PROTEIN SYNTHESIS AND CATABOLISM

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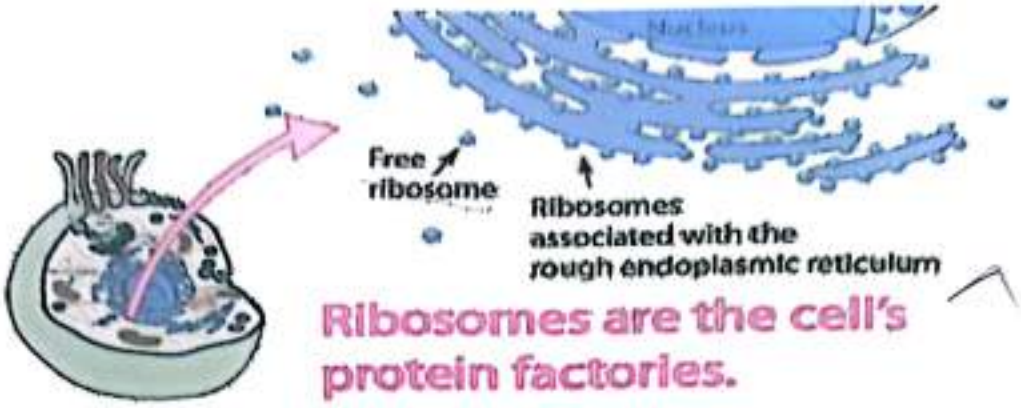
Hepatic protein synthesis proceeds via the subcellular stages of gene transcription (in the nucleus) and gene translation (in the cytoplasm). The DNA is transcribed into various types of RNA by the action of the different DNA-dependent RNA polymerases I (A), II (B) and III (C). RNA polymerase I is responsible for the transcription of ribosomal RNA, RNA polymerase II mediates the transcription of messenger RNA, and RNA polymerase III forms transcriptal RNA. These three different RNA types move out of the nucleus into the cytoplasm. Here the ribosomes acquire the genetic information needed for protein synthesis via mRNA, and tRNA transports the activated amino acids to the ribosomes, which are themselves activated (and if necessary replicated) by rRNA.

Protein metabolism denotes the various biochemical processes responsible for the synthesis of proteins and amino acids (anabolism), and the breakdown of proteins by catabolism.

The steps of protein synthesis include transcription, translation, and post translational modifications. During transcription, RNA polymerase transcribes a coding region of the DNA in a cell producing a sequence of RNA, specifically messenger RNA (mRNA).

In humans, non-essential amino acids are synthesized from intermediates in major metabolic pathways such as the Citric Acid Cycle. Essential amino acids must be consumed and are made in other organisms. The amino acids are joined by peptide bonds making a polypeptide chain. This polypeptide chain then goes through post translational modifications and is sometimes joined with other polypeptide chains to form a fully functional protein.

The sites of proteins synthesis are ribosomes. There are Free ribosomes are located in the cytosol and are able to move throughout the cell, whereas fixed ribosomes are attached to the rER. Free ribosomes synthesize proteins that are released into the cytosol and used within the cell.



Protein catabolism is the process by which proteins are broken down to their amino acids. This is also called proteolysis and can be followed by further amino acid degradation.

Proteolysis in organisms serves many purposes; for example, digestive enzymes break down proteins in food to provide amino acids for the organism, while proteolytic processing of a polypeptide chain after its synthesis may be necessary for the production of an active protein. It is also important in the regulation of some physiological and cellular processes, as well as preventing the accumulation of unwanted or abnormal proteins in cells. Consequently, dis-regulation of proteolysis can cause disease.

CARBOHYDRATE METABOLISM OF THE LIVER

The liver is of central significance for the regulation of carbohydrate metabolism and the maintenance of the physiological glucose concentration within narrow limits. There is an intermittent dietary uptake of carbohydrates which, after resorption in the intestine, are transported primarily to the liver. The liver can take up about 87% of the glucose delivered by the portal blood. When required, the liver is able to release glucose from its stored carbohydrate reserves to compensate for any deficiency and maintain the normal blood sugar value. The adjustment of blood sugar concentration, which is responsible for all intermediary metabolic processes, is regulated by the interplay between insulin and its hormonal antagonists, such as glucagon and adrenalin. Thus the liver contributes in four different ways to the maintenance of **glucose homoeostasis** within the context of carbohydrate metabolism:

(1.) glycogenesis, (2.) glycogenolysis, (3.) gluconeogenesis, and (4.) glucolysis. • The liver therefore functions as a glucostate.

1- Glycogenesis:

Glycogenesis is the formation of glycogen from glucose. Glycogen is synthesized depending on the demand for glucose and ATP (energy). If both are present in relatively high amounts, then the excess of insulin promotes the glucose conversion into glycogen for storage in liver and muscle cells.

