BI/CH 422/622

OUTLINE:
Review, Goals
Membrane Transport
Catabolism of Glucose
Glycogenolysis
Glycolysis
Phase I: HK, PGI, PFK-1, Aldolase, TPI
Exam 1
Phase II; **GAPDH**, PGK, **PGM**, **Enolase**, PK
Summary: labeling studies, logic, energetics
Catabolism of Other sugars
Pasteur: Anaerobic vs Aerobic
Fermentations; Lactate, Acetoacetate, Ethanol
Aerobic
Pyruvate; PDHC
Krebs' Cycle
How did he figure it out?
Overview
8 Steps
Citrate Synthase
Aconitase
Isocitrate dehydrogenase
Ketoglutarate dehydrogenase
Succinyl-CoA synthetase
Succinate dehydrogenase
Fumarase
Malate dehydrogenase
Energetics
Regulation
Summary
Oxidative Phosphorylation
Energetics, Mitochondria, Transport
Electron transport
discovery
Four complexes
Complex I
Complex II
Complex III
Exam 2
Complex IV
Electron Transport
Complex IV: Cytochrome C (Fe^{2+}) → H_2O
Exam 3
Chemiosmotic theory: Phosphorylation
ATP synthesis
ATPase
Mitchell Hypothesis
Binding-Change Model
Connection to the proton motive force
Net ATP production
Regulation

OUTLINE:
Lipid Degradation (Catabolism)
Fat Catabolism
diet
storage
Fatty acid Catabolism
FOUR stages in the catabolism of lipids:
Mobilization from adipose tissues
hormone regulated
specific lipases
glycerol
Activation of fatty acids
Fatty-acyl CoA Synthetase
Transport
carnitine
Oxidation
Rationale
Saturated FA
β-oxidation
4 steps
dehydrogenation
hydration
oxidation
thiolase
energetics
Unsaturated FA
Odd-chain FA
Oxidation of fatty acids in other organelles
Ketone Bodies Catabolism
energetics
Protein Degradation (Catabolism)

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Degradation of Unsaturated Fatty Acids

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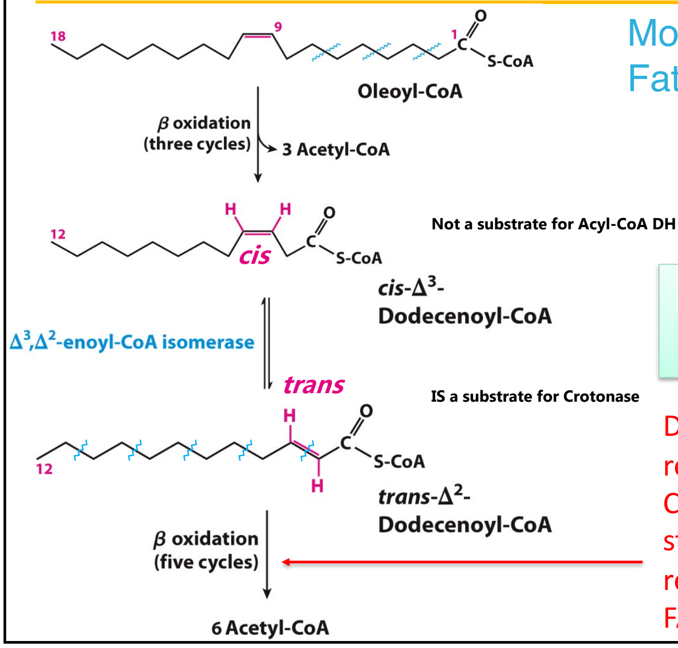
Fatty Acid Degradation



