Journal of Clinical Lipidology (2007) 1, 20–30

Journal of Clinical Lipidology

Intrinsic enzymes of high-density lipoprotein

Ngoc-Anh Le, PhD,* Mary F. Walter, PhD

Emory Lipid Research Laboratory, Emory University School of Medicine, 1670 Clairmont Road, Atlanta Veterans Affairs Medical Center, Mail Code 151 Room 4A187, Decatur, GA 30033, USA

KEYWORDS:
CETP;
Enzymes;
GPx;
HDL;
Inflammation;
LCAT;
Lp-PLA2;
Oxidation;
PLTP;
PON1;
Reverse cholesterol transport

Abstract. Several lines of evidence are available to support the protective effects of high-density lipoproteins (HDL) on atherosclerosis. The exact mechanisms by which HDL protects against atherosclerotic disease development are not understood. In addition to its role in the reverse transport of cholesterol from the peripheral sites to the liver for excretion, HDL also carries a number of enzymes that contribute to the remodeling of plasma lipoproteins and to the protection of other lipoproteins against oxidative modification. Many of these enzymes can play a role in determining the composition of circulating HDL, while others appear to affect specific biologic activities associated with HDL. It is not clear whether the concentrations of HDL particles or the activities associated with this class of particles are more important. One of the problems is that HDL constitutes a heterogeneous population of particles, and analytical tools to characterize the various subpopulations are not widely available. In this article, we will review the enzymes that are associated with plasma HDL and possible mechanisms as to how these may contribute to the protective properties of HDL in humans.

Introduction

Atherosclerosis is a multifactorial disease that is characterized by excess accumulation of lipids, in particular cholesterol, in lesions throughout the arterial tree. With 60% of the cholesterol in the circulation being associated with low-density lipoproteins (LDL), elevated concentrations of LDL-cholesterol (LDL-C) have been identified as the primary risk factor for atherosclerotic diseases. Approximately 20% to 30% of circulating cholesterol is associated with the high-density lipoproteins (HDL) and high levels of HDL-cholesterol (HDL-C) are associated with reduced risk. In spite of the wealth of new data on the pathogenesis of atherosclerosis, the exact role of HDL as an antiatherogenic agent is still unclear. Our current understanding of HDL physiology would suggest at least two mechanisms through which HDL could modulate development and progression of atherosclerotic diseases. HDL can affect the deposition of cholesterol in peripheral tissues by promoting the efflux of cholesterol from cells as part of the process known as reverse cholesterol transport.[1] HDL can also affect the progression of the disease by modulating the responses to oxidative stress and inflammatory insult.[2] A detailed discussion of both these processes is available elsewhere in this issue. In this review, we will focus on the specific enzymes that are present on plasma HDL and can contribute to these processes.

Contrary to common perception, HDL is a heterogeneous mixture of particles ranging in diameter from 7 nm to 10 to 11 nm. By density, as many as five different subpopulations of HDL particles have been characterized. Using the phospholipid contents as a rough estimate of the surface area for the various HDL, it is important to note that the surface area available for interactions with other lipoprotein particles and with cell surfaces could differ by a factor of 5 between large HDL and small HDL.[3,4] Using more sophisticated techniques that take into account differences in size, electrostatic charge and apolipoprotein composition as many as

* Corresponding author.
E-mail address: ale@emory.edu
Submitted January 23, 2007. Accepted for publication January 30, 2007.

1933-2874/$ -see front matter
doi:10.1016/j.jacl.2007.01.005

10 different subspecies of HDL may be identified.[5] From the perspective of the clinical management, however, only total cholesterol contents in HDL and the concentration of apolipoprotein A-I (ApoA-I), the major protein in HDL, are available.

Enzymes of reverse cholesterol transport

There are three key enzymes that are involved in the metabolism of HDL as it relates to the transport of cholesterol from peripheral tissues back to the liver. They are commonly referred to as the lipid transfer proteins, and include phospholipid transfer protein (PLTP), lecithin-cholesterol acyl transferase (LCAT), and cholesteryl ester transfer protein (CETP). They appear to function in a sequential process and complement one another with the product of one enzyme serving as the substrate for the next. In the following sections, current theories will be discussed regarding how alterations in any of the steps in this process can affect the normal and efficient delivery of cholesterol back to the liver.

