Lipid Metabolism

By Inga Borchgrevink

Outline 1

- Types of lipids
- Lipid Synthesis
- Lipid b-oxidation
- TAG synthesis
- Ketones
- Cholesterol

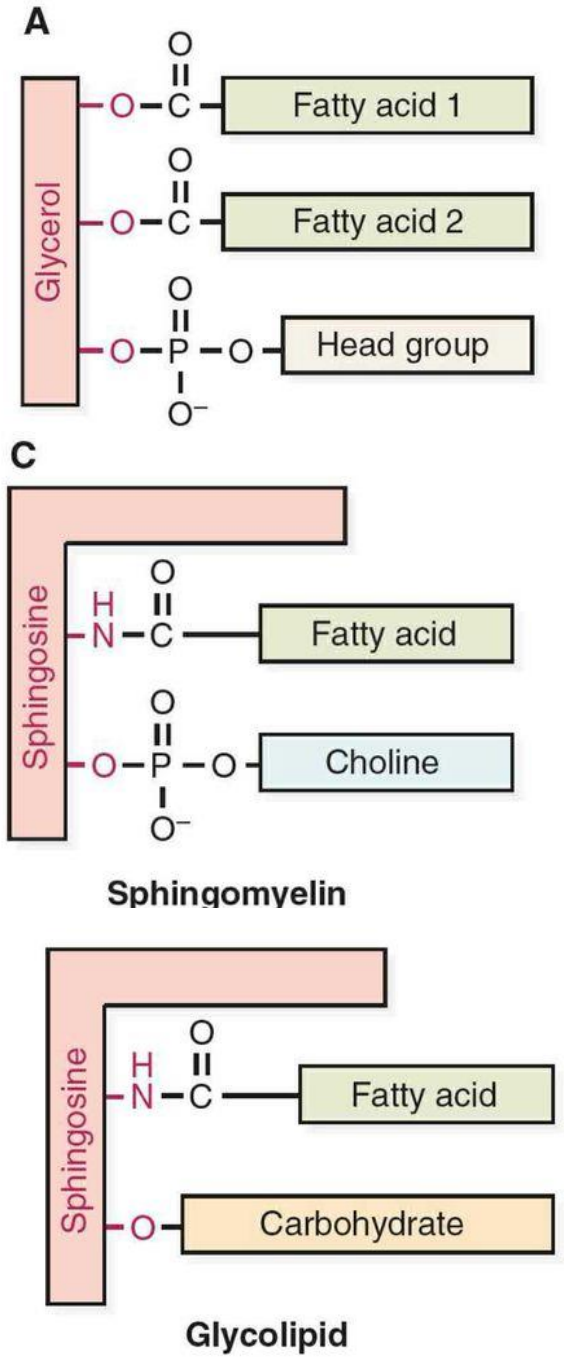
Acyl = FA

Types of lipids

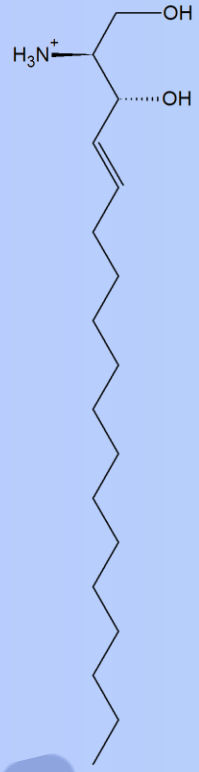
Types	Build from
Fatty acids	
Acylglyserol	Glyserol + FA
Phosphoacylglyserol	Glyserol + FA + P
Sphingolipids	Sphingosine
Steroids	Steroid nucleus

Backbone

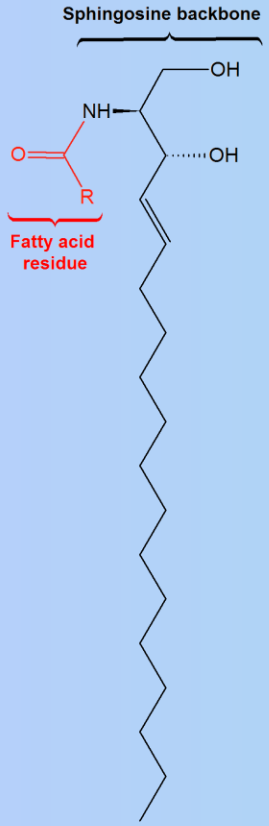
Glyserol **Spingosine**



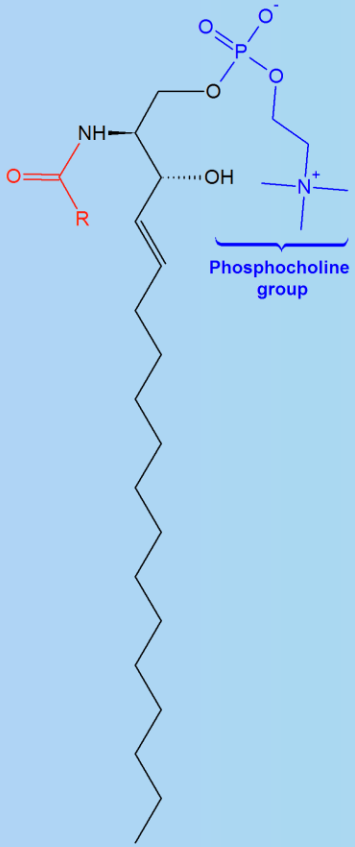
Sphingolipids



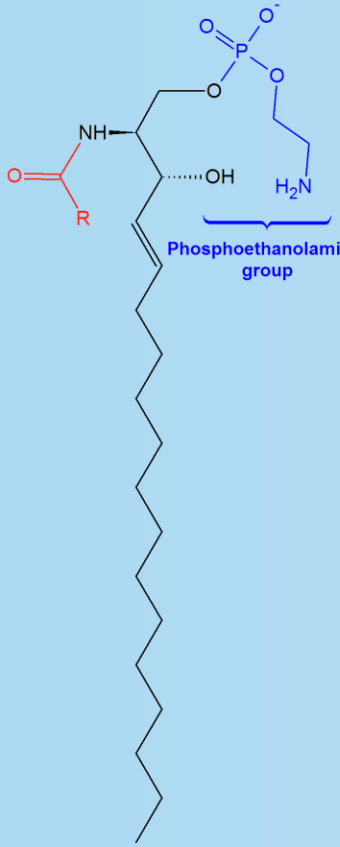
Sphingosine



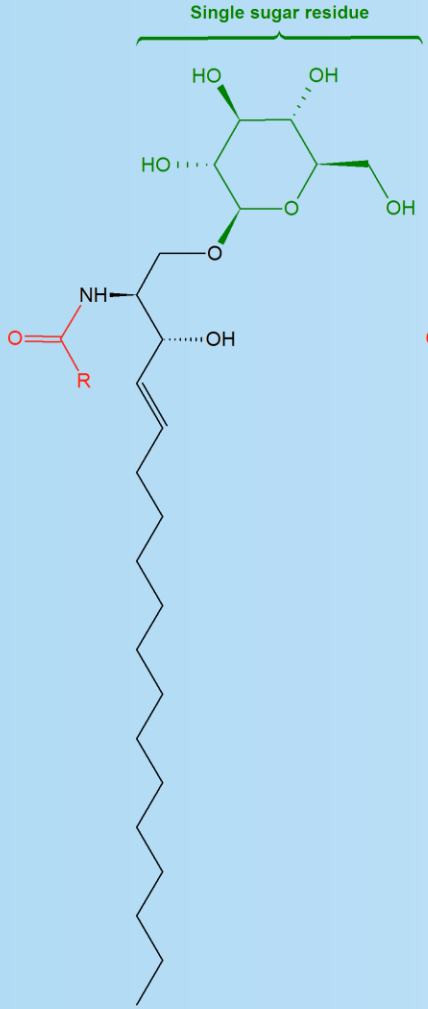
A Ceramide



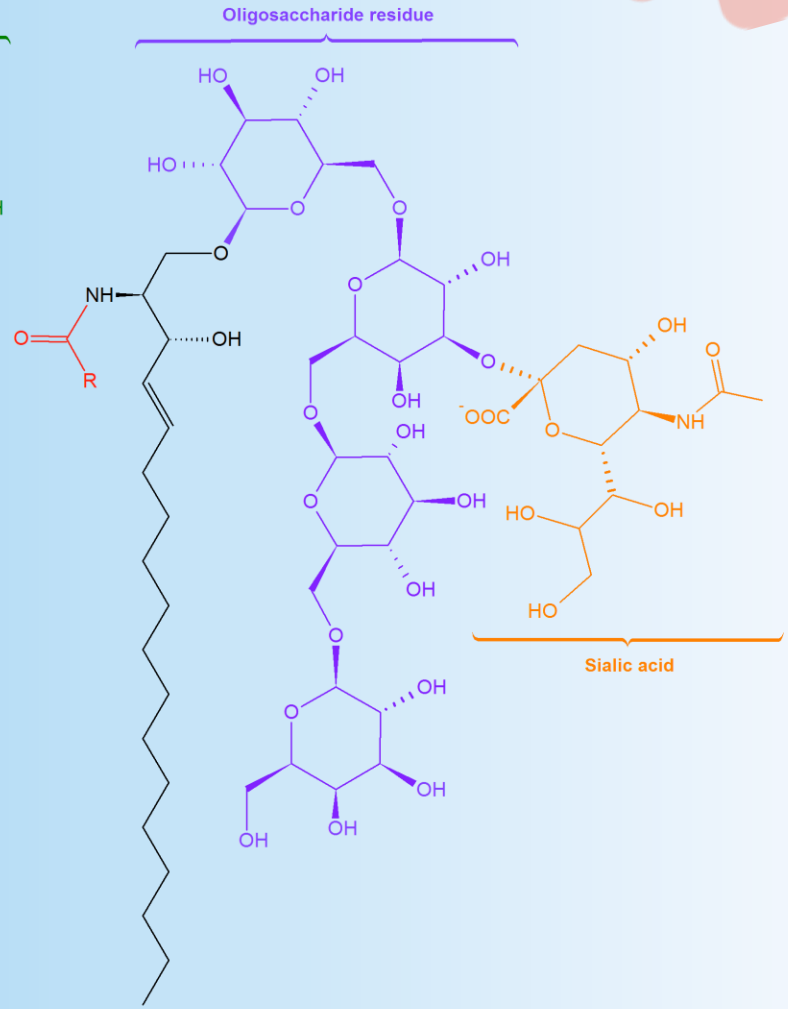
A Sphingomyelin



A Sphingomyelin



A Cerebroside

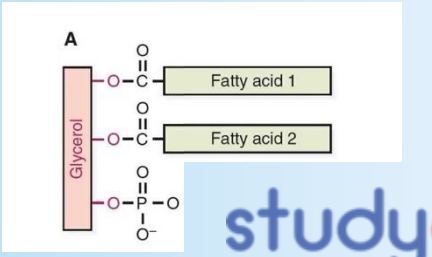


A Ganglioside

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

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

Idyl = glyserol + 2FA



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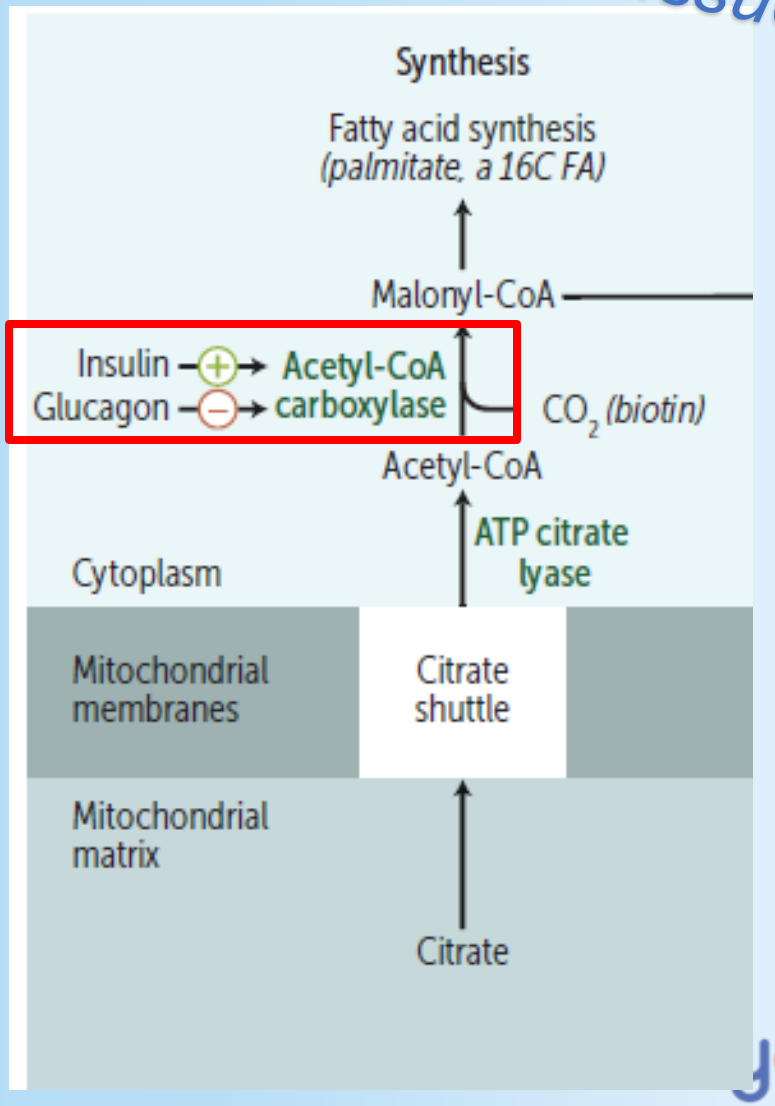
Fatty acid synthesis (de novo)

