METABOLIC BIOCHEMISTRY

Fatty Acid Catabolism (β-oxidation)

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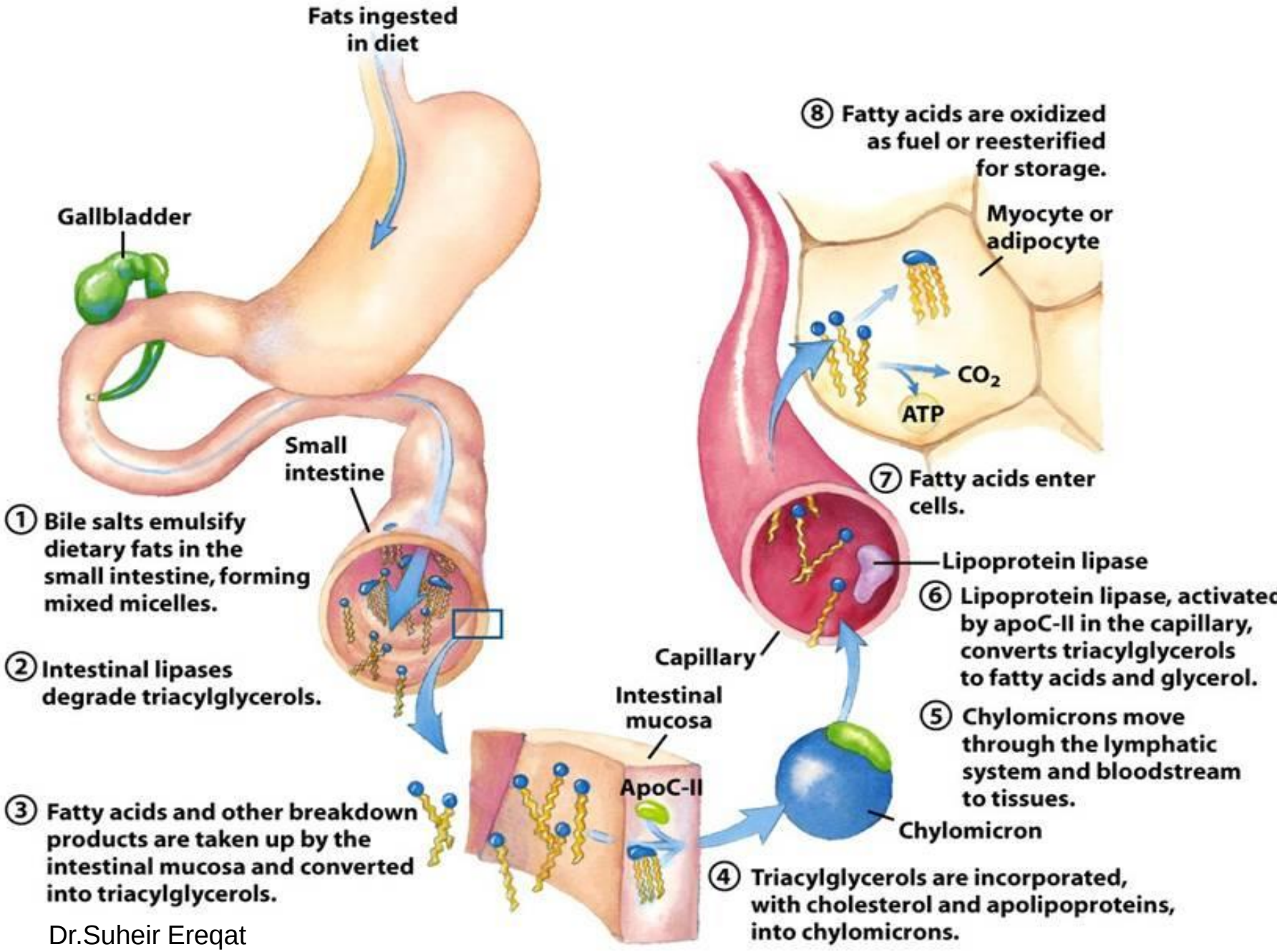
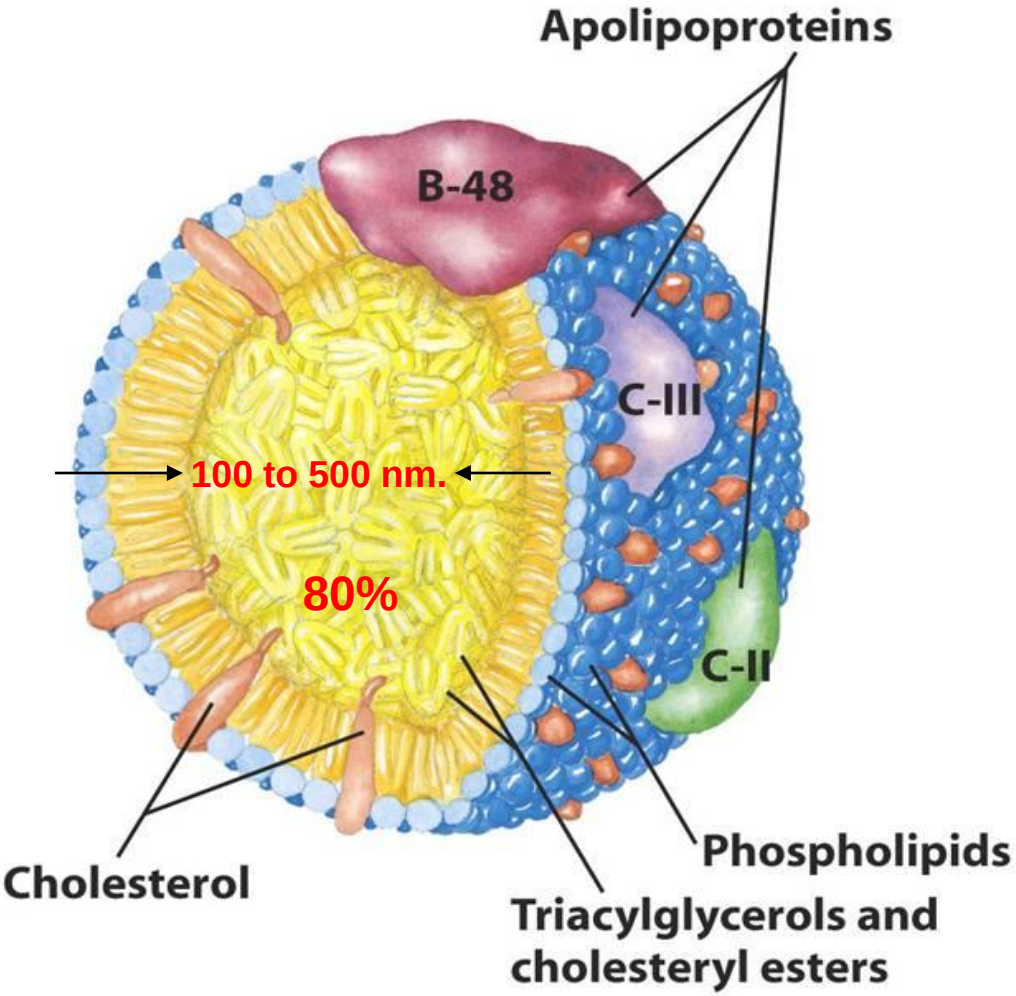
- Greatest fraction of fuel for most organisms and organs
  - Vertebrates
  - Muscle (including heart), liver
- Fat sources for energy
  - Ingested
  - Taken from stores (Adipocytes)
  - Synthesized in liver from carbohydrates

