Metabolism of lipids III:

Degradation of fatty acids

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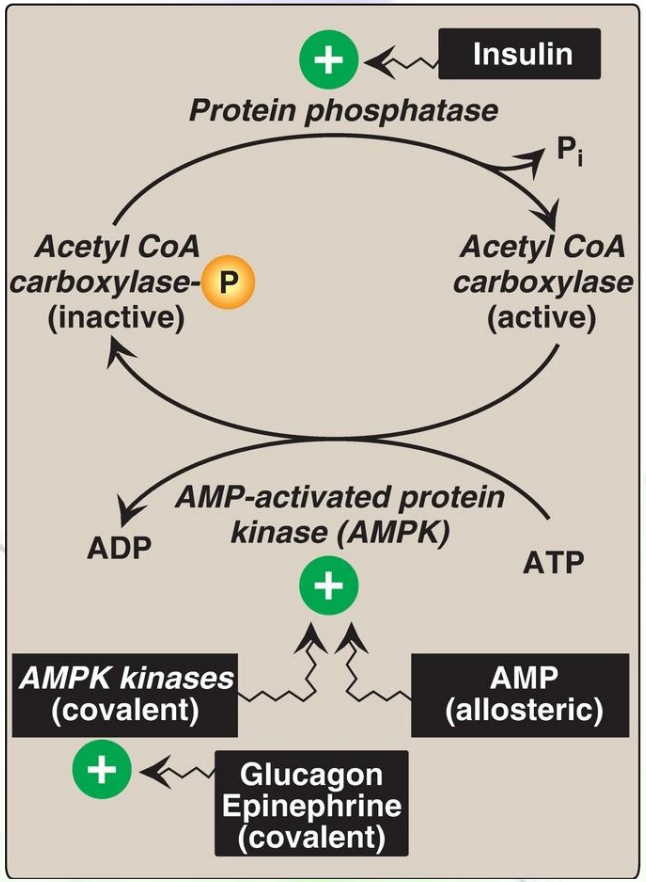
Resources

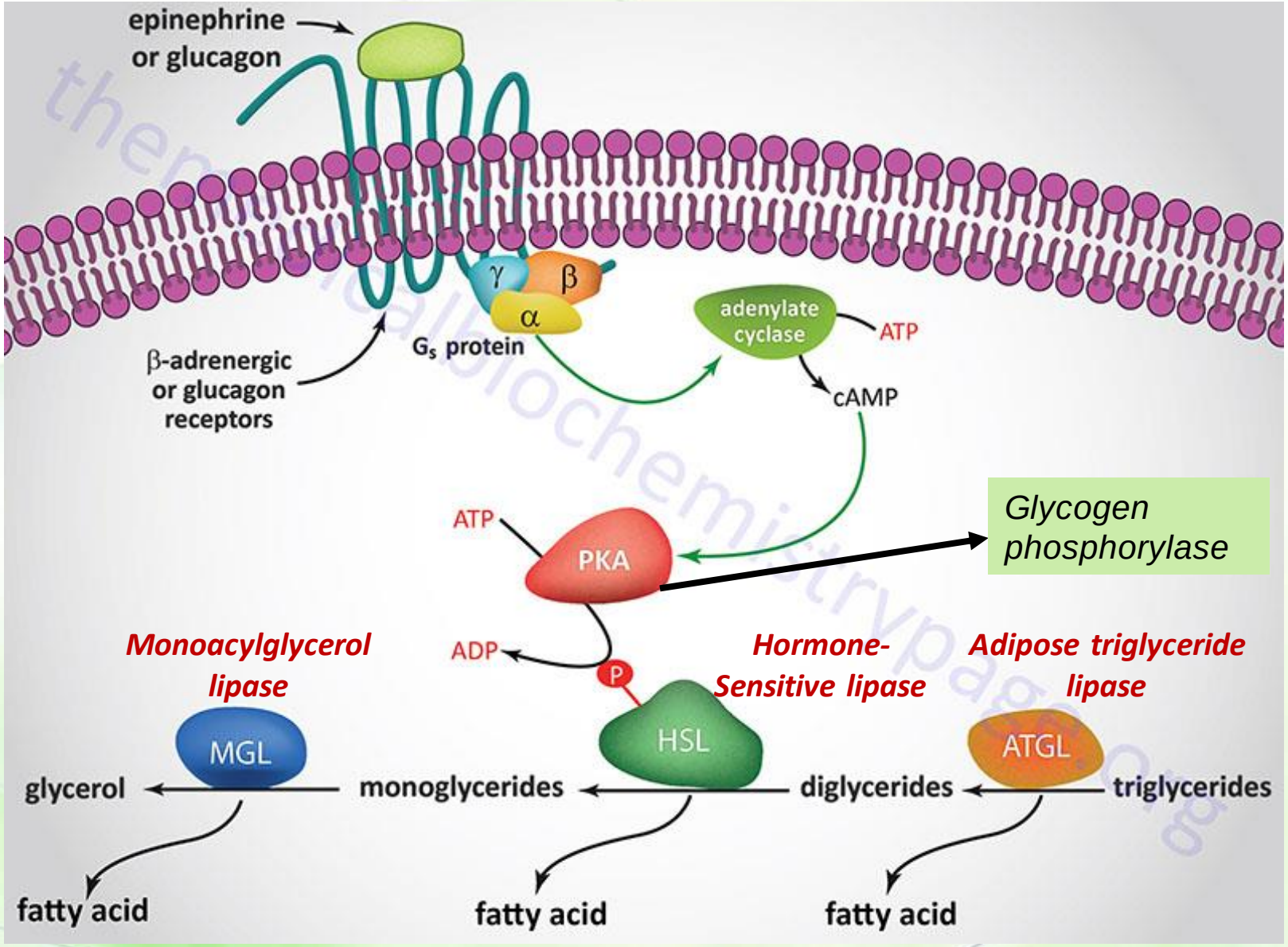
- This lecture
- Lippincott's Biochemistry, Ch. 16

Release of fatty acids from TAG

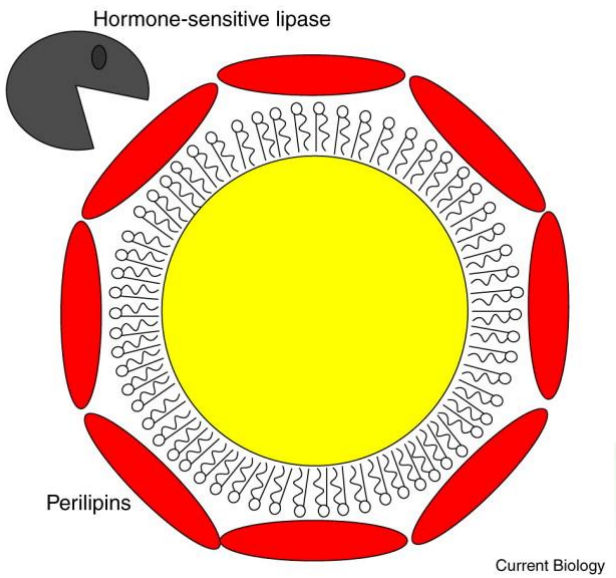
Hormonal regulation



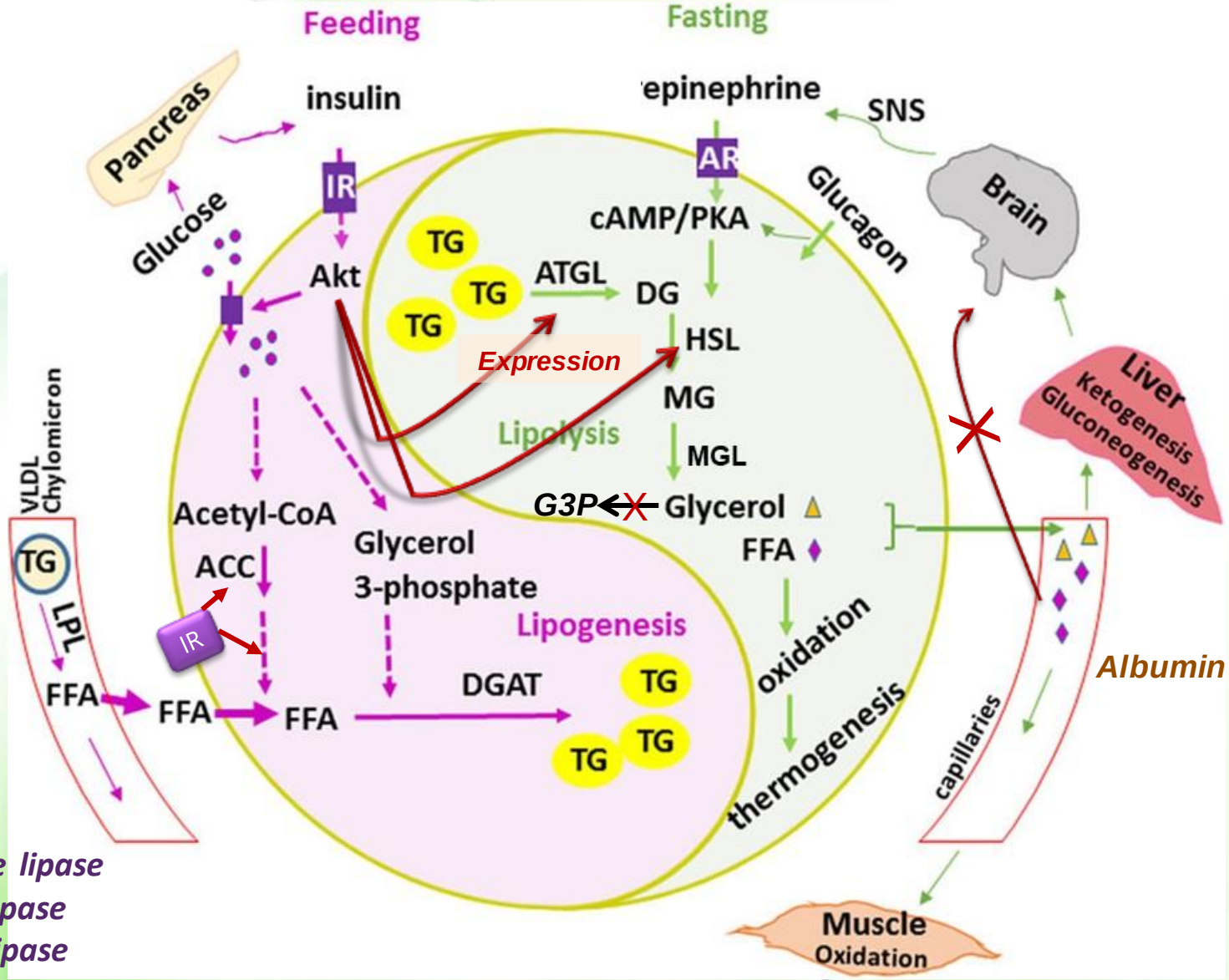
Note: Acetyl CoA carboxylase (ACC) is inhibited by the same signaling pathway



