MEDICINAL BIOCHEMISTRY 818803

Lipid Metabolism

Prepared by

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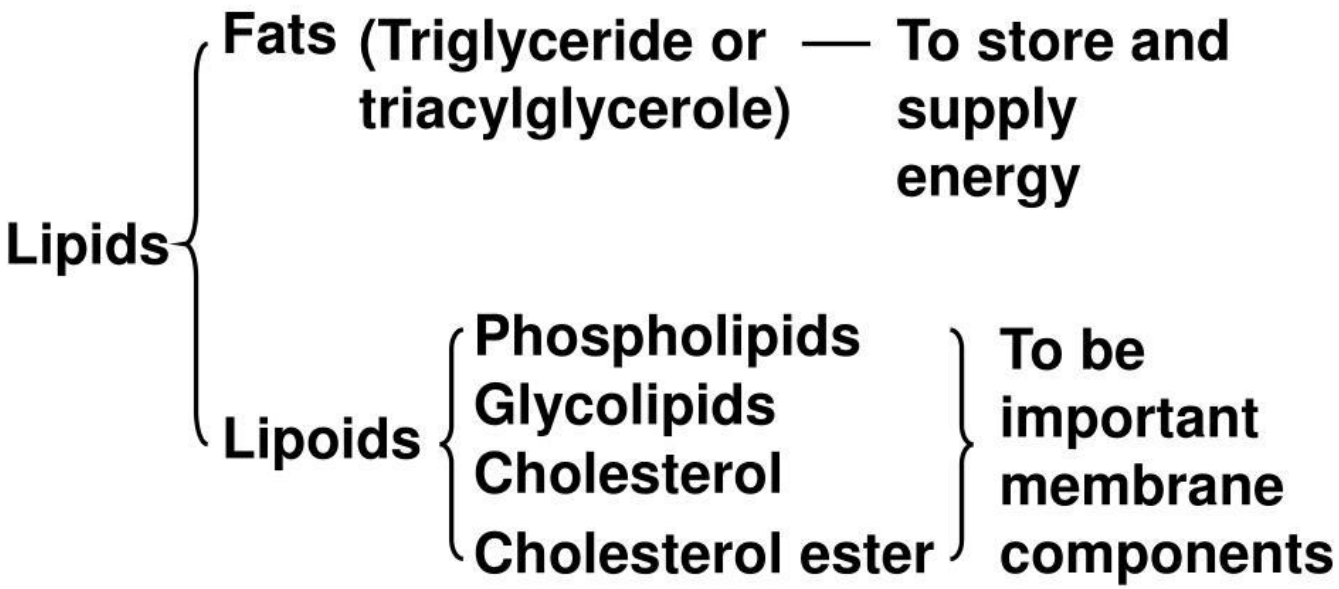
M. Pharm


Lipids
Fats
(Triglyceride or triacylglycerole)
To store and supply energy
Lipoids
Phospholipids
Glycolipids
Cholesterol
Cholesterol ester
To be important membrane components

Lipid Metabolism

Introduction

- Lipids is insoluble in polar solvent and have good solubility in non-polar solvent
- Lipids has hydrocarbon chain and ester group
- Lipids classified as simple and complex lipids
- Lipid composed by ester of fatty acid

Lipid Metabolism

Introduction

- The main function of lipids :
  - Energy storage
  - Structural components of cell membranes
  - As important signalling molecules
- Oxidation of lipids are produced more energy than the oxidation of carbohydrates
- Humans have fat tissue under the skin, in the abdominal cavity, and in the mammary gland

Overview of Lipid Metabolism

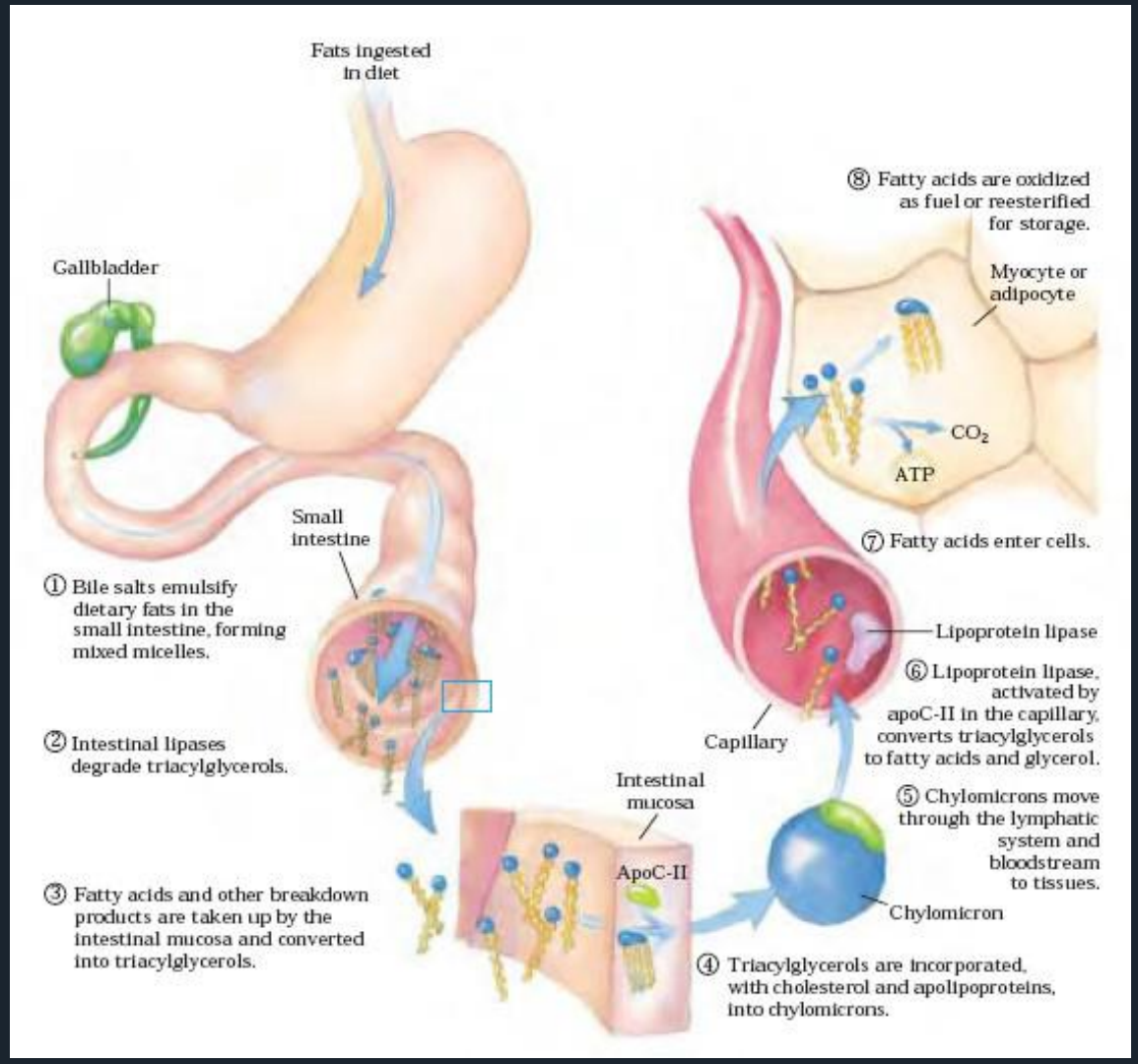
01

Lipid Digestion

02

Lipid Catabolism

01 Lipid Digestion



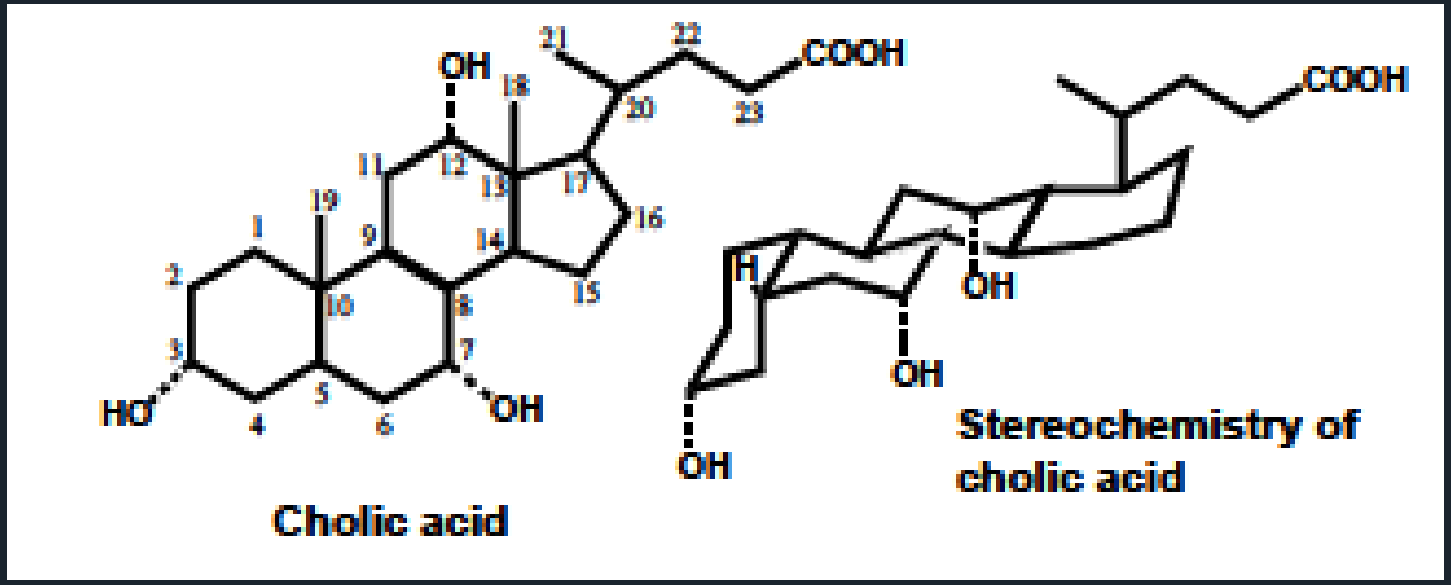
Digestion of Lipids

Emulsification of Fats

Fatty acids can be liberated by simple hydrolysis of the ester bonds in triglycerides, but the **insolubility of the triglycerides presents a problem**; digestion occurs following dispersion of dietary fat into small particles with sufficiently exposed surface area for rapid attack by digestive enzymes. This is achieved by detergent action and mechanical mixing, with the **detergent effect** being supplied by several components, both in the diet and in the digestive juices, but especially by partially digested fats (fatty acid soaps and monacylglycerols) and by **bile salts**.

