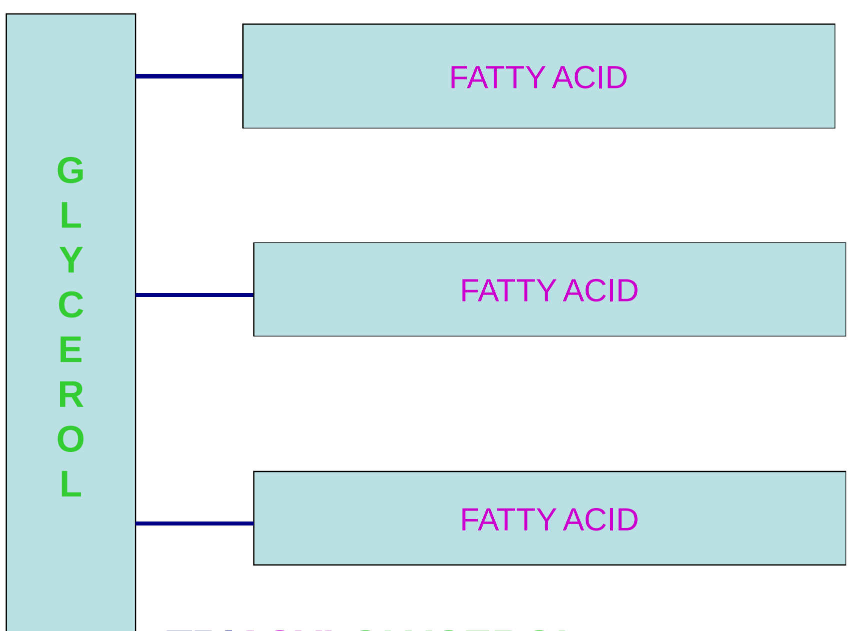
Fatty Acid and Triacylglycerol Metabolism 1

Mobilization of stored fats and oxidation of fatty acids

Lippincott's Chapter 16



TRIACYLGLYCEROL

CH_3-CH_2-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

CH_3-CH_2-CH_2-CH_2-CH_2-CH=CH-CH_2-CH=CH-$(CH_2)_7$-**COO^-**

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

- The major fuel used by tissues but Glucose is the major circulating Fuel

Fuel type	Amount used/ 12 hours (kcal)	Amount in Fluids (kcal)
FA	540	3
Glucose	280	80

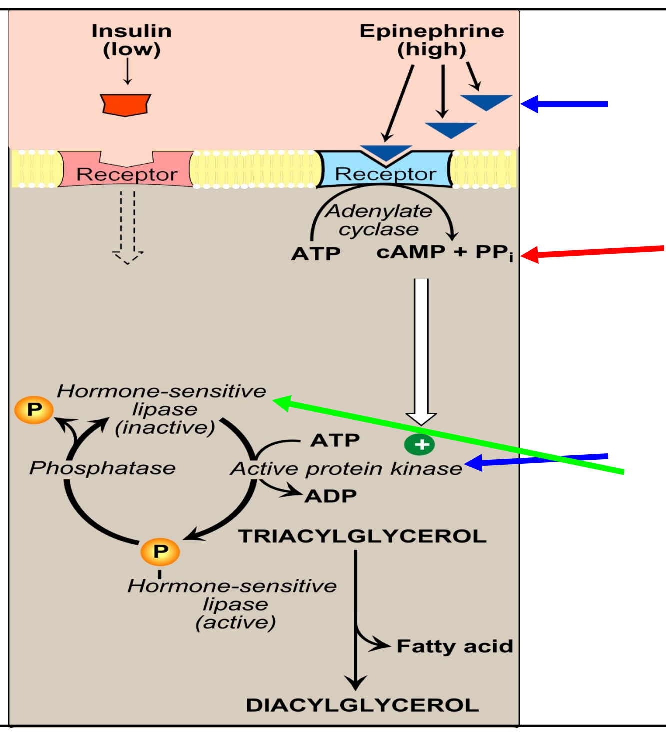
Mobilization of stored fats
The need for hormonal signal

- Fat is stored in Adipose tissue
- When needed a hormonal signal reaches the adipocyte.
- Hydrolysis of TAG