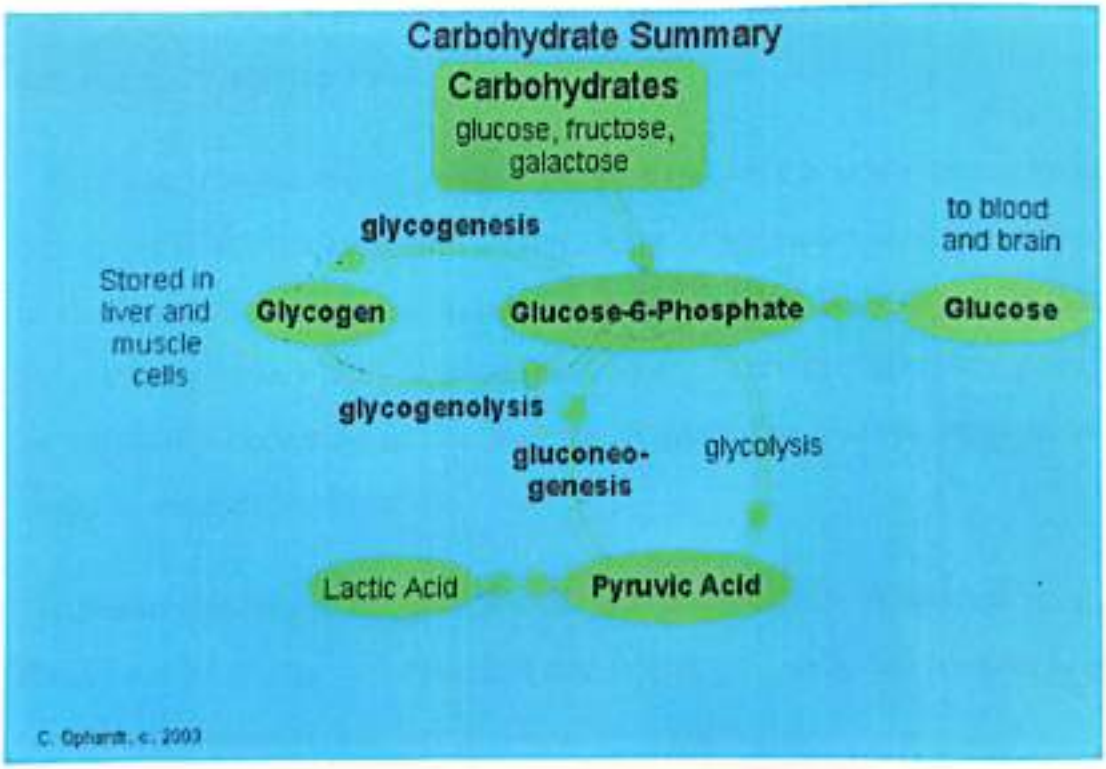
In the synthesis of glycogen, one ATP is required per glucose incorporated into the polymeric branched structure of glycogen. actually, glucose-6-phosphate is the cross-roads compound. Glucose-6-phosphate

is synthesized directly from glucose or as the end product of gluconeogenesis.

2- Glycogenolysis:

In glycogenolysis, glycogen stored in the liver and muscles, is converted first to glucose-1- phosphate and then into glucose-6-phosphate. Two hormones which control glycogenolysis are a peptide, glucagon from the pancreas and epinephrine from the adrenal glands.

Glucagon is released from the pancreas in response to low blood glucose and epinephrine is released in response to a threat or stress. Both hormones act upon enzymes to stimulate glycogen phosphorylase to begin glycogenolysis and inhibit glycogen synthetase (to stop glycogenesis).



3. Gluconeogenesis:

Gluconeogenesis is the process of synthesizing glucose from non-carbohydrate sources. Gluconeogenesis is activated when the glycogen reserves are exhausted. There are three alternative substrates available in the liver cells for glucose synthesis:

1. Lactate (60%) from anaerobic glycolysis

2. Amino acids, mainly alanine (30%) from proteolysis

3. Glycerol (10%) from lipolysis in the fatty tissue.

The starting point of gluconeogenesis is pyruvic acid. Lactic acid, some amino acids from protein and glycerol from fat can be converted into glucose. Gluconeogenesis is similar but not the exact reverse of glycolysis, some of the steps are the identical in reverse direction and three of them are new ones.

