Degradation of fatty acids

Dr. Diala Abu-Hassan

Lippincott's Biochemistry, Ch. 16

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 carbohydrates: 2 grams H_2O

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

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

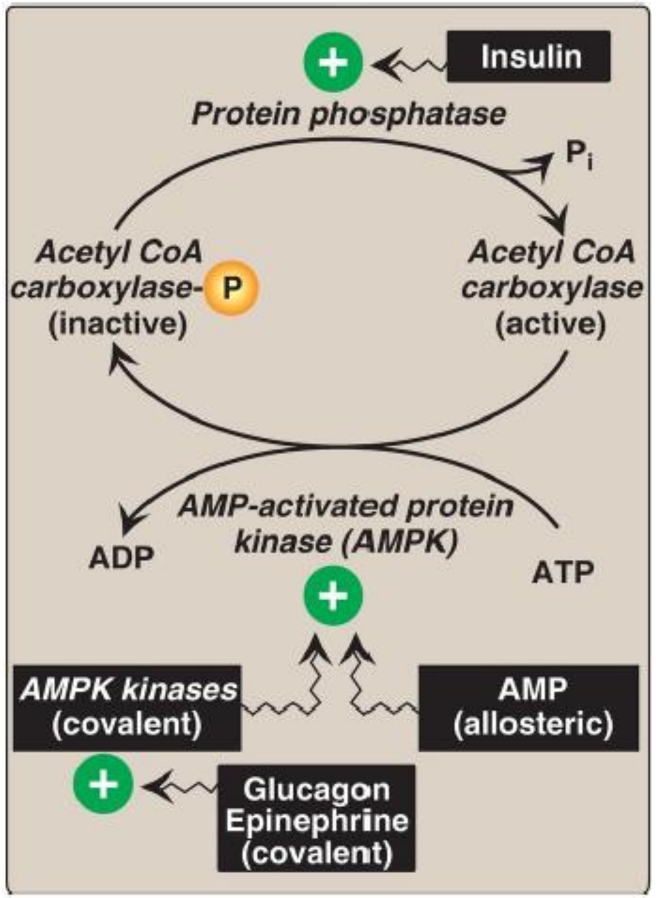
FATTY ACID as FUELS

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

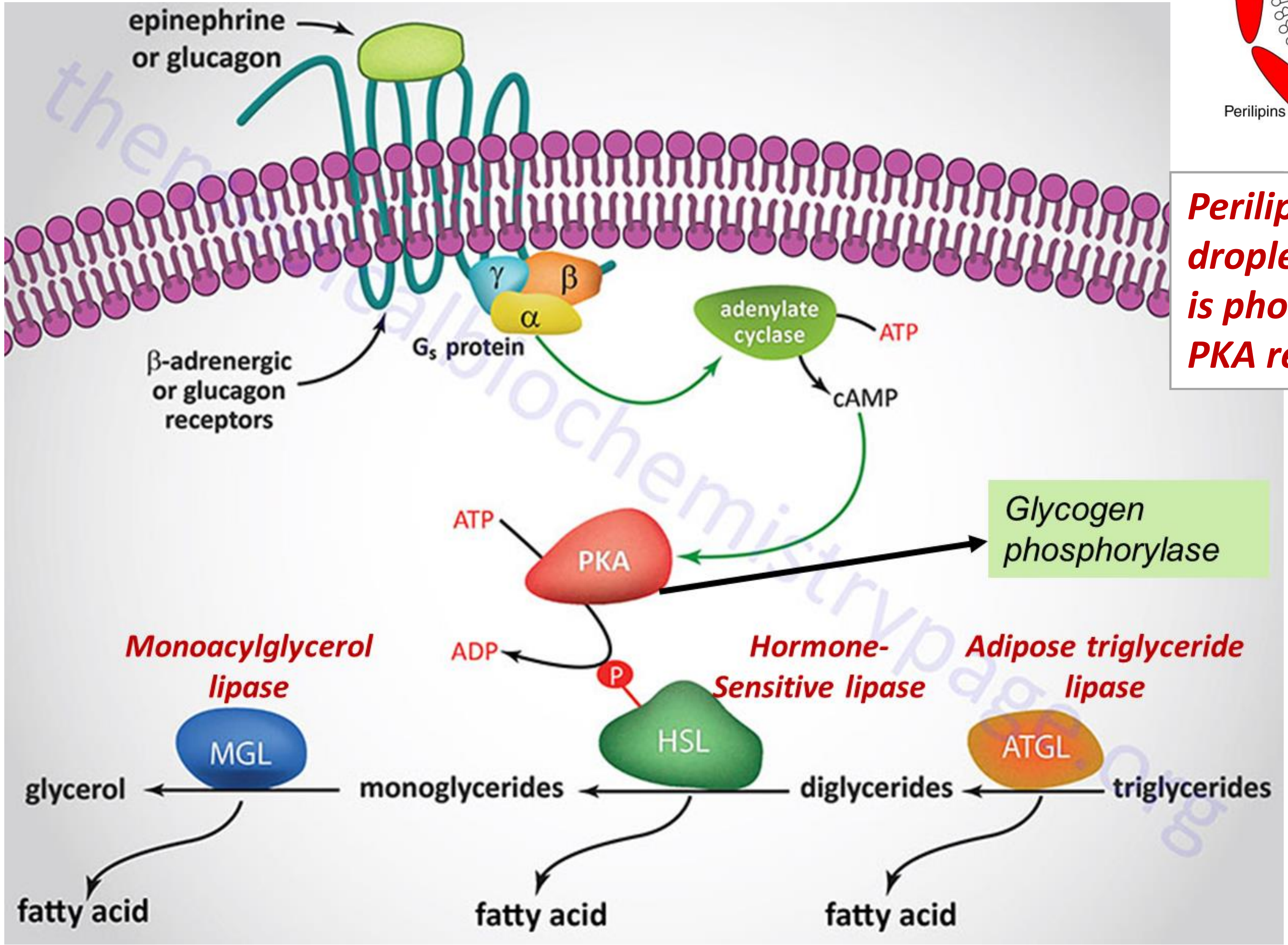
Fuel type	Amount used/kcal/12 hours (gram)
FA	60 (540)
Glucose	70 (280)

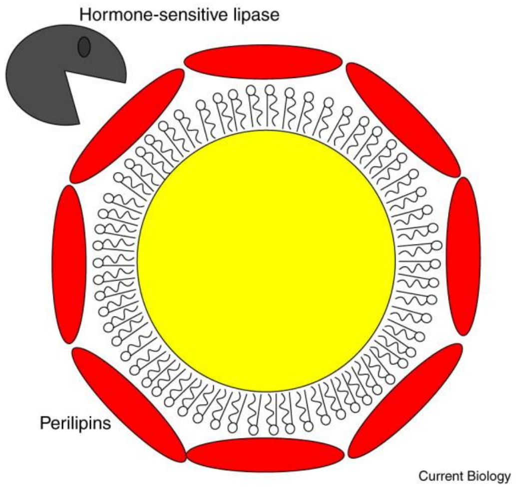
The release of fatty acids from TAG

Hormonal regulation



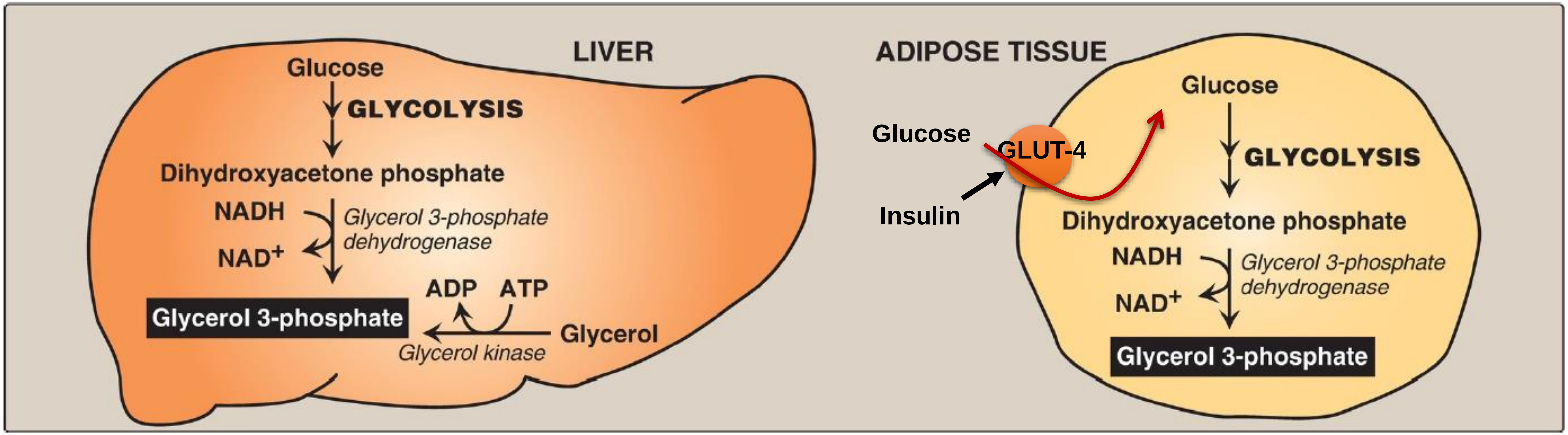
Acetyl CoA carboxylase (important for fatty acid synthesis) is inhibited by the same signaling pathway of glucagon or epinephrine





