Biological Chemistry Department

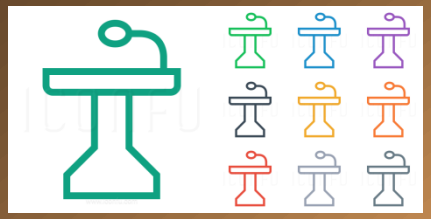
Biological Chemistry

LIPID

Metabolism

Speciality: Pharmacy for foreign students (Language of instructions – English)

Lecturer: ass. prof. Kravchenko G.B.



Lecture Plan

1. Intestinal Uptake of Lipids.
2. β-Oxidation.
3. Regulation of Fatty Acid Oxidation.
4. Ketogenesis. Regulations of Ketogenesis.
5. Lipid Synthesis.

<u>Individual work</u>

1. The Lipid Metabolism Pathology.

Information Resources

1. Biological Chemistry: Textbook / A.L. Zagayko, L.M. Voronina, G.B. Kravchenko, K.V. Strel`chenko. – Kharkiv: NUPh; Original, 2011. – 107-119 p.
2. Training Journal for Licensed Exam "KROK-1": Study Material in Biological Chemistry. – Kharkiv: NUPh, 2017. – 71-80 p.
3. Laboratory Manual on Biochemistry. Kharkiv: NUPh, 2017. - 50-52 p.
4. Lipolysis and the Oxidation of Fatty Acids: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/fatty-acid-oxidation.php.**
5. Cholesterol Metabolism: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/cholesterol.php.**
6. Bile Acid Synthesis and Utilization: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/bileacids.php.**

Fats Digestion

Although some of the fat in our diets is in the form of phospholipids, the major form of dietary lipids is fats. Most natural fats, such as those in vegetable oils, dairy products, and animal fat, are complex mixtures of simple and mixed fats. These contain a variety of fatty acids differing in chain length and degree of saturation. Vegetable oils such as corn and olive oil are composed largely of fats with unsaturated fatty acids, and thus are liquids at room temperature. Fats containing only saturated fatty acids, such as tristearin, the major component of beef fat, are white, greasy solids at room temperature.

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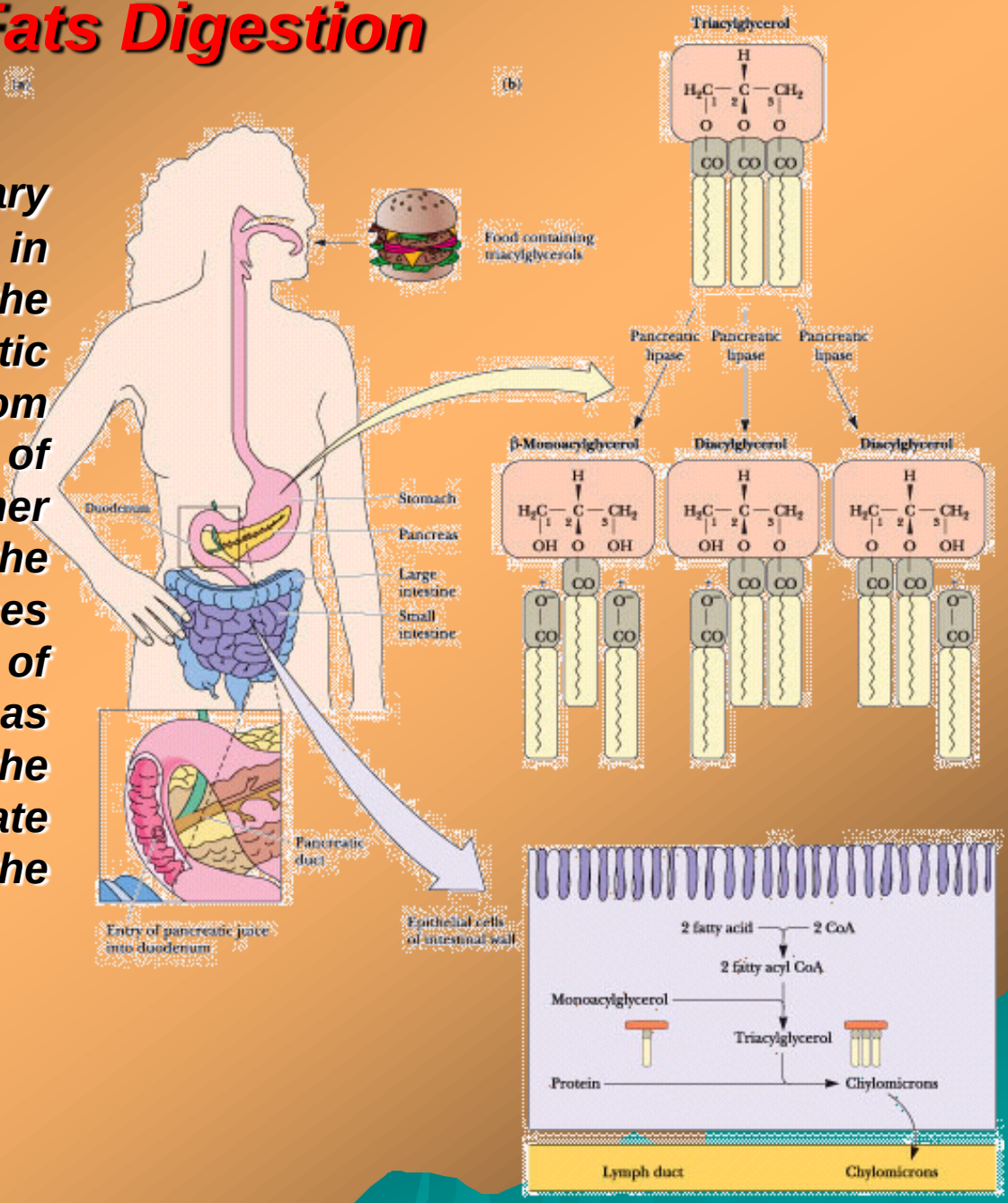
Fats Digestion

Degradation of dietary fatty acids occurs primarily in the duodenum by the pancreatic lipase. Pancreatic lipase cleaves fatty acids from the C-1 and C-3 positions of triacylglycerols, and other lipases and esterases attack the C-2 position. These processes depend upon the presence of bile salts. These agents act as detergents to emulsify the triacylglycerols and facilitate the hydrolytic activity of the lipases and esterases.