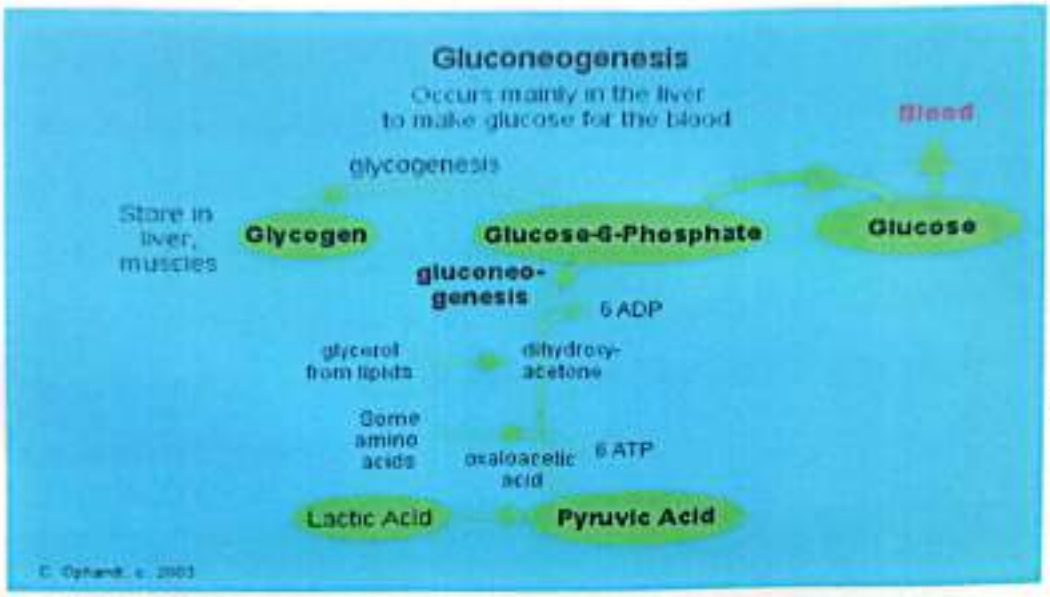
Gluconeogenesis occurs mainly in the liver with a small amount also occurring in the cortex of the kidney. Very little gluconeogenesis occurs in the brain, skeletal muscles, heart muscles or other body tissue. In fact, these organs have a high demand for glucose. Therefore, gluconeogenesis is constantly occurring in the liver to maintain the glucose level in the blood to meet these demands.

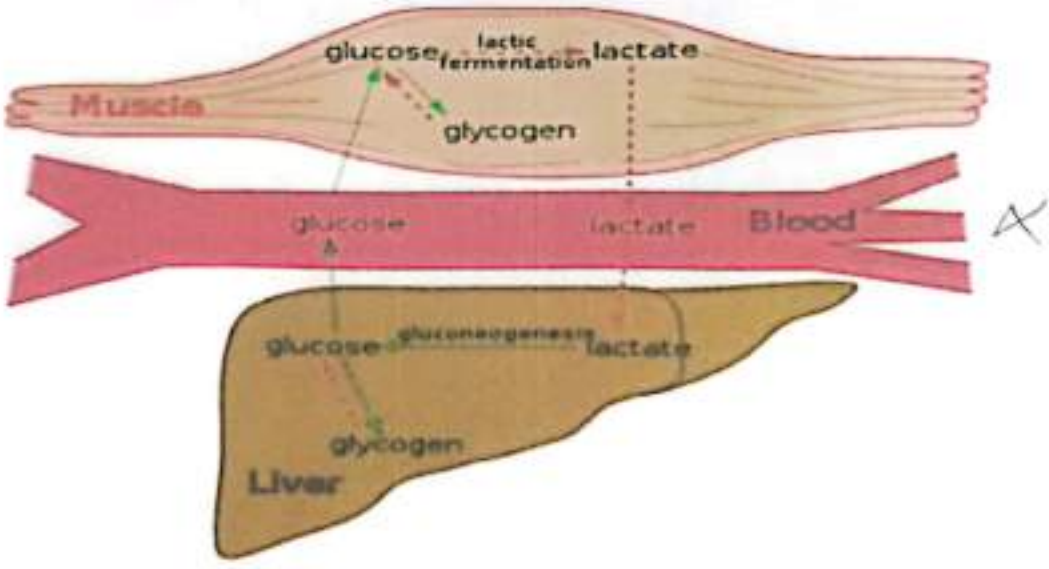
Gluconeogenesis is an energy-rich process which is increased in the short term by glucagon, adrenaline and acetyl-CoA or in the long term by glucocorticosteroids, but it is inhibited by insulin.

Ketogenesis is the biochemical process through which organisms produce ketone bodies through breakdown of fatty acids and ketogenic

amino acids. This process supplies energy under circumstances such as fasting or caloric restriction to certain organs, particularly the brain, heart and skeletal muscle. Insufficient gluconeogenesis can cause hypoglycemia and excessive production of ketone bodies.

