BIOCHEMISTRY **1st Year, 2nd Semester**

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Lecture 7

III. LIPID METABOLISM

Elongation of fatty acids

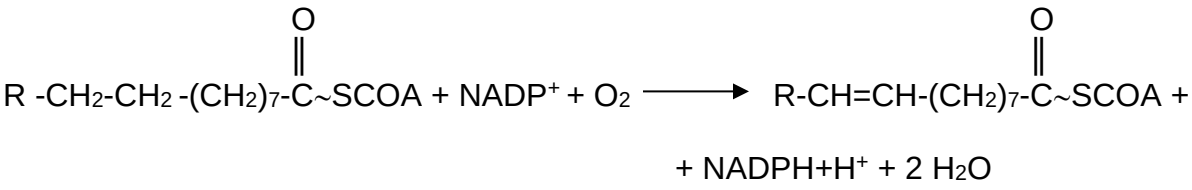
It is the process by which the existing endogenous and exogenous fatty acids are altered by their elongation with a variable number of carbon atoms. The process occurs within the endoplasmic reticulum and within mitochondria and consists in successively adding fragments of two carbon atoms.

Within the **endoplasmic reticulum,** the preferred substrate is palmitoyl ~CoA, the two carbon atoms units are provided by malonyl ~CoA, and the reactions accomplished are such as those catalized by fatty acid–sinthase.

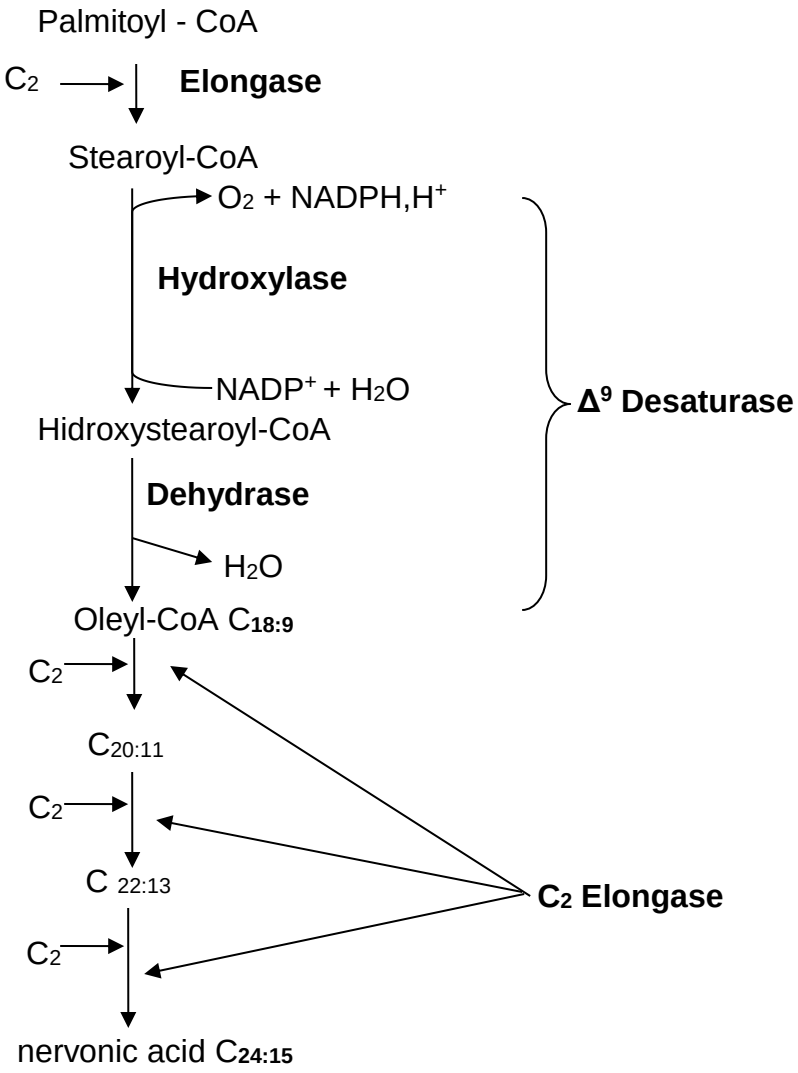
Within **mitochondria**, are elongated especially the acids with a chain smaller than 16 carbon atoms, and the units of two carbon atoms are provided by acetyl ~CoA. The enzymatic system used consists in reversing the β-oxidation pathway except for the last stage, when the action acyl–CoA-dehydrogenase is replaced by that of a NADPH dependent β-enoyl–reductase.

Biosynthesis of the unsaturated fatty acids

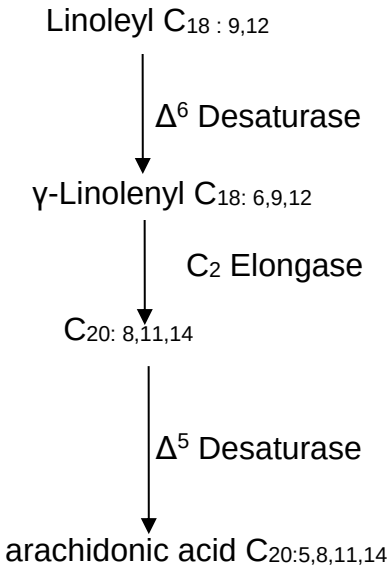
The process takes place within the microsomes from the liver and other organs, where the desaturase system is attached to the membrane; this being a multienzymatic complex with a catalytic activity of monooxygenase, hydroxylase and dehydratase.



The first double bond is inserted at position 9 of the palmitic and stearic acids, these turning into palmitoleic and oleic acid, respectively. The oleic acid may be alongated with 6 carbon atoms, turning into nervonic acid $C_{24:15}$.



The polyunsaturated fatty acids linoleic $C_{18:9,12}$, linolenic $C_{18:6,9,12}$ and arachidonic $C_{20:5,8,11,14}$ also referred to as essential fatty acids are obtained either from food or from the linoleic acid (this also comes from food supply).

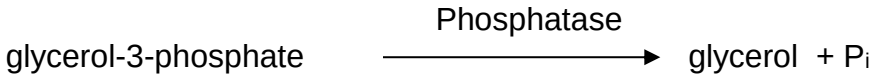


Essential fatty acids deficit occurs first of all due to the insufficient food supply, in the case of patients fed by perfusions for a long time, in case of malabsorption syndrome, and is characterized by dermatitis and longer time for wound healing.

III.4. Glycerol metabolism

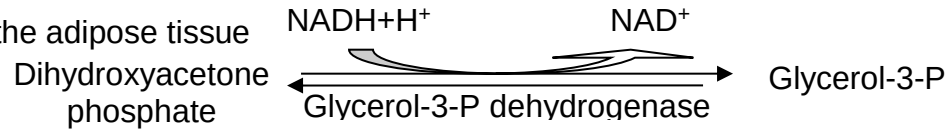
The glycerol sources within the body are:

- triacylglycerols catabolism
- glucose catabolism forming dihydroxyacetone phosphate
- hydrolysis of glycerol-3-phosphate

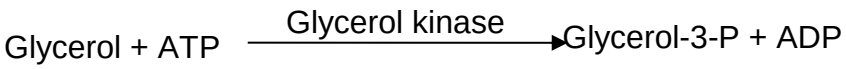


As any precursor of a metabolic pathway, glycerol is first turned into a metabolic active form of glycerol–3–phosphate. This can be done in several ways:

a) In the adipose tissue



b) In the liver and intestine



c) In the cells of the intestinal mucosa 2–monoacylglycerol is the corresponding active form

Within the adipose tissue, glycerol-kinase is not active, so that the only source of glycerol-3-P is dihydroxyacetone phosphate. This explains the dependency of the adipose tissue on the glucose metabolism and on the action of insulin. As active form of glycerol-3-P, the glycerol is used for lipids synthesis (triglycerides, phospholipids, etc), in gluconeogenesis or glycolysis.

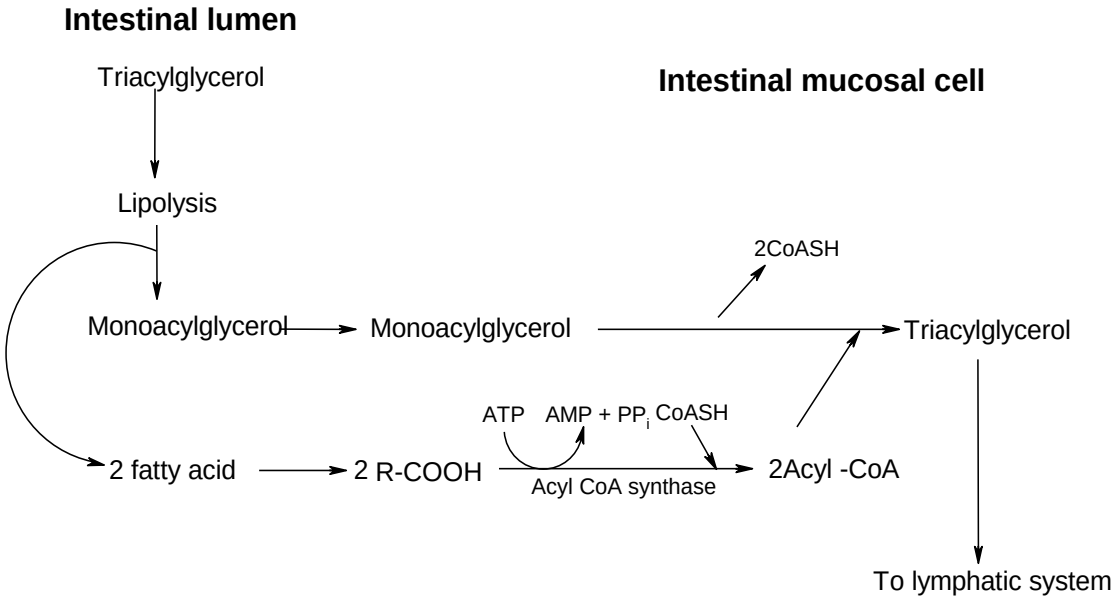
III.5. Triglycerides metabolism

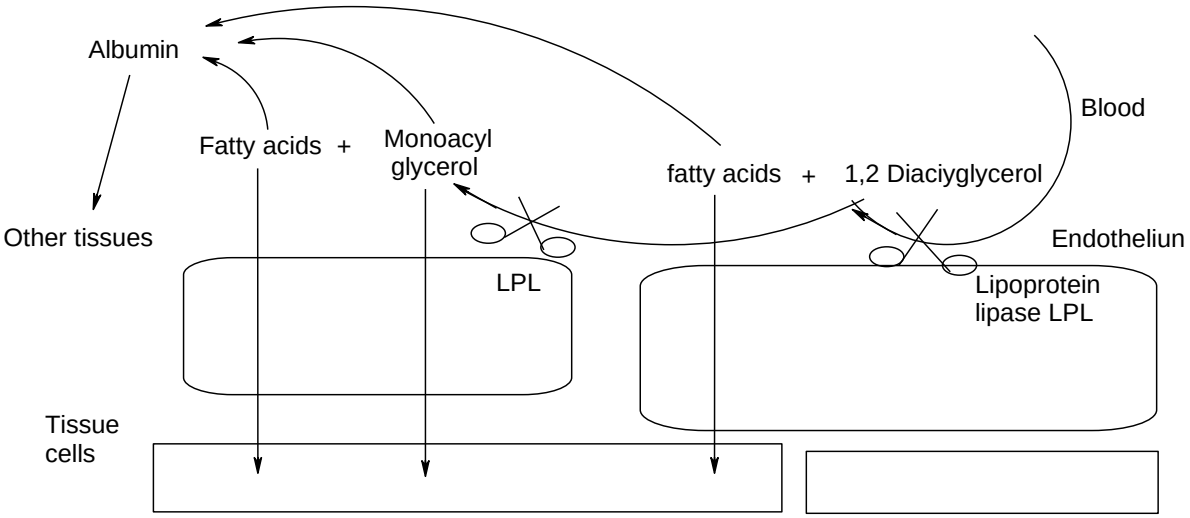
The triglycerides metabolism takes place mostly in the liver, adipose tissue and intestine.

III.5.1. Exogenous triglycerides metabolism

The enzyme lipoprotein lipase (LPL) acts within the adipose tissue, skeletal muscles, myocardium, lungs, kidneys, aorta, but **not** in the liver and brain.

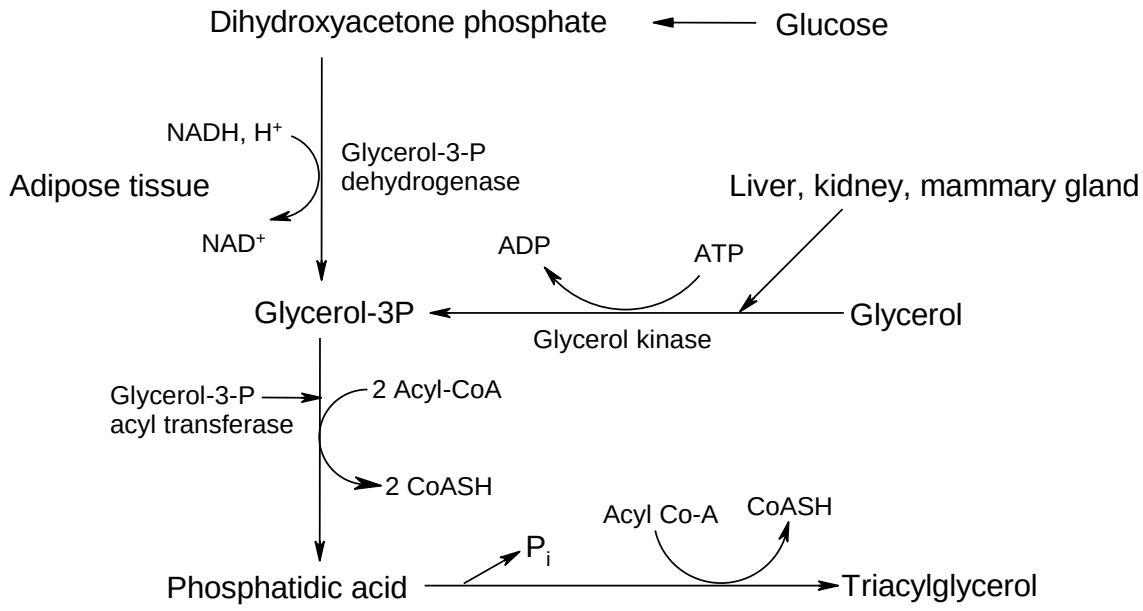
Under the action of LPL, 90% of the triglycerides from chylomicrons are hydrolyzed. K_M of LPL from the adipose tissue is 10 times higher than within the myocardium. Thus, after a meal, when high amounts of triglycerides reach the blood, these are used by the adipose tissue. During the postabsorptive state, the triglycerides are at a much lower plasma concentration and will be used only by the myocardium and skeletal muscles.





