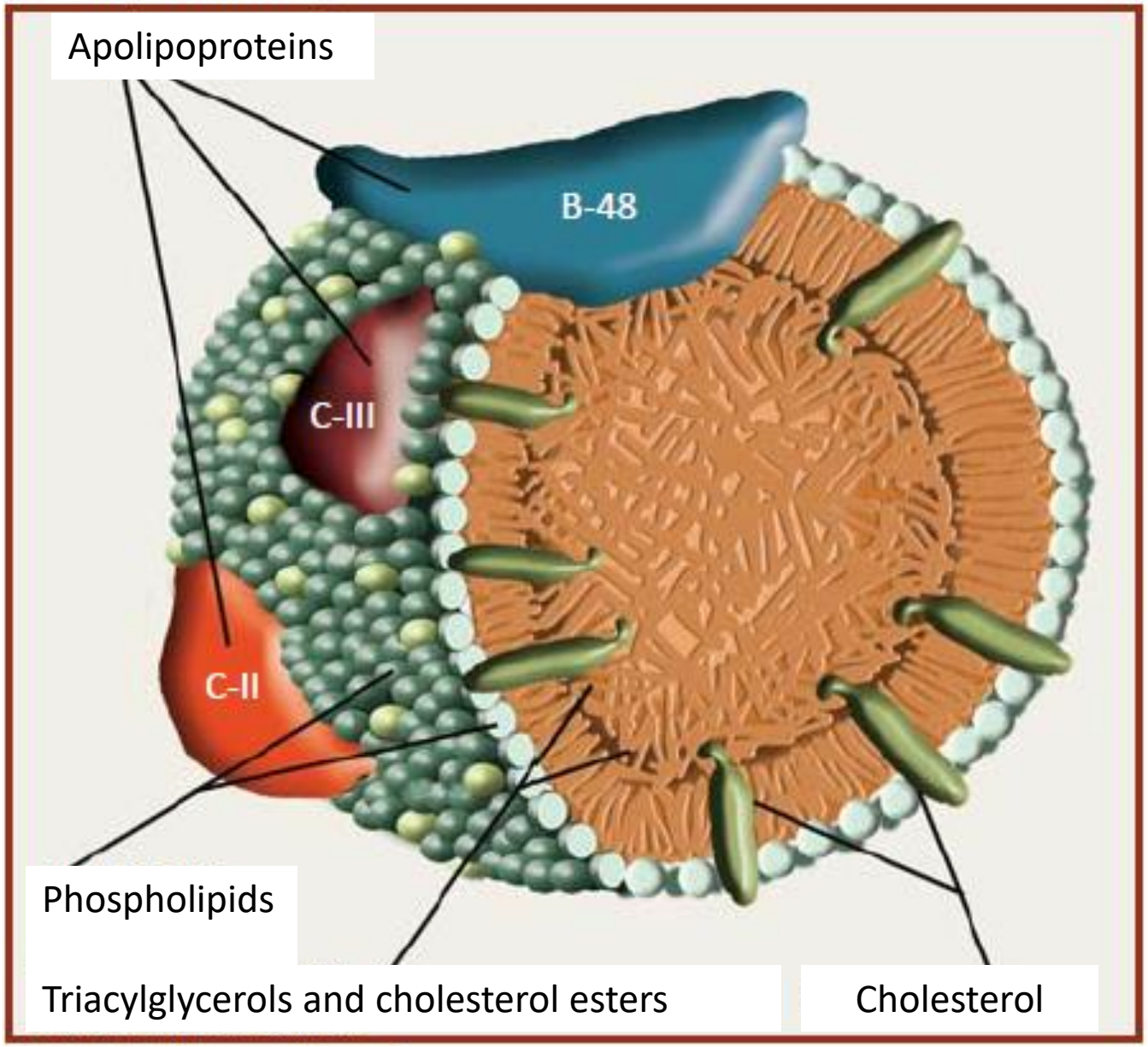
LIPID METABOLISM-2

Secretion of Lipids to Lymphatics

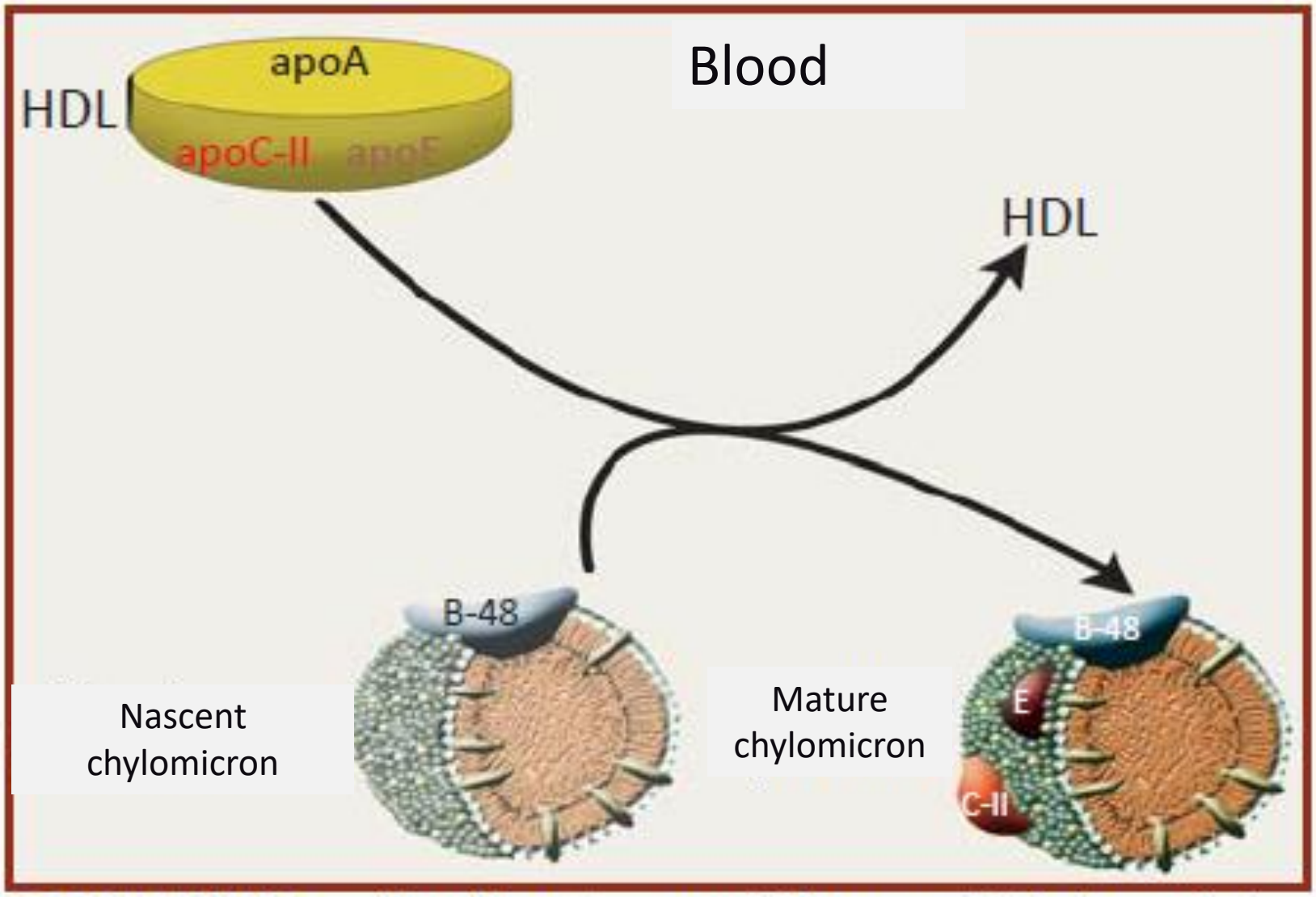
- The newly resynthesized TAGs and cholesteryl esters are very hydrophobic, and aggregate in an aqueous environment.
- So that, they need to be packaged as particles of lipid droplets surrounded by a thin layer of hydrophylic compounds composed of phospholipids, unesterified cholesterol, and a molecule of the characteristic protein, apolipoprotein B-48.



The structure of a mature chylomicron

- This thin layer stabilize the particle, increase its solubility and prevent multiple particles from coalescing.
- Microsomal TAG transfer protein is essential for the assembly of these TAG-rich apolipoprotein B–containing lipoprotein particles in the endoplasmic reticulum.
- The particles are released by exocytosis from enterocytes to the lymphatic vessels.

- The presence of these particles in the lymph after a lipid-rich meal gives it a milky appearance. This lymph is called chyle and the particles are named chylomicrons.
- Chylomicrons reach to the thoracic duct through lymphatics, and then to the circulation system through left subclavian vein.



Transfer of apoC-II and apoE from HDL to nascent chylomicrons

Fate of Chylomicrons in Blood

- Triacylglycerol found in chylomicrons is broken down primarily in the capillaries of skeletal muscle and adipose tissues (but also those of the heart, lung, kidney, and liver).
- Triacylglycerol in chylomicrons is degraded to free fatty acids and glycerol by lipoprotein lipase (Initially, lipoprotein lipase is activated by apolipoprotein C-II).

- Lipoprotein lipase enzyme is synthesized primarily by adipocytes and muscle cells.
- It is secreted and becomes associated with the luminal surface of endothelial cells of the capillary beds of the peripheral tissues.
- Familial lipoprotein lipase deficiency (Type I hyperlipoproteinemia) is a rare, autosomal recessive disorder caused by a deficiency of lipoprotein lipase or its coenzyme, apolipoprotein C-II.
- The result is fasting chylomicronemia and hypertriacylglycerolemia.

