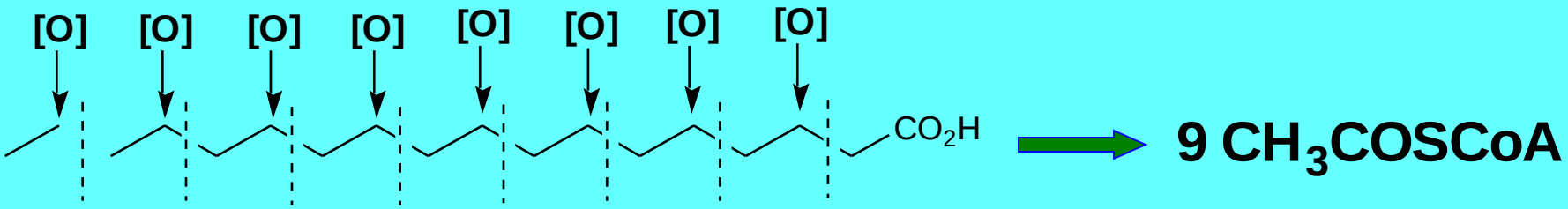
B – oxidation , cholesterol and KBs

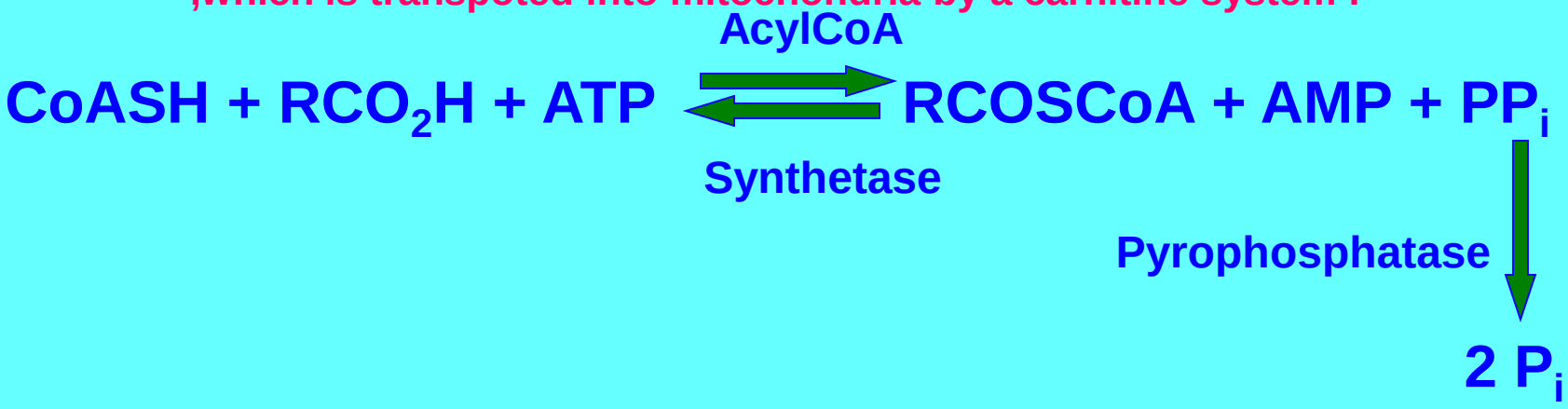
Beta Oxidation

- **Cleavage of fatty acids to acetate in tissues**
- **Occurs in mitochondria**