Digestion of Lipids

Emulsification of Fats



Digestion of Lipids

Emulsification of Fats

The bile salts such as cholic acid contain a hydrophobic side and a hydrophilic side, this allowing bile salts to dissolve at an oil-water interface, with the hydrophobic surface in contact with the nonpolar phase and the hydrophilic surface in the aqueous medium. This detergent action **emulsifies fats and yields mixed micelles, which allow attack by water-soluble digestive enzymes** and facilitate the absorption of lipids through the intestinal mucosa. **Mixed Micelles also serve as transport vehicles for those lipids that are less water-soluble than fatty acids, such as cholesterol or the fat-soluble vitamins A, D, E, and K.** Thus, efficient absorption of lipids depends on the presence of sufficient bile acids to solubilize the ingested lipids.

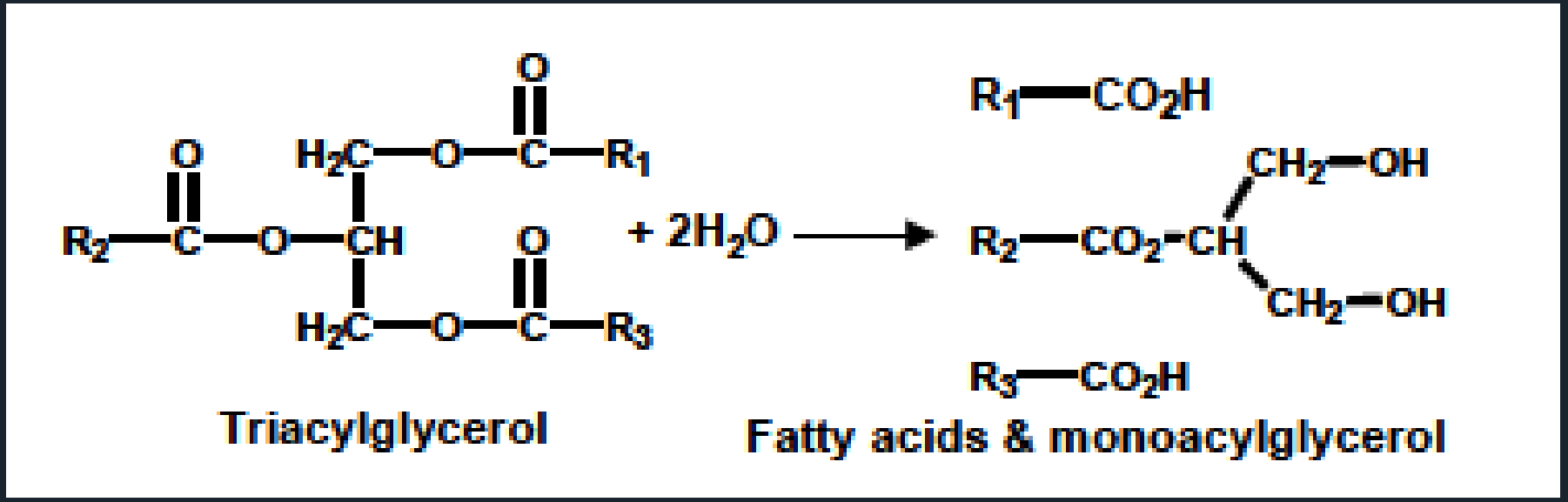
Digestion of Lipids

Digestion of Fats

The emulsification of fats render them susceptible to hydrolysis by enzymes secreted by the pancreas. The most important enzyme involved is **pancreatic lipase**. *Pancreatic lipase is virtually specific for the hydrolysis of primary ester linkages, the 1 or the 3 ester bonds, but not the bond in the central 2 position (see below). As a result of this conversion, 2-monoglycerides (2-monoacylglycerols) are major end-products of triglyceride digestion.* Less than 10% of triglycerides remain unhydrolyzed in the intestine.

Digestion of Lipids

Digestion of Fats



Digestion of Lipids

Control of Fat Digestion

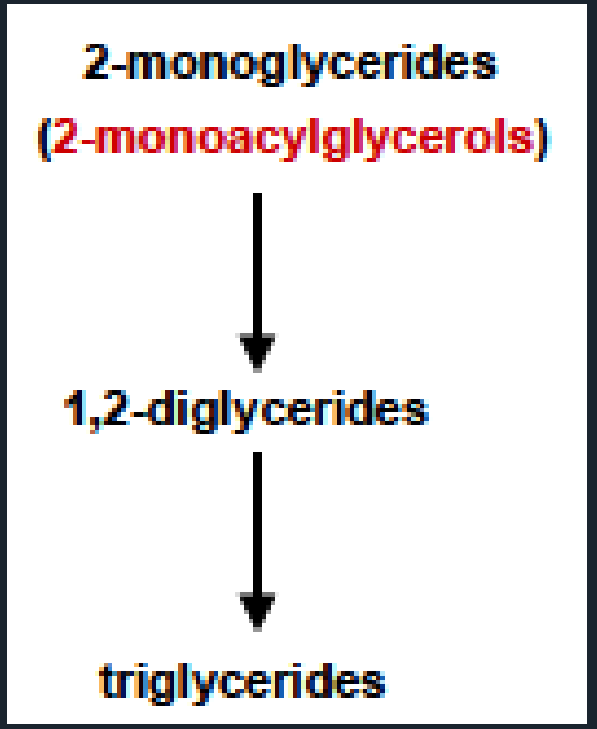
Initial products of digestion (e.g., free fatty acids) stimulates release by the duodenum of the 33 amino acid peptide hormone **pancreozymin-cholecystokinin (PCCK).** The **cholecystokinin** (CCK) activity induces **emptying of the gallbladder**, thuleading to **increased concentration of bile salts** and other bile constituents in the intestine, including cholesterol and phospholipids. The **pancreozymin** (PZ) activitcauses **release of pancreatic digestive enzymes, including pancreatic lipase.**

Absorption of Lipids

Short-chain fatty acids (up to 12 carbons) are absorbed directly through the villi of the intestinal mucosa. They enter the blood via capillaries thaeventually **empty into the portal vein and are transported** via lipid carrier proteins directly to the liver, where they are used for energy production. **2-Monoglycerides, long-chain fatty acids (more than 12 carbons), cholesterol and lysophospholipidsabsorbed from the lumen by intestinal mucosal cells, where they are incorporated into lipoproteins and directed to the lymphatic system.**

Absorption of Lipids

Within the intestinal wall, the triglyceride are resynthesized by the 2-monoacylglycerol pathway as shown on the right. The 2-monoacylglycerol pathway is unique for the intestine. Triglycerides, having been synthesized in the intestinal mucosa, aren't transported to any extent in the portal venous blood. Instead, **the great majority of absorbed lipids, including triglycerides, phospholipids, cholesterol esters, and cholesterol, appear in the form of chylomicrons that pass to the lymphatic vessels of the abdominal region and later to the systemic blood** (Lipoprotein metabolism)