Fate of Free Fatty Acids Degraded from Chylomicrons

- The free fatty acids derived from the hydrolysis of TAG may either directly enter adjacent muscle cells or adipocytes, or they may be transported in the blood in association with serum albumin until they are taken up by cells.
- Serum albumin is a large protein secreted by the liver. It transports a number of primarily hydrophobic compounds in the circulation, including free fatty acids and some drugs.

- Most cells can oxidize fatty acids to produce energy.
- Adipocytes can also reesterify free fatty acids to produce TAG molecules, which are stored until the fatty acids are needed by the body.

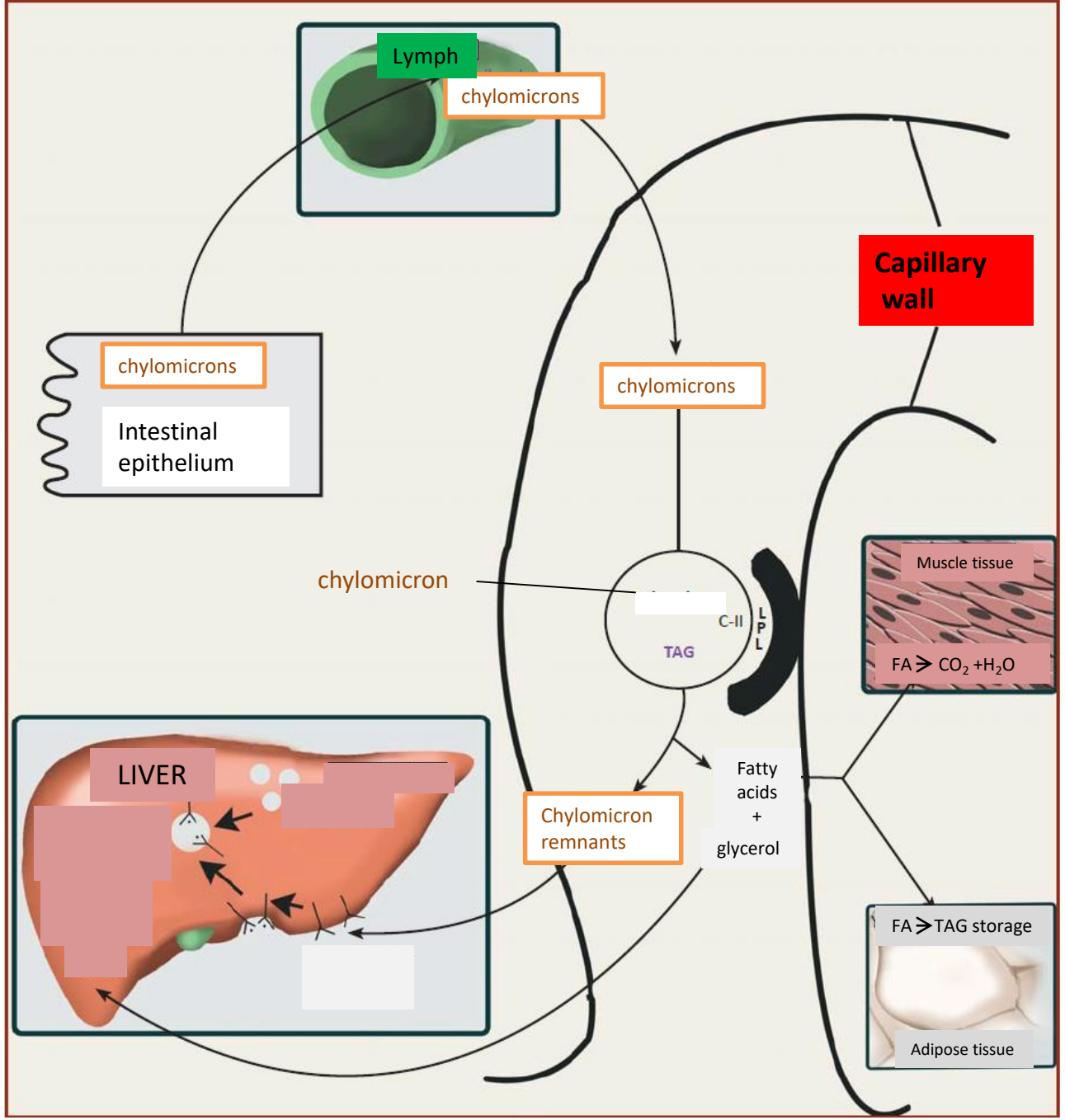
Fate of Glycerol derived due to TAG Degradation from Chylomicrons

- Glycerol that is released from TAG is removed from blood by the liver to produce glycerol 3-phosphate, which is oxidized to dihydroxyacetone phosphate and then can enter either glycolysis or gluconeogenesis.

