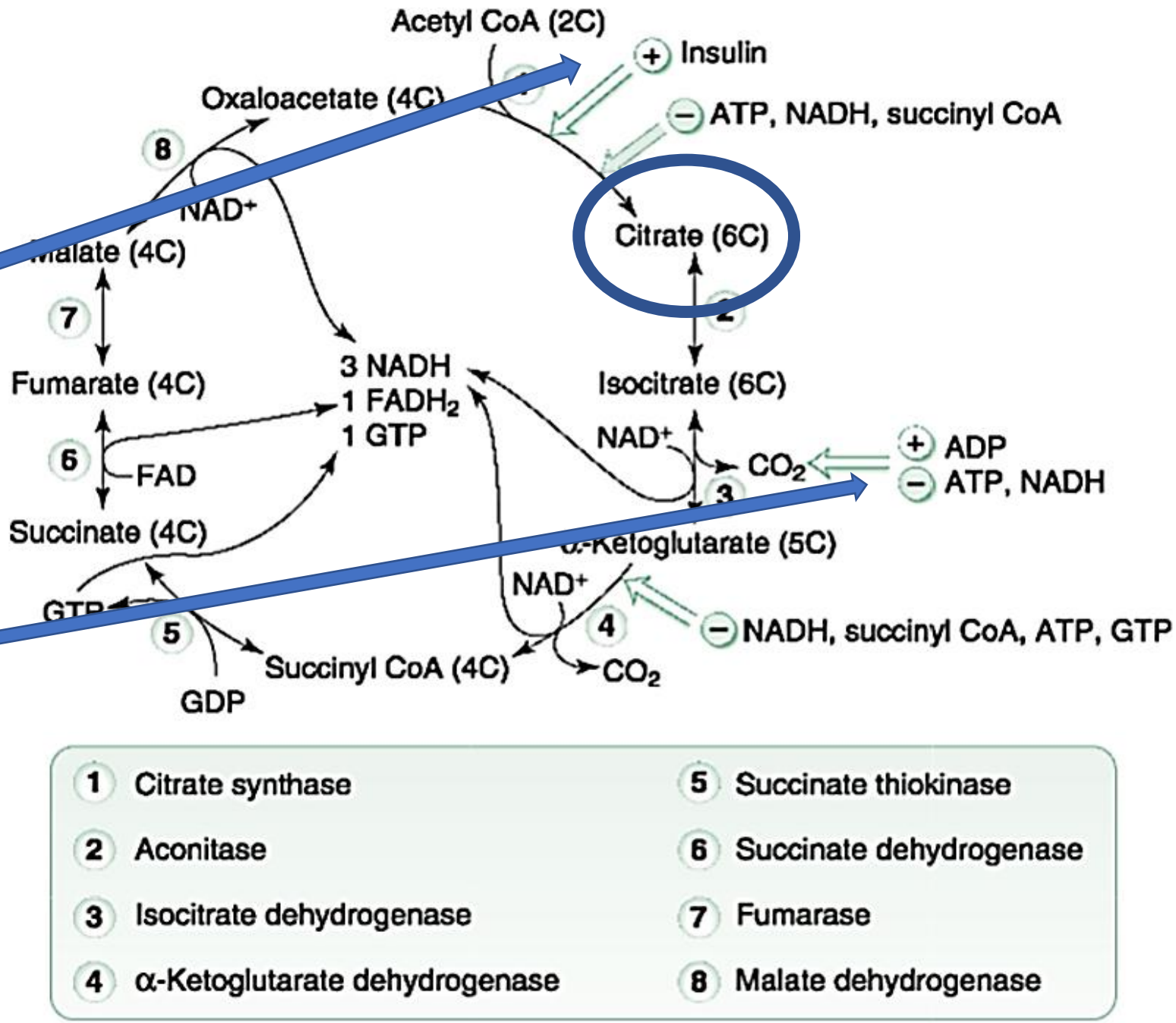
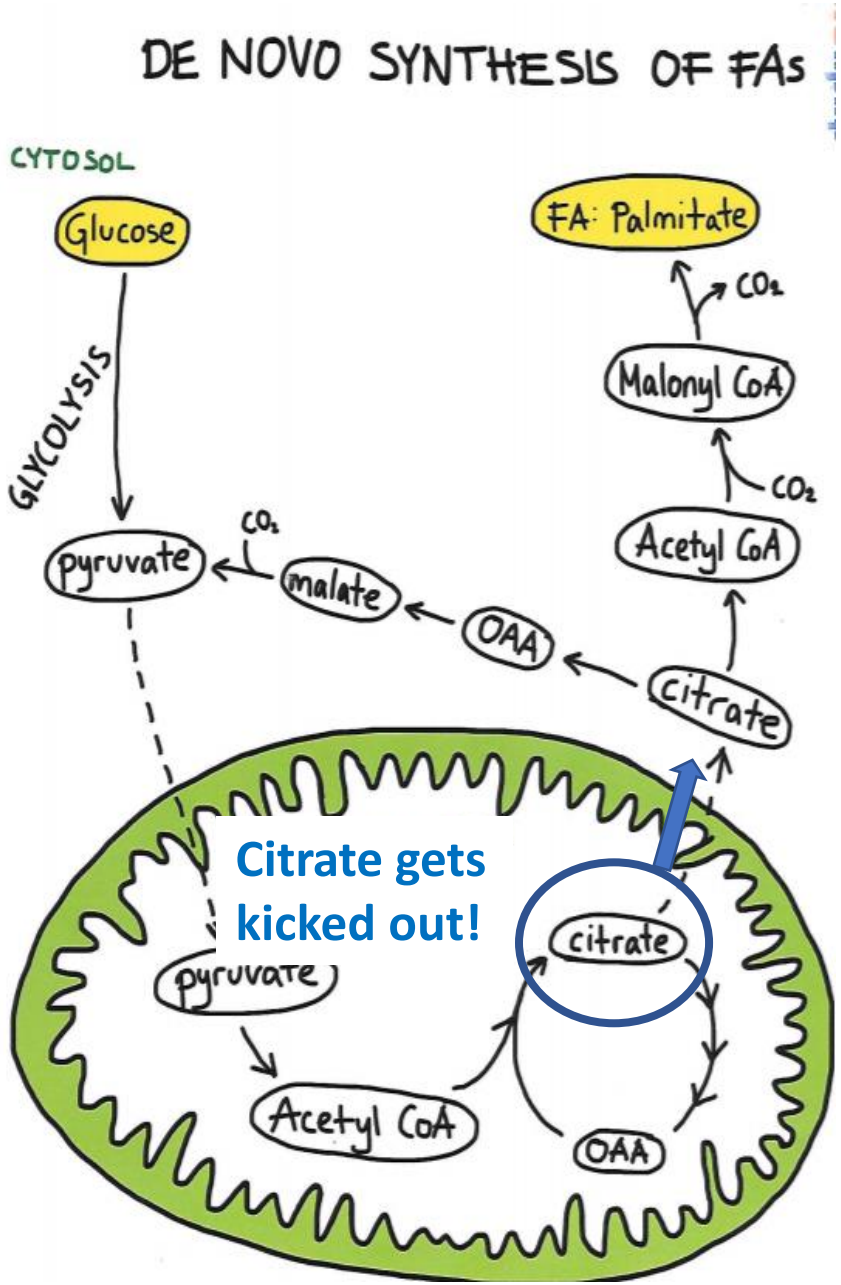
What are we gonna talk about?

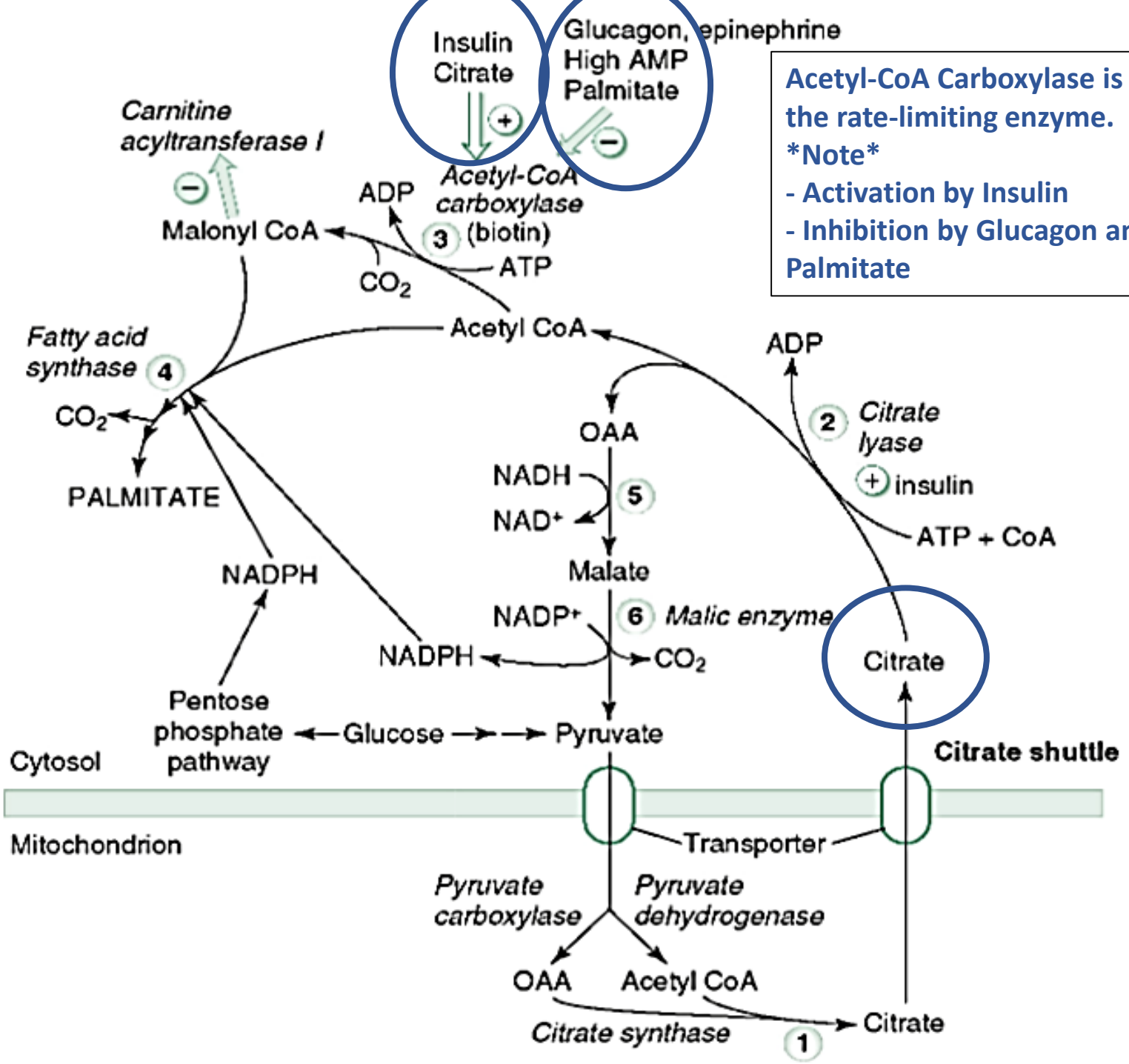
- Lipid synthesis
- Lipid b-oxidation
- Ketones
- Cholesterol synthesis
- Cholesterol breakdown
- Lipid + Cholesterol transportation

Note
Insulin promotes formation of Citrate

Energy in the cell prevents citrate from moving along the TCA







Acetyl-CoA Carboxylase is the rate-limiting enzyme.
Note
- Activation by Insulin
- Inhibition by Glucagon and Palmitate

Fatty acid Synthesis

Steps 1-3 of the Fatty Acid Synthase reaction pathway are catalyzed by the catalytic domains listed in the diagram at right.

