Fatty Acid and Triacylglycerol Metabolism 1

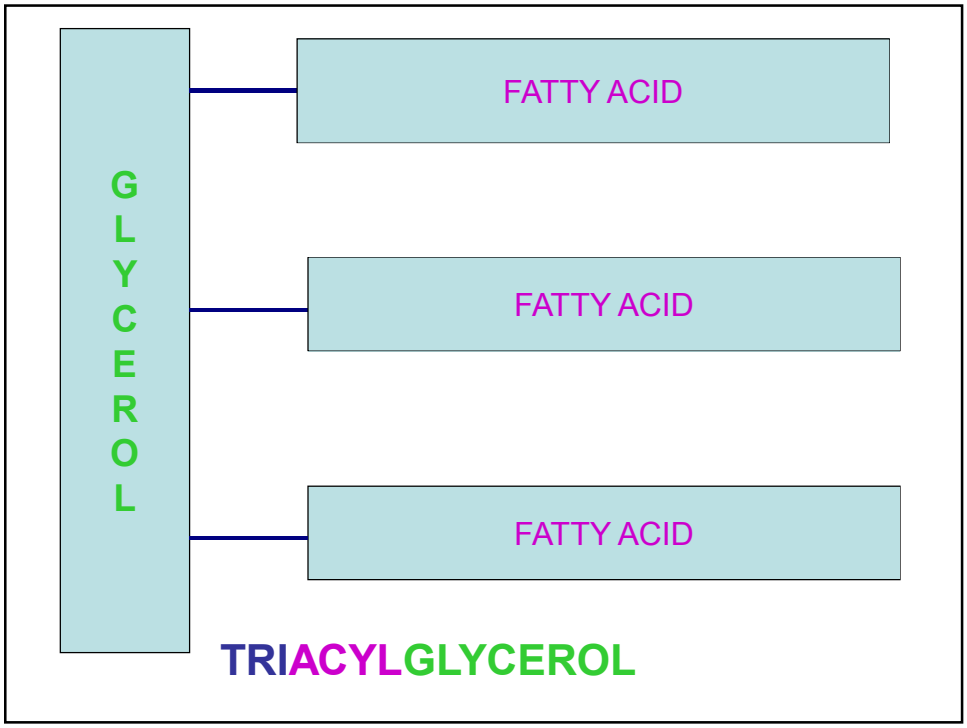
Mobilization of stored fats and oxidation of fatty acids

Lippincott's Chapter 16

What is the first lecture about

- What is triacylglycerol
- Fatty acids structure
- The most common fatty acids
- TAG as the major energy source and reserve
- Mobilization of TAG in response to hormonal signal
- Reactions of β oxidation
  - Activation
  - Transport across inner mitochondrial membrane
  - Sequence of reactions

181-182
189-192
193-197



CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-**COOH**

Fatty acid

The pk_a of carboxyl group in fatty acid ≈ 4.8

So, at physiological pH fatty acid exists as anion

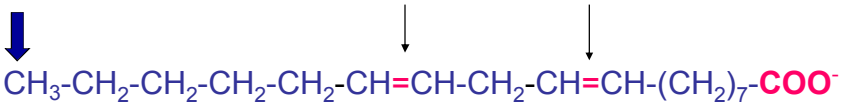
ω β α

CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-**COO^-**

Or

CH_3 $(CH_2)_n$ **COO^-**

The hydrocarbon chain can be saturated or it may contain one or more double bonds



Unsaturated Fatty Acid

$18{:}2\Delta^{9,12}$ or 18:(9,12)

Linoleic Acid

ω6

Some fatty acids of physiological importance

COMMON NAME	STRUCTURE
Formic acid	1
Acetic acid	2:0
Propionic acid	3:0
Butyric acid	4:0
Capric acid	10:0
Palmitic acid	16:0
Palmitoleic acid	16:1(9)
Stearic acid	18:0
Oleic acid	18:1(9)
Linoleic acid	18:2(9,12)
Linolenic acid	18:3(9,12,15)
Arachidonic acid	20:4(5, 8,11,14)
Lignoceric acid	24:0
Nervonic acid	24:1(15)

Triacylglycerol (TAG) or FAT is the major energy reserve in the body

It is more efficient to store energy in the form of TAG

Why FAT not Carbohydrates?

* More reduced:
  9 kcal per gram compared with
  4 kcal per gram of carbohydrates

* Hydrophobic:
  can be stored without H_2O
  carbohydrates are hydrophilic
  1 gram carbohdrates: 2 grams H_2O

Why FAT not Carbohydrates? (Continued)

Average adult has 10 Kg of Fat

How many calories?

90,000 kcal

What is the mass of carbohydrates that produces 90,000 kcal ?

90,000 / 4 = 22.5 Kg

How much water with it?

FATTY ACID as FUELS

- Fatty Acids are the major fuel used by tissues but Glucose is the major Fuel in extracellular fluids

Fuel type	Amount in Fluids gram	Amount used /12 hours gram
FA	0.4	60 (540 Kcal)
Glucose	20	70 (280 Kcal)