In cytosol of liver and adipose tissue

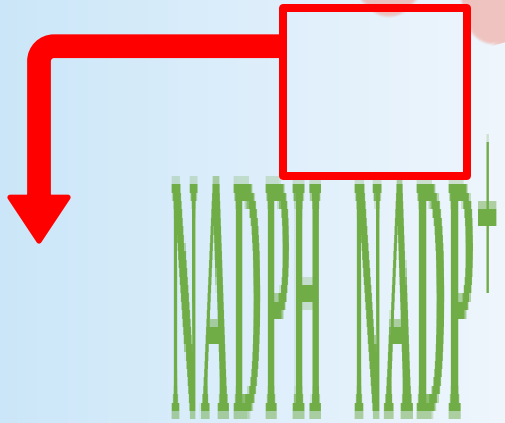
NOTE:

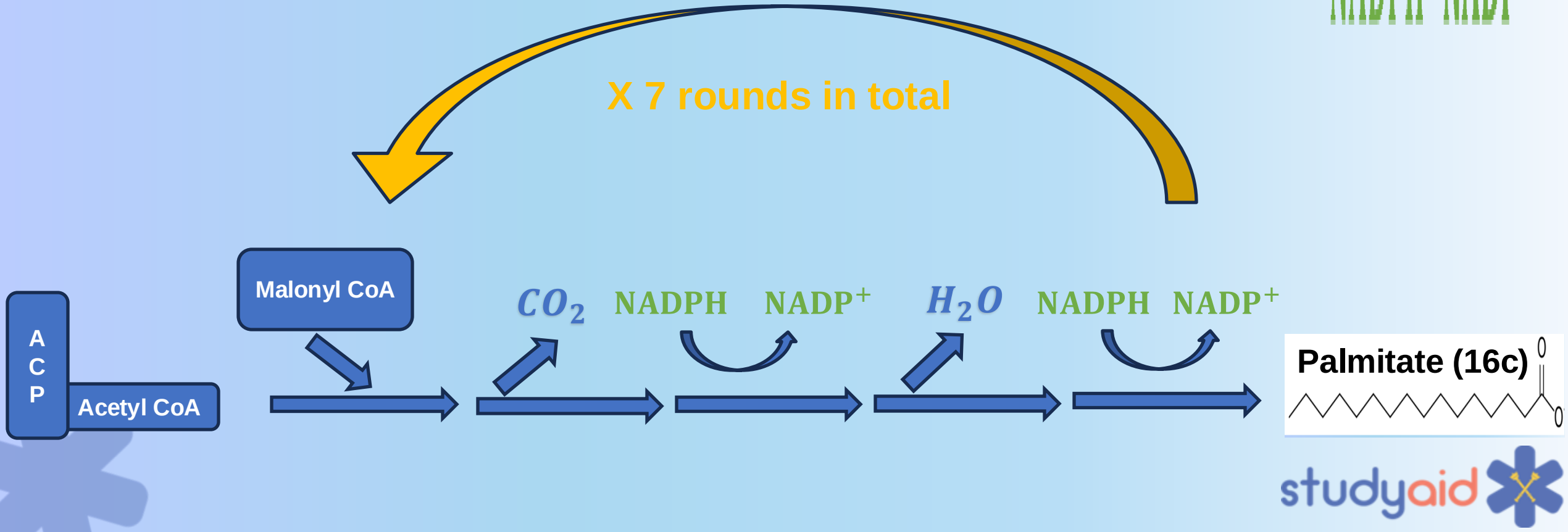
- Citrate shuttle!
- Citrate is an energy marker
- Acetyl-CoA carboxylase = rate limiting step



Fat synthesis (de novo)

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





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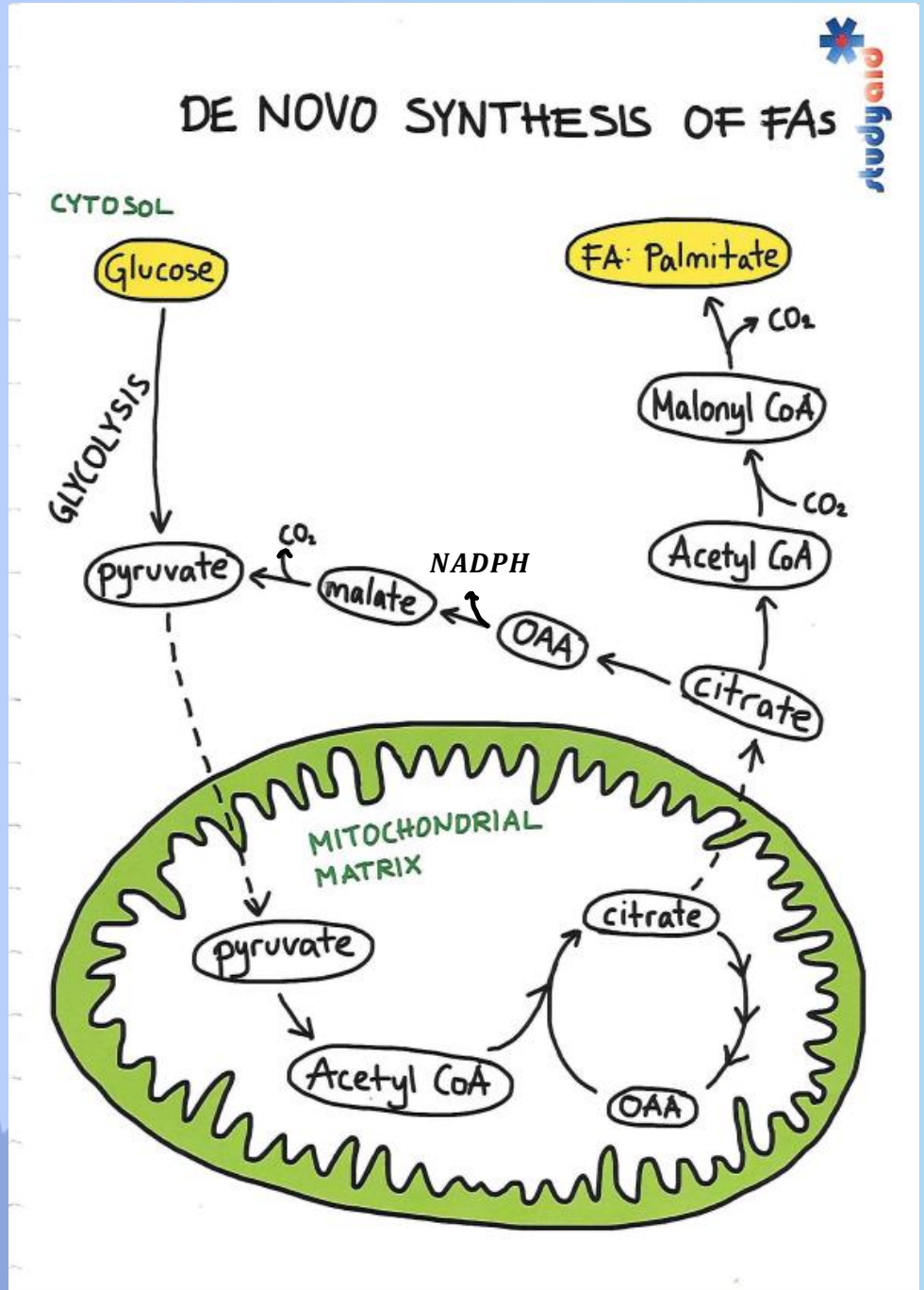
DE NOVO SYNTHESIS OF FAs
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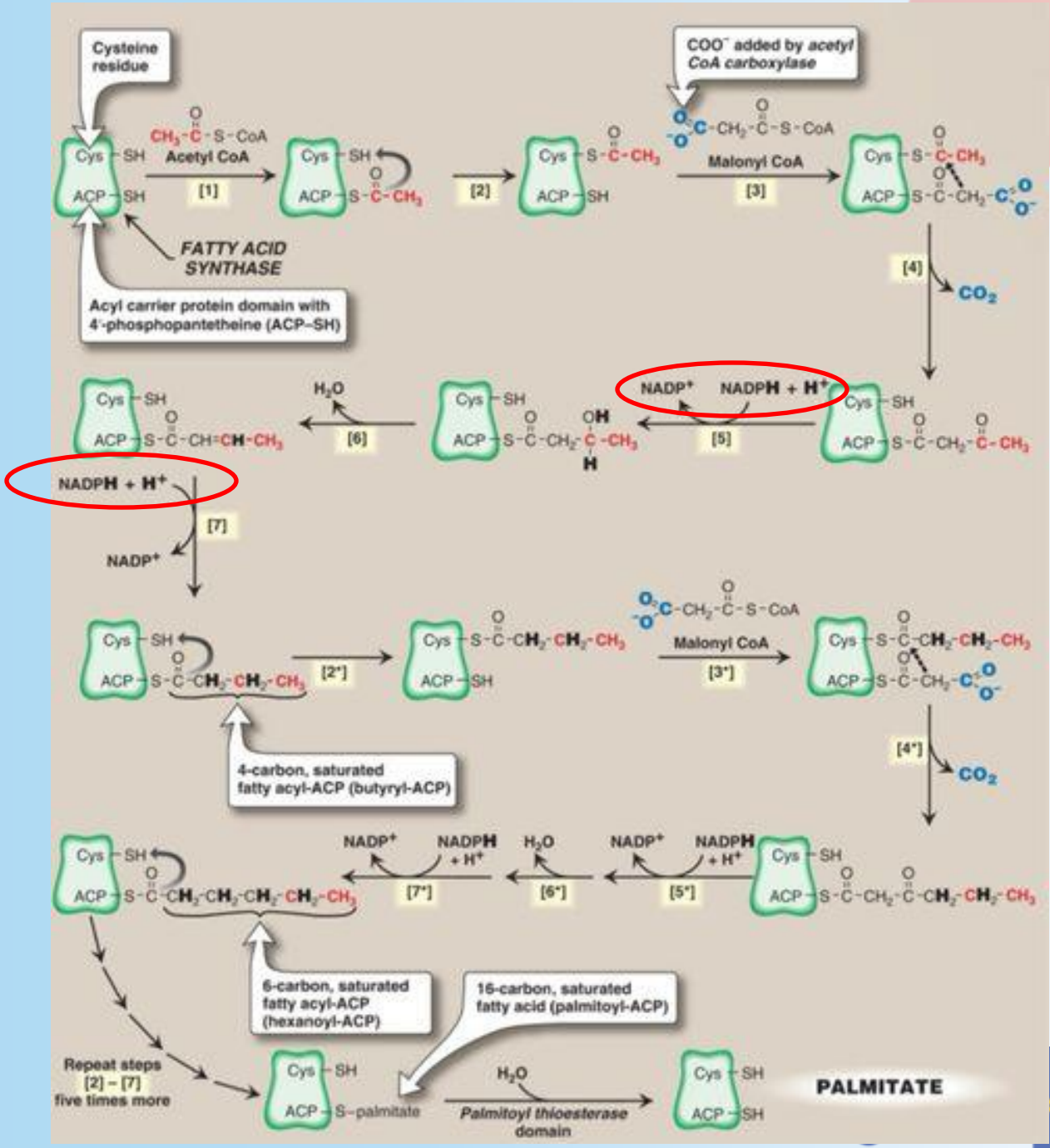
CYTOSOL
Glucose
GLYCOLYSIS
pyruvate
CO₂
malate
NADPH
OAA
citrate
Acetyl CoA
CO₂
Malonyl CoA
CO₂
FA: Palmitate
MITOCHONDRIAL MATRIX
pyruvate
Acetyl CoA
citrate
OAA

