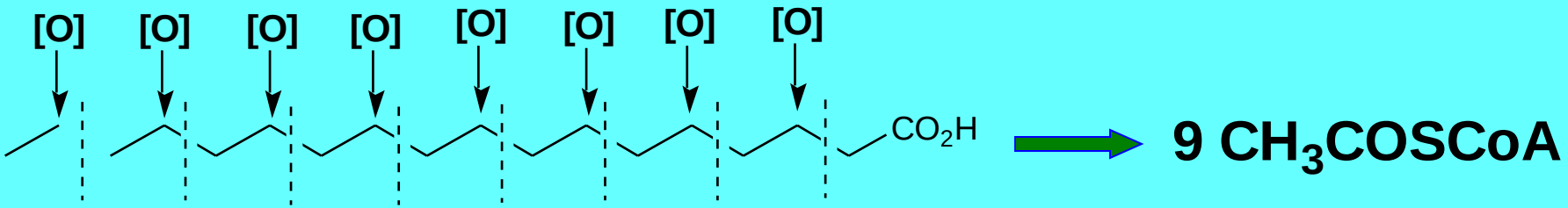
B – oxidation , cholesterol and KBs

prof.dr. zuhair maarouf hussein
biochemistry

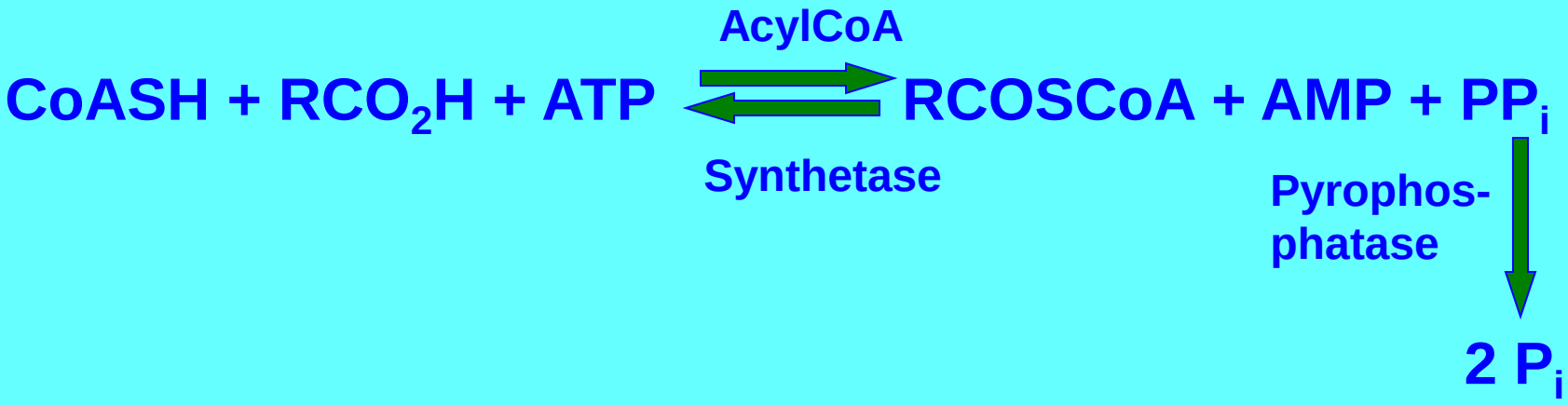
