Lipid Metabolism

By Filip Sadurski 5/6MD

Outline

- Preliminary Info
- Lipid Synthesis
- Lipid b-oxidation
- Ketones & Cholesterol
- Lipid Transport
- Eicosanoids + Structures

Preliminary

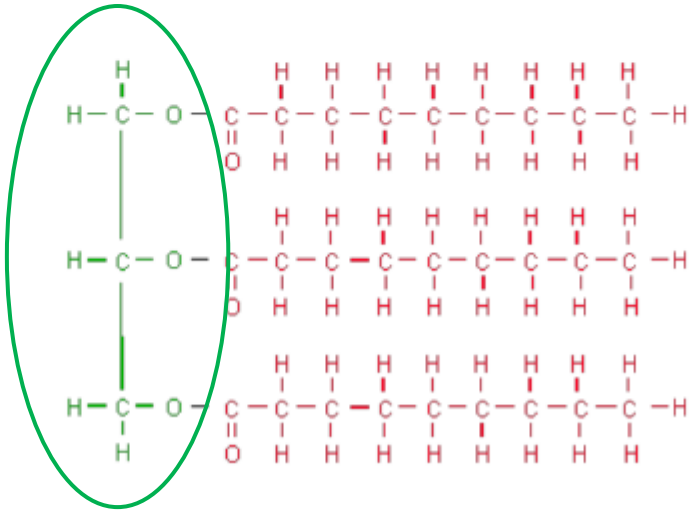
Types of Lipids:
- Triglycerides
  - Fatty Acids
  - Glycerol
- Cholesterol
- Cholesteryl esters
- Phospholipids
- Unestrified FA
- Sphingolipids

Uses of Lipids
- Energy reserve
- Cell membrane components
- Fat-soluble vitamins
- Prostaglandins
- Steroid hormones

Increased chain length: decreased solubility & increased melting temperature

Increased number of double bonds (decreased saturation): increased solubility & decreased melting temperature

TRIGLYCERIDE/TRIAGLYCEROL



- Fats are not soluble in water (hydrophobic)
- Glycerol Backbone

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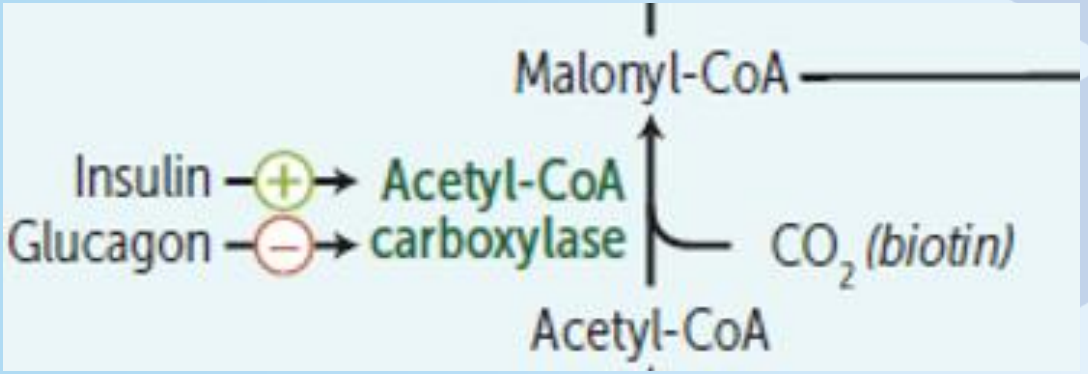
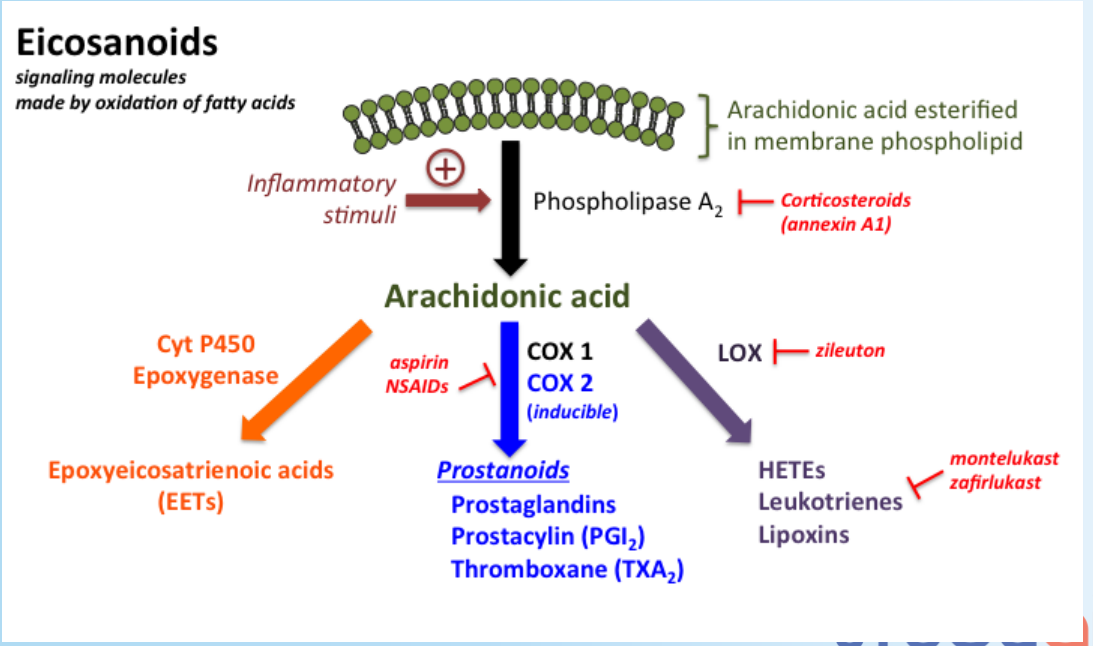
What to look for when studying biochemical pathways

1) Enzymes (+ Possible Cofactors)

2) Rate limiting steps (Usually Require ATP)

3) Pharmacological tie-in [Effects of Insulin and Glucagon]

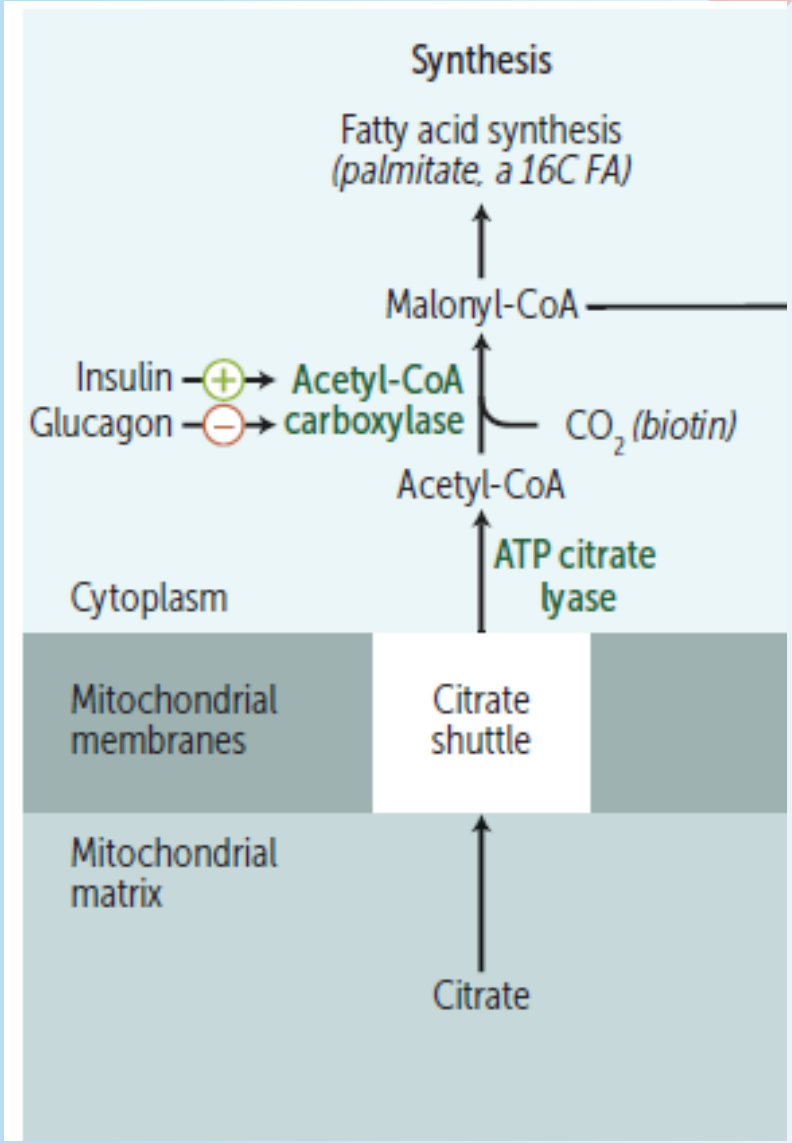




Fat synthesis

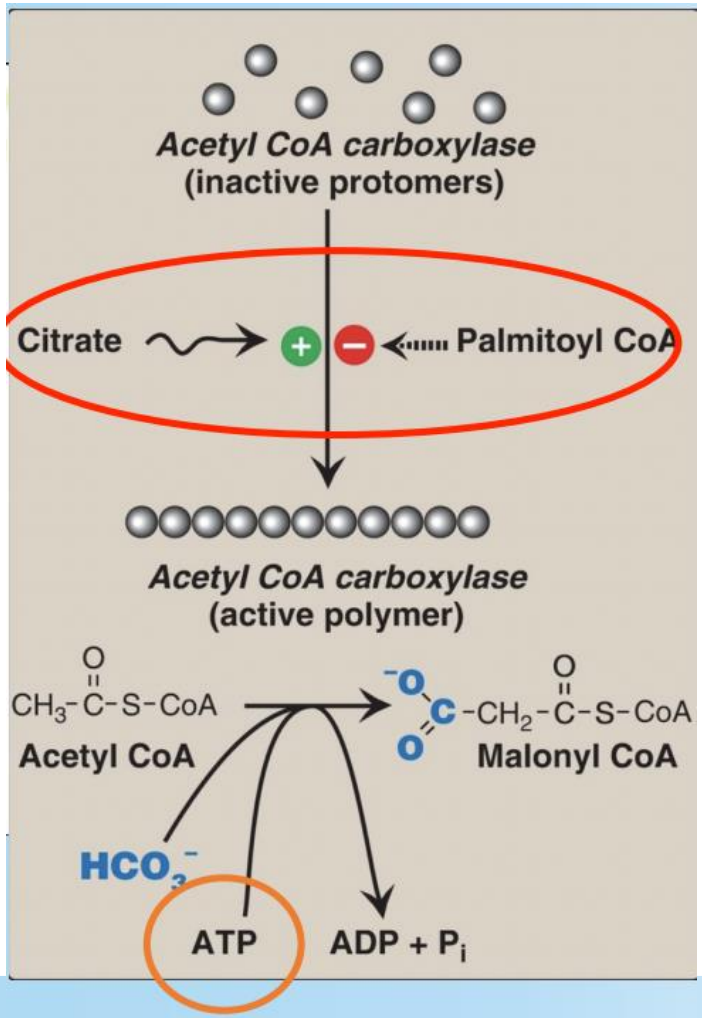
NOTE:

- Citrate shuttle!
- Citrate is an energy marker
- Fatty Acids NOT used by:
  - RBC's: Glycolysis only (no mitochondria for ß-oxidation of FA's
  - Brain: Glucose & Ketones only!
- Predominantly occurs in Liver and Adipose Tissue