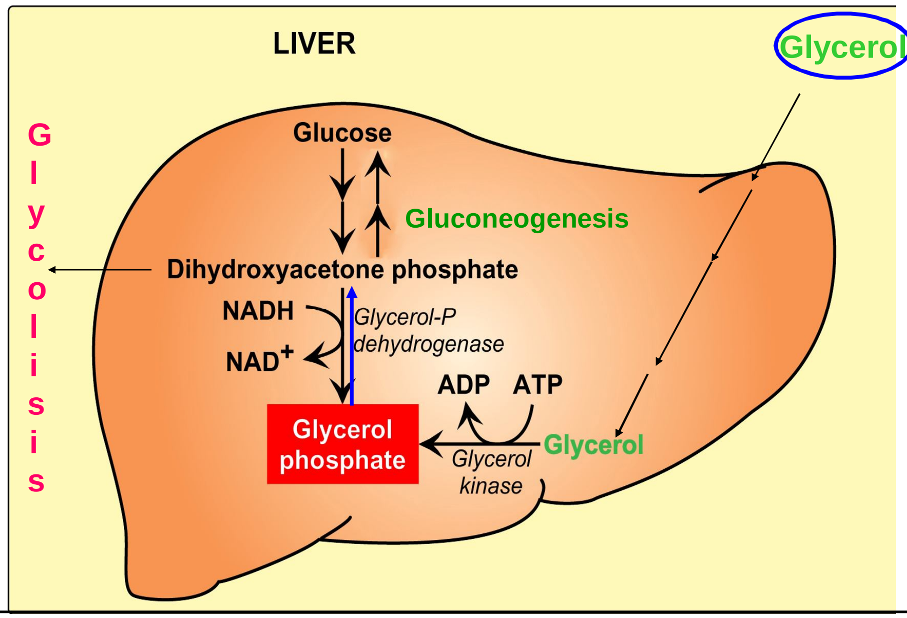
$$TAG + 3\ H_2O \longrightarrow 3\ FA + glycerol$$

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
- $-CH_2- \longrightarrow -\overset{\overset{\displaystyle O}{\|}}{C}-$

β Oxidation of Fatty Acids (overview)

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

↓

$CH_3 (CH_2)_n$ -CH_2-CH_2-**CO** ~CoA

↓

↓

↓

O
||
$CH_3 (CH_2)_n$ -C-CH_2-**CO** ~CoA

↓

$CH_3 (CH_2)_n$ -CO ~CoA + CH_3-**CO** ~CoA

Activation of Fatty Acids

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

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

PP_i + H_2O $\longrightarrow$ 2 P_i

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

AMP + ATP $\rightleftharpoons$ ADP + ADP

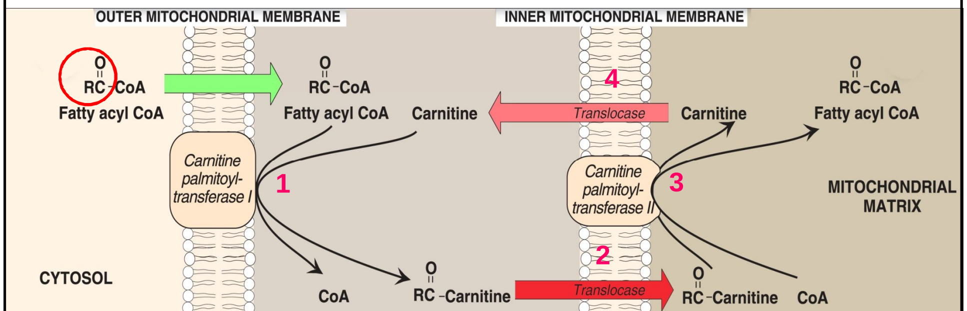
Activation of Fatty Acids (cont.)

- 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

β Oxidation of Fatty Acids (overview)

