Topic: Fatty acid Catabolism Part I

B.Sc (H) Zoology

Sem IV

Paper: Biochemistry of Metabolic Processes

Teacher: Dr. Renu Solanki

Introduction

- The oxidation of long chain fatty acids to acetyl CoA ia central energy yielding pathway in many organisms and tissues.
- In mammalian heart and liver, for example, it provides as much as 80% of the energetic needs under all physiological circumstances. The electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis; the acetyl-CoA produced from the fatty acids may be completely oxidized to CO_2 in the citric acid cycle, resulting in further energy conservation.
- In some species and in some tissues, the acetyl-CoA has alternative fates. In liver, acetyl-CoA may be converted to ketone bodies—water-soluble fuels exported to the brain and other tissues when glucose is not available.

Hormones Trigger Mobilization of Stored Triacylglycerols

- Neutral lipids are stored in adipocytes (and in steroid- synthesizing cells of the adrenal cortex, ovary, and testes) in the form of lipid droplets, with a core of sterol esters and triacylglycerols surrounded by a monolayer of phospholipids.
- The surface of these droplets is coated with **perilipins**, a family of proteins that restrict access to lipid droplets, preventing untimely lipid mobilization.
- When hormones signal the need for metabolic energy, triacyl-glycerols stored in adipose tissue are mobilized (brought out of storage) and transported to tissues (skeletal muscle, heart, and renal cortex) in which fatty acids can be oxidized for energy production.

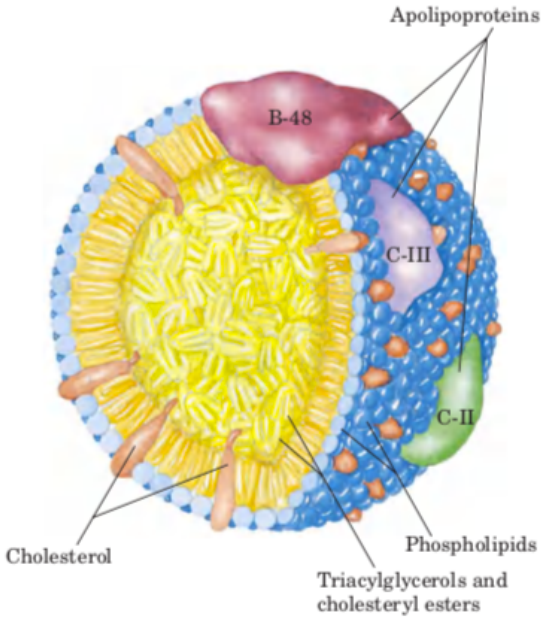


Fig. 1: Molecular structure of a chylomicron. The surface is a layer of phospholipids, with head groups facing the aqueous phase. Triacylglycerols sequestered in the interior (yellow) make up more than 80% of the mass. Several apolipoproteins that protrude from the sur- face (B-48, C-III, C-II) act as signals in the uptake and metabolism of chylomicron contents. The diameter of chylomicrons ranges from about 100 to 500 nm.

- The hormones epinephrine and glucagon, secreted in response to low blood glucose levels, activate the enzyme adenylyl cyclase in the adipocyte plasma membrane **(Fig. 2)**, which produces the intracellular second messenger cyclic AMP. Cyclic AMP–dependent protein kinase (PKA) phosphorylates perilipin A, and the phosphorylated per- ilipin causes **hormone-sensitive lipase** in the cytosol to move to the lipid droplet surface, where it can begin hydrolyzing triacylglycerols to free fatty acids and glycerol. PKA also phosphorylates hormone-sensitive lipase, dou- bling or tripling its activity, but the more than 50-fold increase in fat mobilization triggered by epinephrine is due primarily to perilipin phosphorylation.