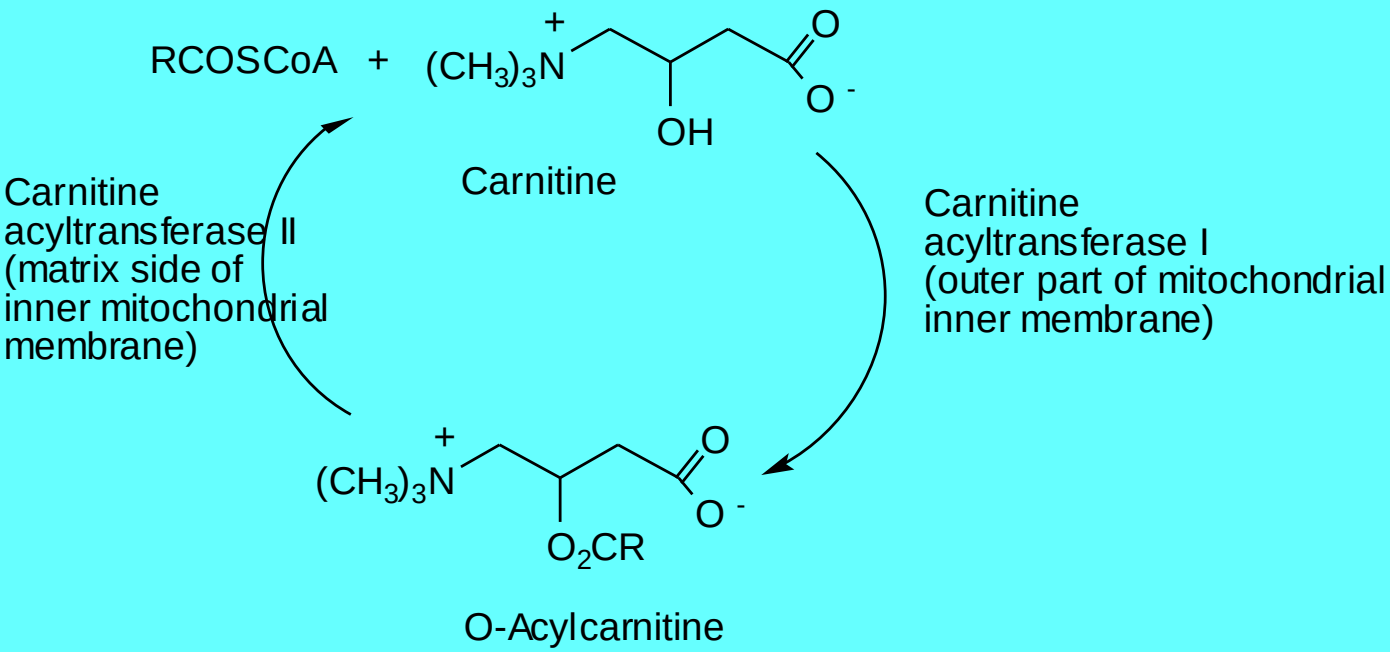


Fatty Acid Activation by Esterification with CoASH

prior to oxidation , long chain fatty acids are activated , forming fatty acyl CoA ,which is transpoted into mitochondria by a carnitine system .

