BIOCHEMISTRY

Fourth Class-First Couse

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The citric acid cycle (Krebs cycle, Tricarboxylic acid cycle).

The citric acid cycle (Krebs cycle, tricarboxylic acid cycle) is a sequence of reactions in mitochondria that oxidizes the acetyl moiety (فرع) of acetyl-CoA and reduces coenzymes that are reoxidized through the electron transport chain, linked to the formation of ATP

The citric acid cycle is the final common pathway for the oxidation of carbohydrate, lipid, and protein because glucose, fatty acids, and most amino acids are metabolized to acetyl-CoA or intermediates of the cycle.

It also has a central role in gluconeogenesis(Produce of glucose), lipogenesis(Produce of lipid), and interconversion of amino acids. Many of these processes occur in most tissues, but the liver is the only tissue in which all occur to a significant extent.

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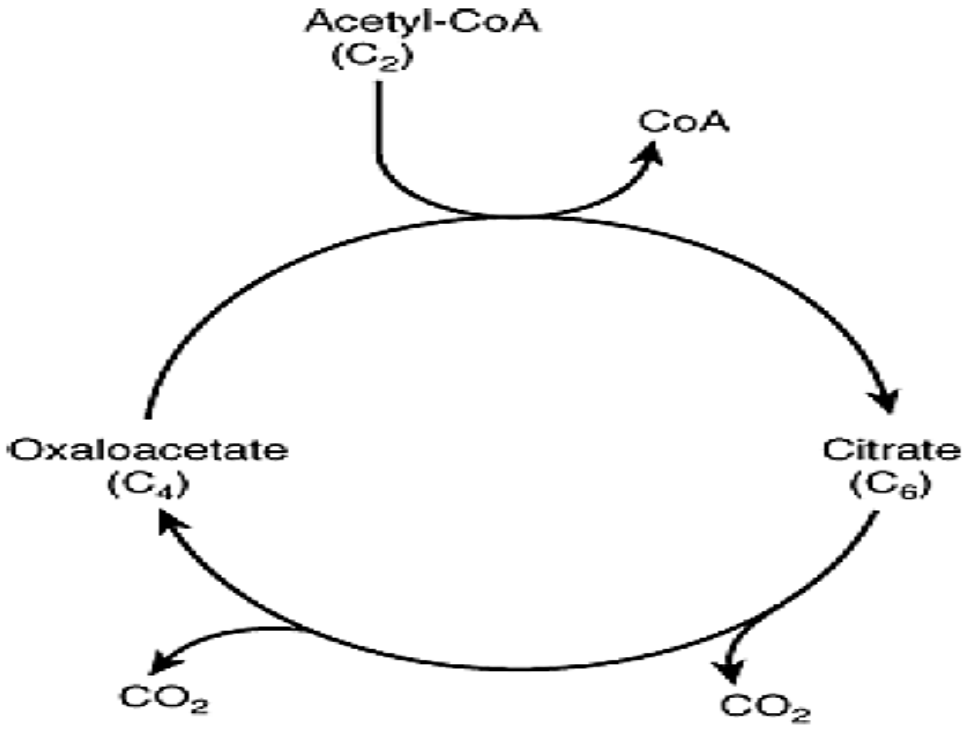
THE CITRIC ACID CYCLE PROVIDES SUBSTRATE FOR THE RESPIRATORY CHAIN