Perilipin



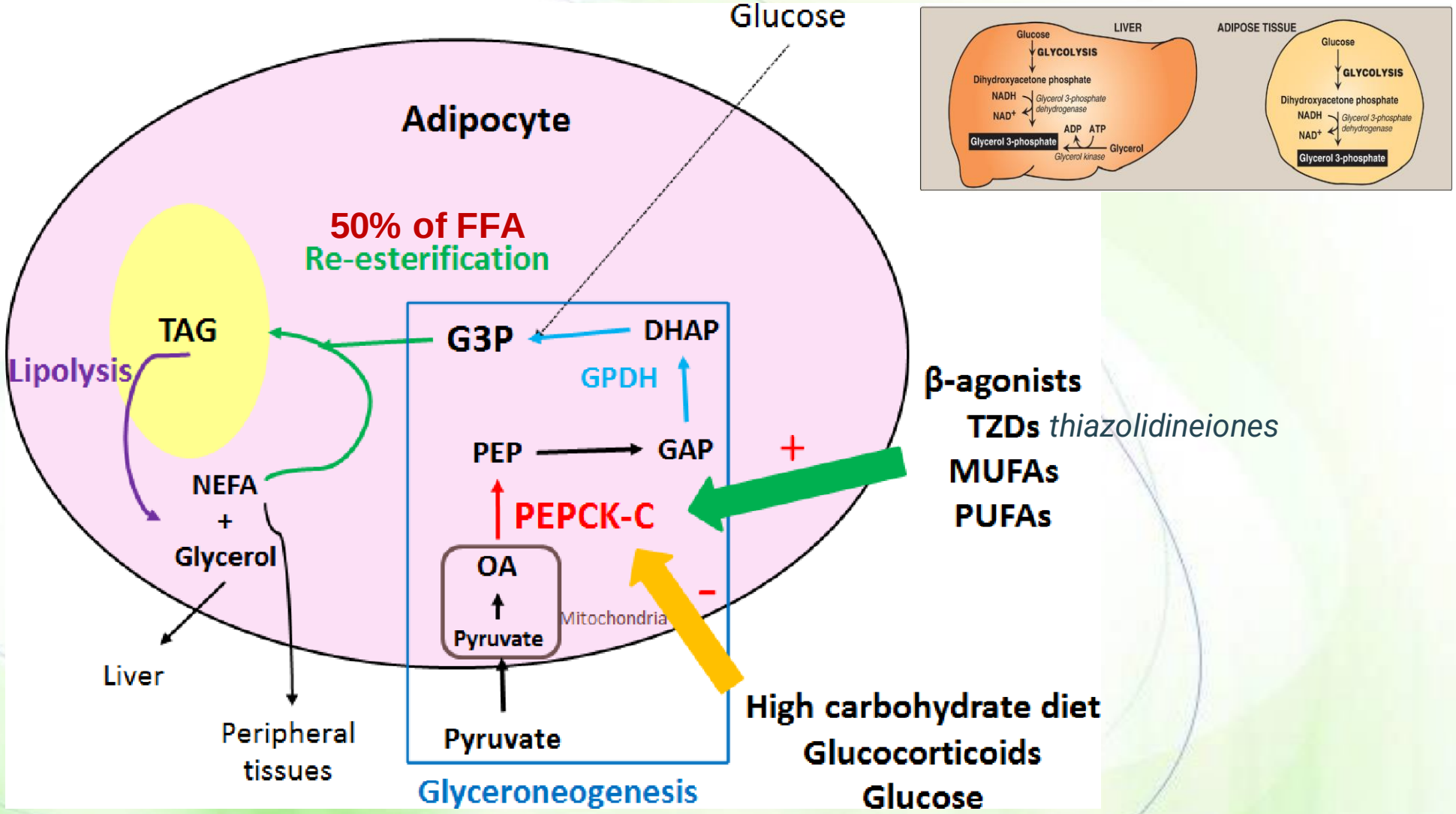
Perilipin (in red) coats fat droplets blocking HSL. It is phosphorylated by PKA releasing it.



ATGL: Adipose triglyceride lipase
HSL: Hormone-sensitive lipase
MGL: Monoacylglycerol lipase

