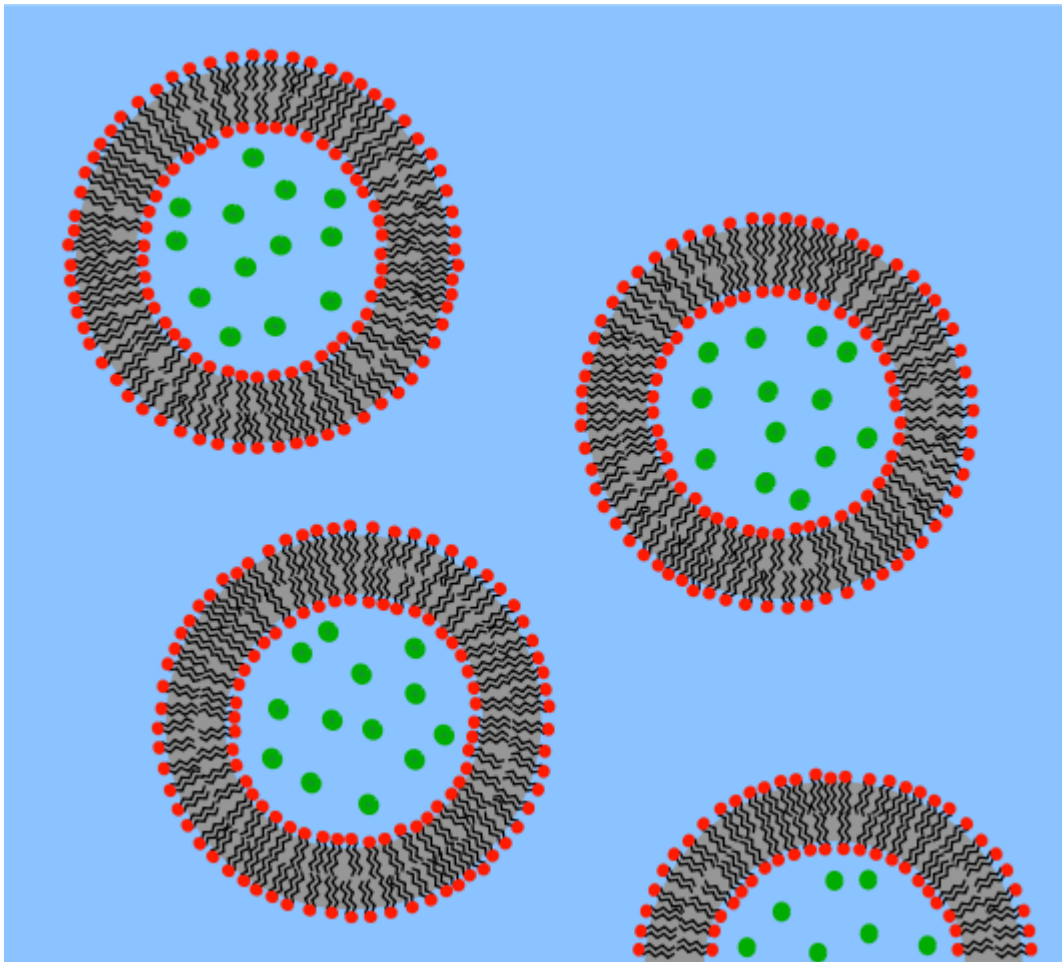


Steroids and Bile Acids: Mevalonate Pathway and Receptor-mediated Endocytosis

[See online here](#)

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 the cases of starvation and diabetes mellitus, the acetyl CoA molecules take an alternate route forming ketone bodies.

Ketone bodies are water-soluble molecules that are produced by the liver from the metabolism of fatty acids. There are three ketone bodies produced during fatty acid

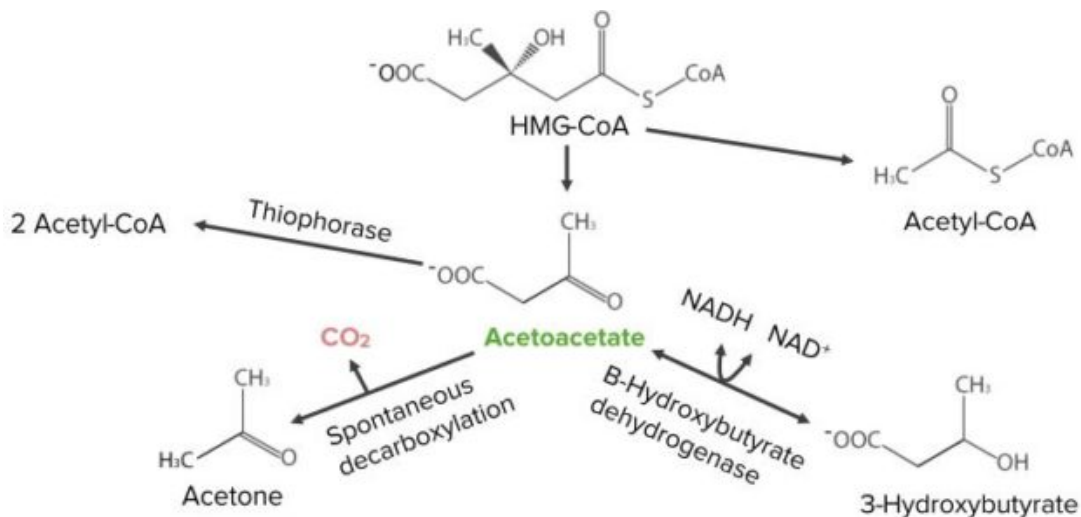
metabolism. These are acetone, acetoacetate, and β -hydroxybutyrate. They are produced by the liver from the fatty acids.