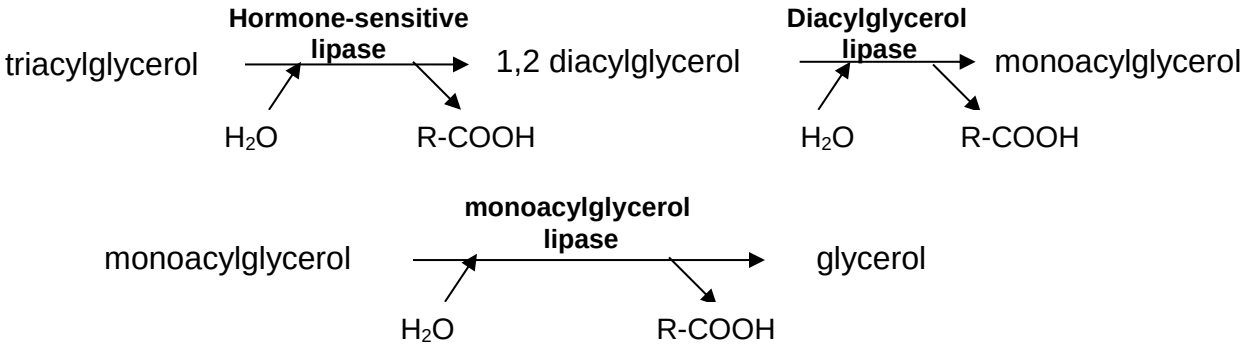
III.5.2. Metabolism of triglycerides from the adipose tissue

Triglycerides synthesis (lipogenesis) – takes place as per the following figure:



The synthesized triglycerides will be stored within the adipocyte under the form of lipid droplets. The stage controlling this metabolic pathway is that of forming glycerol –3– phosphate out of dihydroxyacetone phosphate. Because of the fact that dihydroxyacetone phosphate is an intermediary of glycolisis, which is an insulin controlled metabolic pathway, insulin will also control the synthesis of triglycerides within the adipose tissue.

Catabolism of triglycerides (lipolysis) – takes place according to the following scheme:

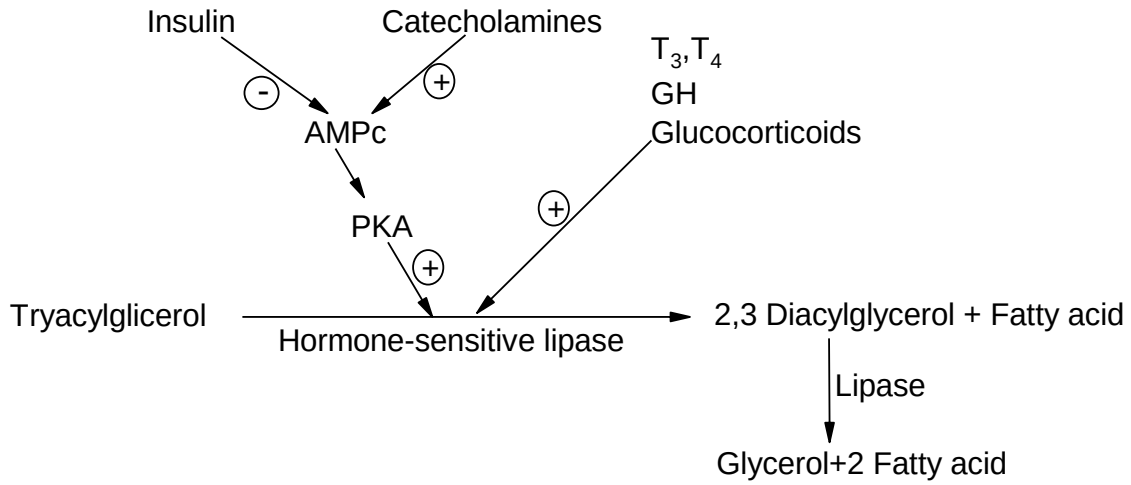


The limitative stage of the pathway is the one catalized by the hormone-sensitive lipase, thus avoiding the accumulation of mono and diacylglycerols within the adipose cell. The triglyceride lipase is regulated by the mechanism of phosphorylation–dephosphorylation, the phosphorylated form being the biologically active one. The enzyme is also regulated hormonally, stimulated by ACTH, TSH, catecholamine, glucagon, vasopressin and inhibited by insulin, prostglandine E, nicotinic acid. The fatty acids and glycerol get into the plasma, where the hydrophobic fatty acids will bond to albumin, being the fraction of free fatty acids (FFA)–normal values 5–20 mg%. The FFA value is the lowest after a meal, but increases afterwards, during the postabsorptive state reaching 5 times higher values. The FFA formed is the energetic alternative of the tissues (except for the glucose–dependent ones) in the cases of a decrease of glucose concentration during starvation. This way, the glucose left for the brains and erythrocytes is being preserved, while for muscles, myocardium, kidneys, the free fatty acids will be the preferred and alternative energy substrate. Within these tissues, after activation and transportation into mitochondria, FFA will be subject to β-oxidation for obtaining energy.

The adipose tissue is considered the main tissue of insulin action, being actually produced under its action (the adipose tissue has very few glucagon receptors). The insulin stimulates the formation of lipogenesis precursors by:

- stimulating lipoprotein lipase which hydrolizes the triglycerides from chylomicrons forming fatty acids that pass into adipocytes
- stimulating the glucose entering into tissues, followed by glycolisis which forms dihydroxyacetone phosphate.

The insulin stimulates the key enzyme of the triglycerides synthesis, glycerol-3-phosphate acyl transferase and inhibits the key enzyme of triglycerides hydrolysis – hormone-sensitive lipase. The lipolysis within the adipose tissue, materialized by triglycerides hydrolysis, begins once the insulin concentration decreases during the postabsorptive state, when the glycerol-3-phosphate acyl transferase is no longer activate, and the hormone-sensitive lipase is activated by phosphorylation. Additionally, the effects are intensified under stress by the action of catecholamines.



III.5.3. Metabolism of triglycerides within the liver

Triglycerides synthesis

The precursor of the triglycerides synthesis within the liver is the excess of FFA from the plasma, which upon reaching the hepatic tissue may suffer 2 types of transformations:

- synthesis of endogenous circulating triglycerides
- ketogenesis.

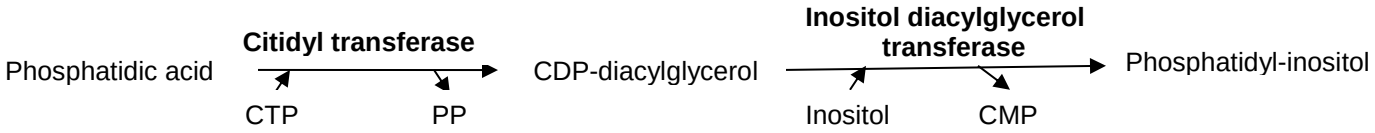
Synthesis of endogenous circulating triglycerides

The fatty acids and the activated glycerol will react, forming triglycerides, the daily quantity being between 25-50 grams. Unlike the adipose system, the glycerol-phosphate does not come only from dihydroxyacetone phosphate, but also from the glycerol phosphorylation. In parallel, glycerophospholipids, cholesterol and proteins are also synthesized within the liver. In case of providing these in sufficient quantities, a lipoprotein complex called VDLD (very low density lipoproteins) is assembled, similar to chylomicrons, but differing by the type and concentration of apoliporoteins (which in this case are mostly apo B_{100} and, in smaller quantities, apo C and apoE). VLDL has ρ=0,97 grams/cm^3 and a structure of 7% proteins and the rest being lipids of which 57 % triglycerides (TG), 20% phospholipids (PL), 15% esterified cholesterol and 8% free cholesterol. The VLDL particles are secreted inside the hepatocytes by exocytosis, then reach the plasma; their life span being of 15–60 minutes. The metabolization of triglycerides from VLDL takes place at the level of tissue capillaries under the action of lipoprotein lipase from the capillary endothelium, similar to chylomicrons catabolism.

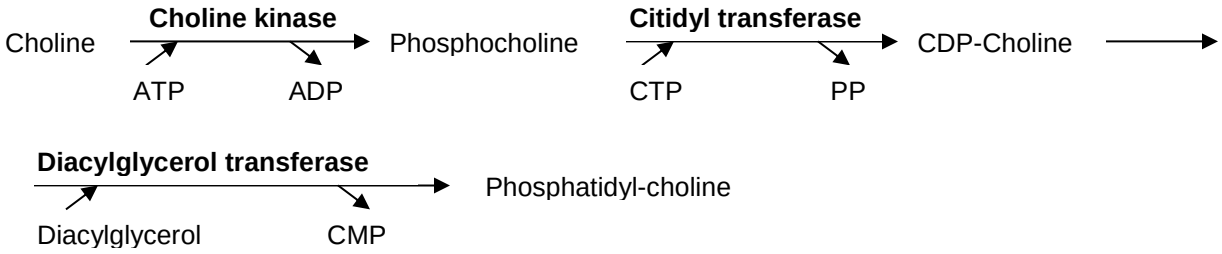
III.6. Glycerophospholipids metabolism

This class of lipids has in common a molecule of glycerol-3-phosphate esterified at positions 1 and 2 with fatty acid residues. Their synthesis may begin either from diacylglycerol-3-phosphate, or from phosphatidic acid. The synthesis takes place within microsomes (esther-phospholipids), peroxisomes (ether-phospholipids or plasmalogens) or the mitochondrial matrix (cardiolipin).

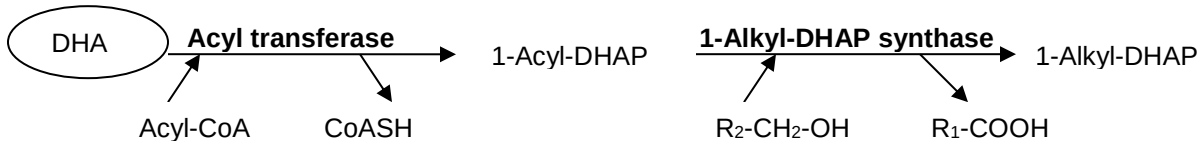
Synthesis of phosphatidyl-inositol



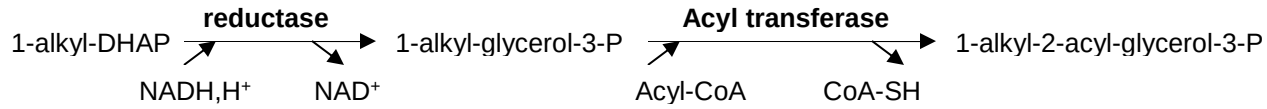
Synthesis of phosphatidyl-choline (lecithin)

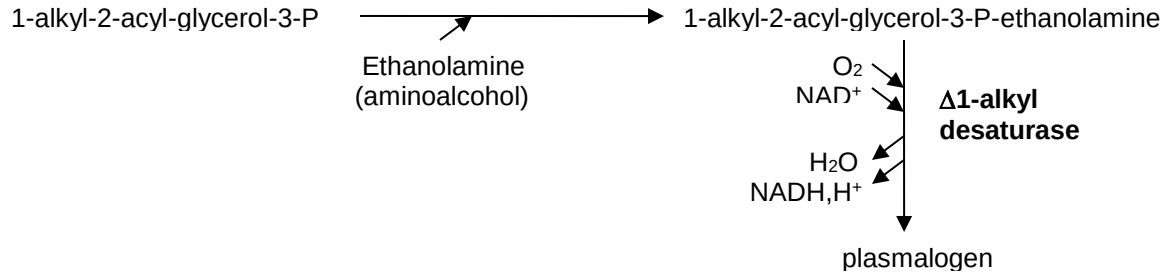


Synthesis of plasmalogens



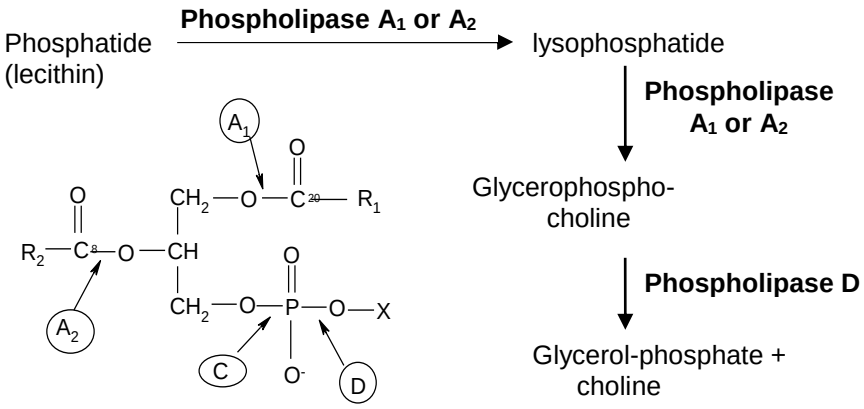
DHAP = dihydroxyacetone phosphate





Glycerophospholipids catabolism

Glycerophospholipids catabolism takes place under the action of phospholipases which hydrolize the ester bonds. The action takes place gradually, in the successive presence of lipases A1, A2, C and D.



The role of phospholipids

The phospholipids play a part within the synthesis of VLDL plasma lipoproteins, where they are the bond between the hydrophobic nucleus, formed of triglycerides, and the hydrophilic area from the outside of the lipoprotein particle, formed of proteins. VLDL eliminates the triglycerides formed within the liver, preventing its fatty infiltration. The factors which will take part to forming the hepatic phospholipids (methionine, B_{12}vitamin, folic acid) will thus have a lipotropic action.

The phospholipids are components of cellular membranes, where they play a functional or structural role. For instance, the erythrocyte membrane contains up to 50% phospholipids. Dipalmitoillecithine acts as surfactant within the liquid layer at the surface of the pulmonary alveoli, thus reducing the superficial tension of the aqueous layer. Lungs can thus accomplish by themselves the complete extension. The phospholipids also play a part in making the cholesterol from the bile soluble, a place where phosphatidylcholine prevents the formation of calculi in the gallbladder.