Shown are the cysteine of one protein subunit and the acyl carrier protein phosphopantetheine (Pant) of the other subunit of the dimeric complex

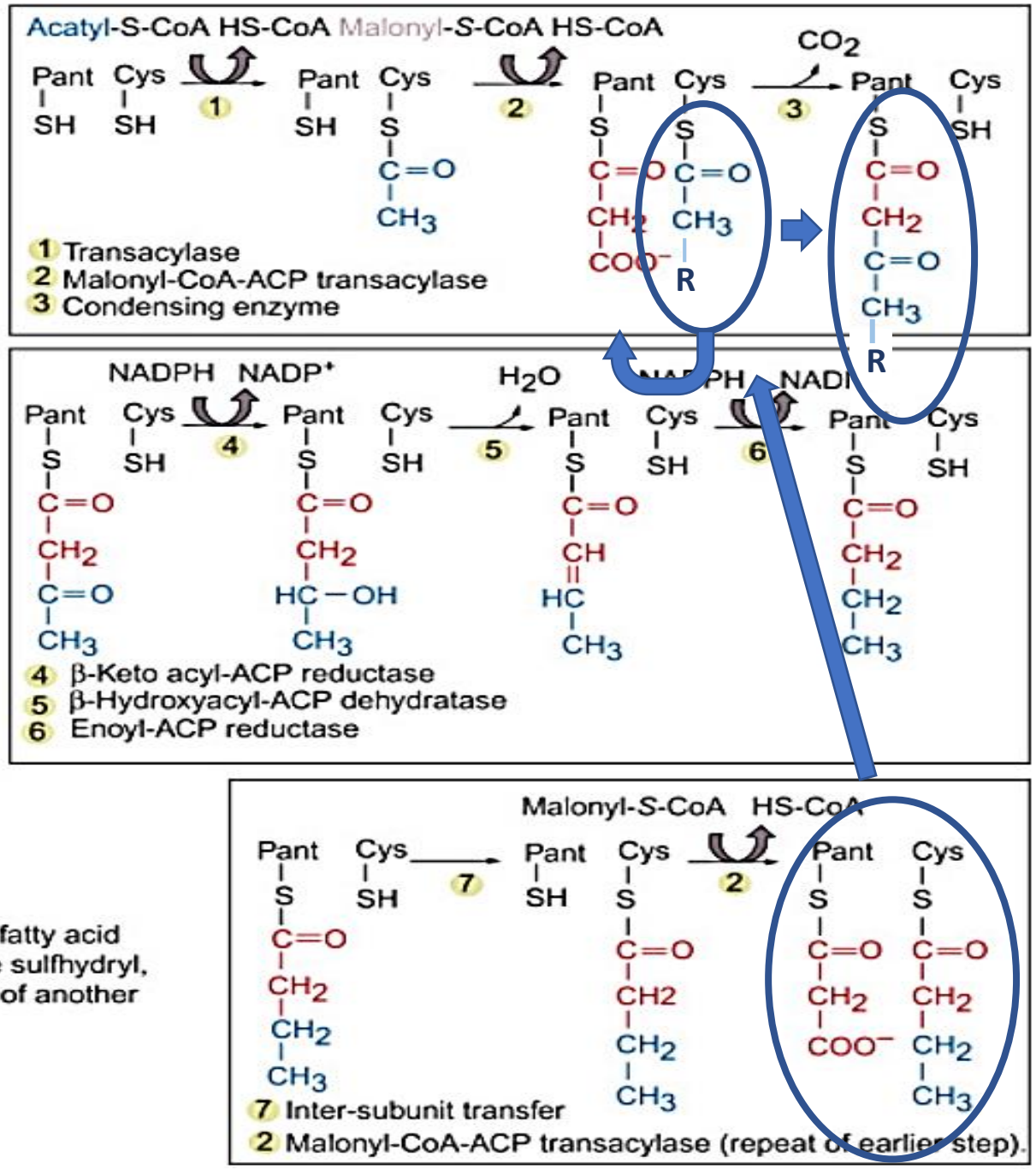
In steps 4-6:

The β-Ketone is reduced to an alcohol, by electron transfer from NADPH.

Dehydration yields a trans double bond.

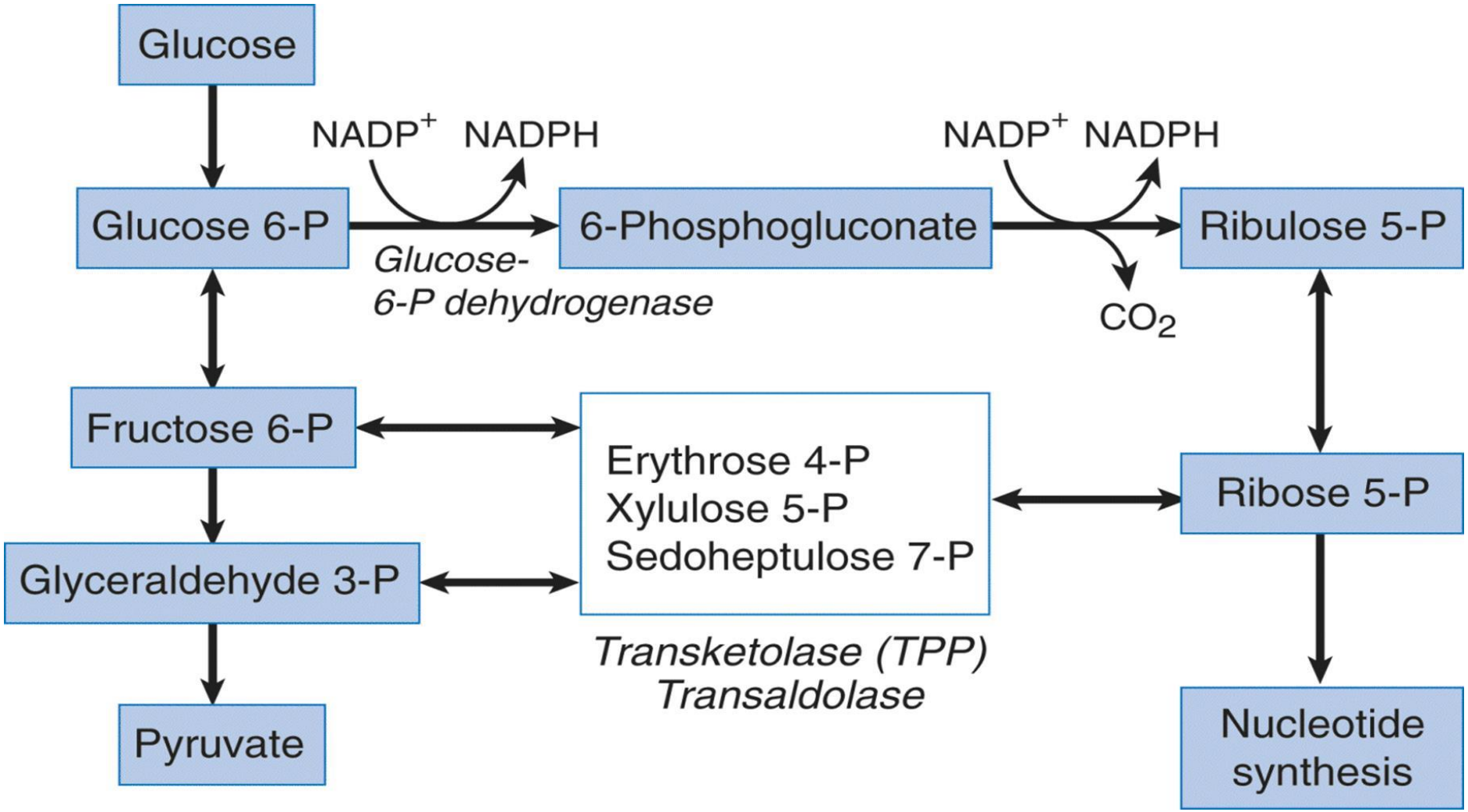
Reduction at the double bond by NADPH yields a saturated chain.

Following intersubunit transfer of the fatty acid from phosphopantetheine to cysteine sulfhydryl, the cycle begins again, with reaction of another malonyl CoA.

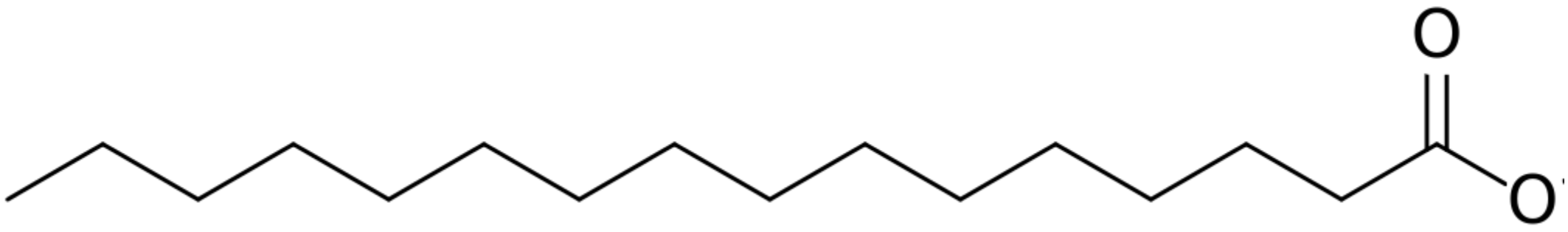


Note
New Acetyl-CoA units are added using Malonyl-CoA at the <u>beginning</u> of the elongating chain (i.e. The one on the right gets added to the butt of the one on the left)

Where do I get NADPH?!



What do we get?