Glyceroneogenesis

Glycerol leaves adipocytes to liver

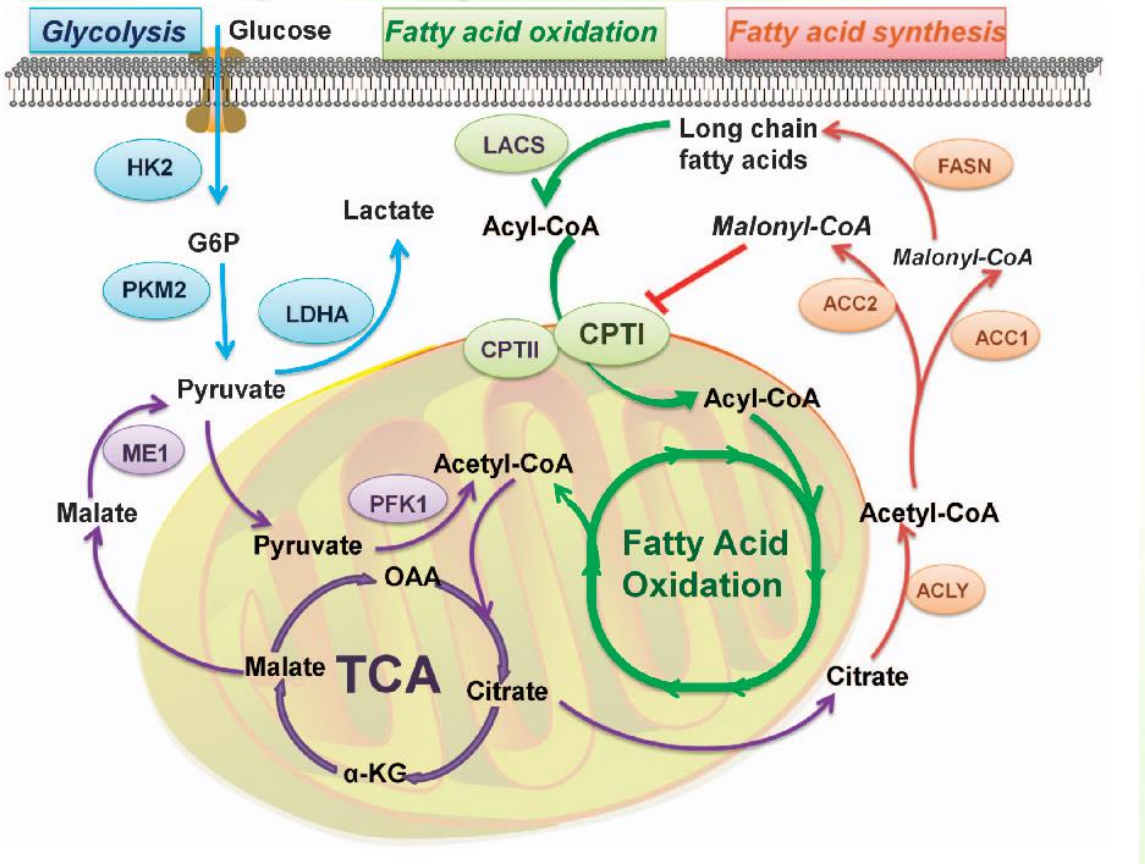


PC: Pyruvate carboxylase

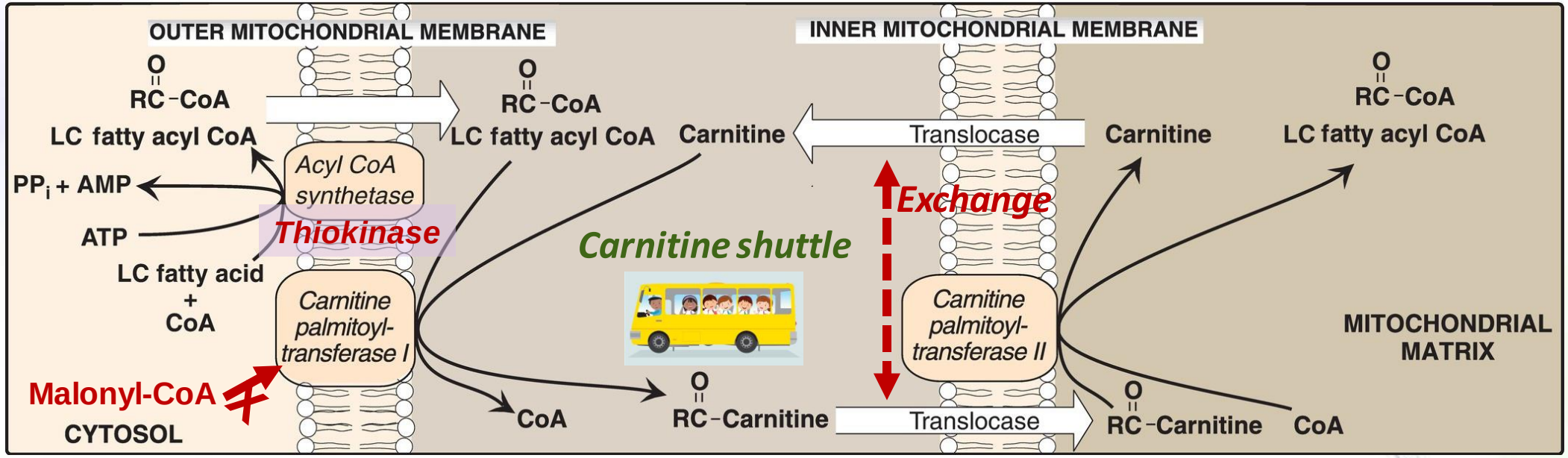
PEPCK:

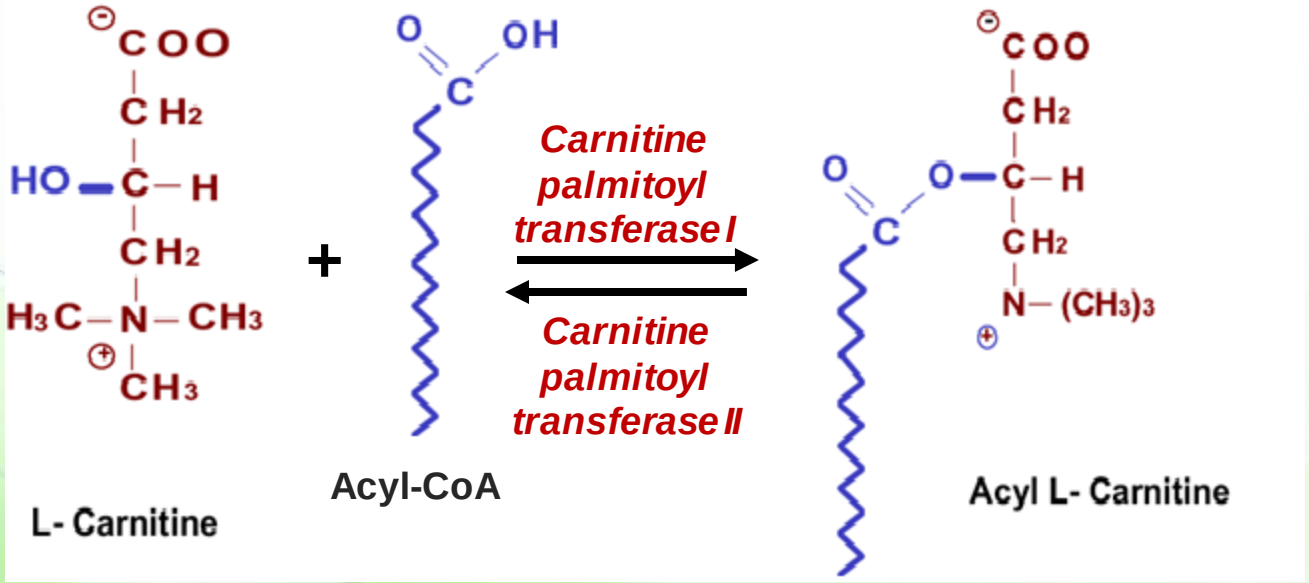
phosphoenolpyruvate *carboxykinase*

Fatty acid β-oxidation

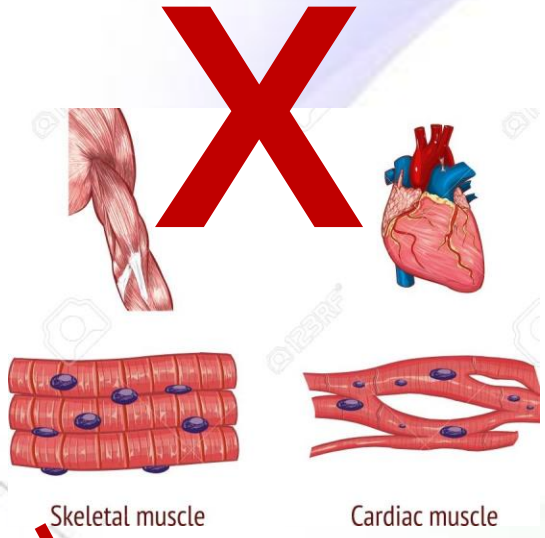


LCFA is mitochondrial



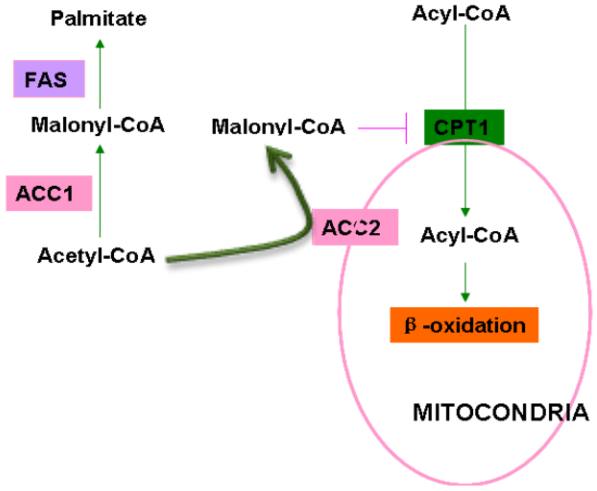


More on carnitine…sources



contains ~97% of all carnitine in the body.

No ACC1, no FA synthesis but contains a mitochondrial ACC2 that is inhibited by acetyl CoA.

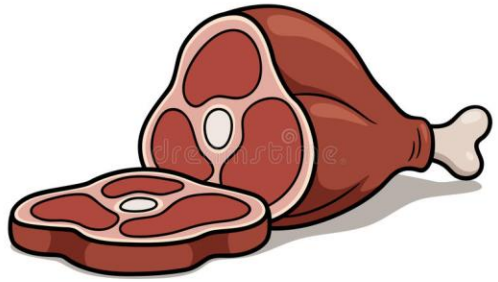


L- methionine — L-lysine

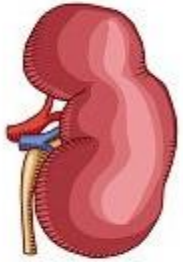
S-adenosyl-methionine — Protein-lysine

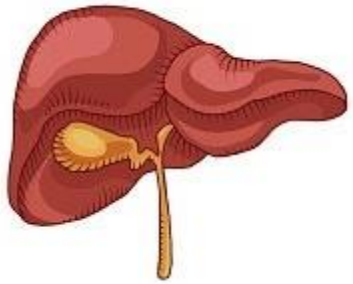
Protein-6-N-trimethyllysine —(Lysosomal hydrolysis)→ 6-N-trimethyllysine (TML)

Do not memorize the pathway



O_2 + 2-oxoglutarate — TMLD, Fe^{2+} → CO_2 + Succinate





NAD+ — HTMLA, PLP → NADH + Glycine

4-trimethilaminobutyroaldehyde (TMABA)

