Review

HDL-Cholesterol: Pro-Inflammatory and Anti-Inflammatory Effects

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The anti-atherogenic properties of high density lipoprotein (HDL) - cholesterol are nowadays widely accepted. The main protective role of HDL lies in its contribution to the reverse cholesterol transport from the peripheral tissues to the liver. In recent years, however, investigations–mainly at the level of basic research–have shown that HDL also exerts its anti-atherogenic effects through other mechanisms. These mechanisms are of particular interest, since their discovery provides indirect confirmation of the latest theories of atherogenesis, which are centred on the oxidation of lipoproteins and inflammation of the vascular wall.

HDL-cholesterol and coronary artery disease

The first indications of the protective role of HDL arose from epidemiological studies during the 1970s.[1,2] The Framingham study subsequently showed that HDL was the lipidaemic factor with the strongest predictive capability for the development of coronary artery disease in men and women over 49 years old.[3] Newer studies confirmed these findings and showed that an increase in HDL by 1 mg/dl leads to a reduction in cardiovascular risk by 2% in men and by 3% in women.[4] The findings of certain clinical trials also showed that therapeutic interventions aimed at increasing HDL levels reduced the risk of coronary heart disease. Thus, the Helsinki Heart Study showed that increasing HDL by 11% via administration of gemfibrozil reduced the risk of coronary events in men.[5] Moreover, in the recent Veteran Affairs HDL Intervention Trial, although the administration of gemfibrozil did not lower LDL levels, HDL increased by 6% and the risk of both death and non-fatal myocardial infarction was reduced significantly.[6] The role, therefore, of HDL-cholesterol in the prevention and treatment of atherosclerosis is coming to seem more and more important. In recent years this has led important international scientific bodies to issue treatment guidelines aimed at increasing HDL levels.[7,8]

The structure of HDL cholesterol

The HDL-cholesterol fraction consists of small, dense, spherical lipoprotein complexes that are formed mainly in the liver and the small bowel. The lipids in the complex include phospholipids, cholesterol, cholesterol esters and triglycerides, while the protein part is made up of apolipoproteins A-I, A-II, E, C, A-IV, J

and D. The HDL particle also includes other small protein compounds that are of particular pathophysiological significance, such as paraoxonase, platelet activating factor-acetylhydrolase (PAF-AH), lecithin: cholesterol acyltransferase (LCAT) and cholesterol ester transfer protein (CETP). The main vascular protective action of HDL-cholesterol is due to these enzymes and to apolipoproteins A-I, A-IV and E. The HDL molecules circulating in the plasma are divided into subgroups according to their density and apolipoprotein composition. Thus, on the basis of density they are divided into HDL_2 (larger and less dense) and HDL_3 (smaller and denser), while agaroze gel electrophoresis further discriminates the basic HDL fraction (α-lipoproteins) and a small fraction, pre-β-HDL.[9] The recognition of these subgroups is important, given that they show differences in their anti-atherogenic action.

Atherosclerosis: An inflammatory disease

Atherosclerosis, according to modern viewpoints, is a chronic inflammatory process in combination with fibrous degeneration that affects the intima of large and medium-sized arteries.[10] The vital importance of vascular inflammation has been recognised in recent years in the light of findings from basic research and epidemiological studies. Indeed, 10 large prospective studies that have been carried out to date have clearly shown that the C-reactive protein is a powerful and independent predictor of future cardiovascular events in healthy men and women.[11,12] Many studies have also shown that treatment for the prevention of coronary artery disease offers a greater benefit to those individuals who have the highest values of inflammatory indices.[13] Based on these data, one can predict with some confidence that inflammation, apart from its already recognised contribution to the appearance and progression of atherosclerosis, may in the future itself become a new therapeutic target in the battle to fight the disease. Indeed, recent efforts to treat coronary artery disease with the use of antibiotics (newer macrolides) have been focused in precisely this direction. Related clinical trials, however, have so far produced conflicting results. Higgins[14] very recently published an extensive review of these studies and concluded that the short duration of macrolide administration to patients with a recent acute myocardial infarction or chronic coronary artery disease has not so far been shown to reduce the incidence of cardiovascular events. The same author notes that in patients with an acute coronary syndrome some studies showed a benefit while others did not. This question, then, remains open, given that in most of these studies antibiotics were given for a short and perhaps insufficient period of time. The definitive answer will come from the results of larger and better organised clinical trials that are still under way.