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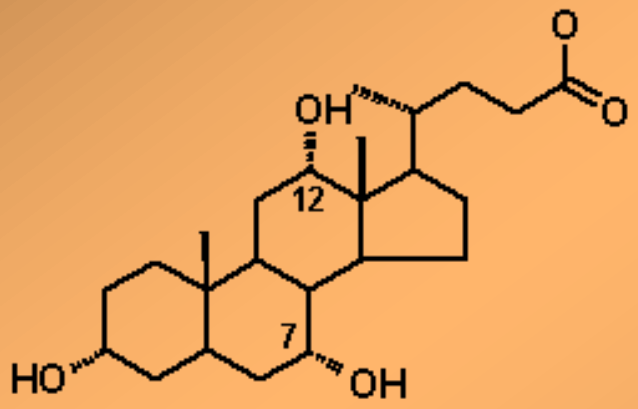
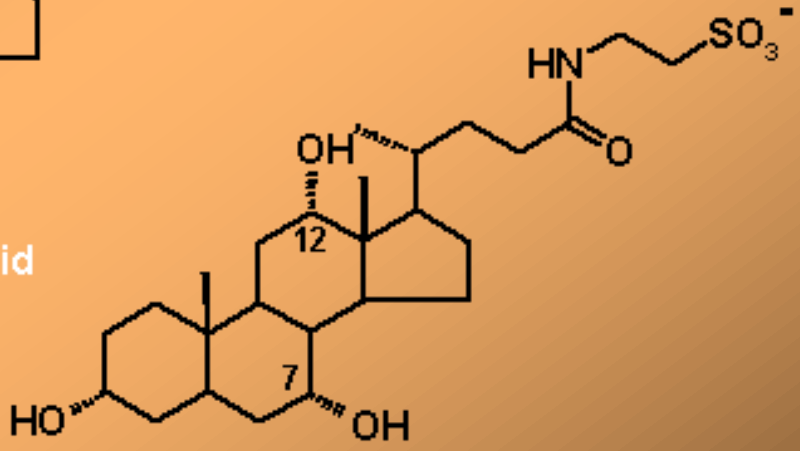
Bile Salts

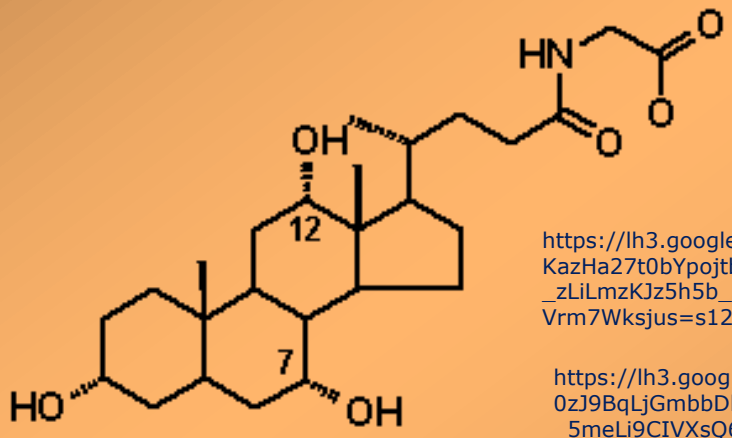
Bile salts synthesized from cholesterol in the liver, stored in gallbladder - released into small intestine and act as detergent, creating micelles of bile salts and triacylglycerols.



Cholic acid



Taurocholic acid



Glycocholic acid

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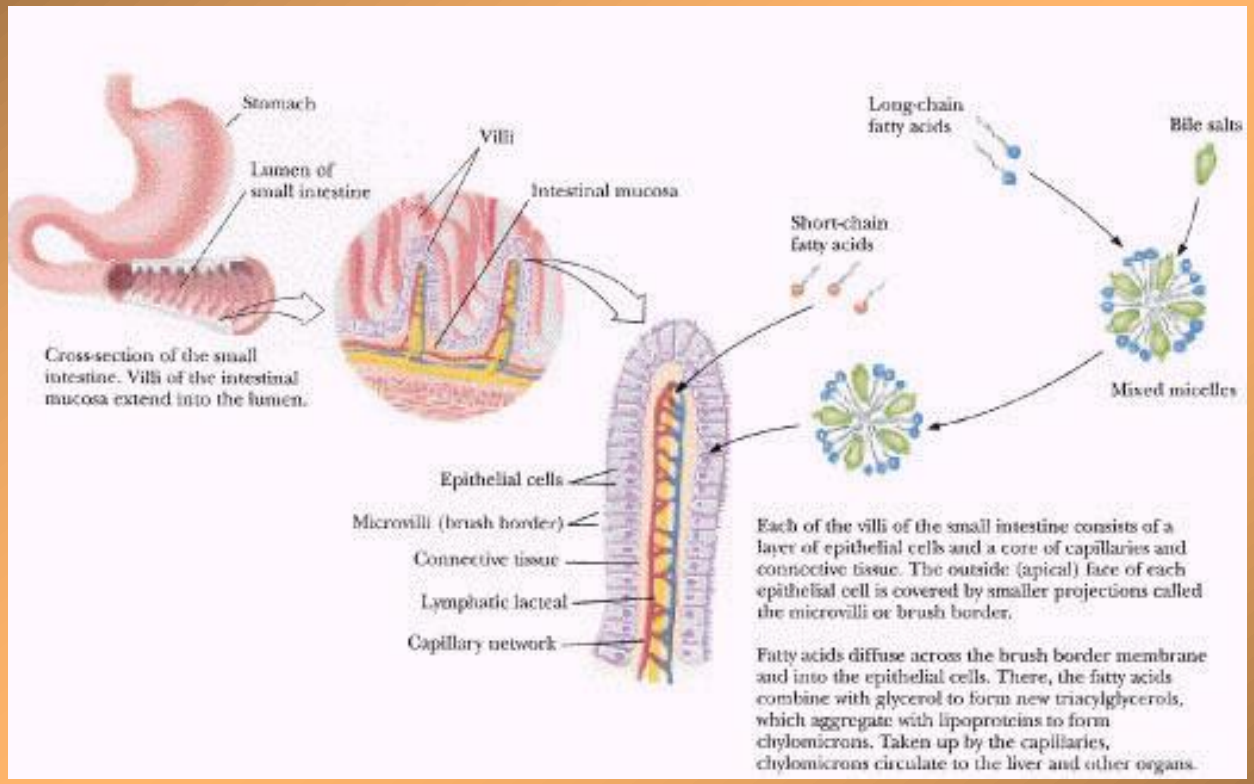
The fatty acids pass into the epithelial cells, where they are condensed with glycerol to form new triacylglycerols. These triacylglycerols aggregate with lipoproteins to form particles called chylomicrons, which are then transported into limphatic system and on to the bloodstream, where they circulate to the liver, lungs, heart, muscles, and other organs.



