2) Fatty acid oxidation

- **Hormone sensitive lipase** releases fatty acids from intracellular TAG stores

- **Lipoprotein lipases** releases fatty acids from lipoproteins into blood stream

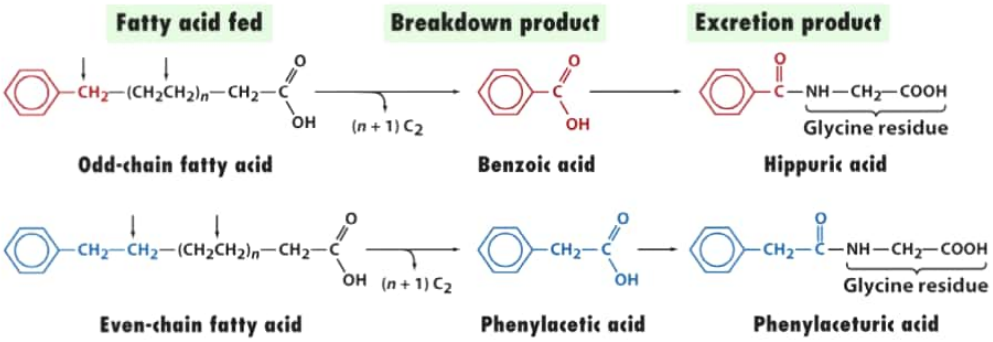
- Fatty acids enter blood stream, kept soluble by binding to albumin, ~10^{-6}M -> 2mM

- But **analbuminemia** is not lethal

- Intracellular catabolism of fatty acids to produce energy

Franz Knoop's classic experiment indicating that fatty acids are metabolically oxidized at their β-carbon atom

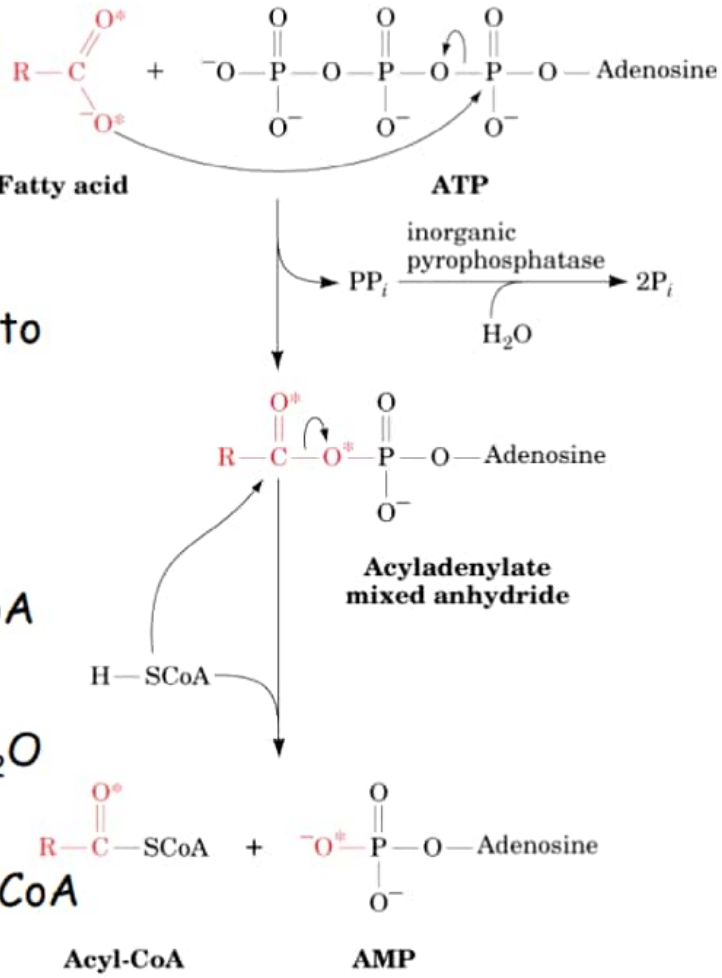
- Phenyl-labeled even- or odd-numbered fatty acids
- Feed to dogs -> what product appears in urine ?