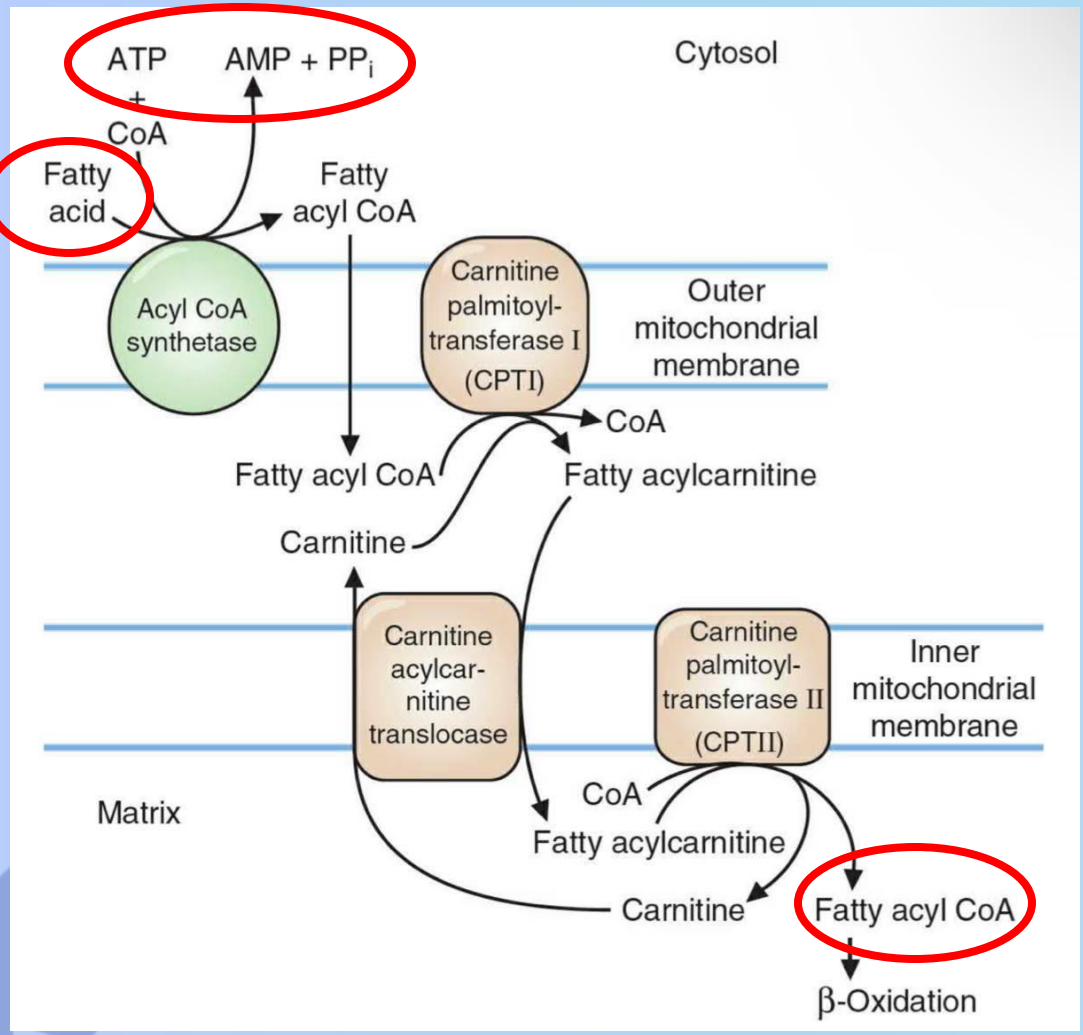

Cysteine residue
Acetyl CoA
[1]
[2]
COO⁻ added by acetyl CoA carboxylase
Malonyl CoA
[3]
[4]
CO₂
FATTY ACID SYNTHASE
Acyl carrier protein domain with 4'-phosphopantetheine (ACP–SH)
NADPH + H⁺
NADP⁺
[5]
H₂O
[6]
NADPH + H⁺
[7]
NADP⁺
[2*]
Malonyl CoA
[3*]
[4*]
CO₂
4-carbon, saturated fatty acyl-ACP (butyryl-ACP)
[5*]
[6*]
[7*]
6-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
16-carbon, saturated fatty acid (palmitoyl-ACP)
Repeat steps [2] – [7] five times more
Palmitoyl thioesterase domain
PALMITATE