At these sites, the triacylglycerols are hydrolyzed to release fatty acids, which can then be oxidized in a highly exergonic metabolic pathway known as β-oxidation.

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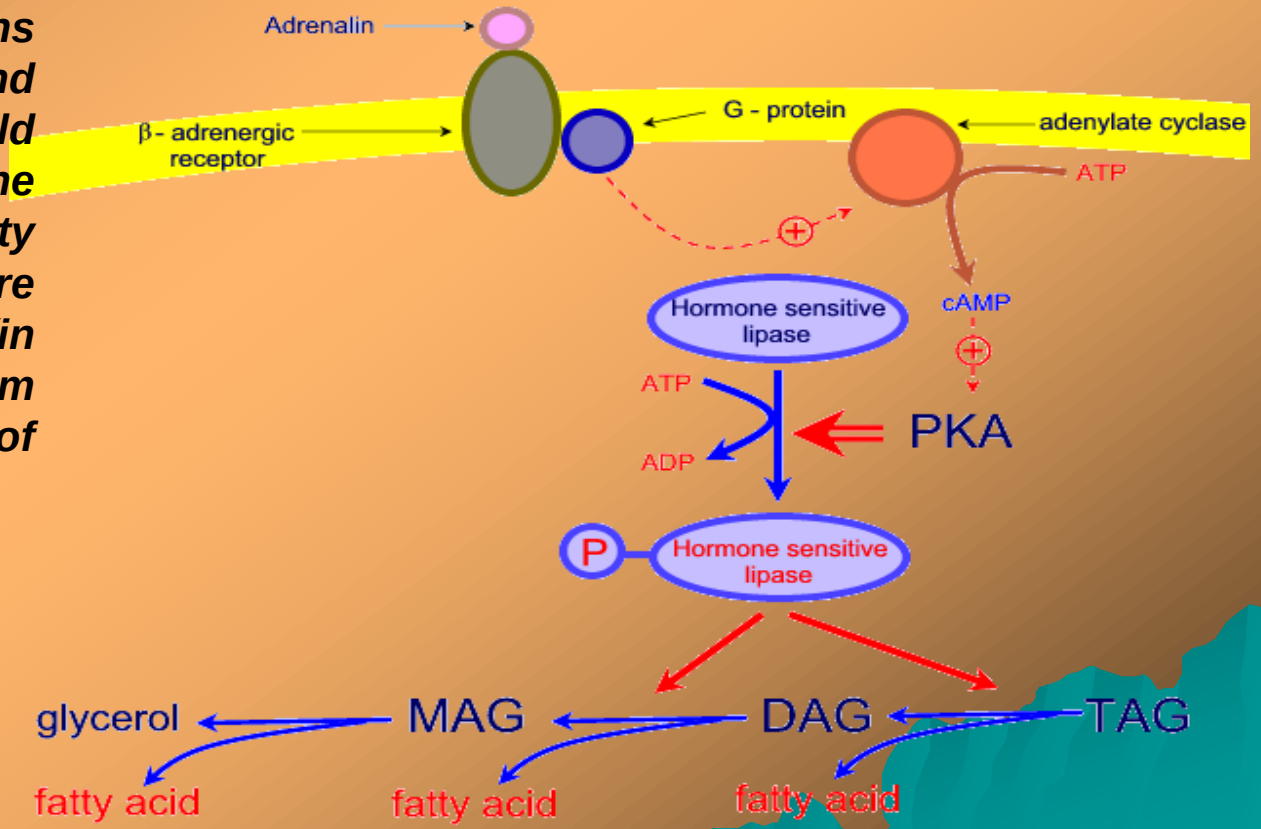
Lipid Mobilization from Cellular Stores

The primary sources of fatty acids for β-oxidation are dietary and mobilization from cellular stores. Fatty acids are mobilized from adipocytes in response to hormone messengers such as adrenaline, glucagon, and adrenocorticotropic hormone. These signal molecules bind to receptors on the plasma membrane of adipose cells and lead to the activation of adenylylate cyclase, which forms cyclic AMP from ATP. In adipose cells, cAMP activates protein kinase A, which phosphorylates and activates a triacylglycerol lipase (also termed hormone-sensitive lipase) that hydrolyzes a fatty acid from C-1 or C-3 of triacylglycerols.

Subsequent actions of diacylglycerol lipase and monoacylglycerol lipase yield fatty acids and glycerol. The cell then releases the fatty acids into the blood, where they are carried (in complexes with serum albumin) to sites of utilization.