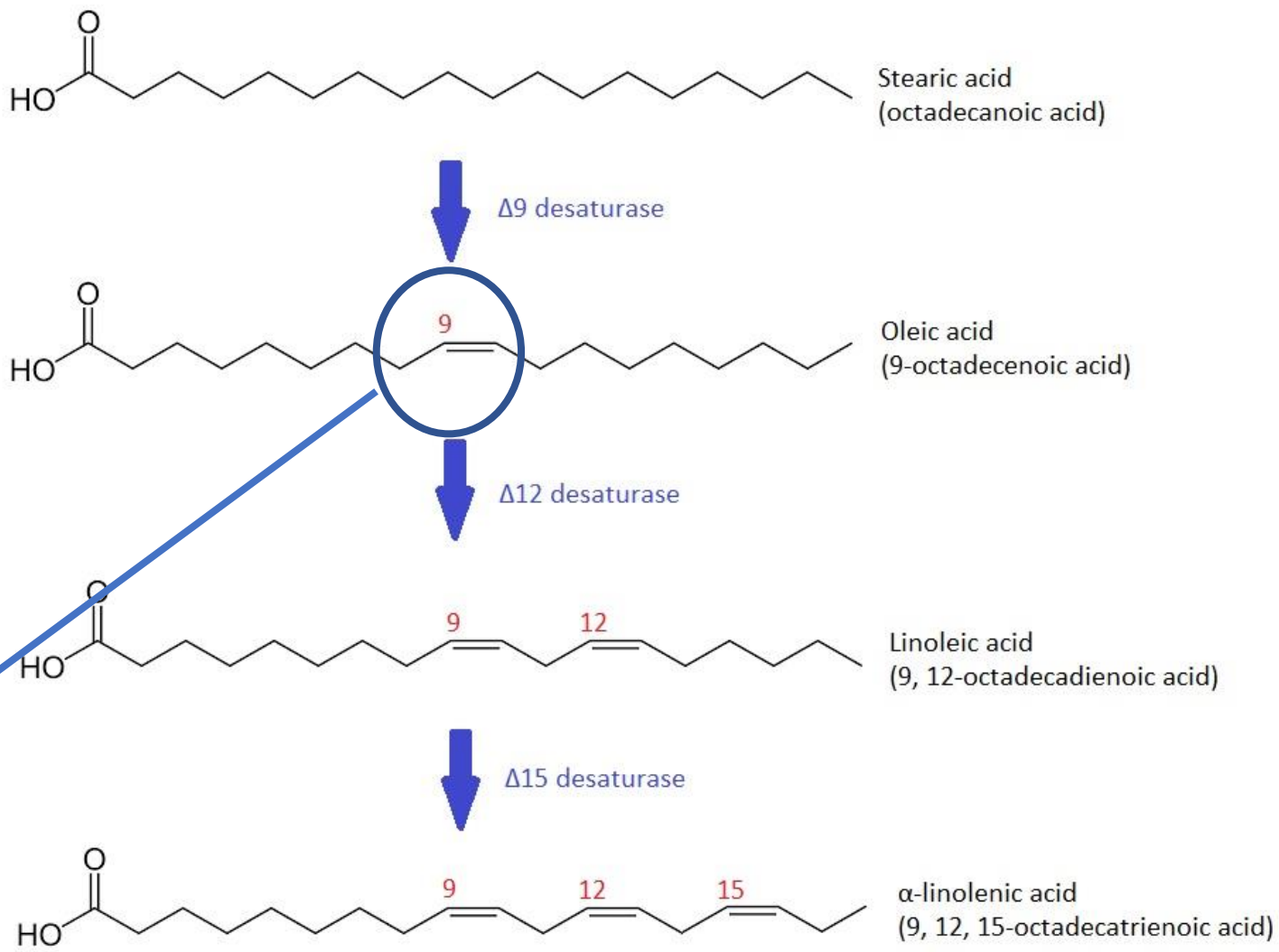


Palmitate C16

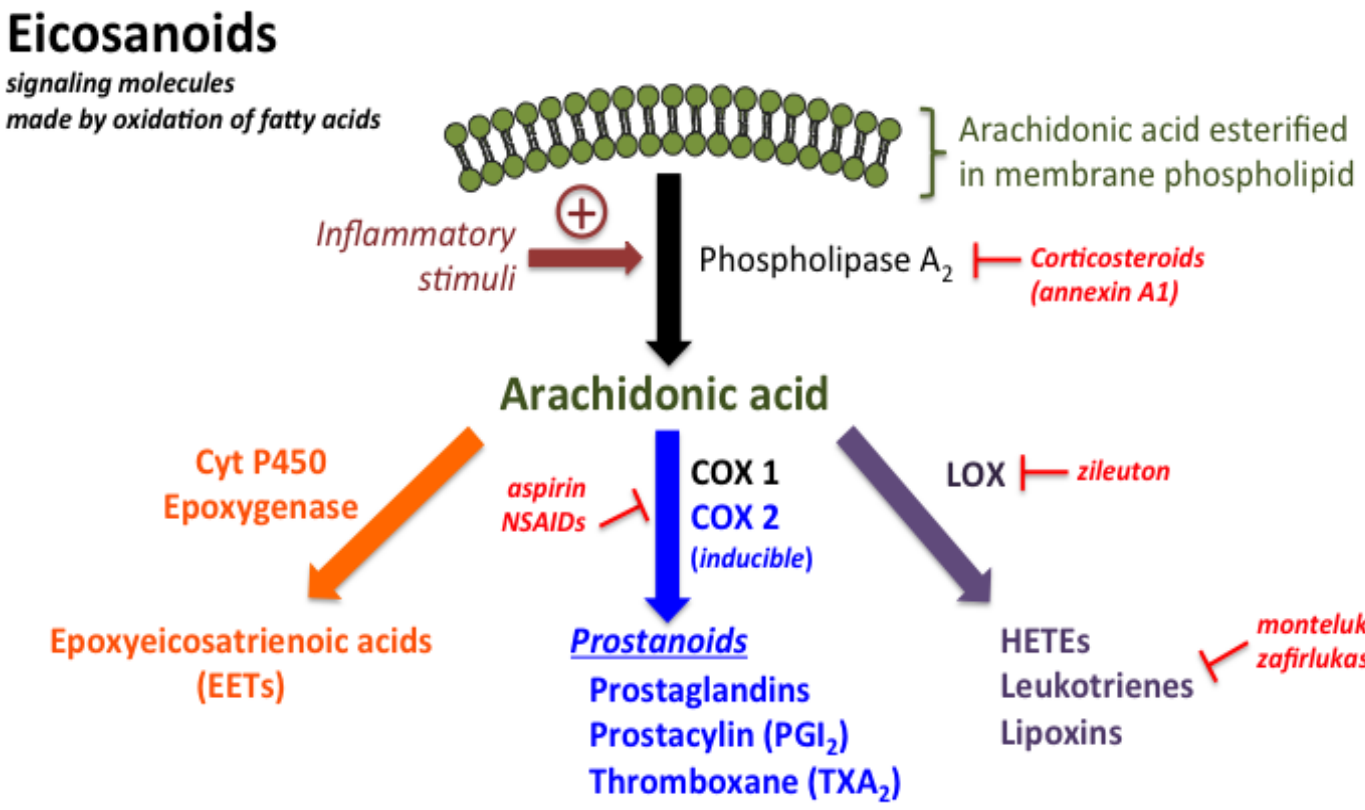
Can we make all unsaturated fatty acids?

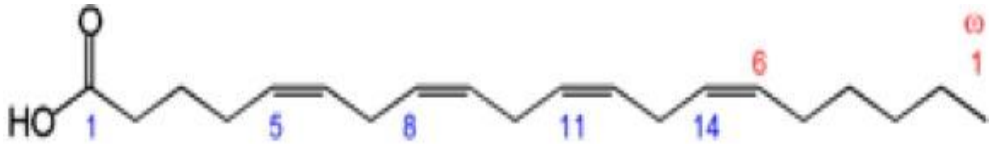
Humans only have Δ9-Desaturase, we can only desaturate 9 carbons from the front, not the back

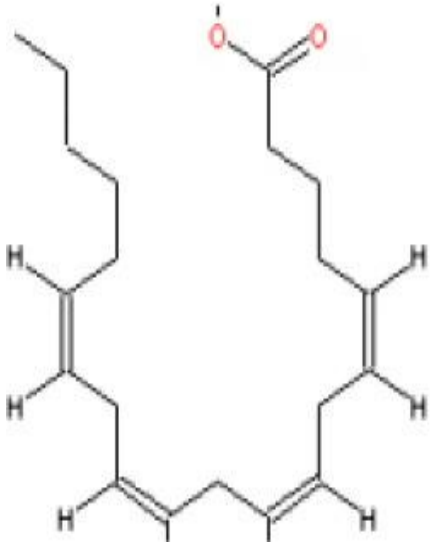
Linoleic and Linolenic acids are essential fatty acids



Arachidonic acid
20 Carbon
omega 6 – 4 double bonds





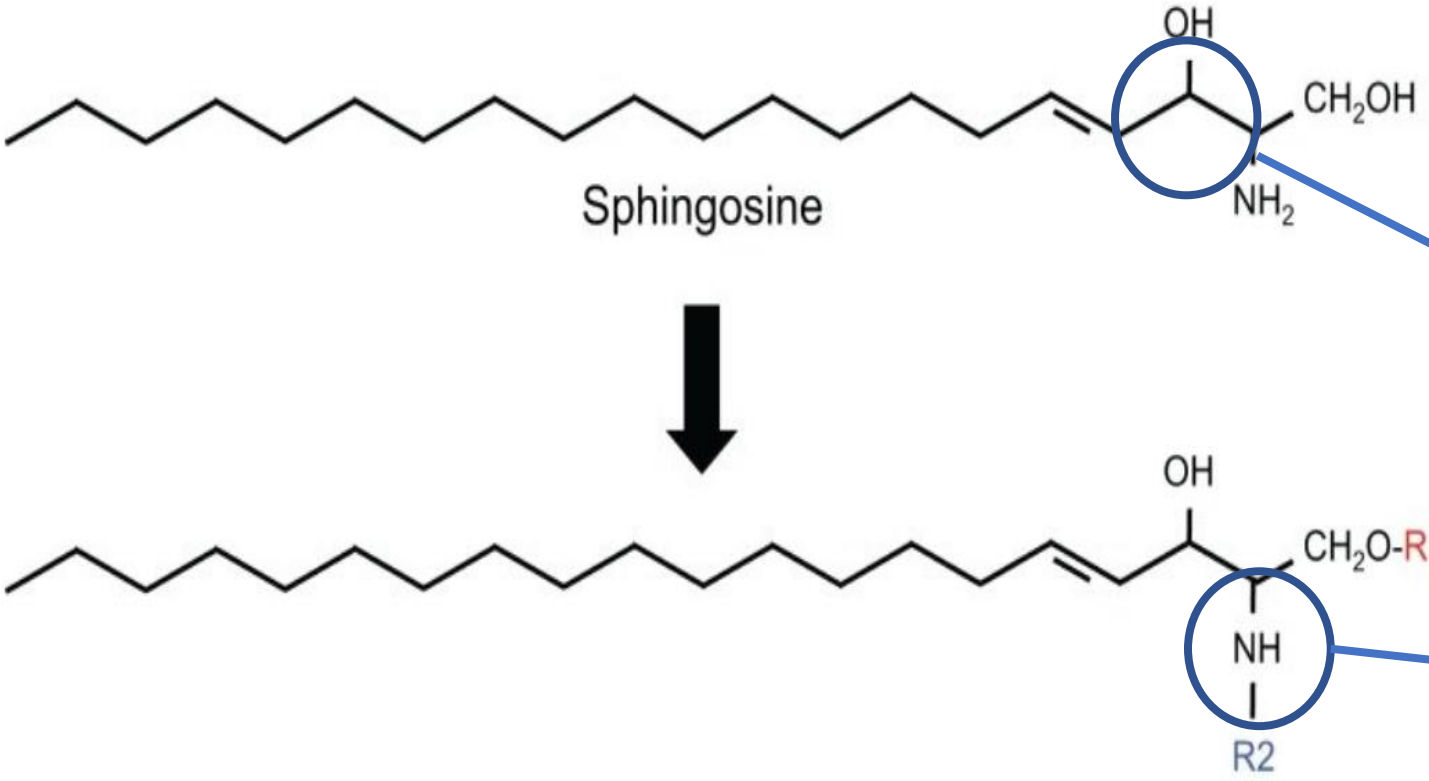


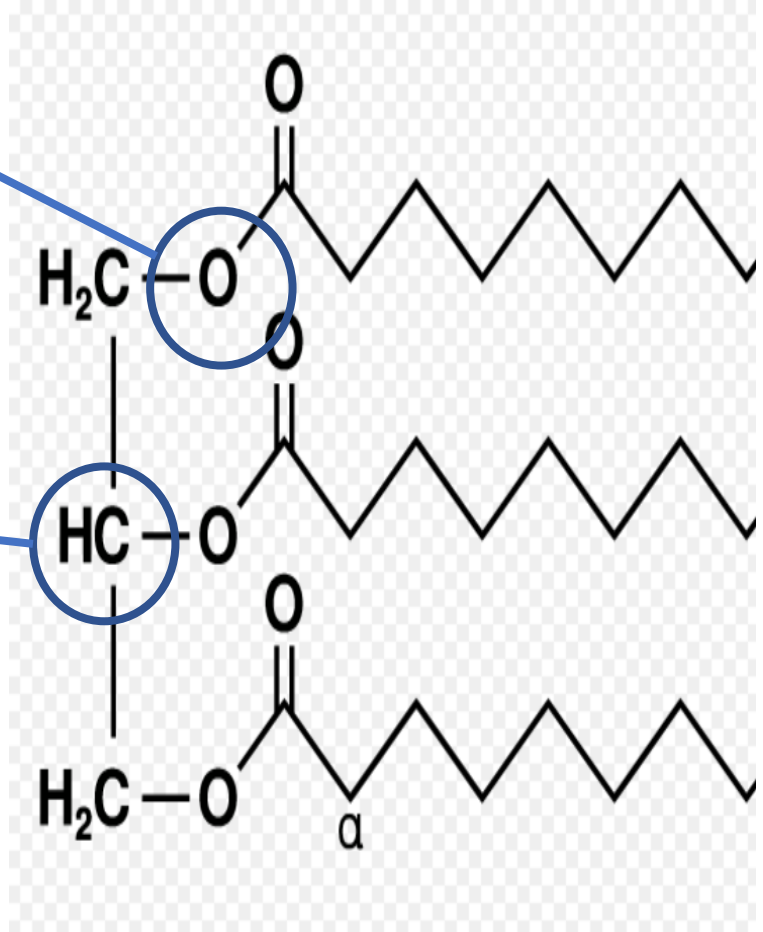
We can make it by elongating and further desaturating Linoleic acid