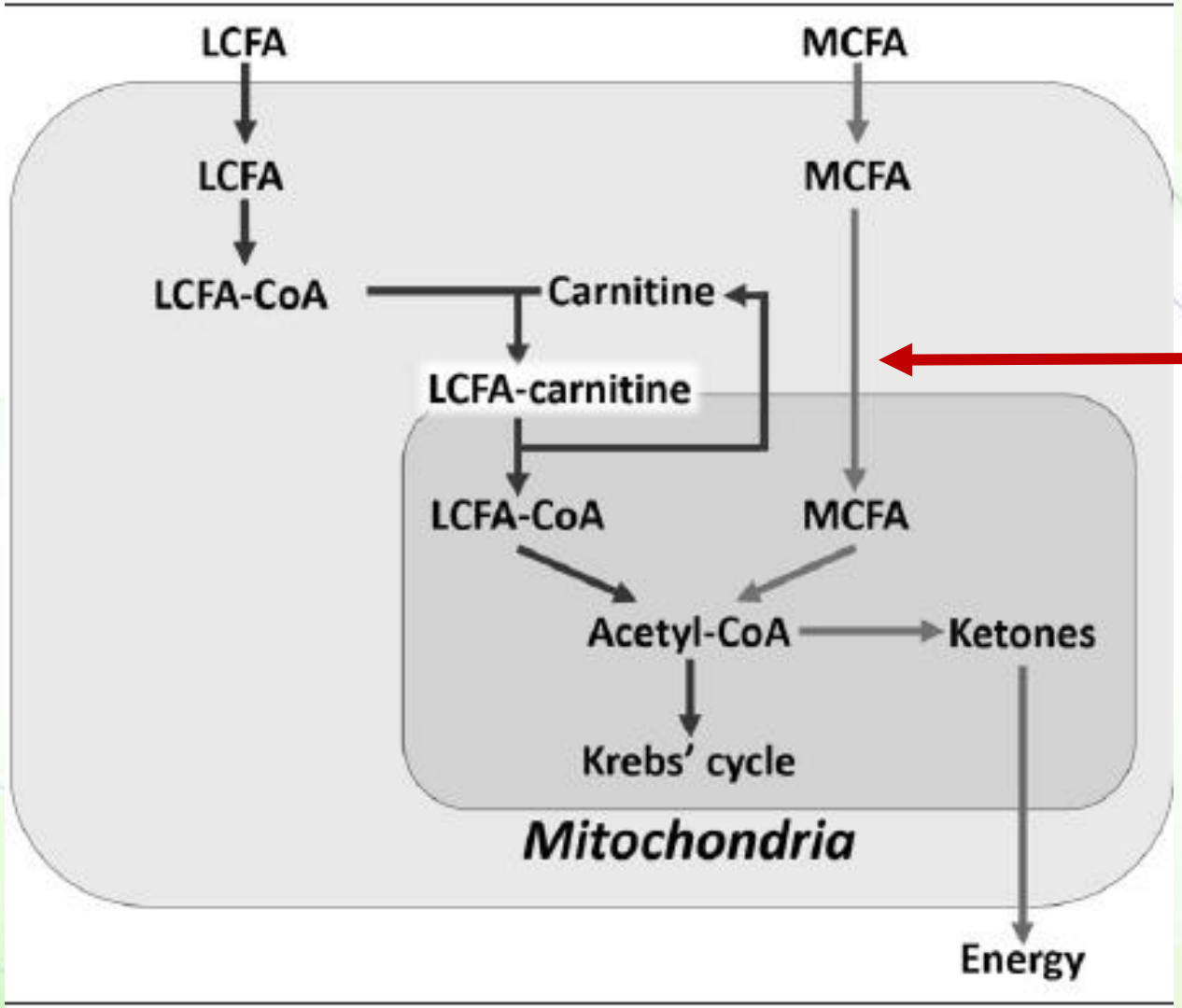
NAD+ — TMABA DH → NADH+ H+

Butyrobetaine (BB) — BBD, Fe^{2+} → L-carnitine + Succinate + CO_2 + 2-oxoglutarate + O_2

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) → decreased renal reabsorption
  - Defective fatty acid oxidation → acyl-carnitines accumulate → urine
  - Liver diseases → decreased carnitine synthesis
  - CPT-I deficiency: affects the liver; no use of LCFA, no energy for glucose synthesis during fasting → severe hypoglycemia, coma, and death
  - CPT-II deficiency: affects the 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.

SCFAs and MCFAs

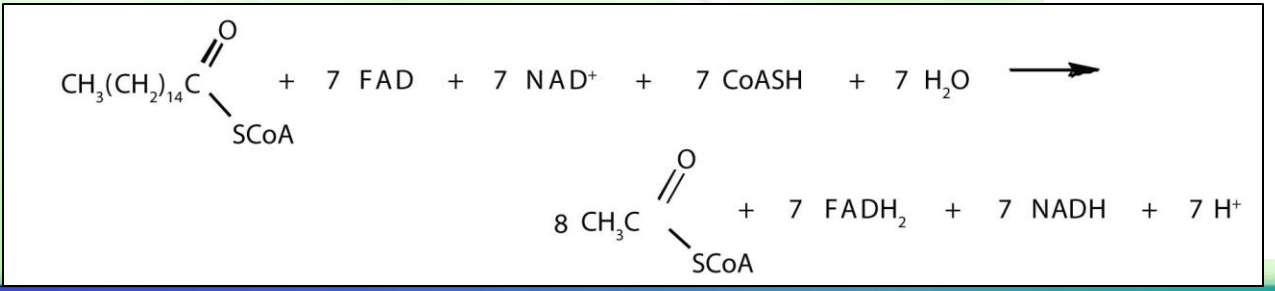


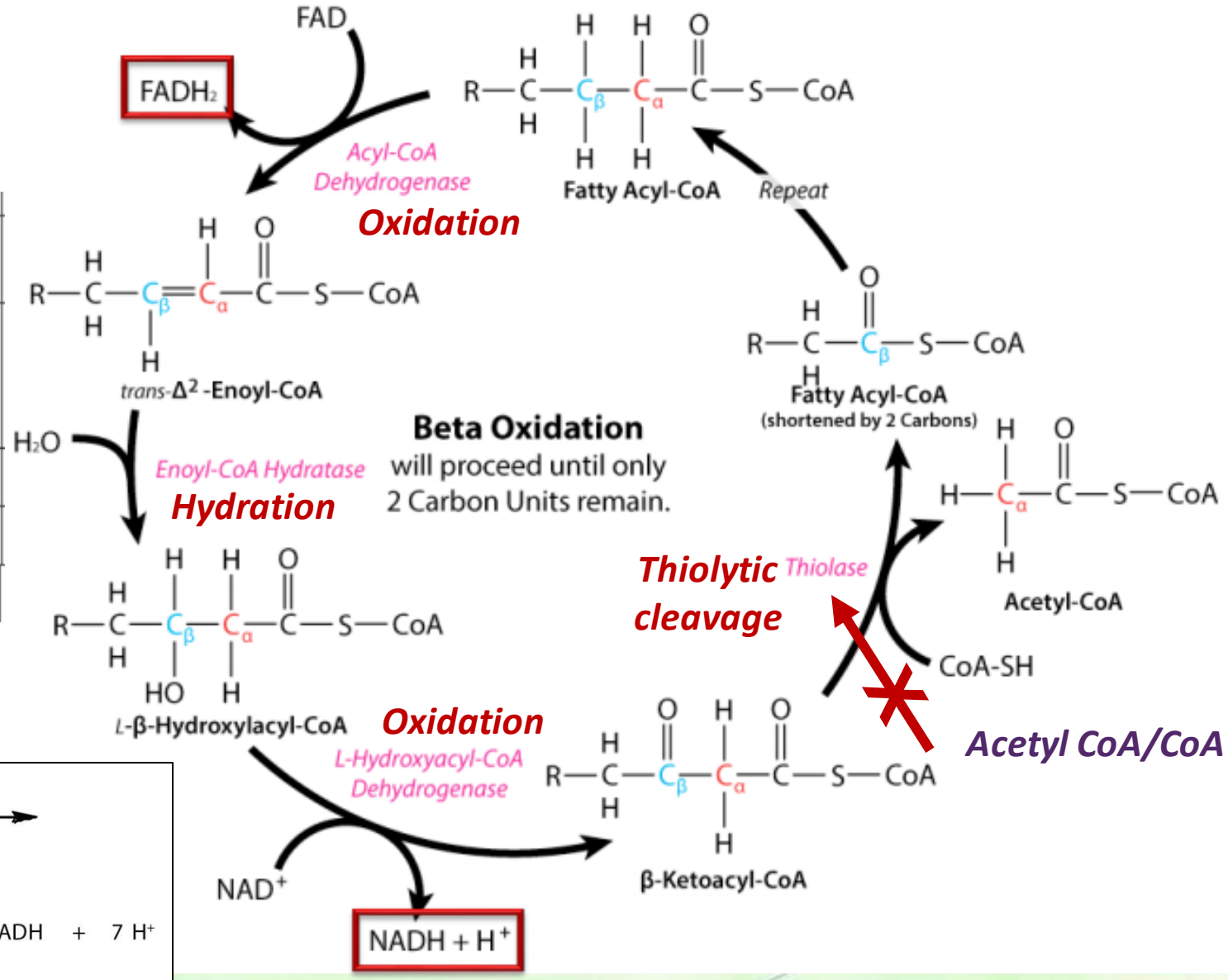
Note: No regulation of entry like that of CPTI by malonyl CoA