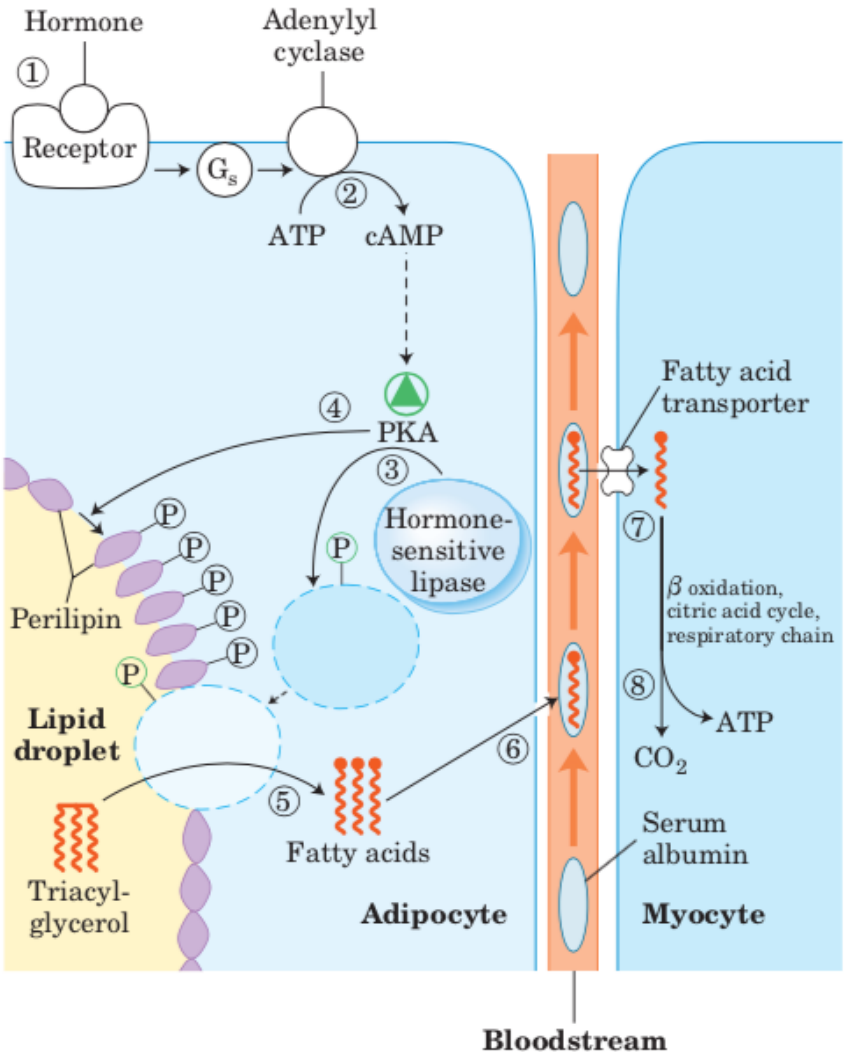


Fig 2: Mobilization of triacylglycerols stored in adipose tissue. When low levels of glucose in the blood trigger the release of glucagon, 1 the hormone binds its receptor in the adipocyte membrane and thus 2 stimulates adenylyl cyclase, via a G protein, to produce cAMP. This activates PKA, which phosphorylates 3 the hormone-sensitive lipase and 4 perilipin molecules on the surface of the lipid droplet. Phospho- rylation of perilipin permits hormone-sensitive lipase access to the sur- face of the lipid droplet, where 5 it hydrolyzes triacylglycerols to free fatty acids. 6 Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood; they are released from the albu- min and 7 enter a myocyte via a specific fatty acid transporter. 8 In the myocyte, fatty acids are oxidized to CO_2, and the energy of oxida- tion is conserved in ATP, which fuels muscle contraction and other en- ergy-requiring metabolism in the myocyte.

- As hormone-sensitive lipase hydrolyzes triacylglycerol in adipocytes, the fatty acids thus released (**free fatty acids, FFA**) pass from the adipocyte into the blood, where they bind to the blood protein **serum albumin**.
- This protein (*M*r 66,000), which makes up about half of the total serum protein, noncovalently binds as many as 10 fatty acids per protein monomer. Bound to this soluble protein, the otherwise insoluble fatty acids are carried to tissues such as skeletal muscle, heart, and renal cortex. In these target tissues, fatty acids dissociate from albumin and are moved by plasma membrane transporters into cells to serve as fuel.
- About 95% of the biologically available energy of tri- acylglycerols resides in their three long-chain fatty acids; only 5% is contributed by the glycerol moiety. The glycerol released by lipase action is phosphorylated by **glycerol kinase (Fig. 3)**, and the resulting glycerol 3-phosphate is oxidized to dihydroxyacetone phos- phate. The glycolytic enzyme triose phosphate iso- merase converts this compound to glyceraldehyde 3-phosphate, which is oxidized via glycolysis.

