Lipid Metabolism

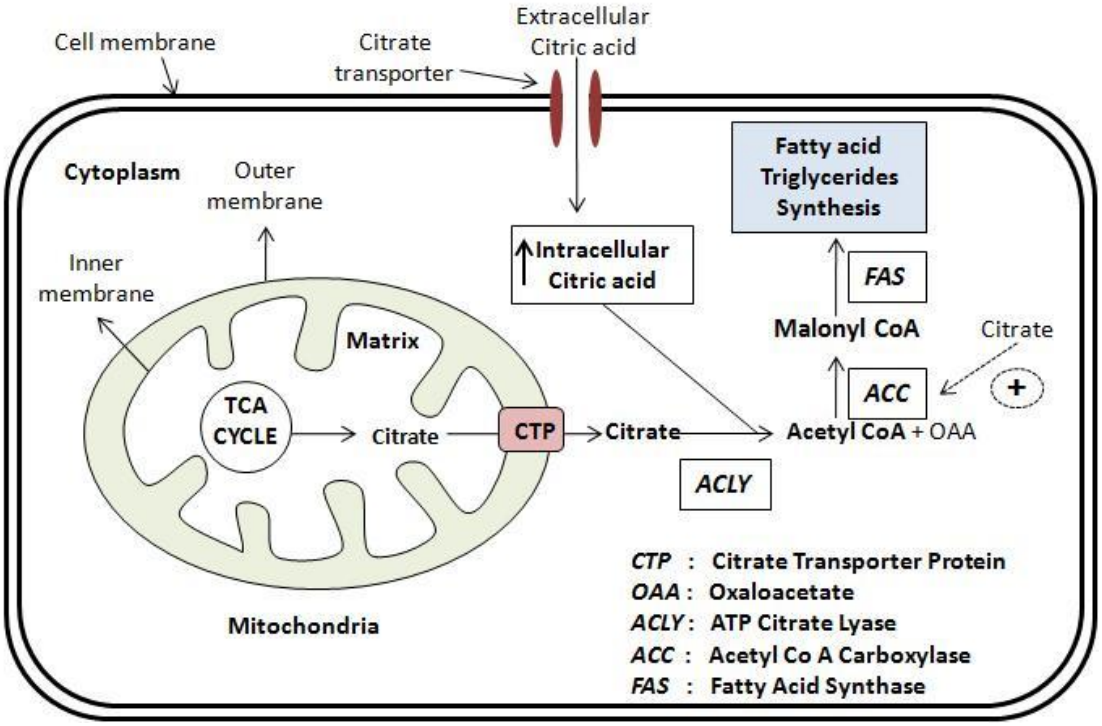
Dietary lipids are fats and complex molecules that the body needs to break down in order to utilize and energy, lipids are absorbed from the intestine and undergo digestion and metabolism,

- Triglycerides and dietary fats are insoluble in water and thus their absorption is difficult therefore hydrolyzed or broken down by enzymes secreted by the pancreas, they undergo emulsification that leads to liberation of fatty acids, the most important enzyme involved is pancreatic lipase that breaks down primary ester linkages.
- This converts triglycerides to diglyceride (2-monoacylglycerols), less than 10% of triglycerides remain unhydrolyzed in the intestine, short chain fatty acids enter the circulation directly but most of the fatty acids are re-esterified with glycerol in the intestines to form triglycerides that enter into the blood as lipoprotein particles called chylomicrons.
- These may be stored as fat in adipose tissue also re-esterified to triglycerides in the liver and exported as lipoproteins called VLDL (very low density lipoproteins), VLDL has a similar outcome as chylomicrons and eventually is converted to LDL (low density lipoproteins).
- During starvation for long periods of time the fatty acids can also be converted to ketone bodies in the liver, these ketone bodies can be used as an energy source by most cells that have mitochondria.
- Fatty acids are broken down by (Beta oxidation), this occurs in the mitochondria and/or in peroxisomes to generate acetyl-CoA, the process is the reverse of fatty acid synthesis (Lipogenesis).
- Beta oxidation which two-carbon fragments are removed from the carboxyl end of the acid to form Acetyl-CoA may undergo several fates:
  1. It is the precursor for synthesis of cholesterol and other steroids.
  2. In the liver, forms ketone bodies (acetone, acetoacetate, and 3-hydroxybutyrate) that are important fuels in prolonged starvation.

