
Fatty Acid Degradation

Oxidation of Polyunsaturated Fatty Acids

Results in 1 fewer $FADH_2$ after isomerization, as the acyl-CoA dehydrogenase step is skipped and goes right to the hydratase.

NADPH reduces the 2 conjugated unsaturated bonds to one trans-double bond between them; but its still at an odd carbon

This bond already made with $FADH_2$ already generated before reductase and isomerization.



Fatty Acid Degradation

Energy from Fatty Acid Catabolism

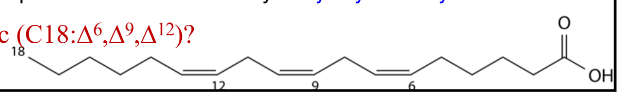
TABLE 17-1a Yield of ATP during Oxidation of One Molecule of Linoleoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step		Number of NADH or $FADH_2$ formed		Number of ATP ultimately formed[a]	
***β* Oxidation**					
Acyl-CoA dehydrogenase		7 $FADH_2$		10.5	
β-Hydroxyacyl-CoA dehydrogenase	(8-1=7; 1 used for reductase)	7 NADH		17.5	
Citric acid cycle			34		→85 ATP
Isocitrate dehydrogenase		9 NADH		22.5	
α-Ketoglutarate dehydrogenase		9 NADH		22.5	
Succinyl-CoA synthetase	16			9[b]	
Succinate dehydrogenase	→24 ATP	9 $FADH_2$		13.5	
Malate dehydrogenase		9 NADH		22.5	
Total				118	– 2 = 116*

[a]These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.
[b]GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 516).

*These 2 "ATP" equivalents were expended in the activation by Fatty acyl–CoA synthetase.

What would it be for γ-linolenic (C18:Δ^6,Δ^9,Δ^{12})?



Degradation of Odd-Chain Fatty Acids

Fatty Acid Degradation

Oxidation of Odd-Numbered Fatty Acids

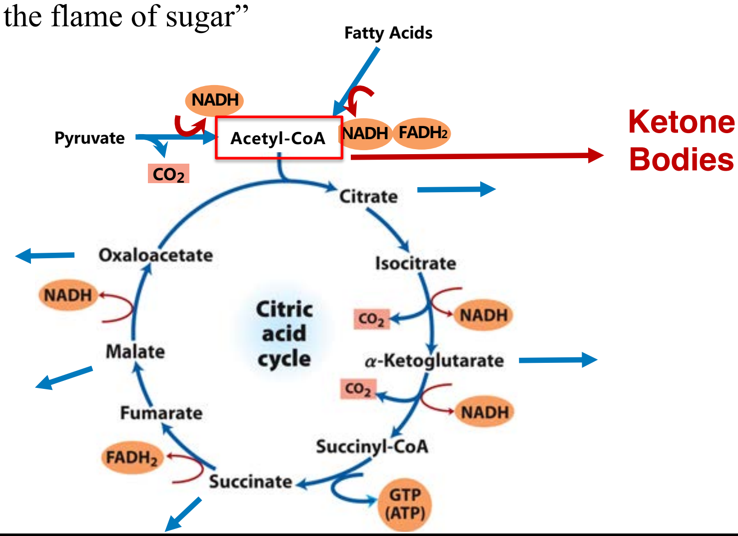
- Most dietary fatty acids are even-numbered.
- Many plants and some marine organisms also synthesize odd-numbered fatty acids.
- The metabolism of oxidation of odd-chain fatty acids CONVERGES with that of some amino acids
- Details will be discussed with amino acids

Ketone Bodies

Ketone Body Degradation

What are Ketone Bodies?

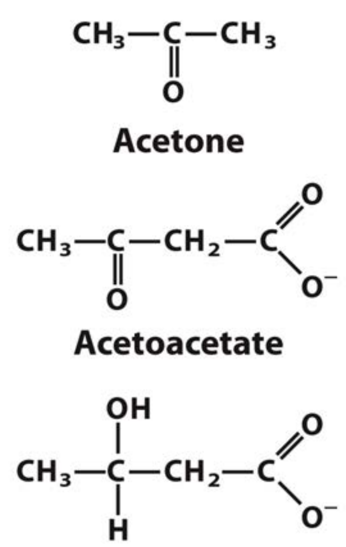
"Fat burns in the flame of sugar"