Sphingolipids

Note differences

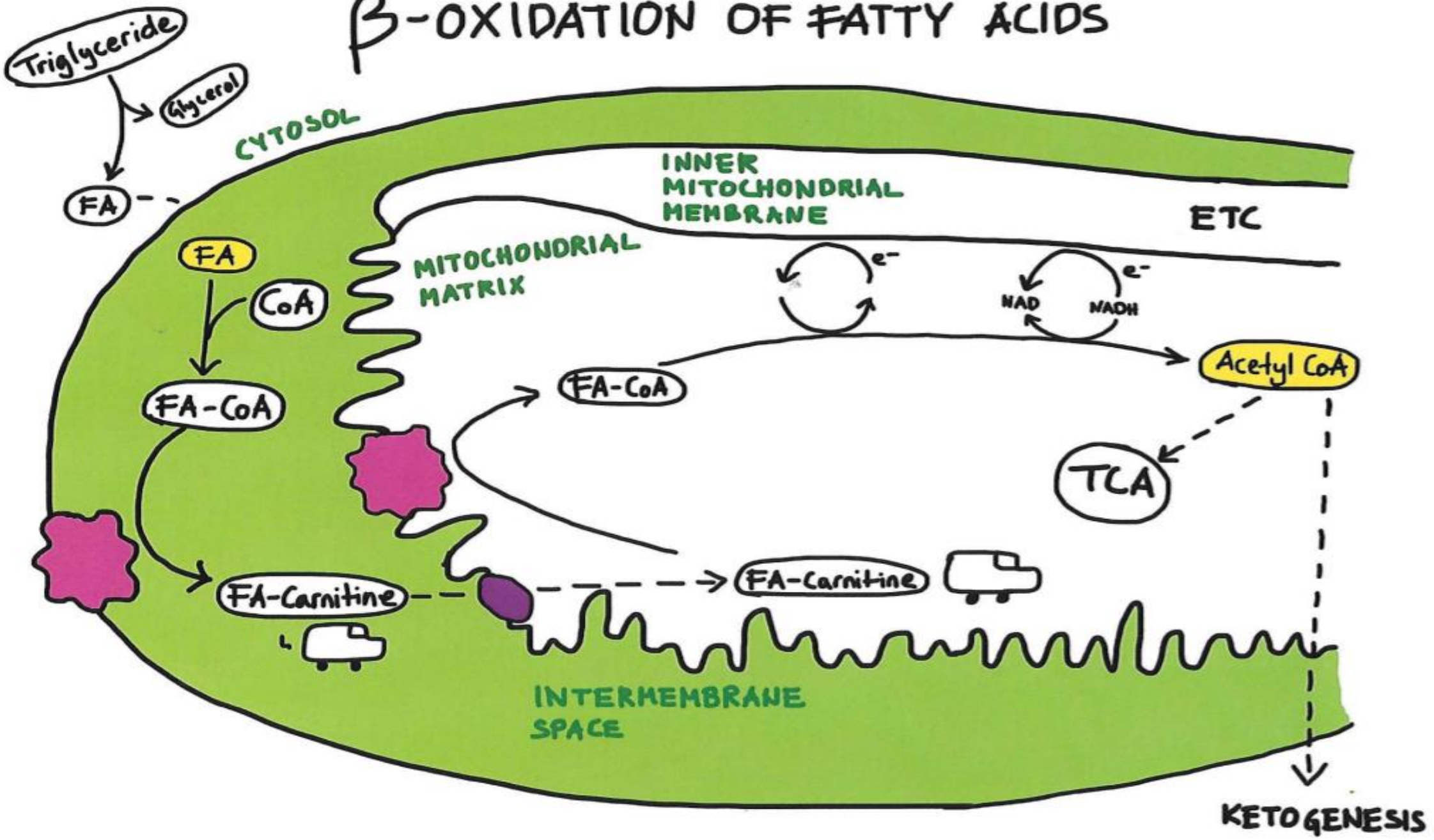
1. No ester bond on Carbon 1
2. Amide bond on carbon 2





Sphingosine + Fatty Acid = Ceramide

β-OXIDATION OF FATTY ACIDS



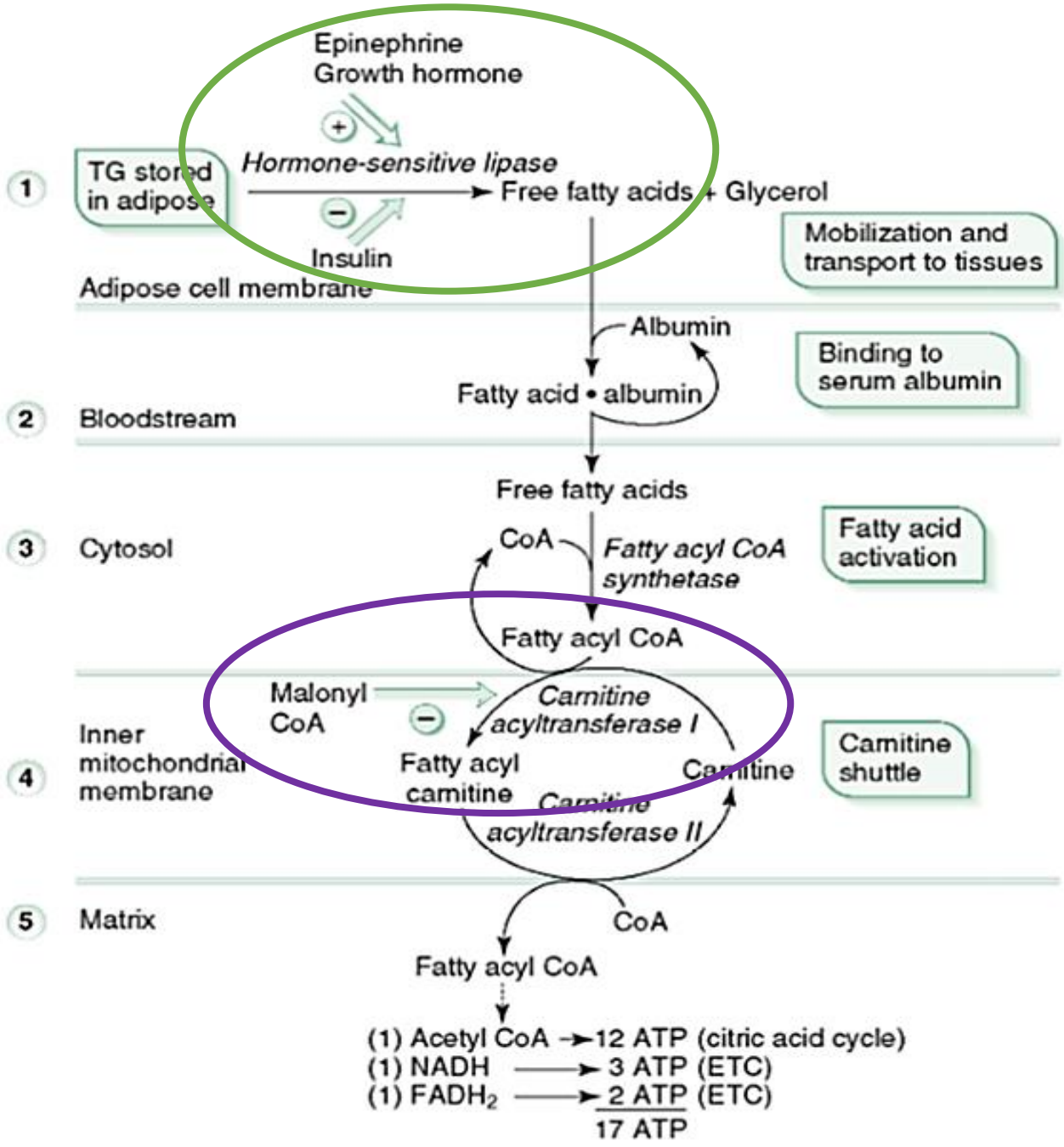
Fatty Acid b-oxidation

Only 2 points of regulation

- In Adipocytes
  - Hormone sensitive lipase
- During shuttling of FAs into the mitochondria
  - Carnitine acyltransferase

Note

Only long chain fatty acids (14 or more carbons) need to be shuttled by carnitine



But!!! What happens if I have odd chain Fatty Acids?

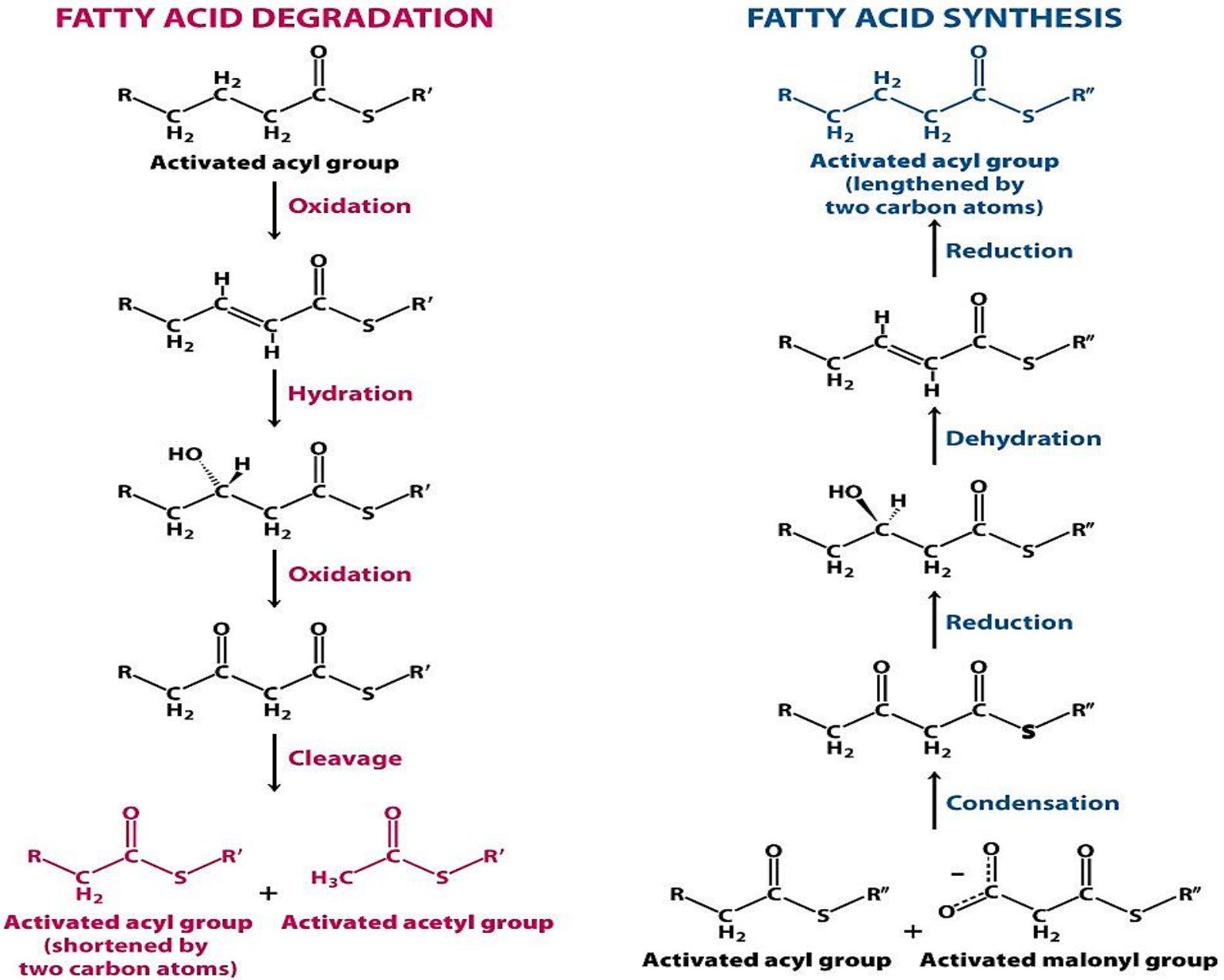
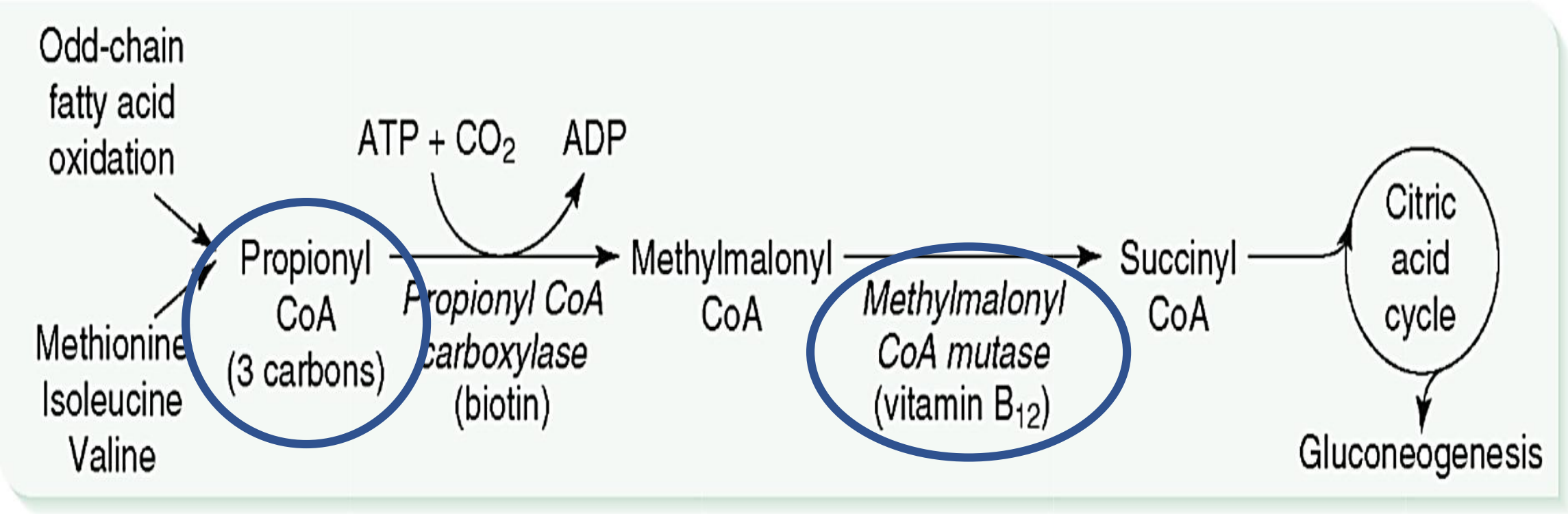