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

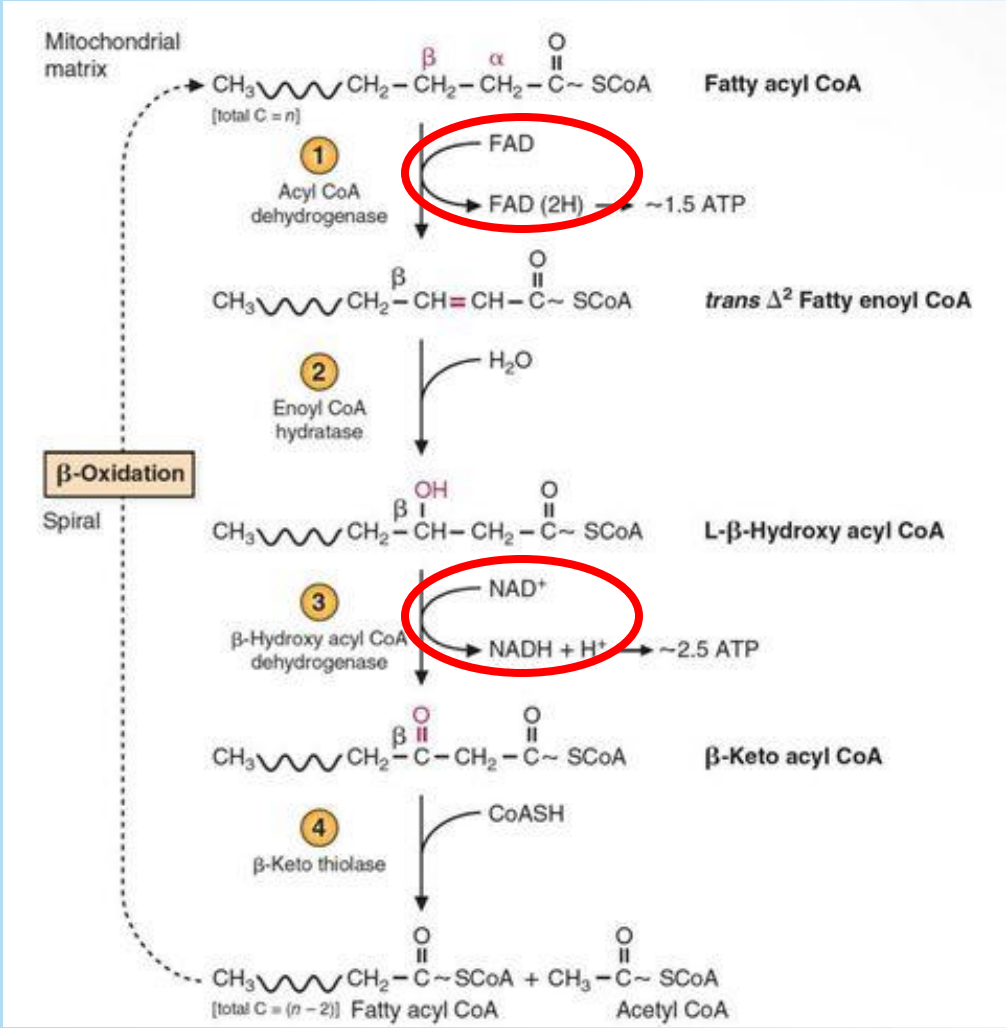
Degreadation of fatty acids

Mitochondria

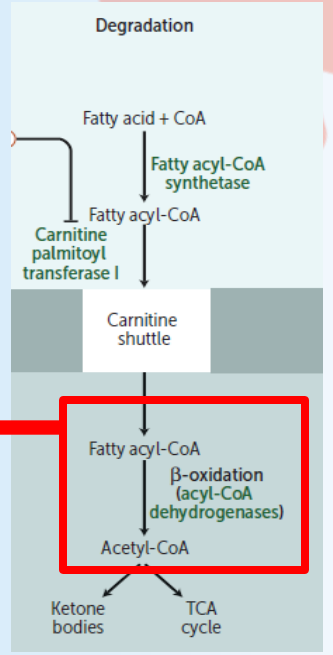
Transfer Fatty acid into mitochondria



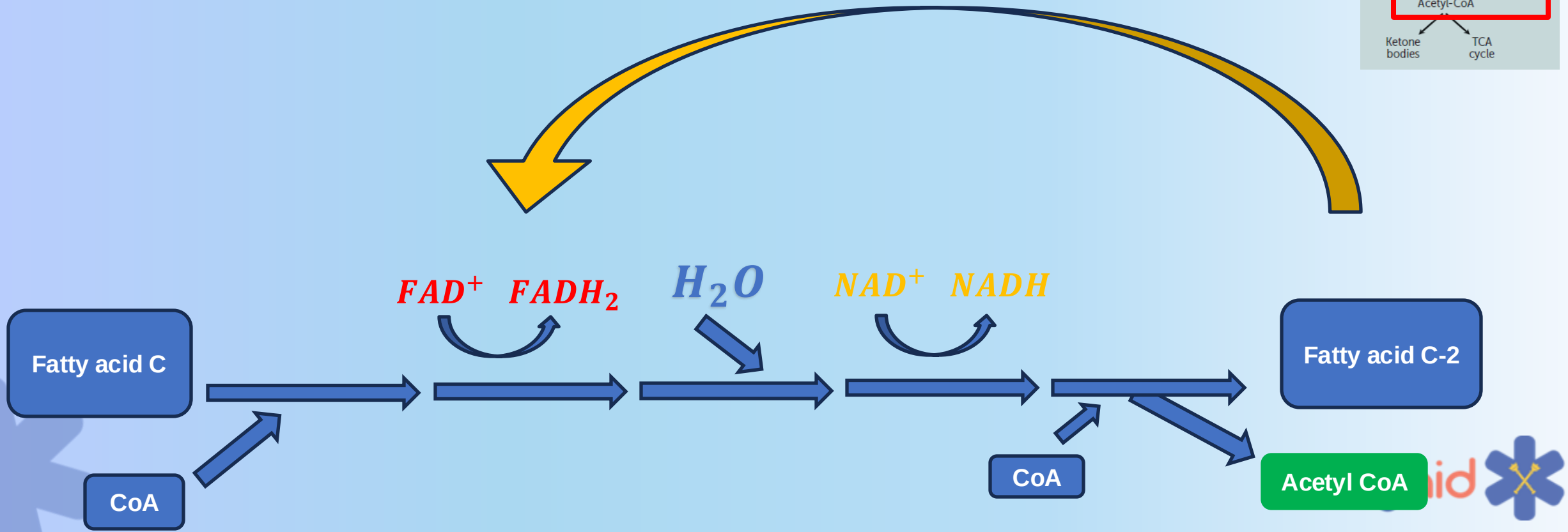
β-oxidation spiral



β-oxidation spiral



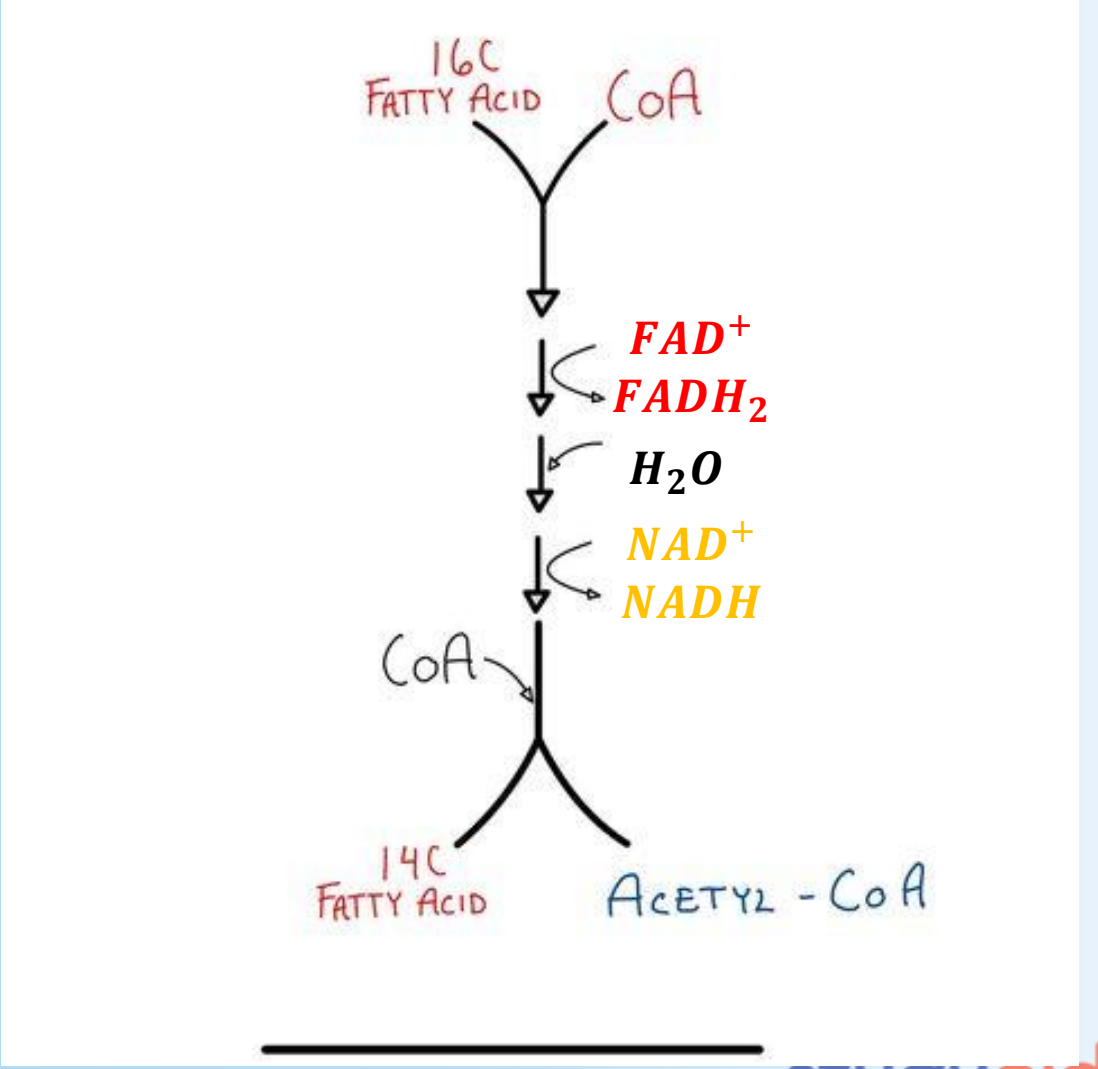
- Oxidate two carbons per round
- Produce 1 $FADH_2$, 1 NADH and 1 Acetyl CoA per round



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

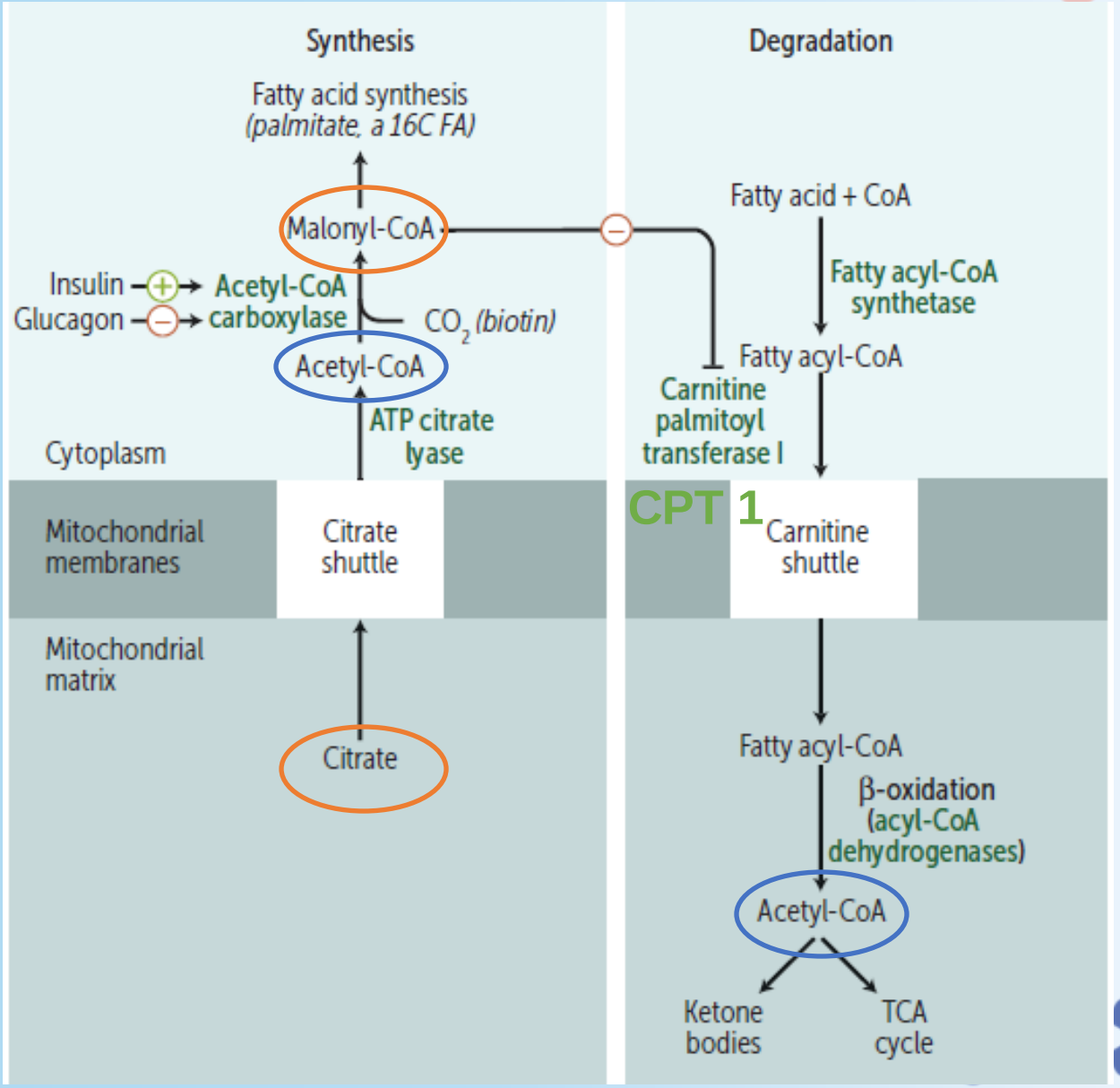
Energy output

- Number of rounds = $\frac{C-2}{2}$
- 16C → 7 rounds of b-oxidation
  - 7 $FADH_2$ → 10,5 ATP
  - 7 $NADH_2$ → 17,5 ATP
  - 8 $Acetyl - CoA$ → 80 ATP
  - → 108 ATP
  - 108 ATP - 2 ATP (for activation)
  - → <u>106 ATP netto</u>



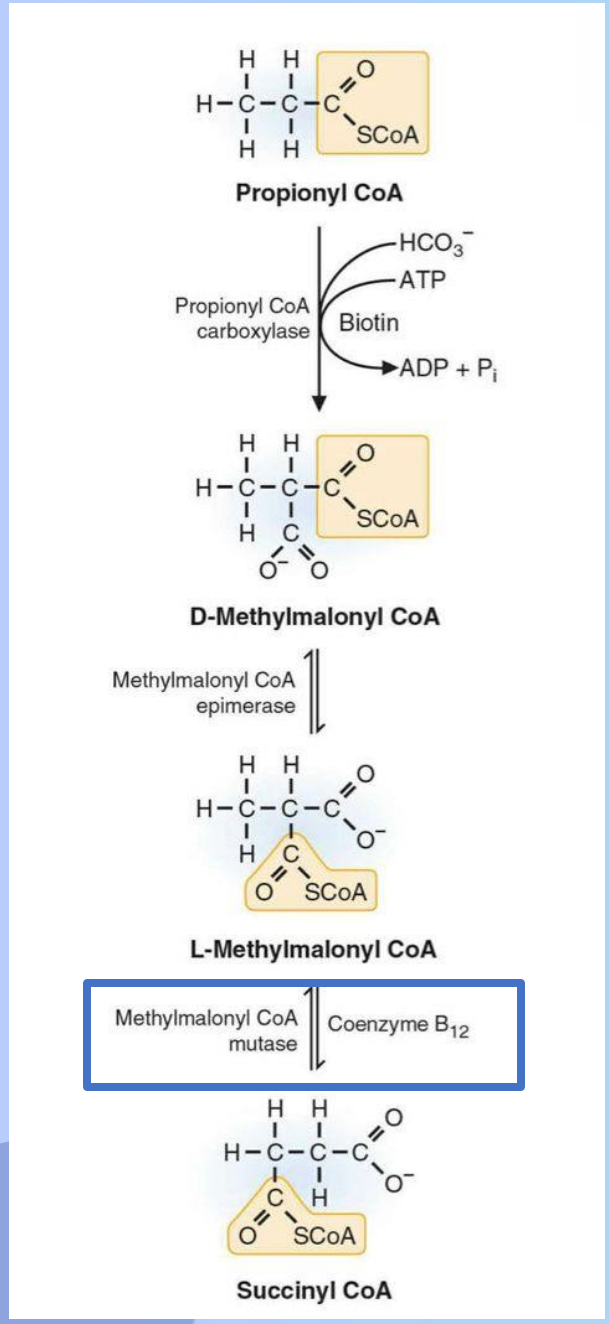
Balace between synthesis and degradation of FA

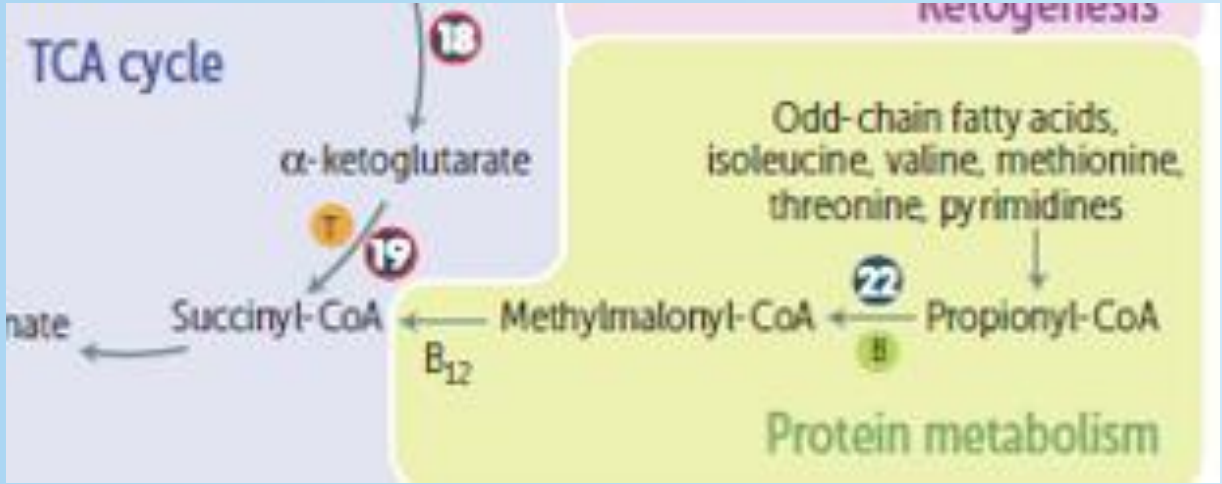
- **Malonyl-CoA** inhibits **CPT1** meaning Fatty Acid synthesis and degradation does not happen simultaneously



What about Odd Chain Fatty Acids?