Fatty acids synthesis from acetyl Co-A (Lipogenesis)

Lipogenesis is the pathway of fatty acids synthesis occur **in cystol,** this system is present in many tissues, including liver, kidney, brain, lung, mammary gland, and adipose tissue, cofactor requirements include NADPH, ATP, Mn2+, biotin, and HCO3 (as a source of CO2).

Fatty acid synthesis begin from acetyl-CoA, via malonyl-CoA, through the action of enzymes called fatty acid synthases, this process takes place in the cytoplasm of the cell, the main sources of NADPH for Lipogenesis is the Pentose Phosphate Pathway



Fatty acids synthesis (Lipogenesis)

Regulates of lipogenesis

1. The nutritional state
   Excess carbohydrate and high-fat diet, or a deficiency of insulin, as in diabetes mellitus these latter conditions are associated with increased concentrations of plasma-free fatty acids.

2. Acyl-CoA causes an inhibition of Acetyl-CoA Carboxylase.

3. Insulin stimulates lipogenesis by several other mechanisms as well as by increasing acetyl-CoA carboxylase activity.

Elongation of Fatty Acid Chains

This pathway occurs in the endoplasmic reticulum elongates saturated and unsaturated using malonyl-CoA as the acetyl donor and NADPH as the reductant.

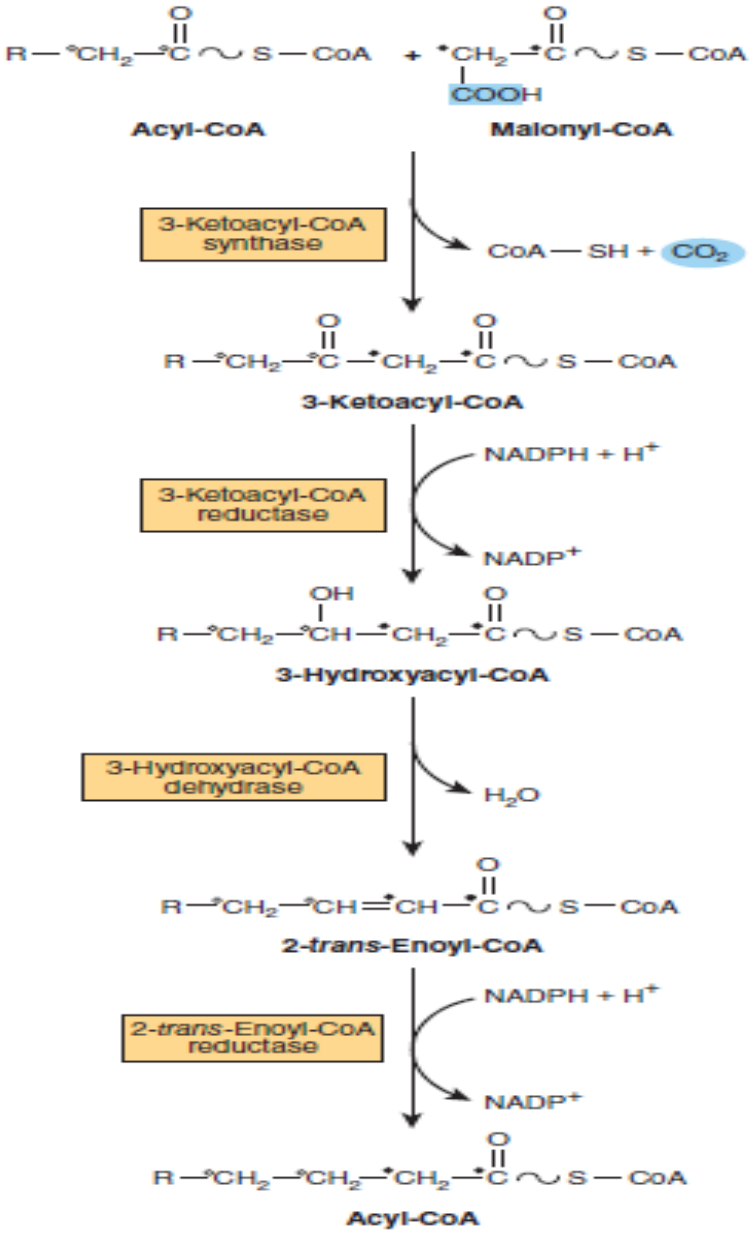
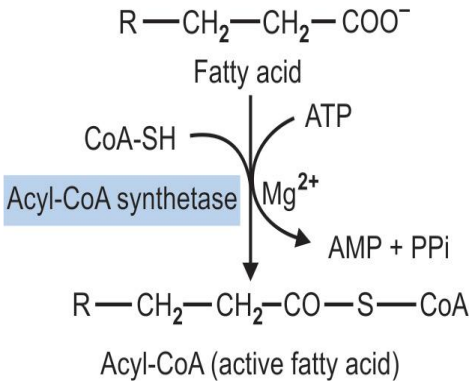


FIGURE 23–5 Microsomal elongase system for fatty acid chain elongation. NADH is also used by the reductases, but NADPH is preferred.

