Chapter 9
Lipid Metabolism

Introduction

- Lipids are biological molecules which dissolve well in organic solvents but they are insoluble in water.

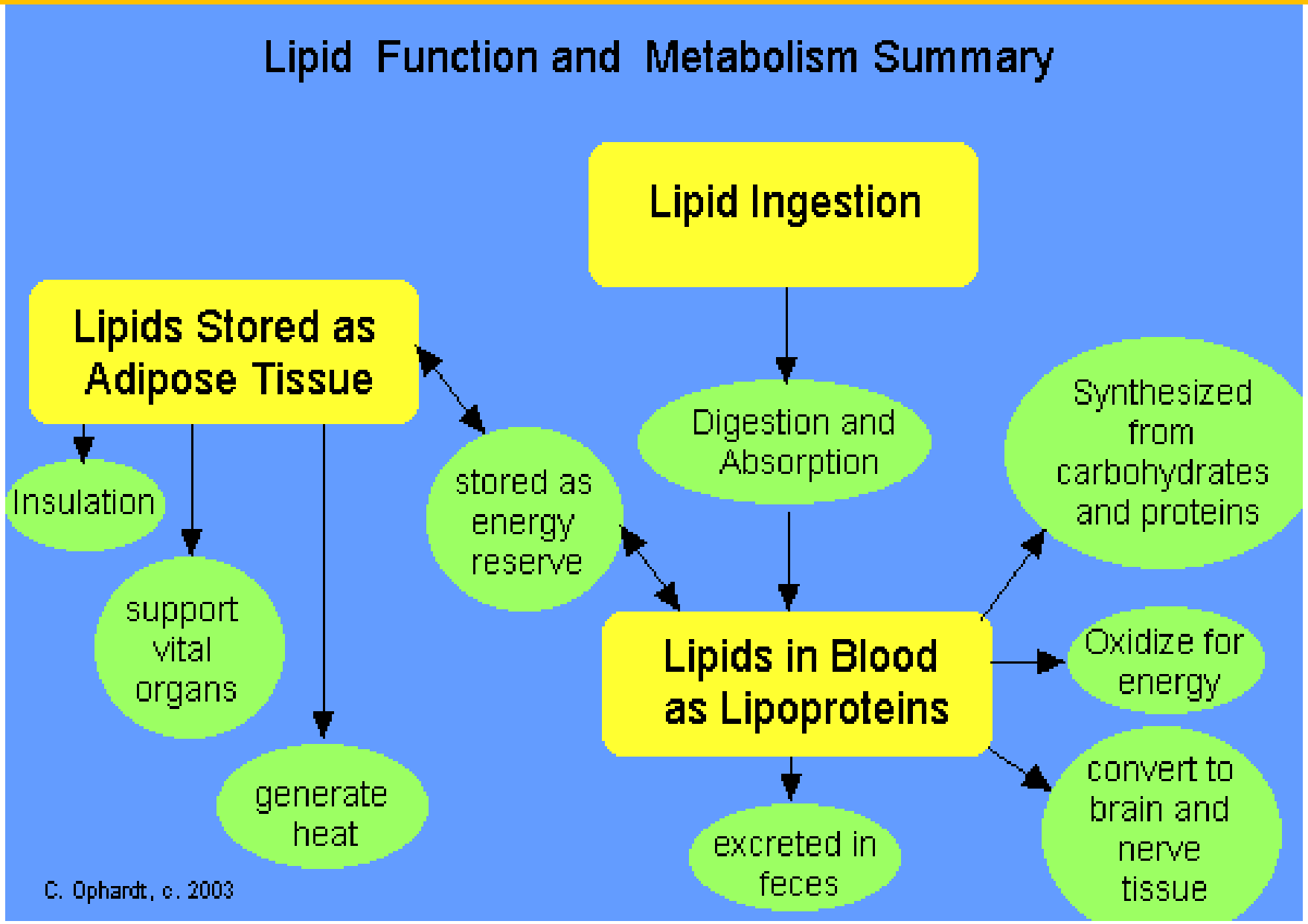
- Generally include
  - Triacylglycerols TAG (fats &)
  - Waxes
  - Glycerophospholipids
  - Sphingolipids
  - Isoprenoids: terpenoids, lipid vitamins, carotenoids
  - Steroids: sterols, bile acids, steroid hormones
  - Eicosanoids etc…

Introduction

Biological roles of lipids

- Source of energy/metabolic fuel
  - Triacylglycerides can provide 40% or more of daily energy requirements
  - Compared to carbohydrates, fats provide twice as much higher energy
    - About 9 kcal/g(for fats) Vs 4 kcal/g(for carbohydrates)
- Building blocks of cellular membranes (amphipathic lipids)
- Substrates for synthesis of other compounds (eicosanoids, bile acids)
- Thermal insulation

Introduction



Digestion, Mobilization and Transport of Lipids

- Digestion of lipids are enhanced if they are converted into finely dispersed microscopic state called emulsion/micelles.
  - By process called **emulsification**

- Emulsification is carried in the small intestine
  - Aided by detergent property of **bile salt** and **peristalsis**

- Emulsification **increase surface area** for lipase activity (digestion)

Digestion, Mobilization and Transport of Lipids

❖ Digestion of various types of lipids give different products

Triacyglycerol hydrolysis (TAG)

➢ Are degraded by **pancreatic lipase** to give FA's attached to C-1 and C-3 as well as a 2-monoacylglycerol

Cholesteryl ester

➢ Are degraded by **cholesterol esterase** producing cholesterol and FA

Phospholipids

➢ Are degraded by **Phospholipase A_2** producting lysophospholipid and FA

❖ The FFA, free cholesterol, 2-monoacylglycerol , lysophospholipid and bile salts form **mixed micelles**

Digestion, Mobilization and Transport of Lipids

Absorption of Lipids by intestinal mucosal cells

- FFA, free cholesterol, 2-monoacylglycerol, lysophospholipid together with bile salts are absorbed at the brush border membrane of SI
  - Short and medium chain FA are directly absorbed

Resynthesis of TAG, CE and PL

- Different lipids in intestinal mucosa are resynthesized again

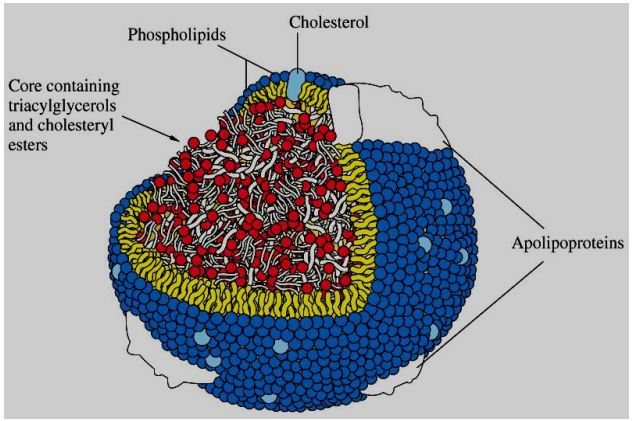
2-monoacylglycerol + fatty acyl-CoA $\xrightarrow{\curvearrowright}$ TAG