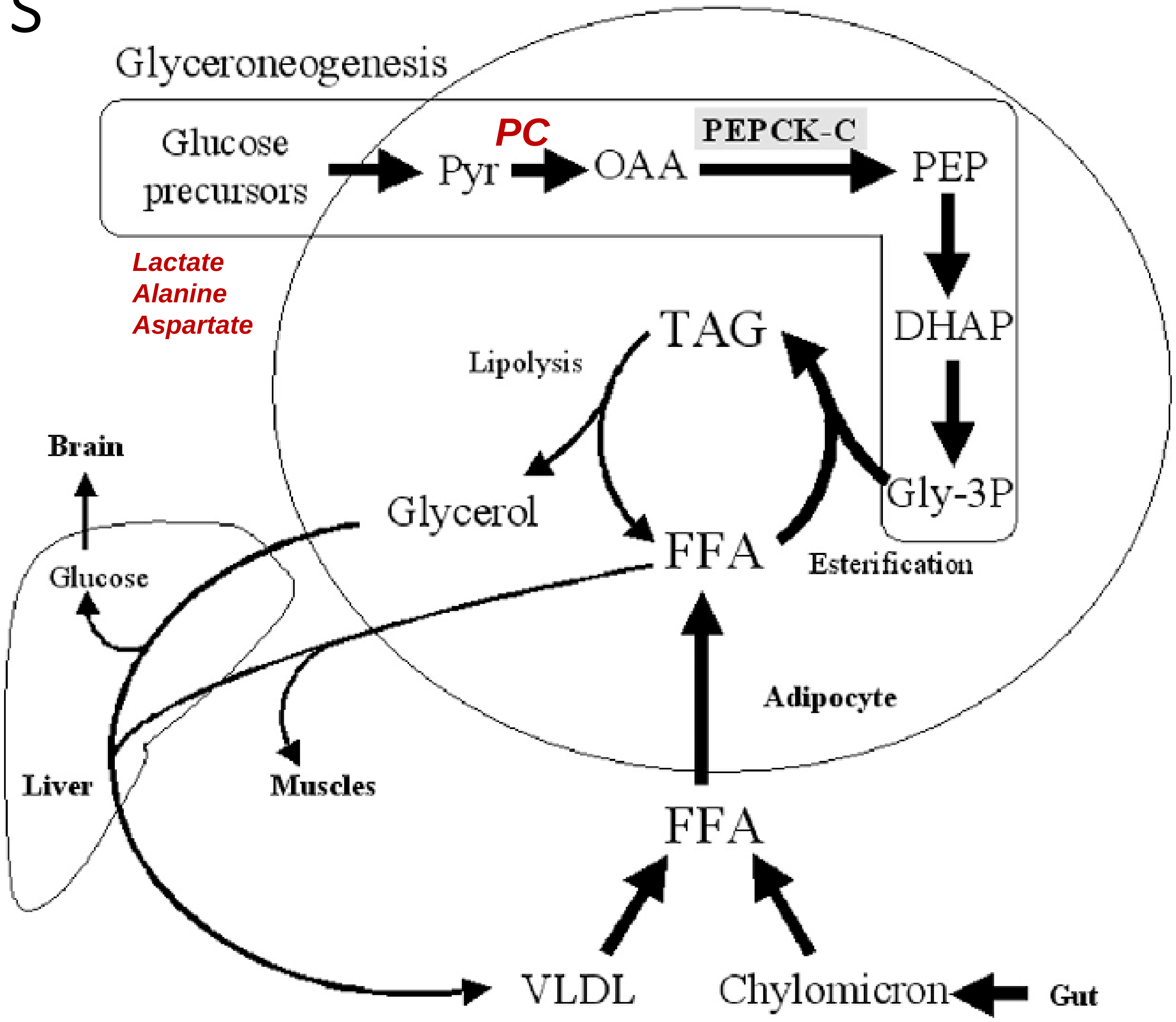
Perilipin (in red) coats fat droplets blocking HSL. It is phosphorylated by PKA releasing it.

Glycerol in liver and adipose tissues



Glyceroneogenesis

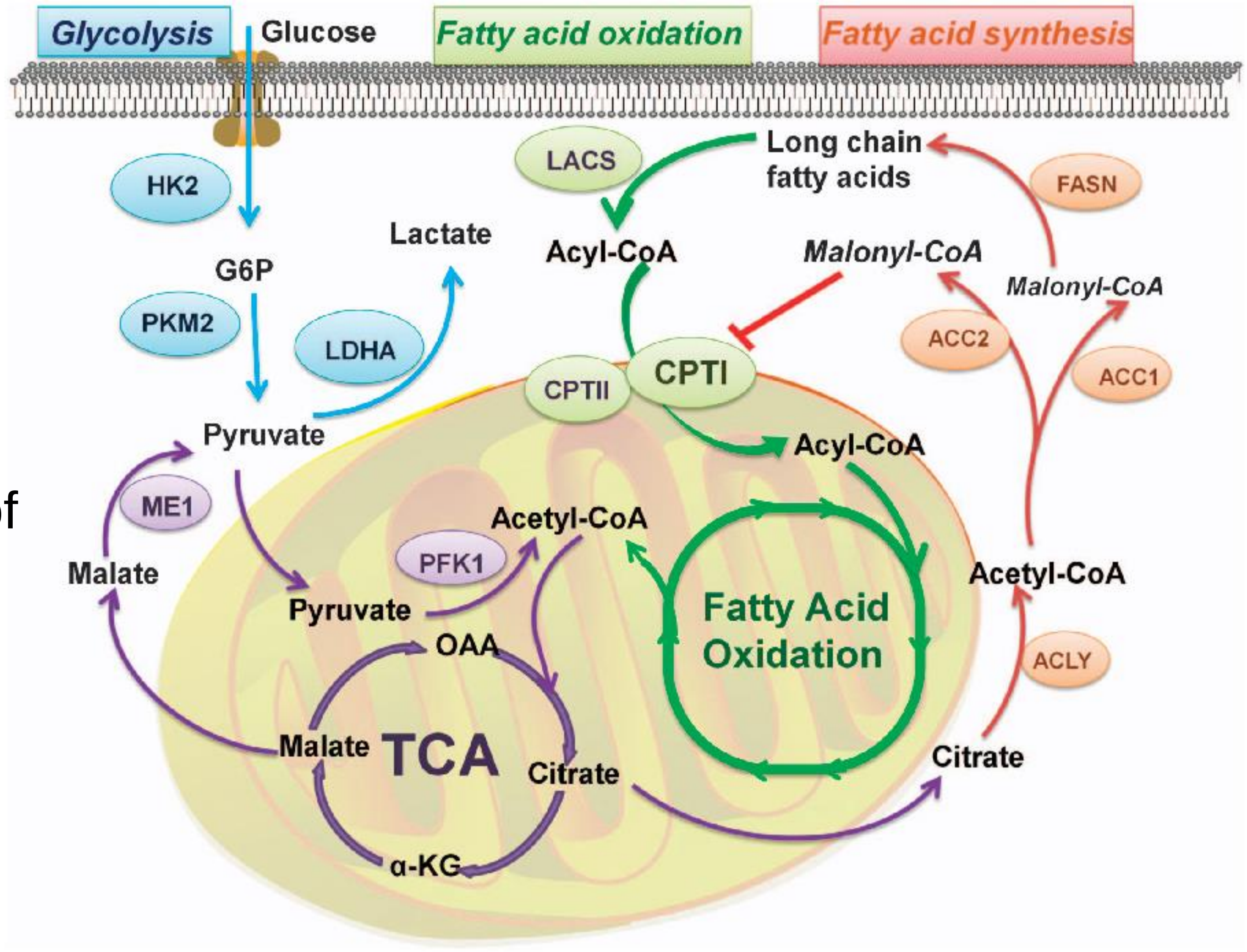
- **Purpose: regulating the levels of FAs in blood.**
- **In liver and adipose tissue**
- **Glycerol leaves the adipocytes into the liver.**
- **Failure in regulating glyceroneogenesis may lead to Type 2 diabetes due to excess fatty acids and glucose in the blood**



PC: Pyruvate carboxylase
PEPCK:* phosphoenolpyruvate *carboxykinase

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)

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

$$\downarrow$$

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

$$\downarrow$$

$$\downarrow$$

$$\downarrow$$

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

$$\downarrow$$

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

Activation of Fatty Acids

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

Thiokinase
(Acyl CoA Synthetase)

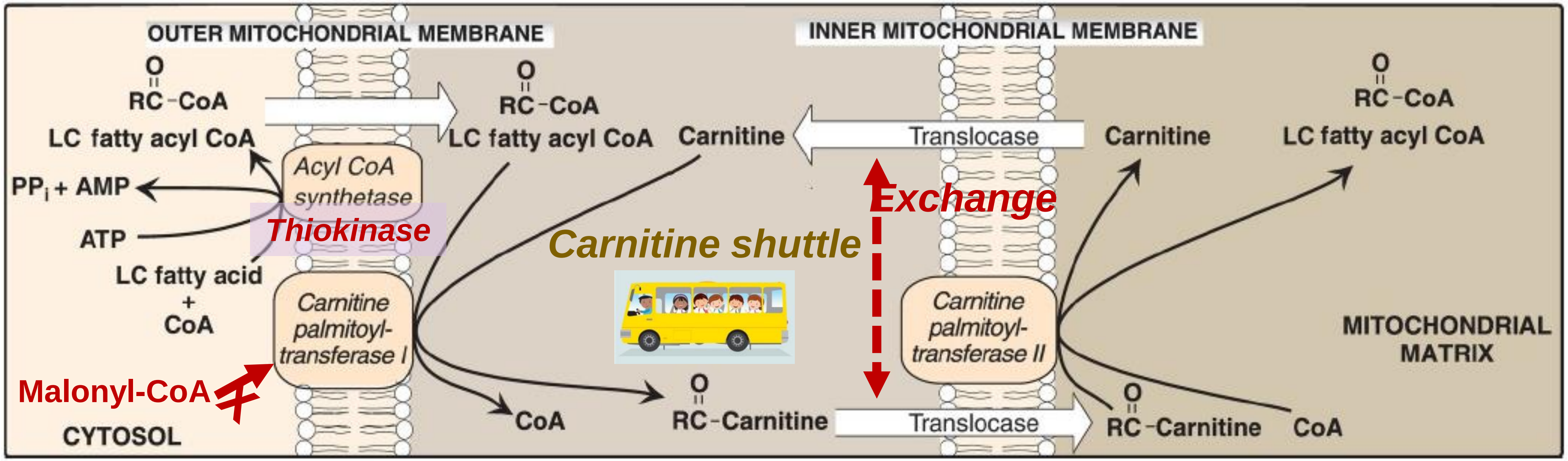
$$FA + HSCoA + ATP \rightleftharpoons FA{\sim}CoA + AMP + PP_i$$

