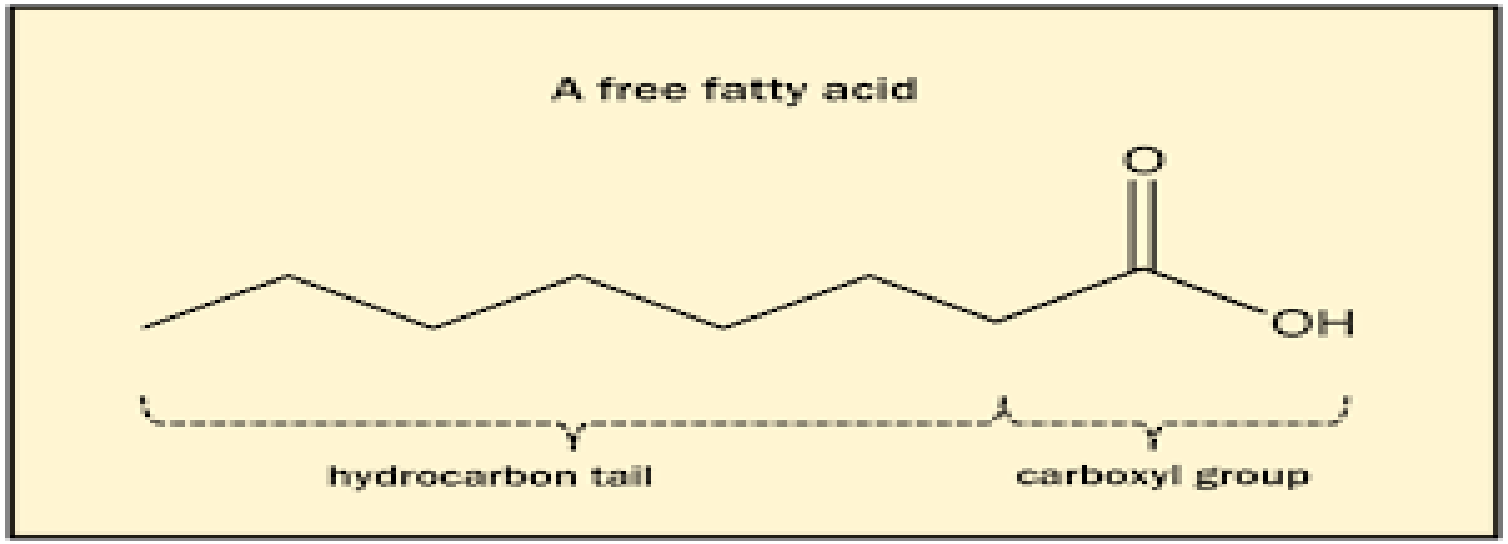
Lipid metabolism



Ass.prof. Dr. Anwar Alabdali

By the end of the lectures you will learn

-What is the lipid ?

-Subdivision of lipids

-lipids nomenclature

-Digestion and absorption of the lipids

-Biosynthesis of fatty acids (lipogenesis)

-Steps of fatty acids synthesis

-Enzymes are involved in the fatty acids synthesis

-Regulation of fatty acids synthesis

-What is the β-oxidation (lipolysis) and the steps of synthesis ?

-Regulation of lipolysis

-What are the ketone bodies ? And what is the ketogenesis ?

What is the lipids ?

- Lipids are a heterogeneous group of water-insoluble (hydrophobic) organic molecules that can be extracted from tissues by nonpolar solvents

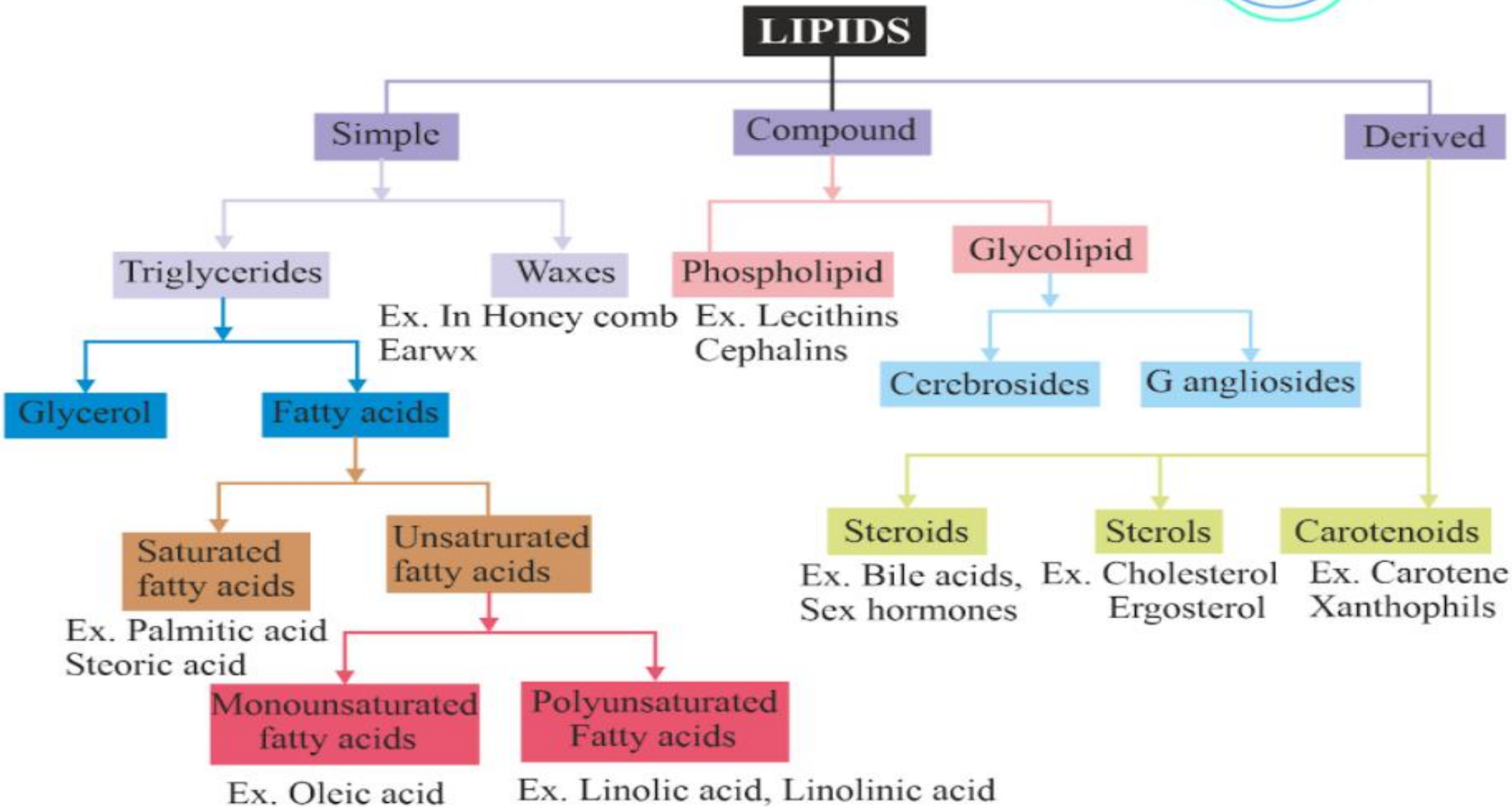
- Lipids are a major source of energy for the body.

