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Peripheral-type benzodiazepine receptor-mediated action of steroidogenic acute regulatory protein on cholesterol entry into Leydig cell mitochondria. *Mol Endocrinol*. 2005;19:540-554. doi: 10.1210/me.2004-0307. [DOI] [PubMed] [Google Scholar] steroidogenesis.svg Farese RV Jr, Walther TC. Lipid droplets finally get a little R-E-S-P-E-C-T. *Cell*. 2009;139:855-860. doi: 10.1016/j.cell.2009.11.005. [DOI] [PMC free article] [PubMed] [Google Scholar] Articles from Nutrition & Metabolism are provided here courtesy of BMC Display options Format AbstractPubMedPMID Steroid hormones regulate diverse physiological functions such as reproduction, blood salt balance, maintenance of secondary sexual characteristics, response to stress, neuronal function and various metabolic processes. They are synthesized from cholesterol mainly in the adrenal gland and gonads in response to tissue-specific tropic hormones. These steroidogenic tissues are unique in that they require cholesterol not only for membrane biogenesis, maintenance of membrane fluidity and cell signaling, but also as the starting material for the biosynthesis of steroid hormones. It is not surprising, then, that cells of steroidogenic tissues have evolved with multiple pathways to assure the constant supply of cholesterol needed to maintain optimum steroid synthesis. The cholesterol utilized for steroidogenesis is derived from a combination of sources: 1) de novo synthesis in the endoplasmic reticulum (ER); 2) the mobilization of cholesteryl esters (CEs) stored in lipid droplets through cholesteryl ester hydrolase; 3) plasma lipoprotein-derived CEs obtained by either LDL receptor-mediated endocytosis and/or SR-BI-mediated selective uptake; and 4) in some cultured cell systems from plasma membrane-associated free cholesterol. Here, we focus on recent insights into the molecules and cellular processes that mediate the uptake of plasma lipoprotein-derived cholesterol, events connected with the intracellular cholesterol processing and the role of crucial proteins that mediate cholesterol transport to mitochondria for its utilization for steroid hormone production. In particular, we discuss the structure and function of SR-BI, the importance of the selective cholesterol transport pathway in providing cholesterol substrate for steroid biosynthesis and the role of two key proteins, StAR and PBR/TSO in facilitating cholesterol delivery to inner mitochondrial membrane sites, where P450scc (CYP11A) is localized and where the conversion of cholesterol to pregnenolone (the common steroid precursor) takes place. Figure 1 Principal steps involved in the... Figure 1 Principal steps involved in the biosynthesis of various steroid hormones . Modified from... Figure 1 Principal steps involved in the biosynthesis of various steroid hormones. Modified from Payne and Hales and website [1,305] Figure 2 Potential sources of cholesterol for... Figure 2 Potential sources of cholesterol for product formation (steroids, vitamin D and bile acids)... Figure 2 Potential sources of cholesterol for product formation (steroids, vitamin D and bile acids) and membrane biogenesis Figure 3 Diagrammatic representation of the molecular... Figure 3 Diagrammatic representation of the molecular and cellular events involved in the selective and... Figure 3 Diagrammatic representation of the molecular and cellular events involved in the selective and endocytic uptake and intracellular processing of the lipoprotein-derived cholesteryl esters for steroid hormone biosynthesis by adrenal and gonadal tissues. ACAT1, acyl-coenzyme A:cholesterol acyltransferase I; CEs, cholesteryl esters; CS, cytoskeleton; CYP11A1, cytochrome P450 side-chain cleavage enzyme (P450scc); FC, free cholesterol; NPC1, Nieman-Pick type C1; NPC2, Nieman-Pick type C2; SCP2, sterol carrier protein2; SREBP, sterol-regulatory element-binding proteins; SCAP, SREBP cleavage-activating protein. StAR, steroidogenic acute regulatory protein; TGS, triglycerides; TSPo, translocator protein. Modified from Chang et al, Rone et al, and Farese and Walther [68,288,306]. Figure 4 Correlation between the cellular levels... Figure 4 Correlation between the cellular levels of SR-BI dimers and the functional efficiency of... Figure 4 Correlation between the cellular levels of SR-BI dimers and the functional efficiency of selective HDL-CE uptake. Appropriate Western blots from various cell types were scanned for SR-BI monomers and dimers and dimer/monomer ratios were plotted against the respective selective HDL-CE uptake data. 