Monounsaturated Fatty Acids

1. Acyl-CoA DH
2. Crotonase (hydratase)
3. βHADH
4. Thiolase

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

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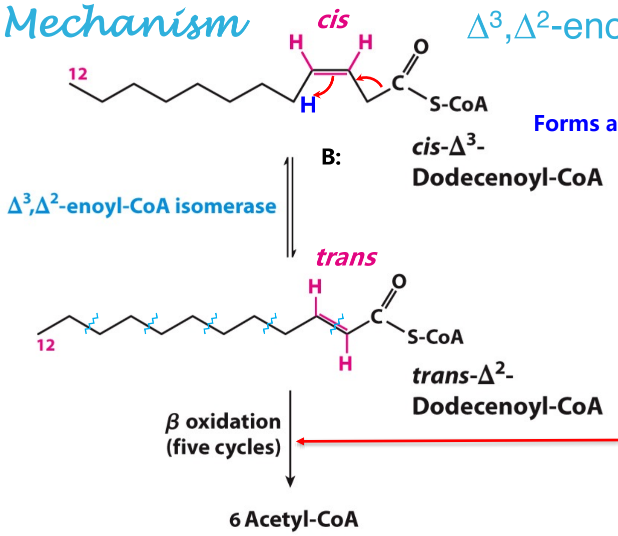
Fatty Acid Degradation

Mechanism

Δ^3,Δ^2-enoyl-CoA isomerase



Forms an enolic intermediate

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

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Fatty Acid Degradation

Energy from Fatty Acid Catabolism

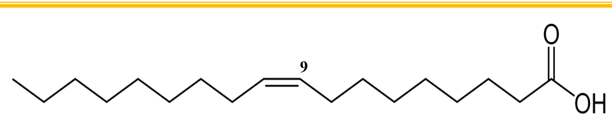
TABLE 17-1a Yield of ATP during Oxidation of One Molecule of Oleoyl-CoA (C18) to CO_2 and H_2O

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed[a]
***β* Oxidation**		
Acyl-CoA dehydrogenase (8-1=7; 1 lost due to isomerase)	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*

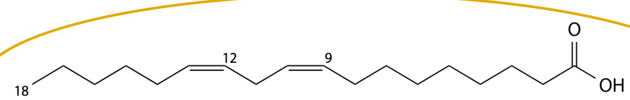
[a]These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.
[b]GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 516).

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

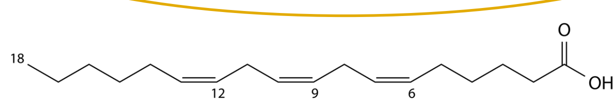
Degradation of Unsaturated Fatty Acids



oleic (C18:1 Δ^9)

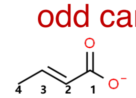


linoleic (C18:2 Δ^9,Δ^{12})



γ-linolenic (C18:3 Δ^6,Δ^9,Δ^{12})

TWO problems:
1. *cis*
2. often at odd carbon



crotonate

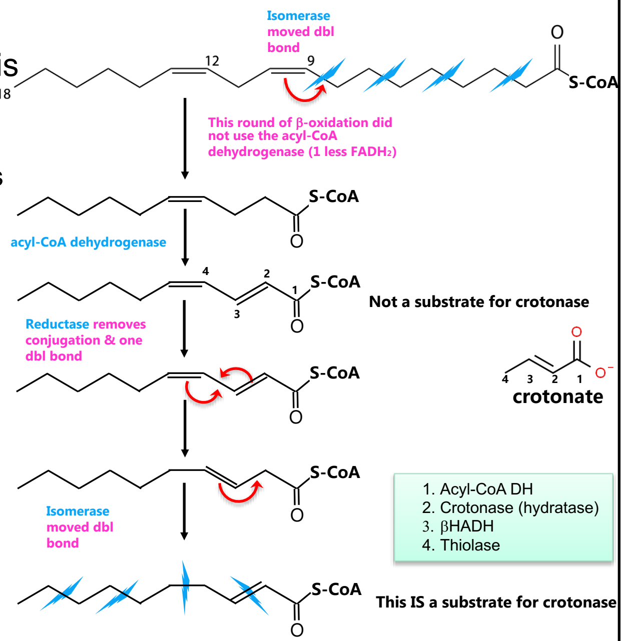
Both linoleic and γ-linolenic (ω6), as well as α-linolenic (ω3; C18:3 Δ^9,Δ^{12},Δ^{15}) are essential fatty acids (EFA)

Fatty Acid Degradation

Linoleic (C18:2 Δ^9,Δ^{12})

- An additional enzyme is required for *cis*-double bonds **not** at carbon 3:
  - **reductase**: reduces cis double bonds at Δ^4
- Polyunsaturated fatty acids, or monounsaturated fatty acids at an even carbon, require both enzymes.