HDL-Cholesterol: Antioxidative and anti-inflammatory action

Based on the data from very recent studies, a part of the anti-atherogenic action of HDL-cholesterol can be attributed to the anti-inflammatory properties of its molecule. This anti-inflammatory action is directly connected with the antioxidative properties of certain compounds that help to make up the HDL molecule, given that an increase in the concentration of the products of lipid oxidation is the main stimulus that starts the inflammatory procedure that leads to the formation of atheromatous plaque. These compounds are apolipoprotein A-I, paraoxonase, PAF-AH and LCAT.

Apolopoprotein A-I

Apolipoprotein A-I has perhaps the greatest biological significance of all the ingredients of the HDL molecule. Apart from the fact that it plays a vital role in reverse cholesterol transport, it has clear antioxidative and anti-inflammatory properties. As Hayek et al showed,[15] insertion of the human apolipoprotein A-I gene into mouse DNA resulted in very high levels of apolipoprotein A-I in the animals' plasma, sufficient to reduce LDL-cholesterol oxidation *in vitro* by 50%.

Furthermore, recently Navab et al[16,17] published the results of a series of experiments that discovered a great deal of evidence about both the pathophysiological mechanism of LDL oxidation and the inhibitory effect of apolipoprotein A on that process. Those researchers proposed the view that LDL oxidation involves 3 stages. In the first stage the LDL molecule is combined with products of linoleic and arachidonic acid metabolism and with cholesterol hydroperoxide. In the second stage the LDL is trapped in the subendothelial region, while other products of oxidation arising from the action of 12-lipoxygenase,

which is produced by the cells of the arterial wall, are added to its molecule. Finally, in the third stage the HDL phospholipids are also oxidised and the oxidised lipids that result cause monocytes to connect to the endothelium, to enter the subendothelial region and to be transformed into macrophages. Apolipoprotein A-I appears to have an inhibitory effect on all 3 stages of LDL oxidation, removing oxidised lipids from its molecule. The same researchers found that the administration of human apolipoprotein A-I makes the LDL–in both animals and humans–resistant to the oxidative action of cells in the vascular wall.

It should be noted, however, that the anti-inflammatory action of apolipoprotein A-I also extends beyond inhibiting the production of toxic oxidised lipids. Recent experimental studies have shown that HDL has an inhibitory effect on the production of adhesion molecules (E-selectin, ICAM-1 and VCAM-1) by endothelial cells that have been exposed to the action of cytokines.[18,19] The central role in this action of HDL appears to be played by apolipoprotein A-I, but in combination with the phospholipids of the lipoprotein molecule.[20] In addition, a new mechanism of action of apolipoprotein was discovered recently by Hyka et al.[21] These researchers found that apolipoprotein A-I inhibits the production of inflammatory cytokines (interleukin-1β and TNF-α), blocking the connection between activated T-lymphocytes and monocytes in the blood. The practical significance of these findings is made more clear by data from animal studies such as the one by Shah et al,[22] who showed that the administration of a dose of recombinant apolipoprotein A-I to apolipoprotein E-deficient mice (which were thus susceptible to rapid development of extensive atherosclerotic lesions when put on a fatty diet) not only reduced the extent of the atherosclerotic plaques by 50% but also decreased their macrophage content by 29-36% over a 48-hour period. Furthermore, the implantation by Rong et al[23] of the human apolipoprotein A-I gene in animals with extensive atherosclerotic lesions led to an 80% reduction in macrophages and a 300% increase in smooth muscle cells in the region of the lesion, suggesting that apolipoprotein A-I is likely to play a positive role in the stabilisation of atheromatous plaque. Finally, in a very recent study by Sampietro et al,[24] who studied a population of 50 individuals with hypoalphalipoproteinemia (characterised by very low levels of HDL and apolipoprotein A-I), it was found that these subjects had very high values of C-reactive protein compared to normal individuals and that these values had a significant negative correlation with levels of both HDL and apolipoprotein A-I.