Digestion and Transport of Fats

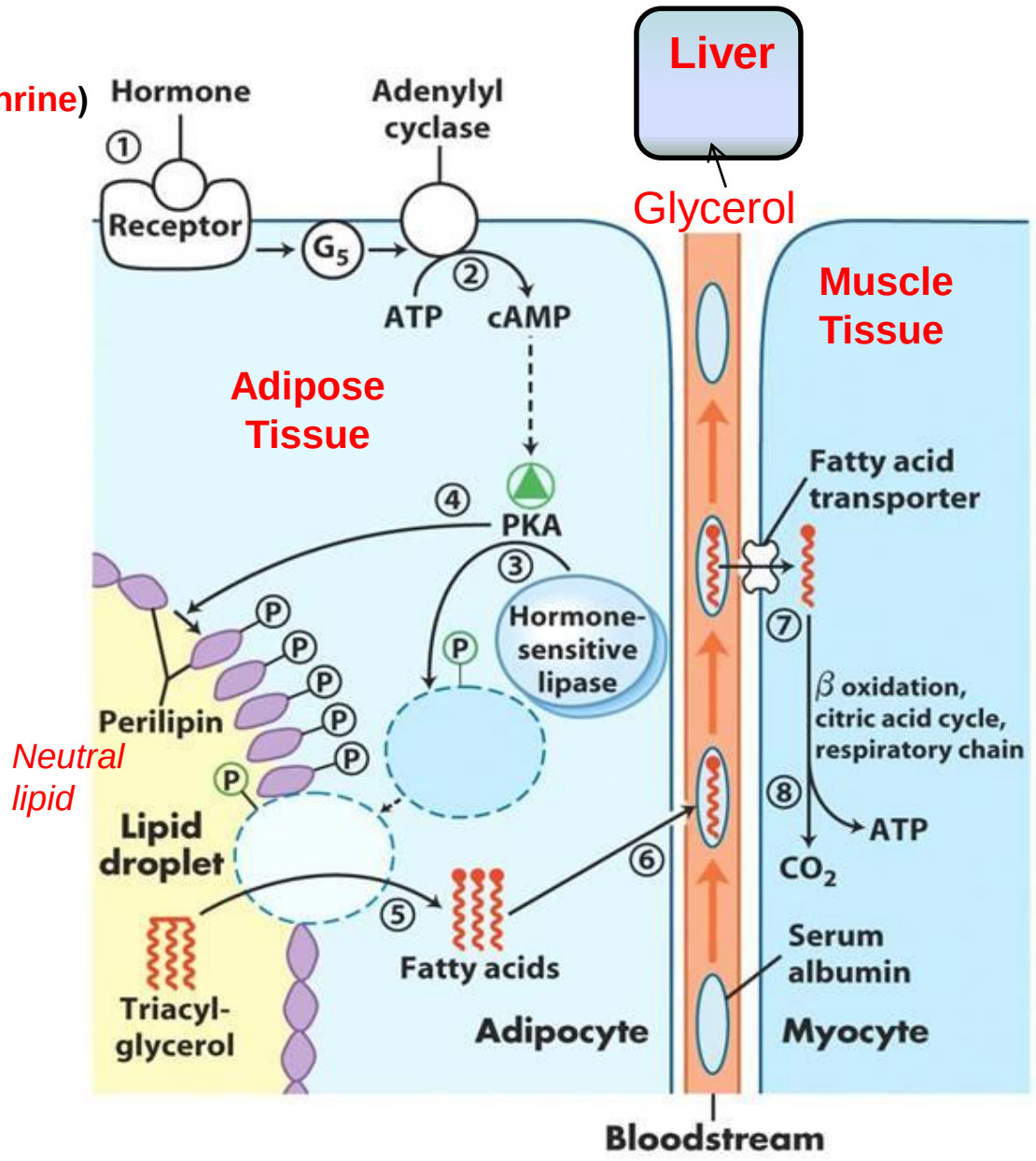


Molecular structure of a chylomicron



Hormones Trigger Mobilization of Stored Triacylglycerols

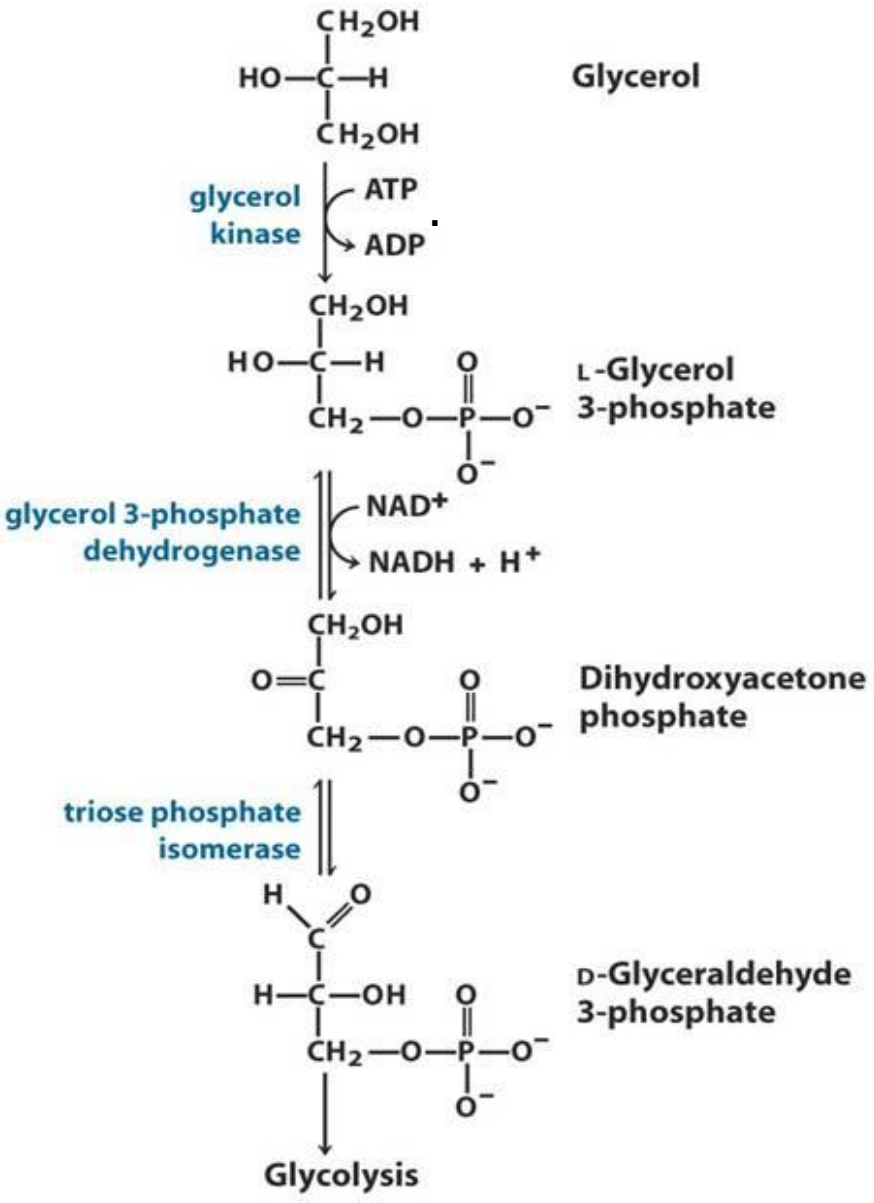
(Glucagon, Epinephrine)