Mitochondria





- B-oxidation until propionyl CoA (3C)
- Vit B12 deficiency causes buildup of Methylmalonyl-CoA
- End product Succinyl-CoA → TCA cycle

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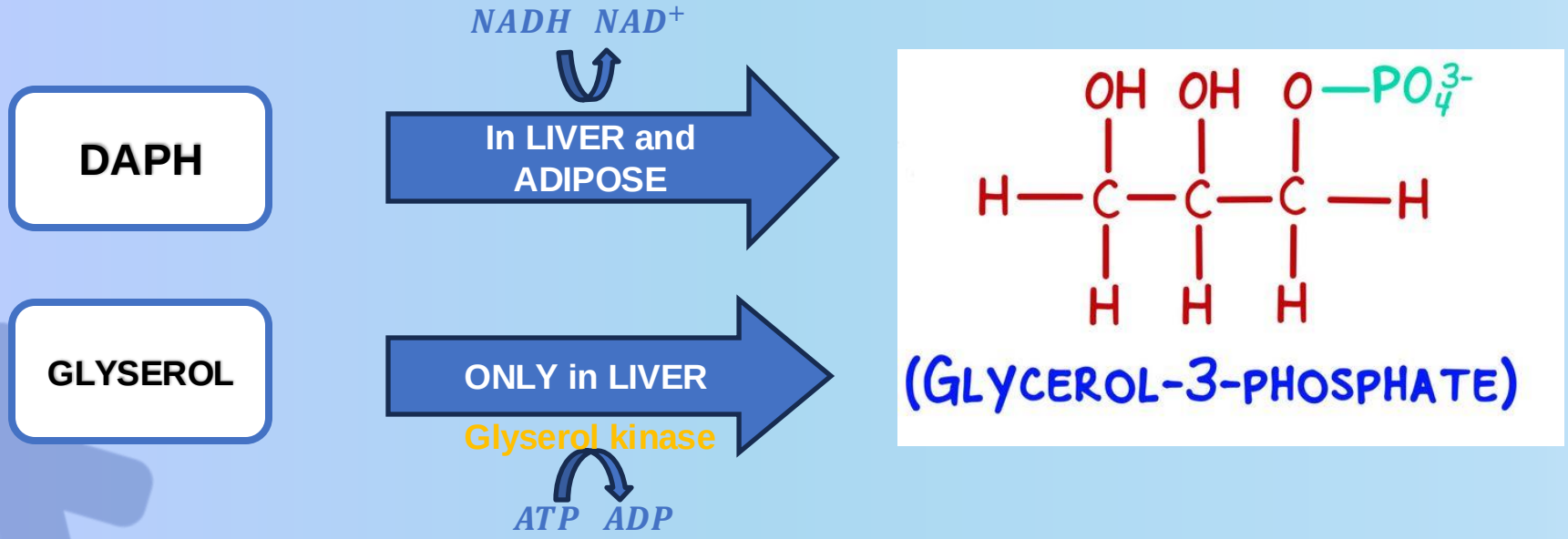
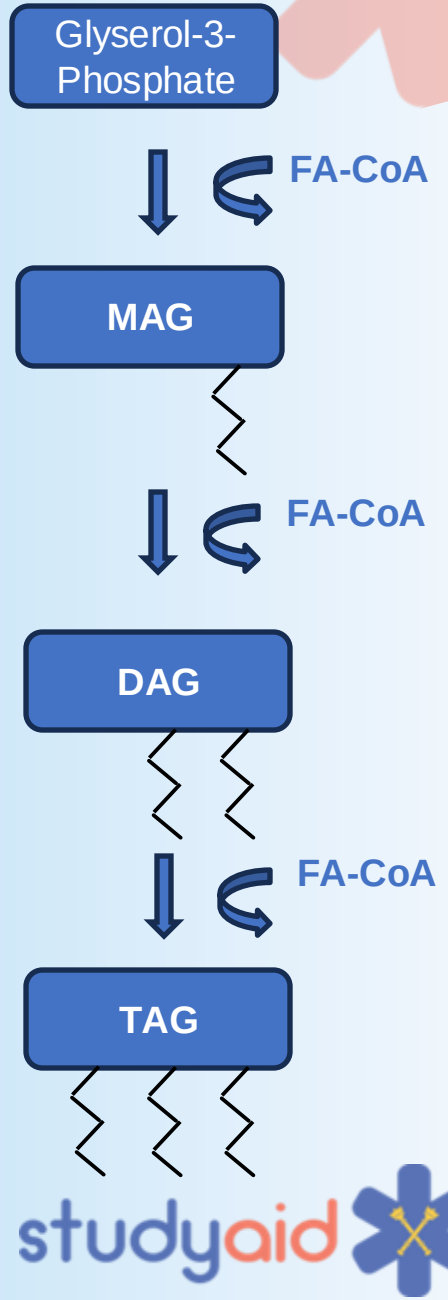
Liver and Adipose ER

TAG synthesis/Lipogenesis

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





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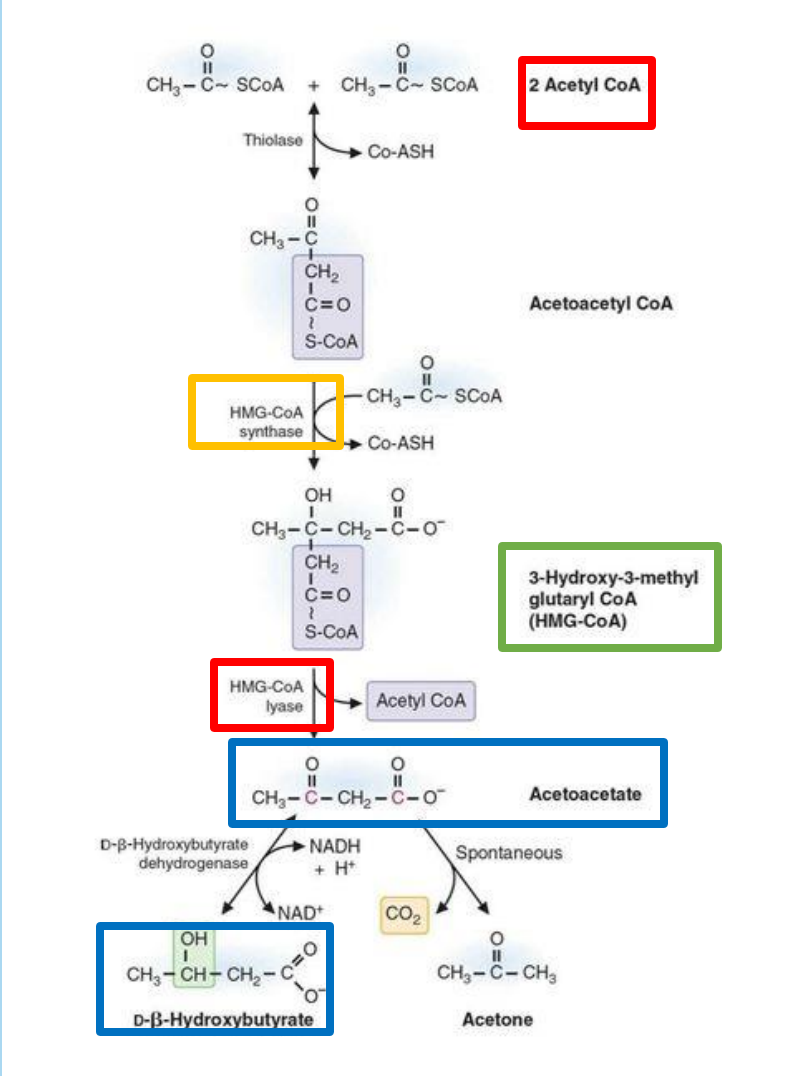
Synthesis of ketone

In liver mitochondria

HMG-CoA synthase = Rate limiting step

HMG-CoA lyase



Acetyl CoA from fatty acid oxidation

HMG-CoA

Ketone bodies

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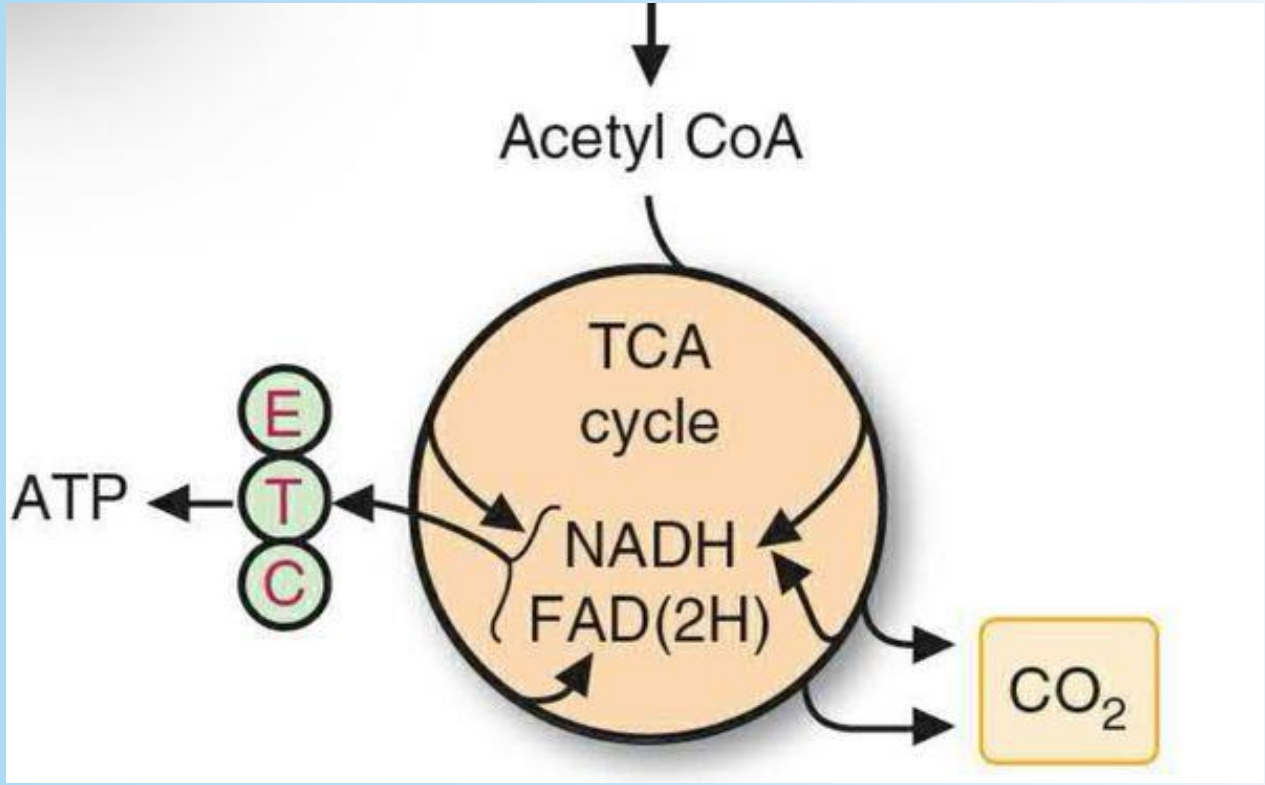
When are Ketones produced?