A) Fatty acid activation catalyzed by acyl-CoA synthetase

- Fatty acids need almost always be activated to Acyl-CoAs for subsequent enzymatic reaction
- Activation by acyl-CoA synthetases via acyladenylate intermediate

Mechanism of fatty acid activation catalyzed by acyl-CoA synthetase

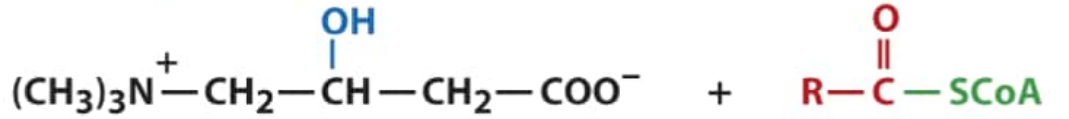


1) Activation of acyl chains to acyl-CoAs in cytosol
2) Requires ATP -> acyl-adenylate intermediated
3) Transesterification to CoA
4) Driven by inorganic pyrophosphatase PP_i -> H_2O $+2P_i$
5) ^{18}O-labels AMP and Acyl-CoA

Acylation of carnitine catalyzed by carnitine palmitoyltransferase

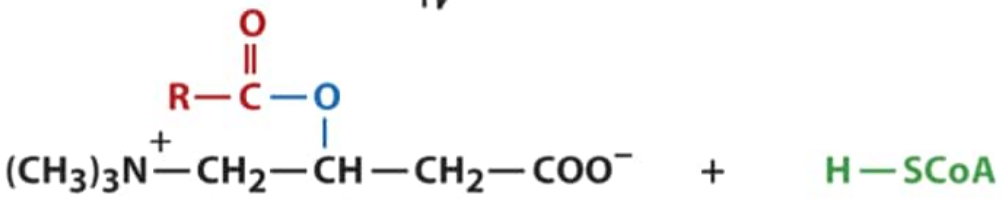
2nd step: preparation for mitochondrial import

- Transesterification of acyl-CoA to carnitine (no AMP intermediate !)
- catalyzed by CPTI (equilibrium close to 1)



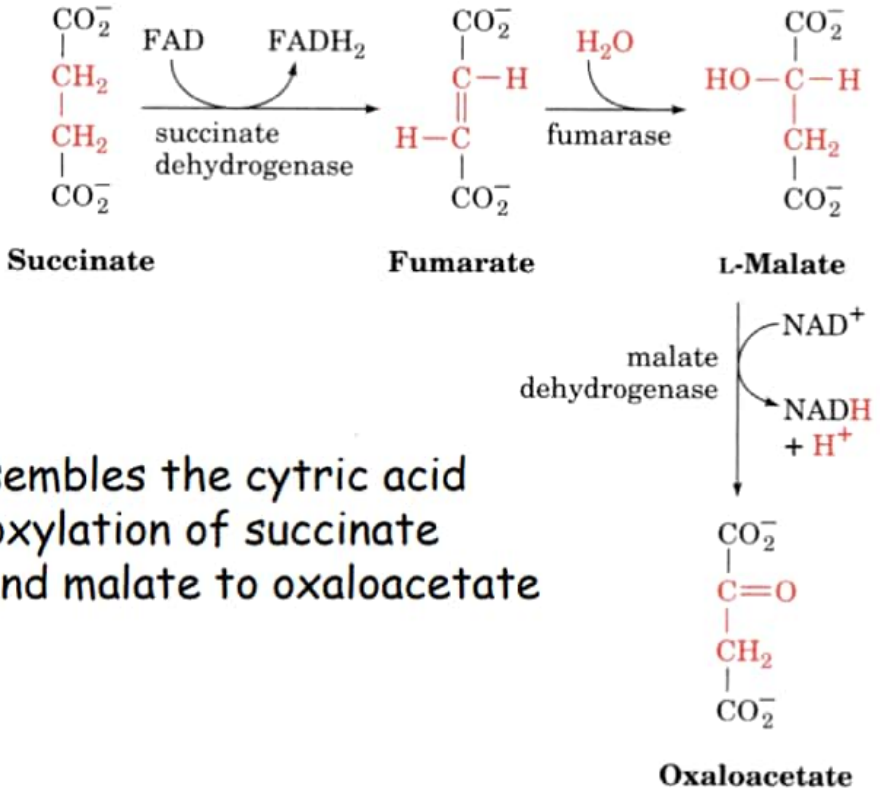
Carnitine (4-trimethylamino-3-hydroxybutyrate)