Cholesterol + FA $\longrightarrow$ CE

Lysophospholipid + FA $\longrightarrow$ Phospholipid

Digestion, Mobilization and Transport of Lipids

- In intestinal mucosa the **different lipids** (FFA,dietary cholesterol, phospholipids) are packaged with **specific proteins** forming lipoprotein aggregates
  - Called **chylomicrons**



- Chylomicrons are spherical aggregates with
  - Hydrophobic lipids at the core
  - Hydrophilic protein side chains and
  - Lipid head groups at the surface
- Chylomicrons move into the lymphatic system
  - Then enter the blood to deliver dietary fats to tissues (muscle and adipose tissue)
    - **In the capillaries**- the extracellular enzyme **lipoprotein lipase,** hydrolyzes TAG to fatty acids and glycerol, which are taken up by cells in the target tissues
    - **In muscle-** fatty acids are oxidized for energy
    - **In adipose tissue**- they are re-esterified for storage as triacylglycerols

Digestion, Mobilization and Transport of Lipids

- Various combinations of lipid and protein produce particles of different densities (lipoproteins)

- Following high fatty acids diet consumption liver converts them to triacylglycerols and package them with specific apolipoproteins into **very low-density lipoproteins (VLDLs)**

- VLDLs are transported in the blood where hydrolytic enzymes convert them into :-
  - Triacylglycerols - stored in lipid droplets within adipocytes
  - **VLDL remnants** (also called **intermediate-density lipoprotein, IDL**)

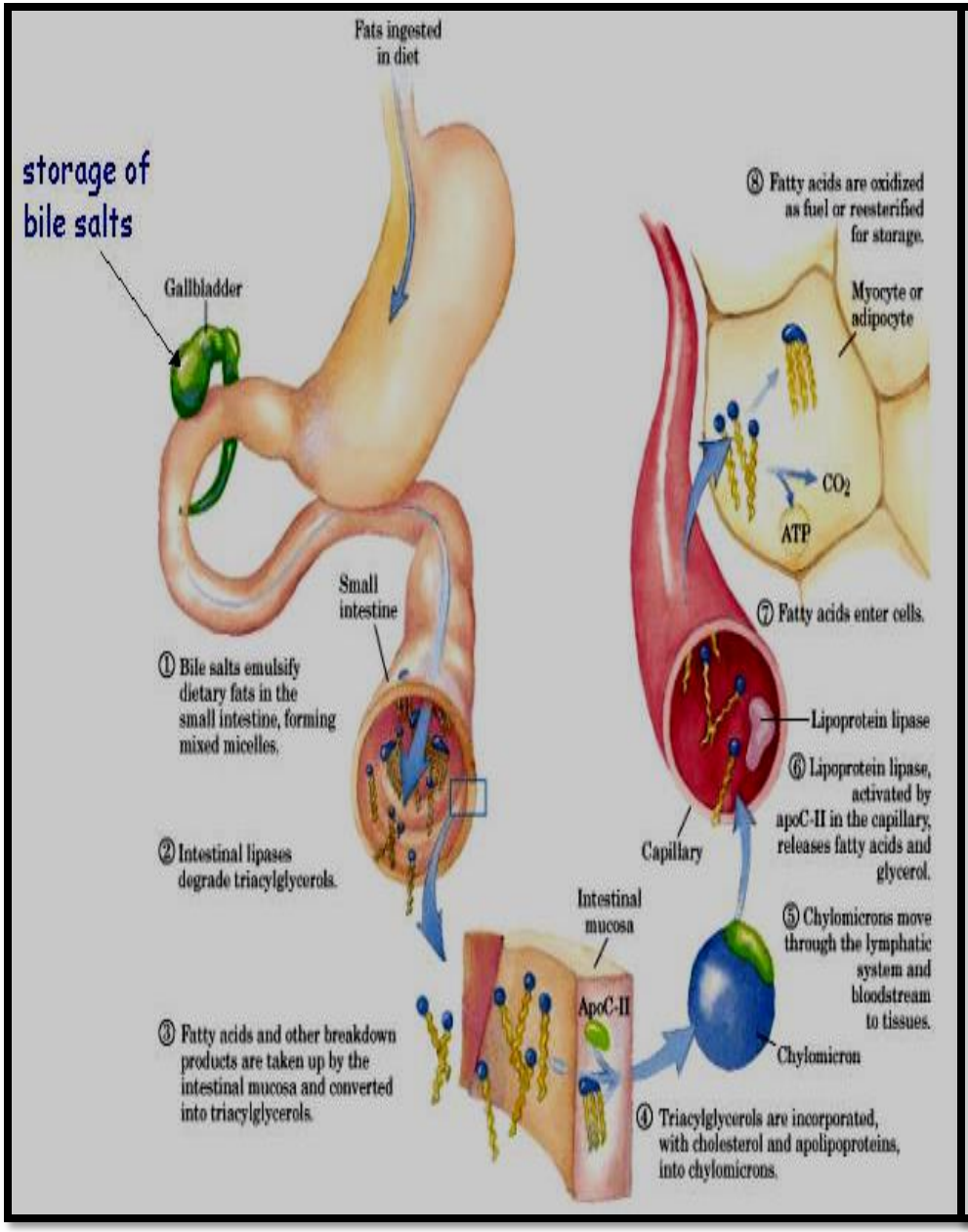
- Removal of TAG fro**m VLDL remnants** give **low-density lipoprotein (LDL)**