- lipids are generally found compartmentalized, as in the case of membrane-associated lipids or droplets of triacylglycerol in white adipocytes, or transported in plasma in association with protein, as in lipoprotein particles ,

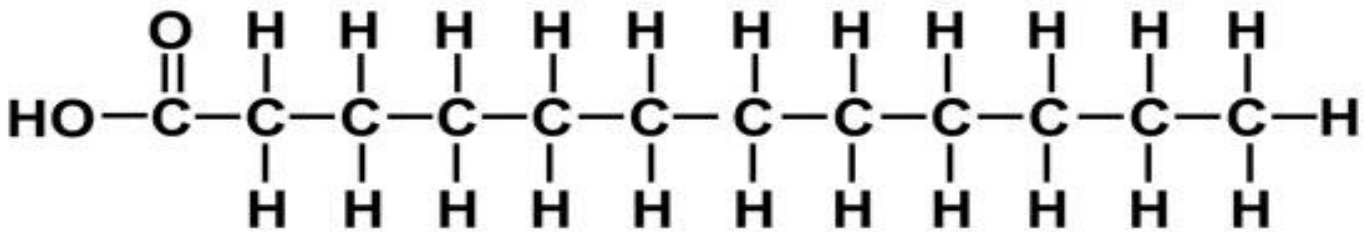
or Free fatty acids (FFA) transported with albumin.

- Lipids serve additional functions in the body, for example, some fat-soluble vitamins have regulatory or coenzyme functions, and the prostaglandins and steroid hormones play major roles in the control of the body's homeostasis

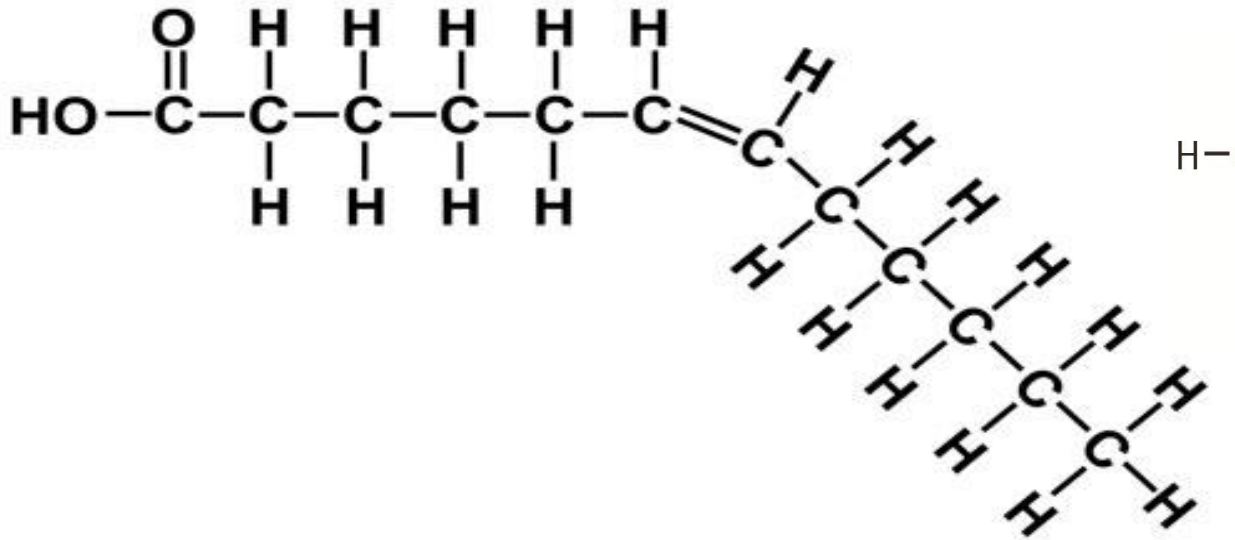
- Deficiencies or imbalances of lipid metabolism can lead to some of the major clinical problems, such as atherosclerosis and obesity.

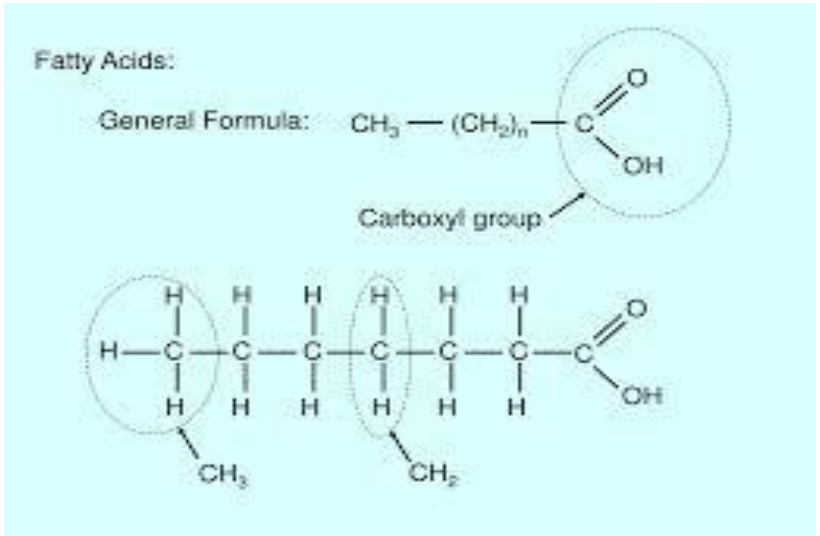

LIPIDS
Simple
Compound
Derived
Triglycerides
Waxes
Phospholipid
Glycolipid
Ex. In Honey comb
Earwx
Ex. Lecithins
Cephalins
Glycerol
Fatty acids
Cerebrosides
G angliosides
Saturated
fatty acids
Unsatrurated
fatty acids
Steroids
Sterols
Carotenoids
Ex. Bile acids,
Sex hormones
Ex. Cholesterol
Ergosterol
Ex. Carotene
Xanthophils
Ex. Palmitic acid
Steoric acid
Monounsaturated
fatty acids
Polyunsaturated
Fatty acids
Ex. Oleic acid
Ex. Linolic acid, Linolinic acid

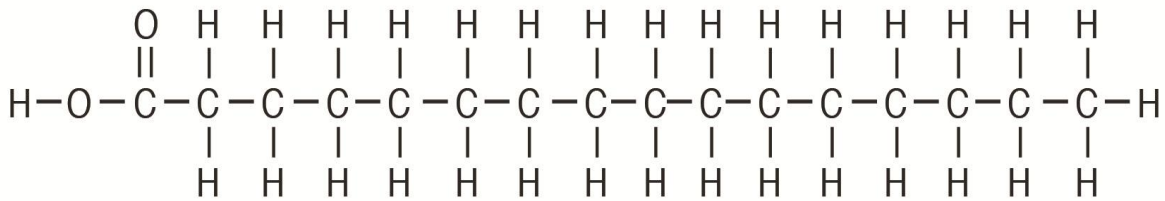
Saturated Fatty Acid



Unsaturated Fatty Acid







Palmitic Acid

****saturated fatty acids (containing no double bonds) e.g., palmitic acid while unsaturated acids (with double bond) e.g., (oleic acid).

**** The most frequently used systematic nomenclature names **.** The carbon atoms adjacent to the carboxyl carbon (Nos. 2, 3, and 4) are also known as the α, β, and γ carbons, respectively, and the terminal methyl carbon is known as the ω or n-carbon.