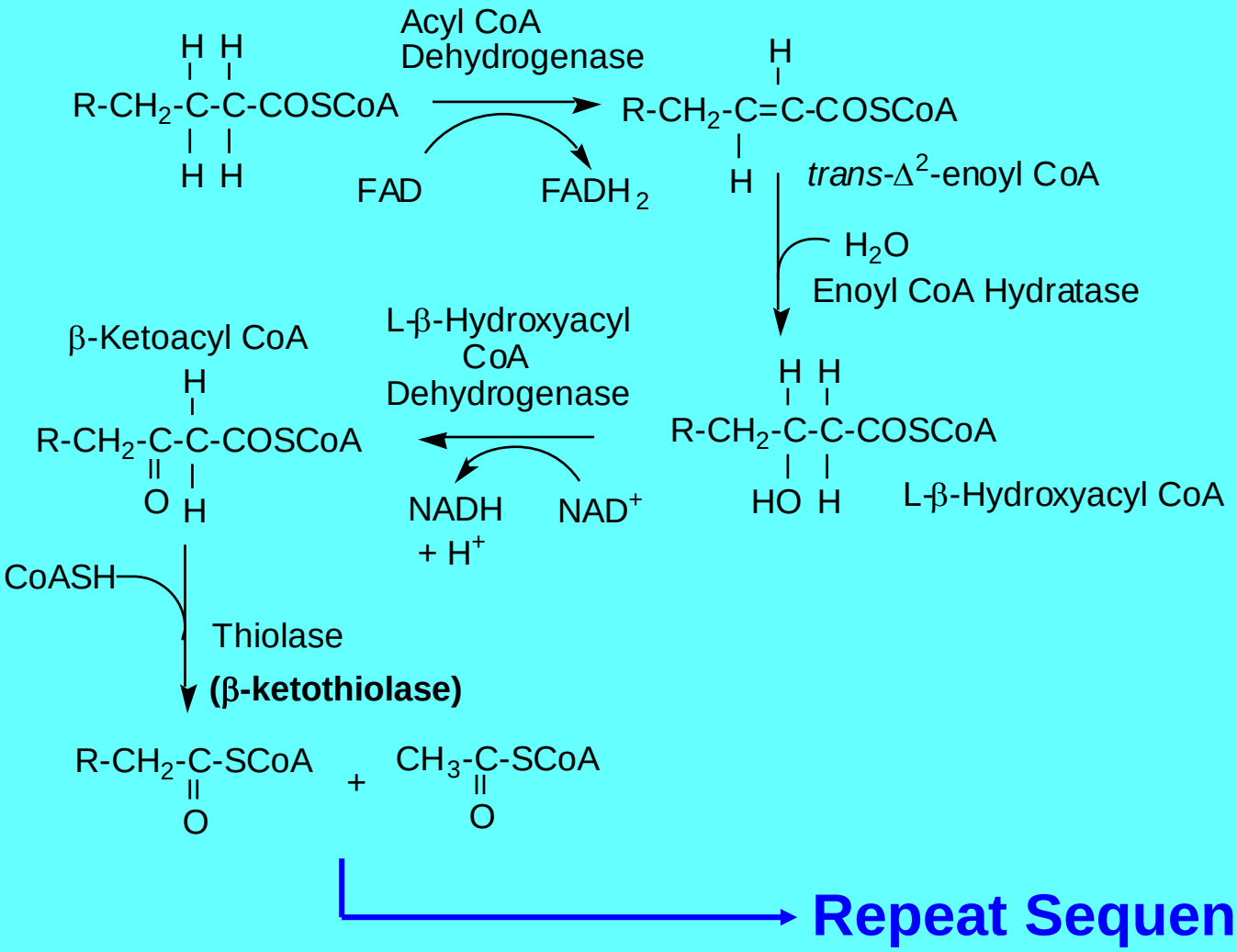


Membrane Transport of Fatty Acyl CoA Esters

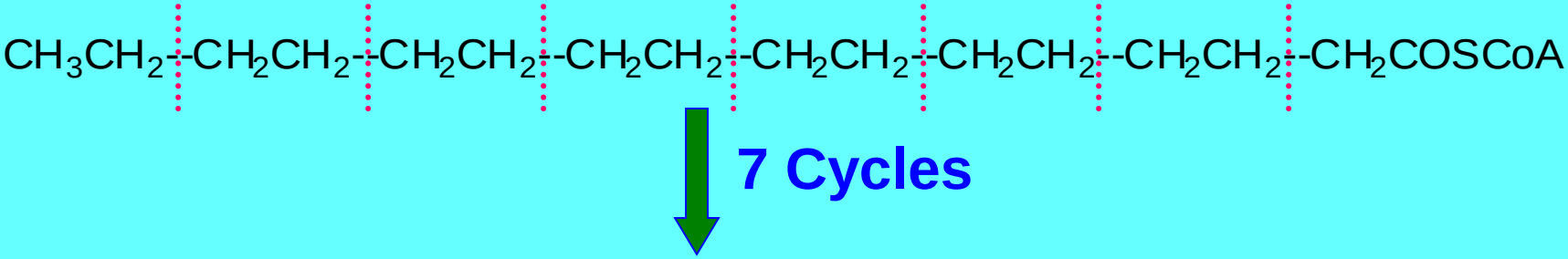


Fatty acyl CoA from the cytosol reacts with carnitine in the outer mitochondrial membrane , forming fatty acyl carnitine .The enzyme is CAT1 .
Fatty acyl carnitine passes to the inner membrane , where it re-forms fatty acyl CoA , which enters the matrix . The second enzyme is CAT 11 .

Beta Oxidation Reaction Sequence



Complete Beta Oxidation of Palmitoyl CoA



8 CH3COSCoA + 7 FADH2 + 7 NADH + 7 H+

1 . The 7 FADH2 each generate approximately 2 ATP for a total of about 14 ATP .

2 . The 7 NADH each generate about 3 ATP , for a total about 21 ATP .

3 . The 8 acetyl CoA can enter the TCA cycle , each producing about 12 ATP , for a total about 96ATP.

4 . From the oxidation of palmitoyl CoA to CO2 and H2O , a total of about 131 ATP are produced .