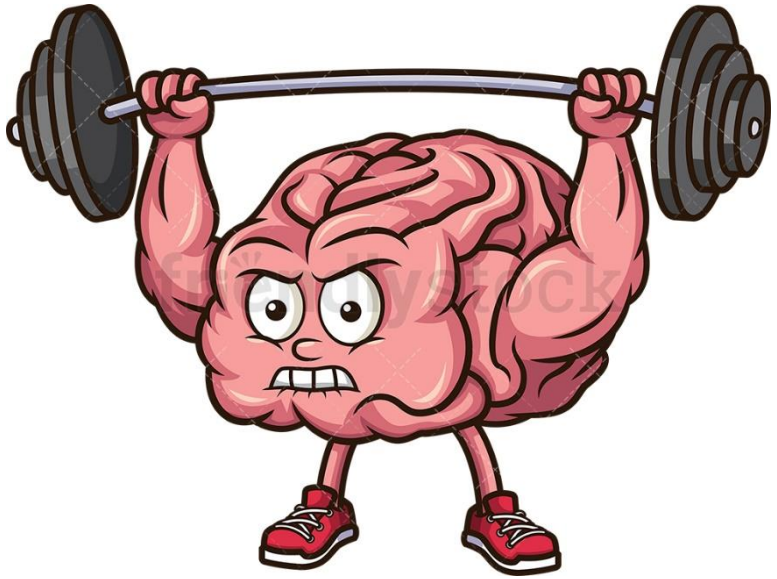
Figure 22.2
Biochemistry, Seventh Edition



Note
Odd-chain fatty acid synthesis requires Vitamin B12

Ketones
Why do we need em?

To save your Brain
and your Gains!



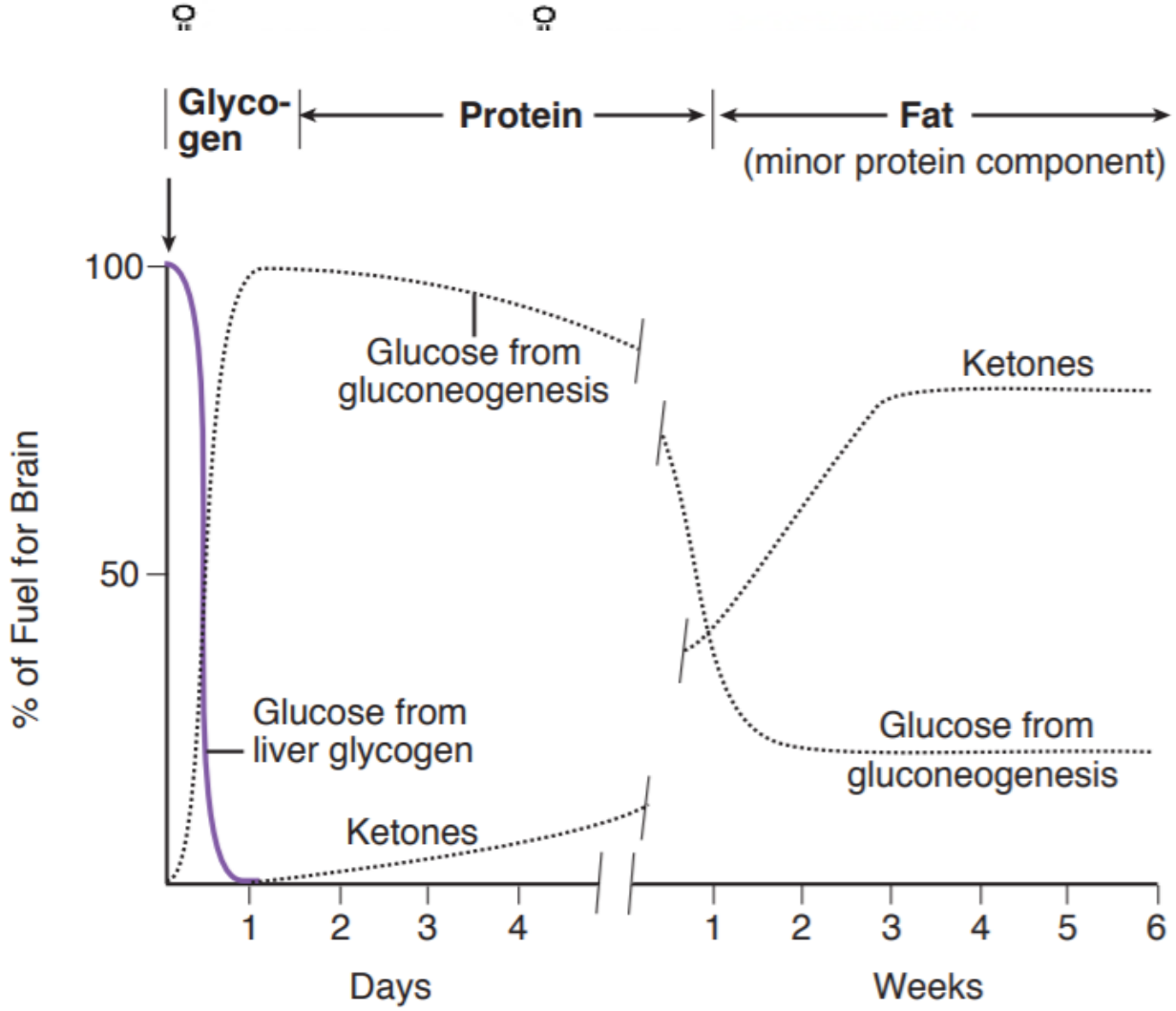
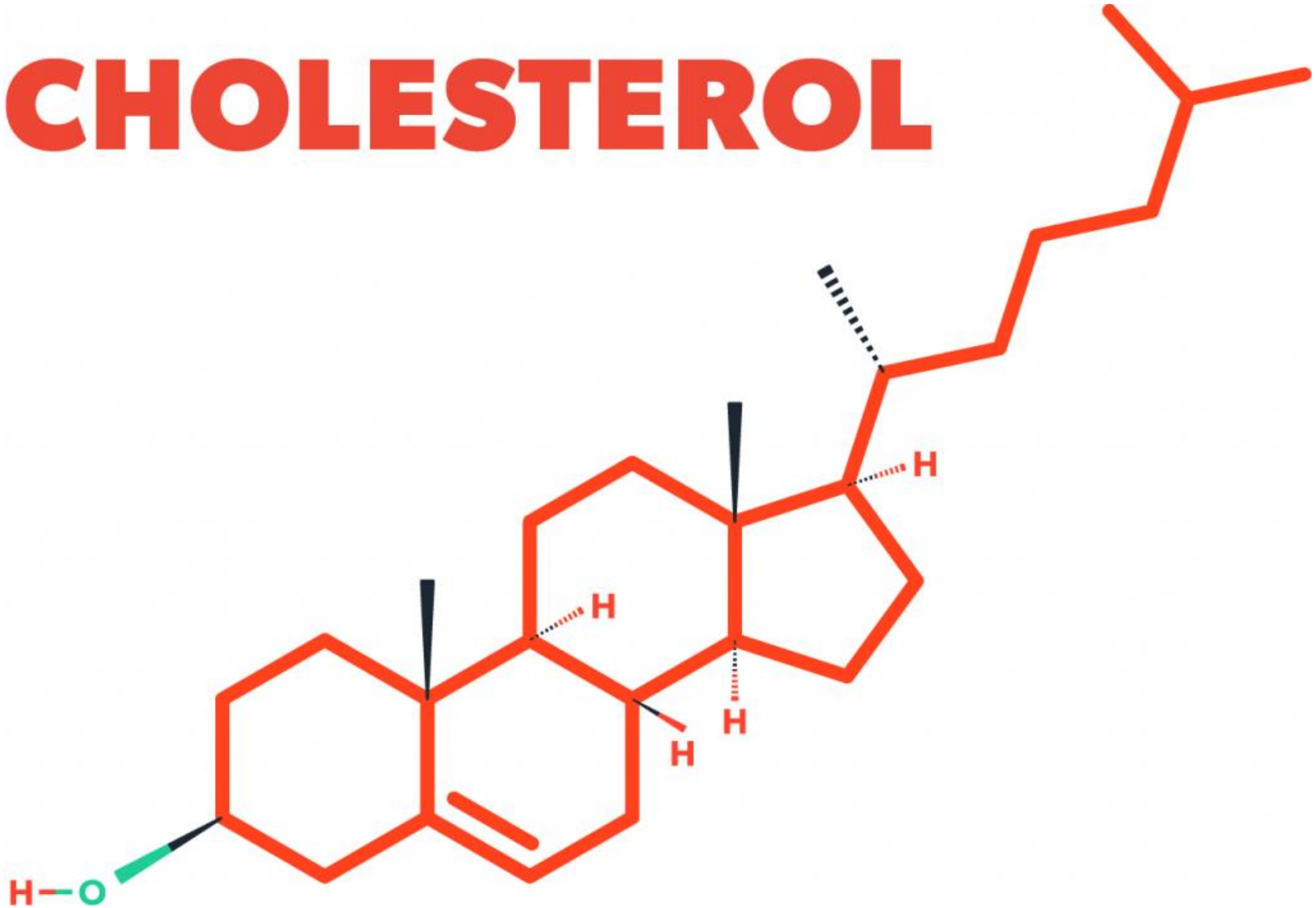


Figure I-16-5. Fuel Use in the Brain During Fasting and Starvation

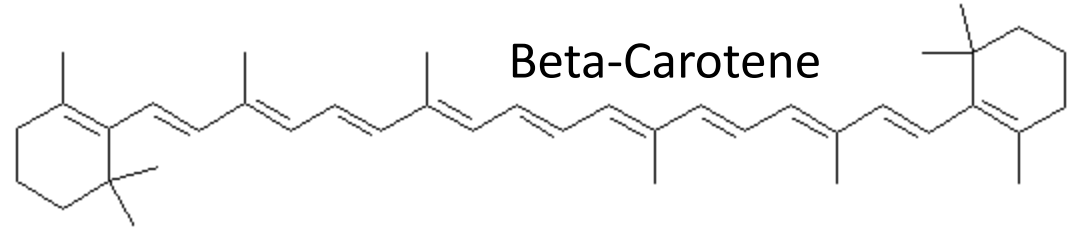
Acetone

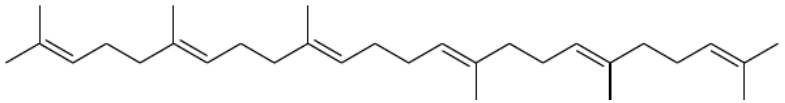
D-β-hydroxybutyrate

Let’s make cholesterol!