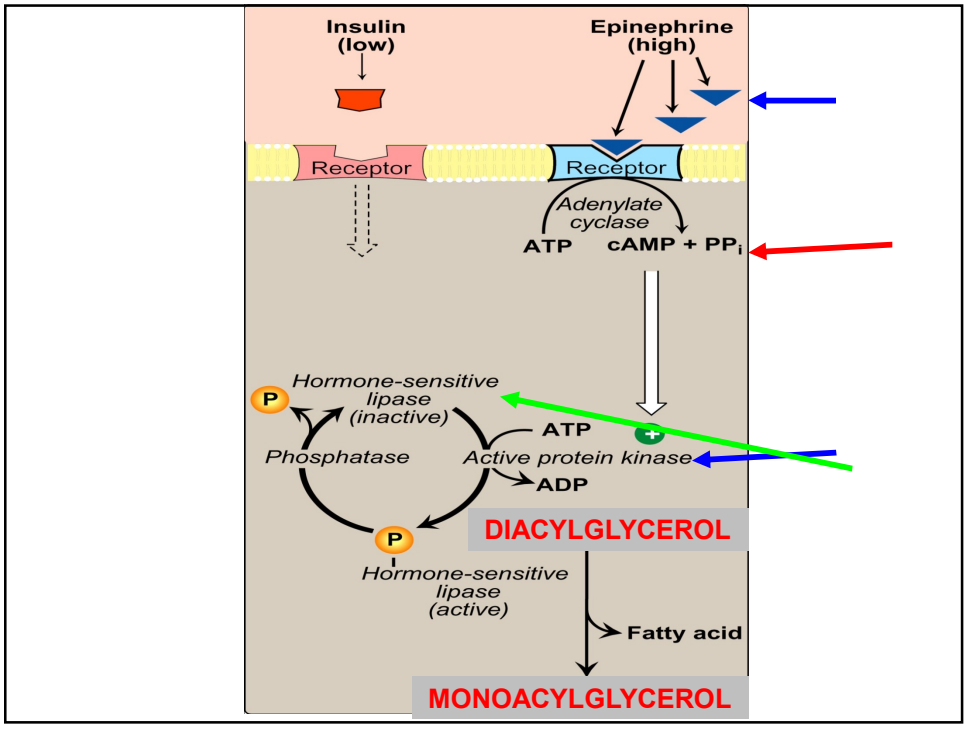
Mobilization of stored fats
The need for hormonal signal

- Fat is stored in Adipose tissue
- When needed a hormonal signal must reach the adipocytes.
- Hydrolysis of TAG