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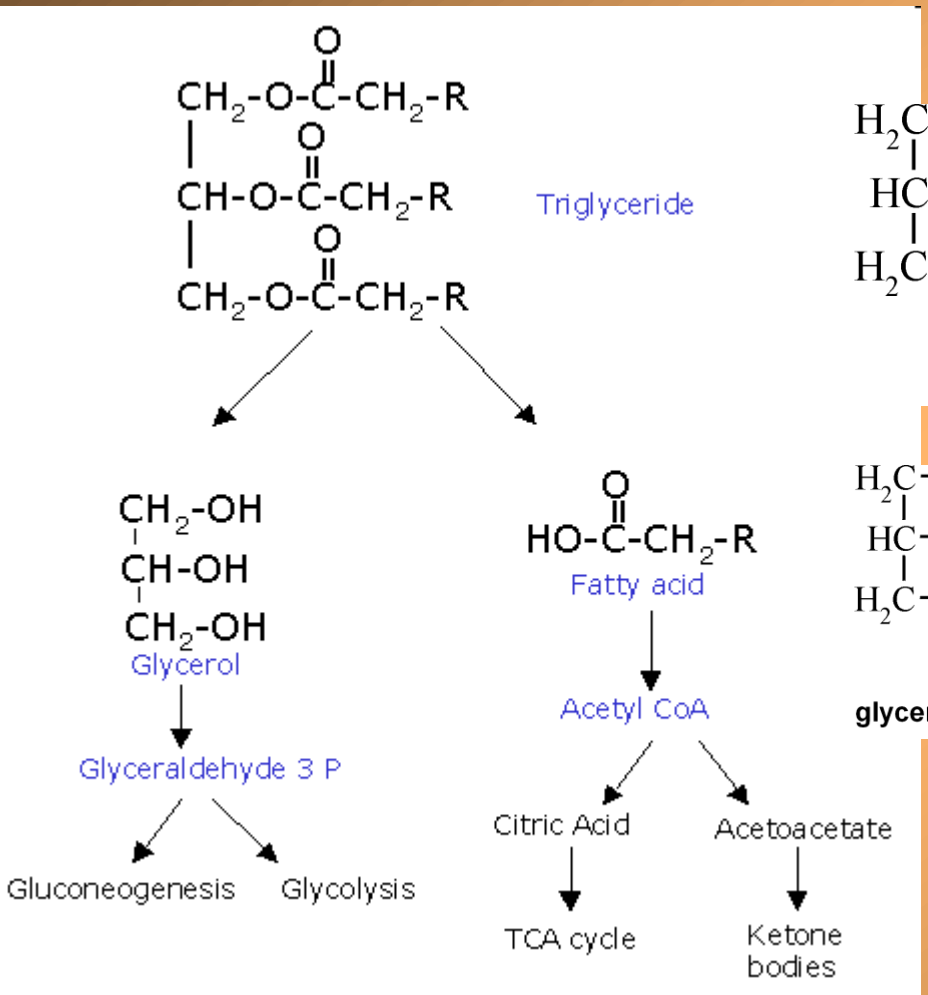
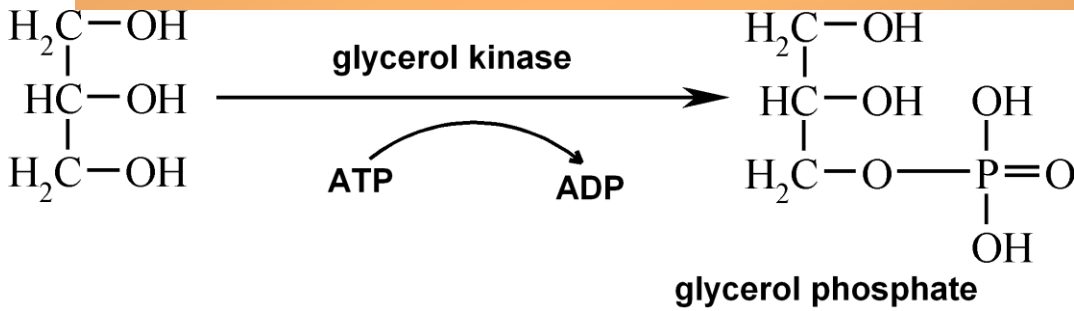
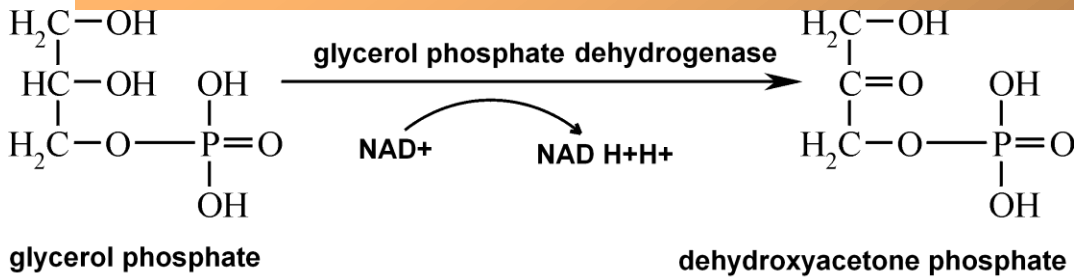
The glycerol is then converted to glyceraldehyde 3-P which is then processed by glycolysis or gluconeogenesis. The fatty acids may be oxidized to acetyl CoA.







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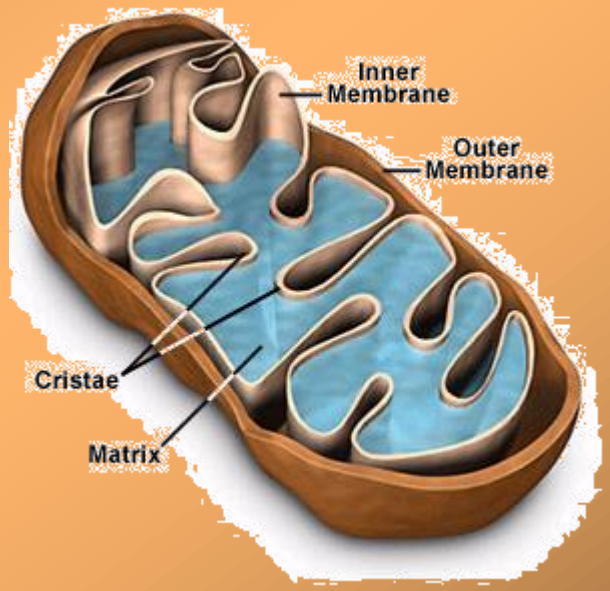
β-Oxidation

β-Oxidation – oxidation at the β-carbon, followed by cleavage of the C-C bond. The 2-carbon unit released in this process is acetyl-CoA. The oxidation of long-chain fatty acids to acetyl-CoA is a central energy-yielding pathway in animals. The β-oxidation takes place in the mitochondria. The electrons removed during fatty acid oxidation pass through the mitochondrial respiratory chain, driving ATP synthesis, and the acetyl-CoA produced from the fatty acids may be completely oxidized to CO2 via the citric acid cycle, resulting in further energy conservation.