Ketone bodies are not obligately produced from fatty acids, but rather any meaningful amount of them is synthesized only in a situation of carbohydrate and protein insufficiency, where fatty acids are the only readily available fuel for their production.

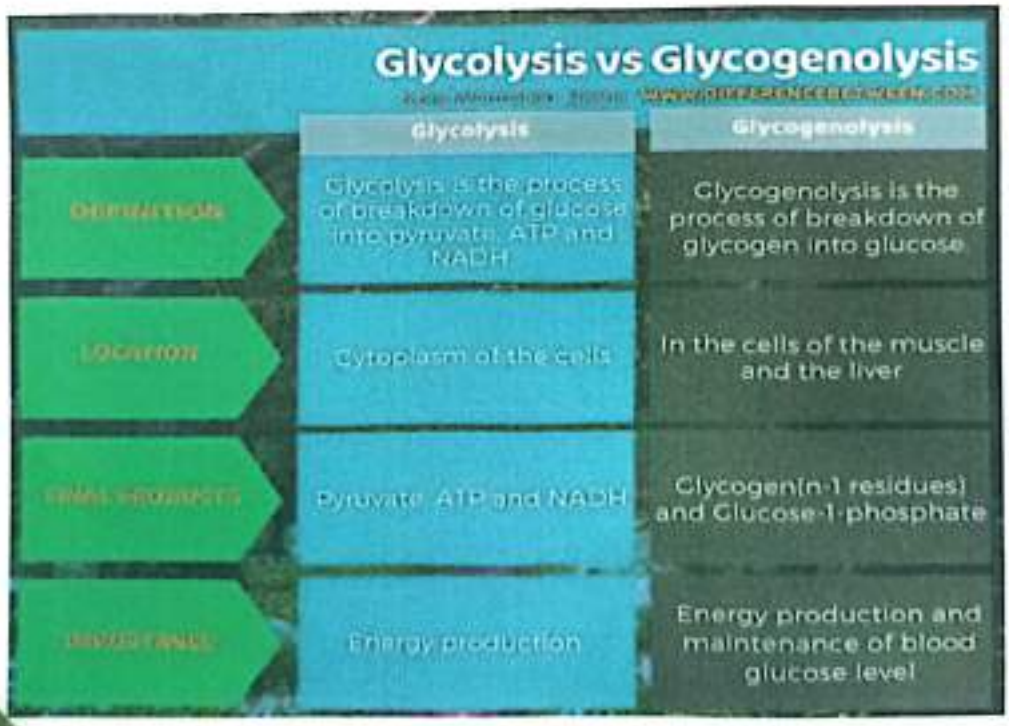




4. Glycolysis

Glycolysis is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate (pyruvic acid), and a hydrogen ion H^+. The free energy released in this process is used to form the high-energy molecules ATP and NADH. Glycolysis is a sequence of ten enzyme-catalyzed reactions.

Most monosaccharides, such as fructose and galactose, can be converted to one of these intermediates. The intermediates may also be directly useful rather than just utilized as steps in the overall reaction. In most organisms, glycolysis occurs in the cytosol. Glucose-6-phosphate is the first step of the glycolysis pathway if glycogen is the carbohydrate source and further energy is needed. If energy is not immediately needed, the glucose-6-phosphate is converted to glucose for distribution in the blood to various cells such as brain cells. The key enzymes of glycolysis are activated by insulin.