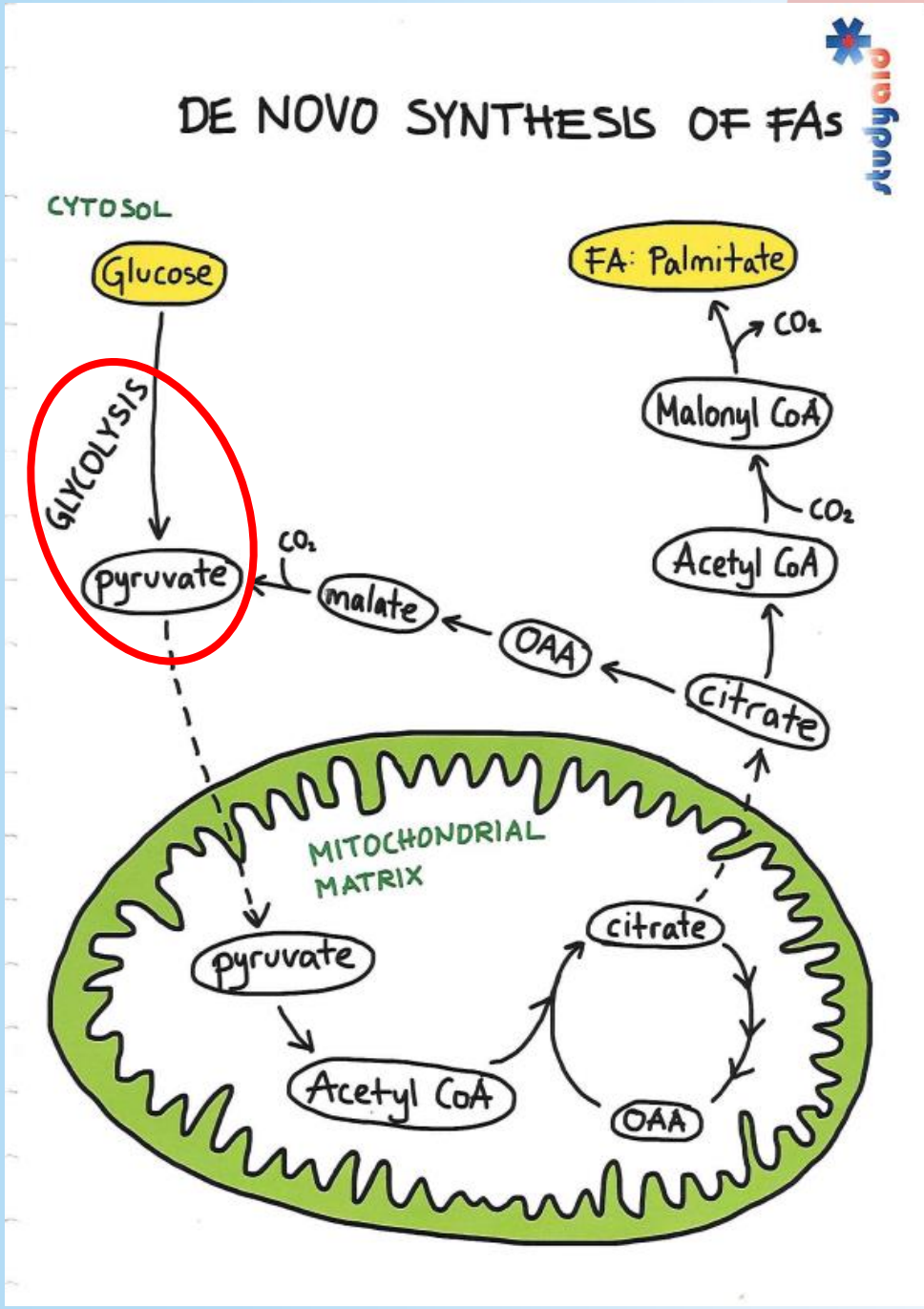
Acetyl CoA carboxylase is the rate limiting enzyme

The rate limiting step is the conversion of Acetyl-CoA to Malonyl-CoA



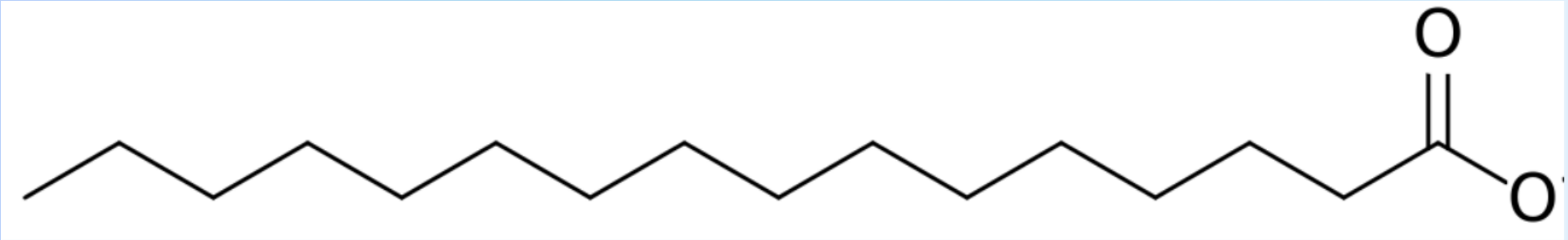
How to Move Acetyl-CoA?

- Well-Fed state = Influx of Insulin = More Glycolysis = More citrate!
- If cell's energy needs are met (enough ATP and NADH) then citrate accumulates
- Oxaloacetate recycled back into mitochondria through malate shuttle



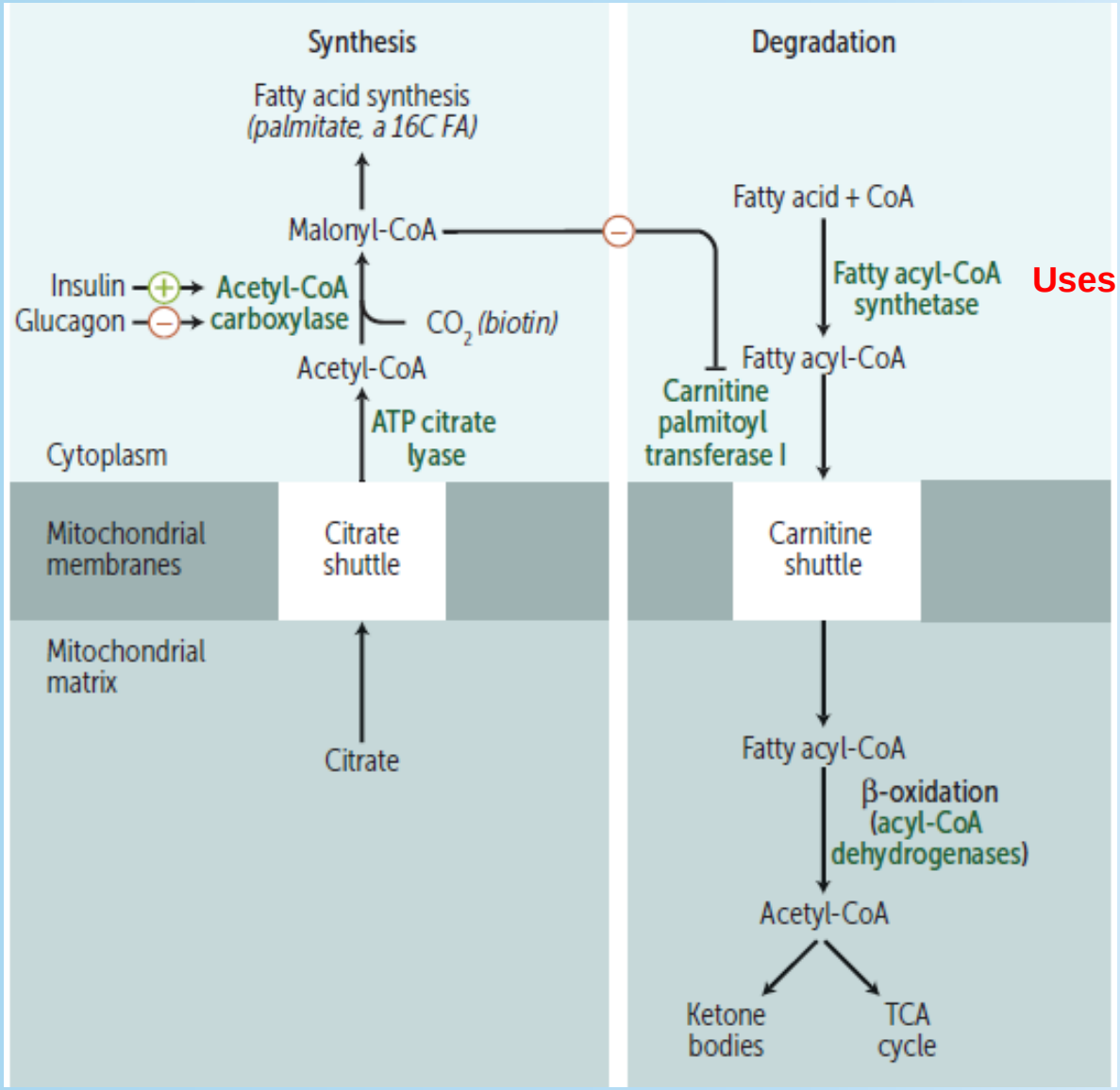
Palmitate (16c)

