

Lipid Metabolism: TAG, ketones and cholesterol

By Inga Borchgrevink

Outline

Types of lipids

Lipid Synthesis

Lipid b-oxidation

TAG synthesis

Ketones

Cholesterol

← *Wooclap*

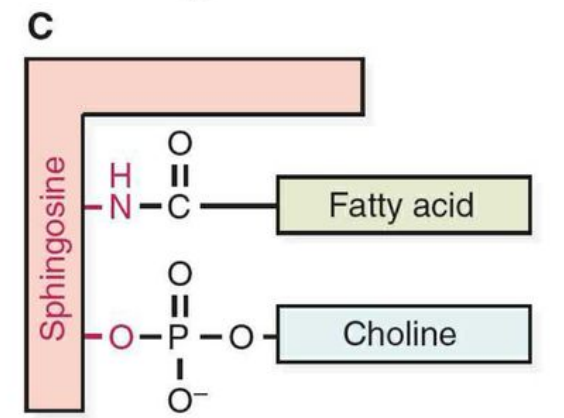
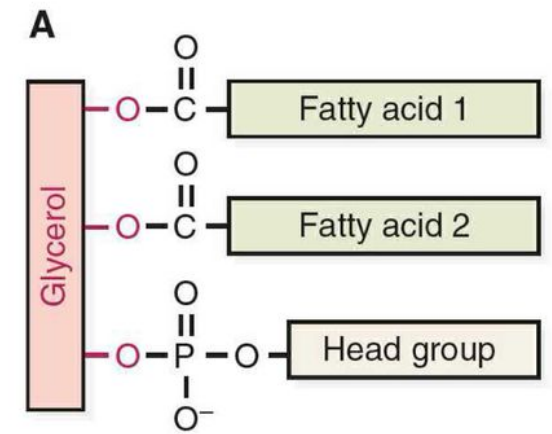
← *Wooclap*



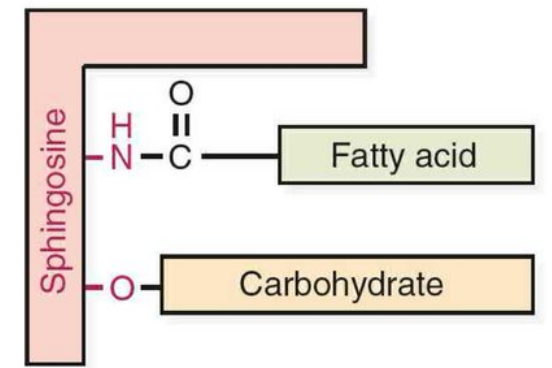
Lipids =
Water insoluble
biomolecules

Types of lipids

Types	Build from
Fatty acids	FA
Acylglycerol	Glycerol + FA
Phosphoacylglycerol	Glycerol + FA + P
Sphingolipids	Sphingosine + FA
Steroids	Steroid nucleus



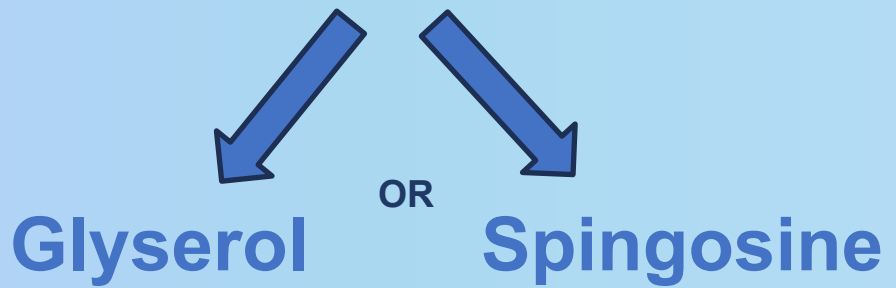
Sphingomyelin



Glycolipid

Acyl = FA

Backbone

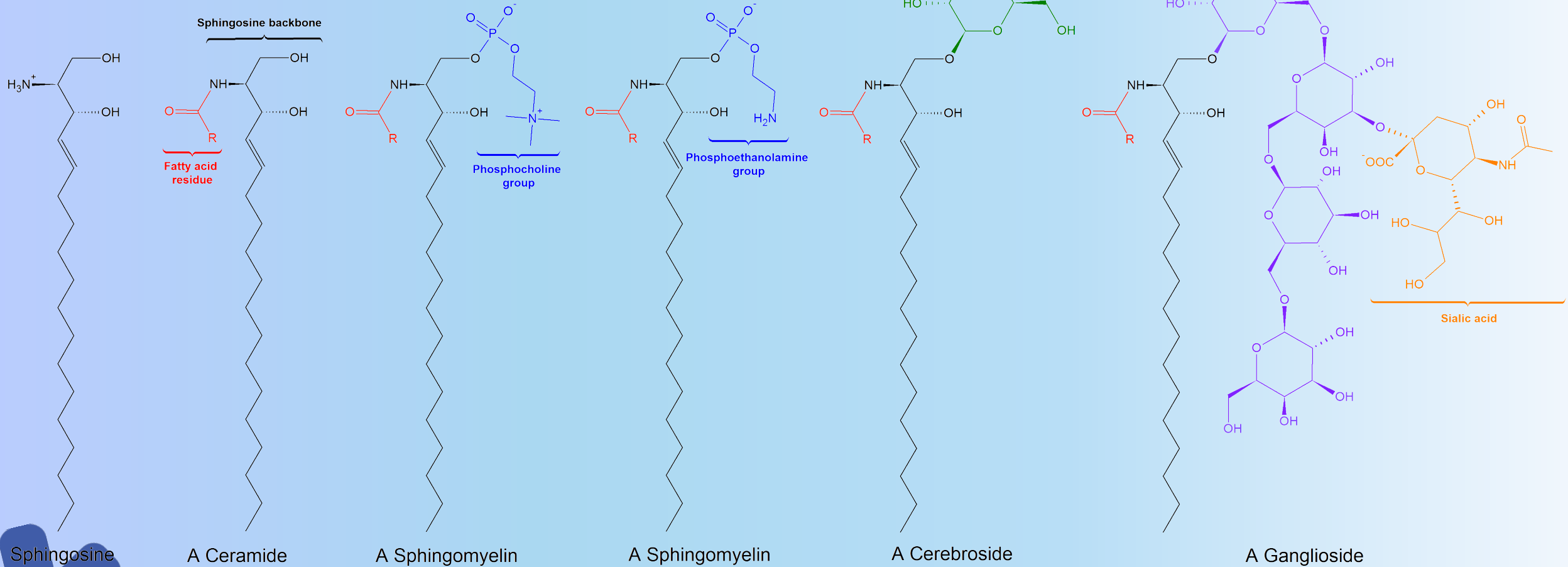


Take-home message - on lipid structure and classification

- **Lipids are diverse molecules crucial for cellular structure, energy storage, and signaling. They are characterized by their hydrophobic nature due to long hydrocarbon chains. They are divided into **simple lipids, complex lipids and precursor and derivative lipids****
- **Key lipid types include:**
 - ✓ **Fatty Acids:** building blocks of lipids, characterized by a hydrophobic tail and a carboxyl group; they vary in chain length and saturation, influencing lipid properties; serve as energetic substrates.
 - ✓ **Triacylglycerols/triglycerides:** main storage form of lipids in animals, composed of three fatty acid chains esterified to a glycerol molecule; they constitute energy storage and insulation.
 - ✓ **Phospholipids:** major components of cell membranes, consisting of a polar phosphate head and two hydrophobic fatty acid tails; they form bilayers, essential for compartmentalization and cell integrity.
 - ✓ **Sphingolipids:** contain a sphingosine backbone, fatty acid chain, and polar head group; found in cell membranes and involved in cell signaling.
 - ✓ **Steroids:** lipids with a characteristic four-ring structure, including cholesterol and hormones like testosterone and estrogen; they regulate membrane fluidity and serve as signaling molecules and emulsifying agents.

