LECTURES

HEPATIC CHOLESTEROL METABOLISM

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The liver is the only organ where cholesterol can be removed irreversibly from the blood. The unique anatomical structure enables uptake of cholesterol-carrying particles (lipoproteins) on the sinusoidal site of hepatocytes, intracellular metabolism and secretion of the metabolic products in the bile canaliculi. Besides hepatocytes, the liver also contains Kupffer, endothelial and fat-storing cells. These latter cell types are highly specialized in receptor-mediated endocytosis (including lipoproteins) and cholesterol initially internalized by the sinusoidal liver cells will be subject to a multicompartment processing system. Cholesterol from exogenous origin is partly esterified in the small intestine and transported from the lymphe to the blood circulation in chylomicrons (relatively large particles containing triglycerides and apolipoprotein B-48). In the blood the high density lipoproteins (HDL) provide the chylomicrons with apolipoproteins E and C, which are required for proper delivery of fatty acids in extrahepatic tissues and subsequent delivery of cholesterol (ester) in liver parenchymal cells. Recognition of the chylomicron remnants occurs by a so-called apo E-receptor which is specific for liver hepatocytes. Intracellularly the uptake of cholesterol inhibits the biosynthesis of cholesterol while excretion in the bile canaliculi or secretion with very low density lipoprotein (VLDL) may occur. The circulation of VLDL by the liver leads to the socalled endogenous cholesterol pathway because also newly synthesized liver cholesterol is transported in these particles. VLDL is extrahepatically metabolized in a similar way as chylomicrons leading to the formation of triglyceride-depleted VLDL (VLDL-remnants). The VLDL-remnants are either converted to low density lipoproteins (LDL), or re-internalized by the liver with the aid of the apo B,E-receptor. Receptor-deficiency (type II-a hypercholesterolemia) leads to increased formation of LDL. Because also LDL is recognized by the apo B,E-receptor, its catabolism is greatly blocked by an apo B,E-receptor deficiency, leading to a 6-8 fold increased level of LDL in these patients. In rats 60-70% of the LDL is catabolized by the liver for which mainly the liver Kupffer cells are responsible. Probably in other species (including man), a higher proportion of LDL will be processed by the liver hepatocytes. In addition to the apo B,E-receptor the liver endothelial cells do possess a highly active scavenger-receptor which recognizes both chemically or biologically modified lipoproteins. Uptake of cholesterol(esters) by liver endothelial or Kupffer cells is coupled to an endocytotic pathway which includes participation of the lysosomes. After processing, resecretion to the hepatocytes and finally to the bile can occur, leading to the concept of intercellular communication in the metabolism of cholesterol inside the liver. Recent therapies designed to lower serum cholesterol levels, utilize drugs which act on reabsorption of bile acids in the intestine (cholestyramine), inhibit endogenous cholesterol synthesis (mevinolin) or are designed to utilize highly active carbohydrate-recognizing receptors (ref. 1,2) for lipoprotein catabolism.

References:

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HEPATIC CATABOLISM OF CHOLESTEROL

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The liver plays a central part in the metabolism of cholesterol. Firstly, the liver shows a relatively high rate of cholesterol synthesis, a process controlled by the rate-limiting enzyme 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase. Secondly, the liver is actively involved in the uptake of various cholesterol-containing lipoproteins from the circulation, which is mediated by specific receptors. Thirdly, the main route of cholesterol elimination from the body is via bile, either as cholesterol as such or after conversion to bile acids.

In the past years we have developed an animal model which allows us to study cholesterol metabolism and biliary bile acid excretion in unanestetized, unrestrained rats with a normal feeding pattern (1). For this purpose, rats are equipped with permanent catheters in bile duct, duodenum and heart. All three catheters are attached on top of the skull. There, bile duct and duodenum-catheter are connected to each other in order to maintain an intact enterohepatic circulation. The heartcatheter allows intracardial administration of compounds and repeated blood sampling. Rats are used for experiments after an 8-days recovery period.

Interruption of the enterohepatic circulation in these rats resulted in a strong decrease in biliary bile acid output, due to exhaustion of the endogenous bile acid pool. After approximately 3 hours bile acid output stabilized at 5% of its initial value, representing hepatic synthesis rate. During long-term bile diversion, bile acid output gradually increased, but never exceeded 13% of its value during intact enterohepatic circulation.

Treatment of rats during long-term bile diversion with mevinolin, a potent blocker op HMG-CoA reductase, caused a rapid, dose-dependent and reversible reduction of hepatic bile acid synthesis, which could be abolished by simultaneous administration of mevalonolactone. Maximal inhibition reached a level of 79% and the formation of chenodeoxycholic acid was affected most. In contrast, the synthesis of β-muricholic acid, a primary bile acid in the rat, was not affected by mevinolin.

Intravenously administered human low density lipoproteins (LDL), radiolabeled with ^{3}H-cholesteryloleate (^{3}H-CO), were cleared slowly by the liver, mainly by Kupffer cells. After 3 hours only 0.9±0.2% of the injected radioactivity had appeared in bile, after 12 hours this value was 4.5±0.5%. Induction of LDL (apo B,E) receptors on hepatocytes by 17α-ethinylestradiol (EE) treatment accelerated hepatic uptake of ^{3}H-CO from LDL. Biliary excretion was increased to 3.9±0.5% after 3 hours and 12.4±2.0% after 12 hours. Both in untreated and EE-treated animals biliary radioactivity derived from ^{3}H-CO was