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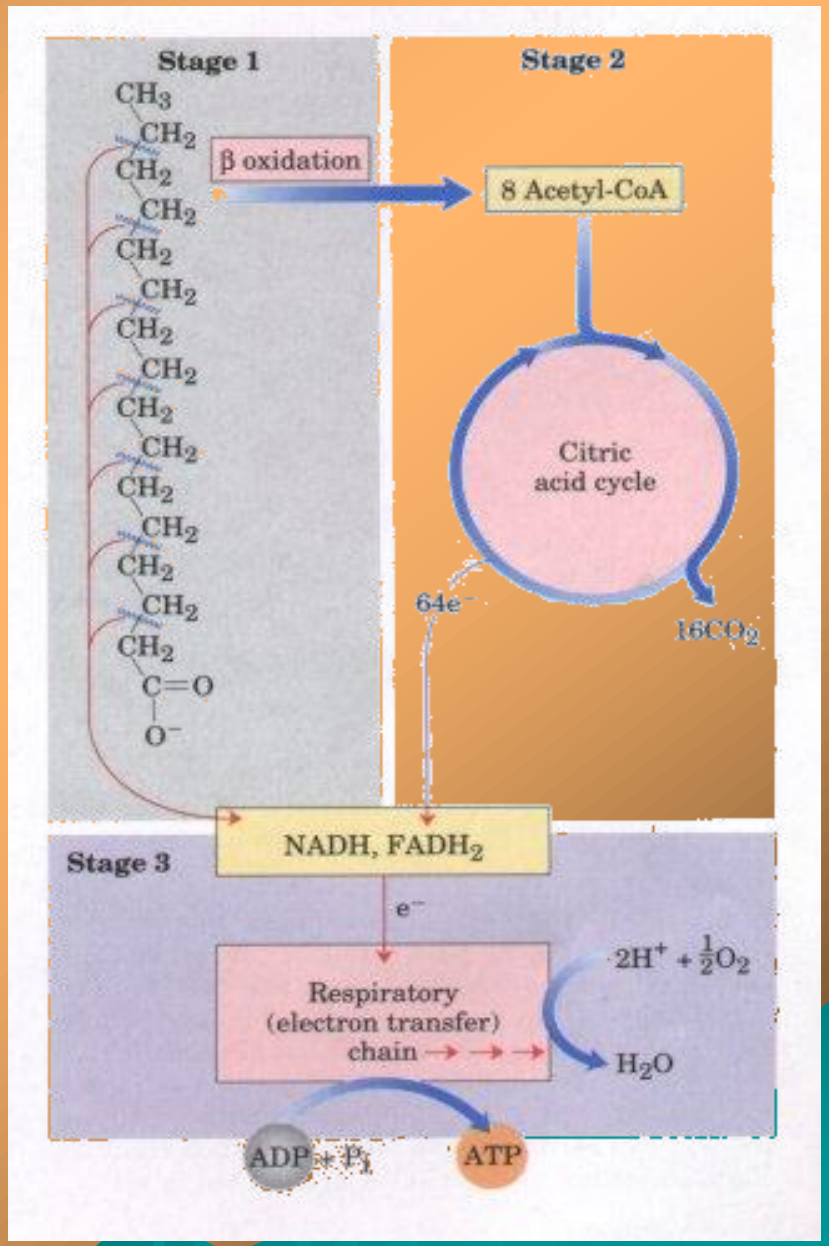
Stages of Fatty Acid Oxidation

Stage 1: ***A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA (β-oxidation).***

Stage 2: ***The acetyl residues are oxidized to CO_2 via the citric acid cycle.***

Stage 3: ***Electrons derived from the oxidations of stages 1 and 2 are passed to O_2 via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation.***



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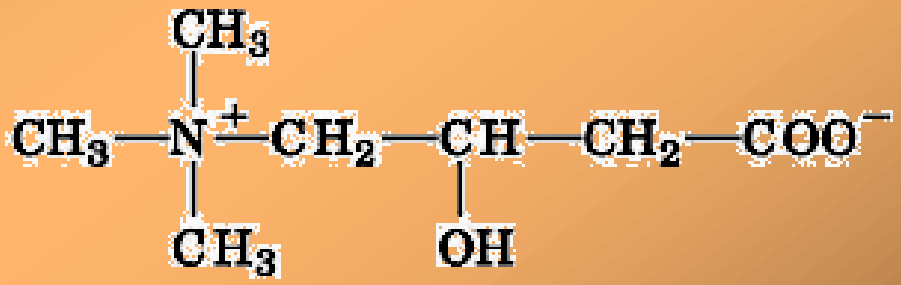
Activation and Transfer of Fatty Acid

Fatty acids must be activated in the cytoplasm before being oxidized in the mitochondria. Activation is catalyzed by acyl-CoA synthetase. The net result of this activation process is the consumption of 2 molar equivalents of ATP.

Fatty acid + ATP + CoA -------> Acyl-CoA + PP_i + AMP

The next step of β-oxidation is the transport fatty acids into mitochondria in complex with carnitine.