Fate of the Remaining Chylomicron Components

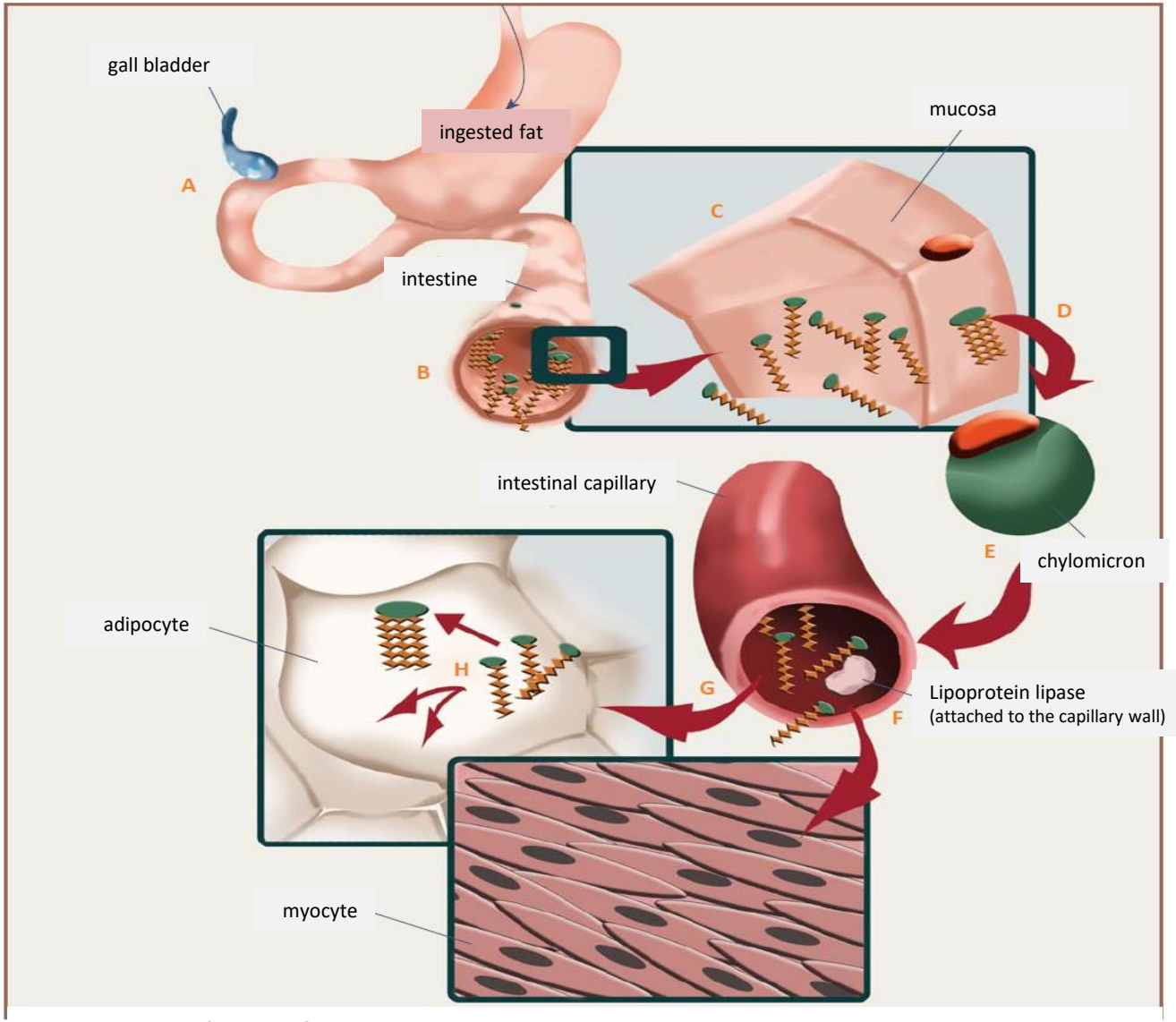
- After most of the TAG has been removed, the chylomicron remnants (containing cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and some TAG) bind to receptors on the liver and endocytosed.
- The remnants are then hydrolyzed to their components.

- Cholesterol and the nitrogenous bases of phospholipids (for example, choline) can be recycled by the body.
- If removal of remnants by the liver is decreased due to impaired binding to their receptor, they accumulate in the plasma.
- This is seen in **Type III hyperlipoproteinemia** (also called **familial dysbetalipoproteinemia**).