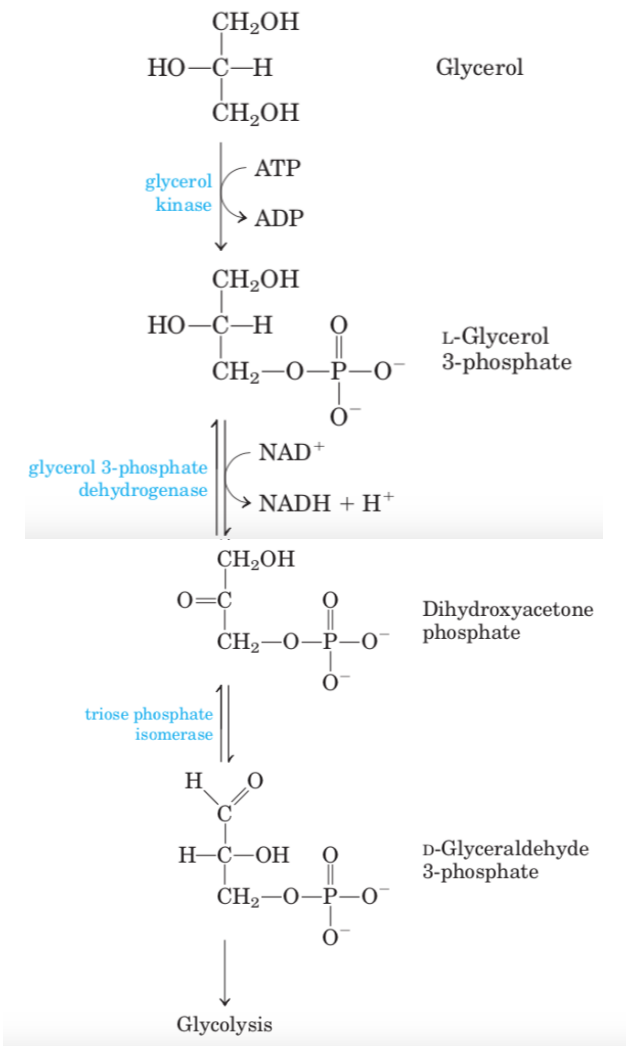


FIG 3: Entry of glycerol into the glycolytic pathway.

Activation of Fatty Acids

- Fatty acids are activated and Transported into Mitochondria
- The enzymes of fatty acid oxidation in animal cells are located in the mitochondrial matrix, as demonstrated in 1948 by Eugene P. Kennedy and Albert Lehninger.
- The fatty acids with chain lengths of 12 or fewer carbons enter mitochondria without the help of membrane transporters.
- Those with 14 or more carbons, which constitute the majority of the FFA obtained in the diet or released from adipose tissue, cannot pass directly through the mitochondrial membranes—they must first undergo the three enzymatic reactions of the **carnitine shuttle**.
- The first reaction is catalyzed by a family of isozymes (different isozymes specific for fatty acids hav- ing short, intermediate, or long carbon chains) present in the outer mitochondrial membrane, the **acyl-CoA synthetases**, which promote the general reaction

$$\text{Fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{fatty acyl–CoA} + \text{AMP} + \text{PP}_\text{i}$$

- Thus, acyl-CoA synthetases catalyze the formation of a thioester linkage between the fatty acid carboxyl group and the thiol group of coenzyme A to yield a **fatty acyl–CoA**, coupled to the cleavage of ATP to AMP and PPi. The reaction occurs in two steps and involves a fatty acyl–adenylate intermediate (Fig 4).

