Steroids and Bile Acids: Mevalonate Pathway and Receptor-mediated Endocytosis

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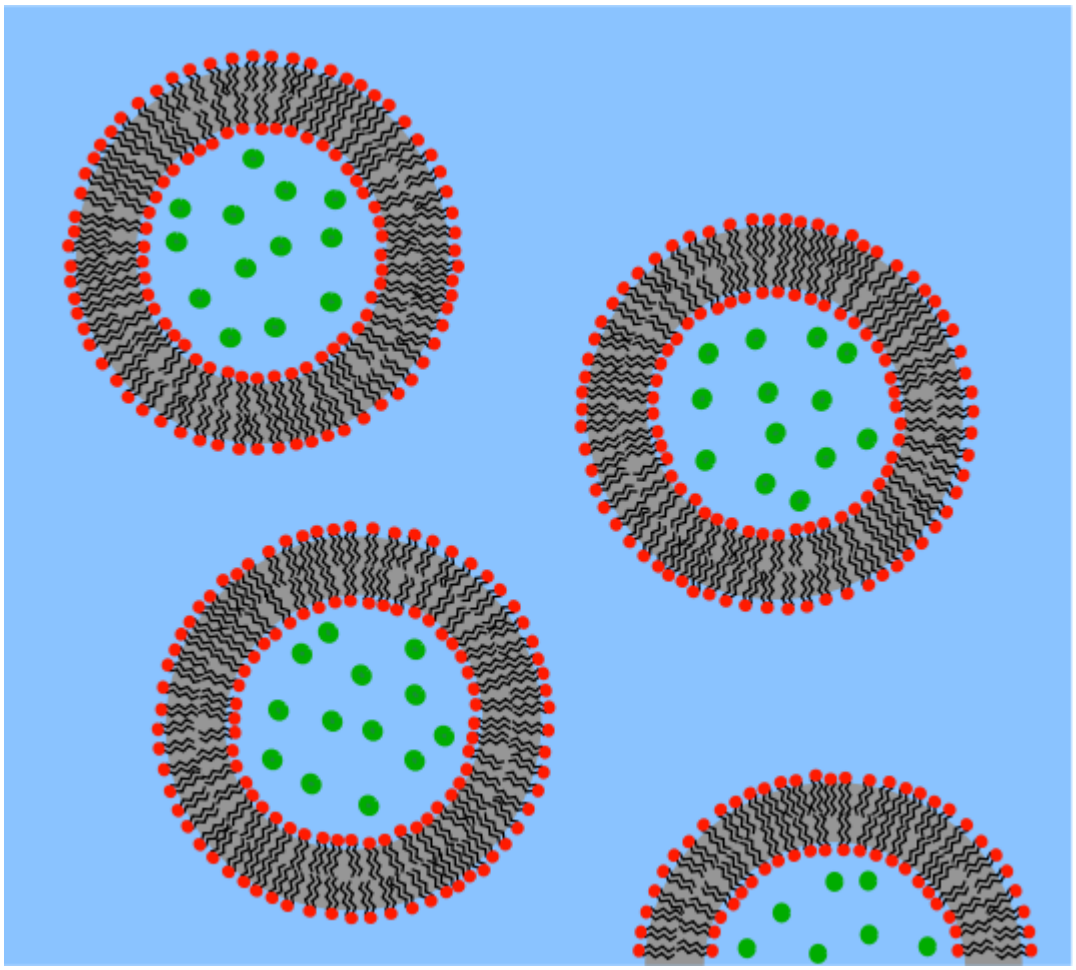
Lipid is one of the biomolecules important to humans. They serve a number of purposes in human metabolism. In the absence of carbohydrates, acetyl CoA does not enter the TCA cycle, instead, are processed to form ketone bodies, cholesterol, steroid hormones, and bile acids. This article focuses on the metabolism of these four compounds.