Carnitine

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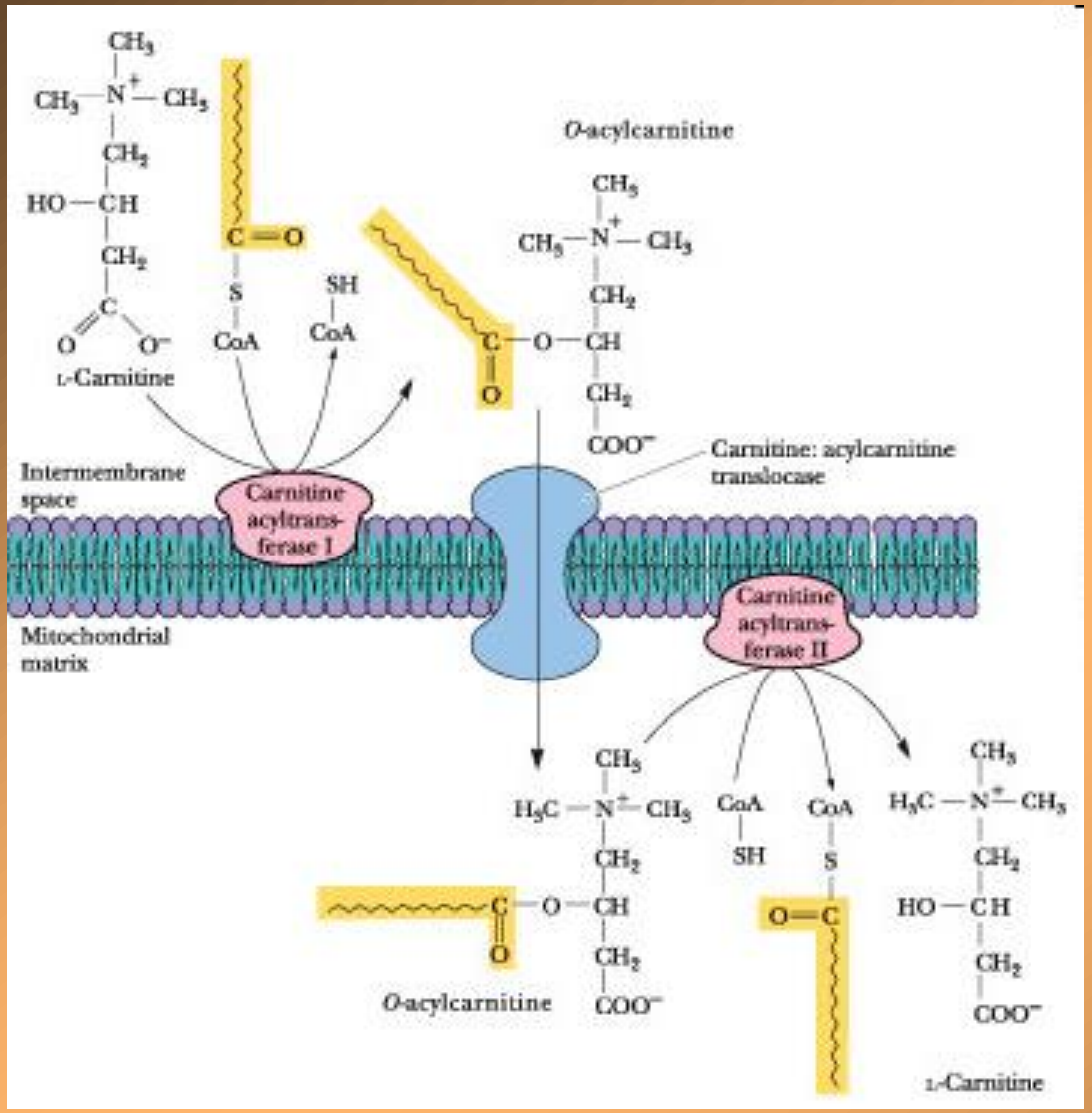

The formation of acylcarnitines and their transport across the inner mitochondrial membrane. The process involves the coordinated actions of carnitine acyltransferases on both sides of the membrane and of a translocase that shuttles O-acylcarnitines across the membrane.

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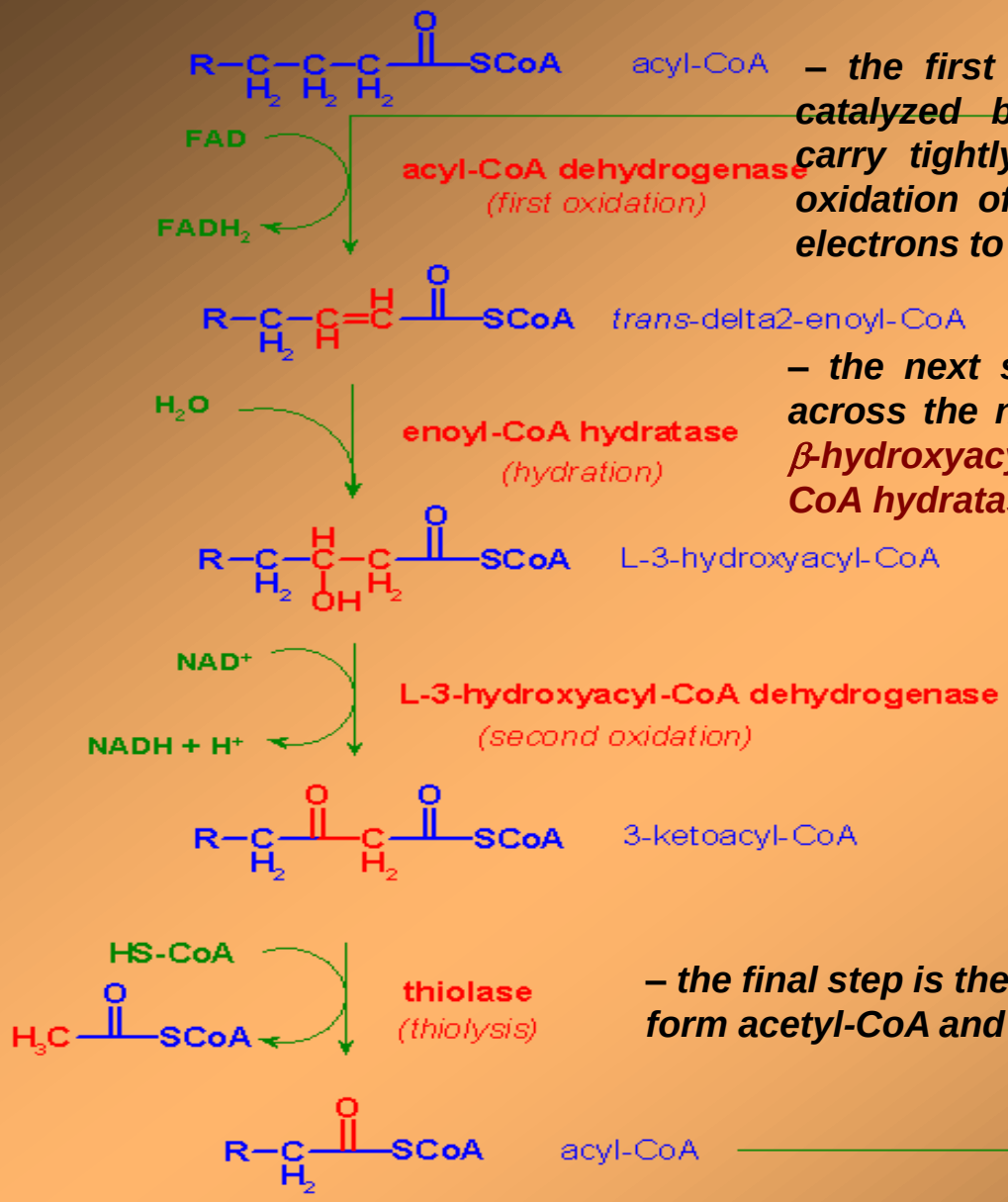
Reaction of β-Oxidation