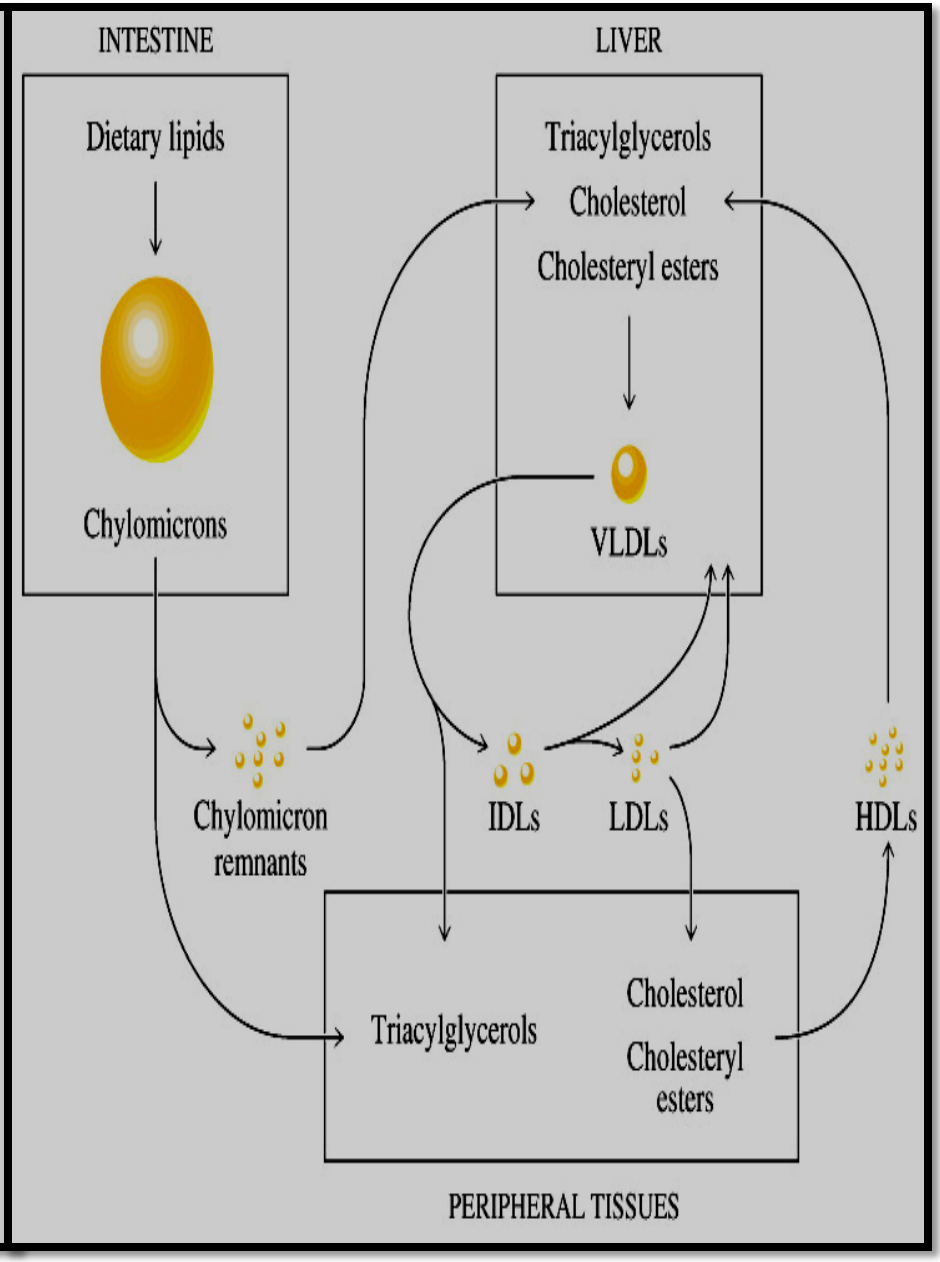
- The **high-density lipoprotein (HDL)** originates in the liver and small intestine as small, protein-rich particles that contain relatively low cholesterol

Note

- Lipoproteins are responsible for transport of lipids b/n organs
- Which can be separated by ultracentrifugation

Digestion, Mobilization and Transport of Lipids





Catabolism of FFA's

- Occur in several tissues, including liver, muscle, and adipose tissue as sources of energy (in mitochondria)

- The process of FA oxidation is called **β-oxidation**
  - Although less common pathways (α & ω oxidation) exist

- β-oxidation reverses the process of fatty acid synthesis (will be discussed later)

Note

- Beta-Oxidation do not occur in erythrocytes and brain (even during fasting they rely on glucose)

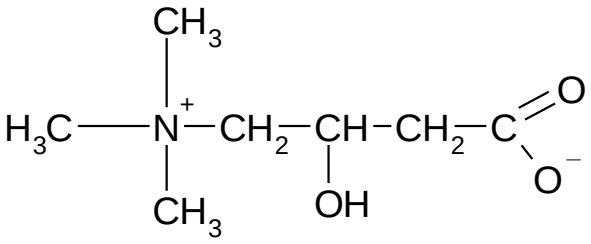
Catabolism of FFA's

- Catabolism of FFA's require prior activation and transport of FFA's (long chain) into mitochondria

- Fatty acids are transported across outer membrane after being acetylated ,driven by Acyl CoA Synthetase

$$FA + CoASH + ATP \rightarrow FA\text{-}SCoA + AMP + Ppi$$

- Transport through inner mitochondrial membrane is possible via carnitine (a □-amino acid)
  - uses specific acyl carnitine transporter