Beta Oxidation

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



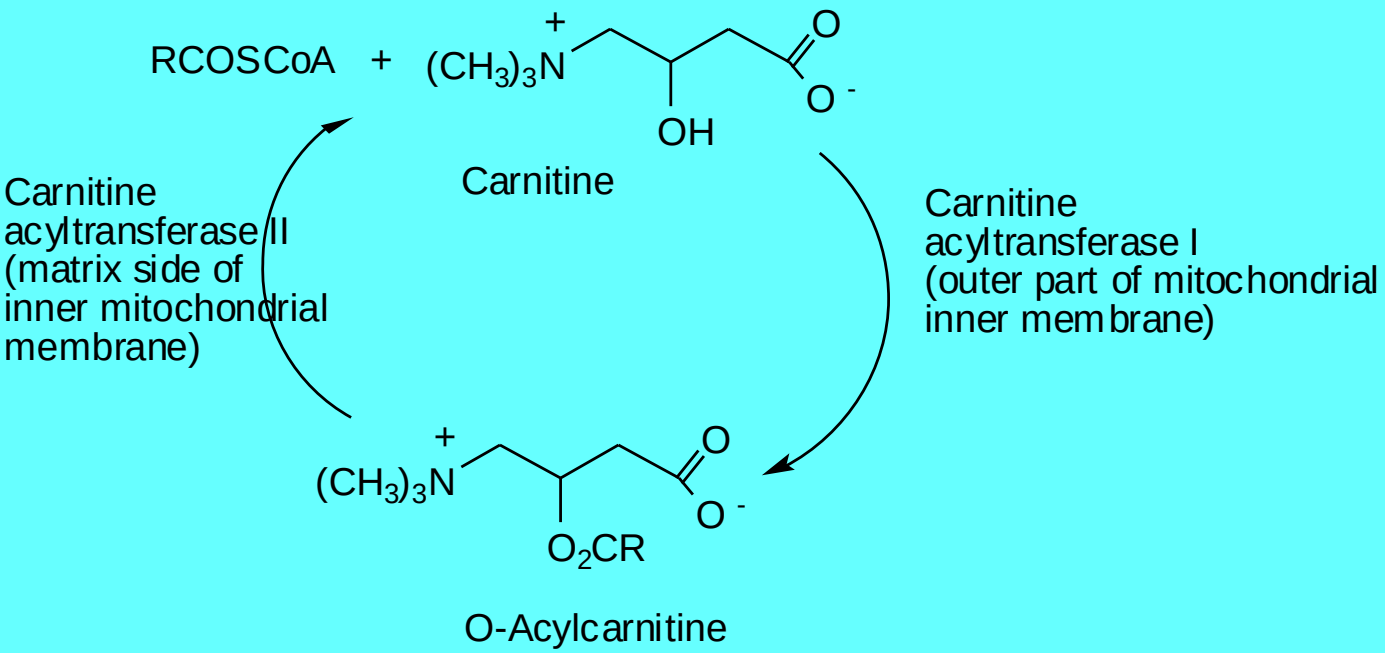
Fatty Acid Activation by Esterification with CoASH