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

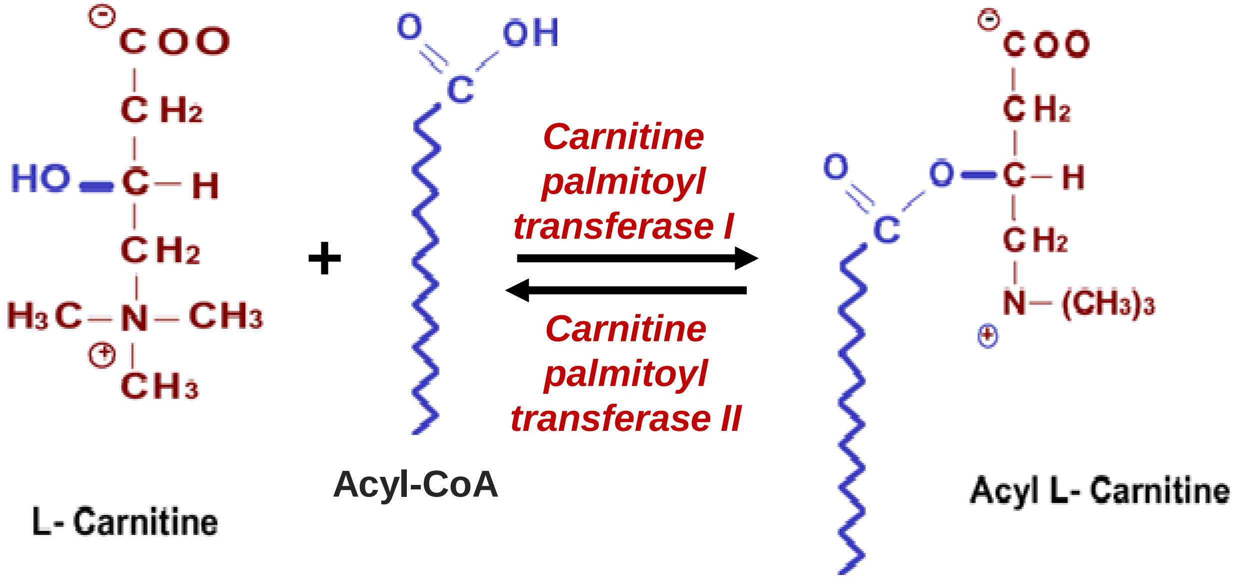
$$FA + HSCoA + ATP \longrightarrow FA{\sim}CoA + AMP + 2\,P_i$$

Location:
LCFA: outer mitochondrial membrane
Short and medium chain FA: mitochondrial matrix

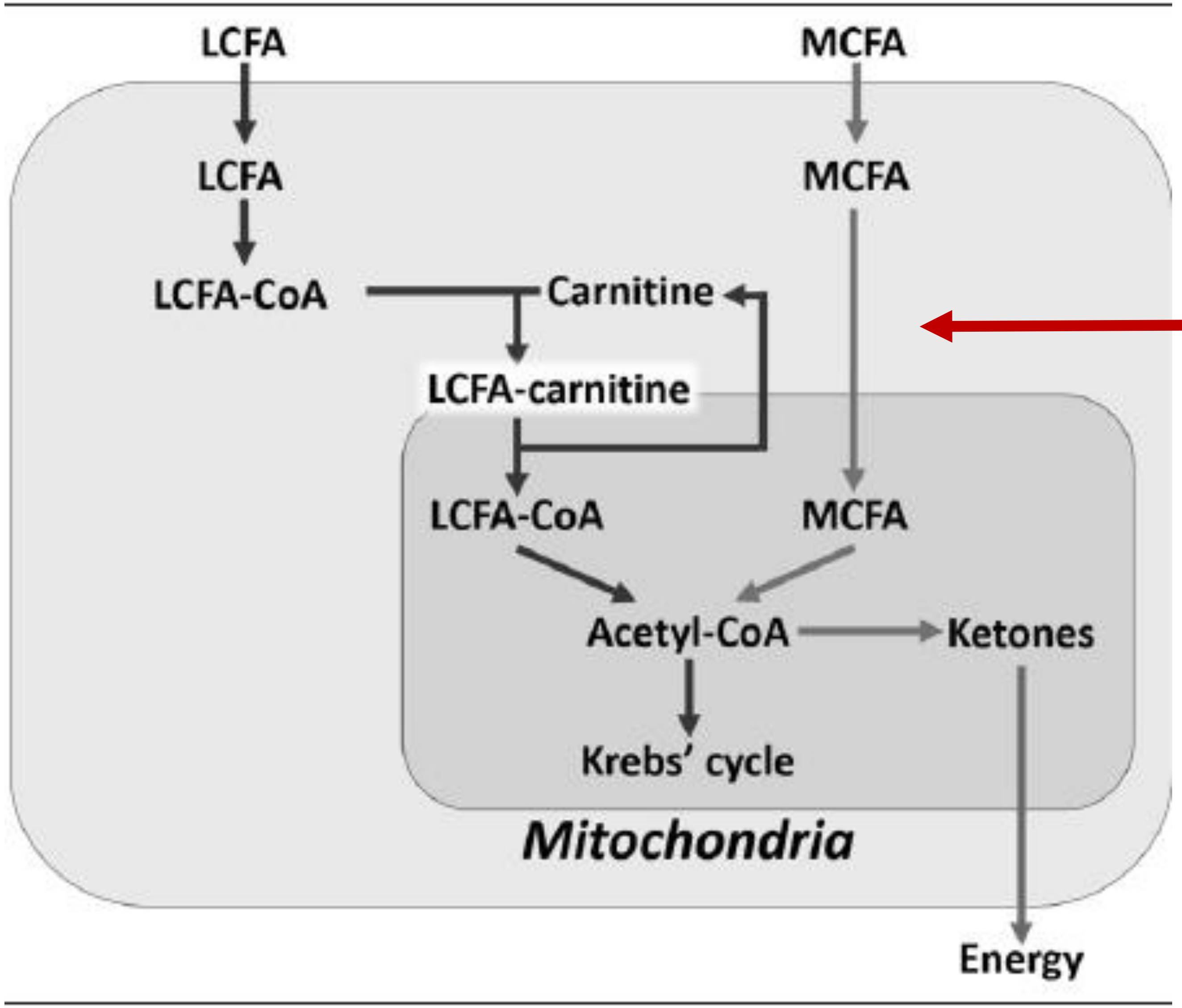
Transport of LCFA



The transport system consists of:
1. A carrier molecule (carnitine)
2. Two enzymes
3. Membrane transport protein (translocase)