Fate of Chylomicrons

Digestion of Triglycerides



A: Bile salts emulsify dietary fats in the small intestine
B: Intestinal lipases degrade triacylglycerols
C: Fatty acids and other breakdown products taken up by the intestinal mucosa and converted to TAGs
D: TAGs are incorporated with cholesterol and apolipoproteins into chylomicrons
E: Chylomicrons move through the lymphatic system and bloodstream to tissues
F: Lipoprotein lipase activated by apoC-II in the capillary releases fatty acids and glycerol
G: Fatty acids enter cells
H: Fatty acids are oxidized as fuel or reesterified for storage

β-Oxidation of Fatty Acids

- The major pathway for catabolism of fatty acids is a mitochondrial pathway called β-oxidation.
- In β-oxidation two-carbon fragments are removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and $FADH_2$.
- Since, β-oxidation takes place in the mitochondrial matrix, fatty acids should be carried into the matrix, first.

- 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 fatty acids, cannot pass directly through the mitochondrial inner membrane.
- Therefore, a specialized carrier (carnitine) transports the long-chain acyl group from the cytosol into the mitochondrial matrix.
- This rate-limiting transport process is called the **carnitine shuttle**.

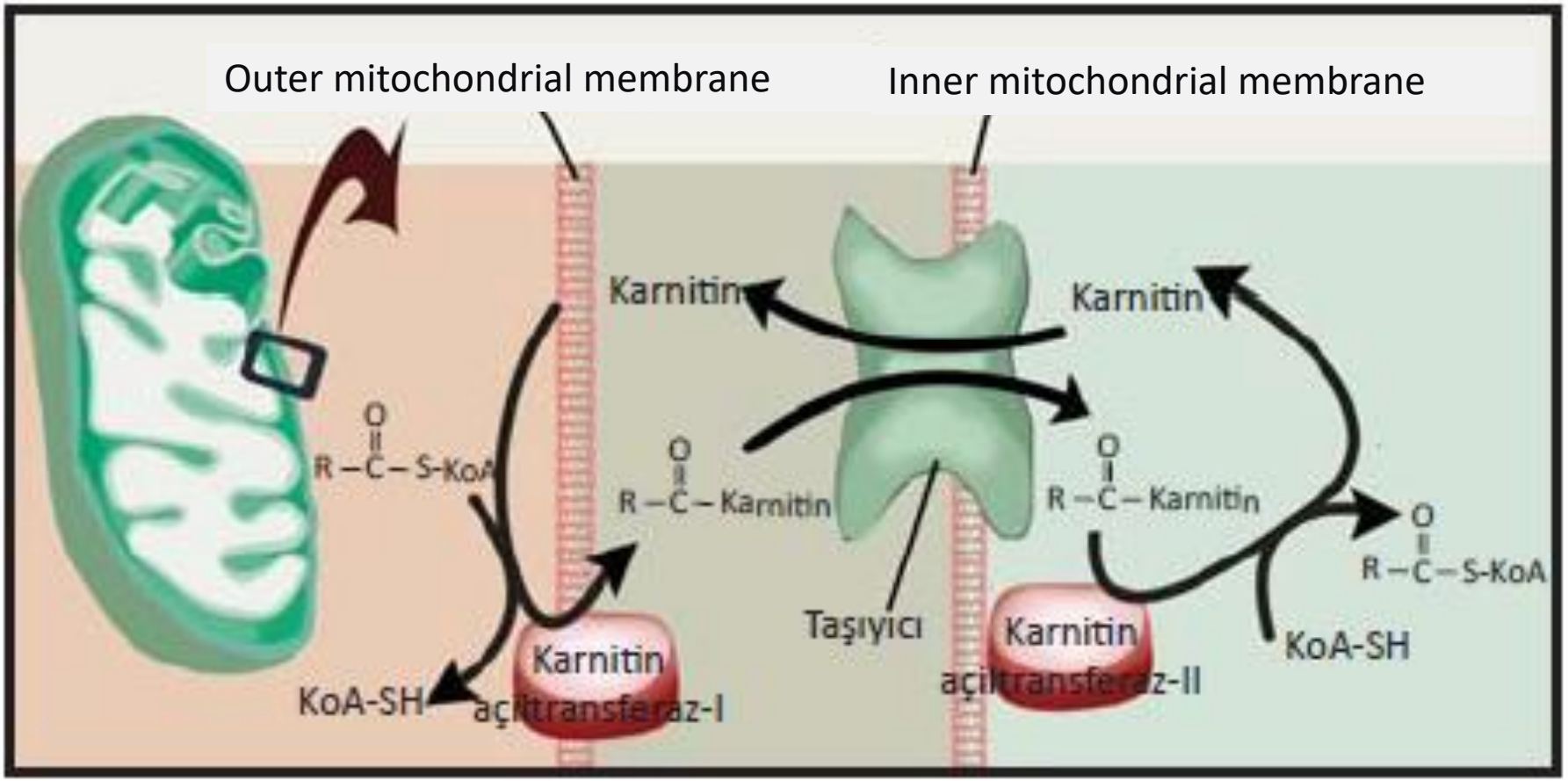
For transport;