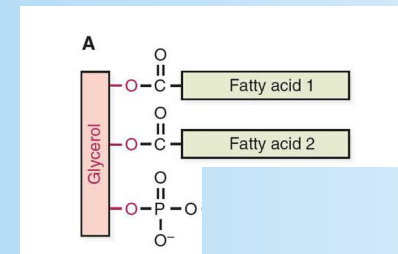
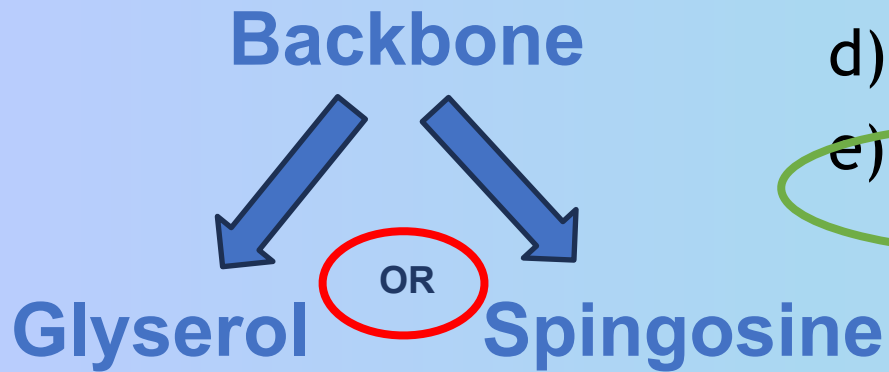


Sphingolipids



Q: Which of the following is needed for the synthesis of all three compounds: triacylglycerol, phosphatidyl and sphingomyelin

- a) Diacylglycerol ✘
- b) Phosphatidic acid ✘
- c) Phosphocholine ✘
- d) Glycerol-3-phosphate ✘
- e) Acyl-CoA

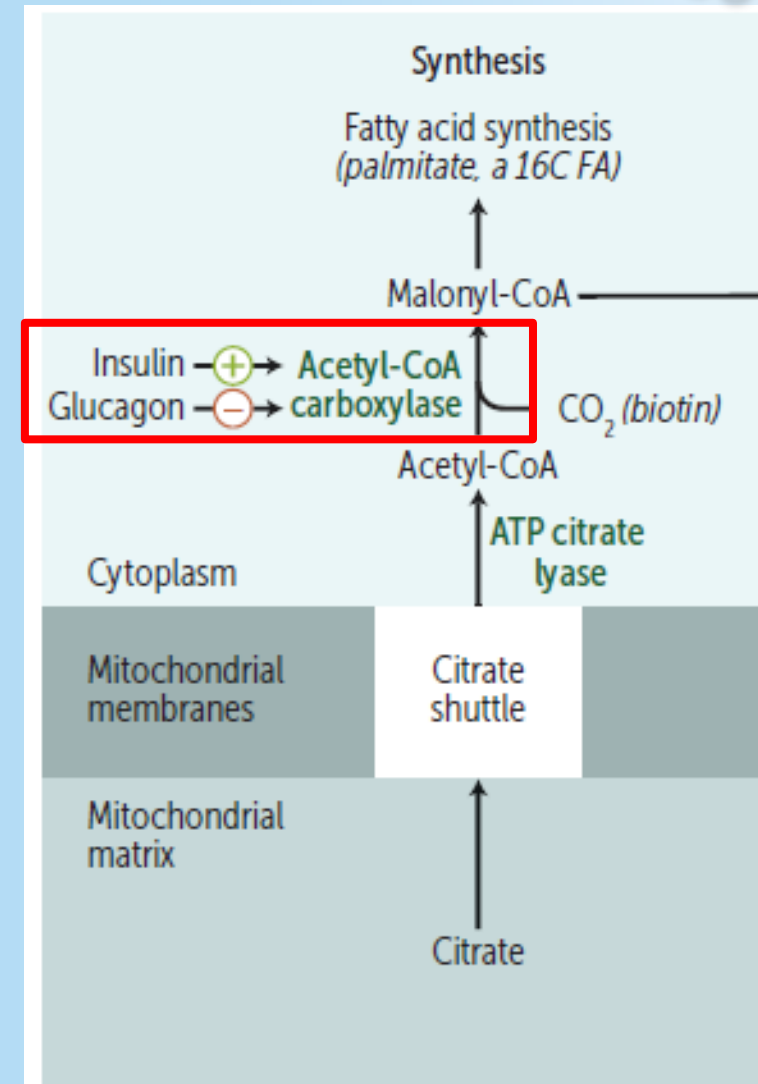


Fatty acid synthesis (de novo)

In cytosol of liver and adipose tissue

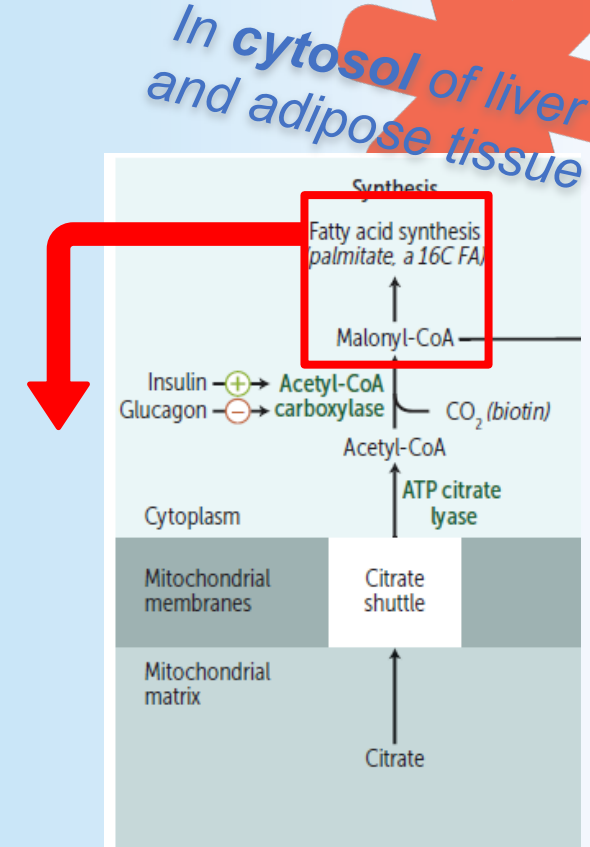
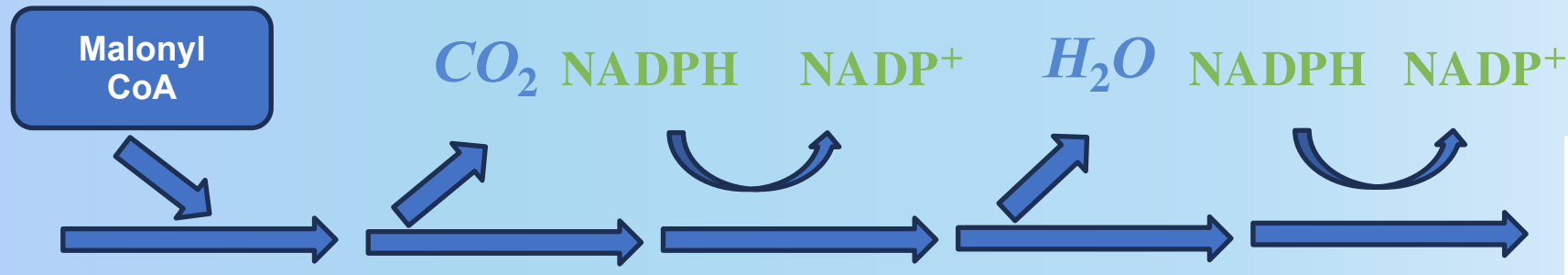
NOTE:

- Citrate shuttle!
- Citrate is an energy marker
- **Acetyl-CoA carboxylase = rate limiting step**