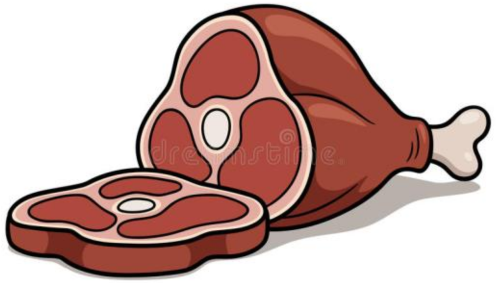


Transport of SCFAs and MCFAs

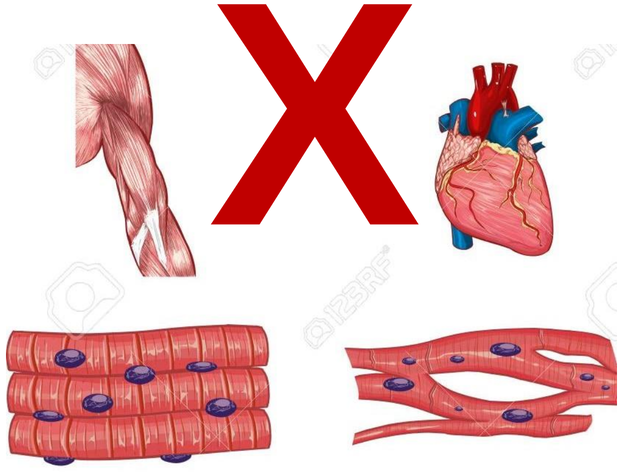


Note: No regulation of entry like that of CPTI by malonyl CoA

Application: Carnitine sources

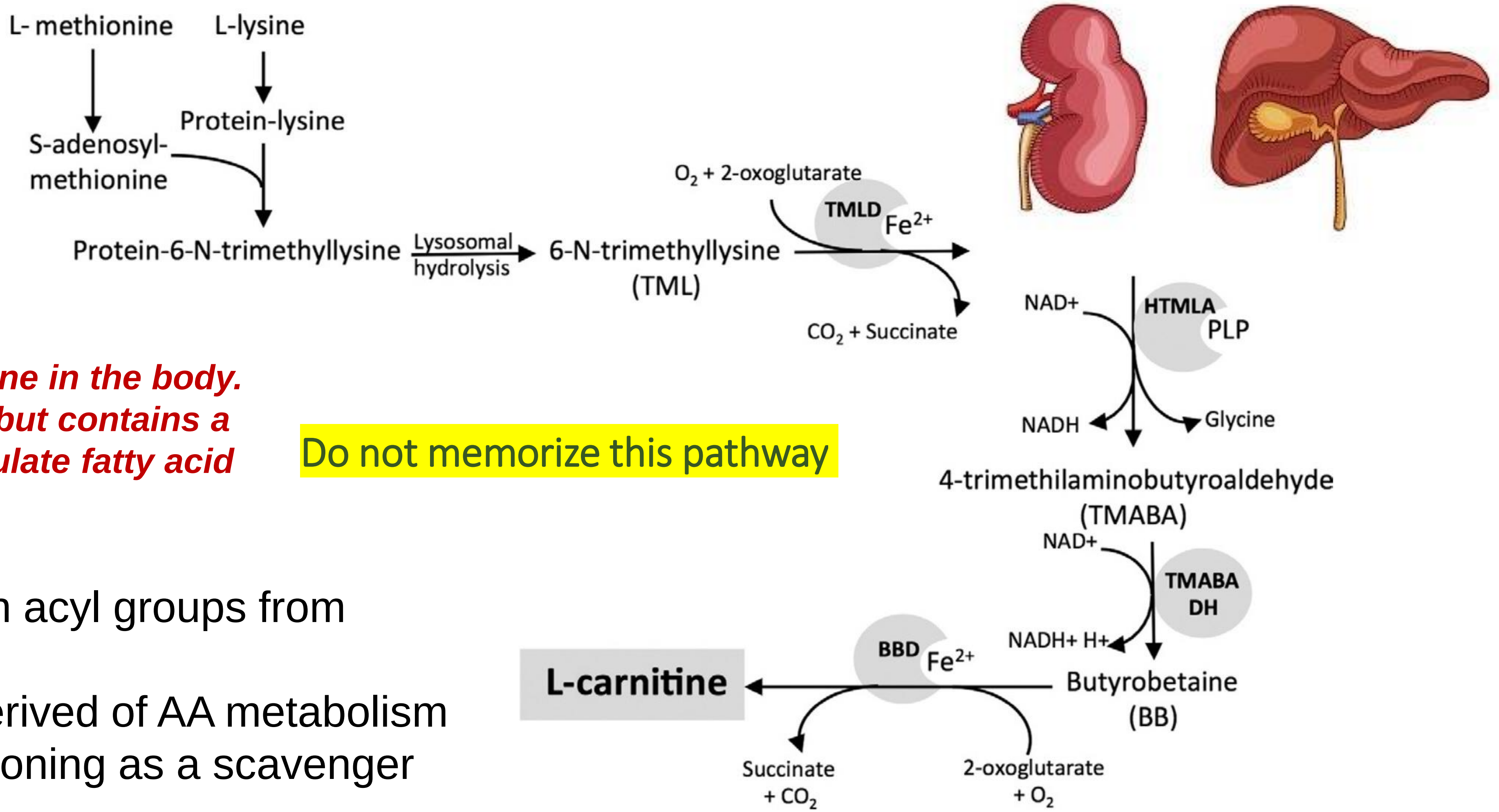


Source: meat product and synthesis from Lys and Met (liver and kidney)



Skeletal muscle Cardiac muscle

contains ~97% of all carnitine in the body. No ACC1, no FA synthesis but contains a mitochondrial ACC2 to regulate fatty acid degradation.



Do not memorize this pathway

Other functions:

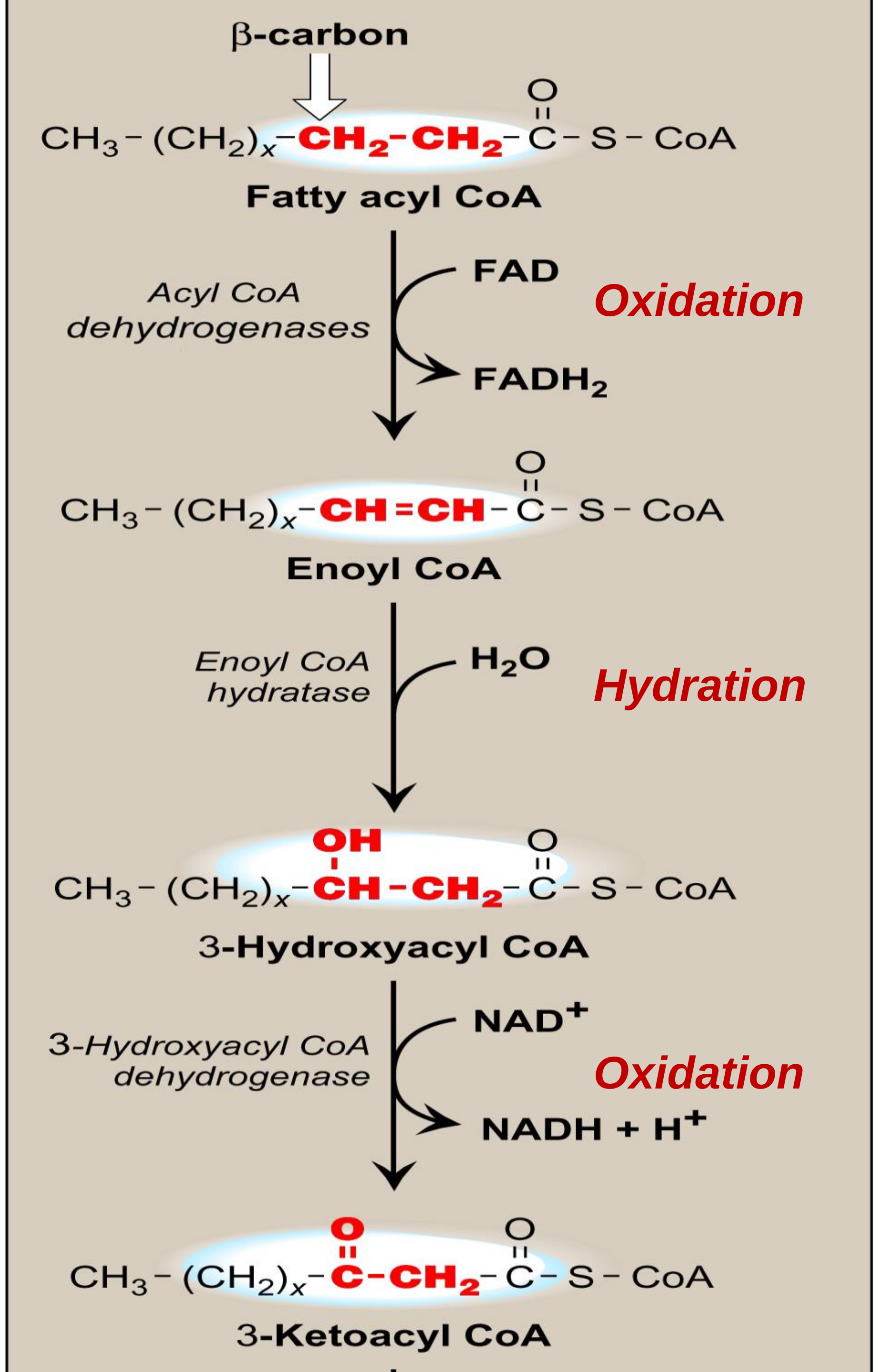
- Export of branched chain acyl groups from mitochondria

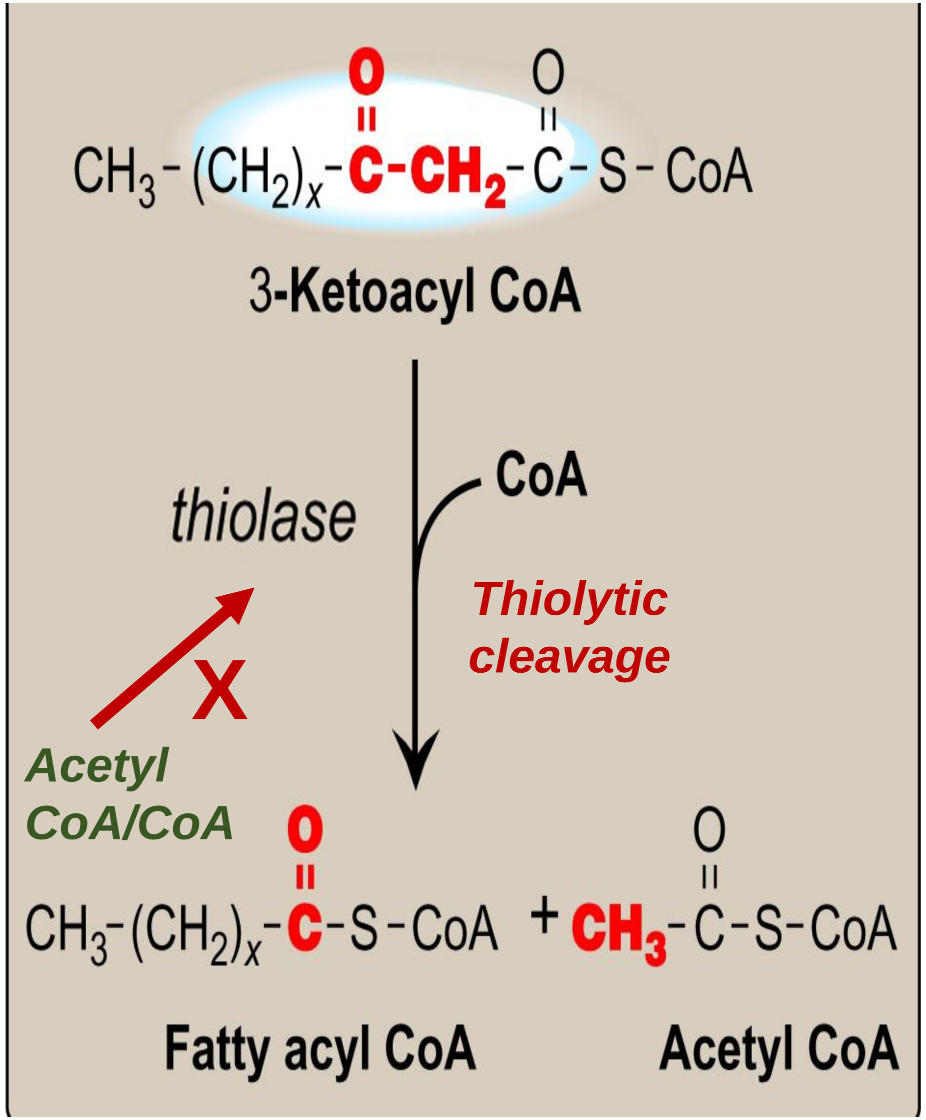
-Binding to acyl groups derived of AA metabolism and their execration functioning as a scavenger