Ketone Bodies

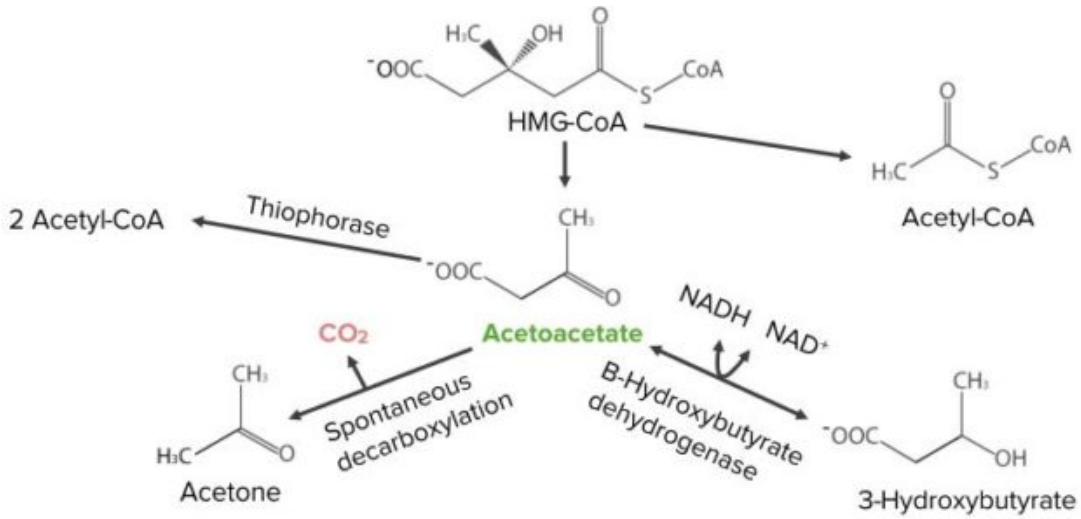
During fatty acid metabolism, acetyl CoA is formed. In the presence of carbohydrates, acetyl CoA gets oxidized in the TCA cycle. In cases of starvation and diabetes mellitus, the acetyl CoA molecules take an alternate route, forming ketone bodies. Three ketone bodies, which are are water-soluble molecules, are produced by the liver during fatty acid metabolism. These are acetone, acetoacetate, and β-hydroxybutyrate.

Ketone Body Synthesis

Ketogenesis is the biochemical process in which organisms produce ketone bodies through the breakdown of fatty acids and ketogenic amino acids. The purpose of ketogenesis is to supply energy to specific organs in the body.

Ketone body biosynthesis occurs in five steps:

1. The first step involves two molecules of acetyl CoA combining to form acetoacetyl CoA. The enzyme thiolase catalyzes the condensation step.
2. The second step involves producing hydroxymethyl glutaryl coenzyme A (HMG-CoA) by combining the acetoacetyl CoA with another acetyl CoA molecule. The enzyme HMG CoA synthase catalyzes the second step.
3. The third step involves lysing the HMG CoA molecule to form acetoacetate and acetyl CoA. This process occurs in the liver because the HMG CoA lyase is only present in the liver.
4. The fourth step in the ketone body synthesis is a reduction step. The ketone body β-hydroxybutyrate is formed by acetoacetate reduction. The ratio of β-hydroxybutyrate and acetoacetate is dictated by the ratio of cellular NAD and NADH.
5. The last step in the process is the spontaneous acetoacetate decarboxylation. This reaction produces acetone.



"Ketone Body Synthesis" Image created by Lecturio

Ketone bodies can be transported easily from the liver to various tissues of the human body. β-hydroxybutyrate and acetoacetate are important energy sources for peripheral tissues, including the cardiac muscles, renal cortex, and skeletal muscles. Only cells containing mitochondria can use ketone bodies.

Cholesterol

Cholesterol is the most abundant sterol in animal tissues. A waxy, fatty substance made in the liver, it is a precursor molecule for several steroid hormones, including androgen, estrogen, and glucocorticoids. Cholesterol is a significant component of lipoproteins and a precursor of bile acids and bile salts. It is found in every cell of the body and plays a vital natural function in food digestion.

Aside from being a precursor for several important molecules in the body, cholesterol plays four major roles:

1. It maintains membrane fluidity over a range of temperatures.
2. It facilitates intracellular transport, nerve conduction, cell communication, and cell signaling.
3. It contributes to the structure of the cell walls.
4. It allows the body to produce vitamin D and ensures certain hormones have suitable growth conditions.

Cholesterol has an important role in lipid transport. Lipids are generally packed in lipoproteins for transport in the human body. Lipoproteins are molecules containing triacylglycerol, phospholipid, apolipoproteins, and cholesterol. They can be generally classified as very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Due to its oil-based nature, cholesterol does not mix with blood, since blood is water-based. Lipoproteins circulate cholesterol around the body. The figure below shows the actions of lipoprotein, cholesterol, and bile acids in the body.