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



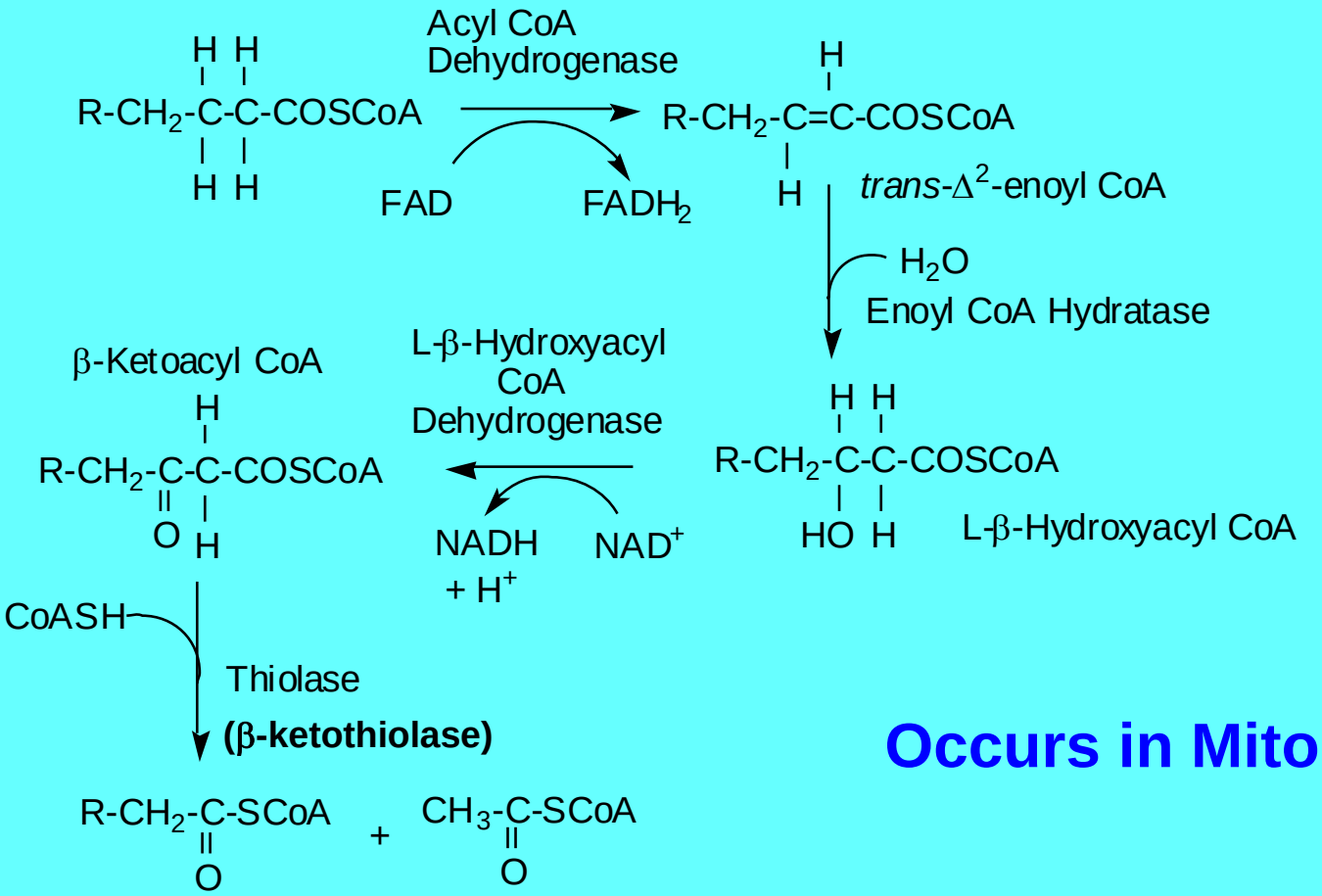
(The process of B- oxidation occurs in mitochondria)

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 .

