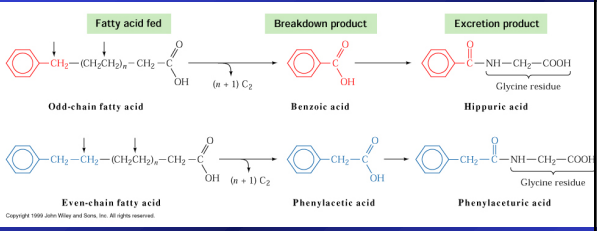
Fatty Acid Metabolism

Oxidation - even or odd



Fatty Acid Oxidation (α, ω and ß-oxidation)

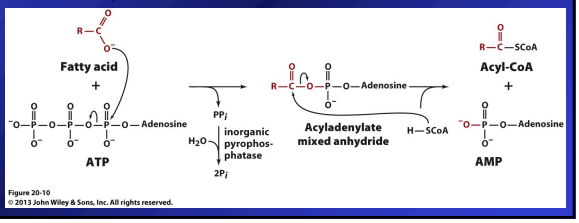
- Three phases to ß oxidation
  - activation with Coenzyme A
  - transport into the mitochondria
  - oxidation of 2 carbon units

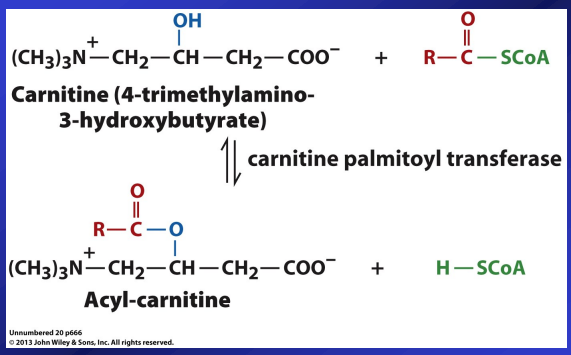
Activation acyl CoA synthetase aka thiokinase

- uses ATP (only energy requiring step)
- 2 part step forming acyl CoA and PPi (drives reaction)
- mixed anhydride forms attack site for CoA

$CH_3\text{-}(CH_2)_n\text{-}COO^- + ATP + HS\text{-}CoA$ ✖

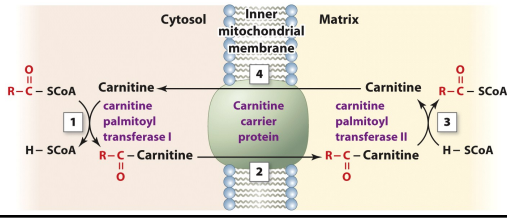
acyl-CoA + AMP + PP_i





Transport

- FA greater than 12 C long need to be transported into mito
- three step reaction 2 transferases and a translocase
- carnatine replaces CoA
- has nearly the same E of hydrolysis and acylCoA
- little change of energy during translocation
- cell keeps separate pools of CoA



ß-oxidation of fatty acids

occurs in the mitochondria (inner membrane)
subtracts 2 carbons from COO- end of ß carbon of FA

- four steps :
  1. oxidation - > acyl-CoA dehydrogenase
     - FAD linked via electron transferring protein
     - feeds to site 2 in ETS
     - double bond formed between C 2 & 3
     - acyl-CoA dehydrogenase isozymes

ß-oxidation of fatty acids

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- four steps :

  2. hydration -> enoyl CoA hydratase
     - puts water across Δ2 carbon

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- four steps :

  3. oxidation -> ß hydroxyacyl CoA dehydrogenase
     - $NADH_2$ linked oxidation of OH from last step
     - $NADH_2$ free to be oxidized at site 1 of ETS
     - specific for the L isomer

ß-oxidation of fatty acids

occurs in the mitochondria (inner membrane)
subtracts 2 carbons from COO^- end of ß carbon of FA

- four steps :

  4. thiolase -> ß keto thiolase
     - similar reaction to hydrolysis uses SH group of CoA
     -leads to new acylCoA (minus 2 carbons)

steps 1 thru 3 are similar to part of the TCA
(succinate->fumarate->malate->oxalacetate)
Repeat cycle until two or 3 Carbons (1 acyl CoA) are left

Energetics of ß oxidation
palmitate (C_{16}) - CoA + 7 CoASH + 7 FAD + 7 NAD^+ +7 H_2O
--> 8 acetyl CoA + 7 $FADH_2$ + 7 NADH
The net yield in ATP currency is:
7 FADH - 14 ATP
7 NADH - 21 ATP
8 Acyl-CoA
8 NADH = 72 ATP
8 FADH = 16 ATP
8 GTP = 8 ATP
with 100% efficiency - 131 ATP
activation costs of 1 fatty acid - 2 ATP (?)
total ATPs from palmitate 107 to 129

Long Chain FA shortened in peroxisomes -> O_2 is the e- acceptor

The double bond problem - remember 2nd step of ß ox has a double bond at the C2

- Even # unsaturation - skip first step and result in one less FADH2
- Odd # unsaturations undergo isomeraton when the double bond gets to delta 3.

