FATTY ACID METABOLISM

lipids are a chemically diverse group of compounds, the common & defining feature of which is their insolubility in water.

Highly soluble in non-polar solvents chloroform, ether, benzene.

Their water-insolubility contributes to much of the complexity in their digestion, transport, and metabolism.

Essential to the overall energy economy of the cell.

Initial step in TG catabolism:

Hydrolysis of a TG by lipases

glycerol + 3 fatty acids

<u>Hormonal regulation of adipose-cell lipase:</u>

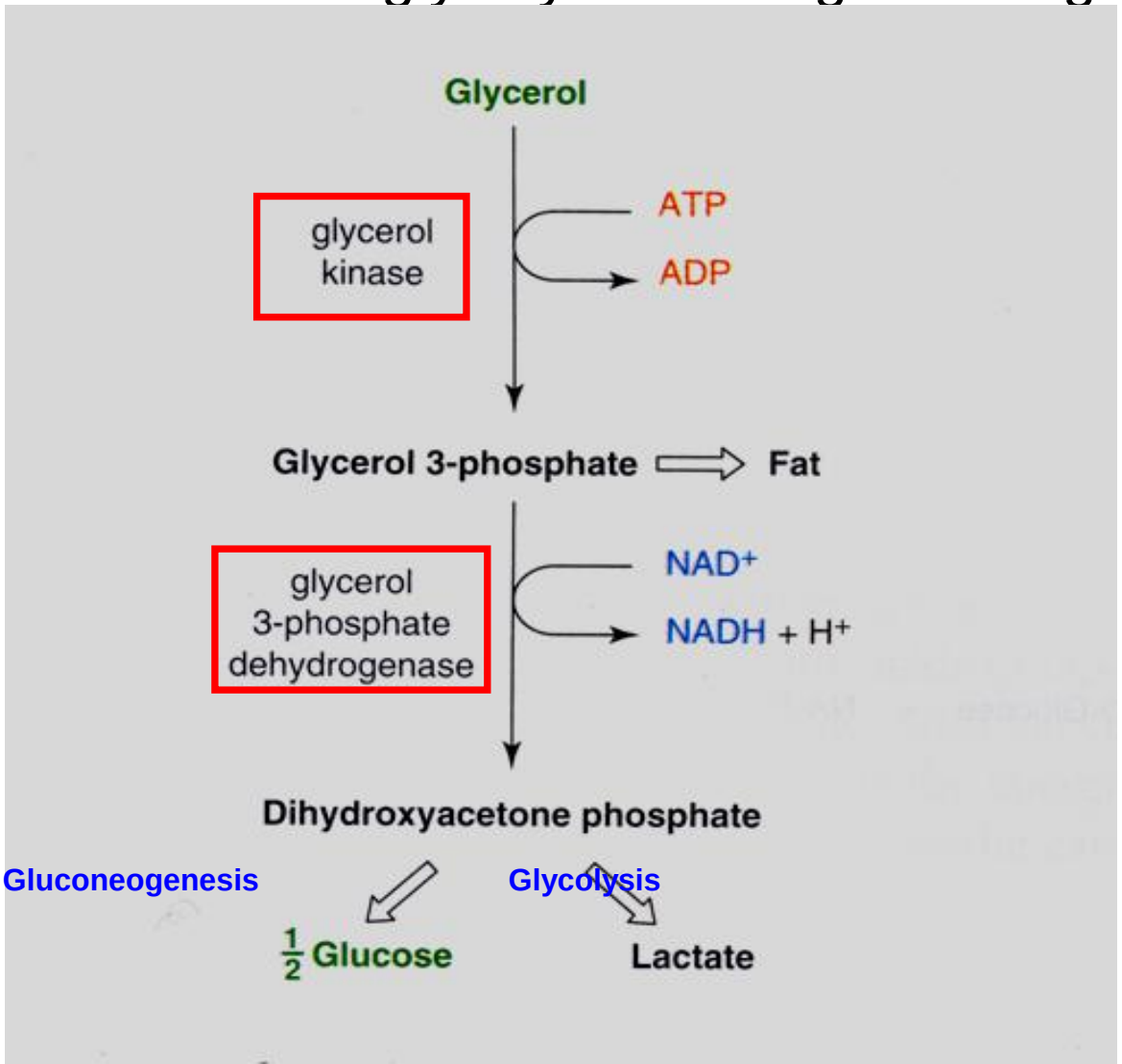
Epinephrine and Glucagon ⟶ adenylate cyclase in adipose cells.

(second messenger) cAMP↑ , activates PKA, phosphorylates lipase and activates it.

Analogues to its role in glycogen degradation, Insulin antagonistic effect.