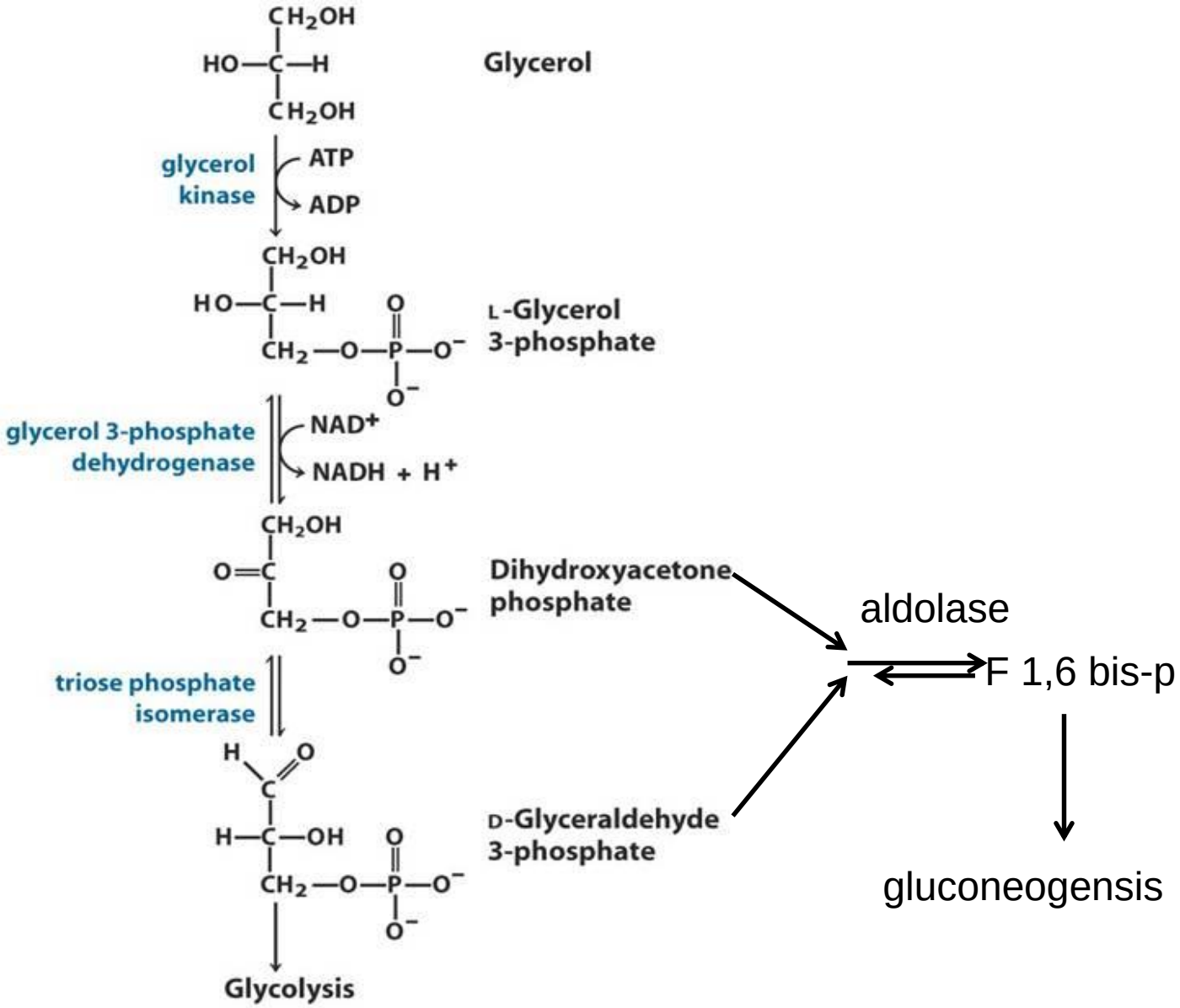
Entry of glycerol into the glycolytic pathway