Application: Carnitine deficiencies

- Primary carnitine deficiency
  - Defects in a membrane transporter: No uptake of carnitine by cardiac and skeletal muscles and the kidneys, causing carnitine to be excreted.
    - Treatment: carnitine supplementation.
- Secondary carnitine deficiency
  - Taking valproic acid (antiseizure) $\rightarrow$ decreased renal reabsorption
  - Defective fatty acid oxidation $\rightarrow$ acyl-carnitines accumulate $\rightarrow$ urine
  - Liver diseases $\rightarrow$ decreased carnitine synthesis
  - CPT-I deficiency: affects liver; no use of LCFA, no energy for glucose synthesis during fasting $\rightarrow$ severe hypoglycemia, coma, and death
  - CPT-II deficiency: affects liver, cardiac muscle, and skeletal muscle
    - Treatment: avoidance of fasting and adopting a diet high in carbohydrates and low in fat but supplemented with medium-chain TAG.

β-Oxidation of fatty acids





Number of cycles: (n/2)-1

Energy Yield from FA Oxidation

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

6 Acetyl CoA

6 $FADH_2$

6 NADH

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

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

- ✓ Oxidation of C 16 FATTY ACID

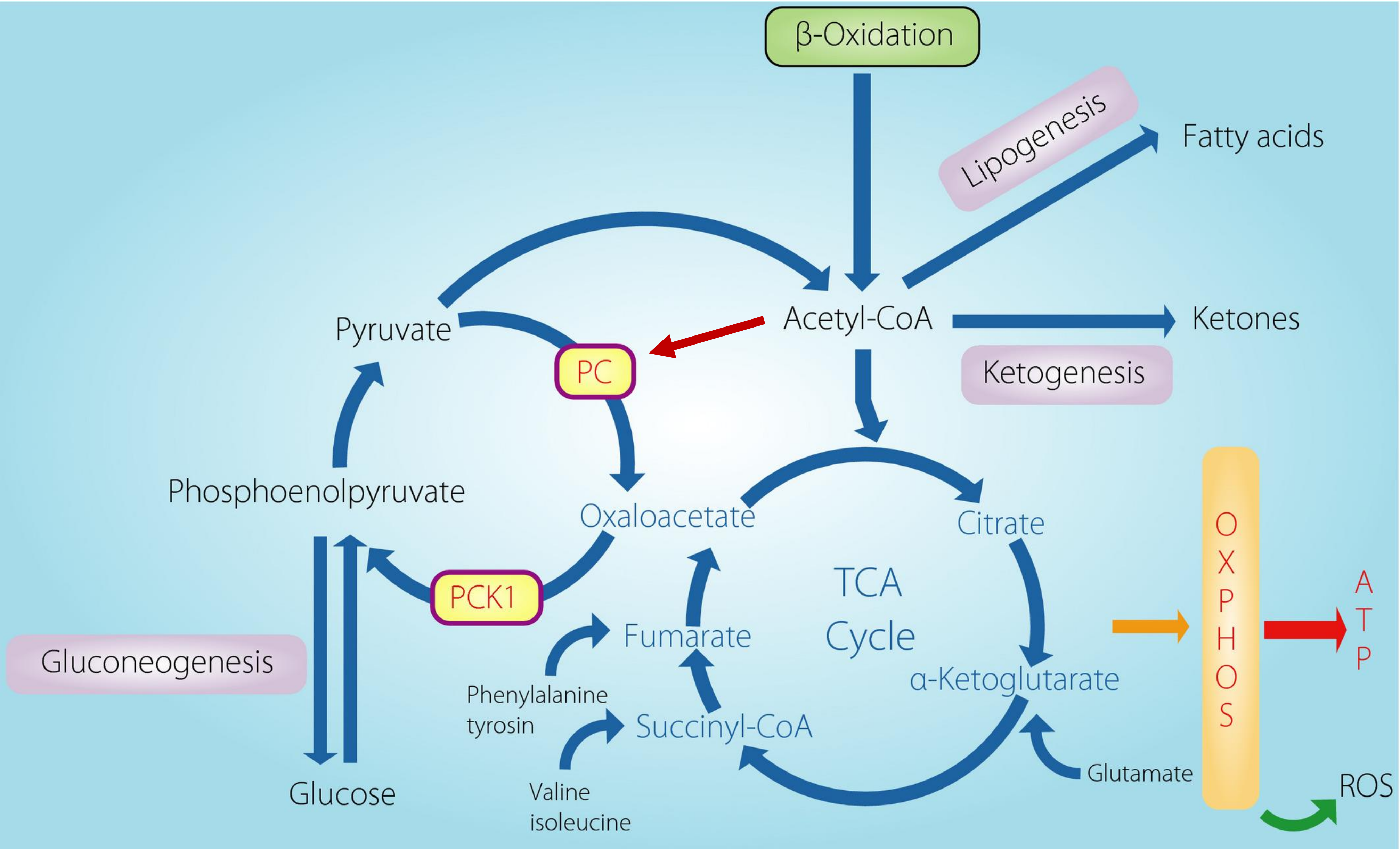
  7 $FADH_2$ → 14 ATP

  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

Induction of gluconeogenesis and fates of acetyl CoA

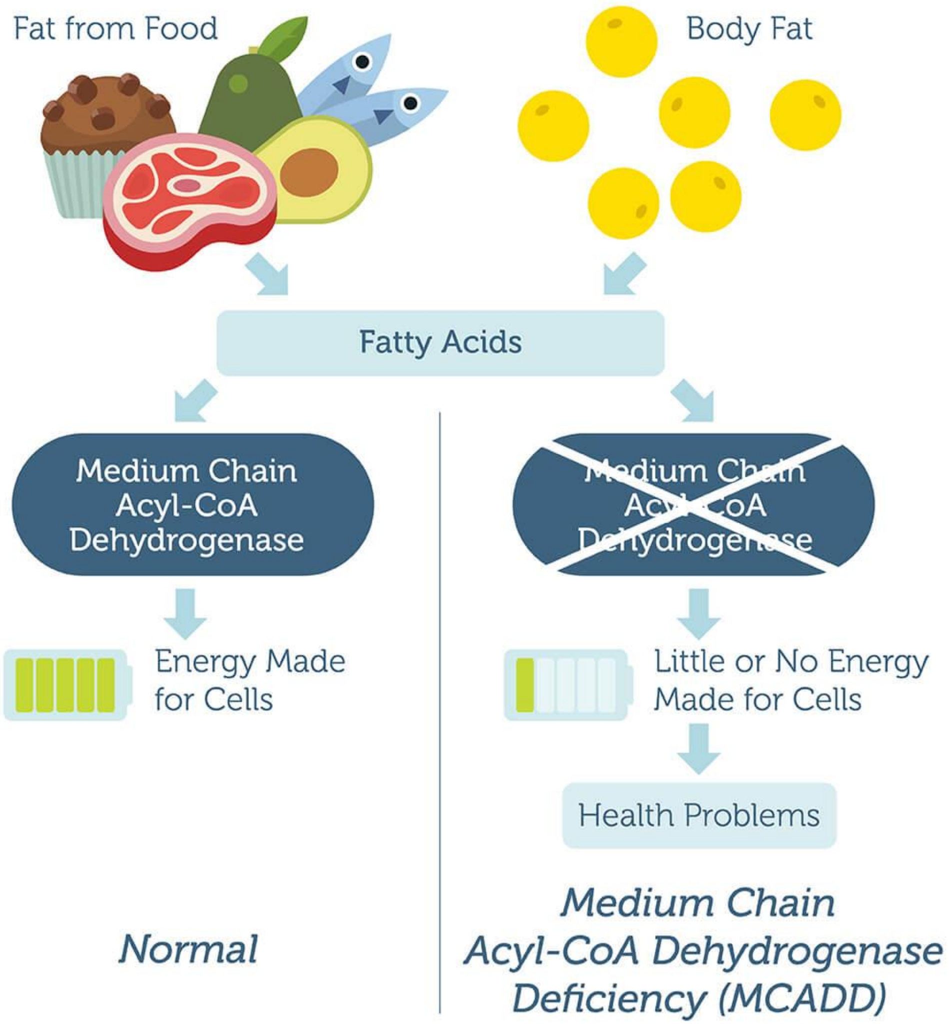


Application: MCAD deficiency

- There are 4 isozymes of fatty acyl CoA dehydrogenase for SCFA, MCFA, LCFA, and VLCFA.
- Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency,
    - An autosomal-recessive disorder
    - Most common inborn error of β-oxidation (1:14,000 births worldwide)
    - Higher incidence among Caucasians of Northern European descent
    - Decreased ability to oxidize MCFAs (lack of energy)
    - Severe hypoglycemia and hypoketonemia
    - Treatment: avoidance of fasting