Paraoxonase

The antioxidative and anti-inflammatory action of the HDL molecule, however, is not related exclusively with the existence of apolipoprotein A-I. Another biologically active element of HDL is the paraoxonase enzyme, an esterase that is used to neutralise the toxic action of organophosphate compounds in the organism, mainly in the liver, and joins with the HDL-cholesterol molecule.[25] The gene responsible for the production of paraoxonase has been described and its location has been determined precisely. In fact, polymorphism of this gene has also been described. More specifically, the existence of the amino acid glutamine in position 192 characterises Isoenzyme Q, which has low paraoxonase activity. In contrast, replacement of glutamine by arginine leads to the creation of Isoenzyme R, which exhibits high paraoxonase activity.[26]

Paraoxonase has a strong antioxidative action, given that it is capable of hydrolysing the oxidised phospholipids that are formed during the third stage of LDL oxidation.[27] In a laboratory setting Shih et al[28] created experimental animals that were completely lacking in the paraoxonase gene. The HDL that was isolated from the homozygote animals was unable to inhibit LDL oxidation in a cell culture model. In addition, the administration of a diet with high fat content led to clearly more extensive aortic atherosclerotic lesions in those animals compared to controls. In humans, too, it has been shown that both the levels and the potency of the enzyme are lower in patients with acute myocardial infarction.[29] Furthermore, studies of patients and controls have shown that polymorphism of the paraoxonase gene is related with a higher risk of coronary atherosclerosis in both diabetics[30] and non-diabetics.[31] In any event, according to many recent studies only a part of the antioxidative action of HDL is due to paraoxonase.[32]

PAF-AH

Another portion of the antioxidative and anti-inflammatory action of HDL is attributable to the

connection of its molecule with the PAF-AH enzyme. Platelet activating factor (PAF) is implicated in the early phase of atherosclerosis, being produced by the endothelial cells under the influence of free oxygen radicals and products of lipid oxidation. PAF itself stimulates the macrophages, which produce peroxide anions, thus perpetuating the vicious circle of increased oxidative stress leading to an intensification of the inflammatory process and promotion of atherosclerosis.[33,34] In addition, as mentioned above, the third phase of LDL oxidation includes the formation of oxidised phospholipids, which also have PAF activity. PAF-AH is an enzyme that hydrolyses PAF and joins with molecules of both LDL and HDL.[35] Since the beginning of the 1990s studies have shown that PAF has a powerful inflammatory action and a little later Tjoelker et al[36] found that administration of PAF-AH to experimental animals inhibited the inflammation process. Subsequent studies connected the anti-inflammatory with the anti-atherogenic effects of PAF-AH. Theilmeir et al[37] used an adenovirus to implant the human PAF-AH gene in apolipoprotein E-deficient mice and found that the PAF-AH significantly reduced the tendency for macrophages to adhere to the aorta in those animals. Furthermore, using similar methods Quark et al[38] showed that PAF-AH reduced the extent of atherosclerotic lesions by 42% and restenosis by 77% in apolipoprotein E-deficient mice. These findings have been confirmed by epidemiological studies showing that mutations of the PAF-AH gene are an independent risk factor for coronary artery disease,[39] while low levels of the enzyme have been found in patients with acute myocardial infarction.[40]