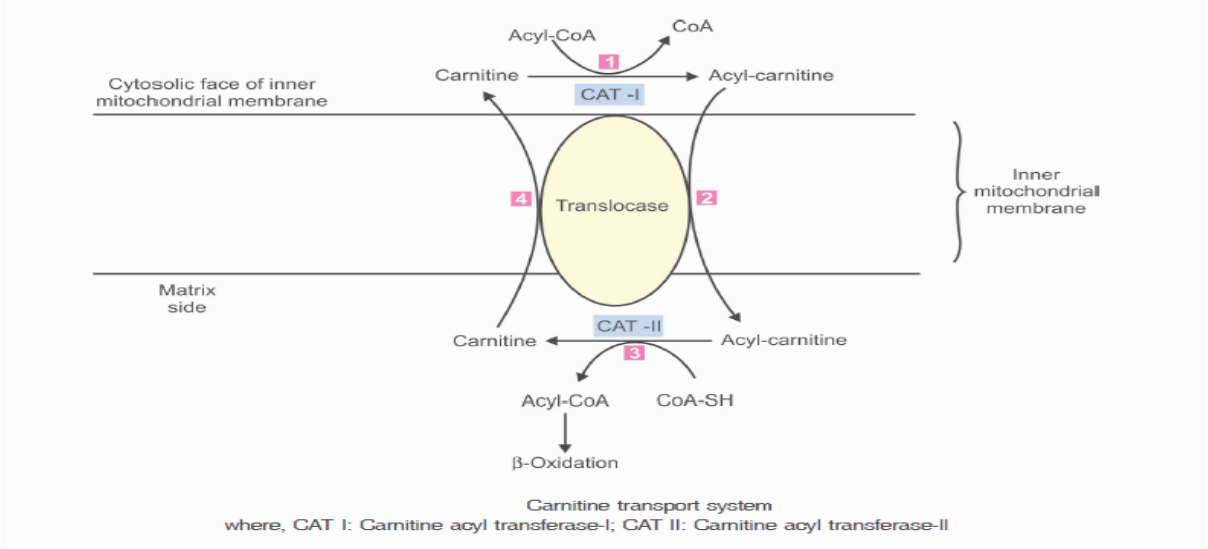
B-oxidation pathway

Although fatty acids are broken down by oxidation to acetyl-CoA and also synthesized from acetyl-CoA, it is an aerobic process, requiring the presence of oxygen, all reactions of β-oxidation occur **in mitochondria.** Increased fatty acid oxidation is a characteristic of starvation, diabetes mellitus and leads to ketone body production by the liver (ketosis), ketone bodies are acidic and when produced in excess over long periods, as in diabetes, cause ketoacidosis, which is ultimately fatal, it involves following three steps:

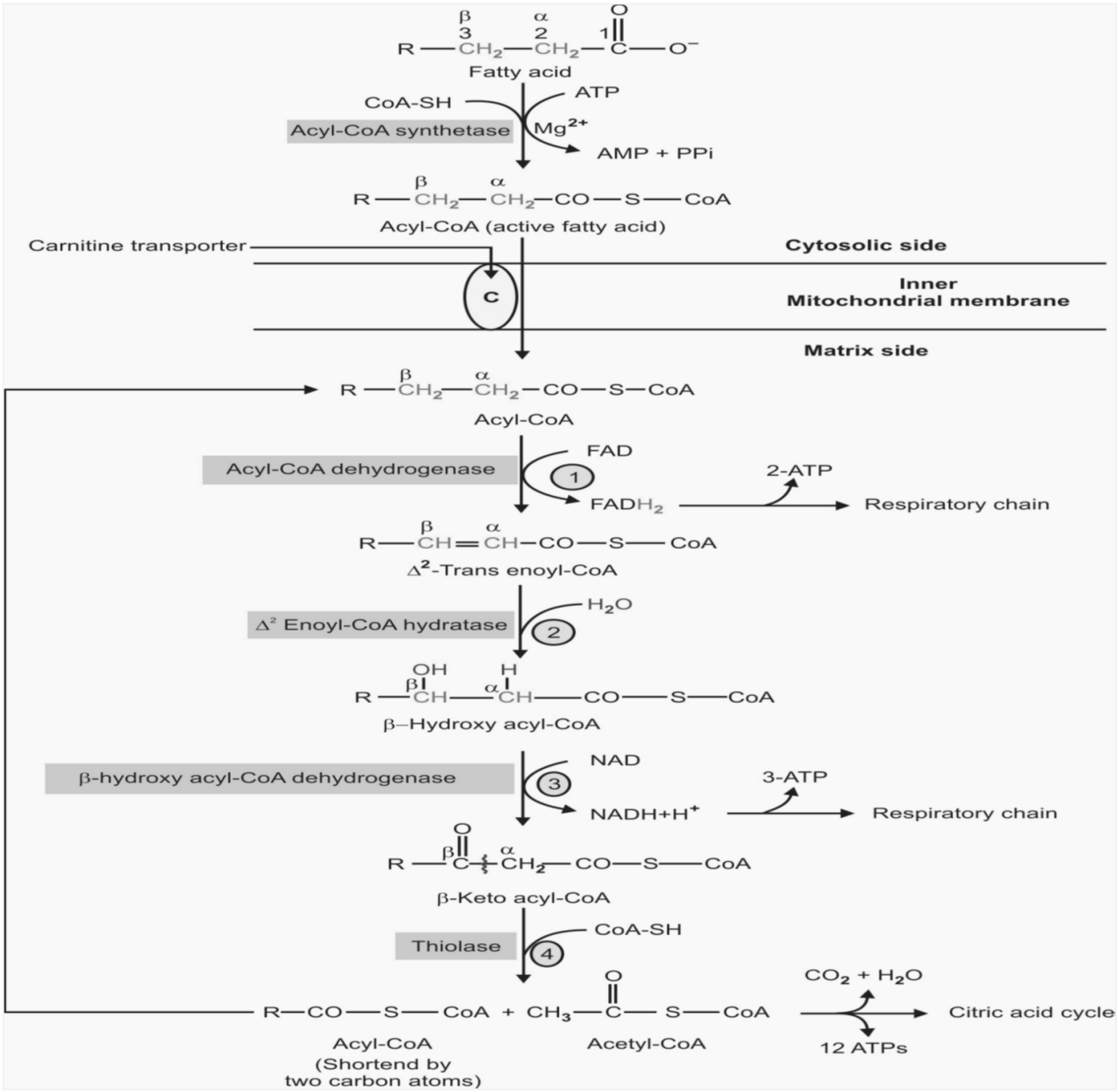
1. Activation of fatty acid to acyl-CoA



2. Transfer of acyl CoA into mitochondria by carnitine transport system, the acyl group of acyl-CoA is transferred to the carnitine to form acyl carnitine, this reaction is catalyzed by carnitine acyltransferase-I .



Carnitine transport system
where, CAT I: Carnitine acyl transferase-I; CAT II: Carnitine acyl transferase-II



B-oxidation pathway occurs in mitochondria.

Quantity of ATP for oxidation of palmitate (16 c):