PLTP

Human PLTP mRNA is most abundant in the placenta, pancreas, and lungs. This is notably different from the distribution of synthetic sites for the other major lipid transfer protein, CETP, which is made primarily in the liver, spleen, and adipose tissue. There are two forms of PLTP present in plasma; the low activity form is associated with ApoA-I, while the high-activity form is associated with ApoE.[6] PLTP is believed to play a key role in the transfer of phospholipids from remnant lipoproteins to ApoA-I−containing particles with pre-β mobility, the preferred acceptor of cellular cholesterol.[7] PLTP can also enhance cholesterol efflux by stabilizing the interactions of ApoA-I and the ATP binding cassette transporter A1 (ABCA-1).[8]

PLTP activity has been reported to be increased in patients with type 1 diabetes mellitus[9] and is positively associated with very-low-density lipoprotein (VLDL), LDL-C, and LDL particle number.[10] Patients with primary hypertriglyceridemia have also been reported to have higher PLTP activity as compared to normotriglyceridemic controls, in spite of lower PLTP concentrations in plasma.[11] With weight loss, reduction in plasma triglycerides (TG) is accompanied by a modest reduction in PLTP activity, which appears to be linked to changes in subcutaneous fat and plasma-free fatty acid levels.[12] In patients with CHD, PLTP activity is a risk factor for future vascular events[13] and a positive correlation has been reported between PLTP activity and ApoA-I−containing HDL particles.[14] Patients with the highest quintile of PLTP activity had a 1.9-fold increase in risk, compared to those in the lowest quintile. PLTP mass, on the other hand, has been suggested to be atheroprotective,[15] but additional studies are required to explain the disparities in the correlations of risk with protein mass and with transfer activity in this system.

Transient overexpression of human PLTP resulted in a fall in HDL lipids and ApoA-I,[16] with most of the ApoA-I being associated with the small pre-β HDL fraction. A 92% reduction in plasma cholesterol has been reported in transgenic mice, which demonstrated a 15-fold overexpression of human PLTP.[17] In these animals, there was a 1.8-fold increase in the cholesteryl ester content of the liver as well as a 40% increase in fecal bile acid secretion. It has been suggested that increased PLTP activity may promote the delivery of cholesterol from lipoproteins to the liver with enhanced excretion of cholesterol into the bile. In the absence of the LDL receptor (LDL receptor−deficient, $LDLR^{-/-}$, mice), overexpression of PLTP is, however, associated with decreased HDL levels and increased atherosclerosis,[18] suggesting the contribution of other metabolic processes in the wild-type mouse, such as enhanced transport of LDL through the LDL receptor in this protective effect of PLTP.

In mice with PLTP deficiency, there was a consistent increase in vitamin-E content in the VLDL-LDL fractions, a prolonged lag time for Cu^{++}-induced oxidation of LDL, and lower titers of autoantibodies to oxidized LDL.[19] Thus, the enhanced protection of the atherogenic lipoproteins from oxidative modification in PLTP deficiency may explain why high PLTP activity is proatherogenic. Whether similar processes can be demonstrated in humans remain unknown.

The current hypothesis that protection from atherosclerosis depends on the availability of high concentrations of the low-activity form of PLTP (LA-PLTP, Fig. 1A) that can stabilize the interactions between ABCA-1 and apoA-I to enhance cholesterol efflux. However, preferential association of the high-activity form of PLTP to ApoE-containing lipoproteins (HA-PLTP, Fig. 1A), possibly the atherogenic remnant lipoproteins, is proatherogenic. It is not clear from available data whether these two forms of PLTP are products from different genes are they are the same protein with the activity being dependent on the carrier lipoproteins.

LCAT

Pre-β HDL are formed in the liver and secreted into the plasma containing ApoA-I with phospholipids and free cholesterol. They can also be formed in the plasma space with the release of ApoA-I during processing of mature HDL followed by the addition of phospholipids by PLTP and cholesterol through interaction with cell surfaces and the ABCA-I transporter. These are typically discoidal in appearance and may aggregate as stacked discs (rouleaux, LCAT deficiency[20]). In the presence of LCAT and plasma lecithin, free cholesterol is readily esterified with the formation of lysolecithin.[21] Because cholesteryl esters (CE) are more hydrophobic, they tend to move away from the surface toward the center of the particle, thus transforming discoidal HDL to a more spherical structure. ApoA-I is preferred for