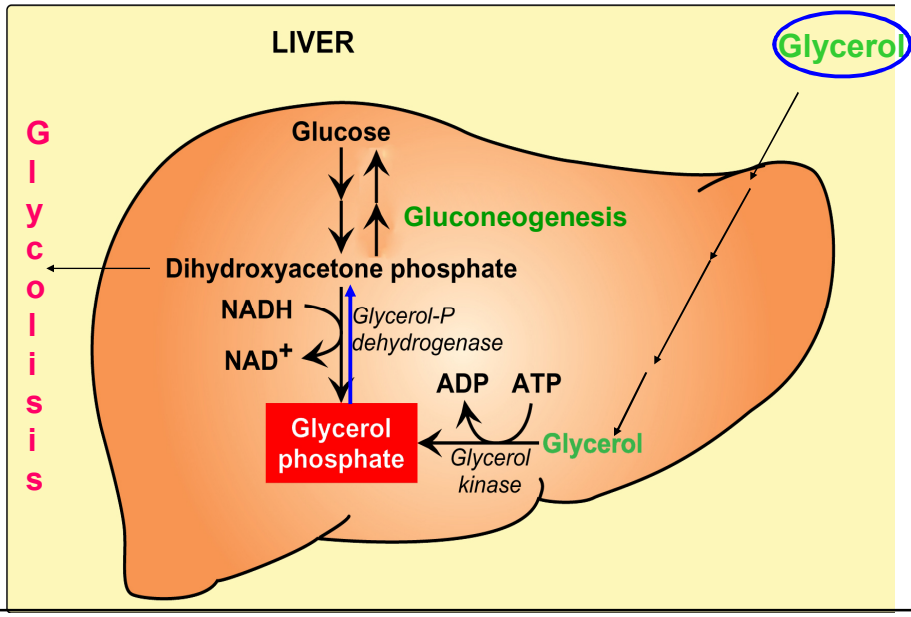
LIPASE :Hormone Sensitive Lipase

Hormones that activate the Hormone Sensitive Lipase

- Glucagon
- Epinephrine
- Norepinephrine
- ACTH

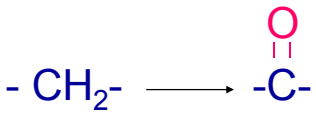


Fate of Glycerol

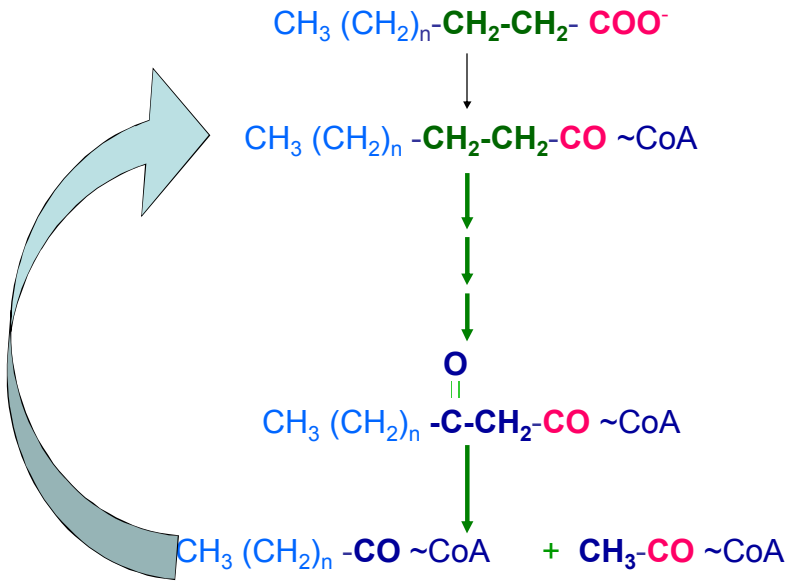


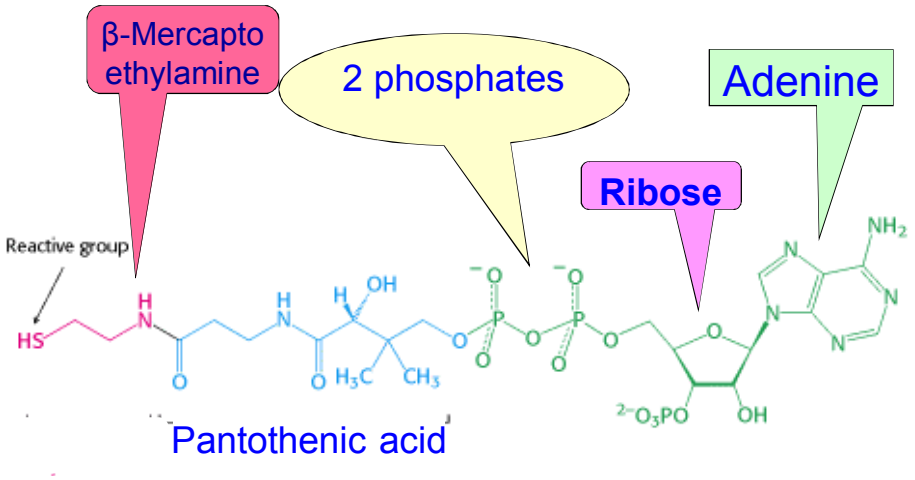
β Oxidation of Fatty Acids

- Fatty Acids are transported to tissues bound to albumin
- Degraded by oxidation at β carbon followed by cleavage of two carbon units



β Oxidation of Fatty Acids (overview)





Activation of Fatty Acids

- Joining F.A with Coenzyme A
- RCO~SCoA (Thioester bond)

$$FA + HSCoA + ATP \rightleftharpoons FA\sim CoA + AMP + PP_i$$

$$PP_i + H_2O \longrightarrow 2\ P_i$$

$$FA + HSCoA + ATP \longrightarrow FA\sim CoA + AMP + 2\ P_i$$

$$AMP + ATP \rightleftharpoons ADP + ADP$$

$$FA + HSCoA + 2ATP \longrightarrow FA\sim CoA + 2ADP + 2\ P_i$$

Activation of Fatty Acids (cont.)

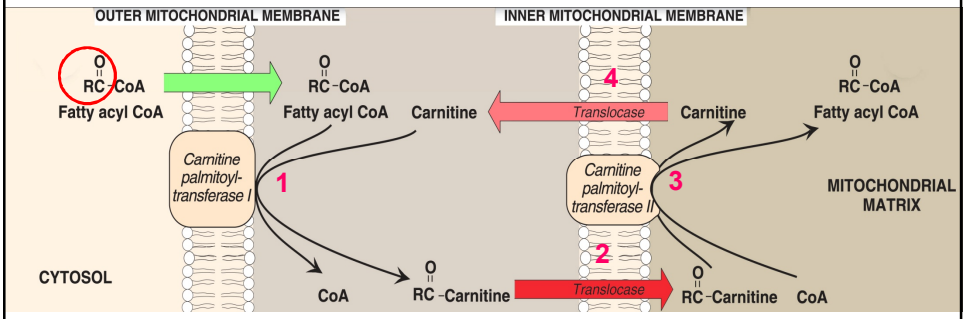
- ATP conversion to AMP + 2 P_i is equivalent to hydrolysis of 2 ATP to 2ADP
- Enzyme: thiokinase (Acyl CoA Synthetase)
- Location: - outer mitochondrial membrane

  - mitochondrial matrix (for short and medium chain FA)

Transport of long chain Acyl CoA across inner mitochondrial membrane

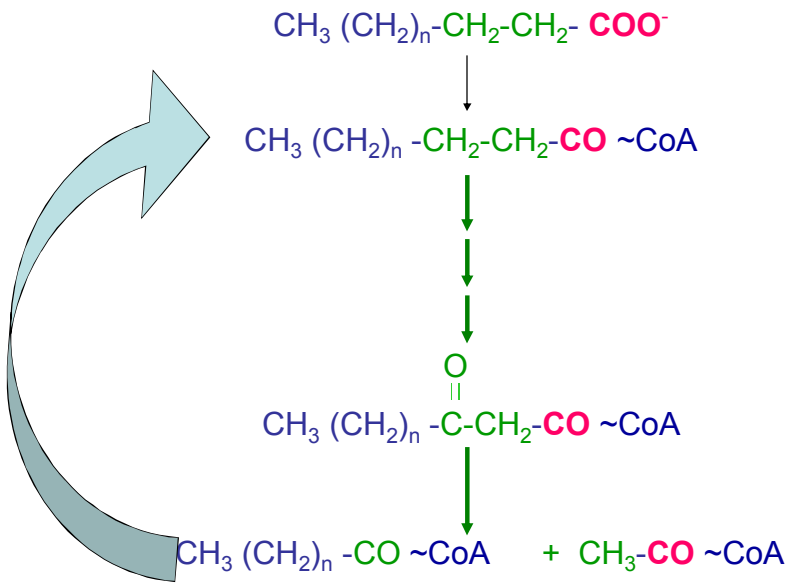
- Inner mitochondrial membrane is impermeable to Acyl CoA
- Carrier system is required (Carnitine Shuttle)
- It consists of:
  - Carrier molecule
  - Two enzymes
  - Membrane transport protein