Glycerol is phosphorylated and oxidized to DHAP

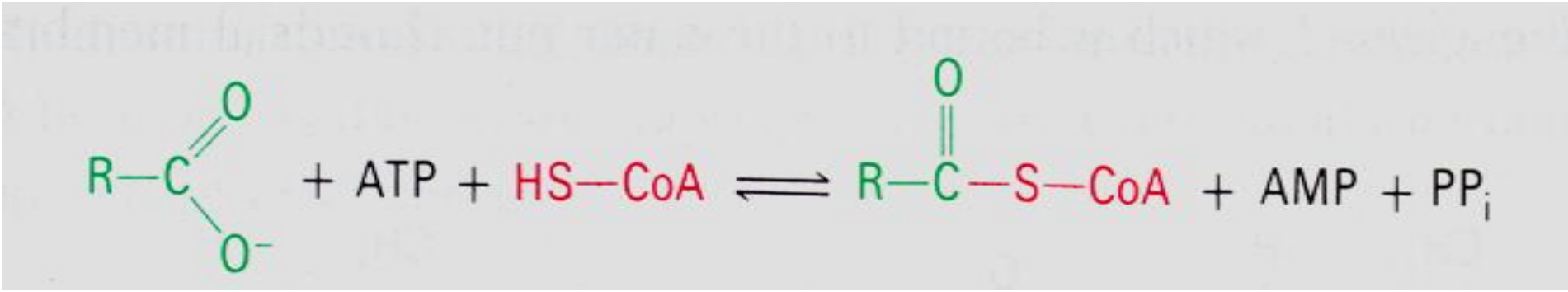
glycolysis gluconeogenesis



Metabolism of Fatty Acids

1. Activation: A FA must be "activated" before it can either be broken down to CO_2 or it can be used for TG synthesis.
FA "activation" is catalyzed by by *acyl CoA synthetase* (also called *fatty acid thiokinase*).

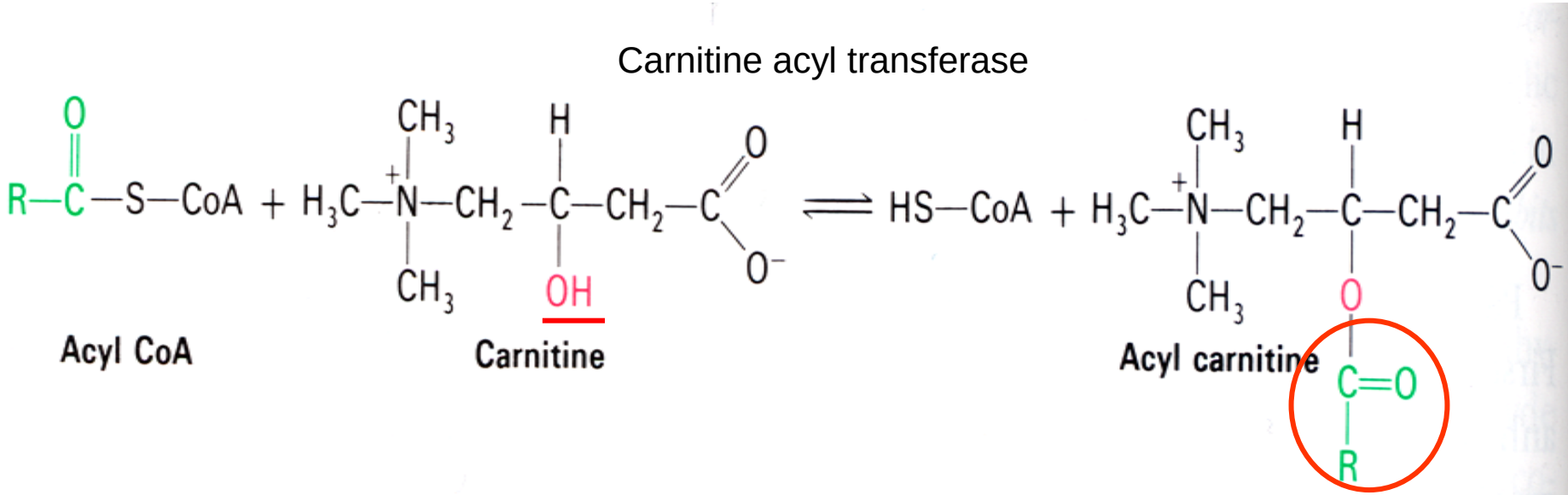
Activation reaction occurs in the outer mitochondrial membrane.