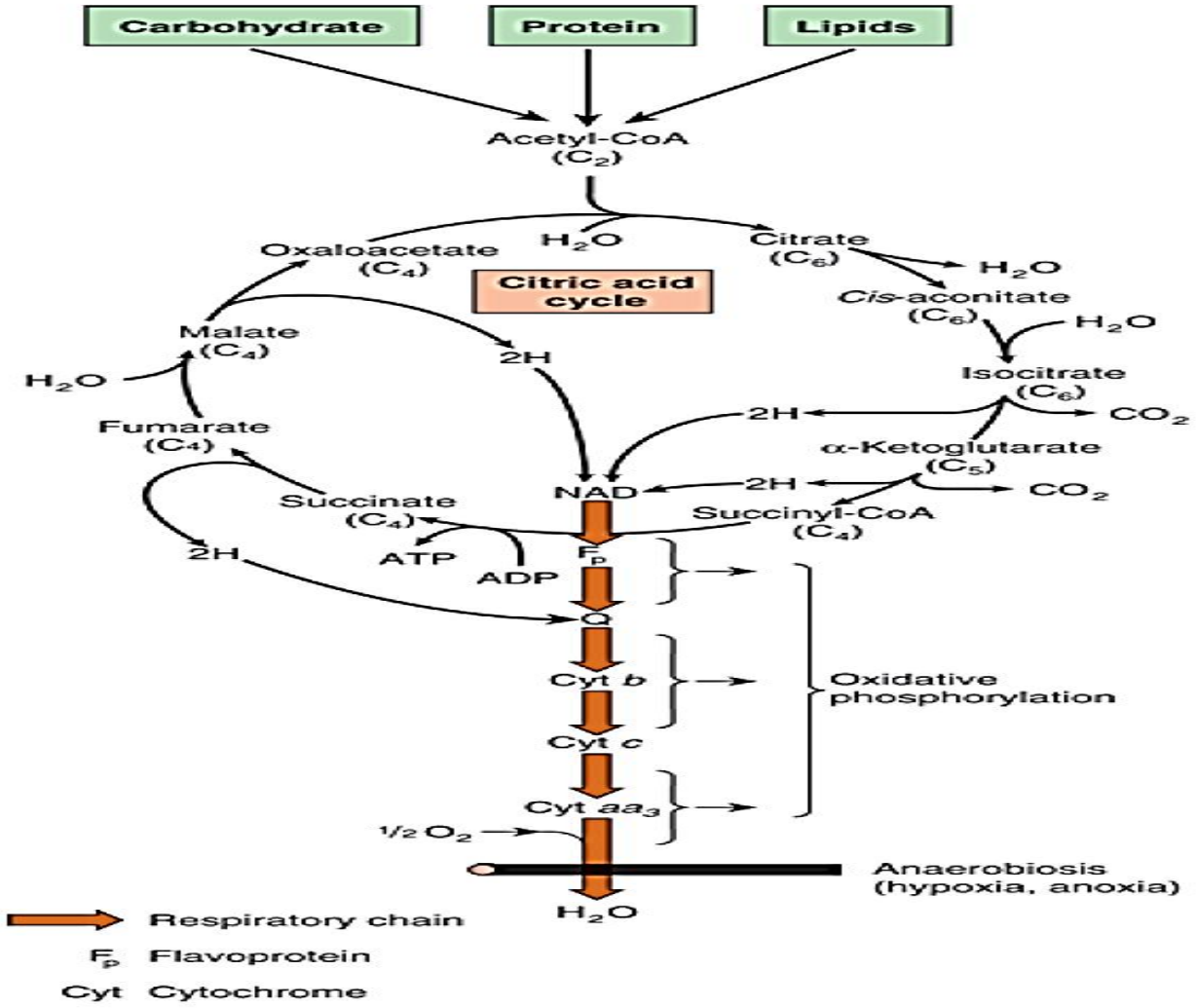
The cycle starts with reaction between the acetyl moiety of acetyl-CoA and the four-carbon dicarboxylic acid oxaloacetate, forming a six-carbon tricarboxylic acid, citrate. In the subsequent reactions, two molecules of CO_2 are released and oxaloacetate is regenerated (Figure 15). Only a small quantity of oxaloacetate is needed for the oxidation of a large quantity of acetyl-CoA; it can be considered as playing a catalytic role

(Figure 15)



[2]