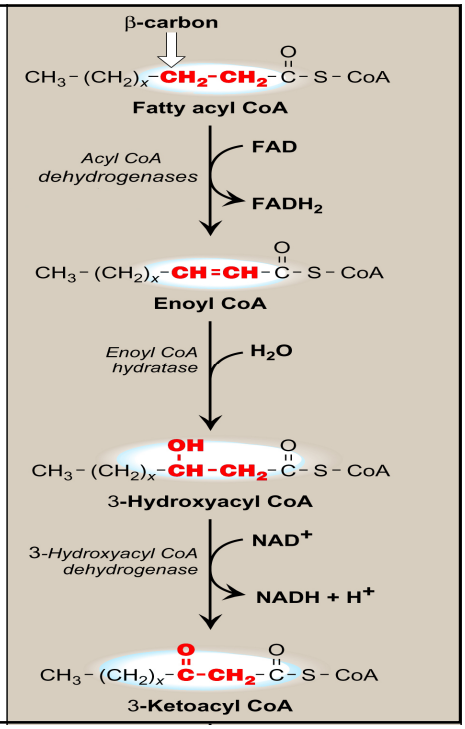
CARNITINE SHUTTLE

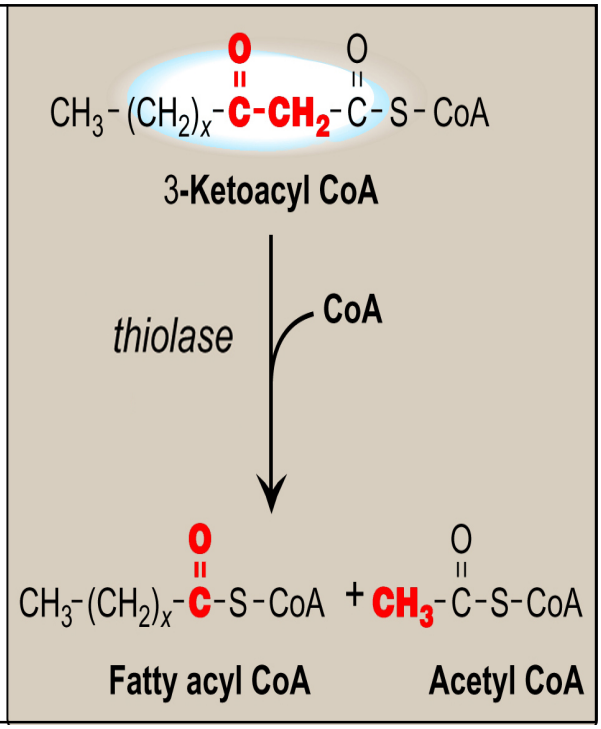


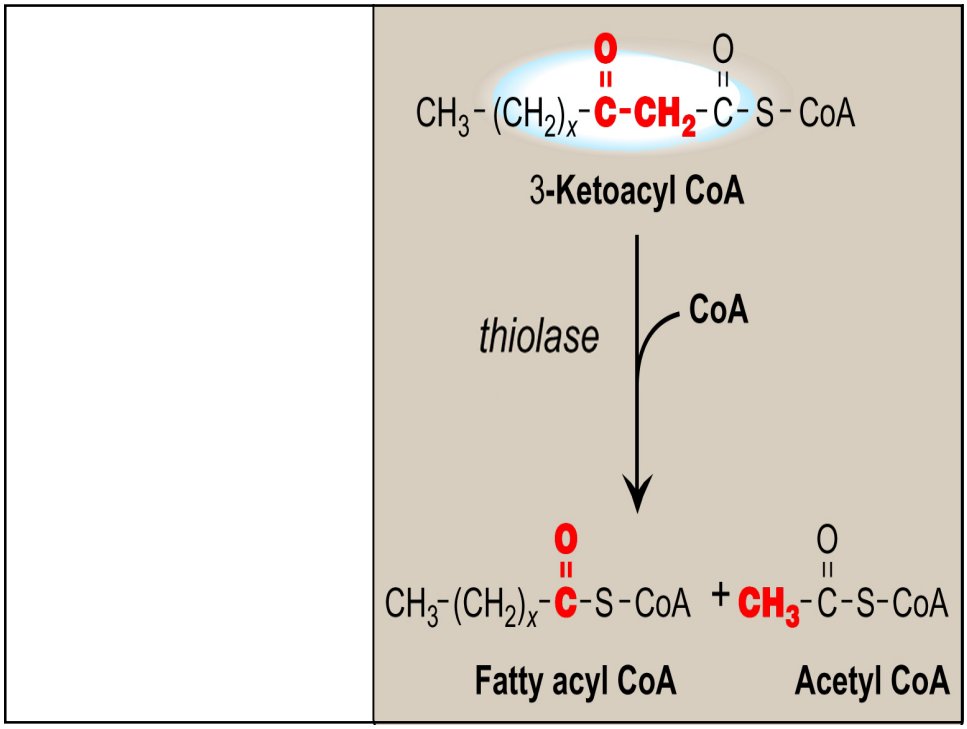
For Long chain fatty acids
Inhibited during fatty acid synthesis
Not required for medium and short chain fatty acids

β Oxidation of Fatty Acids (overview)




β-carbon
CH3-(CH2)x-CH2-CH2-C-S-CoA
Fatty acyl CoA
Acyl CoA dehydrogenases
FAD
FADH2
CH3-(CH2)x-CH=CH-C-S-CoA
Enoyl CoA
Enoyl CoA hydratase
H2O
CH3-(CH2)x-CH(OH)-CH2-C-S-CoA
3-Hydroxyacyl CoA
3-Hydroxyacyl CoA dehydrogenase
NAD+
NADH + H+
CH3-(CH2)x-C(=O)-CH2-C-S-CoA
3-Ketoacyl CoA