- **NADPH** is used for final step of Reducing *Malonyl-CoA* to *Palmitate*



Fatty acid degradation

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



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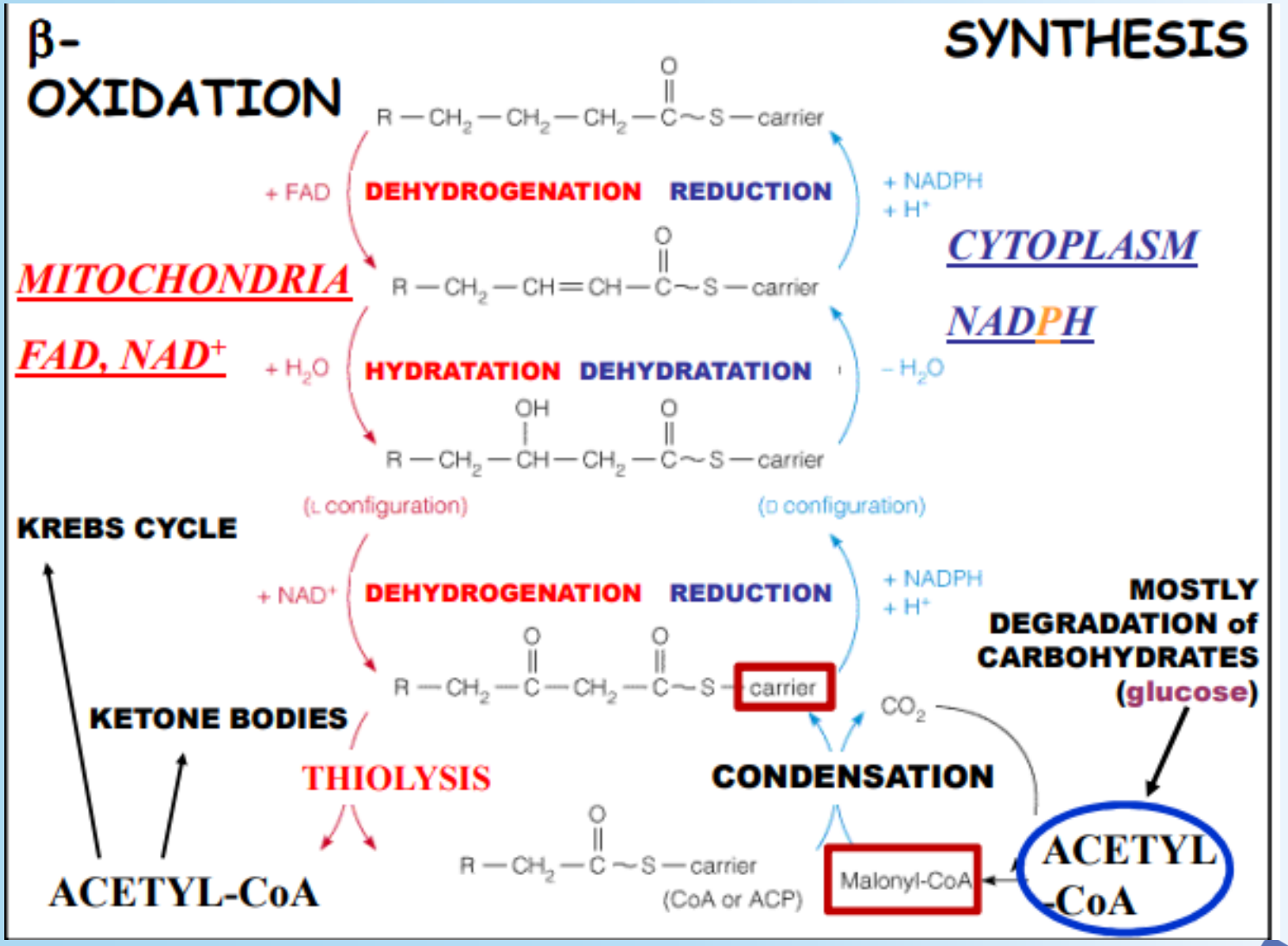
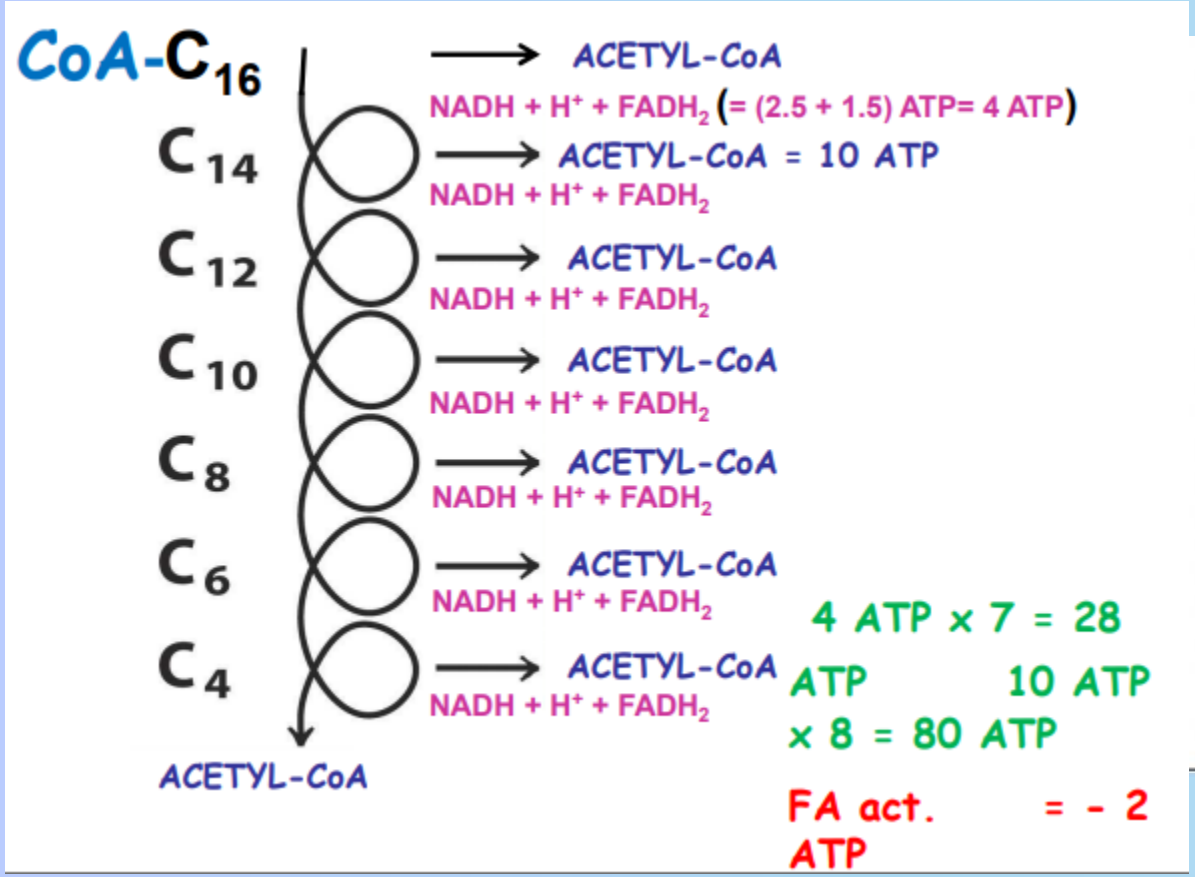
β-oxidation of FA's

- VLCFA (>20 carbons) B-Oxidation in peroxisomes
- Different Acyl CoA Dehydrogenases for different lengths! (ex. Medium-chain acyl-CoA dehydrogenase)

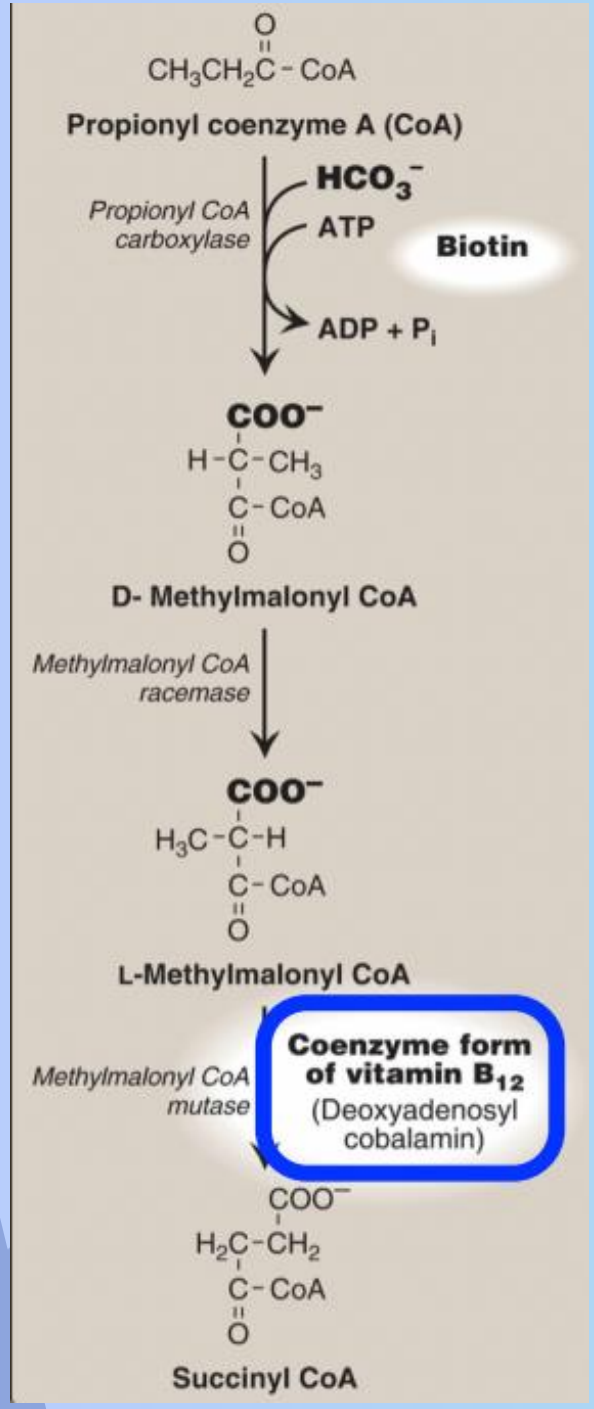


Energy Output

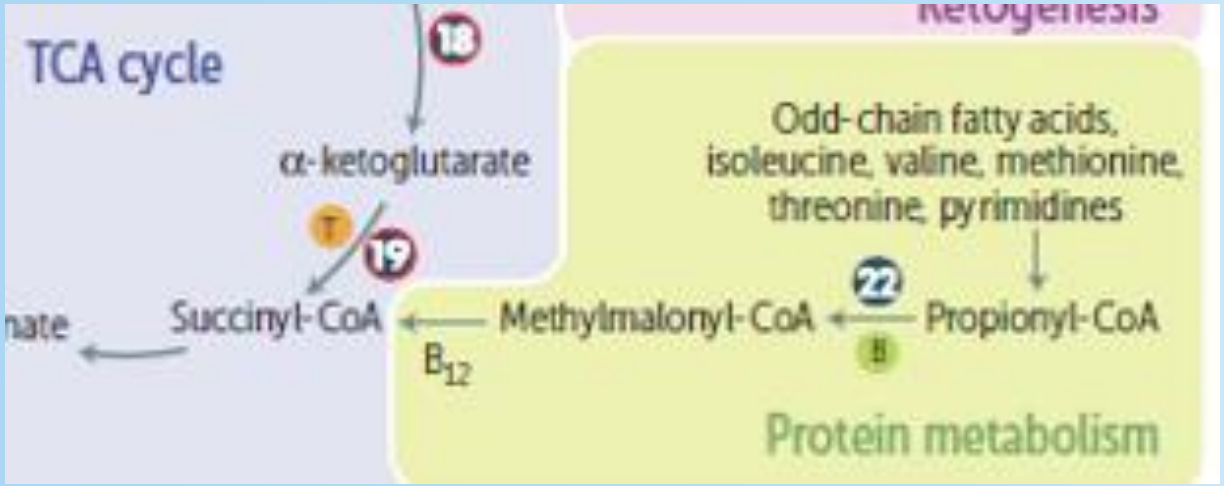


β-OXIDATION ATP YIELD

C_{16} fatty acid $\longrightarrow$ $16CO_2$	129 ATP
Breakdown into steps:	
Activation of fatty acid to fatty acyl-CoA	−2 ATP
7 $FADH_2$ made from forming double bond at C-2 (7 × 2)	14 ATP
7 NADH made from oxidations during formation of 3-ketoacyl-CoA (7 × 3)	21 ATP
8 acetyl-CoA (8 × 12) through TCA cycle	96 ATP



What about Odd Chain Fatty Acids?