Compare FA oxidation vs. synthesis

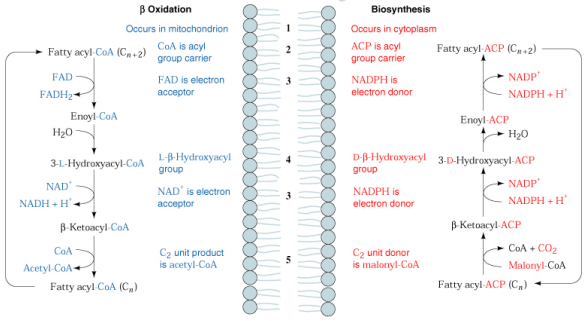
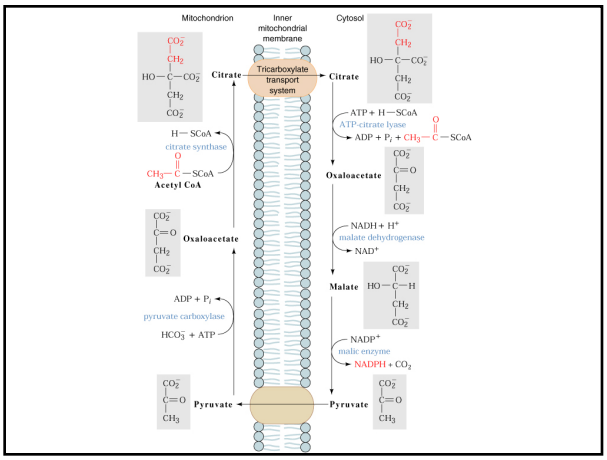


Figure 19-19. A comparison of fatty acid β oxidation and fatty acid biosynthesis.

Biosynthesis of fatty acids

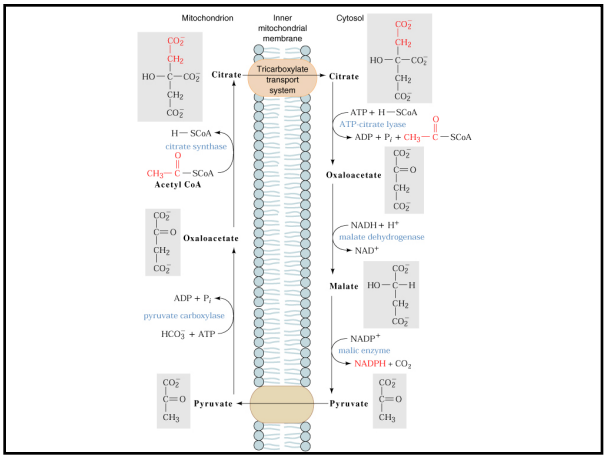
This pathway occurs in the cytosol. 2 carbon are added at a time to produce acetyl CoA. The precursors are from glucose and amino acids. This is distinct from ß oxidation- it is a reductive process and uses NADPH. It takes place in the cytosol. A 3 carbon acid malonyl-CoA as the 2 carbon donar. The growing chain is attached to an acyl-carrier protein rather than Co-A. The enzymes are not shared between either

Acetyl CoA are produced by pyruvate carboxylase from both glycolytic and TCA intermediates. Acetyl CoA, which is is generated by pyruvate dehydrogenase (PDH) in the mitochondrion cannot cross the inner mitochondrial membrane to reach the cytosol. Instead transport occurs by the tricarboxylate transport system.



Acetyl CoA transport

- Acetyl CoA produced in mito - transported out as citrate
- glucose ->->-> pyruvate -> OAA and Acetyl CoA
- pyruvate carboxylase and pyruvate dehydrogenase
- OAA and Acetyl CoA -> Citrate (in mito)
- citrate transfer into cytosol and cleaved to Acetyl CoA and OAA by ATP citrate lyase - cost of ATP to transport
- OAA shuttled back into mito via MDH, Malic enzyme (NADPH)
- pyruvate transport into mito converted to OAA
- produces both 1 NADPH /and Acetyl CoA