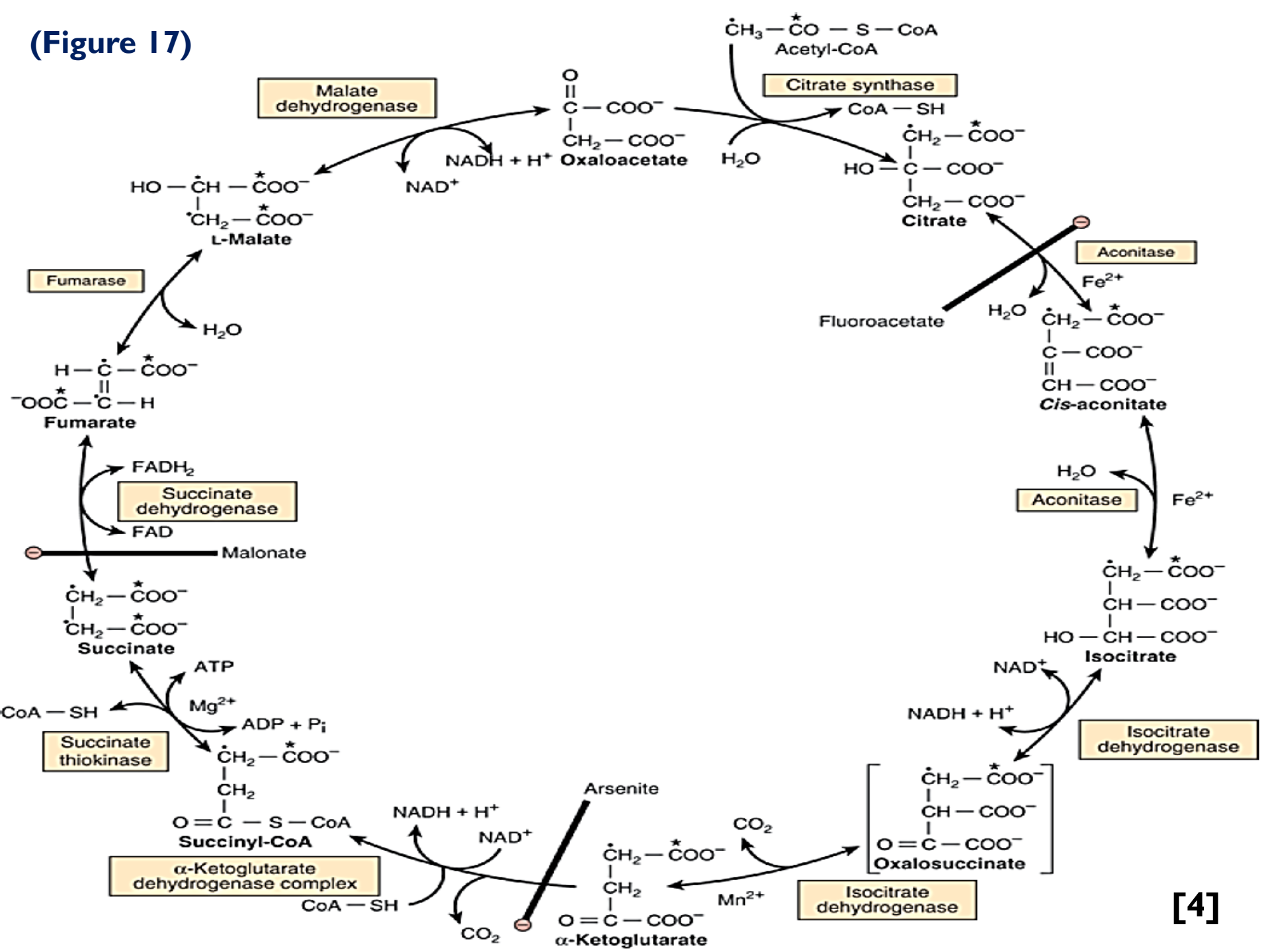
During the oxidation of acetyl-CoA, coenzymes are reduced and subsequently reoxidized in the respiratory chain, linked to the formation of ATP (oxidative phosphorylation, Figure 16). This process is aerobic, requiring oxygen as the final oxidant of the reduced coenzymes. The enzymes of the citric acid cycle are located in the mitochondrial matrix.