- Vit B12 deficiency causes buildup of Methylmalonyl-CoA
- Succinyl-CoA straight to TCA cycle

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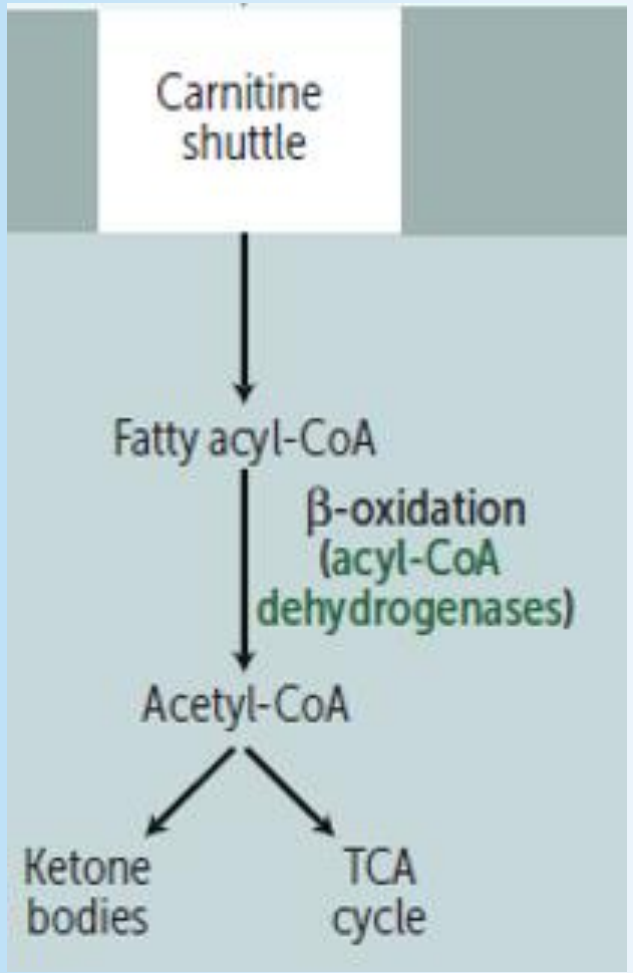
Medium-chain acyl-CoA dehydrogenase deficiency

Autosomal recessive

No enzyme = Impaired fatty acid breakdown ➡ **Decreased acetyl-CoA**
+ Buildup of fatty acyl carnitines.
Hypoketotic Hypoglycemia

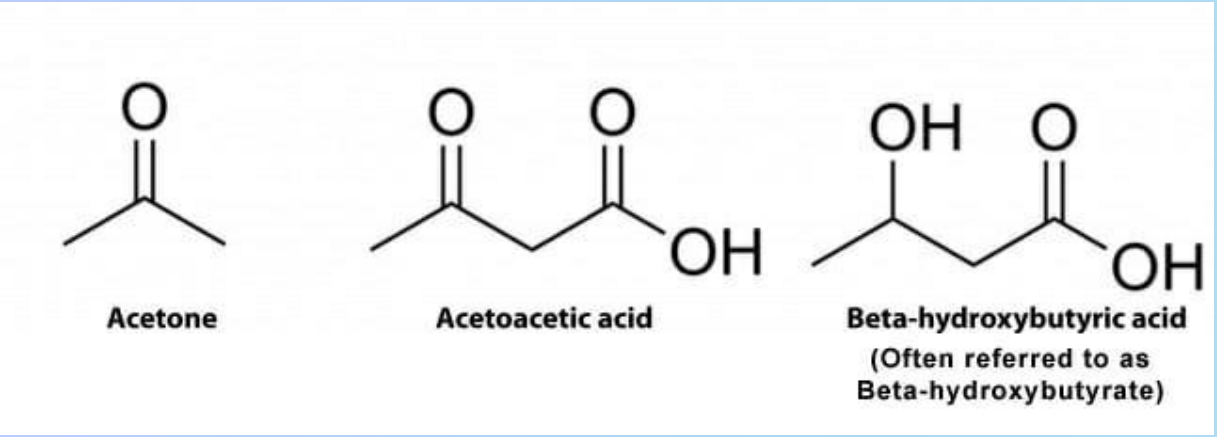
Symptoms: Seizures, vomiting, coma, liver dysfunction, hyperammonemia

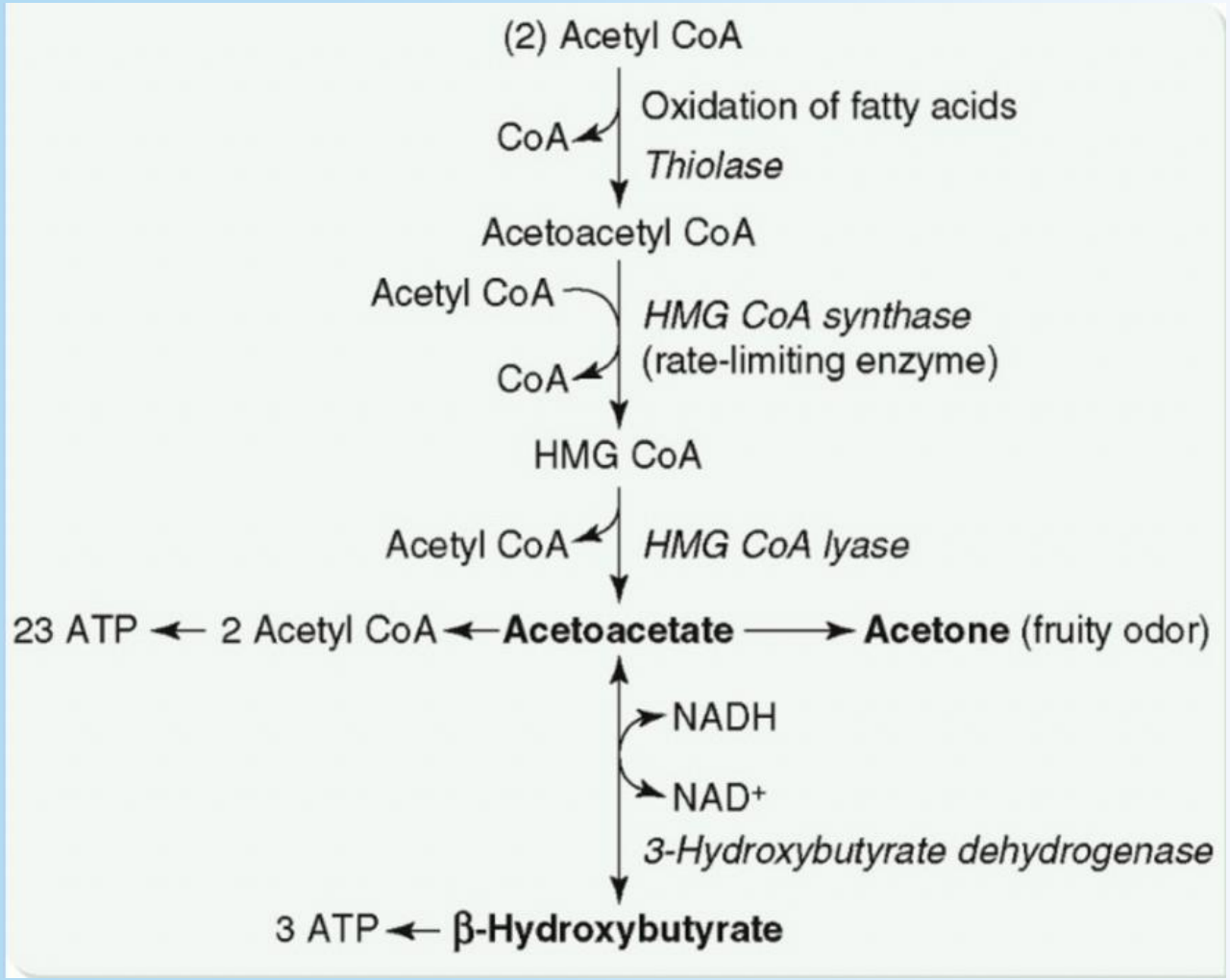
Tx = Avoid fasting



Ketones

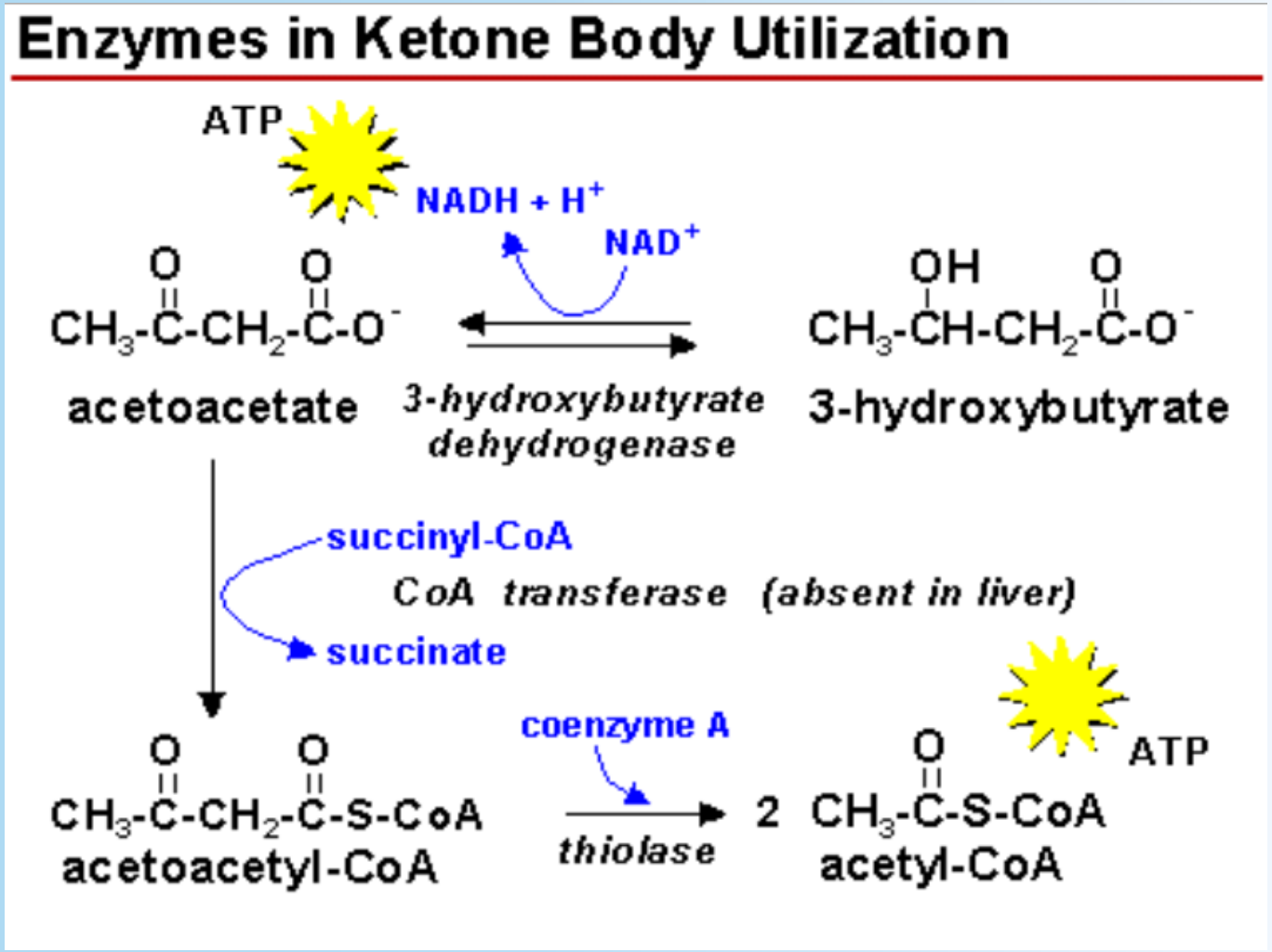
- Generated in the Liver! (Sometimes Kidney too)
- Ketones are used by the brain and muscles.
- RBCs can not use ketones (only glucose)