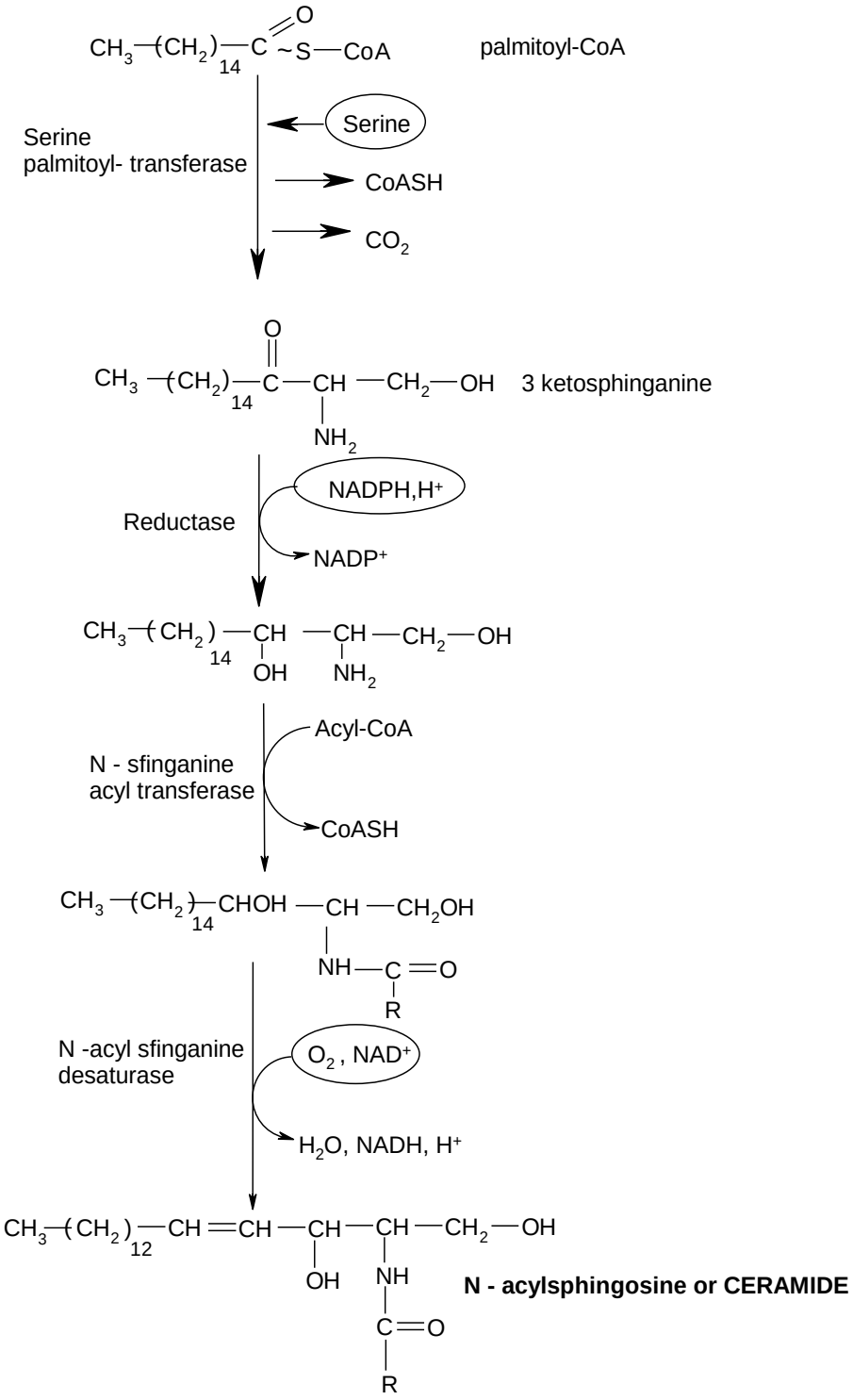
Another important role is intracellular signal transduction at the level of different signaling pathways. The platelet aggregation factor (PAF), a phospholipid of plasmalogen type, is the major mediator of hypersensitivity, of acute inflammatory reactions and the anaphylactic shock. It is synthesized and released by the polymorphonuclear leukocytes, accomplishing platelet aggregation and the chemotaxis of polymorphonuclear leukocytes.

III.7. Sphingolipids metabolism

The sphingolipids are about 25% of the total of lipids in humans, and within the brains they represent about 6% of the fatty mass.

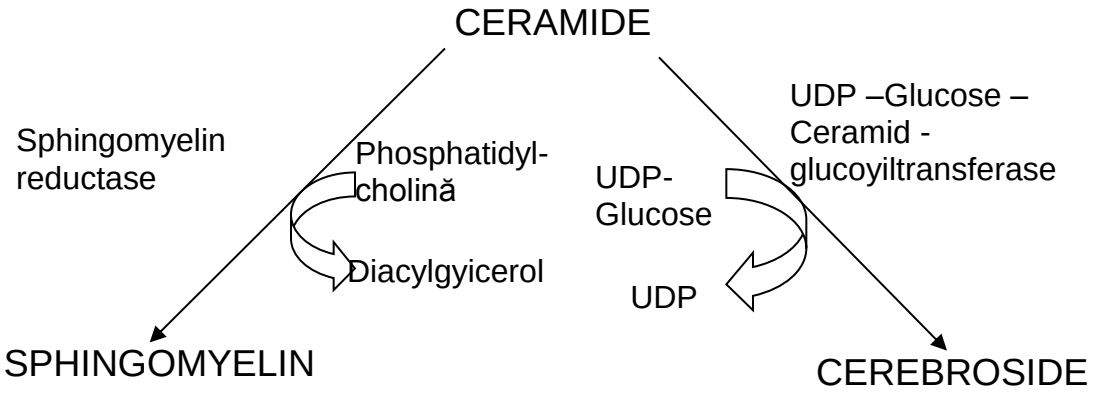
Sphingolipids synthesis

It takes place starting from ceramides (N-acylsphingozines). Their synthesis occurs within the membrane of the endoplasmic reticulum and comprises the stages presented in figure 14:

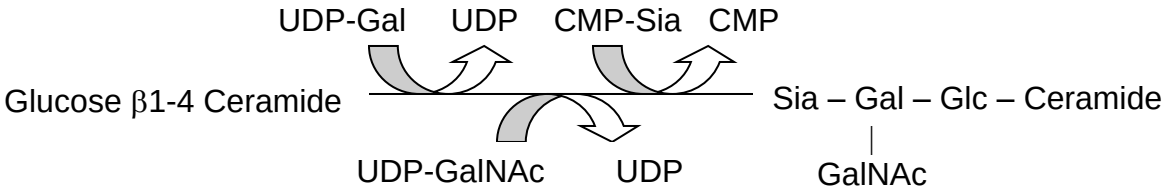


Sphingolipids synthesis

The sphingomyelins are produced by linking a phosphocholine molecule on a ceramide, at the level of C1 hydroxyl groups. In the case of cerebrosides, the precursor will also be a ceramide where the linking of a carbohydrate residue from the primary –OH group will occur by a β-glycosidic bond.



The gangliosides synthesis takes place within the endoplasmic reticulum and the Golgi apparatus, having as precursor a cerebroside to which monosaccharides and their derivatives are added successively.

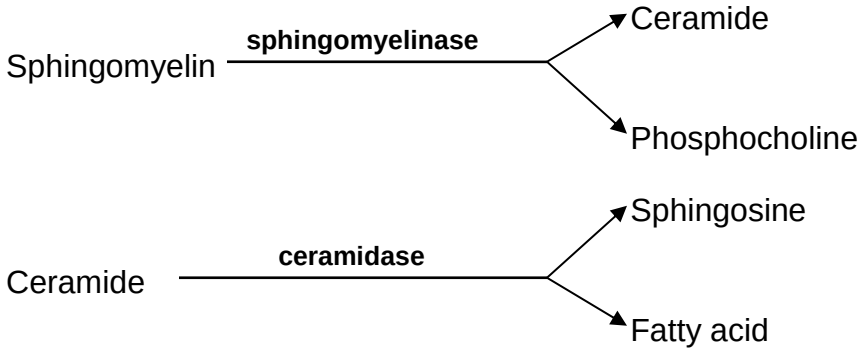


Sia – sialic acids
Glc – glucose
Gal – galactose
GalNAc – N-acetylgalactosamine

For the synthesis of sulfatides, but also for the other sphingolipids containing sulphate groups, sulphate groups are added at the level of –OH and –NH groups. The sulphate groups are inserted as the active sulphate group PAPS (3-phosphoadenosin-5'-phosphosulphate).

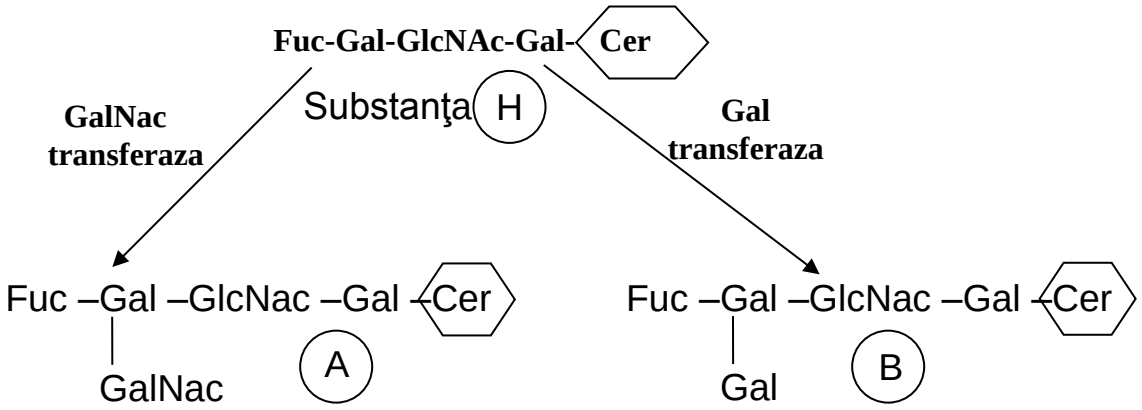
Sphingolipids catabolism

The catabolism occurs at the level of lysosomes under the action of certain hydrolytic enzymes.



The gangliosides are catabolized by the action of a great number of enzymes, each one specialized on detaching a certain glycosidic unit. For instance, β-N-acetylhexozaminidase A hydrolizes the terminal N-acetylgalactosamine from a GM_2 ganglioside. The deficit of this enzyme, a feature of the Tay-Sachs disease, produces the accumulation of this type of ganglioside, which causes pathological phenomena such as blindness, mental retardation, hepatosplenomegaly and early death. A method of diagnosis od this disease is is the determination of the enzyme in cell culture.

Sphingolipids, blood group markers. The blood group substances are components of the erythtocyte membrane, which differ from person to person based on genetic polymorphism. Although there are over 200 substances within this category, the ABO system is the most important, being used as a compatibility marker for transfusions. From a chemical point of view, the markers are glycosphingolipids, and their antigenic specificity is provided by the variations at the terminal sugar level.



The enzymes GalNAc and Gal transferase are codified by 2 allelic variants of the same gene, noted allele A and allele B. A third allelic variant of the gene, named allele 0 codifies an inactive form of transferase so that the marker will remain at the basic form H.

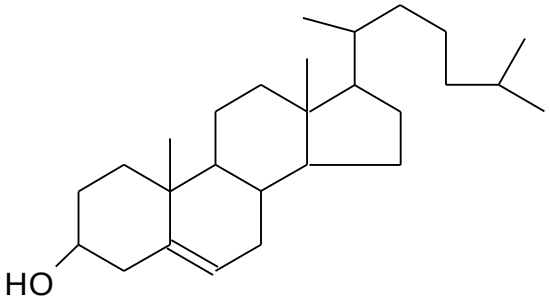
In the case of individuals of Caucasian race, about 40–45% have the OO type of the allelic profile of the gene, so they have markers only of H type and correspond to the O blood group. About 40–45% of the individuals have allele A, either in two copies (homozygote) or in combination AO (heterozygote). In both cases, the individuals express A type markers, corresponding to the A blood group. 10% of the individuals have allele B, either in two copies BB (homozygote), or in combination BO (heterozygote). In both cases, the individuals express B type markers, corresponding to the B blood type. The other 5% of individuals have the profile of AB or BA, expressing both types of markers and belonging to the AB blood group. For other blood groups, the differences are provided additionally by the oligosacharride sequence or by different sequences in amino-acids at the level of membrane glycoproteins.

The pathology of sphingolipids metabolism. It is due to defects at the level of lysosome enzymes which catabolize the sphingolipids. As a result, sphingolipids accumulation within the lysosomes is produced, triggering the sphingolipidoses or lipid storage disorders. The enzymatic deficit appears within all tissues. In case of total deficit

the disease is severe, affecting the nervous system (characterized by a high content of sphingolipids), the liver (hepathosplenomegaly), and producing blindness for instance in the Tay-Sachs malady. In general, the disease is rare, but in some populations (the Askenazi Jewish) the frequency is of 1:3600. In case of a partial defect, for instance in Gaucher's disease, the disease debut occurs within the adult stage, without affecting the nervous system, but generating splenomegaly and thrombocytopenia. The disease is rare, but more frequent within the Askenazi Jewish population (1:600).

III.8. Cholesterol metabolism

The cholesterol, $C_{27}H_{45}$-OH, is a lipid molecule with a special importance for the human body. It is an essential component of the cell membranes, of plasma lipoproteins, the precursor of steroid hormones synthesis, of biliary acids and of D vitamin.



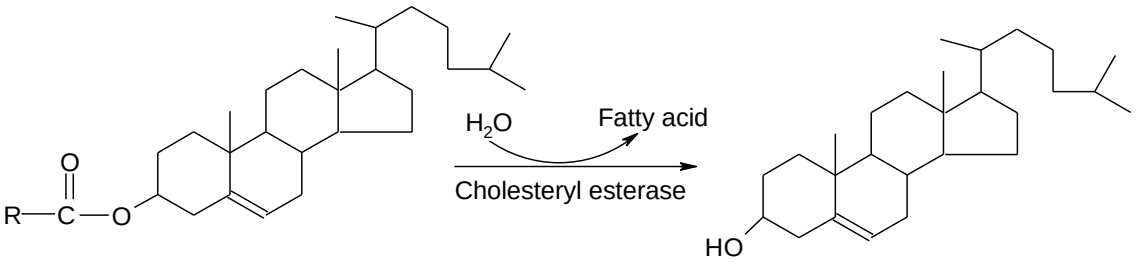
The human body contains about 140 grams of cholesterol, most of it as free form (non-esterified), located within the cell membranes, especially within the nervous tissue. As esterified form it is found within the suprarenal cortex and within the plasma lipoproteins. The cholesterol comes both from food (about ½ of the needs), as well as from endogenous synthesis (within liver and intestine).

Most of the cholesterol synthesized within the liver is exported under three forms: bile cholesterol, bile acids and circulating cholesterol in lipoproteins. Food rich in cholesterol are: egg yolk, liver, brains; the total daily quantity of food cholesterol which reaches the intestine being of about 1 gram.

The food cholesterol, mostly as esterified form, is hydrolyzed by pancreatic cholesterol esterase, then passes into enterocytes where under the action of the enzyme acyl-CoA cholesterol acyltransferase (ACAT) is esterified again and included within the lipoprotein fraction of chylomicrons.

After the triglycerides hydrolysis at the endothelial level, the residual chylomicrons, rich in cholesterol, are captured by the liver. Within the liver, part of the cholesterol, free and esterified, is included within the lipoprotein fraction of VLDL which transfers the lipids synthesized in the liver towards the rest of the tissues.

After the transfer of triglycerides at the endothelial level, the residual VLDL return to the liver, are loaded with cholesterol turning into the LDL fraction, which becomes the main cholesterol supplier at tissue level. The cholesterol excess at a tissue level is collected and brought back to the liver by another type of lipoprotein, HDL.