Note :

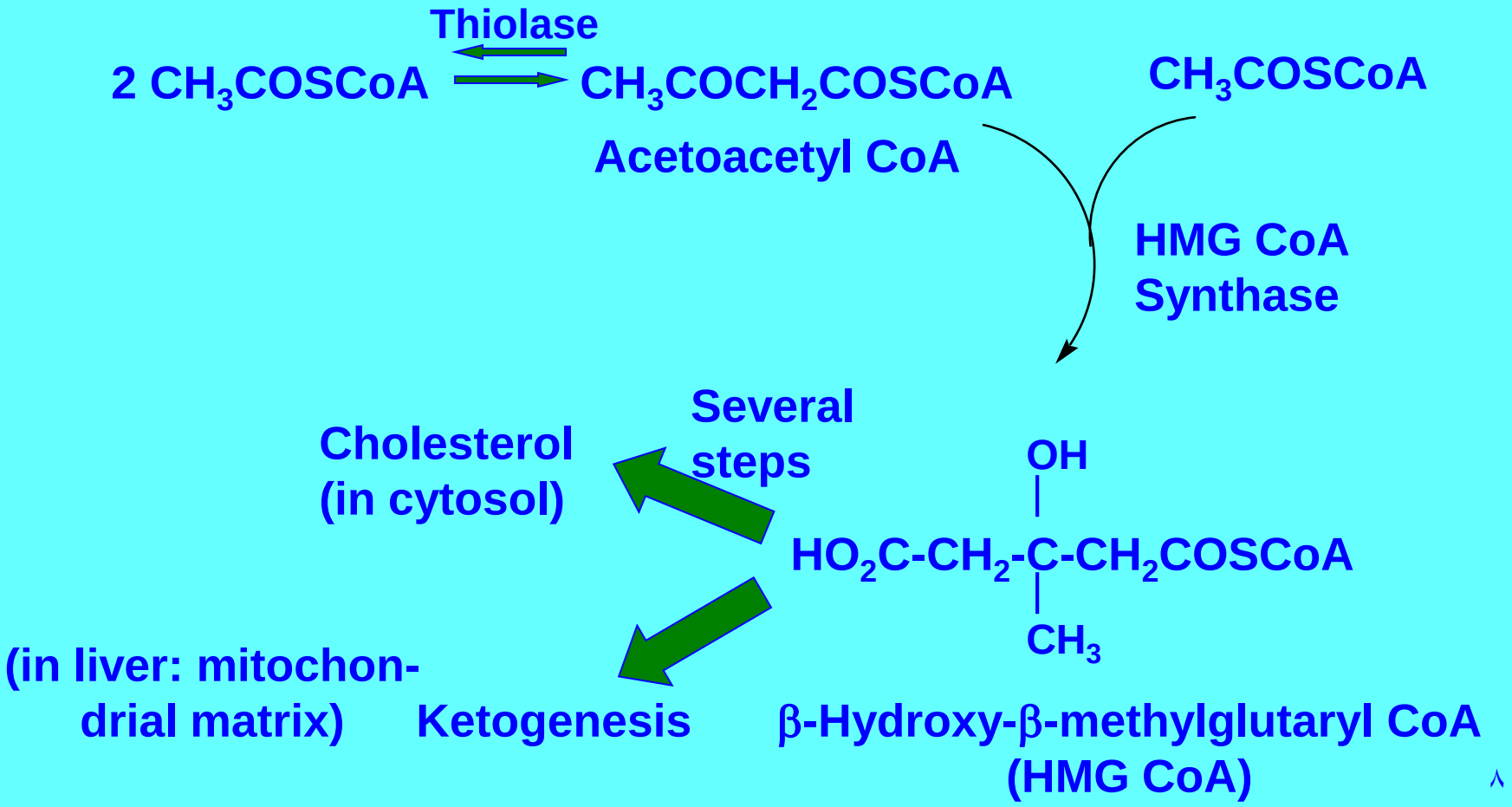
The fates of acetyl CoA formed by B – oxidation of fatty acid are :

1 . Oxidation by citric acid cycle .