Carnitine

Catabolism of FFA's

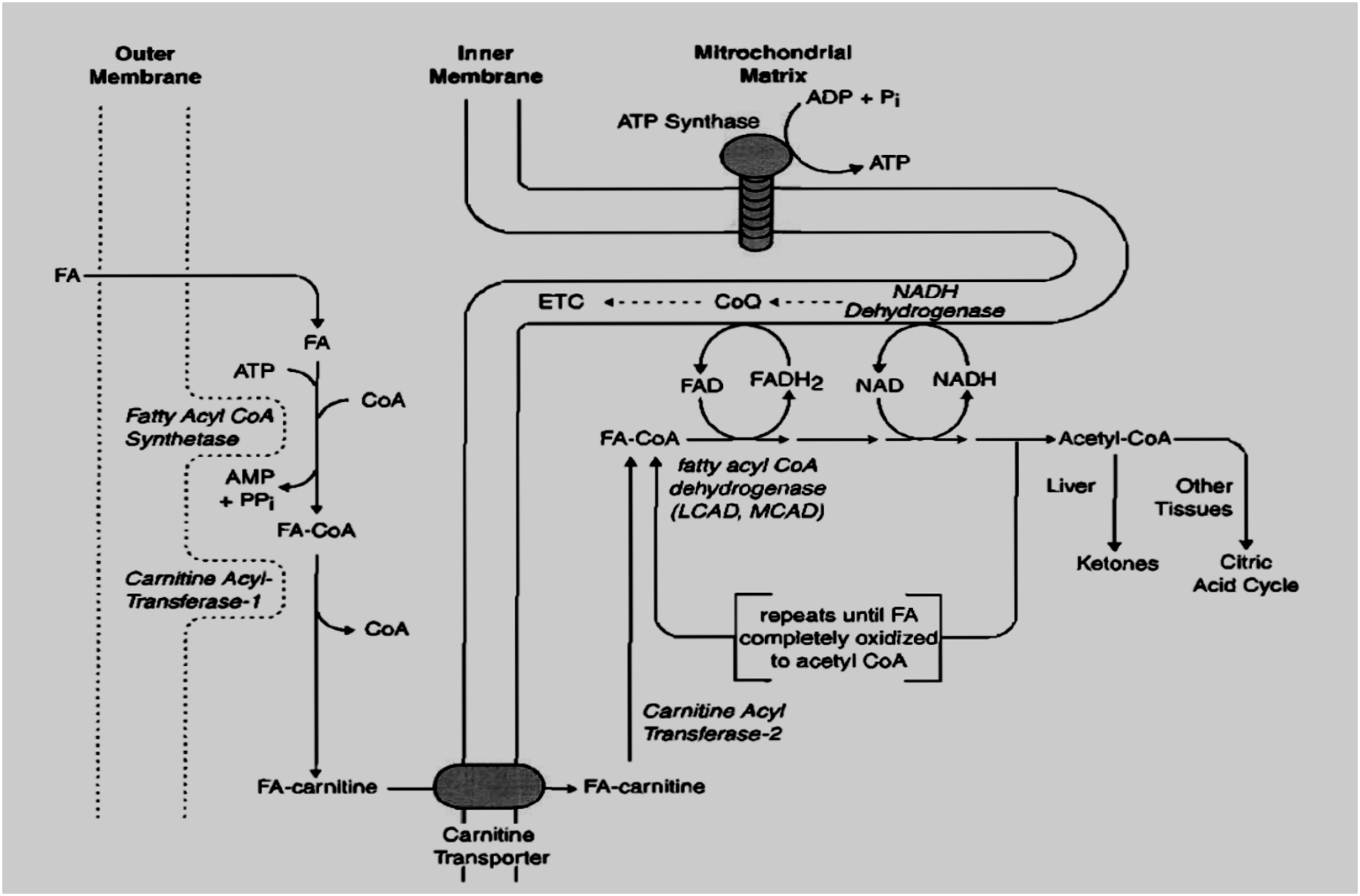


Fig: Fatty acid activation, transport and β-oxidation

Catabolism of FFA's

Beta-Oxidation

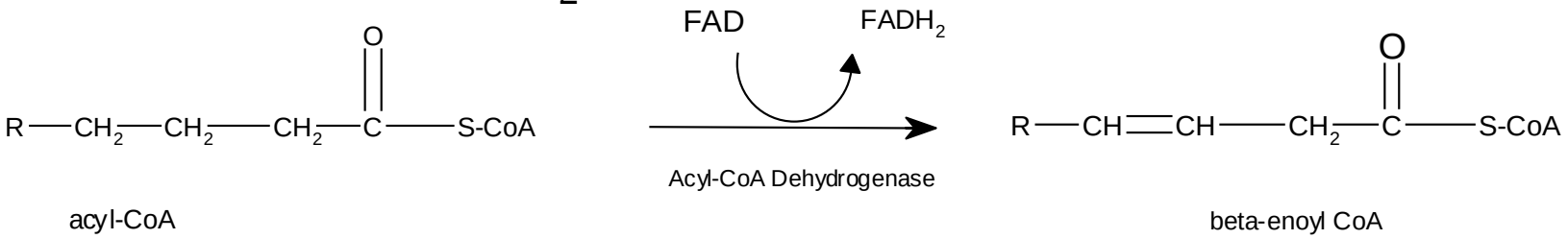
- Breakdown of FFA's into
  - Acetyl coenzyme A :– to join Kreb's Cycle
  - $FADH_2$ & NADH:- to join Oxidative Phosphorylation
- Involve removal of two carbon fragments successively from the carboxyl end of the fatty acylCoA
  - Producing acetylCoA
- The remaining fatty acid goes another round
- Consists of four reactions: shortening of FA by 2 carbons
  - Oxidation: produces $FADH_2$
  - Hydration: produces NADH
  - Thiolytic cleavage: produces 2 acetylCoA

Catabolism of FFA's

Steps in Beta-Oxidation

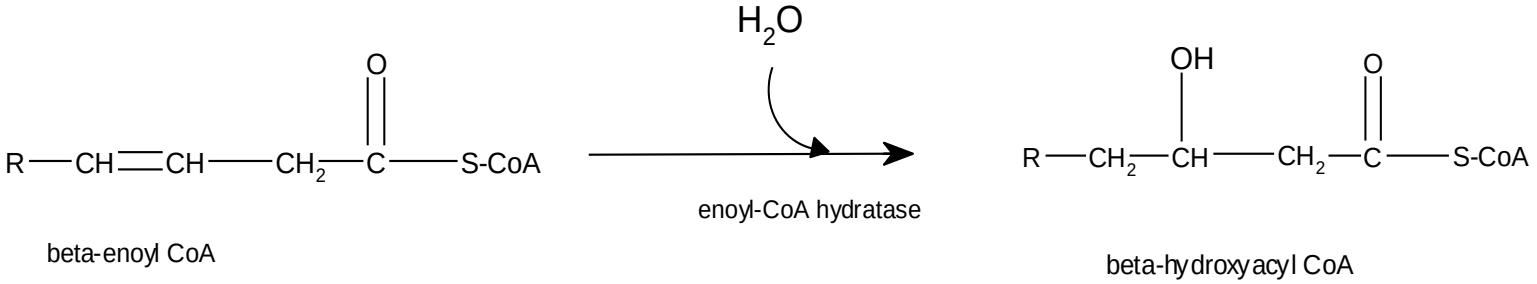
Step 1

- Catalysed by acyl-CoA Dehydrogenase
- Puts in a ß double bond (Oxidizes C-C bond to double bond)
- Produces $FADH_2$