– the first reaction, the oxidation of the C-C bond, is catalyzed by acyl-CoA dehydrogenases. This enzyme carry tightly bound FAD, which is reduced during the oxidation of the fatty acid to $FADH_2$ which transfers its electrons to an electron transfer chain.

– the next step is the addition of the elements of H_2O across the new double bond, yielding the corresponding β-hydroxyacyl-CoA. The reaction is catalyzed by enoyl-CoA hydratase.

– the third reaction is the oxidation of the hydroxyl group at the β-position to produce β-ketoacyl-CoA. This reaction is catalyzed by hydroxyacyl-CoA-dehydrogenase, an enzyme that requires NAD+ as a coenzyme. NADH produced in this reaction is oxidised in the electron transfer chain.

– the final step is the cleavage of the β-ketoacyl-CoA by thiolase to form acetyl-CoA and and acyl-CoA shorted by 2 carbon atoms. .

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Each round of β-oxidation produces one mole of NADH(H+), one mole of FADH2 and one mole of acetyl-CoA.

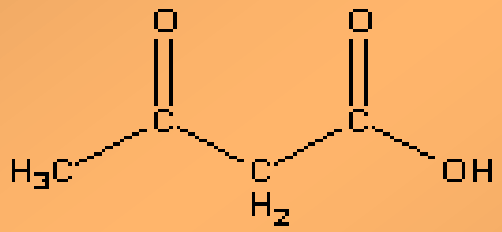
If the acetyl-CoA is directed entirely to the citric acid cycle in mitochondria, it can eventually generate approximately 12 high-energy phosphate bonds—that is, 12 molecules of ATP synthesised from ADP.

Including the ATP formed from $FADH_2$ and NADH, complete β-oxidation of a molecule of palmitoyl-CoA in mitochondria yields 108 molecules of ATP.

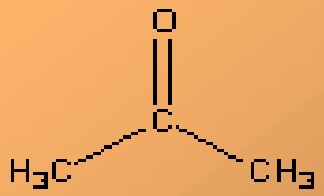
Ketone Bodies

Most of the acetyl-CoA produced by the oxidation of fatty acids in liver mitochondria undergoes further oxidation in the TCA cycle. However, some of this acetyl-CoA is converted to three important metabolites: acetone, acetoacetate, and b-hydroxybutyrate. The process is known as ketogenesis, and these three metabolites are traditionally known as ketone bodies.

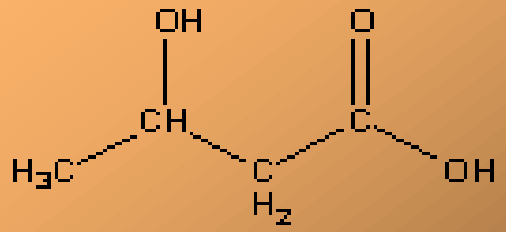
These three metabolites are synthesised primarily in the liver but are important sources of fuel and energy for many peripheral tissues, including brain, heart, and skeletal muscle. The brain, for example, normally uses glucose as its source of metabolic energy. However, during periods of starvation, ketone bodies may be the major energy source for the brain. Acetoacetate and 3-hydroxybutyrate are the preferred and normal substrates for kidney cortex and for heart muscle.



Acetoacetate



Acetone



B-hydroxybutyrate

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REGULATION OF KETOGENESIS

The fate of the products of fatty acid metabolism is determined by an individual's physiological status. Ketogenesis takes place primarily in the liver and may by affected by several factors:

1. Control in the release of free fatty acids from adipose tissue directly affects the level of ketogenesis in the liver. This is substrate-level regulation.

2. Once fats enter the liver, they have two distinct fates. They may be activated to acyl-CoAs and oxidized, or esterified to glycerol in the production of TAG. If the liver has sufficient supplies of glycerol-3-phosphate, most of the fats will be turned to the production of TAG.

3. The generation of acetyl-CoA by oxidation of fats can be completely oxidized in the TCA cycle. Therefore, if the demand for ATP is high the fate of acetyl-CoA is likely to be further oxidation to CO2.

In type I diabetes, increased gluconeogenesis consumes most of the available oxaloacetate, but breakdown of fat produces large amounts of acetyl-CoA. This increased acetyl-CoA would normally be directed into the TCA cycle, but, with oxaloacetate in short supply, it is used instead for production of unusually large amounts of ketone bodies. Acetone can often be detected on the breath of type I diabetics, an indication of high plasma levels of ketone bodies (diabetic ketoacidosis).

THE LIPID METABOLISM PATHOLOGY

Heperlipidemias

In the hyperlipidemias, the blood level of cholesterol or triacylglycerols, or both, are elevated resulting from overproduction of lipoproteins or defects in various stages of their degradation. In familiar hypercholesterolemia, cellular receptors for LDL are defective. Therefore, LDL cannot be taken into the cells. The consequent increase of blood LDL is associated with coronary artery disease. Treatment may involve the diets low in saturated fat and cholesterol, and inhibitors or cholesterol synthesis.

Fatty liver related to alcoholism.