(Figure 16)

[3]

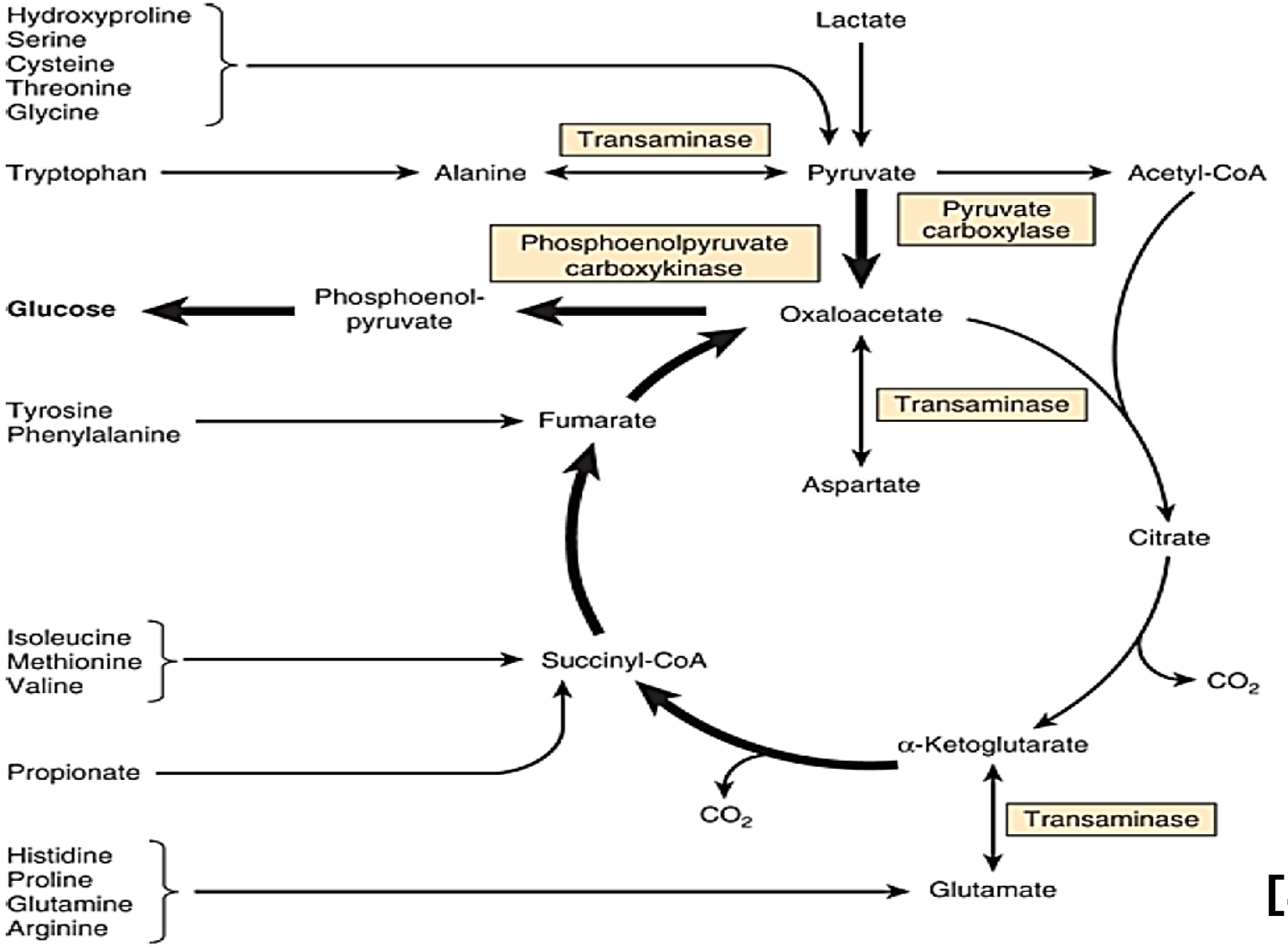
(Figure 17)