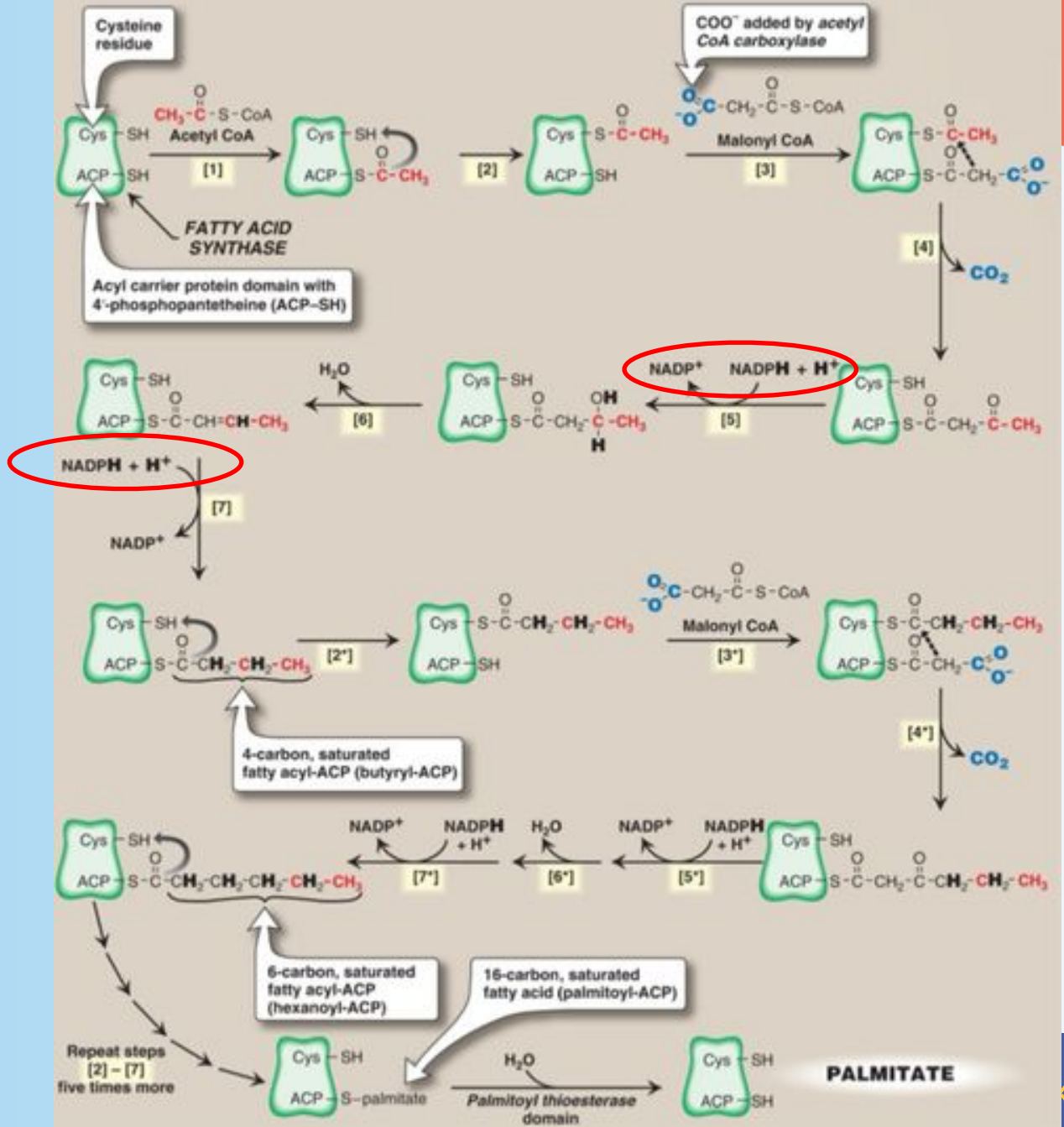
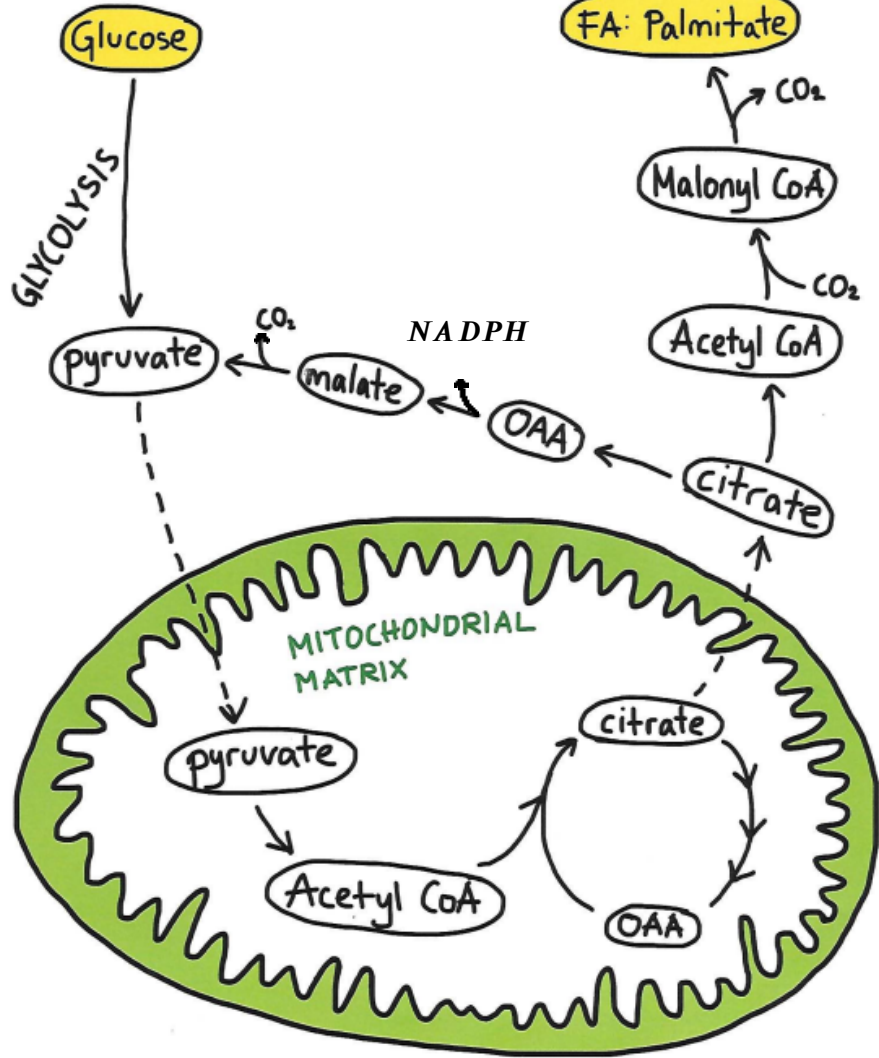
Fat synthesis (de novo)

- ACP = acyl carrier protein
- FAS-I = Enzyme
- Malonyl CoA as building block
- Use **2 NADPH** per round



DE NOVO SYNTHESIS OF FAs

CYTOSOL

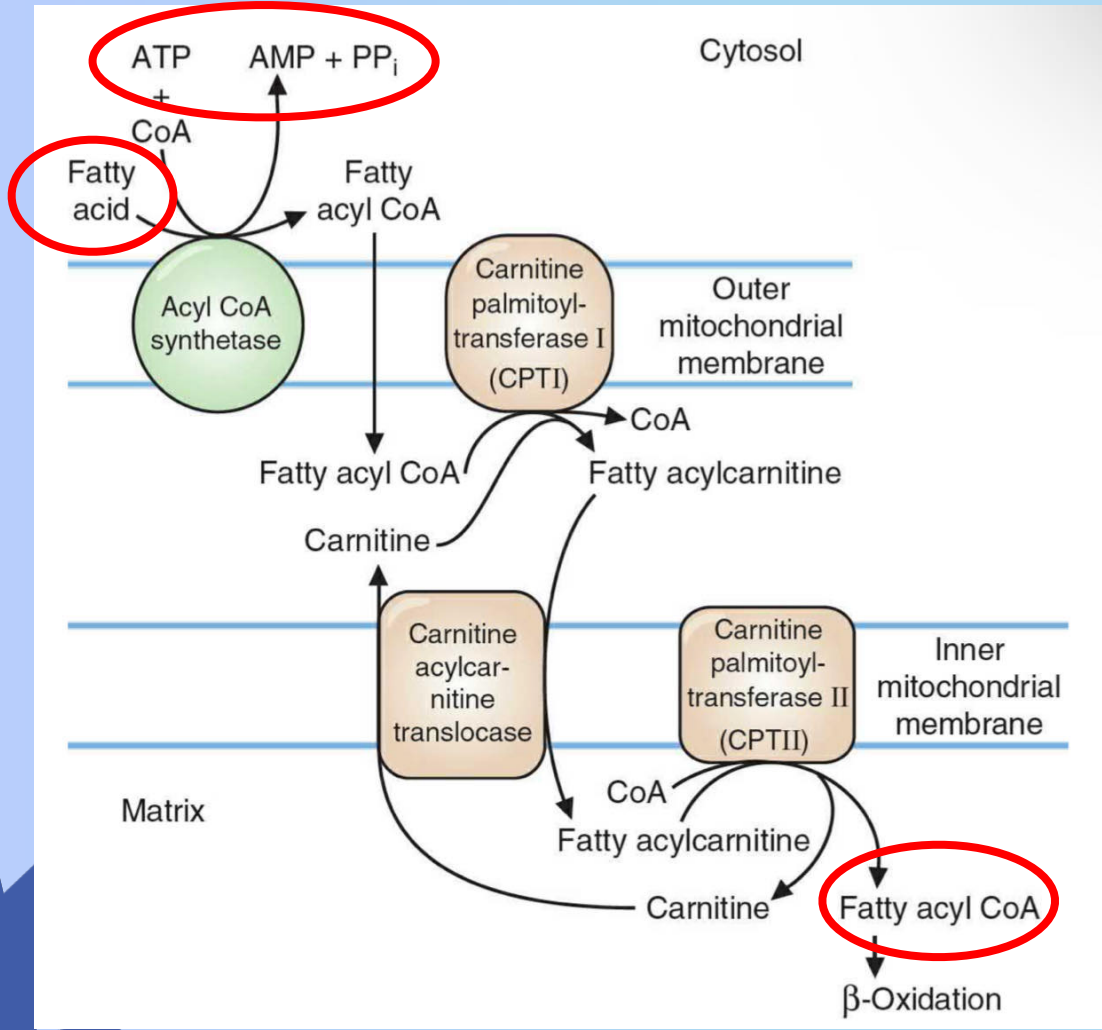


Fatty Acids **NOT** used by:
RBC's: Glycolysis only (no mitochondria)
Brain: Glucose & Ketones only!