LCAT

Finally, LCAT, apart from its role in reverse cholesterol transport, also appears to have antioxidative properties. Klimov et al first showed that the incubation of partially purified LCAT with LDL led to the inhibition of malonyldialdehyde formation.[41] Vohl et al[41] confirmed this finding, showing that LCAT that had been completely purified of other HDL ingredients was able to inhibit the accumulation of oxidised lipids in the LDL molecule. In any event, when oxidised LDL is formed, in its turn it inhibits the activity of LCAT, thus blocking the reverse cholesterol transport process.[42]

HDL during the acute phase of inflammation: A "chameleon" molecule

Recent studies have shown that HDL-cholesterol undergoes structural alteration during the phase of acute inflammation. This leads not only to the loss of its normal antioxidative and anti-inflammatory action, but also to its transformation into an inflammatory agent. The first observations in this respect noted a drop in HDL levels during the acute phase.[43] So far we have no satisfactory explanation for this increased HDL clearance, but it is certain that the most important changes undergone by HDL during the acute phase lie elsewhere and are related to its composition in terms of both lipids and protein factors. As was demonstrated in an important study by Van Lenten et al,[44] during the acute phase HDL loses a large part of both its paraoxonase and its PAF-AH. In contrast, there is a significant increase in the combination of the HDL molecule with ceruloplasmin, which normally transports copper in the plasma and enhances LDL oxidation.[45,46] As the same researchers[45] also showed, in the acute phase HDL loses 73% of its apolipoprotein A-I, whose place is taken by amyloid A. Finally, these changes in composition are also accompanied by changes in the function of HDL, which consist of an inability to inhibit LDL oxidation and an increase in the expression of monocyte chemotactic agents (MCP-1) in cell cultures. Other studies have shown that the LCAT enzymes[47] and CETP[48] have significantly reduced activity during the acute inflammatory phase, which could potentially have a significant influence on the process of reverse cholesterol transport by HDL. In contrast, the activity of phospholipase A2 increases,[49] but this could also promote atherogenesis since the increased rate of hydrolysis and removal and the reduced phospholipid capacity of HDL increase the cholesterol flux from HDL towards the cells.[50]

A more recent study showed additionally that the changes in the acute phase also concern HDL lipids.[51] Specifically, the authors noted a reduction in cholesterol esters, isoprostanoids and acidic phospholipids, whereas there was an increase in triacylglycerol, lysophosphatidylcholine, free cholesterol and free fatty acids. Certain lipids, such as lysophosphatidylcholine, have been shown to promote inflam-

mation via an increase in monocyte chemotaxis[52] as well as an in the production of adhesion molecules in cultures of endothelial cells.[53]

It seems, therefore, that the overall change in the HDL molecule during the acute phase of inflammation converts this lipoprotein from an antioxidative, anti-inflammatory and hence anti-atherogenic factor into an agent that promotes inflammation and atherosclerosis. That this hypothesis seems to hold true in vivo, at least in animals, was shown by Van Lenten et al,[54] who observed that during acute infection by the influenza A virus HDL loses its anti-inflammatory properties.

Conclusions

Today there is a large body of research data to form a foundation for modern views concerning the multiplicity of the anti-atherogenic action of HDL-cholesterol. Its main vascular protective role is still considered to be the removal of cholesterol from the peripheral tissues via its reverse transport mechanism. However, the antioxidative and anti-inflammatory action of HDL, which is due to specific protein elements in its molecule, also appears to be of particular pathophysiological significance. Moreover, the recently demonstrated antioxidative and anti-inflammatory properties of fibrates,[55,56] the only widely used drugs for increasing HDL, provide indirect confirmation of this hypothesis and turn our therapeutic interest towards not only increasing HDL, but also correcting the functional disturbances that characterise its molecule. At the same time, intervention using genetic techniques, such as the transfer of the apolipoprotein A-I gene that has already been accomplished at the experimental level,[57] hold out promise of an amazing future from the therapeutic point of view. Finally, the structural and functional changes that characterise the HDL-cholesterol molecule during the phase of acute inflammation are worthy of further study, which is likely to lead to a deeper understanding of the pathophysiological mechanisms of atherosclerosis.

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