1 FADH=2ATP

1 NADH=3ATP

=5ATP

-for 7 oxidation steps yield: 7×5=35

- 8 of acetyl- CoA is formed yield: 8 × 12 = 96

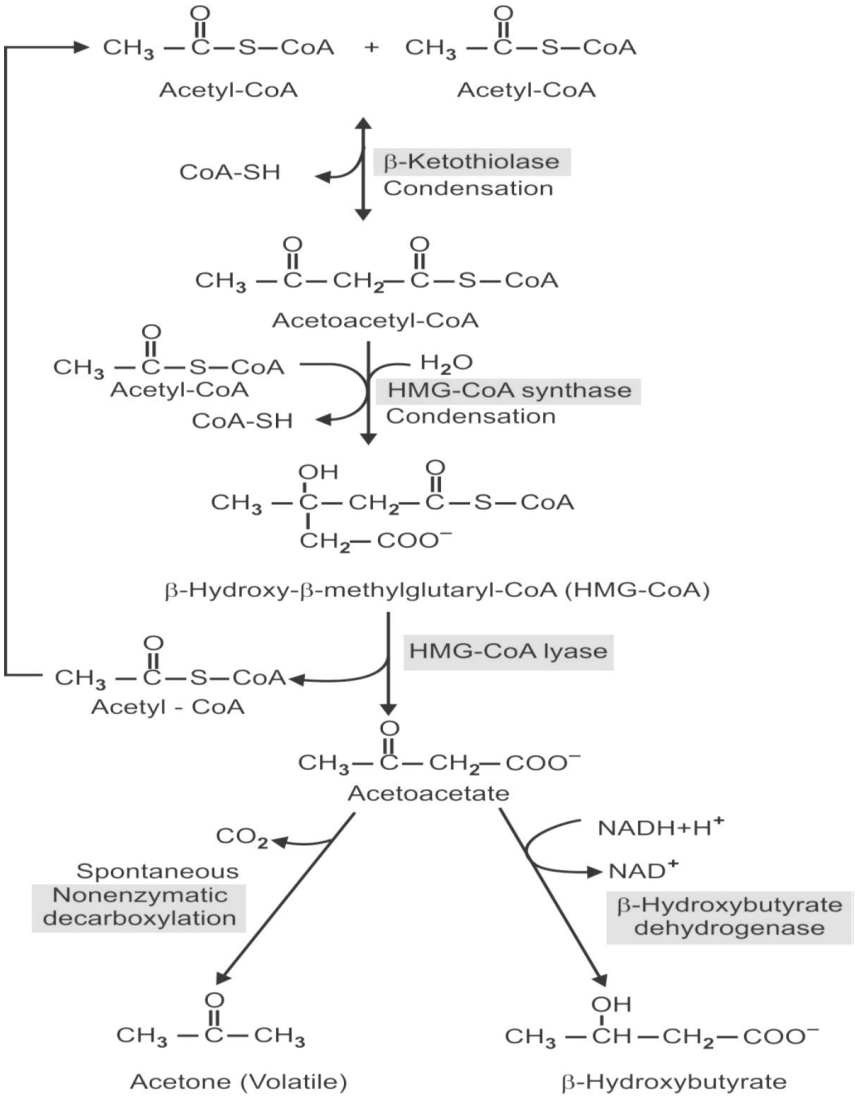
-Yield 35+96=131 ATP

For activation of fatty acid required (2ATP) yield 131-2=129 ATP

-Note that in this step, the ATP is converted to AMP, not ADP, thus, activation uses the equivalent of 2 ATP molecules.

Ketone Bodies

Ketone bodies are three water-soluble molecules that are produced by the liver from fatty acids during periods of low food intake (fasting) of the body to use as energy instead of glucose, ketogenesis means the formation of ketone bodies, liver is the only organ that synthesizes ketone bodies:

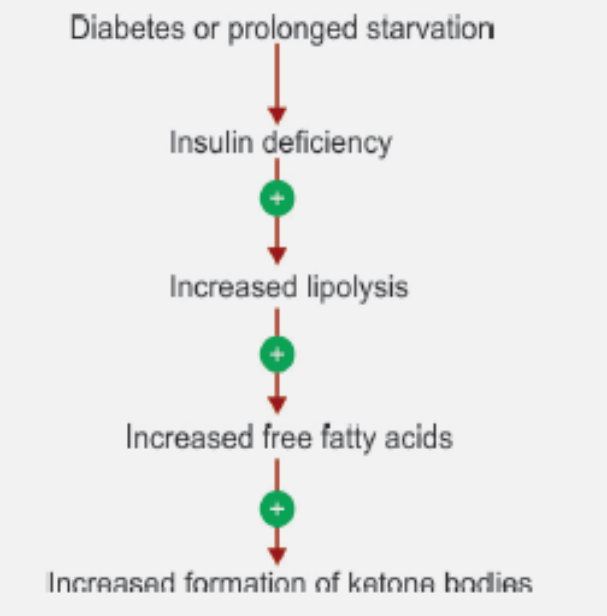


Synthesis of ketone bodies

The three ketone bodies are acetone, acetoacetic acid and beta-hydroxybutyric acid, normally the concentration of ketone bodies in blood is very low, (less than 0.2 mmol/L) but in fasting and in diabetes mellitus it may reach extremely high levels.

During fasting or in diabetes mellitus, when exogenous glucose is unavailable, insulin secretion is inhibited, the plasma insulin concentration is low which causes increased lipolysis and therefore increased production of free fatty acids and hence ketone bodies production is increased, when the rate of formation of the ketone bodies by liver exceeds the capacity of the peripheral tissues to use them up, their levels begin to rise in blood.

An increase in concentration of ketone bodies in blood is called ketonemia and eventually leads to excretion of ketone bodies into the urine called ketonuria, the overall condition (ketonemia and ketonuria) is called ketosis, acetone is very volatile and is present in the breath of diabetics, to which it gives sweet fruity odor.