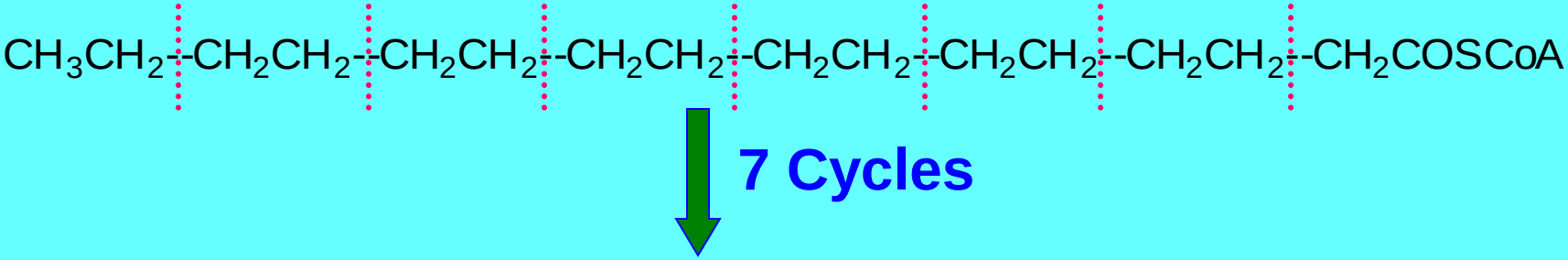
Beta Oxidation Reaction Sequence



Occurs in Mitochondria

Repeat Sequence

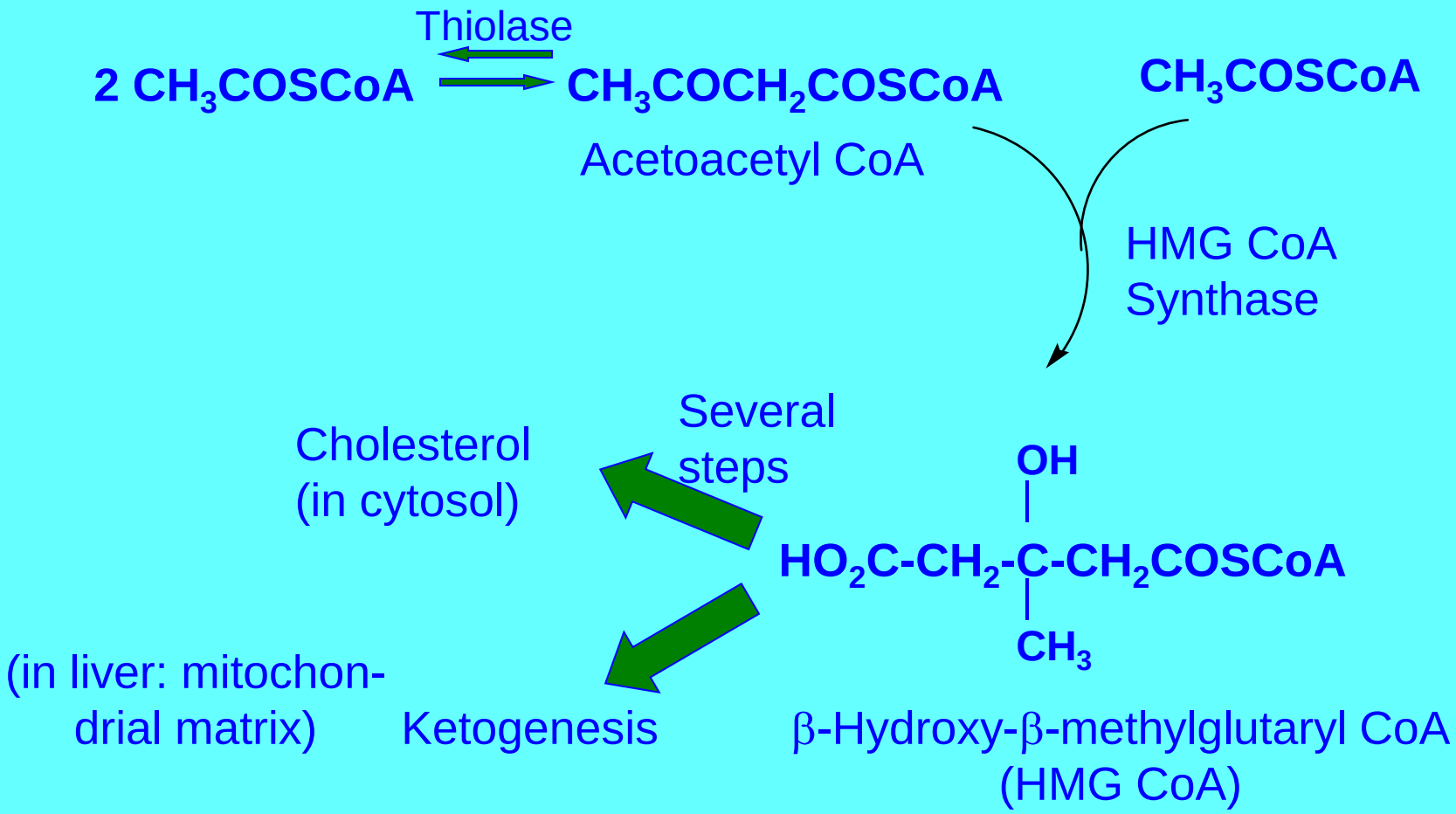
Complete Beta Oxidation of Palmitoyl CoA