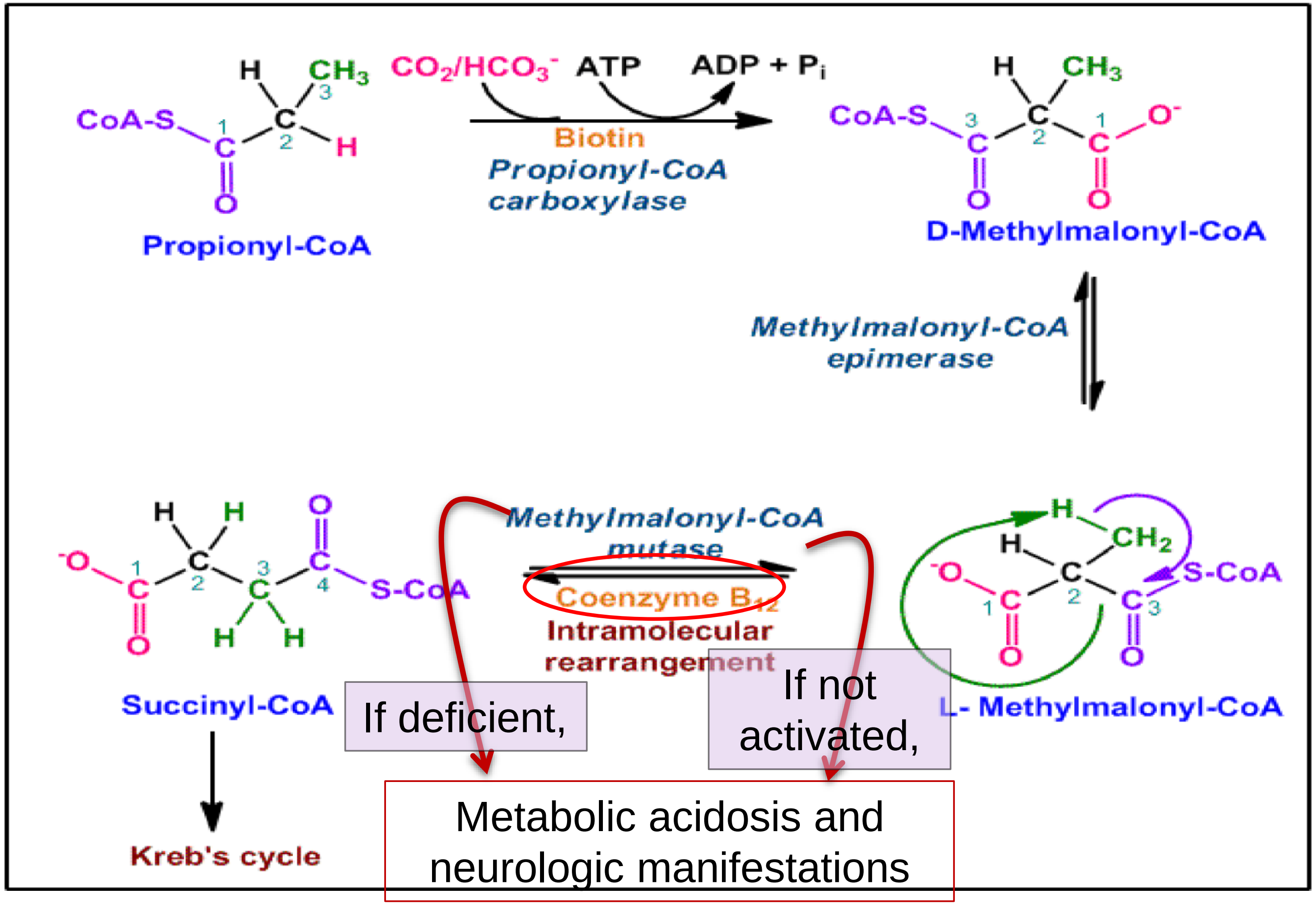
        Regular and frequent meals and snacks

        Diet high in carbohydrates and low in fat

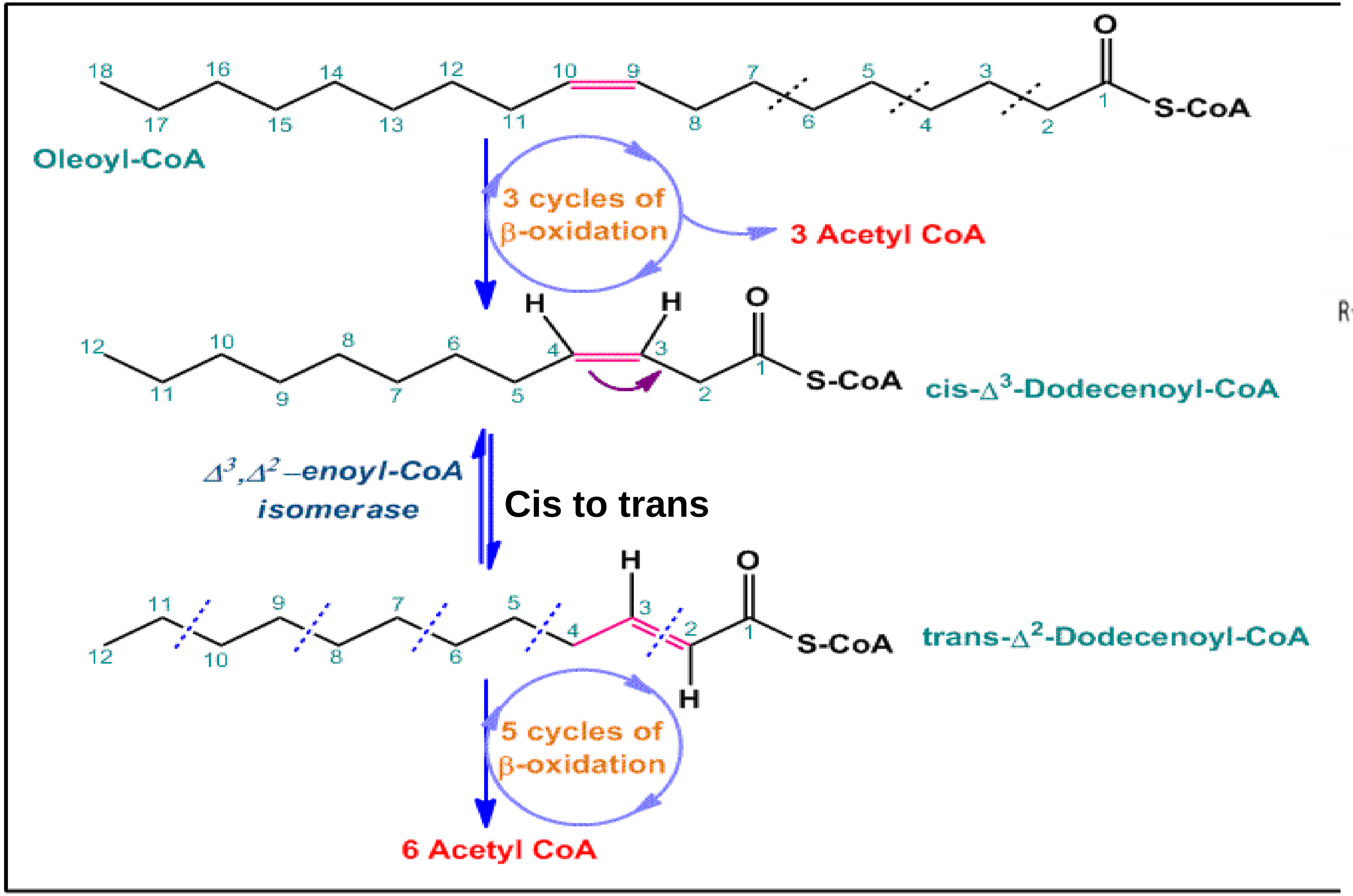


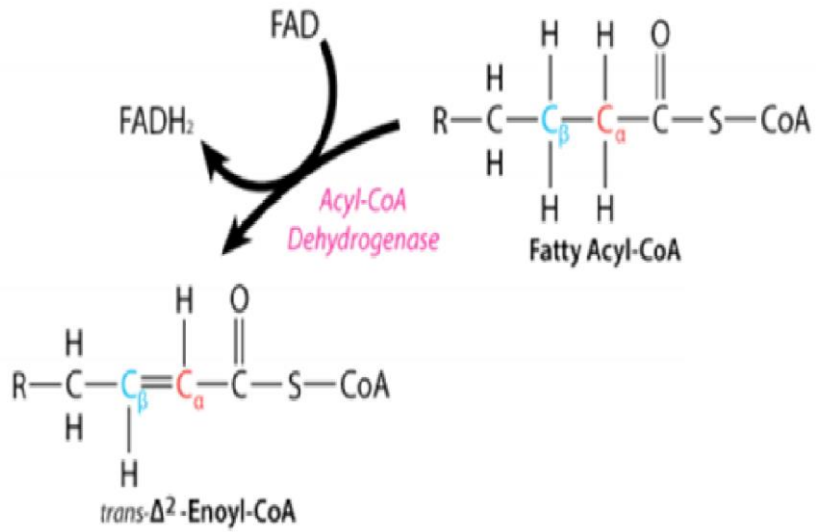
Oxidation of odd-numbered FAs

Starts as cycles of beta-oxidation producing acetyl-CoA and propionyl-CoA



Monounsaturated fatty acid β-oxidation





But this reaction is skipped resulting in one less $FADH_2$ → loss of electrons

Polyunsaturated FA will also need an *NADPH-dependent 2,4-dienoyl CoA reductase* in addition to the *isomerase.*
→ loss of electrons