Ketone Body Synthesis

Ketogenesis, the biochemical process in which organisms produce the ketone bodies through the breakdown of the fatty acids and the ketogenic amino acids, with an aim of supplying energy to certain organs in the body.

Ketone body biosynthesis occurs in 5 steps:

1. The first step involves two molecules of acetyl CoA combining to form acetoacetyl CoA. This condensation step is catalyzed by the enzyme thiolase.
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 as, the enzyme responsible for it, 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 the reduction of acetoacetate. 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 decarboxylation of acetoacetate. In this reaction, acetone is produced.



"Ketone Body Synthesis" Image created by Lecturio

Ketone bodies can be easily transported from the liver to various tissues of the human body. β -hydroxybutyrate and acetoacetate are important sources of energy for peripheral tissues that include the cardiac muscles, renal cortex, skeletal muscles, etc. Not all cells in the body can utilize ketone bodies. Cells should have mitochondria to use up ketone bodies.

Cholesterol

Cholesterol is the most abundant sterol in tissues of animals. It is a waxy, fatty substance made in the liver. It is a precursor molecule for a number of steroid hormones. These

hormones include androgen, estrogen, and glucocorticoids. It is a major component of lipoproteins and is also precursors of bile acids and bile salts. It is found in every cell of the body and plays a vital natural function when it comes to the digestion of foods.

Aside from being precursors for a number of important molecules in the body, cholesterol plays four major roles in the body, which include:

1. Cholesterol serves to maintain membrane fluidity over a range of temperatures.
2. They also serve for intracellular transport, nerve conduction, and cell communication and signaling.
3. Contributing to the structure of the cell walls.
4. Allowing the body to produce vitamin D, as well as to make sure certain hormones have suitable conditions for their growth.

One important role of cholesterol is in lipid transport. Lipids are generally packed in lipoproteins for transport in the human body. Lipoproteins are molecules that contain 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 have the responsibility of circulating cholesterol around the body. The figure below shows the fate of lipoprotein, cholesterol, and bile acids in the body.

Different types of lipoprotein play different functions:

1. VLDL serves to deliver triacylglycerol to cells in the body.
2. LDL, on the other hand, delivers cholesterol to cells in the body.
3. HDL serves as reverse cholesterol transport. In reverse cholesterol transport, excess cholesterol is brought back to the liver for bile acid biosynthesis.