carnitine palmitoyl transferase

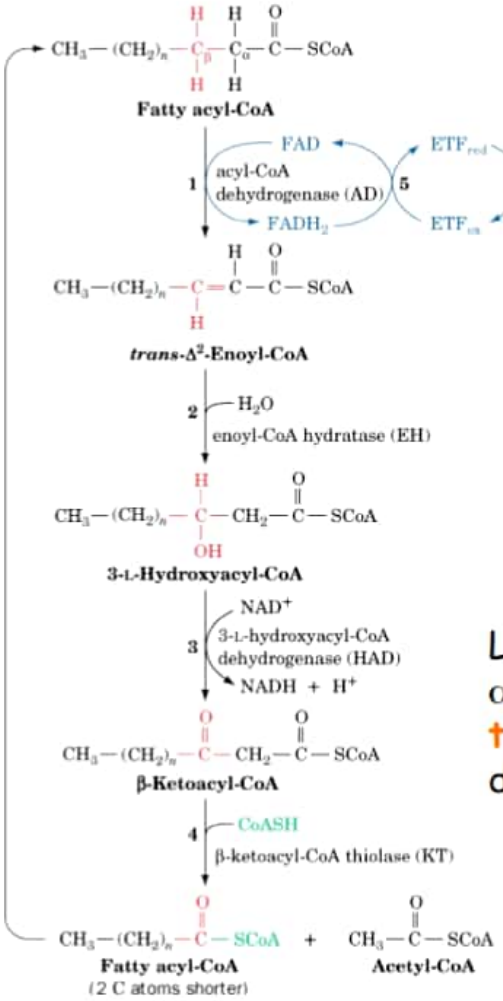


Acyl-carnitine

C) β-oxidation

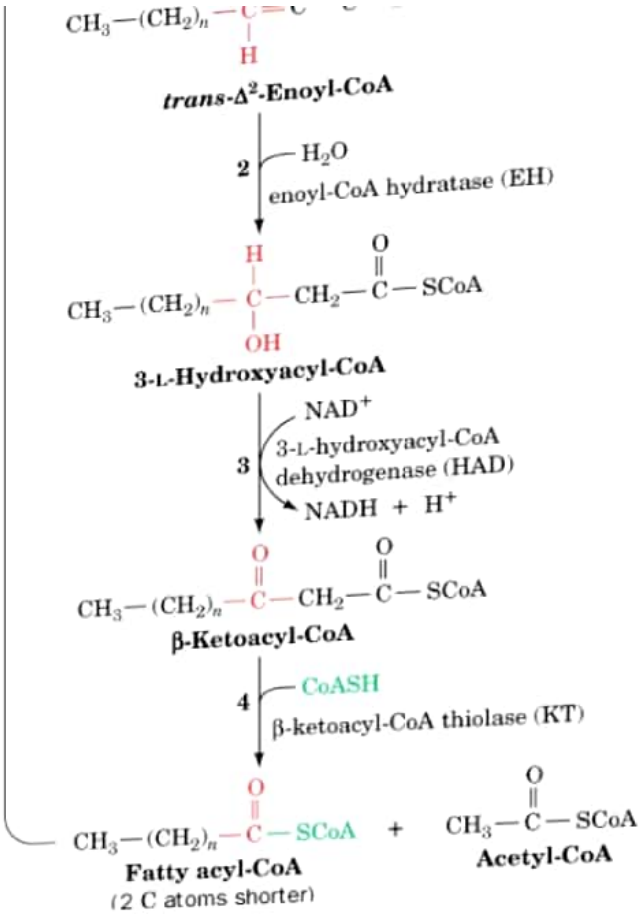


- Chemically resembles the cytric acid cycle: Decarboxylation of succinate via fumarate and malate to oxaloacetate



The β-oxidation pathway of fatty acyl-CoA

Long chain versions of EH, HAD and KTs in $\alpha_4\beta_4$ ocatmeric protein, **mitochondrial trifunctional protein** -> channeling, no detectable intermediates



Each round of β-oxidation produces:

1 NADH -> 3 ATP

1 FADH2 -> 2 ATP

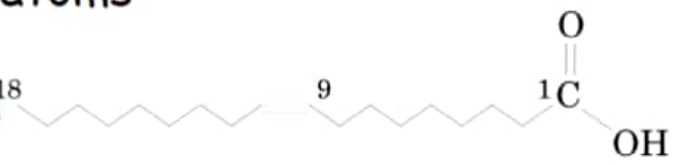
1 acetyl-CoA -> TCA (1 GTP, 3 NADH, 1 FADH2) (respiration only !)