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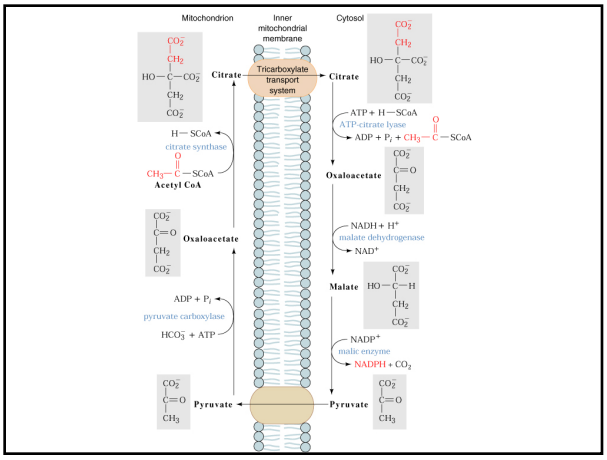

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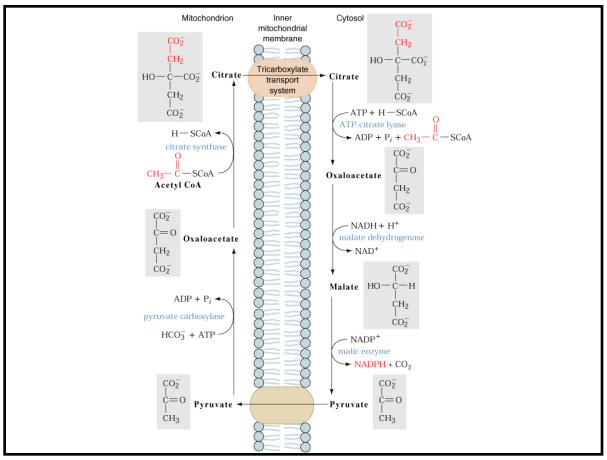

Mitochondrion
Inner mitochondrial membrane
Cytosol
Citrate
Tricarboxylate transport system
Citrate
ATP + H—SCoA
ATP-citrate lyase
ADP + Pi + CH3—C—SCoA
H—SCoA
citrate synthase
CH3—C—SCoA
Acetyl CoA
Oxaloacetate
NADH + H+
malate dehydrogenase
NAD+
Oxaloacetate
Malate
ADP + Pi
pyruvate carboxylase
HCO3− + ATP
NADP+
malic enzyme
NADPH + CO2
Pyruvate
Pyruvate

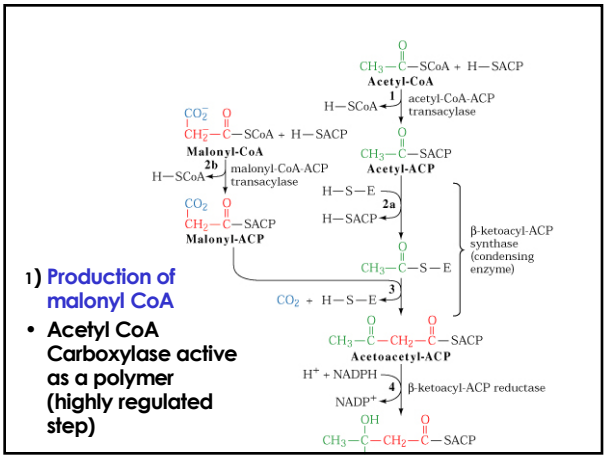
Biosynthesis-

Two phases - malonyl CoA formation and FA complex

1) Production of malonyl CoA

Acetyl CoA Carboxylase active as a polymer (highly regulated step)

- 1st committed step in fatty acid synthesis (FAS)
- biotin cofactor - important point in activated one carbon carriers
- Highly regulated step
- allosteric effectors and covalent modification citrate activates by increasing the Vmax, where long chain FAs inhibit. AMP kinase inactivates (think of why) and insulin activates a phosphatase which relieves this inhibition by promoting the dephosphorylation of ACoA carboxylase