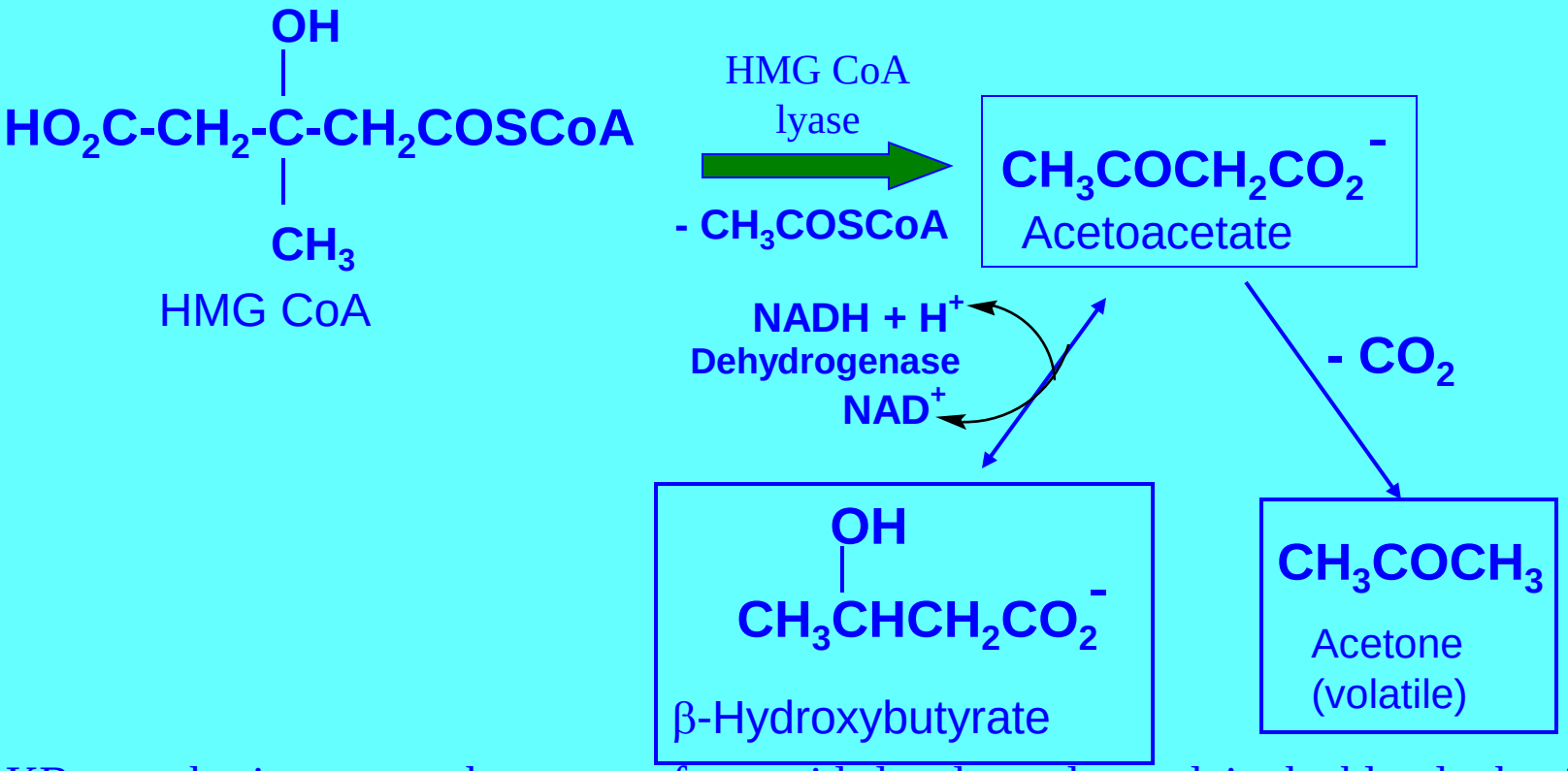
8 CH3COSCoA + 7 FADH2 + 7 NADH + 7 H+

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