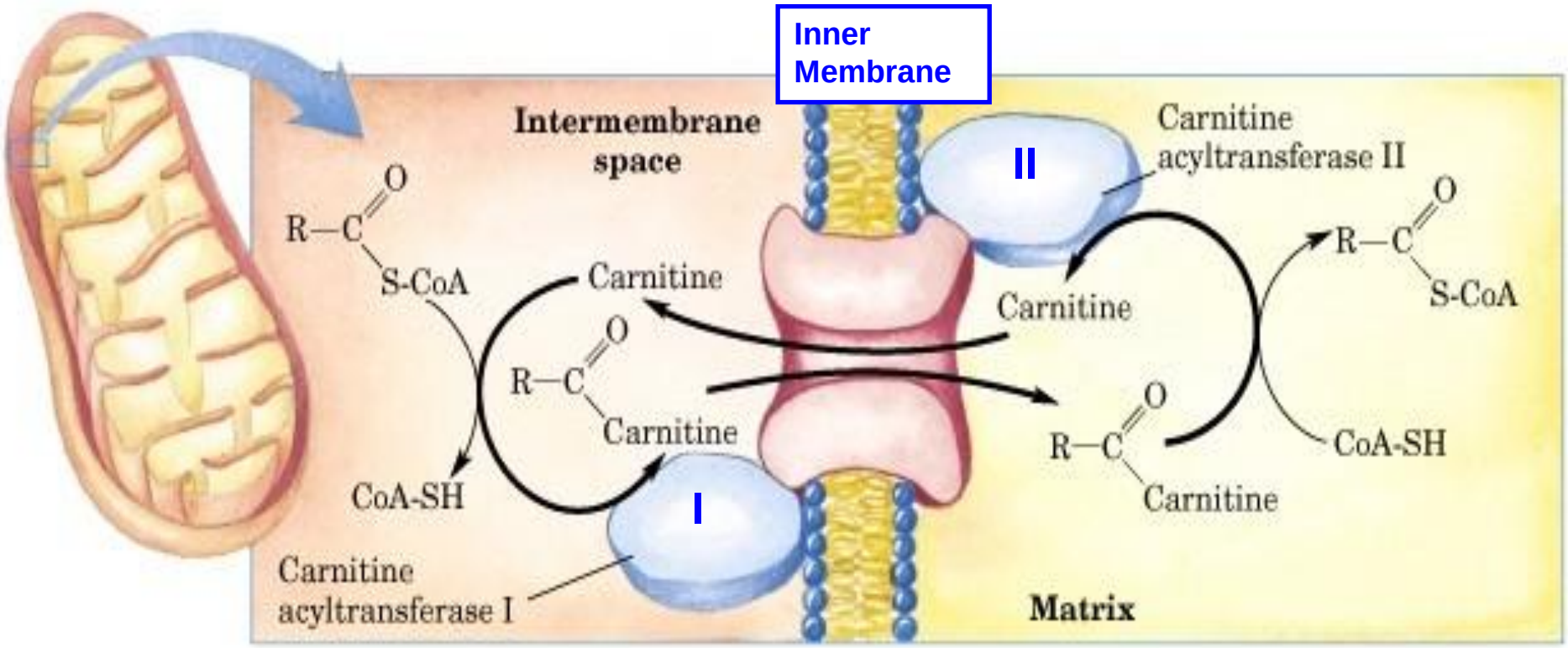


2. Transport of Acyl-CoAs into Mitochondria:

< 12 carbon fatty acyl CoAs passively diffuse through the mitochondrial inner membrane
> 12 carbon fatty acyl CoAs are specifically transported across the inner membrane.

Basic Strategy: Convert acyl CoA to an acyl carnitine derivative, which is then transported, then regenerate the acyl CoA within the mitochondrial matrix.





<u>Regulation:</u> The principal point of regulation of FA oxidation is via inhibition of carnitine acyltransferase I by malonyl CoA.

<u>Two Important Points:</u>

i) Inhibition occurs at the first committed step in the FA oxidation pathway.

ii) Reciprocol regulation of degradative and synthetic pathway. Thus, when FA synthesis occurs (producing malonyl CoA), FA oxidation is inhibited.

3. Catabolism of Fatty Acyl CoAs in the Mitochondrial Matrix

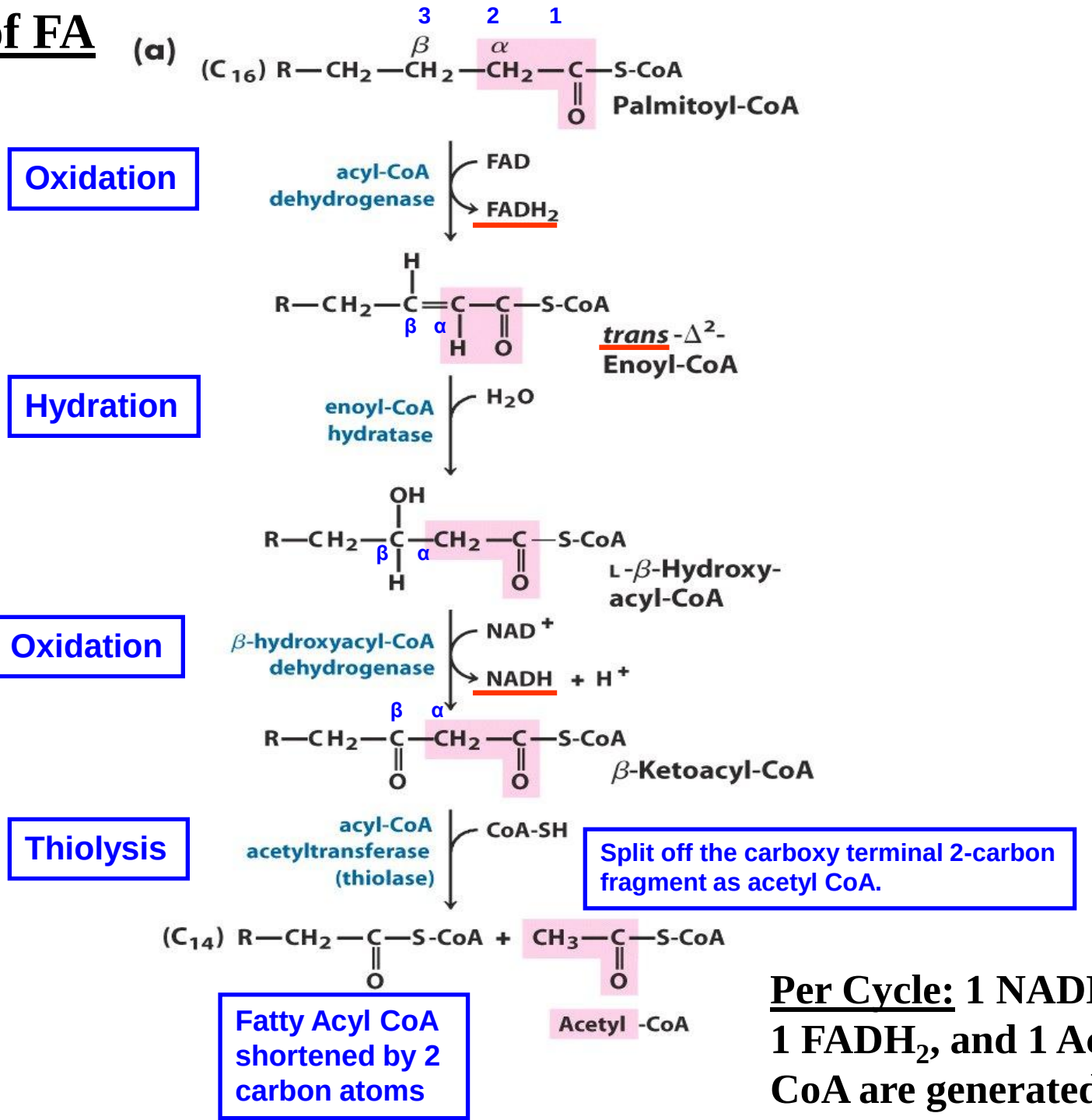
- Degradation of FAs proceeds 2 carbons at a time, starting from the carboxyl end.