Ketone Body Degradation

- Entry of acetyl-CoA into citric acid cycle requires oxaloacetate.
- When oxaloacetate is depleted, acetyl-CoA is converted into ketone bodies.
  - frees coenzyme A for continued β oxidation
- Three forms of ketone bodies can leave the liver: acetone, acetoacetate, and β-hydroxybutyrate.
- Therefore, the anabolism of Ketone Bodies is connect to catabolism of fatty acids and sugars
- For now, we will discuss Ketone Body catabolism

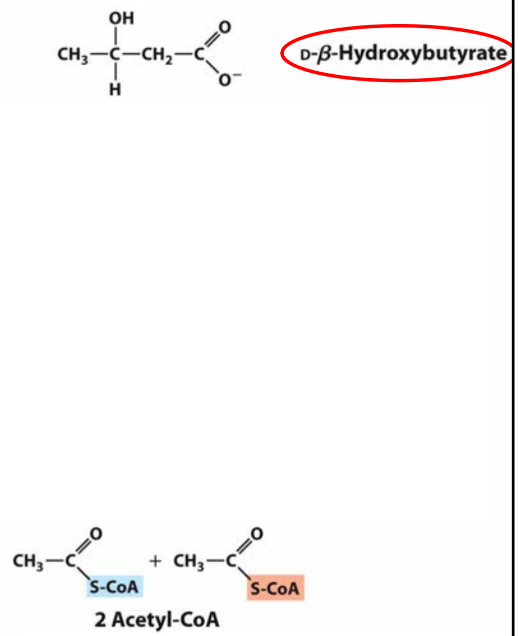
Ketone Bodies



Ketone Body Degradation

Ketone Bodies as Fuel

1. Make CoA derivatives
2. Oxidize alcohol
3. Thiolase reaction



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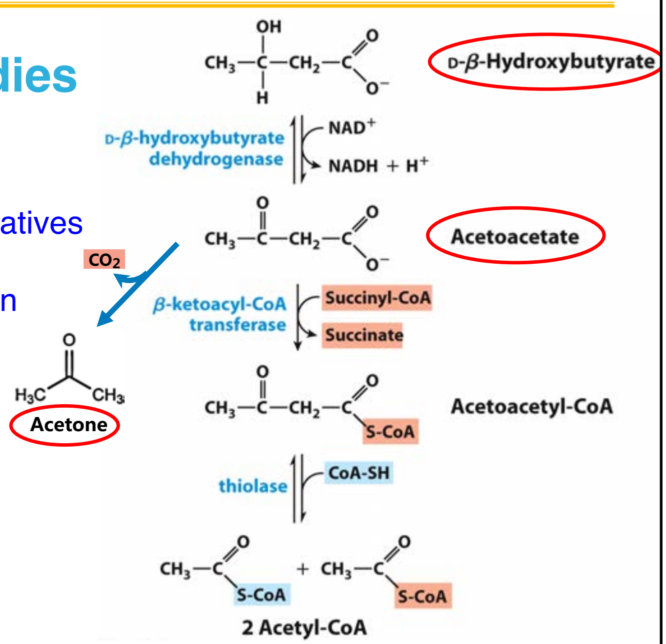
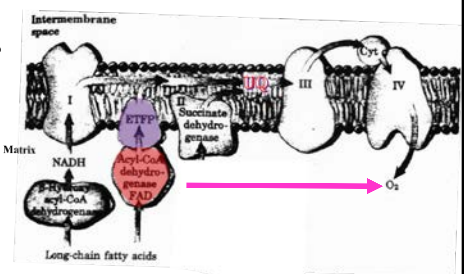


Fatty Acid Oxidation in Other Organelles

Fatty Acid Degradation

β Oxidation in Plants Occurs Mainly in Peroxisomes

- Mitochondrial acyl-CoA dehydrogenase passes electrons into respiratory chain via electron-transferring flavoprotein (ETFP).
  - energy captured as ATP