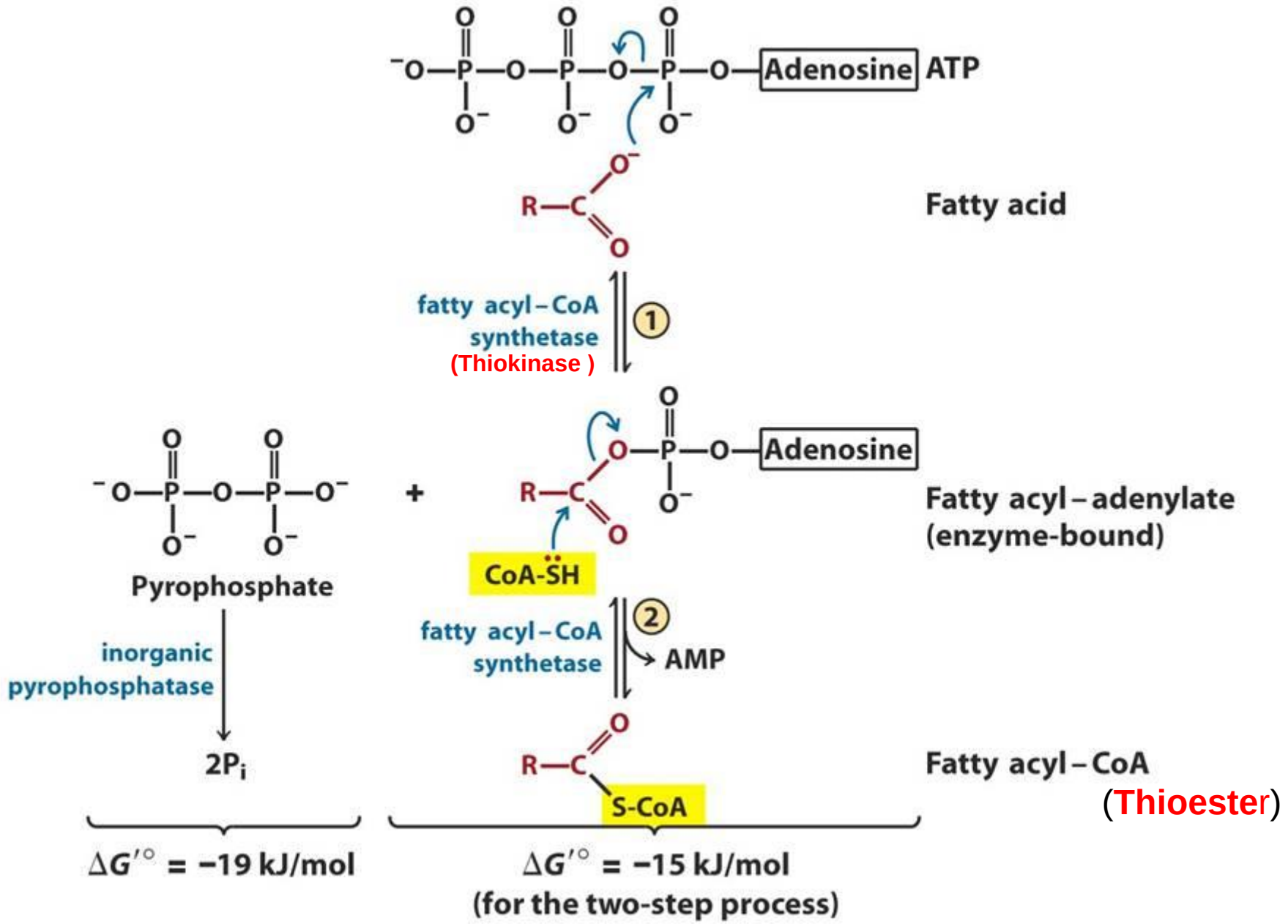
Well fed state

About 95% of the biologically available energy of triacylglycerols resides in their three long-chain fatty acids;
only 5% is contributed by the glycerol moiety



Fasted state

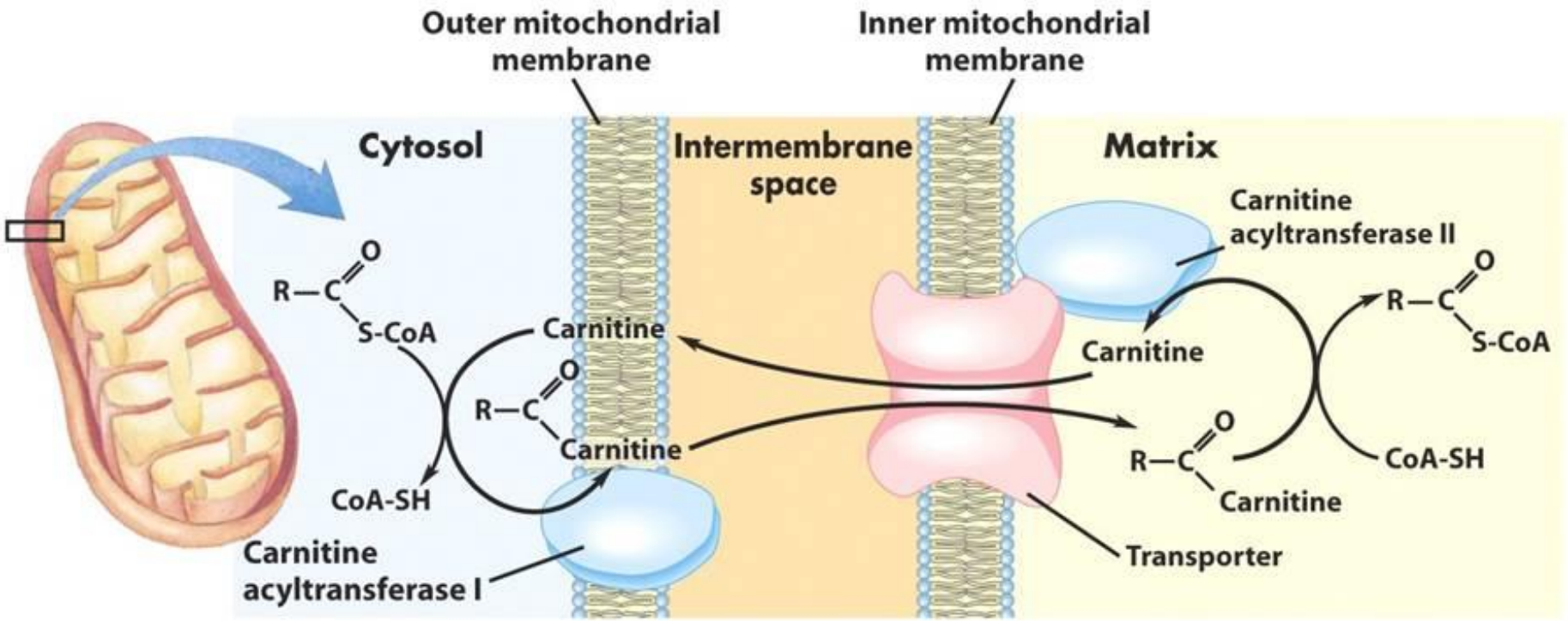



Adenosine
ATP
Fatty acid
fatty acyl–CoA synthetase (Thiokinase)
1
Adenosine
Fatty acyl–adenylate (enzyme-bound)
Pyrophosphate
CoA-SH
fatty acyl–CoA synthetase
2
AMP
inorganic pyrophosphatase
2Pi
Fatty acyl–CoA (Thioester)
S-CoA
ΔG'° = −19 kJ/mol
ΔG'° = −15 kJ/mol
(for the two-step process)

Activation

Carnitine Shuttles

The carnitine-mediated entry process is the **rate limiting step** for oxidation of fatty acids in mitochondria