Regulation of ketogenesis

Ketosis does not occur unless there is an increase uptake by the liver, fatty acids are either a-oxidized to CO2 or ketone bodies or esterified to triacylglycerol and phospholipid, there is regulation of entry of fatty acids into the oxidative pathway by carnitine acyltransferase-I (CPT-I)

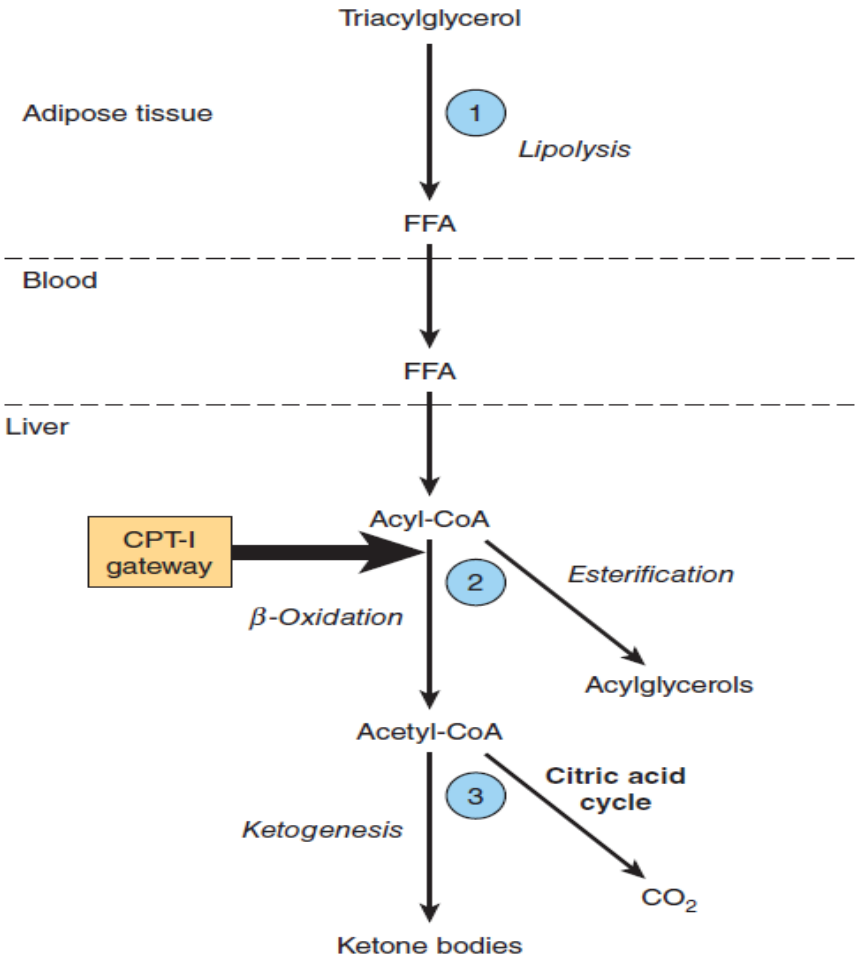


FIGURE 22–9 **Regulation of ketogenesis.** ① to ③ show three crucial steps in the pathway of metabolism of free fatty acids (FFA) that determine the magnitude of ketogenesis. (CPT-I, carnitine palmitoyltransferase-I.)

Lipid Transport

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage, since lipids are insoluble in water, Lipoproteins are responsible of lipid transport in the blood, they classified by their buoyant density, which inversely reflects their size, the greater the lipid to protein ratio, the larger their size and the lower the density, the plasma lipoproteins include chylomicrons, very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs), Furthermore, generally about 70 percent of plasma cholesterol is incorporated as LDL and 20 percent as HDL, the Friedewald equation enables plasma LDL cholesterol concentration to be calculated and is often used in clinical laboratories:

LDL = total cholesterol – HDL –triglyceride

Table 3.3: The four main lipoproteins and their site of synthesis and function

Lipoprotein	*Site of synthesis*	*Function*
Chylomicrons	Intestine	Transport of dietary lipids from intestine to peripheral tissues
VLDL	Liver	Transport of triacylglycerol from liver to peripheral tissues
LDL	Plasma VLDL	Transport of cholesterol from liver to peripheral tissues
HDL	Liver and intestine	Transport of free cholesterol from peripheral tissues to the liver (Reverse cholesterol transport)