- The reactions occur in the mitochondrial matrix.

- Oxidation reactions directly feed reducing equivalents to the respiratory chain to make ATP.

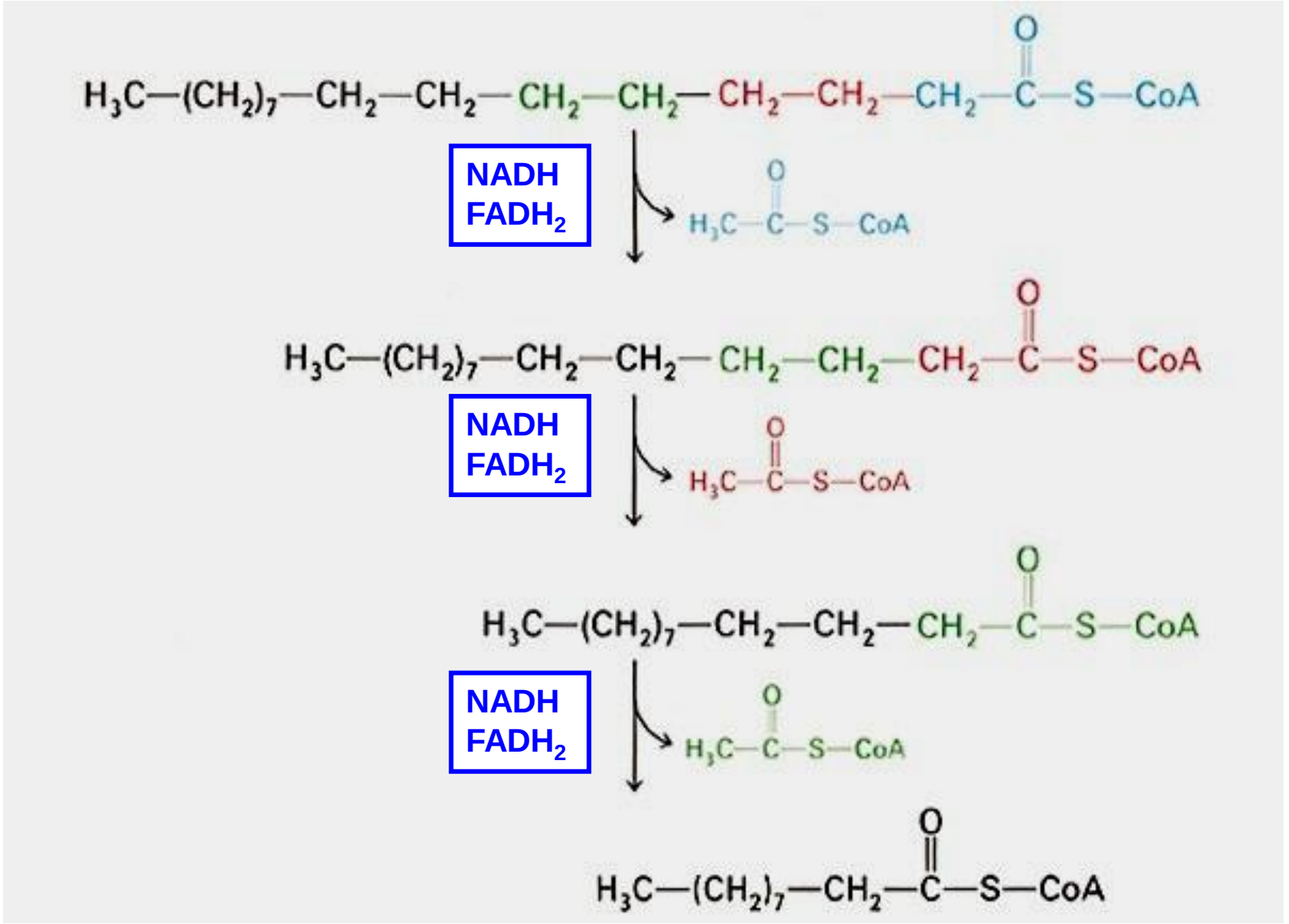
- The released acetyl CoA enters the citric acid cycle which will yield additional ATP.

β-Oxidation of FA



Per Cycle: 1 NADH, 1 $FADH_2$, and 1 Acetyl CoA are generated.