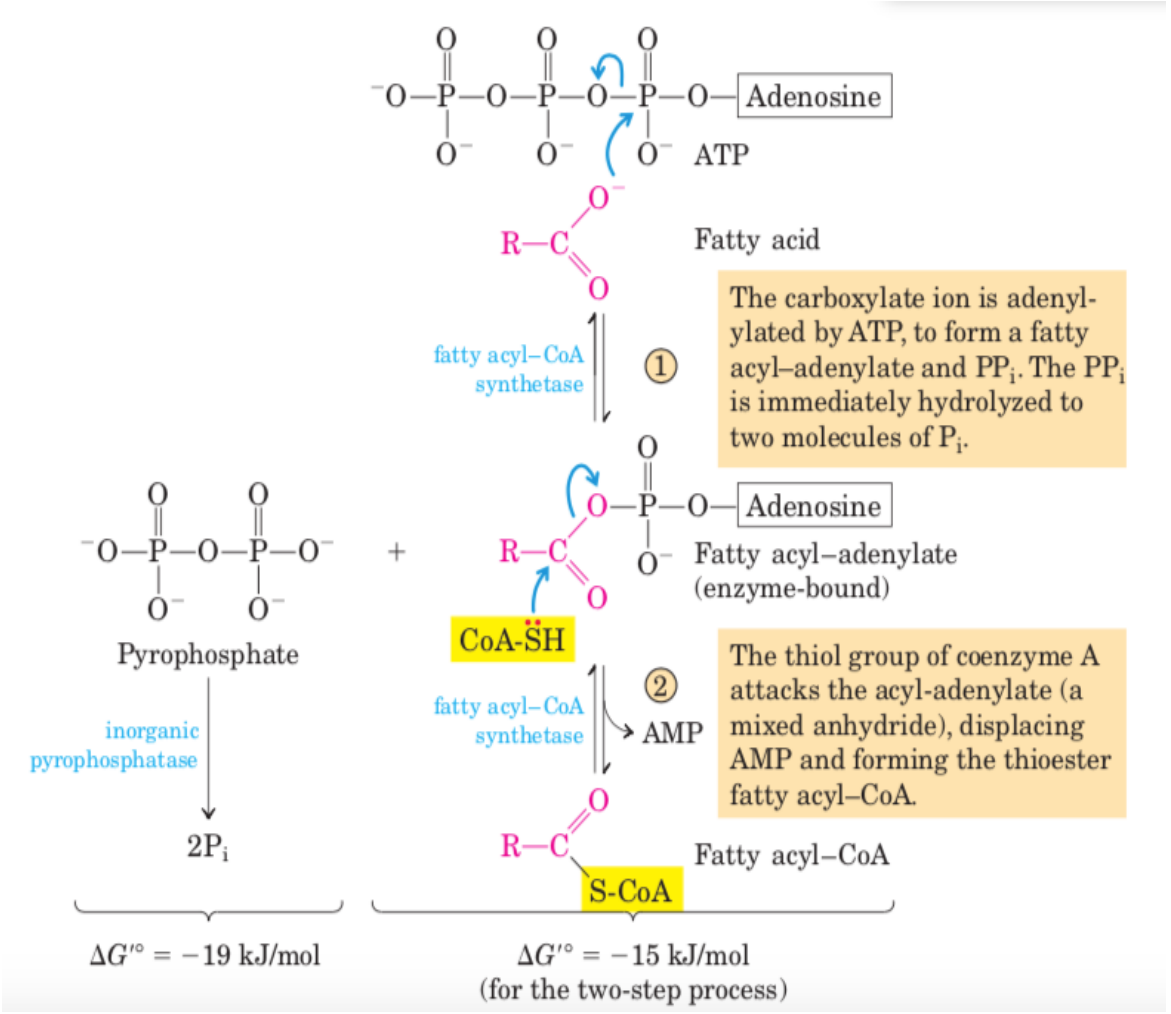


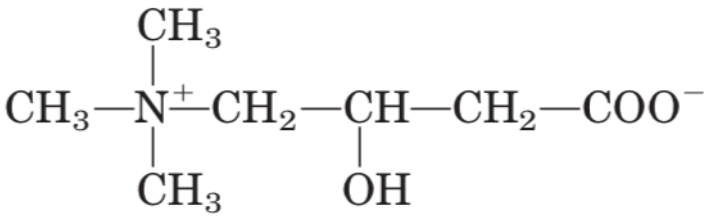
Fig 4: Conversion of a fatty acid to a fatty acyl–CoA.

- Fatty acyl–CoAs, like acetyl-CoA, are high-energy compounds
- The formation of a fatty acyl–CoA is made more favorable by the hydrolysis of *two* high-energy bonds in ATP; the pyrophosphate formed in the activation reaction is immediately hydrolyzed by inorganic pyrophosphatase (left side of Fig. 4), which pulls the preceding activation reaction in the direction of fatty acyl–CoA formation. The overall reaction is

$$\text{Fatty acid} + \text{CoA} + \text{ATP} \longrightarrow \text{fatty acyl–CoA} + \text{AMP} + 2\text{P}_\text{i} \qquad (17\text{–}1)$$

$$\Delta G'^\circ = -34 \text{ kJ/mol}$$

- Fatty acyl–CoA esters formed at the cytosolic side of the outer mitochondrial membrane can be trans- ported into the mitochondrion and oxidized to produce ATP, or they can be used in the cytosol to synthesize membrane lipids. Fatty acids destined for mitochondrial oxidation are transiently attached to the hydroxyl group of **carnitine** to form fatty acyl–carnitine—the second reaction of the shuttle. This transesterification is catalyzed by **carnitine acyltransferase I** (*M*r 88,000), in the outer membrane. Either the acyl-CoA passes through the outer membrane and is converted to the carnitine ester in the in- termembrane space (Fig 5) or the carnitine ester is formed on the cytosolic face of the outer membrane, then moved across the outer membrane to the intermembrane space
- The fatty acyl–carnitine ester then enters the matrix by facilitated diffusion through the **acyl- carnitine/carnitine transporter** of the inner mitochondrial membrane