Acetyl-CoA
Citrate synthase
CoA — SH
Oxaloacetate
Malate dehydrogenase
NADH + H+
NAD+
H2O
Citrate
L-Malate
Aconitase
Fe2+
Fluoroacetate
H2O
Cis-aconitate
Fumarase
H2O
Fumarate
FADH2
Succinate dehydrogenase
FAD
Malonate
Aconitase
Fe2+
H2O
Succinate
Isocitrate
ATP
Mg2+
ADP + Pi
CoA — SH
Succinate thiokinase
NAD+
NADH + H+
Isocitrate dehydrogenase
Succinyl-CoA
Arsenite
NADH + H+
NAD+
CO2
α-Ketoglutarate dehydrogenase complex
CoA — SH
Mn2+
Isocitrate dehydrogenase
Oxalosuccinate
CO2
α-Ketoglutarate

[4]

THE CITRIC ACID CYCLE PLAYS A PIVOTAL ROLE IN METABOLISM

The citric acid cycle is not only a pathway for oxidation of two-carbon units, but is also a major pathway for interconversion of metabolites arising from transamination and deamination of amino acids , and providing the substrates for amino acid synthesis by transamination(Figure 18) , as well as for gluconeogenesis and fatty acid synthesis . Because it functions in both oxidative and synthetic processes, it is amphibolic .



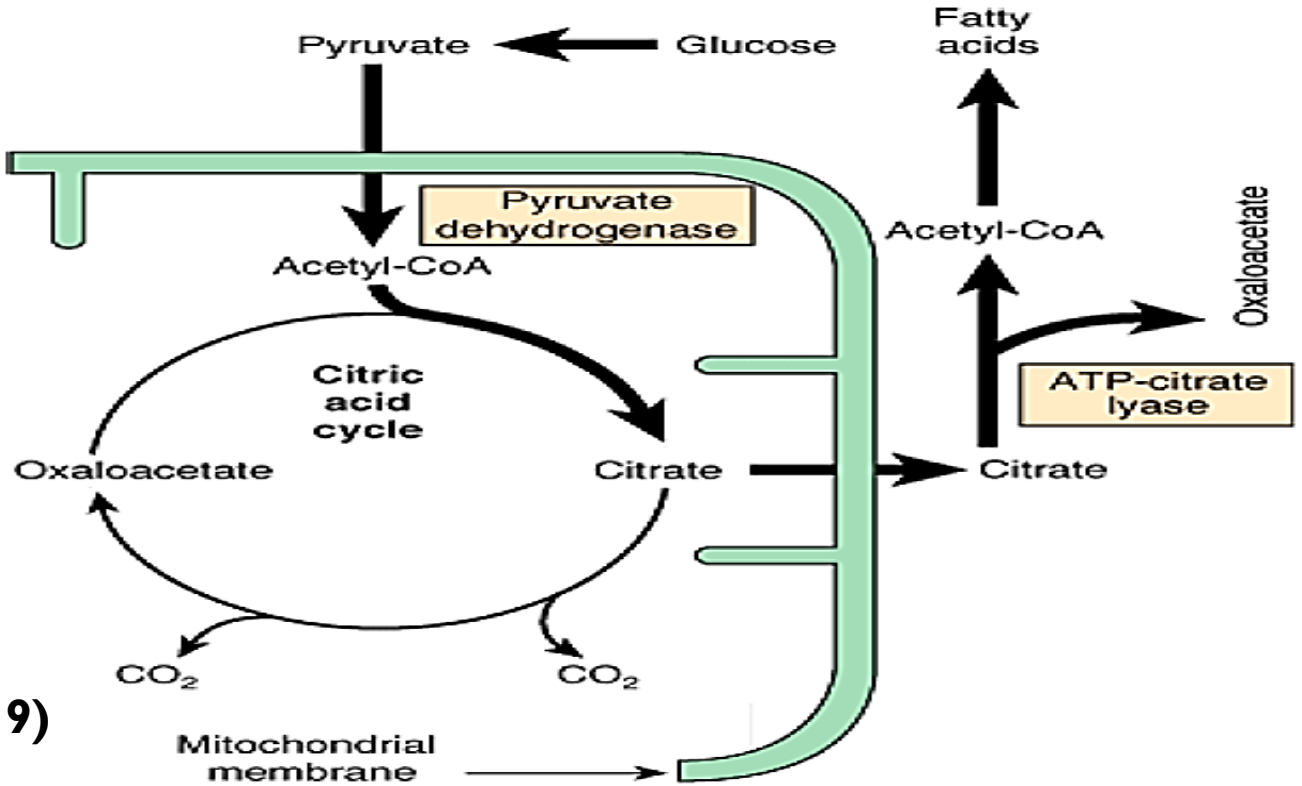
(Figure 18)