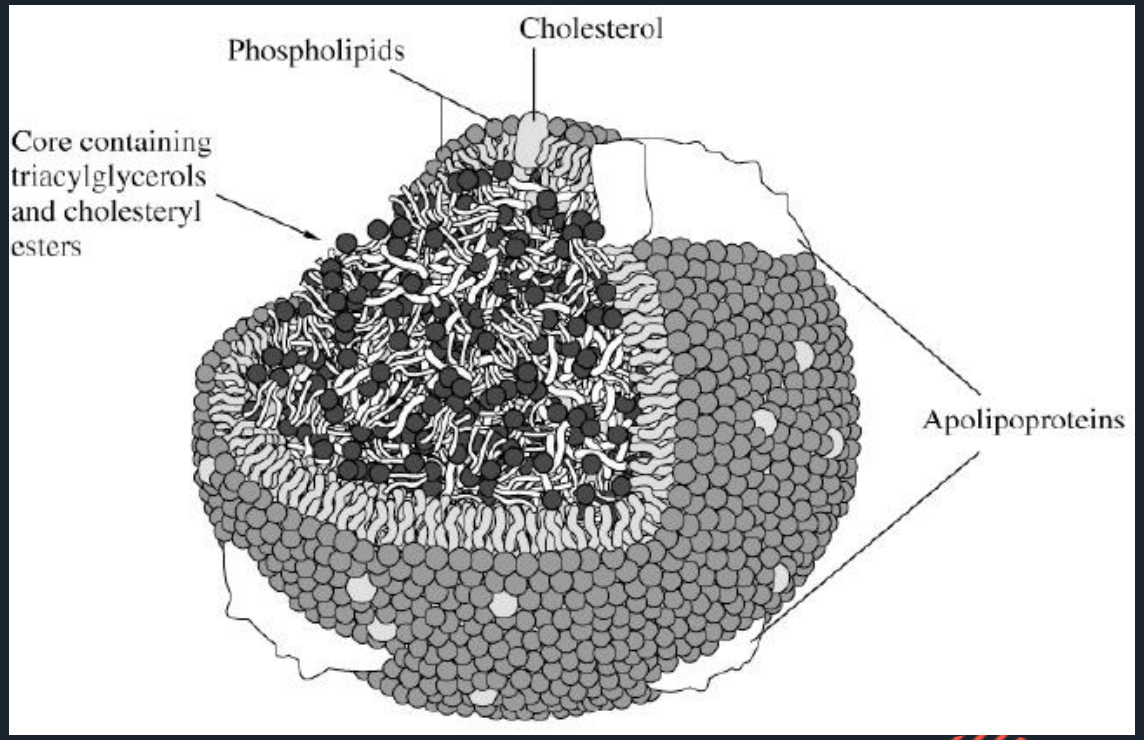


Lipoproteins

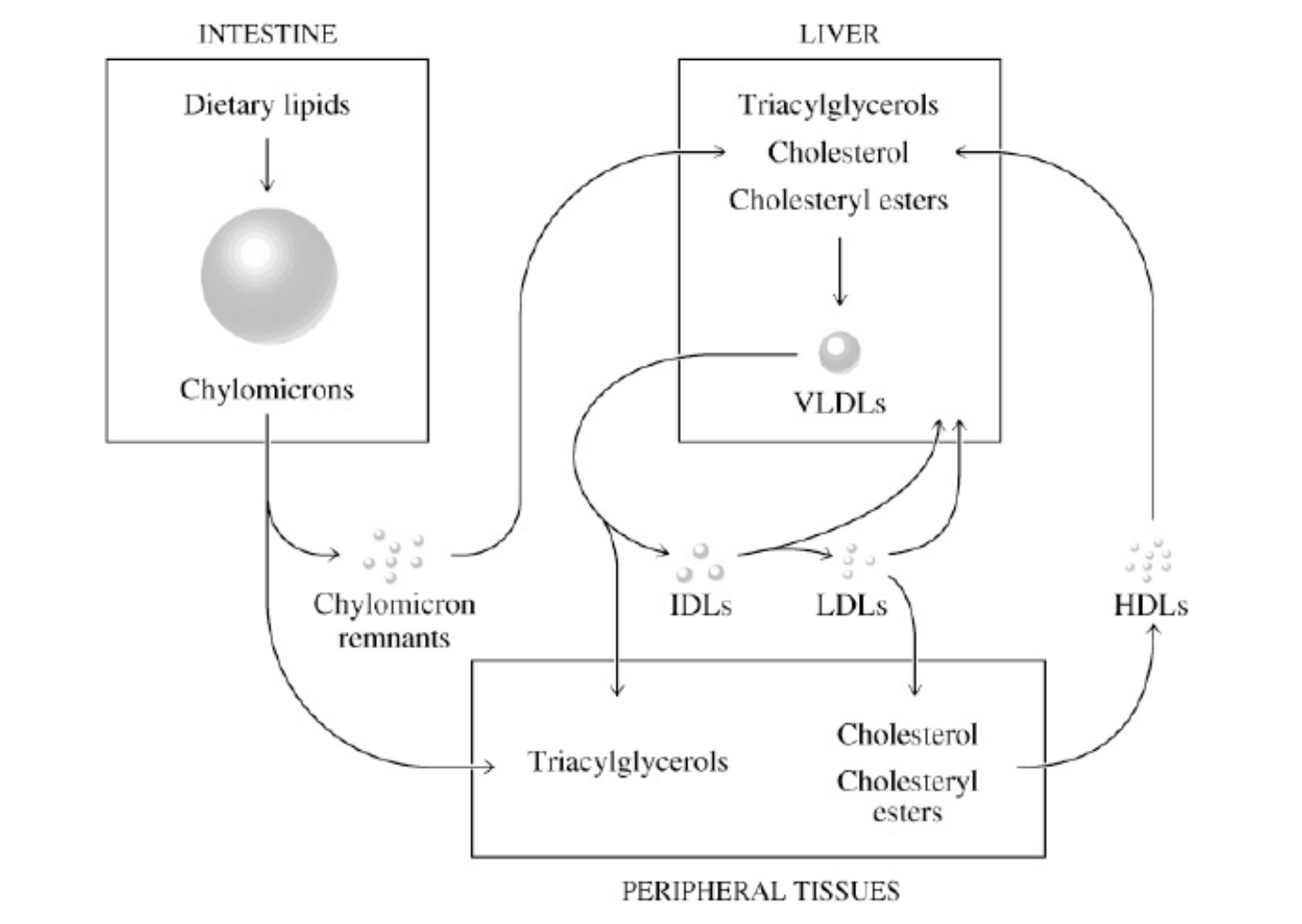
- TGs, cholesterol and cholesterol esters are insoluble in water and cannot be transported in blood or lymph as free molecules
- These lipids assemble with phospholipids and apoproteins (apolipoproteins) to form spherical particles called **lipoproteins** with:

- Hydrophobic cores : TGs, cholesteryl esters

- Hydrophilic surfaces : cholesterol, phospholipids, apolipoproteins



Summary of Lipoproteins Metabolism



02 Lipid Catabolism

01 Fat catabolism (lipolysis)

02 B-Oxidation of Fatty Acids

03 Other Oxidations of Fatty Acids

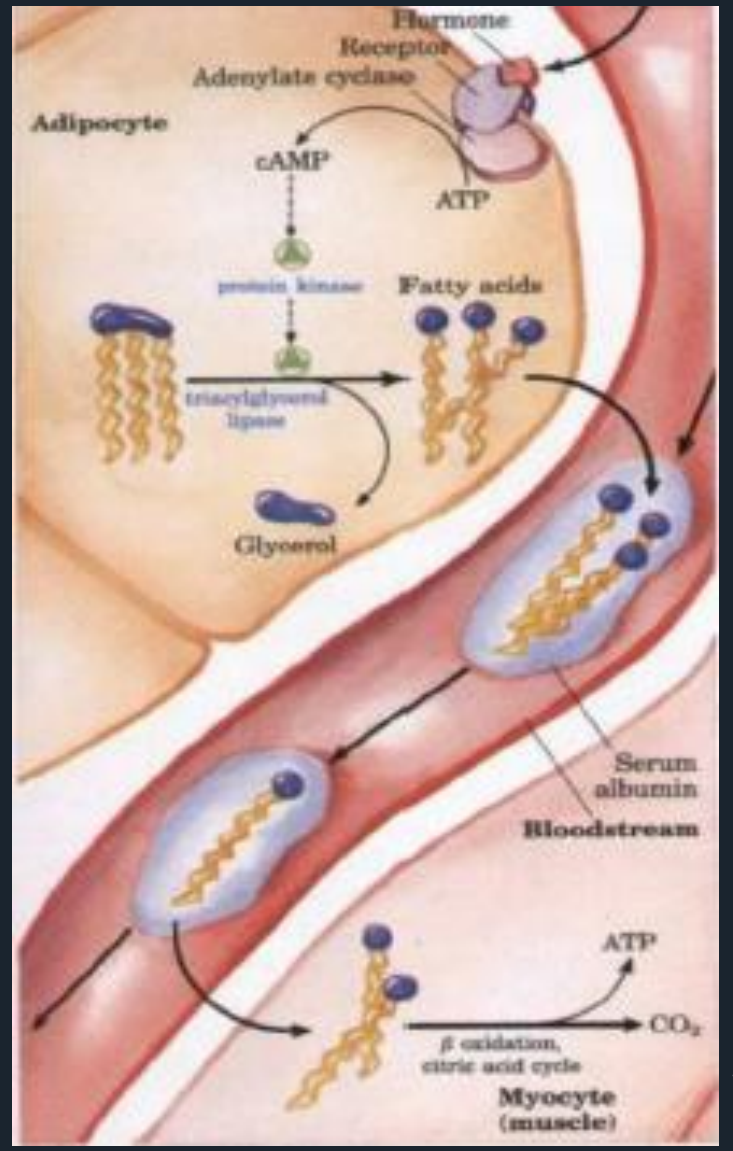
04 Ketone Bodies Formation and Utilization

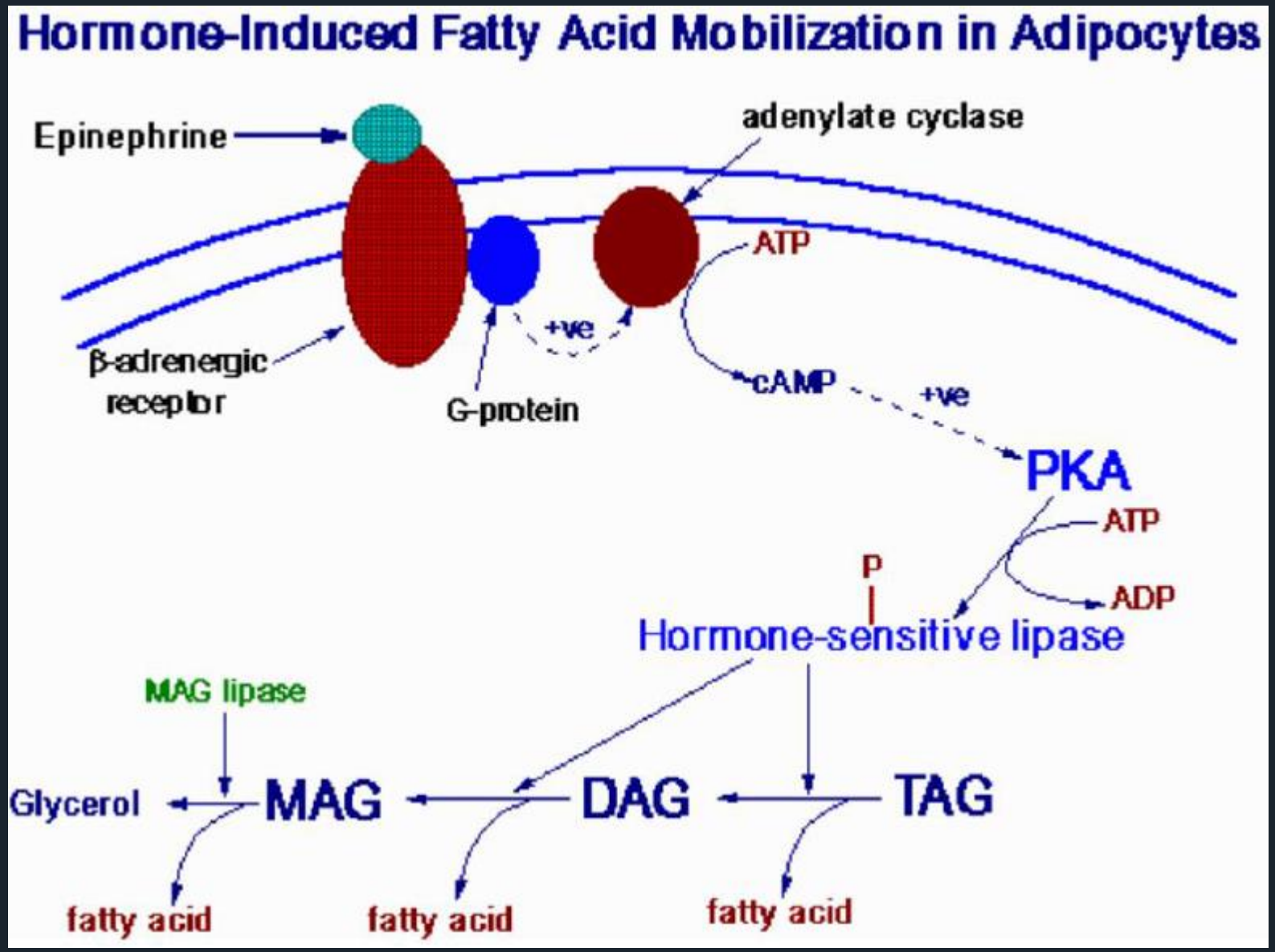
Fat Catabolism (Lipolysis)

Fat mobilization :

The triacylglycerol stored in the adipocytes are hydrolyzed by lipases, to produce free fatty acids (FFA) and glycerol, which are released to the blood, this process is called fat mobilization

The fatty acids thus released diffusively from the adipocyte into the blood, where they bind to the **serum albumin**




Hormone-Induced Fatty Acid Mobilization in Adipocytes
Epinephrine
adenylate cyclase
ATP
β-adrenergic receptor
+ve
G-protein
cAMP
+ve
PKA
ATP
P
ADP
Hormone-sensitive lipase
MAG lipase
Glycerol
MAG
DAG
TAG
fatty acid
fatty acid
fatty acid