β-Oxidation of fatty acids

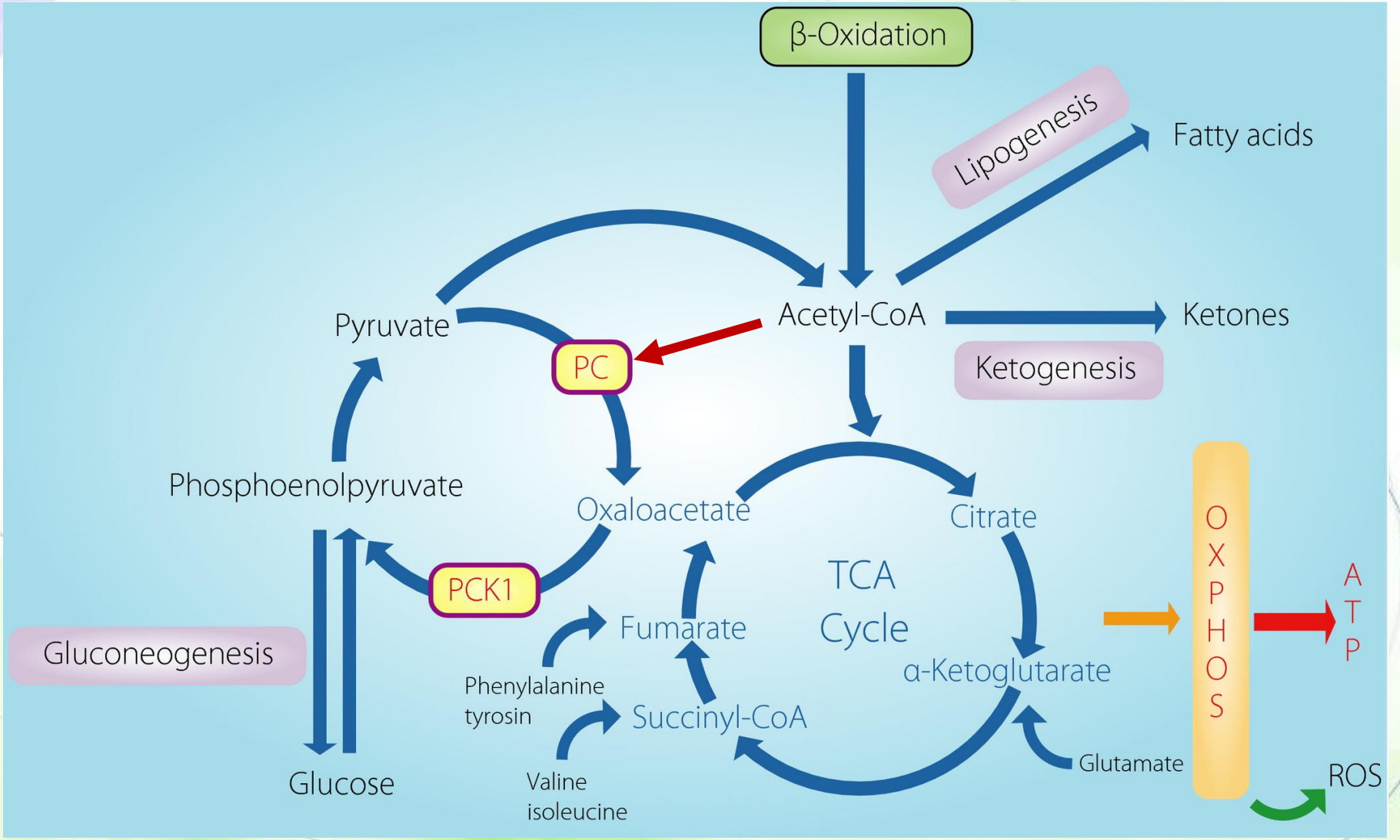
- **Number of cycles: (n-2)-1**

Mechanism	ATP Yield
1. β-oxidation 7 cycles 7 $FADH_2$ and 7 NADH are generated when oxidized by ETC	7$FADH_2$- 7 x 1.5 = 10.5 7 NADH- 7 x 2.5 = 17.5
2. From 8 acetyl CoA 1 acetyl CoA =3 NADH + 1 $FADH_2$ + 1 GTP Oxidized by citric acid cycle, each acetyl CoA provides ATP	10 x 8 = 80
Total Energy from one mole of palmitoyl CoA	**108**
Energy utilized for activation (Formation of Palmitoyl CoA)	2
Net yield of oxidation of one mole of palmitate	108-2 =**106**



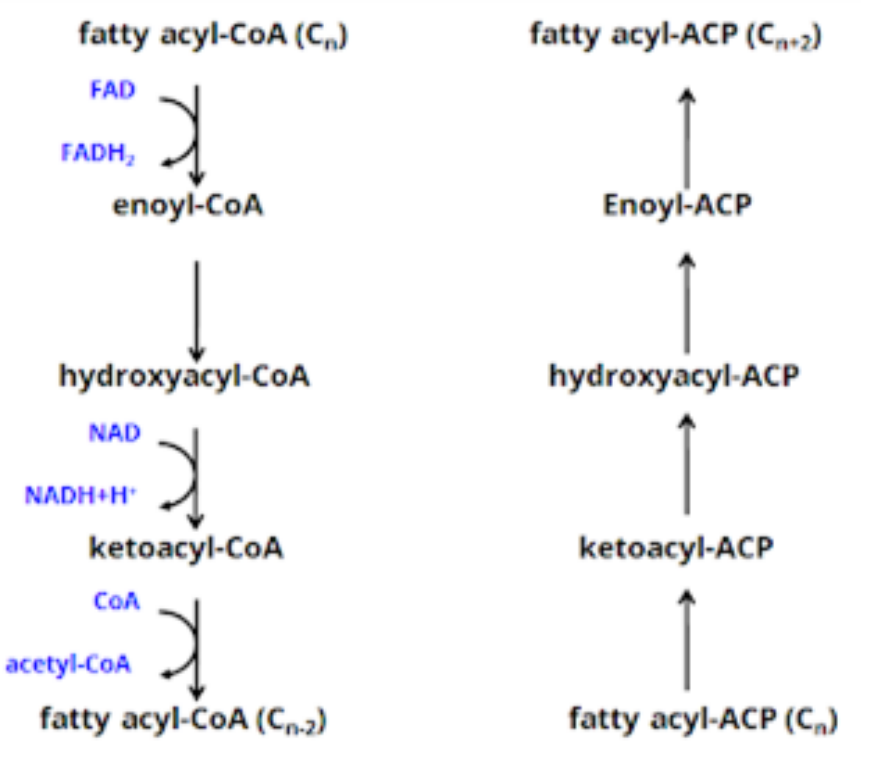


Induction of gluconeogenesis and fates of acetyl CoA



Synthesis vs. degradation

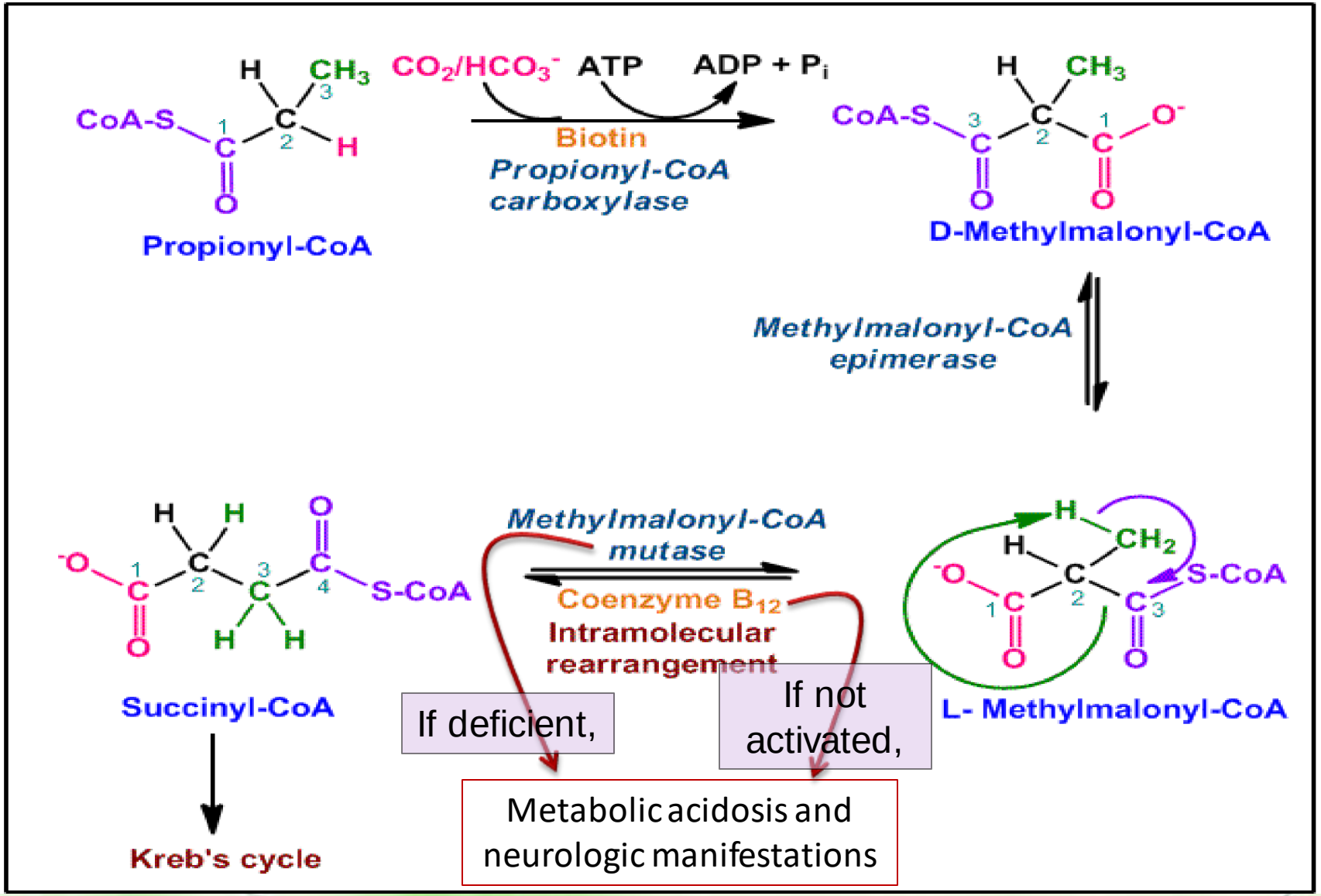
VARIABLE	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymes	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis



MCAD deficiency

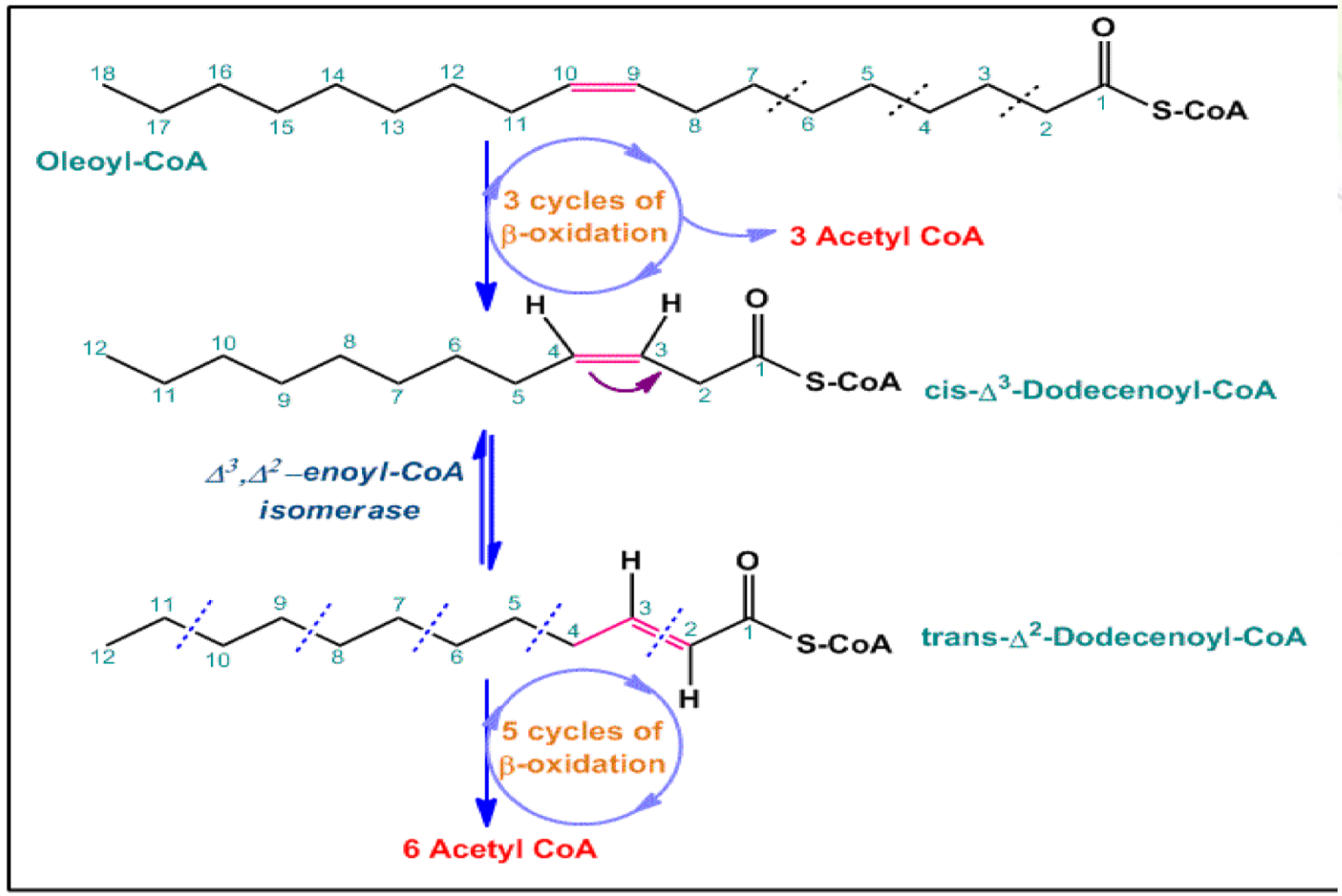
- There are 4 isozymes of fatty acyl CoA dehydrogenase for SCFA, MCFA, LCFA, and VLCFA.
- Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency,
  - An autosomal-recessive disorder
  - Most common inborn error of β-oxidation (1:14,000 births worldwide)
  - Higher incidence in Caucasians of Northern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

Oxidation of odd-numbered FAs

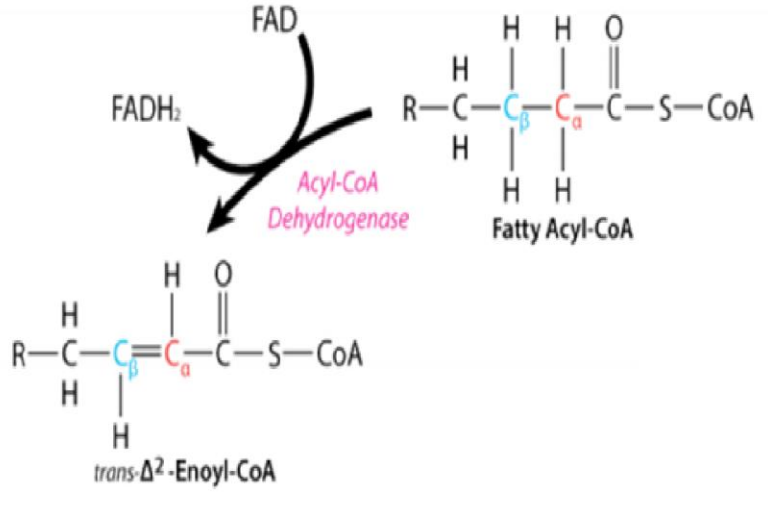


Note: Loss of electrons

Monounsaturated fatty acid β-oxidation

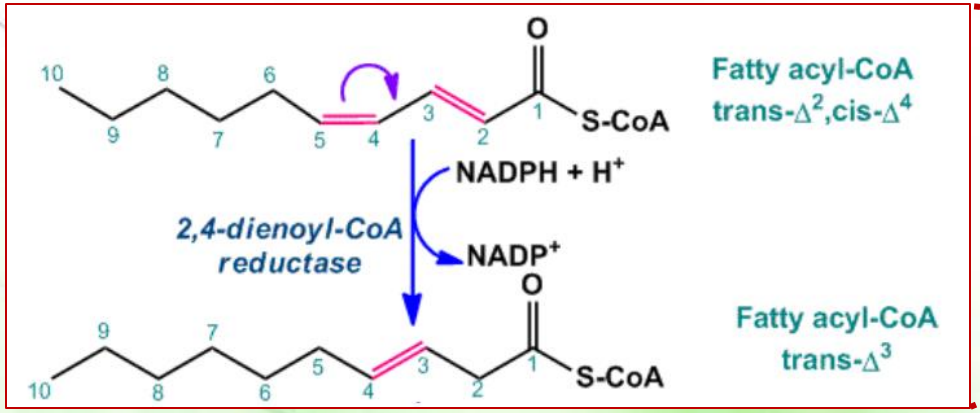


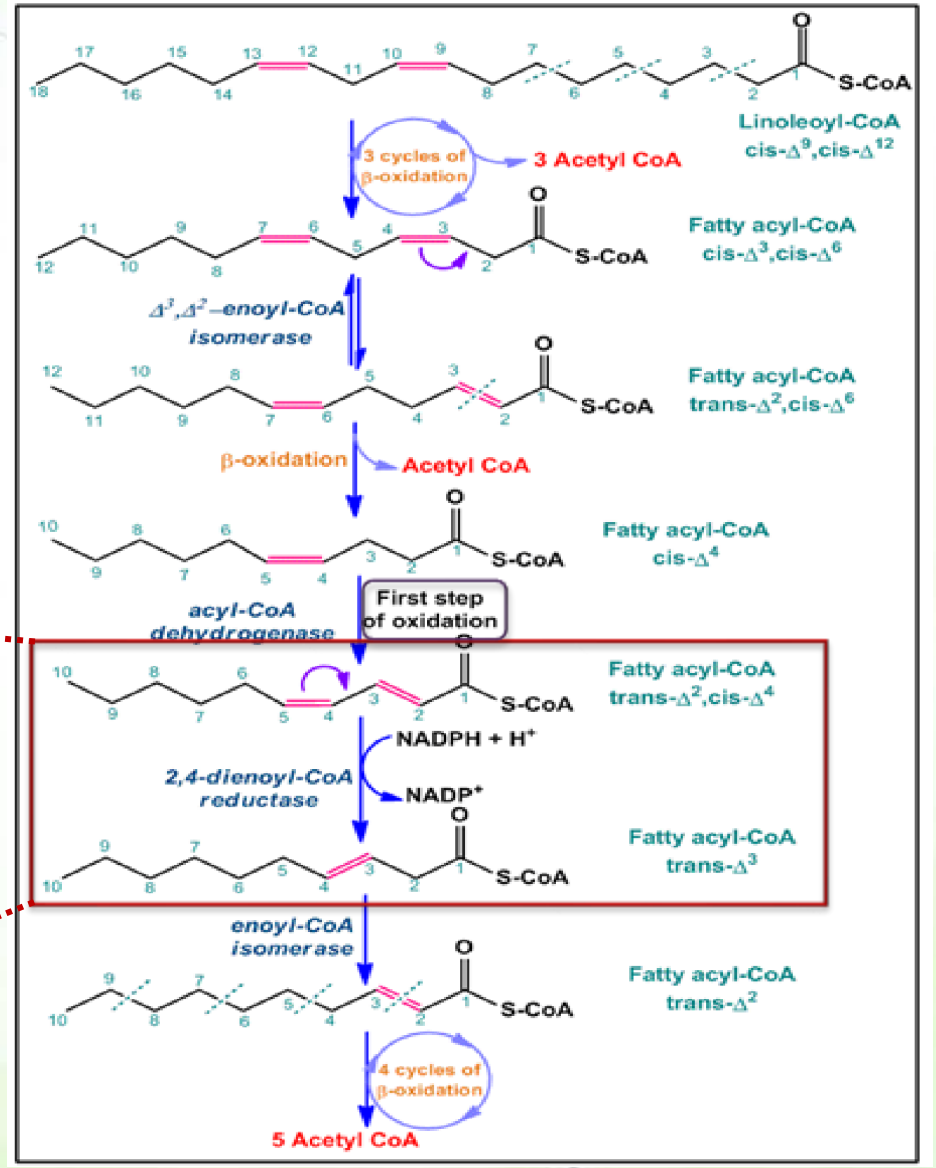
But this reaction is skipped resulting in less FADH2 → loss of electrons