- 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



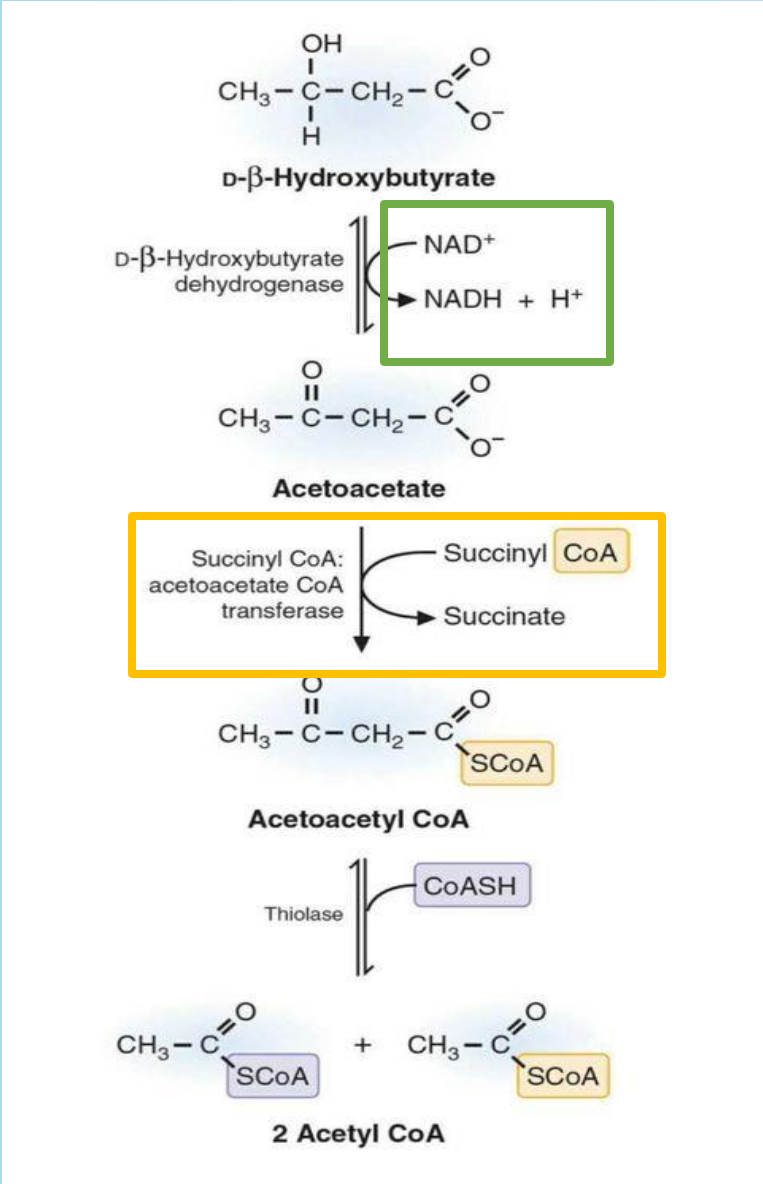
Oxidation of ketones

Broken down in muscle and **brain** → energy

Succinyl CoA: acetoacetate CoA transferase:

ABSENT IN LIVER

Depend on an active TCA cycle to provide succinyl CoA

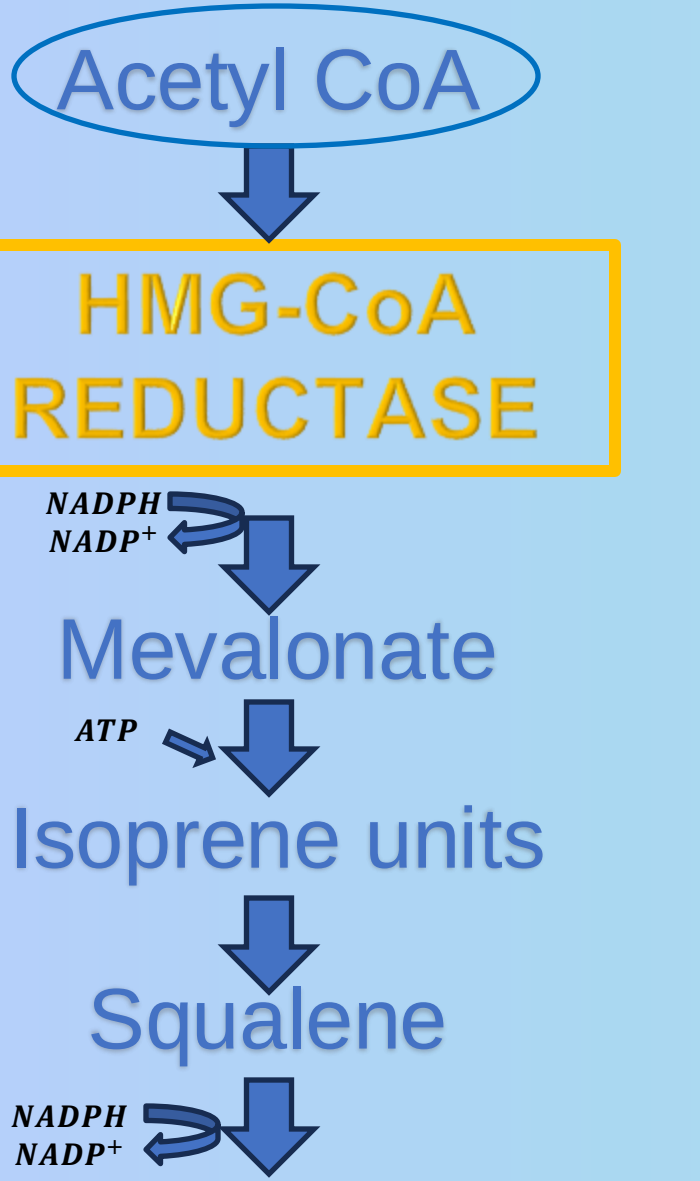


Get more energy (NADH) from *hydroxybutyrate* then from *acetoacetate*

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

Cholesterol synteses

In liver cytocol



- **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

Irriversible prosess!!
Cholesterol can NOT be broken down for energy

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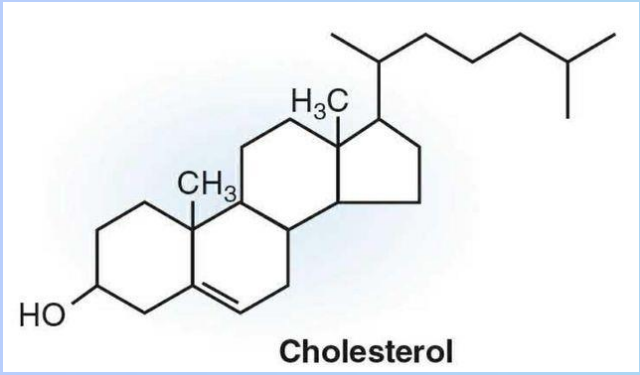
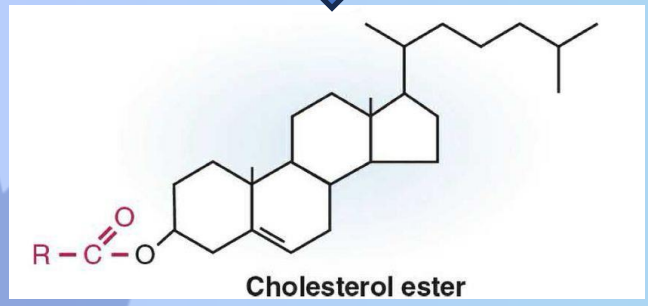
Fates of cholesterol

Made in liver, delivered to tissue by VLDL



Cholesterol

ACAT



Cholesterol ester

In VLDLs

TISSUES

Membrane structure
Production of steroid hormones
Production of vit D

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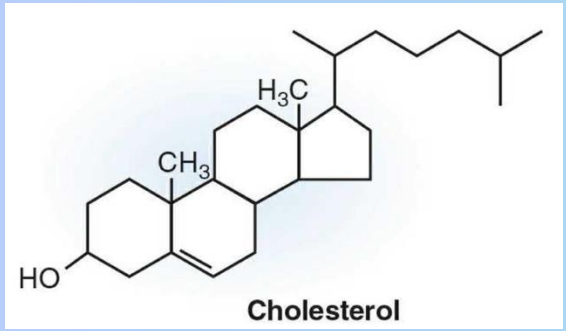
Cholesterol → bile acid/salts

Made in liver, stored in gallbladder

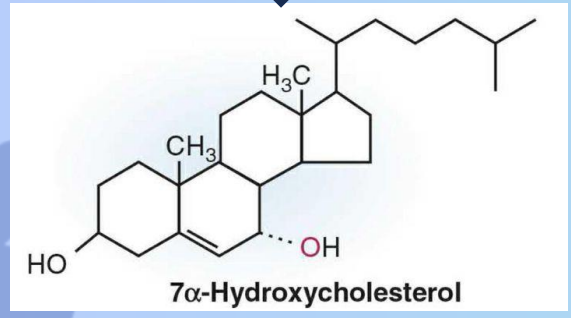


Cholesterol

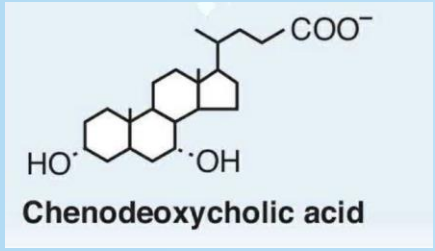
7a-hydroxylase = Rate limiting step

Bile acids inhibit

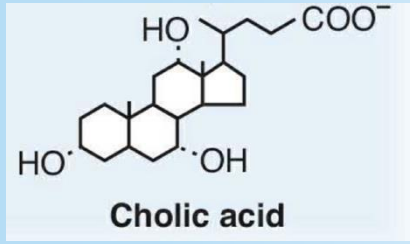
7a-hydroxylase



7α-Hydroxycholesterol



Chenodeoxycholic acid



Cholic acid

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Don’t mix these up!

HMG-CoA **Lyase** = **Ketone** production

HMG-CoA **Reductase** = ***Cholesterol*** synthesis

IMPORTANT

Where are you?

Fasting:

⬇ Insulin *Inhibits enzymes*

⬆ Glugacon Stimulate enzymes

Fed:

⬆ Insulin Stimulate enzymes

⬇ Glugacon *Inhibits enzymes*

What?	Where?	When?
Ketone synthesis	Liver cell 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

Break☺

Outline 2

- Lipoproteins
- Apolipoproteins
- Eicosanoids
- Naming Lipids

What are lipoproteins?

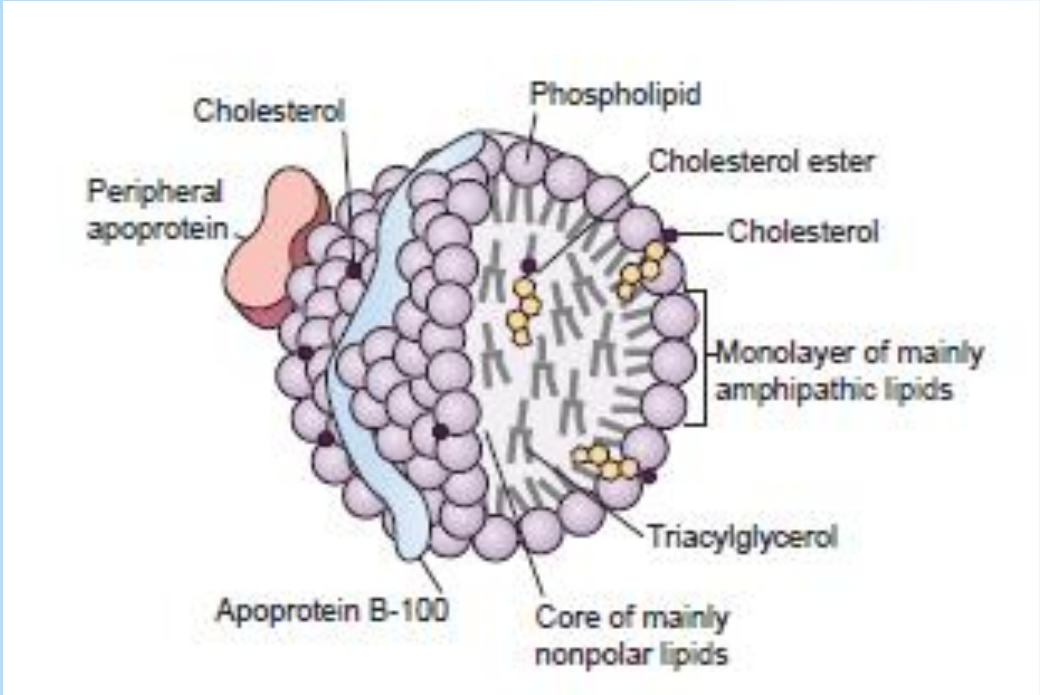
FFA are insoluble in blood → binds to albumin

- Lipoproteins = transporters for hydrophobic lipids in the blood

TAG

Cholesterol

- Chylomicrons
- Very low-density lipoproteins (VLDL)
- Intermediate-density lipoprotein (IDL)
- Low density lipoproteins (LDL)



- High density lipoprotein (HDL) (lowest TAG, high cholesterol) = “good cholesterol”