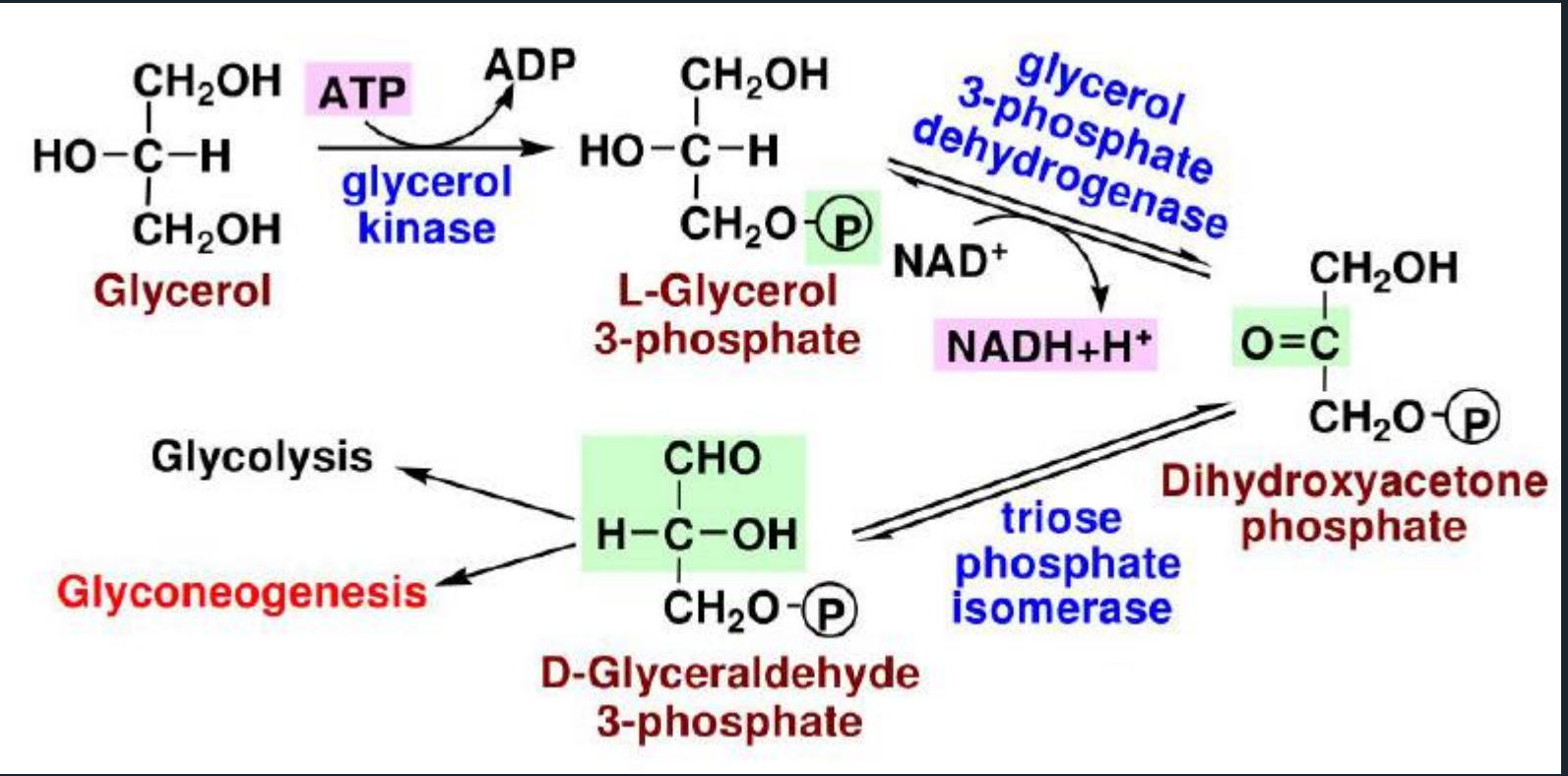
Fat Catabolism (Lipolysis)

- Hormone sensitive lipase (HSL) : TG lipase is the rate-limiting enzyme in the TG degradation in adipose tssie. Its also named HSL because its regulated by some hormones.

- Effect of hormones on lipolysis
  - ❑ Lipolytic Hormones :
  - Epinephrine
  - Norepinephrine
  - Adrenocorticotropic hormone (ACTH)
  - Thyroid stimulating hormone (TSH)
  - Glucagon
  - ❑ Antilipolytic hormone :
  - Insulin

Glycerol Metabolism

- Place : liver, kidney, intestine



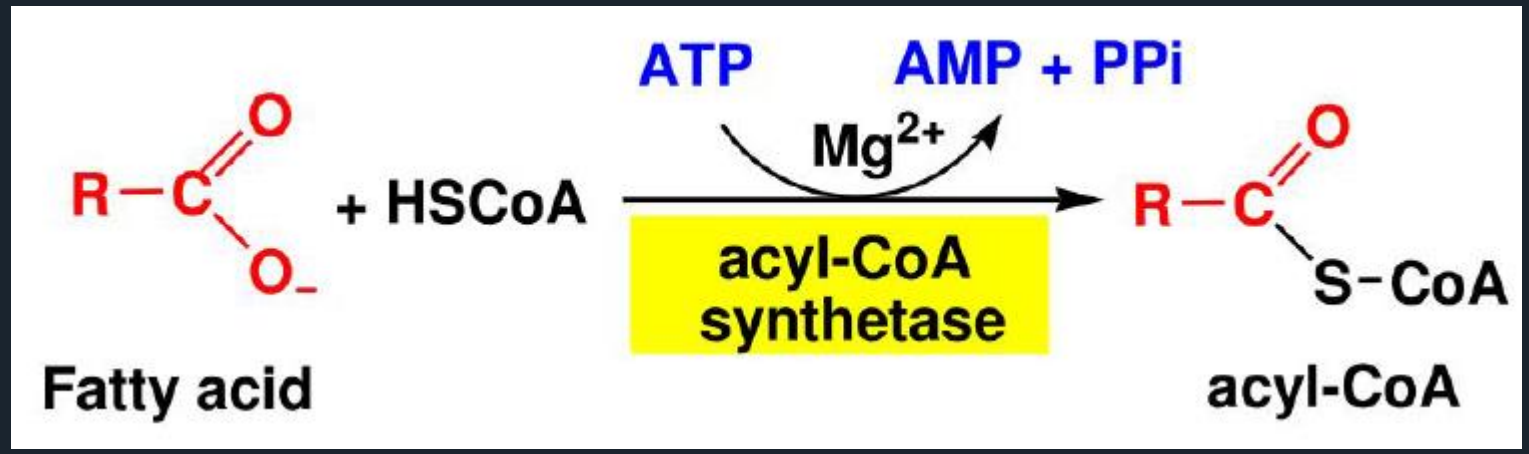
β -Oxidation of Fatty Acids

- Fatty acids are one of the main energy materials of human and other mammalian
- Fatty acid catabolism can be subdivided into 3 stages

β -Oxidation of Fatty Acids

Stage 1. Activation of FAs

Acyl-CoA Synthetase (Thiokinase) which locates on the cytoplasm, catalyzes the activation of long chain fatty acids

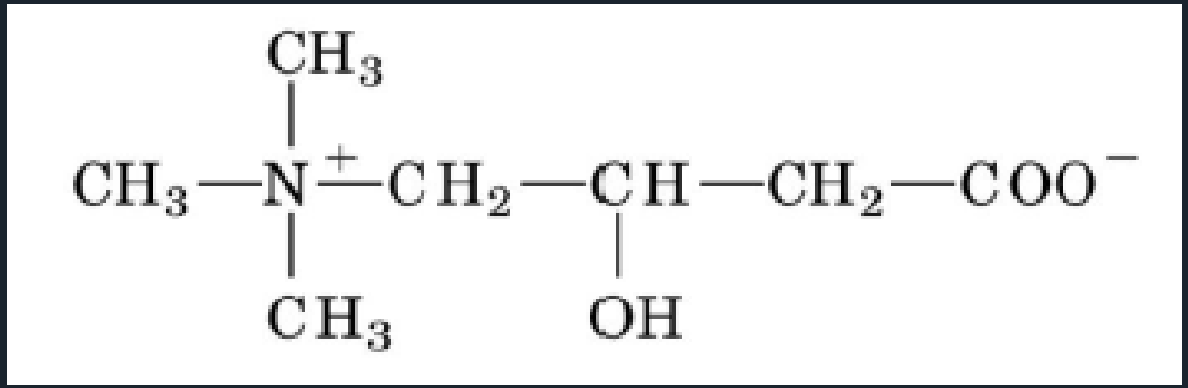


Key points of FA activation : irreversible, consume 2~P, site:cytosol

β -Oxidation of Fatty Acids

Stage 2. Transport of acyl CoA into the mitochondria (rate-limiting step)