Different types of lipoprotein play different functions:

1. VLDLdelivers triacylglycerol to cells.
2. LDL, on the other hand, delivers cholesterol to cells in the body.
3. HDL returns excess cholesterol to the liver for bile acid biosynthesis.

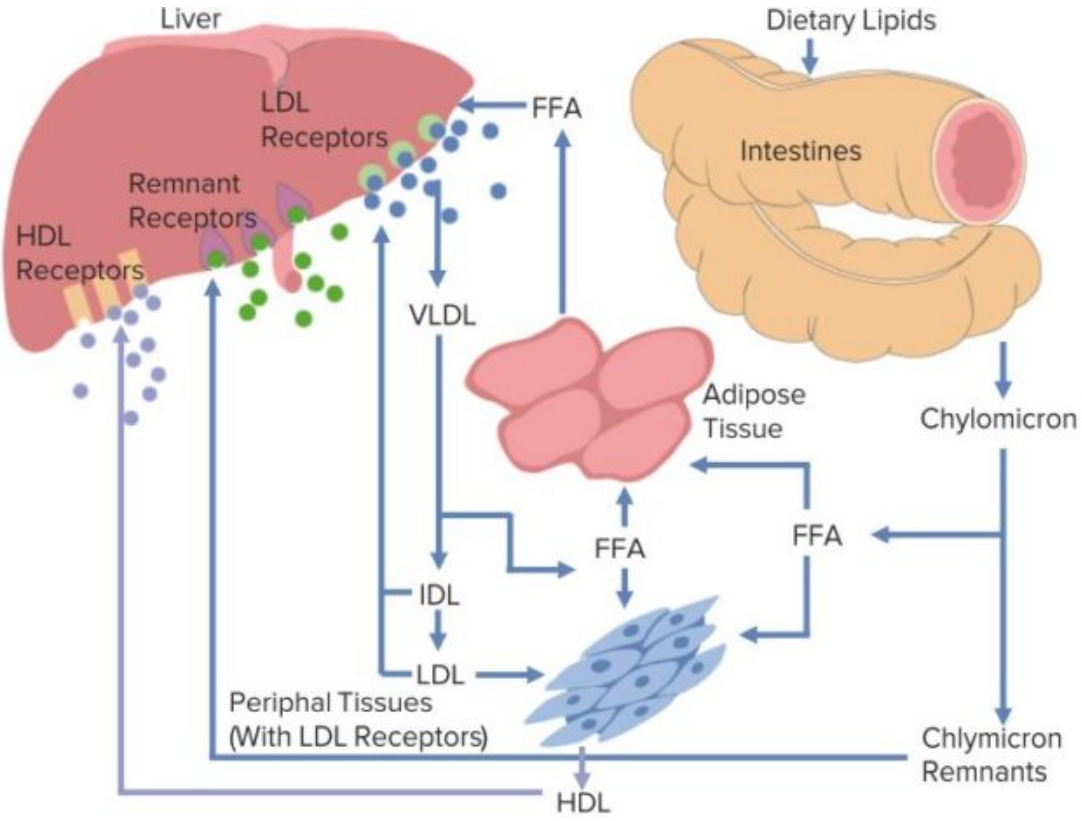
Cholesterol Synthesis

The primary precursor for cholesterol synthesis is hydroxymethyl-glutaryl-coenzyme A (HMG-CoA). During the synthesis of a cholesterol molecule, an HMG CoA is first converted to mevalonate. The enzyme HMG-CoA reductase catalyzes this reaction. This process requires two moles of NADPH as a cofactor.

The mevalonate is then converted to isopentyl pyrophosphate (IPP). Mevalonate is first phosphorylated twice by mevalonate kinase and phosphomevalonate kinase to produce a mevalonate-phosphate and mevalonate-5-diphosphate, respectively. The mevalonate-5-diphosphate then undergoes an ATP-dependent decarboxylation, producing IPP.

The next step is the squalene synthesis. In this step, one molecule of IPP condenses with its isomer, dimethylallyl pyrophosphate (DMPP), to synthesize geranyl pyrophosphate (GPP). Another condensation step occurs with the GPP with another IPP to produce farnesyl pyrophosphate (FPP). Two molecules of FPP then condense to form squalene.