18:1;9 *or* Δ9 18:1

$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$

ω9,C18:1 *or* n–9, 18:1

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH=CH(CH_2)_7COOH$

Fatty acids occur mainly as esters in natural fats and oils

but do occur in the unesterified form as **free fatty**

Esterification :-is the process of combining an organic acid(RCOOH) with an alcohol (ROH) to form an ester(RCOOR) and water

How are dietary lipids digested and absorbed?

Dietary lipid is in the form of •

1- Triacylglycerol(predominant) •

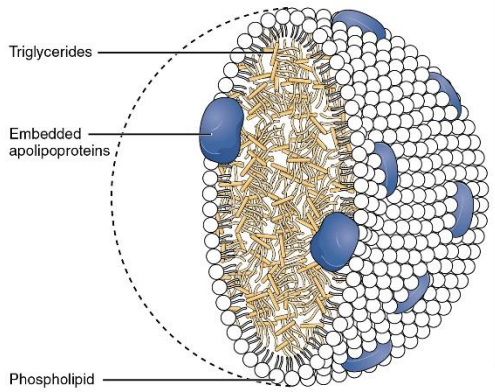
2- Phospholipids •

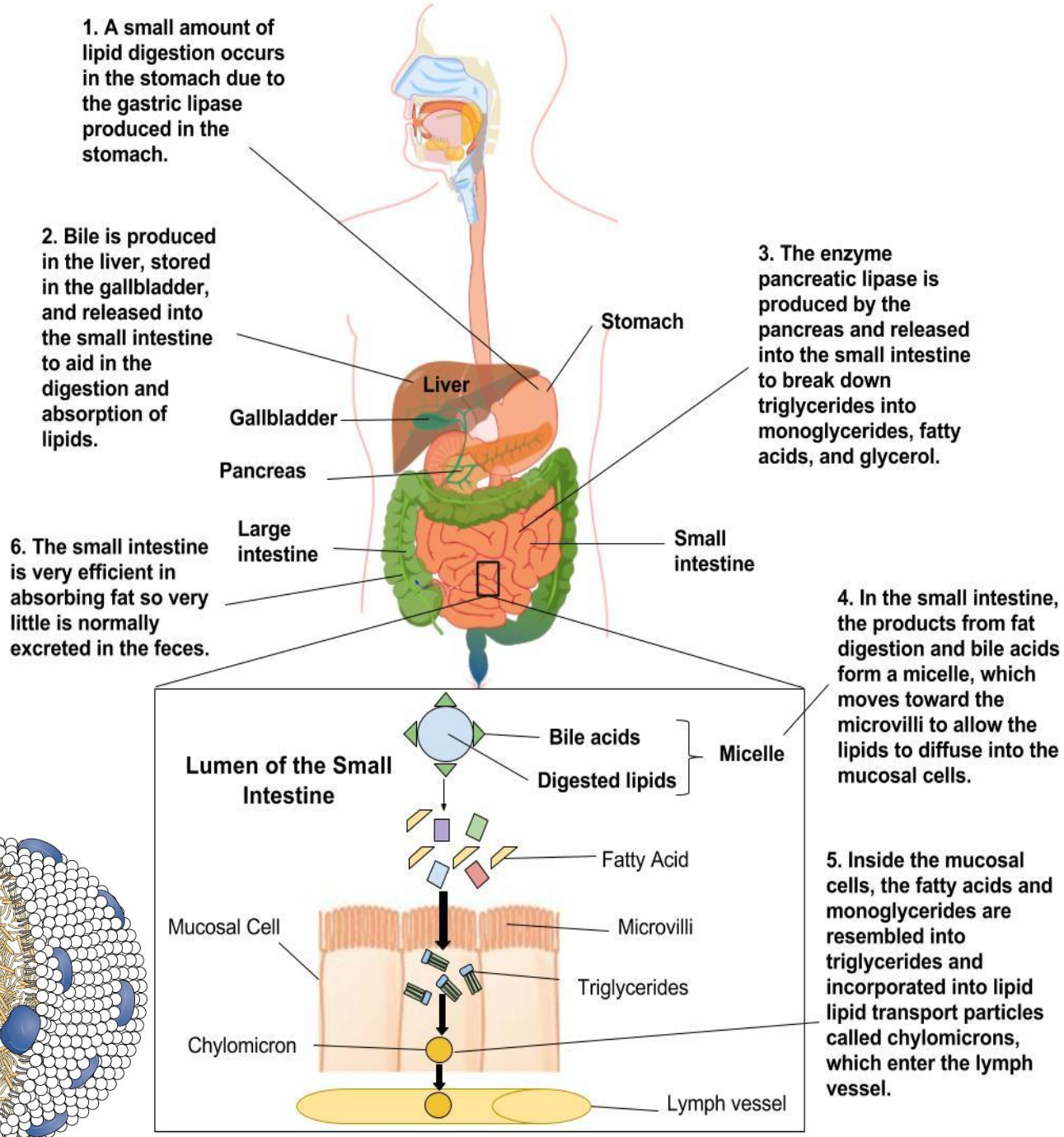
3-Cholesterol and cholesteryel esters •

Emulsification of dietary lipid !! •

It occurs in the duodenum , it increases the surface area of hydrophobic lipid droplet so the interface of these droplets with aqueous solution can act effectively .

The emulsification agents are bile salts





Fatty acid biosynthesis

- A large proportion of the fatty acids used by the body is supplied by the diet.

- Carbohydrates and protein obtained from the diet in excess of the body's needs for these compounds can be converted to fatty acids, which are stored as triacylglycerol's.

-The synthesis of fatty acids involves the condensation of 2-carbon units in the form of acetyl-coA.

During this synthesis, the fatty acids are covalently linked to an acyl carrier protein(ACP).

Sites of synthesis: Liver, kidney and adipose tissue

Subcellular site : Cytosol

Precursor :- Acetyl-coA

Requirements:Fatty acid synthase complex, NADPH as a reductant

Fatty acid biosynthesis

Transfer of acetyl CoA from the mitochondrion to the cytosol •

The inner mitochondrial membrane is not permeable to acetyl CoA. The following • reactions facilitate acetyl CoA transport:

1. Condensation of acetyl CoA with oxaloacetate to form citrate •

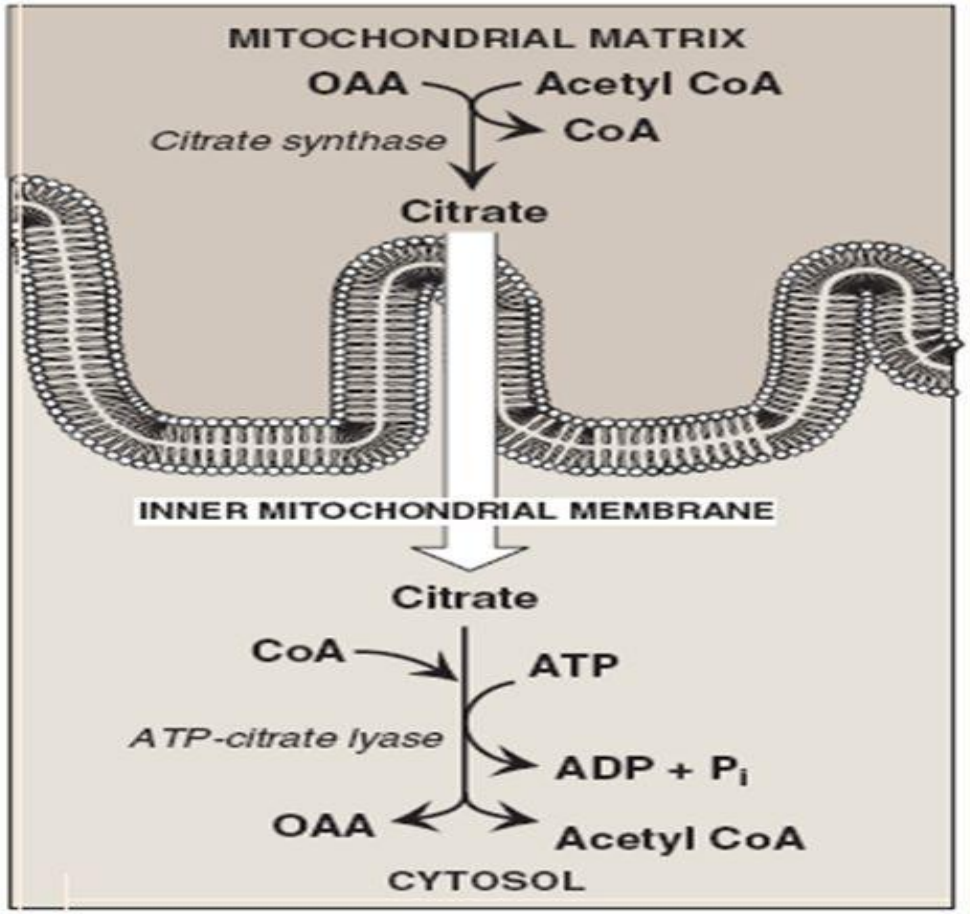
2. Transport of citrate to the cytosol •

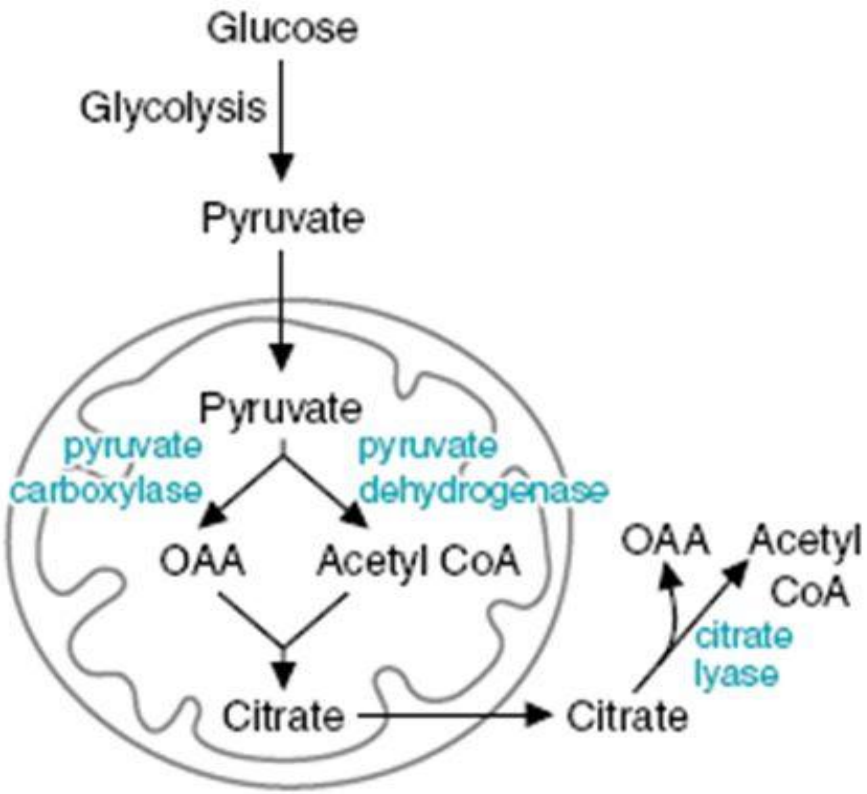
3. Cleavage of citrate by ATP-citrate lyase to regenerate acetyl CoA and • oxaloacetate

4. Re-entry of oxaloacetate to the mitochondria after conversion to malate • generating NADPH.

Fatty acid biosynthesis

Transport of acetyl CoA from mitochondria to cytoplasm:





Fatty acid biosynthesis

Steps in biosynthesis •

1. Carboxylation of acetyl CoA to malonyl CoA by acetyl CoA carboxylase that • contains biotin as a prosthetic group.

2. Conversion of acetyl CoA and malonyl CoA to their corresponding ACP- • derivatives catalyzed by acetyltransacylase and malonyl transacylase , respectively.

3. Elongation cycle involves a repeated sequence of four reactions: •

a. Condensation of acetyl-ACP and malonyl-ACP to yield acetoacetyl-ACP. •

b. Reduction of acetoacetyl-ACP to 3-hydroxybutyryACP by NADPH. •

c. Dehydration to crotonyl ACP. •

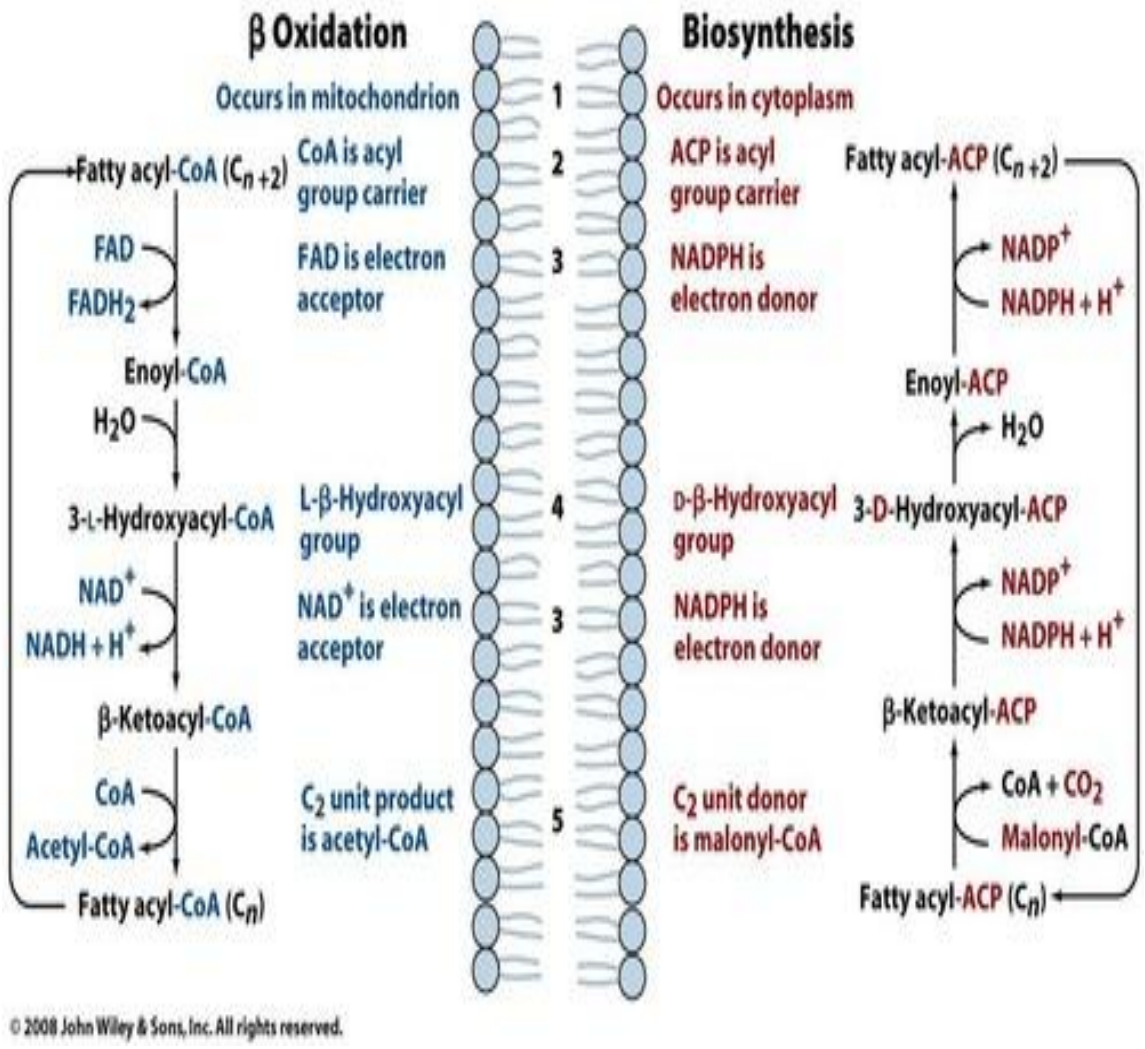
d. Reduction of crotonyl ACP to butyryl-ACP by NADPH. •