First 3 cycles of degradation of palmitoyl-CoA:



4. Energy Yield of FA Oxidation

	One Cycle
NADH	3 ATP
$FADH_2$	2 ATP
Acetyl CoA	12 ATP (generated via citric acid cycle; i.e., 3 NADH + 1 $FADH_2$ +1 GTP)

Example: Palmitoyl CoA (16 carbons)

NADH=21ATP

FADH2=14ATP

7 cycles of oxidation = 35 ATP

8 acetyl CoAs produced = 96 ATP

TOTAL = 131 ATP from palmitoyl CoA

For fa. Activation 2ATP(AMP is rephosphorylated to ADP.

131 ATP-2ATP (activation of fa.) = 129ATP from palmitate

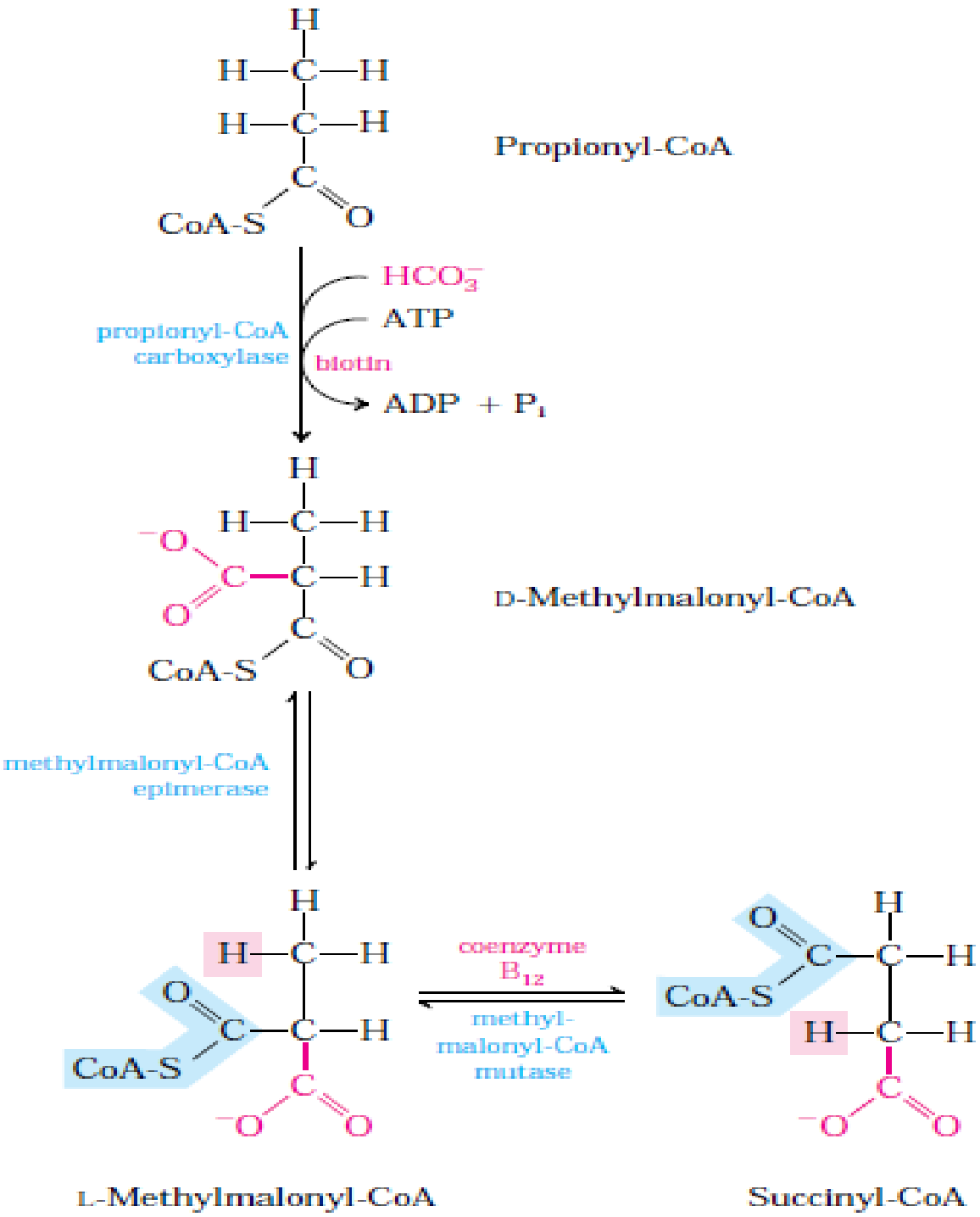
Odd-chain Fatty Acids

- Most naturally occurring lipids contain FA with an even number of carbons

- Lipids of plants & certain marine organisms have FA with an odd number of carbons.

- oxidation of odd number carbon FAs yields acetyl CoA & propionyl CoA in the final round.

- **Propionyl CoA enters citric acid cycle after being converted to succinyl CoA.**



Ketone Body Synthesis and Utilization

Ketone bodies refer to 3 compounds: 3-hydroxybutyrate
acetoacetate
acetone

Produced by the liver & utilized by extrahepatic tissues.

Usually produced in small amounts. But Greatly increased during:

High fat diets:
Increase f.a used by the liver to form ketones .

Starvation/ fasting :
fa from break down of TG in adipose tissue are used to form ketone bodies in the liver & delivered to the brain, muscles & peripheral tissues

Diabetic ketosis:
significant loss of insulin and relative abundance of glucagon leads to strong mobilization of fatty acids from adipose tissue.
Ketone bodies are relatively strong acids, and their increase in blood lowers the pH. The acidification of blood is dangerous because it impairs the ability of hemoglobin to bind oxygen, which might cause coma and death.