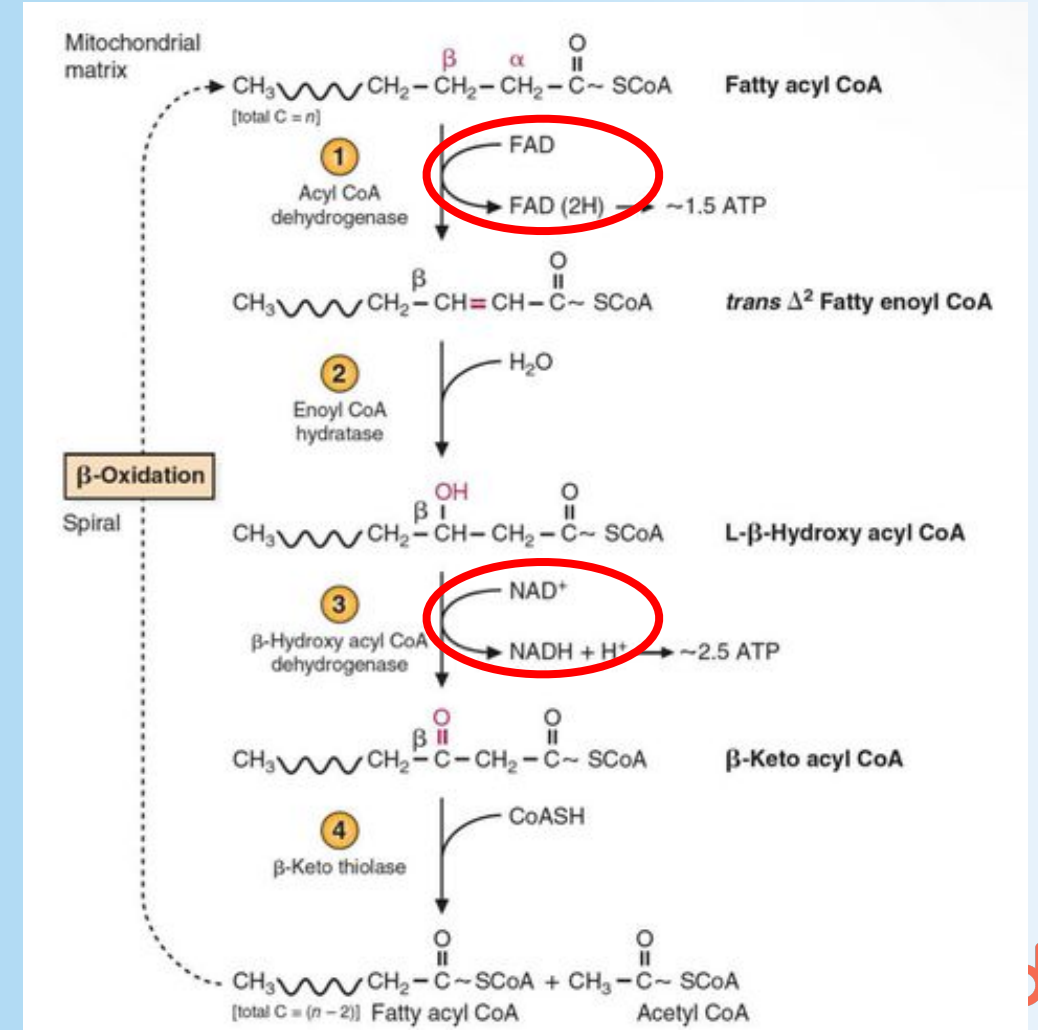
Mitochondria

Degradation of fatty acids

Transfer Fatty acid into mitochondria

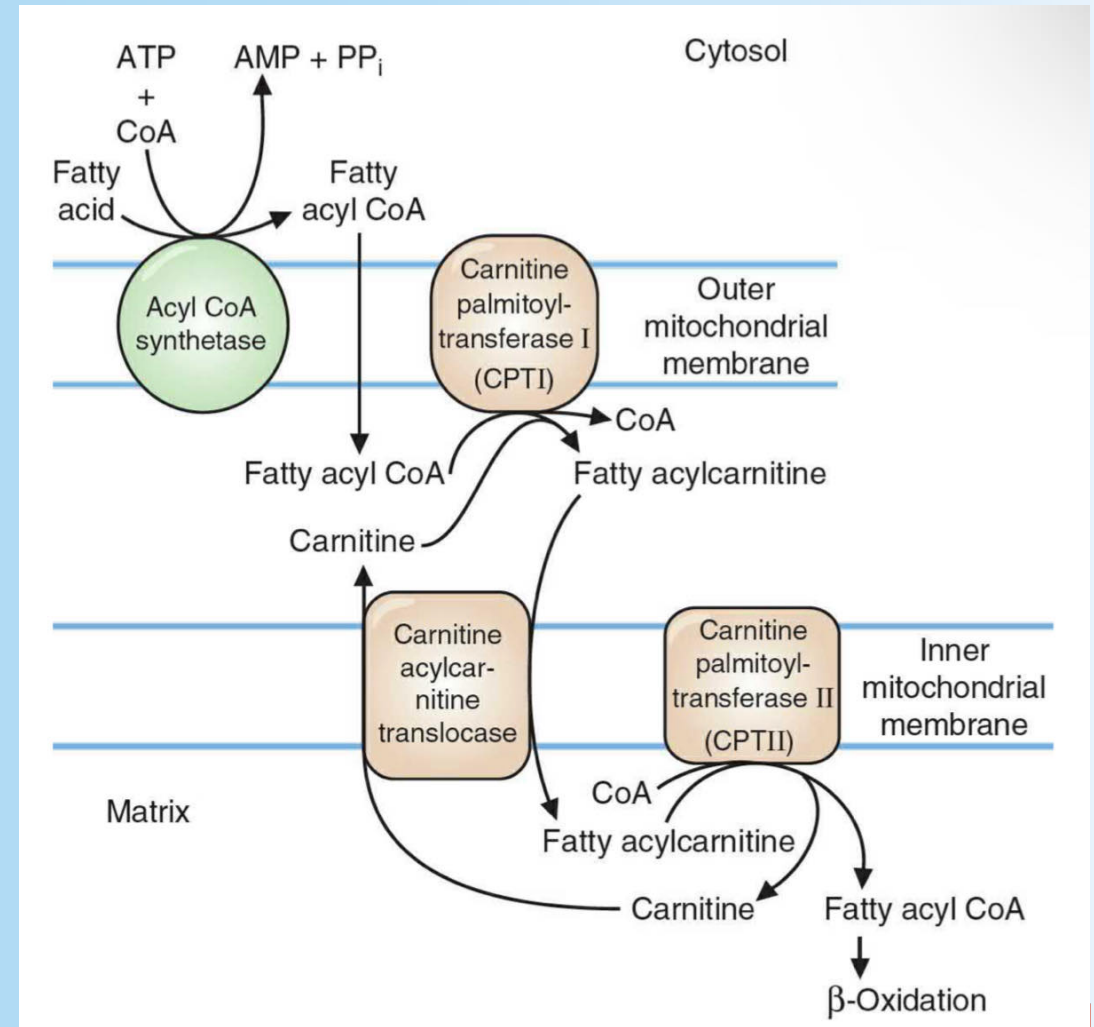


β-oxidation spiral



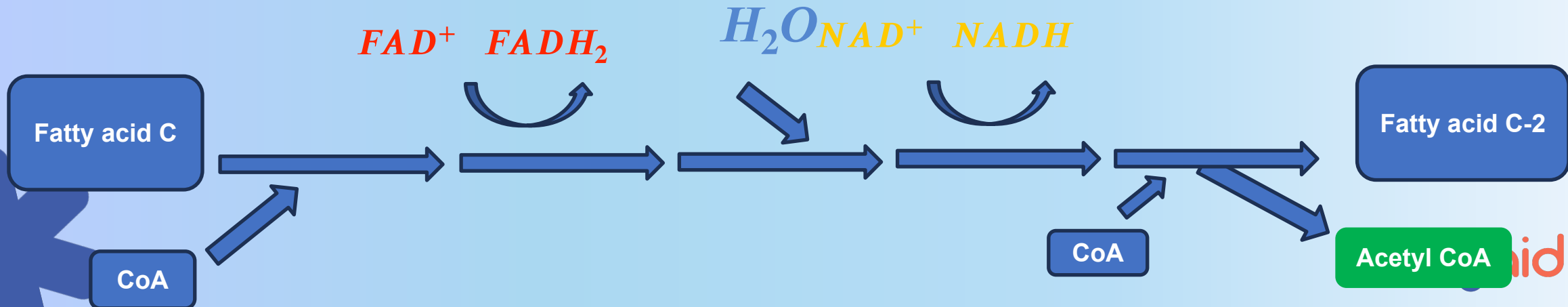
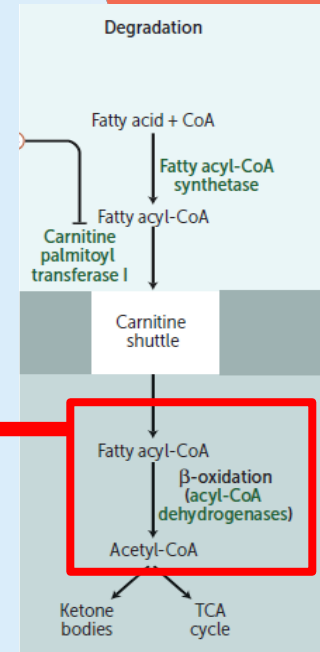
Transfer Fatty acid into mitochondria

- Use (!!) 2 ATP per round
- Carnitine palmitoyl transferase I = rate limiting step



β -oxidation spiral

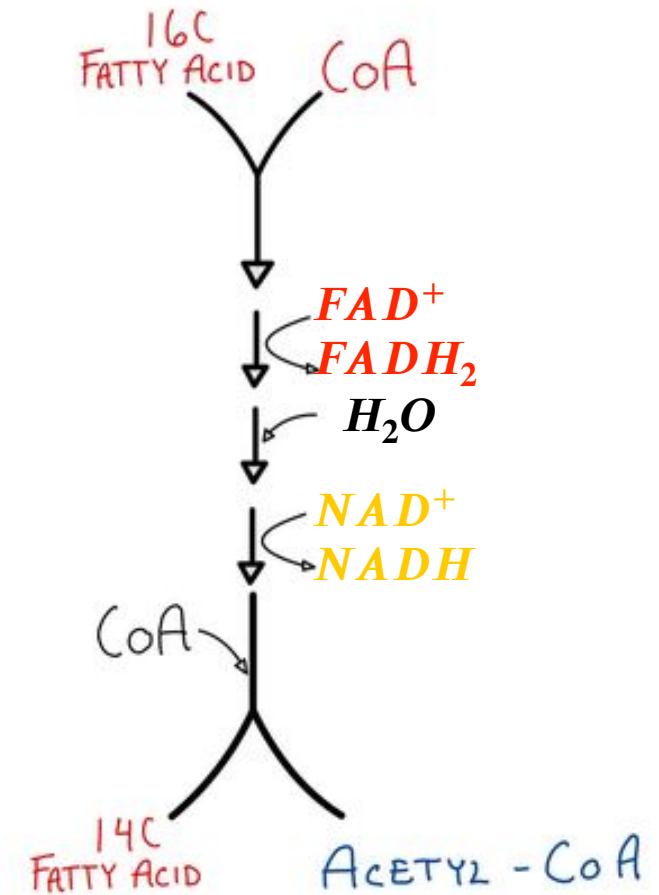
- Oxidate two carbons per round
- Produce **1 $FADH_2$** , **1 $NADH$** and **1 Acetyl CoA** per round