Carrier : carnitine

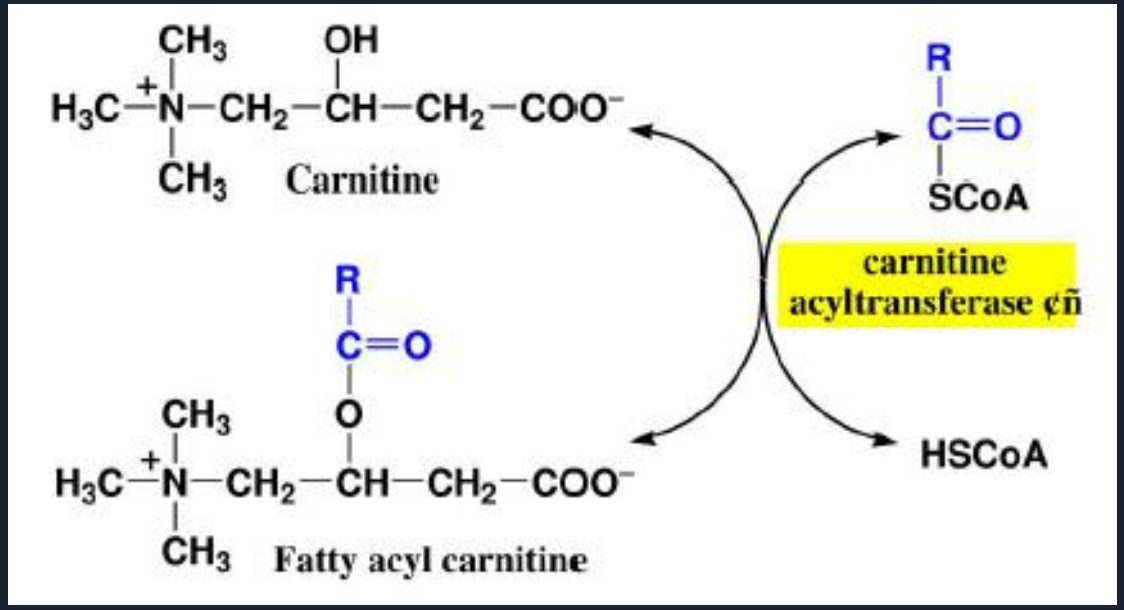


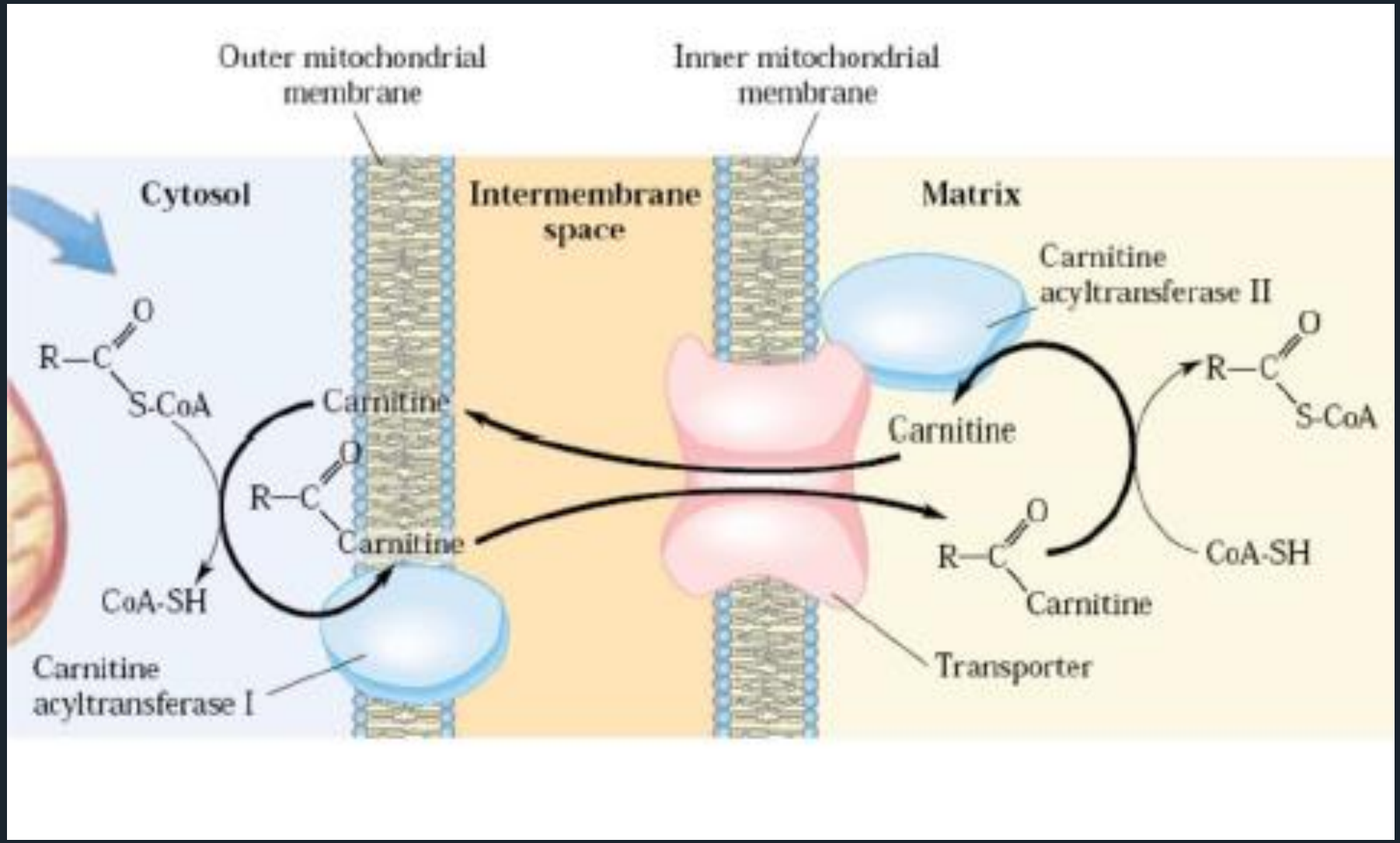
β -Oxidation of Fatty Acids

Stage 2. Transport of acyl CoA into the mitochondria (rate-limiting step)

Rate-limiting enzyme

- Carnitine acyltransferase I




Outer mitochondrial membrane
Inner mitochondrial membrane
Cytosol
Intermembrane space
Matrix
Carnitine acyltransferase II
R—C(=O)—S-CoA
Carnitine
R—C(=O)—Carnitine
CoA-SH
Carnitine acyltransferase I
Carnitine
R—C(=O)—Carnitine
R—C(=O)—S-CoA
CoA-SH
Transporter

β-Oxidation of Fatty Acids

Stage 3. β-oxidation of FAs

B-oxidation means β-C reaction

4 steps in one round :