CH3-(CH2)x-C(=O)-CH2-C-S-CoA
3-Ketoacyl CoA
thiolase
CoA
CH3-(CH2)x-C(=O)-S-CoA + CH3-C-S-CoA
Fatty acyl CoA
Acetyl CoA



Energy Yield from FA Oxidation

$CH_3\text{-}(CH_2)_{14}\text{-}CO\text{-}CoA$

After 6 cycles of β Oxidation

- 6 $FADH_2$
- 6 NADH
- 6 Acetyl CoA

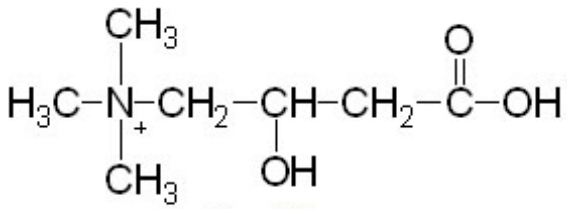
$CH_3\text{-}CH_2CH_2\text{-}CO\text{-}CoA$

$CH_3\text{-}CO\text{-}CoA + CH_3\text{-}CO\text{-}CoA + FADH_2 + NADH$

Energy Yield from FA Oxidation (cont.)

- Oxidation of C 16 FATTY ACID
  - 7 $FADH_2$ ➔ 14 ATP
  - 7 NADH ➔ 21 ATP
  - 8 Acetyl CoA ➔ 96 ATP
- Activation of the Acid consumes 2 ATP
- Net 129 ATP mole per mole of C16 Fatty Acid

Carnitine



Carnitine

* Other functions:
  - Export of branched chain acyl groups from mitochondria
  - Excretion of acyl groups that cannot be metabolized in the body

Carnitine Deficiencies

- ↓ Ability to use FA as a fuel
- Accumulation of F.A and branched Acyl groups in cells

Oxidation of unsaturated F.A: Oleic Acid

$CH3 – (CH_2)_7\text{-}CH = CH\ (CH_2)_7\text{-}CO\sim CoA$

18:cis Δ^9

3 rounds of β oxidation

3 Acetyl CoA

$CH3 – (CH_2)_7\text{-}CH = CH\ CH_2\text{-}CO\sim CoA$

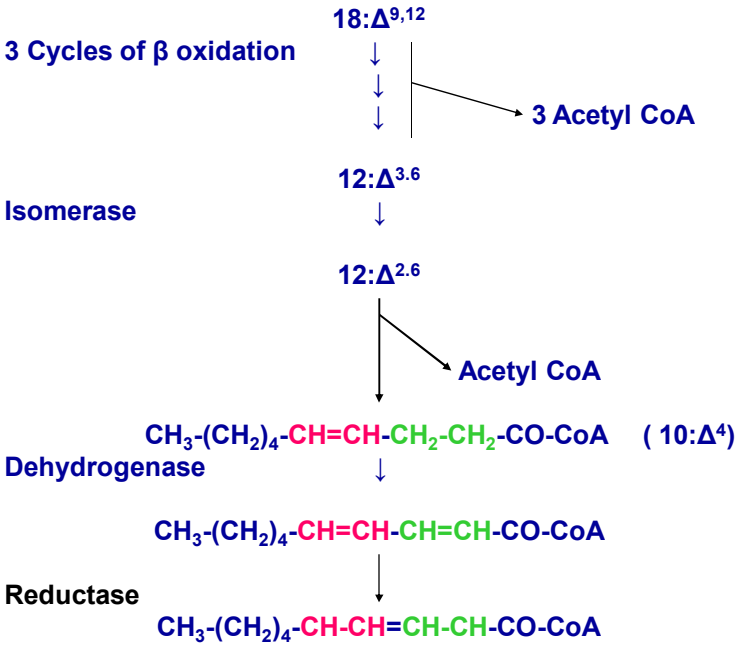
12:cis Δ^3

isomerase

$CH3\ (CH_2)_7\ CH_2\text{-}CH{=}CH\text{-}CO\sim CoA$

12:trans Δ^2

Oxidation of Unsaturated F.A: Linoleic Acid



Oxidation of FA with odd number of carbons

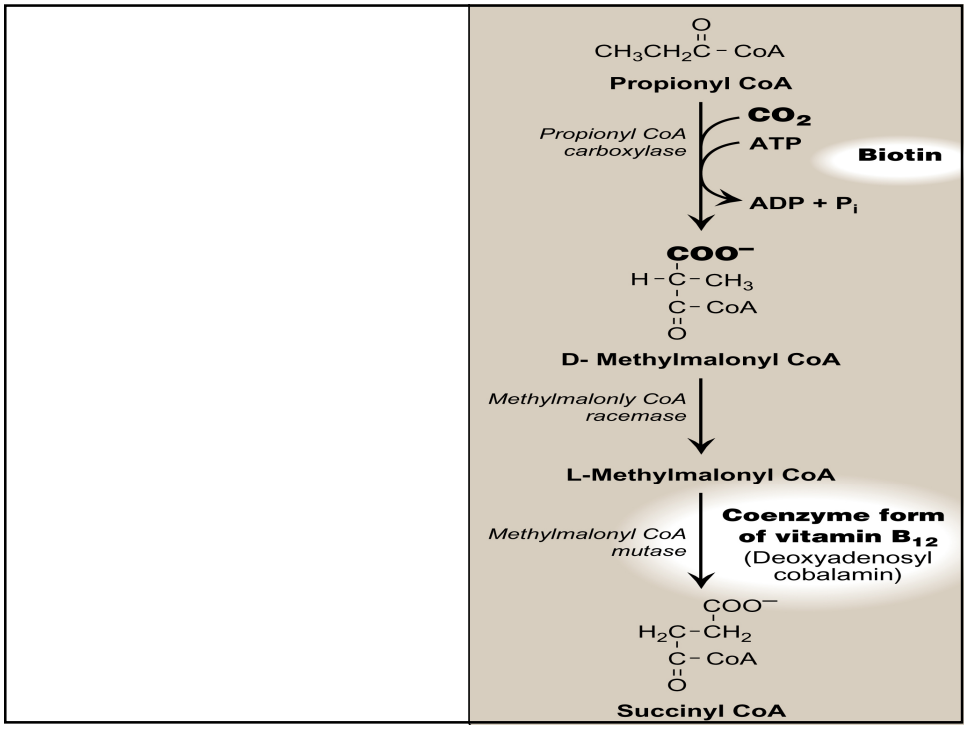
$CH_3\text{-}(CH_2)_{13}\text{-}CO\sim CoA$