Peroxisomal β-oxidation

VLCFA ≥22

FAD Containing acyl CoA Oxidase

Loss of electrons

- **Zellweger syndrome: a peroxisomal biogenesis disorder**
- **X-linked adrenoleukodystrophy: dysfunctional transport VLCFA across the peroxisomal membrane**

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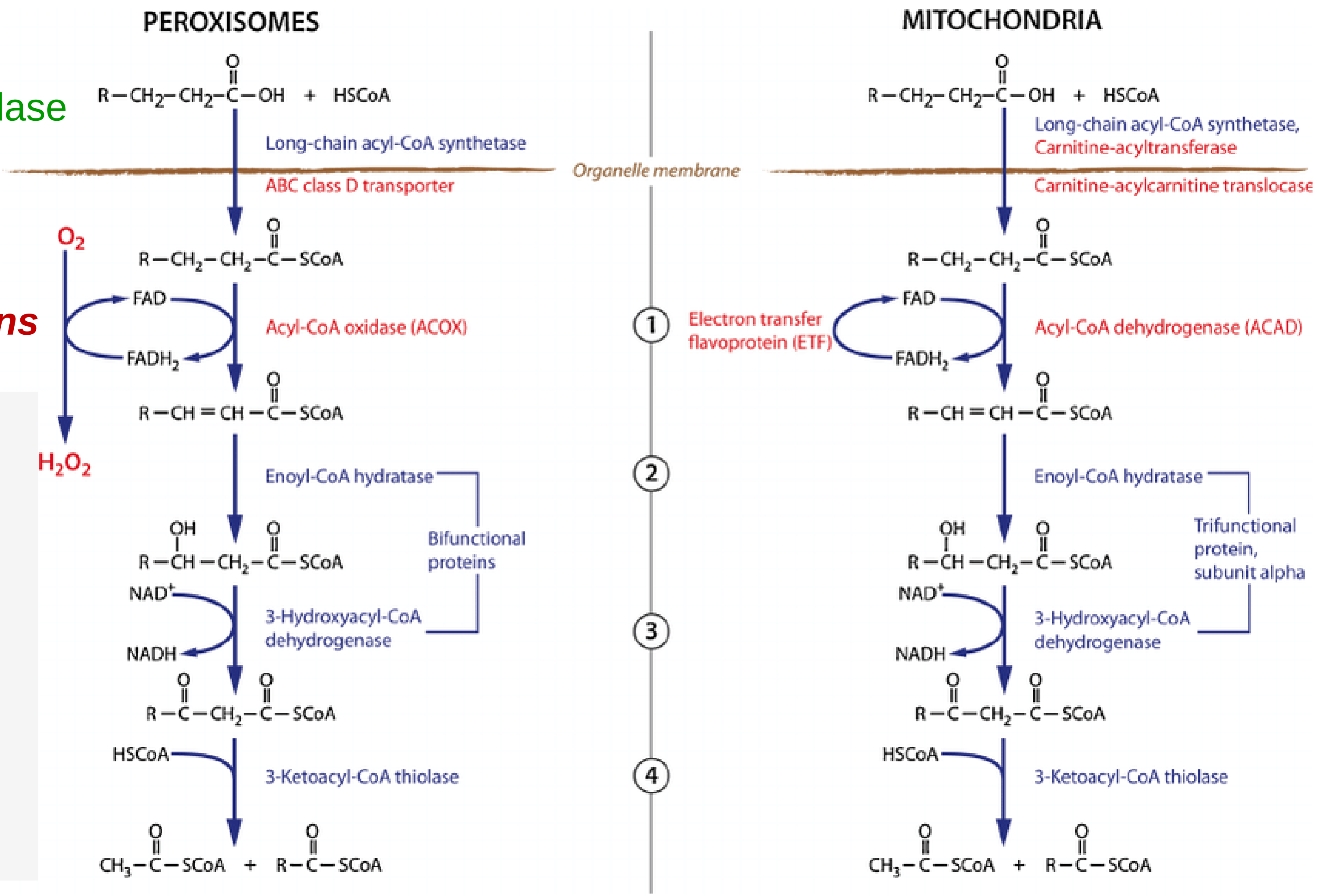
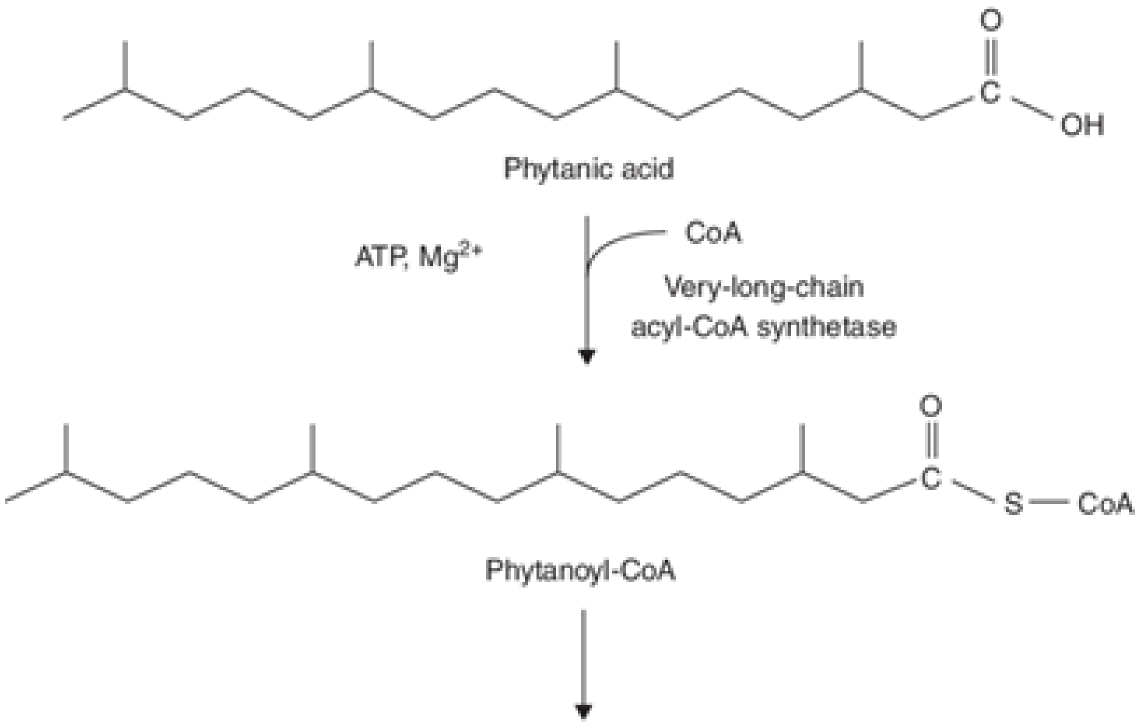
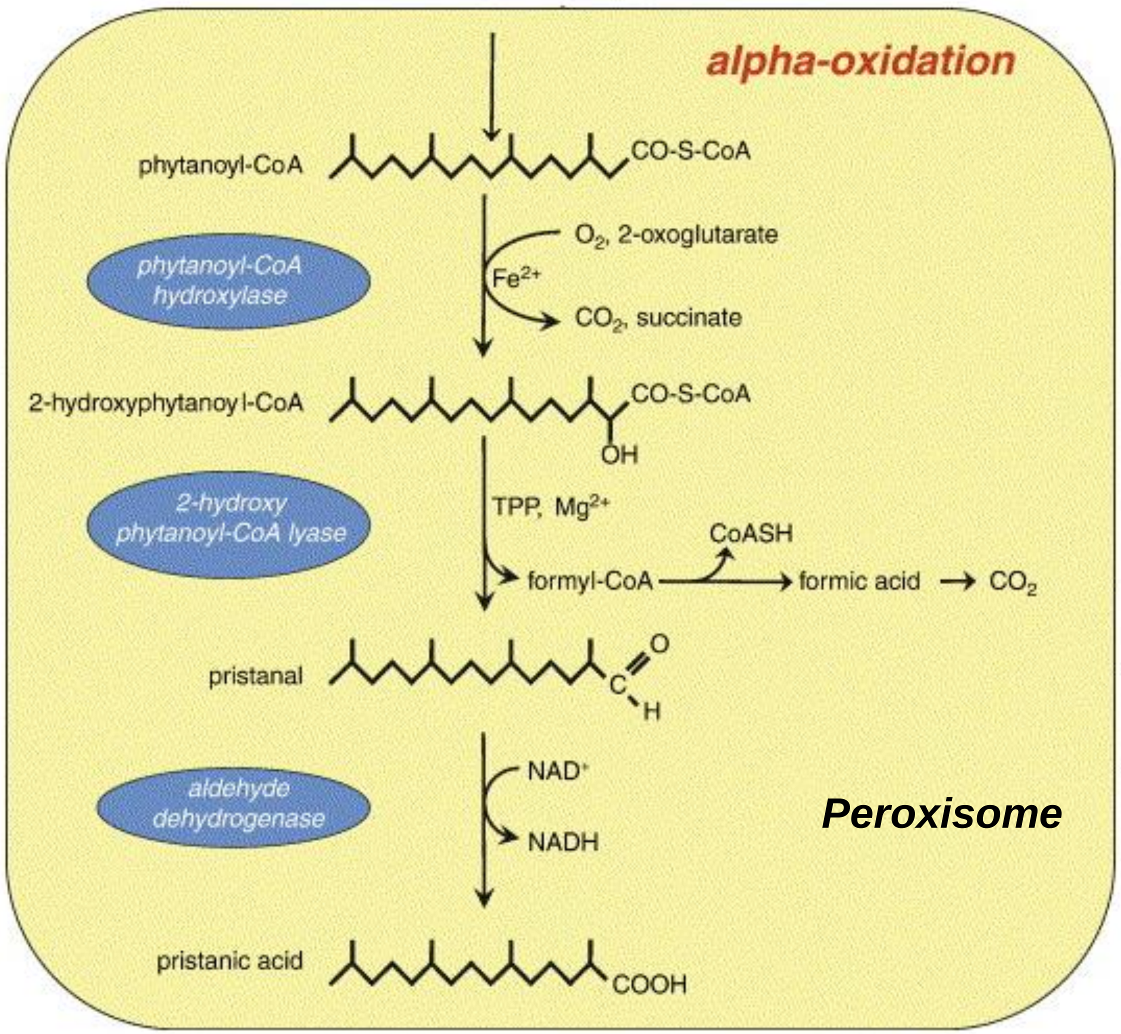
Accumulation of VLCFAs