$FADH_2 = 1,5 \text{ ATP}$
 $NADH = 2,5 \text{ ATP}$
 $Acetyl - CoA = 10 \text{ ATP}$

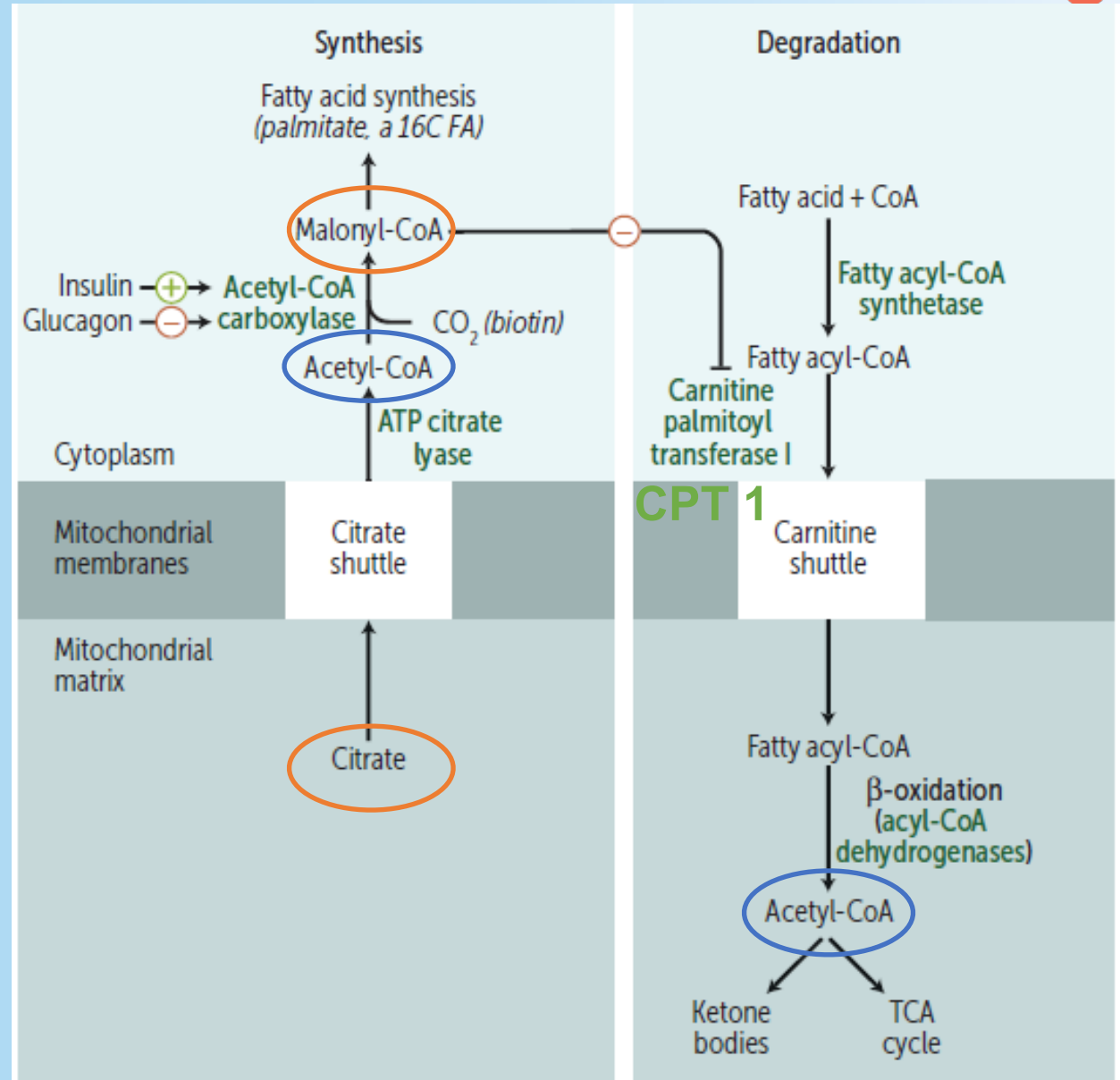
Energy output

- Number of rounds = $\frac{C - 2}{2}$
- $16C \rightarrow 7$ rounds of β -oxidation
 - $7 FADH_2 \rightarrow 10,5 \text{ ATP}$
 - $7 NADH_2 \rightarrow 17,5 \text{ ATP}$
 - $8 \text{ Acetyl} - \text{CoA} \rightarrow 80 \text{ ATP}$
 - $\rightarrow 108 \text{ ATP}$
 - $108 \text{ ATP} - 2 \text{ ATP (for activation)}$
 - $\rightarrow \underline{106 \text{ ATP netto}}$