FA with14 or more carbons

Transport

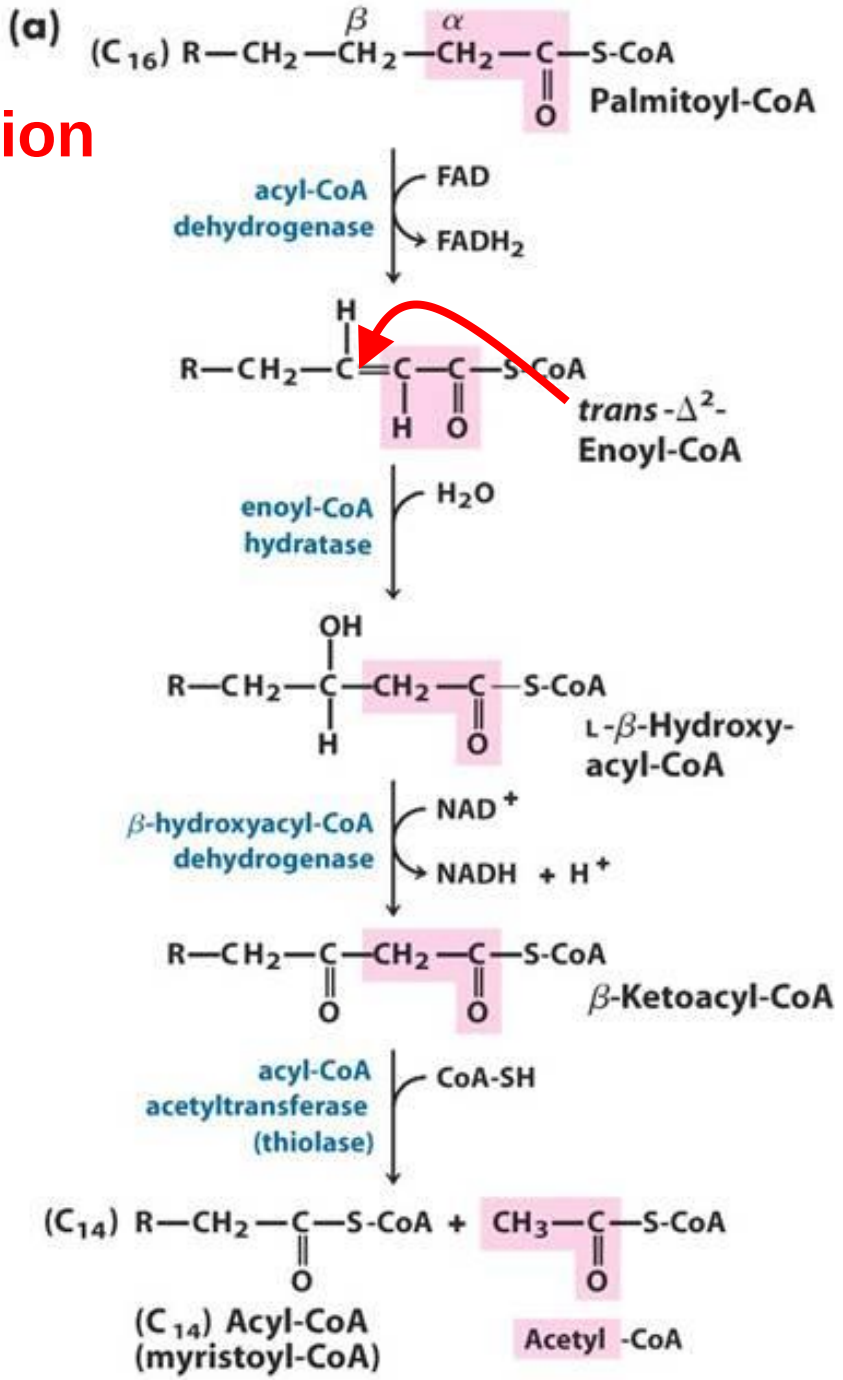
B-Oxidation

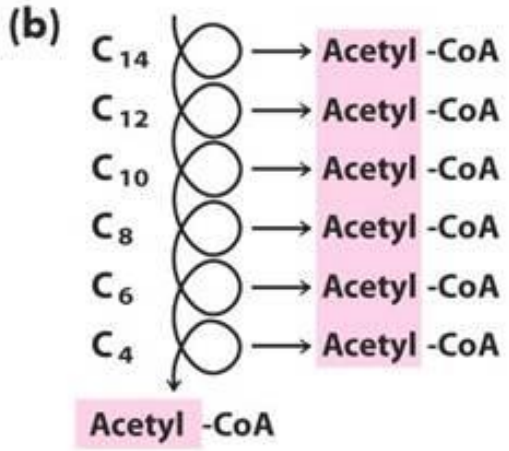
Oxidation

Hydration

Oxidation

thiolysis





Energy Yield

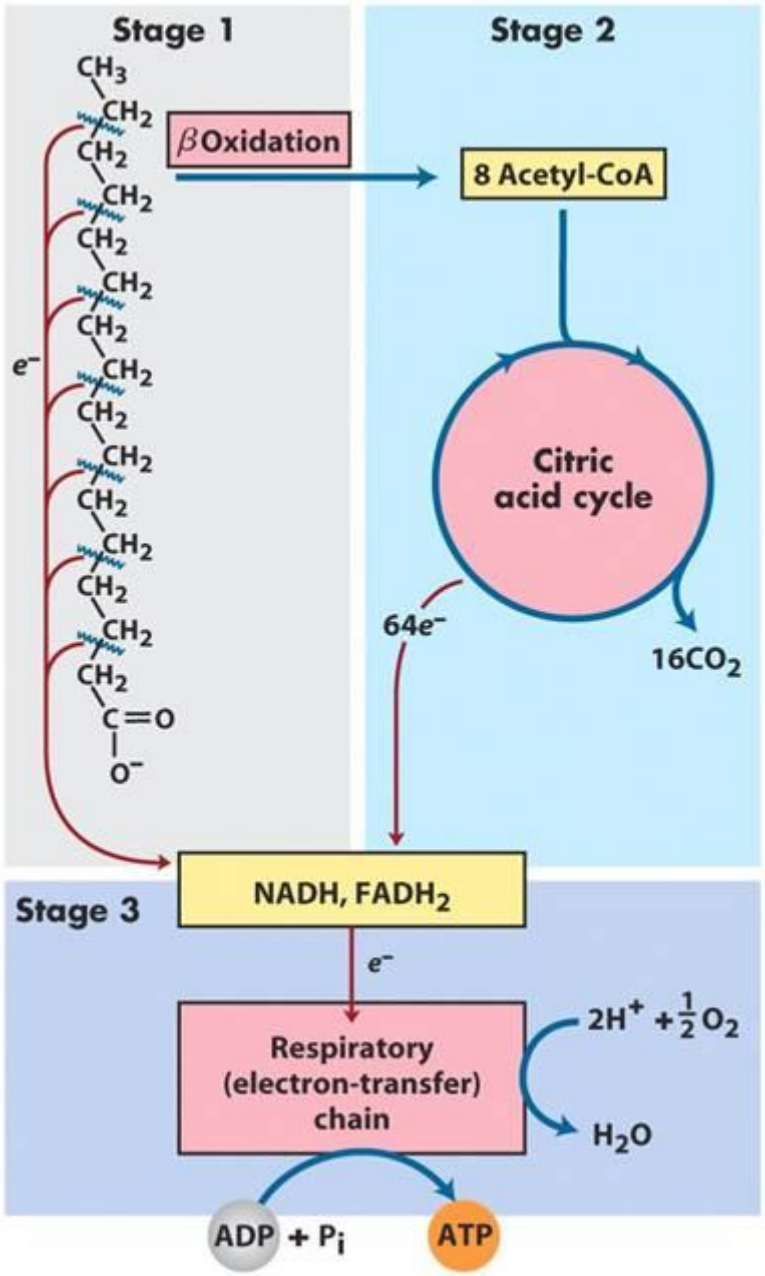


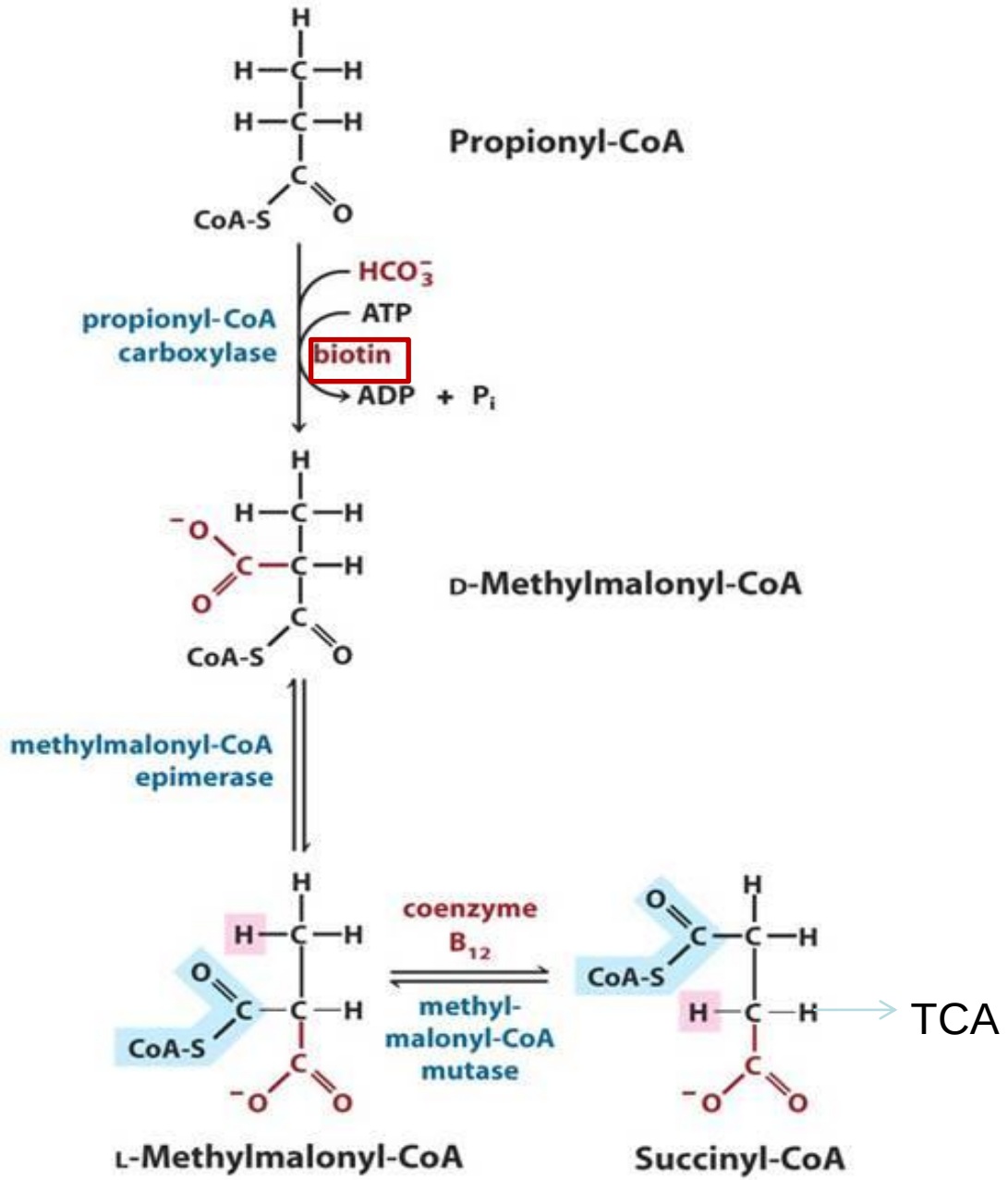
TABLE 17–1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed*
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 510).

Oxidation of propionyl-Co A produced by oxidation of odd-number fatty acids.



In the liver, fatty acyl–CoA formed in the cytosol has two major pathways:

(1) *oxidation* by enzymes in mitochondria
(2) conversion into triacylglycerols and phospholipids by enzymes in the cytosol.

The pathway taken depends on the rate of transfer of long-chain fatty acyl–CoA into mitochondria.

The three-step process (carnitine shuttle) by which fatty acyl groups are carried from cytosolic fatty acyl–CoA into the mitochondrial matrix is rate-limiting for fatty acid oxidation and is an important point of regulation. Once fatty acyl groups have entered the mitochondrion, they are committed to oxidation to acetyl-CoA.