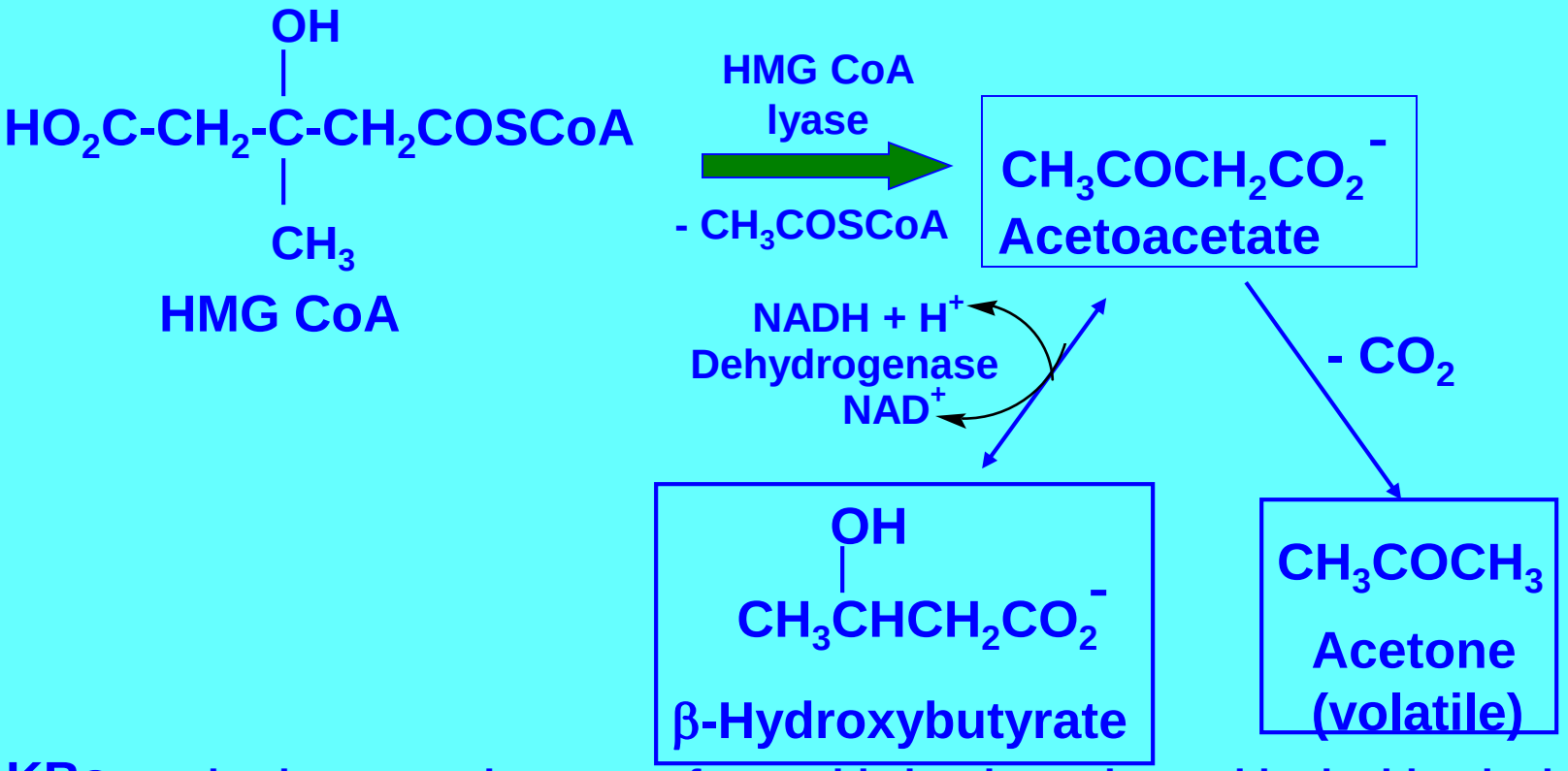
2 . Synthesis of lipids like cholesterol, fatty acids and other steroids .

3 . Formation of ketone bodies in the liver .