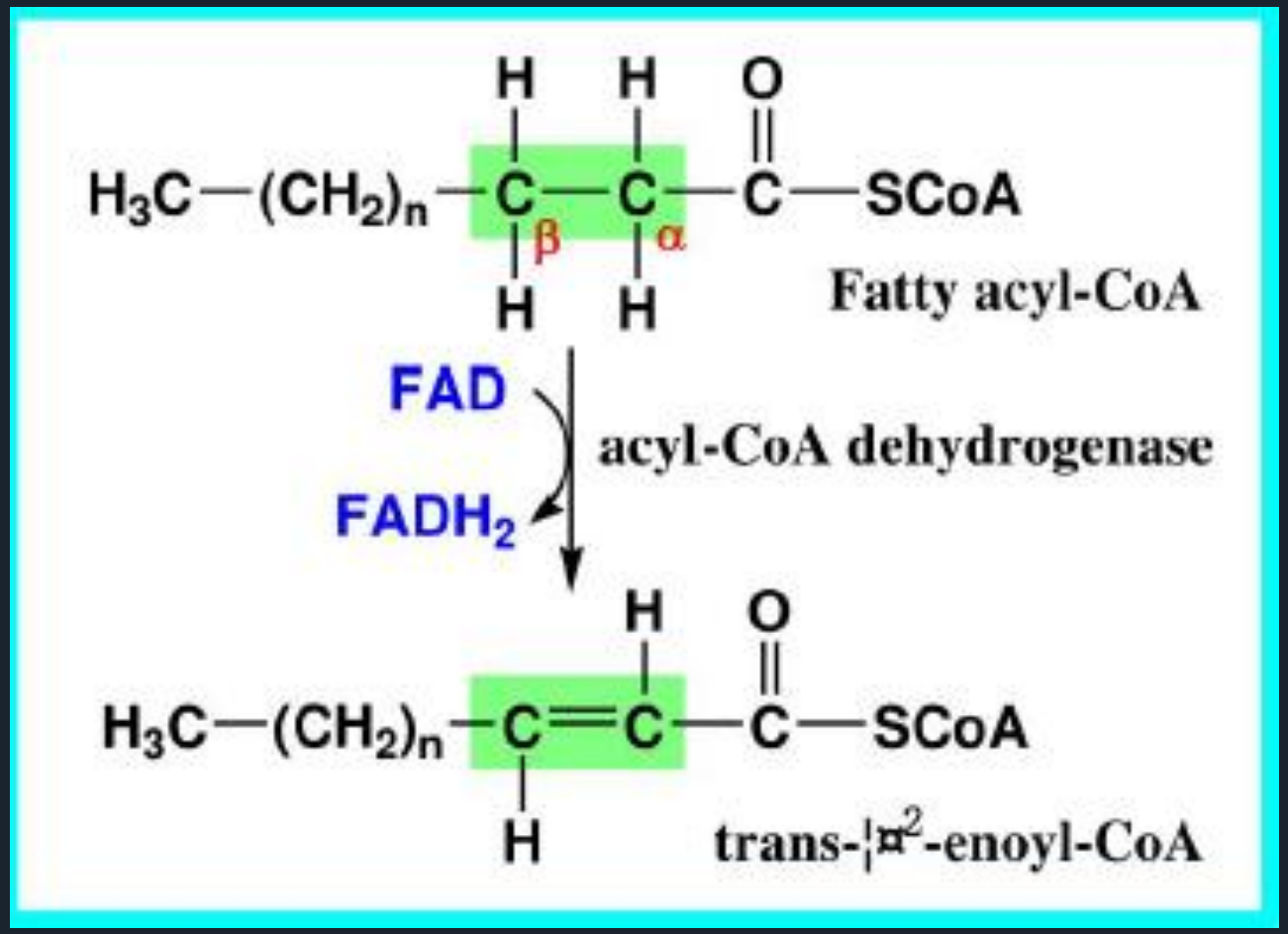
Step 1: Dehydrogenate

Step 2: Hydration

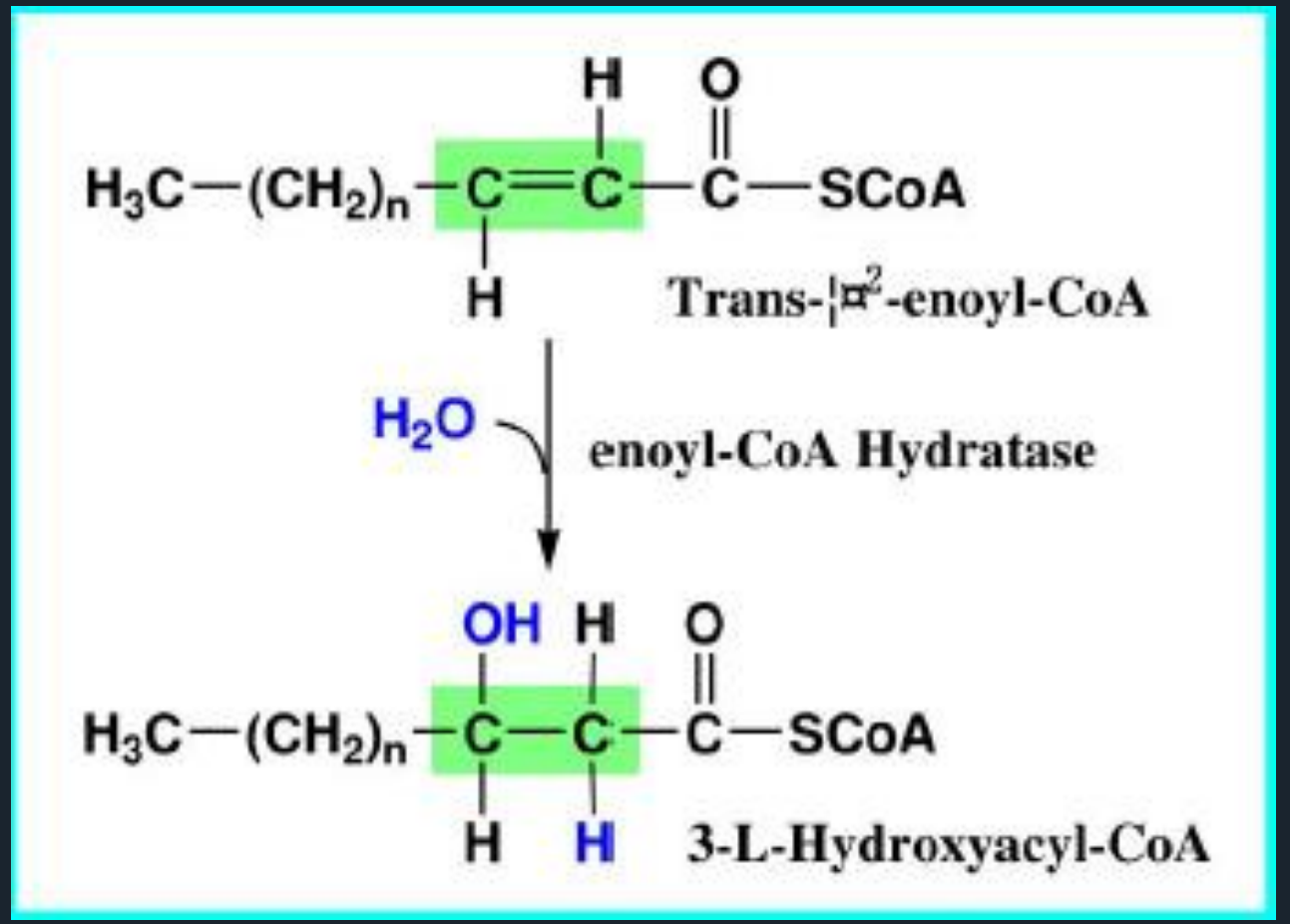
Step 3: Dehydrogenate

Step 4: Thiolytic cleavage

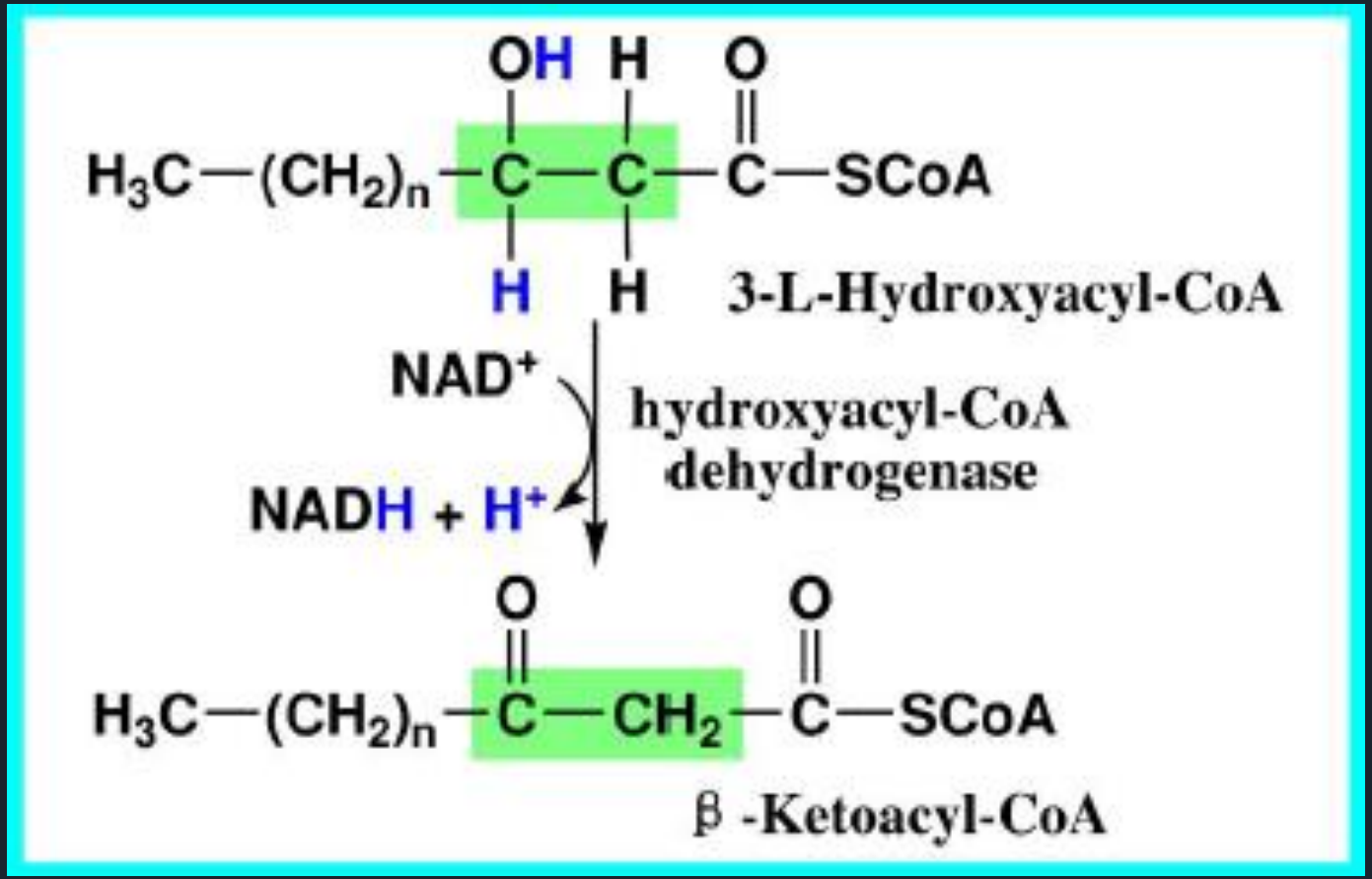
Step 1. Dehydrogenate



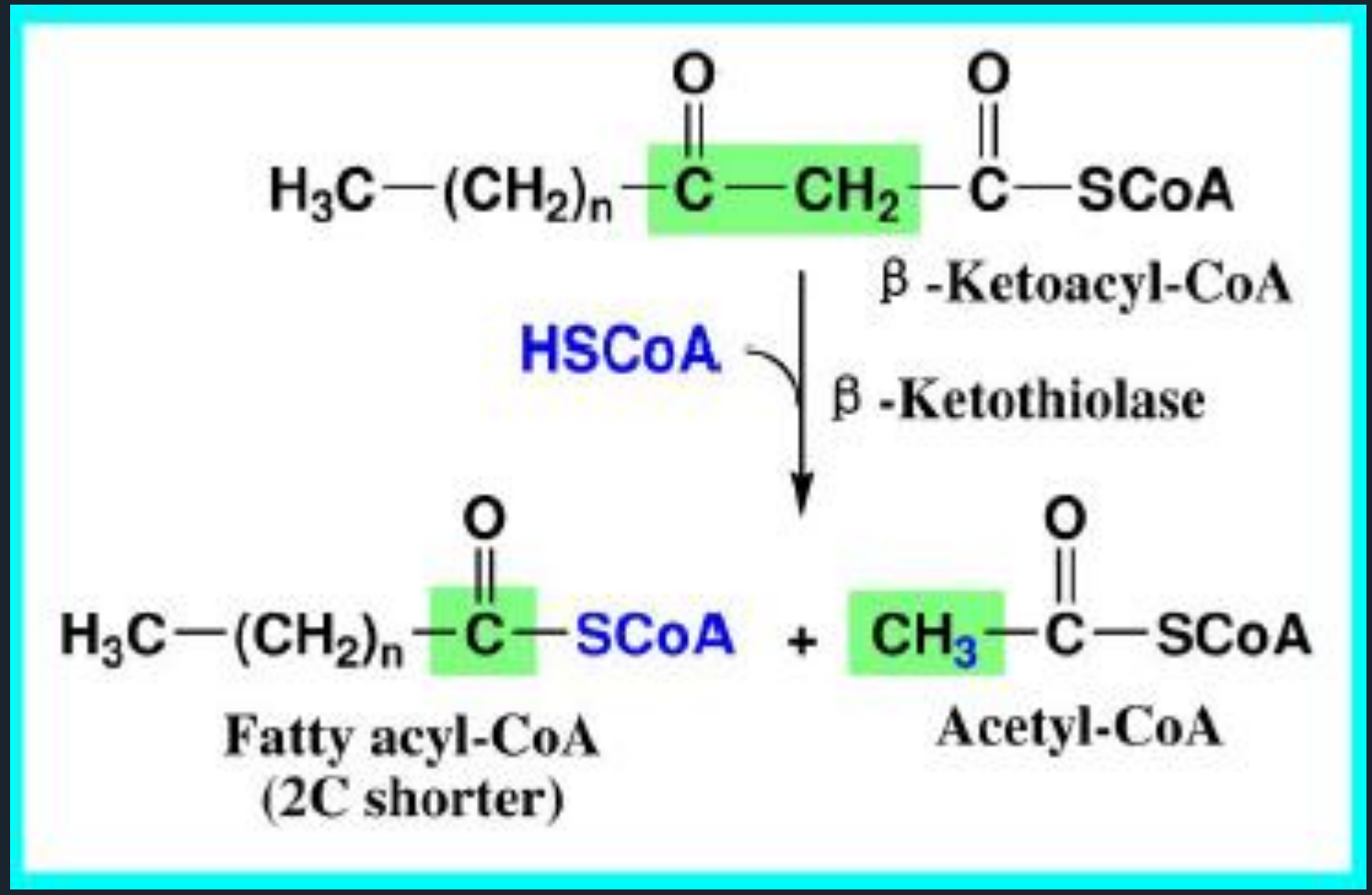
Step 2. Hydration



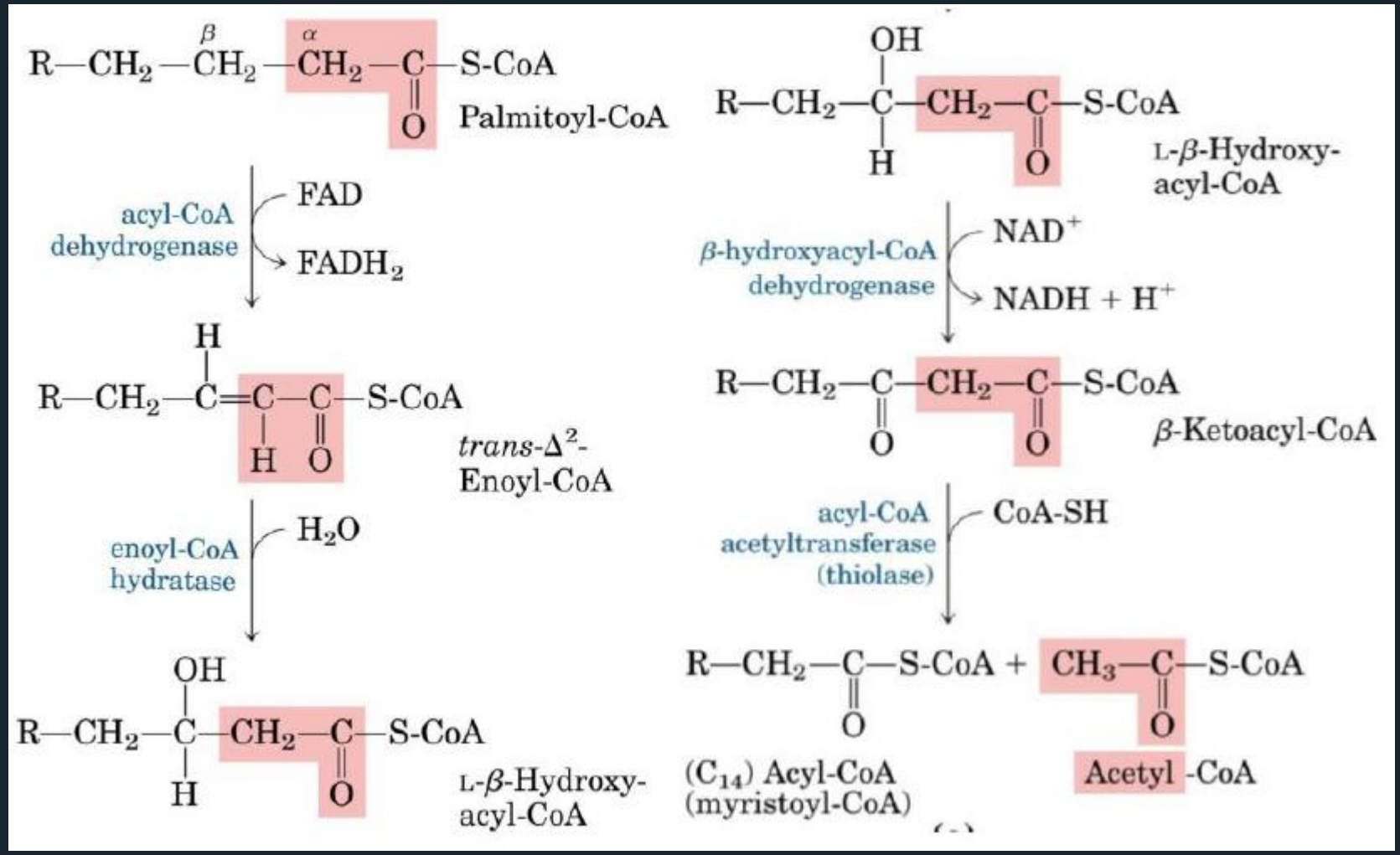
Step 3. Dehydrogenate



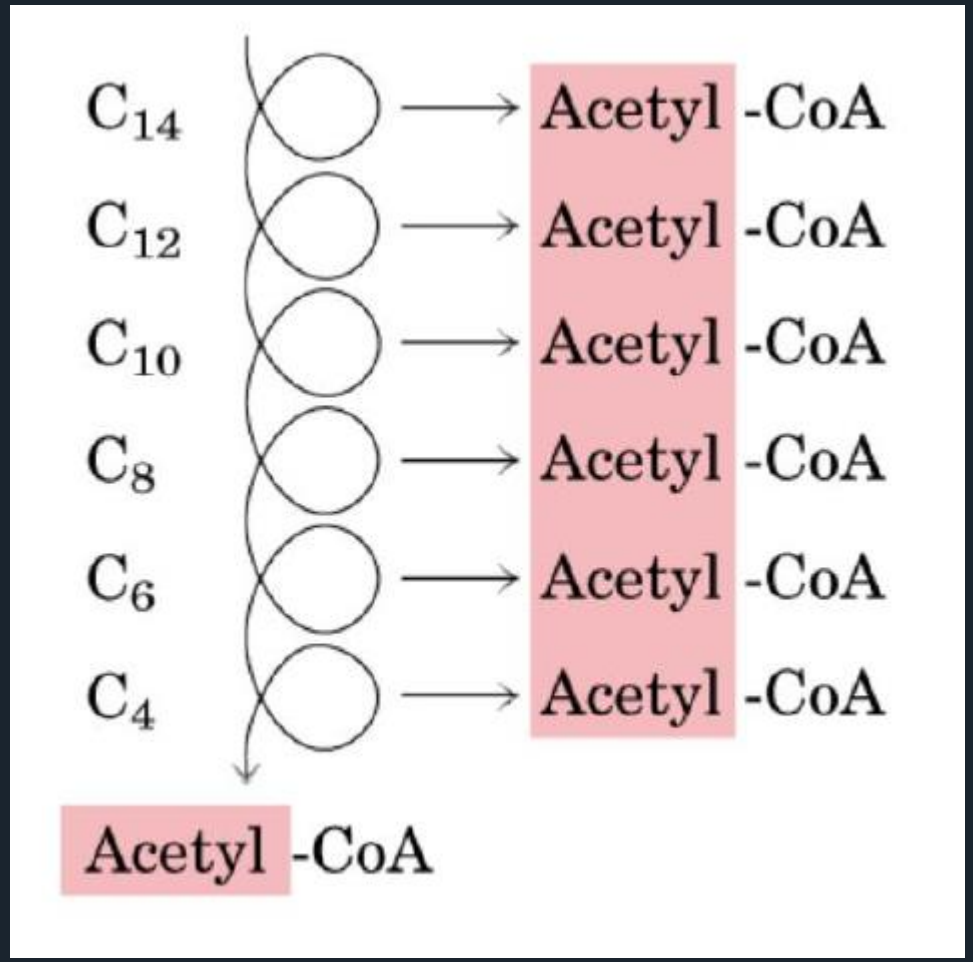
Step 3. Thyolytic Cleavage



β-Oxidation of Fatty Acids



The β-Oxidation pathway is cyclic



β-Oxidation summary

One cycle :

fatty acyl-CoA + FAD + NAD^+ + HS-CoA

→fatty acyl-CoA (2 C less) + $FADH_2$ +

NADH + H^+ + acetyl-CoA