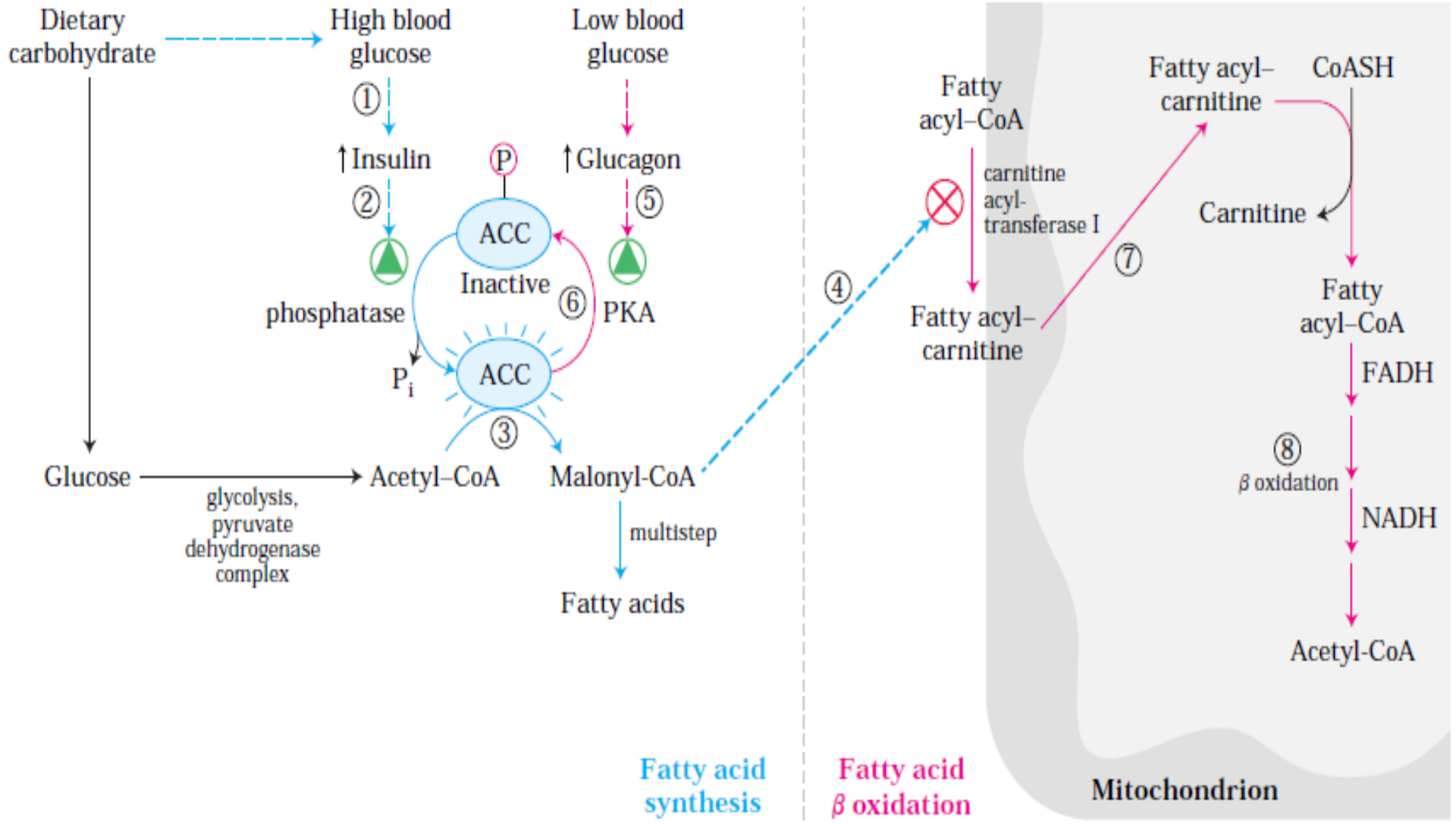
Regulation of B-oxidation

↑↑[malonyl-CoA] (the first intermediate in the cytosolic biosynthesis of long-chain fatty acids from acetyl-CoA) → inhibition of CAT I to ensure that the oxidation of fatty acids is inhibited whenever the liver is amply supplied with glucose as fuel and is actively making triacylglycerols from excess glucose.

Two of the enzymes of oxidation are also regulated by metabolites that signal energy sufficiency.

When the **[NADH]/[NAD]** ratio is **high,** acyl- CoA dehydrogenase is inhibited
in addition, **high** concentrations of **acetyl-CoA** inhibit thiolase