Peroxisomal α-oxidation of branched chain FAs



Peroxisomes

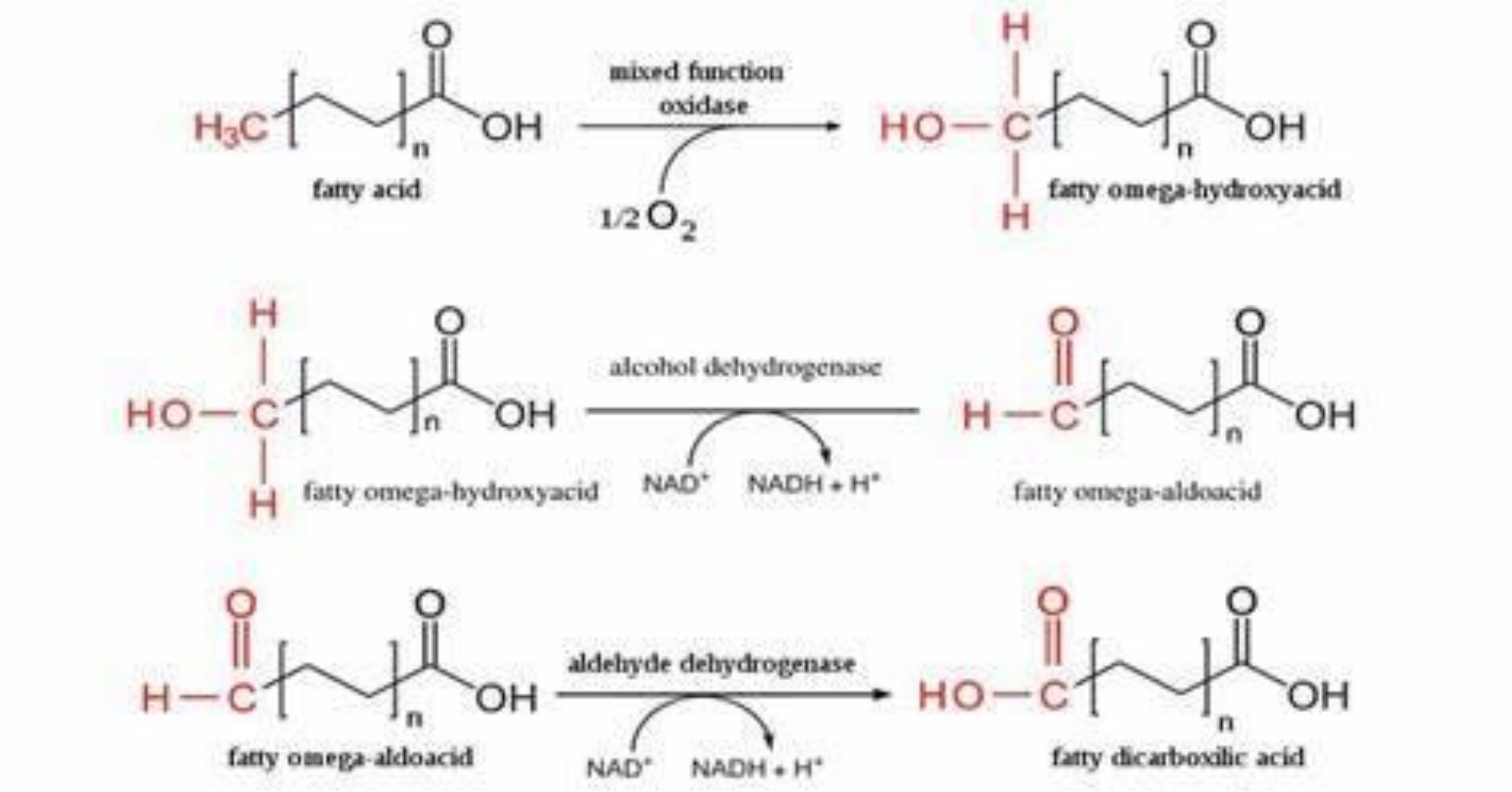


- Phytanic acid is a breakdown product of Chlorophyll.
- It is activated by CoA, transported into peroxisome, hydroxylated by phytanoyl CoA α-hydroxylase (PhyH), and carbon 1 is released as CO_2.
- When fully degraded, it generates formyl-CoA, propionyl-CoA, acetyl-CoA, and 2-methyl-propionyl-CoA.

Refsum disease is an autosomal-recessive disorder caused by a deficiency of peroxisomal PhyH.

ω-Oxidation

- ω-Oxidation is a minor pathway of the SER
- It generates dicarboxylic acids.
- It is upregulated in certain conditions such as MCAD deficiency.



Lipids and energy

- TAGs are the body's major fuel storage reserve.
- The complete oxidation of fatty acids to CO_2 and H_2O generates 9 kcal/g of fat (as compared to 4 kcal/g protein or carbohydrate). Why?

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy

Exercise and sources of energy

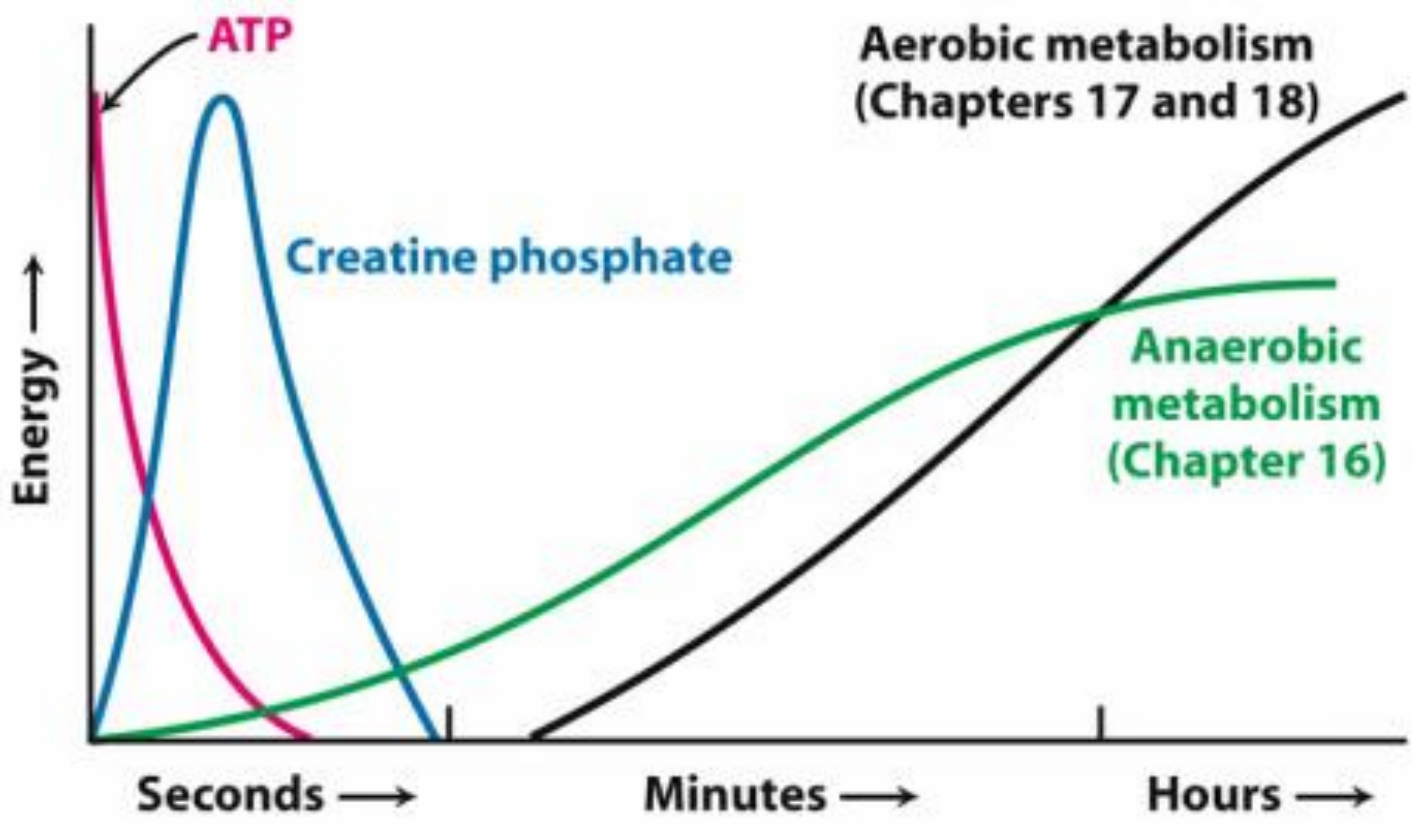


Figure 15.7
Biochemistry, Seventh Edition