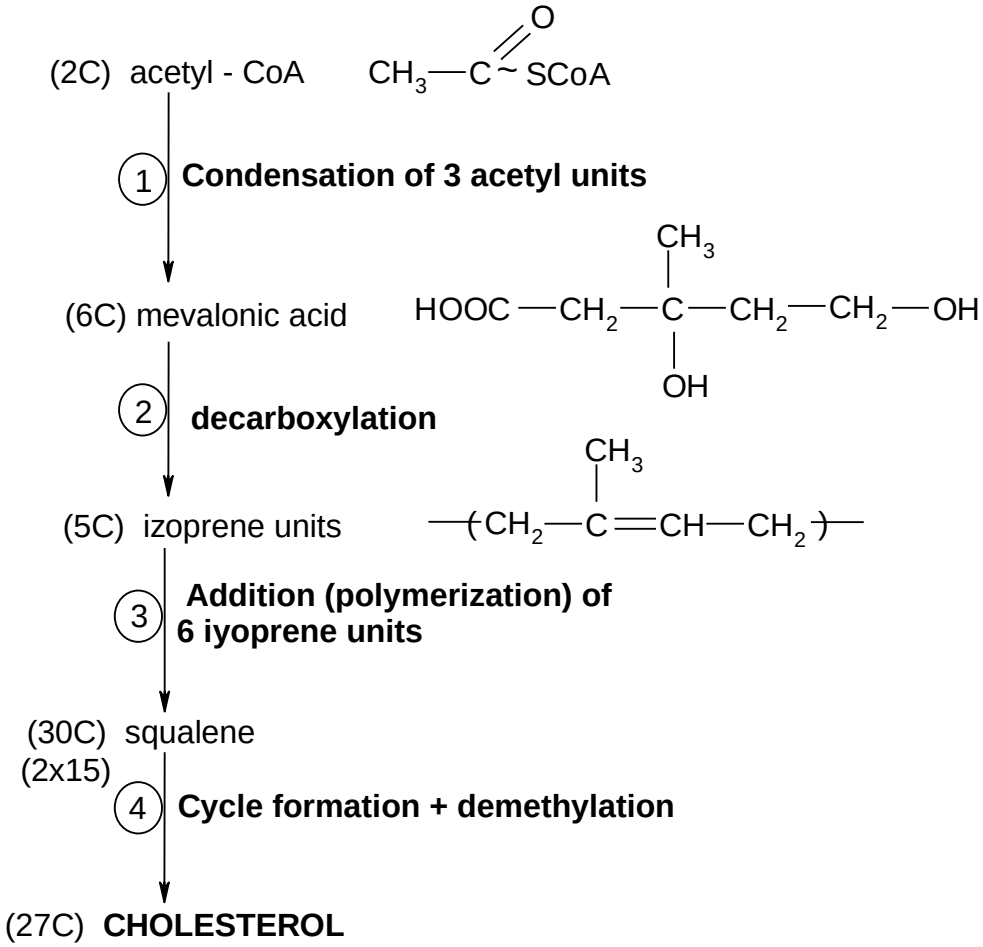
Cholesteryl ester (CE)

Cholesterol

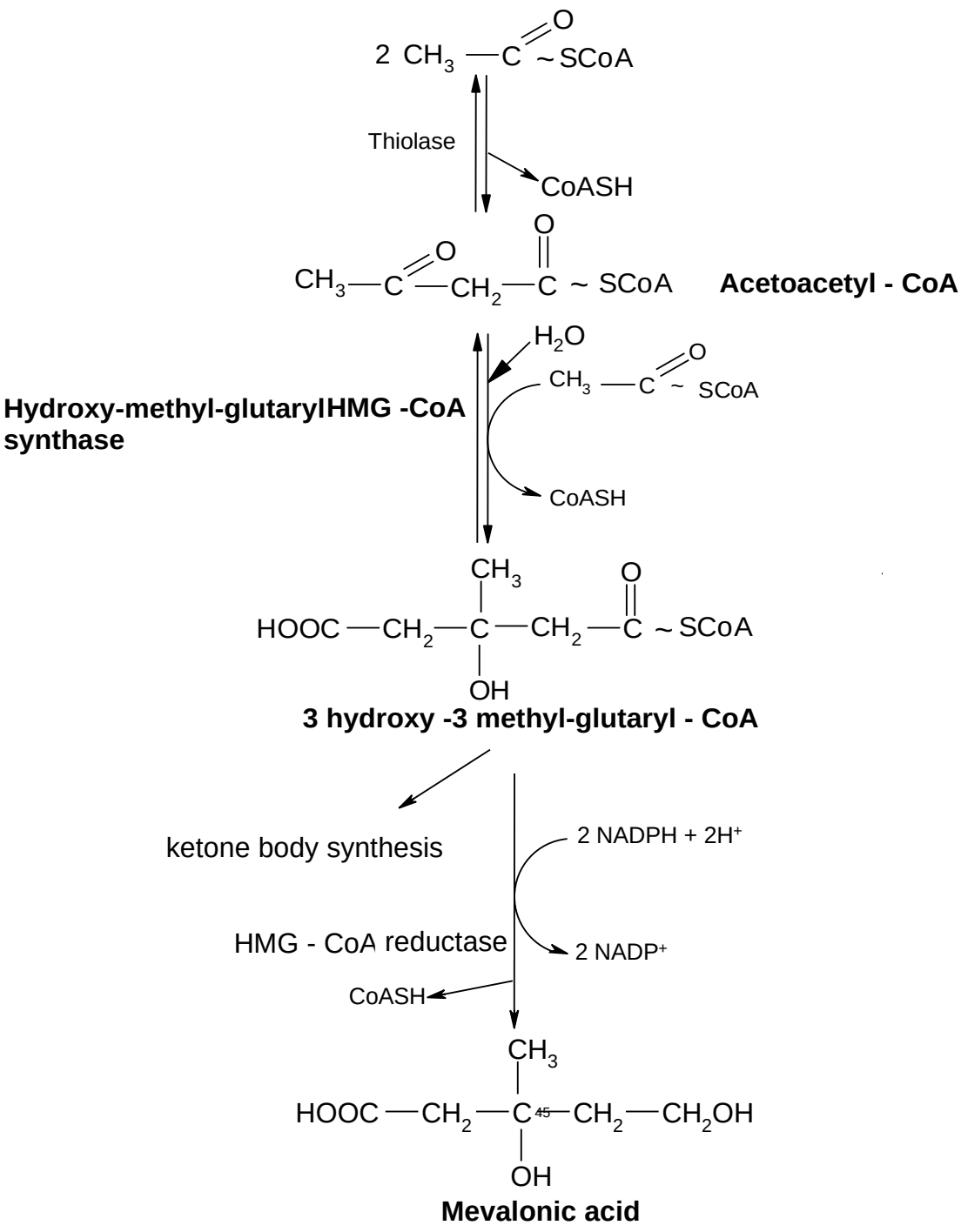
Cholesterol synthesis

The cholesterol biosynthesis depends on the intake and absorption of food cholesterol, there being a reversely proportional relation between the two processes. Thus, biosynthesis at the hepatic level is inhibited by the high concentration of the residual chylomicrons, while the intestinal biosynthesis is inhibited by the bile salts.

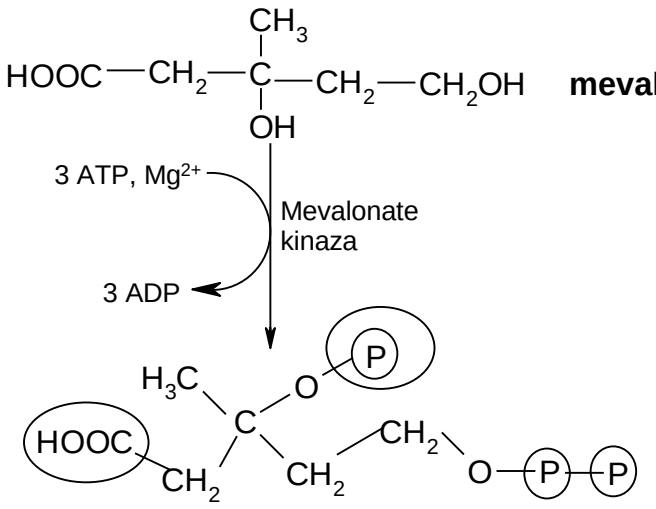
The biosynthesis occurs within all nucleated cells, but mostly within the liver (over 50 %), intestine (about 15%), and the rest within teguments and endocrine tissues: suprarenal cortex, sexual organs, yellow body. At a cellular level, the process occurs within microsomes and within cytoplasm, and comprises the stages:



1. Mevalonic acid synthesis

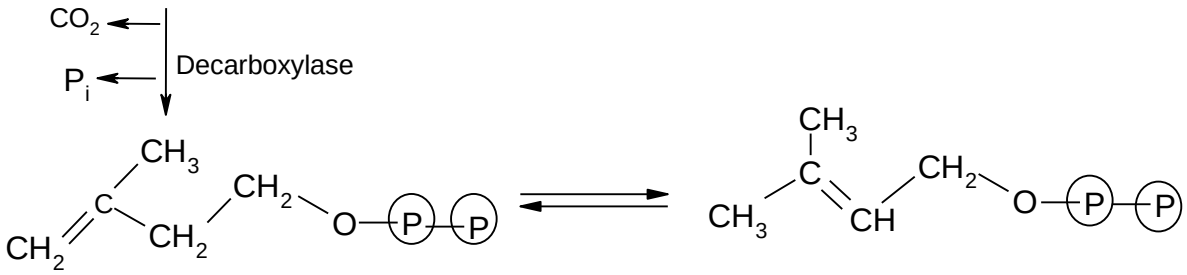


2. Izoprene units synthesis



mevalonic acid

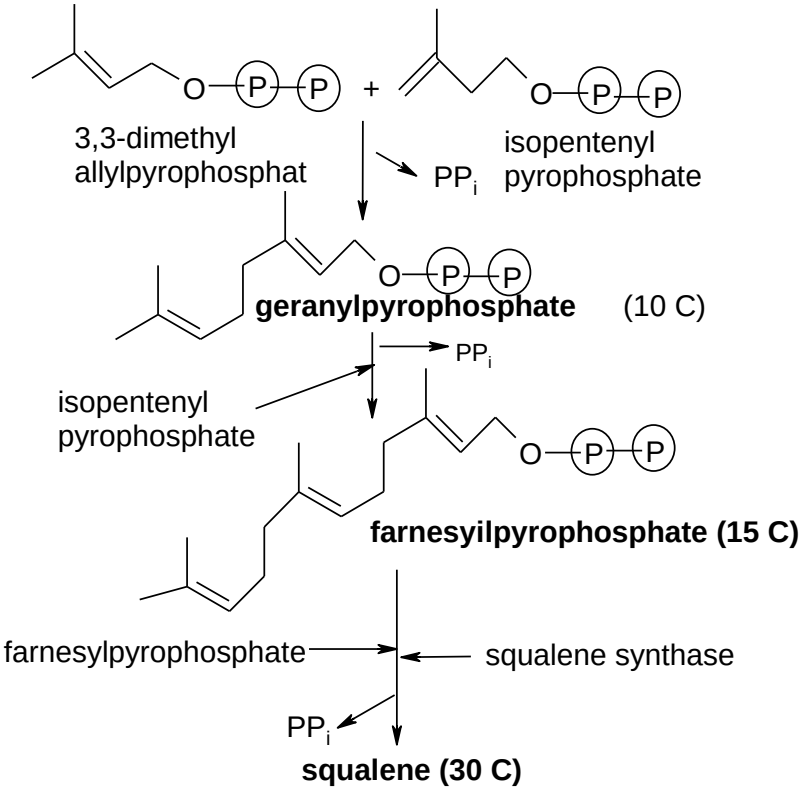
mevalonate 3-P-5-pyrophosphate



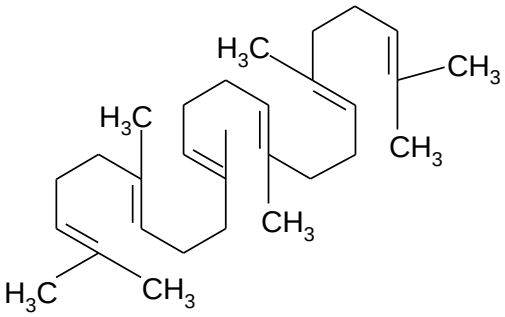
Isopentenyl pyrophosphate

3,3-dimethylallylpyrophosphate

3. Squalene synthesis

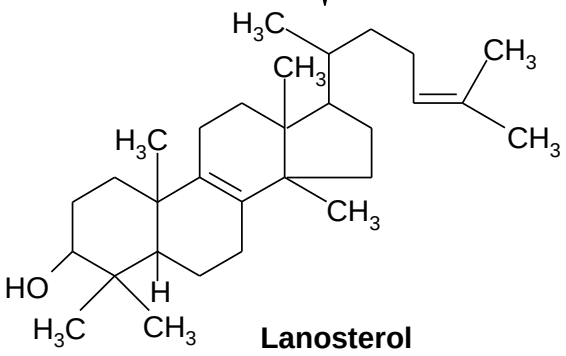


4. Finalizing the cholesterol synthesis

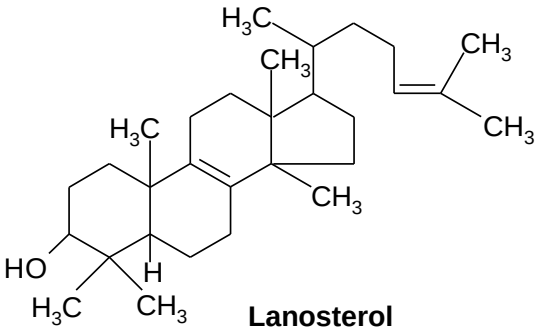


Squalene

1/2 O_2
NADPH + H^+
Monooxygenase
$NADP^+$

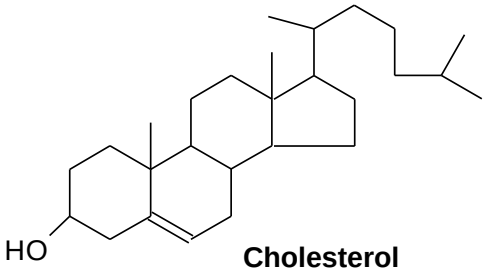


Lanosterol



Lanosterol

2NADPH + $2H^+$
Reduction
Demethylation
Isomerisation
2 $NADP^+$
3 CH_3



Cholesterol

The synthesis of a cholesterol molecule is intensely energy consuming, needing 16 $NADPH+H^+$ molecules and 36 ATP molecules.

The cholesterol catabolism and elimination

Within the human body, there is no metabolic pathway for the steranic nucleus degradation. As a result, the forms under which cholesterol is eliminated from the body are derivatives of the steranic nucleus. The cholesterol can be eliminated from the body in the following ways:

1. Biliary pathway
   - biliary cholesterol→intestine→reduction to coprostanon or cholestanol →fecal matter
   - not reabsorbed biliary acids (0,25 grams/day) →fecal matter
2. Desquamated intestinal ephitelial cells →fecal matter
3. Sebaceous secretion at the tegument level
4. Urinary elimination of the steroid hormones and D vitamins metabolites.