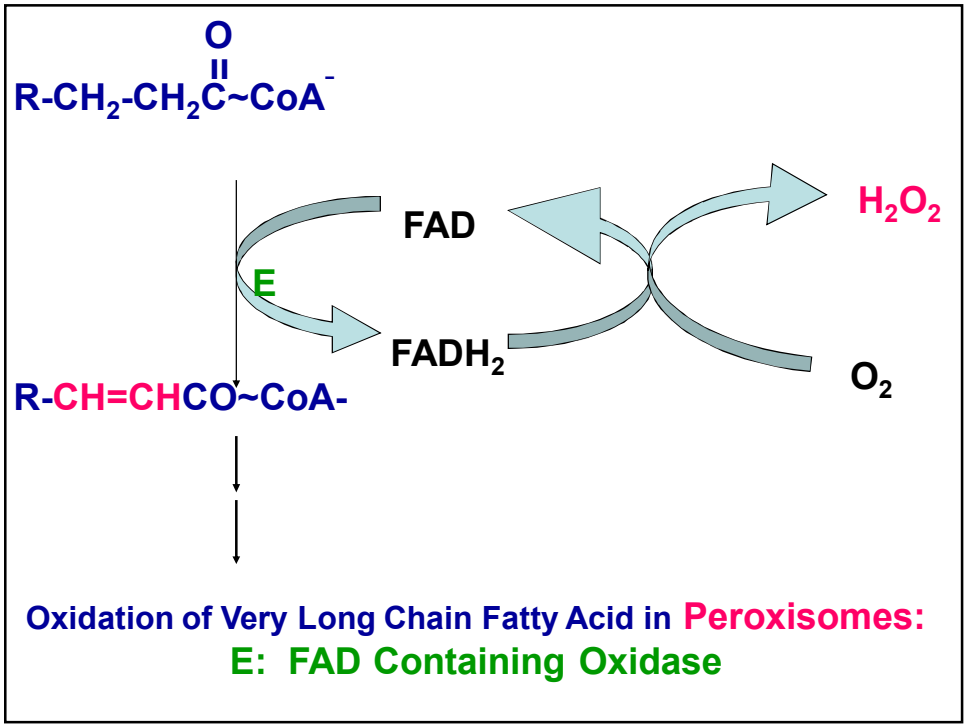
Six Cycles of β oxidation ↓

↓

$CH_3\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\sim CoA$ + 6 Acetyl CoA