• Remember for polyunsaturated fatty acids at the first dbl-bond you lose 1 $FADH_2$ equivalent from first step of β-oxidation and use the isomerase instead & at the second dbl-bond you use an NADPH (NADH) for the reductase



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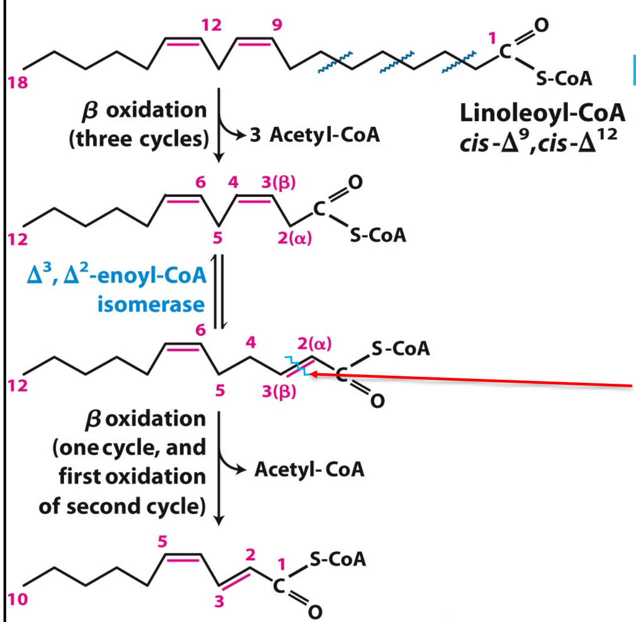
Fatty Acid Degradation

Oxidation of Polyunsaturated Fatty Acids

Isomerization



During this β-oxidation, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer $FADH_2$.

This conjugated situation is not a substrate for the hydratase

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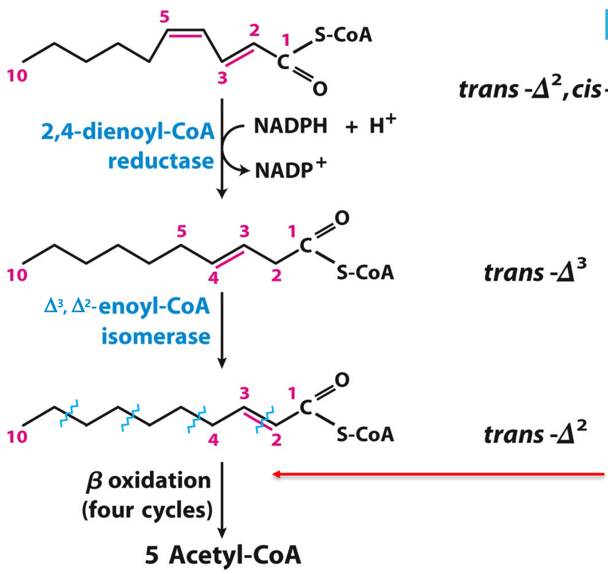
Fatty Acid Degradation

Oxidation of Polyunsaturated Fatty Acids

Reductase



Recall that during first step of four remaining cycles, acyl-CoA dehydrogenase already put in the dbl-bond prior to reductase and isomerase reactions.

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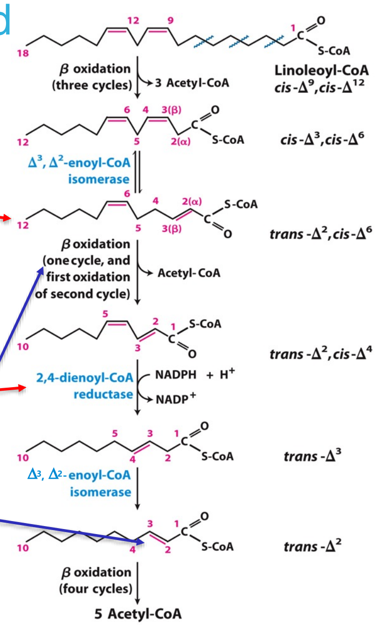
Fatty Acid Degradation

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.