Ketogenesis: Formation of Ketone Bodies



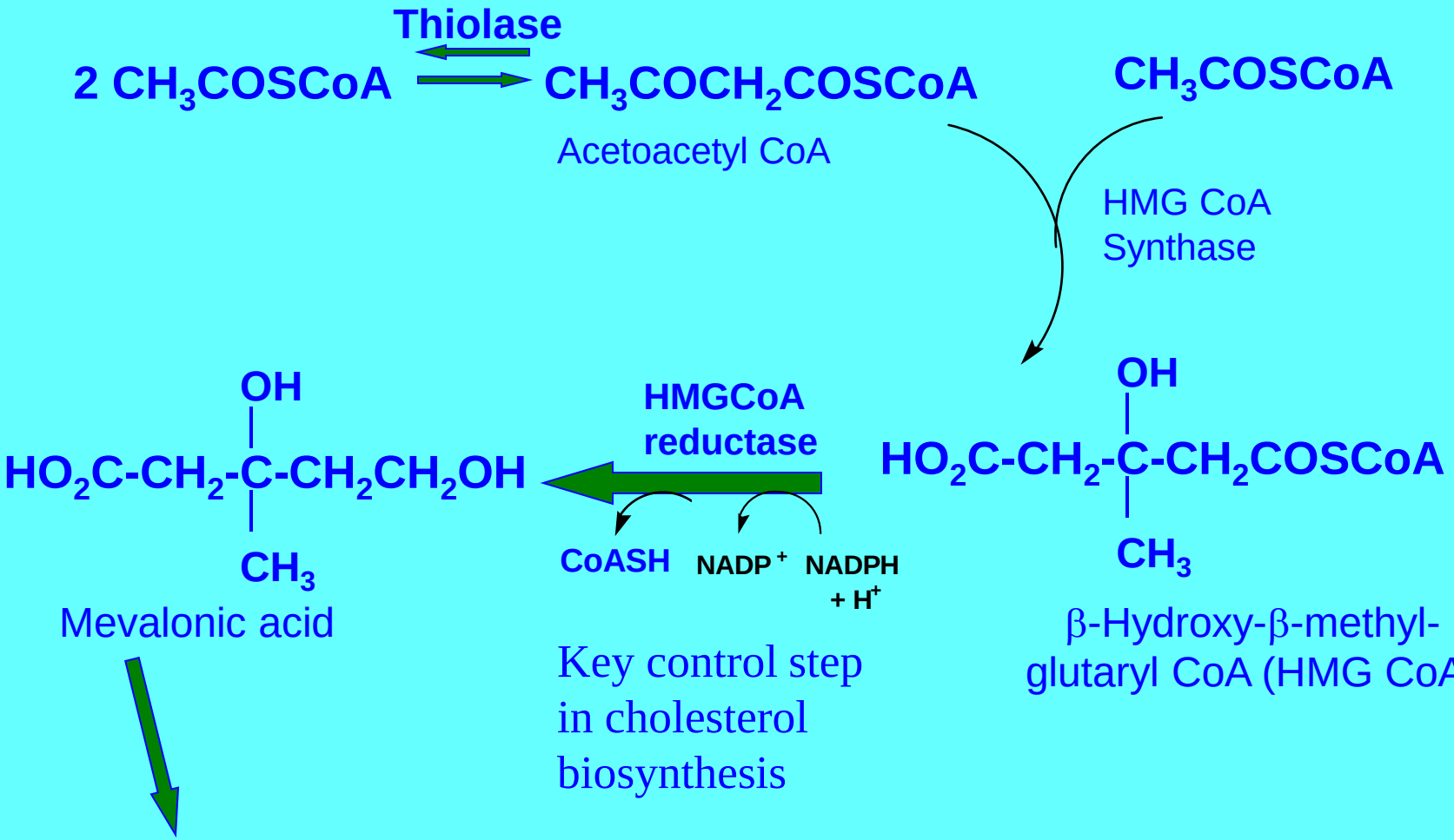
Ketogenesis : Formation of Ketone Bodies