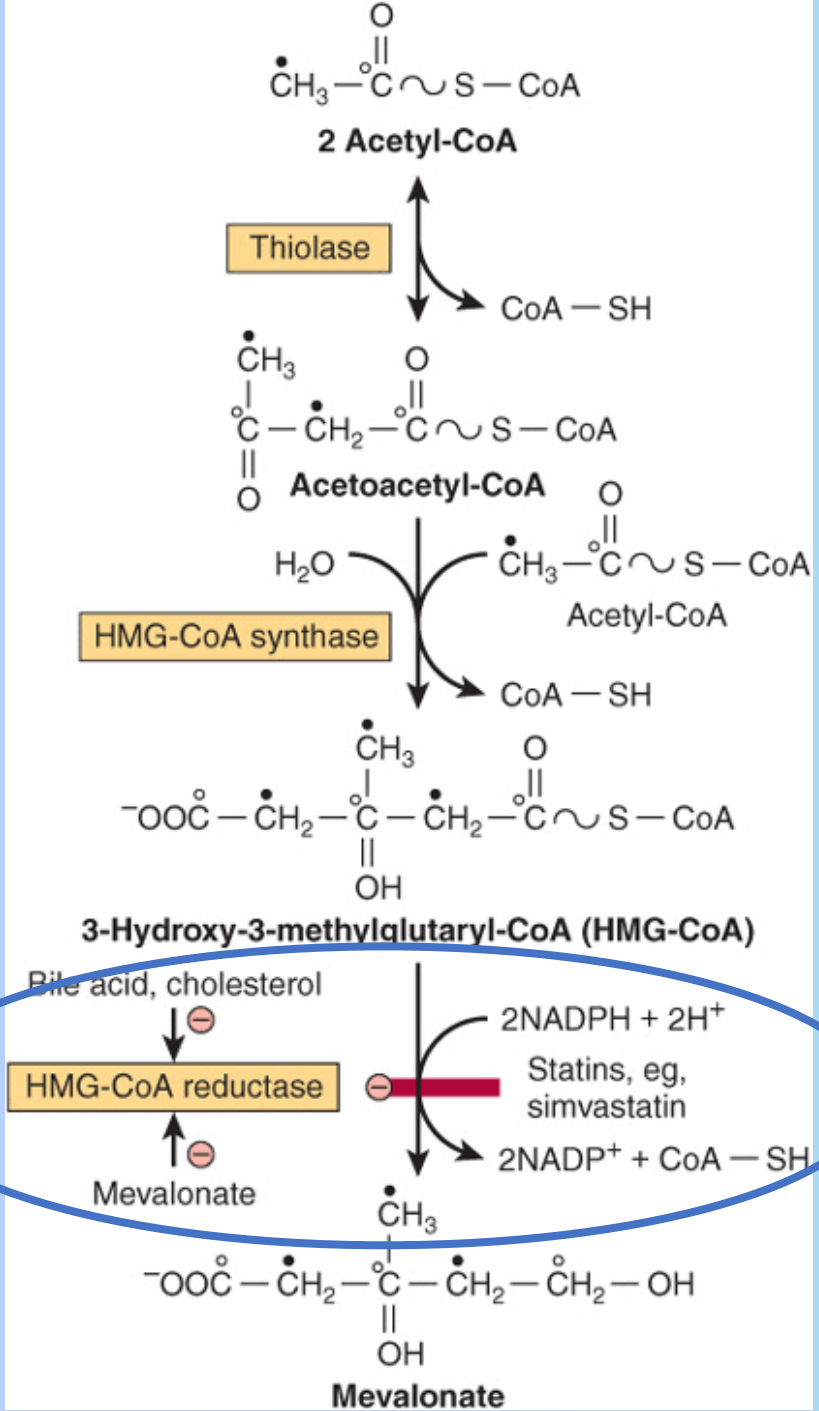


When are Ketones produced?

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



Cholesterol Synthesis



- HMG-CoA reductase = Rate Limiting
- Inhibited by statin drugs and by cholesterol + mevalonate buildup

- Insulin Induces HMG-CoA Reductase
- Glucagon Inhibits HMG-CoA Reductase

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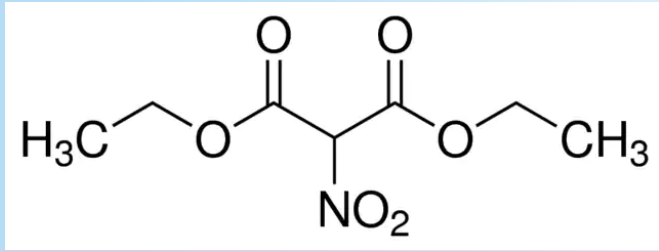
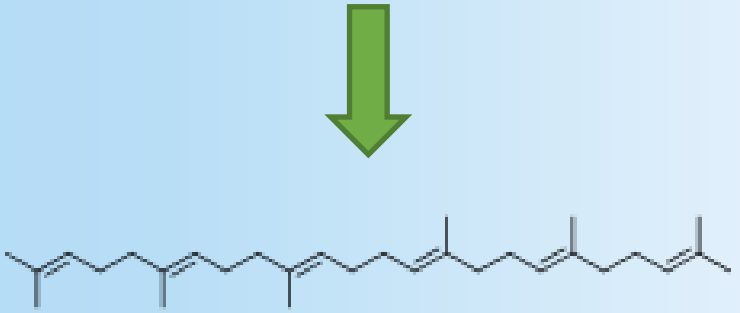
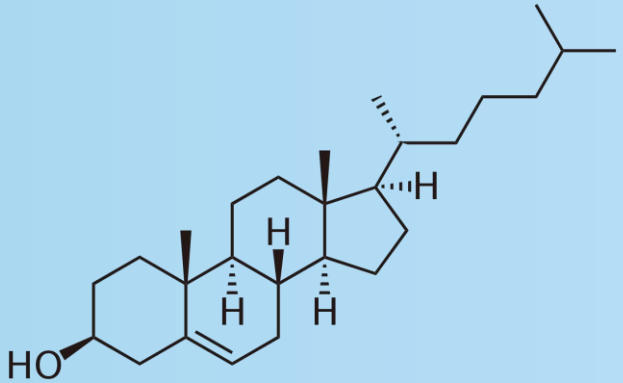
- Cholesterol used for: Vitamin D, synthesis, Bile acid synthesis, Steroid synthesis and Cell-Membrane integrity



Mevalonate



Squalene



Cholesterol

Don’t mix these up!

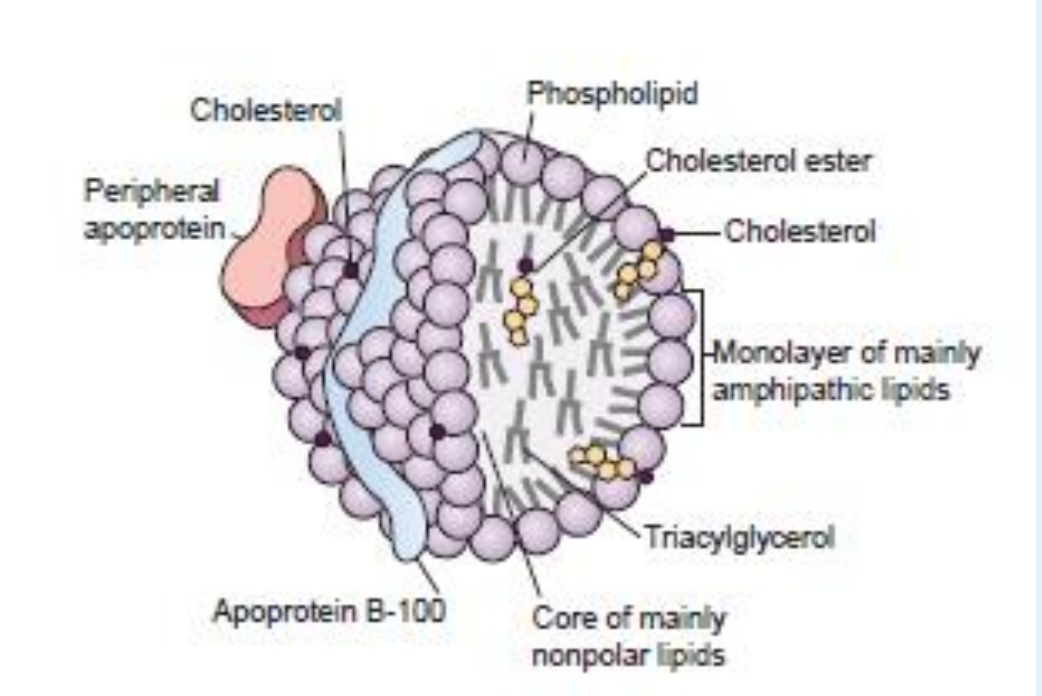
HMG-CoA **Lyase** = **Ketone** production

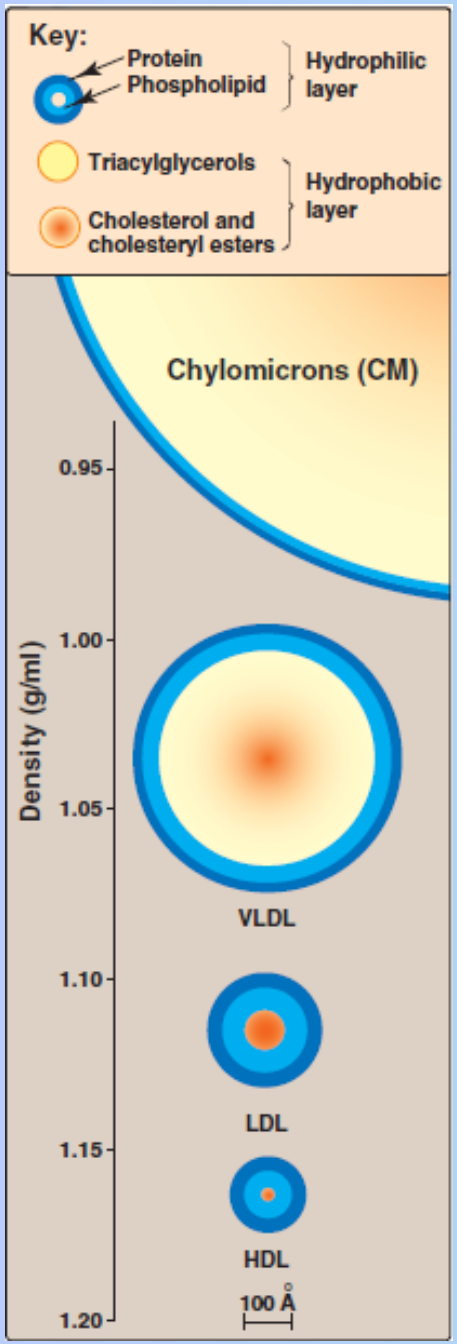
HMG-CoA **Reductase** = ***Cholesterol*** synthesis

What are lipoproteins?