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Fatty Acid Degradation

Energy from Fatty Acid Catabolism

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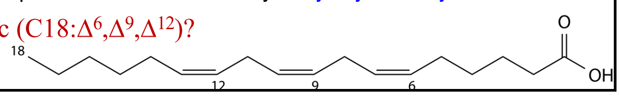
β Oxidation			
Acyl-CoA dehydrogenase	(8-1=7; 1 lost due to isomerase)	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	(8-1=7; 1 used for reductase)	7 NADH	17.5
Citric acid cycle		34	→85 ATP
Isocitrate dehydrogenase		9 NADH	22.5
α-Ketoglutarate dehydrogenase		9 NADH	22.5
Succinyl-CoA synthetase	16		9[b]
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:$\Delta^6,\Delta^9,\Delta^{12}$)?



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Degradation of Odd-Chain Fatty Acids

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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

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Fatty Acid Oxidation in Other Organelles

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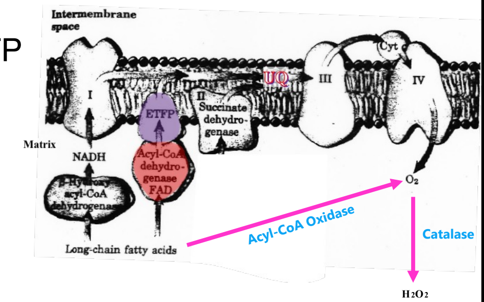
Fatty Acid Degradation

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

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Fatty Acid Degradation

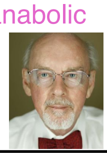
• Acetyl-CoA released from peroxisomal β oxidation is exported to cytosol and then imported to mitochondria (NADH also).

• A peroxisome is also a glyoxysome when enzymes for glyoxylate cycle are present (e.g., germinating seeds).

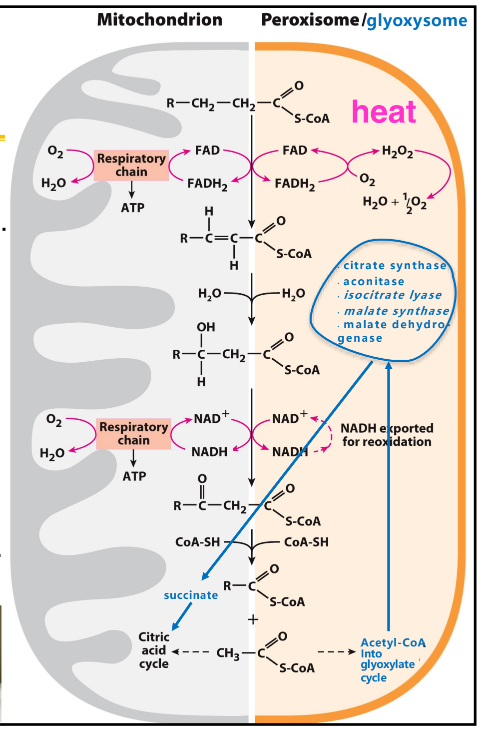
• Acetyl-CoA made from peroxisomal β–oxidation can be used in glyoxylate cycle.

• 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.



We will come back to this pathway when we discuss biosynthesis



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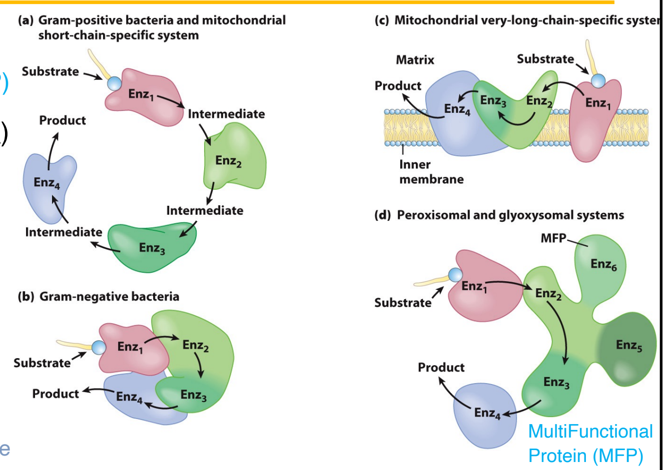
Fatty Acid Degradation