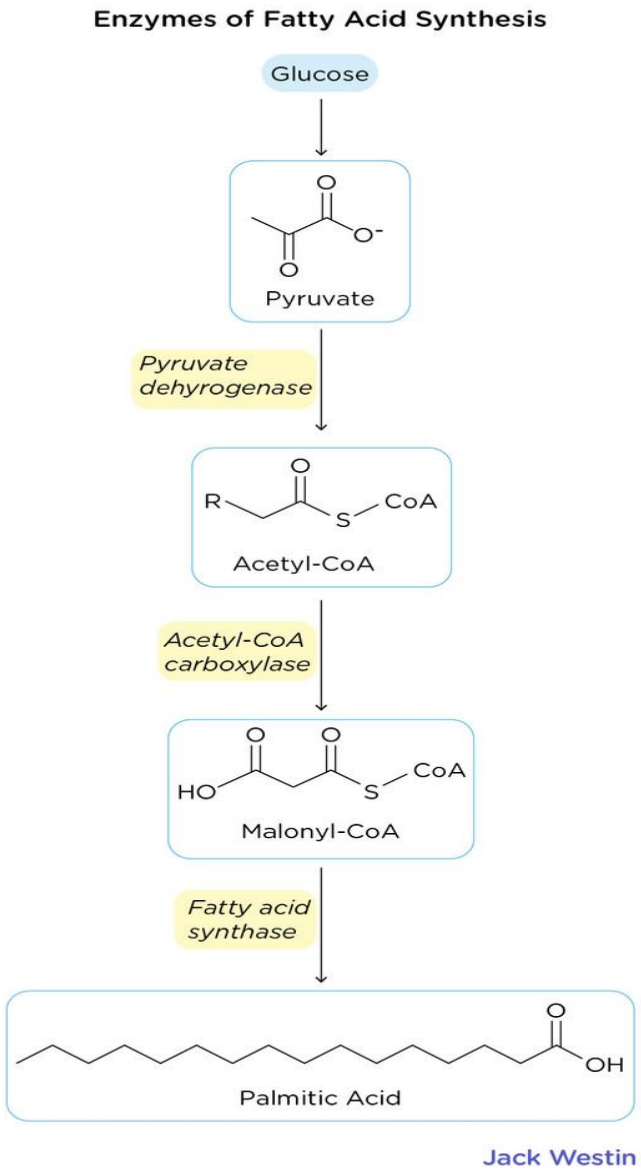
Thus, successive addition of two-carbon units forms the 16C palmitoyl-ACP. •

Hydrolysis of palmitoyl-ACP by a thioesterase generates palmitate and ACP. •

4. Desaturation:Palmitate undergoes chain elongation to form C18 stearate •

Fatty acid biosynthesis





Regulation of fatty acids synthesis

Lipogenesis is regulated by the following factors: •

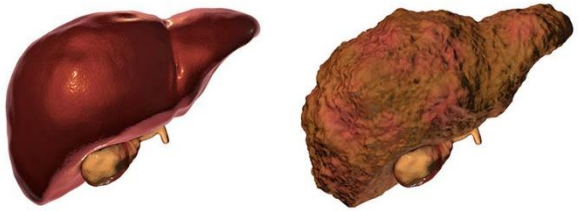
1-Hormones: Insulin stimulates fatty acid synthesis, whereas glucagon and epinephrine • inhibit fatty acid synthesis.

2-Acetyl CoA carboxylase: This is an allosteric enzyme, which is stimulated by citrate and inhibited by long-chain acyl CoA molecules.

**- <u>This enzyme is inhibited in diabetes</u>.

3-Nutritional state: Fatty acid synthesis is decreased by caloric restriction and increased in the well fed state.

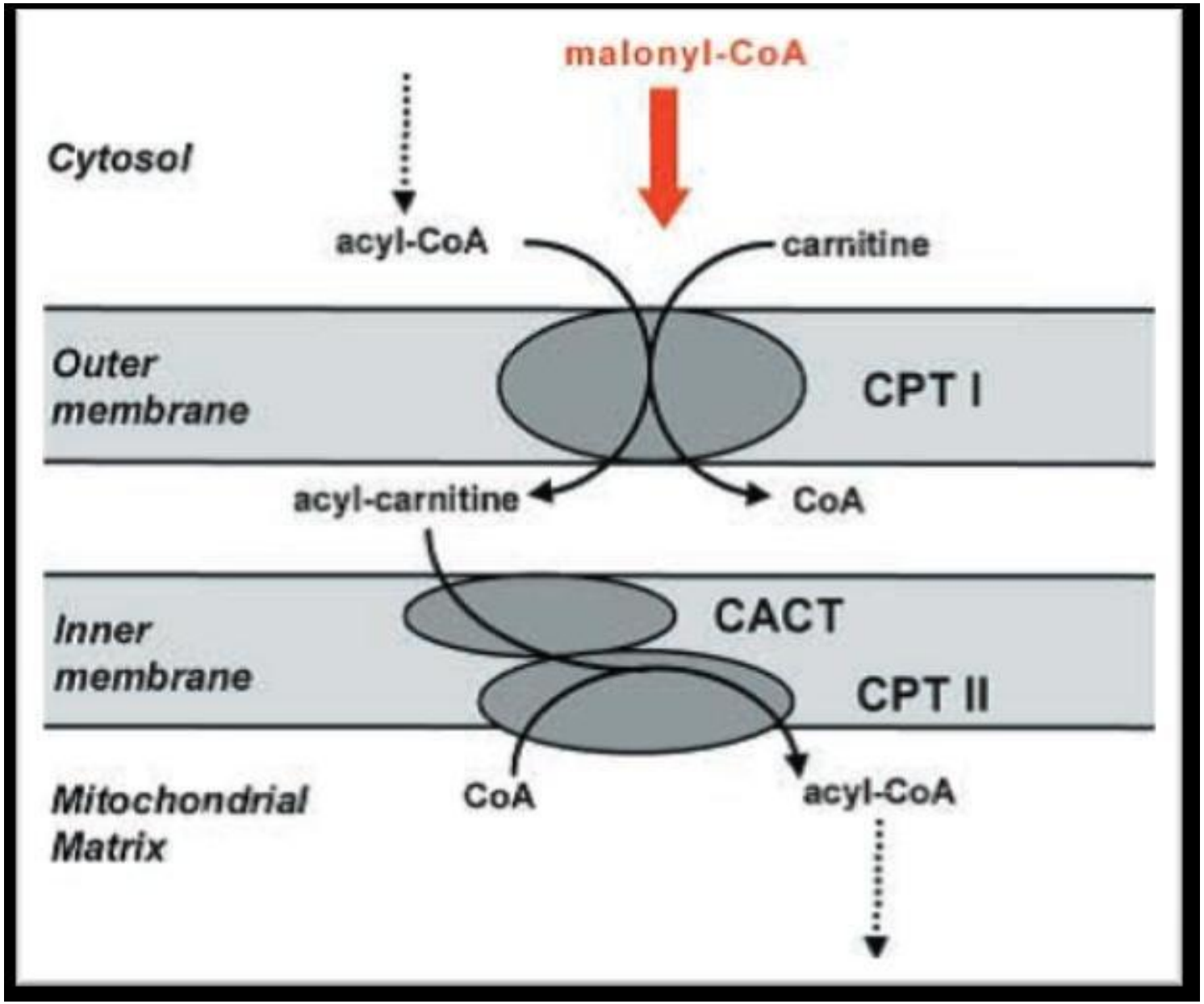
Fatty liver: It's the accumulation of triacylglycerol(T.G) in the liver which lead to liver fibrosis ,it is called cirrhosis and then impaired of liver function. This occurs in excess calories of fat and alcoholism.