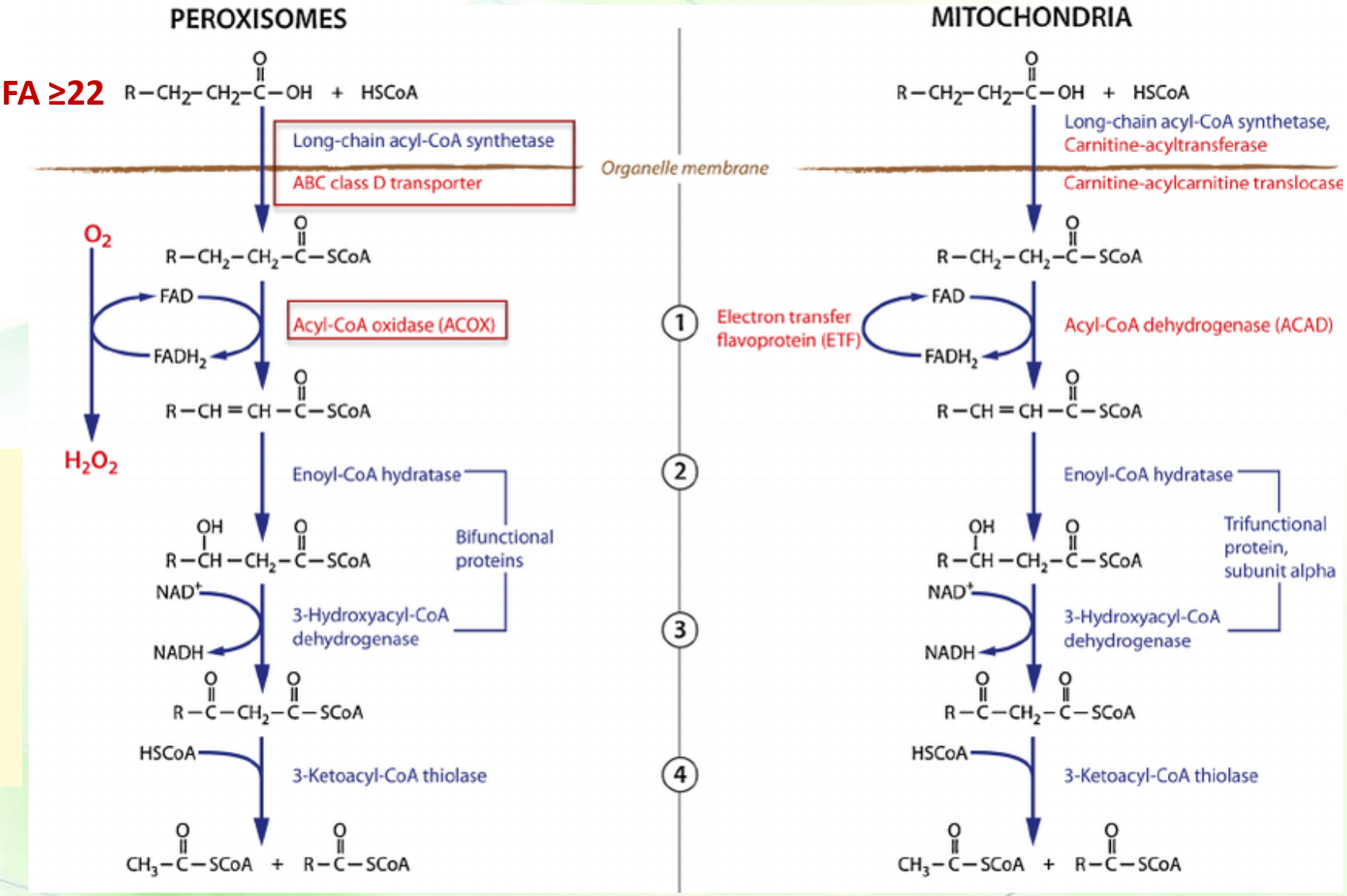
Polyunsaturated fatty acid β-oxidation

- Oxidation of a double bond at an even-numbered carbon, such as 18:2(9,12) (linoleic acid), requires an *NADPH-dependent 2,4-dienoyl CoA reductase* in addition to the *isomerase.*
- Note: loss of electrons





Peroxisomal β-oxidation



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

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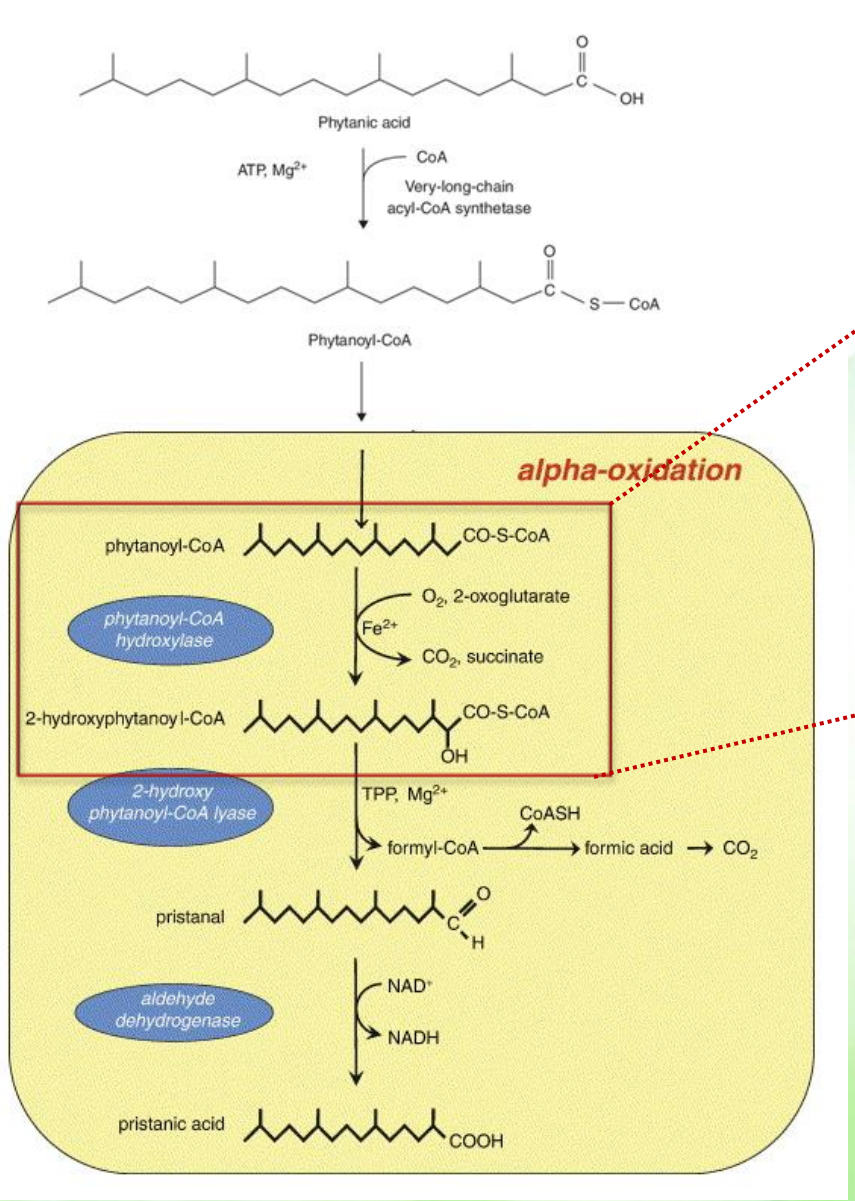
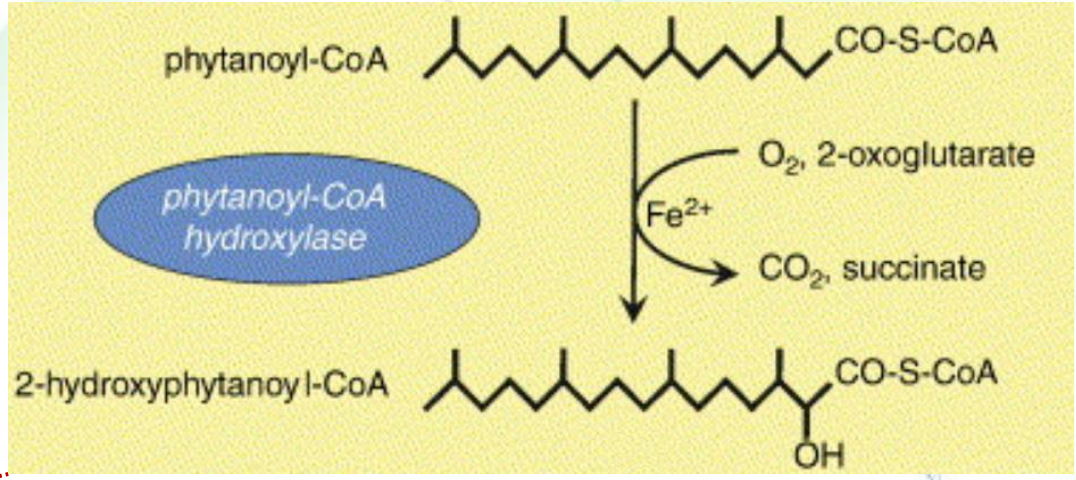
Accumulation of VLCFAs