Step 2

- Catalysed by enoyl CoA Hydratase
- Adds water to form ß-hydroxy product

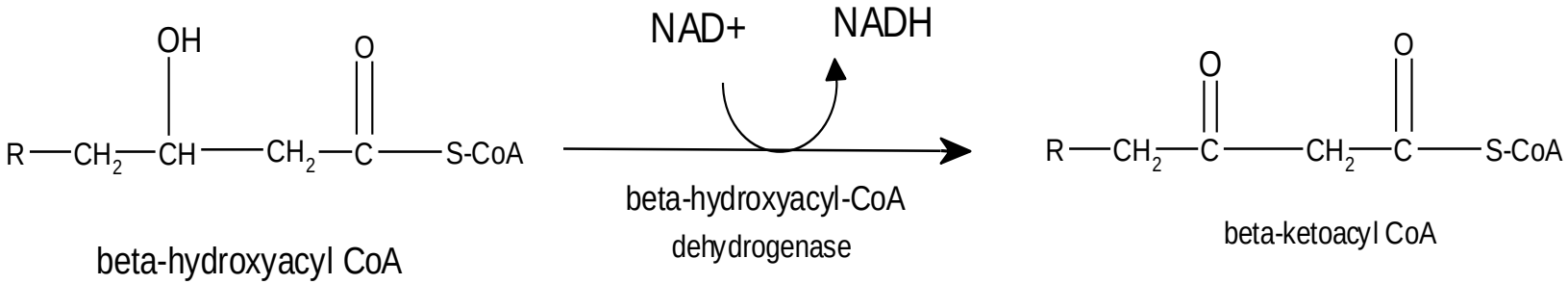


Catabolism of FFA's

Steps in Beta-Oxidation

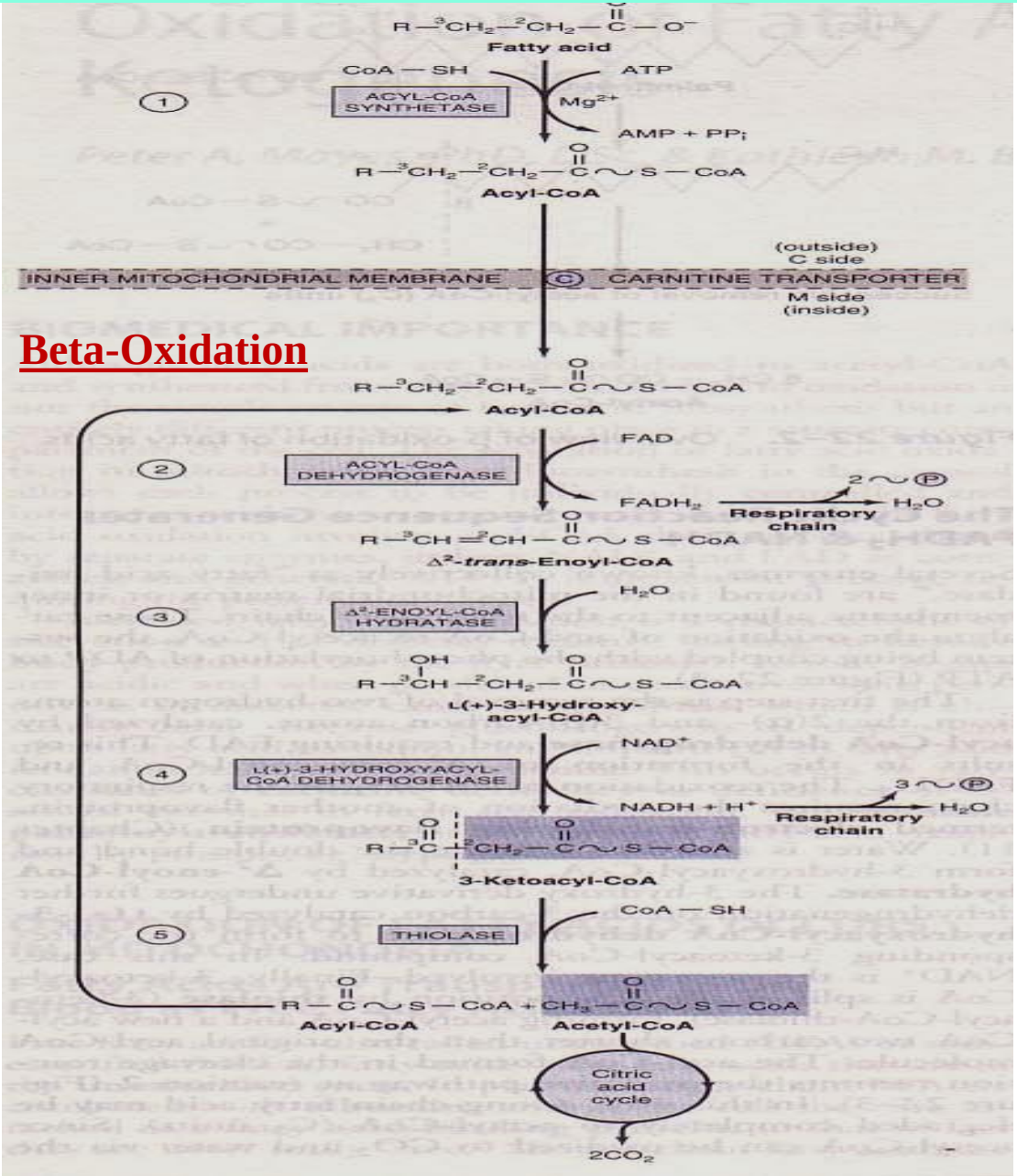
Step 3

- Catalysed by ß-hydroxylacyl-CoA dehydrogenase
- Oxidizes secondary alcohol to ketone
  - Oxygen-containing group
  - Produces NADH



Note:- Metabolism of unsaturated fat require special enzymes to convert cis bonds in fatty acids to trans bonds

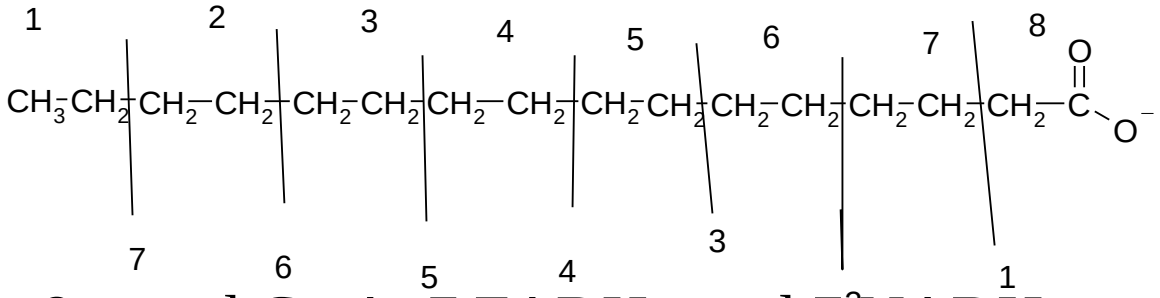
Catabolism of FFA's



Catabolism of FFA's

Beta Oxidation on 16 C fatty Acid

- 7 rounds of Beta oxidation (bottom numbers)



- Form 8 acetyl Co A, 7 $FADH_2$ and 7 NADH

- Energy yields from ß-Oxidation of palmitoylCoA

	ATP Yield
7NADH x 3 ATP by ETC oxidation	21
7 $FADH_2$ x 2 ATP by ETC oxidation	14
8 Acetyl CoA x 12 ATP via Krebs CAC	96
Total (Gross)	131 ATP
Less	2 ATP
NET	129 ATP

Regulation of Fat Metabolism

Regulation of beta oxidation

- Transport is rate-limiting
- Regulation of carnitine acyl transferase
  - off by fat synth products
  - high NADH

Formation of ketone bodies:-Ketogenesis

- Starvation and diabetics cause break down of fat for energy
  - Which leads to accumulation of acetyl CoA
    - not enough carbohydrates to keep Kreb's Cycle going

- High acetyl CoA leads to formation of **ketone bodies**
  - Viz. acetoacetate, ß-hydroxybutyrate & acetone

NB:-Acetone is a spontaneous breakdown product of acetoacetate (decarboxylation), or is formed by enzymatic cleavage of acetoacetate by the enzyme **acetoacetate decarboxylase**