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See all "Cited by" articles Health & Medicine Anatomy & Physiology The steroid hormones consume a very small fraction of the total cholesterol available in the organism, but they are very important physiologically. (See below Biological functions of lipids.) There are five principal classes, all derived from cholesterol: progestins (active during pregnancy), the glucocorticoids (promoting the synthesis of glucose and suppressing inflammatory reactions), the mineralocorticoids (regulating ion balances), estrogens (promoting female sex characteristics), and androgens (promoting male sex characteristics). With the exception of progesterone, all of these closely related biologically active molecules have in common a shortened side chain in ring D and, in some cases, an oxidized OH group on ring A. The individual molecules are synthesized on demand by the placenta in pregnant women, by the adrenal cortex, and by the gonads. High blood levels of cholesterol have been recognized as a primary risk factor for heart disease. For this reason, much research has been focused on the control of cholesterol's biosynthesis, on its transport in the blood, and on its storage in the body. The overall level of cholesterol in the body is the result of a balance between dietary intake and cellular biosynthesis on the one hand and, on the other hand, elimination of cholesterol from the body (principally as its metabolic products, bile acids). As the dietary intake of cholesterol increases in normal persons, there is a corresponding decrease in absorption from the intestines and an increase in the synthesis and excretion of bile acids—which normally accounts for about 70 percent of the cholesterol lost from the body. The molecular details of these control processes are poorly understood. Regulation of cholesterol biosynthesis in the liver and other cells of the body is better understood. The initial enzyme that forms mevalonate in the first stage of biosynthesis is controlled by two processes. One is inhibition of the synthesis of this enzyme by cholesterol itself or a derivative of it. The other is regulation of the catalytic activity of the enzyme by phosphorylation/dephosphorylation in response to intracellular signals. Several pharmacological agents also inhibit the enzyme, with the result that unhealthy levels of cholesterol can be lowered over a period of time. The normal human body contains about 100 grams of cholesterol, although this amount can vary considerably among healthy people. Approximately 60 grams of this total are moving dynamically through the organism. Because cholesterol is insoluble in water, the basis of the bodily fluids, it is carried through the circulatory system by transport particles in the blood called lipoproteins. These microscopic complexes (described in the section Lipoproteins) contain both lipids and proteins that can accommodate cholesterol and still remain soluble in blood. Cholesterol is absorbed into the cells of the intestinal lining, where it is incorporated into lipoprotein complexes called chylomicrons and then secreted into the lymphatic circulation. The lymph ultimately enters the bloodstream, and the lipoproteins are carried to the liver. Cholesterol, whether derived from the diet or newly synthesized by the liver, is transported in the blood in lipoproteins (VLDL and LDL) to the tissues and organs of the body. There the cholesterol is incorporated into biological membranes or stored as cholesteryl esters—molecules formed by the reaction of a fatty acid (most commonly oleate) with the hydroxyl group of cholesterol. Esters of cholesterol are even more hydrophobic than cholesterol itself, and in cells they coalesce into droplets analogous to the fat droplets in adipose cells. Cholesterol is lost from cells in peripheral tissues by transfer to another type of circulating lipoprotein (HDL) in the blood and is then returned to the liver, where it is metabolized to bile acids and salts. low-density lipoprotein (LDL) complexThe LDL complex is essentially a droplet of triacylglycerols and cholesteryl esters encased in a sphere made up of phospholipid, free cholesterol, and protein molecules known as apoprotein B-100 (ApoB-100). The LDL complex is the principal vehicle for delivering cholesterol to body tissues through the blood.Lipoproteins are lipid-protein complexes that allow all lipids derived from food or synthesized in specific organs to be transported throughout the body by the circulatory system. The basic structure of these aggregates is that of an oil droplet made up of triglycerides and cholesteryl esters surrounded by a layer of proteins and amphipathic lipids—very similar to that of a micelle, a spherical structure described in the section Fatty acids. If the concentration of one or another lipoprotein becomes too high, then a fraction of the complex becomes insoluble and is deposited on the walls of arteries and capillaries. This buildup of deposits is called atherosclerosis and ultimately results in blockage of critical arteries to cause a heart attack or stroke. Because of the gravity of this condition, much research is focused on lipoproteins and their functions. The emphasis in the following discussion is therefore placed on human lipoproteins.