Lipid Metabolism of the Liver

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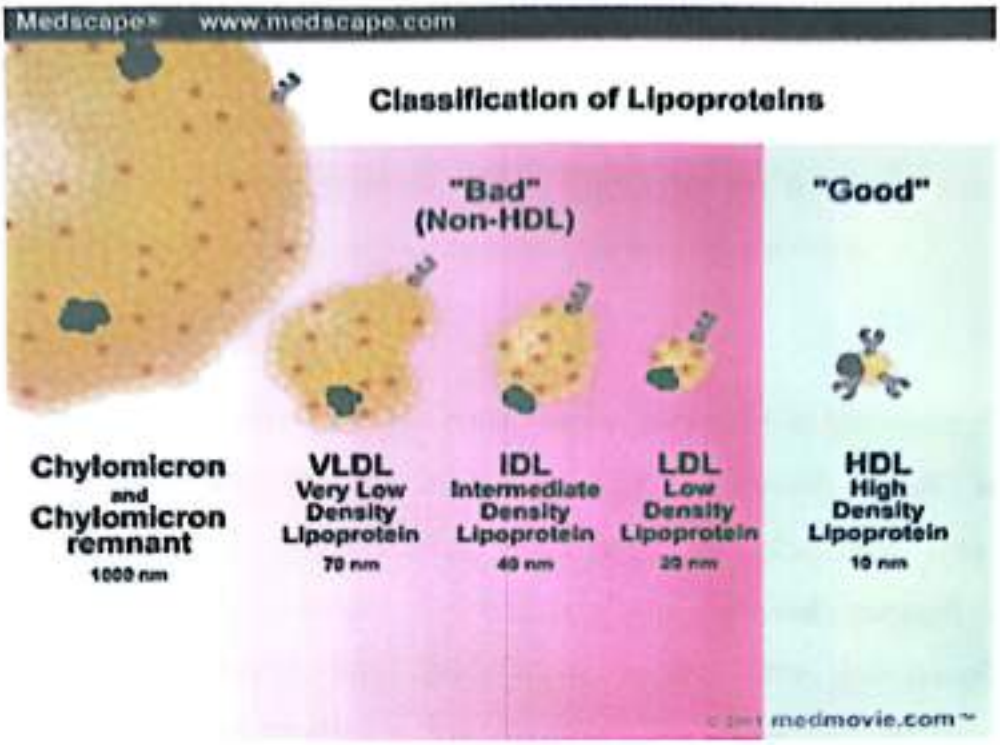
Fats and fat-like compounds of varying chemical structures are classified as lipids. They have a low molecular weight and are insoluble in water. The original substance in fat biosynthesis is acetyl-CoA (so-called activated acetic acid). On the basis of chemical criteria, they may be divided into simple lipids (glycerides, cholesterol, cholesterol esters, bile acids) and complex lipids.

The liver has a variety of functions in lipid metabolism: (1.) uptake, oxidation and transformation of free fatty acids, (2.) synthesis of plasma lipoproteins, (3.) transformation of lipoproteins, (4.) catabolization of LDL, VDL and chylomicron remnants, and (5.) secretion of enzymes for lipoprotein metabolism.

Differences between oils and fats

Differences	Fats	Oils
Sources	Mainly animals	Mainly plants
Fatty acid	Saturated	Unsaturated
Bonding	No double bond	Have double bond
State at room conditions	Solid	Liquid
Melting point	High	Low

Classification of lipoproteins



Lipoproteins are macromolecules comprising proteins (apolipoproteins, apoproteins) and lipids. They transport water-insoluble lipids in the blood, with the exception of the albumin-bound free fatty acids. Only short chain fatty acids are dissolved in plasma. The lipoproteins are formed in the liver and in the mucosa of the small intestine. Many enzymes, transporters, structural proteins, antigens, adhesins, and toxins are lipoproteins. Examples include plasma lipoprotein particles (HDL, LDL, IDL, VLDL and chylomicrons).

Subgroups of these plasma particles are primary drivers or modulators of atherosclerosis. The handling of lipoprotein particles in the body is referred to as lipoprotein particle metabolism. It is divided into two pathways, **exogenous** and **endogenous**, depending in large part on whether the lipoprotein particles in question are composed chiefly of

dietary **(exogenous)** lipids or whether they originated in the liver **(endogenous)**, through de novo synthesis of triacylglycerols.

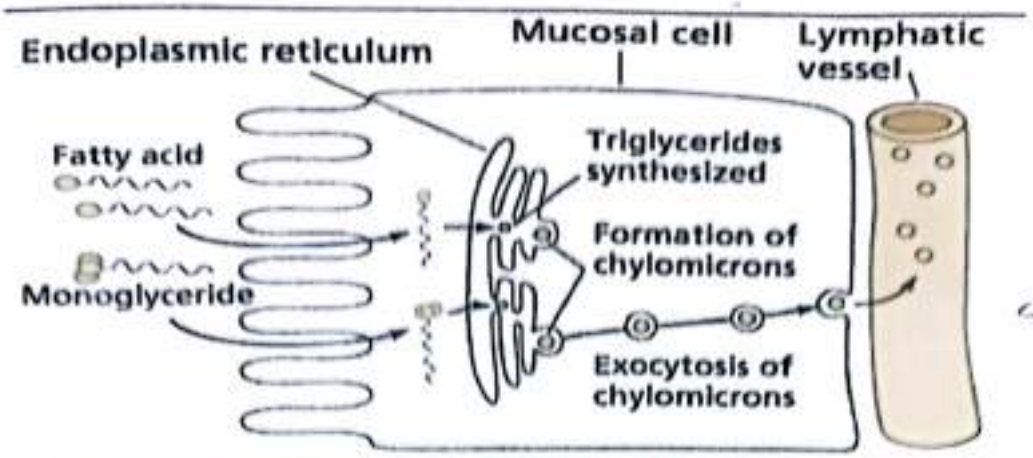
The hepatocytes are the main platform for the handling of triacylglycerols and cholesterol; the liver can also store certain amounts of glycogen and triacylglycerols. While adipocytes are the main storage cells for triacylglycerols, they do not produce any lipoproteins.