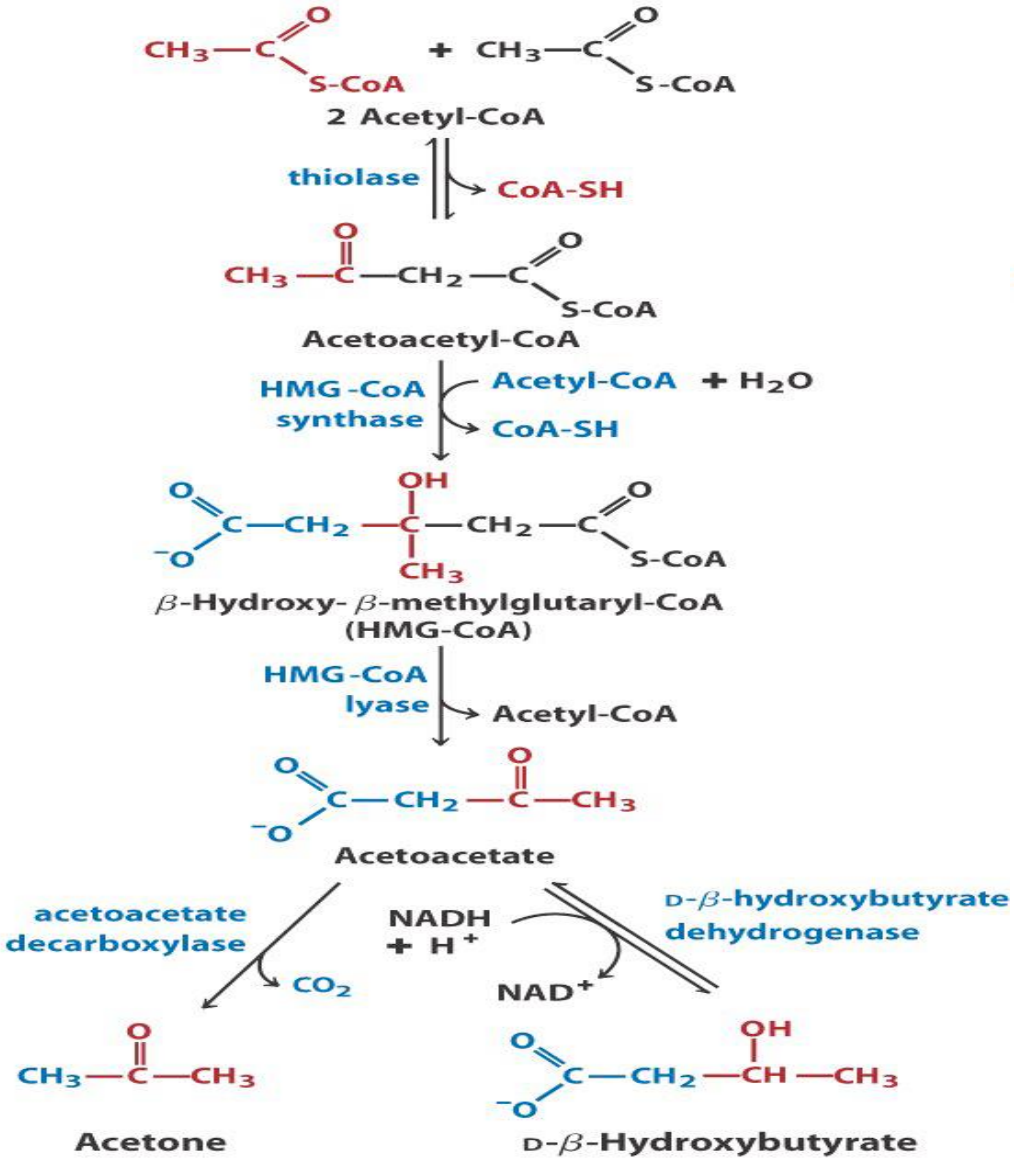
- Ketone bodies are special source of energy
  - For certain tissues (brain, heart, kidney and muscle)
    - ✓ Particularly during starvation

Formation of ketone bodies:-Ketogenesis

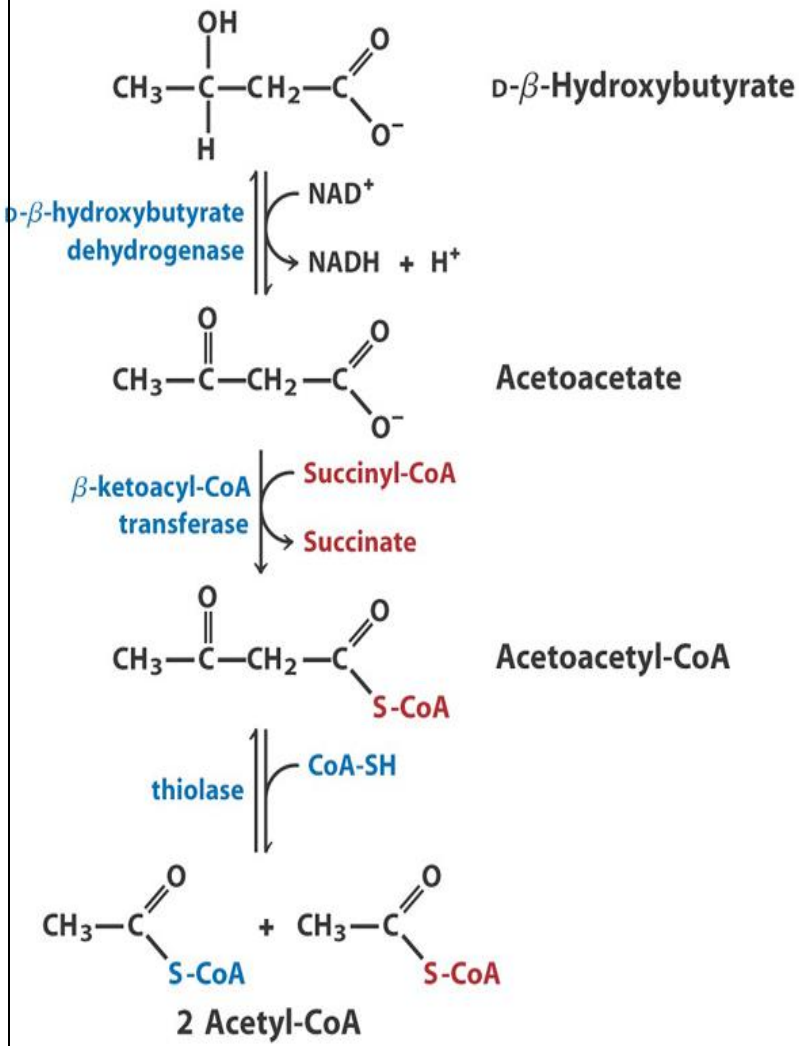
In diabetic patients

- Ketones build up in the blood and then spill over into the urine so that the body can get rid of them.
- Acetone can be exhaled through the lungs.
  - ✓ This gives the breath a fruity odor.
- Ketones that build up in the body for a long time lead to serious illness and coma.
  - ✓ Diabetic ketoacidosis

Formation of ketone bodies:-Ketogenesis



Formation of Ketone bodies



Utilization of ketone bodies

Biosynthesis of fatty acid

- In mammals fatty acid synthesis occurs in
  - Liver and adipose tissues (primarily)
  - Mammary glands during lactation

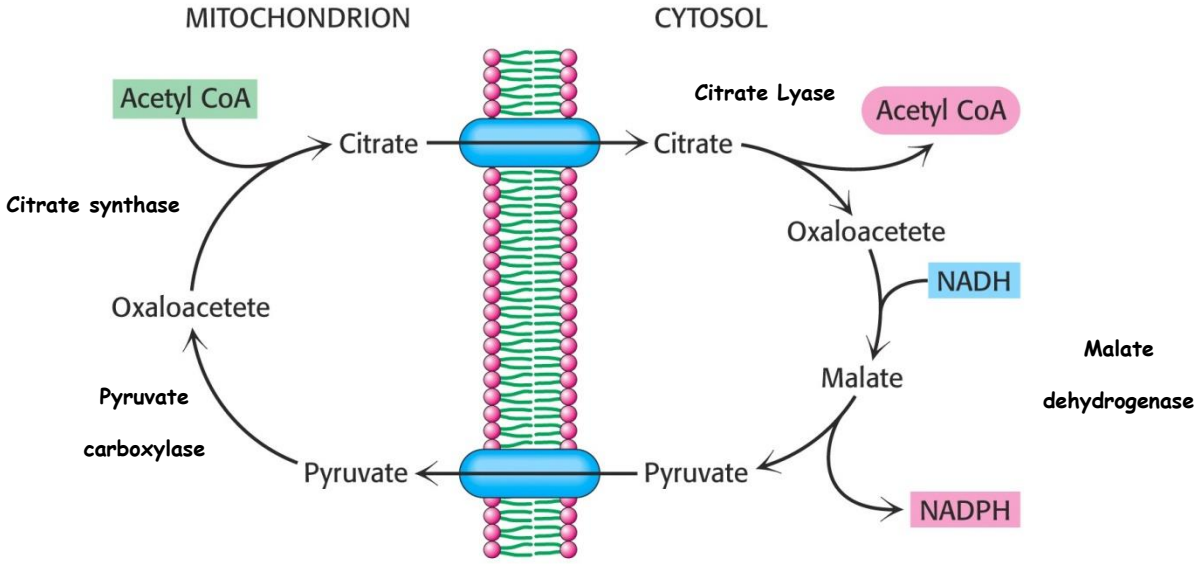
- Synthesis occurs in the cytosol (Where acetyl-CoA is deficient)
  - ✓ From acetyl CoA units