Ways of cholesterol transformation

1. Within teguments — cholesterol→cholecalciferol (D_3 vitamin)
2. Within suprarenals — cholesterol→corticosteroid hormones
3. Within sexual glands — cholesterol→steranic sexual hormones
4. Within liver — cholesterol→primary biliary acids
5. Within liver and intestine — cholesterol→plasma lipoproteins

Regulating the cholesterol metabolism

The regulation comprises 3 important levels:

- regulating the cholesterol synthesis
- regulating the LDL receptors synthesis
- regulating the hepatic synthesis of the bile acids

Regulating the cholesterol synthesis

Regulating the synthesis comprises a metabolic level, an enzymatic one and a hormonal one.

Within the metabolic regulation, an important part is played by supplying precursors such as acetyl-CoA, ATP, $NADPH+H^+$ which shows that the cholesterol synthesis is a component of the anabolic stage of metabolism. Furthermore, the quantity of cholesterol supplied from food is a negative regulating factor of the endogenous synthesis.

The enzymatic regulation is closely related to the hormonal regulation; actually the hormonal action consists in modulating of the activity of the rhythm enzymes within the cholesterol synthesis process. Thus, insulin, a stimulator of the cholesterol synthesis, stimulates the dephosphorylation of the rhythm enzyme HMG-reductase, changing the enzyme into active form. The hyperglycemiant hormones (glucagon, cortisol, oestrogen, thyroxine) stimulate the phosphorylation of HMG–reductase, making the enzyme inactive and thus inhibiting the cholesterol synthesis. The drug Lovastatin, an inhibitor of HMG–reductase, blocks the cholesterol cellular synthesis, favoring this way the absorption of

an increased LDL quantity from the plasma, the effect being the reduction of cholesterolemia.

Regulating the LDL receptors synthesis

The LDL receptors synthesis depends on the intracellular concentration of cholesterol, controlling the transcription of the LDL receptor gene. This way, the cell will absorb cholesterol from the plasma LDL lipoprotein particles only according to the needs.

Regulating the hepatic synthesis of primary bile acids

The liver is the only organ capable of eliminating cholesterol from the body, under the form of cholesterol and bile acids using the bile pathway. The bile acids synthesis will be regulated by the quantity of bile acids reabsorbed at the intestine level that will return to the liver through the enterohepatic cycle. The decrease of their quantities will stimulate the hepatic synthesis.

The medications such as Cholestyramine, Colestipol, etc. are resins that bind the bile acids at the level of the intestine, preventing them from being reabsorbed. Within the bile, the cholesterol is the least soluble component, which is why there are precipitation phenomena – cholelithiasis, a process affecting about 20% of the population during lifetime. The precipitating components are mainly cholesterol and secondarily bile acids.

Utilization of cholesterol

The cholesterol is a component of the cell membranes, and of the myelin sheaths. It is a precursor in the synthesis of bile acids, colecalcipherol and of the steroid hormones from corticosuprarenals, the gonads and placenta. Cholesterol is transported throughout the body by means of plasma lipoproteins. It has a dynamic state, a permanent cholesterol transfer existing between lipoproteins and tissues.

The pathology of cholesterol metabolism

The cholesterol metabolism plays a key role in cardiovascular diseases. In general, the patients with high levels of LDL cholesterol in the blood are at an increased risk of myocardial infarction (heart attack).

1. **Hypercholesterolemia** is a congenital disease which manifests as rapidly instated atherosclerosis. In most cases, the genetic mutations reduce the quantity or the functionality of the LDL receptors at cellular level. The inhibited cellular synthesis will lead to an increase of the LDL within the blood and of the cholesterol quantity in the cells. LDL in excess is accumulated in macrophages (foam cells) at subendothelial level causing distortions which stimulate the thrombocytes aggregation and the stimulation of the of the migration of smooth muscle cells from the media to the intimae. The destruction of the foam cells generates lipid accumulation which stimulates fibrosis. The final effect is an atherosclerotic plaque, broadening of the vascular lumen, with the risk of producing a thrombus which initiates infarction states.
2. **Cholesterol esters storage disease**, due to the genetic deficit of acidic lysosomal lipase which hydrolyzes the cholesterol esters. The disease begins during adulthood and manifests itself by an early severe atherosclerosis.
3. **Bile calculi (cholelithiasis, gallstones)** – the bile cholesterol comes from the liver and is solubilized under the form of micelles that additionally contain

phospholipids and bile salts. The cholesterol excess (oversaturated bile) has the tendency to precipitate and crystallize forming bile calculi. This tendency is more frequent in women and in case of obesity. The therapy under these circumstances consists either in cholecystectomy or in administration of bile salts orally in order to reduce the cholesterol excretion in the bile and to solubilize the gallstones.

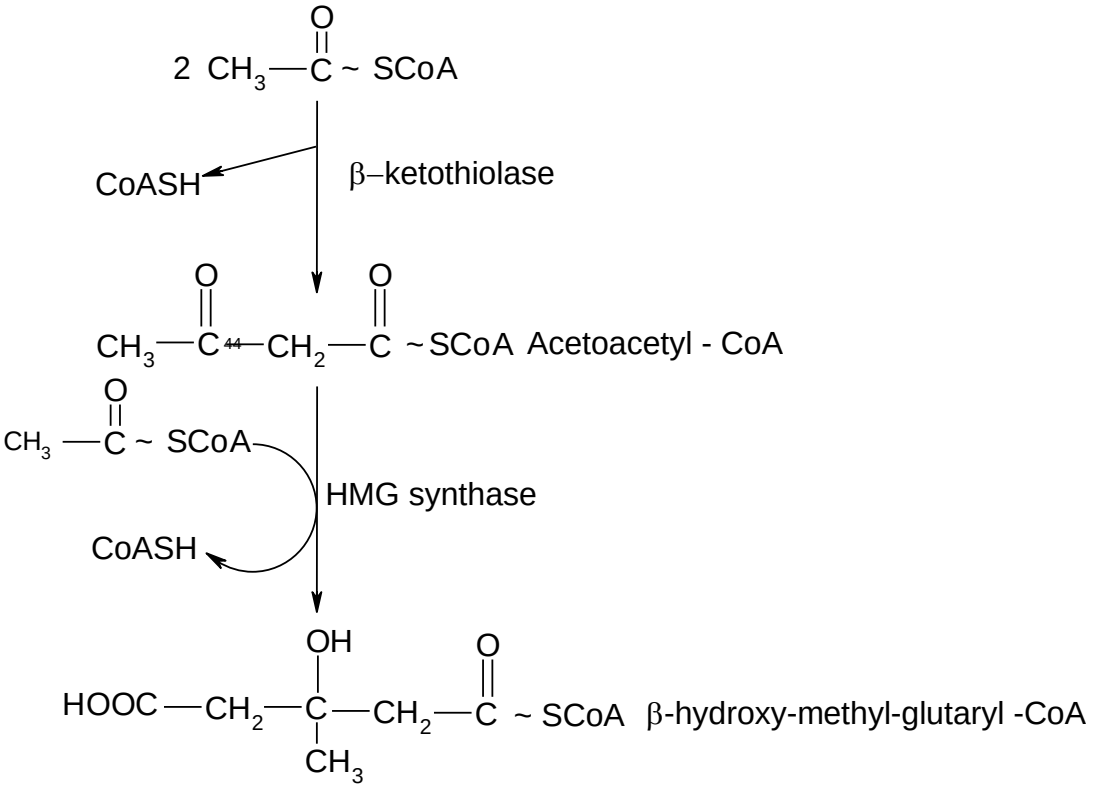
III.9. Ketone bodies metabolism

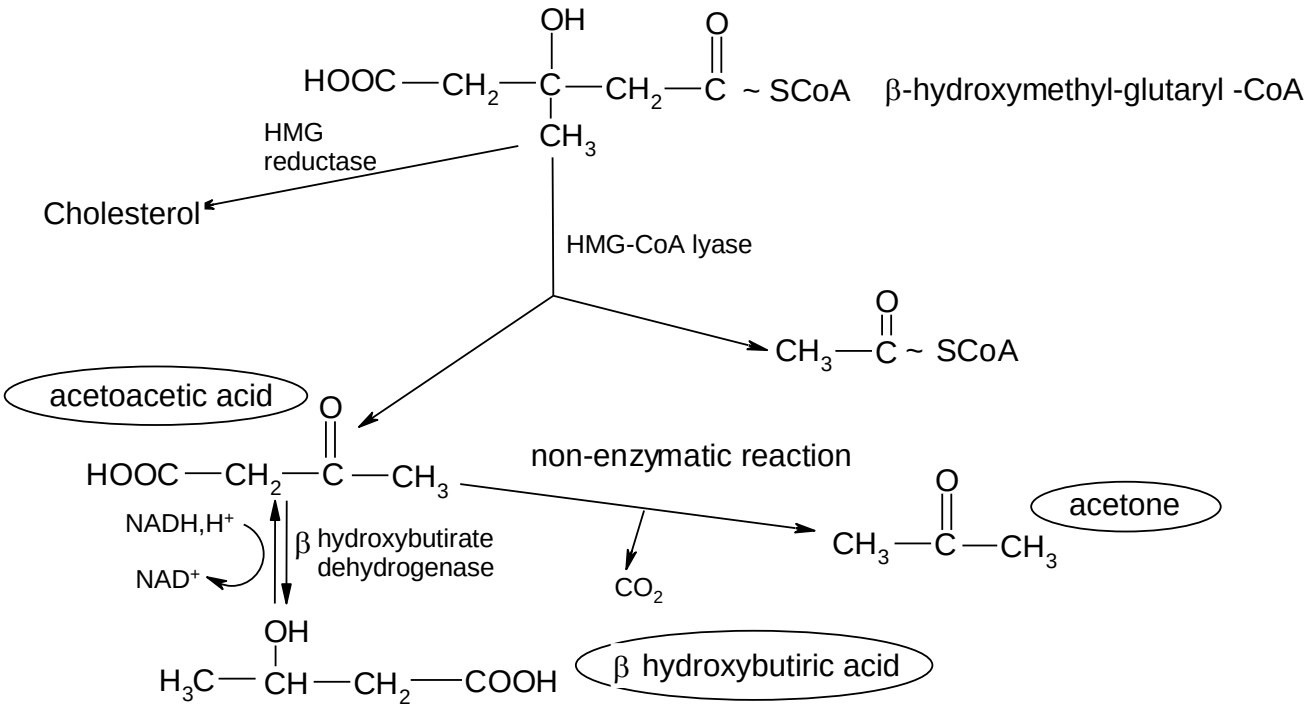
The ketone bodies metabolism (acetoacetic acid, β-hydroxybutyric acid, acetone) has a reduced importance under normal physiological conditions. In case of starvation, in case of pathological hypoglycemia, the ketone bodies metabolism becomes a more intense metabolic pathway with increased amplitude. Under these circumstances, the ketone bodies in great quantity serve as glucose replacement for most of the tissues, including the central nervous system and erythrocytes.

Ketogenesis

The ketone bodies are synthesized exclusively within the hepatic mitochondria from the excessive acetyl–CoA, coming from the excessive fatty acids oxidation. The basic condition of ketogenesis is the existence of this available excessive acetyl-CoA, which cannot be used in the priority metabolic pathways: fatty acids synthesis, cholesterol synthesis or triglycerides synthesis.

Ketogenesis comprises the following stages:

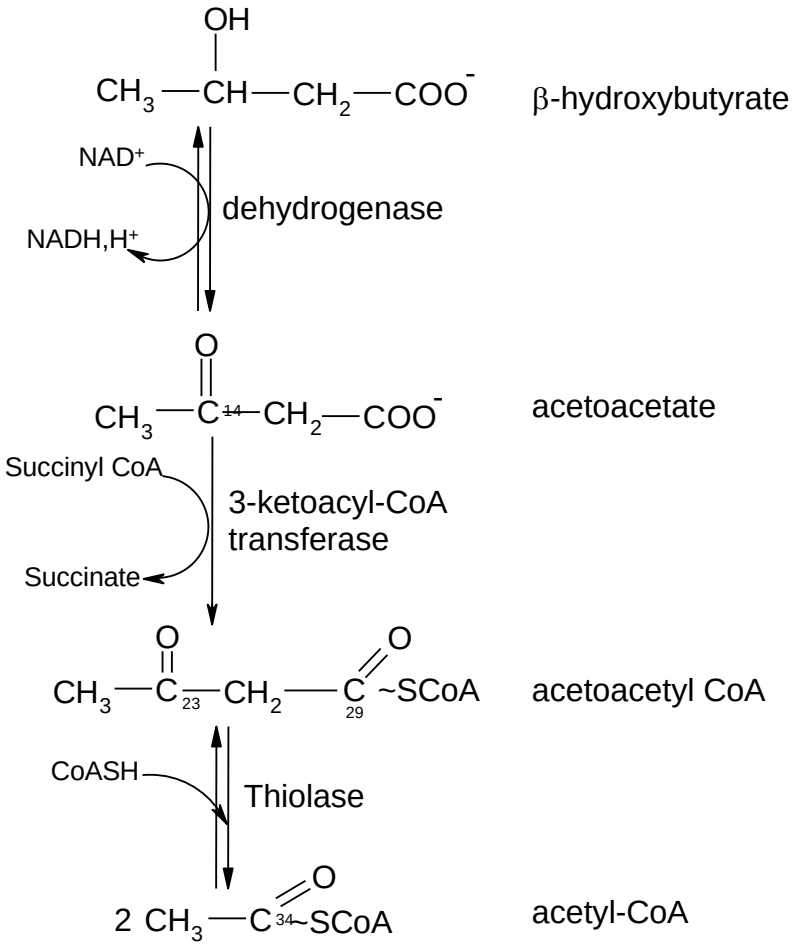




Ketolysis

Ketolysis or ketone bodies catabolism takes place within the mitochondria of all tissues, except for the hepatic one.

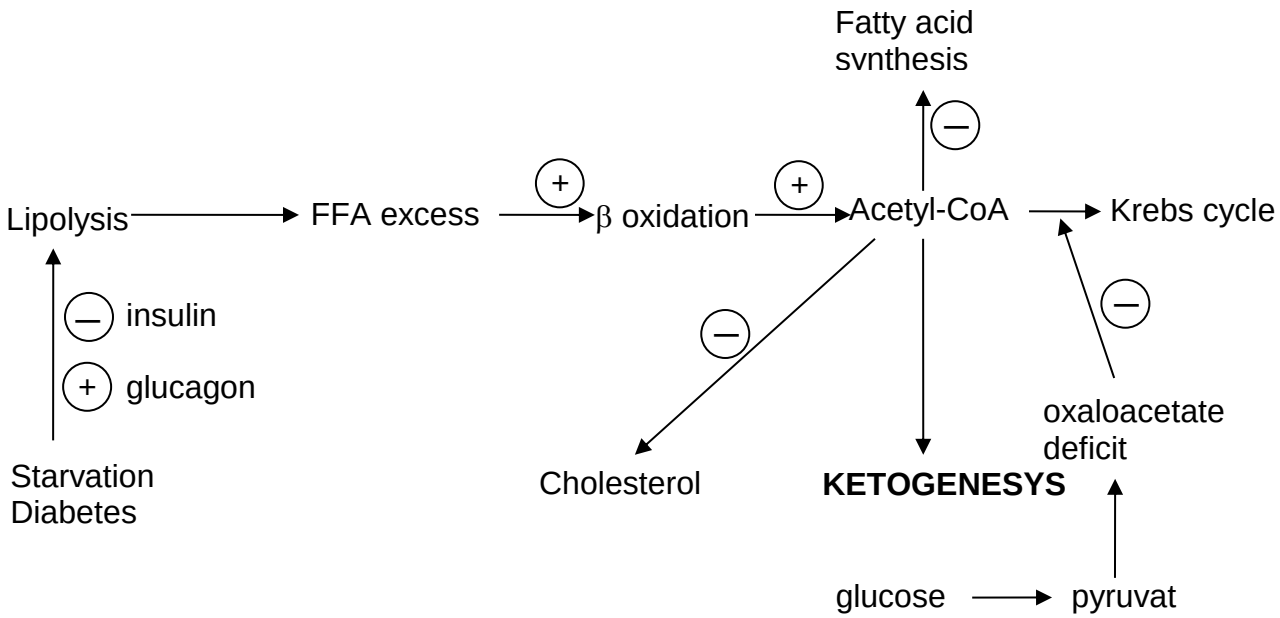
Ketolysis comprises the following stages:



The third ketone bodies representative, acetone, being volatile, is eliminated mainly through breath, or secondarily is converted to pyruvate or lactate.