- Lipoproteins = transporters for hydrophobic lipids in the blood

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




Key:
Protein
Phospholipid
Hydrophilic layer
Triacylglycerols
Cholesterol and cholesteryl esters
Hydrophobic layer
Chylomicrons (CM)
Density (g/ml)
0.95
1.00
1.05
1.10
1.15
1.20
VLDL
LDL
HDL
100 Å

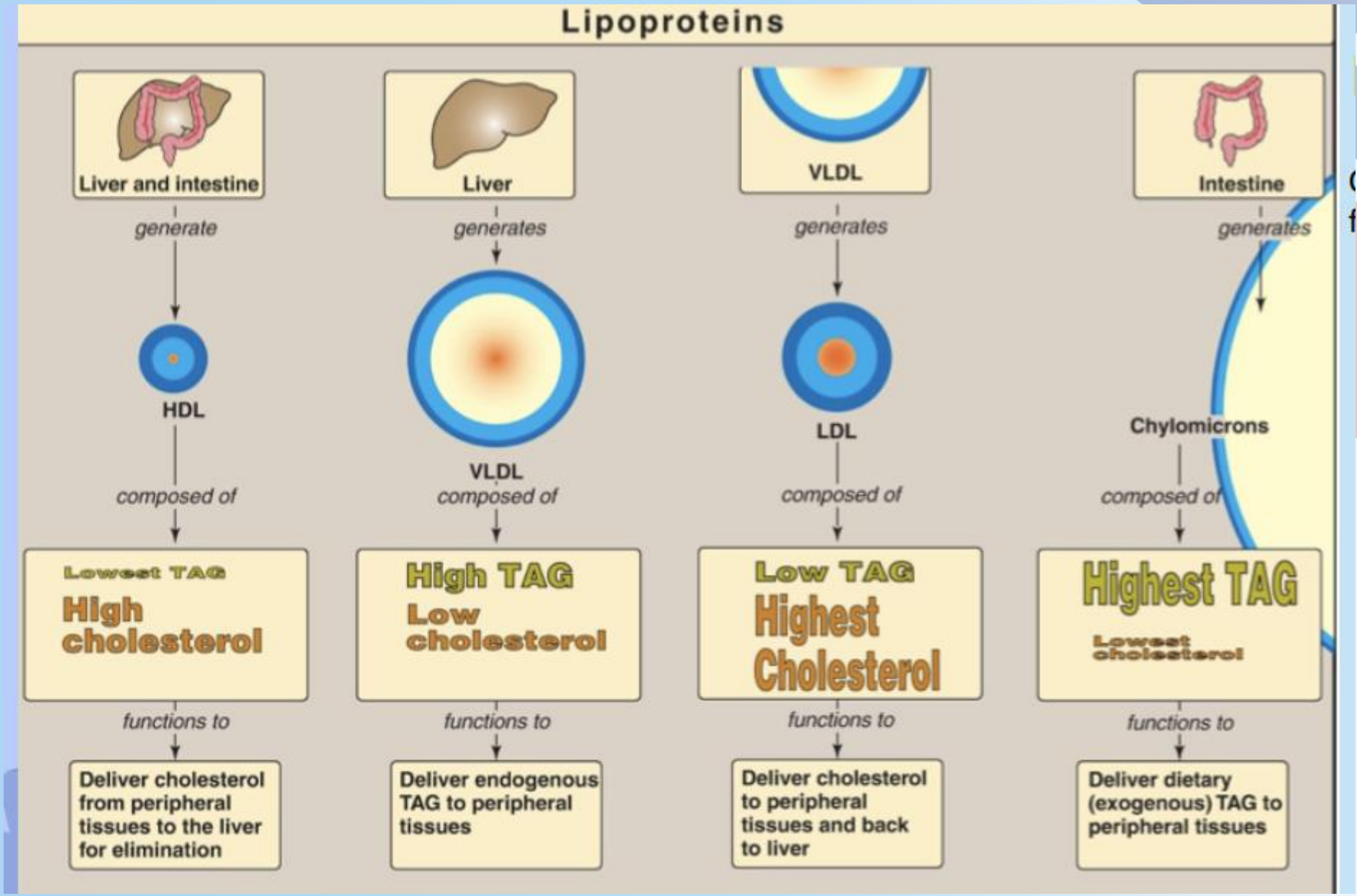

Lipoproteins
Liver and intestine
generate
HDL
composed of
Lowest TAG
High cholesterol
functions to
Deliver cholesterol from peripheral tissues to the liver for elimination
Liver
generates
VLDL
composed of
High TAG
Low cholesterol
functions to
Deliver endogenous TAG to peripheral tissues
VLDL
generates
LDL
composed of
Low TAG
Highest Cholesterol
functions to
Deliver cholesterol to peripheral tissues and back to liver
Intestine
generates
Chylomicrons
composed of
Highest TAG
Lowest cholesterol
functions to
Deliver dietary (exogenous) TAG to peripheral tissues

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

Fat transport

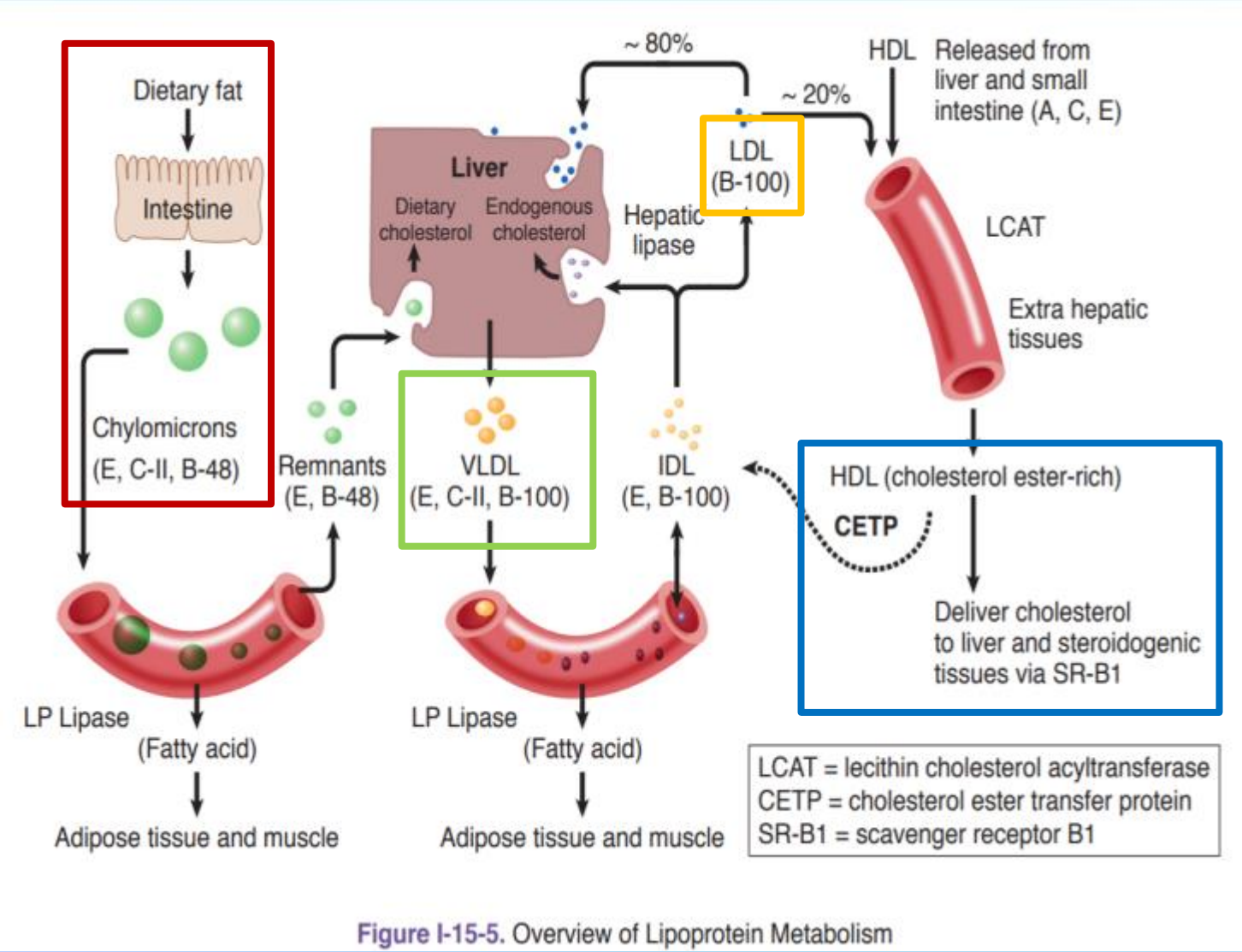


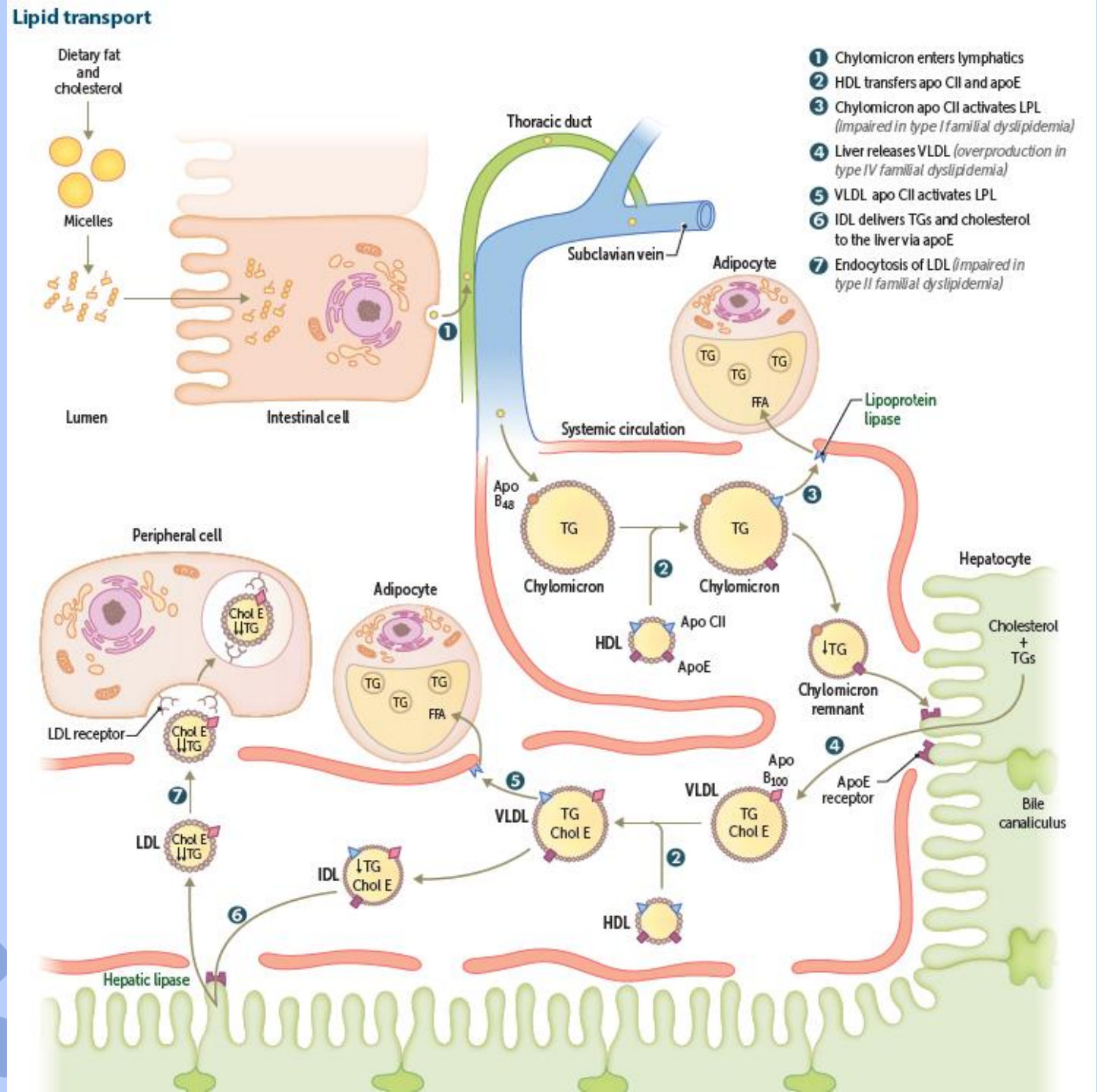
Figure I-15-5. Overview of Lipoprotein Metabolism

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

VLDL: Newly synthesized endogenous triglycerides from liver to tissues.