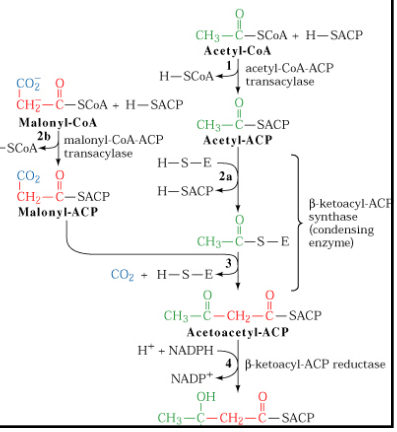
1) **Production of malonyl CoA**

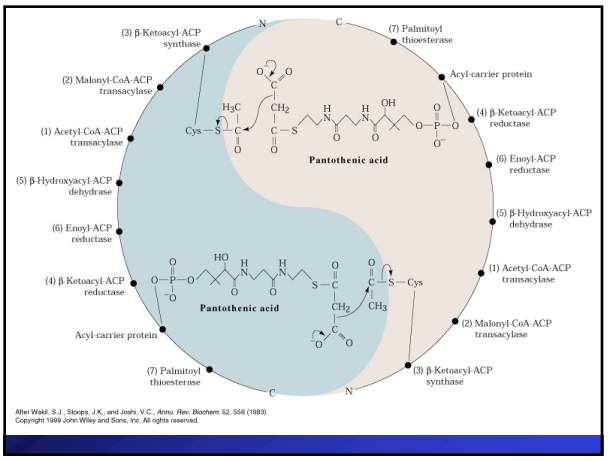
- **Acetyl CoA Carboxylase active as a polymer (highly regulated step)**

2) Fatty acid synthesis

transacylase

- the first reaction starts with a manonyl CoA and an ACoA
- transfer of acyl CoAs to ACP
- ACP - acyl carrier protein (derivative of CoA)
- long flexible arms w/ sulfhydrals
- allows flexibility to different active sites

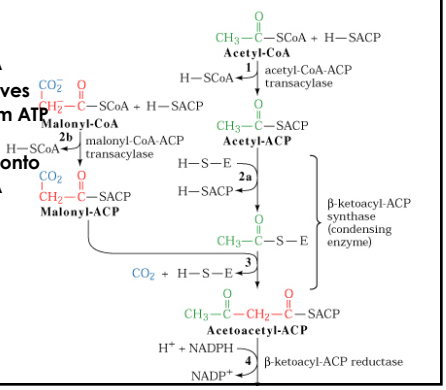




2) Fatty acid synthesis

condensation

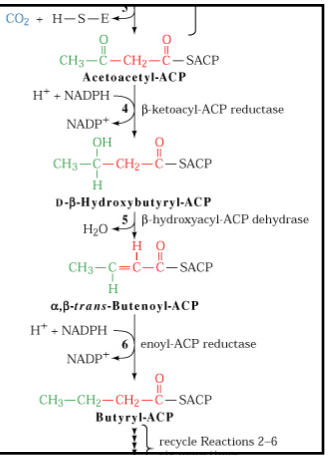
- acetyl CoA + malonyl CoA
- loss of CO_2 drives reaction (from ATP hydrolysis)
- ACoA added onto malonyl CoA
- forms new 2 carbon acetoacetyl group

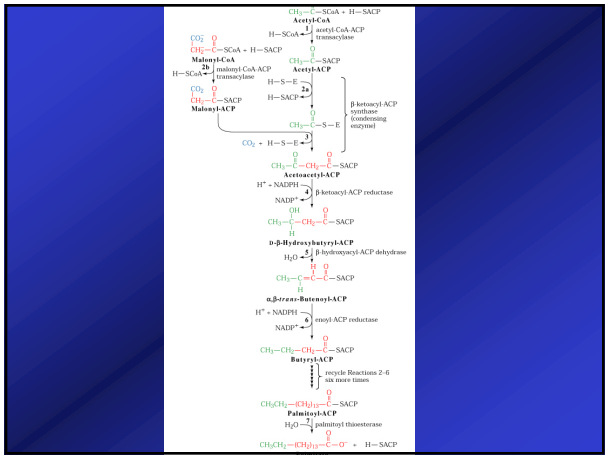


2) Fatty acid synthesis

reductions

- NADPH required
- similar reactions to reversal of ß oxidation
- end up with a new +2 carbon acyl - ACP group

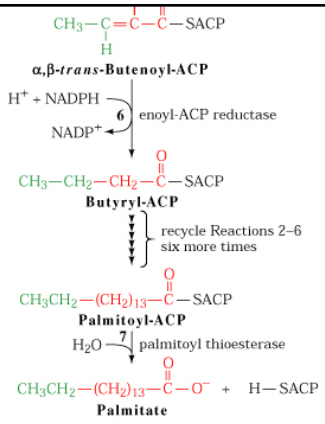




continuation reactions

- the above is one full round of fatty acid synthase
- reactions continues 7 times until 16 carbon chain is formed (palmitate)

termination - by thiolase



Single enzymes or complexes

Two types of FAS systems bacterial and higher organisms. In *E. coli*,. this takes place by several successive different enzymatic reactions. In eukaryotic cells, it takes place on one enzyme with several catalytic activities.