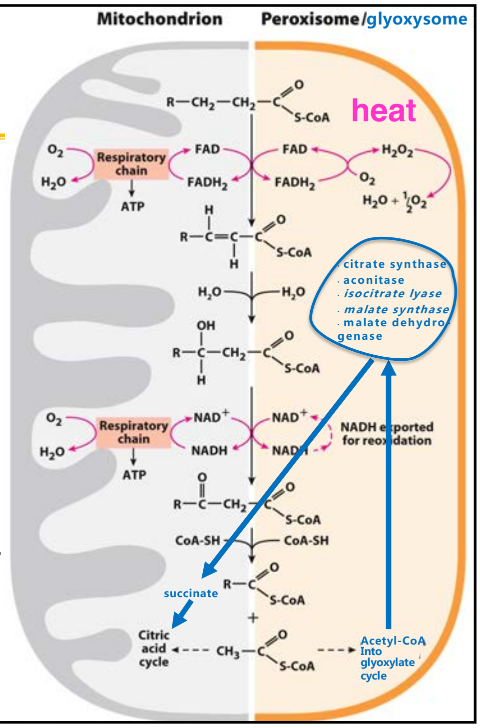


- Peroxisomal/glyoxysomal acyl-CoA oxidase passes electrons directly to molecular oxygen and H_2O_2.
  - energy released as **heat**
  - hydrogen peroxide eliminated by catalase

Fatty Acid Degradation

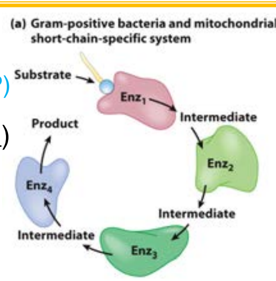
- Acetyl-CoA released from peroxisomal β oxidation is exported to cytosol and then imported to mitochondria.

- A peroxisome is also a glyoxysome when enzymes for glyoxylate cycle are present (e.g., germinating seeds).
- Acetyl-CoA released from peroxisomal β oxidation can be used in glyoxylate cycle.
- The glyoxylate cycle is found in most organisms, but not vertebrate animals.
- The glyoxylate cycle has an anabolic function to synthesize larger molecules from acetyl-CoA.



Fatty Acid Degradation

Fatty Acid Oxidation is Performed by a Single TriFunctional Protein (TFP)



- Hetero-octamer ($\alpha_4\beta_4$)
  - four α subunits
    - enoyl-CoA hydratase activity
    - β-hydroxyacyl-CoA dehydrogenase activity
    - responsible for binding to membrane
  - four β subunits
    - long-chain thiolase activity
- May allow substrate channeling between enzymes
- Associated with inner-mitochondrial membrane
- Processes fatty acid chains with 12 or more carbons
- Shorter chains processed by soluble enzymes in the matrix

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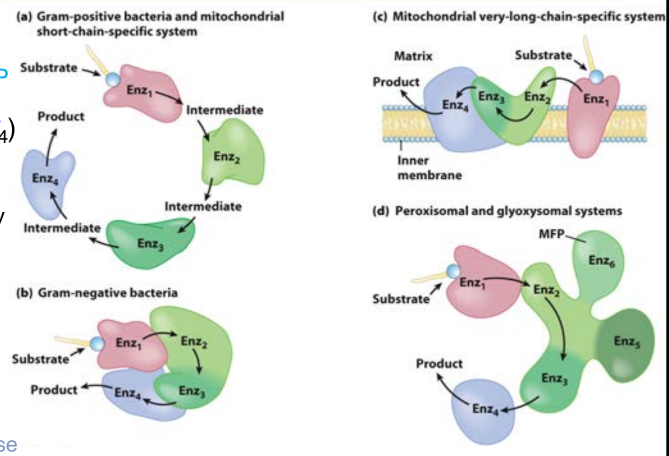

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Fatty Acid Degradation: Summary

We learned that:

- fats are an important energy source in animals
- two-carbon units in fatty acids are oxidized in a four-step β oxidation process into acetyl-CoA
- in the process, a lot of NADH and $FADH_2$ forms; these can yield a lot of ATP in the electron-transport chain
- Mono- and poly-unsaturated fatty acids require additional enzymes and lose an $FADH_2$ for every double bond at an odd carbon, and cost an NADPH for every pair.
- acetyl-CoA formed in the liver can be either oxidized via the citric acid cycle or converted to ketone bodies that serve as fuels for other tissues
- Other organelles can perform fatty-acid oxidation; during peroxisomal oxidation, fats can be oxidized to generate heat