1- Chylomicrons:

Chylomicrons are formed in the endoplasmic reticulum in the absorptive cells **(enterocytes)** of the small intestine. The villi, lined with the microvilli of the brush border, provide a lot of surface area for absorption. Newly formed chylomicrons are secreted through the basolateral membrane into the lacteals, where they join lymph to become chyle. The lymphatic vessels carry the chyle to the venous return of the systemic circulation. From there the chylomicrons supply the tissue with fat absorbed from the diet.

- Chylomicrons transport lipids absorbed from the intestine to adipose, cardiac, and skeletal muscle tissue, where their triglyceride components are hydrolyzed by the activity of the **lipoprotein lipase,** allowing the released free fatty acids to be absorbed by the tissues. When a large portion of the triglyceride core has been hydrolyzed, chylomicron remnants are formed and are taken up by the liver, thereby also transferring dietary fat to the liver.

A lacteal: is a lymphatic capillary that absorbs dietary fats in the villi of the small intestine.



2- Very-low-density lipoprotein (VLDL)

Very-low-density lipoprotein (VLDL), density relative to extracellular water, is a type of lipoprotein made by the liver. VLDL is assembled in the liver from triglycerides, cholesterol, and apolipoproteins. VLDL is converted in the bloodstream to low-density lipoprotein (LDL) and intermediate-density lipoprotein (IDL).

VLDLtransports **endogenous** products,whereas chylomicrons transport exogenous (dietary) products. Very-low-density lipoproteins transport endogenous triglycerides,phospholipids, cholesterol,and cholesteryl esters.**It functions** as the body's internal transport mechanism for lipids.

3- Low density lipoproteins (LDL)

Low density lipoproteins (LDL) are **formed from VLDL** in the plasma when triglycerides are removed from VLDL by the **lipoprotein lipase enzyme** (LPL) and they become smaller and denser. If no VLDL is secreted, there is no synthesis of LDL. **Insulin** and **oestrogen** increase VLDL secretion.

The function of LDL is the transport of cholesterol and cholesterol esters. Cell surface LDL receptors take up LDL-bound cholesterol according to cellular requirements. In the event of increased LDL

availability, scavenger cells (e. g. macrophages) can also act to clear away cholesterol, independently of the LDL receptors. LDL has been associated with the progression of atherosclerosis and blockage of the artery lumen, because it can carry cholesterol into smaller vessels. But LDL is also essential for carrying lipids that keep the human body alive, including in those small vessels.

Atherosclerosis

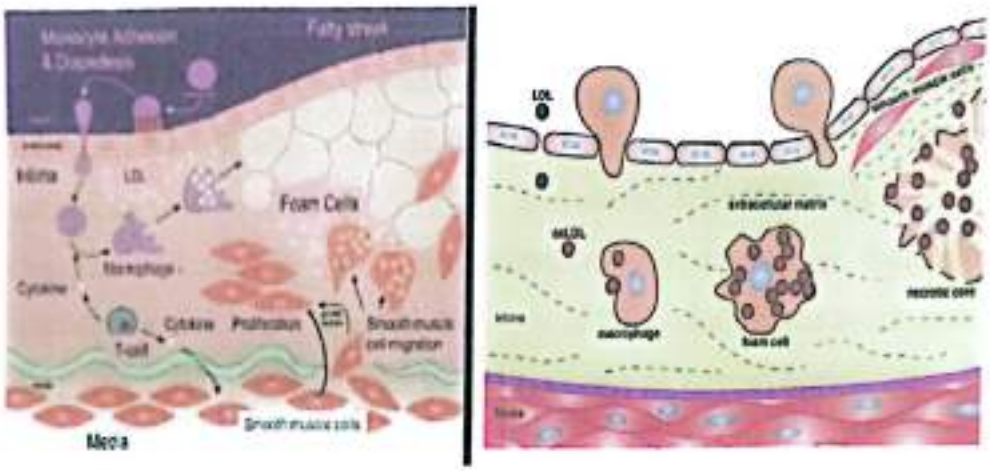
All blood vessels (arteries and veins) have three primary layers: the **intima, media,** and **adventitia**. Normally, the walls of an artery are smooth, allowing unobstructed blood flow. The innermost layer of a blood vessel (**the intima**) is lined with endothelial cells, which are in direct contact with blood.