Healthy liver Cirrhotic liver

β-Oxidation of fatty acid

- Definition:-The major pathway for catabolism of fatty acids, it is a mitochondrial pathway acyl CoA, producing acetyl CoA, NADH, and FADH2.
- Acetyl CoA is completely oxidized to carbon dioxide and water via the TCA cycle.
- Subcellular site: Mitochondrial matrix
- Steps:-Before the oxidation reactions ,the fatty acids are a activated and transported to the mitochondria, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acid .
- The following sequence of events are involved:
- I. Activation of fatty acids to fatty acyl CoA by acyl CoA synthase (fatty acid thiokinase).
- RCOOH + ATP + CoASH F:- R-COS CoA + AMP + PPi
- 2. Transfer of fatty acyl CoA by carnitine acyltransferaseI to carnitine. Carnitine is required as an acyl group carrier because the mitochondrion is impermeable to fatty acyl CoA. The acyl group from acyl carnitine is transferred to CoA in the mitochondrial matrix by carnitine acyltransferaseII


malonyl-CoA
Cytosol
acyl-CoA
carnitine
Outer membrane
CPT I
acyl-carnitine
CoA
Inner membrane
CACT
CPT II
Mitochondrial Matrix
CoA
acyl-CoA

β-Oxidation of fatty acid

3. B-Oxidation involves repeated sequence of the following four reactions

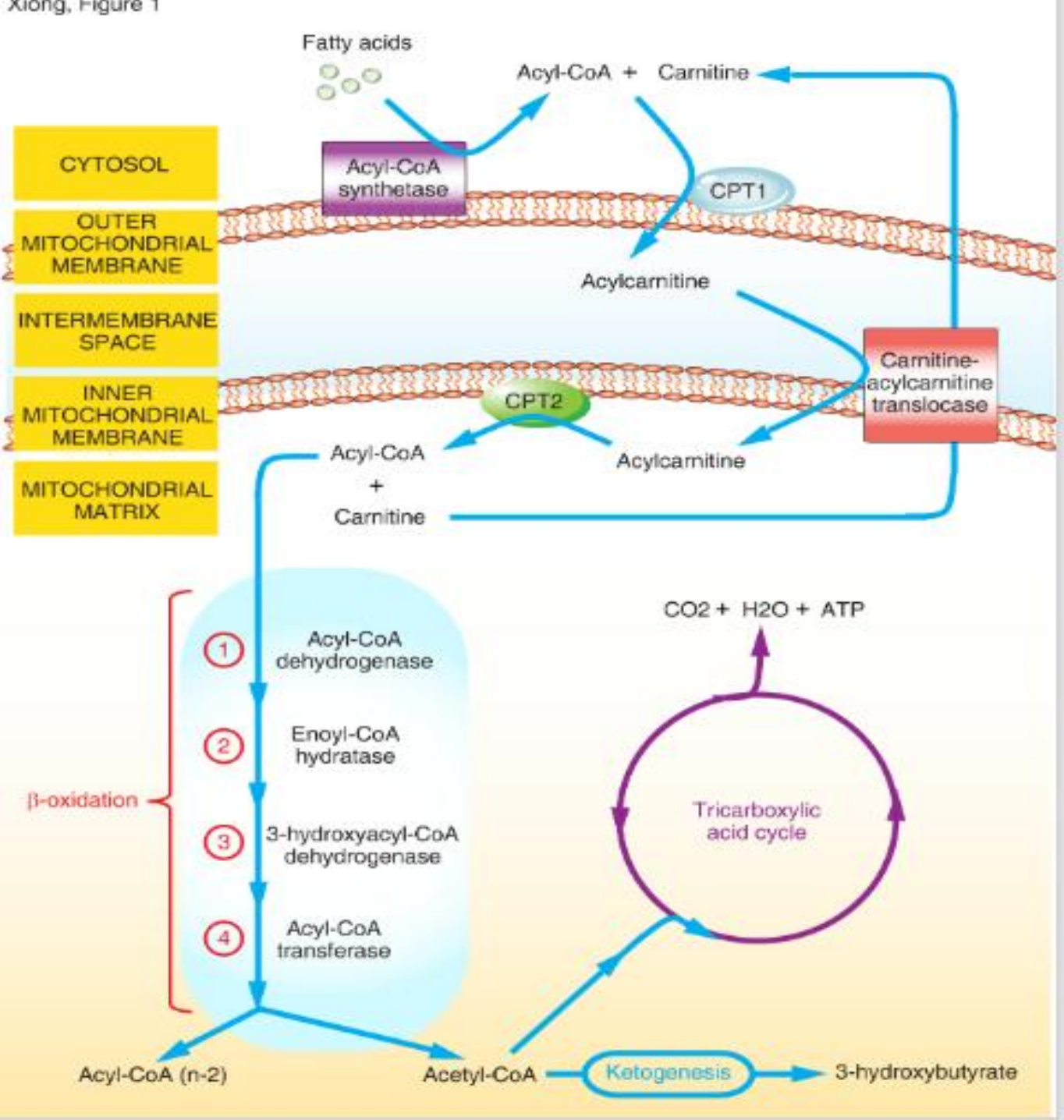
a. Oxidation of the acyl CoA to trans- Δ^2-enoyl CoA by FAD-dependendt dehydrogenase.