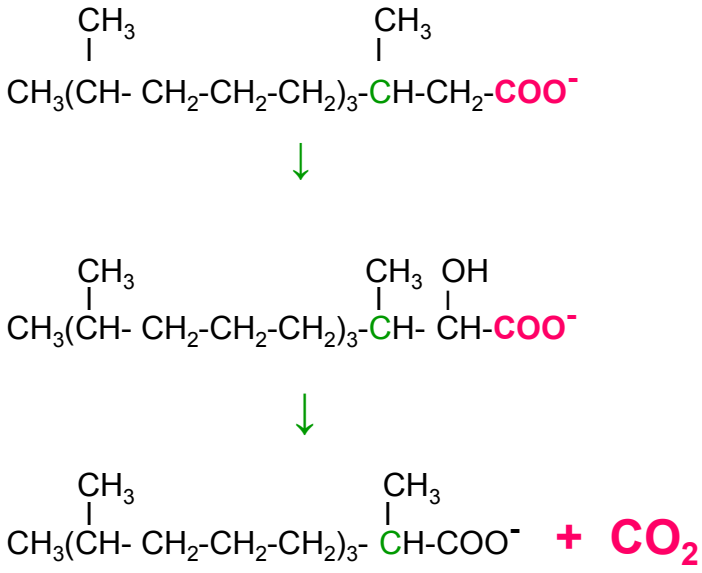
Propionyl CoA



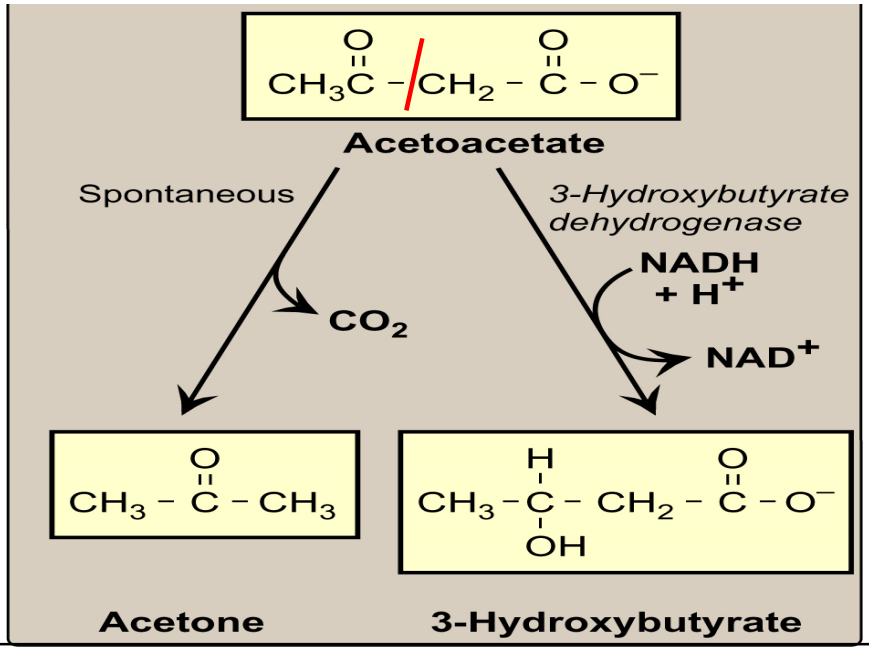


Oxidation of Very Long Chain Fatty Acid in Peroxisomes:
E: FAD Containing Oxidase

α Oxidation of Fatty Acids

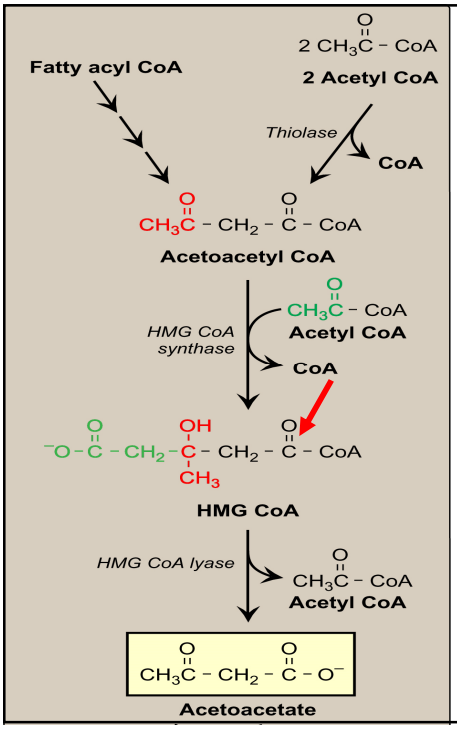


Ketone Bodies



Ketone Bodies

- Synthesis:
  In Liver
- Precursor:
  Acetyl CoA
- At high rate during:
  -Fasting
  - Uncontrolled Diabetes Mellitus



Net Reaction ??