Atherosclerosis is a disease process which is triggered by sometimes subtle physical or chemical insults to the endothelial cell layer of arteries. The endothelial cells begin to produce cell surface adhesion molecules, causing monocytes and T-lymphocytes to adhere to the endothelium and then migrate beneath it by squeezing between the endothelial cells. Circulating monocytes and T-lymphocytes are attracted to the sites of injury by chemoattractant cytokines (chemotaxis).

The endothelial cells also change shape, and the tight junctions between endothelial cells loosen, increasing the permeability to fluid, lipids, and

leukocytes. Lipoprotein particles, and especially low-density lipoprotein (LDL), enter the arterial wall and undergo oxidation.

Oxidation of LDL in the arterial wall occurs as a result of its exposure to nitric oxide, macrophages, and some enzymes. Once they have migrated into the intima, monocytes differentiate into macrophages and begin to take up oxidized LDL that has gotten into the intima. Macrophages retain the lipid they take up, and as they become more lipid-laden, they are referred to as **"foam cells."** Eventually, the foam cell will undergo apoptosis and die, but the lipid will accumulate in the intima.



- Arteriolosclerosis, is the thickening, hardening, and loss of elasticity of the walls of arteries, unlike atherosclerosis, is a sclerosis that only affects small arteries and arterioles, which carry nutrients and blood to the cells.
- Atherosclerosis: is the narrowing of arteries from a build up of plaque, usually made up of cholesterol, fatty substances, cellular waste products, calcium and fibrin, inside the arteries. This affects large and medium-sized arteries.

4-High density lipoproteins (HDL)

is one of the five major groups of lipoproteins. HDL transports cholesterol mostly to the liver or steroidogenic organs such as adrenals, ovary, and testes by both direct and indirect pathways. HDL is removed by HDL receptors such as scavenger receptor BI (SR-BI), which mediate the selective uptake of cholesterol from HDL. In humans, probably the most relevant pathway is the indirect one, which is mediated by cholesteryl ester transfer protein (CETP). This protein exchanges triglycerides of VLDL against cholesteryl esters of HDL. As the result, VLDLs are processed to LDL, which are removed from the circulation by the LDL receptor pathway.

The triglycerides are not stable in HDL, but are degraded by hepatic lipase so that, finally, small HDL particles are left, which restart the uptake of cholesterol from cells. The cholesterol delivered to the liver is excreted into **the bile** and, hence, **intestine** either directly or indirectly after conversion into **bile acids**. Delivery of HDL cholesterol to adrenals, ovaries, and testes is important for the synthesis of steroid hormones.