LDL: Cholesterol to tissues
B-100 binds LDL receptor

HDL: Cholesterol from tissues to liver



ApoE for Exit (everything except LDL)

ApoA-1 for Activation of LCAT

ApoC-2 for Cleaving with Lipoprotein lipase

Chylomicrons from intestines = B48

VLDL and LDL from liver = B100

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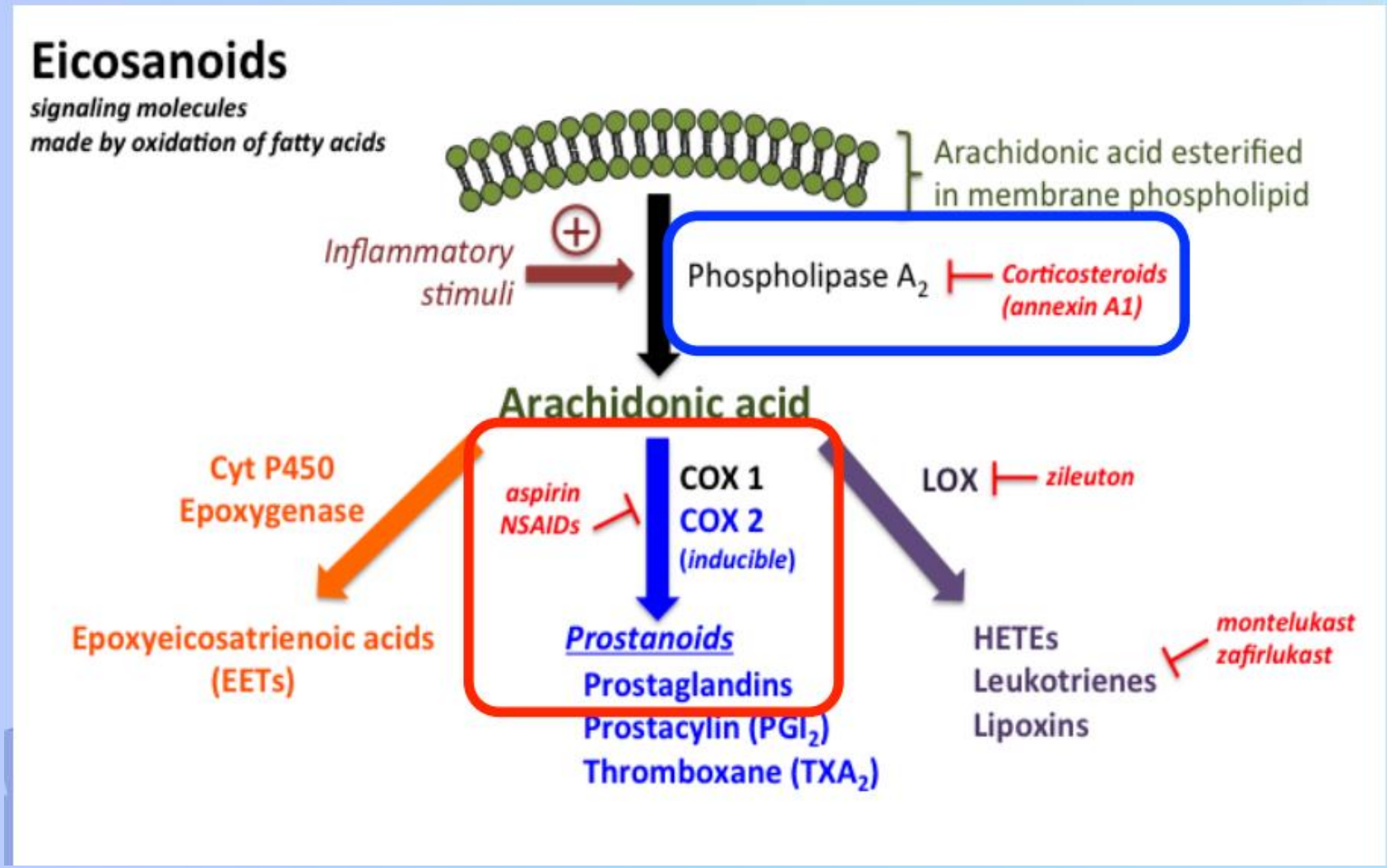
Eicosanoids



- Steroids inhibit all products of Arachidonic acid
- NSAIDs only inhibit Prostanoid formation

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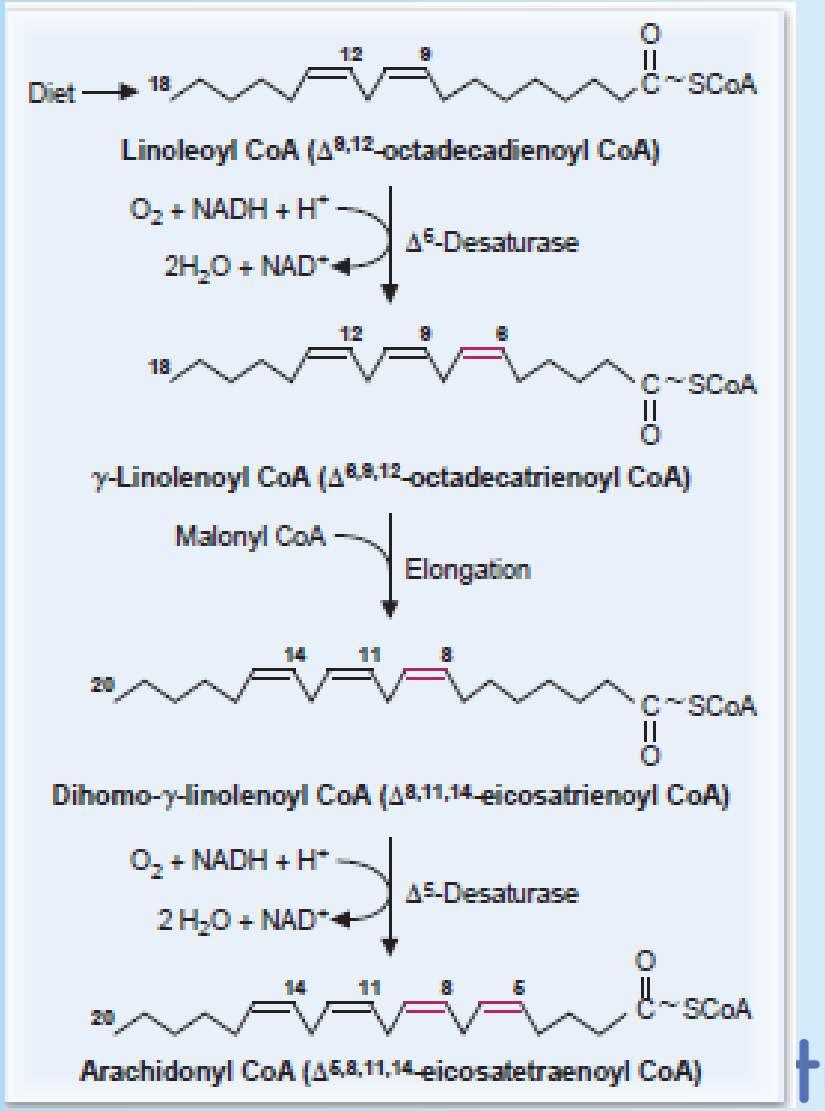
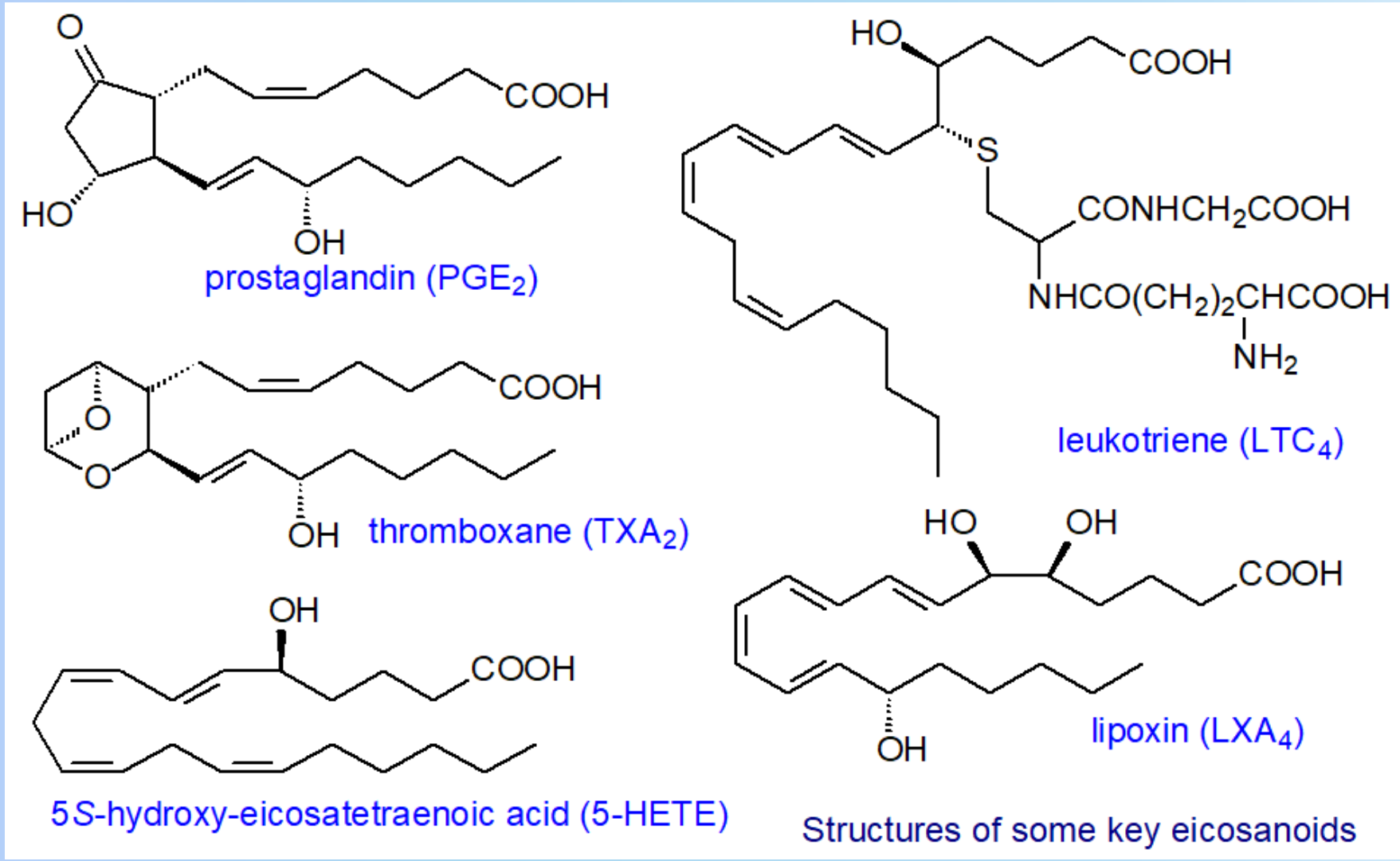
Where does Arachidonic Acid come from?