[5]

The Citric Acid Cycle Takes Part in Fatty Acid Synthesis

Acetyl-CoA, formed from pyruvate by the action of pyruvate dehydrogenase, is the major substrate for long-chain fatty acid synthesis in nonruminants (Figure 19). (In ruminants(المجترات), acetyl-CoA is derived directly from acetate.) Pyruvate dehydrogenase is a mitochondrial enzyme, and fatty acid synthesis is a cytosolic pathway; the mitochondrial membrane is impermeable to acetyl-CoA.

Acetyl-CoA is made available in the cytosol from citrate synthesized in the mitochondrion, transported into the cytosol, and cleaved in a reaction catalyzed by ATP-citrate lyase.



(Figure 19)

[6]

Regulation of the Citric Acid Cycle Depends Primarily on a Supply of Oxidized Cofactors

The most likely sites for regulation are the nonequilibrium reactions catalyzed by **pyruvate dehydrogenase, citrat synthase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase.** The dehydrogenases are activated by Ca^{2+} , which increases in concentration during muscular contraction and secretion, when there is increased energy demand. In a tissue such as brain, which is largely dependent on carbohydrate to supply acetyl-CoA, control of the citric acid cycle may occur at pyruvate dehydrogenase.

Several enzymes are responsive to the energy status as shown by the [ATP]/[ADP] and [NADH]/[NAD+] ratios. Thus, there is allosteric inhibition of citrate synthase by ATP and long-chain fatty acyl-CoA. Allosteric activation of mitochondrial NAD-dependent isocitrate dehydrogenase by ADP is counteracted by ATP and NADH. The α-ketoglutarate dehydrogenase complex is regulated in the same way as is pyruvate dehydrogenase .