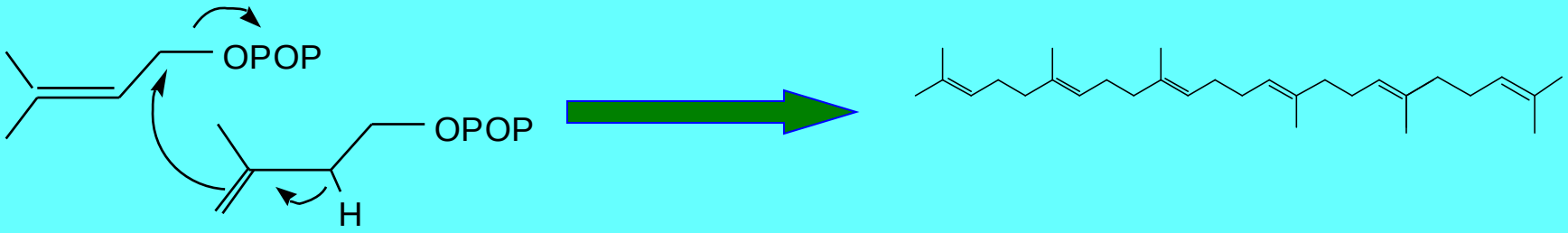


KBs synthesis occur when every fatty acids level are eleveted in the blood , that is during fasting or starvation or as a result of a high fat , low carbohydrate diet . (The enzymes for KBs synthesis are located mainly in liver mitochondria **)** [8]

Cholesterol Biosynthesis

Liver is primary site of cholesterol biosynthesis :





Isoprenes

Squalene

Notes

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

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

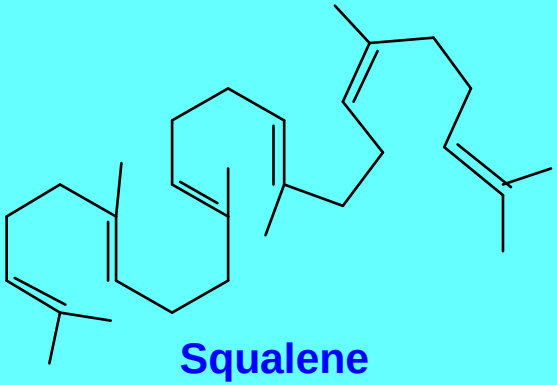
KBs ↑ → Acidity ↑ → pH ↓ → fatal

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

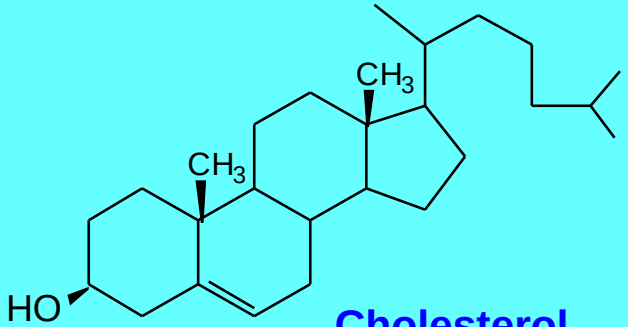
Treatment :