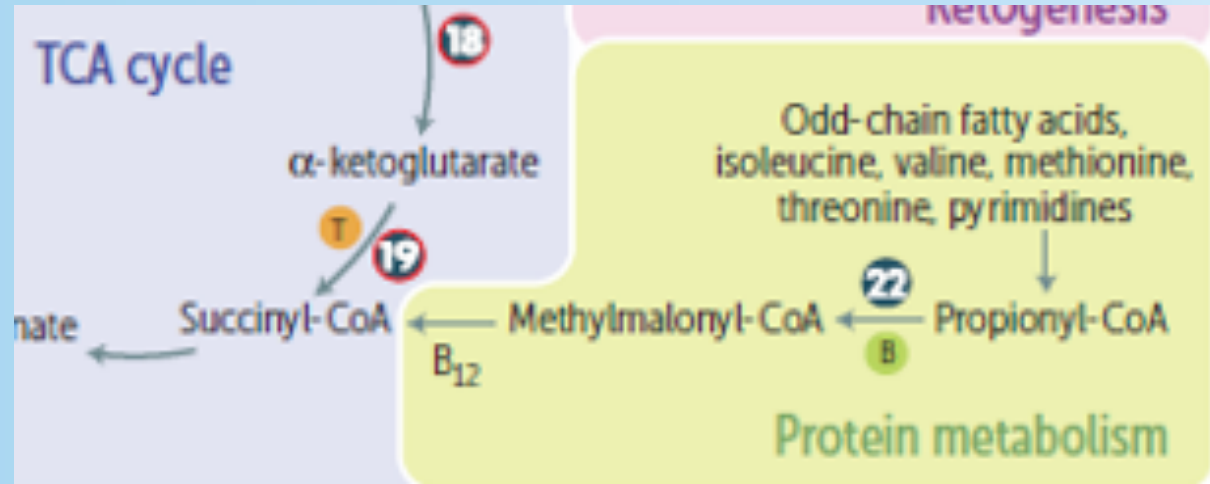
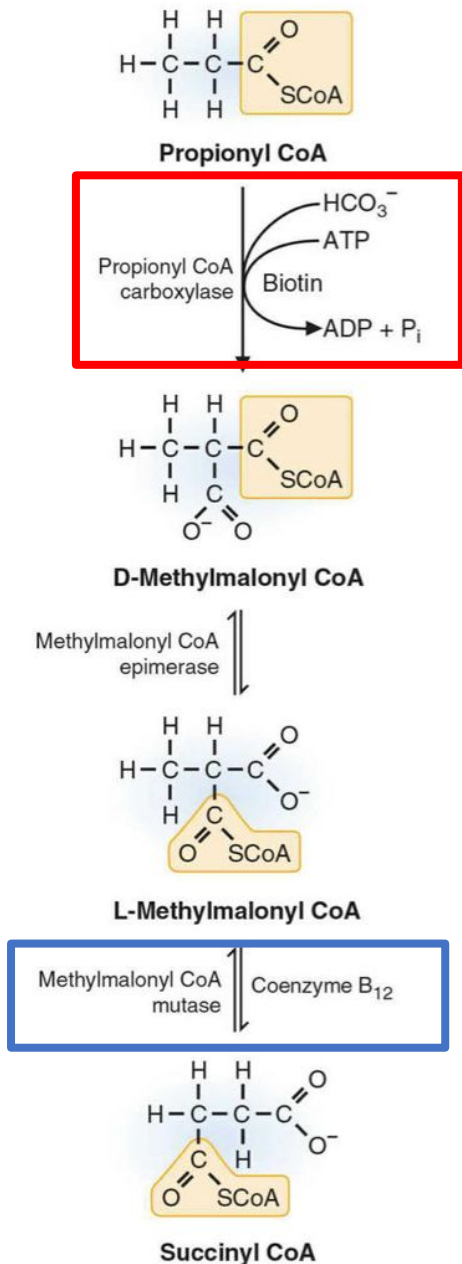


Balace between synthesis and degradation of FA

- Malonyl-CoA **inhibits** CPT1 meaning Fatty Acid synthesis and degradation does not happen simultaneously



What about Odd Chain Fatty Acids?



- 1) B-oxidation until propionyl CoA (3C)
- 2) **Enzyme 1: Need: Biotin, ATP and CO₂**
- 3) **Enzyme 3: Vit B12 deficiency causes buildup of Methylmalonyl-CoA**
- 4) End product Succinyl-CoA → TCA cycle

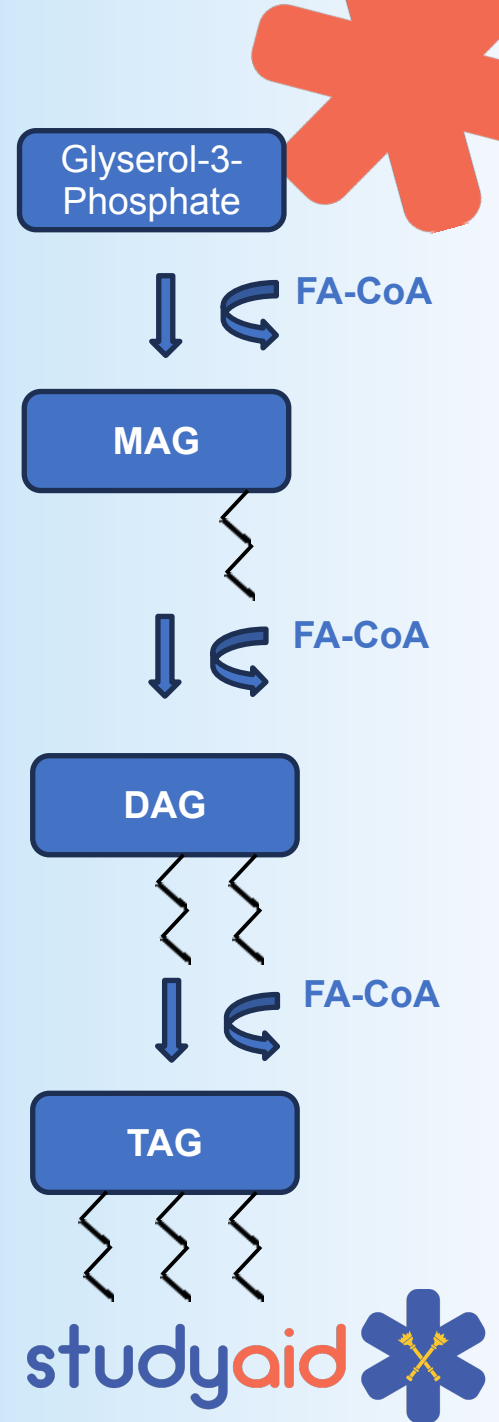
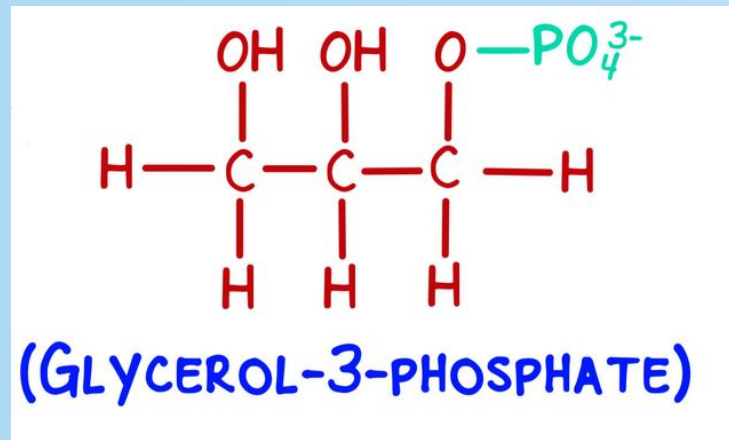
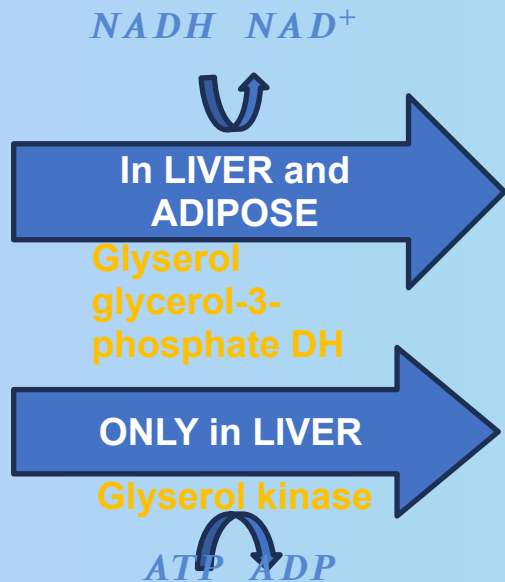
Liver and Adipose ER