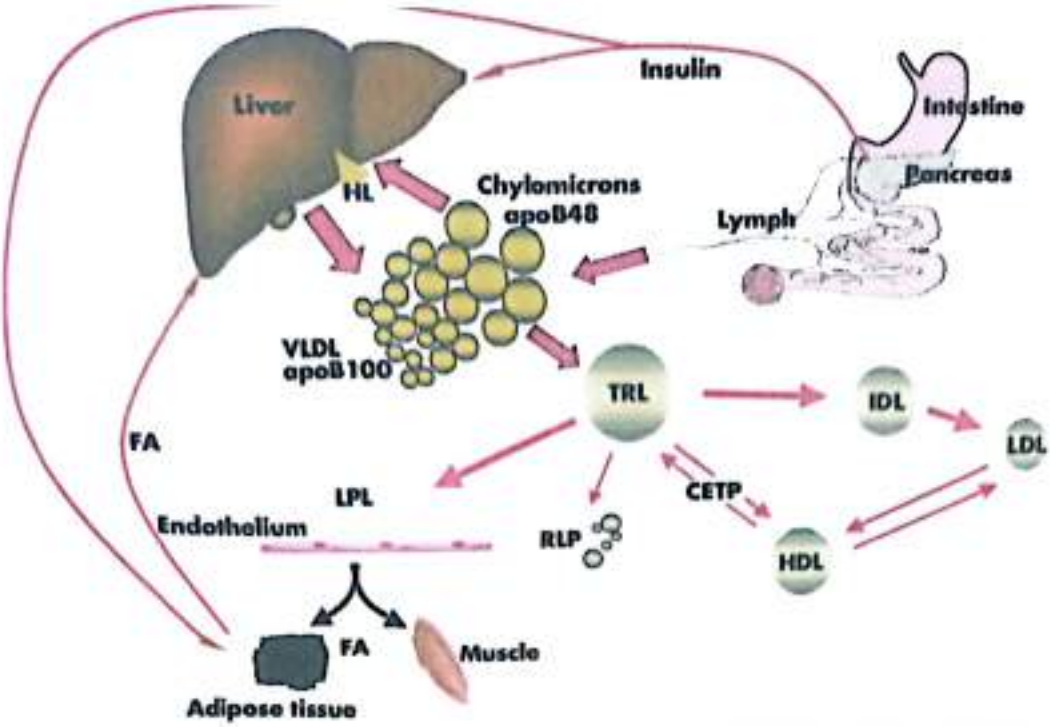


Diagram showing the metabolic exchange of lipids between intestine, fatty tissue, musculature and liver. Dietary fatty acids (FA) are absorbed from the gut and converted to triglycerides to be incorporated into chylomicrons in the intestinal epithelial cells. The triglyceride-rich apolipoprotein (apo) B48 containing chylomicrons enter the plasma via the intestinal lymph. Lipoprotein lipase (LPL) hydrolyses the triglyceride in chylomicrons to fatty acids, which are taken up by muscle cells for oxidation or adipocytes for storage. The remaining particles, the chylomicron remnants, are removed from the circulation by the liver through binding of their surface apoE to the low density lipoprotein (LDL) receptor or LDL receptor related protein. Very low density lipoprotein (VLDL) particles are triglyceride-rich apoB100 containing particles, synthesised by the liver. As with chylomicrons, VLDL triglycerides are hydrolysed by LPL. VLDL remnants or intermediate density lipoproteins (IDL) are taken up by liver receptors via apoE or converted to LDL. Chylomicrons, VLDL and their respective remnants (RLP, remnant lipoproteins) are termed triglyceride-rich lipoproteins (TRL). Under physiological conditions, insulin, which is raised in the postprandial state, suppresses lipolysis from adipose tissue and hepatic VLDL production, however, this insulin action is inappropriate in insulin resistance and type 2 diabetes, resulting in high TRL concentrations. The large amount of TRL and their prolonged residence time in the circulation increase the exchange of esterified cholesterol from high density lipoprotein (HDL) and LDL to TRL and of triglycerides to LDL and HDL particles, which is mediated by cholesterol-ester transfer protein (CETP). Triglyceride enrichment of LDL particles renders them better substrates for hepatic lipase (HL), which hydrolyses triglycerides from the core of LDL and turns them into smaller and denser particles. Small dense LDL are more atherogenic as they readily enter the subendothelial space and become oxidised. Triglyceride enriched HDL particles are smaller and are more rapidly catabolysed, which may explain the observed low plasma HDL in insulin resistance and type 2 diabetes.

cholesterolmetabolism

Cholesterol (from the Ancient Greek chole- (bile) and stereos (solid) is an organic molecule. It is a sterol (or modified steroid), a type of lipid. Cholesterol is formed in the liver (85%) and intestine (12%) .

Cholesterol is biosynthesized by all animal cells and is an essential structural component of animal **cell membranes**. Cholesterol also serves as a precursor for the biosynthesis of **steroid hormones, bile acid** and **vitamin D**. Cholesterol is recycled in the body. The liver excretes cholesterol into biliary fluids, which are then stored in the gallbladder, which then excretes them in a non-esterified form (via bile) into the digestive tract. Typically, about 50% of the excreted cholesterol is reabsorbed by the small intestine back into the bloodstream. **Homocysteine** stimulates the production of cholesterol in the liver cells as well as its subsequent secretion. Cholesterol may be removed from the pool by being channelled into the bile or, as VLDL and HDL particles, into the plasma.

Hormone metabolism and the liver

In minute amounts, hormones engender specific biochemical "**primary reactions**" through cellular metabolic processes, which subsequently trigger "**secondary reactions**" through physiological processes. Hormone synthesis takes place in special cells or tissues either in the form of precursors with storage potential (**prohormones**) or in the form of stored or continuously secreted substances in an active state (hormones). Synthesis, release and activation of the hormones are under the strict

control of a regulatory system, which itself responds according to a variety of endogenous and exogenous stimuli.

Inactivation of the hormones occurs mainly due to enzymes (in the kidney, plasma and target cell) and in the liver as a result of proteolytic or redox reactions. The liver contributes to the maintenance of hormonal homoeostasis. Liver diseases may thus affect the hormone regulation in different ways, giving rise to various and sometimes long-lasting disorders. In the endocrine system the signal substances are called hormones, in the nervous system they are known as neurotransmitters, and in the immune system cytokines.

- **Signals** transferred through the hormones may be **endocrinal, neuroendocrinal, paracrinal** (signal transfer to adjacent cells), and **autocrinal** (signal transfer within the individual cell itself).

- **Receptors**, which are able to detect and bind a substance (e. g. hormones), are required to transmit signals for special cellular activity, including that of hormones. All substances which specifically bind with receptors are termed ligands. Both glycoprotein and peptide hormones, for example, are bound to receptors on the cell membrane, whereas steroid and thyroid hormones bind with cytoplasmic or nuclear receptors.