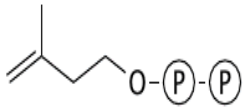
How do we make it?





squalene

HMG-CoA Reductase

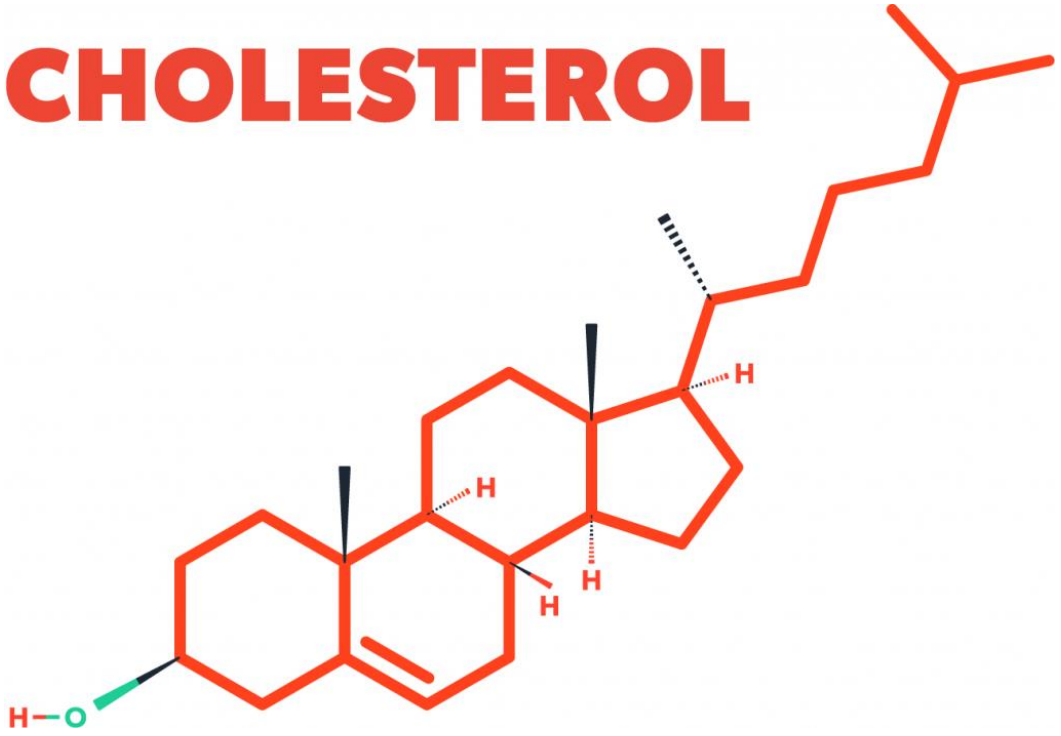


~~isopentenyl-pyrophosphate~~

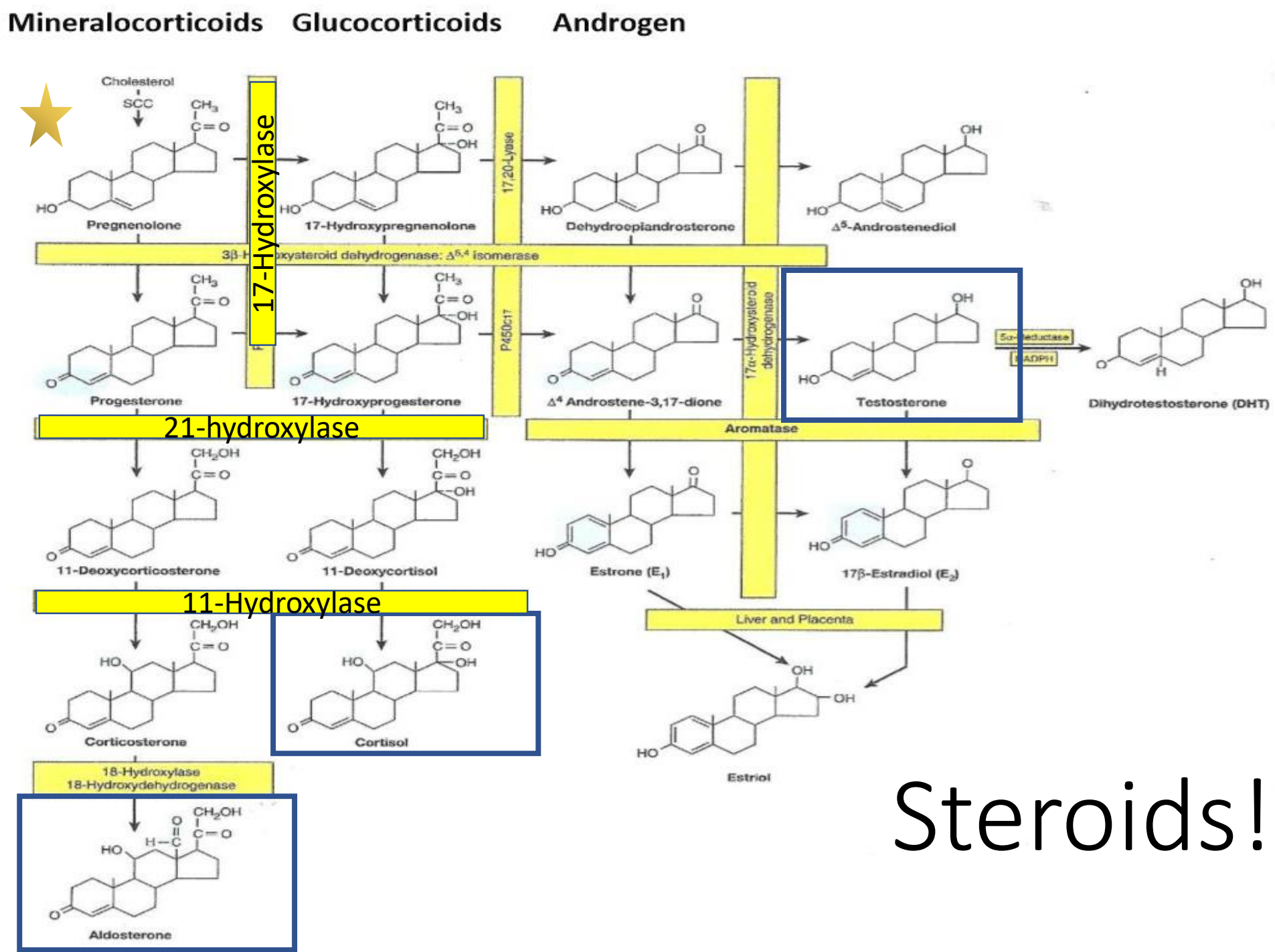
Isoprene units (terpene)

What do we use Cholesterol for?

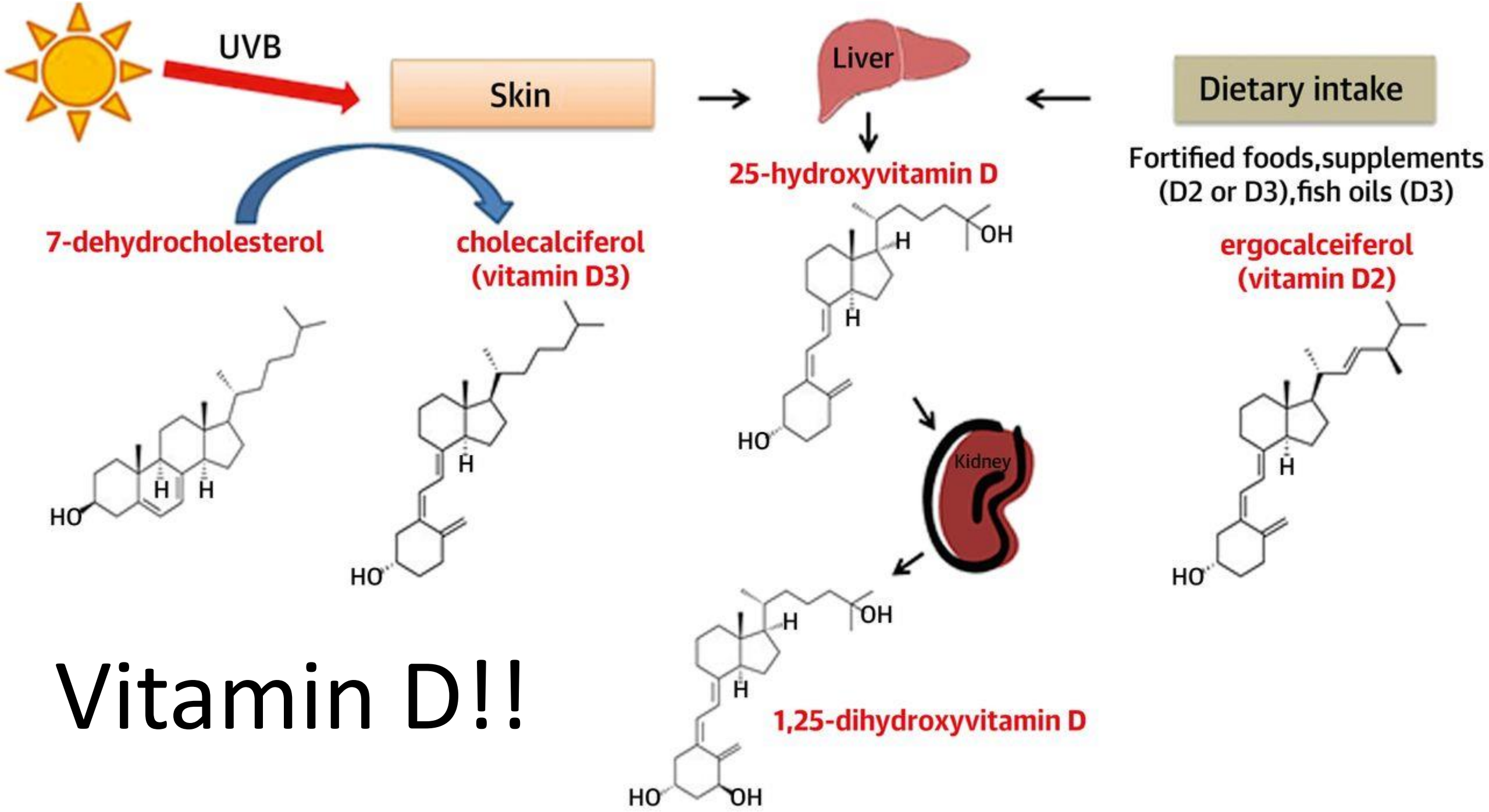
- Membrane integrity
- Steroids
- Vitamin D
- Bile acids



Note
Pregnenolone is Totipotent!



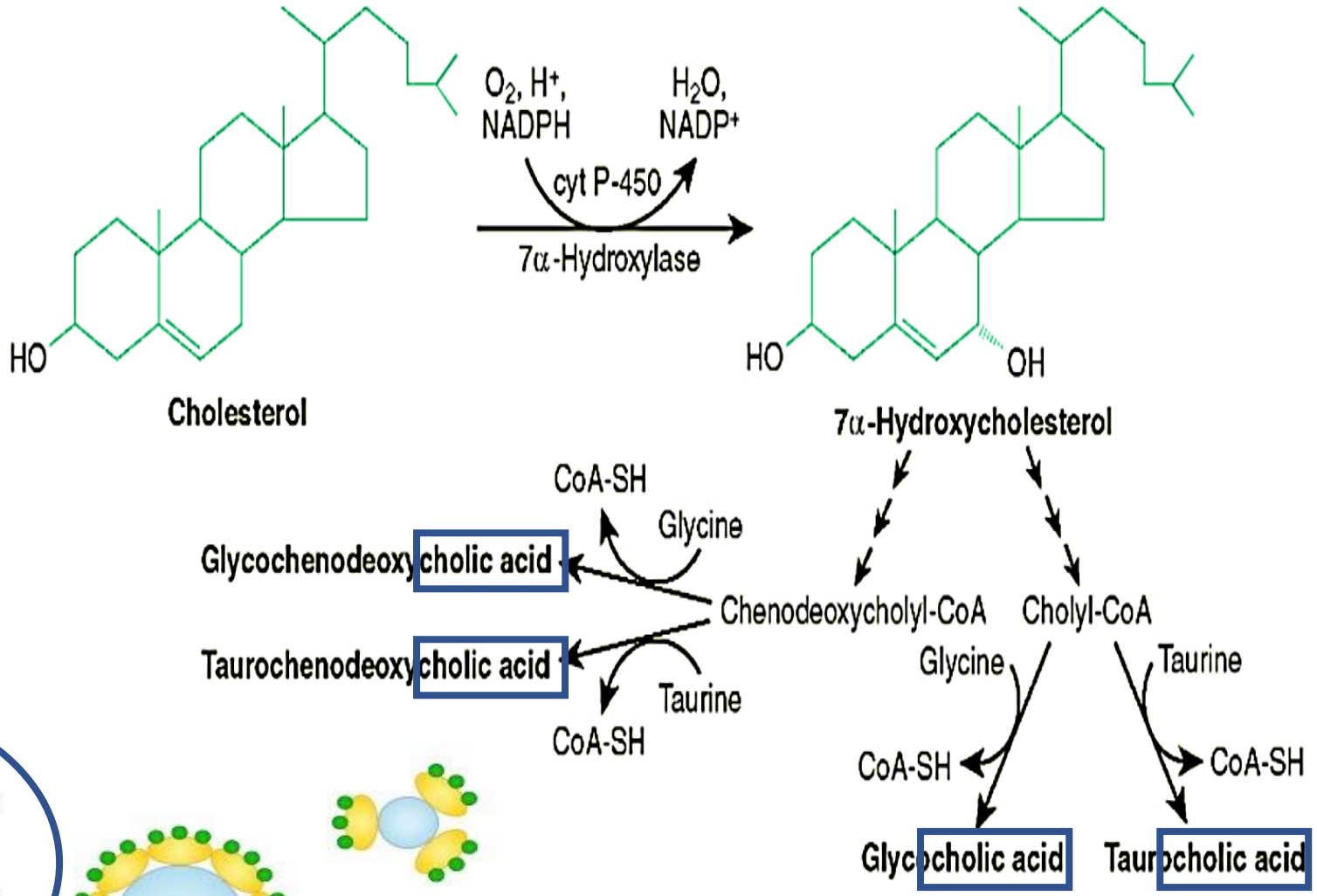
Steroids!!