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

1. Acyl-CoA DH
2. Crotonase (hydratase)
3. βHADH
4. Thiolase

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Ketone Bodies

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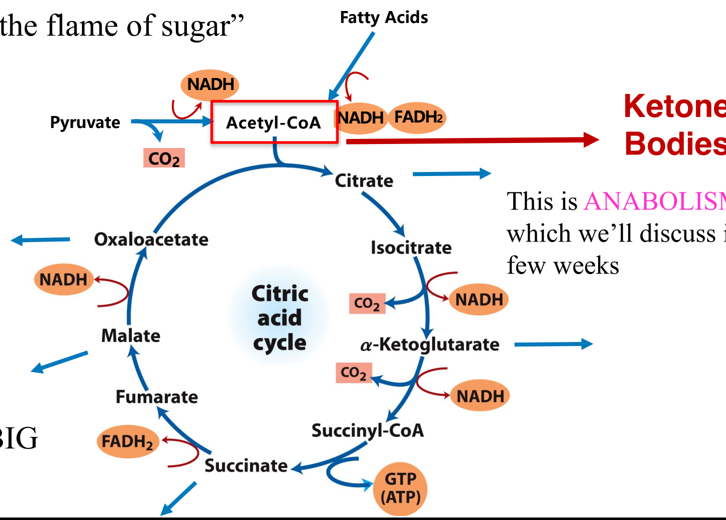
Ketone Body Degradation

What are Ketone Bodies?

"Fat burns in the flame of sugar"



This is ANABOLISM, which we'll discuss in a few weeks

THIS IS A BIG DEAL!!!!

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Ketone Bodies Catabolism

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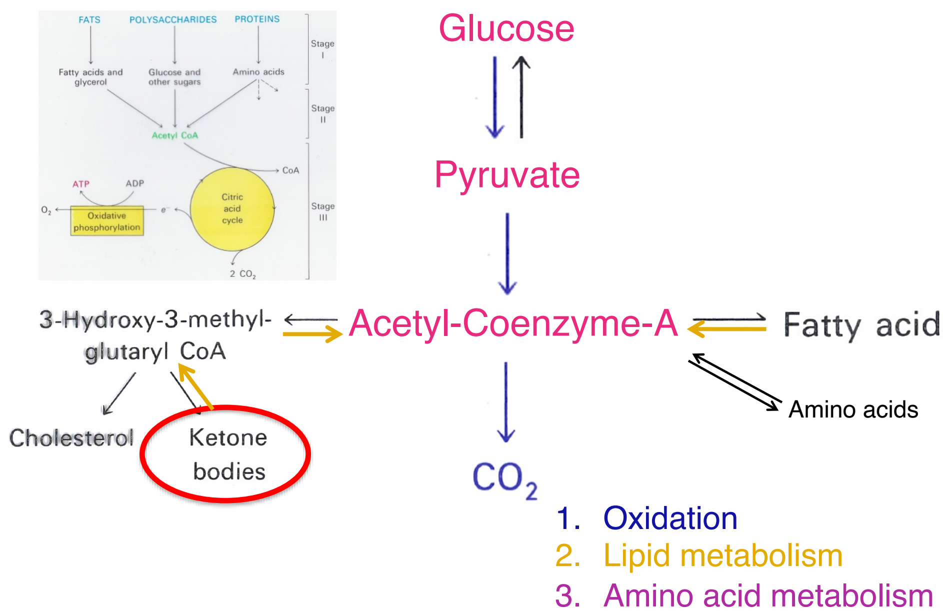
Fates of Acetyl CoA