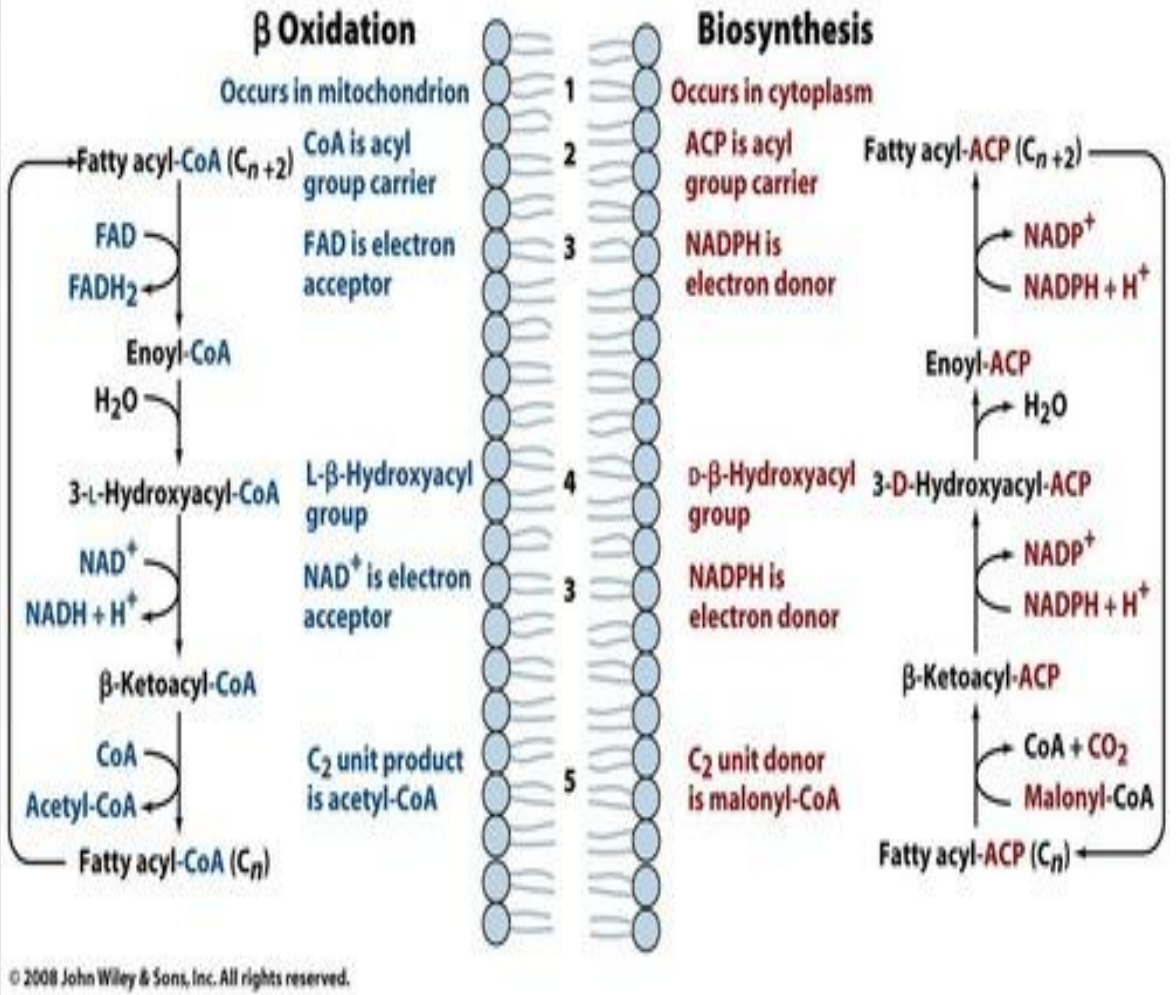
b. Hydration of the trans- Δ^2-enoyl CoA to 3-hydroxy acylCoA by enoylCoA hydratase.

c. Oxidation of 3-hydroxyacylCoA to 3-ketoacylCoA by NADH-dependendt dehydrogenase.

d. Thiolysis(cleavage)o f 3-ketoacylCoA to acetyl CoA by B-ketothiolase.

β-Oxidation of fatty acid





β-Oxidation of fatty acid

- **Oxidation of fatty acids produces large quantity of ATP:**

Oxidation of palmitate by β-oxidation produced 131 ATP as followings :-

1. **No. cycle =** $\frac{no.carbon\ atom}{2}$ **-1 = 16÷2=8-1=7 no.cycle**
2. **FADH2 provide 2 ATP so : 7x2 = 14 ATP**
3. **NADH provide 3 ATP so : 7x 3= 21 ATP**

- **4-Each acetyl- CoA provide 12 ATP so:**
- **No . of acetyl -CoA = no . of cycle +1**
- **= 7+ 1 =8 SO 8x12 = 96 ATP**
-
- **Total of ATP = 14 +21 +96 = 131 ATP**
- **-Because there is activation(consumption 2 ATP) in the first step of fatty acid oxidation, the final energy production is 131-2=129 ATP**

- * Red blood cell (RBC) con not oxidize fatty acids because they don't have mitochondria.
- * The brain it is a poorly oxidize fatty acids because of limited transport across the blood _brain barrier.
- * Fatty acid oxidation is increased in:
- 1-diabetes
- 2-starvation

Leading to ketone body production in liver (ketosis). ketone bodies are acidic and when it produced in excess over long periods as in diabetes , cause ketoacidosis .

The Fate of Glycerol and Fatty Acids •

Once a triglyceride is completely broken down, the free fatty acids • bind to serum albumin in the blood stream and carries the free fatty acids to the tissues that need energy. Glycerol is absorbed by the liver.

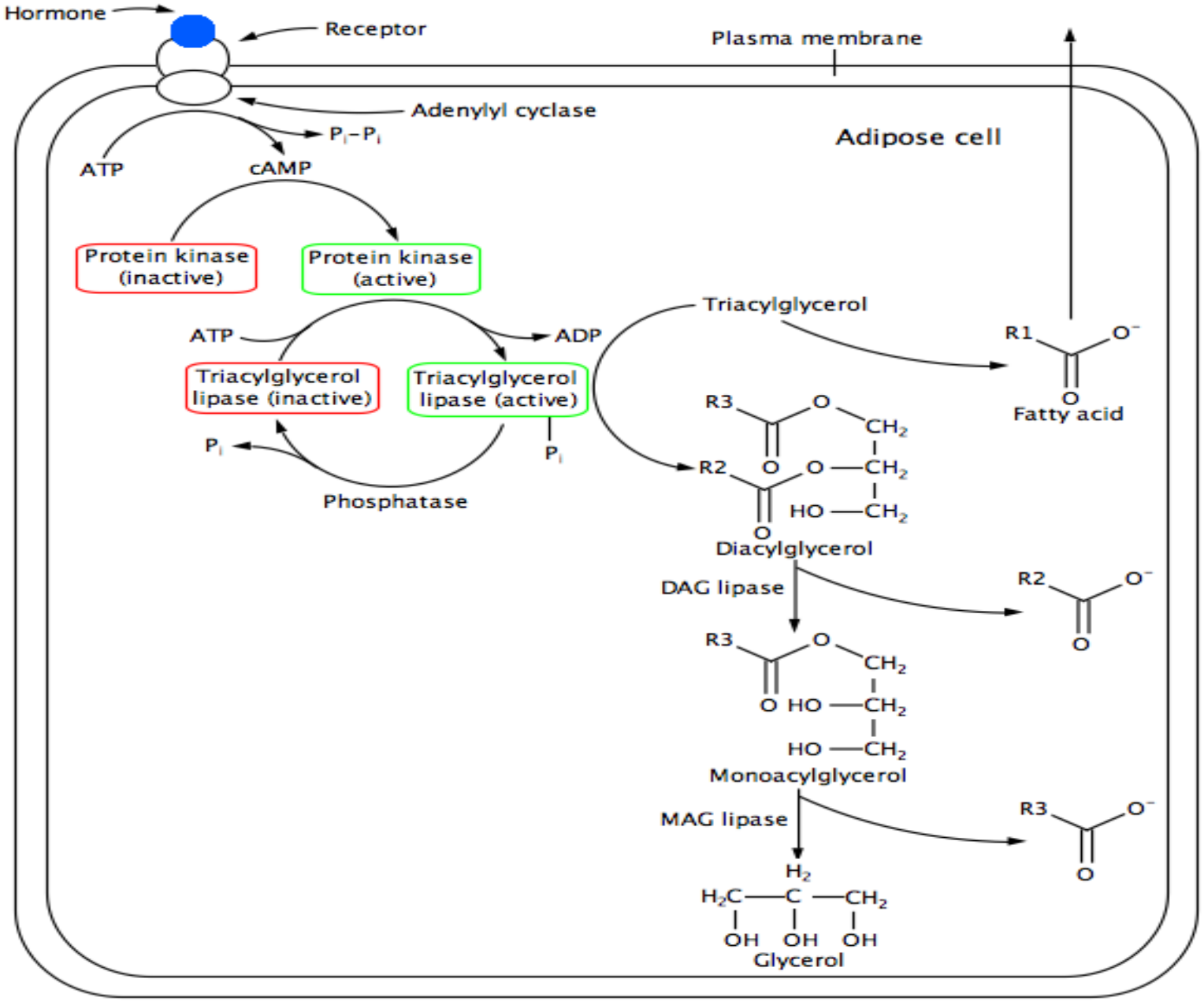
Now that we have glycerols and free fatty acids, what do we do with • them?