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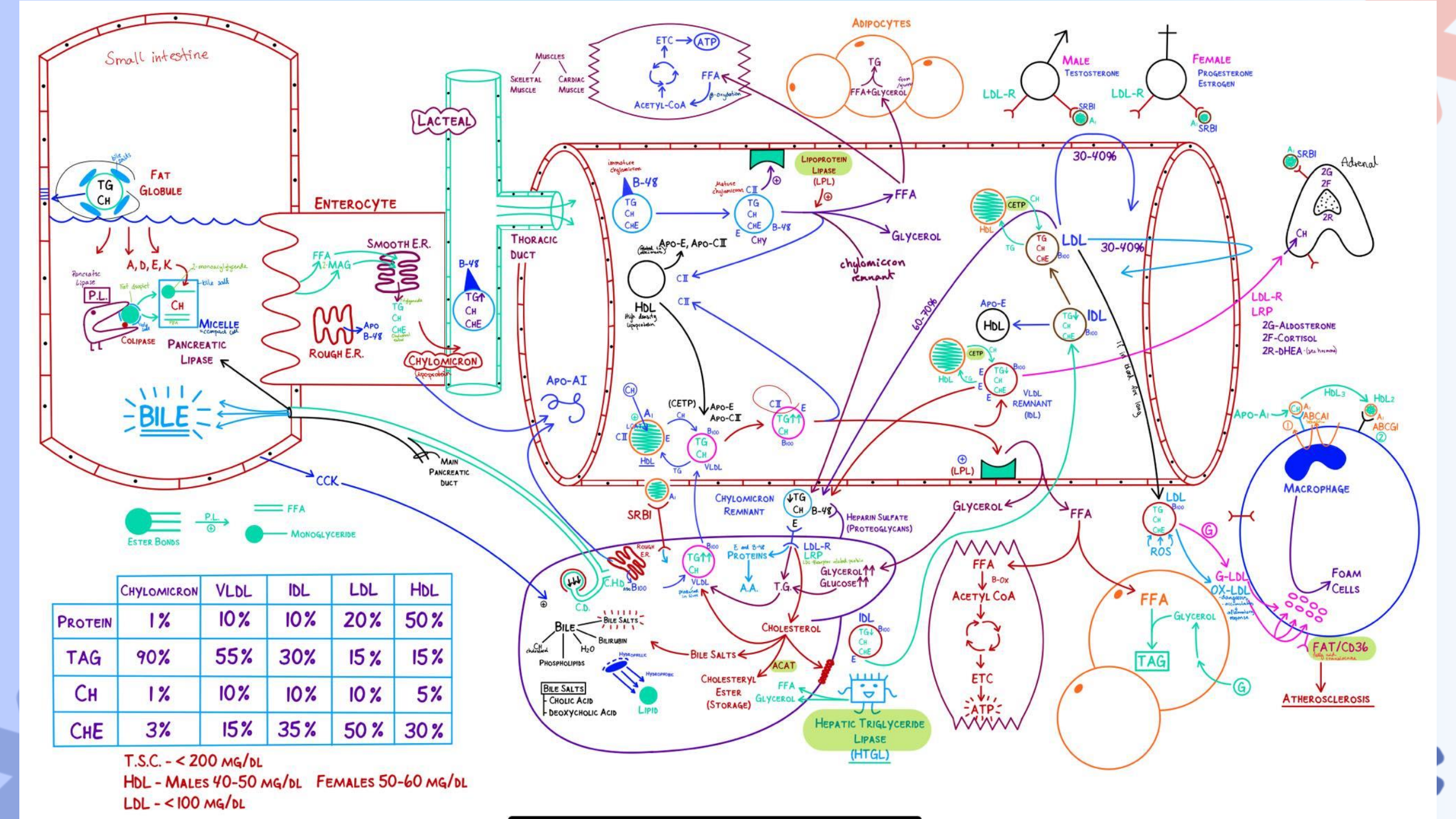

	Chylomicron	VLDL	IDL	LDL	HDL
Protein	1%	10%	10%	20%	50%
TAG	90%	55%	30%	15%	15%
CH	1%	10%	10%	10%	5%
CHE	3%	15%	35%	50%	30%

T.S.C. - < 200 mg/dL
HDL - Males 40-50 mg/dL Females 50-60 mg/dL
LDL - < 100 mg/dL

Fat transport

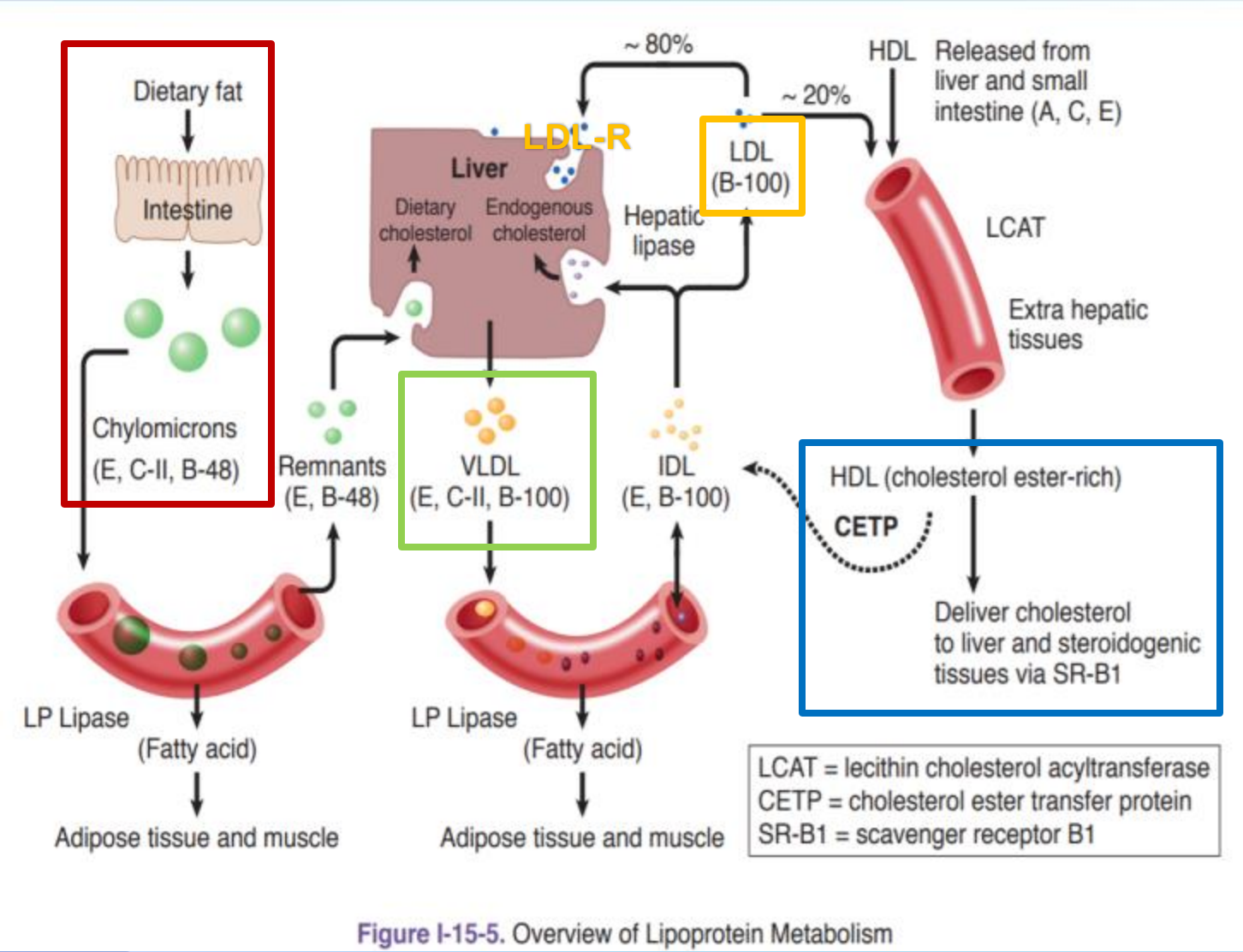

Figure I-15-5. Overview of Lipoprotein Metabolism

Chylomicrons: Bind exogenous dietary fat.
C-II activates LP lipase
B-48 for unique identification
E for entry to liver

VLDL: Newly synthesized endogenous triglycerides from liver to tissues.

LDL: Cholesterol to tissues
B-100 binds LDL receptor

HDL: Cholesterol from tissues to liver

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Apolipoproteins

Only on chylomicrons

Deliverd by HDL

Only on HDL

Apolipoprotein	Function
Apo B-48	«guide» chylomicrons
Apo CII	Activates LPL (TAG → glyserol + FA)
Apo E	Entry into liver
Apo B100	Entry into liver and other tissue (LDL-Receptors)
Apo A1	Activates LCAT (Ch →ChE)

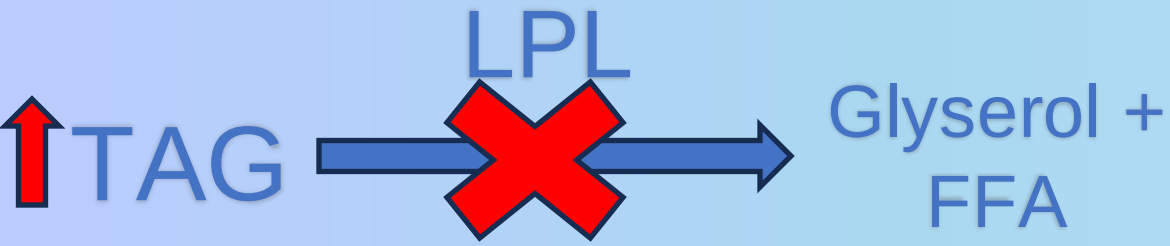
Table I-15-1. Classes of Lipoproteins and Important Apoproteins

Lipoprotein	Functions	Apoproteins	Functions
Chylomicrons	Transport dietary triglyceride and cholesterol from intestine to tissues	apoB-48 apoC-II apoE	Secreted by intestine Activates lipoprotein lipase Uptake of remnants by the liver
VLDL	Transports triglyceride from liver to tissues	apoB-100 apoC-II apoE	Secreted by liver Activates lipoprotein lipase Uptake of remnants (IDL) by liver
IDL (VLDL remnants)	Picks up cholesterol from HDL to become LDL Picked up by liver	apoE apoB-100	Uptake by liver
LDL	Delivers cholesterol into cells	apoB-100	Uptake by liver and other tissues via LDL receptor (apoB-100 receptor)
HDL	Picks up cholesterol accumulating in blood vessels Delivers cholesterol to liver and steroidogenic tissues via scavenger receptor (SR-B1) Shuttles apoC-II and apoE in blood	apoA-1	Activates lecithin cholesterol acyltransferase (LCAT) to produce cholesterol esters

Diseases

- **Type 1 hyperlipoproteinemia**

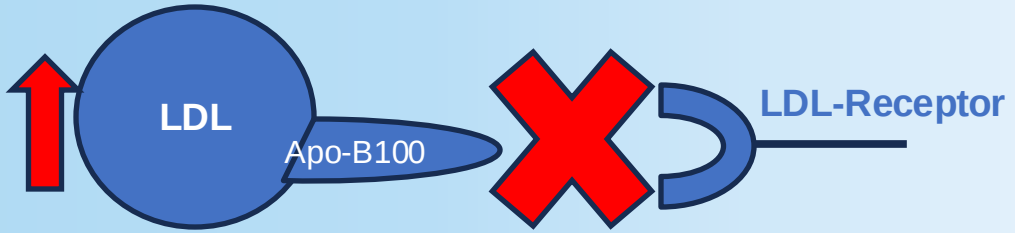
Mutation of apoCII (activates LPL)