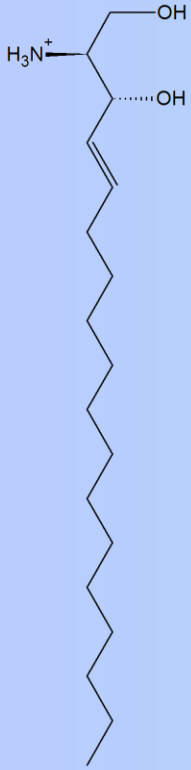
- Elongation + Desaturation of Linoleic acid leads to Arachidonic Acid production



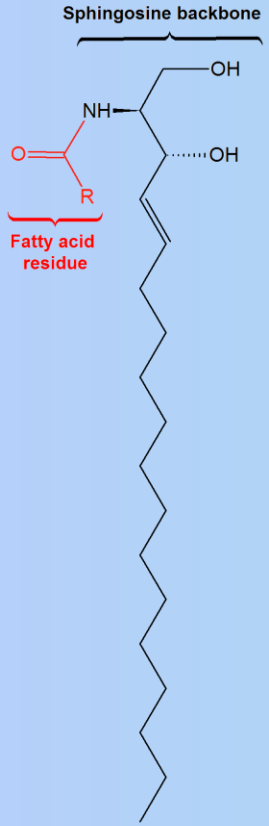
Important Structures



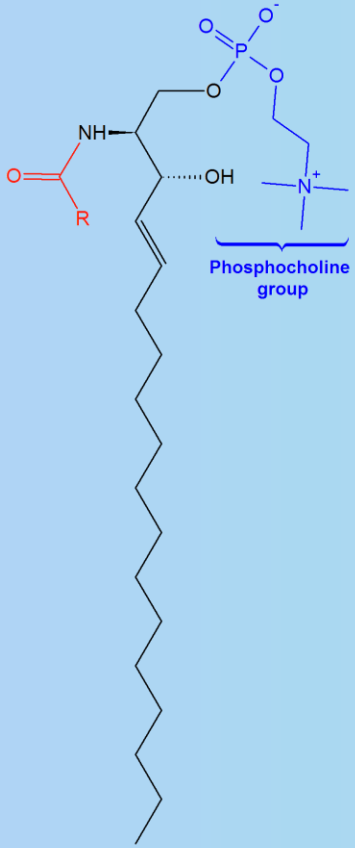
Sphingolipids



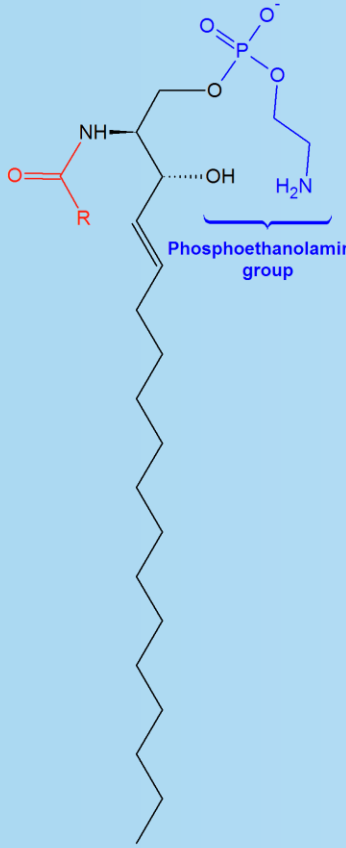
Sphingosine



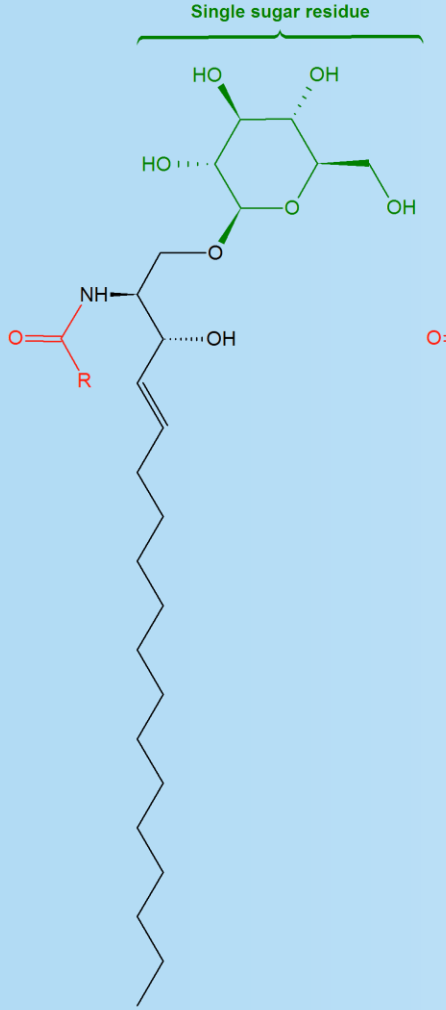
A Ceramide



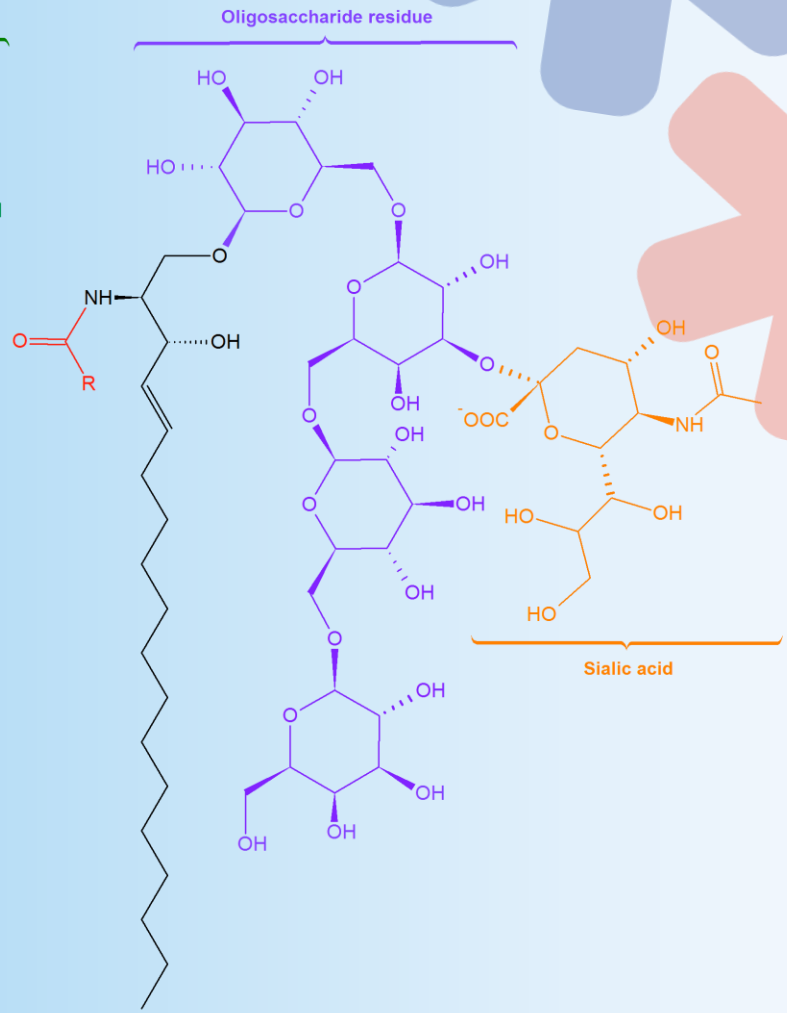
A Sphingomyelin



A Sphingomyelin



A Cerebroside



A Ganglioside

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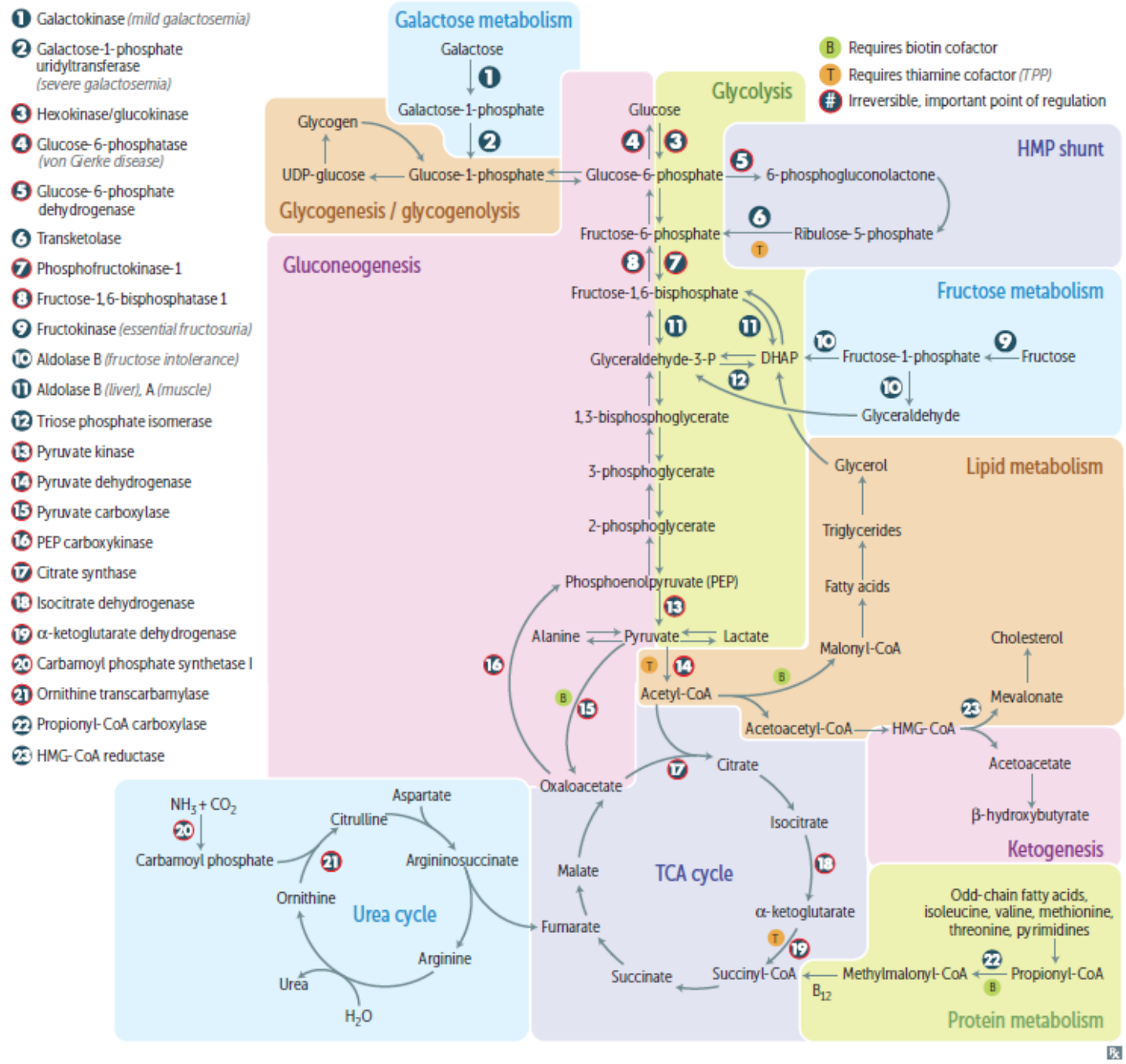
Summary of pathways



Reference: First Aid for the USMLE step 1 2022 pg. 72

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ETSNSL

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