Acetyl CoA produced via FA oxidation can enter the TCA cycle only if sufficient OAA exists.

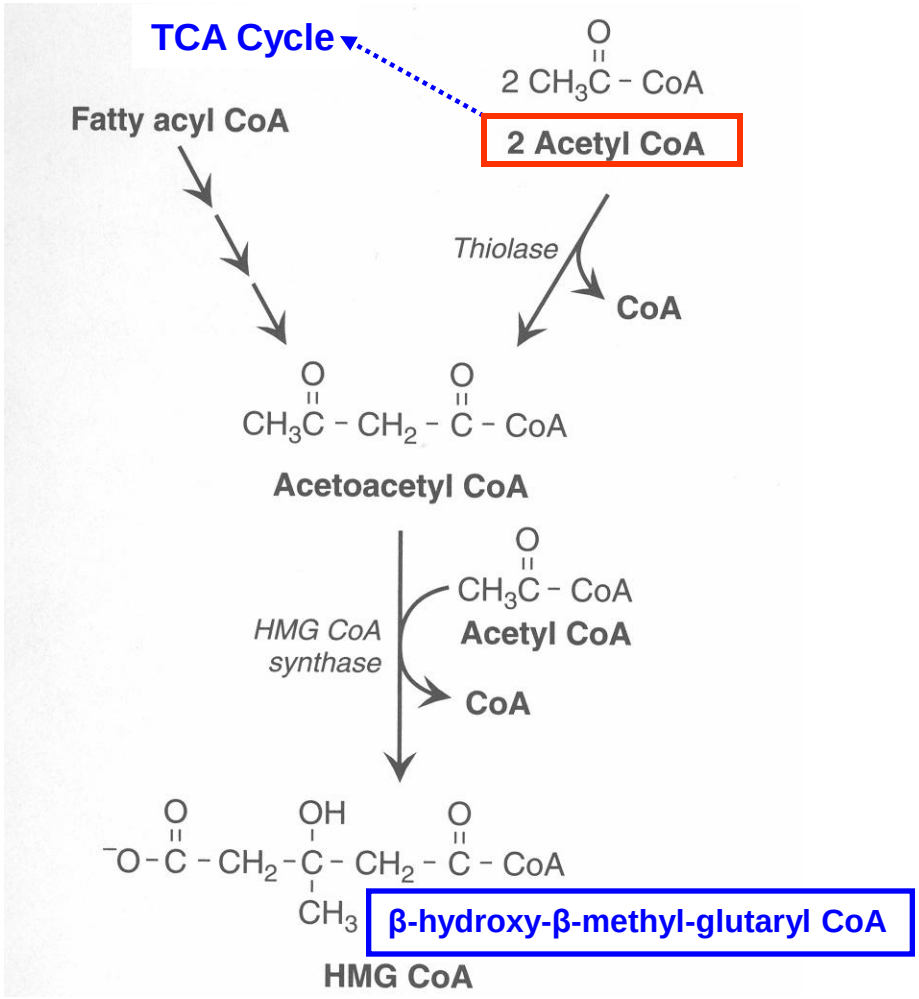
When there is insufficient carbohydrate (fasting / diabetes) OAA consumed to form glucose (via gluconeogenesis).

Note:
OAA⟶PEP catalyzed by PEP-carboxykinase, an enzyme present in liver, absent in muscle & heart.

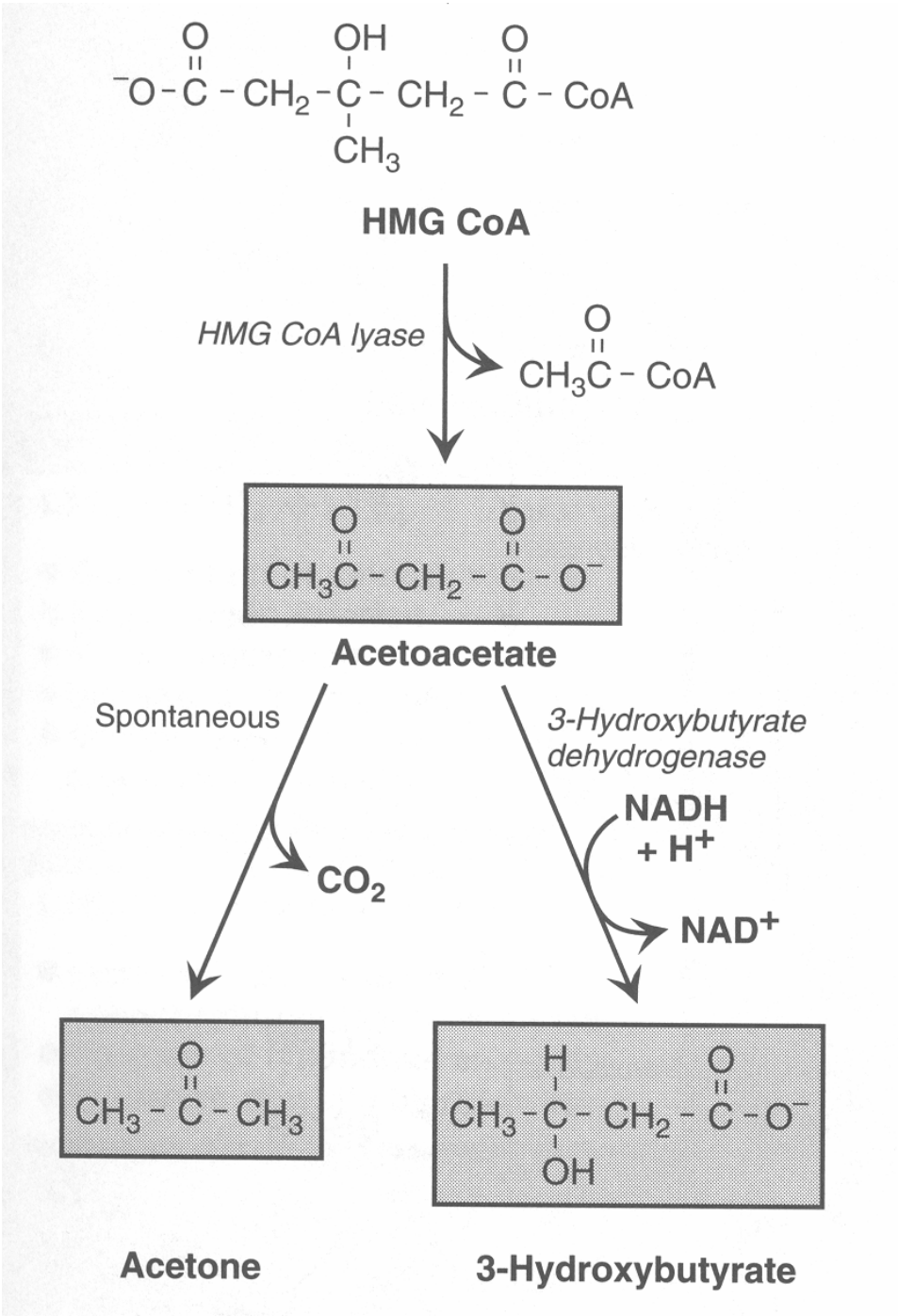
Thus, there is no depletion of OAA in muscle & heart →they can handle incoming acetyl CoA.