Ketogenesis: Formation of Ketone Bodies



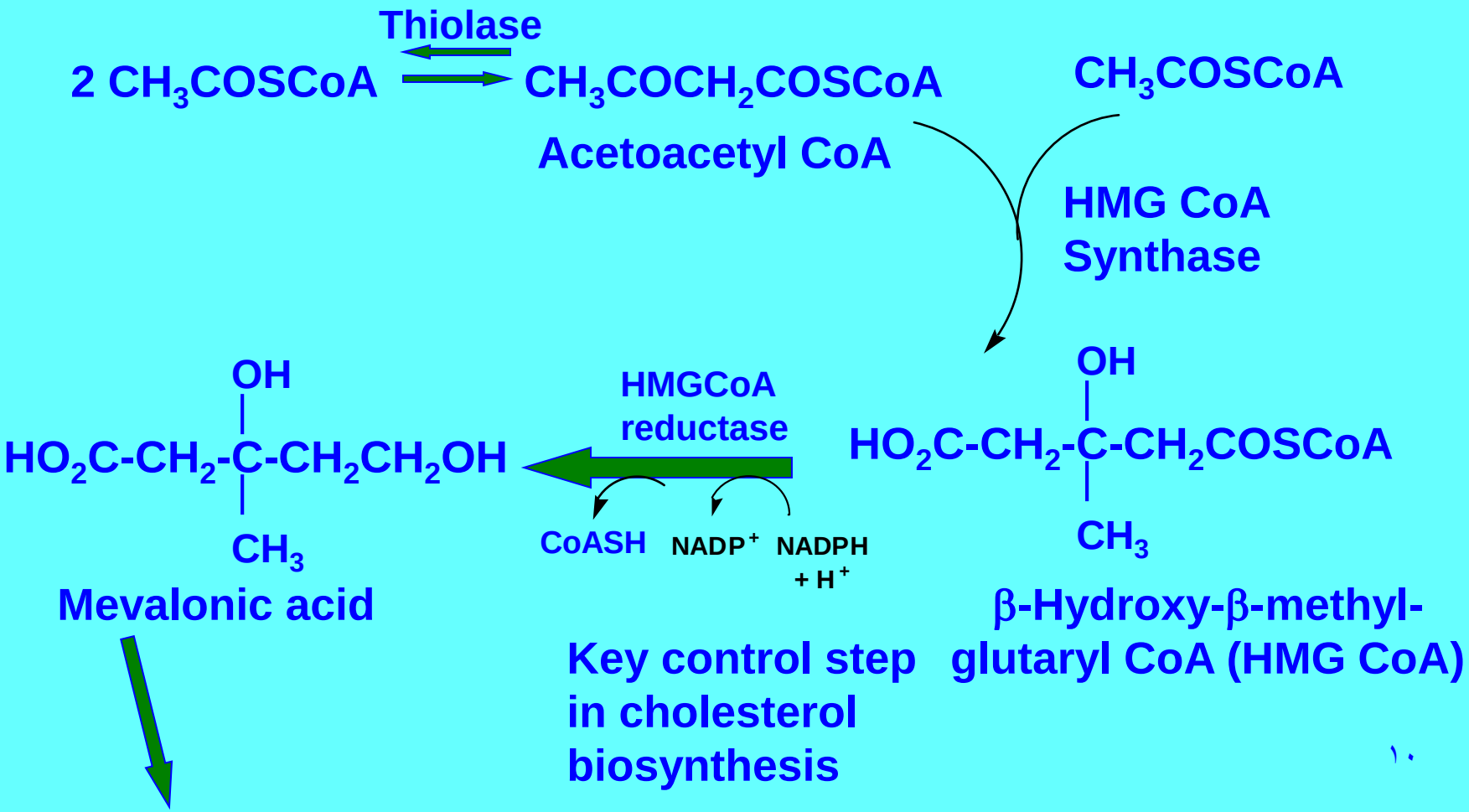
Ketogenesis: Formation of Ketone Bodies

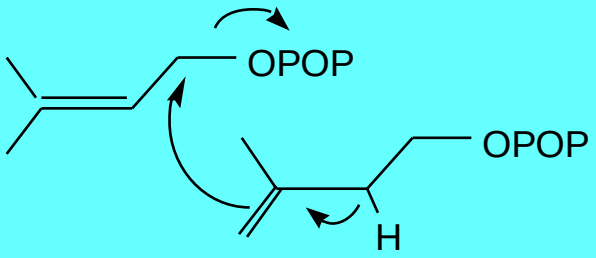


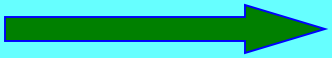
KBs synthesis occur when every fatty acids level are eleveted in the blood , that is during fasting or starvation or as a result of a high fat , low carbohydrate diet .
(The enzymes for KBs synthesis are located mainly in liver mitochondria)

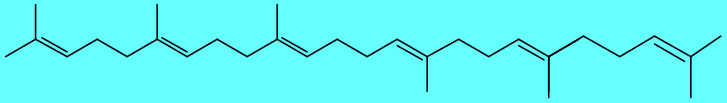
Cholesterol Biosynthesis

Liver is primary site of cholesterol biosynthesis









Isoprenes **Squalene**

Notes

1.Lovastatin and Mevastatin,drugs can be used for inhibited ch. biosynthesis , they are used to decrease plasma ch . level in patients with hypercholesterolemia .