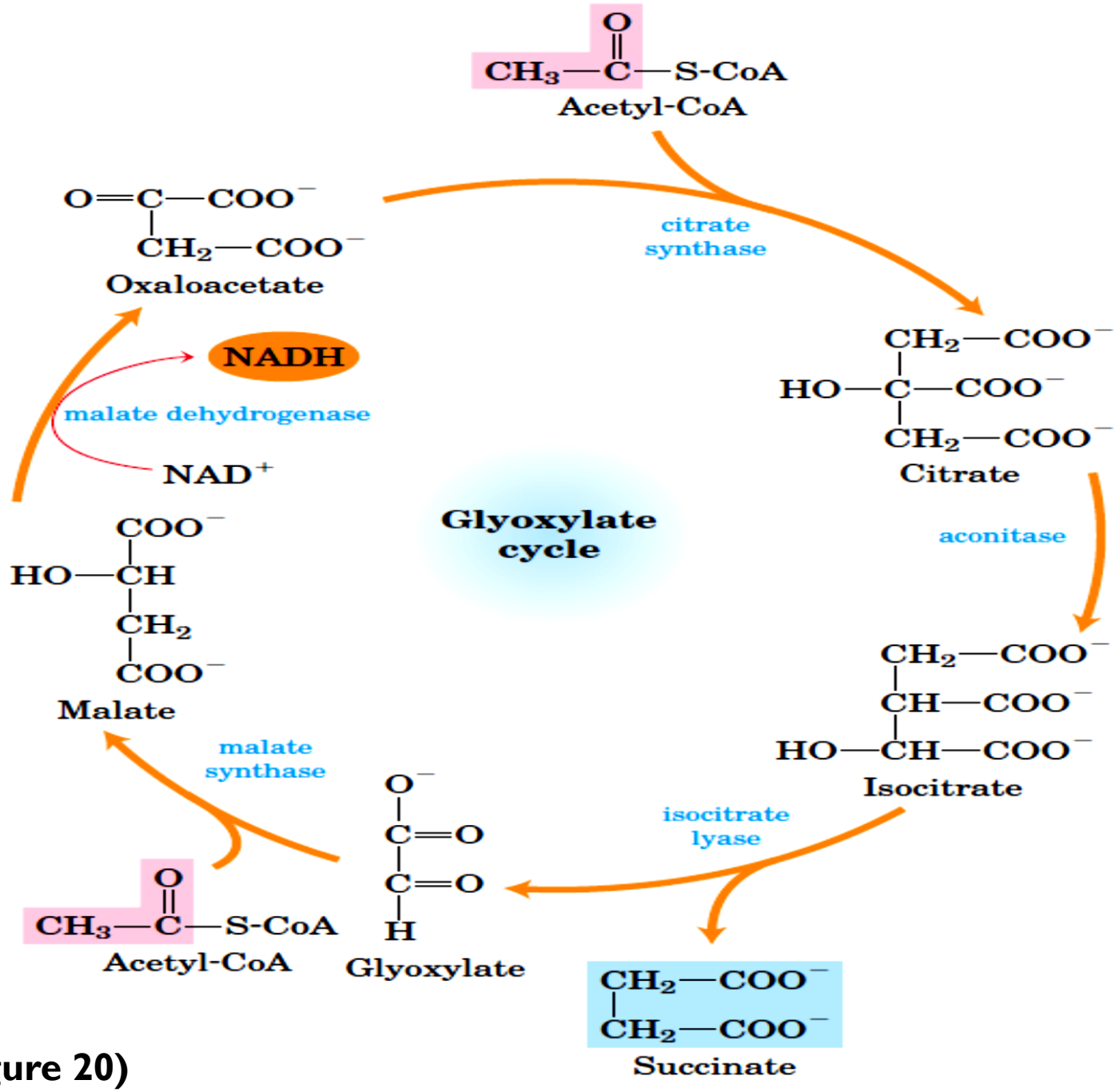
The Glyoxylate Cycle

The Glyoxylate cycle produces Four-Carbon Compounds from Acetate In plants, certain invertebrates, and some microorganisms (including *E. coli and yeast) acetate can serve both* as an energy-rich fuel and as a source of phosphoenolpyruvate for carbohydrate synthesis. In these organisms, enzymes of the glyoxylate cycle catalyze the net conversion of acetate to succinate or other four carbon intermediates of the citric acid cycle:

$$2\text{Acetyl CoA} + \text{NAD}^+ + \text{NAD}^+ + 2\text{H}_2\text{O} \longrightarrow \text{Succinate} + \text{NADH} + \text{H}^+ + 2\text{CoA-SH}$$