Depletion of TCA cycle OAA in liver causes acetyl CoA to be diverted to ketone body production.

Thus, it allows continued FA oxidation even when acetyl CoA is not being oxidized by the cycle.

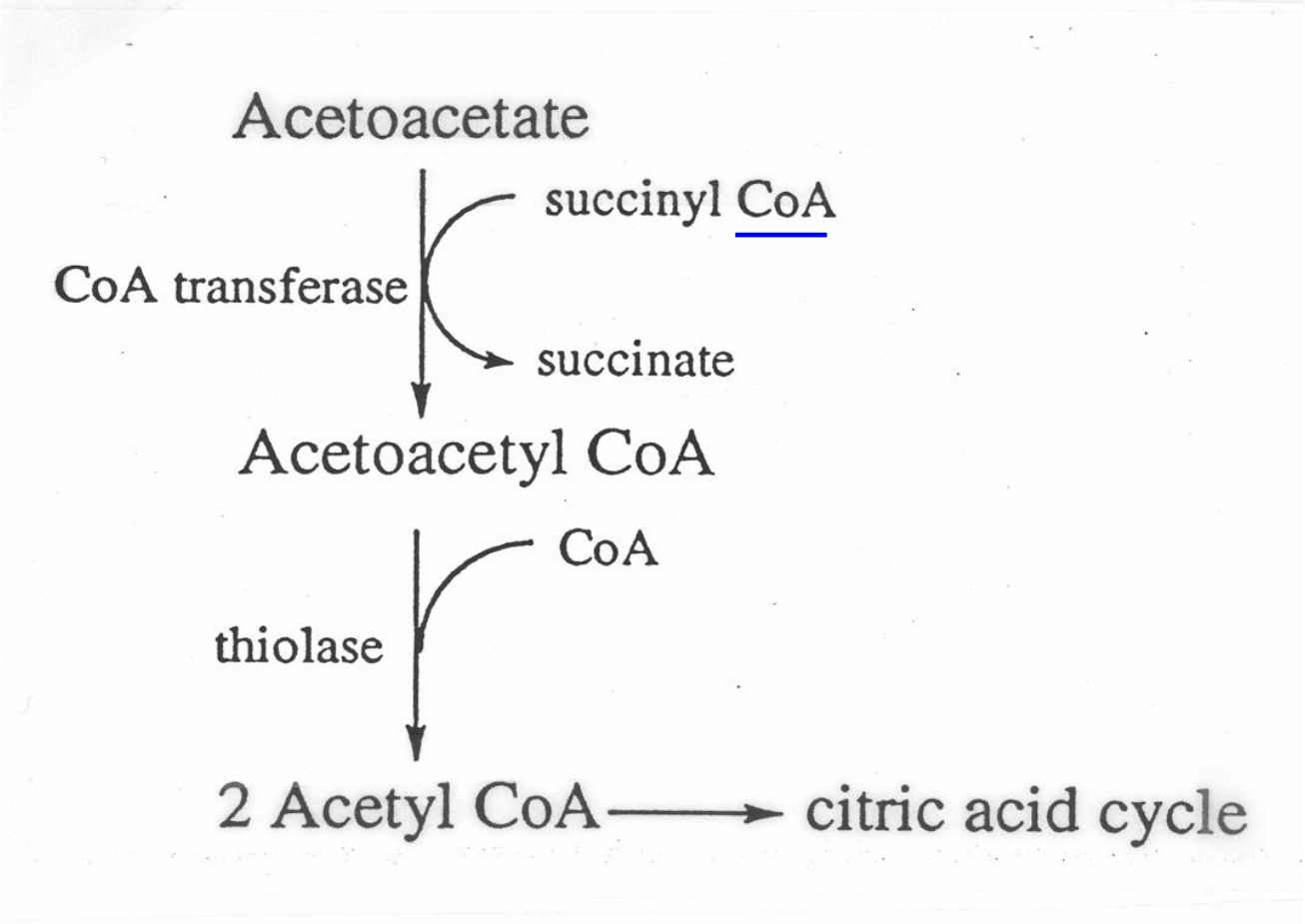


HMG CoA Synthase rate- limiting step & is present in significant quantities only in the liver.