Other Oxidations of Fatty Acids

1. Oxidation of unsaturated fatty acids
2. Peroximal fatty acid oxidation
3. Oxidation of propionyl-CoA

Other Oxidations of Fatty Acids

1. Oxidation of Unsaturated Fatty Acids

- Mitochondria
- Isomerase : *cis* → *trans*
- Epimerase : D (-) → L (+)

Other Oxidations of Fatty Acids

2. Peroximal Fatty Acid Oxidation

Very long chain fatty acids

FAD

Acyl-CoA oxidase

Shorter chain fatty acids

β-oxidation

Other Oxidations of Fatty Acids

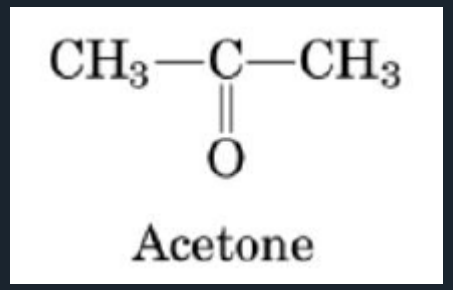
3. Oxidation of Propionyl-CoA

Propionyl-CoA

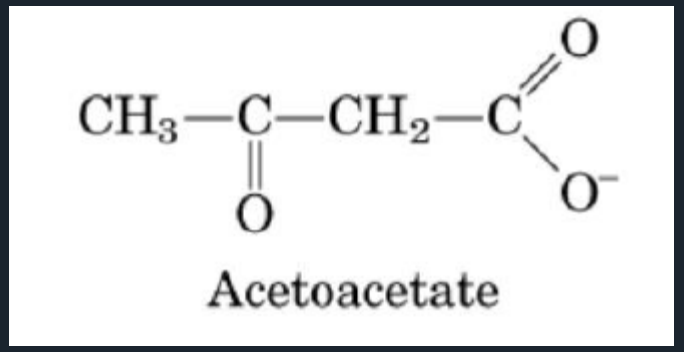
↓ Carboxylase (biotin)
Epimerase
Mutase (VB_{12})