$CH_3\ (CH_2)_n\text{-}CH_2\text{-}CH_2\text{-}\ COO^-$

↓

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

↓

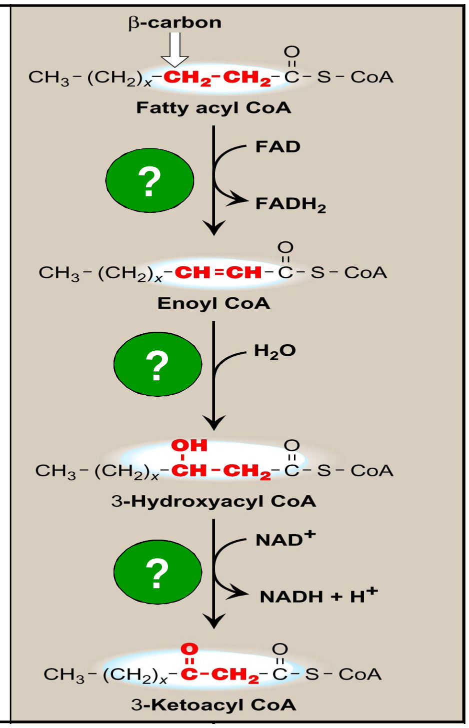
↓

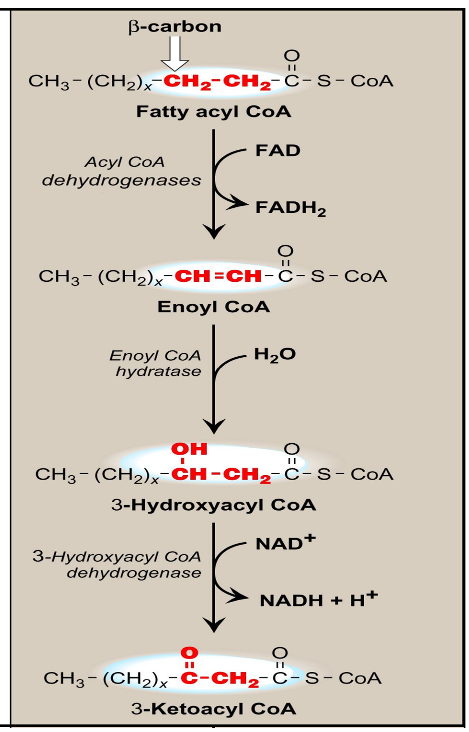
↓

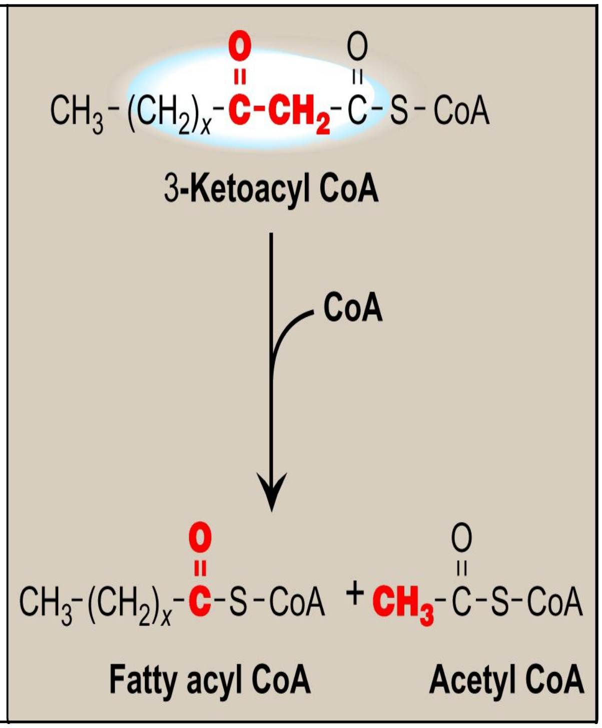
$CH_3\ (CH_2)_n\ \text{-}\overset{\overset{O}{||}}{C}\text{-}CH_2\text{-}CO \sim CoA$

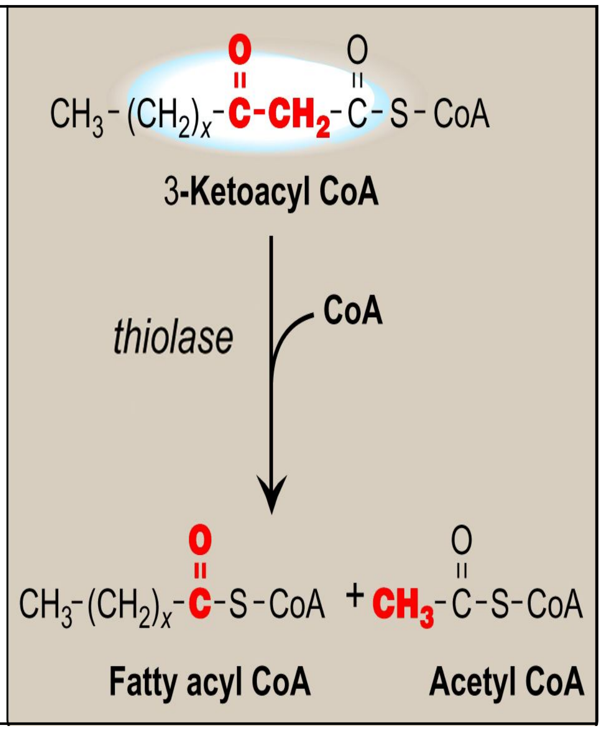
↓

$CH_3\ (CH_2)_n\ \text{-}CO \sim CoA \quad + \quad CH_3\text{-}CO \sim CoA$


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


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


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


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

Energy Yield from FA Oxidation

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

$\downarrow$ → 6 $FADH_2$ → 6 NADH → 6 Acetyl CoA

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

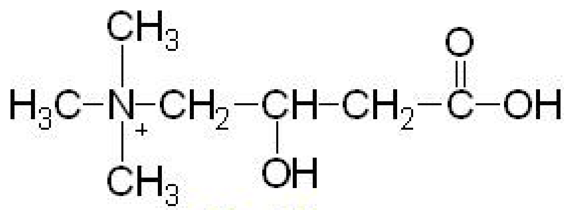
$\downarrow$

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

Energy Yield from FA Oxidation (cont.)

- Oxidation of C 16 FATTY ACID
  - 7 FADH2 ====> 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

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

Oxidation of unsaturated F.A: Oleic Acid

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

↓ 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

$18{:}\Delta^{9,12}$

3 Cycles of β oxidation ↓ ↓ ↓ → 3 Acetyl CoA

$12{:}\Delta^{3.6}$

Isomerase ↓

$12{:}\Delta^{2.6}$

↓ → Acetyl CoA

$CH_3\text{-}(CH_2)_4\text{-}CH{=}CH\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}CoA$ ($10{:}\Delta^4$)

Dehydrogenase ↓

$CH_3\text{-}(CH_2)_4\text{-}CH{=}CH\text{-}CH{=}CH\text{-}CO\text{-}CoA$

Reductase ↓

$CH_3\text{-}(CH_2)_4\text{-}CH\text{-}CH{=}CH\text{-}CH\text{-}CO\text{-}CoA$

Oxidation of FA with odd number of carbons

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

Six Cycles of β oxidation ↓

↓

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

Propionyl CoA