Biosynthesis of fatty acid

Synthesis short chain fatty Acid (palmitic acid)

Step 1:- Translocation of mitochondrial acetate in to cytosol

- Acetyl-CoA is deficient in cytosol
- Hence supplied by from mitochondria through **Citrate-malate-pyruvate** shuttle



Biosynthesis of fatty acid

Synthesis short chain fatty Acid (palmitic acid)

Step 2 :- Activation of acetyl CoA

- By carboxylation of acetyl CoA to malonyl CoA by acetylCoA carboxylase (ACC'se)

- Is a rate limiting step in fatty acid synthesis
- ACC'se can be regulated
  - ✓ Activators: insulin,Inc. CHO intake, fat-free diet
  - ✓ Inhibitors: malonyl CoA, palmitoyl CoA,epinephrine,fasting, high fat diet

Biosynthesis of fatty acid

Synthesis short chain fatty Acid (palmitic acid)

Step 3 :- fatty acid synthesis

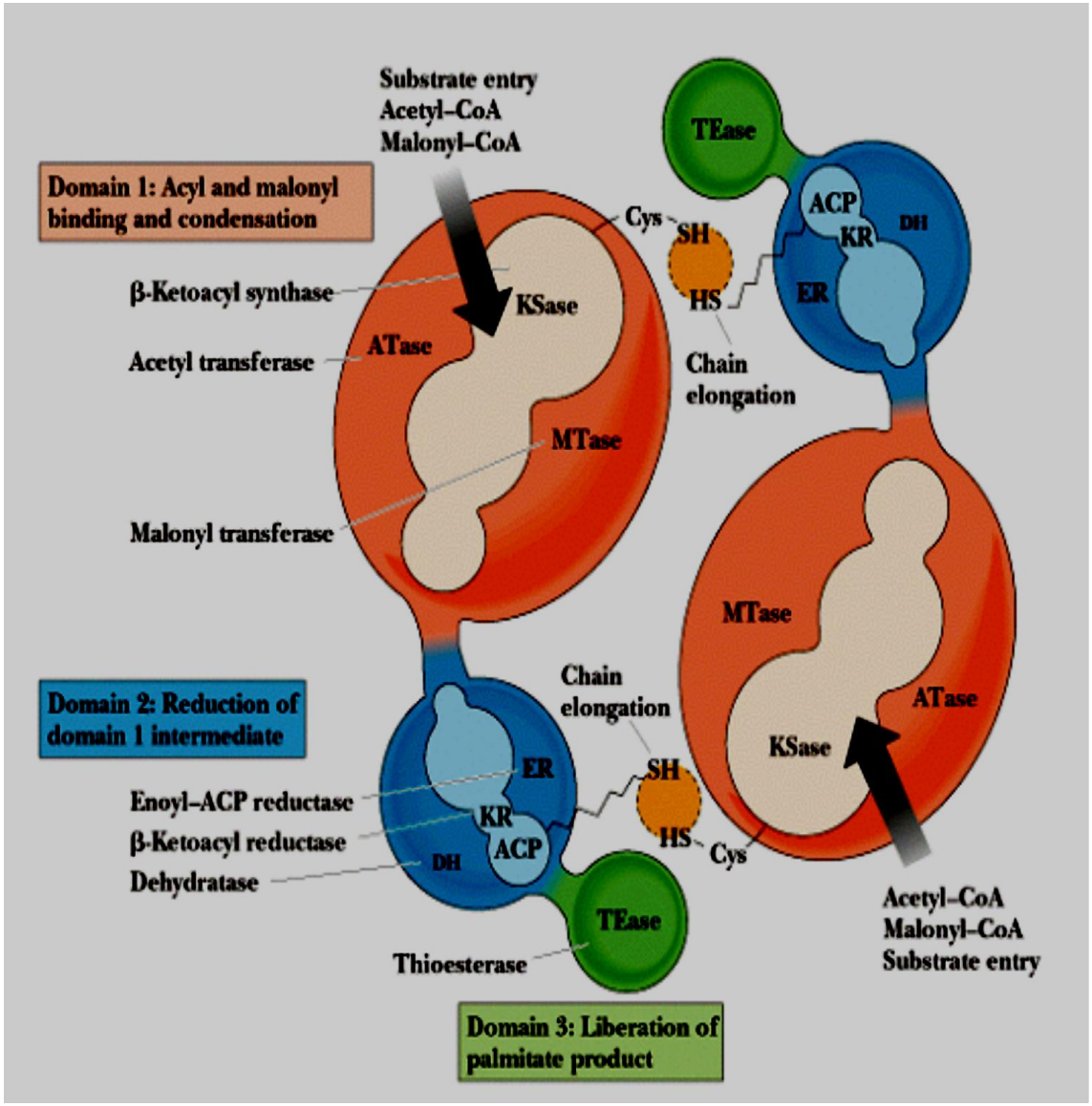
- By **a Fatty acid synthase-a homodimerenzyme composed of**
  - ✓ **seven catalytic centres arranged around a central acyl carrier protein (ACP) bound pantetheine chain**
  - ✓ The catalytic cycle involve the following enzymes
    - ✓ ketoacylACP synthase (KS)
    - ✓ ketoacyl ACP reductase (KR)
    - ✓ **AcetylCoA-ACP transacylase**
    - ✓ **MalonylCoA-ACP transacylase**
    - ✓ **ß-ketoacyl-ACO synthase**
    - ✓ **Palmitoyl thioesterase**