OVERALL NET YIELD: 106 ATP per C16

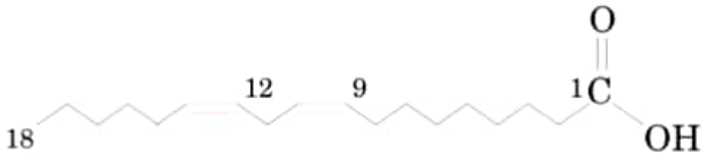
D) Oxidation of unsaturated fatty acids

Structures of two common unsaturated fatty acids,
Usually, *cis* double bond at C9
Additional double bond in C3 intervals, i.e. next at C12
-> odd, even numbered C atoms

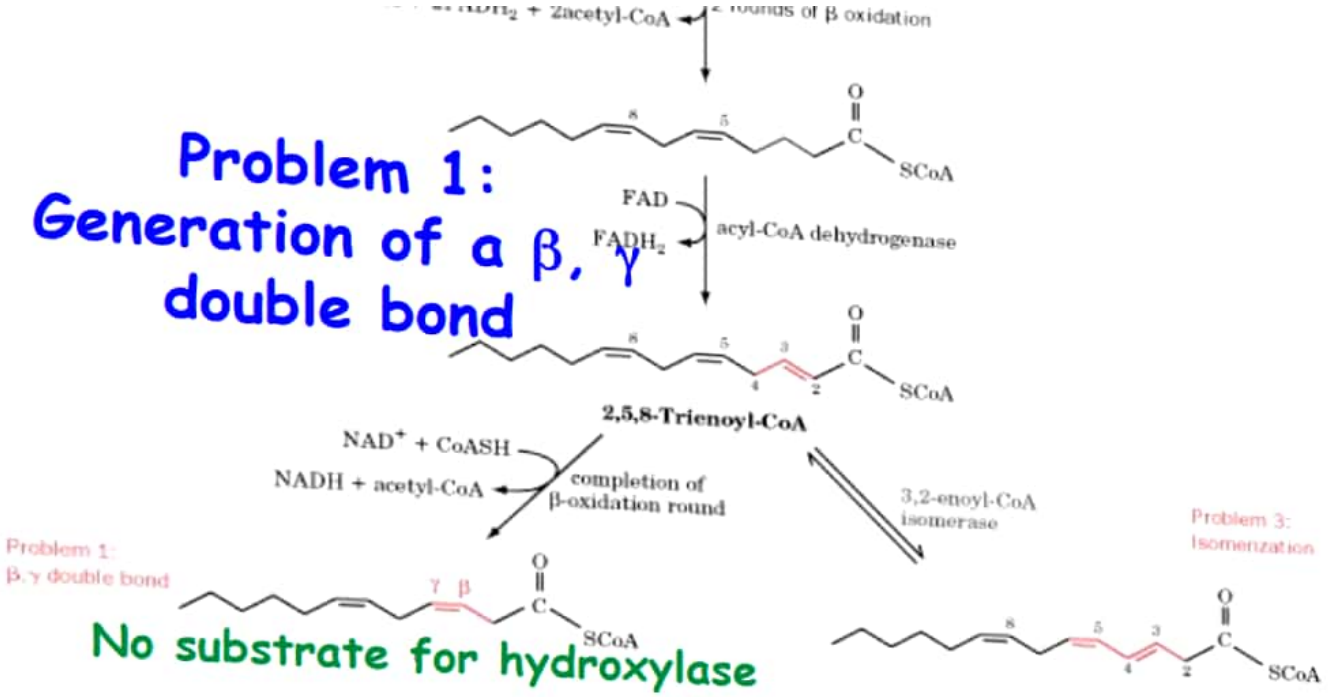
Problems for β-oxidation



Oleic acid
(9-*cis*-Octadecenoic acid)



Linoleic acid
(9,12-*cis*-Octadecadienoic acid)



F) Peroxisomal β oxidation

- β-oxidation occurs both in mitochondria and in peroxisomes
- *Peroxisomes:* Shortening of very-long chain fatty acids (VLCFA) for subsequent transport and oxidation in mitochondria
- **ALD protein** to transport VLCFA into peroxisomes, no carnitine required, VLCFA-CoA synthetase
- *X-adrenoleukodystrophy caused by defects in ALD,* lethal in young boys, 13% reduced efficiency of lignoceric acid (C24:0) to lignoceryl-CoA conversion
- first step in perox. oxid. **Acyl-CoA oxidase** generates H_2O_2 (peroxide) -> name ! Catalase
- carnitine for transport of chain shortened FAs out of peroxisomes and into mito.