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Balancing Cholesterol Synthesis and Absorption in the Gastrointestinal Tract

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Abstract

Cholesterol balance is achieved both by synthesis in the body and by absorption in the gastrointestinal tract. Cholesterol synthesis and absorption are also critical determinants of plasma LDL cholesterol concentrations. In clinical practice, inhibitors of synthesis and inhibitors of absorption are both effective methods of lowering LDL cholesterol concentrations and may be utilized in combination. This review rationalizes these mechanisms of LDL reductions by placing them in the context of cholesterol balance as it is determined by digestive lipid metabolism.

Introduction

Cholesterol is an insoluble lipid molecule that plays a critical role in the structure and function of membrane bilayers. Membrane cholesterol contents that are either too high or too low are detrimental to cell function. When present in excess amounts in cells, cholesterol becomes toxic. Certainly, cholesterol-induced cytotoxicity represents a key initiating event leading to the development of atherosclerotic cardiovascular disease.¹ Cholesterol is also used as a substrate for steroid hormone biosynthesis. Virtually all cells are capable of synthesizing their full complement of cholesterol, despite the capacity of the gastrointestinal tract to absorb large quantities. However, only hepatocytes within the liver are capable of degrading cholesterol and eliminating it in large quantities.

The ongoing requirement for cholesterol turnover in cells necessitates transport to the liver for elimination. Because cholesterol is insoluble, its transport in plasma requires the participation of high density lipoproteins (HDL), which are specialized particles capable of efficient cholesterol transport through an aqueous environment. The liver processes the excess cholesterol for elimination via bile. Transport of cholesterol to the liver for biliary elimination is essential for maintaining cholesterol balance and is sometimes referred to as reverse cholesterol transport.^{2,3}

Digestive lipid metabolism

Following hepatic uptake of lipoprotein cholesterol, a portion is enzymatically converted to bile salt molecules. This is unique to the liver because only hepatocytes express high levels of the enzyme cholesterol 7 α -hydroxylase (a.k.a. CYP7A1), which initiates and rate-limits the

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multi-step conversion process.⁴ Cholesterol and bile salt molecules exhibit strikingly different physical properties: whereas cholesterol is insoluble in water, bile salts are biological amphiphiles, which are very highly soluble by virtue of their capacity to self-associate.⁵ This detergent property allows bile salts to transport cholesterol in the digestive system by forming micelles, which are lipoprotein-like particles.

Micelles are created by interactions between bile salts and the plasma membrane of hepatocytes.^{6,7} Bile salts are first pumped out of the hepatocyte across the canalicular plasma membrane by ABCB11, an ATP-driven membrane transporter. Bile salts then interact with the exterior surface of the canalicular plasma membrane. This interaction appears to activate two other ATP-dependent canalicular plasma membrane transporters, ABCB4 and a heterodimer of ABCG5 and ABCG8, which promote the biliary secretion of phospholipid and cholesterol molecules, respectively. Following their secretion, a complex series of interactions among bile salts, phospholipids and cholesterol ultimately leads to the formation of micelles. The movement of lipids into bile occurs at a very high rate. The secretion of bile salts at 24 g/day (average 1 g/hr) is accompanied by the daily secretion of approximately 11 g of phospholipids and up to 2 g of cholesterol.⁶

Interdigestively, micellar particles are stored within the gallbladder. When food is ingested, the gallbladder is stimulated to contract. This propels bile out of the gallbladder and into the lumen of the small intestine. In addition to transporting cholesterol from the liver into the intestine through the biliary tree, micelles serve an important function in the digestion and absorption of fat, which consists mainly of dietary triglycerides and cholesterol. Lipases secreted by the stomach and intestine partially break down triglycerides into fatty acids and monoglycerides, which are incorporated into micelles.⁸ Dietary cholesterol is also assimilated into micelles, becoming indistinguishable from cholesterol molecules that originate from inside the body and are secreted into bile.

Following fat digestion, micelles facilitate absorption by transporting solubilized lipids to the plasma membrane of enterocytes, which form a single-cell lining of the small intestinal lumen. At the plasma membrane, fatty acids and monoglycerides are taken up into enterocytes and reassembled enzymatically into triglycerides. Cholesterol molecules are simultaneously taken up by a separate mechanism, which begins with facilitated transport of cholesterol into the enterocyte by the protein Nieman-Pick C1 Like 1 (NPC1L1).⁹ A fraction of cholesterol that is taken up is then pumped back into the lumen by the action of a heterodimer of ABCG5 and ABCG8.¹⁰ A portion of this absorbed cholesterol is converted to cholesteryl esters when the enzyme acyl-CoA:cholesterol acyltransferase (ACAT) covalently attaches a fatty acid to the free hydroxyl group on the cholesterol molecule.¹¹ The remaining fraction is absorbed as free cholesterol. Within the enterocyte, triglycerides, cholesterol and cholesterol esters are combined together with apolipoprotein B48 into chylomicrons, which are secreted into the lymph and subsequently enter the plasma.¹²

Cholesterol balance

The digestive system is largely responsible for the maintenance of cholesterol balance in the body. Because bile salt molecules are created by enzymatic modification of cholesterol, an accounting of cholesterol balance requires consideration of both the bile salts and cholesterol.