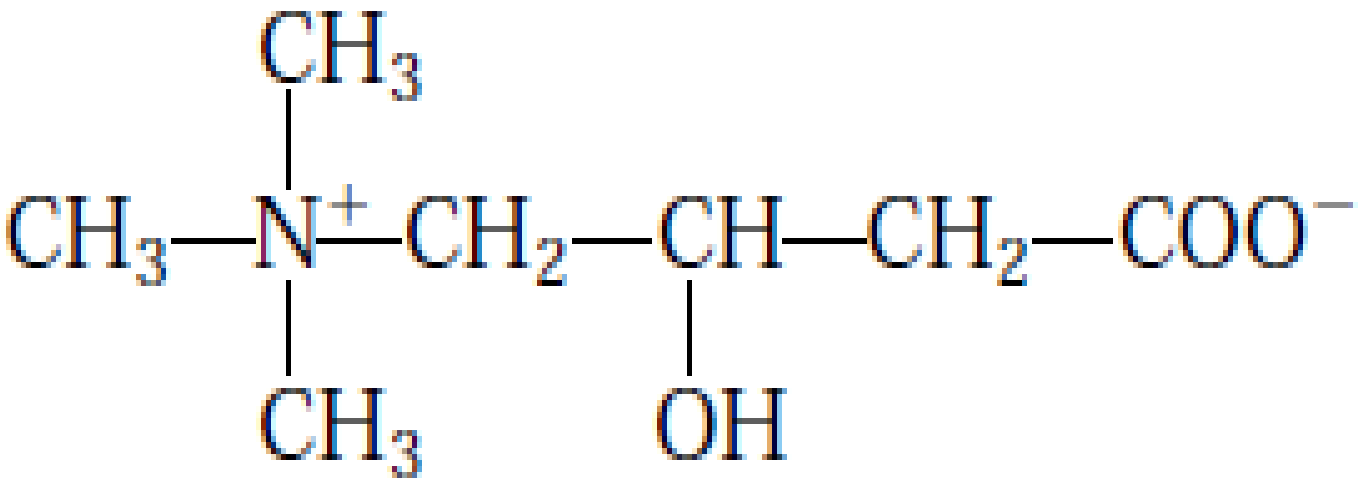
1. ‘acyl-CoA synthetase’-an enzyme located on the outer mitochondrial membrane- binds fatty acid to CoA to yield a fatty acyl-CoA.
2. the acyl group is transferred from CoA to carnitine by carnitine acyltransferase I (CAT-I; an enzyme of the outer mitochondrial membrane). This reaction forms acyl-carnitine, and regenerates free CoA.

3. the acyl-carnitine is transported into the mitochondrial matrix in exchange for free carnitine by **acyl-carnitine/carnitine transporter** of the inner mitochondrial membrane