2 . The KBs (acetoacetate , 3- HBA) are acids , so they form (H^+) . AS a result :

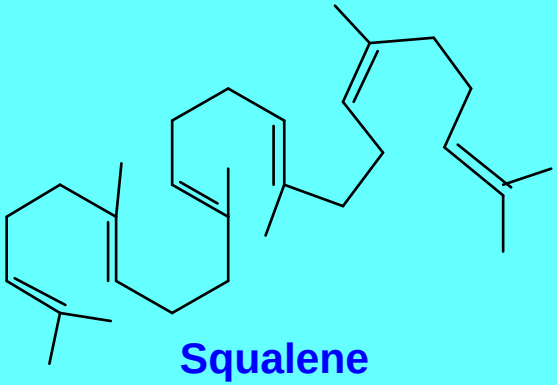
KBs ↑ → H^+ ↑ → pH ↓ → fatal

So the danger is not from KBs but from H that is il produced .

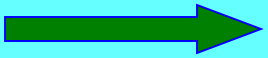
Treatment :

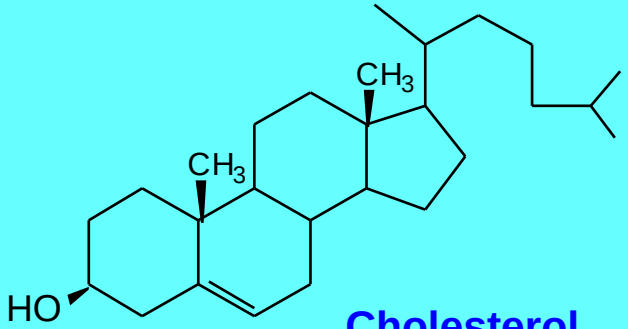
Insulin intake → no lipolysis → FFA ↓

Conversion of Squalene to Cholesterol



Squalene

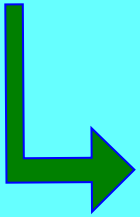


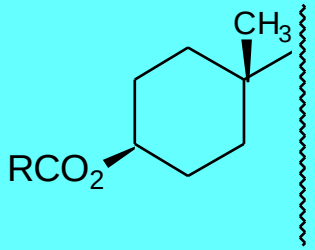


Cholesterol

cholesterolAcyl-CoA:

acyltransferase

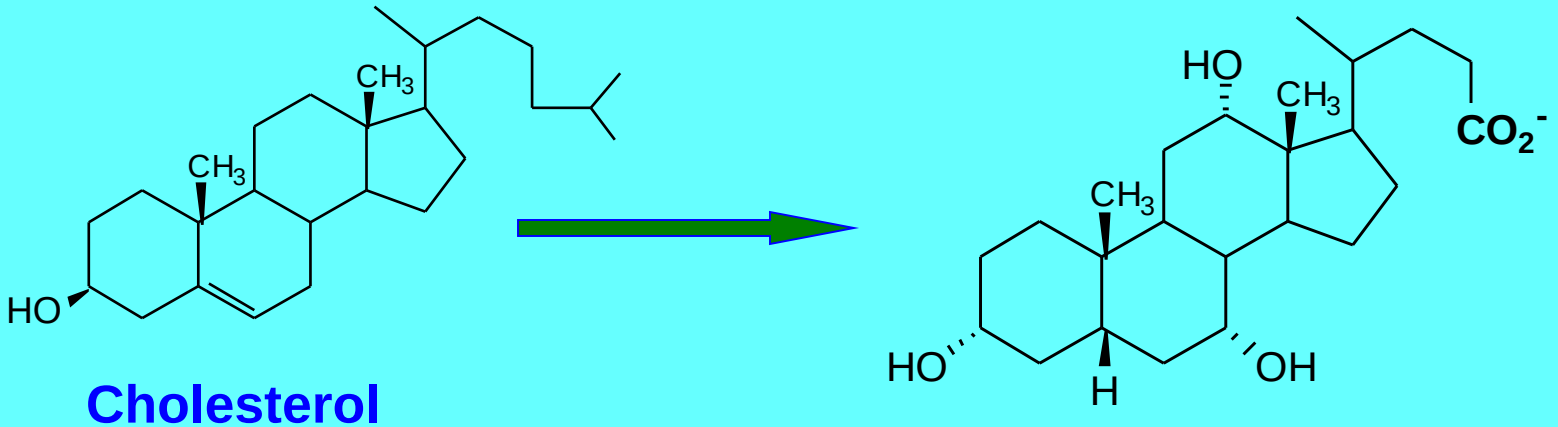




Cholesterol esters
(principal transport form in blood)