TAG synthesis/Lipogenesis

- Glycerol-3-Phosphate → TAG
- Adipose tissue lack **Glycerol kinase**

DAPH

GLYSEROL



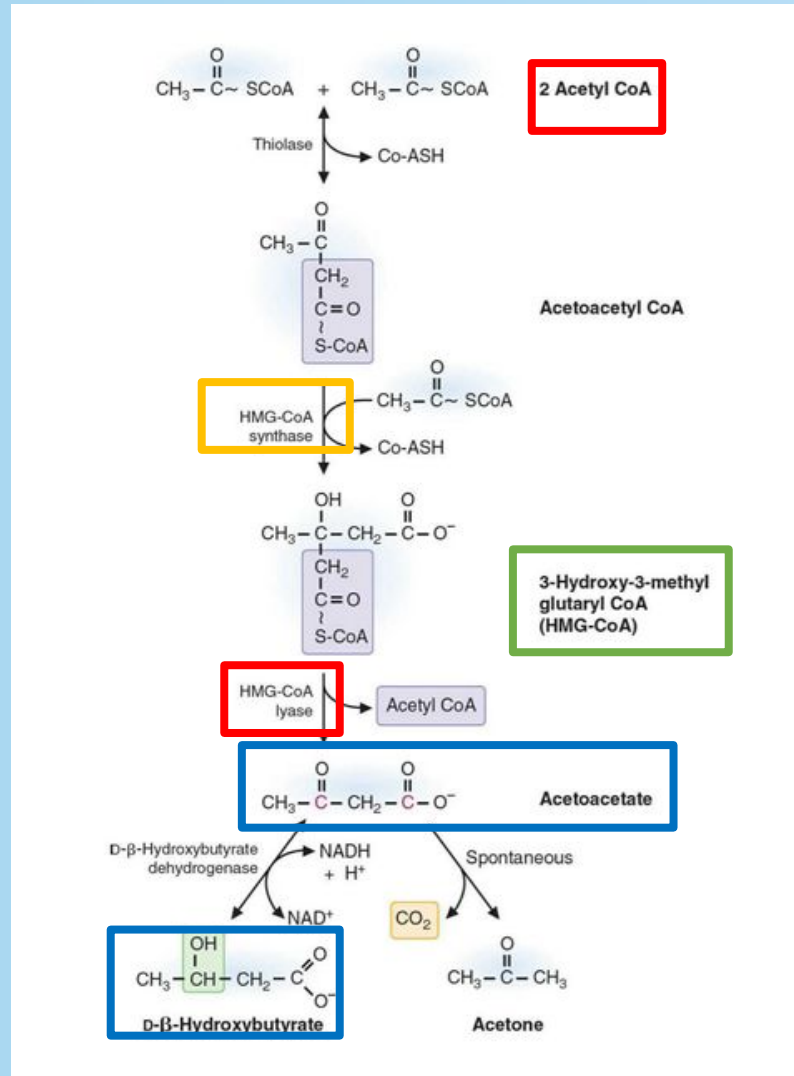
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Synthesis of ketone

In liver mitochondria

HMG-CoA synthase = Rate limiting step

HMG-CoA lyase



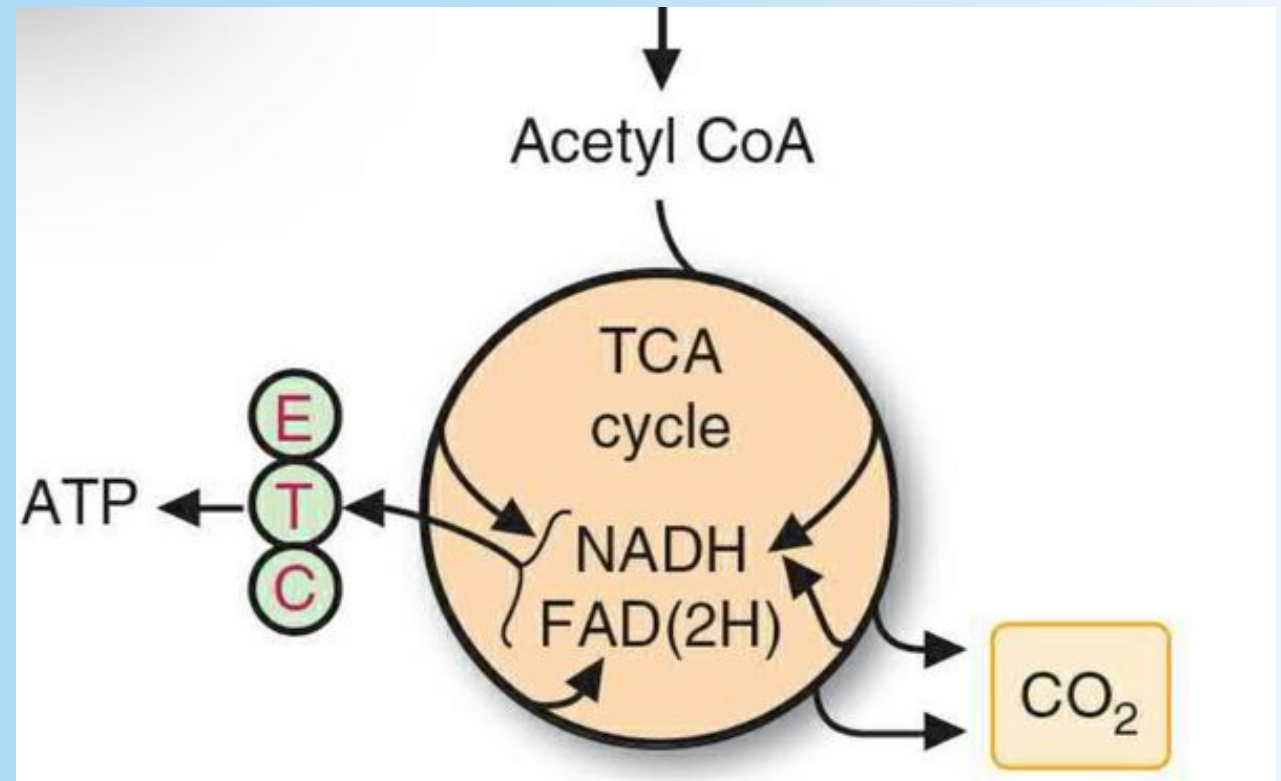
Acetyl CoA from fatty acid oxidation

HMG-CoA

Ketone bodies

When are Ketones produced?

- Prolonged starvation & Diabetic Ketoacidosis = oxaloacetate depleted (TCA)
- Chronic alcohol overuse = NADH excess
- Both of the above processes lead to **acetyl-CoA buildup** which is shunted to ketone synthesis



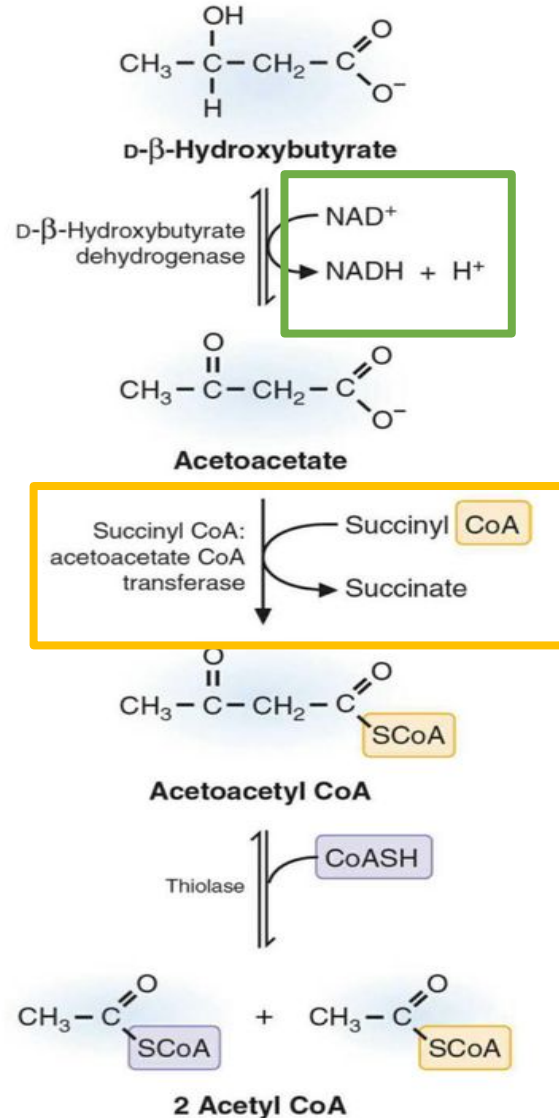
Oxidation of ketones

Broken down in
muscle and brain
mitochondria →
energy
NOT liver and erythrocytes

Succinyl CoA:
acetoacetate CoA
transferase:

ABSENT IN LIVER

Depend on an active TCA
cycle to provide succinyl
CoA!!!