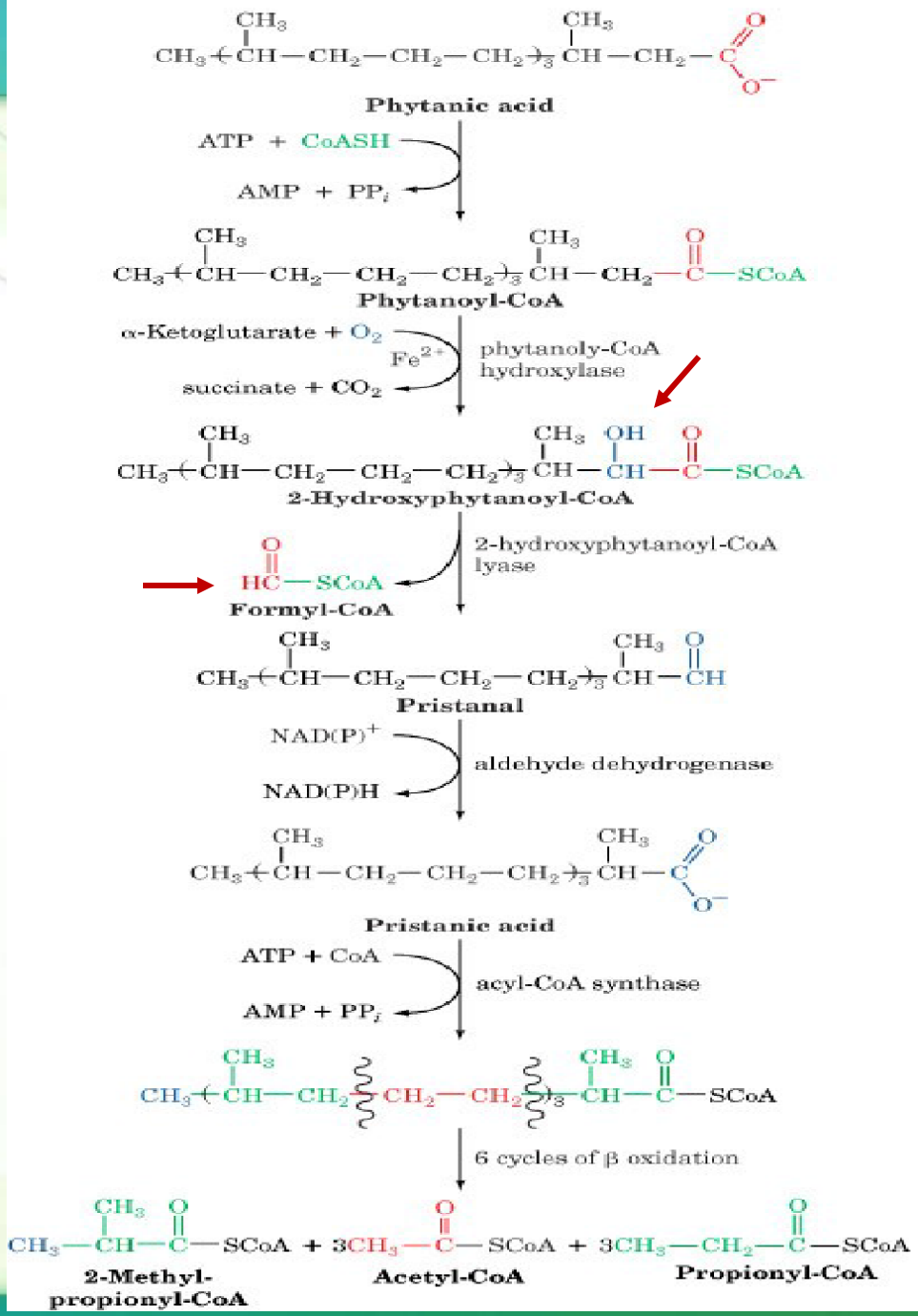
Peroxisomal α-oxidation





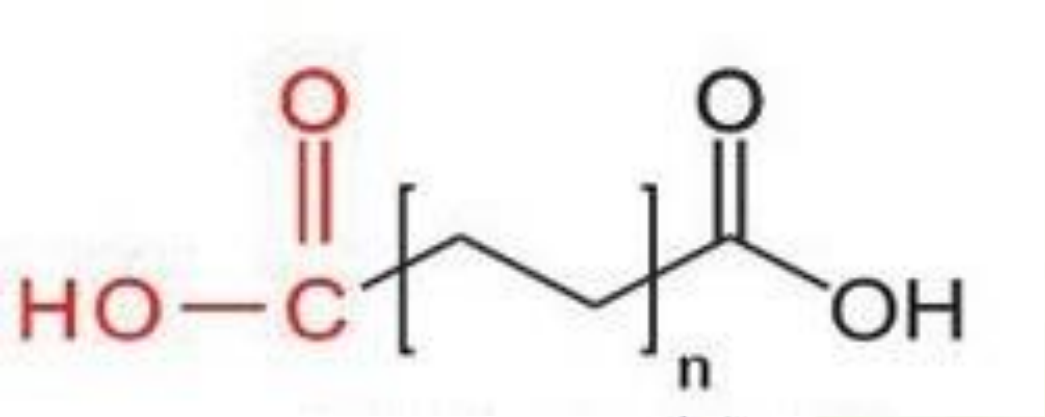
Peroxisomal α-oxidation

- Phytanic acid is a breakdown product of Chlorophyl.
- It is activated by CoA, transported into peroxisome, hydroxylated by phytanoyl CoA α-hydroxylase (PhyH), and carbon 1 is released as CO2.
- When fully degraded, it generates formyl-CoA, propionyl-CoA, acetyl-CoA, and 2-methyl-propionyl-CoA from the methyl-end.
- 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

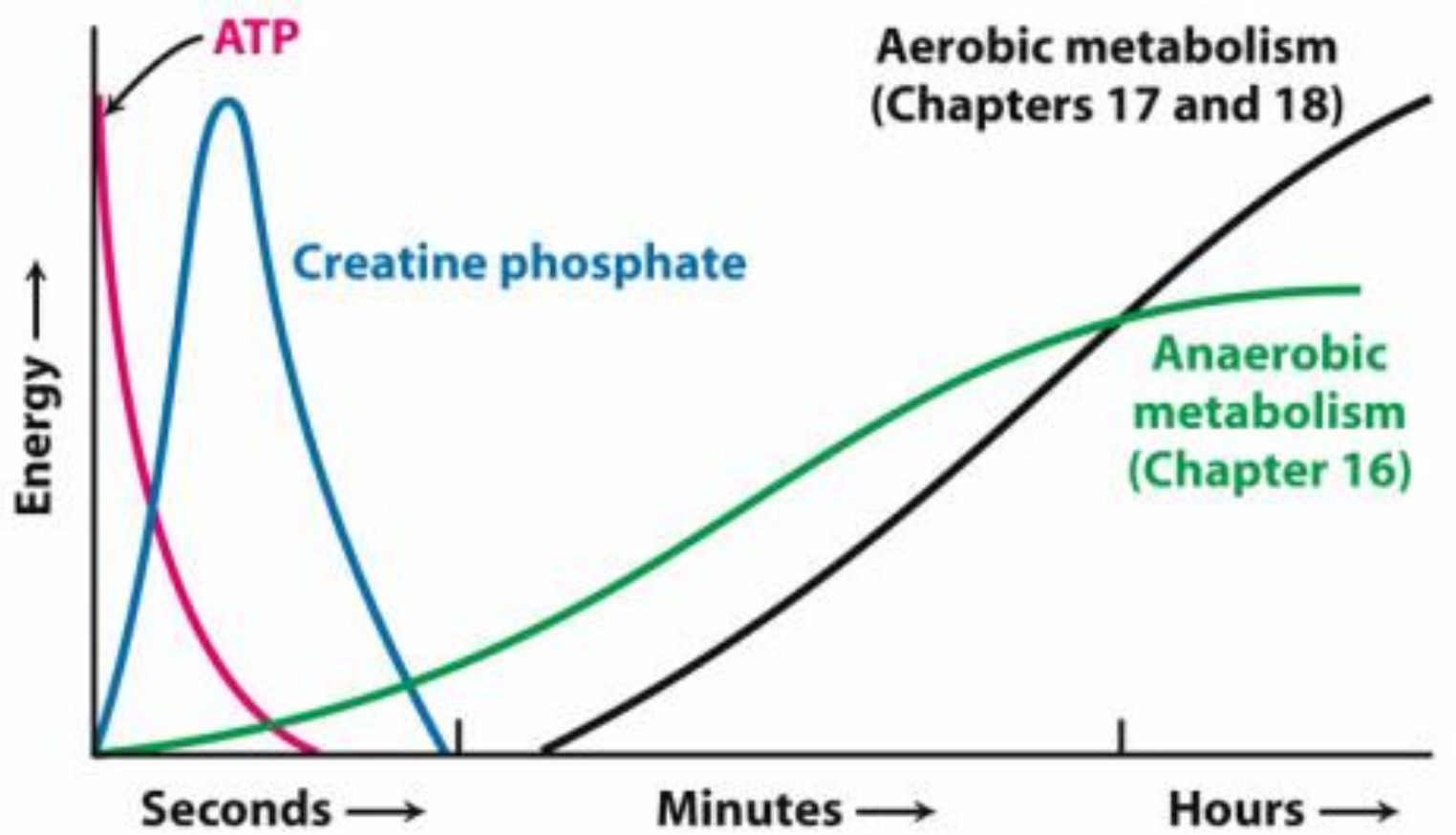


Figure 15.7
Biochemistry, Seventh Edition