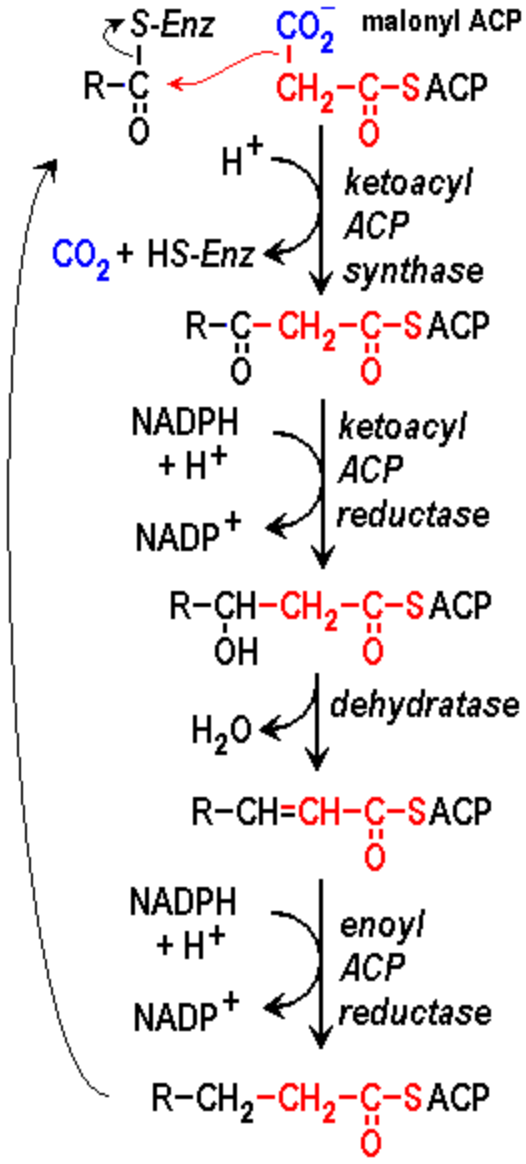
Overall reaction

Acetyl-CoA + 7 malonyl-CoA + 14 NADPH + 14 H+ ⟶ palmitate + 7 CO2 + 8 HSCoA + 14 NADP+ + 6 H2O

Biosynthesis of fatty acid

Synthesis short chain fatty Acid (palmitic acid)





Biosynthesis of fatty acid

Synthesis long chain fatty Acid

- **Precursor(s)**:- Palmitic acid
- **Site**:- Mitochondria and EPR (microsomal membranes)
- **Mechanism**:-
  - ✓ First acyl-CoA /malonyl-CoA conjugate is formed
  - ✓ Results in product with **two carbons longer**
  - ✓ Which undergoes reduction, dehydration and reduction yielding longer saturated FA's

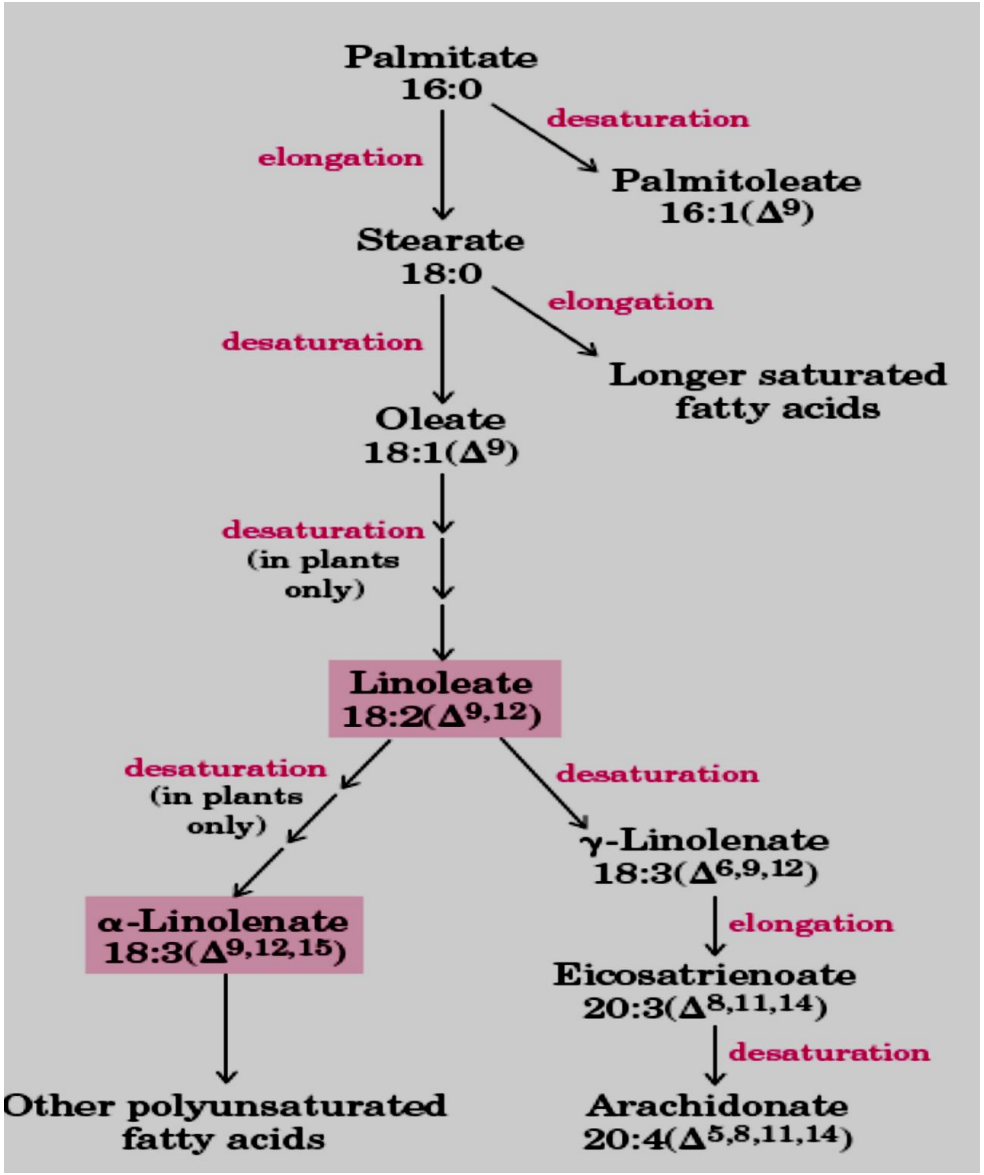
Biosynthesis of fatty acid

Synthesis long chain unsaturated fatty Acid

Desaturation of fatty acid side chain

- Occurs in the ER membranes of mammalian cells
- Involves four broad specificity fatty ***acyl-CoA desaturases***
- Enzymes introduce unsaturation at C_4, C_5, C_6 or C_9
  - ✓but not beyond C_9

Biosynthesis of fatty acid



Biosynthesis of Eicosanoids

- **Physiological role**:- mediators of local cellular changes (local hormones) e.g cell damage
- **Triggers(s)**:- Arachidonic acid is released response to in numerous stimuli (e.g. epinephrine, thrombin and bradykinin)
- **Precursor(s)**:- C-20 unsaturated membrane fatty acids (arachidonic acid, 20:4 ($\Delta^{5,8,11,14}$))
- **Site**:- Cell interior (cytoplasm of all cells)
- **Mechanism** :-Two main pathways are involved

i) The ***cyclo-oxygenase pathway*** (cyclic pathway*):*-For ***PG*** and ***TX*** synthesis

➢Catalyzed by prostaglandin G/H synthase (PGS)

- **COX-1**:- In gastric mucosa, kidney, platelets, and vascular endothelial cells **(constitutive)**
- **COX-2**:- In macrophages and monocytes in response to inflammation **(Inducible)**

ii) The ***lipoxygenase pathway*** (linear pathway):-For ***LT*** synthesis

➢ Catalyzed by 5-lipoxygenase (5-LOX) enzyme

Biosynthesis of Eicosanoids