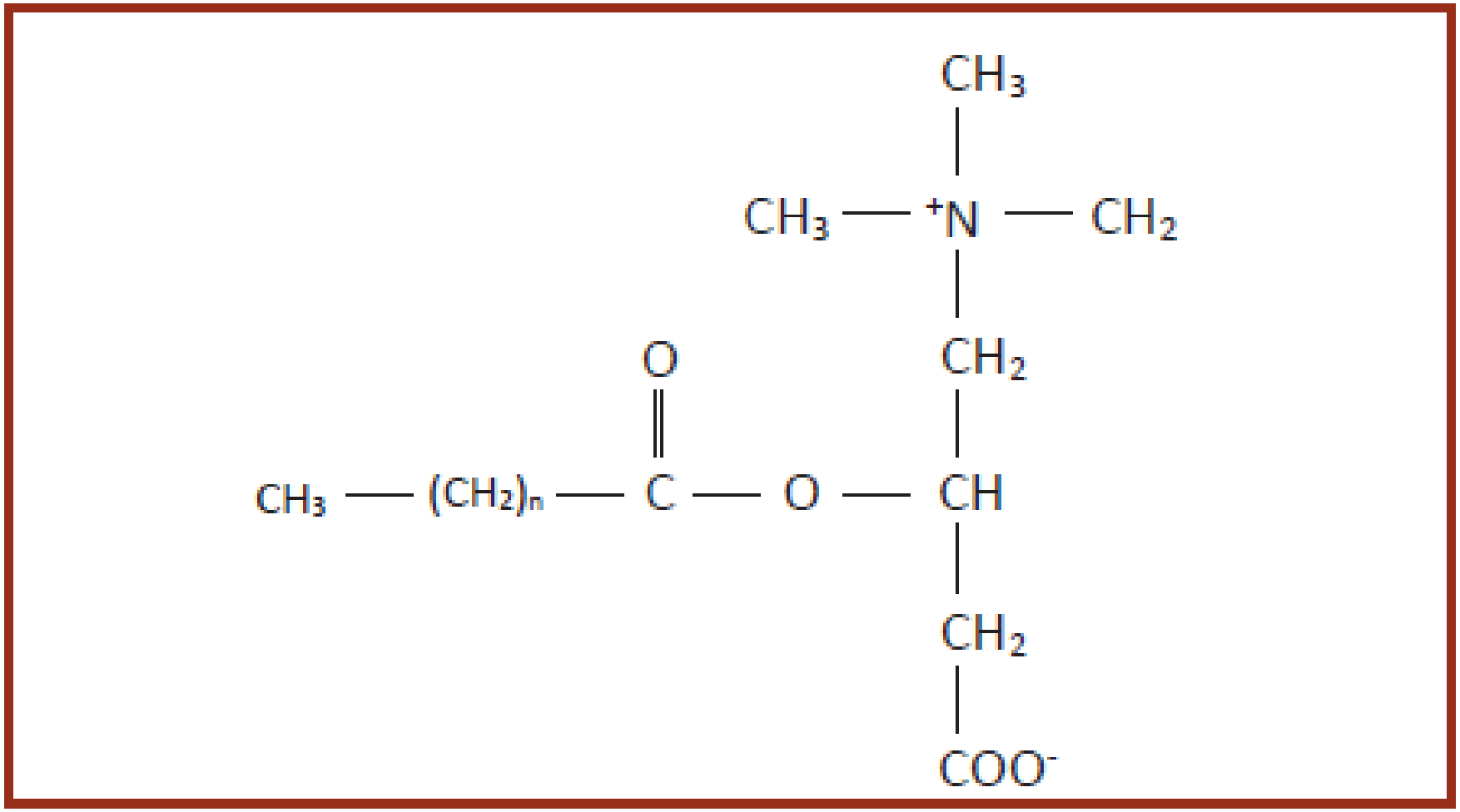
4. Carnitine acyltransferase II (CAT-II ; an enzyme of the inner mitochondrial membrane) catalyzes the transfer of the acyl group from carnitine to CoA in the mitochondrial matrix, thus regenerating free carnitine.

Fatty Acid Entry into Mitochondria via The Acyl-Carnitine/Carnitine Transporter





Carnitine



Acyl-Carnitine

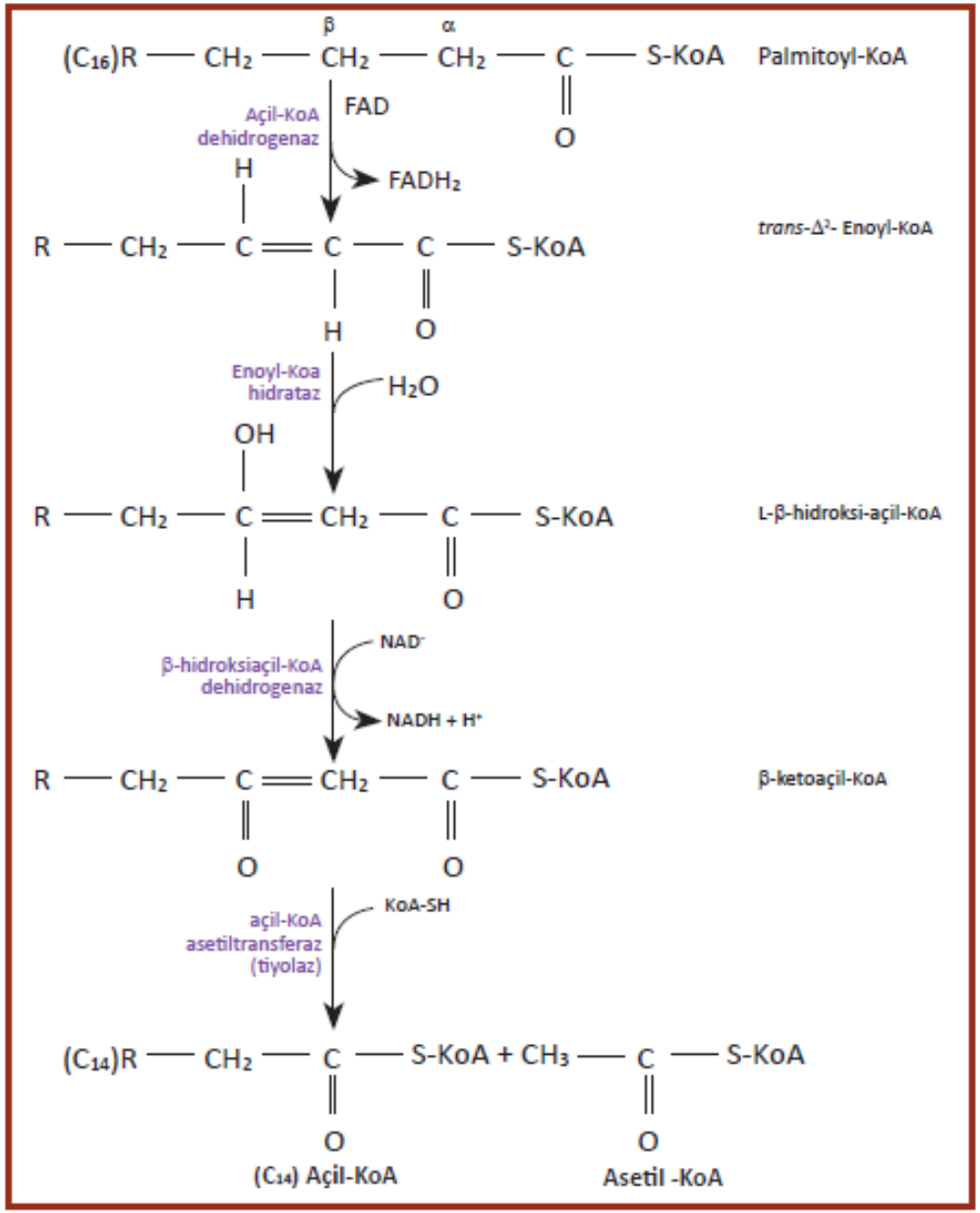
- Carnitine can be obtained from the diet, where it is found primarily in meat products.
- Carnitine can also be synthesized from the amino acids lysine and methionine by an enzymatic pathway found in the liver and kidney but not in skeletal or heart muscle.
- Skeletal muscle contains about 97% of all carnitine in the body.