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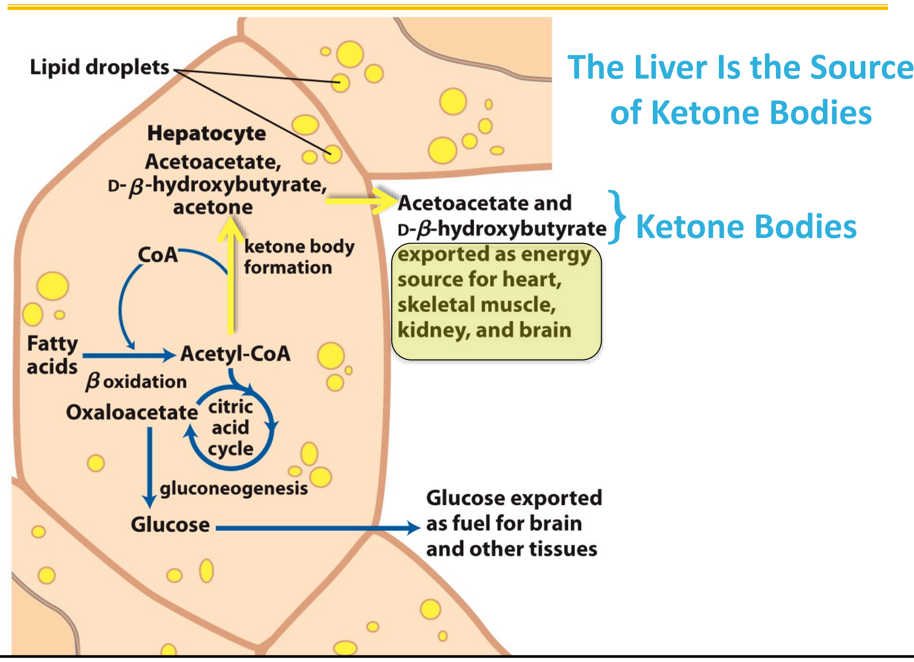
Ketone Body Degradation



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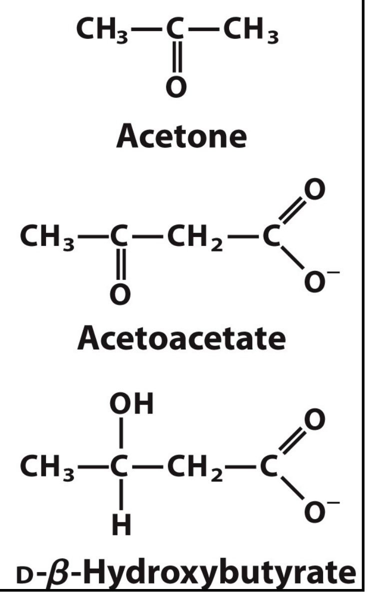
Ketone Body Degradation

- Entry of acetyl-CoA into citric acid cycle requires oxaloacetate.
- When oxaloacetate is depleted, acetyl-CoA is converted into ketone bodies in the LIVER.
  - 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 connected to catabolism of fatty acids and sugars
- For now, we will discuss Ketone Body catabolism

Ketone Bodies



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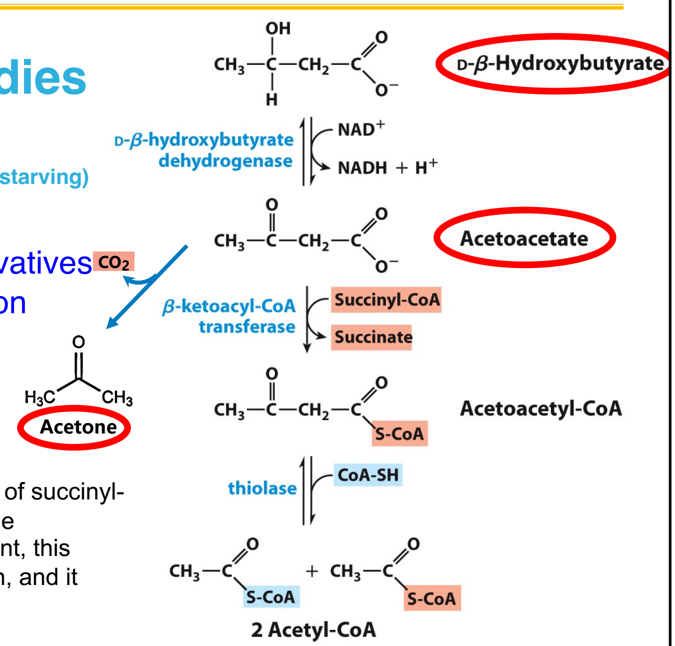
Ketone Body Degradation

Ketone Bodies as Fuel

(heart & muscle, brain if starving)

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



Notice the ingenious use of succinyl-CoA, which is a TCA cycle intermediate. If insufficient, this reaction does not happen, and it backs up…….acidosis

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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 double bond at an even carbon.
- Other organelles can perform fatty-acid oxidation; during peroxisomal oxidation, fats can be oxidized to generate heat
- 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

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