Carnitine

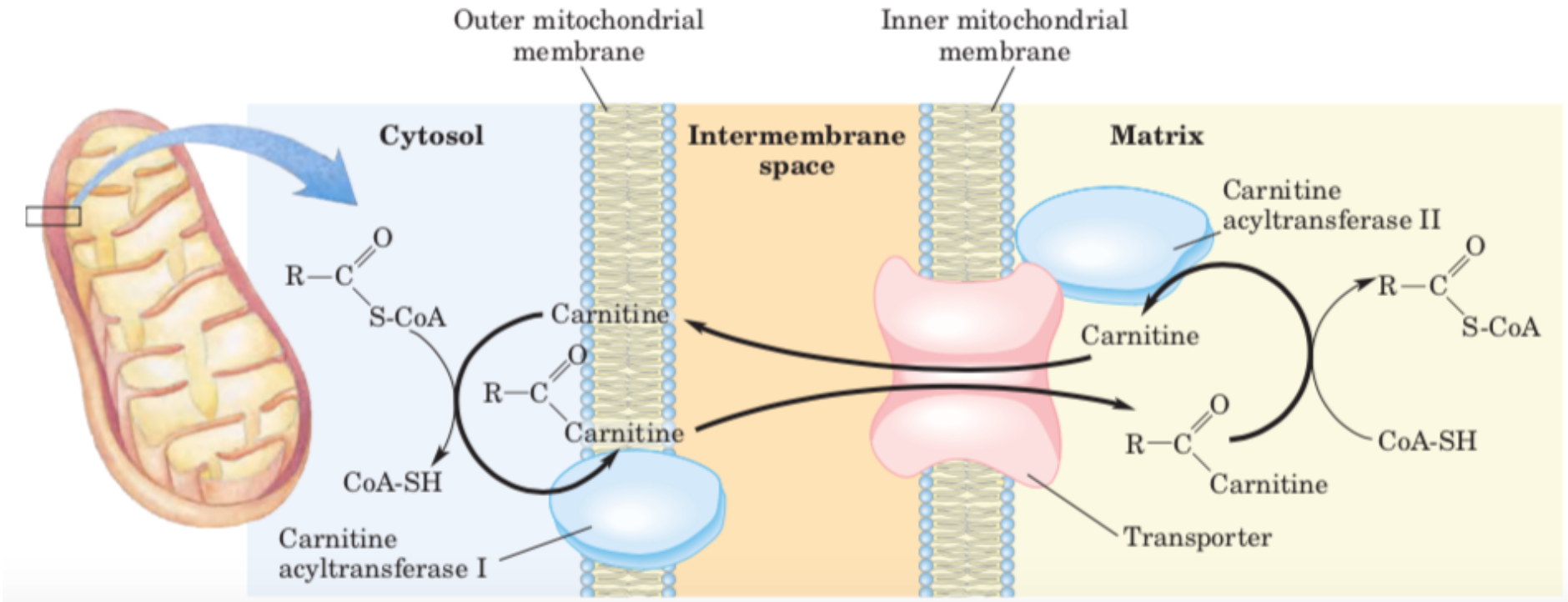


Fig 5: Fatty acid entry into mitochondria via the acyl-carnitine/ carnitine transporter. After fatty acyl–carnitine is formed at the outer membrane or in the intermembrane space, it moves into the matrix by facilitated diffusion through the transporter in the inner membrane. In the matrix, the acyl group is transferred to mitochondrial coenzyme A, freeing carnitine to return to the intermembrane space through the same transporter. Acyltransferase I is inhibited by malonyl-CoA, the first intermediate in fatty acid synthesis. This inhibition prevents the simultaneous synthesis and degradation of fatty acids.

- In the third and final step of the carnitine shuttle, the fatty acyl group is enzymatically transferred from carnitine to intra-mitochondrial coenzyme A by **carnitine acyl- transferase II**. This isozyme, located on the inner face of the inner mitochondrial membrane, regenerates fatty acyl–CoA and releases it, along with free carnitine, into the matrix (Fig. 5). Carnitine reenters the intermembrane space via the acyl-carnitine/carnitine transporter.
- Fatty acyl–CoA in the cytosolic pool can be used for membrane lipid synthesis or can be moved into the mitochondrial matrix for oxidation and ATP production. Conversion to the carnitine ester com- mits the fatty acyl moiety to the oxidative fate.
- The carnitine-mediated entry process is the rate- limiting step for oxidation of fatty acids in mitochondria and, as discussed later, is a regulation point. Once inside the mitochondrion, the fatty acyl–CoA is acted upon by a set of enzymes in the matrix.

Reference:

- Chapter 17: • Cox, M.M and Nelson, D.L. (2008).Lehninger’s Principles of Biochemistry. VEdition, W.H. Freeman and Co., New York.