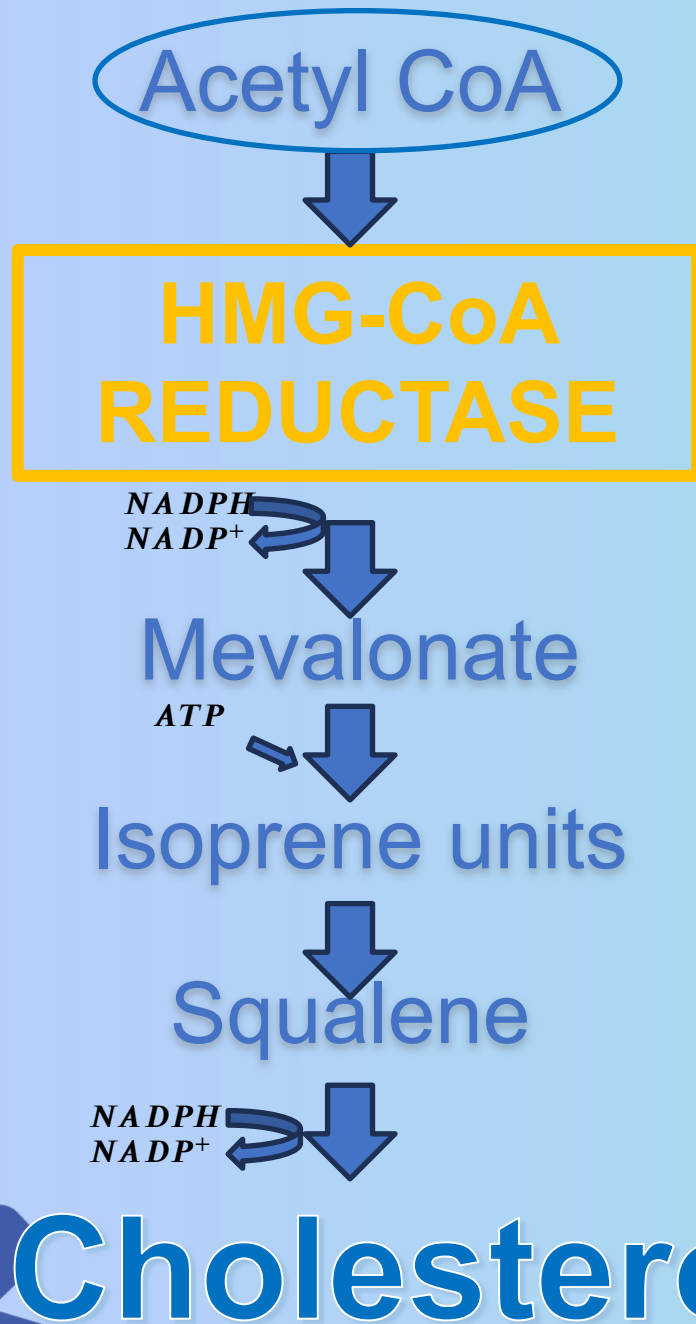


Get more energy (NADH) from
hydroxybutyrate (most common)
then from acetoacetate

Energy output:
2 Acetyl CoA → 20 ATP
1 NADH → 2,5 ATP

In liver
cytocol

Cholesterol synteses



- Start from Acetyl CoA
- Use NADPH and ATP

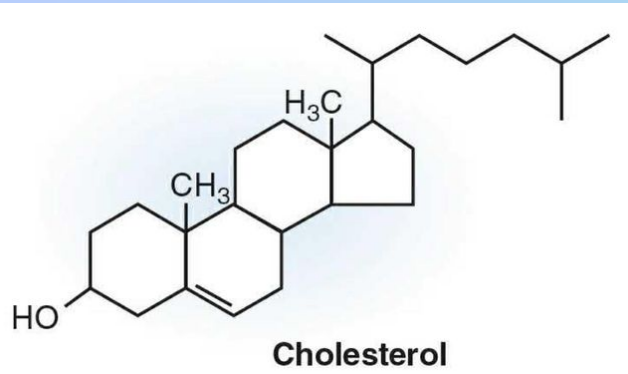
HMG-CoA reductase = Rate Limiting Step

- **Inhibited** by statin drugs and cholesterol + mevalonate buildup
- **Insulin** Induces
- **Glucagon** Inhibits

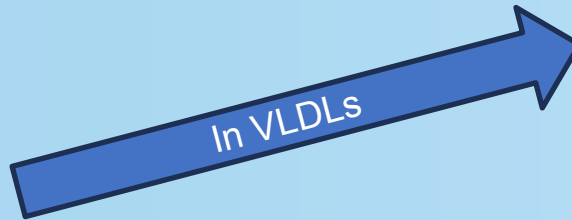
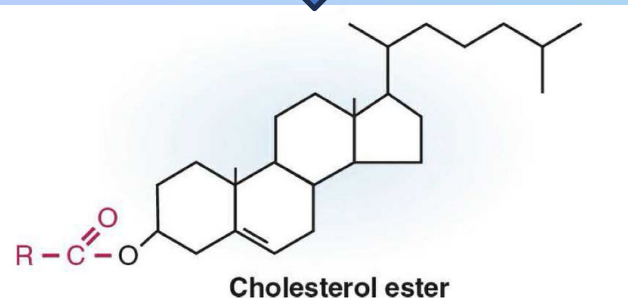
Irrversible proses!!
Cholesterol can NOT be broken down for energy:!

Fates of cholesterol

Made in liver,
delivered to tissue by
VLDL



ACAT

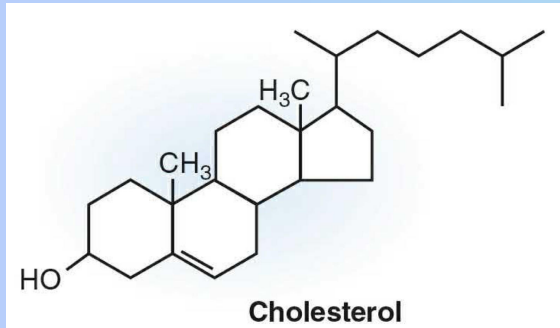


TISSUES

- Membrane structure
- Production of steroid hormones
- Production of vit D

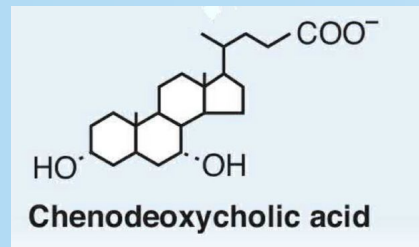
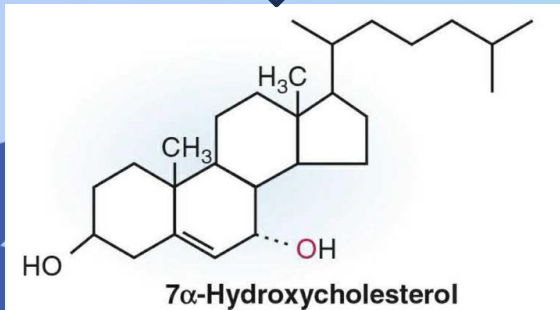
Cholesterol → bile acid/salts

Made in liver,
stored in
gallbladder

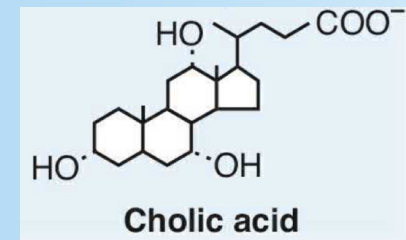


7 α -hydroxylase = Rate limiting step
Bile acids inhibit

7 α -hydroxylase



Bile acids



Don't mix these up!

HMG-CoA **Lyase** (mitochondria) = **Ketone** production

HMG-CoA **Reductase** (cytosol) = **Cholesterol** synthesis

HMG-CoA **Synthase** = **BOTH**




IMPORTANT


Fasting:


Where are you?


Fed:



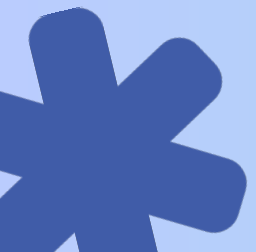
 **Insulin** *Inhibits enzymes*

 **Glugacon** *Stimulate enzymes*

 **Insulin** *Stimulate enzymes*

 **Glugacon** *Inhibits enzymes*

What?	Where?	When?
Ketone synthesis	Liver cell mitochondria	Fasting
Ketone oxidation (break down)	Muscle and brain mitochondria	Fasting
Cholesterol synthesis	Liver cytosol	Fed
TAG synthesis	Adipose + liver, ER	Fed
FA synthesis	Cytoplasm	Fed
FA degradation	Cytosol → Mitochondria (β -oxidation spiral)	Fasting



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