About hormonal regulation of ch. biosynthesis , insulin activate HMG – coA reductase (increase the rate of ch. synthesis) while glucagon inactivate HMG – coA reductase (decrease the rate of ch. synthesis) .

Transformations of Cholesterol: Bile Salts



Cholesterol **Cholic acid**

Bile acids are synthesized in the liver from cholesterol

They are secreted in the bile as sodium salts , conjungated with the amino acids glycine or taurine to form primary bile salt . They are converted by the becterial action in the intestinal lumen to the secondary bile salts . Deficiency of bile salts lead to impaired micelle formation and malabsorption of fat.The functions of bile salts(They are highly emulsifying agent,so they help in digestion a fat and absorption of vit. A,D,K,E)(Lower surface tension of H2O ,so break fat particles into smaller for action of lipase) (facilitate the action of pancreatic lipase by shifting of pH from 6.5 to 8 , thus providing optimal pH)(bile salts stimulate intestinal peristalsis) (bile salts form complex micelles with fatty acids , MAG. and DAG) .

Atherosclerosis

Deposition of lipids in the connective tissues of intima of arteries called atherosclerosis . It cause obstruction to blood flow , leading coronary heart disease , stroke , MI , etc .

Fatty liver

Excess accumulation triglycerides in liver causes fatty liver , liver cirrhosis and failure of liver function .Causes are :

1 . Elevated levels of free fatty acids in blood .
2 . Failure in the secretion of lipoproteins from liver.
3 . Chronic alchoholism .
4 . Prolonged treatment with antibiotics .
5 . Deficiency of lipotropic factors which help in the mobilization of fat from liver .

Gall stones (cholelitiasis)

A hard mass composed of bile pigments , ch. and calcium salts , that can form in the gallbladder and bile duct .

So they may lead to jaundice (obstruction) or damage to gallbladder and bile duct . Gallstones are more favourable to occurs in fatty women especially after 40 years . Absence of bile salts precipitate cholesterol as gallstones .

There are two types of stones according to composition :

1 . Cholesterol stones (Main constituent is cholesterol) .

2 . Bile pigment stones (Main constituent is bililrubin) .

Notes

1.High concentration of blood cholesterol and presence of becterial infection in the gallbladder , are the main causes of gallstones formation .

2 . LDL – ch is the bad ch. , it can contribute with other substance to the formationof plaque buildup in the arteries feeding the heart and brain , known as atherosclerosis .

3 . HDL – ch is a good ch. , that helps to remove ch. from the blood, preventing the fatty buildup and formation of plaque .

4 . If you want your HDL to be as high as possible (or your LDL to be low) :

-- Avoid foods high in saturated fat , dietary cholesterol and excess calories .

-- Exercising for at least 20 minutes three times a weak .

-- Stop smoking .

-- Maintain a healthy weight .

5 . Ketogenesis is refers to the formation of KBs while ketosis is refers to the production of KBs in excessive amount . ketonemia is refers to the accumulation of KBs in blood

while ketonuria is refers to the accumulation of KBs in urine .

6 . The liver actively produces KBs but it can not use them as fuel , because it can not reconvert aceto acetate to aceto acetyl coA . Therefore , aceto acetate and 3-HBA are released into the blood by the liver .

7 . KBs are used as fuel by tissues such as muscle and kidney . During starvation (after about 3 - 5 days of fasting) , the brain also oxidizes KBs .

(Mechanism of gallstones formation)

1 . Change in the relative composition of the major constituent of bile(exess cholesterol) .

2 . Presence of foreign substance (becterial infection in the gallbladder) .

3 . High conc. of blood cholesterol .

4 . Stimulation to secret bile as long as bile salts are absorbed .

5 .The stimulation of intestinal motility.