Bile salts are secreted into bile at a rate of approximately of 24 g/day, but are synthesized at only a fraction of this rate.¹³ This is because bile salts are recycled to the liver from the ileum, where transporters on the plasma membrane of the enterocytes in this distal region of the small intestine very efficiently take up bile salts (~98%) from the lumen and translocate them into the portal blood for return to the liver. Hepatocytes very efficiently clear bile salts from the

portal blood and re-secrete them into bile. The movement of bile salts between the liver and intestine is referred to as the enterohepatic circulation. Although this process is highly efficient, 1–2% of bile salts escape recycling and are spilled into the feces. This amounts to a loss of approximately 0.4 g/day of cholesterol in the form of bile salt molecules. Within the liver, the conversion of bile salts to cholesterol occurs at a rate that precisely balances the loss into the feces. This is accomplished by nuclear hormone receptors that “sense” the concentrations of bile salts in both the liver and intestine.⁴ Bile salt sequestrants, such as colestevlam and cholestyramine, function to increase the fecal loss of bile salts. The liver responds by upregulating bile salt synthesis, and this consumes cholesterol within the liver.

In addition to bile salts, cholesterol is secreted into bile at rates that vary up to 2 g/day.^{6,14} Within the intestine, biliary cholesterol mixes with cholesterol in the diet. The average American diet contains approximately 0.4 g of cholesterol per day. Consequently, most cholesterol within the intestinal lumen is derived from internal sources via bile, whereas the diet contributes a relatively minor fraction.

Rates of cholesterol absorption vary widely in the population from as little as 25% to around 80%, and average approximately 50%.¹⁵ For an individual, the absorption rate appears to be constant over time. If in an individual cholesterol is secreted into bile at the maximal rate of 2 g/day, consumed at 0.4 g/day from the diet, and absorbed at a rate of 50%, then 1.2 g/day will be lost in the feces. If such an individual also loses 0.4 g/day of cholesterol in the form of bile salts, the total cholesterol loss will be 1.6 g/day (i.e., 25% as bile salts and 75% as cholesterol). The net daily synthesis of cholesterol is equal to the amount of cholesterol lost in the feces minus the dietary cholesterol, which in this case amounts to 1.2 g/day. This indicates that the amount of cholesterol absorbed is equal to the amount lost (i.e., the body synthesizes an amount approximately equal to the amount it absorbs).

Mechanisms of LDL lowering by inhibitors of cholesterol synthesis and absorption

Statins are the most commonly administered class of drugs to lower plasma LDL cholesterol. Their primary mechanism of action is to promote clearance of LDL particles from the plasma.¹⁶ This is accomplished because statins reduce the rate of intracellular cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, the rate-limiting step in cholesterol biosynthesis. In most cells, the adaptive response is upregulation of LDL receptors, which clear LDL from plasma and replete the deficit created by the reduced synthetic rate. This mechanism provides a very effective means for exploiting the intrinsic cellular response to reduced synthesis in order to reduce LDL cholesterol concentrations in the plasma.

Cholesterol absorption inhibitors slow the absorption of dietary cholesterol, but more important, they also reduce the reabsorption of biliary cholesterol, which accounts for most of the cholesterol in the intestine. The available cholesterol absorption inhibitors are plant sterols/stanols and ezetimibe.¹¹ Plant sterols/stanols are naturally occurring molecules that diminish dietary cholesterol absorption within the intestinal lumen. They are close molecular mimics of cholesterol, but are much more hydrophobic. As a result, they displace cholesterol from micelles. Moreover, when plant sterols are taken up into enterocytes, they are very efficiently pumped back into the lumen by the action of ABCG5 and ABCG8, which very effectively prevent plant sterols from entering the body. Ezetimibe is also a cholesterol absorption inhibitor, but functions to reduce the uptake of cholesterol into enterocytes by inhibiting NPC1L1.^{9,17}

Inhibition of cholesterol absorption most likely lowers plasma LDL cholesterol by more than one mechanism.^{18,19} Chylomicron cholesterol from the intestinal lumen is ultimately taken

up by the liver. A portion of this cholesterol is incorporated into VLDL particles, which are the source LDL in the plasma. Therefore, inhibiting cholesterol absorption may reduce the rate of LDL formation in the plasma. In addition, hepatocytes respond to decreased chylomicron cholesterol uptake by upregulating LDL receptors on their plasma membranes. This also facilitates clearance of LDL particles from the plasma.

In clinical practice, statins and ezetimibe are often combined to very effectively reduce plasma LDL cholesterol. This is explained in part because their mechanisms of LDL lowering do not completely overlap. However, additional LDL lowering may be achieved because it is observed that when cholesterol absorption is inhibited, hepatic cholesterol synthesis increases¹⁸, and this may offset the effect of ezetimibe. Here, the addition of a statin blocks the compensatory upregulation in cholesterol synthesis and may contribute the potency of LDL lowering attributable to the combination of these two agents.

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