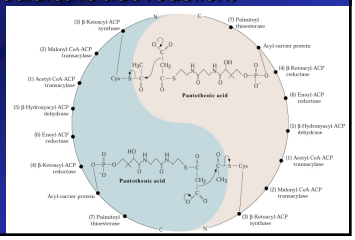
Reactions. The benefits of multienzyme systems:

- channeling of substrates - faster synthesis
- no loss of intermediates to side reactions

Source of reducing equivalents

pentose phosphate pathway

malic enzyme - 1 per acetyl CoA transport



Energetics of FA synthesis

8 acyl CoA + 7 ATP+ 14 NADPH + $6H^+$ -->

palmitate (C_{16}) + 8 CoASH + 14 $NADP^+$ + 6 H_2O + 7 ADP/ Pi

The net yield in ATP currency is from mito is

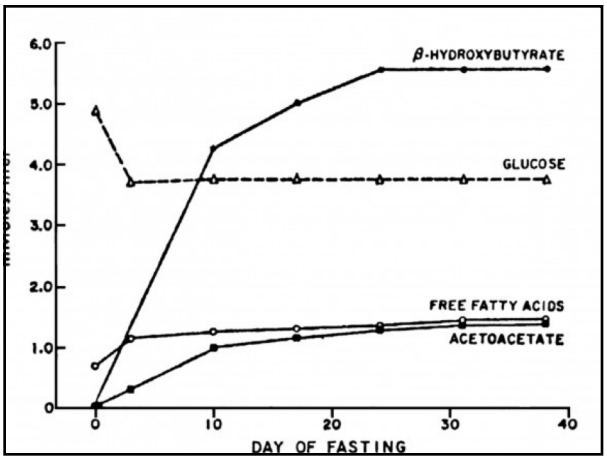
- 8 ATP - citrate lyase
- 7 ATP - Acetyl CoA Carboxylase
- 7 rounds of FAS x NADPH -> 42 ATP

total of 57 ATP to make palmitate / 129 to break down palmitate

Fruity Smelling Breath

Ketogenesis - Acetyl-CoA forms acetoacetate under high fatty acid oxidation (***loss of insulin***) and or prolonged starvation

- Acetoacetate can spontaneously decarboxylate into acetone OR reduce to ß hydroxybutyrate
- These are collectively called ketone bodies
- Acetoacetate and ß hydroxybutyrate serve as alternative fuel sources by the brain and muscle



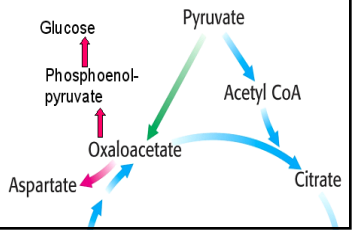
KETONE BODIES

The entry of acetyl CoA into the citric acid cycle depends on the availability of oxaloacetate.

The concentration of oxaloacetate is lowered if carbohydrate is unavailable (starvation) or improperly utilized (diabetes).

Oxaloacetate is normally formed from pyruvate by *pyruvate carboxylase* (anaplerotic reaction).

Fats burn in the flame of carbohydrates.



Fruity Smelling Breath

Synthesis

- Acetoacetyl-CoA forms by the condensation of two acetyl-CoA - thiolase in reverse
- A third Acetyl CoA is added by another condensation reaction to form HMG-CoA (ß-hydroxy-ß-methylglutaryl-CoA) - part of cholesterol synthesis
- HMG CoA is lysed to form acetyl CoA and acetoacetate

Fruity Smelling Breath

Acetoacetate and ß HG formed in the liver are transported in the bloodstream to peripheral tissues and there are converted into two acetyl CoA units. This is still inefficient because succinyl CoA is used and therefore is not available for STK formation of GTP in the Kreb's cycle.

B. Ketone bodies are a major fuel in some tissues

Ketone bodies diffuse from the liver mitochondria into the blood and are transported to peripheral tissues.

Ketone bodies are important molecules in energy metabolism.

Heart muscle and the renal cortex use acetoacetate in preference to glucose in physiological conditions.

The brain adapts to the utilization of acetoacetate during starvation and diabetes.

KETOSIS

The absence of insulin in diabetes mellitus

- liver cannot absorb glucose
- inhibition of glycolysis
- activation of gluconeogenesis
- activation of fatty acid mobilization by adipose tissue
- caused by a deficit of oxaloacetate
- leading to large amounts of acetyl CoA which can not be utilized in Krebs cycle
- large amounts of **ketone bodies** (moderately strong acids)
- Giving rise to severe acidosis **(ketosis)**

Impairment of the tissue function, most importantly in the central nervous system