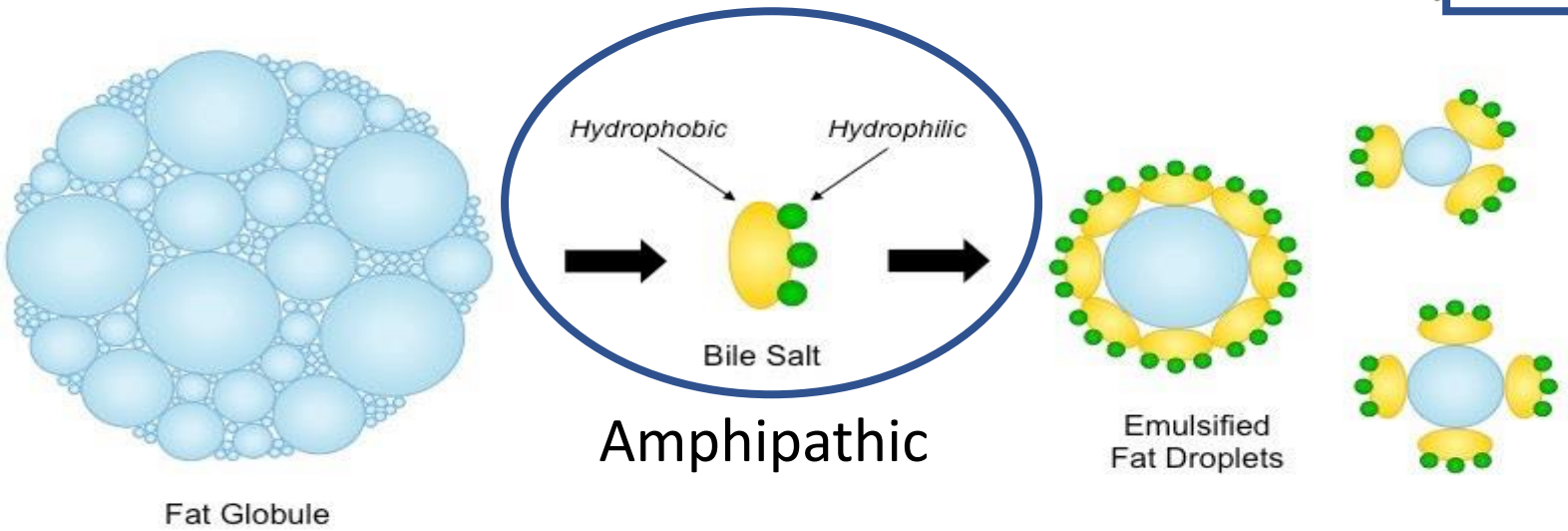

UVB
Skin
Liver
Dietary intake
Fortified foods,supplements (D2 or D3),fish oils (D3)
25-hydroxyvitamin D
7-dehydrocholesterol
cholecalciferol (vitamin D3)
ergocalceiferol (vitamin D2)
Kidney
1,25-dihydroxyvitamin D
Vitamin D!!

Can you break down cholesterol?

NO!

Bile salts!





Note
If you see Cholic acid – it means it's a bile salt

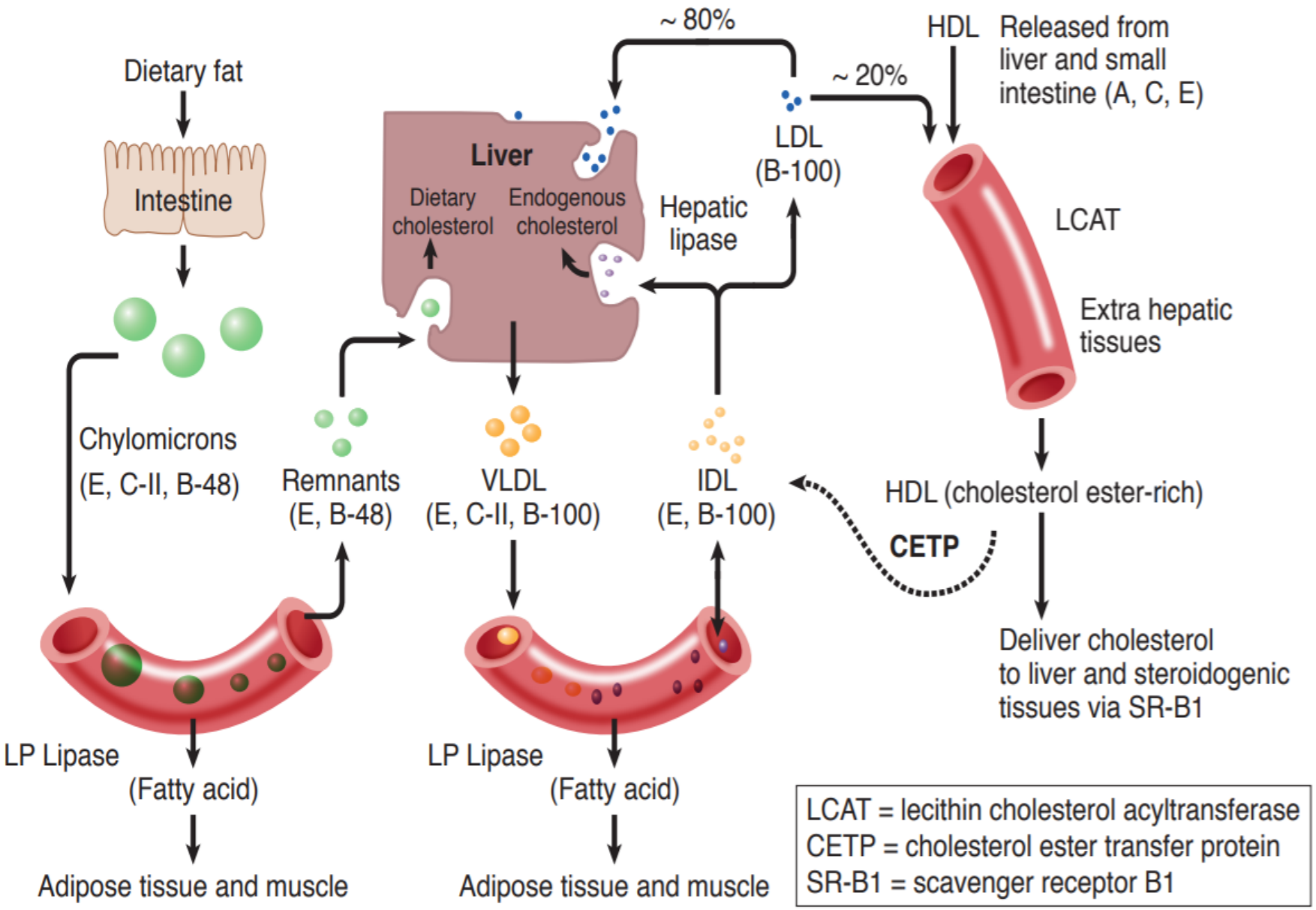


Figure I-15-5. Overview of Lipoprotein Metabolism

*Things to remember

Chylomicrons

- Must obtain Apo C-II, Apo E from HDL
- Apo B48 indentifies

VLDL

- Carries NEWLY synthesized fatty acids from liver to tissues

IDL

- Intermediate between fat/cholesterol transport. Can be converted to LDL by taking up cholesterol from HDL

LDL

- Carries cholesterol to the tissues.
- Apo B-100 binds to the LDL receptor

HDL

- Carries cholesterol from tissues to liver.
- Carries Apo C-II, Apo E to give to nascent Chylomicrons

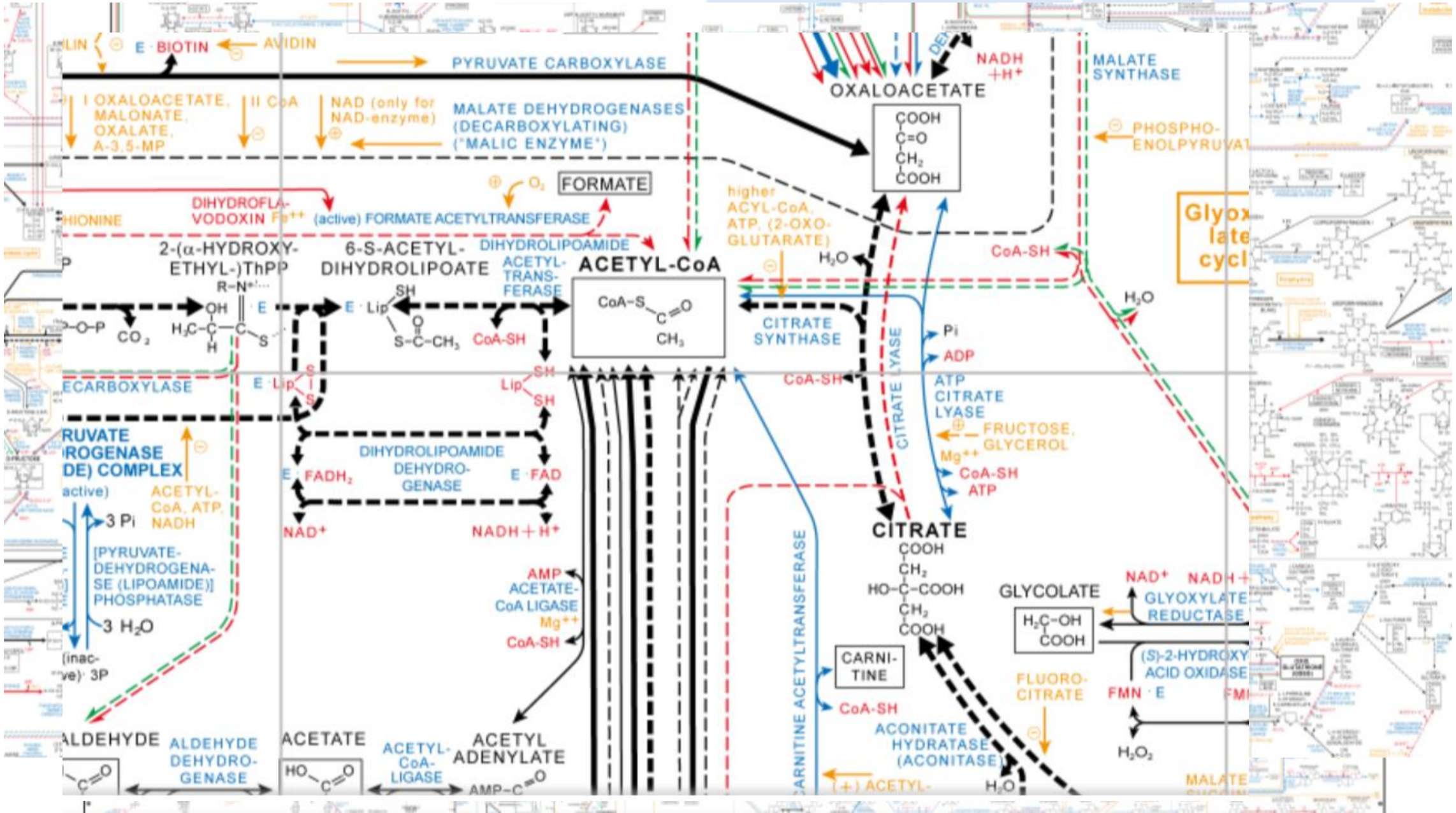
Table I-15-1. Classes of Lipoproteins and Important Apoproteins