The glycerol represents 5% of the energy available from triglycerides. • In order to use the glycerol we need to activate it by phosphorylating it by glycerol kinase(GK),. Glycerol 3-phosphate is oxidized into Dihydroxyacetone phosphate (DHAP), which is then isomerized into Glyceraldehyde 3- phosphate (G3P). You should recognize G3P as an intermediate in the glycolytic and gluconeogenic pathways and can be converted into pyruvate or glucose.

Regulation of lipolysis

- Lipolysis is stimulated by the hormones epinephrin, glycagon, or adrenalcorticaltropic hormone (ACTH). These hormones bind to receptors on the plasma membrane of the cell and initiate a signal cascade. The first step of the signal cascade is the activation of adenylyl cyclase, which is the enzyme required to synthesize cyclic AMP from ATP. High levels of cyclic AMP activate protein kinase A. The protein kinase then uses ATP to activate the triaclyglycerol lipase. The phosphorylated lipase can then catalyze the hydrolysis of triglycerides to free fatty acids. Multiple lipases work to hydrolyze the fatty acids off of the glycerol.

Regulation of lipolysis



ketogenesis

What are ketone bodies? •

- Ketone bodies are acetoacetate, -hydroxybutyrate and acetone that are formed from acetyl CoA. •

- ketone bodies are water-soluble and do not require a carrier protein for transport. •

- They produce within the mitochondria of the liver ,when the amount of acetyl CoA formed exceeds the rate of entry into the TCA cycle during long fasting. •

- Under normal condition , only small amount of ketones are produced, from fatty acid oxidation. •

Outline the process of ketogenesis. •

Ketogenesis refers to the formation of ketone bodies. It occurs in the liver •

Steps: •

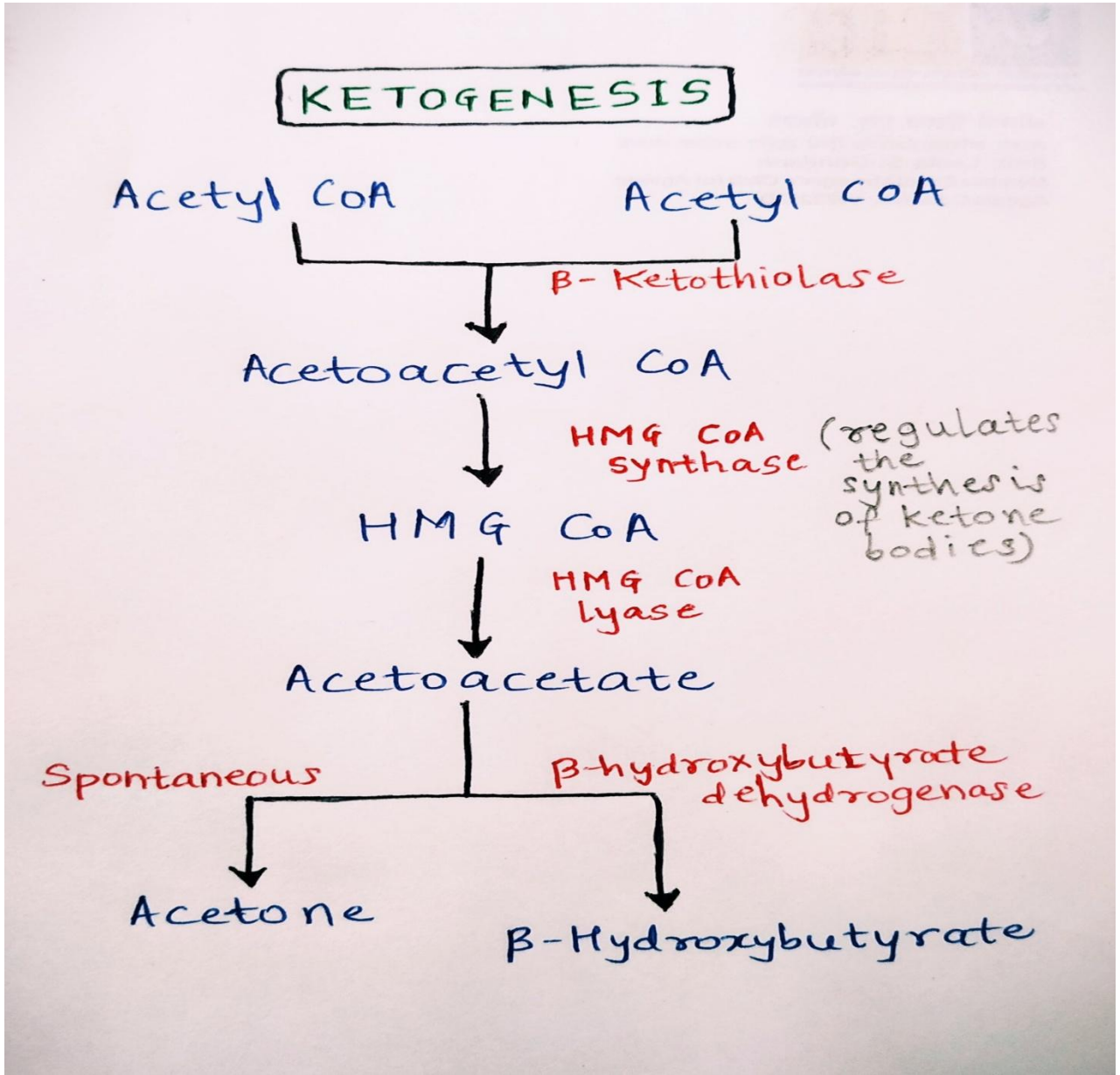
l. Condensation of two molecules of acetyl CoA to form acetoacetyl CoA •

2. Formation of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) by condensation of acetoacetyl •

CoA with another molecule of acetyl CoA •

3. Cleavage of HMG CoA to form A-3-hydroxybutyrate or decarboxylation to acetone. •

ketogenesis



Summary of ketone bodies synthesis, utilization and excretion