→ Increased TAG in serum

- **Familial hypercholesteremia**

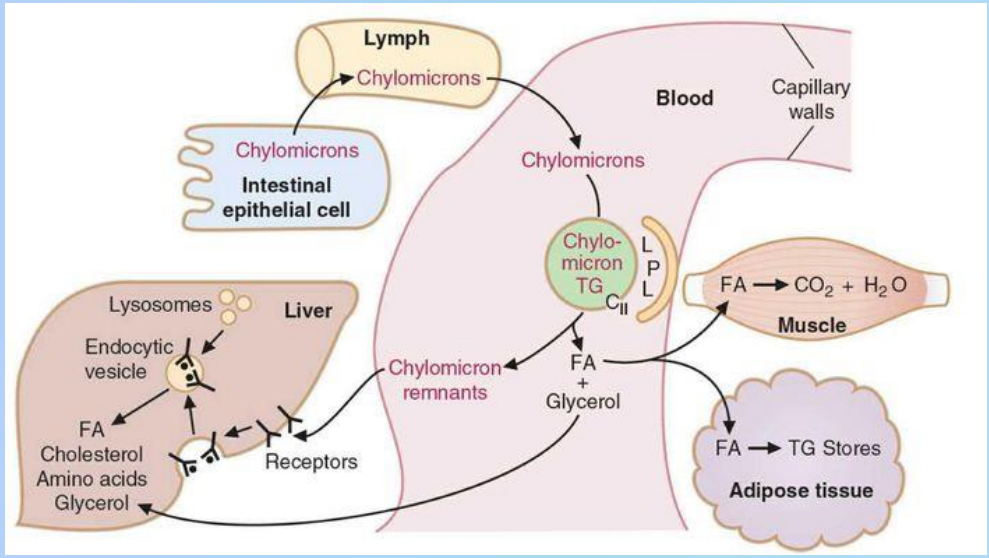
Mutation of LDL-receptor

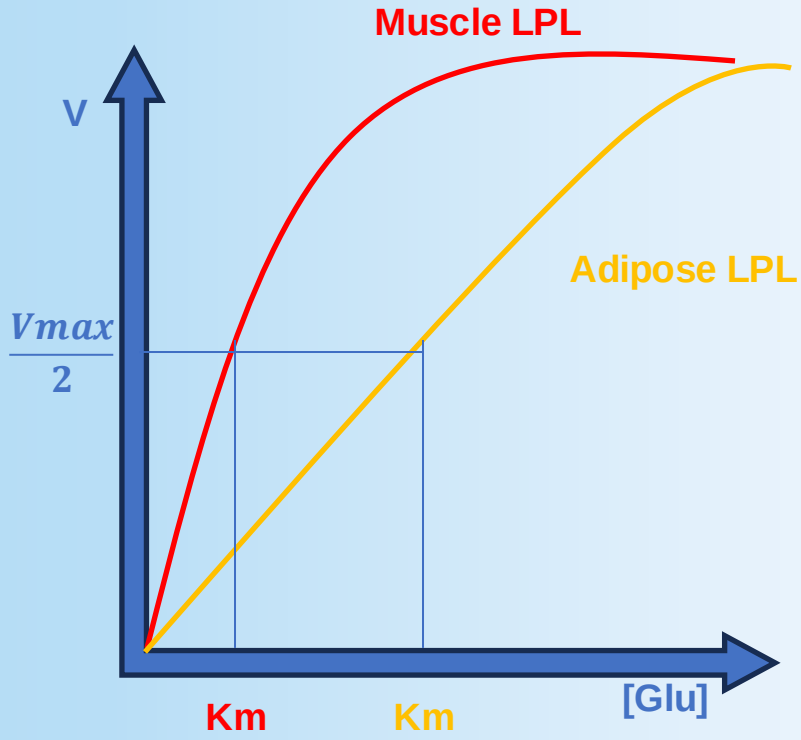


→ increased LDL in serum

Lipoprotein lipase (LPL)

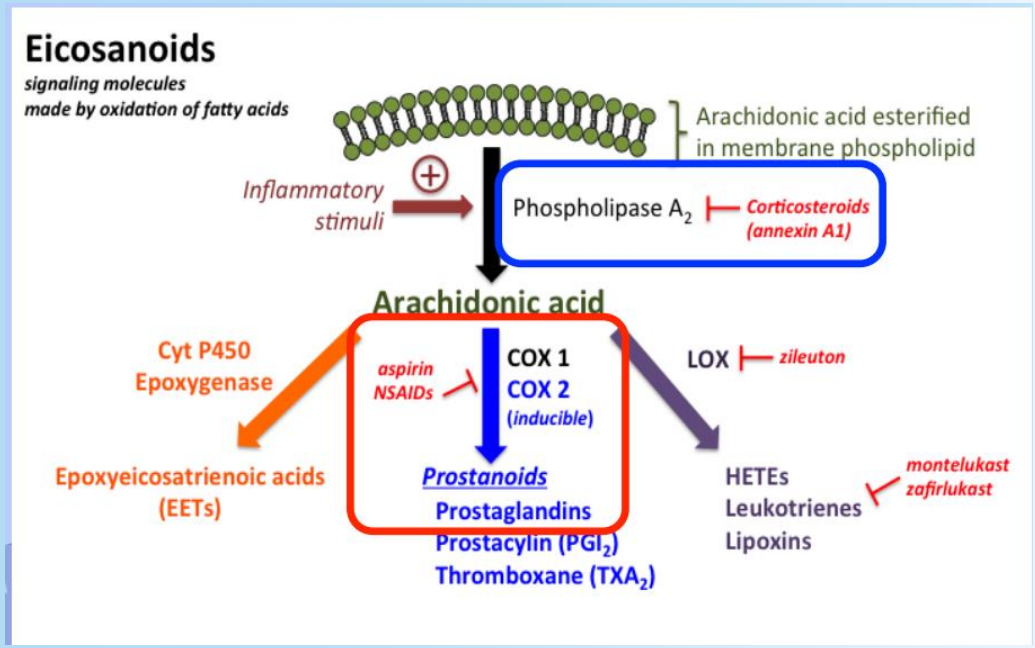
- On capillary endothelial cells, OUTSIDE adipose and muscle cells
- TAG → glyserol + 3FFA
  - Chylomicrones → chylomicrone remnent
  - VLDL → IDL
- Adipose LPL has **HIGHER** Km than muscle LPL
- Insulin stimulate **ONLY** adipose LPL





Eicosanoids

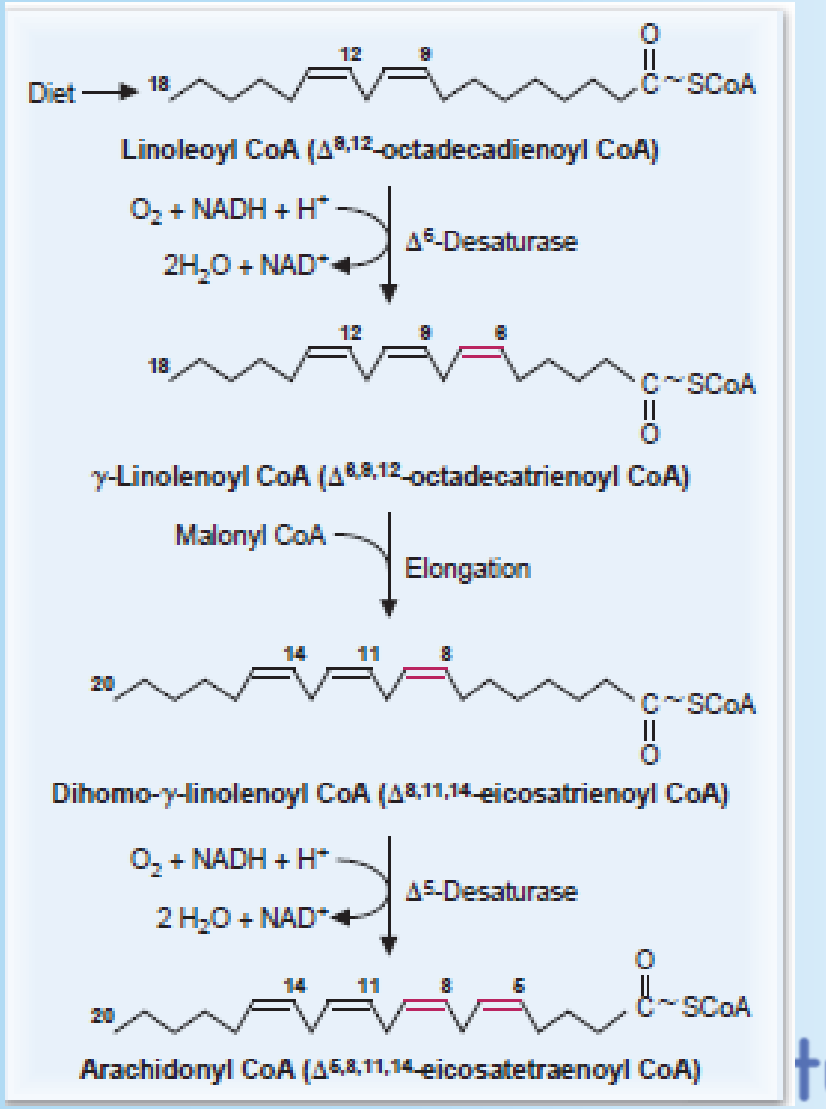
- 20 carbon FA
- Prostaglandins, thromboxanes, and leukotrienes
- Cell signaling
- Inflammatory response
- **Precursor = Arachidonic acid**



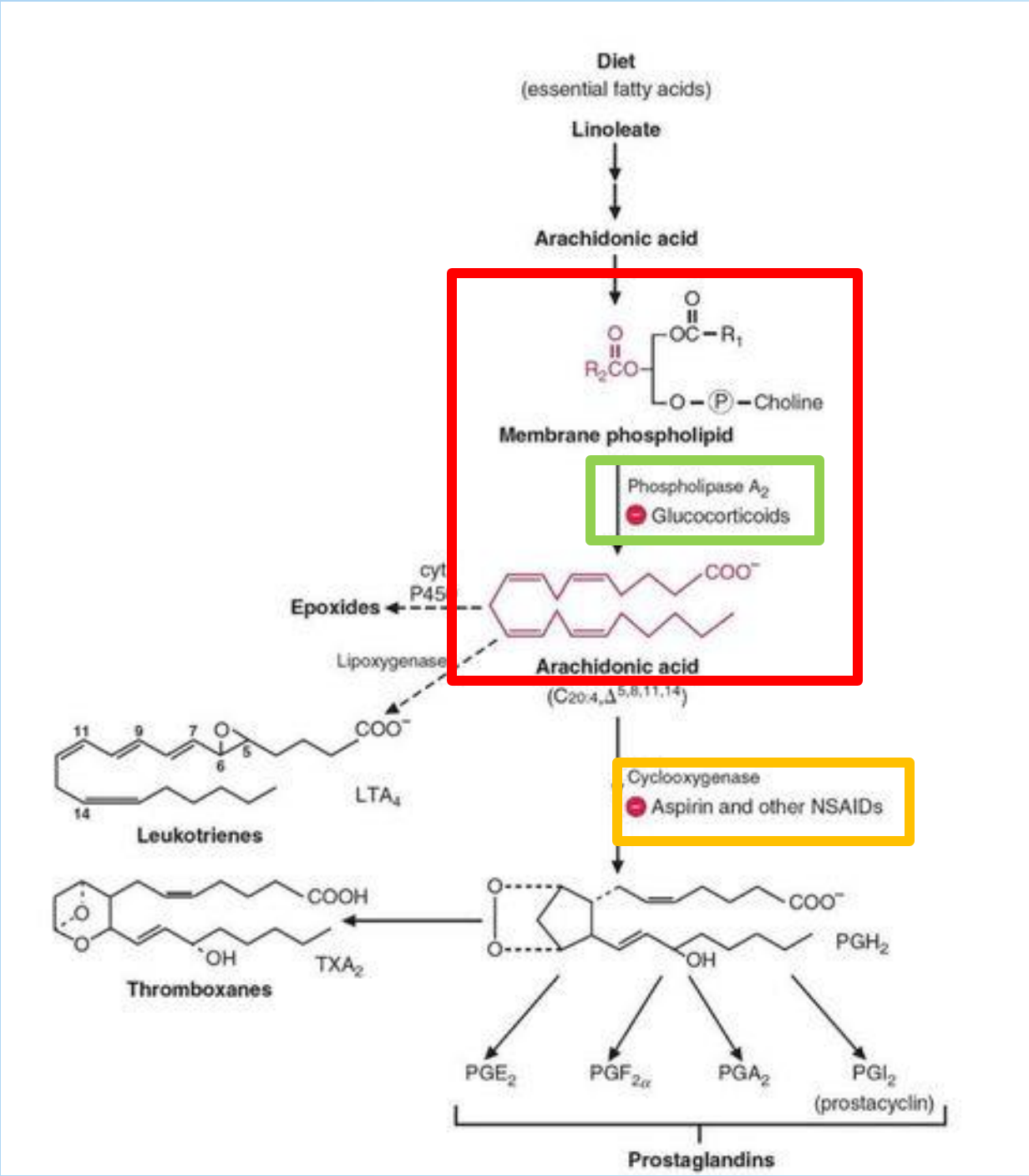
Where does Arachidonic Acid come from?

- Elongation + Desaturation of Linoleic acid leads to Arachidonic Acid production

- **Linoleic acid comes from diet!!**



Membrane phospholipid is cleaved by **Phospholipase A_2** to extract **Arachidonic acid**



Steroids inhibit all products (LT, TX, PG)

NSAIDs only inhibit PG and TX formation

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Naming fatty acids

Number of double bonds

20:4 ω 6

Starting carbon of double bonds

Number of carbons

Δ5,8,11,14

Number of double bonds and their location

Start counting C from CH_3 end

Arachidonic acid

Start counting C from COO^- end

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