The last step in cholesterol synthesis is for squalene to undergo a two-step cyclization to produce lanosterol. Through a series of 19 additional reactions, cholesterol is synthesized from lanosterol.



"Cholesterol Synthesis" Image created by Lecturio

Bile Acid Metabolism

Bile acids are physiological agents that help secrete lipids, toxic metabolites, and xenobiotics. They are signaling molecules that activate G protein-coupled receptors and nuclear receptors to signal regulation of hepatic lipid, glucose, and homeostasis of energy. They are the products of catabolism of excess cholesterol.

The conversion process of cholesterol to bile is critical for maintaining cholesterol homeostasis and preventing the accumulation of cholesterol, triglycerides, and toxic metabolites, which may lead to injuries to the liver and other organs in the body. The enterohepatic circulation of bile acid from the liver to the intestine and back to the liver plays a central role in nutrient absorption and distribution.

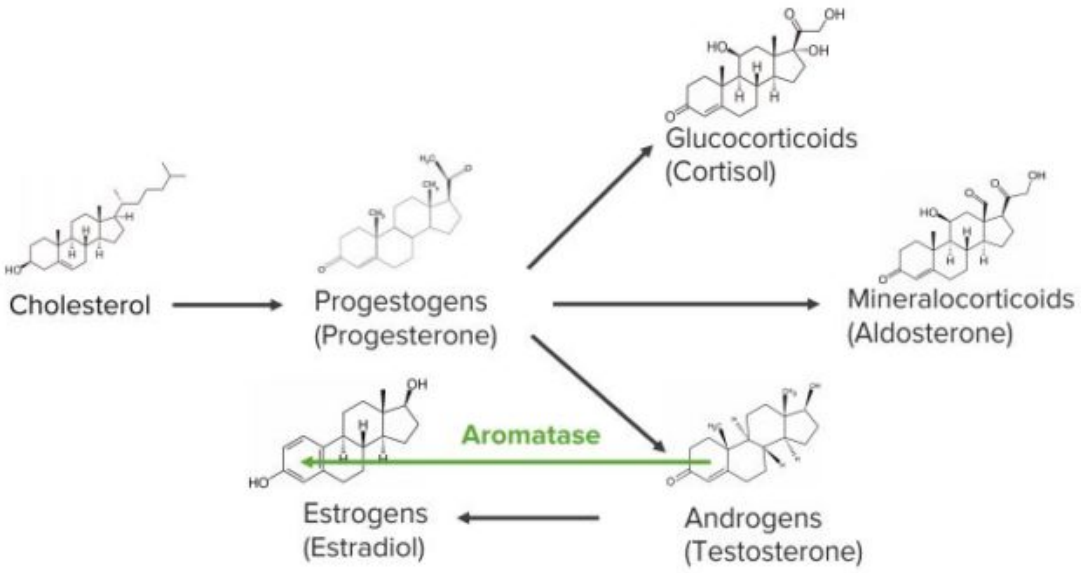
The conversion of cholesterol to bile acids the following processes: hydroxylation, epimerization of the 3-hydroxyl group, a saturation of the double bond at C_5 and C_6, and oxidative cleavage of a 3-carbon unit from the side chain. The conversion is a multi-step process that involves 17 enzymes catalyzing the different processes. The human liver can synthesize about 600 mg of bile acids per day, eventually excreting them in the feces.

Steroid Hormone Metabolism

Steroids are lipophilic compounds derived from cholesterol that serve different important physiological functions. Steroid hormones are steroid compounds synthesized by the endocrine glands, such as the gonads (testis and the ovary) and the adrenals (during the gestation period) by the fetoplacental unit to coordinate physiological and behavioral responses in the body, such as reproduction, sexual maturation, and the modulation of sexual behaviors. Additionally, they act both on peripheral target tissues and the central

nervous system. Some of the important steroid hormones are cortisol, aldosterone, testosterone, and estradiol.

The first step in hormone synthesis is the conversion of cholesterol to pregnenolone. This molecule is then converted to progesterone, which is the precursor of the different hormones.



"Steroid Hormone Metabolism" Image created by Lecturio

References

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Reece, J. B., & Campbell, N. A. (2011). *Campbell biology*. Boston: Benjamin Cummings / Pearson.

Notes