Regulation of B-oxidation

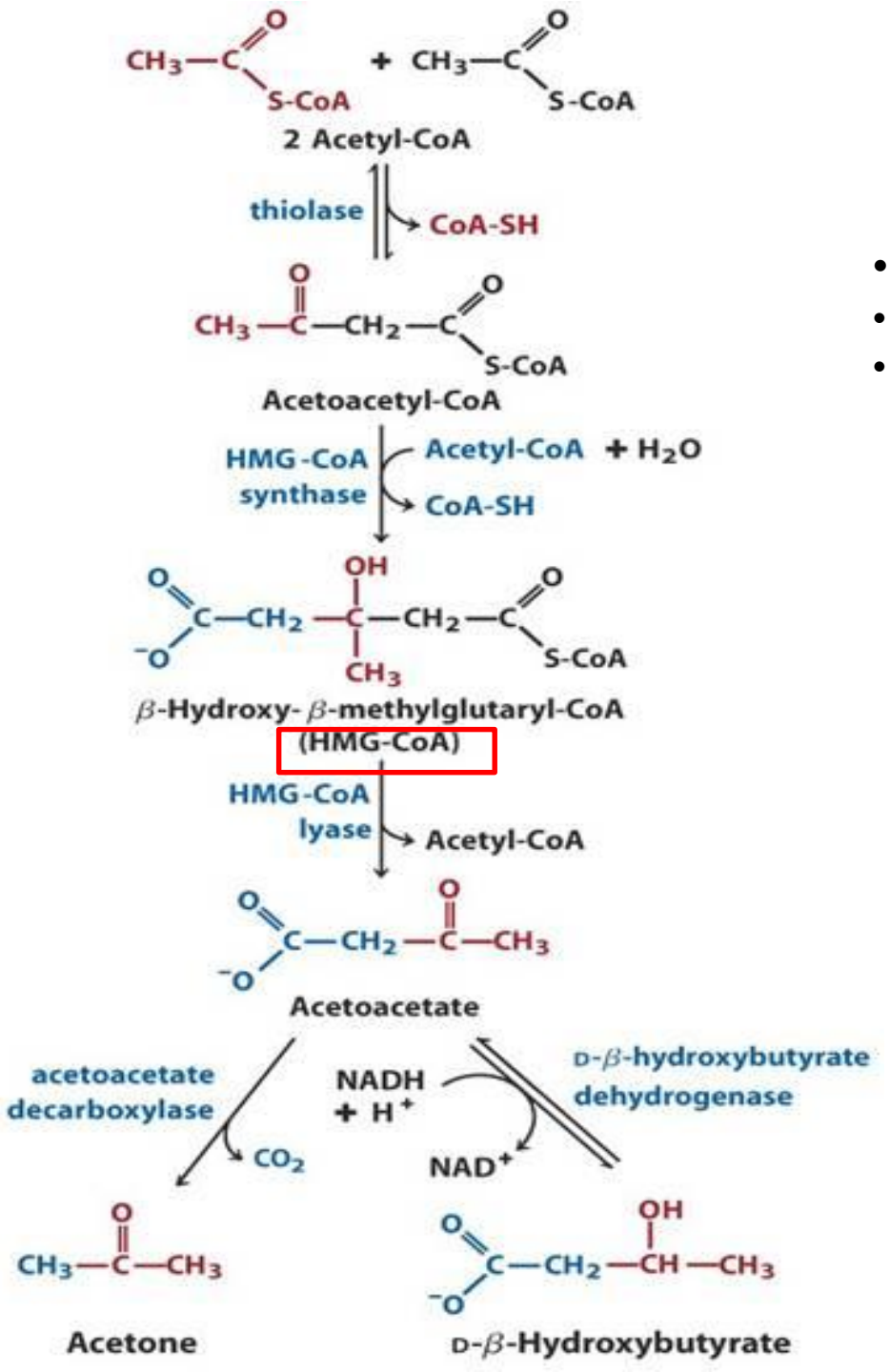


ACC: Acetyl coA carboxylase

Dr.Suheir Ereqat

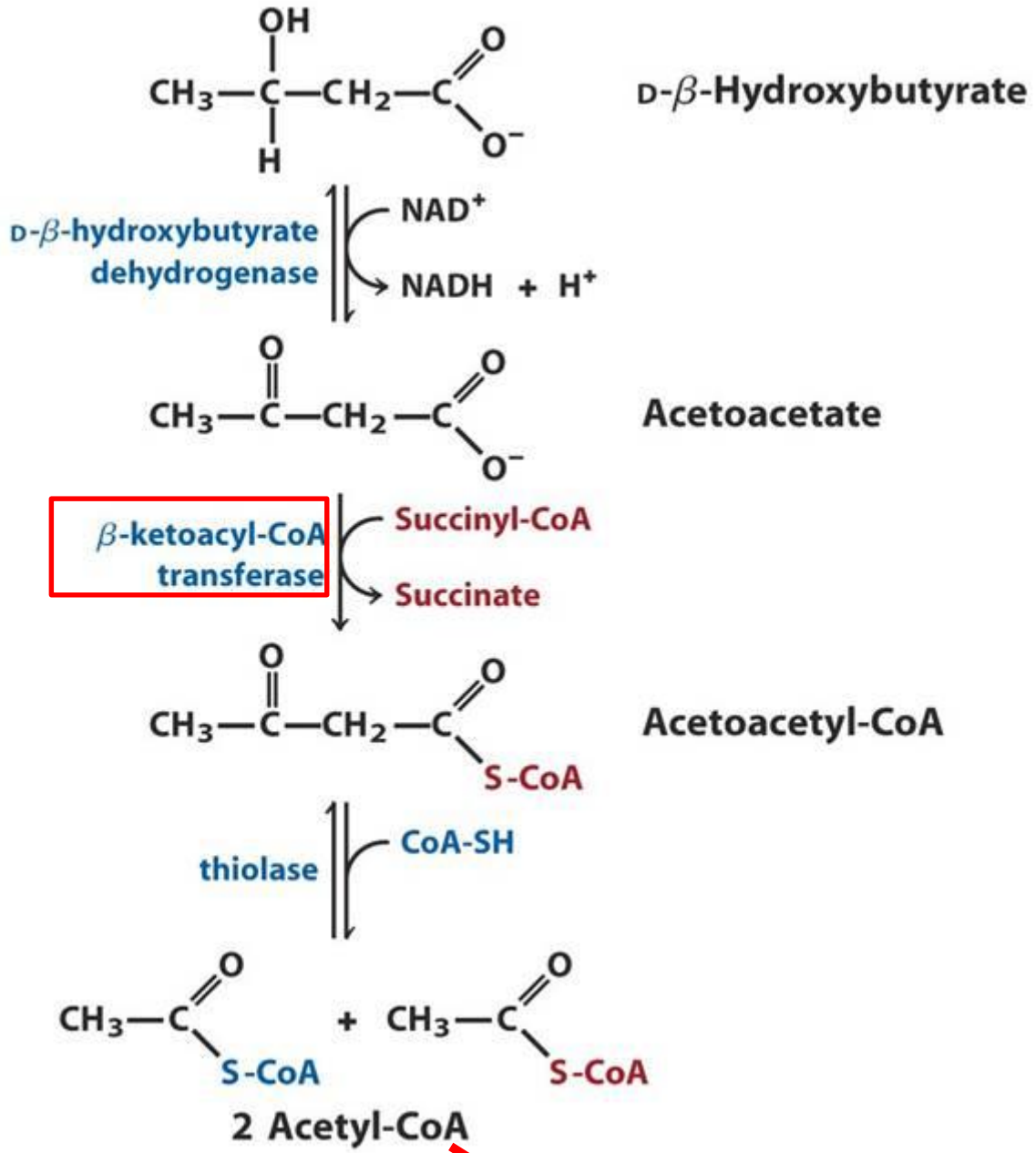
Ketone Bodies

In liver



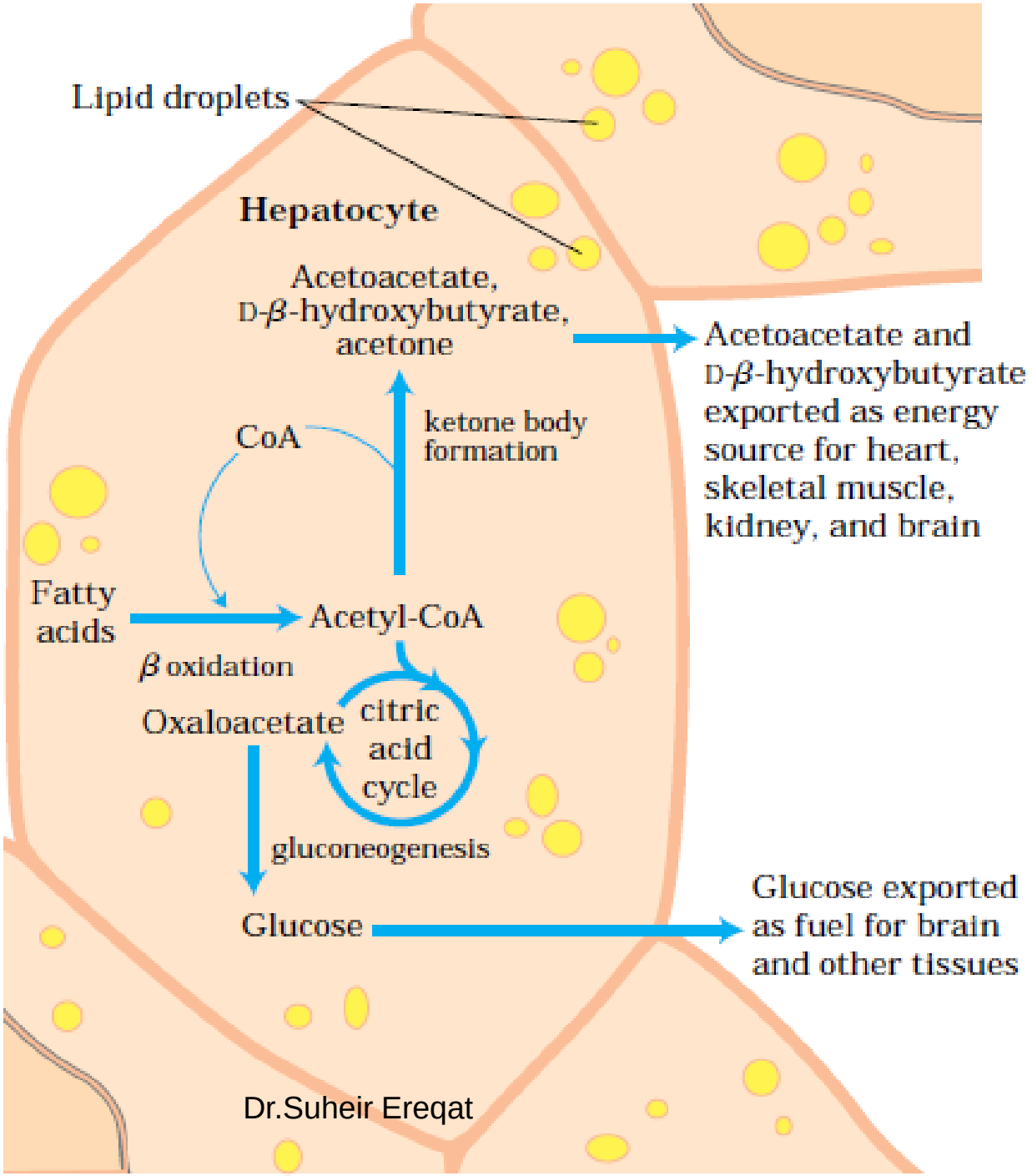
- **Acetone**
- **Acetoacetate**
- **B- Hydroxybutyrate**

In periphery



TCA cycle

Ketone bodies formation and export from the liver



Ketone Bodies Are Overproduced in Diabetes and during Starvation

In untreated diabetes, when the insulin level is insufficient, extrahepatic tissues cannot take up glucose efficiently from the blood, either for fuel or for conversion to fat.

fatty acids enter mitochondria to be degraded to acetyl-CoA—which cannot pass through the citric acid cycle because cycle intermediates have been drawn off for use as substrates in gluconeogenesis.

The resulting accumulation of acetyl-CoA accelerates the formation of ketone bodies beyond the capacity of extrahepatic tissues to oxidize them.

The increased blood levels of acetoacetate and B-hydroxybutyrate (**ketosis)** lower the blood pH, causing the condition known as **acidosis.** acidosis can lead to coma and in some cases death.