- **Carnitine deficiency may ocur;**

1) in patients with liver disease causing decreased synthesis of carnitine;
2) in individuals suffering from malnutrition or those on strictly vegetarian diets;
3) in those with an increased requirement for carnitine as a result of, for example, pregnancy, severe infections, burns, or trauma;
4) in those undergoing hemodialysis, which removes carnitine from the blood.

- Congenital deficiencies in one of the components of the *carnitine shuttle,* in renal tubular reabsorption of carnitine, or in carnitine uptake by cells cause primary carnitine deficiency.

- Genetic *CAT-I* deficiency affects the liver, where an inability to use LCFA for fuel greatly impairs that tissue's ability to synthesize glucose during a fast. This can lead to severe hypoglycemia, coma, and death.
- *CAT-II* deficiency occurs primarily in cardiac and skeletal muscle, where symptoms of carnitine deficiency range from cardiomyopathy to muscle weakness with myoglobinemia following prolonged exercise.



Reaction series of **beta-oxidation**

The first step is catalyzed by three isozymes of **acyl-CoA dehydrogenase**, each specific for a range of fatty acyl chain lengths:

- very-long-chain acyl-CoA dehydrogenase (VLCAD), acting on fatty acids of 12 to 18 carbons;
- medium-chain (MCAD), acting on fatty acids of 4 to 14 carbons;
- short-chain (SCAD), acting on fatty acids of 4 to 8 carbons.

- The last three steps of this four-step sequence are catalyzed by either of two sets of enzymes, with the enzymes employed depending on the length of the fatty acyl chain.
- For fatty acyl chains of 12 or more carbons, the reactions are catalyzed by a multienzyme complex associated with the inner mitochondrial membrane, the **trifunctional protein (TFP)**.

- TFP is a heterooctamer of 4α and 4β subunits.
- Each α subunit contains two activities, the enoyl-CoA hydratase and the β-hydroxyacyl-CoA dehydrogenase;
- the β subunits contain the thiolase activity.
- When TFP has shortened the fatty acyl chain to 12 or fewer carbons, further oxidations are catalyzed by a set of four soluble enzymes in the matrix.

- Fatty acid oxidation does not take place in erythrocytes, brain and adipose tissue, so that, fatty acids can not be used for energy needs by those cells/tissues.

Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

- In mitochondria, there are four fatty acyl CoA dehydrogenase species, each with a specificity for either short-, medium-, long-, or very-long-chain fatty acids.
- MCAD deficiency, an autosomal recessive disorder, is one of the most common inborn errors of metabolism, and the most common inborn error of fatty acid oxidation, being found in 1:14,000 births worldwide, with a higher incidence in Northern Europeans.
- It results in decreased ability to oxidize fatty acids with six to ten carbons and severe hypoglycemia.
- Treatment includes avoidance of fasting.

- Succinyl CoA can enter the tricarboxylic acid cycle.
- This is the only example of a glucogenic precursor generated from fatty acid oxidation.
- The enzyme, methylmalonyl CoA mutase, requires a coenzyme form of vitamin B12 (deoxy - adenosylcobalamin) for its action.
- In patients with vitamin B12 deficiency, both propionate and methylmalonate are excreted in the urine.