Regulating the ketone bodies metabolism

Under normal circumstances, ketone bodies production is reduced, the normal blood concentration being of 1 mg%, and the daily urinary elimination of about 10 mg. The metabolic regulation depends on the normal lipid metabolism, the ketogenesis being favored by the increase of acetyl-CoA concentration at mitochondrial level. Both processes are associated to the catabolic state of the body, characterized by acute lipolysis and the decrease of the anabolic synthesis processes such as fatty acids and cholesterol synthesis. Lipolysis generates great quantities of free fatty acids (FFA) inhibiting lipogenesis by stimulating β-oxidation of FFA to acetyl-CoA. Using acetyl-CoA within the TCA cycle is decreased due to the oxaloacetate deficiency (formed in the reactions glucose→pyruvate→oxaloacetate), so that, as a compensatory mechanism, the ketone bodies and cholesterol synthesis will be amplified.



Pathological ketogenesis

A chronic hunger state (starvation) or, pathologically, the states of advanced uncompensated diabetes have as common features: lack of insulin secretion, excess of hyperglycemic hormones, glucose and oxaloacetate cellular deficiency, increased lipolysis.

This complex of factors exacerbates ketogenesis, the concentration of ketone bodies exceeding 100 mg%, and the ketone bodies become a basic energy source. Even the brain is getting 75% of the energy needs from the ketone bodies. Pathological ketogenesis is an evolving process which produces successively:

Hyperketonemia → ketonuria → ketosis → acidosis and polyuria→diabetic coma.

The state of ketosis is characterized by synthesis and massive acetone elimination, massive body spoliation of alkaline salts, events favoring the development of acidosis.

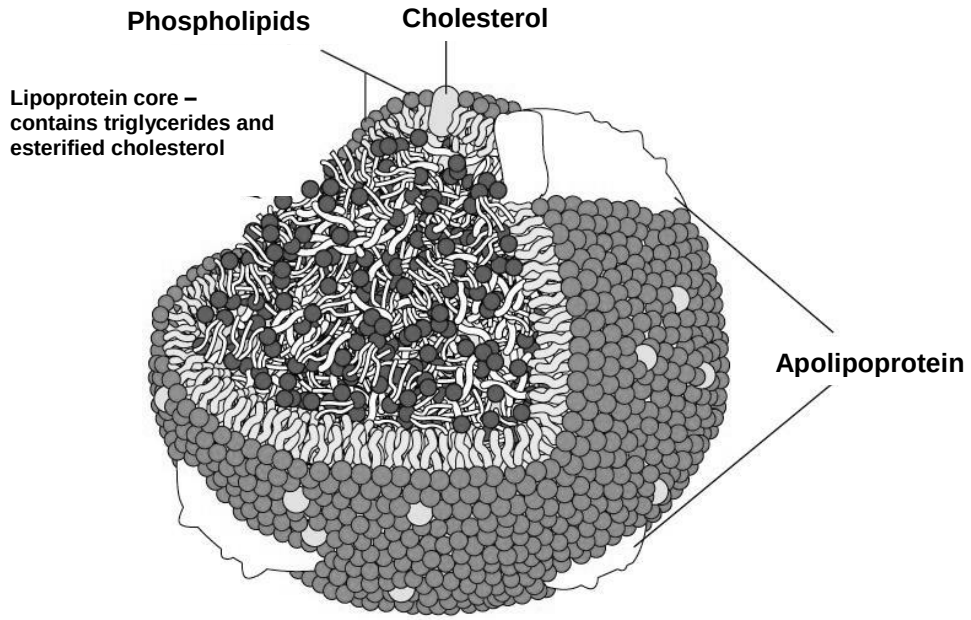
III.10. Plasma lipoproteins

The chemical analysis of the lipids from the plasma provides the following distribution:

- Total lipids 400 – 800 mg%
- Triglycerides 40 – 300 mg%
- Total cholesterol 120 – 280 mg%
- Esterified cholesterol 90 - 200 mg%
- Phospholipids 150 – 380 mg % (lecithin 66%, sphingomyelins 22%, lysolecithin 9%, kephalyn 3%)
- Free fatty acids 5 – 20 mg%

The plasma lipoproteins concentrations vary greatly according to the nutritional state and the individual structure. The free fatty acids are transported attached to serum albumin; to which they are linked by non-covalent bonds. The triglycerides, the phospholipids and the cholesterol form aggregates with proteins, called plasma lipoproteins.

The plasma lipoproteins represent the system for preserving the lipids balance in the body. The plasma lipoproteins provide the transportation of various lipids categories among the main organs involved in the lipid metabolism and the rest of the tissues.



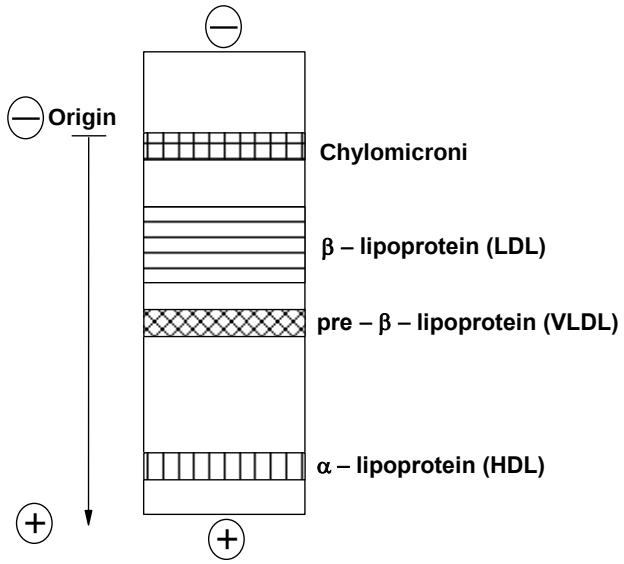
From a structural point of view, a lipoprotein has a lipid core made of triacylglycerols and esterified cholesterol, surrounded by a monolayer of amphipathic phospholipids and cholesterol with the polar chains oriented towards the outside aqueous environment.

In the outside area, there are the protein components called apolipoproteins which can be integrated (they cannot be transferred from a lipoprotein to another), or external or transferable (they can be transferred from one lipoprotein to another). Such integrated proteins are: apo A within HDL, apo B 48 within chylomicrons, apo B 100 within VLDL and LDL, and as transferable proteins: apo C and apo E.

Apoproteins fulfill several roles within the lipoprotein, such as: solubilization and transportation of the lipid fractions, markers for specific cellular receptors, enzymatic cofactors.

The plasma lipotroteins have been identified and characterized using the ultracentrifugation and electrophoresis methods. By ultracentrifugation, the lipoproteins have been separated based on the density difference into 4 main fractions: HDL (high density lipoproteins), LDL (low density lipoproteins), VLDL (very low density lipoproteins) and chylomicrons (Chy). Their density is reversely proportional with the lipids content.

By electrophoresis, the lipoproteins have been separated based on the electric charge difference, into 4 main fractions: Chy, β-lipoproteins, pre-β-lipoproteins, α-lipoproteins. The correspondence between the two methods of analysis is provided by the figure below.



The main features of the lipoprotein fractions are provided below.

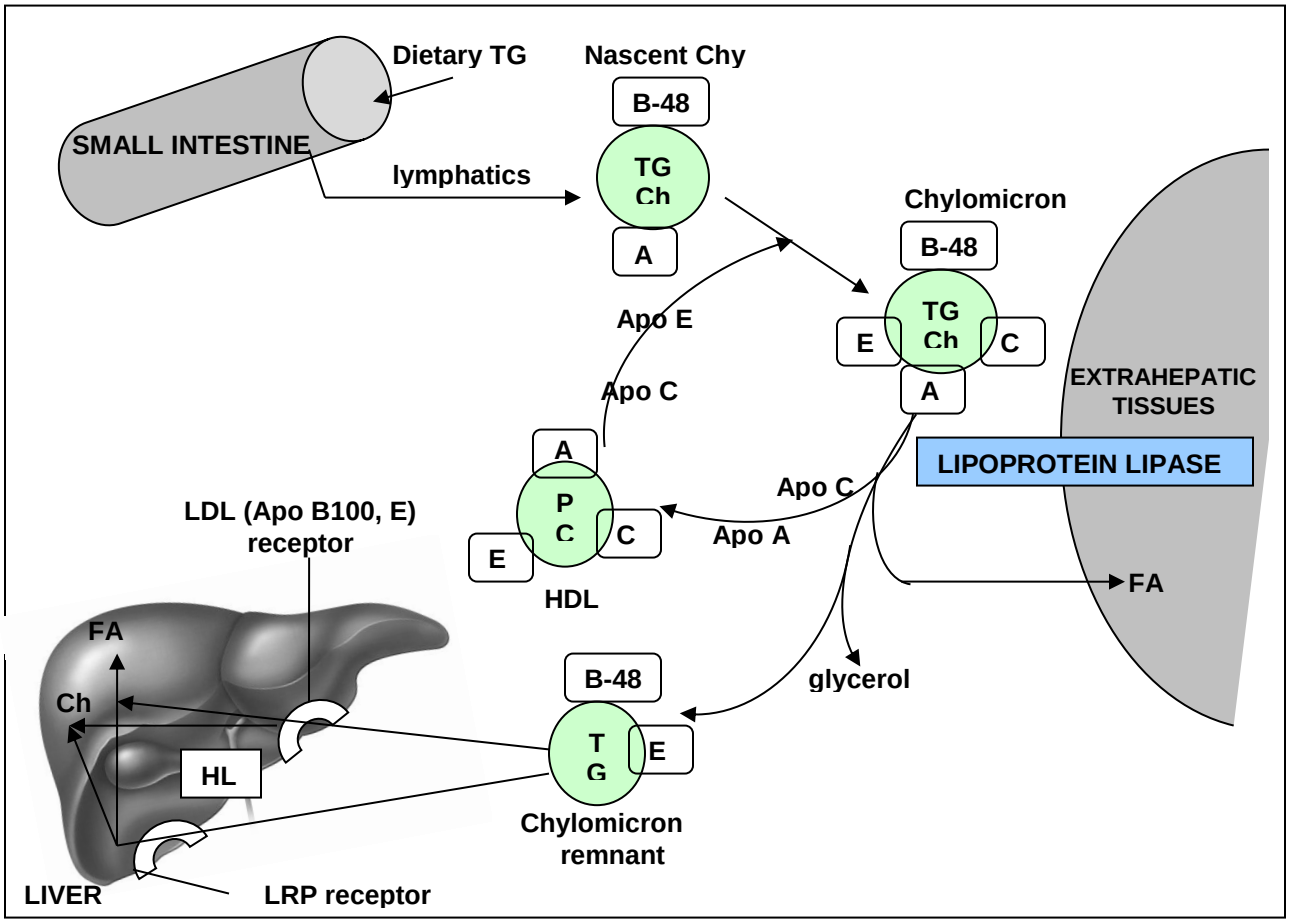
The structure of the plasma lipoprotein fractions

Lipoprotein fraction	ϕ nm	ρ g/ml	Composition %					$T_{1/2}$	Origin	Apolipo-proteins	Role
			Proteins	Lipids							
				Total	PL	CL	TG				
						F E					
Chy	75-1200	< 0.96	1-2	98-99	8	1 3	86	8 minutes	external	A, B 48, C, E	Transport of exogenous TG to tissues
VLDL	30-80	0.96-1.006	9	90-93	20	8 15	56	4 hours	Liver, intestine	B 100, E	Transport of endogenous TG from liver to tissues
LDL	20-40	1.006-1.063	11	89	26	9 34	29	2 days	VLDL and Chy	B 100, E	Transport of cholesterol from liver to tissues
HDL	7-20	1.063 HDL1 1.125 HDL2 1.210 HDL3	33-57	43-67	43-46	6-10 29-31	13-16	4 days	liver, intestine, VLDL and Chy	A I, A II, A III	Transport of cholesterol from tissues to liver
FFA - albumins		1.28	99	1	-	- -	-	-	Adipose tissue	-	energetic substrate

Abbreviations: TG –triacylglycerols
PL – phospholipids
CL – cholesterol
F – free, E – esterified
FFA – free fatty acids

III.10.1. Chylomicrons

They are formed within the enterocytes from the exogenous lipids, include apoB48, pass into the blood where they will be the fraction of primary chylomicrons Chy 1. They travel in the lymphatic system, and at the level of the left subclavian vein pass to the bloodstream where they interact with the HDL1 fraction, from which they acquire apo C and apo E, turning into circulating chylomicrons or Chy 2. These will reach the tissue capillary, where under the action of lipoprotein lipase and apo C, their triacylglycerols are hydrolyzed to fatty acids which pass into the tissues and glycerol which is transported to the liver. When the TG contents of Chy 2 decreases below 20%, these become residual chylomicrons or Chy 3. Chy 3 is captured by the liver, by attaching to specific receptors for apo E, then they are internalized and degraded.



Chylomicrons metabolism.