Succinyl-CoA

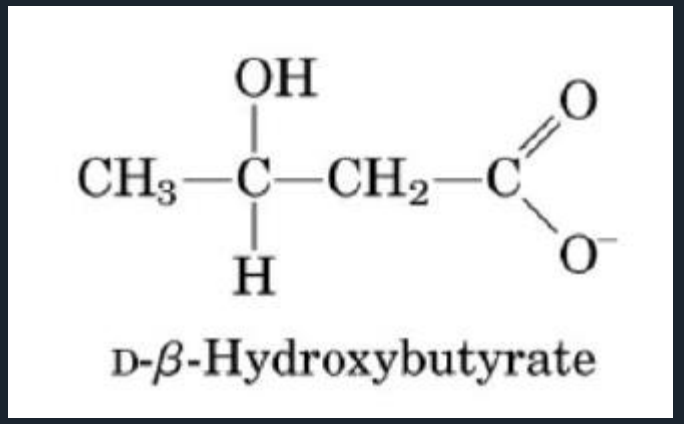
Ketone Bodies
Formation and Utilization



Acetone



Acetoacetate



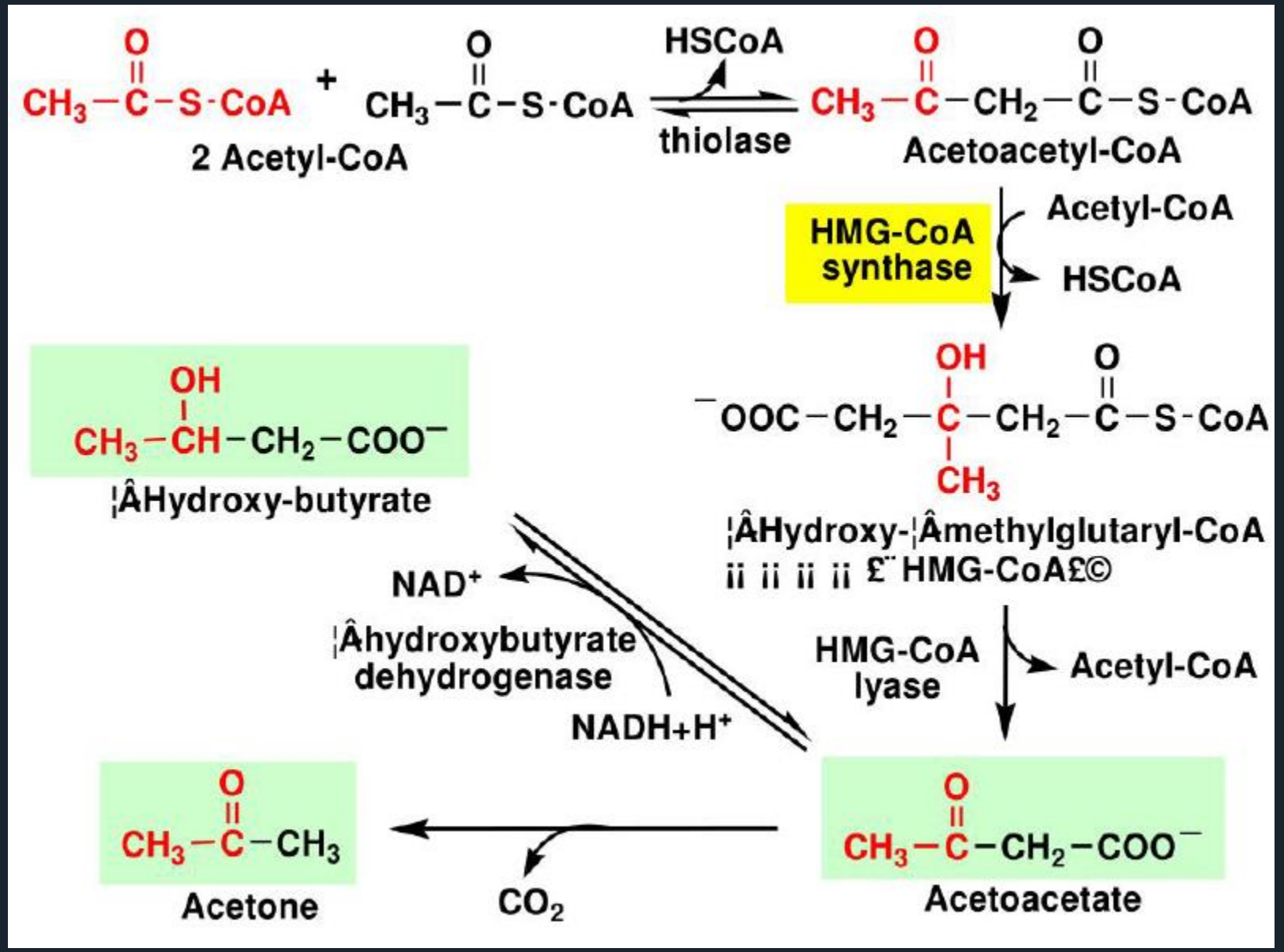
D-β-Hydroxybutyrate

Ketone bodies are water-soluble fuels normally exported by the liver but overproduced during fasting or in untreated diabetes mellitus, including acetoacetate, β-hydroxybutyrate and acetone

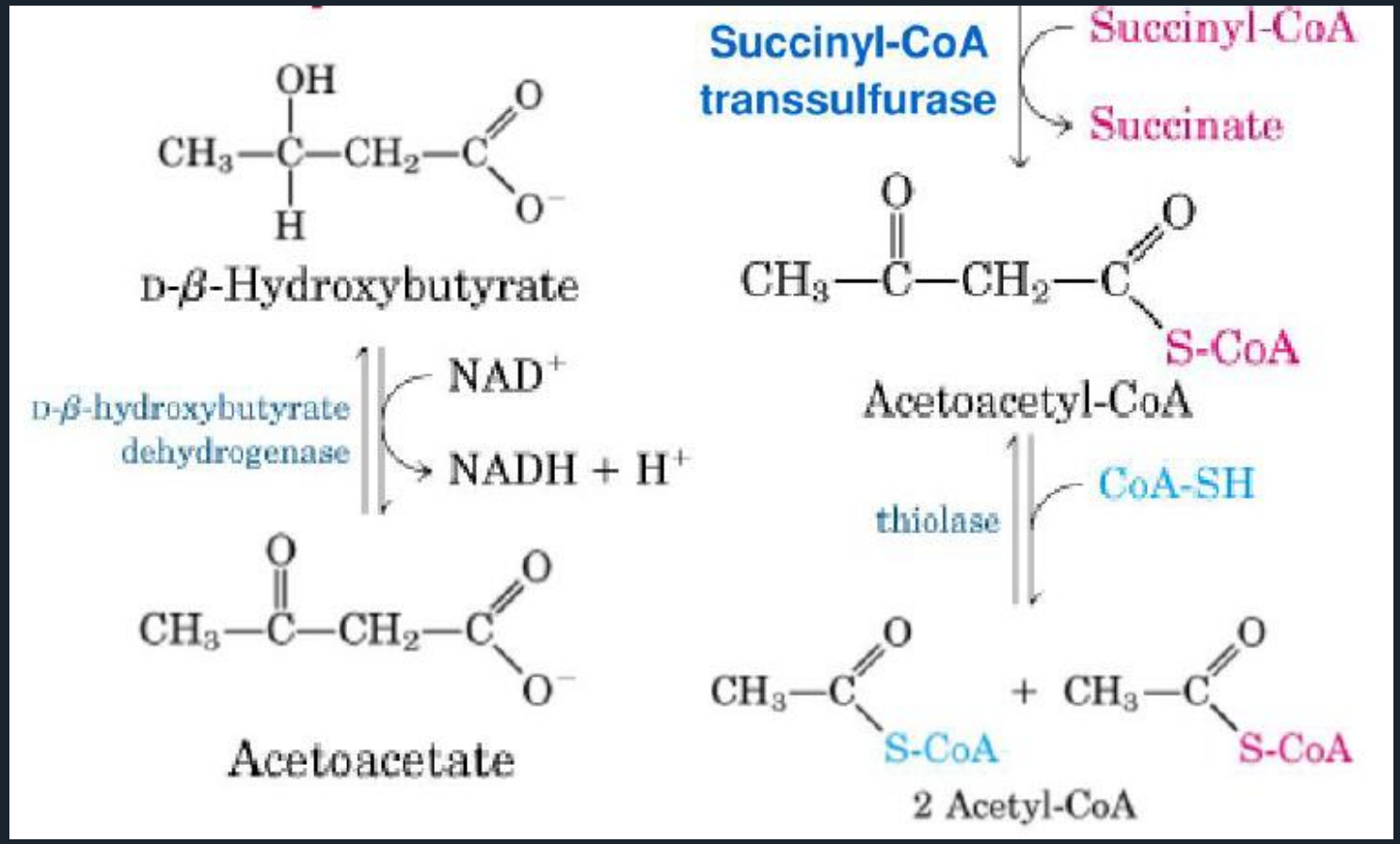
Ketone Bodies Formation and Utilization

The formation of Ketone bodies (ketogenesis)

- Location : hepatic mitochondria
- Material : acetyl CoA
- Rate-limiting enzyme : HMG-CoA synthase

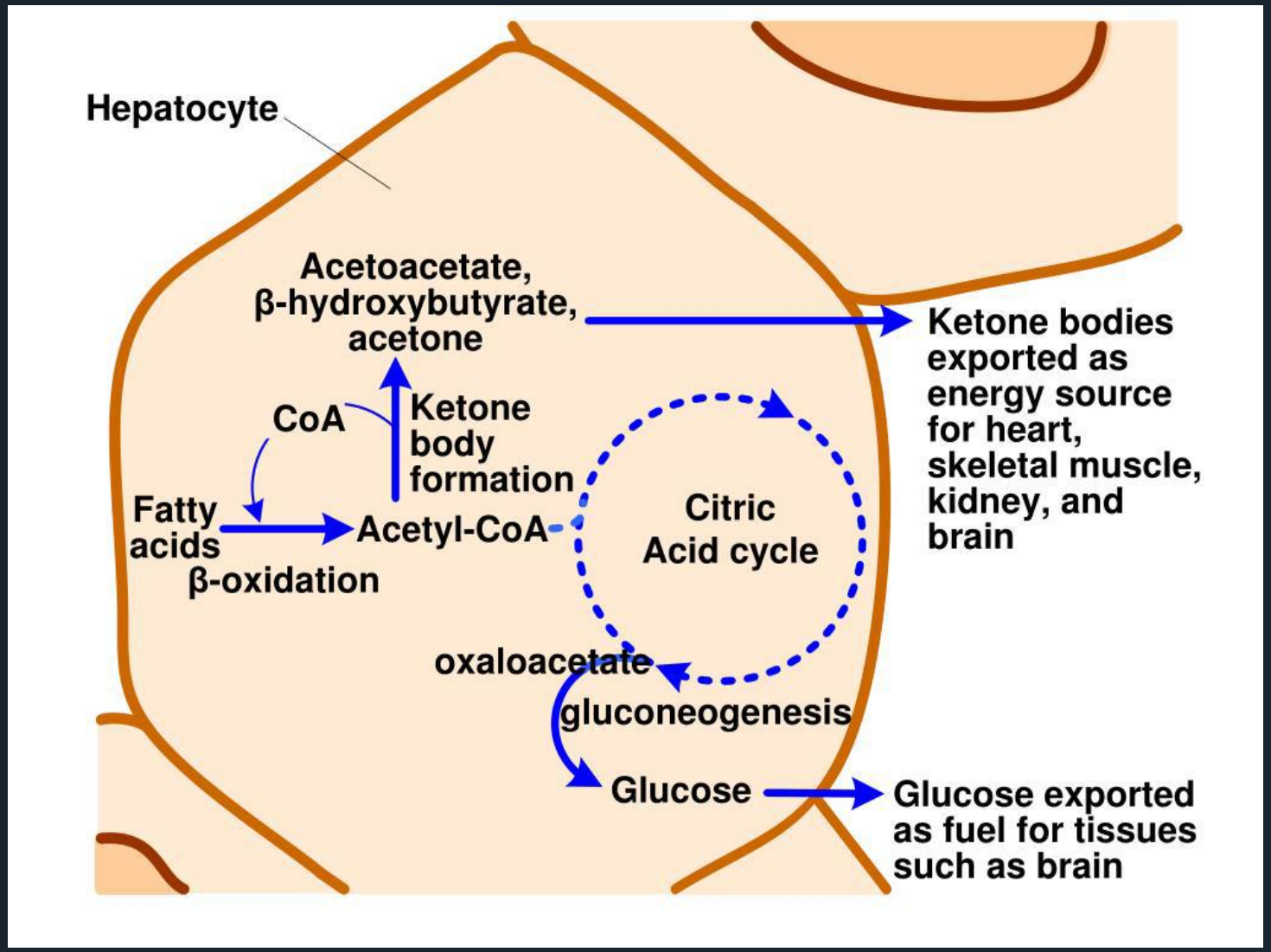

2 Acetyl-CoA
HSCoA
thiolase
Acetoacetyl-CoA
HMG-CoA synthase
Acetyl-CoA
HSCoA
¦ÂHydroxy-butyrate
¦ÂHydroxy-¦Âmethylglutaryl-CoA
ii ii ii ii £¨HMG-CoA£©
NAD+
¦Âhydroxybutyrate dehydrogenase
NADH+H+
HMG-CoA lyase
Acetyl-CoA
Acetone
CO2
Acetoacetate

Utilization of Ketone Bodies at Extrahepatic Tissues



Biological Significance

- Ketone bodies replace glucose as the major source of energy for many tissues especially the brain, heart and muscles during times of prolonged starvation
- Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation


Hepatocyte
Acetoacetate,
β-hydroxybutyrate,
acetone
Ketone bodies
exported as
energy source
for heart,
skeletal muscle,
kidney, and
brain
CoA
Ketone
body
formation
Fatty
acids
β-oxidation
Acetyl-CoA
Citric
Acid cycle
oxaloacetate
gluconeogenesis
Glucose
Glucose exported
as fuel for tissues
such as brain

Thank You

For The Attention