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The Physiology and the Pharmacology of Cholesterol Transfer in Reverse

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ABSTRACT:

In order to maintain cholesterol homeostasis in the body, reverse cholesterol transport refers to a series of metabolic processes that transfer cholesterol from peripheral tissues to the liver. In this reverse transport, cholesterol is carried by high density lipoproteins (HDL), which is thought to account for the negative relationship between plasma HDL levels and atherosclerosis. In the prevention and treatment of vascular disease, an attempt to stimulate this transport process through the use of medicines appears to hold tremendous potential. There are currently very few medications that have the ability to alter the activity of the many elements involved in the process. Although the newer fibric acids are often unsuccessful as anion-exchange resins, clofibrate lowers cholesterol esterification. The physiological process of removing cholesterol from tissues may be improved by probucol, which directly enhances the mass and activity of cholesteryl ester transfer protein. The limited information now available on how medications affect reverse cholesterol transport should encourage researchers to find new treatments that target this antiatherogenic pathway.

Keywords*:* Reverse cholesterol transport; HDL subfractions; Lecithin : cholesterol acyltransferase; Cholesteryl ester transfer protein

INTRODUCTION:

A complicated balance between endogenous synthesis, extracellular cholesterol uptake, primarily from low density lipoproteins (LDL) through the LDL receptor, and efflux of cell cholesterol into the circulatory fluids keeps cholesterol homeostasis in the majority of non-hepatic cells. The migration of cholesterol from peripheral tissues to the liver is known as "reverse cholesterol transport," a phrase that was first coined by Glomset in 1968 [l]. This efflux is the first stage of this process. High density lipoproteins (HDL) are thought to be necessary for reverse cholesterol transfer, which explains why there is a well-known inverse relationship between plasma HDL levels and atherosclerosis 131.

Reverse cholesterol transport has the potential to be anti-atherogenic, hence it must be possible to stimulate this mechanism in order to prevent and/or treat artery disease. The

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physiology of reverse cholesterol transport is covered in this article, and suggestions for clinically useful techniques to modulate this process are given.

Physiology of reverse cholesterol transport

The uptake of cellular cholesterol by HDL is the first step in the reverse cholesterol transport pathway [4,5]. Only a portion of the mechanism(s) through which HDL removes cholesterol from cells is known. The majority of cholesterol that exits cells is not esterified; rather, it can desorb from the plasma membrane into the extracellular fluids by a diffusion-limited process [6, 7], where it is then integrated into HDL, which has a relatively high affinity for lipids [S]. Additionally, HDL can interact with a particular surface receptor found on a number of extrahepatic cell types [9-11].

Although it is not necessary for the transfer of sterol from plasma membranes [12-14], cell binding of acceptor particles may facilitate the translocation of extra cholesterol from intracellular to membrane pools [15,16]. In the cell, cytoplasmic acyl CoA: cholesterol acyltransferase (ACAT) and cholesterol esterase continuously esterify and hydrolyze cholesterol; in vitro inhibition of the esterification cycle improves cholesterol efflux from cells [17–19], suggesting that the availability of free cholesterol is a key factor in the initial stage of reverse cholesterol transport.

Evaluation of the reverse cholesterol transport in man

Reverse cholesterol transport involves numerous metabolic processes that take place in both tissues and plasma, making it nearly impossible to evaluate the entire procedure in its entirety. Even though in vivo kinetic investigations of HDL-CE transport [20] ought to be very instructive, they are challenging to implement in clinical settings. To assess the reverse transport at the tissue level, in vitro measurements of each individual's ability for cholesterol uptake from peripheral cells [15] and for delivery to hepatocytes [6] should be used. However, at this time, the best feasible method for assessing a person's reverse cholesterol transport appears to be the examination of the processes taking place in plasma. Two of the many characteristics that need to be taken into account, cholesterol esterification and cholesteryl ester transfer from HDL to lower density lipoproteins, are particularly important.

Effects of drugs on the reverse cholesterol transPod

Many pharmacological agents, including numerous hypolipidemic medications, antihypertensive medicines, hormones, and inducers of microsomal enzymes, can alter plasma HDL levels in people [21]. Although the precise mechanisms causing these alterations are generally not well known, fibric acid-induced elevations in HDL are probably caused by lipase-stimulating activity [7, 8]. Drug-induced increases in HDL cholesterol have been linked to lower cardiovascular risk [22], possibly as a result of enhanced reverse cholesterol transport. However, only a small number of research have looked at how medications affect the different stages of this process.

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Finally, a number of research [7] have looked at how pharmacological therapies affect the distribution of HDL subfractions in both normo- and hyperlipidemic patients. The utilisation of various HDL fractionation procedures, which frequently produce contradictory results [13], makes it difficult to directly compare the presented data. We were able to show that the fibric acid derivative gemfibrozil raises plasma HDL levels in both hypertriglyceridemic [14] and hypercholesterolemic [15] subjects through the use of rate zonal ultracentrifugation and nondenaturing polyacrylamide gradient gel electrophoresis. HDL levels also rise when patients with mild metabolic disturbances are treated with the H, antagonist cimetidine [16]. Acipimox, a nicotinic acid derivative, had only little effects on hypertriglyceridemic patients [107], whereas pravastatin, an HMGCoA reductase inhibitor, has no effect on the distribution of HDL subfractions in hypercholesterolemic people. Instead, in line with a simulation of the CETP activity, probucol reduces the plasma levels of both HDL subfractions, primarily HDL.

CONCLUSIONS:

The outcome of distinct metabolic pathways and a number of different metabolic stages is reverse cholesterol transfer. The relative impact of these different pathways on the effectiveness of the entire process in vivo, particularly in man, is currently poorly understood. The antiatherogenic potential of the various routes is still a subject of intense debate. The CETP-mediated process may encourage the synthesis of CE-rich chylomicron or remains of VLDL, which ultimately results in the production of foam cells. Although they are rare, familial CETP and LCAT deficiencies may not necessarily offer protection against atherosclerosis because of their lack of association with an elevated prevalence of early CHD. Even in patients with angiographically diagnosed CHD, LCAT activity is elevated. To conclusively demonstrate that promoting reverse cholesterol transport at the plasma level will have an antiatherogenic effect in men, more research is required, especially in vivo research. For the prevention and treatment of atherosclerotic disease, it appears to us that this sector offers interesting targets. An exceptional foundation for developing the pharmacology of reverse cholesterol transport is provided by the recently demonstrated efficacy of HDL supplementation in vivo in improving atherosclerotic regression in experimental animals [llO]. Only a small number of medications that can modify just a few steps of reverse cholesterol transfer are known as of right now. Some of these substances, such as probucol, can promote the regression of tissue lipid deposits in humans and inhibit the development of atherosclerosis in experimental animals. These scant and preliminary results ought to jog researchers' interest in discovering new substances that work particularly to promote reverse cholesterol transfer at the cellular and/or plasma levels.

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