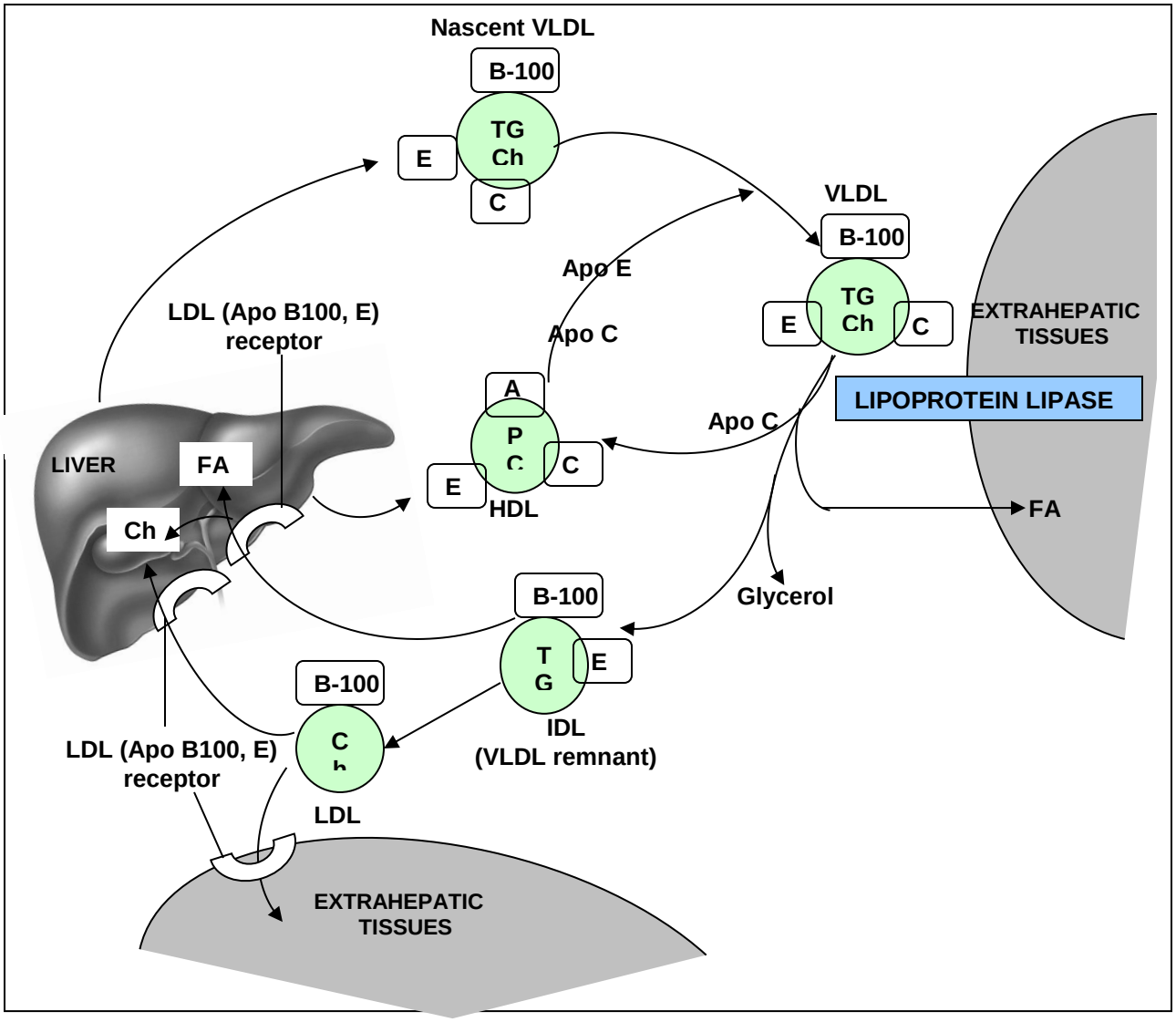
A, Apolipoprotein A; B 48, Apolipoprotein B 48; C, Apolipoprotein C; E, Apolipoprotein E; HDL=high density lipoproteins; TG, triacylglycerol; C, Cholesterol and Triglycerides; P, phospholipid; HL, hepatic lipase; LRP, a protein associated to LDL receptor.

The main role of chylomicrons is to transport exogenous lipids from the intestine to the tissues: triglycerides to most tissues, and phospholipids and cholesterol to the liver.

III.10.2. VLDL

It is formed within the liver, by encapsulation of the endogenous hepatic lipids, having mainly the apolipoprotein apo B100 and secondarily apo C and apo E. The particles reach the capillary endothelium where they are degraded in a similar manner to Chy 2, losing the triglyceride component. The remaining residual particles, called IDL (intermediary density lipoproteins) return to the liver, where at the level of the capillaries, lose apo E and apo C, turning into the LDL fraction.

The main role of VLDL is to transport the endogenous triglycerides to the tissues.



Metabolism of very low density lipoproteins (VLDL)

A, Apolipoprotein A; B-100, Apolipoprotein B-100; C, Apolipoprotein C; E, Apolipoprotein E; HDL = high density lipoproteins; lDL = intermediary density lipoproteins; LDL = low density lipoproteins; TG, triacylglycerol; Ch, Cholesterol; P, phospholipid; FA, fatty acids; HL, hepatic lipase; LRP, LDL receptor-related protein

III.10.3. LDL

It is formed within the liver from the residual VLDL (IDL). LDL gets to the peripheral cells, connects to the specific receptors, becomes internalized and decomposes into lysosomes. The cholesterol brought by LDL inhibits the local synthesis of cholesterol (HMG–reductase), activates the enzyme ACAT (acyl–cholesterol-acyl–transferase) and reduces the number of membrane receptors for LDL. This process of cholesterol transfer from LDL to the cells is called the β-lipoproteins pathway and is a mechanism of regulating cholesterol capture, depositing and synthesis, preventing the liver overloading with cholesterol. Of the total quantity of cholesterol transported, about 65% is absorbed by the peripheral cells and the rest by the macrophages - the scavenger pathway. The main role of LDL is to transport endogenous cholesterol from the liver to the tissues.

III.10.4. HDL

The HDL particles are complexes made of apoproteins (apoA-I, present within all HDL complexes, apoA-II which is found within about 2/3 of the total HDL complexes and other proteins such as the paraoxonase enzyme, apoE), free cholesterol and phospholipids within the external layer of the particle, and esterified cholesterol together with small quantities of triglycerides within the hydrophobic core of the complex.

ApoA-I represents 70% of the total proteins quantity existing within the HDL, located at the level of the external layer. ApoA-I is synthesized within hepatocytes and enterocytes, and **Apo-II** only in hepathocytes.

The two types of apoproteins interact with a **transporter protein** located at the level of the hepatocyte or enterocyte membrane (**ABCA1**), belonging to the superfamily of ATP binding cassette proteins (ABC), transferred to the plasma where by association with the free cholesterol molecules and the phospholipids secreted by the hepatocyte and enterocyte form **nascent HDL**, poor in lipids (**pre-β HDL**).

Nascent HDL, by interaction with ABCA1, will continue to collect free cholesterol (FR) and phospholipids (FL) from the macrophages within the arterial walls or from other cells within the peripheral tissues, as well as from lipoproteic particles rich in ApoB (chylomicrons, VLDL), and phospholipids collection is made in this case through the **phospholipids transfer protein** (**PLTP**).

Within the macrophages from the arterial walls, the transformation of the cholesterol esters (CE) into free cholesterol takes place, under the action of **cholesterol ester hydrolase** (CEH) which will be secreted by means of ABCA1 along with the phospholipids into the plasma where it will be collected by the particles of nascent HDL.

Under the action of the enzyme **LCAT (lecithin-cholesterol acyltransferase),** the free cholesterol located at the surface of the particles of nascent HDL is turned into esterified cholesterol (EC). This will migrate to the core of the particle, which enlarges becoming a spherical particle of **mature HDL** (**α HDL, HDL_3 şi HDL_2**). The mature HDL particle will reach the liver through the blood circulation, where there are two processing possibilities.

One of the ways involves the interaction of the HDL particles with the **SR-BI receptors** (scavenger receptor class B) located within the hepatocyte membrane, by which the molecules of free cholesterol and esterified cholesterol are absorbed within the hepatocyte. Within the hepatocyte, the esterified cholesterol is turned into free cholesterol which is either used for bile acids synthesis to be secreted in the bile, or cholesterol is

directly secreted into the bile, or by means of the protein ABCA1 into the plasma where it can combine with other molecules of apoA-I or apoA-II.

The second processing pathway ensures the transfer of esterified cholesterol from HDL to lipoproteins containing apoB (LDL, VLDL), which in their turn will transfer triglycerides to the HDL particles.

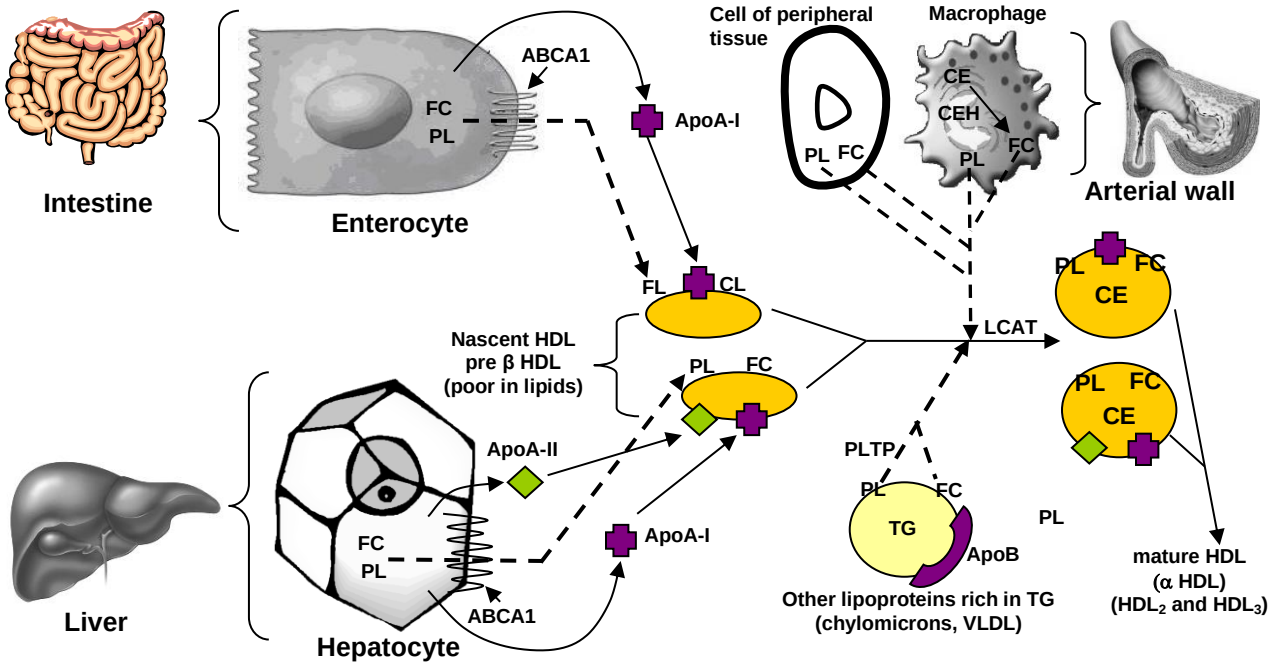
This lipids exchange is mediated by the **cholesteryl ester transfer protein** (**CETP**). The lipoproteins with apoB having absorbed the esterified cholesterol will transfer it to the hepatocyte by means of the LDL receptors where it will be turned into free cholesterol.

It has been found that the subjects with high concentration of cholesterol and apo A within the HDL fraction have a lower risk of atherosclerosis.

The normal cholesterol values of 150-250 mg %, add up all the cholesterol contained within the three main fractions: HDL – (40-60 mg% in women and 35-55 mg% in men), LDL 100-170 mg%, VLDL 20-40 mg %.

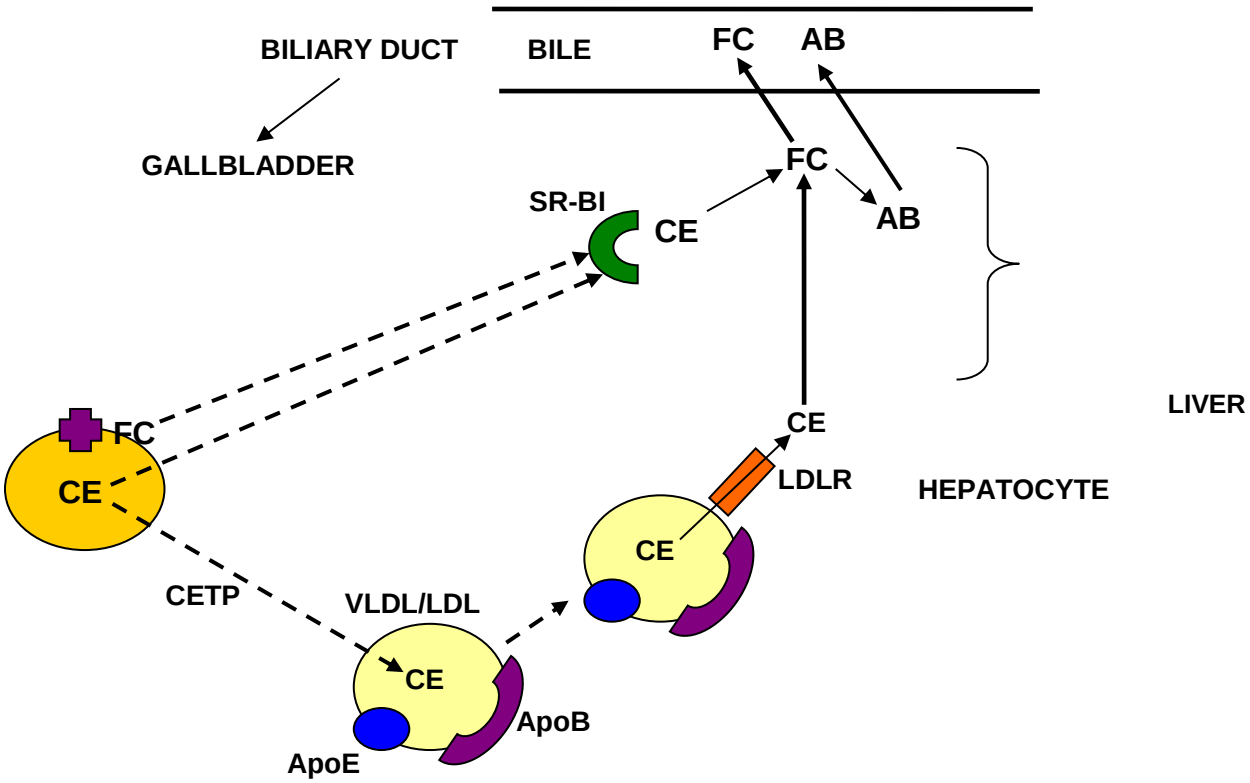
$$\text{Ratio } \frac{totalcholesterol}{HDLcholesterol} = 3{,}5 - 5$$

In the case of a ratio above 5, there is an increased risk of atherosclerosis.



Formation of the HDL lipoprotein particles

ABCA1 – apoproteins transporter protein A1 (transporter from the ATP binding cassette proteins family) ; FC – free cholesterol; PL – phospholipids; EC – ester cholesterol; CEH – cholesterol ester hydrolase; LCAT - lecithin-cholesterol acyltransferase; PTFL – phospholipids transfer protein (PLTP)



Unloading of the HDL lipoprotein particles

III.10.5. Pathology of lipoproteins metabolism

I. Atherosclerosis. Atherosclerosis is a complex of pathological alterations at the level large arteries intimae (coronary disease, acute heart attack, gangrene, cerebrovascular accidents, some cases of senile dementia) whose complications can be fatal. The name of atherosclerosis is due to the atheromatous plaques (injuries typical to the arterial intimae) formed by a cholesterol core surrounded by a fibrous area. The plaque prevents the blood flow from getting through the arterial lumen generating additional calcification, hemorrhage within the plaque and the formation of thrombi. Atheromatosis begins with a deposition of LDL cholesterol within macrophages which become foam cells and generate growth factors of various etiologies which induce fibroblast proliferation.