Insulin intake → no lipolysis → FFA ↓

Conversion of Squalene to Cholesterol

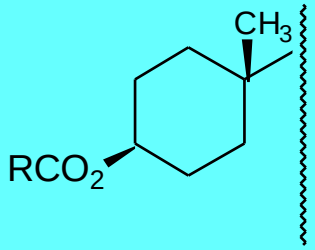


Squalene



Cholesterol

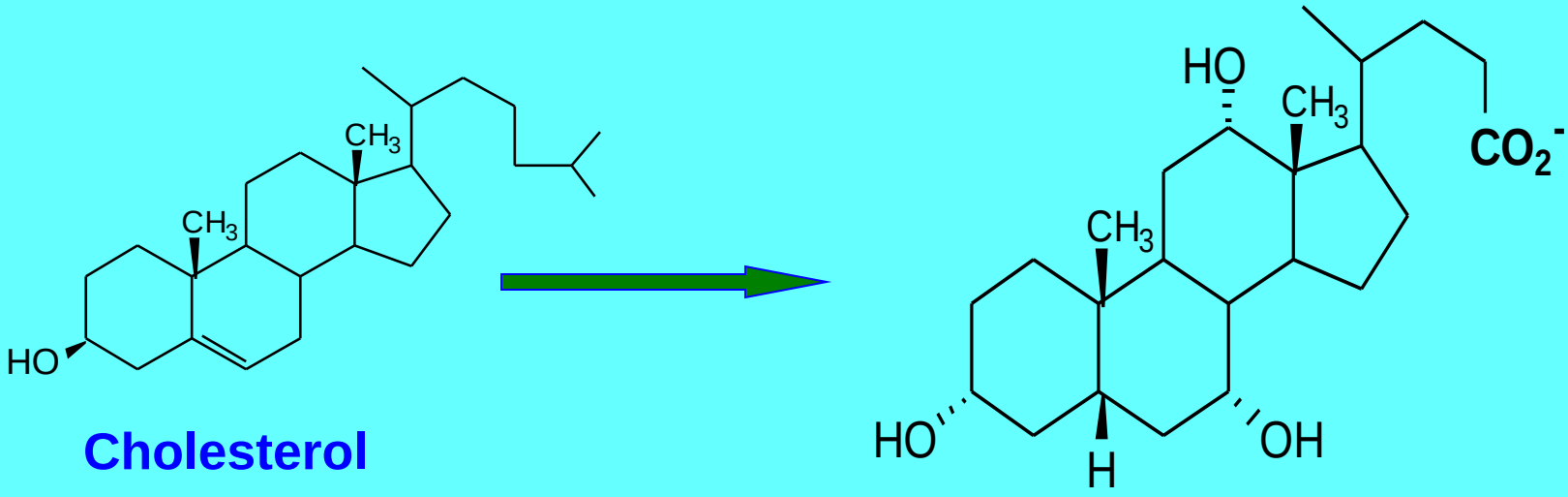
Cholesterol Acyl-CoA: acyltransferase



Cholesterol esters
(principal transport form in blood)

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

Transformations of Cholesterol: Bile Salts



Cholesterol

Cholic acid

Four bile acids are produced in man . Two of these , cholic acid and chenodeoxycholic acid are synthesized in the liver from cholesterol and called primary bile acids .They are secreted in the bile as sodium salts , conjugated with the amino acids glycine or taurine(primary bile salts) . These are converted by bacterial action with in the intestinal lumen to the secondary bile salts , deoxycholate and lithocholate respectively .

Deficiency of bile salts in the intestinal lumen leads to impaired micelle formation and malabsorption of fat .Such deficiency may be caused by cholestatic liver disease (failure of bile salts to reach the intestinal lumen) .

Gall stones

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 .

There aew three types of stones according to composition :

1 . Cholesterol stones (Main constituent is cholesterol) .

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

3 . Calcarous stones (Mix. Of two above + salts of Mg and Ca) .

Notes

1.High concentration of blood cholesterol and presence of bacterial 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 formation of 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 acetoacetate to acetoacetylcoA . Therefore , acetoacetate 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 .

8 . Wilson's disease may cause hepatitis and cirrhosis in young adults and is due to excessive accumulation of copper .

9 . Gilbert's disease is a relatively common condition characterized by plasma unconjugated bilirubin levels of between 1.2 and 5.0 mg / dl . This familial condition may be noticed at any age . It is often discovered when plasma bilirubin levels fail to return to normal after an attack of hepatitis .

(Mechanism of gallstones formation)

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

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

3 . High concentration of blood cholesterol .

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

5 .The stimulation of intestinal motility.