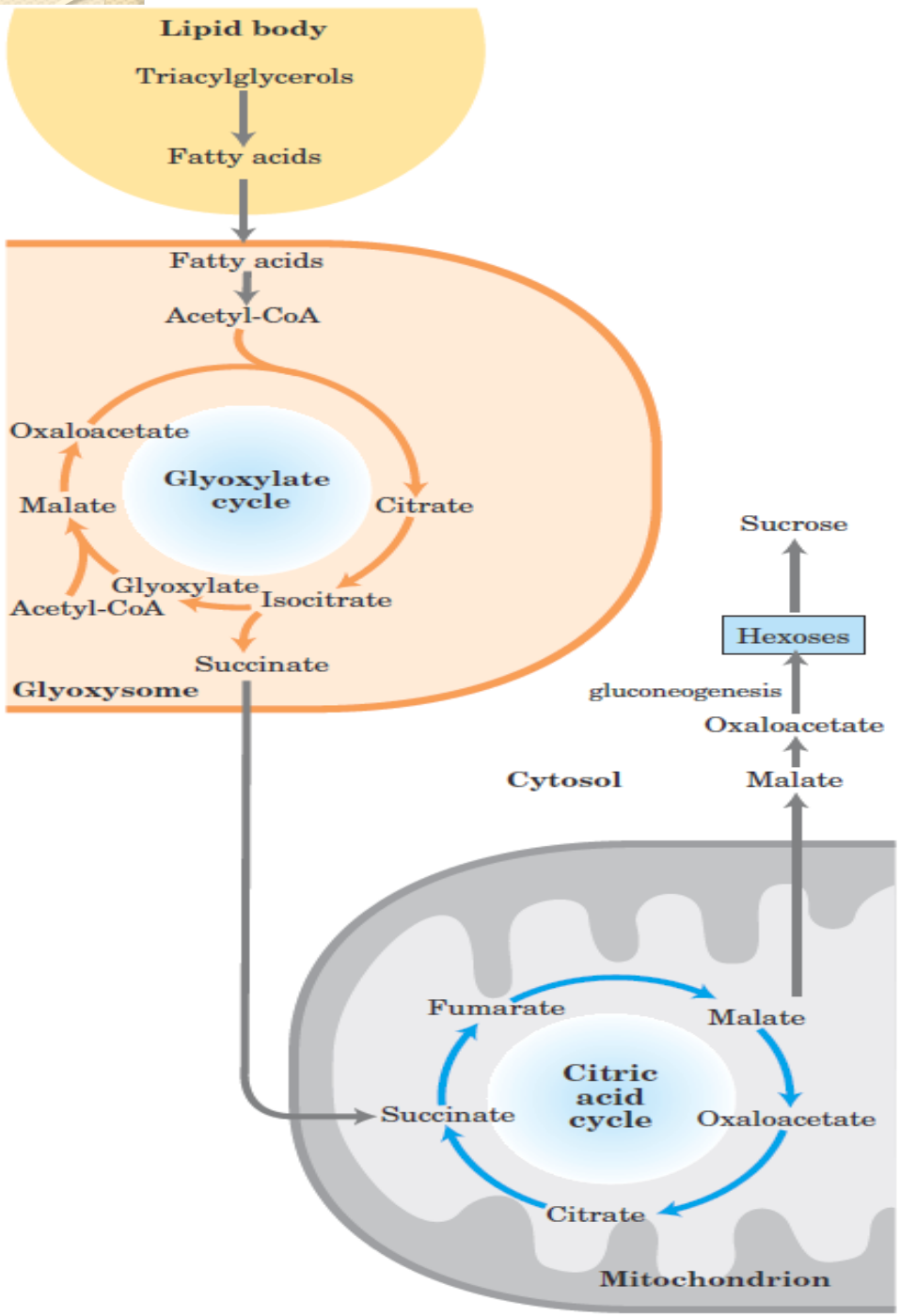
In the glyoxylate cycle, acetyl-CoA condenses with oxaloacetate to form citrate, and citrate is converted to isocitrate, exactly as in the citric acid cycle. The next step, however, is not the breakdown of isocitrate by isocitrate dehydrogenase but the cleavage of isocitrate by **isocitrate lyase,** forming succinate and **glyoxylate.**

The glyoxylate then condenses with a second molecule of acetyl-CoA to yield malate, in a reaction catalyzed by **malate synthase.** The malate is subsequently oxidized to oxaloacetate, which can condense with another molecule of acetyl-CoA to start another turn of the cycle (Figure 21).


Acetyl-CoA
citrate synthase
Oxaloacetate
NADH
malate dehydrogenase
NAD+
Citrate
Glyoxylate cycle
aconitase
Malate
Isocitrate
malate synthase
isocitrate lyase
Acetyl-CoA
Glyoxylate
Succinate

(Figure 20)

[9]



Relationship between the glyoxylate and citric acid cycles.

The reactions of the glyoxylate cycle (in glyoxysomes) proceed simultaneously with, and mesh (يشابك)with, those of the citric acid cycle (in mitochondria), as intermediates pass between these compartments (Figure 21). The conversion of succinate to oxaloacetate is catalyzed by citric acid cycle enzymes. The oxidation of fatty acids to acetyl-CoA is described in second course; the synthesis of hexoses from oxaloacetate is described in later for this course.

(Figure 21)