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

Nucleotide Metabolism
Purines

Nucleotide Metabolism
NAD, NADP

Antibiotics
Penicillin, Cephalosporin



Note
Central role of Acetyl CoA

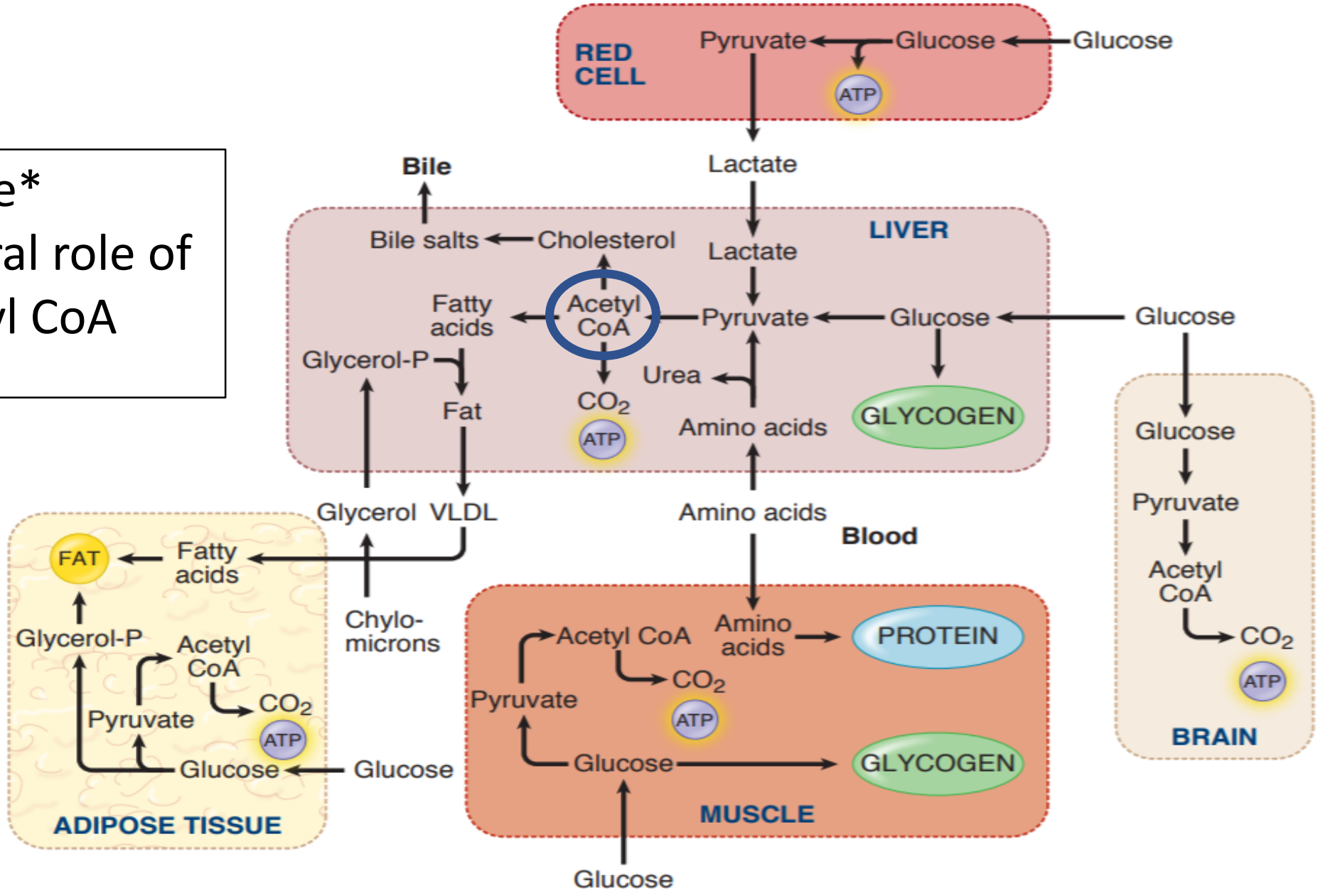


Figure I-11-2. Metabolic Profile of the Well-Fed (Absorptive) State

Note
The carbons from Acetyl CoA cannot be used for Gluconeogenesis

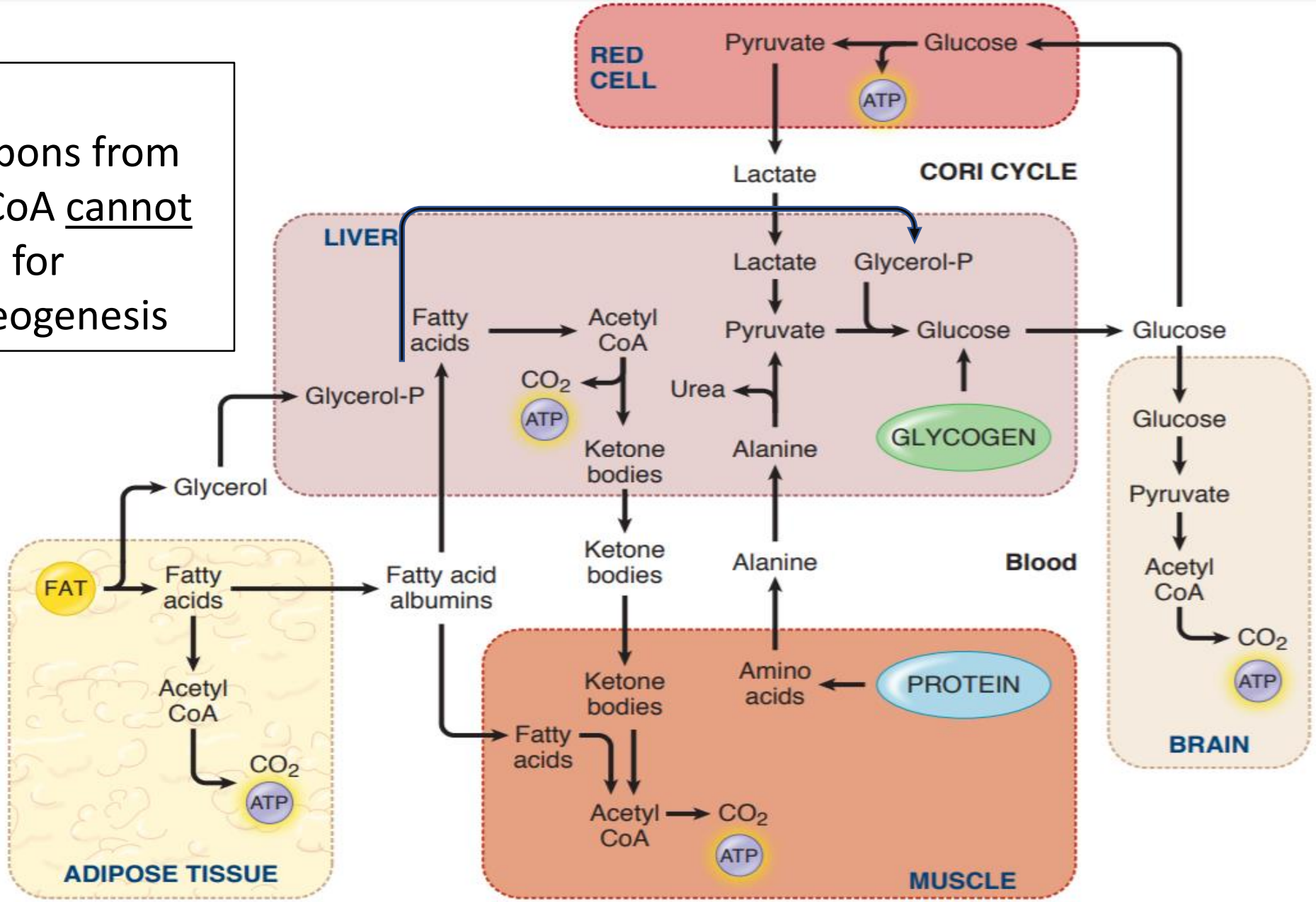


Figure I-11-3. Metabolic Profile of the Postabsorptive State

Overview of Pathways of Carbohydrate and Lipid Metabolism

Pathway	Cell type	Organelle	Final Products
Glycolysis	All cells	Cytosol	Pyruvate
TCA Cycle	All cells with mitochondria	Mitochondria	NADH, FADH, CO2
Electron Transport Chain	All cells with mitochondria	Inner mitochondrial membrane	ATP, H2O
Gluconeogenesis	Liver (Sometimes Kidney)	Cytoplasm (also mitochondrial matrix)	Glucose
Glycogenesis	Liver, Muscle	Cytoplasm	Glycogen
Glycogenolysis	Liver, Muscle	Cytoplasm	Glucose
De Novo Synthesis of Fatty Acids	Liver, Adipocytes	Cytoplasm	Palmitate
Beta-Oxidation	All cells (mainly muscle + liver) EXCEPT erythrocytes	Mitochondrial matrix	NADH, FADH (ATP) Acetyl CoA (ATP)
Ketogenesis	Mainly in Liver (Sometimes Kidney)	Mitochondrial matrix	Ketone bodies

Energy Yield for 1 molecule of glucose

Pathway		ATP Yield
Glycolysis	2 ATP 2 NADH	2 ATP 3/5 ATP
PDH	2 NADH	5 ATP
TCA	2 GTP 6 NADH 2 $FADH_2$	2 ATP 15 ATP 3 ATP
TOTAL		**30 / 32 ATP**

Energy Yield for 1 molecule of palmitate (C16)

	ATP	Multiple	Result
$FADH_2$	2 ATP	7	14
NADH	3 ATP	7	21
Acetyl CoA	12 ATP	8	96
ATP used	-2 ATP		-2
TOTAL			**129**

Enzyme Overview for Carbohydrate and Lipid Metabolism

Carbohydrate Metabolism Enzymes

Process	Enzyme	Substrate	Product	Activation	Inhibition	Comment
Glycolysis	Hexokinase	Glucose	Glucose 6-P		G-6-P	**ATP**
	* Glucokinase	Glucose	Glucose 6-P	insulin		
	Phosphofructokinase-1	Fructose 6-P	Fructose-1,6-BP	AMP (*PFK-2)	ATP Citrate	**ATP**
	*Phosphofructokinase-2	Fructose 6-P	Fructose-1,6-BP	Insulin	Glucagon	Only in liver!
	Pyruvate Kinase	PEP	Pyruvate	Fructose 1,6 BP	ATP Glucagon	Active: dephysphorylated - insulin
Tricarboxylic Acid Cycle (TCA)	Pyruvate dehydrogenase	Pyruvate	Acetyl CoA		Acetyl CoA	Requires Co-factors T, L, C, F, N
	Isocitrate dehydrogenase	Isocitrate	Alpha-ketoglutarate	AMP	ATP NADH Citrate	
Gluconeogenesis	Pyruvate carboxylase	Pyruvate	OAA	Acetyl-CoA	PDH	*ABC enzyme* (requires ATP, biotin and CO2)
	PEP carboxykinase	OAA	PEP	Glucagon, cortisol	Insulin	Requires GTP
	Fructose-1,6-bisphosphatase	Fructose-1,6-BP	Fructose-6-P	ATP	AMP; Fructose-2,6-BP	
Glycogenesis	Glycogen synthase	UDP Glucose	Glycogen	Insulin	Glucagon	Active: dephosphorylated - insulin
Glycogenolysis	Glycogen phosphorylase	Glycogen	Glucose 1-P	Glucagon AMP	Insulin ATP	Active: Phosphorylated - glucagon

Fatty Acids

Process	Enzyme	Substrate	Product	Activating Factors	Inhibiting Factors	Comment
Synthesis of FA	Acetyl CoA Carboxylase	Acetyl CoA	Malonyl CoA	Insulin	Glucagon	Active: Dephosphorylated - Insulin Requires Co-factors A, B, C
TG degradation	Hormone Sensitive Lipase	TG	FA + Glycerol	Epinephrine glucagon Cortisol	Insulin	Active: Phosphorylated - epinephrine
Beta-oxidation	Carnitine acyltransferase-1	FA-CoA	FA-Carnitine		Malonyl CoA	Inhibition prevents entry of FA into mitochondrial matrix