Risk factors for atherosclerosis are: age and gender (older age and male gender), smoking, diabetes mellitus, hypertension and hypercholesterolemia.

II. Familiar hypercholesterolemia (HF), 1:500 incidence.

It is due to the deficiency of LDL receptors from the liver and extrahepatic tissues, caused by mutations, deletions within the LDL receptor gene. It is transmitted mostly autosomal. The heterozygotes have only 50% of the LDL receptors, the LDL accumulating in the plasma where the cholesterol level reaches 250-500 mg/dl. Diagnosis elements: increase of plasma cholesterol > 260 mg%, tendon xanthomas and a family

history of coronary disease. The disease can lead to myocardial infarction. About 5% of all myocardial infarction cases before 60 years old is due to HF.

Hyperlipoproteinemias

They are regarded as the most common biochemical pathological modifications affecting between 5 - 20% of the population. Traditionally, there are 5 types of hyperlipoproteinemias, I - V. These are not diseases per se, but they are complications of certain chronical diseases such as diabetes mellitus, alcoholism, hypothyroidism. The hyperlipoproteinemias depend on the interaction between the genetic structure and a lipid rich diet.

Type I – hyperchylomicronemia (1:10000 incidence), is due to the deficiency of triglycerides hydrolysis within the chylomicrons, the level of TG in the blood exceeding 1000 mg%. This type does not produce atherosclerosis and coronary disease. The patients have cutaneous xanthomas, stomach pains and in extreme cases, pancreatitis risk.

Type II - hypercholesterolemia is characterized by LDL increase. Incidence at 2-8% of the population. High risk for atherosclerosis and coronary disease.

Type III - dysbetalipoproteinemia (1% of the population) is characterized by homozygotism apo E_2, a variant which is not linked to the hepatic receptors apo E. Residual chylomicrons and IDL are accumulated, which are engulfed within the reticuloendothelial cells, which will become foam cells. There are xanthoma eruptions and high risk of atherosclerosis and cardiovascular diseases.

Type IV - VLDL increase is the most common one. It increases the incidence of atherosclerosis.

Type V – both chylomicrons as well as VLDL increase. It is associated to the decompensated diabetes, alcoholism, obesity and renal disease.

For all types, a diet poor in calories and lipids, without alcohol and carbohydrates is the main therapeutic means.

Pharmacologic interventions that alter the plasma lipoproteins levels

Although diet is an efficient therapy in many forms of hyperlipoproteinemias, a large number of patients cannot face this change of lifestyle. For them, especially in the case of hypercholesterolemia, the following medication is used:

LOVASTATIN (MEVIOLINE) a HMG-CoA reductase inhibitor. Blocking the cellular synthesis will increase the number of LDL receptors and will decrease the LDL concentration from the blood.

CHOLESTYRAMIN is an anionic ions exchanger that binds to bile salts at the intestinal level, thus preventing their reabsorption and interrupting the enterohepatic cycle. The bile salts are eliminated through the fecal matter; and at hepatic level, the conversion of cholesterol into bile salts will be increased, diminishing its quantity in the liver and also reducing the LDL from the plasma (LDL is formed at a hepatic level). A diet rich in fibers is recommended. These will increase the intestinal contents volume, preventing the reabsorption of the bile salts. The antioxidant vitamins (C, E) prevent LDL oxidation and turning the macrophages into foam cells, thus avoiding lipid deposits.

III.11. Regulation of the lipid metabolism

The lipid metabolism is tightly related to the energy metabolism; the fatty acids being reserve substances for producing energy within the cell. For this reason, the lipid metabolism is dependent on the energy production from glucose and thus on insulin.

Early postprandial

There is an increase of the energy producing substances in the blood from the food digestion. After the energy needs are met, the excess of glucose and fatty acids is deposited through lipogenesis within the adipose tissue as triacylglycerols. This stage is dominated by insulin, an anabolic hormone which stimulates the energy storage pathways, stimulating this way glycogenogenesis and lipogenesis. The insulin controls the receptors for glucose and the key enzymes of the metabolic pathways which store the excess glucose.

Late postprandial (post-absorptive state)

It is a catabolic phase in which the insulin actions are reduced, increasing the concentration of hyperglycemic hormones (glucagon, catecholamines, glucocorticoids, etc). The lipolysis within the adipose tissue which produces excess fatty acids, used in the tissues as energy source and within the liver for the synthesis of the ketone bodies is stimulated. In starvation, the ketone bodies, which unlike FFA can cross the blood-brain barrier, will replace the glucose and will represent the energy source for the brain.

III.12. The pathology of lipid metabolism

Deficiencies within the fatty acids metabolism

1. deficiency - carnitine (premature babies)→hypoglycemia
   - carnitine palmitoyltransferase I.
2. Dicarboxylic aciduria → excretion of ω-dicarboxylic, hypoglycemia
3. Refsun Disease - accumulation of phytanic acid
   - deficiency of α- oxidation of fatty acids
4. Zellweger syndrome – lack of peroxisomes.

Deficiencies within the complex lipids metabolism

1. Respiratory distress syndrome (dipalmytolecitin-pulmonary surfactant)
2. Multiple sclerosis – phospholipids loss
3. Lipidose - lipid storage diseases – accumulation of various lipids as a result of certain enzymatic deficiencies; Gaucher disease for instance - β-glycoxidation deficiency ↑cerebrosides
   - Metachromatic Leukodystrophy →def. Sulphatase

Deficiencies within the lipoproteins metabolism

Hypolipoproteinemias – rare
Hyperlipoproteinemias – I lipoproteinlipase deficiency
– II apo B-48 deficiency etc.

Metabolic syndrome

The most recent research in the field of the etiology of degenerative metabolic diseases, diabetes and cardiovascular maladies, have shown that the common element is the alteration of the structure and functionality of the vascular endothelium, or endothelial dysfunction. This common element has outlined a new preliminary and predisposing phase to the development of this malady, a phase called **metabolic syndrome**.

The term of metabolic syndrome unites the factors which increase the risk of developing cardiovascular diseases and diabetes:

1. decrease of glucose tolerance, insulin-resistent or type II diabetes;
2. moderate arterial hypertension;
3. central or visceral obesity;
4. dyslipidemia (decrease of HDL cholesterol and triglycerides increase).

The causes of the metabolic syndrome are still little understood and its pathophysiology is extremely complex and partially elucidated. One of the central pathophysiology factors is the dysfunction of the vascular endothelium, while the inflammation and the oxidative stress are the main mechanisms affecting the normal endothelial functionality.

The response of the vascular endothelium to abnormal stimuli (e.g.: dyslipidemia, hyperglycemia, glycosylated proteins, inflammation, oxidative stress) is gradual and involves at first:

- **modulation** of the endothelial constitutive functions (for instance the increase of NO production as a result of stimulation of acetylcholine, increase of permeability for lipoproteins under circumstances of hyperglycemia or hyperlipemia)
- endothelial **dysfunction** by the appearance of new properties
- **endothelial damage** which can be reversible through a process of local tissue regeneration, or can be irreversible, ultimately leading to cell death. For instance, hyperlipidemia finally leads to atherosclerosis, and hyperglycemia leads to diabetes mellitus.

Resistance to insulin (at the level of the adipose, muscular and hepatic tissue) causes the endothelial dysfunction by multiple mechanisms among which the increase of oxidative stress followed by reducing the NO bioavailability, inflammation by producing certain pro-inflammatory compounds, as well as the alteration of the mechanisms of action of insulin with the synthesis of the vasoconstrictor endothelin I.

New therapeutic strategies in the metabolic syndrome

The treatment in case of the metabolic syndrome is meant to prevent the occurrence or the control of diabetes mellitus and to prevent the cardiovascular events by reducing the atherosclerosis risk. When lifestyle modifications and regular exercise are not enough, medication is usually needed. The treatment options for the metabolic syndrome have become more broad by the emergence of certain new medication classes.

There are 5 classes of hypoglycemia medicines on the market:

1. sulphonilureic (glibenclamide - Daonil, glimepiride - Amaryl), stimulate insulin secretion, acting at the level of β-cell receptors within the pancreas.

2. biguanides (Metformin) acts by diminishing the hepatic production of glucose by inhibiting gluconeogenesis and glycogenolysis, reduces insulin-resistance, reduces appetite.
3. inhibitors of α-glucosidase (milglitol - Diastabol), slows down the process of digestion and assimilation of polysaccharides within the proximal small intestine, reducing postprandial hyperglycemia.
4. glinides (RepFFAinida, Nateglinida) stimulate insulin secretion by the pancreas, acting at the level of another receptor from the beta cells membranes than the sulphonylureas do.
5. biosynthetic human insulin, made by genetic engineering on bacterial cultures, is ultrapure and absolutely identical with human insulin. It is the most efficient medicine for reducing glycemia. There is long or medium-term action insulin, used for covering the basic insulin needs, and the quick or short-term action insulin, for covering the postprandial needs. The insulin treatment is beneficial on the level of triglycerides and cholesterol LDL, but causes weight gain.

New medicines have emerged recently, based on new control methods of the biochemical disturbances within the metabolic syndrome:

1. Incretins

Postprandial, specialized intestinal cells secrete hormones known as incretin hormones. These hormones behave as messengers whose target cells are the beta pancreatic cells. The outcome of incretins action is the increase of insulin secretion. This relation between the intestine and pancreas is known as *enteroinsular axis* and is considered responsible for about hlaf of the insulin production which is the peak reached postprandial. The incretins have a peptide structure. Two incretins have been more thoroughly studied and synthesized:

- glucagon-like peptide-1, GLP-1
- insulin-tropic glucose-dependent peptide also known as gastric inhibitory polypeptide (GIP).

Both types can stimulate the insulin secretion, but it has been recently proved that GIP is much less efficient than GLP-1.

The action of GLP-1:

- stimulates insulin secretion;
- inhibits glucagon secretion;
- slows down the process of intestine discharge;
- reduces the hunger feeling;
- stimulates the multiplication of the beta pancreatic cells;
- prevents the programmed cell death (apoptosis) of the beta pancreatic cells allowing for the regeneration of the islets of Langerhans from the pancreas and partially reestablishes the pancreas secretion capacity;
- does not produce hypoglycemia even in great doses.

Disadvantages:

- in oral administration, being a peptide, it is digested, and its action is canceled;

- in intravenous administration, it is quickly inactivated by an enzyme - dipeptidyl-peptidase IV (DPP-IV).

2. DPP-IV (SitFFAiptin, VildFFAiptin-LAF237) inhibitors are compounds which can be administered orally and which inhibit the enzyme DPP-IV. Administering a DPP-IV inhibitor prevents the decomposition of the natural GLP-1 by enzymes, which allows the peptide to exercise its function of stimulating the insulin secretion.

3. Modified GLP (Exenatid, LirFFAutid, CJC1131). In order to permit the action of GLP-1, GLP-1 with a modified chemical structure has been synthesized, being resistant to the action of DPP-IV.

Exenatide, accidentally discovered in reptile saliva, is a peptide having 50% the same chemical structure as GLP-1. Being an analogue of it from a structural point of view, stimulates the insulin secretion, inhibits the glucagon secretion, and slows down gastric motility.

4. The analogues of the human biosynthetic insulin are made by selectively altering the amino-acids succession composing the human insulin in order to make insulin with a better disintegration time within the blood flow, without affecting its action and without causing immune reactions.

- Lispro Insulin (Humalog) – the name comes from the 2 amino-acids (lisine and proline) whose succession has been altered within the beta chain at position 28 and 29. It is quicker and with a shorter action time compared to the human biosynthetic insulin.
- Aspart Insulin (Novorapid) – made by replacing the aspartic acid with proline at position 28 of the beta chain. It is a quick action insulin.
- Glargina Insulin (Lantus)– it is long action insulin, made by the genetic alteration of three amino-acids:
  - asparagine from position 21 of the alpha chain is replaced by glycine;
  - two arginine groups are added at the carboxy-terminal end of the β chain.

These structural alterations slow down the insulin absorption and solubility into the blood. Glargina Insulin has an isoelectric pH modified at 5.4, which makes it insoluble in the blood at a normal pH. It is prepared within a solution with pH = 4.0 to which zinc is added. When injected subcutaneously, it precipitates almost completely, it is slowly absorbed within the circulation in small quantities which provides the basic insulin needs throughout 24 hours.

- Detemir Insulin (Levemir) – fatty acids have been added, by acylation, to the insulin molecule, turning it into a long action insulin.

5. The selective agonists of PPAR γ receptor (peroxisomal proliferator activator receptor γ) – glytasone or tiazolidindions (Glitazonze). PPAR is a family of transcription factors controlling the expression of several genes involved in the control of carbohydrate and lipid metabolism. Their action can be amplified by a substance with a structure similar to (agonists) the natural signal molecules which bind to the PPAR receptors. These are

used for the treatment of insulin resistance or of both types of diabetes, as well as for the dyslipidemia associated to them:

- determines hypoglycemia by increasing muscle, adipose tissue and liver sensitivity to exo- and endogenous insulin (insulin sensitizers);
- determines hypotriglyceridemia by stimulating the catabolism of lipoproteins rich in triglycerides;
- reduces oxidative stress;
- reduces the amplitude of inflammatory response.

6. The selective agonists of PPARα receptor - Fibrates (Fenofibrat, Gemfibrozil, Bezafibrat) alter the atherogenous lipid phenotype, being agonists of PPAR α (expressed in liver, kidneys, heart and skeletal muscles), modulate genes involved in lipid metabolism. Action:

- determines the lipolysis of lipoproteins VLDL by:
    - increasing the activity of lipoprotein lipase (LPL);
    - reducing the contents of apolipoprotein CIII (inhibitor of LPL) by decreasing its synthesis at a hepatic level.
- limits the triglycerides hepatic synthesis by:
    - stimulating the fatty acids capture and metabolism at a hepatic level;
    - reducing the fatty acids synthesis at a hepatic level;
    - stimulating the hepatic synthesis of apolipoprotein A-V.
- stimulates the HDL production by increasing the hepatic synthesis of apolipoproteins AI and AII;
- stimulates the LDL catabolism by:
    - altering the LDL composition;
    - increasing the LDL affinity for specific receptors.

7. Statins (Simvastatin, Lovastatin, Fluvastatin, Pravastatin, Atorvastatin) reduce the circulating cholesterol quantity from the body as well, acting by two mechanisms:

- increase the receptors density for LDL at the hepatocytes level resulting in a marked decrease of LDL, IDL and of the remnant chylomicrons from the circulation, these lipoproteins being more intensely captured by the liver;
- reduce the hepatic production of VLDL, precursors of IDL and LDL by:
    - inhibiting enzyme 3-hydroxy-3methylglutaryl coenzyme A reductase (HMG-CoA reductase) decreasing the synthesis de novo of cholesterol;
    - reducing the synthesis of apolipoprotein B100.