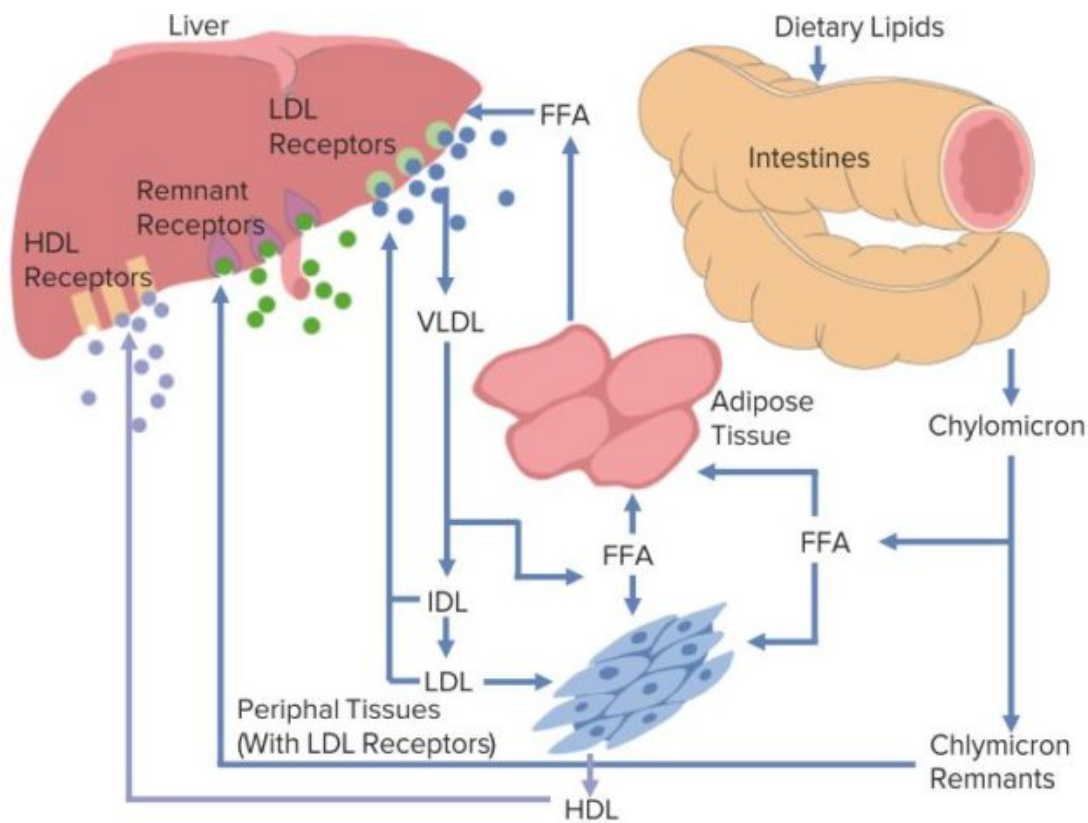
Cholesterol Synthesis

The main 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 NADPH as a cofactor requiring two moles of it to be consumed.

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 synthesis of squalene. 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 aid in the secretion of 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 the maintenance of cholesterol homeostasis and the prevention of the accumulation of cholesterol, triglycerides, as well as the 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.

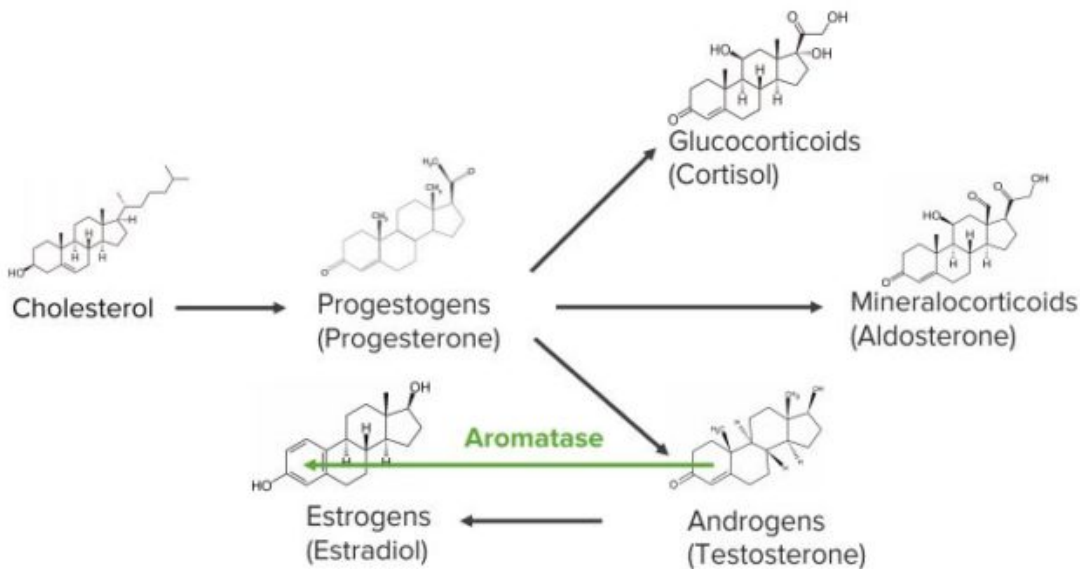
The conversion of cholesterol to bile acids the following processes: hydroxylation, epimerization of the 3-hydroxyl group, saturation of the double bond at C₅ and C₆, and oxidative cleavage of a 3-carbon unit from the side chain. The conversion is a multi-step process that involves 17 enzymes catalyzing the different processes. The human liver is able to synthesize more or less 600 mg of bile acids per day, excreting them eventually in the feces.

Steroid Hormone Metabolism

Steroids are lipophilic compounds derived from cholesterol that serves different important physiological functions. Steroid hormones are steroid compounds synthesized by the endocrine glands, such as the gonads (testis and the ovary), as well as the adrenals (during the gestation period) by the fetoplacental unit to function in co-ordinating physiological and behavioral responses in the body, such as reproduction and sexual

maturation, as well as 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 the synthesis of hormones 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

Review Questions

The answers can be found below the references.

1. What type of lipoprotein functions in reverse cholesterol transport?

- A. Very low-density lipoprotein
- B. Low-density lipoprotein
- C. High-density lipoprotein
- D. Progesterone

2. What is the main precursor for cholesterol synthesis?

- A. Progesterone
- B. HMG-CoA
- C. Acetyl CoA
- D. Mevalonate

References

Voet, D. & Voet, J.G. (2011). *Biochemistry*. 4th ed. New York: J. Wiley and Sons.

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

Correct answers: 1C; 2B

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Notes