Cardioprotection With High-Density Lipoproteins
Fact or Fiction?
Dipak K. Das

Epidemiological studies strongly suggest an inverse correlation between plasma high-density lipoprotein (HDL) concentration and the risk of ischemic heart disease.1,2 Experimental evidence also indicates cardioprotective effects of HDL.3 However, the mechanism for protective effect of HDL against ischemic heart disease is not completely understood. Although the widely accepted mechanism comprises the ability of HDL to enhance reverse cholesterol transport,4 cholesterol-independent mechanisms have also been postulated. For example, lower HDL is associated with endothelial cell injury, which is involved both in the progression of atherogenesis and myocardial ischemia-reperfusion injury. The ability of HDL to inhibit endothelial adhesion molecule expression5 and to potentiate prostacyclin release from the endothelial cells6 further supports cholesterol-independent mechanism of HDL.

Antiatherogenic property of HDL is mediated by its ability to release cholesterol from lipid-containing cells followed by esterification through lecithin:cholesterol acyltransferase and delivery to the liver and to steroidogenic organs for subsequent synthesis of bile acids and lipoproteins.7 Most importantly, HDL can inhibit oxidation of low-density lipoprotein (LDL) as well as the atherogenic effects of oxidized LDL by virtue of its antioxidant property.

Atherosclerosis is an inflammatory disease characterized by adhesion of circulating monocytes to activated endothelial cells followed by migration to the subendothelium with the help of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin.8 Consistent with these reports, there is an increased expression of adhesion molecules in atherosclerotic plaque9 and upregulation of adhesion molecules in the acute thrombotic process.10 Recently, an increased plasma concentration of soluble adhesion molecules has been described as a risk factor for ischemic heart disease.11 The adhesion molecules are synthesized in the endothelial cells by the cytokines including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). An increased expression of TNF-α has been reported in human atherclerosis.12 A recent study showed protection of endothelial cells from TNF-α-induced apoptosis by HDL.13 In that study, the authors demonstrated that HDL prevented apoptosis of human umbilical venous endothelial cells (HUVECs) induced by TNF-α via an inhibition of CPP32-like protease activity. The incubation of HUVECs with TNF-α significantly increased CPP32-like protease activity and induced apoptosis.

Prostacyclin (PGI₂), a vasodilator that contributes to the maintenance of vascular tone, may also function as an endogenous antiatherogenic molecule.14 The antiatherogenic property of PGI₂ is attributed to its ability to inhibit platelet aggregation and adhesion and to block leukocyte activation and adhesion. Several reports exist in the literature indicating PGI₂ release by HDL by a Cox-2–dependent mechanism although Cox-1 may also have some role.15 Cox-2 induction by HDL may be viewed as heart’s own effort to upregulate its own defense to limit the deleterious effects of ischemia and reperfusion.

In this issue of Circulation Research, Calabresi et al16 reported HDL protection of isolated rat hearts from ischemia/reperfusion injury by a mechanism that involves reduction of cardiac TNF-α and enhancement of prostaglandin release. Preperfusion of the isolated hearts with HDL improved posts ischemic functional recovery and reduced creatine kinase release from the heart indicating cardioprotective effects of HDL. These results were corroborated by a reduction in the ischemia-induced expression of TNF-α and enhancement of prostaglandin release. The rate-limiting enzyme for the prostaglandin synthesis is cyclooxygenase, which is present in two different forms. Cyclooxygenase-1 (Cox-1) is ubiquitously present in many tissues, whereas cyclooxygenase-2 (Cox-2) is usually absent in the cells, but induced upon stimulation by agents like cytokines and mitogens.17 A recent study demonstrated that HDL could induce PGI₂ release in Cox-2–dependent manner and that its synthesis is regulated by both transcriptional and translational machineries.18 The study showed several-fold increase in HDL–induced release of PGI₂, which was blocked by a selective Cox-2 inhibitor, (N-(2-cyclohexyloxy-4-nitrophenyl)methanesulphonamide). Cycloheximide, actinomycin D, and dexamethasone downregulated HDL-induced PGI₂ synthesis, suggesting de novo synthesis of protein and mRNA of Cox-2 by HDL.

HDL can differentially modulate cytokine-induced expression of E-selectin and Cox-2.18 Preincubation with HDL completely abolished E-selectin expression in the endothelial cells in response to TNF-α. Transient cotransfection experiments determined that HDL could inhibit cytokine-induced expression of a reporter gene driven by the E-selectin proximal promoter. HDL did not influence the nuclear translocation or DNA binding of NF-κB or alter the kinetics of degradation and resynthesis of the inhibitory protein IκBα.
HDL synergized with cytokine to enhance the expression of Cox-2 and induce the synthesis of PGI₂. Thus, the results of this study indicates that HDL is able to counteract cytokine-induced inflammatory response in the endothelial cells by simultaneous upregulation of Cox-2 and inhibition of the expression of adhesion molecules in an NF-κB–independent pathway.

A recent study showed that enhancement of the cytokine-activated human primary monocytes production of matrix metalloproteinase-1 (MMP-1) by oxidized LDL can be inhibited by adding HDL in conjunction with oxidized LDL. MMPs are composed of a family of proteolytic enzymes that are capable of degrading extracellular matrix components. Recently, MMP-1 has been found to colocalize with monocytes/macrophages in regions of enhanced collagenolysis within rupture-prone plaques. Interestingly, the regulation of HDL- and LDL-induced MMP-1 production in cytokine-activated monocytes is mediated, in part through Cox-2 and PGE₂. Although the mechanism for HDL inhibition of the enhancement of MMP-1 is not clear, CD36 is likely to be involved because similar to oxidized LDL, HDL, and LDL also possess high affinity for this scavenger receptor. It may be possible that high concentration of HDL saturate the binding sites of the CD36 receptor, thereby limiting oxidized LDL uptake and MMP-1 production.

It should be clear from this discussion that a crucial event in atherogenesis is endothelial activation by a variety of factors including cytokines such as TNF-α resulting in the expression of a variety of adhesion molecules. Sphingosine kinase signaling may play a significant role in this process because sphingosine-1-phosphate, generated by sphingosine kinase activation, is a key factor responsible for TNF-α–induced adhesion molecule expression. A recent study demonstrated that HDL could inhibit TNF-α–mediated upregulation of sphingosine kinase activity in endothelial cells resulting in a reduction in sphingosine-1-phosphate production leading to a downregulation of adhesion protein expression. In concert, HDL reduced TNF-α–mediated activation of extracellular signal regulated kinases and NF-κB signaling cascades. Additionally, HDL enhanced the cellular levels of ceramide resulting in the inhibition of endothelial activation. Thus, HDL appears to interrupt a sphingosine kinase signaling pathway, which is involved in endothelial cell activation and adhesion molecule generation.

In summary, the results based on the epidemiological studies indicating an inverse relationship between plasma HDL concentration and the risk of ischemic heart disease is now supported from the experimental evidence. A significant number of reports exist in the literature supporting cardioprotective role of HDL. One of the pioneer studies involved infusion of HDL during ischemia and examining ventricular arrhythmias. In that study, the authors found that HDL significantly inhibited incidence of ischemia/reperfusion-induced ventricular arrhythmias by a mechanism involving PGI₂. It appears that HDL provides cardioprotection through diverse mechanisms including reduction of adhesion molecules, increase in PGE₂ and PGI₂, inhibition of MMP-1, antioxidant action, and interruption of sphingosine kinase signaling pathway (Figure 1). It is tempting to speculate that a direct HDL therapy or using a drug to enhance HDL content may also alleviate the severity of ischemia/reperfusion injury.

References


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