Ketone bodies are released into the circulation & are used by a variety of peripheral tissues as an energy source.

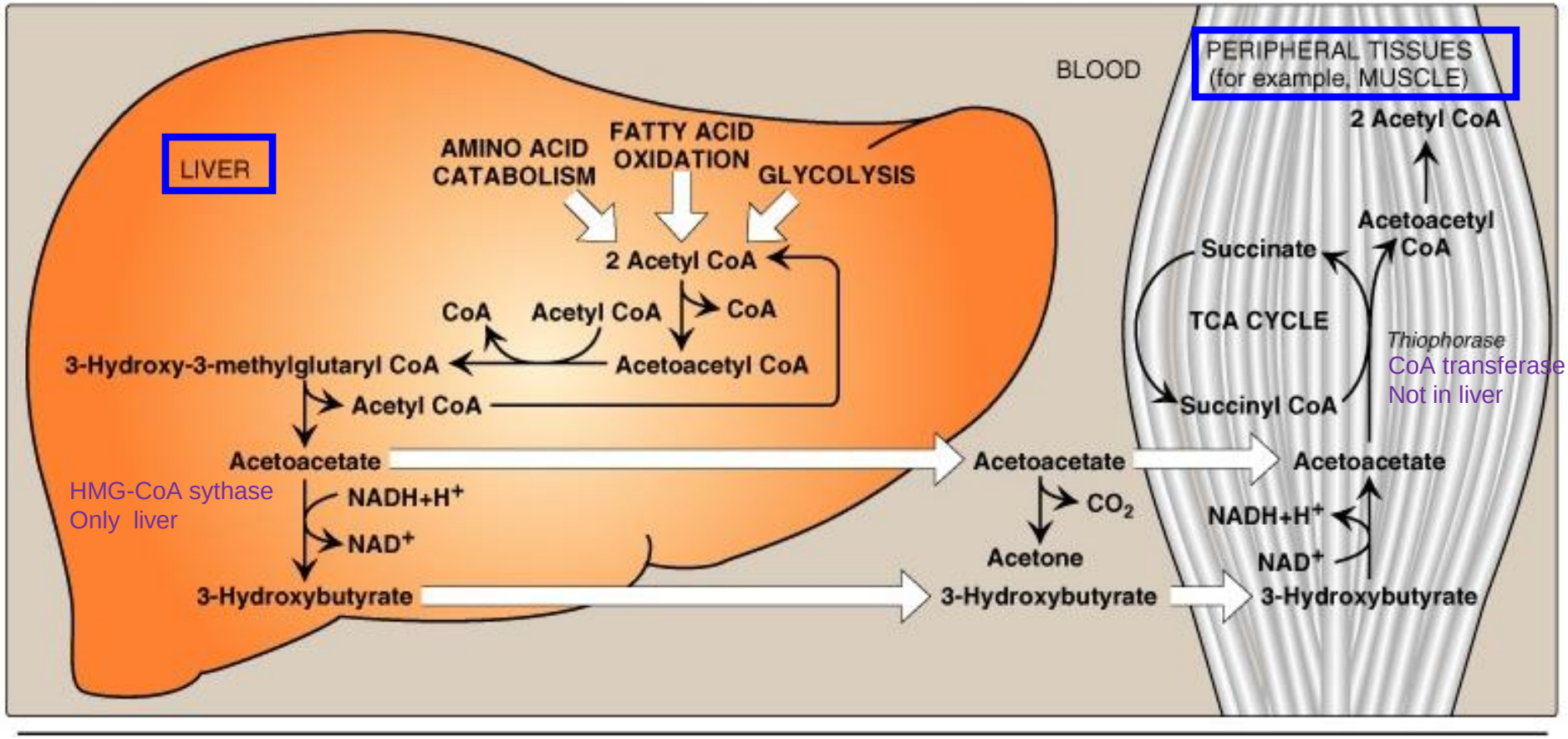
Utilization of Ketone Bodies by the Peripheral Tissues



The liver lacks CoA transferase → it cannot utilize ketone bodies as an energy source for itself.

Ketogenesis : more AcetylCoA than TCA can handle.

Ketone Body Synthesis in the Liver & Utilization in Peripheral Tissues



In starvation 75% of the fuel needs of the brain = acetoacetate.

[acetoacetate] ⇧ in blood decrease lipolysis rate.

Low Insulin/Glucagon ratio stimulates ketogenesis in liver; gluconeogenesis stimulated energy supplied by fat oxidation .Can be especially severe in unregulated diabetic

table 17–2

Ketone Body Accumulation in Diabetic Ketosis

	Urinary excretion (mg/24 h)	Blood concentration (mg/100 mL)
Normal	≤125	<3
Extreme ketosis (untreated diabetes)	5,000	90