Oxidation of ingested alcohol produces acetaldehyde, acetate, and NADH. In same conditions the citric acids cycle and oxidation of fatty acids are inhibited and fatty acid synthesis is stimulated. The net result is that fatty acids react with glycerol 3-phosphate to form triacylglycerols, which accumulate in the liver. Impairment of protein synthesis due to chronic liver dysfunction results in an inability to produce and secrete VLDL and adds to the hepatic overload of fats.

Atherosclerosis

Atherosclerosis involves the formation of lipid-rich plaques in the intima of arteries. The plaques begin as fatty streaks containing foam cells, which initially are macrophages filled with lipids, particularly cholesterol esters. These early lesions develop into fibrous plaques that may occlude an artery and cause a myocardial infarct or a cerebral infarct. Formation of these plagues is often associated with abnormalities in plasma lipoprotein metabolism. In contrast to the other lipoproteins, HDL may have a protective effect.

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Obesity

Obesity is a term used to describe body weight that is much greater than what is considered healthy. There are many ways to determine if a person is obese, but experts believe that a person's body mass index (BMI) is the most accurate measurement of body fat for children and adults. Adults with a BMI greater than 30 are considered obese. Adults with a BMI between 25 and 29.9 are considered overweight.

Consuming more calories than you burn leads to being overweight and, eventually, obesity. The body stores unused calories as fat. Work with your health care provider to determine how many calories you need to consume each day to stay healthy.

Obesity increases a person's risk of illness and death due to diabetes, stroke, heart disease, high blood pressure, high cholesterol, and kidney and gallbladder disease. Obesity may increase the risk for some types of cancer. Genetic factors play some part in the development of obesity - children of obese parents are 10 times more likely to be obese than children with parents of normal weight.

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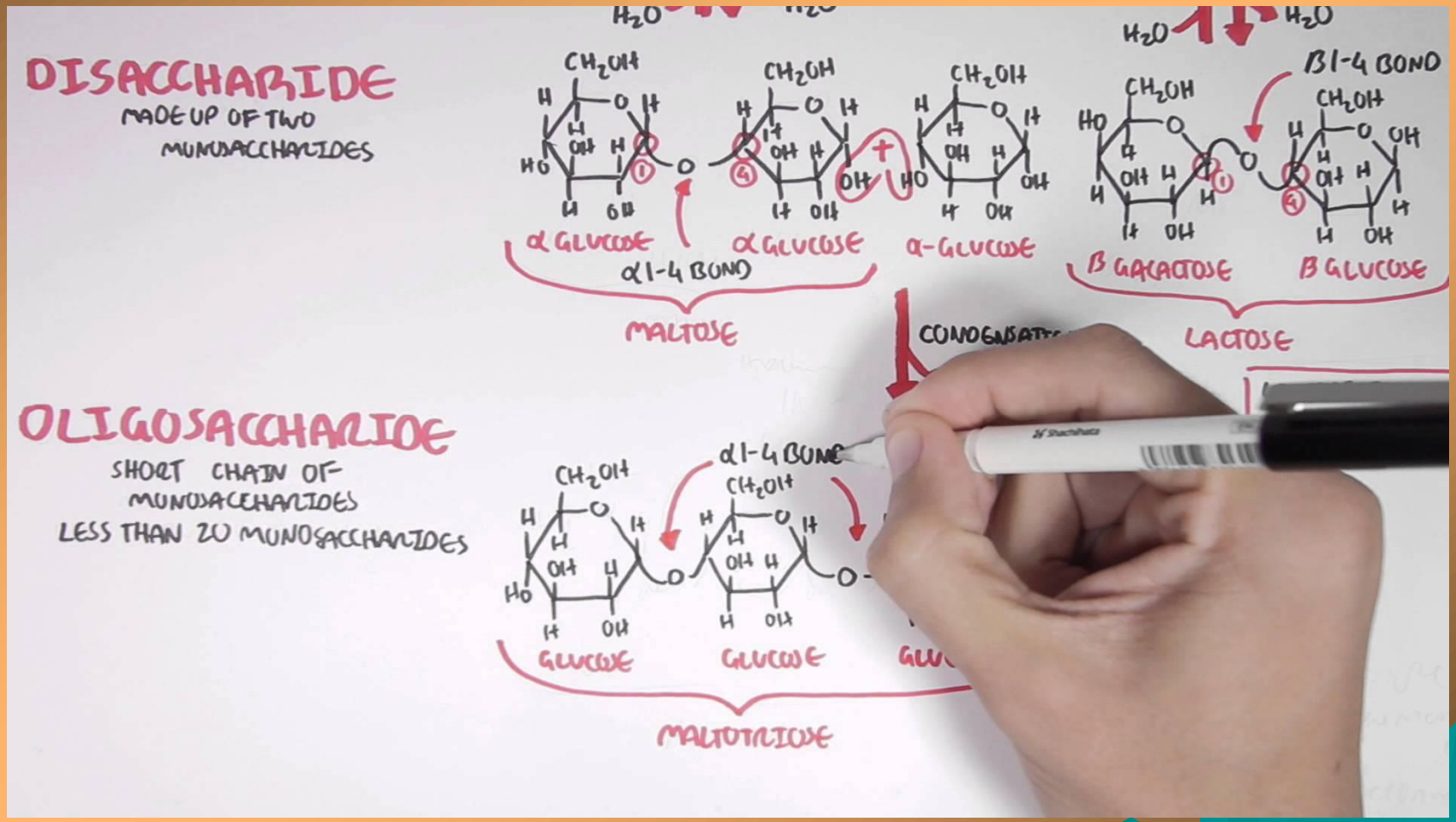
Conclusions

1. Degradation of dietary fats occur primary in the duodenum by the pancreatic lipases. These processes depend upon the presence of bile acids.
2. β-Oxidation – oxidation of the β-carbon, followed by cleavage of the C-C bond. The 2-carbon unit released in this process is acetyl-CoA.
3. In liver some of the acetyl-CoA is converted to ketone bodies; acetone, acetoacetate, and 3-hydroxybutirate.
4. Long-chain fatty acids are synthesized from acetyl-CoA by fatty acid synthase – a cytosolic complex of six enzymes plus acyl carrier protein (ACP), which contains phosphopantetiheine as its prostetic group .

Do you have any questions?

Thank you for your attention!



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