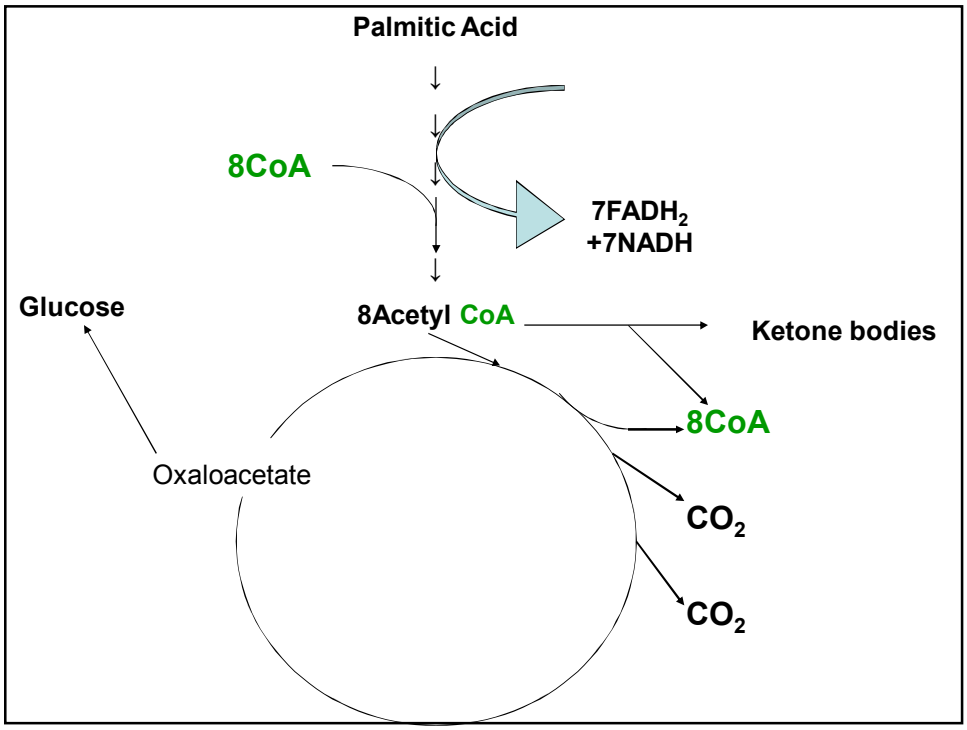
2 Acetyl CoA → Acetoacetate + 2 CoA

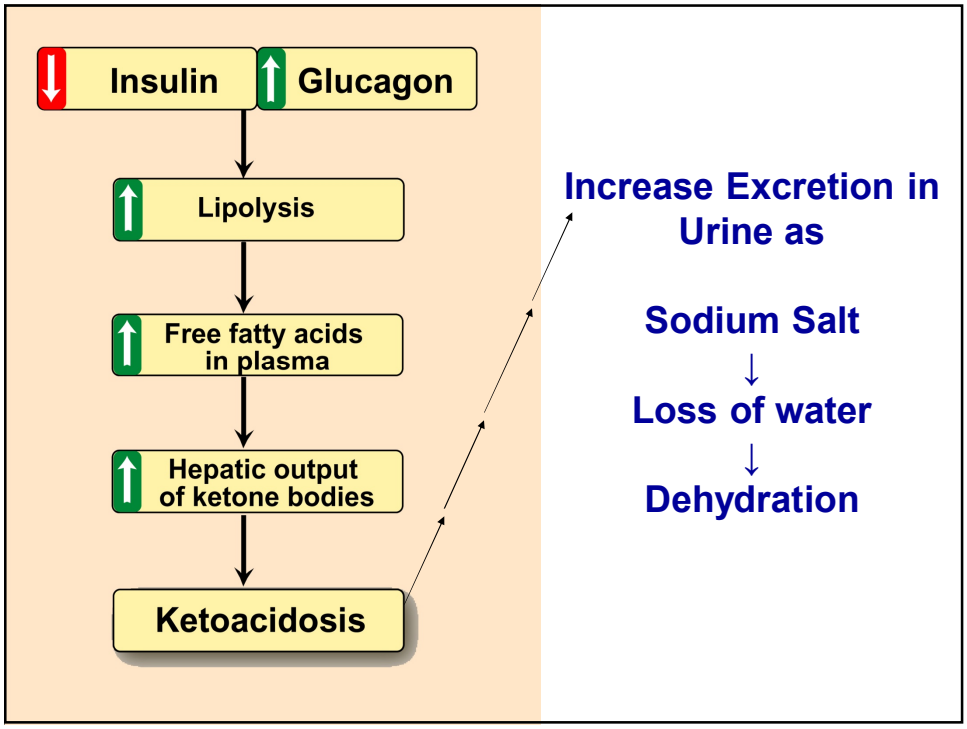
Net Reaction

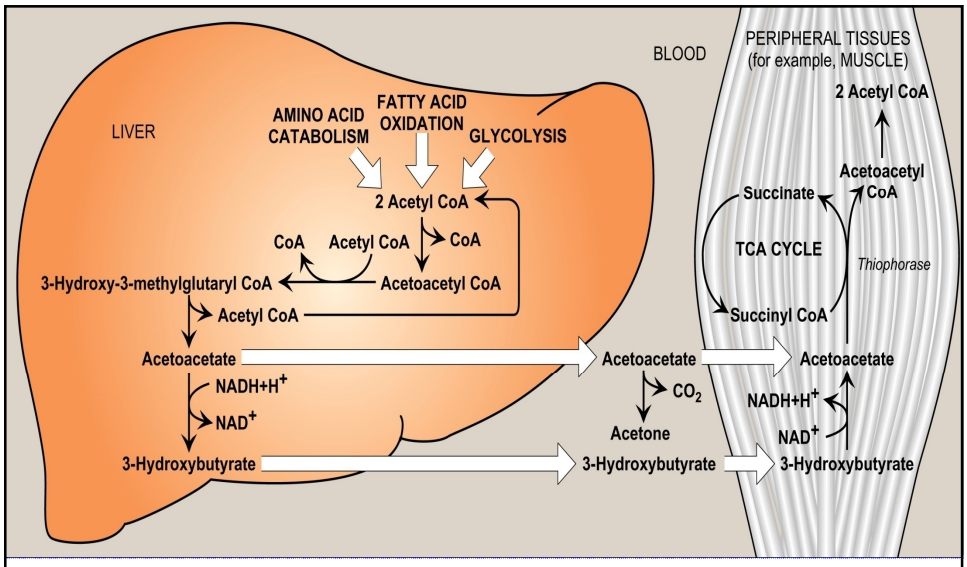
2 Acetyl CoA → Acetoacetate + 2 CoA

Advantage (Purpose) ?

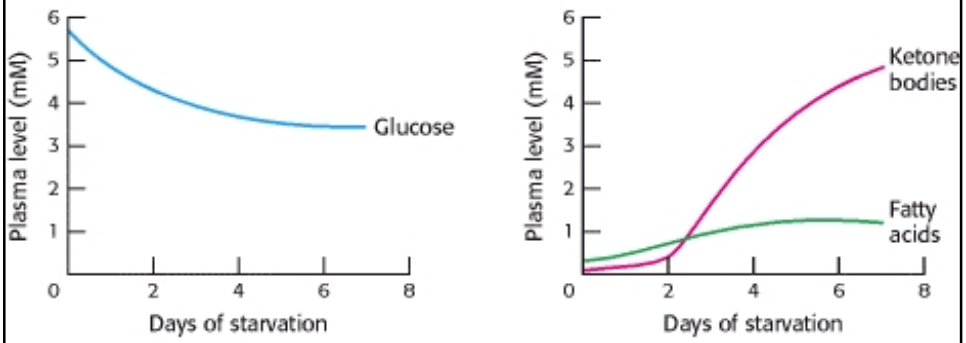
- For the liver
- For the tissues







Use of Ketone Bodies by Peripheral Tissues: Skeletal Muscle, Cardiac Muscle and In Brain During Prolonged Fasting (Starvation)



Fuel metabolism in starvation

	Amount formed or consumed in 24 hours (grams)	
Fuel exchanges and consumption	**3rd day**	**40th day**
Fuel use by the brain		
Glucose	100	40
Ketone bodies	50	100
All other use of glucose	50	40
Fuel mobilization		
Adipose-tissue lipolysis	180	180
Muscle-protein degradation	75	20
Fuel output of the liver		
Glucose	150	80
Ketone bodies	150	150